MedicalXpress

New studies identify novel group of inherited genes of moderate effect, show their links to other behavioral conditions

August 18 2022

Credit: Pixabay/CC0 Public Domain

In a series of articles published in the journal *Nature Genetics*, researchers have used data from the SPARK (Simons Powering Autism Research) research cohort, which was created to advance our understanding of the complex genetics of autism and includes genetic data from nearly 43,000 people with autism. The findings show differences in genetic influences among people all along the autism spectrum.

"Autism is a spectrum, and includes individuals with profound autism who often have cognitive differences and/or epilepsy, as well as individuals who are talented and exceptional, often in specific areas. We are now appreciating that the genetic contributions to different phenotypes vary in terms of the genes involved; when those genes are activated during brain development; and how common some of the genetic variants are in the population," said Wendy Chung, M.D., Ph.D., principal investigator of SPARK.

One study, "Integrating de novo and inherited variants in 42,607 autism cases identifies mutations in new moderate effect genes," was published in *Nature Genetics* on August 18, 2022. Researchers analyzed the DNA of almost 43,000 people with autism, including 35,000 participants from the SPARK autism research study, as part of SPARK's ongoing effort to understand the full spectrum of autism genetics. This largest-ever autism cohort allowed researchers to identify a group of novel "moderate-effect" genes that tend to contribute to autism through inherited variants.

It is widely known that autism is heritable, but previous studies have primarily identified autism genes with de novo variants (DNV)—variants that occur spontaneously in germ cells prior to conception—that are not inherited. Most of these variants are also implicated in other neurodevelopmental disorders (NDDs). Most genetic variants of this type associated with autism have profound effects on the brain in those individuals when they occur. However, only 20 percent of individuals with autism have this type of genetic variant.

"For many years, we have known from twin studies that there must be inherited genetic variants that lead to autism, but we have not been able to systematically identify individual genes until now," said lead author Pamela Feliciano, Ph.D., SPARK's scientific director. "We have now identified a group of genes associated with autism, that can include inherited variants, which begin to explain a different part of the autism spectrum."

To gain a better understanding of the full spectrum of autism genes, the researchers analyzed 19,843 participants with autism, along with one or both of their biological parents, and found that roughly 20 percent of people with autism have de novo genetic variants that affect the function of the associated gene. Nearly 70 percent of this genetic contribution can be attributed to known autism or neurodevelopmental disorder genes. However, this means that although known autism-associated genes are responsible for the majority of de novo variants, there are others still to be identified.

The researchers next added in another 22,764 individuals with autism and 236,000 people without autism from the general population. In this meta-analysis, they identified 60 autism genes whose contribution to autism is largely driven by rare inherited loss of function (LOF) variants transmitted by parents who do not have cognitive differences or autism. Of these genes, five have not previously been implicated in

neurodevelopmental conditions.

Individuals with autism who carry inherited variants in these "moderate effect" genes are less likely to have cognitive differences than people with autism who carry LOF variants in well-established autism genes, such as CHD8 and SCN2A.

"The majority of parents who passed down these genetic variants in our study do not have cognitive differences or autism, but we know that these genes are associated with autism because we find that these variants are more frequently inherited by children with autism. We hypothesized that people with autism who have these inherited genetic variants are not as likely to have seizures and cognitive differences as people with de novo genetic variants. So far our data strongly support[s] this hypothesis," said Dr. Feliciano.

The SPARK cohort's reach

A second study also published in *Nature Genetics*, "Rare coding variation provides insight into the genetic architecture and phenotypic context of autism," led by a team of investigators supported by the Simons Foundation Autism Research Initiative (SFARI) and the Autism Sequencing Consortium (ASC), performed analyses on genetic data from 20,627 people with autism, with new genetic data derived primarily from SPARK.

The team developed new methods to discover gains and losses of DNA, or copy number variants (CNVs), from exome sequencing, and methods to integrate data from these CNVs with other classes of de novo and rare inherited variants, and identified 72 genes associated with autism. Most evidence came from de novo variants, with smaller but significant contributions from rare inherited variants.

The researchers then combined data from the autism studies with a large dataset of 31,000 families in which the child was diagnosed with developmental delay and/or other neurodevelopmental conditions. These analyses discovered 373 genes associated with these diverse neurodevelopmental outcomes, and allowed the team to identify genes more associated with autism than with other neurodevelopmental conditions, and vice versa. They found that genes associated predominantly with developmental delay tend to be important in early neuronal development, whereas autism genes tend to play a role in more mature neurons.

The study's senior author, Michael Talkowski, Ph.D., director, Center for Genomic Medicine at Massachusetts General Hospital and member of the Broad Institute, noted that "the scale of the data collections from SPARK, the ASC and other sources—as well as the newly developed methods—has allowed us to explore the relative contribution of the diverse classes of genetic variants that contribute to a continuum of neurodevelopmental variability across these datasets."

"These analyses suggested that most of the genes identified play a role very early in brain development, though the genes with higher mutation rates in autism displayed slightly greater enrichment in more mature excitatory neurons. There are so many new genes and insights into neurodevelopment to be pursued from these findings, and all of these discoveries were only possible due to the accessibility of [the] rich data that SPARK and other studies provide for the field."

Finally, two other studies (Antaki et al, 2022, Warrier et al, 2022) appearing in a recent issue of *Nature Genetics* analyzed the SPARK datasets. These two studies made use of the ASC and SPARK whole genomes, exomes and single nucleotide polymorphism (SNP) genotypes to determine the contributions of multiple genetic factors to ASD, including de novo mutations, inherited rare variants, common polygenic

variants, and sex.

The study by Antaki et al. found that different forms of genetic contributors are associated with different ASD symptoms, and that the wide variety of clinical presentations of individuals across the autism spectrum can be explained by the combinations of genetic factors they carry. Antaki also found that genetic contributors to ASD influence behavior in all family members, including parents and typically developing siblings.

Jonathan Sebat, Ph.D., professor of psychiatry and cellular and molecular medicine at UCSD and senior author on Antaki et al, said, "The spectrum of symptom severity in ASD is attributable to a spectrum of genetic influence. People who meet diagnostic criteria for autism may have the most genetic factors for autism, but these types of factors are present to varying degrees in all of us. We are all somewhere on a continuum."

Together, the four papers provide new insights into the genetic basis of autism, a condition so varied in its characteristics that it has been difficult to understand its neurobiological basis. Although researchers have yet to identify the fuller picture of brain molecules and pathways that underlie autism, these new studies will lead the way toward an improved understanding of this complicated and common condition.

More information: Wendy Chung, Integrating de novo and inherited variants in 42,607 autism cases identifies mutations in new moderate-risk genes, *Nature Genetics* (2022). DOI: 10.1038/s41588-022-01148-2. www.nature.com/articles/s41588-022-01148-2

Joseph Buxbaum, Rare coding variation provides insight into the genetic architecture and phenotypic context of autism, *Nature Genetics* (2022). DOI: 10.1038/s41588-022-01104-0.

www.nature.com/articles/s41588-022-01104-0

Provided by Simons Foundation

Citation: New studies identify novel group of inherited genes of moderate effect, show their links to other behavioral conditions (2022, August 18) retrieved 11 December 2023 from https://medicalxpress.com/news/2022-08-group-inherited-genes-moderate-effect.html

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.