Mutations causing Factor XIII deficiency in Pakistan

Authors : ***Munira Borhany**[1], Tahir Shamsi[1], Andrea Cairo[2], Flora Peyvandi [2]

Hospitals: 1.National Institute of Blood Diseases & Bone Marrow Transplantation (NIBD),Karachi, Pakistán.
2. Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Luigi Villa Foundation, IRCCS Maggiore Hospital, Mangiagalli and Regina Elena Foundation and University of Milan, Milan, Italy.
*corresponding author email : drmunirashoaib@yahoo.com

OBJECTIVES

To determine the frequency , clinical features and genetic characterization of **FXIII deficiency** among Rare bleeding disorders, as a result of consanguineous marriages.

INTRODUCTION:
Rare bleeding disorders (RBDs) represent 3% to 5% of all inherited coagulation deficiencies, and are usually transmitted as autosomal recessive traits (1, 2). Among it congenital factor XIII (FXIII) deficiency has a prevalence ranging from approximately 1 in 2 million, higher in countries where consanguineous marriages are common like Iran, India as compared to other RBDs. FXIII deficiency is usually due to mutations in the factor 13A (F13A) gene which is located in chromosome 6, at p24-25. Up to now more than 70 mutations on F13A gene are reported (3,4). Consanguinity is common in several populations of the world. In Pakistan close consanguineous unions continue to be extremely common as in South West Asia (5).

METHODS

The study was approved by institutional ethics committee and was done in accordance with declaration of Helsinki. Informed consent was obtained from all adult subjects, parents or legal guardians. In our centre 16 unrelated patients affected with FXIII deficiency with repeated bleeding symptoms are followed. All laboratory coagulation tests showed normal results except FXIII activity, which was undetectable in plasma using 5M urea clot solubility test and Photometric assay (Berichrom). FXIIIA antigen levels were then determined by immunoassay (HemosIL^{TM}). The molecular analysis was performed by direct sequencing of the coding regions, intron/exon boundaries and 5' and 3' untranslated regions of the *F13A* were amplified by polymerase chain reaction (PCR). PCR products were sequenced by the Big Dye Terminator cycle sequencing kit (Applied Biosystems, Warrington, UK) on an ABI 3130 genetic analyzer (PE Applied Biosystems, Foster City, CA, USA). Mutations identified was confirmed by repeated sequencing.

RESULTS

In our centre we have 16 unrelated patients affected with FXIII deficiency. They were referred to us with history of repeated bleeding symptoms. Most common bleeding manifestations were epistaxis , gum bleeds, cutaneous bruises and circumcision bleeding. In females history of repeated abortions was significant . All patients have history of cousin marriages in their parents.
A novel splice site mutation, c.1460+1G>A (IVS11+1G>A) in the core domain was identified in 6 patients (5 homozygote and 1 heterozygote) belonging to three different families. The use of the Berkely Drosophilia Genome Project human database predicted that this mutation would probably result in the complete abolition of the donor splicing site. The other novel mutation, c.1126 C>T, p. Trp376Arg (Exon 9), was also identified in the core domain, present in one patient in homozygous state. The use of Poly Phen-2 predicted that this mutation could be damaging for the protein with a score of 1.0. Both mutations are associated with undetectable FXIII activity and 2% of FXIIIA antigen level in homozygous patients. The one in heterozygous state has 60% of antigen and 53 % of activity.

Fig-1 Family Tree of the Family

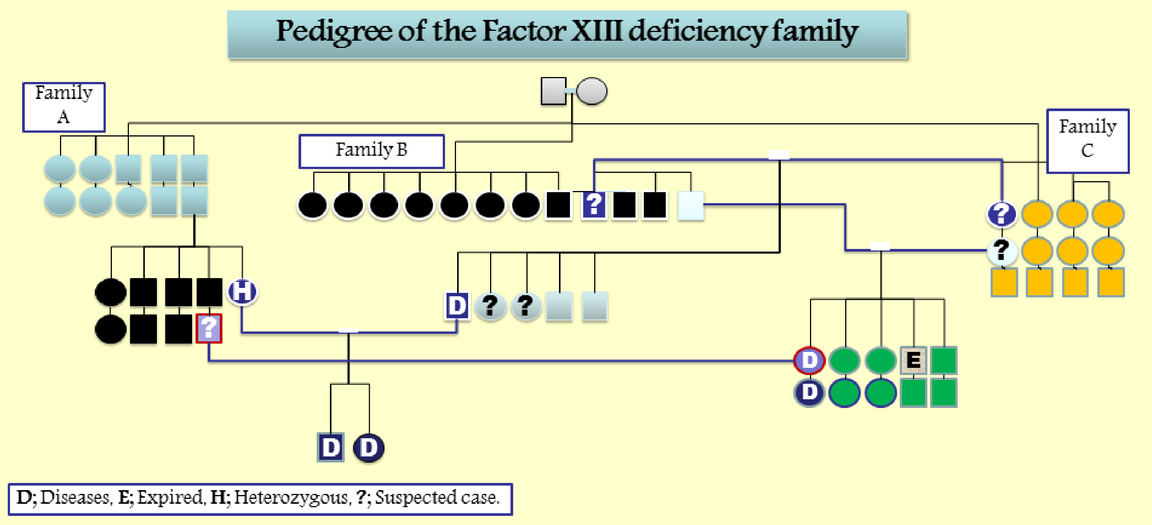


Fig-2 Splice site mutation, c.1460+1G>A (IVS11+1G>A) in the core domain was identified in 5 patients (homozygotes) belonging to three different families.

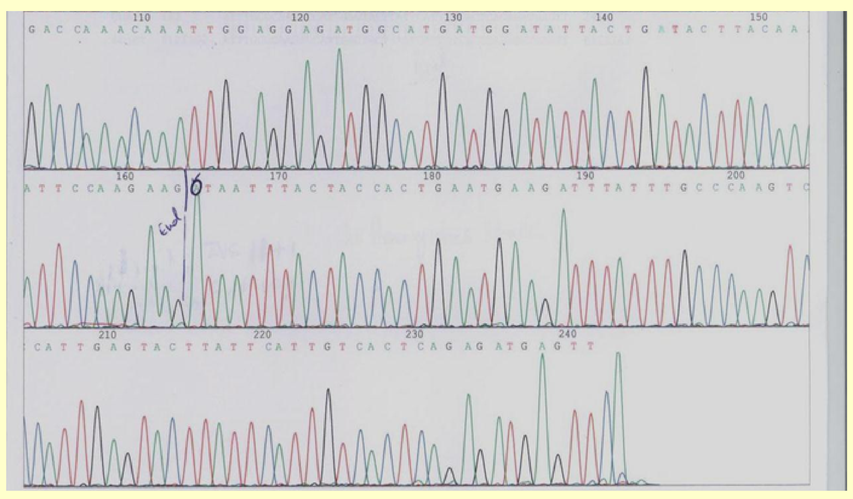


Fig-3 The other novel mutation, c.1126 C>T, p. Trp376Arg (Exon 9), was also identified in the core domain, present in one patient in homozygous state.

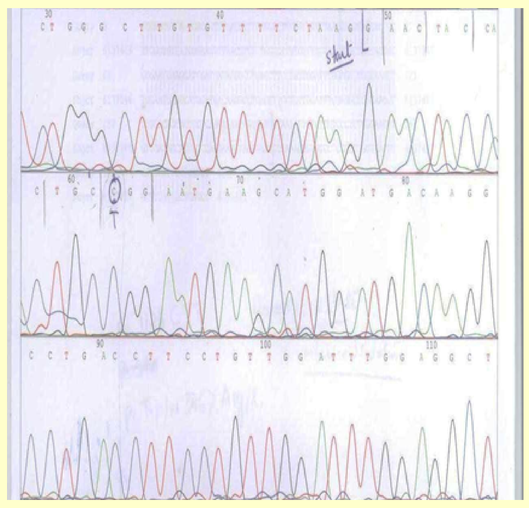
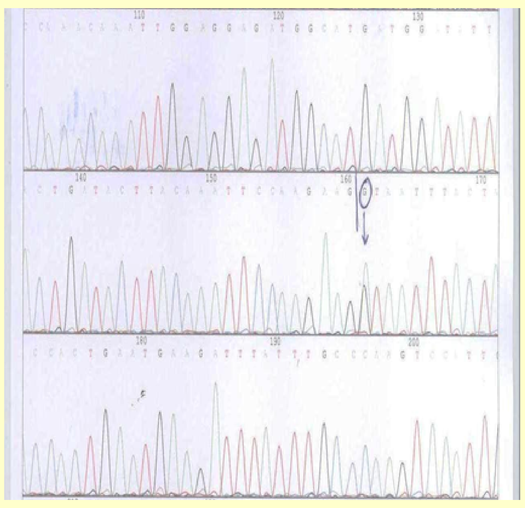


Fig-4 Splice site mutation, c.1460+1G>A (IVS11+1G>A) in the core domain was identified in 1patient (heterozygote).



CONCLUSION

We have identified 2 novel mutations leading to congenital Factor XIII deficiency in Pakistan. We will characterize all other severe affected patients of our centre to verify if these variants could be recurrent mutations in our specific geographic area. This molecular analysis might help for the prevention of these disorders in our region where consanguineous marriages is common through prenatal diagnosis in families with already one severe affected child.

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