

It's Complicated

The Genetics of Schizophrenia and Related Serious Mental Illnesses

Joseph T. Coyle

Findings from family, adoption and twin studies have provided compelling evidence that serious mental disorders including schizophrenia, bipolar disorder and autism have high degrees of heritability. In the case of schizophrenia, concordance for the diagnosis of schizophrenia if one twin is affected is approximately 60%. However, the relative risk for fraternal twins falls to the level observed in first-degree relatives, which is 10–15%. This lack of complete concordance points to important environmental risk factors, and a relative risk well below 25% in first-degree relatives suggests non-Mendelian, i.e., complex, genetics. The high degree of heritability in schizophrenia held forth the promise that identifying risk genes for the disorder would shed light on the underlying pathophysiology and reveal potential targets for therapeutic intervention.

Initial forays into risk gene identification for schizophrenia in the 1990s exploited linkage strategies. Linkage analysis of families with multiple affected members exploited intrafamily correlations between illness and allelic markers that were thought to be close to the disease-related genes (Psychiatric GWAS Consortium Coordinating Committee, 2009). When the sequence of the entire human genome was complete early in this decade, it became possible to determine whether genes that encoded proteins implicated in the pathophysiology of schizophrenia, such as dopamine receptors, were in fact genes of risk. These studies were often carried out with 100 or fewer affected individuals and a comparable number of suitable controls to determine whether a known allelic variant was transmitted more frequently with the disorder. While hundreds of candidate genes appeared significantly associated with risk for schizophrenia, replication studies were often negative. It became clear that these studies were underpowered and

were likely generating false positive findings. Meta-analysis of these studies identified only four “strong” potential gene associations. None involved dopaminergic-related genes, but the gene encoding the NMDA receptor NR2B subunit was implicated.

Lessons learned from research on medical disorders with complex genetics such as type II diabetes indicated that common alleles that conferred a relative risk between 1.1 and 1.4 required the analysis of thousands of subjects for genome-wide association studies (GWAS) to achieve statistical significance. Nevertheless, recent well-powered GWAS studies on schizophrenia and related serious mental disorders have been remarkably unrevealing of common alleles that confer significant risk, with the possible exception of *ZNF804A*, a zinc-finger protein. One possibility for the relatively negative findings is that there is a gene–gene interaction of common alleles such that the association is not detected by testing single nucleotide polymorphisms (SNPs) one at a time.

An alternative hypothesis that is gaining traction is that rare mutations with high penetrance might account for the heritable risk for schizophrenia. Consistent with this hypothesis, several GWAS studies have revealed rare copy number variants (CNVs) associated with the risk for schizophrenia. CNVs are structural genomic variants, stretches of DNA several hundred to several million base pairs in size, consisting of micro-insertions, micro-deletions and transpositions in the human genome (Gershon et al., 2011). Rare deletions were found at 1q 21.1, 15q13.3 and 22q 11. Notably, some of these CNVs are also associated with autism spectrum disorder and developmental disability and often occur *de novo*. Whereas GWAS studies indicated a significantly increased number of CNVs in the schizophrenia genome as compared to that of controls, the density of CNVs in bipolar disorder does not appear to differ from that of controls (Grozeva et al., 2010). Genes contained within the CNVs likely confer the risk, and

understanding their function could reveal “final common pathways to vulnerability” that could be targets for pharmacologic intervention. This difference in CNV density may interact with shared risk alleles to distinguish schizophrenia from bipolar disorder.

References

Gershon et al., 2011 E.S. Gershon, N. Alliey-Rodriguez, C. Liu, After GWAS: Searching for genetic risk for schizophrenia and bipolar disorder. *The American Journal of Psychiatry*. 168 (2011) 253–256.

Grozeva et al., 2010 D. Grozeva, G. Kirov, D. Ivanov, I.R. Jones, L. Jones, E.K. Green, D.M. St Clair, A.H. Young, N. Ferrier, A.E. Farmer, P. McGuffin, P.A. Holmans, M.J. Owen, M.C. O’Donovan, N. Craddock, Rare copy number variants: A point of rarity in genetic risk for bipolar disorder and schizophrenia. *Archives of General Psychiatry*. 67 (2010) 318–327.

Psychiatric GWAS Consortium Coordinating Committee, 2009 Psychiatric GWAS Consortium Coordinating Committee, Genomewide association studies: History, rationale, and prospects for psychiatric disorders. *The American Journal of Psychiatry*. 166 (2009) 540–556.