SPEAKER NOTES

# Mental Illness: Genes vs. Environment

*Summarized by Thomas T. Thomas*

**Isabel Zaror, PhD,** is the recently retired Executive Director at Novartis Biomedical Research in Emeryville, California, and before retirement was head of the Novartis Emeryville Protein Interatomic Center. She is also a member of NAMI East Bay's board. At our October 23 information meeting, she reviewed the basics of genetics and explored the current scientific evidence for how genes play a role in mental illness. She also discussed how the environment influences the onset of these diseases. Dr. Zaror presented to us ten years ago, and it was interesting to hear how much—or little—things have changed.

The human body contains about twenty trillion cells, each containing 23 pairs of chromosomes. Each of these chromosomes contains genes—sequences of the four DNA bases—that are either the recipe for one or more proteins that our body needs, or instructions for how to express them in the different types of cells.

Changes in the genes or chromosomes can cause diseases. For instance, duplication of chromosome 21 is related to Down Syndrome, and deletions in chromosomes are related to many neurodevelopmental diseases. Mutations—changes in the coding of a gene—can change the protein, sometimes resulting in a nonfunctional protein with detrimental effects. For example, a mutation in the gene for the protein hemoglobin on chromosome 11 results in sickle cell disease. Mutations arising in the germline—the eggs and sperm—are inheritable.

Epigenetics is a new field of study relating to changes in gene expression without changing the underlying DNA sequence. This is the mechanism by which cells activate or inhibit specific genes in different types of cells. But epigenetics also captures the effect of environmental factors and can be reversed.

The Human Genome Project (HGP) reported the sequencing of all three billion base pairs in the genome by studying five individuals representing a mix of sexes and racial identities. The project took 13 years to obtain this sequence, which today can be done for an individual in less than a day for less than $1,000. The HGP and subsequent sequencing efforts have shown that the genome is 99.9% the same for all people. Also, almost half of our human proteins share similarities with those of other organisms.

Many heritable diseases—like familial hypercholesterolemia, polycystic kidney disease, neurofibromatosis type I, sickle cell disease, cystic fibrosis, and many more—result from mutation in a single gene. But psychiatric disorders are a totally different ball game.

It has been difficult to understand the role of genes in psychiatric disorders for several reasons. First, the diagnosis is based on reported symptoms, and it is not clear that all of them are biologically valid. We also have no adequate *in vitro* cellular and *in vivo* animal models to replicate these conditions: you can't sample one brain cell or ask a mouse what it's feeling. And we still don't understand the environmental role in and the contribution of epigenetics to psychiatric disorders. Some disorders

display high heritability, but often more than one gene—and frequently many genes—contribute to similar traits. To study the genetic nature of these disorders, we need to sequence the genomes of many individuals—perhaps hundreds of thousands—and then compare them to "normal" controls to find the differences.

One of the drivers behind the effort to find genes associated with mental illness is the Psychiatric Genomics Consortium (PGC), which conducts mega-analyses of genome-wide genetic data for psychiatric disorders. It began in 2007 and includes more than 800 investigators from 36 countries studying close to 400,000 individuals. The PGC initially focused on autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), bipolar disorder (BP), major depression disorder (MDD), and schizophrenia (SCZ). It now includes large studies on anorexia nervosa, drug use, obsessive-compulsive disorder (OCD)/Tourette's syndrome, and post-traumatic stress disorder (PTSD). Original PGC studies focused on single-nucleotide polymorphisms (mutation of a single base pair in a gene, or SNP), but their work has now expanded to include copy number variations and uncommon or rare genetic variations. The results of all their studies are publicly available.

Studies of identical twins, families, and adoptions provide heritability estimates for major psychiatric disorders. Based on studies of identical twins alone, the heritability for SCZ is 81%; ASD, 80%; ADHD, 75%; BP, 75%; and MDD, 37%. Because the concordance even for identical twins is not 100%, clearly there are other factors besides genes.

Schizophrenia affects about one in a hundred people, and symptoms usually first appear between the ages of 16 and 30. Most drugs treat only the overt symptoms of psychosis, such as imaginary voices, and the drugs have serious side effects. (Older drugs blocked dopamine receptors, but the FDA recently approved an M1/M4 muscarinic agonist called Cobenfy.) Heritability studies based on small sets of families could not demonstrate that only one gene or just a few genes were responsible for schizophrenia.

The most recent genome-wide association study (GWAS) of 77,000 individuals against 240,000 controls identified 287 genomic loci and identified 120 genes as likely associated with schizophrenia. So, many of the gene variants likely have a small effect and make only a minor contribution to the risk of schizophrenia. The common variants are concentrated in genes expressed in the excitatory and inhibitory neurons in the central nervous system. One of these genes encodes for the dopamine receptor DRD2. Other genes are implicated in glutamate neurotransmitter pathways. And still others don't have a clear explanation yet: for example, several are associated with the immune system.

Bipolar disorder has a similarly high heritability. A GWAS of 41,917 individuals against 371,549 controls of European ancestry identified variants in 741 genes. Many of these genes are associated with synaptic signaling pathways, especially in the prefrontal cortex, which governs problem solving and decision making, and the hippocampus, which is associated with learning and memory. As with schizophrenia, many genes make only a small contribution to the disorder.

Similar genome-wide studies show that many different gene loci are associated with autism spectrum disorder, ADHD, and major depression.

Epigenetics involves the addition of chemicals—mostly the methyl group ($CH_3$)—to the genome to inhibit gene expression without changing the DNA

sequence. Early life adversities and stressors, either in the womb or postnatal, have been linked to mental health outcomes later in life and increasing risk of psychiatric disorders. Interaction between genetic and non-genetic factors is likely, meaning that certain exposures would only be of consequence with a given genetic makeup.

Based on PGC published studies, the five major mental disorders often share the same genetic variations, and the boundary between a disorder and the "normal" condition is not always clear. Many disorders have overlapping symptoms, such as schizoaffective disorder sharing symptoms with schizophrenia and bipolar disorder. The studies suggest that the genetic variations shared among the five disorders account for between 17% and 28% of the risk for mental illness.

This suggests that the discrete "boxes" of symptoms captured in the DSM-5 manual of mental disorders, published by the American Psychiatric Association, may be an artificial construct. A more dimensional approach, a spectrum, would be a closer understanding of the causes for these disorders. This spectrum would include pathological domains like cognitive impairments, positive and negative symptoms, and mood disturbances, as well as causes like genetic and environmental factors.

In conclusion, the association between genetics and environment in psychiatric disorders is complex. These disorders involve an interplay of several genes and even more complex genetic mechanisms. And inheritance is probabilistic but not deterministic. But, disappointingly, not much progress has been made in understanding the environmental factors associated with mental illness.