Mouse Models of Human Disease: Data & Curation challenges

Achondroplasia

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Mouse Genome Database

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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

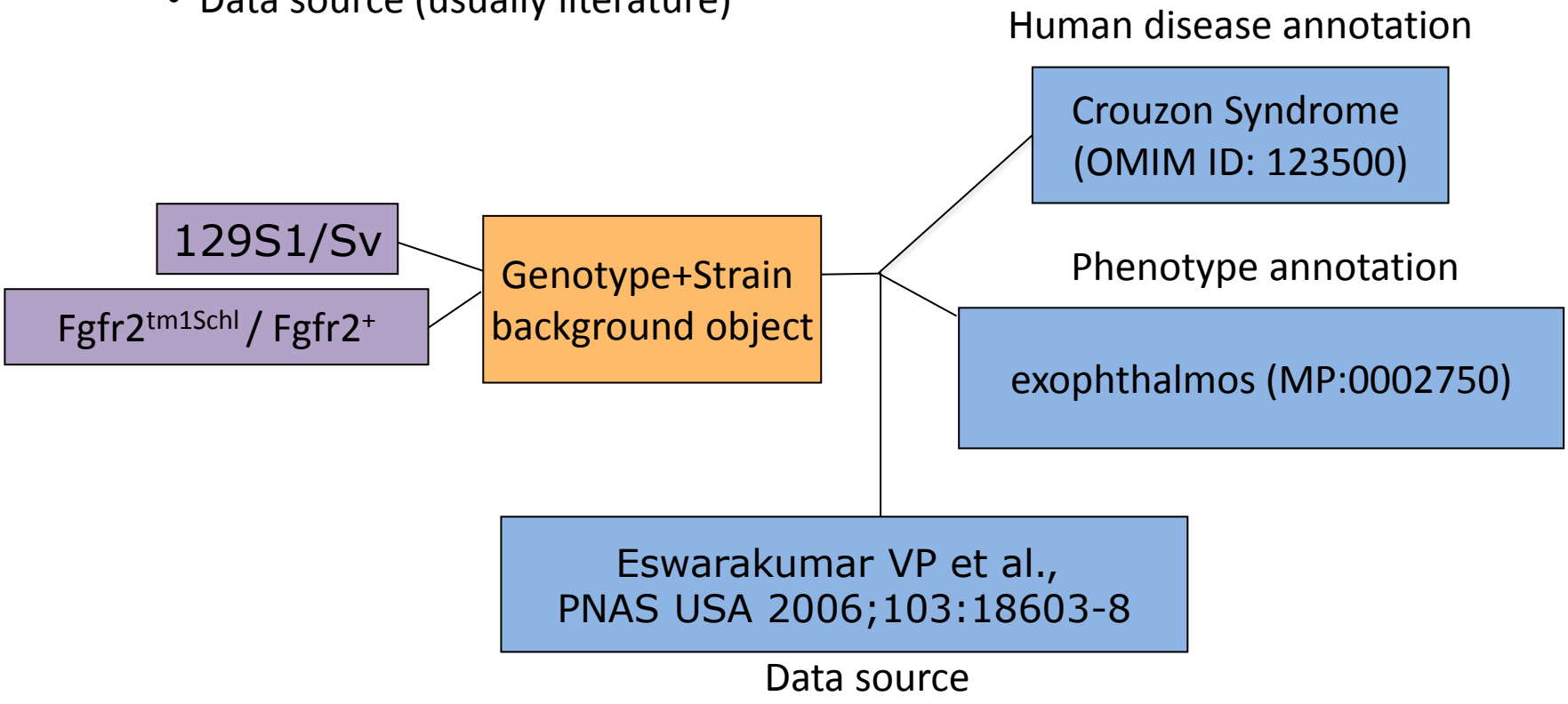
Normal littermate with *Lep^{ob}/Lep^{ob}* mutant

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)

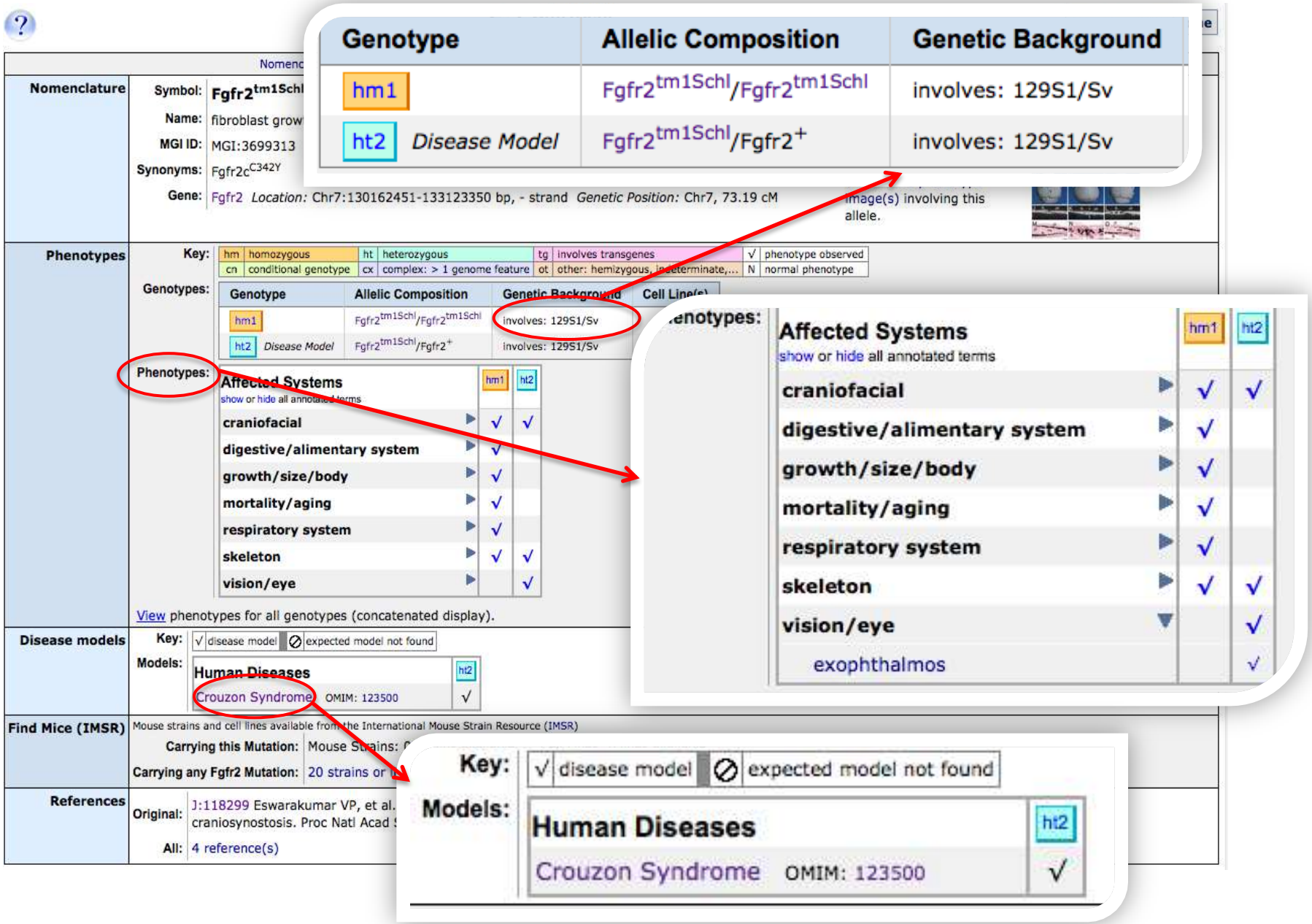


How MGI annotates phenotype and disease?

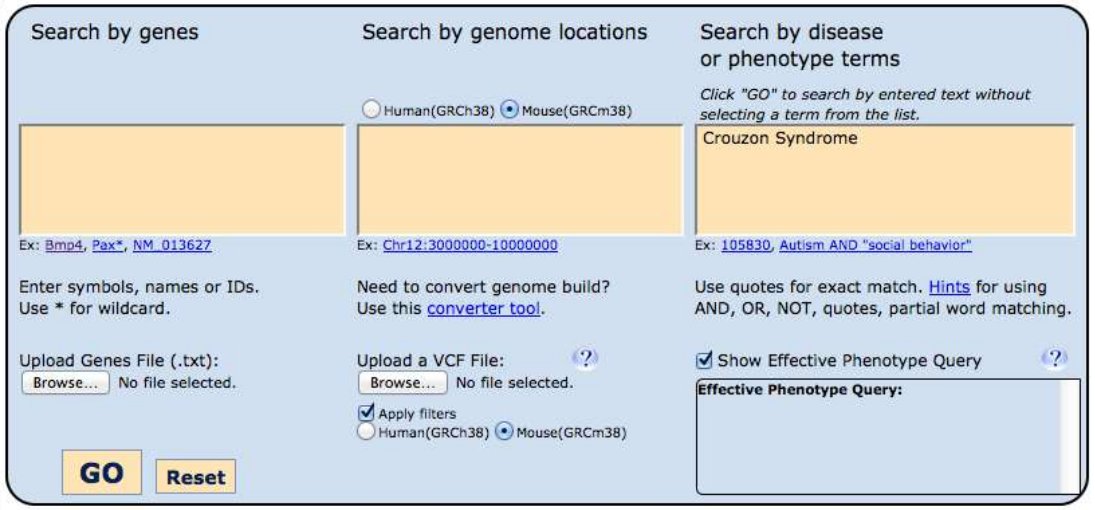
Eswarakumar VP et al., PNAS USA 2006;103:18603-8

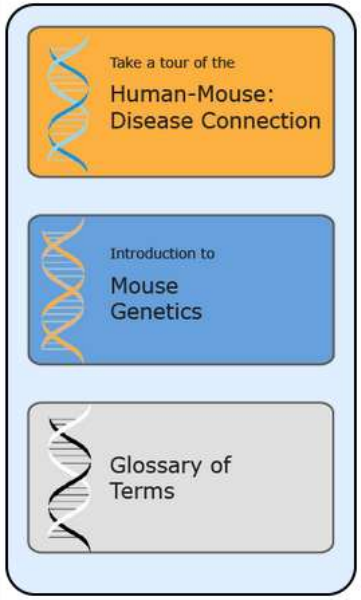
Text States:	Annotate to:
• ..murine model system of Crouzon-like craniosynostosis induced by a dominant mutation in Fgfr2c..	• Crouzon Syndrome (OMIM 123500)
• *..Fgfr2c^{C342Y}/* Crouzon-like mice are characterized by ocular proptosis..	• exophthalmos (MP:0002750)

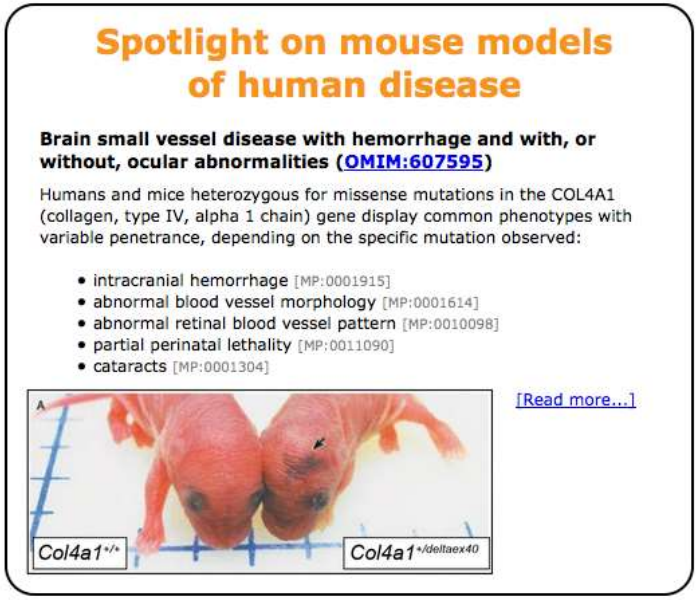
MGI allele detail page:



Human <--> Mouse: Disease Connection







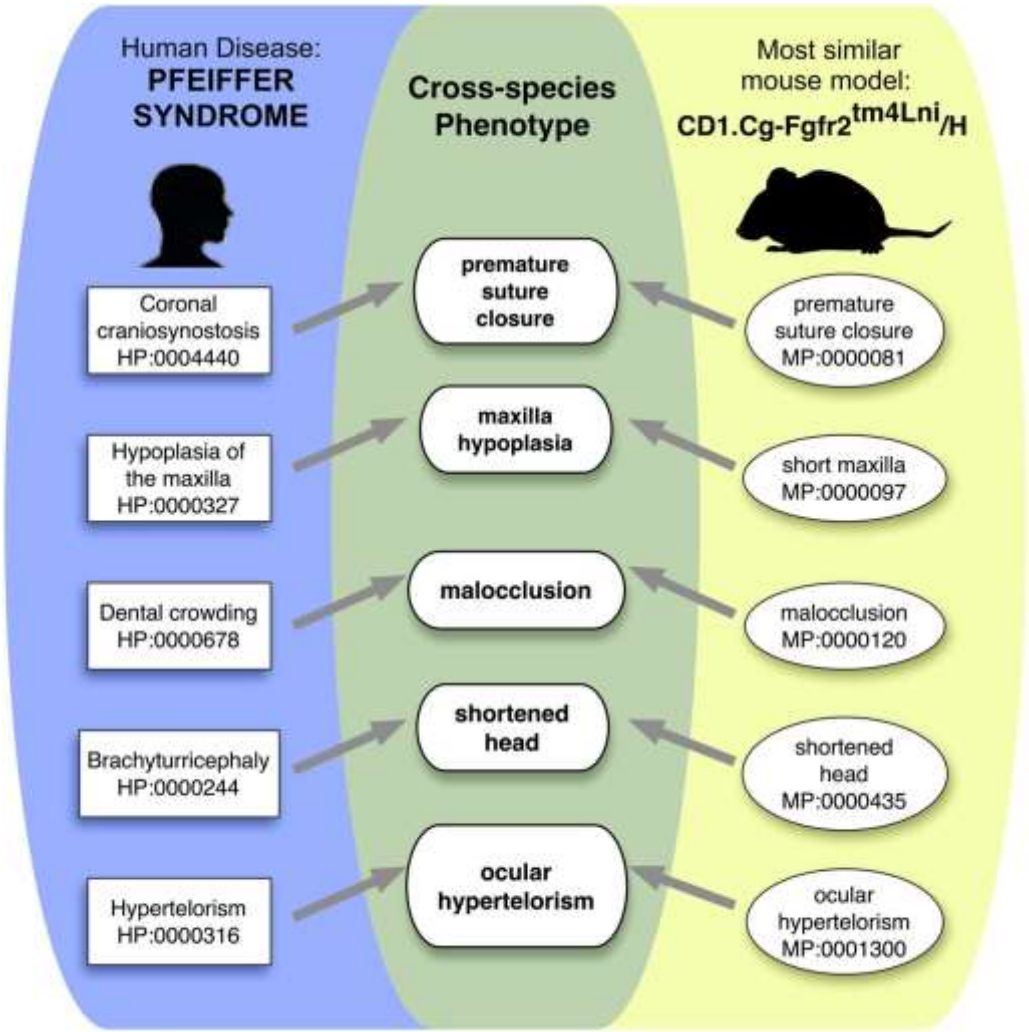
Goal: Make data about mouse models of human disease more accessible to researchers (esp. clinical & translational researchers less familiar with mouse data).

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.

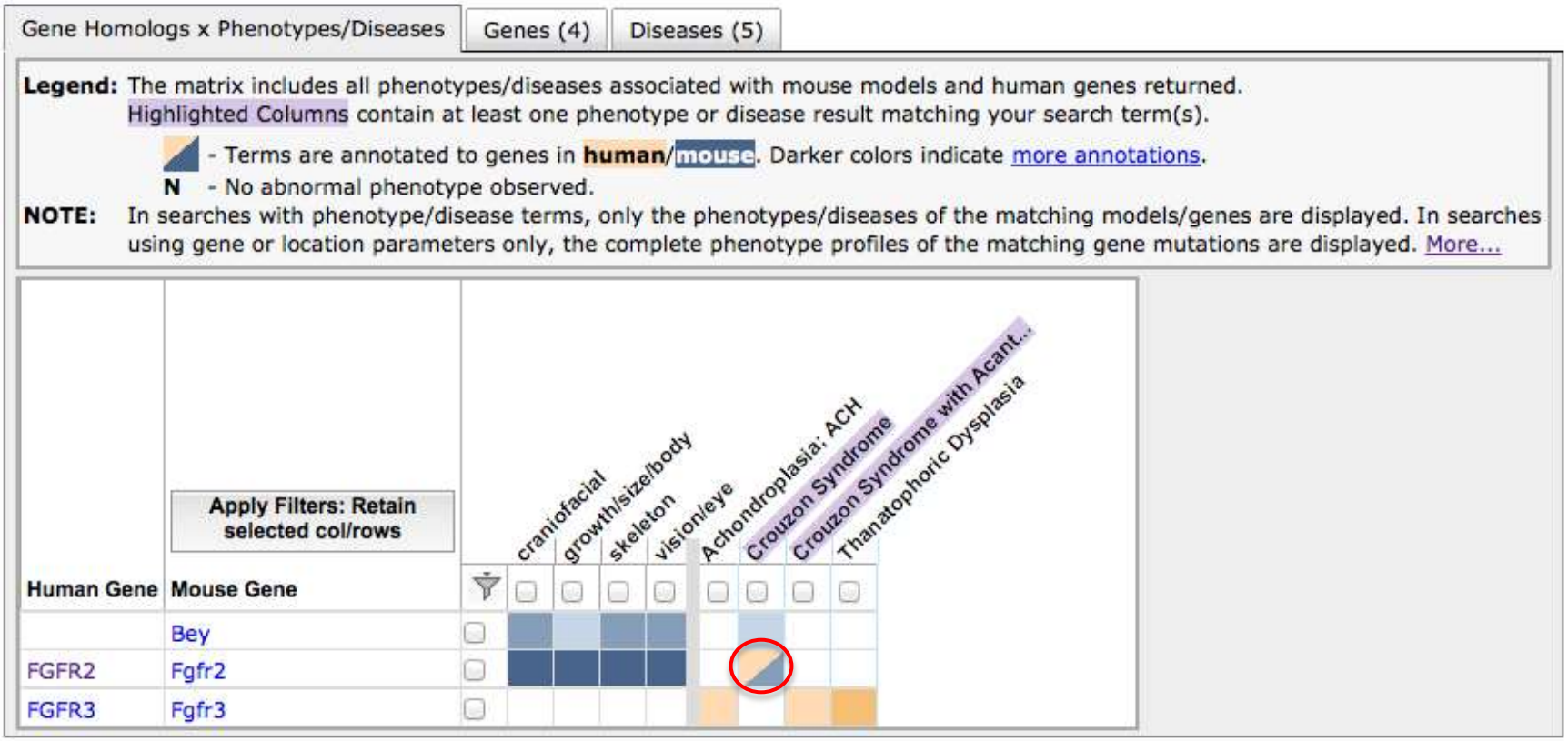


Robinson P N et al. Genome Res. 2014;24:340-348

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



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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