Hemophilia A

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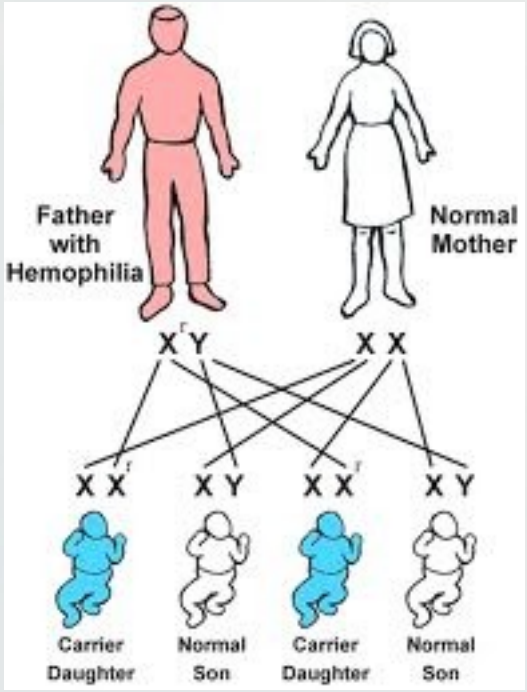
Disease Overview

- Hemophilia A is a blood disorder that affects clotting
- Type A mutation results in abnormal version of Coagulation Factor VIII
- Superficial and subtle dangers- spontaneity
- Biggest danger is in complications from internal bleeding (joints, muscles, brain organs)

Medelian Sex-Linked Trait

- Sex-Linked on X chromosome, recessive
- Any male with a copy is affected, females need homozygous recessive to be full
- Though primarily affects males, can't pass father to son
- 10% heterozygotes develop mild blood disorder



History of Hemophilia

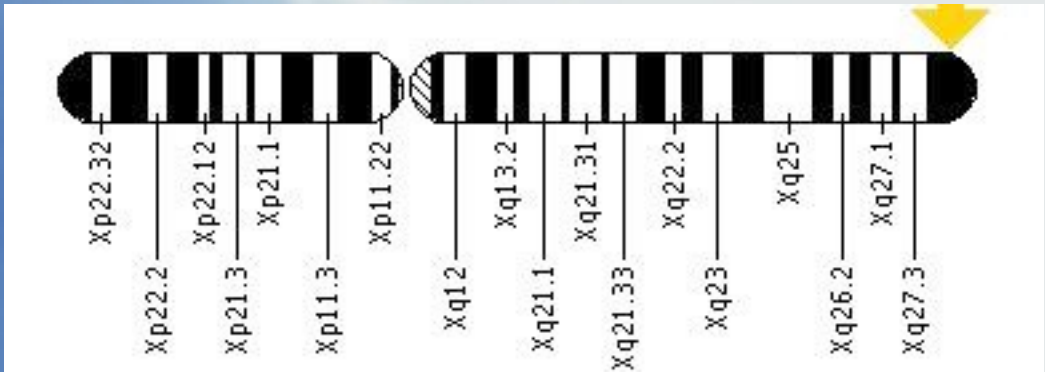
- “The Royal Disease”
  - Russia, Germany, Spain via Victoria
- Today, affects about 1 in 5,000 live male births (equal geographically because of spontaneous mutation)
- Also Hemophilia B which is on the F9 gene, affects other factor

Traditional Treatment

- Gene counseling
- Assessment of situation
- Management of symptoms
  - Lifestyle Changes
  - Vigilance for symptoms

Genetic Basis for Disease

- A mutation of the F8 gene, located on the X chromosome at Xq28
- Mutation between bases 154,064,062 to 154,250,997
- Causes the protein to be deactivated because of improper coding
- Inversion of 1kb introns 1 and 5' leads to severe phenotype. Point mutation stop codons



Penetrance and Expression

- Penetrance is nearly universal in affected males and homozygous females
- Varying levels of expressivity
  - Most severe usually diagnosed in first year
  - Medium severity can be at 5-6 years
  - Mild can be late in life
- Families generally have consistent expressivity

New Diagnosis Options

- Factor VIII level vs. von Willebrand
- Prenatal sequence tests are possible but carry risk
  - Only done when there is reason
- Gene sequencing tests can confirm the disease in 98% of individuals

Contemporary Genetic Treatment

- Understanding the location and coding of the genes allows for infusions of blood with F8 concentrate
- No way to change or replace the gene sequence is in clinical trial, but the disease can be managed effectively
- Pre-clinical experiments in progress
  - Developing viral infections from human clotting factors

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