International Journal of Pharmaceutical and Medicinal Research

Journal homepage: www.ijpmr.org

Research Article

Hemophilia: Genetics, History, and Technology

Nilakshya Rajora

CEO,The Factor Foundation, New Jersey, United States

*Corresponding Author: **Nilakshya Rajora**, CEO,The Factor Foundation, New Jersey, United States*

ARTICLE INFO:

Article history:

Received: 28 January, 2026

Received in revised form: 14 February , 2026

Accepted: 20 March, 2026

Keywords:

Hemophilia, X-linked inheritance, royal disease, Queen Victoria, genetic heritage, clotting factor deficiency, hereditary disorders, Factor VIII

ABSTRACT

This paper is an overview of Hemophilia, what it is, its variants, the history of Hemophilia, and the reason it's called the "royal disease." The term Hemophilia is derived from the Greek words haima (blood) and philia (love).In the context of a 19th-century medical landscape, the term philia didn't refer to love alone but also a way for physicians to denote predisposition. The disease itself is rare but highly devastating, being distinguished by deficiencies in clotting factors [6]. Hemophilia has two distinct variations, one being Hemophilia A and the other being Hemophilia B, both of which result from a lack of clotting factors.The only difference between the two is that Hemophilia A is a result of a lack of Clotting Factor VIII, and Hemophilia B is a result of a lack of Clotting Factor IX. Hemophilia is transmitted via an X-linked recessive pattern, affecting males with higher efficiency while being transmitted by females who are referred to as 'carriers' Historically, Hemophilia was coined the "royal disease" due to it being passed down from Queen Victoria and then spreading to multiple European royals and their families. This further influenced a trifecta of political stability, power, and patient confidentiality at the time. This paper analyses not through a sole scientific lens but a historical one as well, exploring how Hemophilia's connection with royalty provided early ideas about heredity, advancing genetic research. By connecting the biological bases of Hemophilia with the disease's history, this paper shows how Hemophilia has played a large role in a case study intersected with genetics, heritage, and societal influence.

Introduction

Hemophilia & Genetic Concept

Deficiencies in certain clotting factors required for blood coagulation characterize the genetic bleeding disorder Hemophilia [6]. Hemophilia A and Hemophilia B are the two primary forms of the disorder that account for the vast majority of cases [1-4]. Nearly 80% of Hemophilia cases today are accounted for by Hemophilia A, resulting from issues in producing Factor VIII [14].The 'Christmas disease', also known as Hemophilia B, is caused purely by Factor IX deficiencies [13]. These two diseases differ markedly from a genetic standpoint but are similar in clinical severity and symptoms. From a genetic standpoint, the diseases have different treatments as well as completely different underlying genetic mutations. For both Hemophilia A and B, the genes responsible for these conditions are located on the X chromosome, which males have one of and females have two of, resulting in an overall X-linked recessive inheritance pattern.Due to males having only one X chromosome, since they have an XY chromosome pair, a singular defective gene could easily cause the disorder [5]. On the other hand, females will always have two X chromosomes, forming an XX pair, allowing a normal copy of the gene to be able to override the mutated one, inhibiting Hemophilia in females. This means that for females to be actually affected by Hemophilia, they would need both of their parents to have Hemophilia for even a 50% chance of contracting the disorder, as shown in Figure 1. Due to this, females end up being the assymptomatic carrier of the disorder who pass it down, and males tend to be the ones exhibiting the disorder itself.

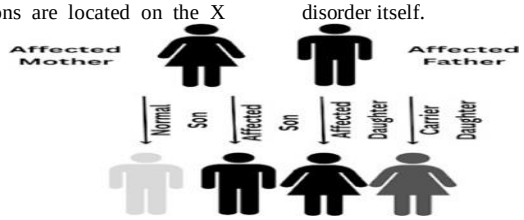

Figure 1. Affected Daughter: Only Possible Scenario

The majority of the time, Hemophilia is inherited from mothers who are asymptomatic carriers of the disorder itself, having one normal X chromosome and one affected X chromosome [17]. In this pattern of inheritance, we would end up seeing the son have a 50% chance of inheriting the disorder, and the daughter would have a 50% chance of becoming an asymptomatic carrier of Hemophilia [17]. I have created this pattern on a Punnett square below for representation, shown as Figure 2, demonstrating how traits that are X-linked recessive are passed down into the next generation when between a carrier female and a normal male. This helps show why sometimes people can mistake Hemophilia to skip generations when, in reality, it's just asymptomatic as a recessive gene. The way in which family lineage and Hemophilia directly intertwine with one another is a testament to the concept of heritage that follows families and bloodlines.[6-9]

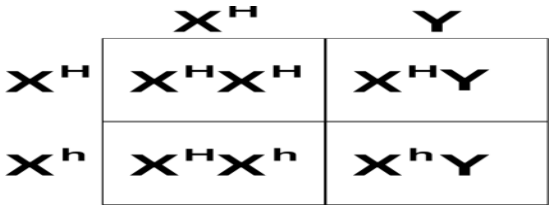

Figure 2. Punnet Square of Carrier Mother x Normal Father

Hemophilia and Royal Bloodlines

Starting with Queen Victoria of the United Kingdom, Hemophilia became historically memorable as it spread throughout Europe's royal families in the 19th century [10]. It is believed that Queen Victoria experienced a genetic mutation that made her a carrier of Hemophilia, as neither of her parents experienced Hemophilia or had any family lineage with the disorder [9].This

defective gene, which she possessed as an asymptomatic carrier of Hemophilia, further spread across Europe through her children and grandchildren, being exposed to multitudes of royal families across Europe [10-12] Specifically, we saw lots of her sons displayed the outright effects of Hemophilia, whereas her daughters unknowingly spread the disease in royal marriages and affiliations. The overall landscape of Hemophilia had changed within 2 generations, plaguing the royal blood of the world's largest monarchies at the time, altering the disease from a 'rare disorder' to a 'transnational issue' as it now affected the elites.The far-reaching effects of Hemophilia impacted the royal families of nations such as Spain, Germany, and Russia, leaving it with the name the 'royal disease' [1]. One of the victims of the royal disease was the son of Tsar Nicholas II of Russia, Tsarevich Alexei Romanov [7].Tsarevich Alexei Romanov is known for being a member of a royal family with well-documented info about his Hemophilia, as his Hemophilia was a major threat to the Russian Monarchy, with his history being kept secret to preserve his image [16]. Due to Tsarevich Alexei Romanov's condition, Tsarina Alexandra (the consort of Tsar Nicholas II and mother of Tsarevich Alexei Romanov) asked Grigori Rasputin for help with her son's condition [16].

Somehow, this mystical and holy man from Siberia, Grigori Rasputin's rituals and hypnosis helped Tsarevich Alexei Romanov make Tsarina Alexandra believe that he was a holy man sent to save the Russian Monarchy. She then started depending on him for guidance on the Russians' governmental affairs, eventually eroding the trust of the public in the government during a volatile period of Russian history [13-16].

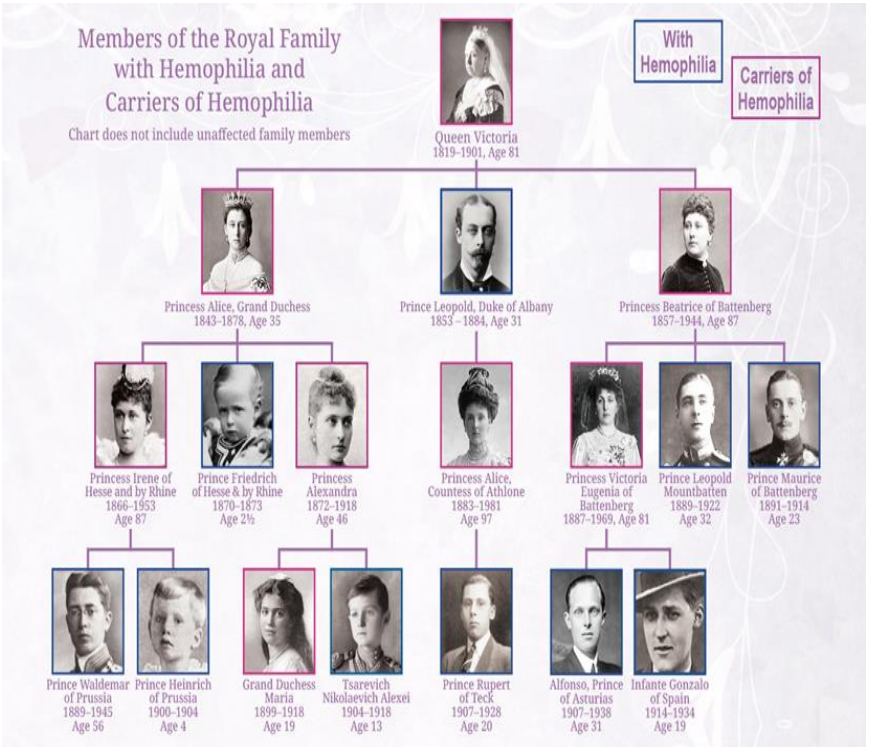

Figure 3. The Royal Bloodline of Hemophilia

When discussing the term 'heritage' on the topic of Hemophilia, you can end up on a completely different topic, depending on whether you analyze it from a biological or a historical perspective. From the biological perspective, Hemophilia is passed down from generation to generation following a strict set of genetic rules. On the other hand, historically, we see that heritage defines the disorder along with secrecy, royalty, and power. History has shown us that Hemophilia was often hidden from the public by royalty in fear that it would be an attack on political authority or even disrupt full-blown monarchies [13]. The fear the royals had about Hemophilia further stimulated secrecy, pushing off needed medicine and creating stigma about inherited disorders, which are long-lasting to this day. As knowledge about scientific fields such as genetics advanced, so did the representation of Hemophilia as it realigned itself away from being a royal vulnerability and towards a milestone in hereditary science-based studies [15].

Modern Understanding and Treatment

Modern medical advancements in the field of Hemophilia changed the prognosis for an individual with the disorder completely [6]. A disease that was originally a fatal disorder that would end the lives of individuals as children has evolved to become a condition that you can live with in your life with considerations, treatment, diagnosis, and hematological research.

These technological changes represent a larger shift to therapy-based solutions to bleeding disorders such as Hemophilia.The ground-level therapy being used by the majority of individuals living with Hemophilia is Clotting Factor Replacement Therapy. This therapy provides patients with a constant supplement of the clotting factors that their body lacks to deal with Hemophilia [4]. This would allow individuals with Hemophilia A to be provided Factor VIII and people with Hemophilia B to be provided Factor IX. These therapies work by stopping long bleeding episodes by effectively allowing the blood in the human body to be able to clot any bleeding taking place. This treatment is effective as it can be used on demand when dealing with an acute bleed, compared to prophylactic therapy, which has infusions that have to be administered regularly before the bleeding even takes place to prevent it. Prophylactic therapy has also been seen as highly useful as it reduced spontaneous bleeding in joints, which could otherwise lead to chronic pain or joint damage [4]. Figure 4, shown below, highlights a blood coagulation cascade showing the role of both Factor VIII and IX used in Hemophilia A and B, as well as how Clotting Factor Replacement Therapy directly provides relief to the human body [9].

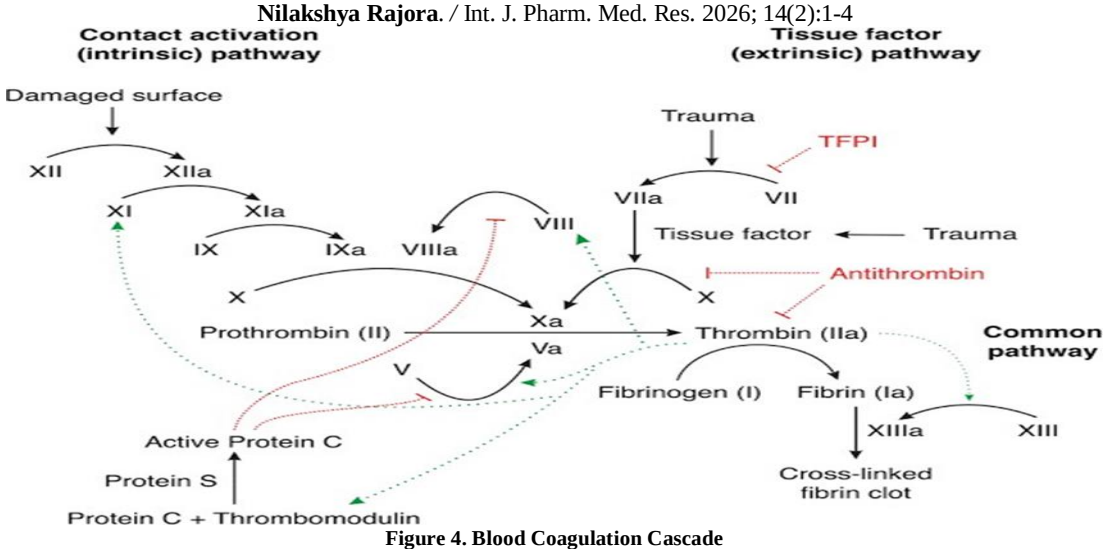

Figure 4. Blood Coagulation Cascade

An older yet cheaper alternative used by individuals from lower-income areas utilizes donated human plasma that provides clotting factors, while at the same time risking viral transmission. Newer biotechnologies have also seen the creation of recombinant clotting factors, which are created by using genetically engineered cells. These products are not created from human blood, allowing them to provide improved safety, improved health for the longterm, and reduce complications by providing precisely dosed medicine with great quality [4]. These modern medicines are made to improve the half-life of dosages, providing patients with a decreasing frequency of infusions. Figure 5, provided below, helps show and compare the differences between plasma-based and recombinant clotting factors [8].

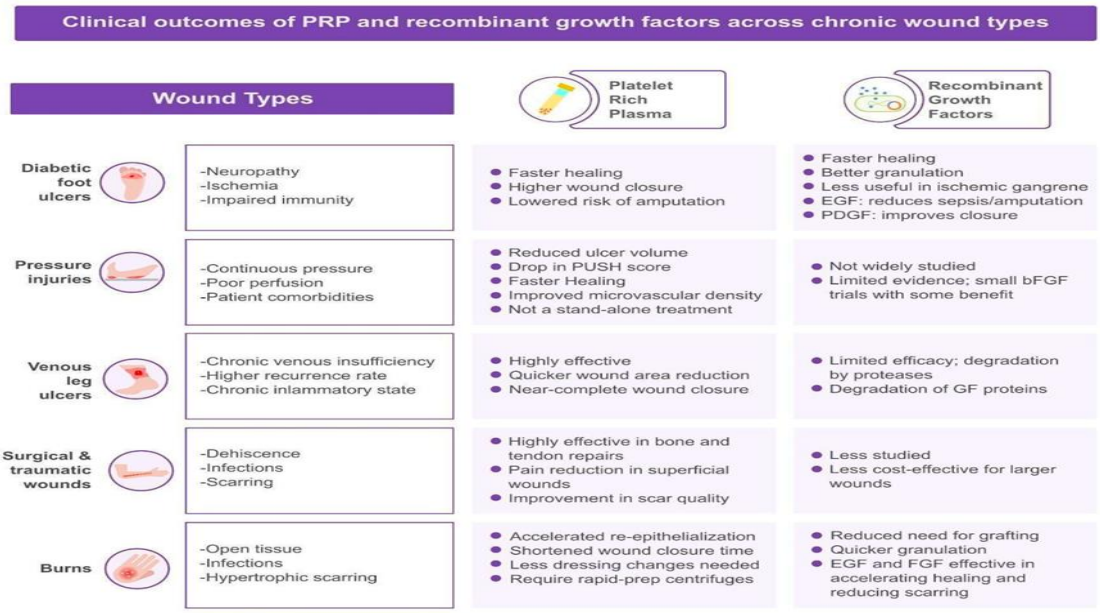

Figure 5. Plasma v. Recombinant Clotting Factors

A new and more promising treatment in the field of Hemophilia is Gene Therapy, which takes a completely new approach when trying to fight Hemophilia [3]. Instead of aiding the body repeatedly with clotting factors, as done in Clotting Factor Replacement Therapy, Gene Therapy attempts to stop the issue at the root. This means providing the liver with a functional copy of the defective gene leading to Hemophilia, further allowing the body to self produce it's own clotting factor. The latest gene therapy utilizes adeno-associated viral (AAV) vectors, which target cells and then deliver the needed genetic material directly to them [5]. Over clinical trials, this has resulted in a mass reduction of bleeding episodes and an increase in clotting factor quantities within the human body [3]. In Figure 5, I have also attached a demonstration of the Gene Therapy process showing how it works step by step, showing how AAVs transport the needed functional genes to the liver cells, allowing for continuous factor production [11]. Though the pricing for Gene Therapy is still quite expensive, this work is a good basis to build toward refined and financially safer technologies[16-18]

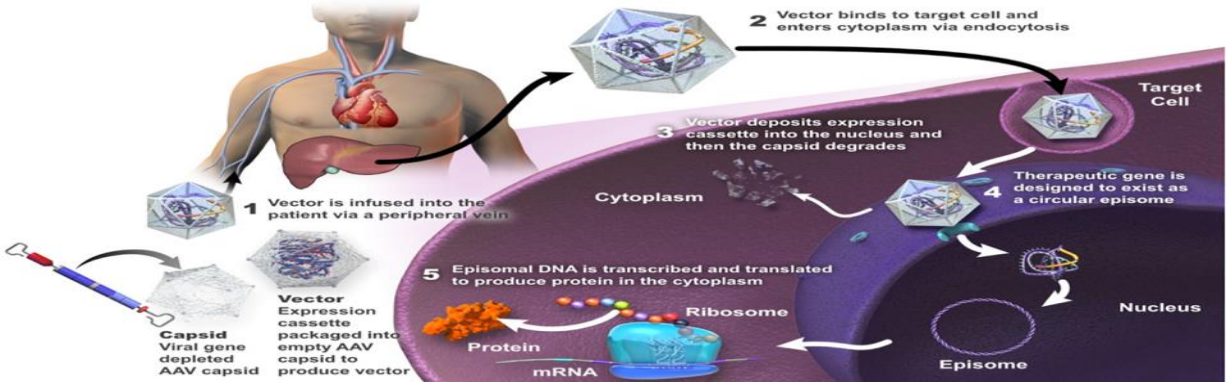

Figure 6. Modern Gene Therapy using AAV

Conclusion

The X-linked recessive disorder Hemophilia illustrates the influence of genetics on health at both the individual and historical levels. The disorders' presence in the royal families of Europe has helped transform a normal disorder into a societal and political issue, eroding public trust as well as royal succession. Time has seen studies of Hemophilia help foster and grow early foundations of heredity and genetics. In present-day modern technological innovations, such as clotting factor replacement and emerging gene therapies, have helped vastly improve the quality of life for individuals living with Hemophilia [4]. To conclude Hemophilia is an example of how a disorder based on heritage can shape history while being reshaped by scientific progress.

References

1. Beheshti, Amin, et al. "The History of Hemophilia: A Review of the Genetic and Social Impact of the Royal Disease." Blood Reviews, vol. 31, no. 3, 2020, pp. 112-124.
2. Evatt, Bruce L. "The History of Hemophilia and Queen Victoria." British Journal of Haematology, vol. 151, no. 4, 2010, pp. 312-322.
3. George, Lindsey A. "Hemophilia Gene Therapy comes of Age." Blood, vol. 130, no. 21, 2017, pp. 2261-2266.
4. Ljung, Rolf, and Christopher A. Ludlam. "Progress in Hemophilia Treatment: From Plasma-Derived to Recombinant Factors and Beyond." Haemophilia, vol. 18, no. s4, 2012, pp. 101-106.
5. Nienhuis, Arthur W., and Amit C. Nathwani. "Adno-Associated Virus-Mediated Gene Transfer for Hemophilia B." Expert Opinion on Biological Therapy, vol. 17, no. 11, 2017,pp. 1325-1334. Google Scholar, doi:10.1080/14712598.2017.1364344.
6. Peyvandi, Flora, et al. "Genetic and Management of Hemophilia: A Case Study Intersecting Heritage and Science." The Lancet, vol. 388, no. 10040, 2016, pp. 187-197. Google Scholar, doi:10.1016/S0140-6736(16)00570-4.
7. Rogaev, Evgeny I., et al. "Genotype Analysis of the Royal Family of Tsar Nicholas II: Identification of the 'Royal Disease' as Hemophilia B." Science, vol. 326, no. 5954, 2009,pp. 817-817.
8. Ahmed, Abu-Bakr, et al. "Platelet-Rich Plasma (PRP) and Recombinant Growth Factor Therapies in Cutaneous Wound Healing: Mechanisms, Clinical Applications, and Future Directions." Journal of Clinical Medicine, vol. 14, no. 23, 2025, p. 8583. MDPI, https://doi.org/10.3390/jcm14238583.
9. "Coagulation." TeachMePhysiology, 18 Sept. 2023, https://teachmephysiology.com/immune-system/haematology/coagulation/.
10. "The Royal Disease." BioMatrix Specialty Pharmacy, 15 Jan. 2018, https://www.biomatrixsprx.com/news/the-royal-disease.
11. Svegliati Baroni, Gianluca, et al. "The Arrival of Gene Therapy for Patients with Hemophilia A." International Journal of Molecular Sciences, vol. 23, no. 18, 2022, p. 10228. MDPI, https://doi.org/10.3390/ijms231810228.
12. Arruda, Valder R., and Katherine A. High. "Gene Therapy for Hemophilia." Cold Spring Harbor Perspectives in Medicine, vol. 2, no. 1, 2012, pp. a007617.
13. Ingram, G. I. C. "The History of Haemophilia." Journal of Clinical Pathology, vol. 29, no. 6, 1976, pp. 469-479. Google Scholar, doi:10.1136/jcp.29.6.469.
14. Lillicrap, David. "The Molecular Biology of Hemophilia." Therapeutic Advances in Hematology, vol. 4, no. 4, 2013, pp. 255-267. Google Scholar, doi:10.1177/2040620713491291.
15. Mannucci, Pier Mannuccio. "Hemophilia: From Art to Science." Haematologica, vol. 89, no. 3, 2004, pp. 338-345. Google Scholar, www.haematologica.org/article/view/3042.
16. Massie, Robert K. Nicholas and Alexandra. Atheneum, 1967. [Scholarly biography cited in Google Scholar for historical context on Alexei Romanov and Rasputin].Oldenburg, Johannes, and Anna Pavlova. "Genetic Basis of Haemophilia and Its Implications for Treatment." Haemophilia, vol. 12, no. s3, 2006, pp. 91-97.
17. Pipe, Steven W. "The Promise of Gene Therapy for Hemophilia." Pediatric Blood & Cancer, vol. 68, no. 2, 2021, e28701. Google Scholar, doi:10.1002/pbc.28701.
18. Rushton, Alan R. "Royal Hemophilia: The Mechanism of Mutation." Journal of Medical Genetics, vol. 18, no. 2, 1981, pp. 90-93. Google Scholar, doi:10.1136/jmg.18.2.90.

Source of support: Nil, Conflict of interest: None Declared