First common risk genes discovered for autism

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A study headed by researchers from the Danish project iPSYCH and the Broad Institute in the U.S., has found the first common genetic risk variants for autism and uncovered genetic differences in clinical

subgroups of autism. The discovery means that we will in future be able to determine the genes that separate the diagnostic groups, make more precise diagnoses, and provide better counseling for the individual person suffering from autism disorders.

Autism is not a new phenomenon, as historical records describe individuals with symptoms that today are associated with this group of disorders. It was not until 1938 that the first person was given that diagnosis. Ever since then, researchers have tried to explain the cause of autism. There have been many suggestions, but one factor has long been established—genes play an important role.

A large-scale international collaboration headed by the Danish iPSYCH project and Broad Institute, together with several international groups organized in the Psychiatric Genomics Consortium, has now identified the first common genetic risk variants for autism, and for the first time, found the genetic differences between different types of autism.

These genes increase risk

"When we look at autism, there is a heredity factor of up to 80 percent, so genes have a great deal of impact overall. Nevertheless, despite many years of work, identifying precisely which genes are involved has been very challenging," says Professor Mark Daly from Broad Institute and Institute for Molecular Medicine Finland, who is one of the leading scientists of the study.

In the study, the researchers compared the genomes of 20,415 people with autism and 174,280 healthy control subjects, and in this way, and report that five genetic variants increase the risk of autism. The results have recently been published in the scientific journal *Nature Genetics*.

"It is known that there are very rare genetic variants that carry a high risk

for autism, but they do not explain many cases. However, according to our estimates, there are common variants that [cause autism] when enough of them act together. In this study, we have examined all the approximately 9 million frequent variants that can be found in the genomes of the people who are included in our study. These are genetic variants which are common in the population at large and where the individual variant's contribution to the risk is very small," explains Associate Professor Jakob Grove from Aarhus University. He is the lead author of the study and a member of the iPSYCH research project.

The genetic findings provide an entirely new insight into the biological processes involved in the development of autism.

"By comparing the genetic risk variants with the genes' expression and the 3-D structure of the genome in the developing brain, we can show that the identified risk genes are important for the development of the brain, and in particular, the development of the cerebral cortex," explains Professor Anders Børglum from Aarhus University, who is research head at iPSYCH and directed the study with Dr. Daly.

The researchers have also found a significant overlap between the genetic background for autism and other mental disorders such as schizophrenia and depression—though also with positive cognitive characteristics such as educational attainment and IQ.

"The positive correlation with educational attainment might seem paradoxical, because some autistic people have reduced cognitive function, and on average, fewer people with an autism diagnosis end up with a higher education. The correlation is seen in several previous studies, and in our data we can confirm that in general, this correlation between the genes for autism and genes that predispose for longer education does exist," says Jakob Grove. "However, we can demonstrate that this does not apply to all subsets of autism. We see that people with

Asperger's syndrome or infantile autism have more of the genes on average that are beneficial for education, while this is not the case for people with so-called atypical autism or unspecified autism disorders."

Better treatment on the horizon

Autism refers to a very mixed group with different autism disorders. Some have very pervasive developmental disorders with mental retardation, while others may be cognitively well-functioning with a normal or high IQ.

"Thanks to a new and highly sensitive method that we've developed, we can for the first time establish genetic differences between the various diagnostic subgroups. This indicates that larger studies in the future will be able to pinpoint genes that separate the diagnostic groups and enable more precise diagnosis and advice for the individual person suffering from an autism disorder. We also hope that the genes we identify can provide an opportunity for developing actual treatment or prevention of the condition, which is something that we unfortunately cannot offer at present," says Anders Børglum.

The scientific article titled "Identification of common genetic risk variants for autism spectrum disorder" was published in *Nature Genetics*, February 2019.

More information: Identification of common genetic risk variants for autism spectrum disorder, *Nature Genetics* (2019). DOI: 10.1038/s41588-019-0344-8

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