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Commentary

A developmental perspective on the convergence of genetic risk factors for neuropsychiatric disorders

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To what extent do genetic risk variants for psychiatric disorders converge on discrete biological processes? In 2013, Kenneth Kendler outlined 4 potential scenarios that might eventually explain the then emerging results from genome-wide association studies (GWAS), exome sequencing and copy number variant (CNV) analyses of these disorders (1). At one extreme, risk variants for a given disorder could show no biological coherence, affecting numerous disparate systems that ultimately give rise to the condition. At the other, risk genes for the disorder could form a single interconnected network, affecting a specific biochemical pathway, neural circuit or cellular function. The continued success of large-scale genomic approaches in identifying risk loci for neuropsychiatric disorders has enabled investigators to shed light on this issue: for schizophrenia, there is now good evidence that associated rare CNVs and smaller *de novo* coding mutations are enriched within (although by no means specific to) genes involved in synaptic function (e.g. 2, 3), while for autism spectrum disorder (ASD) such variants implicate processes such as synapse development and chromatin remodelling (e.g. 4, 5).

The paper of Forsyth and colleagues (6), published in this issue of *Biological Psychiatry*, explores convergence of risk genes for both autism and schizophrenia in terms of developmental co-expression and protein interactions. Like the earlier study of Perikshak et al (4), the authors make use of human brain transcriptomic data from the BrainSpan project in order to construct modules of correlated gene expression across development, but extend these to encompass human brain development in its entirety, from the first trimester of gestation through to adulthood. The paper also advances on earlier studies in that it considers enrichment of genes affected by the full spectrum of risk variants for these disorders – from rare CNVs and protein-damaging point mutations to common alleles of weak effect – within these developmental modules. Although the genes targeted by common (typically non-coding) risk variants are less easily predicted than those disrupted by coding mutations or CNVs, the authors identify 3 modules containing genes enriched

for common variant association with schizophrenia. One of these modules, containing genes involved in synaptic transmission, was found to be additionally enriched for genes disrupted by schizophrenia-associated CNVs, while another, containing genes involved in RNA processing, was also nominally enriched for rare coding variants associated with the disorder. GWASs of ASD are only recently reaching sufficient sample sizes to yield genome-wide significant associations (7), but several developmental modules enriched for rare damaging coding variants in the condition (including one involved in gene regulation and another in neuronal differentiation) are also noted to be enriched for common variant association, albeit at nominal significance.

In considering both schizophrenia and ASD, Forsyth et al highlight similarities and differences between the diagnoses in terms of modules of risk factor enrichment and the timing of their expression. Thus, ASD-associated genetic variation is reported to be enriched in all 3 modules enriched for schizophrenia risk variants, two of which (involved in synaptic transmission and neuronal excitability) exhibit maximal expression in the post-natal brain, while the other (involved in RNA processing) is most highly expressed during early fetal development. In addition, the authors identify 4 modules that appear specifically enriched for ASD risk genes; the expression 3 of these (including those involved in gene regulation and neuronal differentiation) peaks during fetal development, while that of the fourth (involved in synaptic signalling) plateaus in late gestation. As the authors note, it may be speculated that the apparently greater loading of genetic risk factors for ASD on prenatal developmental processes may contribute to the earlier onset of this condition compared to schizophrenia. That the authors identified no schizophrenia-associated modules that were not additionally enriched for ASD risk genes might also provide clues to the relationship between the two conditions - and the overlap could help explain reports of increased risk of psychotic disorders in people diagnosed with ASD in childhood (8).

A major focus of Forsyth and colleagues' study is a region on chromosome 22q11.2 where hemizygous deletions, occurring in ~ 1 in 4000 live births, cause a multisystem syndrome (22q11.2 deletion, or velocardiofacial, syndrome) in which cognitive impairment is a common feature. Typically encompassing around 60 known genes, CNVs in this region are also potent risk factors for schizophrenia and a range of other neuropsychiatric conditions (9, 10), but the responsible gene(s) and mechanisms are unclear. Using protein interaction databases, Forsyth et al construct a protein-protein interaction (PPI) network for genes within the typical (~3Mb) CNV region, restricting these to genes that are mutually expressed in the human brain during at least one developmental period. Intriguingly, they find that this extended chromosome 22q11.2 protein network is over-represented in several gene expression modules enriched for other schizophrenia / ASD genetic risk variants, including those involved in synaptic transmission and the regulation of gene expression. The authors highlight several genes within the deleted region that are connected to these modules (e.g. *SEPT5*, *PI4KA* and *SNAP29* to modules associated with synaptic function, and *DGCR8* and *HIRA* to those associated with gene regulation), thus suggesting these as candidates for increasing risk of neuropsychiatric disorders in chromosome 22q11.2 CNV carriers.

As well as supporting the view that neuropsychiatric phenotypes arising from CNVs at chromosome 22q11.2 result from disruption of more than one gene, the study of Forsyth *et al* also provides a framework through which gene networks underlying other neuropsychiatric traits associated with CNVs in this region (e.g. attention deficit hyperactivity disorder and anxiety) might be explored. Indeed, the variability in cognitive deficits and neuropsychiatric phenotypes in chromosome 22q11.2 CNV carriers suggests that these gene disruptions are amenable to modification, which could be of therapeutic relevance.

As the authors point out, experimental manipulation will be required to elucidate the functional consequences of chromosome 22q11.2 CNV gene disruptions on their implicated gene networks, and the same may also be said for other forms of neuropsychiatric risk variation. However, advances in genome engineering technology (e.g. CRISPR) as well as human neural cell models make high-throughput functional assessments of risk alleles a realistic prospect. In coming years, our understanding of the molecular convergence of genetic risk factors for neuropsychiatric disorders will also be greatly informed by transcriptomic, epigenomic and, potentially, proteomic studies of the human brain using single-cell technology. With even larger sample sizes, improved analytic methods and technologies such as whole genome sequencing, our understanding of the genetic underpinnings of these disorders will also increase. Although risk alleles for neuropsychiatric disorders are unlikely to conform to the most coherent possible biological scenario outlined by Kendler (1), patterns of convergence, such as those highlighted by Forsyth et al, seem likely to emerge, and it may be hoped that some of these can be targeted for patient benefit.

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