Researchers deliver a new understanding into a common cause of syndromic autism

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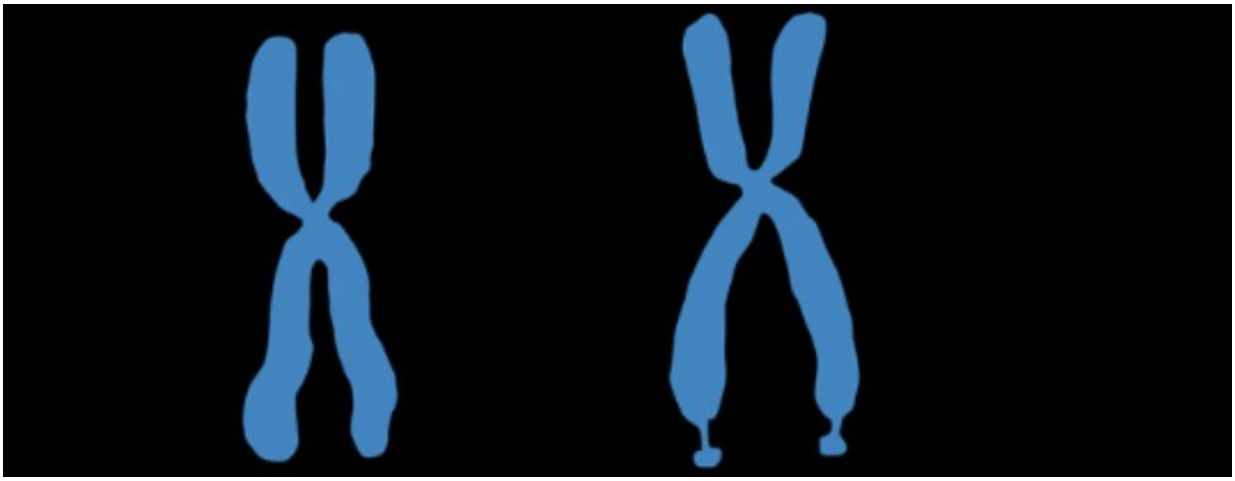

Fragile X is caused by a disruption of the gene, FMR1, and this disruption was previously thought to occur almost exclusively through presence of a repeated DNA sequence called ‘full mutation’, that makes the gene inactive.

Australian and Chilean scientists have made a breakthrough in their understanding of the genetics of a common form of syndromic autism—and they hope their work could one day lead to the development of treatments for the condition.

The Murdoch Children's Research Institute (MCRI) led the research focusing on genes linked to Fragile X syndrome (FXS), one of the most common genetic causes of intellectual disability and autism spectrum

disorder (ASD), particularly in boys. Approximately one in 4000 males are affected.

The international study, published in *Molecular Autism*, looked at 100 children, adolescents and adults with Fragile X, a condition caused by a disruption to a single gene, FMR1.

Half the study participants lived in Australia and half in Chile. The study involved a large network of collaborators in both countries, with the bulk of the recruitment and assessments was performed by MCRI researchers at the Royal Children's Hospital and other locations, in collaboration with teams headed by Dr. Lorena Santa Maria from the Instituto de Nutrición y Tecnología de los Alimentos (INTA), University of Chile and Dr. Michael Field from Hunter Genetics, NSW.

"Within our study group of people with FXS, the gene, FMR1, was completely turned off in some, while in the majority of participants it was partially turned on," Dr. Baker said. "The gene, FMR1, is totally turned on in people without Fragile X syndrome, and so it would be fair to expect that people with the partially turned on gene would have less traits of autism, but we found the opposite."

"Unexpectedly we showed for the first time that people with a partially turned-on FMR1 had intellectual disability and more traits of autism spectrum disorder, whereas people with the gene completely turned off had intellectual disability and much less severe autism. This is possibly because the genetic code of the FMR1 gene in FXS is not the same as in unaffected people. In FXS the gene contains a large repetitive sequence called full mutation. When this full mutation is turned on it may cause autism features worse in FXS. These findings are significant because they enhance our understanding of the biology of autism, and may explain why severity of Fragile X is not the same between affected individuals."

Senior researcher in the study, Associate Professor David Godler, said global pharmaceutical companies have invested millions of dollars trying to develop medications to treat autism and often use Fragile X syndrome as their model.

"In mice these targeted drugs were very effective, but have failed in most human trials. This may be due to the fact that in mice, the FMR1 gene is artificially completely switched off, which is not consistent with the biology of the majority of males with Fragile X as shown in this study," Golder said. "Our breakthrough may explain why trials for drugs treating autism have to date not worked and it may enable researchers in future trials to separate people into those with partially turned-on FMR1 and those with FMR1 turned-off."

Dr. Baker said she hoped the study would have an impact on the development of treatments and interventions aimed at improving behavior in individuals with Fragile X.

"I want the ultimate result of this research to lead to a better quality of life for both the affected individual and the families who support them," Dr. Baker said.

More information: Emma K. Baker et al. Incomplete silencing of full mutation alleles in males with fragile X syndrome is associated with autistic features, *Molecular Autism* (2019). DOI: 10.1186/s13229-019-0271-7

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