Changes in scores of genes contribute to autism risk

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Small differences in as many as a thousand genes contribute to risk for autism, according to a study led by Mount Sinai researchers and the Autism Sequencing Consortium (ASC), and published today in the journal *Nature*.

The new study examined data on several types of rare, genetic differences in more than 14,000 DNA samples from parents, affected children, and unrelated individuals – by far the largest number to date – to dramatically expand the list of genes identified with autism spectrum disorder (ASD).

Most of the genes that contribute to autism remain unknown, but the current study increases the number of definitive autism genes almost fourfold to 33, compared to the 9 genes most closely tied to risk in recent years by similar studies in several labs. It also identified more than 70 additional, likely ASD genes. Each of these genes is mutated in more than 5 percent of individuals with autism, signifying a large, relative contribution to risk for a complex genetic disease.

By casting a wider net, a research team from 37 institutions found that previously unsuspected sets of genes may be involved in ASD risk, including some that control how nerve networks form in the brain. Occurring in one out of 68 children in the U.S., ASD affects a person's social interactions, including communication, as well as behaviors with varying levels of severity.

"The steps we added to our analysis over past studies provide the most complete theoretical picture to date of how many genetic changes pile up to affect the brains of children with autism," said Joseph D. Buxbaum, PhD, Professor of Psychiatry, Neuroscience and Genetics and Genomic Sciences at the Icahn School of Medicine at Mount Sinai and Director of the Seaver Autism Center. Dr. Buxbaum is senior author for the *Nature* study, together with Mark J. Daly, PhD, co-director of the Program in Medical and Population Genetics at the Broad Institute of MIT and Harvard. "Beyond autism, we think this work will yield insights into what makes us social beings," Dr. Buxbaum said.

"While we have very strong findings in these genetic analyses, newfound genetic discoveries must next be moved into molecular, cell and animal studies to realize future benefits for families," added Dr. Buxbaum. "A study like this creates an industry for years to come, with labs worldwide checking the brain changes linked to each new genetic finding, and searching for drugs to counter them."

For the first time, the study authors were able to assess the effects of both inherited genetic differences and those that happen spontaneously in the sperm and eggs that go on to form human embryos. While small, rare genetic differences in the top 107 genes were found to confer a relatively large jump in a person's risk, many more changes in other genes add smaller amounts of risk. According to the authors, the interplay between gene variations, both common and rare, holds the key to understanding autism. Along these lines, the team, by looking at how many times variations occurred in each of the 107 genes, was able to predict that small differences in about 1,000 genes will eventually be found to increase autism risk.

Assembling by far the largest autism study to date, the international research team collected and analyzed data from 3,871 autism cases, 2,270 sets of mothers, fathers and their affected children, and additional

control samples. This was achieved through the Autism Sequencing Consortium (ASC), originally funded by the Beatrice and Samuel A. Seaver Foundation and the Seaver Autism Center within the Icahn School of Medicine at Mount Sinai. The ASC is a multiple Principal Investigator grant funded by the National Institute of Mental Health (NIMH), with additional support from the National Human Genome Research Institute (NHGRI). In addition to Drs. Buxbaum and Daly, the PIs are Drs. Bernie Devlin (University of Pittsburgh School of Medicine)/Kathryn Roeder (Carnegie Mellon University), and Matthew State (University of California, San Francisco). Dr. Buxbaum is the communicating PI.

The consortium shares patient data because no single lab has enough to identify obscure genetic patterns scattered across thousands of genomes. The ASC continues to add patients because so far the number of risk genes found has steadily increased with the number of patients studied. Its many investigators share samples, data, and ideas without first publishing them in medical journals, a unique level of collaboration that is accelerating discovery.

"The genetics underlying ASD are highly complex and having access to large sample sizes is essential to rooting out the many genetic mutations involved, and the biological mechanisms implicated by those mutations," said Dr. Daly, also founding chief of the Analytic and Translational Genetics Unit at Massachusetts General Hospital. "This sort of study cannot be done without the collaboration and cooperation we relied on across the consortium."

Surprise Links

The *Nature* study points to three pathways required for healthy development where variations in genes were linked to greater autism risk, in some cases confirming past study results. Among the surprises

was a newfound association between autism risk and variations in genes that control "chromatin remodeling."

As part of the organization of genetic material within cell nuclei, DNA forms a complex with proteins called histones to become chromatin. Long chains of DNA wrap around histone "spools" that unwind with the right signal. The unwinding makes stretches of genetic instructions accessible to the machinery that builds proteins, which comprise bodily structures and signals.

One group of genes newly linked to autism, for instance, codes for an enzyme that regulates histones by attaching or removing methyl groups to one of their building blocks, lysine amino acids. By doing so, the enzyme influences when specific genes are turned on or off, and the study results support the theory that such mechanisms may be altered in autism, such that developing brain cells may not mature, divide, or migrate the same way.

Other variations linked to autism by the study were in genes that govern synapses, the spaces between nerve cells in pathways that "decide" whether signals travel onward. Nerve cells must be able to execute well-timed maneuvers, such as allowing charged particles to build up or rush out of them, to pass on nerve signals normally. A third set of genes linked to risk by the study regulate basic steps that turn genes into proteins. For a protein to be built based on genetic code, the code must be translated into related molecules (transcription) and cut up and rebuilt (spliced) into the core instructions for protein building.

Study researchers reached their conclusions with the help of new DNA sequencing techniques, which determine the order of the letters (bases) making up the genetic code to reveal rare variations, some linked to disease risk. The current study employed whole exome sequencing, which is a less expensive, more focused version of whole genome

sequencing. By looking at only the protein-coding part of genes, exome sequencing precisely identifies small changes in the gene code that in turn affect specific spots in a resulting protein.

The study results also revolve around genetic mutations. Changes occur in our genetic code at a steady rate thanks to the error-prone processes that copy the code and other factors, and despite mechanisms bent on weeding out faulty code. Part of evolution, changes in the order of the "letters" (base pairs) making up the instructions encoded in DNA are called mutations, with some inherited and others occurring when the egg or sperm are formed (de novo mutations).

Past studies looking at genetic autism risk focused only on de novo mutations that caused any key protein to stop working (loss-of-function mutations). The current study looked at both inherited and de novo loss-of-function mutations, along with de novo "missense" mutations in affected children and their parents. Where loss-of-function mutations are blunt, causing the resultant protein to stop working, missense mutations may make a protein work slightly less well. Being more common and subtle, they are harder to spot, but the current study shows that they make a sizeable contribution to ASD risk.

The new study was also the first to compare the rate of different classes of mutations between girls with ASD and boys with ASD. Feminine genetics somehow protect girls from ASD, so comparing mutations between girls and boys enabled the authors to estimate the risk associated with different kinds of mutations. Using this approach, the study authors found mutations that came with a more than 20-fold increase in risk for autism.

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