Representation of Disease Ontologies

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The Current Picture

The knowledge is in the details

Information about mouse models for human diseases is standardized and integrated in the Mouse Genome Informatics system.

article

Mouse models of Tay-Sachs and Sandhoff diseases differ in neurologic phenotype and ganglioside metabolism

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Tay-Sachs and Sandhoff diseases are clinically similar neurodegenerative disorders. These two sphingolipidoses are characterized by a heritable absence of β-hexosaminidase A resulting in defective G_{M2} ganglioside degradation. Thro... of the *Hexa* and *Hexb* genes in embryonic stem cells, we have established ... models corresponding to each disease. Unlike the two human disorders, t... models show very different neurologic phenotypes. Although exhibiting bio... pathologic features of the disease, the Tay-Sachs model showed no neuro... abnormalities. In contrast, the Sandhoff model was severely affected. The ... difference between the two mouse models is the result of differences in the ... degradation pathway between mice and humans.

The G_{M2} gangliosidoses are a group of heritable lysosomal storage disorders resulting from impaired degradation of G_{M2} ganglioside and related substrates[1]. They are caused by mutations in any of three genes, the *HEXA* gene resulting in Tay-Sachs disease (variant B), the *HEXB* gene resulting in Sandhoff disease (variant 0) and the *GM2A* gene resulting in the G_{M2} activator deficiency (variant AB). The *HEXA* and *HEXB* genes code for the β-... dimeric isozymes, hexosaminidase A and B, respectively, which ... G_{M2} ganglioside to G_{M3} ganglioside[2]. The *GM2A* gene codes for the ... G_{M2} activator, a ganglioside binding protein encoded ... the GM2A gene. Accordingly, in both Tay-Sachs di... (or subunit deficiency) and Sandhoff disease (β-sub... deficiency) there is a deficit of hexosaminidase A ... can be degraded only by the A isozyme in concert with ... and other glycolipids in the lysosomes of neurons. ... glycolipids are stored as multilayer lamellar struct... known as membranous cytoplasmic bodies (MCBs)[3]. ... distort and disrupt neuronal synaptic function. In Sand... disease, the additional absence of β-hexosaminida... results in accumulation of other substrates incl... globoside, oligosaccharides and glycosaminoglycans ... (keratan sulfate)[4].

Tay-Sachs disease and Sandhoff disease, in both t... infantile and later-onset forms, have very similar cli... courses. The infantile forms, caused by a total absence ... β-hexosaminidase A, are rapidly progressi... neurodegenerative disorders resulting in death in e... childhood. The later-onset forms, characterized by ... but detectable levels of β-hexosaminidase A activ... progress more slowly and may display a spectrum ...

clinical manifestations including ataxi... degeneration, motor neuron disease an...

Mouse models of G_{M2} ganglio... invaluable tools for studies of pathogenesi... eventual therapy for these disorders. W... created a mouse model of Tay-Sachs dis... targeted disruption of the mouse *Hexa* gene by homologous recombination[5]. The *Hexa*-/- mice displayed the biochemical and pathologic hallmarks of the disease, a profound β-hexosaminidase A deficiency, G_{M2} ganglioside accumulation in brain and MCBs in neurons

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Curators use controlled terms from structured vocabularies (ontologies) to annotate complex biological systems described in the literature.

Phenotypic Allele Detail

Allele	Symbol: **Hexb^{tm1Rlp}** Name: targeted mutation 1, Richard L Proia ID: MGI:1857438
Synonyms	Hexb-
Allele details	**Allele Type:** Targeted (knock-out) **Strain of Origin:** 129S4/SvJae **ES Cell Line:** J1 **ES Cell Line Strain:** 129S4/SvJae **Mutation:** Disruption caused by insertion of vector A neomycin resistance cassette was inserted into and disrupted exon 13 of the gene. This mutation resulted in the production of no detectable functional protein. (*J:29268*) **Gene Expression in Hexb^{tm1Rlp} mutants** (92 assay results) **International Mouse Strain Resource:** (Search for IMSR strains with Hexb mutations) **Mouse Models of Human Diseases:** (See Below) **References and Additional Notes:** (See Below)
Gene information	**Symbol:** Hexb **Name:** hexosaminidase B **Chromosome:** 13 **Genetic Position:** 46.0 cM **Genome Coordinates:** 93365510-93387341 bp, - strand (From NCBI annotation of NCBI Build 34) **Human Ortholog:** HEXB
Phenotypes	**Phenotypic details for all genotypes that include at least one Hexb^{tm1Rlp} allele**

Phenotype	Genotype: Allelic Composition	Genetic Background
Go To	Hexb^{tm1Rlp}/Hexb^{tm1Rlp}	involves: 129P2/OlaHsd * 129S4/SvJae * C57BL/6
Go To	Hexb^{tm1Rlp}/Hexb^{+}	involves: 129S4/SvJae * C57BL/6
Go To	Hexb^{tm1Rlp}/Hexb^{+}	involves: 129S4/SvJae * C57BL/6
Go To	Fcer1g^{tm1Rav}/Fcer1g^{tm1Rav} Hexb^{tm1Rlp}/Hexb^{tm1Rlp}	involves: 129P2/OlaHsd * 129S4/SvJae * C57BL/6
Go To	Ccl3^{tm1Unc}/Ccl3^{tm1Unc} Hexb^{tm1Rlp}/Hexb^{tm1Rlp}	involves: 129P2/OlaHsd * 129S4/SvJae * C57BL/6
Go To	Ccl3^{tm1Unc}/Ccl3^{+} Hexb^{tm1Rlp}/Hexb^{tm1Rlp}	involves: 129P2/OlaHsd * 129S4/SvJae * C57BL/6
Go To	Galgt1^{tm1Rlp}/Galgt1^{tm1Rlp} Hexb^{tm1Rlp}/Hexb^{tm1Rlp}	involves: 129S4/SvJae * 129S6/SvEvTac * C57BL/6
Go To	Galgt1^{tm1Rlp}/Galgt1^{+} Hexb^{tm1Rlp}/Hexb^{tm1Rlp}	involves: 129S4/SvJae * 129S6/SvEvTac * C57BL/6
Go To	Hexb^{tm1Rlp}/Hexa^{tm1Rlp} Hexb^{tm1Rlp}/Hexb^{tm1Rlp}	involves: 129S4/SvJae * C57BL/6

Allelic Composition	Genetic Background
Hexb^{tm1Rlp}/Hexb^{tm1Rlp}	involves: 129S4/SvJae * C57BL/6

life span/aging
- premature death (*J:53080*)
  - died around 120 to 150 days of age

behavior/neurological
- abnormal motor capabilities/coordination/movement (*J:29268*)
  - beginning at 3 months and progressing with age
  - abnormal gait (*J:29268*)
    - spastic movements of hind limbs starting around 5 months
    - near lack of hind limb movement by 5 months and fore limbs also afflicted
  - impaired righting response (*J:53080*)
    - progressive loss of righting response with age
  - impaired coordination (*J:29268*)
    - performance in a rotarod test is impaired at 9 weeks and declines very rapidly after 11 weeks of age
    - at 16 weeks of age, homozygous mice are unable to stay on a rotarod

nervous system
- abnormal neuron (*J:29268*)
  - neuronal storage vacuoles (PAS positive) found throughout the central nervous system
  - vacuoles very abundant in anterior horn motor neurons of the spinal cord
  - PAS positive granules also found in neuropil and dendrites
  - no granules found in cerebral and cerebellar white matter, nerve fiber tracts, spinal roots or optic nerves

muscle
- muscular atrophy (*J:29268*)
  - at 5 months of age

liver/biliary system
- abnormal liver morphology (*J:29268*)
  - storage vacuoles found in cells in hepatic sinusoids
- abnormal hepatocyte morphology (*J:29268*)
  - PAS positive storage vacuoles found

renal/urinary system
- abnormal renal tubules (*J:29268*)
  - storage vacuoles found in epithelial cells of the proximal tubules

The terms in blue here come from the Mammalian Phenotype ontology.

Human Disease and Mouse Model Detail

Human Disease	Term: **Sandhoff Disease** OMIM ID: 268800
Synonyms	Gm2-Gangliosidosis, Type II
Associated Genes	Orthologous mouse and human markers where mutations in one or both species have been associated with phenotypes characteristic of this disease.

Mouse Gene	Human Gene	Characteristics of this are associated with mutations in...
Hexb	HEXB	...both mouse and human orthologous genes.
Ccl3	CCL3	...the mouse gene.
Fcer1g	FCER1G	OMIM data currently do not associate this disease with the orthologous human gene.

Mouse Models

Genotype: Allelic Composition	Genetic Background	Ref(s)
Models with phenotypic similarity to human disease where etiologies involve orthologs.[1]		
Ccl3^{tm1Unc}/Ccl3^{tm1Unc} Hexb^{tm1Rlp}/Hexb^{tm1Rlp}	involves: 129P2/OlaHsd * 129S4/SvJae * C57BL/6	J:90687
Ccl3^{tm1Unc}/Ccl3^{+} Hexb^{tm1Rlp}/Hexb^{tm1Rlp}	involves: 129P2/OlaHsd * 129S4/SvJae * C57BL/6	J:90687
Fcer1g^{tm1Rav}/Fcer1g^{tm1Rav} Hexb^{tm1Rlp}/Hexb^{tm1Rlp}	involves: 129P2/OlaHsd * 129S4/SvJae * C57BL/6	J:87617
Hexb^{tm1Grv}/Hexb^{tm1Grv}	either: (involves: 129P2/Ola * C57BL/6J) or (involves: 129S1/Sv * 129X1/SvJ * C57L/6J)	J:30899
Hexb^{tm1Rlp}/Hexb^{tm1Rlp}	involves: 129P2/OlaHsd * 129S4/SvJae * C57BL/6	J:87617
Hexb^{tm1Rlp}/Hexb^{tm1Rlp}	involves: 129S4/SvJae * C57BL/6	J:29268

[1]Human genes are associated with this disease. Orthologs of those genes appear in the mouse genotype(s).

Human Disease and Mouse Model Detail displays orthologous mouse and human markers where mutations in one or both species have been associated with phenotypes characteristic of this disease

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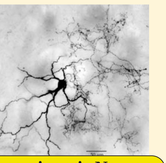
The Challenge

No Ontology is an island

Different core ontologies need to be combined to model complex biological systems.

This example shows that the complex process term "synaptic transmission, dopaminergic" can be decomposed into more elemental classes represented in OBO ontologies. Ontologies that are used to describe complex biological processes do not exist in isolation.

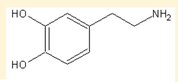


Dopaminergic Neuron CL:0000700

Cell Type Ontology

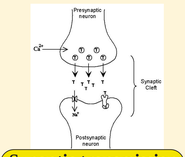
Brain MA:0000168

Anatomical Dictionary



Dopamine CHEBI:18243

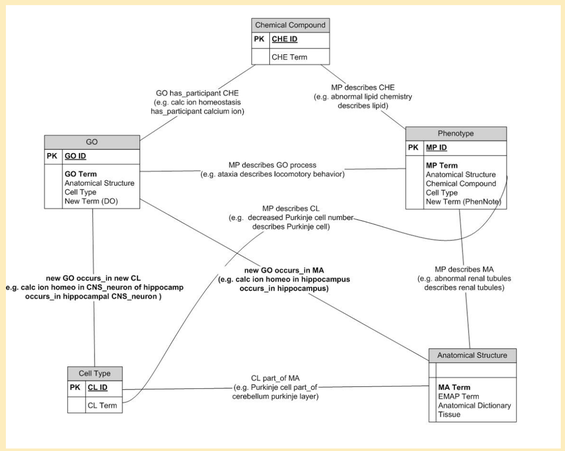
Chemical Ontology



Synaptic transmission GO:0007268

Biological Process

Ontologies can be linked



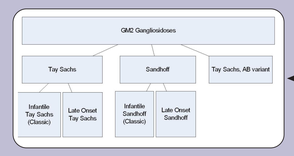
A data model linking five separate OBO ontologies.

Conclusion:

Integration of mouse and human information in the context of a complex ontology structure provides novel access global biological data, here from the view points of anatomy, cell processes, phenotypes, and diseases.

Ontologies can model diseases

We are exploring ontological representations of diseases

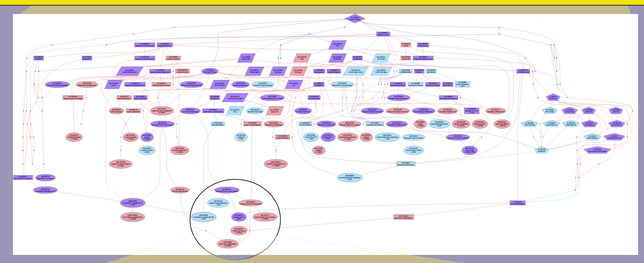


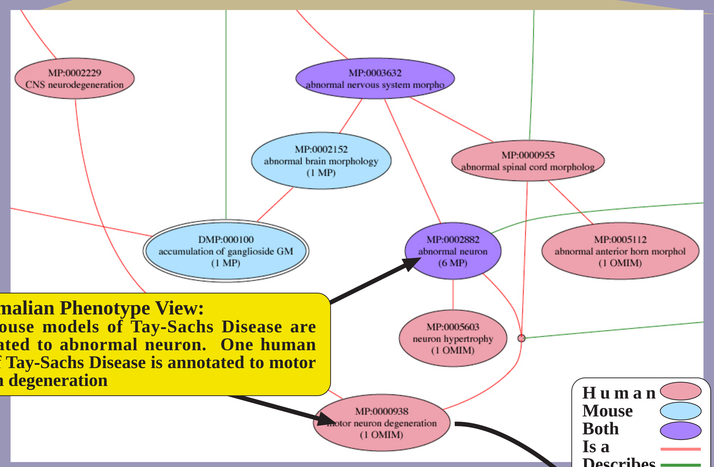
As a disease test case we modeled gangliosidoses. Two types of gangliosidoses are Sandoff and Tay-Sachs diseases

Using the combined ontology, we annotated the biomedical literature and OMIM reports to construct an ontological representation of gangliosidoses. This complex graph represents all of the knowledge we have about mouse and human Sandhoff's Disease.

Graphical representations help humans visualize the complexities

In this subgraph, human and mouse Tay-Sachs Disease annotations are displayed from a phenotypic viewpoint. Zooming in on the graph we can see that mice have not been shown to display the motor neuron degeneration that is typical of the human disease. We can explore the current data using the ontological structure and we can link out to underling global information.





Mammalian Phenotype View:
Six mouse models of Tay-Sachs Disease are annotated to abnormal neuron. One human case of Tay-Sachs Disease is annotated to motor neuron degeneration

Mammalian Phenotype Ontology Annotations
Query Results -- Summary

10 genotypes with 10 annotations displayed

Searched Term: motor neuron degeneration

Allelic Composition (Genetic Background)	Annotated Term	Reference
Atcay^{ji}/Atcay^{ji} (BALB/c)	motor neuron degeneration	J:14903
awg$^{Tg(GBtn1env)832Pkw}$/awg$^{Tg(GBtn1env)832Pkw}$ (involves: C57BL/6J * SJL)	motor neuron degeneration	J:43273
Cln8^{mnd}/Cln8^{mnd} (B6.KB2/Rn-Cln8^{mnd})	motor neuron degeneration	J:8492
Ctrl^{tm1Msd}/Ctrl^{tm1Msd} (Not Specified)	motor neuron degeneration	J:77294
hurl8/hurl8 (Not Specified)	motor neuron degeneration	J:85113
Smn1^{tm1Msd}/Smn1^{tm1Msd} Tg(SMN2.)89Ahmbj? (involves: 129P2/OlaHsd * C57BL/6J * FVB)	motor neuron degeneration	J:60592
Sox2^{tm2Sks}/Sox2^{tm3Sks} (involves: 129S/SvEv * 129S1/Sv * C57BL/6J)	motor neuron degeneration	J:92063
Tg(SOD1-G93A)2Gur/0 (involves: C57BL/6 * SJL)	motor neuron degeneration	J:32665
Ucht1^{tm1}/Ucht1^{tm1} (Not Specified)	motor neuron degeneration	J:28526
wrmod1$^{CAST/Ei}$/wrmod1$^{CAST/Ei}$ (involves: C57BL/6J-wr * CAST/Ei)	motor neuron degeneration	J:89229

Linking disease annotations with MGI phenotypes allows users to compare like phenotypes from diverse genotypes.

Mammalian Phenotype Browser
Term Detail

MP term: **motor neuron degeneration**
Synonym: **loss of motor neurons**
MP id: **MP:0000938**
Definition: **retrogressive impairment of function or destruction of the cells that innervate an effector (muscle or glandular) tissue**
Number of paths to term: **3**

①denotes an 'is-a' relationship
②denotes a 'part-of' relationship

Phenotype Ontology
- ①nervous system phenotype
  - ①abnormal nervous system morphology
    - ①abnormal neuron
      - ①abnormal motor neuron morphology
        - ①abnormal motor neuron innervation
        - ①excessive motor neuron axon growth
        - ①failure of motor neuron target finding
        - ①increased motor neuron number
        - ①motor neuron degeneration [MP:0000938] *(10 genotypes, 10 annotations)*
        - ①reduced motor neuron number

Phenotype Ontology
- ①nervous system phenotype
  - ①abnormal nervous system morphology
    - ①abnormal spinal cord morphology
      - ①abnormal motor neuron morp
        - ①abnormal motor neuron
        - ①excessive motor neuron
        - ①failure of motor neuron
        - ①increased motor neuron
        - ①motor neuron degeneration [MP:0000938] *(10 genotypes, 10 annotations)*
        - ①reduced motor neuron number

10 genotypes in MGI display a phenotype of mortor neuron degenration