NEWS

Rare mutations linked to severity of autism symptoms

BY **JESSICA WRIGHT**

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Boys with autism who carry rare, spontaneous mutations have lower intelligence quotients (IQs) and more severe symptoms than do those who may have inherited the disorder. The finding,

published 21 October in the *Proceedings of the National Academy of Sciences*[1], hints at two classes of autism risk with varying severity.

“Understanding how the genetic heterogeneity is actually leading to phenotypic heterogeneity is a very exciting time in our research,” says lead researcher **Mark Daly**, associate professor of medicine at Harvard University.

The researchers looked at harmful mutations present in 618 boys with autism but not in their parents or unaffected siblings.

The researchers initially included 152 girls with autism in their study. This number turned out to be too low to spot any meaningful trends between spontaneous mutations and IQ.

However, these girls have double the rate of harmful mutations compared with the boys. This is in line with the finding that girls **need a bigger genetic hit** to develop autism than boys do.

Boys with IQs below 100, the population average, have a high rate of spontaneous, or *de novo,* mutations, the study found. They also have more severe symptoms than boys with higher IQs. This suggests that harmful mutations track with both IQ and autism severity.

By contrast, boys with autism who have IQs higher than 100 have the same number of *de novo* mutations as do people without autism. This suggests that themutations do not contribute to autism in these boys.

The boys with higher IQs also tend to have a family history of psychiatric disorders, suggesting that inherited milder mutations may have **combined to cause their autism**.

“It seems as if the higher-IQ boys [have] a different class of genetic mechanism,” says **Michael Wigler**, professor at Cold Spring Harbor Laboratory in New York. Wigler was not involved in this study, but has found similar results.

In a study published last week, he and his colleagues reported that *de novo* mutations are present predominantly in children with low IQs. One harmful *de novo* mutation in an autism gene can lower IQ by about 5 points, and two mutations by about 20 points, they found.

New risk:

Wigler’s study also found that *de novo* mutations may account for just under **one-third of the risk for autism**. This is the latest in a string of results suggesting an important role for *de novo* mutations in autism risk.

Much of the search for harmful *de novo* mutations so far has focused on families that have only

one member with autism. For example, the new study and Wiger's report last week both drew samples from the **Simons Simplex Collection** (SSC) — a database of children with autism whose parents and siblings do not have the disorder[2]. (The SSC is funded by the Simons Foundation, SFARI.org's parent organization.)

By comparing the **exomes** — the protein-coding regions of the genome — of these family members, researchers have tried to pinpoint *de novo* mutations in the child with autism.

Looking instead at boys with autism who have low IQs may be "markedly more productive," says **Elise Robinson**, instructor in medicine at Harvard University and one of the researchers on the new study.

Boys who were unable to complete an IQ test also have an elevated rate of *de novo* mutations, the study found. These boys have the most severe behavioral problems, further reinforcing the link between *de novo* mutations and autism severity.

Not everyone with a *de novo* mutation in an autism gene has severe symptoms, however. And many people with the disorder may carry both *de novo* and inherited risk factors.

"We shouldn't set up a situation where we say only the kids who have severe *de novo* mutations are the ones who are going to be severely affected," says **Brian O'Roak**, assistant professor of molecular and medical genetics at Oregon Health and Science University, who was not involved in the new study. "You can have the same high-risk genetic mutation in kids who have an IQ above 100 and on the other side have a kid who is basically on the low IQ end."

As a proxy for inherited mutations, the researchers looked at the children's family history — up to first cousins — of depression, bipolar disorder and schizophrenia. This is "clever," says **Kathryn Roeder**, professor of statistics?at Carnegie Mellon University in Pittsburgh, who was not involved in the study. "It's a good insight. You see that the people with a family history [of psychiatric disorders] still have autism, but they are high functioning."

The milder symptoms, which may be the result of common variants found throughout the population, may shed light on important aspects of autism, she says.

"Studying the impact of the common variants will give us greater insight into how we develop into social beings," Roeder says. "They're going to get us to the subtle symptoms, which are the pretty interesting part of autism."

References:

1: Robinson E.B. *et al. Proc. Natl. Acad. Sci. USA* **111**, 15161-15165 (2014) **PubMed**

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