HOW DO MENTAL DISORDERS EMERGE FROM THE MIX OF GENES AND ENVIRONMENTS?

Lamar, a man with bad news

Lamar is sitting in a coffee shop, stunned. His fiancée Marta has just broken up with him. She gave him some odd reasons. “It’s important for me to have children and I don’t think you should have them,” she said. She also said, “I don’t think I’ll be able to take care of you.” Before Lamar could respond, Marta fled from the restaurant.

At first Lamar couldn’t make sense of her remarks. Then it occurred to him that this unhappy scene might be connected to the drama already taking place in his family.

About a month ago, Lamar and Marta had plans to meet his mother Adele for dinner at a new restaurant outside of town. Adele never showed up. Lamar spent several hours calling and driving around, trying to locate her. Finally, near midnight, his mother called him from a pay phone. She had no idea where she was or how she had gotten there.

This was not the first time Adele had gotten lost, but before she had always blamed it on being distracted and terrible with directions. This time Lamar did not buy the excuses. He insisted she go to her doctor.

After a thorough exam and several diagnostic tests, Adele was given a dreadful diagnosis. She has Alzheimer’s disease. With this illness, plaques and tangles (two types of protein residue) build up in the brain, destroying cells. Over the course of years, people with Alzheimer’s lose memory, reasoning and language abilities, and their independence. Eventually the brain is unable to carry out basic tasks, causing death. Alzheimer’s usually strikes people over age sixty-five, but some forms, known as early-onset Alzheimer’s, strike people even younger. Adele is forty-eight.

Last week when Lamar learned about his mother’s diagnosis, he immediately shared the sad news with his fiancée. So perhaps Marta has panicked about marrying a man she assumes will be afflicted by Alzheimer’s at an early age.

Lamar wonders if Marta is right to worry. Perhaps he is at extra risk for early Alzheimer’s. Perhaps he should not have a family and perhaps he could become a terrible burden to any spouse. Is Marta right to reject him?
Genotype/phenotype complexity

Many genes interact with many physical and social environments to shape normal traits, but one gene misfiring is sometimes sufficient to produce disorder. This is the case with Alzheimer’s disease — which we will get back to in a moment — but also with other medical conditions. An example is the rare dementing illness called Huntington’s disease, which destroys the fatty lining of nerve cells leading to loss of coordinated movement, emotional instability, psychosis, and mental decline. Huntington’s is a dominant disorder, meaning that only one disease-related allele at a single locus need be present for the disease to manifest itself.

A gene on Chromosome 4 is implicated in Huntington’s. (The chromosomes are numbered in order of their relative length; 4 is a relatively big chromosome.) However, this disease does not result from a single mutation to this gene. Rather, many different alleles for the gene lead to the same problematic result. These alleles differ from each other in one important way: they have a different number of tandem repeats — multiple copies of the same base sequence (sometimes called “stutters”).

Cystic fibrosis is another single-locus disease that results from a great many (some 650) allelic variations of a single gene. Unlike Huntington’s, cystic fibrosis is a recessive disorder; it takes two disease-related alleles at that locus for the disease to manifest.
to emerge. Cystic fibrosis affects the mucus lining of the lungs, leading to breathing problems and other difficulties.

Some single-locus disorders follow a slightly different script: the allele or allelic pair contributing to disorder may occur in any of several different genes. As noted in Chapter 2, this is called genetic heterogeneity, and it is a characteristic of certain rare forms of breast and colon cancer as well as the early-onset form of Alzheimer’s.

The important point is that single-gene disorders may result from one of many different alleles at one or more loci. Furthermore, any particular allele associated with a disorder may sometimes, but not always, lead to that disorder and may sometimes, but not always, lead to either a mild or severe form of the disorder.

The less-than-straightforward association between an allele and a disorder has to do with proteins. Recall that genes code for amino acids that combine into proteins that make up the structure of cells and direct their activities. A so-called “disease gene” has some alleles whose code results in a necessary protein and other alleles whose code does not have the necessary result. The gene “misfires” when the latter type of allele is present. This could mean that as a result of that allele’s instructions, none of, not enough of, or too much of a resulting protein is produced. Or it could mean that the protein is not made properly and quickly becomes degraded.

The same unhappy results can occur when an allele is affected by modifier genes, that is, by alleles at other loci that interact with the allele in question.

Researchers theorize that the genotype/phenotype relationship may be threshold-dependent. Take, for example, a disorder that results when too little of a particular protein is produced. If protein quantities fall below a lower threshold, disorder will follow. When protein quantities rise above an upper threshold, no disorder will follow.

But when protein quantities lie between the two thresholds, disorder may or may not follow. There may be no symptoms, unnoticeable symptoms, mild symptoms, or serious symptoms. In other words, there is no predictable phenotype associated with that genotype. In such cases, whether or how the disorder manifests itself depends on environmental factors.

PKU is a disease that results when the body does not have enough of a particular enzyme; this enzyme is a protein that acts upon the liver. As described in Chapter 3, PKU can cause mental retardation. It also produces other effects, such as the lightening of hair and skin color.

The gene associated with PKU is called PAH (this stands for the enzyme involved, phenylalanine hydroxylase). More than 400 problematic alleles have been identified; according to one scientific report, the mutations include “dele-
tions, insertions, missense mutations, splicing defects, and nonsense mutations." Researchers had hoped that they could match up genotype with phenotype — that is, that based on the problem allele that is present, they could predict the symptoms and severity of the disease. If they could do this, then doctors could adjust treatment plans to each individual. Babies having alleles known to produce severe effects could be put on the highly restricted diet that prevents symptoms from appearing. Babies with alleles associated with milder effects could be put on less restrictive diets.

It has not turned out to be so simple. Many alleles are not consistently associated with any one PKU phenotype, that is, with any one set of symptoms. In the glum words of one research report, “Prognosis may not be predicted with precision based on mutation analysis.”

More genotype/phenotype complexity

PKU is a recessive disorder, like cystic fibrosis and unlike Huntington’s, a dominant disorder. The disease occurs only in persons who inherit two problematic alleles of the same gene, one from each parent. Recessive and dominant disorders of this type illustrate Mendelian inheritance patterns. “Mendelian” refers to Gregor Mendel, a 19th century monk who raised pea plants and carefully recorded various traits that appeared in successive generations (color, shape, texture, size, etc.). Based on his experiments, Mendel proposed the theory that discrete units of heredity (what we now call genes) are passed from generation to generation in dominant and recessive patterns that can be calculated using simple mathematical formulas. All of modern genetics builds upon his original ideas.

Geneticists today realize that inheritance is more complicated than a simple Mendelian passing down of immutable genetic units. For example, with Huntington’s disease, the allele that is passed down in dominant fashion through the generations alters slightly along the way. A sequence of DNA within the allele repeats itself (stutters) each time it gets passed down. When the string of repeats exceeds a certain length, the allele begins to malfunction — fails to properly instruct for the amino acids that will build a needed protein — and disease results. The age at onset of disease and
the speed of decline correlate positively with the number of stutters. Huntington’s disease appears when there are more than 35 repeats but not when there are fewer than 35 repeats. Importantly, there are rare, unexplained exceptions.

**Fragile X syndrome**, the most commonly inherited form of mental retardation, is another disorder that occurs when a string of repeats in a gene lengthens. As with Huntington’s, Fragile X appears when there is a high number of base repeats (above 200) in the relevant gene. There appears to be only a modest relationship between the number of repeats above 200 and the severity of the disease.

There’s a second twist to the inheritance pattern of Fragile X. The disorder is what is known as an X-linked disorder or trait. A gene with the disease-causing alleles appears on the X chromosome that, along with its counterpart the Y chromosome, defines gender. Boys (XY) are more frequently and severely affected by Fragile X because if they have a problematic allele on their X chromosome, they do not have a second X with a normal allele to compensate for the deficiency, the way that girls (XX) do.

The bottom line is that even for a single-locus disorder, inheriting a disease-related allele does not by itself foretell the presence of disease and the severity of symptoms. Once again, genotype may not always predict phenotype.

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**Polygenic disorders: complexity multiplied**

Some mental disorders have no conspicuous genetic component; the loss of memory that we call amnesia is typically caused by a hit to the head, not a genetic problem. And as we emphasized earlier, most genetic disorders do not result from alleles at a single locus. PKU, Huntington’s, and Fragile X are exceptions to the rule.

The vast majority of mental disorders are believed to be polygenic: health problems occur when disease-related alleles are inherited for many different genes. Most mental disorders also are multifactorial, which means that multiple environmental and genetic factors are operating in an intricate, epigenetic fashion to upset the stable development and functioning of cells. (The adjective “complex” is often used in the same sense as “multifactorial.”)

Earlier in this chapter, we pointed out that with most single-gene disorders, a disease-related allele sometimes, but not...
always, leads to the disorder and sometimes, but not always, leads to either a mild or severe form of the disorder. This qualifying statement applies to alleles involved in polygenic disorders, too. Each of the many potentially problematic alleles sometimes, but not always, contributes to triggering a disorder and sometimes, but not always, contributes to a mild or severe form of the disorder.

A polygenic disorder results only when all of the pertinent genetic and environmental factors are in place, and the extent of disorder depends on when those factors occur and how they affect each other. The difficulty of predicting phenotype from genotype is compounded exponentially.

Schizophrenia, a polygenic disorder

Schizophrenia is an example of a polygenic mental disorder with an ambiguous genotype-phenotype relationship. It is a common form of mental illness compared to PKU and Huntington's, affecting about 1 percent of the general population. About half of all cases manifest themselves in adolescence or early adulthood.

Schizophrenia stems from incoordination of brain function. It is as though circuits inside the brain get crossed. The brain loses its ability to process thoughts, words, and emotions as it normally would. Affected persons become confused, paranoid, and/or delusional. They may believe spies are following them or that aliens are beaming them messages. They can become apathetic and emotionally stunted, which causes them to isolate themselves from other people and to abandon cleanliness or other social norms. People affected by an episode of schizophrenia often make no sense to others and can be impossible to reason with. They often become social outcasts. Many of the homeless suffer from this disorder.

With some people the symptoms of schizophrenia appear gradually. With others the symptoms show up in a sudden, dramatic change of behavior. Some people experience schizophrenic symptoms only occasionally, while others are chronically affected. Like many chronic diseases, schizophrenia is not curable, though medicine and behavior therapy can often control some symptoms. In some cases — not predictably — improvement and virtually full recovery occur. Symptoms often decline with age.

For a long time schizophrenia was believed to be the result of faulty parenting, the victim's weak personality, or God's punishment. But beginning in the 1960s, researchers conducting family, twin, and adoption studies recognized that relatives of affected persons are much more likely to themselves become schizophrenic, compared to people in the general population. Indeed, there is a ten-fold increase in risk for persons who have siblings with the disease. This implies that schizophrenia has a familial, perhaps
hereditary component. That research did not lead to a cure for schizophrenia, but it did provide great relief to parents and patients who had previously shouldered the blame for the disease.

Molecular scientists have put a great deal of effort into finding the  

**susceptibility genes** for schizophrenia. A susceptibility gene is one for which certain alleles make you susceptible to — at higher risk for — a disorder, while other alleles make you less liable to have the disorder. A disorder will appear in those instances where a particular allele appears in conjunction with problematic alleles at other loci plus environmental triggers. (“Susceptibility” as an adjective also is used to describe genes that affect traits not associated with disorder, such as a “susceptibility gene” for musicality.)

Studies on schizophrenia have “implicated” various genes and chromosomal regions, but they have produced only tentative results that remain unconfirmed despite replication studies that have been attempted. The failure to pin down schizophrenia susceptibility genes is frustrating, but it does not mean that such genes do not exist. Rather, it underscores the complexity of the disease. It serves as evidence that the disease is genetically heterogeneous: multiple genetic factors provide different pathways to the same disease.

It is important to note here that the vast majority of people who have first-degree relatives with schizophrenia do not end up with the disease themselves. Something besides genes is at play, but it is not clear what that is. So another question is, what environmental factors interact with susceptibility genes to launch the onset of schizophrenia?

Researchers are exploring various causal theories. Viral infections that alter brain chemistry are suspected to play a role in some, but perhaps not all, instances of this disease. Head injuries are another possible factor, in some cases. So are prenatal infections such as rubella, developmental problems triggered by complications at birth, and drug abuse. In short, what we call schizophrenia may have many different causes and is probably several distinct diseases. The search for genetic components to schizophrenia is merely one track in the manifold investigations into this tragic and disabling form of mental disorder.

A significant percentage of the homeless in the U.S. today suffer from schizophrenia or some other mental disorder. It is not yet known which environmental factors interact with genetics to cause these mental disorders to emerge.
Bipolar disorder, also polygenic

Like schizophrenia, bipolar disorder is a polygenic mental disorder with no clear genotype-phenotype relationship. Bipolar, also known as manic-depressive illness, causes extreme swings in mood.

In a depressed state, an affected person is overwhelmingly sad, disinterested in life, indecisive in the extreme, and unable to sleep or, alternatively, unable to stay alert. The person may feel worthless and be filled with despair, leading to suicidal impulses. It is estimated that 15 percent to 20 percent of patients suffering from bipolar disorder kill themselves, even though many are on medication.

In the manic state of bipolar disorder, the same person is highly elated and may also be extremely talkative, distractable, hypersexual, irresponsibly extravagant financially, and unable or unwilling to sleep. The person may feel extremely self-important and be willing to take extraordinary and dangerous risks.

For the person with bipolar disorder, extreme moods alternate with periods of more stable emotions. The mood swings
may occur months or weeks apart, or they may cycle rapidly. The frequency of these mood swings tends to increase over time.

About one in every 100 persons has severe bipolar, and another one in 100 has a milder form of the disease. It occurs equally often in men and women and has its onset primarily in adulthood, though researchers believe it may be underdiagnosed in adolescents. Bipolar disorder is treated with medication and counseling, but these treatments are not effective in all cases nor to the same degree. Each physician has to experiment with treatments until one is found that works.

From this description of bipolar disorder, it should be apparent that its phenotype varies in each affected person. This is because the pathway from cause to disease varies in each person. Systematic studies of families, twins, and adoptees show that the risk of having bipolar disorder is far higher for persons who have close relatives with the disorder, compared to members of the general population.

As has been the case for schizophrenia, finding the specific genes involved in bipolar disorder has proven to be difficult. Later investigations (called replications) have produced lower lod scores for the same genes, suggesting that perhaps they are not so relevant after all. A recent meta-analysis of genome scan studies could find no statistical significance for any nominated site. One reasonable conclusion is that no one gene has such a significant effect that it can be revealed through linkage analysis. Thus, the search continues both for susceptibility genes for mental disorders and also for better methods of finding them.

Research challenges

There are no recognized laboratory tests for schizophrenia or bipolar disorder to help a physician confirm or disconfirm a diagnosis. Researchers know less about the etiology of these disorders (the pathways from cause to effect) than they do about the etiology of non-psychological diseases such as the various forms of cancer and diabetes. The same relative scarcity of knowledge also holds for other mental disorders such as anxiety disorder, post-traumatic stress disorder, eating disorders, and phobias. The etiology of Alzheimer’s is relatively better understood, but not well enough yet to provide for adequate treatments.

Genetic research will help fill in the blanks, and here’s how. As each susceptibility gene of large or small effect is identified, lab techniques can be used to entice the gene to express itself and

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Many studies have sought to identify the susceptibility genes for bipolar (the genes that play some role in the disease), but so far none has been confirmed. Finding them may be difficult if there are many genes, each of small effect.
reveal the amino acids for which it codes and the proteins that result. Through a variety of techniques, researchers can then figure out what the proteins do when they are functioning properly and what happens when they malfunction. Following this trail for each gene, researchers hope to put together a better picture of what happens inside the body to cause the paranoia of schizophrenia, the mood swings of bipolar disorder, and the memory loss of Alzheimer’s. Researchers are also attempting to discover more about the mostly unknown factors that regulate variability in gene expression. With such knowledge could come medicines that substitute for proteins the body needs, but is not able to produce properly itself or produces insufficiently due to problems in genetic coding.

The environmental part of the story may be neglected through this approach, but that is mainly because researchers have not yet found a good way to isolate and study each contributing environmental factor the way a gene can be isolated and studied. The complex interplay that occurs between biological processes and environments also gets neglected, though it is argued that approaching mental disorders through individual genes — as piecemeal and artificial as that may be — is a pragmatic and doable way to get started on this difficult puzzle.

**Lamar’s dilemma**

Despite the considerable effort being expended in behavioral genetic research, results so far offer little practical help to the patient who already has a mental disorder. Very little can be done for Adele, who already suffers from Alzheimer’s, nor for Lamar, who worries that he himself may someday be afflicted with this disease.

Alzheimer’s affects about 4 million Americans. That number is growing because people are living longer and the disease appears late in life. The biggest risk factor for expression of the disease is aging. It is estimated that perhaps as many as 10 percent of all people age 65 and older have the disease and up to 50 percent of all people age 85 and older. People with relatives affected by Alzheimer’s are at somewhat higher risk.
themselves for acquiring the disease.

The form of Alzheimer’s that has a late onset is what afflicts former U.S. President Ronald Reagan. It is a complex disorder, with many genes contributing. One gene identified as a contributing factor sits on Chromosome 19 and is called apoE (for apolipoprotein class E). Although the details remain unclear, researchers believe that the protein associated with this gene repairs connections between cells in the brain. This suggests that the problems of Alzheimer’s occur when these repairs are no longer made properly.

ApoE appears in three different alleles called apoE2, apoE3, and apoE4. People who inherit one copy of apoE4 (about a quarter of the population) have about four times the risk of developing Alzheimer’s compared to the general population. People who inherit two copies of apoE4, one from each parent (about 2 percent of the population) are at a ten-fold increase in risk. The risk declines for people with apoE3 alleles, and it declines even more for people with apoE2 alleles.

About 5 percent of Americans with Alzheimer’s have the rare early-onset varieties that strike people before age 65. This is the form of the disease that has affected Lamar’s mother, Adele. Three different loci have been implicated in early Alzheimer’s, and they are located on Chromosomes 1, 14, and 21. It is a dominant, single-locus disorder, which means that just one copy of a disease-related allele at any one of these three loci is enough to trigger the disease.

A diagnosis of Alzheimer’s, both late-onset and early-onset, rests on a variety of factors, such as tests of cognitive functioning and mood (to gauge symptoms), blood and urine tests (to rule out other health problems), and brain scans (to rule out strokes). As yet there is no cure for Alzheimer’s, although there are drugs that can delay the problems for some people.

Lamar’s mother, with early-onset Alzheimer’s, has obviously inherited one of the alleles associated with the disease. Recall that each person has a pair of alleles for every gene and passes only one
of them down to each child. Lamar may have inherited the problem allele from his mother, in which case he has inherited the disease, or he may have inherited a benign allele from her, in which case he will escape the early onset form of the disease. (He would still share the general population’s risk for the late onset form.)

Lamar could get a genetic test to find out whether he has inherited an allele associated with early-onset Alzheimer’s. If the test shows he is free from such alleles, perhaps his fiancée Marta will reconsider marriage and life will be back to usual.

On the other hand, if the test shows he has an early-onset Alzheimer’s allele, then Lamar has brought upon himself foreknowledge of a sorry fate. Because early-onset Alzheimer’s is a single-gene, dominant disorder, Lamar will most likely succumb to the slow destruction of his mind. How would such information affect his life in the meantime? Probably not well, based on reports in the medical literature on people who have obtained this knowledge.

Lamar may or may not want to know what his future holds, but at least he can choose whether or not to find out. That choice is not available to people concerned about their risks for the predominant forms of Alzheimer’s. Because those forms of the disease are polygenic, the presence of apoE4 or any other allele associated with the disease would only indicate level of risks, not certain diagnosis. No professional medical society recommends screening for the apoE4 allele.

But, as Lamar probably realizes, there is little to be gained from getting tested for any form of Alzheimer’s so long as no cure is known and treatment is palliative at best. In fact, there is much to be risked. Suppose, for example, that Lamar’s employer obtains access to his medical records and learns he has an early-onset Alzheimer allele. The employer could misunderstand the information and presume Lamar is already diseased. Lamar could find himself moved to a position of less responsibility, cut off from promotion. The employer might even be tempted to fire Lamar out of fears that insurance premiums will climb if Lamar stays. This would all be quite unfair for Lamar since he may have left twenty or more years of healthful living.

Lamar’s fiancée, of course, did not even wait for a test before jumping to conclusions and abandoning him. So perhaps Lamar has been spared marriage to someone so flighty. There’s little else positive to see about his situation. But who knows? Before the disease appears in Lamar — if it does — researchers may have found the cure. They may have discovered the environmental factors Lamar should avoid to delay onset of the disease. They may have figured out how to synthesize the proteins his body needs in order to compensate for those his body inadequately produces. They may even know how to repair or replace unwanted alleles through gene therapy.
Normal and abnormal traits

There are opposing ways to look at mental disorder. One view is that they are all-or-none states, like pregnancy or measles. The other view is that disorders represent the extreme end of a continuum ranging from healthy to unhealthy or, to put it in psychological terms, from the normal to the pathological. These competing possibilities lead to such questions as whether the sad or introverted person differs in kind or degree from the depressed person, whether or not someone with an exuberant personality is just a few shades away from being uncontrollably manic, and whether absentmindedness is a preliminary form of dementia.

If a disorder is on a continuum with “order,” then the location of the dividing line becomes important. Otherwise, treatment for disorder could someday extend into treatment for normal conditions.

One way to distinguish mental disorder from normal mental functioning is to say that a disorder is one that has a detrimental effect on a person’s ability to get along in society. But sometimes that’s hard to say. Vincent Van Gogh suffered greatly from severe mental problems, yet he was one of the greatest artists of the 19th century. Many have pointed to a putative link between creative genius and mental disorder. Some researchers say that a feature common to both is greater emotional range. If this is the case, then the quest to eliminate mental disorder could have the unintended effect of eliminating positive traits as well. For a mental disorder such as Alzheimer’s, it is hard to imagine what the related positive trait might be, but someday scientists may prove that it is simply the extreme opposite of some beneficial protein processes rather than a unique aberration.

Notes
3 See for example Williams, H. J. et al (2003), disconfirming the association between the PRODH gene on Chromosome 22 and schizophrenia. See also the vague conclusion of the abstract for a genome scan meta-analysis by Lewis, C. M. et al (2003), p. 34: “The results suggest that some or all of [more than a dozen chromosomal] regions contain loci that increase susceptibility to schizophrenia in diverse populations.”
RESOURCES FOR CHAPTER 5


