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Psychiatric Genetics and the Future of Personalized Treatment

Jordan W. Smoller, MD, ScD

¹ Psychiatric and Neurodevelopmental Genetics Unit, Center for Human Genetic Research, Massachusetts General Hospital, Boston, MA

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

³ Stanley Center for Psychiatric Research, Broad Institute, Boston, MA

Well before the sequencing of the human genome in 2003, family and twin studies had established that psychiatric disorders are both familial and heritable. But identifying the genes involved has been a formidable challenge. At the same time, there has been an urgent need to unlock the biological basis of psychiatric disorders. While psychotropic drugs are helpful for many and life-saving for some, there is a striking fact about available drug therapies: they are all based on serendipitous discoveries and biological insights that date to the 1950s and 1960s. When it comes to treating psychiatric disorders, we are still living in the “Mad Men” era.

Lithium has been the gold standard treatment for bipolar disorder ever since John Cade reported its mood stabilizing effects in 1949. All current antipsychotic medications target the D2 dopamine receptor, just as the first medicines in this class did in the 1950s.

Antidepressants have relied on variations of the monoamine hypothesis that was articulated in the mid-1960s. The shortcomings of available psychotropics are well-known. The results of large-scale effectiveness studies of mood and psychotic disorders (STAR*D, CATIE, and STEP-BD) are sobering: roughly 30% of depressed patients treated for 14 weeks with an SSRI achieved remission [1]; 25% of patients with schizophrenia remained on their initial medication by 18 months [2]; and 50% of bipolar patients who achieved recovery from a mood episode relapsed within two years despite best-practice treatment. [3]

A major hope hanging on genetic studies has been that they can break this therapeutic impasse. There are three main avenues by which genetic research may inform efforts towards personalized medicine. First, by identifying DNA variants associated with risk of disease, genetic studies may point us toward new treatment targets. The discovery that a specific gene or set of genes confers risk for illness raises the possibility that drugs that target that gene (or genes) may have therapeutic effects. Second, genetic studies may clarify diagnostic boundaries in ways that could inform treatment selection or identify etiologically-related subgroups that might preferentially benefit from a given treatment. And third, pharmacogenetic studies may yield genetic profiles that predict response to available

treatments. The following sections address each of these avenues and the state of the science to date.

Prying Open the Black Box of Psychiatric Genetics

Until recently, the search for genes predisposing to psychiatric disorders seemed like an exercise in futility. In the 1980s and 1990s, the predominant approach to gene mapping involved genetic linkage analysis. When a DNA marker is co-inherited with the disease of interest in families, we can infer that a disease-related gene is “linked to” (physically close to) that DNA marker. Thus, linkage studies provide information about the location of disease genes. There was initially great enthusiasm for this approach because of the successful linkage mapping of disease genes for Mendelian disorders like Huntington disease and cystic fibrosis. However, scores of linkage studies of psychiatric disorders failed to yield conclusive results. We now know that the linkage method is best suited to diseases caused by one or more rare mutations of large effect. However, the genetic basis of psychiatric disorders is much more complex than that.

Beginning in the late 1990s, psychiatric genetic studies began to focus on association analysis, which is more powerful for complex disorders. In an association study, we test whether one or more genetic variants are more common among affected individuals (cases) than among unaffected individuals (controls). Thus, association studies aim to identify specific genetic risk factors for a disorder or trait. Early association studies focused on DNA variants in candidate genes—that is, genes that were hypothesized to be involved in the disorder based on prior biological evidence (or, sometimes, based on their location within a region that was reported to be linked to the disorder). Over a period of a decade, many hundreds of candidate gene studies of psychiatric disorders appeared, but the results were equivocal at best. Indeed, by 2006, essentially no genetic variants had been convincingly associated with a psychiatric disorder. In retrospect, the candidate gene era failed because these studies were underpowered to pick up the small effects that are typical of common genetic risk factors and because our understanding of the biological basis of psychiatric disorders was so limited, making most “candidates” little more than wild guesses. But more recently, the field has been transformed.

Several major advances have made this transformation possible. The first was the advent of genomewide association studies (GWAS). Progress in our understanding of the genome as well as “big science” projects that catalogued genetic variation in populations around the world enabled the development of DNA microarrays that capture genomewide common variation. In a typical GWAS, microarrays are used to genotype 500,000 or more single nucleotide polymorphisms (SNPs) in a single experiment. GWAS allows us to move beyond a limited set of hypotheses about candidate genes to discover new and unforeseen associations anywhere in the genome. This “unbiased” approach lets the data speak for themselves. The second major advance was a shift in scientific culture toward widespread collaboration and data sharing. In 2007, independent research groups, recognizing the need for large datasets, joined forces to establish the Psychiatric Genomics Consortium (PGC). [4] Through the PGC, hundreds of researchers around the world have agreed to share and jointly analyze their GWAS datasets for a range of disorders, and this sharing has begun to

bear fruit. In just the last six years, we've gone from having virtually no confirmed genetic associations to roughly 200, including more than 100 SNPs associated with schizophrenia (SCZ) alone. [5] (Figure 1) At the same time, studies of copy number variation (CNVs), a kind of structural variation in which DNA segments are duplicated or deleted, have identified rare CNVs associated with neurodevelopmental disorders including autism spectrum disorder (ASD) and SCZ [6] More recently, with dramatic reductions in the cost of DNA sequencing, rare mutations have been implicated in psychiatric disorders, primarily ASD and SCZ. [7-9]

These discoveries have galvanized the field, though it's important to bear in mind that we have yet to identify the lion's share of genetic risk factors for psychopathology. For example, recent estimates from GWAS data indicate that more than 8,300 common variants contribute to schizophrenia. [10] Thus, the recent discovery of 108 schizophrenia risk loci represents less than 2% of the estimated total. And, for most psychiatric disorders, no risk loci have been established based on GWAS, CNV, or sequencing studies. For example, GWAS of depression and anxiety disorders have yielded few significant results and none have been firmly established. The largest published GWAS of major depressive disorder (MDD), including a discovery sample of more than 9000 cases, failed to identify any significant loci, suggesting that much larger samples may be needed. [11]

Identifying Treatment Targets through Genetic Research

Because GWAS does not involve testing prior hypotheses, it has the potential to identify novel molecular components of disorder etiology. Most importantly, these studies have done more than simply accumulate a list of associated SNPs. As the catalogue of susceptibility loci has grown, the results have begun to coalesce into biological pathways, providing the preliminary outlines of a pathogenetic account. For example, genes involved in immune function and glial cell function have been linked to SCZ [5; 12], genes involved in structural elements of the postsynaptic density have been associated with SCZ and bipolar disorder (BPD) [13] [7], glutamatergic pathway genes have been implicated in SCZ, BPD, ASD, and MDD [7; 14; 15], targets of the fragile X mental retardation protein (FMRP) have been implicated in SCZ and ASD [7; 16], and genes involved in calcium channel signaling have been associated with a broad range with SCZ, BPD, MDD, ASD, and attention deficit/hyperactivity disorder (ADHD) [17].

Each of these findings suggests avenues for developing therapeutics that are designed to impact underlying disease biology, a goal often referred to as "precision medicine." There are precedents for translating genetic findings into targeted treatments. The canonical example of rational drug design based on genetic etiology is imatinib (Gleevec), a tyrosine kinase inhibitor that specifically inhibits the BCRABL fusion protein resulting from the chromosomal translocation that causes chronic myelogenous leukemia. But this translocation is a somatic, rather than inherited event, and its effect is clearly causal.

What about the kinds of low penetrance, inherited alleles that we are detecting through common and rare variant GWAS? There is convincing evidence that GWAS findings include viable treatment targets. For example, variants in the gene encoding HMG-CoA

reductase, the target of statins, are among genomewide significant loci associated with LDL levels. Large-scale GWAS of rheumatoid arthritis have identified numerous genes that are the target of drugs approved for the treatment of the disorder. [18] The same picture is beginning to emerge for psychiatric disorders, at least in the case of SCZ. One of the strongest associations observed in the recent PGC GWAS of SCZ was for variants in the dopamine 2 receptor gene (*DRD2*), the target of all approved antipsychotic drugs. Nevertheless, some risk loci present more “drug-able” than others. Perhaps the most promising targets are risk variants that represent gain-of-function mutations. Inhibition of these gene products might be expected to be therapeutic. A prominent example are mutations in (*PCSK9*), an enzyme involved in the degradation of LDL receptors. Loss-of-function variants in *PCSK9* are associated with reduced LDL cholesterol concentrations and risk of coronary disease, while rare gain-of-function mutations are associated with increased LDL and premature heart disease. [19] PCSK9 inhibitors are now in development and Phase II trials indicate they are an effective option for patients who do not respond to or tolerate statins. [19]

It is worth noting that translation of genetic findings to new therapies can be a long and costly endeavor. Nevertheless, genomic targets can provide a crucial starting point for novel approaches. (Figure 2) With confirmed risk loci in hand, functional studies (e.g. in cellular or experimental animal models) can be used to validate the target. The recent advent of genome editing techniques now makes it possible to engineer specific variants into these assays. Large-scale libraries of compounds can then be screened for their capacity to ameliorate functional phenotypes in these experimental models. Once a suitable compound is identified, the customary steps in drug development—from toxicology and safety studies to proof-of-concept human studies and Phase II-III trials—are needed. In some cases, these steps can be circumvented by repurposing drugs that are already available for other indications. For example, the discovery that calcium channel genes are associated with mood and psychotic disorders motivated a proof-of-concept study that suggested benefit from the calcium channel antagonist isradipine (approved for the treatment of hypertension) in bipolar depression. [20]

Informing Etiology-Based Treatment Matching

The development and application of treatments for psychiatric disorders has been heavily influenced by the syndromic diagnostic categories embodied in the DSM. These categories are based on a consensus of experts, without explicit reference to underlying etiology. There is widespread agreement, however, that these constructs ignore the heterogeneity of patients who receive a given diagnosis. The limited overall efficacy of available treatments may mask the particular benefits that subgroups of patients experience. Defining etiologically-based subgroups could thus enhance treatment efficacy by targeting treatments to those most likely to respond. Genetic research can facilitate this goal by identifying genes and pathways that may be specific to subtypes of psychopathology. Genomic studies have begun to dissect the genetic basis of disorder subtypes and intriguing results (too numerous to review here) have been reported for a variety of phenotypic subsets (e.g. based on early age of onset, comorbidities, and other factors.). However, to date, none of these results has been established to the degree that they could serve as a basis for treatment stratification.

At the same time, genetic research suggests that some etiologic mechanisms transcend diagnostic boundaries. These include findings that specific genes and pathways contribute to the pathogenesis of multiple disorders. For example, results from the PGC's Cross-Disorder Workgroup found loci that influence risk for a range of childhood- and adult-onset disorders (ASD, ADHD, SCZ, MDD, BPD). [17]. As a group, genes involved in calcium channel signaling were also associated with these disorders, suggesting that treatments targeting this pathway might have broad therapeutic effects. Looking beyond diagnostic boundaries may also facilitate the treatment of symptom domains and other phenotypes that cross these boundaries, a goal consistent with the recently launched NIMH RDoC Initiative. For example, identifying genetic mechanisms underlying suicidality could point us toward therapies that target this lethal outcome of many disorders. Recent evidence has also begun to implicate loci influencing functional impairment across mood and psychotic disorders. [21] Large-scale efforts to map transdiagnostic phenotypes are underway and may provide important avenues for personalized medicine.

Genetic Predictors of Treatment Response

Pharmacogenetic studies aim to use genetic profiles to predict individual differences in therapeutic response or risk of adverse effects. For the most part, treatment selection in psychiatric practice remains a trial-and-error proposition. The development of validated predictors of efficacy or toxicity is a central goal of personalized medicine. In other areas of medicine, several genetic variants relevant to drug response have been identified and have demonstrated clinical utility. For example, a SNP (rs4149056) in *SCLO1B3*, whose product regulates hepatic uptake of statins, has been shown to predict risk of simvastatin-induced myopathy. Variants in P450 drug metabolizing enzymes are associated with reduced response and poor outcomes among patients treated with clopidogrel (*CYP2C19*), and with dose requirements for warfarin (*CYP2C9*). However, progress in psychiatric pharmacogenetics has been limited to date. Scores of genetic associations, mostly focused on candidate genes, have been reported for antidepressants, antipsychotics, and mood stabilizers, but none have been established or demonstrated clinical utility. A recently reported dramatic association between variants in *GADL1* and lithium response [22] was rapidly followed by numerous failures to replicate the finding.

Two relatively large GWAS meta-analyses of antidepressant response ($N > 2200$, with some sample overlap) have been reported and neither identified any genomewide significant associations. [23; 24] While these results suggest that individual SNPs of large effect do not exist for antidepressant response, they do not rule out the possibility that loci of modest effect contribute, though identifying them will likely require much larger samples (e.g. on the order of tens of thousands of patients). Consistent with this, Tansey and colleagues, using GWAS data from the first meta-analysis, estimated that 42% of the overall variance in antidepressant response is attributable to common genetic variation. [25] Thus, like psychiatric disorders themselves, antidepressant response appears to be a highly polygenic phenotype. Recent studies have explored genetic predictors of response to psychotherapy, an approach that has been called therapygenetics. [26] To date, however, only a few studies of candidate genes have been reported and no predictors have been established.

Conclusions

As progress in psychiatric genetics has accelerated over the past several years, several themes have emerged.

1. *It's Complicated.* Psychiatric disorders and response to psychotropic drugs are complex, polygenic traits whose genetic basis involves many common and rare variants.
2. *Size Matters.* The successful identification of genetic variants underlying psychiatric disorders and drug response will likely require very large samples (thousands to tens of thousands of subjects).
3. *Unusual Suspects.* Large-scale unbiased genomewide approaches have implicated specific genes and biological pathways beyond the “usual suspects” that were the focus of candidate gene studies.
4. *Our DNA has not read the DSM.* There is increasing evidence that genetic influences transcend the diagnostic boundaries of our current nosology.

Despite these complexities, ongoing genetic discovery can inform the movement toward personalized medicine in psychiatry. First, the identification of novel genes and pathways creates new opportunities for developing treatments that target the underlying pathophysiology of mental disorders. In the past six years, with the advent of large-scale genomewide association analyses, the field has gone from having essentially no confirmed risk loci to approximately 200. The path from genetic discovery to therapeutics is now visible and can capitalize on new tools including cellular (induced pluripotent stem cell) models, genome editing, and massive chemical screening libraries to identify target compounds. Second, uncovering genetic influences that are subtype-specific or transdiagnostic may facilitate the matching of treatment strategies to a given patient's clinical profile. And, finally, genetic predictors of treatment response may allow us to select treatments that maximize benefit and minimize toxicity for individual patients or subgroups. At present, however, all of these approaches are works in progress. We must be humble about the challenging road ahead, but we can also be encouraged by the progress made in the past several years.

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REFERENCES

1. Trivedi MH, Rush AJ, Wisniewski SR, et al. Evaluation of Outcomes With Citalopram for Depression Using Measurement-Based Care in STAR*D: Implications for Clinical Practice. *Am J Psychiatry*. 2006; 163(1):28–40. [PubMed: 16390886]
2. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005; 353(12):1209–23. [PubMed: 16172203]
3. Perlis RH, Ostacher MJ, Patel JK, et al. Predictors of recurrence in bipolar disorder: primary outcomes from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *Am J Psychiatry*. 2006; 163(2):217–24. [PubMed: 16449474]

4. Sullivan PF. The psychiatric GWAS consortium: big science comes to psychiatry. *Neuron*. 2010; 68(2):182–6. [PubMed: 20955924]
5. Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. *Nature*. 2014
6. Malhotra D, Sebat J. CNVs: harbingers of a rare variant revolution in psychiatric genetics. *Cell*. 2012; 148(6):1223–41. [PubMed: 22424231]
7. Purcell SM, Moran JL, Fromer M, et al. A polygenic burden of rare disruptive mutations in schizophrenia. *Nature*. 2014; 506(7487):185–90. [PubMed: 24463508]
8. Fromer M, Pocklington AJ, Kavanagh DH, et al. De novo mutations in schizophrenia implicate synaptic networks. *Nature*. 2014; 506(7487):179–84. [PubMed: 24463507]
9. Neale BM, Kou Y, Liu L, et al. Patterns and rates of exonic de novo mutations in autism spectrum disorders. *Nature*. 2012; 485(7397):242–5. [PubMed: 22495311]
10. Ripke S, O'Dushlaine C, Chambert K, et al. Genome-wide association analysis identifies 13 new risk loci for schizophrenia. *Nat Genet*. 2013; 45(10):1150–9. [PubMed: 23974872]
11. Major Depressive Disorder Working Group of the Psychiatric GC. Ripke S, Wray NR, et al. A mega-analysis of genome-wide association studies for major depressive disorder. *Mol Psychiatry*. 2013; 18(4):497–511. [PubMed: 22472876]
12. Duncan LE, Holmans PA, Lee PH, et al. Pathway analyses implicate glial cells in schizophrenia. *PLoS One*. 2014; 9(2):e89441. [PubMed: 24586781]
13. Pedroso I, Lourdasamy A, Rietschel M, et al. Common genetic variants and gene-expression changes associated with bipolar disorder are over-represented in brain signaling pathway genes. *Biol Psychiatry*. 2012; 72(4):311–7. [PubMed: 22502986]
14. Nurnberger JI Jr, Koller DL, Jung J, et al. Identification of pathways for bipolar disorder: a meta-analysis. *JAMA Psychiatry*. 2014; 71(6):657–64. [PubMed: 24718920]
15. Lee PH, Perlis RH, Jung JY, et al. Multi-locus genome-wide association analysis supports the role of glutamatergic synaptic transmission in the etiology of major depressive disorder. *Translational psychiatry*. 2012; 2:e184. [PubMed: 23149448]
16. Uddin M, Tammimies K, Pellecchia G, et al. Brain-expressed exons under purifying selection are enriched for de novo mutations in autism spectrum disorder. *Nat Genet*. 2014; 46(7):742–7. [PubMed: 24859339]
17. 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(9875):1371–9. [PubMed: 23453885]
18. Okada Y, Wu D, Trynka G, et al. Genetics of rheumatoid arthritis contributes to biology and drug discovery. *Nature*. 2014; 506(7488):376–81. [PubMed: 24390342]
19. Dadu RT, Ballantyne CM. Lipid lowering with PCSK9 inhibitors. *Nat Rev Cardiol*. 2014
20. Ostacher MJ, Iosifescu DV, Hay A, et al. Pilot investigation of isradipine in the treatment of bipolar depression motivated by genome-wide association. *Bipolar Disord*. 2014; 16(2):199–203. [PubMed: 24372835]
21. McGrath LM, Cornelis MC, Lee PH, et al. Genetic predictors of risk and resilience in psychiatric disorders: a cross-disorder genome-wide association study of functional impairment in major depressive disorder, bipolar disorder, and schizophrenia. *Am J Med Genet B Neuropsychiatr Genet*. 2013; 162B(8):779–88. [PubMed: 24039173]
22. Chen CH, Lee CS, Lee MT, et al. Variant GADL1 and response to lithium therapy in bipolar I disorder. *N Engl J Med*. 2014; 370(2):119–28. [PubMed: 24369049]
23. Tansey KE, Guipponi M, Perroud N, et al. Genetic predictors of response to serotonergic and noradrenergic antidepressants in major depressive disorder: a genome-wide analysis of individual-level data and a meta-analysis. *PLoS Med*. 2012; 9(10):e1001326. [PubMed: 23091423]
24. Investigators G, Investigators M, Investigators SD. Common genetic variation and antidepressant efficacy in major depressive disorder: a meta-analysis of three genome-wide pharmacogenetic studies. *Am J Psychiatry*. 2013; 170(2):207–17. [PubMed: 23377640]
25. Tansey KE, Guipponi M, Hu X, et al. Contribution of common genetic variants to antidepressant response. *Biol Psychiatry*. 2013; 73(7):679–82. [PubMed: 23237317]

26. Lester KJ, Eley TC. Therapygenetics: Using genetic markers to predict response to psychological treatment for mood and anxiety disorders. *Biol Mood Anxiety Disord.* 2013; 3(1):4. [PubMed: 23388219]

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Confirmed Psychiatric Risk Variants

Figure 1.

Discovery timeline for psychiatric genetics. GWAS: genomewide association study

Figure 2.

Illustrative pathway from genetic discovery to novel therapeutics. In this example, confirmation of genetic risk variant(s) is followed by functional studies in cellular and animal models. A cell-based assay of a disorder-relevant functional phenotype might then be used to screen libraries of small molecules to identify target compounds that modify or rescue the phenotype. Toxicology studies and animals and Phase I safety studies can then be used to identify safe doses of a lead compound. Small proof-of-concept studies can be used to establish target engagement and therapeutic effects. Finally, traditional Phase II and III trials are undertaken to establish safety and efficacy. iPS: induced pluripotent stem cells