Fragile X Syndrome in a female patient: A case of strong family history and developmental delay

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Introduction

Fragile X Syndrome (FXS) is caused by a triplet repeat expansion in the *Fragile X Mental Retardation 1 (FMR1)* gene on the X chromosome. It manifests with intellectual and developmental disability (especially speech delays and autism spectrum behaviors), macroorchidism in adult males, and a long face with large ears and prognathism.

Given its X-linked recessive inheritance pattern, FXS more commonly affects males and is one of the most common inherited causes of intellectual and developmental disability in this population. Females who inherit a full mutation can also exhibit the characteristic developmental phenotype.

Case Description

A 15mo female patient with an extensive family history of FXS was referred to genetics after developmental delay and hypotonia were noted.

The patient was born at 39 weeks to a 32 year old G4P3>4 mother and a 58 year old father via spontaneous vaginal delivery. Ultrasound and maternal serum screen were unremarkable prior to delivery and there were no pre- or post-natal complications.

She exhibited no apparent dysmorphic features and had been growing appropriately, but had mild diffuse hypotonia and was delayed in reaching speech and motor milestones.

Family history is significant for FMR1 premutation (70 repeats) in her mother and FXS in two maternal half-brothers and a maternal half-sister. Her mother's paternal half-sisters (monozygous twins) are each premutation carriers, and each has a son affected with FXS.

There is no known family history of premature ovarian failure or tremor/ataxia.

The patient's Fragile X repeat analysis confirmed a diagnosis of FXS with 24 CGG repeats on one X chromosome and >200 repeats on the other.

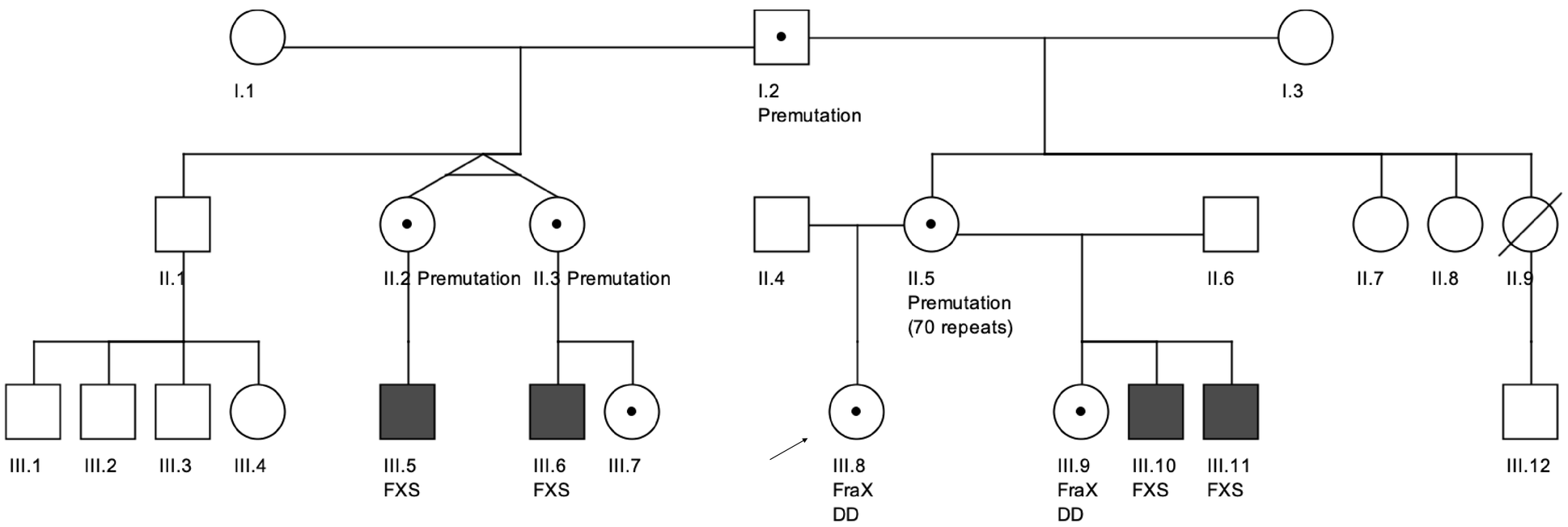

Figure 1: Patient's pedigree

Male family members affected by Fragile X Syndrome (FXS), female family members affected by developmental delay (FraX DD), and several other family members with FRM1 gene premutation.

Discussion

The typically milder phenotype and wide range of severity in female patients with FXS is related to the degree of X inactivation in females who inherit the full mutation. If X inactivation is skewed toward silencing the wild-type FMR1 allele, less protein product is produced and a more severe phenotype would be expected. Although some female patients affected with FXS display the characteristic facial features, intellectual or developmental delay may be the sole sign of FXS in a female patient. Genetic testing should be considered in any such patient.

Conclusion

Fragile X Syndrome is an important diagnostic consideration for any child, male or female, who presents with intellectual or developmental delay.

Molecular testing and genetic counseling should be considered for patients and their families in cases of unexplained intellectual or developmental disability, or where a family history of FXS, POI, or FXTAS exists.

References

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