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# How to Assess Founder Effect in Patients with Congenital Factor XIII Deficiency

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**ABSTRACT**

Congenital factor XIII (FXIII) deficiency is an extremely rare bleeding disorder (RBD) with estimated prevalence of one per 2 million in the general population. The disorder causes different clinical manifestations such as intracranial hemorrhage (ICH), recurrent miscarriage, umbilical cord bleeding, etc. High incidence of the disorder might be due to founder effect. To assess founder effect, haplotype analysis is an important step. For this purpose, suitable and reliable genetic markers such as microsatellites (Hum FXIIIA01 and HumFXIIIA02) and single nucleotide polymorphisms (SNP) are suggested. In the present study we tried to describe evaluation of founder effect in patients with congenital FXIII deficiency via haplotype analysis using suitable genetic markers.

**Keywords:** Factor XIII deficiency; Intracranial hemorrhage; Founder effect; Genetic markers

## INTRODUCTION

Factor XIII (FXIII) deficiency is a rare inherited disorders with an incidence of one per 2 million. The disorder is higher in some regions like Iran, Pakistan, Tunisia, Indian, etc. [1, 2]. Patients with FXIII deficiency have different clinical manifestations like recurrent and delayed bleeding, intracerebral hemorrhage (ICH), umbilical cord blood (UCB), defected wound healing and recurrent miscarriages [3,4]. There are specific and common mutations of factor XIII gene in different geographic areas. Due to autosomal recessive pattern of inheritance and rate of consanguineous marriages, disease causing mutations may inherited to children by their parents[5]. On the other words, the presence of a same mutation in different non-consanguineous families in a particular area may indicate a common ancestor or a founder effect. Founder effect causing mutation is called founder mutation. For example, Trp187Arg is a suitable example for FXIII deficiency associated with founder mutation in southeast Iran. These types of mutations usually occur in one or more founders of a new and different population and are inherited to next generations, which finally

make a great alteration in DNA. In other words, pathogenic alleles will be displayed in next generations in homozygote form and probably founder effect could be the reason of high incidence disorder[6,7]. For assessment of founder effect if: 1) candidate microsatellites and single nucleotide polymorphisms (SNPs) are meaningfully different in patient and control groups, 2) a unique haplotype is observed in the majority of the patients, these can indicate genetic linkage between microsatellites and polymorphisms with causative mutation[8-10]. Our goal in the present study was to describe how founder effect influences FXIII deficiency in areas with particular mutation by using haplotype analysis and suitable genetic markers.

**Diagnosis of factor XIII deficiency**

Routine coagulation tests like bleeding time, prothrombin time, activated partial thromboplastin time, fibrinogen level and platelets count are normal[11]. The primary and the most commonly used test is clot solubility test. This is a qualitative test and is positive only in patients with a very low of FXIII [1, 12]. Measuring FXIII activity is a decisive diagnosis[13]. Commercial ELISA kits are available for measuring of FXIII-$A_2B_2$, FXIII-A and FXIII-B antigenic levels[14]. Finally, genetic analysis can help to find associated mutations of FXIII gene. Carrier detection is very important to prevent marriage of these patients and to recognize FXIII suspected individuals in haplotype aspects [15, 16].

More than 170 mutations have been identified within *F13A* and *F13B* genes, most belongs to *F13A* subunit [17,18]. Sanger sequencing is the most common DNA sequencing method, but next-generation sequencing (NGS) is a more advanced sequencing technology, which can increase the rate of mutation detection [16, 19].

**Founder effect**

Founder effect is one of the important topics in population genetics and it is one of the ways that nature uses to generate new species from primary populations [10, 20]. In a simple word, sometimes, a few number of a large population immigrate to specific locations. Others cannot enter to these population to make change in their genetic pool that leads to lower genetic diversity and occurring of defected pathogenic mutation that is actually called founder effect [10]. Over the time, new populations genetically and phenotypically become thoroughly differentiated from the primary population .Founder effect causing mutation is called founder mutation.

**Founder effect in congenital factor XIII deficiency**

There are *F13A* common mutations in the different geographic areas. For example, Trp187Arg and Arg77His are common in Iran, Ser295Arg and c.2045G>A in Pakistan, c.869insC in Tunisia, Arg77Cys in Switzerland, and Arg661X in Finland [3, 7, 21-33]. In India, IVS1 A246G polymorphisms seems to be the most common FXIII polymorphisms [34]. The IVS5-1G>A mutation was observed in European countries, including Poland, Czech Republic, Turkish, Greek, UK, Macedonia and the Netherlands [7, 30, 35, 36]. According to the inheritance pattern of mutation, disease-associated mutations may happen in previous generations. Presence of a same mutation in different non-consanguineous families in a special area may show common ancestor. For example, Trp187Arg is a suitable example for FXIII deficiency associated with founder mutation in southeast Iran[37]. These types of mutations usually occur in one or more founders of a new and different population and are inherited to next generation, and finally make great alterations in DNA. In other words, pathogenic alleles will be displayed in next generations in homozygote forms. One important population example is congenital FXI deficiency in Ashkenazi Jews [38].

**How to evaluate association of founder effect and FXIII deficiency**

We can use haplotype analysis in order to evaluate founder effect which is caused by inbreeding in populations of a certain area [9,39]. Haplotype is a combination of alleles in different locus of a chromosome that inherit together. In simple word, haplotype is a set of a mononucleotide polymorphisms like SNPs, microsatellites, variable number tandem repeats (VNTRs) on one chromosome of homologous chromosomes [40,41]. These markers are sequences of DNA and they inherit together due to their closeness to disease-

associated gene, therefore if an individual or a group possesses a set of linked markers, the presence of disease-associated gene in their genome is assumable. Therefore, haplotype analysis via SNP, microsatellite and VNTRs can be used to assess the association of founder effect with specific and considered mutation as the most incident type of FXIII deficiency causing mutation in particular region[42,43]. It's important that selected polymorphic markers should be informative and be close to disease-causing gene to achieve the best results [44, 45].

**First step: Diagnosis of FXIII deficiency**

-Providing questionnaires, including individual's characteristics such as age, gender, city of residence, family history, clinical symptoms

-Sample collection

-Routine coagulation tests: At first all FXIII deficiency suspected individuals have to be examined by common coagulation tests like bleeding time (BT), prothrombin time (PT), activated partial thromboplastin time (PTT), platelet count and fibrinogen level. Those patients with low FXIII level who showed a significant decrease (1 to 2%) should enter to molecular laboratory phase (Figure 1)[2].

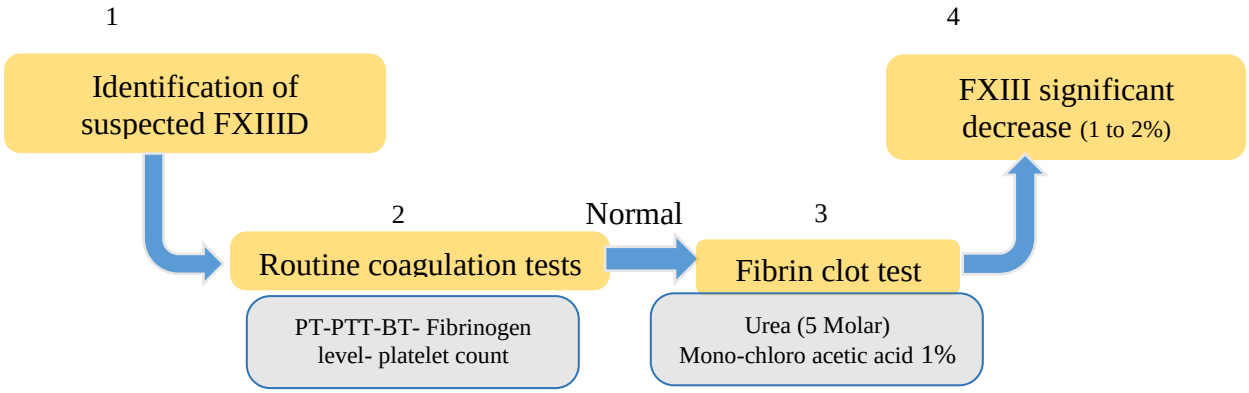


**Figure 1:** How to diagnose FXIII deficiency suspected individuals
BT: Bleeding Time, PT: Prothrombin Time, PTT: Activated Partial Thromboplastin Time

**Second step: Detection of molecular defect in patients with congenital FXIII deficiency**

- Bioinformatics studies: To find FXIII gene in NCBI data bank.
- DNA extraction

-Quantitative and qualification assessment of extracted DNA

-Polymerase chain reaction-Restriction fragment length polymorphisms (PCR-RFLP): To select suitable restriction enzymes, after bioinformatics analysis based on candidate enzyme selected, different fragments of DNA are observable on electrophoresis gel, which indicates homozygote, heterozygote and normal gene (Table 1) [46-48].

**Table 1:** Characteristics of important features most common mutation of congenital factor XIII deficiency

| Most common mutation | Origin of patient | Chromosome location | Genotype | Type | Domain | Gene subunit | Functional information | References |
|---|---|---|---|---|---|---|---|---|
| Trp187Arg | Iran | Exon 4 | Homozygous | Missense | Core | FXIII A-subunit | Steric clashes of arginine with side chains | (3, 6, 21, 22, 37, 49) |
| Arg77His | Iran | Exon 3 | Homozygous | b-sandwich | Missense | FXIII A-subunit | Disruption of most H-bonds | (2, 21, 22, 47, 49) |
| Ser295Arg | Pakistan | Exon 7 | Homozygous | Missense | Core | FXIII A-subunit | Incorrect folding resulting in an unstable FXIIIA polypeptide | (7, 24-27) |
| c.2045G>A | Pakistan | Exon 14 | Homozygous | Splicing | Barrel 2 | FXIII A-subunit | Probably splicing defect | (7, 25-27) |
| Arg77Cys | Switzerland | Exon 3 | Homozygous | Missense | b-sandwich | FXIII A-subunit | Disruption of most H-bonds | (7, 30) |
| c.869insC | Tunisia | Exon 7 | Homozygous | Frameshift | Core | FXIII A-subunit | Stop after 8 altered amino acid | (26, 28, 29) |
| Arg661X | Finland | Exon 14 | Heterozygous | Nonsense | Barrel 2 | FXIII A-subunit | Decrease of FXIII mRNA levels | (31-33) |
| IVS5-1G>A | European Countries: Netherland, Poland, UK, Czech Republic, Macrdonia, Greek, German and Turkish | Intron 5 | Homozygous | Splicing | intronic | FXIII A-subunit | Effect on RNA splicing | (1, 2, 7, 30, 35, 36) |
| A246G | India | Intron 14 | Heterozygous | Splicing | intronic | FXIII A-subunit | Probably splicing defect | (34) |

**Third step: selection of suitable microsatellites**

Microsatellites are highly polymorphic and repetitive DNA sequences. These sequences are 2 to 6 base pair repeats that place along DNA [50]. Microsatellites are highly polymorphic and mutation prone. Because of microsatellite uniqueness in different populations and high number of them in the genome, they can be used as informative markers to investigate genetic association among human ethnics, population genetics and haplotype analysis [39,51]. There is a criterion named polymorphic informative content (PIC), which indicates allele frequency in the population and relates with mean repeat length. PIC < 0.7 represents that microsatellite is informative and this is important in microsatellite option [45, 52].

-Candidate microsatellite: based on previous studies and bioinformatics analysis in NCBI databank and FXIII Database, 2 microsatellites could be selected in *F13A* gene (Table 2).

-Microsatellite Hum FXIII A01 has repeated sequence of AAAG in chromosomal location of 6p24-25 and in 5`UTR(-2775/ATG) region [44, 53].

-Microsatellite Hum FXIII A02 has repeated sequence of AC (poly AC) in chromosomal location of 6p24-25 and in intron 8 region [29].

For visiting the most practical microsatellites in details, go to http://www.cstl.nist.gov/biotech/strbase.

- DNA extraction
-Quantitative and qualitative assessment of extracted DNA
-PCR along labeled primers with fluorescent substance (FAM)
- Capillary electrophoresis
- Data analysis using Gene marker software

**Fourth step: Selection of suitable SNPs for haplotype analysis**

SNPs occur with frequency of 1% in general population and they span all the human genome, because of this, these markers are widely used in diagnosis of different cancers and congenital genetic disorders [40, 54, 55].

-Candidate SNPs: SNPs are selected after bioinformatics analysis in NCBI database. Candidate SNPs should be verified by Hapmap project, Cluster, 1000 genomes project and frequency databases. Furthermore, these SNPs are mostly locate in FXIIIA gene (6:6144077-6320590). It is better to select SNPS with global minor allele frequency (Global MAF) near to 0.5 to have fewer differences between SNPs allele incidence (Table 3) [9, 40, 42].

- DNA extraction
- Qualitative and quantitative assessment of extracted DNA
- PCR
- Sequencing or PCR-RFLP
- Data analysis by CLC sequencer and Chromas software

**Fifth step: Haplotype analysis**

After data analysis, we have to determine similarity of haplotypes in FXIII deficiency patients. Generally microsatellites are more reliable markers than SNPs[9,44,45]. On the other hand, larger number of genetic markers in a study results in more reliable and informative results. The important point is that in haplotype analysis, shorter distances between genetic markers and considered mutations will achieve to more reliable results. We can differentiate haplotypes by comparing results of patients and normal individuals[56]. Schematic figure of chromosomal location of candidate SNPs and STRs for FXIII haplotype analysis are shown in Figure 2.

**Table 2:** Features of Hum FXIII A01 and Hum FXIII A02 microsatellites

| Microsatellite | Human FXIIIA01 (FXIIIA01) | Human FXIIIA02 (FXIIIA02) |
|---|---|---|
| Repeat sequence | AAAG | AC |
| Chromosomal location | 6p24-25 | 6p24-25 |
| Gene bank accession | M21986 | - |
| Expected range of allele | 281-331 | 204-236 |
| PCR primers | 5′-TTTTCTCTGCCTTCCCATGT-3′<br>3′-ATGCCATGCCAGATTAGAAA-5′ | 5′-GAGGTTGCACTCCAGCCTTT-3′<br>3′-CCCCCAGTGCAGTGTTTTAT-5′ |
| Primer concentration | 0.1 Micromolar | 0.1 Micromolar |

* No accession number was reported for this STR and it was mentioned in article [29].

**Table 3**: Features of candidate Single Nucleotide Polymorphism (SNPs)

| SNP | rs3024317 | rs4960181 | rs63778360 | rs7757882 | rs1781794 | rs1674044 |
|---|---|---|---|---|---|---|
| Number | 1 | 2 | 3 | 4 | 5 | 6 |
| Chromosomal location | 6:6319146 | 6:6269065 | 6:6150132 | 6:6189967 | 6:6241547 | 6:6310481 |
| Hap map | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Intron Site | 3 | 3 | 14 | 11 | 6 | 2 |
| Frequency | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Global MAF | 0.4688 | 0.4854 | 0.4842 | 0.4553 | 0.4888 | 0.4535 |
| 1000 G | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Cluster | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |

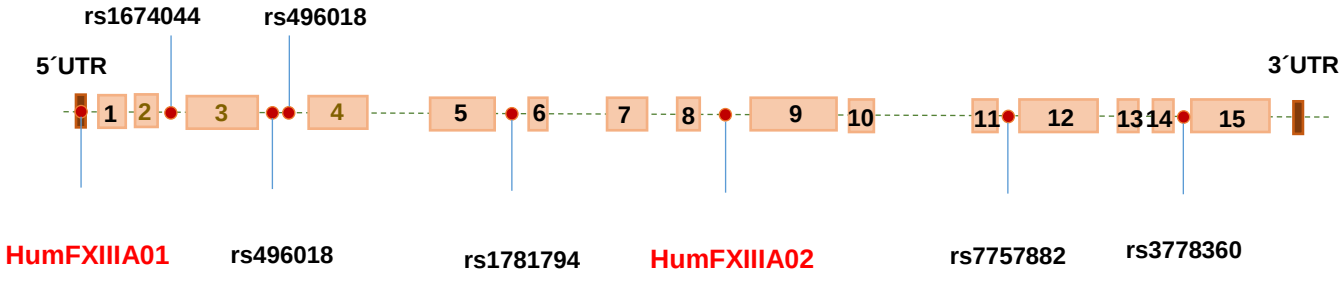


Figure 2. Schematic figure of chromosomal location of candidate microsatellites and SNPs of *F13A* gene

## CONCLUSION

When we are evaluating impact of founder effect in congenital FXIII deficiency, we have to notice that if:

-Candidate microsatellites and SNPs were meaningfully different in patients and control groups

-A unique haplotype was observed in most of the patients

These can indicate genetic linkage between microsatellites and polymorphisms with considered mutation and subsequently this genetic linkage can imply a kind of founder effect for the disease, which means that previous generations increased FXIII deficiency via consanguineous marriage. Generally, it is considered some circumstances like consanguineous marriage; ethnic and place of residence can prominently increase pathogenic mutations, founder effect and subsequently raise FXIII deficiency.

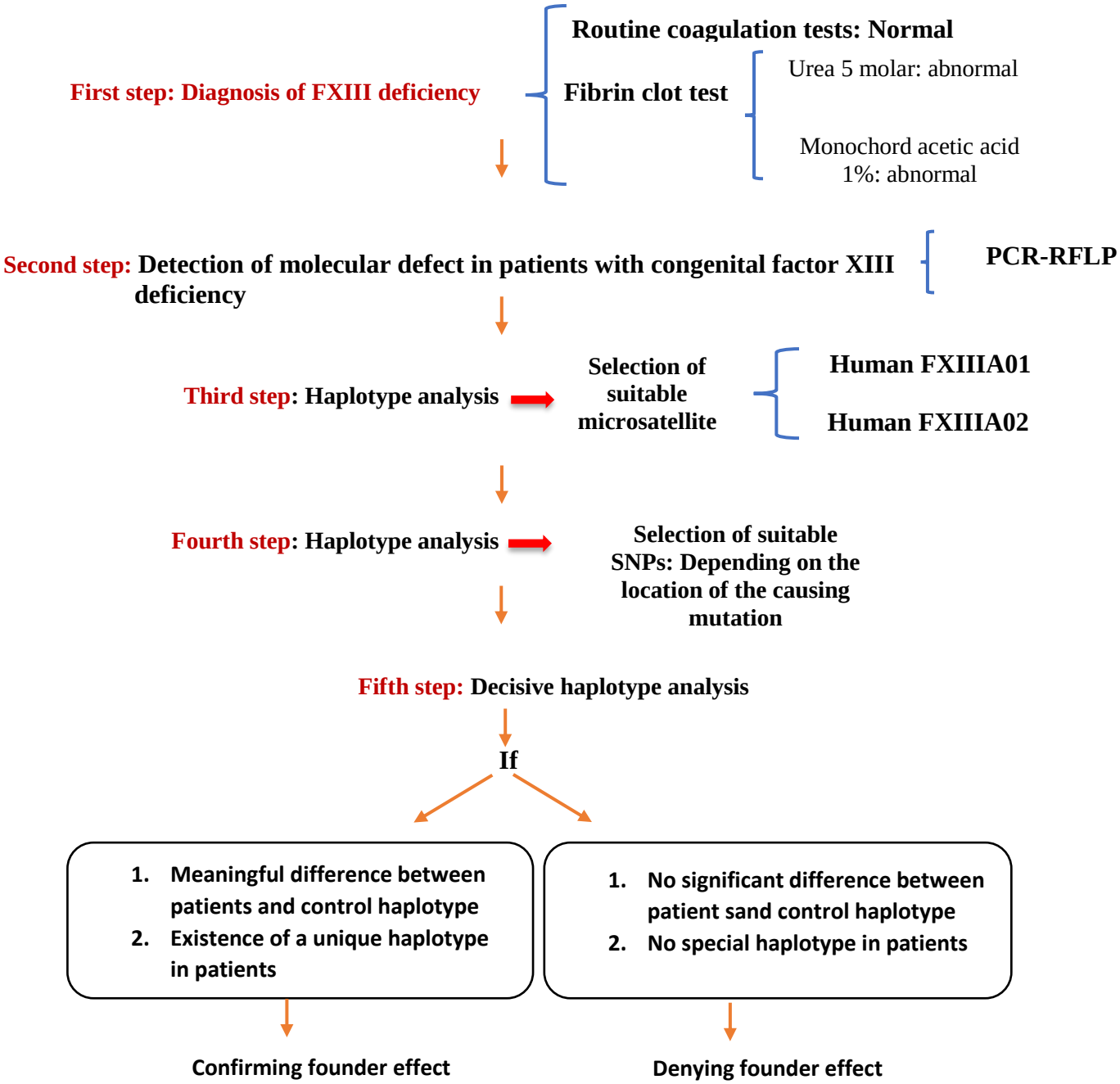


Figure 3: Evaluating association of founder effect with FXIII deficiency by step-by-step diagnostic algorithm

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**CONFLICTS OF INTEREST**

There are no conflicts of interest.

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