# Schizophrenia genetics: a model

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The Kraepelinian dichotomy – the broad division of major mood and psychotic illnesses of adulthood into schizophrenia and manic depressive illness (bipolar disorder) – has been enshrined in Western psychiatry for over a century and continues to influence clinical practice, research and public perceptions of mental illness. There have been several important research findings in genetics over the last 5 years that will help to improve understanding of schizophrenia and radically change the way we think about its relationship with other major psychiatric disorders. This article will provide a brief introductory overview. The aim is to avoid being technical, to get across major points and, hopefully, to "whet the appetite" so that some readers will want to look at other papers. This article is based on an editorial published last year in the British Journal of Psychiatry.

## Important recent findings

Major recent findings of relevance include:

**1) Family study** - The largest family study of schizophrenia ever conducted, a Swedish population register study of 2 million nuclear families, shows overlap in genetically inherited susceptibility across bipolar disorder and schizophrenia. In other words, some genes influence risk to both schizophrenia and bipolar disorder.

**2) Molecular study of common DNA variants** - Large-scale molecular genetic studies of common DNA variants spread across all the chromosomes (so called "genome-wide association studies") have started to pinpoint some of the genes and biological systems that influence susceptibility to schizophrenia. Typically these studies use 1000s of cases and controls and examine 500,000+ common DNA variants. There is now direct molecular genetic support for a substantial genetic overlap between schizophrenia and bipolar disorder. This evidence includes analyses of specific risk loci including ZNF804A, a gene that encodes a zinc finger protein, and CACNA1C a gene encoding a voltage-gated calcium channel. It is of interest that there is evidence that variation at CACNA1C, also influences risk of recurrent unipolar depression. More broadly, there is molecular genetic evidence for overlap in the identity of several other specific genes influencing risk of both schizophrenia and bipolar disorder. There is also strong evidence from analyses of the aggregate "polygenic" contribution of many common variants of small effect that many of these variants influence susceptibility to schizophrenia and bipolar disorder. These findings are unlikely to surprise clinicians who frequently have to decide how to categorise and treat individuals with a mixture of prominent mood and psychotic symptoms.

**3) Molecular study of rare DNA copy number variants** - Several recent studies have shown that rare structural chromosomal variants (stretches of DNA of length 1000 base pairs or more that vary in number between individuals – some missing a copy, some having an extra copy) are more common in some neuropsychiatric phenotypes than in controls. Such "copy number variants" (CNVs) have been shown to increase the risk of autism, attention deficit hyperactivity disorder (ADHD), learning disability (mental retardation) and schizophrenia, but seem to play a much lesser role in bipolar disorder. The most well-known and studied example is a rare deletion of part of chromosome 22 that causes a developmental syndrome known as Velo-cardiofacial Syndrome (VCFS), one feature of which is mental retardation. Neuropsychiatric diagnoses in both childhood and adulthood occur at a greatly increased rate in individuals with VCFS, with 25% of adults having psychosis diagnoses, usually schizophrenia.

However, mood episodes are common and children have increased rates of autism, ADHD and mood diagnoses. Several other specific copy number variant regions on other chromosomes have similarly been shown to increase risk of schizophrenia and other "neurodevelopmental" neuropsychiatric diagnoses. This indicates an overlap of genetic susceptibility and pathogenesis across the categories of schizophrenia, autism and other neurodevelopmental disorders and challenges the view that these are completely unrelated diagnostic entities.

***Despite important genetic overlaps, schizophrenia and bipolar do not have a single underlying cause and are not the same clinical entity***

These new genetic data show that schizophrenia and bipolar disorder (and autism etc) are not completely separate, unrelated disease categories. However, the data do not support a model of a single disease category that is undifferentiated with respect to the relationship between clinical expression and genetic susceptibility and, hence, underlying biological mechanisms. For example, the same large Swedish family study mentioned above that demonstrated a substantial overlap in genetic susceptibility to bipolar disorder and schizophrenia also provided clear evidence for the existence of *non-shared* genetic and environmental risk factors. These findings are fully consistent with earlier genetic data suggesting that there are relatively specific as well as shared susceptibility genes. Recent molecular studies suggest some of this specificity might be due to structural genomic variation (CNVs) and some studies of common DNA variants also show relative specificity. For example, common genetic variation at genes that encode the GABAA receptor family (a site of action of benzodiazepines, alcohol and some anti-epileptics) influence risk of illness with mixed features of schizophrenia and bipolar disorder (so-called "schizoaffective disorder").

***Approaching a time when we can move towards more biologically plausible and clinically useful models of psychosis***

The main clinical aims of diagnosis include the optimisation of treatments and allowing useful prognostic statements to be made. The history of medicine suggests that therapeutic and prognostic decision-making are usually facilitated, often greatly, as classifications move closer to the underlying biological mechanisms. For this reason it is desirable to move towards a classification that maps the expression of illness onto the underlying biological systems. It is not yet clear whether this will be most usefully achieved by using multiple overlapping "categorical" domains of psychopathology or multiple dimensions. Clinicians benefit from the simplest, most user-friendly model that is clinically useful. Of course, the traditional dichotomy is simple but perhaps the time is finally coming to begin thinking seriously of alternatives.

## A simplified schematic of a complex set of relationships

In the accompanying figure, we show a simplified schematic that relates genetic variation to clinical syndromes, via the complexities of the biological systems and neural mechanisms (modules) of the brain. The brain is a highly complex structure in which high levels of anatomical and functional connectivity occur at many levels. Plasticity occurs at all stages of development and environmental influences cause important short- and long-term effects on brain function. Psychiatry will have to integrate evidence from various levels of neuroscientific investigation – including molecular biology, cognitive neuroscience and affective neuroscience- to move towards a coherent understanding of psychiatric illness that can appropriately use models from each area of inquiry for the benefit of patients. The evidence coming from molecular genetics is but one part – albeit an extremely important part – of the process of piecing together the complex jigsaw that will help to explain the mental illness from which patients suffer. The key messages for the purposes of this article are shown in the boxes around the figure. Interested readers should consult the editorial in the British Journal of Psychiatry for more details about the model (article available freely).

## Conclusion

Recent genetic studies reinforce the view that current approaches to the diagnosis and classification of major psychiatric illness are inadequate. These findings challenge the traditional distinction between schizophrenia and bipolar disorder and suggest that more attention should be given to the relationship between the functional psychoses and neuro-developmental disorders such as autism. We are entering a transitional period of several years during which psychiatry will need to move

from using traditional descriptive diagnoses to clinical entities (categories and/or dimensions) that relate more closely to the underlying workings of the brain. During the transition it will be necessary to be open-minded and flexible. Research will need to move ahead of clinical practice and it is likely to be a little time yet before the traditional dichotomous prototypes will make an exit from official classifications, even though evidence and thinking is moving on.

## GP Comment

**What have I learned from this paper?**

1. The ultimate aim of genetics and related scientific studies on schizophrenia is to provide information on treatment and prognosis but that aim has yet to be achieved.

2. There is an overlap between genetic susceptibility to schizophrenia and bipolar disorder but there are distinctions between the two conditions. There are also overlaps between the genetic predisposition to schizophrenia and other conditions.

3. A number of genetic susceptibilities for schizophrenia have been identified but the interaction between genetics and environment remains important in determining whether an individual develops the condition.

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Bedfordshire.

## Further reading

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**Figure: Schematic hypothesized model of the complex relationship between biological variation and some major forms of psychopathology (reprinted by kind permission of the British Journal of Psychiatry).**

This is a simplified model of a highly complex set of relationships between genotype and clinical phenotype. The key messages for this article are shown in the five light blue boxes arranged around the schematic diagram. More details can be found in the editorial in the British Journal of Psychiatry.