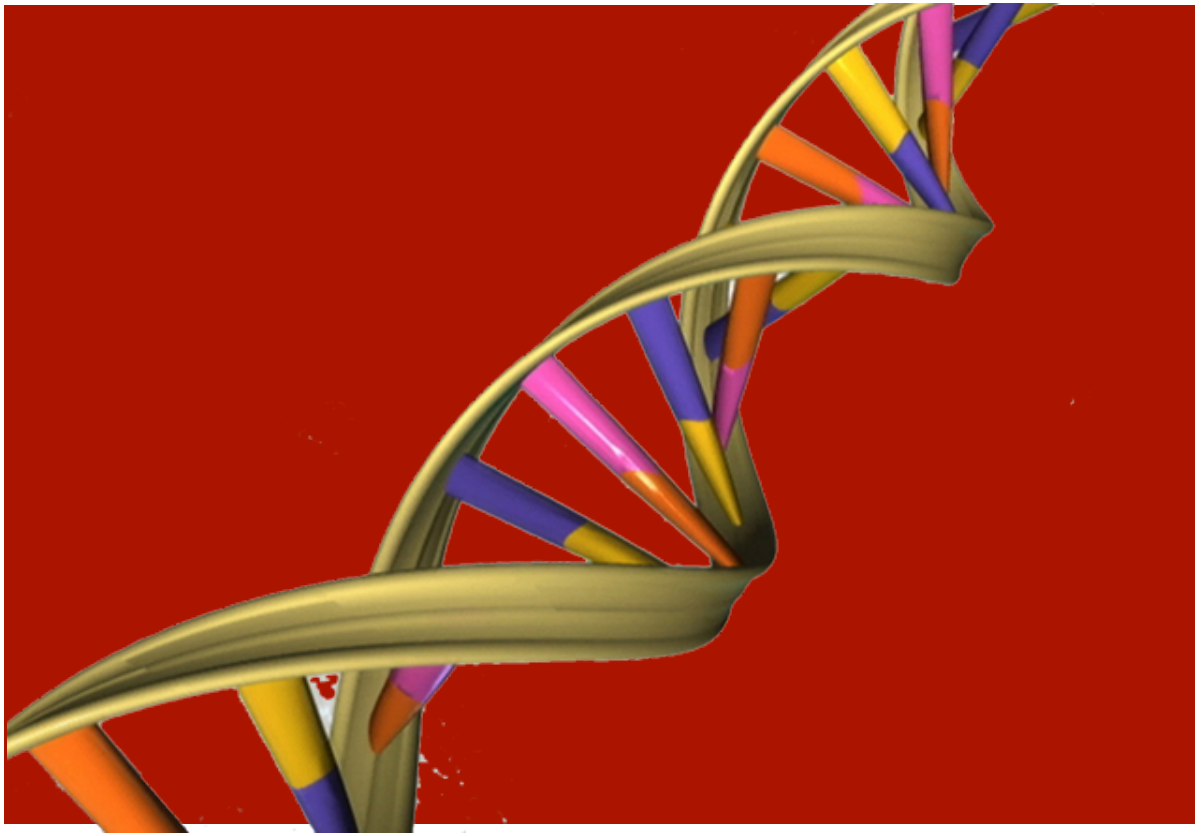
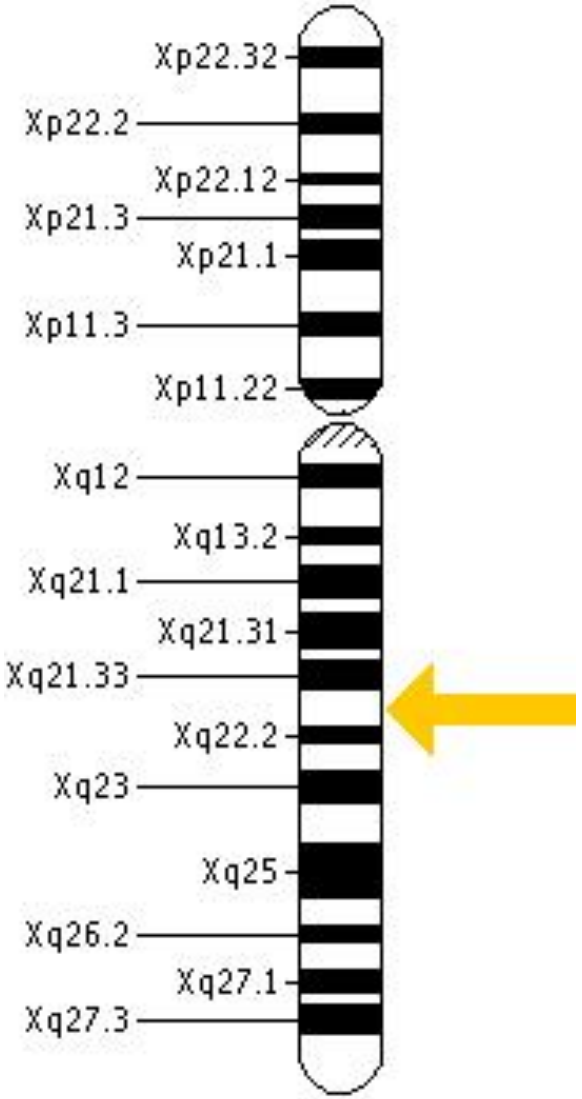


Fabry Disease

Lauren Sweet
Genomics and Medicine 2012

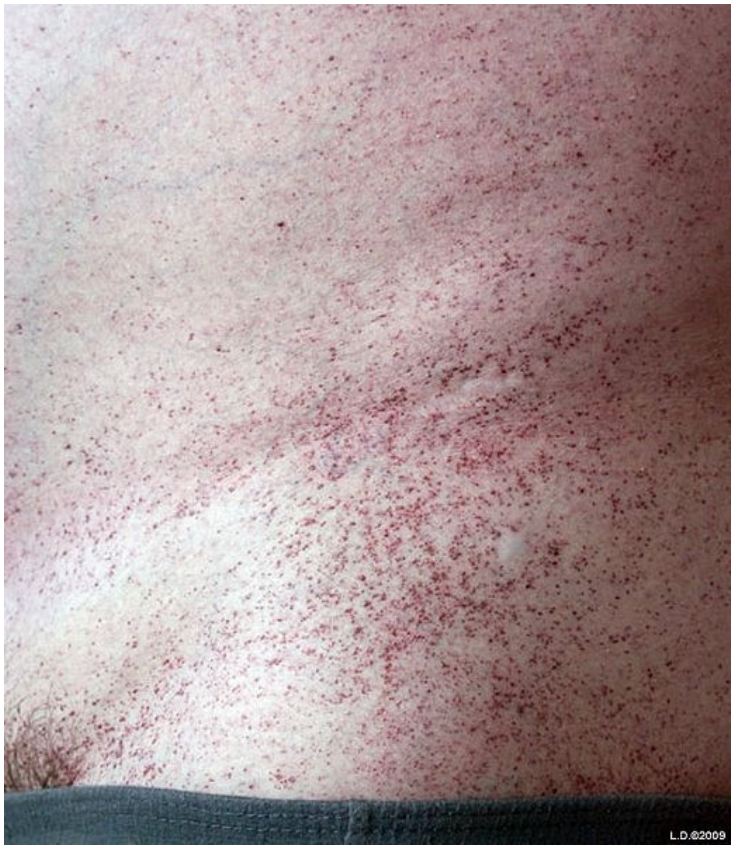
The Gene

- Galactosidase, alpha (GLA)
- ~12kb base pairs
- Contains 7 exons
- Location: Xq22.1
- Codes for the enzyme α-Gal A



Classic Signs and Symptoms

- Angiokeratomas
- Severe Pain
  - Acroparesthesia
- Inability to sweat
  - Anhidrosis
- Eye Problems
  - Opacity of the lens and cornea
- Later Stage: Cardiovascular issues
- Cerebrovascular issues
  - Including thrombosis, , aneurysm, seizures, hemiplegia, aphasia and hemorrhage
- Progressive Renal failure
- Other: gastrointestinal, pulmonary, auditory problems, psychological issues



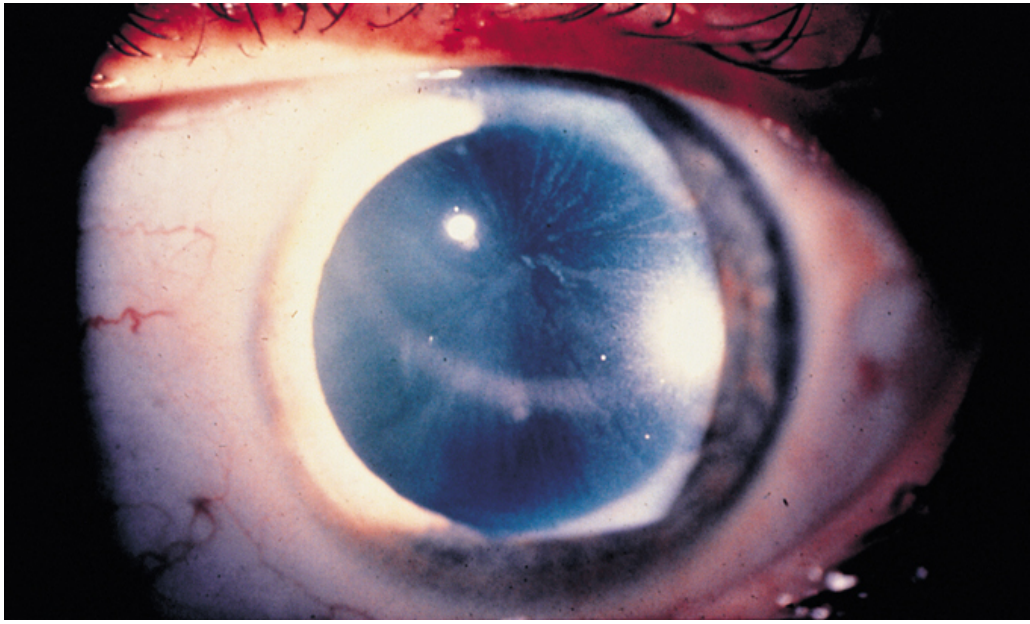
Carrier Variants

- Heterozygous (carrier) females range from asymptomatic to as sever disease as males

- In most cases females have a more milder case of the disease

- Common symptoms among carriers
  - Cornea/lens issues
  - Pain or tingling in extremities
  - Slight angiokeratomas
  - Hypohidrosis
  - Only about 10% of carriers develop renal failure

- Psychological impacts: guilt, fatigue, depression, suicidal thoughts



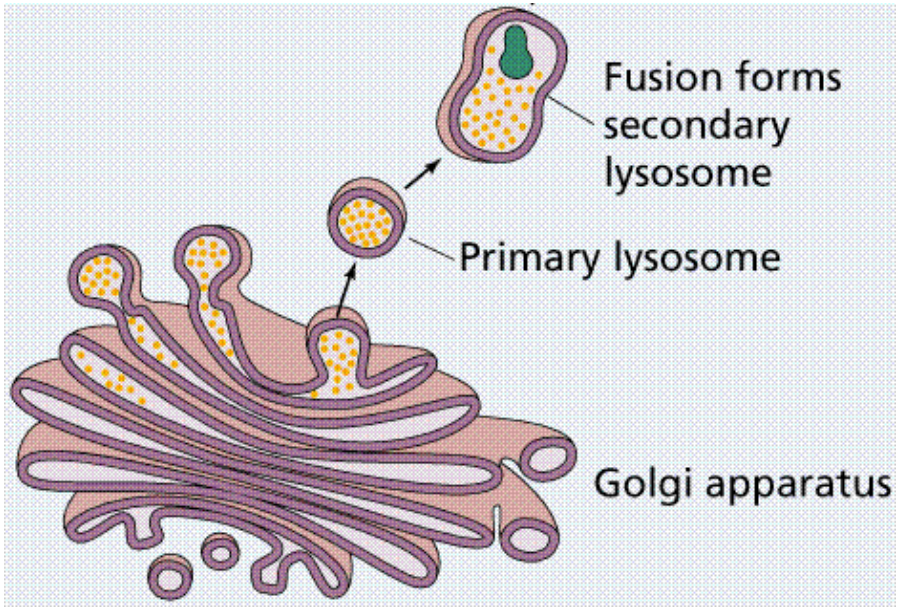
A Genetic Deficiency

- Mutation in GLA leads to improperly functioning α-Gal A

- α-Gal A works in lysosomes
  - Breaks down globotriaosylsphingosine (Gb3), a by product of recycling old cells like red blood cells

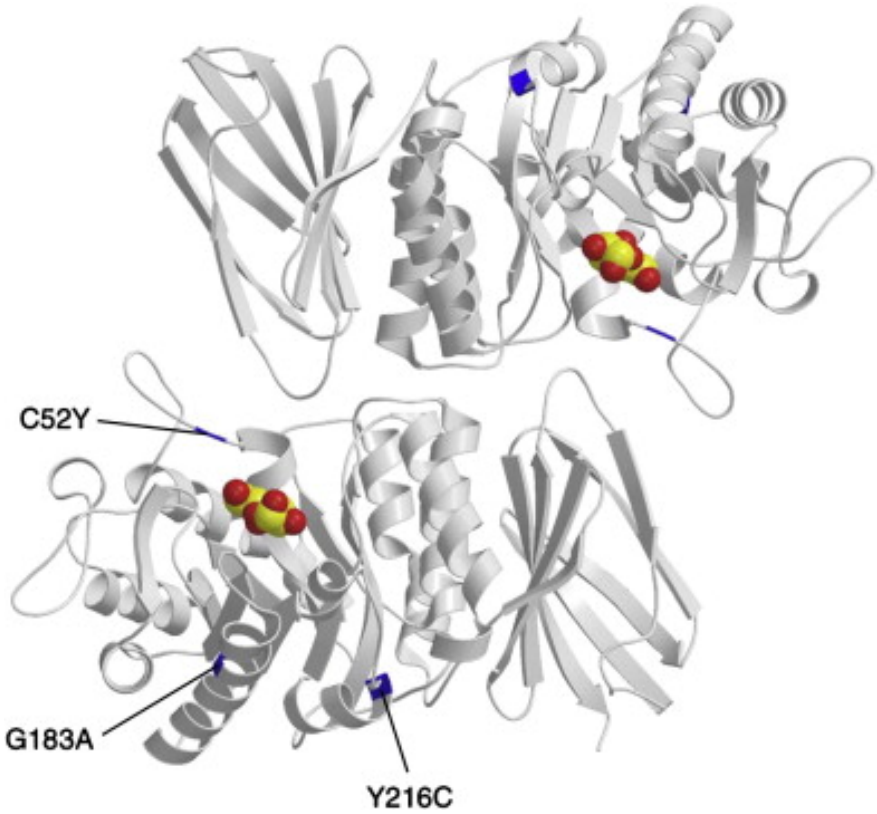
- Fabry GLA gene defect causes Gb3 to build up in the cells, damaging tissues

- Other regulatory functions:
  - Catalytic activity
  - Binding(cations, proteins, receptors, galactoside)
  - Hydrolase activity



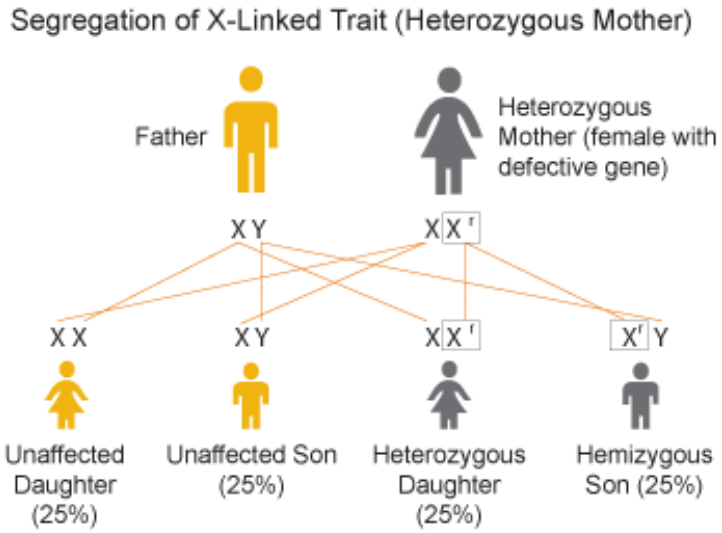
Genetic Diagnosing

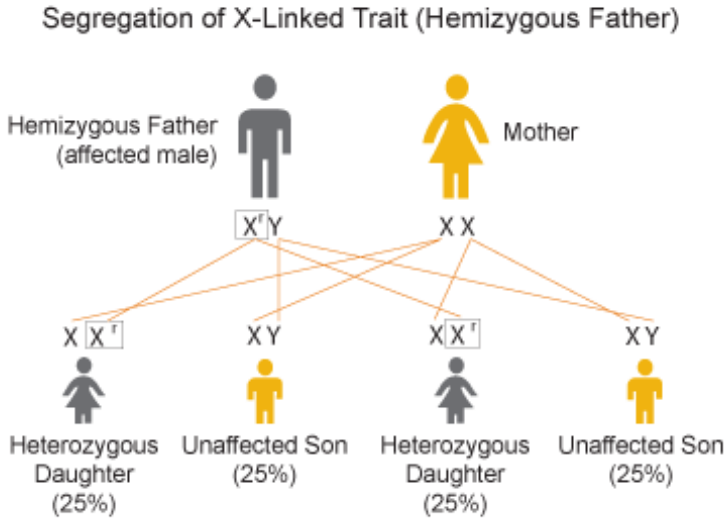
- Best way (in males) to detect Fabry disease is to measure their α-Gal A levels
  - <1% a-Gal A activity=classic
  - >1% a-Gal A activity= cardiac or renal variant
- In carriers the only way to reliably test for Fabry is through sequencing and looking for the GLA gene
- No one type of mutation in GLA responsible for Fabrys
  - Nearly every family has a different mutation of their GLA gene
  - Science still in the stage of trying to identify all the mutatiosn



Treatment and Inheritance

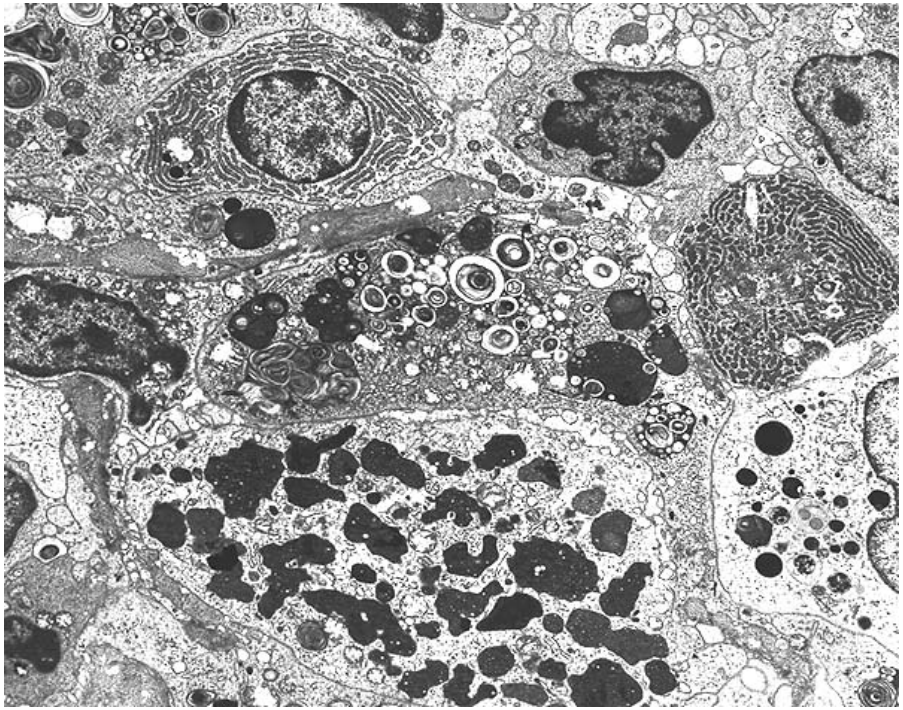
- Currently limited to treating the manifestations
  - Enzyme replacement therapy (ERT) used, but with mixed results
  - Dialysis, renal transplant
  - More localized approach being tested
- Inherited on the X chromosome
  - Mother of affected son is obligate carrier
- Carrier female has 50% chance of passing it on to each pregnancy
- Occasionally de novo mutations in males seen





An Under-diagnosed Disease?

- Traditional estimates:
- 1:50,000 males
- 1:80,000 females
- Italian Study (Spada et al. 2006) : incidence may be as high as 1:3100
- Why?
- Looks like other diseases
- Can not show up until late in life
- Especially under diagnosed in the cerebro, cardio, renal versions of the disease



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