SPEAKER NOTES

Causes of Mental Health Disorders: Genes, Environment, or Both?

Summarized by Thomas T. Thomas

The etiology of mental illness is a matter of great interest to many family members and friends of people with mental disorders. It is also a topic in the ongoing dialogue between activist consumers and family leaders. NAMI East Bay has a valuable resource on the biological side of the question: board member and family member **Isabel Zaror, PhD,** who is a researcher in cellular and molecular biology and who serves as research director in oncology protein sciences with a local pharmaceutical company. She spoke at our November 19 meeting about recent discoveries in genetics relating to brain chemistry.

ISABEL ZAROR, PHD

Zaror started with the basics of human genetics: that the nucleus of each cell in our bodies contains 23 pairs of chromosomes, one member of the pair from our fathers, the other from our mothers. These chromosomes are made of DNA, a molecule that presents a continuous sequence of four bases labeled A, C, G, and T that makes up our genes. The order of these bases in a gene is the recipe for a protein, and proteins perform all the functions needed for us to be human.

An error in the sequence, like a typo in text, may change its meaning, creating a protein whose function may be different. Such an error, or mutation, may be inherited, which means it arrived in the sperm or egg from your parents, is present in every cell in your body, and may be passed on to your children. Or the mutation may be acquired during embryonic development or later in life, which means it occurs in some but not all of your cells, may have been caused by an environmental factor or an error in DNA duplication during cell division, and will not be passed on to your children. Not all mutations change the protein that the DNA makes. Not all changes are bad, "but we notice more the ones that cause diseases," she said. "We study them more."

A mutation can be small, a single-letter change in the DNA sequence, or large, such as duplication or deletion of all or part of a chromosome. Examples of the latter include Down Syndrome, caused by a third copy of chromosome 21, or Wolf-Hirschhorn Syndrome—a condition of skull and facial deformities, stunted growth, intellectual disability, and other defects—caused by deletion of part of chromosome 4. For this discussion of mental disorders, the single-letter or "point" mutations in a gene and having duplicate copies of a gene are most important. Such a mutation can cause a nonfunctional or missing protein, and many familiar diseases are caused in this way: sickle cell anemia, cystic fibrosis, polycystic kidney disease, and hemophilia.

When a gene makes a protein, it is said to be "expressed," but obviously not every gene in the nucleus should be expressed by every cell in the body. Only in the last few years have researchers begun to learn about how genes are turned on and off, or "regulated," through the mechanism of *epigenetics*. These are modifications of the DNA that do not change its sequence. In some cases, epigenetic changes are stable and can be passed on to future generations; in others, they are dynamic, respond to environmental stimuli, and may be reversible. This is the most rapidly emerging field in genetics and it helps explain how environmental factors can affect cell function, including the brain's neurons and neural circuits.

The Human Genome Project created the first complete genome, drawn from just five individuals, whose sequencing required an international project taking many years and costing more than $3 billion.[1] This first sequence revealed that, of the genome's three billion bases, just a tiny fraction represents protein coding, using only about 20,000 genes. The rest of the DNA at first appeared to be "junk," but subsequent research has shown that most of it involves gene regulation and cell differentiation and development. Still, sequencing an entire genome requires tremendous computing power and memory to make sense of it.[2]

One of the reasons it is so hard to understand the role of genetics in psychiatric disorders is that the current diagnoses are descriptive. They deal in signs and symptoms that tend to occur together, but we don't know if they have a basis in biology. And the symptoms tend to overlap, so that many disorders do not present a unique set of symptoms but a spectrum. So, for example, we have schizo-affective disorder, which has symptoms of both schizophrenia and bipolar disorder. And some disorders appear to run in families, while others do not.

Psychiatric disorders combine complex genetic variations—not the Mendelian inheritance we studied in school, where one gene controls one trait. "Many genes are involved," Zaror said, "and each may have only a small effect, contributing in ways we don't yet understand. We will need to study the complete genomes of a large number of individuals in order to identify these genes and their combinations if we are to understand mental disorders."

Another problem is that we have inadequate cellular and animal models for these disorders. For example, we can grow a tumor in a petri dish or in a mouse, but we can't induce depression in a mouse. We can force it to live under stressful circumstances, then see how it responds through its behavior and socialization patterns, but is this really depression? We don't have biometrics for psychiatric disorders in the same way we can measure blood glucose to test people for diabetes.

New technologies are allowing researchers to scan large swaths of the human genome in thousands of individuals to reveal unexpected links to diseases. Started in 2007, the Psychiatric Genomics Consortium (PGC) has gathered more than 500 researchers at 80 institutions in 25 countries to conduct large-scale analyses of

[1] Today, through technical advances, we can sequence an individual genome in one to two weeks for about $1,000.

[2] Genomic services like 23andMe, which will examine your DNA for about $100, do not sequence the entire genome but just a complement of individual genes with the most interesting or common point mutations.

genome-wide data for psychiatric disorders. More than 170,000 individuals are being studied—and this number is growing rapidly. The effort was originally divided into five "working groups," each with its own diagnosis: autism spectrum disorders (ASD), attention deficit/hyperactivity disorder (ADHD), bipolar disorder, major depression, and schizophrenia.[3]

We know from the study of twins, families, and adoptions that many disorders are inheritable. For example, identical twins have an 81% chance of both having schizophrenia, 80% chance for autism, 75% for bipolar and ADHD, and so on. But since the concordance is not 100%, other factors than genes are clearly involved. The chances of inheritance are greatest for individuals whose parents or siblings have the disorder; less so for those whose aunts, uncles, or grandparents had it; and the chance among first cousins is comparable to the general population.

New methods that allow genome-wide association studies among thousands of people are showing that most psychiatric disorders result from many gene variants, each making only a minor contribution to the condition. For example, a study by the Schizophrenia Working Group in July 2014 among 150,000 people—37,000 with the diagnosis, 113,000 without—found 128 gene variants in 108 different distinct locations to be associated with the disorder.

One of these genes codes for a protein in the dopamine receptor—a target for drugs treating schizophrenia—but others affect glutamate neurotransmitter pathways and elements of neuronal signaling, function, plasticity, and development. Other genes are involved with the immune system, suggesting that onset of the disorder may be associated with infections and inflammation.

A study from the Bipolar Disorder Working Group sampled 50,000 people both with and without a diagnosis and discovered genes related to various ion channels in the neuron, development of the neuron and its myelin sheath, response to valproic acid, and many other functions.

Of the five major mental disorders in the PGC's original working groups, a 2013 study of more than 60,000 people worldwide found the same inherited genetic risk factors accounting for 17% to 28% of the risk for a mental disorder. The highest overlap was between schizophrenia and bipolar, moderate for either bipolar or ADHD and depression, and lowest for schizophrenia and depression. This suggests the hypothesis—which the psychiatric community is not yet ready to adopt—that these diseases may be on a spectrum.

Genes also appear to govern how susceptible a person may be to a mental disorder. An earlier study identified two gene variants, "s" and "l," that correlated individuals having a large number of stressful life events with later developing a mental disorder.

Finally, studies of mouse brains have shown that mice under stress and showing depression-like symptoms have epigenetic changes in the genes associated with neurons. And treating them with the antidepressant imipramine reversed both the symptomatic behavior and the epigenetic markers. Post-mortem studies of human brains have shown that epigenetic changes in the genes associated with

[3] More recently, the PGC has also taken on anorexia nervosa, drug abuse, obsessive/compulsive disorder and Tourette syndrome, and post-traumatic stress disorder.

brain development and communication between neurons are higher in people diagnosed with schizophrenia and bipolar disorder than in those without diagnosis.

Zaror concluded that the association between genetics and environmental factors in mental disorders is complex. It no longer makes sense to look for one gene or environmental factor as the cause of any of these disorders, because several genes, complex genetic mechanisms, and the effect of environmental risk factors are all involved. And finally, that the diagnosis of discrete and different disorders based on observed symptoms, as in the *Diagnostic and Statistical Manual,* is an artificial construct, and that a spectrum approach may be closer to the truth.

"But we have to keep an open mind," Zaror said. "We don't have all the answers, and research in this area is changing rapidly."