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Nurturing the Genius of Genes: The New Frontier of Education, Therapy, and Understanding of the Brain

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Abstract. Genes dance. They dance with culture. They dance with environment. Genes act on the world through the brain, mind and behavior. Historically, psychologists, therapists, educators and most lay people have understood genes in the context of Gregor Mendel's experiments, which were only partially explained to us. While many studies show that brain structures and behaviors have quite robust influences from inheritance, most behavior is not influenced in the classic way we were taught in our introduction to genetics – which has been revolutionized by molecular studies and understandings that most of the important genes of everyday life are quantitative, or polygenic. Popular culture and naïve theory has a very simplistic view of genes. They are bad, impolite and vaguely anti-democratic if not sinister. A very simple truth exists, however. Were it not for the genes of our grandparents, no one would be reading this article. This article introduces the reader to an idea that emerges from evolutionary psychology and behavior genetics, which may turn our thinking inside out. For the most part, genes are gifts of nature to solve problems, and to hedge a bet on the future. Most true genetic diseases, regulated by the classic processes that Mendel observed, are extremely rare – typically below one in several hundred. Most of the behaviors that cause us grief or joy in our homes, schools and communities and with some form of genetic contribution happen far more often – 3%, 5%, 10% or more of the time in the population. If such behaviors were "defects" harming our reproductive success, Mother Nature would have quickly made short work of those genes in a handful of generations. The fact that many of the genes related to these behaviors and subtle changes in the brain seem to have been recent changes (pejoratively called by some "mutations") in the past few thousand years implies that these changes are in some sense Nature's Gifts. Gifts are to be treasured, saved and perhaps passed on. Sometimes a gift may be burdensome. This paper is about reframing and explaining advances in science in the past 10 years or so, parallel to the brain imaging studies. The molecular studies, explored in the context of evolutionary psychology and behavioral genetics provide a new model for human development, enhancing our understanding of more traditional views of human phylogeny and ontogeny. The same molecular studies, when framed in the context of twin, adoption and longitudinal studies, provide new insights for parenting, schools, community and therapy.

Genes were the dancers, providing clever answers, for our distant ancestors.

Culture was the muse, and sometimes the fuse, for the heritable new.

From the DNA tango of gene and culture, the brain wired itself and grew.

It's not exactly scientific, but ask any grandmother. She'll say, "No two children, honey, even from the same family, are alike." Parents of course attest to this, puzzling over the differences in their children who had similar family experiences. "We gave them the same advantages, but they are so different." One child may be forever on the go, and grows up to be a day trader in the stock market. Another child seems shyer, more withdrawn. That child grows up to be more sedate in lifetime work choice.

Childhood differences show up early in some longitudinal studies, lasting well into adulthood. These differences show up strongly in the twin studies who may be reared apart or together (e.g., Karkowski *et al.*, 2000; Kendler *et al.*, 1999; Maes *et al.*, 1999; Schulsinger, 1972; Slutske *et al.*, 1997). When such consistent similarities show up in twin studies, a good possibility exists that that trait or pattern of behavior has genetic roots.

Genes scare many people. Perhaps, it is our own fear of whether our own genes contain seeds of problems like cancer or other diseases. We may fear the proverbial crazy relative not because of the risk of their behavior, but because of the fear they live incipiently inside us. Genes humble us, too. Personally, I will never have a great mop of thick hair like the men's fashion models – unless there is some miracle as a result of the Human Genome project. Secretly, we hope our genes have given us gifts – some talent, some immunity, some prowess. Gene combinations seem to be the result of a dice throw, yet Einstein believed that God and Nature rarely did so.

This article is about understanding how genes do give us gifts. This article frames scientific advances of genetics in ways that we might better understand why or how certain traits are manifested today, based on evolutionary theory. This article also aims to clarify what educators and therapists must do to address the disorders *du jour* – depression, attention deficit, learning disabilities, violence, and substance abuse. This article provides a genetic context for understanding advances in neuroscience and behavioral science. The article is not, however, an argument about nature versus nurture, a pointless straw argument. This article aims to bridge the distance between major advances in basic science and applications for policy, helping make good intentions a reality. The article also introduces a new concept, braingenomics, to describe the role of genes, culture, and brain in manifesting behavior.

Contemporary Scientific Context

Catalogues and brochures tout "brain-compatible learning." The advertisements speak of intelligences, and entrepreneurial therapists put trademarks on some putative revolutionary treatment. All of these efforts appeal to the revolution in neuroscience, which largely began with the commercial sales of brain scanning equipment in 1989 – just a decade ago. Unnoticed by even the most studious of educators, psychologists, and even medical doctors is a volcanic eruption of knowl-

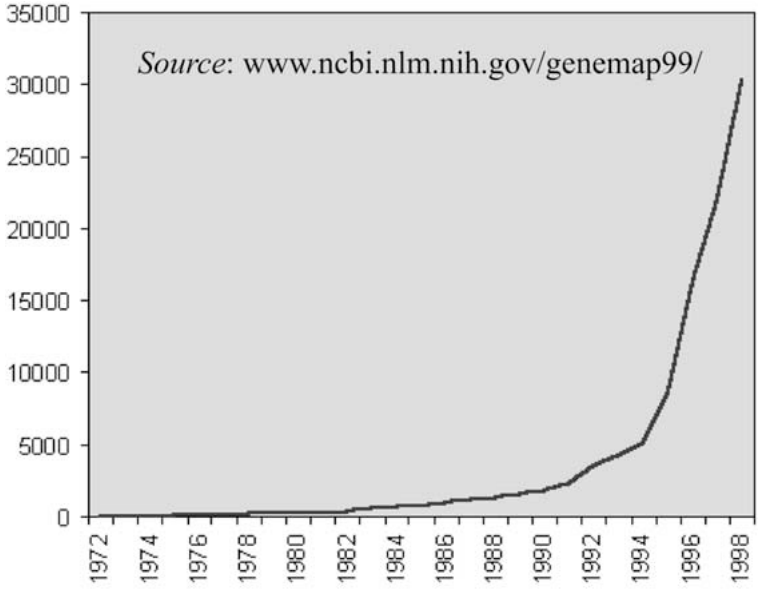

Figure 1. Human genome progress.

edge of gene mechanisms that orchestrate the unfolding of behavior, cognition, and emotion whose provenance is the brain. These genes – even bits of genes – were unknown to but a few earnest researchers a few years ago. The instrumentation and processes that have made these gene discoveries – the Human Genome Project, for example – only became available in the mid-1990s. Genes are not what they used to be.

The Human Genome Project has exploded our knowledge of genes, which can be seen from a graph in Figure 1. Prior to the start of that project, about 5,000 genes had been mapped. By 1998, the number had nearly doubled to a total of 30,261 mapped genes.

It's not just the number of genes mapped that has changed our knowledge. It is our understanding of the very mechanics of genetics. Most of us know genetics from high-school biology. We remember Gregor Mendel. We remember recessive and dominant genes. We remember different colored flowers on sugar peas. While these basic understandings are useful, it is about as informative as a junior chemistry kit from elementary school compared to modern molecular biology. Most of us are stuck in those darn sugar peas.

Certainly no educators, no therapists, not even many doctors think of genes in their daily practice. Pity. In those delicate bits of organic matter is the dance of life, partnering with the social and physical environment in ways that make "brain compatible learning" seem like the cognitive stage of a preschooler. The brain is the gene's way of *acting on* the environment.

Even hundreds of years ago, noted by Mendel in his own experiments, there were different models of genetics than the now textbook cases of dominant and recessive genes. The experiments made no clear sense at the time. For example, Mendel found that some peas were shades of in-between colors, which is not predicted by a *single* gene model. The single gene model is what most of us learned in school, however. Early experiments showed that some traits could be continuous, much like height from very short people all through the spectrum to very tall people. Two armies eventually emerged from these observations, one the "classic Mendelians" and the other composed of statistical folks who claimed there were no genes in the classic sense. How to reconcile these observations?

My colleague, David Comings, tells the story (in press):

> A number of geneticists such as Johannsen, Yule, Nilsson-Ehle, and East produced some of the early studies of plants that helped to resolve the conflict (Strickberger, 1968). Johannsen attributed variation in weight of the beans that were greater than the variation in the weight of the parent strains as due to environmental factors, thus suggesting that quantitative traits were due to both genetic and environmental factors. In 1906, Yule suggested that continuous quantitative variation might be due to the interaction of many individual genes, each with a small effect. This was demonstrated by Nilsson-Ehle in his studies of the color of wheat grains. In the second generation, the observed ratio of 1 white to 63 red grains conformed to the expectation for the segregation of 3 genes and 6 alleles in a diploid organism. The uniqueness of this experiment was that for the first time, a quantitative trait was shown to be due to discrete, individually segregating genes. Thus, very early in the 20th century all of the key elements of polygenic inheritance had been identified i.e., continuous quantitative traits were due to the additive effect of multiple genes, each with a small effect, interacting with the environment.

The continuous traits, described by Comings, represent the arrow of evolution. They are adaptations to the past, that when combined in new ways, offer low-risk reserve for adaptation to the future. Polygenic genes are typically polymorphic – showing in multiple forms. Genes are predictions about the present and future world, based on the past. Were it not for the genes of your grandparents, you would not be reading this page. Our genes bestow gifts that enable us to create symbolic speech, throw an object at a target, recognize emotions on human faces, and experience pleasure at the taste of a sweet. Our genes are gifts, not curses, enabling complex behaviors. Polygenic inheritance may be one of the least understood gifts in human education, therapy, medicine, and other knowledge areas.

Genetic defects are rare, especially dangerous ones. Dangerous genes quickly vanish. Genes survive because they have had value. Genes are inheritances from past successes, much like a family estate passed on to the grandchildren as a bequest that might hedge the future. Framing genes as a gift – a Nature's genius – can help us better understand how to nurture brains and behavior. Genes contain

the greatest potential gifts for human brains and behavior, which may startle folks who are used to thinking of genes as politically incorrect dinner conversation.

Polite dinner conversation limits most talk of genes to the noises that folks make upon seeing a new baby. "Oh, she has your eyes"; or, "Ah, his nose is just like his grandfather." Sometimes, when we are mad at our children or spouses, we hurl genetic insults. "You are acting just like your father"; or "You sound just like your mother."

Scientists know that behavior as well as looks can be inherited. These are not the findings of social Darwinists from the turn of the 19th century, fascist rubes of the World War II era, or modern-day Bubbas. These are the findings of reputable, peer-reviewed articles published in virtually every language. Often, journalists and pundits incorrectly report information. Sometimes, headlines claim something like, "scientists find gene *for* ADHD, crime, or substance abuse." This comment incorrectly reports science. What is more accurate is to say that scientists have found that certain patterns of behavior are heritable. Genes do not typically code for disease or disorder; genes code or gift for advantage for certain circumstances. At the risk of hyperbole, the greatest of circumstances for humans are the ones created intentionally or unintentionally by other humans. Advantage is not what we *say* it is; advantage is what Mother Nature decides. A review of some issues of polygenic inheritance will help understanding.

POLYGENIC INHERITANCE NOT VISIBLE BY COUNTING BODY PARTS IN THE GYM SHOWER

Polygenic mechanisms are quite different from what most adults have learned. Multiple genes affect one trait such as diabetes, cardio-vascular disease, and cancer. The traits are quantitative, varying along a continuum such as height or skin color. The polygenic traits show a bell-shaped distribution. Figure 2 illustrates the polygenic normal curve associated with skin pigment.

If "toe-ness" were a polygenic trait, there would be a distribution along a normal curve of 1, 2, 3, 4, 5, 6, and even 7 toes per foot! Quite obviously toes are not inherited in this manner, as anyone who has gone to a public-school shower can attest. There are equally obvious body parts that do vary on a continuum – easily visible in the same locker room shower, either for boys or girls. Height, weight, athletic prowess, reaction time, ability to track moving targets are, however, polygenic traits that can be measured in the gym or on playing fields. Polygenic traits are not necessarily the province of those settings.

POLYGENES AND THE BRAIN

Mice and men share much from mammalian evolution (e.g., Plomin *et al.*, 2001). Where the basics of biochemistry not the same, virtually no modern pharmaceut-

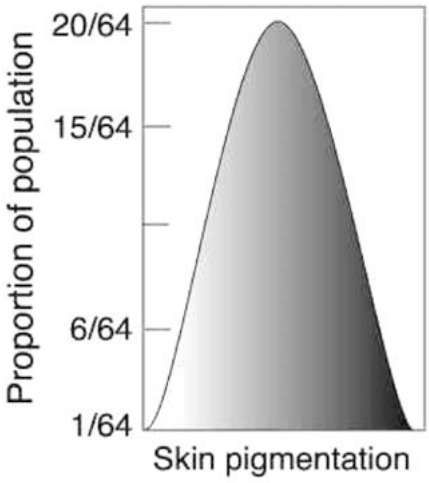

Figure 2. Polygenic example of skin pigmentation.

icals would be available to humans today. Most every drug was first tested on mice or rats. In an odd way, some strains of mice or rats owe their reproductive success, indeed their very lives, to the ecological niche of laboratory research. We have even closer relatives.

It is often stated in popular literature that the chimpanzee shares 98.7% of its genes with us (*New York Times*, April 12, 2002, A18), and the primatology studies by Frans de Waal and Jane Goodall shows us how much the modular components of behavior exist in our distant cousins. The politics, the parental care or lack thereof, war and conflict, peacemaking skills, and problem solving among the chimpanzee look eerily familiar to the home, school, office, and family reunions of *homo sapiena.* Where lies the subtle difference?

The difference and similarities glow on a gene chip, a recent invention. Fluids from living cells are dropped on a glass slide, embedded with genes in an array. Each location on the array lights up on the array, depending on the presence of the genes.

Is there a difference on the gene array? Absolutely. In particular, the gene differences show up in the area of the brain genes. That is, genes for chimps versus people vary mostly in the area of the brain and the "clock speed" of evolution (Pennisi, 2002). This difference is not surprising based on early work that showing subtle structural differences in chimpanzees, monkeys, and man (e.g., Buxhoeveden *et al.*, 2001). The difference appears to be the result of evolutionary differences in gene and protein expression, the manner in which coded information in genes is activated in the brain, and then converted into proteins that carry out many cellular functions. The brain differences are more a matter of quantity than quality. Differences in the amount of gene and protein expression – partic-

Table I. Heritability ratios of some mental disorders. The risk ratio λ denotes the ratio of risk to siblings or identical twins to the general population prevalence

Disorders	Risk ratio λ	
	Siblings	Identical twins
Autism	50–150	2000
Tourette's	200	1000 (?)
Bipolar disorders	7	60
Schizophrenia	9	48
Type II diabetes	2–3	16
Depression	2–5	8

These ratios show increasing recurrence risk with increasing genetic similarity. The question mark of Tourette's reflects the dearth of twin studies. See Genetics Workgroup, NIMH (1999).

ularly RNA messengers, rather than differences in the structure of the genes or proteins themselves, distinguish chimpanzees and people (Enard *et al.*, 2002). Thus, humans seem to have sped up the rate of change of gene expression selectively in their brains, accumulating expression differences at least five times faster than chimpanzees.

This rapid rate of human gene changes in the brain would suggest that differences in human behavior, emotions, ability to learn, and so forth would have a fertile ground to grow from on the genes governing neurotransmitters, hormones, and neuropeptides. Indeed, these "brain genes" might well have changed as a result of ecological, climate, migrations, or other social changes faced by our ancestors, with different individuals or groups having acquired different "genetic gifts" to solve problems of survival and adaptation. Some evidence already exists from the study of disorders described in the Diagnostic and Statistical Manual of the American Psychiatric Association.

Most psychological events described in DSM-IV have substantial genetic loadings, which was recently overviewed by none other than Dr. Steven Hyman of the National Institute of Health. A table of just a few interactions from Hyman's article appears in Table I.

My purpose here is not to review that literature, argue the various loads and interactions, or the politically correctness of mental disorders, but simply to tell the reader that *the essence* of what Dr. Hyman says is demonstrably true. A very large number of behaviors, which some describe as disordered, are clearly heritable (see Plomin *et al.*, 2001). Dr. Hyman's numbers are probably outdated, in the rapid pace of knowledge with the risk ratios for Tourette's being nearer 10 for siblings and 80–100 for identical twins, because Tourette's is much more common than previously

thought (Comings, personal communication, April, 2002). This certainly means that a far more subtle range of behaviors related to the brain must be regulated by genes, which have survival value, and which may be turned off or on as a result of social-biological-physical events in the course of individual development. These differences must be expressed across a continuum of additive effects via polygenic mechanisms.

Human behavioral development is often presented as a linear event, with stages based on age. These are presented as invariant processes. This leaves a puzzle of all the behaviors that emerge that cause grief to parents, families, teachers, and clinical staffs. Certainly 3-year olds tend to do things differently than 1-year olds and 13-year olds. However, some 3-year olds and some 13-year olds, let alone 30-year olds feel, think, and act quite differently than their age mates. It is clear that "normal" and "abnormal" development interact with the present social-physical and biological environment to affect developmental outcome profiles of individuals. Developmental theory embraces evolutional theory of how we have come to be the same or similar through the process of adaptation to common problems during evolutionary history; behavioral genetics attempts to explain how groups or individuals might likewise have adaptations that result in differences. Both the evolutionary theory and behavioral genetics interact with the present environment to produce the enormous variation in how people feel, think, and act. This is a three-dimensional rather than two-dimensional model of human development, and it is represented in the Figure 3.

POLYGENIC BEHAVIORS AND REGULATORS

The 3-D Human Development Model predicts that developmental outcome will be a function of evolutionary forces common for all humans, some evolutionary forces faced by our unique ancestors, and modified in response to the present environment. People and other mammals are complicated. We move. We fight. We mate. We give birth. We learn. We feel. We think. We change our environment by our behavior. There are only a tiny handful of *single* genes that regulate behavior. Thus, there is no gene *for* learning, *for* fighting, *for* thinking or feeling, *for* spelling or language, or *for* virtually any behavior that would be of everyday interest to a parent, teacher, or doctor.

Ah, but there is inheritance. It is obvious to even the unschooled. "You know, substance abuse seems to run in that family." Or, "They are all pretty much a feisty lot." This list is extensive from lay observations. Serious scientific studies concur.

Twin, adoption, and molecular studies from all over the world show substantial heritability of all sorts of traits and behavioral or personality characteristics (e.g., Bouchard and Loehlin, 2001). Some of the them include: (1) aggression, (2) novelty seeking, (3) attention, (4) activity levels, (5) extroversion, (6) shyness, (7)

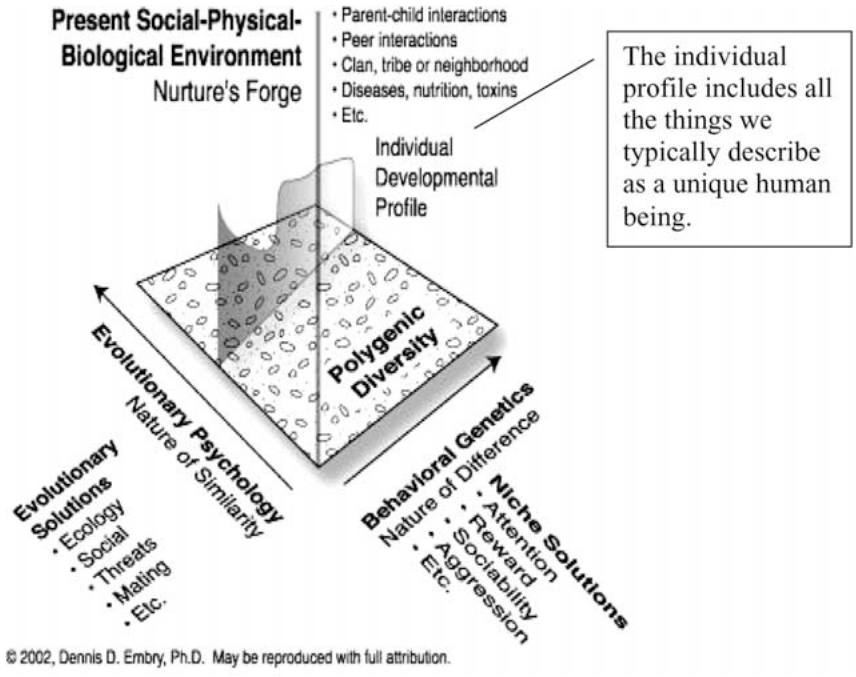

Figure 3. 3-D model of human development.

language, (8) susceptibility to reward immediacy, (9) response to stressors; (10) dominance, (11) openness, and (12) conscientiousness. What is important to note is that the personality or behavioral variables are distributed along a normal curve, and not necessarily an aberrant mutation or disorder. What, however, might be the link between personality, brain, neurotransmitters and genetics? The annual report (www.grc.nia.nih.gov/branches/lpc/chief.htm) from Laboratory of Personality and Cognition at the National Institute on Aging provides some useful insights of what is happening scientifically.

> Two independent studies reported in the January issue of *Nature Genetics* provided evidence suggesting a link between scales from two personality inventories – the Tridimensional Personality Questionnaire (TPQ) and the Revised NEO Personality Inventory (NEO-PI-R) – and alleles of the D4 dopamine-receptor gene (D4DR) located on the short arm of chromosome 11, which encodes for one of the five known subtypes of human dopamine receptors. 124 normal adult Israelis (69 men and 55 women) completed Cloninger's TPQ. The 34 subjects with an allele containing 7 repeats in the exon III region of D4DR scored significantly higher on the Novelty Seeking scale than subjects with a shorter allele.
>
> Jonathan Benjamin, Dean Hamer, and colleagues at the NIH administered the NEO-PI-R to 217 American subjects with short (2 to 5) D4DR exon III

repeat sequences and 98 subjects with long (6 to 8) repeats. Subjects with the long allele had higher scores than subjects with the short allele on 3 of the 6 facets of Extraversion, namely Positive Emotions, Warmth, and Excitement-Seeking, and had lower scores on Deliberation, a facet of Conscientiousness. Because Extraversion and low Consciousness are known to be related to TPQ Novelty Seeking, these two studies both suggest that long allele subjects are more cheerful and spontaneous, possibly as a result of the functioning of their dopamine systems.

Although twin studies have long suggested that normal personality traits must have some genetic basis, these studies demonstrate a direct link and open the way for a series of studies on the genetic basis of personality and other psychosocial variables.

Future studies will investigate the relations of other central nervous system (CNS) receptor alleles to personality traits and other psychosocial variables. These analyses will provide a more complete understanding of the personality traits related to D4DR and possibly other CNS receptor alleles. That in turn may suggest hypotheses about the functioning of the dopamine system and its behavioral expression, and about the broader genetic basis of normal variations in personality.

Even subtle behaviors, as in the way an infant responds to strange situations and attaches to its mother are affected by polygenes (Lakatos *et al.*, 2001). As we once blamed parents for schizophrenia, the issues of attachment disorder can make a parent or adoptive parent feel terrible shame as the mental health profession microscopes their behavior. The issue is far more complicated than early bonding or brain stimulation. The DRD4 7 repeat allele happens four-times more often among infants with disorganized attachment. Yet, the modifying effect of a *single* nucleotide polymorphism (–521 C/T) in the regulatory region of the same DRD4 gene can reduce rate of transcription of the DRD4 gene by approximately 40% – affecting dopaminergic neurotransmission. If the "T" version of this allele and the DRD4 7 repeat happen together, the relative risk for disorganized attachment increases 12-fold. Obviously, the dance that happens between a mother and an infant will be different, and this will take some very meticulous study to find a solution.

Polygenic mechanisms could be viewed as behavioral rheostats. At one level, they may set the "temperature", "humidity" or "frequency." Thus, these polygenic mechanisms affect many neurotransmitters such as serotonin, dopamine, norepinephrine, GABA, opioids, hormones (e.g., Comings *et al.*, 1999, 2000). For example, a collection of genes regulates our individual preference for rewards right now versus rewards down the line (e.g., Cloninger *et al.*, 1996). Why might this be so? Of what use is this gift or difference? Other gene constellations determine our individual range of response to aggression, stress, or sexual maturity. Again, why? How do we use this gift of Nature?

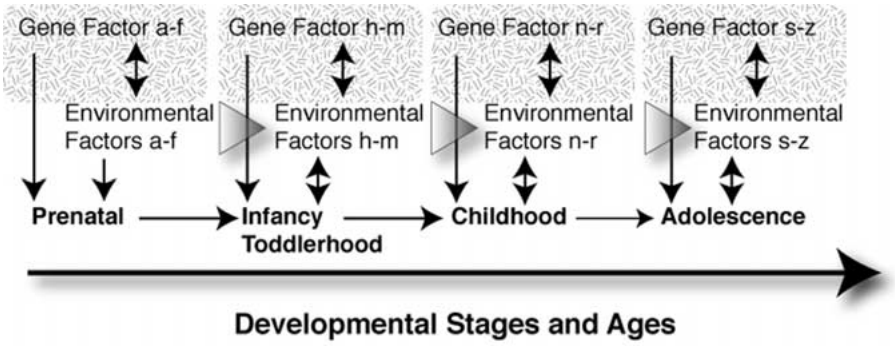

Figure 4. Gene, environment and developmental stage diagram.

Rheostats are useful metaphors, quite unlike the yes-no distinction of Mendelian genetics. A rheostat can be fast or slow. A rheostat can have a narrow or wide range. A rheostat can be set low, high, or in between. A rheostat can have a winter or summer setting. Most importantly, a rheostat can be adjusted, and rheostats have U-shaped curve functions. That is, rheostats typically try to make sure there is not too much or too little for *a given circumstance*. The purpose of this article is not to detail the various mechanics of genes. That can be left to any number of resources on the Internet or textbooks (e.g., Plomin *et al.*, 2001). The true purpose of this article is to reveal how the mind is sculpted by a dance between polygenes and the environment, how brain and behavior interact with those genes, and how micro and macro-level social events can be changed to alter the expression of polygenes, maximize the gifts of those polygenes, or even alter their future distribution. Polygenes are among the greatest gift of Mother Nature. What will be discussed here is how we can use this bequest to liberate the genius of genes or how we might squander or misunderstand the gift.

Is there evidence of a rheostat function in genetic mechanisms? Yes, indeed. Most people think of genes as some sort of a fixed property. That is not entirely true. While each of us carries the genes we got at the moment of conception (though, this may not always be true as genetic re-engineering advances), genes can turn on in response to signals or events from life. Conceptually, the rheostat function might have sensitivities governed by different genes at different developmental stages, triggered by different environmental or social events. The genes might even operate directly on the environment, and the effect of the environment-gene interaction might have a valence or directional slope over time. Figure 4 provides a conceptual diagram.

Are there any data to support this type of interaction? Yes, and "anti-social behavior" provides a case example. Consider a sample of 14,000 children, some born to one or more parents with a documented history of antisocial behavior, some born to families with no antisocial parental histories. Imagine that such children are put up for adoption, some to adoptive parents with antisocial tendencies and

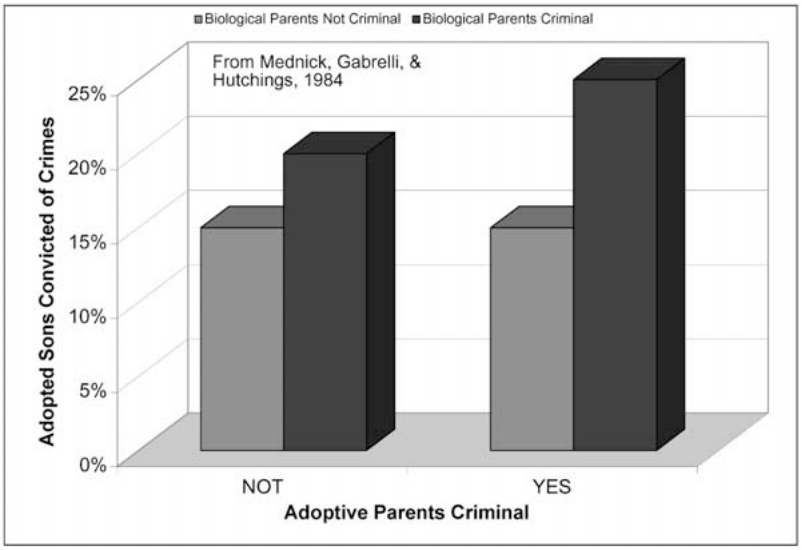

Figure 5. Influence of adoptive environment on genetic risk.

some without. What will the outcomes be? Mednick *et al.* (1984) provide some evidence of genetic influence on criminal behavior in a Danish adoption study. Figure 5 is adapted from that study. What the study suggests is that the genetic influence is "turned on" substantially by environmental circumstances, which has many implications for social policy.

More sophisticated studies are like to reveal timing mechanisms for certain behaviors, which unfold differently based on genes, environment and developmental stage. Why might this be so? Genes are not turned on necessarily at birth; some genes "turn on" in response to sex hormones, environmental stressors, or other environmental factors.

POLYGENES AS EVOLUTIONARY MECHANISMS

Evolutionary psychology describes solutions to common problems; behavioral genetics describes solutions to unique situations. How is that possible? Historically, humans were far more isolated than today's humans who move across continents in 6–12 hours. Historically, human populations have had to solve adaptive problems. For example, several thousand years ago, humans faced a terrible malaria epidemic in Africa. This catastrophic event caused many people to die, but there were some who had a difference in their hemoglobin that caused "sickle" and did not die. The difference in hemoglobin provided a protection from malaria, and is of recent origin (e.g., Tishkoff *et al.*, 2001). While this example is relatively well known, there are others such as the immune system adaptation among some Northern Europeans that confers protection against HIV infection, which apparently happened several

centuries ago. Here is that story as described by Reiness (2000), which nicely summarizes the studies published in *Lancet* and *Science*. A group of individuals have been known to have been exposed to HIV many times, and yet never seem to have developed a serious HIV infection. For example, about 10% of hemophiliacs who received HIV-contaminated blood didn't become infected with HIV. Some people test positive for HIV, yet have remained symptom free for 15 years or more. One such person is a personal friend. Is there some characteristic that enables some to fight HIV infection better than most people? Yes, about 20% of people in the long-term survival group do not have a working *CCR5* gene, which appears to provide protection against HIV. Consider the evidence. Not one in 1300 infected individuals was homozygous for the non-working *CCR5* genes while 3% of the uninfected group were homozygous for this trait, a highly significant difference. Reiness further observed in his write-up that the rate of progression from HIV infection to AIDS was demonstrably slower in individuals heterozygous for the non-working *CCR5* gene. Some people may have natural resistance to HIV infection – mostly people of northern European origin. The non-working *CCR5* gene is absent among Africans, Asians, or Native Americans, but about 20% of northern Europeans carry one or two copies of the non-working gene. This ethnic distribution suggests that the *CCR5* polymorphism results from a relatively recent mutation with high survival advantage, possibly because it offers protection against another infectious agent. An editorial review in the *Journal of the American Medical Association* provides an excellent synopsis of the *CCR5* gene variations in HIV infections (O'Brien and Goedert, 1998). This, however, is not the only variation relevant to HIV distributed by populations.

HIV invades the immune system via a clever set of tricks involving co-receptors. One variation of a co-receptor, controlled by a specific gene also confers resistance to infection as shown in a study of several thousand patients (Winkler *et al.*, 1998). Using a polymerase chain reaction assay, Bing and colleagues (1998) investigated the distribution the *SDF1-3'A* allele in 16 worldwide representative populations. Their results showed that the *SDF1-3'A* gene allele frequencies vary drastically among the world populations surveyed, ranging from 2.9% to 71.4%. African populations exhibit lowest frequencies (2.9–9.1%), rates that agree with the reported frequency in African Americans. No individuals were found in African samples in their study to have the variation. The frequency of the allele increases in American Indians, Europeans, and Asians, ranging from 12.2% to 36.6%. The greatest frequency for the HIV-resistant allele happened among New Guinean Highlanders.

If there are polymorphic genes that show adaptation for diseases among populations, are there behavioral adaptations with possible genetic linkages? The answer appears to be yes.

A multi-national research team from the University of California at Irvine, the Chinese Academy of Sciences, and Yale University studied genes from 600 people around the world in an effort to pinpoint the basis of attention deficit

hyperactivity disorder. They found 56 variations of the gene DRD4; which controls dopamine, the neurotransmitter that manages movement, learning, and responding to rewards. Their study showed that a specific variation, 7R, was especially prominent and looks to have popped up spontaneously from 10,000 to 40,000 years ago. That corresponds to the time when humans were building complex societies that included agriculture, the first governments, and the first cities. They were also exploring the planet. The study team argue that those societal changes, led our ancestors to favor the behaviors expressed by 7R, which led to it being so common today (at least 3% of elementary school children evidence these behaviors). Half of all children with ADHD now carry the 7R variation, which is also linked to novelty seeking and addictions – but not in all studies, which is a common "statistical" sort of problem wherein a particular gene variation accounts for a small amount of variance. This important technical issue is explained in other places (e.g., Comings, in press). It is important to restate that this variation in a gene that favors a common constellation of behaviors has been favored by natural selection, yet does not exist in every person – the difference between evolutionary psychology and behavioral genetics.

Before the advent of polygenic technologies, other investigators have documented interactions between human ecologies (e.g., pastoral economies) and the expression of aggression related to other human threats (e.g., Nisbett, 1993). In this earlier work, Nisbett reported that individuals whose migration patterns originated from pastoral economies tended to very sensitive to perceived threats, insults, and implications that resources might be taken by others. For example, the South is more violent than the North because Southerners have different, culturally acquired beliefs about personal honor than Northerners. Nisbett tested his theory in the context of differential patterns of violence between the North and South in America. Scotch-Irish, people with an animal herding background, largely settled the South; the Northern settlers were English, German and Dutch peasant farmers. Most herders originally migrated from sparsely populated, lawless regions. Since livestock are easy to steal, herders found that reputations for willingness to engage in violent behavior deterred rustling and other predatory behavior. Of course, predatory men used the same strategy to intimidate their victims. As this arms race proceeds, arguments over trivial acts can rapidly escalate if a man (less often a woman) thinks his honor is at stake, and the resulting "culture of honor" leads to high rates of violence. Nisbett has demonstrated his theory quite elegantly, and subsequently showed significant cortisol and testosterone elevations among individuals sensitive to insults and affronts (Cohen *et al.*, 1996). Could this cultural and biological interaction, with sensitivity to threats and human predators, have a genetic loading? The answer is not definitive, but certainly the evidence is congruent with this hypothesis (e.g., Wuest *et al.*, 2000; Young *et al.*, 2000).

Polygenes are clearly relevant to medicine, yet they were barely understood even five years ago in medical Epidemiology – mostly because the technology has zoomed along with the study of the human genome. One wonders if the discoveries are relevant to us in our homes, classrooms, and communities.

POLYGENES IN THE HOME, CLASSROOM, AND COMMUNITY

"Billy," not his real name, is presently in the state prison of Wyoming. It's not a nice place to be, and Billy's history is a map of the impact of polygenes interacting at home, in the classroom, and the community. During a major effort to develop a comprehensive, science-based blueprint to prevent and treat substance abuse and related problems in the state of Wyoming, I had to review most of the science on genes that led to my thinking about this article. The overall report (Embry and McDaniel, 2001) can be downloaded at www.paxtalk.com/news. The preparation of the report exposed me to the reality of the new brain and genetic sciences in everyday life. Part of the activity of preparing a huge blueprint involved creating case studies of Wyoming young people, and "Billy" is one such person, though he is a construct from a number of details. Figure 6 maps multiple aspects of Billy's life from the perspective of different parties – law enforcement, mental health, doctors, schools, and even self-report.

When I present Billy's record, the gasps are audible from the audience. People typically say, "Look at all those missed opportunities for prevention or early intervention." An amazing event happened the first time I showed this construct. A 50-year-old recovering man who was hired by the project to help in assorted ways said: "That's my life, with only minor differences." Billy's case is textbook in detailing the cognitive, social, emotional differences of children at risk for multi-problem behavior (e.g., Embry and Flannery, 1999). What is latent in his case history is the documented interaction between his genes and his environment. The biological side of the equation, especially considering the mechanism of polygenic inheritance, is much more evident when one examines a genogram, as shown below. I am very thankful to my colleague, David Comings, for introducing me to the use of the genogram for the purpose of illustrating polygenic mechanism. Few of us think of how the genes of different "problems" or disorders might combine in novel ways to produce different outcomes across generations. Intellectually, we want either a simple gene or a no-gene solution. The genogram in Figure 7 is a composite of Dr. Coming's patient (A.J.) and teenagers like him who could easily be "Billy." What the genogram show us is that the issue is more intellectually challenging, and mysterious in some ways as the poly genes combine to produce different results.

The combination of the records map and the genogram for Billy suggest many opportunities for prevention and intervention strategies at home, school, and in the community. Those missed opportunities were just that, missed. Thus, the DNA tango between gene and culture produced a result that was aimed at a survival

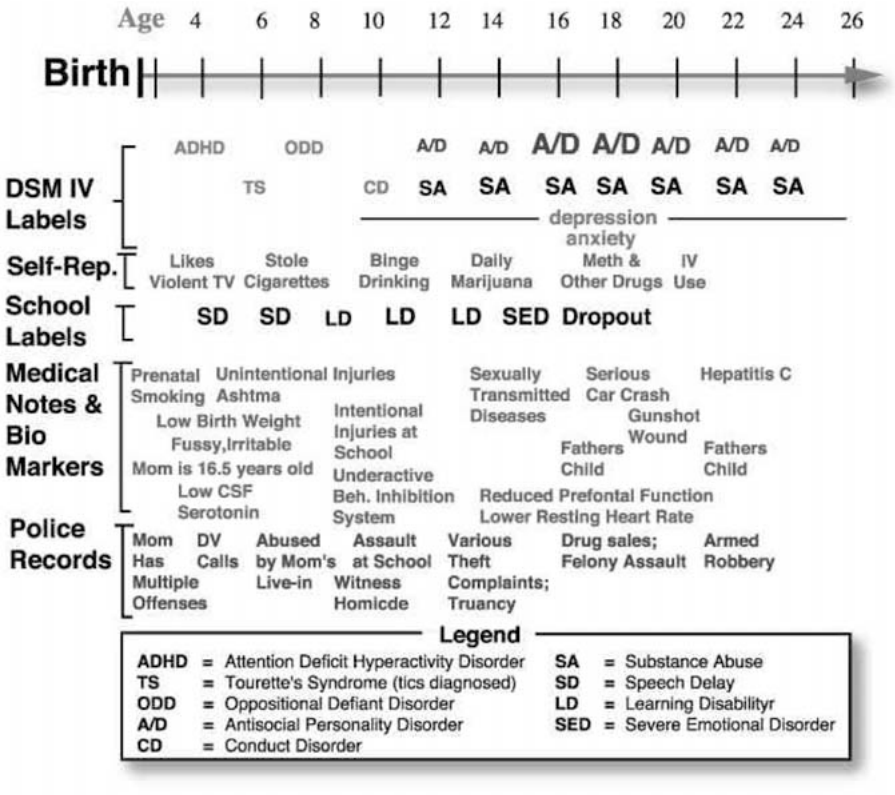

Figure 6. Billy's case history records map.

solution engineered long ago under the threat assumption that other humans are highly predatory, life is short, and reward today is better than reward tomorrow. Given that assumption or prediction, Billy's life is not deviant, defective, or bad. It is the genius of Mother Nature, not playing with dice, to assure a good outcome. Unfortunately, for the people around Billy at home, school, or in the community, the solution presents some serious challenges. Mother Nature does not judge the outcome by how much Billy or we like it, however. Mother Nature judges the outcome based on successful adaptation to circumstances. By the scorecard of biology, Billy is reasonably successful. By human laws and cultural convention, Billy is a mess.

There are millions of Billy's in the world. There are millions of other people with different genes interacting with culture to produce adaptive solutions. Some of the solutions we subjectively like and others we dislike. Because we are living on the gene-times-culture plane or ship as it flies or sails, we have difficulty seeing the workings of either. Huge advances in machines make the working visible. With the exception of some very nasty things, most of the adaptive solutions are

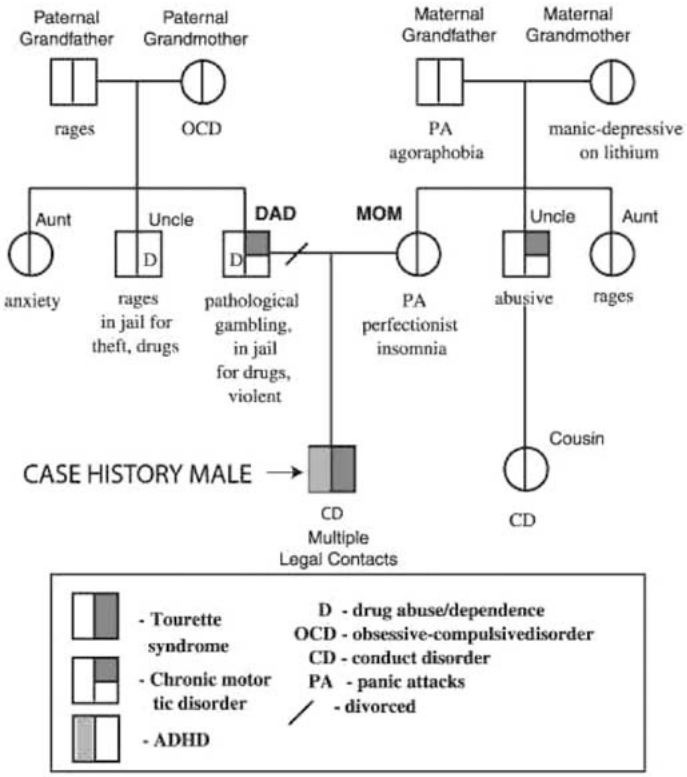

Figure 7. The family history genogram of a teenager who could be a "Billy."

genius of nature "trying to" solve a problem, which may be cultural, biological, environmental, or some combination.

If we began to see the differences as potential gifts bestowed by Nature, we might possibly do a better job of evoking the genius of those gifts at home, in the classroom, or throughout the community. Right now, we have the rather arrogant notion that we can legislate Mother Nature into obedience or ignore Her. Even our language of describing genes or their behavioral manifestations as defective or disordered when Mother Nature obviously has selected them for some purpose, is about as wise as the Captain of Titanic insisting that, "Not even God could sink her."

Let us, therefore consider some issues of evoking the genius of genes.

Evoking the Genius of Genes at Home, Classroom, and in the Community

By any reckoning, attention deficit and hyperactivity is happening a lot in developed society. It appears rare, as a problem, in anthropological society. The

case of ADHD provides fertile ground for the discussion of evoking the genius of genes.[1]

One can go on and on about over-diagnosis and the evils of marketing by pharmaceutical companies. That is not the purpose of this article. Rather, this article looks differently at the issue. The behaviors described by the Diagnostic and Statistical Manual of the American Psychological Association for "problems of attention and Activity" happen quite a lot. Estimates vary from 3% to 10%, depending on the criteria. The "symptoms" can be clearly caused by many things, including such things as airborne exposure to lead, which happens more to African Americans by virtue of where people who are poor live and something about a polygenic variation in African American calcium metabolism, possibly coupled with diet.

All ADHD forms are not the same. Some children show up as inattentive, some hyper-aroused, and others as impulsive. Some people have all of the observed clinical components. These differences appear to be linked to different neurotransmitters and different parts of the brain, and there is evidence of different genetic mechanisms involved.

Dopamine and norepinephrine are key neurotransmitters regulating attention. The two, together, are called catecholamine – chemically similar small molecules from the amino acid, tyrosine. Dopamine is a neurotransmitter (a chemical used to transmit impulses between nerve cells), mainly found in the brain. It seems to regulate reward, goal setting, and movement. Norepinephrine is the primary neurotransmitter in the sympathetic nervous system, controls "fight or flight" reactions plus orientation to reward or threat. Epinephrine is not only a brain neurotransmitter, but also a major hormone in the body. Figure 8, I have adapted from some major research on the mapping of the effects of those neurotransmitters related to ADHD. The structures, however, are only part of the story. Different dopamine genes determine the structures, such as different receptor configurations.

After 1996, reports of Dopamine Receptor 4 (DRD4) variations led to investigations of *DRD4*, a gene located on chromosome 11p15.5, as a risk factor for ADHD.

[1] ADHD has been presented by some as a potentially positive evolutionary trait, possibly related to hunting and gathering (e.g., Shelley-Tremblay and Rosen, 1996). But, Goldstein and Barkley (1998) argue hogwash and that these are "just so" stories. Both camps in this argument spend a fair bit of time arguing whether the obnoxious or cognitive manifestations of ADHD might or might not be advantageous, while both seeming miss the point. Goldstein and Barkley aptly point out that most of the symptoms of ADHD are not particular advantageous from most people's view, but Mother Nature doesn't always care what we think. The stories about hunting and gathering are provocative, but probably not right (though testable). Both parties seem to miss the issues of polygenics and non-random mating. The genes that foster or trigger ADHD are seemingly robust, and are still with us. What is striking from multiple camps is implicit observation that the behaviors typical of ADHD seem to have been less prevalent in Paleolithic times, observations of which are not possible or testable, of course. Both camps seem to be looking at evolution as a sort of flat file, not puzzling why reproductive rates appear to be higher (the measure of the game of genes) and why the genes might be "turned on" with exposure to serious stress (Madrid *et al.*, 1999).

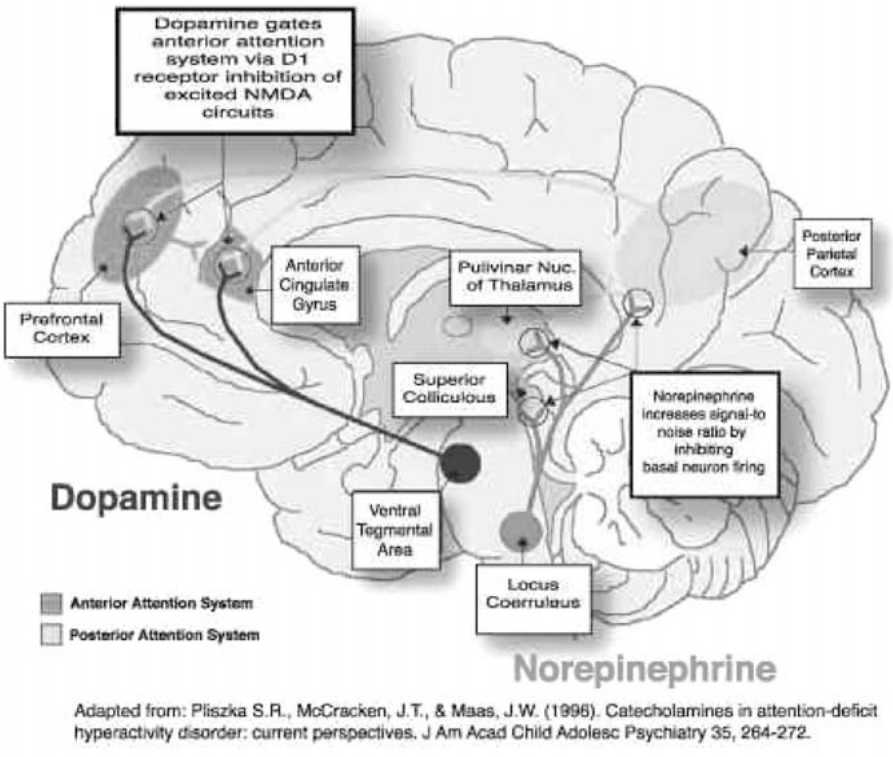

Figure 8. Catecholamine pathways and attention.

The first study used a case-control design and found an increased frequency of the 7-repeat allele in the ADHD sample compared with an ethnically matched control group. These authors subsequently collected DNA samples from affected children and parents. The same 7-repeat allele was found to occur at a higher frequency in affected children and parents than other alleles (variations) from the parents and children who did not show the behaviors. This type of study helps control for potentially ethnically diverse individuals in which normal polymorphisms (different alleles) are often found, and siblings have to be added for additional controls. The reader can glimpse this idea (but not the DRD4 gene) in the genogram of Billy-like children, because the parents do not show all the behaviors that the child shows.

Other diverse studies have happened in the last few years on the relationship between variations of *DRD4* in ADHD, such as those by Rowe and colleagues. The most interesting finding comes from Swanson and co-workers in 2000 on association of the dopamine receptor D4 (DRD4) specific allele [the 7-repeat of a 48-bp variable number of tandem repeats (VNTR) in exon 3]. They evaluated ADHD subgroups defined by the presence or absence of the 7-repeat allele of the DRD4 gene, using neuropsychological tests with reaction time measures designed to probe attention networks of D4-rich brain regions. Despite the same

severity of symptoms on parent and teacher ratings for the ADHD subgroups, the average reaction times of the 7-present subgroup showed normal speed and variability of response, whereas the average reaction times of the 7-absent subgroup showed the expected abnormalities (slow and variable responses). The 7-present sub-group seemed largely free of the *neuropsychological* problems that describe ADHD.

To someone who is familiar with the neuroscience, classrooms, and behavioral interventions, I find the implications profound and striking. Some children need interventions that inhibit their motor overflow and wandering; other children clearly need much more "exciting and challenging" instruction to engage their inquisitive brains. To an average counselor, teacher, or school administrator, the two types of kids may look the same. Because of a whole host of reasons that putatively act on the dopamine and norepinephrine structures and receptors in the brain (and body), which were engineered by culture and genes, some children are not "acting bad" nor even have a mental disorder. They are acting and behaving because of Mother's Nature's gifts that emerged as selective advantage several thousand years ago.

Engaging the latent talent or gift of such children is certainly well documented in the behavior analytic literature, though the intervention science has no measures of the genes in question. For example, the problems of inhibition can be easily reduced by a simple intervention called the Good Behavior Game, which provides frequent group-based rewards for inhibiting all the disruptive behaviors of ADHD. The Game is a simple but powerful behavior modification protocol, in which students are divided into teams. They help induce the rules in the classroom, and if a team member breaks a rule, a point is scored against the team. One or more teams score below a criterion win a brief activity prize, such as passing notes, tipping the chair, humming a tune while the "loosing" team watches. The Game is played while the teacher teaches, and typically time in engaged learning zooms up. Rates of classroom disruption typically drop from about 100–200 per hour to 5–10 per hour. The Game has about 20 studies supporting its efficacy, including ones with nearly 10 years of longitudinal follow up. The mechanisms, studies, and results of the Good Behavior Game are described in review (Embry, in press), and the Game is listed as a "best practice" in the Surgeon General's Report on Mental Health and Youth Violence.

Unfortunately, the Good Behavior Game is largely unknown by schools and professionals, unlike stimulant medication. In 1991, Greenwood published a review of a simple-to-use class-wide peer tutoring process, which dramatically improves behavior, improves academic success, and reduces placement in special services – all for about $40 dollars per classroom. Class-wide peer tutoring works by having the class divided into teams again, with children taking 10-minute turns as tutor or tutee with very rapid pace and feedback. The team with the most points wins, and lives to play again the next day for 30 minutes. The model is also listed as a best practice, yet is used in only a handful of American schools – despite world-

class research supporting its efficacy in helping children who would receive the diagnosis of ADHD. These are but two simple examples. Both are characterized by rapid pace, lots of feedback, group pressure, public positing, low reaction to negatives, and fun competition – all of these are characteristics of computer games in way. Both provide novelty, but in a controlled way. Imagine there are hundreds of very well-done Studies – exceeding or meeting the same standards of science of medications – that can be used to evoke the talents of children and adults in the home, classroom, or community. What is surprising, too, is that many of these scientifically tested and validated strategies cost almost nothing to use or implement, compared to hundreds of dollars a month for medications (which, of course, are necessary in some cases).

Some children need different behavioral interventions, quite possibly from birth, than other children. They are "wired" for a different world, while we as educators or therapists stubbornly insist that all children *should* be treated the same. Unfortunately (and paradoxically) treating them the same exaggerates their differences. No rational adult objects to a child receiving medication or altered diet to make life manageable with diabetes (insulin), and no rational adult *should* deny the needed extra reinforcement (dopamine), whether it must be delivered socially, medically or both if needed for a child to succeed with what Nature may have bestowed.

Many readers might speculate, what can a parent do if the genes point in a certain way? In the case of Billy's, actually there is evidence for how parent-child interaction might affect the outcomes. Recently, Johnston and colleagues (2002) reported on the interactions of "responsive parenting" on children with ADHD, from the Multi-Modal Treatment Study of Children with ADHD (MTA) – the largest such study in the world presently. In investigation of the parenting behaviors, Johnston and colleagues observed parents and children in: "(1) free play; (2) during a pencil and paper task while their sons were instructed to sit quietly; (3) a teaching task in which mothers instructed their sons to work on a math or handwriting exercise; and (4) a clean up period in which all toys and materials were supposed to be put away." During the activities, the investigators measured the following variables, which are quoted here (cf. Damon, 1988):

- *Authoritative control* – the extent to which the mother encouraged her child to participate in decision-making and offered explanation for commands, as opposed to using control strategies that relied on direct and harsh commands;
- *Sensitivity of control* – the degree to which the mother exerted control in a manner that was sensitive to the child's needs, as opposed to making demands that were unreasonable for the situation;
- *Responsiveness* – the mother's ability to appropriately adapt her behaviors to the child's abilities, needs, requests, interests, and ongoing behavior;
- *Positive affect* – the degree to which the mother displayed frequent and/or intense positive affect towards the child, as opposed to expressions of negative emotion;

- *Acceptance of the child* – the degree to which the mother expressed approval, praise, and positive affection towards her child, as opposed to appearing cold and rejecting; and
- *Involvement with the child* – the amount of time the mother spent in verbal and non-verbal interactions with her child, as opposed to engaging in solitary activities.

Several measures were highly correlated in the data analysis: authoritative control, sensitivity of control, responsiveness, positive affect, and acceptance of child. This lead to a composite measure of "maternal responsiveness." While responsiveness was not related to the child's severity of ADHD, responsiveness was related to reduced risk of conduct disorders and maternal depression. This large-scale study strongly fits the trailblazing work of Gerald Patterson and colleagues (e.g., Patterson, 1982; Dishion *et al.*, 1991), who previously showed that harsh, negative and inconsistent interactions by the parent tend to evoke a cycle of aggression and problem behavior over the child's lifetime.

What is missing in practice, training, and promotion is a sort of guide like the Moerk Manual or the Physician's Desk Reference (PDR) for drugs, which provides the same kind of information about science-based behavioral or cultural strategies to evoke positive behavior or inhibit negative behavior at home, school, or in the community. Virtually any citizen can buy a Moerk Manual or a PDR at the local discount store or bookstore. In many cases, the same information is on-line. In college, my doctor at the university health clinic used to joke with me that anyone who could read the Moerk Manual and the PDR could do a lot of decent medical things. She was right, yet we have no similar documents for everyday behaviors of humans.

What is happening for the future, even with the PDR or the Moerk Manual will be the inclusion of genetic information for medical treatments. For example, Evan and Johnson (2001) detail the idea of pharmacogenomics – the inherited basis for interindividual differences in medication responses. Instead of writing off side-effects or idiosyncratic responses, polygene assessments provide the capacity to tailor or maximize treatment effects. Something similar is possible for behavior change issues.

I propose a new field of endeavor, which I will call *Braingenomics*. The idea is to provide information that integrates the medical advances in the study of the brain and genes with the huge corpus of knowledge about changing human behavior. This endeavor is sort of like mapping how behavioral, cultural, and medical knowledge overlap.

Braingenomics is fundamentally revolutionary for policy planning issues, and will take some effort to flesh out the details. The central idea cannot be ignored, however, because the science is so compelling.

Consider an example application. In Wyoming, for example, a statewide needs assessment survey suggests that sensation seeking is well above average compared to other states. Moreover, the rate of substance abuse and misuse is quite high in

Table II. Braingenomics table illustration for prevention and policy

	Gene Allele Negative	**Gene Allele Neutral**	**Gene Allele Positive**
Family			
Classroom			
School			
Community Setting			

Behavioral Options and Strategies

the state, compared to other states. The state must have a coherent, cost-effective strategy to reduce substance abuse.

Sensation seeking is a factor with substantial genetic loading related to substance abuse, alcohol and tobacco use (e.g., Thombs *et al.*, 1994; Kraft and Rise, 1994; Cloninger *et al.*, 1996), and there is reason to believe that sensation seeking is not randomly distributed in cultures or political units based on geographic patterns of substance use, antisocial behavior and other factors. Sensation seeking has been linked to at least one variation of monoamine oxidases (MAO) gene alleles (e.g., Garpenstrand *et al.*, 2001), and such sensation seeking related variables can be seen via technological measures of brain function (e.g., Wang and Wang, 2001). One might be inclined to say, "So what, we can't do anything about these issues anyway."

The response is, "Not so. We can do something to address the genetic differences, even at the scale of the community. The National Institute on Drug Abuse reports that researchers have demonstrated that television public service announcements (PSAs) designed for and targeted to specific teen personality-types can significantly reduce their marijuana use.

In a study published in the February 2001 issue of the American Journal of Public Health, researchers report that PSAs with an anti-marijuana use message resulted in at least a 26.7 percent drop in the use of that drug among the targeted teen population. The PSAs were designed to appeal to the 50 percent of teens who tested high (above the median) on sensation seeking, who are more likely to use drugs at an earlier age than are adolescents who test low as sensation seekers.

The PSA's had several components, including designing high-sensation-value prevention messages that were novel, dramatic, and attention-getting, and placing these messages in high-sensation-value contexts, such as TV programs that are favorites of high sensation seekers. The study showed that sensation seeking-based campaign got the attention of high sensation seeking teens and changed their drug

use behaviors from the previous 30 days. The estimated drop in the relative proportion of high-sensation seekers using marijuana was 26.7 percent. The PSAs had no effect on teens who were low sensation seekers, a group that already exhibited low levels of marijuana use.

Wyoming would do well to design its treatment, intervention and prevention strategies to address the high sensation seeking among its young people, since evidence suggests that this would be a sound "braingenomic" strategy with modest risk of backfires. If the idea of braingenomics can be applied to prevention, can it be applied to therapy?

Evoking the Genius of Genes in Therapy

The professional literature in psychiatry and psychology is beginning to take note of gene allele issues interacting with diagnoses and treatment. For example, a web site now lists many of the gene studies on both bipolar disorder and schizophrenia. The web site is http://archive.uwcm.ac.uk/uwcm/mg/psychemap/. This type of mapping is the beginning of a powerful knowledge base. The introduction of discussion of genes therapy has triggered a whole article on the subject in the flagship publication of the American Psychological Association (Patenaude *et al.*, 2002). Anyone engaged in therapy cannot for long try to pretend that a discussion of genes is something Calvin Klein sells at the department store. The matrix for braingenomics used in therapy will, in the future, look not too dissimilar from the one suggested for prevention. Table III illustrates the options for therapy and medication.

The development of braingenomics in therapy will involve the development of several tools for therapists and professionals. First, the knowledge base will require an artificial intelligence engine, just like is beginning to happen in the treatment of various cancers. Such an engine could be loaded onto a personal digital assistant (PDA). Second, therapists and professionals will likely start taking a much more detailed genogram (not just family "issues"), as well as request a buccal (cheek) smear that will be processed through a DNA chip array. Such a test will cost several hundred dollars, and will require that therapists begin to master some of the exponentially growing knowledge (though the PDAs can make much of the detail transparent). Already, this type of screening is entering the discussion and planning for pharmaceuticals, which has a name – pharmacogenomics (e.g., Evans and Johnson, 2001).

These developments in both medication and therapy have been long needed. The issues involve treatment efficacy, client improvement, and risk management.

About 50 years ago, clinicians started to notice that there might be inherited reactions to medications. The mechanisms for this were not understood, however. Of course, clinicians had noticed that some people had serious, life threatening to mild reactions to drugs. These reactions were thought to be idiopathic, meaning arising from some unknown reactions. For example, I, myself, have adverse reac-

Table III. Braingenomics table illustration for therapy

	Gene Allele Negative	**Gene Allele Neutral**	**Gene Allele Positive**
DSM Category 1		Therapy and Drug Options	
Sub-type			
Sub-type			
DSM Category *N*			

tions to Darvon and synthetic codeine, but did not understand how or why until I learned more about polygenic mechanisms a couple of years ago.

Since the development of sophisticated molecular methods, we can now "see" the effects of genes on drugs, largely as a result of the genome projects. This field is called pharmacogenetics. This area of study has started to explain why some people and drugs can be toxic or have to have much higher doses. Let's consider a hypothetical case, which I have adapted from the elegant article by Evans and Johnson, 2001. There are human genes that metabolize drugs. There are at least 28 families of genes related to drug metabolism, which must have arisen based on the ecology that our distant ancestors lived in. Some people may be highly efficient in how they use drugs; that is, they may convert most of the drug into an "active ingredient." Some people may convert only a small amount of drug into an "active ingredient." There are also genes that regulate how many receptors a cell may have for a type of drug, from a few receptors to a lot of receptors. This means that some people may have a lot of "active ingredient" but a low functioning dose, because the cell cannot receive the drug. Other people may have a lot of receptors (like a powerful antenna), which cause the cell to burn out from the "active ingredient." In some cases, a highly efficient metabolizing gene coupled with high expression of receptors can be toxic and cause serious effects, which is thought to be the case in some of the psychotropic drugs causing violence. Figure 9 shows the polygenic interactions.

These type of gene interactions with medications mean that the next generation of pharmacology will be chosen based on who you are not just a general prescription. I think something similar will happen for both drugs and behavioral interventions. How will this be managed as a system?

Over time, it will be necessary to build a knowledge engine. This will be difficult, but offers considerable hope for evoking the genius of genes. What might it look like? I suggest that the knowledge engine be called, "Hierarchical Optimiza-

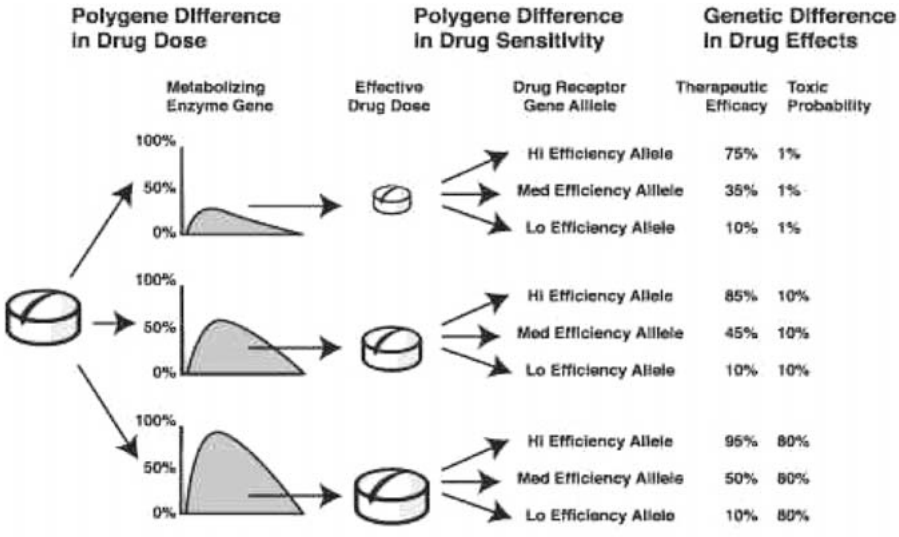

Figure 9. Polygene drug interactions and differences.

tion for Personal Effectiveness" or "HOPE" for short. A diagram of how "HOPE" might work, along with a stylized implementation on a personal digital assistant are modeled in Figure 10.

Generating something like HOPE will be as bold as the genome project. It is possible by virtue of modern mathematics, and the use of a rapid cohort study whereby people of different ages are measured both for age and genes, then followed over time. The study needs to sample both folks with and without evident risk for various diagnoses. In the meantime, a temporary version of the HOPE algorithm can be built from meta-analyses studies as a test bed. It will have to be built as a cooperative project across a number of investigators. It is important that the model be built using both drugs and behavioral interventions as components in the database, since considerable evidence exists for synergistic benefits for more severe diagnoses. The strategies for building the HOPE algorithm merits a very detailed article its own right, far beyond the scope of appealing for the idea alone.

Summary

The special issue on the brain and caring behavior offers some of the most spectacular insights from experts in the United States and Canada. This article details how the brain, behavior and mind are expressed as the result of ancient gifts of genes, interacting with the environment. In the past the knowledge of genetics based in Mendelian mechanics, that most of us learned in college or even high school, has shaped an extremely limited understanding of how genetics might have created the gifts of the brain, mind and behavior. This limited understanding fostered an absurd debate of nature *versus* nurture. What is clear now is that nurture can cause the

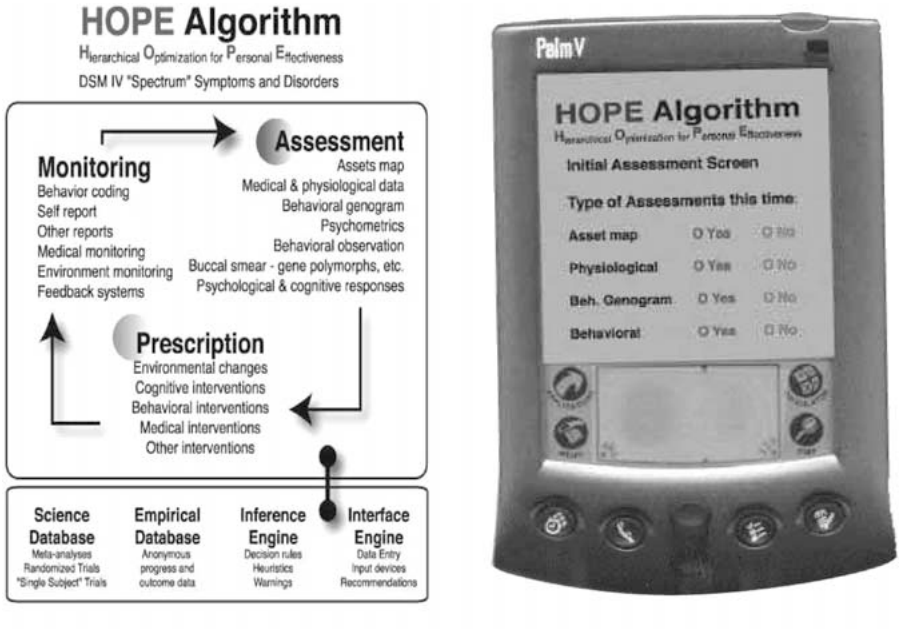

Figure 10. Algorithm for evoking success in therapy.

expression of certain genes during human development, and that culture (nurture, writ very large) has probably selected certain genes even in relatively recent times, especially because people do not choose their sexual partners randomly. What is also clear is that nature – the genes each of us possess – shapes our environment; that is, how other people respond to us, the physical and biological environment, too. Modern social and medical science has allowed us to see and hear the endless tango between genes and environment, especially in the case of human brains, minds and behaviors.

References

Bernstein, G.A., Borchardt, C.M., and Perwien, A.R., 1996: Anxiety disorders in children and adolescents: A review of the past 10 years, *Journal of American Academy of Child & Adolescent Psychiatry* **35**, 1110–1119.

Biederman, J., Rosenbaum, J.F., Hirshfeld, D.R. *et al.*, 1990: Psychiatric correlates of behavioral inhibition in young children of parents with and without psychiatric disorders, *Archives of General Psychiatry* **47**, 21–26.

Bing Su, B., Chakraborty, R., Jin, L., Xiao, J., and Lu, D., 1998: An HIV-resistant allele Is exceptionally frequent in New Guinean highlanders, *Journal of American Medical Association* **280**, 1830.

Birmaher, B., Yelovich, A.K., and Renaud, J., 1998: Pharmacologic treatment for children and adolescents with anxiety disorders, *Pediatric Clinics of North America* **45**, 1187–1204.

Bouchard, T.J., and Loehlin, J.C., 2001: Genes, evolution and personality, *Behavior Genetics* **11**, 243–273.

Brady, E.U., and Kendall, P.C., 1992: Comorbidity of anxiety and depression in children and adolescents, *Psychological Bulletin* **111**, 244–255.

Buxhoeveden, D.P., Switala, A.E., Roy, E., Litaker, M., and Casanova, M.F., 2001: Morphological differences between minicolumns in human and nonhuman primate cortex, *American Journal of Physical Anthropology* **115**, 361–371.

Chhabildas, N.A., Pennington, B.F., & Willcutt, E.G., in press: A comparison of the cognitive deficits in the DSM-IV subtypes of ADHD, *Journal of Abnormal Child Psychology.*

Cloninger, C. R., Adolfsson, R, & Svrakic, N. M., 1996: Mapping genes for human personality, *Nature Genetics* **12**, 3–4.

Cohen, D., Nisbett, R.E., Bowdle, B.F., & Schwarz, N., 1996: Insult, aggression, and the southern culture of honor: An "experimental ethnography", *Journal of Personality & Social Psychology* **70**, 945–960.

Comings, D.E., in press: The real problem in association studies, *American Journal of Medical Genetics (Neuropsychiatric Genetics).*

Comings, D.E., Gade-Andavolu, R., Gonzalez, N., Wu, S., Muhleman, D., Blake, H., Chiu, F., Wang, E., Farwell, K., Darakjy, S., Baker, R., Dietz, G., Saucier, G., and MacMurray, J.P., 2000:. Multivariate analysis of associations of 42 genes in ADHD, ODD and conduct disorder, *Clinical Genetics* **58**, 31–40.

Comings, D.E., Gade-Andavolu, R., Gonzalez, N., Wu, S., Muhleman, D., Blake, H., Mann, M.B., Dietz, G., Saucier, G., and MacMurray, J.P., 2000: A multivariate analysis of 59 candidate genes in personality traits: the temperament and character inventory, *Clinical Genetics* **58**, 375–385.

Damon, W., 1988: *The Moral Child: Nurturing Children's Natural Moral Growth*, Free Press, New York.

Dishion, T., Patterson, G.R., Stoolmiller, M., and Skinner, M.L., 1991: Family, school, and behavioral antecedents to early adolescent involvement with antisocial peers, *Developmental Psychology* **27**, 172–180.

Dummit E.S. 3rd, Klein, R.G., Tancer, N.K. *et al.*, 1997: Systematic assessment of 50 children with selective mutism, *Journal of the American Academy of Child and Adolescent Psychiatry* **36**, 653–660.

Ellis, L., 1988: Criminal behavior and r/K selection: An extension of gene-based evolutionary theory, *Personality & Individual Differences* **9**, 697–708.

Embry, D.D., and Flannery, D.J., 1999: Two sides of the coin: Multi-level prevention and intervention to reduce youth violent behavior, in D.J. Flannery and C. Ronald Huff (eds), *Youth Violence: Prevention, Intervention and Social Policy*, American Psychiatric Press, Washington, DC.

Embry, D.D., and McDaniel, R., 2001: *Reclaiming Wyoming: A Comprehensive Blueprint for Substance Abuse Treatment, Intervention and Prevention*, Wyoming Department of Health, Substance Abuse Division, Cheyenne, WY.

Enard, W., Khaitovich, P., Klose, J., Zöllner, ß., Heissig, F., Giavalisco, P., Nieselt-Struwe, K., Muchmore, K., Varki, A., Ravid, R., Doxiadis, G.M., Bontrop, R.E., and Pääbo, S., 2002: Intra- and interspecific variation in primate gene expression patterns, *Science* **296**, 340–343.

Garland, E.J., and Weiss, M., 1996: Case study: obsessive difficult temperament and its response to serotonergic medication, *Journal of the American Academy of Child Adolescent Psychiatry* **35**, 916–920.

Garpenstrand, H., Ekblom, J., Forslund, K., Rylander, G., and Oreland, L., 2000: Platelet monoamine oxidase activity is related to MAOB intron 13 genotype, *Journal of Neural Transmission* **107**, 523–530.

Ginsburg, G.S., LaGreca, A.M., and Silverman, W.K., 1998: Social anxiety in children with anxiety disorders: Relation with social and emotional functioning, *Journal of Abnormal Child Psychology* **26**, 175–185.

Hartung, C.M., Willcutt, E.G., Lahey, B.B., Pelham, W.E., Keenan, K., Loney, J., and Steiner, R., in press: Gender differences in attention-deficit / hyperactivity disorder in preschool children, *Journal of Clinical Child Psychology*.

Hyman, S., 2000: Mental illness: Genetically complex disorders of neural circuitry and neural communication, *Neuron* **28**, 321–323.

Johnston, C. *et al.*, 2002: Responsiveness in interactions of mothers and sons with ADHD: Relations to maternal and child characteristics, *Journal of Abnormal Child Psychology* **30**, 77–88.

Kagan, J., Reznick, J.S., and Gibbons, J., 1989: Inhibited and uninhibited types of children, *Child Development* **60**, 838–845.

Kagan, J., Snidman, N., and Arcus, D., 1998: Childhood derivatives of high and low reactivity in infancy, *Child Development* **69**, 1483–1493.

Karkowski, L.M., Prescott, C.A., and Kendler, K.S., 2000: Multivariate assessment of factors influencing illicit substance use in twins from female-female pairs, *American Journal of Medical Genetics* **96**, 665–670.

Kaufer, D., Friedman, A., and Soreq, H., 1999: The vicious circle: long-lasting transcriptional modulation of cholinergic neurotransmission following stress and anticholinesterase exposure, *The Neuroscientist* **5**, 173–183.

Kendall, P.C., Flannery-Schroeder, E., Panichelli-Mindel, S.M. *et al.*, 1997: Therapy for youths with anxiety disorders: A second randomized clinical trial, *Journal of Consulting and Clinical Psychology* **65**, 366–380.

Kendler, K.S., Karkowski, L.M., and Prescott, C.A., 1999: Hallucinogen, opiate, sedative and stimulant use and abuse in a population-based sample of female twins, *Acta Psychiatrica Scandinavica* **99**, 368–376.

Kendler, K.S., Karkowski, L.M., Neale, M.C., and Prescott, C.A., 2000: Virginia Twin study of Adolescent Behavioral Development, *Archives of General Psychiatry* **57**, 261–269.

Kraft, P., and Rise, J., 1994: The relationship between sensation seeking and smoking, alcohol consumption and sexual behavior among Norwegian adolescents, *Health Education Research* **9**, 193–200.

La Greca, A.M., and Lopez, N., 1998: Social anxiety among adolescents: linkages with peer relations and friendships, *Journal of Abnormal Child Psychology* **26**, 83–94.

Lahey, B.B., Pelham, W.E., Stein, M., Loney, J., Trapani, C., Nugent, K., Kipp, H., Schmidt, E.G., Lee, S., Cale, M., Gold, E.G., Hartung, C., Willcutt, E.G., and Baumann, B., 1998: Validity of DSM-IV attention-deficit/hyperactivity disorder for young children, *Journal of the American Academy of Child and Adolescent Psychiatry* **37**, 695–702.

Lewohl, J.M., Wang, L., Miles, M.F., Zhang, L., Dodd, P.R., and Harris, R.A., 2000: Gene expression in human alcoholism, *Alcoholism: Clinical & Experimental Research* **24**, 1873–1882.

Maes, H.H., Woodard, C.E., Murrelle, L., Meyer, J.M., Silberg, J.L., Hewitt, J.K., Rutter, M., Simonoff, E., Pickles, A., Carbonneau, R., Neale, M.C., and Eaves, L.J. (1999). Tobacco, alcohol and drug use in eight- to sixteen-year-old twins: the Virginia Twin Study of Adolescent Behavioral Development, *Journal of Studies on Alcohol* **60**, 293–305.

Manassis, K., Bradley, S., Goldberg, S. *et al.*, 1995: Behavioural inhibition, attachment and anxiety in children of mothers with anxiety disorders, *Canadian Journal of Psychiatry* **40**, 87–92.

Manassis, K., Mendlowitz, S., and Menna, R., 1997: Child and parent reports of childhood anxiety: Differences in coping styles, *Depression and Anxiety* **6**, 62–69.

March, J., 1998: *Multidimensional Anxiety Scale for Children (MASC)*, Multi Health Systems Inc., Toronto.

McBurnett, K., Pfiffner, L.J., Willcutt, E., Tamm, L., Lerner, M., Ottolini, Y.L., and Furman, M.B., 1999: Experimental cross-validation of DSM-IV types of Attention-Deficit Hyperactivity Disorder, *Journal of the American Academy of Child and Adolescent Psychiatry* **38**, 17–24.

Mednick, S.A., Gabrielli, W.E., and Hutchings, B. (1984). Genetic factors in criminal behavior: Evidence from an adoption cohort, *Science* **224**, 891–893.

Mohler, H. *et al.*, 1999: Decreased GABAA-receptor clustering results in enhanced anxiety and a bias for threat cues, *Nature Neuroscience* **2**, 833–839.

Nisbett, R.E., 1993: Violence and U.S. regional crime, *American Psychologist* **48**, 441–449.

O'Brien, T.R., and Goedert, J.J., 1998: Chemokine receptors and genetic variability, *Journal of the American Medical Association* **279**, 317–318.

Palmgreen, P., 2001: Sensation seeking and public service announcements, *American Journal of Public Health* **91**, 292–296.

Patterson, G., 1982: *A social Learning Approach to Family Intervention: III. Coercive Family Process*, Castalia, Eugene, OR.

Pennisi, E., 2002: PRIMATE EVOLUTION: Gene activity clocks brain's fast evolution, *Science* **296**, 233–235.

Pine, D.S., and Grun, J., 1999: Childhood anxiety: integrating developmental psychopathology and affective neuroscience, *Journal of Child Adolescent Psychopharmacology* **9**, 1–12.

Plomin, R., DeFries, J.C., McClearn, G.E., and McGuffin, P., 2001: *Behavioral Genetics* (4th ed), Worth Publishers, New York.

Reiness, G., Nov. 26, 2000: AIDS. http://www.lclark.edu/dimreiness/immuno/lectures/lect21.htm

Rowe, D.C., Stever, C., Giedinghagen, L.N. *et al.*, 1998: Dopamine DRD4 receptor polymorphism and attention deficit hyperactivity disorder, *Molecular Psychiatry* **3**, 419–426.

Ryabinin, A.E., 1998: Microarray analysis of frontal cortex, *Psychopharmacology* **139**, 34–43.

Schulsinger, F., 1972: Psychopathy: Heredity and environment, *International Journal of Mental Health* **1**, 190–206. (Reprinted in 1977 in S.A. Mednick and K.O. Christiansen (eds.), *Biosocial Bases of Criminal Behavior*, Gardner Press.)

Schwartz, C.E., Snidman, N., and Kagan, J., 1999: Adolescent social anxiety as an outcome of inhibited temperament in childhood, *Journal of American Academy of Child Adolescent Psychiatry* **38**, 1008–1015.

Silverman, W.K., Ginsburg, G.S., and Goedhart, A.W., 1999: Factor structure of the childhood anxiety sensitivity index, *Behavior Research and Therapy* **37**, 903–917.

Simonton, D.K., 1999: Talent and its development: An emergenic and epigenetic model, *Psychological Review* **106**, 435–457.

Simonton, D.K., 2001: Talent development as a multidimensional, multiplicative, and dynamic process, *Current Directions in Psychological Science* **10**, 39–43.

Slutske, W.S., Heath, A.C., Dinwiddie, S.H., Madden, P.A., Bucholz, K.K., Dunne, M.P., Statham, D.J., and Martin, N.G., 1997: Modeling genetic and environmental influences in the etiology of conduct disorder: A study of 2,682 adult twin pairs, *Journal of Abnormal Psychology* **106**, 266–279.

Strickberger, M.W., 1968: *Genetics*, New York, London.

Swanson, J., Oosterlaan, J., Murias, M., Schuck, S., Flodman, P., Spence, M.A., Wasdell, M., Ding, Y., Chi, H.-C., Smith, M., Mann, M., Carlson, C., Kennedy, J.L., Sergeant, J.A., Leung, P., Zhang, Y.-P., Sadeh, A., Chen, C., Whalen, C.K., Babb, K.A., Moyzis, R., and Posner, M.I., 2000: Attention deficit/hyperactivity disorder children with a 7-repeat allele of the dopamine receptor D4 gene have extreme behavior but normal performance on critical neuropsychological tests of attention, *Proceedings of the National Academy of Sciences* **97**, 4754–4759.

Swanson, J.M., McBurnett, K., Wigal, T., Pfiffner, L., Lerner, M., Williams, L., Willcutt, E., Christian, D., Tamm, L., Crowley, K., Clevenger, W., Khouzam, N., Woo, C., and Crinella, F., 1993: Effect of stimulant medication on children with Attention Deficit Disorder: A "review of Reviews", *Exceptional Children* **60**, 154–162.

Thombs, D.L., Beck, K.H., Mahoney, C.A., Bromley, M.D., and Bezon, K.M., 1994: Social context, sensation seeking, and teen-age alcohol abuse, *Journal of School Health* **64**, 73–79.

Tishkoff, S.A., Varkonyi, R., Cahinhinan, N., Abbes, S., Argyropoulos, G., Destro-Bisol, G., Drousiotou, A., Dangerfield, B., Lefranc, G., Loiselet, J., Piro, A., Stoneking, M., Tagarelli, A., Tagarelli, G., Touma, E.H., Williams, S.M., and Clark, A.G., 2001: Haplotype diversity and

linkage disequilibrium at human G6PD: Recent origin of alleles that confer malarial resistance, *Science* **293**, 455–462.

Wadsworth, S.J., Davis, C.J., Knopik, V.S., Willcutt, E.G., and DeFries, J.C., in Press: Genetics of reading disabilities, in *Proceedings of the 12th Postgraduate Course in Pediatric Neurology: Learning Disabilities in Reading and Writing*.

Wang, W., and Wang, Y.H., 2001: Sensation seeking correlates of passive auditory P3 to a single stimulus, *Neuropsychologia* **39**, 1188–1193.

Whitfield, J.B., Zhu, G., Duffy, D.L., Birley, A.J., Madden, P.A.F., Heath, A.C., and Martin, N.G., 2001: Illict psychoactive substance use, heavy use, abuse, and dependence in a US population-based sample of male twins, *Alcoholism: Clinical & Experimental Research* **25**, 1257–1263.

Willcutt, E.G., and Pennington, B.F., 1998: Assessment of DSM-IV reading disorder, *Clinical Child Psychology Newsletter* **13**, 6–11.

Willcutt, E.G., and Pennington, B.F., 2000: Comorbidity of reading disability and attention-deficit/hyperactivity disorder: Differences by gender and subtype, *Journal of Learning Disabilities* **33**, 179–191.

Willcutt, E.G., and Pennington, B.F., 2000: Psychiatric comorbidity in children and adolescents with reading disability, *Journal of Child Psychology and Psychiatry* **41**, 1039–1048.

Willcutt, E.G., Chhabildas, N., and Pennington, B.F., 2001: Validity of the DSM-IV subtypes of ADHD, *The ADHD Report* **9**, 2–5.

Willcutt, E.G., DeFries, J.C., Pennington, B.F., Olson, R.K., Smith, S.D., and Cardon, L.R., in press: Comorbidity of reading difficulties and ADHD, in R. Plomin, J.C. DeFries, P. McGuffin, and I. Craig (eds), *Behavioral Genetics in the 21st Century*.

Willcutt, E.G., Hartung, C.M., Lahey, B.B., Pelham, W.E., and Loney, J., 1999: Utility of behavior ratings made by examiners during assessments of children with attention-deficit/hyperactivity disorder, *Journal of Abnormal Child Psychology* **27**, 463–472.

Willcutt, E.G., Pennington, B.F., Boada, R., Tunick, R.A., Ogline, J., Chhabildas, N.A., and Olson, R.K., 2001: A comparison of the cognitive deficits in reading disability and attention-deficit/hyperactivity disorder, *Journal of Abnormal Psychology* **110**, 157–172.

Willcutt, E.G., Pennington, B.F., Chhabildas, N.A., Friedman, M.C., and Alexander, J., 1999: Psychiatric comorbidity associated with DSM-IV ADHD in a nonreferred sample of twins, *Journal of the American Academy of Child and Adolescent Psychiatry* **38**, 1355–1362.

Willcutt, E.G., Pennington, B.F., and DeFries, J.C., 2000: A twin study of the etiology of comorbidity between reading disability and attention-deficit/hyperactivity disorder, *American Journal of Medical Genetics (Neuropsychiatric Genetics)* **96**, 293–301.

Willcutt, E.G., Pennington, B.F., and DeFries, J.C., 2000: Etiology of inattention and hyperactivity/impulsivity in a community sample of twins with learning difficulties, *Journal of Abnormal Child Psychology* **28**, 149–159.

Willcutt, E.G., Pennington, B.F., Smith, S.D., Cardon, L.R., Gayþn, J., Knopik, V.S., Olson, R.K., and DeFries, J.C., in press: Quantitative trait locus for reading disability on chromosome 6p is pleiotropic for ADHD, *American Journal of Medical Genetics (Neuropsychiatric Genetics)*.

Winkler, C., Modi, W., Smith, M.W. *et al.*, 1998: Genetic restriction of AIDS pathogenesis by an SDF-1 chemokine gene variant, *Science* **279**, 389–393.

Wong, M.L., and Licinio , J., 2001: Search and treatment approaches to depression, *Nature Reviews Neuroscience* **2**, 343–351.

Wuest, S., Federenko, I., Hellhammer, D.H., and Kirschbaum, C., 2000: Genetic factors, perceived chronic stress, and the free cortisol response to awakening, *Psychoneuroendocrinology* **25**, 707–720.

Young, E.A., Aggen, S.H., Prescott, C.A., and Kendler, K.S., 2000: Similarity in saliva cortisol measures in monozygotic twins and the influence of past major depression, *Biological Psychiatry* **48**, 70–74.

Yule, G.U., 1906: Changes in the marriage and birth rates in England and Wales during the past half century, *Journal of the Royal Statistical Society* **69**, 66.

Zahn-Waxler, C., Robinson, J., and Emde, R.N., 1992: The development of empathy in twins, *Developmental Psychology* **28**, 1038–1047.

Zahn-Waxler, C., Schiro, K., Robinson, J., Emde, R.N., and Schmitz, S., in press: Empathy and prosocial patterns in young MZ and DZ twins: Development, genetic, and environmental influences, in J. Hewitt, R. N. Emde, and J. Robinson (eds), *The Transition from Infancy to Early Childhood: The MacArthur Longitudinal Twin Study*, Oxford University Press, Oxford, UK.