

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

David Curtis MD PhD FRCPsych

Honorary Professor

Centre for Psychiatry, Queen Mary University of London

UCL Genetics Institute, University College London

UCL Genetics Institute, Darwin Building, Gower Street, London WC1E 6BT.

d.curtis@ucl.ac.uk

David Curtis is a retired consultant psychiatrist who continues to carry out research in psychiatric and statistical genetics.

Summary

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

Key words

Schizophrenia; genes; exome; NMDA receptor.

Relevance statement

A newly published study implicates damaging variants in ten genes as having a causative effect on risk of developing schizophrenia. This provides psychiatrists with a solid example of how disrupted biological processes can result in mental illness. This will support them to have conversations with patients and their relatives regarding the relevance of the “medical model”, i.e. a biopsychosocial approach, to the management of schizophrenia and also other mental illnesses. The findings throw light on the way we think about the diagnosis of schizophrenia and of psychiatric diagnosis in general. New treatment approaches are also suggested.

Results from a large collaborative study, termed SCHEMA, clearly implicate ten genes in schizophrenia aetiology. For each of these genes, the finding is that rare genetic variants which damage functioning are found more often in people with schizophrenia than controls. The effect sizes are large, with estimates for some genes that 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.

Key findings

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 [1]. Attention was focussed on extremely rare coding variants which were expected to either cause complete loss of function of a gene or else result in a severely damaged protein product. They found that in ten genes there was an excess of such variants in cases which was statistically significant even after correction for testing thousands of genes. The effect sizes were large, with estimated odds ratios (ORs) ranging from 3 to over 50. These genes included some of obvious biological relevance. Among these are *GRIA3*, which codes for a subunit of the glutamatergic AMPA receptor, *GRIN2A*, which codes for a subunit of the glutamatergic NMDA receptor, and *SP4*, which is necessary for normal expression of a gene coding for a different subunit of the NMDA receptor, *GRIN1*. Also implicated was *SETD1A*, which has been reported previously and which consequently has already been the subject of some laboratory investigations. There is evidence that rare damaging variants in other genes can also contribute to risk, with the expectation that some of these will be conclusively implicated as additional samples become available.

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. While 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 this 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 recognize 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 which is different in terms of presentation, severity or response to treatment.

Conversely, this study and other investigations demonstrate that, while 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 which 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 diagnosis 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 which results from sundry pathological processes and which 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 through impacting 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 [4]. One of those used was tranylcypromine, which has this function in addition to its action as a monoamine 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 [5]. As the results are followed up and better understood novel interventions may be devised.

Conclusion

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.

Declaration of interest

The author has spent over thirty years involved in research attempting to identify genes affecting susceptibility to schizophrenia and other diagnoses. He is one of the authors of the report referred to. He is on the *BJPsych* editorial board but did not take part in the review or decision-making process regarding publication. He declares no other interest.

Funding

This work received no specific grant from any funding agency, commercial or not-for-profit sectors.

References

- 1 Singh T, Poterba T, Curtis D, *et al.* Exome sequencing identifies rare coding variants in 10 genes which confer substantial risk for schizophrenia. medRxiv. 2020;:2020.09.18.20192815. doi:10.1101/2020.09.18.20192815
- 2 Anttila V, Bulik-Sullivan B, Finucane HK, *et al.* Analysis of shared heritability in common disorders of the brain. *Science (80-)* 2018;**360**:eaap8757. doi:10.1126/science.aap8757
- 3 Lynch DR, Rattelle A, Dong YN, *et al.* Anti-NMDA Receptor Encephalitis: Clinical Features and Basic Mechanisms. In: *Advances in Pharmacology*. Academic Press Inc. 2018. 235–60. doi:10.1016/bs.apha.2017.08.005
- 4 Mukai J, Cannavò E, Crabtree GW, *et al.* Recapitulation and Reversal of Schizophrenia-Related Phenotypes in Setd1a-Deficient Mice. *Neuron* 2019;**104**:471-487.e12.

doi:10.1016/j.neuron.2019.09.014

- 5 Ulrich S, Messer T. Review and meta-analysis of add-on tranylcypromine with antipsychotic drugs for the treatment of schizophrenia with predominant negative symptoms: a restoration of evidence. *Curr Med Res Opin* 2021;:1–1. doi:10.1080/03007995.2021.1895095