

NEWS

Genetics underscores importance of motor deficits in autism

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Spontaneous mutations that impair proteins can cause motor problems in children with autism even in the absence of intellectual disability, a new study suggests¹. The findings indicate that motor problems are an inherent feature of autism.

“People should pay more attention, when making the diagnosis [of autism], to look carefully at the kids’ physical disabilities,” says lead researcher **Michael Wigler**, professor at Cold Spring Harbor Laboratory in New York.

The presence of motor deficits in a child with autism might also indicate that the child has a spontaneous mutation. The work appeared 6 February in the *Proceedings of the National Academy of Sciences*.

Severe spontaneous mutations are linked to both intellectual disability and motor problems. In a 2015 study, Wigler and his colleagues showed that harmful mutations increase the likelihood that a child with autism **has intellectual disability**².

The new findings suggest that problems with motor skills arise more readily in children with autism than intellectual disability does, says **Ivan Iossifov**, associate professor at Cold Spring Harbor Laboratory.

The findings are in line with those from a study last year showing that children who carry a harmful mutation in an autism gene **walk later** than those who don’t have these mutations³.

Moving target:

Both studies drew on data from the **Simons Simplex Collection** (SSC), a repository of clinical

information from 2,760 families and genetic sequencing data for nearly 2,500 of them. These families have one child with autism and unaffected parents and siblings. (The collection is funded by the Simons Foundation, *Spectrum's* parent organization.)

Wigler and his colleagues looked for correlations among any of 10 measures of motor function and the presence of a harmful spontaneous mutation in children with autism. The measures of motor skills included the age when the child first walked, as well as scores for fine and gross motor skills on two parent-report questionnaires.

The researchers also ranked the severity of the spontaneous, or *de novo*, mutation. They ranked a mutation as more severe if it was identified in more than one child with autism in the SSC or was found in a gene regulated by FMRP (the protein missing in **fragile X syndrome**) or a gene regulated by **CHD8**, a top autism gene. They also rated how **vulnerable the gene** is to becoming mutated.

In each case, the more severe a mutation, the more it tracks with motor deficits, the researchers found. The most severe mutations, based on the genes' vulnerability, tend to lead to both intellectual disability and motor deficits; less severe mutations tend to track with motor deficits but not intelligence.

The team then looked at spontaneous 'missense' mutations, which alter the protein code but don't erase a protein's function. Missense mutations in vulnerable genes track with motor deficits but not intellectual disability, the team found.

Severity markers:

The results emphasize the importance of motor problems in autism, which often receive less scientific attention than social skills do.

"The findings show that future research as well as clinical evaluations should be including good measures of motor functioning," says **Helen Tager-Flusberg**, director of the Center for Autism Research Excellence at Boston University, who was not involved in the study.

The study relied on parent reports, but researchers can also track motor skills with automated measures to flag autism early.

Motor skills may also offer a convenient way to measure autism severity because they are apparent at a young age and are more quantifiable than social skills, says **Stewart Mostofsky**, director of the Center for Neurodevelopmental Medicine and Research at the Kennedy Krieger Institute in Baltimore, Maryland, who was not involved in the study.

The researchers also found that social problems and **repetitive behaviors** are equally severe

among children with autism who have de novo mutations and those who do not.

That result is contrary to the 2017 study, which found that children with harmful de novo mutations have milder social problems than those with a similar intelligence quotient (IQ) who do not have those mutations. However, that study looked only at children from the SSC who carry a de novo mutation in a known autism gene.

The difference between the studies may be due to the fact that the earlier study held IQ constant in the comparison. Removing IQ as a variable skews the data, the researchers on the new study say, as it cannot be cleanly separated from other features of autism.

But it is important to hold IQ constant to better understand the specific relationship between motor deficits and autism mutations, because IQ correlates with motor deficits in children with autism, says **Stephan Sanders**, a researcher on the 2017 study. “In this context, controlling for IQ is the more informative approach,” he says. Sanders is assistant professor of psychiatry at the University of California, San Francisco. For now, the two teams disagree.

A next step, says Iossifov, is to see whether motor deficits also track with spontaneous harmful mutations in children who do not have autism. If they do, motor deficits might not be useful as an early marker of autism.

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