scientific reports

Check for updates

OPEN

A familial study of a de novo FGG gene mutation causing congenital hypofibrinogenaemia and intervention during pregnancy and childbirth

Zehui Xie[1], Hongrui Li[2], Yarong Guo[1], Bin Mao[2,3], Jing Wang[1,2], Min Gao[1] & Xiaoling Ma[1,2,3]✉

To investigate the family line of a pregnant woman with congenital hypofibrinogenaemia due to a de novo mutation in the fibrinogen gamma (FGG) gene and experimentally explore its molecular pathological mechanisms. Peripheral blood specimens were collected from the proband and her family members for coagulation tests to assess their coagulation function. Whole exome sequencing was used to determine the gene mutation in the family lineage. SDS-PAGE was utilized to analyze the plasma of the proband and her mother for their congenital hypofibrinogenaemia. Structural distribution was analyzed by scanning electron microscopy. Molecular modeling was performed to predict the effect of mutation sites on fibrinogen structure and function. A de novo heterozygous mutation in the FGG gene was identified: c.702G>T, with a markedly prolonged thrombin time. The thromboelastography results showed that her fibrinogen function was essentially normal. LC-MS/MS showed no plasma or mutant chains in the plasma. Molecular modeling showed that this de novo mutation altered the structure of fibrinogen in the patient and her fibrinogen was heterogeneous in diameter and sparsely networked under electron microscopy. An intermittent infusion of 6 g of fibrinogen in the prenatal period of the proband brought the fibrinogen level of the patient to 2.13 g/L. No significant haemorrhage was detected between and after the caesarean section. The FGG gene NM_021870.3: c.702G>T (p.Trp234Cys) mutation is a de novo mutation, which is heterozygous in both the proband and her mother. It's the biogenetic basis for the pathogenicity of this congenital hypofibrinogenaemia family line.

Keywords FGG gene, Fibrinogen, Congenital hypofibrinogenemia, Maternal interventions

Also known as coagulation factor I, fibrinogen is the most abundant coagulation factor in plasma that binds to each other to form fibrin clots, mediates platelet aggregation and plays a vital role in the process of blood clotting[1]. It is a symmetrical dimeric molecule consisting of two similar subunits. The three peptide chains that make up the subunits are encoded by fibrinogen alpha, beta and gamma (FGA, FGB and FGG) genes.

Among the three genes, the FGG gene encodes the gamma chain, the gamma chain plays a crucial role in determining fibrinogen concentration, whose concentration is associated with coagulation disorders[2], which may result in either impaired coagulation or thrombosis.

Congenital hypofibrinogenemia is a rare inherited disease characterized by mutations leading to impaired fibrinogen synthesis or secretion[3]. The clinical presentation of patients is complex and variable, including no symptoms[4], haemorrhage, thrombosis and the coexistence of haemorrhage and thrombosis, with a spontaneous haemorrhage rate of nearly 20%[5]. In women, the main clinical manifestations are excessive menstruation, fibrinogen hydration below 1.5 g/L, and complications such as placental abruption, recurrent miscarriage, postpartum haemorrhage and thrombosis during pregnancy and childbirth[6–8]. Fibrinogen replacement therapy is the primary maternal intervention for pregnant women with congenital hypofibrinogenemia. However,

[1]The First School of Clinical Medicine of Lanzhou University, Lanzhou 730000, Gansu, China. [2]Reproductive Medicine Center, The First Hospital of Lanzhou University, Lanzhou 730000, Gansu, China. [3]Clinical Research Center for Reproductive Diseases of Gansu Province, Lanzhou 730000, Gansu, China. ✉email: maxl2005@163.com

its clinical use remains controversial as it may lead to an increased risk of thrombosis[9]. The most important maternal intervention for congenital hypofibrinogenemia is fibrinogen replacement therapy.

In this study, a pregnant woman with congenital hypofibrinogenemia was phenotypically validated and genotyped. Possible molecular pathogenesis was elucidated by validation experiments such as gene sequencing, coagulation index tests, molecular modeling, sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE), LC-MS/MS, thromboelastography and scanning electron microscopy. Possible molecular pathogenesis was explored in a pregnant woman with this disease. Maternal intervention strategies were proposed for pregnant women with the disease.

Methodology

Blood sample collection and coagulation measurement

Peripheral blood was sampled from the proband and her mother, uncle and cousin. Informed consent was obtained from all study participants in accordance with the tenets of the Declaration on Helsinki, and gained the approval of the Ethics Committee of the First Hospital of Lanzhou University (LDYYSZLLKH2024-12). Blood samples were measured by the Department of Laboratory Medicine of the First Hospital of Lanzhou University. Additionally, they were analyzed for prothrombin, activated partial thromboplastin and thrombin time (PT, APTT and TT), as well as fibrinogen levels using an ACL TOP700 fully automated haematology analyzer (Werfen Company, China). Fibrinogen was detected using Clauss and PT-derived methods.

Deoxyribonucleic acid extraction and whole exome sequencing

Blood samples from the family line of the proband collected in 2.1 were sent to Suzhou Yikang Medical Testing Co., Ltd. for whole exome gene sequencing. Genomic deoxyribonucleic acid (DNA) was extracted from family members using a blood genomic DNA extraction kit (Tiangen Biotech, Beijing, China) to prepare sample DNA templates. Whole-exome library capture was performed after synthesis by TWIST using custom probes to construct the whole-exome libraries of the proband and her family lineages. Bipartite sequencing was performed using the PE150 mode on the lllumina NovaSeq 6000 (San Diego, California (CA)) sequencing platform. Then, the genome of proband and her family lineages was sequenced using the Burrows-Wheeler Aligner software with the reference sequence of the hg19 version of the human genome provided by UCSC (http://genome.ucsc.edu/). Finally, the variants were identified by GATK v3.70 (Genome Analysis Toolkit). The pathogenicity of the variants was analyzed with reference to the American Society for Medical Genetics and Genomics Standards and Guidelines for the Classification of Genetic Variants.

Extraction and purification of fibrinogen

Fibrinogen was extracted from the sodium citrate anticoagulated plasma of the proband, the proband's mother and healthy controls using a 25% saturated ammonium sulphate solution. After that, the fibrinogen concentration was determined using the bicinchoninic acid (BCA) Protein Concentration Assay Kit (Coolaber, Beijing, China). Fibrinogen from the plasma of the proband individual and her mother was used as a control. Plasma fibrinogen from the proband individual and her mother was subjected to SDS-PAGE on 10% separating gel. The samples were photographed after silver staining.

Liquid chromatograph mass spectrometer/mass spectrometer

The samples were mashed using a glass rod and then decolored sequentially using double distilled water (ddH_2O), decolorizing solution and CAN. The mixture was shaken for 5 min. Then, the sample was centrifuged and the supernatant was discarded. After the addition of Tris(2-carboxyethyl)phosphine hydrochloride (TCEP) and 2-Chloroacetamide (CAA), the mixture underwent 30-min incubation at 60 °C to complete reduction and alkylation. After the addition of Acetonitrile (ACN), the sample was shaken for 5 min and centrifuged, and the supernatant was discarded. An appropriate amount of trypsin was added in accordance with the sample volume, and incubated and shaken at 37 ℃ overnight for digestion. The next day, the peptide extract was added and sonicated for 10 min, followed by the centrifugation and vacuum-drying of the supernatant. Finally, the supernatant was desalted using a C18 desalting column, vacuum-dried and frozen at -20 °C. Then, it was incubated at 37 °C for 10 min. Samples were detected by mass spectrometry using an UltiMate 3000RSLCnano nanolitre liquid tandem Q Exactive HF mass spectrometer (Thermo, the United States of America (USA)).

Thrombus elastography

Samples were assayed using a thromboelastograph (HAS-100; Haemonetics Corporation, USA) within 2 h of sample collection. All reagents were kept at 37 °C before testing. A reagent bottle containing clay was added with citrate anticoagulated blood (1 ml), inverted to mix the contents and then left to incubate. Afterwards, the reaction cup was placed in the test channel, and its bottom was added with 20 µL of calcium chloride ($CaCl_2$). The bottle was stirred to mix the reaction bottle, followed by the addition of 340 µL of whole blood along the top edge of the cup into the cup. After that, the test was performed on the machine.

Scanning electron microscopy of fibrin clots

In this step, 3 µL of plasma was incubated with 1 µL of thrombin (final concentration: 2 U/mL) at 37 °C for 3 h and washed three times with 0.1 M phosphate-buffered saline (PBS; pH 7.4). Next, the samples were fixed for 2 h at 4 °C. The fixed samples were washed three times with 0.1 M PBS (pH 7.4) for 15 min each time, fixed with 1% osmium acid prepared in 0.1 M PBS (pH 7.4) at room temperature and protected from light for 1–2 h. Then, the samples were rinsed again three times with 0.1 MPBS (pH 7.4) for 15 min each time. They were sequentially passed through a graded alcohol series (30%, 50%, 70%, 80%, 90%, 95% and 2 times 100%) for dehydration, each time for 15 min, and finally into isoamyl acetate for 15 min. Later, the samples were put into a critical point dryer

for drying. The dried samples were put into the sample stage of the ion sputterer for gold spraying for about 30 s by tightly sticking to the conductive carbon film on the double-sided tape and then observed under a scanning electron microscope (Hitachi, Japan). The average fiber diameter within the fibrinogen network was analyzed using Image Pro Plus 6.0 software (Media Cybernetics company, Silver Springs, Maryland (MD), USA).

Results

Basic medical history of the family of the patient with prior evidence

The proband was a 32-year-old woman who underwent Intracytoplasmic sperm injection (ICSI) for male factor in 2021–2022. Fibrinogen concentration was 0.65 g/L by the Clauss method and 0.77 g/L by the Fib-derivative method in the forensic patient. Thrombin time (TT) was 22.3 s (Standard Value: 14–21 s), Prothrombin time (PT) was 11.5 s (Standard Value: 10–14 s), and Activated partial thrombin time (APTT) was 22.9 s (Standard Value: 22–38 s), PT and APTT were not significantly abnormal. In addition, 2 g of fibrinogen was given as an intravenous infusion before egg retrieval after a comprehensive evaluation, and 2 u of red blood cells were given for excessive bleeding during the removal of embryos at 6^{+3} weeks of gestation after the 2nd implantation. One child was delivered by caesarean section at 38^{+4} weeks of gestation in the designated hospital. The proband had no history of spontaneous bleeding with normal menstrual flow in the past, but had a long duration of compression at the venipuncture to stop bleeding, namely about 15–30 min. She was given 6 g of fibrinogen in three doses before caesarean section. Fib was regularly tested during pregnancy and delivery (Fig. 1). In addition, the mother of the proband complained of a history of haemorrhage during normal delivery, with FIB: 0.58 g/L. The aunt of the proband had died of a previous cerebral haemorrhage (details unknown), and her uncle and cousin did not complain of any obvious haemorrhagic clinical symptoms (the family tree diagram in Fig. 2).

DNA sequencing results of proband and her family lines

DNA sequencing revealed a missense mutation at chr4:155529767 (NM_021870.3) in the FGG gene of the proband and her mother: c.702G > T, which mutates tryptophan (TGG) at position 234 to cysteine (TGT). It is a mutation that has not been reported in the literature or included in the gnomAD East Asian General Population Database and was assessed as a mutation of unknown clinical significance. However, the uncle and cousin of the proband did not detect any mutation at this locus, and her son was also subjected to locus validation after birth. Again, no mutation was detected (Fig. 3).

Multiple sequence comparison of mutant loci

ClustalX2.1 software (http://www.clustal.org/clustal2/) in the National Center for Biotechnology Information (NCBI) database was used to evaluate conserved amino acid residues in the sequences of 10 species, including humans, chimpanzees, rhesus monkeys, og, mice, rats, pheasants, zebrafish, Xenopus tropicalis and cattle, and find them highly conserved at the mutation site (Fig. 4).

Molecular modeling of amino acid mutations

Molecular simulations showed that a stable hydrogen bond was formed between wild-type Trp234 and Glu296 via NH and carboxyl groups. After Trp234 was replaced by Cys234, however, the change in the nature of the

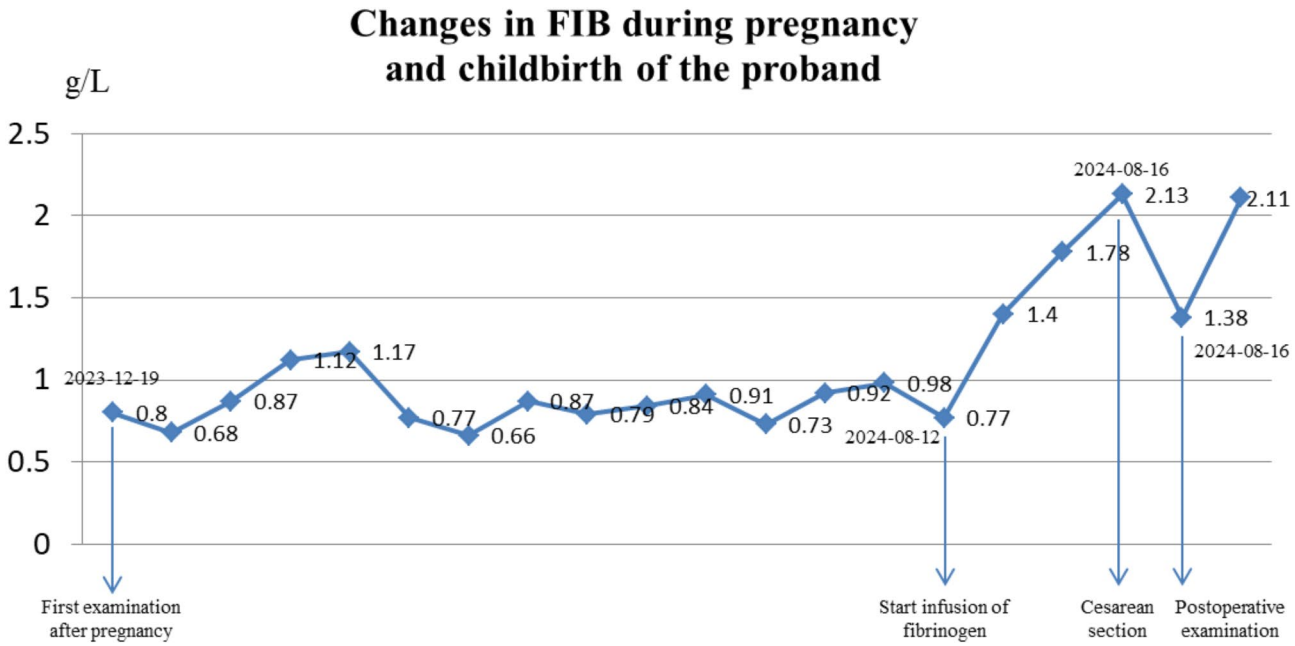

Fig. 1. Changes in FIB during pregnancy and labor in proband.

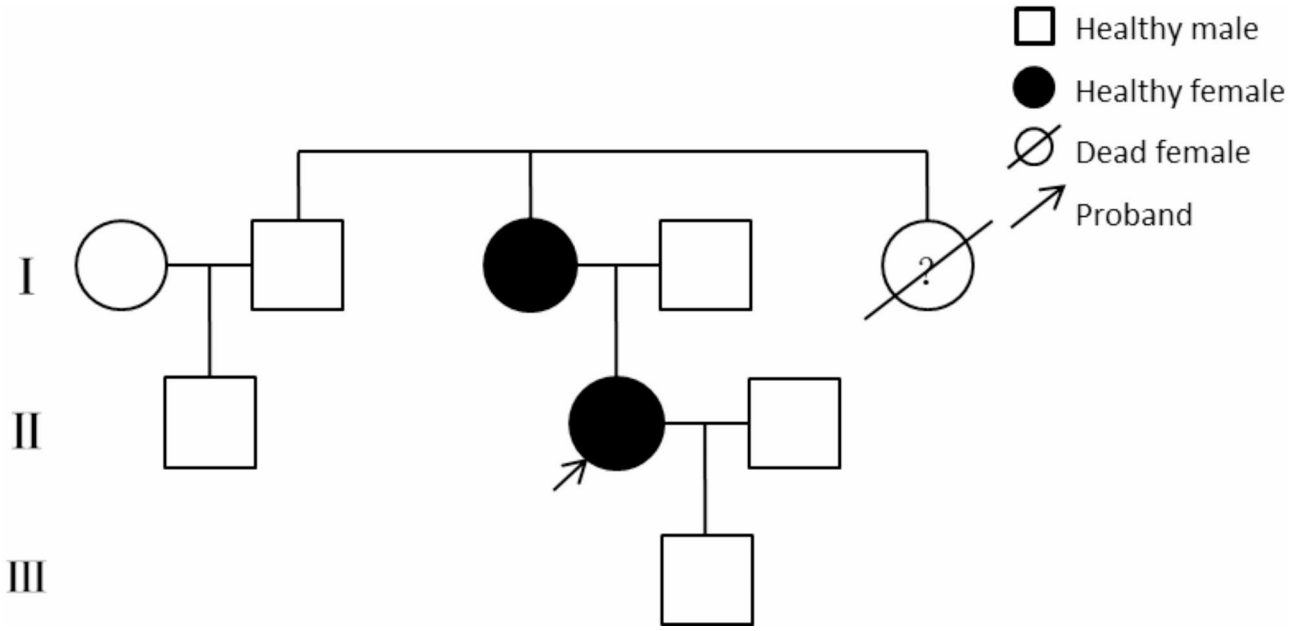

Fig. 2. Family chart of proband.

amino acid resulted in the loss of hydrogen bonding between the two and the inability to continue to maintain the interaction with Glu296 (Figure 5).

SDS-PAGE analysis of proband and her mother

Fibrinogen levels were significantly lower in proband and her mother compared to healthy controls, but no significant difference could be seen in the relative molecular mass of the three fibrinogen peptide chains (Aα, Bβ, and γ) (Fig. 6). This was a result consistent with the detection of fibrinogen levels in proband by the Clauss method.

Mass spectrometry analysis of proband and her mother

The analysis of the fibrinogen fragments of proband showed that only normal peptides were present in plasma and no mutated peptides were detected. This suggested the absence of the mutated peptides in the plasma of the patient (Fig. 7).

Thromboelasticity testing in proband

The pre-pregnancy thromboelastography of the precedent showed that her R value was 4.8 min (normal reference range: 5–10 min), K value was 2.6 min (normal reference range, 1–3 min), Angel was 56.7° (normal reference range: 53–72°), and MA was 34.6 mm (normal reference range: 50–70 mm). These results indicated that the coagulation factor activity of the precedent was essentially normal; fibrinogen function was good but fibrillogenesis and reinforcement were reduced; the coagulation index of proband was − 3.4 (normal reference range: -3 to 3). This suggested that she had a low level of coagulation. Nevertheless, all the abnormal indices improved significantly after the pregnancy of the attestant and continued to do that until she gave birth (Table 1).

Structural changes in the fibrin network of proband and her mother

The fibers of proband and her mother were heterogeneous in thickness and loosely arranged compared with those of normal controls (Fig. 8). The mean fiber diameter was 0.061 ± 0.009, 0.066 ± 0.010 and 0.088 ± 0.008 μm in the fibrin networks of proband, her mother and normal controls, respectively. The mean fiber diameters of fiber networks of proband and her mother were significantly ($P < 0.05$) different from those of normal controls, which indicated significant differences ($P < 0.05$).

Discussion

Congenital hypofibrinogenemia belongs to the type I congenital fibrinogen disorder, namely abnormal fibrinogen content type, with autosomal dominant inheritance as the genetic mode. The relationship between clinical phenotype and genotype is unclear. Among the gene variants included in the human fibrinogen database, FGA gene variants account for the highest proportion, while FGG gene variants account for about 30%, mainly concentrated on exon 8 of the FGG gene. Hypofibrinogenemia is mainly caused by missense mutations of FGG and FGB genes[10]. Congenital hypofibrinogenemia has strong clinical heterogeneity, where some patients have no obvious clinical symptoms, while others show bleeding and/or thrombosis. Therefore, clinical management plans need to be individualized.

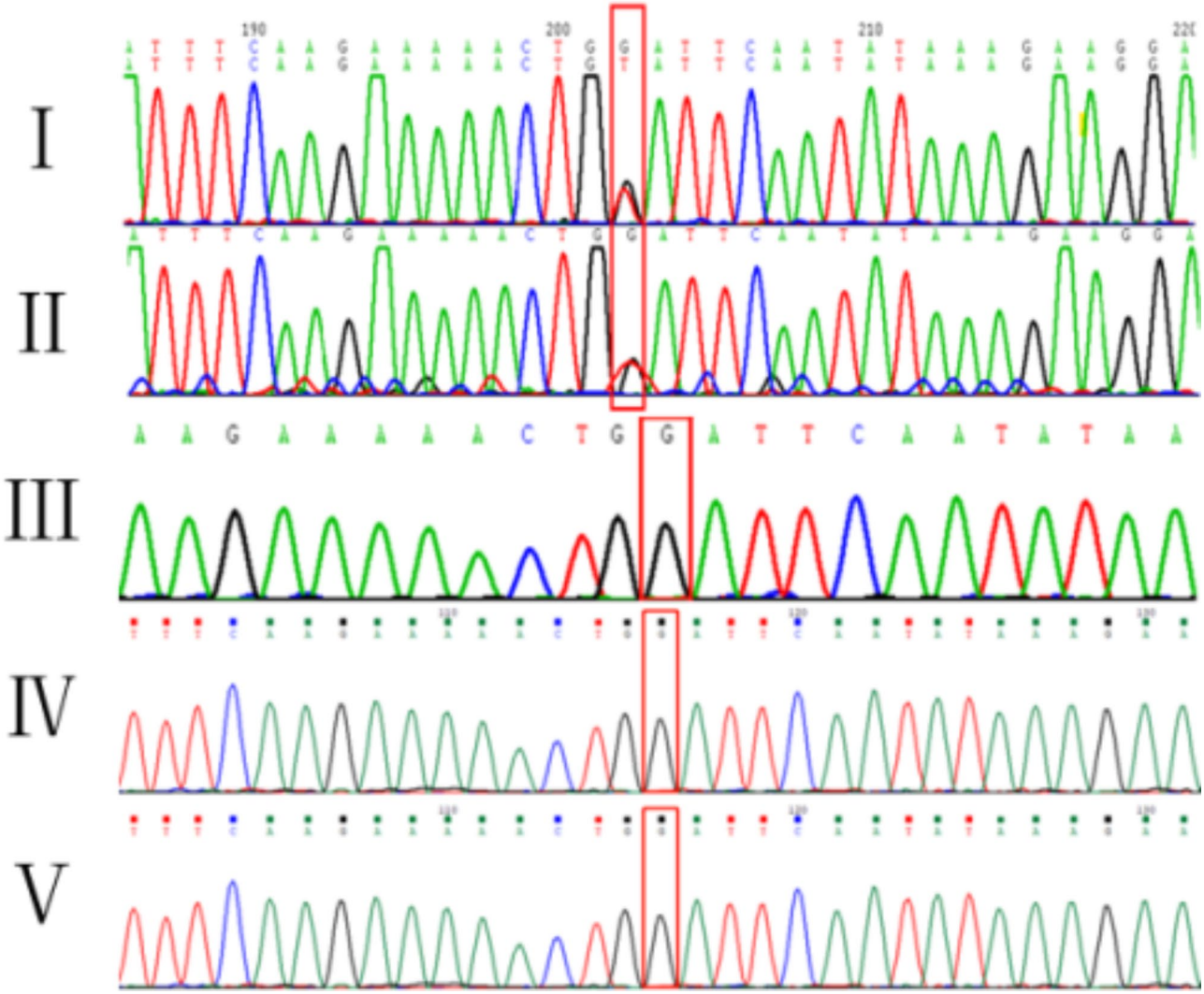

Fig. 3. DNA sequencing results (I: proband; II: mother; III: son; IV: uncle; V: cousin).

In the present study, the patient had no history of excessive menstruation or spontaneous bleeding. The main clinical manifestations were prolonged hemostasis on pressure at the venous puncture site and easy bleeding from the gingiva. In retrospect, the patient had a history of two chemical pregnancy and early pregnancy embryo abortion. The thromboelastography results showed normal fibrinogen activity. The typical coagulation findings in patients with congenital hypofibrinogenemia are a normal or mild prolongation of TT、APTT and PT, and markedly reduced fibrinogen activity by the Clauss method and Fib-Diffraction method[11,12]. Patients' blood test results were consistent with it, which further confirmed the diagnosis of congenital hypofibrinogenemia. Meanwhile, the liquid chromatograph mass spectrometer (LC-MS/MS) results showed the absence of mutant chains in the plasma of the patient, which also confirmed the diagnosis of congenital hypofibrinogenemia instead of congenital hypodysfibrinogenemia[13,14].

The SDS-PAGE analysis showed no significant change in the molecular weight of the three fibrinogen peptide chains and a significant decrease in fibrinogen levels in the proband compared to normal subjects. The results of the proband's mother were in line with those of the proband. The scanning electron microscopy analysis of the proband and her mother showed that the structural fibers of the normal control fibrin clot were of uniform thickness, neatly aligned and overlapped to form thick fibers. However, the fibers of the proband and her mother were of uneven thickness and irregularly aligned, and the fiber network was sparsely and loosely packed. Molecular modeling showed that a very stable hydrogen bonding originally existed between Trp234 and Glu296. Nevertheless, it lacked the corresponding hydrogen bond donor capacity to maintain this interaction after mutation to Cys234. The loss of hydrogen bonding weakened the local structural stability of fibrinogen, which in turn affected its overall structure. The D: D interaction is an important determinant of the structure of the fibrin clot network[15]. This may have led to impaired D: D interactions, which in turn affected the network structure of the fibrin clot. Protein modeling conducted by Tomas et al.[16] suggested that the gamma chain and its C-terminal domain are important for hepatocyte secretion of fibrinogen, and thus the mutations in the gamma chain may affect blood fibrinogen content. Upon the analysis of genetic mutation testing, the proband and her

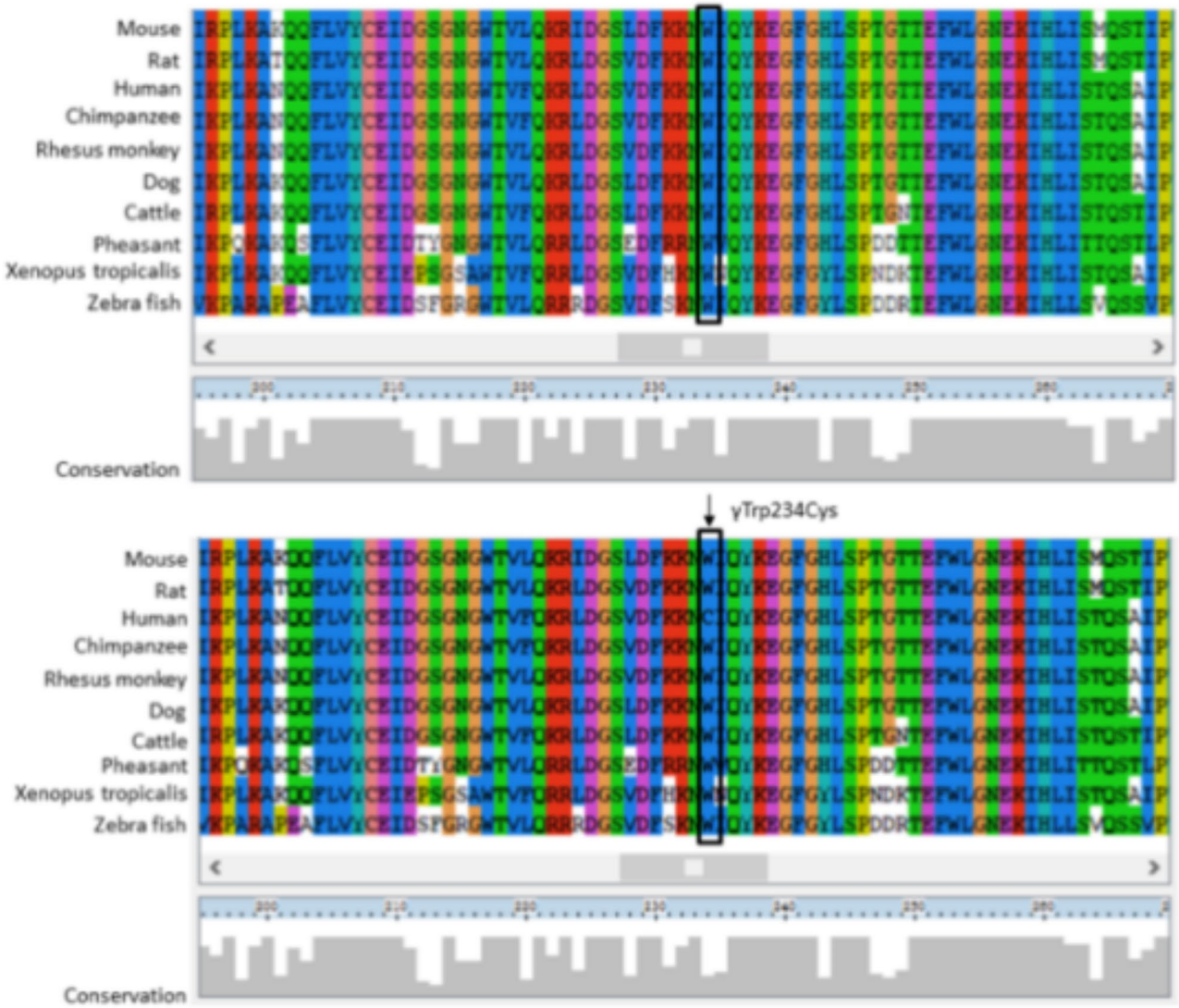

Fig. 4. Multiple sequence comparisons of mutant loci.

mother had a missense mutation at chr4:155529767 (NM_021870.3): c.702G > T. This resulted in a mutation of tryptophan at position 234 (TGG) to cysteine (TGT). Multiple sequence comparisons showed that this site was highly conserved in the amino acid sequence of fibrinogen between species, which indicates that it has an extremely important function for the survival and activity of organisms. This mutation may seriously affect the structure and function of fibrinogen molecules, which was present in the proband and her mother, but normal in her uncle and cousin. Her father and husband refused to undergo genetic testing. (In the pre-pregnancy genetic counseling, considering that congenital hypofibrinogenemia is a rare genetic disease with a low incidence, and a clear maternal heterozygous mutation has been detected in the proband, it is not considered that the father of the proband also carries the same mutation.) The proband complained of the death of her sister-in-law from a previous intracranial haemorrhagic disease. Without definitive genetic testing, however, whether the death of her sister-in-law was related to congenital hypofibrinogenemia was unsure.

Fibrinogen maintains the integrity of the placenta and promotes the completion of the development of the fetal-maternal vasculature. Therefore, pregnancy in women with congenital hypofibrinogenemia is an extremely high-risk condition[17], with the potential for early vaginal bleeding, early miscarriage[18], placental abruption, preterm labor, placenta previa[19] and postpartum haemorrhage and thrombosis[7,20]. Previous studies generally consider that the rate of abortion is higher in congenital hypofibrinogenemia than in normal persons[21,22]. However, a multicenter study in 2023[23] indicates the abortion rate is similar to the general population, but the incidences of retroplacental hematoma, postpartum hemorrhage and thrombosis are higher. In the case of congenital haemorrhage, early miscarriage or vaginal bleeding in early pregnancy is ascribed to unstable blood clots caused by a significant increase in the rate of fibrinogen breakdown during pregnancy[24]. Studies have shown that the most important means of reducing the risk of haemorrhage in pregnant women with congenital hypofibrinogenemia throughout pregnancy and childbirth is to maintain their fibrinogen levels[25,26]. In this case, patients can reach a physiological state of hypercoagulation. Thus, fibrinogen levels need to be closely

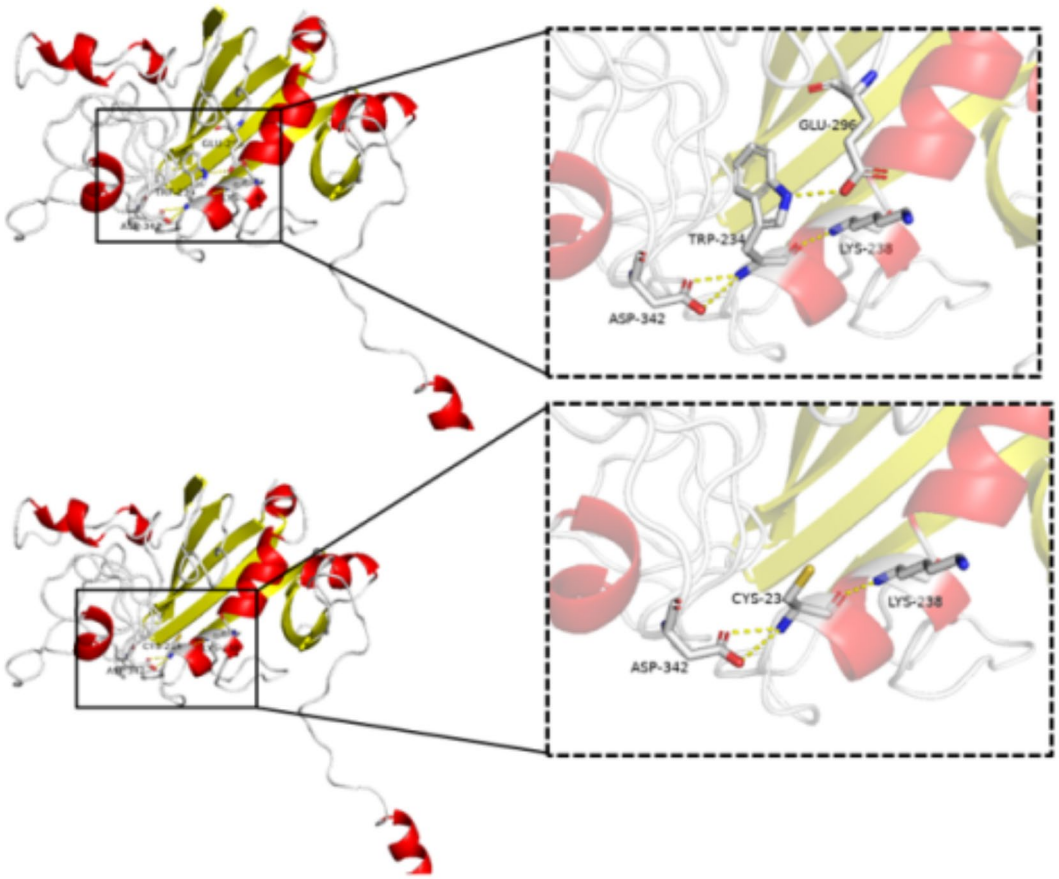

Fig. 5. Schematic representation of the tertiary structure of the wild type (top) and mutant (bottom).

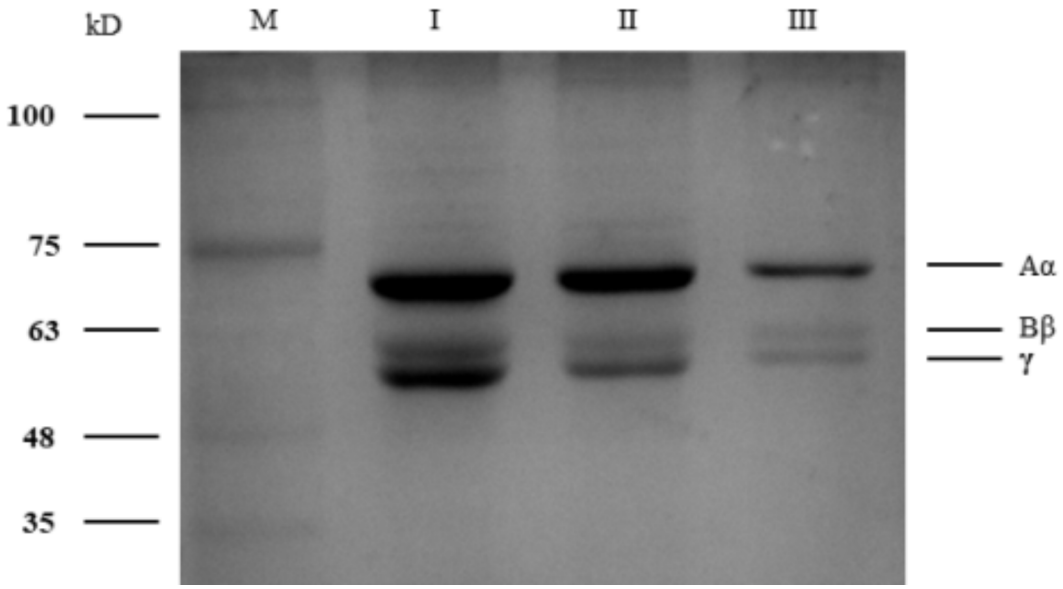

Fig. 6. SDS-PAGE analysis of the proband person and her mother (I: normal; II: proband person; III: mother).

monitored throughout pregnancy[27]. Fibrinogen can be supplemented at the discretion of the blood transfusion service, which can also prevent placental abruption at the middle to late stages of pregnancy[13,28]. Fibrinogen supplementation can be used to prevent placental abruption in the second and third trimesters. However, care should be taken in terms of both duration and dose to avoid thrombosis when fibrinogen is supplemented.

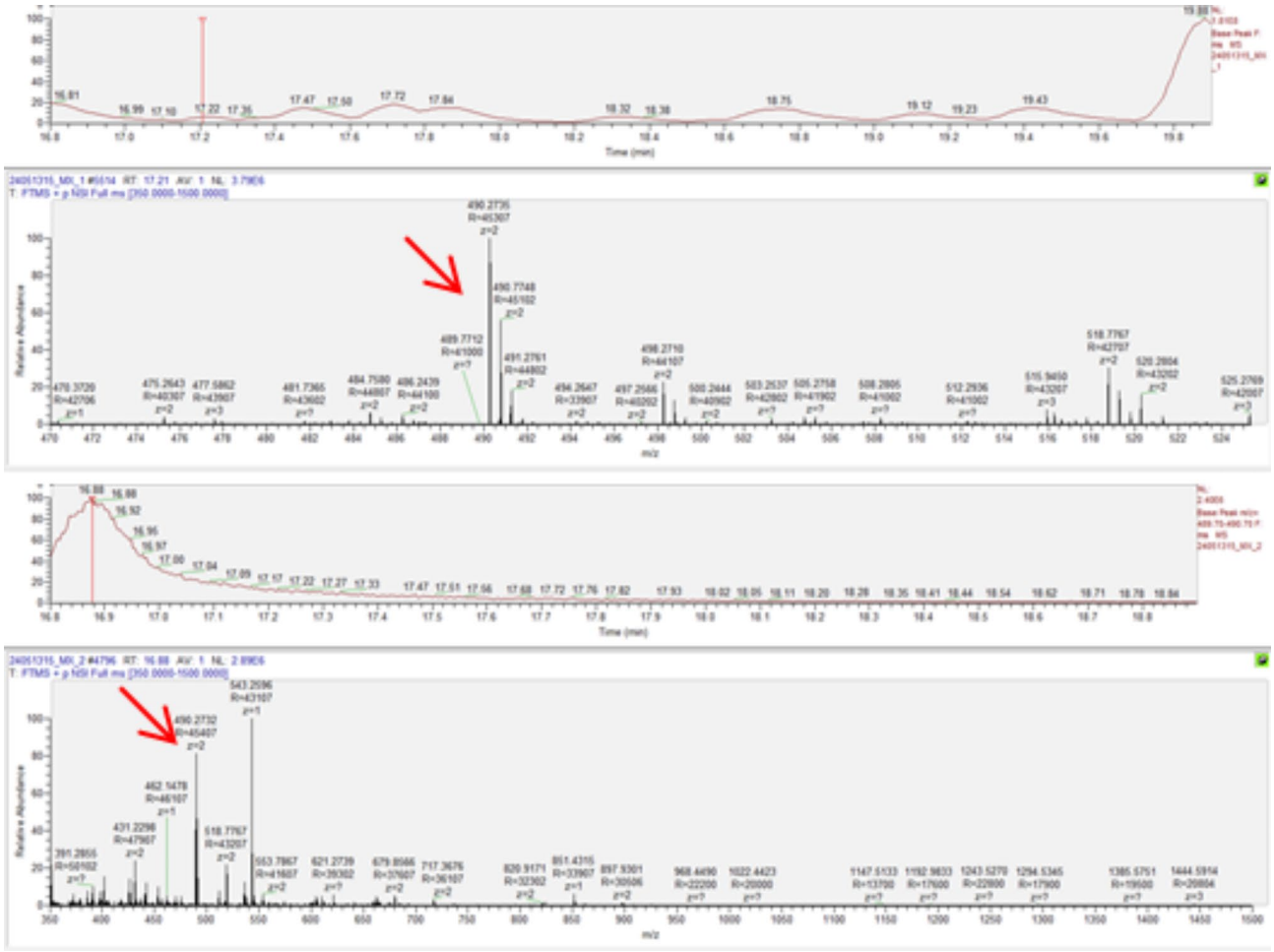

Fig. 7. Mass spectra of the proband and her mother (top: proband, bottom: mother, normal peptides indicated by arrows).

	Before pregnancy	After pregnancy	Standard value
R (min)	4.8	5.1	5–10
K (min)	2.6	2.4	1–3
Angle (deg)	56.7	56.2	53–72
MA (mm)	34.6	53.8	50–70
EPL (%)	0.2	0.0	0–15
CI	-3.4	-1.2	-3-3
LY30 (%)	0.2	0.0	0-7.5

Table 1. Changes in thromboelastography before and after pregnancy in proband.

The reason is that patients with congenital hypofibrinogenemia are at risk of spontaneous thromboembolic complications[29] and childbirth also significantly increases the risk of thrombotic episodes[30].

In this study, the obstetrician ultimately chose cesarean section as the first evidence to end the pregnancy. Fibrinogen was given intermittently intravenously three times at 2 g/d before cesarean section and after the increase of fibrinogen supplementation from 0.77 g/L to 2.13 g/L. Charbitic's study in 2007 was the first to suggest that fibrinogen concentrations below 2 g/L may cause severe postpartum haemorrhage[28]. In 2015, Karlsson et al. concluded that plasma fibrinogen concentration before delivery does not predict severe postpartum haemorrhage[31]. However, fibrinogen was still supplemented to above 2 g/L for the proband patients as recommended by the European Consensus Group on Postpartum Haemorrhage[32]. Fibrinogen supplementation is not predictive of severe postpartum haemorrhage. A case of pulmonary embolism after fibrinogen infusion in a patient with congenital hypofibrinogenemia misdiagnosed as hypofibrinogenemia was reported by Zhou et al.[33]. Studies have also suggested that asymptomatic patients with congenital hypofibrinogenemia do not

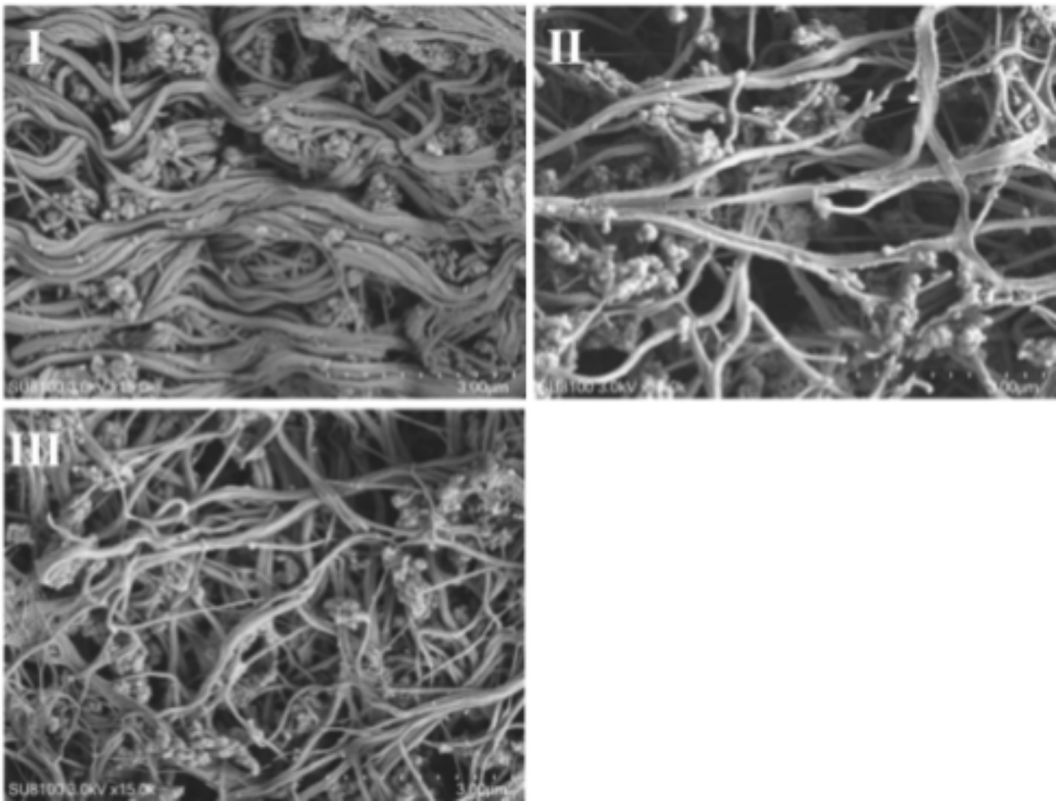

Fig. 8. Scanning electron micrographs of fibrin networks (I: normal, II: preexisting, III: mother).

require intravenous fibrinogen supplementation[34]. In the current study, the patient was not supplemented with fibrinogen before being admitted to the hospital for delivery. This was mainly because she had a stable fibrinogen level and no obvious clinical symptoms except for occasional vaginal bleeding in early pregnancy. The researchers wanted to avoid unnecessary blood transfusion to avert all the possible risks of allergy and infections and take into account the poor financial situation of the patient's family. No clinical guidelines are provided for the treatment of congenital hypofibrinogenemia. The rationale for prenatal prophylactic transfusion in pregnant women with this disease is controversial[35]. If the patient has a history of thrombosis or a relevant family history, anticoagulation with low molecular heparin may be used in conjunction with fibrinogen supplementation[36].

The pregnant woman with congenital hypofibrinogenemia in this study was heterozygous for the mutation. The diagnosis was not confirmed by amniocentesis during pregnancy due to the high risk of bleeding. There was a 50% chance that her child would be a patient. The first clinical symptom that neonates with this condition show is usually umbilical cord bleeding[37,38]. The main cause of death is intracranial haemorrhage. Hence, neonates need to have a cranial examination completed after birth to rule out intracranial haemorrhage, close observation of milk intake, mental and pupil conditions, and fibrinogen supplementation if necessary, and complete genetic testing as soon as possible. The son of the proband was very lucky not to have inherited his mother's disease-causing mutation, but the prevention of congenital hypofibrinogenemia in newborns should be done in primary prevention. Carriers of the mutation with clear pathogenicity can undergo preimplantation genetic testing (PGT) for the birth of a completely healthy newborn, which is also applicable to patients with "mutations of unknown significance". Patients with "mutations of undetermined significance" can also undergo PGT with full informed consent and multidisciplinary discussion.

In summary, a family study was conducted on a congenital hypofibrinogenemia patient with a de novo c.702G > T (p.Trp234Cys) mutation in the FGG gene. The mutation database of the FGG gene was supplemented. The means of intervention were provided in the maternal period for female patients with this type of disease. Meanwhile, this study conducted functional validation experiments on this de novo mutation, to upgrade its pathogenicity and provide an example and theoretical basis for genetic counseling and maternal intervention in congenital hypofibrinogenemia.

Data availability

The datasets generated and/or analysed during the current study are available in the Sequence Read Archive repository, PRJNA1189500.

Received: 10 November 2024; Accepted: 24 February 2025
Published online: 01 March 2025

References

1. Sang, Y. et al. Interplay between platelets and coagulation. *Blood Rev.* **46**, 100733 (2021).
2. Pineda, A. O. et al. Crystal structure of thrombin in complex with fibrinogen gamma' peptide. *Biophys. Chem.* **125**(2–3), 556–559 (2007).
3. Callea, F. et al. Hepatic endoplasmic reticulum storage diseases. *Liver* **12**(6), 357–362 (1992).
4. Hanss, M. F. & Biot A database for human fibrinogen variants. *Ann. N Y Acad. Sci.* **936**, 89–90 (2001).
5. Acharya, S. S., Coughlin, A. & Dimichele, D. M. Rare bleeding disorder registry: Deficiencies of factors II, V, VII, X, XIII, fibrinogen and dysfibrinogenemias. *J. Thromb. Haemost* **2**(2), 248–256 (2004).
6. Chafa, O. et al. Severe hypofibrinogenemia associated with bilateral ischemic necrosis of toes and fingers. *Blood Coagul. Fibrinolysis* **6**(6), 549–552 (1995).
7. Frenkel, E. et al. Congenital hypofibrinogenemia in pregnancy: Report of two cases and review of the literature. *Obstet. Gynecol. Surv.* **59**(11), 775–779 (2004).
8. Neerman-Arbez, M., Casini, A. & de Moerloose, P. Congenital fibrinogen disorders: An update. *Semin. Thromb. Hemost.* **39**(06), 585–595 (2013).
9. Korte, W. et al. Thrombosis in inherited fibrinogen disorders. *Transfus. Med. Hemother.* **44**(2), 70–76 (2017).
10. Casini, A. et al. Mutational epidemiology of congenital fibrinogen disorders. *Thromb. Haemost.* **118**(11), 1867–1874 (2018).
11. Pietrys, D. et al. Two different fibrinogen gene mutations associated with bleeding in the same family (A αGly13Glu and γGly16Ser) and their impact on fibrin clot properties: Fibrinogen Krakow II and Krakow III. *Thromb. Haemost.* **106**(3), 558–560 (2011).
12. Arai, S. et al. Screening method for congenital dysfibrinogenemia using clot waveform analysis with the Clauss method. *Int. J. Lab. Hematol.* **43**(2), 281–289 (2021).
13. Kobayashi, T. et al. Prenatal and peripartum management of congenital afibrinogenaemia. *Br. J. Haematol.* **109**(2), 364–366 (2000).
14. Aygören-Pürsün, E. et al. Retrochorionic hematoma in congenital afibrinogenemia: resolution with fibrinogen concentrate infusions. *Am. J. Hematol.* **82**(4), 317–320 (2007).
15. Sugo, T. et al. A classification of the fibrin network structures formed from the hereditary dysfibrinogens. *J. Thromb. Haemost.* **4**(8), 1738–1746 (2006).
16. Simurda, T. et al. Congenital hypofibrinogenemia associated with a novel heterozygous nonsense mutation in the globular C-terminal domain of the γ-chain (p.Glu275Stop). *J. Thromb. Thrombolysis* **50**(1), 233–236 (2019).
17. Zhang, Y., Zuo, X. & Teng, Y. Y. Women With congenital hypofibrinogenemia/afibrinogenemia:From birth to death. *Clin. Appl. Thromb. Haemost.* **26** (2020).
18. Saes, J. L. et al. Pregnancy outcome in afibrinogenemia: are we giving enough fibrinogen concentrate? A case series. *Res. Pract. Thromb. Haemost.* **4**(2), 343–346 (2020).
19. Peterson, W. et al. Hemorrhagic, thrombotic and obstetric complications of congenital dysfibrinogenemia in a previously asymptomatic woman. *Thromb. Res.* **196**, 127–129 (2020).
20. Ikejiri, M. et al. Protection from pregnancy loss in women with hereditary thrombophilia when associated with fibrinogen polymorphism Thr331Ala. *Clin. Appl. Thromb. Hemost.* **23**(5), 494–495 (2016).
21. Valiton, V. et al. Obstetrical and postpartum complications in women with hereditary fibrinogen disorders: A systematic literature review. *Haemophilia* **25**(5), 747–754 (2019).
22. Casini, A. et al. Natural history of patients with congenital dysfibrinogenemia. *Blood* **125**(3), 553–561 (2015).
23. Obstetrical complications in hereditary fibrinogen.pdf.
24. Roqué, H. et al. Pregnancy-related thrombosis in a woman with congenital afibrinogenemia: A report of two successful pregnancies. *Am. J. Hematol.* **76**(3), 267–270 (2004).
25. Peyvandi, F. et al. Incidence of bleeding symptoms in 100 patients with inherited afibrinogenemia or hypofibrinogenemia. *J. Thromb. Haemost* **4**(7), 1634–1637 (2006).
26. Casini, A. et al. Management of pregnancy and delivery in congenital fibrinogen disorders: Communication from the ISTH SSC subcommittee on factor XIII and fibrinogen. *J. Thromb. Haemost.* **22**(5), 1516–1521 (2024).
27. Marchi, R. et al. Perinatal stroke and hypofibrinogenemia: IS the new missense fibrinogen variant γ p.Gly310Glu the cause of the procoagulant State?? *Thromb. Res.* **241**, 109106 (2024).
28. Charbit, B. et al. The decrease of fibrinogen is an early predictor of the severity of postpartum hemorrhage. *J. Thromb. Haemost.* **5**(2), 266–273 (2007).
29. Casini, A. et al. Genetics, diagnosis and clinical features of congenital hypodysfibrinogenemia: A systematic literature review and report of a novel mutation. *J. Thromb. Haemost.* **15**(5), 876–888 (2017).
30. Stanciakova, L. et al. Congenital afibrinogenemia: From etiopathogenesis to challenging clinical management. *Expert Rev. Hematol.* **9**(7), 639–648 (2016).
31. Karlsson, O. et al. Fibrinogen plasma concentration before delivery is not associated with postpartum haemorrhage: a prospective observational study. *Br. J. Anaesth.* **115**(1), 99–104 (2015).
32. Muñoz, M. et al. Patient blood management in obstetrics: prevention and treatment of postpartum haemorrhage. A NATA consensus statement. *Blood Transfus.* **17**(2), 112–136 (2019).
33. Zhou, J., Zhu, P. & Zhang, X. A Chinese family with congenital dysfibrinogenemia carries a heterozygous missense mutation in FGA: Concerning the genetic abnormality and clinical treatment. *Pak J. Med. Sci.* **33**(4), 968–972 (2017).
34. Yan, J. et al. Congenital dysfibrinogenemia in major surgery: A description of four cases and review of the literature. *Clin. Chim. Acta***528**, 1–5 (2022).
35. Tarantino, M. D., Ansteatt, K. & Mistretta, J. Prophylaxis and treatment of bleeding or thrombosis with fibrinogen concentrate (Fibryga) in patients with congenital hypofibrinogenemia or dysfibrinogenemia. *Blood* **142**(Supplement 1), 5483–5483 (2023).
36. Casini, A. et al. Dysfibrinogenemia: From molecular anomalies to clinical manifestations and management. *J. Thromb. Haemost.* **13**(6), 909–919 (2015).
37. Abolghasemi, H. E. & Shahverdi Umbilical bleeding: a presenting feature for congenital afibrinogenemia. *Blood Coagul. Fibrinolysis* **26**(7), 834–835 (2015).
38. Simurda, T. et al. Yes or no for secondary prophylaxis in afibrinogenemia? *Blood Coagul. Fibrinolysis*. **26**(8), 978–980 (2015).

Author contributions

X.Z. and L.H. completed the main experiment, G.Y. conducted part of the experiment, X.Z.,L.H.and G.Y. completed the main manuscript writing, M.B. designed the experimental scheme, W.J. provided the case information, G.M. reviewed and revised the manuscript, M.X. conducted the overall planning and provided financial support, All authors reviewed the manuscript.

Funding

Science and Technology Programme of Gansu Province (21JR7RA391, 21YF1FA115).

Declarations

Competing interests
The authors declare no competing interests.

Additional information
Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-025-91740-3.

Correspondence and requests for materials should be addressed to X.M.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.