NOTE TO USERS

The Development of Contemporary Medical Genetics Research Models and the Need for Scientific Responsibility

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ABSTRACT

Current medical genetics research is dominated by a single theory that supports the Human Genome Project rationale. This thesis investigates this and several alternative hypotheses and the ethical context related to their development. Firstly, the hypotheses are discussed in detail followed by a sub-section in which research evidence based on each hypothesis is cited. Secondly, these medical genetics hypotheses are situated within the contemporary medical paradigm. To conclude, the thesis examines in depth the ethical and practical implications of medical genetics research. A framework of analysis of scientific responsibility is used to explore these implications. Scientific responsibility, as presented in this thesis, is a process consisting of three steps: 1) scientific discourse; 2) the development of the nature of scientific responsibility; and, 3) effective criticism. Once scientific responsibility is defined, the term is applied specifically to the field of medical genetics research.

RÉSUMÉ

La recherche médicale en génétique est actuellement dominée par une hypothèse qui soutient le raisonnement que l'on retrouve à la base du Projet sur le Génome Humain (HGP). Cette dissertation examine cette hypothèse principale, présente plusieurs hypothèses alternatives et analyse le contexte éthique inhérent à leur développement. Les hypothèses associées à la recherche médicale en génétique sont en premier lieu analysées en détail et ensuite appuyées par des exemples de recherche concrets. En deuxième lieu, ces hypothèses sont analysées à l'intérieur d'un paradigme médical contemporain. Finalement, cette dissertation examine de façon détaillée les implications morales et pratiques de la recherche médicale en génétique au moyen du cadre d'analyse de la responsabilité scientifique. La responsabilité scientifique, telle que présentée dans cette dissertation, se compose de trois éléments: 1) le discours scientifique; 2) le développement du caractère de la responsabilité scientifique; 3) la critique efficace. Une fois l'expression « responsabilité scientifique » définie, elle est appliquée spécifiquement au domaine de la recherche médicale en génétique.

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LIST OF ABBREVIATIONS

AD	Alzheimer disease
APOE4	apolipoprotein E4
BRCA1/2	Breast Cancer 1 and 2 genes
CFTR	Cystic Fibrosis transmembrane receptor
CD/CM	common disease/common mechanism
CD/CV	common disease/common variant
CD/FV	common disease/fixed variant
CD/RV	common disease/rare variant
CV/MD	common variant/multiple disease
DNA	deoxyribonucleic acid
DOE	US Department of Energy
HGP	Human Genome Project
HD	Huntington disease
LD	linkage disequilibrium
LDLR	low density lipoprotein receptor
MHC	major histocompatibility complex
NAS	US National Academy of Sciences
NAT2	N-acetyltransferase 2
NCBI	US National Center for Biotechnology Information
NHGRI	US National Human Genome Research Institute
NIH	US National Institutes of Health
RNA	ribonucleic acid
SNP	single nucleotide polymorphism

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INTRODUCTION

The Human Genome Project's International Human Genome Sequencing Consortium announced the completion of the sequencing of the human genome in the spring of 2003. The Human Genome Project (HGP) was co-sponsored by the U.S. Department of Energy (DOE) and National Institutes of Health (NIH) with a final cost of about US$3 billion (Anon, 2003). The project's researchers announced that, with the knowledge of the sequence of each gene, the human genome and all its complexities could now be studied and deciphered. Genomics[1] would allow a greater understanding of human biology and, in turn, human health and disease.

According to an article by Francis Collins [director of the National Human Genome Research Institute (NHGRI) of the NIH] and colleagues (2003), the relationship of genomics to health necessarily rests on the foundation of the HGP. The project was the first step in the process of a "revolution in biological and medical research." Collins et al (2003) list several challenges to the active translation of the HGP into medical advances. One such challenge is the need to compile a "comprehensive and comprehensible catalogue of all of the components encoded in the human genome" through the creation of various public databases. The catalogue would entail an exhaustive "parts list" not only of every gene, its protein counterpart and its function(s) but also of regulatory elements.

Francis Collins and his colleagues note two more challenges (relevant to this thesis) to the greater understanding of genetics and health: the elucidation of the "organization of genetic networks and protein pathways and how they contribute to phenotypes" and the development of "a detailed understanding of the heritable variation in the human genome." The authors explain that all genes and their products must be assigned to functional pathways in order to gain "a complete understanding

of systems biology" and to establish "how organized molecular pathways and networks give rise to normal and pathological...phenotypes." With the same logic, the authors state the necessity of cataloguing through databases all genetic variation in the human genome in order to study DNA variants and their relationship to health and disease.

The main anticipated advances by the HGP would be: improved abilities to predict disease and ascertain individual disease risk via identification of genetic profiles[2] and the creation of potential "designer" treatments via pharmacogenomics. These individualized genetic profiles depend on the development of extensive genetic cataloguing. A recent review in the *New England Journal of Medicine* (*NEJM*) stated, "Over the next decade or two, it seems likely that we will screen entire populations or specific subgroups for genetic information in order to target interventions to individual patients that will improve their health and prevent disease" (Khoury et al, 2003). The aim is, in about ten to fifty years, to create a medicine and a pharmacology that are individualized and predictive as opposed to generalized and reactive.

The methods of categorization of the human genome are intended to lead to a clearer understanding of the mechanisms and pathways that mediate disease. This in turn "will lead to the definition of distinct disease subtypes, and may resolve many questions relating to variable disease symptoms, progression and response to therapy seen within current diagnostic categories [providing] a new taxonomy for human disease" (Bell, 2003). Clinicians are being called to "think mechanistically about disease" and to achieve a "better understanding...at a molecular level" allowing for a more accurate prognosis (Bell, 2003). Yet, nowhere is it explained why molecular medicine would be simpler and more accurate. For this to be true, the relationship

between genetics and disease would depend on this underlying accuracy and simplicity.

The promise inherent with the provision of the massive HGP budget is that human genetics will lead to treatments and cures for disease[3]. Yet, critics have for a long time complained that discovered genes and even sequenced genomes do not necessarily lead directly to cures (Holtzman & Marteau, 2000; Lindee, 2003). After 13 years of HGP activity, the relationship between genetics and medicine has not been adequately determined[4]. The main question of the researchers has been until now, simply, how to sequence 3 billion DNA base pairs. Questions related to the purpose of this initiative have rarely been raised.

This method of categorization and classification of each piece of the human genomic (and "proteomic") puzzle contradicts the versatile and less narrowly determined (even messy) genomic networks we now believe to exist. Whether or not a gene is categorized as important depends on the context including, interactions with other alleles, environmental factors and chance. Yet, HGP researchers contend that the "parts list" is a tool that will aid researchers in the unequivocal elucidation of medical genomics. This molecular level catalogue will be made understandable through the obligatory use of "increasingly powerful technological tools" (Collins et al, 2003).

The HGP could not have been completed ahead of schedule without technological developments created primarily for the facilitation of the project and its spin-offs. Advances in instrumentation, automation and computation have increased sequencing capacity (especially through the use of capillary-based DNA sequencing), and increased the number of genes analyzed via expression analysis with DNA chips containing tens of thousands of DNA and RNA fragments. Developments have also

provided new methods for genotyping single nucleotide polymorphisms (SNPs) that are thought to be associated with disease. Research technology and computational biology have been successful in helping to fulfill the goals of the first phase of the HGP; our future abilities to sort through the complexities of medical genetics are thought to rely on further technological development and new mathematical models. To be of real medical value, the HGP and its technologies will have to provide a substantial foundation on which to build future medical research rather than simply being boldly ambitious and of commercial potential.

Simple, precise diagnosis via genetic profiles would be a useful tool for health professionals. One of the goals of research in the field of medical genetics is to identify clinically important genetic effects in "typical" patients. Yet, complexity and variation are integral to human biology and describe most of our diseases. Gaps between the medical genetics ethos and its practice may occur because of lack of knowledge, lack of adequate attention to serious methodological questions or unrealistic expectations. The result is that health professionals, researchers and patients do not know how to approach or use much genetic information efficaciously. While genetic information may be presented as more accurate than traditional diagnostics, genetic diagnoses are always probabilistic, often carrying with them wide-ranging lifetime risk estimates that may be difficult to interpret at the individual level.

The current medical paradigm within which medical genetics is set influences the direction of research. The HGP has captured the imagination of many researchers, physicians and the public alike, because it corresponds well with a particular biomedical paradigm that emphasizes biotechnological development, individual control over one's own health and focuses on biological processes rather than social

and environmental aspects of disease. Ideal genetic explanations of disease would be simple and applicable to the average patient. Many researchers agree that rendering human genetics into a simplified disease model will be a great challenge (Terwilliger & Weiss, 2003; Wright et al, 2003). Many other investigators believe that the development of new and more powerful technologies will meet this challenge and personalized medicine will become a reality (Collins et al, 2003; Bell, 2003). Unfortunately, our current mainstream medical paradigm does not take into account human biological complexity or complexities beyond our biology. For example, the concentration on technology and commercial forces rather than the practical uses of genetics may lead to its misuse or misinterpretation. Additionally, medicine that focuses on the individual presumes a strong degree of personal agency and ignores the powerful social and economic forces exerted on each individual.

Researchers at the NHGRI and elsewhere champion a massive catalogue of genes, proteins and genetic variation as well as detailed maps of biological networks and pathways. The idea is that a detailed understanding comes from cataloguing and classification. However, the gathered information also needs to be interpreted. According to the group at the NHGRI, interpretation will occur through the technological and computational development and better mathematical models. Yet, whether or not technological models will significantly revolutionize medicine depends, in large part, on the reliability of the HGP foundation. Although the interpretation stage of the HGP is still in its infancy, some models and research results indicate that genetics will be medically useful only in a very narrow sense, for example, those rare circumstances when DNA variants have severe phenotypic consequences (usually associated with founder populations or within families). The concomitant medical revolution promises individualized medicine and designer

therapies (Collins et al, 2003; Khoury et al, 2003). Yet, we do not know for certain how genetic information can be used. The gaps in our understanding need to be acknowledged and various disease models need to be examined in order to provide useful and thoughtful research results.

Section one of this thesis will investigate several medical genetics hypotheses that I have characterized as thus: 1) the common disease/common variant hypothesis that is currently a popularly held medical genetics theory and is connected with the goals of the HGP; 2) the common disease/rare variant hypothesis which is a rival medical genetics model; 3) the polygenic disease model; 4) hypotheses surrounding the environmental influences on disease and the genetics of disease; 5) ideas on chance events and the related limitations of accurate genetic predictions. All of these hypotheses and ideas will be discussed in detail followed by a sub-section in which research evidence based on each hypothesis is cited. Many of the references used in this thesis represent investigations of novel interpretations and ways of conceiving complex disease and genetics research models. Only a limited number of investigators are writing on the alternative research models and even fewer are openly critical of the current trends in genetics research. For this reason, this thesis can only quote from a small pool of researchers who are otherwise respected and whose commentaries are important to this field of inquiry. The second section situates the medical genetics hypotheses within the current medical paradigm that I describe as: individualized, technologized and focused on the biological processes of disease manifestation. The third section of the thesis examines the ethical and practical implications of medical genetics research (under the current medical paradigm). A framework of analysis of scientific responsibility will be used to explore these implications. Scientific responsibility, as presented in this thesis, is a process consisting of three steps. The

first step consists of an active scientific discourse. Section one documents the current scientific discourse within the medical genetics field. Step two includes the development of awareness, professional commitment and humility while step three describes effective scientific criticism. This third step of scientific responsibility results from the infusion of a political consciousness into scientific discourse. Once scientific responsibility is defined, the term will be applied to the field of medical genetics research. In this case, scientific responsibility ought to lead to a more useful and equitable distribution of funds for various medical genetics research models. In other words, no single research model should be favoured at the expense of another model of equal promise but less commercial potential. Thus, scientific responsibility would promote a medical genetics that better reflects the needs of the greater community. The final sub-section of the ethical analysis asks whether scientists are capable of scientific responsibility. Researchers make ethical decisions throughout the scientific process and also have a special understanding of their subject. This sub-section concludes that investigators need to be aware of the responsibilities inherent in scientific knowledge and *must* be scientifically responsible.

SECTION ONE

THE RESEARCH MODELS

The HGP and related medical genetics research are carried out with the expectation that human genetic variation will be explainable. If so, this variation may describe differences in disease outcomes and differences between sick and healthy individuals. People may respond, not respond or have toxic reactions to drugs based on their particular DNA profile. The common disease/common variant (CD/CV) hypothesis suggests that the cataloguing of all genetic variation will permit the

cataloguing of individual health and disease. The common disease/rare variant (CD/RV) model illustrates the complexity of genetic variation and the difficulty, if not the impossibility, of application in the medical clinic.

Other descriptions of disease complexity (not necessarily divorced from the theories mentioned above) are also being developed. For example, the polygenic model refers to the large number of genes involved with disease that interact and have multiple functions. No statistical model or technology has been able to precisely follow polygenic contribution to complex disease. Additionally, environmental influences, which are often lumped into a catchall category, are fundamental to the study of individual and collective health and disease. Beyond genetics, environmental factors are thought to be major, if not the major, contributors to complex disease risk, even if there is a gene-environment interaction (Terwilliger & Weiss, 2003). Finally, another illustration of disease complexity is the role of chance in disease manifestation. If our contemporary large-scale genetics projects promise accurate genetic categorization and precise diagnosis of disease for individuals, the examination of chance events and the limitations of genetic control are important. This section will describe these hypotheses—CD/CV, CD/RV, the polygenic nature of common disease, environmental contributors, and chance events—that are used in the attempts to explain the genetic architecture of disease (the number and frequencies of susceptibility alleles at complex disease loci) and the variability of disease expression. The following section is arranged in a point-counterpoint manner. The "point" represents a popular medical genetic research hypothesis against which the "counterpoint" argues for several alternative hypotheses that emphasize biological and environmental complexity.

POINT

I) Common disease/common variant

The common disease/common variant (CD/CV) hypothesis, as interpreted by Reich and Lander (2001), predicts that there are few disease-predisposing alleles of high frequency in the human population. Alleles influencing common, late-onset diseases have a moderate effect on fitness allowing them to become common (of high frequency) in the human population. Widely distributed or common causative alleles would most likely be of ancient origin and stem from a founder population (Harrap, 2003). If the typical patient carries these ancient disease alleles, genomic information may conceivably be harnessed for future medical use via pharmaceutical development or more precise disease diagnoses.

The CD/CV hypothesis not only depends on the existence of common variants maintained in the human population but also on a limited number of disease loci (or an "oligogenic" basis of common disease). According to the CD/CV model, the rapid population expansions of modern humans from a small founder population lead to low allelic diversity (Wright & Hastie, 2001). The CD/CV hypothesis questions why common disorders are indeed common and why they are maintained in the population at such high frequency (Becker, 2004). According to this model, the reply is that the underlying disease-influencing alleles must be common themselves. Thus, the authority of the CD/CV model is based on the dynamics of ancient founder populations and on the idea that common diseases are necessarily caused by common alleles.

"Clinical characterization and design of diagnostic and therapeutic interventions are substantially easier when the allelic spectrum is simple" (Reich & Lander, 2001). The CD/CV model is popular because it is tractable and would lead to

a medically useful genetics. In fact, this model inspires much of the research into medical genetics. The CD/CV hypothesis proposes that the allelic architecture of disease loci is simple, common across human populations and collectively highly informative. Susceptibility alleles[6], in this case, would be potentially detectable, classifiable and informative for disease prediction or understanding. The CD/CV model facilitates the incorporation of genetics into everyday medicine. This model provides an explanation of how human variation may influence health and disease. The CD/CV hypothesis also provides grounds for sanctioning the development of the HGP, its sub-projects, the massive funding and technological developments of medical genomics. Yet, serious concerns about this disease model have surfaced in recent publications detailed below.

COUNTERPOINT

II) Common disease/rare variant

The common disease/rare variant (CD/RV) model proposes that susceptibility to common disease results from numerous rare variants at many loci. This allelic spectrum is often associated with mendelian diseases. However, recently, some investigators have asked why the architecture of complex disease loci should differ from that of mendelian loci (Pritchard & Cox, 2002; Wright et al, 2003). The proportion of rare variants, according to this point of view, is thought to be high for two reasons. "First, most mutations with phenotypic effects are deleterious, so that their frequency is reduced by selection. Second, the human population has been expanding, generating large numbers of rare alleles by mutation" (Wright et al, 2003). The majority of disease-causing alleles in early-onset mendelian disorders are recent, diverse and rare, resulting in extreme allelic heterogeneity [which] is expected for

deleterious alleles exposed to early selection, but is also found in late-onset diseases (Wright et al, 2003). The CD/RV model, "predicts extensive allelic heterogeneity" (Wright & Hastie, 2001).

The CD/CV model represents the ideal scenario for contemporary medical genetics research. The CD/RV hypothesis presents a much less optimistic formula for modern methods of disease allele detection. The CD/RV model presents major obstacles to the methods outlined by the researchers at the NHGRI such as, extensive cataloging, individualized DNA profiling and association studies (Pritchard & Cox, 2002; Wright et al, 2003). A large and diverse group of rare susceptibility alleles would be difficult to detect in the typical patient since "the typical patient" would not exist. Current strategies depend on the idea that genetic profiles, strongly associated with disease, will be detectable. The CD/RV theory proposes that any allele with strong effects on fitness would be rare in the population due to selection pressures and a high mutation rate (Pritchard & Cox, 2002). Disease loci underlying physiologically complex diseases (caused by numerous determinants) "are likely to be so numerous and of such small effect that gene identification will be either impossible or unhelpful" (Wright et al, 2003).

The CD/RV hypothesis clearly raises many questions about the direction of current medical genetics research. The CD/RV model, as opposed to the tractable CD/CV model, reflects the complexity of human disease. Many prominent researchers favour the CD/CV hypothesis because (among other reasons explored further below) this approach to disease genetics would be more useful in the clinic. Yet, current evidence (presented as examples below) challenges the idea of genetic simplicity, representing a complex human genetics that may not be readily determinable.

III) Polygenic nature of common disease

Polygenic implies disease that is determined by a large number of loci. The number of polygenes (and their alleles) contributing to the disease phenotype is unknown but "will have important consequences for the discovery and use of genetic information" (Harrap, 2003). Overall, if a trait is complex and multidimensional and its variance is high (true of most common diseases), the genetics of the trait is likely to be polygenic and heterogeneous (Wright et al, 2003). A polygenic disease model consists of interactive genetic networks, each locus within the network having many possible variants that differ from individual to individual and population to population. "Presumably, for each polygene, DNA variants exist that alter the function or expression of the gene or its encoded protein" (Harrap, 2003). The researchers that support the CD/CV hypothesis contest that the cumulative effect of a few common oligogenes associated with common disease will be determinable. In contrast, according to the polygenic model, the large number of loci at which mutations can arise intractably complicates disease-gene identification. For instance, "the genetic basis of disease could vary greatly among individuals with the same disease." (Wright et al, 2003).

The polygenic model assumes that the common complex disease phenotype is explained by upwards of hundreds of genes (Lifton et al, 2001; Rudan et al, 2003a; Rudan et al, 2003b). The exact number of alleles/loci influencing disease manifestation is difficult to estimate. However, "a common, often implicit, assumption in mapping studies of complex traits is that relatively few genetic loci of moderate to large effect [i.e. the oligogenic model] account for a large component of the underlying genetic variance despite the paucity of empirical data to support this"

(Rudan et al, 2003a). This statement implies that an alternative polygenic interpretation of complex disease ought to be explored in greater detail.

IV) Environmental factors

Those researchers studying the genetics of disease often do not wholly consider the influence of environmental factors on disease. "Molecular genetics, which has deeply influenced the philosophical framework of biology, often assumes that the primary threats to health are programmed in our DNA rather than our social environment, with disease being transmitted through abnormal physiology rather than food, air, microorganisms and our place in the social hierarchy" (Cooper & Psaty, 2003). Yet, many researchers question the overall significance of genetics. The magnitude of genetic effects in complex disease is frequently dwarfed by known environmental factors (Wright et al, 2003).

While environmental factors can be complex and change frequently over time, these factors otherwise have strong disease effects. Removal of an environmental factor can dramatically reduce disease risk. Examples include, infection for polio, smoking and lung cancer, diet and exercise for obesity, key types of asbestos for mesothelioma, and thalidomide for birth defects (Terwilliger & Weiss, 2003). Genetically speaking, strong effects are found only in very rare cases of monogenic forms of complex disease (e.g. breast and colon cancer). Additionally, research investigating the genetic architecture of disease may be complicated by environmental factors because "opportunities for disentangling interactions between genetics and environment are often limited" (Wright et al, 2003).

V) Chance

In their book, *Chance, Development, and Aging*, Caleb Finch and Thomas Kirkwood (both biological gerontologists) present another theme on genetic variation. They investigate "the sources of individual variations in postnatal development and in aging that cannot be attributed to genes or the environment." In their view, the processes that cannot be explained by genetics and/or the environment are attributed to chance events. They use 'chance' as "the most generic term to describe the generating force that lies behind the variations that cannot (at least, not yet) be explained." Chance, according to the authors, can also be related to 'randomness' that describes "outcomes that are essentially unpredictable" (Finch & Kirkwood, 2000). Finch and Kirkwood explain further that,

> "[c]hance is an essential ingredient of the chemical reactions that sustain life. Molecules moving through intracellular space are subject to all kinds of random encounters; some, such as collisions with free radicals, are highly destructive. The very interactions between molecules that influence key outcomes in cell differentiation and development are inescapably governed by chance. We wish to know at a fundamental, mechanistic level how chance affects the development of tissues, and how these fluctuations can have a long-term impact on viability and fertility throughout adult life."

The hypothesis developed by Finch and Kirkwood states that chance variations in form (cell number, organ structure) and function (organ system physiology) can affect individual responses to the environment, modifying outcomes of disease.

Finch and Kirkwood state, "no matter how precisely the genetic library is copied from cell to cell, degrees of randomness as cells carry out their genetic instructions are still allowed." Gene expression in the complex human biological milieu is variable and is often beyond genetic control. Chance events in development "result in wide-ranging variation [so that] every organism is the outcome of a unique interaction between genes and environmental sequences modulated by the random chance of cell growth and division" (Lewontin, 1990).

This hypothesis, while conceding that genetics is an important subject, raises concern about the limitations of genetics in determination of disease. The Finch and Kirkwood thesis does not propose that human biology is chaotic and uncontrolled, since many regulatory and scaffolding systems[7] exist to restrict morphogenesis, disease manifestation and other functions. Chance plays a role within the constraints of the genome, human biology and the external environment (Finch & Kirkwood, 2000). Within the limits of human biological regulatory and repair systems, degrees of variation in form and function exist. Consequently, the explanatory power of medical genetics at the individual level would be reduced and would allow multiple interpretations.

EXAMPLES

Each hypothesis documented above comes with a body of evidence based on research undertaken by investigators supporting said hypotheses. At this stage of medical genetics research, no particular hypothesis can be unequivocally recognized as "proven" or even "well-established." Currently, the favoured theory is the CD/CV hypothesis that, some researchers maintain, rests on weak evidence. However, as already mentioned, various assumptions about population structure, genetic architecture and external influences on health and disease are made for each theory. These assumptions are based on ideas that are not confirmed but are simply preferred for various (strong or weak) reasons by particular investigators. Research evidence based on each hypothesis/theory from the current medical genetics discourse is cited below.

I) Common disease/common variant

The development of haplotype studies and the burgeoning field of pharmacogenomics are two areas that may hold promise for those supporting the CD/CV hypothesis. A haplotype is a "specific combination of adjacent polymorphisms on a single chromosome" (Lee, 2002). Rather than investigate an arbitrary group of variable alleles, ancestral haplotype "blocks" can be determined and their patterns linked to disease. If haplotype blocks are typical, and the blocks are shared globally, a modest number of common variants selected from each block might suffice to define mapping haplotypes that will be useful in any population, reducing the cost and complexity of mapping studies (Weiss & Clark, 2002). Haplotypes have been linked to Crohn disease (Rioux et al, 2001) and type II diabetes (Horikawa et al, 2000).

Pharmacogenomics, is based on expected associations between individual DNA profiles and drug absorbance and clearance. According to the NIH, National Center for Biotechnology Information (NCBI) web page, "in the future, the most appropriate drug for an individual could be determined in advance of treatment by analyzing a patient's DNA profile [this] would allow pharmaceutical companies to bring many more drugs to market and allow doctors to prescribe individualized therapies specific to a patient's needs" (NCBI, 2004). More than 20 polymorphisms have been identified in drug-metabolizing enzymes, one example, the NAT2 enzyme form of N-acetyltransferase, influences adverse drug reactions in those individuals carrying specific *NAT2* polymorphisms (Tsai & Hoyme, 2002). Insights into the structure and function of the Philadelphia chromosome in chronic myelogenous leukemia has lead to the identification of a new drug target and, consequently, genetic variations that confer resistance to the new drug (Kantarjian et al, 2002). "Compared

with the chemotherapeutic model in which the most toxic drugs are given at the highest possible doses to kill the cancer, this therapy is nontoxic and represents an astonishing achievement. Whether it will be possible to develop a similar approach to the treatment of other cancers remains unknown" (Cooper & Psaty, 2003).

II) Common disease/rare variant

The many rare disease variants predicted by the CD/RV hypothesis would make human genetic variation extremely difficult to study. These alleles would be too rare to be detected except in particular populations such as founder populations (Wright et al, 2003). Common variants, according to this model, are considered to carry no significant disease risk. In fact, common variants, as per the CD/RV hypothesis, are more likely to be neutral or even beneficial since these variants have not been filtered out by natural selection[8].

Studies to identify individual alleles associated or linked to particular diseases have generated inconclusive and disappointing results. "Often, strong associations are reported that are later not confirmed in larger and better-designed studies. For example...initial reports of associations between a polymorphism in the apolipoprotein B gene and coronary heart disease were not supported in subsequent larger studies" (Willett, 2002). Additionally, *BRCA1/2* were originally mapped and associated with disease through studies in families with high risk. Attempts to apply the results of such studies to wider, more heterogeneous populations have proven "to have less direct public health impact than initially predicted from the rarefied samples in which they were first identified" (Weiss & Terwilliger, 2000). These results support the CD/RV hypothesis in that extensive allelic heterogeneity and complex genetic interactions render gene identification extremely difficult.

The CD/RV model appears to be supported in two research studies investigating hypertension. Two large-scale genome-scanning studies, in which 3599 hypertensive patients and 6000 individuals from hypertensive families were genotyped, were unable to provide evidence of disease-associated oligogenes (Harrap, 2003). These results confirm that hypertension (a common, late-onset disease) is causatively complex. If one or a small number of common alleles had sufficient effect(s) on blood pressure, the two studies mentioned above should have located the allele(s) (Harrap, 2003). However, the results are not surprising if, according to the CD/RV hypothesis, a large number of infrequent and population-specific alleles influence disease manifestation.

Haplotype mapping depends on common variants and on clearly defined patterns of linkage disequilibrium (LD). According to the CD/RV hypothesis, common alleles capable of significantly influencing health or drug response are unlikely to exist in the general population. These common, ancient alleles would most likely be functionally neutral or even beneficial (Terwilliger & Weiss, 2003). The more recent, rare disease alleles may be missed if not associated with ancient haplotypes and "disease associations will be hard to detect especially if alleles of opposite effect arise on the same haplotype" (Wright et al, 2003). The HapMap project is based on very minimal knowledge of haplotype structure within the human population. "LD is a highly stochastic measure difficult to predict in advance (that is, in designing the sites to be typed in a study), and is a function of the histories of the alleles being compared" (Terwilliger & Weiss, 2003). Thus, the strategies used in the HapMap project may not be easily modeled or globally applicable. In general, the CD/RV hypothesis does not support the large-scale genomic strategies that are currently being developed for disease-gene or haplotype identification.

III) Polygenic nature of common disease

"Strategies for identifying disease susceptibility genes depend both on the balance of common and rare variants maintained in the population, and on whether these occur at a limited (oligogenic) or a large (polygenic) number of loci" (Wright et al, 2003). In general, the number and nature of genes that contribute to complex disease is presently unknown. However, the number of genes (and alleles) that contribute to complex disorders such as coronary artery disease and asthma are, indisputably, orders of magnitude larger than "simple" mendelian diseases (Wright & Hastie, 2001). The low success rate of complex trait mapping stems from a recipe of factors not the least of which is the large number of genes that influence these traits in different combinations in different individuals (Weiss & Terwilliger, 2000).

Researchers at the NHGRI purport that the problem of genetic heterogeneity can be solved through better statistical models and new technology. "But inflated claims based on [a technological] approach can divert attention from the critical issue of how to deal with complexity on its own terms, and fuels false hopes for simple answers to complex questions" (Weiss & Terwilliger, 2000). If the polygenic disease model were correct, the numerous individual genetic effects would be too small to detect in finite samples of 'typical' patients by any known technological standards. This supposition was supported in a study of inbreeding effects and the genetic basis of blood pressure (Rudan et al, 2003a). Yet, determining the number of genes involved with disease is based on many assumptions about which we are not certain. Additionally, large numbers of susceptibility genes compound statistical calculations so that demonstrating a clear link between genotype and phenotype is difficult. Indeed, more needs to be known about disease mechanisms and genetic architecture

before we say with any confidence whether disease is caused by few or hundreds of genes.

IV) Environmental factors

Both genetics and environmental factors play a role in complex disease yet population and clinical studies are regarded as "the poor intellectual cousins" to molecular genetics (Cooper & Tsaty, 2003). Geneticists often treat the environment as a nuisance parameter, to be integrated out of their analyses (Weiss & Terwilliger, 2000). Yet, the various environmental factors involved in disease manifestation are important to consider because, in addition to constituting strong effects, they can also confound genetics research results.

Cataloguing all disease related alleles and the sequencing of the human genome do not necessarily lead to the discovery of novel treatments of, or prevention strategies for, disease. Additionally, while the contribution of individual genetic factors to complex disease, in most cases, is seldom greater than a few percent of the trait variance and a small percentage of cases, environmental factors such as diet, physical inactivity and tobacco have been proposed to account for 75% of new cases of cardiovascular disease (Wright et al, 2003). The traits that geneticists focus on "frequently have heritabilities of less than 50% meaning most of the variation in the traits is not genetic in any simple sense" (Weiss & Terwilliger, 2000). "Geneticists focus little effort on controlling for potential environmental confounders, which may be more important than genetic factors in terms of having an impact on public health because they are more easily modified in many cases" (Weiss & Terwilliger, 2000).

"Many environmental factors affect gene expression [for example] regulation of blood pressure changes daily in response to many factors, levels of growth

hormone and cortisol change in response to exercise, and nutritional factors during growth and development may affect metabolism and susceptibility to disease throughout later life" (Weiss & Terwilliger, 2000). The effects of disease related alleles could also be obscured by environmental conditions that constrain their expression in particular populations (Harrap, 2003). The ability to determine the genetic contribution to complex disease under varying environmental conditions is extremely challenging. Furthermore, heritability may be overestimated when family data is used. Heritability is assumed to be present if siblings share a trait. However, relatives are exposed to more similar environments than random controls. Furthermore, as noted, genetic and environmental effects frequently interact leading to results that are difficult to decipher (Wright et al, 2003).

V) Chance

If chance events modify individual disease thresholds, extensive heterogeneity in penetrance[10] of genetic factors in late-onset diseases is expected. Indeed, genetic tests may be difficult to interpret due to variability at the individual level. Even alleles considered to be strongly penetrant such as, *APOE4* associated with cardiovascular and AD and the *huntingtin* gene in Huntington disease (HD) can be inaccurate in disease prognosis. As stated in the book, *Chance, development and aging*, the genetic test for HD does not predict age of onset. Additionally, normal and HD genotypes overlap, "such that some individuals with clinical HD have *huntingtin* mutations in the normal range; conversely some individuals with repeats in the diagnostic HD range have reached advanced ages in good health" (Finch & Kirkwood, 2000). In the same way, individuals who carry *APOE4* alleles may function normally because of variable allele penetrance. The *huntingtin* and *APOE4* examples could generalize to

numerous other genetic risk factors in which the extent of penetrance depends on other genes, on the external environment and, for example, on chance variations in brain architecture that modify disease thresholds or the amount of damage that can be sustained (Finch & Kirkwood, 2000).

If chance were an important mechanism in human biology and disease, the usefulness of genomics as a determinant of disease would be limited. The hopes that genomics may provide precise diagnoses and prognoses at the individual level could be questioned. Additionally, the classification of complex diseases via genetic categories presumes an unrealistic genotypic and phenotypic homogeneity. The determination of disease not only depends on identifying genes but increased knowledge of (and respect for) genetic variability, wider environmental influences and the role of chance in human biology.

SECTION TWO

A MEDICAL PARADIGM

Medical genetics research exists within the present medical paradigm. The current paradigm reflects a personalized, biomedical approach. This approach influences the types of research carried out, the framing of research questions and the interpretation of research data. The reasons why one medical genetics theory gains popularity over others can be partially explained by the overarching medical system and its biases. Currently, a certain view of medical genetics—the CD/CV hypothesis—is widely endorsed. The popularity of the hypothesis can be related to its potential conformity with the personalized biomedical paradigm. This paradigm is technology-dependent, favours a biological approach to disease and focuses on tailored therapies for the individual with less attention to the social and

environmental. In this section, the biomedical paradigm is described in detail in order to position the aforementioned medical genetics research models within the contemporary medical landscape.

I) How we frame research questions

The way we view genetic architecture and medical genetics influences (consciously or not) the way in which we frame research questions and analyze and interpret genetic data. "Scientific reductionists are trained to minimize complexity" (Wright & Hastie, 2001). Disease diagnosis and prognosis would be simplified if reduced to genetic causes, and further simplified if genetic causes were catalogued and categorized. In addition, "clinicians can visualize and use and are, therefore, in favour of simple approaches" (Choi, 2002). If genetics were to be useful in the clinic, it would have to be practical, easy to use, and provide consistent and useful results. The ideal scenario would, therefore, reflect the views of the NHGRI and the success of the CD/CV hypothesis. Thus, despite the many challenges to these views such as the CD/RV hypothesis and disease models that illustrate human biological complexity, researchers continue to look for ideal, tractable genetic explanations.

The ability to attach meaning to our genetics through classification would lend greater facility to medical genetics. Mapping is portrayed as an aid to disease-gene identification, classification and the cataloging of genetic variation. Unfortunately, very little is known about the mechanisms of disease or the functions of most genes and their alleles. By HGP reasoning, future technology and statistical models will be the potential simplifiers and the genetic categorizers of disease. The implicit hope is that future developments will make sense of the accumulated genetic information. However, since there are attempts to promptly use this knowledge in the clinic to

provide diagnoses and potentially alleviate illness, there is a need to exercise caution with the types of labels used. Genetic classification of health and illness needs to be more than simply an "arbitrary dividing line drawn between conditions that form a continuum to construct categories of convenience" (Lippman, 1998).

Current mainstream genetics research focuses on a single, dominant paradigm reflected by the aims of the HGP. Research questions are thus framed by the desire to reach an ideal goal. Our gaze becomes directed toward models or explanations of models that would best facilitate this desire. But, why should the genetic architecture of complex disease be different from that of mendelian diseases which have surprised many investigators by their complexity and heterogeneity (Scriver & Waters, 1999; Pritchard & Cox, 2001). Joseph Terwilliger and Kenneth Weiss are two vocal critics of the current direction of medical genetics research who point out that our genetic architecture may be less than ideal for the purposes proposed by medical genetics forecasters. Terwilliger and Weiss (2003) have brought attention to the politics of medical genetics research and characterize the situation thus: "Naturally, questioning the system and its vested interests does not generate friendly responses, in this [medical genetics/genetic epidemiology] or any other field of human endeavour."

Despite reams of information via mapping projects, genetic linkage, association studies, and theoretical development, the gap between existing genetic data and its clinical relevance remains wide. The result of the HGP focus on technology development "is an inundation of data whose amount far exceeds our capacity to understand [and] has driven us in confusion away from real hypotheses towards bioinformatics to sift through [and] search for patterns" (Terwilliger & Weiss, 2003). The result is that health professionals, researchers and patients do not know how they should interpret genetic information. "Expert consultation is decisive

information consisting either of good or bad news, but at present genetic knowledge is fragmentary and incomplete" (Smith et al, 2000). Yet, according to the CD/RV model, genetic information describing health and disease for the majority of individuals may never be more than fragmentary and incomplete. Furthermore, polygenes, environmental contributors and chance events all add layers of complexity so that each disease and each case may require their own course of action.

Population-based methods of gene discovery (such as association and LD studies), as well as the clinical characterization and design of disease interventions, depend on the existence of a relatively simple allelic spectrum (Reich & Lander, 2001). The CD/CV supporters hope that their theories will provide the basis on which medical genetics can be used in the clinic. The NCBI boasts that, in the near future, physicians will use "hand-held instruments" containing SNP profiles[9] "to quickly diagnose cancer or other diseases during routine office visits" (NCBI, 2004). Theoretically, genomic classification of individuals could lead to prevention, diagnosis and treatment of disease. "[These] hopes for the revolutionizing effect of genomics have been pinned on the gene chip or affordable ways to sequence each patient's genome, leading to tailored therapy" (Cooper & Psaty, 2003). However, in order to reach this stage, researchers espousing the CD/CV model will need to face many challenges. Most researchers agree that the deciphering of complex disease from a genetic basis will be extremely difficult.

"The reason experimental animals provide such a powerful tool is [that] they experimentally eliminate all variation other than at a single locus...essentially making a complex trait monogenic" (Terwilliger & Weiss, 2003). This procedure can be mimicked in humans by studying homogenous populations, pedigrees or large numbers of affected individuals or relatives. Of course, researchers cannot control for

variation in human subjects as well as they can in laboratory animals. Nevertheless, in order to achieve a more than marginal genetic-signal to noise ratio, medical geneticists have largely confined themselves to the clinical extremes (Wright & Hastie, 2001). So as to fulfill the simplified CD/CV goal, researchers have restricted their attention to particular subtypes of disease, in specific populations (Terwilliger & Weiss, 2003). Thus, the practical problem, the need for a clinically simple genetic-disease correlation, could be realized only very rarely (context and population dependent). Genetics becomes generally less informative than the average risk factor that is "neither necessarily nor sufficiently causal at the individual level [and has] only modest associations at the population level" (Rockhill, 2001).

The CD/RV model (and the other disease models that focus attention on the complexity of disease) claims that genetic variation is not easily simplified or interpreted and genetic classification of disease is of limited applicability. "To date, both association studies and genome-wide scans have identified only weak and inconsistent genetic signals for the underlying conditions, such as hypertension and diabetes (Cooper & Psaty, 2003). Yet despite the challenges, large-scale genetics projects continue to be funded and the idea that genetics is a useful indicator of disease continues to be favoured. Rather than focusing on a single dominant research model with a only few investigators defining the research questions to be explored, more evidence is needed to demonstrate that the CD/CV model could work, that human genetics could be applied reliably in the medical clinic and is worth the attention.

II) Personalized genetics

The individual level and population level are two separate entities with two different objects of explanation. The "Prevention Paradox" illustrates this distinction of levels: "A preventive measure which brings much benefit to the population offers little to each participating individual" (Rose, 1985). However, overall patterns are capable of being detected at the level of populations or society. When delineating the genetic architecture of disease, it is conceivable that patterns may emerge at the population level, if the particular genetics were common. From the perspective of medical genetics, the 'population attributable risk[11]' would be greater if an allele had high population prevalence. The level of the population attributable risk of a specific risk factor helps determine the public health significance of that risk factor (Merikangas & Risch, 2003). However, as mentioned earlier, genetic factors can be highly variable, display plasticity and, according to some researchers, are often rare in the general population. Many rare, variable genetic risk factors can be isolated (under very controlled conditions) but do not carry with them a measurable degree of effect on disease risk (Terwilliger & Weiss, 2003).

In attempts to apply medical genetics to individuals within the general population, it is important to keep in mind that each person has their own genetics, physiology, culture, psychology, and profession. There is a plethora of possible causes for illness or health within each individual. Knowing the precise causal sequence of events that lead to a particular individual's disease state (if indeed this were possible) would not provide an appropriate explanation of the disease nor would it necessarily lead to prevention or cure. "Disease pathogenesis at the individual level is a very complex process" (Rockhill, 2001). Regardless of the difficulties in delineating the multi-factorial causes of disease at the individual level, attempts at

explanation have been made. "Studies have focused on the testing of risk factors as causes, in an attempt to explain why some individuals get sick while others remain healthy" (Rose, 1985). Risk measurement procedures allow the "circumscription of individual pathology" (Dean, 1999). The idea is, with a greater understanding of genetic risk factors and what they imply (quantitatively and qualitatively) a "uniquely defined disease risk" for each individual will surface (Risch et al, 2002).

Personalized medicine is based on the idea that individual genetic variation will be classifiable and associated with a degree of risk for disease. Future personalized (or individualized) medicine entails screening each patient for disease risk by analyzing their genetic profile for specific SNP patterns associated with disease susceptibility (NCBI, 2004). However, "risk individualization denies the prevention paradox and implies that most epidemiological risk models are accurate in predicting the future of a specific individual" (Rockhill, 2001). As per the individualized medicine model, population level studies will lead to the identification of common genes of known disease risk and accordingly, this information will be used to more accurately diagnose or treat the patient. Yet, the link between population, aggregate level risk and individual level risk has not been clearly explained (Rockhill, 2001). Causation at the individual level is more difficult to ascertain. Additionally, if the CD/RV hypothesis is correct and many, rare variants of weak effect are involved in disease manifestation, no generalizations about allele effect on disease risk will be possible. "To pretend that we can make elaborate predictions of disease at the individual level is to make rather immodest claims of our understanding of causation" (Tam & Lopman, 2003).

The design of studies in which susceptibility genes are isolated necessarily complicates estimations of risk in individuals who bear these genetic variants

(Terwilliger & Weiss, 2003). Researchers use strategies that inflate the apparent effect of genes on disease risk in order to increase the power to detect and map genetic variants. Classic genetic studies involve the investigation of families and ethnic groups with high disease incidence for shared genetic variants. Specific families and ethnic groups are studied with "non-independent exposures to the risk factors [sought], irrespective of the risk factor exposure distribution in the population" (Terwilliger & Weiss, 2003). This allows the identification of genes and their alleles in rarified populations but does not explain why people become diseased and does not approach the population attributable risk. In addition, rare alleles of weak effect will not be useful at the population level because they confer only small relative risks[12]. Alternatively, "it may be possible to identify many polymorphisms that each weakly predict risk of disease and combine them into a risk score that more effectively predicts disease" (Willett, 2002). Unfortunately, correcting the effects of many variants may be immensely difficult since the variants themselves may have multiple mechanisms (detrimental and beneficial in the same individual and variable across populations), not to mention the fact that genetic risk factors are at present "non-removable" (Terwilliger & Weiss, 2003).

Inferring genetic associations from the population to the individual or from rarified groups to the general public is not entirely legitimate. Unless susceptibility genotypes are common and have a moderately large relative risk, they will be of limited screening or testing use in the clinic (Holtzman & Marteau, 2000). Otherwise, many individuals could be labeled high risk while remaining free of disease and many cases of disease could be missed. To the clinician, genetic susceptibility would resemble a myriad of symptoms (like that of many late-onset diseases) common in patients but only slightly more so than in persons without the condition, yielding weak

predictive values (Cooper & Psaty, 2003). Before clinical use may be sanctioned, genetic associations and their related risks require a greater degree of certainty than currently exists.

III) Societal health versus the biomedical disease model: who will benefit from the "genetics revolution?"

The biomedical model of disease[13] has ethical implications for public health and genetics. The biomedical model focuses attention primarily on the individual and individual risk. According to this model, once one's personal risk is known, disease can be prevented or treated through the correction of faulty biological processes. Furthermore, "this system gives primacy to personal autonomy and action and seeks to induce personal behaviour change rather than to promote social interventions" (Rockhill, 2001). The genetics of disease, which belongs to the biomedical model, also focuses attention on the individual as the point of action. "The alleged predictive ability of genetic testing...feeds into current notions of individual responsibility for health and health improvement" (Lippman, 1991). Control over one's own health is expected to arise simply by knowing one's genetics and subsequently manipulating defective biological mechanisms, most likely, via drug interventions. Yet, this perspective is descriptive rather than explanatory, reactive as opposed to proactive in application and does not provide insights into the underlying factors that influence biological processes (Tam & Lopman, 2003). Rockhill (2001) notes three potential dangers in designating the individual the sole locus of risk: 1) the "amplification of existing socioeconomic health inequities;" 2) the "labeling of risk factors as the 'causes' of individual cases of disease;" and 3) the resultant "indifference to the social determinants of risk factor distributions [that leads] to ineffectual disease prevention

policies at the population level." These three potential problems will be discussed further with respect to medical genetics.

The focus of the biomedical disease model on the individual can lead to the "exaggeration of personal agency" (Farmer, 1999). Risk factor epidemiology can bring about the "victimization of individuals [through] the assumption that behavioural change alone is a realistic intervention given the strong cultural, social and economic forces that are exerted on individuals" (Tam & Lopman, 2003). This framework assumes that all individuals have access to immediate medical care and that all individuals have the ability to change their "lifestyles" or avoid the risks thought to be associated with genetics. Personal responsibility for illness can lead to a "moralistic tendency to blame individuals for their own poor health outcomes" (Rockhill, 2001). "The transfer of accountability from society to the individual potentially redefines 'being ill' as 'being guilty' and makes illness a matter of personal responsibility (Gillick, 1984; Lippman, 1998). However, unemployed or low-income individuals do not have equal access to healthcare and may have little ability to change their circumstances (Farmer, 1999). In addition, as genetic medicine focuses more on individual risk it becomes less practical for low-income countries (WHO, 2002).

"Gen[etics] gives undeserved attention to the idea of discrete causes and the silver bullet" (Cooper & Psaty, 2003). The focus on individual genetics as an indicator of potential disease and the discussions of the potential use of "hand-held DNA profile devices" in the clinic tend to imply that our genetics are causal or deterministic. Bell (2003) has written that "[a]n understanding of genetic basis of maladies is providing a new taxonomy of disease, free from the risk that the diagnostic criteria related to events are secondary to the disease process, rather than to

its cause." The idea insinuates that our genetics can either be used as a drug target to "cure" disease or that the biological process affected by the genetic mutation can be "fixed" using preventive drug therapies. "The genetic approach seems to provide a 'quick fix' to what is posed as a biological problem" (Lippman, 1991). In this way, the promotion of expensive individualized therapies takes precedence over complicated social and environmental determinants of disease that warrant greater exploration as factors contributing to fundamental health inequalities.

"Simply looking at differences between decontextualized groups of individuals can lead to what could be termed 'outcome bias,' a failure to recognize that disease distributions in different populations can be affected by a whole host of social factors that influence individual risk (e.g. local food production, global food trade, marketing of foodstuffs, and social changes leading to decreased physical activity)" (Tam & Lopman, 2003; Farmer, 2004). As mentioned in previous sections, the design of medical genetic studies not only creates difficulties for the estimation of disease risk in the general population but also creates decontextualized genetic categories. Additionally, by focusing attention on the genetics of disease and on biological differences, health determinants beyond the individual are ignored. Within the biomedical/genetics disease model, biological variations that create differences between individuals are often seen as preventable or avoidable while social conditions that create similar distinctions are likely to be perceived as intractable givens (Lippman, 1991). The perceived points of manipulation are the biological processes or the genetic markers that indicate imminent disease. Yet, risk factors are not merely attached to individuals but are conditions with a collective dynamic (Lippman, 1998).

Given the many challenges facing the proponents of the HGP, it is fair to ask whether there is sufficient evidence that genetic categories and classifications will be

useful. The current favoured genetics disease model, the CD/CV model, conveniently represents the best-case scenario for isolating disease-associated alleles for future medical uses. Beyond biology, "the process of 'geneticization[14]' is political because it redefines what we take to be significant differences between people and empowers new people and institutions to make these redefinitions.... Health, however we define it, cannot be conceptualized without reference to politics and the power to name" (Lippman, 1998). The call for the redefinition of disease via genetics (Collins et al, 2003; Bell, 2003) brings with it the potential to divert attention away from important social and environmental disease determinants forcing many investigations under the genetic mantle. The questioning of the accuracy of the CD/CV hypothesis by those who support other disease models, most notably the CD/RV hypothesis, begs the scientific community to broaden its view. "It is important to take realistic stock of what we know, where we are, where we want to be going and how to get there" (Terwilliger & Weiss, 2003).

SECTION THREE

ETHICAL ANALYSIS: SCIENTIFIC RESPONSIBILITY

The way in which genetic variation and disease are viewed has broad ethical implications. This section will use a framework of analysis of scientific responsibility to explore these implications and how to address them. Scientific responsibility is presented in this thesis as a process involving three steps where the goal is to lead to a more critically aware scientific community and a more useful and equitable medical genetics research. Thus far, I have documented several contemporary medical genetics models and a popular biomedical disease model. I have argued that the CD/CV hypothesis is favoured, not necessarily because it presents the most powerful

evidence, but because it represents the ideal model fitting squarely within the biomedical paradigm. The CD/RV hypothesis, the polygenic model of disease and other models that take into consideration the effects of social and environmental factors on disease manifestation are alternative models. Most notably, these genetics models would not be useful to physicians treating the majority of patients nor to drug companies searching for genetic targets for the reasons described above.

The HGP and its related projects have received plenty of attention and funding. Francis Collins et al (2003) stated, "genomics has become a central and cohesive discipline of biomedical research." Promises have been made by researchers as to their ability to provide unequivocal associations between genetic variants and an individual's health or health prospects. Additionally, "revolutionary claims have been made about the ultimate impact of genetics on clinical medicine" (Holtzman & Marteau, 2000). As stated above, the model that best fits the promises and hopeful future is the CD/CV model. Most contemporary large-scale genetics research projects are based on this model and the idea that a "genetics parts list" will delineate normal/abnormal or healthy/diseased individuals. Some researchers have stated, "further investment in 'whole genome' genetic analysis as a way to predict someone's future disease should wait until we have positive examples of how this information will be useful" (Cooper & Psaty, 2003).

In the discourses directed to decision makers, and to other audiences as well, in view of promoting and explaining the HGP and related projects, medicine is providing most of the rhetorical justification (Limoges, 1994). Thus, medical genetics research bases most of its value on the connection of scientific knowledge with the potential application in preventive or therapeutic interventions, programs and policies. "The ultimate goal of all medical research is the reduction of morbidity and mortality

through prevention and treatment" (Merikangas & Risch, 2003). Additionally, "the health of the public is a social good [and] the same can be said of scientific knowledge" (Weed & McKeown, 2003). Many scientists believe that they ought to "have the right to follow their curiosity in understanding the causes and determinants of diseases" (Weed & McKeown, 2003). Yet, while this allows science to be free, this does not necessarily promote a reflective science (Funari, 2002). Scientific knowledge and medical research are social goods in themselves; however these goods carry responsibilities. These responsibilities can be to any number of entities including the general public (who are partners in research as subjects, potential beneficiaries of research and indirectly major funders through government), and to their profession (in the search of new theoretical avenues and in the free and open expression of opinions or reservations).

Lippman (1998) finds, "no clear separation of research, medical practice, politics and health." As noted above, scientists, thus, have a responsibility to be aware of these interwoven subjects and to appreciate their relevance to everyday professional (research and clinical) practice. For example, in Britain, the difference in lifespan between the most and the least affluent is eleven years, which dwarfs anything that genetics might explain (Jones, 2000). Health, disease and medical genetics are necessarily political because they are social, reflect societal values, affect communities as well as individuals, reveal power inequalities and involve policy at the government or professional level and choice (or lack thereof) at the public level. Yet, genetics researchers often do not discuss power relationships or social and environmental influences on disease manifestation—essentially, that which is political. Nonetheless, "scientific knowing [has a] social context that shapes what we know, how we know and what we ask; it is also a context in which we dwell in a

mutual relationship with society and other scientists" (Weed & McKeown, 2003). Genetics researchers have specialized knowledge and the power to name and classify. "Key questionings occur, and ought to, upstream, while and where the science is being done, in the scientific process itself: before the technologies and procedures have been packaged and black-boxed, crucial conceptual decisions, as well as strategic choices, are already being made" (Limoges, 1994). Without scientific responsibility, our theories are open to becoming biased, exclusionary and unwise. An ethical approach to medical research allows an evaluation of how researchers ought to act and aids investigators to make the best choices. Ethical guidelines for health professionals are usually based on general ethical principles and obligations such as, respect for persons, beneficence and nonmaleficence. Scientific responsibility suggests, further, a way of thinking and acting so that researchers may place themselves within the wider community and appreciate the relevance of ethical principles and responsibility to everyday professional practice.

This section will discuss the steps in the process to achieve scientific responsibility in the research environment. Scientific responsibility not only requires a more vigilant education at all levels of study but also requires a new way of thinking and acting within the research community. The first step, scientific discourse, is at present taking place among geneticists and, to a lesser degree, physicians within the medical genetics field. The second step consists of the development of awareness, professional commitment and humility. The third step returns to scientific discourse but with an added element, the politicization of this discourse through effective self-criticism. This final step fosters meaningful debate among scientists, allows for the development of more germane medical genetics research models and ethically prioritizes distribution of funding to those projects deemed useful and robust. Once

scientific responsibility has been defined, a link will be made between scientific responsibility and justice issues. Additionally, scientific responsibility will be discussed specifically with respect to medical genetics research. Finally, I will ask whether researchers are capable of being scientifically responsible. Although all scientific research needs to be carried out responsibly, medical research is especially in need of an ethical approach because it has direct impact on the public and public health. Researchers involved with the HGP justify the project through its future medical benefits. However, as I have documented, many uncertainties and complexities surround the potential medical uses of genetic information for most common diseases in the general population. Scientific research carried out to acquire knowledge about our human genetics or our evolutionary history is integral to the development of the subject of genetics. In a more modest role of seeking basic understanding, genetics may not necessarily create information of immediate medical or commercial interest but simply of use to our biological understanding.

I) What is scientific responsibility?

Scientific responsibility, as defined in this thesis, is a social and professional conscientiousness and accountability necessary to the good practice of scientific research. From the medical genetics perspective of this thesis, "good practice" refers to research that is just, effective and based on healthcare needs. Scientific responsibility is especially, but not exclusively, important to the sciences attached to public health, clinical medicine and other medical applications. For this reason, the development of medical genetics research models requires a responsibility of good practice within the research profession and toward the public. The implication of scientific responsibility at the level of basic research may not be obvious since

responsibility has rarely been considered a prerequisite to the development of basic medical research models. Currently, researchers do not feel compelled to abandon scientific theorizing or project development because some of their uses may have questionable social consequences or because they raise ethical dilemmas (Limoges, 1994). Yet, if science is to be carried out for the social good, the critical examination of the directions of basic research is crucial, especially in medical science. Below I examine the process of scientific responsibility realized in three essential steps that of: 1) scientific discourse; 2) the development of the nature of scientific responsibility; and, 3) effective criticism.

Step one: scientific discourse

Basic scientific research is not consistently objective or devoid of value judgments. As Limoges (1994) documents, "matters of 'ethical' significance might already have been given shape in actual scientific processes." Limoges (1994) discusses Erwin Schrodinger (1944), one of the forefathers of molecular biology and genetics,

> "[Who] did not conceptualize mutations as errors of copying or replication, but rather as different 'readings' or 'versions' of the 'code-script.' [Schrodinger] even emphasized that while it might be tempting, it would nevertheless be entirely wrong to regard the original version as 'orthodox,' and the mutant version as 'heretic.'"

Limoges continues, ideas about 'normal' and 'abnormal' genes or allelic variation did not surface until many years after Schrodinger's writings. The value-laden language describing "error" or "damage" to the DNA molecule leads to calls for "correction" or "repair" (Limoges, 1994). "Questions relative to normality, to the biological differential characteristics of our species, to the characterization of mutations as genetic 'errors,' to the polymorphisms that contribute toward differentiating each of

us as individuals to what counts as normal or abnormal variation—these are questions to be dealt with in the process of doing science" (Limoges, 1994). The way in which scientists name genetic processes and variations reflect value judgments and power wielded. Importantly, power and knowledge brings with it a corresponding scientific responsibility for how they are used.

As Limoges (1994) maintains, while the language of "categorical thinking" in molecular genetics still exists, and may have found reinforcement in the wake of the HGP movement, such language may not be unproblematic for scientists. Researchers are capable of taking part in scientific discourses where opposing views are aired and defended. In fact, the first part of this thesis documents the discussions between researchers on the relative importance of human genetic variation in disease manifestation. While the CD/CV hypothesis is popular within the genetics field, pockets of alternative discourses have arisen. I argued earlier how the CD/CV theory reflects the mechanical, categorical thinking that has influenced the development of genetics. The language used to describe the "classification of genetic variation," the search for a "simple allelic spectrum" that reflects the "typical" patient and the ability to identify mutant "disease/susceptibility genes" to "cure, treat, prevent" or fix disease exemplifies what has become the traditional genetics discourse. The language implies that genetics is simple and could be easily used to classify healthy and diseased individuals. The diseased individuals could then be targeted and treated with drug interventions or with a change in lifestyle.

An alternative discourse has been assumed by the CD/RV, polygenic, and other theories that draws attention to the complexities of human genetics through its relation to health and disease. Genes, according to these theories, are part of a myriad of factors and pathways that lead to illness and may even be an irrelevant factor to the

development of disease in most individuals. In fact, under these circumstances, it is difficult to classify individual genetic risk because the risk factor distribution in the general population and in the disease population overlap. "Average patients have average genetic effects" (Wright et al, 2003). Some scientific researchers themselves are questioning the direction and methods of large-scale genetics and "the logic behind it" (Terwilliger & Weiss, 2003).

While scientific discourse reflects a healthy dialogue amongst researchers, our goal of "scientific responsibility" would fail if we were to stop at this level. This is only a first step. While many researchers have objected to a focus on the CD/CV hypothesis within the scientific discourse and have offered alternatives, genetics research continues in much the same way. Even as these scientists provide alternative points of view, they are not effectively critical. Those authors writing the alternative discourse dilute their arguments by being equivocal. In almost all cases, the most argumentative scientists conclude that their opinions "do not diminish the far greater potential of genetics for prevention and treatment" (Harrap, 2003), or that geneticists may be to blame for "overstatements and false hopes" but others may stand to gain from "exaggerating" the difficulties with genetics research (Jones, 2000). Other scientists mount very strong arguments only to conclude with statements such as, "there is no doubt the DNA science will continue in an incremental fashion to make important contributions to health and wellbeing" (Cooper & Psaty, 2003). Wright et al (2003) use their entire paper to state that large genetic effects will not be found in most cases of disease and yet they weaken their CD/RV argument by concluding that, "identifying genes with the largest effects, and which contribute most to the extremes of the disease or trait distribution, might be the most robust [genetics] approach." Thus, proposing in their conclusion that we embark on, what they claimed to be in the

body of their article, a mostly futile enterprise ultimately requiring a reanalysis of the "big genetics" research approach. In this way, scientific discourse is useful and important but does not go far enough in challenging the status quo.

Step two: the nature of scientific responsibility: development of awareness, professional commitment and humility

The second step in the process of developing scientific responsibility is crucial in order to adequately investigate the ethical implications of the current progress and funding of medical genetics research. The exploration of the nature of scientific responsibility will lead successfully to the final step of effective criticism and to a more useful and equitable medical genetics research. Awareness, professional commitment and humility are three parts that, I consider, compose the nature of scientific responsibility. These three parts are greatly derived from Weed and McKeown's work discussing scientific and social responsibility in public health (Weed & McKeown, 2003), the writings of Van Rensselaer Potter (1971) and a critique of Van Rensselaer Potter's *Bridge to the Future* (Funari, 2002).

The development of awareness, professional commitment and humility among scientific researchers can be undertaken in many ways. Traditionally, scientific responsibility has focused on integrity. In the United States, the National Academy of Sciences (NAS) published a volume in 1992 on responsible science called *Ensuring the integrity of the research process*. This report dealt specifically with misconduct in science defined as the "fabrication, falsification or plagiarism, in proposing, performing or reporting research." While the investigation of misconduct is an important enterprise, the report did not address the meaning of responsible science or methods by which scientific responsibility could be fostered and promoted. A recent

report by the NAS (2002) entitled, *Integrity in scientific research: creating an environment that promotes responsible conduct*, went further than the 1992 report in describing responsibility at the individual and institutional levels and by suggesting methods for the implementation of scientific responsibility. The NAS found that "no established measures for assessing integrity in the research environment exist." The report defined integrity in research (similar to scientific responsibility in this thesis) as that which "embodies above all the individual's commitment to intellectual honesty and personal responsibility [as] an aspect of moral character and experience." Institutions must provide "leadership and example, training and education, and policies and procedures, as well as tools and support systems" so that research teams may conduct research responsibly (NAS, 2002). According to this report, the main method of providing instruction in the responsible conduct of research is through educational programs "in the context of the research rather than as a separate entity." While this NAS report was more detailed than the 1992 report, the 2002 report did not describe fundamentally how the scientist's approach to research would change after the implementation of the NAS recommendations in order to allow for a more responsible research environment. In Canada, the Tri-Council Policy Statement for Human Research (a code of research ethics; MRC, 2003) and the development of Research Ethics Boards (the means by which the code of ethics is implemented) both fulfill a crucial role in the development of scientific responsibility.

As important as they are, improved integrity education and the development of guidelines for all basic medical research is insufficient to implement the process I propose. A change in attitude requiring a fundamental shift in how medical research is undertaken is required. Additionally, in accordance with the recommendations of the NAS (2002) the "responsibility of knowledge" (Funari, 2002) needs to be

incorporated into the science education curriculum at the undergraduate and graduate levels.

i) Awareness

The opposite of awareness in the context of scientific responsibility is a type of scientific "tunnel vision." Presently, most of the genetics research funding has been focused on the HGP and related projects. Researchers intimately connected to the HGP generally favour the CD/CV model. The alternative models that investigate the complexities of human biology need a stronger voice. The "new genetics" rather than being portrayed as "no more than another form of high-tech medicine, of importance to a few but irrelevant to the many" (Jones, 2000) is more often depicted as the leading edge of a medical revolution (Collins et al, 2003). In addition, the various medical genetics hypotheses call for different public health responses that could have different effects on healthcare in the long-term. For this reason, researchers need to be aware of the multiple hypotheses and their potential consequences.

Awareness can be described as "the need to look around [oneself]" (Potter, 1971) in order "to understand where our knowledge comes from and where it is leading" (Funari, 2002). Scientists ought to step back and take a more realistic view of contemporary genetics research and realize that we need a broader foundation of knowledge (Terwilliger and Weiss, 2003). We also need to be mindful of the cultural, political and social use to which our thoughts may be put (Calhoun, 1988). Thus, researchers need to not only be aware of the history of their subject, its present and potential applications, but also to its long-term consequences. To be able "to step back" or "to be mindful" allows the researcher to place herself in a greater context beyond her chosen field or area of study and to realize the wider implications of her

work. "Rather than leading us back to the ascetic surroundings of the laboratory, such considerations invite us on a longer journey, towards a consideration of the real responsibilities of knowledge" (Funari, 2002).

ii) Professional commitment

Professional commitment involves "commitment to positive action, to the pursuit and achievement of something of value, such as a social good" (Jonas, 1984). Professional commitment goes beyond commercial or self interest. This responsibility "involves a commitment to the fundamental ends of a profession itself" (Weed & McKeown, 2003). The goals of medical genetics and most human genetics research would be to identify, treat and prevent genetic disease. Yet, those researchers involved in the field of medical genetics are not just accountable to individual patients with genetic disease. In addition, their work has an effect upon the public. In attempting to apply medical genetics research findings to the general public as the HGP and large-scale genetics projects do, the scope of accountability of the medical genetics field expands beyond specific families, communities or individuals. Thus, researchers have a commitment to society as a whole.

Medical genetics researchers need to be committed to reliability. For many years, "geneticists have issued a stream of promises about what they will achieve; few have been fulfilled [and] medical providers must realize that the molecular biology business is as adept at promoting its wares as is any other" (Jones, 2000). Many claims and overstatements have been made about the potential usefulness of genetics in determining health and disease based on insufficient evidence. For example, association studies have been widely touted as an accurate means to isolate susceptibility genes. In a recent review of 603 reported disease associations (166 of

these associations had been studied three or more times), ascribed to 268 genes, only six associations were reproduced consistently (Hirschhorn et al, 2002). Whether the inconsistent results reflected false-positives or genetic effects too weak to be significant, is unknown. Regardless, the authors of the review expressed surprise at the lack of reproducibility of the genetic association research results and were concerned by the level of uncertainty surrounding these studies. Geneticists have a responsibility to their profession to speak reliably based on solid research and not on "wishful thinking" (Weiss & Terwilliger, 2000). General guidelines such as the Canadian Tri-Council Policy are important for research involving humans, but new tools and new ways of thinking and teaching also need to be developed for basic research in medical genetics. Of course, not only do researchers need to follow professional and research guidelines but they also must understand the ethical foundations of the guidelines and must have "an appreciation of their relevance to everyday professional practice" (Weed and McKeown, 2003).

iii) Humility

As mentioned earlier, many claims have been made about the revolutionary power of medical genetics. Projects are underway to create a DNA catalogue of all genetic variation. Once all the molecular level information has been gathered, "powerful technological tools" and statistical models will be developed in order to process the information. Genetic data, according to many researchers, will also give vital information about human biological processes and networks. In other words, we will know everything about human disease. This type of thought pattern comes, in most cases, from an excessive arrogance. Potter (1971) states aptly: we do not have "the knowledge of how to use knowledge." The consequence of this arrogance is not

favourable and could lead to the misuse of genetics research. "The beginning of wisdom...may invoke in us a decent respect for the far-flung web of life and a humility as to our limited ability to comprehend [human biology and] all the repercussions of our technological arrogance" (Potter, 1971). If the components of scientific responsibility discussed thus far were incorporated into the education and professional conduct of scientific researchers and a more open scientific discourse were encouraged, more scientists may be humble and cautious in the face of human biological complexity and would be in a better position to see how medical genetics research is ethically and socially placed.

Step three: effective criticism

Scientific discourse and effective criticism are similar yet fundamentally different. The main difference between the two is that effective criticism is political. Those researchers who are effectively critical of the current dominant medical genetics models use political language in describing their position in the scientific landscape. These researchers are also critical about the dominant biomedical paradigm that affects the wider community and environment. Probably the most political criticizers of the current large-scale genetics projects are Joseph D. Terwilliger (Department of Psychiatry and Columbia Genome Center, Columbia University) and Kenneth M. Weiss (Departments of Anthropology and Biology, Pennsylvania State University) whom I have quoted liberally in this thesis. Terwilliger and Weiss refer often to the obligation of scientists to question the course of recent medical genetics research and to remember their responsibility to the public and to their patients. However, even these well-established researchers complain that, "questioning the system and its vested interests does not generate friendly responses"

(Terwilliger & Weiss, 2003). Most investigators criticizing the current dominant genetics models and paradigms dilute their arguments with caveats to their continued support of (perhaps a less aggressive form of) those same models and paradigms. Yet, if a scientific discourse were encouraged, along with the above-mentioned awareness, professional commitment and humility, in everyday laboratory work and student learning environments, effective criticism may become more accepted within the scientific community.

Farmer and Gastineau Campos (2004) talk of "resocializing" the medical ethics field. Their views could also be applied to medical genetics for the purposes of this thesis. In effect, the authors' resocializing or positioning medical ethics within a greater social and political context allows for a more effective criticism of dominant medical models and paradigms. Largely, medical genetics does not address the basic needs of the poor since their immediate needs include such essentials as, access to food, healthcare, education, housing and clean water. "The research enterprise…is a fundamentally inegalitarian exercise in the sense that medicine and science are expanding rapidly, but in a social context of growing global inequality, which ensures that the fruits of medicine and science are not available to many who need them most" (Farmer & Gastineau Campos, 2004). Farmer and Gastineau Campos (2004) quote Brody (1992) in that, "the word *power* is essentially absent from the vocabulary that scholars of medical ethics have constructed for their discipline." It would also be fair to state that the discussion of power is absent from the medical genetics discourse. Yet, Holtzman and Marteau (2000), two medical geneticists, have brought attention to the idea that,

> "In our rush to fit medicine with the genetic mantle, we are losing sight of other possibilities for improving the public health. Differences in social structure, lifestyle and environment account for much larger proportions of diseases than genetic differences[15]."

Medical genetics would take a more realistic back seat to greater, more obvious medical problems "by restoring to these problems more of the social and historical complexities inherent in each of them" (Farmer & Gastineau Campos, 2004). In this way, using political language and advocating on behalf of unempowered communities would be part of effective criticism in the field of medical genetics research.

II) Why is scientific responsibility needed in medical genetics research?

Thus far, I have documented the current scientific discourse surrounding medical genetics research models. I have explored a popular research model—the CD/CV hypothesis—that exists within the prevailing medical paradigm—the biomedical model. This hypothesis fits well within the biomedical model and, ideally, could provide physicians with an easy method for disease diagnosis and prognosis and, conveniently, could also be economically viable. The other models are less optimistic about the possible use of genetics in the medical clinic for the general public. Far from presenting an ideal scenario, the CD/RV, polygenic and other marginal disease models bring attention to the complexities of human genetics, biology and the social environmental factors that impact on health and disease of individuals. These alternative hypotheses do not predict obvious drug targets or powerful DNA chips to revolutionize medicine. However, they provide research evidence that suggests a more restricted, modest and realistic path for genetics research.

Even if the CD/CV hypothesis proves to be fallacious, we could still acquire knowledge from the research being carried out in its name. Ultimately, is it mistaken to follow the CD/CV model approach? While it is true that we have and probably will continue to learn something more about human genetics through the research done by

the investigators who support the HGP related projects, this approach has only a narrow reach. The allocation of research resources is to a small group whose research methods are technologically dependent. This approach minimizes biological complexities, focuses on the individual and attempts to genetically classify and categorize illness and health. Investigators and investors are interested in the identification of genetic variants that can accurately inform about disease risk, leading in turn to the development of tests and drug targets. However, while all medical genetics research models are at a strictly theoretical level and cannot provide definitive information on individual genetic risk, some researchers may exaggerate promises in order to obtain research funding. "A decision to invest in one concept of disease inevitably is a decision not to invest in something else" (Terwilliger & Weiss, 2003). When all our expectations are placed on one theory, this jeopardizes the development of other theories. Also researchers cannot embark on alternative investigations. This ultimately negatively affects vulnerable populations to whom scientists should be responsible.

Presently, as the first part of this thesis has shown, scientific discourse exists amongst medical genetics researchers. However, this discourse stops short of being aware, publicly accountable or humble. The scientific discourse is not sufficiently critical. Without these characteristics of scientific responsibility medical genetics research has followed almost entirely a single, exclusive theory that precludes thorough investigation of other research avenues and may even be detrimental to the effectual advancement of medical genetics itself. The next subsection will illustrate how scientific responsibility may be implemented in order to improve medical genetics (and other medical) research and hopefully impact the types of research

done, the application and interpretation of genetic information intended for the clinic and address research inequalities.

i) Scientific responsibility and justice: resource allocation in medical genetics research

Theorists have written on various approaches to justice such as social justice, corrective justice and, discussed in this section, distributive justice which is most relevant to this thesis. The principles of distributive justice are "normative principles designed to allocate goods in limited supply relative to demand" (Lamont, 2003). "A theory of distributive justice is an attempt to establish a connection between the properties or characteristics of persons and the morally correct distribution of benefits and burdens in society" (Beauchamp & Childress, 1989).

Scientific responsibility and justice are linked in that the former directs medical genetics (and other) research toward just outcomes. Medical genetics researchers are responsible to the general public for a variety of reasons. The public indirectly funds, through government, most research. Scientists have a responsibility to conduct the best possible research that is in no way frivolous and that will benefit the public as a whole. The research carried out by medical genetics investigators has effects on the public. Healthcare may be affected, not to mention the classification and meaning of disease. If, some medical genetics models (because of their lack of commercial viability) are marginalized, the public will eventually bear the consequences of the lost potential due to a narrow research focus. Lastly, if the medical genetics researcher were also a physician, this researcher would have a fiduciary duty to his or her patients and a therapeutic obligation to members of the general public.

Researchers are especially responsible to the least advantaged. The way in which the "least advantaged" has been defined in this thesis is related to those within society whose healthcare needs are marginalized. As mentioned earlier, presently, the biomedical model focuses attention on the individual through personalized prognosis and diagnosis using, for example, DNA profiles. The assumption is that the public's basic medical needs are met and that all individuals have equal access to medical care. Medical genetics concentrates on this idealized, individual patient to the detriment of the marginalized patient who does not have access to services and could greatly benefit from basic public health research. Public health research would be of more immediate benefit to the marginalized group since the idealized individual would, regardless of their DNA profile, have greater access to all diversities of modern medical care and likely be more healthy. In this way, investigators and funders would favour research that aided the marginalized patient and research fields such as medical genetics that benefits the most advantaged individuals would receive less funding than it presently enjoys.

Scientific responsibility is also linked to justice with regards to the promotion of equal opportunity for all scientists reflected in the scientific discourse surrounding the various medical genetics research models described above. At present, an elite group of medical genetics researchers promoting the dominant research model receive most of the funding and attention within this field. The allocation of funding and review of public research needs to take into account the marginalized medical genetics models that warrant greater notice. Those projects with no obvious financial benefit need also to be funded and equal opportunity needs to be given to those alternative points of view in order to promote vigorous medical genetics research. Other marginal subjects such as evolutionary studies should receive a greater

percentage of the funding because it could aid in fundamental knowledge of human population structure which is integral to medical genetics model development. The level of our understanding of genetic architecture continues to be rudimentary and until we develop our knowledge of basic genetics it is not just or wise to favour one hypothesis over another.

The current distribution of resources may not give sufficient consideration to need, usefulness and contribution to knowledge. Those scientists and policymakers who render decisions about the types of research undertaken or who formulate criteria for the projects that receive funding, are those who have power to determine the scientific "agenda." These decision-makers ought to give greater consideration to a broader range of topics. For example, I would argue that because the CD/CV hypothesis, by many standards, has not been sufficiently substantiated, it is not possible to justify the degree of attention it has received. The research community and policymakers need to be open to alternative theories that may lead to fruitful research. Medical genetics investigators need to be encouraged to pursue research committed to the promotion of health for those populations in need, not simply to those industries with the deepest pockets. Additionally, those with decision-making power should ask whether the current use of resources diverts funds from areas that critically need development.

In the conclusion of their paper entitled, *Genomic priorities and public health*, Merikangas and Risch (2003) propose several criteria to establish priorities for genetics research. The highest priority for medical genetics research, according to the authors, should be complex diseases with the strongest genetic effects, where there is limited ability to modify environmental or other external risk factors and of high public health impact. In addition, for those disorders with weak or questionable

genetic effects and for which genetic tools may have less impact, non-genetics public health approaches may ultimately lead to far more effective prevention and intervention (Merikangas & Risch, 2003). Thus, those in need of basic public health resources would greatly benefit while the development of, for example, DNA medical profiles benefiting few, would be scaled back. Through these criteria, medical genetics research is therefore set in more realistic terms and, consequently, becomes situated humbly and fairly within the health sciences. This article by Merikangas and Risch goes some way toward articulating what might constitute a just and scientifically responsible goal of research.

ii) The implementation of effective criticism

As stated above, the primary difference between scientific discourse and effective criticism is that the latter is political. Effective criticism encourages the scientist to place herself within society and the greater environment. From this position, the researcher can act on her position within the scientific discourse and feel comfortable in questioning (or upholding) the status quo. By restoring to scientific and especially medical research the social and historical complexities inherent in them, related ethical dilemmas will have a greater chance to be uncovered, discussed and acted upon. The egoism and bias associated with considering the human race as one big pedigree, easily deciphered through "categories of convenience," ignores important biological, social, historical and environmental complexities.

"The genetic approach seems to provide a 'quick fix' to what is posed as a biological problem, directing attention away from society's construction of a biological reality...and leaving the conditions that create social disadvantage [such as poverty, racism, etc] largely unchallenged" (Lippman, 1991). From the genetic

perspective, health is individual and medical, not public and political. To challenge medical genetics research and the biomedical paradigm, researchers need to be at ease with criticism and questioning "big science." Presently, alternative discourses are being posed in the scientific literature but we also need a more prominent position for the questioning of specialist knowledge and what lies behind it. In addition, we need to reexamine the role of science and the relationship between ethics and science (Funari, 2002).

The HGP-related research focuses on technological answers to health problems, DNA profiles and individual optimization of health. If serious criticism were encouraged, other theories that present a more wholistic and realistic genetics may gain some clemency as opposed to suspicion. Effective criticism could encourage more types of research and the examination of other avenues altogether. Rather than bringing medical genetics research to a halt, criticism could create more research opportunities that reach more people.

III) Are scientists capable of scientific responsibility?[16]

Scientific responsibility is needed within medical genetics research in order to emphasize conditions in which people and communities can be healthy. Medical genetics research is not solely based on genetics discoveries; the goal is for research findings to be applied to improve the health of the population. Medical genetics researchers are almost universally engaged in the practice of laboratory research but are not equally active in the scientific discourse surrounding their subject. Very few geneticists are effectively critical or actively committed to the promotion of the social good of the knowledge which they assume. Is commitment to scientific knowledge alone sufficient to the actualization of health or is more required? Investigations

undertaken in a medical genetics laboratory may eventually be applied in the form of decisions made in a clinician's office. The responsible researcher with specialist knowledge is well situated to assure that their work is put to the best possible use. In fact, medical genetics researchers, because of their training and expertise, have a special responsibility to participate in public health action.

An actively endorsed scientific responsibility is imperative in the face of demands to meet commercial and other funding needs. Open and responsible communication (i.e. critical discourse) and the pursuit of basic research can be compromised by the possibility of profit or loss of funding. Scientific responsibility needs to be taught at all levels of education and reflected in public policy. Effective criticism needs to be encouraged in order to bring scientific research into the wider political discourse. If this role of responsibility is increasingly encouraged and taught, researchers would practice science with more of a consideration for the ethical, social and political aspects of their work. Society should ask medical genetics researchers to be thoughtful of potential consequences of their studies and to be ready to accurately see all potential future uses of current scientific knowledge. Yet, scientists may only be able to foresee a limited number of potential consequences. Very few researchers (very few individuals for that matter) can possess such wisdom. Humility, thus, plays an important role within the framework of scientific responsibility. According to Jonas (1984), we must admit "a new type of humility: a humility induced...not by our limitations, but by the abnormal size of our power.... The ignorance of the ultimate consequences itself becomes a reason for assuming an attitude of responsible reserve." Unlike the rhetoric of the writings surrounding the HGP and related projects where humans will eventually know everything about disease and health usually via our technological prowess, this responsibility emphasizes the complexities inherent in

knowledge and in the use of knowledge. Scientific responsibility is a fundamental concern for the ethical practice of medical genetics research. Not only are researchers capable of being scientifically responsible, they *must* be, for the purposes of good scientific practice and for the good of all populations.

CONCLUSION

According to Collins et al (2003), the scientific community post-HGP faces the surmountable challenges of: 1) the compilation of an extensive genome catalogue or genetics parts list; 2) the classification of genetic networks and protein pathways; leading to, 3) a detailed understanding of genetic variation and its influence on normal and pathological phenotypes. The main justification for the large amounts of funding for these projects is their potential medical benefits. The ideal scenario would consist of a simple, accurate genetics (preferably a readable DNA profile) prognostication and diagnosis applicable at the level of the clinic. The recipe for this ideal is devised from improved technology and statistical models. Yet, how solid is the HGP foundation?

The HGP's potential medical use would be best demonstrated by the CD/CV hypothesis which states that the human allelic spectrum is common across populations and collectively highly informative. However, serious criticisms of this disease model have surfaced in recent publications. The CD/RV hypothesis predicts extensive allelic heterogeneity underlying disease. Essentially, from this point of view, "selection does not specify a single good sequence" for a few common variants, "but, instead, is a tolerant process that allows as much variation as can survive to survive" (Weiss, 1998). A large and diverse group of rare susceptibility alleles would be difficult to detect. The polygenic model also brings attention to the difficulty of detecting

individual genetic effects amongst a variable, yet influential, genetic background. This model assumes that the common complex disease phenotype is explained by upwards of hundreds of genes. If common diseases were polygenic, most individual allelic effects would be too small to be useful. Environmental backgrounds are also important to disease manifestation and add a layer of complexity to medical genetics. Difficulties arise when interactions between genetics and the environment confound research results and attempts to disentangle these interactions prove restricted. Finally, at the extreme bounds of complexity, chance events may affect the explanatory power of medical genetics and need to be further investigated. The supporters of the above-mentioned hypotheses cannot claim that their preferred model has been definitively established. Conversely, researchers may contest that enough valuable evidence has been amassed to warrant further investigation of all of these theories. Nevertheless, the CD/CV theory is favoured in the field while the other theories are marginalized. Why have these alternative points of view been so far ignored?

The popularity of the CD/CV hypothesis is related to its conformity with the biomedical paradigm. This paradigm is technology-dependent, favours a biological approach to disease and focuses on tailored therapies for the individual with less attention to the social and environmental. Control over one's own health is expected to arise simply by knowing one's genetics and subsequently manipulating defective biological mechanisms, most likely, via drug interventions or future development of gene therapies. Yet, this viewpoint does not provide insights into the underlying factors that influence biological processes and is reactive as opposed to proactive in application. The alternative hypotheses present much less optimistic formulae as well as major obstacles to the methods outlined by those researchers who support the

CD/CV model. The alternatives draw attention to the complexities of human biology and the problematic attempts at identifying genetically typical patients. The biomedical model of disease and the partiality for the CD/CV hypothesis have ethical implications for public health and genetics research. How can we address these ethical implications?

This thesis used a framework of analysis of scientific responsibility to address the ethical implications of the study and perception of human genetic variation. Scientific responsibility was presented in this thesis as a three-step process. The first step, scientific discourse, reflects a variety of views expressed by the research community. The current scientific discourse in the field of medical genetics was documented in section one of this thesis. Common opinion surrounding the pursuit of science is that this study is objective and unbiased. Yet, health, disease and medical genetics reflect societal values, affect communities as well as individuals and reveal power inequalities. In addition, scientists have the capacity to name genetic processes and variation in a way that reflects their own values and beliefs. Step two and three of the process of scientific responsibility aim to admit this research subjectivity and shape it into a more aware, committed, humble and "resocialized" undertaking. Ethical guidelines and education are effective avenues in which to encourage scientific responsibility. However, the process of scientific responsibility also includes an encouragement of a greater awareness of the connection between ethics and science and a fundamental change in how medical research is carried out. As I have previously stated, without these characteristics of scientific responsibility, medical genetics research has followed almost entirely a single theory without sufficient investigation of other research avenues. Additionally, those individuals without access to healthcare become further marginalized while the medical genetics

focus rests on the "idealized" patient or the medical "extremes." The goal of scientific responsibility is to help researchers make better decisions, to improve the variety and quality of (medical genetics) research and to help place researchers within a wider societal context.

ENDNOTES

1. Genomics is a new term usually referring to the study of the entire human genome (all known human genes contained in the nucleus of a cell) rather than the study of a single gene. The field of genetics is a subtopic of biology referring, in my thesis, to all genetic studies, either of single genes, or of whole genome studies (genome scans, microarrays, etc.). For the purposes of my thesis, I decided, on the whole, to use the word 'genetics' as opposed to 'genomics' in order to avoid confusion.
2. Genetic profiles are thought to consist of multiple alleles (the number of which is not known) that act together to "modulate physiological systems that control the risk factors contributing to...disease" (Harrap, 2003).
3. Those researchers who support further development of the HGP and related projects, base their support on the prediction that the HGP will be useful in the elucidation of complex disease. The study of genetics has been very valuable in understanding the diseases in which the gene determines, is directly causal to, disease manifestation (although the trait or disease may vary from individual to individual). These diseases are called monogenic or mendelian and occur rarely in the human population. Complex disorders represent the large majority of human diseases including, psychiatric diseases, metabolic disorders, autoimmune disease and hypertension, among many others. "Unlike conditions involving single gene defects...the genetic contributions to common complex disorders are generally considered to be susceptibility loci, influencing but not determining overall disease risk" (Becker, 2003). The genetics of complex disease is thought to consist of multiple genes that interact in an influential environmental context.
4. I believe I need to qualify this statement. I am referring to a concept that Terwilliger and Weiss (2003) call, the "second meaning of the word 'genetic.'" The first meaning of the word 'genetic' "refers to the role of genes as basic units of biological 'information' and has to do with physiology...of their action" (Terwilliger & Weiss, 2003). Humans cannot live without genes. Our genetics are fundamentally involved in the development of many human traits. Thus, genetics is an important subject in the field of biology and can contribute very much to the understanding of human biological processes. The second meaning of the word 'genetic' "has to do with heritable DNA sequence *variation* and its influence on phenotypic variation" (Terwilliger & Weiss, 2003). Different, inherited DNA variants or, in other words, allelic variation in genes, can influence to some extent the variations in phenotype from one individual to another. However, there is an enormous difference between, for example, having a colon and having a risk of colon cancer. Genetics is fundamentally involved in colon development, whereas, genetic variation is not the fundamental cause of colon cancer. A direct line between genetic variation and its medical application for complex diseases in the general population has not been elucidated.
5. Genetic association is simply a statistical statement about the co-occurrence of alleles or phenotypes (Strachan & Read, 1999). Allele A is associated with disease D if people who have D also have A more often than would be predicted from the individual frequencies of D and A in the population. An association can have many possible causes, not all genetic (Strachan & Read, 1999).

6. "By definition, common disease susceptibility alleles should *not* be considered disease genes because although necessary, they are not sufficient to cause disease. [However, researchers believe that these] molecular variants are components in complex multi-component networks that contribute in additive ways to the ultimate disease phenotype. Individually, they may have little or no disease effect" (Becker, 2003).
7. Scaffolding systems are proteins that are part of the cytoskeleton and protein trafficking systems of cells involved with signaling and structural molecules. The scaffolding system is an important regulator of cell morphogenesis.
8. "Gene frequencies are subject to the control of natural selection, such that alleles which have substantially negative effects on reproductive fitness will not become common except under some restricted circumstances" (Terwilliger & Weiss, 2003). The trade-off theory states that an allele may become common if harmful in some contexts but helpful in others. The variant may also have positive effects on traits other than the disease trait. Additionally, a common variant can have negative effects on fitness if it had previously been neutral or beneficial under the environmental conditions prevalent through most of human history. This latter case refers to the common disease/fixed variant (CD/FV) hypothesis in which "genetic factors are essentially invariant in [usually specific ethnic] populations as a result of strong selective advantages in the past" (Wright et al, 2003). Conventional mapping studies would thus fail to detect these variants.
9. SNP profiles represent, for each individual, an SNP pattern that is made up of many different genetic variations. Most SNPs are not usually responsible for a disease state. The aim is to used SNPs as markers for pinpointing a disease on a genome map since these polymorphisms may be located near a gene that has been found to be associated with a certain disease. It is thought that eventually SNP profiles, characteristic of a variety of diseases, will be established and used to screen individuals for susceptibility for disease (NCBI, 2004).
10. Penetrance refers to the characteristic phenotypic effect of a genotype. If the phenotype is always expressed in the presence of the genotype, the genotype is completely penetrant. If it is not always expressed, it is incompletely penetrant.
11. The population attributable risk measures the potential impact of control measures in a population, and is relevant to decisions in public health (Coggon et al, 1997). The *attributable proportion* is the proportion of disease that would be eliminated in a population if its disease rate were reduced to that of unexposed persons. It is used to compare the potential impact of different public health strategies (Coggon et al, 1997).
12. Relative risk is the ratio of the disease rate in exposed persons to that in people who are unexposed (Coggon et al, 1997). For example, if a person has a relative risk of two for breast cancer this means their risk of disease is double that in the general population.
13. The biomedical disease model is the current dominant medical paradigm: medicine as a branch of applied biology. The model focuses on biological processes such as, pathology, biochemistry and genetics of disease. This model does not take into account the role of sociology or other external factors in the cause or treatment of illness.
14. "Geneticization is a term coined (Lippman, 1991) to capture the ever-growning tendency to distinguish people one from another on the basis of

genetics; to define most disorders, behaviours and physiological variations as wholly or in part genetic in origin" (Lippman, 1998).

15. This article has been condemned and praised in equal measure by the research community and quoted widely as a critical commentary of the "genetic revolution."
16. This section is taken greatly from Weed and McKeown (2003

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