Fibrinogen Bonn (p. Arg510Cys) in the Aα-Chain Is Associated with High Risk of Venous Thrombosis

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Abstract

Introduction   Inherited dysfibrinogenemia is a qualitative defect of fibrinogen caused by various mutations among three fibrinogen genes. Dysfibrinogenemia can be associated with an increased risk of thrombosis, bleeding, or both. Here, we report a 36-year-old female with dysfibrinogenemia who experienced two successful pregnancies under thromboprophylaxis after cerebral venous sinus thrombosis (CVST).

Patients and Methods   In addition to plasmatic coagulation tests, fibrinogen genes *FGA*, *FGB*, and *FGG* were screened using direct genomic DNA sequencing. The structural-functional implications of the detected mutation were analyzed in silico.

Results   Inherited dysfibrinogenemia was diagnosed in an index patient after CVST in a risk situation. Anticoagulation with warfarin was stopped after 12 months when the first pregnancy was planned. Pregnancy and spontaneous delivery (2020) was uncomplicated. A second pregnancy was interrupted because of acute cytomegalovirus infection and the third pregnancy was successful in 2022. Pregnancies were accompanied by thromboprophylaxis with enoxaparin 40 mg once daily until 6 weeks postpartum. Substitution of fibrinogen has not become necessary in the index patient so far. Genetic analysis revealed a novel missense mutation (p. Arg510Cys) in the *FGA* gene ("fibrinogen Bonn") in the index patient, as well as an asymptomatic sister, and their father who experienced recurrent pulmonary embolism. Surface exposure of wild-type Arg510 suggested the mutated Cys510 to form nonnative disulfide bonds with surface-exposed reactive cysteines from other plasma proteins like albumin leading to formation of aggregates and impaired fibrinolysis.

Conclusions   Fibrinogen Bonn might be associated with an increased risk of thrombosis, possibly due to impaired polymerization.

Keywords
► dysfibrinogenemia
► thrombosis
► genetics
► pregnancy
► anticoagulation

Zusammenfassung

Schlüsselwörter
► Dysfibrinogenämie
► Thrombose
► Genetik
► Schwangerschaft
► Antikoagulation

Bei der Dysfibrinogenämie handelt es sich um einen qualitativen Defekt des Fibrinogens, der mit einem erhöhten Thromboserisiko, einer Blutungsneigung oder einer Kombination beider einhergehen kann. Als Ursache sind verschiedene Mutationen beschrieben, die jedes der drei Fibrinogen-Gene betreffen können. Wir schildern den Fall einer 36jährigen Patientin mit Dysfibrinogenämie und zwei erfolgreichen Schwangerschaften unter prophylaktischer Antikoagulation nach einer cerebralen Venen- und Sinusthrombose (CVST).

Methoden   Zusätzlich zur plasmatischen Gerinnungsdiagnostik erfolgte eine Sequenzierung der Fibrinogen-Gene *FGA*, *FGB* und *FGG*. Die Struktur-Funktions-Analyse der erstmalig beschriebenen Mutation erfolgte in silico.

Ergebnisse   Die Dysfibrinogenämie der Patientin wurde nach Auftreten einer Risiko-assoziierten CVST diagnostiziert. Eine Antikoagulation mit Warfarin wurde 12 Monate nach CVST bei Kinderwunsch beendet. 2020 und 2022 erfolgten jeweils unter prophylaktischer Antikoagulation mit Enoxaparin 40 mg täglich zwei komplikationslose Schwangerschaften und Entbindungen, die Substitution von Fibrinogen war nicht erforderlich. Eine dazwischenliegende Schwangerschaft wurde aufgrund einer Cytomegalievirus-Infektion beendet. Molekulargenetisch ließ sich bei der Indexpatientin, einer asymptomatischen Schwester und dem Vater, der rezidivierende Lungenembolien erlitten hatte, eine Missense-Mutation (p. Arg510Cys) des *FGA*-Gens („Fibrinogen Bonn") erstbeschreiben. Die Oberflächenexposition von Wildtyp Arg510 lässt vermuten, dass mutiertes Cys510 nicht-native Disulfid-Brücken mit reaktiven Cysteinen auf der Oberfläche anderer Plasmaproteine wie Albumin bildet. Dies könnte zur Bildung von Aggregaten und einer beeinträchtigten Fibrinolyse führen.

Schlussfolgerung   Fibrinogen Bonn ist aufgrund einer gestörten Polymerisationsfähigkeit möglicherweise mit einem erhöhten Thromboserisiko assoziiert.

Introduction

Fibrinogen, a 340-kDa plasma protein, is composed of two identical molecular halves each consisting of three non-identical Aα-, Bβ-, and γ-chain subunits held together by multiple disulfide bonds. Fibrinogen is shown to have a trinodular structure; that is, one central nodule, the E domain, and two identical outer nodules, the D-domains, linked by two coiled-coil regions.[1]

The fibrinogen protein chains are encoded by three genes (OMIM: *FGA* *134820, *FGB* *134830, *FGG* *134850) grouped in a cluster of about 50 kb on chromosome 4q23-32.[2] After full processing and construction inside the endoplasmic reticulum (ER) and Golgi organelles, there are 610, 461, and 411 amino acids in the final configurations of the human Aα, Bβ, and γ chains, respectively.[3] Fibrinogen is synthetized by hepatic parenchymal cells[4] and its plasma concentration ranges between 150 and 350 mg/dL.

Fibrinogen plays an important role in coagulation by supporting platelet aggregation in primary hemostasis and fibrin clot formation as its substrate in secondary hemostasis. Moreover, fibrinogen participates in other biological actions such as immune response, tissue repair, angiogenesis, and maintenance of pregnancy.[5]

Because of the complexity of the fibrinogen molecule, both quantitative (afibrinogenemia, hypofibrinogenemia) and qualitative (dysfibrinogenemia and hypodysfibrinogenemia) fibrinogen deficiencies may cause a large spectrum of symptoms associated with hemorrhage and thrombosis.[5] Several types and subtypes of inherited dysfibrinogenemia have been recently classified according to recommendations of the International Society of Thrombosis and Hemostasis.[6] Dysfibrinogenemia may cause structural fibrinogen changes leading to either defective fibrin polymerization or impaired fibrinolysis.[7] In the majority of cases, dysfibrinogenemia is an autosomal dominant disease caused predominantly by heterozygous mutations in one of the fibrinogen genes (*FGA*, *FGB*, or *FGG*). The prevalence of dysfibrinogenemia is unknown. Nevertheless, this type of fibrinogen deficiency is less common than hypofibrinogenemia (Ivaskevicius et al, unpublished data). For the management of dysfibrinogenemia patients, there is no evidence-based guidance available, which is especially true in the case of pregnancy.

Here, we report clinical data, including the management of two successful pregnancies, and provide a characterization of a novel potentially pathogenic missense mutation in the *FGA* gene in a 36-year-old female with inherited dysfibrinogenemia.

Methods

Functional and Immunological Analysis of Fibrinogen Levels in Plasma

Peripheral venous blood samples were collected in tubes with citrate anticoagulant (10.5 millimolar [mM] final concentration; Sarstedt, Nümbrecht, Germany) and centrifuged for 10 minutes at $2,500 \times g$ within 4 hours after blood collection. The obtained plasma was introduced to analysis or frozen at $-40\,°C$ until the measurement was performed. Both functional and immunological analysis of fibrinogen was performed using an Atellica Coag 360 coagulation analyzer (Siemens Healthineers, Erlangen, Germany).

The Clauss method was applied for functional measurements using the Dade Thrombin reagent (Siemens). In brief, diluted plasma was incubated at 37 °C prior to the addition of the pre-warmed (37 °C) thrombin reagent. Functionally active fibrinogen was calculated from measured clotting times based on a fibrinogen standard curve. The measurement

Table 1 Sequencing primers

FGA	Sequence (5′–3′)
FGA 1F	TGG GAT ACC AAC AGC ATA GG
FGA 1R	AGG CCT GGG GTC ATA AAG
FGA 2F	TAA GAA ACC TGA AGC TTG CC
FGA 2R	AAA CAG TGC TCT TGG GAG TAG
FGA 3F	CCT ACT TTT AAG CCA ACT TAT CTG
FGA 3R	TCA GGG ATA TTA TGA AGG TAT GTG
FGA 4F	GCC CCA TAG GTT TTG AAC TC
FGA 4R	GAC AGG GAC TGA ACA TTT GC
FGA 5.0 F	TGA AAC CAG TTT CCA GAA GGA
FGA 5.0 R	CTG CGG CAT GTC TGT TAA TG
FGA 5.1F	CCA GTT CCA GAC TTG GTT CC
FGA 5.1R	CCG GTA CTA CCA GGT CTA GGG
FGA 5.2F	AAC CCT GGG AGC TCT GG
FGA 5.2R	CAG ACA ATG TGC CTA AAT CC
FGA 5.3F	TCG TTC ATG CTC TAA AAC CG
FGA 5.3R	TTT CAA TGA CGT GTA ACA GAG AG
FGB	**Sequence (5′–3′)**
FGB 1F	CCT AAC TTC CCA TCA TTT TGT CC
FGB 1R	AAA ACA CAT CTT ACA TTA GCT AAG CC
FGB 2F	CAC TAT CAC CAA CCA GCC AG
FGB 2R	AAG CCT AAA CCA AAG GCC C
FGB 3F	TTG CCA CTG CCT TTG TTT AG
FGB 3R	CTT GCT GAT GTC AGA CTG GG
FGB 4F	GCG CCA AAT CAT TTC CAC
FGB 4R	GCC AGT CCA AAA CAC AAC TG
FGB 5F	TCC TCA AAA CTG GGT TGG AC
FGB 5R	GGC TCA AGC TAT CAG CCC AC
FGB 6F	AAG CAC TTG CAG TTT CCA AAG
FGB 6R	TTT CCA AGC CAA TAT TCA CC
FGB 7F	TGG AAG CCT GTT TTA GGC AG
FGB 7R	GAA ATG CTT TCG AGT GAT GC
FGB 8F	TAG GGC ACA GGA GGT CTT TG
FGB 8R	AAA AGT CAC ACT CAC GTC TGC
FGG	**Sequence (5′–3′)**
FGG 1 + 2F	GGT AAT TCA GGT GAT GGC AG
FGG 1 + 2R	GCC AGA TGA TAT TTA TGA GGG
FGG 3 + 4F	TCC CTC ATA AAT ATC ATC TGG C
FGG 3 + 4R	AAT CAG GCA TAA TGT CAC TGG
FGG 5F	TCA GGT CCA CAT TGT ATT CC
FGG 5R	GCT ATT CAA GAA AGG TCT AGA CAA C
FGG 6F	TTT AAA AGG AAT GCT GAT GTG
FGG 6R	CTC TTA GGG CTA TTG CAA GG
FGG 7F	GGC CAA GAT CAC TTA GTT GG

Table 1 (*Continued*)

FGA	Sequence (5′–3′)
FGG 7R	GGC TGG ATG TGC TGT TTG
FGG 8F	TCA ATG AGC AAA TTT CAG CC
FGG 8R	TCC ACT TCC AGT TTC AAA GAA C
FGG 9F	TTGA TAT TTT AGG AAT CTT TGG AG
FGG 9R	GAG TTT TAA TTT CCA TTG AAG GC
FGG 10F	TTT AGA GTT TCA AAT TCC CAG G
FGG 10R	TGT AAC TCC CAA AGA GTT AGG C

range was 40 to 900 mg/dL, and the reference interval was 180 to 355 mg/dL.

Immunological analysis of fibrinogen was performed using the LIAPHEN FG assay kit (Hyphen Biophen, Neuville-sur-Oise, France). In brief, latex particles coated with a polyclonal rabbit antihuman fibrinogen antibody were mixed with the diluted patient sample. Measured agglutination was proportional to the immunological content of fibrinogen in the sample as determined by the use of a corresponding standard curve. Other coagulation tests were done using standard procedures.

DNA Isolation, PCR, and Sequencing

All genetic analyses were performed in the Department of Molecular Haemostaseology, Institute for Experimental Hematology and Transfusion Medicine, University Hospital Bonn.

Genomic DNA was isolated from peripheral whole blood using the Blood Core Kit (Qiagen, Hilden, Germany).

Molecular genetic analyses included sequencing of all coding regions and intron/exon boundaries of the following genes: *FGA*, *FGB*, *FGG*. The sequencing analyses were carried out on ABI Prism 3130 genetic analyzer (Thermo Fisher Scientific, Langenselbold, Germany). Data were evaluated by SeqScape Version 2.7 (Thermo Fisher Scientific). Primers are listed in ►Table 1.

For the description of sequence variations at the DNA and protein level, the guidelines of the Human Genome Variation Society (HGVS) were used. The genetic variant interpretation and criteria used to establish variant pathogenicity was performed according to ACMG (American College of Medical Genetics) and AMP (Association for Molecular Pathology) guidelines for the interpretation of sequence variants.[8] The disease causality of genetic variants was compared in Human Gene Mutation Database (HGMD)[9] and ClinGen database.[10]

Informed patient consent was obtained in accordance with the Declaration of Helsinki.

In Silico Analysis

The structural-functional implications of the mutation (new nomenclature: p. Arg510Cys, old nomenclature: Aα Arg491Cys) were analyzed in silico using the alpha fold full model of fibrinogen alpha chain (https://alphafold.ebi.ac.uk/entry/P02671), since the regions in which the

mutation has been reported are missing in fibrinogen's main crystal structure (PDB ID: 3GHG). Visual analysis and image rendering was done on the YASARA platform.

Results

The propositus was a 36-year-old Caucasian female from Belgium. Because of increased menstrual bleeding she received oral contraceptives containing ethinylestradiol (Microgynon) from the age of 18 years onward. A periorbital hematoma provoked by a bicycle accident required no further medical treatment. At the age of 30 years she was admitted to the hospital in the United Kingdom with severe sudden-onset headache 3 days prior to admission. In the preceding 2 weeks she had been suffering from mild headache, which became increasingly worse. These symptoms appeared after a flight of more than 6 hours while under hormonal contraception. A head CT venogram revealed acute thrombosis within the vein of Galen, straight, right, transverse, and sigmoid sinuses in the brain. An initial thrombophilia screen showed no abnormalities. Initial anticoagulant treatment consisted of intravenous heparin infusion which was later converted to warfarin with subcutaneous enoxaparin as bridging therapy. Combined oral contraceptives were replaced by desogestrel pills to avoid menorrhagia. In the same year, a further thrombophilia screening was performed in another laboratory in Germany showing a decreased functional fibrinogen level (128 mg/dL, normal range: 170–420 mg/dL). Nevertheless, no further investigations (immunological fibrinogen, thrombin time [TT] and reptilase time [RT]) were performed. An MRI with contrast 7 months after CVST showed a significant reduction of the thrombosis and incomplete recanalization. Anticoagulation with warfarin was continued. Eventually, dysfibrinogenemia was diagnosed in 2019 in our institution. The patients' fibrinogen levels (Clauss method) were mildly decreased (129–138 mg/dL, normal range: 180–355 mg/dL) and the fibrinogen antigen levels were within the normal range (276–301 mg/dL). TT and RT were slightly prolonged, 24.9 to 28.6 seconds and 22.8 to 23.4 seconds, respectively (normal ranges for both parameters: < 20.5 seconds). Genetic analysis revealed a heterozygous missense mutation in the terminal part of the FGA gene (c.1528C > T, p. Arg510Cys) encoding the αC domain (►Fig. 1). No mutations were found in the FGB and FGG genes. The same genetic defect in the FGA gene was confirmed in the patients' father and sister who also showed a phenotype of dysfibrinogenemia.

Approximately 12 months after the CVST she discontinued warfarin and desogestrel and switched to SC administration of enoxaparin (40 mg once daily [OD]), and became pregnant within a few months. From the second trimester (►Fig. 2), functional fibrinogen levels normalized (178–260 mg/dL) and fibrinogen antigen levels remained stable (278–390 mg/dL). TT and RT also normalized. The entire course of the pregnancy was uncomplicated. No fibrinogen substitution was required. Spontaneous delivery in 2020 was uncomplicated and not associated with increased bleeding. Thrombosis prophylaxis with enoxaparin was continued
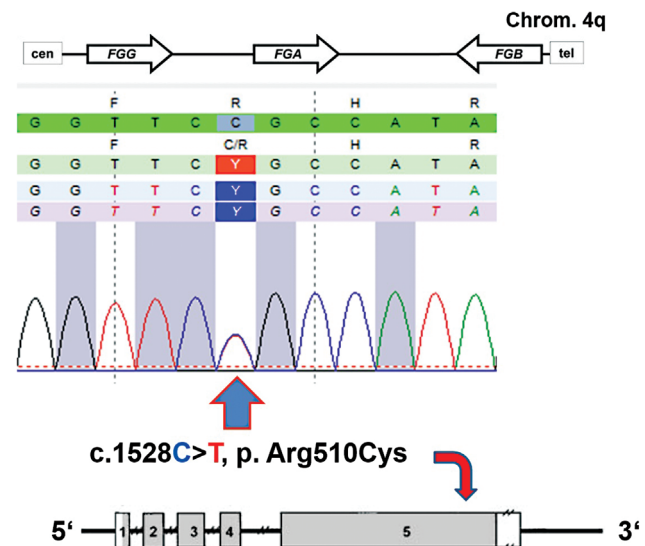

Fig. 1 Identification of a missense mutation in exon 5 of the FGA gene. A point mutation was detected in the terminal part of exon 5 resulting in cytosine (C) exchange to thymine (T) at nucleotide position 1528 (c.1528) and at codon 510 (CGC- > TGC, Arg- > Cys).

postpartum for 6 weeks. The patient became pregnant again in 2021 and thrombosis prophylaxis with enoxaparin in the same dosage as before was reinitiated. Because of a cytomegalovirus infection, the pregnancy was discontinued in the 10th week of gestation (WoG). Enoxaparin was stopped prior to curettage. Nine days after the procedure, she experienced Hb-relevant vaginal bleeding with massive coagulated discharge. A single dosage of 1 g tranexamic acid was administered intravenously without substitution of fibrinogen. Approximately 6 months later (December 2021), she became pregnant again. Again, thromboprophylaxis with enoxaparin was reinitiated (40 mg OD). Due to vaginal bleeding (spotting) in the 7th WoG, the enoxaparin dose was reduced from 40 to 20 mg for several weeks and thereafter continued at the previous dosage. The further course of the pregnancy and a spontaneous delivery (2022) were uncomplicated. Enoxaparin was discontinued 6 weeks postpartum. To date, the patient is still breastfeeding and has no menstrual bleeding. We are planning to initiate gestagen-based contraception and anticoagulation with low-dose rivaroxaban in the future.

Family Data

The pedigree of the index patient (III.6) is shown in ►Fig. 3. The paternal grandfather (I.2) experienced ischemic stroke at the age of 53 years. The father II.4 (born 1961) experienced two unprovoked events of pulmonary embolism (2011 and 2015) and is under long-term anticoagulation (acenocoumarol). So far, he has experienced no surgery. His fibrinogen level (Clauss) was reduced (145 mg/dL) and his fibrinogen antigen level was normal (287 mg/dL). An asymptomatic sister (III.8) was born in 1989 and has been under oral contraceptives (containing estrogen) for more than 15 years. Prior to oral contraception, she experienced heavy menstrual bleeding. She has no children. An appendectomy (2010)
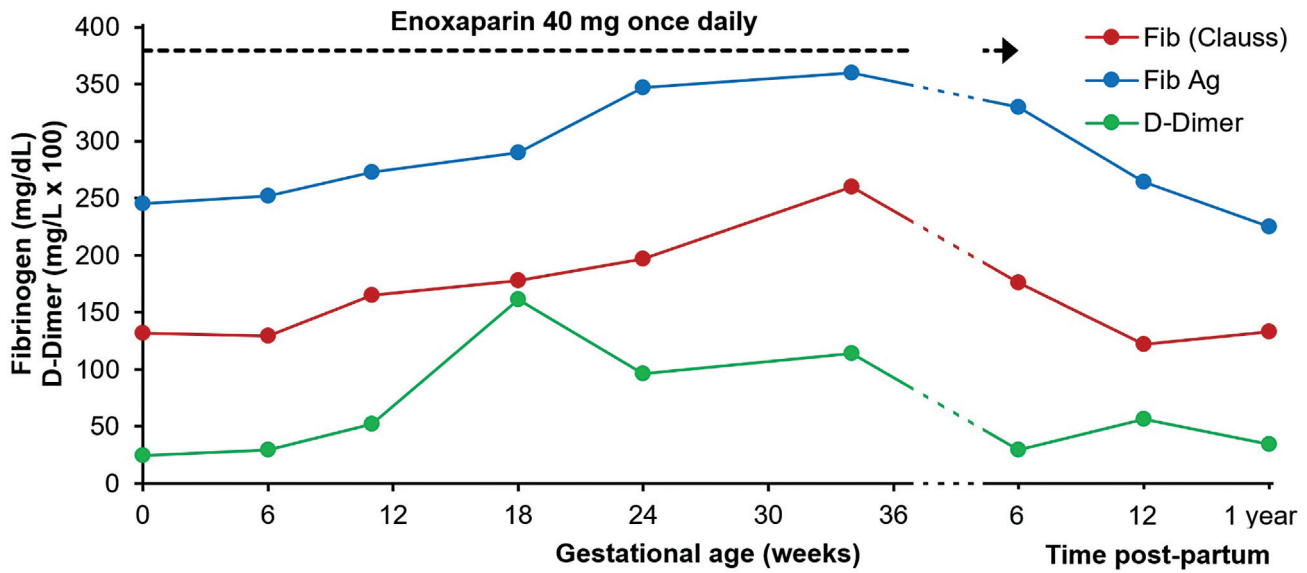
Fig. 2 Fibrinogen values and D-dimer levels during the first pregnancy. From the second trimester fibrinogen values started proportionally to increase. The D-dimers were unexpectedly low during the whole pregnancy.
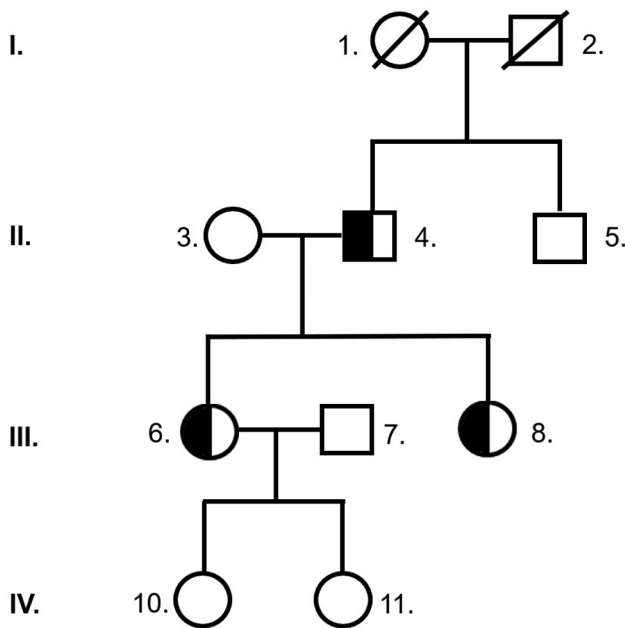

Fig. 3 Pedigree of the propositus (III.6). Among index patient, two further family members (II.4 and III.8) with dysfibrinogenemia were investigated in this study.

was uncomplicated. Her fibrinogen level (Clauss) was reduced (148 mg/dL) and fibrinogen antigen level was normal (312 mg/dL). Both daughters (IV.10 and IV.11) of the propositus have not been investigated so far. A potentially pathogenic missense mutation in the *FGA* gene (p. Arg510Cys) was identified in the propositus (III.6), her father (II.4), and sister (III.8). Other family members have not been investigated.

In Silico Analysis

The local structural environment of the affected residue Arg510, as observed on the alpha fold model of fibrinogen alpha chain, showed that it is located on a surface-exposed short helix located within an essentially long disordered region extending from residue 485 all the way to residue 630 (►Fig. 4). The flexibility of this long disordered region suggests that when folding, this part, unless it is restrained by contacts with other regions of the alpha chain will act as a very flexible bridge between residues 485 and 630 which are on the opposite surface ends of the primary long helix of the fibrinogen alpha chain. Mutation to a cysteine residue at this location can prompt the formation of nonnative disulfide bonds with proximally located unpaired cysteines like Cys491 during the folding process. The surface-exposed character of the wild-type Arg510 also means that, if the mutated cysteine residue is also surface exposed, it could possibly form the nonnative disulfide bonds with surface-exposed reactive cysteines from other proteins like albumin leading to formation of aggregates and possibly thrombosis (►Fig. 4).

Discussion

Here we describe a family with inherited dysfibrinogenemia (type 3B, according to the new ISTH classification, Casini et al[6]) caused by a novel potentially pathogenic missense mutation in the *FGA* gene. To the best of our knowledge, this mutation was not reported elsewhere. We may propose to denominate p. Arg510Cys variant as "Fibrinogen Bonn," since it was detected and described in Bonn (Germany). The p. Arg510Cys variant seems to be associated with a high risk of venous thrombosis. Two of three family members with this mutation experienced thrombosis. Along with the increased risk of thrombosis, affected females experienced increased menstrual bleeding (Hb relevant), although functional fibrinogen levels were above 120 mg/day in both sisters.
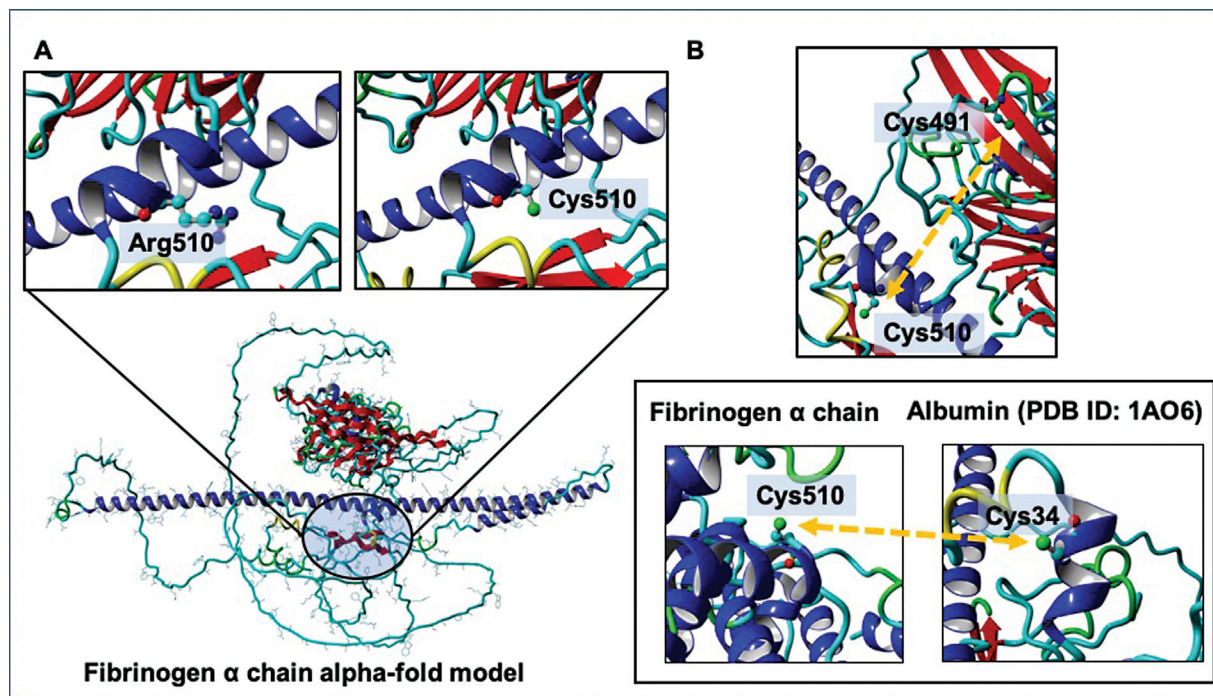
Fig. 4 The figure has two panels: Panel **A** shows the local molecular environment of residue 510 in the alpha fold model of the fibrinogen α chain in the presence or absence of the Cys substitution. Panel B shows the two possibilities of nonnative disulphide bond formation when there is a substitution to Cys at the residue 510.

Management of pregnancy in dysfibrinogenemia is challenging. There are no evidence-based guidelines on how to perform treatment. Because of prior thrombotic events in the personal and familial history of our propositus, we decided to initiate thrombosis prophylaxis with enoxaparin at standard dosage (4,000 IE daily) and fibrinogen supplementation or treatment with antifibrinolytics to consider only in case of bleeding events. Fortunately, functional fibrinogen levels during the first pregnancy (and third pregnancy) normalized from 128 mg/dL in the 6th WoG to 260 mg/dL in the 34th WoG, thereby reducing the risk of spontaneous bleeding. This data are especially valuable since so far, not enough data have been available on the variation of fibrinogen levels during pregnancy in the setting of dysfibrinogenemia.[11] Because of the increased risk of both thrombosis and bleeding in pregnant women with known dysfibrinogenemia, management should be performed by a multidisciplinary team consisting of obstetricians, hematologists (coagulation specialists), and anesthesiologists.[11,12]

Dysfibrinogenemia is usually associated with either defective fibrin polymerization or impaired fibrinolysis.[7] As shown by in silico analysis, fibrinogen Bonn is located in a terminal part of the αC domain and might predict formation of nonnative disulfide bonds with surface-exposed reactive cysteines from other plasma proteins like albumin. As reviewed by Soria et al,[13] abnormal fibrinogens with either a point mutation in the αC domain or a frameshift mutation resulting in the absence of a part of the αC domain are often

associated with either thrombotic events or bleeding. Mutation of an amino acid into cysteine or a frameshift mutation yielding an unpaired cysteine in the αC domain is often responsible for thrombotic events. Covalent binding of albumin to the unpaired cysteine via a disulfide bridge leads to decreased accessibility to the fibrinolytic enzymes, hence formation of poorly degradable fibrin clots, which explains the high incidence of thrombosis.

A previously described p. Arg573Cys (according to old nomenclature: Aα Arg554Cys) molecular defect in the *FGA* gene, also known as fibrinogen "Dusart," was found to be associated with thrombophilia showing thinner fibers compared to normal fibrin in electron microscopy and immunoblot analysis of plasma fibrinogen demonstrated a substantial part of the fibrinogen Dusart molecules to be disulfide linked to albumin. Molecular abnormality in fibrinogen Dusart resulted in defective lateral association of the fibrin fibers and disulfide-linked complex formation with albumin and was associated with a family history of recurrent thrombosis in the affected individuals.[14]

A further missense mutation (p. Ser551Cys, according to old nomenclature: Aα Ser532Cys) in the αC domain, also known as "Caracas V," also was associated with thrombophilia.[15]

To summarize, due to possibly impaired polymerization, fibrinogen Bonn might be associated with increased thrombosis requiring long-term anticoagulation and also thrombosis prophylaxis in pregnancy. Contraceptives containing estrogens should be, if possible, avoided in females with fibrinogen Bonn.

What is known about this topic?

- Dysfibrinogenemia is a rare coagulation disorder resulting in qualitative fibrinogen deficiency.
- There is no evidence-based guidance for the treatment of inherited dysfibrinogenemia, especially during pregnancy.

What does this paper add?

- Fibrinogen Bonn (p. Arg510Cys) in the αC domain might be associated with increased thrombosis risk possibly due to impaired fibrinolysis phenomena.
- Thromboprophylaxis in pregnancy (in case of fibrinogen Bonn) is essential to prevent thrombotic events.
- Fibrinogen Bonn seems "to keep" acute phase protein status in pregnancy preventing bleeding complications.

Conflict of Interest

VI, AB, SS, US, SR, HR and AP have no conflict of interest. BP received grants for research from Biotest and Octapharma, Consulting fees from NovoNordisk and Octapharma as well as personal fees for lectures from Octapharma and travel support from NovoNordisk and Octapharma.
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