Identification of specific genes involved in schizophrenia aetiology – what difference does it make?

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Summary
Genes in which rare, damaging variants substantially increase risk of developing schizophrenia have now been identified. These findings can influence how we think about mental illness in general as well as yielding specific insights into schizophrenia aetiology. Better understanding of underlying biology might eventually lead to improved treatments.

Key findings of SCHEMA
The SCHEMA (Schizophrenia Exome Sequencing Meta-Analysis) consortium analysed exome sequence data from a total of 24,248 individuals with schizophrenia and 97,322 controls. Attention was focused on extremely rare coding variants which were expected either to cause complete loss of function of a gene or to result in a severely damaged protein product. They found that in ten genes there was an excess of such variants in people with schizophrenia which was statistically significant even after correction for testing thousands of genes. The effect sizes were large, with estimates that for some genes such variants increase risk of developing illness by a factor of ten or more. These findings, considered alongside others emerging from complementary approaches, have important implications for psychiatry.

Impact on our understanding of the nature of mental illness
These findings allow psychiatrists to state unequivocally that specific genetic variants can cause mental illness in the same way that smoking can cause heart disease. Not everybody who smokes will develop heart disease, not everybody with heart disease is a smoker and even if a smoker develops heart disease we cannot say with certainty that the smoking caused the disease in that individual. Nevertheless, we are still happy with the claim that smoking causes heart disease. Although psychiatrists may already feel comfortable with the notion that at least some mental illnesses may arise from physical processes, this proposition has been by no means universally accepted and is still under challenge from anti-psychiatrists. It is now legitimate to point to the SCHEMA study as an example and say that biological abnormalities, here pathological changes in DNA sequence, can at least sometimes result in a severe illness characterised entirely by abnormalities in mental functioning.

That said, it is important to keep the findings in perspective. The observed variants are seen in only a very small proportion of cases included in the sample. The best estimate is that if one included similar variants acting in genes yet to be conclusively identified then only about 5% of cases would be accounted for. Most cases of schizophrenia are not due to genetic variants with very large effect sizes, although many other cases might be due to variants with smaller effect sizes acting in combination. Genetic variants will make a smaller contribution to the risk of some other psychiatric diagnoses and it may well be that some forms of mental illness are best considered as being primarily abnormalities of psychological functioning rather than brain diseases. Thus, the importance of these findings is to insist that the ‘bio’ not be excluded completely from a biopsychosocial approach to psychiatry, not that it should be considered to explain away other relevant factors.

Impact on our understanding of psychiatric diagnoses
The fact that variants in several different genes can separately cause schizophrenia should not be taken to imply that there are different subtypes of schizophrenia. It is now commonplace in genetics to recognise that a particular syndrome can be caused by variants in different genes. Sometimes these relate to more or less severe forms of the condition or a tendency to have a somewhat different...
manifestation. However, often this is not the case, with there being no clear correlation between genetic cause and phenotypic effect. From the results obtained so far, there is very little to suggest that people who have one of these identifiable variants have a form of schizophrenia that is different in terms of presentation, severity or response to treatment.

Conversely, this study and other investigations demonstrate that, although some effects seem fairly specific to schizophrenia, certain genetic variants can be a risk factor for more than one different psychiatric diagnosis. Variants in SETD1A can increase risk of schizophrenia or of intellectual disability. The same is true for 22q11 deletion syndrome. There are common genetic variants that contribute to risk of both schizophrenia and bipolar disorder and more broadly there seems to be a good deal of overlap between some forms of genetic risk across a range of psychiatric disorders.2

The fact that there can be multiple different risk factors for the same disorder or that some exposures may be risk factors for multiple different diagnoses should not be taken as a challenge to the validity of diagnosis. Variants in different genes can cause familial hyperlipidaemia, which may result in myocardial infarction. Other risk factors for myocardial infarction include diet and smoking. Myocardial infarction shares some risk factors with intermittent claudication, kidney failure, stroke and cancer. The identification of diverse risk factors for individual psychiatric diagnoses and the recognition that risk factors are shared in different ways across psychiatric diagnoses reinforces rather than undermines the traditional medical view of a diagnosis. A diagnosis represents a characteristic, though variable, set of signs and symptoms that result from sundry pathological processes and that has usefulness in terms of guiding treatment choices and informing prognosis.

Impact on our understanding of schizophrenia

It is reasonable to expect that as these results are followed up new insights will emerge. However, one finding is worth highlighting even at this stage, which is that there is now convergent and persuasive evidence that hypofunction of the NMDA receptor can produce symptoms characteristic of schizophrenia. This has been reported in the short term to result from intoxication with phencyclidine or attack by antibodies in autoimmune encephalitis.3 Now we see that genetic variants resulting in sustained impairment over time can result in a diagnosis of schizophrenia.

The functions of other implicated genes suggest that some may manifest their effect by affecting normal development and other evidence strongly supports a neurodevelopmental contribution to schizophrenia risk. The relative contributions of neurodevelopmental factors and ongoing problems such as neurotransmitter receptor dysfunction will hopefully be further elucidated as additional findings emerge.

Impact on research

The clear identification of genes whose loss of function can cause disease is extremely valuable in terms of allowing the exploration of pathogenic processes. For SETD1A, this has led to the study of the effects of knocking this gene down in mice, leading to the identification of abnormalities in neuronal architecture and in behaviour as well as a wealth of other findings.4 Although some of the genes implicated, such as GRIN2A, have already been subject to intensive investigation, little is known about the function of some of the others and one would expect and hope that considerable resources will be invested in exploring their role in schizophrenia aetiology.

Impact on treatment

The promise of personalised medicine was that gaining detailed information about a patient, including genetic information, would enable doctors to devise an ideal treatment plan for them. Frankly, this promise seems unlikely to be fulfilled. Patients with familial hyperlipidaemia are not treated according to which gene is responsible but are given the same lipid-lowering medications as anybody else. Only a small percentage of people with schizophrenia will have an identifiable genetic cause and even if they do there is no evidence that treatment should be targeted accordingly. It is not necessarily the case that patients with a variant identified to reduce NMDA receptor functioning will benefit more from a treatment targeting this than any other patients might.

The main hope is that understanding what systems can be involved in schizophrenia aetiology might guide treatment development in general. For example, these results might incentivise trials of NMDA receptor enhancers such as sarcosine. Another example is that SETD1A codes for a histone methylase and effects of its loss in mice can be ameliorated by histone demethylase antagonists.5 One of those used was tranylcypromine, which has this function in addition to its action as a monamine oxidase inhibitor. Perhaps this observation will give greater weight to recent calls to re-examine whether tranylcypromine has a role in the treatment of schizophrenia.6 As the results are followed up and better understood novel interventions may be devised.

Conclusions

The identification of genes causally involved in schizophrenia represents an important landmark for psychiatric genetics and, arguably, for psychiatry as a whole. Hopefully these findings may change both how we think about mental illness and also, one day, what we are able to do about it.

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References


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