NEWS

Massive sequencing studies reveal key autism genes

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Master regulators: The strongest autism gene candidates to emerge from two large sequencing studies regulate the expression of other genes.

Analyzing the sequences of more than 20,000 people, researchers have unearthed the largest and most robust list of autism genes so far, they reported today in *Nature*[1, 2].

These 50 ‘high-confidence’ autism genes may help researchers understand the biological underpinnings of autism.

“This is just absolutely thrilling,” says **Matthew State**, chair of psychiatry at the University of California, San Francisco, who was involved in both studies. “For so many years it felt incredibly challenging to figure out how we were going to identify autism genes. Now we can begin to see the biology clarify itself through these papers.”

The researchers found these genes by scouring the **exomes**, the protein-coding regions of the genome, looking for rare genetic glitches unique to people with autism.

One study sequenced members of 2,517 families — a child with autism and his or her unaffected siblings and parents — and pinpoints 27 candidate genes.

The other bears the fruit of an international consortium that has compiled data from nearly 4,000

people with autism from across the world. It highlights 33 autism risk genes.

The two lists share only ten genes, but overall the genes point to two key functions: communication between neuronal junctions, or **synapses**, and control of gene structure and expression. The latter, virtually unheard of in autism five years ago, is emerging as the strongest pathway involved in the disorder.

“The two studies have complementary but certainly distinctive designs, and they point to basically the same biological processes,” says **Patrick Sullivan**, professor of genetics at the University of North Carolina at Chapel Hill, who was not involved with either study. “It will give some important clues to work from.”

Autism genes:

The family study relied on data from the **Simons Simplex Collection** (SSC) — a database of families that have one child with autism and unaffected parents and siblings. (The SSC is funded by the Simons Foundation, SFARI.org’s parent organization.) This collection is designed to identify *de novo*, or spontaneous, mutations, which are present only in the affected child.

Hitting high confidence

Learn more about a selection of the strongest new autism genes:

- ***CHD8***
- ***DYRK1A***
- ***GRIN2B***
- ***SCN2A***
- ***ANK2***

In 2012, three teams of researchers independently analyzed a subset of more than **800 families** from the SSC. In the new study, they collaborated to analyze the exomes of 2,517 people with autism, their 5,034 parents and 1,911 unaffected siblings.

The researchers found 27 genes that have so-called ‘loss-of-function’ mutations — which abolish function of the corresponding protein — in at least two people with autism. “Around here, we call

them killers," says lead researcher **Michael Wigler**, professor at Cold Spring Harbor Laboratory in New York.

Of the 27 genes, 6 are mutated in three or more people with autism. This makes these six — **CHD8**, **DYRK1A**, **ANK2**, **GRIN2B**, DSCAM and **CHD2** — the strongest autism candidates so far.

Overall, the researchers found 391 killer mutations in 353 genes in children with autism. By looking at the rates of these mutations in unaffected siblings, they estimate that roughly 40 percent of the *de novo* loss-of-function mutations contributed to autism diagnoses.

In each case, the mutation affects only one copy, or allele, of the gene, which is encouraging, says Wigler. "That means there is at least some hope that symptoms can be lessened by targeting the remaining good allele," he says.

The children with autism also carry another 1,500 *de novo* 'missense' mutations of unknown significance. Because of the large sample size, the researchers were able to estimate that about 13 percent of these mutations are likely to lead to symptoms, says Wigler. This was impossible in the smaller SSC studies published two years ago, in which the sequences were split among three research groups.

The estimate suggests that missense mutations are less valuable for identifying autism risk genes than are the killer mutations, says Wigler. "Missense is a sticky ball of wax. We don't know what point mutations are disruptive for a gene, and most are not," he says.

Family risk:

In their paper, the members of the research consortium looked at mutations whose impact is even more difficult to interpret: mutations inherited from family members. This **collaboration of more than 20 teams**, called the Autism Sequencing Consortium, has collected sequences from across the globe, including Costa Rica, Finland and the Middle East.

The teams analyzed sequences from 3,871 people with autism and 9,937 controls of the same ancestry. This includes 2,270 children with autism — including 825 from the SSC — whose unaffected parents served as controls.

To analyze these mixed data, they used a **statistical method called TADA**. This approach merges information about inherited and *de novo* loss-of-function and harmful missense mutations to rate the significance of a particular autism gene.

Using this method, the researchers identified 33 genes that have at least a 90 percent chance of being true autism genes, including 13 genes that have a 99 percent chance or more of being so. The latter list includes **ADNP**, ANK2, CHD8, DYRK1A, GRIN2B, SCN2A, **SYNGAP1** and **TBR1**.

The researchers also uncovered seven genes that have never been linked to autism before.

To further strengthen the genes' link to autism, the researchers looked at their prevalence in males and females with the disorder. Because it takes **a bigger genetic hit** to lead to autism in women than in men, mutations with a true link to autism would be expected to be more prevalent in women with the disorder than in men.

The study found that mutations in the 33 autism genes are more prevalent in females than in males, and increase the risk of autism by at least 20-fold.

"This shows us that these are the uniquely high-impact set," says **Mark Daly**, associate professor of medicine at Harvard University.

The set of genes is merely the first step to revealing the biology of autism, however. "We want not just to collect genes and genetic variants in a stamp-collecting mode, but to derive potential hypotheses," Daly says.

To find patterns among their data, the researchers used another statistical tool, called DAWN, that identifies genes expressed **at the same time and place** in the developing brain. This tool points to regulation of the synapse and of gene expression as key pathways in autism. The strongest signal, the researchers say, comes from genes that modify chromatin, which helps package DNA in the nucleus of the cell.

"It's breathtaking," says **Joseph Buxbaum**, director of the Seaver Autism Center at the Icahn School of Medicine at Mount Sinai in New York City, of the data linking chromatin-modifying genes to autism. "The entire universe of these genes is less than a couple dozen and I have four of them right in front of me."

The SSC study also identified genes that influence transcription and chromatin modification. Genes important in fetal development and targets of the protein involved in **fragile X syndrome** also figured in both lists of genes.

Taken together, the studies suggest clear starting points in the search for autism treatments, Buxbaum says. "Genetics is not the end; it's the beginning. Here we're finally coming to the point where we can think about that beginning."

References:

1: Iossifov I. *et al. Nature* Epub ahead of print (2014) **Abstract**

2: De Rubeis S. *et al. Nature* Epub ahead of print (2014) **Abstract**