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Genetic association studies in psychiatry: time for pay-off

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“For of those to whom much is given, much is required”

John F Kennedy

Such is the state of schizophrenia genetics. After many years of searching, we now have 108 loci associated with schizophrenia at stringent, genome-wide levels of significance.¹ Additional genes have been implicated by studies of copy number variants,² de-novo mutations,³ and rare coding variants.⁴ Compared with the state of schizophrenia genetics 10 years ago, we have indeed been given much!

Now much is required. Working out the individual genes and their functions in the brain will be a challenge, but this is now becoming more feasible thanks to projects such as ENCODE,⁵ PsychENCODE,⁶ and the CommonMind Consortium.⁷ These projects provide basic information about how genetic variation affects gene expression and regulation. Methods to integrate this information with the results of genetic association studies are also developing rapidly.^{8,9} Additional work with animal and cellular models will be needed, but the route from genome-wide association study (GWAS) hit to the identification of genes and pathways is becoming clearer.

Despite this considerable progress, the long-term goal of using the findings from genetic association studies to develop new treatments remains elusive. Douglas Ruderfer and colleagues¹⁰ provide a valuable advance peek into one way this might work.

The authors assembled a list of drug targets from two different databases and used it to derive 167 gene sets. They then tested these sets for evidence of enrichment for loci previously implicated in schizophrenia. Loci were defined as genes near common SNPs associated with schizophrenia by GWAS, or genes in which people with schizophrenia seem to carry an excess of very rare coding variants predicted to disrupt protein function. The contribution of such variants to treatment resistance was also examined.

Among 70 genes that encode known targets of antipsychotics, three genes (about 4%) lay within a schizophrenia GWAS locus—no more than would be expected by chance alone. However, when 277 genes predicted to encode novel drug targets were included, ten genes (about 3%) overlapped a schizophrenia GWAS locus—significantly more than expected by chance alone. Genetic variants identified by sequencing made the enrichment signals more

significant. Additionally, the most treatment-resistant patients were about twice as likely to carry rare disruptive variants within 347 genes encoding proteins predicted to be targets of antipsychotics.

The investigators conclude that the results support genetic overlap between schizophrenia pathogenesis and antipsychotic mechanism of action. Let us examine what is meant here by “genetic overlap”. Neither schizophrenia pathogenesis nor antipsychotic mechanism is a trait in the usual sense. Instead, they are constructs that involve sets of genes, their protein products, and many unobserved variables. The authors assume that genetic markers associated with schizophrenia point to genes that have a causal role in the illness. This assumption is sensible when the genetic marker directly alters the protein-coding sequence of a gene, as is the case with many coding variants. When the genetic marker lies elsewhere, however, as with most common variants implicated by GWAS, causality may be quite indirect and can involve many genes. For example, the 108 distinct loci that were associated with schizophrenia in the *Nature* study¹ actually encompass more than 300 known genes; some undoubtedly contribute to risk but many probably do not. Much experimental work will be needed to bring clarity to this area.

The results also suggest that the most treatment-resistant patients carry an increased burden of very rare variants predicted to disrupt proteins that are likely targets of antipsychotics. Although intriguing, it is not intuitively obvious what this reveals. Most disruptive mutations lead to a loss of function, whereas antipsychotics block various dopamine and serotonin receptors. Thus it might seem that disruptive mutations in antipsychotic target proteins would enhance, rather than reduce, treatment response. One could quibble with the definition of treatment resistance here, which relies on repeated prescription of clozapine in a centralised health-care system, but this is probably not a major limitation. Ruderfer and colleagues argue that their results are consistent with the notion that treatment response is moderated by many factors that include—but also extend beyond—dopamine and serotonin receptors. This is one of the great strengths of genetic association studies, revealing genes whose functions may never have been considered in prevalent models of aetiology or treatment, including genes whose functions are essentially unknown.

Ruderfer and colleagues demonstrate a creative strategy for detecting unexpected correspondences between genetic studies and predicted drug targets. This will be of interest to researchers who seek to translate genetic findings into better treatments for psychiatric disorders. The results also suggest that the road from genetic association to new drugs may be long and difficult. These are challenging enterprises, with weak signals and considerable noise. The reported enrichment, while significant, is quite modest, suggesting that we still know too little about the genetics of schizophrenia and its treatment. The proportion of overlapping genes should improve as additional genetic associations—and drug targets—are identified, but there is no guarantee that genes involved in aetiology will have that much to do with genes involved in treatment.

Still, this study shows how genetic association studies can open new windows, some of which look toward unheralded therapeutic opportunities. In a devastating disorder such as

schizophrenia, where existing treatments are only modestly effective and offer no hope of cure, any new window is welcome—and desperately needed.

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References

1. Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. *Nature*. 2014; 511:421–27. [PubMed: 25056061]
2. Malhotra D, Sebat J. CNVs: harbingers of a rare variant revolution in psychiatric genetics. *Cell*. 2012; 148:1223–41. [PubMed: 22424231]
3. Gulsuner S, Walsh T, Watts AC, et al. Spatial and temporal mapping of de novo mutations in schizophrenia to a fetal prefrontal cortical network. *Cell*. 2013; 154:518–29. [PubMed: 23911319]
4. Purcell SM, Moran JL, Fromer M, et al. A polygenic burden of rare disruptive mutations in schizophrenia. *Nature*. 2014; 506:185–90. [PubMed: 24463508]
5. ENCODE Project Consortium. The ENCODE (ENCyclopedia Of DNA Elements) project. *Science*. 2004; 306:636–40. [PubMed: 15499007]
6. Akbarian S, Liu C, Knowles JA, et al. The PsychENCODE project. *Nat Neurosci*. 2015; 18:1707–12. [PubMed: 26605881]
7. CommonMind Consortium. <http://commonmind.org/WP/> (accessed Dec 30, 2015)
8. Giallourakis C, Henson C, Reich M, Xie X, Mootha VK. Disease gene discovery through integrative genomics. *Annu Rev Genomics Hum Genet*. 2005; 6:381–406. [PubMed: 16124867]
9. Akula N, Wendland JR, Choi KH, McMahon FJ. An integrative genomic study implicates the post-synaptic density in the pathogenesis of bipolar disorder. *Neuropsychopharmacol*. 2016; 41:886–95.
10. Ruderfer, DM.; Charney, AW.; Readhead, B., et al. Polygenic overlap between schizophrenia risk and antipsychotic response: an analysis of genetic registry data. *Lancet Psychiatry*. 2016. published online Feb 22. [http://dx.doi.org/10.1016/S2215-0366\(15\)00553-2](http://dx.doi.org/10.1016/S2215-0366(15)00553-2)