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Opinion
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The Hidden Side of *FMR1* Instability: Are CGG Repeat Contractions Truly Rare, or Rarely Seen?

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Opinion

Fragile X Syndrome (FXS) is the most common inherited form of intellectual disability, caused by a dynamic mutation in the *FMR1* gene on chromosome Xq27.3. The disease is associated with the expansion of CGG trinucleotide repeats in the 5' UTR: normal alleles have up to 54 repeats, premutation alleles range from 55 to 200, and full mutations exceed 200.

The expansion of premutation alleles during maternal transmission is well documented. Yrigollen et al. [1,2] showed that the risk of expansion increases steeply with the number of repeats, approaching 100% beyond 99. A striking case by Fernández-Carvajal et al. [3] reported a 56-repeat premutation in a mother expanding to 538 repeats in her son within a single generation.

By contrast, contraction events — in which CGG repeats are reduced from full or premutation to normal range — have received limited attention. In a prenatal diagnosis study, Manor et al. [4] identified a fetus who inherited a 19-repeat allele from a mother with a mosaic full mutation (>200 repeats), suggesting a reversion to normal range via contraction.

Repeat instability is modulated by AGG interruptions within the CGG tract. These interruptions enhance repeat stability and reduce expansion risk but their role in contraction remains unclear [5,6]. It is plausible that specific repeat-AGG configurations may predispose to contractions under certain conditions, yet this hypothesis remains largely unexplored.

The rarity of reported contractions may reflect not only true biological infrequency, but also a profound diagnostic bias. Current genetic testing protocols primarily target symptomatic individuals or those with a family history of FXS. Silent contractions that revert the allele to normal range are clinically invisible and unlikely to trigger testing. As a result, these events may go undetected, contributing to a skewed perception of repeat dynamics [7,8].

To address this knowledge gap, we propose systematic investigations of *FMR1* transmission across extended pedigrees — including asymptomatic individuals — and the use of advanced technologies such as long-read sequencing, AGG profiling, and methylation-sensitive assays. These tools could identify rare contraction events and clarify their frequency and molecular drivers [9,10].

Furthermore, the epigenetic implications of such contractions deserve attention. Could contraction restore a normal methylation profile and prevent silencing of *FMR1*? If so, contraction might not only normalize repeat size, but also gene function, a possibility that opens new avenues in understanding *FMR1* gene regulation.

Ultimately, a deeper exploration of contraction events may improve genetic counseling for families with *FMR1* premutations or mosaicism and reshape our understanding of dynamic repeat disorders. What we perceive as rare might simply be unobserved.

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