An unexpected finding: Two different coagulation factor VIII gene mutations in brothers

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Summary

Introduction and Objectives: Inherited hemophilia A in females is rare and female hemophilia A patients are at risk of being misdiagnosed as acquired hemophilia A or as von Willebrand disease type 2N. Here we report a female patient with moderate factor VIII deficiency due to compound heterozygosity for two different coagulation factor VIII gene mutations.

Material and Methods: A 41-year-old mother presented her three sons aged 5, 8, and 12 years with moderately decreased factor VIII activity (20 to 24 %) for genetic counseling and testing. Genomic DNA was obtained from anticoagulated blood. All factor VIII gene exons and flanking regions were amplified and PCR products were purified and sequenced.

Results: Initial mutational screening identified the previously identified hemizygous factor VIII gene mutation p.Met2183Val (p.Met2164Val) located in exon 23 in the 12-year-old first son. Unexpectedly, the mutation could not be demonstrated in his two brothers prompting further full sequencing studies. A hemizygous mutation p.Arg2016Gln (p.Arg1997Gln) in exon 19 was identified in the 8-year-old and in the 5-year-old boys. Investigation of both mutations was conducted in the mother and confirmed the rare diagnosis of a compound heterozygous female hemophilia A patient. Her residual factor VIII activity was similar to that of her sons (23 %) leading to the diagnosis of mild hemophilia A.

Conclusions: Female cases of hemophilia A are rare. Among the potential genetic mechanisms leading to hemophilia A in females, compound heterozygosity affecting both factor VIII alleles has been demonstrated only in a few cases. Here we report a female patient mother to three hemophilia A sons displaying two different missense mutations in exon 19 and exon 23, respectively. Compound heterozygosity was confirmed in the mother causing mild hemophilia A.

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Introduction

Hemophilia A is the most common X-chromosome linked recessive disease resulting from mutations of the factor VIII coding gene. The estimated incidence is approximately 1 case per 5000 males. Most of the mutations in hemophilia A patients can be traced back to parents/grandparents while 10 % of mutations develop spontaneously. Due to the X-linked recessive mode of inheritance, hemophilia A predominantly affects males, and females usually are carriers who may pass the disease on to their progeny. Female hemophilia A cases have only rarely been reported. Here we report the unusual case of two different factor VIII gene mutations in brothers leading to the diagnosis of hemophilia A in their mother due to underlying compound heterozygous mutations affecting both of her factor VIII alleles.

Material and Methods

A 41-year-old mother presented her three sons aged 5, 8, and 12 years with moderately decreased factor VIII activity (20 to 24 %) for genetic counseling and testing. Genomic DNA was obtained from anticoagulated blood. All factor VIII gene exons and flanking regions were amplified and PCR products were purified and sequenced by standard procedures.

Results

Initial mutational screening identified the previously described hemizygous factor VIII gene missense mutation c.6547A>G leading to p.Met2183Val (p.Met2164Val) located in exon 23 (Tavassoli et al. 1998) in the 12-year-old first son (Figure 1). The boy with a factor VIII residual activity of approximately 21 % (mild hemophilia A) had repeatedly suffered bleeding episodes (soft tissue and joint bleeds) and was on prophylactic treatment.

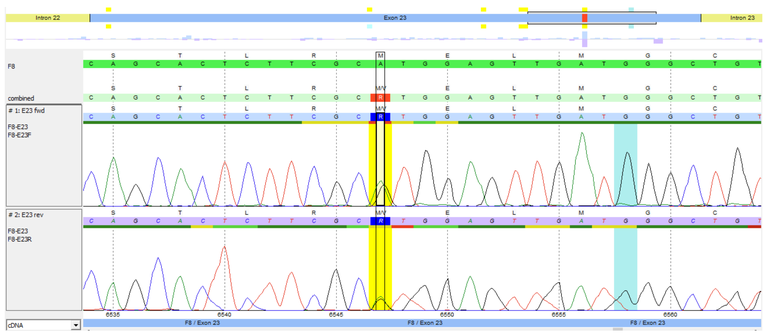

Figure 1: Genomic DNA sequencing analysis demonstrating c.6547A>G (yellow box) missense mutation in codon 2183 (Met/Val).

Having identified the mutation in the first-born son, a targeted sequencing approach was employed to detect the mutation in his two brothers. Unexpectedly, the mutation could not be demonstrated in his two brothers prompting further full sequencing studies. A hemizygous factor VIII gene missense mutation c.6047G>A leading to p.Arg2016Gln (p.Arg1997Gln) in exon 19 was identified in the 8-year-old and in the 5-year-old boys (Figure 2). This mutation has been described in the Factor VIII Variant Database (www.factorviii-db.org) in a patient with mild hemophilia A (residual factor VIII activity 38 %). The residual factor VIII activity in the two boys was slightly lower (12 % and 20 %, respectively). Both boys had suffered soft tissue bleeds in the past and are on-demand therapy.

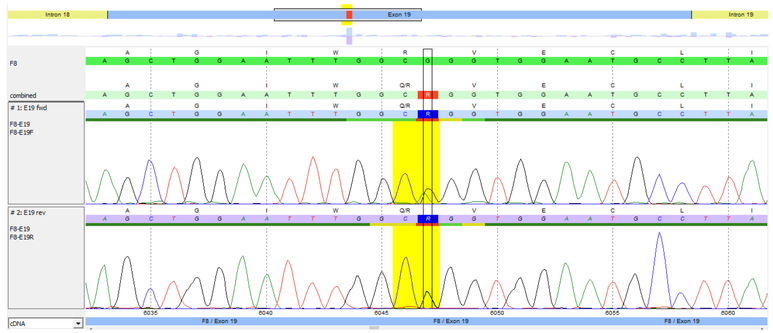

Figure 2: Genomic DNA sequencing analysis demonstrating c.6047G>A (yellow box) missense mutation in codon 2016 (Arg/Gln).

Investigation of both mutations was conducted in the mother and confirmed the rare diagnosis of a compound heterozygous female hemophilia A patient. Her residual factor VIII activity was similar to that of her sons (23 %) leading to the diagnosis of mild hemophilia A. Her bleeding history consisted of menorrhagia.

Conclusions

As a classic X-chromosome linked recessive disorder, hemophilia A affects very few females. Different pathogenic mechanisms have been described (Pavlova et al. 2009) including compound heterozygous mutations as in the mother to three hemophilic sons reported here. The identification of compound heterozygous factor VIII gene mutations in a female hemophilia A patient is important as she has 100 % certainty for giving birth to hemophilic sons.

References

Pavlova A, Brondke H, Müsebeck J, et al.: J Thromb Haemost 2009;7:976-82.
Tavassoli K, Eigel A, Wilke K, et al.: Hum Mutat 1998;12:301-3.