Research identifies frequent genetic causes of cerebral palsy

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Researchers have discovered a strong link between genetic changes known to cause neurodevelopmental disabilities and cerebral palsy.

Cerebral palsy affects movement and posture and often co-occurs with other neurodevelopmental disorders, including intellectual disability, epilepsy and autism spectrum disorder. Individual cases of cerebral palsy are often attributed to birth asphyxia, although recent studies indicate that asphyxia accounts for less than 10% of cases. A growing body of research indicates that cerebral palsy may be caused by genetic changes, as is the case in other neurodevelopmental disorders.

The research team, which included investigators from Geisinger and GeneDx Inc., a wholly owned subsidiary of BioReference Laboratories Inc., an OPKO Health company and global leader in genetic diagnostics, studied the DNA sequence of 1,526 children and adults with cerebral palsy. The team found disease-causing changes in 229 genes, several of which have been previously identified in people with both cerebral palsy and other neurodevelopmental disorders. Disease-causing genetic changes were found in 32.7% of a primarily pediatric group of patients from GeneDx and in 10.5% of a primarily adult group from Geisinger.

"Finding a genetic cause for cerebral palsy not only provides an answer to the family, but also informs recurrence risk estimates for future children born to the same parents," said Christa Martin, Ph.D., senior co-author of the study and professor and director of Geisinger's Autism & Developmental Medicine Institute.

"Previous studies in families with children with CP have found a risk of recurrence of 1-2%. Identifying a genetic change that causes the CP in a

child and is not present in either parent decreases the risk to less than 1% for future children born to the same parents. When the genetic change that causes CP is inherited from one or both of the parents, that risk increases to 50% and 25%, respectively," Martin said.

"At GeneDx, we were able to test three-fourths of patients along with both parents, allowing us to establish the inheritance of the genetic changes," said Francisca Millan, M.D., co-first author of the study and associate director of neurogenetics at GeneDx. "For approximately a third of the families where a causative genetic change was identified, the family recurrence risk increased to 25% to 50%."

The identification of these genetic changes in multiple patients and replication of these findings across different settings and cohort types provided strong evidence for their role in cerebral palsy, the research team wrote. The findings were published in the *Journal of the American Medical Association* (*JAMA*).

"DNA sequencing is recommended as a first-tier clinical diagnostic test for individuals with neurodevelopmental disorders, which are known to co-occur with cerebral palsy," said Andres Moreno De Luca, M.D., physician-scientist and clinical neuroradiologist at Geisinger and co-first author of the study. "Since cerebral palsy can be identified earlier than other neurodevelopmental disorders, such as intellectual disability and autism spectrum disorder, genetic testing for individuals with cerebral palsy may allow for quicker identification of genetic changes and facilitate early interventions and treatment."

"This study re-iterates the value of genetic testing for neurodevelopmental disorders and highlights the utility of genetic testing for cerebral palsy patients," said Kyle Retterer, senior co-author of the study and senior vice president and chief technology officer at GeneDx. "Increasing utilization of and access to DNA sequencing for these

patients will lead to earlier diagnoses and improved care in many cases."

More information: Andrés Moreno et al. Molecular Diagnostic Yield of Exome Sequencing in Patients With Cerebral Palsy. *JAMA* February 2, 2021 DOI: 10.1001/jama.2020.26148

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