NEWS

Chromosome 16 mutations augur distinct developmental paths

BY **NICHOLETTE ZELIADT**

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Children missing a stretch of DNA on chromosome 16 show worsening motor and social skills in the first eight years of life, a new study suggests[1]. Those with an extra copy of the strip, called **16p11.2**, do not show this decline.

The findings suggest that deletion and duplication of 16p11.2 lead to distinct developmental trajectories. About **1 percent of people with autism** have one of these mutations.

The new study is unique in that it followed 56 children with the mutations for several years.

“This helps us understand what these kids look like over time,” says lead investigator **Raphael Bernier**, associate professor of psychiatry and behavioral sciences at the University of Washington in Seattle. “So many of our studies about the genetics of autism are looking at a single time point; if we don’t consider the developmental change in behaviors, then it can be a little confusing.”

Deletions or duplications in 16p11.2 are rare, each occurring in about 3 out of 10,000 people. Deletions typically lead to an **enlarged head** and **obesity**, whereas duplications result in a **smaller head** and **low body weight**. Both mutations are associated with **language problems, intellectual disability** and autism.

The new findings highlight features clinicians should look for early in the child’s life, when treatments may be most effective. The study was published 27 March in the *American Journal of Medical Genetics: Part B, Neuropsychiatric Genetics*.

“If we know what’s likely to happen, we can be monitoring those things closely,” says **Cheryl Klaiman**, assistant professor of pediatrics at Emory University in Atlanta, Georgia, who was not involved in the study.

Different paths:

Bernier and his colleagues followed 33 children with a 16p11.2 deletion and 23 with a duplication. They began tracking the children as early as 6 months of age, up to age 8. Eight of the children with a deletion and five with a duplication have autism. All of the children are part of the **Simons Variation in Individuals Project**, a cohort of hundreds of people who carry mutations tied to autism. (The project is funded by the Simons Foundation, *Spectrum's* parent organization.)

The researchers assessed each child at least three times over the course of the study. (They aimed to assess the children every six months for the first two years and once a year after that, but some children missed assessments.)

The team used standardized tests to measure verbal and nonverbal intelligence quotients (IQ), as well as parent reports to assess internalizing behaviors, such as anxiety, and externalizing behaviors, such as hyperactivity. The researchers also measured 'adaptive functioning,' which refers to daily-living skills such as communication, social and motor abilities.

The team compared the children at ages 2, 3, 4, 5, 6 and 7, the time points for which data from the most children were available. There were no significant differences at any age in IQ scores, behaviors or adaptive functioning between children with a deletion and those with a duplication.

However, each group's average profile changed over time. The children with a deletion showed declines in motor and social skills, whereas those with a duplication remained relatively stable in these areas. Both groups of children showed an increase in verbal IQ — which is expected with age — but their behaviors and nonverbal IQ remained relatively stable.

Autism trajectory:

The findings help to fill an important gap in clinicians' understanding of children with these mutations, says **Anne Maillard**, a neuropsychologist at the Lausanne University Hospital in Switzerland, who was not involved in the study. "This paper is important because it looks at early development," she says. "That is the age range that we've been missing in the description of the phenotype."

The researchers did not detect any patterns that distinguish the subset of deletion carriers with autism from the rest of the children with the deletion.

However, among children with a duplication, those who have autism have weaker communication and social skills and lower verbal and nonverbal IQs at age 2 than do those without autism. They also show losses in motor skills and greater gains in verbal IQ with age than those without autism.

The number of children with autism in each group is so small that this analysis is "exploratory,"

Bernier says. Still, the pattern in children with a duplication mirrors the motor delays broadly **seen in children with autism**.

Bernier plans to explore the trajectories of children with other genetic risk factors for autism. He says he would also like to continue following children with 16p11.2 mutations into adolescence and adulthood.

REFERENCES:

1. Bernier R. *et al. Am. J. Med. Genet. B Neuropsychiatr. Genet.* **174**, 367-380 (2017)
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