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Editorial / Editoryal

The Genomics Revolution in Psychiatry: A Lesson from Bipolar Disorder

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April 14, 2013 was the 10th anniversary of the completion of the first draft of the Human Genome Project (http://www.genome.gov/). Results are still far from the revolution "in the diagnosis, prevention and treatment of human disease" forecasted by president Clinton. However, in the last decade psychiatric genetics has seen unprecedented advances in understanding the mechanisms underpinning many severe disorders, including bipolar disorder.

Genetics of Bipolar Disorder

The clinical wisdom that bipolar disorder runs in family has been confirmed by a great amount of research. Genetic epidemiological studies estimate that the heritability of bipolar disorder ranges from about 60% to more than 90% (1,2).

In the past decade great research efforts have been involved in the exploration of these inherited factors. Several molecular genetic approaches have been developed to identify genetic variants related to common complex traits.

In the first studies linkage analyses were conducted on few large families. Genetic markers on the DNA were used in an effort to find the rough location of postulated rare gene variants ("mutations") associated with a risk of a disease.

Another widely employed strategy was to look at candidate genes, which were selected on the basis of pathophysiological theories of disease involving their coded proteins (for example genes encoding for neurotransmitters).

With a sharp drop in the costs and a fast increase in the resolution of DNA mapping, new and more powerful techniques have emerged. In the past decade, genome-wide association studies (GWASs) have become the most popular approach to genetics of complex disorders. These studies rely on a more intensive DNA sequencing across the entire genome. By comparing subjects with a disorder to healthy controls, GWASs statistically link common genetic variants, known as single nucleotide polymorphisms (SNPs), to the disorder of interest. GWASs require big sample sizes of the order of thousand of participants. For this reason, research efforts from different centres have been unified under collaborative consortia.

The Psychiatric GWAS Consortium – Bipolar Disorder Working Group reported results from the largest study to date, including 11,974 cases with bipolar disorder and 51,792 controls (3). It confirmed the genome-wide significant evidence of association for the gene CACNA1C (encoding an alpha-1 subunit of a voltage-dependent calcium channel) and found a new locus in ODZ4 (a highly conserved gene encoding for a protein with dimerization activity),

while it did not replicated the significant associations for several loci, including ANK3 (encoding for an ankyrin found in the axonal initial segment and nodes of Ranvier of neurons) and SYNE1 (a spectrin repeat containing protein that localizes to the nuclear membrane) that had emerged in previous and smaller GWASs studies (4). It is possible that the failure in replicating some previous genome-wide significant loci is due to true effect sizes that are actually smaller than originally estimated and thus larger samples are needed for replication.

Despite these robust results, GWASs currently explain only a very small amount of the genetic risk. For example, about 30% of the general population carries the susceptibility allele within CACNA1C and this variant increases the risk of developing bipolar disorder by only about 18%. Evidence converges on a polygenic component in the pathogenesis of bipolar disorder, with a large number (hundreds or thousands) of genetic variants of small effect accounting for approximately 20-30% of the heritability estimated from family and twin studies (5).

Pathway analysis has been used to extract meaning from long lists of SNPs produced by GWASs studies by identifying groups of genes that function in the same biological pathways. The Psychiatric GWAS Consortium – Bipolar Disorder Working Group reported significant enrichment for genes involving voltage gated calcium channel activity. The robust findings of an involvement of voltage-dependent calcium channel in the pathogenesis of bipolar disorder are of great interest. There are in fact clinical reports on the mood stabilizing effects of L-type calcium channels blockers (e.g. Verapamil) and on their direct efficacy in bipolar disorder (6).

SNPs are not the only source of variation in human DNA. Copy number variants (CNVs) are deletions or duplication of large segments of DNA sequence consisting of between one thousand and five million bases. Despite the promising results in other severe psychiatric disorders such as schizophrenia, the role of CNVs in bipolar disorder is still unclear, but certainly is less than in schizophrenia or autism.

Rethinking Bipolar Disorder

The association between genotype and phenotype for psychiatric disorders is complex. There is no place for reductionism (7) or dualistic views that contrast supposedly pure genetic models against supposedly pure environmental models.

Bipolar disorder is a heterogeneous group of conditions that involves in the majority of cases the interaction of multiple genes or more complex genetic mechanisms – together with the effects of environmental risk factors. The way genetic and non-genetic components interact during brain development and function is better explained by stochastic than deterministic models. Moreover, the genetic risk to bipolar disorder is mainly given by multiple genes of small effect and therefore findings of susceptibility loci are not useful in creating predictive tests, especially if used on their own. However, psychiatric genetics offers a privileged window on the pathophysiology of mental disorders and gives important clues for understanding the biological mechanisms causing mental disorders and the relationships between psychiatric illnesses.

The current psychiatric nosology is based on clinical observations from the late 19th century. However, genetics has provided new criteria for the definition and classification of psychiatric disorders. An example of phenotype refinement using genetic information is the evidence of a specific association between the gene encoding the GABA-A β1 receptor and schizoaffective disorder, bipolar type (8). Other studies of phenotypic aspects included mood incongruent psychotic symptoms, suicidality and temperament. Although some have reported signals that just achieve genome-wide significance, they need to be interpreted with caution.

Consistent evidence from epidemiological (2) and molecular genetic (5,9) studies have also provided insight in the nosology of psychosis, showing an overlapping susceptibility between bipolar disorder and schizophrenia. Combining GWASs results from schizophrenia and bipolar, significant genome-wide loci were discovered for ZNF804A (encoding for an intracellular zinc finger protein), ITIH3-ITIH4 (encoding

for inter-alpha-trypsin inhibitors, a family of structurally related plasma serine protease inhibitors), ANK3, CACNA1C and MAPK3 (encoding for a mitogen-activated protein kinase 3, involved in signaling cascades that regulates various cellular processes).

Interestingly, none of the genes directly involved in classical neurotransmitters pathways (such as monoaminergic transmission) has emerged in any study using hypotheses-free approach.

In the last decade there has been a revolution in the way we conceptualize mental disorders. The picture that emerges from genetic studies is much more complex than the reductionist views of discrete disease-entities caused by imbalances in the neurotransmission. However, a satisfactory understanding of severe mental disorders is still far away.

A range of genetic and non-genetic research approaches is required to help us to better understand psychiatric illness. Genetic data from different experiments need to be integrated with information about gene interactions, regulation and expression, knowledge of proteomics and biological pathways and the broader understandings of neuroscience, including neuroimaging studies.

A promising approach come from human induced pluripotent stem cells. They are generated from adult somatic cells that are reprogrammed to exhibit the characteristics of embryonic stem cells, including the ability to differentiate into specialized cell types, such as neurons. Manipulated experimentally, they have already proved a powerful intermediate for developing and testing pathophysiological understanding (10).

To conclude, genetics, with the help of other research methodologies, is contributing to a revolution in psychiatry. It will lead to diagnoses and treatment based on the biological mechanisms involved in the pathogenesis, with great benefit for patients.

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