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Genetic defect causing fragile X-related disorders more common than thought

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A single genetic defect on the X chromosome that can result in a wide array of conditions—from learning and emotional difficulties to primary ovarian insufficiency in women and tremors in middle-aged men—occurs at a much greater frequency than previously thought, research led by the UC Davis MIND Institute has found.

The research is based on the first large-scale, multi-center newborn screening effort for the defect in the United States, conducted in a group of more than 14,200 male and female infants at three research university medical centers piloting a new infant screening test developed at UC Davis.

The study, "FMR1 CGG Allele Size and Prevalence Ascertained Through Newborn Screening in the United States," was led by Flora Tassone, professor-in-residence in the Department of Biochemistry and Molecular Medicine, and was conducted using blood spots obtained from infant heel pricks as part of the normal newborn genetic screening process. It is published online today in the journal *Genome Medicine*.

The investigators examined the prevalence of expanded alleles of the fragile X mental retardation 1 (FMR1) gene. Defects in FMR1 cause conditions as diverse as fragile X syndrome—the leading cause of intellectual disability and the leading known single-gene cause of autism—and a Parkinson's disease-like condition called fragile X-associated tremor/ataxia syndrome, or FXTAS. The term "fragile X" is used because of the altered appearance of the X chromosome among

sufferers from the conditions.

"This study demonstrates that there is a higher frequency of mutations of the FMR1 gene across racial and ethnic groups than previously believed," said Randi Hagerman, medical director of the UC Davis MIND Institute and one of the world's leading experts on fragile X-related conditions. "It also demonstrates that newborn screening for fragile X mutations is technically feasible in a large-scale setting using the blood spot technique developed by Dr. Tassone."

The degree of disability from defects in FMR1 depends upon the number of repetitions of the sequence of the proteins cytosine-guanine-guanine (CGG) in the promoter region of the gene. The range of repeats in normal individuals is between six and 40. CGG repeats greater than 200 cause what is called the full mutation and fragile X syndrome. Fewer repeats—in the range of 55 to 200—result in a variation called a premutation.

The current study found the estimated prevalence of the premutation to be 1 in 200 females, a finding somewhat greater than earlier estimates. However, it estimates the prevalence among males to be 1 in 400—double what had previously been reported. The researchers said that the sample size in the current study was not great enough to estimate the true prevalence of the full fragile X mutation, currently estimated at between 1 in 2,500 and 1 in 8,000 females and 1 in 5,000 males.

While most people with the premutation appear normal, some individuals can have mild difficulties in childhood, such as such as learning problems or emotional difficulties including social anxiety and attention deficit hyperactivity disorder (ADHD), said Hagerman, a professor in the Department of Pediatrics. Individuals with the premutation also can suffer from FXTAS, which causes debilitating tremors, balance problems and dementia primarily in older men, and

premature ovarian insufficiency in women.

Tassone, a researcher affiliated with the MIND Institute, is one of the world's leading experts on screening and identification of the FMR1 mutation. Her polymerase chain reaction (PCR)-based test used in the current study was described in January 2008 in the Journal of Molecular Diagnostics.

"This study shows that newborn screening for the FMR1 mutation is technically possible on a large scale," Tassone said. "However, the screening will identify far more carrier and gray-zone infants than those with a full fragile X mutation. As we now know that there may be clinical involvement with these individuals, such as FXTAS, we need to better understand the impact of identifying these mutations on families before widespread newborn screening can be instituted."

Hagerman said that the study is important because early intervention can be helpful for children with these mutations who experience developmental problems. In addition, a baby who is positive for the mutation will have other family members who also carry mutations. Genetic counseling is essential for the family members, in addition to treatment for the medical or psychiatric problems associated with the premutation or full mutation, she said.

More information: FMR1 CGG allele size and prevalence ascertained through newborn screening in the United States Flora Tassone, Ka Pou Iong, Joyce Lo, Louise W Gane, Elizabeth Berry-Kravis, Danh Nguyen, Lisa Mu, Jennifer Laffin, Don Bailey Jr., Randi J Hagerman and Tzu-Han Tong Genome Medicine (in press)

Provided by UC Davis