Fabry Disease

Lauren Sweet
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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 severe 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 $\alpha$-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 mutations
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
Bibliography


