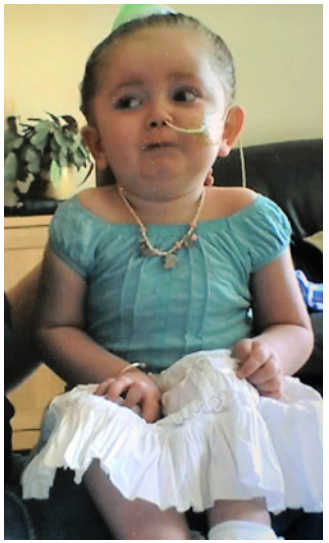
TAY-SACHS DISEASE

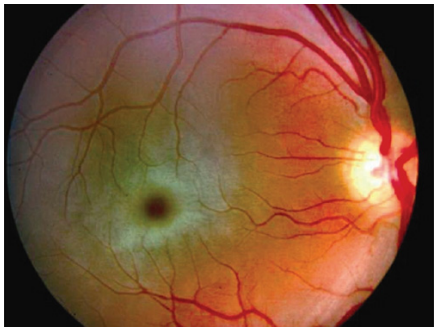
KIRIT LIMPERIS

P3

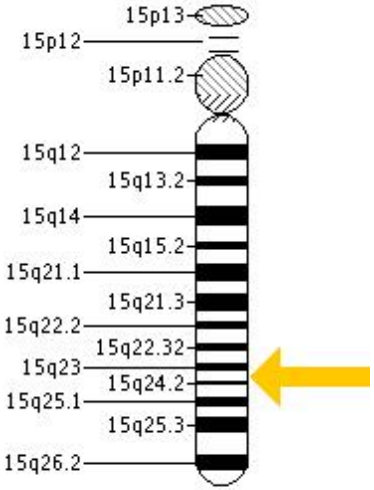
PHYSIOLOGY AND SYMPTOMS

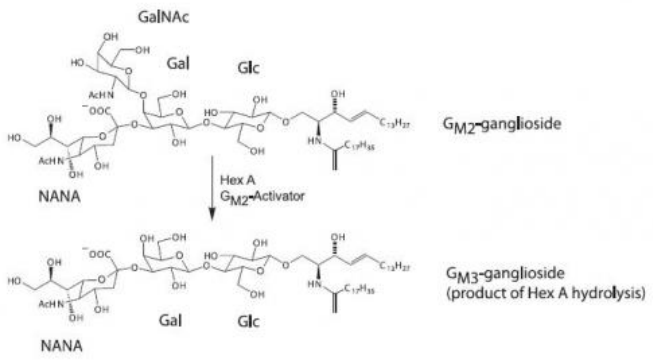
- **1/250 people in general population is a carrier (1.2 mil Americans)**
- **Most common in Eastern European Jews (and French-Canadians)**
- **Lysosomal storage disease**
    - loss of motor skills and muscle function followed by possible paralysis
    - possibly deafness and blindness
    - **Infantile (Classic) Tay-Sachs**: Begins ~6 months
        - Diagnosis: motor delays, Cherry-red spot due to gangliolside buildup
        - Seizures
        - Definite paralysis
        - diminishes mental and social skills, and slows growth
        - Eventual respiratory shut down
        - *Lethal by age 6*
            - Hexosaminidase A enzyme nonfunctional in lysosomes
    - **Juvenile:** Begins 5 – 10 years old
        - Rarest
        - Same symptoms as infantile
        - *Lethal* (Hexosaminidase A is in smaller quantities → delays death)
    - **Late-Onset:** patient appears healthy until teens-30 years old
        - decreased muscle strength, can develop into paralysis
        - extreme emotions (40% have bipolar disorder)
        - Suffered from speech difficulties and were athletically less capable in childhood
        - *Not lethal – life expectancy is the same as that of wild type*
            - Hexosaminidase A enzyme semi-functional

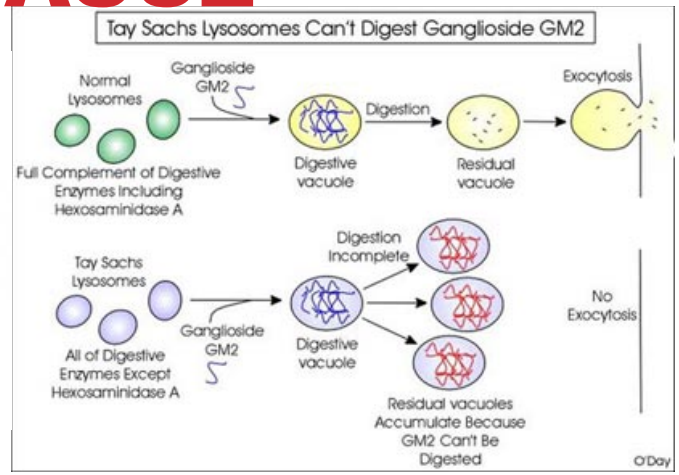




MOLECULAR CAUSE



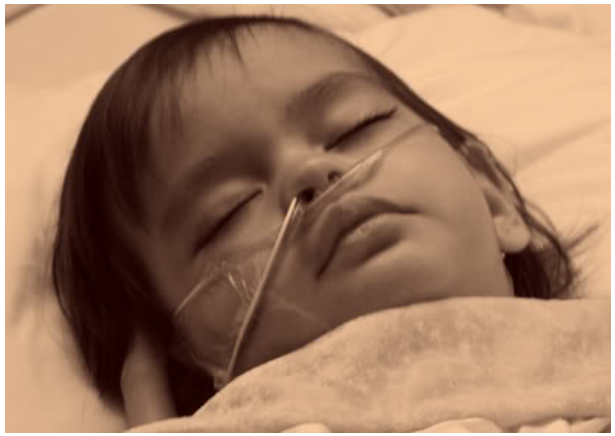


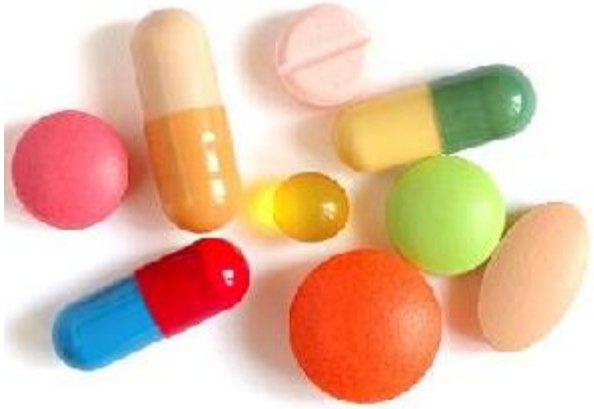


- **HEXA gene is located on Chromosome 15, 15q24.1**
  - 72,635,777 to 72,668,519 base pairs (32,742 base pairs)
- **HEXA gene codes for Hexosaminidase A enzyme in the lysosomes of nerve cells**
  - Beta-hexosaminidase A portion of enzyme is destroyed in mutation
- **Hexosaminidase A protein breaks down the fatty GM2 Ganglioside substance into GM3**
  - GM3 is essential in brain development, its presence prevents seizures
- **HEXA mutation causes GM2 buildup in nerve cell lysosomes → death of nerve cells in brain and spine**
  - Causes blindness, deafness, and paralysis
- **5 "Novel Mutations"**
  - deletions: a two base deletion of TC in exon 5, and the five base deletion of TCTCC (common lesion in E European Jews)
  - Insertion: stop codon in exon 1
  - Substitution: amino acid exon 5
  - Point mutation: G to C at position 1 of IVS-2
- **pattern of a 7.5 kilobase deletion is common in French Canadian Tay-Sachs patients**

TREATMENTS: CURRENT…

- **Only current solution is to help relieve symptoms**
  - For seizures: antiepileptic drugs, also known as anticonvulsants, such as benzodiazepines, phenytoins, and/or barbiturates
  - For emotions (bipolar disorder and depression): antidepressant medication and conventional antipsychotics
  - If necessary: breathing tubes and ways to clear excess mucus





…AND ON THE HORIZON

- **Enzyme replacement therapy**
  - Inject missing enzyme (Hexosaminidase A) into brain
  - Lifelong therapy
  - already been tested: on a 14-month-old baby, and another time on a 7-week-old baby. Neither trial was successful
  - Why didn't it work?
    - blood-brain barrier
    - enzyme replacement therapy may only be temporary. The injected enzymes might have died off quickly, before having any effect on the children
    - quality of the enzymes used; the response of white blood cells to foreign objects
- **Stem Cell Injections**
  - Create new nerve cells
  - Inject into spine
  - Risks and complications:
    - immune system of the individual rejecting the stem cells
    - the transmission of the donor's own personal diseases into the Tay-Sachs patient.
    - stem cells are not easily obtained, and there is major controversy over embryonic stem cells
      - Come from three to five day old embryos

MY PROPOSAL:

GENE THERAPY

- **buildup of GM2 ganglioside causes paralysis and death in the disease: cure should find a way to stop the buildup of GM2.**
- **Have to find a way to fix HEXA gene locus**
  - Scientists obtain vector (AAV virus) insert correct HEXA gene (extracted from a person with a error-free HEXA gene) into AAV virus
  - Inject virus into brain
    - Virus attacks faulty brain cells and spinal cord cells
    - DNA of these cells is now altered: able to create Hexosaminidase A enzyme → can now convert GM2 into GM3
  - And it gets better:
    - The corrected cells will excrete the enzyme to cells that were not infected by virus
    - These cells will absorb it → now also have the Hexosaminidase A enzyme
  - No more GM2 buildup → no more nerve cell death → no more paralysis → no more tay-Sachs! *And it's a permanent cure (DNA is altered)*
- **Timing:**
  - Injection has to occur within first few weeks of life
  - Telltale signs do not occur until 6 months (for Classic) → prenatal screening for those who are prone to Tay-Sachs.
- **Possible Complications:**
  - Blood brain barrier may not let vector into brain
    - Solution: inject into "circumventricular organs" where the blood-barrier is weaker
  - DNA in the virus is incorrect, then it would further harm the Tay-Sachs patient
    - Solution: very precise screening of the DNA donors

MY PROPOSAL:
GENE THERAPY

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