Medical Xpress

MSSNG study expands understanding of autism's complex genetics

August 4 2016

A new study from Autism Speaks' MSSNG program expands understanding of autism's complex causes and may hold clues for the future development of targeted treatments. The report, appearing in *npj Genomic Medicine* is the largest-ever whole genome study of autism, involving 200 children with the condition and both their unaffected parents.

The new research focuses on newly arising, or de novo, gene changes in the germline cells that produce a parent's eggs or sperm. Previous studies have shown that these mutations can be major contributors to autism through their effects on early brain development.

The 600 fully sequenced genomes came from MSSNG (pronounced "missing"), the world's largest collection of autism genomes and a collaborative effort of Autism Speaks and The Hospital for Sick Children (SickKids), in Toronto. More than halfway to its goal of sequencing more than 10,000 autism genomes, MSSNG has made this unprecedented resource freely available for worldwide research into the causes and personalized treatments for autism.

Geneticists Stephen Scherer and Ryan Yuen, of SickKids, led the study team, which also included scientists with the University of Toronto, Google, BGI-Shenzhen (China) and Autism Speaks.

The researchers found:

- An abundance of autism-linked changes in DNA outside of the gene-coding regions of the genome. Traditional genetic testing largely ignores the non-coding regions of the genome—which make up 98 percent of our DNA. Coding DNA spells out our genes. Non-coding DNA had long been considered "junk," with no known function. Geneticists now appreciate that it helps regulate the activity of our genes. This regulation is particularly crucial for healthy brain development, which involves genes turning on and off at precisely the right times.

"This represents the most comprehensive assessment to date on the contribution of non-coding variants to autism," Dr. Yuen says. "As such, it provides an important road map on how whole genome sequencing can advance autism research in the future."

- A clear difference between the de novo mutations that come from the mother versus the father. The study confirmed previous findings that most autism-linked de novo mutations come from the father and tend to increase with his age.

However, the researchers also found that clustered, or concentrated, stretches of de novo mutations tend to come from the mother. "This new finding may be evidence that different types of gene-change and gene-repair mechanisms are at work in men versus women," Dr. Yuen says. Indeed, the clustered mutations from the mother tended to occur near stretches of deleted or repeated DNA called copy number variations (CNVs)—a type of mutation that the research team had previously linked to autism.

In addition to genetic changes in egg and sperm, the analysis turned up autism-associated mutations that likely occurred in the embryo soon after fertilization. "These genetic changes can arise due to environmental insults [such as exposure to toxic chemicals]," Dr. Yuen says.

- A new way to explore epigenetic risk factors for autism. The team also developed new methods to look at changes in the epigenetic control of gene expression. Epigenetics is the study of proteins that wrap around our DNA to help regulate gene activity. These epigenetic controls can be disrupted by some—perhaps many—of the environmental influences suspected of increasing autism risk. Examples include exposure to certain pollutants, nutritional deficiencies and inflammation during pregnancy. Using their new test, the researchers found significantly disrupted epigenetic patterns in just over 1 percent of the genomes they analyzed.

- A cascade effect, with one altered gene affecting the expression of many other genes involved in brain development. "Using new statistical methods and the whole genome sequence as a framework, we found genes with mutations that led to a cascade of changes in gene expression," Dr. Yuen says. This may help explain how the hundreds of rare gene changes associated with autism may converge to affect a few vital pathways in early brain development, he notes.

"These findings advance our efforts to improve diagnostics and precision healthcare for autism," says geneticist Mathew Pletcher, Autism Speaks interim chief science officer and a co-author on the report. "There's so much about the causes of autism that we would miss if we focused only on the gene-coding regions of the genome. This demonstrates again why whole genome sequencing is so important."

"These findings represent a step toward better understanding the interplay between the genetic and non-genetic factors that contribute to autism risk," Dr. Scherer adds. "But we need to analyze many more whole genomes - such as the number being sequenced through MSSNG - to fully understand these intriguing findings." Dr. Scherer is project

director for the Autism Speaks MSSNG program and directs the Centre for Applied Genomics at Toronto's Sick Children's Hospital. Dr. Yuen's research was supported by an Autism Speaks Meixner Postdoctoral Fellowship in Translational Research.

More information: Read more about Autism Speaks research fellowships here.

Ryan KC Yuen et al. Genome-wide characteristics of de novo mutations in autism, *npj Genomic Medicine* (2016). DOI: 10.1038/npjgenmed.2016.27

Provided by Autism Speaks