Intermediate *FMR1* CGG repeat sizes (35-54) may also contribute to fertility issues in women with potential premature ovarian insufficiency

Authors: Tiffiney G. Carter, Elaine C. Weltmer, Amal Yussuf, Zoe Powis, Jing Wang
Ambry Genetics Laboratory, Aliso Viejo, CA

Introduction: Approximately 20% of women who carry a *FMR1* premutation allele of 55-200 CGG repeats will experience premature ovarian insufficiency (POI) causing them to experience menopause before the age of 40. Although the mechanism responsible for POI is unknown, one hypothesis is that an increase in *FMR1* mRNA is likely pathogenic in POI. Studies have shown an association with slightly increased *FMR1* mRNA levels in intermediate allele carriers with 45-54 repeats compared with those in the normal range of 6-44 repeats. Although alleles of <45 repeats are considered within normal range, alleles at the higher end of this range ($\geq$35 repeats) are relatively rare in the general population (2-3%). To evaluate the relationship between alleles in the high end of the normal range and POI, we examined *FMR1* repeat size in our clinical cohort of samples sent for fragile X carrier screening in patients with a suspected indication of infertility.
Methods/Materials: Retrospective analysis of 1,141 female samples submitted between 7/1/15-3/31/16 for fragile X carrier screening was performed. Screening performed by PCR of *FMR1*, capillary electrophoresis, and methylation status. Our lab received samples from facilities specializing in infertility. Statistical analysis performed via Fisher's exact test.
Results: We identified 172 (15.1%) female patients with at least one CGG allele size between 35-54 repeats, 6 (0.53%) premutation carriers and 963 (85.4%) patients with both alleles $\leq$34 repeats. Similar studies found the general population rate for 35-54 repeats was approximately 6.5-7.8%($p<0.002$). Number is highly statistically significant for 35-54 repeats.
Conclusion: Currently, CGG repeat alleles $\geq$55 are known to be associated with infertility/POI. However, our results may suggest that smaller *FMR1* CGG repeats between 35-54 repeats might also contribute to these issues; and this may potentially alter the way patients are counseled regarding their risk. Our findings are consistent with previous studies in smaller cohorts; more research is needed to elucidate this association.