Paroxysmal Nocturnal Hemoglobinuria

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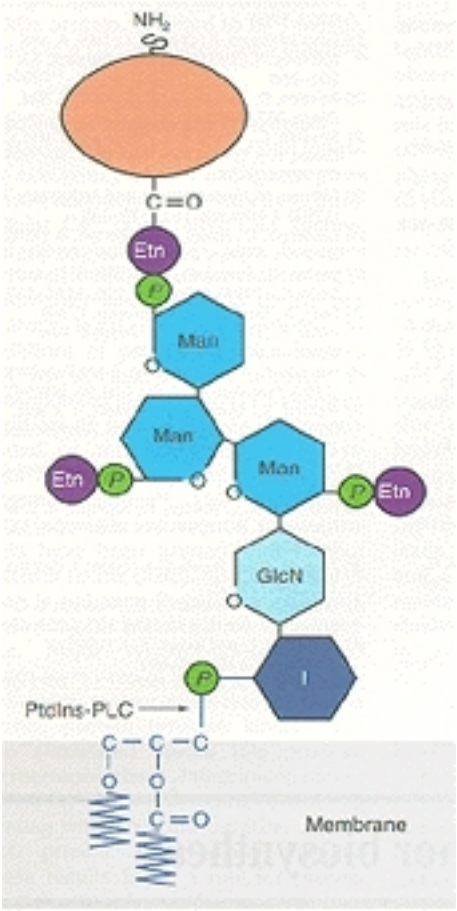
PNH

- A rare, acquired, potentially life-threatening disease of the blood
  - Anemia
  - Hemoglobinuria
  - Hemoglobinemia
  - Thrombotic events
- PNH is the only hemolytic anemia caused by an acquired defect in the cell membrane
- It may develop on its own ("primary PNH") or in the context of other bone marrow disorders such as aplastic anemia ("secondary PNH")


07:00
09:00
12:00
15:00
19:00

Pathophysiology

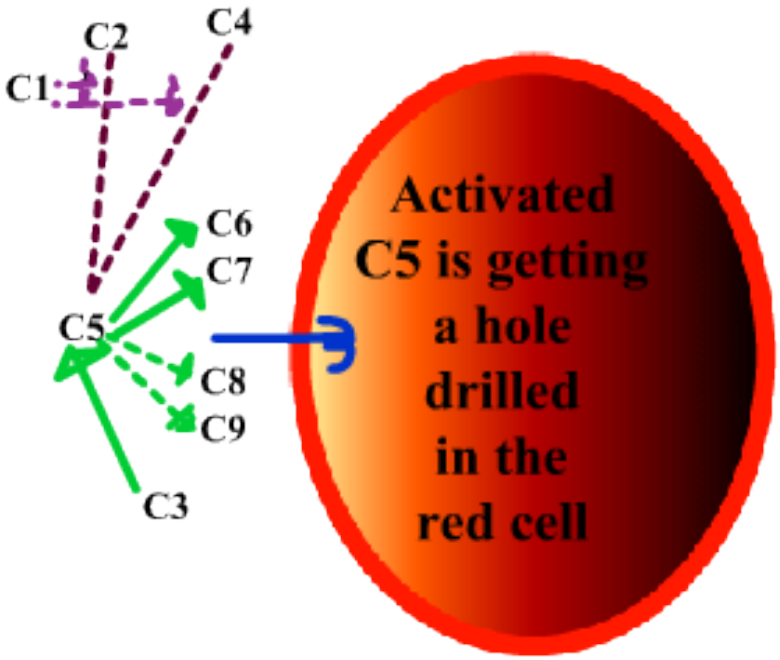
- The enzyme phosphatidylinositol glycan A (PIGA) is needed to make glycosylphosphatidylinositol (GPI)
- A mutated PIGA gene leads to deficiency of surface expressions of GPI-anchored complement inhibitors leads to complement-mediated hemolysis



A glycosylphosphatidylinositol (GPI) anchor - people with paroxysmal nocturnal hemoglobinuria (PNH) have a mutation in the first enzyme in the GPI anchor synthesis pathway. [Reproduced with permission from Takeda, J. and Kinoshita, T. (1995) Trends Biochem. Sci. 20, 367-371.]

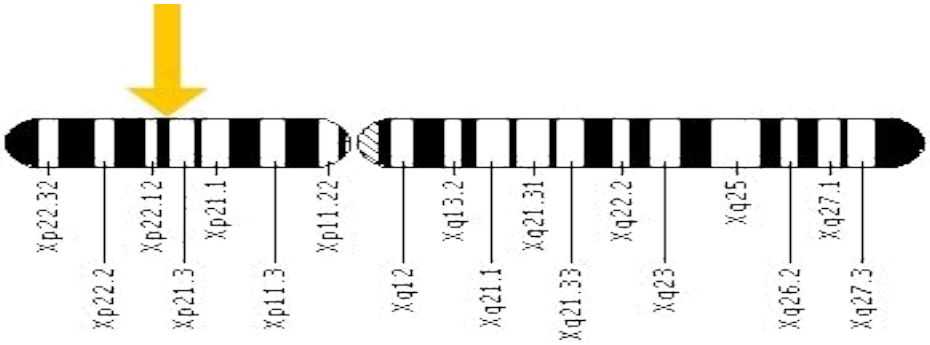
The Complement System

- Proteases in the system cleave specific proteins to release cytokines and initiate an amplifying cascade of further cleavages
  - Massive amplification
  - C5 protein leads to activation of the cell-killing membrane attack complex.



Genetics

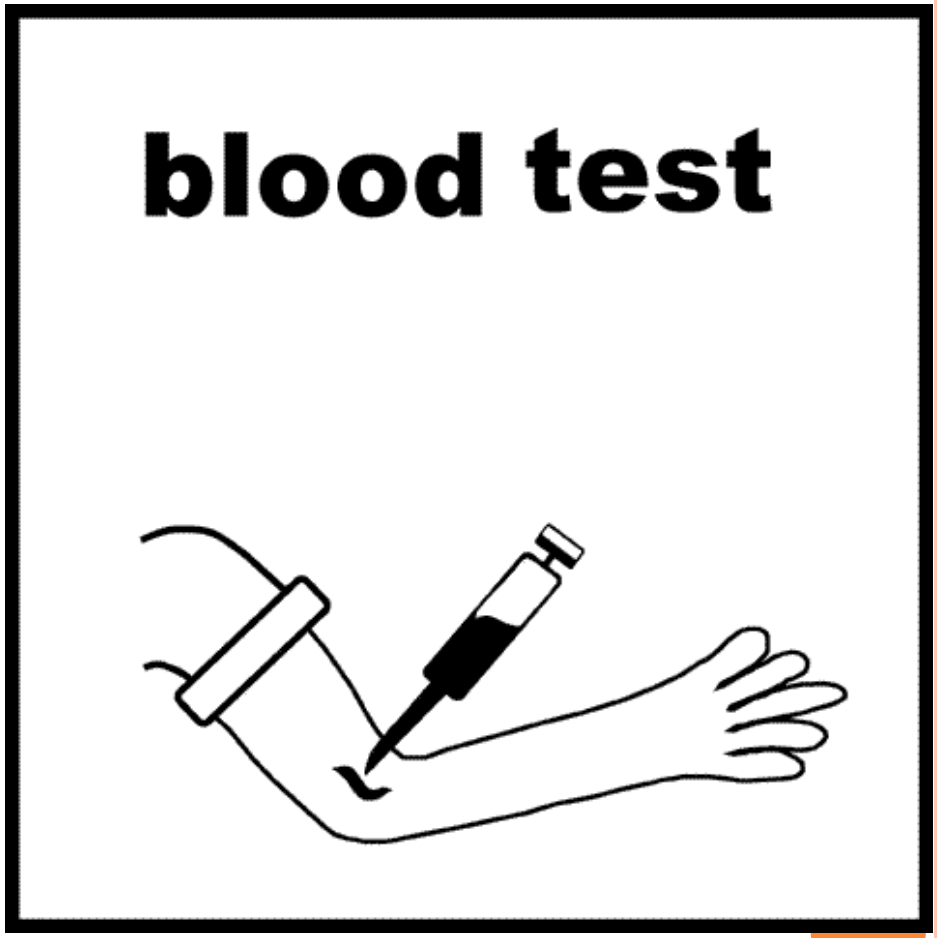
- Mutation of the PIGA gene on the X chromosome
  - Somatic mutation in only one X chromosome is necessary to produce the mutation in a male cell or female cell if it occurs on the active X chromosome.



- All patients with PNH is have PIGA defect, but PIGA is but 1 of at least 10 genes involved in GPI synthesis.

Classical Diagnosis

- Blood tests:
  - Low hemoglobin
  - Raised lactate dehydrogenase
  - Raised reticulocytes (immature red cells)
  - Raised bilirubin (a breakdown of hemoglobin)
  - Sucrose test/Ham's test

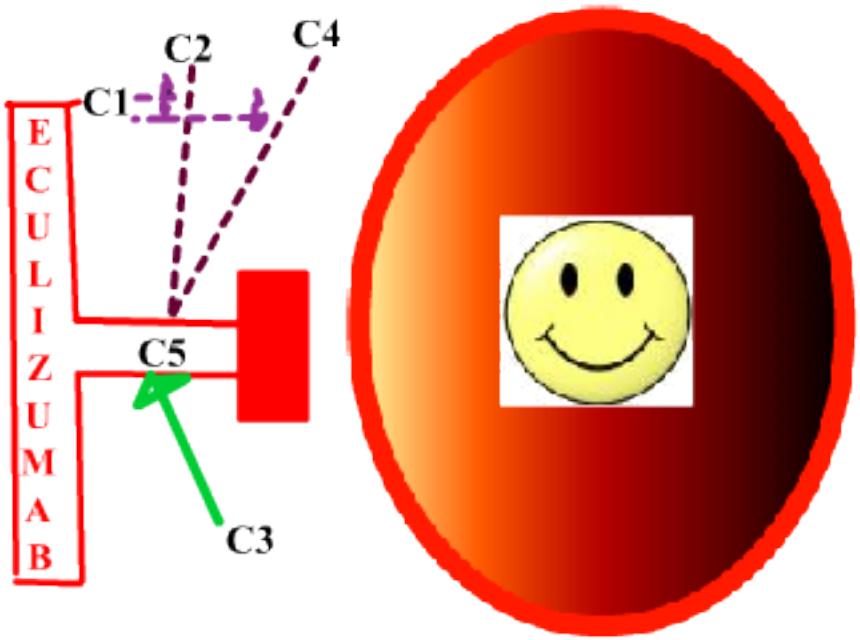


Modern Diagnosis

- Flow cytometry for CD55 and CD59
- …

Treatment

- Eculizumab, or Soliris, is a monoclonal antibody directed against the complement protein C5.



Treatment

- According to Forbes magazine, Soliris, at $409,500 a year, is the world's single most expensive drug.

Sources

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- http://www.ncbi.nlm.nih.gov/books/NBK22166/
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