

Hemophilia and the Royal Bloodlines

Study Case

This case study complements the virtual reality (VR) game Protein Mission and will help you understand pedigrees, x-linked diseases and how a single defective protein can impact physiological processes... and history!

Watch the following video before reading the case study:
https://www.youtube.com/watch?v=xMNm7XY_m_s

Part I: When a Mutation Affects History

Hemophilia is sometimes referred to as the Royal Disease, and it all started with Queen Victoria of Great Britain who wanted to add strong blood to the family and married her sons and daughters to Spaniards, Russians and Prussians. However, Queen Victoria was a carrier of a mutated gene coding for a clotting factor, and the mutation spread in imperial and royal families, affecting male descendants. The rest is history... Figure 1 on the next page shows a pedigree of her descendants and how the mutation was passed on.

Hemophilia is a disease characterised by the incapacity to normally form blood clots. Blood clotting is a process by which blood coagulates to prevent excessive bleeding, possibly fatal, when a blood vessel is damaged. The coagulation cascade contains several proteins called clotting factors (clotting factors XII, XI, IX, VIII, X, V, II [prothrombin], and I [fibrinogen]), which are all necessary to induce blood clots and prevent excessive bleeding. Hemophilia is now treatable with

blood transfusions, but it is an expensive and intrusive process that greatly affects the quality of life of patients. In the recent years, genetic treatments have successfully been used to increase blood clot factor concentrations in hemophiliac patients (Wolfgang et al., 2022). One type of gene therapy for hemophilia is using a non-pathogenic virus as a vector to deliver the gene in the cells. In this case, the viral DNA is replaced by a bioengineered 'corrected' gene.

1. What is the correct definition of a codon:

- a) A sequence of three nucleotides on the tRNA that is codes for a specific amino acid
- b) A sequence of three nucleotides on the mRNA that is codes for a specific amino acid.
- c) A sequence of three nucleotides on the DNA that is codes for a specific amino acid
- d) A sequence of three amino acids on the polypeptide chain that is codes for a specific protein.

2. **Discussion** : Explain how a mutation may affect an individual's ability to prevent excessive bleeding?

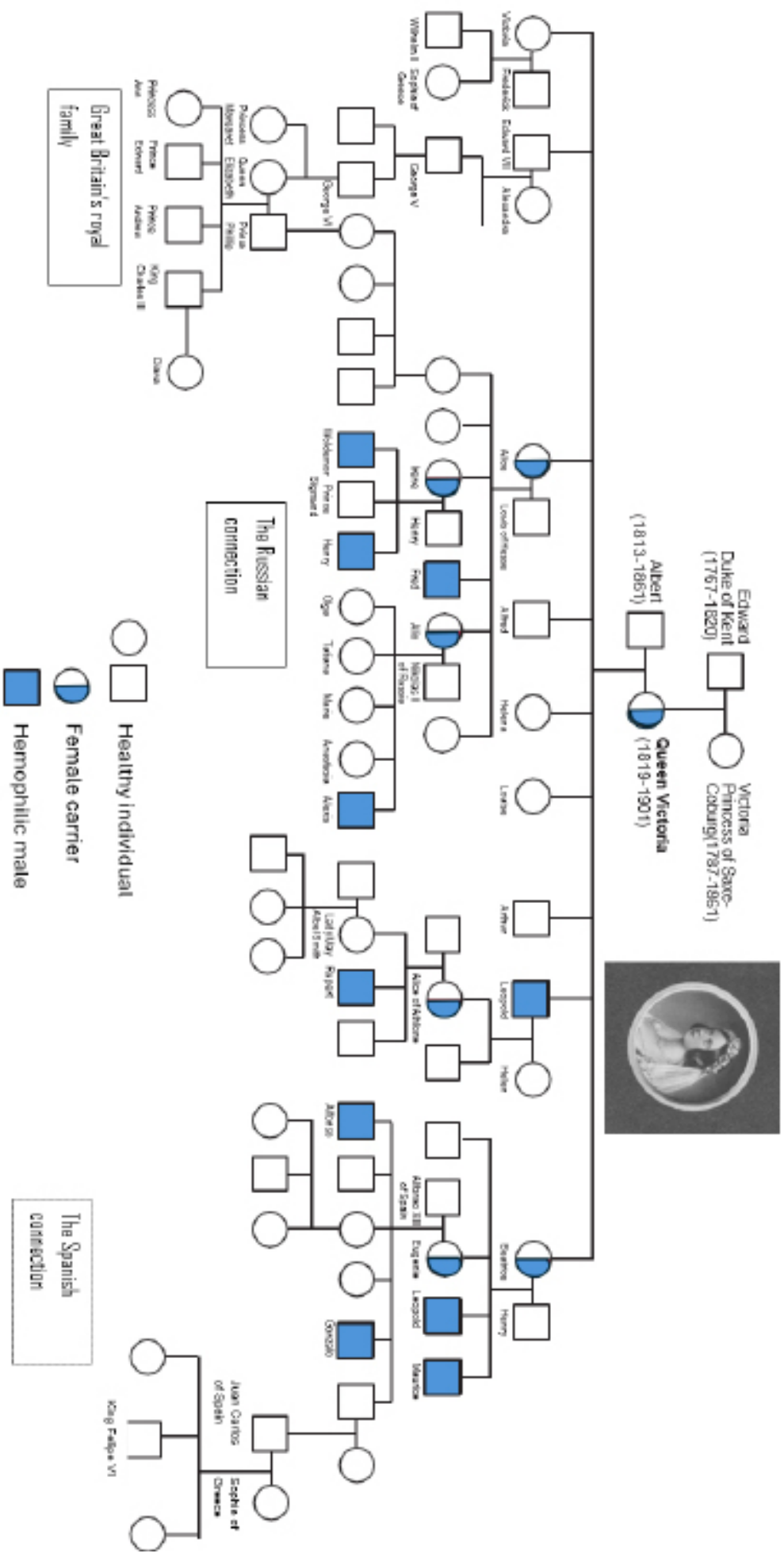


Figure 1. Pedigree montrant la phylogénie de l'hémophilie dans les familles impériales d'Europe. Adapté de « Hemophilia, The Royal Disease » par Aronova-Tiuntseva et Herreid, National Centre for Case Study Teaching in Science.

Part II: X-linked recessive disease

3. In figure 1, can you see more males or females affected?

4. Why are x-linked recessive diseases more common in males?

The Russian connection

Take a closer look at the Russian connection in figure 1. You can see that Victoria's daughter Alice passed hemophilia to the Russian imperial family, the Romanov, killed during the Russian revolution. Rumour has it that Tsar Nikolas II of Russia and his wife Alix were often calling on a now famous healer called Rasputin to take care of their hemophilic son Alexis, their awaited and sole male descendant. The role that Rasputin took in the Russian revolution and the fall of the Romanov family is debated but given that Alexis' health was greatly affected by hemophilia, one can suppose that the tsar and tsarina may have lost focus of what was happening in Russia!

5. Given that hemophilic males at the time died before reproductive age, we can assume that Nikolas II was not hemophilic. What was the likelihood that Alexis be hemophilic?

6. What was the likelihood that Alexis' sister Anastasia be hemophilic?

6 b. What was the likelihood that Anastasia be a carrier?

The Spanish Connection

Now take a closer look at the Spanish connection.

7. If you learnt that the current king of Spain, Felipe VI, had hemophilia, could you say that it is coming from the royal bloodline or can there be another explanation?

Conclusion and practice

Now take a closer look at Queen Victoria at the origin of this pedigree and remember that hemophilic males' life expectancy at the time was very low. Duke of Kent was 50 years old when he conceived Victoria. Victoria's mother was married before she married the Duke of Kent and none of her offspring or offspring's family showed signs of hemophilia.

8. Give a hypothesis that would account for Victoria being a carrier.

Practice

Now it's your turn to practice.

9. Draw a pedigree using the following information and draw a Punnett square for the parents. Indicate carriers only when you are certain that the individual is a carrier.

Informations :

- a) A man with hemophilia has children with a woman without hemophilia.
- b) They have 2 daughters and 2 sons, none of them have hemophilia.
- c) The first daughter has a son with hemophilia