Tay - Sachs Disease: Childhood Killer

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Introduction

- Discovered in 1881 by Warren Tay (1843 - 1927), a British ophthalmologist
- Named also for Bernard Sachs (1858 - 1944), New York neurologist
- described first cellular changes in Tay-Sachs
- familial nature of disease
- high propensity in East European Jews
Introduction

- Disease isolated to three ethnic groups
  - East European (Ashkenazi) Jews
  - Non-Jewish French Canadians living near the St. Lawrence River
  - Cajun population of Louisiana
- Other cases are isolated to specific families only
Classic TSD Symptoms

- Children are normal at birth
  - appear to develop normally
  - symptoms appear ~ 6 months old

- Initially
  - development slows
  - loss of peripheral vision
  - dramatic startle response
Symptoms (Cont’d)

• By 2 years
  - recurrent seizures
  - loss of mental functions
  - disappearance of acquired skills
  - restricted coordination and movement
Symptoms (Cont’d)

• Eventually
  - Blindness
  - Mental retardation
  - Paralysis
  - Nonresponsiveness to environment or other stimulation
  - Death at ~ 6 years old
Molecular Information

- TSD stems from mutation in β-hexosaminidase A enzyme
- β-hexosaminidase A comprised of α/β heterodimer
- Mutations in α (HEX A gene) cause TSD, mutant β causes Sandhoff Disease
- Autosomal recessive disease
- Gene frequency 1/27 for Jews, 1/300 for general population
Molecular Information

- HEX A is a 35 KB gene
- 14 exons
- Hex A mapped to 15q23-q24
- Mutations cause storage of GM2 Ganglioside in lysosomes of neurons
β-Hexosaminidase

GM2 Activator
Reduction of GM2 to GM3

GM2 Ganglioside

GM3 Ganglioside

N-Acetylgalactoseamine
TSD Mutations

- Many mutations that cause some form of TSD
  - caused by various mutations in $\alpha$ or $\beta$ subunits
  - many not yet identified
Common Variations

1. Ashkenazi Jewish Population
   - 4 bp (TATC) at number 1277 in exon 11
   - 70% of Jewish TSD cases
   - Causes a 9 bp downstream stop signal and
   - mRNA is deficient

2. 69% of Cajun TSD patients have the same 4 bp insertion in exon 11
Common Variations

3. French Canadians
   - found in 82% of TSD cases
   - 7.6 KB deletion
   - loss of entire exon 1 and part of intron 1
   - extends 2000 bp into putative promoter
Diagnosis

- Two methods of diagnosis of TSD carriers
  1. Enzyme Assay
     - blood is drawn to determine $\beta$ hexosaminidase A levels
     - Carriers have lower levels than normal individuals
  2. DNA Test
     - use known mutations as probes on cultured DNA extracts
Treatment

- No cure has been brought forth as of yet
- Animal model has been developed in mice
  - knocked out $\alpha$ subunit on chromosome 9
  - GM2 is stored, but no neurological abnormalities are apparent
  - mice have minor pathway to degrade GM2
- have created adenoviral vector which transforms in vivo liver cells
- full or partial restoration of enzyme
Prevention of TSD

• Accent on prevention because there is no cure
• Genetic counseling for high risk ethnic groups
  - easy prenatal diagnosis
  - possible therapeutic abortion


