Published in final edited form as:

Harv Rev Psychiatry. 2017 ; 25(6): 256–258. doi:10.1097/HRP.0000000000000180.

A Quarter Century of Progress in Psychiatric Genetics

Jordan W. Smoller, MD, ScD^{1,2,3}

¹Psychiatric and Neurodevelopmental Genetics Unit, Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA

²Department of Psychiatry, Massachusetts General Hospital, Boston, MA

³Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard, Cambridge, MA

Keywords

Psychiatric genetics; GWAS; genomics; DNA; schizophrenia; polygenic

In 1993, when the *Harvard Review of Psychiatry*'s inaugural issue was published, the field of psychiatric genetics was both well-established and facing a crisis of sorts. Family studies had already documented that essentially all of the major psychiatric disorders run in families. Twin studies had established that for most of these disorders, the familial component was largely attributable to genetic influences. Thus, genetic epidemiologic approaches had provided a firm basis for the hypothesis that genes contribute to the risk for psychiatric illness. With that evidence base in place, the field had begun a search for the genes themselves. Initially, hopes were high that gene finding would be a relatively straightforward process. By 1993, the mapping of human disease genes by linkage analysis had seen a decade of several high profile successes, beginning with the localization of the Huntington Disease locus in 1983. By the late 1980s, a growing number of linkage studies of major mental illness had appeared, and initial reports of significant linkage to schizophrenia and bipolar disorder in extended pedigrees fueled optimism that psychiatric disease genes were at hand. Early estimates suggested that as few as 8–10 moderate-sized pedigrees might be required to map single major loci underlying psychiatric disorders.¹

But as more studies appeared, the results were sobering. Initial findings were not replicated, and most findings proved weak and unstable. The field began to confront a disappointing reality: the genetic basis of mental illness is not as simple as that of Mendelian disorders like Huntington disease and cystic fibrosis for which linkage studies were able to map the single causal genes. Rather, psychiatric disorders are “complex disorders”, reflecting the interplay of numerous genes and environmental risk factors. The field had begun to move on to association studies, in which the frequencies of genetic variants (alleles) are compared between cases and controls. In 1996, an influential paper by Risch and Merikangas² demonstrated that this method was more powerful for finding genes underlying complex traits. And so, a second wave of psychiatric genetic studies began to appear using

association methods. But there was another problem: what genetic variants should be studied? Before the availability of genomewide genotyping that allows surveying variation across the genome, researchers were limited to studying variants in “candidate genes”—that is, genes suspected to be involved based on prior knowledge of their biological relevance. Unfortunately, our limited understanding of the biological basis of psychiatric disorders meant that any gene might be a candidate, but none were especially compelling. A flood of studies were published that tended to focus on a small set of candidates—mainly genes encoding receptors, transporters, and synthetic enzymes involved in neurotransmitter systems that are the target of therapeutic agents (e.g. serotonin, norepinephrine, glutamate, dopamine), neuropeptides, and a few others. Scores of gene associations were claimed, once more raising expectations that the field was finally cracking the genetic code of psychiatric disorders. But, again, replication of these findings proved elusive and, by 2006, ten years after Risch and Merikangas’ paper appeared, the picture was again bleak. After two decades of linkage and association studies, thousands of publications, and the hard work of dedicated scientists and trainees, the field had few if any robust discoveries. And then things began to change.

Psychiatric Genetics in the 21st Century

The transformation of psychiatric genetics resulted from the convergence of several key advances. The first was a deepening understanding of the structure of the human genome enabled by “big science” efforts. The sequencing of the human genome in 2003 was followed by the International HapMap Project and 1000 Genomes Project that provided a catalog of genetic variation in populations around the world. The discovery that human genomic variation includes stretches of correlated single nucleotide polymorphisms (SNPs) facilitated the development of genotyping microarrays that allowed genomewide genotyping of SNPs that captured most of the genome’s common genetic variation. Now, researchers could conduct genomewide association studies (GWAS) that enabled an “unbiased” search for risk loci by examining variants across the genome instead of limiting the search to hypothesized candidate genes. Around the same time, genomewide investigations of rare copy number variants (CNVs), in which large chunks of DNA sequence (typically 500 kilobases, kb) are deleted or duplicated, became possible. The first large-scale studies of genomewide SNPs and CNVs began to appear around 2007–2008, and their value was quickly apparent. Significant associations, achieving stringent thresholds of statistical significance, were discovered for several SNPs (for schizophrenia and bipolar disorder) and CNVs (for autism and schizophrenia).

But real success required a second advance which was more about scientific culture than genomics or technology: the formation of large collaborative consortia. Genomewide association analyses require statistical correction for the large number of tests entailed by examining variation across the genome. For genomewide SNP studies, this means correcting the standard significance threshold of $p < 0.05$ for the one million effective tests involved, resulting in a nominal threshold of $p < 5 \times 10^{-8}$. At the same time, the effect sizes (e.g. odds ratios, ORs) observed for common variants that showed significant association with complex disorders were very small—on the order of an OR of 1.5 or less for each risk allele. Reliably detecting such effects while correcting for multiple testing would clearly require very large

sample sizes, much larger than those available to any individual research group. The same challenge applies to studies of rare risk variants and CNVs: they often have stronger individual effects but their rarity again necessitates large samples to detect. Recognizing that progress would require collaboration on an unprecedented scale, psychiatric genetic researchers began to form consortia, combining data and centralizing their analysis. The largest of these, the international Psychiatric Genomics Consortium (PGC) (<http://www.med.unc.edu/pgc>), currently includes more than 800 investigators from 38 countries and genomic datasets comprising nearly 1 million individuals.

The shift to genomewide analysis and large-scale studies has clearly paid off for the field of psychiatric genetics. The sections that follow highlight several major discoveries and emerging themes from this research over the past decade.

The Discovery of Common and Rare Genetic Contributions to Psychiatric Disorders

While essentially no confirmed common risk variants influencing psychiatric disorders were identified before 2007, the past decade has seen the discovery of more than 200 such genetic loci across a range of psychiatric disorders, and the list is expanding every year. A landmark 2014 report by the PGC's Schizophrenia Workgroup, that included nearly 37,000 cases, identified 108 risk loci for schizophrenia alone.³ In 2017, analyses by the PGC have added more than 40 loci for major depressive disorder, 30 for bipolar disorder, and 12 for ADHD. At the same time, studies of rare *de novo* CNVs have convincingly identified specific deletions and duplications in neurodevelopmental psychiatric disorders—most extensively in autism and schizophrenia with a smaller number for ADHD. More recently, direct DNA sequencing has become feasible on a large scale, allowing comprehensive analyses of rare single nucleotide mutations across the exome or whole genome. Although these studies have not yet reached the scale of common variant GWAS, rare mutations contributing to autism and schizophrenia have been identified. As ever-larger sample sizes become available, the discovery of additional loci is certain to follow.

Psychiatric Disorders are Highly Polygenic

It is now clear that the genetic component of psychiatric disorders includes variations in hundreds or even thousands of genes. For example, simulations based on GWAS of schizophrenia indicate that more than 8000 common variants can affect risk of the disorder.⁴ The “polygenic” basis of psychiatric disorder includes both common SNP variants of small effect and rare mutations and CNVs variants with larger effects. We have thus far identified only a sliver of the full pie. What does this mean for the prospect of genetic risk prediction or diagnostic testing? Clearly, individual variants of small effect are not useful for this purpose. In some cases, rare (often *de novo*) higher penetrance mutations or CNVs might be useful in diagnostic evaluations. Indeed, testing for such variants is now a recommended component of the diagnostic workup for autism.⁵ A more uncertain but emerging issue concerns the predictive value of so-called “polygenic risk scores” where the effects of multiple (often tens of thousands) individual common SNPs are aggregated into a single index of risk. By definition, these scores account for a substantially larger portion of genetic

risk compared to single SNPs, but to date they fall short of clinical utility. Whether such polygenic profiles will ultimately achieve clinically useful levels of predictive power as larger studies improve their precision remains to be seen.

Genes Do Not Respect Our Diagnostic Boundaries

In 1993, the year that the *Harvard Review of Psychiatry* was launched, Tsuang and colleagues⁶ proposed the notion of a “psychiatric genetic nosology”, noting that “it seems unlikely that there will be a one-to-one correspondence between genetically influenced processes in the brain and the clinical phenomena that we observe.” One of the most intriguing themes to emerge from recent psychiatric genetic research has been the discovery that genetic influences transcend our traditional clinical categories of disorder. As its often stated, “our DNA has not read the DSM.” Although such effects had been suggested by family and twin studies, it took the new era of genomic research to demonstrate cross-disorder genetic overlap at the level of our DNA. For example, specific rare CNVs have been shown to confer risk to a range of neurodevelopmental disorders including autism, intellectual disability, and schizophrenia. In terms of common variants, the PGC’s Cross-Disorder Workgroup used GWAS data to identify specific genetic loci that overlap among childhood- and adult-onset disorders, including ADHD, autism, bipolar disorder, major depressive disorder, and schizophrenia.⁷ Genomewide studies have also allowed us to estimate the overall genetic correlation between SNPs affecting multiple disorders. The results have shown that a broad range of disorders including the five noted above as well as anorexia, PTSD, obsessive-compulsive disorder, and substance use disorders overlap genetically to varying degrees. In some cases, such as schizophrenia and bipolar disorder, the degree of overlap is strikingly high. Other studies have found that genetic signals for specific pathways (e.g. calcium channel signaling, synaptic structural proteins) have cross-disorder effects. Taken together, these studies are revealing patterns of shared genetics and biology across disorders that are often assumed to be clinically distinctive. The implications of these discoveries for refining psychiatric nosology are intriguing though controversial.

Genetic Studies Reveal Novel Biology and Possible Treatment Targets

Beyond amassing a list of genetic risk variants, research in psychiatric genetics has begun to focus on the functional role of these loci. So-called network and pathway analyses have begun to sketch the biologically story that ties genes to molecular pathways. By applying other tools of neuroscience, gene expression and the broader domain of systems biology, researchers have also begun to unravel unforeseen mechanisms of disease. In a breakthrough study, Sekar and colleagues⁸ focused on the strongest common variant association with schizophrenia—a variation at the major histocompatibility complex (MHC) locus on chromosome 6. In a series of experiments, they localized the genetic signal to functional alleles of component 4 (C4) genes and found that they play a role in microglia-mediated synaptic pruning. The implication, that these DNA variations confer risk by promoting synaptic loss, has provided a new window onto the etiology of schizophrenia and, possibly, a novel target for the development of mechanism-based therapeutics. Such discoveries can give us cause for optimism that genetic research will ultimately have important implications for diagnosis and treatment of mental illness.

The Future of Psychiatric Genetics

As this brief review of the last 25 years of psychiatric genetics suggests, the field has traveled far since the Harvard Review of Psychiatry first appeared. We have seen the discovery of robust and replicated genetic risk factors and new insights into the biology of mental disorders. Recent advances, including the feasibility of low-cost genome sequencing and the harnessing of stem cell biology and gene editing, have created unprecedented opportunities to capitalize on the insights from genomic research. And yet, we are still in the early days of understanding the genetic architecture and etiology of psychiatric disorders. With the rapid pace of technological advances, a commitment to large-scale collaboration, and new tools of functional genomics, the field is poised to make an even more transformative impact on the mental health of patients and families who struggle with these disorders.

Acknowledgments

Dr. Smoller is a Tepper Family MGH Research Scholar. He is an unpaid member of the Scientific Advisory Board of PsyBrain, Inc. and the Bipolar/Depression Research Community Advisory Panel of 23andMe.

References

1. Gershon ES, Goldin LR. The outlook for linkage research in psychiatric disorders. *J Psychiatr Res* 1987;21:541–50. [PubMed: 3326940]
2. Risch N, Merikangas KR. The future of genetic studies of complex human diseases. *Science* 1996;273:1516–7 Erratum: 997, 275, 329–330. [PubMed: 8801636]
3. Schizophrenia Working Group of the Psychiatric Genomics C. Biological insights from 108 schizophrenia-associated genetic loci. *Nature* 2014;511:421–7. [PubMed: 25056061]
4. Ripke S, O'Dushlaine C, Chambert K, et al. Genome-wide association analysis identifies 13 new risk loci for schizophrenia. *Nat Genet* 2013;45:1150–9. [PubMed: 23974872]
5. Schaefer GB, Mendelsohn NJ, Professional P, Guidelines C. Clinical genetics evaluation in identifying the etiology of autism spectrum disorders: 2013 guideline revisions. *Genet Med* 2013;15:399–407. [PubMed: 23519317]
6. Tsuang M, Faraone S, Lyons M. Identification of the phenotype in psychiatric genetics. *European archives of psychiatry and clinical neuroscience* 1993;243:131–42. [PubMed: 8117756]
7. Cross-Disorder Group of the Psychiatric Genomics C. Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. *Lancet* 2013;381:1371–9. [PubMed: 23453885]
8. Sekar A, Bialas AR, de Rivera H, et al. Schizophrenia risk from complex variation of complement component 4. *Nature* 2016;530:177–83. [PubMed: 26814963]