Chapter 23: Schizophrenia

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Introduction

In 1971, Eliot Slater (at that time, the foremost psychiatric geneticist in the world) and Valerie Cowie published *The Genetics of Mental Disorders*. The book was encyclopedic—it synopsized all the world’s empirical literature on schizophrenia, the affective disorders, the neuroses (as they were called then), mental retardation, and personality disorders. Today, such an undertaking would surpass the capabilities of even the most talented scholarly duo and would require a volume each for every major form of psychopathology. Hence, a single chapter cannot summarize a single disorder. To avoid diluting knowledge by discussing a number of disorders, I focus exclusively on schizophrenia. It serves as a good model for the genetics of psychopathology in general.

Schizophrenia: the Phenotype

No one is born with schizophrenia. Instead, the psychopathology develops over time—sometimes slowly and mysteriously but other times abruptly. Onset before puberty and after age 50 are rare, but deserving of attention when encountered; most cases appear between ages 15 and 35. For males, the average age of first symptoms
occurs around 22 with first admission at 28; females have a delayed onset for reasons that are not understood. The respective figures for women are 25 (age of onset) with admission at 32 (Harner et al., 1999—GET EXACT REF FROM IRV). Despite the age difference in onset, schizophrenia is not a sexist disorder—males and females are affected equally. About 1% of the general population will develop schizophrenia at some point in their lives, making it a “common” genetic disorder. Prognosis can be grim, including a very high risk of death from suicide. Although there are well-documented cases of social recoveries, many schizophrenics are so changed by the illness that they require extensive mental health assistance to function in society. Hence, schizophrenia places a deep burden on health resources, not to say the families of victims.

The behavior of schizophrenics before their onset is statistically different from that of their normal peers (Cornblatt et al., 1999), but the differences are so small and so diffuse that there is no practical way as yet of predicting who will and will not develop the disorder in the general population. Sometimes the disorder develops insidiously. Gradually, normal positive and negative affect may give way to a lack of any affect, the ability to experience pleasure slowly diminishes, the person could experience feelings of unreality, and and problems with concentration and attention emerge. Thereafter, s/he may develop overvalued ideas (e.g., extreme preoccupation with a health food fad or joining a cult) and become socially isolated. To the friend or relative, the person seems to be developing eccentricities. Eventually, overt delusions and hallucinations\(^1\) appear.

\(^1\) Delusions are ideas and feelings that are very incongruent with reality (e.g., feeling that there is a vast governmental conspiracy specifically directed at oneself). Hallucinations are sensory perceptions that do not arise from a physical stimulus (e.g., hearing voices).
They can take many different forms, but friends and relatives now recognize that something serious is the matter and bring the schizophrenic into treatment.

Other cases may have a more abrupt onset. There is little of the gradual deterioration marking the hypothetical case given above. Rather, an otherwise normal person becomes convinced that s/he is receiving personal messages from the television, is being spied on by the government, or has been given a special mission to count all the books in the local library. Irving Gottesman (1991), an erudite scholar of schizophrenia, highlights the extraordinary variability in the clinical signs and symptoms of the disorder. Schizophrenia affects cognition (memory and executive functioning), attention, affect (which can range from its total absence to episodes of silly and inappropriate laughter), motivation, personality, and even motor behavior (e.g., stereotyped movements). Still, there is no single symptom that is found in all schizophrenics, and a single person may show different constellations of symptoms at different times during the illness.

Neither is there a single biological marker that can be used to diagnose schizophrenia. Despite a century of research on the brains of schizophrenics, there is no visible pathology such as the neuronal plaques and tangles that characterize Alzheimer’s disorder or the death of glial cells that mark other neurodegenerative disorders.² Within the schizophrenic brain, the ventricles (i.e., fluid-filled sacks deep within the brain) are larger on average than those of normals³, but there is so much overlap between the two types of brains that ventricle size cannot be used as a diagnostic measure. The absence of

² Glia cells (AKA neuroglia) are connective tissues that bind and support neurons in the central nervous system.
³ There is also a concomitant decrease in the volume of the cortical matter and certain other structures in the brains of schizophrenics
detectable neuropathology has led many to posit that schizophrenia is a neurodevelopmental disorder and not a neurodegenerative one.

A large number of biochemical (e.g., amino acid levels in certain brain regions), physiological (e.g., eye tracking, reaction time, certain evoked potentials from the brain), and psychological (e.g., attention span, language functioning) variables have been researched and there are indeed many replicable findings. Invariably schizophrenics lie toward the “bad” end of the variables (e.g., aberrant eye tracking, short attention span, poor communication skills). However, none of these biochemical, physiological or psychological variables are powerful enough to be used to diagnose schizophrenia.

Many, but not all experts suspect that schizophrenia is a collection of heterogeneous disorders. In this sense, one should speak of the schizophrenias instead of schizophrenia. At present, there is no way to differentiate any one of the disorders from the others by simply examining the phenotype. Researchers who hold this view try to find subsets of schizophrenics who might show one or more specific abnormalities that might distinguish them from the others. To date, identification of subtypes has not been successful.

A considerable amount has been learned in the past century of schizophrenia research, but much of this knowledge boils down to a simple aphorism—if one can measure a physiological variable related to the nervous system, a cognitive trait, or anything that has to due with human affect, personality or social interaction, then schizophrenics tend to score on the abnormal end of the variable. Separating potential causes of schizophrenia from the consequences of such a devastating illness still remains
difficult. In many ways, the disorder remains almost as mysterious today as it did to those who first described it in the late 1800s.

**Genetic Epidemiology of Schizophrenia: I. Heritability**

Shortly after the disorder was first classified by Emil Kraepelin as *dementia praecox* and given the name schizophrenia by Eugen Bleuler in 1908, it was observed that schizophrenia would often run in families. Table 23.1 gives the risk for schizophrenic in different types of genetic relatives of a schizophrenic. Gottesman (1991) compiled the data from the best Western European studies reported over the past century. Risk for cousins (2%) is only slightly greater than the general population risk. Second-degree relatives have a risk of around 5%, while first-degree relatives have a risk close to 10%. These figures clearly indicate that schizophrenia is not a simple, fully penetrant recessive (e.g., PKU) or dominant disorder (e.g., Huntington’s Disease).

![Insert Table 23.1 about here]

Several of the risk figures deserve comment. The risk to children (13%) is significantly higher than the risk for parents (6%). This discrepancy is attributed to the well-documented fact that schizophrenics have a lower reproductive fitness than normals, producing only half the children of normals. In addition, it is usually the less severe schizophrenics that marry and have children. A second noteworthy discrepancy is the fact that DZ twins have a higher risk than full siblings (17% versus 9%) do despite the

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4 Previously the disorder was called dementia praecox (premature dementia). Bleuler, noting that the course of the illness was not always consistent with dementia (a chronic and irreversible deterioration of cognitive functioning), renamed it schizophrenia from the Greek roots schizo (split) and phrenos (mind). In the popular mind, schizophrenia is often equated with "split personality," a concept that is not justified scientifically.
The fact that DZ twins and sibs have the same degree of genetic relatedness. The reasons for this are unknown but are likely to include the fact that the DZ cotwins have been studied more intensively than sibs and the possibility of pre- and/or perinatal effects on schizophrenia. Finally, the fact that risk for parents is about 6% carries the necessary implication that most schizophrenics—in fact, over 90%—will be born to nonschizophrenic parents.

Risk for MZ cotwins is almost 50%, suggesting that genes play an important role in the familial aggregation of schizophrenia. Adoption studies confirm the genetic influence. Schizophrenia in biological relatives—not in adoptive relatives—predicts schizophrenia in adoptees (Heston, 1966; Ingraham & Kety, 2000).

The strength of the genetic influence is difficult to quantify because estimation of heritability depends on the mode of transmission for schizophrenia and we simply do not know the mode of transmission. Working on the assumption of the polygenic-threshold model described in chapter X, McGue, Gottesman, and Rao (1983) estimated heritability at close to .70 with negligible influence from the shared family environment. However, if there is marked heterogeneity in schizophrenia, this figure could be misleading.

**Genetic Epidemiology of Schizophrenia: II. Beyond Heritability**

Family and twin studies provide much more important information about schizophrenia than providing numerical estimates of heritability. Concordant MZ twins have similar ages of onset, similar profiles of clinical signs and symptoms, and similar

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5 In fact, if there is marked heterogeneity, an argument could be made that heritability should not be calculated in the first place. A more important goal would be to identify the sources of heterogeneity.
courses of illness (Abe, 1969; Cardno et al., 1999; Gottesman & Shields, 1972). Some family studies also report familial clustering of signs and symptoms. These observations are consistent with the hypothesis that schizophrenia is a heterogeneous collection of disorders. However, there are so many differences in clinical manifestation among concordant sibs, DZ twins, and MZ twins that no one has been able to conclusively subdivide schizophrenia into separate familial disorders based exclusively on symptoms. Also, a familial correlation for symptoms is also consistent with the hypothesis of modifying loci—i.e. genes that might not contribute to schizophrenia per se but may influence the form it takes.

A second important finding is that 5% to 10% [CHECK WITH IRV OVER FIGURES HERE—USE KIMLING AND KENDLER REFS] of first-degree relatives exhibit eccentricities, peculiar ideas, suspiciousness, and/or odd social behavior but never seem to develop full-blown delusions and hallucinations of the full psychosis. Various names—schizoid, schizophreniform, schizophrenic spectrum—have been used over the years to describe this subclinical phenomenon, the currently favored phrase being schizotypal personality disorder (SPD). The available data suggest that SPD is familially and genetically related to full-blown schizophrenia. The reasons why someone with SDP does not decompensate into schizophrenia are unknown.

Severity of schizophrenia in a proband is associated with familial risk—the relatives of severely affected schizophrenics are at higher risk than relatives of less severe probands. The situation is best illustrated in the Maudsley twin series (Gottesman and Shields, 1972; Gottesman, 1991). No matter how severity was measured—number of hospitalizations, length of treatment, outcome, or global ratings of
psychopathology—there was a consistent tendency for twin concordance to be associated with proband severity. The reason for the severity-concordance relationship is not understood but it may come from some combination of three different factors. First, if there is marked heterogeneity in schizophrenia, the less severe cases may contain more phenocopies than severe schizophrenics may. Second, to the extent that there is multifactorial, polygenic transmission, the more severe cases may have a greater genetic loading than the mild cases. Finally, difficulties in diagnosis could influence the relationship. Severely affected schizophrenics have longer and more detailed case history information that might increase accuracy in diagnosis. Mild cases, on the other hand, may include more false positive diagnoses.

One of the most intriguing aspects of the genetic epidemiological literature has been the study of MZ twins discordant for schizophrenia. Indeed, this type of research highlights how genetic studies can be used for much more than simply calculating heritability. Differences between the well and the ill twin reflect facets of the idiosyncratic environment that play a causal role in schizophrenia or they can tap the consequences of the illness itself. Variables that occur long before the onset of illness are more likely to be causal than those measured after the illness. An example of each type of variable is given.

Early twin researchers reported an association between laterality and discordance—MZ twins discordant for schizophrenia also tend to be discordant for handedness (Gottesman and Shields, 1971). A recent study reported that fingerprint (AKA dermatoglyphic) differences are greater in discordant MZ twins than concordant MZ twins (Davis & Bracha, 1996). Because fingerprints develop before birth and
handedness develops in late infancy, these variables are probably manifestations of unknown, but early, developmental processes that may play a role in schizophrenia.

Differences in personality and some cognitive variables in discordant pairs probably measure the effects of the illness. The ill twin of the pair shows more deviance in traditional personality measures than the well twin (DiLalla & Gottesman, 1995). More importantly, the moderate to strong personality resemblance found among ordinary twin pairs is missing in discordant MZ twins. A very similar pattern occurs for neuropsychological functioning (Goldberg et al., 1995). These findings suggest that the personality aberrations and some aspects of unusual cognitive functioning may be consequences of the disease.

The causal versus consequential role for many other variables that differentiate the well from the ill MZ twin is unclear. Ill twins tend to have larger brain ventricles (fluid filled “lakes” within the brain) than well twins. They also show more EEG abnormalities (Stassen et al., 1999), abnormal auditory information processing (Weisbrod et al., 1999), and neurological soft signs (Cantor et al., 1994). Are these parts in the causal network of schizophrenia or are they consequences of the illness? Currently, there is no unambiguous answer. Instead, these factors must be pieced together with the results from other research to develop hypotheses that guide future research. To give an example, McNeil et al. (2000) report that enlarged ventricles were associated with birth trauma and prolonged labor. Given that pregnancy and birth complications are weakly associated with schizophrenia, the McNeil et al results support the notion that ventricle size may be a facet of idiosyncratic environmental experiences (birth complications) that play an etiological role in the disorder.
A final important result from discordant MZ twins comes from the risk for schizophrenia in their offspring. If the ill twins are largely environmental phenocopies, then the risk to the offspring of the \textit{well} twin should be close to the population base rate. On the other hand, if both members of the twin pair have elevated genetic loadings on schizophrenia but the ill twin experienced some adverse unique environmental events to make him/her break down, then \textit{both} twins should transmit the same above-average genetic liability to their offspring. In this case, the offspring of both the well and the ill twin would have the same, elevated risk of developing schizophrenia. Study of a series of Danish discordant twins suggests that the latter hypothesis fits the data better than the former (Gottesman & Bertelson, 1989).

\textbf{The Multifactorial Threshold Model Revisited: Diathesis-stress}

Let us revisit the multifactorial threshold model that we briefly examined in the discussion of disorders with complex genetics and examine its application to schizophrenia. Figure 23.1 is an adaptation of the original threshold model proposed by Gottesman and Shields (1967, 1972)\textsuperscript{6}. It depicts four different components of liability. According to Gottesman and Shields, \textit{specific} genetic liability is a quantitative scale that measures the propensity to develop schizophrenia \textit{per se}. That is, the genes for this liability dimension make a person vulnerable to \textit{schizophrenia}\textemdash not necessarily to anxiety disorders, general stress resistance, emotional instability or any other of a large number of traits that might influence the probability that someone develops psychopathology. The central empirical evidence for specific genetic liability is that the

\textsuperscript{6} The mathematics of the threshold model were developed by the Douglas Falconer and were applied to schizophrenia by Gottesman and Shields.
most common form of psychopathology seen in the MZ cotwins of schizophrenic probands (allowing for base rates of other psychopathology) is schizophrenia or schizophrenic-like disorders such as SPD.

[Insert Figure 23.1 about here]

The mean of the general population for specific genetic liability is 0. Individuals with negative values are protected from developing schizophrenia, although they may have little protection from developing other forms of psychopathology. Those with high positive scores are at high risk for breaking down with schizophrenia, but not necessarily with manic-depressive disorder, antisocial personality, etc.

The genes in the specific genetic liability dimension do not operate in a vacuum. Their biological activity works in concert with the background music provided by the rest of the genome and the environment. Several of those other loci may contribute to the development of schizophrenia but not in a direct way. The quantitative effects of these genes form the scale of general genetic liability. Gottesman and Shields hypothesized that a number of different background traits influence the development of many different forms of psychopathology. As an example, take the personality dimension of neuroticism. People high on this trait may be at risk for many different disorders—panic disorder, generalized anxiety disorder, obsessive compulsive disorder, depression, and even schizophrenia. The particular form of the disorder in any given person, however, depends on the specific liabilities of that person. Again, the population mean for general genetic liability is 0, those with strong genetic assets will score on the negative (i.e., less vulnerable) end of the scale, and those with genetic liability factors will have positive scores.
Specific and general environmental liabilities work in analogous ways to the genetic liabilities but apply to environmental factors. There is not the strong empirical evidence for specific environmental liability as there is for specific genetic liability. It is included here to allow for the possibility that factors like a virus may influence schizophrenia per se. Many researchers speculate that most of the environmental influences on schizophrenia fall under the general environmental liability dimension. One of the most salient variables contributing to this dimension is environmental stress. Hence, the multifactorial threshold model is often referred to as the *diathesis-stress model* in psychopathology, the word *diathesis* being a fancy synonym for liability.

In its simplest form, the diathesis-stress or polygenic threshold model assumes that everyone has a latent phenotype (called total liability) that is a combination of all the specific and general liabilities mentioned above. That is, total liability = $\beta_1 \times$ specific genetic liability + $\beta_2 \times$ general genetic liability + $\beta_3 \times$ specific environmental liability + $\beta_4 \times$ general environmental liability. The subscripted $\beta$s are unknown weights that specify how important one of the liabilities contributes to total liability. Once the total liability exceeds a certain point (the first threshold), a process begins and the person develops some signs and symptoms of schizophrenia and SPD becomes apparent. When the liability is very large, the person crosses a second threshold and the overt hallucinations and delusions of schizophrenia become apparent. This is an example of a *two-threshold model* in which passing the first threshold leads to the development of a mild form of the disorder but passing the second threshold results in a more severe form. One could

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7 The model described is a simple additive one. In principle, it can be expanded to account for other factors such as an interaction between specific genetic liability and some environmental factor.
generalize this principle to a *multiple-threshold* model that may have more than two thresholds.

The diathesis-stress model has two important uses in psychopathology. First, the mathematics of the model can be used to calculate the *correlation in liability* for relatives. When data on twins and/or adoptees are available, then these correlations can be used to calculate heritability in a manner identical to calculating heritability for personality or intelligence. In this case, the heritability is termed the *heritability of liability*. It is not strictly the heritability of schizophrenia *per se*. Instead, it is the heritability of *all* those multifactorial factors that go into the predisposition for developing schizophrenia. In terms of the model in Figure 23.1, heritability of liability includes both the specific genetic liability and the general genetic liability. Analogously, one could compute the environmentability of liability (or $e^2$) as well as the correlation in environmental liability for relatives ($\eta$).

The second importance of the diathesis-stress model as outlined above is that it guides scientific research. Thinking in a multifactorial mode requires discipline because according to this train of thought, there is no such critter as *the* cause of schizophrenia. Instead there are several causes—perhaps as few as three or maybe as many as 300—that work together. The same may be said about the consequences of the disorder. Hence, cognitive psychologists are not backing a different horse than biochemists in researching schizophrenia. They are likely to be exploring different pathways of complicated etiology and/or symptomatology of the disorder. [SEE IRVS COMMENTS ABOUT KEITH NUECHTERLEIN’S MODEL IN VOL 3 OF HAFNER/GATTAZ. GET BOOK].
Diathesis-Stress and Lemonade

Stress takes many forms. Negative life events such as the death of a loved one are one type of stress. Other life events may be pleasurable or aversive, depending on their context and the individual affected by them. For example, leaving home to attend a distant college involved trials as well as rewards. In terms of the diathesis-stress model, separation from family and friends in this case could be a specific environmental stressor for depression, a general environmental stressor for schizophrenia, or perhaps even an environmental asset.

Other types of stress may be self-imposed rather than an external event. Negative life events themselves show some heritability, suggesting that we can assist in the creation of our own stressors. Poor job performance can result in a person being fired that itself can lead to anxiety about money and worries over self-worth. And general genetic and general environmental liabilities may have influenced the poor job performance in the first place.

Lastly, environmental stress must be evaluated with consideration for its biological and even genetic influence on the organism. One consequence of stress is the excretion of large amounts of cortisol. As we saw in the chapter on genetic regulation, cortisol has the effect of enhancing and inhibiting transcription. Hence, all those genetic and environmental factors that influenced job performance will also influence the probability of getting fired. Once fired, the stresses about money, finding a new job, self-esteem, etc. can increase cortisol excretion that, in turn, regulates expression of a number of different genes in different bodily tissues. Thus, the genes and environmental factors
for job performance can assist in a cascade of events that ultimately influence many other genes. Once again, it is lemonade.

**Molecular Genetics Studies of Schizophrenia**

The best way to introduce this topic is to quote directly from the abstracts of recent journal articles on the molecular genetics of schizophrenia.

“Studies of schizophrenia kindreds have yielded robust evidence for susceptibility at 18p11.2 and 22q11-13 ... Similarly, confirmed schizophrenia vulnerability loci have been mapped, too, for 6p24, 8p, and 13q32.” (Berrettini, 2000)

“As with most complex inheritance diseases, there are at this time no identified susceptibility genes for schizophrenia ... Nonetheless, progress has occurred. ... Genetic linkages and associations have been reported and replicated, although there have been inconsistencies between studies ...” (Gershon, 2000)

“In the last decade, a new wave of molecular genetic studies of families with schizophrenia has yielded unconvincing evidence for the involvement of multiple putative loci.” (DeLisi, 2000)

Pretty confusing, isn’t it? Opinion ranges from “confirmed loci” to “unconvincing evidence” with many more researchers occupying various intermediate positions. To illustrate the current state of molecular-genetic studies of schizophrenia, let us examine one chromosome (number 6) and review the empirical findings.

The reason for exploring chromosome 6 for genes in schizophrenia began with the report of a single pedigree where a chromosomal translocation between chromosomes 6
and 11 segregated with a vaguely defined psychotic illness (Holland & Gosden, 1990).

Five years later, Wang et al. (1995) and then Straub et al. (1995) reported positive findings of linkage for a schizophrenia susceptibility locus in the p arm of chromosome 6. Figure 23.2 depicts chromosome 6 and the region of the p arm where this gene may lie. (Also depicted is a region of the q arm that is currently being investigated for another susceptibility gene.)

Soon thereafter, a flurry of results on chromosome 6 hit the journals, some of which supported the original finding to various degrees (e.g., Lindholm et al., 1999; Moises et al., 1995; Schwab et al., 1995) while others failed to detect linkage (e.g., Daniels et al., 1997; Garner et al., 1996; Gurling et al., 1995). The last published overview of all the linkage results to chromosome 6 (Nurnberger et al., 1999) concluded that there is tentative but not conclusive evidence for linkage and that the results need to be pursued with more vigor.

What might be the possible reasons for the inconsistency in the literature? One answer may simply be sample size. Several of the studies that failed to replicate the finding involved a small number of families (e.g., Daniels et al., 1997). Small samples reduce the statistical power of linkage analysis. That is, they make it more difficult to detect a linkage when in fact the linkage is present.

Secondly, the actual effect of the locus on chromosome 6 may be very small. Most researchers regard this as a “susceptibility” gene—one that increased risk, but only slightly increases it. A third possibility is an association of the schizophrenia susceptibility locus on 6 with ethnicity. The strongest evidence for linkage comes from the initial reports of Straub et
al. (1995) and Wang et al. (1995) that were dominated by a large number of Irish pedigrees. Perhaps the susceptibility allele has a higher frequency among Celtic peoples than other populations.

Whatever the cause, the overall story of chromosome 6 is not a one-of-a-kind tale. Almost all reported linkages have followed the same pattern. Sobering failures to replicate dampens the enthusiasm following an initial positive report. It is tempting for the novice scientist to dismiss entirely this line of research, but that is a serious error. These results may be telling us something very, very important—there may not be single genes of very large effect for schizophrenia and possibly for most other forms of psychopathology. Most geneticists in the field interpret the data as supporting a polygenic mode of inheritance—several genes contribute to the liability of developing schizophrenia and the effect size for each locus is relatively small. Thus, linkage studies require a very large number of pedigrees to detect these loci.

The biggest advantage of these confusing results is that they can guide future research based on emerging genetic knowledge and technologies. As more and more human genes are identified and characterized at the molecular level, the strategy to detect vulnerability loci will switch from the linkage design to the more powerful association design. Instead of blindly assessing the tens of thousands of human loci for their relevance for schizophrenia, the linkage results point to areas of the genome that should first be explored. The 6p region in Figure 23.2 potentially implicated in schizophrenia contains several hundreds of genes to perhaps a thousand or so genes, not many thousands. Searching for one needle in one haystack is much easier than searching for that needle in a hundred different haystacks.
Other Forms of Psychopathology

Although schizophrenia is the most studied disorder in the genetics of psychopathology, there have been twin and (a few) adoption studies on other disorders. With the exceptions noted below, the results are similar to those for schizophrenia in the following ways: (1) MZ twins are never 100% concordant for a disorder; this clearly implicates the environment for all forms of psychopathology studied thus far. Hence, statements like “alcoholism is a genetic disorder” or “bipolar manic-depression is due to heredity” are very misleading. (2) The risks to relatives do not follow the pattern of simple Mendelian inheritance, even if that pattern is “souped up” by espousing incomplete penetrance and variable expressivity. The results of almost all forms of segregation analysis (a statistical attempt to find major Mendelian loci for disorders with complex genetics) have been mixed (Carey, 1987). (3) Hence, all forms of psychopathology studies thus far are DCGs (disorders with complex genetics). (4) Although many researchers—perhaps even the majority of them—suspect heterogeneity, no subdivision of any disorder into “types” has been so compelling as to put them into a textbook. The best example is depression. Despite attempts to classify depression into “exogenous versus endogenous,” “reactive versus nonreactive,” and “neurotic versus psychotic,” the data suggest that they do not run true to type within families. (5) To date, no genes of large effect have been reported by a large and replicated body of linkage or association results. To be sure, there are interesting leads here and there, but no single result has passed the crucial test of replication in a large number of independent labs. The reasons for this state of affairs are unclear, but the empirical data have certainly dampened the initial enthusiasm of investigators who hoped to detect such phenomenon
as a “chromosome 13 form of schizophrenia.” On the other hand, the confusing results should not lead to a state of despair in which linkage and association studies are abandoned as being unproductive. The puzzling results are telling us something important—it is just that we have not been clever enough to figure out what that important something is. Currently the most favored hypothesis is that polygenic transmission is responsible for the lion’s share of the genetic diathesis. Hence, the effect of any single locus will be on the small side and hard to detect in studies that lack very large numbers of pedigrees.

Here and there, we do find exceptions to these (over)generalizations. MZ twins are not 100% concordant for severe forms of agoraphobia and social phobia, but careful clinical study of the well cotwins suggest that most—perhaps even all—of them show subclinical features similar to the full-blown syndrome (Carey & Gottesman, 1981). These cotwins may be fearful enough to shun subway trains or avoid open places, but their anxiety fails to cause sufficient interference in ordinary behavior to merit the diagnosis of a “disorder.” The discussion of ALDH deficiency in the chapter on Mendelian traits is a clear example of a major locus influencing the susceptibility to alcohol problems; it is the best-documented exception to number (4) above. Also, there is a body of consist linkage results suggesting that an important gene on chromosome 6 contributes to reading disability (Gayan et al., 1999).

As we learn more about the human genome, we will eventually develop more and more exceptions to these generalizations. What we cannot anticipate, however, is how long it might take to develop a large body of well-replicated genetic associations with psychopathology.
References


Gershon, E. S. (2000). Bipolar illness and schizophrenia as oligogenic diseases: implications for the future. *Biol Psychiatry, 47*(3), 240-244.


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### Table 23.1. Risks for schizophrenia in genetic relatives of schizophrenics. Adapted from Gottesman (1991, Figure 10).

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<thead>
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<th>Genetic Relation:</th>
<th>Type of relation:</th>
<th>Risk:</th>
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<td>General Population</td>
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<td>Third-degree</td>
<td>Cousins</td>
<td>2%</td>
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<td>Second-degree</td>
<td>Uncles/aunts</td>
<td>2%</td>
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<td></td>
<td>Nieces/nephews</td>
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Figure 23.1. The multifactorial-threshold model for liability to schizophrenia and schizotypal personality disorder.
Figure 23.2. Schematic of chromosome 6 showing the areas of reported linkage in the p arm (short arm) and the q arm (long arm).