

Mouse Models of Human Disease: Data & Curation challenges



Achondroplasia



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Mouse Genome Database

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The Jackson Laboratory
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Workshop 5: Genotype-2-phenotype:

Curation challenges in translational & reverse translational informatics

Why mouse is a primary tool?

- mammal (share virtually the same set of genes with human)
- small (easy to raise & maintain)
- all life stages can be accessed (e.g. prenatal stages)
- fully sequenced & annotated reference genome (C57BL/6J)
- easy to genetically engineer to specification, including spatiotemporal control of gene expression
- myriad inbred strains & population based crosses



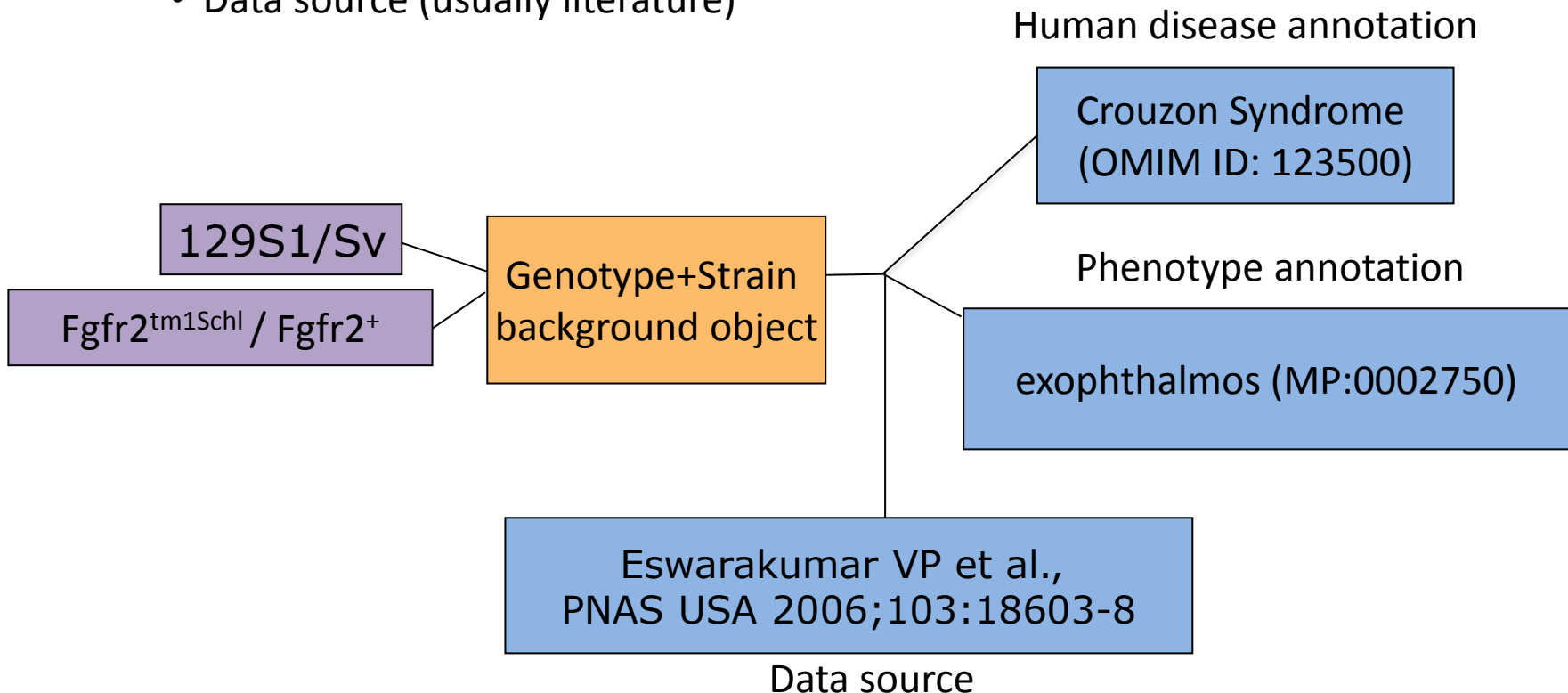
Normal littermate with *Lep^{ob}/Lep^{ob}* mutant

Challenges of Annotating Disease to the Mouse

- Different alleles of the same gene on the same genetic background may or may not model the same disease.
- The same alleles of a given gene on different genetic backgrounds may or may not be disease models.
- Therefore, disease models are associated to “mouse objects” that describe the mutant allelic state and the strain (genetic) background of the mice analyzed.
- Disease annotation consists of OMIM term, MP terms and data reference/source.

How MGI annotates phenotype and disease?

- A disease annotation in MGD consists of
 - Mouse strain background & mutant allele composition. Together these provide the Genotype+Strain object describing the whole mouse.
 - The disease annotation (blue) consists of
 - The OMIM human disease term
 - Phenotype annotation with mammalian phenotype terms
 - Data source (usually literature)



How MGI annotates phenotype and disease?

Eswarakumar VP et al., PNAS USA 2006;103:18603-8

Text States:

- ..murine model system of Crouzon-like craniosynostosis induced by a dominant mutation in *Fgfr2c*..
- ..*Fgfr2c*^{C342Y}/ Crouzon-like mice are characterized by ocular proptosis..

Annotate to:

- Crouzon Syndrome (OMIM 123500)
- exophthalmos (MP:0002750)

MGI allele detail page:

Nomenclature

Symbol: **Fgfr2^{tm1Schl}**
 Name: fibroblast growth factor receptor 2, transmembrane domain 1, conditional allele
 MGI ID: MGI:3699313
 Synonyms: Fgfr2^{C342Y}
 Gene: **Fgfr2** Location: Chr7:130162451-133123350 bp, - strand Genetic Position: Chr7, 73.19 cM

Genotype | **Allelic Composition** | **Genetic Background**

hm1	Fgfr2 ^{tm1Schl} /Fgfr2 ^{tm1Schl}	involves: 129S1/Sv
ht2 Disease Model	Fgfr2 ^{tm1Schl} /Fgfr2 ⁺	involves: 129S1/Sv

Key: hm homozygous, ht heterozygous, tg involves transgenes, cn conditional genotype, cx complex: > 1 genome feature, ot other: hemizygous, isodisomic, ...

Phenotypes

Genotypes:

Genotype	Allelic Composition	Genetic Background	Cell Line(s)
hm1	Fgfr2 ^{tm1Schl} /Fgfr2 ^{tm1Schl}	involves: 129S1/Sv	
ht2 Disease Model	Fgfr2 ^{tm1Schl} /Fgfr2 ⁺	involves: 129S1/Sv	

Phenotypes:

Affected Systems	hm1	ht2
craniofacial	✓	✓
digestive/alimentary system	✓	
growth/size/body	✓	
mortality/aging	✓	
respiratory system	✓	
skeleton	✓	✓
vision/eye		✓

Disease models

Key: disease model expected model not found

Models:

Human Diseases	ht2
Crouzon Syndrome OMIM: 123500	✓

Find Mice (IMSR)

Carrying this Mutation: Mouse Strains: 0
 Carrying any Fgfr2 Mutation: 20 strains or more

References

Original: J:118299 Eswarakumar VP, et al. Craniosynostosis. Proc Natl Acad Sci U S A. 2003;100(12):7033-7038.
 All: 4 reference(s)

Human <--> Mouse: Disease Connection

Search by genes Search by genome locations Search by disease or phenotype terms

Human(GRCh38) Mouse(GRCm38)

Ex: [Bmp4, Pax*, NM_013627](#) Ex: [Chr12:30000000-10000000](#) Ex: [105830, Autism AND "social behavior"](#)

Enter symbols, names or IDs. Use * for wildcard. Need to convert genome build? Use this [converter tool](#). Use quotes for exact match. [Hints](#) for using AND, OR, NOT, quotes, partial word matching.

Upload Genes File (.txt): No file selected. Upload a VCF File: No file selected. Show Effective Phenotype Query

Apply filters Human(GRCh38) Mouse(GRCm38)

Effective Phenotype Query:

Goal: Make data about mouse models of human disease more accessible to researchers (esp. clinical & translational researchers less familiar with mouse data).

Take a tour of the Human-Mouse: Disease Connection

Introduction to Mouse Genetics

Glossary of Terms


Spotlight on mouse models of human disease

Brain small vessel disease with hemorrhage and with, or without, ocular abnormalities (OMIM:607595)

Humans and mice heterozygous for missense mutations in the COL4A1 (collagen, type IV, alpha 1 chain) gene display common phenotypes with variable penetrance, depending on the specific mutation observed:

- intracranial hemorrhage [MP:0001915]
- abnormal blood vessel morphology [MP:0001614]
- abnormal retinal blood vessel pattern [MP:0010098]
- partial perinatal lethality [MP:0011090]
- cataracts [MP:0001304]

[\[Read more...\]](#)



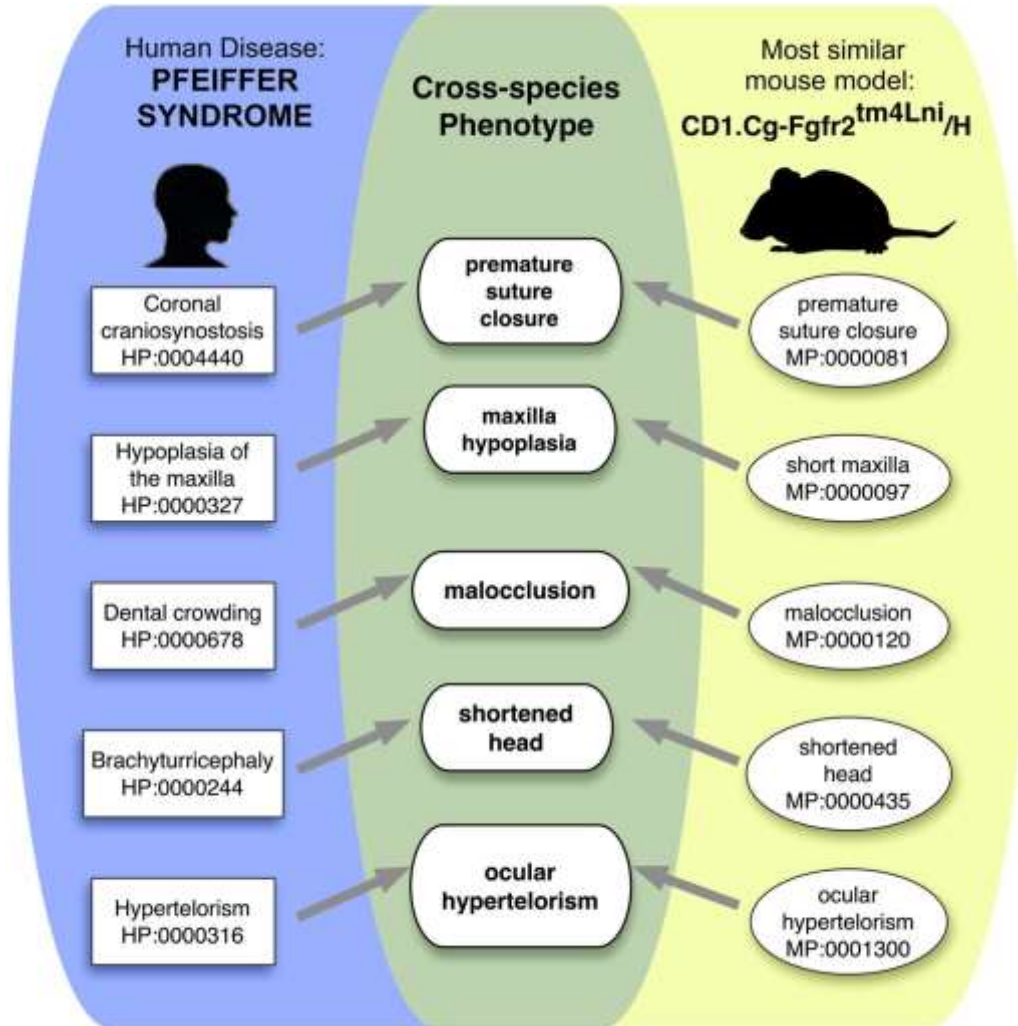
Col4a1^{+/-} Col4a1^{+/-deltaex40}

What did we develop?....

1. infrastructure to support data relationships.
2. Behind-the-scenes filtering of mouse data
3. New interface with very simple search parameters

Addition of Human Phenotype Ontology (HPO) to HMDC

Phenotype matching algorithm.



Collaboration with Peter Robinson and Chris Mungall *et al.* to map MP to HPO

This will allow the “Grid” to display both species associations in the phenotype

Addition of Human Phenotype Ontology (HPO) to HMDC

Gene Homologs x Phenotypes/Diseases Genes (4) Diseases (5)

Legend: The matrix includes all phenotypes/diseases associated with mouse models and human genes returned. Highlighted Columns contain at least one phenotype or disease result matching your search term(s).
■ - Terms are annotated to genes in **human/mouse**. Darker colors indicate [more annotations](#).
N - No abnormal phenotype observed.

NOTE: In searches with phenotype/disease terms, only the phenotypes/diseases of the matching models/genes are displayed. In searches using gene or location parameters only, the complete phenotype profiles of the matching gene mutations are displayed. [More...](#)

Human Gene	Mouse Gene		craniofacial	growth/size/body	skeleton	vision/eye	Achondroplasia: ACH	Crouzon Syndrome	Thanatophoric Dysplasia
		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Bey	<input type="checkbox"/>	■	■	■	■	■	■	■
FGFR2	Fgfr2	<input type="checkbox"/>	■	■	■	■	■	■	■
FGFR3	Fgfr3	<input type="checkbox"/>					■	■	■

Apply Filters: Retain selected col/rows

→ Crouzon Syndrome patients have craniofacial development defects and the mouse model shows abnormal craniofacial morphology

Human phenotype data will be available in a future release.

Many other challenges remain :

- The human disease / mouse model matrix is sparse
 - Many human diseases (even simple Mendelian diseases) have unknown or multiple suspected etiologies.
 - No systematic effort in mouse to recapitulate disease mutations known or suspected in human.
 - Multiple gene contributions are being captured/analyzed, but slowly.
 - Variable penetrance, genetic background effects, expand complexity
- Need for a true Human Disease Vocabulary/Ontology
 - MGI is Working with many groups:
 - Providing feedback on issues found, particular missing terms or incorrect term relationships
 - Using available terminology as best we can

Aknowledegment

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