COMMENTARY

Advances in the Genetics of Attention-Deficit/Hyperactivity Disorder

Stephen V. Faraone

One of the most replicated findings in studies of attention-deficit/hyperactivity disorder (ADHD) is its very high heritability, which averages approximately 75% across 20 twin studies conducted on three continents (1). ADHD's high heritability kick-started a search for DNA variants with the hope that their discovery would lead to advances in diagnosis and treatment. During the dark decades of linkage and candidate gene studies, progress was slow, but in the past few years, boosted by genome-wide association studies (GWAS), the ADHD research community has made real breakthroughs. GWAS taught us that 25% to 30% of ADHD's heritability could be accounted for by a polygenic liability consisting of many common DNA variants (2). GWAS also gave us replicated discoveries of rare deletions and insertions known as copy number variants (CNVs) (3). These GWAS data confirmed what many had suspected from epidemiologic data, that ADHD's genetic liability consists of a complex mixture of common and rare DNA variants.

In this issue of Biological Psychiatry, two articles address ADHD's complex inheritance. Martin et al. (4) illustrate the use of the recently developed “polygenic paradigm,” which, remarkably, was conceptually foreshadowed by Gottesman and Shields (5) more than 40 years ago. The polygenic paradigm uses a discovery sample (in this case ADHD cases and controls) to discover and define a polygenic liability score indexing the number of ADHD risk alleles carried by an individual. Each risk allele or risk variant is the nucleotide that is more frequently observed among ADHD cases, using an arbitrary (and typically liberal) level of statistical significance. When defined like this, many of the risk variants comprising the polygenic liability score will be true risk variants, but many will be false positives. It is the statistical significance of the polygenic score that assures us that it has captured many true positives in the mix.

ADHD's polygenic liability score is a molecular genetic tease. On the one hand, it confirms that many common DNA variants (defined by single nucleotide polymorphisms) are associated with ADHD, but it cannot tell us if “many” means hundreds or thousands or even more, and it cannot tell us which of the many variants comprising the score are truly associated with the disorder. Despite this limitation, polygenic scores provide a valuable tool. For example, when the Psychiatric Genomics Consortium applied this method to schizophrenia, bipolar disorder, depression, ADHD, and autism spectrum disorders (ASDs), a polygenic background defined by single nucleotide polymorphisms accounted for 17% to 29% of the variance in liability to these disorders (http://www.med.unc.edu/pgc/) (2). Moreover, for some disorders, the correlation among their polygenic liabilities was moderate to high (e.g., schizophrenia and bipolar disorder [68], schizophrenia and depression [43], bipolar disorder and depression [47], and ADHD and depression [32]). These findings confirmed, at a molecular level, genetic associations between disorders that had been posited from family and twin studies.

In the hands of Martin et al. (4), the polygenic paradigm yields insights about the well-known comorbidity between ADHD and ASDs, which share neurobiological features and some CNV risk variants (for a review see (6)). As expected, the ADHD children in that study’s sample showed ASD-related social communication traits. The novel finding in the study by Martin et al. (4) is that ADHD’s polygenic liability derived from a clinical sample predicted these ASD traits in the population sample. Therefore, just as previous data showed that ADHD and ASDs share CNVs (3), these new data suggest that ADHD and ASD traits share common DNA risk variants. The sample in Martin et al. (4) was too small to accurately assess the magnitude of overlap. Such estimates must await the large sample analyses expected from the Psychiatric Genomics Consortium, whose initial analyses did not report a positive correlation between ADHD’s and ASD’s polygenic liabilities (2).

The work of Martin et al. (4) yielded another notable result. The polygenic liability score derived from their ADHD case compared to that of the control clinical sample predicted both inattention and hyperactivity in the general population. This result confirms conclusions from twin studies that the liability for clinically defined ADHD is the extreme of a trait that varies continuously in the population (for a review see ref. (1)). We can also intuit the continuous nature of ADHD symptoms from population twin studies of ADHD which have used continuous measurements of symptoms; those studies found that ADHD’s heritability is of the same magnitude as that found from twin studies using categorical diagnostic methods (1). The dimensional nature of ADHD has wide-ranging implications. If we view ADHD as being analogous to cholesterol levels, then diagnostic approaches should focus on defining the full continuum of ADHD traits along with clinically meaningful thresholds for defining who does and does not require treatment and who has clinically subthreshold traits that call for careful monitoring. Moreover, just as physicians integrate other risk factors to determine whether a given cholesterol level requires treatment, perhaps the mental health professions should adapt a multilayered approach to defining diagnoses. The dimensional nature of ADHD should also shift the debate about the increases in ADHD prevalence in recent years. Instead of decreeing increases in misdiagnosed ADHD, perhaps critics should be discussing why the threshold for diagnosis has decreased over time and whether changes in the threshold are clinically sensible or not.

A shift from categorical to dimensional constructs harmonizes with the Research Domain Criteria (RDoC) (7) initiative of the National Institute of Mental Health. RDoC seeks to define and validate the dimensional constructs mediating psychopathology along with the neurobiological underpinnings of these constructs. Again, we hear echoes from the past. Two decades ago, Tsuang et al. (8) and other investigators urged researchers to create a

From the Department of Psychiatry and Behavioral Sciences, SUNY Upstate Medical University, Syracuse, New York.

Address correspondence to Stephen Faraone, Ph.D., SUNY Upstate Medical University, Department of Psychiatry and Behavioral Sciences, 750 East Adams Street, Syracuse, NY 13210; E-mail: sfaraone@child psyresearch.org.

Received and accepted Jul 16, 2014.

0006-3223/$36.00
http://dx.doi.org/10.1016/j.biopsych.2014.07.016

BIOL PSYCHIATRY 2014;76:599–600 © 2014 Society of Biological Psychiatry
genetic nosology to replace clinical diagnoses for research studies. RDoC takes the idea from Tsuang et al. (8) several steps farther by applying novel nosological ideas to a broader range of neuroscience studies.

The emerging genetic nosology in psychiatry includes endophenotypes, which Gottesman and Gould (9) defined as neurobiological, biochemical, endocrinological, cognitive, or neuropsychological phenotypes mediating the link between disease cause and disease expression. Because endophenotypes are way stations on the pathway between genes and disease, Gottesman and Gould (9) surmised they would have a simpler genetic architecture than disorders and thus would have a useful tool for genetic studies. In this issue of Biological Psychiatry, Pironti et al. (10) use family study methodology to validate neuropsychological and neuroanatomical dimensional endophenotypes for ADHD. The family study design infers an endophenotype when a trait is heritable, is associated with the disorder, and is more extreme in unaffected relatives of patients than in suitable controls. Pironti et al. (10) show that the non-ADHD first-degree relatives of ADHD patients have sustained attention deficits that are significantly worse than those of controls and comparable to deficits seen in ADHD patients. The authors found the same pattern of results for several regions previously implicated in ADHD or the regulation of attention: decreased gray matter volume in the right inferior frontal gyrus; increased gray matter volume in the left middle occipital gyrus and right superior occipital gyrus and left dorsal mid cingulate cortex; and increased white matter volume in the right inferior fronto-occipital fusciulus.

As we saw in the results of the study by Martin et al. (4), the work by Pironti et al. (10) supports RDoC’s guiding premise, which is that dimensional measures of neurobiological dysfunction mediate the link between genes and psychopathology. The discovery of endophenotypes may move the field forward in three ways. If, compared with diagnoses, many fewer genes mediate the expression of endophenotypes, then they might increase the power of molecular genetic studies. Endophenotypes might also provide information about the pathway from DNA risk variants to psychopathology. For example, the work by Pironti et al. (10) suggests that some DNA variants regulate brain volumes and that aberrant brain volumes lead to ADHD. This study cannot, however, rule out the possibility that the brain changes are epiphenomena. Because endophenotypes also provide a method for identifying people at risk for psychopathology, they could be used for studies of primary prevention (11), although that would require that the endophenotypes were sufficiently accurate in predicting disease onset.

It is, perhaps, the sign of a maturing science that ideas from several decades ago, derived from the relatively low-tech methods of epidemiology, have been confirmed and extended in the high-tech era of molecular genetics and neuroimaging. This maturation offers hope that that a new generation of research will finally solve the conundrum of ADHD’s genetic causes and lead to breakthroughs in how we diagnose and treat the disorder and its comorbidities.

Dr. Faraone has received income, travel expenses, and/or research support from and has been an advisory board member for Pfizer, Ironshore, Shire, Akili Interactive Labs, CogCubed, Alcobra, VAYA Pharma, Neurovance, Impax, and NeuroLifeSciences and research support from U.S. National Institutes of Health. His institution is seeking a patent for the use of sodium-hydrogen exchange inhibitors in the treatment of ADHD. Previously he received consulting fees or has been on advisory boards or participated in continuing medical education programs sponsored by Shire, Alcobra, Otsuka, McNeil, Janssen, Novartis, Pfizer and Eli Lilly. Dr. Faraone receives royalties from books published by Guilford Press.