Evidence of germline mosaicism in Hemophilia A: implication of genetic counseling

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Introduction

- Hemophilia A is an X-linked, recessive disorder caused by deficiency of functional plasma clotting factor VIII (FVIII), which may be inherited or arise from spontaneous mutation.

- This study reports a family with an affected hemophilia boy in which germline mosaicism in the mother complicates the X-linked inheritance of the disease.

- There was no family history of hemophilia in the family.

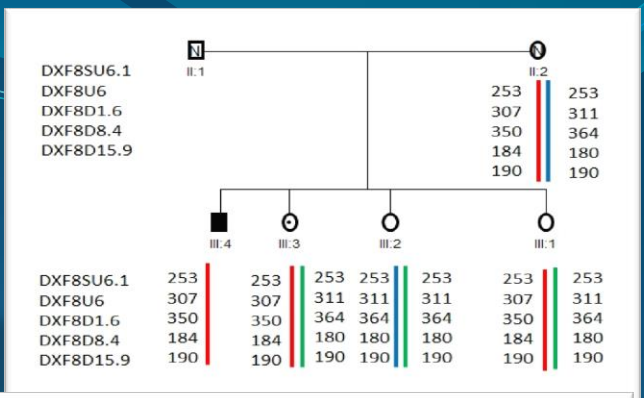
- It seems that denovo mutation or germline mosaicism could be responsible for the disease occurrence.

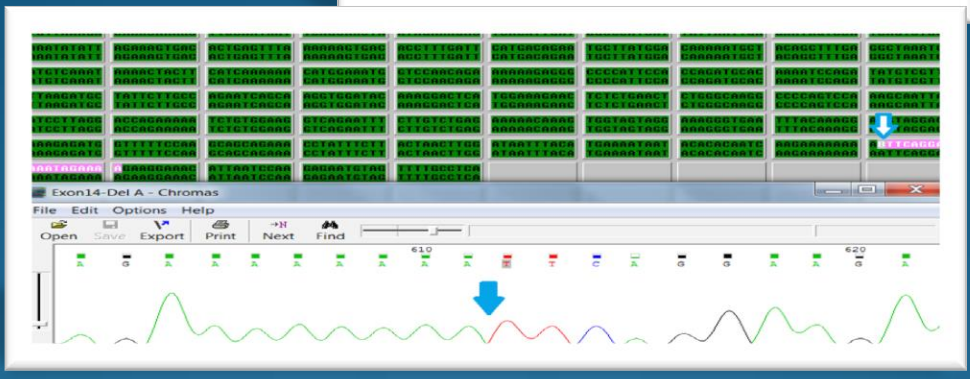
Materials & Methods

- Genetic counseling & drawing pedigree
- Blood sample collect & getting **informed consent**
- Direct sequencing of FVIII gene in proband
- Genetic testing of mother
- Track the mutated allele using linkage analysis with the help of STR (Short Tandem Repeat) markers linked to the FVIII gene.
- Haplotype analysis

Results

- Direct sequencing in proband revealed c.3637delA (p.I1213>Ffs5) mutation in the 14th exon.
- genetic testing of the mother showed no mutation.
- Haplotype & linkage analysis showed his mother was a carrier
- One of his sisters was normal with direct mutation analysis but haplotype mapping suggested her as a carrier.
- The second sister was normal with the direct and indirect approaches.
- The third one was carrier with both methodologies.





Discussion

- Based on the obtained results, one possible mechanism could be germline mosaicism of the mother
- Gonadal mosaicism usually occurs in females and can complicate data analysis.
- DNA testing may help carrier detection but negative results will not rule out the possibility of mosaicism.
- This observation suggests the importance of confirming the carrier status of the family members with different strategies
- Since mosaicism after having an affected child is consistent with gonadal/somatic mosaicism, the recurrence risk is significantly increased. The results have important implication in genetic counseling in X-linked disorders