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# Five Novel SNPs in the Factor XIII A Subunit Gene Causing Hereditary Factor XIII Deficiency in Three Related Families

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**Abstract:** Factor XIII deficiency (FXIIID) is an extremely rare autosomal recessive disorder, which cause coagulation distribution and it's mostly the mutations in *FXIII A* subunit. The aim of this study is to identify some mutations in the factor XIII *(FXIII)* gene among three related families originating from Baghdad-Iraq. The studied group consisted of nine people from three family's relatives' patients with FXIII deficiency, and the control groups of nine healthy people. Including the sex (female: 5 and male: 4) and mean age34.9±, the controls sex (female: 4 and male; 5) and age mean 35.5±. The patients' demographic profiles, in the first family, the daughter suffered from muscle and joint bleeding, and poor wound healing, without symptoms appearing in the parents. In the second family, the father suffered from skin bleeding, the son from post-traumatic bleeding, and the daughter from childbirth bleeding, joints, nosebleeds, skin, and muscles. In the third family, the father and daughter did not show any symptoms. Genetic variants were determined using the sanger sequencing method, Polymerase chain reaction (PCR) was used, the distribution of SNPs location on exon 9 was, rs5977, rs5978, and exon 10 was, rs2274391, rs41302861, and rs924669371. Polymorphisms in patients with deficiency of coagulation factor XIII A Subunit. All SNPs of family appear heterozygous and homo recessive genotype.

**Keywords:** Blood Coagulation, Factor XIII subunit A, Polymorphism, FXIII deficiency.

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## Introduction

Fibrin is the final product of the coagulation cascade and it is made by the Coagulation factor *XIIIA* gene. This gene codes for a protransglutaminase enzyme that is turned into a transglutaminase enzyme by thrombin in the presence of calcium ions (1). People who have FXIII deficiency inherit it as an autosomal recessive disease and they have a rare bleeding disorder that lasts for their whole life (2). It affects individuals of all genders and races (3). In plasma, FXIII circulates as a heterotetramer involving of subunits paired (A, B), where A behavior as a catalytic domain, and subunits B bearing ($A_2B_2$) that serve as a carrier that defends, and become stable the A subunits (4). Hereditary Bleeding Disorder (HBDs) are a set of inherited disorders that affect two types first, and second of homeostasis. These disorders arise from deficiencies or functional abnormalities of plasma proteins incorporated in normal coagulation (5). The dimensional (3D) structure of Factor *XIII A* is composed of several domains, including β-barrel domains 1 and 2 (residues 516–628 and 629–727, respectively), a β sandwich (residues 43–184), and

catalytic core domain (residues 185–515) (6). This unusual bleeding disorder has been reported in more (300) cases worldwide to date. It is more prevalent in relatives with FXIII defective consanguinity, and patients (7). A higher prevalence observed in families with FXIII deficient patients and consanguinity (8). FXIIID symptoms can range from milder forms, including, umbilical cord bleeding, skin bleeding and soft tissue hematoma are the most common and often the first symptoms to higher symptoms that life-threatening hemorrhages, such as intracranial hemorrhage (9). The prothrombin time, activated bleeding time, platelet count, and partial thromboplastin time routine represent a first-line testing laboratory for clotting blood in patient with FXIIID (10). Most congenital FXIII deficiencies are a result of FXIII-A subunit deficiency (11). The A-subunit of Factor XIII *(FXIII)* is encoded by the *F13A1* gene, which is located on the short arm of chromosome 6p25.3- p24.3(12). The *F13A1* gene consists of fifteen exons that code for a 731 residues-long polypeptide. This polypeptide comprises an activation peptide, which is cleaved by thrombin during activation, a β-sandwich domain, a core domain, and two β-barrel domains (13). In inherited deficiency of Factor XIII (FXIII), the A subunit is absent from platelets, monocytes, and plasma . Over fifty mutations in the *FXIII A* gene have been reported, including twenty-five missense, nine splice site mutations, twenty small deletions/insertions, four nonsense, and one gross deletion (14). In compare, just a few modifications have been explained in the *B subunit* (15). Family history theatres a crucial role in determining the risk of autosomal recessive conditions. It is important to consider both history and family patient, beside with clinical assessment, to raise suspicion and qualify early identification (16).

## Materials and methods

### Family study and data collection

In the current study, there are three families of relatives with Factor XIII deficiency have been characterized based on clinical and laboratory features. Most patients had severe bleeding events. The patients were recruited from the Child Protection Hospital's Department of hemorrhagic disorders in Medicine City, Baghdad, Iraq. Also, nine healthy control samples were randomly chosen from the general population during the period of November 2022 to January 2023. The healthy.

Controls were unrelated to patients but were of the same ethnicity, the healthy controls were identified with no bleeding complaints or hereditary familial hemorrhage. The ethics committee of the Hospital approved the study. Also, the Biotechnology Department, College of Science, University of Baghdad, CSEC/0222/0023, approved the study. Depending on the time of diagnosis, factor XIII deficiency was diagnosed and classified by the 2010 EULAR/ACR criteria. All participants gave informed consent and completed a questionnaire about each patient and control information.

### DNA extraction and genotyping

By using a standard procedure DNA genomic was extracted from peripheral blood leukocytes. Exon 9, exon 10, and exon 13 of *FXIIIA gene*. Genomic DNA were amplified by polymerase chain reaction (PCR) using Taq DNA polymerase (macro gene company, Korea) and specifically designed primers as shown in (Table 1).

**Table (1): The sequence of the *FXIIIA* gene primer**

| Primer Name | Sequence nucleotide | Annealing Temp. (°C) | Product size (bp) |
|---|---|---|---|
| **F13-F1** | TGTAAAACGACGGCCAGTGCAGAGTAGATGCAGGAATAG | **60** | **828** |
| **F13-R1** | CAGGAAACAGCTATGACGGATGGCAGGA CATAGATTG | | |
| **F13-F2** | TGTAAAACGACGGCCAGTATCCTCCAGTC AAAGCAATC | | **721** |
| **F13-R2** | CAGGAAACAGCTATGACGACCATACGTG AGTAGGTAGTA | | |

## Statistical analysis

The comparison of the studied groups, including all clinical data was performed using the statistical software package (SPSS and WinPep) version 26 and Student's t-test for age. P-value significance was established at 0.05. The distribution of genotypes was analyzed in autosomal recessive inheritance and the P-value for an association was calculated.

## Results and discussion

The PCR products were purified using High Pure PCR Product Purification kit (Promega, USA) and subjected to direct sequencing (Macrogen Corporation; South Korea) . The procedure of polymerase chain reactions (PCRs) was conducted using a 25µl total volume, which consisted of a 10µl mixture of the GoTaq Green Master Mix (Promega, USA) and 1µl of the forward primer solution. After that, 1µl of reverse primer (10pmol/µl), and 2 µl of the DNA template, and 6 µl of the distilled nuclease-free water. The temperature program utilized in this study involved an initial denaturation step at 94°C for 4 min, followed by a series of 30 cycles. Each cycle consisted of denaturation at 94°C for 30 sec, annealing at 55°C for 30 sec, and extension at 72°C for 30 sec. The ultimate incubation temperature was sustained for 7 min, followed by a 10 min incubation at 4°C to cease the reactions. The products amplified by PCR were undergone to forward and reverse Sanger DNA sequencing. After aligning with reference-DNA-sequences in the National Centre for biotechnology Information (NCBI), Geneious software was employed to recognize the FXIIIA gene SNPs.

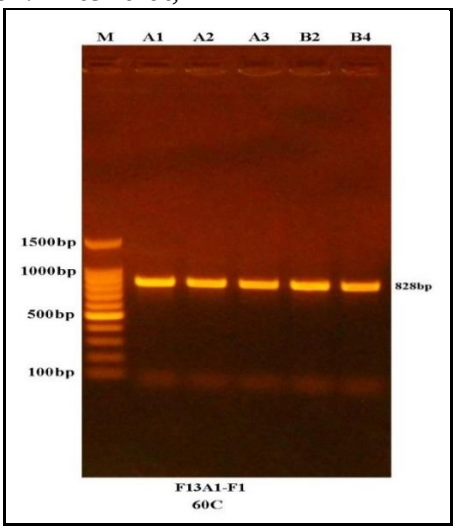


**Figure (1): Results of the amplification of F13A1-1 primer of Human samples species were fractionated on 1.5% agarose gel electrophoresis stained with Eth.Br. M: 100bp ladder marker. Lanes C3-4 resemble 828bp PCR products**

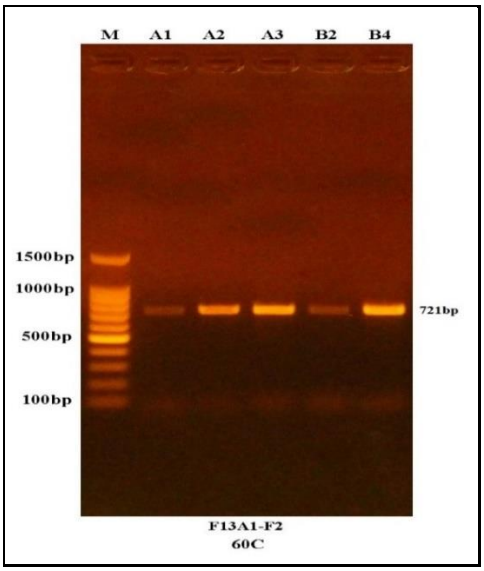


**Figure (2): Results of the amplification of F13A1-2 primer of Human samples species were fractionated on 1.5% agarose gel electrophoresis stained with Eth.Br. M: 100bp ladder marker. Lanes C3-4 resemble 721bp PCR products.**

In the present study, three families with FXIII deficiency have been characterized. calcium level was performed in a Dirrui device a (Chinese company). The result showed non-significant differences between the two groups (patients and controls) with a (P > 0.021), as shown in (Tables 2,3).

**Table (2): Calcium serum levels (mg/dl) in patients and controls**

| Groups | N | Ca (mg/dl) Mean ± S.D. | P-value | Reference rang (mg/dL) |
|---|---|---|---|---|
| **Patients** | 9 | 9.8±1.21 | 0.021 | 8.5 - 10.2 |
| **Controls** | 9 | 9.2±0.44 | | |

**(Ca): Calcium**

***FXIII A* gene sequence analysis**

**Table (3): genotype and allele frequency of factor XIII distribution SNPs of three families of relative.**

| Region | SNP | Variation | Genotype | Family 1 (N=3) N (%) | Family 2 (N=4) N (%) | Family 3 (N=2) N (%) |
|---|---|---|---|---|---|---|
| **Exon 9** | **rs5977** | **C>T** | **CC** | 3 (100) | 3 (75) | 1 (50) |
| | | | **CT** | 0 (0) | 1 (25) | 1 (50) |
| | **rs5978** | **C>T** | **CT** | 2 (66.7) | 0 (0) | 1 (50) |
| | | | **TT**** | 1 (33.3) | 4 (100) | 1 (50) |
| **Exon 10** | **rs2274391** | **G>A** | **AG** | 0 (0) | 3 (75) | 1 (50) |
| | | | **GG** | 3 (100) | 1 (25) | 1(50) |
| | **rs41302861** | **G>A** | **AG** | 1 (33.3) | 0 (0) | 0 (0) |
| | | | **GG** | 2 (66.7) | 4 (100) | 2(100) |
| | **rs924669371** | **A>G** | **AA** | 0 (0) | 2 (50) | 1 (50) |
| | | | **AG** | 3 (100) | 2(50) | 1 (50) |

Several single nucleotide polymorphisms (SNP) were identified in the exon 9, and exon 10, regions of the *FXIII A* gene through direct sequencing. Nine patients with FXIII deficiency from three families of relatives had their DNA examined, and variants of genotypes in each family

suffered from this disease. The relationship between the fathers of the first and second families is that of brothers, the father of the third family is a cousin to the fathers of the first and second families. In the first family, which consisted of three (father, mother, and daughter), the parents were relatives. The SNP rs5978 genotype located in exon 9, this SNP rs5978 was heterozygous (CT) for both parents (66.7%), but the daughter exhibited a homozygous recessive (TT) genotype (33.3%). This variation appeared for the first time in Iraqi patients and was statistically significant as it was associated with factor XIII deficiency. The genotype of the SNP rs41302861 was heterozygous (CT) in the daughter. The second family consisted of four (father, a mother, and two children). Given that the parents were related, it's interesting to note that all family members exhibited a homozygous recessive (TT) genotype for the SNP rs5978. The SNP rs2274391 genotype was heterozygous (CT) in three family members (father, mother, and son), accounting for 75% of the family. Additionally, for SNP rs924669371, two family members (the mother and son) carried a heterozygous (CT) genotype, representing 50% of the family. The third family consisted of three (father, daughter and granddaughter). The father and daughter were a carrier for the disease, the daughter married a man who had carrier the disease also and gave birth to an infected daughter. The genotype of the SNP rs5977, rs5978, rs2274391, and 924669371 was for daughter 1(50%) heterozygous (CT), as shown in Table (3).

**Characteristic features of F13-deficient patients and their family**

There is one affected patient in first family. The parents were consanguineous, FXIII deficiency was diagnosed in the index patient, a 25 years-old girl, symptoms appeared three days after giving birth, her parents were asymptomatic, Musculoskeletal hematomas, joint bleeding, and poor wound healing were observed, as shown in (Table 4). She had normal PT and APTT. She had not received routine replacement therapy. However, she received transfusion of fresh frozen plasma, as shown in (Figure3).

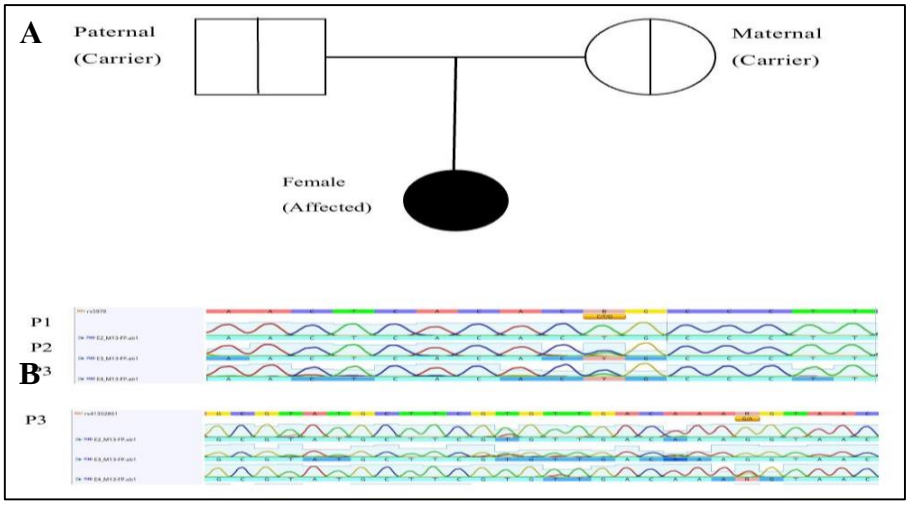


**Figure (3): Mutation in F13A1. A: family (1) tree. B: Sanger sequences for the Proband (homozygote), maternal/paternal (heterozygous). The first sequence, where all family members participated in SNP number rs5978. The second sequence, it was only the daughter who had SNP rs41302861. P: Patient, P1 (paternal), P2 (maternal)**

In the second family, four affected patients were found. Both parents were disease carriers and had consanguineous marriages. The symptoms for the thirteen-year-old male appeared after the trauma, whereas for the fifteen-year-old girl, they appeared seven days after her birth where musculoskeletal hematomas, joint bleeding, skin bleeding and epistaxis bleeding were observed, as shown in (Figure 4).

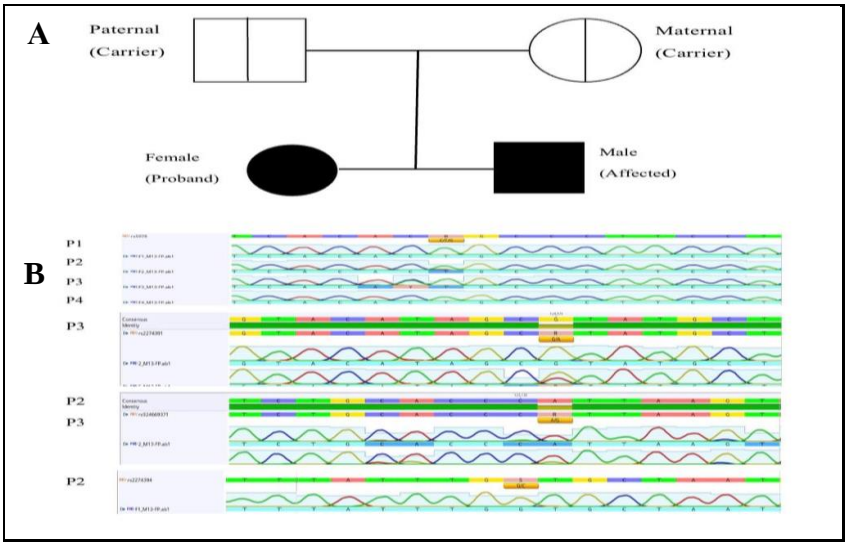


**Figure (4): Mutation in F13A1. A: family 2 tree. B: Sanger sequences for the Proband (homo recessive), maternal/paternal (heterozygote). The first sequence, where all family members participated in SNP number rs5978. In the second sequence, it was only the son who had SNP rs5977, and rs924669371. The third sequence, mother and son carried SNP rs924669371.**

The third family consisted of a father, and daughter. The father, and daughter were carriers of the FXIII deficiency gene. However, no symptoms were observed in the thirty-two-year-old daughter, as shown in (Figure 5).

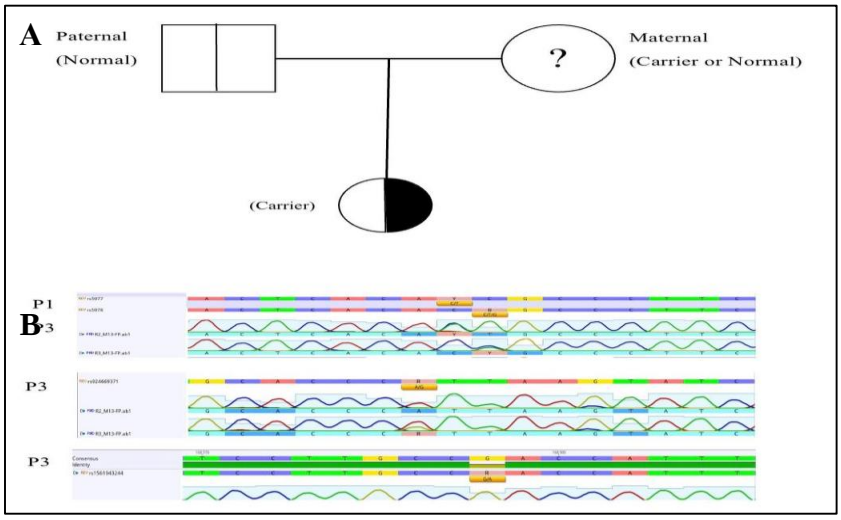


**Figure (5): Mutation in F13A1. A: family 3 tree. B: Sanger sequences for the Proband (heterozygote), maternal (heterozygote or homozygote) /paternal (homozygote). The sequences, where daughter participated in SNP number rs5978, rs5977, rs924669371, and rs2274391.**

**Table (4)**: **Family data showing genetic transmission of the F-XIII deficiency alleles to offspring.**

| Family–Patient | Gender | Age | Clinical phenotype | Genetic result |
|---|---|---|---|---|
| P1 | | | | |
| 1-Father | M | 69 | No symptoms | rs5978 rs41302861. |
| 2-Mother | F | 56 | No symptoms | |
| 3-Dautgher | F | 25 | Musculoskeletal hematomas, joint bleeding, and poor wound healing | |
| P2 | | | | |
| 1-Father | M | 42 | Skin bleeding | rs5978 rs2274391 rs924669371 |
| 2-Mother | F | 37 | No symptoms | |
| 3-Sun | M | 13 | Trauma bleeding | |
| 4-Dautgher | F | 15 | Musculoskeletal hematomas, joint bleeding, childbirth bleeding, skin bleeding and epistaxis bleeding | |
| P3 | | | | rs5977 |
| 1-Fater | M | 55 | No symptoms | rs5978 rs2274391 |
| 2-Dautgher | F | 32 | | rs924669371 |

**M: Male, F: Female and P: Patient**

Factor 13-A1 deficiency is a rare genetic bleeding disorder that is inherited in an autosomal recessive pattern, that differ from other bleeding disorder that have X-linked inheritance such as Hemophilia B (17). The autosomal recessive disease is characterized by a non-random inheritance pattern, where the two mutant alleles appear only in consanguineous marriages. The percentage of trait crossing over is 25% and transcends generations. However, in consanguineous marriages, the offspring are more likely to inherit diseased alleles from their parents and grandparents, which can lead to an increased severity of genetic disorders. This is due to the higher probability of sharing common genetic material between closely related individuals (18). Among the demographic factors in this study used for diagnosis include, skin bleeding, bleeding after trauma, joint hemorrhage, muscle bleeding, and family history, which were significant between the patients and control groups. In patients with bleeding diathesis, the severity of symptoms can vary, but it often includes a range of bleeding-related issues such as: intramuscular, postnatal umbilical cord bleeding, postoperative hemorrhage impaired wound healing, cutaneous bruising hematomas, spontaneous abortions in early

pregnancy and joint hemorrhage (19). In this study family history is positive in 100% of patients due to higher incidence of interfamilial marriages. Family history was positive in more than half of the patients (20). The calcium was examined; the p-value level appears 0.021 showing significant differences between patients and controls. Nine patients with *FXIIIA* gene deficiency from three families of relatives were studied. Six SNPs were found in the exon 9, exon 10, and exon 13 regions of the coagulation factor *XIII* gene A. The distribution of SNPs location on exon 9 were rs5977 and rs5978**,** on exon 10 were rs2274391, rs41302861, and rs924669371. Polymorphisms between individuals revealed the presence of a congenital homozygous (wild type) and heterozygous (mutant type) deficiency in the individuals. In the first family, FXIII deficiency was diagnosed in the index patient, a 25-year-old girl. Symptoms appeared three days after giving birth as she had joint bleeding and muscle bleeding. Her parents were asymptomatic. In the second family, both parents were disease carriers and had a consanguineous marriage. The symptoms for the boy, who was thirteen, arose after the trauma, but for the girl, who was fifteen, they appeared seven days after she was born; Severe Factor XIII (FXIII) deficiency typically manifests during the neonatal period, while individuals with mild FXIII deficiency may present later in life1. When evaluating patients with suspected FXIII deficiency, it is important to obtain a family history, especially regarding a history of consanguineous marriage (21). The genetic results showed that in SNP rs5978, all four members of the family had a (mutant type) (TT) genotype, which was highly significant. Since the entire family was a carrier of the disease. The presence of the T/T genotype has been associated with an increased risk of peripheral venous thrombosis, as shown in a study by (Reuner *et al*.). The TT genotype of the functional factor XII (FXII) C46T gene polymorphism is associated with an increased risk of peripheral venous thrombosis (22). The third family consisted of a father and a daughter. The result of genotype showed, homozygous (Wild type) (50%), and heterozygous (Mutant type) (50%). Because not have information about the mother, it is expected from the genetic results of the daughter and father that the mother was a carrier of the disease. These SNPs occurred in the intron region; they did not affect the kind of amino acid from one acid to another. The study you mentioned by (Spencer *et*, Al),discusses the fact that single nucleotide polymorphisms (SNPs) within a coding sequence do not necessarily change the amino acid sequence of the protein produced1. This is due to the degeneracy of the genetic code (23). There haven't been any prior studies done on this polymorphism in the population of Iraq, thus the research on it may be limited globally, and the current study is the first to demonstrate a link between the, rs5977, rs5978, rs2274391, rs41302861, rs92466937, and rs2274391 gene and the risk of the *FXIIIA* gene. Although the SNPs rs5977, rs5978, rs2274391, rs41302861, and rs92466937 are listed in NCBI, they are considered risk factors in Iraqi patients. However, the polymorphism also depends on race, and they may not be risk factors in other countries, and no articles have been made about them. Due to the disease's rarity and the

insufficient number of samples available in Baghdad, as well as the lack of information regarding the cause of the disease's emergence in the SNPs, it is impossible to draw conclusions from this comparison.

## Conclusion

Three families with FXIII deficiency have been genotyped, and five rare SNPs affecting the *FXIII A*-subunit have been identified. These SNPs, namely rs5977, rs5978, rs2274391, rs41302861, and rs92466937 have been described for the first time in Baghdad samples. They are located in exon 9, exon 10, and exon 13 on the *gene A* on chromosome 6p24-25. The SNP rs5978 was found in all three families. Its appearance was concentrated in the second family for all family members, making it a risk factor for the emergence of the disease. The percentage of TT (mutant type) was 100%, meaning that all family members had the disease. Meanwhile, the SNPs rs2274391 and 924669371 were found in family 2 and family 3 . Because more than one common trait appeared in the three families, it is possible that this SNPs is considered a risk factor and related to the disease. Therefore, to confirm these results, we recommend using a technique NGS. In these families, the diagnosis has been confirmed through genetic testing. Molecular analyses have been conducted and the results are consistent with functional studies and clinical observations.

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