PERSPECTIVE

Revealing molecular secrets

The more we study the genetics of schizophrenia, says **Steven E. Hyman**, the more daunting — and exciting — are the challenges we see ahead.

The genetic analysis of schizophrenia and other psychiatric disorders, such as bipolar disorder and autism, has begun to yield replicable and informative results at the molecular level[1–3]. These successes are creating epochal opportunities to understand disease mechanisms and allow us to envisage an era of therapeutics directed at pathogenic processes — unlike current antipsychotic and antidepressant drugs that merely control symptoms.

But the emerging picture reveals great challenges ahead for translational neurobiology. Schizophrenia is highly heritable, but unlike diseases caused by a single, highly penetrant mutation (causing a phenotype with high probability), in schizophrenia the large aggregate risk attributable to genes is seen to have a polygenic basis. Disease liability is being mapped to hundreds, perhaps ultimately more than a thousand, genetic loci, each contributing a small increment of risk[1,2,4]. Further, many of the risk-associated genetic variants (risk alleles) for schizophrenia also contribute to the risk of bipolar disorder, autism, depression and other psychiatric disorders[5].

Copy number variants (CNVs), duplications or deletions of DNA segments affecting up to 40 genes have been found in the genomes of 2.5% of people with schizophrenia (but only 0.9% of healthy subjects). Some CNVs are potent risk factors for schizophrenia (increasing risk 10–25-fold), but even the highest-risk CNVs tell a muddled story, as they are also associated with intellectual disability and autism spectrum disorders[6]. So risk of schizophrenia is polygenic, heterogeneous across individuals, and overlaps with risk of other disorders depending on the genetic background and exposure to environmental risk factors.

As the genetic analysis of schizophrenia proceeds with ever more subjects, the list of schizophrenia-associated genes, already large, will grow further and the results will gain in certainty. However, it would be a Pyrrhic victory if the resulting list of genes yielded no biological insights that ultimately led to effective treatments.

It is not yet clear how to achieve the desired outcomes. Current tools to study gene function have been optimized to investigate highly penetrant mutations with large effects on phenotype. Typically, researchers study the effects on phenotype that result from either knocking a gene out entirely or inserting a highly penetrant allele into an animal model. But given the low penetrance of schizophrenia-associated alleles, and their ability to contribute to different diseases depending on the genetic background of the organism, inserting one or even several into an animal model may yield a phenotype that is ambiguous with respect to human disease — or no phenotype at all.

The large number of genes involved in schizophrenia, and their combinatorial interactions, require models that permit efficient testing of many different hypotheses. Moreover, many loci that contribute to polygenic disorders including schizophrenia occur in non-coding parts of the genome, which are less well conserved in evolution than segments of DNA that encode proteins. For this reason, and because many features of schizophrenia pathogenesis occur in evolutionarily recent neural cell types and circuits, it is critical to take evolution into account in matching a model to the question being asked. Given such constraints, the kinds of genetic mouse models that have been used for decades to study diseases caused by single, highly penetrant mutations are likely to have severe limitations for the study of schizophrenia.

According to a model for how polygenic risk factors operate, the products of allelic variants appear in key protein networks and biochemical pathways in cells and perturb their function, causing disease. Each individual is likely to have a different combination of variants that produce pathological tweaks in these networks. The ability to study these networks is more likely than studying individual genes to yield insight into schizophrenia mechanisms and to suggest drug targets. For example, a possible protein network arising from the schizophrenia genetic data is involved in the postsynaptic specialization of excitatory neurons[2–4].

Despite a wealth of genetic findings, further investment in gene discovery is needed. Each risk allele discovered identifies a gene with some role in pathogenesis, and provides a new piece in the jigsaw puzzle from which important networks and pathways emerge[4].

A more difficult question concerns the selection of living systems, cells or animal models for the functional analysis of alleles and pathways. Thanks to advances in genome engineering, it should be possible to insert DNA sequences of interest into many models, and enable researchers to engineer many mutations at once[7]. Models may include induced pluripotent cell lines and human embryonic stem-cell lines reprogrammed into neurons to study molecular and cellular mechanisms, and serve as a platform for chemical screens. Progress is being made in reprogramming such cells into relevant neuronal and glial cell types, although questions remain over the cell types most involved in various psychiatric disorders.

Invertebrates, zebrafish, mice and non-human primates may all prove to be useful genetic models. It is too early to say what combination of approaches will work. All we know is that the emerging genetic discoveries will call for innovation and a willingness by foundations, government funding agencies and scientists to try new things. ■

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