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GUEST EDITORIAL

Travails of psychiatric genetics

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Psychiatric genetics has received plenty of attention recently, at least in some psychiatric journals. For example, the *American Journal of Psychiatry* routinely publishes articles on psychiatric genetic research, and devoted an entire issue to genetic studies in November 2022. Most of the articles and accompanying editorials were quite optimistic, with titles such as, "A revolution is brewing in how we understand the shared genetic causes of psychiatric disorders."[1] In that same issue, Kalin[2] stated that "Considerable progress has been achieved in clarifying the complexity and polygenic nature of psychiatric illnesses and the shared generic variations across different illnesses and their medical and psychiatric comorbidities."

These statements sound full of promise, but what do they mean in the clinical sense? Are these genetic findings game changers in patient care, or just smoke and mirrors? This led me to muse about the achievements of psychiatric genetics over the last 50 years, since the publication of a book on genetics in psychiatry by Zvolsky,[3] one of my teachers in Europe, which was the first psychiatric genetics text I ever read.

Psychiatric genetics of the past

The methodology and technology of psychiatric genetics were a bit different a few decades ago. The core methods were family/pedigree studies, twin studies, adoption studies, population genetics, and estimates of the risk of illness among proband relatives. Some of these estimates are still used today to describe risks to patients' relatives. Examples include the risk of schizophrenia being 40% to 50% in offspring if both parents have been diagnosed with schizophrenia; the risk of schizophrenia being 50% if one identical twin has schizophrenia; the chance of developing schizophrenia being 5% to 10% if one family member has schizophrenia (compared to the approximately 1% risk in the entire population); the increased risk of depression, suicidality, bipolar disorder, substance abuse and attention-deficit/hyperactivity disorder in patients with familial occurrence of these

conditions; or that the response to long-term lithium therapy appears to be a familial trait.[4]

At times we also select a specific antidepressant based on a family member's responsiveness to it. These are clinically useful pieces of information that can be helpful to patients, and at times may help in the management of the disease(s).

Psychiatric genetics of the present

Contemporary psychiatric genetics has been boosted, like the entire field of genetics, by the completion of the Human Genome Project. There are numerous more sophisticated methods available, including genome-wide association studies (GWAS); polygenic risk studies; cross-disorder studies; optogenetics; chromosomal microarray analyses (CMA) and other molecular techniques that can detect different copies, small duplications, or deletions of genetic material number variants (the CMA along with fragile X testing is used in the assessment of autism spectrum disorder [ASD]); epigenetic studies; and pharmacogenetics/pharmacogenomic studies. Other than CMA studies of ASD, these data are of limited or no clinical usefulness.

Some of these methodologies have significant limitations. For example, GWAS looks for certain genes associated with a particular disease in a large sample of patients, seeking small variations called single nucleotide polymorphisms. While interesting and sophisticated, these studies have many limitations, including a small effect size. The fact they cannot predict disease status or fully explain the risk of common diseases are additional problems. They also have underlying confounding environmental and genetic background variables.[5] Finally, these studies need to be replicated.

Two excellent review articles by Smoller et al[6] and Zeier et al[7] addressed 2 useful areas of modern-era psychiatric genetics: the biology/etiology of mental illness, and clinical implementation of pharmacogenetics.

Smoller et al[6] focused on genetics and the structure of psychopathology, asking how molecular genetics confirms and extends genetic epidemiologic findings. One conclusion is that the GWAS document that psychiatric disorders "are highly polygenic, reflecting a combination of thousands of common variants of individually small effect and rarer variants of larger effects … it is increasingly clear that a substantial fraction of genetic risk is the result of common SNP (single nucleotide polymorphism) variation."[6] In discussing cross-disorder studies, Smoller et al[6] noted initial clues of the shared biology of schizophrenia and bipolar disorder. Importantly, the results suggest that "susceptibility to each psychiatric disorder, as currently defined by DSM, is influenced by many genetic risk factors rather than a single cause, and that any given psychiatric disorder will share some genetic risk factors with others." Smoller et al[6] also observed that psychiatric disorders are highly polygenic, that genetic studies challenge the DSM paradigm, that genetic complexity is a challenge for identifying clinically relevant biomarkers, and that discovering biological mechanisms from common variants will be challenging: "When we hear only ten or even 100 notes, we cannot reconstruct a symphony." They also add that "Efforts to dissect the fundamental intermediate phenotypes underlying risk of psychiatric disorder face important challenges … we still do not know which are the most relevant levels of analyses …"[6] This is a somber and realistic evaluation of the psychiatric genetic state of art and results.

In their review that addresses the state of the art of pharmacogenetics, Zeier et al[7] asserted that, "at present, there are insufficient data to support the widespread use of combinatorial pharmacogenetic testing in clinical practice, although there are clinical situations in which the technology may be informative, particularly in predicting side effects." In other words, the authors discourage the widespread use of this testing.

In an article focused on what psychiatrists should know about genetics, Nurnberger et al[8] suggested that genetic knowledge is already required in estimating empirical risk for psychiatric illness from family studies and epidemiological data; ordering and interpreting genetic tests for ASD and intellectual disability (which prompts me to ask: which one?); evaluating the results of pharmacogenomic testing and commercial genetic testing; and knowing when to refer for genetic testing and counseling. That is not much. They also suggest that in 1 to 2 decades we may expect to apply genetic risk scoring in a clinical framework, ordering and interpreting genetic tests for rare variants in schizophrenia and bipolar disorder, and developing personal genetic profiles for patients and interpretation for treatment decisions and personal prognosis. I am skeptical of this timeline, considering the article by Nurnberger et al[8] was published in 2018, and we have seen no suggestion for the realization of these goals.

Conclusion

Despite decades of considerable efforts and new methodologies and technology, the achievements of psychiatric genetics seem overstated and overemphasized. This

questions what psychiatric geneticists expect to achieve and whether they can actually achieve it. The genetic findings certainly question our nosology and the DSM paradigm. However, can psychiatric genetics provide a better or more clinically useful system and paradigm? I do not think a genetics-based clinically useful nosology is possible in classifying polygenic "multiple etiology" diseases, which most mental disorders/diseases are. Present-day psychiatric genetics is deeply rooted in biology and in biological reductionism. Yet psychology or nurture play a similarly important role in the multiple etiologies and expressions of mental diseases. It seems that right now the approach of psychiatric genetics is like the approach of the blind men in the Indian parable, each of whom attempt to draw a conclusion about an elephant by touching only 1 part of it.

Psychiatric genetics should clarify its goals and their achievability and figure out the involvement of "nurture" or psychology in its methodological approaches. Its achievements to date have, with the notable exception of ASD, had very little (if any) clinical significance. I do not believe we will see any clinically applicable results within the next 1 or 2 decades, as some optimists claim. I agree with Paris[9] that some psychiatric genetics research may lead to practical results, perhaps such as gene therapy, in the future. However, like Paris, by "the future" I do not mean within the next 5 to 10 years but by the end of the 21st century, if even that soon. ■

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