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### **Mental Illness and Addiction Genes: Answers Remain Elusive**

Fifty years after Watson and Crick discovered the structure of DNA, and three years after the draft sequence of human DNA was published, “genomics” (the study of genes and their functions) unquestionably has begun to transform medicine. But what has genomics taught us about mental disorders and addictions, which affect one in five Americans, and which current treatments are for the most part inadequate?

As with many of the most common diseases that affect humans, unraveling the genetics of mental illnesses has turned out to be an incredibly complex task. Though conditions such as bipolar disorder, schizophrenia, autism, depression, anxiety, eating disorders, and substance abuse certainly have a genetic component—studies that compare identical with fraternal twins suggest a very significant role for inherited factors—these illnesses cannot be traced to a single gene. Rather, they appear to develop from a complex interplay of inherited and non-genetic factors, both environmental and “chance.” Illnesses’ “multigenic” nature is one reason that, despite years of concerted effort and undeniable recent progress in some areas, scientists have yet to precisely identify any gene that

can be unequivocally linked to the major mental illnesses.

“In the aggregate, genes have an enormous amount to say about one’s risk for mental illness,” says Steven E. Hyman, former director of the National Institute for Mental Health and currently the provost at Harvard University. “The problem is that each gene may contribute only a small increment to one’s total risk. That makes the hunt for these genes extremely difficult.”

That’s not to say progress hasn’t been made. So-called “linkage” studies, which compare the genomes of people affected by mental illness with both unaffected and affected family members, have narrowed the search to likely target regions on chromosomes that may harbor the genes involved in individual disorders. Still, none of the genes that will ultimately be found are expected to be “causative,” meaning all those who inherit the gene will eventually develop the disease. (The genes for Huntington’s disease and cystic fibrosis, for example, are causative genes.)

Instead, genes for mental illnesses and substance abuse, as with other common disorders such as diabetes, coronary

artery disease and prostate cancer, will confer risk. As such, they are termed “susceptibility” genes, or “vulnerability” genes. An example of a susceptibility gene is APOe4, the only gene so far associated with the common, late-onset form of Alzheimer’s. Carrying the APOe4 gene increases one’s risk for Alzheimer’s, but not everyone who carries it develops the disease. Moreover, not everyone who has Alzheimer’s carries APOe4, which suggests that other factors—genetic and environmental—play a role.

Like Alzheimer’s and others, most mental diseases are the result of “multiple genetic pathways,” says Hyman. “Just as there are many ways to become a high-risk person for, say, heart disease, there are many ways to become high-risk for major depression, as one example,” he says. “That fact decreases the influence of any individual gene, further complicating the search.”

In practical terms, this means that genetic studies must be conducted on huge numbers of families with an affected relative in order to focus in on a short list of genes from among the 30,000 or so in the human genome.

### ***Underestimating the Enemy***

Wade Berrettini, a genetics specialist at the University of Pennsylvania, has been searching for the gene for bipolar disorder since the early 1980s. Inspired by a paper by genetics pioneer James Gusella describing the method Gusella and colleagues used to find the gene for Huntington’s disease, Berrettini applied the same method to his hunt for bipolar genes. Two decades later, he’s still searching.

“We seriously underestimated our foe,” says Berrettini. The genetic roots of bipolar disorder have turned out to be far more complex and elusive than those of Huntington’s, which is a classic autosomal dominant disease (i.e., if either parent carries the gene and passes it along to an offspring, the offspring will develop the disease). Berrettini has just completed a four-year collaboration with nine other medical centers in which DNA samples were collected from 700 families with at least one relative who has bipolar disorder. He predicts that at least 1,000 families—a minimum of 2,000 genomes—will be needed to get the answers he seeks.

The effort has already resulted in several “hits”: Berrettini says the teams have identified “at least 10 [chromosomal] sites around the genome where there is a high probability that susceptibility genes for bipolar disorder reside.” Each of these sites consists of roughly 10 million to 20 million base pairs, the individual linked units that are the fundamental building blocks of DNA. To pinpoint the genes within those target regions, researchers (armed with powerful computers) must sift through more than 100 million to 200 million base pairs in order to find the particular sequence that is repeated in affected people. As if that’s not difficult enough, it’s likely that each gene has several different variants—or alleles—that confer varying degrees of risk.

### ***Finding the “Needle”***

If this sounds like the proverbial “needle-in-a-haystack” search, it is. But, says George Uhl of the National Institute of Drug Abuse (NIDA), “The haystack is finite—30,000 or so genes. The problem is, it’s also a small needle, and

the needle looks a lot like the straw that's all around it.”

These high hurdles are not unique to mental illness or addiction gene searches. The experts point out that gene hunts for heart disease, diabetes, and a host of other common conditions include the same dilemmas. But, as Berrettini says, “It’s different because it’s mental illness, and we know so much less about the brain than we do about heart disease, for example.”

Collecting enough DNA samples is also a challenge that pervades genetics research. Bipolar disorder is one of the most common mental conditions, affecting about 1 percent of the population. Anorexia nervosa, which Berrettini also studies, affects about one-tenth of 1 percent of the population, making it even more critical to establish networks of researchers and “to build bridges with patient groups” to locate enough affected families and achieve the statistical power needed to make meaningful progress. In the case of autism, a patient advocacy group called Cure Autism Now has taken the lead in identifying families and collecting DNA samples; this initiative is viewed as a model strategy for speeding gene searches.

### ***“Overlap” in Addiction Genes***

As with the major mental illnesses, concrete evidence is lacking for a single gene that has a major effect on one’s vulnerability to substance abuse, says NIDA’s Uhl. Yet, while the search for addiction genes is relatively young compared to the search for bipolar genes, there has been a “remarkable convergence” of data from independent groups that point to more than a dozen

chromosomal regions that may harbor susceptibility genes, he says.

Recently, various groups of NIDA-funded researchers have identified possible gene loci for alcoholism, nicotine addiction, and “polysubstance abuse,” that is, vulnerability to various drugs of abuse. In addition, researchers studying families and unrelated individuals have identified several chromosomal regions that harbor “relatively common” gene variants that each may contribute to addiction vulnerability, Uhl says. This apparent overlap in the genomic regions of interest suggests a common genetic link that may manifest differently depending on other inherited traits or environmental factors.

The impact that environmental factors have on the development of mental illness and addiction confounds even the most thorough genetic studies. In most cases, scientists simply don’t understand how environmental factors that increase or decrease one’s risk interact with inherited tendencies.

### ***The Payoffs***

For all the unknowns, what is clear is that much can be gained from identifying these genes. First and foremost, says Hyman, finding disease genes enables a better understanding of the molecular events that cause the disorder.

Gene identification can also drive therapeutic advances, both by pointing to potential new targets for interrupting the processes that lead to disease and by using the gene to create animal models. Even though such models would be “imperfect” because it’s impossible to

precisely model psychiatric illnesses in animals, Hyman says, “Even partial animal models are important for testing and developing drugs, and we are sorely in need of new medicines for mental illnesses.”

A better understanding of the genetic underpinnings of mental illnesses also should allow scientists to unravel the timing of gene expression, which Hyman says might give clues to environmental factors that come into play at various points in development to trigger certain genes to turn “on” or “off.” This in turn could lead to intervention strategies that could potentially interrupt these triggers.

Without doubt, experts in this area say, genome-sequencing efforts have made a significant impact on the search for mental illness genes. Despite the imperfections of the draft sequence, it has provided a rough road map that researchers can refer to once they have identified regions of interest through linkage studies. Berrettini likens the situation to early explorers who were trying to discover a new land without a map to show its location. Like them, he says, “We need a good map of the world.”

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