HEXA and Tay-Sachs Disease

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http://www.ldnz.org.nz/news_and_issues/conference_reports/national_tay_sachs_and_allied_diseases
Background on Tay-Sachs Disease (TSD)

- Autosomal recessive disorder
- Due to missing Hexoaminidase A (an enzyme that remove acetylglucosamine residues from polysaccharides)
- Carrier rate: 1 in 300
- Occurrence in Eastern European, Central European and Askhenazi Jewish heritage
Model for the lysosomal metabolism of GM2

Hex A
- heterodimer
- interact with GM2 indirectly.
- Remove the terminal N-acetylgalactosamine from GM2

GM2 activator protein
- Extracts the glycolipid

Tay Sachs Lysosomes Can’t Digest Ganglioside GM2

Normal Lysosomes

Ganglioside GM2

Digestive vacuole

Digestive vacuole

Exocytosis

Full Complement of Digestive Enzymes Including Hexosaminidase A

Tay Sachs Lysosomes

All of Digestive Enzymes Except Hexosaminidase A

Ganglioside GM2

Digestion Incomplete

Residual vacuoles Accumulate Because GM2 Can’t Be Digested

Residual vacuoles

No Exocytosis

http://www.utm.utoronto.ca/~w3bio315/lecture15.htm
## Types of TSD

<table>
<thead>
<tr>
<th>Types of Tay-Sachs</th>
<th>Age of Symptoms Appearance</th>
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</thead>
<tbody>
<tr>
<td>Classic Infantile</td>
<td>Around 6 months of age</td>
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<tr>
<td>Juvenile</td>
<td>Between ages 2 and 5, or anytime during childhood.</td>
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<tr>
<td>Late Onset</td>
<td>Adolescence or early adulthood or even later.</td>
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Information adapted from National Tay-Sachs & Allied Diseases
What are the symptoms of TSD?

- Loss of muscle coordination
- Speech problems
- Seizures
- Mental retardation
- Paralysis
- Dementia
- Eye abnormality
  → cherry-red spot

Figure from http://flipper.diff.org/app/items/info/2950
Mutations of the HEXA gene reduce the activity of β-hexosaminidase A (Hex A)
HEXA protein domain

Two domains were found on the HEXA sequence by SMART.

Two domains were found in HEXA protein by Pfam.

Glycoside hydrolase family 20, domain 2

Glycoside hydrolase family 20, catalytic domain
How is *HEXA* associated with TSD?

- TSD is caused by a mutation that leaves the body unable to produce an enzyme known as hexosaminidase-A (Hex-A).
- Fat metabolism in nerve cells.
- By the absence of this enzyme, central nervous system degeneration ensues due to the accumulation of lipid called GM2 ganglioside in the nerve cells of the brain.
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- TSD is caused by a mutation that leaves the body unable to produce an enzyme known as hexosaminidase-A (Hex-A).
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- By the absence of this enzyme, central nervous system degeneration ensues due to the accumulation of lipid called GM2 ganglioside in the nerve cells of the brain.
Hexa -/- mice show the neuropathology characteristic of Tay-Sachs disease.

(A) Membranous cytoplasmic bodies (MCBs) in the parietal cortex.

(B) Neurons are immunostained with anti-Gm2 ganglioside antibody.

(C) Multilayered lamellae in a cerebral cortical neuron
Phenotype of Late Onset TSD (LOTS) mice.

(A) The phenotype of a presymptomatic 8-month old bred female

(B) A symptomatic 18-month-old bred female

Why use a mouse model?

- Human protein domain HEXA
- Mouse protein domain Hexa

Identities = 84%

The mutant phenotypes expressed in the mice are the closest characteristics of the human Tay-Sachs disease.
Hexa Protein Phylogeny

Phylogenetic tree made using ClustalW2
Hexa Protein Phylogeny

Phylogenetic tree made using Phylogeny.fr
HEXA Interaction Network

http://string.embl.de/newstring_cgi/show_network_section.pl
Experimental Questions

1. What is the Gene Ontology (GO) for the proteins involved in the degradation of GM2 in the HEXA interaction network?

2. What domain are found in the related proteins located at the lysosome? Are Glycoside hydrolase family 20, catalytic domain found in those protein?
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(1) What is the GO for the proteins involved in the degradation of GM2 in the HEXA interaction network?

**Method:** Using the AMIGO database to find out the gene ontology of each related proteins in the degradation of GM2 and categorize them into different cellular component.
(1) Hypothesis

- The GO for the related proteins in the HEXA interaction network is categorized based on cellular component. There are categorized into groups like lysosome, lysosomal lumen, membrane, nucleus, cytosol, Golgi apparatus, and mitochondrial matrix.
(1) Collected Data

http://string.embl.de/newstring_cgi/show_network_section.pl
Experimental Questions

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- Are Glycoside hydrolase family 20, catalytic domain found in those protein?

**Method:** Using the SMART database to find the domains of the related proteins that are located in the lysosome.
(2) Hypothesis

• The Glycoside hydrolase family, catalytic domain should be observed in some of the proteins located at the lysosome in the HEXA interaction network because this domain play an important role in degrading GM2 ganglioside.
(2) Collected Data

HEXA

HEXB

CHIT1

GLB1
(2) Expected Data

NAGA

Melibiase

GM2A
Model for the lysosomal metabolism of GM2

Hex A
- heterodimer
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GM2 activator protein
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Activator-lipid complex

Future Directions

1. What mechanism of action of GM2-AP causes the recognition of Hex-A?
   – Method: TAP-tag
     → Label GM2-AP and determine how it is recognize HEXA

2. Chaperone Therapy
   - Different kind of chaperone to treat TSD with different mutant variations.

3. To create effective GM2 ganglioside inhibitors.
Conclusion

- **Tay-Sachs Disease (TSD)** is an autosomal recessive disease caused by mutations in both alleles of a gene (*HEXA*) on chromosome 15.

- The Glycoside hydrolase family 20, catalytic domain could play an important role in degrading GM2 ganglioside.


3. MGI


5. National Tay-Sachs & Allied Diseases

6. String: [http://string.embl.de](http://string.embl.de)


8. PFAM: [http://pfam.sanger.ac.uk/](http://pfam.sanger.ac.uk/)
Video

• http://www.cbs42.com/content/localnews/story/Little-Girl-Gets-Stem-Cell-Treatment-For-Deadly/goY5hrZWkkS7yfOENWxsdA.cspx