NEWS

Dispatches from ASHG 2015

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*These short reports from **Jessica Wright** give you the inside scoop on developments at the 2015 American Society of Human Genetics Annual Meeting.*

Isolated islands offer new glimpse into autism genetics

Halfway between Iceland and Norway lie the Faroe Islands, a smattering of 18 isles that, if pushed together, would be smaller than the city of Houston. The islands provide a unique opportunity to examine the genetics of autism in an unusual isolated population, researchers reported at the **2015 American Society of Human Genetics Annual Meeting** in Baltimore.

The Faroe islands, which now represent a single country in the Danish Realm, were first colonized by Irish monks and the Vikings in the 1300s. Today, roughly 49,000 people call them home and nearly 92 percent of these citizens are considered native Faroese. Because few people immigrate to the country, the Faroese people are like one big family, genetically speaking, says Coralie Carton, a graduate student in **Thomas Bourgeron**'s lab at the Pasteur Institute in Paris, who presented an ongoing analysis of autism in the Faroe Islands Friday.

Because the researchers took an unbiased selection of all people with autism, the study represents an epidemiological profile of autism across the Faroe islands, says Bourgeron, professor of genetics.

The researchers identified 66 individuals who were diagnosed with autism between 1985 and 1994 on the islands. They looked at the genetic architecture of half of those individuals compared with 105 of their relatives, as well as 201 unrelated controls, using gene sequencing and mapping genetic variants.

Because most people on the Faroe Islands are distantly related, the researchers found more genetic regions to be identical on both copies of a chromosome compared with populations from Asia, Africa and Europe. Genetic similarity among chromosome copies boosts the likelihood of

having two of the same mutation. Recessive mutations are only harmful when both copies of a gene carry the mutation, and little is known about their contribution to autism.

The researchers found that the individuals with autism living in the Faroe Islands are more likely than controls to inherit similar swaths of DNA from both of their parents. This suggests that **recessive mutations contribute to autism risk**, but the data is preliminary, says Bourgeron. “I would be cautious to say that inbreeding is a risk factor for autism,” he says.

In a subset of the families, the researchers also looked at *de novo* mutations or deletions, which arise spontaneously and are found in an individual with autism but not in that person's parents or siblings.

Despite the unique population, this analysis fingered the usual suspects: known mutations in autism-linked genes or chromosomal regions. For instance, they found one individual with a deletion of the **NRXN1** gene, another with a **MeCP2** mutation and a third person with a deletion of the 22q11.1 chromosomal region.

“It looks like the genetic architecture is not that different,” says Bourgeron.

The researchers also found some inherited mutations in autism-associated genes, such as **ADNP** and **TBL1X**. These mutations are rare, present in less than 1 percent of the population. It is possible that the individuals with autism who carry these rare mutations inherited additional mutations from their parents that tipped the scales towards autism, says Carton.

Although the work is preliminary, it is a first step toward unraveling how both inherited and spontaneous mutations may work together to lead to autism risk, says Bourgeron. Much of the focus of autism research has been on *de novo* mutations, but these are like nature’s “car accidents,” he says. They do not explain why autism is a heritable genetic disorder.

“This kind of setting is exactly right to see what is the contribution of different types of mutations,” he says.

— Jessica Wright / 12 October

Molecular scissors can mimic large gene variants in people

Using sophisticated genome-editing technology, researchers can engineer cells to sport the complex duplications and deletions that some people with autism carry. The method allows them to more accurately assess the ripple effects of these large variations.

These **copy number variations** (CNVs) include multiple genes and may have widespread effects on gene expression. For example, a 2014 study found that deletion or duplication of a swath of

DNA known as 16p11.2 **changes the expression levels of hundreds of genes** — well beyond the 29 genes in the **16p11.2** region itself. In this study, researchers measured gene expression changes in neurons derived from induced pluripotent stem (iPS) cells, which they reprogrammed from the skin cells of people with 16p11.2 deletions or duplications.

The best place to look for the effect of CNVs on people is in their own cells. But because people are not genetically identical, it is difficult to know which of the observed changes in expression result from the CNV and which reflect natural variation in expression patterns, says Derek Tai, a postdoctoral associate in **Michael Talkowski's lab** at Harvard University. Tai presented the unpublished results Thursday at the **2015 American Society of Human Genetics Annual Meeting** in Baltimore.

To solve this problem, Tai and his colleagues found a way to introduce CNVs into iPS cells, allowing them to compare the same exact cells with and without the mutation.

To do this, the researchers used the gene-editing tool **CRISPR**, which can cut and paste sequences into DNA. To make a deletion, the researchers used two methods. In one, they simply used CRISPR to snip out the 16p11.2 region. But they also used a more sophisticated process that recapitulates the steps that lead to CNVs in people.

CNVs originate in cells when identical regions of DNA, which are themselves a series of repeats, flank another stretch of DNA. During cell division these repeats can stick to each other, causing the DNA to break and reassemble, which can delete or duplicate the stretch between the repeats.

The researchers used CRISPR to mimic this natural process by inserting identical flanking regions on either side of the 16p11.2 segment. This technique produces deletions about 10 percent of the time and duplications about 4 percent of the time — an efficient yield, says Tai.

So far, these engineered cells show differences in expression of 16p11.2 genes that are similar to the differences seen in people with the CNVs.

The method can be used for any kind of CNV. Tai and his colleagues are already working on engineering duplications of a DNA segment on chromosome 15 known as **15q11.3**, which leads to problems such as seizures, intellectual disability and autism.

— Jessica Wright / 9 October

*For more reports from the 2015 American Society of Human Genetics Annual Meeting, please **click here**.*