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Commentary

Parsing psychosis subtypes through investigations of rare genetic variants

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While we have now identified >100 common single nucleotide polymorphisms (SNPs) contributing to risk for the umbrella diagnosis of schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014), the genetic contribution to variation in clinical expression for schizophrenia is far less clear. Most prior work in this area has focused on common variants (Bergen et al., 2009; Fanous and Kendler, 2008), often in selected candidate genes, although, some recent studies have used genome-wide association studies (GWAS) to investigate symptom variation in schizophrenia (Docherty et al., 2015; Bergen et al., 2014; Edwards et al., 2016; Fanous et al., 2012). The findings thus far are inconclusive or unreplicated.

The role of rare genetic variants (<1% frequency) has been much more challenging to study. Evidence is mounting for their involvement in schizophrenia risk, but their rarity often necessitates aggregation across genes or biological pathways for analyses (Purcell et al., 2014). The study by Kranz et al. represents a much-needed step forward as the first to explicitly explore the role of rare genetic variation in expression of schizophrenia (Kranz et al., 2016).

For four genes (PTPRG, SLC39A13, TGM5, and ARMS/KIDINS220) previously shown to have *de novo* or rare mutations in people with schizophrenia, a sample of 48 ancestrally diverse familial and sporadic schizophrenia cases were examined for novel or rare missense-coding variants and their relationship to clinical characteristics (Kranz et al., 2015a, 2015b). Fifteen of these patients carried at least one such variant. The four or five individuals carrying altered forms of these genes in functional domains were compared to non-carrier cases as well as controls for a range of symptoms, IQ measures, memory task performance, and other characteristics. For each gene, carriers exhibited somewhat different features than non-carriers, suggesting two possible models: 1) they confer risk for forms of schizophrenia with distinct clinical profiles (i.e. susceptibility-modifier genes) or 2) these genes merely modify the presentation of schizophrenia (i.e. modifier genes). The correct model may depend on the gene or variant in question and will require additional investigation.

The main innovation of this study lies in its connection of rare sequence-derived variants to an impressive array of clinical features. Like most trail-blazing studies, replication and use of larger samples will be essential to solidify these tenuous initial findings. For future studies, the few genes studied so far will almost certainly grow to encompass all gene coding regions (known as the exome) and ultimately involve the whole human genome. As the scope of these studies increases, the scale will need to, as well. Since rare genetic variants are, by definition, not observed often, the number of subjects that will be needed for sufficient statistical power to detect associations will be even greater than the large samples currently used in GWAS.

Furthermore, while common genetic variants are often observed across populations, rare variants are more likely to be population specific. Therefore, combining subjects of different ancestry is an even greater concern for studies of rare variants and their effects than for most genetic studies. The diversity in ancestry represented in this study is a refreshing change from most genetic association studies, but potentially clouds interpretation when the frequencies of the observed variants are not precisely known across populations. False associations due to "population stratification" may occur. Furthermore, rare missense-coding variants and novel missense-coding mutations are not compatible with currently used GWAS methods, since only genetic polymorphisms a) above 1% minor allele frequency are analyzed and b) most lie in the non-coding regions of the human genome.

Another difficulty facing this and other studies is the lack of annotation detailing the effects of genetic polymorphisms and novel mutations. Many times, changes of one single base to another have no influence at all, while other times this could reduce (or increase) gene expression, change or inactivate a protein, or even have lethal effects. Predictions of the effects are predominantly carried out "in silico" through computational algorithms (e.g. PolyPhen2 and SIFT) with relatively little substantiation from laboratory experimentation. Consequently, we have only a rough idea of the true biological effects of most genetic variation in humans. Improvements in annotation will concomitantly enhance the interpretation of studies connecting genetic variants and clinical features.

As noted by the authors, identifying gene-phenotype relationships within psychosis will facilitate precision medicine efforts. Patients may respond well to one medication but not another, and clinicians currently have little to guide their decisions besides trial and error. The different

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biological pathways leading to psychosis will undoubtedly be amenable to different pharmacological manipulations, and understanding these connections is critical to improving care for the affected patients. However, much more research needs to occur before translation of these provisional findings into clinical practice can occur.

The study by Kranz et al. (2016)) is an exciting peek into the future of psychiatric genetics as we work towards a more fine grained understanding of the ways in which genetic variation contributes to the immense variability in expression of psychotic illnesses. Investigations of relationships between genetic variants and clinical features will shed light on the etiology of schizophrenia in ways that will facilitate studies of the different biological mechanisms leading to this diagnosis and ultimately generate targeted therapeutics for the different schizophrenia subtypes.

Disclosure

The author declared no conflicts of interest.

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