# Role of Immune System in Chronic Primary Pain Conditions

Vivek Verma

Integrated Program in Neuroscience

Faculty of Medicine

McGill University

Montréal, Québec, Canada

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# List of abbreviations

| Abbreviation | Description |
|---|---|
| **ADNKA** | Antibody-Dependent NK cell Activation |
| **AECRP** | Alan Edwards Centre for Research on Pain |
| **AF** | Alexa-fluor |
| **AIDS** | Acquired Immune Deficiency Syndrome |
| **AMPA** | α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid |
| **ANOVA** | Analysis of variance |
| **APC** | Allophycocyanin |
| **ATP** | Adenosine Tri-Phosphate |
| **BAI** | Beck Anxiety Inventory |
| **BDI** | Beck Depression Inventory |
| **BDNF** | Brain-Derived Neurotrophic Factor |
| **BMD** | B-Mono-Dc |
| **BMI** | Body Mass Index |
| **CCL** | Chemokine (C-C motif) Ligand |
| **CCR** | CC chemokine receptor |
| **CD** | Cluster of Differentiation |
| **CERC** | Canada Excellence Research Chairs |
| **CFA** | Complete Freund's Adjuvant |
| **CIM-11** | Classification Internationale des Maladies-11 |
| **CPI** | Characteristic Pain Intensity |
| **CPSQ** | Comprehensive Pain Symptom Questionnaire |
| **CNS** | Central Nervous System |
| **$CO_2$** | Carbon dioxide |
| **COX** | Cyclo-OXygenase |
| **CRP** | C-reactive protein |
| **CV** | Cross-Validation |
| **CXCL** | chemokine (C-X-C motif) Ligand |
| **CXCR** | chemokine (C-X-C motif) Receptor |
| **DC** | Dendritic Cells |
| **DMSO** | Dimethyl Sulfoxide |
| **DNA** | DeoxyriboNucleic Acid |
| **DNAM** | DNAX Accessory Molecule |
| **DRG** | Dorsal Root Ganglion / Dorsal Root Ganglia |
| **EDTA** | Ethylenediaminetetraacetic acid |
| **EGFR** | Epidermal growth factor receptor |
| **EM** | Expectation Maximization |
| **EQTL** | Expression Quantitative Trait Loci |

| | |
|---|---|
| **EREG** | Epiregulin |
| **ESR** | Erythrocyte Sedimentation Rate |
| **FBS** | Fetal Bovine Serum |
| **FDR** | False Discovery Rate |
| **FITC** | Fluorescein isothiocyanate |
| **FMO** | Fluorescent Minus One |
| **FMS** | Fibromyalgia Syndrome |
| **GAP** | Global Assessment of Pain |
| **HIV** | Human Immunodeficiency Virus |
| **HLA** | Human Leukocyte Antigen |
| **HW** | Hardy-Weinberg |
| **IASP** | International Association for the Study of Pain |
| **ICD** | International Classification Of Diseases |
| **IENF** | intra-epidermal nerve fiber |
| **IENFD** | intra-epidermal nerve fiber deficiency |
| **IG** | Immunoglobulin |
| **IL** | Interleukin |
| **IMDM** | Iscove's Modified Dulbecco's Media |
| **IRB** | Institutional Review Board |
| **ITIM** | immunoreceptor tyrosine-based inhibitory motif |
| **IU** | International Units |
| **IV** | Intravenous |
| **LASER** | Light Amplification by Stimulated Emission of Radiation |
| **LPS** | lipopolysaccharide |
| **MD** | Maryland |
| **MHC** | Major Histocompatibility Complex |
| **MS** | Multiple Sclerosis |
| **MUHC** | McGill University Health Centre |
| **NCAM** | Neural Cell Adhesion Molecule |
| **NIAID** | National Institute for Allergy and Infectious Diseases |
| **NIH** | National Institutes of Health |
| **NJ** | New Jersey |
| **NK** | Natural Killer |
| **NKA** | NK Activation |
| **NLR** | NOD-like |
| **NMDA** | N-Methyl-D-aspartate |
| **NOD** | Nucleotide-binding Oligomerization Domain |
| **NRS** | Numeral Rating Scale |
| **NSAIDs** | Non-Steroidal Anti-Inflammatory Drugs |
| **NY** | New York |
| **ON** | Ontario |

| | |
|---|---|
| **OPPERA** | Orofacial Pain: Prospective Evaluation and Risk Assessment |
| **OR** | Odds Ratio |
| **PBMC** | Peripheral Blood Mononuclear Cells |
| **PBS** | Phosphate-Buffered Saline |
| **PE** | Phycoerythrin |
| **PILL** | Pennebaker Inventory for Limbic Languidness |
| **PMT** | PhotoMultiplier Tubes |
| **PSQI** | Pittsburgh Sleep Quality Index |
| **PSS** | Perceived Stress Scale |
| **QC** | Quality Control |
| **QTL** | Quantitative Trait Loci |
| **RA** | Rheumatoid Arthritis |
| **RDC** | Research Diagnostic Criteria |
| **REDCap** | Research Electronic Data Capture |
| **REF** | Reference |
| **RI-MUHC** | Research Institute of the McGill University Health Centre |
| **RNA** | RiboNucleic Acid |
| **RPMI** | Roswell Park Memorial Institute |
| **SCL90R** | Symptom Checklist-90-Revised |
| **SD** | Standard Deviation |
| **SE** | Standard Error |
| **SEM** | Standard Error of the Mean |
| **SEP** | Sub-Epidermal nerve plexus |
| **SNI** | Spared Nerve Injury |
| **SNP** | Single nucleotide polymorphism |
| **TACTILE** | T-cell Activation, Increased Late Expression |
| **TIGIT** | T-cell Immunoreceptor With Ig And ITIM Domains |
| **TLR** | Toll-Like Receptors |
| **TMD** | TemporoMandibular Disorders |
| **t-SNE** | t-distributed Stochastic Neighbor Embedding |
| **UK** | United Kingdom |
| **UKB** | UK Biobank |
| **ULBP** | UL16 Binding Protein |
| **UMAP** | Uniform Manifold Approximation and Projection |
| **UNC** | University of North Carolina |
| **US** | United States |
| **USA** | United States of America |
| **UTR** | UnTranslated Region |
| **UV** | Ultra-Violet |
| **WHO** | World Health Organization |
| **WT** | Wild Type |

# Abstract

International classification of diseases-11 (ICD-11) classifies chronic primary pain conditions like temporomandibular pain disorders and fibromyalgia syndrome under Chapter 21 ("*symptoms, signs or clinical findings, not elsewhere classified*"). such conditions lack well-defined etiology and diagnosis. Our understanding of chronic primary pain conditions is incomplete, and these conditions are not just limited to anomalies in sensory perception of pain but involve multiple systems. The immune system is one of those contributors to the pathophysiology of chronic primary pain. This thesis explores the role of the immune system in pain modulation. Specifically, we will focus on two chronic primary pain conditions: temporomandibular disorder (TMD) and fibromyalgia syndrome (FMS). Chapter I would summarize the literature on the general involvement of the immune system in enhancing and resolving pain, and how immune cells and neurons interact due to neuro-immune molecular overlap.

Chapter II will describe my first research project representing an important example of reverse translational research in the area of pain genetics and immunology. Here, we found an association between an inflammatory mediator, epiregulin (EREG), and chronic TMD through statistical genetics approaches. TMD, a major cause of nondental pain in the orofacial region, is characterized by craniofacial pain involving the joint, masticatory muscles, or muscle innervations of the head and neck. We found that loss of function EREG genetic variants are associated with chronic TMD and chronic pain intensity. Next, we found that the same genetic variants are analgesic during the acute stages of pain development. We then validated these associations in the large independent cohort.

Finally, we were able to confirm this dichotomous role of EREG in pain through animal pain models.

Chapter III deciphers the role of the immune response in another chronic musculoskeletal pain condition-fibromyalgia syndrome (FMS). FMS, a common rheumatic disease, is characterized by chronic widespread pain, fatigue, and, sleep and cognitive difficulties. Pathogenesis of this syndrome remains elusive leading to a lack of objective diagnosis and specific treatment. Although the immune system's involvement in FMS is irrefutable, the specifics are yet to be deciphered. Furthermore, numerous studies have described the presence of small fiber neuropathy in FMS patients, but the mechanism of development of this neuropathy is unknown. In chapter III, we investigate peripheral blood mononuclear cells (PBMCs) through flow cytometry and differential gene expression in a case-control manner. We found that the FMS cases have fewer circulating natural killer (NK) cells. Furthermore, these cells were activated and exhausted in FMS patients. Co-culturing these cells with HLA-/- cell line (an activation stimulus for NK cells) showed that the NK cells from FMS patients are hyperactive compare to controls. Lastly, skin biopsies from an independent cohort showed increased expression of ULBP (NK activation ligand) and recruitment of NK cells on the peripheral nerves of the patients.

In summary, this thesis advances our current understanding of the immune system's involvement in chronic primary pain conditions. Firstly, it demonstrates the dichotomies role of EREG in pain development being protective against acute pain but contributing to chronic pain. Secondly, we found the contribution of NK cells to FMS through its association with peripheral nerves in FMS. Both of these findings are novel

steppingstones on our understanding of the pathophysiology of chronic pain and have therapeutics implementations in the treatment of chronic primary pain conditions.

# Résumé

La 11ième version de la classification internationale des maladies (CIM-11) classe les affections chroniques de la douleur primaire, comme les troubles de la douleur temporomandibulaire et le syndrome de fibromyalgie, au chapitre 21 ("symptômes, signes ou constatations cliniques, non classés ailleurs"). Ces affections n'ont pas d'étiologie et de diagnostic bien définis. Notre compréhension des affections primaires de la douleur chronique est incomplète, et ces affections ne se limitent pas qu'aux anomalies de la perception sensorielle de la douleur mais impliquent aussi de multiples systèmes. Le système immunitaire est l'un de ceux qui contribuent à la physiopathologie de la douleur primaire chronique. Cette thèse explore le rôle du système immunitaire dans la modulation de la douleur. Plus précisément, nous nous concentrerons sur deux conditions de douleur primaire chronique: le trouble temporomandibulaire (TMD) et le syndrome de fibromyalgie (FMS).

Le chapitre I résumera la littérature sur l'implication générale du système immunitaire dans l'amélioration et la résolution de la douleur, et sur la manière dont les cellules immunitaires et les neurones interagissent en raison du chevauchement moléculaire neuro-immunitaire.

Le chapitre II décrira mon premier projet de recherche qui représente un exemple important de recherche translationnelle inverse dans le domaine de la génétique et de l'immunologie de la douleur. Nous y avons trouvé une association entre un médiateur inflammatoire, l'épireguline (EREG), et la TMD chronique par le biais d'une approche statistique de la génétique. Nous avons découvert que des variantes génétiques de

l'EREG de type perte de fonction sont associées à la TMD chronique et à l'intensité de la douleur chronique. Ensuite, nous avons découvert que les mêmes variantes génétiques sont analgésiques pendant les stades aigus du développement de la douleur. Nous avons ensuite validé ces associations dans une grande cohorte indépendante. Enfin, nous avons pu confirmer ce rôle dichotomique de l'EREG dans la douleur grâce à des modèles animaux de douleur.

Le chapitre III décrypte le rôle de la réponse immunitaire dans un autre état de douleur musculo-squelettique chronique, le FMS. Le FMS, une maladie rhumatismale courante, se caractérise par une douleur chronique généralisée, de la fatigue et des troubles cognitifs et du sommeil. La pathogenèse de ce syndrome reste insaisissable, ce qui entraîne un manque de diagnostic objectif et des traitements spécifiques. Bien que l'implication du système immunitaire dans le FMS soit irréfutable, les spécificités restent encore à être déchiffrés. En outre, de nombreuses études ont décrit la présence d'une neuropathie des petites fibres chez les patients atteints du FMS, mais le mécanisme de développement de cette neuropathie est inconnu. De plus, dans ce chapitre, nous étudions les cellules mononucléaires du sang périphérique (PBMC) par cytométrie de flux et par expression différentielle de l’expression des gènes. Nous avons constaté que les cas de FMS ont moins de cellules immunitaires de type « tueuses naturelles » (NK, pour « Natural Killer » en anglais) en circulation. De plus, ces cellules étaient activées et épuisées chez les patients atteints du FMS. La co-culture de ces cellules avec la lignée cellulaire HLA-/- (un stimulus d'activation pour les cellules NK) a montré que les cellules NK des patients atteints du FMS sont hyperactives par rapport à celles chez les témoins. Enfin, des biopsies de la peau provenant d'une cohorte indépendante ont montré une

expression accrue de l'ULBP (ligand d'activation des NK) et un recrutement de cellules NK sur les nerfs périphériques des patients.

En résumé, cette thèse fait progresser notre compréhension actuelle de l'implication du système immunitaire dans les affections chroniques de la douleur primaire. Tout d'abord, elle démontre le rôle des dichotomies de l'EREG dans le développement de la douleur, étant protectrice contre la douleur aiguë mais contribuant à la douleur chronique. Deuxièmement, nous avons découvert la contribution des cellules NK au FMS par son association avec les nerfs périphériques dans le FMS. Ces deux découvertes constituent de nouvelles étapes dans notre compréhension de la physiopathologie de la douleur chronique et ont des applications thérapeutiques dans le traitement des affections primaires de la douleur chronique.

# Acknowledgments

First and foremost, I am grateful to my supervisor, Prof. Luda Diatchenko. She believed in me even during times of self-doubt. Luda's philosophical quotes are not only famous in our lab but also among other faculty members. *"As a researcher, 95% of what you'll do, you'll fail in it. But it will teach you something for sure, 100%"* helped me to keep sailing through this academic odyssey. "*Perseverance is harmful after a point*" taught me how and when to decide to pull brakes, switch lanes, and update my destinations. *"In today's world, one can find one journal article about anything"* made me realize how important it is to be a critique of the information in front of us and to be aware of our own biases. Along with learning how to do research, being Luda's student has contributed to my emotional maturity. Thanks to her humility, debating with her over scientific hypotheses is like having a heart-to-heart talk with a colleague, no filters, no hierarchy, just science, and often, humor. Her commendable feedbacks and extraordinary efficiency are noteworthy.

Secondly, I would like to thank my advisory committee members, Prof. Irah King and Prof. Ji Zhang for their continuous support. Dr. King's involvement in the development and maturation of my research project was beyond the responsibilities of a committee member which surely stems from his passion for immunology. Here, I would like to thank Prof. Laura Stone for being an excellent PhD mentor and getting me involved in chronic pain, even before my PhD enrollment.

Next, I would like to thank Prof. Carolina Beraldo Meloto. As my first mentor in Diatchenko's lab, she helped me in transitioning from a dentist to a researcher. While

Luda was the beacon, Carol was in the lab with me, training me from pipetting to thinking like a clinician-scientist. Dr. Katerina Zorina-Lichtenwalter, PhD student in Luda's lab then, was my "fellow inmate" in the grad life who exposed me to the new "North American" social life and guided me throughout the PhD process. Dr. Ryan Lichtenwalter, a geek with astonishing skillsets, taught me many complex concepts (like Principal Component Analysis) through easier-to-understand explanations. Dr. Marc Parisien, a maverick bioinformatician, exposed me to the world of computer coding. Nothing was more fun in the lab than having "coffee mug" discussions with Marc on topics like the future of the universe and the simulation theory of existence. I am grateful to Dr. Marc Parisien for proofreading the French abstract of this thesis and providing his valuable feedbacks. In addition, Dr. Samar Khoury, Dr. Alex Samoshkin, Dr. Pavel Gris, Dr. Stefano Cattaneo, Francesca Montagna, Sarah Jane Martinez, Dr. Rodrigo Benavides, Dr. Anne-Julie Chabot-Doré, Shawn Wen, Nicol Tugarinov, Masha Verner, Richie Klares, and Alex Linton have been a very supportive lab-mates.

I would like to thank my friends: Rahul, Ravi, Prabir, Karan, Janaki, Akanksha, Fahad, Mahendra, and Sreenath: thank you for putting up barbecues in the middle of winters; you guys rock! Lastly, I am grateful to my parents and my wife, Aparna. I couldn't imagine any achievement in my life without your benevolent support.

# Preface

## 1. Contribution of authors

This thesis describes the mechanistic involvement of the immune system in chronic pain conditions through three manuscripts.

Chapter I is a literature review summarizing our current understanding of the immune system, inflammation, and neuroimmune interactions in the perception of pain and its establishment as a chronic ailment. This chapter originally appeared as:

**Verma V, Sheikh Z, Ahmed AS. *Nociception and role of the immune system in pain*. Acta Neurol Belg. 2015 Sep;115(3):213-20. doi: 10.1007/s13760-014-0411-y. Epub 2014 Dec 30. PMID: 25547878.**

This manuscript was conceived and written entirely by me. Sheikh Z and Ahmed AS helped with the discussion and proofreading of the manuscript. Dr. Luda Diatchenko has provided her valuable feedbacks for this review post-publication. Her feedbacks are included in this thesis.

Chapter II focuses on epiregulin, an inflammatory mediator and a growth factor, and its contrasting effect on pain during acute and chronic stages of pain. This chapter originally appeared as:

**Verma V, Khoury S, Parisien M, Cho C, Maixner W, Martin LJ, Diatchenko L. *The dichotomous role of epiregulin in pain*. Pain. 2020 May;161(5):1052-1064. doi: 10.1097/j.pain.0000000000001792. PMID: 31917773**

This manuscript was conceived and written by me under Dr. Diatchenko's active guidance. Khoury S and Parisien M provided their expertise in statistical genetics. Maixner W contributed through proofreading and critical corrections before the manuscript submission. The animal experiments were performed by Martin LJ and Cho C at the University of Toronto.

Chapter III is a case-control study of fibromyalgia, a common and debilitating chronic pain condition. It includes immunophenotyping of peripheral blood mononuclear cells this is currently a manuscript that is being prepared for submission:

**Verma V, Drury G, Al-Aubodah T, Özdağ AN, Nijnik A, Wen X, Tugarinov N, Verner M, Klares RIII, Linton A, Piccirillo C, Fitzcharles MA, Ingelmo PM, Parisien M, Zhang J, Bernard N, Üçeyler N, Sommer C, King IL, Meloto CB, Diatchenko L. *An unbiased immune profiling approach reveals a Natural Killer cell-peripheral nerve axis in fibromyalgia*. 2021**

I have been involved with this project even before joining Dr. Diatchenko's lab as a PhD student (as a research assistant in 2014). Under the supervision of Diatchenko L and Meloto CB, I have worked on the research proposal, informed consent forms, patient recruitment and data collection, processing of blood samples, and analysis of the data. Drury G contributed through her background in immunology and expertise in flow cytometry. Parisien M provided his valuable inputs for mRNA data analysis. Fitzcharles MA and Ingelmo PM helped us with the evaluation and recruitment of the study participants. Piccirillo C and Al-Aubodah T aided in designing and conducting three immunophenotyping panels. Sommer C, Özdağ AN, and Üçeyler N planned and conducted skin biopsies, imaging, and quantification. King IL and Zhang J are my

advisory committee members and have been intellectually contributing towards the development of the experiments and the manuscript. Natural killer (NK) cell activation assays were performed by Bernard N and her team. Nijnik A helped with setting up the protocol for processing blood samples. Wen X, Tugarinov N, Verner M, Klares R III, and Linton A helped with the processing of blood samples. The work on this manuscript was ongoing at the time of thesis submission.

## 2. Novel contributions to knowledge

Chapter II (The dichotomous role of epiregulin in pain) elaborates the role of epiregulin (EREG) in pain. It shows for the first time that EREG could be analgesic during acute stages of pain development but increases the risk of establishment of chronic pain. This discovery was first made through a statistical genetic approach, validated in an independent population cohort, and was confirmed in animal models of pain. In addition, this chapter identifies two mutations of the *EREG* gene as novel response biomarkers for EREG–based pharmacotherapy of chronic pain.

Chapter III (An unbiased immune profiling reveals a Natural Killer cell-peripheral nerve axis in fibromyalgia.) proposes an original heuristic model of natural killer (NK) cells' contribution to fibromyalgia syndrome (FMS) pathogenesis. Through unbiased evaluation of human peripheral blood mononuclear (PBMC) cells in FMS and matched controls, we found that the depletion of NK cells is the strongest immune cell disturbance in FMS. The NK cells were activated, exhausted, but hyperactive. Lastly, NK cells in FMS patients were recruited to peripheral nerve fibers, which expressed NK activation ligand.

# I. Introduction

The most vital function of the nervous system is to provide information about the occurrence or threat of an injury. One of the ways this is done is in the form of pain. However, sometimes established pain can go beyond its protective role, thus becoming a disease than just being a symptom. Such painful conditions usually remain refractory to available treatments. Likewise, as part of the immune system response, inflammation is a protective reaction involving host cells, blood vessels, proteins, and other mediators, which is intended to eliminate the initial cause of cell injury, the necrotic cells and tissues resulting from the original insult, and to initiate the process of repair. Pain scientists have studied intensely the chemical mediators released during inflammation that are responsible for the associated abnormal pain states. Moreover, it is well established that the immune system can alter sensory and emotional processing and plays a pivotal role in the development and maintenance of persistent pain. Hence, addressing the intricate interplay between the immune system and the nervous system, understanding immunity's role in nociception, and knowledge about the establishment of pain following inflammation can provide novel pharmacological pathways to effectively manage various painful conditions.

## 1. Pain

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage. Unlike other sensory modalities, it is not the direct expression of a sensory event but rather the product of elaborate processing by the brain of a variety of

neural signals. Pain can be nociceptive or neuropathic. Neuropathy is characterized by pathological ectopic electro-chemical discharges from the involved sensory nerves. Direct nerve injury, damage, or dysfunction causes neuropathic pain. Nociceptive pain can be an acute physiological response to injury or pathophysiological in origin, due to inflammation. The excitation threshold of polymodal nociceptors drops during inflammation. Moreover, initially, mechano-insensitive nerves (silent nociceptors) become mechano-sensitive, adding to the nociceptive input to the central nervous system (CNS). These changes in the neuronal response during inflammation are known as peripheral sensitization. By virtue of neuroplasticity, neurons in the spinal cord undergo central sensitization, thereby increasing the response to stimuli, decreasing the threshold for nociceptive firing, and expansion of the receptive field. Central sensitization can persist from weeks to months and is more common during neuropathic pain conditions [1].

## 2. Inflammation

Any transient and early response to injury, characterized by inflammation, is associated with the activation of stereotypical leukocytes namely, neutrophils and monocytes, blood vessel reactions, and the release of numerous chemical mediators. The vascular and cellular reactions during inflammation are triggered by soluble factors. These factors are generated or activated in response to the inflammatory stimulus, such as infection, tissue necrosis, immune reactions, foreign bodies, hypoxia, etc., and are produced by immune cells and/or derived from the plasma proteins. When acute inflammation is successful in eliminating the offenders, the reaction subsides. However, if the response fails to clear the invaders, it can progress to a chronic phase. Chronic inflammation is an inflammation

of prolonged duration (weeks or months) in which inflammation, tissue injury, and attempts to repair coexist in varying combinations. It may follow acute inflammation or can begin insidiously, as a low-grade, smoldering response without any manifestations chronologically prior to acute reaction. Normally, inflammation is terminated when the offending agent is eliminated. The reaction resolves rapidly because the mediators are broken down and dissipated. Also, the leukocytes have a short life span in the tissues. In addition, anti-inflammatory mechanisms are activated that serve to control the immune response and prevent it from causing any excessive damage to the host.

Dolor (Pain) has always been recognized as a cardinal sign of inflammation. Recent evidence supports the notion that the immune cells, glia, and neurons form an integrated network in which immune responses modulate the excitability of pain pathways [2]. The interplay of specific leukocyte subpopulations, resident cells, pro-algesic mediators, and downstream products results in pain during inflammation [3]. Peripheral nerves also affect the tissue by releasing neuropeptides like substance P (SP), calcitonin gene-related peptide (CGRP), somatostatin, vasoactive intestinal polypeptide, and galanin from their sensory endings. This release causes vasodilatation, plasma extravasation, migration and recruitment of macrophages, and degranulation of mast cells, leading to aggravation of tissue injury. This phenomenon is called neurogenic inflammation, where the nerves antidromically contribute towards peripheral inflammation [4].

# 3. Neuro-immune molecular overlap

Neuroimmune interactions play a critical role both in the initiation and propagation of peripheral inflammation. These interactions are not only significant in influencing the perception of pain but are also associated with emotions like depression associated with pain [5]. Many inflammatory mediators influence the functioning of sensory nerves and central processing of nociception. Similarly, neurogenic inflammation is evidenced by the role of neurotransmitters in aggravating inflammation. The co-existence of receptors for a considerable number of molecules in both the nervous and immune system suggests functional integration of these two distinct systems.

Interleukin 1 (IL-1) and tumor necrosis factor-α (TNF-α) are the most important proinflammatory cytokines. IL-1 is a known pyrogen and induces transcription of cyclooxygenase-2 (COX-2). This, in turn, increases the production of prostaglandin E2 (PGE2). On the other hand, TNF-α is involved in a bidirectional cause-effect relationship with activation of inflammasomes [6]. High sensitivity C-reactive protein (hs-CRP) is another marker of inflammation with well-established diagnostic significance. Serum levels of inflammatory mediators and hs-CRP are positively associated with pain [7, 8].

Immune mediators directly influence neurons through their specific receptors, thus expressing effects from peripheral nerve modulation to complex cognitive alterations. These chemicals can also induce vagal or circumventricular organ-mediated reflexes, thus modulating the autonomous nervous system [9]. On the other hand, the immune system is influenced by the nervous system through the hormonal and neuronal

pathways. The hormonal pathway majorly consists of the hypothalamic-pituitary-adrenal axis (HPAA) which is stimulated by IL-1 [10] and hypothalamic-pituitary-gonadal axis (HPGA) [11]. Glucocorticoids are the end products of HPAA and are crucial in the suppression of the immune system. End products of HPGA are majorly, estrogen, and androgens in females and males, respectively. Estrogen instigates and androgens suppress immune responses. Consequently, inflammatory and autoimmune disorders are more common in females [12]. It is also noteworthy that chronic pain conditions are considerably more prevalent among females [13]. In addition to neurogenic inflammation, the nerves influence the immune system through the autonomous nervous system. Catecholamines exert an anti-inflammatory effect by facilitating the Th2 immune response. The presence of β2 adrenergic receptors on lymphocytes further corroborates this direct interaction [14]. An inflammatory reflex of the parasympathetic system and acetylcholine through α-nicotinic receptors on macrophages [15] inhibit the production of pro-inflammatory cytokines. Thus, the influence of the nervous system on the immune system and vice versa is complex and multi-directional and is associated with multiple outcomes.

## 4. The interaction

The following event descriptions attempt to explain interactions between the nervous system and the immune system during generation, propagation, perception, and establishment of pain in consideration with participating anatomical sites:

## 4.1. Peripheral nociceptor sensitization during inflammation

Inflammatory mediators with pro-nociceptive functions [16] are generated during inflammation. These include prostaglandins, bradykinin, serotonin, histamine, SP, thromboxanes, platelet-activating factor (PAF), purines and its derivatives [17] (such as adenosine and adenosine triphosphate (ATP)), protons (H+), free radicals, cytokines [18] (such as interleukins (ILs) and TNF), and neurotrophins, especially nerve growth factor (NGF) [19]. Some of these agents can directly activate nociceptors, while others by acting through immune cells. Inputs from the resident immune cells (like mast cells and resident macrophages) and immune-related cells (including keratinocytes and fibroblasts) recruit systemic immune cells, leading to peripheral sensitization. This condition is further exacerbated by direct and indirect consequences of inflammatory mediators (like decrease in pH, increase in temperature, vasodilatation, etc.).

Mast cells are the sentinels and the first responders of peripheral inflammation. They also play a crucial role in the establishment of pain [20]. Damaged nerves release TNF-α [21] and IL-15 [22], leading to the recruitment of macrophages and T cell infiltration. Cytokines, ATP, bradykinin, NGF (which also stimulates mast cells to release histamine and serotonin), PGE2, and PGI2 stimulate peripheral Aδ and C nerves. This leads to the release of neuropeptides, SP, CGRP, prostaglandins, and glutamate, which in turn aggravates inflammation. As these events are caused due to active participation of peripheral nerves, it is known as neurogenic inflammation [23]. Hence, nerves and immune cells are involved in a vicious cycle with a feed-forward mechanism, stimulating each other and propagating both inflammation and nociception.

## 4.2. Sensory ganglia and inflammation

Cytons of the peripheral sensory nerves lie in the trigeminal ganglion (TG) and dorsal root ganglia (DRG) along with glial cells. Microglia (MG) are derived from distinct macrophage populations and play a crucial role in the immunity of the nervous system [24]. Microgliosis (increase in density of MG due to migration and local proliferation associated with rapid change in morphology, gene expression profile, and physiology) is a common finding in case of nerve injury, neuropathy, and painful conditions [25]. Involved primary afferent nerves release neuregulin-1 which binds to erbB2 receptors on MG and contributes towards hypersensitivity and allodynia. Moreover, up-regulation of matrix metalloproteinase-9 (MMP-9) in involved nerves causes increased expression of CD11b and P38 mitogen-activated protein kinases (p38MAPK) phosphorylation in MG. This has been linked with the associated mechanical hypersensitivity [26]. As MG expresses both CCR7 and CXCR3; the release of CCL21 (exclusively during the noxious event) leads to purinergic receptor P2X4 up-regulation which is associated with allodynia [27], whereas CCL2 is released from nerves during pain and causes monocyte migration in CNS. The presence of CCR2 on both neurons and MG hints towards its possible role in nociception and central sensitization [28].

Additionally, a series of obvious immune-related activities of MG is associated with the occurrence of hypersensitivity and allodynia. These include activation of toll-like receptors (TLRs) and nod-like receptors (NLRs) in MG during painful conditions, [29] interferon (IFN-γ)-mediated stimulation of MG [30], synthesis and release of cytokines [31], brain-derived neurotrophic factor (BDNF) and nitric oxide, expression of MHC-II on pain

activated MG [32] and CD40-CD154-mediated communication between MG and T cells [33].

Noxious stimulation also leads to the formation of gap junctions between central neurons and satellite glial cells (SGC). This pathological communication between neurons and SGC leads to increased afferent input and enhanced neuronal excitability, which can spread to neighboring dermatomes as well [25, 34]. Reduced expression of inward rectifying K+ Channel, Kir 4.1 on SGC during pain is also been linked to increased mechanical hypersensitivity [35]. Reciprocal paracrine signaling loop involving CGRP and PGE2 (Fig. 1) further accentuates the noxious stimulus perception by CNS [36].

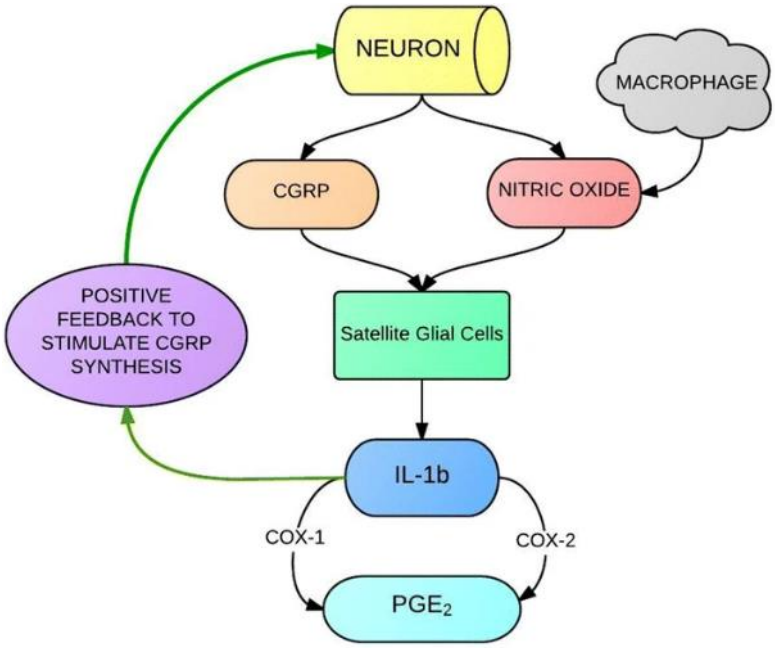



**Figure I-1: Pain amplification through reciprocal paracrine signaling**

This series of neuro-immuno-glial interactions alter the central processing of somatosensory inputs leading to widespread, longer-lasting allodynia and secondary hyperalgesia. This eventually contributes to central sensitization [37].

## 4.3. Central nervous system's response to peripheral inflammation

Time-dependent and somatotopically relevant glial activation in CNS is related to inflammatory injury and pain. Soluble mediators released by reactive immune-competent cells diffuse and bind to receptors on presynaptic and postsynaptic terminals to modulate excitatory and inhibitory synaptic transmissions, resulting in a nociceptive hypersensitivity. Growing evidence suggests that, apart from aiding communication between the immune cells, specific cytokines play a role in brain signaling to produce neurochemical, neuroendocrine, neuroimmune, and behavioral changes related to inflammation [38]. 'Sickness response', a well-documented effect of peripheral inflammation, and its role in the aggravation of pain perception and associated psychiatric conditions like depression is a well-described clinical condition.

Cytokines like IL-1, TNF, IL-6, and IL-10 are known to centrally influence nociception. Circulating IL-6, released during the peripheral inflammatory event, elicits the release of PGE2 through the COX-2 pathway from the endothelial cells in the CNS [39]. Physical remodeling of the neuronal cytoarchitecture (aided by glial cells) occurs after the onset of persistent acute pain and leads to the transition from acute pain into a chronic pain state. These pain-transmitting neurons become more sensitive, react more intensely to stimuli, and grow more connections to second-order neurons within the CNS [40]. This phenomenon, known as neuroplasticity, along with neuronal priming due to inflammatory mediators plays a crucial role in the prognosis of any painful condition (including its resolution or chronification).

## 5. Transformation to chronic pain

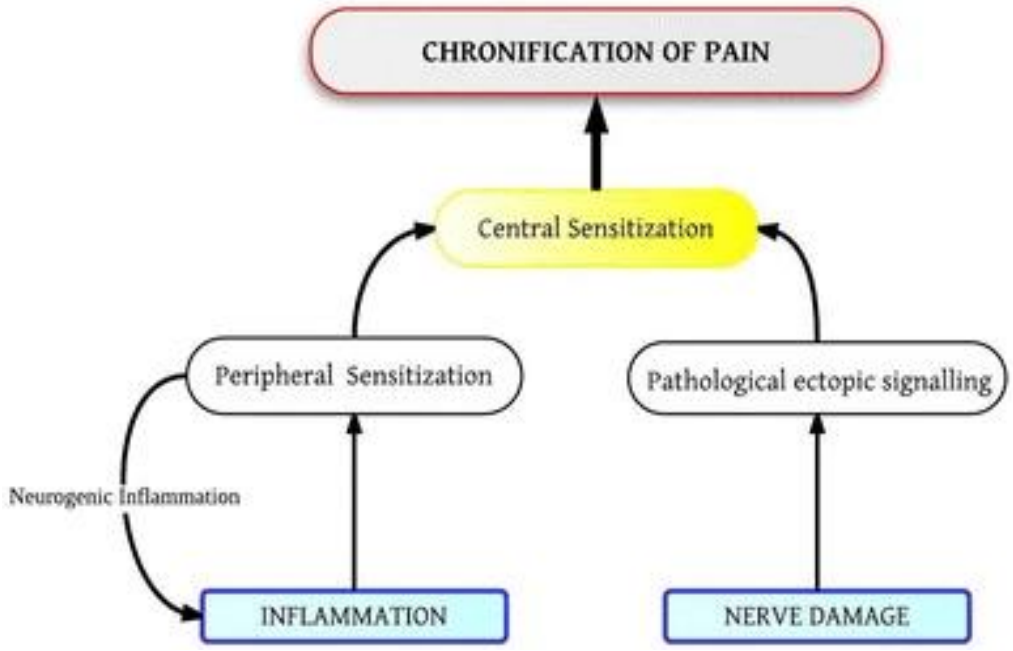



**Figure I-2: Chronification of nociceptive and neuropathic pain**

The prevalence of chronic pain can range from 10.1 to 55.2 % where often a prolonged experience of acute pain leads to chronic pain [13]. The transition of acute to chronic pain (chronification) occurs in discrete pathophysiological steps (Fig. 2). Apart from the genetic predisposition, the intensity and the duration of initial noxious stimuli play a critical role in this process. Unlike acute pain, which is usually a symptom of inflammation or/and tissue damage, chronic pain is a poorly understood disease in itself. In such cases, the pain goes way beyond its protective purpose and affects the quality of life of the patient. A disproportion of pro-inflammatory and anti-inflammatory cytokines is known to be a contributory cause of chronic pain and associated pain behavior. For example, TNF-α causes a release of CCL-2, which interacts positively with both NMDA and AMPA receptors in the neurons. This adversely affects central descending pain modulation, leading to failure of resolution state [40]. Moreover, co-localization of IL-1β and NMDA

receptors on neurons, and phosphorylation of NMDA on being stimulated by IL-1, explains the direct role of the immune system in establishing the nociceptive neuronal circuit [41]. Thus, being embedded into psycho-neuro-endocrine feedback loops, cytokines can perpetuate a vicious connection between inflammation and pain/sickness behavior, contributing towards the chronification of pain [42].

## 6. Analgesic effects of the immune system

Contrary to the villainous projection of the immune system, the pieces of evidence also support the analgesic effects of immune cells and mediators in painful conditions. During inflammation, neutrophils containing opioid peptides migrate into the tissue. Chemokines, adhesion molecules, neurokinins, such as SP recruit these ‘analgesic’ cells. Recent research has also confirmed the expression of endorphins in T cells, macrophages, and fibroblasts [43]. Additionally, Endothelin-B receptor activation during inflammation leads to the release of β-endorphin from keratinocytes [44]. Moreover, the expression of opioid receptors on peripheral nerves increases in response to inflammation and this further exaggerates the analgesic effect of endogenous immune-derived opioid peptides [45].

Certain specialized mediators (lipoxins, resolvins, and neuroprotectins) aid in the resolution of inflammation [46]. Lipoxins (LXA4 and LXB4) are generated from arachidonic acid via the phospholipase A2–lipoxygenase pathway. It facilitates the resolution of inflammation by stopping the recruitment of neutrophils, attenuating nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation, and blocking phosphorylation of p38MAPK and extracellular signal-regulated kinase (ERK) [47].

Lipoxin receptors are expressed on astrocytes and administration of lipoxin A4, or its stable analogs attenuate inflammation-induced pain [48]. Resolvins (RvD1, AT-RvD1, and RvE1) are a family of pro-resolution mediators that are biosynthesized from the omega-3 fatty acids. Resolvin-specific G-protein-coupled receptors (GPCRs) are expressed not only on neutrophils and macrophages but also on microglia, nociceptors, neuronal body, and, pre- and post-synaptic nerve endings. It directly inhibits transient receptor potential channels, TRPV1, TRPV3, TRPV4, and TRPA1 (nociceptors) activity, and downregulates ERK, COX2, and NF-κB activities in the central neurons, therefore, demonstrating analgesic effects in spontaneous, inflammatory, and post-operative pain models [49]. Similarly, neuroprotectins prevent glial proinflammatory responses and reverse nerve injury-induced neural plasticity and long-term potentiation, thus protecting against neuropathic pain [50]. The purinergic system also participates in the neuro-immune interplay to decrease pain perception. P1R, which is activated by adenosine, facilitates central analgesia [51]. Also, in DRG, P2X7R in SGC inhibits P2X3R expression by activation of P2Y1Rs via SGC-derived ATP, thus preventing inflammatory pain in rats [52]. Lastly, immune modulation through cytokines like IL-4, IL-10, and TNF soluble receptors (TNFSR) could provide novel strategies for pain therapeutic development.[65]

## 7. Therapeutic opportunities

Most commonly used painkillers belong to the class of non-steroidal anti-inflammatory drugs (NSAIDs) and target inflammation to control pain. Currently available drugs of other therapeutic categories, like amitriptyline, ceftriaxone, methotrexate, minocycline, and rifampin are being explored as analgesics due to their effect on the neuroimmune

interface [53]. For example, in a recent *in vivo* study, minocycline, a broad-spectrum antibiotic drug, prevented lipopolysaccharide-induced microglia/macrophage activation and cytokine responses in the spinal cord and DRG, thus relieving hyperalgesia [54].

Consistent with the potent role of the immune system mediators in the pain, specific cytokine inhibitors like IL-1 receptor antagonists and TNF inhibitors, primarily developed as anti-inflammatory drugs, demonstrate their potential as novel analgesics as well [55, 56]. Moreover, intra-thecal gene therapy augmenting IL-10 (an anti-inflammatory cytokine released by TH2 cells) expression has shown promising results in neuropathic pain conditions [57]. Similarly, CCR2 antagonization has demonstrated its *in vivo* efficacy too [58]. The kinins, bradykinin, kallidin, and their metabolites are vasoactive peptides that are implicated in the propagation of pain and inflammation. Identification and optimization of aryl sulfone-based bradykinin (B1) antagonists and confirmation of their analgesic effects in various animal models promise a new class of novel pain killers [59]. Microglial CX3CL1 release is mediated through cathepsin S and is regulated by the P2X7 receptor [60]. Therefore, (1) P2X7 receptor antagonism or (2) protease cathepsin S inhibition [61], or (3) direct CX1CL3 antagonism can potentially provide pain control. Likewise, complement C5a antagonism exhibited inhibition of inflammatory hyperalgesia in animal models [62]. Another promising area of research is the pharmacological utilization of anti-inflammatory and pro-resolution immune mediators. Investigating this, researchers confirm that intrathecal bolus injection of lipoxins and resolvins attenuates cytokine release from astrocytes, leading to potent suppression of inflammation-induced mechanical hypersensitivity [63].

Due to the heavy involvement of inflammatory mediators in pain mechanisms [64] and given the redundancy in and robustness of the immune system, the expectation of profound analgesia by antagonizing a single mediator appears impracticable.

## 8. Conclusion

Current research demonstrates the multi-dimensional involvement of the immune system and inflammation in the generation, potentiation, and chronification of pain. Immune cells and mediators play well-defined roles at various physio-anatomical landmarks of the pain pathways. Understanding of participation of glial cells and their role in the regulation of pain also provide a promising avenue in studying pain mechanisms. Additionally, glial modulators and their efficacy confirm glia-mediated immune system involvement in nociception. On one hand, antagonizing various immune responses (and mediators) appears as an inconclusive approach to manage pain. On the other hand, independent anti-inflammatory and pro-resolution immune mediators provide new domains for pharmacological exploration in the development of safer and effective analgesics. To summarize, our understanding of the role of the neuro-immune interface in pain is still juvenile. Furthermore, our incomplete understanding of the nervous system architecture further complicates our comprehension of various pain conditions. Future work in understanding the intricacies of the two systems promises a premise for long-waited effective pain management strategies.

# 9. References


1. Baranauskas G, Nistri A (1998) Sensitization of pain pathways in the spinal cord: cellular mechanisms. Prog Neurobiol 54:349–365
2. Ren K, Dubner R (2010) Interactions between the immune and nervous systems in pain. Nature Med 16(11):1267–1276
3. Hackel D, Pflücke D, Neumann A, Viebahn J, Mousa S, Wischmeyer E, Roewer N, Brack A, Rittner HL (2013) The connection of monocytes and reactive oxygen species in pain. PLoS ONE 8(5):2
4. Schaible HG, Richter F (2004) Pathophysiology of pain. Langenbecks Arch Surg
5. Walker AK, Kavelaars A, Heijnen CJ, Dantzer R (2014) Neuroinflammation and comorbidity of pain and depression. Pharmacol Rev 66(1):80–101. doi:10.1124/pr.113.008144. Print 2014. Review. PubMed PMID: 24335193; PubMed Central PMCID: PMC3880465
6. Singhal G, Jaehne EJ, Corrigan F, Toben C, Baune BT (2014) Inflammasomes in neuroinflammation and changes in brain function: a focused review. Front Neurosci 8:315. doi:10.3389/fnins.2014.00315. eCollection 2014. Review. PubMed PMID: 25339862; PubMed Central PMCID: PMC4188030
7. Ren K, Torres R. (2009) Role of interleukin-1beta during pain and inflammation. Brain Res Rev 60(1):57–64. doi:10.1016/j.brainresrev.2008.12.020. Epub 2008 Dec 31. Review. PubMed PMID: 19166877; PubMed Central PMCID: PMC3076185

8. Stannus OP, Jones G, Blizzard L, Cicuttini FM, Ding C (2013) Associations between serum levels of inflammatory markers and change in knee pain over 5 years in older adults: a prospective cohort study. Ann Rheum Dis 72(4):535–40. doi:10.1136/annrheumdis-2011-201047. Epub 2012 May 12. PubMed PMID: 22580582
9. Otmishi P, Gordon J, El-Oshar S, Li H, Guardiola J, Saad M, Proctor M, Yu J (2008) Neuroimmune interaction in inflammatory diseases. Clin Med Circ Respirat Pulm Med 2:35–44. PubMed PMID: 21157520; PubMed Central PMCID: PMC2990232
10. Eskandari F, Webster JI, Sternberg EM (2003) Review: neural immune pathways and their connection to inflammatory diseases. Arthritis Res Ther 5(6):251–265
11. Cutolo M, Wilder RL (2000) Review: different roles for androgens and estrogens in the susceptibility to autoimmune rheumatic diseases. Rheum Dis Clin North Am 26(4):825–839
12. Olsen NJ, Kovacs WJ. Gonadal steroids and immunity. Endocr Rev. 1996 Aug;17(4):369–84. Review. PubMed PMID: 8854050
13. Voscopoulos C, Lema M (2010) When does acute pain become chronic? Br J Anaesth 105(Suppl 1):i69–i85
14. Kin NW, Sanders VM (2006) Review: it takes nerve to tell T and B cells what to do. J Leukoc Biol 79(6):1093–1104
15. Wang H, Yu M, Ochani M, Amella CA, Tanovic M, Susarla S, Li JH, Wang H, Yang H, Ulloa L, Al-Abed Y, Czura CJ, Tracey KJ (2003) Nicotinic acetylcholine receptor alpha7 subunit is an essential regulator of inflammation. Nature 421(6921):384–388

16. Momin A, McNaughton PA (2009) Regulation of firing frequency in nociceptive neurons by pro-inflammatory mediators. Experimental Brain Res 196:45–52
17. Burnstock G (2009) Purinergic receptors and pain. Curr Pharm Des 15:1717–1735
18. Miller RJ, Jung H, Bhangoo SK et al (2009) Cytokine and chemokine regulation of sensory neuron function. Handb Exp Pharmacol 194:417–449
19. Watson JJ, Allen SJ, Dawbarn D (2008) Targeting nerve growth factor in pain: what is the therapeutic potential? BioDrugs 22:349–359
20. Chatterjea D, Martinov T (2014) Mast cells: versatile gatekeepers of pain. Mol Immunol. pii: S0161–5890(14)00054–6. doi:10.1016/j.molimm.2014.03.001. [Epub ahead of print]
21. Shubayev VI et al (2006) TNFα-induced MMP-9 promotes macrophage recruitment into injured peripheral nerve. Mol Cell Neurosci 31:407–415
22. Gómez-Nicola D, Valle-Argos B, Suardíaz M, Taylor JS, Nieto-Sampedro M (2008) Role of IL-15 in spinal cord and sciatic nerve after chronic constriction injury: regulation of macrophage and T-cell infiltration. J Neurochem 107:1741–1752
23. Richardson JD, Vasko MR (2002) Cellular mechanisms of neurogenic inflammation. J Pharmacol Exp Ther 302(3):839–845
24. Ginhoux F, Lim S, Hoeffel G, Low D, Huber T (2013) Origin and differentiation of microglia. Front Cell Neurosci 7:45
25. Calvo M, Zhu N, Tsantoulas C, Ma Z, Grist J, Loeb JA, Bennett DL (2010) Neuregulin-ErbB signaling promotes microglial proliferation and chemotaxis contributing to microgliosis and pain after peripheral nerve injury. J Neurosci 30:5437–5450

26. Kawasaki Y, Xu ZZ, Wang X, Park JY, Zhuang ZY, Tan PH, Gao YJ, Roy K, Corfas G, Lo EH, Ji RR (2008) Distinct roles of matrix metalloproteases in the early- and late-phase development of neuropathic pain. Nat Med 14:331–336
27. Thalakoti S et al (2007) Neuron-glia signaling in trigeminal ganglion: implications for migraine pathology. Headache 47:1008–1023
28. Zhang J, Shi XQ, Echeverry S, Mogil JS, De KY, Rivest S (2007) Expression of CCR2 in both resident and bone marrow-derived microglia plays a critical role in neuropathic pain. J Neurosci 27:12396–12406
29. Kim D, Kim MA, Cho IH, Kim MS, Lee S, Jo EK, Choi SY, Park K, Kim JS, Akira S, Na HS, Oh SB, Lee SJ (2007) A critical role of toll-like receptor 2 in nerve injury-induced spinal cord glial cell activation and pain hypersensitivity. J Biol Chem 282:14975–14983
30. Tsuda M, Masuda T, Kitano J, Shimoyama H, Tozaki-Saitoh H, Inoue K (2009) IFN-gamma receptor signaling mediates spinal microglia activation driving neuropathic pain. Proc Natl Acad Sci USA 106:8032–8037
31. Kawasaki Y, Zhang L, Cheng JK, Ji RR (2008) Cytokine mechanisms of central sensitization: distinct and overlapping role of interleukin-1beta, interleukin-6, and tumor necrosis factor-alpha in regulating synaptic and neuronal activity in the superficial spinal cord. J Neurosci 28:5189–5194
32. Sweitzer SM, White KA, Dutta C, DeLeo JA (2002) The differential role of spinal MHC class II and cellular adhesion molecules in peripheral inflammatory versus neuropathic pain in rodents. J Neuroimmunol 125:82–93

33. Cao L, Palmer CD, Malon JT, De Leo JA (2009) Critical role of microglial CD40 in the maintenance of mechanical hypersensitivity in a murine model of neuropathic pain. Eur J Immunol 39:3562–3569
34. Thalakoti S et al (2007) Neuron-glia signaling in trigeminal ganglion: implications for migraine pathology. Headache 47:1008–1023
35. Vit JP, Ohara PT, Bhargava A, Kelley K, Jasmin L (2008) Silencing the Kir4.1 potassium channel subunit in satellite glial cells of the rat trigeminal ganglion results in pain-like behavior in the absence of nerve injury. J Neurosci 28:4161–4171
36. Capuano A et al (2009) Proinflammatory-activated trigeminal satellite cells promote neuronal sensitization: relevance for migraine pathology. Mol Pain 5:43
37. Mifflin KA, Kerr BJ (2014) The transition from acute to chronic pain: understanding how different biological systems interact. Can J Anaesth 61(2):112–122
38. Kronfol Z, Remick DG (2000) Cytokines and the brain: implications for clinical psychiatry. Am J Psychiatry 157(5):683–694
39. Oka Y et al (2007) Interleukin-6 is a candidate molecule that transmits inflammatory information to the CNS. Neuroscience 145:530–538
40. Wei F, Guo W, Zou S, Ren K, Dubner R (2008) Supraspinal glial-neuronal interactions contribute to descending pain facilitation. J Neurosci 28:10482–10495
41. Guo W et al (2007) Glial-cytokine-neuronal interactions underlying the mechanisms of persistent pain. J Neurosci 27:6006–6018

42. Ahrens C, Schiltenwolf M, Wang H (2012) Cytokines in psychoneuroendocrine immunological context of nonspecific musculoskeletal pain. Schmerz 26(4):383–388
43. Jessop DS et al (2010) Endomorphins in rheumatoid arthritis, osteoarthritis, and experimental arthritis. Ann NY Acad Sci 1193:117–122
44. Khodorova A et al (2003) Endothelin-B receptor activation triggers an endogenous analgesic  cade at sites of peripheral injury. Nat Med 9:1055–1061
45. Stein C (1993) Peripheral mechanisms of opioid analgesia. Anesth Analg 76:182–191
46. Serhan CN, Chiang N, Van Dyke TE (2008) Resolving inflammation: dual anti-inflammatory and pro-resolution lipid mediators. Nat Rev Immunol 8:349–361
47. Serhan CN (2005) Lipoxins and aspirin-triggered 15-epi-lipoxins are the first lipid mediators of endogenous anti-inflammation and resolution. Prostaglandins Leukot Essent Fatty Acids 73:141–162
48. Svensson CI, Zattoni M, Serhan CN (2007) Lipoxins and aspirin-triggered lipoxin inhibit inflammatory pain processing. J Exp Med 204:245–252
49. Yoo S, Lim JY, Hwang SW (2013) Resolvins: endogenously-Generated Potent Painkilling Substances and their Therapeutic Perspectives. Curr Neuropharmacol 11(6):664–676
50. Xu ZZ, Liu XJ, Berta T, Park CK, Lü N, Serhan CN, Ji RR (2013) Neuroprotectin/protectin D1 protects against neuropathic pain in mice after nerve trauma. Ann Neurol 74(3):490–5. doi:10.1002/ana.23928. Epub 2013 Sep 4

51. Zylka MJ et al (2008) Prostatic acid phosphatase is an ectonucleotidase and suppresses pain by generating adenosine. Neuron 60:111–122
52. Chen Y et al (2008) Activation of P2X7 receptors in glial satellite cells reduces pain through downregulation of P2X3 receptors in nociceptive neurons. Proc Natl Acad Sci USA 105:16773–16778
53. Grace PM, Hutchinson MR, Maier SF, Watkins LR (2014) Pathological pain and the neuroimmune interface. Nat Rev Immunol 14:217–231. doi:10.1038/nri3621
54. Yoon SY, Patel D, Dougherty PM (2012) Minocycline blocks lipopolysaccharide induced hyperalgesia by suppression of microglia but not astrocytes. Neuroscience 221:214–224
55. Listing J et al (2005) Infections in patients with rheumatoid arthritis treated with biologic agents. Arthritis Rheum 52:L3403–L3412
56. Torres R et al (2009) Hyperalgesia, synovitis and multiple biomarkers of inflammation are suppressed by interleukin 1 inhibition in a novel animal model of gouty arthritis. Ann Rheum Dis 68:1602–1608
57. Soderquist RG et al (2010) Release of plasmid DNA encoding IL-10 from PLGA microp s facilitates long-term reversal of neuropathic pain following a single intrathecal administration. Pharm Res 27:841–854
58. Serrano A, Paré M, McIntosh F, Elmes SJ, Martino G, Jomphe C, Lessard E, Lembo PM, Vaillancourt F, Perkins MN, Cao CQ (2010) Blocking spinal CCR2 with AZ889 reversed hyperalgesia in a model of neuropathic pain. Mol Pain 6:90
59. Biswas K, Aya T, Qian W, Peterkin TA, Chen JJ, Human J, Hungate RW, Kumar G, Arik L, Lester-Zeiner D, Biddlecome G, Manning BH, Sun H, Dong H, Huang M,

Loeloff R, Johnson EJ, Askew BC (2008) Aryl sulfones as novel bradykinin B1 receptor antagonists for treatment of chronic pain. Bioorg Med Chem Lett 17:4764–4769

60. Clark AK, Wodarski R, Guida F, Sasso O, Malcangio M (2010) Cathepsin S release from primary cultured microglia is regulated by the P2X7 receptor. Glia 14:1710–1726

61. Clark AK, Yip PK, Grist J, Gentry C, Staniland AA, Marchand F, Dehvari M, Wotherspoon G, Winter J, Ullah J, Bevan S, Malcangio M (2007) Inhibition of spinal microglial cathepsin S for the reversal of neuropathic pain. Proc Natl Acad Sci USA 104(25):10655–10660

62. Ting E et al (2008) Role of complement C5a in mechanical inflammatory hypernociception: potential use of C5a receptor antagonists to control inflammatory pain. Br J Pharmacol 153:1043–1053

63. Abdelmoaty S, Wigerblad G, Bas DB, Codeluppi S, Fernandez-Zafra T, El-Awady el-S, Moustafa Y, Abdelhamid Ael-D, Brodin E, Svensson CI (2013) Spinal actions of lipoxin A4 and 17(R)-resolvin D1 attenuate inflammation-induced mechanical hypersensitivity and spinal TNF release. PLoS ONE 8(9):e75543

64. Block BM, Hurley RW, Raja SN (2004) Mechanism-based therapies for pain. Drug News Perspect 17(3):172–186

65. Vanderwall AG and Milligan ED (2019) Cytokines in Pain: Harnessing Endogenous Anti-Inflammatory Signaling for Improved Pain Management. Front Immunol. 2019; 10: 3009

# II. The dichotomous role of epiregulin in pain

## 1. Abstract

It has recently been shown that epidermal growth factor receptor (EGFR) contributes to the pathogenesis of pain. We scanned genetic markers within genes coding for receptors of the EGFR family (*EGFR, ERBB2, ERBB3*, and *ERBB4*) and their ligands (*AREG, BTC, EGF, EPGN, EREG, HBEGF, MUC4, NRG1, NRG2, NRG3, NRG4*, and *TGFA*) for association with self-reported pain intensity in patients with chronic facial pain who participated in the Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) cohort. We found that only epiregulin (EREG) was associated with pain. The strongest effect was observed for a minor allele at rs6836436 in *EREG*, which was associated with lower chronic pain intensity. However, the same allele was associated with higher facial pain intensity among cases with recent onset of facial pain. Similar trends were observed in an independent cohort of UK Biobank (UKB) where the minor allele at rs6836436 was associated with a higher number of acute pain sites but a lower number of chronic pain sites. Expression quantitative trait loci analyses established rs6836436 as a loss-of-function variant of *EREG*. Finally, we investigated the functional role of EREG using mouse models of chronic and acute pain. Injecting mice with an EREG monoclonal antibody reversed established mechanosensitivity in the complete Freund's adjuvant and spared nerve injury models of chronic pain. However, the EREG monoclonal antibody prolonged allodynia when administered during the development of complete

Freund's adjuvant-induced mechanosensitivity and enhanced pain behavior in the capsaicin model of acute pain.

## 2. Introduction

The establishment of chronic pain is often a result of the body's inability to restore physiological homeostasis after acute pain.[24] Both acute and chronic pain states have a large genetic component, which we have now started to identify.[31,51] The Orofacial Pain Prospective Evaluation and Risk Assessment (OPPERA) study was designed to examine and identify biopsychosocial, environmental, and genetic factors that contribute to the onset and chronicity of orofacial pain.[26] In the OPPERA cohort, case-control association analysis that focused on a common orofacial pain condition, temporomandibular disorders (TMDs), using a panel of 358 pain-relevant candidate genes, revealed that the genes encoding for the epidermal growth factor receptor (EGFR) and its ligand epiregulin (EREG) had the highest association with TMD risk.[30] However, genes of other EGFR ligands and receptors have not been tested for their association with human pain phenotypes.

Epiregulin, a member of the epidermal growth factor (EGF) family of peptide growth factors, plays important role in angiogenesis and vascular remodeling. It is a potent mitogen with direct and indirect proinflammatory effects.[37] Epiregulin binds to EGFR (ErbB1) and ErbB4 (HER4) but also stimulates the signaling of ErbB2 (HER2/Neu) and ErbB3 (HER3) through ligand-induced heterodimerization with a cognate receptor. Blocking EGFR with pharmacologically available small molecules and monoclonal

antibodies produce analgesia in animals[30] and chronic pain patients.[19–21] For the current study, we hypothesized that the EREG–EGFR pathway uniquely contributes to the development and persistence of pain.

For the first time, we systematically screened single-nucleotide polymorphisms (SNPs) in all gene loci belonging to EGFR family receptors (namely, *EGFR, ERBB2, ERBB3,* and *ERBB4*) and their ligands (namely, *AREG, BTC, EGF, EPGN, EREG, HBEGF, MUC4, NRG1, NRG2, NRG3, NRG4,* and *TGFA*) for their association with reported clinical pain in the OPPERA cohort. We chose to use characteristic pain intensity (CPI) as an outcome measure because of its clinical significance.[11] Our analysis indicated that from the 16 genes screened, only *EREG* gene SNPs were associated with CPI. Next, we characterized the association between *EREG* variants and other pain severity phenotypes, namely, acute pain intensity and the number of other chronic painful comorbidities in OPPERA. The same *EREG* variant that was protective for chronic pain intensity increased the risk for acute pain intensity in OPPERA. We then validated the dichotomous effect of EREG using an independent cohort from the UK Biobank (UKB). We also demonstrated the direction of the genetic effect of the identified SNPs on the corresponding mRNA expression level through subsequent cis-expression quantitative trait loci (eQTL) analyses from 2 independent studies. Finally, the dichotomous role of EREG for pain phenotypes was tested using mouse models of chronic and acute pain sensitivity.

# 3. Methods

## 3.1. Cohort description

The OPPERA cohort was used as a discovery cohort for this study. The study methods have been described in detail elsewhere.[2] In summary, the prospective cohort study enrolled 3263 participants between May 2006 and November 2008 at 4 US study sites: Baltimore, Maryland; Buffalo, New York; Chapel Hill, North Carolina; and Gainesville, Florida, from which 3161 were genotyped. To be eligible for enrollment, the participants had to satisfy the selection criteria determined during telephone screening and at the baseline clinical visit. The facial pain characteristics were collected using the OPPERA Comprehensive Pain Symptom Questionnaire (CPSQ), and TMD was diagnosed by trained examiners using the Research Diagnostic Criteria for TMD (RDC/TMD).10 Participants were followed at quarterly (3 monthly) intervals after the baseline visit with questionnaires and clinical visits. The project's protocol was approved by the institutional review boards at each OPPERA study site and McGill University. Written informed consent was obtained from each participant before their enrollment.

To replicate our findings from OPPERA, data from UKB were used. Described in detail elsewhere,[44] the UKB study is a large prospective multicenter study of people living in the United Kingdom that had recruited [503,325] individuals between 2006 and 2010. Follow-up data were collected after 2012. Ethics approval for the UK Biobank study was obtained from the northwest Centre for Research Ethics Committee (11/NW/0382), and all participants provided written informed consent. Their participation involved completing

questionnaires, undergoing an interview with a trained nurse during which a range of physical measures was collected, and donating samples of blood, urine, and saliva.

## 3.2. Outcome measures

The OPPERA study used the Research Diagnostic Criteria to define TMD cases.[10] According to this criteria, an individual was deemed as a chronic TMD case if an examiner had confirmed pain in the orofacial area for at least 5 days a month for ≥6 months and either ≥3 temporomandibular muscle groups or ≥1 temporomandibular joint painful to palpation or jaw movement. In addition, the OPPERA study used the CPSQ questionnaire, a self-report instrument, to assess the presence of multiple pain symptoms and associated characteristics.[40]

Comprehensive Pain Symptom Questionnaire asked the following screening question:

“Have you ever had pain in your face, jaw, temple, in front of the ear, or the ear, not including toothache or ear infection?”

If the participant answered “yes” to the aforementioned question, s/he was asked the following:

(1) “How many years or months ago did your facial pain begin?”
(2) “How would you describe the duration of your facial pain?”
(3) “How would you rate your facial pain at the present time, i.e., right now?”
(4) “In the past 6 months, how intense was your worst facial pain?”
(5) “In the past 6 months, on average, how intense was your facial pain?”

The responses to the above-mentioned question (1) were numerical (years and months) The responses to question (2) were collected as either “persistent,” “recurrent,” or “one time,” whereas, the responses to the questions (3) to (4) were collected using a numerical rating scale (NRS) where 0 was marked as “no pain” and 10 was “pain as bad as it could be.” Measuring pain intensity on an NRS is a valid and clinically meaningful measure of pain severity.[13] Characteristic pain intensity is an arithmetic mean of the 3 NRS ratings, namely, pain right now, worst pain in 6 months, and average pain in 6 months. Contrary to NRS alone, CPI is temporally stable,[33] provides a more reliable estimation of pain severity,[11,47] and has been demonstrated to be a significant predictor of TMD chronicity.[12] Hence, we chose CPI as our primary outcome measure. Of 3161 genotyped OPPERA participants, 399 participants were excluded due to missing or poor-quality phenotype data. Of the remaining 2762 participants, 1626 never had pain in the facial region. Characteristic pain intensity scores were not calculated for these 1626 participants. Eight hundred ninety-four of the remaining 1136 participants had facial pain for more than 3 months. We restricted our analysis to the participants with either persistent (n = 124) or recurrent (n = 264) facial pain to comply with the latest definition of chronic pain according to the International Association for the Study of Pain (IASP).[45] The CPI scores of these 388 OPPERA participants at baseline were considered as the chronic pain intensity (Fig. 1A). Follow-up CPI scores of the controls with a CPI at baseline of zero were considered as an acute pain intensity marker (n = 213) (Fig. 1A), and participants with acute CPI >0 were considered as acute facial pain cases (n = 112). Other phenotypes from OPPERA included the number of comorbid pain conditions present from

fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, interstitial cystitis, arthritis, and chronic pelvic pain, and TMD caseness, as described earlier.

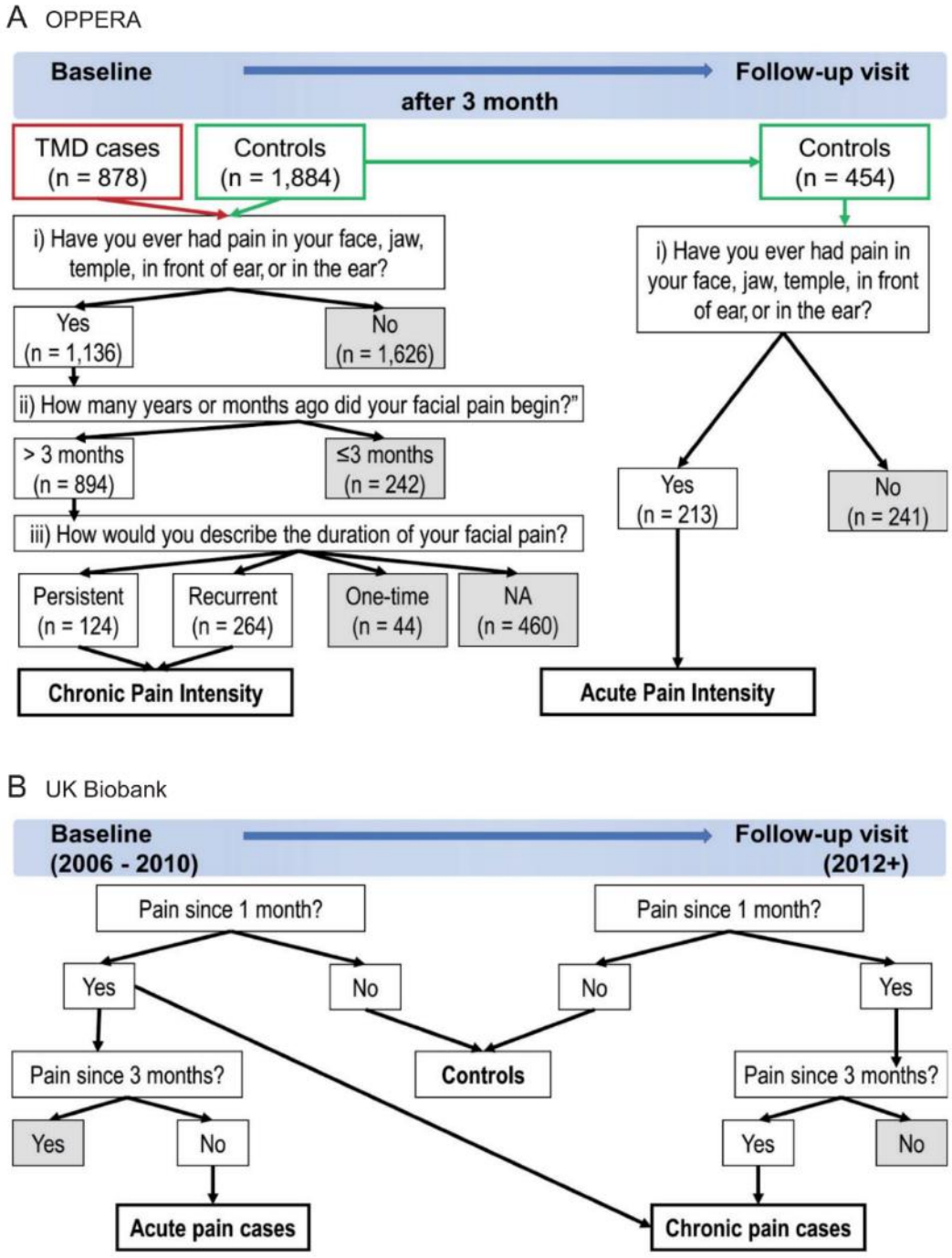



**Figure II-1: Selection of acute and chronic pain phenotypes in the (A) OPPERA and (B) UKB cohorts.**

As part of the UKB data collection framework, participants were asked: “In the last month, have you experienced any of the following that interfered with your usual activities?” (UKB data-field ID: 6159). Participants could choose all that apply from the following options: headache, facial pain, neck or shoulder pain, back pain, stomach or abdominal pain, hip pain, knee pain, pain all over the body, none of the above, and prefer not to answer. We generated a quantitative trait ranging from 0 to 8, corresponding to the number of sites reported as painful. Those reporting to have “pain all over the body” were assigned the maximum score of 8. If the site was painful for not more than a month, it was counted as an acute pain site. If a bodily site remained painful on follow-up after 2 or more years, then it was counted as a chronic pain site.

Caseness for participant's pain sites were established as follows in UKB (Fig. 1B):

(1) Participants who reported no pain sites at baseline and follow-up were treated as controls.
(2) If a participant reported pain at a particular body site for 1 month but not for 3 months, s/he was classified as an acute pain case for that particular site.
(3) If a participant reported pain at a particular site for 1 month at baseline and at the same site for more than 3 months at follow-up, s/he was classified as a chronic case for that particular site.

## 3.3. Genotyping

Peripheral venous whole blood was collected at each OPPERA site into 5-mL polyethylene tubes containing ethylenediaminetetraacetic acid (EDTA) (Vacutainer; Beckton Dickinson and Company, Franklin Lakes, NJ), and the tubes were stored in a

−80°C freezer.[41] Genomic DNA was purified using the protocols of Qiagen extraction kits. Samples were genotyped using the Illumina HumanOmni2.5Exome-8v1A array (Illumina, Inc, San Diego, CA) at the Center for Inherited Disease Research (Johns Hopkins University, Baltimore, MD). The details of genotyping and QC procedures have been described elsewhere.[42] Genotyping results were returned for 3221 unique samples, representing the study participants. All the genotyped SNPs with minor allele frequency (MAF) greater than 5% in gene loci belonging either to EGF-family receptors (namely, EGFR, ERBB2, ERBB3, and ERBB4) or ligands (namely, AREG, BTC, EREG, EGF, EPGN, EREG, HBEGF, MUC4, NRG1, NRG2, NRG3, NRG4, and TGFA) were chosen for the association analyses (n = 2407).

UKB's genetic data for 488,288 participants were used. As described in detail elsewhere,[8] blood samples were collected from participants on their visit to a UKB assessment center, and the samples were stored at the UKB facility in Stockport, UK. Over a period of 18 months, samples were retrieved, DNA was extracted, and shipped to Affymetrix Research Services Laboratory for genotyping. A subset of 49,940 participants was genotyped using the Applied Biosystems UK BiLEVE Axiom Array by Affymetrix (now part of Thermo Fisher Scientific).[48] The remaining 438,348 participants were genotyped using the closely related Applied Biosystems UK Biobank Axiom Array that shares 95% marker content with the UK BiLEVE Axiom Array. Routine quality checks were performed during the process of sample retrieval, DNA extraction, and genotype calling.

## 3.4. Mouse subjects

Male adult (7-9 weeks of age) CD1 [Crl:CD1 (ICR)] mice were acquired from Charles River Laboratories (Saint Constant, QC, Canada) and used for all experiments. All mice were housed in groups of 4 upon arrival, and procedures were conducted in accordance with the animal care standards set forth by the Canadian Council on Animal Care and were approved by the University of Toronto's Biosciences Panel on Laboratory Animal Care. All animals were maintained within a temperature-controlled environment (23 ± 1°C) with a 12:12 h light:dark cycle. A compressed cotton nesting square and crinkled paper bedding were provided in each cage as a source of environmental enrichment. All mice had access to food (Harlan Teklad 8604) and water ad libitum.

### 3.4.1. Anti-EREG monoclonal antibody

A blocking/neutralizing EREG monoclonal antibody (mAb) (NBP2-21992; Novus Biologicals, Oakville, ON, Canada) was diluted in phosphate-buffered saline (PBS) and administered directly into the tail vein (5 µg/5 µL). Control mice were injected with an equivalent volume of PBS.

### 3.4.2. Mouse behavioral assays

#### 3.4.2.1. von Frey tests

Mechanosensitivity was measured using the simplified up-down (SUDO) method with von Frey hairs to estimate the 50% withdrawal threshold in pressure units (g/mm2).[7] Mice were placed on a perforated metal floor (with 5-mm-diameter holes placed 7 mm apart) within small Plexiglas cubicles (9 × 5 × 5-cm high), and a set of 8 calibrated von Frey

fibers (Stoelting Touch Test Sensory Evaluator Kit no. 2 to no. 9; ranging from ~0.015 to ~1.3 g of force) was applied to the plantar surface of the hind paw until the fibers bowed and then held for 3 seconds. The threshold force required to elicit withdrawal of the paw (median 50% withdrawal) was determined twice on each hind paw (and averaged) for all measurements, with sequential measurements separated by at least 20 minutes.

#### 3.4.2.2. Complete Freund's adjuvant

Complete Freund's adjuvant (CFA) (50%; Sigma-Aldrich, Oakville, ON, Canada) was injected intraplantar in a volume of 20 µL into the left hind paw using a 100-µL microsyringe with a 30-gauge needle. Mice were tested for mechanical thresholds of the injected hind paw using the von Frey test as described above, before, and at selected time points after CFA injection. The EREG mAb or vehicle control was injected 1 or 3 days after CFA injection.

#### 3.4.2.3. Spared nerve injury

Spared nerve injury (SNI), an experimental nerve injury designed to produce neuropathic pain, was performed under isoflurane/oxygen anesthesia as described previously.[6,9] Briefly, using an operating microscope (X40), the 3 terminal branches of the sciatic nerve (tibial, sural, and common peroneal) were exposed. The tibial and common peroneal nerves were cut, after tight ligation with 6.0 silk, “sparing” the sural nerve. The incisions were closed in layers using interrupted sutures (6-0 Vicryl). Mice recovered on a heating pad—carefully monitored to prevent overheating—until ambulatory as per standard operating procedures. Mice were tested for mechanical sensitivity before and 14 days after surgery using the von Frey test as described above, except that the “spared” sural

region was targeted for SNI by applying the fibers to the hind paw. After von Frey's mechanical testing on day 14, mice were injected (intravenously) with the EREG mAb or vehicle control and then tested for mechanical sensitivity 16, 19, 21, and 23 days after surgery.

#### 3.4.2.4. Capsaicin assay

Mice were placed on a tabletop within Plexiglas cylinders (30-cm high and 30-cm diameter) and allowed to habituate for 15 minutes. Mice then received a subcutaneous injection of capsaicin (2.5 μg; Sigma-Aldrich) into the plantar left hind paw (20 μL) and were digitally videotaped for 10 minutes. Video files were later scored for the total duration (s) of licking/biting (ie, nocifensive behavior) of the injected paw. Two hours after capsaicin behavior, mechanosensitivity was measured using the SUDO method (as described above). Care was taken to avoid the capsaicin injection site when testing mechanosensitivity. In these experiments, mice were pretreated with the EREG mAb or vehicle control 2 days before capsaicin injection. Withdrawal thresholds for the uninjected paw were also measured to determine whether the EREG mAb altered mechanical thresholds per se.

### 3.4.3. Antibody measurements

The concentration of the EREG mAb antibody conjugated to Alexa-647 (NBP2-21992AF647; Novus Biologicals) was determined using the Cytation 5 Cell Imaging Multi-Mode Reader (Biotek, Winooski, VT). In brief, either PBS or the EREG mAB-Alexa-647 was injected intravenously, and after 2, 5, or 7 days, mice were euthanized to collect

blood. Blood was centrifuged at 5000 rpm for 20 minutes at 4°C to separate plasma and kept at −80°C until analysis. Plasma samples (100 µL/well) along with known standard concentrations of the EREG mAb were loaded into a 96-well microplate for fluorescence-based intensity measurement (Invitrogen, Burlington, ON, Canada). Using the multimode plate reader, the fluorescence intensity of Alexa-647 was measured with a bandwidth of 20 nm (640-nm excitation and 681-nm emission). A standard curve was generated based on the fluorescence intensity values from the known standard concentrations, which was then used to calculate the concentration of the EREG mAB in the plasma samples.

## 3.5. Data analyses

The additive model of inheritance was assumed for all genetic analyses. The family-wise error rate was controlled using the Benjamini–Hochberg's false discovery rate (FDR) method5 at a 5% threshold. Pain phenotypes were considered as dependent variables, and minor allele counts of SNPs were independent variables for Poisson and logistic regression models for count and binary outcome measures, respectively. For initial screening of all the 2407 SNPs in the EGFR family of receptors and ligands against chronic pain intensity, multivariate linear regression was conducted using PLINK (Broad Institute, Cambridge, MA), version 1.09.35 Haplotype analyses were performed using Haplo.stats v1.7.7 (R-package),[23] which implements an expectation-maximization–derived score to test for a statistically significant association between haplotypes and outcome measurements. The statistical methods implemented in this R-package assume that all subjects are unrelated and that haplotypes are ambiguous (due to the unknown linkage phase of the genetic markers), while also allowing for missing alleles. Hence, unrelated participants from the OPPERA and UKB cohorts were selected using a second-

degree relatedness threshold as implemented in Kinship-based INference for Genome-wide association studies (KING).[28] The effects of all rare haplotypes with the estimated frequency >5% in OPPERA and >2% in UK Biobank were compared against the effect of one ancestral haplotype. Generalized linear modeling was used to test for an association between genotypes and phenotypes. As the OPPERA participants were recruited in 4 study sites, recruitment sites were introduced as covariates in the regression models. Age, sex, and the first 3 principle components (the markers of ancestry) were also included as covariates to adjust for population stratification. Similarly, the UKB data analyses were corrected for sex, age, ethnic background, and genotyping platforms. R v3.5.2 was used as the language and environment for statistical computation. Haplotype structure of EREG was analyzed using Haploview v 4.2.4

For eQTL analysis, 2 large-scale data sets, namely, the Framingham Heart Study (FHS)18 and the Genotype-Tissue Expression (GTEx) project14 (version 7), were used. The FHS data are available at dbGaP under the accession numbers phs000342 and phs000724. The GTEx data are also available at dbGAP under the accession number phs000424.v7.p2.

For mouse experiments, von Frey's data were analyzed using repeated-measures analysis of variance (ANOVA), followed where appropriate by Tukey's honest significant difference post hoc test. Capsaicin nocifensive behavior was analyzed using independent t-tests.

# 4. Results

## 4.1. Among all EGFR receptors and ligands, only EREG was associated with pain

Our primary outcome measure, CPI, was well characterized in the OPPERA study. Hence, we used OPPERA as our discovery cohort. A total of 2407 genotyped SNPs with MAF >5% situated within the 16 genes of EGFR family receptors (ie, EGFR, ERBB2, ERBB3, and ERBB4) and their ligands (AREG, BTC, EGF, EPGN, EREG, HBEGF, MUC4, NRG1, NRG2, NRG3, NRG4, and TGFA) were screened for an association with CPI in OPPERA (Fig. 2; supplementary Table 1, available at http://links.lww.com/PAIN/A937). Only 7 SNPs passed the FDR threshold of 5% after correcting for age, sex, recruitment site, and the first 3 principal components (Table 1). All significantly associated SNPs were located in the EREG gene with their minor alleles associated with less pain. Therefore, EREG was chosen as our primary candidate gene for further investigation.

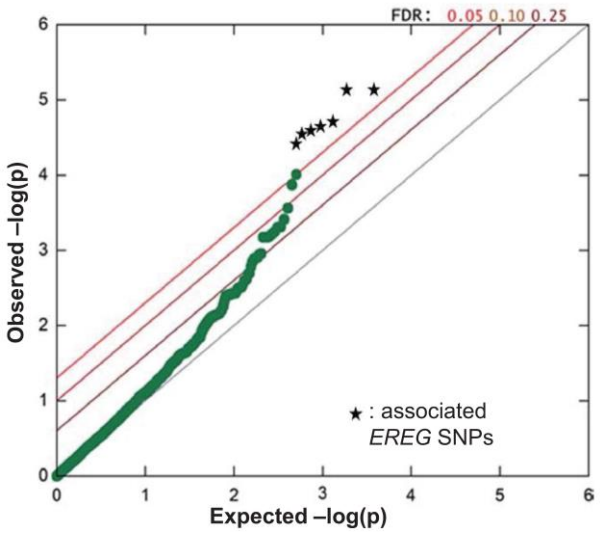



**Figure II-2: Quantile–quantile plot of 2407 SNPs in genes coding for EGFR superfamily receptors and ligands, showing a significant association (FDR < 0.05) between 7 EREG SNPs and chronic characteristic pain intensity (CPI) in OPPERA cohort. EGFR, epidermal growth factor receptor; EREG, epiregulin; FDR, false discovery rate.**

**Table 1**

**Linear regression analyses of all the genes in EGFR receptor family and its ligands, and chronic characteristic pain intensity (CPI) in OPPERA cohort, corrected for age, sex, and the first 3 principal components.**

| Gene | SNP | Ref | Min | Base pair location | β | *P*-value | FDR |
|---|---|---|---|---|---|---|---|
| *EREG* | rs10518126 | G | A | 75,243,119 | −11.09 | 0.0000078 | 0.00944** |
| *EREG* | rs57839099 | G | A | 75,243,813 | −11.09 | 0.0000078 | 0.00944** |
| *EREG* | rs200889776 | G | A | 75,240,770 | −10.41 | 0.00002 | 0.011* |
| *EREG* | rs57933408 | G | A | 75,243,828 | −10.51 | 0.00002 | 0.011* |
| *EREG* | rs201835071 | G | A | 75,237,587 | −9.99 | 0.00003 | 0.011* |
| *EREG* | rs72859363 | A | G | 75,246,112 | −10.24 | 0.00003 | 0.011* |
| *EREG* | rs6836436 | A | C | 75,230,930 | −8.84 | 0.00013 | 0.041* |

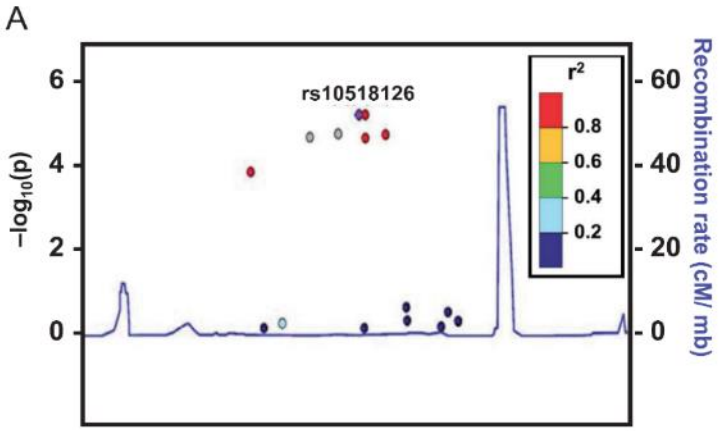
FDR ≤ 0.01: "**" 0.05: "*". Only significant results (FDR ≤ 5%) are presented.

β, slope of least-squares line; EGFR, epidermal growth factor receptor; EREG, epiregulin; FDR, false discovery rate; Min, minor allele; Ref, reference allele; SNP, single-nucleotide polymorphism (rs ID).

## 4.2. *EREG* gene has two functional minor haplotypes

Of 2407 tested SNPs in the EGFR family of receptors and ligands, 7 SNPs within EREG were found to be significantly associated with CPI. The association results of the EREG SNPs were visualized along with their local linkage disequilibrium (LD), recombination patterns, and genomic region position. This regional plot of EREG (Fig. 3A) uncovered substantial LD structure between EREG SNPs, with one LD block within the gene (Fig. 3B; Supplementary Table 2, available at http://links.lww.com/PAIN/A937). Furthermore, haplotype analysis identified 2 minor haplotypes, herein referred to as H2 and H3, with frequencies 17.3% and 5.8%, respectively, in OPPERA. All 7 significant SNPs were markers for the H3 haplotype of EREG (Fig. 3C), while we have previously reported the association of the H2 haplotype of EREG, marked by the functional SNP, rs2367707 with TMD,30 and the H3 haplotype of EREG was not detected in our earlier analysis due to its relatively low frequency. A marker of the H3 haplotype, rs6836436, was deemed potentially functional because it was located in the 5′UTR region of EREG. Finally, the presence of reference allele (A) at rs1993665 exclusively marked the major haplotype (herein referred to as H1). Hence, rs1993665, rs6836436, and rs2367707 were chosen as the markers of H1, H2, and H3 haplotypes of EREG for haplotype association analyses in both OPPERA and UKB cohorts. Their minor allele counts and frequencies in OPPERA and UK Biobank are shown in Table 2. Haplotype frequencies based on the 3 marker SNPs in EREG as derived using expectation–maximization (E-M) algorithm were 67.33% and 74.65% for H1, 20.39% and 19.91% for H2, and 7.61% and 2.77% for H3 in OPPERA and UKB, respectively (Table 3). Expression quantitative trait loci databases, namely, FHS and GTEx, were scanned for the H2 (rs2367707) and H3 (rs6836436) SNP markers.

Expression quantitative trait loci analyses revealed that both minor alleles at rs2367707 and rs6836436 were associated with decreased mRNA levels of EREG in the peripheral blood (Table 4).




| | SNP (major / minor alleles) | H1 | H2 | H3 |
|---|---|---|---|---|
| 1 | rs6836436 (A/C) | A | A | **C** |
| 2 | rs7662139 (A/C) | A | C | A |
| 3 | rs1993665 (A/G) | **A** | G | G |
| 4 | rs201835071 (G/A) | G | G | A |
| 5 | rs200889776 (G/A) | G | G | A |
| 6 | rs10518126 (G/A) | G | G | A |
| 7 | rs4694683 (G/A) | G | A | G |
| 8 | rs57839099 (G/A) | G | G | A |
| 9 | rs57933408 (G/A) | G | G | A |
| 10 | rs72859363 (A/G) | A | A | G |
| 11 | rs2367707 (G/A) | G | **A** | G |
| 12 | rs2367708 (A/G) | A | G | A |
| 13 | rs1017733 (A/G) | A | G | A |
| 14 | rs1017734 (C/A) | C | A | C |
| 15 | rs1460007 (A/G) | A | G | A |
| 16 | rs1460008 (A/G) | A | G | A |

**Figure II-3: The EREG gene has 2 minor haplotypes. (A) Regional plot of EREG. (B) Illustration of the 16 SNPs in EREG linkage disequilibrium plot, numbers inside each cell indicate r2 values, and color reflects D′ value, ranging from white to red, (ie, 0-1). (C) The sequence of 3 haplotypes with frequency >5% within EREG gene locus. Major and minor alleles of EREG SNPs genotyped in OPPERA, and SNPs significantly associated with CPI from Figure 2 are highlighted in green. Marker SNPs, namely, rs1993665, rs2367707, and rs6836436, for haplotypes H1, H2, and H3, respectively, are highlighted in yellow. CPI, characteristic pain intensity; EREG, epiregulin.**

**Table 2**

**Minor allele counts of the marker SNPs in OPPERA and UK Biobank cohorts.**

| MAC | Cohort | H1 marker SNP (rs1993665) | | H2 marker SNP (rs2367707) | | H3 marker SNP (rs6836436) | |
|---|---|---|---|---|---|---|---|
| | | n | Frequency | n | Frequency | n | Frequency |
| 0 | OPPERA | 1361 | 49.4% | 1672 | 60.7% | 2368 | 86.0% |
| 1 | | 1082 | 39.3% | 956 | 34.7% | 349 | 12.7% |
| 2 | | 312 | 11.3% | 127 | 4.6% | 38 | 1.4% |
| 0 | UK Biobank | 267,521 | 58.5% | 281,970 | 61.7% | 432,835 | 94.7% |
| 1 | | 163,181 | 35.7% | 154,109 | 33.7% | 23,650 | 5.2% |
| 2 | | 26,568 | 5.8% | 21,191 | 4.6% | 785 | 0.2% |

MAC, minor allele counts; n, number of participants.

**Table 3**

**Haplotype frequencies of *EREG* as estimated through expectation–maximization (E-M) algorithm.**

| Haplotype* | OPPERA (n = 2755) | UK Biobank (n = 473,879) |
|---|---|---|
| H1 | 67.33% | 74.65% |
| H2 | 20.39% | 19.91% |
| H3 | 7.61% | 2.77% |
| Log-likelihood | −4400.5 | −563884.5 |
| lr stat for no LD† | 3404.9 | 588,766.6 |
| *P* | $8.63 \times 10^{-08}$ | $4.99 \times 10^{-23}$ |

* Haplotypes with frequencies > 5% in OPPERA and > 2% in UK Biobank.
† Likelihood ratio test statistic contrasting the log-likelihood for the estimated haplotype frequencies vs the log-likelihood under the null assuming that the alleles from all the 3 loci are in linkage equilibrium.
EREG, epiregulin; LD, linkage disequilibrium.

**Table 4**

**Cis-eQTL in blood for the marker SNPs of minor haplotypes in *EREG*.**

| Cohort | n | SNP | Haplotype | β | *P* |
|---|---|---|---|---|---|
| FHS | 2770 | rs2367707 | H2 | −0.14 | $1.2 \times 10^{-16}$ |
| | | rs6836436* | H3 | NA | NA |
| GTEx | 369 | rs2367707 | H2 | −0.09 | $2.4 \times 10^{-02}$ |
| | | rs6836436 | H3 | −0.27 | $1.4 \times 10^{-04}$ |

* H3 marker SNP, rs6836436, was not genotyped in Framingham Heart Study cohort.
eQTL, Expression quantitative trait loci; EREG, epiregulin; FHS, Framingham heart study; GTEx, Genotype-Tissue Expression project; n, number of participants; SNP, single-nucleotide polymorphism; β, slope of least-squares line.

## 4.3. H3 and H2 haplotypes of *EREG* protects from chronic pain

We hypothesized that genetic variability within the EREG locus may affect chronic pain intensity. From the OPPERA cohort, chronic pain intensity at baseline, TMD case status, and the number of chronic pain comorbidities were chosen as the chronic pain phenotypes for this study. Haplotype association analyses confirmed our previously reported protective role for the H2 haplotype for TMD case status (n = 2,755, OR = 0.84, FDR = 0.032, Fig. 4A).[30] Furthermore, the H3 haplotype of EREG was associated with lower chronic pain intensity (n = 388, β = −8.06, FDR = 0.033, Fig. 4B) and was marginally protective against the number of chronic pain comorbidities (n = 2,748, β = −0.07, FDR = 0.08). For validation of these results, we used the UKB cohort. Pain intensity was not collected in the UKB cohort. Hence, we used the number of reported chronic pain body sites as a substitute for chronic pain intensity. Although pain severity in terms of intensity and anatomical extent are different phenotypes, they are correlated.[3,49] Painful sites were considered chronic if the pain persisted at the same site for at least 2 years, and the number of reported chronic pain body sites was used as a substitute for chronic pain intensity. In addition, the substantial size of the UKB cohort allowed us to consider pain at each of the 8 reported body sites as individual chronic pain phenotypes for this analysis. H2 was protective for the report of at least one chronic pain site (n = 196,534, OR = 0.95, FDR = 0.031, Fig. 4C) in UKB, whereas the presence of the H3 haplotype was associated with a decrease in the number of chronic pain sites (n = 196,534, β = −0.21, FDR = 0.003, Fig. 4D) and was protective for chronic hip pain (n = 191,669, OR = 0.66, FDR = 0.028). The results of all chronic pain phenotypes are summarized in Table 5. Together, both the H2 and H3 haplotypes showed protective properties towards chronic pain with the H3

haplotype displaying a stronger effect size consistent with its eQTL strength (defined by the slope, β, of the eQTL analysis, Table 4).

**Table 5**

**Haplotype association to analyze the relationship between chronic pain phenotypes and *EREG* haplotypes.**

| Cohort | Chronic pain phenotype | n | Prevalence | Haplotype II | | Haplotype III | |
|---|---|---|---|---|---|---|---|
| | | | | Estimate | FDR | Estimate | FDR |
| OPPERA | Chronic pain intensity | 388 | 88.66%† | β = −3.11 | 0.245 | β = −8.06 | 0.033* |
| | TMD case status | 2755 | 31.87% | OR = 0.84 | 0.032* | OR = 0.79 | 0.083 |
| | No. of chronic pain comorbidities | 2748 | 78.93%‡ | β = −0.04 | 0.174 | β = −0.07 | 0.080 |
| UK Biobank | Chronic pain all over the body | 190,866 | 0.05% | OR = 1.08 | 0.660 | OR = 0.95 | 0.913 |
| | Chronic stomach or abdominal pain | 191,111 | 0.18% | OR = 1.09 | 0.340 | OR = 0.50 | 0.055 |
| | Chronic headache | 191,859 | 0.56% | OR = 0.91 | 0.112 | OR = 0.96 | 0.804 |
| | Chronic neck or shoulder pain | 192,507 | 0.90% | OR = 0.96 | 0.309 | OR = 0.80 | 0.082 |
| | Chronic back pain | 192,922 | 1.11% | OR = 0.98 | 0.521 | OR = 0.83 | 0.081 |
| | Chronic hip pain | 191,669 | 0.47% | OR = 0.98 | 0.700 | OR = 0.66 | 0.028* |
| | Chronic knee pain | 192,796 | 1.05% | OR = 0.94 | 0.138 | OR = 0.99 | 0.966 |
| | Chronic facial pain | 190,832 | 0.03% | OR = 0.77 | 0.305 | OR = 0.27 | 0.204 |
| | No. of chronic pain sites | 196,534 | 2.93%‡ | β = −0.031 | 0.107 | β = −0.15 | 0.003* |
| | At least one chronic pain site | | | OR = 0.95 | 0.031* | OR = 0.90 | 0.131 |

FDR < 0.001: "***" 0.05: "*."

† Prevalence of TMD cases among n with valid chronic pain intensity scores at baseline.

‡ Prevalence of at least one chronic pain comorbidity/chronic pain site among total number of participants.

β, slope of least-squares line; CPI, characteristic pain intensity; EREG, epiregulin; FDR, false discovery rate; n, valid number of participants; OR, odds ratio.

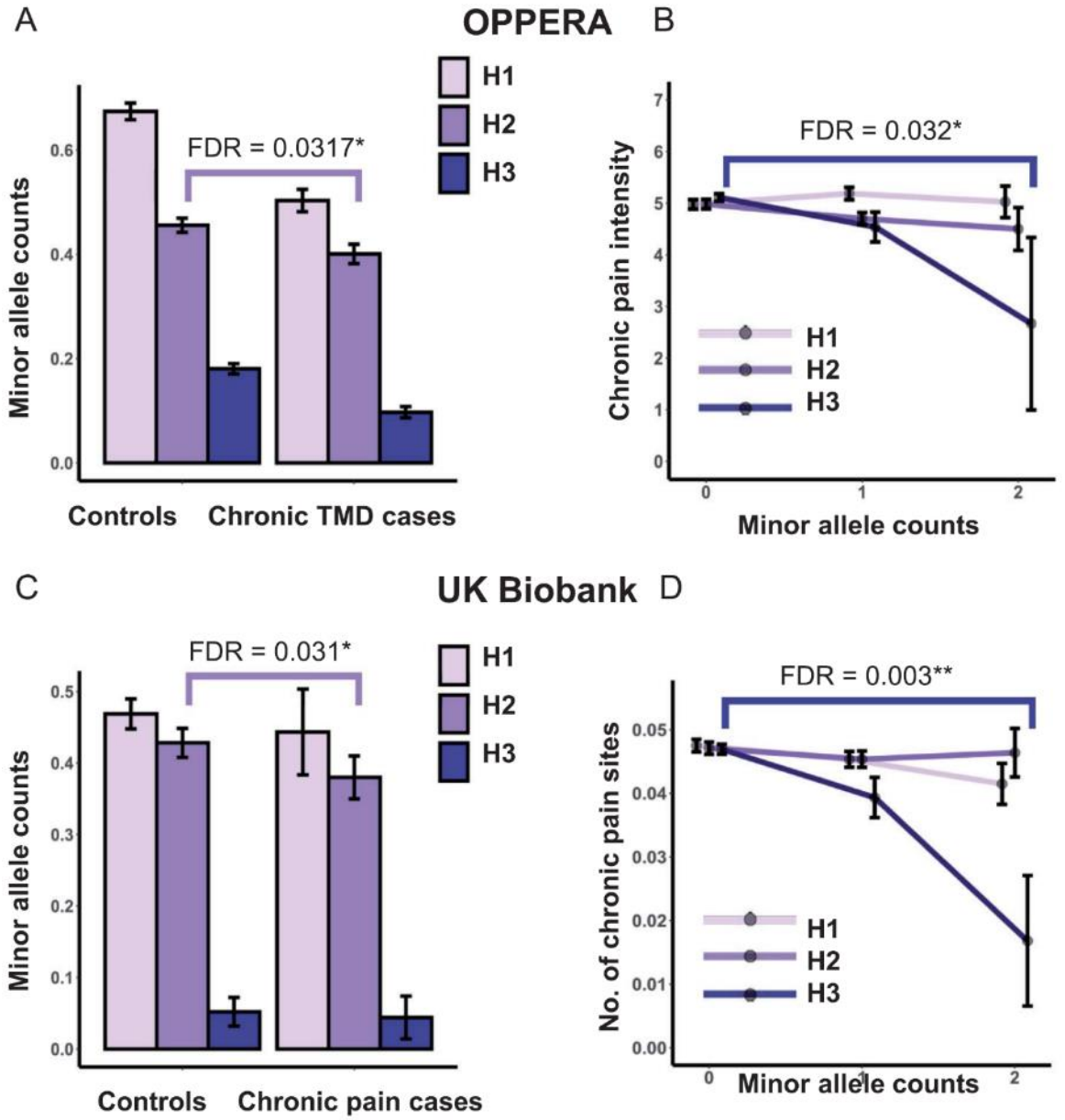



**Figure II-4: H3 and H2 haplotypes of EREG protects from chronic clinical pain. (A and B) OPPERA cohort. (A) Bar plot of average minor allele counts of rs1993665, rs2367707, and rs6836436, (markers for haplotypes H1, H2, and H3, respectively) among chronic TMD cases and controls and (B) plot of mean chronic pain intensity at baseline for minor allele counts of rs1993665, rs2367707, and rs6836436, (markers for haplotypes H1, H2, and H3, respectively) in the OPPERA cohort. (C and D) UKB cohort. (C) Bar plot of average minor allele counts of rs1993665, rs2367707, and rs6836436, (markers for haplotypes H1, H2, and H3, respectively) among chronic pain cases (at least one chronic pain site) and controls and (D) plot of mean number of chronic pain sites for minor allele counts of rs1993665, rs2367707, and rs6836436, (markers for haplotypes H1, H2, and H3, respectively) in the UKB cohort. Symbols represent mean ± SEM; false discovery rates (FDRs) were derived by generalized linear modelling for haplotype association; *FDR < 0.05; **FDR < 0.01. EREG, epiregulin; TMD, temporomandibular disorders.**

## 4.4. H3 haplotype of *EREG* is a risk for acute pain

Next, we tested the association of functional EREG haplotypes with acute clinical pain. To study the effects of minor haplotypes of EREG on acute pain, the first quarterly follow-up CPI scores measured in controls with baseline CPI = 0 were chosen as acute pain phenotype from the OPPERA cohort. Participants with no facial pain at baseline but CPI >0 after 3 months were considered acute facial pain cases (Fig. 5A). The number of reported acute (not more than 3 months) painful body sites was used as a marker of acute pain severity in UKB. In addition, participants with at least one reported acute painful site (n = 137,852) were contrasted against participants with no reported pain at all (n = 333,921). Haplotype H3 was strongly associated with acute pain but, unexpectedly, in the opposite direction compared with chronic pain. The presence of minor haplotype H3 was associated with an increase in acute pain intensity at follow-up (n = 213, $\beta = 8.68$, FDR = 0.039, Fig. 5B) in the OPPERA cohort. In the UKB, H3 was a risk factor for self-reported acute pain of at least one site (n = 471,773, OR = 1.34, FDR = 0.0002, Fig. 5C) and the total number of acute pain sites (n = 471,773, $\beta = 0.028$, FDR = 0.003, Fig. 5D). Moreover, haplotype H3 was associated with increased odds of having acute pain all over the body (n = 335,565, OR = 1.33, FDR = 0.0003). No significant association was detected between acute pain phenotypes and haplotype H2. The results of acute pain phenotypes are summarized in Table 6.

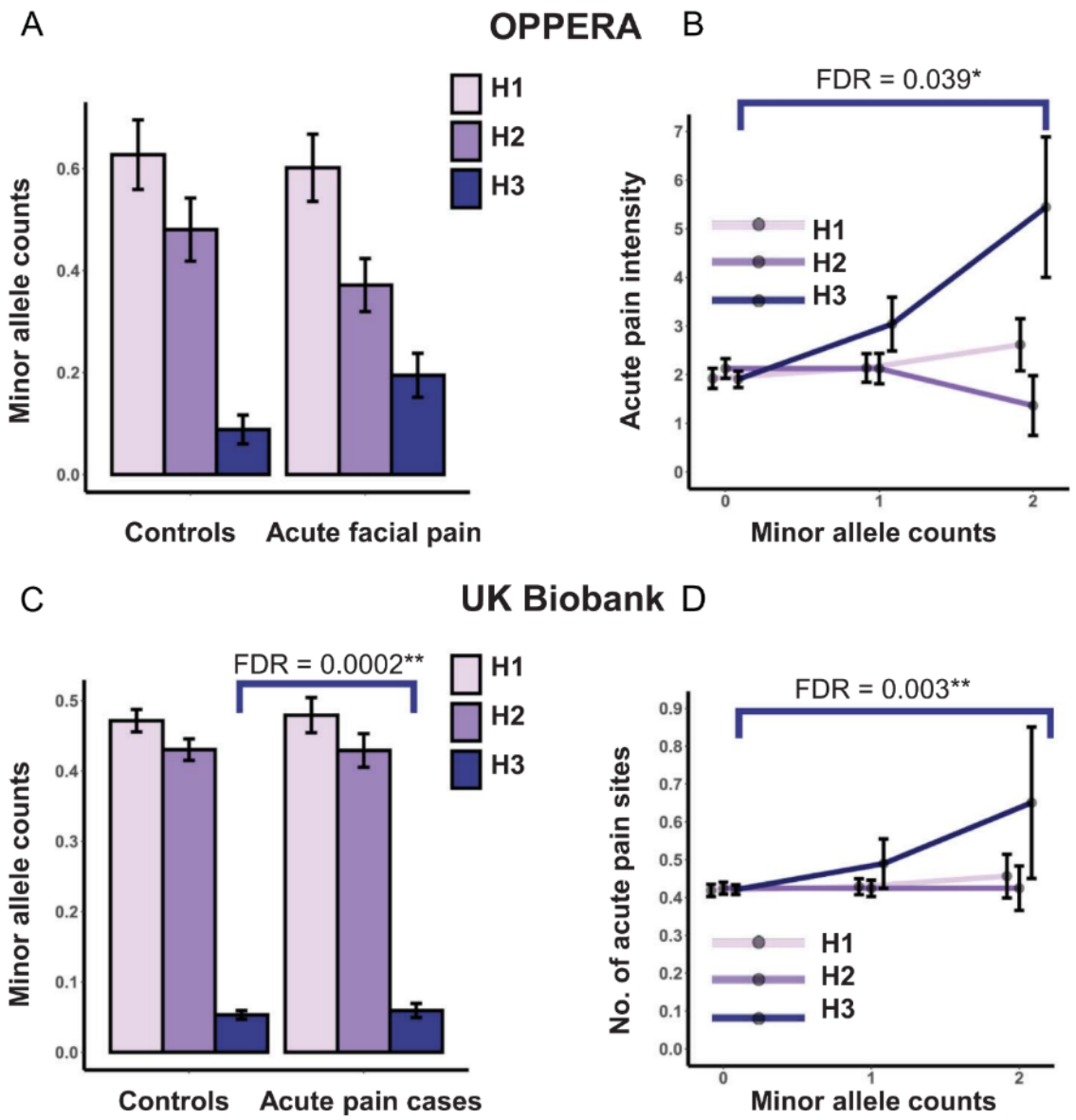



**Figure II-5: H3 haplotype of EREG is a risk for acute clinical pain. (A and B) OPPERA cohort. (A) Bar plot of average minor allele counts of rs1993665, rs2367707, and rs6836436, (markers for haplotypes H1, H2, and H3, respectively) among acute facial pain cases and (B) plot of mean of acute pain intensity at follow-up in controls for minor allele counts of rs1993665, rs2367707, and rs6836436, (markers for haplotypes H1, H2, and H3, respectively) in the OPPERA cohort. (C and D) UKB cohort. (C) Bar plot of average minor allele counts of rs1993665, rs2367707, and rs6836436, (markers for haplotypes H1, H2, and H3, respectively) among acute pain cases (at least one acute pain site) and controls. (D) A plot of the mean number of acute pain sites for minor allele counts of rs1993665, rs2367707, and rs6836436, (markers for haplotypes H1, H2, and H3, respectively) in the UK Biobank (UKB) cohort. Symbols represent mean 6 SEM; false discovery rates (FDRs) were derived by generalized linear modelling for haplotype association; *FDR, 0.05; **FDR , 0.01. EREG, epiregulin.**

Table 6

**Haplotype association to analyze the relationship between acute pain phenotypes and EREG haplotypes.**

| Cohort | Acute pain phenotype | n | Prevalence | Haplotype II | | Haplotype III | |
|---|---|---|---|---|---|---|---|
| | | | | Estimate | FDR | Estimate | FDR |
| OPPERA | Acute pain intensity | 213 | 52.58%† | β = −1.83 | 0.517 | β = 8.68 | 0.0390* |
| | Acute facial pain | | | OR = 0.76 | 0.289 | OR = 1.99 | 0.121 |
| UK Biobank | Acute pain all over the body | 335,565 | 0.87% | OR = 1.01 | 0.909 | OR = 1.33 | 0.0003** |
| | Acute stomach or abdominal pain | 352,780 | 5.34% | OR = 0.99 | 0.261 | OR = 0.94 | 0.066 |
| | Acute headache | 388,126 | 13.96% | OR = 0.99 | 0.246 | OR = 1.00 | 0.771 |
| | Acute neck or shoulder pain | 369,264 | 9.57% | OR = 1.02 | 0.083 | OR = 1.01 | 0.611 |
| | Acute back pain | 373,432 | 10.58% | OR = 0.99 | 0.672 | OR = 0.98 | 0.447 |
| | Acute hip pain | 346,291 | 3.57% | OR = 0.99 | 0.820 | OR = 0.98 | 0.758 |
| | Acute knee pain | 356,768 | 6.40% | OR = 1.00 | 0.810 | OR = 1.03 | 0.408 |
| | Acute facial pain | 338,577 | 1.37% | OR = 0.97 | 0.405 | OR = 0.95 | 0.541 |
| | No. of acute pain sites | 471,773 | 29.22%‡ | β = −0.001 | 0.752 | β = 0.028 | 0.003* |
| | At least one acute pain site | | | OR = 1.01 | 0.909 | OR = 1.34 | 0.0002** |

FDR < 0.001: "***" 0.05: "*."

† Prevalence of participants with acute pain intensity at follow-up > 0 among n with valid acute pain intensity scores at follow-up.

‡ Prevalence of at least one acute pain site.

β, slope of least-squares line; CPI, characteristic pain intensity; EREG, epiregulin; FDR, false discovery rate; n, valid number of participants/cases and controls; number of controls (no pain at all) is 333,936 for all the UK Biobank phenotypes; OR, odds ratio.

## 4.5. EREG has a dichotomous role in pain behavior in mice

Because our human genetic association results indicated that the H2 and H3 haplotypes may have a protective role against chronic pain and that these haplotypes were associated with lower EREG mRNA in the blood (Table 4), we hypothesized that blocking EREG would reduce pain hypersensitivity in mouse models of chronic pain. For these experiments, we blocked EREG by peripheral administration of an EREG mAb (5 μg) directly into the tail vein. Strikingly, mice injected with a single intravenous injection of the EREG mAb recovered quicker than control mice when the mAb was administered 3 days after CFA (ie, the peak of allodynia) (two-way ANOVA, treatment × repeated measures: $F_{3,42} = 5.53$, $P = 0.003$, Fig. 6A). Since mice recovered from CFA-induced hypersensitivity by day 7 ($t_{14} = 1.35$, $P = 0.2$), it was difficult to determine whether the EREG mAb had long-lasting effects on allodynia or was specific for inflammatory pain. Thus, we assessed whether the EREG mAb reversed mechanosensitivity using the SNI model. For the SNI experiments, we administered the mAb 14 days after surgery to

ensure that postoperative inflammation had resolved and that chronic mechanosensitivity had been established. As shown in Figure 6B, administration of the EREG mAb reversed mechanical hypersensitivity produced by SNI for up to 1 week after administration (two-way ANOVA, treatment × repeated measures: $F_{5, 84} = 10.49$, $P < 0.001$). In a subset of mice, we tracked the levels of the EREG mAb (conjugated to Alexa-647) by measuring fluorescence intensity in the blood plasma 2, 5, and 7 days after mAb administration. The concentration of the EREG mAb was significantly elevated at all time points after injection compared with control mice (two-way ANOVA, treatment × day after injection: $F_{2, 17} = 4.4$, $P = 0.027$, Fig. 6C).

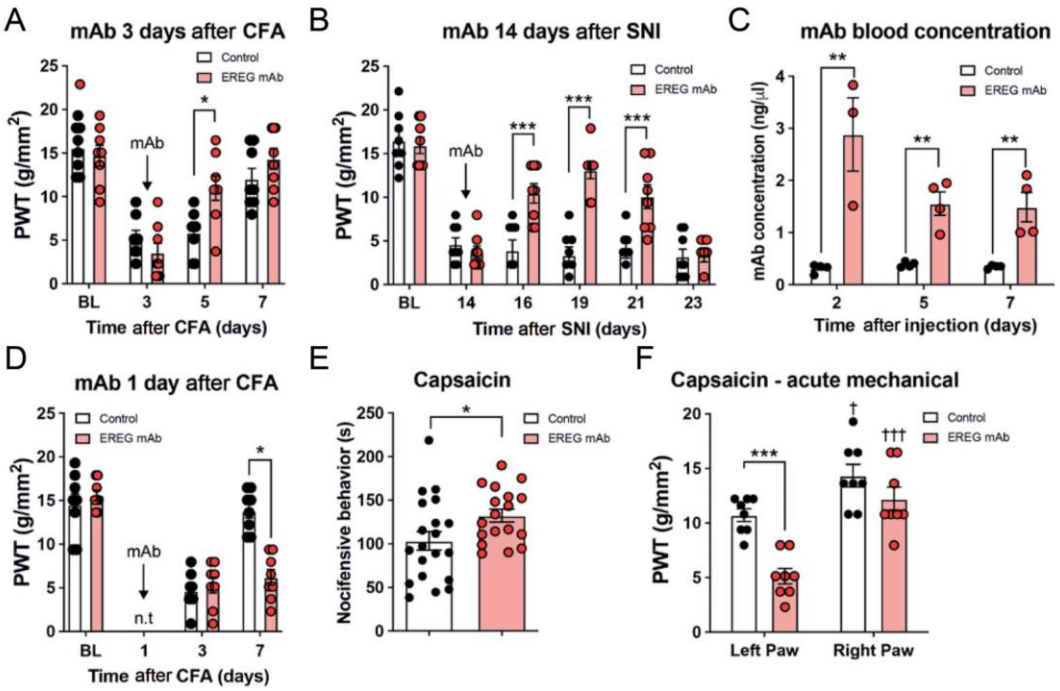



**Figure II-6: The effects of systemically administering an EREG monoclonal antibody (mAb, 5 μg) in mouse models of pain. (A) Mice injected with the EREG mAb 3 days after CFA, as indicated by the arrow have higher paw withdrawal thresholds (g/mm2) compared with control mice 5 days after CFA; n = 8/group. (B) The EREG mAb or vehicle control was administered 14 days after SNI surgery, as indicated by the arrow. A single administration of the mAb reverses mechanical allodynia for up to 1 week. (C) The concentration of EREG mAb in the blood plasma of mice after a single tail vein**

**administration; n = 4/group. (D) Mice injected with the EREG mAb 1 day after CFA, as indicated by the arrow have lower paw withdrawal thresholds (g/mm2) than control mice 7 days after CFA; n = 8/group. (E) Pretreatment with the EREG mAb, 2 days before testing increases nocifensive behavior in the intraplantar capsaicin test of acute pain; n = 18 to 20/group. (F) A subset of mice from E was tested for mechanosensitivity after intraplantar capsaicin injection; n = 8/group. Mice injected with the EREG mAb have lower paw withdrawal thresholds (g/mm2) in the capsaicin injected paw, but not the uninjected paw when compared with controls. BL: baseline. *P < 0.05; **P < 0.001; ***P < 0.001 compared with vehicle at the indicated time points. †P < 0.05; ††P < 0.001 compared with capsaicin-injected paw in F. CFA, complete Freund's adjuvant; EREG, epiregulin.**

Considering that the human genetic association results indicated that lost function H2 and H3 haplotypes were a risk for acute pain, we further hypothesized that blockade of EREG during the development of pain states may prolong or enhance hypersensitivity. Administration of the EREG mAb 1 day after CFA (ie, during the development of hypersensitivity) delayed the natural recovery time course of mechanosensitivity (two-way ANOVA, treatment × repeated measures: $F_{2, 28} = 5.4$, $P = 0.001$, Fig. 6D). This effect seemed to be independent of an inflammatory state per se, as levels of white blood cells were not different in mice that received the EREG mAb or vehicle control (supplementary Table 3, available at http://links.lww.com/PAIN/A937). Next, we injected capsaicin as a model of acute pain (measuring both nocifensive and mechanical withdrawal thresholds). Pre-treatment with the EREG mAb 2 days before capsaicin increased nocifensive behavior ($t_{14} = 2.54$, $P = 0.02$, Fig. 6E) and decreased mechanical pain thresholds in the injected, but not un-injected paw (two-way ANOVA, treatment × paw: $F_{1, 28} = 4.91$, $P = 0.03$, Fig. 6F).

# 5. Discussion

In this study, we report the results of genetic screening within 16 genes of the EGFR family of receptors and ligands for their association with acute and chronic pain states. First, we identified EREG as the strongest sole contributor with 2 functional genetic variants and discovered a new haplotype H3 of EREG marked by the presence of a minor allele at SNP rs6836436. Second, and more surprisingly, we found that EREG has a dichotomous role in the pathophysiology of pain with its loss-of-function variants associated with decreased chronic pain severity but increased acute pain severity. We validated the results of this association analysis using mouse models of pain, where we found that neutralizing EREG with a mAb either reversed or enhanced pain behavior in chronic vs acute pain models, respectively.

Together, our results combined with previous reports[22,30] suggest that EREG mitigates pain during the early stages of its development but eventually contributes to the establishment of chronic pain. Therefore, in addition to current pharmacotherapy of chronic pain conditions with nonsteroidal anti-inflammatory drugs, opioids, corticosteroids, anxiolytics, muscle relaxants, antidepressants, anticonvulsants, and benzodiazepines, inhibition of EREG-EGFR complex formation could serve as a novel strategy to control chronic pain. Epiregulin-targeted therapy would not only be efficient in managing chronic pain but may provide a safer alternative to currently available drugs for EGFR inhibition because EGFR inhibitors have side effects such as skin rash.[20] Nonetheless, more definitive studies such as functional assays for rs6836436, preclinical experiments to further explore the role of EREG in acute and chronic pain, and clinical

trials for EREG inhibitors as analgesics are required to substantiate the role of EREG in the pathogenesis of pain.

Like other chronic diseases, early intervention is associated with better outcomes with chronic pain. Hence, there is a need to identify potential chronic pain patients during the acute stage for timely and optimal disease management. On one hand, a risk biomarker indicates the potential for developing a disease in an individual who does not currently have an identifiable clinical disease. Being associated with increased chronic pain severity and risk for developing chronic TMD, the presence of a major allele at rs6836436 or rs2367707 in acute pain patients might serve as a risk biomarker of chronic pain development. Nevertheless, it is important to recognize that pain is a highly polygenic trait, and the contribution of each allele to the appreciable minor allelic frequency is expected to be modest. That is, why we do not suggest rs6836436 or rs2367707 by themselves will act as sole predictors of pain states but could be useful inclusions into a screening panel of genetic markers for pain profiling. Conversely, a response biomarker could identify individuals who are more likely to experience a favorable or unfavorable effect from drug treatment. The current findings suggest that the presence of a major allele at rs6836436 or rs2367707 may serve as a favorable response biomarker for EREG-EGFR–based pharmacotherapy of chronic pain. Thus, studying EREG gene polymorphism could accelerate the development of personalized pain medicine.

Although we used a TMD-centric cohort (OPPERA) as a discovery cohort, our results do not suggest that the association between EREG and pain phenotypes is specific to TMD or orofacial pain. We identified an association between EREG SNPs and a number of

chronic pain conditions, independent of body site. This suggests that EREG contributes to TMD through mechanisms overlapping with other chronic pain conditions.[27] Symptoms of chronic TMD such as generalized pain sensitivity, sleep, concentration difficulties, depression, bowel complaints, and headaches often overlap with those of more generalized chronic pain conditions such as fibromyalgia and chronic fatigue syndrome.[1] However, our conclusions may be limited based on the statistical power of the discovery cohort, OPPERA. With a TMD incidence rate of 8% and MAF of EREG's H2 and H3 haplotype at 17.3% and 5% in the OPPERA follow-up cohort, respectively, the data lacked sufficient power to analyze the association between EREG and the onset of TMD in OPPERA or other associated pain phenotypes. Moreover, because of limited acute CPI at follow-up data, we could not confirm whether captured patients would resolve TMD in the OPPERA cohort or whether they would remain chronic.

It is important to recognize the absence of a good replication cohort for our discovery findings. We used CPI as a pain intensity marker in OPPERA, but this phenotype is rarely collected in large community cohorts such as UKB. Thus, we used the number of painful sites as markers of acute and chronic pain severity in UKB. Although pain severity in terms of intensity and anatomical extent are correlated[3,49], these are clearly different phenotypes with potentially overlapping pathophysiology. Furthermore, the original discovery cohort was TMD-centric, while the UKB subjects reported pain across all body sites. Here, we viewed orofacial pain as an idiopathic pain condition and assumed that EREG contributes to it through molecular mechanisms shared by other chronic pain conditions, as suggested in our previous work.[30] Overall, our second analysis in the UKB cohort was a validation of the primary findings from OPPERA rather than a true

replication. It, however, unambiguously supported the dichotomous nature of EREG's contribution to pain.

We previously showed that both EGFR and EREG displayed a genetic association with chronic TMD where EREG showed the strongest association.[30] The current study confirms the association of haplotype H2 with chronic TMD in a different subset of OPPERA subjects (Table 5) and also demonstrated that the same haplotype H2 was associated with the presence of at least one chronic pain site in UKB. Although haplotype H3 was not identified in our earlier studies—due to its low frequency—it has a stronger effect than H2, as is evident from the strength of associations with pain phenotypes (Tables 5 and 6) and eQTL analysis (Table 4). However, both haplotypes, H2, and H3 are loss-of-function variants. Although we do not know the exact molecular mechanisms through which haplotypes H2 and H3 control EREG mRNA levels, we have shown earlier that rs2367707 (a marker of H2) reduces the stability of the mRNA, and the 5′UTR location of rs6836436 (a marker of H3) suggests control of transcription. The absence of association of haplotype H2 with acute pain phenotypes (Table 6) is likely a reflection of its effect size rather than evidence for a unique contribution of H3, but not H2 to acute pain. An inverse relationship exists between the effect sizes and the allele frequencies for all phenotypic traits.[34] It is also possible that state-dependent stimuli regulating EREG transcription and mRNA stability contribute equally to chronic pain, but only regulation of transcription contributes to acute pain.

Our current results are also in line with our previous report on the effect of EREG in animal pain models. We previously showed that administration of EREG but not other EGFR

ligands to mice in the late phase of the formalin test increased pain sensitivity.[30] Mouse experiments in this study assessed the impact of blocking EREG in different pain models at different time points and were designed to support and complement the human genetic analysis. Mice treated with the EREG mAb during peak CFA allodynia (i.e., 3 days after CFA) recovered quicker than control mice; SNI-induced allodynia was also reversed for up to 1 week after EREG mAb administration. These results provide generalizability across chronic pain assays and suggest that EREG neutralization may offer a novel analgesic strategy for established chronic pain. Furthermore, the EREG mAb delayed recovery from CFA when administered during the development of CFA-induced allodynia (i.e., 1 day after CFA). EREG neutralization also enhanced nocifensive pain behavior and acute mechanosensitivity in mice injected with capsaicin. Broadly, these data support the findings from the human genetic analysis, where the H3 haplotype was found to be protective for chronic pain, but a risk marker for acute pain.

Although the signaling mechanisms of EREG on acute and chronic pain have yet to be discovered, a recently published independent study has reported similar dichotomous effects of EREG, where the application of EREG onto the spinal dorsal nerve roots of rats reduced evoked c-fiber responses but increased spontaneous activity in spinal dorsal horn neurons.[22] Furthermore, immune system dysfunctions including allergic and autoimmune disease comorbidities[16,29,36,46] and elevated levels of proinflammatory cytokines[38,43,50] are common among chronic pain conditions. Because EREG is temporally15 and causally[17,32] associated with activation of the immune system and inflammation,[37] EREG may contribute to pain through a systemic process. For instance, EREG is involved with the production of proinflammatory cytokines in macrophages,[39],

and EREG is increased during cutaneous wound inflammation and healing.[25] Thus, EREG production may be necessary for the resolution of inflammation and the natural recovery from pain; however, EREG may trigger the expression of signaling cascades in primary afferent nerves or in the dorsal horn that promotes long-term changes in neuronal excitability.[15,30,32] Nevertheless, a full understanding of the role of EREG in modulating pain severity through the immune and/or nervous system will require simultaneous study of EREG, immune cells, inflammation, and pain responses, both preclinically and clinically.

In conclusion, this study confirms the previously reported role of EREG in the pathogenesis of human chronic pain and preclinical pain models.[30] In addition, this study discovered an analgesic role for EREG during the early stages of pain, while an opposite-pronociceptive role in establishing chronic pain. Explicitly, this study is an example of a human → mouse translational research that further affirms EREG's potential as a biomarker of chronic pain, demystifies EREG-mediated pathogenesis of pain, and suggests a novel, nonopioid therapy for chronic pain.

## 6. Conflict of interest statement

The authors have no conflicts of interest to declare.

## 7. Supplemental content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/A937 and also as Appendix 2 of this thesis.

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# 9. References

[1]. Aaron LA, Burke MM, Buchwald D. Overlapping conditions among patients with chronic fatigue syndrome, fibromyalgia, and temporomandibular disorder. Arch Intern Med 2000;160:221–7.

[2]. Bair E, Brownstein NC, Ohrbach R, Greenspan JD, Dubner R, Fillingim RB, Maixner W, Smith SB, Diatchenko L, Gonzalez Y, Gordon SM, Lim PF, Ribeiro-Dasilva M, Dampier D, Knott C, Slade GD. The study protocol, sample characteristics, and loss to follow-up: the OPPERA prospective cohort study. J Pain 2013;14(12 suppl):T2–19.

[3]. Barbero M, Fernandez-de-Las-Penas C, Palacios-Cena M, Cescon C, Falla D. Pain extent is associated with pain intensity but not with widespread pressure or thermal pain sensitivity in women with fibromyalgia syndrome. Clin Rheumatol 2017;36:1427–32.

[4]. Barrett JC, Fry B, Maller J, Daly MJ. Haploview: analysis and visualization of LD and haplotype maps. Bioinformatics 2005;21:263–5.

[5]. Benjamini Y, Hochberg Y. Controlling the false discovery rate—a practical and powerful approach to multiple testing. J R Stat Soc B 1995;57:289–300.

[6]. Bennett GJ, Xie YK. A peripheral mononeuropathy in rat that produces disorders of pain sensation like those seen in man. PAIN 1988;33:87–107.

[7]. Bonin RP, Bories C, De Koninck Y. A simplified up-down method (SUDO) for measuring mechanical nociception in rodents using von Frey filaments. Mol Pain 2014;10:26.

[8]. Bycroft C, Freeman C, Petkova D, Band G, Elliott LT, Sharp K, Motyer A, Vukcevic D, Delaneau O, O'Connell J, Cortes A, Welsh S, Young A, Effingham M, McVean G, Leslie S, Allen N, Donnelly P, Marchini J. The UK Biobank resource with deep phenotyping and genomic data. Nature 2018;562:203–9.

[9]. Decosterd I, Woolf CJ. Spared nerve injury: an animal model of persistent peripheral neuropathic pain. PAIN 2000;87:149–58.

[10]. Dworkin SF, LeResche L. Research diagnostic criteria for temporomandibular disorders: review, criteria, examinations and specifications, critique. J Craniomandib Disord 1992;6:301–55.

[11]. Dworkin SF, Von Korff M, Whitney CW, Le Resche L, Dicker BG, Barlow W. Measurement of characteristic pain intensity in field research. PAIN 1990;41:S290.

[12]. Epker J, Gatchel RJ, Ellis E III. A model for predicting chronic TMD: practical application in clinical settings. J Am Dent Assoc 1999;130:1470–5.

[13]. Farrar JT, Young JP Jr, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. PAIN 2001;94:149–58.

[14]. GTEx_Consortium. The genotype-tissue expression (GTEx) project. Nat Genet 2013;45:580–5.

[15]. Harada M, Kamimura D, Arima Y, Kohsaka H, Nakatsuji Y, Nishida M, Atsumi T, Meng J, Bando H, Singh R, Sabharwal L, Jiang JJ, Kumai N, Miyasaka N, Sakoda S, Yamauchi-Takihara K, Ogura H, Hirano T, Murakami M. Temporal expression of growth factors triggered by epiregulin regulates inflammation development. J Immunol 2015;194:1039–46.

[16]. Hoffmann RG, Kotchen JM, Kotchen TA, Cowley T, Dasgupta M, Cowley AW Jr. Temporomandibular disorders and associated clinical comorbidities. Clin J Pain 2011;27:268–74.

[17]. Homma T, Kato A, Sakashita M, Takabayashi T, Norton JE, Suh LA, Carter RG, Harris KE, Peters AT, Grammer LC, Min JY, Shintani-Smith S, Tan BK, Welch K, Conley DB, Kern RC, Schleimer RP. Potential involvement of the epidermal growth factor receptor ligand epiregulin and matrix metalloproteinase-1 in pathogenesis of chronic rhinosinusitis. Am J Respir Cell Mol Biol 2017;57:334–45.

[18]. Joehanes R, Zhang X, Huan T, Yao C, Ying SX, Nguyen QT, Demirkale CY, Feolo ML, Sharopova NR, Sturcke A, Schaffer AA, Heard-Costa N, Chen H, Liu PC, Wang R, Woodhouse KA, Tanriverdi K, Freedman JE, Raghavachari N, Dupuis J, Johnson AD, O'Donnell CJ, Levy D, Munson PJ. Integrated genome-wide analysis of expression quantitative trait loci aids interpretation of genomic association studies. Genome Biol 2017;18:16.

[19]. Kersten C, Cameron MG. Cetuximab alleviates neuropathic pain despite tumour progression. BMJ Case Rep 2012;2012:bcr1220115374.

[20]. Kersten C, Cameron MG, Laird B, Mjaland S. Epidermal growth factor receptor—inhibition (EGFR-I) in the treatment of neuropathic pain. Br J Anaesth 2015;115:761–7.

[21]. Kersten C, Cameron MG, Mjåland S. Epithelial growth factor receptor (EGFR)-inhibition for relief of neuropathic pain—a case series. Scand J Pain 2013;4:3–7.

[22]. Kongstorp M, Schjølberg T, Jacobsen DP, Haugen F, Gjerstad J. Epiregulin is released from intervertebral disks and induces spontaneous activity in pain pathways. PAIN Rep 2019;4:e718.

[23]. Lake SL, Lyon H, Tantisira K, Silverman EK, Weiss ST, Laird NM, Schaid DJ. Estimation and tests of haplotype-environment interaction when linkage phase is ambiguous. Hum Hered 2003;55:56–65.

[24]. Loeser JD, Melzack R. Pain: an overview. Lancet 1999;353:1607–9.

[25]. Magnusson JE, Fisher K. The involvement of dopamine in nociception: the role of D(1) and D(2) receptors in the dorsolateral striatum. Brain Res 2000;855:260–6.

[26]. Maixner W, Diatchenko L, Dubner R, Fillingim RB, Greenspan JD, Knott C, Ohrbach R, Weir B, Slade GD. Orofacial pain prospective evaluation and risk assessment study—the OPPERA study. J Pain 2011;12(11 suppl):T4–11.e12.

[27]. Maixner W, Fillingim RB, Williams DA, Smith SB, Slade GD. Overlapping chronic pain conditions: implications for diagnosis and classification. J Pain 2016;17(9 suppl):T93–107.

[28]. Manichaikul A, Mychaleckyj JC, Rich SS, Daly K, Sale M, Chen WM. Robust relationship inference in genome-wide association studies. Bioinformatics 2010;26:2867–73.

[29]. Marchand F, Perretti M, McMahon SB. Role of the immune system in chronic pain. Nat Rev Neurosci 2005;6:521–32.

[30]. Martin LJ, Smith SB, Khoutorsky A, Magnussen CA, Samoshkin A, Sorge RE, Cho C, Yosefpour N, Sivaselvachandran S, Tohyama S, Cole T, Khuong TM, Mir E, Gibson DG, Wieskopf JS, Sotocinal SG, Austin JS, Meloto CB, Gitt JH, Gkogkas C, Sonenberg N, Greenspan JD, Fillingim RB, Ohrbach R, Slade GD, Knott C, Dubner R, Nackley AG, Ribeiro-da-Silva A, Neely GG, Maixner W, Zaykin DV, Mogil JS, Diatchenko L. Epiregulin and EGFR interactions are involved in pain processing. J Clin Invest 2017;127:3353–66.

[31]. Meloto CB, Benavides R, Lichtenwalter RN, Wen X, Tugarinov N, Zorina-Lichtenwalter K, Chabot-Dore AJ, Piltonen MH, Cattaneo S, Verma V, Klares R III, Khoury S, Parisien M, Diatchenko L. Human pain genetics database: a resource dedicated to human pain genetics research. PAIN 2018;159:749–63.

[32]. Murakami M, Harada M, Kamimura D, Ogura H, Okuyama Y, Kumai N, Okuyama A, Singh R, Jiang JJ, Atsumi T, Shiraya S, Nakatsuji Y, Kinoshita M, Kohsaka H, Nishida M, Sakoda S, Miyasaka N, Yamauchi-Takihara K, Hirano T. Disease-association analysis of an inflammation-related feedback loop. Cell Rep 2013;3:946–59.

[33]. Ohrbach R, Turner JA, Sherman JJ, Mancl LA, Truelove EL, Schiffman EL, Dworkin SF. The research diagnostic criteria for temporomandibular disorders. IV: evaluation of psychometric properties of the Axis II measures. J Orofac Pain 2010;24:48–62.

[34]. Park JH, Gail MH, Weinberg CR, Carroll RJ, Chung CC, Wang Z, Chanock SJ, Fraumeni JF Jr, Chatterjee N. Distribution of allele frequencies and effect sizes and their interrelationships for common genetic susceptibility variants. Proc Natl Acad Sci U S A 2011;108:18026–31.

[35]. Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA, Bender D, Maller J, Sklar P, de Bakker PI, Daly MJ, Sham PC. PLINK: a tool set for whole-genome association and population-based linkage analyses. Am J Hum Genet 2007;81:559–75.

[36]. Ren K, Dubner R. Interactions between the immune and nervous systems in pain. Nat Med 2010;16:1267–76.

[37]. Riese DJ II, Cullum RL. Epiregulin: roles in normal physiology and cancer. Semin Cell Dev Biol 2014;28:49–56.

[38]. Rodriguez-Pintó I, Agmon-Levin N, Howard A, Shoenfeld Y. Fibromyalgia and cytokines. Immunol Lett 2014;161:200–3.

[39]. Shirasawa S, Sugiyama S, Baba I, Inokuchi J, Sekine S, Ogino K, Kawamura Y, Dohi T, Fujimoto M, Sasazuki T. Dermatitis due to epiregulin deficiency and a critical role of epiregulin in immune-related responses of keratinocyte and macrophage. Proc Natl Acad Sci USA 2004;101:13921–6.

[40]. Slade GD, Bair E, By K, Mulkey F, Baraian C, Rothwell R, Reynolds M, Miller V, Gonzalez Y, Gordon S, Ribeiro-Dasilva M, Lim PF, Greenspan JD, Dubner R, Fillingim RB, Diatchenko L, Maixner W, Dampier D, Knott C, Ohrbach R. Study methods, recruitment, sociodemographic findings, and demographic representativeness in the OPPERA study. J Pain 2011;12(11 suppl):T12–26.

[41]. Smith SB, Maixner DW, Greenspan JD, Dubner R, Fillingim RB, Ohrbach R, Knott C, Slade GD, Bair E, Gibson DG, Zaykin DV, Weir BS, Maixner W, Diatchenko L. Potential

genetic risk factors for chronic TMD: genetic associations from the OPPERA case control study. J Pain 2011;12(11 suppl):T92–101.

[42]. Smith SB, Parisien M, Bair E, Belfer I, Chabot-Dore AJ, Gris P, Khoury S, Tansley S, Torosyan Y, Zaykin DV, Bernhardt O, de Oliveira Serrano P, Gracely RH, Jain D, Jarvelin MR, Kaste LM, Kerr KF, Kocher T, Lahdesmaki R, Laniado N, Laurie CC, Laurie CA, Mannikko M, Meloto CB, Nackley AG, Nelson SC, Pesonen P, Ribeiro-Dasilva MC, Rizzatti-Barbosa CM, Sanders AE, Schwahn C, Sipila K, Sofer T, Teumer A, Mogil JS, Fillingim RB, Greenspan JD, Ohrbach R, Slade GD, Maixner W, Diatchenko L. Genome-wide association reveals contribution of MRAS to painful temporomandibular disorder in males. PAIN 2019;160:579–91.

[43]. Sommer C, Kress M. Recent findings on how proinflammatory cytokines cause pain: peripheral mechanisms in inflammatory and neuropathic hyperalgesia. Neurosci Lett 2004;361:184–7.

[44]. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, Downey P, Elliott P, Green J, Landray M, Liu B, Matthews P, Ong G, Pell J, Silman A, Young A, Sprosen T, Peakman T, Collins R. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med 2015;12:e1001779.

[45]. Treede RD, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, Cohen M, Evers S, Finnerup NB, First MB, Giamberardino MA, Kaasa S, Korwisi B, Kosek E, Lavand'homme P, Nicholas M, Perrot S, Scholz J, Schug S, Smith BH, Svensson P, Vlaeyen JWS, Wang

SJ. Chronic pain as a symptom or a disease: the IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11). PAIN 2019;160:19–27.

[46]. Verma V, Sheikh Z, Ahmed AS. Nociception and role of immune system in pain. Acta Neurol Belg 2015;115:213–20.

[47]. Von Korff M, Ormel J, Keefe FJ, Dworkin SF. Grading the severity of chronic pain. PAIN 1992;50:133–49.

[48]. Wain LV, Shrine N, Miller S, Jackson VE, Ntalla I, Soler Artigas M, Billington CK, Kheirallah AK, Allen R, Cook JP, Probert K, Obeidat M, Bosse Y, Hao K, Postma DS, Pare PD, Ramasamy A, Consortium UKBE, Magi R, Mihailov E, Reinmaa E, Melen E, O'Connell J, Frangou E, Delaneau O, Ox GSKC, Freeman C, Petkova D, McCarthy M, Sayers I, Deloukas P, Hubbard R, Pavord I, Hansell AL, Thomson NC, Zeggini E, Morris AP, Marchini J, Strachan DP, Tobin MD, Hall IP. Novel insights into the genetics of smoking behaviour, lung function, and chronic obstructive pulmonary disease (UK BiLEVE): a genetic association study in UK Biobank. Lancet Respir Med 2015;3:769–81.

[49]. Wolfe F. Pain extent and diagnosis: development and validation of the regional pain scale in 12,799 patients with rheumatic disease. J Rheumatol 2003;30:369–78.

[50]. Zhang JM, An J. Cytokines, inflammation, and pain. Int Anesthesiol Clin 2007;45:27–37.

[51]. Zorina-Lichtenwalter K, Meloto CB, Khoury S, Diatchenko L. Genetic predictors of human chronic pain conditions. Neuroscience 2016;338:36–62.

# III. Unbiased immune profiling reveals a Natural Killer cell-peripheral nerve axis in fibromyalgia.

## 1. Abstract

Fibromyalgia syndrome (FMS) is a common rheumatic disease characterized by chronic widespread pain, fatigue, and, sleep and cognitive difficulties. Pathogenesis of this syndrome remains elusive leading to a lack of objective diagnosis and specific treatment, although the association of immune system abnormalities and small fiber neuropathy have been reported. To advance our understanding of FMS pathophysiology, a case-control study using unbiased genome-wide approaches at cellular and mRNA levels was conducted. Evaluation of peripheral blood mononuclear cells found circulating natural killer (NK) cells to be depleted in FMS patients. Immunophenotyping and functional testing of NK cells in FMS patients revealed a hyperactivated, yet exhausted profile including decreased expression of CD16, CD96, and CD226 and increased CD107a and TIGIT expression. Whole blood transcriptomics showed marked similarities between FMS and infectious, autoimmune, malignant, and neurodegenerative diseases. Lastly, skin biopsies from an independent cohort showed increased expression of the NK activation ligand, ULBP, on the subepidermal nerves in FMS that correlated with the presence of NK cells near the peripheral nerves and reduced epidermal nerve density. Collectively, our results suggest that chronic activation and redistribution of NK cells from the circulation to the peripheral nerves contribute to the pathology associated with FMS.

# 2. Introduction

Fibromyalgia syndrome (FMS) is the second most common rheumatic disease[1] with global prevalence ranging from 1-12.5% in women and 0-5.1% in men.[2, 3] It is characterized by chronic widespread pain, fatigue, sleep disturbance, anxiety, depression, and cognitive difficulties. This syndrome is often associated with an array of other symptoms like restless leg syndrome, irritable bowel syndrome, vulvodynia, irritable bladder, xerostomia, and dry eyes.[4] The diagnosis of FMS is given to individuals with chronic widespread pain for which no alternative cause can be identified.[5] Vague diagnostic criteria often lead to misdiagnosis and contribute to heterogeneity among the patient group. Moreover, FMS, being one of the functional somatic syndromes that are otherwise medically unexplained[6], lacks a definitive treatment. Incomplete understanding of the etiology and pathogenesis of FMS is a major obstacle in modeling the disease in animal assays, further hampering the pre-clinical research. In summary, the lack of objective diagnosis and poorly understood aetiopathogenesis of FMS are the two most important hindrances in identifying and treating FMS patients.

Both, central and peripheral nervous systems are affected in FMS. Changes in gray matter volume in the specific regions of the brain, decreased functional connectivity in the descending pain-modulating system, and increased activity in the pain matrix are suggestive of central sensitization in FMS.[7-9] Increased peripheral nerve demyelination, decreased dermal and intra-epidermal nerve fibers in FMS patients[10-12], and, presence of sensorial symptoms[13] such as paraesthesia, hyperalgesia, and allodynia are suggestive of peripheral neuropathy in FMS. Moreover, similarities between FMS and

chronic inflammatory demyelinating polyneuropathy (CIDP) are suggestive of chronic immunologic dysregulation in FMS.[11, 14]

There is a plethora of evidence demonstrating immune dysregulation in FMS. Epidemiological studies have shown that allergic[15-17] and autoimmune[18, 19] comorbidities are more common among FMS patients. Targeted exome sequencing [20], and proteome-wide[21] studies have identified molecular signatures consistent with low-grade chronic inflammation in FMS patients. Transcriptome-wide approaches found the relevance of immune response pathways and homeostasis to the experience of FMS.[22] Previous studies also hint towards defective cytotoxic immune response [23], increased activation of lymphocytes, and increased expression of cell adhesion molecules on neutrophils and monocytes[24] in FMS. However, specific immune players and neuro-immune interactions involved in the pathogenesis of FMS remain to be discovered.[25]

# 3. Methods

## 3.1. The Canadian cohort

### 3.1.1. Study population

The Canadian cohort was collected under the research project approved by the institutional review board (IRB), Faculty of Medicine, McGill University (IRB Study Number A05-M50-14B). PS: Power and Sample Size Calculation tool [26] was used to calculate the sample size based on a previous study[27] (Supplementary Figure 1). Forty-four FMS patients and 46 matched controls were deemed sufficient to reject the null hypothesis that the population means of the experimental and control groups are equal with probability

(power, 1 - β) 80% and type I error (α) ≤ 5%. The participants were recruited at the rheumatology clinics of McGill University, Alan Edwards Centre for Research on Pain's (AECRP) clinic, and the Research Institute of the McGill University Health Centre (RI-MUHC). The participants were enrolled by advertising the study in the local newspapers, at MUHC and McGill University bulletin boards and websites, and through mass emails.

The following inclusion criteria were applied to determine eligibility to participate in this study: (1) ability to write and speak in English and/or French, (2) agrees to provide signed and dated informed consent form, (3) willingness to comply with all study procedures and to be available for the duration of the study, and, (4) aged 40 years and more. An individual was excluded from the study if s/he had: (1) medical or psychiatric condition that is uncontrolled, (2) participated in a clinical study that may interfere with participation in this study, (3) had prior or current drug and/or alcohol abuse, or (4) had anything that would place the individual at increased risk or preclude the individual's full compliance with or completion of the study. As the specific inclusion criterion for FMS cases, patients were required to have a clinical diagnosis of fibromyalgia made by a rheumatologist, based on the 2010 criteria.[5] Lastly, a participant must have been never diagnosed with any chronic pain condition and should not have a history of depression to be deemed as a control.

### 3.1.2. Outcome measures

The primary outcome measure for this study was the case status of FMS. The secondary outcome measure was the global assessment of pain[28]. Apart from age, body mass index, and detailed medical history, other tertiary outcome measures collected are

summarized in Supplementary Table 1. All demographic, anthropometric, clinical, and patient-reported outcomes were collected and managed using Research Electronic Data Capture (REDCap) electronic data capture tools [29] which is a secure, web-based application designed to support data capture for research studies hosted at RI-MUHC.

### 3.1.3. Blood sample collection

Fifteen mL of peripheral blood samples were collected in ethylene diamine tetraacetic acid (EDTA) vacutainer tubes from each participant through the median cubital vein. Two and a half mL of whole blood was preserved in PAXgene™ blood RNA tubes (Qiagen, Hilden, Germany) and stored in a -80˚C freezer for RNA extraction. PBMCs were fractionated from the remaining whole blood using Ficoll™-based density gradient.[30] PBMCs (3 vials with 5 million cells in each) were resuspended in heat-inactivated human plasma-derived serum (H4522, Sigma-Aldrich, Canada) and 10% dimethyl sulfoxide (DMSO, D128-500, Fisher Scientific, Ontario, Canada), and, cryopreserved in liquid nitrogen for flow cytometry and NK activation assay.

### 3.1.4. mRNA sequencing

RNA from whole blood was isolated from PAXgene collection tubes according to the provider's protocol (PreAnalytiX GmbH, 08/2005, REF: 762174). The average mRNA concentration was 120 ng/µL and 25 µL of mRNA per sample was sequenced using Illumina's NovaSeq™ 6000 S2 SR100 platform at Génome Québec, Montreal, QC, Canada.

### 3.1.5. Flow cytometry

One vial of the cryopreserved PBMCs was split into three to stain for cytokines, chemokines, and regulatory T-cells (Tregs). Another vial was split into two to stain for B-cells, monocytes and dendritic cells (DCs), and, natural killer (NK) cells. Experimental design, selection of the antibodies and fluorochromes, antibody concentrations, and flow cytometer photomultiplier tubes' (PMTs) voltages were optimized to minimize technical artifacts in downstream computational analysis.[31] Details of the excitation LASER, channel filters, clones, antibody isotype, fluorochromes, manufacturer and catalog number, and the quantity of reagents used for all the flow cytometry panels are summarized in Supplementary Table 2. Cryopreserved PBMCs were rapidly thawed in a 37˚C water bath, resuspended in IMDM with 10% fetal bovine serum (FBS), and incubated in 37˚C with 5% $CO_2$ for 1 hour to improve detection of cell surface markers.[32] Viability staining was performed using Zombie NIR™ (423106; BioLegend, San Diego, CA, USA) and nonspecific mAb binding was minimized by the use of TruStain FcX reagent™ (422302; BioLegend, San Diego, CA, USA), as per the manufacturer's instructions. Subsequently, the cells were stained for extracellular markers. Intracellular staining was preceded with permeabilization as per the manufacturer's protocol (421002; BioLegend, San Diego, CA, USA). Following the staining, the PBMCs were fixed in 2% paraformaldehyde and stored at 4˚C in dark for data acquisition on the next day. Unstained cells, single-stained cells, and fluorescent minus one controls (FMOs) were used as controls. UltraComp eBeads™ were used for compensation of all fluorochromes. Using SPHERO™ alignment particles, the coefficients of variation (CVs), peak channels, and histogram distributions were aligned before every flow cytometry run to standardize

data acquisition across all the batches. Around two million total events were acquired from each sample on LSRFortessa™ (BD Biosciences) at the Flow Cytometry and Cell Sorting Facility of McGill University and the Immunophenotyping platform of RI-MUHC. Acquisitions of all the batches were performed within 24 hours of staining.

### 3.1.6. NK activation assay

Cryopreserved PBMCs from randomly chosen 14 cases and 14 controls were thawed, counted, and resuspended in RPMI 1640 medium supplemented with 10% FBS, 2 mM l-glutamine, 50 IU/ml penicillin, and 50 mg/ml streptomycin (henceforth, R10 medium) at 4 x $10^6$/mL for overnight resting. Each sample was split into four: two (one for stimulation and the other as unstimulated control) for human leukocyte antigen null ($HLA^{-/-}$) assay and two for antibody-dependent NK activation (ADNKA) assay.

$HLA^{-/-}$ assay is described in detail elsewhere.[33] For this assay, lymphoblastoid cell line (LCL) 721.221, a kind gift from Dr. Galit Alter (Ragon Institute, Harvard University, Cambridge, MA, USA) to Dr. Nicole Bernard, was used as the stimulant. In short, rested PBMCs (effector) were cocultured with 221 cells (target) at an E:T ratio of 5:1 in 200 µL of R10 in V-bottom 96-well plates. PBMCs cultured alone in R10 served as an unstimulated negative control.

Details of the ADNKA assay are described elsewhere.[34] In short, NKr.CCR5 (CEM) cells infected with HIV (iCEM; from the NIH AIDS Reagent Program, Division of AIDS, NIAID, NIH, Germantown MD, USA, from Dr. Alexandra Trkola) cells, recombinant gp120 (HIV-1 Env rgp120 from HIV-1Bal), and HIVIG pooled plasma from HIV infected donors

(Catalog #3957, HIV-IG from NABI and NHLBI) were obtained from the NIH AIDS Reagent Program. $1x10^6$ cells (50 µL) iCEM cells and 50 µL of pre-diluted opsonizing Abs (HIV+Ig or HIV-Ig, 50 µg/mL in R10) were added to the rested PBMCs (effector) in V-bottom 96-well plates (E:T ratio of 1:1).

One hour after the initiation of the cocultures, 1.33 µL (final dilution of 1:1500) of GolgiStop™ (pre-diluted 1:10 in PBS; cat. 554724; BD Biosciences, Mississauga, ON, Canada) and 2 µL (final dilution 1:1000) of Golgiplug™ (pre-diluted 1:10 in PBS; cat. 555029; BD Biosciences, Mississauga, ON, Canada) were added. BV711-conjugated anti-CD107a (5 µL/well; cat. 328640; BioLegend) was also added at the beginning of the coculture. Both the cocultures ($HLA^{-/-}$ and ADNKA) were incubated for six hours at 37°C in a humidified 5% CO2 incubator. After incubation, the plates were wrapped in aluminum foil and stored in a 4°C fridge overnight. The next day, the cells were stained with UV Live/Dead™ Fixable Blue cell stain kit, as per manufacturer's directions (cat. L34961; Thermofisher, Waltham, MA) and with reagents described in Supplementary Table 1.

## 3.2. The German cohort

The details of the study population and skin biopsy procedures are summarized elsewhere.[12] In short, 382 participants were screened and 117 women (median age of 52 years, range: 22-75 years) with FMS were enrolled. Six mm skin punch biopsies were obtained from the right lateral lower leg and upper thigh of the participants. The skin biopsies from 17 FMS patients and 11 controls were randomly selected for this study. The project was approved by the Ethics Committee of the University of Würzburg, Medical Faculty Germany, (#121/14), and all study participants gave written informed consent.

### 3.2.1. Skin microscopy

Twenty µm thick sections were prepared and two sections were loaded per slide. The slides were blocked with 10% bovine serum albumin (BSA) in phosphate buffer saline (PBS) for 30 minutes at room temperature. Anti-ULBP goat monoclonal antibody(mAb,1:50; R&D 1298), anti-CD3 (168; BIO-RAD, MCA1477) with rat anti-human 1:500 with Cy3 (54; Dianova, 112-165-167), goat anti-rat 1:100 and anti-CD56 goat mAb (1:100; R&D AF2408) along with PGP9.5 rabbit anti-human mAb (1:200; Zytomed 516-3344) were used as primary antibodies in 10% BSA/PBS and 0.3 Triton. The sections were incubated overnight at 4°C with the primary antibodies. Followed by incubation, staining was performed with Cy3 donkey anti-goat mAb (1:50; Dianova 705-165-147) and Alexa Fluor 488 donkey anti-rabbit mAb (1:400; Dianova 711-545-152). Nuclei were stained with 1.5 µg/mL 4′,6-diamidino-2-phenylindole di-lactate (DAPi), and Vectashield™ (Vectorlabs, H-1000-10) was used as mounting medium. Quantification of intra-epidermal nerve fiber deficiency (IENFD), ULBP+ sup-epidermal plexus (SEP), and CD56+ nucleated cells was performed by an independent investigator blinded to subject group allocation. IENFD was assessed on an Axioplot™ microscope (Zeiss, Oberkochen, Germany) and was defined as normal if there were ≥ 5.4 fibers/mm. All other Immunofluorescence microscopy was performed on ApoTome™ microscope (Zeiss, Oberkochen, Germany). Both the microscopes were equipped with an AxioCam™ MRm camera (Zeiss) and SPOT software (Diagnostic Instruments, Sterling Heights, MI) was used. The area of interest was 100 µm from the dermis-epidermis border. All the assessments were performed with a 40x objective and optical sectioning. Images from the whole sample were Z-stacked to follow the nerve fibers and NK cells. The

subepidermal neural plexus (SEP), located in the zone of 100 µm from the basement membrane, were counted regardless of the individual length of nerve segments. Then, each segment was checked for ULBP positivity one by one, as the ratio and degree of ULBP staining of SEP could show variability even within a section. If the shape of SEP could be distinguished from the ground, they were marked as positive regardless of their staining strength. Then, the percentage of ULBP positive SEP was calculated by dividing the number of ULBP stained SEPs by the number of total SEPs. The $CD56^{+}$ NK cells, which were alone or in contact with subepidermal neural plexus segments, were counted manually. As Schwann cells may also be stained by CD56, the cells that had a discus-shaped nucleus were excluded.

## 3.3. Data analysis

### 3.3.1. Flow cytometry

Flow cytometry data was compensated using Flowjo v10.7.3 (Treestar, Ashland, OR). Cells of interest were identified as per the gating strategy described in Supplementary Figure 2. Data from all five flow cytometry panels were analyzed using VoPo[35]. In brief, the cells were clustered into coherent subpopulations based on the expression of all cell phenotype markers using a robust bootstrapped meta-clustering algorithm. A random forest algorithm was applied to the dataset comprised of all cell cluster features to estimate the magnitude of differences in features separating the controls from the patients. Using a leave-group-out cross-validation procedure the Random Forest model predicted the probability that each sample belonged to the patient group. The p-value (p) from a Wilcoxon Rank Sum Test was used to test the null hypothesis that the predicted

probabilities of a sample to be from a patient or control were equal. As this approach does not rely on an individual cell-to-population partition but instead integrates multiple clustering solutions to predict patient phenotype, it has less variability compared to individual solutions. Finally, cells were projected using t-Distributed UMAP (t-UMAP) into two dimensions for visualization using uwot R package v0.1.9.

### 3.3.2. Pathway analyses

The Enrichment of hematopoietic cell type activation pathways in FMS patients compared to healthy controls was estimated via two genome-wide approaches, namely at the transcriptomics level and at the genomics level. Total mRNA from the whole blood was sequenced as described earlier, section 3.1.4. The transcriptomics data were mapped on the human genome GRCh37/hg19 using the STAR aligner[36], then featureCount was used to count reads mapped to each gene[37]. The analysis for differential gene expression between FMS and healthy controls performed using DEseq2[38] in each sex separately, then combined using the inverse variance-based approach proposed in METAL[39]. Pathway analyses were performed using the Gene Ontology (GO)[40] for cell types of hematopoietic origin for genes involved in cell activation (December 2020 version from http://baderlab.org/GeneSets) using fgsea.[41]

At the genetics level, we first performed a genome-wide association study (GWAS) in the UK Biobank (UKB) project.[42, 43] Cases were defined as individuals reporting “fibromyalgia” for field 20002 “Non-cancer illness code, self-reported” or with generalized pain all over the body (n=8,086), while controls defined as individuals with no reported pain (n=197,050). The GWAS was computed using SAIGE, taking into account the

disproportionate case-to-control ratio and cryptic relatedness.[44] Sex, age, age squared, genotyping array, dummy-coded recruitment centers, and the largest 40 principal components were used as co-variables. The second GWAS was performed in the HUNT study.[45] There, cases were defined as per the American College of Rheumatology's 2016 criteria (n=2,818), while controls as individuals with no pain (n=16,901). The GWAS was computed using BOLT-LMM[46], with birth-year, sex, genotyping batch, and the first four principle components as co-variables. Single nucleotide polymorphism (SNP)-level summary results from both UKB and HUNT were given as input to MAGMA[47], to derive gene-level summary results for each cohort. MAGMA was used again to perform a meta-analysis of both UKB and HUNT studies, still at the gene level. Finally, the gene-level summary information was used by MAGMA to infer pathway-level summaries in the same GO version as above. Because of enhanced power to detect differences at the transcriptomics level compared to at the genetic level where effect sizes are more subtle, we focused at the genomics level on pathways with “regulation of <cell type> activation”, while for genetics we required larger gene sets, so we focused on pathways without the regulation, thus simply “<cell type> activation”, where <cell type> is a cell type of hematopoietic origin. The current study was conducted under UK biobank application no. 20802.

### 3.3.3. Other data analyses

Results from NK activation assays were analyzed using mixed model analyses with age, sex, and BMI as fixed effects, and, batch and sample ID as random effects. R package lme4 v1.1.26 was used. Analysis of variance (ANOVA) with Tukey's correction and

Pearson's product-moment correlation was used for analyzing skin biopsy results. R package ggplot2 v3.3.2 was used for making the plot. All statistical analyses were performed using R v4.0.3. Lastly, the entire experiment plan is illustrated in Figure 1.

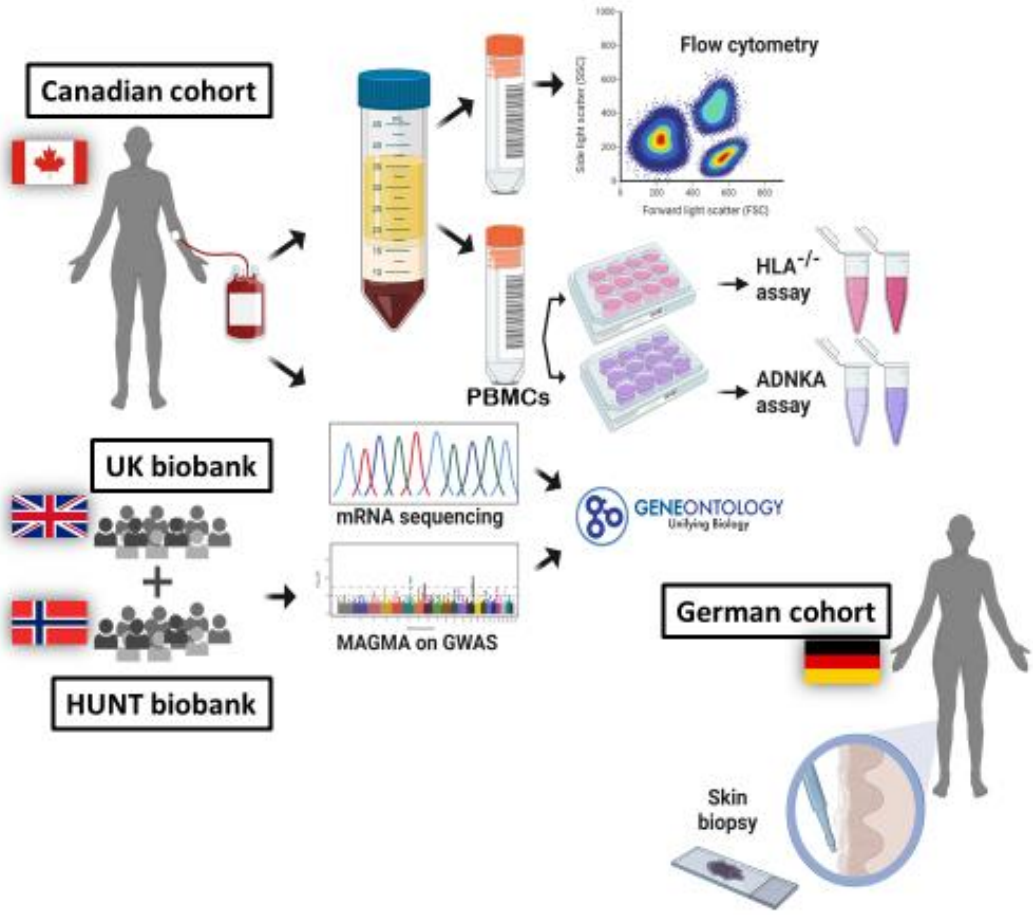


**Figure III-1: The summary of the experimental flow. Whole blood from the Canadian cohort was split for isolating peripheral blood mononuclear cells (PBMCs) and for mRNA sequencing. PBMCs were aliquoted for cryopreservation and used for immunophenotyping using flow cytometry and NK activation assays. mRNA was isolated and sequenced from the whole blood of the same cohort and was used for differential pathways analysis using Gene Ontology (GO) database. GWAS results derived from the UK biobank and the HUNT cohorts and were used along with the differential pathways analysis using Gene Ontology (GO) database as well. Microscopic analysis was performed on the skin biopsies from the German cohort. (Created with BioRender.com)**

# 4. Results

## 4.1. Characteristics of the Canadian cohort

The blood samples were collected from 90 participants, of which 44 were diagnosed as fibromyalgia patients. Similar to the previously reported prevalence of FMS[2], 97.7% of the cases were women. Hence, the majority of the recruited controls were women (91.3%) to match the number of cases. Mean age and BMI did not differ significantly between the control group and the FMS patients.

FMS patients had significantly higher pain scores, a higher proportion of their days were in pain, and had more painful body sites than the controls. Cases were 2.9 times more likely to suffer from headaches (p-value: 0.023), 4.5 times more likely to suffer from abdominal cramps (p-value: 0.0008), and 5.3 times more likely to suffer from depression (p-value: 0.0005). Fatigue and poor sleep quality were more common among the cases. The detailed description of the study population is summarized in Table 1.

**Table 1: Characteristics of the Canadian cohort**

| | Controls (n = 46) | Cases (n = 44) | Total (N = 90) | p-value |
|---|---|---|---|---|
| **Age** | | | | 0.960 |
| Mean (SD) | 55.6 (9.7) | 55.5 (8.3) | 55.6 (9.0) | |
| Range | 40.0 - 77.0 | 40.0 - 73.0 | 40.0 - 77.0 | |
| **Gender** | | | | 0.361 |
| Women | 42 (91.3%) | 43(97.7%) | 85 (94.4%) | |
| Men | 4 (8.7%) | 1 (2.3%) | 5 (5.6%) | |
| **BMI** | | | | 0.170 |
| N-Miss | 3 | 2 | 5 | |
| Mean (SD) | 26.4 (5.8) | 28.4 (7.8) | 27.3 (6.6) | |
| Range | 17.9 - 40.9 | 18.8 - 57.1 | 17.9 - 57.1 | |
| **Highest pain**[†] | | | | **< 0.001** |
| Mean (SD) | 2.7 (6.3) | 24.9 (19.9) | 13.5 (18.3) | |
| Range | 0.0 - 28.5 | 1.0 - 90.0 | 0.0 - 90.0 | |

| | | | | |
|---|---|---|---|---|
| **Average pain**[†] | | | | **< 0.001** |
| Mean (SD) | 2.4 (4.5) | 17.6 (13.6) | 9.7 (12.5) | |
| Range | 0.0 - 24.0 | 0.0 - 52.5 | 0.0 - 52.5 | |
| **Lowest pain**[†] | | | | **< 0.001** |
| Mean (SD) | 1.0 (2.7) | 6.7 (8.8) | 3.8 (7.0) | |
| Range | 0.0 - 15.0 | 0.0 - 50.0 | 0.0 - 50.0 | |
| **% day in pain**[*] | | | | **< 0.001** |
| Mean (SD) | 37.3 (44.6) | 96.2 (17.6) | 65.7 (45.2) | |
| Range | 0.0 - 100.0 | 12.0 - 100.0 | 0.0 - 100.0 | |
| **No. of painful sites**[*] | | | | **< 0.001** |
| N-Miss | 0 | 1 | 1 | |
| Mean (SD) | 2.8 (3.0) | 13.0 (3.5) | 7.7 (6.1) | |
| Range | 0.0 - 12.0 | 5.0 - 19.0 | 0.0 - 19.0 | |
| **Headache**[*] | | | | **0.023** |
| No | 20 (44.4%) | 9 (21.4%) | 29 (33.3%) | |
| Yes | 25 (55.6%) | 33 (78.6%) | 58 (66.7%) | |
| **Abdominal cramps**[*] | | | | **< 0.001** |
| No | 29 (64.4%) | 12 (28.6%) | 41 (47.1%) | |
| Yes | 16 (35.6%) | 30 (71.4%) | 46 (52.9%) | |
| **Depression**[*] | | | | **< 0.001** |
| No | 38 (84.4%) | 21 (50.0%) | 59 (67.8%) | |
| Yes | 7 (15.6%) | 21 (50.0%) | 28 (32.2%) | |
| **Fatigue**[*] | | | | **< 0.001** |
| No problem | 12 (26.7%) | 0 (0.0%) | 12 (13.8%) | |
| Slight or mild problem | 25 (55.6%) | 5 (11.9%) | 30 (34.5%) | |
| Moderate problem | 2 (4.4%) | 7 (16.7%) | 9 (10.3%) | |
| Severe problem | 6 (13.3%) | 30 (71.4%) | 36 (41.4%) | |
| **Trouble thinking/remembering**[*] | | | | **< 0.001** |
| No problem | 25 (55.6%) | 1 (2.4%) | 26 (29.9%) | |
| Slight or mild problem | 17 (37.8%) | 16 (38.1%) | 33 (37.9%) | |
| Moderate problem | 0 (0.0%) | 2 (4.8%) | 2 (2.3%) | |
| Severe problem | 3 (6.7%) | 23 (54.8%) | 26 (29.9%) | |
| **Overall sleep quality**[#] | | | | **< 0.001** |
| Very good | 11 (24.4%) | 3 (7.1%) | 14 (16.1%) | |
| Fairly good | 26 (57.8%) | 9 (21.4%) | 35 (40.2%) | |
| Fairly bad | 7 (15.6%) | 17 (40.5%) | 24 (27.6%) | |
| Very bad | 1 (2.2%) | 13 (31.0%) | 14 (16.1%) | |
| **Waking up tired (unrefreshed)** [*] | | | | **< 0.001** |
| No problem | 19 (42.2%) | 1 (2.4%) | 20 (23.0%) | |
| Slight or mild problem | 19 (42.2%) | 2 (4.8%) | 21 (24.1%) | |
| Moderate problem | 2 (4.4%) | 6 (14.3%) | 8 (9.2%) | |
| Severe problem | 5 (11.1%) | 33 (78.6%) | 38 (43.7%) | |

† Global assessment of pain (GAP); * Patient Self-report Survey for the Assessment of Fibromyalgia; #component 1 of Pittsburgh Sleep Quality Index (PSQI); BMI: body mass index; SD: standard deviation; N-Miss: no. of missing data points.

## 4.2. Assessment of immune cell subsets in fibromyalgia

We started with analyzing differential immunophenotypes of the PBMCs in FMS compared to matched cases in a hypothesis-free manner. No significant batch effects between flow cytometry runs were observed as there were no evident batch-specific cell clusters on the t-SNE plot (Supplementary Figure 3A). Neither the total cell count nor the viability differed between FMS cases and controls ($t = -1.08$, p-value = 0.283 and $t = 0.87$, p-value = 0.388; Supplementary Figure 3B and 3C, respectively). Assignment of PBMC phenotypes was based on the presence of expression of various immunophenotypical markers (supplementary figures 4-8).

With the available choice of markers, we were able to evaluate T helper cell subsets (Th1, Th2, Th17, and Treg), T cytotoxic cells (Tc1, Tc2, and Tc17), B cell subsets (plasmablast, naïve, translational, marginal zone, and memory B cells), monocyte subsets (classical, intermediate and non-classical), dendritic cells (DC, plasmacytoid DC and myeloid DC), NK cell subsets ($CD56^{bri}$, transitional and terminal NK cells), and, NKT cells (CD4+ and CD8+ NKTs). Cyto panel, chemo panel, Treg panel, BMD panel, and NK panel had 10, 12, 11, 14, and 14 markers, respectively, apart from viability staining. To quantify novel immune cells, unsupervised gating strategies were implemented, which in theory, could explore 39,936 immune cell subsets. (with 10, 12, 11, 14 and 14 markers per panel, $2^{10} + 2^{12} + 2^{11} + 2^{14} + 2^{14}$ marker combinations are possible.) Single cells across samples were projected into two dimensions using t-distributed UMAP for all the panels (Figure 2). Among all the PBMCs investigated, NK cell subsets were best able to differentiate FMS

cases and controls (p-value < $10^{-4}$). Specifically, there were significantly fewer circulating CD56$^{bri}$ NK cells in FMS patients (Figure 2E).

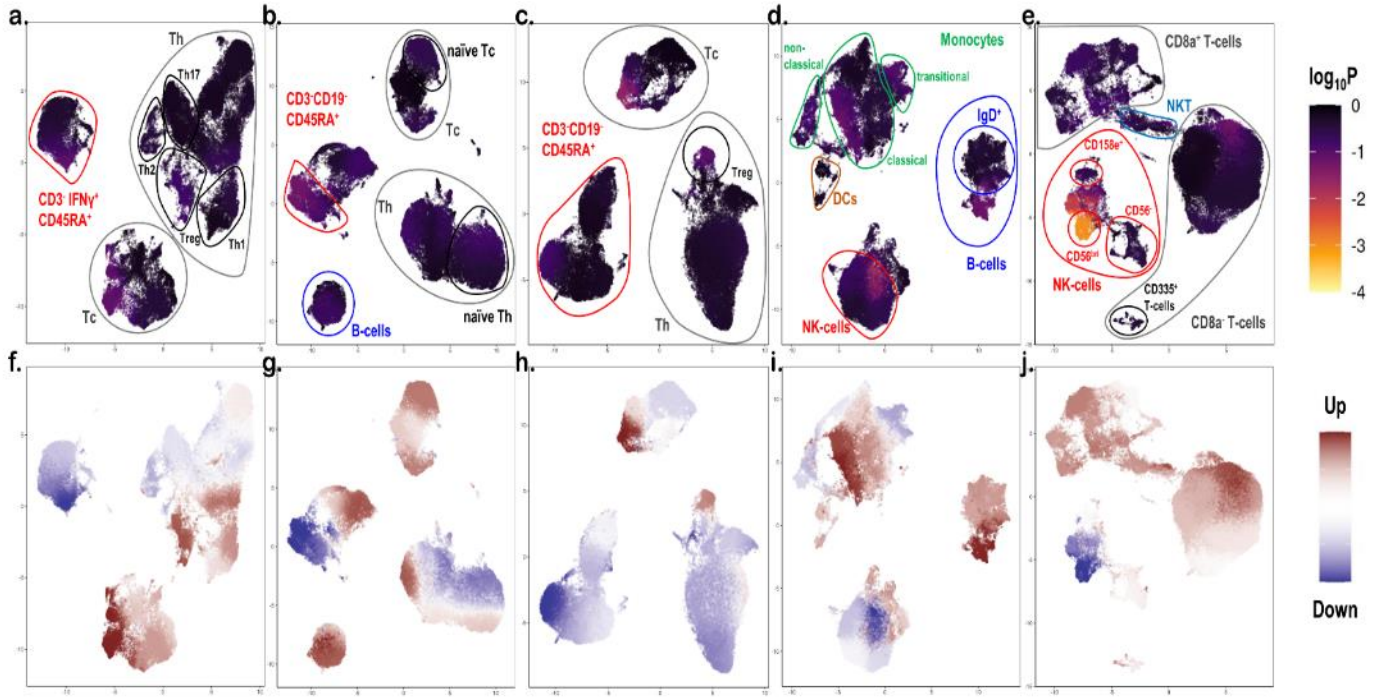


**Figure III-2: Differential abundance of immune cells in fibromyalgia syndrome (FMS) compare to controls. Single cells across samples were projected into two dimensions using t-distributed UMAP in the Cyto (a), Chemo (b), Treg (c), BMD (d) and NK (e) flow cytometry panel datasets. Cells were colored by their computed differentiation score, which depicts the degree of association with FMS, where lighter the color, more significant is the association. The direction of frequency differences between case and control samples is shown in Figures f-j where red and blue represent increased and decreased frequencies in cases, respectively.**

## 4.3. State of circulating NK cells in fibromyalgia

As depletion of circulating NK cells was associated with FMS, we examined a number of the surface markers on NK cells: CD16, CD107a, TIGIT, CD96, CD226, CD158e, CD159a, CD159c, and CD314. We observed the difference in expression of CD16, CD107a, TIGIT, CD96, and CD226 with type I error < 5%. Specifically, circulating NK cells had decreased surface expression of CD16, and, increased surface expression of

degranulation marker, CD107a, and TIGIT (Figure 3), suggesting a hyperactive state of NK cells in FMS.

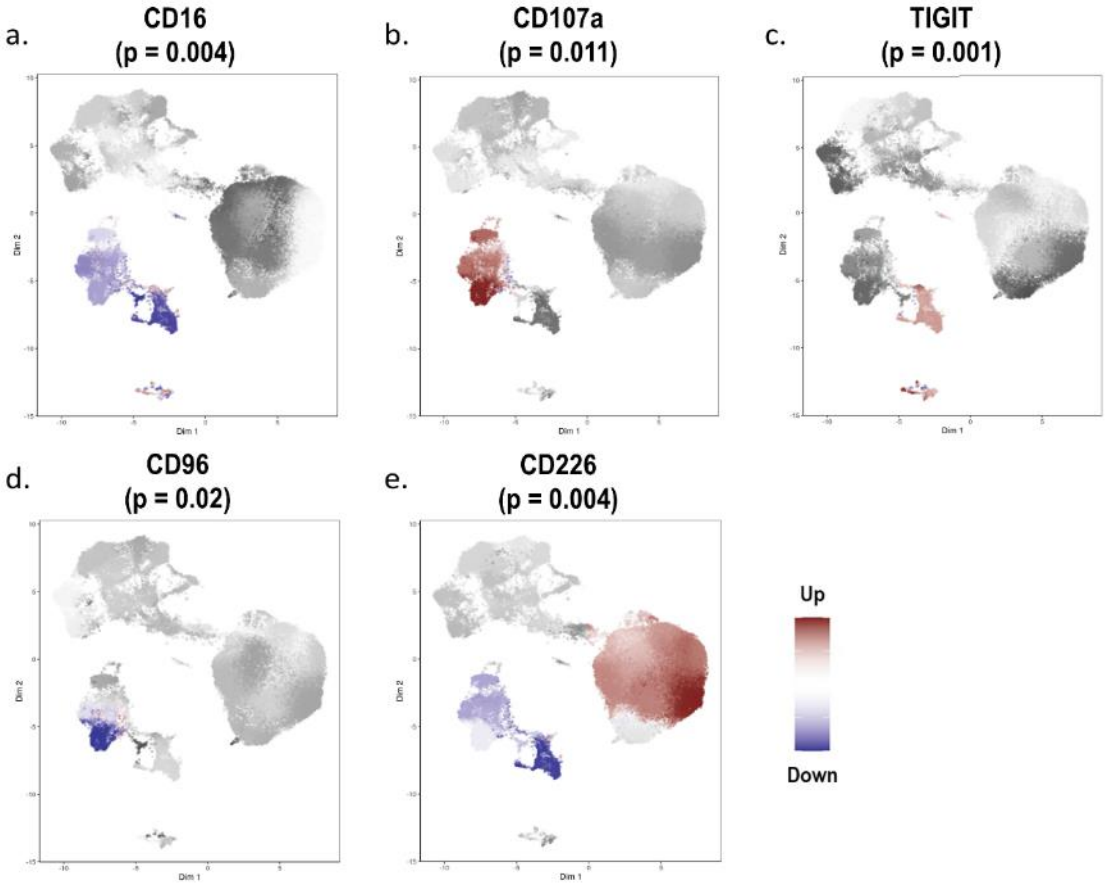


**Figure III-3: Differential states of NK cell subsets in fibromyalgia syndrome compare to controls. The direction of differences in expression between case and control samples for CD16, CD107a, TIGIT, CD96 and CD226 are shown in figures a-e. Red and blue represent increased and decreased frequencies in cases, respectively.**

Next, we investigated if the *in-vitro* activation profile of the circulating NK cells from FMS patients differed from that of the controls. Two assays to activate NK cells were implemented. Co-culturing with $HLA^{-/-}$ cells stimulates NK cells to reveal their direct cytotoxicity functional potential. Whereas, antibody-dependent NK cell activation

(ADNKA) measures NK cell activation following incubation with Ab opsonized targets cells. Alive $CD3^{-}CD14^{-}CD19^{-}$ but $CD16^{+}CD56^{+}$ were identified as NK cells (Supplementary Figure 9a). Responses measured by CCL4, CD107a, and IFNγ production were quantified as the proportion of NK cells positive for the aforesaid markers. A typical response of stimulated and unstimulated cells for CCL4, CD107a, and IFNγ production is shown in Supplementary Figure 9B, 9C, and 9D, respectively. There were no differences in CCL4+, CD107a+ and IFNγ+ NK cells proportions between FMS cases and controls in unstimulated samples (t-stat = 1.33, 0.98 and 0.18, and, p-value = 0.19, 0.33 and 0.86 for CCL4+, CD107a+ and IFNγ+ NK cells, respectively; Supplementary Figures 10a-c). Incubation of NK cells with activating stimuli led to significant increase in expression of CCL4, CD107a and IFNγ (t-stat = 13.30, 15.35 and 6.52, and, p-value = $2.8x10^{-24}$, $1.9x10^{-28}$ and $2.6x10^{-9}$ for $CCL4^{+}$, $CD107a^{+}$ and $IFN\gamma^{+}$ NK cells, respectively; Supplementary Figures 11a-c).[48]

Response to activating stimulus, $HLA^{-/-}$ cells, differed between FMS patients and controls. Significantly more NK cells of FMS patients became $CCL4^{+}$ (β = 13.98, p-value = 0.02; Figure 7A) and $CD107a^{+}$ (β = 17.04, p-value = 0.0006, Figure 4b) after activation. IFNγ response did not differ between FMS cases and controls in $HLA^{-/-}$ assay (β = 0.13, p-value = 0.96, Figure 4c). ADNKA assay did not show statistically significant difference between cases and controls, although similar trends of hyperactive response in FMS cases were seen for CCL4 and CD107a response (β = 2.00, 10.27 and -1.63, and, p-value = 0.67, 0.10 and 0.55 for $CCL4^{+}$, $CD107a^{+}$ and $IFN\gamma^{+}$ NK cells, respectively; Figures 4d-f).

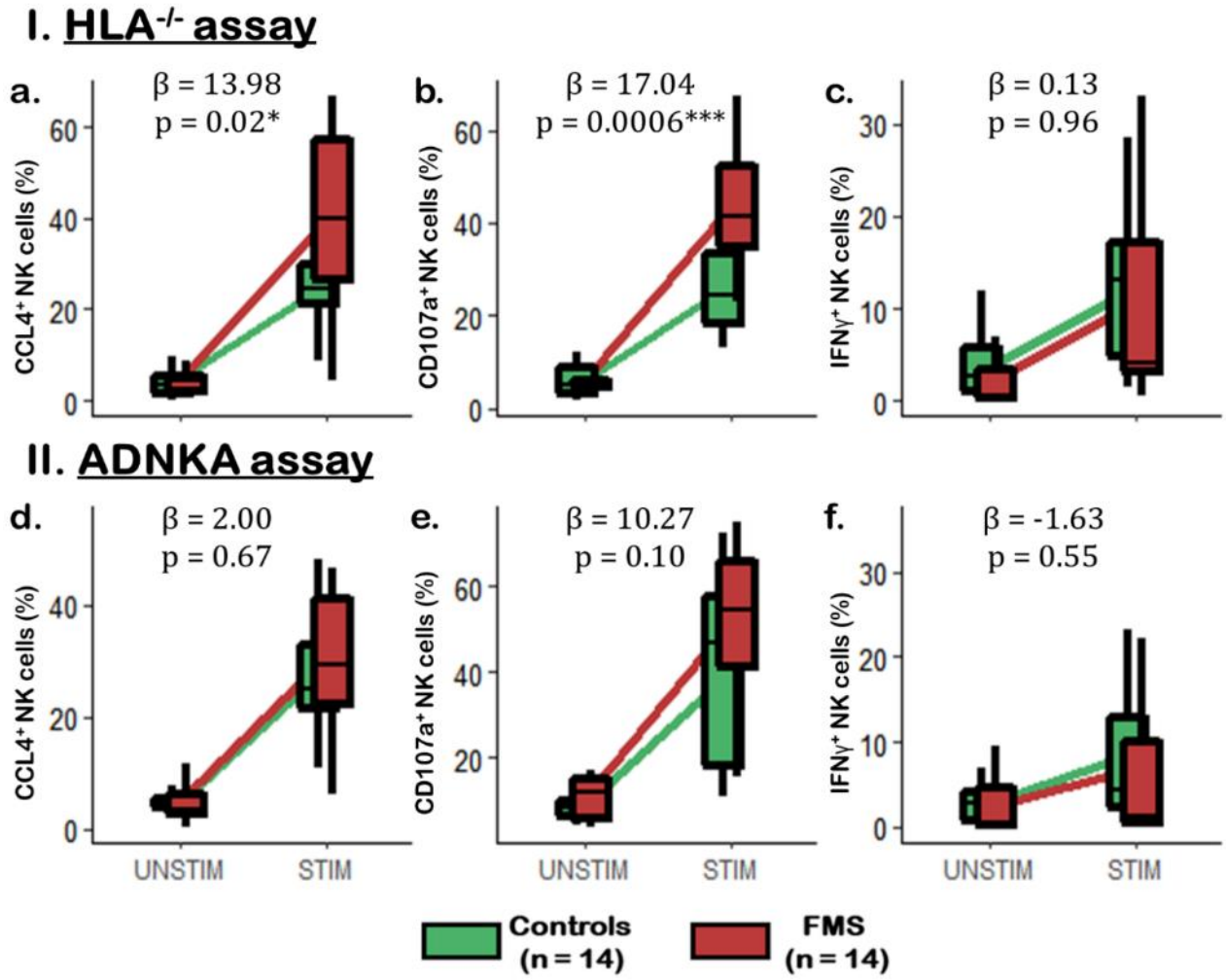


**Figure III-4: NK cells activation assay in fibromyalgia syndrome (FMS) and control subjects. The NK cells were co-cultured with either I. Human Leukocyte Antigen null ($HLA^{-/-}$) cell line or II. opsonized HIV+ cells (antibody-dependent NK activation (ADNKA) assay). Changes between unstimulated and stimulated NK cells in expression of NK activation markers, CCL4 (a and d), CD107a (b and e) and IFNγ (c and f) are shown. Green boxplot depicts controls and red boxplots depicts FMS cases. Whiskers represent interquantile range, horizontal black lines represent group medians. Green and red lines connect group means of controls and FMS cases, respectively. P-values and β values represent the interaction term: *condition x case-status* of the mixed model with age, sex and BMI as fixed effects, and, batch and sample ID as random effects. UNSTIM: unstimulated; STIM: stimulated.**

## 4.4. Enriched immune cell type activation pathways in fibromyalgia

To corroborate our findings of circulating NK cell activation in FMS, mRNA was extracted from the peripheral whole blood of FMS patients and controls of the Canadian cohort and was sequenced using Illumina's NovaSeq™ 6000 S2 SR100 platform. Pathway analysis was performed on the differentially expressed genes to test for enrichment of immune cell activation pathways. At the whole blood transcriptomics level, FMS patients showed significant enrichment for cell activation and with strongest and only significant contribution by NK cell activation pathways (enrichment scores of 0.26 and 0.5 with FDR 0.02 and 0.06, respectively, Figure 5A). Similarly, at the genetics level, a meta-analysis of the GWAS summary results from both UKB and HUNT, FMS patients showed significant enrichment for cell activation pathway primarily driven by activation of NK cells (FDR=0.02 and 0.05 for cell activation and NK cell activation, respectively, Figure 5B).

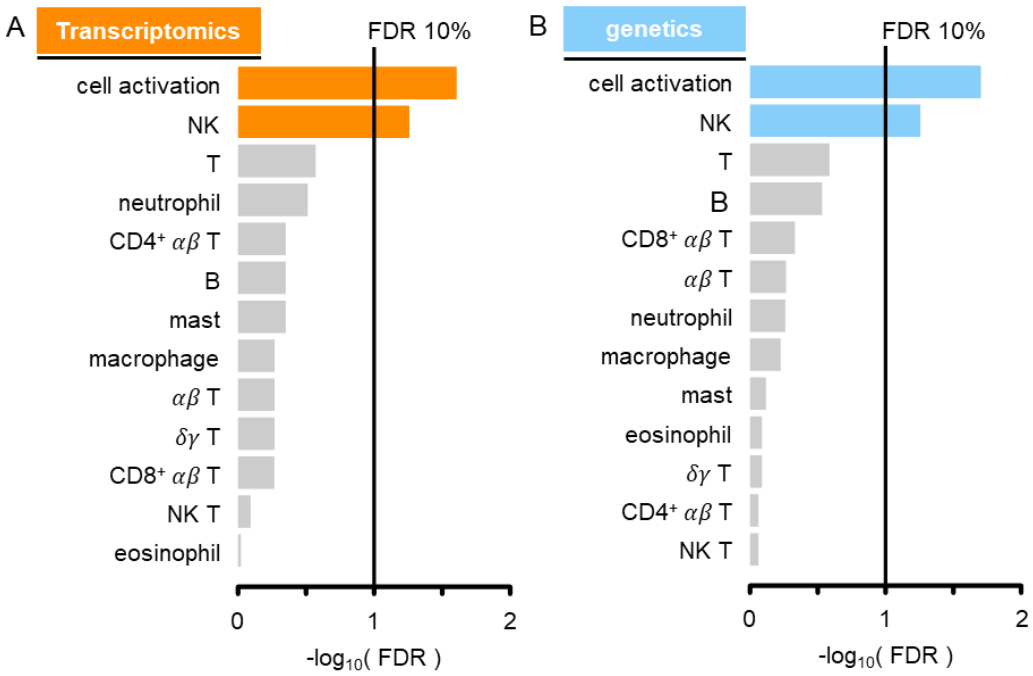


**Figure III-5: Enrichment of hematopoietic cell type activation pathways in FM patients compared to healthy controls. (A) Enrichment at the genomics level, from transcriptomics of white blood cells from the Canadian cohort. (B) Enrichment at the genetics level, from combined genome-wide association studies in the UKB and the HUNT.**

**Abbreviations for cell types are natural killer (NK), alpha-beta ($\alpha\beta$), and gamma-delta ($\delta\gamma$).**

## 4.5. Peripheral recruitment of NK cells in fibromyalgia

Peripheral nerve pathologies are often reported in fibromyalgia syndrome.[49] Hence, we hypothesized that depletion of circulating NK cells, and, its activated and exhausted profile is associated with its recruitment to and consequent degeneration of peripheral nerves in FMS patients. Using immunofluorescent microscopy, we found increased expression of NK activation ligand, UL16 binding protein (ULBP) in the subepidermal nerve plexus of FMS patients (Figure 6A and B). Moreover, recruitment of NK cells (nucleated $CD56^+$ cells) near peripheral nerves was seen in the skin biopsies of FMS patients but not in control (Figure 6C and D). Keratinocytes and subepidermal nerves are

expected to express ULBP[50] (Figure 6A and B) and CD56[51] (Figure 6C and D), respectively.

When evaluated quantitatively, there were significantly more ULBP+ subepidermal plexus in FMS patients (p-value = 0.01, Figure 6E). Interestingly, this increased ULBP expression in FMS was not associated with the diagnosis of intra-epidermal nerve fiber (IENF) deficiency (p-value = 0.91, Supplementary Figure 12). ULBP expression was also correlated with Fibromyalgia Severity Questionnaire (FSQ) scores ($\rho$ = 0.5, p-value = 0.01, Figure 6H). Although recruitment of NK cells was not significantly associated with the case-status (Figure 6F), it was correlated with ULBP expression on the nerves ($\rho$ = 0.5, p-value = 0.01, Figure 6G) and was significantly associated with FSQ score ($\rho$ = 0.4, p-value = 0.04, Figure 6I).

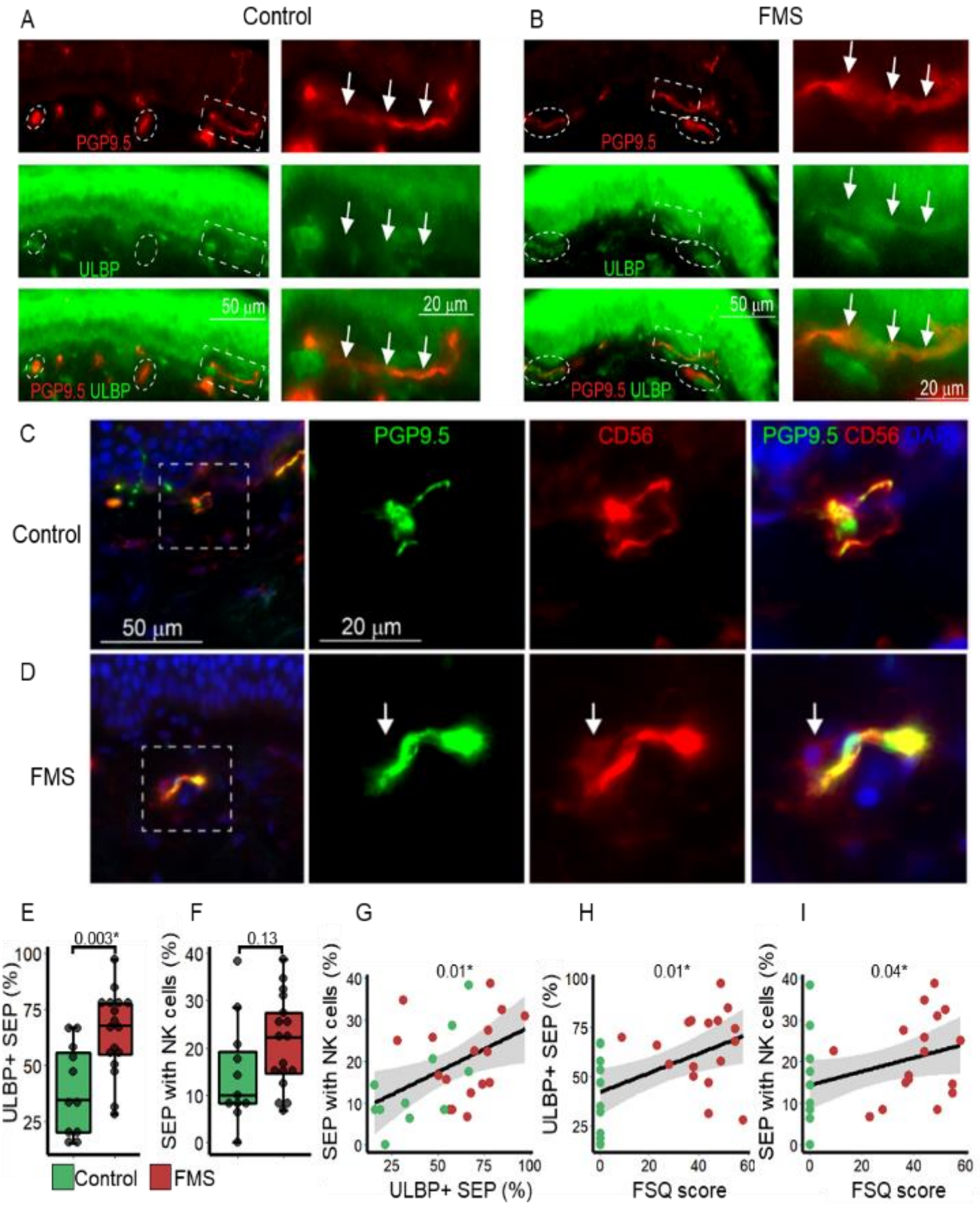
A
Control
B
FMS
PGP9.5
ULBP
PGP9.5 ULBP
50 μm
20 μm
C
Control
D
FMS
PGP9.5
CD56
PGP9.5 CD56 DAPI
E
F
G
H
I
0.003*
0.13
0.01*
0.01*
0.04*
ULBP+ SEP (%)
SEP with NK cells (%)
FSQ score
Control
FMS

**Figure III-6: ULBP expression and NK cell recruitment at the peripheral nerves are associated with FMS**

**Immunostaining of the skin from (A) a control and (B) an FMS patient with nerves stained with anti-PGP9.5 (red) and NK activation ligand stained with anti-ULBP (green). High magnification image of the area in the white dashed box shows co-staining (marked with arrows) of PGP9.5 and ULBP in FMS but not in control. White dashed ovals show SEP. (C) and (D) are micro-images from a control and an FMS patient stained for PGP9.5 (green), nuclei (DAPI in blue) and CD56 (red). Arrows mark NK cells seen in proximity of an SEP in FMS but not in control. Boxplots showing distribution of (E) ULBP+ SEP and (F) SEP with NK cells, stratified by case-status. Whiskers represent standard errors and numbers are the p-values derived from Welch's two-sample t-test. (G) depicts correlation between NK cells and ULBP near SEP. (H) and (I) show correlations between ULBP expression on SEP and NK cell recruitment at SEP, with FSQ scores (symptom severity), respectively. Green and red depict controls (n=11) and FMS cases (n=17), respectively. Linear regression and it's 95% confidence interval are shown as a black line and gray shaded area, respectively. Numbers denote p-values from Kendall's rank correlation. *p < 0.05.**

**FMS: fibromyalgia syndrome; ULBP: UL16 binding protein; SEP: Subepidermal plexus; NK: natural killer; IENFD: intra-epidermal nerve fiber deficiency; FSQ: fibromyalgia screening**

# 5. Discussion

Although a recent meta-analysis showed upregulated immune-inflammatory and compensatory immune-regulatory system in FMS, the precise involvement of the immune system in the pathogenesis of FMS remains elusive.[52] At the cellular level, previous studies have demonstrated alternation of several blood cell types,[53, 54] including depletion of circulating NK cells[53, 54] in FMS patients. Furthermore, NK cell activity has been shown to correlate negatively with right hemisphere activity in the secondary somatosensory and motor cortices, thalamus, and, bilaterally related to activity in the posterior cingulate cortex in FMS.[55] Here, we employed the unbiased multiparametric flow cytometry data from all the PBMCs to evaluate immune cell subset contributions to FMS. We found that the circulating NK cells display the strongest difference between

FMS cases and controls. Specifically, we found the circulating $CD56^{bri}$ NK subset to be depleted in FMS patients.

We have explored the differential state of circulating NK cells and found that these cells were exhausted yet activated in FMS patients with decreased CD16 expression, and increased CD107a and TIGIT expression. Similar to CD16 expression, decreased expression of CD226 (DNAX Accessory Molecule-1, DNAM-1) and CD96 (T Cell-Activated Increased Late Expression Protein, TACTILE) are associated with NK cell activation.[56] This profile of circulating NK cells is typically associated with their prolonged activation and exhaustion.[57, 58]

We then questioned where the $CD56^{bri}$ NK cells can be redistributed and hypothesized that they are recruited to peripheral nerves in FMS patients where they consequently degenerate the peripheral nerves. This hypothesis was based on the high prevalence of small fiber neuropathy in FMS patients ranges from 45-59%, depending on the method of estimation.[49, 59] Most FMS patients show a variable degree of intraepidermal nerve fiber deficiency, irrespective of neuropathy.[8] Ligands for the activating NK receptor, CD314, MHC class I chain-related protein A (MICA) and B (MICB), and UL16-binding proteins (ULBP1-6) are not physiologically expressed on mature sensory neurons.[60] Nevertheless, extravasation of circulating NK cells and its CD314 (NKG2D)-mediated recruitment is associated with partially damaged peripheral nerves in mice.[60] We have identified a higher expression of NK activation ligand, ULBP, on the peripheral nerves of FMS patients. Furthermore, we found recruitment of the NK cells at the peripheral nerves of these patients. Being derived from an independent FMS cohort, our

immunofluorescence data on ULBP expression and NK cell's peripheral recruitment validates our initial discovery and hypothesis of the potential re-distribution of NK cells from the circulation to the peripheral nerves.

Based on our results, we propose a new heuristic model of the pathogenesis of FMS (Figure 7). According to this model, in FMS, peripheral nerves express NK activation ligand(s), leading to the extravasation and peripheral recruitment of circulating NK cells. Notably, ULBP expression on the intraepidermal nerve fibers is associated with FMS caseness both with and without IENF deficiency (Figure 8a) and there is only a weak anti-correlation between ULBP expression and IENF density ($\rho = -0.4$, p-value = 0.07, Figure 8g). However, because of the significant association of ULBP expression with FMS severity (Figure 8d), it is possible that in some FMS patients even when the nerves are being marked by ULBP for removal by the NK cells, they continue to regrow, masking IENF deficiency but not preventing the pain symptoms. Lastly, the site of this neuroimmune interaction between NK cells and subepidermal nerve plexuses could justify some of the dermatological manifestations[48] of FMS. Nevertheless, the cause of NK-ligand expression on the peripheral nerve of FMS patients is unknown and will require

further investigation. Moreover, it is unclear if ULBP expression is a cause, consequence, or exacerbator of the nerve damage in FMS.

There are striking similarities between FMS and other autoimmune diseases.[61] A recent study has demonstrated that FMS pain is caused by IgG autoantibodies that sensitize peripheral sensory neurons, thus providing direct evidence favoring autoimmunity in FMS.[62] NK cells play multiple crucial roles in linking innate and adaptive immune responses to either promote or protect against the onset of autoimmune conditions. Reduction in peripheral blood NK cells reported in autoimmune patients is related to their

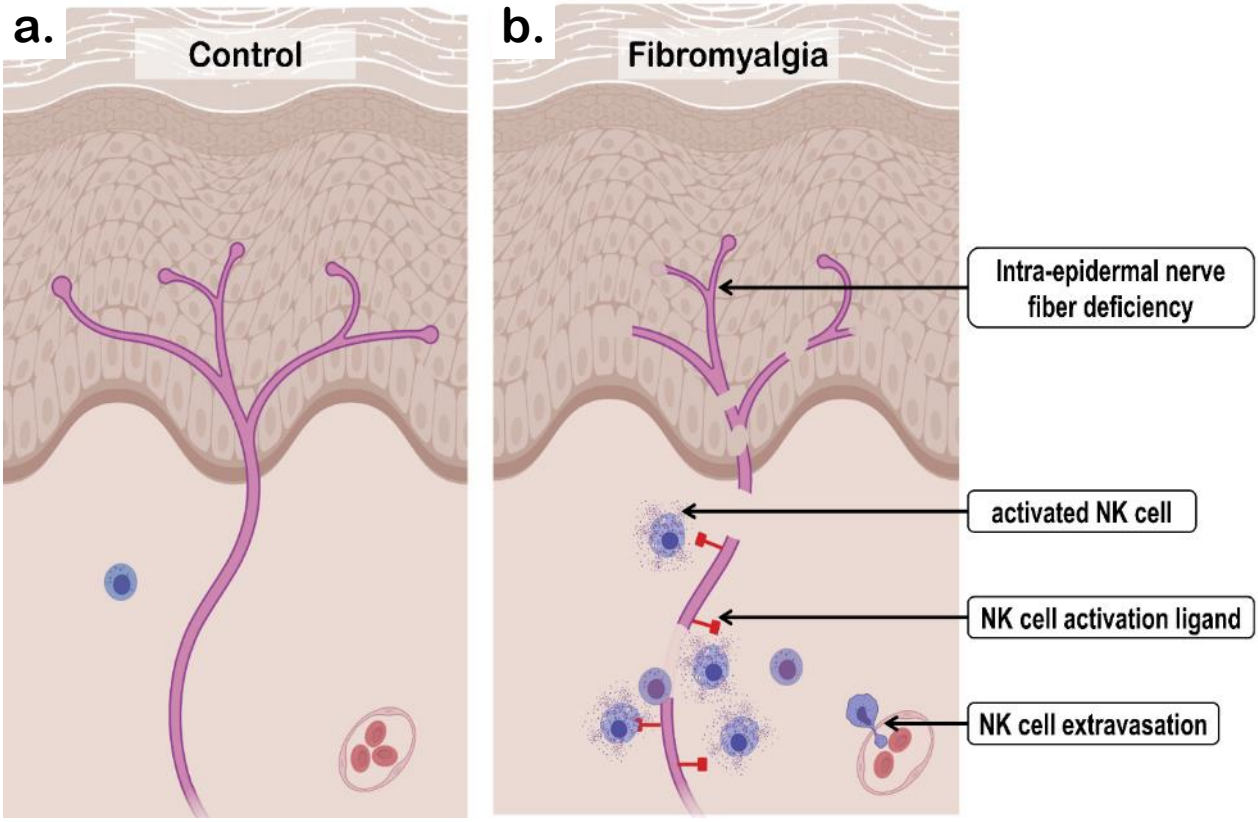


**Figure III-7: Heuristic model of natural killer (NK) cells' contribution to fibromyalgia syndrome (FMS) pathogenesis. Compare to controls (a), FMS patients (b) express the natural killer (NK) activation ligand on the peripheral nerves, promoting extravasation, recruitment, and activation of the circulated NK cells. (Created with BioRender.com)**

trafficking to damaged tissues[63]. $CD56^{bri}$ NK cell subset has been shown to play a role

in different disease states, such as cancer, neuroinflammation, and infection.[64] In addition, the $CD56^{bri}$ NK cell subset has been associated with tissue-specific recruitment in multiple autoimmune diseases.[63, 64] Hence, our results can provide an additional link to the autoimmune hypothesis of FMS. Nevertheless, the most important piece of this puzzle, the antigen invoking immune response in FMS remains to be discovered.

Transcriptomics data from the whole blood show that FMS shares similarities with infectious diseases, autoimmune diseases like rheumatoid arthritis and multiple sclerosis, malignancies, and neurodegenerative diseases. NK cell activation and exhaustion have been reported in various infections, chronic inflammation conditions, autoimmune disorders, and cancers.[65] Hyperactivation of NK cells, as was observed in our *in-vitro* activation assay for FMS patients (Figure 4), has been reported in multiple autoimmune diseases.[63]

It is important to stress that although our findings suggest a critical role of NK cells in the pathogenesis of FMS, it does not exclude the possibility that other immune cell types could also contribute to this process in either consequent, inter-dependent, or independent manner. Our flow cytometry, genetics, and transcriptomics data support immune dysregulation in FMS where NK cell-neuron interaction could be a partial explanation for FMS etiopathogenesis. The contribution of multiple immune cells to chronic inflammation that drives neurodegeneration has been reported[66] when the role of NK cells in neurodegeneration and pain modulation is only recently been recognized[60]. Hence, Immune system exploration using holistic approaches such as immune cell profiling with mass cytometry and single-cell RNA sequencing in FMS over

the course of the disease development are needed to further explore the immune system's involvement in FMS. Similarly, the causes of NK activation ligand expression by peripheral nerves in FMS warrants further investigations.

To conclude, this study identified a novel neuro-immune interface between peripheral nerves and NK cells in FMS patients that suggests a mechanism for FMS pathogenesis and a new direction in the development of therapeutic options to treat this poorly managed syndrome.

## 6. Conflict of interest statement

The authors have no conflicts of interest to declare.

## 7. Supplemental content

Supplemental content associated with this manuscript is attached as Appendix 3 of this thesis.

## 8. Acknowledgments

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# 9. References

1. Clauw DJ. Fibromyalgia: a clinical review. JAMA-J Am Med Assoc. 2014;311(15):1547-55. Epub 2014/04/17. doi: 10.1001/jama.2014.3266

2. Queiroz LP. Worldwide epidemiology of fibromyalgia. Curr Pain Headache Rep. 2013;17(8):356. Epub 2013/06/27. doi: 10.1007/s11916-013-0356-5

3. Creed F. A review of the incidence and risk factors for fibromyalgia and chronic widespread pain in population-based studies. Pain. 2020;161(6):1169-76. Epub 2020/02/11. doi: 10.1097/j.pain.0000000000001819

4. Arnold LM, Bennett RM, Crofford LJ, Dean LE, Clauw DJ, Goldenberg DL, et al. AAPT Diagnostic Criteria for Fibromyalgia. J Pain. 2019;20(6):611-28. doi: 10.1016/j.jpain.2018.10.008

5. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Hauser W, Katz RS, et al. Fibromyalgia criteria and severity scales for clinical and epidemiological studies: a modification of the ACR Preliminary Diagnostic Criteria for Fibromyalgia. J Rheumatol. 2011;38(6):1113-22. Epub 2011/02/03. doi: 10.3899/jrheum.100594

6. Borchers AT, Gershwin ME. Fibromyalgia: A Critical and Comprehensive Review. Clinical Reviews in Allergy & Immunology. 2015;49(2):100-51. Epub 2015/10/09. doi: 10.1007/s12016-015-8509-4

7. Cagnie B, Coppieters I, Denecker S, Six J, Danneels L, Meeus M. Central sensitization in fibromyalgia? A systematic review on structural and functional brain MRI. Seminars in Arthritis and Rheumatism. 2014;44(1):68-75. Epub 2014/02/11. doi: 10.1016/j.semarthrit.2014.01.001

8. Vecchio E, Lombardi R, Paolini M, Libro G, Delussi M, Ricci K, et al. Peripheral and central nervous system correlates in fibromyalgia. Eur J Pain. 2020;24(8):1537-47. Epub 2020/06/02. doi: 10.1002/ejp.1607

9. Yunus MB. Editorial Review: An Update on Central Sensitivity Syndromes and the Issues of Nosology and Psychobiology. Current Rheumatology Reviews. 2015;11(2):70-85. Epub 2015/07/04. doi: 10.2174/1573397111021507021122236

10. Evdokimov D, Dinkel P, Frank J, Sommer C, Uceyler N. Characterization of dermal skin innervation in fibromyalgia syndrome. PLoS One. 2020;15(1):e0227674. Epub 2020/01/14. doi: 10.1371/journal.pone.0227674

11. Caro XJ, Winter EF. Evidence of abnormal epidermal nerve fiber density in fibromyalgia: clinical and immunologic implications. Arthritis Rheumatol. 2014;66(7):1945-54. Epub 2014/04/11. doi: 10.1002/art.38662

12. Evdokimov D, Frank J, Klitsch A, Unterecker S, Warrings B, Serra J, et al. Reduction of skin innervation is associated with a severe fibromyalgia phenotype. Ann Neurol. 2019;86(4):504-16. Epub 2019/08/04. doi: 10.1002/ana.25565

13. Kosehasanogullari M, Erdinc Gunduz N, Akalin E. Is Fibromyalgia Syndrome a Neuropathic Pain Syndrome? Arch Rheumatol. 2019;34(2):196-203. doi: 10.5606/ArchRheumatol.2019.7244

14. Caro XJ, Winter EF, Dumas AJ. A subset of fibromyalgia patients have findings suggestive of chronic inflammatory demyelinating polyneuropathy and appear to respond to IVIg. Rheumatology (Oxford). 2008;47(2):208-11. Epub 2008/01/23. doi: 10.1093/rheumatology/kem345

15. Baraniuk JN, Zheng Y. Relationships among rhinitis, fibromyalgia, and chronic fatigue. Allergy Asthma Proc. 2010;31(3):169-78. Epub 2010/07/10. doi: 10.2500/aap.2010.31.3311

16. Baraniuk JN, Clauw D, Yuta A, Ali M, Gaumond E, Upadhyayula N, et al. Nasal secretion analysis in allergic rhinitis, cystic fibrosis, and nonallergic fibromyalgia/chronic fatigue syndrome subjects. Am J Rhinol. 1998;12(6):435-40. Epub 1999/01/12. doi: 10.2500/105065898780707964

17. Tuncer T, Butun B, Arman M, Akyokus A, Doseyen A. Primary fibromyalgia and allergy. Clin Rheumatol. 1997;16(1):9-12. Epub 1997/01/01. doi: 10.1007/BF02238757

18. Giacomelli C, Talarico R, Bombardieri S, Bazzichi L. The interaction between autoimmune diseases and fibromyalgia: risk, disease course and management. Expert Rev Clin Immunol. 2013;9(11):1069-76. Epub 2013/10/31. doi: 10.1586/1744666X.2013.849440

19. Clauw DJ. Fibromyalgia and related conditions. Mayo Clin Proc. 2015;90(5):680-92. Epub 2015/05/06. doi: 10.1016/j.mayocp.2015.03.014

20. Zhang Z, Feng J, Mao A, Le K, La Placa D, Wu X, et al. SNPs in inflammatory genes CCL11, CCL4 and MEFV in a fibromyalgia family study. PLoS One. 2018;13(6):e0198625. Epub 2018/06/22. doi: 10.1371/journal.pone.0198625

21. Han CL, Sheng YC, Wang SY, Chen YH, Kang JH. Serum proteome profiles revealed dysregulated proteins and mechanisms associated with fibromyalgia syndrome in women. Sci Rep. 2020;10(1):12347. Epub 2020/07/25. doi: 10.1038/s41598-020-69271-w

22. Lukkahatai N, Walitt B, Espina A, Wang D, Saligan LN. Comparing Genomic Profiles of Women With and Without Fibromyalgia. Biol Res Nurs. 2015;17(4):373-83. Epub 2015/05/28. doi: 10.1177/1099800415589785

23. Behm FG, Gavin IM, Karpenko O, Lindgren V, Gaitonde S, Gashkoff PA, et al. Unique immunologic patterns in fibromyalgia. BMC Clin Pathol. 2012;12:25. Epub 2012/12/19. doi: 10.1186/1472-6890-12-25

24. Macedo JA, Hesse J, Turner JD, Ammerlaan W, Gierens A, Hellhammer DH, et al. Adhesion molecules and cytokine expression in fibromyalgia patients: increased L-selectin on monocytes and neutrophils. J Neuroimmunol. 2007;188(1-2):159-66. Epub 2007/07/03. doi: 10.1016/j.jneuroim.2007.06.002

25. Sluka KA, Clauw DJ. Neurobiology of fibromyalgia and chronic widespread pain. Neuroscience. 2016;338:114-29. Epub 2016/10/27. doi: 10.1016/j.neuroscience.2016.06.006

26. Dupont WD, Plummer WD, Jr. Power and sample size calculations. A review and computer program. Control Clin Trials. 1990;11(2):116-28. Epub 1990/04/01. doi: 10.1016/0197-2456(90)90005-m

27. Russell IJ, Vipraio GA, Michalek JE, Craig FE, Kang YK, Richards AB. Lymphocyte markers and natural killer cell activity in fibromyalgia syndrome: effects of low-dose, sublingual use of human interferon-alpha. J Interferon Cytokine Res. 1999;19(8):969-78. Epub 1999/09/07. doi: 10.1089/107999099313523

28. Carlsson AM. Assessment of Chronic Pain .1. Aspects of the Reliability and Validity of the Visual Analog Scale. Pain. 1983;16(1):87-101. doi: Doi 10.1016/0304-3959(83)90088-X

29. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow

process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377-81. doi: 10.1016/j.jbi.2008.08.010

30. Tripodi D, Lyons S, Davies D. Separation of peripheral leukocytes by Ficoll density gradient centrifugation. Transplantation. 1971;11(5):487-8. Epub 1971/05/01. doi: 10.1097/00007890-197105000-00010

31. Brummelman J, Haftmann C, Nunez NG, Alvisi G, Mazza EMC, Becher B, et al. Development, application and computational analysis of high-dimensional fluorescent antibody panels for single-cell flow cytometry. Nat Protoc. 2019;14(7):1946-69. Epub 2019/06/05. doi: 10.1038/s41596-019-0166-2

32. Lemieux J, Jobin C, Simard C, Neron S. A global look into human T cell subsets before and after cryopreservation using multiparametric flow cytometry and two-dimensional visualization analysis. J Immunol Methods. 2016;434:73-82. doi: 10.1016/j.jim.2016.04.010

33. Tremblay-McLean A, Coenraads S, Kiani Z, Dupuy FP, Bernard NF. Expression of ligands for activating natural killer cell receptors on cell lines commonly used to assess natural killer cell function. BMC Immunology. 2019;20(1):8. doi: 10.1186/s12865-018-0272-x

34. Lisovsky I, Kant S, Tremblay-McLean A, Isitman G, Kiani Z, Dupuy FP, et al. Differential contribution of education through KIR2DL1, KIR2DL3, and KIR3DL1 to

antibody-dependent (AD) NK cell activation and ADCC. J Leukoc Biol. 2019;105(3):551-63. Epub 2019/01/31. doi: 10.1002/JLB.4A0617-242RRR

35. Stanley N, Stelzer IA, Tsai AS, Fallahzadeh R, Ganio E, Becker M, et al. VoPo leverages cellular heterogeneity for predictive modeling of single-cell data. Nat Commun. 2020;11(1):3738. Epub 2020/07/29. doi: 10.1038/s41467-020-17569-8

36. Dobin A, Davis CA, Schlesinger F, Drenkow J, Zaleski C, Jha S, et al. STAR: ultrafast universal RNA-seq aligner. Bioinformatics. 2013;29(1):15-21. Epub 2012/10/30. doi: 10.1093/bioinformatics/bts635

37. Liao Y, Smyth GK, Shi W. featureCounts: an efficient general purpose program for assigning sequence reads to genomic features. Bioinformatics. 2014;30(7):923-30. Epub 2013/11/15. doi: 10.1093/bioinformatics/btt656

38. Love MI, Huber W, Anders S. Moderated estimation of fold change and dispersion for RNA-seq data with DESeq2. Genome Biol. 2014;15(12):550. Epub 2014/12/18. doi: 10.1186/s13059-014-0550-8

39. Willer CJ, Li Y, Abecasis GR. METAL: fast and efficient meta-analysis of genomewide association scans. Bioinformatics. 2010;26(17):2190-1. Epub 2010/07/10. doi: 10.1093/bioinformatics/btq340

40. Gene Ontology C. The Gene Ontology resource: enriching a GOld mine. Nucleic Acids Res. 2021;49(D1):D325-D34. Epub 2020/12/09. doi: 10.1093/nar/gkaa1113

41. Korotkevich G, Sukhov V, Budin N, Shpak B, Artyomov MN, Sergushichev A. Fast gene set enrichment analysis. bioRxiv. 2021:060012. doi: 10.1101/060012

42. Allen NE, Sudlow C, Peakman T, Collins R, Biobank UK. UK biobank data: come and get it. Sci Transl Med. 2014;6(224):224ed4. Epub 2014/02/21. doi: 10.1126/scitranslmed.3008601

43. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med. 2015;12(3):e1001779. Epub 2015/04/01. doi: 10.1371/journal.pmed.1001779

44. Zhou W, Nielsen JB, Fritsche LG, Dey R, Gabrielsen ME, Wolford BN, et al. Efficiently controlling for case-control imbalance and sample relatedness in large-scale genetic association studies. Nat Genet. 2018;50(9):1335-41. Epub 2018/08/15. doi: 10.1038/s41588-018-0184-y

45. Krokstad S, Langhammer A, Hveem K, Holmen TL, Midthjell K, Stene TR, et al. Cohort Profile: the HUNT Study, Norway. Int J Epidemiol. 2013;42(4):968-77. Epub 2012/08/11. doi: 10.1093/ije/dys095

46. Loh PR, Tucker G, Bulik-Sullivan BK, Vilhjalmsson BJ, Finucane HK, Salem RM, et al. Efficient Bayesian mixed-model analysis increases association power in large cohorts. Nat Genet. 2015;47(3):284-90. Epub 2015/02/03. doi: 10.1038/ng.3190

47. de Leeuw CA, Mooij JM, Heskes T, Posthuma D. MAGMA: generalized gene-set analysis of GWAS data. PLoS Comput Biol. 2015;11(4):e1004219. Epub 2015/04/18. doi: 10.1371/journal.pcbi.1004219

48. Laniosz V, Wetter DA, Godar DA. Dermatologic manifestations of fibromyalgia. Clin Rheumatol. 2014;33(7):1009-13. Epub 2014/01/15. doi: 10.1007/s10067-014-2488-3

49. Martinez-Lavin M. Fibromyalgia and small fiber neuropathy: the plot thickens! Clin Rheumatol. 2018;37(12):3167-71. Epub 2018/09/22. doi: 10.1007/s10067-018-4300-2

50. Jan Chalupny N, Sutherland CL, Lawrence WA, Rein-Weston A, Cosman D. ULBP4 is a novel ligand for human NKG2D. Biochemical and Biophysical Research Communications. 2003;305(1):129-35. doi: 10.1016/s0006-291x(03)00714-9

51. Panicker AK, Buhusi M, Thelen K, Maness PF. Cellular signalling mechanisms of neural cell adhesion molecules. Front Biosci. 2003;8:d900-11. Epub 2003/04/18. doi: 10.2741/1014

52. Andres-Rodriguez L, Borras X, Feliu-Soler A, Perez-Aranda A, Angarita-Osorio N, Moreno-Peral P, et al. Peripheral immune aberrations in fibromyalgia: A systematic review, meta-analysis and meta-regression. Brain Behav Immun. 2020;87:881-9. Epub 2019/12/31. doi: 10.1016/j.bbi.2019.12.020

53. Kwiatkowska KM, Bacalini MG, Sala C, Kaziyama H, de Andrade DC, Terlizzi R, et al. Analysis of Epigenetic Age Predictors in Pain-Related Conditions. Front Public Health. 2020;8:172. Epub 2020/06/26. doi: 10.3389/fpubh.2020.00172

54. Landis CA, Lentz MJ, Tsuji J, Buchwald D, Shaver JL. Pain, psychological variables, sleep quality, and natural killer cell activity in midlife women with and without fibromyalgia. Brain Behav Immun. 2004;18(4):304-13. Epub 2004/05/26. doi: 10.1016/j.bbi.2003.11.001

55. Lekander M, Fredrikson M, Wik G. Neuroimmune relations in patients with fibromyalgia: a positron emission tomography study. Neurosci Lett. 2000;282(3):193-6. Epub 2000/03/16. doi: 10.1016/s0304-3940(00)00901-0

56. Martinet L, Smyth MJ. Balancing natural killer cell activation through paired receptors. Nat Rev Immunol. 2015;15(4):243-54. Epub 2015/03/07. doi: 10.1038/nri3799

57. Romee R, Foley B, Lenvik T, Wang Y, Zhang B, Ankarlo D, et al. NK cell CD16 surface expression and function is regulated by a disintegrin and metalloprotease-17

(ADAM17). Blood. 2013;121(18):3599-608. Epub 2013/03/15. doi: 10.1182/blood-2012-04-425397

58. Judge SJ, Murphy WJ, Canter RJ. Characterizing the Dysfunctional NK Cell: Assessing the Clinical Relevance of Exhaustion, Anergy, and Senescence. Front Cell Infect Microbiol. 2020;10:49. Epub 2020/03/03. doi: 10.3389/fcimb.2020.00049

59. Grayston R, Czanner G, Elhadd K, Goebel A, Frank B, Uceyler N, et al. A systematic review and meta-analysis of the prevalence of small fiber pathology in fibromyalgia: Implications for a new paradigm in fibromyalgia etiopathogenesis. Semin Arthritis Rheum. 2019;48(5):933-40. Epub 2018/10/14. doi: 10.1016/j.semarthrit.2018.08.003

60. Davies AJ, Kim HW, Gonzalez-Cano R, Choi J, Back SK, Roh SE, et al. Natural Killer Cells Degenerate Intact Sensory Afferents following Nerve Injury. Cell. 2019;176(4):716-28 e18. Epub 2019/02/05. doi: 10.1016/j.cell.2018.12.022

61. Meester I, Rivera-Silva GF, Gonzalez-Salazar F. Immune System Sex Differences May Bridge the Gap Between Sex and Gender in Fibromyalgia. Front Neurosci. 2019;13:1414. Epub 2020/02/06. doi: 10.3389/fnins.2019.01414

62. Goebel A, Gentry C, Cuhadar U, Krock E, Vastani N, Sensi S, et al. Passive transfer of fibromyalgia pain from patients to mice. 2019:713495. doi: 10.1101/713495 %J bioRxiv

63. Gianchecchi E, Delfino DV, Fierabracci A. NK cells in autoimmune diseases: Linking innate and adaptive immune responses. Autoimmun Rev. 2018;17(2):142-54. Epub 2017/11/29. doi: 10.1016/j.autrev.2017.11.018

64. Michel T, Poli A, Cuapio A, Briquemont B, Iserentant G, Ollert M, et al. Human CD56bright NK Cells: An Update. J Immunol. 2016;196(7):2923-31. Epub 2016/03/20. doi: 10.4049/jimmunol.1502570

65. Vivier E, Tomasello E, Baratin M, Walzer T, Ugolini S. Functions of natural killer cells. Nat Immunol. 2008;9(5):503-10. Epub 2008/04/22. doi: 10.1038/ni1582

66. Yang Q, Wang G, Zhang F. Role of Peripheral Immune Cells-Mediated Inflammation on the Process of Neurodegenerative Diseases. Front Immunol. 2020;11:582825. Epub 2020/11/13. doi: 10.3389/fimmu.2020.582825

# IV. Discussion and integrative summary

## 1. Chronic primary pain

Chronic primary pain (CPP) is defined as pain in one or more anatomical regions that persists or recurs for longer than 3 months and is associated with significant emotional distress or functional disability (interference with activities of daily life and participation in social roles) and that cannot be better accounted for by another chronic pain condition. [1] CPP is idiopathic, meaning, the etiology of CPP remains unknown and the biological findings contributing to the pain problem may or may not be recognized. According to the International Classification of Diseases (ICD) 11$^{th}$ revision[2] by World Health Organization (WHO), major group (MG) 30.0: CPP is further classified as follows:

| MG | CONDITION | EXAMPLE |
|---|---|---|
| **30.00** | Chronic primary visceral pain | Chronic primary pelvic pain syndrome |
| **30.01** | Chronic widespread pain | Fibromyalgia syndrome |
| **30.02** | Chronic primary musculoskeletal pain | Chronic primary lower back pain |
| **30.03** | Chronic primary headache or orofacial pain | Chronic primary temporomandibular disorder pain |

High co-prevalence and similar epidemiological profile of CPP could be explained by overlapping biopsychosocial vulnerabilities and common underlining mechanisms.[3] In this thesis, we have focused on temporomandibular disorder (TMD) and fibromyalgia syndrome (FMS). The comorbidity of FMS in TMD patients is 24%[4] and 75%[5] of FMS patients suffer from TMD. Along with high co-prevalence between TMD and FMS, the following clinical symptoms of the two CPP conditions overlap considerably[6]:

i. presence of trigger points in taut bands of muscles
ii. presence of consistent tender points in defined soft tissue locations
iii. dull-aching pain
iv. fluctuating pain intensity
v. presence of psychological comorbidities such as fatigue, depression, insomnia, and anxiety
vi. allergic and autoimmune comorbidities[7-12]

All CPP conditions are unequivocally multifactorial syndromes with overlapping pathways of vulnerability.[13] CPP is associated with a prolonged but reversible increase in the excitability and synaptic efficacy of neurons in central nociceptive pathways, known as central sensitization.[14] Nociceptors are the primary sensory neurons innervating skin, muscle, joints, and viscera that selectively respond to noxious or potentially tissue-damaging stimuli.[15] The term, peripheral sensitization is used to describe the hyperexcitability and hypersensitivity of nociceptors which precedes central sensitization. The immune system’s involvement in both central and peripheral sensitizations is well

recognized.[16, 17] This thesis describes the involvement of the immune system in CPP modulation using TMD and FMS cohorts as prototypical examples.

## 2. Epiregulin: an important modulator of pain

Chapter II (The dichotomous role of epiregulin in pain) demonstrates that epiregulin (EREG) is an analgesic during acute stages of pain but contributes to chronic pain. EREG is expressed predominantly in the placenta and peripheral blood leukocytes.[18] Tissue inflammation and repair are complementary biological processes.[19, 20] Even though EREG is classified as a growth factor, multiple studies are favoring its role as an inflammatory mediator. These studies can be summarized in the following categories:

1. Increased EREG expression in chronic inflammatory conditions: EREG levels are reported to be increased in:
    1.1. Chronic kidney disease[21],
    1.2. Hypoxic stress[22],
    1.3. UVB-exposed skin[23],
    1.4. Multiple sclerosis (MS) and rheumatoid arthritis (RA),[24] and,
    1.5. Oral lichen planus[25]
2. EREG causes inflammation: EREG is causally associated with inflammation and its expression temporally precedes inflammatory response:
    2.1. EREG induces sinus inflammation through matrix metallopeptidase-1 (MMP-1).[26]

2.2. EREG induces neuroinflammation through Mitogen-activated protein kinase (MAPK) and Nuclear Factor-kappa B (NF-κB) pathways.[27]

2.3. EREG contributes to lung inflammation.[28]

2.4. Pro-inflammatory effects of EREG in MS and RA are mediated through interleukin (IL)-6.[24]

3. Inflammation induces EREG expression: Various inflammatory mediators are known to increase EREG levels through feed-forward loops:

3.1. IL-1β increases EREG levels.[29]

3.2. Lipopolysaccharides (LPS) induce EREG production through toll-like receptor-4 (TLR-4).[30]

3.3. IL-6 and IL-17 exacerbate EREG transcription and secretion.[31]

3.4. Suppression of inflammation with dexamethasone reduces EREG levels.[32]

Hence, the analgesic role of EREG during acute stages of pain could be at least partially mediated through its inflammatory effects. In other words, inflammation could be protective during the acute stages of pain. This has been observed not only in the UK Biobank dataset, where anti-inflammatory drugs are associated with increased chronic lower back pain but also through animal experiments, where suppressing inflammation with dexamethasone interferes with pain resolution (unpublished). Monitoring the effects of EREG blockage on the systemic biomarkers of inflammation such as plasma levels of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), the levels of TNFα, IL-1β, and IL-6, and immune cell recruitment at the site of inflammation in inflammatory pain animal models like CFA-induced hyperalgesia could test if the dichotomous role of EREG is indeed mediated through inflammation.

Secondly, it would be appropriate to assume that the observed dichotomy of EREG in pain depends on its site of action and time of release. A recently published study[33] reports that the application of EREG onto the spinal dorsal nerve roots of rats reduced evoked c-fiber responses, but increased spontaneous activity in spinal dorsal horn neurons. This corroborates the findings of Chapter III and supports the hypothesis of time-dependent, tissue-specific modulation of pain by EREG. Lastly, the tissue remodeling role of EREG may contribute to its immediate analgesic function while its high concentration and/or prolonged exposure could sensitize the nociceptors. Notably, our results do not suggest that the association between EREG and pain phenotypes is specific to TMD or orofacial pain. We identified an association between *EREG* SNPs and a number of chronic pain conditions, independent of the anatomical site of the symptom. This suggests that EREG contributes through the mechanisms common for different chronic pain conditions. Nevertheless, a full understanding of the role of EREG in modulating pain severity through the immune and /or nervous system will require simultaneous study of EREG, immune cells, inflammation, and pain responses, both preclinically and clinically.

While Chapter II demonstrates an analgesic role for EREG during the early stages of pain, but an opposite-pronociceptive role in establishing chronic pain, Chapter III deciphers the role of the immune response in another chronic musculoskeletal pain condition - fibromyalgia.

# 3. Peripheral neuroimmune interaction in fibromyalgia

Chapter III (Unbiased immune profiling reveals a Natural Killer cell-peripheral nerve axis in fibromyalgia) describes peripheral neuroimmune interaction in FMS. It shows that FMS is associated with the depletion of circulating NK cells and their activation and exhaustion. In addition, it shows that the peripheral nerves express NK activation ligand, ULBP, which leads to the extravasation and peripheral recruitment of NK cells at subepidermal nerve plexuses in FMS. Cytotoxicity is an essential element of the immune response to infections, cancers, inflammation, and tissue repair. The role of cytotoxic immunity in form of NK cell response to nerve injury and pain modulation has been described only recently.[34, 35] Chapter III advances our understanding of cytotoxic immunity in CPP such as FMS.

Davies A. et. al.[35] has demonstrated that anatomically restricted expression of RAE1 protein, another NK activation ligand, on the peripheral axons of injured sensory neurons, leads to NK cell recruitment and clearance of the damaged nerve fibers in mice. According to this study, NK cell-mediated clearance of damaged nerves protects from pain in the mouse neuropathic pain model. Our results suggest that the expression of ULBP leads to the recruitment of NK cells at the peripheral nerves in FMS. However, expression of ULBP by the peripheral nerves in FMS could either be a cause or consequence of damaged (or potentially damaged) nerves. Cellular stress has been attributed as the cause of CD314 (NKG2D) ligand expression, leading to activation of the NK cells. This

stress could be caused by numerous conditions such as rapid cell replication (either physiological, e.g. embryological development, physiological response to pathology, e.g. repair and regeneration, or pathological, e.g. tumorigenesis), activation of cellular pathways that are associated with infections (e.g. signaling pathways triggered by Toll-like receptors and NOD-like receptors), or metabolic markers of oxidation, aging or chronic inflammation (e.g. oxidized low-density lipoproteins, advanced glycation end product or heat shock proteins).[36] Lastly, EGFR agonism can upregulate the expression of CD314 activation ligands[37] and expression of these ligands could be diminished using anti-EGFR molecules[38]. Hypothetically, EGFR-mediated NK-activation ligand expression could link the findings of Chapter II and Chapter III of this thesis. Nevertheless, this hypothesis warrants further research.

## 4. Limitations

Like any research project, both the projects described in Chapters II and III of this thesis have their limitations. The EREG project (Chapter II) lacks analyses from a follow-up cohort of pain patients. As at least some individuals identified as acute pain patients would fail to resolve their pain, labeling them as acute patients is inaccurate. Secondly, although we were able to infer the functionality of the EREG gene variants (H2 and H3) through eQTL databases, more definitive functional assays are needed to confirm that H2 and H3 are loss-of-function mutations.

The FMS project (Chapter III) attempts to holistically investigate the contribution of immune cells to FMS. However, due to the limitations of the current experimental design,

granulocytes (neutrophils, basophils, and eosinophils) were excluded from the downstream analyses. Similarly, other innate lymphoid cells (ILC2 and 3) and γδT cells were not considered due to the limitations on the number of markers that can be included on the flow cytometry panels. Lastly, I acknowledge that the proposed heuristic model of NK cells' contribution to FMS lacks causal associations to establish NK cells' role in FMS.

# 5. Conclusion

To conclude, this thesis underscores the importance of the immune system in pain modulation. Firstly, with the example of EREG, we demonstrate that inflammation, a cardinal immune response often associated with chronic pain, could be protective during the early stages of pain development. An important therapeutic implication of this finding would be to use anti-inflammatory drugs with caution in acute pain conditions. Besides, these findings suggest a new non-opioid-based pain management strategy that utilizes EREG-EGFR pathways of pain modulation.

Secondly, this thesis describes the novel pathophysiological roles of NK cells and suggests a heuristic model of NK cells' contribution to FMS pathogenesis. Without preclinical studies to establish causation, it would be too precarious to predict clinical applications of these findings. Nonetheless, it warrants further exploration of the peripheral neuroimmune interactions in FMS.

Overall, both the projects described in Chapters II and III highlight the importance of taking research from "bedside" to bench. In Chapter I, statistical genetic approaches identified the dichotomous role of EREG which stimulated basic science investigation in animal pain

models. Similarly, discoveries of Chapter III are from observational studies in humans and these results are suggestive of animal experiments to develop novel fibromyalgia animal models and subsequent therapies. Consequently, this thesis is a testament to the utility of reverse translational research.

# 6. References


1. Nicholas M, Vlaeyen JWS, Rief W, Barke A, Aziz Q, Benoliel R, et al. The IASP classification of chronic pain for ICD-11: chronic primary pain. Pain. 2019;160(1):28-37. Epub 2018/12/27. doi: 10.1097/j.pain.0000000000001390

2. International Classification of Diseases 11th Revision: World Health Organization (WHO); [cited 2021, 27-Jan]. 09/2020:[Available from: https://icd.who.int/browse11/l-m/en#/http%3a%2f%2fid.who.int%2ficd%2fentity%2f1326332835.

3. Maixner W, Fillingim RB, Williams DA, Smith SB, Slade GD. Overlapping Chronic Pain Conditions: Implications for Diagnosis and Classification. J Pain. 2016;17(9 Suppl):T93-T107. Epub 2016/09/03. doi: 10.1016/j.jpain.2016.06.002

4. Yunus MB. The prevalence of fibromyalgia in other chronic pain conditions. Pain Res Treat. 2012;2012:584573. Epub 2011/12/23. doi: 10.1155/2012/584573

5. Plesh O, Wolfe F, Lane N. The relationship between fibromyalgia and temporomandibular disorders: prevalence and symptom severity. J Rheumatol. 1996;23(11):1948-52. Epub 1996/11/01.

6. Fricton JR. The relationship of temporomandibular disorders and fibromyalgia: implications for diagnosis and treatment. Curr Pain Headache Rep. 2004;8(5):355-63. Epub 2004/09/14. doi: 10.1007/s11916-996-0008-0

7. Baraniuk JN, Zheng Y. Relationships among rhinitis, fibromyalgia, and chronic fatigue. Allergy Asthma Proc. 2010;31(3):169-78. Epub 2010/07/10. doi: 10.2500/aap.2010.31.3311

8. Baraniuk JN, Clauw D, Yuta A, Ali M, Gaumond E, Upadhyayula N, et al. Nasal secretion analysis in allergic rhinitis, cystic fibrosis, and nonallergic fibromyalgia/chronic fatigue syndrome subjects. Am J Rhinol. 1998;12(6):435-40. Epub 1999/01/12. doi: 10.2500/105065898780707964

9. Tuncer T, Butun B, Arman M, Akyokus A, Doseyen A. Primary fibromyalgia and allergy. Clin Rheumatol. 1997;16(1):9-12. Epub 1997/01/01. doi: 10.1007/BF02238757

10. Giacomelli C, Talarico R, Bombardieri S, Bazzichi L. The interaction between autoimmune diseases and fibromyalgia: risk, disease course and management. Expert Rev Clin Immunol. 2013;9(11):1069-76. Epub 2013/10/31. doi: 10.1586/1744666X.2013.849440

11. Clauw DJ. Fibromyalgia and related conditions. Mayo Clin Proc. 2015;90(5):680-92. Epub 2015/05/06. doi: 10.1016/j.mayocp.2015.03.014

12. Fredricson AS, Khodabandehlou F, Weiner CK, Naimi-Akbar A, Adami J, Rosen A. Are there early signs that predict development of temporomandibular joint disease? J Oral Sci. 2018;60(2):194-200. Epub 2017/11/23. doi: 10.2334/josnusd.17-0073

13. Diatchenko L, Nackley AG, Slade GD, Fillingim RB, Maixner W. Idiopathic pain disorders--pathways of vulnerability. Pain. 2006;123(3):226-30. Epub 2006/06/17. doi: 10.1016/j.pain.2006.04.015

14. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain. 2011;152(3 Suppl):S2-S15. Epub 2010/10/22. doi: 10.1016/j.pain.2010.09.030

15. Gold MS, Gebhart GF. Nociceptor sensitization in pain pathogenesis. Nat Med. 2010;16(11):1248-57. Epub 2010/10/16. doi: 10.1038/nm.2235

16. Matsuda M, Huh Y, Ji RR. Roles of inflammation, neurogenic inflammation, and neuroinflammation in pain. J Anesth. 2019;33(1):131-9. Epub 2018/11/19. doi: 10.1007/s00540-018-2579-4

17. Ji RR, Nackley A, Huh Y, Terrando N, Maixner W. Neuroinflammation and Central Sensitization in Chronic and Widespread Pain. Anesthesiology. 2018;129(2):343-66. Epub 2018/02/21. doi: 10.1097/ALN.0000000000002130

18. Toyoda H, Komurasaki T, Uchida D, Morimoto S. Distribution of mRNA for human epiregulin, a differentially expressed member of the epidermal growth factor family. Biochem J. 1997;326 ( Pt 1):69-75. Epub 1997/08/15. doi: 10.1042/bj3260069

19. Eming SA, Wynn TA, Martin P. Inflammation and metabolism in tissue repair and regeneration. Science. 2017;356(6342):1026-30. Epub 2017/06/10. doi: 10.1126/science.aam7928

20. Pastore S, Mascia F, Mariani V, Girolomoni G. The epidermal growth factor receptor system in skin repair and inflammation. J Invest Dermatol. 2008;128(6):1365-74. Epub 2007/12/01. doi: 10.1038/sj.jid.5701184

21. Fouli GE, Gnudi L. The Future: Experimental Therapies for Renal Disease in Diabetes. Nephron. 2019;143(1):3-7. Epub 2018/09/27. doi: 10.1159/000492825

22. Kyotani Y, Takasawa S, Yoshizumi M. Proliferative Pathways of Vascular Smooth Muscle Cells in Response to Intermittent Hypoxia. Int J Mol Sci. 2019;20(11). Epub 2019/06/05. doi: 10.3390/ijms20112706

23. Zhang N, Zhong Z, Wang Y, Yang L, Wu F, Peng C, et al. Competing endogenous network analysis identifies lncRNA Meg3 activates inflammatory damage in UVB induced murine skin lesion by sponging miR-93-5p/epiregulin axis. Aging (Albany NY). 2019;11(22):10664-83. Epub 2019/11/26. doi: 10.18632/aging.102483

24. Harada M, Kamimura D, Arima Y, Kohsaka H, Nakatsuji Y, Nishida M, et al. Temporal expression of growth factors triggered by epiregulin regulates inflammation development. J Immunol. 2015;194(3):1039-46. Epub 2015/01/04. doi: 10.4049/jimmunol.1400562

25. Kumagai K, Horikawa T, Gotoh A, Yamane S, Yamada H, Kobayashi H, et al. Up-regulation of EGF receptor and its ligands, AREG, EREG, and HB-EGF in oral lichen planus. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2010;110(6):748-54. Epub 2010/10/19. doi: 10.1016/j.tripleo.2010.06.022

26. Homma T, Kato A, Sakashita M, Takabayashi T, Norton JE, Suh LA, et al. Potential Involvement of the Epidermal Growth Factor Receptor Ligand Epiregulin and Matrix Metalloproteinase-1 in Pathogenesis of Chronic Rhinosinusitis. Am J Respir Cell Mol Biol. 2017;57(3):334-45. Epub 2017/04/12. doi: 10.1165/rcmb.2016-0325OC

27. Yang XP, Fu JY, Yang RC, Liu WT, Zhang T, Yang B, et al. EGFR transactivation contributes to neuroinflammation in Streptococcus suis meningitis. J Neuroinflammation. 2016;13(1):274. Epub 2016/10/21. doi: 10.1186/s12974-016-0734-0

28. Bauer AK, Fostel J, Degraff LM, Rondini EA, Walker C, Grissom SF, et al. Transcriptomic analysis of pathways regulated by toll-like receptor 4 in a murine model of chronic pulmonary inflammation and carcinogenesis. Mol Cancer. 2009;8:107. Epub 2009/11/21. doi: 10.1186/1476-4598-8-107

29. Massip-Copiz M, Clauzure M, Valdivieso AG, Santa-Coloma TA. Epiregulin (EREG) is upregulated through an IL-1beta autocrine loop in Caco-2 epithelial cells with reduced CFTR function. J Cell Biochem. 2018;119(3):2911-22. Epub 2017/11/02. doi: 10.1002/jcb.26483

30. Hsu D, Fukata M, Hernandez YG, Sotolongo JP, Goo T, Maki J, et al. Toll-like receptor 4 differentially regulates epidermal growth factor-related growth factors in response to intestinal mucosal injury. Lab Invest. 2010;90(9):1295-305. Epub 2010/05/26. doi: 10.1038/labinvest.2010.100

31. Murakami M, Harada M, Kamimura D, Ogura H, Okuyama Y, Kumai N, et al. Disease-association analysis of an inflammation-related feedback loop. Cell Rep. 2013;3(3):946-59. Epub 2013/02/26. doi: 10.1016/j.celrep.2013.01.028

32. Kadmiel M, Janoshazi A, Xu X, Cidlowski JA. Glucocorticoid action in human corneal epithelial cells establishes roles for corticosteroids in wound healing and barrier function of the eye. Exp Eye Res. 2016;152:10-33. Epub 2016/09/08. doi: 10.1016/j.exer.2016.08.020

33. Kongstorp M, Schjolberg T, Jacobsen DP, Haugen F, Gjerstad J. Epiregulin is released from intervertebral disks and induces spontaneous activity in pain pathways. Pain Rep. 2019;4(2):e718. Epub 2019/05/02. doi: 10.1097/PR9.0000000000000718

34. Davies AJ, Rinaldi S, Costigan M, Oh SB. Cytotoxic Immunity in Peripheral Nerve Injury and Pain. Front Neurosci-Switz. 2020;14:142. Epub 2020/03/11. doi: 10.3389/fnins.2020.00142

35. Davies AJ, Kim HW, Gonzalez-Cano R, Choi J, Back SK, Roh SE, et al. Natural Killer Cells Degenerate Intact Sensory Afferents following Nerve Injury. Cell. 2019;176(4):716-28 e18. Epub 2019/02/05. doi: 10.1016/j.cell.2018.12.022

36. Raulet DH, Gasser S, Gowen BG, Deng W, Jung H. Regulation of ligands for the NKG2D activating receptor. Annu Rev Immunol. 2013;31(1):413-41. Epub 2013/01/10. doi: 10.1146/annurev-immunol-032712-095951

37. Vantourout P, Willcox C, Turner A, Swanson CM, Haque Y, Sobolev O, et al. Immunological visibility: posttranscriptional regulation of human NKG2D ligands by the EGF receptor pathway. Sci Transl Med. 2014;6(231):231ra49. Epub 2014/04/11. doi: 10.1126/scitranslmed.3007579

38. Okita R, Wolf D, Yasuda K, Maeda A, Yukawa T, Saisho S, et al. Contrasting Effects of the Cytotoxic Anticancer Drug Gemcitabine and the EGFR Tyrosine Kinase Inhibitor Gefitinib on NK Cell-Mediated Cytotoxicity via Regulation of NKG2D Ligand in

Non-Small-Cell Lung Cancer Cells. PLoS One. 2015;10(10):e0139809. Epub 2015/10/07. doi: 10.1371/journal.pone.0139809

# Appendices

## 1. Contribution of the thesis author to other projects

1. Parisien M, Dagostino C, Samoshkin A, El-Hachem N, Drury G, Huising J, **Verma V**, Grant AV, Meloto CB, Mogil J, Allegri M, Diatchenko L. *Impaired inflammatory response in people with acute low back pain increases risk of pain chronicity* . [Manuscript in preparation.]
2. van Tilburg MAL, Parisien M, Boles RG, Drury GL, Smith-Voudouris J, **Verma V**, Khoury S, Chabot-Doré AJ, Nackley AG, Smith SB, Whitehead WE, Zolnoun DA, Slade GD, Tchivileva I, Maixner W, Diatchenko L. (2020). *A genetic polymorphism that is associated with mitochondrial energy metabolism increases risk of fibromyalgia.* Pain, 161(12):2860-2871. PMID: 32658146
3. Benavides R., Vsevolozhskaya O., Cattaneo S, Zaykin D., Brenton A., Parisien M., **Verma V.**, Khoury S., Gilron I., Diatchenko L. (2020). *A Functional Polymorphism in the ATP-Binding Cassette B1 Transporter Predicts Pharmacologic Response to Combination of Nortriptyline and Morphine in Neuropathic Pain Patients.* Pain, 161 (3), 619-629. PMID: 31738228
4. Meloto CB., Benavides R., Lichtenwalter RN., Wen X., Tugarinov N., Zorina-Lichtenwalter K., Chabot-Doré AJ., Piltonen MH., Cattaneo S., **Verma V.**, Klares R. 3rd, Khoury S., Parisien M., Diatchenko L. (2018). *Human pain genetics database: a resource dedicated to human pain genetics research.* Pain, 159(4):749-763. PMID: 29300278

# 2. Supplementary materials of chapter II

**Supplementary Table 1: Evaluation of receptor and ligand genes in Epithelial Growth Factor family**

| | | |
|---|---|---|
| **GENES** | RECEPTORS: | EGFR, ERBB2, ERBB3, ERBB4 |
| | LIGANDS: | AREG*, BTC, EGF, EPGN, EREG, HBEGF, MUC4, NRG1, NRG2, NRG3, NRG4, TGFA |
| PHENOTYPE: | | CHARACTERISTIC PAIN INTENSITY |
| MODEL | | ADDITIVE |
| COVARIATES: | | RECRUITMENT SITE, GENDER, AGE, PCA (first three eigenvectors) |
| FDR THRESHOLD: | | FDR < 5% |
| MAF: | | >5% (total 2407 unimputed SNPs, *none in AREG) |

| GENE | SNP | Chromosome | BASE PAIR | BETA | P-val | FDR |
|---|---|---|---|---|---|---|
| **EREG** | **rs10518126 (G/A)** | **4** | **75243119** | **-11.09** | **0.0000078** | **0.00944** |
| **EREG** | **rs57839099 (G/A)** | **4** | **75243813** | **-11.09** | **0.0000078** | **0.00944** |
| **EREG** | **rs200889776 (G/A)** | **4** | **75240770** | **-10.41** | **0.00002** | **0.011** |
| **EREG** | **rs57933408 (G/A)** | **4** | **75243828** | **-10.51** | **0.00002** | **0.011** |
| **EREG** | **rs201835071 (G/A)** | **4** | **75237587** | **-9.99** | **0.00003** | **0.011** |
| **EREG** | **rs72859363 (A/G)** | **4** | **75246112** | **-10.24** | **0.00003** | **0.011** |
| **EREG** | **rs6836436 (A/C)** | **4** | **75230930** | **-8.84** | **0.00013** | **0.0405** |
| NRG3 | rs1764075 (A/G) | 10 | 83968400 | -5.51 | 0.00028 | 0.07365 |
| TGFA | rs79124432 (C/A) | 2 | 70676332 | 6.56 | 0.001 | 0.3396 |
| NRG3 | rs1764074 (G/A) | 10 | 83968230 | -4.05 | 0.00114 | 0.27392 |
| NRG3 | rs1764077 (A/C) | 10 | 83973325 | -4.92 | 0.00131 | 0.28342 |
| ERBB4 | rs61197595 (C/A) | 2 | 213192590 | 6.02 | 0.00141 | 0.28342 |
| ERBB4 | rs1505366 (C/A) | 2 | 213191389 | 5.49 | 0.00201 | 0.3552 |
| ERBB4 | rs4146051 (G/A) | 2 | 213189994 | 5.49 | 0.00207 | 0.3552 |
| ERBB4 | rs16775 (A/G) | 2 | 213189297 | 4.44 | 0.00315 | 0.49118 |
| TGFA | rs3771515 (G/A) | 2 | 70695562 | 5.03 | 0.00327 | 0.49118 |
| ERBB4 | rs17335169 (G/A) | 2 | 212437161 | -7.22 | 0.00368 | 0.49477 |
| NRG1 | rs4458836 (C/A) | 8 | 31578885 | 4.02 | 0.0037 | 0.49477 |
| NRG3 | rs1739764 (G/A) | 10 | 83946635 | -4.71 | 0.00403 | 0.51054 |
| NRG2 | rs443587 (A/C) | 5 | 139290232 | -3.86 | 0.00483 | 0.58069 |
| ERBB4 | rs10199212 (A/G) | 2 | 212345416 | 6.43 | 0.00628 | 0.64118 |
| ERBB4 | rs60764990 (A/G) | 2 | 213159957 | 7.25 | 0.00667 | 0.64118 |
| ERBB4 | rs905882 (A/C) | 2 | 213188733 | 4.76 | 0.00703 | 0.64118 |
| EGFR | rs11977660 (A/G) | 7 | 55162336 | -2.94 | 0.00722 | 0.64118 |
| NRG1 | rs7006093 (G/A) | 8 | 31519062 | 7.64 | 0.00735 | 0.64118 |
| ERBB4 | rs6727114 (G/A) | 2 | 212752193 | -3.36 | 0.00759 | 0.64118 |
| NRG3 | rs2255228 (A/G) | 10 | 84403376 | -4.20 | 0.00762 | 0.64118 |
| NRG3 | rs12269018 (G/A) | 10 | 83882883 | -4.17 | 0.00768 | 0.64118 |
| NRG3 | rs76122081 (A/G) | 10 | 83798079 | -5.11 | 0.00773 | 0.64118 |
| NRG2 | rs3777102 (A/G) | 5 | 139257603 | -3.33 | 0.00814 | 0.65318 |
| TGFA | rs11466229 (G/A) | 2 | 70722763 | 3.98 | 0.00914 | 0.7096 |
| ERBB4 | rs77945488 (A/G) | 2 | 213225704 | 4.10 | 0.00953 | 0.71646 |
| NRG3 | rs12248317 (G/A) | 10 | 83792458 | 6.32 | 0.01032 | 0.74405 |
| NRG1 | rs4552856 (G/A) | 8 | 31555139 | 4.00 | 0.01051 | 0.74405 |
| NRG3 | rs4933819 (G/A) | 10 | 83764742 | -2.73 | 0.01111 | 0.76405 |
| EGFR | rs11971051 (A/T) | 7 | 55170578 | -2.93 | 0.01179 | 0.78829 |
| ERBB4 | rs10497961 (G/A) | 2 | 213043071 | 5.10 | 0.01338 | 0.81733 |
| NRG1 | rs2919373 (G/A) | 8 | 32431859 | -3.08 | 0.01435 | 0.81733 |
| NRG3 | rs594418 (A/G) | 10 | 84385052 | -3.46 | 0.01474 | 0.81733 |
| NRG3 | rs11192604 (A/G) | 10 | 83880996 | 4.79 | 0.01495 | 0.81733 |
| ERBB4 | rs13407198 (A/G) | 2 | 212712835 | -3.03 | 0.01515 | 0.81733 |
| ERBB4 | rs72933751 (C/A) | 2 | 212779081 | -5.04 | 0.01535 | 0.81733 |
| NRG2 | rs6868928 (C/A) | 5 | 139270729 | -3.17 | 0.01571 | 0.81733 |
| NRG3 | rs1764073 (C/A) | 10 | 83965348 | -2.97 | 0.01586 | 0.81733 |

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|---|---|---|---|---|---|---|
| ERBB4 | rs2371438 (A/G) | 2 | 212965531 | 4.99 | 0.01627 | 0.81733 |
| NRG3 | rs59144097 (A/C) | 10 | 84473414 | 6.41 | 0.01666 | 0.81733 |
| NRG2 | rs6860347 (G/A) | 5 | 139262117 | 2.53 | 0.01735 | 0.81733 |
| EPGN | rs6821364 (A/G) | 4 | 75176692 | 4.72 | 0.01748 | 0.81733 |
| NRG3 | rs12772014 (A/C) | 10 | 83954965 | -2.61 | 0.01775 | 0.81733 |
| ERBB4 | rs9283525 (C/A) | 2 | 213360073 | -3.36 | 0.01866 | 0.81733 |
| NRG1 | rs6468121 (C/A) | 8 | 32500809 | 2.52 | 0.0187 | 0.81733 |
| ERBB4 | rs1394799 (A/G) | 2 | 213230879 | 4.00 | 0.01883 | 0.81733 |
| NRG1 | rs4733362 (A/G) | 8 | 32428968 | -2.45 | 0.01912 | 0.81733 |
| TGFA | rs3771502 (A/G) | 2 | 70717507 | 3.50 | 0.01958 | 0.81733 |
| NRG3 | rs11815249 (G/A) | 10 | 83764410 | -3.51 | 0.01977 | 0.81733 |
| ERBB4 | rs12104709 (C/G) | 2 | 213264873 | 3.44 | 0.01998 | 0.81733 |
| ERBB4 | rs6747637 (A/C) | 2 | 212406789 | 2.47 | 0.01999 | 0.81733 |
| ERBB3 | rs877636 (A/G) | 12 | 56480583 | -2.57 | 0.02044 | 0.81733 |
| NRG1 | rs4236710 (A/G) | 8 | 32428759 | -2.44 | 0.02052 | 0.81733 |
| ERBB4 | rs1439248 (A/G) | 2 | 212687395 | -2.75 | 0.02125 | 0.81733 |
| NRG2 | rs10515509 (G/A) | 5 | 139290054 | -3.56 | 0.02205 | 0.81733 |
| NRG1 | rs2466059 (A/G) | 8 | 32472617 | -4.30 | 0.02233 | 0.81733 |
| ERBB4 | rs75401106 (G/A) | 2 | 212272475 | -4.22 | 0.02233 | 0.81733 |
| NRG1 | rs7012268 (G/A) | 8 | 31560051 | 6.02 | 0.02253 | 0.81733 |
| EGFR | rs2110290 (A/G) | 7 | 55172768 | -2.65 | 0.02263 | 0.81733 |
| ERBB4 | rs1025753 (C/A) | 2 | 212722915 | -2.84 | 0.02286 | 0.81733 |
| NRG1 | rs7838546 (G/A) | 8 | 31947880 | 3.85 | 0.02292 | 0.81733 |
| NRG3 | rs7907146 (G/A) | 10 | 83819987 | 3.97 | 0.02319 | 0.81733 |
| EGFR | rs3778866 (C/A) | 7 | 55166368 | -2.57 | 0.02343 | 0.81733 |
| NRG1 | rs2919378 (G/A) | 8 | 32569669 | 3.32 | 0.02398 | 0.82432 |
| NRG1 | rs4733359 (G/A) | 8 | 32424651 | -2.36 | 0.02445 | 0.82432 |
| MUC4 | rs56703338 (A/C) | 3 | 195496198 | -3.72 | 0.0248 | 0.82432 |
| ERBB4 | rs7572366 (G/A) | 2 | 213119367 | 4.94 | 0.025 | 0.82432 |
| NRG1 | rs73239840 (A/G) | 8 | 31570464 | 3.38 | 0.02581 | 0.83796 |
| NRG3 | rs67093168 (A/C) | 10 | 84398084 | 3.08 | 0.02611 | 0.83796 |
| ERBB4 | rs10932383 (A/G) | 2 | 212409676 | 2.42 | 0.02776 | 0.86159 |
| ERBB4 | rs4321319 (A/C) | 2 | 212361511 | -3.89 | 0.02817 | 0.86159 |
| NRG1 | rs6989889 (G/A) | 8 | 31987432 | 2.61 | 0.02852 | 0.86159 |
| EGFR | rs4947974 (G/A) | 7 | 55168912 | -2.63 | 0.02866 | 0.86159 |
| ERBB2 | rs4252596 (C/A) | 17 | 37855834 | -4.02 | 0.02953 | 0.86159 |
| NRG2 | rs76328935 (G/A) | 5 | 139401520 | -4.80 | 0.02953 | 0.86159 |
| NRG3 | rs1649940 (A/G) | 10 | 83953623 | -2.63 | 0.02959 | 0.86159 |
| NRG3 | rs12572464 (A/G) | 10 | 84000985 | 3.33 | 0.02971 | 0.86159 |
| NRG3 | rs1739779 (G/A) | 10 | 83933057 | -2.89 | 0.03097 | 0.86682 |
| ERBB4 | rs55663096 (G/A) | 2 | 212406723 | 3.00 | 0.03105 | 0.86682 |

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|---|---|---|---|---|---|---|
| ERBB4 | rs839509 (C/A) | 2 | 212822297 | 2.93 | 0.03125 | 0.86682 |
| NRG1 | rs7007662 (G/A) | 8 | 31952745 | 2.41 | 0.03179 | 0.86682 |
| ERBB4 | rs6435629 (G/A) | 2 | 212367912 | -2.39 | 0.03194 | 0.86682 |
| ERBB4 | rs7601515 (G/A) | 2 | 213190493 | 2.40 | 0.03282 | 0.86682 |
| NRG1 | rs34841210 (A/C) | 8 | 31545671 | -2.34 | 0.03306 | 0.86682 |
| NRG3 | rs56697116 (A/G) | 10 | 84469791 | 5.66 | 0.03309 | 0.86682 |
| NRG1 | rs6468085 (G/A) | 8 | 32000665 | -3.38 | 0.03347 | 0.86682 |
| ERBB4 | rs3791689 (A/G) | 2 | 212259223 | 2.24 | 0.035 | 0.86682 |
| ERBB4 | rs4672617 (A/C) | 2 | 212364807 | -2.66 | 0.03536 | 0.86682 |
| NRG3 | rs9419959 (G/A) | 10 | 83977442 | -2.94 | 0.03541 | 0.86682 |
| ERBB4 | rs35159481 (G/A) | 2 | 212378456 | 3.23 | 0.03604 | 0.86682 |
| TGFA | rs1448927 (A/G) | 2 | 70702233 | -2.29 | 0.03694 | 0.86682 |
| NRG3 | rs10884116 (G/A) | 10 | 83823067 | 3.58 | 0.03698 | 0.86682 |
| ERBB4 | rs7571561 (A/G) | 2 | 213386267 | -2.44 | 0.03806 | 0.86682 |
| ERBB4 | rs13010155 (A/C) | 2 | 212366429 | -2.30 | 0.0383 | 0.86682 |
| ERBB4 | rs2204070 (A/G) | 2 | 213043927 | -2.80 | 0.03973 | 0.86682 |
| NRG1 | rs1996563 (A/C) | 8 | 32239586 | 2.98 | 0.04015 | 0.86682 |
| NRG1 | rs16879153 (G/A) | 8 | 32192397 | 2.69 | 0.04038 | 0.86682 |
| ERBB4 | rs839530 (A/G) | 2 | 212802765 | 3.46 | 0.0405 | 0.86682 |
| NRG3 | rs544711 (G/A) | 10 | 84647566 | -2.17 | 0.04078 | 0.86682 |
| NRG1 | rs10156318 (G/A) | 8 | 32177114 | 3.46 | 0.04189 | 0.86682 |
| NRG3 | rs1649942 (A/G) | 10 | 83951691 | -2.40 | 0.04209 | 0.86682 |
| TGFA | rs1880039 (A/G) | 2 | 70687052 | 3.28 | 0.04264 | 0.86682 |
| ERBB4 | rs13423636 (G/A) | 2 | 213354898 | -3.31 | 0.0429 | 0.86682 |
| NRG1 | rs7813211 (G/A) | 8 | 31526127 | 5.50 | 0.04325 | 0.86682 |
| ERBB4 | rs10190653 (A/G) | 2 | 213366879 | -3.30 | 0.04326 | 0.86682 |
| EGFR | rs62459764 (G/A) | 7 | 55186800 | 3.68 | 0.04353 | 0.86682 |
| ERBB4 | rs10932382 (G/A) | 2 | 212395971 | 2.71 | 0.04358 | 0.86682 |
| NRG3 | rs10884060 (G/A) | 10 | 83789830 | -2.61 | 0.04373 | 0.86682 |
| NRG3 | rs12266991 (A/G) | 10 | 83784487 | 5.03 | 0.04448 | 0.86682 |
| ERBB4 | rs73073372 (C/A) | 2 | 212772374 | 3.12 | 0.04456 | 0.86682 |
| NRG2 | rs34566928 (C/A) | 5 | 139406956 | -3.49 | 0.04558 | 0.86682 |
| NRG3 | rs12251206 (A/G) | 10 | 84516525 | -4.03 | 0.04597 | 0.86682 |
| NRG3 | rs594530 (G/A) | 10 | 84394945 | -3.21 | 0.04676 | 0.86682 |
| ERBB3 | rs10876870 (C/A) | 12 | 56478002 | -2.19 | 0.04683 | 0.86682 |
| EGFR | rs2472520 (G/C) | 7 | 55265940 | -2.16 | 0.04834 | 0.86682 |
| ERBB4 | rs74911002 (A/C) | 2 | 213270590 | -3.71 | 0.04839 | 0.86682 |
| ERBB4 | rs13409739 (G/A) | 2 | 212580184 | 2.32 | 0.04879 | 0.86682 |
| NRG1 | rs56716642 (G/A) | 8 | 32170923 | 2.43 | 0.04921 | 0.86682 |
| NRG3 | rs34290487 (G/A) | 10 | 84489286 | 4.13 | 0.04923 | 0.86682 |
| NRG1 | rs6468090 (G/A) | 8 | 32076049 | 2.57 | 0.04952 | 0.86682 |

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|---|---|---|---|---|---|---|
| ERBB4 | rs4278873 (A/G) | 2 | 212361074 | -2.57 | 0.04966 | 0.86682 |
| ERBB4 | rs201425105 (C/A) | 2 | 212998148 | 3.62 | 0.04986 | 0.86682 |
| NRG3 | rs1983680 (A/G) | 10 | 83792004 | -3.42 | 0.04993 | 0.86682 |
| ERBB4 | rs13034566 (A/G) | 2 | 213240767 | -2.17 | 0.05004 | 0.86682 |
| ERBB4 | rs839520 (A/G) | 2 | 212817095 | 2.27 | 0.05054 | 0.86682 |
| NRG1 | rs2466075 (G/A) | 8 | 32432949 | -2.07 | 0.05063 | 0.86682 |
| ERBB4 | rs73073370 (G/A) | 2 | 212772221 | 2.98 | 0.05129 | 0.86682 |
| ERBB4 | rs62182566 (A/G) | 2 | 213049183 | -2.68 | 0.0515 | 0.86682 |
| ERBB4 | rs1482381 (A/G) | 2 | 213399007 | -3.19 | 0.05193 | 0.86682 |
| NRG1 | rs16879801 (A/G) | 8 | 32570493 | 3.58 | 0.05255 | 0.86682 |
| NRG3 | rs10786907 (A/C) | 10 | 83908249 | 3.64 | 0.05279 | 0.86682 |
| NRG3 | rs4326733 (A/G) | 10 | 84650672 | 2.66 | 0.05285 | 0.86682 |
| ERBB4 | rs13391359 (A/G) | 2 | 212771670 | -2.78 | 0.05378 | 0.86682 |
| ERBB4 | rs6732969 (A/G) | 2 | 212437072 | -2.49 | 0.05429 | 0.86682 |
| NRG1 | rs62506865 (A/C) | 8 | 31501160 | -2.43 | 0.05501 | 0.86682 |
| ERBB4 | rs17344252 (G/A) | 2 | 212973223 | 4.58 | 0.05646 | 0.86682 |
| NRG3 | rs7922851 (A/G) | 10 | 84463852 | 4.85 | 0.05705 | 0.86682 |
| ERBB4 | rs839523 (G/A) | 2 | 212816089 | 2.22 | 0.0571 | 0.86682 |
| NRG3 | rs7903899 (A/G) | 10 | 84502161 | -4.09 | 0.0582 | 0.86682 |
| NRG1 | rs2466093 (G/A) | 8 | 32448785 | -5.95 | 0.05856 | 0.86682 |
| ERBB4 | rs16848584 (A/G) | 2 | 213316592 | 4.95 | 0.05894 | 0.86682 |
| NRG1 | rs1462902 (A/G) | 8 | 31927566 | -2.26 | 0.05923 | 0.86682 |
| ERBB4 | rs59043430 (G/A) | 2 | 212283669 | -2.16 | 0.05925 | 0.86682 |
| NRG3 | rs73320364 (A/G) | 10 | 83902826 | 5.36 | 0.05939 | 0.86682 |
| ERBB4 | rs62182574 (A/C) | 2 | 213057843 | -2.53 | 0.05988 | 0.86682 |
| ERBB4 | rs17413177 (A/G) | 2 | 212419760 | -4.52 | 0.06004 | 0.86682 |
| NRG3 | rs1649947 (C/A) | 10 | 83874965 | -2.51 | 0.06005 | 0.86682 |
| NRG1 | rs16879304 (A/G) | 8 | 32240840 | 3.38 | 0.0607 | 0.86682 |
| ERBB4 | rs13413099 (A/G) | 2 | 212573962 | -2.08 | 0.06109 | 0.86682 |
| ERBB4 | rs12470850 (A/C) | 2 | 212414621 | -2.53 | 0.06113 | 0.86682 |
| NRG1 | rs4295616 (G/A) | 8 | 31521424 | 5.17 | 0.06154 | 0.86682 |
| ERBB4 | rs3791697 (G/A) | 2 | 212272614 | -2.16 | 0.06157 | 0.86682 |
| NRG1 | rs1462900 (A/C) | 8 | 31927638 | -2.31 | 0.06178 | 0.86682 |
| NRG1 | rs1081062 (A/G) | 8 | 31500264 | 2.25 | 0.06188 | 0.86682 |
| ERBB4 | rs1521653 (A/T) | 2 | 213028042 | 2.09 | 0.06191 | 0.86682 |
| NRG2 | rs1800954 (A/G) | 5 | 139245086 | -2.64 | 0.06195 | 0.86682 |
| TGFA | rs3771514 (G/A) | 2 | 70697667 | 2.38 | 0.06254 | 0.86682 |
| TGFA | rs446086 (C/A) | 2 | 70756057 | -2.33 | 0.06257 | 0.86682 |
| EGFR | rs2293348 (G/A) | 7 | 55266757 | -2.26 | 0.06285 | 0.86682 |
| ERBB4 | rs12994961 (A/G) | 2 | 212576980 | 3.49 | 0.06342 | 0.86682 |
| NRG1 | rs10100667 (G/A) | 8 | 32099102 | -2.03 | 0.06358 | 0.86682 |

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|---|---|---|---|---|---|---|
| NRG4 | rs1499063 (G/A) | 15 | 76274512 | -2.28 | 0.06444 | 0.86682 |
| TGFA | rs374640 (A/G) | 2 | 70753882 | 2.34 | 0.0647 | 0.86682 |
| NRG3 | rs1649943 (G/A) | 10 | 83950665 | -2.06 | 0.06532 | 0.86682 |
| NRG3 | rs2114818 (G/A) | 10 | 83876526 | 2.44 | 0.06574 | 0.86682 |
| NRG1 | rs56080487 (A/G) | 8 | 31574045 | -2.38 | 0.06621 | 0.86682 |
| NRG1 | rs11778887 (A/G) | 8 | 32156724 | 2.28 | 0.06624 | 0.86682 |
| ERBB4 | rs73077353 (A/C) | 2 | 212773893 | 2.78 | 0.0668 | 0.86682 |
| ERBB4 | rs1394782 (A/G) | 2 | 213200920 | 2.05 | 0.06704 | 0.86682 |
| NRG1 | rs66743588 (A/G) | 8 | 31596882 | -2.39 | 0.06827 | 0.86682 |
| EGFR | rs6958497 (A/G) | 7 | 55161746 | -3.18 | 0.06838 | 0.86682 |
| NRG3 | rs12774724 (G/A) | 10 | 83958152 | -1.99 | 0.06857 | 0.86682 |
| ERBB4 | rs905879 (C/A) | 2 | 213189366 | 2.04 | 0.06955 | 0.86682 |
| NRG1 | rs2466068 (G/A) | 8 | 32436680 | -2.14 | 0.06993 | 0.86682 |
| NRG1 | rs13258892 (G/A) | 8 | 32423537 | 2.05 | 0.07051 | 0.86682 |
| ERBB4 | rs7568763 (A/G) | 2 | 213351973 | -2.86 | 0.07069 | 0.86682 |
| NRG1 | rs10103952 (A/G) | 8 | 32556270 | 3.32 | 0.0707 | 0.86682 |
| EGFR | rs1140475 (G/A) | 7 | 55266417 | 3.05 | 0.07122 | 0.86682 |
| NRG3 | rs661469 (A/G) | 10 | 84386093 | -2.59 | 0.07133 | 0.86682 |
| TGFA | rs378322 (G/A) | 2 | 70762905 | 2.88 | 0.07241 | 0.86682 |
| ERBB4 | rs6744796 (A/G) | 2 | 212828793 | 2.13 | 0.07244 | 0.86682 |
| ERBB4 | rs62182572 (G/A) | 2 | 213057695 | -2.40 | 0.0726 | 0.86682 |
| NRG3 | rs11816151 (A/G) | 10 | 83704329 | 4.85 | 0.07312 | 0.86682 |
| ERBB4 | rs6435660 (G/A) | 2 | 212571939 | 1.93 | 0.07396 | 0.86682 |
| TGFA | rs199690423 (G/A) | 2 | 70744008 | 2.40 | 0.07476 | 0.86682 |
| NRG1 | rs4733094 (G/A) | 8 | 31597593 | -2.43 | 0.07489 | 0.86682 |
| ERBB4 | rs6745717 (A/G) | 2 | 212577231 | 2.50 | 0.0751 | 0.86682 |
| NRG3 | rs7894461 (C/A) | 10 | 83963016 | -2.02 | 0.07528 | 0.86682 |
| NRG2 | rs17208017 (A/G) | 5 | 139342616 | 4.41 | 0.07542 | 0.86682 |
| NRG1 | rs1481762 (G/A) | 8 | 31991227 | 1.95 | 0.07571 | 0.86682 |
| ERBB4 | rs201340763 (C/A) | 2 | 213202606 | 2.01 | 0.07589 | 0.86682 |
| NRG3 | rs2644212 (A/C) | 10 | 84519876 | 2.41 | 0.0759 | 0.86682 |
| ERBB4 | rs16847171 (A/G) | 2 | 212765359 | 3.13 | 0.07612 | 0.86682 |
| NRG3 | rs10509459 (G/A) | 10 | 84484387 | -3.73 | 0.07627 | 0.86682 |
| ERBB4 | rs1394792 (A/G) | 2 | 213178165 | 2.42 | 0.0763 | 0.86682 |
| ERBB4 | rs13417149 (G/A) | 2 | 213353515 | 5.30 | 0.07654 | 0.86682 |
| NRG1 | rs13270788 (A/G) | 8 | 31630983 | -2.01 | 0.07696 | 0.86682 |
| NRG1 | rs73239823 (A/G) | 8 | 31555911 | 2.23 | 0.07739 | 0.86682 |
| TGFA | rs10489984 (G/A) | 2 | 70772455 | 2.93 | 0.0775 | 0.86682 |
| ERBB4 | rs707284 (G/A) | 2 | 212839046 | 2.03 | 0.07787 | 0.86682 |
| ERBB4 | rs62182583 (A/G) | 2 | 213060796 | -2.36 | 0.07794 | 0.86682 |
| ERBB4 | rs839521 (G/A) | 2 | 212817010 | 2.10 | 0.07795 | 0.86682 |

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|---|---|---|---|---|---|---|
| ERBB4 | rs62182978 (T/A) | 2 | 212581721 | -3.54 | 0.07822 | 0.86682 |
| TGFA | rs34079678 (G/A) | 2 | 70726852 | 2.55 | 0.07909 | 0.86682 |
| NRG3 | rs1832586 (A/C) | 10 | 84400246 | -2.10 | 0.07918 | 0.86682 |
| EGFR | rs17290392 (G/A) | 7 | 55247610 | 2.75 | 0.07925 | 0.86682 |
| NRG3 | rs932512 (G/A) | 10 | 83933812 | -3.84 | 0.0793 | 0.86682 |
| TGFA | rs1807968 (A/G) | 2 | 70708261 | -1.92 | 0.07987 | 0.86682 |
| TGFA | rs426081 (A/G) | 2 | 70750531 | 2.36 | 0.07987 | 0.86682 |
| ERBB4 | rs62178826 (G/A) | 2 | 212370790 | -3.27 | 0.08006 | 0.86682 |
| ERBB4 | rs10174412 (G/A) | 2 | 212570416 | -2.05 | 0.08045 | 0.86682 |
| ERBB4 | rs7607086 (A/G) | 2 | 213105651 | 4.33 | 0.08149 | 0.86682 |
| NRG1 | rs7014221 (A/G) | 8 | 31582959 | 2.19 | 0.08156 | 0.86682 |
| NRG1 | rs7845525 (G/C) | 8 | 32295728 | 2.36 | 0.08174 | 0.86682 |
| NRG1 | rs3802158 (G/A) | 8 | 32404896 | -1.90 | 0.08206 | 0.86682 |
| NRG3 | rs2820110 (G/A) | 10 | 84519695 | 2.36 | 0.08266 | 0.86682 |
| NRG1 | rs7844425 (A/C) | 8 | 32375617 | -2.05 | 0.0828 | 0.86682 |
| ERBB4 | rs17344915 (A/G) | 2 | 213052379 | -2.39 | 0.08317 | 0.86682 |
| NRG1 | rs200685858 (T/A) | 8 | 32104629 | 1.92 | 0.08342 | 0.86682 |
| NRG1 | rs9297178 (G/A) | 8 | 31542212 | -2.22 | 0.08355 | 0.86682 |
| ERBB4 | rs3828243 (A/C) | 2 | 212276710 | 1.88 | 0.0836 | 0.86682 |
| NRG3 | rs2132377 (G/A) | 10 | 84638905 | 2.07 | 0.08395 | 0.86682 |
| NRG1 | rs4733130 (A/G) | 8 | 32406994 | -1.89 | 0.08436 | 0.86682 |
| NRG3 | rs543506 (A/C) | 10 | 84520727 | 2.34 | 0.08451 | 0.86682 |
| NRG3 | rs10786964 (G/A) | 10 | 83967446 | -1.89 | 0.08516 | 0.86682 |
| NRG3 | rs1010875 (G/A) | 10 | 84501184 | -3.59 | 0.08532 | 0.86682 |
| NRG3 | rs12358407 (A/C) | 10 | 83769695 | -2.35 | 0.08551 | 0.86682 |
| NRG1 | rs66560030 (A/C) | 8 | 31515559 | 2.16 | 0.08563 | 0.86682 |
| ERBB4 | rs1025752 (A/G) | 2 | 212723459 | -1.86 | 0.08606 | 0.86682 |
| NRG3 | rs7908131 (G/A) | 10 | 83966320 | -1.95 | 0.08611 | 0.86682 |
| NRG3 | rs646282 (G/A) | 10 | 84385067 | -2.25 | 0.08657 | 0.86682 |
| NRG3 | rs1336287 (C/A) | 10 | 83953716 | -1.89 | 0.08659 | 0.86682 |
| NRG3 | rs678139 (G/A) | 10 | 84416129 | -2.84 | 0.08713 | 0.86682 |
| NRG3 | rs586982 (A/G) | 10 | 84417577 | -2.84 | 0.08713 | 0.86682 |
| ERBB4 | rs839519 (G/A) | 2 | 212817319 | 2.19 | 0.08744 | 0.86682 |
| NRG3 | rs1010874 (G/A) | 10 | 84501091 | -3.62 | 0.08748 | 0.86682 |
| ERBB4 | rs62182573 (A/G) | 2 | 213057811 | -2.34 | 0.08751 | 0.86682 |
| NRG3 | rs4933824 (C/A) | 10 | 83819125 | 3.33 | 0.08818 | 0.8674 |
| ERBB4 | rs80175157 (G/A) | 2 | 212969727 | 4.06 | 0.08829 | 0.8674 |
| EGFR | rs887824 (C/A) | 7 | 55206861 | -3.30 | 0.08886 | 0.86798 |
| NRG1 | rs7833971 (A/G) | 8 | 32420054 | -2.27 | 0.08907 | 0.86798 |
| NRG1 | rs57495084 (C/A) | 8 | 31543081 | -2.17 | 0.08976 | 0.87118 |
| ERBB4 | rs1836719 (A/G) | 2 | 212259228 | -1.88 | 0.09037 | 0.87321 |

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|---|---|---|---|---|---|---|
| NRG1 | rs13266217 (G/A) | 8 | 31764280 | -2.18 | 0.09076 | 0.87321 |
| NRG1 | rs1081063 (G/A) | 8 | 31500222 | -2.20 | 0.09129 | 0.87321 |
| NRG3 | rs12357753 (G/A) | 10 | 83920714 | -2.99 | 0.09142 | 0.87321 |
| ERBB4 | rs16847178 (A/G) | 2 | 212766642 | -2.30 | 0.09199 | 0.87473 |
| NRG3 | rs10884217 (A/C) | 10 | 83872700 | 2.54 | 0.09248 | 0.87473 |
| NRG3 | rs4933811 (A/G) | 10 | 83675990 | -2.05 | 0.09267 | 0.87473 |
| NRG3 | rs11192136 (G/A) | 10 | 83763784 | 3.55 | 0.09489 | 0.89219 |
| ERBB4 | rs73985878 (A/G) | 2 | 212670359 | 3.51 | 0.09666 | 0.89942 |
| NRG3 | rs1649956 (A/G) | 10 | 83927984 | -2.33 | 0.09667 | 0.89942 |
| ERBB3 | rs2292239 (C/A) | 12 | 56482180 | -1.83 | 0.09678 | 0.89942 |
| ERBB4 | rs7586610 (A/G) | 2 | 213119487 | 3.98 | 0.09811 | 0.90181 |
| NRG1 | rs4733313 (G/A) | 8 | 32118416 | 1.81 | 0.09902 | 0.90181 |
| ERBB4 | rs57566572 (A/G) | 2 | 212747035 | 2.48 | 0.09904 | 0.90181 |
| NRG2 | rs75949957 (G/A) | 5 | 139280113 | 3.17 | 0.09928 | 0.90181 |
| MUC4 | rs6792437 (G/A) | 3 | 195479226 | -2.65 | 0.0996 | 0.90181 |
| EGFR | rs17172433 (G/A) | 7 | 55142435 | 2.59 | 0.09961 | 0.90181 |
| NRG2 | rs1800953 (A/C) | 5 | 139251469 | -2.07 | 0.09966 | 0.90181 |
| NRG3 | rs12571344 (A/G) | 10 | 83898148 | -2.52 | 0.1004 | 0.90373 |
| NRG3 | rs1555241 (G/A) | 10 | 83901664 | -1.90 | 0.101 | 0.90373 |
| ERBB4 | rs13384518 (G/A) | 2 | 212573365 | -1.90 | 0.1015 | 0.90373 |
| NRG2 | rs6885391 (A/C) | 5 | 139254229 | -3.86 | 0.102 | 0.90373 |
| NRG1 | rs79027555 (G/A) | 8 | 32055223 | -3.83 | 0.1022 | 0.90373 |
| ERBB4 | rs75981138 (G/A) | 2 | 212760650 | 2.77 | 0.1023 | 0.90373 |
| NRG3 | rs12261149 (A/G) | 10 | 83968703 | -1.80 | 0.1025 | 0.90373 |
| NRG3 | rs1739778 (G/A) | 10 | 83931542 | -2.32 | 0.1032 | 0.90658 |
| NRG3 | rs7090079 (A/G) | 10 | 84634637 | 2.42 | 0.1041 | 0.9068 |
| NRG3 | rs10736177 (G/A) | 10 | 83839348 | -2.23 | 0.1053 | 0.9068 |
| ERBB4 | rs73985830 (G/A) | 2 | 212607788 | 3.46 | 0.1055 | 0.9068 |
| NRG1 | rs1381871 (G/A) | 8 | 31935302 | -2.06 | 0.1063 | 0.9068 |
| NRG3 | rs11598813 (G/A) | 10 | 83993952 | 3.16 | 0.1063 | 0.9068 |
| ERBB4 | rs73073344 (A/G) | 2 | 212760472 | 2.38 | 0.1068 | 0.9068 |
| NRG1 | rs60806417 (A/C) | 8 | 31525033 | -1.95 | 0.1071 | 0.9068 |
| NRG1 | rs62506914 (G/A) | 8 | 31548360 | -2.10 | 0.1071 | 0.9068 |
| ERBB4 | rs707283 (G/A) | 2 | 212834170 | 2.14 | 0.1073 | 0.9068 |
| ERBB4 | rs73073183 (G/A) | 2 | 212407500 | 2.70 | 0.1074 | 0.9068 |
| NRG1 | rs28556775 (G/A) | 8 | 31523036 | -2.06 | 0.1083 | 0.9068 |
| NRG1 | rs7463426 (A/G) | 8 | 31523972 | -2.06 | 0.1083 | 0.9068 |
| ERBB4 | rs10191397 (A/G) | 2 | 213127742 | 4.31 | 0.1084 | 0.9068 |
| NRG3 | rs4140411 (G/A) | 10 | 83866166 | -2.16 | 0.1085 | 0.9068 |
| NRG3 | rs7899474 (G/A) | 10 | 83775626 | -1.97 | 0.1089 | 0.907 |
| EGFR | rs845559 (G/A) | 7 | 55247960 | 2.26 | 0.1095 | 0.90885 |

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|---|---|---|---|---|---|---|
| NRG3 | rs688413 (C/A) | 10 | 84385896 | -2.04 | 0.1104 | 0.91044 |
| NRG3 | rs2024785 (A/C) | 10 | 83664796 | 3.56 | 0.1108 | 0.91044 |
| NRG1 | rs2466062 (A/G) | 8 | 32443090 | -1.84 | 0.1113 | 0.91044 |
| NRG3 | rs1333208 (C/A) | 10 | 84666081 | 2.77 | 0.1116 | 0.91044 |
| NRG3 | rs10786961 (G/A) | 10 | 83964123 | -1.80 | 0.1128 | 0.91044 |
| NRG1 | rs17645417 (A/G) | 8 | 32351333 | -1.69 | 0.1131 | 0.91044 |
| NRG3 | rs2494026 (A/C) | 10 | 84442373 | 2.15 | 0.1136 | 0.91044 |
| TGFA | rs375668 (A/C) | 2 | 70737888 | 2.05 | 0.1139 | 0.91044 |
| NRG1 | rs4733267 (G/A) | 8 | 31504639 | -2.07 | 0.114 | 0.91044 |
| ERBB4 | rs11679499 (T/A) | 2 | 212729377 | 1.77 | 0.114 | 0.91044 |
| NRG1 | rs2466066 (G/A) | 8 | 32438416 | 2.01 | 0.1141 | 0.91044 |
| NRG3 | rs17098803 (C/A) | 10 | 83714374 | 2.83 | 0.1145 | 0.91044 |
| ERBB4 | rs3791692 (A/G) | 2 | 212264598 | 1.71 | 0.1147 | 0.91044 |
| ERBB4 | rs3791686 (A/G) | 2 | 212258353 | -1.74 | 0.1153 | 0.91044 |
| ERBB4 | rs6740652 (G/A) | 2 | 212405590 | -1.79 | 0.1155 | 0.91044 |
| NRG1 | rs2976525 (A/C) | 8 | 32572983 | 2.31 | 0.1159 | 0.91044 |
| ERBB4 | rs9288433 (G/A) | 2 | 212407077 | -1.80 | 0.1163 | 0.91044 |
| ERBB4 | rs7559679 (A/G) | 2 | 212471642 | -2.57 | 0.1165 | 0.91044 |
| NRG1 | rs1038280 (G/A) | 8 | 31992258 | 1.72 | 0.1171 | 0.91217 |
| NRG3 | rs12260741 (A/G) | 10 | 83670914 | 2.75 | 0.118 | 0.91362 |
| ERBB4 | rs62178805 (A/G) | 2 | 212359302 | -3.08 | 0.1189 | 0.91362 |
| ERBB4 | rs905883 (A/G) | 2 | 213188470 | 2.17 | 0.1198 | 0.91362 |
| EGFR | rs17336765 (G/A) | 7 | 55228379 | 3.36 | 0.1201 | 0.91362 |
| ERBB4 | rs62184542 (G/A) | 2 | 212781787 | -2.25 | 0.1203 | 0.91362 |
| NRG1 | rs2439273 (A/G) | 8 | 32490310 | -2.18 | 0.1208 | 0.91362 |
| NRG1 | rs4733329 (A/G) | 8 | 32274540 | 2.67 | 0.1209 | 0.91362 |
| NRG3 | rs61858778 (C/A) | 10 | 84645510 | 1.83 | 0.1209 | 0.91362 |
| ERBB4 | rs1910866 (A/C) | 2 | 213183696 | 2.09 | 0.1217 | 0.91362 |
| NRG3 | rs910584 (A/G) | 10 | 83662187 | -2.25 | 0.122 | 0.91362 |
| ERBB4 | rs6435693 (A/G) | 2 | 213009160 | 3.12 | 0.1221 | 0.91362 |
| ERBB4 | rs78568172 (G/A) | 2 | 212775465 | 2.81 | 0.1224 | 0.91362 |
| NRG3 | rs11191761 (G/A) | 10 | 83669286 | 2.72 | 0.1226 | 0.91362 |
| ERBB4 | rs10165449 (A/G) | 2 | 212303073 | 1.67 | 0.1226 | 0.91362 |
| NRG1 | rs7825175 (G/A) | 8 | 32416274 | -2.06 | 0.1237 | 0.91628 |
| NRG3 | rs1609605 (G/A) | 10 | 84655185 | -1.69 | 0.1239 | 0.91628 |
| EGFR | rs58711464 (A/G) | 7 | 55092322 | 2.01 | 0.1241 | 0.91628 |
| EGFR | rs10245472 (G/A) | 7 | 55147478 | 2.14 | 0.1249 | 0.91937 |
| ERBB4 | rs2043888 (A/G) | 2 | 212768779 | -2.34 | 0.126 | 0.92088 |
| ERBB4 | rs62178790 (A/G) | 2 | 212327460 | -2.92 | 0.1267 | 0.92088 |
| TGFA | rs450419 (A/G) | 2 | 70744107 | 1.78 | 0.1269 | 0.92088 |
| NRG3 | rs1764094 (A/C) | 10 | 83988809 | -2.93 | 0.1274 | 0.92088 |

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|---|---|---|---|---|---|---|
| NRG3 | rs1764096 (G/A) | 10 | 83990050 | -2.93 | 0.1274 | 0.92088 |
| NRG3 | rs1649978 (G/A) | 10 | 83990684 | -2.93 | 0.1274 | 0.92088 |
| ERBB4 | rs4300779 (G/A) | 2 | 213183765 | 2.06 | 0.1282 | 0.92233 |
| NRG3 | rs10883909 (A/C) | 10 | 83680766 | -1.85 | 0.1299 | 0.92233 |
| ERBB4 | rs16846917 (C/A) | 2 | 212697542 | 1.81 | 0.1303 | 0.92233 |
| NRG1 | rs327329 (A/G) | 8 | 31853498 | -1.89 | 0.1305 | 0.92233 |
| ERBB4 | rs62178804 (A/G) | 2 | 212358064 | -3.04 | 0.1309 | 0.92233 |
| NRG3 | rs1649933 (A/G) | 10 | 83885277 | -1.77 | 0.1317 | 0.92233 |
| NRG1 | rs4733319 (G/A) | 8 | 32235881 | -2.40 | 0.1318 | 0.92233 |
| NRG3 | rs73320389 (G/A) | 10 | 83916033 | 4.35 | 0.1318 | 0.92233 |
| TGFA | rs17639251 (A/G) | 2 | 70776281 | 2.64 | 0.132 | 0.92233 |
| ERBB4 | rs72941345 (C/A) | 2 | 212409600 | -1.97 | 0.1321 | 0.92233 |
| NRG3 | rs2132375 (G/A) | 10 | 84550812 | -2.85 | 0.1322 | 0.92233 |
| NRG3 | rs11195974 (A/G) | 10 | 84551558 | -2.85 | 0.1322 | 0.92233 |
| NRG1 | rs16878405 (G/A) | 8 | 31750300 | -3.20 | 0.1328 | 0.92384 |
| NRG2 | rs11746363 (G/A) | 5 | 139353857 | -2.16 | 0.1337 | 0.92418 |
| ERBB4 | rs1851196 (A/G) | 2 | 212470620 | -2.32 | 0.1338 | 0.92418 |
| ERBB4 | rs16846519 (G/A) | 2 | 212440969 | -3.51 | 0.134 | 0.92418 |
| TGFA | rs3771494 (A/G) | 2 | 70725352 | 1.97 | 0.1348 | 0.9244 |
| ERBB4 | rs2030458 (G/A) | 2 | 212376761 | 1.59 | 0.1348 | 0.9244 |
| NRG1 | rs2466094 (A/G) | 8 | 32448731 | -1.71 | 0.1364 | 0.92812 |
| ERBB4 | rs7597007 (A/C) | 2 | 212592044 | -1.73 | 0.1364 | 0.92812 |
| ERBB4 | rs2030457 (G/A) | 2 | 212376745 | 1.57 | 0.1365 | 0.92812 |
| NRG3 | rs7069209 (A/G) | 10 | 84589789 | -1.85 | 0.1373 | 0.93093 |
| EGFR | rs2075102 (A/C) | 7 | 55253305 | 1.62 | 0.1384 | 0.93187 |
| NRG1 | rs2346770 (A/G) | 8 | 31964752 | -3.36 | 0.1385 | 0.93187 |
| NRG3 | rs74146712 (A/G) | 10 | 83763627 | -2.32 | 0.1386 | 0.93187 |
| NRG3 | rs7100526 (G/A) | 10 | 83719888 | 2.06 | 0.1398 | 0.93636 |
| NRG1 | rs2466049 (G/A) | 8 | 32514916 | -2.61 | 0.1406 | 0.93636 |
| NRG3 | rs1649962 (G/A) | 10 | 83982090 | -2.80 | 0.1412 | 0.93636 |
| ERBB4 | rs10164675 (C/A) | 2 | 213187034 | -2.64 | 0.1418 | 0.93636 |
| NRG1 | rs12056766 (G/A) | 8 | 31513887 | -1.89 | 0.1429 | 0.93636 |
| NRG3 | rs2207773 (A/G) | 10 | 83793043 | -1.52 | 0.143 | 0.93636 |
| ERBB4 | rs4673661 (G/A) | 2 | 213205047 | 1.75 | 0.143 | 0.93636 |
| ERBB4 | rs16847170 (C/A) | 2 | 212764825 | 2.62 | 0.1451 | 0.93636 |
| NRG1 | rs2439292 (G/A) | 8 | 32446882 | 1.59 | 0.1475 | 0.93636 |
| NRG3 | rs61863009 (G/A) | 10 | 84003522 | 2.32 | 0.1475 | 0.93636 |
| NRG2 | rs4912894 (G/A) | 5 | 139236962 | 1.66 | 0.1479 | 0.93636 |
| ERBB4 | rs17878516 (C/G) | 2 | 212654554 | -1.70 | 0.1482 | 0.93636 |
| EGF | rs6840890 (A/G) | 4 | 110912940 | 3.28 | 0.1502 | 0.93636 |
| NRG1 | rs1481736 (G/A) | 8 | 31980642 | 1.61 | 0.1511 | 0.93636 |

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|---|---|---|---|---|---|---|
| EGFR | rs6593210 (G/A) | 7 | 55254186 | -1.89 | 0.1513 | 0.93636 |
| NRG3 | rs490164 (G/A) | 10 | 84597496 | 2.14 | 0.1525 | 0.93636 |
| NRG1 | rs13252152 (A/G) | 8 | 31955149 | 1.58 | 0.1526 | 0.93636 |
| NRG2 | rs7734418 (C/A) | 5 | 139405701 | -2.88 | 0.1528 | 0.93636 |
| ERBB4 | rs13006832 (G/A) | 2 | 213223044 | -1.72 | 0.1529 | 0.93636 |
| NRG3 | rs9664256 (A/G) | 10 | 83777755 | -1.49 | 0.153 | 0.93636 |
| ERBB4 | rs1347889 (A/G) | 2 | 212781914 | -1.53 | 0.1544 | 0.93636 |
| NRG3 | rs34979473 (A/G) | 10 | 84530942 | 2.09 | 0.1549 | 0.93636 |
| NRG3 | rs342371 (A/G) | 10 | 84589285 | 1.64 | 0.155 | 0.93636 |
| NRG1 | rs79035035 (G/A) | 8 | 32219907 | 2.51 | 0.1552 | 0.93636 |
| TGFA | rs6708768 (A/C) | 2 | 70752195 | 2.64 | 0.1554 | 0.93636 |
| ERBB4 | rs9808028 (A/G) | 2 | 212305314 | 1.59 | 0.1564 | 0.93636 |
| NRG3 | rs35702195 (A/G) | 10 | 83889114 | 4.16 | 0.1565 | 0.93636 |
| ERBB4 | rs3942465 (A/G) | 2 | 213042489 | 1.94 | 0.1569 | 0.93636 |
| NRG2 | rs75043106 (A/G) | 5 | 139382248 | -2.27 | 0.1575 | 0.93636 |
| ERBB4 | rs6711391 (A/G) | 2 | 213162300 | 2.15 | 0.1575 | 0.93636 |
| ERBB4 | rs6711487 (A/G) | 2 | 212597041 | -1.62 | 0.1581 | 0.93636 |
| NRG1 | rs10503892 (A/G) | 8 | 31705433 | -2.08 | 0.1588 | 0.93636 |
| NRG1 | rs2466073 (G/A) | 8 | 32433312 | 1.48 | 0.1588 | 0.93636 |
| NRG1 | rs11786653 (G/A) | 8 | 32106774 | -1.54 | 0.1591 | 0.93636 |
| EGFR | rs2075109 (G/A) | 7 | 55218903 | -1.46 | 0.1599 | 0.93636 |
| EGF | rs6810393 (C/A) | 4 | 110912687 | 3.20 | 0.1603 | 0.93636 |
| NRG1 | rs17706408 (A/G) | 8 | 32208121 | 2.59 | 0.1604 | 0.93636 |
| EGFR | rs1050171 (A/G) | 7 | 55249063 | 1.54 | 0.1606 | 0.93636 |
| NRG3 | rs11191796 (A/G) | 10 | 83678141 | 3.37 | 0.1609 | 0.93636 |
| NRG3 | rs10884225 (G/A) | 10 | 83880290 | 2.65 | 0.161 | 0.93636 |
| ERBB4 | rs7422053 (A/T) | 2 | 212563738 | -1.70 | 0.1626 | 0.93636 |
| NRG3 | rs17100442 (G/A) | 10 | 84423731 | 2.26 | 0.1628 | 0.93636 |
| NRG1 | rs901561 (A/G) | 8 | 32143462 | -1.63 | 0.1639 | 0.93636 |
| NRG4 | rs10851884 (G/A) | 15 | 76290042 | 1.52 | 0.1647 | 0.93636 |
| NRG3 | rs77967961 (G/A) | 10 | 83784627 | -1.90 | 0.1649 | 0.93636 |
| NRG1 | rs13255747 (G/A) | 8 | 31763811 | -1.80 | 0.1655 | 0.93636 |
| NRG3 | rs1614787 (A/C) | 10 | 83959179 | -1.58 | 0.1656 | 0.93636 |
| NRG3 | rs10884099 (G/A) | 10 | 83815369 | 2.56 | 0.1662 | 0.93636 |
| NRG1 | rs6993043 (G/A) | 8 | 31965188 | 1.55 | 0.1669 | 0.93636 |
| ERBB4 | rs72933754 (A/G) | 2 | 212781536 | -2.46 | 0.1672 | 0.93636 |
| NRG1 | rs1545961 (G/A) | 8 | 32173356 | 1.57 | 0.1676 | 0.93636 |
| NRG1 | rs35233333 (A/G) | 8 | 32429734 | 1.67 | 0.1677 | 0.93636 |
| ERBB4 | rs10208623 (A/G) | 2 | 212703221 | -1.56 | 0.1684 | 0.93636 |
| NRG1 | rs6468086 (A/C) | 8 | 32000759 | -1.90 | 0.1693 | 0.93636 |
| NRG3 | rs12240519 (G/A) | 10 | 83878316 | 2.75 | 0.17 | 0.93636 |

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|---|---|---|---|---|---|---|
| NRG1 | rs13250687 (C/A) | 8 | 31721106 | -2.90 | 0.171 | 0.93636 |
| NRG3 | rs11192423 (C/A) | 10 | 83839893 | 3.52 | 0.1715 | 0.93636 |
| NRG3 | rs74143892 (G/A) | 10 | 83729383 | 3.65 | 0.1716 | 0.93636 |
| NRG1 | rs17716295 (C/A) | 8 | 32317917 | -1.61 | 0.1722 | 0.93636 |
| ERBB2 | rs35797841 (G/A) | 17 | 37850777 | 2.70 | 0.1725 | 0.93636 |
| NRG1 | rs28406305 (G/A) | 8 | 32357923 | -1.60 | 0.1726 | 0.93636 |
| NRG1 | rs1503499 (A/G) | 8 | 31655026 | 1.73 | 0.1729 | 0.93636 |
| ERBB4 | rs78325609 (G/A) | 2 | 212555195 | 2.87 | 0.1734 | 0.93636 |
| NRG3 | rs2207778 (G/A) | 10 | 83773214 | -2.12 | 0.174 | 0.93636 |
| NRG1 | rs4733325 (A/G) | 8 | 32247220 | -1.45 | 0.1745 | 0.93636 |
| NRG3 | rs10732795 (G/A) | 10 | 83826122 | -2.13 | 0.1745 | 0.93636 |
| EGFR | rs763317 (G/A) | 7 | 55095197 | -1.47 | 0.175 | 0.93636 |
| NRG1 | rs12680844 (G/A) | 8 | 31991415 | -2.46 | 0.1758 | 0.93636 |
| EGFR | rs17172438 (A/G) | 7 | 55151537 | 1.88 | 0.1759 | 0.93636 |
| NRG2 | rs13165725 (A/G) | 5 | 139279459 | -1.71 | 0.1765 | 0.93636 |
| NRG1 | rs723811 (A/G) | 8 | 32527281 | 1.91 | 0.1768 | 0.93636 |
| TGFA | rs3755377 (G/A) | 2 | 70732852 | 1.52 | 0.1768 | 0.93636 |
| EGFR | rs58786160 (G/A) | 7 | 55185301 | -1.64 | 0.1771 | 0.93636 |
| EGFR | rs2058502 (A/G) | 7 | 55177869 | 1.48 | 0.178 | 0.93636 |
| ERBB4 | rs16848108 (G/A) | 2 | 213120523 | -1.71 | 0.1781 | 0.93636 |
| NRG1 | rs3924999 (G/A) | 8 | 32453358 | 1.58 | 0.1787 | 0.93636 |
| NRG1 | rs4733272 (A/G) | 8 | 31612816 | -1.78 | 0.179 | 0.93636 |
| NRG3 | rs2281471 (G/A) | 10 | 83690009 | 3.51 | 0.1791 | 0.93636 |
| NRG3 | rs12569561 (G/A) | 10 | 83865848 | 1.46 | 0.1793 | 0.93636 |
| NRG1 | rs13265568 (C/A) | 8 | 31651944 | -2.96 | 0.1794 | 0.93636 |
| NRG1 | rs10095694 (G/A) | 8 | 32499740 | -1.49 | 0.1795 | 0.93636 |
| EGFR | rs2280653 (A/G) | 7 | 55276094 | 1.76 | 0.1796 | 0.93636 |
| ERBB4 | rs73066385 (A/G) | 2 | 213151653 | -2.57 | 0.1796 | 0.93636 |
| NRG1 | rs7014535 (A/G) | 8 | 32569803 | 2.55 | 0.1798 | 0.93636 |
| EGFR | rs202028278 (A/G) | 7 | 55156803 | -1.61 | 0.1798 | 0.93636 |
| NRG3 | rs7913415 (A/G) | 10 | 83677849 | 2.45 | 0.1807 | 0.93636 |
| NRG1 | rs4422736 (G/A) | 8 | 32370520 | 2.42 | 0.1809 | 0.93636 |
| NRG2 | rs1422187 (A/G) | 5 | 139276748 | -1.54 | 0.181 | 0.93636 |
| NRG1 | rs7824399 (G/A) | 8 | 32141515 | -1.57 | 0.1814 | 0.93636 |
| NRG1 | rs60559257 (A/G) | 8 | 32172176 | -1.79 | 0.1838 | 0.93636 |
| NRG4 | rs8036952 (G/A) | 15 | 76284238 | 2.92 | 0.1838 | 0.93636 |
| NRG3 | rs17095111 (A/G) | 10 | 83989092 | -2.40 | 0.1839 | 0.93636 |
| NRG1 | rs11776959 (G/A) | 8 | 31948864 | 1.50 | 0.1841 | 0.93636 |
| ERBB4 | rs13019524 (A/G) | 2 | 213251503 | -1.61 | 0.1863 | 0.93636 |
| NRG1 | rs199942240 (T/A) | 8 | 32279530 | -1.94 | 0.1866 | 0.93636 |
| NRG1 | rs34861396 (G/A) | 8 | 31498467 | -1.55 | 0.187 | 0.93636 |

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|---|---|---|---|---|---|---|
| NRG1 | rs1503486 (G/A) | 8 | 31609577 | -1.47 | 0.187 | 0.93636 |
| ERBB4 | rs1394780 (A/C) | 2 | 213283190 | -1.64 | 0.1874 | 0.93636 |
| NRG1 | rs9297191 (A/G) | 8 | 32283471 | 1.51 | 0.1875 | 0.93636 |
| NRG4 | rs1874953 (C/G) | 15 | 76236837 | 1.44 | 0.1877 | 0.93636 |
| NRG1 | rs2221349 (G/A) | 8 | 31650609 | 1.67 | 0.1881 | 0.93636 |
| NRG1 | rs7833021 (A/G) | 8 | 32016694 | 1.77 | 0.1888 | 0.93636 |
| NRG1 | rs983598 (C/A) | 8 | 32163416 | -1.38 | 0.1891 | 0.93636 |
| NRG1 | rs981817 (G/A) | 8 | 31986192 | -1.44 | 0.1894 | 0.93636 |
| NRG3 | rs2065539 (G/A) | 10 | 84537562 | 1.45 | 0.1895 | 0.93636 |
| ERBB4 | rs12998591 (G/A) | 2 | 212787427 | 2.38 | 0.1899 | 0.93636 |
| ERBB4 | rs12478244 (G/A) | 2 | 213226396 | -2.41 | 0.1899 | 0.93636 |
| NRG1 | rs12679454 (G/A) | 8 | 31612756 | -2.88 | 0.19 | 0.93636 |
| NRG3 | rs10884342 (G/A) | 10 | 83974586 | -1.50 | 0.1906 | 0.93636 |
| ERBB4 | rs11680307 (G/A) | 2 | 212997024 | -1.43 | 0.1913 | 0.93636 |
| NRG3 | rs2256108 (A/G) | 10 | 84472269 | 1.41 | 0.1914 | 0.93636 |
| EGFR | rs917880 (G/A) | 7 | 55162011 | 1.45 | 0.1917 | 0.93636 |
| ERBB4 | rs17347530 (A/G) | 2 | 213222446 | -2.07 | 0.1926 | 0.93636 |
| NRG2 | rs6580288 (A/G) | 5 | 139245762 | -1.65 | 0.1929 | 0.93636 |
| EGFR | rs7801956 (G/A) | 7 | 55214443 | 2.80 | 0.1937 | 0.93636 |
| NRG1 | rs4531002 (G/A) | 8 | 32501987 | 1.47 | 0.1939 | 0.93636 |
| ERBB4 | rs71422750 (C/A) | 2 | 212542930 | 2.23 | 0.1942 | 0.93636 |
| NRG3 | rs17100804 (G/A) | 10 | 84571432 | -1.93 | 0.1945 | 0.93636 |
| NRG1 | rs1481744 (A/G) | 8 | 32020990 | 1.74 | 0.1949 | 0.93636 |
| NRG1 | rs13282123 (A/G) | 8 | 32377064 | 1.83 | 0.1952 | 0.93636 |
| NRG3 | rs17100775 (C/A) | 10 | 84524550 | 2.63 | 0.1956 | 0.93636 |
| EGF | rs113097224 (A/G) | 4 | 110837520 | 2.89 | 0.1957 | 0.93636 |
| ERBB4 | rs16847741 (C/A) | 2 | 212987580 | 2.62 | 0.196 | 0.93636 |
| ERBB4 | rs839517 (G/A) | 2 | 212817777 | 1.58 | 0.1961 | 0.93636 |
| EGFR | rs11979158 (A/G) | 7 | 55159349 | 1.84 | 0.1962 | 0.93636 |
| ERBB4 | rs201596760 (A/G) | 2 | 212328438 | -1.43 | 0.1966 | 0.93636 |
| NRG1 | rs10954827 (A/G) | 8 | 31952710 | 1.47 | 0.1973 | 0.93636 |
| ERBB4 | rs1836717 (A/G) | 2 | 212292699 | -1.56 | 0.1973 | 0.93636 |
| ERBB4 | rs6755568 (G/A) | 2 | 213283749 | -1.82 | 0.1976 | 0.93636 |
| NRG1 | rs1685117 (C/A) | 8 | 32197182 | -2.13 | 0.1977 | 0.93636 |
| ERBB4 | rs60194994 (A/C) | 2 | 212297335 | -1.60 | 0.1982 | 0.93636 |
| TGFA | rs3771481 (A/C) | 2 | 70759302 | 3.48 | 0.1988 | 0.93636 |
| NRG1 | rs13249321 (A/G) | 8 | 31688285 | 1.63 | 0.1992 | 0.93636 |
| NRG1 | rs3847131 (G/A) | 8 | 32282019 | -1.44 | 0.1997 | 0.93636 |
| TGFA | rs2215020 (A/C) | 2 | 70745840 | 3.73 | 0.1999 | 0.93636 |
| NRG1 | rs16878890 (A/G) | 8 | 32020891 | 2.27 | 0.2001 | 0.93636 |
| NRG1 | rs10503904 (A/G) | 8 | 32164687 | -2.46 | 0.2002 | 0.93636 |

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|---|---|---|---|---|---|---|
| ERBB4 | rs1818755 (G/A) | 2 | 212375171 | 1.37 | 0.2003 | 0.93636 |
| ERBB4 | rs16847747 (G/C) | 2 | 212990837 | 2.59 | 0.2011 | 0.93636 |
| ERBB4 | rs11689233 (G/A) | 2 | 213317794 | -1.96 | 0.2026 | 0.93636 |
| ERBB4 | rs11684546 (G/A) | 2 | 212695511 | 2.16 | 0.2042 | 0.93636 |
| EGFR | rs2192293 (G/A) | 7 | 55098289 | -1.37 | 0.2043 | 0.93636 |
| NRG2 | rs4912936 (G/A) | 5 | 139293166 | 1.70 | 0.205 | 0.93636 |
| ERBB4 | rs16846100 (C/A) | 2 | 212278218 | -1.63 | 0.2056 | 0.93636 |
| NRG1 | rs2126613 (G/A) | 8 | 31961283 | -1.39 | 0.2059 | 0.93636 |
| ERBB4 | rs10196652 (A/C) | 2 | 213330413 | -1.93 | 0.2059 | 0.93636 |
| ERBB4 | rs6435632 (G/A) | 2 | 212378524 | 1.48 | 0.206 | 0.93636 |
| ERBB4 | rs13395652 (A/G) | 2 | 212303506 | 1.46 | 0.2062 | 0.93636 |
| NRG2 | rs73271418 (G/A) | 5 | 139261005 | -1.79 | 0.2063 | 0.93636 |
| EPGN | rs72654839 (A/C) | 4 | 75181247 | 2.05 | 0.2067 | 0.93636 |
| NRG1 | rs7829124 (A/G) | 8 | 31509494 | 1.60 | 0.2074 | 0.93636 |
| NRG3 | rs10885506 (A/C) | 10 | 84681635 | 1.37 | 0.2078 | 0.93636 |
| NRG1 | rs2466058 (G/A) | 8 | 32507149 | -2.17 | 0.2089 | 0.93636 |
| ERBB4 | rs12466141 (G/A) | 2 | 213029233 | 2.24 | 0.2091 | 0.93636 |
| ERBB4 | rs13020474 (G/A) | 2 | 212866473 | 2.11 | 0.2097 | 0.93636 |
| NRG1 | rs13273150 (G/A) | 8 | 32429174 | 2.62 | 0.2104 | 0.93636 |
| NRG1 | rs2439327 (A/G) | 8 | 32512309 | -2.21 | 0.2105 | 0.93636 |
| NRG1 | rs1481765 (G/A) | 8 | 32078971 | 1.88 | 0.2108 | 0.93636 |
| NRG3 | rs61858783 (G/A) | 10 | 84659477 | -2.13 | 0.2108 | 0.93636 |
| NRG1 | rs1473438 (A/G) | 8 | 31733759 | 1.39 | 0.2114 | 0.93636 |
| ERBB4 | rs56388911 (A/G) | 2 | 213116827 | -1.62 | 0.2115 | 0.93636 |
| EGFR | rs17172435 (G/A) | 7 | 55146471 | 1.75 | 0.2117 | 0.93636 |
| ERBB4 | rs12990694 (G/A) | 2 | 212695924 | 2.13 | 0.2121 | 0.93636 |
| NRG1 | rs6995821 (C/A) | 8 | 31970568 | 1.54 | 0.2125 | 0.93636 |
| EGFR | rs10277413 (A/C) | 7 | 55238464 | -1.43 | 0.2125 | 0.93636 |
| EREG | rs2367707 (G/A) | 4 | 75248434 | 1.65 | 0.2126 | 0.93636 |
| NRG1 | rs10103750 (A/C) | 8 | 32596998 | 1.67 | 0.213 | 0.93636 |
| NRG1 | rs1503491 (G/A) | 8 | 31642106 | -1.63 | 0.2138 | 0.93636 |
| ERBB4 | rs11305823 (A/C) | 2 | 213316734 | 1.53 | 0.214 | 0.93636 |
| EGFR | rs4947986 (G/A) | 7 | 55221655 | -1.55 | 0.2141 | 0.93636 |
| EGFR | rs4947979 (A/G) | 7 | 55195625 | -1.60 | 0.2152 | 0.93636 |
| TGFA | rs62151581 (A/C) | 2 | 70768180 | -2.16 | 0.2166 | 0.93636 |
| NRG3 | rs11192252 (A/G) | 10 | 83798259 | 2.16 | 0.2177 | 0.93636 |
| ERBB4 | rs2135160 (A/G) | 2 | 213214467 | -2.35 | 0.2182 | 0.93636 |
| NRG3 | rs55670857 (G/A) | 10 | 84498654 | 2.51 | 0.2184 | 0.93636 |
| NRG1 | rs2976527 (G/A) | 8 | 32577452 | 1.47 | 0.2191 | 0.93636 |
| NRG3 | rs1577464 (A/G) | 10 | 84533447 | -2.12 | 0.2191 | 0.93636 |
| ERBB4 | rs6435690 (G/A) | 2 | 212975239 | 1.34 | 0.2192 | 0.93636 |

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|---|---|---|---|---|---|---|
| ERBB4 | rs1357139 (C/A) | 2 | 213050781 | -1.37 | 0.2198 | 0.93636 |
| NRG1 | rs75016101 (A/C) | 8 | 31879230 | -1.40 | 0.2202 | 0.93636 |
| NRG1 | rs7836913 (A/G) | 8 | 32068180 | -1.59 | 0.2205 | 0.93636 |
| NRG1 | rs2929484 (G/A) | 8 | 31866079 | -1.43 | 0.221 | 0.93636 |
| NRG3 | rs59698716 (A/G) | 10 | 83983440 | 2.90 | 0.2212 | 0.93636 |
| NRG3 | rs12416296 (A/G) | 10 | 84428646 | 2.06 | 0.2213 | 0.93636 |
| ERBB4 | rs7570124 (C/A) | 2 | 213319545 | 3.15 | 0.2219 | 0.93636 |
| NRG1 | rs2466044 (A/G) | 8 | 32501626 | -2.36 | 0.222 | 0.93636 |
| NRG1 | rs16879552 (G/A) | 8 | 32411216 | 2.67 | 0.2222 | 0.93636 |
| NRG3 | rs2494021 (A/G) | 10 | 84477066 | 1.48 | 0.2243 | 0.93636 |
| ERBB4 | rs7603379 (A/C) | 2 | 213345437 | 2.83 | 0.2244 | 0.93636 |
| NRG3 | rs7085170 (A/G) | 10 | 84038059 | 1.36 | 0.2248 | 0.93636 |
| ERBB4 | rs1566926 (A/G) | 2 | 213220898 | 1.37 | 0.2249 | 0.93636 |
| NRG2 | rs7707550 (A/T) | 5 | 139410945 | -1.33 | 0.2251 | 0.93636 |
| NRG4 | rs11072567 (A/G) | 15 | 76298744 | 1.30 | 0.2255 | 0.93636 |
| NRG1 | rs10954822 (A/G) | 8 | 31907266 | -2.05 | 0.2258 | 0.93636 |
| NRG3 | rs61858784 (A/G) | 10 | 84661523 | 3.01 | 0.2265 | 0.93636 |
| NRG1 | rs10503901 (G/A) | 8 | 32085171 | 1.91 | 0.2274 | 0.93636 |
| EGFR | rs2740761 (G/A) | 7 | 55255986 | -1.58 | 0.2282 | 0.93636 |
| NRG1 | rs16879085 (G/A) | 8 | 32132644 | -2.48 | 0.2286 | 0.93636 |
| NRG3 | rs659561 (C/A) | 10 | 84303712 | -2.27 | 0.2286 | 0.93636 |
| ERBB4 | rs1595062 (G/A) | 2 | 212251070 | 1.40 | 0.2286 | 0.93636 |
| ERBB4 | rs6730119 (G/A) | 2 | 212519028 | -1.29 | 0.2288 | 0.93636 |
| NRG1 | rs2045796 (A/C) | 8 | 31949047 | 1.52 | 0.2298 | 0.93636 |
| NRG1 | rs1680167 (G/A) | 8 | 31778474 | 1.33 | 0.2303 | 0.93636 |
| ERBB4 | rs17347606 (A/C) | 2 | 213226977 | -2.10 | 0.2309 | 0.93636 |
| NRG1 | rs6981660 (A/G) | 8 | 32298476 | -1.36 | 0.2313 | 0.93636 |
| NRG3 | rs11194700 (C/A) | 10 | 84255527 | 3.00 | 0.2317 | 0.93636 |
| EGFR | rs4140770 (A/G) | 7 | 55141476 | 1.32 | 0.2323 | 0.93636 |
| EPGN | rs16850898 (A/G) | 4 | 75175677 | 2.93 | 0.2327 | 0.93636 |
| EPGN | rs75967466 (A/G) | 4 | 75176983 | 2.93 | 0.2327 | 0.93636 |
| NRG3 | rs11192402 (A/C) | 10 | 83835232 | -1.41 | 0.2331 | 0.93636 |
| BTC | rs10005235 (A/G) | 4 | 75697820 | 1.80 | 0.2334 | 0.93636 |
| NRG1 | rs2439313 (G/A) | 8 | 32533316 | 1.25 | 0.2336 | 0.93636 |
| ERBB4 | rs77159266 (G/A) | 2 | 213364056 | -2.22 | 0.2337 | 0.93636 |
| ERBB4 | rs10185729 (A/G) | 2 | 212842777 | -1.63 | 0.2351 | 0.93636 |
| NRG1 | rs2466064 (G/A) | 8 | 32441203 | -1.37 | 0.2358 | 0.93636 |
| NRG3 | rs1937969 (A/G) | 10 | 84223444 | -1.43 | 0.2361 | 0.93636 |
| ERBB4 | rs34306926 (G/A) | 2 | 212826392 | 1.78 | 0.2361 | 0.93636 |
| NRG1 | rs10109194 (C/A) | 8 | 32537995 | 2.18 | 0.2369 | 0.93636 |
| ERBB4 | rs2371272 (A/G) | 2 | 212329352 | -1.31 | 0.2369 | 0.93636 |

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|---|---|---|---|---|---|---|
| MUC4 | rs9832033 (G/A) | 3 | 195538901 | 2.10 | 0.237 | 0.93636 |
| TGFA | rs3849383 (A/C) | 2 | 70710420 | 1.31 | 0.2371 | 0.93636 |
| NRG1 | rs2439315 (G/A) | 8 | 32530811 | 1.91 | 0.2372 | 0.93636 |
| ERBB4 | rs186694905 (G/A) | 2 | 213239209 | -2.15 | 0.2375 | 0.93636 |
| NRG3 | rs479772 (G/A) | 10 | 84624927 | -1.43 | 0.2378 | 0.93636 |
| ERBB4 | rs72946560 (G/A) | 2 | 212581988 | -2.55 | 0.238 | 0.93636 |
| MUC4 | rs842226 (G/A) | 3 | 195478861 | -2.61 | 0.2384 | 0.93636 |
| NRG1 | rs10503926 (C/A) | 8 | 32541216 | 1.24 | 0.2392 | 0.93636 |
| NRG1 | rs7827391 (G/A) | 8 | 32542912 | 1.24 | 0.24 | 0.93636 |
| ERBB4 | rs13413335 (A/C) | 2 | 213288664 | -1.95 | 0.2402 | 0.93636 |
| NRG3 | rs1040674 (A/G) | 10 | 83681283 | -1.68 | 0.2404 | 0.93636 |
| ERBB4 | rs76666265 (T/A) | 2 | 212855248 | 1.37 | 0.2404 | 0.93636 |
| NRG3 | rs10748994 (G/A) | 10 | 84237629 | -1.42 | 0.2415 | 0.93636 |
| NRG1 | rs11775675 (G/A) | 8 | 32262505 | -1.39 | 0.2418 | 0.93636 |
| NRG1 | rs116111265 (A/C) | 8 | 32482753 | -2.01 | 0.2419 | 0.93636 |
| NRG1 | rs4733363 (T/A) | 8 | 32451286 | 1.34 | 0.2427 | 0.93636 |
| ERBB4 | rs16847879 (A/G) | 2 | 213067535 | -1.61 | 0.2428 | 0.93636 |
| NRG3 | rs342390 (C/A) | 10 | 84582514 | 1.72 | 0.2434 | 0.93636 |
| NRG1 | rs12548924 (A/G) | 8 | 32383339 | 1.62 | 0.2436 | 0.93636 |
| ERBB4 | rs4673629 (A/G) | 2 | 212586244 | -1.24 | 0.2437 | 0.93636 |
| ERBB4 | rs72949534 (G/A) | 2 | 213199479 | -1.75 | 0.2442 | 0.93636 |
| TGFA | rs17005644 (A/G) | 2 | 70696953 | 1.68 | 0.2449 | 0.93636 |
| NRG1 | rs17721282 (G/A) | 8 | 32443025 | -1.42 | 0.245 | 0.93636 |
| NRG1 | rs989735 (G/A) | 8 | 31916730 | -1.28 | 0.246 | 0.93636 |
| NRG3 | rs10748869 (G/A) | 10 | 83776091 | -1.19 | 0.2462 | 0.93636 |
| ERBB4 | rs6732730 (A/G) | 2 | 213009392 | 2.54 | 0.2466 | 0.93636 |
| NRG1 | rs1481742 (C/A) | 8 | 32021186 | 1.53 | 0.2471 | 0.93636 |
| NRG1 | rs1487155 (A/G) | 8 | 32195259 | 1.30 | 0.2471 | 0.93636 |
| NRG1 | rs6999843 (G/A) | 8 | 32447277 | -1.42 | 0.2472 | 0.93636 |
| NRG2 | rs6893652 (G/A) | 5 | 139270855 | -1.57 | 0.2473 | 0.93636 |
| ERBB4 | rs839536 (G/A) | 2 | 212810155 | 1.56 | 0.2474 | 0.93636 |
| NRG1 | rs2347507 (G/A) | 8 | 32235025 | -1.83 | 0.2476 | 0.93636 |
| ERBB4 | rs75592307 (A/G) | 2 | 213255912 | -2.06 | 0.2483 | 0.93636 |
| NRG1 | rs2976514 (G/A) | 8 | 32538038 | 1.21 | 0.2484 | 0.93636 |
| ERBB4 | rs6746949 (C/A) | 2 | 212360994 | -1.26 | 0.2492 | 0.93636 |
| NRG1 | rs10113308 (A/G) | 8 | 32492391 | 1.77 | 0.2493 | 0.93636 |
| NRG1 | rs7822564 (A/G) | 8 | 32132882 | -1.33 | 0.2499 | 0.93636 |
| NRG1 | rs2466092 (A/G) | 8 | 32464939 | -1.92 | 0.2499 | 0.93636 |
| ERBB4 | rs16848751 (A/G) | 2 | 213389346 | -1.33 | 0.25 | 0.93636 |
| ERBB4 | rs13427258 (G/A) | 2 | 213076051 | 1.21 | 0.2501 | 0.93636 |
| NRG1 | rs7841220 (G/A) | 8 | 31943664 | -1.33 | 0.2506 | 0.93636 |

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|---|---|---|---|---|---|---|
| ERBB4 | rs1965462 (A/G) | 2 | 212464224 | -2.15 | 0.2506 | 0.93636 |
| ERBB4 | rs36040938 (G/A) | 2 | 212412272 | -1.56 | 0.2515 | 0.93636 |
| NRG1 | rs756265 (A/G) | 8 | 31769937 | -1.27 | 0.2518 | 0.93636 |
| NRG1 | rs67993561 (G/A) | 8 | 32437234 | -1.40 | 0.2522 | 0.93636 |
| EPGN | rs75220201 (A/G) | 4 | 75176211 | 2.92 | 0.2529 | 0.93636 |
| ERBB4 | rs28529590 (A/G) | 2 | 213241394 | 1.43 | 0.2532 | 0.93636 |
| ERBB4 | rs7556879 (A/G) | 2 | 212465328 | -1.68 | 0.2533 | 0.93636 |
| ERBB4 | rs4435392 (A/G) | 2 | 212411658 | -1.63 | 0.2536 | 0.93636 |
| ERBB4 | rs17406681 (G/A) | 2 | 212403387 | -1.56 | 0.2539 | 0.93636 |
| NRG3 | rs1414767 (G/A) | 10 | 83972768 | 1.30 | 0.254 | 0.93636 |
| ERBB4 | rs13002712 (A/G) | 2 | 212587321 | -1.27 | 0.254 | 0.93636 |
| NRG3 | rs1577463 (C/A) | 10 | 84551067 | -1.78 | 0.2541 | 0.93636 |
| BTC | rs6842284 (G/A) | 4 | 75717119 | -1.23 | 0.2547 | 0.93636 |
| EGFR | rs759160 (A/G) | 7 | 55181442 | -1.41 | 0.2552 | 0.93636 |
| NRG3 | rs3903435 (A/C) | 10 | 83776457 | -1.17 | 0.2564 | 0.93636 |
| NRG3 | rs56163553 (G/A) | 10 | 84479425 | 2.14 | 0.2564 | 0.93636 |
| NRG1 | rs56362701 (C/A) | 8 | 31671457 | -1.23 | 0.2575 | 0.93636 |
| ERBB4 | rs16848458 (A/G) | 2 | 213227254 | -1.73 | 0.2579 | 0.93636 |
| NRG1 | rs4733342 (A/G) | 8 | 32349236 | 1.77 | 0.258 | 0.93636 |
| NRG3 | rs6584612 (G/A) | 10 | 84038461 | 1.28 | 0.2581 | 0.93636 |
| NRG4 | rs334951 (A/G) | 15 | 76300995 | 2.49 | 0.2582 | 0.93636 |
| ERBB4 | rs16846127 (G/A) | 2 | 212285785 | -1.37 | 0.2585 | 0.93636 |
| NRG3 | rs1739765 (C/A) | 10 | 83950540 | -1.33 | 0.2589 | 0.93636 |
| NRG1 | rs1481628 (G/A) | 8 | 31779265 | 1.26 | 0.2593 | 0.93636 |
| NRG3 | rs17099325 (A/C) | 10 | 83826908 | 2.55 | 0.2606 | 0.93636 |
| NRG3 | rs2144393 (A/G) | 10 | 83851010 | -1.77 | 0.261 | 0.93636 |
| ERBB4 | rs73073158 (G/A) | 2 | 212383724 | -1.27 | 0.2617 | 0.93636 |
| EGFR | rs729969 (G/A) | 7 | 55128207 | 1.71 | 0.2618 | 0.93636 |
| NRG3 | rs79319236 (A/G) | 10 | 84674420 | -2.60 | 0.2618 | 0.93636 |
| NRG3 | rs12250654 (A/G) | 10 | 84646857 | -2.21 | 0.262 | 0.93636 |
| ERBB4 | rs4673613 (A/G) | 2 | 212264642 | -1.32 | 0.262 | 0.93636 |
| NRG1 | rs6986716 (C/A) | 8 | 32247739 | 1.54 | 0.263 | 0.93636 |
| EGFR | rs10228436 (G/A) | 7 | 55238268 | -1.28 | 0.2635 | 0.93636 |
| ERBB4 | rs11895509 (G/A) | 2 | 212412738 | 1.95 | 0.2635 | 0.93636 |
| ERBB4 | rs16847207 (A/G) | 2 | 212791249 | 1.90 | 0.2635 | 0.93636 |
| NRG1 | rs13249578 (G/A) | 8 | 31945918 | -1.27 | 0.2638 | 0.93636 |
| NRG3 | rs7078253 (A/C) | 10 | 84136681 | -1.64 | 0.2648 | 0.93636 |
| NRG1 | rs1111307 (G/A) | 8 | 32092536 | 1.92 | 0.2654 | 0.93636 |
| NRG3 | rs12416404 (G/A) | 10 | 84685218 | -1.30 | 0.266 | 0.93636 |
| ERBB4 | rs4145961 (A/G) | 2 | 213074216 | 1.33 | 0.2667 | 0.93636 |
| NRG1 | rs1462904 (C/A) | 8 | 31926881 | -1.23 | 0.2674 | 0.93636 |

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|---|---|---|---|---|---|---|
| NRG1 | rs16878772 (A/C) | 8 | 31941211 | -2.51 | 0.2683 | 0.93636 |
| EGFR | rs2302534 (A/G) | 7 | 55136397 | 1.14 | 0.2683 | 0.93636 |
| NRG3 | rs597803 (G/A) | 10 | 84395625 | -1.32 | 0.2688 | 0.93636 |
| NRG3 | rs12572315 (A/G) | 10 | 83775851 | 2.47 | 0.2695 | 0.93636 |
| NRG1 | rs2439320 (A/G) | 8 | 32524802 | 1.17 | 0.2696 | 0.93636 |
| NRG1 | rs2439275 (A/T) | 8 | 32488687 | 1.26 | 0.2708 | 0.93636 |
| ERBB4 | rs12470608 (A/G) | 2 | 212737233 | 1.74 | 0.2717 | 0.93636 |
| ERBB4 | rs11679952 (G/A) | 2 | 212621848 | -1.28 | 0.2718 | 0.93636 |
| NRG3 | rs4329625 (G/A) | 10 | 84035428 | 1.88 | 0.2725 | 0.93636 |
| EGFR | rs11506105 (G/A) | 7 | 55220177 | -1.17 | 0.273 | 0.93636 |
| NRG1 | rs2919382 (A/G) | 8 | 32560765 | 1.37 | 0.2733 | 0.93636 |
| ERBB4 | rs16825005 (G/A) | 2 | 212304565 | -1.37 | 0.2735 | 0.93636 |
| ERBB4 | rs10188926 (G/A) | 2 | 213275304 | -1.85 | 0.2736 | 0.93636 |
| ERBB4 | rs7423708 (A/C) | 2 | 212645885 | -1.26 | 0.274 | 0.93636 |
| ERBB4 | rs10932377 (A/G) | 2 | 212362263 | -1.20 | 0.2741 | 0.93636 |
| ERBB4 | rs12616932 (A/C) | 2 | 212824999 | 1.37 | 0.2742 | 0.93636 |
| NRG1 | rs2466067 (A/G) | 8 | 32437994 | -1.26 | 0.2749 | 0.93636 |
| NRG1 | rs1965365 (G/A) | 8 | 31650080 | 1.36 | 0.2754 | 0.93636 |
| ERBB4 | rs13383863 (A/C) | 2 | 213284021 | -1.77 | 0.2763 | 0.93636 |
| NRG3 | rs72819813 (A/G) | 10 | 83775532 | 2.44 | 0.2764 | 0.93636 |
| ERBB4 | rs12620169 (G/A) | 2 | 212362328 | -1.30 | 0.2777 | 0.93636 |
| ERBB4 | rs10180494 (A/G) | 2 | 212796981 | -1.23 | 0.2777 | 0.93636 |
| ERBB4 | rs7574462 (A/G) | 2 | 212888988 | -1.24 | 0.2784 | 0.93636 |
| NRG3 | rs1333217 (G/A) | 10 | 84579830 | -1.30 | 0.279 | 0.93636 |
| TGFA | rs1851610 (G/A) | 2 | 70699159 | -1.18 | 0.2791 | 0.93636 |
| NRG3 | rs17099862 (G/A) | 10 | 84121782 | -1.50 | 0.2795 | 0.93636 |
| NRG3 | rs73311340 (A/C) | 10 | 84675910 | -2.46 | 0.2798 | 0.93636 |
| NRG3 | rs2225809 (G/A) | 10 | 84051375 | 1.21 | 0.2802 | 0.93636 |
| ERBB4 | rs17414466 (C/A) | 2 | 212796443 | -1.39 | 0.2802 | 0.93636 |
| EGFR | rs12669749 (C/A) | 7 | 55235804 | 1.76 | 0.2803 | 0.93636 |
| ERBB4 | rs1568519 (A/C) | 2 | 213006392 | -2.00 | 0.2815 | 0.93636 |
| BTC | rs10009801 (A/G) | 4 | 75694208 | 1.42 | 0.2817 | 0.93636 |
| NRG3 | rs10884065 (A/G) | 10 | 83794761 | -1.53 | 0.2817 | 0.93636 |
| NRG3 | rs17101193 (C/A) | 10 | 84744926 | 2.14 | 0.2822 | 0.93636 |
| NRG3 | rs17101196 (A/G) | 10 | 84745040 | 2.14 | 0.2822 | 0.93636 |
| ERBB4 | rs16848454 (A/G) | 2 | 213226366 | 2.29 | 0.2826 | 0.93636 |
| TGFA | rs7562947 (A/G) | 2 | 70758123 | -1.65 | 0.2833 | 0.93636 |
| EGFR | rs6969570 (A/G) | 7 | 55203838 | -1.69 | 0.2835 | 0.93636 |
| ERBB4 | rs6435707 (C/A) | 2 | 213386112 | 1.20 | 0.2835 | 0.93636 |
| EREG | rs1017734 (C/A) | 4 | 75253120 | 1.36 | 0.2852 | 0.93636 |
| NRG1 | rs2347501 (G/A) | 8 | 32294151 | 1.24 | 0.2857 | 0.93636 |

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|---|---|---|---|---|---|---|
| ERBB4 | rs114549502 (C/A) | 2 | 212782888 | 2.61 | 0.2858 | 0.93636 |
| NRG1 | rs9297186 (C/A) | 8 | 31960376 | -1.74 | 0.2859 | 0.93636 |
| ERBB4 | rs714393 (G/A) | 2 | 212698718 | -1.17 | 0.286 | 0.93636 |
| ERBB4 | rs1394788 (A/G) | 2 | 213211349 | 1.46 | 0.2867 | 0.93636 |
| ERBB4 | rs10166403 (A/G) | 2 | 213291199 | -1.66 | 0.2871 | 0.93636 |
| ERBB3 | rs10783779 (A/C) | 12 | 56491880 | -1.15 | 0.2877 | 0.93636 |
| NRG3 | rs12243071 (G/A) | 10 | 84675278 | 1.29 | 0.2878 | 0.93636 |
| NRG1 | rs17665212 (G/A) | 8 | 32448542 | -1.26 | 0.2881 | 0.93636 |
| NRG3 | rs17101130 (C/A) | 10 | 84698466 | 1.90 | 0.2884 | 0.93636 |
| ERBB4 | rs6733265 (A/G) | 2 | 212428192 | -1.79 | 0.2885 | 0.93636 |
| NRG3 | rs10883934 (A/G) | 10 | 83689496 | -1.25 | 0.2888 | 0.93636 |
| ERBB4 | rs979124 (A/G) | 2 | 213384978 | 1.18 | 0.2888 | 0.93636 |
| NRG3 | rs17099667 (A/G) | 10 | 84019116 | 2.33 | 0.2889 | 0.93636 |
| NRG1 | rs4373483 (A/G) | 8 | 32242079 | 1.13 | 0.289 | 0.93636 |
| NRG3 | rs17101125 (G/A) | 10 | 84693490 | 2.08 | 0.2894 | 0.93636 |
| NRG1 | rs2919370 (G/A) | 8 | 32476816 | 1.20 | 0.2895 | 0.93636 |
| NRG1 | rs13260545 (A/G) | 8 | 32417600 | 1.31 | 0.2897 | 0.93636 |
| ERBB4 | rs2118891 (A/G) | 2 | 212679643 | 2.29 | 0.2904 | 0.93636 |
| NRG1 | rs1481758 (G/A) | 8 | 32131798 | 1.39 | 0.2907 | 0.93636 |
| NRG2 | rs3756675 (G/A) | 5 | 139238893 | -1.61 | 0.2913 | 0.93636 |
| NRG3 | rs2248956 (G/A) | 10 | 84485323 | 1.19 | 0.2923 | 0.93636 |
| NRG1 | rs4733308 (G/A) | 8 | 32082436 | 1.16 | 0.2925 | 0.93636 |
| ERBB4 | rs11689581 (G/C) | 2 | 212598084 | 1.41 | 0.2927 | 0.93636 |
| NRG1 | rs17646307 (A/G) | 8 | 32398122 | 2.13 | 0.2928 | 0.93636 |
| NRG2 | rs6859144 (A/G) | 5 | 139237341 | -1.59 | 0.2941 | 0.93636 |
| NRG3 | rs12763193 (G/A) | 10 | 84740839 | -1.15 | 0.2942 | 0.93636 |
| ERBB4 | rs7578784 (A/G) | 2 | 212807645 | 1.15 | 0.2943 | 0.93636 |
| ERBB4 | rs17334842 (C/A) | 2 | 212407857 | -1.44 | 0.2947 | 0.93636 |
| ERBB4 | rs7598440 (G/A) | 2 | 212793198 | -1.19 | 0.2948 | 0.93636 |
| NRG3 | rs10883973 (A/G) | 10 | 83717632 | 1.67 | 0.2949 | 0.93636 |
| TGFA | rs58635657 (G/A) | 2 | 70729314 | -1.25 | 0.2964 | 0.93636 |
| NRG1 | rs1685102 (A/G) | 8 | 32199128 | 1.17 | 0.2966 | 0.93636 |
| NRG3 | rs11192840 (A/G) | 10 | 83935947 | 2.02 | 0.2967 | 0.93636 |
| NRG1 | rs4566990 (G/A) | 8 | 31573695 | 1.16 | 0.2971 | 0.93636 |
| NRG3 | rs1764072 (A/G) | 10 | 83964496 | 1.62 | 0.2972 | 0.93636 |
| EGFR | rs17289984 (G/A) | 7 | 55227510 | 1.67 | 0.2975 | 0.93636 |
| NRG3 | rs342365 (A/C) | 10 | 84500019 | 1.18 | 0.2983 | 0.93636 |
| NRG3 | rs79642569 (G/A) | 10 | 84511025 | 2.42 | 0.2983 | 0.93636 |
| NRG3 | rs1937970 (A/G) | 10 | 84223466 | -1.24 | 0.2991 | 0.93636 |
| ERBB4 | rs13417523 (G/A) | 2 | 213282779 | -1.69 | 0.2992 | 0.93636 |
| NRG3 | rs12413431 (A/G) | 10 | 84362174 | -1.77 | 0.2993 | 0.93636 |

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|---|---|---|---|---|---|---|
| EGFR | rs984654 (A/G) | 7 | 55144156 | -1.32 | 0.2995 | 0.93636 |
| ERBB4 | rs114304818 (A/G) | 2 | 212513114 | -2.22 | 0.3 | 0.93636 |
| ERBB2 | rs2643194 (A/G) | 17 | 37853048 | -1.15 | 0.3003 | 0.93636 |
| NRG2 | rs17118539 (A/G) | 5 | 139303341 | -1.41 | 0.3005 | 0.93636 |
| NRG1 | rs34998122 (G/A) | 8 | 32281229 | -1.15 | 0.3007 | 0.93636 |
| BTC | rs28576102 (A/G) | 4 | 75704143 | 1.36 | 0.3007 | 0.93636 |
| ERBB4 | rs10804195 (A/G) | 2 | 212327353 | -1.16 | 0.3009 | 0.93636 |
| NRG1 | rs73232416 (G/A) | 8 | 31833651 | 1.86 | 0.301 | 0.93636 |
| NRG1 | rs201848136 (A/C) | 8 | 32472569 | 1.18 | 0.3012 | 0.93636 |
| ERBB4 | rs1026882 (A/G) | 2 | 213387389 | 1.15 | 0.3015 | 0.93636 |
| ERBB4 | rs12694281 (G/A) | 2 | 213314038 | -1.13 | 0.3018 | 0.93636 |
| ERBB4 | rs6743565 (A/G) | 2 | 212381610 | 2.95 | 0.3028 | 0.93636 |
| ERBB4 | rs62186270 (A/G) | 2 | 213261454 | 2.20 | 0.3028 | 0.93636 |
| NRG1 | rs1383966 (A/C) | 8 | 32084692 | 1.26 | 0.303 | 0.93636 |
| NRG3 | rs9943299 (A/G) | 10 | 83640808 | 1.47 | 0.3031 | 0.93636 |
| EGFR | rs12535578 (G/A) | 7 | 55154586 | -1.28 | 0.3032 | 0.93636 |
| TGFA | rs2862851 (G/A) | 2 | 70712802 | -1.15 | 0.3033 | 0.93636 |
| NRG3 | rs75508896 (G/A) | 10 | 84668677 | 2.65 | 0.3034 | 0.93636 |
| ERBB4 | rs60630046 (A/G) | 2 | 213243275 | -1.85 | 0.3041 | 0.93636 |
| NRG3 | rs7078771 (G/A) | 10 | 84689060 | 2.00 | 0.3044 | 0.93636 |
| ERBB4 | rs13018333 (G/A) | 2 | 212546810 | 1.78 | 0.305 | 0.93636 |
| NRG3 | rs7079963 (A/C) | 10 | 84666953 | 1.24 | 0.3053 | 0.93636 |
| NRG1 | rs7005124 (A/C) | 8 | 32167730 | -1.15 | 0.3062 | 0.93636 |
| NRG3 | rs1474 (G/C) | 10 | 83974642 | -1.13 | 0.3062 | 0.93636 |
| ERBB4 | rs6725395 (A/C) | 2 | 212375386 | 1.10 | 0.3062 | 0.93636 |
| NRG1 | rs6996957 (G/A) | 8 | 32306984 | 1.14 | 0.3066 | 0.93636 |
| NRG1 | rs2439322 (A/G) | 8 | 32520472 | 1.09 | 0.3072 | 0.93636 |
| NRG3 | rs11191834 (G/C) | 10 | 83688360 | -1.32 | 0.3073 | 0.93636 |
| NRG1 | rs12056821 (A/C) | 8 | 31966653 | 1.27 | 0.3077 | 0.93636 |
| NRG1 | rs1685101 (G/A) | 8 | 32197913 | -1.76 | 0.3078 | 0.93636 |
| NRG1 | rs16878370 (G/A) | 8 | 31719490 | -1.50 | 0.3084 | 0.93636 |
| ERBB2 | rs2934971 (A/C) | 17 | 37854507 | -1.13 | 0.3086 | 0.93636 |
| NRG1 | rs35767550 (C/A) | 8 | 31507844 | -1.35 | 0.3098 | 0.93636 |
| ERBB4 | rs11892564 (A/G) | 2 | 213226544 | 1.29 | 0.3098 | 0.93636 |
| ERBB4 | rs13030304 (C/A) | 2 | 212283146 | 1.39 | 0.3108 | 0.93636 |
| NRG3 | rs12416668 (A/G) | 10 | 83655048 | -2.13 | 0.3113 | 0.93636 |
| ERBB4 | rs13032114 (C/A) | 2 | 212578978 | -1.10 | 0.3113 | 0.93636 |
| ERBB4 | rs2204853 (A/G) | 2 | 213316826 | -1.52 | 0.3114 | 0.93636 |
| ERBB4 | rs35248812 (A/C) | 2 | 212567389 | 1.48 | 0.3124 | 0.93636 |
| ERBB4 | rs7573807 (C/A) | 2 | 212687864 | 1.34 | 0.3124 | 0.93636 |
| ERBB4 | rs2289086 (A/G) | 2 | 212285103 | -1.12 | 0.3127 | 0.93636 |

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|---|---|---|---|---|---|---|
| ERBB4 | rs4673618 (G/A) | 2 | 212310843 | 1.17 | 0.3127 | 0.93636 |
| NRG3 | rs926929 (G/A) | 10 | 83847988 | -1.37 | 0.3131 | 0.93636 |
| NRG4 | rs201770710 (A/C) | 15 | 76246609 | 1.32 | 0.3132 | 0.93636 |
| NRG1 | rs2919391 (C/A) | 8 | 32525041 | -1.47 | 0.3136 | 0.93636 |
| ERBB4 | rs73087372 (G/A) | 2 | 212895680 | 1.97 | 0.3138 | 0.93636 |
| ERBB4 | rs979042 (G/A) | 2 | 213146827 | 1.15 | 0.3139 | 0.93636 |
| NRG2 | rs197197 (A/C) | 5 | 139348915 | -1.11 | 0.3149 | 0.93636 |
| NRG3 | rs7914963 (A/G) | 10 | 83732122 | 2.45 | 0.3151 | 0.93636 |
| ERBB4 | rs73076904 (G/A) | 2 | 212439576 | 2.90 | 0.3151 | 0.93636 |
| ERBB4 | rs17416620 (G/A) | 2 | 213033533 | -1.64 | 0.3154 | 0.93636 |
| NRG1 | rs1947734 (G/A) | 8 | 31937903 | -1.16 | 0.3155 | 0.93636 |
| EGF | rs11569017 (T/A) | 4 | 110902111 | -2.39 | 0.3156 | 0.93636 |
| ERBB4 | rs1836724 (A/G) | 2 | 212244952 | 1.10 | 0.316 | 0.93636 |
| NRG3 | rs1333211 (A/G) | 10 | 84545849 | -1.87 | 0.3163 | 0.93636 |
| ERBB4 | rs13387495 (A/G) | 2 | 213285057 | -1.77 | 0.3167 | 0.93636 |
| ERBB4 | rs13401244 (A/G) | 2 | 213125563 | 2.62 | 0.3168 | 0.93636 |
| NRG1 | rs12678940 (A/G) | 8 | 31958544 | 1.25 | 0.3169 | 0.93636 |
| EGFR | rs17172430 (G/A) | 7 | 55122650 | 1.57 | 0.3174 | 0.93636 |
| NRG1 | rs13271344 (A/G) | 8 | 31919990 | -1.13 | 0.3181 | 0.93636 |
| ERBB4 | rs6718189 (A/G) | 2 | 213264247 | 1.09 | 0.3181 | 0.93636 |
| NRG1 | rs7827456 (G/A) | 8 | 31888494 | -1.14 | 0.3187 | 0.93636 |
| ERBB4 | rs6435667 (C/A) | 2 | 212627805 | 2.33 | 0.3187 | 0.93636 |
| EGFR | rs17335808 (A/G) | 7 | 55112112 | 2.09 | 0.3191 | 0.93636 |
| ERBB4 | rs839539 (A/C) | 2 | 212811801 | -1.54 | 0.3193 | 0.93636 |
| NRG1 | rs10096770 (A/G) | 8 | 32325220 | -1.14 | 0.3198 | 0.93636 |
| NRG3 | rs342393 (A/G) | 10 | 84515820 | 1.22 | 0.3202 | 0.93636 |
| NRG3 | rs12783350 (A/G) | 10 | 84530063 | 1.18 | 0.3206 | 0.93636 |
| NRG3 | rs12411365 (G/A) | 10 | 83837703 | 1.08 | 0.3215 | 0.93636 |
| NRG1 | rs10097263 (G/A) | 8 | 32071743 | 1.08 | 0.3217 | 0.93636 |
| ERBB4 | rs13409719 (C/A) | 2 | 212814557 | -1.73 | 0.3224 | 0.93636 |
| BTC | rs6813883 (A/C) | 4 | 75717808 | -1.07 | 0.324 | 0.93636 |
| NRG1 | rs10503907 (A/G) | 8 | 32172010 | -1.13 | 0.3243 | 0.93636 |
| EGFR | rs12668175 (A/C) | 7 | 55178579 | 2.22 | 0.3245 | 0.93636 |
| ERBB4 | rs3791704 (A/G) | 2 | 212284621 | -1.18 | 0.3247 | 0.93636 |
| ERBB4 | rs12988214 (G/A) | 2 | 212650241 | 1.43 | 0.3248 | 0.93636 |
| NRG1 | rs62500194 (A/G) | 8 | 32403057 | -1.43 | 0.3249 | 0.93636 |
| ERBB4 | rs201832813 (G/A) | 2 | 213218533 | 1.33 | 0.3253 | 0.93636 |
| NRG1 | rs394738 (A/G) | 8 | 31807295 | 2.65 | 0.3255 | 0.93636 |
| ERBB4 | rs2371444 (A/G) | 2 | 212975953 | -1.13 | 0.3257 | 0.93636 |
| NRG3 | rs168200 (A/G) | 10 | 84604557 | 1.46 | 0.3258 | 0.93636 |
| ERBB4 | rs10176432 (G/A) | 2 | 212861363 | 1.43 | 0.3261 | 0.93636 |

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|---|---|---|---|---|---|---|
| ERBB4 | rs12104833 (G/A) | 2 | 212965276 | 1.33 | 0.3262 | 0.93636 |
| NRG1 | rs35110336 (A/G) | 8 | 32169540 | -1.10 | 0.3263 | 0.93636 |
| NRG1 | rs17624592 (A/G) | 8 | 32122424 | -2.25 | 0.3271 | 0.93636 |
| ERBB4 | rs12694267 (G/A) | 2 | 213069051 | 1.03 | 0.3277 | 0.93636 |
| BTC | rs2864668 (A/G) | 4 | 75717660 | -1.06 | 0.3285 | 0.93636 |
| NRG3 | rs7091020 (G/A) | 10 | 83796920 | -2.14 | 0.3286 | 0.93636 |
| NRG1 | rs57941555 (A/C) | 8 | 32024269 | -2.28 | 0.33 | 0.93636 |
| NRG1 | rs59501354 (A/G) | 8 | 32190403 | 1.71 | 0.33 | 0.93636 |
| EGFR | rs17290225 (G/A) | 7 | 55238253 | -2.32 | 0.3302 | 0.93636 |
| NRG1 | rs7002024 (A/G) | 8 | 32079552 | 1.16 | 0.3307 | 0.93636 |
| ERBB4 | rs7563378 (C/A) | 2 | 212846898 | -1.23 | 0.3314 | 0.93636 |
| NRG1 | rs2062055 (A/G) | 8 | 31743113 | -1.15 | 0.3317 | 0.93636 |
| ERBB4 | rs1857796 (A/G) | 2 | 213164837 | 1.48 | 0.3317 | 0.93636 |
| ERBB4 | rs12464239 (G/A) | 2 | 212896904 | 1.68 | 0.3325 | 0.93636 |
| ERBB4 | rs7564926 (A/G) | 2 | 212961992 | 1.31 | 0.3326 | 0.93636 |
| NRG3 | rs193178 (C/A) | 10 | 84583413 | 1.29 | 0.3328 | 0.93636 |
| ERBB4 | rs6435628 (A/G) | 2 | 212319043 | -1.38 | 0.333 | 0.93636 |
| NRG1 | rs1383895 (A/G) | 8 | 31703542 | -1.07 | 0.3343 | 0.93636 |
| NRG3 | rs12249088 (G/A) | 10 | 83922529 | 2.19 | 0.3346 | 0.93636 |
| NRG3 | rs1339797 (A/C) | 10 | 84404982 | 1.18 | 0.335 | 0.93636 |
| NRG3 | rs7342133 (G/A) | 10 | 83790207 | 1.01 | 0.3351 | 0.93636 |
| ERBB4 | rs35633854 (A/G) | 2 | 212421476 | -1.22 | 0.3355 | 0.93636 |
| NRG1 | rs11774962 (A/G) | 8 | 32256384 | -1.01 | 0.336 | 0.93636 |
| NRG1 | rs7844483 (A/G) | 8 | 32263846 | 1.06 | 0.3361 | 0.93636 |
| NRG2 | rs7723119 (A/G) | 5 | 139411703 | -1.09 | 0.3362 | 0.93636 |
| NRG3 | rs11195990 (A/G) | 10 | 84557079 | 2.45 | 0.3367 | 0.93636 |
| ERBB4 | rs16847425 (G/A) | 2 | 212853298 | -2.12 | 0.3368 | 0.93636 |
| TGFA | rs3771475 (A/G) | 2 | 70769328 | -1.70 | 0.337 | 0.93636 |
| NRG3 | rs6584400 (G/A) | 10 | 83656526 | 1.36 | 0.3373 | 0.93636 |
| ERBB4 | rs16848535 (C/A) | 2 | 213292130 | 2.08 | 0.3381 | 0.93636 |
| ERBB4 | rs80044823 (A/G) | 2 | 212887517 | -2.41 | 0.3385 | 0.93636 |
| NRG3 | rs12358815 (C/A) | 10 | 83668325 | -1.74 | 0.3391 | 0.93636 |
| NRG3 | rs10883951 (G/A) | 10 | 83697630 | -1.12 | 0.3391 | 0.93636 |
| NRG1 | rs7006475 (A/C) | 8 | 32353970 | 1.04 | 0.3395 | 0.93636 |
| NRG2 | rs3777106 (A/G) | 5 | 139247971 | -1.38 | 0.3395 | 0.93636 |
| NRG3 | rs11195073 (A/G) | 10 | 84333628 | -1.63 | 0.34 | 0.93636 |
| NRG1 | rs13279876 (A/G) | 8 | 31638990 | -1.40 | 0.3401 | 0.93636 |
| NRG1 | rs6986789 (G/A) | 8 | 32250029 | -1.02 | 0.3402 | 0.93636 |
| ERBB4 | rs13408475 (G/A) | 2 | 212379238 | -1.22 | 0.3406 | 0.93636 |
| NRG1 | rs10954821 (G/A) | 8 | 31898990 | -1.08 | 0.341 | 0.93636 |
| NRG3 | rs12358632 (G/A) | 10 | 84111459 | -2.09 | 0.3411 | 0.93636 |

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|---|---|---|---|---|---|---|
| NRG1 | rs7815226 (A/G) | 8 | 31964189 | 1.08 | 0.3412 | 0.93636 |
| ERBB4 | rs17337014 (A/G) | 2 | 212864752 | 1.77 | 0.3413 | 0.93636 |
| ERBB4 | rs2135159 (G/A) | 2 | 213214465 | 1.53 | 0.3416 | 0.93636 |
| ERBB4 | rs10175279 (G/A) | 2 | 212859518 | -1.08 | 0.342 | 0.93636 |
| NRG1 | rs16879067 (G/A) | 8 | 32121424 | 1.33 | 0.3432 | 0.93636 |
| NRG1 | rs4733373 (A/G) | 8 | 32605583 | 1.47 | 0.3432 | 0.93636 |
| NRG2 | rs4404729 (G/A) | 5 | 139407044 | -1.07 | 0.3434 | 0.93636 |
| NRG4 | rs10444808 (G/A) | 15 | 76272822 | 2.15 | 0.3435 | 0.93636 |
| ERBB4 | rs11898476 (G/A) | 2 | 212397409 | 1.75 | 0.3442 | 0.93636 |
| ERBB4 | rs10497966 (C/A) | 2 | 213113079 | -1.38 | 0.3443 | 0.93636 |
| NRG3 | rs11195057 (A/G) | 10 | 84329093 | 1.30 | 0.3444 | 0.93636 |
| EGFR | rs11772801 (A/C) | 7 | 55204196 | 2.09 | 0.3459 | 0.93636 |
| NRG1 | rs13259768 (A/G) | 8 | 31579119 | -1.11 | 0.3463 | 0.93636 |
| NRG1 | rs72612103 (G/A) | 8 | 31969872 | -1.69 | 0.3463 | 0.93636 |
| NRG1 | rs73234156 (A/G) | 8 | 32425102 | 2.00 | 0.3466 | 0.93636 |
| NRG3 | rs11192849 (A/G) | 10 | 83938041 | 1.84 | 0.3468 | 0.93636 |
| ERBB4 | rs10205863 (A/T) | 2 | 213237665 | -1.69 | 0.3468 | 0.93636 |
| NRG3 | rs17682831 (A/G) | 10 | 84497360 | 1.33 | 0.3474 | 0.93636 |
| NRG3 | rs1649952 (A/G) | 10 | 83920935 | 1.16 | 0.3475 | 0.93636 |
| ERBB4 | rs200382732 (G/A) | 2 | 212243614 | 1.03 | 0.349 | 0.93636 |
| NRG1 | rs4602844 (G/A) | 8 | 32451898 | -1.51 | 0.3495 | 0.93636 |
| ERBB4 | rs2135161 (A/G) | 2 | 213136747 | -1.46 | 0.3499 | 0.93636 |
| TGFA | rs4852604 (A/G) | 2 | 70694437 | -1.06 | 0.35 | 0.93636 |
| NRG3 | rs4933836 (G/A) | 10 | 84137873 | -1.06 | 0.35 | 0.93636 |
| ERBB4 | rs10192485 (A/G) | 2 | 212556137 | -1.02 | 0.35 | 0.93636 |
| NRG1 | rs78672160 (G/A) | 8 | 32509782 | -2.01 | 0.3503 | 0.93636 |
| NRG3 | rs12414020 (C/A) | 10 | 83978303 | -1.73 | 0.3506 | 0.93636 |
| EGFR | rs6950826 (A/G) | 7 | 55223176 | -0.98 | 0.3511 | 0.93636 |
| NRG1 | rs61156846 (A/G) | 8 | 32467567 | -2.48 | 0.3515 | 0.93636 |
| NRG3 | rs17760956 (A/C) | 10 | 84690341 | -1.01 | 0.3515 | 0.93636 |
| NRG3 | rs10749058 (G/A) | 10 | 84401508 | -1.06 | 0.3522 | 0.93636 |
| ERBB4 | rs4302167 (A/C) | 2 | 212333423 | 1.16 | 0.3528 | 0.93636 |
| EGF | rs3733625 (A/G) | 4 | 110933004 | -1.98 | 0.3532 | 0.93636 |
| NRG3 | rs7079037 (G/A) | 10 | 84535582 | 1.07 | 0.3536 | 0.93636 |
| NRG1 | rs73582342 (A/G) | 8 | 32187756 | 1.63 | 0.3537 | 0.93636 |
| ERBB4 | rs12052282 (A/C) | 2 | 213045240 | 1.00 | 0.354 | 0.93636 |
| NRG1 | rs7000397 (A/G) | 8 | 32383863 | -1.05 | 0.3542 | 0.93636 |
| NRG1 | rs2919384 (A/G) | 8 | 32559943 | 1.10 | 0.3559 | 0.93636 |
| NRG1 | rs17713685 (A/G) | 8 | 32261582 | -1.10 | 0.356 | 0.93636 |
| EGFR | rs17337023 (T/A) | 7 | 55238874 | -1.05 | 0.3563 | 0.93636 |
| ERBB4 | rs6722322 (G/A) | 2 | 212604921 | 1.07 | 0.3563 | 0.93636 |

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|---|---|---|---|---|---|---|
| NRG3 | rs4933837 (G/A) | 10 | 84242262 | -1.10 | 0.3568 | 0.93636 |
| ERBB4 | rs6738304 (G/A) | 2 | 212989308 | -1.00 | 0.3568 | 0.93636 |
| ERBB4 | rs1851179 (G/A) | 2 | 212399084 | 1.07 | 0.3578 | 0.93636 |
| NRG1 | rs4543501 (A/C) | 8 | 32496505 | 1.06 | 0.3579 | 0.93636 |
| ERBB4 | rs61424783 (A/C) | 2 | 213084876 | 0.96 | 0.3584 | 0.93636 |
| ERBB4 | rs9288448 (C/A) | 2 | 213085697 | 0.96 | 0.3584 | 0.93636 |
| ERBB4 | rs4292044 (A/G) | 2 | 212761152 | 1.99 | 0.3585 | 0.93636 |
| NRG1 | rs4733346 (G/A) | 8 | 32369226 | 1.58 | 0.3591 | 0.93636 |
| ERBB4 | rs6755027 (G/A) | 2 | 213053239 | 0.99 | 0.3594 | 0.93636 |
| NRG1 | rs12548779 (A/G) | 8 | 31912250 | -1.00 | 0.3599 | 0.93636 |
| ERBB4 | rs10174916 (A/G) | 2 | 212439695 | -1.21 | 0.3601 | 0.93636 |
| NRG1 | rs16878368 (C/A) | 8 | 31718367 | 1.58 | 0.3608 | 0.93636 |
| ERBB4 | rs71422758 (A/G) | 2 | 212652224 | -1.09 | 0.3608 | 0.93636 |
| NRG1 | rs10093107 (G/A) | 8 | 32026449 | -1.02 | 0.3611 | 0.93636 |
| NRG3 | rs2820100 (C/A) | 10 | 84491173 | 1.04 | 0.3611 | 0.93636 |
| NRG1 | rs1542517 (G/A) | 8 | 31959943 | -1.65 | 0.3612 | 0.93636 |
| NRG1 | rs1158105 (A/C) | 8 | 32130916 | 1.19 | 0.3616 | 0.93636 |
| NRG3 | rs10884019 (G/A) | 10 | 83757021 | 1.57 | 0.3616 | 0.93636 |
| ERBB4 | rs10932384 (A/C) | 2 | 212409848 | -1.01 | 0.3623 | 0.93636 |
| NRG1 | rs1487145 (A/G) | 8 | 32134461 | -1.07 | 0.3625 | 0.93636 |
| NRG2 | rs265165 (A/G) | 5 | 139353723 | 1.05 | 0.3638 | 0.93636 |
| EGFR | rs2017000 (A/G) | 7 | 55242609 | -1.12 | 0.3646 | 0.93636 |
| NRG1 | rs16878394 (C/A) | 8 | 31727061 | -2.39 | 0.3647 | 0.93636 |
| NRG3 | rs3740350 (C/A) | 10 | 84151515 | -1.07 | 0.365 | 0.93636 |
| ERBB4 | rs16848380 (G/A) | 2 | 213194322 | 1.72 | 0.3654 | 0.93636 |
| ERBB4 | rs10192302 (A/C) | 2 | 212408179 | 1.03 | 0.3657 | 0.93636 |
| NRG1 | rs13259346 (A/G) | 8 | 32511006 | -1.00 | 0.366 | 0.93636 |
| NRG3 | rs17099306 (A/C) | 10 | 83823289 | -1.60 | 0.3663 | 0.93636 |
| NRG1 | rs1503488 (G/A) | 8 | 31691010 | 1.10 | 0.3664 | 0.93636 |
| EGFR | rs17289099 (A/G) | 7 | 55123214 | 1.86 | 0.3664 | 0.93636 |
| NRG3 | rs72829364 (G/A) | 10 | 84431429 | 1.12 | 0.3668 | 0.93636 |
| ERBB4 | rs6725181 (G/A) | 2 | 212530466 | 1.40 | 0.3674 | 0.93636 |
| NRG3 | rs7075400 (A/G) | 10 | 84131104 | -1.25 | 0.3675 | 0.93636 |
| NRG3 | rs1335624 (A/C) | 10 | 84440148 | 1.03 | 0.3678 | 0.93636 |
| NRG1 | rs10107049 (G/A) | 8 | 32035502 | -1.00 | 0.3683 | 0.93636 |
| NRG1 | rs4733327 (C/A) | 8 | 32254397 | -0.96 | 0.3683 | 0.93636 |
| NRG1 | rs1481761 (G/A) | 8 | 32008253 | -1.01 | 0.3686 | 0.93636 |
| EGFR | rs17172448 (G/A) | 7 | 55207220 | -1.98 | 0.369 | 0.93636 |
| NRG1 | rs1471387 (G/A) | 8 | 31935612 | -1.00 | 0.3691 | 0.93636 |
| NRG1 | rs10092307 (A/G) | 8 | 32332633 | 0.98 | 0.3695 | 0.93636 |
| NRG3 | rs7895428 (A/G) | 10 | 84122467 | -1.10 | 0.3705 | 0.93636 |

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|---|---|---|---|---|---|---|
| NRG3 | rs9971107 (C/A) | 10 | 84122925 | -1.10 | 0.3705 | 0.93636 |
| NRG3 | rs34499222 (G/A) | 10 | 84223349 | 1.88 | 0.3705 | 0.93636 |
| NRG1 | rs7009043 (A/G) | 8 | 31524553 | -0.98 | 0.3707 | 0.93636 |
| NRG1 | rs1081064 (C/A) | 8 | 31500207 | -1.08 | 0.3708 | 0.93636 |
| EGFR | rs6593206 (A/C) | 7 | 55180110 | -1.02 | 0.371 | 0.93636 |
| NRG2 | rs2060296 (G/A) | 5 | 139323257 | 1.02 | 0.371 | 0.93636 |
| ERBB4 | rs17413728 (A/G) | 2 | 212508093 | -1.87 | 0.3712 | 0.93636 |
| NRG3 | rs73320353 (A/G) | 10 | 83896099 | 1.97 | 0.3715 | 0.93636 |
| NRG1 | rs10097555 (A/G) | 8 | 32346295 | 0.97 | 0.3719 | 0.93636 |
| NRG3 | rs17099627 (A/G) | 10 | 83978695 | -1.64 | 0.3719 | 0.93636 |
| EGFR | rs11773818 (G/A) | 7 | 55123968 | -1.13 | 0.3726 | 0.93692 |
| NRG1 | rs11774564 (A/G) | 8 | 32316935 | 1.38 | 0.3729 | 0.93692 |
| BTC | rs28517341 (A/G) | 4 | 75700367 | 1.44 | 0.3735 | 0.93698 |
| NRG3 | rs2065538 (A/G) | 10 | 84537367 | 1.02 | 0.3738 | 0.93698 |
| ERBB4 | rs2371315 (C/A) | 2 | 212393907 | -1.02 | 0.3751 | 0.93698 |
| NRG3 | rs519003 (A/G) | 10 | 84598255 | 1.07 | 0.3754 | 0.93698 |
| NRG1 | rs4733108 (G/A) | 8 | 31947675 | -0.99 | 0.377 | 0.93698 |
| NRG3 | rs11192921 (G/A) | 10 | 83952106 | -0.98 | 0.3771 | 0.93698 |
| ERBB4 | rs7562782 (A/G) | 2 | 213192268 | 1.09 | 0.3771 | 0.93698 |
| NRG3 | rs10884648 (A/G) | 10 | 84141592 | -1.04 | 0.3772 | 0.93698 |
| TGFA | rs3732247 (G/A) | 2 | 70692557 | -1.16 | 0.3777 | 0.93698 |
| ERBB4 | rs114609408 (A/C) | 2 | 213143171 | -1.99 | 0.378 | 0.93698 |
| NRG3 | rs11196259 (A/G) | 10 | 84620787 | 1.20 | 0.3781 | 0.93698 |
| ERBB4 | rs16847218 (G/A) | 2 | 212795233 | 1.62 | 0.3788 | 0.93698 |
| NRG1 | rs6468104 (A/C) | 8 | 32303612 | 0.98 | 0.379 | 0.93698 |
| NRG1 | rs12677942 (G/A) | 8 | 31539942 | -1.18 | 0.38 | 0.93698 |
| ERBB4 | rs72946542 (A/G) | 2 | 212577157 | -1.70 | 0.3801 | 0.93698 |
| NRG1 | rs11777461 (G/A) | 8 | 32364970 | 1.53 | 0.3803 | 0.93698 |
| EGFR | rs12535226 (A/T) | 7 | 55156419 | -0.92 | 0.3809 | 0.93698 |
| NRG3 | rs1335625 (A/G) | 10 | 84479555 | -0.94 | 0.3811 | 0.93698 |
| NRG3 | rs72177668 (A/G) | 10 | 83857812 | -1.07 | 0.3816 | 0.93698 |
| NRG1 | rs2439279 (A/G) | 8 | 32466409 | 1.01 | 0.3821 | 0.93698 |
| ERBB4 | rs7426206 (A/G) | 2 | 212984455 | -1.01 | 0.3825 | 0.93698 |
| NRG1 | rs13260061 (A/C) | 8 | 31585000 | -1.03 | 0.3828 | 0.93698 |
| NRG1 | rs6468096 (A/G) | 8 | 32165687 | -0.97 | 0.3832 | 0.93698 |
| ERBB4 | rs35785239 (A/G) | 2 | 212355255 | -0.96 | 0.3835 | 0.93698 |
| NRG1 | rs1481763 (C/A) | 8 | 31993810 | -0.98 | 0.3847 | 0.93698 |
| ERBB4 | rs12470836 (G/A) | 2 | 213209008 | 1.40 | 0.3849 | 0.93698 |
| NRG1 | rs9642725 (A/C) | 8 | 32147878 | 0.93 | 0.3855 | 0.93698 |
| ERBB2 | rs2952155 (G/A) | 17 | 37861718 | -1.00 | 0.387 | 0.93698 |
| NRG3 | rs7477796 (G/A) | 10 | 84538744 | 1.00 | 0.3875 | 0.93698 |

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|---|---|---|---|---|---|---|
| HBEGF | rs2237077 (A/G) | 5 | 139720400 | -1.04 | 0.3875 | 0.93698 |
| NRG3 | rs72197632 (G/A) | 10 | 83781542 | -1.02 | 0.3881 | 0.93698 |
| NRG1 | rs17624997 (G/A) | 8 | 32137649 | 1.44 | 0.3892 | 0.93698 |
| TGFA | rs12473408 (A/G) | 2 | 70776384 | -0.93 | 0.3894 | 0.93698 |
| NRG3 | rs2245896 (A/G) | 10 | 84463662 | 0.97 | 0.3901 | 0.93698 |
| ERBB4 | rs1357127 (G/A) | 2 | 212948287 | -1.47 | 0.3903 | 0.93698 |
| NRG3 | rs72827304 (A/C) | 10 | 84022385 | -1.23 | 0.391 | 0.93698 |
| ERBB4 | rs13019783 (A/C) | 2 | 212538415 | 1.59 | 0.3911 | 0.93698 |
| NRG2 | rs264350 (A/G) | 5 | 139362321 | 0.95 | 0.3912 | 0.93698 |
| NRG3 | rs584702 (A/C) | 10 | 84315531 | 1.23 | 0.3913 | 0.93698 |
| TGFA | rs432203 (A/C) | 2 | 70764688 | 0.94 | 0.3924 | 0.93698 |
| NRG3 | rs12769829 (G/A) | 10 | 83958312 | -0.94 | 0.3925 | 0.93698 |
| ERBB4 | rs7576673 (A/G) | 2 | 212423302 | -1.18 | 0.3928 | 0.93698 |
| NRG3 | rs7923865 (A/G) | 10 | 84461072 | -1.07 | 0.3932 | 0.93698 |
| NRG1 | rs9801737 (G/A) | 8 | 31912379 | -0.93 | 0.3933 | 0.93698 |
| ERBB4 | rs6719517 (G/A) | 2 | 212979399 | -0.93 | 0.3933 | 0.93698 |
| NRG1 | rs1842637 (A/G) | 8 | 31722926 | -1.25 | 0.3934 | 0.93698 |
| NRG3 | rs4586096 (A/C) | 10 | 84430088 | 0.95 | 0.3934 | 0.93698 |
| NRG1 | rs327416 (G/A) | 8 | 31826219 | -1.27 | 0.3941 | 0.93698 |
| NRG3 | rs10884943 (C/A) | 10 | 84328619 | -1.46 | 0.3944 | 0.93698 |
| ERBB4 | rs6753466 (A/G) | 2 | 213248130 | 0.94 | 0.3957 | 0.93698 |
| MUC4 | rs2246901 (A/C) | 3 | 195489009 | 0.95 | 0.3958 | 0.93698 |
| ERBB4 | rs34706082 (G/A) | 2 | 212712046 | 1.49 | 0.3958 | 0.93698 |
| NRG3 | rs7084937 (G/A) | 10 | 83993404 | 0.97 | 0.3972 | 0.93698 |
| NRG1 | rs10808318 (A/G) | 8 | 31919211 | -0.96 | 0.3974 | 0.93698 |
| MUC4 | rs12630536 (G/A) | 3 | 195480414 | 0.97 | 0.3974 | 0.93698 |
| ERBB4 | rs60268595 (G/A) | 2 | 212819976 | 2.28 | 0.3975 | 0.93698 |
| EGFR | rs1554718 (G/A) | 7 | 55255963 | 0.93 | 0.398 | 0.93698 |
| NRG2 | rs56354014 (G/A) | 5 | 139260292 | -2.10 | 0.3981 | 0.93698 |
| ERBB4 | rs1948877 (A/G) | 2 | 213219641 | 0.99 | 0.3981 | 0.93698 |
| TGFA | rs77291713 (G/A) | 2 | 70720450 | 2.06 | 0.3983 | 0.93698 |
| NRG1 | rs16878885 (G/A) | 8 | 32019682 | 1.06 | 0.3988 | 0.93698 |
| NRG1 | rs4624987 (G/A) | 8 | 32396704 | 1.85 | 0.3988 | 0.93698 |
| EGFR | rs4947491 (G/A) | 7 | 55169291 | 0.97 | 0.3991 | 0.93698 |
| ERBB4 | rs10932432 (G/A) | 2 | 213164193 | 0.98 | 0.3991 | 0.93698 |
| ERBB4 | rs6435661 (A/G) | 2 | 212572127 | 0.98 | 0.3993 | 0.93698 |
| BTC | rs72867579 (A/G) | 4 | 75698204 | 1.36 | 0.3999 | 0.93698 |
| ERBB4 | rs6435663 (G/A) | 2 | 212575671 | 0.97 | 0.4004 | 0.93698 |
| NRG1 | rs1386440 (G/A) | 8 | 32177531 | -0.93 | 0.4006 | 0.93698 |
| ERBB4 | rs6707285 (C/A) | 2 | 213067749 | 0.89 | 0.4009 | 0.93698 |
| ERBB4 | rs10204324 (A/G) | 2 | 212984466 | -0.91 | 0.401 | 0.93698 |

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|---|---|---|---|---|---|---|
| NRG1 | rs1383961 (C/A) | 8 | 32098055 | 0.98 | 0.4015 | 0.93698 |
| ERBB4 | rs1505353 (C/A) | 2 | 213203057 | -0.95 | 0.4017 | 0.93698 |
| MUC4 | rs3096333 (A/G) | 3 | 195496792 | 0.90 | 0.4023 | 0.93698 |
| NRG1 | rs2439282 (G/A) | 8 | 32462701 | -1.33 | 0.4024 | 0.93698 |
| ERBB4 | rs76812495 (A/G) | 2 | 212882485 | -2.09 | 0.4026 | 0.93698 |
| NRG3 | rs915345 (A/G) | 10 | 84459894 | 0.92 | 0.4029 | 0.93698 |
| NRG3 | rs8421 (A/G) | 10 | 84746621 | -0.93 | 0.4045 | 0.93698 |
| ERBB4 | rs3883913 (A/C) | 2 | 212566034 | 0.89 | 0.4047 | 0.93698 |
| TGFA | rs4852608 (A/C) | 2 | 70698531 | 0.92 | 0.4048 | 0.93698 |
| NRG3 | rs12776248 (A/C) | 10 | 84490409 | 1.18 | 0.4049 | 0.93698 |
| BTC | rs6532366 (C/A) | 4 | 75683103 | -1.47 | 0.4055 | 0.93698 |
| NRG1 | rs2919390 (A/C) | 8 | 32526955 | -0.90 | 0.4056 | 0.93698 |
| ERBB4 | rs3748962 (A/G) | 2 | 212251864 | -0.97 | 0.4065 | 0.93698 |
| NRG3 | rs2068877 (A/G) | 10 | 83651520 | -1.71 | 0.4066 | 0.93698 |
| ERBB4 | rs72931605 (A/G) | 2 | 212693775 | -1.42 | 0.407 | 0.93698 |
| HBEGF | rs13385 (G/A) | 5 | 139712878 | 1.10 | 0.4072 | 0.93698 |
| NRG1 | rs7839597 (A/G) | 8 | 32188594 | -1.03 | 0.4074 | 0.93698 |
| NRG3 | rs645769 (G/A) | 10 | 84263757 | -1.02 | 0.4076 | 0.93698 |
| NRG1 | rs17665441 (C/A) | 8 | 32455027 | -0.94 | 0.4084 | 0.93698 |
| NRG1 | rs7001942 (C/A) | 8 | 32287232 | 0.98 | 0.4086 | 0.93698 |
| NRG3 | rs72825440 (G/A) | 10 | 83861185 | -1.74 | 0.4086 | 0.93698 |
| NRG2 | rs11955691 (G/A) | 5 | 139313021 | -1.16 | 0.4093 | 0.93698 |
| MUC4 | rs729593 (C/A) | 3 | 195517909 | 1.30 | 0.4095 | 0.93698 |
| ERBB4 | rs10932426 (A/G) | 2 | 213073599 | 0.99 | 0.41 | 0.93698 |
| ERBB4 | rs7605095 (A/C) | 2 | 212308833 | -1.07 | 0.4107 | 0.93698 |
| EGFR | rs4947490 (G/A) | 7 | 55160538 | 0.92 | 0.4109 | 0.93698 |
| TGFA | rs77982178 (C/A) | 2 | 70768922 | 0.90 | 0.4115 | 0.93698 |
| ERBB4 | rs72946572 (G/A) | 2 | 212585204 | 1.61 | 0.4127 | 0.93698 |
| EGF | rs2298999 (G/A) | 4 | 110911907 | 0.91 | 0.4129 | 0.93698 |
| ERBB4 | rs2128322 (C/A) | 2 | 213384313 | -1.37 | 0.4129 | 0.93698 |
| NRG3 | rs7902158 (A/G) | 10 | 83723457 | 1.01 | 0.4134 | 0.93698 |
| NRG1 | rs13279596 (A/G) | 8 | 31736024 | -0.97 | 0.4136 | 0.93698 |
| NRG3 | rs1764076 (A/G) | 10 | 83969034 | 1.71 | 0.4139 | 0.93698 |
| ERBB4 | rs7579502 (G/A) | 2 | 212986680 | -0.88 | 0.4144 | 0.93698 |
| NRG1 | rs16879099 (A/G) | 8 | 32137313 | -1.61 | 0.4152 | 0.93698 |
| ERBB4 | rs1879637 (A/G) | 2 | 212868624 | 0.92 | 0.4154 | 0.93698 |
| NRG3 | rs10884204 (G/A) | 10 | 83867428 | -0.99 | 0.416 | 0.93698 |
| MUC4 | rs2641773 (C/A) | 3 | 195528226 | -0.85 | 0.416 | 0.93698 |
| NRG3 | rs2484452 (A/G) | 10 | 84464685 | 0.92 | 0.4162 | 0.93698 |
| TGFA | rs454305 (A/G) | 2 | 70736219 | 0.93 | 0.417 | 0.93698 |
| NRG2 | rs62383916 (A/G) | 5 | 139395099 | -1.42 | 0.4171 | 0.93698 |

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|---|---|---|---|---|---|---|
| NRG1 | rs10100501 (G/A) | 8 | 32254835 | 1.76 | 0.418 | 0.93698 |
| NRG1 | rs55973232 (C/A) | 8 | 32231597 | -1.45 | 0.4186 | 0.93698 |
| ERBB4 | rs55866026 (A/G) | 2 | 212796378 | 0.92 | 0.419 | 0.93698 |
| NRG1 | rs16879088 (G/A) | 8 | 32133284 | -1.64 | 0.4198 | 0.93698 |
| NRG1 | rs10503929 (A/G) | 8 | 32613983 | -1.23 | 0.4199 | 0.93698 |
| EREG | rs2367708 (A/G) | 4 | 75248544 | 1.12 | 0.4203 | 0.93698 |
| NRG3 | rs7072670 (G/A) | 10 | 84045401 | 0.91 | 0.4207 | 0.93698 |
| ERBB4 | rs839524 (C/A) | 2 | 212815801 | -1.25 | 0.4207 | 0.93698 |
| NRG3 | rs72823898 (G/A) | 10 | 83787261 | 1.73 | 0.4209 | 0.93698 |
| NRG1 | rs2347503 (A/G) | 8 | 32232827 | -1.36 | 0.4211 | 0.93698 |
| NRG3 | rs3740349 (A/C) | 10 | 84151628 | -1.77 | 0.4216 | 0.93698 |
| NRG3 | rs594612 (A/G) | 10 | 84267826 | -0.96 | 0.4225 | 0.93698 |
| ERBB4 | rs6719664 (A/G) | 2 | 212525039 | 1.30 | 0.4226 | 0.93698 |
| NRG3 | rs1024193 (G/A) | 10 | 83852321 | -0.92 | 0.4228 | 0.93698 |
| ERBB4 | rs12473131 (G/A) | 2 | 212845292 | 1.15 | 0.4229 | 0.93698 |
| NRG3 | rs489466 (A/G) | 10 | 84648966 | 0.87 | 0.423 | 0.93698 |
| ERBB4 | rs16847406 (G/A) | 2 | 212845314 | 1.59 | 0.4233 | 0.93698 |
| NRG3 | rs10509454 (G/A) | 10 | 84260043 | -1.27 | 0.424 | 0.93698 |
| NRG1 | rs975199 (G/A) | 8 | 31700703 | 0.97 | 0.4249 | 0.93698 |
| ERBB4 | rs58905892 (C/A) | 2 | 212586970 | -1.59 | 0.4252 | 0.93698 |
| EGFR | rs56208956 (G/A) | 7 | 55167063 | 1.57 | 0.4256 | 0.93698 |
| ERBB4 | rs10200942 (A/G) | 2 | 212378991 | 0.93 | 0.4258 | 0.93698 |
| NRG1 | rs6987816 (G/A) | 8 | 31896196 | 1.84 | 0.426 | 0.93698 |
| ERBB4 | rs74409401 (A/G) | 2 | 212878653 | -1.14 | 0.4265 | 0.93698 |
| ERBB4 | rs12475523 (G/A) | 2 | 212245284 | 0.87 | 0.4267 | 0.93698 |
| BTC | rs6843005 (G/A) | 4 | 75684474 | 0.83 | 0.4271 | 0.93698 |
| ERBB4 | rs11903508 (G/A) | 2 | 212825238 | 2.14 | 0.4271 | 0.93698 |
| NRG3 | rs4143817 (C/A) | 10 | 84099660 | -1.28 | 0.4275 | 0.93698 |
| NRG1 | rs2919392 (G/A) | 8 | 32524451 | 0.84 | 0.4277 | 0.93698 |
| NRG1 | rs201709327 (A/G) | 8 | 31993497 | -0.89 | 0.4281 | 0.93698 |
| ERBB4 | rs13021712 (G/A) | 2 | 212565358 | -0.93 | 0.4282 | 0.93698 |
| ERBB4 | rs1394791 (C/A) | 2 | 213297810 | 1.13 | 0.4287 | 0.93704 |
| ERBB4 | rs7426203 (G/A) | 2 | 212555823 | -0.90 | 0.4297 | 0.93704 |
| ERBB4 | rs10172967 (A/G) | 2 | 212787989 | -0.89 | 0.4297 | 0.93704 |
| ERBB4 | rs7591137 (G/A) | 2 | 212585422 | -0.87 | 0.4311 | 0.93704 |
| ERBB4 | rs2062937 (G/A) | 2 | 213218396 | -0.89 | 0.4315 | 0.93704 |
| ERBB4 | rs13385826 (A/G) | 2 | 212295478 | -0.94 | 0.4318 | 0.93704 |
| NRG2 | rs35740825 (G/A) | 5 | 139311588 | -1.22 | 0.4324 | 0.93704 |
| NRG2 | rs34596629 (G/A) | 5 | 139320512 | -1.22 | 0.4324 | 0.93704 |
| NRG1 | rs17624670 (G/A) | 8 | 32126374 | 1.08 | 0.4325 | 0.93704 |
| NRG1 | rs372373 (G/A) | 8 | 31847539 | -1.15 | 0.4326 | 0.93704 |

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|---|---|---|---|---|---|---|
| NRG1 | rs13275885 (G/A) | 8 | 32071975 | -0.87 | 0.4328 | 0.93704 |
| ERBB4 | rs75719406 (G/A) | 2 | 213187448 | -1.15 | 0.4329 | 0.93704 |
| NRG3 | rs2246165 (A/C) | 10 | 84461630 | 1.31 | 0.434 | 0.93858 |
| NRG4 | rs334941 (G/A) | 15 | 76294870 | 1.79 | 0.4357 | 0.93924 |
| NRG1 | rs6983573 (C/A) | 8 | 31602067 | 1.07 | 0.4359 | 0.93924 |
| EGFR | rs6970029 (C/A) | 7 | 55252226 | 0.86 | 0.436 | 0.93924 |
| NRG1 | rs4403369 (A/G) | 8 | 31544898 | 1.17 | 0.4363 | 0.93924 |
| MUC4 | rs201296070 (G/A) | 3 | 195505739 | -2.01 | 0.4372 | 0.93924 |
| EREG | rs1460008 (A/G) | 4 | 75254282 | 1.05 | 0.4374 | 0.93924 |
| NRG1 | rs7825588 (G/A) | 8 | 32504401 | 1.34 | 0.4378 | 0.93924 |
| NRG1 | rs74354821 (G/A) | 8 | 32158293 | -0.88 | 0.4383 | 0.93924 |
| NRG3 | rs7085184 (A/G) | 10 | 84038093 | 0.89 | 0.4384 | 0.93924 |
| ERBB4 | rs12162287 (C/A) | 2 | 212579897 | -0.99 | 0.4385 | 0.93924 |
| EREG | rs1460007 (A/G) | 4 | 75254258 | 1.08 | 0.4386 | 0.93924 |
| NRG3 | rs12265466 (G/A) | 10 | 84001018 | -1.22 | 0.4397 | 0.93952 |
| ERBB4 | rs10497945 (A/C) | 2 | 212418110 | -0.97 | 0.4397 | 0.93952 |
| NRG1 | rs2129533 (A/C) | 8 | 32161552 | -0.87 | 0.4399 | 0.93952 |
| NRG3 | rs715687 (A/G) | 10 | 84571953 | -0.88 | 0.4406 | 0.93982 |
| ERBB4 | rs13383860 (A/G) | 2 | 213253930 | 0.99 | 0.4412 | 0.93982 |
| NRG1 | rs16879273 (G/A) | 8 | 32231847 | -1.39 | 0.4415 | 0.93982 |
| EGFR | rs2075106 (A/G) | 7 | 55253425 | 0.84 | 0.4416 | 0.93982 |
| ERBB4 | rs6435701 (G/A) | 2 | 213283512 | 0.86 | 0.4423 | 0.94047 |
| NRG1 | rs10087434 (A/G) | 8 | 31983067 | 0.85 | 0.4427 | 0.94049 |
| NRG3 | rs61862999 (A/G) | 10 | 83991403 | -0.94 | 0.4438 | 0.94119 |
| ERBB4 | rs2090863 (G/A) | 2 | 213078668 | 0.80 | 0.4439 | 0.94119 |
| NRG3 | rs10884546 (C/A) | 10 | 84082731 | -1.22 | 0.4442 | 0.94119 |
| NRG1 | rs2881544 (G/A) | 8 | 32112409 | 0.88 | 0.4448 | 0.94135 |
| NRG3 | rs41412145 (G/A) | 10 | 83844839 | -1.78 | 0.4453 | 0.94135 |
| ERBB4 | rs1521545 (A/C) | 2 | 212938165 | 1.18 | 0.4457 | 0.94135 |
| TGFA | rs7568707 (G/A) | 2 | 70777550 | 0.93 | 0.4463 | 0.94135 |
| EGF | rs11569061 (A/G) | 4 | 110913193 | 1.89 | 0.4467 | 0.94135 |
| NRG3 | rs56161908 (A/C) | 10 | 84570531 | -1.52 | 0.4472 | 0.94135 |
| BTC | rs28822209 (G/A) | 4 | 75690673 | 1.00 | 0.4476 | 0.94135 |
| NRG1 | rs72612106 (C/A) | 8 | 32280768 | 1.80 | 0.4485 | 0.94135 |
| NRG1 | rs11775517 (A/G) | 8 | 31663923 | 0.98 | 0.4486 | 0.94135 |
| ERBB4 | rs6435654 (G/A) | 2 | 212547935 | -0.81 | 0.4487 | 0.94135 |
| NRG1 | rs66963240 (G/A) | 8 | 32392283 | -0.82 | 0.4496 | 0.94135 |
| NRG1 | rs939077 (C/A) | 8 | 32245538 | -0.82 | 0.4497 | 0.94135 |
| NRG3 | rs56304721 (G/A) | 10 | 84227466 | -1.19 | 0.4497 | 0.94135 |
| NRG1 | rs10098433 (T/A) | 8 | 32600843 | 1.10 | 0.4507 | 0.94135 |
| NRG3 | rs568271 (A/C) | 10 | 84631585 | -0.86 | 0.4508 | 0.94135 |

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|---|---|---|---|---|---|---|
| NRG2 | rs3822741 (G/A) | 5 | 139238921 | -1.05 | 0.4508 | 0.94135 |
| ERBB4 | rs7569142 (G/A) | 2 | 213294557 | -0.87 | 0.4511 | 0.94135 |
| ERBB2 | rs2952156 (G/A) | 17 | 37876835 | -0.82 | 0.4518 | 0.94135 |
| ERBB4 | rs13021324 (A/G) | 2 | 212350245 | 0.98 | 0.4522 | 0.94135 |
| NRG3 | rs2475797 (A/G) | 10 | 84690140 | -0.86 | 0.4528 | 0.94135 |
| NRG1 | rs1481756 (G/A) | 8 | 31967245 | 0.82 | 0.4534 | 0.94135 |
| NRG1 | rs4590398 (C/A) | 8 | 31850576 | -0.88 | 0.4535 | 0.94135 |
| TGFA | rs1523300 (A/C) | 2 | 70769365 | -0.82 | 0.4535 | 0.94135 |
| NRG3 | rs7087569 (C/A) | 10 | 84100509 | 1.20 | 0.4543 | 0.94135 |
| TGFA | rs72912113 (G/A) | 2 | 70774248 | 1.21 | 0.4549 | 0.94135 |
| NRG2 | rs7736276 (G/A) | 5 | 139335948 | -1.15 | 0.4552 | 0.94135 |
| NRG3 | rs505087 (G/A) | 10 | 84502803 | -0.97 | 0.4553 | 0.94135 |
| NRG4 | rs10851885 (A/G) | 15 | 76304503 | 0.96 | 0.4562 | 0.94135 |
| NRG3 | rs72831329 (A/G) | 10 | 84565780 | -1.49 | 0.4562 | 0.94135 |
| TGFA | rs201827816 (C/G) | 2 | 70778627 | 0.92 | 0.4564 | 0.94135 |
| TGFA | rs199985861 (A/C) | 2 | 70778629 | 0.92 | 0.4564 | 0.94135 |
| EGFR | rs6964705 (C/A) | 7 | 55209637 | 0.83 | 0.4575 | 0.94187 |
| NRG3 | rs12573797 (G/C) | 10 | 83764714 | 1.56 | 0.4579 | 0.94187 |
| ERBB4 | rs61631854 (G/A) | 2 | 212377672 | -0.95 | 0.4581 | 0.94187 |
| NRG3 | rs10748842 (A/G) | 10 | 83649739 | 1.23 | 0.4586 | 0.94187 |
| NRG1 | rs1023910 (A/G) | 8 | 31825486 | -0.94 | 0.4588 | 0.94187 |
| ERBB4 | rs77200750 (G/A) | 2 | 212465243 | 1.67 | 0.459 | 0.94187 |
| ERBB4 | rs67044368 (A/G) | 2 | 212573895 | 1.09 | 0.4605 | 0.94377 |
| NRG2 | rs2916092 (A/G) | 5 | 139414752 | -0.91 | 0.4609 | 0.94377 |
| ERBB4 | rs10192514 (G/A) | 2 | 213216431 | 1.17 | 0.4611 | 0.94377 |
| ERBB4 | rs1384289 (G/A) | 2 | 213339192 | -1.62 | 0.4628 | 0.94644 |
| NRG3 | rs200838641 (G/A) | 10 | 84158436 | -0.86 | 0.4642 | 0.94751 |
| ERBB4 | rs57445671 (A/G) | 2 | 212377043 | -1.16 | 0.4642 | 0.94751 |
| NRG3 | rs10509451 (G/A) | 10 | 84032154 | 1.23 | 0.4647 | 0.94751 |
| HBEGF | rs7268 (C/A) | 5 | 139712550 | 0.78 | 0.4649 | 0.94751 |
| NRG1 | rs16878500 (A/C) | 8 | 31801518 | -1.37 | 0.4663 | 0.94787 |
| NRG1 | rs71512629 (A/G) | 8 | 32308302 | -1.02 | 0.4663 | 0.94787 |
| NRG1 | rs7835014 (A/G) | 8 | 31995958 | -1.13 | 0.4675 | 0.94787 |
| NRG1 | rs733230 (G/C) | 8 | 31802582 | 1.01 | 0.4679 | 0.94787 |
| ERBB4 | rs6435692 (A/G) | 2 | 213008886 | -0.83 | 0.4685 | 0.94787 |
| NRG1 | rs7001060 (A/C) | 8 | 32066467 | -1.35 | 0.4689 | 0.94787 |
| NRG3 | rs342395 (G/A) | 10 | 84622010 | 1.16 | 0.4691 | 0.94787 |
| ERBB4 | rs16825008 (A/G) | 2 | 212304841 | -0.88 | 0.4694 | 0.94787 |
| ERBB4 | rs10196354 (A/G) | 2 | 212382646 | -0.87 | 0.4695 | 0.94787 |
| NRG3 | rs72825496 (A/G) | 10 | 84011500 | 1.19 | 0.4697 | 0.94787 |
| NRG3 | rs11194491 (G/A) | 10 | 84225687 | -0.83 | 0.4698 | 0.94787 |

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|---|---|---|---|---|---|---|
| ERBB4 | rs13014726 (G/A) | 2 | 213224540 | -1.04 | 0.4698 | 0.94787 |
| NRG1 | rs57627142 (A/C) | 8 | 32193198 | -1.05 | 0.4708 | 0.94816 |
| NRG2 | rs192371066 (A/G) | 5 | 139311848 | -1.10 | 0.4708 | 0.94816 |
| TGFA | rs443120 (A/G) | 2 | 70743064 | -1.28 | 0.4717 | 0.94816 |
| NRG3 | rs7082760 (A/G) | 10 | 83828745 | -0.96 | 0.4724 | 0.94816 |
| NRG3 | rs10884110 (A/G) | 10 | 83820418 | -1.01 | 0.4726 | 0.94816 |
| ERBB4 | rs7569828 (G/A) | 2 | 212243534 | 1.76 | 0.4726 | 0.94816 |
| NRG2 | rs9686629 (A/G) | 5 | 139329066 | -1.10 | 0.4727 | 0.94816 |
| NRG1 | rs12546943 (G/A) | 8 | 32170223 | -0.99 | 0.4731 | 0.94817 |
| NRG1 | rs7819063 (G/A) | 8 | 31499408 | 0.93 | 0.4743 | 0.94978 |
| NRG1 | rs28392732 (G/A) | 8 | 32267235 | 1.06 | 0.4755 | 0.95063 |
| NRG3 | rs585597 (A/G) | 10 | 84315759 | -0.83 | 0.476 | 0.95063 |
| NRG1 | rs6468095 (G/A) | 8 | 32164476 | -0.99 | 0.4761 | 0.95063 |
| ERBB4 | rs4530297 (A/G) | 2 | 212453661 | 1.00 | 0.4763 | 0.95063 |
| NRG3 | rs4341481 (A/G) | 10 | 84713797 | 0.75 | 0.4768 | 0.95083 |
| NRG1 | rs35216206 (A/G) | 8 | 31854803 | -1.23 | 0.4794 | 0.95388 |
| NRG1 | rs1487146 (A/G) | 8 | 32134420 | 0.88 | 0.4794 | 0.95388 |
| NRG2 | rs17118604 (A/G) | 5 | 139375692 | 1.39 | 0.4796 | 0.95388 |
| NRG3 | rs201423217 (A/G) | 10 | 84457944 | 0.78 | 0.48 | 0.95388 |
| NRG3 | rs17559164 (G/A) | 10 | 83875533 | -1.03 | 0.4808 | 0.95388 |
| NRG2 | rs2436389 (A/C) | 5 | 139416265 | 0.84 | 0.4809 | 0.95388 |
| NRG1 | rs13266401 (A/G) | 8 | 31887758 | 1.40 | 0.4811 | 0.95388 |
| ERBB4 | rs12467708 (A/G) | 2 | 212689053 | 1.12 | 0.4831 | 0.95627 |
| ERBB4 | rs16848137 (A/G) | 2 | 213136366 | -0.90 | 0.4833 | 0.95627 |
| ERBB4 | rs4630710 (A/G) | 2 | 213211617 | 0.95 | 0.4835 | 0.95627 |
| ERBB4 | rs4673664 (G/A) | 2 | 213277649 | 0.78 | 0.4842 | 0.95687 |
| ERBB4 | rs1818752 (C/A) | 2 | 212507648 | -1.41 | 0.485 | 0.95767 |
| ERBB4 | rs1972820 (A/G) | 2 | 212243422 | 0.77 | 0.4869 | 0.96004 |
| NRG3 | rs2483299 (G/A) | 10 | 84652722 | 0.77 | 0.487 | 0.96004 |
| ERBB4 | rs13026255 (A/G) | 2 | 212596915 | -0.80 | 0.4879 | 0.96065 |
| NRG1 | rs989465 (A/C) | 8 | 32105334 | 0.79 | 0.4883 | 0.96065 |
| NRG3 | rs17099777 (A/C) | 10 | 84075777 | -0.84 | 0.4887 | 0.96065 |
| NRG1 | rs16879366 (A/G) | 8 | 32286041 | -1.22 | 0.4892 | 0.96065 |
| ERBB4 | rs55951977 (G/A) | 2 | 212602010 | -0.80 | 0.4903 | 0.96065 |
| NRG1 | rs17620153 (G/A) | 8 | 31976837 | -0.74 | 0.4905 | 0.96065 |
| NRG3 | rs2144468 (C/G) | 10 | 83684106 | -0.90 | 0.4905 | 0.96065 |
| NRG2 | rs67151903 (G/A) | 5 | 139363583 | 1.57 | 0.4909 | 0.96065 |
| ERBB4 | rs4673616 (A/C) | 2 | 212281381 | -0.84 | 0.4909 | 0.96065 |
| EGFR | rs723527 (A/G) | 7 | 55134872 | 0.74 | 0.4913 | 0.96065 |
| MUC4 | rs2688515 (G/A) | 3 | 195527471 | -0.71 | 0.494 | 0.96431 |
| ERBB4 | rs16848048 (G/A) | 2 | 213110812 | -1.55 | 0.4941 | 0.96431 |

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|---|---|---|---|---|---|---|
| NRG3 | rs1889709 (A/C) | 10 | 84469007 | -0.83 | 0.4944 | 0.96431 |
| NRG3 | rs11193683 (A/C) | 10 | 84079184 | -0.85 | 0.4959 | 0.96431 |
| ERBB4 | rs4672612 (G/A) | 2 | 212245489 | 0.76 | 0.4964 | 0.96431 |
| ERBB4 | rs839533 (G/A) | 2 | 212808107 | -0.93 | 0.4965 | 0.96431 |
| ERBB4 | rs6757068 (A/G) | 2 | 212615516 | -0.73 | 0.4966 | 0.96431 |
| NRG1 | rs7841677 (A/C) | 8 | 32078855 | 0.77 | 0.4971 | 0.96431 |
| NRG1 | rs956203 (A/G) | 8 | 31910758 | -0.79 | 0.4976 | 0.96431 |
| NRG3 | rs7083829 (A/G) | 10 | 83719445 | 1.24 | 0.4979 | 0.96431 |
| NRG3 | rs7099000 (G/A) | 10 | 83719507 | 1.24 | 0.4979 | 0.96431 |
| NRG2 | rs35342155 (G/A) | 5 | 139300789 | -0.92 | 0.4984 | 0.96431 |
| NRG3 | rs10509440 (G/A) | 10 | 83736634 | 1.29 | 0.4993 | 0.96431 |
| EGFR | rs845550 (G/A) | 7 | 55236774 | -1.28 | 0.4995 | 0.96431 |
| EGFR | rs17586344 (A/G) | 7 | 55140398 | -1.08 | 0.4996 | 0.96431 |
| NRG3 | rs4933830 (A/G) | 10 | 83873131 | -0.85 | 0.5 | 0.96431 |
| EGFR | rs78265168 (G/A) | 7 | 55114589 | 1.80 | 0.5006 | 0.96431 |
| NRG3 | rs6584407 (A/G) | 10 | 83676409 | -0.82 | 0.5016 | 0.96431 |
| NRG1 | rs11782671 (G/A) | 8 | 32290601 | 0.72 | 0.5031 | 0.96431 |
| ERBB4 | rs7586570 (A/C) | 2 | 212243737 | 1.79 | 0.5034 | 0.96431 |
| ERBB4 | rs10932386 (A/G) | 2 | 212450199 | 1.12 | 0.5036 | 0.96431 |
| ERBB4 | rs55988979 (A/G) | 2 | 212684970 | 0.82 | 0.5043 | 0.96431 |
| TGFA | rs3771492 (G/A) | 2 | 70728877 | -1.40 | 0.5044 | 0.96431 |
| MUC4 | rs67175307 (G/A) | 3 | 195479237 | 1.56 | 0.5045 | 0.96431 |
| NRG1 | rs9297190 (A/G) | 8 | 32258926 | -0.79 | 0.5048 | 0.96431 |
| NRG3 | rs11196077 (A/G) | 10 | 84574375 | -1.00 | 0.5054 | 0.96431 |
| EGFR | rs2072454 (A/G) | 7 | 55214348 | -0.69 | 0.5057 | 0.96431 |
| EGFR | rs10258429 (G/A) | 7 | 55238087 | -1.27 | 0.5057 | 0.96431 |
| ERBB4 | rs7565960 (G/A) | 2 | 212242434 | -0.79 | 0.5059 | 0.96431 |
| ERBB4 | rs116254091 (G/A) | 2 | 213114344 | -1.49 | 0.5059 | 0.96431 |
| NRG1 | rs2919385 (G/A) | 8 | 32557831 | 1.73 | 0.506 | 0.96431 |
| EGFR | rs1013127 (A/G) | 7 | 55139068 | 0.90 | 0.5062 | 0.96431 |
| NRG1 | rs16879882 (C/A) | 8 | 32584095 | 1.83 | 0.5068 | 0.96431 |
| NRG3 | rs10883898 (G/A) | 10 | 83670126 | -0.80 | 0.5075 | 0.96431 |
| ERBB4 | rs61250365 (A/G) | 2 | 212428646 | -0.83 | 0.5077 | 0.96431 |
| ERBB4 | rs78307325 (G/A) | 2 | 212892543 | -1.64 | 0.5085 | 0.96431 |
| NRG3 | rs2246633 (A/G) | 10 | 84457148 | 0.73 | 0.5087 | 0.96431 |
| BTC | rs10029520 (G/A) | 4 | 75680724 | 0.70 | 0.5089 | 0.96431 |
| NRG1 | rs13276200 (A/G) | 8 | 31835829 | -1.22 | 0.5093 | 0.96431 |
| NRG1 | rs4352806 (A/G) | 8 | 32238916 | 1.41 | 0.5096 | 0.96431 |
| NRG2 | rs265161 (G/A) | 5 | 139391486 | -0.92 | 0.5096 | 0.96431 |
| NRG1 | rs1381874 (G/A) | 8 | 31942557 | -1.16 | 0.5106 | 0.96545 |
| ERBB4 | rs55651117 (C/A) | 2 | 212467401 | -1.43 | 0.5133 | 0.96735 |

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|---|---|---|---|---|---|---|
| EGFR | rs17172446 (G/A) | 7 | 55202598 | 0.83 | 0.5137 | 0.96735 |
| NRG1 | rs28569837 (G/A) | 8 | 32285094 | 0.77 | 0.514 | 0.96735 |
| BTC | rs13129461 (A/G) | 4 | 75705267 | 0.78 | 0.514 | 0.96735 |
| ERBB4 | rs1836712 (A/G) | 2 | 212312191 | -1.48 | 0.5141 | 0.96735 |
| EGFR | rs7795564 (G/A) | 7 | 55124829 | -0.72 | 0.515 | 0.96735 |
| ERBB4 | rs4672614 (A/G) | 2 | 212350088 | 0.84 | 0.5151 | 0.96735 |
| ERBB4 | rs6735769 (A/G) | 2 | 212434037 | -0.82 | 0.5158 | 0.96735 |
| NRG1 | rs72586969 (G/A) | 8 | 32536429 | 0.70 | 0.5169 | 0.96735 |
| ERBB4 | rs7608189 (A/G) | 2 | 212382106 | -0.91 | 0.5187 | 0.96735 |
| NRG1 | rs776401 (A/G) | 8 | 31716962 | 0.74 | 0.5193 | 0.96735 |
| NRG1 | rs1979565 (A/G) | 8 | 32102493 | 0.74 | 0.5193 | 0.96735 |
| ERBB4 | rs13024094 (G/A) | 2 | 212560354 | -0.93 | 0.5197 | 0.96735 |
| ERBB4 | rs71422752 (A/G) | 2 | 212575971 | -1.11 | 0.5199 | 0.96735 |
| ERBB4 | rs12613571 (A/G) | 2 | 212845994 | 1.25 | 0.5199 | 0.96735 |
| ERBB4 | rs17325821 (G/A) | 2 | 213336689 | 0.85 | 0.52 | 0.96735 |
| NRG1 | rs10808317 (G/A) | 8 | 31816746 | -0.82 | 0.5208 | 0.96735 |
| ERBB4 | rs1371203 (A/G) | 2 | 212683946 | 0.82 | 0.5212 | 0.96735 |
| ERBB4 | rs75605905 (G/A) | 2 | 212333563 | 0.83 | 0.5213 | 0.96735 |
| EREG | rs1993665 (A/G) | 4 | 75234486 | -0.79 | 0.5216 | 0.96735 |
| NRG3 | rs7915217 (A/G) | 10 | 84098115 | 1.02 | 0.5217 | 0.96735 |
| ERBB4 | rs3791699 (G/A) | 2 | 212274447 | -0.80 | 0.5225 | 0.96735 |
| ERBB4 | rs1910861 (G/A) | 2 | 213211407 | -0.72 | 0.5227 | 0.96735 |
| ERBB4 | rs12475861 (A/G) | 2 | 212415948 | 0.81 | 0.5232 | 0.96735 |
| EGFR | rs1468726 (G/A) | 7 | 55165999 | 0.77 | 0.5234 | 0.96735 |
| ERBB4 | rs11895168 (C/A) | 2 | 212242192 | 0.72 | 0.5235 | 0.96735 |
| ERBB4 | rs9678219 (G/A) | 2 | 212937649 | -0.93 | 0.5256 | 0.96735 |
| NRG3 | rs7358197 (G/A) | 10 | 84030522 | 1.23 | 0.5263 | 0.96735 |
| ERBB4 | rs4490118 (A/C) | 2 | 212330865 | -0.77 | 0.5266 | 0.96735 |
| ERBB4 | rs7588431 (G/A) | 2 | 212650985 | 0.69 | 0.527 | 0.96735 |
| EGFR | rs11238354 (A/G) | 7 | 55227064 | 0.77 | 0.5275 | 0.96735 |
| ERBB4 | rs7419310 (G/A) | 2 | 212583563 | -0.78 | 0.528 | 0.96735 |
| EGFR | rs11760524 (A/G) | 7 | 55221167 | 1.04 | 0.5282 | 0.96735 |
| TGFA | rs7579830 (A/G) | 2 | 70711183 | 1.49 | 0.5282 | 0.96735 |
| NRG1 | rs900103 (A/G) | 8 | 32001009 | 0.89 | 0.5285 | 0.96735 |
| NRG3 | rs342372 (G/A) | 10 | 84589336 | -0.67 | 0.5285 | 0.96735 |
| NRG3 | rs7476649 (G/A) | 10 | 84087761 | -0.92 | 0.5286 | 0.96735 |
| NRG3 | rs7072481 (A/G) | 10 | 84030537 | 0.73 | 0.53 | 0.96735 |
| NRG3 | rs514237 (G/A) | 10 | 84505577 | 0.75 | 0.53 | 0.96735 |
| ERBB4 | rs75469068 (A/C) | 2 | 213171575 | -1.02 | 0.5302 | 0.96735 |
| NRG3 | rs342375 (G/A) | 10 | 84590820 | -0.67 | 0.5303 | 0.96735 |
| MUC4 | rs863582 (A/G) | 3 | 195478694 | -0.68 | 0.5307 | 0.96735 |

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|---|---|---|---|---|---|---|
| ERBB4 | rs16847152 (G/A) | 2 | 212736394 | 0.68 | 0.5309 | 0.96735 |
| ERBB4 | rs16847082 (A/G) | 2 | 212718670 | 0.83 | 0.5312 | 0.96735 |
| ERBB4 | rs13382194 (A/G) | 2 | 212378743 | -0.68 | 0.5318 | 0.96735 |
| NRG3 | rs7069578 (G/A) | 10 | 84179887 | -0.87 | 0.5319 | 0.96735 |
| ERBB4 | rs1402711 (C/A) | 2 | 212863006 | 0.70 | 0.5334 | 0.96735 |
| ERBB4 | rs72948566 (C/A) | 2 | 212687528 | 0.77 | 0.534 | 0.96735 |
| NRG1 | rs6468091 (G/A) | 8 | 32087606 | -1.25 | 0.5343 | 0.96735 |
| ERBB4 | rs2177035 (C/A) | 2 | 212891401 | -0.79 | 0.535 | 0.96735 |
| EGFR | rs6593207 (A/G) | 7 | 55196855 | 1.02 | 0.5357 | 0.96735 |
| NRG3 | rs10884361 (G/A) | 10 | 83981964 | 1.07 | 0.5362 | 0.96735 |
| NRG3 | rs2246879 (A/G) | 10 | 84455202 | 1.04 | 0.5364 | 0.96735 |
| NRG1 | rs201525202 (A/G) | 8 | 32310209 | 0.67 | 0.5366 | 0.96735 |
| NRG3 | rs11192447 (G/A) | 10 | 83848397 | -1.31 | 0.5366 | 0.96735 |
| ERBB4 | rs17415079 (A/G) | 2 | 212856363 | -1.05 | 0.5369 | 0.96735 |
| ERBB4 | rs62178819 (G/A) | 2 | 212370193 | -1.02 | 0.5371 | 0.96735 |
| NRG1 | rs10503919 (C/A) | 8 | 32399742 | -0.88 | 0.5378 | 0.96735 |
| ERBB4 | rs62178817 (C/A) | 2 | 212368624 | -1.07 | 0.5381 | 0.96735 |
| NRG3 | rs1937968 (A/C) | 10 | 84222280 | -0.73 | 0.5383 | 0.96735 |
| BTC | rs5028443 (A/G) | 4 | 75678122 | 0.65 | 0.5397 | 0.96735 |
| ERBB4 | rs7604206 (C/A) | 2 | 212584780 | 0.70 | 0.5398 | 0.96735 |
| TGFA | rs12617813 (G/A) | 2 | 70778190 | 0.66 | 0.5399 | 0.96735 |
| NRG1 | rs2347496 (A/C) | 8 | 32288932 | 0.67 | 0.5405 | 0.96735 |
| NRG3 | rs2348332 (C/A) | 10 | 84389603 | 1.08 | 0.5405 | 0.96735 |
| ERBB4 | rs17259208 (A/G) | 2 | 213316586 | 0.74 | 0.5413 | 0.96735 |
| EGFR | rs2075108 (A/G) | 7 | 55254322 | -1.17 | 0.5415 | 0.96735 |
| ERBB4 | rs12622730 (A/G) | 2 | 212435213 | -0.79 | 0.5416 | 0.96735 |
| ERBB4 | rs17344065 (A/G) | 2 | 212947759 | -0.89 | 0.5421 | 0.96735 |
| ERBB4 | rs12694263 (G/A) | 2 | 213003179 | -1.04 | 0.5423 | 0.96735 |
| ERBB4 | rs62182993 (G/A) | 2 | 212599288 | 0.74 | 0.5428 | 0.96735 |
| NRG3 | rs12570292 (G/A) | 10 | 83755561 | -0.90 | 0.5429 | 0.96735 |
| ERBB4 | rs6714941 (C/A) | 2 | 212539997 | -0.66 | 0.5432 | 0.96735 |
| ERBB4 | rs1439235 (G/A) | 2 | 212709028 | 0.81 | 0.5432 | 0.96735 |
| ERBB4 | rs6754899 (G/A) | 2 | 212576043 | -0.64 | 0.5441 | 0.96735 |
| ERBB4 | rs2371283 (A/G) | 2 | 212386868 | -1.10 | 0.5458 | 0.96735 |
| NRG3 | rs652183 (A/C) | 10 | 84381535 | 0.68 | 0.5459 | 0.96735 |
| NRG1 | rs7844698 (G/A) | 8 | 32345693 | 0.66 | 0.5468 | 0.96735 |
| NRG1 | rs4501543 (A/G) | 8 | 32454484 | -0.68 | 0.5469 | 0.96735 |
| TGFA | rs1597253 (A/G) | 2 | 70765713 | -0.87 | 0.5477 | 0.96735 |
| BTC | rs72660307 (A/C) | 4 | 75678027 | -1.40 | 0.5481 | 0.96735 |
| NRG3 | rs1080293 (G/A) | 10 | 83896260 | 0.75 | 0.5481 | 0.96735 |
| NRG1 | rs10088313 (C/A) | 8 | 32390061 | 1.30 | 0.5483 | 0.96735 |

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|---|---|---|---|---|---|---|
| NRG3 | rs11813781 (A/G) | 10 | 83718762 | 1.10 | 0.5483 | 0.96735 |
| NRG1 | rs56129386 (G/A) | 8 | 32129651 | 1.00 | 0.5486 | 0.96735 |
| NRG1 | rs7005288 (A/G) | 8 | 32620467 | -0.82 | 0.5493 | 0.96735 |
| EGFR | rs9692301 (A/G) | 7 | 55243754 | -0.73 | 0.5504 | 0.96735 |
| ERBB4 | rs1521657 (G/A) | 2 | 213023438 | -0.79 | 0.5511 | 0.96735 |
| ERBB4 | rs985995 (G/A) | 2 | 213341614 | -0.78 | 0.5512 | 0.96735 |
| NRG1 | rs6651144 (A/G) | 8 | 32382668 | -0.65 | 0.5514 | 0.96735 |
| NRG3 | rs11196606 (A/C) | 10 | 84706653 | 0.63 | 0.5518 | 0.96735 |
| NRG1 | rs10503913 (A/G) | 8 | 32234113 | 0.87 | 0.5519 | 0.96735 |
| NRG3 | rs7909484 (G/A) | 10 | 84206002 | -0.74 | 0.5521 | 0.96735 |
| MUC4 | rs79077800 (G/A) | 3 | 195537660 | 0.87 | 0.5523 | 0.96735 |
| NRG3 | rs6584426 (A/G) | 10 | 83732093 | 0.73 | 0.5532 | 0.96735 |
| EGFR | rs17336282 (G/A) | 7 | 55203978 | 0.75 | 0.5534 | 0.96735 |
| NRG1 | rs16878763 (A/G) | 8 | 31936063 | -0.69 | 0.5536 | 0.96735 |
| NRG1 | rs111450459 (G/A) | 8 | 31844866 | -0.75 | 0.554 | 0.96735 |
| EGFR | rs845561 (A/G) | 7 | 55252708 | -0.77 | 0.554 | 0.96735 |
| NRG3 | rs77891870 (G/A) | 10 | 83709730 | -1.33 | 0.5558 | 0.96735 |
| ERBB4 | rs62178818 (A/G) | 2 | 212370172 | -0.99 | 0.5563 | 0.96735 |
| MUC4 | rs56065813 (G/A) | 3 | 195520719 | 0.68 | 0.5568 | 0.96735 |
| NRG1 | rs201837009 (G/A) | 8 | 31903654 | -0.63 | 0.5574 | 0.96735 |
| ERBB4 | rs4561599 (G/A) | 2 | 212356281 | -0.69 | 0.5578 | 0.96735 |
| NRG3 | rs639839 (C/A) | 10 | 84363327 | -1.03 | 0.5579 | 0.96735 |
| NRG1 | rs4733330 (C/A) | 8 | 32274960 | -0.62 | 0.5583 | 0.96735 |
| NRG1 | rs13253155 (G/A) | 8 | 32368723 | -0.81 | 0.5587 | 0.96735 |
| NRG2 | rs265158 (A/G) | 5 | 139390467 | -0.81 | 0.5587 | 0.96735 |
| NRG1 | rs3735775 (G/A) | 8 | 32585423 | 0.80 | 0.5588 | 0.96735 |
| ERBB4 | rs10932414 (G/A) | 2 | 212893219 | -1.01 | 0.5589 | 0.96735 |
| NRG3 | rs2249964 (G/A) | 10 | 84452076 | 0.66 | 0.559 | 0.96735 |
| NRG1 | rs13255716 (A/G) | 8 | 31842475 | 0.66 | 0.5592 | 0.96735 |
| MUC4 | rs9837428 (A/G) | 3 | 195486869 | 0.66 | 0.5596 | 0.96735 |
| NRG3 | rs342374 (G/A) | 10 | 84590002 | -0.62 | 0.5606 | 0.96735 |
| NRG1 | rs900102 (G/A) | 8 | 32120188 | 0.62 | 0.5607 | 0.96735 |
| EGFR | rs67652465 (A/G) | 7 | 55258033 | -0.76 | 0.5607 | 0.96735 |
| NRG3 | rs3904726 (A/G) | 10 | 84091078 | -0.86 | 0.5611 | 0.96735 |
| NRG3 | rs11192265 (C/A) | 10 | 83801263 | -0.65 | 0.5614 | 0.96735 |
| NRG3 | rs6584870 (G/A) | 10 | 84431179 | -0.64 | 0.5617 | 0.96735 |
| MUC4 | rs2291652 (G/A) | 3 | 195477791 | 0.65 | 0.5617 | 0.96735 |
| NRG3 | rs17100097 (A/G) | 10 | 84218664 | -0.69 | 0.5622 | 0.96735 |
| NRG3 | rs7069222 (G/A) | 10 | 83756102 | 0.70 | 0.5631 | 0.96735 |
| BTC | rs977266 (A/G) | 4 | 75717601 | -0.61 | 0.5634 | 0.96735 |
| ERBB4 | rs1394783 (A/G) | 2 | 213201725 | -0.69 | 0.5639 | 0.96735 |

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|---|---|---|---|---|---|---|
| BTC | rs11938093 (T/A) | 4 | 75675841 | -0.71 | 0.5644 | 0.96735 |
| NRG1 | rs57944175 (G/A) | 8 | 32474242 | -1.20 | 0.5647 | 0.96735 |
| NRG3 | rs7068082 (G/A) | 10 | 84458075 | -0.73 | 0.565 | 0.96735 |
| NRG1 | rs810284 (A/G) | 8 | 31768052 | 0.87 | 0.5651 | 0.96735 |
| BTC | rs61604859 (G/A) | 4 | 75718619 | 1.15 | 0.5662 | 0.96735 |
| NRG3 | rs617738 (C/A) | 10 | 84322815 | -0.66 | 0.5674 | 0.96735 |
| NRG3 | rs492203 (A/G) | 10 | 84678512 | -0.64 | 0.5674 | 0.96735 |
| NRG3 | rs10787129 (T/A) | 10 | 84168912 | -0.65 | 0.5675 | 0.96735 |
| ERBB4 | rs2033647 (A/G) | 2 | 212302127 | -0.67 | 0.5681 | 0.96735 |
| NRG3 | rs6584402 (G/A) | 10 | 83663215 | -0.69 | 0.5682 | 0.96735 |
| NRG3 | rs1937984 (A/G) | 10 | 84152990 | -0.67 | 0.5683 | 0.96735 |
| NRG3 | rs3908834 (G/A) | 10 | 84078217 | -0.83 | 0.5686 | 0.96735 |
| NRG3 | rs7068961 (A/G) | 10 | 84000308 | -0.90 | 0.5689 | 0.96735 |
| ERBB4 | rs1829615 (A/G) | 2 | 212547777 | -0.61 | 0.5693 | 0.96735 |
| NRG2 | rs6864507 (A/C) | 5 | 139237379 | -1.48 | 0.5696 | 0.96735 |
| HBEGF | rs4912711 (C/A) | 5 | 139718525 | -0.97 | 0.5696 | 0.96735 |
| NRG1 | rs57310164 (G/A) | 8 | 31732302 | -0.65 | 0.5701 | 0.96735 |
| MUC4 | rs1806440 (G/A) | 3 | 195517124 | 0.83 | 0.5701 | 0.96735 |
| ERBB4 | rs7603039 (A/G) | 2 | 212788895 | -0.73 | 0.5702 | 0.96735 |
| ERBB4 | rs10183757 (G/A) | 2 | 212539559 | -0.61 | 0.5706 | 0.96735 |
| NRG1 | rs73252749 (A/G) | 8 | 32316734 | -0.71 | 0.5707 | 0.96735 |
| MUC4 | rs56350323 (C/A) | 3 | 195525746 | -1.08 | 0.5708 | 0.96735 |
| ERBB4 | rs75989563 (A/G) | 2 | 213350702 | -1.32 | 0.5717 | 0.96735 |
| TGFA | rs930655 (G/A) | 2 | 70684451 | -0.65 | 0.5718 | 0.96735 |
| ERBB4 | rs34819491 (G/A) | 2 | 212561232 | -0.77 | 0.5721 | 0.96735 |
| NRG2 | rs12520398 (G/A) | 5 | 139405072 | -0.61 | 0.5724 | 0.96735 |
| BTC | rs4352548 (A/G) | 4 | 75683594 | -0.82 | 0.5728 | 0.96735 |
| EGFR | rs9649847 (G/A) | 7 | 55187138 | 0.97 | 0.573 | 0.96735 |
| NRG1 | rs4288331 (A/G) | 8 | 31520547 | -0.65 | 0.5734 | 0.96735 |
| ERBB3 | rs705708 (G/A) | 12 | 56488913 | -0.62 | 0.574 | 0.96735 |
| NRG3 | rs581628 (G/A) | 10 | 84265169 | -0.67 | 0.5742 | 0.96735 |
| NRG1 | rs2976532 (G/A) | 8 | 32594251 | 0.67 | 0.5743 | 0.96735 |
| MUC4 | rs3103954 (A/C) | 3 | 195516630 | 0.83 | 0.5751 | 0.96795 |
| NRG1 | rs4373486 (G/A) | 8 | 31791685 | 0.79 | 0.5758 | 0.96795 |
| ERBB4 | rs1851168 (A/G) | 2 | 212535145 | -0.60 | 0.5766 | 0.96795 |
| NRG3 | rs7077048 (G/A) | 10 | 84111105 | -0.83 | 0.577 | 0.96795 |
| NRG1 | rs12056925 (A/C) | 8 | 32486892 | -1.46 | 0.5776 | 0.96795 |
| EGFR | rs3752651 (A/G) | 7 | 55229543 | -0.80 | 0.5782 | 0.96795 |
| ERBB4 | rs34621071 (A/G) | 2 | 212522651 | 1.01 | 0.5784 | 0.96795 |
| NRG2 | rs11738832 (G/A) | 5 | 139294677 | 0.64 | 0.5799 | 0.96795 |
| EGFR | rs6970262 (G/A) | 7 | 55259763 | -0.62 | 0.5802 | 0.96795 |

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|---|---|---|---|---|---|---|
| ERBB4 | rs6727581 (A/G) | 2 | 212299979 | -1.11 | 0.5802 | 0.96795 |
| NRG1 | rs17630744 (A/G) | 8 | 32145945 | 1.34 | 0.5806 | 0.96795 |
| ERBB4 | rs2076818 (A/G) | 2 | 212261968 | 0.99 | 0.5811 | 0.96795 |
| ERBB4 | rs11693914 (A/G) | 2 | 212867025 | -0.94 | 0.5814 | 0.96795 |
| ERBB4 | rs1595066 (G/A) | 2 | 212241725 | -0.67 | 0.5815 | 0.96795 |
| ERBB4 | rs201134330 (A/G) | 2 | 212983286 | -0.61 | 0.5815 | 0.96795 |
| NRG3 | rs10884538 (G/A) | 10 | 84080228 | -0.69 | 0.5821 | 0.96795 |
| MUC4 | rs2259331 (G/A) | 3 | 195501258 | 0.64 | 0.5822 | 0.96795 |
| ERBB4 | rs58138021 (C/A) | 2 | 213135289 | -1.08 | 0.5824 | 0.96795 |
| EGFR | rs940810 (G/A) | 7 | 55277387 | -0.73 | 0.5825 | 0.96795 |
| EGFR | rs4947973 (G/A) | 7 | 55161056 | 0.63 | 0.5827 | 0.96795 |
| NRG1 | rs67222611 (A/G) | 8 | 32469506 | -1.12 | 0.5841 | 0.96924 |
| NRG3 | rs4933814 (A/C) | 10 | 83755315 | -0.81 | 0.5845 | 0.96924 |
| NRG3 | rs1739766 (C/A) | 10 | 83875762 | 0.59 | 0.5848 | 0.96924 |
| TGFA | rs200348663 (A/C) | 2 | 70683994 | -0.62 | 0.5865 | 0.96924 |
| NRG1 | rs4535704 (A/G) | 8 | 32474622 | -0.62 | 0.587 | 0.96924 |
| EREG | rs1017733 (A/G) | 4 | 75252350 | 0.73 | 0.5872 | 0.96924 |
| NRG3 | rs7069393 (A/C) | 10 | 83875405 | -0.92 | 0.5872 | 0.96924 |
| NRG1 | rs796549 (G/A) | 8 | 31768217 | 0.82 | 0.5884 | 0.96924 |
| ERBB4 | rs1521636 (A/G) | 2 | 213117976 | -0.63 | 0.5888 | 0.96924 |
| ERBB4 | rs12471583 (A/G) | 2 | 212244718 | 0.67 | 0.5905 | 0.96924 |
| NRG3 | rs1763060 (G/A) | 10 | 84571876 | -0.63 | 0.5928 | 0.96924 |
| NRG3 | rs74147915 (G/A) | 10 | 84120739 | 1.23 | 0.5931 | 0.96924 |
| ERBB4 | rs77824825 (A/G) | 2 | 212948255 | -0.78 | 0.5942 | 0.96924 |
| NRG1 | rs776385 (G/A) | 8 | 31736625 | -0.61 | 0.5949 | 0.96924 |
| ERBB3 | rs2229046 (A/G) | 12 | 56487201 | 1.03 | 0.595 | 0.96924 |
| NRG3 | rs10884056 (G/A) | 10 | 83788206 | 0.67 | 0.5951 | 0.96924 |
| NRG1 | rs10808324 (G/A) | 8 | 32295903 | 0.61 | 0.5952 | 0.96924 |
| ERBB4 | rs68029722 (A/G) | 2 | 212692219 | 0.66 | 0.5954 | 0.96924 |
| NRG2 | rs265148 (A/G) | 5 | 139400779 | 0.65 | 0.5959 | 0.96924 |
| NRG1 | rs28374316 (A/G) | 8 | 32562293 | -0.83 | 0.5969 | 0.96924 |
| NRG3 | rs4933812 (A/C) | 10 | 83688892 | -0.63 | 0.5977 | 0.96924 |
| NRG3 | rs7070560 (A/G) | 10 | 84048346 | 0.97 | 0.5979 | 0.96924 |
| NRG3 | rs10509449 (G/A) | 10 | 84022458 | 1.00 | 0.5985 | 0.96924 |
| NRG4 | rs76466466 (A/G) | 15 | 76289451 | -1.11 | 0.5988 | 0.96924 |
| NRG3 | rs11193401 (G/A) | 10 | 84040843 | -0.78 | 0.5988 | 0.96924 |
| ERBB4 | rs6435681 (G/A) | 2 | 212783175 | 0.68 | 0.5988 | 0.96924 |
| EGFR | rs12535536 (A/G) | 7 | 55154381 | -0.63 | 0.5997 | 0.96924 |
| MUC4 | rs2688482 (G/A) | 3 | 195529118 | -0.57 | 0.5999 | 0.96924 |
| ERBB4 | rs59197841 (G/A) | 2 | 212241339 | 1.29 | 0.5999 | 0.96924 |
| EGF | rs10023272 (A/G) | 4 | 110886804 | 0.61 | 0.6008 | 0.96924 |

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|---|---|---|---|---|---|---|
| ERBB4 | rs13035133 (A/G) | 2 | 212654817 | 0.57 | 0.6009 | 0.96924 |
| NRG1 | rs12542743 (G/A) | 8 | 32318355 | -0.55 | 0.6011 | 0.96924 |
| NRG1 | rs11989919 (A/G) | 8 | 32502626 | -1.17 | 0.602 | 0.96924 |
| ERBB4 | rs7588792 (C/A) | 2 | 212626917 | 0.73 | 0.6025 | 0.96924 |
| NRG2 | rs265151 (C/A) | 5 | 139378986 | 0.72 | 0.6027 | 0.96924 |
| NRG3 | rs12220854 (A/G) | 10 | 83954600 | -1.00 | 0.6038 | 0.96924 |
| NRG1 | rs16879814 (A/G) | 8 | 32573583 | -0.60 | 0.6041 | 0.96924 |
| MUC4 | rs67882058 (A/G) | 3 | 195485439 | 0.58 | 0.6045 | 0.96924 |
| NRG3 | rs11193797 (G/A) | 10 | 84093995 | 0.77 | 0.6047 | 0.96924 |
| ERBB4 | rs6757140 (G/A) | 2 | 213279029 | -0.58 | 0.6048 | 0.96924 |
| ERBB4 | rs1521662 (A/C) | 2 | 213129211 | -0.62 | 0.6049 | 0.96924 |
| NRG3 | rs17099329 (A/C) | 10 | 83828693 | 1.18 | 0.6055 | 0.96924 |
| NRG1 | rs28712850 (C/A) | 8 | 31769225 | 0.79 | 0.6073 | 0.96924 |
| NRG3 | rs560083 (G/A) | 10 | 84614844 | -0.62 | 0.6079 | 0.96924 |
| TGFA | rs17005666 (G/A) | 2 | 70705402 | 1.21 | 0.6083 | 0.96924 |
| TGFA | rs17005692 (G/A) | 2 | 70712860 | 1.21 | 0.6083 | 0.96924 |
| ERBB4 | rs6435689 (G/A) | 2 | 212975064 | -0.62 | 0.6084 | 0.96924 |
| NRG1 | rs117470596 (G/A) | 8 | 32201394 | -1.06 | 0.6092 | 0.96924 |
| NRG1 | rs17731664 (A/G) | 8 | 32586085 | 0.89 | 0.6092 | 0.96924 |
| NRG1 | rs10092449 (G/A) | 8 | 32563363 | -0.80 | 0.6094 | 0.96924 |
| ERBB4 | rs10207020 (G/A) | 2 | 213107619 | 0.61 | 0.6104 | 0.96924 |
| EGFR | rs17172451 (G/A) | 7 | 55222755 | -0.63 | 0.6108 | 0.96924 |
| NRG3 | rs973634 (G/A) | 10 | 83871324 | 0.56 | 0.6114 | 0.96924 |
| ERBB4 | rs1851185 (G/A) | 2 | 212527729 | -0.62 | 0.6117 | 0.96924 |
| ERBB2 | rs2643195 (G/A) | 17 | 37853118 | -0.56 | 0.6118 | 0.96924 |
| ERBB4 | rs6747405 (A/C) | 2 | 212574618 | -0.82 | 0.6133 | 0.96924 |
| NRG1 | rs13255161 (G/A) | 8 | 31921721 | -0.55 | 0.6135 | 0.96924 |
| EGFR | rs712831 (G/A) | 7 | 55242782 | 0.63 | 0.6135 | 0.96924 |
| NRG1 | rs7822917 (C/A) | 8 | 32190881 | -0.65 | 0.6144 | 0.96924 |
| MUC4 | rs2550271 (G/A) | 3 | 195484916 | -0.54 | 0.6149 | 0.96924 |
| NRG3 | rs2644207 (A/C) | 10 | 84489741 | 0.54 | 0.6152 | 0.96924 |
| MUC4 | rs2641776 (G/C) | 3 | 195515617 | -1.19 | 0.6173 | 0.96924 |
| ERBB4 | rs6435639 (A/G) | 2 | 212403323 | 0.61 | 0.6175 | 0.96924 |
| ERBB4 | rs72945096 (G/A) | 2 | 212553271 | -0.80 | 0.6175 | 0.96924 |
| ERBB4 | rs1402708 (G/A) | 2 | 212832434 | 1.10 | 0.6176 | 0.96924 |
| ERBB4 | rs1521648 (C/A) | 2 | 213039476 | 0.57 | 0.6177 | 0.96924 |
| NRG3 | rs2348553 (G/A) | 10 | 84601325 | -0.66 | 0.6184 | 0.96924 |
| ERBB4 | rs13390226 (G/A) | 2 | 212739861 | 0.86 | 0.6184 | 0.96924 |
| NRG3 | rs910585 (G/A) | 10 | 83662048 | -0.61 | 0.6186 | 0.96924 |
| ERBB4 | rs7595473 (A/G) | 2 | 212428439 | -0.62 | 0.619 | 0.96924 |
| EGFR | rs2293347 (G/A) | 7 | 55268916 | 0.94 | 0.6191 | 0.96924 |

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|---|---|---|---|---|---|---|
| NRG3 | rs520775 (A/G) | 10 | 84680228 | -1.07 | 0.6192 | 0.96924 |
| ERBB4 | rs16846013 (G/A) | 2 | 212250195 | -0.68 | 0.6198 | 0.96924 |
| NRG3 | rs524577 (G/A) | 10 | 84642168 | 1.06 | 0.6202 | 0.96924 |
| ERBB4 | rs1464443 (A/C) | 2 | 212914726 | -0.59 | 0.6203 | 0.96924 |
| ERBB4 | rs2017322 (A/G) | 2 | 212723516 | -0.74 | 0.6209 | 0.96924 |
| ERBB4 | rs62182564 (G/A) | 2 | 213040280 | 0.61 | 0.6212 | 0.96924 |
| MUC4 | rs13095016 (G/C) | 3 | 195515594 | 0.66 | 0.6215 | 0.96924 |
| ERBB4 | rs12476100 (G/A) | 2 | 212534520 | -0.56 | 0.6218 | 0.96924 |
| BTC | rs967875 (G/A) | 4 | 75718067 | 0.53 | 0.6219 | 0.96924 |
| BTC | rs4585380 (G/A) | 4 | 75673363 | -0.61 | 0.622 | 0.96924 |
| NRG3 | rs342368 (A/C) | 10 | 84565851 | 0.56 | 0.6221 | 0.96924 |
| NRG3 | rs7099976 (G/A) | 10 | 83865764 | -0.61 | 0.6228 | 0.96924 |
| NRG1 | rs7012841 (A/G) | 8 | 32102970 | 0.72 | 0.6235 | 0.96924 |
| NRG1 | rs776387 (A/G) | 8 | 31738051 | -0.53 | 0.6238 | 0.96924 |
| NRG1 | rs1565031 (G/A) | 8 | 32201135 | -0.71 | 0.6239 | 0.96924 |
| NRG3 | rs1576987 (A/G) | 10 | 84680499 | 0.54 | 0.6239 | 0.96924 |
| ERBB4 | rs16848640 (A/C) | 2 | 213338904 | -1.02 | 0.6241 | 0.96924 |
| ERBB4 | rs13018908 (A/C) | 2 | 213221111 | 0.74 | 0.6258 | 0.96924 |
| NRG1 | rs6468067 (G/A) | 8 | 31629500 | 0.61 | 0.6265 | 0.96924 |
| NRG3 | rs7094235 (G/A) | 10 | 83802818 | 0.92 | 0.6268 | 0.96924 |
| NRG3 | rs7099539 (G/A) | 10 | 83804209 | 0.92 | 0.6268 | 0.96924 |
| NRG1 | rs970998 (G/A) | 8 | 32201084 | -0.54 | 0.6271 | 0.96924 |
| NRG3 | rs581354 (C/A) | 10 | 84647206 | 0.78 | 0.6272 | 0.96924 |
| EGF | rs72676957 (A/G) | 4 | 110902684 | -1.00 | 0.6274 | 0.96924 |
| ERBB4 | rs1521654 (T/A) | 2 | 213027954 | 0.79 | 0.6276 | 0.96924 |
| ERBB4 | rs13432680 (A/C) | 2 | 213068720 | -0.54 | 0.6277 | 0.96924 |
| NRG1 | rs13257203 (G/A) | 8 | 31541283 | 0.53 | 0.6279 | 0.96924 |
| MUC4 | rs842223 (G/A) | 3 | 195483076 | 0.62 | 0.6293 | 0.96924 |
| ERBB4 | rs10221912 (A/G) | 2 | 212322368 | 1.11 | 0.6296 | 0.96924 |
| ERBB4 | rs4580336 (A/G) | 2 | 213090009 | 0.53 | 0.6296 | 0.96924 |
| NRG3 | rs12249883 (A/G) | 10 | 83995904 | -0.61 | 0.6298 | 0.96924 |
| ERBB4 | rs4673649 (A/G) | 2 | 212956761 | -0.66 | 0.6298 | 0.96924 |
| NRG3 | rs73319118 (G/A) | 10 | 83658507 | 1.32 | 0.6302 | 0.96924 |
| NRG1 | rs10102746 (C/A) | 8 | 32046770 | 0.67 | 0.6304 | 0.96924 |
| NRG2 | rs12515886 (C/G) | 5 | 139394586 | -0.51 | 0.6309 | 0.96924 |
| ERBB4 | rs10185241 (A/G) | 2 | 213244124 | 0.52 | 0.631 | 0.96924 |
| ERBB4 | rs58853206 (C/A) | 2 | 212243380 | 1.28 | 0.6311 | 0.96924 |
| NRG3 | rs11195188 (G/A) | 10 | 84359114 | 0.65 | 0.6317 | 0.96924 |
| ERBB4 | rs1836715 (A/G) | 2 | 212307077 | -0.60 | 0.6323 | 0.96924 |
| NRG1 | rs10097712 (G/A) | 8 | 32133418 | 0.93 | 0.6324 | 0.96924 |
| MUC4 | rs73891120 (G/A) | 3 | 195536430 | 1.18 | 0.6324 | 0.96924 |

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|---|---|---|---|---|---|---|
| NRG1 | rs17635931 (A/C) | 8 | 32264311 | -0.56 | 0.633 | 0.96924 |
| NRG3 | rs2347331 (C/G) | 10 | 83737461 | 0.58 | 0.6336 | 0.96924 |
| NRG1 | rs17728839 (A/G) | 8 | 32517515 | 1.10 | 0.6339 | 0.96924 |
| EGF | rs2298982 (A/G) | 4 | 110846796 | -0.78 | 0.6339 | 0.96924 |
| EGF | rs11568978 (A/G) | 4 | 110889909 | 0.87 | 0.6342 | 0.96924 |
| NRG3 | rs571797 (G/A) | 10 | 84503055 | -0.65 | 0.6343 | 0.96924 |
| NRG3 | rs2494023 (A/C) | 10 | 84484985 | 0.51 | 0.6344 | 0.96924 |
| NRG1 | rs1354334 (C/A) | 8 | 31680070 | 0.51 | 0.6352 | 0.96924 |
| TGFA | rs3732253 (G/A) | 2 | 70676098 | 0.62 | 0.6352 | 0.96924 |
| TGFA | rs11466212 (A/G) | 2 | 70757358 | -0.89 | 0.636 | 0.96924 |
| ERBB4 | rs10445735 (A/G) | 2 | 212913183 | -0.79 | 0.6363 | 0.96924 |
| EGFR | rs1558542 (G/A) | 7 | 55134272 | 0.67 | 0.6364 | 0.96924 |
| NRG3 | rs10786762 (G/A) | 10 | 83670102 | -0.60 | 0.6364 | 0.96924 |
| NRG1 | rs2200033 (G/A) | 8 | 31815670 | -0.58 | 0.637 | 0.96924 |
| NRG1 | rs7006674 (G/A) | 8 | 31575884 | -0.60 | 0.6378 | 0.96924 |
| NRG3 | rs342398 (G/A) | 10 | 84620220 | 0.69 | 0.6383 | 0.96924 |
| ERBB4 | rs10207288 (A/G) | 2 | 212541377 | -0.55 | 0.6391 | 0.96924 |
| TGFA | rs731461 (G/A) | 2 | 70748334 | -0.61 | 0.6394 | 0.96924 |
| NRG2 | rs6895139 (G/A) | 5 | 139295821 | 0.92 | 0.64 | 0.96924 |
| NRG2 | rs58447715 (G/A) | 5 | 139355739 | 1.02 | 0.6403 | 0.96924 |
| NRG3 | rs7089781 (G/A) | 10 | 84566090 | -0.70 | 0.6406 | 0.96924 |
| ERBB4 | rs7419259 (C/A) | 2 | 212620510 | 0.55 | 0.6406 | 0.96924 |
| NRG1 | rs113490374 (A/G) | 8 | 31898477 | 0.92 | 0.6407 | 0.96924 |
| EGFR | rs4947492 (A/G) | 7 | 55187992 | -0.50 | 0.6413 | 0.96924 |
| ERBB4 | rs839498 (A/C) | 2 | 212828771 | 1.01 | 0.6414 | 0.96924 |
| NRG3 | rs201345318 (A/C) | 10 | 83908532 | -0.60 | 0.6416 | 0.96924 |
| NRG3 | rs10884251 (G/A) | 10 | 83908565 | -0.60 | 0.6416 | 0.96924 |
| NRG2 | rs34308038 (G/A) | 5 | 139396184 | 0.96 | 0.6421 | 0.96924 |
| NRG1 | rs28662908 (A/G) | 8 | 31507015 | 0.61 | 0.6423 | 0.96924 |
| NRG3 | rs17098797 (C/A) | 10 | 83709652 | 0.88 | 0.6423 | 0.96924 |
| NRG3 | rs10884066 (G/A) | 10 | 83794963 | -0.54 | 0.6423 | 0.96924 |
| ERBB4 | rs16847917 (G/A) | 2 | 213080786 | 0.93 | 0.6423 | 0.96924 |
| NRG1 | rs73578505 (A/G) | 8 | 31721340 | -0.69 | 0.6425 | 0.96924 |
| NRG3 | rs10748871 (G/A) | 10 | 83790407 | -0.49 | 0.6429 | 0.96924 |
| NRG2 | rs264347 (G/A) | 5 | 139360590 | 0.51 | 0.6432 | 0.96924 |
| EGFR | rs56246439 (A/C) | 7 | 55103964 | -0.65 | 0.6433 | 0.96924 |
| NRG3 | rs1124305 (A/G) | 10 | 83900555 | -0.52 | 0.6443 | 0.96924 |
| EREG | rs7662139 (A/C) | 4 | 75232431 | 0.66 | 0.6452 | 0.96924 |
| EREG | rs4694683 (G/A) | 4 | 75243702 | 0.66 | 0.6452 | 0.96924 |
| NRG3 | rs74146134 (G/A) | 10 | 84393476 | 0.88 | 0.6453 | 0.96924 |
| NRG1 | rs17669617 (A/G) | 8 | 32579109 | 0.63 | 0.6454 | 0.96924 |

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|---|---|---|---|---|---|---|
| ERBB4 | rs4672648 (A/G) | 2 | 213399917 | -0.63 | 0.6458 | 0.96924 |
| NRG3 | rs10786760 (G/A) | 10 | 83664575 | -0.56 | 0.6461 | 0.96924 |
| NRG1 | rs73578534 (G/A) | 8 | 31750239 | -0.68 | 0.6465 | 0.96924 |
| NRG1 | rs4733303 (A/G) | 8 | 32019288 | 0.50 | 0.647 | 0.96924 |
| NRG3 | rs1416851 (G/A) | 10 | 84335691 | 0.56 | 0.6471 | 0.96924 |
| ERBB4 | rs62184480 (G/A) | 2 | 212654200 | 0.55 | 0.6489 | 0.97012 |
| ERBB4 | rs6734836 (A/G) | 2 | 213233631 | 0.51 | 0.649 | 0.97012 |
| BTC | rs77548995 (A/G) | 4 | 75693867 | -0.95 | 0.6491 | 0.97012 |
| ERBB4 | rs1098065 (A/G) | 2 | 212835954 | 0.99 | 0.6493 | 0.97012 |
| NRG1 | rs1948098 (A/G) | 8 | 32184932 | -0.52 | 0.65 | 0.97056 |
| ERBB4 | rs7425448 (G/A) | 2 | 212558540 | -0.66 | 0.6518 | 0.97096 |
| ERBB4 | rs1473636 (G/A) | 2 | 212882190 | -0.69 | 0.6518 | 0.97096 |
| MUC4 | rs2688513 (A/G) | 3 | 195505664 | 0.67 | 0.6529 | 0.97096 |
| ERBB4 | rs1505372 (A/C) | 2 | 213316470 | -0.52 | 0.6531 | 0.97096 |
| NRG1 | rs7839411 (A/G) | 8 | 31996755 | -0.91 | 0.6533 | 0.97096 |
| ERBB4 | rs6732128 (A/C) | 2 | 212528298 | 0.60 | 0.6533 | 0.97096 |
| NRG2 | rs265147 (A/G) | 5 | 139400532 | 0.56 | 0.654 | 0.97096 |
| ERBB4 | rs76168336 (A/G) | 2 | 212384219 | -0.88 | 0.6542 | 0.97096 |
| NRG1 | rs2466052 (A/G) | 8 | 32511640 | -0.98 | 0.6547 | 0.97096 |
| NRG3 | rs2224076 (A/G) | 10 | 83852072 | -0.55 | 0.6547 | 0.97096 |
| NRG3 | rs11196399 (A/G) | 10 | 84665013 | 0.51 | 0.6547 | 0.97096 |
| NRG3 | rs1649949 (G/A) | 10 | 83916424 | 0.55 | 0.6562 | 0.97107 |
| ERBB4 | rs17335043 (A/C) | 2 | 212426466 | 0.74 | 0.6563 | 0.97107 |
| ERBB4 | rs6712126 (G/A) | 2 | 212916157 | 0.64 | 0.6564 | 0.97107 |
| NRG3 | rs4360649 (A/G) | 10 | 84661601 | 0.51 | 0.6568 | 0.97107 |
| NRG3 | rs34321233 (A/G) | 10 | 84351856 | -0.75 | 0.657 | 0.97107 |
| NRG3 | rs604482 (C/A) | 10 | 84412569 | -0.74 | 0.6572 | 0.97107 |
| ERBB4 | rs12475812 (A/C) | 2 | 212688964 | 0.66 | 0.658 | 0.97165 |
| ERBB4 | rs13002674 (A/G) | 2 | 212733164 | 0.59 | 0.6584 | 0.97165 |
| NRG3 | rs10885239 (G/A) | 10 | 84470658 | -0.54 | 0.66 | 0.97342 |
| ERBB4 | rs3791691 (G/A) | 2 | 212264560 | -0.58 | 0.662 | 0.97376 |
| ERBB4 | rs13421680 (A/G) | 2 | 212416029 | -0.52 | 0.6622 | 0.97376 |
| ERBB4 | rs2371277 (A/G) | 2 | 212554979 | -0.57 | 0.6628 | 0.97376 |
| ERBB4 | rs11887237 (A/C) | 2 | 212305570 | -0.84 | 0.6634 | 0.97376 |
| NRG3 | rs11193663 (C/A) | 10 | 84076732 | -0.62 | 0.664 | 0.97376 |
| NRG3 | rs17100444 (G/A) | 10 | 84424078 | -0.55 | 0.6648 | 0.97376 |
| ERBB4 | rs4366846 (G/A) | 2 | 213379537 | -0.57 | 0.6651 | 0.97376 |
| NRG1 | rs170576 (G/A) | 8 | 31793055 | 0.69 | 0.6657 | 0.97376 |
| ERBB4 | rs35762488 (A/G) | 2 | 212546559 | 0.71 | 0.667 | 0.97376 |
| NRG3 | rs10884936 (C/A) | 10 | 84321914 | -0.76 | 0.6674 | 0.97376 |
| ERBB4 | rs66522864 (A/G) | 2 | 212966947 | 0.47 | 0.6677 | 0.97376 |

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|---|---|---|---|---|---|---|
| EGFR | rs1024748 (A/C) | 7 | 55128339 | 0.61 | 0.668 | 0.97376 |
| NRG1 | rs7012325 (A/G) | 8 | 32545333 | -0.96 | 0.6681 | 0.97376 |
| NRG3 | rs1649934 (G/A) | 10 | 83884894 | -0.47 | 0.6682 | 0.97376 |
| ERBB4 | rs10932398 (A/G) | 2 | 212627259 | -0.47 | 0.6687 | 0.97376 |
| NRG3 | rs12241441 (G/A) | 10 | 84008661 | -0.67 | 0.6691 | 0.97376 |
| ERBB4 | rs13413659 (A/C) | 2 | 212382319 | 1.06 | 0.6693 | 0.97376 |
| NRG1 | rs13276181 (G/A) | 8 | 32242498 | 0.47 | 0.6694 | 0.97376 |
| NRG3 | rs11595839 (A/C) | 10 | 84205078 | -0.68 | 0.6712 | 0.97376 |
| NRG3 | rs74920288 (C/A) | 10 | 84231001 | -0.51 | 0.6734 | 0.97376 |
| TGFA | rs77929275 (G/A) | 2 | 70707199 | -0.51 | 0.6737 | 0.97376 |
| ERBB4 | rs2371275 (A/G) | 2 | 212555154 | 0.46 | 0.6737 | 0.97376 |
| EGF | rs10002971 (A/C) | 4 | 110896050 | 0.51 | 0.6738 | 0.97376 |
| ERBB4 | rs7560730 (A/G) | 2 | 212990868 | -0.64 | 0.674 | 0.97376 |
| TGFA | rs3911077 (G/A) | 2 | 70717078 | -0.51 | 0.6741 | 0.97376 |
| NRG3 | rs679571 (G/A) | 10 | 84329838 | 0.48 | 0.6743 | 0.97376 |
| ERBB4 | rs17744862 (A/G) | 2 | 212244520 | 0.94 | 0.6754 | 0.97376 |
| NRG3 | rs660464 (G/A) | 10 | 84350877 | 0.47 | 0.6756 | 0.97376 |
| NRG1 | rs13252799 (A/G) | 8 | 32379953 | -0.59 | 0.6769 | 0.97376 |
| ERBB4 | rs2102996 (G/A) | 2 | 212841868 | -0.95 | 0.6775 | 0.97376 |
| EGFR | rs845560 (G/A) | 7 | 55250794 | 0.53 | 0.6776 | 0.97376 |
| ERBB4 | rs62184063 (G/C) | 2 | 213203096 | 0.75 | 0.678 | 0.97376 |
| NRG1 | rs6985581 (A/G) | 8 | 32319538 | -0.44 | 0.6786 | 0.97376 |
| ERBB4 | rs13423759 (A/C) | 2 | 212245972 | 1.17 | 0.6787 | 0.97376 |
| BTC | rs72855860 (G/A) | 4 | 75714054 | 0.63 | 0.6794 | 0.97376 |
| NRG3 | rs7081891 (G/A) | 10 | 83821592 | -0.45 | 0.6799 | 0.97376 |
| ERBB4 | rs12694259 (G/A) | 2 | 212895366 | 0.46 | 0.6801 | 0.97376 |
| NRG3 | rs614287 (G/A) | 10 | 83931937 | 0.47 | 0.6805 | 0.97376 |
| NRG1 | rs1699125 (A/G) | 8 | 31781905 | 0.61 | 0.681 | 0.97376 |
| TGFA | rs11466191 (C/G) | 2 | 70780081 | -0.51 | 0.681 | 0.97376 |
| BTC | rs11734944 (A/G) | 4 | 75681217 | -0.45 | 0.6813 | 0.97376 |
| ERBB4 | rs7570613 (A/G) | 2 | 212629579 | 0.53 | 0.6817 | 0.97376 |
| EGFR | rs1015793 (A/G) | 7 | 55114316 | 0.61 | 0.682 | 0.97376 |
| TGFA | rs199828822 (G/A) | 2 | 70723562 | -0.45 | 0.6825 | 0.97376 |
| NRG3 | rs578080 (A/G) | 10 | 84501882 | -0.51 | 0.6826 | 0.97376 |
| NRG2 | rs171951 (C/A) | 5 | 139372149 | 0.45 | 0.6826 | 0.97376 |
| ERBB4 | rs201229648 (A/T) | 2 | 212552218 | -0.45 | 0.6828 | 0.97376 |
| NRG3 | rs2783413 (A/G) | 10 | 84455315 | 0.46 | 0.6829 | 0.97376 |
| ERBB4 | rs200822862 (A/C) | 2 | 213151322 | -0.44 | 0.683 | 0.97376 |
| ERBB4 | rs13414946 (G/A) | 2 | 212296470 | -0.74 | 0.6832 | 0.97376 |
| EGF | rs11568993 (G/A) | 4 | 110897315 | -0.84 | 0.6833 | 0.97376 |
| ERBB4 | rs12151481 (G/A) | 2 | 213111238 | 0.52 | 0.6835 | 0.97376 |

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|---|---|---|---|---|---|---|
| EGFR | rs759159 (C/A) | 7 | 55179400 | 0.46 | 0.6837 | 0.97376 |
| ERBB4 | rs17346713 (A/G) | 2 | 213156498 | 0.55 | 0.6839 | 0.97376 |
| EGFR | rs13244925 (C/A) | 7 | 55192256 | -0.44 | 0.6842 | 0.97376 |
| NRG1 | rs186649104 (G/A) | 8 | 32153473 | 0.99 | 0.6847 | 0.97376 |
| NRG1 | rs16878953 (A/G) | 8 | 32044425 | 0.59 | 0.6856 | 0.97376 |
| NRG1 | rs76369822 (A/G) | 8 | 32061785 | 0.93 | 0.6859 | 0.97376 |
| NRG3 | rs7101028 (A/C) | 10 | 83785860 | -0.44 | 0.6867 | 0.97376 |
| ERBB4 | rs7567959 (G/A) | 2 | 212521325 | -0.43 | 0.6878 | 0.97376 |
| NRG1 | rs435904 (G/A) | 8 | 31789101 | 0.64 | 0.688 | 0.97376 |
| NRG1 | rs7845510 (A/G) | 8 | 32579646 | 0.68 | 0.6881 | 0.97376 |
| NRG2 | rs77864329 (G/A) | 5 | 139256795 | 0.91 | 0.6881 | 0.97376 |
| NRG3 | rs2434068 (G/A) | 10 | 83974607 | -0.90 | 0.6883 | 0.97376 |
| NRG1 | rs327359 (G/A) | 8 | 31803458 | 0.64 | 0.6891 | 0.97376 |
| NRG3 | rs1764065 (A/G) | 10 | 83942004 | -0.46 | 0.6892 | 0.97376 |
| NRG3 | rs201735485 (C/A) | 10 | 84495694 | 0.43 | 0.6894 | 0.97376 |
| BTC | rs1452310 (A/G) | 4 | 75715125 | 0.61 | 0.6897 | 0.97376 |
| NRG3 | rs2820107 (A/G) | 10 | 84494274 | 0.43 | 0.6897 | 0.97376 |
| NRG3 | rs7069367 (A/G) | 10 | 84074976 | 0.52 | 0.6901 | 0.97376 |
| NRG1 | rs199974185 (A/G) | 8 | 32364690 | 0.47 | 0.6907 | 0.97376 |
| NRG2 | rs975642 (A/G) | 5 | 139384490 | 0.42 | 0.6909 | 0.97376 |
| EGF | rs12506362 (G/A) | 4 | 110922680 | 0.92 | 0.6911 | 0.97376 |
| MUC4 | rs75411247 (G/A) | 3 | 195533190 | 0.86 | 0.6916 | 0.97376 |
| ERBB4 | rs16846352 (G/A) | 2 | 212378242 | -0.64 | 0.6918 | 0.97376 |
| NRG3 | rs981776 (G/A) | 10 | 83872165 | 0.43 | 0.692 | 0.97376 |
| NRG3 | rs12218527 (A/G) | 10 | 84026285 | -0.59 | 0.6921 | 0.97376 |
| NRG1 | rs56126917 (A/G) | 8 | 32590992 | 0.60 | 0.6922 | 0.97376 |
| ERBB4 | rs62182999 (A/G) | 2 | 212605745 | 0.48 | 0.6923 | 0.97376 |
| BTC | rs1349634 (G/A) | 4 | 75718547 | 0.43 | 0.6928 | 0.97376 |
| MUC4 | rs1104760 (A/G) | 3 | 195517321 | -0.54 | 0.693 | 0.97376 |
| NRG3 | rs2483300 (A/G) | 10 | 84653084 | 0.44 | 0.6937 | 0.97417 |
| EGFR | rs10241326 (G/A) | 7 | 55248787 | 0.44 | 0.6942 | 0.97431 |
| ERBB4 | rs13423577 (A/G) | 2 | 212520563 | -0.69 | 0.6948 | 0.97444 |
| NRG3 | rs12265039 (G/A) | 10 | 84578104 | -0.44 | 0.6951 | 0.97444 |
| EGFR | rs7795743 (A/G) | 7 | 55250130 | 0.43 | 0.6961 | 0.97484 |
| NRG1 | rs13254149 (G/A) | 8 | 32348088 | -0.53 | 0.6962 | 0.97484 |
| MUC4 | rs11922145 (T/A) | 3 | 195520807 | -0.57 | 0.6966 | 0.97484 |
| NRG3 | rs17655972 (G/A) | 10 | 83825479 | 0.44 | 0.6972 | 0.97511 |
| NRG1 | rs76558928 (A/G) | 8 | 31862492 | -0.97 | 0.6977 | 0.97524 |
| NRG1 | rs62497650 (G/A) | 8 | 32238984 | 0.43 | 0.6993 | 0.97642 |
| NRG1 | rs28547336 (A/G) | 8 | 32576545 | 0.52 | 0.6994 | 0.97642 |
| NRG3 | rs10884421 (G/A) | 10 | 84017046 | 0.43 | 0.7 | 0.97642 |

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|---|---|---|---|---|---|---|
| NRG1 | rs73592164 (A/C) | 8 | 32255924 | 0.61 | 0.7004 | 0.97642 |
| TGFA | rs408990 (G/A) | 2 | 70744617 | 0.64 | 0.7016 | 0.97642 |
| NRG1 | rs4733304 (G/A) | 8 | 32023292 | 0.65 | 0.7022 | 0.97642 |
| NRG1 | rs16878764 (A/C) | 8 | 31936552 | -0.45 | 0.7025 | 0.97642 |
| NRG1 | rs113074948 (A/C) | 8 | 31806295 | -0.71 | 0.7031 | 0.97642 |
| ERBB3 | rs2292238 (A/C) | 12 | 56493822 | -0.42 | 0.7033 | 0.97642 |
| NRG3 | rs2881608 (A/G) | 10 | 83812026 | -0.43 | 0.7033 | 0.97642 |
| ERBB4 | rs6715314 (G/A) | 2 | 213017607 | -0.44 | 0.7034 | 0.97642 |
| EGFR | rs76692262 (A/G) | 7 | 55089831 | 0.62 | 0.7036 | 0.97642 |
| NRG1 | rs7013361 (C/A) | 8 | 32363288 | 0.45 | 0.7041 | 0.97642 |
| ERBB4 | rs10200506 (A/G) | 2 | 213040853 | 0.58 | 0.7048 | 0.97642 |
| NRG3 | rs342367 (T/A) | 10 | 84565339 | -0.42 | 0.7056 | 0.97642 |
| NRG3 | rs580298 (A/G) | 10 | 84678397 | 0.58 | 0.7057 | 0.97642 |
| ERBB4 | rs62182615 (G/A) | 2 | 213111971 | 0.48 | 0.706 | 0.97642 |
| NRG3 | rs10883899 (A/G) | 10 | 83670383 | -0.75 | 0.7092 | 0.97642 |
| NRG1 | rs1383893 (G/A) | 8 | 31724648 | 0.43 | 0.7093 | 0.97642 |
| NRG1 | rs200427989 (G/A) | 8 | 31508288 | -0.44 | 0.7098 | 0.97642 |
| EGFR | rs845551 (G/A) | 7 | 55237283 | 0.46 | 0.7105 | 0.97642 |
| NRG1 | rs34442697 (A/G) | 8 | 32008543 | -0.74 | 0.7112 | 0.97642 |
| NRG3 | rs910583 (G/A) | 10 | 83741277 | 0.46 | 0.7123 | 0.97642 |
| NRG3 | rs10736175 (G/A) | 10 | 83824944 | -0.45 | 0.7124 | 0.97642 |
| ERBB4 | rs16848675 (A/G) | 2 | 213349997 | -0.87 | 0.7132 | 0.97642 |
| NRG1 | rs28719657 (G/A) | 8 | 32234017 | 0.50 | 0.7136 | 0.97642 |
| NRG3 | rs12767156 (G/A) | 10 | 83813595 | -0.45 | 0.7137 | 0.97642 |
| NRG1 | rs73590130 (A/G) | 8 | 31614608 | -0.53 | 0.7138 | 0.97642 |
| ERBB4 | rs1505369 (A/G) | 2 | 213318593 | 0.40 | 0.7142 | 0.97642 |
| EGFR | rs2330951 (A/C) | 7 | 55174342 | 0.49 | 0.7147 | 0.97642 |
| NRG1 | rs2347502 (A/C) | 8 | 32231416 | 0.39 | 0.7148 | 0.97642 |
| ERBB4 | rs7585000 (A/C) | 2 | 212264818 | -0.43 | 0.7154 | 0.97642 |
| NRG3 | rs56117798 (G/A) | 10 | 83978031 | 0.77 | 0.7155 | 0.97642 |
| NRG1 | rs10093683 (C/G) | 8 | 32528312 | -0.61 | 0.7157 | 0.97642 |
| NRG3 | rs10786787 (G/A) | 10 | 83730893 | 0.44 | 0.7158 | 0.97642 |
| ERBB4 | rs6435670 (C/A) | 2 | 212655885 | 0.44 | 0.7161 | 0.97642 |
| ERBB4 | rs10189506 (G/A) | 2 | 213239858 | -0.50 | 0.7164 | 0.97642 |
| ERBB4 | rs10469656 (G/A) | 2 | 212486350 | -0.54 | 0.717 | 0.97642 |
| NRG1 | rs13251778 (A/G) | 8 | 31815427 | 0.59 | 0.7171 | 0.97642 |
| EGFR | rs6593211 (G/A) | 7 | 55277964 | 0.42 | 0.7177 | 0.97642 |
| NRG1 | rs1947911 (G/A) | 8 | 32081795 | -0.70 | 0.7185 | 0.97642 |
| NRG3 | rs505079 (A/G) | 10 | 84623627 | -0.41 | 0.7186 | 0.97642 |
| ERBB4 | rs12618175 (A/C) | 2 | 212864886 | 0.39 | 0.7191 | 0.97642 |
| NRG1 | rs10216782 (G/A) | 8 | 32234759 | -0.51 | 0.7203 | 0.97642 |

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|---|---|---|---|---|---|---|
| ERBB4 | rs4439896 (A/G) | 2 | 212345458 | -0.44 | 0.7203 | 0.97642 |
| ERBB4 | rs2033646 (G/A) | 2 | 212322858 | -0.56 | 0.7204 | 0.97642 |
| MUC4 | rs2641772 (A/G) | 3 | 195531841 | 0.38 | 0.7206 | 0.97642 |
| NRG3 | rs17099657 (A/G) | 10 | 84005517 | 0.66 | 0.7207 | 0.97642 |
| ERBB4 | rs7573568 (A/G) | 2 | 213391696 | -0.51 | 0.7208 | 0.97642 |
| ERBB4 | rs1351593 (G/A) | 2 | 213394605 | -0.51 | 0.7208 | 0.97642 |
| NRG1 | rs2975503 (T/A) | 8 | 32574124 | 0.42 | 0.7209 | 0.97642 |
| EGFR | rs4947978 (C/A) | 7 | 55186456 | -0.40 | 0.721 | 0.97642 |
| NRG1 | rs75263811 (A/G) | 8 | 31919857 | -0.88 | 0.7213 | 0.97642 |
| NRG3 | rs7919853 (G/A) | 10 | 84556953 | 0.52 | 0.7214 | 0.97642 |
| NRG3 | rs11195879 (A/G) | 10 | 84531521 | -0.56 | 0.7219 | 0.97642 |
| BTC | rs1869172 (A/C) | 4 | 75718366 | 0.55 | 0.7226 | 0.97642 |
| NRG2 | rs2436387 (C/A) | 5 | 139419985 | -0.41 | 0.7233 | 0.97642 |
| BTC | rs11097375 (C/A) | 4 | 75695676 | 0.52 | 0.7238 | 0.97642 |
| NRG3 | rs2644202 (G/A) | 10 | 84501148 | 0.55 | 0.7238 | 0.97642 |
| ERBB4 | rs10194693 (A/C) | 2 | 212945761 | 0.56 | 0.724 | 0.97642 |
| NRG3 | rs71483400 (G/A) | 10 | 83873157 | -0.67 | 0.7251 | 0.97642 |
| NRG3 | rs12767327 (C/A) | 10 | 83813700 | -0.43 | 0.7252 | 0.97642 |
| ERBB4 | rs10164682 (G/A) | 2 | 213062018 | -0.39 | 0.7254 | 0.97642 |
| ERBB4 | rs10188703 (G/A) | 2 | 212379150 | -0.39 | 0.7276 | 0.97642 |
| NRG1 | rs28366800 (G/A) | 8 | 32255252 | -0.40 | 0.7277 | 0.97642 |
| TGFA | rs538118 (A/G) | 2 | 70676639 | -0.39 | 0.728 | 0.97642 |
| TGFA | rs61025727 (A/G) | 2 | 70756681 | -0.57 | 0.7281 | 0.97642 |
| ERBB4 | rs6749560 (G/A) | 2 | 212256192 | -0.45 | 0.7288 | 0.97642 |
| MUC4 | rs11928440 (A/G) | 3 | 195500758 | 0.53 | 0.7293 | 0.97642 |
| TGFA | rs416254 (G/A) | 2 | 70766404 | -0.37 | 0.7303 | 0.97642 |
| NRG3 | rs512064 (C/A) | 10 | 84623726 | -0.39 | 0.7306 | 0.97642 |
| MUC4 | rs73079395 (C/A) | 3 | 195481111 | 0.98 | 0.7306 | 0.97642 |
| NRG3 | rs1414771 (G/A) | 10 | 84013558 | -0.80 | 0.7307 | 0.97642 |
| ERBB4 | rs10932374 (G/A) | 2 | 212244403 | -0.45 | 0.7307 | 0.97642 |
| NRG3 | rs6421337 (G/A) | 10 | 83747396 | 0.43 | 0.7309 | 0.97642 |
| NRG3 | rs12265675 (A/G) | 10 | 84079745 | -0.50 | 0.7317 | 0.97642 |
| MUC4 | rs882605 (C/A) | 3 | 195517553 | -0.47 | 0.7317 | 0.97642 |
| ERBB4 | rs6742399 (G/A) | 2 | 212300055 | -0.37 | 0.7317 | 0.97642 |
| TGFA | rs62151575 (A/G) | 2 | 70734687 | 0.58 | 0.7321 | 0.97642 |
| NRG1 | rs2466103 (A/C) | 8 | 32412304 | 0.42 | 0.7323 | 0.97642 |
| ERBB4 | rs2371279 (C/A) | 2 | 212553703 | -0.41 | 0.7329 | 0.97642 |
| NRG3 | rs73312903 (G/A) | 10 | 84158251 | -0.48 | 0.7331 | 0.97642 |
| NRG2 | rs2560711 (A/G) | 5 | 139394941 | 0.43 | 0.7331 | 0.97642 |
| MUC4 | rs2177336 (G/A) | 3 | 195516878 | -0.46 | 0.7332 | 0.97642 |
| MUC4 | rs1106502 (A/G) | 3 | 195517258 | -0.46 | 0.7332 | 0.97642 |

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|---|---|---|---|---|---|---|
| NRG1 | rs6987310 (A/G) | 8 | 31675630 | 0.47 | 0.7338 | 0.97642 |
| ERBB4 | rs4132462 (G/A) | 2 | 212635589 | 0.42 | 0.7341 | 0.97642 |
| NRG3 | rs999889 (G/A) | 10 | 84279949 | -0.41 | 0.7346 | 0.97642 |
| ERBB4 | rs4569408 (A/G) | 2 | 212330564 | 0.42 | 0.7367 | 0.97642 |
| NRG1 | rs7010141 (A/C) | 8 | 31925511 | 0.99 | 0.7384 | 0.97642 |
| NRG3 | rs2881607 (A/G) | 10 | 83809837 | 0.38 | 0.7385 | 0.97642 |
| NRG3 | rs7917405 (A/G) | 10 | 84618072 | 0.45 | 0.7386 | 0.97642 |
| TGFA | rs404420 (G/A) | 2 | 70733526 | -0.40 | 0.7393 | 0.97642 |
| NRG1 | rs34423096 (A/T) | 8 | 32548077 | 0.39 | 0.7394 | 0.97642 |
| NRG3 | rs7922963 (G/A) | 10 | 84445140 | -0.43 | 0.7396 | 0.97642 |
| ERBB4 | rs10205553 (A/G) | 2 | 212559948 | -0.36 | 0.7398 | 0.97642 |
| NRG1 | rs2881542 (C/A) | 8 | 32058903 | 0.84 | 0.74 | 0.97642 |
| NRG1 | rs34195089 (A/G) | 8 | 31870957 | 0.53 | 0.7407 | 0.97642 |
| EGFR | rs10280515 (A/G) | 7 | 55173700 | 0.71 | 0.741 | 0.97642 |
| NRG3 | rs7096123 (A/G) | 10 | 84033986 | 0.38 | 0.7411 | 0.97642 |
| ERBB4 | rs12373751 (G/A) | 2 | 212936891 | 0.43 | 0.7415 | 0.97642 |
| NRG1 | rs6992907 (A/G) | 8 | 32227926 | -0.35 | 0.7427 | 0.97642 |
| NRG1 | rs5006809 (G/A) | 8 | 32228088 | -0.35 | 0.7427 | 0.97642 |
| NRG1 | rs1383888 (A/G) | 8 | 31758989 | -0.43 | 0.7428 | 0.97642 |
| NRG1 | rs1462874 (A/C) | 8 | 31851335 | 0.41 | 0.743 | 0.97642 |
| NRG1 | rs1626771 (G/A) | 8 | 32220852 | 0.37 | 0.7431 | 0.97642 |
| ERBB4 | rs1851184 (A/G) | 2 | 212523424 | 0.34 | 0.7431 | 0.97642 |
| NRG3 | rs673049 (G/A) | 10 | 84386973 | 0.36 | 0.7434 | 0.97642 |
| NRG3 | rs2249075 (A/G) | 10 | 84483977 | 0.50 | 0.7441 | 0.97642 |
| ERBB4 | rs9288445 (G/A) | 2 | 212847371 | -0.43 | 0.7444 | 0.97642 |
| NRG3 | rs1764097 (G/A) | 10 | 83991317 | -0.59 | 0.7445 | 0.97642 |
| NRG1 | rs7840880 (G/A) | 8 | 31840506 | 0.94 | 0.7447 | 0.97642 |
| NRG1 | rs1714422 (G/A) | 8 | 32212219 | -0.50 | 0.745 | 0.97642 |
| NRG3 | rs1739768 (G/A) | 10 | 83881713 | -0.68 | 0.7452 | 0.97642 |
| EGFR | rs884225 (A/G) | 7 | 55274084 | -0.58 | 0.7455 | 0.97642 |
| NRG1 | rs10108099 (A/T) | 8 | 32232651 | -0.48 | 0.7456 | 0.97642 |
| ERBB4 | rs4321317 (A/G) | 2 | 212346739 | 0.38 | 0.7467 | 0.97733 |
| NRG1 | rs17603876 (A/G) | 8 | 31668404 | -0.64 | 0.7472 | 0.97745 |
| NRG3 | rs10509445 (A/G) | 10 | 83795839 | -0.36 | 0.7482 | 0.97823 |
| NRG3 | rs17656252 (G/A) | 10 | 83832049 | 0.58 | 0.7492 | 0.97859 |
| NRG1 | rs55694684 (A/G) | 8 | 31859236 | -0.65 | 0.7495 | 0.97859 |
| ERBB4 | rs961593 (A/G) | 2 | 212408554 | 0.36 | 0.75 | 0.97859 |
| ERBB4 | rs57878911 (A/G) | 2 | 212582994 | -0.68 | 0.7501 | 0.97859 |
| BTC | rs1377032 (A/G) | 4 | 75712104 | 0.49 | 0.7511 | 0.9792 |
| ERBB4 | rs4100599 (G/A) | 2 | 212308372 | -0.42 | 0.7519 | 0.9792 |
| NRG3 | rs7073972 (G/A) | 10 | 84237349 | -0.38 | 0.752 | 0.9792 |

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|---|---|---|---|---|---|---|
| NRG3 | rs951204 (A/G) | 10 | 84048765 | -0.45 | 0.7522 | 0.9792 |
| ERBB4 | rs16846200 (A/C) | 2 | 212311744 | -0.46 | 0.7529 | 0.97958 |
| NRG1 | rs12216802 (A/G) | 8 | 32340967 | 0.41 | 0.7537 | 0.98003 |
| NRG2 | rs74505169 (G/A) | 5 | 139358324 | 0.68 | 0.7544 | 0.98003 |
| ERBB4 | rs6721178 (C/A) | 2 | 212845714 | 0.40 | 0.7548 | 0.98003 |
| NRG3 | rs2253822 (A/G) | 10 | 84443346 | 0.49 | 0.7554 | 0.98003 |
| NRG3 | rs10786827 (C/A) | 10 | 83787265 | -0.33 | 0.7558 | 0.98003 |
| BTC | rs10005089 (G/A) | 4 | 75694606 | 0.41 | 0.7559 | 0.98003 |
| NRG2 | rs60293875 (G/A) | 5 | 139413164 | -0.52 | 0.7562 | 0.98003 |
| NRG1 | rs776398 (A/G) | 8 | 31765337 | 0.34 | 0.7565 | 0.98003 |
| ERBB4 | rs6710350 (A/G) | 2 | 213073735 | -0.50 | 0.7573 | 0.98014 |
| NRG2 | rs12163954 (A/G) | 5 | 139299907 | 0.59 | 0.7574 | 0.98014 |
| NRG1 | rs16879327 (G/A) | 8 | 32257621 | 0.50 | 0.7584 | 0.98031 |
| ERBB4 | rs11901482 (A/C) | 2 | 212381919 | 0.39 | 0.7587 | 0.98031 |
| MUC4 | rs73892864 (A/G) | 3 | 195487537 | -0.73 | 0.7593 | 0.98031 |
| NRG3 | rs12259197 (G/A) | 10 | 84028006 | 0.67 | 0.7596 | 0.98031 |
| NRG1 | rs34566719 (C/G) | 8 | 31693944 | -0.66 | 0.7598 | 0.98031 |
| NRG3 | rs6584594 (A/G) | 10 | 84014053 | 0.40 | 0.761 | 0.98031 |
| NRG3 | rs73306568 (G/A) | 10 | 83721941 | 0.58 | 0.7613 | 0.98031 |
| NRG1 | rs1564126 (A/C) | 8 | 31925867 | -0.34 | 0.7614 | 0.98031 |
| NRG3 | rs10885087 (G/A) | 10 | 84409894 | -0.33 | 0.7614 | 0.98031 |
| BTC | rs28431134 (G/A) | 4 | 75688733 | 0.40 | 0.7616 | 0.98031 |
| NRG3 | rs11192502 (G/A) | 10 | 83859375 | -0.58 | 0.763 | 0.98062 |
| EGF | rs3822286 (G/A) | 4 | 110925459 | -0.78 | 0.763 | 0.98062 |
| HBEGF | rs2074611 (G/A) | 5 | 139722345 | -0.53 | 0.7634 | 0.98062 |
| ERBB4 | rs7421820 (G/A) | 2 | 212588627 | 0.44 | 0.7643 | 0.98062 |
| TGFA | rs13393308 (G/A) | 2 | 70744323 | 0.92 | 0.7644 | 0.98062 |
| ERBB4 | rs12987596 (G/A) | 2 | 212856539 | 0.33 | 0.7646 | 0.98062 |
| NRG3 | rs635481 (A/G) | 10 | 84311992 | 0.34 | 0.7647 | 0.98062 |
| NRG1 | rs80062976 (G/A) | 8 | 32602697 | 0.56 | 0.7655 | 0.98113 |
| NRG1 | rs7823498 (A/G) | 8 | 32403573 | 0.39 | 0.7669 | 0.98188 |
| NRG3 | rs7093158 (C/A) | 10 | 84065441 | 0.36 | 0.7669 | 0.98188 |
| NRG1 | rs16879886 (A/G) | 8 | 32584857 | 0.48 | 0.7679 | 0.98191 |
| NRG3 | rs112309006 (A/C) | 10 | 84332354 | 0.31 | 0.7685 | 0.98191 |
| NRG1 | rs2439312 (G/A) | 8 | 32412359 | 0.39 | 0.7693 | 0.98191 |
| ERBB4 | rs77762486 (A/G) | 2 | 212385664 | -0.59 | 0.7698 | 0.98191 |
| NRG1 | rs12541309 (G/A) | 8 | 32545001 | -0.42 | 0.77 | 0.98191 |
| EGFR | rs11976696 (A/G) | 7 | 55232333 | 0.38 | 0.77 | 0.98191 |
| NRG1 | rs17721043 (G/A) | 8 | 32436875 | -0.39 | 0.7701 | 0.98191 |
| NRG2 | rs12655558 (A/T) | 5 | 139395233 | 0.55 | 0.7704 | 0.98191 |
| ERBB4 | rs7604094 (A/C) | 2 | 212378925 | -0.31 | 0.7706 | 0.98191 |

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|---|---|---|---|---|---|---|
| ERBB4 | rs960824 (A/G) | 2 | 212871592 | -0.34 | 0.7725 | 0.98273 |
| NRG1 | rs4733347 (G/A) | 8 | 32376010 | -0.36 | 0.7735 | 0.98273 |
| ERBB4 | rs1020126 (C/A) | 2 | 212703601 | -0.42 | 0.7735 | 0.98273 |
| NRG1 | rs2466048 (A/C) | 8 | 32516055 | -0.31 | 0.7738 | 0.98273 |
| NRG3 | rs17727747 (A/G) | 10 | 83790082 | -0.32 | 0.774 | 0.98273 |
| BTC | rs9307118 (A/G) | 4 | 75682484 | -0.31 | 0.7741 | 0.98273 |
| ERBB4 | rs1505377 (G/A) | 2 | 213304043 | 0.38 | 0.7741 | 0.98273 |
| NRG3 | rs10736173 (G/A) | 10 | 83822865 | 0.38 | 0.7772 | 0.98556 |
| NRG3 | rs1414753 (G/A) | 10 | 84031455 | 0.33 | 0.7778 | 0.98556 |
| NRG3 | rs17687943 (A/G) | 10 | 84696792 | 0.29 | 0.7782 | 0.98556 |
| NRG1 | rs11998291 (A/G) | 8 | 31984536 | -0.81 | 0.779 | 0.98556 |
| NRG1 | rs59861679 (A/G) | 8 | 32295287 | -0.37 | 0.779 | 0.98556 |
| NRG1 | rs11993611 (G/A) | 8 | 32305720 | 0.32 | 0.7805 | 0.98556 |
| NRG2 | rs4440417 (G/A) | 5 | 139332206 | 0.61 | 0.782 | 0.98556 |
| ERBB4 | rs57053115 (G/A) | 2 | 212717793 | -0.42 | 0.7822 | 0.98556 |
| NRG1 | rs62500167 (G/A) | 8 | 32269907 | -0.33 | 0.7824 | 0.98556 |
| ERBB4 | rs62182968 (A/C) | 2 | 212579954 | 0.37 | 0.7824 | 0.98556 |
| NRG1 | rs7819870 (A/C) | 8 | 31575497 | -0.35 | 0.7834 | 0.98556 |
| NRG1 | rs9918832 (A/G) | 8 | 32282597 | 0.34 | 0.7839 | 0.98556 |
| NRG3 | rs17688475 (A/G) | 10 | 84724996 | 0.44 | 0.7859 | 0.98556 |
| ERBB4 | rs10177211 (A/C) | 2 | 212475771 | -0.40 | 0.7861 | 0.98556 |
| NRG3 | rs12771529 (A/C) | 10 | 84625558 | 0.52 | 0.7869 | 0.98556 |
| NRG3 | rs11193660 (G/A) | 10 | 84076497 | 0.53 | 0.7876 | 0.98556 |
| ERBB4 | rs7422464 (A/C) | 2 | 212511895 | -0.56 | 0.7877 | 0.98556 |
| EGFR | rs759169 (G/A) | 7 | 55154636 | -0.41 | 0.7878 | 0.98556 |
| MUC4 | rs62282509 (G/A) | 3 | 195529431 | 0.34 | 0.7878 | 0.98556 |
| ERBB4 | rs12994785 (G/A) | 2 | 212857425 | -0.30 | 0.7885 | 0.98556 |
| NRG1 | rs17690742 (G/A) | 8 | 31914399 | 0.29 | 0.7888 | 0.98556 |
| NRG3 | rs9804192 (G/A) | 10 | 84611008 | 0.34 | 0.789 | 0.98556 |
| TGFA | rs11466297 (A/C) | 2 | 70675707 | -0.57 | 0.7898 | 0.98556 |
| MUC4 | rs2293232 (G/A) | 3 | 195497143 | 0.38 | 0.7898 | 0.98556 |
| NRG3 | rs1937977 (G/A) | 10 | 84185858 | -0.37 | 0.7902 | 0.98556 |
| ERBB4 | rs6722300 (G/A) | 2 | 212544685 | -0.32 | 0.7906 | 0.98556 |
| NRG3 | rs17100728 (A/G) | 10 | 84511080 | 0.59 | 0.7917 | 0.98556 |
| ERBB4 | rs16846896 (G/A) | 2 | 212695168 | -0.48 | 0.7918 | 0.98556 |
| ERBB4 | rs1521539 (G/A) | 2 | 212889635 | -0.59 | 0.7932 | 0.98556 |
| NRG1 | rs17603821 (G/A) | 8 | 31667034 | -0.38 | 0.7935 | 0.98556 |
| ERBB4 | rs10497960 (G/A) | 2 | 212952125 | 0.35 | 0.7936 | 0.98556 |
| NRG1 | rs16879922 (G/A) | 8 | 32611221 | -0.40 | 0.7941 | 0.98556 |
| ERBB4 | rs7564414 (A/G) | 2 | 212585498 | -0.56 | 0.7945 | 0.98556 |
| NRG1 | rs2919381 (A/G) | 8 | 32563924 | -0.29 | 0.7948 | 0.98556 |

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|---|---|---|---|---|---|---|
| ERBB4 | rs13412270 (C/A) | 2 | 212586298 | 0.54 | 0.795 | 0.98556 |
| NRG2 | rs265150 (G/A) | 5 | 139376819 | 0.49 | 0.7955 | 0.98556 |
| NRG1 | rs6999872 (A/C) | 8 | 32024994 | 0.45 | 0.7956 | 0.98556 |
| NRG2 | rs76178519 (G/A) | 5 | 139295721 | 0.55 | 0.7958 | 0.98556 |
| ERBB4 | rs72933746 (A/G) | 2 | 212777973 | -0.38 | 0.7959 | 0.98556 |
| NRG3 | rs2453688 (G/A) | 10 | 84592691 | 0.34 | 0.7961 | 0.98556 |
| NRG3 | rs4073987 (A/G) | 10 | 84427307 | 0.39 | 0.7963 | 0.98556 |
| ERBB4 | rs10176100 (A/G) | 2 | 212545621 | 0.28 | 0.7964 | 0.98556 |
| ERBB4 | rs1009142 (A/G) | 2 | 212440500 | 0.44 | 0.7969 | 0.98556 |
| ERBB4 | rs1402766 (C/A) | 2 | 213033301 | -0.29 | 0.7977 | 0.98556 |
| NRG1 | rs12680129 (A/G) | 8 | 32443145 | 0.59 | 0.7985 | 0.98556 |
| ERBB4 | rs144265625 (G/A) | 2 | 213016573 | 0.49 | 0.7987 | 0.98556 |
| NRG1 | rs10954811 (G/A) | 8 | 31586453 | -0.33 | 0.799 | 0.98556 |
| MUC4 | rs73081320 (G/A) | 3 | 195495721 | 0.66 | 0.799 | 0.98556 |
| NRG3 | rs10884515 (G/A) | 10 | 84071965 | -0.31 | 0.7994 | 0.98556 |
| ERBB4 | rs6710946 (A/G) | 2 | 212295875 | -0.32 | 0.7994 | 0.98556 |
| NRG3 | rs10884296 (G/A) | 10 | 83933237 | 0.57 | 0.8004 | 0.98556 |
| MUC4 | rs9844491 (G/A) | 3 | 195521531 | 0.28 | 0.8007 | 0.98556 |
| NRG1 | rs73672011 (A/G) | 8 | 31823564 | 0.58 | 0.801 | 0.98556 |
| TGFA | rs11126273 (A/C) | 2 | 70715824 | -0.50 | 0.801 | 0.98556 |
| ERBB4 | rs10048673 (A/G) | 2 | 213083282 | 0.27 | 0.8018 | 0.98556 |
| NRG3 | rs7915399 (A/C) | 10 | 83996992 | -0.39 | 0.8019 | 0.98556 |
| EGFR | rs2227983 (G/A) | 7 | 55229255 | 0.32 | 0.8021 | 0.98556 |
| EGF | rs2298989 (G/A) | 4 | 110891673 | 0.28 | 0.8031 | 0.98556 |
| EGF | rs4444903 (G/A) | 4 | 110834110 | 0.27 | 0.8033 | 0.98556 |
| TGFA | rs6546610 (G/A) | 2 | 70771302 | -0.27 | 0.8038 | 0.98556 |
| NRG1 | rs10103976 (G/A) | 8 | 32481673 | -0.29 | 0.8041 | 0.98556 |
| NRG1 | rs1386438 (C/A) | 8 | 32195543 | 0.27 | 0.8045 | 0.98556 |
| NRG1 | rs7835765 (G/A) | 8 | 32549845 | 0.28 | 0.8056 | 0.98556 |
| NRG1 | rs66775327 (G/A) | 8 | 31552367 | -0.45 | 0.8058 | 0.98556 |
| NRG1 | rs67883841 (A/G) | 8 | 31721830 | 0.32 | 0.8059 | 0.98556 |
| MUC4 | rs73204000 (A/C) | 3 | 195479681 | 0.36 | 0.8059 | 0.98556 |
| NRG1 | rs6990973 (A/G) | 8 | 32010945 | 0.53 | 0.8062 | 0.98556 |
| NRG3 | rs4297406 (A/G) | 10 | 84048527 | -0.35 | 0.8062 | 0.98556 |
| NRG1 | rs4504593 (A/G) | 8 | 31689095 | 0.28 | 0.8064 | 0.98556 |
| NRG3 | rs72827348 (G/A) | 10 | 84084069 | 0.32 | 0.8066 | 0.98556 |
| NRG1 | rs4276645 (G/A) | 8 | 32257673 | -0.29 | 0.8076 | 0.98556 |
| NRG1 | rs7001724 (A/C) | 8 | 32212426 | -0.28 | 0.808 | 0.98556 |
| ERBB4 | rs1402716 (A/C) | 2 | 212882926 | -0.29 | 0.8086 | 0.98556 |
| NRG1 | rs10503915 (A/G) | 8 | 32285177 | 0.32 | 0.809 | 0.98556 |
| ERBB4 | rs4673628 (A/G) | 2 | 212543924 | -0.26 | 0.8102 | 0.98556 |

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|---|---|---|---|---|---|---|
| ERBB4 | rs939645 (A/G) | 2 | 212916758 | 0.34 | 0.8104 | 0.98556 |
| NRG1 | rs17631978 (G/A) | 8 | 32181948 | -0.28 | 0.8106 | 0.98556 |
| EGF | rs11568943 (G/A) | 4 | 110883121 | -0.43 | 0.8109 | 0.98556 |
| ERBB4 | rs1402770 (G/A) | 2 | 213114560 | 0.30 | 0.8112 | 0.98556 |
| NRG3 | rs12255719 (A/G) | 10 | 83974087 | 0.38 | 0.8113 | 0.98556 |
| ERBB4 | rs13028597 (A/G) | 2 | 212719203 | 0.30 | 0.8114 | 0.98556 |
| ERBB4 | rs6731193 (A/G) | 2 | 213379961 | -0.26 | 0.8114 | 0.98556 |
| NRG1 | rs12550153 (G/A) | 8 | 32260010 | 0.30 | 0.8115 | 0.98556 |
| NRG1 | rs7831866 (G/A) | 8 | 32264966 | -0.29 | 0.8118 | 0.98556 |
| TGFA | rs10178514 (G/A) | 2 | 70745446 | 0.71 | 0.8126 | 0.98556 |
| TGFA | rs3771504 (G/A) | 2 | 70712005 | -0.28 | 0.8132 | 0.98556 |
| EGF | rs17253063 (A/G) | 4 | 110894449 | 0.28 | 0.8133 | 0.98556 |
| ERBB4 | rs12329252 (A/C) | 2 | 212385723 | 0.28 | 0.8134 | 0.98556 |
| NRG3 | rs17100439 (A/G) | 10 | 84423164 | 0.63 | 0.8137 | 0.98556 |
| ERBB4 | rs7595207 (G/A) | 2 | 212452598 | 0.32 | 0.8138 | 0.98556 |
| NRG3 | rs10884462 (G/A) | 10 | 84040680 | -0.33 | 0.814 | 0.98556 |
| ERBB4 | rs6708035 (A/G) | 2 | 212516742 | -0.29 | 0.814 | 0.98556 |
| ERBB4 | rs2371573 (G/A) | 2 | 213214303 | -0.26 | 0.8148 | 0.98557 |
| ERBB4 | rs7591480 (G/A) | 2 | 213040865 | -0.27 | 0.8152 | 0.98557 |
| NRG1 | rs9297180 (A/G) | 8 | 31592637 | 0.60 | 0.8156 | 0.98557 |
| NRG2 | rs6896087 (A/G) | 5 | 139375932 | 0.25 | 0.8158 | 0.98557 |
| NRG3 | rs7069727 (A/G) | 10 | 83798469 | 0.24 | 0.8162 | 0.98557 |
| NRG1 | rs1623372 (A/G) | 8 | 32215602 | -0.27 | 0.8166 | 0.98557 |
| NRG1 | rs4733323 (C/A) | 8 | 32239849 | -0.25 | 0.8171 | 0.98557 |
| ERBB4 | rs10168303 (A/G) | 2 | 213097913 | -0.24 | 0.8177 | 0.98557 |
| NRG1 | rs16879809 (G/A) | 8 | 32572873 | -0.37 | 0.8181 | 0.98557 |
| ERBB4 | rs13395352 (A/G) | 2 | 212959784 | 0.31 | 0.8181 | 0.98557 |
| ERBB4 | rs12473610 (C/A) | 2 | 213192198 | 0.32 | 0.8187 | 0.9858 |
| ERBB4 | rs12467225 (G/A) | 2 | 212244657 | 0.28 | 0.82 | 0.98677 |
| ERBB4 | rs6745160 (C/A) | 2 | 213130540 | -0.24 | 0.8207 | 0.98677 |
| NRG1 | rs1503495 (G/A) | 8 | 31684724 | 0.26 | 0.821 | 0.98677 |
| ERBB4 | rs72933744 (A/G) | 2 | 212777775 | -0.33 | 0.8212 | 0.98677 |
| NRG3 | rs72819694 (G/A) | 10 | 84605536 | 0.47 | 0.8225 | 0.98677 |
| NRG3 | rs7074029 (G/A) | 10 | 84210756 | -0.33 | 0.8233 | 0.98677 |
| ERBB4 | rs11676241 (C/G) | 2 | 212308141 | -0.25 | 0.824 | 0.98677 |
| NRG3 | rs4562759 (A/G) | 10 | 83835639 | -0.25 | 0.8249 | 0.98677 |
| ERBB4 | rs17336942 (A/G) | 2 | 212861073 | 0.24 | 0.8252 | 0.98677 |
| ERBB4 | rs12466094 (A/G) | 2 | 213117008 | -0.37 | 0.8252 | 0.98677 |
| ERBB4 | rs35880620 (G/A) | 2 | 213243651 | 0.31 | 0.8252 | 0.98677 |
| ERBB4 | rs12992515 (A/C) | 2 | 212267373 | -0.26 | 0.826 | 0.98677 |
| ERBB4 | rs72945031 (A/G) | 2 | 212534921 | -0.34 | 0.8264 | 0.98677 |

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|---|---|---|---|---|---|---|
| ERBB4 | rs6752616 (A/G) | 2 | 212535653 | -0.34 | 0.8264 | 0.98677 |
| NRG1 | rs62500235 (G/A) | 8 | 32484731 | -0.39 | 0.8265 | 0.98677 |
| NRG1 | rs79008058 (G/A) | 8 | 32016151 | 0.52 | 0.8266 | 0.98677 |
| NRG1 | rs16879927 (A/G) | 8 | 32612705 | -0.36 | 0.8267 | 0.98677 |
| NRG3 | rs17100701 (A/G) | 10 | 84509231 | 0.64 | 0.8273 | 0.98677 |
| NRG3 | rs17100713 (G/A) | 10 | 84510336 | 0.64 | 0.8273 | 0.98677 |
| NRG1 | rs12155594 (G/A) | 8 | 31606595 | -0.43 | 0.8295 | 0.9872 |
| ERBB4 | rs10932375 (A/G) | 2 | 212340022 | -0.27 | 0.8301 | 0.9872 |
| NRG1 | rs7815849 (G/A) | 8 | 31833448 | -0.27 | 0.8305 | 0.9872 |
| NRG1 | rs2347506 (G/A) | 8 | 32234929 | 0.24 | 0.8305 | 0.9872 |
| ERBB4 | rs984773 (A/G) | 2 | 212723026 | -0.27 | 0.831 | 0.9872 |
| NRG3 | rs17099664 (A/G) | 10 | 84016070 | 0.42 | 0.8312 | 0.9872 |
| ERBB4 | rs6435699 (G/A) | 2 | 213061726 | -0.34 | 0.8319 | 0.9872 |
| EGFR | rs917881 (G/A) | 7 | 55162305 | 0.31 | 0.832 | 0.9872 |
| NRG3 | rs11812850 (G/A) | 10 | 84173117 | -0.29 | 0.8326 | 0.9872 |
| NRG1 | rs12546380 (A/G) | 8 | 32535920 | 0.25 | 0.833 | 0.9872 |
| ERBB4 | rs1357142 (G/A) | 2 | 213017462 | -0.26 | 0.8331 | 0.9872 |
| EGF | rs2298978 (G/A) | 4 | 110837667 | -0.23 | 0.8333 | 0.9872 |
| ERBB4 | rs12694262 (A/G) | 2 | 212931980 | 0.34 | 0.8333 | 0.9872 |
| NRG1 | rs11996981 (G/A) | 8 | 32271517 | -0.25 | 0.8334 | 0.9872 |
| NRG3 | rs480220 (C/A) | 10 | 84504702 | 0.25 | 0.8343 | 0.98741 |
| NRG3 | rs645168 (G/A) | 10 | 84395218 | 0.34 | 0.8344 | 0.98741 |
| NRG3 | rs2207768 (A/G) | 10 | 83802403 | 0.24 | 0.8351 | 0.98763 |
| NRG1 | rs7832999 (G/A) | 8 | 32247244 | 0.34 | 0.8354 | 0.98763 |
| NRG1 | rs1016165 (A/G) | 8 | 31824555 | 0.24 | 0.837 | 0.98885 |
| ERBB4 | rs62182620 (A/G) | 2 | 213127670 | -0.36 | 0.8379 | 0.98885 |
| ERBB4 | rs11889311 (C/A) | 2 | 213040887 | 0.25 | 0.838 | 0.98885 |
| NRG3 | rs10884989 (G/A) | 10 | 84357748 | 0.23 | 0.8381 | 0.98885 |
| ERBB4 | rs2860059 (A/G) | 2 | 212852895 | -0.26 | 0.8387 | 0.98885 |
| NRG1 | rs6982890 (G/A) | 8 | 32615098 | 0.27 | 0.8389 | 0.98885 |
| ERBB4 | rs2371303 (A/G) | 2 | 212443357 | 0.34 | 0.8397 | 0.98931 |
| NRG3 | rs11194106 (A/G) | 10 | 84148715 | -0.36 | 0.8417 | 0.98985 |
| EGF | rs11568994 (G/A) | 4 | 110897535 | 0.23 | 0.8418 | 0.98985 |
| EGF | rs2298991 (C/A) | 4 | 110892012 | -0.22 | 0.8424 | 0.98985 |
| EGFR | rs7796139 (A/G) | 7 | 55175876 | 0.26 | 0.8436 | 0.98985 |
| NRG2 | rs59615734 (A/G) | 5 | 139411146 | -0.25 | 0.8437 | 0.98985 |
| NRG3 | rs61864200 (C/A) | 10 | 84068130 | 0.33 | 0.8439 | 0.98985 |
| NRG3 | rs17100953 (G/A) | 10 | 84621316 | -0.29 | 0.8444 | 0.98985 |
| NRG2 | rs11167875 (G/A) | 5 | 139384602 | 0.21 | 0.8449 | 0.98985 |
| ERBB4 | rs72948506 (G/A) | 2 | 212618440 | 0.24 | 0.845 | 0.98985 |
| ERBB4 | rs13428633 (A/G) | 2 | 212820953 | -0.45 | 0.8461 | 0.98985 |

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|---|---|---|---|---|---|---|
| ERBB4 | rs73070304 (A/C) | 2 | 213202226 | 0.55 | 0.8468 | 0.98985 |
| NRG1 | rs7000590 (G/A) | 8 | 32400628 | 0.24 | 0.8469 | 0.98985 |
| EGFR | rs6972246 (G/A) | 7 | 55159983 | -0.29 | 0.8476 | 0.98985 |
| NRG2 | rs265152 (G/A) | 5 | 139379707 | 0.24 | 0.8479 | 0.98985 |
| ERBB4 | rs2008506 (G/A) | 2 | 213207306 | 0.54 | 0.8481 | 0.98985 |
| MUC4 | rs2550241 (A/G) | 3 | 195498942 | -0.21 | 0.8482 | 0.98985 |
| ERBB4 | rs10497948 (A/G) | 2 | 212492126 | 0.27 | 0.8485 | 0.98985 |
| ERBB4 | rs16848412 (A/G) | 2 | 213215340 | 0.54 | 0.8485 | 0.98985 |
| ERBB4 | rs17418814 (C/A) | 2 | 213164792 | 0.28 | 0.8488 | 0.98985 |
| ERBB4 | rs10164847 (G/A) | 2 | 212379145 | -0.21 | 0.849 | 0.98985 |
| NRG3 | rs4933265 (A/G) | 10 | 83712877 | -0.27 | 0.8492 | 0.98985 |
| MUC4 | rs3107764 (C/G) | 3 | 195518330 | -0.21 | 0.8495 | 0.98985 |
| NRG1 | rs4129581 (A/G) | 8 | 32298100 | -0.26 | 0.8501 | 0.98985 |
| ERBB4 | rs57038689 (A/G) | 2 | 212682706 | -0.31 | 0.8504 | 0.98985 |
| EGFR | rs2075101 (G/A) | 7 | 55250026 | 0.21 | 0.8512 | 0.98985 |
| ERBB4 | rs7608095 (G/A) | 2 | 213070451 | -0.21 | 0.8519 | 0.98985 |
| NRG3 | rs2494028 (G/A) | 10 | 84465162 | 0.35 | 0.8521 | 0.98985 |
| NRG1 | rs16875654 (A/G) | 8 | 31913615 | -0.54 | 0.8522 | 0.98985 |
| NRG1 | rs73234154 (G/A) | 8 | 32424829 | 0.32 | 0.8523 | 0.98985 |
| ERBB4 | rs17344783 (G/A) | 2 | 213040157 | 0.22 | 0.8525 | 0.98985 |
| NRG1 | rs1383887 (A/G) | 8 | 31753156 | 0.20 | 0.8534 | 0.99028 |
| NRG3 | rs11817202 (C/A) | 10 | 83809752 | -0.22 | 0.8537 | 0.99028 |
| NRG1 | rs1481624 (G/A) | 8 | 31779956 | -0.22 | 0.8541 | 0.99028 |
| NRG2 | rs12517577 (A/C) | 5 | 139240190 | 0.33 | 0.8547 | 0.9905 |
| ERBB4 | rs2371572 (A/C) | 2 | 213214174 | 0.20 | 0.8557 | 0.99064 |
| NRG1 | rs28707215 (G/A) | 8 | 31503226 | -0.24 | 0.8567 | 0.99064 |
| NRG1 | rs2919389 (G/A) | 8 | 32588901 | -0.19 | 0.8568 | 0.99064 |
| ERBB4 | rs13022952 (C/A) | 2 | 213125175 | 0.30 | 0.8571 | 0.99064 |
| ERBB4 | rs974968 (A/C) | 2 | 213318641 | -0.20 | 0.8572 | 0.99064 |
| ERBB4 | rs10174063 (A/G) | 2 | 212864338 | 0.20 | 0.8574 | 0.99064 |
| NRG1 | rs7002063 (A/G) | 8 | 31803534 | -0.23 | 0.8577 | 0.99064 |
| ERBB4 | rs34687398 (A/C) | 2 | 213023995 | -0.20 | 0.859 | 0.99152 |
| NRG1 | rs16878344 (C/A) | 8 | 31702323 | -0.26 | 0.8599 | 0.99152 |
| NRG1 | rs1481728 (C/A) | 8 | 32116927 | -0.25 | 0.8612 | 0.99152 |
| NRG1 | rs6992010 (A/G) | 8 | 32117412 | -0.25 | 0.8612 | 0.99152 |
| NRG1 | rs62500177 (G/A) | 8 | 32280225 | -0.19 | 0.8612 | 0.99152 |
| NRG3 | rs7088954 (C/A) | 10 | 84088903 | 0.22 | 0.8613 | 0.99152 |
| NRG1 | rs4733305 (A/G) | 8 | 32035790 | -0.24 | 0.8614 | 0.99152 |
| NRG3 | rs6584455 (A/C) | 10 | 83759053 | 0.20 | 0.8618 | 0.99152 |
| ERBB4 | rs4672626 (G/A) | 2 | 212670425 | -0.29 | 0.8632 | 0.99152 |
| NRG3 | rs71483383 (G/A) | 10 | 83794591 | -0.22 | 0.8636 | 0.99152 |

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|---|---|---|---|---|---|---|
| NRG3 | rs12267711 (G/A) | 10 | 84350913 | 0.41 | 0.8648 | 0.99152 |
| EGF | rs11569121 (G/A) | 4 | 110929128 | 0.30 | 0.8664 | 0.99152 |
| ERBB4 | rs77536379 (C/A) | 2 | 212492021 | -0.32 | 0.8664 | 0.99152 |
| MUC4 | rs79706438 (A/G) | 3 | 195497121 | 0.43 | 0.8667 | 0.99152 |
| ERBB4 | rs1992026 (G/A) | 2 | 212281672 | -0.37 | 0.8667 | 0.99152 |
| ERBB4 | rs1505376 (A/G) | 2 | 213303947 | -0.18 | 0.8667 | 0.99152 |
| NRG1 | rs59110554 (A/C) | 8 | 32120353 | -0.21 | 0.8671 | 0.99152 |
| NRG3 | rs7073820 (A/C) | 10 | 84177024 | -0.23 | 0.8675 | 0.99152 |
| ERBB4 | rs13008370 (A/C) | 2 | 212642374 | 0.19 | 0.8675 | 0.99152 |
| NRG1 | rs10096667 (G/A) | 8 | 32150982 | -0.24 | 0.8678 | 0.99152 |
| NRG1 | rs10503887 (C/A) | 8 | 31633447 | 0.24 | 0.8679 | 0.99152 |
| ERBB4 | rs12995889 (A/G) | 2 | 213050763 | -0.38 | 0.8686 | 0.99152 |
| EGFR | rs6954351 (G/A) | 7 | 55171190 | 0.28 | 0.8689 | 0.99152 |
| NRG1 | rs4733332 (C/A) | 8 | 32288374 | 0.20 | 0.869 | 0.99152 |
| NRG3 | rs12267852 (A/C) | 10 | 84470373 | 0.35 | 0.8692 | 0.99152 |
| NRG1 | rs553950 (C/A) | 8 | 31791362 | -0.30 | 0.8694 | 0.99152 |
| NRG3 | rs60695870 (C/G) | 10 | 84559415 | -0.25 | 0.8697 | 0.99152 |
| MUC4 | rs2291650 (G/A) | 3 | 195478188 | 0.22 | 0.87 | 0.99152 |
| ERBB4 | rs10197270 (G/A) | 2 | 212929113 | 0.21 | 0.8724 | 0.9935 |
| NRG3 | rs73314451 (G/A) | 10 | 84113016 | -0.29 | 0.8733 | 0.9935 |
| ERBB4 | rs60490270 (G/A) | 2 | 212641601 | -0.25 | 0.8733 | 0.9935 |
| NRG3 | rs12773117 (A/C) | 10 | 84559886 | -0.24 | 0.8737 | 0.9935 |
| NRG3 | rs72827384 (G/A) | 10 | 84155774 | -0.21 | 0.8738 | 0.9935 |
| TGFA | rs10489985 (A/G) | 2 | 70772720 | 0.23 | 0.8744 | 0.99371 |
| NRG1 | rs6468122 (G/A) | 8 | 32539327 | -0.18 | 0.876 | 0.99429 |
| ERBB4 | rs3791700 (A/G) | 2 | 212275020 | -0.20 | 0.8776 | 0.99429 |
| ERBB4 | rs10173683 (G/C) | 2 | 212545562 | 0.17 | 0.8783 | 0.99429 |
| NRG3 | rs4933818 (C/A) | 10 | 83760211 | 0.19 | 0.8785 | 0.99429 |
| NRG1 | rs16879060 (C/A) | 8 | 32118296 | 0.23 | 0.8793 | 0.99429 |
| EGFR | rs845558 (G/A) | 7 | 55247588 | 0.16 | 0.8795 | 0.99429 |
| TGFA | rs11466285 (A/G) | 2 | 70677439 | -0.30 | 0.8798 | 0.99429 |
| EGF | rs2255355 (A/C) | 4 | 110891543 | -0.27 | 0.8806 | 0.99429 |
| TGFA | rs6749533 (A/G) | 2 | 70691766 | -0.24 | 0.8815 | 0.99429 |
| ERBB4 | rs7423124 (C/A) | 2 | 212867291 | 0.16 | 0.8816 | 0.99429 |
| ERBB4 | rs17416172 (A/G) | 2 | 212974828 | -0.16 | 0.8817 | 0.99429 |
| NRG4 | rs17428804 (C/A) | 15 | 76260430 | -0.28 | 0.8821 | 0.99429 |
| NRG3 | rs2347332 (G/A) | 10 | 83746494 | 0.18 | 0.8821 | 0.99429 |
| ERBB3 | rs812826 (G/A) | 12 | 56495306 | -0.24 | 0.883 | 0.99429 |
| ERBB4 | rs17346754 (G/A) | 2 | 213159671 | 0.21 | 0.8834 | 0.99429 |
| EGF | rs9992755 (A/G) | 4 | 110882590 | 0.16 | 0.8835 | 0.99429 |
| NRG1 | rs984633 (C/A) | 8 | 32166816 | -0.23 | 0.8841 | 0.99429 |

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|---|---|---|---|---|---|---|
| NRG2 | rs6891114 (A/G) | 5 | 139372521 | 0.26 | 0.8848 | 0.99429 |
| NRG1 | rs16878243 (A/C) | 8 | 31609048 | -0.22 | 0.885 | 0.99429 |
| EGFR | rs1404908 (G/A) | 7 | 55262627 | -0.16 | 0.8853 | 0.99429 |
| NRG1 | rs28411153 (A/G) | 8 | 31993038 | -0.18 | 0.8857 | 0.99429 |
| ERBB4 | rs1482378 (A/C) | 2 | 213347104 | -0.26 | 0.8857 | 0.99429 |
| ERBB4 | rs4672615 (G/A) | 2 | 212356992 | -0.16 | 0.8885 | 0.99429 |
| ERBB4 | rs11675580 (C/A) | 2 | 213333945 | -0.16 | 0.8894 | 0.99429 |
| ERBB4 | rs73988941 (A/G) | 2 | 212882867 | 0.19 | 0.89 | 0.99429 |
| NRG3 | rs7921634 (C/G) | 10 | 83637304 | -0.17 | 0.8914 | 0.99429 |
| NRG1 | rs34825962 (G/A) | 8 | 31731475 | 0.15 | 0.8916 | 0.99429 |
| NRG3 | rs7916696 (C/A) | 10 | 84089539 | 0.24 | 0.8918 | 0.99429 |
| ERBB3 | rs2271189 (G/A) | 12 | 56494991 | -0.16 | 0.8919 | 0.99429 |
| EGF | rs10470911 (A/C) | 4 | 110865271 | 0.15 | 0.8933 | 0.99429 |
| NRG1 | rs2683768 (A/C) | 8 | 31738311 | -0.14 | 0.8955 | 0.99429 |
| NRG1 | rs7818821 (A/G) | 8 | 32153164 | -0.15 | 0.8956 | 0.99429 |
| ERBB4 | rs12996976 (A/G) | 2 | 212726694 | 0.17 | 0.8956 | 0.99429 |
| ERBB4 | rs62184037 (A/G) | 2 | 212977114 | -0.15 | 0.8957 | 0.99429 |
| NRG1 | rs10503899 (A/G) | 8 | 31947234 | -0.15 | 0.8964 | 0.99429 |
| TGFA | rs428225 (A/G) | 2 | 70759161 | 0.14 | 0.8969 | 0.99429 |
| NRG1 | rs7000201 (A/G) | 8 | 32224779 | -0.21 | 0.897 | 0.99429 |
| NRG3 | rs57647976 (A/G) | 10 | 84405406 | 0.24 | 0.8972 | 0.99429 |
| EGFR | rs10235245 (G/A) | 7 | 55192617 | -0.15 | 0.8979 | 0.99429 |
| EGFR | rs845552 (A/G) | 7 | 55245507 | -0.14 | 0.898 | 0.99429 |
| TGFA | rs2166975 (G/A) | 2 | 70677994 | -0.16 | 0.8986 | 0.99429 |
| NRG3 | rs10884061 (G/A) | 10 | 83790221 | 0.16 | 0.8988 | 0.99429 |
| NRG1 | rs3735776 (C/A) | 8 | 32585434 | 0.18 | 0.8989 | 0.99429 |
| ERBB4 | rs16846161 (A/G) | 2 | 212297838 | -0.23 | 0.899 | 0.99429 |
| NRG3 | rs1475706 (G/A) | 10 | 84685244 | 0.20 | 0.8993 | 0.99429 |
| ERBB4 | rs7421024 (G/A) | 2 | 212604663 | -0.25 | 0.8994 | 0.99429 |
| MUC4 | rs73085337 (A/G) | 3 | 195529087 | 0.25 | 0.8995 | 0.99429 |
| NRG1 | rs10092055 (G/A) | 8 | 32381411 | -0.16 | 0.8996 | 0.99429 |
| NRG3 | rs12246695 (G/A) | 10 | 83974268 | 0.23 | 0.8998 | 0.99429 |
| NRG3 | rs6585084 (G/A) | 10 | 84733869 | -0.27 | 0.9005 | 0.99429 |
| NRG3 | rs915349 (A/G) | 10 | 84477898 | 0.14 | 0.9016 | 0.99429 |
| NRG3 | rs2172939 (G/A) | 10 | 84607824 | -0.14 | 0.902 | 0.99429 |
| NRG3 | rs342386 (A/G) | 10 | 84611100 | -0.14 | 0.902 | 0.99429 |
| ERBB4 | rs16847346 (A/G) | 2 | 212827279 | 0.26 | 0.9031 | 0.99429 |
| NRG3 | rs1739769 (A/G) | 10 | 83883951 | -0.13 | 0.9032 | 0.99429 |
| NRG3 | rs35422267 (A/G) | 10 | 83998003 | 0.20 | 0.9039 | 0.99429 |
| ERBB4 | rs34156842 (A/C) | 2 | 212577264 | -0.16 | 0.9039 | 0.99429 |
| ERBB4 | rs35145864 (G/A) | 2 | 212359600 | -0.14 | 0.9041 | 0.99429 |

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|---|---|---|---|---|---|---|
| NRG1 | rs7830159 (A/G) | 8 | 31645028 | 0.13 | 0.9042 | 0.99429 |
| TGFA | rs3821261 (A/C) | 2 | 70729253 | -0.21 | 0.9045 | 0.99429 |
| NRG3 | rs3862550 (A/G) | 10 | 84094771 | 0.15 | 0.9048 | 0.99429 |
| NRG3 | rs7092994 (A/G) | 10 | 84735241 | -0.13 | 0.9049 | 0.99429 |
| ERBB4 | rs6435655 (A/G) | 2 | 212562538 | 0.13 | 0.9051 | 0.99429 |
| NRG3 | rs7894092 (C/A) | 10 | 84066560 | -0.15 | 0.9054 | 0.99429 |
| ERBB4 | rs10932439 (A/G) | 2 | 213242374 | 0.13 | 0.9055 | 0.99429 |
| ERBB4 | rs62182562 (G/A) | 2 | 213030170 | -0.16 | 0.9059 | 0.99429 |
| ERBB4 | rs16848312 (G/A) | 2 | 213173172 | -0.18 | 0.906 | 0.99429 |
| ERBB4 | rs6745249 (G/A) | 2 | 213130571 | -0.12 | 0.9063 | 0.99429 |
| EGFR | rs13222385 (A/G) | 7 | 55251593 | 0.14 | 0.9067 | 0.99429 |
| EGFR | rs10244108 (G/A) | 7 | 55152337 | 0.14 | 0.9072 | 0.99429 |
| NRG3 | rs7099749 (A/G) | 10 | 84576414 | 0.21 | 0.9077 | 0.99429 |
| NRG1 | rs12678982 (G/A) | 8 | 32296794 | -0.15 | 0.9078 | 0.99429 |
| ERBB4 | rs62184548 (A/C) | 2 | 212808309 | 0.17 | 0.9086 | 0.99429 |
| NRG2 | rs13173983 (A/G) | 5 | 139410510 | 0.14 | 0.9087 | 0.99429 |
| ERBB2 | rs1136201 (A/G) | 17 | 37879588 | -0.15 | 0.9088 | 0.99429 |
| NRG1 | rs1462891 (G/A) | 8 | 31830933 | -0.14 | 0.9092 | 0.99429 |
| ERBB4 | rs1521647 (A/G) | 2 | 213040127 | -0.20 | 0.9098 | 0.99429 |
| NRG1 | rs7826312 (G/A) | 8 | 32400115 | 0.13 | 0.9099 | 0.99429 |
| NRG3 | rs342396 (G/A) | 10 | 84621666 | 0.13 | 0.9099 | 0.99429 |
| EGFR | rs7786831 (G/A) | 7 | 55190489 | -0.22 | 0.9102 | 0.99429 |
| EGFR | rs12718937 (T/A) | 7 | 55089451 | -0.13 | 0.9105 | 0.99429 |
| NRG3 | rs11192970 (C/A) | 10 | 83961273 | -0.21 | 0.9106 | 0.99429 |
| ERBB4 | rs6740117 (A/G) | 2 | 212384231 | 0.12 | 0.9107 | 0.99429 |
| NRG3 | rs17099789 (A/G) | 10 | 84088573 | 0.14 | 0.912 | 0.99429 |
| NRG3 | rs6585083 (C/A) | 10 | 84732356 | -0.24 | 0.9123 | 0.99429 |
| ERBB4 | rs6754240 (G/A) | 2 | 212764141 | -0.13 | 0.9129 | 0.99429 |
| NRG1 | rs12547858 (G/A) | 8 | 32487053 | 0.16 | 0.9132 | 0.99429 |
| EGF | rs3796947 (A/G) | 4 | 110870765 | -0.18 | 0.9133 | 0.99429 |
| ERBB4 | rs62184064 (G/A) | 2 | 213215895 | 0.19 | 0.9133 | 0.99429 |
| ERBB4 | rs10168850 (G/A) | 2 | 213334523 | -0.13 | 0.9133 | 0.99429 |
| ERBB4 | rs74894709 (A/G) | 2 | 212956433 | -0.18 | 0.9134 | 0.99429 |
| ERBB4 | rs78068641 (G/A) | 2 | 212788333 | -0.24 | 0.9137 | 0.99429 |
| ERBB4 | rs13027737 (G/A) | 2 | 212718757 | 0.14 | 0.9138 | 0.99429 |
| ERBB4 | rs199532836 (G/A) | 2 | 212719804 | 0.14 | 0.9138 | 0.99429 |
| NRG2 | rs6580353 (G/A) | 5 | 139410687 | -0.13 | 0.9145 | 0.99429 |
| ERBB4 | rs6758063 (G/A) | 2 | 212582246 | -0.12 | 0.9147 | 0.99429 |
| NRG1 | rs6999862 (G/A) | 8 | 32194497 | 0.12 | 0.9153 | 0.99429 |
| NRG3 | rs2250933 (A/C) | 10 | 84444585 | 0.20 | 0.9157 | 0.99429 |
| NRG1 | rs7011105 (A/G) | 8 | 32537461 | -0.12 | 0.9158 | 0.99429 |

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|---|---|---|---|---|---|---|
| ERBB4 | rs4511675 (C/A) | 2 | 213233739 | -0.12 | 0.9166 | 0.99433 |
| NRG3 | rs7902584 (A/G) | 10 | 84207574 | 0.15 | 0.9172 | 0.99433 |
| ERBB4 | rs72935738 (G/A) | 2 | 212826952 | 0.15 | 0.9178 | 0.99433 |
| NRG3 | rs35860440 (G/A) | 10 | 84587947 | 0.16 | 0.9179 | 0.99433 |
| ERBB4 | rs13383927 (C/A) | 2 | 212336730 | -0.12 | 0.919 | 0.99433 |
| ERBB4 | rs13028369 (G/A) | 2 | 212360399 | -0.15 | 0.9195 | 0.99433 |
| NRG1 | rs4733281 (A/G) | 8 | 31778618 | -0.13 | 0.9198 | 0.99433 |
| NRG1 | rs17705398 (G/A) | 8 | 32195932 | -0.15 | 0.9199 | 0.99433 |
| ERBB4 | rs11695227 (A/G) | 2 | 212982171 | -0.12 | 0.9203 | 0.99433 |
| NRG1 | rs10101580 (A/G) | 8 | 32468951 | -0.11 | 0.9205 | 0.99433 |
| ERBB4 | rs1949652 (A/G) | 2 | 213110424 | -0.10 | 0.9205 | 0.99433 |
| NRG1 | rs12546350 (G/A) | 8 | 32397189 | 0.16 | 0.9208 | 0.99433 |
| NRG3 | rs11596426 (A/G) | 10 | 84071127 | 0.16 | 0.9228 | 0.99594 |
| EGFR | rs7796872 (G/A) | 7 | 55179844 | -0.16 | 0.9239 | 0.99594 |
| NRG1 | rs1462892 (G/A) | 8 | 31830996 | -0.12 | 0.9249 | 0.99594 |
| NRG3 | rs983086 (C/A) | 10 | 84354158 | 0.10 | 0.9249 | 0.99594 |
| EGFR | rs4947963 (A/G) | 7 | 55088415 | -0.11 | 0.9253 | 0.99594 |
| NRG1 | rs62508561 (A/G) | 8 | 31610270 | -0.12 | 0.9256 | 0.99594 |
| NRG1 | rs4489283 (G/A) | 8 | 32399662 | 0.10 | 0.926 | 0.99594 |
| NRG3 | rs2348754 (G/A) | 10 | 84715289 | 0.15 | 0.9263 | 0.99594 |
| ERBB4 | rs12469375 (A/G) | 2 | 212492708 | 0.14 | 0.9268 | 0.99594 |
| NRG1 | rs73234151 (C/A) | 8 | 32423538 | 0.12 | 0.9274 | 0.99594 |
| NRG1 | rs6999977 (A/G) | 8 | 32173061 | -0.14 | 0.9279 | 0.99594 |
| ERBB4 | rs17335518 (A/G) | 2 | 212526025 | 0.10 | 0.9281 | 0.99594 |
| EGF | rs4698756 (G/A) | 4 | 110866442 | 0.10 | 0.9284 | 0.99594 |
| NRG1 | rs4584111 (A/G) | 8 | 32299316 | -0.10 | 0.9285 | 0.99594 |
| NRG1 | rs35544675 (A/C) | 8 | 32422857 | -0.12 | 0.9285 | 0.99594 |
| NRG3 | rs10883976 (A/G) | 10 | 83720231 | 0.18 | 0.9291 | 0.99614 |
| EGFR | rs759167 (C/A) | 7 | 55127784 | 0.11 | 0.93 | 0.99644 |
| ERBB4 | rs77509092 (A/G) | 2 | 213003783 | -0.16 | 0.9302 | 0.99644 |
| ERBB4 | rs75051161 (A/G) | 2 | 213131988 | -0.16 | 0.931 | 0.99646 |
| EGFR | rs1024750 (G/A) | 7 | 55128731 | 0.12 | 0.9317 | 0.99646 |
| NRG3 | rs10884143 (G/A) | 10 | 83840139 | 0.15 | 0.9324 | 0.99646 |
| MUC4 | rs842460 (A/G) | 3 | 195536040 | 0.09 | 0.9324 | 0.99646 |
| ERBB4 | rs939224 (A/G) | 2 | 213089095 | 0.09 | 0.9325 | 0.99646 |
| ERBB4 | rs12475565 (A/G) | 2 | 213074560 | 0.12 | 0.9332 | 0.99646 |
| EGF | rs6825106 (G/A) | 4 | 110904502 | 0.13 | 0.9335 | 0.99646 |
| NRG1 | rs7821017 (C/A) | 8 | 31607509 | 0.11 | 0.9336 | 0.99646 |
| EGF | rs6824594 (A/G) | 4 | 110904448 | -0.09 | 0.9348 | 0.99646 |
| ERBB4 | rs6729362 (G/A) | 2 | 212581902 | -0.14 | 0.9354 | 0.99646 |
| NRG3 | rs1475707 (C/A) | 10 | 84684932 | -0.09 | 0.9356 | 0.99646 |

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|---|---|---|---|---|---|---|
| NRG2 | rs265160 (A/C) | 5 | 139390914 | 0.10 | 0.9361 | 0.99646 |
| ERBB4 | rs17262115 (C/A) | 2 | 213398354 | 0.10 | 0.9367 | 0.99646 |
| ERBB4 | rs6756725 (A/C) | 2 | 212650162 | 0.10 | 0.9372 | 0.99646 |
| EGF | rs7670908 (G/A) | 4 | 110892625 | 0.15 | 0.9373 | 0.99646 |
| EGF | rs9991367 (G/A) | 4 | 110894301 | 0.15 | 0.9373 | 0.99646 |
| NRG1 | rs17642273 (A/C) | 8 | 32292231 | -0.13 | 0.9378 | 0.99646 |
| EGFR | rs12718939 (G/A) | 7 | 55105320 | -0.09 | 0.9381 | 0.99646 |
| ERBB4 | rs6435665 (G/A) | 2 | 212591641 | -0.12 | 0.9382 | 0.99646 |
| ERBB4 | rs201059849 (C/A) | 2 | 213180395 | 0.11 | 0.9385 | 0.99646 |
| EGF | rs4698803 (A/T) | 4 | 110914427 | 0.11 | 0.9395 | 0.99649 |
| NRG1 | rs57086312 (A/G) | 8 | 32026489 | 0.09 | 0.9402 | 0.99649 |
| NRG2 | rs2916093 (A/G) | 5 | 139415532 | -0.09 | 0.9402 | 0.99649 |
| ERBB4 | rs77488258 (A/G) | 2 | 212308490 | -0.18 | 0.9415 | 0.99649 |
| NRG1 | rs9297192 (G/A) | 8 | 32283517 | 0.10 | 0.9417 | 0.99649 |
| NRG2 | rs71581525 (A/C) | 5 | 139392069 | 0.14 | 0.9418 | 0.99649 |
| EGFR | rs7780270 (A/C) | 7 | 55151886 | -0.08 | 0.9421 | 0.99649 |
| ERBB4 | rs4673633 (G/A) | 2 | 212658297 | -0.10 | 0.9421 | 0.99649 |
| ERBB4 | rs73985811 (G/A) | 2 | 212571407 | 0.12 | 0.9426 | 0.99649 |
| ERBB4 | rs78047850 (G/A) | 2 | 212389664 | 0.15 | 0.943 | 0.99649 |
| NRG3 | rs12415063 (A/C) | 10 | 84560528 | 0.11 | 0.9432 | 0.99649 |
| EGFR | rs13234622 (A/G) | 7 | 55211879 | -0.08 | 0.9435 | 0.99649 |
| ERBB4 | rs6719811 (G/A) | 2 | 213194405 | -0.15 | 0.9443 | 0.99657 |
| NRG1 | rs73592185 (G/A) | 8 | 32276102 | 0.11 | 0.9444 | 0.99657 |
| NRG3 | rs12262500 (G/A) | 10 | 84047246 | -0.14 | 0.9454 | 0.99719 |
| NRG1 | rs6982316 (A/G) | 8 | 32534755 | -0.08 | 0.9462 | 0.99723 |
| NRG1 | rs1383890 (A/G) | 8 | 31721207 | 0.07 | 0.9467 | 0.99723 |
| NRG3 | rs649536 (A/G) | 10 | 84330895 | 0.07 | 0.9469 | 0.99723 |
| MUC4 | rs2259292 (A/G) | 3 | 195501149 | -0.07 | 0.9473 | 0.99723 |
| NRG3 | rs1649967 (G/A) | 10 | 83907724 | -0.07 | 0.9487 | 0.99723 |
| ERBB4 | rs13015805 (A/G) | 2 | 213249244 | -0.09 | 0.9497 | 0.99723 |
| NRG2 | rs6580323 (A/G) | 5 | 139340779 | -0.07 | 0.9499 | 0.99723 |
| NRG3 | rs10736174 (G/A) | 10 | 83822961 | -0.08 | 0.95 | 0.99723 |
| ERBB4 | rs4672621 (G/A) | 2 | 212529506 | -0.07 | 0.9502 | 0.99723 |
| NRG1 | rs2347505 (G/A) | 8 | 32234782 | -0.08 | 0.951 | 0.99723 |
| NRG1 | rs12549199 (G/A) | 8 | 32548970 | -0.09 | 0.9511 | 0.99723 |
| MUC4 | rs6809312 (A/G) | 3 | 195479068 | -0.07 | 0.9511 | 0.99723 |
| ERBB4 | rs62184493 (G/A) | 2 | 212705127 | 0.10 | 0.9513 | 0.99723 |
| MUC4 | rs2259419 (A/G) | 3 | 195505417 | -0.06 | 0.9517 | 0.99723 |
| ERBB4 | rs16845990 (A/G) | 2 | 212243011 | -0.07 | 0.9519 | 0.99723 |
| ERBB4 | rs35853366 (A/G) | 2 | 212940153 | -0.08 | 0.9524 | 0.99723 |
| ERBB4 | rs72949628 (G/C) | 2 | 212302122 | -0.12 | 0.9526 | 0.99723 |

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|---|---|---|---|---|---|---|
| ERBB4 | rs7561282 (G/A) | 2 | 212453901 | 0.08 | 0.9529 | 0.99723 |
| NRG3 | rs12243625 (G/A) | 10 | 84328538 | 0.14 | 0.9541 | 0.99805 |
| MUC4 | rs73205722 (A/G) | 3 | 195485225 | 0.11 | 0.9547 | 0.99806 |
| EGF | rs929446 (A/G) | 4 | 110883344 | 0.06 | 0.956 | 0.99806 |
| ERBB4 | rs1357136 (G/A) | 2 | 213103721 | -0.06 | 0.9564 | 0.99806 |
| NRG3 | rs201178935 (G/A) | 10 | 84561763 | -0.06 | 0.9567 | 0.99806 |
| ERBB4 | rs16846210 (G/A) | 2 | 212322255 | 0.08 | 0.9567 | 0.99806 |
| ERBB4 | rs1505357 (A/G) | 2 | 213210229 | -0.06 | 0.9573 | 0.99806 |
| EGF | rs2237051 (A/G) | 4 | 110901198 | -0.06 | 0.9576 | 0.99806 |
| MUC4 | rs59408218 (G/C) | 3 | 195515550 | 0.10 | 0.9586 | 0.99806 |
| ERBB4 | rs73071355 (G/C) | 2 | 212744099 | -0.06 | 0.9589 | 0.99806 |
| NRG1 | rs6468119 (G/A) | 8 | 32401561 | 0.05 | 0.959 | 0.99806 |
| ERBB4 | rs10187387 (A/G) | 2 | 212772588 | 0.06 | 0.9593 | 0.99806 |
| NRG3 | rs981168 (C/A) | 10 | 84547861 | 0.06 | 0.9598 | 0.99806 |
| NRG3 | rs665296 (G/C) | 10 | 84332163 | 0.05 | 0.9609 | 0.99806 |
| EGFR | rs10251909 (A/T) | 7 | 55262189 | 0.06 | 0.9612 | 0.99806 |
| NRG1 | rs10954810 (G/A) | 8 | 31555743 | -0.06 | 0.9628 | 0.99806 |
| ERBB4 | rs1546717 (G/A) | 2 | 212902339 | 0.07 | 0.9628 | 0.99806 |
| NRG3 | rs17100087 (A/G) | 10 | 84213251 | 0.05 | 0.9649 | 0.99806 |
| NRG3 | rs17746622 (A/G) | 10 | 84571247 | 0.07 | 0.9653 | 0.99806 |
| ERBB4 | rs16847102 (G/A) | 2 | 212722988 | -0.07 | 0.9657 | 0.99806 |
| NRG3 | rs60827755 (A/G) | 10 | 83647518 | 0.07 | 0.9659 | 0.99806 |
| NRG3 | rs11191965 (A/G) | 10 | 83726634 | 0.08 | 0.9668 | 0.99806 |
| ERBB4 | rs10193855 (A/G) | 2 | 212382485 | 0.05 | 0.9675 | 0.99806 |
| NRG1 | rs16879773 (G/A) | 8 | 32551304 | 0.05 | 0.9676 | 0.99806 |
| ERBB4 | rs12694256 (A/G) | 2 | 212858137 | 0.05 | 0.9679 | 0.99806 |
| NRG3 | rs7074306 (G/A) | 10 | 84210966 | 0.05 | 0.9686 | 0.99806 |
| NRG3 | rs4933813 (G/A) | 10 | 83689125 | -0.05 | 0.9687 | 0.99806 |
| ERBB4 | rs9288450 (A/G) | 2 | 213093843 | -0.09 | 0.9697 | 0.99806 |
| NRG3 | rs12262125 (G/A) | 10 | 84676828 | -0.06 | 0.9699 | 0.99806 |
| ERBB4 | rs55890667 (A/C) | 2 | 212667493 | 0.05 | 0.9709 | 0.99806 |
| ERBB4 | rs13017883 (C/A) | 2 | 213054058 | 0.07 | 0.9712 | 0.99806 |
| NRG1 | rs72634868 (G/A) | 8 | 32489391 | 0.08 | 0.9716 | 0.99806 |
| NRG1 | rs17671089 (A/C) | 8 | 32621094 | -0.07 | 0.9719 | 0.99806 |
| ERBB4 | rs4672620 (G/A) | 2 | 212489679 | -0.05 | 0.9729 | 0.99806 |
| BTC | rs74657106 (G/A) | 4 | 75711789 | -0.07 | 0.9739 | 0.99806 |
| NRG3 | rs2247247 (A/G) | 10 | 84383277 | 0.04 | 0.9743 | 0.99806 |
| MUC4 | rs3096336 (A/G) | 3 | 195534013 | -0.03 | 0.9743 | 0.99806 |
| NRG3 | rs12267229 (A/G) | 10 | 83639303 | 0.08 | 0.9745 | 0.99806 |
| MUC4 | rs2258447 (G/A) | 3 | 195479256 | -0.05 | 0.975 | 0.99806 |
| NRG3 | rs2483307 (A/G) | 10 | 84564127 | 0.03 | 0.9752 | 0.99806 |

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|---|---|---|---|---|---|---|
| ERBB4 | rs10932387 (A/G) | 2 | 212458206 | 0.04 | 0.9754 | 0.99806 |
| ERBB4 | rs7565327 (G/A) | 2 | 212542748 | -0.03 | 0.9759 | 0.99806 |
| ERBB4 | rs35419573 (A/G) | 2 | 212624172 | 0.05 | 0.9759 | 0.99806 |
| TGFA | rs1058211 (A/C) | 2 | 70677819 | 0.07 | 0.9765 | 0.99806 |
| ERBB4 | rs13032986 (A/C) | 2 | 212519135 | 0.04 | 0.9766 | 0.99806 |
| NRG1 | rs11984751 (G/A) | 8 | 32273529 | -0.04 | 0.9767 | 0.99806 |
| NRG3 | rs168201 (A/G) | 10 | 84610081 | 0.03 | 0.9769 | 0.99806 |
| NRG1 | rs17719687 (A/G) | 8 | 32414166 | 0.05 | 0.9776 | 0.99806 |
| NRG3 | rs59384209 (C/A) | 10 | 84425342 | -0.05 | 0.9779 | 0.99806 |
| NRG3 | rs72825487 (G/A) | 10 | 83973760 | -0.05 | 0.978 | 0.99806 |
| NRG1 | rs776404 (A/C) | 8 | 31706695 | -0.03 | 0.9782 | 0.99806 |
| NRG3 | rs2207767 (A/G) | 10 | 83802473 | 0.03 | 0.9783 | 0.99806 |
| NRG1 | rs7841599 (A/G) | 8 | 32199572 | 0.03 | 0.9784 | 0.99806 |
| ERBB4 | rs1521550 (G/A) | 2 | 212958457 | 0.03 | 0.9795 | 0.99806 |
| NRG3 | rs501376 (A/C) | 10 | 84570188 | 0.03 | 0.9797 | 0.99806 |
| NRG3 | rs576966 (C/A) | 10 | 84678060 | 0.03 | 0.9798 | 0.99806 |
| ERBB4 | rs73986915 (G/A) | 2 | 213135079 | -0.05 | 0.98 | 0.99806 |
| ERBB4 | rs2170529 (G/A) | 2 | 213328749 | -0.03 | 0.98 | 0.99806 |
| NRG3 | rs3924461 (G/A) | 10 | 84433391 | 0.03 | 0.9801 | 0.99806 |
| ERBB4 | rs201176747 (A/T) | 2 | 212308965 | -0.03 | 0.9801 | 0.99806 |
| NRG1 | rs11776203 (A/C) | 8 | 32419119 | 0.03 | 0.9804 | 0.99806 |
| ERBB4 | rs2371276 (A/G) | 2 | 212555085 | 0.03 | 0.9813 | 0.99806 |
| ERBB4 | rs6435659 (A/G) | 2 | 212564895 | -0.02 | 0.9826 | 0.99806 |
| NRG3 | rs12415782 (A/G) | 10 | 84604382 | 0.04 | 0.9827 | 0.99806 |
| NRG3 | rs11196301 (A/G) | 10 | 84634847 | -0.03 | 0.9827 | 0.99806 |
| NRG1 | rs10106329 (A/G) | 8 | 32214317 | 0.03 | 0.9833 | 0.99806 |
| NRG1 | rs13439861 (A/G) | 8 | 32220702 | 0.03 | 0.9833 | 0.99806 |
| ERBB4 | rs73081389 (C/A) | 2 | 212870284 | 0.03 | 0.9833 | 0.99806 |
| EGFR | rs2740764 (A/C) | 7 | 55267458 | -0.03 | 0.9834 | 0.99806 |
| EGF | rs28672708 (A/C) | 4 | 110845886 | -0.02 | 0.9841 | 0.99806 |
| NRG1 | rs62500191 (C/A) | 8 | 32382264 | 0.03 | 0.9843 | 0.99806 |
| NRG3 | rs2644206 (A/G) | 10 | 84493564 | -0.02 | 0.9847 | 0.99806 |
| EGF | rs4698800 (G/A) | 4 | 110866508 | -0.02 | 0.9854 | 0.99806 |
| ERBB4 | rs10189716 (A/G) | 2 | 212380586 | 0.02 | 0.9854 | 0.99806 |
| TGFA | rs3771507 (G/A) | 2 | 70701923 | -0.02 | 0.9867 | 0.99806 |
| NRG1 | rs3757930 (G/A) | 8 | 32589118 | 0.02 | 0.9872 | 0.99806 |
| ERBB4 | rs10198754 (G/A) | 2 | 212440041 | -0.02 | 0.9872 | 0.99806 |
| EGFR | rs12667668 (C/A) | 7 | 55187053 | -0.02 | 0.9877 | 0.99806 |
| ERBB4 | rs7594072 (G/A) | 2 | 212380125 | 0.02 | 0.9879 | 0.99806 |
| ERBB4 | rs7594200 (G/A) | 2 | 212380226 | 0.02 | 0.9879 | 0.99806 |
| ERBB4 | rs931817 (A/G) | 2 | 213137150 | -0.04 | 0.988 | 0.99806 |

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|---|---|---|---|---|---|---|
| NRG1 | rs17705671 (A/G) | 8 | 32198296 | -0.02 | 0.9883 | 0.99806 |
| ERBB4 | rs35330898 (G/A) | 2 | 212351335 | 0.02 | 0.9886 | 0.99806 |
| EGFR | rs7781264 (G/A) | 7 | 55230840 | 0.02 | 0.9896 | 0.99806 |
| NRG2 | rs1422188 (C/A) | 5 | 139276664 | -0.02 | 0.9896 | 0.99806 |
| NRG1 | rs1487152 (A/G) | 8 | 32217225 | 0.01 | 0.9903 | 0.99806 |
| ERBB4 | rs1473638 (A/C) | 2 | 212883383 | -0.02 | 0.9903 | 0.99806 |
| EGFR | rs11770506 (A/G) | 7 | 55090379 | 0.01 | 0.9905 | 0.99806 |
| NRG3 | rs12244925 (A/G) | 10 | 84049409 | 0.01 | 0.9906 | 0.99806 |
| NRG1 | rs117211909 (C/A) | 8 | 31747717 | -0.02 | 0.9916 | 0.99812 |
| MUC4 | rs73205719 (G/A) | 3 | 195485085 | -0.02 | 0.9916 | 0.99812 |
| NRG1 | rs73239835 (G/A) | 8 | 31559986 | -0.01 | 0.9919 | 0.99812 |
| NRG3 | rs4506582 (G/A) | 10 | 84126885 | -0.01 | 0.9932 | 0.99814 |
| ERBB4 | rs11901525 (A/G) | 2 | 212382015 | 0.01 | 0.9937 | 0.99814 |
| NRG1 | rs2010243 (A/G) | 8 | 31846380 | 0.01 | 0.9939 | 0.99814 |
| NRG1 | rs10103255 (C/G) | 8 | 32488351 | 0.01 | 0.9939 | 0.99814 |
| NRG3 | rs2246386 (G/A) | 10 | 84459893 | 0.01 | 0.9948 | 0.99814 |
| NRG3 | rs12256472 (C/A) | 10 | 84668708 | -0.01 | 0.9952 | 0.99814 |
| ERBB4 | rs10203022 (A/G) | 2 | 212458790 | -0.01 | 0.9953 | 0.99814 |
| ERBB4 | rs10932380 (A/G) | 2 | 212390350 | -0.01 | 0.9958 | 0.99814 |
| NRG3 | rs2152594 (G/A) | 10 | 83952753 | -0.01 | 0.9961 | 0.99814 |
| ERBB4 | rs6711080 (G/A) | 2 | 213317329 | 0.01 | 0.9961 | 0.99814 |
| ERBB4 | rs6743763 (G/A) | 2 | 213200363 | -0.01 | 0.9966 | 0.99814 |
| NRG1 | rs17683983 (C/A) | 8 | 31846839 | 0.00 | 0.9969 | 0.99814 |
| NRG1 | rs6987996 (G/A) | 8 | 31506771 | 0.00 | 0.998 | 0.99851 |
| NRG3 | rs11192134 (G/A) | 10 | 83763015 | 0.00 | 0.9981 | 0.99851 |
| NRG1 | rs4733372 (A/G) | 8 | 32605388 | 0.00 | 0.9993 | 0.9993 |

**Supplementary Table 2: Haplotype analysis of *EREG* gene**

| SNP1 | SNP2 | D' | LOD | $R^2$ | 95%CI_low | 95%CI_hi | Distance | T stat |
|---|---|---|---|---|---|---|---|---|
| rs6836436 | rs7662139 | 1 | 18.93 | 0.018 | 0.9 | 1 | 1501 | 1317.16 |
| rs6836436 | rs1993665 | 0.971 | 148.35 | 0.176 | 0.94 | 0.99 | 3556 | - |
| rs6836436 | rs201835071 | 0.929 | 367.82 | 0.771 | 0.9 | 0.96 | 6657 | - |
| rs6836436 | rs200889776 | 0.982 | 392.24 | 0.818 | 0.96 | 1 | 9840 | - |
| rs6836436 | rs10518126 | 0.982 | 389.82 | 0.811 | 0.96 | 1 | 12189 | - |
| rs6836436 | rs4694683 | 1 | 18.84 | 0.018 | 0.9 | 1 | 12772 | - |
| rs6836436 | rs57839099 | 0.982 | 388.93 | 0.811 | 0.96 | 1 | 12883 | - |
| rs6836436 | rs57933408 | 0.985 | 380.91 | 0.798 | 0.96 | 1 | 12898 | - |
| rs6836436 | rs72859363 | 0.942 | 371.46 | 0.78 | 0.91 | 0.97 | 15182 | - |
| rs6836436 | rs2367707 | 1 | 19.28 | 0.023 | 0.89 | 1 | 17504 | - |
| rs6836436 | rs2367708 | 0.934 | 15.92 | 0.017 | 0.8 | 0.98 | 17614 | - |
| rs6836436 | rs1017733 | 0.769 | 10.79 | 0.013 | 0.61 | 0.87 | 21420 | - |
| rs6836436 | rs1017734 | 0.057 | 0.46 | 0.001 | 0 | 0.13 | 22190 | - |
| rs6836436 | rs1460007 | 1 | 20.18 | 0.02 | 0.9 | 1 | 23328 | - |
| rs6836436 | rs1460008 | 0.76 | 10.23 | 0.012 | 0.59 | 0.87 | 23352 | - |
| rs7662139 | rs1993665 | 1 | 410.93 | 0.486 | 0.99 | 1 | 2055 | 2644.66 |
| rs7662139 | rs201835071 | 0.882 | 11.51 | 0.013 | 0.72 | 0.96 | 5156 | - |
| rs7662139 | rs200889776 | 1 | 15.86 | 0.016 | 0.88 | 1 | 8339 | - |
| rs7662139 | rs10518126 | 1 | 15.74 | 0.015 | 0.88 | 1 | 10688 | - |
| rs7662139 | rs4694683 | 0.999 | 873.55 | 0.995 | 0.98 | 1 | 11271 | - |
| rs7662139 | rs57839099 | 1 | 15.61 | 0.015 | 0.88 | 1 | 11382 | - |
| rs7662139 | rs57933408 | 1 | 15.32 | 0.015 | 0.88 | 1 | 11397 | - |
| rs7662139 | rs72859363 | 1 | 16.83 | 0.016 | 0.89 | 1 | 13681 | - |
| rs7662139 | rs2367707 | 0.985 | 607.74 | 0.755 | 0.97 | 1 | 16003 | - |
| rs7662139 | rs2367708 | 0.984 | 730.24 | 0.893 | 0.97 | 1 | 16113 | - |
| rs7662139 | rs1017733 | 0.979 | 660.26 | 0.821 | 0.96 | 0.99 | 19919 | - |
| rs7662139 | rs1017734 | 0.972 | 414.12 | 0.526 | 0.95 | 0.99 | 20689 | - |
| rs7662139 | rs1460007 | 0.972 | 712.02 | 0.882 | 0.95 | 0.99 | 21827 | - |
| rs7662139 | rs1460008 | 0.971 | 643.56 | 0.811 | 0.95 | 0.99 | 21851 | - |
| rs1993665 | rs201835071 | 0.963 | 129.86 | 0.156 | 0.92 | 0.99 | 3101 | 3447.98 |
| rs1993665 | rs200889776 | 1 | 139.65 | 0.159 | 0.98 | 1 | 6284 | - |
| rs1993665 | rs10518126 | 1 | 139.2 | 0.158 | 0.98 | 1 | 8633 | - |
| rs1993665 | rs4694683 | 1 | 410.24 | 0.485 | 0.99 | 1 | 9216 | - |
| rs1993665 | rs57839099 | 1 | 139.11 | 0.158 | 0.98 | 1 | 9327 | - |
| rs1993665 | rs57933408 | 1 | 136.09 | 0.154 | 0.98 | 1 | 9342 | - |
| rs1993665 | rs72859363 | 0.977 | 133.09 | 0.157 | 0.94 | 1 | 11626 | - |
| rs1993665 | rs2367707 | 0.897 | 395.63 | 0.503 | 0.87 | 0.92 | 13948 | - |
| rs1993665 | rs2367708 | 0.895 | 315.87 | 0.422 | 0.86 | 0.92 | 14058 | - |
| rs1993665 | rs1017733 | 0.88 | 332.69 | 0.44 | 0.85 | 0.91 | 17864 | - |
| rs1993665 | rs1017734 | 0.806 | 463.06 | 0.566 | 0.78 | 0.83 | 18634 | - |
| rs1993665 | rs1460007 | 0.886 | 302.29 | 0.409 | 0.85 | 0.91 | 19772 | - |
| rs1993665 | rs1460008 | 0.88 | 329.93 | 0.438 | 0.85 | 0.91 | 19796 | - |

| SNP1 | SNP2 | D' | LOD | $R^2$ | 95%CI_low | 95%CI_hi | Distance | T stat |
|---|---|---|---|---|---|---|---|---|
| rs201835071 | rs200889776 | 1 | 458.46 | 0.945 | 0.99 | 1 | 3183 | 5295.83 |
| rs201835071 | rs10518126 | 1 | 457.14 | 0.942 | 0.99 | 1 | 5532 | - |
| rs201835071 | rs4694683 | 0.881 | 11.45 | 0.013 | 0.71 | 0.96 | 6115 | - |
| rs201835071 | rs57839099 | 1 | 456.19 | 0.942 | 0.99 | 1 | 6226 | - |
| rs201835071 | rs57933408 | 1 | 441.48 | 0.922 | 0.99 | 1 | 6241 | - |
| rs201835071 | rs72859363 | 0.955 | 426.88 | 0.896 | 0.93 | 0.98 | 8525 | - |
| rs201835071 | rs2367707 | 0.772 | 9.26 | 0.013 | 0.59 | 0.88 | 10847 | - |
| rs201835071 | rs2367708 | 0.792 | 9.76 | 0.011 | 0.62 | 0.89 | 10957 | - |
| rs201835071 | rs1017733 | 0.558 | 4.61 | 0.006 | 0.36 | 0.71 | 14763 | - |
| rs201835071 | rs1017734 | 0.258 | 1.23 | 0.002 | 0.08 | 0.43 | 15533 | - |
| rs201835071 | rs1460007 | 0.861 | 11.94 | 0.013 | 0.7 | 0.94 | 16671 | - |
| rs201835071 | rs1460008 | 0.548 | 4.38 | 0.006 | 0.34 | 0.7 | 16695 | - |
| rs200889776 | rs10518126 | 1 | 487.3 | 0.997 | 0.99 | 1 | 2349 | 7149.27 |
| rs200889776 | rs4694683 | 1 | 15.79 | 0.016 | 0.88 | 1 | 2932 | - |
| rs200889776 | rs57839099 | 1 | 486.34 | 0.997 | 0.99 | 1 | 3043 | - |
| rs200889776 | rs57933408 | 1 | 466.12 | 0.977 | 0.99 | 1 | 3058 | - |
| rs200889776 | rs72859363 | 0.994 | 455.84 | 0.949 | 0.97 | 1 | 5342 | - |
| rs200889776 | rs2367707 | 1 | 16.03 | 0.02 | 0.87 | 1 | 7664 | - |
| rs200889776 | rs2367708 | 0.89 | 12.33 | 0.013 | 0.73 | 0.96 | 7774 | - |
| rs200889776 | rs1017733 | 0.709 | 7.38 | 0.009 | 0.52 | 0.83 | 11580 | - |
| rs200889776 | rs1017734 | 0.367 | 2.3 | 0.004 | 0.17 | 0.53 | 12350 | - |
| rs200889776 | rs1460007 | 1 | 17.08 | 0.017 | 0.89 | 1 | 13488 | - |
| rs200889776 | rs1460008 | 0.701 | 7.08 | 0.009 | 0.51 | 0.83 | 13512 | - |
| rs10518126 | rs4694683 | 1 | 15.67 | 0.015 | 0.88 | 1 | 583 | 6977.84 |
| rs10518126 | rs57839099 | 1 | 490.11 | 1 | 0.99 | 1 | 694 | - |
| rs10518126 | rs57933408 | 1 | 468.56 | 0.979 | 0.99 | 1 | 709 | - |
| rs10518126 | rs72859363 | 0.997 | 459 | 0.952 | 0.98 | 1 | 2993 | - |
| rs10518126 | rs2367707 | 1 | 15.91 | 0.02 | 0.87 | 1 | 5315 | - |
| rs10518126 | rs2367708 | 0.889 | 12.21 | 0.013 | 0.73 | 0.96 | 5425 | - |
| rs10518126 | rs1017733 | 0.706 | 7.26 | 0.009 | 0.51 | 0.83 | 9231 | - |
| rs10518126 | rs1017734 | 0.365 | 2.27 | 0.004 | 0.17 | 0.53 | 10001 | - |
| rs10518126 | rs1460007 | 1 | 16.94 | 0.017 | 0.89 | 1 | 11139 | - |
| rs10518126 | rs1460008 | 0.698 | 6.97 | 0.009 | 0.5 | 0.83 | 11163 | - |
| rs4694683 | rs57839099 | 1 | 15.53 | 0.015 | 0.88 | 1 | 111 | 6746.08 |
| rs4694683 | rs57933408 | 1 | 15.25 | 0.015 | 0.87 | 1 | 126 | - |
| rs4694683 | rs72859363 | 1 | 16.76 | 0.016 | 0.89 | 1 | 2410 | - |
| rs4694683 | rs2367707 | 0.989 | 614.97 | 0.759 | 0.97 | 1 | 4732 | - |
| rs4694683 | rs2367708 | 0.987 | 737.76 | 0.897 | 0.97 | 1 | 4842 | - |
| rs4694683 | rs1017733 | 0.982 | 664.15 | 0.824 | 0.96 | 1 | 8648 | - |
| rs4694683 | rs1017734 | 0.973 | 415.48 | 0.527 | 0.95 | 0.99 | 9418 | - |
| rs4694683 | rs1460007 | 0.973 | 712.52 | 0.882 | 0.95 | 0.99 | 10556 | - |
| rs4694683 | rs1460008 | 0.973 | 644.34 | 0.811 | 0.95 | 0.99 | 10580 | - |
| rs57839099 | rs57933408 | 1 | 467.59 | 0.979 | 0.99 | 1 | 15 | 5822.15 |
| rs57839099 | rs72859363 | 0.997 | 458.06 | 0.952 | 0.98 | 1 | 2299 | - |
| rs57839099 | rs2367707 | 1 | 15.75 | 0.02 | 0.87 | 1 | 4621 | - |

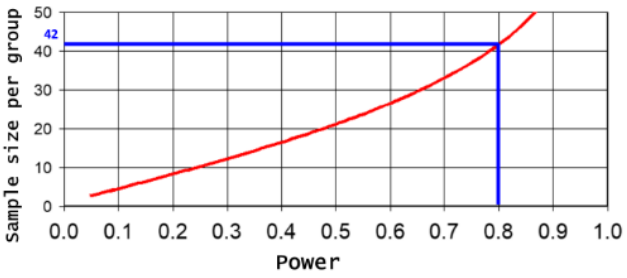
| SNP1 | SNP2 | D' | LOD | $R^2$ | 95%CI_low | 95%CI_hi | Distance | T stat |
|---|---|---|---|---|---|---|---|---|
| rs57839099 | rs2367708 | 0.888 | 12.08 | 0.013 | 0.73 | 0.96 | 4731 | - |
| rs57839099 | rs1017733 | 0.704 | 7.15 | 0.009 | 0.51 | 0.83 | 8537 | - |
| rs57839099 | rs1017734 | 0.36 | 2.19 | 0.004 | 0.16 | 0.53 | 9307 | - |
| rs57839099 | rs1460007 | 1 | 16.8 | 0.017 | 0.89 | 1 | 10445 | - |
| rs57839099 | rs1460008 | 0.696 | 6.86 | 0.009 | 0.5 | 0.83 | 10469 | - |
| rs57933408 | rs72859363 | 0.997 | 442.65 | 0.932 | 0.98 | 1 | 2284 | 4419.18 |
| rs57933408 | rs2367707 | 1 | 15.3 | 0.019 | 0.86 | 1 | 4606 | - |
| rs57933408 | rs2367708 | 1 | 16.51 | 0.016 | 0.88 | 1 | 4716 | - |
| rs57933408 | rs1017733 | 0.697 | 6.86 | 0.009 | 0.5 | 0.83 | 8522 | - |
| rs57933408 | rs1017734 | 0.425 | 2.98 | 0.005 | 0.23 | 0.59 | 9292 | - |
| rs57933408 | rs1460007 | 1 | 16.47 | 0.016 | 0.88 | 1 | 10430 | - |
| rs57933408 | rs1460008 | 0.689 | 6.58 | 0.008 | 0.49 | 0.82 | 10454 | - |
| rs72859363 | rs2367707 | 0.826 | 10.09 | 0.014 | 0.65 | 0.92 | 2322 | 3361.28 |
| rs72859363 | rs2367708 | 0.892 | 12.75 | 0.014 | 0.74 | 0.96 | 2432 | - |
| rs72859363 | rs1017733 | 0.704 | 7.79 | 0.009 | 0.52 | 0.83 | 6238 | - |
| rs72859363 | rs1017734 | 0.233 | 0.97 | 0.002 | 0.05 | 0.41 | 7008 | - |
| rs72859363 | rs1460007 | 1 | 18.12 | 0.017 | 0.89 | 1 | 8146 | - |
| rs72859363 | rs1460008 | 0.697 | 7.5 | 0.009 | 0.51 | 0.82 | 8170 | - |
| rs2367707 | rs2367708 | 0.989 | 686.67 | 0.824 | 0.97 | 1 | 110 | 6495.89 |
| rs2367707 | rs1017733 | 0.933 | 635.85 | 0.79 | 0.91 | 0.95 | 3916 | - |
| rs2367707 | rs1017734 | 0.967 | 561.89 | 0.67 | 0.95 | 0.98 | 4686 | - |
| rs2367707 | rs1460007 | 0.987 | 671.6 | 0.812 | 0.97 | 1 | 5824 | - |
| rs2367707 | rs1460008 | 0.929 | 624.02 | 0.782 | 0.91 | 0.95 | 5848 | - |
| rs2367708 | rs1017733 | 0.983 | 756.17 | 0.897 | 0.97 | 1 | 3806 | 5402.54 |
| rs2367708 | rs1017734 | 0.988 | 483.24 | 0.591 | 0.97 | 1 | 4576 | - |
| rs2367708 | rs1460007 | 0.987 | 834.48 | 0.963 | 0.97 | 1 | 5714 | - |
| rs2367708 | rs1460008 | 0.975 | 735.02 | 0.885 | 0.96 | 0.99 | 5738 | - |
| rs1017733 | rs1017734 | 0.989 | 535.04 | 0.637 | 0.97 | 1 | 770 | 6176.11 |
| rs1017733 | rs1460007 | 0.996 | 780.45 | 0.911 | 0.98 | 1 | 1908 | - |
| rs1017733 | rs1460008 | 0.993 | 897.75 | 0.983 | 0.98 | 1 | 1932 | - |
| rs1017734 | rs1460007 | 0.999 | 496.85 | 0.596 | 0.98 | 1 | 1138 | 5619.06 |
| rs1017734 | rs1460008 | 0.999 | 553.27 | 0.647 | 0.98 | 1 | 1162 | - |
| rs1460007 | rs1460008 | 1 | 795.41 | 0.921 | 0.99 | 1 | 24 | 3605.47 |

**Supplementary Table 3: Percentage of white blood cells at baseline and following CFA injection (Day 3 and Day 7) for mice treated with vehicle control or the epiregulin mAb. The p-values are shown for Tukey's post-hoc testing comparing the different time-points.**

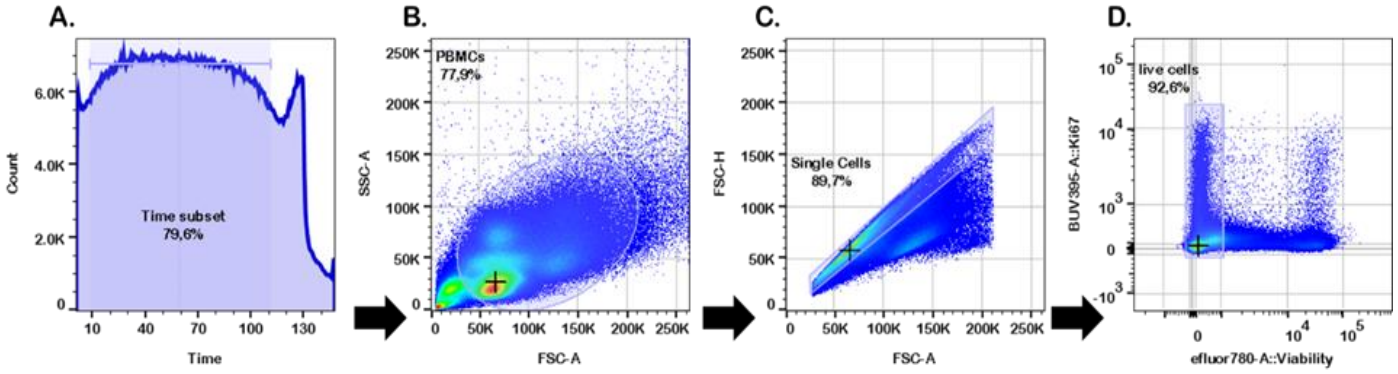
| Blood cell type | Time-point | Control (% ± S.D.) | Epiregulin mAb (% ± S.D.) | p-value |
|---|---|---|---|---|
| **Lymphocyte** | Baseline | 78.75 ± 27.37 | 80.0 ± 24.67 | 0.98 |
| | Day 3 | 71.86 ± 24.31 | 68.25 ± 20.31 | 0.67 |
| | Day 7 | 70.37 ± 22.61 | 73.37 ± 22.97 | 0.85 |
| **Monocyte** | Baseline | 4.38 ± 3.33 | 2.45 ± 0.86 | 0.93 |
| | Day 3 | 4.0 ± 3.29 | 3.96 ± 1.44 | 0.99 |
| | Day 7 | 8.0 ± 3.10 | 4.48 ± 1.15 | 0.10 |
| **Neutrophil** | Baseline | 14.0 ± 9.74 | 12.5 ± 4.16 | 0.96 |
| | Day 3 | 21.75 ± 10.30 | 24.88 ± 8.10 | 0.76 |
| | Day 7 | 17.63 ± 6.36 | 17.13 ± 2.79 | 0.99 |

# 3. Supplementary materials of chapter III

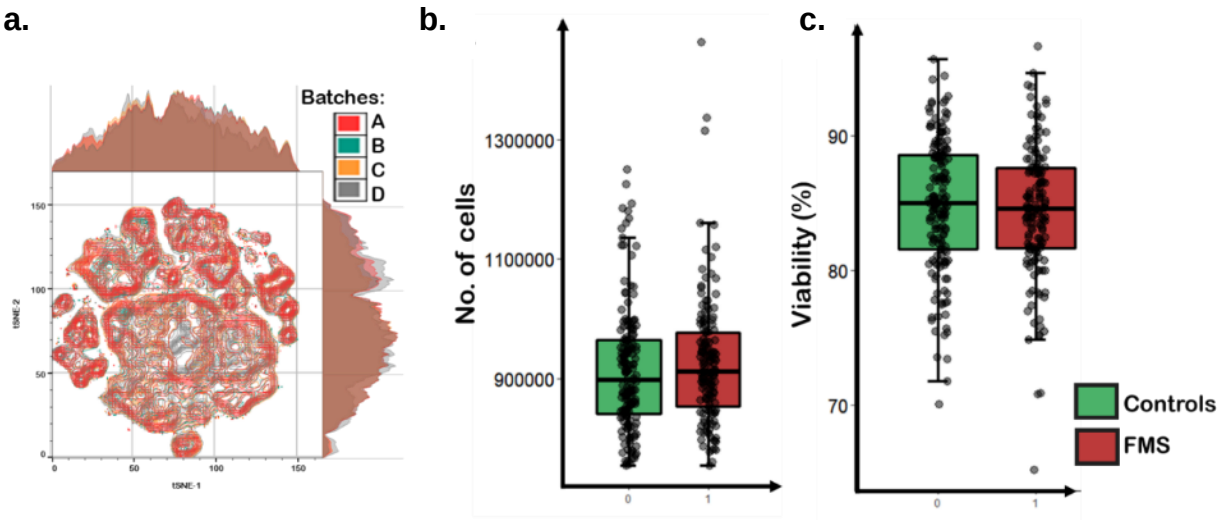
Supplementary Figure 1: Sample size calculation to capture immunophenotype difference with 80% power and 5% type-I error.



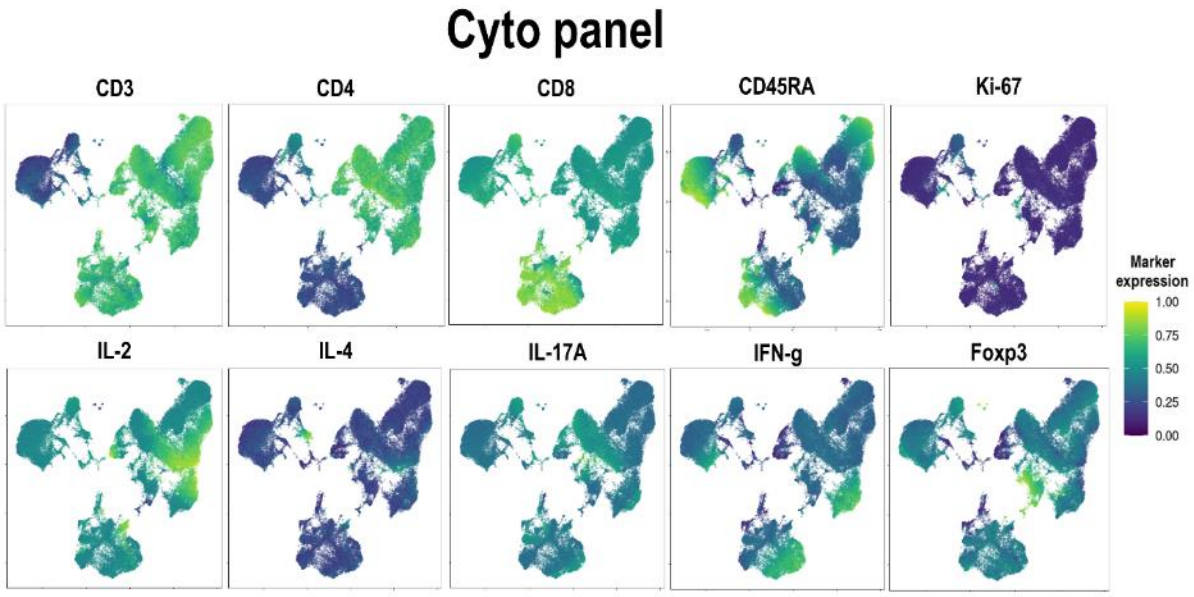

Supplementary Figure 2: Gating strategy to export cells of interest for further flow cytometry data analyses.



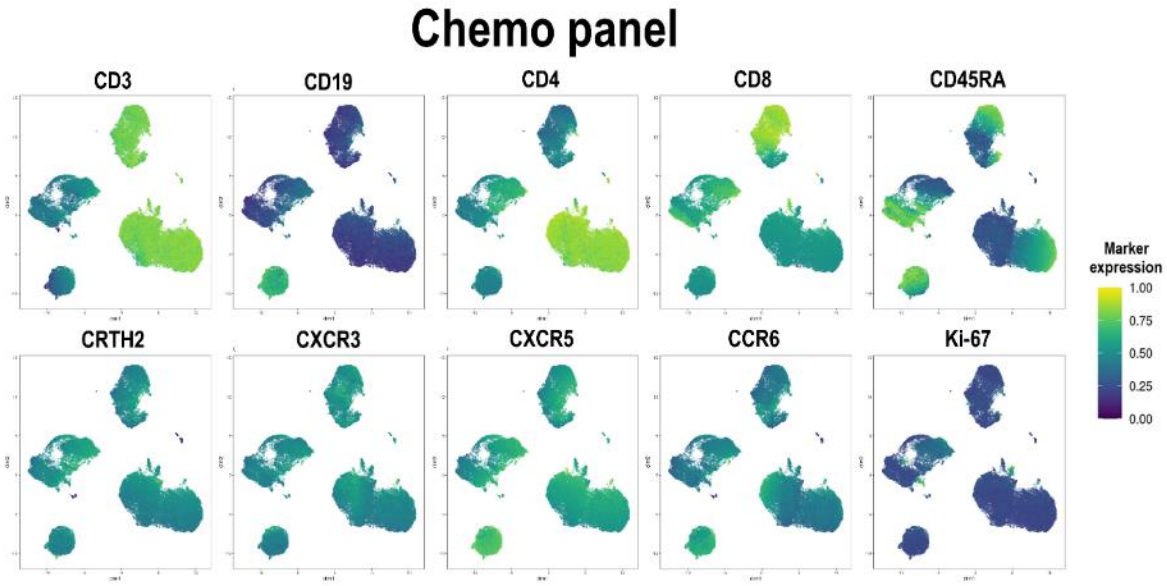
Supplementary Figure 3: Quality control of the flow cytometry data. (A) t-SNE projection of cells stratified according to the batch. Boxplots showing (B) the total number of cells acquired and viability. Colors, green and red are used to depict controls and fibromyalgia syndrome (FMS) cases.



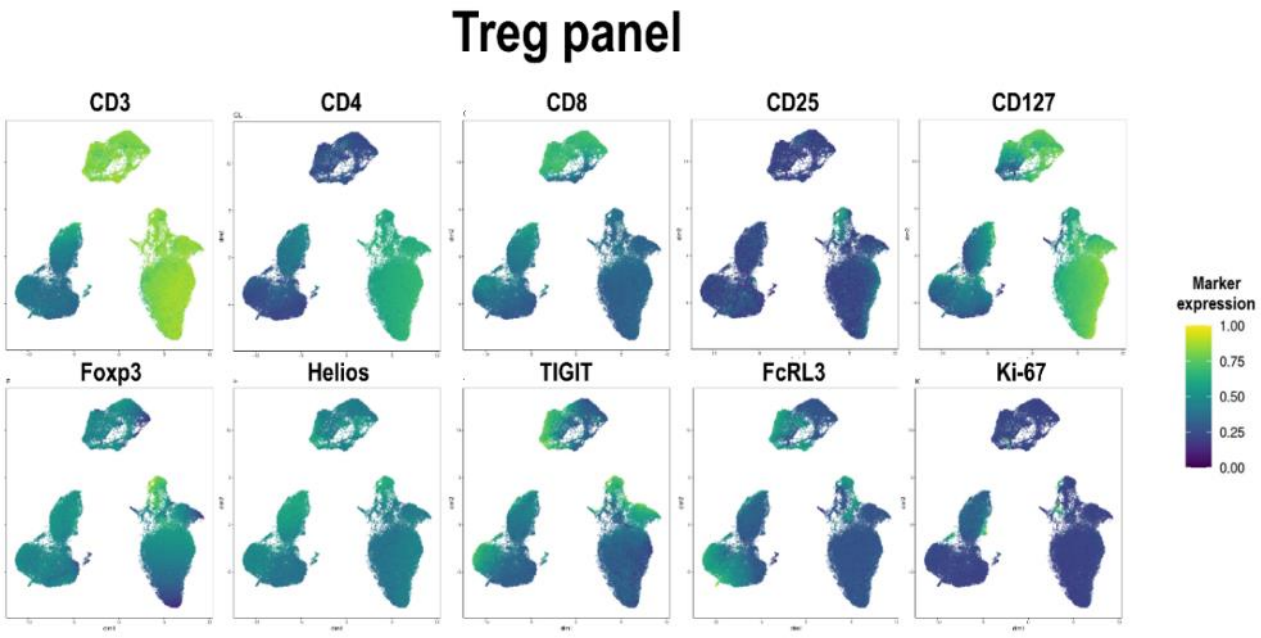
Supplementary Figures 4: Markers' Expression in the Cyto panel dataset. Single peripheral blood mononuclear cell samples projected on t-distributed Uniform Manifold Approximation and Projection (UMAP) dimensions. Normalized expressions of all the functional and phenotypic markers are represented through a color scale (low, dark blue to high, yellow).



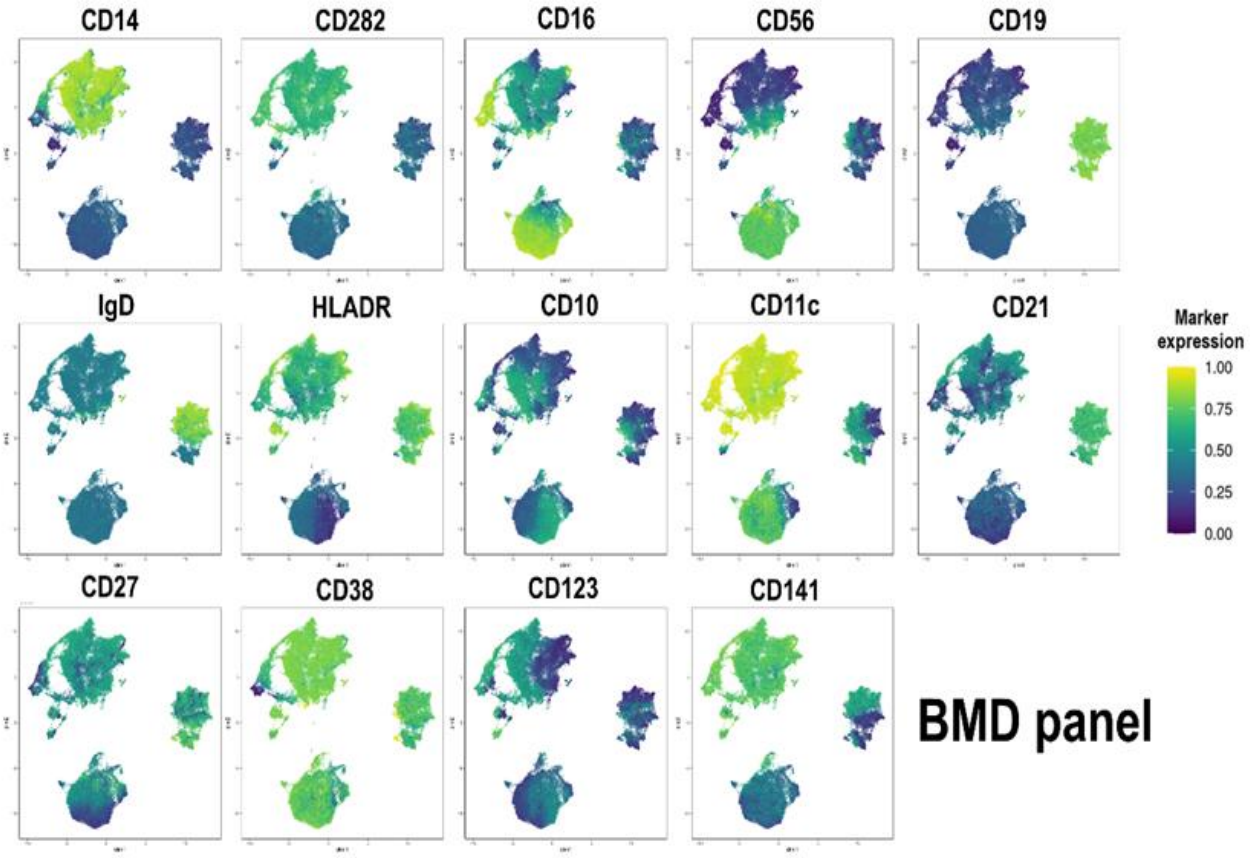
Supplementary Figures 5: Markers' expression in the Chemo panel dataset. Single peripheral blood mononuclear cell samples projected on t-distributed Uniform Manifold Approximation and Projection (UMAP) dimensions. Normalized expressions of all the functional and phenotypic markers are represented through a color scale (low, dark blue to high, yellow).



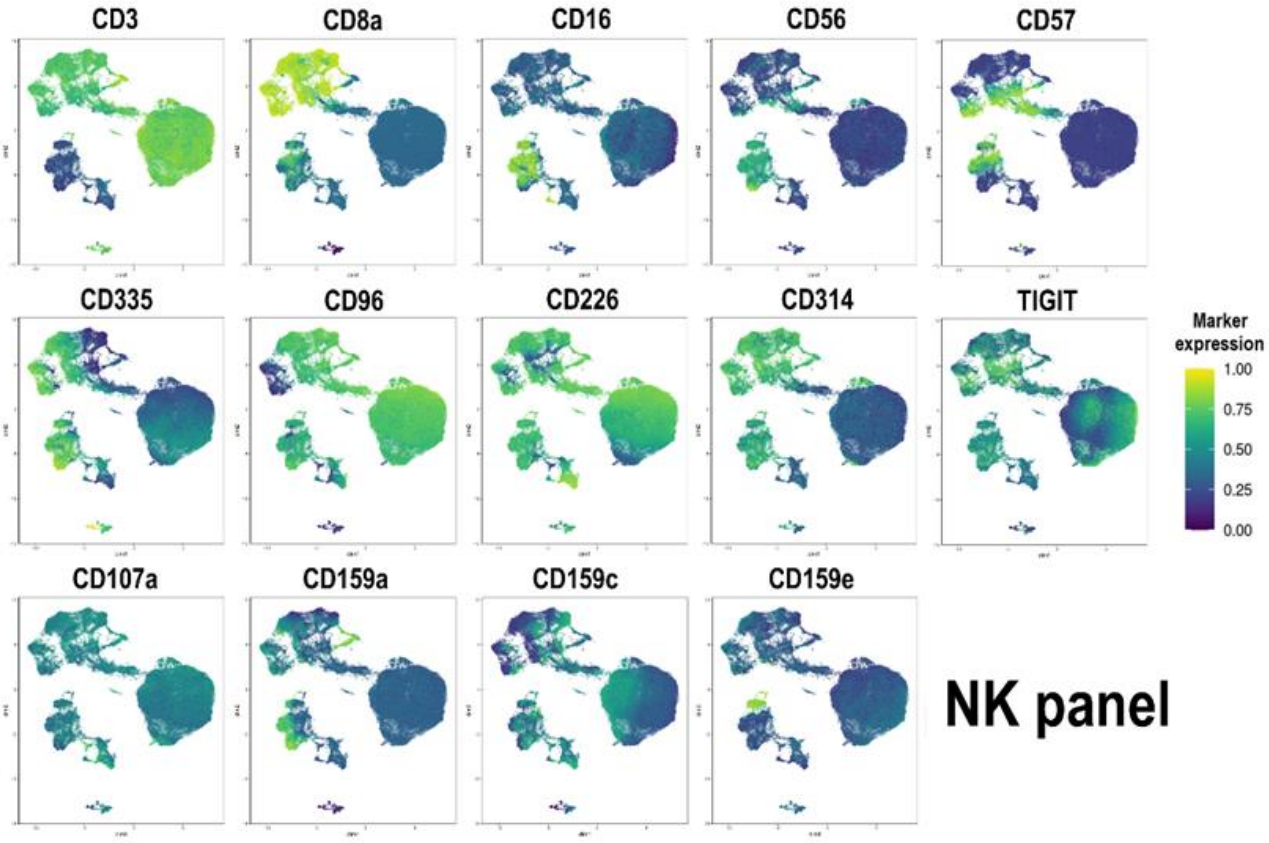
Supplementary Figures 6: Markers' Expression in the Treg panel dataset. Single peripheral blood mononuclear cell samples projected on t-distributed Uniform Manifold Approximation and Projection (UMAP) dimensions. Normalized expressions of all the functional and phenotypic markers are represented through a color scale (low, dark blue to high, yellow).



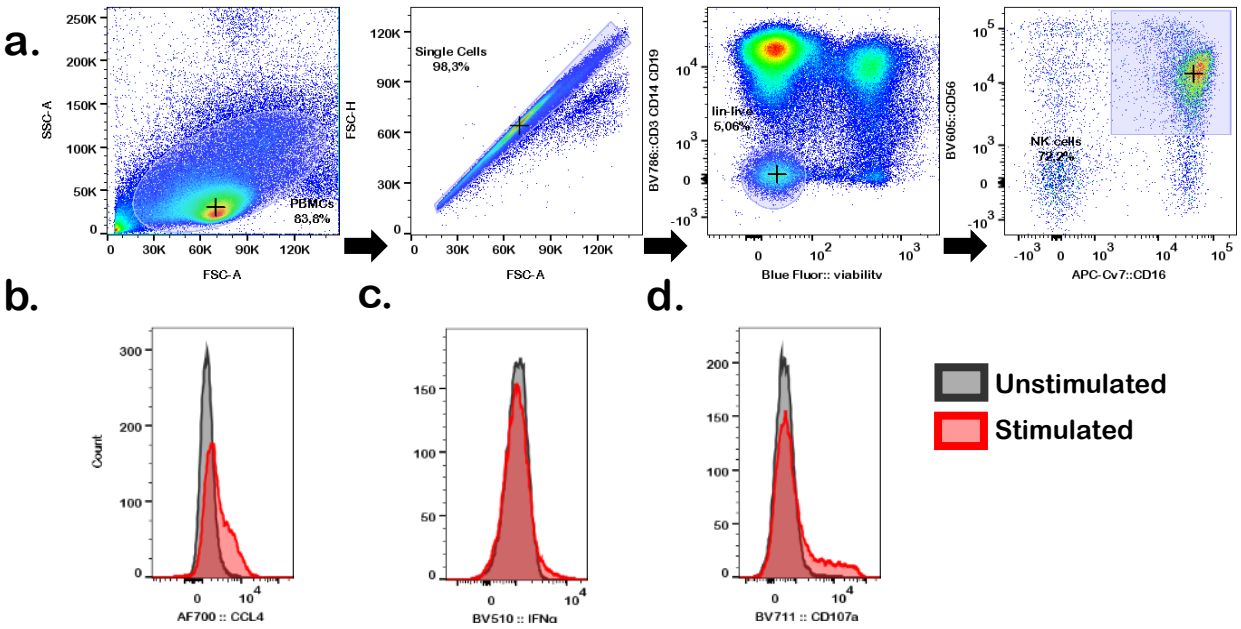
Supplementary Figures 7: Markers' Expression in the BMD panel dataset. Single peripheral blood mononuclear cell samples projected on t-distributed Uniform Manifold Approximation and Projection (UMAP) dimensions. Normalized expressions of all the functional and phenotypic markers are represented through a color scale (low, dark blue to high, yellow).



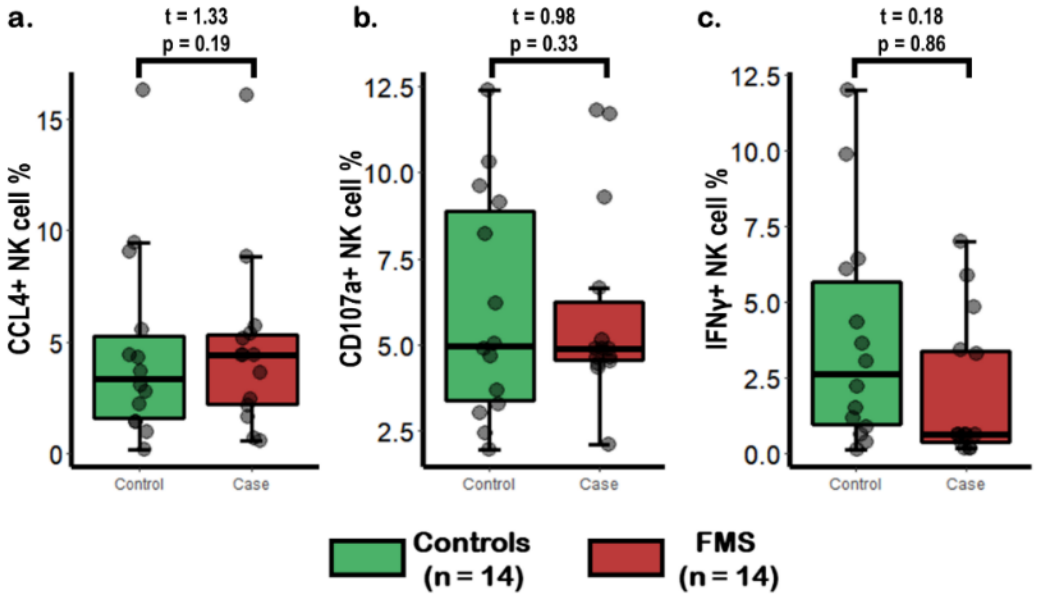
Supplementary Figures 8: Markers' Expression in the NK panel dataset. Single peripheral blood mononuclear cell samples projected on t-distributed Uniform Manifold Approximation and Projection (UMAP) dimensions. Normalized expressions of all the functional and phenotypic markers are represented through a color scale (low, dark blue to high, yellow).



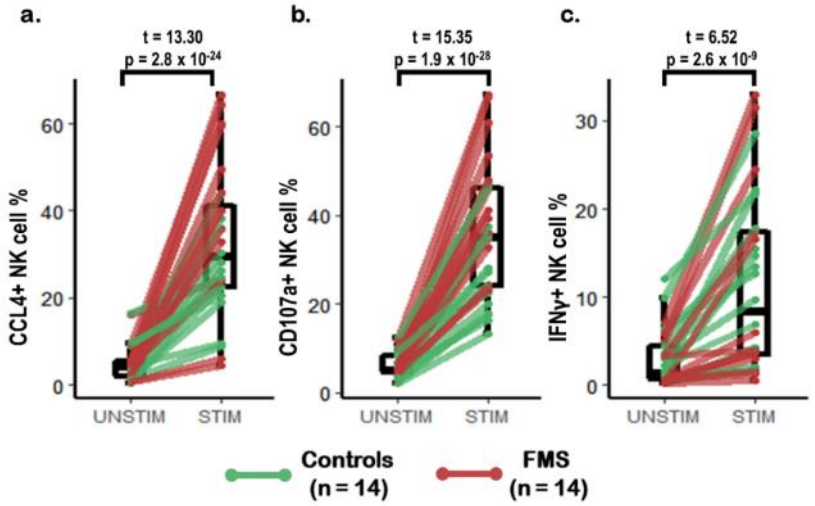
Supplementary Figure 9: NK activation assay: gating strategy and effect of stimulation



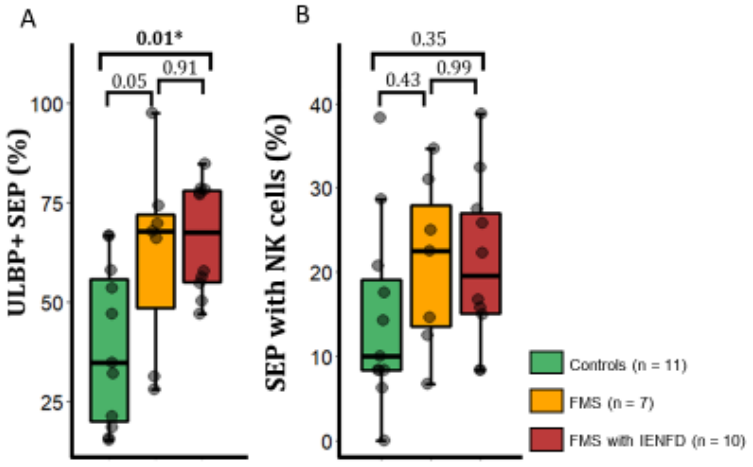

Supplementary Figure 10: Difference in NK activation markers between FMS cases and controls at baseline (unstimulated cells).



Supplementary Figure 11: Effect of stimulation on NK cells with either HLA$^{-/-}$ cells or opsonized cells on NK cells.




Supplementary Figure 12: ULBP expression and NK cell recruitment at the peripheral nerves are associated with FMS. Boxplots showing the distribution of (A) ULBP + SEP and (B) SEP with NK cells are stratified by the case status. Green, yellow and red depict controls, FMS cases, and FMS cases with IENFD, respectively. Statistics in (h) and (i) are based on one-way ANOVA followed by Tukey's posthoc comparison. Boxplots are presented as mean ± s.e.m. FMS: fibromyalgia syndrome; ULBP: UL16 binding protein; SEP: Subepidermal plexus; NK: natural killer; IENFD: intra-epidermal nerve fiber deficiency



Supplementary Table 1: Tertiary Outcome Measures

| No. | Title | Description | Ref. |
|---|---|---|---|
| 1 | Pennebaker Inventory for Limbic Languidness (PILL) | PILL measures the tendency of people to notice and report a broad array of physical symptoms and sensations. | [1] |
| 2 | Symptom Checklist-90-Revised (SCL90R) | SCL90R helps in evaluating a broad range of psychological problems and symptoms of psychopathology. | [2] |
| 3 | Pittsburgh Sleep Quality Index (PSQI) | Pittsburgh Sleep Quality Index (PSQI) is a self-administered questionnaire that assesses sleep quality and disturbances over a one-month time interval. | [3] |
| 4 | Perceived Stress Scale (PSS) | PSS measures the degree to which situations in one's life are appraised as stressful. | [4] |
| 5 | Beck’s Anxiety Index (BAI) | BAI is a self-report measure of anxiety | [5] |
| 6 | Beck’s Depression Index (BDI) | BDI is a self-report measure of anxiety | [6] |

## References

1. Pennebaker JW. Putting Stress into Words - Health, Linguistic, and Therapeutic Implications. Behaviour research and therapy. 1993;31(6):539-48. doi: Doi 10.1016/0005-7967(93)90105-4

2. Derogatis LR. SCL-90-R : symptom checklist-90-R : administration, scoring & procedures manual. 3 ed. Minneapolis: National Computer Systems; 1994.

3. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989;28(2):193-213. doi: 10.1016/0165-1781(89)90047-4

4. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav. 1983;24(4):385-96.

5. Beck AT, Steer RA. Manual for the Beck anxiety inventory. San Antonio, TX: Psychological Corporation. 1990.

6. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Archives of general psychiatry. 1961;4(6):561-71. doi: 10.1001/archpsyc.1961.01710120031004

Supplementary Table 2: Flow cytometry panels

| Cyto Panel | | | | | | | |
|---|---|---|---|---|---|---|---|
| LASER-channel (nm) | Antibody | Isotype | Clone | Fluorochrome | Manufacturer | Catalog no. | µl/test |
| 355 - 379/28 | Ki-67 | IgG1, κ | B56 | BV395 | BD Biosciences | 564071 | 6 |
| 405 - 450/40 | IL-17A | IgG1, κ | N49-653 | V450 | BD Biosciences | 560610 | 4 |
| 405 - 525/50 | CD8a | IgG1, κ | RPA-T8 | V500 | BD Biosciences | 560774 | 3 |
| 405 - 780/60 | CD3 | IgG2a, κ | OKT3 | BV785 | Biolegend | 317330 | 3 |
| 488 - 530/30 | CD4 | IgG1, κ | RPA-T4 | FITC | BD Biosciences | 555346 | 3 |
| 488 - 695/40 | IL-2 | IgG2a, κ | MQ1-17H12 | PerCP-Cy5.5 | BD Biosciences | 560708 | 4 |
| 561 - 582/15 | FoxP3 | IgG1, κ | 236A/E7 | PE | Thermofisher (eBio) | 12-4777-42 | 6 |
| 561 - 780/60 | IFNγ | IgG1, κ | 4S.B3 | PE-Cy7 | BD Biosciences | 560741 | 1 |
| 640 - 670/14 | IL-4 | IgG1, κ | 8D4-8 | APC | BD Biosciences | 561233 | 4 |
| 640 - 730/45 | CD45RA | IgG2b, κ | HI100 | AF700 | BD Biosciences | 560673 | 4 |
| 640 -780/60 | Viability | n/a | n/a | eFluor780 | Thermofisher (eBio) | 65-0865-18 | 1 |

| Chemo Panel | | | | | | | |
|---|---|---|---|---|---|---|---|
| LASER-channel (nm) | Antibody | Isotype | Clone | Fluorochrome | Manufacturer | Catalog no. | µl/test |
| 355 - 379/28 | Ki-67 | IgG1, κ | B56 | BV395 | BD Biosciences | 564071 | 6 |
| 405 - 450/40 | CXCR3 | IgG1, κ | 1C6/CXCR3 | BV421 | BD Biosciences | 562558 | 5 |
| 405 - 525/50 | CD8a | IgG1, κ | RPA-T8 | V500 | BD Biosciences | 560774 | 3 |
| 405 - 660/20 | CXCR5 | IgG2a, κ | 2G8 | BV650 | BD Biosciences | 563981 | 5 |
| 405 - 780/60 | CD3 | IgG2a, κ | OKT3 | BV785 | Biolegend | 317330 | 3 |
| 488 - 530/30 | CD4 | IgG1, κ | RPA-T4 | FITC | BD Biosciences | 555346 | 3 |
| 488 - 695/40 | CD19 | IgG1, κ | HIB19 | PerCP-Cy5.5 | Biolegend | 302230 | 2 |
| 561 - 582/15 | FoxP3 | IgG1, κ | 236A/E7 | PE | Thermofisher (eBio) | 12-4777-42 | 6 |
| 561 - 610/20 | CRTH2 | IgG2a, κ | BM16 | PE-CF594 | BD Biosciences | 563501 | 5 |
| 561 - 780/60 | CCR6 | IgG1, κ | 11A9 | PE-Cy7 | BD Biosciences | 560620 | 5 |
| 640 - 670/14 | CD25 | IgG1, κ | M-A251 | APC | BD Biosciences | 555434 | 4 |
| 640 - 730/45 | CD45RA | IgG2b, κ | HI100 | AF700 | BD Biosciences | 560673 | 4 |
| 640 -780/60 | Viability | n/a | n/a | eFluor780 | Thermofisher (eBio) | 65-0865-18 | 1 |

| Treg Panel | | | | | | | |
|---|---|---|---|---|---|---|---|
| LASER-channel (nm) | Antibody | Isotype | Clone | Fluorochrome | Manufacturer | Catalog no. | µl/test |
| 355 - 379/28 | Ki-67 | IgG1, κ | B56 | BV395 | BD Biosciences | 564071 | 6 |
| 405 - 450/40 | Helios | IgG | 22F6 | Pacific Blue | Biolegend | 137220 | 2 |
| 405 - 525/50 | CD8a | IgG1, κ | RPA-T8 | V500 | BD Biosciences | 560774 | 3 |
| 405 - 610/20 | CD3 | IgG2a, κ | OKT3 | BV785 | Biolegend | 317330 | 3 |
| 405 - 660/20 | CD4 | IgG1, κ | RPA-T4 | FITC | BD Biosciences | 555346 | 3 |
| 488 - 695/40 | TIGIT | IgG1, κ | MBSA43 | PE-eFluor710 | Thermofisher (eBio) | 46-9500-42 | 2 |
| 561 - 582/15 | FoxP3 | IgG1, κ | 236A/E7 | PE | Thermofisher (eBio) | 12-4777-42 | 6 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 561 - 610/20 | CD127 | IgG1, κ | eBioRDR5 | PE-eFluor610 | Thermofisher (eBio) | 61-1278-42 | 2 |
| 561 - 780/60 | FcRL3 | IgG2b, κ | H5 | Biotin* | BD Biosciences | 565056 | 1 |
| | *Streptavidin | n/a | n/a | PE-Cy7 | Thermofisher (eBio) | 25-4317-82 | 5 |
| 640 - 670/14 | CD25 | IgG1, κ | M-A251 | APC | BD Biosciences | 555434 | 4 |
| 640 - 730/45 | CD45RA | IgG2b, κ | HI100 | AF700 | BD Biosciences | 560673 | 4 |
| 640 -780/60 | Viability | n/a | n/a | eFluor780 | Thermofisher (eBio) | 65-0865-18 | 1 |

| **BMD Panel** | | | | | | | |
|---|---|---|---|---|---|---|---|
| LASER-channel (nm) | Antibody | Isotype | Clone | Fluorochrome | Manufacturer | Catalog no. | µl/test |
| 355 - 379/28 | CD14 | IgG2b, κ | MFP9 | BUV395 | BD Biosciences | 563561 | 5 |
| 355 - 740/35 | CD21 | IgG1, κ | B-ly4 | BUV737 | BD Biosciences | 564437 | 2.5 |
| 405 - 450/40 | CD38 | IgG1, κ | HIT2 | BV421 | Biolegend | 303526 | 5 |
| 405 - 610/20 | CD56 | IgG1, κ | HCD56 | BV605 | Biolegend | 318334 | 5 |
| 405 - 660/20 | CD16 | IgG1, κ | 3G8 | BV650 | Biolegend | 302042 | 1.25 |
| 405 - 710/50 | CD10 | IgG1, κ | HI10a | BV711 | Biolegend | 312226 | 5 |
| 405 - 780/60 | CD27 | IgG1, κ | M-T271 | BV786 | BD Biosciences | 740972 | 2.5 |
| 488 - 530/30 | CD19 | IgG1, κ | HIB19 | BB515 | BD Biosciences | 564457 | 5 |
| 488 - 695/40 | HLA-DR | IgG2a, κ | G46-6 | BB700 | BD Biosciences | 566480 | 5 |
| 561 - 582/15 | CD282 | IgG2a, κ | TL2.1 | PE | Biolegend | 309708 | 10 |
| 561 - 610/20 | IgD | IgG2a, κ | IA6-2 | PE-CF594 | BD Biosciences | 562540 | 5 |
| 561 - 780/60 | CD11c | IgG1, κ | Bly6 | PE-Cy7 | BD Biosciences | 561356 | 5 |
| 640 - 670/14 | CD123 | IgG1, κ | 32703 | APC | R&D Systems | FAB301A | 10 |
| 640 -780/60 | CD3 | IgG1, κ | UCHT1 | APC-Cy7 | Biolegend | 300426 | 5 |
| 640 -780/60 | Viability | n/a | n/a | Zombie NIR™ | Biolegend | 423106 | 0.005 |

| **NK Panel** | | | | | | | |
|---|---|---|---|---|---|---|---|
| LASER-channel (nm) | Antibody | Isotype | Clone | Fluorochrome | Manufacturer | Catalog no. | µl/test |
| 355 - 379/28 | CD226 | IgG1, κ | DX11 | BUV395 | BD Biosciences | 742498 | 10 |
| 355 - 670/25 | CD3 | IgG1, κ | UCHT1 | BUV661 | BD Biosciences | 565065 | 0.32 |
| 355 - 740/35 | CD56 | IgG2b, κ | NCAM16 | BUV737 | BD Biosciences | 564447 | 5 |
| 405 - 450/40 | CD107a | IgG1, κ | H4A3 | BV421 | Biolegend | 328626 | 5 |
| 405 - 610/20 | CD335 | IgG1, κ | 9E2 | BV605 | Biolegend | 331926 | 5 |
| 405 - 660/20 | CD159c | IgG1, κ | 134591 | BV650 | BD Biosciences | 748165 | 5 |
| 405 - 710/50 | CD158e | IgG1, κ | DX9 | BV711 | BD Biosciences | 564102 | 5 |
| 405 - 780/60 | CD314 | IgG1, κ | 1D11 | BV785 | Biolegend | 320830 | 5 |
| 488 - 530/30 | CD57 | IgM, κ | TBO1 | BB515 | BD Biosciences | 565285 | 1.25 |
| 561 - 582/15 | CD96 | IgG1, κ | 6F9 | PE | BD Biosciences | 562379 | 5 |
| 561 - 610/20 | CD8a | IgG1, κ | RPA-T8 | AF594 | Biolegend | 301056 | 5 |
| 561 - 780/60 | CD159a | IgG1, κ | REA110 | PE-Vio770 | Miltenyi Biotec | 130-113-567 | 1 |
| 640 - 670/14 | TIGIT | IgG1, κ | MBSA43 | APC | Thermo Fisher Sci. | 17-9500-42 | 5 |
| 640 - 730/45 | CD16 | IgG1, κ | 3G8 | AF700 | Biolegend | 302026 | 1.25 |
| 640 -780/60 | CD19 | IgG1, κ | HIB19 | APC-Cy7 | Biolegend | 302218 | 5 |
| 640 -780/60 | CD14 | IgG2b, κ | MFP9 | APC-Cy7 | BD Biosciences | 333945 | 5 |
| 640 -780/60 | Viability | n/a | n/a | Zombie NIR™ | Biolegend | 423106 | 0.005 |

| NKA Panel | | | | | | | |
|---|---|---|---|---|---|---|---|
| LASER-channel (nm) | Antibody | Isotype | Clone | Fluorochrome | Manufacturer | Catalog no. | µl/test |
| 355 - 450/40 | Viability | n/a | n/a | Blue fluor. | Thermo Fisher Sci. | L34961 | 0.3 |
| 405 - 525/50 | IFNγ | IgG1, κ | B27 | BV510 | BD Biosciences | 563287 | 5 |
| 405 - 610/20 | CD56 | IgG1, κ | HCD56 | BV605 | Biolegend | 318334 | 4 |
| 405 - 710/50 | CD107a | IgG1, κ | H4A3 | BV711 | Biolegend | 328640 | 5 |
| 405 - 780/60 | CD3 | IgG2a, κ | OKT3 | BV785 | Biolegend | 317330 | 3 |
| 405 - 780/60 | CD14 | IgG2a, κ | M5E2 | BV785 | Biolegend | 301840 | 1 |
| 405 - 780/60 | CD19 | IgG1, κ | HIB19 | BV785 | Biolegend | 302240 | 1 |
| 561 - 582/15 | CD57 | IgM, κ | TBO1 | PE | Thermo Fisher Sci. | 12-0577-42 | 2 |
| 561 - 780/60 | CD159c | IgG1 | REA205 | PE-Vio770 | Miltenyi Biotec | 130-120-449 | 1 |
| 640 - 670/14 | CD159a | IgG1, κ | REA110 | APC | Miltenyi Biotec | 130-114-089 | 1 |
| 640 - 730/45 | CCL4 | IgG1, κ | D21-1351 | AF700 | BD Biosciences | 561278 | 2.5 |
| 640 -780/60 | CD16 | IgG1, κ | 3G8 | APC-Cy7 | BD Biosciences | 557758 | 2 |