First study to directly compare gene mutation type in individuals with CHAMP1 disorder indicates key differences

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Researchers in the lab. Credit: Mount Sinai Health System

New research led by the Seaver Autism Center for Research and Treatment at Mount Sinai has illuminated genetic differences among children with a rare neurodevelopmental condition and could point the way toward a precision medicine approach to caring for these children.

The study is the first of its kind to directly assess differences between individuals with mutations in the CHAMP1 gene and those with deletions of the gene. The analysis was published in *Human Genetics* on July 17.

CHAMP1 disorder is a genetic, neurodevelopmental condition associated with intellectual disability, medical comorbidities (e.g., seizures, gastrointestinal problems), and dysmorphic features. The disorder is caused by mutations or deletions of the CHAMP1 gene.

Researchers from the Seaver Autism Center performed clinical evaluations of two groups of subjects: 16 individuals with CHAMP1 coding mutations (spelling changes in the gene), and eight individuals with deletions of CHAMP1.

The group with CHAMP1 gene mutations revealed significantly lower adaptive functioning skills than those with deletions across all areas assessed, including communication, daily living skills, socialization, and motor skills. Those in the mutation group also had more severe developmental delays and were more likely to have low muscle tone and gastrointestinal abnormalities.

Researchers hypothesize that the variation in symptoms is likely attributable to differences in the mechanisms behind the deletions and mutations of the CHAMP1 gene. Deletions act through CHAMP1 haploinsufficiency, which occurs when the remaining functioning copy of the CHAMP1 gene is not adequate to preserve normal function alone. Mutations may be acting through dominant negative or gain-of-function mechanisms, which actively interfere with the normal gene function and lead to more severe clinical symptoms.

"Hearing parents describe the challenges and strengths their children experience and possess has showed us that while these children share the

diagnosis of CHAMP1 disorder, their presentations and behaviors often differ," said Thariana Pichardo, Clinical Research Coordinator at the Seaver Autism Center, who completed many of the study's key clinical assessments.

The study results illustrate the importance of understanding the mechanisms of mutations and deletions prior to treatment development for CHAMP1 and other disorders, like autism, that have broad diagnosis with differing genetic causes.

"This analysis unveils valuable insight into potential therapeutics that may lead to successful symptom improvement," said Tess Levy, CGC, Assistant Professor of Psychiatry at the Icahn School of Medicine at Mount Sinai and first author of the paper. "Pinpointing the mechanisms that are the source of this disorder will enable a precision medicine approach to treatment for the two groups of patients with different presentation but ultimately the same CHAMP1 disorder diagnosis."

More information: Tess Levy et al, Prospective phenotyping of CHAMP1 disorder indicates that coding mutations may not act through haploinsufficiency, *Human Genetics* (2023). DOI: 10.1007/s00439-023-02578-6

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