FRAGILE X CLINICAL CHARACTERISTICS AND PARENTAL INHERITANCE; DATA FROM 100 PGT-M FAMILIES

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Abstract Body

PGT-M for Fragile X syndrome (FXS) is commonly performed. Information regarding Fragile X family history and prior genetic testing is typically gathered prior to PGT-M analysis; however, these data have largely been unreported. This study reviews the clinical characteristics and inheritance patterns for a large cohort of FXS PGT-M families. This cohort represents 100 families for which both female patient and parental Fragile X repeat sizes had been determined by diagnostic testing prior to PGT-M analysis.

The average age of patients at time of referral was 32.5 years. 24% of patients had prior family history of FXS clinical disease. 29% of patients reported a personal history of infertility, either unexplained or consistent with premature ovarian failure (POF). Most patients (78%) inherited Fragile X risk alleles in the premutation range (55-200 repeats). The average size of expanded Fragile X alleles in patients was 95 repeats. Surprisingly, 58% of women in this cohort inherited Fragile X risk alleles from their fathers ($p=0.02$). All full mutation range alleles (8/8 patients) were maternally inherited. Allele expansion events were more common than contraction events (44% of cases vs. 8% of cases, respectively). Maternal risk alleles expanded more frequently than paternally inherited alleles (53% vs. 38% of cases, respectively). Maternal expansion events were larger, on average (6.2 repeats, maternal vs. 2.1 repeats, paternal).

Some previously reported FXS inheritance patterns were observed in this 100 PGT-M family cohort: exclusive transmission of full mutation alleles by mothers and common expansion or premutation range alleles. However, most women in this cohort inherited FXS risk alleles from their fathers, which challenges some widely accepted beliefs regarding maternal inheritance predominance. This result warrants further investigation and, possibly, consideration of broader FXS risk assessment for males.