

NEWS

Spectrum of autism traits spans general population

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Genetic variants tied to autism may also influence social skills in people without the condition, supporting the notion that autism lies along a continuum of typical traits.

The findings, published Monday in *Nature Genetics*, also bolster the idea of a **broad autism phenotype**, or mild features of autism, in ‘unaffected’ family members of people with the condition¹.

“It’s not just a spectrum within cases that ends at an obvious cutoff point,” says **Elise Robinson**, instructor in medicine at Harvard University. “The spectrum extends into what we consider the typically unaffected population.”

The study runs counter to the vanishing idea that individual autism-linked genetic variants act as switches that determine whether someone has autism. Rather, each variant contributes incrementally to autism-related traits, and the the right combination of variants can push a person across the threshold for a diagnosis.

The findings also run against the traditional “medical model of illness,” in which certain traits exist only in people with a diagnosis, says **Robert Plomin**, professor of behavioral genetics at King’s College London, who was not involved in the study. “Disorders are not a matter of us ‘normal’ people versus those other people who are ‘disordered,’” Plomin says. “We all have many of the risk alleles for disorders.”

Common risk:

Robinson and her colleagues explored two types of genetic variants implicated in autism: **common, mild variants** found in at least 1 percent of the population, and **rare, harmful variants**

that are not inherited.

To find common variants underlying social ability in the general population, the researchers analyzed data from a genome-wide association study of nearly 6,000 children at age 8. The study identified variants that are more common among children who score poorly on a parent questionnaire of their social skills, called the Social and Communication Disorders Checklist, than they are in controls.

The researchers then looked for overlap between this set of variants and those linked to autism in two other association studies that together include more than 13,000 people with autism and 16,000 controls. In both datasets, more than one-quarter of the variants that contribute to autism risk are also associated with poor social skills in 8-year-old children.

This roughly 30 percent in overlap in variants is greater than **the shared risk** between autism and schizophrenia, and much greater than the overlap between autism and bipolar disorder or depression — conditions that often co-occur. In fact, it is as large as the genetic overlap between obesity and type 2 diabetes, Robinson says.

The overlap might be even bigger if the researchers were to look for variants tied to other features of autism, such as **repetitive behaviors**, Robinson says.

The evidence of a continuum would be more convincing if the researchers had assessed the same behaviors across a single group of individuals, some of whom have autism, says **Thomas Frazier**, director of the Cleveland Clinic's Center for Autism. Despite the new findings, there might still be a threshold at which the risk for autism increases in a nonlinear way, he says.

Strong hits:

To examine whether rare, harmful mutations also have the same effects in people with and without autism, Robinson and her colleagues used data from **a large sequencing study** of more than 2,800 people with autism, along with their unaffected family members. They calculated the proportion of people who carry a non-inherited, or *de novo*, mutation that is likely to harm the corresponding protein. They then excluded any variants found in a large database of **more than 60,000 controls**.

Roughly 19 percent of people with autism and nearly 10 percent of controls carry these rare variants, the researchers found. And in both groups, the more of these variants a person has, the lower he scores on a test called the Vineland Adaptive Behavior Scales, which measures social, communication and daily living skills.

The highest Vineland scores among people with autism overlap with the lowest scores in people without the condition. The individuals who share Vineland scores have a similar number of rare

mutations regardless of whether they have autism.

The work is “impressive” in that it leverages statistical power to find overlap within a set of rare variants, says **Bernie Devlin**, professor of psychiatry at the University of Pittsburgh, who was not involved in the work.

The findings suggest that certain harmful mutations lead to autism-related traits, but are not sufficient on their own to lead to the condition. The background of common variants almost certainly plays a role in this cumulative risk, Robinson says.

“In order to actually understand at any level what’s going on [in autism], be it epidemiologically or biologically, we have to start integrating this information,” she says.

REFERENCES:

1. Robinson E.B. *et al. Nat. Genet.* Epub ahead of print (2016) **PubMed**