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Fragile X gene's prevalence suggests broader health risk

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The first U.S. population prevalence study of mutations in the gene that causes fragile X syndrome, the most common inherited form of intellectual disability, suggests the mutation in the gene – and its associated health risks – may be more common than previously believed.

Writing this month (June 2012) in the *American Journal of Medical Genetics*, a team of Wisconsin researchers reports that the cascade of genetic amino acid repeats, which accumulate over generations and culminate in the mutation of a single gene causing fragile X, is occurring with more frequency among Americans than previously believed. The study also shows that as the genetic basis for the condition is passed from generation to generation and amplified, risks to neurological and reproductive health emerge in many carriers.

"The premutation of this condition is much more prevalent than we previously thought and there are some clinical risks associated with that," explains Marsha Mailick Seltzer, director of the University of Wisconsin-Madison Waisman Center, who led the new study.

Fragile X is caused by the unexplained runaway expansion of a set of amino acid repeats in a single X chromosome gene known as FMR1. When fully mutated, the gene fails to express and produce a protein that's required for healthy brain development. The syndrome, which is more common in boys, results in a spectrum of intellectual disability.

However, before the gene fully mutates, carriers of the faulty gene

exhibit a smaller number of elevated repeats, which expand as the gene is passed from generation to generation. Normal FMR1 genes exhibit anywhere from five to 40 repeats. Carriers with a premutation may have anywhere from 55 to 200. Those with between 45 and 54 repeats are characterized as falling into a "gray zone." Carriers of gray zone expansions often pass the mutation on to their children who themselves are at greater risk of having the premutation, and in subsequent generations the risk of a full mutation causing fragile X syndrome is high.

The goal of the new study was to calculate the prevalence in a U.S. population of the premutation and the gray zone. The research was based on data from the Wisconsin Longitudinal Study (WLS), also known as the "Happy Days study," which for more than 50 years has tracked the careers, family life, health and education of more than 10,000 graduates of Wisconsin's high school class of 1957.

Using genetic samples from 6,747 WLS participants, the team led by Seltzer, an expert on developmental disability and family life, found that 1 in 151 females and 1 in 468 males carry the fragile X premutation while 1 in 35 females and 1 of every 42 males fall into the gray zone.

"The prevalence is high, the second highest reported in the world literature," says Seltzer, noting that the incidence of fragile X varies by population and is higher in some places such as Israel, and lower in others like Asia.

The expansion of the FMR1 gene is known to vary across ethnic groups. The sample in the WLS study is primarily white and of northern European descent.

People with the premutation are more likely to have a child with disability; to have neurological symptoms such as numbness, dizziness

and faintness; and, for women, to experience early menopause. Although these symptoms have been recognized previously in clinical studies, the WLS data represent an unbiased sample and supports those observations.

"This study confirms that there are health risks associated with the premutation," says Seltzer. "People with the premutation have a higher probability of neurological and reproductive problems. There is a significant public health burden."

Provided by University of Wisconsin-Madison