Box S2 | Genetics of schizophrenia: insights into identification of clinically high-risk subjects and potential course-altering therapeutics

In light of the high heredity of schizophrenia, there has been considerable interest in the use of genetics for identifying people at a high risk of transition. However, this is proving a challenging task since the genetic architecture of schizophrenia is complicated, with few or no clear-cut and simple signals of risk. Rather, schizophrenia involves a spectrum of risk alleles, with the vast majority of small individual effect sizes such that each contributes only a tiny fraction to total population variance and individual risk. Thus, genome-wide association studies have so far identified more than 120 common, small-effect risk loci at genome-wide levels of significance corresponding to about half the heritability of schizophrenia. In addition, there are around a dozen very rare but recurrent copy number variants that confer a somewhat higher individual risk, although not greater than 1 or 2%. Recent whole-exome sequencing studies have also established a role for rare, de novo (<1 per 10,000 chromosomes) disruptive mutations distributed across many genes. Additional studies with larger samples should hopefully pinpoint other risk alleles with a spectrum of allele frequencies, and it is likely that only a fraction of genes linked to schizophrenia have as yet been identified. Several observations with interesting implications for course-alteration may be highlighted.

First, certain genes may nonetheless be consistently linked to schizophrenia such as Neurexin-1. Furthermore, Neuregulin-1 was specifically associated with risk of conversion, a result warranting confirmation and extension to other individual genes.

Second, hundreds of genes nonetheless modify the risk of schizophrenia and understanding their relevance to transition is challenging. Success will require a number of approaches including bioinformatic analyses of convergence of individual genes into functionally related clusters. For example, there is a particular significance of interacting proteins controlling synaptic plasticity which is developmentally disrupted prior to conversion. Post-synaptic scaffolding proteins modulating glutamatergic signalling, proteins that regulate cytoskeletal dynamics, and proteins comprising L-type calcium channels also appear to be of special significance. In view of these interactions, gene/protein networks may yield more robust links to risk of schizophrenia than individual genes, as recently demonstrated. Indeed, a polygenic signature (embracing certain consistently associated genes as well as specific, rare, high-penetrance alleles) may eventually aid in the characterisation and stratification of subjects at risk of conversion to psychosis. In particular, if coupled to other readouts of risk (see main text).

Third, certain gene variants and proteins linked to schizophrenia confer accrued susceptibility for other psychiatric disorders like autism and bipolar disorder.

Experimental studies should seek to identify specific developmental and functional anomalies on which genetic risk factors converge, not only a direct link to schizophrenia per se. In this way, it may be possible to find reliable genetic biomarkers of domains of dysfunction manifest prior to diagnosis and predictive of eventual conversion. As implied above, certain domains of dysfunction may be shared by other — ostensibly distinct — diagnostic entities, so this approach is tempered by a possible lack of specificity in predictions of transition.

Finally, complicating matters further, it is a long way from the gene to the protein: many genetic links to the genesis of schizophrenia may be overwitten by epigenetic factors likewise incriminated in its aetiology.