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ARTICLE

Monogenic disorders associated with motor speech phenotypes in children and adolescents undergoing clinical exome sequencing

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About the Authors:
The main author, Marissa Mitchel, M.S., CCC-SLP, is a pediatric speech-language pathologist and researcher at the Geisinger Autism & Developmental Medicine Institute. She specializes in augmentative and alternative communication for children with limited speech, with research focused on the genetics of motor speech disorders and speech-language profiles in children with rare genetic conditions. This research article is the result of a collaborative effort between researchers and medical professionals at the Geisinger Institute, GeneDX, the Broad Institute of MIT and Harvard, and the University of Florida.

Background:
Some kids and teens have serious problems with speaking clearly because the muscles and brain signals that help them talk don't work well together. These are called motor speech disorders (MSDs). Two common examples are childhood apraxia of speech (trouble planning speech movements) and dysarthria (weak or poorly controlled speech muscles). These conditions often happen with other neurodevelopmental challenges like autism or learning problems.

Past studies looking into associations between speech and genetic changes were small and did not look at lots of kids with different kinds of motor speech issues. They mainly focused on childhood apraxia of speech. To expand, this study looked at a larger group of children and teens to try to find specific genetic changes linked to these speech disorders using information from a DNA test called clinical exome sequencing. Exome sequencing allows scientists to test

important parts of thousands of genes at the same time to find possible causes of genetic disorders. These parts are called the exome, and give instructions for how the body and brain grow and work. Most known genetic disorders are caused by changes in the exome. Many children with serious speech difficulties look similar on the outside, even though the reasons for their problems may be very different. Exome sequencing helps doctors look under the surface to find genetic causes that cannot be seen just by watching how a child talks.

This research study combined the results from exome sequencing and observations from doctors on appearance, behavior, and other characteristics to uncover new insights between single gene diseases, such as SETBP1-HD and speech disorders. This research is the largest investigation to date of children and young adults with MSDs

Main Findings:
In general, about 1 in 4 kids (~26%) of the 2,004 included in this study with motor speech problems had a clear genetic change (pathogenic or likely pathogenic variant) that could explain their condition. This means many kids had a single-gene change likely responsible for their respective speech issue.

The researchers found many of the pathogenic or likely pathogenic variants in 262 different genes– previously known to have neurodevelopmental disorders associated with them– had never been linked to MSDs before.

The researchers wanted to see if certain genes show up more often in kids with motor speech disorders (MSDs) than in kids who had genetic testing for other reasons. They looked at children with motor speech disorders (about 2,000 kids) and compared them to a much larger group of children (about 66,000 kids) who had genetic testing but did not have speech motor problems. They focused on gene changes that are known to cause disease, called pathogenic or likely pathogenic (P/LP) variants. If a gene shows up much more often in the speech disorder group, it suggests that gene is strongly linked to speech problems.

They tested 182 genes that were already suspected to be related to speech or movement. 30 genes showed up more often in kids with motor speech disorders. But when the researchers used stricter math rules (to avoid false alarms), only 2 genes stood out as truly important: *SETBP1 and ADCY5*. These genes were much more common in children with motor speech disorders than in other children.

One of the most important findings was the strong connection between changes in the *SETBP1* gene and MSDs.

Children with SETBP1 changes were about 17 times as often in the group of children with motor speech disorders than children compared to the group of children undergoing exome sequencing for reasons other than speech disorders. SETBP1 remained significant even after

comparing it to all ~19,000 human genes, which is a very strict test. This means the connection between SETBP1 and motor speech problems is extremely strong and unlikely to be due to chance.

Furthermore, children with changes in SETBP1 often had reported severe speech difficulties, especially problems planning and producing speech sounds. This study suggests that motor speech difficulties are a key feature of this SETBP1 haploinsufficiency disorder (SETBP1-HD), not just a sporadic occurence.

What does this mean for SETBP1-HD:

The study found that changes in the SETBP1 gene—especially in children with SETBP1-HD—are strongly linked to severe motor speech problems, making SETBP1 an important gene to check when a child has serious difficulty speaking.

Knowing the genetic cause early can help doctors and families plan more targeted support — like starting intensive and specialized speech therapy sooner — and helps researchers understand how these disorders work. In addition this gives families a clearer picture on the cause of their child's speech challenges.

Accessing the Review article:
The full review article titled "Monogenic disorders associated with motor speech phenotypes in children and adolescents undergoing clinical exome sequencing," published in *Genetics in Medicine* on February 7, 2025, can be accessed here:
https://www.gimjournal.org/article/S1098-3600(25)00021-8/fulltext

Other related resources:
Childhood apraxia of speech - Symptoms and causes - Mayo Clinic

Motor Speech Disorders: Apraxia and Dysarthria - Northwestern University Center for Audiology, Speech, Language, and Learning

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