CHAPTER ELEVEN

# Genetic Causation: A Cross Disciplinary Inquiry

**Sheldon Krimsky**
Department of Urban and Environmental Policy and Planning, Tufts University, Medford, MA, USA
E-mail: sheldon.krimsky@tufts.edu

## Contents



## Abstract

The growth of genome-wide and Candidate Gene Association Studies have elevated genetic causality in medicine and behavioral science. This chapter explores the concept of causality as it has been applied in genetic explanations and distinguishes the varieties of methods used to establish genetic causation. The essay ends with a cautionary note on applying genetic causation to compelx human behaviors and neurocognitive abnormalities.

*"Science is about causes, period."*

***E. Turkheimer (Turkheimer, 2011).***

*"Causality in any particular form does not need to be a feature of all successful scientific explanations."*

***D. Noble (Noble, 2008).***

## 1. INTRODUCTION

How we ascertain causes and find agreement about causes depends largely on the methods and tools of science—methods that vary among the disciplines. The issue of genetic causation began to gnaw at me when

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I started to read published studies that found genetic causes or genetic determinants for: breakfast eating patterns, (Keski-Rahkoren et al., 2004) loneliness, (Boomsma et al., 2006) religiousness, (Koenig et al., 2005) agreeableness, (Garpenstrand et al., 2002) voting behavior, novelty seeking, (Strobel, Wehr, Michel, & Brocke, 1999) altruism, cooperation, (Mertins et al., 2011) credit card debt, (De Neve & Fowler, 2010) antisocial behavior, binge eating and drinking, criminal behavior, (DeLisi, Beaver, Vaughn, & Wright, 2009) attitudes of fairness, attitudes toward infidelity, aggression, (McDermott et al., 2009) individualism vs collectivism, number of sexual partners, political ideology, shyness, utilitarian moral judgments, and social networking (Fowler, Settle, & Christakis, 2011). Genetics is beginning to play a prominent role in subdisciplines of political science, developmental and behavioral psychology, and anthropology. Genetic causation, whether weak or strong, deterministic or probabilistic, is a term introduced through a variety of methods in these disciplines, the results of which have gained little attention in the field of genetics itself. Nevertheless, the papers connecting genes to behavior are published in some of the premier journals in the social and behavioral sciences. Genetic causation is also used in disciplines that seek a genetic etiology of disease. This chapter begins with a discussion of "causality" generally and then focuses on "causality" in genetics. I shall argue that for many claims the concept of "genetic cause" does not stand up to critical scrutiny.

## 2. CAUSALITY IN SCIENCE

The term "causality" has a long lineage in philosophy and in the history of science. Aristotle introduced four causes: material, formal, efficient, and final cause. The material cause is the composition of an object—thus in biochemistry the material cause of a protein is its composition of amino acids. Its formal cause is the arrangement of the matter in it or the three-dimensional structure of the amino acids making up the protein. The efficient cause of a substance is what changes its motion—forces acting on it like an electric field acting on a molecule. The final cause is the purpose it serves or the end to which it is directed. For example, a protein designed to deliver oxygen through the blood stream would be its final cause. During the growth of modern science with its emphasis on the physics of moving bodies, the efficient and material causes became the primary focus of philosophical discussion. The expression "A is the Cause of B" meant that "A" preceded "B" in time and that "A" was a sufficient condition for the determination of "B". Newtonian causality was based on law-like or nomological statements such

as "all metals expand when heated." Some classical views of causality locate a power in the cause such as "A has the power to bring about B." In other views, A and B are causally related when they appear together, but not necessarily before or after—as in an antecedent and consequent events.

Newtonian causality also manifests a functional relationship between A and B. For example, the ball "B" of mass "*m*" was brought to acceleration "*a*" by force A (efficient cause) according to the relationship "F = *ma*". Certain fields of natural science connect causality to prediction and claim there is symmetry between causal explanation and prediction. To say that "A" is the cause of "B" is to say that from "A" and law L we can predict the occurrence of "B" by logic or statistical inference.

## 3. CAUSALITY IN MODERN GENETICS

Modern genetics, both in its scientific and cultural discourse, has introduced causality in various forms. Genes are said to be the templates for the synthesis of proteins. In response to the question, "what caused this protein to be abnormal?", the answer is "the gene that codes for the protein had a mutation." Causality, in this sense, means that the mutated gene is the reason for the appearance of the abnormal protein.

It is also common to hear the term "genes" used as the cause of a trait, such as "She has a gene for blue eyes," that suggests that her genes caused or were determinative of her "blue eyes". In addition, genes are cited as a cause of a disease or developmental abnormality such as the genes for amyotrophic lateral sclerosis or achondroplasia (dwarfism). Genetic causes have also been cited for behavioral characteristics, such as aggression, infidelity, and political choices. Finally, the idea that a gene or a group of genes can predispose someone to an effect is another form of a causal statement. To say that A presupposes someone to an effect B is to declare A necessary (with some probability) but not sufficient for B. Before we can fully understand the different forms of causality used in genetics, it would be useful to provide an overview of the changes that have taken place in the theory of molecular genetics over the past 50 years.

## 4. GENETIC THEORY IN TRANSITION

During the last half century in which genetic theory developed many hypotheses and revisions to those hypotheses were made regarding the nature of the animal and plant genomes, the relationship between the genes and phenotype (such as disease, behavior, physical traits), gene–environment interactions,

the process by which cells decode the information stored on DNA, and the estimated number of genes in the human chromosome. Even the concept of the gene has been revised. The early concept of the genome was likened to a Lego structure, composed of segments of DNA linked together and differentiated by the sequence of four nucleotides (the bases A, G, C, T).

An early physical model of the DNA molecule, which James Watson and Francis Crick had fabricated, consisted of metallic double helix "made of flat plates of galvanized metal with narrow brass tubes for bonds."(Ridley, 2003, p. 70). This static model served as an early representation of the structure of the DNA molecule. Initially, genes were viewed as the segments of DNA, which held coding information about proteins.

While some segments of the DNA in the human genome have a coding function, most of the 3 billion base pairs were considered junk DNA with no coding or regulatory functions—the flotsam and jetsam of evolution. The remaining functional DNA (estimated at about 2% of the genome) was divided into discrete segments, each assigned to the coding for one of the unique 100,000 proteins in the human body. Recently the junk DNA hypothesis has been questioned as scientists have discovered that more and more of the non-coding DNA is transcribed into RNA with uncharacterized functions. Also, new estimates put the number of human genes at between 20,000–30,000, signaling that some DNA segments contain the code for more than one protein.

Francis Crick postulated the Central Dogma of molecular genetics theory in 1958 at a meeting of the Society of Experimental Biology in a talk titled "On Protein Synthesis". According to Crick, genetic information transfers from nucleic acid (DNA or RNA) to nucleic acid, or from nucleic acid to protein, but never from protein to nucleic acid. In other words, proteins do not contain the information for duplicating themselves. The Central Dogma has often been simplified as "DNA makes RNA makes Protein." Early popular conceptions of the genetic mechanism gave the false impression that DNA is a self-actualizing master molecule. In fact, proteins play a critical role in directing the orchestral process of protein synthesis (Proteins). "DNA may be a large complex molecule, but alone it does nothing. It does not have powers of self-replication, nor [does it have power] to create new generations of life"(Richards, 2002). In a popular magazine article, Barry Commoner gave a more realistic view of the role of proteins in all aspects of DNA replication and transcription. "...in the living cell the gene's nucleotide code can be replicated faithfully only because an array of specialized proteins intervenes to prevent most of the errors—which DNA by itself is prone to make and or repair the few remaining ones...genetic information arises not from DNA alone but through its essential collaboration with protein enzymes—a contradiction

of the central dogma's precept that inheritance is uniquely governed by the self-replication of the DNA double helix."(Commoner 2002).

Initially, molecular geneticists believed that the function of a gene was to control the production of a single polypeptide. Then it was discovered that genes carried the code for forms of RNA that do not become polypeptides. From the late 1960s to the present, the details of the Central Dogma have been filled in or revised with some variations in how information flows in viruses and retroviruses. An example of replication without nucleic acid is given by prions, newly discovered molecules responsible for mad cow (kuru) disease. Prions can replicate even though they do not contain nucleic acid. They alter normal brain proteins to adapt to the prion's shape, thus in a sense, replicating themselves. If information can be transferred from protein to protein, then this raises in question one of the core ideas in the Central Dogma of molecular biology.

The Lego model of the genome is as simplistic as the Bohr model of the atom. Rather than genes being fixed entities in a static structure waiting to be self-activated, the current conception views the genome as more characteristic of an ecosystem—more fluid, more dynamic, and more interactive than the Lego model implies. "...the assumption that identifiable bits of DNA sequence are even"genes"for particular proteins has turned out not to be generally true. Alternative splicing of fragments of particular sequences, alternative reading frames, and post-transcriptional editing—some of the things that happen between the transcription of DNA and the formatting of a final protein product—are among the processes the discovery of which had led to a radically different view of the genome"(Dupré, 2008).

Within a decade, scientists began to acknowledge that such a view was far too simplistic and the complexity of the genome began to reveal itself. To begin, gene–gene interactions defy a linear model of genetic causality represented by: DNA → RNA → Protein → Disease. Second, DNA sequences may express different products when situated in different parts of the chromosome (the position effect), which means that the role of DNA must be seen in the context of other parts of the cell and organism. Also, the same segment of DNA may be read differently in the same location because of different reading frames (Li et al., 2011). Furthermore, genes may function differently during different periods in a person's life.

By 2001, scientists at the Food and Drug Administration recognized this complexity when reviewing food safety issues arising from genetically modified crops. An agency document included the following statement: "It is also possible with bioengineering that the newly introduced genetic material may be inserted into the chromosome of a food plant in a location that causes the food derived from the plant to have higher levels than

normal of toxins, or lower levels of a significant nutrient. In the former case the food may not be safe to eat, or may require special preparation to reduce or eliminate the toxic substance. In the latter case the food may require special labeling, so that consumers would know that they were not receiving the level of nutrients they would ordinarily expect from consuming a comparable food."(Food and Drug Administration, 2001) This model of the plant genome is far afield from the piano metaphor where the added or subtracted key does not interact with the other keys or affect the system as a whole, other than to add a new protein. Also, there are other reasons to revise the idea of DNA → RNA → Protein. According to a study published in 2001, the authors found that information in DNA is not always faithfully transferred to RNA in transcription—RNA bases did not match the corresponding DNA sequence (Mingyao et al., 2011).

DNA once thought to be the fixed components of heredity is now viewed as a much more fluid idea. Genes may change during a person's development. Genes interact with one another as well as with the environment. Genes may be turned on and off resulting from factors outside the DNA, as exemplified by loss-of-function (LoF) variants in the human genome with at least 20 genes having been completely lost (Quintana-Murci, 2012). The epigenome, which regulates how and when genes get expressed, can be inherited through the germline.

## 5. VARIETIES OF GENETIC CAUSATION

Causality in genetics is determined by different methods used by scientists in different disciplines. For my first example, genetic causality can be inferred from laboratory experiments. In knock-out mice certain genes are removed from the egg before fertilization. Those mice can be compared with the non-knock out variety (the controls). Scientists can examine gene expression, a particular pathway in the gene–protein complex or phenotypic effects—even behavioral change in the animal. Replicability and the use of controls are expected of such experiments for establishing causation.

The argument that causation can be established is as follows. A and B are genetically identical mice except that B has one gene ($g_x$) deleted. A has characteristic C; B lacks characteristic C. The studies can be replicated and the effects are totally deterministic. When $g_x$ then "C" is observed; when not-$g_x$ then "C" is not observed. Therefore, $g_x$ causes "C"(Dyck et al., 2009; Quintana-Murci, 2012). Even in this highly controlled experiment, the

gene in question does not act independently of the proteins, lipids, and cellular machinery such as the ribosomes that go into synthesizing the protein—whether normal or defective. Strictly speaking, the gene is never a sufficient cause of the abnormality. But, as a matter of convention, we can call it the cause if everything else remains constant. This may be traced to John Stuart Mill's Method of Difference in his Methods of Induction.

> *"If an instance in which the phenomenon under investigation occurs, and an instance in which it does not occur, have every circumstance in common save one, that one occurring only in the former; the circumstance in which alone the two instances differ, is the effect, or the cause, or an indispensable part of the cause, of the phenomenon."*
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> ***(Mill, 1859, p. 225).***

A simple model of genetic causation in human disease is illustrated by Phenylketonuria (PKU). This is an autosomal recessive metabolic genetic disorder characterized by a mutation in the gene for the liver enzyme phenylalanine hydroxylase (PAH), rendering it nonfunctional. This enzyme is necessary to metabolize the amino acid phenylalanine (Phe) to the amino acid tyrosine. Without the enzyme, the Phe builds up and can cause mental retardation. Recessive Gene Mutation + phenylalanine → disease. This causal factor is fully predictable based on a genetic marker. One author explained the use of "causality" in such cases. "The Causal nature of Mendelian (recessive or dominantly acting) mutations is fairly easy to establish because there is essentially a strong correspondence between the presence of a mutation and a disease phenotype" (Geschwind, 2011). While it is not probabilistic, the intensity of the effect can vary depending on the amount of the amino acid Phe in the diet. Phe must also be seen as a "necessary" but not sufficient cause. In a world where Phe were ubiquitous in the diet, the cause would be both necessary and sufficient as discussed above in Mill's Methods.

When we get to diseases involving many genes, causality is much more complex not only because the genetic components are acting nonlinearly, but because the disease phenotype is diverse and may be arising from different pathways. This is the case with autism spectrum disorder (ASD). The language of the neurogeneticists is cautious with respect to causality. The methods of analysis include whole genome association studies seeking to find Copy Number Variants that could correlate with ASD. Instead of "causality," scientists speak about "susceptibility genes." "Several dozen ASD susceptibility genes have been identified in the past decade, collectively accounting for 10–20% of ASD cases" (Geschwind, 2011). No specific gene

could be found for the majority of ASD; the most common susceptibility genes account for not more than 1–2% of cases.

A third method of establishing some form of causation in the social sciences involves the use of statistical techniques in combination with twin studies. Although in other behavior genetics work, estimates are made of shared and nonshared environmental variance, in this instantiation of behavior genetics research, monozygote and dizygote twins are compared for some variable, and the environment is assumed constant for each twin pair. If the phenotype is more highly correlated with monozygote twins than dizygote twins then it is deemed heritable—or genetically caused. The National Longitudinal Study of Adolescent Health had a sample of 90,000 adolescents and 1,110 twins that continues to be mined because the survey contains genetic factors (Fowler, Dawes, & Christakis, 2009).

There has been considerable debate about the methodology of twin studies, especially the assumption of environmental uniformity among twins and "whether the influences of genes as opposed to environment on a given trait can be neatly partitioned into percentages...."(Charney, 2008a). Among the claims made by using twin methodology are: "Genes predict voter turnout"; "Genes found for congeniality"; and "genes influence social networks".

A fourth method for establishing genetic causality, albeit indirect causality, is the method of Candidate Gene Associations (CGA). This involves large datasets of genetic information (polymorphisms). Candidate genes are selected from prior studies where associations have been found. Investigators use statistical techniques to correlate particular alleles with a phenotype and ascertain whether a gene is more frequently seen in participants with the disease than in participants without the disease. No one claims that the candidate gene studies by themselves yield causality. The phenotype could be a disease or a behavior. If there is a strong correlation between the gene variant and the phenotype, the gene is said to predict the behavior in question. Some of the results from these studies have claimed: "gene said to predict voting behavior,"(Fowler & Dawes, 2008) "...we hypothesize that people with more transcriptionally efficient alleles of the MAOA and 5HTT genes are more likely to vote"(Fowler & Dawes, 2008). Other studies assert that genes account for "punishing behavior" in an experimental setting, (McDermott et al., 2009) partisanship and party identification, (Dawes & Fowler, 2009) liberal political ideology, (Settle et al., 2010) credit card debt, (De Neve & Fowler, 2010) antisocial personality, (DeLisi et al., 2009)

leadership, (De Neve & Fowler, 2010), and preferences for the voluntary provision of social goods (Mertins et al., 2011).

Familial studies have been used to determine whether a phenotype is manifest in family members at a higher frequency than in the general public—if so, suggesting a genetic cause.

Causality has also been inferred from proxy variables when a direct genetic variable was not found. For example, in the case of the heart drug BiDil, the Food and Drug Administration approved the use of a clinical trial where "race" was a proxy for some as yet undetermined genetic factor (Kahn, 2011).

They used self-reporting of race as the independent variable and correlated it with outcome measures of a drug treatment for congestive heart failure. When the statistics showed a sufficient correlation from self-identified African Americans enrolled in the study, the drug was approved. It was inferred that the drug improved the patients treated more effectively than a placebo and thus was considered to have had a therapeutic effect.

While social scientists have discussed "causal" or "quasi-causal relationships" between genes and complex human behaviors, many medical geneticists have not found genetic links to schizophrenia, diabetes and hypertension.

Genetic causality is complicated by the fact that "gene–environment interactions" have become part of the new genetic paradigm shift. Back in 1968, MacMahon summarized the complexity of the gene–environment interaction making the sorting out of these two factors in a causal analysis an unlikely enterprise. He wrote:

1. It has become clear that there is no disease that is determined entirely by either genetic or environmental factors.
2. There is evidently more overlap in the time of operation of genetic and environmental factors than was previously suspected.
3. Just as the environment may exert its effect through the genetic mechanism of mutation, so may genetic factors operate by changing the environment.
4. The role of gene and environment and the nature of specific factors involved may be quite different in individuals with identical manifestations.

He cites the case of "yellow shanks", a characteristic observed in certain fowl when fed on yellow corn. He noted that a farmer using only yellow corn as feed and owning several strains of fowl would observe the trait appeared in select strains. He believed the trait was genetically determined.

Another farmer feeding some of his flock on yellow and some on white corn would note that the trait only appeared on those fed yellow corn. He concluded that the trait was environmentally determined. Neither environment nor genetics accurately described the cause of the condition. It is more accurate to say, that within a specified range of genetic background, environmental factors determine the occurrence; within a specified range of environment, the trait is genetically determined. Denis Noble notes that "genetic causality" is vexing "not only because the concept of the gene has become problematic,...but also because it is not usually a proximal cause."(Noble, 2008).

## 6. COMPLEX BEHAVIOR AND GENES

Let's consider the study by James Fowler and Christopher Dawes published in the *Journal of Politics* titled "Two Genes Predict Voter Turnout"(Fowler, Baker, & Dawes, 2008). They reported results of their study that a gene and a gene–environment interaction increased the likelihood of voting. Before we enter into the nature of their methodology and how they infer causality, let's first consider what genes do.

They provide a code (CGAT sequences) that the cell uses to synthesize a protein—from its component amino acids that circulate in the cells. How does a protein get turned into voting behavior? Also, given the multitude of ways that a person's voting behavior can be affected, such as peers, family, education, political affiliation, type of employment (farm worker who is peripatetic versus a banker), if someone were to develop a hypothesis that a gene causes voting behavior, it would have to be indisputable given that common sense suggests that this behavior is embedded in a complex culture that is far more likely to affect behavior than a protein.

The authors of the study were able to access genetic data from a National Adolescent Study of Adolescent Health. They had information on eight genes from twins and full siblings from 2,574 respondents. They looked at variants of a gene called MAOA, which encodes the enzyme monamine oxidase. Variants of this gene produce more or less quantities of serotonin, which affect the brain. They also correlated the MAOA variant with religious affiliation. A difference in transcription rates is supposed to exhibit different levels of bioavailable MAOA in the brain, which is supposed to correspond to different levels of bioavailable serotonin, which can be associated with different behavior. Their analysis includes a gene–environment interaction where religious affiliation and MAOA are supposed to work

together. This type of gene–environment interaction requires another quite imaginative causal framework where proteins and religious affiliation co-interact to produce a behavioral outcome.

Their use of the Candidate Gene Association method is based on a case–control design. The gene frequency that is associated with certain behavior in one group is compared to another group, which does not exhibit the behavior. You can either go backwards (explain) or forwards (predict) the results. One group has the requisite candidate gene and you observe the behavior; the other group lacks the candidate gene and you observe the behavior. You can also divide two groups by behavior and then look at the genes to determine whether a correlation exists. This method of inferring causality is highly inductive. It is based purely on statistical correlations and not on deep neurological science where causal connections can be found between serotonin levels and human choice. There is no telling what type of correlations we can find with a .05 significance criterion if we generate enough statistical tests. But for such a result to really hold our attention at a causal level, we need an explanatory framework that is so powerful that it excludes all other more reasonable possibilities between proteins and behavior.

The genetic model used in these studies, and in particular the causal view of genes, is part of the old paradigm and not the new paradigm. The new view, which dramatically affects the idea of genetic causality, includes the epigenome—the proteins wrapped around DNA that provide the switching mechanisms for genes. As one author puts it: "the extent to which a gene can be transcribed is controlled by the epigenome, the complex biochemical regulatory system that turns genes on and off, is environmentally responsive, can influence phenotype via environmentally induced changes to gene transcribability with no changes to the DNA sequence"(Charney & English, 2012). Even at the rudimentary level of protein synthesis, DNA alleles do not tell the story. Therefore, correlating DNA to behavior has more problems than the multiple levels of causation between protein synthesis and human choice. There is no linear, unidirectional, DNA → protein causality.

Second, there is nothing stable about DNA. Its role in an organism changes through time and through environmental interactions; there are jumping genes, mutations and that "one and the same allele in one and the same individual might be completely inactivated in one set of tissues (e.g., the brain), partially inactivated in another, and completely active in a third."(Charney & English, 2012).

Third, one commentator notes that most human traits with genetic components are affected by a vast number of genes—each with a small effect. This framework would substantially discount the idea there is one gene, one cause, one effect. "There is an ever-growing consensus that complex traits, among which certainly be included all politically relevant behaviors, are influenced by hundreds or thousands of proteins encoded in hundreds or thousands of genes of small effect that interact with one another, the environment and the epigenome in complex ways"(Charney & English, 2012).

Let's take a closer look at the twin-studies method. John Alford, Carolyn Funk, and John Hibbing published a paper in 2005 using twin studies in which they found that political orientations are highly heritable and thus strongly determined by genetics (Alford, Funk, & Hibbing, 2005). How far can twin studies take you in asserting genetic causality of behavior? The twin studies typically use sets of monozygote (identical) and dizygote (fraternal) twins. If a behavioral trait correlated more highly with monozygote twins over dizygote twins, then it is presumed to be an indication of higher heritability of that behavior. Alford et al. (2005) reached their conclusion that genes shape political behavior when they found significantly higher correlations for MZ twins vs. same sex DZ twins on the Wilson-Patterson Attitude Inventory Score. The environment is assumed equal or randomly distributed among the twins.

Psychiatric geneticists have reported for decades that twin studies are confounded and that one's conclusions come at considerable risk (Rosenthal, 1979). One of the most important assumptions of such studies is the "equal environment assumption." Identical twins may be treated differently than fraternal twins, which could affect behavioral phenotypes. Some critics of the twin method are in wonderment that it has survived and believe that its survival is no longer a scientific question. "The twin method survives today not because the critics have been successfully'rebuffed' but rather [because it is] the outcome of a power struggle, not the resolution of a debate among scientists" (Joseph, 2010).

Familial studies may be a source of hypotheses about genetic causation—but findings among family members may equally suggest a hypothesis of environmental causation. As one behavioral geneticist observed "Many behaviors run in families," but family resemblance can be due to nature or nurture (Plomin et al., 2008, p. 70). The question remains of how methodologically to disentangle environmental from genetic factors in causation.

There are so many levels of structure and development and so many possible interactions between the production of the hormone or the structure

of a brain region and any behavior that, without irrefutable causal evidence, it would take an act of pure imagination to make a leap that there is a voting gene or a social network gene. Or as Richard Lewontin noted: "It is a sign of the foolishness into which an unreflective reductionism can lead us that we seriously argue from protein similarity to political similarity." In a genocentric framework, there is a tendency to draw the simplest reductionist explanation for a behavior or trait and neglect the complexities of multigenetic, gene-environment, epigenetic interactions or some complex combination involving multiple causation. As Martin Richards noted: "molecular genetics often has the feel of greedy reductionism, trying to explain too much, too fast, under-estimating the complexity and skipping over whole levels of process in the rush to link everything to the foundations of DNA" (Richards, 2002).

Turkheimer does not believe that current methods can disentangle genetic and environmental causation for complex human behavior. I am inclined to agree.

> *"...individual differences in complex human characteristics do not in general, have causes, neither genetic nor environmental. Complex human behavior emerges out of a hyper-complex developmental network into which individual genes and individual environmental events are inputs. The systemic causal effects of any of these inputs are lost in the developmental complex of the network."*
>
> ***(Turkehimer, 2001).***

> *"Causal explanations of complex difference among humans are therefore not going to be found in individual genes or environments any more than explanations of plate tectonics can be found in the chemical composition of individual rocks."*
>
> ***(Turkehimer, 2001).***

There is a rancorous debate among political scientists and between some political scientists and geneticists and behavioral psychologists. Referring to the study by Alford, Funk, and Hibbing (AFH) that political orientation can be genetically transmitted, Evan Charney wrote:

> *"I could perform the exact same study as AFH using a different questionnaire and claim to have determined what percentage of an individual's belief concerning the doctrine of the Trinity is due to genes and what percentage to environment—or to what extent whether one favors the New York Yankees or the Boston Red Sox, or Mercedes or BMWs, or Lowes or Home Depot is "heritable"".*
>
> ***(Charney, 2008b).***

Political scientists are introducing causality for political behavior by a hotly contested method (Twin Studies) or the use of statistical correlations without biological pathways by citing gross neurological hypotheses that would be unrealistic to medical geneticists. After 15–20 years of research on the genetic basis of autism spectrum disorders, which is characterized by a combination of abnormalities in language, social cognition, and mental agility, one neurogeneticist concluded: "Several dozen QASD susceptibility genes have been identified in the past decades, collectively account for 10–20% of ASD cases." This is after an army of researchers have done case-controlled studies. Yet, in far more complex and subtle human developmental behavior, political scientists make stronger claims about the genetic basis of political choices. No one assumes that autism is a personal choice, rather a neurological condition that affects or comes along with other organ pathologies. Nearly everyone assumes we have free will to determine whether, when, and for whom we vote—notwithstanding the fact that there are environmental influences. To make a claim about the genetic basis of political choice flies against all the a priori, personal and empirical knowledge we have accumulated over centuries about human choice.

A growing number of geneticists do not hold DNA to have sole primacy in causation of building a molecule, much less a phenotype. "Genes, as we now define them in molecular biological terms, lay a long way from their phenotypic effects, which are exerted through many levels of biological organization and subject to many influences from both those levels and the environment" (Noble, 2008). Some geneticists are more explicit about avoiding causal language in candidate gene studies or genome-wide studies. "I avoid using terms such as "due to" or "caused by" when referring to the statistical relations between an independent variable and a dependent variable, but instead use terms such as "associated with" to avoid deterministic implications" (Stoltenberg, 1997). What is often neglected in the association studies of individual alleles or polymorphisms is the context in which the genetic pathways operate. One commentator notes that a single genetic variant may have a different impact on the health depending on the other genetic variants that exist in the genome, environmental factors, or a combination of both (Drmanac, 2012).

## 7. CONCLUSION

In some very important respects, nothing happens in a living organism without its DNA and genes playing a role. Almost all illnesses, even those we

attribute to viruses or bacteria, have a genetic component to them. Some of the infectious agents will be deactivated by the immune system. In other cases, the foreign agents will overcome the body's defenses resulting in a disease outcome.

Notwithstanding the close linkage of genetics and environment with disease, we may speak solely of an environmental or genetic cause of a disease. In cases where an individual's genetics is not unusual, we may speak of an environmental cause, even though the genetic–environmental interaction is a sufficient cause of the outcome. On the other hand, if the genetic factor (polymorphism or mutation) is rare, even though it is not itself a sufficient cause, we speak of a genetic cause. In these cases, there is usually a well-defined mechanism that supports the causal language.

In Candidate Gene Association studies, where statistical methods are used to identify probabilistic connections between a genetic locus and a phenotype, the use of causal language is problematic for several reasons. First, the statistical association could be a secondary correlate to another factor that is part of a causal network. As an analogy, if we find an association between the stock market and the crime rate, that could be a spurious causal relationship with the real cause being a rise in poverty. Second, as was previously mentioned, the factor that has been identified as "statistically associated with" may not be proximate to the effect. Therefore, there may be many intervening variables that may or may not diminish the efficacy of the genetic factor. Third, there may be numerous nonlinear genetic interactions, each of which may contribute to a small part of the effect. Only one locus in the genetic quilt of interactions can mistakenly be viewed as *the cause*. Autism is a case in point. "The candidate genes most strongly implicated in NDD [neurodevelopmental disabilities] causation encode for proteins in synaptic architecture, neurotransmitter synthesis…No single anomaly predominates. Instead, autism appears to be a family of diseases with common phenotypes, linked to a series of genetic anomalies, each of which is responsible for no more 2–3% of cases" (Landrigan, Lambertini, & Birnbaum, 2012). The authors argue that the causal mechanism for neurodevelopmental diseases like autism defy most of the classical models of causality. They postulate that genes and environmental factors are responsible for an effect, but how much of each and what combination makes up the causal tree is unknown and may be unknowable.

Large DNA databanks have provided the grist for associational studies that seek genetic determinants of human phenotype. If my analysis is correct then the methods, by themselves, at best can produce testable

hypotheses that some alleles or mutations may contribute to one of the pathways in the complex system linking genetic, somatic, neurological, and environmental components. Failing to account for the complex quilt of interactions, mistakenly, affords DNA causal efficacy that cannot be supported.

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## Part A: Philosophical, Theoretical, and Biological Dimensions

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