**Original Article** *Iran J Ped Hematol Oncol. 2025, Vol 15, No 2, 456-464*

# Molecular Characterization of Coagulation Factor V and Combined Factors V and VIII Deficiencies in the Northeast of Iran

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**Received:** 02 October 2024 **Accepted:** 11 March 2025

**Abstract**

**Background:** The deficiencies of Factor V (F5) and combined Factors V and VIII (F5F8D) are known as two rare bleeding disorders. This study aimed to evaluate the studied patients' demographic, laboratory data, and nucleotide changes.

**Materials and Methods:** This is a cross-sectional study of twelve and five patients affected by F5 deficiency and F5F8D, respectively. The study was conducted at Mashhad University of Medical Sciences, from 2015 to 2016. The mean age of the patients with F5 deficiency was 33.91 ± 18.94 years, and that of the patients with F5F8D was 29.40 ± 9.20 years. The coagulation factor assay was performed, and all the exons and intron-exon junctions of LMAN1, MCFD2, and Factor V genes were amplified and subsequently sequenced.

**Results:** The prevalence of F5 deficiency and F5F8D in the Khorasan Razavi population was 7 and 5 per 1,000,000, respectively, which is higher than the estimated worldwide prevalence of 1 per 1,000,000 to 2 per 2,000,000. There were c.2051 G > A, c.6305 G > A, and c.1340 C > G found in the patients with F5 deficiency. Also, those with F5F8D were found to have c.822 G > A and c.149 +1 G > A.

**Conclusion:** The most common nucleotide change in the patients with F5 deficiency was the missense mutation c.6305 G>A in the C2 domain of exon 23 of the factor V gene. In contrast, patients with F5F8D exhibited splice site mutations, specifically c.822 G>A and c.149 +1 G>A, with homozygous inheritance. These findings suggest a distinct genetic pattern for each disorder within the Khorasan Razavi population. To better understand the correlation between factor levels and these nucleotide changes, and to explore the genetic background of other patients, further research involving a larger cohort and more advanced genetic tools, such as whole exome sequencing, is recommended.

**Keywords:** Combined deficiency of Factor V and Factor VIII, Factor V deficiency, F5F8D, Hemorrhagic Disorders

## Introduction

The deficiencies of Factor V (F5) and combined Factors V and VIII (F8) (F5F8D) are two rare bleeding disorders with autosomal recessive inheritance (1). The prevalence of inherited F5 deficiency is estimated to be 1 in 1,000,000 in the general population (1-4). Its prevalence is much higher in areas of the world where consanguineous marriage is common, such as the Middle East and India (1-4). In this regard, a considerable number of patients are reported from Iran. Various mutations in the F5 gene lead to decreased expression of the gene or the expression of mutated F5, which may interfere with the gene function or secretion or may cause intracellular degeneration. Accordingly, Factor V deficiency is classified into types I and II. Type I is associated with low F5 antigen levels (F5: Ag) and reduced procoagulant F5 activity (F5: C). Type II is associated with normal F5 antigen levels and decreased procoagulant activity. The severe type of F5 deficiency is more



[ DOI: 10.18502/ijpho.v15i2.18175 ]

common among individuals with homozygous or compound heterozygote mutations with a plasma level below 10-15%, while it's mild to moderate types are seen in individuals with heterozygous mutations and the factor level of more than 20-30% in the plasma (2). The deficiency of combined Factors V and VIII (F5F8D, OMIM 227300) is characterized by a concomitant decrease in the plasma levels of both Factor V and Factor VIII (5, 6). It was first reported by Oeri's team in a Swiss sister and brother in 1954 (6, 7). It is an autosomal recessive disorder caused by a single gene mutation in proteins that are involved in the secretion pathway of the coagulation factors (5). To date, different types of mutation in one of the two proteins called the lectin mannose binding protein type 1 (LMAN1, previously referred to as ERGIC-53) and the multiple coagulation factor deficiency 2 (MCFD2) have been reported as the causative mutations in the majority of patients. The F5F8D is very rare, and its prevalence is estimated to be one in 1 million in the general population. However, its prevalence is higher in some areas of the world where consanguineous marriage is common, including the Middle East. The disorder is usually associated with Factor V and Factor VIII levels ranging from 5% to 20%, which leads to mild to moderate bleeding symptoms (5, 8). Despite the higher prevalence of F5 deficiency and combined F5 and FVIII deficiency in Iran than in most other areas in the word, there are no data regarding the prevalence and underlying molecular changes of these factors in the northeast of Iran. This study aimed to investigate the demographic, clinical and laboratory data as well as the molecular background of the patients with these two rare bleeding disorders in Khorasan Razavi Province in the northeast of Iran.

# Materials and Methods

## Patients and data collection

This research is a cross-sectional study of patients with Factor V deficiency and F5F8D in northeastern Iran (Khorasan Razavi Province). It was conducted at the Hemophilia and Thalassemia Research and Treatment Center (Sarvar Clinic) affiliated to Mashhad University of Medical Sciences from 2015 to 2016. The study also benefited from the collaboration of Hemophilia Center in Bonn, Germany. The participants were 45 cases of Factor 5 deficiency and 29 cases of F5F8D registered at Sarvar Clinic. Of them, 12 patients with Factor 5 deficiency and five with F5F8D were included in the molecular study. The other patients had incomplete clinical records or were not interested in participating in molecular testing. The research protocol was approved by the Research Ethics Committee of Mashhad University of Medical Sciences (IR.MUMS.REC.1393.107), and written informed consent was obtained from all the participants. Clinical and demographic data including sex, age, familial relationship, history of family marriage, and the type of the first bleeding event were collected from all the patients using a questionnaire. Peripheral citrated (0.105 M or 3.3%) blood (3-5 ml) with a ratio of 1 to 9 (citrate tri sodium to patient blood) was collected from all the patients to check the coagulation factors assay, and 2 ml of peripheral blood was taken with EDTA for DNA extraction.

## Factor assay

The citrated samples were centrifuged at 3200 g and at 15 to 30°C for 15 minutes. The resultant plasma was used for to assay the factors. The assaying was done using a one-stage technique with the STA-R Diagnostica stago analyzer at the local clinical laboratory of the Hemophilia and Thalassemia Research and Treatment







[ DOI: 10.18502/ijpho.v15i2.18175 ]

Center (Sarvar Clinic), Mashhad University of Medical Sciences. In terms of the Diagnostica Stago kit, the normal range was 70-180 IU / dl for F5 and 60 to 180 IU / dl for F8.

**PCR amplification and DNA sequencing**

DNA was extracted from the peripheral blood leukocytes using the FavorPrepTM Blood Genomic DNA Extraction Mini Kit through the columnar method. The concentration of the extracted DNA was evaluated using a nanodrop device. All the exons and intron-exon junctions of LMAN1, MCFD2, and F5 genes were amplified using PCR. Genome sequencing was carried out by the University of Bonn. In this center, the amplicons were sequenced through the Sanger method with the Big Dye Terminator Cycle Sequencing kit (Applied Biosystems, Warrington, UK) and the ABI 3130 sequencer (PE Applied Biosystems, Foster City, California, USA). The Mutations were searched at http://www.hgmd.cf.ac.uk, and http://www.mutationtaster.org/ to determine the type and prevalence of the mutations identified. Then, the identified mutations were confirmed by repeated sequencing.

**Statistical analysis**

The data analysis was done using the SPSS16 software. Spearman´s correlation test was also used to determine the significant relationships among the variables and the correlation between F5 and FVIII levels. Statistical significance was set at P value $\leq 0.05$.

## Results

**Demographic data and clinical phenotype of the patients**

In Khorasan Razavi Province, the prevalence of F5 deficiency and F5F8D was found to be approximately 7 per 1,000,000 and approximately 5 per 1,000,000, respectively. (According to the latest census in Iran, the population of the province is 6,434,501 people). The patients affected by F5 deficiency were from six families including nine men and three women (with a ratio of 3:1). The age range was 7-68 years with the mean of 33.91 ± 18.94 years. The mean age of the patients at the diagnosis was 21.58 ± 18.15. The patients affected by the deficiency of combined Factors V and VIII (F5F8D) were from three families including four men and one woman (with a ratio of 4:1). The age range of this group was 18-42 years with the mean of 29.40 ± 9.20 years. The mean age of the patients at the diagnosis was 13.60 ± 12.44 years. In both groups of the patients, the primary diagnosis of the disease was followed by bleeding, especially traumatic bleeding. Moreover, 83.3 percent of the patients affected by F5 deficiency and 100 percent of those affected by F5F8D had a history of family marriages.

**Coagulant factor assay analysis**

The mean F5: C level for the patients affected by F5 deficiency was 10.14 ±1.30%, ranging from 1% to 32% (normal level 70–150%). The mean F5: C level and FVIII: C level for the patients with F5F8D was 14.60 ± 1.01% and 27.00 ± 2.10, respectively, ranging from 7% to 32% and 10% to 57%, respectively. The patients were then divided into three groups based on the plasma activity levels of F5 and FVIII as follows: mild (> 5%), moderate (1–5%), and severe (<1%). Regarding the F5 plasma level in the patients affected by F5 deficiency, 16.7, 50.0, and 33.3 percent of the patients could be classified as severe, moderate, and mild, respectively. According to F5 level in the patients affected by F5F8D, 20 and 80 percent of the patients could be classified as moderate and mild, respectively. Considering the FVIII level, all the patients could be classified as mild. Also, a decrease in the activity levels of both F5 and FVIII was seen in all the patients affected by F5F8D, as well as a direct correlation between the







[ DOI: 10.18502/ijpho.v15i2.18175 ]

F5 and FVIII activity levels (Spearman's Correlation coefficient= 0.95, P value= 0.014). Notably, the activity levels of both factors had decreased linearly in plasma (Figure 1).

**Mutations analysis**

In this study, a total of 13 nucleotide changes were observed among all the patients, which included four different mutations among the patients affected by F5 deficiency and two different mutations among the patients affected by F5F8D. In the patients affected by F5 deficiency, there were three types of mutation including NM_000130.5 (F5): c.6305G > A, NM_000130.5 (F5): c. 2051G > A, and NM_000130.5 (F5): c.1340C > G with the frequency of 70%, 20%, and 10%, respectively. In addition, in two patients, no mutation was observed on the F5 gene. All of the found mutations were missense, and most of them occurred on exon 23 with an incidence rate of 70%. The other mutations occurred in exon 13 (20%) and 9 (10%). Moreover, it was shown that 71.43% (5 cases) of the NM_000130.5 (F5): c.6305G > A mutations were homozygous and 28.75% (2 cases) were heterozygous. These mutations cause the substitution of Amino Acid Arginine with Amino Acid Histidine at the 2102 position. The two cases of the NM_000130.5 (F5): c. 2051G > A mutation showed heterozygote inheritance. This Nucleotide change causes the substitution of Amino Acid Cysteine with Amino Acid Tyrosine at the 684 position. There was only one case of the NM_000130.5 (F5): c.1340C > G mutation to observe; it was homozygous and caused the substitution of Amino Acid Proline with Amino Acid Arginine at the 447 position (Table I).

Two patients affected by F5F8D had the NM_139279.6 (MCFD2): c.149+5G > A mutation on the MCFD2 gene. One patient had an NM_005570.4 (LMAN1): c. 822G > A mutation on the LMAN1 gene. In two patients, no mutation was observed on LMAN1 and MCFD2 genes. Both of the found mutations were of the splice site type and were inherited in a homozygous form. The NM_005570.4 (LMAN1): c. 822G > A mutation occurred at the end of the nucleotide of exon 7 on the LMAN1 gene (Table II).



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*Table I: Clinical and laboratory findings of the patients affected by F5 deficiency*

| Patient | Relatives | Sex (M/F) | Age (year) | F5: C (%) | Mutation type | Heterozygote/ Homozygote | Nucleotide Change | Amino acid Change | Exon | History Of Family Marriage | Known/ In Database |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **1** | No | F | 68 | 1 | Missense | Homozygote | c.6305G>A | Arg2102His | 23 | Yes | Yes |
| **2** | No | M | 18 | 2 | Missense | Homozygote | c.1340C>G | Pro447Arg | 9 | No | Yes |
| **3** | Daughter of 04 | F | 7 | 31 | Missense | Heterozygote | c.2051G>A | Cys684Tyr | 13 | Yes | Yes |
| **4** | Father of 03 | M | 31 | 3 | Missense | Heterozygote | c.2051G>A | Cys684Tyr | 13 | Yes | Yes |
| **5** | No | M | 66 | 3.3 | Missense | Homozygote | c.6305G>A | Arg2102His | 23 | Yes | Yes |
| **6** | Father of 08 | M | 35 | 1.8 | Missense | Homozygote | c.6305G>A | Arg2102His | 23 | Yes | Yes |
| **7** | Sister of 06 | F | 42 | 7 | Missense | Homozygote | c.6305G>A | Arg2102His | 23 | Yes | Yes |
| **8** | Son of 06 | M | 9 | 1 | Missense | Homozygote | c.6305G>A | Arg2102His | 23 | No | Yes |
| **9** | Brother of 06 | M | 31 | 32 | Missense | Heterozygote | c.6305G>A | Arg2102His | 23 | Yes | Yes |
| **10** | Brother of 06 | M | 27 | 32 | Missense | Heterozygote | c.6305G>A | Arg2102His | 23 | Yes | Yes |
| **11** | Uncle of 12 | M | 39 | 5 | - | - | No Mutation Found | - | - | Yes | - |
| **12** | Cousin of 11 | M | 34 | 2.6 | - | - | No Mutation Found | - | - | Yes | - |

**Abbreviations: C: Concentration, F5: Factor V, F8: Factor VIII, F: Female, M: Male**

*Table II: Clinical and laboratory findings of the patients affected by F5F8D*

| Patient | Relatives | Sex (F/M) | Age (year) | FV: C / FVIII: C (%) | Gene | Mutation Type | Heterozygote / Homozygote | Nucleotide change | Amino acid Change | Exon | History Of Family Marriage | Known/ In database |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **1** | Sister of 02 | F | 34 | 7 / 10 | MCFD2 | Splice site | Homozygote | c.149+1G>A | Not Applicable | Intron 2 | Yes | Yes |
| **2** | Brother of 01 | M | 24 | 8 / 10 | MCFD2 | Splice site | Homozygote | c.149+1G>A | Not Applicable | Intron 2 | Yes | Yes |
| **3** | No | M | 29 | 13 / 17 | LMAN1 | Splice site | Homozygote | c.822G>A | - | 7 | Yes | Yes |
| **4** | Father of 05 | M | 42 | 32 / 57 | - | - | - | - | - | - | Yes | - |
| **5** | Son of 04 | M | 18 | 13 / 41 | - | - | - | - | - | - | Yes | - |

**Abbreviations: C: Concentration, F5: Factor V, F8: Factor VIII, F: Female, LMAN1: Lectin, Mannose Binding 1, M: Male, MCFD2: Multiple Coagulation Factor Deficiency 2**



[ DOI: 10.18502/ijpho.v15i2.18175 ]

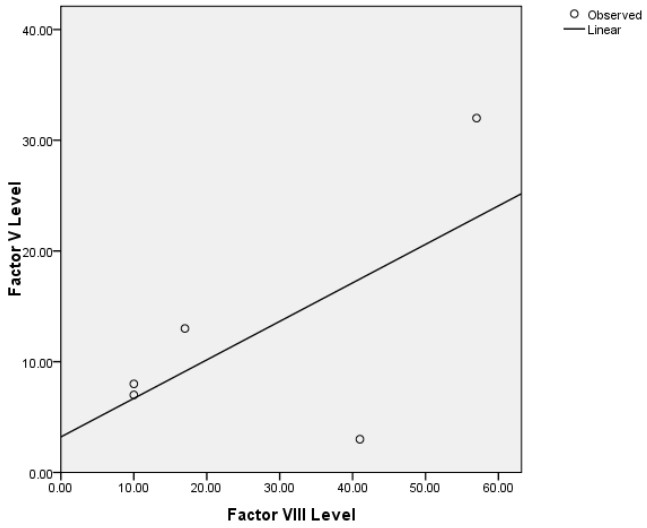


Figure 1. Correlation between F5 and FVIII levels in the patients with F5F8D

## Discussion

F5 deficiency and combined deficiency of F5 and FVIII are rare bleeding disorders (1). While most bleeding disorders are caused by a defect in the coagulation factor encoding gene, in F5F8D, the defect is in the genes encoding the intracellular carrier proteins, which leads to decreased plasma levels of these factors (5). This study was conducted to investigate the clinical and molecular basis of patients with F5 deficiency and combined deficiency of F5 and FVIII in the northeast of Iran. Few studies to date have been done regarding the genetic backgrounds of hemorrhagic disorders in Iran (9, 12, and 17). In the present study, the prevalence of F5 deficiency and F5F8D was found to be approximately 7 and 5 per 1,000,000, respectively, in the Khorasan Razavi population. According to a review by Palla et al. (1), the prevalence of F5 deficiency and F5F8D was 1 per 1,000,000 in the public population, while Paraboschi et al. (10) estimated a worldwide prevalence of 1 in 2,000,000 in the general population for the severe deficiency of Factor V. Compared to these reports, there is a higher prevalence of the disorder in Khorasan Razavi. It has been claimed that, in the areas where consanguineous marriage is more common, the prevalence is higher (1, 2). Despite the decrease of consanguineous marriage in most parts of the world, it is still high in Iran, reaching about 40% in some areas (11), which can explain the higher prevalence of blood disorders. Compared to other rare bleeding disorders, molecular changes behind the Factor V deficiency have been barely characterized. In the present study, molecular analyses were conducted on 12 patients with F5 deficiency, and three types of mutations were observed among 10 patients, all of which were missense mutations. No mutations were observed in two patients. All of the found mutations have already been reported; according to the literature, NM_000130.5 (F5):c.6305G > A (p.Arg2102His) mutation, which was seen in seven of the cases (58%) in the present study, has been reported in nine other patients to date (10, 12, 13). The homozygote patients in this study showed a moderate decrease (1-3%), while the heterozygotes showed a mild decrease







[ DOI: 10.18502/ijpho.v15i2.18175 ]

(32%) in the Factor V level. Both homozygote and heterozygote forms, with various severity from asymptomatic to severe, have been previously reported, and no association has been found between inheritance type and factor level or severity (10, 12, 13). The NM_000130.5 (F5): c.1340C > G (p. Pro447Arg) mutation was seen in one of the studied patients in the homozygote state, which caused a moderate decrease in the factor level. This mutation has been reported in five other patients with a moderate to severe decrease in the factor level (10, 14). Neither homozygote nor heterozygote inheritance has been reported with an association to severity (10, 14). According to the literature, there has been only one patient with NM_000130.5 (F5): c. 2051G > A (p.Cys684Tyr) so far (15). The data on factor level and inheritance were not available. This mutation was seen in two of the studied patients in a heterozygote form. One of them showed a moderate decrease (3%), and the other had a mild (31%) decrease in the factor level. Molecular analysis was conducted on five patients with F5F8D. The causative mutations were found in three patients, and no mutations were observed in two patients. All of the mutations were of the splice site type. The NM_005570.4 (LMAN1): c. 822G > A mutation in the LMAN1 was found in one of the patients. It affects the last nucleotide of exon 7 and causes no amino acid change, but it disrupts the splice site (16). This mutation has already been reported in several Iranian families and other ethnicities (17, 18). According to a study by Neerman-Arbez et al. (17) performed on 35 patients with F5F8D, the NM_005570.4(LMAN1): c. 822G > A mutation was observed in four out of 17 Iranian patients, which is consistent with the results of this study. Two patients showed the NM_139279.6 (MCFD2): c.149 + 5G > A mutation in the MCFD2. This mutation, which also affects the splice site, was previously reported (16). All the patients were homozygote for this mutation, and their factor levels ranged from 7% to 17%, which is in agreement with other reports (5, 16). Several types of mutation including nonsense, deletion/duplication, and splice-site mutations, all of which lead to a null phenotype, have been reported in LMAN1 (5, 16). In contrast, the genetic alterations in MCFD2 consist of both null and missense variants, including nonsense, missense, deletion/duplication, and splice-site mutations (16). To date, most of the reported mutations in F5F8D patients are found in LMAN1, and it has been suggested that molecular evaluation in these patients can be started with LMAN1 evaluation (5).

## Conclusion

In the study of genes, four patients with F5 deficiency and F5F8D proved to have no mutation. Since only exons and intron-exon junctions were amplified and evaluated in this study, the mutations affecting other regulatory domains might have been encountered. This can also be due to the mutations in other genes affecting the level or function of the factors which are not introduced yet. Evaluation of a larger group of patients and employing comprehensive tools such as whole exome sequencing can elucidate the genetic background in other patients.

## Ethical Considerations

The Ethics Committee of Mashhad University of Medical Sciences approved the study with the ethics code of IR.MUMS.REC.1393.107.

## Acknowledgments

This study was conducted with a grant from Mashhad University of Medical Sciences, Mashhad, Iran. The authors greatly appreciate the cooperation of the







[ DOI: 10.18502/ijpho.v15i2.18175 ]

Hemophilia Center of the University of Bonn, Germany, and the Hemophilia and Thalassemia Research and Treatment Center in Mashhad, Iran. We didn't use artificial intelligence (AI) in this study.

## Authors' Contributions

ZB, HF, and MRK conceived and planned the study. FB, HK, ZB and SBN contributed to the sample preparation. FB and SBN contributed to the analysis and interpretation of the results. FB, HK, and, SBN wrote the primary draft of the manuscript. All the authors had a critical review of the final draft of the manuscript and accepted it. ZB and FB contributed equally in this study.

## Funding

This study was conducted with a grant from Mashhad University of Medical Sciences, Mashhad, Iran.

## Conflict of Interest

The authors declare no conflict of interests regarding this study.

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[ DOI: 10.18502/ijpho.v15i2.18175 ]