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Case Report

# New and de novo Biallelic Variant Associated with Owren's Disease: Precision Medicine in Coagulation Disorders

**Michel Alejandra Ewonds Jimenes[1,3]*; Lina Johanna Moreno Giraldo[2-4]**

[1]Resident Specialization in Pediatrics, Universidad Libre seccional Cali, Colombia

[2]MD,Pediatrician, MSc and PhD. Medical genetics, Universidad Libre seccional Cali, Colombia

[3]Researcher Pediatric Research Group (GRINPED)

[4]Leader of the Neurogenetics and Metabolic Diseases Research Line (NEUROMET) of GRINPED

***Corresponding author:** Michel Alejandra Ewonds Jimenes, Resident Specialization in Pediatrics, Universidad Libre seccional Cali, Colombia.

Email: michelleewonds@gmail.com

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**Abstract**

**Introduction:** Coagulation factor V deficiency, also called Owren's disease or parahemophilia [1], is a genetic disease with an autosomal recessive inheritance pattern that causes moderate to severe bleeding [2]. It can be classified into type I when the deficiency is quantitative and type II when the deficiency is qualitative [3]. Currently, it is associated with variants in the F5 gene. According to recent database searches, 450 clinically significant variants and approximately 3942 variants related to the F5 gene have been identified [2].

**Materials & Methods:** 3A 10-year-old female patient who required hospitalization on three occasions due to frequent bleeding (bleeding after dental extraction, hematoma of the iliopsoas and hemarthrosis of the knee) requiring management with fresh frozen plasma. The child was born to a non-consanguineous father, without known illnesses in the family, who was with stunted growth and thinness. In view of the clinical data, paraclinical tests are performed and coagulation factor is studied, finding low factor V activity (< 4 %). Given the complexity of the clinical manifestations, and the relevance to confirm the clinical and paraclinical suspicion, in a patient with no related family history, a molecular study was requested (CNV-seq) by next-generation sequencing of the F5 gene, related to factor V deficiency in order to establish a phenotype-genotype correlation.

**Results:** A probably pathogenic, homozygous variant was identified in the F5 gene, consisting of a thymine nucleotide deletion at position 2,809 of the cDNA in exon 13, (c.2809 del) which at the protein level produces a reading frameshift change leading to a premature stop codon at amino acid 958 (p.Ser937ValfsTer22) in a 2224 amino acid protein so it is expected to result in an absent protein product.

**Discussion & Conclusion:** The genomic variant c.2809del is a single nucleotide deletion that occurs within the coding sequence of the F5 gene. This deletion leads to a reading frame shift variant, designated as p.Ser937ValfsTer22, which indicates that the serine at position 937 is replaced by a valine, and a 22 amino acid premature termination codon is introduced into the translated protein. The reading frame shift variants result in a truncated factor V protein which is likely to be nonfunctional due to the loss of critical sequences of C-terminal amino acids. The F5 gene encodes coagulation factor V, a protein that plays a crucial role in the blood coagulation cascade. Factor V consists of 2224 amino acids and functions as a cofactor for the prothrombinase complex, which is responsible for the conversion of prothrombin to thrombin, a key step in the formation of a blood clot.

When performing an updated search in different databases (HGMD, ClinVar, LOVD, dbSNP and gnomAD v.4), there is no description of a variant as the one reported in this case. Until January 2024, 450 clinically significant variants and approximately 3942 variants related to F5 gene have been reported.

When searching for this variant in artificial intelligence assistants, according to the first genetic variant assistant of GenAI, VarChat, others such as Alphafold, Mastermind, the latter reported that it searched over 36 million abstracts, and over 9 million genomic full-text articles and did not find related articles.

(https://mastermind.genomenon.com/articles?gene=f5&mutation=f5%3Ac.2809del&keyword=F5+c.2809del&gene_op=and&mutation_op=and&keyword_op=and).





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Only two in silico predictors (autoPVS1 and MutationTaster) report this variant as deleterious.

The Uniprot platform, Alliance of Genome Resources which predicts that this gene allows copper ion binding activity and signaling receptor activity. It is predicted to be involved in blood circulation and blood clotting. Located in extracellular vesicle and membrane.

It was reported in enzyme and pathway databases: BioCyc MetaCyc: G66-30677-MONOMER.

In gene interaction databases, a relationship of F5 with 25 other genes has been found, mainly related to Binding, Expression, and Modification mechanisms. Using the genomic platform of artificial intelligence Mastermind, PVS1, PS3, PM2, PM4, PM6 are classified: Pathogenic Classification IA: PM1, PS1, PVS1, PM2, which is the reason to establish genotype/endotype/phenotype correlation. Given the great genotypic heterogeneity and phenotypic expression: variant - dependent, it is important to characterize these pathologies genomically, in order to give a specific diagnosis, indicate targeted treatments, prognosis, monitoring, genetic counseling, in addition to generate knowledge through reports of new and de novo variants, as in the case of our patient, contributing to precision medicine, personalized, predictive, preventive, participatory as a means to seek that it can be standardized at the population level through implementation of screening, carrier search, and continuing education on the great variability of gene expression.

## Introduction

Coagulation factor V deficiency, also called Owren's disease or parahemophilia [1], is a genetic disease of autosomal recessive inheritance pattern that causes moderate to severe bleeding and was first reported in 1943 by Dr. Paul Owren who described a patient with recurrent severe epistaxis and severe menstrual bleeding [2].

This disease has an estimated prevalence of 1 in 1 million people without ethnic predisposition [1,4]. However, a high presentation is described in Caucasians, being less frequent in North Americans [2]. According to the annual report 2022 of the World Federation of Hemophilia, it was found that 80 countries reported cases of factor V deficiency, for a total population of 3664, which corresponds to 36% males and 39% females, mostly reported from the United Kingdom with 303 cases, The United States of America with 163 cases [5].

Factor V deficiency is associated with variants in the F5 gene, the first was described in 1998(2). Currently, according to recent database searches, 450 clinically significant variants and approximately 3942 variants related to the F5 gene have been identified. This disease has an autosomal recessive inheritance and it is generally symptomatic only in the homozygous or compound heterozygous state [2]. It can be classified into type I when the deficiency is quantitative and type II when the deficiency is qualitative [3]. According to reviews conducted in different databases: the International Society on Thrombosis and Hemostasis mutation database (http://www.isth.org/?MutationsRareBleedin), Human Gene Mutation Database (http://www.hgmd.cf.ac. uk/ac/index.php), International Registry of RBDs in Milan (http://www.rbdd.org), the FV Mutation Database (http://www. lumc.nl/4010/research/factor_V_gene.html), and Genome Aggregation Database (https://gnomad.broadinstitute.org/), it was found that, during 2022, the variants are mostly missense, 51.4%; frameshift, 22.9%; nonsense, 13.9%; splicing, 6.5%; finally, inframe insertions/deletions and duplications accounting for 2.5% (2). Sedighe Satari et al., in an Iranian study performed in 7 patients, identified three variants already reported and 4 de novo variants: IVS9-1 G>C, Y478D, L1844P, and I1556T in the FV gene [6].

The F5 gene is located on the long arm of chromosome 1 at location 1q23 band 1. (Figure 1) This gene is expressed in hepatocytes and megakaryocytes. It is approximately 80 kb in length, contains 25 exons and 24 introns, producing a 7 kb messenger RNA which is translated into 2224 amino acids, the resulting protein is compressed into a 28-residue peptide and a mature polypeptide with 2196 amino acids, containing six domains (A1, A2, B, A3, C1 and C2). Exon 13, where most of the variants are found, and it is described as the longest, codes for the B domain [7] (Figure 2). In 2022, Yueh-Shih Chang found a new variant described in exon 16 in a Taiwanese family of homozygous trait, as well as multiple variants in members of the same family [8] (Figure 3).

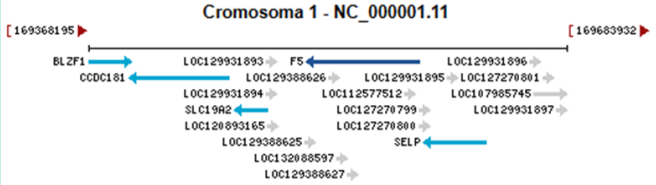


**Figure 1:** FV gene chromosomal location [9].

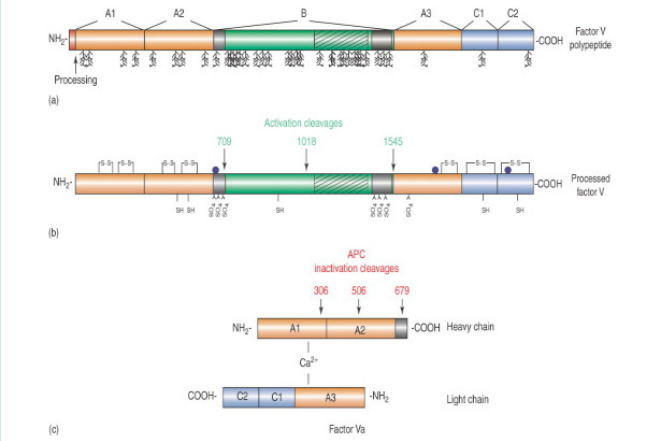


**Figure 2:** Characteristics of the FV gene [10].

The functional product of the F5 gene is activated factor V. It is 40% homologous to FVIII in function and structure [2].

This factor is a key point in homeostasis, it has a procoagulant and anticoagulant role, 80% is maintained in the liver and 20% in platelets; it disposes its B domain through thrombin proteolysis, it interacts with FXa, prothrombin and a light chain (A3 C1 and C2 domain) with membrane phospholipids as co-receptors. FVa concentrates FXa levels on the cell membrane surface and accelerates the conversion of prothrombin to thrombin [2].

Factor V activity has a limited correlation with bleeding severity [1].

Factor V deficiency type I is characterized by a quantitative deficiency and is defined by a low clotting activity and low antigen levels, type II is qualitative and is characterized by a low clotting activity with normal antigens [2].

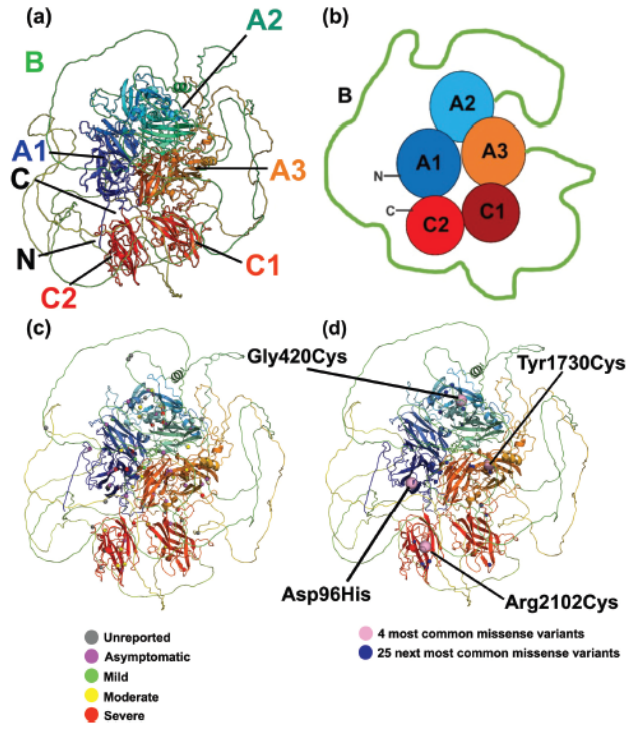


**Figure 3:** FV gene variants [11].

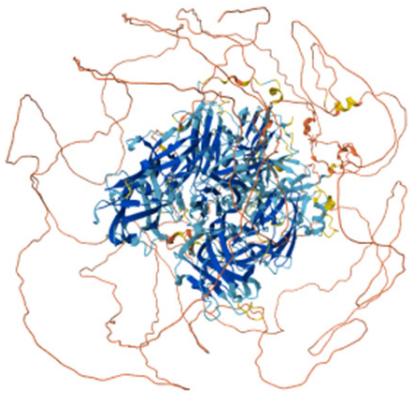

**Figure 4:** 3D prediction of the AlphaFold structure of protein F5 (https://alphafold.ebi.ac.uk/entry/P12259).

The clinical manifestations have a spectrum of presentation from mild to severe, mild with a function higher than 10%, moderate function from 1 - 10% and severe function lower than 1%, the symptoms begin around six years of age, being mucocutaneous bleeding and hematomas the most common symptoms. However, profuse nasal and menstrual bleeding may occur, massive bleeding during surgical procedures; among the most severe cases there is hemarthrosis, pulmonary bleeding, gastrointestinal and central nervous system bleeding, which are rare [7,12]. Farj M A Sarhan described a case of bleeding in an early stage of life after circumcision where a de novo variant was found [13,2].

Acquired factor V deficiency is caused by the formation of antibodies against the factor, leading to hemorrhagic complications with varying degrees of severity. This condition is idiopathic in 15% of the cases, it can also follow a surgical procedure, labor, medications and the use of thrombin sera [14].

The diagnosis is of exclusion. When bleeding is found, secondary hemostasis tests are performed. They correspond to coagulation times, finding the presence of a slight prolongation of prothrombin time and partial thromboplastin time, with normal thrombin time. Specific factor V activity should be measured and factor levels should be measured as well, considering that some patients may have normal factor levels without being functional [15,14].

Molecular genetics is of relevant importance to determine the diagnosis and the type of variant involved, there are different types of tests, such as sanger sequencing, complete sequencing of the coding region through NGS (Next Generation Sequencing), deletion/duplication analysis technique based on MLPA (Multiplex Ligation-dependent Probe Amplification) or methods based on PCR (Polymerase Chain Reaction).

Differential diagnosis with Von Willebrand's disease and other platelet disorders should be performed [14].

Factor V concentrates do not exist; for its treatment, fresh frozen plasma is used at doses of 15 - 25 ml/kg during moderate to severe bleeding episodes; with subsequent monitoring of factor levels to determine the need for other doses; the average life is 24 to 36 hours [14].

Patients who will be taken to surgical interventions should be guaranteed a factor safety level higher than 25% and in the postoperative period receive treatment from 3 to 10 days, evaluating bleeding data. During dental extraction procedures, administration of fresh frozen plasma with local hemostatic measures is also indicated [14].

On some occasions, depending on the magnitude of the bleeding, platelets are administered [16]; for mild mucocutaneous bleeding, fibrinolytic agents are indicated [1]. Prophylactically, it is indicated to administer fresh frozen plasma twice a week [16]. In 2021, Jingjing Yang reported a case of intracranial bleeding in a patient with factor V deficiency with poor response to conventional treatment, considering the possibility of liver transplant [17].

The implementation of gene therapy correcting variants with the use of pluripotential cells has been studied in this type of patients, which is currently being tested [14].

Gene editing tests are also being used in animals using the model CRISPR/CAS (clustered regularly spaced short palindromic repeats), where the normal function of the gene responsible for factor V production has been tested, especially with nonsense variants, but so far with little success since the factor has important roles in embryogenesis and is currently a subject of ongoing research [18].

## Case Report

A 10-year-old female patient, product of a 37-year-old mother, G2P2V2, second gestation, non-consanguineous parents. Born at term by vaginal delivery without complications. Anthropometry at birth: Weight 2440 grams, Height 48 cm. Weight for gestational age (P10) and height for gestational age (P10 - 50).

Who has required hospitalization on three occasions due to frequent bleeding: bleeding after dental extraction, hematoma of the iliopsoas and hemarthrosis of the knee, requiring management with fresh frozen plasma. In the case of major bleeding, red blood cell transfusion was required on four occasions. In initial follow-up by clinical hematology finding a deficiency in the activity of coagulation factor V (4% activity). For the above-mentioned reasons, she is treated as needed with tranexamic acid.

Physical examination revealed a risk of stunted growth and thinness, an increase in the size of the thyroid gland and multiple hyperchromic lesions on the skin, with no suggestive clinical signs of bleeding. Within the multidisciplinary management, evaluations by other specialties are indicated, such as endocrinology that does not find alterations in thyroid function, dermatology that does not find alterations in skin and infectiology that adjusts vaccination in the presence of risk factors. Given the clinical history of the patient, complexity of the manifestations, relevance of confirming the clinical-paraclinical suspicion, phenotypic heterogeneity dependent on the variant, in a patient with no related family history, a molecular study was requested (sequencing + CNV) through NGS of the F5 gene, related to factor V deficiency in order to establish phenotype-genotype correlation.

## Results

It is obtained a genetic study report by sequencing the coding regions of the genome (exome > 20,000 genes), with a coverage of more than 98% and a minimum depth of 20 x. From these data, the gene sequence was analyzed. The sequencing results were analyzed bioinformatically using the Varsome Clinical software and the aligned and filtered sequences, complying with specific quality criteria, they were analyzed with respect to the hg19 reference genome for annotation and variant calling.

The analysis performed was directed to the identification of variants included in exonic regions or splicing regions (at least 20 bp), insertions and small deletions. This analysis allows the identification of exonic deletions and duplications (also known as Copy Number Variants, or CNV) and variants involving large regions of the gene.

The study reported a probably pathogenic, homozygous variant in the F5 gene, consisting of a thymine nucleotide deletion at position 2,809 of the cDNA in exon 13, (c.2809del) which at the protein level produces a frameshift change leading to a premature stop codon at amino acid 958 (p.Ser937ValfsTer22) in a 2224 amino acid protein and is expected to result in an absent or altered protein product.

This variant is not reported in the databases ClinVar, the human gene mutation database (HGMD), Leiden open Variation Databe (LVOD) nor in the scientific literature consulted. Its allele frequency is unknown in the general population (gnomAD v.4) and, *in silico* predictors (autoPVS1 and MutationTaster) classify it as deleterious; there is no data from other individual predictors or high bioinformatic performance.

Pathogenic variants in the F5 gene (OMIN*612309) are associated according to HPO (Human Phenotype Ontology), NCBIGene:2153: Congenital factor V deficiency ORPHA:326 with mechanism of inheritance AR; Factor V deficiency OMIM:227400 with mechanism of inheritance AR; Thrombophilia due to deficiency of activated protein C cofactor OMIM: 188055 with mechanism of inheritance AD; Budd-Chiari syndrome OMIM:600880 with mechanism of inheritance AR; Pregnancy loss, recurrent, susceptibility to, 1 OMIM:614389 with mechanism of inheritance AD; Budd-Chiari syndrome ORPHA:131 with mechanism of inheritance AR, Ischemic stroke, susceptibility to OMIM:601367 multifactorial mechanism of inheritance.

## Discussion

The factor V gene encodes for a protein comprising a leader peptide and heavy chain encoded by exons 1-12, a B domain encoded by exon 13 and a light chain encoded by exons 14-25. Factor V deficiency (also called Owren's disease or parahemophilia) is a bleeding disorder where heterozygous individuals, for a FV deficiency, may remain asymptomatic and homozygous individuals exhibit a moderate to severe bleeding disorder consisting of ecchymosis, epistaxis, and menorrhagia. Bleeding may also occur after trauma, surgery or dental extraction, but is usually easily controlled. Pathogenic variants in this gene have been linked to susceptibility to various medical conditions constituting a large phenotypic heterogeneity that includes not only Factor V deficiency with autosomal recessive inheritance mechanism, but also susceptibility to autosomal dominant recurrent pregnancy loss 1 (RPRGL1) which is defined as more than 3 consecutive losses before 24 weeks of gestation; susceptibility to ischemic cerebrovascular event of multifactorial inheritance which is described as an acute neurological event leading to neuronal death and resulting in loss of motor, sensory and cognitive function; susceptibility to thrombophilia due to autosomal dominant factor V Leiden, which is significantly related to venous thromboembolism; thrombophilia 2 due to autosomal dominant activated protein c cofactor deficiency related to recurrent thromboembolic events; autosomal recessive Budd Chiari syndrome characterized by anatomical abnormalities and hypercoagulability disorders, patients present with hepatomegaly, right hypochondrium pain and ascites.

This gene has Synonyms: activated protein C cofactor; proaccelerin labile factor, with Accession IDs: G66-30677 (MetaCyc), P12259 (UniProt), Mint P12259.

According to UNIPROT (https://www.uniprot.org/), this protein: Coagulation Factor V, consisting of 2224 amino acids, is a central regulator of hemostasis. It serves as a critical cofactor for the prothrombinase activity of factor Xa resulting in the activation of prothrombin to thrombin. Regulation of activity Inhibited by SERPINA5.

Coagulation factor Va is a protein of the coagulation system that is not enzymatically active. Rather, it functions as a coenzyme for factor Xa. The protein, which is homologous to factor VIII, consists of six domains: A1-A2-B-A3-C1-C2. The A domains are homologous to the A domains of the copper-binding protein ceruloplasmin and bind copper. The C domains belong to the family of discoidin domains of phospholipid-binding (unrelated to the C2 domain), and the C2 domain mediates membrane binding. The C-terminal end of the B domain acts as a cofactor for the activation of the anticoagulant Protein for the Protein S [Thorelli98, MacedoRibeiro99].

The protein circulates in the bloodstream in an inactive form until it encounters activated platelets, to which it binds. Upon binding, it is cleaved and activated by thrombin. Activation consists of cleavage and release of the B domain, leaving two chains: a heavy chain, consisting of domains A1-A2, and a light chain, consisting of domains A3-C1-C2. The two chains associate non-covalently in a calcium-dependent manner, forming the active factor Va.

Coagulation factor Va associates with factor Xa to form the prothrombinase complex, which catalyzes the conversion of prothrombin to thrombin. The assembly of the complex takes place in negatively charged phospholipid membranes in the presence of calcium ions.

Coagulation factor Va is inactivated by protein C-catalyzed proteolysis.

Additionally, a search for this variant was carried out in artificial intelligence assistants. According to the first genetic variant of GenAIs, VarChat, the c.2809del genomic variant is a single nucleotide deletion that occurs within the coding sequence of the F5 gene. This deletion leads to a reading frameshift variant, designated as p.Ser937ValfsTer22, which indicates that the serine at position 937 is replaced by a valine, and a 2224 amino acid premature termination codon is introduced into the translated protein. The reading frameshift variants result in a truncated factor V protein that is likely to be nonfunctional due to the loss of critical C-terminal amino acid sequences.

Introduction of a premature stop codon triggers the nonsense-mediated mRNA decay (NMD), a cellular quality control mechanism that degrades mRNAs containing premature termination codons to prevent the synthesis of truncated and potentially harmful proteins. If the mRNA escapes NMD, the truncated protein may be subject to proteasomal degradation or may have dominant-negative effects if it interferes with the function of the wild-type protein.

## Gene Function

The F5 gene encodes coagulation factor V, a protein that plays a crucial role in the blood coagulation cascade. Factor V functions as a cofactor for the prothrombinase complex, which is responsible for the conversion of prothrombin to thrombin, a key step in the formation of a blood clot. Factor V is synthesized as an inactive precursor and activated by thrombin or factor Xa through specific cleavage. The active form of Factor V (Factor Va) is essential for the amplification of thrombin generation. Given its central role in coagulation, variants in the F5 gene may lead to bleeding disorders such as factor V deficiency or may contribute to thrombophilia, as observed in factor V Leiden thrombophilia, depending on the nature of the variant and its impact on protein function. This variant is not described in the literature.

In accordance with various genomic intelligence platform as Mastermind, they reported a search over 36 million abstracts, and over 9 million genomic full-text articles and did not find related articles.

(https://mastermind.genomenon.com/articles?gene=f5&mutation=f5%3Ac.2809del&keyword=F5+c.2809del&gene_op=and&mutation_op=and&keyword_op=and).

According to Alliance of Genome Resources, it predicts that this gene enables copper ion binding activity and signaling receptor activity. It is predicted to be involved in blood circulation and blood clotting. Located in extracellular vesicle and membrane. Involved in several diseases, including arterial disease (multiple); end-stage renal disease; factor V deficiency; liver disease (multiple); and nonarteritic anterior ischemic optic neuropathy. Biomarker of colorectal adenoma; hepatitis; liver cirrhosis; and portal hypertension.

Gene reported in genetic variation databases: BioMuta F5, DMDM 308153653, ClinGen HGNC:3542, GenCC HGNC:3542.

Bases de datos de enzimas y vías: BioCyc MetaCyc: G66-30677-MONÓMERO.

Enzyme and pathway databases: BioCyc MetaCyc: G66-30677-MONOMER.

It has canonical transcript in RefSeq or Ensembl database:

-Transcripts NM_000130.5 - Frameshift MANE Select, Germline Classification, Exomes Frequencies: not found (CoV: 81.4) Genomes: not found (CoV: 30.8), Scores Chromosome CHR1, Position 169542281, UCSC Genome Browser REF T Sequence, Variant Type Deletion; Cytoband 1T24.2, HGVS F5(NM_000130.5):c.2809 p.(Ser937ValfsTer22) conservation: phyloP100: 4.019; PhastCons100way 0.951.

- F5(ENST00000367797.9): c.2809del: Exomes Frequencies: Not found (CoV: 81.4); Genomes: Not found (CoV: 30.8). This variant is found on Chromosome CHR1 Position 169542281 Navigator of the UCSC genome, Sequence REF T, Variant Type Deletion, Cytoband 1T24.2, HGVS F5(ENST00000367797.9):c.2809del p.(Ser937ValfsTer22).

Reactome: R-HSA-114608 Platelet degranulation; R-HSA-140875 Common pathway of fibrin clot formation; R-HSA-204005 COPII-mediated vesicle transport; R-HSA-381426 Regulation of insulin-like growth factor (IGF) transport and uptake by insulin-like growth factor binding proteins (IGFBP); R-HSA-5694530 Charge concentration in the ER; R-HSA-8957275 post-translational phosphorylation of proteins.

Proteomes Identifier UP000005640.

Protein-protein interaction databases: BioGRID 10845217 interactians ComplexPortal CPX-6216; Coagulation Factor Complex Va, DIP DIP-47331N; IntAct P122599 interactans; MINT P12259; STRING 9606.ENSP00000356771.

Chemistry: BindingDB P12259, RNAct P12259Protein.

Genomic annotation databases:

Ensembl ENST00000367797,9ENSP00000356771,3ENSG00000198734,12; GeneID 2153; KEGG has:2153;

MANE-Select ENST00000367797,9ENSP00000356771,3NM_000130,5NP_000121,2

UCSC: UC001GGG.2.

This article reports the case of an adolescent patient with heterogeneous clinical manifestations associated with hematologic involvement, with suspected coagulation disorder, due to altered paraclinical findings, but with no related family history, no consanguinity; therefore, a molecular study for the FV gene is requested.

This patient has a homozygous genomic variant causing inheritance autosomal recessive factor V deficiency, which explains her phenotype. The risk of inheriting this variant to her offspring is 100%. However, the probability of her children inheriting the disease will depend on the carrier status of her partner. The F5 gene variant reported in this case was c.2809del; p.Ser937ValfsTer22; homozygous, frameshift type, when consulting the different databases - genetic registries describe more missense type variants [3].

In the year 2022 in Taiwan, the first report of simultaneous variants found in the same sequencing of the F5 gene of two patients from the same family was made, where 8 different variants were found, of which 7 were heterozygous some located in exon 13 and one homozygous located in exon16 (Met1736Val) which correlates with the clinical manifestations reported; where their carriers had no history of major bleeding, with factor V activity of 3.2% and 2% classified as moderate deficiency, who required fresh frozen plasma for major bleeding related to surgical interventions [8].

In 2023, an analysis of 363 genetic variants related to F5 was performed, which explained the different phenotypes described, the most reported pathogenic variants are c.6304C>T (p.Arg2102Cys), c.1258G>T (p.Gly420Cys), c.5189A>G (p.Tyr1730Cys) and the probably most reported pathogenic is c.6304C>T (p.Arg2102Cys) [3].

Bleeding can also occur after trauma, surgery or dental extraction, but is usually easily controlled. Pathogenic variants in this gene have been linked to susceptibility to various medical conditions constituting a large phenotypic heterogeneity, not only factor V deficiency with autosomal recessive inheritance mechanism, but also to susceptibility to recurrent gestational loss 1 (RPRGL1) of autosomal dominant inheritance which is defined as more than 3 consecutive losses before 24 weeks of gestation; susceptibility to ischemic cerebrovascular event of multifactorial inheritance which is described as an acute neurological event leading to neuronal death and resulting in loss of motor, sensory and cognitive function; susceptibility to thrombophilia due to inherited autosomal dominant factor V Leiden, which is significantly associated with venous thromboembolism; thrombophilia 2 due to activated protein c cofactor deficiency of dominant autosomal inheritance associated with recurrent thromboembolic events; autosomal recessive Budd Chiari syndrome characterized by anatomical abnormalities and hypercoagulability disorders, patients present with hepatomegaly, right hypochondrium pain and ascites. HPO (Human Phenotype Ontology), NCBIGene:2153.

By performing updated search in different databases (HGMD, ClinVar, LOVD, dbSNP and gnomAD v.4), there is no description of a variant as the one reported in this case. Until January 2024, 450 clinically significant variants and approximately 3942 variants related to F5 gene have been reported.

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(https://mastermind.genomenon.com/articles?gene=f5&mutation=f5%3Ac.2809del&keyword=F5+c.2809del&gene_op=and&mutation_op=and&keyword_op=and).

Two in silico predictors report this variant as deleterious.

The Uniprot platform, Alliance of Genome Resources which predicts that this gene enables copper ion binding activity and signaling receptor activity. It is predicted to be involved in blood circulation and blood coagulation. Located in extracellular vesicle and membrane.

Reported in enzyme and pathway databases: BioCyc MetaCyc: G66-30677-MONOMER.

It has canonical transcription in the RefSeq or Ensembl database:

In gene interaction databases it has been found relationship of F5 with 25 other genes mainly related to Binding, Expression, Modification mechanisms. This explains its great phenotypic heterogeneity.

## Conclusions

Factor V deficiency, also called Owren's disease or parahemophilia [1], is a potentially inheritable genetic disease, which causes moderate to severe bleeding, it is a rare disease, which has an autosomal recessive inheritance pattern where there is a risk of heritability of 25%, which increases if parents are consanguineous, but multiple de novo variants have also been described in recent years [4]. It can be classified into type I when the deficiency is quantitative and type II when the deficiency is qualitative [6]. The clinical manifestations are heterogeneous and depend on the degree of function of the factor, which, if it is lower than 1%, it has severe manifestations; between 1% and 10%, moderate; and more than 10%, mild [8]. In mild cases, patients remain asymptomatic, with risk of bleeding during surgical interventions, as well as moderate cases can present with gingival bleeding or epistaxis in a persistent manner with greater risk of bleeding during surgical interventions and require prophylactic therapy with previous fresh frozen plasma [9]. There are currently molecular diagnostic methods and various therapeutic options, some in different phases of research (clinical trials) that seek to learn progressively more about the correlation in view of a hyper-personalized medicine.

The different databases, bioinformatics algorithms, along with knowledge about functionality, biological bases, genomic annotation data, molecular, protein structure and function, functional studies, use of artificial intelligence tools and according to Richards et al., Standards and guidelines for the interpretation of sequence variants. 2015 [5],

American College of Medical Genetics and Genomics, Association for Molecular Pathology, ClinGen, this variant is classified as probably pathogenic, and by using the artificial intelligence genomics platform Mastermind, it is classified PVS1, PS3, PM2, PM4, PM6: Pathogenic Classification IA: PM1, PS1, PVS1, PM2 reason for which genotype/ endotype/ phenotype correlation is established.

Given the great genotypic heterogeneity and phenotypic expression: dependent variant, it is important to characterize these pathologies genomically, in order to provide a specific diagnosis, indicate targeted treatments, prognosis, follow-up, genetic counseling, in addition to generating knowledge through reports of new and de novo variants, as in the case of our patient, contributing to precision, personalized, predictive, preventive and participatory medicine, in the interest to seek to standardize at the population level through the implementation of screening, carrier search, and continuing education on the great variability of gene expression, as in the case of the patient in which this variant is not only associated with factor V deficiency with autosomal recessive inheritance mechanism, but also with susceptibility to recurrent gestational loss 1 (RPRGL1) of autosomal dominant inheritance; susceptibility to ischemic cerebrovascular event of multifactorial inheritance; susceptibility to thrombophilia due to factor V of Leiden of autosomal dominant inheritance; thrombophilia 2 due to activated protein c cofactor deficiency of autosomal dominant inheritance; Budd Chiari syndrome of autosomal recessive inheritance; thus performing a holistic, integral, anticipatory and preventive approach reducing the risks of morbidity and mortality associated with this pathology.

## References

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