NATIONAL HEMOPHILIA FOUNDATION
for all bleeding disorders

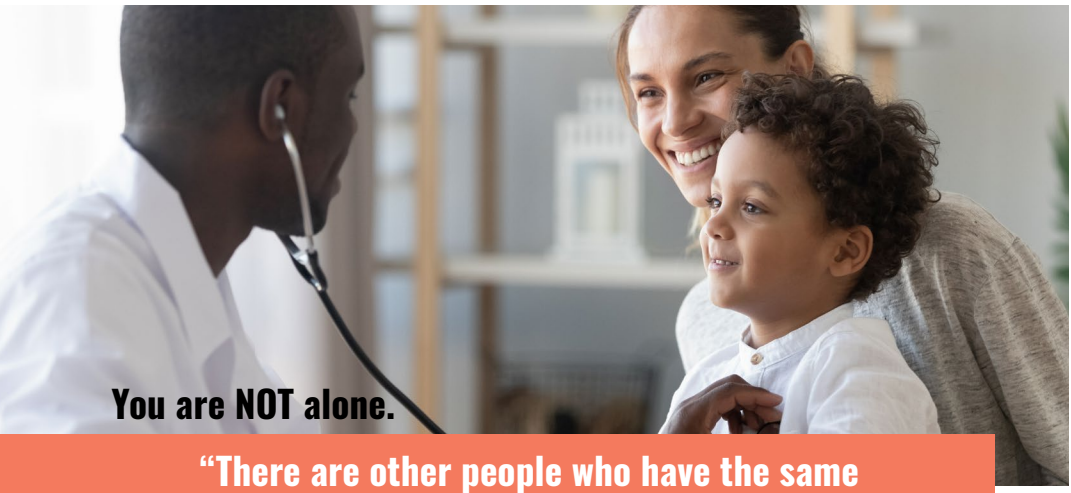
FACTOR XIII (F13) DEFICIENCY

YOU ARE NOT ALONE

Factor XIII Deficiency

WHAT YOU SHOULD KNOW

Whether you are newly diagnosed with **Factor XIII Deficiency (FXIII Deficiency)** or have been diagnosed for some time, it is common to go through many ups and downs. We want to share information that you should know and some resources about this condition that can help you on your path to improved health and quality of life. When you are first given a new diagnosis, one as rare as FXIII Deficiency, it is understandable to have many emotions or feel overwhelmed. The good thing is that you're not alone. There are other people who have the same condition and lead full lives. They have had their lives enriched by becoming closer to other people who are traveling on a similar path. **With the care of an experienced team, you will find support from your healthcare providers as well as from the vibrant and caring bleeding disorders community.** You can be involved in this community and build meaningful relationships with your new extended family.



"There are other people who have the same condition and lead full lives. They have had their lives enriched by becoming closer to other people who are traveling on a similar path."

The National Hemophilia Foundation (NHF) is here to provide you with education and support as you manage your bleeding disorder whether you are a child, a teen, or an adult. In this spirit, NHF and the bleeding disorders community have selected some of the most frequently asked questions and answers below to empower you.

What Is Factor XIII Deficiency?

FXIII Deficiency is an ultra-rare bleeding disorder. Bleeding disorders are a group of medical conditions that share an inability or decreased ability to form a stable blood clot. When the body is injured and an area bleeds, a clot is formed to stop the bleeding. Clot formation is a multistep process called coagulation. When the blood clots properly, the blood clot is held together firmly at the site of the injury to prevent ongoing blood loss. People with a bleeding disorder are unable to form strong clots, which can lead to ongoing bleeding. Improper clotting can be caused by abnormalities in blood components such as platelets and/or blood clotting proteins, also called clotting factors. Platelets are small blood cells that help blood clot normally. Platelets act like first responders and stop bleeding by clumping and forming plugs in blood vessel injuries. If one or more of the blood components is defective or deficient or even absent, blood clotting is affected. FXIII is one of the clotting factors that is an important part of this process and works by making the clot strong or stable, therefore it is also known as Fibrin Stabilizing Factor. FXIII Deficiency is caused by an abnormal function or decreased amount of the FXIII protein. **It affects about 1 in every 3-5 million people, although it is believed that some mild to moderate forms of FXIII Deficiency may go undiagnosed.**[1]

> **"Bleeding disorders are a group of medical conditions that share an inability or decreased ability to form a stable blood clot."**

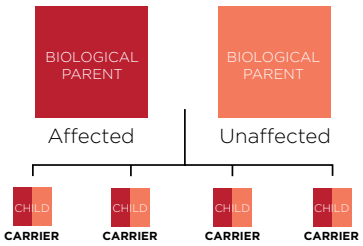
If you have FXIII Deficiency that means you have lower than normal FXIII clotting factor levels. The normal level of FXIII in the blood ranges from 50-220%. A level less than 50% of the normal amount would give you a diagnosis of FXIII Deficiency.[1] FXIII is composed of two parts called subunits: subunit A and subunit B. The subunit that is deficient or abnormal plays a role in determining your treatment plan. Most people who are affected with FXIII Deficiency have a defect in subunit A. You can ask your healthcare provider which subunit deficiency you have.

How does someone get Factor XIII Deficiency?

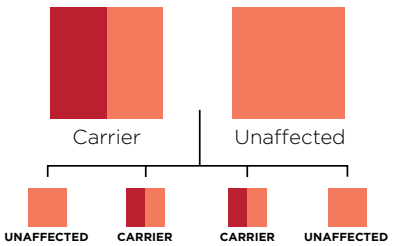
FXIII Deficiency is an inherited bleeding disorder, meaning that it is passed on from biological parents to child at the time of conception.

- It affects both males and females equally.
- A severely affected person has two abnormal copies of a defective gene.
- A carrier has only one copy of a defective gene. Typically, carriers may not have bleeding symptoms.
- For someone to inherit severe FXIII subunit A or B Deficiency, they must get a copy of the defective subunit gene from both biological parents. This means both biological parents must be affected or must be carriers of the same subtype of FXIII Deficiency.
- This pattern of inheritance is called Autosomal Recessive. It is different from what is called X-linked inheritance, as in the case of some other bleeding disorders like hemophilia. The different forms of autosomal recessive inheritance are illustrated on the next page.

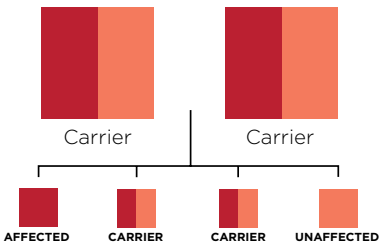
Family Inheritance of an Autosomal Recessive Disorder



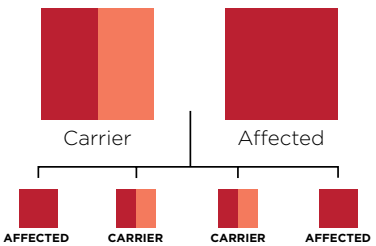
All children will be carriers (**100%**)



2 in 4 chance of being a carrier (**50%**)
2 in 4 chance of being unaffected (**50%**)



1 in 4 chance of being affected (**25%**)
2 in 4 chance of being a carrier (**50%**)
1 in 4 chance of being unaffected (**25%**)



2 in 4 chance of being a carrier (**50%**)
2 in 4 chance of being affected (**50%**)

SUMMARY

If you are **AFFECTED** with severe Factor XIII Deficiency, you probably got one defective gene from each of your biological parents.

If you are a **CARRIER** of Factor XIII Deficiency, you received only one copy of a defective gene from a biological parent.

You can use the same logic to figure out the likelihood of your children being impacted by this deficiency, depending on your and your partner's genes. Genetic testing and counseling are available if you are interested in figuring out where the deficiency came from, or who else in the family might be at risk of having the same condition.

Sometimes a person might develop FXIII Deficiency, rather than being born with it. Such an "acquired deficiency" is still quite rare. It is usually caused by an antibody, which is a protein produced by the body's immune system. The antibody interferes with the way FXIII works in the body. If you have acquired FXIII Deficiency you may have variable bleeding symptoms ranging from mild to severe. The development of acquired FXIII Deficiency may be associated with certain medications, such as isoniazid (an antibiotic used to treat tuberculosis), penicillin (an antibiotic), and phenytoin (a medication used to treat seizures), as well as other medical conditions.[1]

What are the symptoms of
Factor XIII Deficiency?

The symptoms of FXIII Deficiency may depend (but not always) upon how much FXIII you have circulating in your blood or how well it functions. Normal FXIII activity levels range from 50-220%.[1] **If you have FXIII levels that are not able to be measured in the laboratory test, you are considered to have a severe deficiency**. A severe deficiency is usually associated with severe bleeding symptoms including spontaneous (meaning occurring without injury or trauma) bleeding in the brain (intracranial hemorrhage or ICH), poor wound healing, and miscarriages. **An early sign that a child may be affected with a severe FXIII Deficiency is significant bleeding from their belly button (umbilical stump bleeding)** which is reported in approximately 80% of cases.[2] Bleeding in the brain is reported in up to 30% of severe cases, and occurs more often in FXIII Deficiency than in other bleeding disorders.[1] It is often difficult to tell if a brain bleed is going on, especially before a child is able to speak. You need to be aware of other signs such as excessive sleepiness, vomiting, gait changes, and irritability. **Other symptoms of this bleeding disorder include easy bruising, gum and mouth bleeding, heavy menstrual bleeding, nose bleeds (epistaxis), bleeding into joints and muscles, and prolonged bleeding after surgery.** Because of the current limitations of laboratory tests, it is often difficult to accurately measure FXIII levels below 5%.[2]

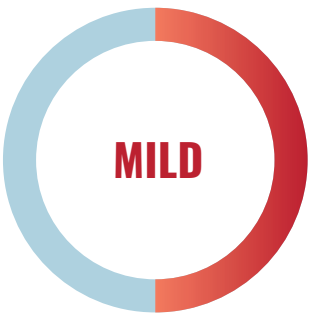
Classification of FXIII Deficiency[3]

less than 1%
cannot be detected by currently available tests

May have unprompted, severe, and even life-threatening bleeding

1% - 29%

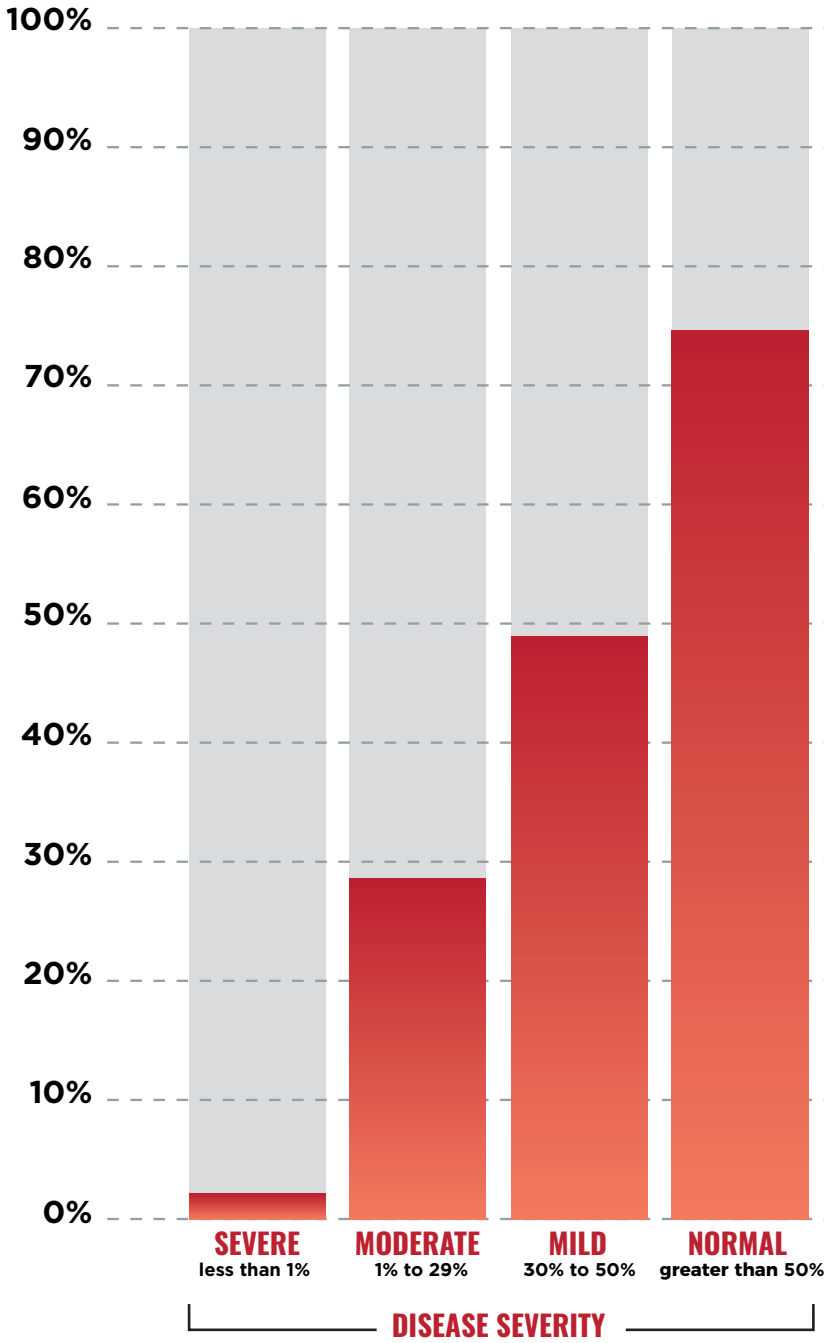
Mostly triggered by trauma, surgery, or pregnancy /delivery



30% - 50%

Often don't show symptoms, but can have problems with bleeding during trauma, a surgical procedure or with pregnancy/delivery

FXIII Activity Level



How is Factor XIII Deficiency diagnosed?

The diagnosis of FXIII Deficiency is challenging because it is rare and the common lab tests to look for this bleeding disorder may show results that are normal. **Some people are not diagnosed for several years because when they have problematic (or acute) bleeding, they may receive a blood component like fresh frozen plasma (FFP) or cryoprecipitate for treatment.** Receiving this treatment affects the test results when they are obtained around the time of these treatments. FXIII has a very long half-life of around 9-14 days, so when given treatment, the effects of the treatment can last for a few weeks and make testing very difficult.

"The diagnosis of FXIII Deficiency is challenging because it is rare and the common lab tests to look for this bleeding disorder may show results that are normal."

If FXIII Deficiency is suspected based on symptoms:

- A FXIII assay (assessing both the amount of FXIII protein and the adequate functioning of this protein) can be done where they draw your blood to test it.
- Your provider may start with a test called "clot lysis or solubility assay", which is a quick screening tool that is most useful if it comes out abnormal, indicating that FXIII levels are close to zero. However, it has low sensitivity, and may come out normal when FXIII levels are low (but not absent).
- Further testing is required to determine which subunit deficiency you have and the type of genetic mutation causing this condition.[2]

How is Factor XIII Deficiency treated?

For optimal care, it is recommended that you find a specialized doctor, or hematologist (a doctor specializing in the study of blood), who is experienced in the treatment of FXIII Deficiency. These doctors often work at a "Hemophilia Treatment Center" or HTC.

There are two medications to treat FXIII Deficiency that are available in the US. These medications replace the missing factor or make up for its activity. They are called "factor concentrates," which means that they have a large amount of FXIII.

The plasma-derived product can be used to treat bleeding episodes and to prevent bleeding (prophylaxis). This can be used in persons who lack either subunit A or subunit B.[4] Plasma-derived concentrates are produced using plasma donations. **Plasma is the liquid part of the blood that includes the plasma proteins, such as FXIII.** This manufacturing process undergoes viral treatment processes to lessen the risk of viruses being transmitted from a treatment with these products.

The other FXIII concentrate is produced in a laboratory (recombinant). It is approved for the prevention of bleeding (prophylaxis) only in subunit A deficiency.[1]

"There are two medications to treat FXIII Deficiency that are available in the US."

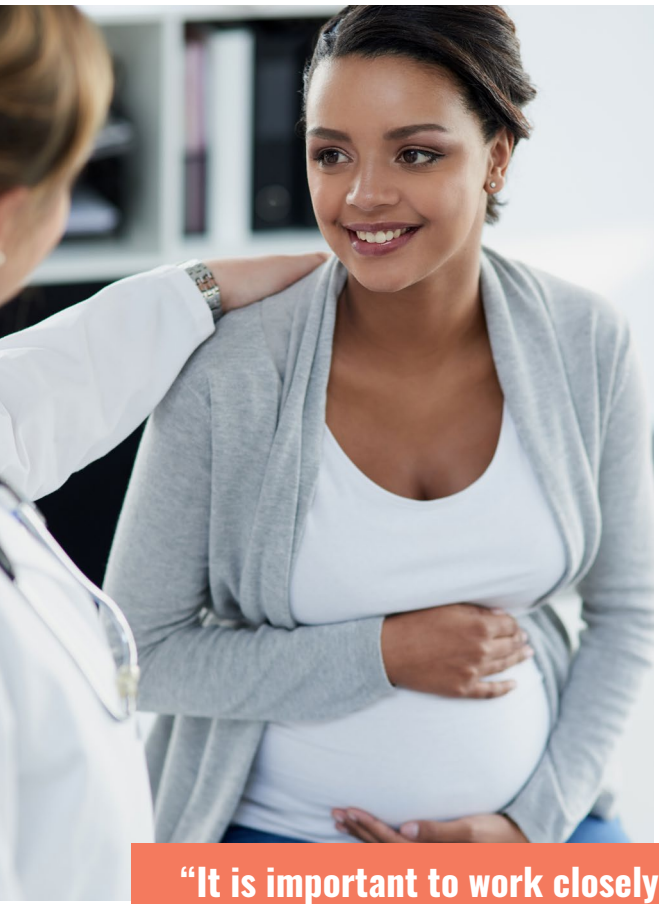
As FXIII lasts in the body for several days, preventative treatment only needs to be given every 3 to 4 weeks.

Historically, two blood components that have FXIII in the circulation (cryoprecipitate and fresh frozen plasma, or FFP) were recommended for the treatment of FXIII Deficiency. Today these blood products are only used when factor concentrates are not available.[1]

For the most current list of FDA-approved treatments for all bleeding disorders, including FXIII Deficiency, visit: **https://www.hemophilia.org/healthcare-professionals/guidelines-on-care/products-licensed-in-the-us**

What special precautions need to be taken when considering pregnancy?

Most pregnancies in women with a severe FXIII Deficiency who are not treated, end in miscarriages. Some studies have found that women who are carriers of FXIII or who have a very mild deficiency, may also have a higher rate of miscarriage than women in the general population.[2] Once pregnant, FXIII concentrates may be needed throughout pregnancy for a healthy outcome. Maintaining a FXIII level greater than 10% is ideal to prevent miscarriages.[1]



Meeting with your hematologist is essential prior to getting pregnant. It is important to work closely with a hematologist who is experienced in the treatment of FXIII Deficiency.

Often these specialized doctors are found at a HTC. They can guide your women's health doctor (OB/GYN) to help develop a treatment plan during your pregnancy, labor and delivery, and up to 4-6 weeks after delivery (the postpartum period).

HTC hematologists will also be able to provide care to your baby and provide testing as needed.

"It is important to work closely with a hematologist who is experienced in the treatment of FXIII Deficiency."

ADVICE FROM OTHER FXIII COMMUNITY MEMBERS

> At first, it felt like the worst case scenario - super scary. Then life kicks in - it ain't nothing, just becomes your normal - out of our 3 boys, he's the easiest."
>
> **Parent of a Child with FXIII Deficiency**

> I was born with FXIII Deficiency, everyone told me I couldn't do it, but here I am 37 years later with my 10 year old daughter--living proof! That they told me I couldn't have. So all you people out there with FXIII Deficiency, I believe in YOU, you can get through this, so you got this! Don't let no one tell you can't! BECAUSE YOU CAN!!!!"
>
> **FXIII Patient**

> Raising a child with a rare bleeding disorder doesn't mean that you and your child can't lead a near-normal lifestyle. My son is eight years old, had severe bleeding issues at a young age, and now lives a near-normal life. He is in 2nd grade and continues to learn how to advocate for himself as he grows."
>
> **Parent of a Child with FXIII Deficiency**

Where else can I obtain additional information?

You are now part of a family known as the bleeding disorders community. You are not alone and you can turn to other members of this community for support if needed:

- Know how to navigate disclosing your or your child's bleeding disorder to daycare, school, work, emergency rooms, and non-hematology specialists.
- Learn more about advocating for appropriate treatment in an emergency room (ER) or with other healthcare providers who may not know much about FXIII Deficiency. Always carry your treatment plan letter provided by your HTC when travelling or going to the emergency room.
- Find out where to connect with others with bleeding disorders locally.

Resources:

The National Hemophilia Foundation

- **Factor 13 webpage:** https://www.hemophilia.org/bleeding-disorders-a-z/types/other-factor-deficiencies/factor-xiii
- **Educational Resources:** https://stepsforliving.hemophilia.org/
- **HemAware magazine:** https://hemaware.org/
- **HANDI toll-free hotline:** 1-800-42-HANDI

Foundation for Women & Girls with Blood Disorders

- **Website directory of specialty women's clinics:** https://www.fwgbd.org/clinics

Hemophilia Federation of America

- **The Learning Central:** https://www.hemophiliafed.org/the-institute/

The Canadian Hemophilia Society

- **Factor XIII Deficiency; An Information Booklet:** https://www.hemophilia.ca/factor-xiii-deficiency/

Rare Coagulation Disorders

- **Factor XIII Deficiency:** http://www.rarecoagulationdisorders.org/diseases/factor-xiii-deficiency/disease-overview

The National Institute of Health

- **Genetic and Rare Diseases Information Center:** https://rarediseases.info.nih.gov/diseases/10766/factor-xiii-deficiency

Mayo Clinic

- **Autosomal Recessive Inheritance Pattern:** https://www.mayoclinic.org/autosomal-recessive-inheritance-pattern/img-20007457

Comprehensive Health Education Services (CHES)

- **Website:** https://www.ches.education/rare-bleeding-disorders

National Organization for Rare Disorders (NORD)

- **Rare Disease Database:** https://rarediseases.org/rare-diseases/factor-xiii-deficiency/

References:

1. Hsieh, L and Nugent, D. Factor XIII deficiency. Haemophilia. 2008; 1190-1200.
2. Karimi, M. et al. Factor XIII deficiency diagnosis: challenges and tools. International Journal of Laboratory Hematology. 2017; 3-11.
3. Peyvandi F, et al. Classification of rare bleeding disorders (RBDs) based on the association between coagulant factor activity and clinical bleeding severity. Journal of Thrombosis and Haemostasis. 2012; 1938-1943.
4. Ashley, C. et al. Efficacy and safety of prophylactic treatment with plasma-derived factor XIII concentrate (human) in patients with congenital factor XIII deficiency. Haemophilia. 2015; 102-108.

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This booklet is intended for informational purposes only. It is not intended to be used to make healthcare coverage or treatment determinations. NHF's Medical and Scientific Advisory Council (MASAC) recommends that the product and corresponding treatment regimen used by an individual should remain a decision between patient and physician.

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