After decades of research, genetics in psychiatry may finally be coming of age. Genetic models now exist that are generating rapid and significant progress in the quest to explain the role of genes in mental illnesses. The answers are not simple and the questions remain numerous and complex, but the results are exciting and have the potential to transform the practice of psychiatry and psychopharmacology.

Here we discuss the new paradigm for genes and psychiatry that has recently emerged. That paradigm conceptualizes genes not so much as direct causes of mental illness but as direct causes of subtle molecular abnormalities that create risk for mental illness. Genes may thus act by “biasing” an individual’s brain circuits toward inefficient information processing and possible breakdown into psychiatric symptoms under certain environmental circumstances.

Soon the modern psychopharmacologist in clinical practice may have tools to assess the risk of patients and their family members for various psychiatric disorders, the risk of suffering specific side effects of various drug treatments, and the likelihood that specific drugs will act effectively on their symptoms. In the future, a psychopharmacologist may even be able to investigate mental illness with information from the DNA of their patients, much as a crime scene investigator (CSI) already does for solving a mystery. Therefore, understanding the state of the art for genes and psychiatry can position psychopharmacologists to become early “CNS-Is” (“central nervous system investigators”) who, as the results of research pour into clinical practice, are able to utilize data from genetic analysis of their patients’ DNA.
Genes and psychiatry: the classic theory

Not too many years ago, researchers were looking for the single genetic abnormality thought to cause a specific psychiatric disorder. This model has proven successful in defining other disorders, such as Huntington's disease (Figure 6-1) and cystic fibrosis. Why not, therefore, an abnormal inherited gene as the cause of schizophrenia or depression (Figure 6-2)? Decades of research and new scientific developments now make that paradigm look overly simplistic.

Why have genes for mental illnesses been so hard to find? The answer is that genes do not encode mental illnesses (Figure 6-2). This is not so hard to believe, since mental illnesses are defined as mixtures of symptoms packaged into syndromes. These syndromes are consensus statements from committees writing the nosologies of psychiatric disorders for the Diagnostic and Statistical Manual of Mental Disorders (DSM) of the American Psychiatric Association and the International Classification of Diseases (ICD). Thus, mental illnesses are not diseases.

When you think about it, the genome obviously did not evolve out of the DSM; rather, the writers of the DSM evolved out of the genome! It is no wonder that committees of experts have so far failed to define the symptoms and syndromes that have evolved out of numerous genes, since in many ways they have been working backwards – that is, from the syndrome to the gene. We are just in the earliest days of working in the other direction – namely, from the genome to the mental illness. Thus, although the DSM and ICD nosologies are useful in communicating about the symptoms of mental illness syndromes, modern genetics in many ways has freed clinicians from the tyranny of nosology in order to focus on symptoms, as we will see below in this chapter and throughout the rest of this book.
The next stage in trying to unravel the contribution of genes to mental illness was to look for genes for personality, temperament, behaviors or symptoms of a mental illness but not for a mental illness per se (Figure 6-3). However, no such genes have been found. Why have genes for personality and behaviors also been so hard to find? The answer is that genes also do not encode personality or behavior (Figure 6-3).

**Genes and psychiatry: the new paradigm**

Well, if genes encode neither mental illness nor behavior, what do they encode? The answer is that genes encode proteins, and that in mental illnesses, individual genes code for a subtle molecular abnormality caused by a genetically altered protein (Figure 6-4). This could include proteins that regulate neurodevelopment, such as neuronal selection, migration, differentiation, or synaptogenesis. It could also include proteins ranging from enzymes to transporters to signal transduction molecules, synaptic plasticity machinery, axonal and dendritic protein transport machinery, and many more (Figure 6-6).

It is a fact that many of the most common and puzzling illnesses of the twenty-first century are no longer thought to be caused by a huge biological contribution from
Symptom Endophenotype Model:
Genes Cause Psychiatric Symptoms, Behaviors, Personalities, and Temperaments

FIGURE 6-3 Symptom endophenotype model. Another theory, the symptom endophenotype model, posits that, rather than genes causing mental illness, genes instead cause individual symptoms, behaviors, personalities, or temperaments. Thus, an abnormal gene encoding for a symptom, behavior, or trait would cause neuronal malfunction leading to that symptom, behavior, or trait. However, no genes for personality or behavior have been identified, and there is no longer any expectation that such a discovery might be made – as indicated by the red cross-out sign over this theory.

a single gene (Figure 6-1). No such abnormality is sufficient to cause any known mental illness.

So what is the pathway from gene to mental illness (Figure 6-5 and 6-6)? The hypothesis is that mental illnesses are caused not by a single gene nor by a single subtle genetic abnormality but by multiple small contributions from several genes, all interacting with environmental stressors. This is sometimes called “complex genetics,” for obvious reasons. It is not simple dominant or recessive genetics, but a complex set of risk factors that bias a person toward an illness but do not cause it.

This concept applies not only to mental illnesses such as schizophrenia and bipolar disorder but also to hypertension and diabetes mellitus. In this model, a person inherits risk, not illness, and there are several possible ways to combine sufficient risk with sufficient opportunity to express that risk in the environment by summing all of these factors, reaching the tipping point, and then developing the illness.
Hypothetical Gene for Subtle Molecular Abnormalities

FIGURE 6-4 Subtle molecular abnormalities. Genes do not directly encode mental illnesses, behaviors, or personalities. Instead, they encode proteins. In some cases, genes may produce genetically altered proteins that code for subtle molecular abnormalities, which in turn may be linked to the development of psychiatric symptoms. Thus, a gene may code for an abnormality in the neurodevelopmental process or in the synthesis or activity of enzymes, transporters, receptors, components of signal transduction, synaptic plasticity machinery, and other neuronal components. Each subtle molecular abnormality may convey risk for the development of mental illness rather than directly causing a mental illness.

Endophenotypes

Scientists exploring along the path from gene to mental illness have discovered a few important intermediaries that assist in unraveling the contribution of genes (Figure 6-5). Lying on this pathway between the subtle molecular abnormality encoded by a gene that
FIGURE 6-5 Hypothetical path from gene to behavior. On the hypothetical path from gene to behavior lie endophenotypes, or "intermediate phenotypes," which are measurable intermediaries more closely linked to the gene than is the disease. Abnormal cortical activity in response to stimuli (abnormal information processing) is an example of a biological endophenotype. A single symptom associated with a mental illness is an example of a symptom endophenotype. In the path from gene to mental illness, a genotype may code for a subtle molecular abnormality that is closely linked to a biological endophenotype (such as abnormal information processing in specific neuronal circuits), which, in turn, may be linked to a symptom or behavior (symptom endophenotype) associated with a mental illness.

Contributes risk for a mental illness and the mental illness itself are intermediaries called "endophenotypes" (Figures 6-5 and 6-6). They are also sometimes called "intermediate phenotypes."

If the illness is the phenotype, lying at the end of the path, then there are two classes of intermediate phenotypes, called biological endophenotypes and symptom endophenotypes,
FIGURE 6-6 Hypothetical path from genes to mental illness. This figure depicts the hypothetical path from genes via molecules, circuits, and information processing to symptoms, syndromes, and mental illnesses. On the far left, the example of risk gene 1 leads to altered enzyme activity for monoamine degradation, while in the center, risk gene 2 leads to altered synaptic plasticity machinery. Both of these molecular abnormalities in this example affect the same circuit (circuit A). If only one of the genes is abnormal, the circuit may be able to compensate and prevent symptoms despite inefficient information processing. However, because both genes have caused molecular abnormalities in circuit A, this circuit can no longer compensate, and a symptom is produced (in this example, executive dysfunction). On the far right, risk gene 3 causes altered development in the prefrontal cortex, preventing adequate activation of a second circuit (circuit B) and thus producing a symptom (delusions). Multiple malfunctioning circuits expressed as multiple biological endophenotypes can cause the expression of multiple symptoms that, taken together, constitute a formally defined syndrome such as schizophrenia.
lying along the path (Figure 6-5). Both are thus intermediates between the gene and the disease and are measurable, but not always by the unaided eye of the clinician. Importantly, endophenotypes are inherited with and closely linked to the disease. They are often more precisely and reproducibly measurable than are the illnesses themselves, since each psychiatric diagnosis probably describes many different illnesses or at least many different biological routes to the same illness. Reproducibly measuring a biological endophenotype can thus reduce variability and allow scientists to link the gene to the biological endophenotype more clearly than linking the gene to the DSM illness, also known as the phenotype itself.

**Biological endophenotypes** are measurable biological phenomena and can range from the electrophysiological response to startle to the neuroimaging response to information processing, as well as many more. Throughout this text, we will frequently refer to the biological endophenotype of activation of brain circuits. These are now often measured by functional magnetic resonance imaging (fMRI) as a sign of information processing in specifically localized brain circuits, often in the prefrontal cortex.

**Symptom endophenotypes**, on the other hand, are single symptoms associated with a mental illness and usually one of the DSM criteria for that illness. Thus, guilt and insomnia are symptom endophenotypes, but the diagnosis of major depressive disorder is not; the symptoms of hallucinations and executive dysfunction are symptom endophenotypes, but the diagnosis of schizophrenia is not. Behaviors can also be more than just the symptom endophenotype of a mental illness and can range from how well you calculate something in your head, to how frightened you are of a scary face, to your temperament – that is, your heritable personality pattern present early in life and persisting throughout life, such as novelty seeking, harm avoidance, conscientiousness, etc.

Behaviors are obviously difficult to define because they have many complex functional interactions and emergent phenomena, but they are nevertheless often simpler to define than mental illnesses themselves, which include many different abnormal behaviors, and not the exact same abnormal behaviors in every patient with the same illness, but just several from a number of possibilities off the same diagnostic list. This variability makes it just too tough to link a subtle gene effect to a complex and multiply defined mental illness.

**Traveling the hypothetical path from gene to mental illness**

The hypothetical path from gene to mental illness goes from the gene via molecules, circuits, and information processing (a biological endophenotype), to symptom endophenotypes (a single symptom of a mental illness), to the full syndrome of symptoms of a mental illness (Figure 6-6). In the hypothetical example shown in Figure 6-6, two risk genes – one for altered enzyme activity for monoamine degradation and another for altered synaptic plasticity – conspire to bias the same circuit, “A,” toward inefficient information processing. This hypothetically results in the cognitive symptom of executive dysfunction. In this case, the biological endophenotype is inefficiency of information processing in circuit A, and the symptom endophenotype is executive dysfunction. A hypothetical third risk gene – one that regulates a protein critical for prefrontal cortex neurodevelopment – acts alone to simultaneously bias circuit “B” toward breakdown of its information processing with the resulting symptom of delusions (Figure 6-6). The biological endophenotype here is loss of adequate information processing in circuit B. The symptom endophenotype is the formation of delusions. Putting these together, the patient hypothetically develops schizophrenia due to the combination of symptoms resulting from multiple abnormal circuits.
Thus, Figure 6-6 summarizes the contemporary model for how genes are hypotheti-
cally linked to mental illnesses along a pathway from gene through subtle molecular abnor-
malities, to biological endophenotypes, to symptom endophenotypes, and then to a set
of symptoms constituting a syndrome known as a mental illness. It should be apparent
from Figure 6-6 that anything on this pathway lying closer to the gene should be more
readily linked to that gene. That is why genes are closely linked to the subtle molecular
abnormalities they encode but only partially linked to the biological endophenotypes these
genes cause and only loosely linked to symptoms and illnesses associated with these bio-
logical endophenotypes. Exact quantitative methods are emerging to measure the presence
of subtle genetic abnormalities, to know what molecular abnormality they encode, and to
see where they cause abnormal information processing in the brain (Figure 6-6), whereas
measurement of symptoms and syndromes tends to be more qualitative and descriptive,
adding to the loose nature of the linkage between genes and mental illness.

What is complicated here is that because of the loose nature of this linkage, not
everyone with a subtle molecular abnormality that causes abnormal information processing
in a specific circuit has a symptom, but everyone with a symptom is presumed to have,
somewhere, abnormal information processing caused by a subtle molecular abnormality.
Furthermore, the same inefficient information processing that causes a symptom can be
cased by a whole variety of subtle molecular abnormalities working alone or along with
additional subtle molecular abnormalities.

One could reasonably ask why the inherited subtle molecular abnormalities are not
more “penetrant" at the behavioral level. That is, why do some people with the same subtle
molecular abnormalities and the same abnormal biological endophenotypes of inefficient
information processing in the same circuits have a symptom, or abnormal behavior, whereas
others do not? A technical way to ask this is why, if the gene penetrates reliably to its molec-
ular abnormality and its molecular abnormality penetrates reliably to inefficient information
processing, does that gene not as reliably penetrate to abnormal behavior or a symptom?

The answers are simple. First, genes exert variable effects throughout life; second, no
one has just one gene; and finally, it depends on whether you have healthy compensatory
backup systems for your subtle molecular abnormality or if you have additional genetic
biases, additional molecular abnormalities, and additional independent causes of inefficient
information processing in that same circuit.

For example, if someone expresses an abnormal form of a gene for neurodevelopment
after the brain has already developed, it might not have any clinical consequence. However,
if someone else in the family expresses that same abnormal gene within a critical window
of time, it could have a much more profound effect. Also, there are multiple copies of each
gene and multiple genes that may have complementary or redundant effects, so that it may
be possible to have an abnormal gene in the presence of other normal genes that render
the abnormality clinically silent, whereas that same genetic abnormality in the presence of
certain other critical abnormalities could lead to manifest malfunctioning of brain circuits.

Stress diathesis hypothesis

Adding to the complexity of “complex genetics” is the observation that genes alone are
not necessarily enough to cause a mental illness. Something else generally has to occur
from the environment to make the inheritance of silent risk become manifest as illness.
That “something else” is often known as “stress.” Environmental stressors are often life
events, such as abusive childhood experiences, difficult adult experiences such as divorce or
Normal Functioning of a Circuit:
Normal Activation Under Stress

Development of psychiatric symptoms is often the function of both genetic and environmental influences; this is known as the stress-diathesis model. Environmental stressors—such as childhood abuse, divorce, viruses, or toxins—can increase the risk, or diathesis, of developing a mental illness. However, individuals with a normal genome and thus normal circuits may experience only normal activation of circuits in response to stressful events; that is, they have a normal biological endophenotype. Such individuals would not express a mental illness, exhibiting instead a normal phenotype with no adverse behavioral symptoms.

Individuals with a risk gene for a mental illness, however, will react differently to a life stressor, but you might never know it (Figure 6-8). That is, the same stressor may cause no adverse behavioral symptoms and thus there is a “normal” phenotype (Figure 6-8) just as shown previously for the genetically and mentally healthy individual with a normal genome (Figure 6-7). However, if you had the ability to measure the effect the stressor
Genetically Biased Circuit but No Symptoms: able to compensate for genetically inefficient information processing by overactivation

FIGURE 6-8 Genetically biased circuit but no symptoms. Environmental stress coupled with a risk gene for mental illness may lead to inefficient information processing of the “biased” circuit; however, this does not necessarily mean that behavioral symptoms will ensue. Genetically inefficient information processing may be behaviorally “silent” if it is compensated by overactivation via backup systems. In this case, the individual may still have a normal behavioral phenotype despite having an abnormal biological endophenotype. Thus, abnormal circuit activation may be detectable with functional brain scanning, but clinical interview would reveal no psychiatric symptom.

has on information processing of the circuit in the individual with the subtle molecular abnormality, you would see that there is overactivation of that circuit (Figure 6-8). Luckily in this individual, there are compensatory backup systems in place and no other critical genetic flaws, so that the circuit is behaviorally silent (Figure 6-8). Technically speaking, the abnormal biological endophenotype has a normal behavioral phenotype.

Now comes an individual with multiple genetic risk factors and with multiple life stressors who is reaching the tipping point, so that the circuit either underperforms or overactivates (Figure 6-9). The overactivation is the same biological endophenotype as that
Stress-Diathesis Model of Psychiatric Symptoms:

too many genetic biases combined with too many stressors results in psychiatric symptoms

FIGURE 6-9 Stress-diathesis model of psychiatric symptoms. An individual with multiple stressors and multiple genetic risks may not have sufficient backup mechanisms to compensate for inefficient information processing within a genetically "biased" circuit. The circuit may either be unsuccessfully compensated by overactivation or it may break down and not activate at all. In either case, the abnormal biological endophenotype would be associated with an abnormal behavioral phenotype and thus a psychiatric symptom. Such abnormal circuit activation would be potentially detectable with functional brain scanning, and psychiatric symptoms would be manifest on clinical interview.

FIGURE 6-10 Stress-diathesis model. Figures 6-10 through 6-13 illustrate the stress-diathesis model using the analogy of a suspension bridge. Each suspension cable is analogous to a gene, while the vehicles that pass over the bridge represent types of environmental stressors. In this figure, there are no risk genes; thus all the suspension cables are normal and the bridge is fully intact. This allows the bridge to handle both mild stressors (small car in middle panel) and severe stressors (large truck in right panel).
Stress-Diathesis Model Part 2:
one risk gene, normal function

FIGURE 6-11 Stress-diathesis model. The presence of a single risk gene can lead to a subtle molecular abnormality (shown as a single cable snapping in the left panel). However, if only a single abnormality is present, the bridge remains intact and can still handle both mild (middle panel) and severe (right panel) stress loads because the other cables compensate for the broken one.

Stress-Diathesis Model Part 3:
two risk genes, slowing of function but compensation and no breakdown

FIGURE 6-12 Stress-diathesis model. If two risk genes are present (shown as two cables snapping in the left panel), the bridge remains intact and can handle light loads (middle panel) because of compensatory actions of the other cables. The bridge can even handle heavy loads (right panel), but less efficiently and with much greater difficulty.

Stress-Diathesis Model Part 4:
multiple risk genes, slowing of function with mild stressor, but decompensation and breakdown with severe stressor

FIGURE 6-13 Stress-diathesis model. The presence of multiple risk genes and consequently multiple broken cables (left panel) puts the bridge at grave risk if any significant stressors are encountered. The bridge may remain intact in the absence of any stressors and may even accommodate light loads (middle panel), but the remaining cables may not be able to compensate for the broken ones in the event of a heavy load (left panel), causing the bridge to break and, by analogy, symptoms of a mental illness to occur.
of the individual with just one subtle molecular abnormality and no symptoms in Figure 6-8. An fMRI scan of both overactivated circuits would look the same. However, the patient in Figure 6-9 lacks successful compensatory mechanisms and has additional molecular flaws in backup systems; thus the abnormal biological endophenotype in this case is not silent but produces a psychiatric symptom, perhaps anxiety (Figure 6-9).

Figures 6-7 through 6-9 thus outline the idea of stress diathesis. The diathesis is the biological risk, whether one or many or none. The same stress with different diathesis can yield normal biological endophenotype and no symptoms (Figure 6-7), abnormal biological endophenotype and no symptoms (Figure 6-8), or abnormal biological endophenotype plus symptoms (Figure 6-9). It all depends on reaching the breaking point.

This idea of reaching the breaking point in the stress diathesis model of mental illnesses is illustrated in Figures 6-10 through 6-13, using the analogy of a suspension bridge holding up various loads. In the first panel of Figure 6-10, all the suspension cables, analogous to all the genes, are normal structures, and the bridge holds up not only itself but also a light stressor (small car load in the middle panel) as well as a severe stressor (big truck load in the right panel). In fact, the bridge is so well built that it has backup systems engineered into its design. If one cable snaps (analogous to one gene encoding a subtle molecular abnormality; Figure 6-11, first panel), the bridge does not fall down, and it can process any stressor loads (middle and right panels). The other cables may be working harder, but they are built for that extra load, so no problem (Figure 6-11).

Things begin to get problematic with two broken cables (analogous to two defective genes). The bridge does not fall down (Figure 6-12, left panel), and it can process a light stressor (middle panel) without problems; however, it begins to have problems processing a heavy stressor (right panel). Things therefore slow down and there is some difficulty with the speed and efficiency of processing the heavy load. Nevertheless, even the heavy stressor is successfully processed by the backup systems still in place (Figure 6-12).

However, when multiple cables are broken, as in Figure 6-13, there is too great a “diathesis” or risk if a heavy load is ever encountered. The backup systems keep the bridge up (Figure 6-13, left panel) and can even process a light load successfully if inefficiently (Figure 6-13, middle panel); but when a heavy load comes along and there are multiple broken cables, compensation is no longer possible. With functioning backup systems no longer in place, the breaking point is reached (Figure 6-13 right panel). The bridge falls down, the stressor load fails to be processed, and, by analogy, a mental illness occurs.

**Personality as buffer or amplifier of stress**

Even the combination of genes coding for subtle molecular abnormalities and environmental stressors is not the whole story (Figure 6-14). To add another level of complexity to the situation, the net outcome of a stressor is determined to some extent by the personality of the person experiencing that stressor, not just the genes of that person. In fact, the development of personality and temperament themselves is determined both genetically and environmentally in its own “complex genetics.” Thus, if the same stressor is “filtered” through the personality of someone with good coping skills, adaptive responses to adverse circumstances, and a healthy lifestyle, the stressor is mitigated; and the effects on the genome are so subtle that there is no decompensation of information processing in the vulnerable circuit, and no symptoms appear (thus, a normal phenotype). This is shown on the left
FIGURE 6-14 Stress and personality. In addition to genetically determined molecular abnormalities and environmental stressors, personality factors such as coping skills and lifestyle can also affect the impact of stressors on an individual's genome and thus his or her total risk of mental illness. As shown on the left, adaptive coping skills and healthy lifestyles may mitigate the effects of stressful life events on genetic risk, so that, despite a "biased" circuit, the individual still exhibits a normal phenotype (on the left). However, in an individual with poor coping skills and an unhealthy lifestyle, stressful life events may exacerbate the effects of genetic risk and render the "biased" circuit unable to compensate; such a person may therefore develop psychiatric symptoms (on the right).

Imagine, however, someone with poor coping skills, bad habits, and maladaptive responses to stress, such as arguing, drinking, or fighting, and so on. In that case, the same stressor can be amplified rather than mitigated (Figure 6-14 on the right). A stressor that would be silent in the person on the left may cause breakdown into the symptom of a mental illness on the right (Figure 6-14).
FIGURE 6-15 Subtle molecular abnormalities and schizophrenia. The "subtlety" of molecular abnormalities may vary, with some leading to psychiatric symptoms in the presence of minimal environmental stress and others requiring multiple major stressors to cause mental illness. For example, the aggregate of symptoms that make up the schizophrenia syndrome may be more biologically determined than that of other psychiatric illnesses. In this case, perhaps only minor stressors acting on very high risk circuits would be enough to activate symptoms of schizophrenia.

Degrees of genetic abnormalities and environmental stressors

Finally, some molecular abnormalities are by nature more subtle than others. This concept is shown in Figures 6-15 through 6-17. Whatever the molecular lesions in schizophrenia, they are very highly biologically determined. Thus it may be that little or no stressor is necessary for this illness to be expressed (Figure 6-15).

On the other hand, many of us may be carrying around the genes for major depression. This is one of the most common psychiatric disorders, the "common cold" of psychiatry. What determines who, among the vulnerable, will experience a major depressive episode? The idea here is that an illness such as depression is moderately biologically determined in many individuals – not enough to manifest without environmental input but vulnerable to breakdown in the presence of major stressors (Figure 6-16).
Along this continuum, there may also be conditions to which even a normal genome is vulnerable, as when an individual experiences overwhelming stress, like combat, rape, or a natural disaster. It may take someone “better than normal” – with resilience genes rather than vulnerability genes – to resist responding to such a situation with symptoms of a mental illness, such as an acute stress reaction or posttraumatic stress disorder (Figure 6-17). Thus, both stress load and genetic load interact to determine the final outcome of whether a person has no problems processing information, silent brain circuit inefficiencies, or manifest symptoms.

Summary

Genes encode proteins, not psychiatric symptoms or mental illnesses. The subtle molecular abnormalities encoded by genes do not cause mental illness but can bias brain circuits toward inefficient information processing, which may lead to mental illness under certain circumstances. The hypothetical path from gene (genotype) to mental illness (phenotype)
passes through some important intermediaries called endophenotypes, which are inherited with and closely linked to the illness. Biological endophenotypes are measurable biological phenomena such as brain imaging, whereas symptom endophenotypes are single symptoms that are components of a mental illness syndrome. The stress diathesis model integrates all this information by formulating the idea that sufficient genetic bias toward inefficient information processing combined with a stressful load from the environment that exceeds the capacity of brain circuits to process that load can result in breakdown into symptoms of a mental illness. In the future, it may be possible to measure a portfolio of critical genes to assess risk for mental illness in individual patients and their families, and this may someday help guide treatment selection as well.