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Genetics and psychosis

REFRESHMENT

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SUMMARY

Genetic research into psychotic disorders is advancing rapidly. On the basis of general evidence for genetic influences from family, twin and adoption studies, molecular genetic studies, particularly genome-wide association studies (GWAS), are identifying a range of common genetic risk factors that each have a small effect on risk, while certain chromosomal copy number variants (CNVs) are rarer, but have a larger effect on risk. There is also evidence for partial overlap of genetic influences among psychotic disorders and with non-psychotic disorders. This brief article summarises the main themes, current findings and potential future directions.

DECLARATION OF INTEREST

None.

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Among the key issues for research into genetic influences on psychotic disorders are: defining the phenotype, i.e. the observable characteristics or symptoms of the illness; investigating general evidence for genetic influences with family, twin and adoption studies; and determining the chromosomal location of DNA risk variants using linkage and association studies. These lead to investigations into the functional/physiological effects of risk variants, with the potential for identifying new targets for treatment.

Phenotypes

The most common phenotype is a lifetime diagnosis of a particular psychotic disorder or group of disorders. Complementary approaches include the use of endophenotypes such as brain imaging or cognitive measures genetically related to psychotic disorders (Gottesman 2003) and of quantitative clinical phenotypes such as symptom scores.

Family, twin and adoption studies

There is strong evidence for familial influences on psychotic disorders. Family studies show that, compared with a lifetime risk for schizophrenia of 0.8–1% in the general population, the risk in siblings of someone with the disorder is around 8–10%, and it increases as more relatives are affected (Gottesman 1991; Lichtenstein 2009).

Twin studies suggest that at least part of this familial effect is due to genetic influences, in that monozygotic (MZ) twin pairs have considerably higher concordance for schizophrenia (~45%) than dizygotic (DZ) pairs (~5–10%) (Cardno 2000). Adoption studies also support genetic influences, in that biological relatives show an elevated risk of schizophrenia despite being separated by adoption and so having little sharing of environmental influences (Lichtenstein 2009). However, the fact that over 50% of MZ co-twins are unaffected, despite being virtually identical genetically, indicates that non-inherited risk factors are also important.

The degree of genetic influences is often investigated by calculating heritability on the basis of concordances in MZ and DZ twins (or other relatives) and the lifetime risk of the disorder. Heritability estimates for schizophrenia are substantial (60–80%) (Cardno 2000; Sullivan 2003; Lichtenstein 2009).

It is likely that the aetiology is usually multifactorial, i.e. many genetic and environmental factors act together to influence risk, and a single risk factor is unlikely to cause the disorder on its own.

Similar patterns of heritability and risks in relatives are also seen for schizoaffective disorder and bipolar disorder. In addition, there is evidence that genetic influences on schizophrenia and mania/bipolar disorder partly overlap (Cardno 2002; Lichtenstein 2009) and are shared with schizoaffective disorder and other psychotic and non-psychotic disorders.

Molecular genetics

On the basis of this general evidence, molecular genetic investigations are conducted to localise DNA risk variants on particular chromosomes. These investigations use genetic markers – DNA sequences that vary between individuals and whose chromosomal location is known – which act as signposts to causal DNA variants close by.

Linkage studies and association studies

Linkage studies are based on families with more than one affected member, and investigate whether genetic markers and the disorder are inherited together more frequently than expected. Association

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studies are population based and are commonly case–control studies employing single nucleotide polymorphisms (SNPs) as genetic markers. This involves investigating whether, at a particular point in the DNA sequence, a particular DNA base occurs more commonly in cases than controls.

Initial linkage studies and small-scale association studies gave inconsistent results, so current research focuses on large-scale genome-wide association studies (GWAS) involving tens of thousands of participants and a million or more measured and estimated SNP genetic markers (Craddock 2013).

GWAS

The first substantive GWAS finding for schizophrenia was for a marker in the zinc finger binding protein 804A gene (*ZNF804A*) on chromosome 2 (O'Donovan 2008), and further associations have followed as sample sizes have increased. Currently, the most consistent GWAS association is in the major histocompatibility complex (MHC) on chromosome 6 (Ripke 2013). This region contains many immune system genes, but the exact location and function of the schizophrenia risk variant(s) are not yet known.

There are also GWAS associations for bipolar disorder, including in the ion channel gene *CACNA1C* (Sklar 2011), and evidence for partial overlap of genetic influences on schizophrenia, bipolar disorder and other psychiatric disorders (Sullivan 2012; Cross-Disorder Group of the Psychiatric Genomics Consortium 2013). As GWAS sample sizes increase, many more associations are expected.

Chromosomal variants

Genome-wide association studies focus on detecting common genetic variants that each have a very small effect on risk. In contrast, larger-scale chromosomal variants, particularly deletions or duplications known as copy number variants (CNVs), are rarer but have a larger effect on risk. Copy number variants are associated with schizophrenia (Sullivan 2012) as well as intellectual disabilities and autism spectrum disorders, but are less associated with bipolar disorder.

There are probably also other types of risk variant (Sullivan 2012), and large-scale DNA sequencing studies are underway to identify these.

Once risk variants are identified, their physiological consequences are investigated with the aim of improving our understanding of the pathophysiology and identifying new targets for treatment. There is also potential to gain insights into gene–environment interplay, including effects acting through epigenetic mechanisms, and to inform the classification of psychotic disorders. Molecular genetic risk factors do not currently have a practical role in predicting risk of developing psychotic disorders, but this may change in the future, for example through combined analyses of multiple genetic and environmental factors.

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