FROM A GENETIC PREDISPOSITION TO AN INTERACTIVE PREDISPOSITION: RETHINKING THE ETHICAL IMPLICATIONS OF RESEARCH ON GENE-ENVIRONMENT INTERACTIONS

by

James Gregory Tabery

BS in Biology, Fairfield University, 2000

PhD in History and Philosophy of Science, University of Pittsburgh, 2007

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This thesis was presented

by

James Gregory Tabery

It was defended on

October 12, 2007

and approved by

Lisa Parker, Director of Graduate Education, Center for Bioethics and Health Law

Erik Parens, Associate for Philosophical Studies, The Hastings Center

Kenneth Schaffner, University Professor, Department of History and Philosophy of Science

Mark Wicclair, Professor of Philosophy, West Virginia University

From a Genetic Predisposition to an Interactive Predisposition: Rethinking the Ethical Implications of Research on Gene-Environment Interactions

James Gregory Tabery

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The concept of *gene-environment interaction*, or G×E, refers to cases where different genetic groups respond differently to the same array of environments for a particular phenotypic trait. In a widely acclaimed study from 2002, researchers found a case of G×E for a gene associated with neuroenzymatic activity (low vs. high), exposure to childhood maltreatment, and the development of antisocial personality disorder (ASPD), or sociopathy. Cases of G×E are generally characterized as evincing a *genetic predisposition* to the trait under consideration; for example, individuals with low neuroenzymatic activity are generally characterized as having a genetic predisposition to ASPD. Bioethical commentators in turn have asked: Should parents test their embryos or fetuses for this genetic predisposition to ASPD in order to screen against the gene associated with low-MAOA activity? Should the state test all newborns for this genetic predisposition to ASPD in order to identify and treat individuals with the gene associated with low-MAOA activity from birth?

I first show that the concept of a genetic predisposition fundamentally misconstrues the ASPD study. That concept is appropriately applied only to cases of G×E that result in a change of scale, but the ASPD study resulted in a change of rank. For cases of G×E that result in a change of rank, I introduce a new concept—*interactive predisposition*. Then, I show how this switch from a genetic predisposition to an interactive predisposition reconfigures old questions and raises new questions in the confines of the ethical discussions about the implications of such studies. For the ASPD study, attempts to screen against the gene associated with low-MAOA

activity potentially fall prey to the *myth of pre-environmental prediction*, and attempts to screen all newborns for the gene associated with low-MAOA activity with an eye towards early intervention will have to face the *interventionist's dilemma*. Moving beyond the ASPD study, traditional cost-benefit analyses involved in deciding whether or not to undertake the genetic testing of a child will have to be reweighed when the disease/disorder of concern results from an interactive predisposition rather than a genetic predisposition.

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1. INTRODUCTION

This thesis is about gene-environment interaction, or G×E. G×E refers to cases where different genetic groups respond differently to the same array of environments. For instance, a very early example of research on G×E is depicted in Figure 1.1 (Hogben 1933). Cases of G×E are often visually displayed by means of a reaction norm graph such as this.[1] In this case, different strains of the fruit fly *Drosophila* (low-bar and ultra-bar) were raised at a number of different temperatures (x-axis) and then measured for how many eye-facets developed on the flies' compound eyes (y-axis). These phenotypic curves revealed how the different strains of *Drosophila* responded to the varying array of environments.

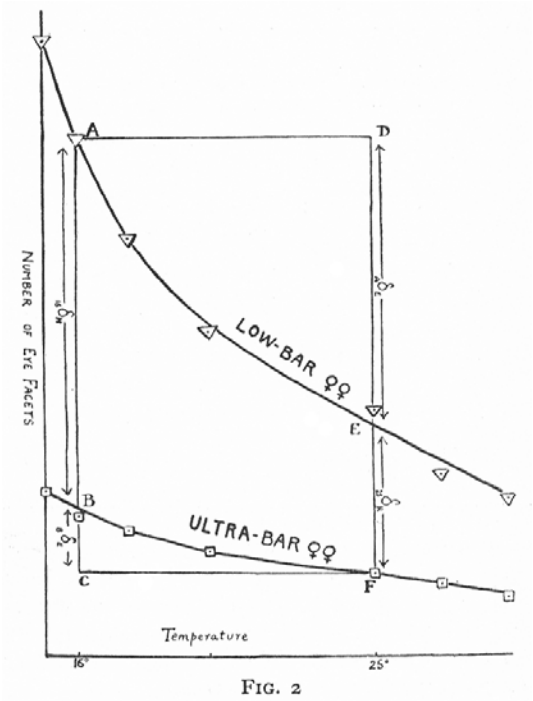


FIG. 2

Figure 1.1. Norms of reaction for low-bar and ultra-bar *Drosophila* strains raised in different temperatures. Figure from Hogben (1933, Figure 2).

[1] For histories of the reaction norm concept, see Griffiths and Tabery (Forthcoming) and Sarkar (1999).

Cases of G×E have figured prominently in the history of the nature-nurture debate. For most of this history, cases of G×E figured into debates about the *group differences between populations*. With the onset of molecular genetics, however, cases of G×E are now figuring into debates about the *predispositions of individuals*. This introductory chapter is meant to explicate this shift and consider how arguments from the older debate might play out in the contemporary one.

1.1. Gene-Environment Interaction in the Nature-Nurture Debate

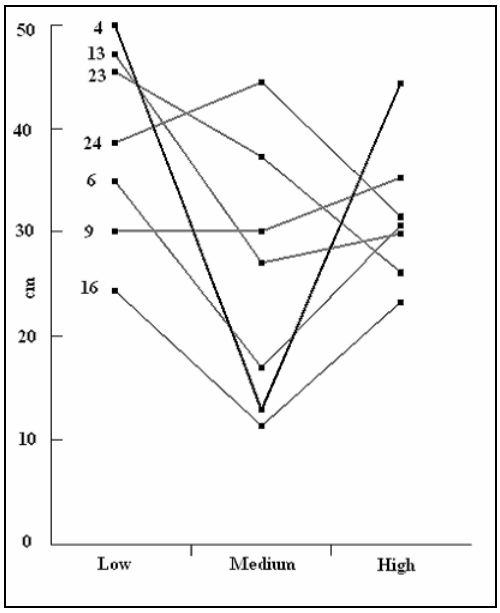
Quantitative behavioral geneticists traditionally investigate the causes of variation responsible for individual differences in a population; they are interested in the relative contributions of genetic differences and environmental differences to total phenotypic variation in a population. Statistical methodologies, such as the analysis of variance (ANOVA), are then employed in an attempt to partition the relative contributions of these factors. These quantitative studies have been undertaken for nearly a century now. For example, population geneticist R. A. Fisher, the creator of ANOVA, undertook these statistical studies in the early-20th century in order to investigate the relative contributions of nature and nurture to physical traits such as stature as well as personality traits such as conscientiousness (Fisher 1918, 1924). Agricultural geneticist Jay Lush undertook these statistical studies in the mid-20th century in order to investigate the relative contributions of nature and nurture to agricultural traits such as milk yield in cattle (Lush 1937). And educational psychologist Arthur Jensen undertook these statistical studies in the late-20th century in order to investigate the relative contributions of nature and nurture to general intelligence (Jensen 1969). These studies were undertaken as a means to answer questions about the causes of group differences between populations. Fisher, a eugenicist, was interested in

different social classes in the United Kingdom; Lush was interested in different breeds of cattle; and Jensen was interested in different races in the United States (Kevles 1995). If phenotypic variation for a trait was largely the result of genetic differences, the inference went, then the differences in the trait between classes, cattle, or races could largely be attributed to genetic differences.

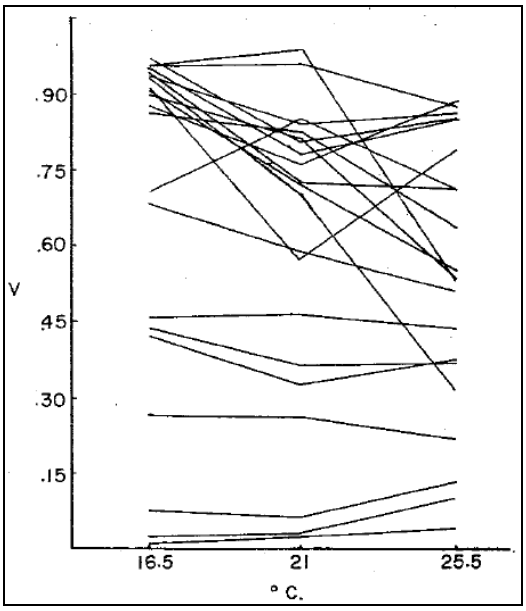
This inference only held up, however, if genetic differences and environmental differences fully accounted for the total phenotypic variation in the trait under investigation. In statistical terms, the "main effects" of genotype and environment must be "additive." If the genetic variation and the environmental variation were interdependent, then this additivity would break down. G×E is precisely this interdependence in genetic variation and environmental variation; as a result, it is sometimes referred to as "non-additive variation." If the total phenotypic variation in a trait under investigation results, in part or in whole, from the interdependence of genetic variation and environmental variation—that is, from G×E—then inferences made about group differences become suspect because total phenotypic variation can no longer be attributed to the separate actions of the main effects (Falconer and Mackay 1996).

Not surprisingly, then, critics of quantitative behavioral genetics have often pointed to G×E as a fundamental problem for those statistical methodologies. British statistician and experimental embryologist Lancelot Hogben introduced Figure 1.1 specifically to attack Fisher's statistical techniques for partitioning variation and to undermine the eugenic conclusions about class differences inferred from his statistical studies (Hogben 1933). Forty years later, evolutionary geneticist Richard Lewontin emphasized the importance of G×E in order to attack Jensen's statistical techniques for partitioning variation and to undermine educational policy conclusions about race differences inferred from his statistical studies (Lewontin 1974).

Lewontin, like Hogben, provided empirical examples of reaction norms from plant and non-human animal studies that displayed the divergent phenotypic curves often found in nature (Figure 1.2).



(a)



(b)

Figure 1.2. Reaction norm graphs. (a) Yarrow genotype, altitude during development (x-axis), and plant height in centimeters (y-axis) (Derived from Clausen, Keck, and Hiesey 1948). (b) Fruit fly genotype, temperature during development (x-axis), and viability of that genotypic group (y-axis) (From Lewontin 1974, Figure 2).

Hogben's and Lewontin's arguments were remarkably similar; they both pointed out that complex behavioral traits (such as conscientiousness or general intelligence) resulted from complicated developmental interactions between genes and the environment, and so variation due to G×E should be expected. And if variation in a complex behavioral trait was the result of G×E, they argued, then inferences made about the causes of group differences between populations as being either genetic or environmental in origin were unfounded. They both were

particularly interested in cases of G×E where the reaction norms of different genotypic groups crossed each other (as in Figure 1.2a and 1.2b), signifying the fact that the *higher-ranking* genotype in one environment could actually be the *lower-ranking* genotype in another environment.[2] Inferences about group differences between populations in unknown or untested environments were extremely dangerous, Hogben and Lewontin argued, for a higher-ranking genotype in current environments might actually become a lower-ranking genotype in other environments.

Defenders of the statistical methodologies, however, were unimpressed by the problem. Fisher, Lush, and Jensen all dismissed cases of G×E as only a *possible*, but *unproved*, complication for the evaluation of group differences. It was a possible complication; they readily admitted that this non-additive variation did complicate their statistical analyses. But it was also an unproved complication; as far as they were concerned, there was insufficient evidence of such cases of G×E, and so they put the burden of proof on their critics to show that the possible complication was an empirical reality. Hogben pointed Fisher to the *Drosophila* example from Figure 1.1, but Fisher questioned whether this was anything but an exceptional case in the natural world. Forty years later, Lewontin pointed Jensen to plant and non-human animal studies such as those in Figure 1.2, but Jensen questioned whether the same phenomenon should be expected in human populations. For years, defenders and critics argued over whether or not we should *assume* that G×E is common in human populations for complex behavioral traits (Tabery 2007). Are cases of G×E common in human populations, or are the cases identified by critics such as Hogben and Lewontin unusual occurrences?

[2] I will say more about this cross-over effect and its relationship to cases of G×E that do not involve a cross-over effect in the following chapter, where it will be critical to the argument there.

1.2. Gene-Environment Interaction in the Age of Molecular Genetics

This question began to be answered by Avshalom Caspi, Terrie Moffitt, and their colleagues with a series of empirical studies published between 2002 and 2005.[3] Caspi and Moffitt found cases of G×E in human populations for three complex human traits. The first study identified a case of G×E for a gene controlling neuroenzymatic activity, exposure to childhood maltreatment, and the subsequent development of antisocial personality disorder (Caspi et al. 2002). The second study identified a case of G×E for a gene controlling serotonin binding activity, exposure to stressful life events, and the subsequent development of depression (Caspi et al. 2003). And the third study identified a case of G×E for a gene involved in the metabolism of dopamine, exposure to cannabis use in adolescents, and the subsequent development of schizophrenia (Caspi et al. 2005). Cases of G×E, it seemed, *were* to be found in human populations.

Hogben and Lewontin, in their criticisms of quantitative behavioral genetics, could only point to cases of G×E in plant and non-human animal studies, while Caspi and Moffitt published a series of empirical studies on G×E in humans. Why? The answer, in short, was the onset of molecular genetics. Geneticists have long been able to raise plants and non-human animals with identical (or virtually identical) genomes in a varying environment, so as to obtain reaction norm data such as that depicted in Figures 1.1 and 1.2. But, for obvious ethical reasons, these same studies cannot be performed on humans. Twin studies are one potential method for avoiding this problem, but even twins reared apart only provide a geneticist with identical genomes in two environments. What if the geneticist is interested in how genomes respond to an array of environments involving three or four separate measurements? Cases of triplets or quadruplets

[3] I only mention these studies in passing here; the 2003 study and, in particular, the 2002 study will be discussed in detail in the subsequent chapters.

raised apart and available for genetic research are uncommon, making such studies virtually impossible.

Caspi and Moffitt's solution to this problem was to stop investigating what different *genomes* did in different environments and instead investigate what different *genes* did in different environments. With the onset of molecular genetics, particular genes may be identified in anyone's genome, and information about his or her environment along with his or her phenotype may also be gathered. So now you and I, even though we are unrelated, could both be recruited for a molecular genetics study. Perhaps we share the same variant of the gene controlling serotonin binding activity but have experienced different numbers of stressful life events. We can now be placed in the same genetic group (presumably with many other study participants who also share the same genetic variant) in order to see how individuals with this particular gene respond to varying levels of stressful life events, providing the data to construct a reaction norm for our genetic group. Our genetic group can also be contrasted with individuals from another genetic group, with a different variant of the gene controlling serotonin binding activity, in order to compare our genetic group's response to the varying levels of stressful life events with the other genetic group's response to this same array of environments.

Molecular genetics, in addition to opening the door to new genetic methodologies, also lends itself to talk of the genetic predispositions of individuals. If it turns out that individuals with our variant of the gene controlling serotonin binding activity are more likely to develop depression than individuals from the other genetic group across the range of environments tested, then should we say that you and I carry a *genetic predisposition to depression*? If the reaction norm for our genetic group is identical to that of the other genetic group, with the only exception being that individuals from our genetic group are consistently at increased risk of developing

depression, then it does seem to make sense to say our genetic group bears a genetic predisposition to depression in the tested environments. But what if the reaction norm for our genetic group looks quite different from the reaction norm of the other group? That is, what if there is G×E for this particular genetic variant, this array of environments, and depression? And what if the reaction norm for our group is so different from the reaction norm of the other group, that our group is *more* likely to develop depression in some environments than the other group but *less* likely to develop depression in other environments? That is, what if the G×E is so extreme that there is a cross-over effect like that found in Figure 1.2? As it turns out, this cross-over effect is precisely what Caspi and Moffitt found in their study of depression. Now who bears the genetic predisposition to depression?

This thesis is, in part, an effort to bring the arguments of Hogben and Lewontin concerning G×E to this new era of molecular genetics. The domain has changed. Hogben and Lewontin were interested in debates over group differences between populations; they were arguing against unwarranted generalizations made about different classes and different races. The debates that I will be considering are over individual predispositions based upon specific genes. Still, the basic point made by Hogben and Lewontin—that G×E can sometimes be so extreme that the reaction norms cross over—is applicable to the domain of individual predispositions. If reaction norms cross over, then we should be wary of generalizations made about the genetic basis of group differences. Likewise, if reaction norms cross over, then we should be wary of generalizations about the genetic basis of individual predispositions. But what can we say beyond this wariness of such generalizations?

1.3. Thesis Outline

The cases of G×E that result in a change of rank identified by Caspi and Moffitt have been characterized as if they display an instance of a *genetic predisposition* to antisocial personality disorder, depression, and schizophrenia. The concept of a genetic predisposition to these complex traits has shaped the subsequent bioethical discourse concerning the ethical implications of testing for the genetic variants involved in those studies. In chapter 2 I argue that this concept of a genetic predisposition fundamentally misconstrues the results of those studies because they exhibit the cross-over effect mentioned above. The purpose of chapter 2 is to reveal how the concept of a genetic predisposition misconstrues such cases and to then offer up an alternative concept—an interactive predisposition—to correct for the conceptual incoherence.

Chapters 3 and 4 then explore the implications of this switch from a genetic predisposition to an interactive predisposition in the context of the ethical debates surrounding genetic testing. In chapter 3, I focus on the ethical questions specifically raised by bioethical commentators on the Caspi-Moffitt MAOA study. These commentators have framed the discussion as if the ethical questions raised by the MAOA study stem from the fact that Caspi and Moffitt identified a genetic predisposition to antisocial personality disorder. But since Caspi and Moffitt identified an interactive predisposition to antisocial personality disorder, not a genetic predisposition, these ethical questions must be reconceived. I argue there that cases of interactive predispositions raise questions quite distinct from the more traditional questions raised by genetic predispositions. In particular, I claim that embryonic and fetal screening for MAOA activity falls victim to what I call "the myth of pre-environmental prediction" if such testing proceeds without considering information about the environmental variable involved in the interactive predisposition. I also claim that a mandatory program of newborn screening for

MAOA activity must face what I call "the interventionist's dilemma"; here, the problem is that an early intervention program designed to first identify those at risk of developing antisocial personality disorder with a genetic test for MAOA activity and then pharmacologically alter that MAOA activity will both *decrease* the risk of developing antisocial personality disorder in some individuals who receive the pharmacological treatment while simultaneously *increasing* the risk of developing antisocial personality disorder in other individuals who receive the pharmacological treatment.

Then, in chapter 4, I expand the discussion of the bioethical implications beyond the MAOA study and beyond the ethical questions raised by commentators on that study. I consider cases of interactive predispositions for a number of complex traits: asthma, depression, and schizophrenia. More specifically, I consider how cases of interactive predispositions should be figured into the ongoing debate over providing genetic tests for children at parental requests. The bioethical discussion surrounding genetically testing children has focused exclusively on cases of genetic determinism (think Huntington's disease) and genetic predisposition (think hereditary breast/ovarian cancer). The purpose of chapter 4 is to draw on the resources developed from these bioethical discussions and update them so as to incorporate potential genetic tests for interactive predispositions requested by parents for their children.

2. FROM A GENETIC PREDISPOSITION TO AN INTERACTIVE PREDISPOSITION: RECONCEPTUALIZING GENE-ENVIRONMENT INTERACTION

Abstract. The concept of *gene-environment interaction*, or G×E, refers to cases where different genetic groups respond differently to the same array of environments for a particular phenotypic trait. In a widely acclaimed study from 2002, researchers found a case of G×E for a gene controlling neuroenzymatic activity (low vs. high), exposure to childhood maltreatment, and the development of antisocial personality disorder (ASPD). Cases of G×E are generally characterized as evincing a *genetic predisposition* to the particular trait under investigation; for example, individuals with low neuroenzymatic activity are generally characterized as having a genetic predisposition to ASPD. This chapter will argue that the concept of a genetic predisposition *fundamentally misconstrues* these cases of G×E. This misconstrual will be diagnosed, and then a new concept—*interactive predisposition*—will be introduced to treat this conceptual incoherence.

2.1. Introduction

The concept of *gene-environment interaction*, or G×E, refers to cases where different genetic groups (i.e., two or more populations differentiated based upon a genetic difference) phenotypically respond differently to the same array of environments. For example, Avshalom Caspi, Terrie Moffitt, and their colleagues found a case of G×E for a gene controlling neuroenzymatic activity (low vs. high MAOA activity), exposure to childhood maltreatment (none vs. probable vs. severe), and the development of antisocial personality disorder (ASPD) (Caspi et al. 2002). MAOA is a metabolic enzyme that inactivates neurotransmitters such as dopamine, norepinephrine, and serotonin (Shih, Chen, and Ridd 1999); deficiencies in the enzyme have been associated with aggression (Rowe 2001). In the Caspi-Moffitt study, childhood maltreatment consisted in physical and sexual abuse. However, other experiences also counted as childhood maltreatment: harsh discipline (e.g. parents "smack him or hit him with something"), multiple changes in the primary caregiver, and poor mother-child interactions (e.g. rough handling of the child, consistent negative affect toward the child, indifference to child's performance). Individuals with none of these incidents in their past were classified as having no

experience with childhood maltreatment; individuals with one of these incidents in their past were classified as having experience with probable childhood maltreatment; and individuals with two or more of these incidents in their past were classified as having experience with severe childhood maltreatment.[4] As illustrated in Figure 2.1, Caspi and Moffit found that individuals with high-MAOA activity *gradually* increased their risk of developing ASPD as incidents of childhood maltreatment increased, whereas individuals with low-MAOA activity *drastically* increased their risk of developing ASPD as incidents of childhood maltreatment increased.

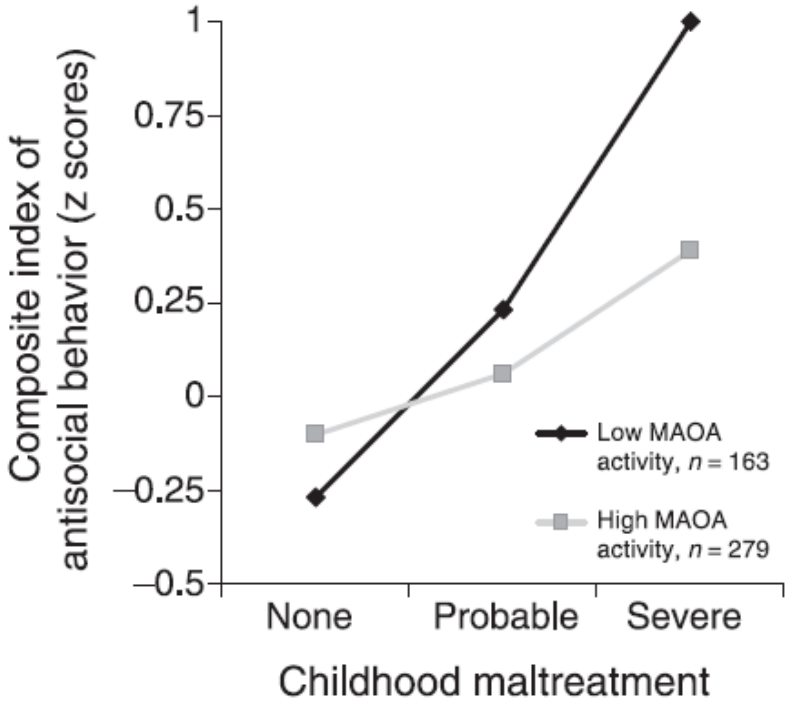


Figure 2.1. Reaction norm graph for MAOA activity, childhood maltreatment, and ASPD. (From Caspi et al. 2002, Figure 1).

[4] 'Probable', in this case, should be read as 'moderate'; it is a measure of severity or frequency, not a measure of certainty or probability. Also, it will be important to keep the less severe forms of childhood maltreatment in mind when we turn to the discussion of the ethical implications of this study in subsequent chapters.

The Caspi-Moffitt results, showing significant G×E for ASPD in a human population, were instantly recognized by scientists, the popular press, and academic commentators as a landmark achievement in the history of human genetics. Behavioral geneticist Dean Hamer, in a review article for *Science* just two months after Caspi and Moffitt published their results, identified the Caspi-Moffitt study as one of three examples paving the way for the future of behavioral genetics (Hamer 2002).[5] The *Economist* hailed the results that same week: "The first study has just been published showing how a particular gene and a particular environment interact to produce violent individuals" (*Economist* 2002, 71). Bioethicist Erik Parens wrote, "It might not be an exaggeration to say that, if replicated, the Caspi-Moffitt MAOA study will turn out to have been a watershed event in the history of behavioral genetics" (Parens 2004, S22). And legal scholar Robert Stone forecasted, "Although the predictive power of genetics has been discussed many times before, the Caspi Study may prove to be the beginning of a new era" (Stone 2003, 1559).

Why such enthusiasm? The enthusiasm can be attributed to two factors. First, as mentioned in the introductory chapter, the excitement was, in part, a function of the fact that Caspi and Moffitt identified a case of G×E in a human population; one aspect of the nature-nurture debate hinged on whether or not G×E was present in human populations, and their MAOA study offered an empirical answer to that question. Second, the fact that Caspi and Moffitt were studying MAOA, in combination with their particular experimental design, is also responsible for the attention. It has long been known that deficiencies in the metabolism of neurotransmitters were connected with aggressive behavior, but what part genes played in this deficiency and what the connection was between gene, neurotransmitter, and aggression

[5] The other two studies that Hamer identified as significant involved a neuroimaging study of differences in amygdale activity correlated with a genetic difference (Hariri et al.), and an examination of different patterns of gene expression for different alleles in a single person (Yan et al.).

remained a mystery. This connection began to be understood in 1993 with the publication of "Abnormal Behavior Associated with a Point Mutation in the Structural Gene for Monoamine Oxidase A" (Brunner et al. 1993). Han G. Brunner and his associates found a point mutation in the males of a large Dutch family, in which a cytosine base (**C**) was switched to a thymine base (**T**) in the individuals' DNA, thus switching the corresponding product from the amino acid glutamine (**C**AG) to a termination codon (**T**AG). The biochemical result of the point mutation was the complete and selective deficiency of MAOA in the 5 affected males of the family. The behavioral result was borderline mental retardation along with a tendency towards aggression and impulsivity manifested in the form of arson, attempted rape, and exhibitionism.

The paper, published in *Science*, attracted much attention and generated intense debate. The result, spun into a tale of a gene *for* aggression, naturally fascinated and outraged many in the legal, scientific, and lay communities. Stephen Mobley, a convicted murderer from Georgia, who robbed a Domino's Pizza in 1991, and then executed the store manager with a gun shot to the back of his neck, sought genetic testing to determine if he too was MAOA deficient, so that his death sentence might be revised, in light of genetically mitigating circumstances, to life in prison (***Mobley v. State***). Legal discussions of this 'genetic defense' quickly ensued (Andrews 2002; Coombs 1999; Denno 1996). Importantly, but less dramatically, the behavioral genetics community itself took a step back and reevaluated what it was researching, what it could reliably reveal about the causes of complex behaviors, and how that information could be put into practical use (Mann 1994). Indeed, Brunner himself, at a conference on the genetics of criminal and antisocial behavior, felt the need to deliver a paper on why his study was emphatically *not* the discovery of an aggression gene (Brunner 1996).

The Brunner et al. (1993) study raised much interest, but also had limitations. The study was confined to a single, Dutch family. There were only 5 affected individuals with the extreme metabolic deficiency. And the affected individuals also were afflicted with mental retardation, suggesting that the ensuing aggression may have just as easily been a result of the lowered intelligence rather than the lowered MAOA.

The Caspi-Moffitt study, in contrast, drew on the resources available from the Dunedin Multidisciplinary Health and Developmental Study in New Zealand, which has been tracking the lives of over 1000 New Zealanders from birth (April 1972-March 1973). In addition to constituting a large sample, the members also offered a representative sample of the general population, thus eliminating the confounding effects of samples drawn from single families or multiple families from isolated social or economic brackets. Drawing on this history, Caspi and Moffitt determined that 8% of the male participants experienced severe maltreatment between the ages of 3 and 11; 28% experienced probable maltreatment between these ages; and 64% experienced no maltreatment. All participants were then evaluated for antisocial behavior, based on convictions for violent crimes, psychological evaluations, and reports from others who knew the participants well. With this environmental and phenotypic information in place, the behavioral geneticists then established genotypic information for all the participants, determining whether the participants had genotypes associated with low or high MAOA activity. Thus, in contrast to the Brunner et al. (1993) study, which investigated a rare and severe genetic phenomenon in an isolated population, Caspi and Moffitt investigated a more common, variable, and less severe genetic phenomenon in a representative sample. This examination of MAOA with a highly valued experimental design is the other reason that the Caspi-Moffitt results received so much attention.

It was the significance of Caspi and Moffit's empirical *results* that received the wide attention. But what was just as significant, though less scrutinized, was *the way in which those results were conceptualized*. Individuals with low-MAOA activity were characterized as having a *genetic predisposition* to ASPD or, because of the correlation between ASPD and violent behavior, a *genetic predisposition* to violence. In his consideration of the familial cycle of abuse, Robert Stone wrote, "The Caspi Study demonstrates that, in addition to free will, the difference between those who break the cycle of abuse and those who do not turns on the victim's genetic predisposition" (Stone 2003, 1562). David Wasserman titled an article on the bioethical implications of the Caspi-Moffitt study, "Is There Value in Identifying Individual Genetic Predispositions to Violence?" (Wasserman 2004). Crucially, and as will be explored in more detail in subsequent chapters, this concept of a genetic predisposition has framed the ethical and legal reflections on this case of G×E. Jonathan Moreno, for instance, pointed to the Caspi-Moffitt study and advised, "If [MAOA] or other neurotransmitters are roughly associated with socially offensive behaviour, even under less extreme environmental insults, they could be brought into the controversy over preimplantation genetic diagnosis. Prospective parents might therefore test embryos for the MAOA marker before implantation to avoid giving birth to a child with this particular potential for criminality" (Moreno 2003, 151). And, considering the possible implications of the Caspi-Moffitt study on the criminal justice system, Paul Appelbaum asked, "Should genetic propensities mitigate punishment for criminal behavior?" (Appelbaum 2005, 26).

The thesis of this chapter will be that this concept of a genetic predisposition *fundamentally misconstrues* cases of G×E such as that found in the Caspi-Moffitt study. In turn, the ethical discussions of a "genetic predisposition to violence" have been equally misconceived.

In the next section of this chapter, I focus on exposing how the concept of a genetic predisposition fundamentally misconstrues these cases of G×E. With that diagnosis made, I then offer in section 2.3 a remedy for the conceptual incoherence by introducing a new concept for these cases of G×E—*interactive predisposition*. The conceptual shift from a genetic predisposition to an interactive predisposition will pave the way for the subsequent chapters in which I explore how this shift reframes questions concerning the incorporation of research on G×E into ethical discussions of screening embryos, fetuses, and newborns for an interactive predisposition to ASPD (chapter 3), or testing children for interactive predispositions to a wider variety of complex traits, such as asthma, depression, and schizophrenia (chapter 4).[6]

2.2. G×E and the Concept of a Genetic Predisposition

As described in the introduction, cases of G×E are generally characterized in terms of a genetic predisposition to the trait under investigation; for example, individuals with low-MAOA activity from the Caspi-Moffitt study are characterized as having a genetic predisposition to violence. The goal of this section is to convey how this concept *fundamentally misconstrues* cases of G×E. Understanding this misconstrual begins by recognizing the fact that cases of G×E come in two forms: those resulting in a change in *scale*, and those resulting in a change in *rank* (Lynch and Walsh 1997). The traditional concept of a genetic predisposition, I will argue, is appropriately applied only to cases of a change in scale; the misconstrual arises when it is also applied to cases of a change in rank.

[6] The grouping of embryos, fetuses, and newborns here should not be interpreted as an implicit argument for the moral equivalence of humans at these developmental stages. Rather, it is a practical grouping; the commentators who I will discuss in chapter 3 have raised the prospect of screening humans at each of these developmental stages. As we will see, the group will be divided between pre-implantation genetic diagnosis and fetal screening, on the one hand, and newborn screening, on the other hand.

2.2.1. A Change in Scale

An instance of G×E resulting only in a change of scale refers to cases where different genetic groups respond differently to the same array of environments, but that difference in phenotypic response does not alter the fact that the higher-ranking group maintains that higher ranking across *all* tested environments (Lynch and Walsh 1997). An example will help to display this phenomenon, so consider the reaction norm graph in Figure 2.2. This is a hypothetical, modified version of the original graph from the Caspi-Moffitt study. Everything in Figure 2.2 is identical to the original graph except that the high-MAOA group has been lowered by 0.25 on the antisocial behavior index for each environment. That is, the high-MAOA group has been bumped down on the y-axis. Now the low-MAOA group maintains its higher ranking on the antisocial behavior index in each of the tested environments. This is still a case of G×E because the two groups do still respond to the array of environments quite differently, but all that has changed is the *scale* of the difference between the two groups in the different environments. That is, the two reaction norms are not parallel; the high-MAOA group increases on the antisocial behavior index as incidents of childhood maltreatment increase but only gradually in comparison to the low-MAOA group, which increases on the antisocial behavior index quite drastically as incidents of childhood maltreatment increase.

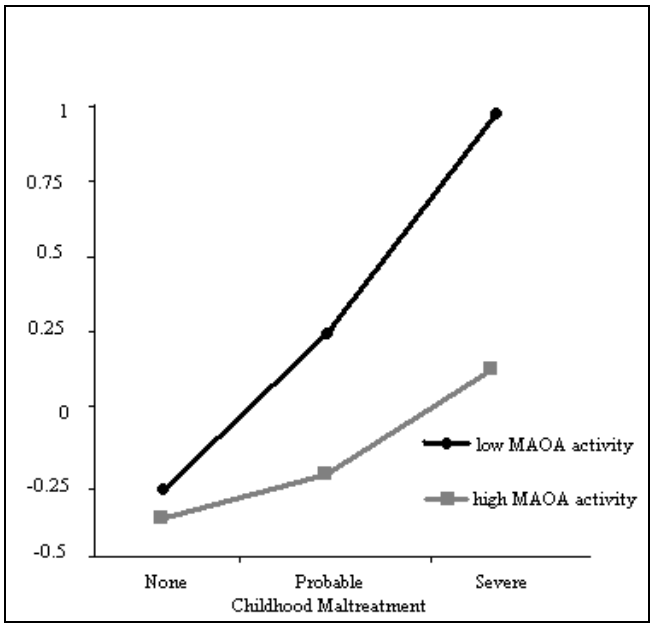


Figure 2.2. Hypothetical reaction norm graph for MAOA activity, childhood maltreatment, and ASPD.

To begin evaluating the appropriateness of the concept of genetic predisposition as applied to cases of G×E, a definition of this concept must first be afforded. "Genetic predisposition" may be defined as follows:

> **Genetic Predisposition**: The presence of a genetic difference between various groups *consistently* increases the probability of individuals from one group, *in comparison to individuals from the other group(s)*, developing a particular phenotypic trait regardless of the tested environmental conditions of development.

Note the relational nature of this definition. Members of *any* group may be susceptible to developing the particular phenotypic trait under investigation if exposed to the environmental stressor. But attaching "genetic" to "predisposition" is only appropriate if it is the *genetic* difference that consistently increases the probability of individuals from one group developing the phenotypic trait relative to individuals from the other group(s). Also note the fact that the relative predisposition is only justifiably applicable within the *tested* environmental conditions of

development. Under unknown or untested environmental conditions of development, the relationship between the groups might change quite drastically. Thus, one cannot assume that just because individuals in a particular group are relatively genetically predisposed to a particular phenotypic trait under known environmental conditions of development that this relationship will hold true under any environmental conditions of development.

Cases of G×E resulting in a change of scale may be appropriately characterized with the concept of a genetic predisposition as defined above. Consider the hypothetical Caspi-Moffitt case graphed in Figure 2.2: in every tested environment (none, probable, and severe childhood maltreatment), individuals in the low-MAOA group maintained their relatively elevated risk for ASPD; moreover, the slope of the low-MAOA group was much steeper than that of the high-MAOA group as the instances of childhood maltreatment increased. What "genetic predisposition" implied in this case, then, was that the presence of the *genetic* difference between the two groups *consistently* put individuals from the low-MAOA group at an increased risk of developing ASPD relative to the individuals from the high-MAOA group. And again, notice that the account here was necessarily relational. As the instances of childhood maltreatment increased, both groups significantly increased on the antisocial behavior index. In statistical terminology, the environmental variable was a statistically significant main effect. Thus, individuals from both genetic groups were susceptible to developing ASPD in the presence of childhood maltreatment. But there still remained a *consistent* phenotypic difference between the genetic groups in each tested environment, and this difference itself increased drastically as the instances of childhood maltreatment increased. There was a change between the groups across the different environments, but it was only a change in *scale*. Or, for an empirical example, consider the BRCA1 and BRCA2 alleles responsible for increased risk of breast and ovarian

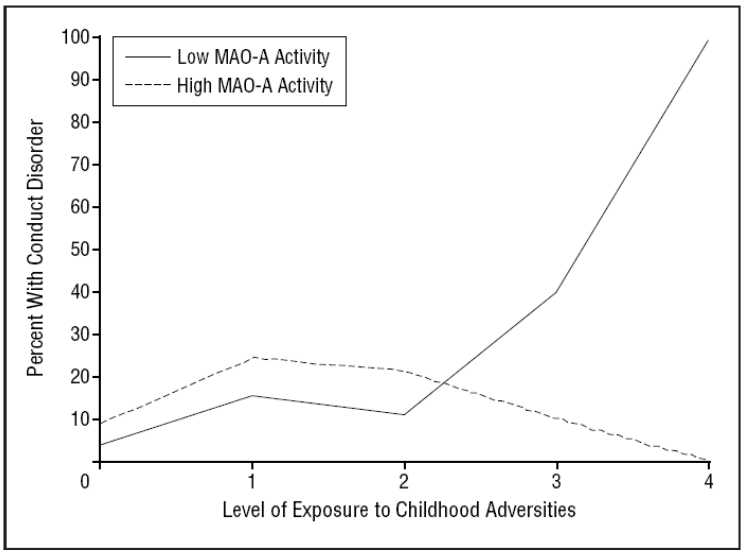
cancers. A ‘genetic predisposition to breast/ovarian cancer’ is appropriately linked with these alleles, since bearing these alleles consistently increases the risk of developing breast/ovarian cancer in the known environments.

2.2.2. A Change in Rank

But notice that the above account is decidedly *not* what occurs in the actual Caspi-Moffitt study. Caspi and Moffitt’s MAOA study is instead an instance of G×E resulting in a change of *rank*. An instance of G×E resulting in a change of rank refers to cases where different genetic groups respond differently to the same array of environments, and that difference in phenotypic response is so extreme that the *higher-ranking* group in one environment becomes the *lower-ranking* group in a different environment (Lynch and Walsh 1997). Notice that this is precisely what we find in the actual reaction norms for the Caspi-Moffitt study’s low- and high-MAOA groups graphed above in Figure 2.1. In the environments with probable and severe childhood maltreatment, the low-MAOA group did in fact score higher on the antisocial behavior index than the high-MAOA group. However, in the environment with no childhood maltreatment the low-MAOA group actually scored *lower* than the high-MAOA group on the index. Importantly, this case of G×E did not display the *consistency* in the relationship between the two groups across all of the tested environments, which was described in the hypothetical case of a change in scale described above.

The original Caspi-Moffitt study has now been replicated several times. In 2004, a group of behavioral geneticists at the University of Virginia investigated the phenomenon in a new population from the United States (Foley et al. 2004). Their replication was slightly altered. They still differentiated genetic groups based on low- vs. high-MAOA activity; however, they instead

tracked childhood conduct disorder (CD), the childhood equivalent of ASPD. Nevertheless, their results were *consistent with the change in rank*, as can be seen in Figure 2.3. More recently, Caspi and Moffitt themselves participated in a replication study with a new population from Britain (Kim-Cohen et al. 2006). And again, their results were *consistent with the change in rank*. There have also been two failures to replicate the interaction effect (Haberstick et al. 2005; Young et al. 2006); however, the study by Kim-Cohen et al. (2006) also included a meta-analysis of the data from the multiple sources, and the interaction effect was significant.



Prevalence of conduct disorder as a function of monoamine oxidase A activity and level of exposure to childhood adversities.

Figure 2.3. Reaction norm graph for MAOA activity, childhood adversity, and conduct disorder. (From Foley et al. 2004).

Interestingly, while the reaction norms in both Figures 2.1 and 2.3 do clearly cross each other (or change in rank), the difference between the two genetic groups in environments with no childhood maltreatment/adversity is *not* statistically significant. In other words, the gap between the two groups could conceivably be the result of chance. If the gap really is due to chance and

there is no actual difference between these two genetic groups, then my analysis in this chapter is inapplicable to the case of MAOA, childhood maltreatment, and the development of ASPD, since the case would be reduced to one of a change in *scale*. To be clear, it would not mean that my analysis of the inappropriateness of the concept of a genetic predisposition to cases of G×E resulting in a change of rank is mistaken, but it would mean that the MAOA case does not fall within this category. However, there is good reason to attribute the lack of significance to a different explanation—insufficient sample size. It is notoriously difficult to detect interaction effects without very large sample sizes. Starting with the Caspi-Moffitt study and continuing with the multiple replications, the results of these studies repeatedly display the change in rank for the genetic groups across the array of environments. However, these studies generally include only several hundred participants with only a proportion in each environment, providing relatively little statistical power to tease apart a genetic difference in the separate environments. Foley et al., in the discussion of their results, reached a similar conclusion: "An interaction without a significant main effect of genotype results in a crossing-over or reordering of risk among groups contingent on environmental exposure. In this case, risk associated with a specific genotype differs qualitatively in association with different environments. Variation in exposure to environmental risks reorders genotypic effects. Our data are consistent with [this] explanation, but a larger study is required to definitively address this possibility" (Foley et al. 2004, 742). It seems prudent, then, to assume that the change in rank is a very real possibility. Such prudence is especially justified when we remember that the identification of these cases of G×E in humans is a fairly young enterprise, while the identification of these cases of G×E in plants and non-human animals has been quite common in the history of genetics. As mentioned in chapter 1, Lewontin

pointed to two cases of G×E that resulted in a change of rank in the context of the IQ Controversy—one for the plant yarrow and one for the fruit fly *Drosophila*.

With regard to the human study by Caspi and Moffitt, ignoring the very real possibility that their results reflect at true change in rank and not just chance, would have a terrible impact on efforts to utilize this data for purposes of genetic testing any population—embryos, fetuses, newborns, or children. The relevance of the Caspi-Moffitt results for genetic testing will be the topic that I take up in the subsequent chapters. In the meantime, I will proceed in this chapter as if the change in rank is real for the MAOA case and continue to diagnose the fundamental misconstrual that arises from characterizing it with the concept of a genetic predisposition.

The concept of genetic predisposition, as defined above, captures cases where a genetic difference between groups consistently increases the probability of individuals from one of these groups developing a phenotypic trait regardless of the tested environmental conditions experienced during development. But in the Caspi-Moffitt study the environmental conditions were crucial for assessing the relationship between the low-MAOA and the high-MAOA groups with regard to risk of developing ASPD. Prior to an individual actual experiencing—or otherwise determining the environmental conditions (i.e., the degree of childhood maltreatment) that the individual faces, there is simply no way to assess whether an individual with low-MAOA activity will be more or less prone to developing ASPD than an individual with high-MAOA activity. The low-MAOA individual is *less* likely to develop ASPD in environments with no childhood maltreatment, while s/he is *more* likely to develop ASPD in environments with probable and severe childhood maltreatment. Employing the concept of a *genetic predisposition* to ASPD when the environmental conditions of development are unknown, we are forced *incoherently* to say that individuals in the low-MAOA group are simultaneously *more* prone to

developing ASPD and, at the same time, *less* prone to developing ASPD. In short, the concept of a genetic predisposition fundamentally misconstrues these cases of G×E resulting in a change of rank because it leads to this incoherent result.

2.3. G×E and the Concept of an Interactive Predisposition

Several bioethicists have rightly stressed the need to promote conceptual clarity concerning G×E research and behavioral genetic research more generally in light of the looming social, ethical and legal implications of this research. Parens warned, "…the consequences of new information about genetic influences on the sorts of people we are will to a large extent be determined by the interpretations we arrive at in the course of our public conversation" (Parens 2004, S27). He thus called for "conceptual tools—basic concepts and distinctions" that will guide this public conversation (ibid, S30). Likewise, Richard Sharp wrote, "Clarifying these emerging areas of concern is an important step in minimizing the potential harms of deciphering complex gene-environment interactions" (Sharp 2001, 146). Suggestions such as these should be heeded, for there is already an indication that G×E results can be quickly morphed into interpretations of 'genes for' complex behavioral traits, reverting to a naïve genetic essentialism (Dreyfuss and Nelkin 1992). Parens has pointed to alarming distillations of the Caspi-Moffitt study in the popular press. "That behavioral geneticists are studying such interactions is good news," Parens reminded his readers; however, "the bad news is that the MAOA study was the subject of a piece in *Popular Mechanics* titled 'Criminal Genes.' The piece in *Time* about the MAOA study was entitled, 'The Search for the Murder Gene.' Although both reporters told subtler stories than the titles announced, the idea that some kids are simply born bad persists. Even though the Caspi and Moffitt MAOA study is about the interaction between genes and child abuse, the story titles in

the popular press suggest that genes 'cause' criminality" (Parens 2004, S8). And the *Economist*, though not encouraging a 'gene for' interpretation of the results of the Caspi-Moffitt study, did warn of the 'gene for' interpretation that could easily follow: "Low-activity promoter regions could be regarded as 'genes for violence' that need a violent context to be expressed. That might make sense in evolutionary terms, since a child brought up in violent surroundings will probably live in a violent world as an adult and might therefore need to employ violence to thrive. On the other hand, high-activity promoter regions could be regarded as genes for the suppression of violence" (*Economist* 2002, 71).

Should we really be surprised that the Caspi-Moffitt study has been morphed into a story about "Criminal Genes" when the concept of a *genetic predisposition* to violence has been used to characterize the results? With the concept of a genetic predisposition to violence, the rigidly deterministic nature of the genetic element may have been abandoned, but it is still the "genetic" that is in the driver's seat. That is, it is still the "genetic" that is doing the predisposing. Or, more accurately, it is still the genetic difference that is associated with the difference in relative predisposition. It may be inappropriate to title articles in the popular press about the Caspi-Moffitt study "Criminal Genes" or "The Search for the Murder Gene," but what about "Criminal Susceptibility Genes" or "The Search for the Murder-Liability Gene"? Would these alternatives be acceptable? If one were entitled to employ the concept of a genetic predisposition to violence, then I do not see how one *could* criticize such distillations. But when we realize that the Caspi-Moffitt study was a case of G×E resulting in a change of *rank*, then we clearly see that even the non-deterministic alternative titles are misleading. Which variant of the gene associated with MAOA activity is the criminal susceptibility gene—low or high? Which variant of the gene associated with MAOA activity is the murder-liability gene—low or high? The lesson of the last

section was that these questions are meaningless unless the environmental conditions are specified.

I am in agreement with Parens's and Sharp's diagnoses. Conceptual clarity is exactly what is needed to properly discuss instances of G×E and convey the ethical and legal implications of this phenomenon. In this spirit, I suggest jettisoning the concept of a genetic predisposition from the discussions of G×E that result in a change of rank. As Parens suggested, "conceptual tools" are needed here. A new concept is needed to capture the different, unique relationship between gene, environment, and phenotype found in these cases and to set this relationship (and the implications of this relationship) apart from cases of genetic predisposition or genetic determinism. I propose employing the concept of an *interactive predisposition* for such cases. "Interactive predisposition" may be defined as:

> **Interactive Predisposition**: The presence of a genetic difference between various groups can either *increase* or *decrease* the probability of individuals from one group, *in comparison to individuals from the other group(s)*, developing a particular phenotypic trait *depending on the environmental conditions experienced during development*.

A genetic predisposition is relational in one sense, whereas an interactive predisposition is relational in *two* senses. Like the concept of a genetic predisposition, the concept of an interactive predisposition is relational in the sense that the probability of individuals from one group developing the phenotypic trait under investigation is always considered *in comparison to* individuals from the other group(s) developing the phenotypic trait. For a genetic predisposition, however, that relation between the groups maintains a consistency (between which is higher and which is lower ranking) across all tested environments, whereas this is not the case for an interactive predisposition. For an interactive predisposition, the relation between the groups is *itself relative* to the environmental conditions experienced during development.

Before concluding this chapter focused on the conceptualization of G×E, a few words should be said about the relationship between the concept of an interactive predisposition and already existing concepts. Why not, for instance, just use the already existing concept of *genetic sensitivity* to describe cases of G×E resulting in a change of rank? Introduced by Kenneth Kendler and Lindon Eaves (1986), "genetic sensitivity to the environment" has become the standard phrase to apply to cases of G×E. Notice, though, the difference between the concepts of genetic *predisposition* and genetic *sensitivity*. These concepts are capturing quite different relationships. *Predisposition* refers to the relationship between a gene and the probabilistic development of a *phenotypic* trait. *Sensitivity*, in contrast, refers to the intimate relationship between a gene and the *environmental* conditions experienced by an individual during development. In short, *predisposition* refers to the gene-phenotype relationship, while *sensitivity* refers to the gene-environment relationship. Likewise, the cognates of genetic predisposition, such as genetic *propensity*, genetic *liability*, and genetic *risk*, refer to the gene-phenotype relationship, while the cognates of genetic sensitivity, such as genetic *vulnerability* and genetic *susceptibility* (to environmental stressors), refer to the gene-environment relationship. Genetic sensitivity, then, is a general concept that captures all cases where the environment moderates gene action. That is, the concept of genetic sensitivity is applicable to all cases of G×E, be they changes in scale or changes in rank.

However, in capturing the general gene-environment relationship, the concept of genetic sensitivity cannot distinguish between the different instantiations of G×E (change in scale vs. change in rank). The concept of a *genetic predisposition* (or propensity, liability, or risk) is applicable to cases of G×E resulting in a change of scale; it incorporates the implied *genetic sensitivity* of all cases of G×E, but it also specifies the way in which that general gene-

environment relationship manifests itself in the form of the phenotype for different groups. That is, the gene-environment relationship for one group (i.e., its genetic sensitivity) *consistently* increases the probability (in comparison to the other group(s)) of developing the phenotypic trait under investigation regardless of the environmental conditions of development. The concept of an *interactive predisposition* is applicable to cases of G×E resulting in a change of rank. Like genetic predisposition, interactive predisposition also incorporates the implied *genetic sensitivity* of all cases of G×E, but it also specifies the way in which that general gene-environment relationship manifests itself in the form of the phenotype for different groups. That is, the gene-environment relationship for one group (i.e, its genetic sensitivity) can either *increase* or *decrease* the probability (in comparison to the other group(s)) of developing the phenotypic trait under investigation depending on the environmental conditions experienced during development. The relationship between cases of G×E and the concepts of genetic sensitivity, genetic predisposition, and interactive predisposition is diagrammed in Figure 2.5. Within this figure, I have represented instances of G×E resulting in a change of scale and instances of G×E resulting in a change of rank both occupying equal portions of all cases of G×E; however, it is of course an empirical question as to which of these is more common in nature.

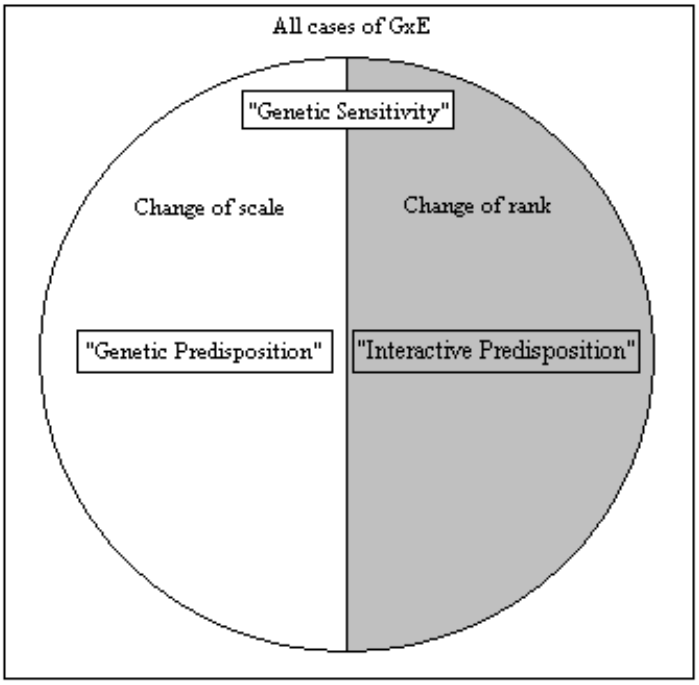


Figure 2.4. The relationship between cases of G×E and the concepts of genetic sensitivity, genetic predisposition, and interactive predisposition.

2.4. Conclusion

This chapter examined how cases of G×E are conceptualized. Cases of G×E, such as that found in the Caspi-Moffitt study, are generally characterized as representing a *genetic predisposition* to the trait under investigation. I argued that this concept of a genetic predisposition, while appropriate for cases of G×E resulting in a change of scale, *fundamentally misconstrues* cases of G×E resulting in a change of rank. For cases of G×E resulting in a change of rank, individuals are incoherently understood to be simultaneously *more* and *less* genetically predisposed to the trait under investigation. With this diagnosis made, I then offered a remedy for this conceptual incoherence—a new concept for cases of G×E resulting in a change of rank: *interactive predisposition*.

This conceptual shift from a genetic predisposition to an interactive predisposition paves the way for investigating how this shift reframes the ethical discussions of a G×E for neuroenzymatic activity, childhood maltreatment, and ASPD. Since the publication of the Caspi-Moffitt study, ethical discussions of the implications of their results have been framed in terms of individuals having a genetic predisposition to ASPD and violence. The conclusion of this chapter, however, has been that employing this concept of a genetic predisposition fundamentally misconstrues the results of the Caspi-Moffitt study, since it is an instance of a G×E resulting in a change of rank. It is time, then, to investigate how the shift from a genetic predisposition to an interactive predisposition translates into a shift in how the ethical implications of the Caspi-Moffitt study should be understood. It is to this task that I now turn.

3. GENETIC SCREENING FOR AN INTERACTIVE PREDISPOSITION: THE MYTH OF PRE-ENVIRONMENTAL PREDICTION AND THE INTERVENTIONIST'S DILEMMA

Abstract. Antisocial Personality Disorder (ASPD) takes a significant toll on those who suffer from the disorder and on those who are forced for whatever reason to interact with those who suffer from the disorder. So it is not surprising that efforts are made to prevent the development of ASPD by predicting who is at risk of developing ASPD and intervening on those variables deemed responsible for this development. The 2002 study by Avshalom Caspi, Terrie Moffitt, and their colleagues on a gene controlling MAOA activity (low vs. high), childhood maltreatment, and ASPD has been highlighted by commentators as a possible empirical basis for preventing ASPD. The thought is to identify those predicted to be "genetically predisposed to ASPD" (i.e., the low-MAOA individuals) either through preimplantation diagnosis, fetal screening, or newborn screening. Then, parents could avoid giving birth to low-MAOA children by selecting against low-MAOA embryos and fetuses. And states could identify low-MAOA newborns and implement an early intervention program to provide an "MAOA boost" to those in need. The problem with these analyses is that they mistakenly assume that Caspi and Moffitt identified an instance of a *genetic predisposition* when in fact they identified an instance of an *interactive predisposition*. Screening for interactive predispositions raises a series of ethical questions that are distinct from the standard ethical questions raised by screening for genetic predispositions. This chapter will explore these ethical questions. Screening embryos or fetuses with an eye towards selecting against low-MAOA individuals will be shown to suffer from the trappings of the *myth of pre-environmental prediction*. Screening newborns with an eye towards early intervention will be shown to face the *interventionist's dilemma*.

3.1. Introduction

Antisocial Personality Disorder (ASPD) is the clinical term for sociopathy. According to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR), ASPD is defined by a pervasive pattern of disregard for and violation of the rights of others. It is diagnosed in an individual when there is evidence of three or more of the following: (1) failure to conform to social norms with respect to lawful behaviors as indicated by repeatedly performing acts that are grounds for arrest, (2) deceitfulness, as indicated by repeated lying, use of aliases, or conning others for personal profit or pleasure, (3) impulsivity or failure to plan ahead, (4) irritability and aggressiveness, as indicated by repeated physical fights or assaults, (5) reckless disregard for safety of self or others, (6) consistent irresponsibility, as indicated by repeated failure to sustain

steady work or honor financial obligations, and (7) lack of remorse, as indicated by being indifferent to or rationalizing having hurt, mistreated, or stolen from another (American Psychiatric Association 2000).[7]

ASPD, which affects roughly 3% of males and 1% of females (Fishbein 2000a), takes a significant toll on those who suffer from the disorder and on those who are forced for whatever reason to interact with those who suffer from the disorder. In disregarding and violating the rights of others, those with ASPD regularly engage in actions that are deemed inappropriate and potentially illegal by the society in which they live; such actions, in turn, lead to broken relationships, and possibly to incarceration or a more extreme punishment. Friends and family members of those with ASPD must interact with and perhaps even care for these individuals despite the fact that they are in constant threat of being lied to, manipulated, or physically abused. Members of society in which those with ASPD live also must co-exist with these individuals; they are also in danger of having their rights violated, and they are responsible for funding the state's criminal justice system which captures, judges, and incarcerates these individuals, as well as the state's mental health institutions which also often house them.

So it is not surprising that efforts are made to prevent the development of ASPD (Fishbein 2000a; McCord and Tremblay 1992; Reid and Eddy 1997). These preventative strategies generally consist in the *prediction* of those individuals deemed at risk of developing ASPD and the *intervention* on those factors deemed pertinent to this development. For better or worse, the prediction of those who are at risk of developing ASPD is thoroughly probabilistic. Quantitative behavioral genetic studies reveal a heritable element for the disorder (Carey and Goldman 1997; Goldman and Fishbein 2000; McGuffin and Thapur 1998). But there are no

[7] A personality disorder like ASPD is classified as Axis II of the DSM-IV-TR, as oppose to clinical/mental disorders such as schizophrenia or posttraumatic stress disorder, which are classified as Axis I.

single genes that deterministically ensure the development of ASPD (Carey 1996; Ridenour 2000); candidate genes have been identified, but most individuals with these genes still do *not* develop ASPD (Goldman 1996). There are also no natural environments that deterministically ensure the development of ASPD. Certain environmental variables, like childhood maltreatment or coercive parenting, do account for a significant portion of variation for ASPD in a population, but still most children who are maltreated or coerced do *not* develop ASPD (Reid, Patterson, and Snyder 2002).

What made the study by Avshalom Caspi, Terrie Moffitt, and their colleagues so exciting, then, was the fact that they found a particular genetic variable and a particular environmental variable which, when joined, led to *almost all* individuals developing ASPD (Caspi et al. 2002). More specifically as shown in Figure 3.1, Caspi and Moffitt found that 85% of the individuals in their sample who both had low-MAOA activity and experienced severe childhood maltreatment (see highlighted portion on Figure) subsequently engaged in antisocial behavior. To relate this finding to the question of societal impact, Caspi and Moffitt found that, while only 12% of the sample fell into this low/severe sub-group, they accounted for a full 44% of the violent convictions of the entire study population.

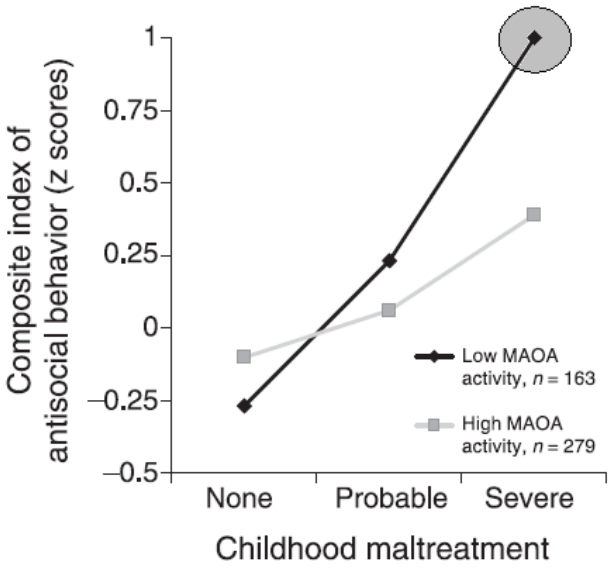


Figure 3.1. Reaction norm graph for MAOA activity, childhood maltreatment, and ASPD with low/severe sub-group highlighted. (Modified from Caspi et al. 2002, Figure 1).

In light of the striking results from the Caspi-Moffitt study, how might their findings be incorporated into the ethical discussions of genetic screening for a complex behavioral trait? Commentators on the Caspi-Moffitt study have pointed to two potential venues for such a genetic test: (a) *parents* interested in screening either embryos or fetuses with an eye toward implantation or termination, and (b) *states* interested in a policy of mandatory newborn screening with an eye toward prediction and intervention.

"I've taken the liberty of eradicating any potentially prejudicial conditions: premature baldness, myopia, alcoholism and addictive susceptibility, *a propensity for violence*, obesity, etcetera" (emphasis added). This line was spoken by a genetic counselor portrayed in the "not-too-distant" future in the 1997 movie *GATTACA*. In this fictional future, parents can choose either to engage in a "faith-based" pregnancy and leave their child's phenotypic future to chance, or to visit a genetic counselor such as the one mentioned above and select which genes he or she

will have. How distant is this "not-too-distant" future? Perhaps surprisingly, steps are already being taken to bring this future into the present. Neuromark, a Colorado-based company founded in 2001 by CEO Kim Bechthold, is currently seeking FDA approval to make available to the public a genetic test for the gene controlling MAOA activity—the gene which figured so crucially in the Caspi-Moffitt study. So, rather than considering some abstract future, we are now in a position to ask very real questions with looming answers: Will genetic counselors soon offer prospective parents the choice between a child with low- or high-MAOA activity? Will a state soon be able to utilize the results of the Caspi-Moffitt study to predict and intervene on those with an alleged propensity for violence?

The purpose of this chapter is to address these questions that have been raised by commentators by drawing on the lesson of chapter 2 and then exploring the ethical questions that are raised by screening for interactive predispositions rather than genetic predispositions. The moral will be that screening for interactive predispositions raises a series of ethical questions that are distinct from those raised by screening for genetic predispositions. Attempts to appropriate the results from the Caspi-Moffitt study for preimplantation or fetal diagnosis will suffer from what I call the *myth of pre-environmental prediction* in the next section. Attempts to appropriate the results from the Caspi-Moffitt study in order to implement a policy of mandatory newborn screening will have to face what I discuss as the *interventionist's dilemma* in section 3.3.

3.2. Preimplantation Genetic Diagnosis, Fetal Screening, and the Myth of Pre-Environmental Prediction

The preimplantation genetic diagnosis of embryos and the genetic screening of fetuses both raise interesting ethical questions. Is the utilization of genetic information to determine who should

and should not be born a reversion to the negative eugenic practices of the early-20th century (Paul 1994)? The utilization of genetic information in order to select against potential humans with undesirable traits certainly smacks of eugenic motivations (Duster 1990). But now it is the *parents* of embryos and fetuses doing the selecting, not the *state*, so if the threat of eugenics is real, it is certainly of a different sort (Buchanan, Brock, Daniels, and Wikler 2000; Kitcher 1996). The purpose of this section will not be to carve out a position on this broad social debate. Rather, the purpose will be to assess how the results of the Caspi-Moffitt study *are being* and *should be* incorporated into this broad social debate. That is, the question to be addressed is the following: What precisely are the implications of the Caspi-Moffitt study for the ethical discussions of preimplantation genetic diagnosis and fetal screening? The argument will be that these implications are being misconceived by commentators who misunderstand the Caspi-Moffitt study to reveal a genetic predisposition to ASPD or violence, when instead the Caspi-Moffitt study reveals an interactive predisposition. Screening for an interactive predisposition raises ethical questions that are distinct from those raised by screening for a genetic predisposition.

Jonathan Moreno, in his discussion of the Caspi-Moffitt study, warns, "if [MAOA] or other neurotransmitters are roughly associated with socially offensive behaviour, even under less extreme environmental insults, they could be brought into the controversy over preimplantation genetic diagnosis. Prospective parents might therefore test embryos for the MAOA marker before implantation to avoid giving birth to a child with this particular potential for criminality" (Moreno 2003, 151). And David Wasserman, asking "Is There Value in Identifying Individual Genetic Predispositions to Violence?", introduces his article with a similar question. Since Caspi and Moffitt found that the 12% of their research participants who were both maltreated and

carrying the gene for low-MAOA activity accounted for 44% of all convictions for violent crimes, Wasserman wonders, "what if we could identify some individuals in that 12% not only at birth, but in utero, or before implantation?" (Wasserman 2004, 24). Wasserman warns against using such information to selectively implant, abort, or intervene on those with a "violence propensity"; for instance, Wasserman argues that a society may want to have these low-MAOA, violence-prone individuals around: "maybe Kitty Genovese, who was murdered on a New York City street while more than thirty witnesses did nothing would have been more likely to survive her attack if there were more low MAOA men on her block" (ibid, 29).

It is important to note that Moreno and Wasserman do *not* advocate utilizing the results of the Caspi-Moffitt study for the purposes of preimplantation genetic diagnosis or fetal screening. Rather, they are simply drawing attention to the ethical questions raised by the possibility that these results could be utilized for screening purposes because it may seem reasonable to select against low-MAOA individuals with a genetic predisposition (or "propensity" for Moreno and Wasserman) to violence. My claim is that, by framing these ethical questions in terms of the concept of a genetic predisposition to violence, they have both fallen trap to the *myth of pre-environmental prediction* and thereby misconceived the ethical questions raised by the Caspi-Moffitt study.

For example, should parents want to screen their embryos or their fetuses for the gene controlling MAOA activity in order to identify and select against those embryos or fetuses with low-MAOA activity, as Moreno warns? *Only if the parents are already intending to maltreat their children!* That is, if the children are not likely to experience childhood maltreatment, then it is in fact the low-MAOA embryos or fetuses that are *less* likely than the high-MAOA embryos or fetuses to develop into adults with ASPD. Would Kitty Genovese, as Wasserman wonders, have

been better off if there were more low-MAOA men living on her block? *Only if we assume that those men experienced childhood maltreatment.* That is, if the men on her block had not experienced childhood maltreatment, then it would have been the high-MAOA men who were more likely to develop ASPD.[8] Slipping into the myth of pre-environmental prediction arises when one forgets that Caspi and Moffitt found an instance of an interactive predisposition and assumes that the genetic information alone is enough to label the low-MAOA individuals "genetically predisposed to ASPD or violence."

Importantly, once we keep the myth of pre-environmental prediction in sight and avoid slipping into its trappings, it does not follow that the ethical questions raised by genetic screening disappear. Instead, a new series of questions arise. For example, if parents can reasonably predict that their children will not experience childhood maltreatment, then it would be the *high*-MAOA embryos or fetuses that will be selected against if the parents wanted to protect against ASPD. This is because, in the environments with no childhood maltreatment, Caspi and Moffitt found the high-MAOA sub-group to have the elevated risk of developing ASPD. Consider parents in the "not-too-distant" future who visit their genetic counselor and decide that they want to select against the high-MAOA genetic variant. Should this request be predicated on proof of no history of engaging in childhood maltreatment? How would a genetic counselor secure this information? Or what about parents who *do* have a history of maltreating children but who have now turned over a new leaf? Should they now be allowed to select against the high-MAOA genetic variant as

[8] In fact, the MAOA status of the men on Ms. Genovese's block would most likely have had little impact on her survival regardless of whether or not those men experienced childhood maltreatment. The kind of violence that individuals with ASPD engage in generally amounts to physical assault and rape, not the kind of violence that amounts to intervening in a situation to save a victim. Indeed, the MAOA status of the men on her block (along with the environmental conditions of development) would be more likely correlated with the person who *murdered* her rather than with who might have *saved* her. The danger of slipping from MAOA status to take-charge-kind-of-guy comes from both incorrectly equating ASPD with a propensity for violence and equating all types of violent action (i.e., assuming violence, is violence, is violence).

well, or is the risk of childhood maltreatment and then the subsequent risk of developing ASPD just too high for the low-MAOA child-to-be?

This question of confirming or disconfirming childhood maltreatment is complicated when we remember that, in the Caspi-Moffitt study, childhood maltreatment included physical and sexual abuse, as well as neglect, harsh punishment, and poor mother-child interactions. With the severe forms of childhood maltreatment, social service departments have the authority to intervene in the family and remove children from this abusive environment. But this is not the case with these less severe forms of maltreatment. Consider a parent who smacks or ignores their child in public. The parent may be socially sanctioned, but it is unlikely that any legal action would be taken against the family. Or, less judgmentally, consider an impoverished, single parent who must work more than one job and spend hours away from home. In this case, neglect might be predictable even though it is entirely unintentional—a consequence of the parent's socioeconomic status. What of the parents who fully admit that they often smack their current children with something and intend to continue this practice with their subsequent children? Or what of the parents who admit that their socioeconomic situation unintentionally leads to the neglect of their current children and will likely lead to the neglect of their subsequent children?

Notice that these particular ethical questions regarding screening for an interactive predisposition are not raised by screening for a genetic predisposition.[9] If there were a true genetic predisposition for ASPD or violence regardless of childhood maltreatment status, then a set of prospective parents whose child is likely to experience maltreatment and a set of prospective parents whose child is unlikely to experience maltreatment should both reach the

[9] Of course, this does not imply that testing for genetic predispositions is at all easy. Judy Garber (1999), for instance, warns of the complex variety of considerations that must be made in testing for hereditary breast/ovarian cancer. My concern here is just to display how these variety of considerations become even more complex when a prediction must also be made about the environment.

same conclusion. If these two sets of parents both go to a genetic counselor in order to avoid, insofar as it is possible, having a child with behavioral problems, then a genetic counselor should make the same recommendation to both sets of parents: select against the low-MAOA embryo or fetus in order to lower the risk of having a child who develops ASPD. But with the interactive predisposition, the environmental conditions expected to be experienced during development must be figured into the decision.

Caught by the trappings of the myth of pre-environmental prediction and assuming that the Caspi-Moffitt study displays a genetic predisposition to ASPD or violence, these different ethical questions are overlooked. It is only when we realize that the researchers found an instance of an interactive predisposition that we can appreciate the unique problems raised by their results. This is crucial information for the genetic counselor and the prospective parents who have visited their genetic counselor in order to reduce the chance of their child having ASPD. If parents can predict the presence or absence of childhood maltreatment, then this must be figured into the decision between selecting against the low- or the high-MAOA embryo or fetus. If the parents do not intend to maltreat the child and do not foresee that maltreatment will be a problem, then the genetic counselor would suggest selecting against the high-MAOA embryo or fetus. If the parents do intend to maltreat the child in spite of efforts to convince them otherwise, or if conditions are such that their child is likely to experience maltreatment in some form, then the genetic counselor would suggest selecting against the low-MAOA embryo or fetus.

3.3. Newborn Screening and the Interventionist's Dilemma

The mandatory screening of newborns for genetic disorders raises interesting ethical questions (Newborn Screening Taskforce 2000; Pass et al. 2000). What is the purpose of such tests? For

whose benefit are the tests undertaken? What requirements in terms of predictive accuracy and treatment options must be met before a test is required? As of 2007, there are a handful of genetic tests mandated in the United States, with a great deal of variation between states (Green, Dolan, and Murray 2006; Therrell 2001). There are, however, increasing efforts to expand this pool (Hampton 2004; Howell 2006), along with pleas for caution (Botkin et al. 2006; Kerruish and Robertson 2005).

Could the results of the Caspi-Moffitt study be implemented in a policy of mandatory newborn screening program? The prospect is not as far-fetched as it might sound. The criteria for assessing a potential screening program proposed by Wilson and Jungner (1968) for the World Health Organization four decades ago remain the gold standard. Regarding *knowledge of the disease*, the condition must be an important health problem; there should be an identifiable latent or early symptomatic stage; and the natural history of the disease should be adequately understood. Regarding *knowledge of the test*, there should be a suitable test; the test should be acceptable to the population; and case finding should be an on-going process (i.e., the test should be made available on a continuing basis, and not just as a one-time search for cases). Regarding *treatment for the disease*, there should be an acceptable treatment for patients; facilities for treatment and diagnosis should be available; and there should be an agreed upon policy concerning who to treat as patients. Finally, regarding *cost considerations*, the costs of case finding should be economically balanced in relation to expenditures on medical care as a whole (Wilson and Jungner 1968).[10]

We can evaluate the possibility of a screening program based on the results of the Caspi-Moffitt study by assessing how well the case of ASPD meets the Wilson-Jungner criteria.

[10] It is worth noting that many of the 29 conditions recommended for testing by the Newborn Screening Task Force (2000) do not meet these criteria.

Regarding knowledge of the disease, ASPD certainly qualifies as an important health problem, both to the *individual* with ASPD and to the *society* in which the individual with ASPD lives. Violent crime is often characterized as a public health problem (Mercy, Rosenberg, Powell, Broome, and Roper 1999; Moore 1999). In turn, ASPD through its association with violent crime has also been characterized as a threat to public health (Fishbein 2000b; Potter and Mercy 1997). There is also a recognizable latent or early symptomatic stage for ASPD, namely childhood conduct disorder (Frick 1998; Reid, Patterson, and Snyder 2002). Now, admittedly, the full causal-mechanical explanation of the development of ASPD remains a mystery; its natural history is not completely understood. However, there is some debate about what the criterion of being "adequately understood" actually requires. Must the full causal mechanisms of the disease be understood? Or do we only need to know what causal variables are implicated in the development of the disorder? For a complex behavioral trait like ASPD, it is doubtful that the full causal-mechanical explanation will ever be elucidated; however, few diseases for which there already are screening programs meet this level of adequate understanding (Howell 2004). So there is reason to believe that even partial understanding of the causal story will satisfy this criterion.

Regarding knowledge of the test, the fact that Neuromark is already seeking FDA approval for such a genetic test obviously makes this a very real possibility. What it means for the test to be "acceptable to the population" is another debatable criterion. Screening for ASPD would clearly be a controversial step for any state to take, and it is very unlikely that any consensus position would form. However, a large portion of the population still may very well find such a measure acceptable in light of the potential decrease in violent crime that might result.

Regarding treatment for the disease, this remains the most elusive achievement for researchers studying ASPD. An effective treatment for ASPD still does not exist in 2007, and without such an intervention, it is clear that this Wilson-Jungner criterion would not be met. Nevertheless, it seems prudent to consider the *possibility* of such a treatment. The most commonly mentioned possibility for treatment involves some form of pharmacological intervention, presumably altering an individual's MAOA activity by, say, increasing MAOA activity for an individual with the low-MAOA genetic variant (call it an "MAOA boost"). Indeed, Caspi and Moffitt themselves conclude their empirical study with the line, "Both attributable risk and predictive sensitivity indicate that these findings could inform the development of future pharmacological treatments." (Caspi et al. 2002, 853)

Finally, regarding cost considerations, it is worth reminding ourselves that 85% of the individuals from the low/severe sub-group in the Caspi-Moffitt study engaged in some form of antisocial behavior. And this sub-group, although amounting to only 12% of the study population, accounted for 44% of the study population's convictions for violent crimes. Weighing the costs of identifying those at risk of developing ASPD against the costs of care for those who do develop ASPD is not a simple calculus. If, as Wilson and Jungner suggest, the costs are kept to purely *medical* concerns, then it is unclear that the balance would tip in favor of implementing such a screening program. However, if the costs of care also include such considerations as finding and then either treating or prosecuting/incarcerating those individuals with ASPD who engage in violent crimes, as well as the costs of care for those individuals who suffer from these violent crimes, then it is clear that a screening program would economically pay for itself with even a minimal decrease in violent crimes.

The possibility of a screening program based on the results of the Caspi-Moffitt study has not escaped the notice of commentators. Ravinesh Kumar, for instance, suggests that "although likely to be highly controversial, we may decide to identify 'at-risk' individuals prone to developing antisocial tendencies by screening for the MAOA functional polymorphism and recognizing those who harbour the 'low-activity' variant" (Kumar 2003, 183). Paul Appelbaum, discussing the Caspi-Moffitt study, warns that "the pressure to screen is likely to increase if intervention can be shown to actually reduce crime. If effective treatment becomes available, the pressure to identify [at-risk] individuals through screening at birth may be irresistible" (quoted in Moran 2006). And Wasserman notes, "It would be tempting for the state to set a low threshold for pharmacological prevention for large categories of potentially vulnerable young men. For example 'prescribing' MAOA supplements for all young men screened as low MAOA, regardless of social class or family circumstances, would avoid blatant class bias, as well as intrusive and expensive inquiries into maltreatment [that] fell short of abuse and neglect" (Wasserman 2004, 28).

Again, Kumar, Applebaum, and Wasserman are *not* endorsing the implementation of a screening program based on the Caspi-Moffitt results. They are simply trying to draw attention to the ethical issues that would arise if a program were implemented to identify and intervene on the "at-risk" individuals deemed "genetically predisposed to violence." But the lesson for preimplantation and fetal diagnosis is also applicable here: There is no way to determine who the individuals "at risk" for ASPD are before the environmental conditions are experienced (or at least reliably predicted). The genotype alone does not establish the relative risk of developing ASPD.

But again, as with preimplantation and fetal diagnosis, recognizing the switch from a genetic predisposition to an interactive predisposition does not eliminate the ethical questions; instead, it raises a new dilemma unique to interactive predispositions—what I will call the *interventionist's dilemma*. Briefly, the idea is the following: Early environmental stressors such as childhood maltreatment contribute to the development of CD and then ASPD, and so there is a premium on early intervention to combat the effects of these stressors; however, interventions that generalize and treat all individuals with low-MAOA (say, by pharmacologically increasing MAOA activity with the MAOA boost) would *decrease* the risk of developing ASPD for some individuals while *simultaneously increasing* the risk of developing ASPD for others. The developmental story is critical.[11]

Genes and the environment both contribute to the development of ASPD (Farrington 1997; Rutter 1997). Cases of G×E reveal an interdependent causal relationship between the genetic variable and the environmental variable during the process of individual development (Tabery 2007, In Press). For ASPD, this developmental story starts early, manifesting itself first as CD and transitioning to ASPD once the individual turns 18. This developmental story is affirmed by the Caspi-Moffitt study. During childhood, an individual learns the process of moral deliberation from those who care for him or her. This process of learning occurs at multiple levels: social, organismal, brain-system, cellular, and molecular. In emotionally charged situations, neurotransmitters are released throughout the brain and controlled by the limbic system. MAOA, a neuroenzyme, is then responsible for breaking down those neurotransmitters

[11] There is, of course, another option: use the genetic information as a guide to identify who is most in need of intervention on the *environmental* variable (i.e., prevention of exposure to childhood maltreatment). This chapter is devoted to the possibilities raised by the *commentators* on the ASPD study, and since none of the commentators have raised this possibility for this case, I will let it pass here too. However, environmental intervention is the main issue that I deal with in the next chapter (in the context of genetic tests for children), where I will argue that environmental interventions are rarely costless. Even in this case of ASPD, one can see how intervening on this environmental variable would lead to intrusions on family privacy and infringements on parental autonomy. But more on this later.

once the threat has passed. If caregivers maltreat the child through either neglect or abuse, these charged situations can become commonplace; and, without a sufficient supply of MAOA, heightened emotional response can persist for some time, ultimately having an impact on how the child learns to deal with conflict and resolution. Not surprisingly then, a premium is placed on *early* intervention in discussions of ASPD treatment—focusing on children and adolescents (McCord and Tremblay 1992). The rationale is that, once the environmental stressors are experienced and the disorder has developed, there is little hope of effective treatment in adults, who generally do not respond well to standard psychotherapy and suffer a high rate of recidivism for crime (Hemphill, Templeman, Wong, and Hare 1998). So the promise of a pharmacological intervention that could be implemented early in this developmental process is naturally appealing. The thought is that increasing MAOA activity for the low-MAOA individuals with an MAOA boost, thereby making them high-MAOA individuals, could act to buffer them against the environmental stressors that cause ASPD. After the environmental stressors have already been experienced, then the damage may be irrevocably done, thereby rendering the MAOA boost ineffective. If, however, the MAOA boost comes early—say, *starting at birth*—then the individuals may have the neurochemical resources to withstand the stress even at its earliest onset.

But notice that the warrant for this early intervention program requires ignoring the presence or absence of childhood maltreatment and treating all low-MAOA individuals at birth as if they are the at-risk population. For those low-MAOA individuals who experience childhood maltreatment, the potential advantage of early intervention is clear. In the Caspi-Moffitt study, individuals with low-MAOA activity were much more likely to develop ASPD in the presence of moderate and severe childhood maltreatment than were high-MAOA individuals. The

implication seems to be that an early intervention program that provided a pharmacological MAOA boost to those individuals might have prevented many of them from going on to engage in antisocial behavior. But if the early intervention program starts at birth and ignores the presence or absence of childhood maltreatment, then this means that the individuals in the environment *without* childhood maltreatment will also receive the pharmacological MAOA boost. Recalling Figure 3.1, note what will happen to the rate of ASPD for that population: It will *increase*. That is, the pharmacological intervention boosting all low-MAOA individuals to high-MAOA individuals will *decrease* the risk of developing ASPD for those individuals who experienced maltreatment while *simultaneously increasing* the risk of developing ASPD for those individuals who do not experience maltreatment.

The two horns between which the interventionist is caught should now be clear. On the one hand, the fact that ASPD is a developmental disorder with early onset militates for an early intervention program in order to provide a treatment before the environmental stressors take their toll. On the other hand, embracing this early intervention strategy necessitates treating all low-MAOA individuals from birth before knowledge of childhood maltreatment is known, thereby decreasing the risk of some while increasing the risk of others. The way past the second horn is to wait and see who does and does not experience childhood maltreatment, and to intervene pharmacologically only once the presence of the environmental stressor can be confirmed. However, waiting pushes the interventionist back on the first horn of the dilemma: Wait until childhood maltreatment can be confirmed, and the damage may already be done.

Now, one response to the interventionist's dilemma might be a kind of utilitarian comparison of sub-groups. The thought here would be to first note how many MAOA/maltreatment sub-groups there are in the Caspi-Moffitt study—6: low/none,

low/probable, low/severe, high/none, high/probable, and high/severe. Then, turning to Figure 3.1, a comparison is made at each environment (none, probable, and severe) of whether the switch from low- to high-MAOA activity leads to an increase or a decrease in risk of ASPD. If it leads to a decrease, then that is a point in favor of the early intervention program; if it leads to an increase, then that is a point against the early intervention program. On this calculus, the interventionist pushes through the dilemma and decides to intervene. In two of the environments (probable and severe), the switch from low- to high-MAOA activity leads to a decrease in risk. In only one of the environments (none), the switch from low- to high-MAOA activity leads to an increase in risk. Two beats one. But this solution belies important information about the constitution of these sub-groups. The switch from low- to high-MAOA activity does decrease the risk of developing ASPD in two of the environments measured. *But only 1/3 of the population from the Caspi-Moffitt study fell into these two environments, whereas 2/3 of the population from the Caspi-Moffitt study fell into the environment without childhood maltreatment.* This should not be surprising; most parents do not maltreat their children. Ultimately, then, implementing the early intervention program would lead to a decrease in risk for 1/3 of the population and an increase in risk for 2/3 of the population. Admittedly, the decrease in risk is substantial, while the increase in risk is slight. But even a slight increase in risk for a full 2/3 of the population should suggest taking pause before any early intervention program is implemented. If such a public policy was implemented, then some form of consensus committee would need to be formed in order to work through the implications of this dilemma.

3.4. Conclusion

This chapter explored several of the ethical questions that arise when efforts are made to screen for an interactive predisposition to ASPD. Commentators reflecting on the Caspi-Moffitt study have treated the case as if the ethical questions arise from the problems posed by screening for a "genetic predisposition to ASPD or violence" in order to identify the "at-risk" population with the low-MAOA variant. Thus, the analyses have been framed around the standard questions raised by screening for genetic predispositions.

The lesson of chapter 2 was that Caspi and Moffitt identified an instance of an interactive predisposition, not a genetic predisposition. This chapter has been devoted to tracking a few of the ethical implications of that conceptual shift. The ethical questions surrounding genetic screening must be reframed in cases of interactive predispositions. With regard to preimplantation diagnosis or fetal screening, the thought that screening against low-MAOA individuals will lead to a decreased risk in developing ASPD suffers from the myth of pre-environmental prediction. There is simply no way to assess whether low- or high-MAOA individuals are more or less at risk of developing ASPD until the environmental conditions of development are either experienced or reliably predicted. With regard to newborn screening, the thought that identifying and pharmacologically treating low-MAOA individuals from birth, as part of an early intervention program aimed towards preventing the development of ASPD, must face the interventionist's dilemma. A successful treatment program seems to require an early intervention, perhaps even beginning at birth; however, an MAOA boost to low-MAOA individuals from birth would both *decrease* the risk of developing ASPD for some individuals while *simultaneously increasing* the risk of developing ASPD for many more individuals.

4. TESTING CHILDREN FOR INTERACTIVE PREDISPOSITIONS

Abstract. Genetically testing a child for susceptibility to a disease or disorder involves many potential benefits and burdens. Typically, the ethical analysis of such cases involves, in part, a cost-benefit analysis to determine whether the advantages outweigh the disadvantages of obtaining the genetic information about a child. Commentators thus far have focused exclusively on cases of genetic determinism (think Huntington's disease) and genetic predisposition (think hereditary breast/ovarian cancer). In such cases there is a clear *at-risk genotype*, and the analysis of testing for the genotype proceeds by considering potential burdens such as negative psychosocial impacts alongside potential benefits such as preventive intervention. In cases of interactive predisposition, however, there are no at-risk genotypes; there are *at-risk gene-environment combinations*. The purpose of this chapter is to explore how the cost-benefit analysis involved in decisions concerning genetically testing children must be adapted in light of this switch from risky genotypes to risky gene-environment combinations. Cases of interactive predispositions for a variety of diseases and disorders are becoming commonplace, making such an adaptation a necessary anticipation of the ethical considerations that will follow from available tests for these cases.

4.1. Introduction

So far in the thesis I have focused solely on the MAOA study by Caspi and Moffitt (2002), as well as on the ethical questions raised by commentators who have considered that study. The goal of chapter 2 was to show that the Caspi-Moffitt MAOA study identified an interactive predisposition, not a genetic predisposition. And the goal of chapter 3 was to explore how that switch reconfigured the ethical questions raised by commentators concerning embryonic, fetal, and newborn screening for MAOA status.

In this chapter I open up the discussion to consider cases of interactive predispositions beyond the MAOA study, as well as ethical questions beyond those raised by the commentators on the MAOA study. There is good reason to expand the discussion in this manner, since discoveries of interactive predispositions for a variety of complex traits are becoming commonplace. Consider three recent cases. In 2005, Sabine Hoffjan and her colleagues published a study on the relationship between functional polymorphisms at several loci, exposure to daycare, and the subsequent development of immunologic responses predictive of asthma

(Hoffjan et al. 2005). For instance, the *NOS3_298* polymorphism (Glu → Asp) results in three possible genetic variants: Glu/Glu, Glu/Asp, and Asp/Asp. Children with these genetic variants were then monitored by Hoffjan and her colleagues in an array of environments—namely, exposure to or lack of exposure to daycare in the first year of life. The phenotypic trait under investigation, then, was the change in interleukin-13 (IL-13) response levels over the course of that year. IL-13, one of the many Th2 cytokines (or messenger cells) in the immunological system, has been identified as a necessary and sufficient cause for allergic asthma; increased levels of IL-13 activity lead to the subsequent development of allergic asthma, while decreased levels apparently ensure its absence (Wills-Karp and Chiaramonte 2003). With the data on each genetic variant's IL-13 response level in each environment, Hoffjan and her colleagues then constructed a reaction norm graph for the phenotypic curves (Figure 4.1). They concluded, "[o]verall, the children with the Asp/Asp genotype who did not attend day care had the highest levels of and greatest increases in Th2 cytokine responses, whereas the children with the Asp/Asp genotype who attended day care had the lowest levels of and smallest increases in Th2 cytokine responses"—the hallmark of an interactive predisposition (Hoffjan et al. 2005, 698). Also note the fact that the effect of daycare exposure led to the drastic *decrease* in IL-13 response for the individuals with the Asp/Asp genotype, while simultaneously leading to a slight *increase* in IL-13 response for the individuals with the Glu/Glu and the Glu/Asp genotype.

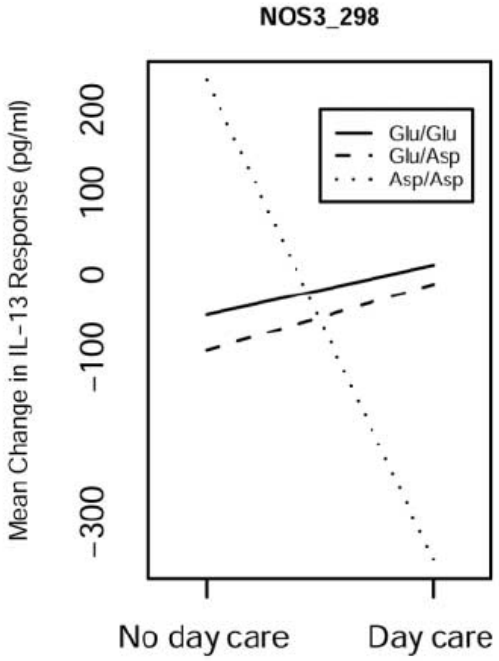


Figure 4.1. Reaction norm graph for *NOS3_298* polymorphism, exposure to day care, and IL-13 response (From Hoffjan et al. 2005, Figure 1A).

In another study, Karl-Erik Wahlberg and his colleagues investigated the relationship between adoptees' genotypes, exposure to communication deviance from the adoptive parents, and the subsequent development of cognitive processes symptomatic of schizophrenia (Wahlberg et al. 1997). The adoptees were classified as carrying either a high-risk genotype or a low-risk genotype based upon whether or not their biological mothers were schizophrenic. The high- and low-risk adoptees were then monitored for how they responded to patterns of communication deviance in their adoptive parents. Communication deviance is a pattern of communication on the part of a speaker that systematically befuddles and distracts a listener, who is attempting to join in a shared focus of attention with the speaker; communication deviance is essentially language that is ambiguous and difficult for a listener to follow, although it would not by itself be taken as evidence of a psychiatric disorder in the speaker (Singer and Wynne 1966). The

phenotypic trait that Wahlberg and his colleagues studied in the adoptees, then, was thought disorder (generally taken to be either an indicator of susceptibility to developing schizophrenia or even as a part of the extended schizophrenic spectrum), measured by means of Rorschach tests. With the data on evidence of thought disorder for individuals with each genotype in each environment, Wahlberg and his colleagues then constructed a reaction norm graph for each of the phenotypic curves (Figure 4.2), revealing the change in rank between the genotypes. Again, note the fact that exposure to increasing levels of communication deviance drastically increased the proportion of high-risk adoptees developing thought disorder, while simultaneously decreasing the proportion of low-risk adoptees developing thought disorder.

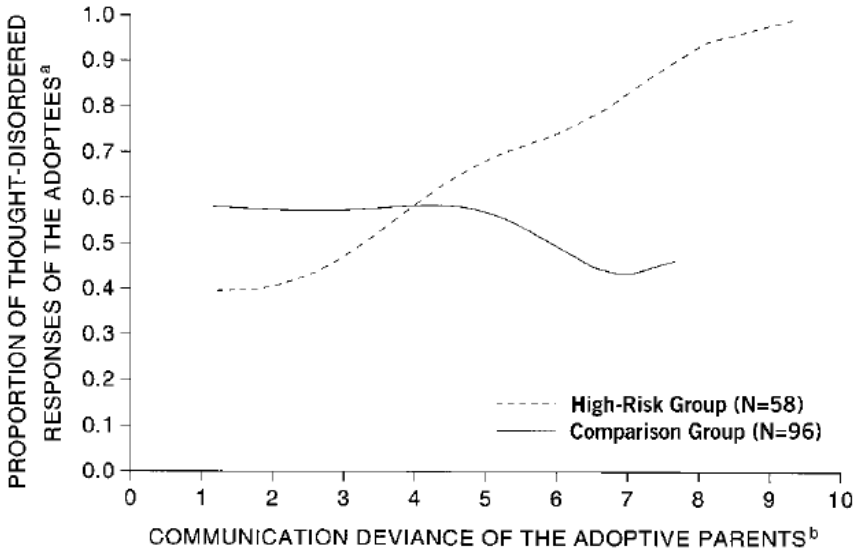


Figure 4.2. Reaction norm graph for high- vs. low- genotypic risk in adoptees, exposure to communication deviance in adoptive parents, and subsequent development of thought disorder (From Wahlberg et al. 1997, Figure 1).

One more example. A year after Caspi and Moffitt published their MAOA study, they published another study examining the relationship between a functional polymorphism in the promoter region of the serotonin transporter gene, exposure to stressful life events, and the subsequent development of depression (Caspi et al. 2003). Serotonin transporters are proteins on the synaptic membranes of neurons involved in the reuptake of neurotransmitters after they have been released in the synapse. The number of these proteins produced at a synapse is regulated by the promoter region of the serotonin transporter gene, which is itself based on the length of that promoter region. Individuals receive one copy from each of their parents, which can be either short (*s*) or long (*l*); thus, individuals can be classified as either s/s, s/l, or l/l. Individuals with the various polymorphisms were then monitored for how they responded to stressful life events, such as the death of a loved one or the loss of a job. The phenotypic trait that Caspi, Moffitt and their colleagues examined in this study was major depression. With the data on genotype, exposure to stressful life events, and the subsequent development of depression, Caspi, Mofitt, and their colleagues constructed reaction norm graphs for each of the phenotypic curves (Figure 4.3a), revealing the change in rank between the genotypes. This study has since been replicated by T.C. Eley and colleagues in an adolescent population (Eley et al. 2004), with results consistent with the change in rank (Figure 4.3b).[12] Interestingly, the researchers conducting the replication in adolescents only found the associated risk of depression in female participants. (Note also that in Figure 4.3b it is now the environmental variable plotted across the array of genotypes; thus, this is actually a phenotypic curve for the environments, not the genotypes. Nevertheless, the change in rank is still apparent. Individuals with the s/s genotype are at the lowest risk of depression in the low-risk environment and at the highest risk of depression in the high-risk environment; and

[12] Replications of the interaction effect have also been reported by Grabe et al. (2005), Kaufman et al. (2004), Kaufman et al. (2006), Kendler et al. (2005), and Wilhelm et al. (2006). Two failures to replicate have been reported as well by Gillespie et al. (2005) and Surtees et al. (2005).

this risk increase is in the opposite direction for individuals with the l/l genotype, who experience the increased risk of depressive symptoms as they move from the high-risk environment to the low-risk environment.)

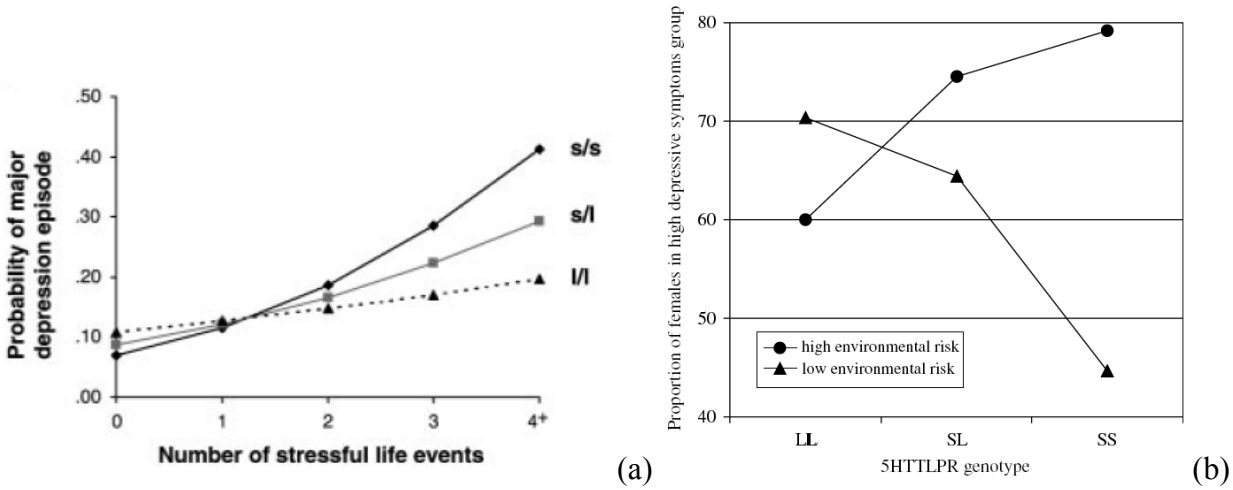


Figure 4.3. Reaction norm graphs for the serotonin transporter gene, exposure to stressful life events, and the subsequent development of depression or depressive symptoms. (a) In an adult population of both males and females (From Caspi et al. 2002, Figure 1B). (b) In an adolescent population of females (From Eley et al. 2004, Figure 1).

Like the Caspi-Moffitt study on ASPD, the asthma study, the schizophrenia study, and the depression study all are cases of G×E resulting in a change in rank; all are cases of an interactive predisposition. But in spite of this commonality, the ASPD study has certainly stolen the spotlight.[13] Perhaps this should not be surprising. The very prospect of a 'gene for violence' or even a 'genetic predisposition to violence' raises a host of obvious ethical questions, as was

[13] As evidence of this overshadowing by the ASPD study, a September 2007 citation survey of these articles found Caspi et al. (2002) cited 503 times, while Hoffjan et al. (2005) was only cited 30 times, and Wahlberg et al. (1997) was only cited 74 times (www.isiwebofknowledge.com). Caspi et al. (2003) is an exception to this rule; it was cited 800 times. However, it has not received the same attention from bioethical and legal scholars as the ASPD study.

documented in the last chapter. But if we focus our attention on preventing the development of ASPD, then that case is actually a fairly easy one to solve: *just don't maltreat the children!* While there may be some debate over the appropriateness of physical punishment, most reasonable adults will agree that the sexual assault, physical abuse, and neglect of children are reprehensible. If parents or a society want to prevent the development of ASPD, simply combat the environmental stressor…a stressor that most agree is repugnant in the first place.

Ironically, as we shift our attention from the highly-publicized ASPD study to the less-scrutinized asthma, schizophrenia, and depression studies, the ethical questions become more difficult to answer precisely because the environmental stressors in these cases lack the reprehensibility identified in the ASPD study. The decision to send a child to daycare is a complex parental decision; available finances, available time, and philosophies of life and parenting all come into consideration. Are parents parenting poorly if they send their child to daycare? Are they parenting poorly if they do not? Should genetic information about a child figure into this parental decision? Communication deviance, though a headache for the listener, is not a crime; it is not even evidence of a psychiatric disorder in the speaker. For some adoptees, communication deviance in their adopted parents apparently lowers the risk of thought disorder; while, for other adoptees, communication deviance in their adopted parents apparently increases the risk of thought disorder. Are adoptive parents harming their adopted child if they *do* engage in communication deviance with a high-risk adoptees? Are adoptive parents harming their adopted child if they do *not* engage in communication deviance with a low-risk adoptees? Should genetic information about adoptees be gathered for the sake of matching them with the appropriate adoptive parents based upon the adoptive parents' communication styles? Stressful life events are often out of anyone's control. Who do we blame for the death of a loved one or

the loss of a job? Should genetic information be gathered from children in order to determine who among them are most susceptible to the trauma from these stressful but unpredictable life events?

Neuromark, the same company seeking FDA approval for a genetic test of MAOA status, is also seeking FDA approval for a genetic test of the serotonin transporter gene. Importantly, when CEO Kim Bechtold was asked about the use of such a test, she offered up the possibility of parents testing their children as a potential venue.[14] Thus, as was the case with the discussion of MAOA in the previous chapter, the discussion here is more than abstract speculation; a test for the serotonin transporter gene may very well be available to parents in the near future.

In this chapter I consider how cases of interactive predispositions should figure into the ongoing debate over genetically testing children. Few argue that genetically testing children should *never* be done, or that it should *always* be permitted. Instead, the ethical analysis of such tests generally follows a cost-benefit analysis of undertaking the test and acquiring the child's genetic information. The ethical debate revolves around *what* these costs and benefits are, *how* costly and beneficial they actually are, and *who* is in the best position to weigh the two. So far, the ethical debate has focused exclusively on cases of genetic determinism (think Huntington's disease) and genetic predisposition (think hereditary breast/ovarian cancer). In such cases, there is a clear *at-risk genotype*, and the cost-benefit analysis proceeds by considering the costs and benefits of identifying the risk status associated with an individual's genotype, such as the threat of genetic discrimination or the promise of medical intervention. In cases of interactive predisposition, however, there are no at-risk genotypes. There are only *at-risk gene-environment*

[14] I undertook a phone interview with Bechthold on Friday, June 9, 2006. Information obtained in that conversation is not to be further cited or discussed with other parties.

combinations. The goal of this chapter is to explore how this switch reconfigures the cost-benefit analysis involved in deciding whether or not to genetically test a child.

4.2. Testing Children for Genetic Predispositions: Weighing the Burdens and Benefits

A 1993 survey of 49 geneticists and 260 pediatricians by the UK Working Party of the Clinical Genetics Society found that the majority of these healthcare providers would, upon parental request, provide presymptomatic genetic testing for a 5-year old child for a host of disorders including Huntington's disease (Working Party 1994). This information quickly elicited a series of publications from physicians, moral philosophers, and legal scholars, who questioned the ethical foundation upon which such tests were warranted (Andrews et al. 1994; Hoffmann and Wulfsberg 1995; Wertz, Fanos, and Reilly 1994). There were differences in foci for these commentators; however, they reached something of a consensus regarding the appropriateness of genetically testing children for diseases, such as cystic fibrosis, Huntington's disease, or phenylketonuria (PKU).

The essence of a genetic predisposition is that there is a clear at-risk genotype. The purpose of a genetic test, then, is to determine whether an individual (in this case, a child) bears that risky genotype. The various teams of authors responding to the UK Working Party's findings noted that there are a number of benefits and burdens that potentially follow from learning that a child has a risky genotype. On the beneficial side, obtaining this genetic information about a child ideally suggests a timely course of medical treatment that can prevent the development of a disease (see also Kodish 1999). For instance, a positive genetic test for PKU in a newborn suggests a course of medical treatment involving a dietary modification that

eliminates phenylalanine, since children with PKU cannot metabolize this amino acid. Eliminating phenylalanine from the diet thereby prevents the mental retardation and seizures that follow from the buildup of this amino acid. Or, a positive genetic test for familial adenomatous polyposis (FAP) in a child suggests a course of medical monitoring and intervention involving regular colonoscopies and ultimately a colectomy, since an adolescent or young adult with FAP will likely develop hundreds of pre-cancerous polyps on their colon without this surgery.

The authors responding to the UK Working Party's findings, however, were much more concerned with the burdens that might come with obtaining genetic information from children. A positive genetic test for, say, mutations in either the BRCA1 or BRCA2 genes (implicated in hereditary breast/ovarian cancer) might have *social* costs. The children could be stigmatized long before they are ever symptomatic. Or, the children could experience discrimination from insurance companies or employers, which translates into a financial cost as well. A positive genetic test might also have *familial* costs. Parents might treat their child as if their future is limited, shift familial resources away from this child, or become overprotective of the child (vulnerable child syndrome) (see also Farrell et al. 1991). There may also be severe stress placed on the parent-child bond. A parent or the parents may feel personally responsible for the positive result. Or, a positive result in one child and a negative result in a sibling may lead to feelings of 'survivor's guilt' in the low-risk sibling, thereby straining the sibling bond (see also Wexler 1985; Biesecker et al. 1993). A positive genetic test might also have *psychological* costs (see also Marteau and Croyle 1998). The child may experience the negative effects of altered family dynamics, feel unworthy, experience a loss of self-esteem, become depressed, or even come to question his/her own sense of self (see also Bloch and Hayden 1990; Koocher 1986). In short, the child, the members of the family, and the members of the larger social network may begin

treating the genetic result as an inevitability, despite the probabilistic nature of the information (see also Dreyfuss and Nelkin 1992). There is also the cost of *lost autonomy*. In genetically testing a child, parents and the health care provider(s) take away the child's ability to make the decision about whether or not to be tested in the future, perhaps violating the child's right to an 'open future' (see also Bloch and Hayden 1990; Davis 1997; Feinberg 1980).

With these potential benefits and burdens under consideration, Andrews et al. (1994), Hoffman and Wulfsberg (1995), and Wertz, Fanos, and Reilly (1994) encouraged undertaking a cost-benefit analysis of these factors. As Hoffman and Wulfsberg summarize, "The decision by a physician to offer or perform a presymptomatic genetic test and by a parent to have their child tested will require weighing the possible benefits of the test with its impact on the child's quality of life" (ibid, 334). With the *best interests of the child* as the guide, the authors made the following recommendations based on the availability of timely medical treatments:

- In the case of a disease with childhood-onset and with a known, medical, preventive treatment/intervention (such as PKU), physicians and parents should undertake genetic testing.
- In the case of a disease with adult-onset and with no known, medical, preventive treatment/intervention (such as Huntington's disease), physicians and parents should not undertake genetic testing.
- Children should be included in the decision-making process to the extent that they are developmentally capable of engaging in the process of assent.[15]

So what if parents want to undertake genetic testing on their child for an adult-onset disease, or for a disease with no known, medical, preventive treatments/interventions? Are

[15] The authors also discuss genetic testing for carrier status and for the benefit of another family member. These other situations, however, are less relevant to the cases of interactive predispositions that I will be discussing, so I will focus my attention on the recommendations above.

physicians obligated to comply with the parents' request? Legally, the answer is, no; physicians are not obligated to provide therapeutic/diagnostic tests such as genetic tests (Clayton 1995). However, we may proceed to ask whether they are morally obligated to comply. For the authors responding to the UK Working Party's findings, the answer is again, no. For instance, Wertz, Fanos, and Reilly advise, "Sometimes the physician must reject a request, whether from a parent or a minor, if in the physician's judgment it serves no useful purpose and may lead to harm. For example, a parental request to test a 7-year-old for predisposition to familial Alzheimer's disease provides no medical benefit to the child and may lead to stigmatization. Decisions that challenge parental autonomy may be necessary to prevent harm and to preserve a minor's future autonomy, which should be the paramount considerations" (ibid, 878). Denying such tests, they explain, is justified medical paternalism. And Hoffman and Wulfsberg concur: "Although parents generally know their child best and care most about the child's welfare, we believe that physicians and health care providers have an obligation to provide them with sufficient information to make a true informed decision about the benefits and risks associated with testing for a genetic predisposition" (ibid, 336).

These authors apply the same reasoning to cases of adoption. Testing should be undertaken with the best interests of the child in mind. Of course, a negative test result for a disease may make the child more likely to be adopted, but a positive test result will simultaneously make the child less likely to be adopted. Wertz, Fanos, and Reilly, for instance, warn, "Testing for untreatable adult-onset disorders prior to adoption makes the child into a commodity undergoing quality control" (ibid, 879)

The analysis provided by Andrews et al. (1994), Hoffman and Wulfsberg (1995), and Wertz, Fanos, and Reilly (1994) has been largely adopted, nationally and internationally, by

professional organizations considering the genetic testing of children. Ethics committees from the American Academy of Pediatrics (2001), the American Medical Association, AMA (1996), the American Society of Human Genetics and the American College of Medical Genetics, ASHG/ACMG (2000), the Canadian Pediatric Society, CPS (2003), and the World Health Organization, WHO (2003) have reaffirmed the potential burdens and benefits of testing children for genetic diseases as well as the subsequent cost-benefit analysis of those factors.[16] The AMA's statement is representative of this group. Noting the potential burdens and benefits of genetic testing in children, the AMA explains, "…there must be some potential benefit from the testing that can reasonably be viewed as outweighing the disadvantages of testing…" (AMA 1996, E-2.138). The AMA then reaches the expected conclusions: test children for diseases with childhood-onset and which have known, medical, preventive treatments/interventions; do not test children for diseases with adult-onset and which have no known, medical, preventive treatments/interventions. The Association also warns, "If parents unreasonably request or refuse testing of their child, the physician should take steps to change or, if necessary, use legal means to override the parents' choice." (ibid)[17]

The medical associations also reached similar conclusions regarding the testing of adoptees. The joint recommendations from ASHG/ACMG, which dealt specifically with genetic testing in adoption, warned that identifying an at-risk genotype in adoptees may adversely affect the chances of adoption. Thus, they suggested keeping the best interests of the child in mind and only testing for childhood-onset diseases with a timely course of preventive intervention available. Interestingly, the ASHG/ACMG statement also recommended, "In the adoption

[16] Though not official recommendations from professional organizations, Cline (1999) and Bove, Fry, and MacDonald (1997) also affirmed for nursing communities the analysis laid out by Andrews et al. (1994), Hoffman and Wulfsberg (1995), and Wertz, Fanos, and Reilly (1994).
[17] And, again, the AMA discusses testing for carrier status or for the benefit of another family member reaching conclusions similar to those mentioned above.

process newborns and children should not be tested for the purpose of detecting genetic variations of or predispositions to physical, mental, or behavioral traits within the normal range" (ASHG/ACMG 2000, 761).

More recently several authors, though not questioning the general cost-benefit analysis involved in the decision, do encourage a more complex appreciation for the burdens and benefits (Clayton 1997; Cohen 1998; Ross 2002). In general, they suggest moving beyond the standard cases of cystic fibrosis, Huntington's disease, and PKU, in order to frame and specify the ethical analysis around the greater variety of tests available for diseases that do not have the same penetrance as these diseases. Moreover, they draw attention to the variety of benefits obtained from positive and negative test results that are overlooked by earlier authors. Cynthia Cohen (1998), for instance, argues that the purported social, familial, and psychological costs of genetic testing are either anecdotal or derive from research on testing for Huntington's disease, making questionable the evidence of burdens associated with testing for genetic predispositions more generally. Cohen suggests that, rather than violating the child's autonomy, testing may actually enhance it; obtaining the genetic information makes apparent certain risks or lack of risks, thereby allowing the child (and the parents) to have the knowledge necessary to make decisions about how to prepare for and ultimately live with (or without) a disease. Rather than following rigid recommendations that consider only the dichotomy between childhood and adult-onset, as well as the rigid dichotomy between a timely medical treatment/intervention or the lack thereof, Cohen suggests taking into account a complex of factors when considering a genetic test for a child, such as the remoteness of disease onset, the severity of the disease, the potential development of future medical technologies, the maturity of the child, the availability of genetic counseling, and the likelihood of occurrence alongside the rate of occurrence in the general

population. Ultimately, Cohen advises, the cost-benefit analysis results in a draw; therefore, the value-laden nature of the decision must be recognized, and parents should be given wide room to decide when and when not to test their children.

Ellen Wright Clayton (1997) and Lainie Friedman Ross (2002) reach a similar conclusion, although their focus is less on reconsidering the benefits/burdens and more on reconsidering who is in the best position to identify and weigh those benefits/burdens when the analysis becomes increasingly complicated and value-laden. While Clayton and Ross agree that genetic testing should be avoided when the test presents clear and substantial harm to a child, they counter that parents are in the best position to weigh the factors when the risk is not so obvious and dire. In U.S. culture, Clayton notes, parents are given substantial leeway to decide what is in the best interests of their child; for instance, there is quite a bit of disagreement over the physical punishment of children, yet parents are permitted to engage in or refrain from physically punishing their children without outside interference. Clayton and Ross also both point out that parents, in making medical decisions about members of the family, must consider a variety of familial factors some of which involve the best interest of individuals in the family (such as a child) and some of which involve the best interest of the family as a unit, which ultimately affects the individuals in the family (see Ross 1998 more generally on this issue). Ross, for example, points out that results from a genetic test can shape decisions about where to buy a home based on its proximity to appropriate, disease-specific health care, or about what style of a home to buy based upon whether or not, say, stairs will present a problem for a child with a specific disease.

I find the contributions from Clayton (1997), Cohen (1998), and Ross (2002) particularly applicable to cases of interactive predispositions, such as those mentioned in the introduction to

this chapter. Take, for instance, the cases of depression or schizophrenia. Psychiatric diseases and disorders do not fit easily onto the rigid dichotomy between childhood-onset and adult-onset diseases. There is quite a bit of variation in onset for these cases, as there is for a host of diseases and disorders. Moreover, the nature of interactive predispositions suggests that the diseases and disorders themselves involve complex interactions between genes and the environment which play out over time; a final diagnosis of schizophrenia may come in adulthood, but other traits symptomatic of the disease (such as thought disorder) may develop in childhood or adolescence. Or consider the case of asthma. A decision about daycare forces parents to consider a variety of familial factors, which include both the direct best interests of the child as well as indirect familial interests pertaining to finances, schedules, and parenting philosophies that ultimately affect the child anyway. In this situation, the rigid dichotomy between the existence or absence of a timely medical treatment/intervention breaks down. The treatment, in this case, is not pharmacological or surgical; it is educational/developmental—exposure to daycare. In turning, then, to potential tests for interactive predispositions, I will keep the recommendations of Clayton (1997), Cohen (1998), and Ross (2002) in focus as a guide for evaluating the complex medical, social, familial, and psychological factors involved in analyzing whether or not to undertake such tests.

4.3. Testing Children for Interactive Predispositions: Reconsidering the Burdens and Benefits

The essence of a genetic predisposition is that there is an at-risk genotype. The essence of an interactive predisposition is that there is an at-risk gene-environment combination. What are the implications of this switch from risky genotypes to risky gene-environment combinations in the

context of genetic tests for children? One of the lessons from Clayton (1997), Cohen (1998), and Ross (2002) is that genetic tests for children must be evaluated individually in order to tailor the cost-benefit analysis to the test at hand (as opposed to extrapolating from tests for Huntington's disease or cystic fibrosis). This is good advice; however, it does not prevent us from making some general observations about testing children for interactive predispositions. Let me begin, then, by drawing attention to several general features of tests for interactive predispositions and then take this general analysis to specific cases, such as tests for the interactive predispositions mentioned in the introduction to this chapter—asthma, depression, and schizophrenia.

4.3.1. Reconfiguring the Benefits and Burdens: General Considerations

The risk status associated with an interactive predisposition requires knowledge of both the genetic variable and the environmental variable; the risk status may only be determined once the values of both these variables are known. The genetic test is designed to determine the value of the genetic variable; for example, a test for the *NOS3_298* polymorphism would be designed to determine whether this genetic variable takes the value of Glu/Glu, Glu/Asp, or Asp/Asp for an individual. But the genetic test undertaken in the case of an interactive predisposition supplies only half of the information required for evaluating risk status. There must be something of an *environmental test* as well. That is, information must also be sought concerning the value of the environmental variable; for example, an evaluation of the risk associated with the interactive predisposition for asthma would involve information about whether or not the individual will be exposed to daycare. Incorporating this environmental test into the equation raises a series of questions alongside the usual questions raised about obtaining information about the genetic variable:

- Can information about the environmental variable be reliably obtained? That is, is the environmental variable under someone's control, so that the value of this variable can be intentionally selected, or is there some degree of chance involved in what value the environmental variable may take?
- If the environmental variable is under someone's control, what does avoiding or attaining a particular environmental value entail? For instance, are there financial or scheduling commitments that must be made in order to ensure that the environmental variable takes a certain value for the child, or are there psychological or social costs of ensuring that the environmental variable does not take a certain value for the child?
- What does obtaining this environmental information entail? That is, is it simply a matter of asking parents a yes/no question, or does it involve acquiring information in a more complicated or invasive manner?

When the determination of an individual's risk status requires information about both the genetic and the environmental variables, the cost-benefit analysis involved in deciding whether or not to test the individual, especially a child, is reconfigured. As discussed above, many of the costs associated with a positive result in a genetic test stem from embracing a genetic essentialism and treating the probabilistic genetic information as if it was a deterministic inevitability (Dreyfuss and Nelkin 1992). Perhaps this should not be surprising. Without a viable genetic engineering program, the value that the genetic variable takes for an individual is fixed. As of 2007, it is not currently possible to change an individual's genotype from Asp/Asp to Glu/Glu at the site of the *NOS3_298* polymorphism. Of course, various dietary, pharmacological, surgical, or environmental manipulations may be made to react to the products of a genetic variable, but the value itself is not manipulated.

With an interactive predisposition, however, there is a very real sense in which the value of the environmental variable may be manipulated. It is, in principle at least, possible to decide whether or not a child is exposed to day care. Of course, as mentioned above, one of the important questions to consider pertains to the costs of practically manipulating this variable. Nevertheless, the very possibility of it should not be overlooked or treated lightly. With cases of interactive predisposition, the genetic information alone does not confer risk status, and so costs such as stigmatization, discrimination, or loss of self-esteem should not (in principle) follow from information about genetic status alone. In this sense, then, the costs of obtaining the genetic information about a child in cases of interactive predisposition are reconfigured since that genetic information alone does not lend itself to the potential burdens in the same way as cases of genetic predisposition.

That said, cases of interactive predisposition, since they incorporate a genetic *and* an environmental variable in the risk analysis, may actually lend themselves to even costlier burdens than cases of genetic predisposition. Consider the burdens associated with fatalistic attitudes. An individual with a risky genotype in a risky environment may feel as if s/he has been hit with a double-dose of bad luck; perhaps this will be perceived as an even greater inevitability than just a genetic predisposition even though the information is still probabilistic. Or, consider feelings of responsibility on the part of parents who learn of a positive test result for their child. In the case of a genetic predisposition, this can be combated with educational information about the unavoidable element of chance involved in genetics; parents should not feel responsible if a genetic roll of the dice fell unfavorably for their child. But with an interactive predisposition, the environmental variable is in play, and so there is the in-principle ability to manipulate that value. The practical costs of such manipulation, however, may be very high; for example, manipulating

the value of the environmental variable may have financial costs beyond those that the parents can afford. The appeal to genetics, described as a factor beyond parental control, made to reduce guilt associated with genetic contributions to their child's condition may now reinforce guilt associated with environmental factors.

Another general feature to keep in mind in cases of interactive predisposition pertains to the extent to which parents will understand the nature of the risk status that incorporates both a genetic and an environmental variable. There are a number of empirical studies suggesting that clinicians and patients alike have difficulty understanding probabilistic information, that clinicians and patients have different interpretations of what is and is not risky, that clinicians and patients have different preferences for probability expressions, and that patients ultimately do not understand the probabilistic information given to them (Chase, Faden, Holtzman et al. 1986; Gigerenzer 2002; Kessler and Levine 1987; Michie, Lester, Pinto, and Marteau 2005; Wertz and Fletcher 1987; Wertz, Sorenson, and Heeren 1986). Moreover, these studies involve cases with probabilities associated with only *one* variable—the genetic. So it is reasonable to assume that these problems of comprehension, appreciation, and deliberation will only be magnified in cases of interactive predisposition where both genetic and environmental variables, each probabilistic in nature, are involved. Fortunately, Celeste Condit and her colleagues at the University of Georgia have begun empirically investigating how well members of the general public process information about cases of gene-environment interaction (personal communication). We will have to wait for the results of her studies. In the meantime, there is reason to be skeptical about how well members of the general public will interpret cases of gene-environment interaction; consider the fact that the scientific, ethical, and legal experts discussed

in chapters 2 and 3 have themselves misinterpreted the Caspi-Moffitt MAOA study as a 'genetic predisposition to violence'. Should we expect members of the general public to do any better?

4.3.2. Reconfiguring the Benefits and Burdens: Cases to Consider

Consider the following hypothetical case:

> A husband and wife approach their pediatrician, seeking information about their infant regarding risk of allergic asthma. The mother suffers from severe allergic asthma, while the father does not. Upon further questioning, the physician learns that the mother did not attend daycare as a child, while the father did. The parents would like to know if there are any predictive tests available to gauge their child's risk of developing allergic asthma, as well as whether there are preventive measures that they can take so as to combat the development of allergic asthma. The physician informs the parents that there is a known interactive predisposition for allergic asthma involving a functional polymorphism (*NOS3_298*) in coordination with exposure to daycare. He also informs them that there is a genetic test available for *NOS3_298* status. The parents had not yet made any decision regarding daycare. They would like to test the child for his *NOS3_298* status.

This case is hypothetical in that there is not now a readily available test for the *NOS3_298* polymorphism studied by Hoffjan and her colleagues (2005). Nevertheless, it is worth considering the situation in which our pediatrician now finds herself, since it is likely that such a case would arise if a genetic test became available. Should she provide the test for the parents and acquire the infant's genetic information, or is she justified in exercising a justified medical paternalism since the test is not being offered for the sake of any preventive medical intervention?

When we apply the analyses of Clayton (1997), Cohen (1998), and Ross (2002) to the interactive predisposition identified by Hoffjan and her colleagues (2005), I claim that there is good reason to allow parents to test their child for *NOS3_298* status. The parents in our hypothetical case are particularly good candidates. The lack of exposure to daycare on the mother's part combined with her allergic asthma suggests that she may carry the Asp/Asp

genotype. The father's exposure to daycare and his lack of allergic asthma suggests that he may carry any of the other possible variants: Glu/Glu, Glu/Asp, or Asp/Asp. Thus, their child may carry either the Glu/Asp or the Asp/Asp variant of the *NOS3_298* genotype. If the parents remain undecided about whether or not to expose their child to daycare, determining whether s/he carries the Glu/Asp or the Asp/Asp genotype could be a decisive factor in making that decision. With the Glu/Asp genotype, exposure to daycare slightly increases his risk of developing allergic asthma. With the Asp/Asp genotype, exposure to daycare drastically decreases his risk of developing allergic asthma. Of course, the potential intervention in this case is not a standard medical intervention; the test is not being undertaken for the purposes of potentially implementing a known, timely, medical intervention along the lines of a phenylalanine-free diet. But as Clayton (1997) and Ross (2002) point out, this need not be the only criterion of potential benefit for the child. Deciding whether or not to send their child to daycare will be a complicated parental decision involving the consideration of a number of financial, occupational, and philosophical factors that affect the family as a unit and the child as an individual. Obtaining the genetic information about the child could be a valuable contribution to this parental decision; if the child carries the Asp/Asp genotype, then there is a very good reason to lean towards daycare even in the face of financial or occupational costs. If the child carries the Glu/Asp genotype, then the threat is not so pressing, and the parents will have to decide whether the slight increase in risk associated with daycare attendance outweighs the costs of not attending.

The fact that the parents in this case also have control over manipulating the value of the environmental variable in this interactive predisposition also makes it a good candidate for going forward with the genetic test. The psychosocial burdens normally associated with a positive test result for a risky genotype need not apply to this case of an interactive predisposition. That is,

even if the child carries the Asp/Asp genotype, exposure to daycare ultimately makes the child relatively unlikely to develop allergic asthma. So there need not be stigmatization, discrimination, or a self-fulfilling prophecy in response to the genetic information. Of course, the pediatrician may be concerned that the parents will still fall trap to vulnerable child syndrome—in this case, interpreting every bout of congestion or wheezy breath as the onset of asthma. The pediatrician can counteract this danger by ensuring that the parents do in fact understand the nature of this interactive predisposition for asthma, using it as a case to explicitly debunk the genetic essentialism that may motivate such an interpretation of the results.

Of course, if the parents have less control over manipulating the value of the environmental variable in this case, or if the parents have decided ahead of time to seek out or forgo daycare based on a particular parenting philosophy, then the cost-benefit analysis is altered. For instance, suppose our parents had decided ahead of time to forgo daycare because one of the parents does not work, and they cannot afford to send their child to daycare on the other parent's salary. Should the physician still provide the genetic test to the parents even with the value of the environmental variable now essentially as fixed as the genetic variable? I think the analyses of Clayton (1997), Cohen (1998), and Ross (2002) still run their course here in favor of providing the genetic test; however, the calculus does not proceed in the same fashion. If the child bears the Glu/Asp genotype, then the parents can be comforted in the fact that lack of daycare actually decreases the child's risk of developing allergic asthma. If the child bears the Asp/Asp genotype, then the parents can both prepare for the potential costs associated with a child with asthma and also take other measures which might take the place of daycare, such as exposure to social environments that include other young children.

Consider another hypothetical case based upon the interactive predisposition associated with depression:

> A father approaches his 9-year-old daughter's pediatrician, asking to have her genotyped to determine which variant of the serotonin transporter gene she carries. His wife, his daughter's mother, was recently killed in an automobile accident, and the father is concerned that this stressful life event, in coordination with certain allelic variants of the serotonin transporter gene, may make his daughter at high risk of developing depression in subsequent years. He would like to genotype his daughter so as to determine whether she is at increased risk of developing depression in light of this environmental stressor.

This case is also hypothetical in that there is not now a readily available test for the serotonin transporter gene. Still, as mentioned in the introduction to this chapter, Neuromark is seeking FDA approval for such a test with the expressed idea being that parents may want to utilize such information by genotyping their children. Should our pediatrician provide the genetic test for the daughter? For this particular case, I do not believe that even the revisionist analyses of Clayton (1997), Cohen (1998), and Ross (2002) support providing the test. To begin, the child has thus far experienced only *one* stressful life event. If we recall the reaction norm graph found in Figure 3.3a above, we see that all three variants of the serotonin transporter gene (s/s, s/l, and l/l) are virtually identical in their risk-status at exposure to one stressful life event. The probability of depression given one stressful life event for individuals from the Caspi-Moffitt study was 0.11 regardless of which genetic variant s/he carried. Obtaining the child's genetic information, then, in no way suggests a relatively elevated or decreased risk of developing depression at this point. Of course, we are all at risk of experiencing stressful life events, and if this young girl subsequently experiences one or more stressful life events on top of this first stressor, then carrying the s/s genotype would put her at a relatively increased risk of developing depression compared to either the s/l or the l/l genotypes. At four or more stressful life events, for instance, individuals from the Caspi-Moffitt study bearing the s/s genotype had a probability of 0.43 of

developing depression; individuals bearing the s/l genotype had a probability of 0.28 of developing depression; and individuals bearing the l/l genotype had a probability of 0.21 of developing depression. Might not the father argue that life is stressful, and thus he should obtain his daughter's genetic information, so that if these subsequent stressful life events *do* unfold, then he will know that she is at increased risk of developing depression? On the one hand, we should be sympathetic to this father's concern for his daughter and appreciate his interest in anticipating future stressors in light of the one he and his daughter have already experienced. Yet, what preventive or responsive action can the father, daughter, or health care provider take for the daughter if she carries the s/s genotype that they would not already take if she carries the l/l genotype in the face of subsequent stressful life events? Suppose, for instance, the father subsequently loses his job and is forced to sell their home and move with his daughter to a smaller apartment in another state, or suppose the daughter loses a close friend to a tragic accident. Should the father treat his daughter any differently in response to these stressful life events if she carries the s/s genotype than if she carries the l/l genotype? Not at all. In both cases, he should respond with appropriate familial, social, and perhaps psychiatric support systems that help her cope with the mounting stressful life events that she is experiencing. The increasing number of stressful life events puts her at increased risk of developing depression *regardless* of her genotypic status. So there is no sense in which obtaining the genetic information provides a potential benefit in the form of suggesting a course of preventive intervention that would not already be employed for any of the other genetic variants.

Moreover, there is also a clear and significant risk associated with a genetic test revealing that the child bears the s/s genotype. Bearing the s/s genotype, in coordination with exposure to multiple stressful life events, does point to a relatively increased risk of developing depression.

Though the outcome of depression is by no means a certainty, there is the very real danger that the daughter, her father, and those in their social network will begin treating depression as an inevitability. She may be seen as getting hit with that double-dose of bad luck: the high-risk genotype in the high-risk environment. Almost all adolescents experience brief periods of depression; with the double-dose, though, even these normal bouts of depression may be interpreted as the onset of clinical depression. Thus, the standard burdens associated with testing a child for a genetic predisposition, such as fears of stigmatization, discrimination, or a self-fulfilling prophecy, are likely to be magnified in this case of an interactive predisposition. When we consider the fact that the value of the environmental variable is out of anyone's control, that responding to the environmental variable would not be changed with information about the genetic variable, and that information about the genetic variable lends itself to clear and significant risks, I argue that the genetic test should not be offered in this case even if requested by the parent.

Consider one more hypothetical case, this time for the interactive predisposition associated with schizophrenia:

> A couple has approached an adoption agency seeking a child for adoption. Before accepting a child for adoption, however, they would like to know whether or not the child is at high-risk of developing schizophrenia. They are not prepared to deal with a child with a severe psychiatric disease, and so they would like to rule out that risk. Thus, they explain to the agency that they will eagerly adopt a child at low-risk of developing schizophrenia but will be unwilling to adopt a child at high-risk of developing schizophrenia.

Should the adoption agency provide the prospective adoptive couple with information about the risk status of an adoptee? In this case, the interactive predisposition associated with schizophrenia identified by Wahlberg and his associates is particularly relevant (Wahlberg et al. 1997). The danger with incorporating genetic information about an adoptee into the adoption

decision, remember, is that it risks making the child a "commodity undergoing quality control" (Wertz, Fanos, and Reilly 1994), and that it may adversely affect the child's chances of adoption (ASHG/ACMG 2000). With an interactive predisposition, though, the genotype alone does not confer risk status; that is, the adoptee cannot yet be labeled 'high risk' or 'low risk' until the environmental conditions of development have been experienced. In the Wahlberg et al. (1997) study, those conditions of development concerned the communication patterns in the adoptive parents. The adoption agency, then, could comply with the prospective adoptive parents request and obtain information about the adoptee's familial history of schizophrenia. However, in turn, the adoption agency would also need to request that the prospective adoptive parents undergo testing for evidence of communication deviance. Because we are dealing with a case of interactive predisposition, the risk status of the adoptee can only be predicted once information about both the genetic and the environmental information are obtained. If the prospective adoptive parents show evidence of communication deviance, then the adoption agency can seek out a potential adoptee without a familial history of schizophrenia.

Ultimately, then, I claim that the adoption agency should obtain the genetic information about the adoptee as it applies to this interactive predisposition for schizophrenia. In this case, there is no at-risk genotype; there is only an at-risk gene-environment combination. Thus, the familial history for the adoptee does not by itself predict his or her risk status, and so the standard burden associated with genetically testing adoptees is eliminated. The risk status comes from joining that family history with information about the communication patters in the prospective adoptive parents. The challenge, then, is pairing adoptees with prospective adoptive parents so as to minimize the risk of schizophrenia.

4.4. Conclusion

This chapter has been devoted to considering how cases of interactive predisposition should be taken into account in the ongoing debates over genetic testing in children. Thus far, the ethical debates have focused solely on cases of genetic determinism and genetic predisposition. As cases of known interactive predisposition become commonplace, however, the ethical considerations must be expanded so as to anticipate tests for genes implicated in these cases. Cases of interactive predisposition reconfigure the cost-benefit analysis involved in deciding whether or not to genetically test a child. In general, the need to incorporate information about the environmental variable into the evaluation of risk status raises important questions about the extent to which the value of that variable can be manipulated and the extent to which information about the value of that variable can actually be obtained. Moreover, the need to incorporate information about the environmental variable into the evaluation of risk status requires updated empirical studies about the extent to which parents will understand the probabilistic information involved in cases of interactive predisposition. The real challenge involves applying these general considerations to particular cases of interactive predisposition. I have considered several hypothetical cases and argued that the reconfigured cost-benefit analysis warrants genetic testing children in some cases, and does not warrant genetic testing children in other cases.

5. CONCLUSION

A conclusion can serve different purposes. One common function involves looking backwards and restating the arguments/conclusions of the earlier chapters so as to bring them all together in one place. Another function involves looking forwards and considering issues that could not be discussed directly in the earlier chapters but which are related in some way and deserve attention, perhaps pointing to directions for future research. Throughout the thesis, I have tried to tie the arguments/conclusions of the earlier chapters into the subsequent chapters. Thus, the backwards-looking function would be redundant here. Instead, I will consider some of the issues related to interactive predispositions which did not fit neatly into the earlier chapters. I will frame these considerations around two possible criticisms that might be leveled against my discussion of interactive predispositions, one criticism suggesting that I have overcomplicated the problem, one criticism suggesting that I have oversimplified the problem.

First, a critic might argue that I have overcomplicated the analysis of interactive predispositions by placing so much emphasis on the change in rank and demanding that a new concept be introduced to capture these cases as distinct from cases of a change in scale. A more nuanced concept of genetic predisposition, the critic argues, will work just fine. Consider the Caspi-Moffitt study on depression. The critic admits that the norms of reaction change rank. But the critic then argues that we can still say that, *in general*, individuals with the s/s genotype are the genetically predisposed population relative to individuals with either the s/l or the l/l genotypes. That is, if we *average* the probabilities of depression across all of the environments, then individuals with the s/s genotype are at a relatively increased risk of developing depression in comparison to individuals with either the s/l or the l/l genotypes. Why not, the critic asks, just forget about the change in rank and the concept of an interactive predisposition and instead focus

on the average risk across the environments and then return to the concept of a genetic predisposition, albeit an *averaged genetic predisposition*?

This criticism is essentially a variant on the utilitarian comparison of subgroups introduced in the context of screening newborns for MAOA status (see section 3.3 above). And, as such, it faces the same problem that the utilitarian comparison of subgroups faced. The utilitarian comparison of subgroups, remember, pushed through the interventionist's dilemma by comparing subgroups in the Caspi-Moffitt MAOA study and noting that, in two of the three environments, the low-MAOA activity population was at the relatively increased risk of developing ASPD, thus concluding that an MAOA boost for all individuals with low-MAOA activity would be in order. The problem with this analysis, however, was the fact that only 1/3 of the population in the Caspi-Moffitt study actually fell into these two environments; *most* of the study population did not experience childhood maltreatment, and so an MAOA boost would actually increase the risk of developing ASPD for *most* of the population. The same can be said for the depression study. Even though individuals with the s/s genotype are at a relatively increased risk of depression in environments with multiple stressful life events, we should not then assume that individuals with the s/s genotype are the ones who most often develop depression in the general population. If most of the population falls into environments with zero or one stressful life event, then individuals with the s/s genotype are, in general, not more at risk than the individuals with the other genotypes. So the concept of an average genetic predisposition fails to capture the relative frequency with which individuals actually find themselves in the different environments.

Now, the critic could here opt for an even more nuanced interpretation of genetic predisposition so as to continue applying this concept to cases of G×E resulting in a change of

rank. We shouldn't focus on average risk across the environments, treating each subgroup as equal; we should focus on *weighted* average risk across the environments, weighting each subgroup based upon how many individuals in the population actually fall into that subgroup. The result, the critic now points out, would be a *weighted average genetic predisposition*. This is certainly a legitimate response to the problem. But why go to such extremes to salvage the concept of a genetic predisposition? The whole point of chapters 3 and 4 was to draw attention to the unique ethical questions that arise when the norms of reaction change rank. Reverting to a weighted average genetic predisposition completely ignores this cross-over effect and generalizes across all of the environments, thereby missing the ethical questions that were raised in those chapters. As Parens points out, "conceptual tools—basic concepts and distinctions" are needed in the scientific, public, and ethical discourses about behavioral genetics (Parens 2004, S30). In light of the important difference between cases of G×E resulting in a change of scale and cases of G×E resulting in a change of rank, differentiating between genetic predispositions and interactive predispositions draws attention to this difference, whereas a weighted average genetic predisposition, nuanced or not, only ignores the difference.

Another critic of my analysis might suggest that, rather than overcomplicating the problem, I have actually oversimplified it. The criticism here would be that my analyses of the diseases and disorders resulting from interactive predispositions only contain information about the particular genetic and environmental variables involved in the studies that I discuss; in fact, the diseases and disorders are probably also affected by many other genetic and environmental variables that do not play out in the same manner. Consider the interactive predisposition for thought disorder, the trait symptomatic of schizophrenia. Wahlberg and his colleagues (1997) found an interactive predisposition for genetic risk, exposure to communication deviance, and

the subsequent development of thought disorder. Children of biological mothers who were schizophrenic were *more likely* to develop thought disorder than children of biological mothers who were not schizophrenic when these two groups were exposed to communication deviance from adoptive parents. Children of biological mothers who were schizophrenic were *less likely* to develop thought disorder than children of biological mothers who were not schizophrenic when these two groups were not exposed to communication deviance from adoptive parents. Still, an adoptee's adoptive environment consists of many factors, communication patterns in the adoptive parents only being one of them. There are also environmental factors involving nutrition, education, and socioeconomic status, to name just a few. The critic admits that there may be an interactive predisposition for thought disorder involving genetic risk and *this particular* environmental variable. But, the critic continues, in general the children of biological mothers who were schizophrenic are consistently at increased risk of developing thought disorder relative to the children of biological mothers who were not schizophrenic across *most of the other environmental variables*. That is, there may be an *interactive* predisposition with this one environmental variable, but the norm is a *genetic* predisposition with most other environmental variables.

I take this to be a valid point, but I do not see it as fundamentally undermining my analysis of interactive predispositions. The conclusion to draw from this criticism is simply the fact that *all* of the empirical information regarding the genetic and environmental variables implicated in the development of schizophrenia (or any trait for that matter) should be incorporated into the analysis, be it an analysis concerning the genetic screening of embryos, fetuses, newborns, or children. If there are interactive predispositions involving some genetic and environmental variables and genetic predispositions involving others, then the analysis must

proceed by taking into consideration both the traditional questions raised about genetic predispositions as well as the new questions I have raised concerning interactive predispositions. Consider the adoption agency deciding whether or not to inform the prospective adoptive couple about the risk status of potential adoptees with regards to schizophrenia. If there is an interactive predisposition involving communication deviance but a genetic predisposition involving most of the other environmental variables present in the adoptive home, then the adoptive agency would be wise to essentially treat the case as a genetic predisposition and consider all of the potential burdens associated with testing adoptees for genetic predispositions to psychiatric disorders alongside the issues raised by the interactive predisposition. The point is that empirical information about an interactive predisposition for a particular trait only provides information regarding the particular genetic and environmental variables involved in the study. This can be valuable when deciding how (or whether or not) to manipulate that particular environmental variable or the product of that particular genetic variable, but it should not be taken to imply that there is an interactive predisposition for that particular trait for *all* genetic and environmental variables.

Ultimately, I have argued in this thesis that the difference between cases of G×E that result in a change of scale and cases of G×E that result in a change of rank warrants distinct concepts. This argument was based both on the conceptual incoherence that follows from characterizing cases of G×E that result in a change of rank with the concept of a genetic predisposition, and also the unique ethical questions surrounding embryonic, fetal, newborn, and childhood genetic screening that arise for these cases of G×E that result in a change of rank. Even a nuanced concept of genetic predisposition, such as weighted average genetic predisposition, will miss these unique questions. However, that being said, the analysis of any

particular case will most likely involve a mix of the traditional questions relating to genetic predispositions and the questions that I have raised relating to interactive predispositions.

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