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FMR1 CGG allele size and prevalence ascertained through newborn screening in the United States

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Abstract

Background: Population screening for *FMR1* mutations has been a topic of considerable discussion since the *FMR1* gene was identified in 1991. Advances in understanding the molecular basis of fragile X syndrome (FXS) and in genetic testing methods have led to new, less expensive methodology to use for large screening endeavors. A core criterion for newborn screening is an accurate understanding of the public health burden of a disease, considering both disease severity and prevalence rate. This article addresses this need by reporting prevalence rates observed in a pilot newborn screening study for FXS in the US.

Methods: Blood spot screening of 14,207 newborns (7,312 males and 6,895 females) was conducted in three birthing hospitals across the United States beginning in November 2008, using a PCR-based approach.

Results: The prevalence of gray zone alleles was 1:66 females and 1:112 males, while the prevalence of a premutation was 1:209 females and 1:430 males. Differences in prevalence rates were observed among the various ethnic groups; specifically higher frequency for gray zone alleles in males was observed in the White group compared to the Hispanic and African-American groups. One full mutation male was identified (>200 CGG repeats).

Conclusions: The presented pilot study shows that newborn screening in fragile X is technically feasible and provides overall prevalence of the premutation and gray zone alleles in the USA, suggesting that the prevalence of the premutation, particularly in males, is higher than has been previously reported.

Background

Fragile X syndrome (FXS), the most common single gene cause of inherited intellectual disabilities and autism, is characterized by a CGG-repeat expansion (>200 CGG repeats, full mutation) in the portion of the first exon of the fragile X mental retardation 1 gene (*FMR1*), which encodes the 5' UTR of the *FMR1* mRNA. When the full mutation is present, epigenetic modification of the CGG rich region turns off the gene, which results in absence or deficit of the encoded product, FMRP, leading to defects in synaptic plasticity. *FMR1* premutation carriers have an unstable expansion containing 55 to 200 CGG repeats and gray zone or intermediate allele carriers have small expansions of 45 to 54 repeats [1].

The *FMR1* full mutation can cause a broad spectrum of involvement, including intellectual disability, behavior problems, social deficits and autism spectrum disorders (ASD) [2-4]. Significant clinical involvement has also been reported in some premutation carriers, including medical, neurological and psychiatric problems such as ASD, attention deficit-hyperactivity disorder (ADHD), depression and anxiety [5-12]. Moreover, fragile X-associated primary ovarian insufficiency (FXPOI) occurs in approximately 20% of female carriers [13,14] and fragile X-associated tremor ataxia syndrome (FXTAS) affects approximately 40% of older male carriers, and approximately 8 to 16% of older female carriers [8,15-17]. Risks associated with gray zone or intermediate alleles still need to be verified, but these alleles may be associated with an increased risk for FXTAS and FXPOI, and can be unstable when transmitted across generations [18-21].

The reported prevalence of the full mutation in the general population ranges from 1:2,500 to 1:8,000 in females and approximately 1:4,000 to 1:5,000 in males [22-28]. Premutation carriers (55 to 200 CGG repeats) are more common, with estimates ranging between 1:130

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