Prevalence of Fragile X Premutation Carriers Among Female Patients Seeking Fertility Treatments

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Rachel Allen, MS, CGC[1], Kailey Owens, MS, CGC.[1], Catherine Terhaar, MS, CGC[1], Christina Settler, MS, CGC[1], Jessica Omark, BS[2], Priscilla Fernandes, PhD[1], Nina Resetkova, MD[3]
[1]Progenity, Inc., Ann Arbor, MI, United States; [2]University of Texas Genetic Counseling Program; [3]Boston IVF, Waltham, MA, United States

Background

Fragile X syndrome is an X-linked condition that is almost always caused by full mutations (>200 CGG repeats; table 1) and aberrant methylation within the *FMR1* gene. It is typically associated with intellectual disability and behavioral issues of variable clinical severity.

Carrier testing is routinely available for detection of CGG repeat number by polymerase chain reaction (PCR). In addition to the reproductive risk of having an affected child, female premutation carriers (55–200 repeats) are also at risk of primary ovarian insufficiency, which is associated with higher rates of infertility among young women. Women with intermediate or gray zone alleles (45–54 repeats) are not at increased risk for an affected child, although future generations may be at increased risk.

Current societal guidelines recommend fragile X testing for women with a history of primary ovarian insufficiency, but it is unclear whether the prevalence of fragile X alleles is higher among women with general fertility issues than the general population.

TABLE 1: *FMR1* ALLELE SIZES

Results	CGG Repeats
Normal	<45
Intermediate (Gray Zone)	45–54
Premutation	55–200
Full Mutation	>200

Objective and Design

This study compares the prevalence of fragile X premutation and/or gray zone allele carriers in reproductive medicine versus the general referral population which consists mostly of ob/gyn clinics. A retrospective review was conducted of fragile X carrier testing results for over 200,000 female samples referred for testing at a large commercial laboratory. Results were grouped by type (premutation vs. gray zone) and practice type (reproductive medicine vs. other).

Methods

The prevalence of premutation and gray zone alleles in samples referred for Preparent® carrier testing by reproductive medicine clinics were compared to the prevalence among samples referred by other clinics. Binomial confidence intervals (CI) for both groups were approximated using Agresti-Coull intervals and compared using A/B (split-run) testing.

Results

The prevalence of premutation carriers within the general referral population was 1 in 211, and the prevalence within the reproductive medicine population was 1 in 141. This difference was statistically significant (p<0.005). The prevalence of gray zone alleles within the general population was 1 in 50, compared to 1 in 44 in the reproductive medicine population. This difference was not statistically significant (p=0.089).

Conclusion

Our results from a large clinical testing laboratory indicate that there is a statistically significant difference in the prevalence of premutation alleles in the reproductive medicine group versus the general population, but not for gray zone alleles. This data adds to the previous literature on the prevalence of fragile X premutation alleles among females seeking fertility evaluations. Current societal guidelines recommend fragile X testing for women with a history of primary ovarian insufficiency. These data suggest that expanding recommendations to include testing for women with a fertility-related indication will help identify more fragile X carriers, allowing for critical counseling and family planning discussions for these patients.