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Gonadal mosaicism in grandfather leading to the transmission of severe hemophilia A in the grandson

Khosravipour K[1], Zafarghandi motlagh F[1], Abiri M*[3, 2], Zeinali S*[2,1]

[1] Dr. Zeinali's Medical Genetics Laboratory, Kawsar Human Genetics Research Center, Tehran, Iran

[2] Departments of Medical Genetics, School of Medicine, Iran University of Medical Sciences, Tehran, Iran

[3] Department of Molecular Medicine, Biotechnology Research Center, Pasteur Institute of Iran, Tehran, Iran

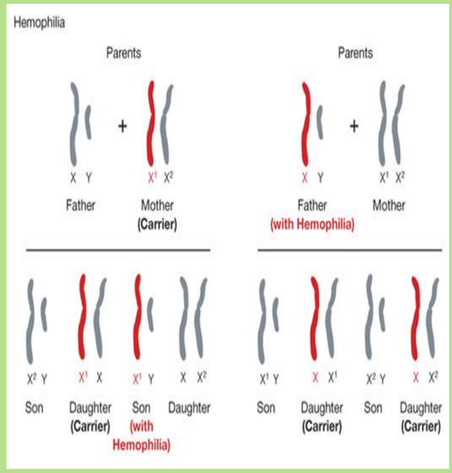
Corresponding authors: [2] Mary_abiri86@yahoo.com [3] Zeinali@kawsar.ir

Medical Genetics Laboratory of Dr.Zeinali

Introduction:

Hemophilia A is caused by a defective or absence of factor VIII protein which is responsible for blood clotting. It is an x-linked disorder with a worldwide frequency of 1 in 5,000 male. The rate of de novo mutations is approximately one third of all patients.

Usually causing mutations in hemophilia A appear in germ cells and leads to heterozygosity or hemizygosity of the mutation in the offspring/s. De novo mutations can also occur during early embryogenesis and may represent in germ line and/or somatic mosaicism. The degrees of mosaicism are determined by the developmental stage and cell lineage.



Result and Discussion:

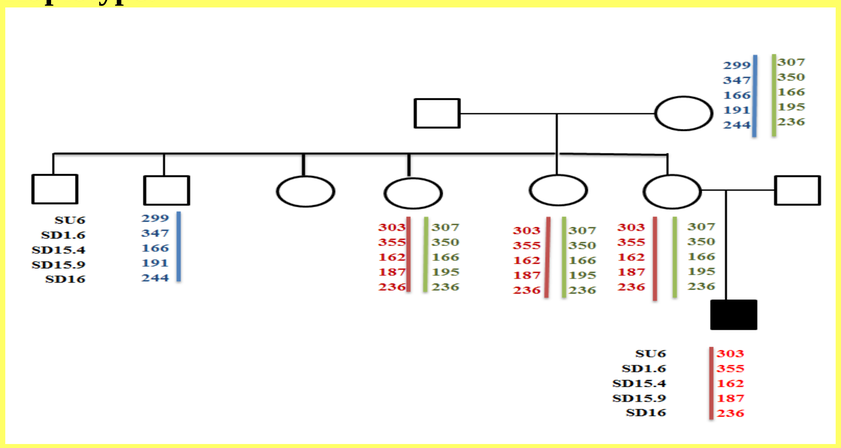
Gonadal mosaim of the male individual is a rare event which usually occurs in female. According to the results, the only mechanism which could justify the scenario would be differential somatic or germline mosaicism of the grandfather. DNA testing may help carrier detection but negative results will not rule out the possibility of mosaicism.

Differential gonadal mosaicism in a male is rare event but can be occurred in x- linked disorders. Pedigree analysis in x-linked disorder highly is recommended. This observation suggests the importance of confirming the carrier status of the family members with different approches. The results have important implication in pedigree analysis and genetic counseling.

Materials and methods:

A pregnant woman with a previous history of a hemophilic son was referred to Dr.zeinali's medical genetic laboratory for the purpose of prenatal diagnosis. Pedigree analysis suggested that the proband would be a new and sporadic case. Genetic testing of the proband showed the common mutation of inversionI. There for, mother would be the obligate carrier of the mutation which confirmed by linkage analysis and also direct investigation of the gene. Linkage analysis was performed using STR markers linked to the VIII gene. Testing four aunts revealed normal results with direct methods and also linkage analysis confirmed the obtained results. On the other hand, one of the aunts were carrier by haplotype analysis but were negative for the familial mutation. Maternal grandmother also was investigated.

Haplotype:



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