**Mutation**

Hemophilia A is caused by a plasma deficiency in the coagulation factor VIII. Factor VIII is a glycoprotein that is also a very important blood coagulation protein. (Mazurkiewicz-Pisarek *et al.* 2016). The plasma deficiency is caused by a mutation in the *F8* gene. The *F8* gene encodes factor VIII. There is variation in the mutation of the *F8* gene. It can be mutated by repeat inversions, duplications, deletions, point mutations, and other genetic alterations. These cases of genetic alterations can be put into three categories. The first category of genetic alteration is when the sequence of gene variants, such as exons and introns, changes. The second category of genetic alteration is chromosome variants. It is the cause of the wide variety of large genetic alterations that are usually seen in hemophilia A patients. Due to the *F8* gene’s large size, it has a higher rate of small mutations. It is located at the tip of the long arm of the X chromosome. Within this area, are highly repetitive sequences that are close to one another, which leaves this area more open to rearrangement in chromosome variants. Another way of genetic alteration is when mobile elements are inserted. This has been shown to damage DNA in individuals with hemophilia A (Lannoy and Hermans 2016). The most common mutation that is seen in patients with severe hemophilia A is a large inversion with a translocation of exons 1-22. This occurs because of a homologous recombination between the *F8* gene in intron 22 and another copy of *F8* at the factor VIII gene. This occurs mostly in male germ cells (Mazurkiewicz-Pisarek *et al.* 2016).

**Transmission**

Hemophilia A is an X-linked disorder. It is caused by an absence or a dysfunction in factor VIII due to gene mutations (Lannoy and Hermans 2016). Individuals who acquire hemophilia A genetically must have a parent who has at least one affected X-chromosome. Those who do not have a family history of hemophilia have it caused by *de novo* mutations or spontaneous mutations. *De novo* mutations are the first time it is seen in the family. About a third of hemophilia A cases are point mutations. Within these point mutations, about eighty-five percent are missense mutations and fifteen percent are nonsense mutations (Mazurkiewicz-Pisarek *et al.* 2016). There are some mutations that increase the chances of developing alloantibodies, which are *F8* inhibitors, and this increases the chances for an individual to have more severe hemophilia A. Although there is still not a lot known about what causes inhibitor development for certain, it is likely that these inhibitors develop from genetic factors, like a mutation or a family history, or it develops from environmental factors, such as the type of treatment the individual is receiving. To create these inhibitors, it needs the activation of T follicular helper cells. These cells are specific for *F8*. However, researchers are still trying to find out what causes the inhibitor development for certain (Garagiola *et al.* 2018).

**Symptoms**

Hemophilia A ranges from mild to moderate to severe. Symptoms include abnormal bleeding, pain, anxiety and depression, emotional distress, and a decrease in psychological health. Symptoms, such as pain, tend to be worse during bleeding episodes. Repetitive bleeding episodes can lead to more frequent pain, and other symptoms, such as joint pain, arthropathy, and chronic synovitis. Patients who have more severe anxiety and depression symptoms have also been reported to have more frequent and severe pain (Pinto *et al.* 2018). In mild cases, individuals are much less common bleeding episodes, usually ranging from one to ten years. People with mild hemophilia A have increased bleeding with surgery. In moderate cases, bleeding episodes are more common, ranging from once a month to once a year. They typically have longer or delayed bleeding after minor trauma. In severe cases of hemophilia A, bleeding is much more frequent and excessive. Severe bleeding and pain can be caused by minor injuries. Bleeding episodes can occur about two to five times a month. Individuals are not affected but are heterozygous for hemophilia A might show symptoms as well. About thirty percent of females who are heterozygous have a factor VIII clotting activity that is below forty percent, which makes them at risk for bleeding even if they do not necessarily have the disease. Even those who are heterozygous but have a normal factor VIII clotting activity level have been reported to having increased bleeding, longer bleeding periods than average, and more frequent or reoccurring bleeding (Konkle and Fletcher 2017). Patients with *F8* inhibitors are more likely to develop more severe hemophilia and their quality of life significantly changes (Garagiola *et al.* 2018).

**Epidemiology**

Hemophilia is the most common type of hemophilia. It is more common than hemophilia B. Hemophilia A accounts for about eighty to eighty-five percent of cases of hemophilia. Hemophilia is the most common severe bleeding disorder (Doncel *et al.* 2023). People with a family history are more likely to have it. About sixty percent of people who have hemophilia A have a family history of it, the rest of the cases are considered to be sporadic (Lannoy and Hermans 2016). About forty-five percent of severe hemophilia A patients had a family history of it. Familial hemophilia accounted for approximately seventy percent of mild and moderate hemophilia patients. Sporadic hemophilia seems to be more common in younger patients. There has been an increase in sporadic hemophilia A (Santana *et al.* 2022). This disorder is more common in males since they only have one X chromosome. It occurs in about one in five thousand males. Females have a chance of getting it as well, but they are less likely to be affected because they have two x chromosomes. Even when females are affected, most cases are mild. Even if a female does not have the disease, she may become a carrier for hemophilia A if she is heterozygous. If the father is affected, she would be a carrier. About thirty percent of individuals with hemophilia A have the *F8* inhibitor development. *F8* mutations happen during embryogenesis in about thirty percent of cases. A decrease in birth rate in many countries has caused hemophilia to be less prevalent in those countries. On the other hand, there are longer life expectancies for hemophilia patients, so there has been an increase in the number of offspring that could be affected (Santana *et al.* 2022).

**Screening**

Genetic testing is used to diagnose individuals with hemophilia A. If a hemizygous *F9* pathogenic variant is found on the male proband, then that male is believed to have hemophilia A. In a female, if a heterozygous *F8* pathogenic variant is found, then she is believed to have it. Someone may be genetically tested if they have a normal von Willebrand factor level and have low factor VIII activity (Konkle and Fletcher 2017). The age at which an individual is diagnosed with hemophilia A often depends on the severity of the case. Patients with mild cases of hemophilia A are usually not diagnosed until later on in their life. Moderate patients are usually diagnosed before they are six years old. Patients that have a severe case are often diagnosed earlier on in their life, usually by the time they are two years old. It is common for people with mild cases to be undiagnosed and get a diagnosis after an event such as a surgery (Konkle and Fletcher 2017).

**Treatment**

Treatment depends on the severity of the disease. Standard therapies of hemophilia A involve administrating factor VIII every other day. Many affected individuals are referred to a hemophilia treatment center for treatment. At the center, they can be treated with an infusion of factor VIII concentrate. Some are taught to conduct home infusions. Mild hemophilia patients should be evaluated at a hemophilia treatment center every one to two years. Patients with moderate to severe hemophilia should be evaluated at the hemophilia treatment center every six to twelve months. People who have hemophilia and other additional diseases may have to follow up more often (Konkle and Fletcher 2017). Another form of treatment is replacement therapy. This form of therapy supplies the coagulation factor that is deficient in hemophilia patients (Weyand and Pipe 2019). About twenty-five to forty percent of patients may not be able to have replacement therapy as an option due to the inhibitors that block factor VIII activity. These individuals who have these inhibitors need to be treated with bypassing agents and immune tolerance induction to get rid of these inhibitors. Even with these options to get rid of the inhibitors, these patients still have a lower quality of life and life expectancy (Weyand and Pipe 2019). Safer and more efficient factor products have become more widespread and available. These products prevent the bleeding and reduce or sometimes avoid altogether the physical trauma that comes with severe bleeding, resulting in benefits such as healthier joints. Hemostatic rebalancing therapy is another form of treatment. It is designed to keep the hemostatic system at an equilibrium by targeting natural anticoagulant pathways. In nonaffected individuals, the hemostatic system is balanced to where the coagulation mechanisms do not have to be activated as long as it is at homeostasis, but it can be activated at times of injury. In individuals with hemophilia, the hemostatic system is not balanced and tends to lean towards bleeding due to a coagulation factor deficiency (Weyand and Pipe 2019). Researchers are trying to find ways to overcome the flaws of current treatments. For example, new recombinant factor VIII products have been discovered that may have more efficient responses to immune tolerance induction. Other new treatments have been developed or are being researched currently. Researchers are close to developing the first substitution therapy that does not depend on factor VIII. Substitution therapy works by using emicizumab, an antibody that joints factor X and factor IXa. This restores the missing function of factor VIII, and it does not have the negative of developing inhibitors like factor VIII since it does have the same structural homology. Investigational gene therapy is also looking more promising with more research (Weyand and Pipe 2019).

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