Tay Sachs Disease

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What is Tay Sachs?

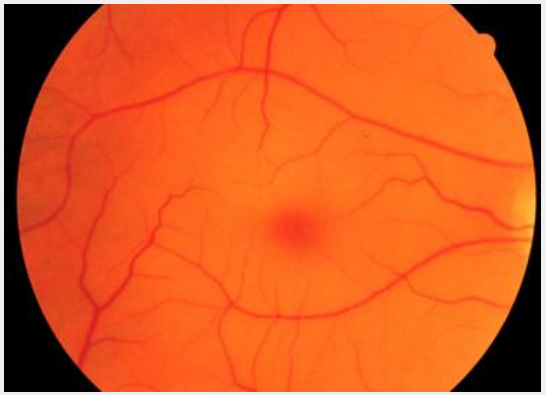
- Rare genetic disorder
- Deletion of Hex A enzyme
- Destroys the nervous system in a progressive manner

(GHR, 2012)

SIGNS & SYMPTOMS

What to look out for

Early/Infantile Onset (~6 months)



- Mild muscle weakness
- Myoclonic jerks/twitches
- Acoustic hypersensitivity
  - Easily startled in response to unexpected noises
- Inability to hold eye contact
- Gradual loss of vision
  - “Cherry red spots” → macular cell degeneration caused by choroid exposure
    - Apparent in ~90% of Tay Sachs cases (NORD, 2016)

Childhood Onset (~2-10 years)

- Lack of coordination and motor skills
  - Clumsiness
  - Unable to walk properly
- Reduction in intellectual abilities
- May develop retinitis pigmentosa
  - Degeneration of the retina
- Loss of speech

(NORD, 2016)

Late Onset (Adolescence--)

- Reduction in motor coordination
  - Muscle weakness
  - Involuntary muscle contractions
  - Tremors
- Slurred speech
- Changes in mood and mental health
- Unable to complete daily tasks

(NORD, 2016)

EPIDEMIOLOGY

Distribution and determinants of Tay-Sachs disease

Genetic Risk Factors

Individuals of the following ethnicities are at a higher risk for being affected by Tay-Sachs or being heterozygous for the mutated allele:

- Ashkenazi Jewish
- French-Canadians of Quebec
- Old Order Amish in Pennsylvania
- Cajuns of Louisiana
- Family history of condition

(Koeslag, 1984)

Tay-Sachs Map

Theories

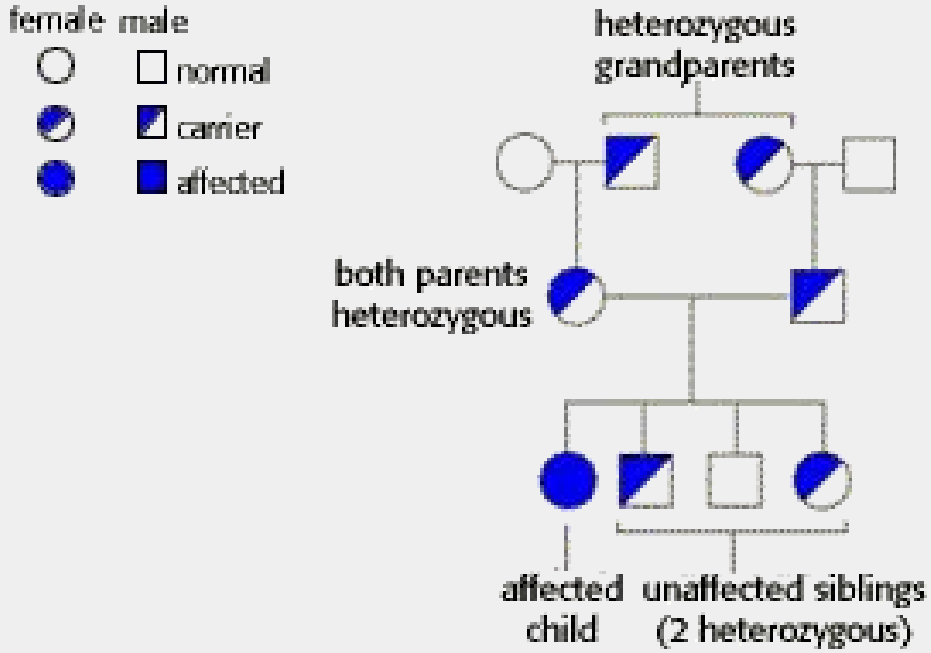
- Heterozygote advantage
  - Being a carrier of mutated gene provides resistance against tuberculosis
- Random genetic drift
  - Change in allele frequencies due to chance
- Founder effect
  - Isolated populations
  - Small initial population: high genetic mutation frequency
- Reproductive compensation
  - Parents who have children affected by Tay-Sachs may continue reproducing

(Withrock, 2015)(Chakravarti, 1978)

Case Study

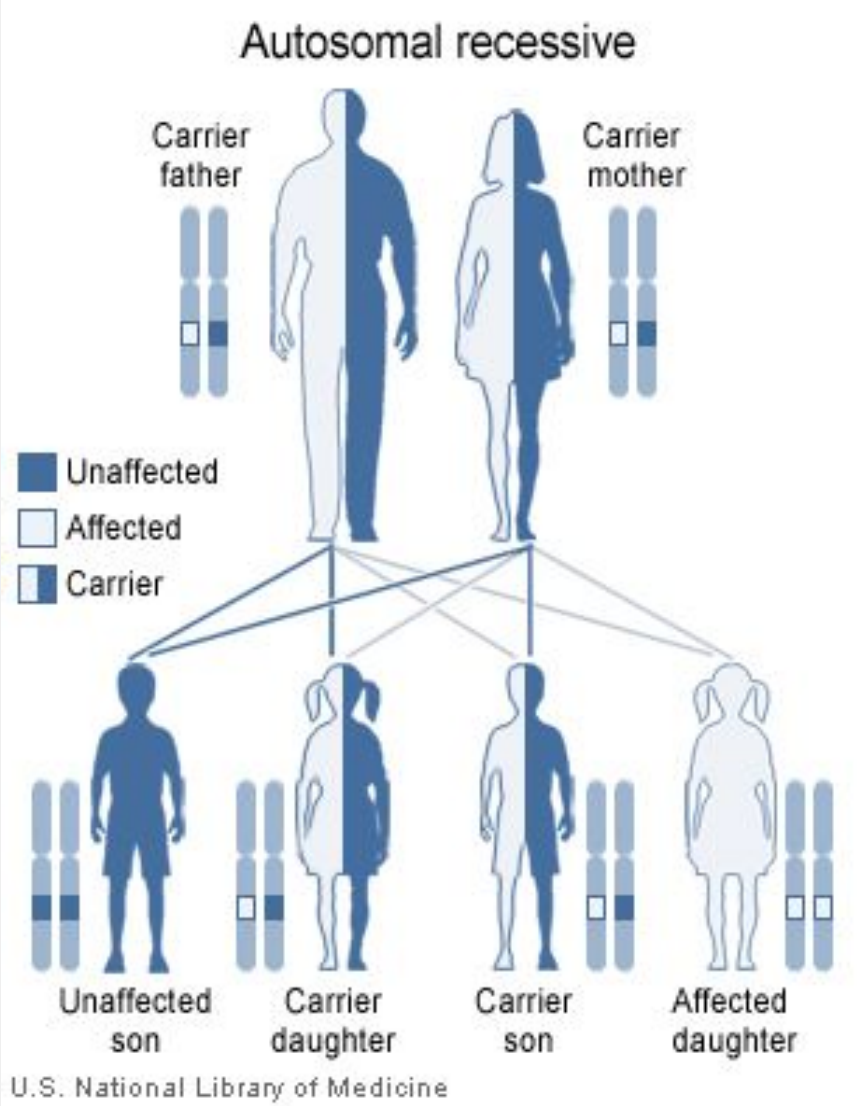
A couple has a female child with Tay-Sachs disease, and three unaffected children. Neither parent nor any of the biological grandparents of the affected child has had this disease.

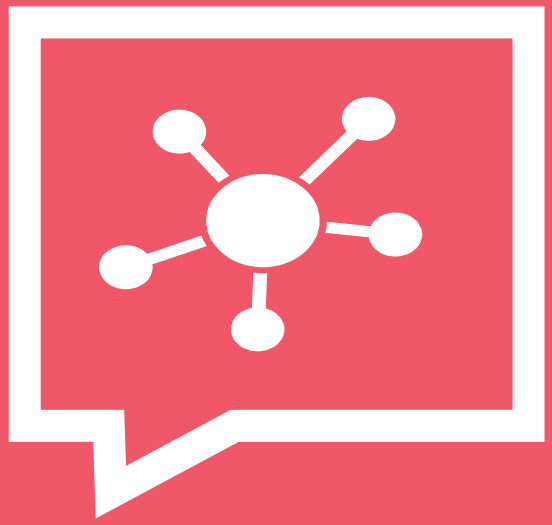
- Dominant or recessive?
- Autosomal or X-linked?



(The University of Arizona, 1998)

Genetic Inheritance



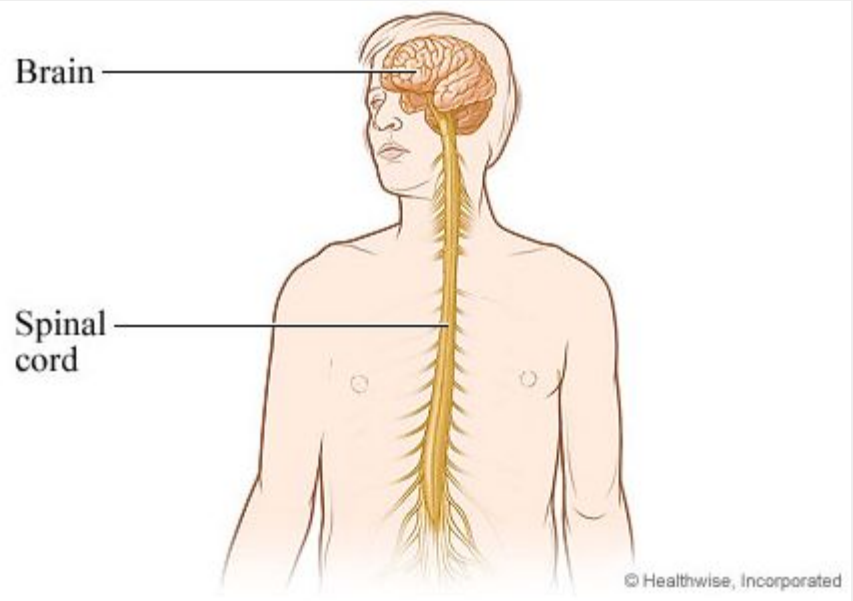


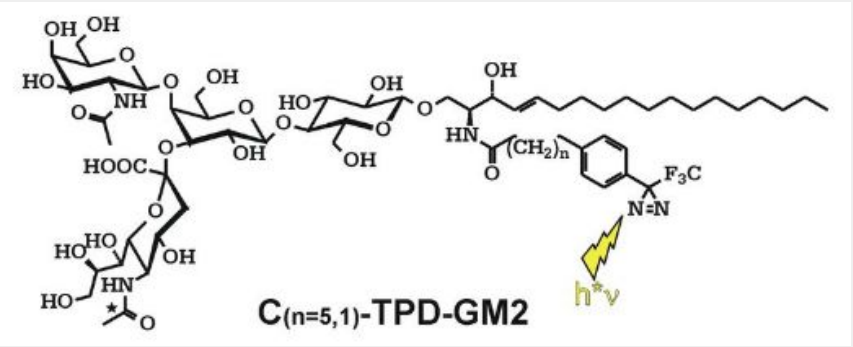
PATHOPHYSIOLOGY

Underlying Mechanisms of Disease

Neurophysiology

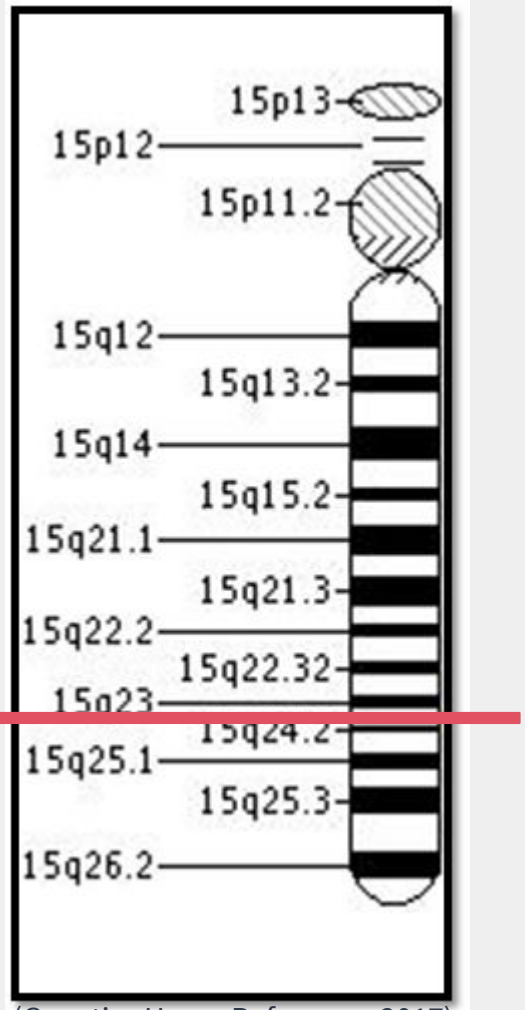
- Central Nervous System
  - Brain & Spinal Cord
- Gangliosides
  - Plasma Membrane
  - Cell-cell recognition, adhesion and signal transduction
  - GM2 gangliosides





(Yu, Tsai, Ariga, & Yanagisawa, 2013) (Sandhoff & Harzer, 2013)

HEXA Gene



(Genetics Home Reference, 2017)

Chromosome 15

15q24.1

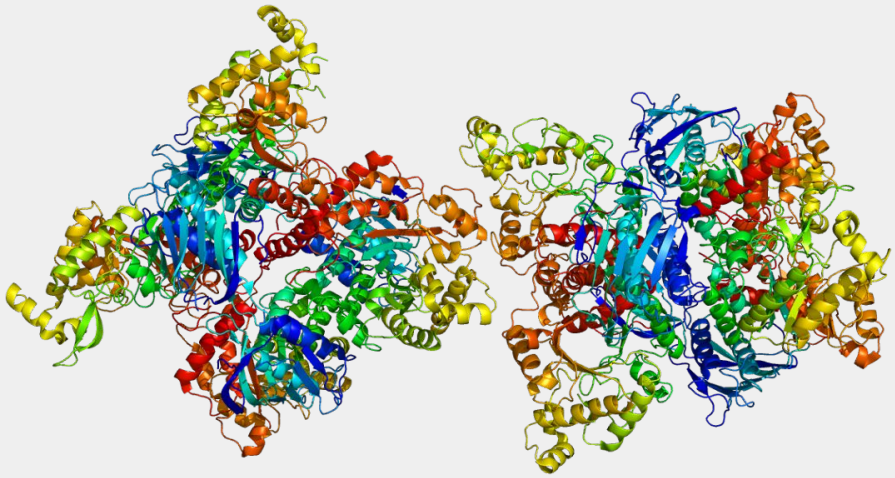
Encodes

β Hexosaminidase A

(Neudorfer et al., 2005)

Beta Hexosaminidase A

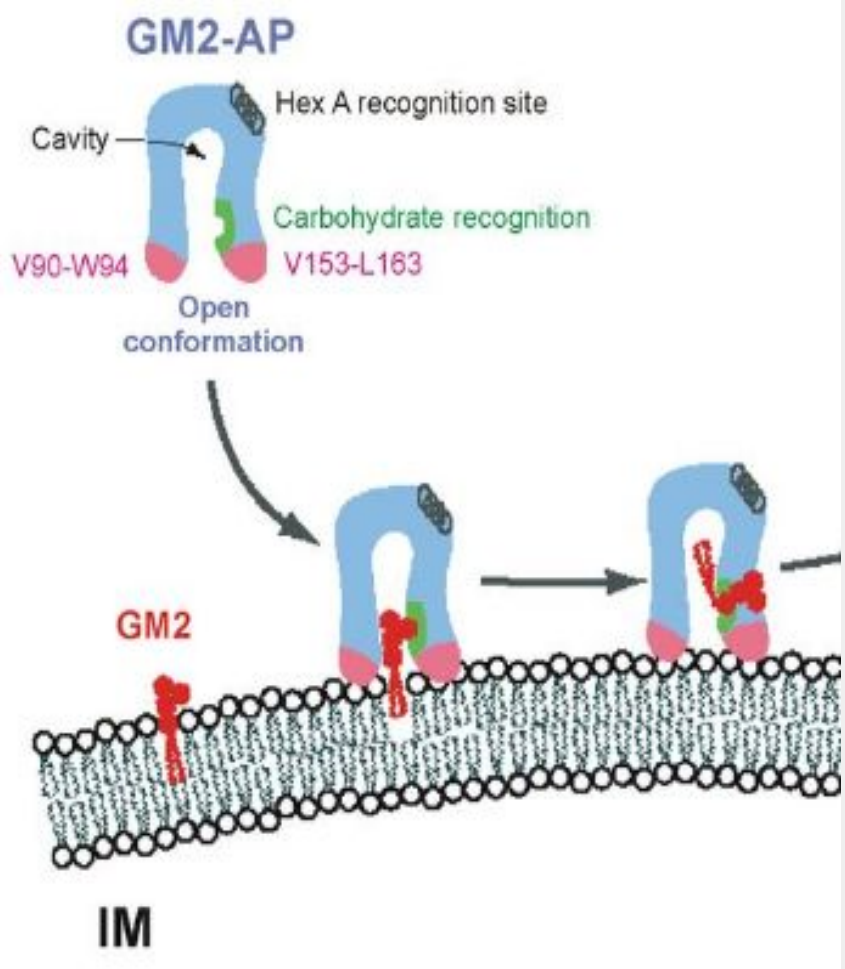
- Lysosomal Enzyme
  - Degrades GM2 gangliosides
- Two subunits
  - α/β heterodimer
- Tay-Sachs Disease
  - α - subunit

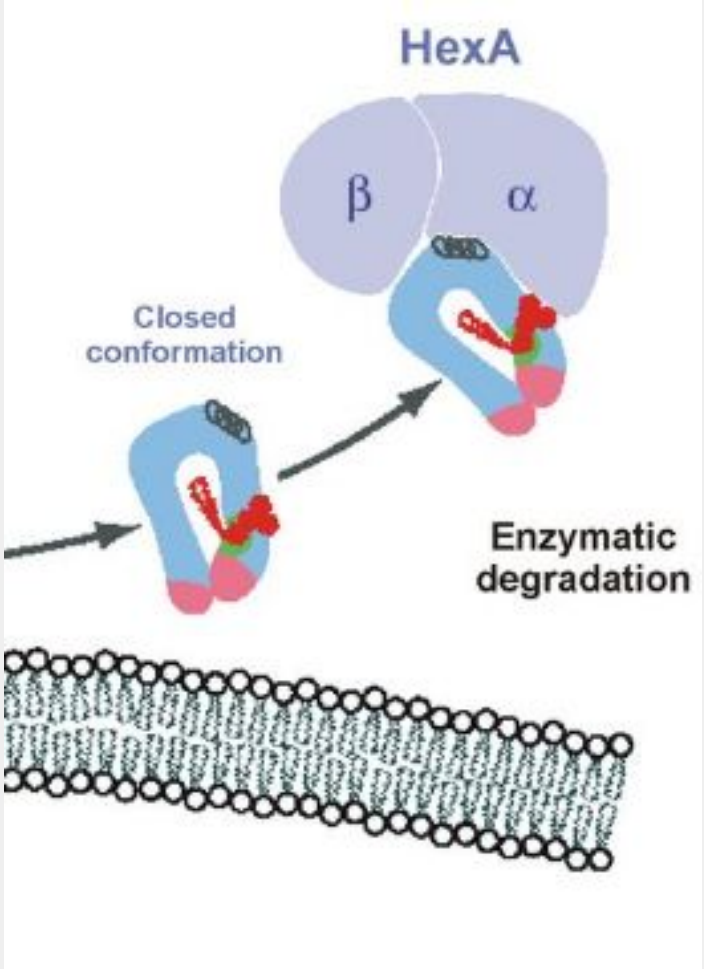


(Pymol, 2009)

(Sandhoff & Harzer, 2013) (Myerowitz, 1997)

Cellular Pathway

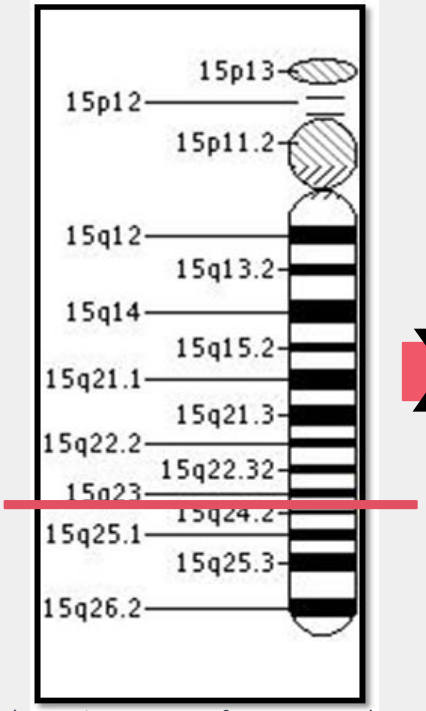




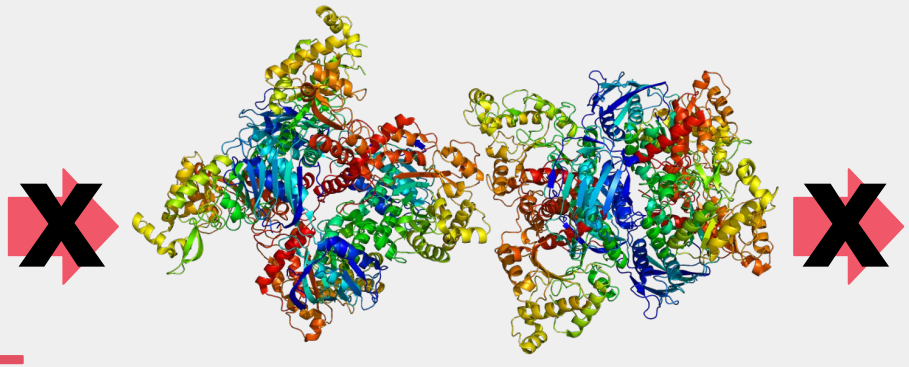
(Sandhoff, 2013)

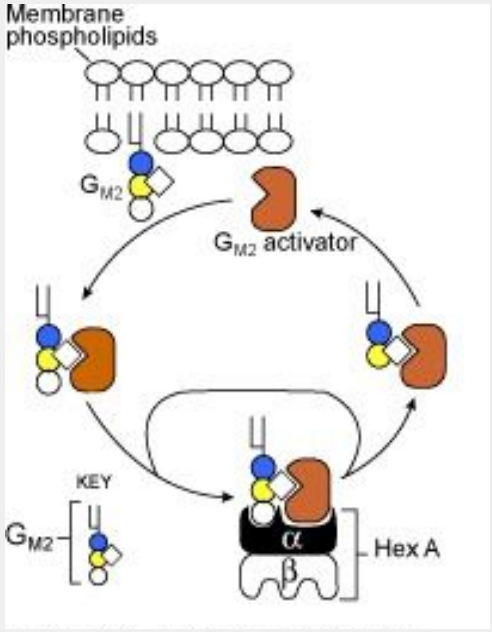
Mutation

- Single Point Mutation
  - Affect Lysosomal Catalytic Activity



(Genetics Home Reference, 2017)


(Pymol, 2009)

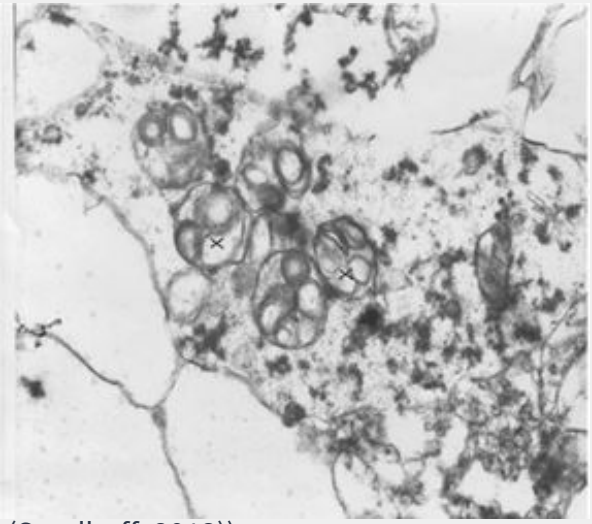


(Chavany & Jendoubi, 1998)

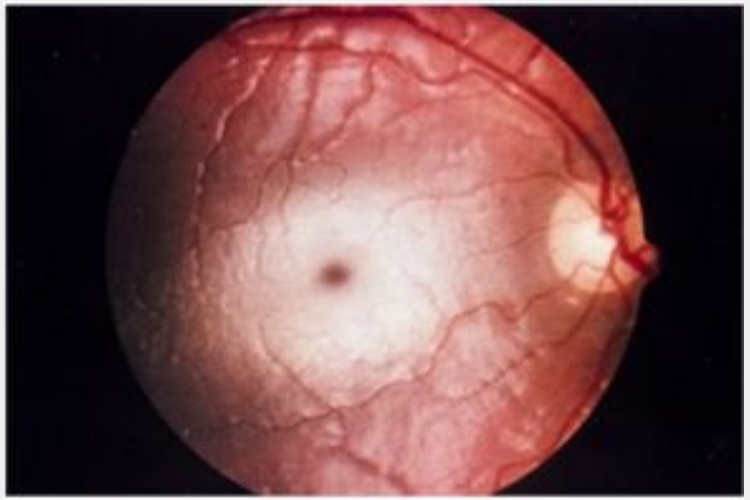
(Myerowitz, 1997)

Result

- GM2 Gangliosidosis
  - Neural Degeneration



(Sandhoff, 2013))



Red Macular Spot (Sandhoff, 2013))

(Sandhoff, 2013) (Sandhoff & Harzer, 2013)

DIAGNOSIS

Various screening methods

Diagnosis

- Blood tests
  - Measures hexosaminidase A levels in the body
  - Reduced levels in people with Tay-Sachs
- Molecular genetic testing
  - Detect mutation in *HEXA* gene
- Testing prenatally
  - Chorionic villi sampling (CVS)
  - Amniocentesis

(NIH, 2011) (NORD, 2016)

Carrier screening in schools

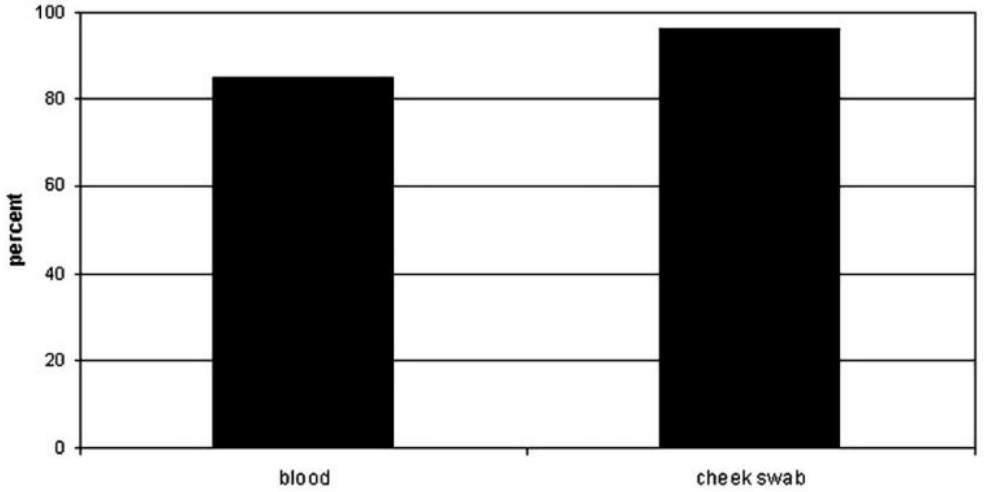


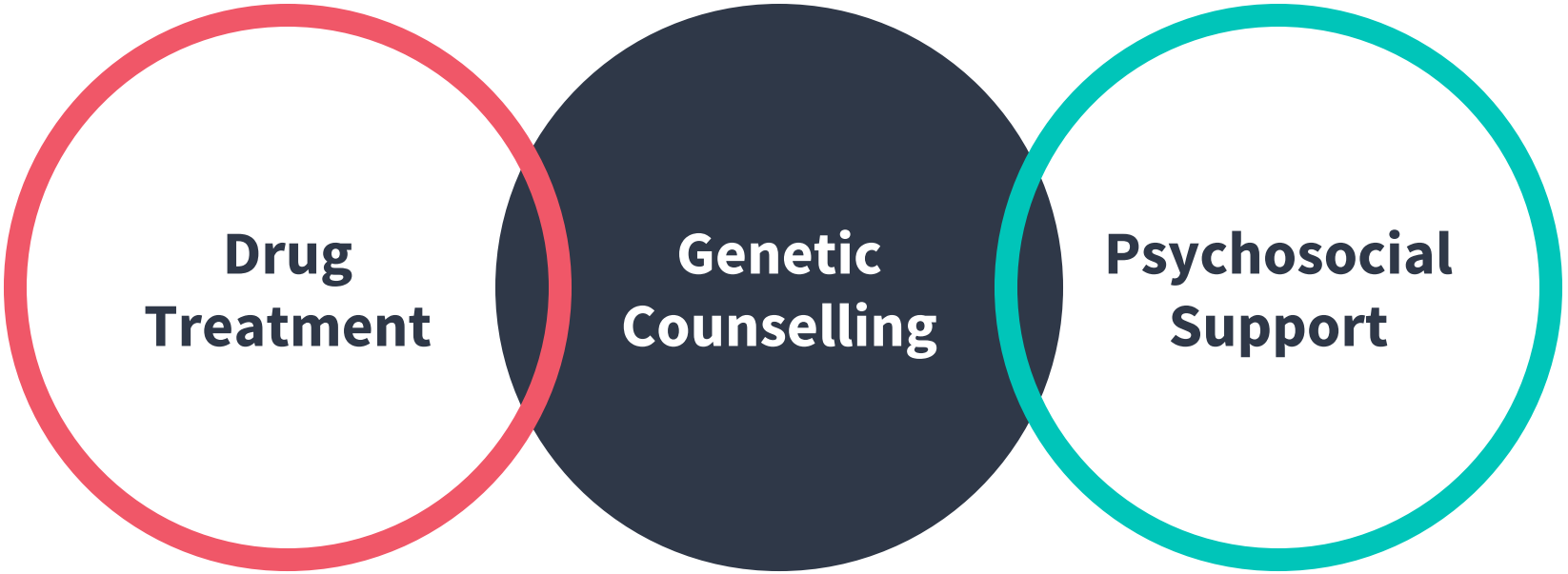
Figure 3. Test uptake for TSD carrier status. The proportion of students who had a carrier test was 84.9% (N = 163) with blood sampling, whereas 96.0% (N = 214) of students accepted testing with a cheekbrush; $\chi^2 = 15.2$, $df = 1$, $P < .0001$.

(Gason et al., 2005)

TREATMENT

Treatment aimed at relieving symptoms

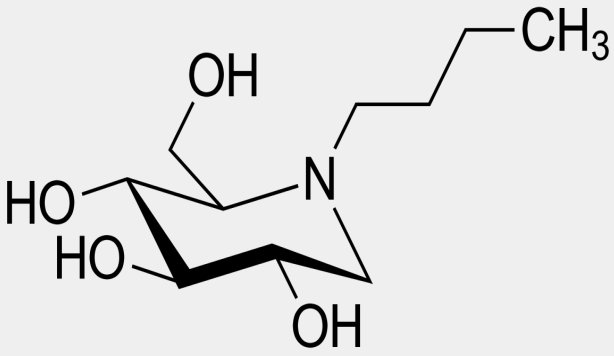
Treatment Approach



Current Therapeutic Options

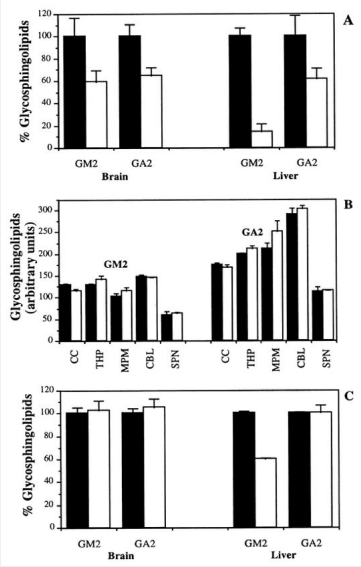
Anticonvulsants

- Anticonvulsants may be used to treat seizures
- Miglustat (synthetic analogue of D-glucose)



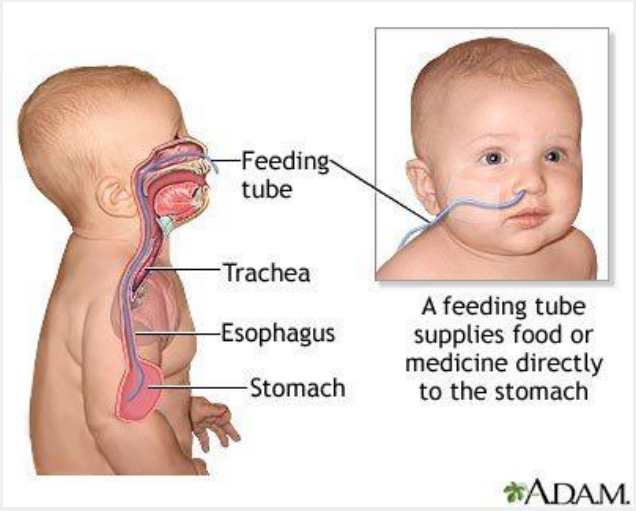
Substrate Deprivation

- N-butyldeoxynojirimycin (inhibitor of glycosphingolipid synthesis)



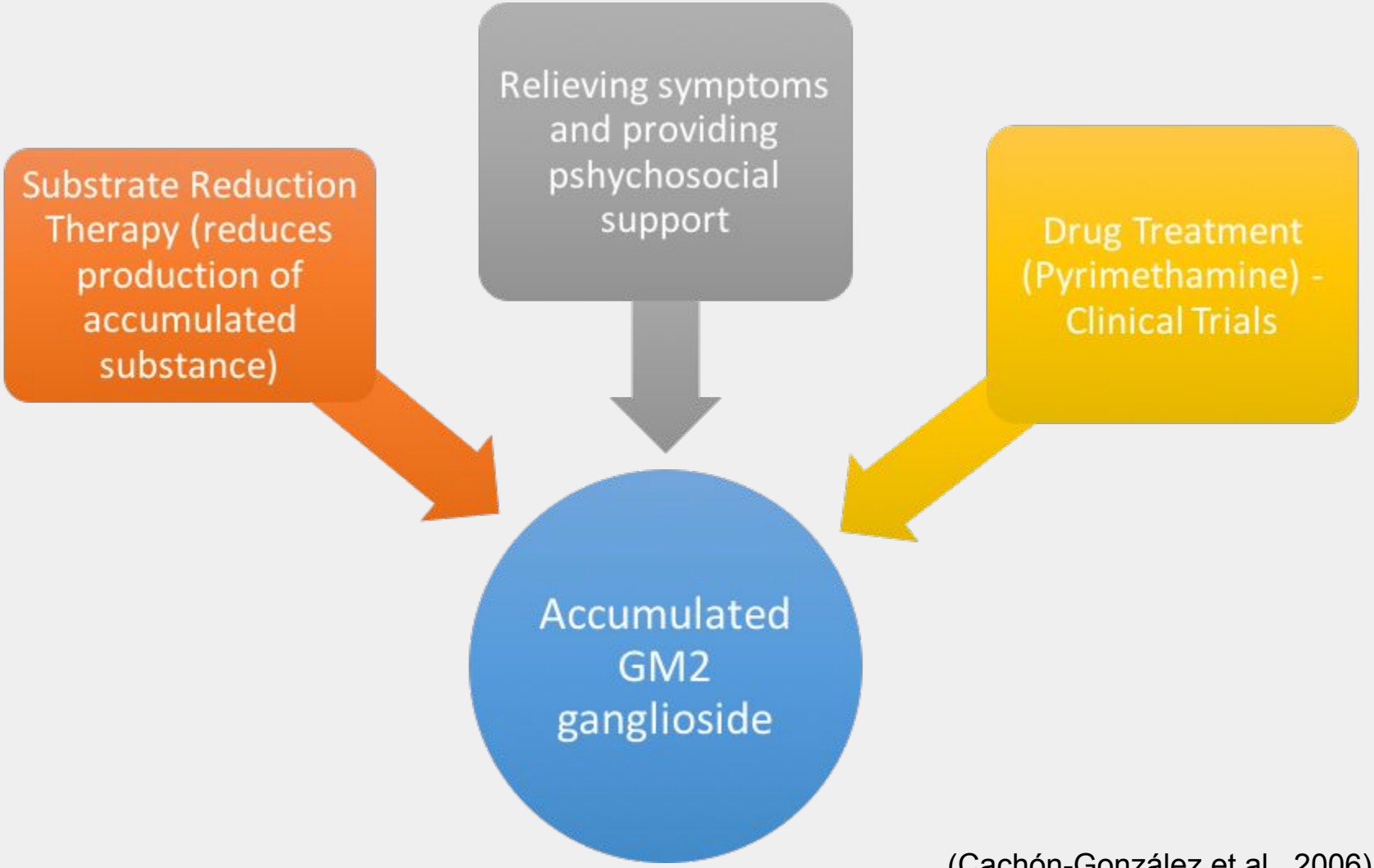
Nutritional Support

- Infants monitored for proper nutrition and hydration
- Feeding tube may be necessary



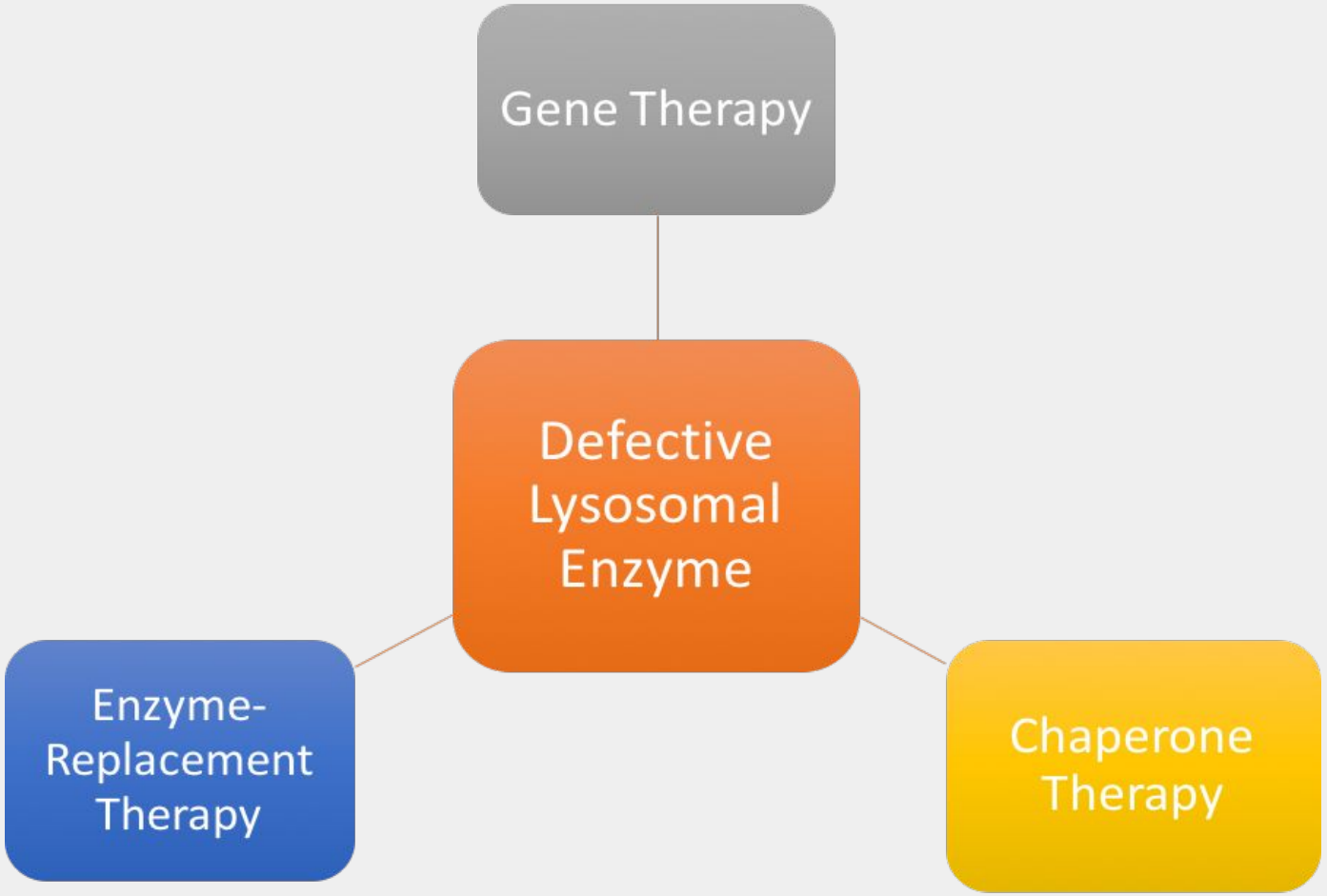
(Osher et al., 2011)

Investigational Therapies



(Cachón-González et al., 2006)

Investigational Therapies...cont'd



(Cachón-González et al., 2006)

Conclusion

What can we do moving forward?

Family Battles Tay-Sachs Disease

National Tay-Sachs & Allied Diseases Association

4 key areas of focus:

- Education
- Advocacy
- Research
- Family Services

(NTSAD, n.a.)

Questions

1. How is this disease inherited?
    a. Autosomal Dominant
    b. Autosomal Recessive
    c. X-linked Dominant
    d. X-linked Recessive

2. What gene is mutated in Tay-Sachs Disease?
    a. HEXA gene
    b. HEXB gene
    c. GM2 ganglioside
    d. β Hexosaminidase A

Thanks!

Any questions?

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