

# The Evolutionary Persistence of Genes That Increase Mental Disorders Risk

Matthew C. Keller

*Department of Psychology and Institute for Behavioral Genetics, University of Colorado at Boulder*

**ABSTRACT**—*Natural selection constantly removes those genetic variants (alleles) that even slightly decrease average reproductive success. Yet, given the high heritabilities and prevalence rates of severe mental disorders, human populations seem to be awash in deleterious alleles. Evolutionary genetics offers an illuminating framework for understanding why mental disorder risk alleles have persisted despite natural selection, and this framework can help guide future research in behavioral and psychiatric genetics.*

**KEYWORDS**—*mental disorders; genetics; evolution; mutation-selection; balancing selection; schizophrenia*

Despite the praise heaped upon the human design by theologians, philosophers, and evolutionists over the years, several aspects of it appear decidedly suboptimal. Humans suffer from myriad seeming design flaws, from fever and vomiting to nearsightedness and back pain to Alzheimer's and heart disease. The last 30 years has seen an awakening in our scientific understanding of these diseases and susceptibilities—not just in terms of their proximate medical causes but also in the deeper sense of why they have evolved despite—or because of—natural selection.

Darwinian medicine has made it clear that many such diseases and susceptibilities are best understood in the context of evolutionary adaptations (Nesse & Williams, 1994). Unpleasant as they may be, fever, nausea, diarrhea, and coughing are bodily defenses crafted by natural selection to deal with infections and toxins (though these symptoms may sometimes be co-opted by pathogens for their own selfish ends). Nearsightedness, obesity, and heart disease probably reflect mismatches between the environments our bodies evolved to deal with and modern ones that pose novel challenges. Age-related diseases such as Alzheimer's likely reflect the fact that genes with “antagonistic” effects that benefit the young

at a cost to the old tend to spread throughout the population, making anyone, should they live long enough, susceptible to diseases of old age.

However, certain human maladies do not fit so easily into the adaptive framework provided by Darwinian medicine. Perhaps this is best exemplified by the most severe mental disorders (see Table 1), which seem to be neither defenses, mismatches, nor age-related trade-offs. Unlike diseases that reflect age-related trade-offs, the mental disorders in Table 1 tend to strike in childhood to the early 30s, periods that precede or are coterminous with best estimates of when ancestral humans were reproducing. Nor do the mental disorders in Table 1 fit the profiles of diseases primarily caused by mismatches between ancestral and modern environments. Diseases caused by such mismatches tend to be highly variable across time and between cultures and should be virtually absent in traditional societies lacking the novel (moderating) environmental factors. While data on mental disorder rates in the few remaining traditional societies are lacking and much needed, what evidence we do have implies that the rates of mental disorders in Table 1 (with the probable exception of autism) are paradoxically high the world over, from the United States to Palau, China to Botswana, and India to Argentina (e.g., for schizophrenia, see Saha, Chant, Welham, & McGrath, 2005).

Finally, the mental disorders listed in Table 1 share little similarity to known defenses, such as fever and nausea, which are reliably triggered by environmental threats and which subside when threats have passed. It is possible that certain reactions, the extreme forms of which are deemed mental disorders, represent adaptive defenses. For example, Keller and Nesse (2006) hypothesized that *normal* depressive reactions—the types that most people experience following deaths, failures, and so forth—serve specific adaptive functions in the situations that arouse them, much as other unpleasant defenses such as normal fever or pain serve situation-specific functions. Persistent depressive reactions (clinical depression) may represent either extreme/intractable situations (perhaps more common in modern environments) or dysregulated neurological systems (which may have strong genetic

Address correspondence to Matthew C. Keller, Department of Psychology, Muenzinger Hall, 345 UCB, Boulder, CO, 80309; e-mail: matthew.c.keller@gmail.com.

TABLE 1

*Genetic Basis, Fitness Effects, and Prevalence Rates of a Small Subset of Single-Locus Disorders and Severe Mental Disorders*

Disorder	Genetic basis	Modern fertility estimates	Lifetime prevalence per 100,000 in U.S.
Disorders caused by mutations at a single locus			
Platyspondylic skeletal dysplasia	Dominant mutations at 12q13	unknown (very low)	< 1
Granulomatous disease Type I	Recessive mutations at 7q11.23	unknown (low)	< 1
Apert's syndrome	Dominant mutations at 10q26	unknown (very low)	1.5
Achondroplastic dwarfism	Dominant mutations at 4q	unknown (low)	2–4
Severe mental disorders			
Autism	unknown; $h^2 \cong .90$	unknown	200 (variable)
Bipolar disorder	unknown; $h^2 \cong .60$	63% (2 studies)	800
Schizophrenia	unknown; $h^2 \cong .80$	47% (12 studies)	800
Mental retardation	unknown; $h^2 \cong .65$	80% (3 studies)	2,000

**Note.** Genetic basis and prevalence estimates obtained from Online Mendelian Inheritance in Man (n.d.) for single-locus disorders and from the National Institute of Mental Health (1998) for severe mental disorders. Modern fertility estimates are the average fertility estimates (percentage of those with the disorders compared to control samples) from all available studies from 1960 to 2005. Shown in parentheses are the numbers of studies on which estimates are based (for severe mental disorders) or the subjective judgments of these estimates (for single-locus disorders).  $h^2$  = heritability estimate.

underpinnings, requiring an evolutionary explanation for why such genes exist; see below). However, the mental disorders in Table 1 are not reliably triggered by environmental factors, and they tend to persist, often for life, rather than to subside. Moreover, whereas virtually everyone has the *capacity* to have a fever or feel sad given the “right” situation, it is very unlikely that more than a small minority of people have the capacity to develop autism or schizophrenia, for example, no matter what their circumstances.

In short, the adaptive explanations that elucidate many other seeming human design flaws fail when it comes to severe mental disorders. At its core, this is because traditional Darwinian medicine explanations explain *universal* adaptive capacities, not heritable differences in risk.

### THE EVOLUTIONARY PARADOX OF SEVERE MENTAL DISORDERS

One of the most robust findings in modern psychiatric research has been that common, severe mental disorders are moderately to highly heritable (Table 1), meaning that differences in genetic variants (alleles) between people cause differences in risk. From an evolutionary perspective, this heritability and commonality poses a paradox. Natural selection constantly removes from the population alleles that tend to decrease, even imperceptibly, their carriers' fitness (expected number of surviving offspring). Therefore, one might expect heritable disorders either to be rare or else not truly harmful to fitness. Yet severe mental disorders are puzzlingly common from an evolutionary perspective, being hundreds and even thousands of times more prevalent than the 2,000 or so single-locus diseases known to harm fitness (Table 1). Severe mental disorders have a cumulative prevalence of some 6% in the United States (Kessler, Chiu, Demler, & Walters, 2005), and nearly 50% of people meet criteria for a less severe mental disorder such as depression during their lifetimes (Kessler

et al., 2005). Moreover, mental disorders account for nearly two thirds of the total disease burden among reproductively aged persons, and almost every investigation on the topic has found that the severest of them are associated with profound social impairments and reductions in reproductive success (Table 1).

Why were the alleles that predispose to severe mental disorders (hereafter, risk alleles) not purged long ago by natural selection? If, over all the environments and all the genomes an allele finds itself in, it has an even slightly negative or positive effect, it will either go extinct or reach fixation, respectively—and will confer no heritability to traits. This happens surprisingly rapidly, within tens to hundreds of generations for even small positive or negative fitness effects. So the paradox boils down to this: Why do seemingly detrimental (but the paradox is every bit as salient if they are beneficial) risk alleles hang around at intermediate frequencies, where they confer heritability to mental disorders? Some simple resolutions to this paradox—that ancestral humans reproduced earlier than modern ones do, that risk alleles are strongly epistatic (moderated by other alleles) and hidden from selection, that mental disorders were benign ancestrally—do not hold up well to theoretical and empirical scrutiny (reviewed in Keller & Miller, 2006). Three mechanisms better grounded in modern evolutionary genetics—each of which leaves different, albeit messy, signatures in the genome—are reviewed below.

### POTENTIAL RESOLUTIONS TO THE PARADOX

#### Mutation-Selection

Mutations are copying errors that occur during DNA replication. These can be substitutions of a single base pair (point mutations) or deletions, duplications, inversions, or translocations of many base pairs in a row. Of evolutionary relevance are those mutations that occur when sperm or egg cells are created. These mutations

can be passed on to fertilized ova. If so, they will be copied into every cell in the offspring's body, including the offspring's own sperm or egg cells and thus potentially transferred to any descendant thereafter. This is how new mutations are "introduced" into a population. Very rarely, through blind luck, new mutations happen to increase their carriers' average reproductive success, and over time can spread through a population, forming the genetic basis of new, universal adaptations. Almost always, however, mutations that affect organic machinery degrade rather than improve its tightly coordinated performance.

Mutation-selection models describe the equilibrium between new mutations being introduced into the population and their removal, usually many generations later, by natural selection. Across individuals at a given time, a gene harbors one or a few functionally equivalent "normal" allele(s) at a very high frequency and many different rare, deleterious mutations. While each individual deleterious mutation is destined for eventual extinction, new ones are constantly arising, creating an equilibrium in the population between normal alleles (which most people have at a given gene) and rare, deleterious mutations (which a tiny minority of people have at that gene). These mutations create maladaptive noise—and heritability—in traits.

After years of being discounted as a major force, many evolutionary geneticists now consider mutation selection to be the principal factor explaining the heritability of complex traits (Houle, 1998). The key insight was to realize that although mutations are rare per gene, hundreds or even many thousands of genes can influence complex traits, and so the cumulative number of mutations affecting such traits could be high enough to explain their heritability. This insight has, in turn, been used as a basis for resolving the paradox of common, heritable mental disorders (Gangestad & Yeo, 1997; Keller & Miller, 2006; McClellan, Susser, & King, 2007).

Supporting this view are findings indicating that the number of genes harboring deleterious mutations is quite large: Proper cellular functioning is disrupted by the action of some 500 old, slightly deleterious mutations passed down from great, great . . . grandparents (Fay, Wyckoff, & Wu, 2001) as well as one or two new deleterious mutations that arose for the first time in the parent's egg or sperm cells (Eyre-Walker & Keightley, 1999). Of course, these are just averages; some people inherit many more mutations than average and some many fewer, and mutations vary enormously in their effect sizes, creating individual differences in the degree to which organs (including the brain) are disrupted by them. The phenotypic effects of these mutations range from the drastic and tell-tale, causing the single-gene disorders so successfully mapped by geneticists, to individually small, unnoticeable ones, which tend to be more common because they are removed more slowly by selection.

The variation in the cumulative effect of mutations might serve as an important substrate to the heritability of mental disorders. By this view, mutations that degrade the brain's performance differentiate everyone on a panoply of behavioral dimensions, making some people slow at learning, others bad at remembering,

others too anxious or not anxious enough, and so forth. But some people inherit an especially high "load" of mutations (from hundreds of small-effect ones to a single large-effect one) that disrupt particular neurodevelopmental pathways, increasing the risk of aberrant behaviors and psychiatric categorization. According to mutational models, mental disorders are not "natural kinds" with clear boundaries and common causes, but rather are umbrella concepts covering a heterogeneous group of similar-appearing phenotypes.

The empirical evidence that mutations play at least some role in the etiology of severe mental disorders is compelling (Table 2). Also telling is what has *not* been found. Despite 20 years of gene hunting, scientists have not found clear links between specific alleles and severe mental disorders, which might suggest that many different risk alleles exist, no one of which accounts for much population risk—exactly what would be predicted from a mutational model. However, methods to find risk alleles to date have been less than optimal. The next 5 years, when results from a large number of whole-genome association studies will be released, will clarify whether many different, individually rare alleles (consistent with mutation-selection balance) or a handful of individually common alleles (consistent with either of the evolutionary processes reviewed next) are the most important in explaining the heritability of mental disorders.

### Evolutionary Time Lags

Mutation-selection is unlikely to be the sole explanation for the heritability of severe mental disorders, nor is it inconsistent with other processes. One class of explanation that may be particularly important is evolutionary time lags. When environments change quickly, as many aspects of human environments have, there can be mismatches such that ancestral alleles are poorly adapted to current environments. Given the increasing awareness that allelic effects can depend on the environmental context (Moffitt, Caspi, & Rutter, 2005), alleles that were once neutral or adaptive may be today's risk alleles.

The *ancestral-susceptibility model* (Di Rienzo & Hudson, 2005) proposes that many current risk alleles are ancestral and are being driven to extinction due to rapid changes in human environments. Consistent with this, rates of allelic substitution (reflecting natural selection) are over 100 times higher in the last 10,000 years than they were during most of human evolution (Hawks, Wang, Cochran, Harpending, & Moyzis, 2007). Several risk alleles for common diseases, such as Alzheimer's and hypertension, are ancestral (Di Rienzo & Hudson, 2005), and Lo et al. (2007) found that schizophrenia risk alleles in the GABA-A receptor  $\beta 2$  gene have been under recent negative selection.

Another type of time-lag explanation involves the coevolution between pathogens and their hosts (Gangestad & Yeo, 1997). Pathogens rapidly evolve new adaptations to better thrive in human bodies. This causes many different defense alleles—some better than others—to exist in the population at a given time.

**TABLE 2**  
**Strength of Various Lines of Evidence Consistent With a Mutational Role in the Risk of Four Mental Disorders**

Evidence	Interpretation	SZ	MR	BD	AU
<b>Indirect Methods</b>					
Low modern fitness	Traits whose genetic variation is maintained by mutation-selection should demonstrate low fitness, although modern and ancestral fitness have unknown relationships.	***	***	*	
Brain trauma	Major phenotypic disruptions increasing mental-disorder risk is consistent with the hypothesis that genetic disruptions (mutations) can do likewise.	**	***	**	*
Paternal age effects	New mutations accumulate in sex (sperm/egg) cells as males (but not as females) age.	***	**		**
Known parental inbreeding	Natural selection weeds out deleterious mutations with dominant or additive effects, leaving extant deleterious mutations skewed toward recessivity; by increasing homozygosity, inbreeding reveals their full harmful effects.	**	***	*	
<b>Direct (molecular) methods</b>					
Chromosomal abnormalities	These can be considered mutations of large effect, affecting multiple genes at once, causing more pronounced phenotypic effects than point mutations and making them easier to detect in pedigrees.	**	***	*	**
Rare deletions and duplications	Like new or rare point mutations, new or rare deletions and duplications are likely to be deleterious to fitness.	**	**	*	**

**Note.** Numbers of stars (0 to 3) represent the author's appraisal of strength of evidence for various lines of evidence for mutation-selection maintaining the genetic variation in schizophrenia (SZ), mental retardation (MR), bipolar disorder (BD), and autism (AU). It is unknown whether a paucity of evidence reflects null and unreported findings or little investigation. For technical reasons, it is not yet possible to directly assess the impact of point mutations, but this is not the case for deletions and duplications.

Pathogens, which can affect neurodevelopment, are known risk factors for several mental disorders. For example, several studies have found that childhood *Streptococcal* infections are weakly associated with adult obsessive-compulsive disorder (Kim et al., 2004). If resistance to *Streptococcal* infections is heritable, then part of the heritability of obsessive-compulsive disorder could be due to *Streptococcal*–human coevolution. This example illustrates that the risk alleles responsible for the heritability of mental disorders need not directly increase mental-disorder risk. Rather, they may make one vulnerable to factors such as pathogens that *do* increase risk.

### Balancing Selection

Balancing selection occurs when natural selection actively maintains two or more equally fit alleles at a gene. This usually occurs because the fitness of the alleles increases as they become rarer: If one allele drifts to a lower frequency than its equilibrium value, its fitness increases, which then nudges its frequency back toward the equilibrium. Heterozygote advantage—in which individuals who are heterozygote (*Aa*) at a gene have higher fitness than those with either homozygote (*AA* or *aa*)—is a special case of this process. For example, individuals in equatorial Africa who are heterozygous at the  $\beta$ -hemoglobin locus are protected against malaria, whereas homozygous individuals are either vulnerable to malaria or at risk of sickle-cell anemia. Each allele—as well as sickle-cell anemia—is maintained in equatorial Africa because if one allele becomes infrequent by chance, it more often finds itself paired with the opposite allele, increasing its fitness and frequency.

Although balancing selection has been a favored explanation for the persistence of risk alleles, my own view is that its popularity outstrips its support. One type of evidence for balancing selection would come from finding high-frequency alleles—a prediction from practically every model of balancing selection—that affect mental disorder risk. Gene-mapping studies have not had much success yet matching specific alleles to severe mental disorders, however, which suggests (but does not prove) that such risk alleles are individually rare rather than common. Moreover, a recent whole-genome scan designed to detect signatures of ancient balancing selection in humans discovered no loci under balancing selection apart from those few already known to exist (Bubb et al., 2006).

Another type of evidence consistent with the balancing-selection hypothesis would be finding that relatives of those with mental disorders have some sort of fitness advantage. This might suggest that low doses of risk alleles (typically found in relatives) have positive effects that counterbalance their high-dose negative effects. Several studies on schizophrenia have looked at this issue, and although mixed, the weight of evidence indicates that relatives of schizophrenics have equal or lower fitness than average, not higher fitness as required by balancing-selection arguments (Keller, 2008). Nevertheless, modern reproductive success may correlate poorly with ancestral reproductive success. More intriguing support comes from studies showing that schizotypy (a personality dimension, the extreme of which may constitute schizophrenia) is higher among highly creative individuals (Nettle & Clegg, 2006). One interpretation is that low doses of schizophrenia risk alleles increased creativity and fitness in ancestral environments.

## CONCLUSIONS

Why do the alleles that predispose to severe mental disorders exist? We don't yet know, but mutation selection, time lags, and balancing selection probably all play roles to different degrees. My own view is that mutation-selection explanations enjoy the strongest support to date, but the weight of evidence may shift as new data become available. Given the rapidity with which the genetic code is being deciphered and the increasing ability to test evolutionary hypotheses using genetic data, it is likely that, within the next 10 to 20 years, we will have a good understanding of why the alleles that increase risk for severe mental disorders have persisted over evolutionary time. Stay tuned.

## Recommended Reading

- Barton, N.H., & Keightley, P.D. (2002). Understanding quantitative genetic variation. *Nature Reviews Genetics*, 3, 11–21. A very good, accessible review of how evolutionary geneticists explain heritability in traits.
- Gangestad, S.W., & Yeo, R.W. (1997). Behavioral genetic variation, adaptation and maladaptation: An evolutionary perspective. *Trends in Cognitive Sciences*, 1, 103–108. An early paper introducing the mutation-selection view of mental disorder risk.
- Keller, M.C., & Miller, G. (2006). Resolving the paradox of common, harmful, heritable mental disorders: Which evolutionary genetic models work best? *Behavioral and Brain Sciences*, 29, 385–452. A thorough overview of the topics in this article, including critical commentaries.
- Mealey, L. (1995). The sociobiology of sociopathy: An integrated evolutionary model. *Behavioral and Brain Sciences*, 18, 523–599. A well-reasoned paper arguing that balancing selection has maintained sociopathy.
- Nesse, R.M., & Williams, G.C. (1994). *Why we get sick: The new science of Darwinian medicine*. New York: Times Books. A user-friendly book that introduced Darwinian medicine to the mainstream.

## REFERENCES

- Bubb, K.L., Bovee, D., Buckley, D., Haugen, E., Kibukawa, M., Paddock, M., et al. (2006). Scan of human genome reveals no new Loci under ancient balancing selection. *Genetics*, 173, 2165–2177.
- Di Rienzo, A., & Hudson, R.R. (2005). An evolutionary framework for common diseases: The ancestral-susceptibility model. *Trends in Genetics*, 21, 596–601.
- Eyre-Walker, A., & Keightley, P.D. (1999). High genomic deleterious mutation rates in hominids. *Nature*, 397, 344–347.
- Fay, J.C., Wyckoff, G.J., & Wu, C. (2001). Positive and negative selection on the human genome. *Genetics*, 158, 1227–1234.
- Gangestad, S.W., & Yeo, R.W. (1997). Behavioral genetic variation, adaptation and maladaptation: An evolutionary perspective. *Trends in Cognitive Sciences*, 1, 103–108.
- Hawks, J., Wang, E.T., Cochran, G.M., Harpending, H.C., & Moyzis, R.K. (2007). Recent acceleration of human adaptive evolution. *Proceedings of the National Academy of Sciences, USA*, 104, 20753–20758.
- Houle, D. (1998). How should we explain variation in the genetic variance of traits? *Genetica*, 102, 241–253.
- Keller, M.C. (2008). Problems with the imprinting hypothesis of schizophrenia [commentary]. *Behavioral and Brain Sciences*, 31, 273–274.
- Keller, M.C., & Miller, G. (2006). Resolving the paradox of common, harmful, heritable mental disorders: Which evolutionary genetic models work best? *Behavioral and Brain Sciences*, 29, 385–452.
- Keller, M.C., & Nesse, R.M. (2006). The evolutionary significance of depressive symptoms: Different adverse situations lead to different depressive symptoms patterns. *Journal of Personality and Social Psychology*, 91, 316–330.
- Kessler, R.C., Chiu, W.T., Demler, O., & Walters, E.E. (2005). Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry*, 62, 617–627.
- Kim, S.W., Grant, J.E., Kim, S.I., Swanson, T.A., Bernstein, G.A., Jaszcz, W.B., et al. (2004). A possible association of recurrent streptococcal infections and acute onset of obsessive-compulsive disorder. *Journal of Neuropsychiatry and Clinical Neuroscience*, 16, 252–260.
- Lo, W.S., Xu, Z., Yu, Z., Pun, F.W., Ng, S.K., Chen, J., et al. (2007). Positive selection within the schizophrenia-associated GABA(A) receptor beta2 gene. *PLoS ONE*, 2, e462.
- McClellan, J.M., Susser, E., & King, M.C. (2007). Schizophrenia: A common disease caused by multiple rare alleles. *British Journal of Psychiatry*, 190, 194–199.
- Moffitt, T.E., Caspi, A., & Rutter, M. (2005). Strategy for investigating interactions between measured genes and measured environments. *Archives of General Psychiatry*, 62, 473–481.
- National Institute of Mental Health. (1998). *Genetics and Mental Disorders: Report of the National Institute of Mental Health's Genetic Workgroup* (NIH Publication No. 98-4268). Bethesda, MD: Author.
- Nesse, R.M., & Williams, G.C. (1994). *Why we get sick: The new science of Darwinian medicine*. New York: Times Books.
- Nettle, D., & Clegg, H. (2006). Schizotypy, creativity and mating success in humans. *Proceedings of the Royal Society of London, Series B*, 273, 611–615.
- Online Mendelian Inheritance in Man. (n.d.). Baltimore, MD: McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University; and Bethesda, MD: National Center for Biotechnology Information, National Library of Medicine. Retrieved October 13, 2007, from <http://www.ncbi.nlm.nih.gov/omim/>
- Saha, S., Chant, D., Welham, J., & McGrath, J. (2005). A systematic review of the prevalence of schizophrenia. *PLoS Medicine*, 2, 413–433.