

Implications of Genetic Findings for Understanding Schizophrenia

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From the perspective of those of us working on the genetics of schizophrenia, recent progress in identifying specific genetic risk factors at highly robust levels of statistical significance has been striking. However, the prevailing response among other schizophrenia researchers and some funders, families, and sufferers is often one of disappointment. In particular, it is often claimed that these discoveries explain only a small proportion of the genetic risk and hence tell us little about the nature of schizophrenia. The purpose of this article is to persuade you that recent genetic findings, while only revealing the tip of a complex genetic iceberg, already have profound implications for our general understanding of the classification and pathogenesis of schizophrenia and related disorders and that these have implications for schizophrenia research of all kinds.

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Genetic Architecture and Genetic Findings

It is not my purpose to provide a detailed review of recent genetic findings in schizophrenia; these can be found elsewhere.^{1–4} The headline is that, in accordance with population genetic theory and genetic epidemiological predictions, we now have molecular genetic evidence that a very large number of genes, possibly thousands, contain risk alleles for schizophrenia in the population and that genetic susceptibility involves a spectrum of risk alleles, from common to rare, with individual effect sizes ranging from small to large, but with each allele contributing only a small fraction to the total population variance. Genome-wide association studies (GWAS) have identified a number (c20) of specific common risk alleles at stringent genome-wide levels of significance and evidence for a substantial contribution (at least 25% of total risk) from many unidentified common risk alleles when the effects of many genetic variants are measured *en*

masse.^{5,6} Comparison with other common diseases, such as type 2 diabetes, suggests that schizophrenia is not atypical in this respect³ and that larger studies, in of the order of 50–100 000 cases, compared to the c12 000 cases that have undergone GWAS to date, will likely detect many other risk loci at stringent levels of statistical significance.

As well as indicating the role of common genetic variants in risk of schizophrenia, GWAS have also pointed to a substantial genetic overlap with bipolar disorder in regards both to specific risk alleles and to unidentified common risk alleles measured *en masse*. This overlap is supported by recent genetic epidemiological studies, and it challenges traditional assumptions that the two disorders are genetically distinct.⁷

The second major advance in the genetics of schizophrenia has been the convincing demonstration in a number of studies that risk is conferred by a class of relatively uncommon variant often referred to as copy number variations (CNVs). CNVs are submicroscopic deletions and duplications of segments of DNA that are important sources of individual genomic variation. These can disrupt gene function by increasing or decreasing gene dosage, by perturbing normal regulation of expression, and possibly by as yet unknown mechanisms. There is evidence both for an increased burden of large rare CNVs in schizophrenia and that risk is conferred by a number (at least 10 identified to date) of specific CNV loci. These individually confer relatively high risks of schizophrenia (odds ratio [ORs] 3–30) compared with the common risk alleles identified by GWAS (ORs < 1.3), but, because they are rare, the population risk conferred by each is small and in fact comparable to common risk alleles identified by GWAS.⁶ There is also evidence that CNVs occur more frequently as *de novo* mutations in schizophrenia than in controls, and thus that new, as well as transmitted, mutations contribute to disease.^{8,9}

Many of the specific CNVs implicated impact on multiple genes with the notable exception of deletions affecting *NRXN1*.¹⁰ Many more CNVs including very rare

and even unique variants are likely also to confer risk, and the larger studies recommended above will identify more associated CNVs implicating more individual genes and pathways. In addition, the role of uncommon and rare single nucleotide variants and small insertion/deletions in schizophrenia is currently being addressed by many groups using whole exome and genome sequencing though few such studies have been published to date and their findings are inconclusive due to the small samples studied.

The finding of most general importance to psychiatry to have emerged from the study of CNVs is that the specific variants that are significantly associated with schizophrenia are also associated with a range of other neurodevelopmental disorders such as autism spectrum disorders, intellectual disability (ID), and attention-deficit hyperactivity disorder (ADHD), as well as other phenotypes such as generalized epilepsy.¹¹

In conclusion, the application of new methods in large well-powered studies is yielding robust findings. These suggest that many genes are involved and that risk alleles occupy a spectrum of frequency from common to rare, with individual effect sizes ranging correspondingly from small to large, but with each allele contributing only a small fraction to the total population variance. These findings not only indicate the tractability of schizophrenia to genomic analysis but also indicate that very large studies will be required, whether rare or common variants are sought, in order to satisfy the necessarily conservative burden of statistical proof.¹ Another obvious conclusion is that the effects of risk alleles are highly pleiotropic at the level of clinical presentation with repeated examples of both common and rare risk alleles conferring risk across current diagnostic categories.

Impact of Genetic Findings on Classification and Nosology

In the absence of a solid understanding of pathophysiology, psychiatric diagnoses are descriptive and largely syndromic in nature. Genetics, in the form of family history and other genetic epidemiological data, has traditionally been regarded as a cornerstone of psychiatric nosology forming one of the three criteria proposed by Robins and Guze¹² for validating nosological categories. It follows that recent genetic findings strongly challenge the etiological basis of current diagnostic approaches. In fact, there is a wealth of evidence from other areas of research suggesting that the predominant view of schizophrenia as a discrete disorder, or set of disorders, with specific causes, symptoms, and consequences is incorrect.^{11,13} Obstetric complications and other factors such as maternal infection and prenatal nutrition, which are associated with early cerebral insult, have been consistently implicated as environmental risk factors for a range of neurodevelopmental disorders including non-syndromal ID, autism, ADHD, epilepsy, and schizophrenia. The similarity between this range of outcomes and

that seen in association with pathogenic CNVs is striking. In the 1950s,¹⁴ Pasamanick and colleagues proposed the hypothesis of a “continuum of reproductive causality” consisting of brain damage incurred during pregnancy or during or around birth leading to a gradient of injury extending from fetal and neonatal death through cerebral palsy, epilepsy, ID, and behavioral disorder including schizophrenia. Given recent genetic findings, it seems reasonable to modify this concept to encompass a continuum of genetically *and* environmentally induced neurodevelopmental causality along which lie what we currently define as ID, epilepsy, autism, ADHD, schizophrenia, and possibly the major affective disorders.^{7,11} This view recognizes the degree of etiological and symptomatic overlap between diagnostic groups and the lack of clear diagnostic boundaries and sees the major clinical syndromes reflecting in part the severity and predominant pattern of abnormal brain development and resulting functional abnormalities and the modifying effects of other genetic and environmental factors.¹¹

Impact of Genetic Findings on Understanding Pathogenesis

The occurrence of psychosis is still thought by many to be the predominant and defining feature of schizophrenia. Yet, psychosis occurs in many psychiatric syndromes and is common in the general population occurring in many who never seek psychiatric treatment. In fact, schizophrenia shares a number of clinical features with other disorders and is often associated with an impairment of cognition that increasingly seems to be generalized rather than specific.¹⁵ There is general consensus that psychotic symptoms reflect, at least in part, a hyperdopaminergic state.¹⁶ However, this seems to lie downstream of more fundamental defects, and dopaminergic drugs, while partly effective in treating positive symptoms, have little or no effect on the negative and cognitive symptoms.

While we have only identified a small fraction of the genes likely to be implicated in risk for schizophrenia, we can ask to what extent findings to date can illuminate disease biology. It is incorrect to assume, as some do, that the identification of relatively common but small effect risk alleles by GWAS cannot point to specific biology, and refutations of this assumption can be found for other complex disorders.¹ In schizophrenia, associated genes (*CACNA1C*, *NRGN*, *TCF4*) implicate ion channels and synaptic function, as well as a specific miRNA (*MIR137*) and its downstream targets. There is also some evidence from gene set analyses of GWAS data implicating neuronal adhesion molecules and other synaptic proteins.^{17,18} There is also optimism, founded on experience in other genetically complex phenotypes, that these types of analyses will be more informative when applied to much larger samples. The relative complexity of the brain and our general ignorance about the ways in which proteins combine and interact also suggests that this work will benefit from more

detailed annotation of the brain proteome, and recent data from CNVs support this view.⁸

Rare alleles associated with higher individual risk are more attractive targets for animal and cellular studies of disease biology, but the problem here is many schizophrenia-associated CNVs involve multiple genes and it is usually not immediately clear which are relevant to pathogenesis. As we have seen, an exception here is *NRXN1* deletions, which are robustly associated with schizophrenia and other neurodevelopmental disorders. *NRXN1* encodes the presynaptic neuronal cell adhesion molecule neurexin 1, and these findings, together with gene set analyses of GWAS data, point to the importance of this class of molecule and abnormalities of synaptic development and function in schizophrenia and related disorders. Another approach to gain biological insights from the association with CNVs is to identify gene sets representing biological pathways that are over represented among those genes disrupted by CNVs. The involvement of well known synaptic proteins in disease associated CNVs has long been recognized,^{19,20} but these studies have been hampered by the fact that brain genes are larger than average and hence more likely to be hit by a CNV and the fact that many CNVs are not common enough in the population to have been statistically robustly implicated in risk. Two recent studies have tackled the latter problem by focussing on CNVs occurring *de novo* in cases of schizophrenia that are highly enriched for pathogenic events and by using appropriate statistical correction for gene size. One study using manually curated gene sets based on proteomic studies found that case *de novo* CNVs were significantly enriched for genes encoding members of the postsynaptic density proteome, specifically those involved in N-methyl-D-aspartate receptor signaling complexes and synaptic plasticity.⁸ A second study using independent samples and methods²¹ identified several functional categories (defined by the Gene Ontology project) to be enriched among case *de novo* CNVs, and a subsequent analysis that tested the enrichment of these groups in a large case control data set showed enrichment of genes encoding proteins or involved in synaptic function and neurodevelopment.

It might seem premature to try and draw strong conclusions from these studies given the small proportion of genetic susceptibility accounted for by alleles in specific genes. However, the findings to date appear to be pointing to synaptic mechanisms that are of fundamental importance to brain development and function. This is congruent with findings suggesting that schizophrenia and related disorders are associated with fairly generalized cognitive dysfunction and with the widespread abnormalities seen in imaging studies. Thus the complex constellation of symptoms and syndromes that we see in individual patients likely reflect developmental and functional disturbances in a wide range of brain systems and psychological

processes and are unlikely to be understandable in terms of a single pathway from pathology to diagnosis.

Conclusions and Implications

As I hope, I have persuaded you that recent genetic findings, while providing a far from comprehensive catalog of specific risk genes, challenge some of our cherished notions about the nature of schizophrenia and its relationship to other disorders. The specific risk variants identified to date confer risk to a range of neurodevelopmental disorders such as schizophrenia, autism, ADHD, and ID, as well as other phenotypes such as generalized epilepsy.¹¹ Taken together with a wealth of evidence for symptomatic and familial overlap and for shared environmental factors, these findings suggest that it is no longer tenable to regard these as discrete disorders, or sets of disorders, with specific causes, symptoms, and consequences.^{11,13} Rather we can conceive a continuum of genetically and environmentally induced neurodevelopmental causality along which these disorders lie.^{7,11} These findings strongly suggest that research on disease pathogenesis should not focus on specific diagnostic categories but should rather seek to identify the cross-diagnostic processes upon which the effects of these and other as yet undiscovered risk alleles converge. Moreover, the genetic findings strongly suggest that we should initially seek such convergence in alterations of synaptic and neuronal network plasticity.

This is not to say that we are yet in a position to jettison current criteria from the clinic and replace them with a new neuroscience-based approach. Current diagnostic categories are likely to remain clinically useful to the extent that they best inform management and prognosis, but these will require modification as future research indicates closer relationships between specific phenotypes and to mechanism and will likely need to include dimensional and categorical entities. We can also envisage psychiatrists of the future using multidimensional (syndromic/symptomatic and etiological) diagnoses similar to those in use to day by oncologists. However, researchers need to appreciate the complexities and shortcomings of psychiatric nosology; current categories will remain useful for research so long as we expect heterogeneity and overlapping risk factors and mechanisms. But we must also be prepared to explore novel dimensional and categorical approaches that cut across current diagnostic groups and better capture underlying psychology and biology. It is likely that mechanistic insights will be most fruitfully sought by studying endophenotypes and by taking a cross-disorder or diagnostically neutral approach. These will likely be both top-down, relating specific psychopathological syndromes to phenotypes defined by cognitive psychology and neuroscience rather than diagnosis,²² and bottom-up, relating genotype to fundamental measures of neuronal and synaptic function in human, animal, and cellular studies. In regard to the

latter, the recent identification of highly penetrant risk alleles offers the opportunity for the first time to develop animal and cellular models of high construct validity for the study of psychiatric disorders. The development of these informative models is essential for the identification of endophenotypes, the understanding of mechanism, and the testing of novel therapeutics. But work in this area can only lead to translatable outcomes if it is linked to parallel and integrated program of work in human volunteers and patients. This will enable the validation of findings across species and the identification of endophenotypes and biomarkers that will be essential for understanding mechanism and developing new treatments.

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