All *FMR1* premutations are not equal: Impact of frequency and repeat distribution on fragile X syndrome risk

Gabriel A. Lazarin, MS; Kenny K. Wong, MS; Imran S. Haque, PhD
Presented by Michelle Gilats, MS

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Background

Instability in the *FMR1* gene can result in CGG repeat expansion, which in turn causes fragile X syndrome (FXS, OMIM 300624) when the repeat count exceeds 200 ("full mutation"). Premutations (55–200 repeats) have a greater risk of next-generation expansion to full mutation.

Previous large studies have reported panethnic FXS prevalence of 1 in 4,000–6,000. There have been some suggestions of ethnic predilection, but this has not been well defined to date. Since the actual reproductive risk in a population for fragile X syndrome is dependent on both premutation frequency and allele sizes, we retrospectively analyzed this data derived from our population based carrier screening.

Methods

Samples were considered only if no family history, known carrier status, or infertility history were reported. We also excluded samples originating from ART clinics to avoid bias from premutation induced fragile X premature ovarian insufficiency (MIM 300624). We report data from 134,840 individuals passing the above filters who were screened for FXS, including at least 2,789 in each of ten self-reported ethnicities. *FMR1* 5'UTR CGG repeat count was assessed by PCR and capillary electrophoresis. A risk of expansion to full mutation was assigned to each repeat count and we calculated the absolute risk for FXS in each ethnic population by weighting the CGG count frequencies and their associated full mutation expansion risks (Yrigollen 2012).

Results

Average frequency of all premutations was 1/383, with substantial ethnic variation: the minimum was 1/2857 in East Asians, and the maximum was 1/182 in Middle Easterners. Our largest ethnic subgroup, Northern Europeans, exhibited a premutation frequency of 1/315. Premutation repeat size distribution also differed by ethnicity. Cumulatively, 46.1% of premutation alleles were in the smallest repeat count group (50–55), but by ethnicity, this ranged from 22.6% – 75.0%.

This provides a more accurate indication of reproductive risk than reliance on simple carrier frequency. As an example, even though the premutation frequency was higher in Northern Europeans (1/316) than Southern Europeans (1/393), the latter's repeat distribution more heavily favored alleles with high transmission risk: 18.2% of premutations were between 90–200 repeats, compared with 4.1%. The outcome of this phenomenon is actually a higher absolute risk for FXS in Southern Europeans, 1/2224, compared to 1/3805.

The highest FXS risk identified was among Middle Easterners (1/1353) and the lowest was among Southeast Asians (1/81745).

Conclusion

Premutation frequency and repeat length must be considered in tabulating risk for fragile X syndrome. Our large carrier screening database enables tabulation of more accurate risk estimations and reveals wide ethnic variability. This variability is generally unrecognized in clinical practice, and may be henceforth considered since certain ethnic groups are disproportionately affected by the disease.

Figure 1: Distribution of FMR1 premutation range (55-200) CGG repeat counts for selected ethnic groups.

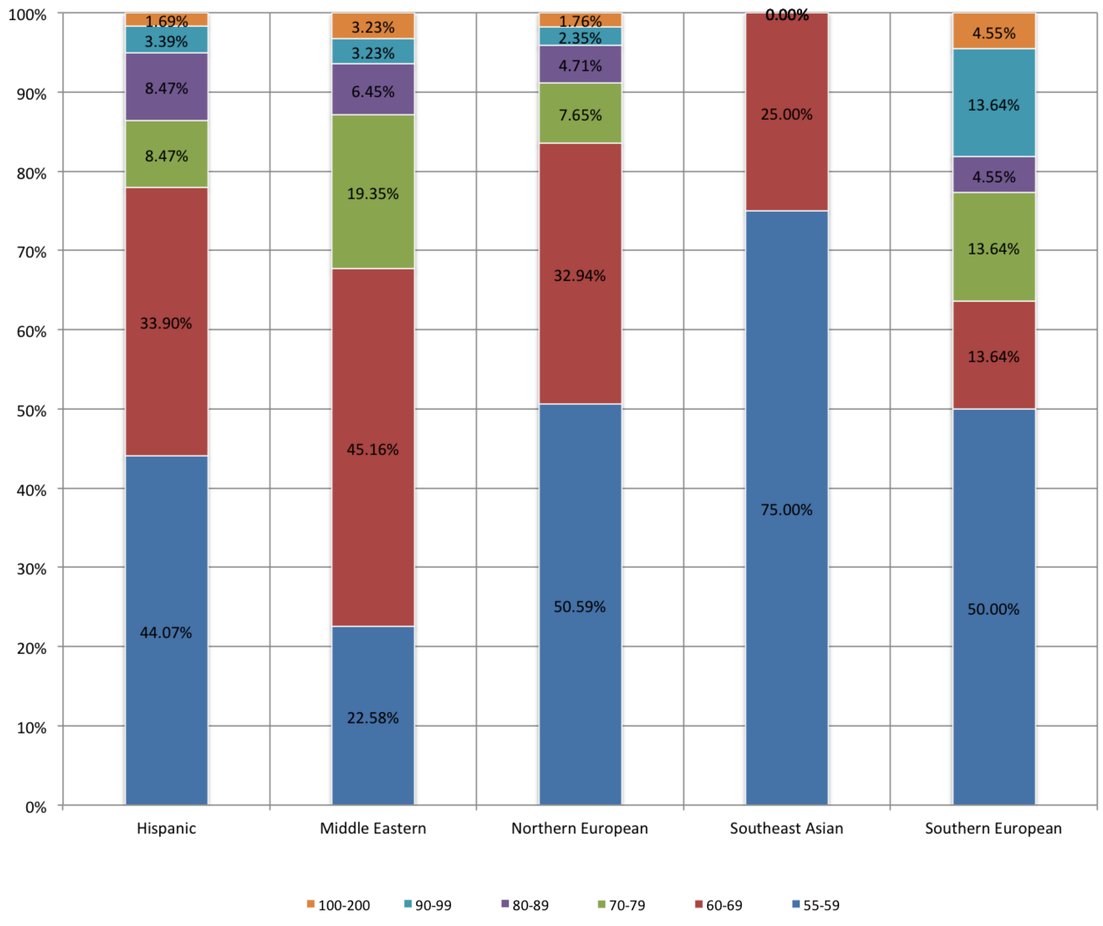

Table 1: Number tested (*n*) by ethnicity

Ethnicity	*n*
Mixed/Other Caucasian	34,465
Northern European	26,910
Unknown	19,889
Hispanic	13,515
Ashkenazi Jewish	9,489
African	7,713
East Asian	7,098
South Asian	5,611
Southern European	4,535
Middle Eastern	2,826
Southeast Asian	2,789

Table 2: Observed premutation allele frequency and predicted fragile X syndrome incidence, by ethnicity

Ethnicity	Pre-mutation Freq. (1 in)	Incidence (1 in)
African	514	3229
Ashkenazi Jewish	211	1783
Mixed Caucasian	415	4521
East Asian	2838	28440
Hispanic	450	3944
Middle Eastern	182	1353
Northern European	316	3805
South Asian	590	3960
Southeast Asian	1390	81745
Southern European	393	2224