Clinically Responsible Genetic Testing in Neuropsychiatric Patients: A Bridge Too Far and Too Soon

Genetic testing for neuropsychiatric disorders has been a visionary goal of psychiatrists and geneticists for many years. Its objectives include identifying risk before the onset of illness, clarifying diagnosis in difficult cases, and improving choice of treatment by identifying individuals who are more likely to respond to, or less likely to have side effects from, a given medication. Genetics offers a unique and powerful insight into the biology of the brain that should make these goals achievable in the future. Despite the genomic revolution of the past decade, however, we still lack the requisite information to create genetic tests for psychiatric risk, diagnosis, and treatment that are robust enough to use responsibly and in a valid manner in psychiatric practice. Nonetheless, scientific entrepreneurs are launching genetic testing companies that make explicit and implicit promises that are premature and currently impossible to fulfill. There is as yet no evidence that a positive or negative genetic test should be used to alter risk, diagnosis, or treatment.

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About 1% of the 3,000,000,000 base pairs in the human genome act as genes to code the synthesis of proteins, the building blocks of life. Of the 30,000 human genes, 16,000 are expressed in the brain and 6,000 are expressed only in the brain (1). Additionally, genes have gene-gene and gene-environment interactions as well as epigenetic methylation events (2) that can influence their effect on the brain. Normal human gene function is expressed in the brain as an elegant symphony of neurons firing across widespread neural circuits that underlie the motor, cognitive, and emotional expression that forms the basis of the CNS's ability to maintain the singular and rich experience of being a person.

Simple and Complex Mendelian Disorders

The gene that is abnormal in the classical Mendelian disorder of Huntington's disease was one of the first mental illness genes to be discovered. One altered copy (H) of the two chromosomal copies of the Huntington's gene (genotype H/h) causes an individual to be 100% likely to develop Huntington's disease and, on average, to transmit the illness to 50% of his or her offspring (assuming that the other parent is the usual h/h genotype). Huntington's disease and most other illnesses caused by single gene mutations are relatively rare in the population, in part because the effect of the mutation is so devastating. There are no genetic treatments available for the few unfortunate patients who have these illnesses, although dietary and other interventions can modulate the consequences of being an affected gene carrier for some disorders.

When scientists discuss complex genetic diseases, they are usually referring to common disorders with a prevalence of about 1% or more, such as diabetes, hypertension, schizophrenia, and bipolar disorder. These common disorders are not simple Mendelian disorders; rather, their complex inheritance reflects polygenic contributions as well as gene-gene and gene-environment interactions. Complex illnesses are common because they result from the combination of many small genetic changes, any one of

which causes little damage to physiological function and thus can exist in high frequency in the general population. The illness results not from an unusual powerfully expressed genetic variant but rather from a combination of several common variants, each in itself usually relatively benign, even if it is expressed as a slightly altered brain physiology in clinically unaffected relatives of patients (3). This complexity means that it is unlikely that a single genetic test, reflecting an alteration in only one of these genes, will be closely related to one of these illnesses.

Standards for Clinically Useful Tests

The validation of tests used in modern medical practice involves several statistical concepts. *Prevalence* is the percentage of afflicted individuals in the general population. Schizophrenia and bipolar I disorder each have a prevalence of about 1%, making them common disorders; diabetes has a prevalence of about 2% (4). *Sensitivity* is the probability of a test being positive in the affected group; *specificity* is the probability of a negative test result in unaffected individuals. A test is clinically useful if sensitivity, specificity, or both are very high, typically over 95% (5). For many tests, it is reasonable to emphasize positive results. *Positive predictive value* is the likelihood that a positive result on the test indicates the true presence of the disorder.

GRK3 is one gene for which genetic testing for bipolar disorder is now offered commercially. In a sample of 181 European American families in which a family member had bipolar disorder, three sets of genetic variants of *GRK3* were found to be transmitted (6). These three genetic variants were transmitted to about 10% of patients with bipolar disorder; about 3% of healthy comparison subjects had these genetic "signatures." Positive predictive value depends not only on the rates of positive tests in the disorder and control groups but also on the prevalence of the illness in the population. One scenario is the testing of individuals who might be at risk for bipolar illness, where the assumption is often made that the likelihood of bipolar disorder is about 50%—for example, alcohol-dependent men with a vague family history of bipolar disorder and dysfunctional mood swings. For 1,000 people in this population, you would expect about 500 with bipolar disorder and 500 without. For 1,000 tests in this population, there would be 50 true positives (10% of 500 bipolar patients) and 15 false positives (3% of healthy subjects), for a positive predictive value of 77% (50 true positives out of 65 [50+15] positive tests). Thus, many people with positive tests will not have bipolar disorder. Also, 450 of the bipolar patients would have false negative tests, reflecting profoundly poor sensitivity (only 10% versus the desired 95% [5]).

If the test were used to screen an entering class of 1,000 high school students to predict future bipolar disorder, then the lifetime population prevalence of bipolar disorder, about 1%, affects the positive predictive value. Of the 10 individuals who would be expected to develop bipolar disorder, only one is likely to have one of the bipolar *GRK3* variants. Thirty of those who will not develop the disorder are also likely to have the genetic variant. Therefore the test's positive predictive value is only about 3%. That value is far too low for the test to be useful, since over 90% of students with positive tests would not develop the disorder.

Commercialization of Psychiatric Genetics

The statistics cited above are not unique to *GRK3* and bipolar disorder. Similar statistics exist for genes associated with other common illnesses, such as type 2 diabetes and colon and breast cancers. Through the Internet, individuals who want to know about their genetic risk and other genomic information can order their own genotyping for some variants across the genome. Navigenics (for $2,500 and $250/year for counseling), 23andMe, and deCODEme (for about $1,000 each) all offer genome-wide scans to the general population. They generally claim that they are not in the health risk business,

but health risk genes are explicitly included in their screening panels. There are now also web sites that offer testing specifically for genes that have been associated with specific psychiatric illnesses in research studies, such as *GRK3*. Psynomics, Neuromark, Suregene, and a host of emerging new companies are offering genetic testing that explicitly targets psychiatric disease risk. Sometimes the marketing is directed to consumers, who might order the "bipolar test" and list the name of a doctor to receive the results (7). In addition to the problems described above in interpreting a positive result, the cost of $400 or more per test needs to be balanced against—in the case of *GRK3*, for example—the 90% likelihood that the test will produce a false negative result, since even in families known to have bipolar disorder, the frequency of a *GRK3* variant associated with bipolar disorder is only about 10% (6).

Proponents of these tests may offer several arguments in their defense. First, genetics is modern medicine, and it is worthwhile to start a process that will be refined as databases grow larger to include more patients, more variants, and different ethnic and racial groups, whose variants may be different. Second, patients are desperate for more thorough answers about their illnesses, and if additional information exists, it should be freely available to them. It may not be definitive, but it may add to the information provided by a clinical evaluation, which itself often seems a somewhat tarnished standard that may vary as patients or loved ones see doctor after doctor for opinions.

Responsible genetic testing in modern medicine has to take into account not only the promise but also the consequences of offering information to patients. A false negative bipolar test may reinforce an ambivalent patient's failure to take medication. Likewise, a false positive "suicide gene" test may have terrible consequences for already depressed and frightened patients by increasing their fear of harming themselves. This need for caution is not reflected in many of the Internet advertisements for gene testing, where tests are being marketed as "behavioral disorders panels." One mental health genetic test battery promises to uncover genes mediating brain signals, stress responses, and "regulation of energy balance"; the web site further claims that "knowing which gene variants you carry will help you to determine your predisposition to various disorders such as susceptibility to alcohol dependence, depression, obsessive-compulsive disorder, schizophrenia, and seasonal affective disorder, among others" (8). No specific information is disclosed about this unreferenced, seemingly inflated claim. If the tests are marketed directly to consumers, the results may be sent to clinicians who do not understand the test's meaning, or do understand it and think that it is not worthwhile (7). Quite a conundrum (and possible liability) is foisted on a physician who may well never have wanted the direct-to-consumer test ordered in the first place. Thus, this direct-to-consumer platform seems especially risky. This risk is increased when leading academic institutions add their imprimatur to this endeavor (7, 9).

Some scientists argue that genomic risk information comes with "special behavior-changing clout" (9). But this argument flies in the face of facts: In one study, for example, even identification of genetic variants that predict lung cancer in smokers did not lead many study subjects to stop smoking (10). In fact, only 36% of smokers accurately remembered their genetic test results 6 months after testing—and 45% misinterpreted the results. Few stopped smoking. Identifying a gene that predisposes to bipolar disorder does not even lead to an obvious behavioral or other ethically acceptable strategy to prevent the onset or progression of illness.

Next Steps

Authoritative statements by people who have no financial or other vested interests in genetic tests are needed to alert psychiatrists to the positive and negative aspects of new treatments and technology. It is overwhelmingly clear that neuropsychiatric genetic testing is likely to be important for our field, and it is timely to begin a process for deciding when genetic information is robust enough to justify testing specifically and when test re-

sults correctly lead to an altered course of action. Genetic research itself obviously needs to continue. Despite the current dubious value of *GRK3* in clinical genetic testing, the *GRK3* finding is among those that have produced evidence for a defect in signaling pathways in bipolar disorder. Dissecting the pathophysiology of bipolar disorder through genetic research is a critical step toward improving detection and implementing early treatment of this devastating illness. A few valid tests already exist for genetic testing-based individualized medicine for the treatment of a limited number of cancers (11) and for creating dosing algorithms for multiethnic populations in the use of warfarin, which has a narrow therapeutic range (12). Hopefully, neuropsychiatric genetics will soon have similarly valid and useful tests based on continuing important genetic research.

We must move forward with developing responsible genomic testing in psychiatry, but the current premature marketing of insensitive and confusing genetic tests is misleading to consumers and may cause human suffering and societal mistrust of what will ultimately be a valuable tool for psychiatric practice and science. Our profession and our science need unambiguously to identify commercial marketing at this time as beyond the pale of good and acceptable practice.

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