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Genetic causes of cerebral palsy uncovered through whole-genome sequencing

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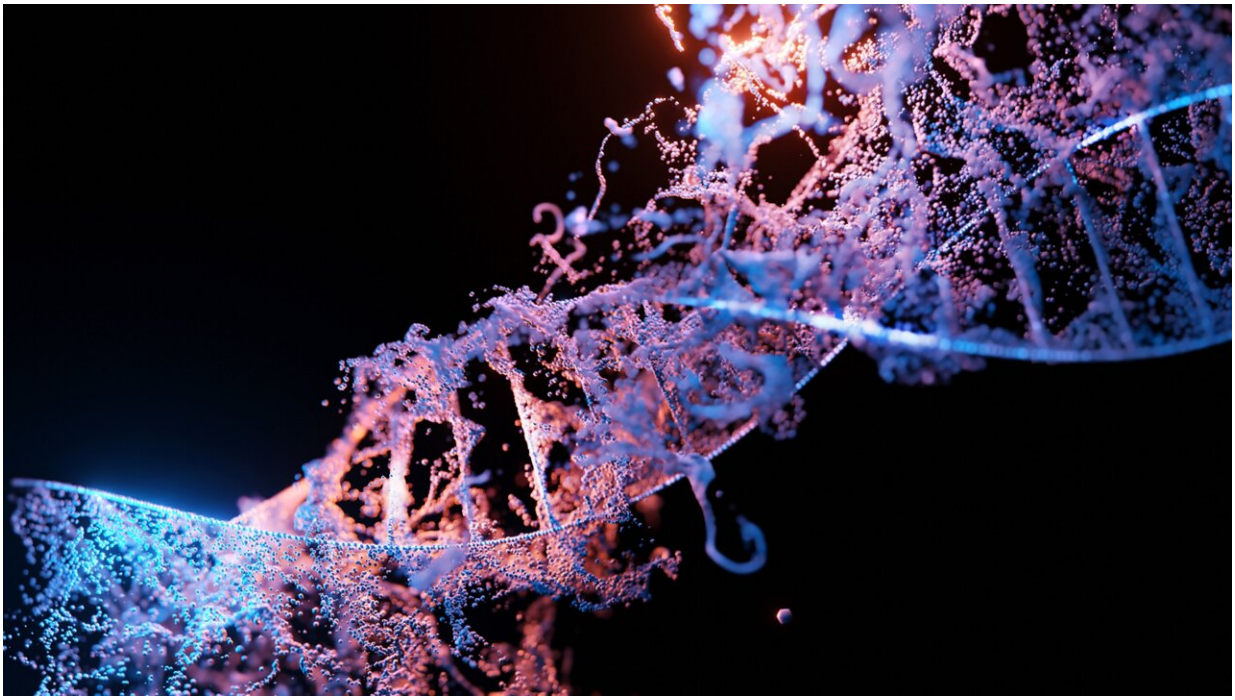

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A Canadian-led study has identified genes which may be partially responsible for the development of cerebral palsy.

Cerebral palsy (CP), a condition that affects the development of motor skills in children, is the most common childhood-onset physical disability. CP can have different causes, such as infections, injuries, or

lack of oxygen before or during birth, but the genetic contributors to CP have remained largely unknown.

Novel research from scientists at The Hospital for Sick Children (SickKids), the Research Institute of the McGill University Health Centre (RI-MUHC) and Holland Bloorview Kids Rehabilitation Hospital, who led a multi-site Canadian project, provides a more detailed look into the genetic causes of the condition. Their findings suggest the existence of many genetic variants contributing to CP, which may inform future diagnosis and treatment.

"For 100 years cerebral palsy was mostly thought to be the result of entirely environmental factors during birth," says study co-lead Dr. Stephen Scherer, Chief of Research and Senior Scientist in the Genetics & Genome Biology program at SickKids and Director of The Centre for Applied Genomics. "Now that we have a better understanding into the complex relationship between cerebral palsy's genetic and environmental factors, we hope we can improve care for these children."

One in ten children with CP have a genetic variant associated with their condition

Published in Nature Genetics, the scientists conducted whole-genome sequencing in 327 children with CP, including their biological parents, and compared it to three independent clinical cohorts as well as two pediatric control cohorts, to identify whether genetic variants may be involved in CP.

The seven-year study found that more than one in ten children (11.3 percent) had a genetic variant or likely genetic variant for their CP, and 17.7 percent of children had variants of uncertain significance that may be linked with CP after further research. Many of the variants also

overlapped with other neurodevelopmental conditions, including autism spectrum disorder (ASD), which is highly prevalent in children with CP.

The findings suggest that CP and its causes may be much more diverse than previously thought and showcases the strength of combining precision medicine programs, including Bloorview Research Institute's precision health program and Precision Child Health at SickKids, a movement to deliver individualized care to each patient.

"Our findings are a step forward in better understanding the complex genetic and environmental risk factors that may determine an individual's chance of developing this complex condition to help individualize future treatment approaches," says study co-lead Dr. Maryam Oskoui, Senior Clinician Scientist of the Fonds de Recherche du Québec Santé at the Research Institute of the McGill University Health Centre and Director of the Neurology Division at the Montreal Children's Hospital.

"Our rich dataset of deeply genotyped and phenotyped trios offers the best available evidence to shift clinical practice to include genetic testing in all children with CP."

Open data provides the foundation for future research

The data collected through this study are the first whole-genome sequencing data to be made available in the Brain-CODE analytics and informatics platform, managed by the Ontario Brain Institute. This initiative aims to improve access to genome sequencing data for scientists around the world.

"Many of the children we see come through our doors have genetic

variations that are associated with their cerebral palsy," explains co-first-author Dr. Darcy Fehlings, a Senior Clinician Scientist at Holland Bloorview Kids Rehabilitation Hospital. "This opportunity for precision medicine is of utmost importance to accurately diagnose etiology across all children with CP, improve family counseling, and choose interventions (medical and rehabilitation) best suited for the child."

The research teams hope the data can also help other scientists identify new genes and pathways that are involved in CP and stimulate more research to understand how they affect the brain and how they can be targeted for intervention.

"Holland Bloorview is excited to co-lead this new research disrupting the CP treatment landscape. Drs. Scherer's and Fehlings' work is laying the foundation for more targeted treatment options through the power of precision health—and transforming the lives of children, youth, and families locally, nationally, and internationally," says Dr. Evdokia Anagnostou, Vice President of Research and Director of the Bloorview Research Institute.

More information: Comprehensive whole-genome sequence analyses provide insights into the genomic architecture of cerebral palsy, *Nature Genetics* (2024). DOI: 10.1038/s41588-024-01686-x. www.nature.com/articles/s41588-024-01686-x

Provided by The Hospital for Sick Children

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