Interactions of childhood maltreatment and genetic variations in adult depression: A systematic review

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Abstract

Background. Childhood maltreatment (CM) significantly increases the risk of adulthood psychopathology. Interplay between susceptible genetic variations and CM contributes to the occurrence of depression. This review aims to systematically synthesize the relationships between genetic variations and depression among those exposed to CM.

Methods. Electronic databases and grey literature to March 31st, 2020 were searched for literature on the topic of depression and CM limited to English-language. Data extraction and quality assessment of key study characteristics were conducted. Qualitative approaches were used to synthesize the findings.

Results. The initial search resulted in 9,185 articles. A total of 29 articles that met the eligibility criteria were included in this review. High heterogeneity was identified regarding the study sample ages, candidate genes and SNPs, the categorization of CM and depression. The findings of this review include several frequently studied genes (5-HTTLPR, CRHR1, BDNF, CREB1, FKBP5, IL1B, NTRK2, and OXTR). Both consistent and inconsistent findings were identified. Overall, the interplay of CM with CREB1-rs2253206 significantly increased the risk of depression. In contrast, CRHR1-TCA haplotype (rs7209436, rs4792887, rs110402), CRHR1-rs17689882, and CRHR1-rs110402 showed protective effects on depression and depressive symptoms among individuals with a history of maltreatment.

Limitations. Due to clinical and methodological diversity of the studies a qualitative approach was used.

Conclusion. This review firstly provides a comprehensive overview of the interplay between CM and genetic variations in adult depression. Future etiological explorations should focus on the above-identified genes for down-stream exploration and address the issues and challenges of gene by environment studies.

Key words: childhood maltreatment, depression, genetic variation, candidate gene, SNP

1. Introduction

Depression, major depressive disorder, or clinical depression, refers to a state of low mood and aversion to activity and is a common and serious mental disease. More than 300 million people across the world are suffering from depression (WHO, 2018). With core symptoms of persistent sadness and hopelessness and loss of interest in activities once enjoyed, depression could lead to sleeping problems, reduce concentration, and even cause some serious consequences such as self-harm and suicide (WHO, 2018). According to the global burden of disease report 2017, depressive disorders accounted for 35% of disability-adjusted life years caused by mental disorders (Kyu et al., 2018), and new cases increased from 172 million in 1990 to 258 million in 2017 (Liu et al., 2019).

Childhood maltreatment (CM) refers to the abuse and neglect that occurs to children before 18 years of age and is a major ethical, public health, human rights, legal and social problem (Butchart et al., 2006). It consists of several subtypes including sexual abuse, physical abuse, emotional or psychological abuse, and neglect. It is estimated that 1 in 5 women and 1 in 13 men worldwide have been sexually abused during childhood, while 25% of adults report being physically abused (WHO, 2016). CM can cause various kinds of both short-term and long-term negative health consequences, for instance, variations of brain structure, dysfunction of stress-responsive neurobiological systems (Anda et al., 2006) and immediate effects on drugs and alcohol misuse (Gilbert et al., 2009).

Research has consistently confirmed the relationship between CM and later-on mental health problems (Li et al., 2016). Studies have found that physical abuse, sexual abuse, and exposure to intimate partner violence, are associated with several mental illnesses, including depression, bipolar disorder, generalized anxiety disorder, alcohol and drug abuse, suicidal ideation and attempts (Afifi et al., 2014; Cerda et al., 2010; Rehan et al., 2017). In addition, children of abusive families were at higher risk of reporting depressive symptoms than those of non-abusive homes (Toth et al., 1992). Exposure to CM increased the risk of depressive disorders by 2- to 3-fold (Chapman et al., 2004; Li et al., 2016). It is estimated that over one-half of global depression and anxiety cases were potentially attributable to self-reported CM (Li et al., 2016). It has been shown that early life adversities are associated with the atypical development of the hypothalamic-pituitary-adrenal (HPA) axis stress response, which makes victims more susceptible to subsequent psychiatric disorders (Heim et al., 2008; McCrory et al., 2012). Also, early adversities have been reported to associate with both structural and functional brain changes (e.g. prefrontal cortex, hippocampus, etc.), which are critical for emotional and behavioural regulation (McCrory et al., 2012; Tottenham et al., 2010). It has also been reported that many genetic variants may be responsible for subtle alterations in the structure and functioning of neural circuitry and hormonal systems, that are critically involved in the response to affections and in regulating stress response (Caspi et al., 2002).

In recent years, researchers have been focusing on the influences of the interaction of genetic variations and stressful life events to the occurrence of depression (Hosang et al., 2014; Sharpley et al., 2014; Wang et al., 2018). Identification of possible genetic variations offers a promising solution to pinpoint disease mechanisms and new targets for clinical therapy (Gonda et al., 2019). Recent research has also convinced that environmental factors could trigger epigenetic changes at particular gene loci, which contributes to neuronal plasticity and function (Misra et al., 2019; Vialou et al., 2013). With the advancement in high-throughput sequencing approaches, progresses in genetics and genomics, more genome-wide association studies (GWAS) have been conducted (Aberg et al., 2018; Dunn et al., 2015; Rietschel et al., 2010). However, the candidate gene

approach is still being used to explore particular gene loci for its contribution to depression (Samaan et al., 2013; Zhang et al., 2014). Some of the most frequently studied genes have been selected because of their relationships to the regulation of serotonin (5-HT) and dopamine (DA) neurotransmission, which are considered to be a part of the pathophysiology of depression and are targets of antidepressants (Dunlop et al., 2007; Thase, 2009) such as Solute Carrier Family 6 Member 4 (SCL6A4), or due to their involvement in the regulation of stress and the HPA axis (Gonda et al., 2019), such as Corticotropin Releasing Hormone Receptor 1 (CRHR1) and Oxytocin Receptor (OXTR).

Single Nucleotide Polymorphisms (SNPs) are the most common genetic variations being studied (Genetics Home Reference, 2019). In 2003, the first study on the interplay of childhood adversities and candidate genes in depression suggested that early life adversities combined with susceptible genetic variations in 5-HTT could contribute to the occurrence of depression (Caspi et al., 2003). Since then, numerous studies of the interplay between childhood adversities or CM and genetic variations in depression have emerged. However, findings on the interplay haven been inconsistent (Carver et al., 2011; Grabe et al., 2010; Harkness et al., 2015; Ressler et al., 2010; Van der Auwera et al., 2018). Even though several reviews were designed to comprehensively synthesize the relevant findings, they all targeted the interplay of genetic variations and general environmental adversities or early-life stress in depression. (Hosang et al., 2014; Uher and McGuffin, 2008; Wang et al., 2018). Wang et al. (2018) concluded that in FKBP prolyl isomerase 5 (FKBP5) gene, rs1360780 (T allele), rs3800373 (C-allele) or rs9470080 (T-allele) promoted the chances of later depression or post-traumatic stress disorder (PTSD) among individuals with early-life trauma history. Another review focusing on the serotonin transporter (5-HTT) gene's effect proved its significant moderator role in the relationship between environmental adversities and depression. In a review of nine original studies the Met allele of Brain Derived Neurotrophic Factor (BDNF) Val66Met polymorphism did not moderate the association between stress and later depression but showed a trend towards significant influence ($P = 0.051$) (Hosang et al., 2014). Overall, although previous reviews examined different forms of early or general life stress as related to specific genes in depression, we are unaware of any systematic review conducted or published on common genetic variations in the relationship between specific CM and depression.

This systematic review aims to summarize the literature on common genetic variations in the relationship between CM and depression, that would provide possible directions for the exploration of disease mechanisms and antidepressant targets for depression intervention, prevention, and treatment success.

2. Methods

The process and reporting of results from this systematic review were guided by the PRISMA guidelines, 2009 revision (Moher et al., 2009).

2.1 Search strategy

To ensure a thorough and systematic review of the literature, computerized and manual searches were used to retrieve relevant studies. First, six bibliographic databases, including PubMed, EMBASE, HealthStar, PsychInfo, Medline, and Cochrane Library, were comprehensively searched by ML & SL. Appendix 1 provides the detailed searching strategies for each database. The literature searched for articles up to March 31, 2020.

Second, we also manually searched the reference lists of selected articles, review articles on relevant topics, and gray literature.

2.2 Eligibility criteria

All suitable articles were evaluated with regards to their internal validity and the following five selection criteria: 1) used an observational study design (case-control, cohort or cross-sectional); 2) examined the interaction effect of child maltreatment and genetic variation on adult depression; 3) used well-accepted measurements for child maltreatment (e.g. official records, reliable and valid structured interview, or self-administered questionnaire, such as Childhood Trauma Questionnaire (CTQ) and depression (e.g. structured clinical interviews based on the Diagnostic and Statistical Manual of Mental Disorders III/IV, (DSM-III/IV), such as Diagnostic Interview Schedule (DIS), Composite International Diagnostic Interview (CIDI), or questions from published health surveys/screening instruments); 4) explored genetic variations in human bio-specimens; and, 5) provided statistical indicators to examine the impact of the interaction of maltreatment during childhood and genetic variation on adult depression. Articles were excluded if they 1) did not provide the information on child maltreatment, genetic variations, or depression; 2) were not written in English; or 3) did not provide quantitative data on research findings.

2.3 Data extraction and synthesis

Two authors (ML & SL) independently evaluated the relevance of titles, abstracts and full texts. Group discussions with the third author (XM) were used to solve inconsistent records. Figure 1 presents a summary of literature retrieval.

Data on author(s), year of publication, sample size, study designs, measurements of child maltreatment, genetic sites, experimental approaches for genetic arrays, diagnoses of depression, covariates (if any), and major results were extracted independently by reviewers ML and SL. For multiple reports of a single study, they were coded onto a single data extraction form. Any disagreements among reviewers were solved by group discussions with the third author (XM). For those studies with missing information authors of these articles were contacted in order to gather complete and consistent study information.

We assessed the heterogeneity of included studies for the following study characteristics: study populations, measurements of childhood maltreatment, genetic loci, experimental approaches, and diagnoses of depression. High heterogeneity was noted for the above-mentioned characteristics. It precluded the use of meta-analysis in this review. Differences in study characteristics violated the assumption of random-effects models, which assume that all the included studies of a systematic review with meta-analysis are drawn from a normally distributed population (Higgins et al., 2009). Consequently as recommended, we used a qualitative approach to summarize the common genetic variations involved in the relationship between CM and depression.

2.4 Evaluation of study quality

The methodological quality of included studies was evaluated by a quality checklist, derived from the STREGA (‘Strengthening the Reporting of Genetic Association Studies’) and STROBE (‘Strengthening the Reporting of Observational Studies in Epidemiology’) checklists (Little et al., 2009; von Elm et al., 2007), which have been used by other meta-analyses of gene-environment interactions (Hosang et al., 2014; Karg et al., 2011). In accordance with current guidelines and previous reviews of gene-environment interaction

studies (Hosang et al., 2014; Karg et al., 2011), the studies were not weighted by quality scores. Appendix 2 provides detailed information on study quality.

3. Results

A total of 29 articles met our eligibility criteria and were included in this review. There were 20 studies that used clinically applied diagnostic criteria to assess depression and 15 articles used questionnaires/scales to assess depressive symptoms. Some articles had more than one outcome. Given that the measures of clinical depression and depressive symptoms can be clinically different in terms of severity and diagnostic criteria, the literature also suggested that depressive symptoms are risk factors for major depression (Horwath, Johnson, Klerman, Weissman, 1992; Pine, Cohen, Cohen, Brook, 1999), we summarized the findings separately by depression outcomes. Some articles were involved in multiple separate analyses as their data permitted. Table 1 summarizes study characteristics of the selected studies. Appendix 3 provides a list of the references for all the selected articles corresponding to their order in Table 1. Most of these selected articles were published between 2008-2020 (28/29), conducted in European countries (20/29), studied Caucasian or European descent population (20/29), used blood, saliva, or buccal swabs as biological samples (24/29), and applied cross-sectional (13/29) or cohort (11/29) study designs. The reviewed articles involved a wide age range (18 to 81 years), a list of genes (30) and SNPs (177+), and multiple phenotypes of depression, including major depressive disorder, depressive episode, unipolar depressive disorder, recurrent and lifetime depression.

We assessed study quality of these selected articles based on their study designs, sample size, implementation (source of participants, selection of participants, genotyping method and platform), statistical analysis (assessment of ethnicity, methods to control confounding, methods to address multiple comparisons), and reporting and interpretation of results (appropriateness of data report, report of genotype frequencies, and result interpretation) (details are in Appendix 2). Most articles applied appropriate study designs and implementation but failed to address multiple comparison issues or to report descriptive data in accordance with suggested reporting guidelines.

*3.1 Interplay of childhood maltreatment (CM) and genetic variations in **depression***

There were 20 articles conducted to explore the interplay between CM and common genetic variations on depression (Appel et al., 2011; Bradley et al., 2008; Brown et al., 2013; Brown et al., 2014; Caspi et al., 2003; Carver et al., 2011; Cohen-Woods et al., 2017; Fisher et al., 2013; Özçürümez et al., 2019; Gutierrez et al., 2015; Juhasz et al., 2011; Polanczyk et al., 2009; Ressler et al., 2010; Border et al., 2019; Sharpley et al., 2013; Tollenaar et al., 2017; Uher et al., 2011; Van der Auwera et al., 2018; Wang et al., 2015; Yin et al., 2020). 26 genes were studied, including Solute Carrier Family 6 Member 4 (SLC6A4), Corticotropin Releasing Hormone Receptor 1 (CRHR1), BDNF, FKBP5, CAMP Responsive Element Binding Protein 1 (CREB1), Neurotrophic Receptor Tyrosine Kinase 2 (NTRK2), Oxytocin Receptor (OXTR), Interleukin 1 Beta (IL1b), Interleukin 6 (IL6), Interleukin 11 (IL11), C-Reactive Protein (CRP), Tumor Necrosis Factor (TNF), TNF Receptor 1 (TNFR1), TNF Receptor 2 (TNFR2), Gamma-Aminobutyric Acid Type A Receptor Subunit Gamma2 (GABRG2), Catechol-O-Methyltransferase (COMT), HTR2A (5-Hydroxytryptamine Receptor 2A), TPH1 (Tryptophan Hydroxylase 1), Dopamine Receptor D2 (DRD2), Apolipoprotein E (APOE), Methylenetetrahydrofolate Reductase (MTHFR), Clock Circadian Regulator (CLOCK), Angiotensin I Converting Enzyme (ACE), ATP Binding Cassette Subfamily B Member 1(ABCB1), Dopamine Receptor D3 (DRD3), and Dopamine Beta-

Hydroxylase (DBH). Table 2 provides a list of genetic loci studied on these genes. There were 143 SNPs and 2 haplotypes, with some of them frequently studied (by at least two cohorts) and others only being examined once. Among those SNPs that were more frequently investigated, we found that people with A allele carriers of CREB1-rs2253206 and CM experiences were more likely to suffer from depression in adulthood (Juhasz et al., 2011; Wang et al., 2014). No significant association was found between depression and the interaction of CM and NTRK2-rs1187323 or OXTR-rs2254298. Detailed statistics of all the frequently investigated SNPs were summarized in Table 4.

Some inconsistent findings among those frequently investigated SNPs were also found (e.g. 5-HTTLPR, CRHR1-rs110402, BDNF-rs6265, FKBP5-rs1360780, etc.) Both significant and non-significant results were shown in terms of their interplay with CM on depression. Although eight out of ten studies showed that people exposed to CM and with S allele of 5-HTTLPR were significantly associated with adult depression (Brown et al., 2013; Caspi et al., 2003; Carver et al., 2011; Fisher et al., 2013; Özçürümez et al., 2019; Gutierrez et al., 2015; Ressler et al., 2010; Border et al., 2019; Sharpley et al., 2013; Uher et al., 2011), this relationship was not supported by the recent study with a large population-based sample (Border et al., 2019). Similarly, among the six studies analyzing the role of the interplay between CM and BDNF-rs6265 in depression, three of them demonstrated the interplay significantly increased the risk of depression (Carver et al., 2011; Gutierrez et al., 2015; Juhasz et al., 2011), whereas the rest three studies with population-based cohort study designs did not find significance (Brown et al., 2014; Border et al., 2019; Van der Auwera et al., 2018) (see Table 4).

*3.2 Interplay of childhood maltreatment (CM) and genetic variations in **depressive symptoms***

There were 15 studies examining the interplay between CM and common genetic variations in adult depressive symptoms (Aguilera et al., 2009; Appel et al., 2011; Bradley et al., 2008; Caspi et al., 2003; de Castro-Catala et al., 2017; Cattaneo et al., 2018; Grabe et al., 2010; Grabe et al., 2012; Heim et al., 2009; Juhasz et al., 2011; Kovacs et al., 2016; Laucht et al., 2013; Ressler et al., 2010; Border et al., 2019; Wichers et al., 2008), including 21 genes (e.g. SLC6A4, BDNF, CRHR1, FKBP5, CREB1, NTRK2, and IL1B) and over 57 SNPs and 4 haplotypes. There were seven genetic loci studied by two or more studies, including 5-HTTLPR, BDNF-rs6265, CRHR1-TAT haplotype (rs7209436, rs110402, rs242924), CRHR1-TCA haplotype (rs7209436, rs4792887, rs110402), CRHR-rs17689882, CRHR1-rs110402, and CRHR-rs242924, and others only investigated by a single study. Table 3 provides the full list of SNPs included in the analysis of the interplay between CM and common genetic variations in depressive symptoms.

Similarly, both consistent and inconsistent findings were found among those frequently investigated SNPs. Consistent findings were all from CRHR1 gene. For TCA haplotype (rs7209436, rs4792887, rs110402) (Bradley et al., 2008; Ressler et al., 2010), rs17689882 (Grabe et al., 2010; Laucht et al., 2013), and rs110402 (Bradley et al., 2008; Grabe et al., 2010; Heim et al., 2009; Ressler et al., 2010), the reviewed studies identified the protective effect of their interaction with CM on depressive symptoms. See table 4 for detailed statistics for each study.

Inconsistent and controversial findings were found from studies testing the interplay between CRHR1-TAT haplotype (rs7209436, rs110402, rs242924), CRHR1-rs242924, 5-HTTLPR, and BDNF-rs6265 and CM in depressive symptoms. For instance, three studies examined the association between the interplay of CRHR1-TAT haplotype (rs7209436, rs110402, rs242924) and CM and depressive symptoms. Two of them found that the interplay was linked to an increased risk of depressive symptoms (Grabe et al., 2010; Laucht et al.,

2013), whereas the other study found a reverse relationship (Bradley et al., 2008). Two studies tested the interplay between CRHR1-rs242924 and CM in depressive symptoms, with one having a protective effect of the interplay on depressive symptoms (Grabe et al., 2010), and another having a non-significant result (Bradley et al.). For 5-HTTLPR, two out of five studies identified that the S allele carriers exposed to early life maltreatment significantly linked with increased depressive symptoms (Aguilera et al., 2009; Grabe et al., 2012; Ressler et al., 2010), whereas three other studies failed to detect such relationship (Border et al., 2019; Wichers et al., 2008; Ressler et al., 2010). Among the five studies on the interplay of BDNF-rs6265 and CM, three studies found that the interplay was positively related to depressive symptoms (Aguilera et al., 2009; Grabe et al., 2012; Wichers et al., 2008), and two others reported non-significant results (Juhasz et al., 2011; Border et al., 2019).

4. Discussion

This systematic review provides the first overview of common genetic variations studied in the relationship between CM and depression. Even though the interplay of gene and environment in depression has been proposed over two decades, the replication of these findings is the issue to be solved. This review included a total of 29 articles of moderate to good quality. In general, the selected studies focused on the neurobiological function of the targeted genes and those genes were relevant to the stress-induced hypotheses of depression (Vialou et al., 2013). So far, most of the study findings had not been frequently replicated and some findings were based on one-time only testing.

4.1 Study findings

The studies reviewed reported many gene loci interacted with CM in clinically depression and depressive symptoms. This is consistent with the findings reported by recent large GWAS findings (Dalvie et al., 2020), although in which the small correlations were found could be attributable to potential confounders, such as parental abusive experience in their childhoods.

For the studies of clinically depression, findings on CREB1-rs2253206, NTRK2-rs1187323, OXTR-rs2254298, IL-6-rs1818879 and CRP-rs3093077 were consistently reported in this review, whereas there were inconsistent findings for 5-HTTLPR, CRHR1-rs110402, BDNF-rs6265, and FKBP5-rs1360780.

In depressive symptom studies, the interplay of CRHR1 and CM protected against depressive symptoms for those carriers with the TCA haplotype (rs7209436, rs4792887, rs110402), rs17689882, rs7209436, and rs110402. Similar to the findings in the depression group, the interplay effects of 5-HTTLPR, CRHR1-TAT haplotype (rs7209436, rs110402, rs242924), BDNF-rs6265, and CRHR1-rs242924 were not consistent.

We also found that A allele carriers of CREB1-rs2253206 with exposure to CM had a significantly higher risk for depression. CREB1 encodes a transcription factor that is a kind of DNA binding protein and is an important mediator of the biological responses to electroconvulsive seizure (Gene, 2019a). Literature has also stated that some genetic polymorphisms in CREB1, including rs2253206, could be associated to depression-related issues and other mental health problems, such as treatment resistance (Serretti et al., 2011) and response to antidepressant drugs (Blendy, 2006; Lim et al., 2013) in major depression, prospective memory (Avgan et al., 2017), and bipolar disorder (Xiao et al., 2018).

A protective effect of interaction between CM and CRHR1 haplotypes and SNPs on depressive symptoms was noted in this review, including TCA haplotype, rs17689882, and rs110402. These findings are consistent with previous experimental studies (McGaugh,

2004). It has been hypothesized that emotional memories in childhood may be influenced by CRHR1, which may precipitate depression (Polanczyk et al., 2009). CRHR1 is essential for the activation of signal transduction pathways that regulate diverse physiological processes including stress, reproduction, immune response and obesity (Gene, 2019b). Experimental evidence has shown the importance of CRHR1 in the impairment of emotional memory consolidation after stressful events (Hubbard et al., 2007; Roozendaal et al., 2002), which may be crucial in the developmental aetiology of depression.

Some previous studies on CM and gene loci did not find any significant findings, for instance, 5-HTTLPR, NTRK2-rs1187323 and OXTR-rs2254298. These genes have an important function in modulating various behaviors, including stress, anxiety, social memory, recognition, sexual and aggressive behaviors (Gene, 2019c; Gene, 2019d). The explanation of these frequently studied but non-significant genes could be the fact that these gene loci may not directly contribute to the relationship between CM and depression, but rather may be the target for epigenetic modifications, such as DNA methylation, histone modifications, and small RNA, which will then change chromatin structure and gene expression (Misra et al., 2019).

4.2 Challenges and mitigation strategies for inconsistent findings

The major challenge for genetic association studies, especially for common genetic variations, is replication (Ioannidis et al., 2001). There are a number of factors, such as characteristics of study populations, gene loci, experimental quality, and statistical analysis potentially attributable to the inconsistent results.

First, the age range of subjects in the studies reviewed is wide (from 18 to 81 years). Like many other illnesses, the incidence and aetiology of depression vary by age and sex/gender (Carli et al., 2011; Murphy et al., 2000). The measurement of depression and depressive symptoms can not accurately classify people with extreme age ranges, some measures were specially designed for younger age groups (Johnson et al., 2002), whereas others for older adults (Kroenke et al., 2001). The quality of these measurements inevitably influenced the homogeneity of the phenotype, which has an impact on results replications. In addition, depression is a wide spectrum disorder. Individuals in different age groups are at various levels of risk for having a depression (Schaakxs et al., 2017). The wide age range could also dilute the distinction and strength of the association as the stressful life events have stronger effects on the first onset of depression than on recurrences (Kendler et al., 2000).

Second, people may have different sensitivity when exposed to early life maltreatment at a different time of life or as a result of life experiences (Heim et al., 2012). Throughout brain development, there are periods of increased plasticity. During these periods, the brain may be particularly sensitive to experiences that may have profound effects both positively and negatively – beneficial effects of enriching experiences and destructive effects of adverse experiences (Andersen et al., 2008; Weiss et al., 1989). Both prospective (Thornberry et al., 2010; Keiley et al., 2001) and retrospective studies (Dunn et al., 2013; Dunn et al., 2017) have supported the theory of sensitive periods for CM exposure and suggested that maltreatment occurring before age 5 is linked to a greater risk of depression, while other studies expanded the sensitive period to the age of 12 (Maercker et al., 2004; Schoedl et al., 2010). In addition, puberty and increased sex steroid levels could also critically affect the neural plasticity and endocrine stress responses (Blakemore et al., 2010; Paus et al., 2008; Romeo and McEwen, 2006). Current gene by environment studies did not take into account the timing of maltreated experiences. This could be a crucial source of hidden heterogeneity and inconsistent findings.

Third, three-way interactions (gene-gene-environment) could also be involved in depression (Heim et al., 2012), for instance, 5-HTTLPR*BDNF*environment (Uher and McGuffin, 2008). Interaction among BDNF and 5-HTT on brain monoamine levels, stress response and anxiety-like behavior have been identified in animal models (Ren-Patterson et al., 2005). In humans, it has been reported that the three-way interaction of environmental adversity, 5-HTTLPR, and BDNF val66met polymorphism contributed more than two-way interaction in depression (Kaufman et al., 2006; Kim et al., 2007). Therefore, research findings may be not consistent when certain gene loci were not included in the study.

Fourth, the distribution of gene loci and environmental factors in the study sample can impact on research findings. For example, for those studies that used a population with a high trauma rate, the main effect of the studied gene will be more likely to be identified than a gene-environment interaction. In contrast, if the environmental exposure is rare, no main effect of gene or gene-environment will be identified (Uher and McGuffin, 2008). Investigations of epigenetic modifications in the gene by environment may help to disentangle the role of genes in the relationship between CM and depression (Vialou et al., 2013). In addition, it is critical to have a valid and reliable measure of environmental risk factor and make sure it is within a reasonable distribution range in a particular population sample, by which gene-environment interaction is to be tested (Uher and McGuffin, 2008).

Fifth, inconsistent and controversial findings on the same gene locus may also result from the different vulnerability to adverse exposure due to the mechanism of resilience (Meng et al., 2018). Several studies have shown that carriers with the same genotypes reported different levels of vulnerability to CM, because positive environmental factors, such as social support could buffer the negative consequences of CM (Kaufman et al., 2006; Kaufman et al., 2007). It suggests that genetic polymorphisms are sensitive to both positive and negative aspects of the environment. It remains unclear whether this sensitivity extends to adolescence and adulthood and what the underlying neural and psychological mechanisms are (Uher and McGuffin, 2008).

Last, but not the least, focusing on a single phenotype may lead to a decrease in the power to detect general aetiological pathways. Psychological disorders rest on a spectrum. One particular aetiological pathway is attributable to a number of psychopathologies (Kendler et al., 2000). Previous studies have suggested to simultaneously exploring multiple phenotypes, including depression, substance use, risk-taking and self-destructive behaviors, which may help to resolve inconsistencies and broaden our current understanding of gene-environment interactions on mental health (Uher and McGuffin, 2008).

A recent study used data from large population-based and case-control samples with a total of over 620,000 individuals to test candidate gene and candidate gene by environment interaction in depression. In contrast to early hypotheses and previous findings, they suggested that no clear evidence to support historical candidate gene or gene-by-environment interaction associated with depression phenotypes (Border et al., 2019). Before making a decision on whether or not to accept in the above statement, there are several issues to consider. First, there are several well-established confounders, such as population stratification, age, sex and gender, depression phenotypes, the accuracy of measurements of maltreatment and depression, not fully controlled or adjusted in the analysis. Research findings are prone to the bias and confounding introduced by these factors. Second, the process from robust genetic discoveries to a better understanding of depression's aetiological mechanisms is a standing discussion (Sestan and State, 2018). Third, there are very few, if not absent, identified genetic risk factors for depression in low-income countries and in non-European ancestries (McIntosh et al., 2019). The statement of "no historical candidate gene for depression" needs to be revisited when the above issues are solved.

4.3 Strengthens and limitations

This review provides an overview of common genetic variations in the relationship between CM and depression. The systematic search allowed us to include comprehensive and high-quality studies on this topic. Despite high heterogeneity, we found frequently studied candidate gene loci and articulated the potential explanations for consistent and inconsistent findings, which could direct future research in the field of neurobiological exploration and pharmacological investigation.

However, several limitations should be noted. First, this review was designed to provide an overview of the relationship between the interplay of common genetic variations and CM in depression. It included studies with a wide range of genetic loci. Because several key study characteristics were heterogeneous, we used qualitative approaches to pool the research results. Second, the accuracy of CM needs to be considered in the interpretation of results. Self-report and retrospective measurements of CM could be influenced by the depressed state (Hardt & Rutter, 2004) and can be experimentally manipulated by mood induction (Cohen et al., 1988). Third, potential publication bias may be an issue and may affect the quality of the studies. Studies with small sample-size cohorts (a total number of study subjects in a study is relatively small when considering a total number of genetic variations tested) are more likely to identify positive results, whereas studies with large sample-size cohorts tend to have negative results, which are more likely to be rejected by re-selection of publications. Fourth, it is not easy to have a large sample sizes (for example, over 1000 subjects) in genetic studies, except in the meta-analyses of multiple cohorts. This limits the power of individual studies. Another methodological concern is that functional-based and/or hypothesis-driven candidate gene approaches have not been seen as successful (Border et al., 2019) due to its limited statistical power and inconsistent findings. Finally, only English databases were searched, which may limit the comprehensiveness of eligible studies.

5. Conclusion

This review firstly provides a comprehensive overview of common genetic variations examined in the relationship between CM and depression. 5-HTTLPR and CREB1-rs2253206, interacted with CM to increase the risk of depression, whereas haplotypes and SNPs of CRHR1 may reduce the risk of depression and depressive symptoms for those people with the history of CM. These findings underscore the importance of genetic factors in clinical interventions for depression. For those who were exposed to CM, it is critical to have genomic testing conducted to assess their genetic susceptibility for depression. Those individuals carrying susceptible genotypes, which are reported to have significantly statistical interplay with CM, should be closely followed by health professionals. This is meaningful not only from selective prevention perspectives but also for personalized medical treatments since the response to specific antidepressant treatments can be affected by genetic variations (Serretti et al., 1998).

Future research could target these identified gene loci for an in-depth exploration of their roles in depression by using a large random representative sample, prospective cohort study design, examining the roles of epigenetic modifications, gene expressions, and gene networks, and adoption of objective records of maltreated experiences and standardized measures of depression. Additionally, GWAS approach, which is a null-hypothesis driven approach and allows a systematic way to analyze millions of variants across the entire genome, should be used in the future studies. In order to facilitate cross comparisons between genetic association studies, an agreement upon a list of standard items is timely needed for reporting and synthesizing for genetic association studies, similar to those for the reporting of

clinical trials, systematic reviews and meta-analysis (Moher et al., 2009; Schulz et al., 2010). The standardized guideline would significantly advance the field by providing a firm base of a synchronized procedure of knowledge generation in the field of genetic association studies. A global initiative of registration for genetic association studies should also be developed to facilitate data sharing and analyzing.

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Authors' contributions

SL conducted the search, together with ML reviewed the articles returned by the search for eligibility. SL, ML and TG conducted the data extraction. ML analyzed the data and prepared the draft of this manuscript with the assistant of SL. XM and CD designed this review. XM oversaw the project, provided feedback on all steps of the search, data extraction and interpretation. All authors contributed to the editing of the manuscript and all of them approved the final version.

Conflict of Interest

The authors declare no conflict of interest.

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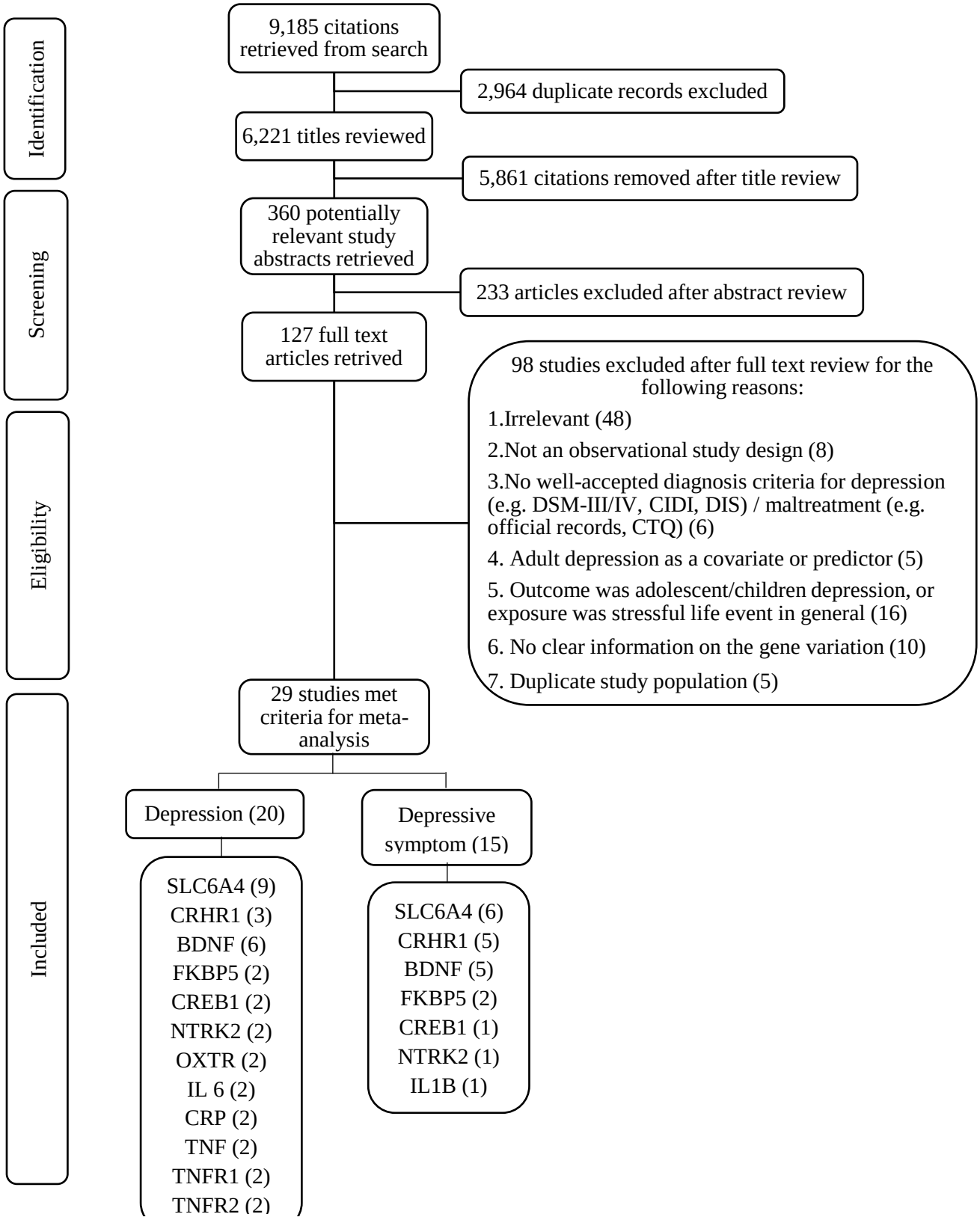
Figure 1 PRISMA flow diagram



Note: SLC6A4, Solute Carrier Family 6 Member 4; CRHR1, Corticotropin Releasing Hormone Receptor 1; BDNF, Brain Derived Neurotrophic Factor; FKBP5, FKBP prolyl isomerase 5; CREB1, CAMP Responsive Element Binding Protein 1; NTRK2, Neurotrophic Receptor Tyrosine Kinase 2; OXTR, Oxytocin Receptor; IL-6, Interleukin 6; CRP, C-Reactive Protein; TNF, Tumor Necrosis Factor; TNFR1, Tumor Necrosis Factor Receptor 1; TNFR2, Tumor Necrosis Factor Receptor 2; IL 6, Interleukin 6; DSM-III/IV, Diagnostic and Statistical Manual of Mental Disorders; DIS, Diagnostic Interview Schedule; CIDI, Composite International Diagnostic Interview.

Table 1
Summary of study characteristics.

First author	Year	Country	Age (range, mean)	Sample Size	Ethnic	Sample resource/ cohort	Study design	Measurement of child maltreatment	Diagnosis of adult depression/ depressive symptom	Biological Sample	Candidate gene	SNP ID	Genotype method	Direction of the solo effects of childhood abuse to depression*	Direction of the solo effect of genetic variation to depression*	Direction of G × E effects of depression*
Aguilera	2009	Spain	18-50, 22.9	534 healthy individuals; 5-HTT 475; BDNF 470	Spanish (Caucasian)	77% university students	cross-sectional	CTQ	SCL-90-R	saliva	5-HTTLPR; BDNF	BDNF, rs6265; 5-HTTLPR	Biosystems TaqMan technology	↑	not mentioned	5-HTTLPR ↑; rs6265 ↑
Laucht	2012	Germany	depression was measured at 23 years old	300	European descent	Hospital-based	cohort	CTQ	BDI & BDI-II	blood or saliva	CRHR1	TAT haplotype (rs7209436, rs110402, rs242924); rs17689882	TaqMans procedure	not mentioned	not mentioned	TAT haplotype ↑; rs17689882 ↓
Carver	2011	USA	18.71 (mean)	133	Mixed	Undergraduates at the University of Miami	cross-sectional	Risky Families	SCID	blood	5-HTTLPR; BDNF	5-HTTLPR; BDNF, rs6265	Biosystems TaqMan technology	not mentioned	not mentioned	5-HTTLPR ↑; rs6265 ↑
Wang	2014	China	case: 44.16; control: 42.93	1,172	Chinese Han	Hospital-based	case-control	CTQ	DSM-IV	blood	CREB1	rs6740584, rs2551941, rs2253206, rs11904814	TaqMan allelic discrimination assays	not mentioned	n.s.	↑ for all SNPs
Sharpley	2013	Australia	mean 32.53	120	not mentioned	general population	cross-sectional	ACE	ZSDS	mouthwash sample	5-HTTLPR	5-HTTLPR	not mentioned	↑	n.s.	↑
Auwera	2017	Germany & Netherland,	not mentioned	maximum 3944	European ancestry	NESDA; Radiant-UK; SHIP-0; SHIP-TREND-0	cohort	CTQ	direct interviews or DSM-IV	not mentioned	26 genes (e.g. BDNF, CRHR1, FKBP5, OXTR, NTRK2)	268 SNPs (e.g. rs6265, rs110402, rs2254298, rs1360780, rs4713916, rs1187323)	Following cohorts' local protocols	not mentioned	not mentioned	n.s.

Castro-Catala	2017 Spain	17–54, 20.79	808	European origin	university students	cross-sectional	CTQ	SCL-90-R	mucosa	FKBP5	haplotypic block 1 (rs3800373, rs9296158, rs1360780); block 2 (rs9470080, rs4713916)	TaqMan 5′ exonuclease assay (Applied Biosystems)	↑	n.s.	Haplotypic block 1 n.s.; block 2 ↑ (physical abuse with non-TA carriers)
Fisher	2013 UK	case: 20-82, 45.5; control: 25-62, 47.2	455	Caucasian/white European origin	Cardiff and London sites of the Depression Case–Control (DeCC) multi-centre study	case-control	CTQ	SCAN & BDI-II	blood or cheek swabs	5-HTTLPR	5-HTTLPR	PCR	↑	n.s.	↑ (sexual abuse and SS)
Ressler	2009 America	18-65+	1,392	African-American	urban population of low socioeconomic status	cross-sectional	CTQ	BDI & SCID	saliva	5-HTTLPR; CRHR1	5-HTTLPR; CRHR1−TCA haplotype (rs7209436, rs4792887, rs110402) & rs110402	CRHR1, TaqMan allelic discrimination assay; 5-HTTLPR, PCR	↑	not mentioned	5-HTTLPR ↑ for depression diagnosis; CRHR1 ↓ for both TCA haplotype and rs110402
Tollenaar	2017 Netherland	18-65, 42.2	2567	North-European descent	NESDA cohort	cohort	Semi-structured childhood trauma interview and CTQ	CIDI	blood	OXTR	rs2254298, rs53576, rs2268498	not mentioned	↑ for all	n.s. for all	n.s. for all
Juhasz	2011 UK	level 1: 18-60, 34.04; level 2: 18-60, 33.56	level 1, 1269; level 2, 264	Caucasian origin	general practices and a website	cross sectional	Level 1, CHA; level 2, CTQ	level 1, lifetime - BGR, symptom - BSI; level 2, lifetime - SCID, symptom - MADRS	Buccal mucosa cells	BDNF, CREB1, NTRK2	BDNF, rs12273363, rs962369, rs988748, rs7127507, rs6265, rs1519480; CREB1, rs2253206; NTRK2, rs1187323, rs1187326	Sequenom MassARRAY technology	not mentioned	n.s.	rs6265 ↑ (MDD); rs988748 ↑; rs12273363 ↓; rs962369 ↓; rs7127507 ↓; rs1519480 ↓; rs2253206 ↑; rs1187326 ↓ (MDD & symptom); n.s. for the rest SNPs

Heim	2009	America	study1, male mean 44.4; female mean 37.8	78	Not mentioned	Atlanta metropolitan area	cross-sectional	CTQ	BDI	saliva	CRHR1	rs110402	Not mentioned	↑	n.s.	↓ (physical abuse)
Appel	2011	German	20–79	2157	Caucasian	SHIP-LEGEND (German general population)	cross-sectional	CTQ	BDI-II & M-CIDI	not mentioned	FKBP5	rs1360780	SHIP group, Affymetrix Human SNP Array 6.0 platform	↑	n.s.	↑ (physical abuse with TT genotype)
Grabe	2010	German	20–79	1,638	Caucasian	SHIP-LEGEND (German general population)	cross-sectional	CTQ	BDI-II	leukocytes	CRHR1	TAT haplotype (rs7209436, rs110402, rs242924) and other 28 SNPs	Affymetrix Genome-Wide Human SNP Array 6.0 platform	not mentioned	n.s. for all	TAT haplotype ↑ (physical neglect); rs17689882 ↓; rs7209436 ↓; rs110402 ↓; rs242924 ↓
Polanczyk	2009	England	Female 26-55, 33	1116	90% White	Mothers of the children in the E-Risk Longitudinal Twin Study	cohort	CTQ	DIS	Buccal swabs	CRHR1	TAT haplotype (rs7209436, rs110402, rs242924)	Applied Biosystems 7900HT TaqMan genotyping platform (Applied Biosystems) in Allelic Discrimination mode	↑	n.s.	↑ (past-year MDD)
Uher	2011	England	Female 26-55, 33	930	Caucasians	Mothers of the children in the E-Risk Longitudinal Twin Study	cohort	CTQ	DIS	Buccal swabs	5-HTTLPR	5-HTTLPR	Not mentioned	↑	not mentioned	↑
Caspi	2003	UK	not mentioned	847	Caucasian	Birth cohort	cohort	behavioral observations, parental reports, and retrospective reports by the study members	DIS	blood & buccal swabs	5-HTTLPR	5-HTTLPR	PCR	↑	n.s.	↑

Brown	2013	UK	19–51, 37	273; a subset of 220 women was followed	not mentioned	From 4 cohorts in London, UK	cohort	CECA	SCAN	saliva	5-HTTLPR	5-HTTLPR	not mentioned	↑	not mentioned	↑
Grabe	2012	German	20-79	2035	Caucasian	SHIP-LEGEND (German general population)	cross-sectional	CTQ	BDI-II	not mentioned	BDNF; 5-HTTLPR	BDNF, rs6265; 5-HTTLPR (rs25531)	PCR	not mentioned	not mentioned	5-HTTLPR ↑ (biallelic); rs6265 ↑
Wichers	2008	Belgium	18-46	BDNF 464; 5-HTTLPR 394	White and Belgian origin	General population twin study	cohort	CTQ	SCL-90, and SCID	Placental tissue, blood, or buccal cell	BDNF, 5-HTTLPR	5-HTTLPR, rs25531; BDNF, rs6265	BDNF, TaqMan allelic discrimination assay	not mentioned	n.s. for all	5-HTTLPR n.s.; rs6265 ↑
Brown	2014	UK	19-51, 37	258 for 12-month depression; 233 for chronic depression	not mentioned	general population	cohort	CECA	SCAN	saliva	BDNF	rs6265	TaqMan allelic discrimination assay	n.s. for 12-month depression; ↑ for chronic depression	n.s.	n.s.
Gutierrez	2015	Spain	mean 50.33	2679	Spanish	population sample throughout Spanish provinces	cohort	CTQ	CIDI	blood and/ or saliva	5-HTTLPR; BDNF	5-HTTLPR, rs25531; BDNF, rs6265	BDNF, TaqMan allelic discrimination assay	↑	n.s. for both SNPs	↑ for both SNPs
Bradley	2008	USA	18-81, 38.4; supportive sample, 31.9	maximum 422; supportive sample, 199	97.4% African American; supportive sample, 87.7% Caucasian or White	Public urban hospital and Emory University; supportive sample, mental health centre at Emory University	cross-sectional	CTQ	BDI; SCI for supportive sample	saliva	CRHR1	rs7209436, rs110402, rs242924, rs242940, rs173365, rs4792887, rs242948, rs4076452, rs12942300, rs242950, haplotype TCA & TAT	TaqMan allelic discrimination assay	↑	not mentioned	↓ for TAT & TCA haplotype, rs110402, rs7209436, rs242940 in both depression and symptom; ↓ for rs4792887, rs242924 in depression only; n.s. for the rest SNPs
Kovacs	2016	Hungary	18-60, 31.21	907 for rs16944; 832 for rs1143643	European White	advertisement	cross-sectional	CHA derived from CTQ	BSI with 4 additional items	Buccal mucosa cells	IL1B	rs16944, rs1143643	Sequenom MassARRAY technology	not mentioned	n.s. for both SNPs	rs16944 ↑; rs1143643 n.s.

Cohen-Woods	2017	Australia	Discovery: 32.4-57.1, 46.2; Replication: 23-52,1, 37.08	Discovery: 550; Replication: 593	European White	Radiant MDD cohort for discovery and the Münster Depression cohort for replication	Cross-sectional	CTQ	DSM-IV and interview	Discovery: saliva; Replication: blood	IL1b, IL-6, IL11, CRP, TNF, TNFR1, TNFR2	120 SNPs tested, 7 of which were replicated: rs1818879, rs3093077, rs1041981, rs4149576, rs616645, rs17882988, rs1061622	Discovery: Illumina HumanHap610-Quad BeadChips; Replication: Sequenom MassARRAY_ iPLEX Gold assay	↑	Not mentioned	↑ for IL-6-rs1818879 and CRP-rs3093077 (meta-analysis of discovery and replication findings)
Yin	2020	China	18–65	362	Han Chinese	Hospital cases and advertisement for health control	Case-control	CTQ	CB-SCID-I/P	blood	GABRG2	rs211034	Sanger sequencing	↑ in emotional neglect	Not mentioned	↓ in emotional neglect
Özçürümez	2019	Turkey	MDD cases: (29.3 ,46.22) 37.67; Healthy controls: (30.4, 49.18) 39.79	MDD cases: 70; Health controls: 67	Caucasian	Clinical cases & matched controls	Case-control	CTQ	CIDI and BDI	blood	5-HTTLPR	5-HTTLPR	PCR	↑	n.s	n.s
Richard Border	2019	UK	Not mentioned	157,146	European ancestry	UK BioBank	Cohort	Not mentioned	DSM-5	blood	13 Genes (e.g. SLC6A4, BDNF, COMT, etc.)	13 SNPs (e.g. 5-HTTLPR, BDNF-rs6265, COMT-rs4680, etc.)	Affymetrix UK Biobank Axiom array or the Affymetrix UK BiLEVE Axiom array	↑ for both MDD diagnosis and depressive symptoms	MDD diagnosis: ↓ in HTR2A-rs6311 and DRD2-rs1800497; depressive symptoms: n.s.	n.s. for MDD diagnosis; depression symptoms: ↑ for TPH1-rs1800532, ↓ for DRD3-rs6280, n.s. for the rest SNPs
Cattaneo	2018	USA	40.1, 13.9	4791	Not mentioned	Grandy Trauma Project	Cross-sectional	CTQ	BDI	Saliva & blood	FoxO1, A2M, TGF-β1	All the SNPs within these 3 genes	Human Gene 2.1st Array Strips on GeneAtlas platform (Affy metrix), following the WT Expression Kit protocol	Not mentioned	Not mentioned	Significant GxE interactions: FoxO1, 6 SNPs with sexual abuse, 40 SNPs with physical abuse, 40 SNPS with emotional abuse; A2M, 7 SNPs with emotional abuse; TGF-β1, 4 SNPs with sexual abuse, 1 SNP with emotional abuse

Notes: *↑, increased risk; ↓, decreased risk; n.s., not significant
CTQ, Childhood Trauma Questionnaire; CECA, Childhood Experience of Care and Abuse interview; ACE, Adverse Childhood Events questionnaire; CHA, Childhood Adversity questionnaire; BGR, Background Quesionnaire; SCL-90-R, Symptom Check List 90 Revised; BDI, Beck Depression Inventory; SCID, Structured Clinical Interview for DSM-IV; DSM-IV, Diagnostic and Statistical Manual of Disorders Fourth Edition; CIDI, Composite Interview Diagnostic Instrument; BSI, Brief Symptom Inventory; MADRS, Montgomery Asberg Depression Rating Scale; M-CIDI, Munich-Composite International Diagnostic Interview; DIS, Diagnostic Interview Schedule; SCAN, Schedule for Clinical Assessment in Neuropsychiatry; ZSDS, Zung Self-Rating Depression Scale

Table 2
Genes and SNPs included in the interplay of childhood maltreatment and genetic variation in *depression group*.

Gene	Frequently investigated SNP (number of studies/cohorts)	Less frequently investigated SNP
SLC6A4	5-HTTLPR (10)	None
CRHR1	rs110402 (3)	TAT haplotype (rs7209436, rs110402, rs242924); TCA (rs7209436, rs4792887, rs110402); rs7209436; rs4792887; rs242924; rs242940
BDNF	rs6265 (6)	rs12273363; rs962369; rs988748; rs7127507; rs1519480
FKBP5	rs1360780 (2)	rs3800373; rs4713916
CREB1	rs2253206 (2)	rs6740584; rs2551941; rs11904814
NTRK2	rs1187323 (2)	rs1187326
OXTR	rs2254298 (2)	rs53576; rs2268498
IL1B	None	rs3917365, rs2853550, rs1143642, rs1143637, rs1143634, rs1143630, rs1143629, rs1143627, rs16944, rs1143625, rs1143623, rs4848306, rs12621220
IL-6	rs1818879 (2)	rs7801617, rs4719714, rs2056576, rs2056577, rs12700386, rs2069824, rs1800797, rs1800795, rs2069832, rs2069833, rs2069837, rs1474347, rs2069840, rs1554606, rs2069845, rs35610689, rs10242595, rs7787893, 7-22774590, rs34880821, rs35436671, rs11766273
IL11	None	rs897799, rs2124920, rs11673515, rs4252568, rs4252565, rs1126757, rs4252546, rs12980914, rs6509940
CRP	rs3093077 (2)	rs2794520, rs3093077, rs3093075, rs2808630, rs3093068, rs1205, rs1130864, rs1417938, rs2794521, rs3093059, rs3116636, rs3116635, rs2369251, rs2808632, rs2794522, rs12084589, rs2808633, rs3122012
TNF	rs1041981 (2)	rs2844482, rs2071590, rs180068, rs2239704, rs909253, rs746868, rs2229094, rs1799964, rs1800630, rs1799724, rs361525, rs1800610, rs3093662, rs3093664, rs769178, rs3093553
TNFR1	rs4149576 (2)	rs12426675, rs1800693, rs1860545, rs4149581, rs4149580, rs4149570
TNFR2	rs17882988 (2); rs1061622 (2)	rs496888, rs3766730, rs616645, rs6697733, rs587406, rs17879121, rs17037696, rs542282, rs512996, rs505844, rs478143, rs500734, rs945439, rs945438, rs1815530, rs1201157, rs5746009, rs525891, rs548580, rs683240, rs683171, rs550523, rs5746014, rs653667, rs1768642, rs7522295, rs235249, rs235219, rs1061631, rs235214

GABRG2	None	rs211034
COMT	None	rs4680
HTR2A	None	rs6311
TPH1	None	rs1800532
DRD2	None	rs1800497
APOE	None	rs429358/rs7412
MTHFR	None	rs1801133
CLOCK	None	rs1801260
ACE	None	in/del
ABCB1	None	rs1045642
DRD3	None	rs6280
DBH	None	rs1611115

Note: SLC6A4, Solute Carrier Family 6 Member 4; 5-HTTLPR, serotonin-transporter-linked polymorphic region; CRHR1, Corticotropin Releasing Hormone Receptor 1; BDNF, Brain Derived Neurotrophic Factor; FKBP5, FKBP Prolyl Isomerase 5; CREB1, CAMP Responsive Element Binding Protein 1; NTRK2, Neurotrophic Receptor Tyrosine Kinase 2; IL1B, Interleukin 1 Beta; IL 6, Interleukin 6; IL 11, Interleukin 11; CRP, C-Reactive Protein; TNF, Tumor Necrosis Factor; TNFR1, TNF Receptor 1; TNFR2, TNF Receptor 2; GABRG2, Gamma-Aminobutyric Acid Type A Receptor Subunit Gamma2; COMT, Catechol-O-Methyltransferase; HTR2A, 5-Hydroxytryptamine Receptor 2A; TPH1, Tryptophan Hydroxylase 1; DRD2, Dopamine Receptor D2; APOE, Apolipoprotein E; MTHFR, Methylenetetrahydrofolate Reductase; CLOCK, Clock Circadian Regulator; ACE, Angiotensin I Converting Enzyme; ABCB1, ATP Binding Cassette Subfamily B Member 1; DRD3, Dopamine Receptor D3; DBH, Dopamine Beta-Hydroxylase.

Table 3
Genes and SNPs included in the interplay effect of childhood maltreatment and genetic variation in *depressive symptom group*.

Gene	Frequently investigated SNP (number of studies/cohorts)	Less frequently investigated SNP
SLC6A4	5-HTTLPR (5)	None
BDNF	rs6265 (5)	rs12273363, rs962369, rs988748, rs7127507, rs1519480
CRHR1	TAT haplotype (rs7209436, rs110402, rs242924) (3); TCA haplotype (rs7209436, rs4792887, rs110402) (2); rs17689882 (2); rs110402 (4); rs242924 (2)	rs12942300; rs242950; rs171440; rs17762769; rs17689471; rs173365; rs242948; rs4076452; rs16969853; rs16940646; rs4792888; rs8072451; rs81189; rs4277389; rs4566211; rs17689653; rs242936; rs1912151; rs1396862; rs17689824; rs17763086; rs16940677; rs1876829; rs17763104; rs1876831; rs16940665; rs17689918; rs16940674; rs7209436; rs4792887
FKBP5	None	rs1360780; haplotypic block (rs3800373, rs9296158, rs1360780); haplotypic block (rs4713916, rs9470080)
CREB1	None	rs2253206
NTRK2	None	rs1187323, rs1187326
IL1B	None	rs16944, rs1143643
COMT	None	rs4680
HTR2A	None	rs6311
TPH1	None	rs1800532
DRD2	None	rs1800497
APOE	None	rs429358/rs7412
MTHFR	None	rs1801133
CLOCK	None	rs1801260
ACE	None	in/del
ABCB1	None	rs1045642
DRD3	None	rs6280
DBH	None	rs1611115
FOXO1	None	All SNPs
A2M	None	All SNPs
TGF-β1	None	All SNPs

Note: SLC6A4, Solute Carrier Family 6 Member 4; 5-HTTLPR, serotonin-transporter-linked polymorphic region; CRHR1, Corticotropin Releasing Hormone Receptor 1; BDNF, Brain Derived Neurotrophic Factor; FKBP5, FKBP Prolyl Isomerase 5; CREB1, CAMP Responsive Element Binding Protein 1; NTRK2, Neurotrophic Receptor Tyrosine Kinase 2; IL1B, Interleukin 1 Beta; COMT, Catechol-O-Methyltransferase; HTR2A, 5-Hydroxytryptamine Receptor 2A; TPH1, Tryptophan Hydroxylase 1; DRD2, Dopamine Receptor D2; APOE, Apolipoprotein E; MTHFR, Methylenetetrahydrofolate Reductase; CLOCK, Clock Circadian Regulator; ACE, Angiotensin I Converting Enzyme; ABCB1, ATP Binding Cassette Subfamily B Member 1; DRD3, Dopamine Receptor D3; DBH, Dopamine Beta-Hydroxylase; FOXO1, Forkhead Box O1; A2M, Alpha-2-Macroglobulin; TGF- β1, Transforming Growth Factor Beta 1.

Table 4 Statistics of frequently investigated SNPs in the interplay effect of childhood maltreatment and genetic variation in depression and depressive symptoms

Gene	SNP	First author, year	Findings on G×E effect* (effect size, 95% CI/p-value, corrections for multiple comparisons (if applicable))
Depression			
SLC6A4	5-HTTLPR	Brown et al., 2013	RD=0.264, 95% CI: 0.113–0.414, p=0.0006
		Caspi et al., 2003	(ss) β=0,60, P=0.02; (sl) β=0.45, p=0.01; (ll) β= -0.01, P=0.99
		Carver et al., 2011	(s carrier) OR=2.29, p=0.08; (ll) OR=0.03, p=0.05
		Fisher et al., 2013	RD=0.273, p<0.001
		Özçürümez et al., 2019	OR=1.91, p=0.28
		Gutierrez et al., 2015	OR=1.680, p = 0.037
		Ressler et al., 2009	β=1.36, p<0.001
		Border et al., 2019	OR=0.998, p=0.919
		Sharpley et al., 2013	(ss) β= -0.073, p=ns; (sl) β=0.100, p=0.048; (ll) β=0.115, p=ns
		Uher et al., 2011	(Additive model) RD=0.054, p-0.0516; (Recessive s allele model) RD=0.1285, p<0.001 (Dominant s allele model) RD=0.0262, p=0.6115
CRHR1	rs110402	Van der Auwera et al., 2018	β= -0.0063, p=0.9687, correction for multiple testing conducted
		Ressler et al., 2009	Not significant, no data
		Bradley et al., 2008	Significantly protective effect after correction for multiple testing, data only available in the figures of this original article
BDNF	rs6265	Carver et al., 2011	(met carrier) OR=5.37, p=0.04; (val/val) OR=0.29, p=0.11
		Gutierrez et al., 2015	OR=1.576, p = 0.07 (emotional abuse)

		Juhasz et al., 2011	(Additive model) β= -0.078, p=0.009, q=0.048; (Recessive s allele model) β= -0.118, p=0.15, q=0.17; (Dominant s allele model) β= -0.091, p=0.01, q=0.048
		Brown et al., 2014	RD= -0.021, p=0.8620
		Border, 2019	OR=1.007, p=0.803
		Van der Auwera et al., 2018	β=0.0804, p=0.6361, correction for multiple testing conducted
FKBP5	rs1360780	Van der Auwera et al., 2018	β=0.0425, p=0.7713, correction for multiple testing conducted
		Appel et al., 2011	(no physical abuse, CC or CT) reference (no physical abuse, TT) OR=1.0, 95% CI=0.7–1.6; (physical abuse, CC or CT) OR=1.3, 95% CI= 0.8–2.3; (physical abuse, TT) OR=8.2, 95% CI=1.9–35.0
CREB1	rs2253206	Wang et al., 2014	(GG, no abuse) reference; (GA/AA, no abuse) OR=1.02, 95% CI=0.73-1.42; (GG, abuse) OR=2.19, 95% CI=0.39-12.50; (GA/AA, abuse) OR=1.37, 95% CI =(0.78-2.41)
		Juhasz et al., 2011	(Additive model) β= -0.060, p=0.01, q=0.048; (Recessive s allele model) β= -0.078, p=0.05, q=0.11; (Dominant s allele model) β= -0.083, p=0.03, q=0.09
NTRK2	rs1187323	Van der Auwera et al., 2018	β=0.0192, p=0.9068, correction for multiple testing conducted
		Juhasz et al., 2011	(Additive model) β=0.029, p=0.34, q=0.22; (Recessive s allele model) β= -0.019, p=0.82, q=0.39;

			(Dominant s allele model) β=0.043, p=0.22, q=0.21
OXTR	rs2254298	Van der Auwera et al., 2018	β=0.0287, p=0.9218, correction for multiple testing conducted
		Tollenaar et al., 2017	OR=0.86, p=0.75
IL-6	rs1818879	Cohen-Woods, 2017 (discovery cohort)	RD=0.060, p=0.006, Meff-Li p<=0.006[a]
		Cohen-Woods, 2017 (replication cohort)	RD=0.044, p=0.043, q=0.129[b]
CRP	rs3093077	Cohen-Woods, 2017 (discovery cohort)	RD=0.098, p=0.009, Meff-Li p<=0.009[a]
		Cohen-Woods, 2017 (replication cohort)	RD=0.102, p=0.021, q=0.126[b]
TNF	rs1041981	Cohen-Woods, 2017 (discovery cohort)	RD=0.070, p=0.005, Meff-Li p<=0.006[a]
		Cohen-Woods, 2017 (replication cohort)	RD=0.011, p=0.762, q=0.762[b]
TNFR1	rs4149576	Cohen-Woods, 2017 (discovery cohort)	RD=-0.064, p=0.004, Meff-Li p<=0.015[a]
		Cohen-Woods, 2017 (replication cohort)	RD=-0.015, p=0.668, q=0.762[b]
TNFR2	rs17882988	Cohen-Woods, 2017 (discovery cohort)	RD=0.086, p=0.001, Meff-Li p<=0.005[a]
		Cohen-Woods, 2017 (replication cohort)	RD=-0.021, p=0.639, q=0.762[b]
	rs1061622	Cohen-Woods, 2017 (discovery cohort)	RD=0.053, p=0.006, Meff-Li p<=0.005[a]
		Cohen-Woods, 2017 (replication cohort)	RD=0.014, p=0.705, q=0.762[b]
Depressive symptoms			
SLC6A4	5-HTTLPR	Aguilera et al., 2009	β=0.21, p=0.016
		Border, 2019	β=-0.012, p=0.601
		Grabe et al., 2012	p=0.008
		Ressler et al., 2010	Nonsignificant, no data reported
		Wichers et al., 2008	(LS–LL) β=0.06, p=0.4; (SS–LL) β=0.07, p=0.4
BDNF	rs6265	Aguilera et al., 2009	β=0.23, p=0.015
		Border, 2019	β=0.006, p=0.843
		Grabe et al., 2012	p=0.430
		Wichers et al., 2008	β=0.13, p=0.031
		Juhasz et al., 2011	(Additive model) β= 0.004, p=0.752, q=0.344; (Recessive s allele model) β= -0.023, p=0.470, q=0.265;

			(Dominant s allele model) β= 0.012, p=0.455, q=0.265
CRHR1	TAT haplotype (rs7209436, rs110402, rs242924)	Grabe et al., 2010	β=1.4, p=0.0229, corrected α=0.00386
		Laucht et al., 2013	β=0.187, p<0.001
		Bradley et al., 2008	Significantly protective effect after correction for multiple testing, data only available in the figures of this original article
	TCA haplotype (rs7209436, rs4792887, rs110402)	Bradley et al., 2008	Significantly protective effect after correction for multiple testing, data only available in the figures of this original article
		Ressler et al., 2010	β=1.59, p=0.039
	rs17689882	Grabe et al., 2010	Significant interaction with physical abuse, corrected α=0.00386, data presented in a figure
		Laucht et al., 2013	β=0.386, p<0.001
	rs110402	Bradley et al., 2008	Significantly protective effect after correction for multiple testing, data only available in the figures of this original article
		Grabe et al., 2010	No significant interaction, corrected α=0.00386, data presented in a figure
		Heim et al., 2009	(men) $F_{2,423}$=3.50, p=0.031; (women) no significant interaction; data presented in a figure
		Ressler et al., 2010	β=3.53, p=0.010
	rs242924	Grabe et al., 2010	No significant interaction, corrected α=0.00386, data presented in a figure
		Bradley et al., 2008	Significantly protective effect after correction for multiple testing, data only available in the figures of this original article

Note: *Statistics across studies applied various indicators and controlled for different confounders.

OR, odds ratio; RD, risk difference;
[a]Meff-Li p-value represents SNPSpD identified p-value threshold for each gene;
[b]q-value represents false discovery rate corrected p-value;

Appendix 1 Search strategy

PubMed

((((((((depressive disorder[MeSH Terms]) OR major depressive disorder[Text Word]) OR major depression[Text Word]) OR unipolar depression[Text Word]) OR depression[Text Word]) OR depressed[Text Word]) OR depressive[Text Word])) AND (child* AND (abus* OR maltreat* OR neglect OR abandon* OR illtreat* OR ill-treat* OR mal-treat* OR advers* OR trauma* OR ACE*))AND (GWA* OR genetic* OR SNP* OR genome* OR WGA* OR gene*)
Filters: Humans

EMBASE, Medline, PsychoInfor, HealthStar

1 ("depressive disorder" OR"major depressive disorder" OR"major depression" OR"unipolar depression" OR"depression"OR"depressed"OR"depressive").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
2 limit 1 to human, humans
3 1 and 2
4 ("genome-wide" OR "GWA*" OR "genetic*" OR "SNP*" OR "genome*" OR "WGA*" OR "gene*").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
5 ("child*" AND ("abus*" OR "maltreat*" OR "neglect" OR "abandon*" OR "illtreat*" OR "ill-treat*" OR "mal-treat*" OR "advers*" OR "trauma*" OR "ACE*")).ti,ab,kw. [ti,ab,kw=title, abstract, keyword]
6 3 and 4 and5

Cochrane Library

#1 MeSH descriptor: [Depressive Disorder] explode all trees
#2 "major depressive disorder" or "major depression" or "unipolar depression" or "depressed" or "depression" (Word variations have been searched)
#3 #2 or #1 or "depressive" (Word variations have been searched)
#4 MeSH descriptor: [Genome-Wide Association Study] explode all trees
#5 GWA* OR genetic* OR SNP* OR genome* OR WGA* OR gene* (Word variations have been searched)
#6 #4 or #5
#7 MeSH descriptor: [child maltreatment] explode all trees
#8 child* AND (abus* OR maltreat* OR neglect OR abandon* OR illtreat* OR ill-treat* OR mal-treat* OR advers* OR trauma* OR ACE*)
#9 #7 or #8
#10 #3 and #6 and #9

Appendix 2
Quality assessment of reviewed articles.

	Design			Measurement			Analysis			Result		
Study (first author, year)	Sample size[1]	Study design[2]	Source of participants[3]	Selection of participants[4]	Assessment of ethnicity[5]	Genotyping method & platform[6]	Appropriate statistical analysis[7]	Appropriate methods to control confounding[8]	Appropriate methods to address multiple comparisons[9]	Descriptive data on depression reported by maltreatment and genotpye[10]	Genotype frequencies reported[11]	Appropriate result interpretation[12]
Aguilera, 2009	+	+	+	+	+	+	+	+	-	-	+	+
Laucht, 2012	+	+	+	+	+	+	+	+	-	-	+	+
Carver, 2011	-	+	+	-	+	+	+	+	-	-	+	+
Wang, 2014	+	+	+	+	+	+	+	+	-	+	+	+
Sharpley, 2014	-	+	+	-	-	+	+	-	-	-	+	+
Auwera, 2017	+	+	+	-	-	+	-	-	-	-	-	+
Castro-Catala, 2017	+	-	+	-	+	+	+	+	-	-	+	+
Fisher, 2013	+	+	+	+	+	+	+	+	+	+	+	+
Ressler, 2009	+	+	+	-	+	+	+	+	-	+	+	+
Tollenaar, 2017	+	+	+	+	+	+	+	+	+	-	+	+
Juhasz, 2011	+	+	+	+	+	+	+	+	+	-	-	+
Heim, 2009	+	+	+	-	+	+	-	+	-	+	+	+
Appel, 2011	+	+	+	+	+	+	+	+	+	+	+	+
Grabe, 2010	+	+	+	+	+	+	+	+	-	-	-	+
Polanczyk, 2009	+	+	+	+	-	+	+	+	-	+	+	+
Uher, 2011	+	+	+	+	+	+	+	-	-	+	+	+
Caspi, 2003	+	+	+	+	+	+	+	+	-	-	+	+
Brown, 2012	+	+	+	+	-	+	+	-	-	+	+	+
Grabe, 2011	+	+	+	+	+	+	+	+	-	-	+	+
Wichers, 2008	+	+	+	+	+	-	+	+	-	-	+	+
Brown, 2014	+	+	+	+	-	+	+	-	-	-	+	+
Gutierrez, 2015	+	+	+	+	+	+	+	+	-	-	+	+
Bradley, 2008	+	+	+	-	-	+	+	+	+	+	+	+
Kovacs, 2016	+	+	+	-	+	+	+	+	+	-	-	+

Cohen-Woods, 2017	+	+	+	+	+	+	+	+	+	-	+	+
Yin, 2020	+	+	+	+	+	+	+	+	+	-	+	+
Gamze, 2019	+	+	+	+	+	+	+	+	-	-	+	+
Richard, 2019	+	+	+	+	+	+	+	+	-	-	-	+
Cattaneo, 2018	+	+	+	+	-	+	+	+	+	-	-	+

Notes. 1 Sample size provides enough power for analysis; 2 Whether the study being conducted appropriately considering the nature of study design; 3 Clear sources of participants; 4 Eligible and reasonable selection methods of participants, which might include the selection criteria; 5 Ethnic origin was identified, and mixed ethnicity was addressed statistically; 6 Clear genotyping methods and platforms, which could include the allele calling algorithm used, and its version; 7 Appropriate statistical analysis, including assessment of Hardy-Weinberg Equilibrium (HWE) and proper regression model; 8 Analysis was adjusted for potential confounders (e.g. age, sex); 9 Multiple comparisons were addressed to control risk of false positive findings, such as Bonferroni correction and False Detective Rate (FDR) with bootstrapping; 10 Enough data to be included in a meta-analysis: exposure or outcome numbers by genotype in each maltreatment group; 11 Genotype frequencies were examined and summarized; 12 Analysis results were appropriately interpreted, neither over- nor under-interpreted from findings.

Appendix 3

Data references for selected 29 articles in this systematic review

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