WFH
WORLD FEDERATION OF HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA

# What are **fibrinogen disorders?**

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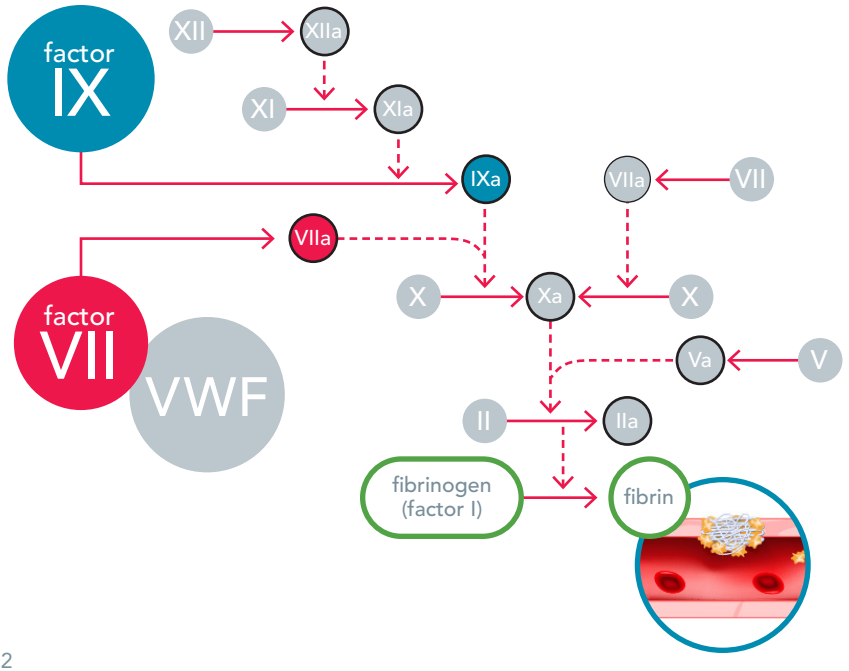
# What are **fibrinogen disorders?**

Fibrinogen disorders are rare inherited bleeding disorders that can be mild, moderate, or severe. The most severe form has an estimated prevalence of 1 in 1,000,000 people. Milder forms have a higher prevalence. Both men and women can have fibrinogen disorders.

There are different types of fibrinogen disorders. They are all caused by a problem with the blood clotting protein, fibrinogen (also referred to as Factor I). Some individuals with fibrinogen disorders do not have enough fibrinogen (i.e., quantitative fibrinogen disorder, hypofibrinogenemia or afibrinogenemia). In other individuals, fibrinogen does not work the way it should (i.e., qualitative fibrinogen disorder, dysfibrinogenemia). Some individuals have both (i.e., fibrinogen does not work they way it should and they do not have enough fibrinogen, hypodysfibrinogenemia).

Fibrinogen is an abundant blood clotting protein. It helps platelets and other clotting proteins stick together to form the initial clot to stop bleeding after an injury. During the coagulation cascade, fibrinogen is converted to fibrin, which forms the stable clot. Some people think of fibrin as being a "scaffold" which supports and gives structure to a blood clot.



People with a fibrinogen disorder may have increased bleeding or may form abnormal clots (thrombosis) due to abnormal fibrinogen. Some individuals may have both.

Bleeding can vary between people with fibrinogen disorders. People with more severe forms experience frequent major bleeding episodes which affect their quality of life. Others with less severe forms may have no symptoms unless they experience a serious injury or have surgery. Some people with fibrinogen disorders may not know that they have the disorder because they have no bleeding or only minor bleeding, and may only be diagnosed after a family member is.

# What are the different types of fibrinogen disorders?

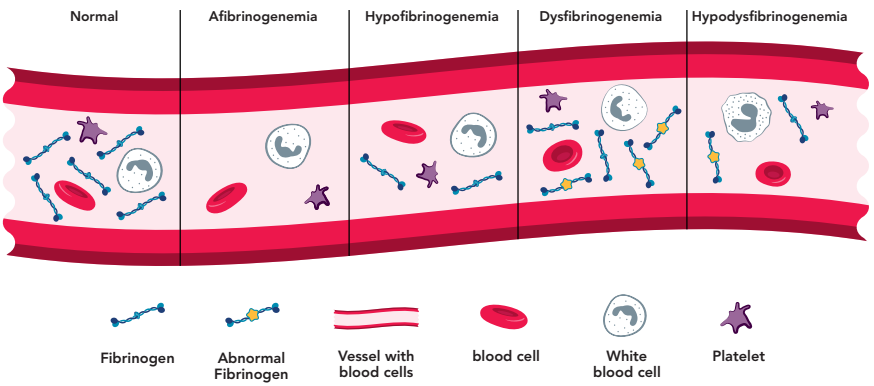
There are several types and subtypes of fibrinogen disorders and treatment should be tailored to each type. Within each type, the disorder can be mild, moderate, or severe and can cause specific symptoms. It is important to know which type of fibrinogen disorder a person has, because treatment and inheritance may differ.

**Afibrinogenemia** is a quantitative fibrinogen disorder and is the rarest and the most severe form. In people with afibrinogenemia, fibrinogen is completely absent leading to frequent bleeding and sometimes formation of blood clots (although the mechanism is largely unknown, this may be due to unstable platelet clots due to lack of fibrin).

**Hypofibrinogenemia** is another quantitative fibrinogen disorder. In people with hypofibrinogenemia, fibrinogen is present but below the levels needed for normal clotting. A subtype of hypofibrinogenemia, called *fibrinogen storage disease*, can lead to liver disease.

**Dysfibrinogenemia** is a qualitative fibrinogen disorder. It results in changes in the structure of fibrinogen which may affect how fibrinogen works, even if levels are normal. Some subtypes of dysfibrinogenemia can increase the risk of forming blood clots.

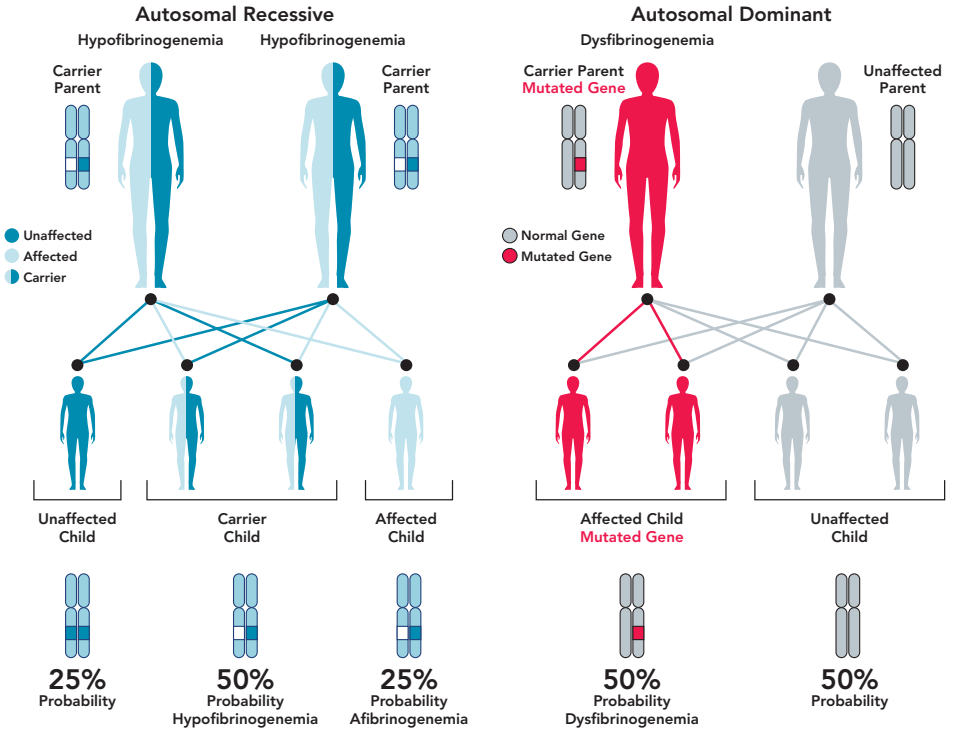
**Hypodysfibrinogenemia** is a combined defect that involves both lower levels of fibrinogen as well as changes in the fibrinogen structure.



# How do people get fibrinogen disorders?

Fibrinogen disorders are inherited, meaning they are passed down through the genes from the parent to the child. There is often a family history of bleeding, although bleeding symptoms may vary a lot in the same family.

Humans have twenty-three pairs of chromosomes: twenty-two pairs of autosomal chromosomes (also called autosomes) and one pair of sex chromosomes (X or Y). Unlike hemophilia, which is due to gene variants or mutations on the X chromosome, fibrinogen disorders are due to gene variants or mutations on the autosomes. Each person has two fibrinogen genes, one from each parent. Afibrinogenemia is inherited in an autosomal recessive fashion, which means that when both parents carry the gene there is a 25% chance they will have a child with a fibrinogen disorder. Hypofibrinogenemia and hypodysfibrinogenemia are inherited in a recessive manner. Some forms of dysfibrinogenemia are inherited in a recessive manner. Other forms of dysfibrinogenemia are inherited in an autosomal dominant manner, which means that if only one parent carries the gene, there is a 50% chance it will be passed on to the child.



# What are the signs and symptoms of fibrinogen disorders?

Signs and symptoms differ according to the type and the subtype of the fibrinogen disorder. People with hypofibrinogenemia and dysfibrinogenemia may have few or no symptoms, while people with afibrinogenemia usually have more severe bleeding. However, it is still possible for someone with any type to have serious bleeding or to experience bleeding or clotting that affects their quality of life. Even people from the same family can have different symptoms and/or severity.

The most common symptoms are:

- frequent or prolonged nosebleeds (epistaxis)
- spontaneous bleeds in oral cavity (particularly after dental surgery or tooth extraction)
- easy and/or long-lasting bruising
- abnormal bleeding during or after injury, surgery or childbirth
- bleeding from the umbilical cord in neonates*
- heavy menstrual bleeding, or bleeding during pregnancy
- prolonged bleeding from minor cuts or after taking blood samples
- bleeding after vaccination or intramuscular injections*
- bleeding into the gastrointestinal and urinary tracts*
- bleeding into the joints (hemarthrosis) or muscles*
- intra-peritoneal bleeding from ovary cyst rupture in females or spontaneous spleen rupture in both males and females*
- spontaneous bleeding into the central nervous system (the brain and spinal cord)*
- formation of bone cysts (which can result in bone pain)*
- delayed healing of wounds*
- external or internal bleeding into the eye*
- formation of blood clots (thrombosis)†

* Especially in those with severe fibrinogen disorders

† Although the mechanism is largely unknown, this may be due to unstable platelet clots due to lack of fibrin.

# How are fibrinogen disorders diagnosed?

If your doctor suspects that you suffer from a bleeding disorder, it is important to refer you to a hematologist trained in the field of bleeding disorders, preferably affiliated with a Bleeding Disorder Treatment Centre and a specialized laboratory. The diagnosis of a fibrinogen disorder relies on a blood test.

Testing includes the measurement fibrinogen levels (fibrinogen antigen) and activity. The fibrinogen activity test looks at how well the fibrinogen works, and the fibrinogen antigen test shows the amount of fibrinogen in the circulation. These tests help your doctor diagnose a fibrinogen disorder:

| TYPE OF FIBRINOGEN DISORDER | APTT/PT | FIBRINOGEN ACTIVITY | FIBRINOGEN ANTIGEN | DESCRIPTION |
|---|---|---|---|---|
| **Afibrinogenemia** | ↑ | ↓↓↓ | ↓↓↓ | Complete absence of fibrinogen |
| **Hypofibrinogenemia** | ↑ or ↔ | ↓ | ↓ | Lower levels of a fibrinogen that works properly |
| **Dysfibrinogenemia** | ↑ or ↔ | ↓ | ↔ or ↑ | Normal levels of a fibrinogen that does not work properly |
| **Hypodysfibrinogenemia** | ↑ or ↔ | ↓ | ↓ | Lower levels of a fibrinogen that does not work properly |

aPTT, activated partial thromboplastin time; PT, prothrombin time.

The measurement of the fibrinogen antigen is available only in some laboratories. If it is not available, your doctor can perform other tests to replace it. Sometimes, to determine the subtype of fibrinogen disorder, your doctor may refer you for genetic testing.

# How are fibrinogen disorders treated?

As a rule, all individuals with fibrinogen disorders should be referred to a Bleeding Disorder Treatment Centre, where a multidisciplinary team develops a comprehensive treatment plan to suit your individual condition and needs. The main goal of treatment is to prevent or stop acute bleeding by giving treatments that support or replace fibrinogen, and to limit the risk of blood clots.

The type of treatment depends on the type of fibrinogen disorder, the severity of the bleeding, the risk of the surgery and the availability of products. People with mild forms of fibrinogen disorders often do not require treatment except during or after surgery or dental work. In people with afibrinogenemia who have a history of severe and frequent bleeds, long-term prophylaxis (i.e., regular administration) is sometimes proposed.

There are three treatments available for fibrinogen disorders:

- *Plasma derived fibrinogen (factor I) concentrate* contains only fibrinogen purified from human blood donations. This is the preferred treatment; however, it is not widely available.
- *Cryoprecipitate/pathogen-reduced cryoprecipitate* contains fibrinogen and other coagulation proteins derived from human blood donations.
- *Fresh frozen plasma (FFP)/pathogen-reduced FFP* contains all coagulation proteins but has lower quantities of fibrinogen, derived from human blood donations.

As with all medications, these treatments may have side effects. People with fibrinogen disorders should talk to their doctor about possible side effects of treatment.

Mucocutaneous bleeding and many minor bleeding episodes can be controlled and prevented by antifibrinolytic drugs, such as tranexamic acid or aminocaproic acid, which help prevent the blood clot from breaking down. Heavy periods in women with fibrinogen disorders may be controlled with antifibrinolytic drugs, or with hormonal contraceptives (such as birth control pills, or levonorgestrel releasing intrauterine device/system [IUD or IUS]) in women who do not wish to conceive.

Some people may be at an increased risk of thrombosis (blood clots). In case of thrombosis, an anticoagulation (blood thinner) treatment can be necessary. Anticoagulation medication increases the length of time it takes for your blood to clot. There are currently various treatment options available and your doctor will discuss the options with you. Symptoms of a thrombosis are a painful, red or swollen limb, shortness of breath or chest pain. If you have any of these symptoms you should attend medical services immediately for assessment.

### Call your Bleeding Disorder Center if:

- pregnant or planning pregnancy
- trauma or planning surgery
- planning invasive dental work
- experiencing bleeding
- experiencing pain, swelling in a limb or chest pain with breathing difficulty
- having heavy menstrual bleeding

# Special issues for women, girls, and those with the potential to menstruate

Women, girls, and those with the potential to menstruate with fibrinogen disorders may face unique challenges due to excessive bleeding, particularly during menstruation and childbirth.

## MENSTRUAL BLEEDING

Women with fibrinogen disorders can experience heavy menstrual bleeding (i.e., excessive or prolonged menstrual bleeding). The average amount of blood lost during a "normal" period is 30–40 ml. Blood loss of 80 ml or more is considered heavy. If your menses (period) lasts longer than 7 days, if you change pads or tampons more frequently than every 2 hours, if you experience a sensation of "flooding" or if you have blood clots larger than the size of a pecan, you are suffering from excessive bleeding. Prolonged bleeding can also lead to iron deficiency. If iron levels are low, iron tablets should be taken, or iron infusion should be administered to increase iron levels and prevent anemia.

## PREGNANCY AND CHILDBIRTH

Fibrinogen plays a crucial role in preventing excessive bleeding during pregnancy and childbirth, and in maintaining a normal placenta. Women with fibrinogen disorders should be informed and counselled about inheritance and risks during pregnancy, and formulate a management plan with the Bleeding Disorder Treatment Centre. In women with severe fibrinogen disorders, a treatment to increase fibrinogen levels may be necessary throughout the pregnancy. In women with mild fibrinogen disorders, a fibrinogen treatment and/or antifibrinolytics such as tranexamic acid may be necessary during delivery. After the baby is born, it is normal to experience period-type bleeding. However, if the bleeding continues for longer than 6 weeks, you may need treatment to increase fibrinogen or antifibrinolytic drugs, and you should contact your Bleeding Disorder Treatment Centre.

## PSYCHOSOCIAL IMPACT

Living with a rare bleeding disorder may have some psychosocial implications for women and girls. If you feel isolated and embarrassed, particularly during the menstrual years, and you have concerns regarding your reproductive health and overall well-being, contact your Bleeding Disorder Treatment Centre.

# Important points for people with fibrinogen disorders

- Register at a Bleeding Disorder Treatment Centre near your home. It will provide you information about your disorder, the treatment you have been prescribed, and the contact details that you should always carry with you.
- Give teachers and friends information about your fibrinogen disorder and how to handle bleeding that may arise.
- Check all medications with your doctor. Some over-the-counter medications should be avoided because they interfere with clotting (such as aspirin or nonsteroidal anti-inflammatory drugs).
- When travelling, find the addresses and telephone numbers of the **Bleeding Disorder Treatment Centre (wfh.org/find-local-support)** at your destination(s) and bring your information with you.
- If you are planning a pregnancy, if you experience prolonged or abnormal menstrual bleeding, or if you are pregnant and want to plan delivery, contact your Bleeding Disorder Treatment Centre.
- If you have abnormal or prolonged bleeding, if you have trauma, or if a surgery or dental work is planned, contact your Bleeding Disorder Treatment Centre.
- People with fibrinogen disorders can develop symptoms at any age, which can show differently in different age groups (for more details, see the section "What are the signs and symptoms of fibrinogen disorders?"). If you have any of these symptoms, contact your Bleeding Disorder Treatment Centre.
- People with fibrinogen disorders can also develop blood clots inside their blood vessels. If you have a concern regarding a possible blood clot, contact your Bleeding Disorder Treatment Centre.
- If you experience recurrent bleeding, keep detailed records of the bleeds as it may help your treating physician develop or update an individualized management plan.

## PATIENT'S PERSPECTIVE

"I was diagnosed with afibrinogenemia when I was born. Getting a diagnosis early on enabled my parents to get information from my hematologist, which helped them understand the complications of this disorder. However, the complexities of growing up, especially being a woman, required consultation with other physicians (gynecologist, neurologists, dentists, orthopedists) in different stages of my life. Through the various bleeding episodes I experienced, we learned it is imperative that doctors work together as one multidisciplinary team so that everyone understands afibrinogenemia and can inform how to adapt and tailor treatments to ensure the best outcome for my health. From a personal perspective, I realized the importance of listening to my body. Everyone manifests symptoms in a different way, so it is important that you stay tuned in to what your body is telling you, sending you signals when something is wrong. It is through listening and communicating to doctors that I have been able to navigate the juxtaposition of bleeding and clotting. Lastly, it is possible to have a normal life, if you prioritize your health above everything else, make peace with the limitations you have and embrace the endless possibilities of what your life can be."

—Joana B.

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