Largest-ever genetic study of schizophrenia cements genetic links

Schizophrenia is a disease almost as mysterious as it is terrible. Almost. The symptoms usually manifest in young adults, including the dramatic and well known hallucinations and delusions as well as subtle and insidious ones like mood changes and chronic apathy. It may only affect approximately 1 percent of the population, but it is a deeply damaging disease.

And science has so far let these people down; dopamine suppression is the only option "despite 60 years of pharmaceutical research," wrote Cardiff University psychiatric geneticist Michael O'Donovan at The Conversation. "In other areas of medicine, like cancer and heart disease, improved understanding of disease mechanisms has led to the identification of a wide range of drug targets." Not so with schizophrenia, whose mechanisms have remained mysterious.There may finally be hope of a breakthrough however.

O'Donovan is part of a team of about 300 scientists in the Schizophrenia Working Group of the Psychiatric Genomics Consortium that just published the results of a massive, global analysis of the genomes of over 150,000 people. It is the largest single genetic study of schizophrenia ever, and it revealed more than 100 genetic regions associated with the disease, emphasizing the biological basis of schizophrenia and revealing new potential for research.

A firm genetic basis

First and foremost, the study cements the importance of genetics in schizophrenia. An editorial accompanying the paper's publication in Nature called it no less than "the culmination of a long debate about the genetic basis of a disorder sometimes considered psychiatry's heartland […] laying to rest forever the idea that genetics is not an important cause of the illness."

The editorial's authors, Oxford neuroscientist Jonathan Flint and University of Bristol psychologist Marcus Munafo, go on to explain that "progress in this area has been marked by false starts, and by more than 800 genetic associations of dubious value."

If the previous research is so dubious, then why should we trust these associations? "The short answer is that the tests for associations between each gene in the human genome and disease are now mature. The correct criteria for determining significance in these tests are as familiar to human geneticists as their two-times table, and are exhaustively documented in the consortium's paper."

Flint told the Wall Street Journal the study's findings were "about as robust as you can get."

This "culmination" is all the more notable given that, during the height of the anti-psychiatry movement in the 1970s, people were outright denying the existence of schizophrenia. Even within the realms of psychiatry the debate over the genetic underpinnings of the disease has been fierce and fraught.

Now, it might be over.

Flint and Munafo write: “This is a tremendous advance, of the sort that rewrites textbooks. Given the turbulent history of the field, this is a point that deserves emphasis.”

New avenues

In the more than 100 genetic regions (i.e. loci) the team identified as associated with schizophrenia, many were associated with the brain chemical called dopamine — a well-established player in the disease and the main target of treatment. Another subset could be traced to glutamate, another brain chemical tentatively tied to schizophrenia. But many were also tied to agents of unknown effect, hinting at possibly unexplored brain chemistry relating to the disease. And another group were linked to tissues that influence the immune system, adding fuel to the theory that the immune system may play an important role in the disease.

What is certain is that there is much left to learn. From the Wall Street Journal:

> The disease is thought to be highly heritable but has been difficult to study because large numbers of those affected are needed to reliably find mutations. The new findings likely account for just 3% to 4% of the total contribution of genetic and nongenetic factors in schizophrenia, Dr. O’Donovan said.

That leaves some 96 percent or more of the factors in schizophrenia unknown. But even illuminating a few more percentage points worth of the genetic factors has the potential to give schizophrenia research a shot in the arm. It’s a firm biological basis, a strong leaping-off point for 100 new projects exploring each of these loci and its associations with schizophrenia in depth. And through it all runs a thread of humanity and hope.

Hope

It’s O’Donovan himself who captures the human stakes of the research best:

> There are lots of medicines available to help with the symptoms of schizophrenia. Some are a bit more effective than others. Some have side effects that make them better suited to particular patients. But fundamentally, they all work pretty much in the same way; they all reduce the activity of a chemical in the brain called dopamine.
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> [B]ut a sizable proportion of people don’t respond well to available treatments and instead develop lifelong disability, tormented by their symptoms, socially withdrawn to the point of isolation, unemployed and financially impoverished – even homeless. Many only function by reliance on their parents.

For these individuals, the stumbling nature of schizophrenia research thusfar has real-world

consequences. And so O’Donovan sums up why such a tremendous collaborative effort was worthwhile:

> Converting even one gene finding into a new and effective treatment for schizophrenia would more than justify the generous donation of time and DNA provided by the tens of thousands of patient volunteers, the efforts of the researchers and the financial support from government bodies, charities and private donations, that it has taken to get to this stage of genetic discovery.

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Additional Resources:

- Video: Schizophrenia study reveals new clues to illness cause, BBC News
- Schizophrenia gene study may point to new treatment, Forbes
- Innovations in neuroscience trigger shifting views in the treatment of mental illness, Genetic Literacy Project