New test improves diagnosis of a common genetic cause of autism

October 28 2019, by Bridie Byrne

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A new stand-alone test can more precisely diagnose people with a common genetic cause of autism than the current testing regime.

The international study, led by the Murdoch Children's Research Institute (MCRI) in collaboration with Lineagen, Inc., an innovative diagnostic genetic testing and clinical information services company based in Utah, published in *Scientific Reports*, describes a trial of a more cost-effective, accurate and timely way to identify those with Fragile X syndrome, one of the most common genetic causes of intellectual disability and autism spectrum disorder.

Fragile X associated costs to raise one affected child have been estimated at more than $2.5 million to the health system.

Fragile X affects about one in 4,000 children with about 90,000 Australians and over one million Americans impacted in some way. A large proportion of these are women who themselves are not affected with Fragile X, but carry a DNA 'premutation' in their FMR1 gene. This premutation predisposes these women to have children with Fragile X.

A major issue with Fragile X is that at a young age the syndrome is not clinically distinct, with an average age of diagnosis in Australia about five years, and, according to the Centers for Disease Control and Prevention, over three years in the US.

As a result of delayed diagnosis, affected children do not receive the medical care they need in a timely manner, and families may end up having multiple affected children before they receive a diagnosis for their first child.

Lead study researcher MCRI's Associate Professor David Godler said families that have carriers of 'premutation' could have an option of having unaffected children, if provided timely advice regarding alternative reproductive options.

"The impact of delayed diagnosis is significant and potentially

preventable not only to the families but also for our health system," he said.

"This is why we developed our new test, called Methylation Specific Quantitative Melt Analysis (MS-QMA). This is a one step process, to assist in more accurate and timely diagnosis of Fragile X in affected children referred for genetic testing."

The one-step test looks at the number of chemical modifications or "marks," called methylation, added to a patient's FMR1 gene in Fragile X, which are not present in typically developing children without Fragile X syndrome. Increasing these marks reduces the production of a protein called FMRP required for healthy brain development and function. This study for the first time shows that the number of these marks can be increased, even in people without the usual genetic changes seen in Fragile X syndrome (called CGG repeats). Until now, this was not known, in part because current standard testing does not involve looking at these marks as part of the initial CGG screen.

The current standard testing only examines these marks using a second separate test, and only on the limited number of patients suspected of having the typical genetic change (CGG repeats) associated with Fragile X, called full mutation, and 'large' permutation alleles. One reason for this is that this second methylation test is too expensive to be used to test all patients initially suspected of having Fragile X and therefore, some patients affected with Fragile X go undetected.

In this study, Lineagen and MCRI compared DNA test results on more than 300 patients from pediatric clinics in the United States and Australia. These patients were known to either contain Fragile X mutations as detected by standard testing or no mutations detected by standard testing. While the second group of patients had no Fragile X mutations detected by standard CGG repeat testing, they were likewise

diagnosed by physicians as having a form of intellectual disability with/or without autism.

All genetic testing was carried out in Associate Professor Godler's laboratory at MCRI using MS-QMA on male and female samples blinded by Lineagen. Once the blind was lifted, all male and female patients with known Fragile X diagnosis received correct diagnosis using MS-QMA.

The study also identified one additional female patient with a Fragile X full mutation in a small proportion of cells, which wasn't detected by the standard two-step testing process.

"We also identified, for the first time, smaller more common FMR1 alleles that are not usually tested for methylation (a tell-tale sign of Fragile X), that had abnormal methylation signatures in a significant number of affected patients," Associate Professor Godler said.

"These abnormal signatures were confirmed to be present by the current standard confirmatory methylation test performed by Lineagen. These signatures may compromise function of the FMR1 gene, and potentially lead to Fragile X like clinical features, and is an active area of research for my group."

Lineagen CEO Dr. Michael Paul said even after a series of the best possible clinical genetic tests, almost half of children with autism spectrum disorders don't receive a genetic diagnosis, so anything we can do to improve genetic diagnostic precision is important for families and their children.

Dr. Paul also said, "We are pleased to have collaborated with Associate Professor Golder and his team to identify up to 15 percent of patients with Fragile X syndrome than is currently revealed through the current

testing paradigm which includes FMR1 CGG repeat analysis as the front-line Fragile X test currently performed for children who are suspected of having the condition."

"Lineagen's mission is to help provide more accurate and precise genetic diagnoses of pediatric neurodevelopmental disorders sooner, so this is a community we must help and a challenge we cannot ignore."

More information: Charles H. Hensel et al. Abnormally Methylated FMR1 in Absence of a Detectable Full Mutation in a U.S.A Patient Cohort Referred for Fragile X Testing, *Scientific Reports* (2019). DOI: 10.1038/s41598-019-51618-7

Provided by Murdoch Children's Research Institute