



NATIONAL CENTER FOR
BIOMEDICAL ONTOLOGY

Promise and Peril of Phenotype Annotation using Ontologies to link Human Diseases to Animal Models

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Lawrence Berkeley National Laboratory
National Center for Biomedical Ontology

<http://www.phenote.org>

Talk Outline

- Current methods to link human diseases to animal models
- Ontologies can help
- NCBO: Creating new tools for recording, storing, accessing phenotypic data (Phenote, OBD)
- Annotation of Phenotypes
 - The “annotation model”
 - Ontologies
 - Human disease annotations - a triple-blind experiment
 - Cross-species comparative analysis
- Promise & Peril

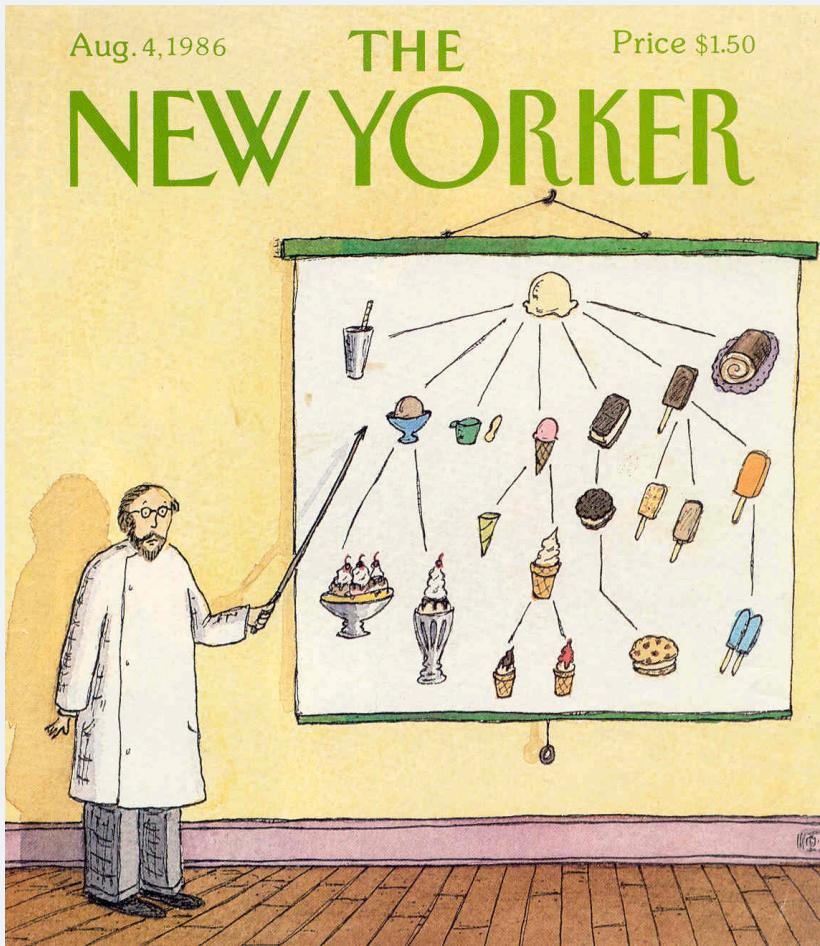
Data mining = text searching

- Gene resources:
 - Entrez/Genbank
 - Ensembl
 - MODs
 - (link by sequence similarity)
- Text-based phenotype resources:
 - OMIM (NCBI)
 - DECIPHER (Sanger)
 - HGMD (Cardiff)
 - Disease-specific DBs
 - MODs
 - PubMed
 - (link by ...? Text-mining?)

Information retrieval from text-based resources (OMIM) is not straightforward:

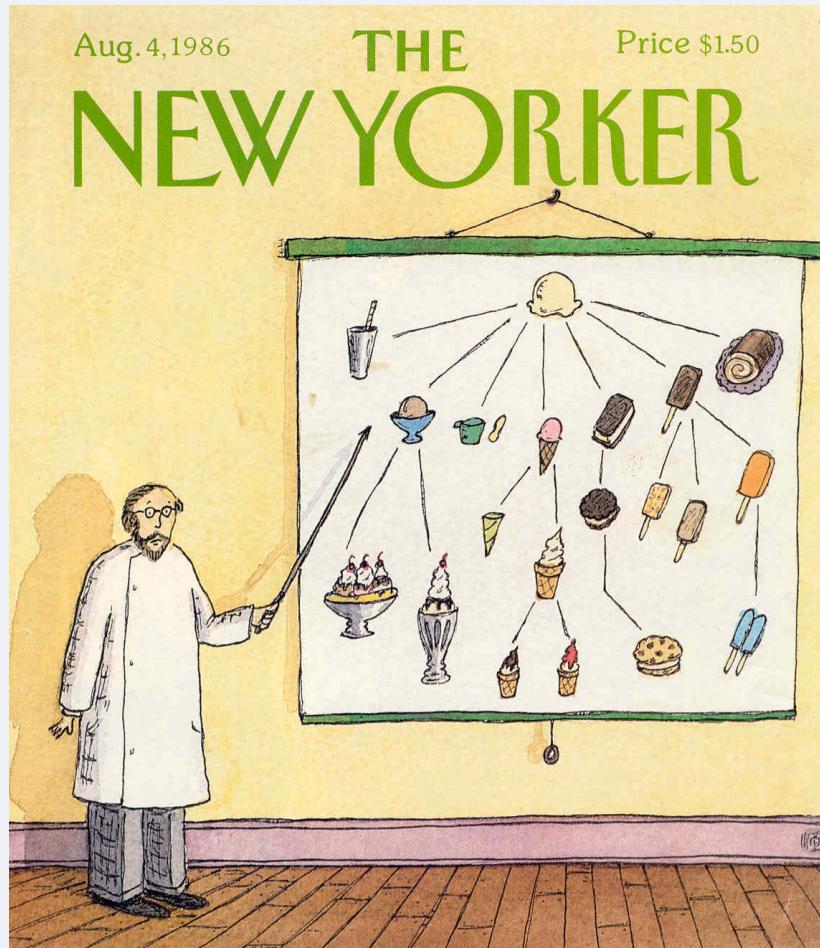
Query	# of records
"large bones"	251
"large bone"	713
"enlarged bones:"	75
"enlarged bone"	136
"big bones"	16
"huge bones"	4
"massive bones"	28
"hyperplastic bones"	8
"hyperplastic bone"	34
"bone hyperplasia"	122
"increased bone growth"	543

Ontologies, what are they, and why do we *need* them?



- "To support the sharing and reuse of formally represented knowledge among AI systems, it is useful to define the common vocabulary in which shared knowledge is represented". A specification of a representational vocabulary for a shared domain of discourse - definitions of classes, relations, functions, and other objects - is called an **ontology**." (Gruber 1993)

An *ontology* is a classification vocabulary



Biological ontologies have two key features:

1. Hierarchical constrained vocabulary
2. Relationships between terms of different types

Ontologies used for describing biology

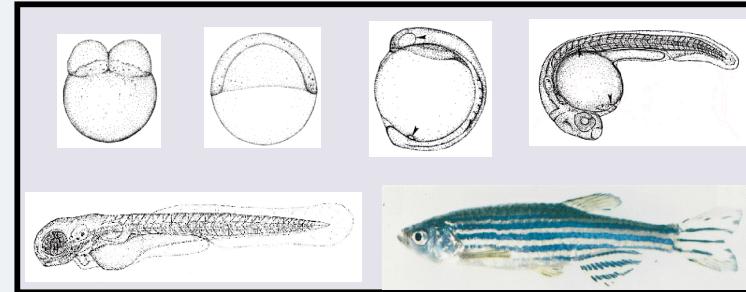
Anatomy ontologies

Cardiovascular system

heart

atrium

ventricle



Phenotype ontology

morphology

size

length

decreased length



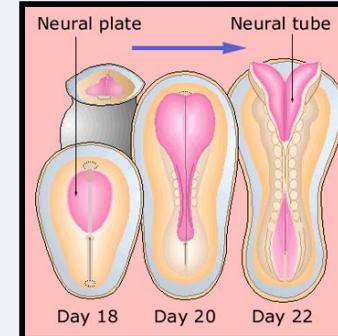
Gene ontology

CNS development

brain development

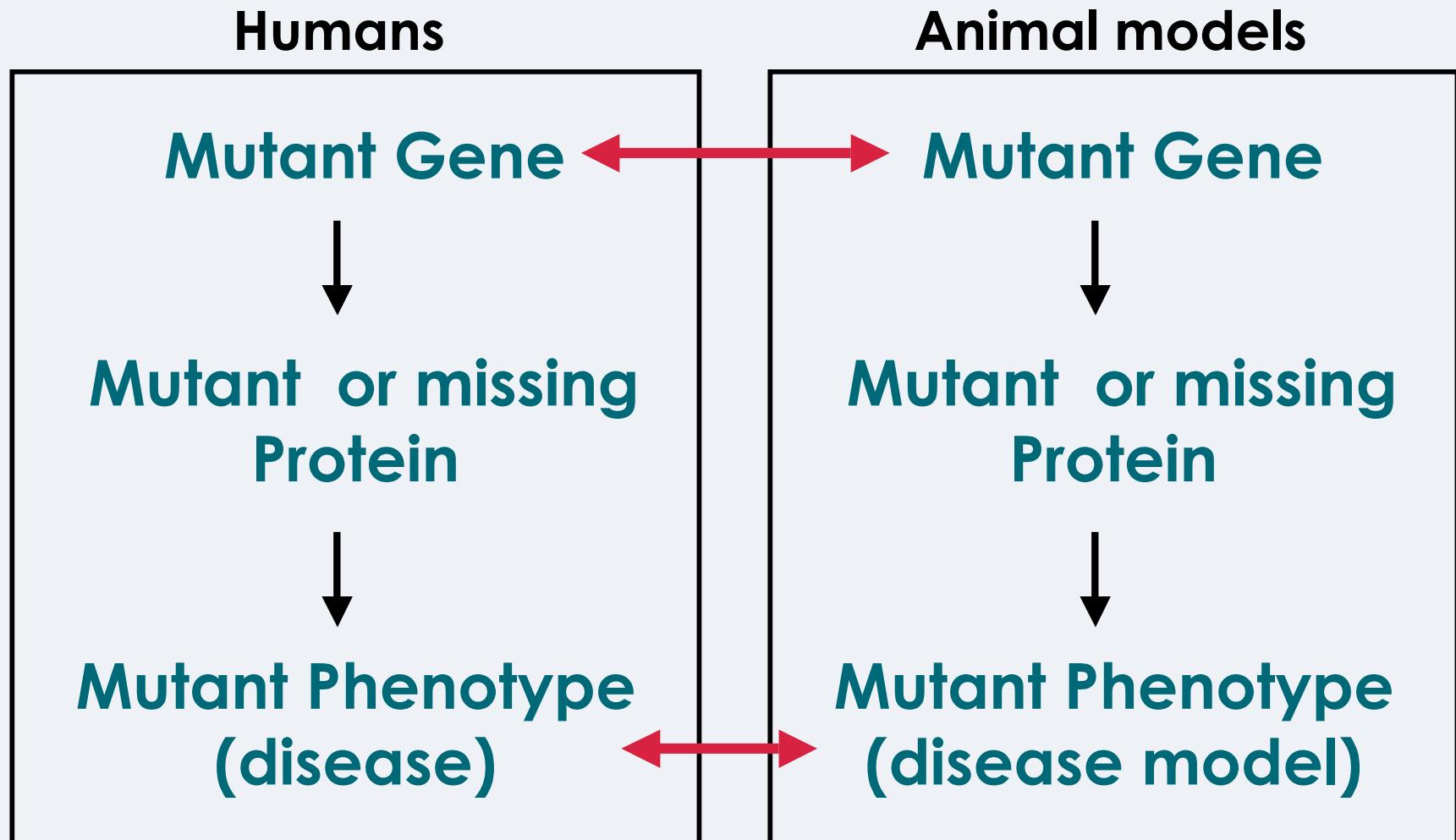
forebrain development

hindbrain development



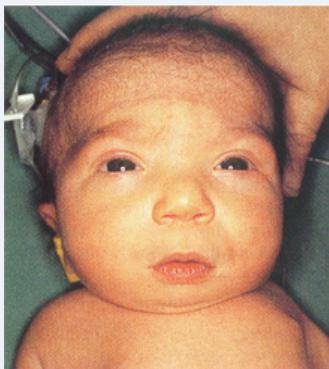
Ontologies allow different data types to be classified in a systematic way understandable by both computers and humans

A common syntax connects mutant phenotypes to candidate human disease genes



Human and zebrafish sox9 mutations curated in PATO syntax

Human, SOX9 (Campomelic dysplasia)



Zebrafish, sox9a (jellyfish)



Scapula: hypoplastic ↔ Scapulocoracoid: aplastic
Lower jaw: decreased size ↔ Cranial cartilage: hypoplastic
Heart: malformed or edematous ↔ Heart: edematous
Phalanges: decreased length ↔ Pectoral fin: decreased length
Long bones: bowed ↔ Cartilage development: disrupted
Male sex determination: disrupted

Curation of mutant phenotypes and human diseases using a common vocabulary can provide candidate genes and mutant models of disease

Goals

- Turn text-based phenotypes into ontology-based computable annotations
- Annotate mutant phenotypes
 - OMIM records
 - Cooperation/synergy between MODs
- Collect & store annotations in a common resource (OBD)
- Collect a set of guidelines for biocurators across disciplines
- Develop additional tools & resources for mining data for novel discovery

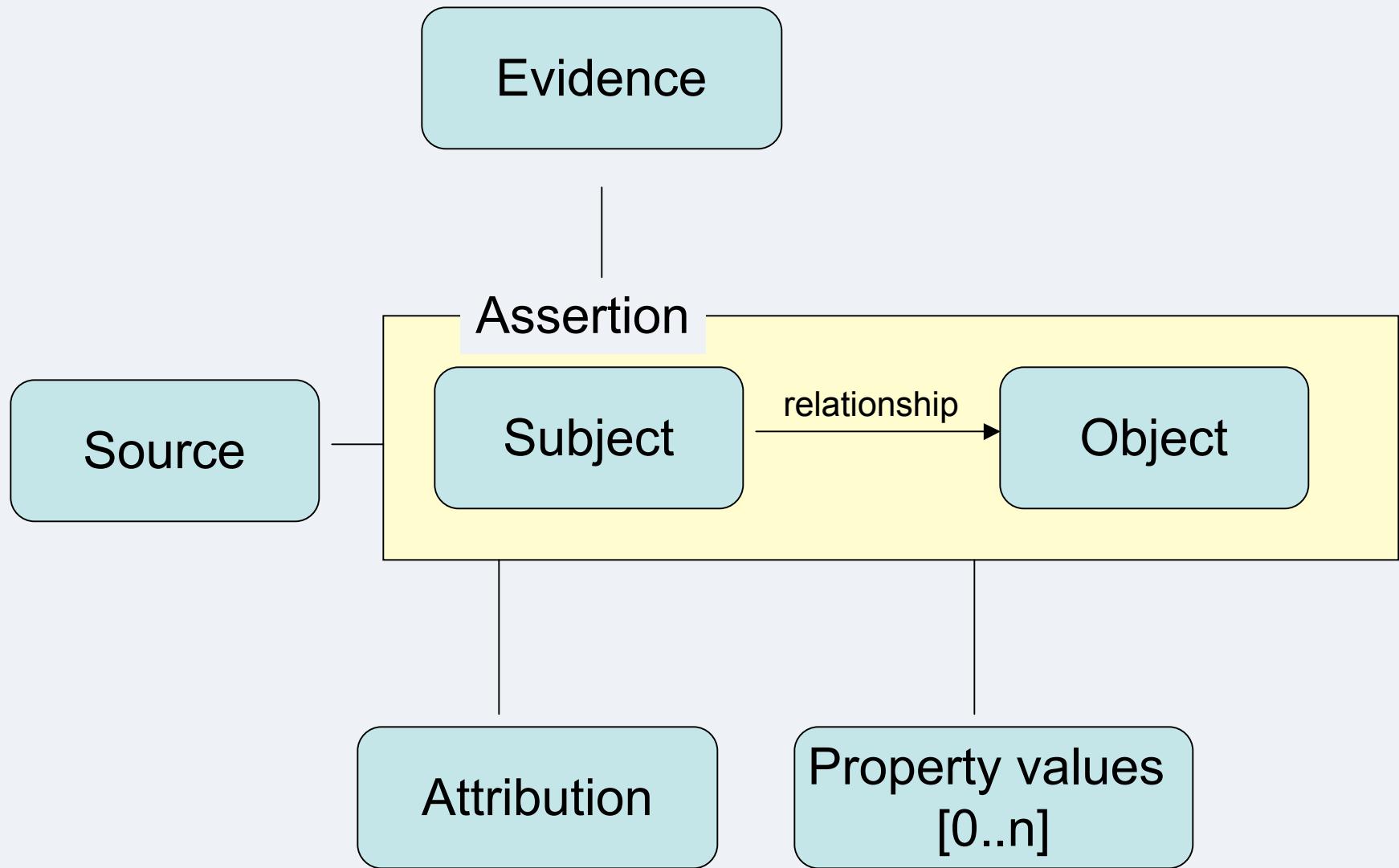
National Center for Biomedical Ontology

- Purpose of the NCBO
 - A centralized resource for biomedical ontologies, tools, applications, data, etc.
 - (<http://www.bioontology.org>)
- Berkeley group contribution:
 - “Annotation model”
 - Tools for recording, storage, analysis of data: Phenote & OBD
 - Ontology development (for annotation)

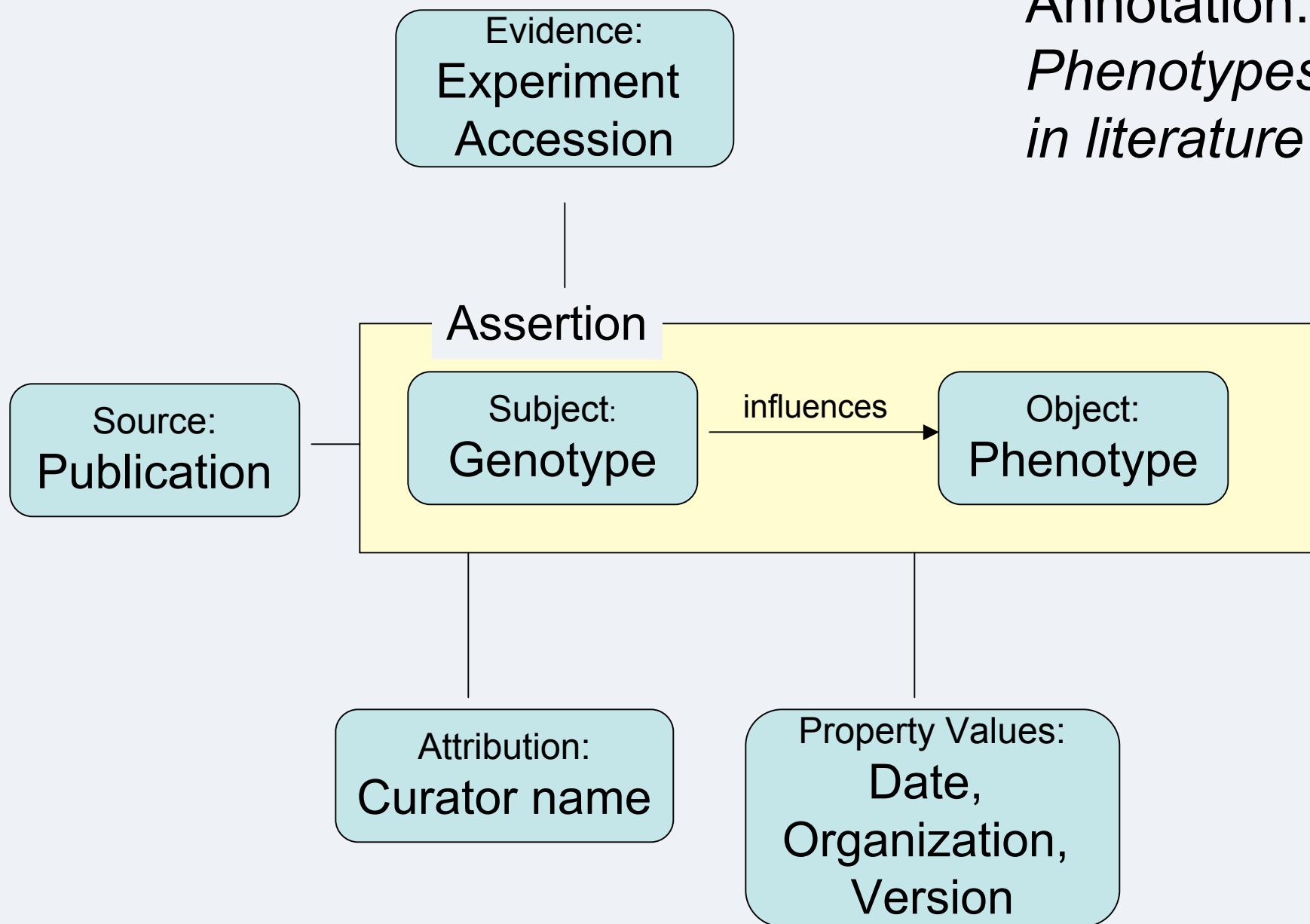
What is an annotation?

- What types of concepts are captured?
 - Assertions A-->B
 - Evidence
 - Source
- Using CVs in annotation
- Interoperability
- Types of annotations:
 - Class-class
 - Class-instance
 - Instance-instance

Annotation



Annotation: *Phenotypes* *in literature*

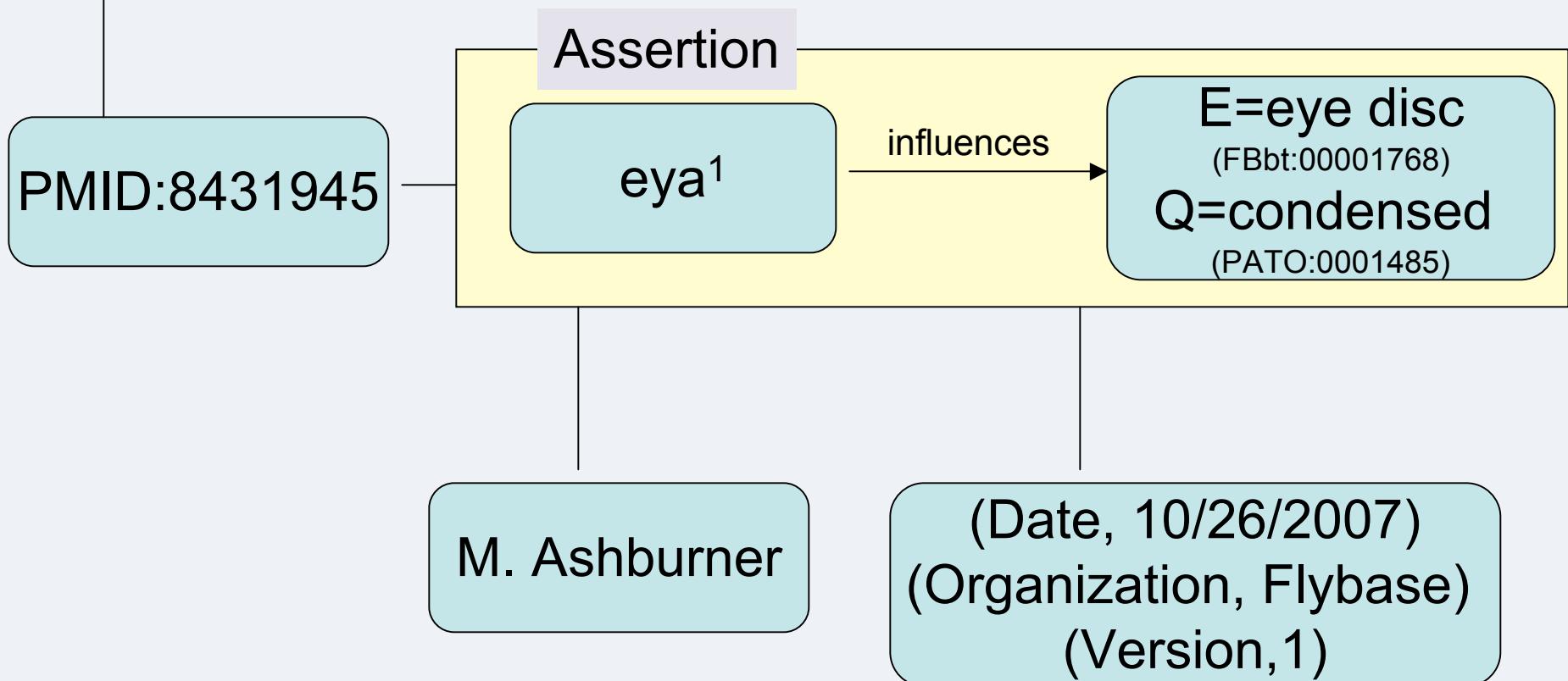


Annotation: *Phenotypes in Literature*

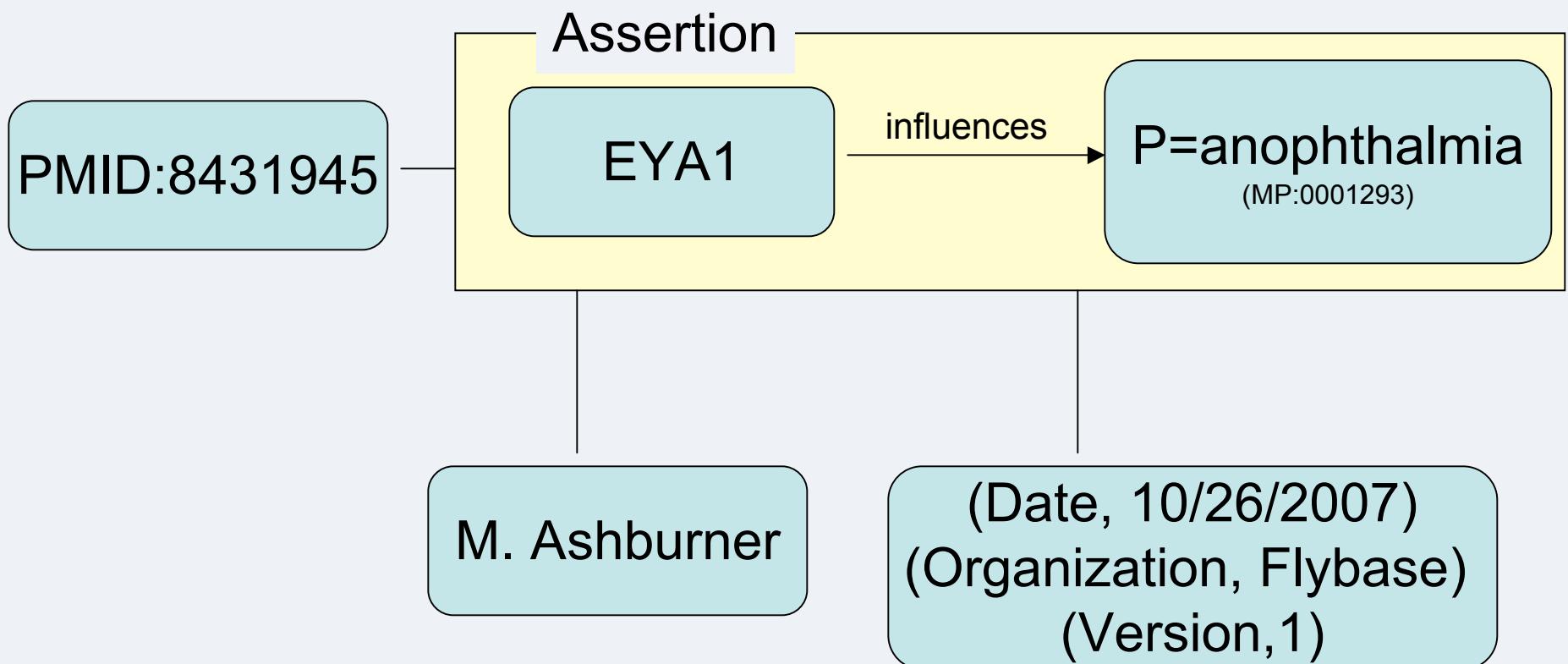
- EQ style: Entity + Quality
 - Entity = Anatomy, GO process, Disease
 - Quality = PATO
- Precomposed-phenotypes:
 - Entity = Mouse anatomy (refining Q)
 - Quality = Mammalian Phenotype

Annotation: *Phenotypes in literature*

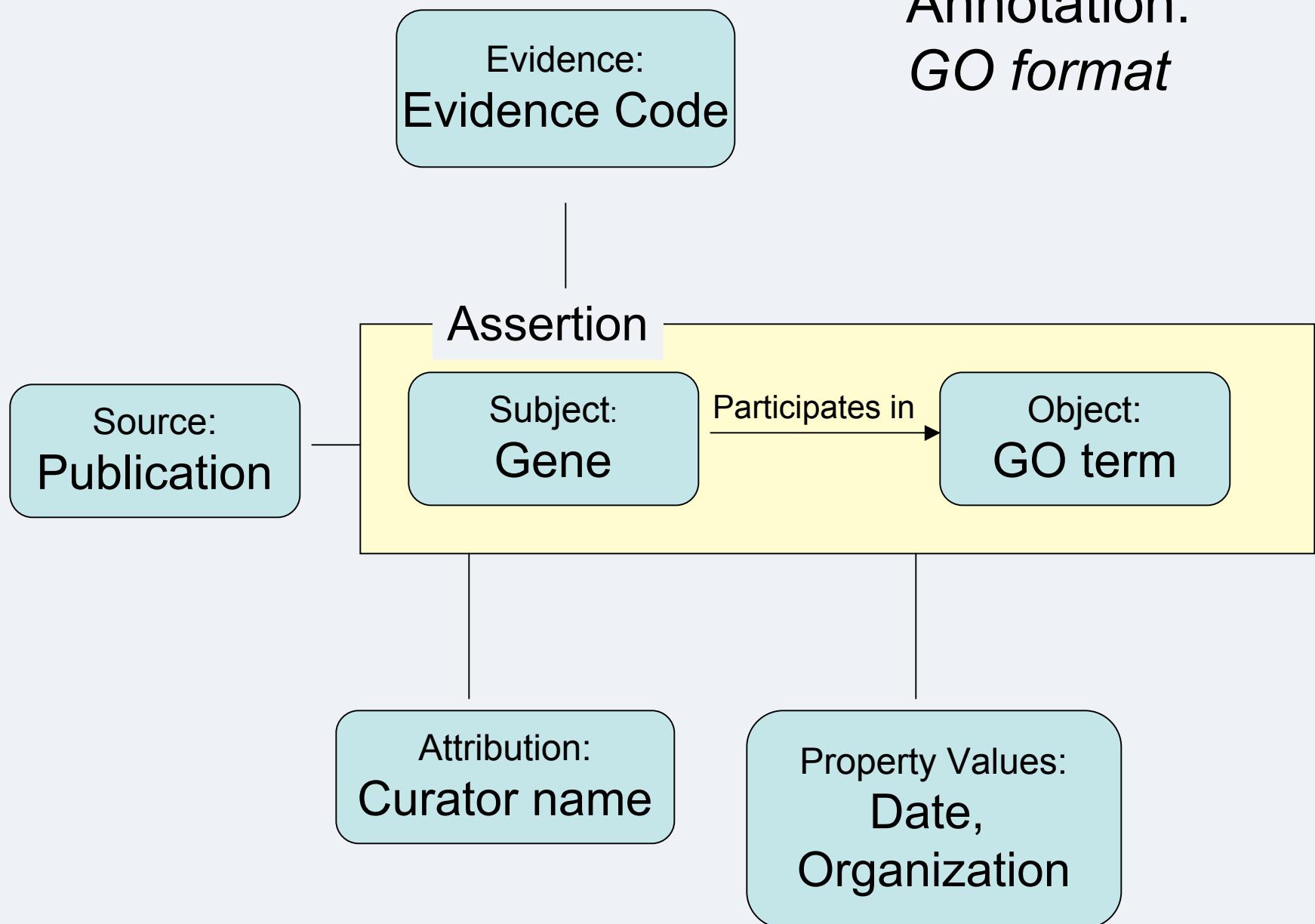
In contrast, eye discs of eya¹ animals reveal a dramatic increase in cell death during the third instar larval stage. Cells are present in the eya¹ eye disc that appear condensed and refractile by light microscopy, reminiscent of



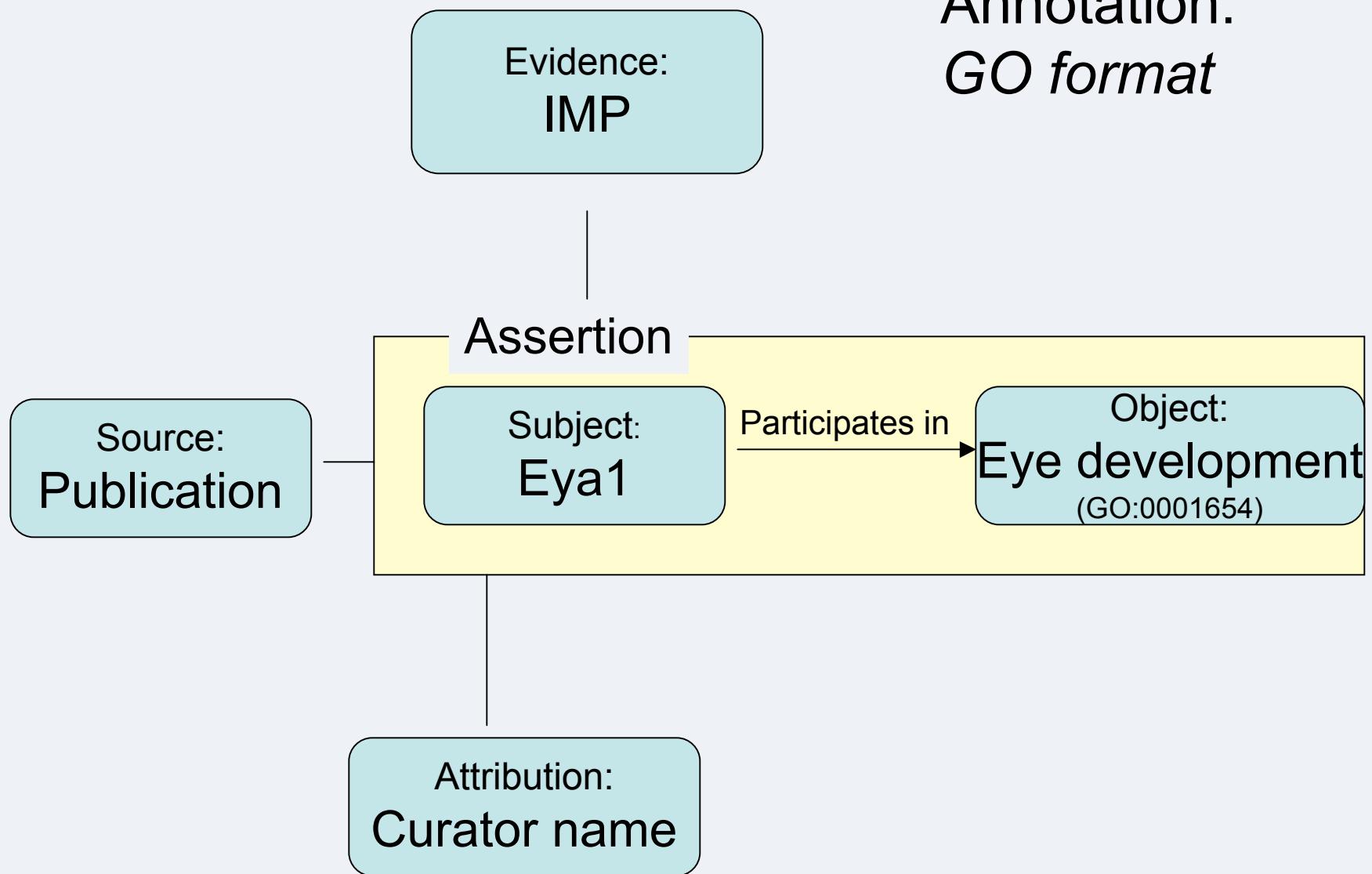
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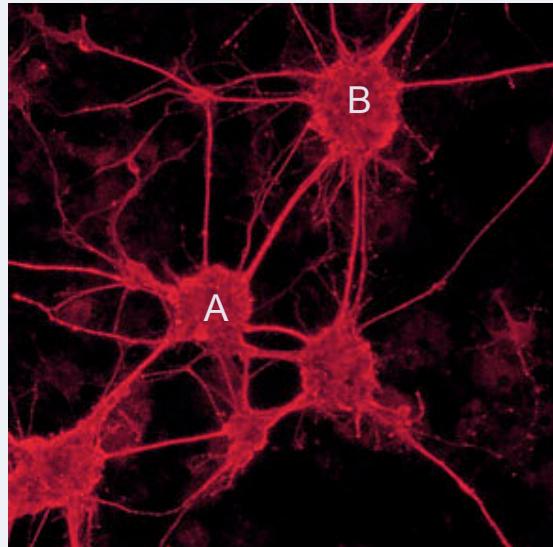


Annotation: *GO format*



Annotation: *GO format*





Evidence:
Assay ID

Annotation: *Image Data*

Assertion

Source:
ImageID

Subject:
NeuronA

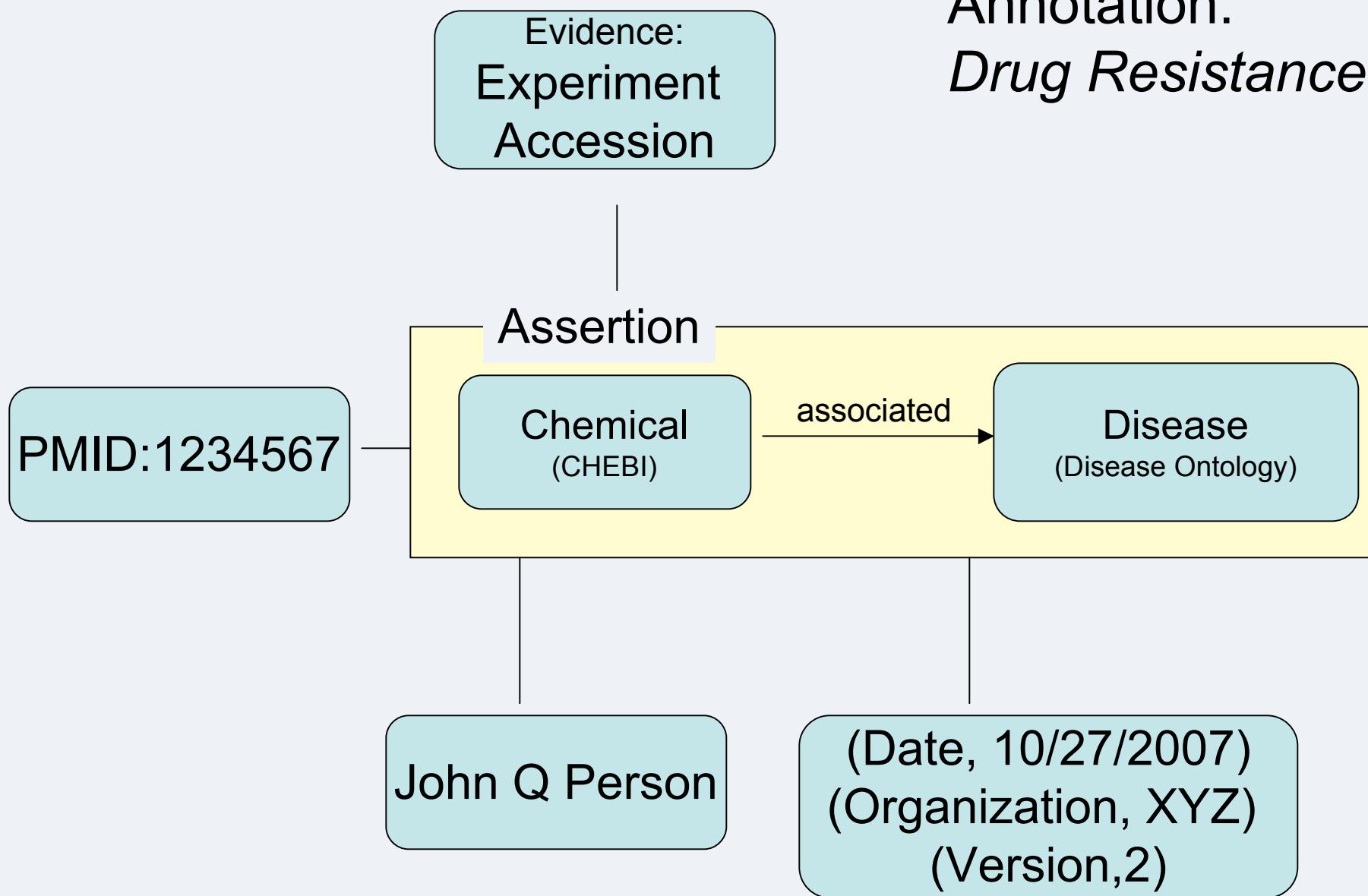
targets

Object:
NeuronB

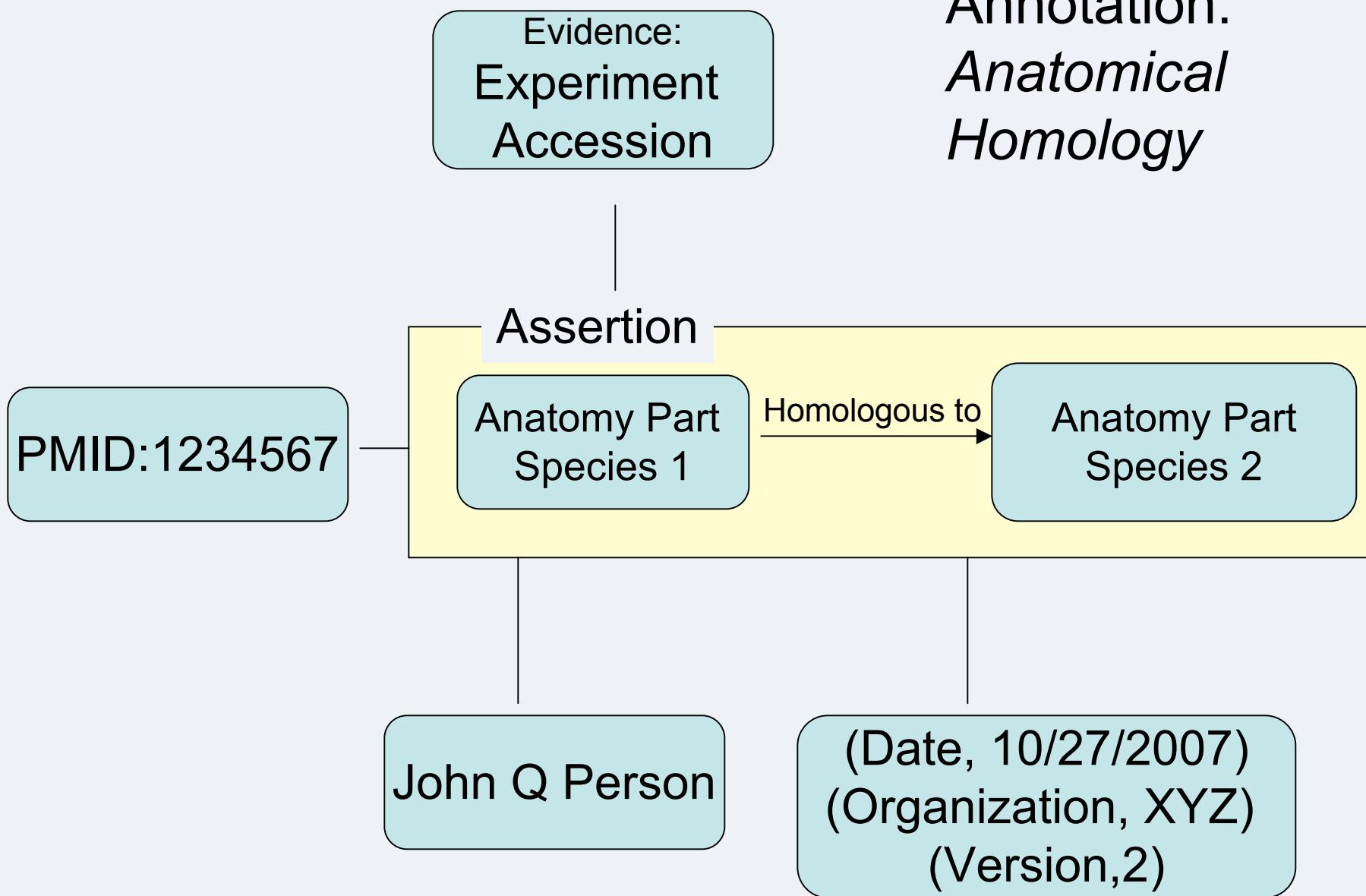
Attribution:
Curator name

Property Values:
Date,
Organization

Annotation:
Drug Resistance



Annotation: *Anatomical Homology*



Refining terms on-the-fly

- Post-composition:
 - Join together 2+ terms for specificity:
 - Apoptosis of neuron in skin (GO,CL,FMA)
 - S-phase of colon cancer cell (GO,CL)
 - Aster of human spermatocyte (GO,FMA)
 - Combine terms from different ontologies
 - Increase “information content” of an annotation

Phenote: Simple software for annotating using ontologies

- Provide tool for ontology-based annotation
 - Standardized model to record annotations for increased compatibility of data between disparate communities.
- Simple & intuitive user interface
 - (especially for users that don't know/care about what an ontology is)
- Easy-to-configure for different user-communities
- Pluggable architecture for external applications to interface/embed in application
- Provide interfaces with external SOAP and REST services for streamlined workflow (BioPortal, OBD, NCBI, EBI, etc).

Phenote tour

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Quality	PATO	increased curvature	<input type="button" value="Comp"/>
Add'l Entity	ALL	<input type="button" value="▼"/>	<input type="button" value="Comp"/>
Abnormal	abnormal		<input type="button" value="▼"/>
Description	CAMPOMELIC DYSPLASIA		

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Ontology: fma
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External Annotations:

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Exact Inherit

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Term Info Browser

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PMID:10951468	OMIM:608160.0006	Plantar that has part Groove	deep			abnormal	deep plantar creases
PMID:10951468	OMIM:608160.0006	Little finger	curved			abnormal	mild clinodactyly
PMID:10951468	OMIM:608160.0006	Nail	convex			abnormal	hyperconvex nails
PMID:10951468	OMIM:608160.0006	Nail	decreased size			abnormal	small nails
PMID:10951468	OMIM:608160.0006	Elbow joint	decreased flexibility			abnormal	limited elbow extension

New Duplicate Delete Undo Save Data Simple Filter Exact Inherit

Article: Campomelic dysplasia ...

JW Foster, MA Dominguez-Steglich, S Guioli, G Kowk, PA Weller, M Stevanović, J Weissenbach, S Mansour, ID Young, PN Goodfellow. 1994. *Campomelic dysplasia and autosomal sex reversal caused by mutations in an SRY-related gene.. Nature* 372:525-30

Abstract: Induction of testis development in mammals requires the presence of the Y-chromosome gene SRY. This gene must exert its effect by interacting with other genes in the sex-determination pathway. Cloning of a translocation chromosome breakpoint from a sex-reversed patient with campomelic dysplasia, followed by mutation analysis of an adjacent gene, indicates that SOX9, an SRY-related gene, is involved in both bone formation and control of testis development. (PMID: 7990924)

Phenote Editor

PUB PMID:7990924
 Genotype OMIM:608160.0001
 Genetic Context
 Entity FMA Long bone
 Quality PATO increased curvature
 Add'l Entity ALL
 Abnormal abnormal
 Description CAMPOMELIC DYSPLASIA

Term Info: Long bone

Term: Long bone
 ID: FMA:7474
 Ontology: fma
 Definition: (no definition provided)
 External Annotations:

Links (21)

Parents

is_a [Bone organ](#)
[Appendicular skeleton](#)

Children

is_a [Fibula](#), [Phalanx of finger](#), [Tibia](#), [Femur](#), [Rib](#), [Metatarsal bone](#), [Radius](#), [Humerus](#), [Clavicle](#), [Metacarpal bone](#), [Phalanx of toe](#), [Ulna](#), [Cartilage of long bone](#), [Compact bone of long bone](#), [Medullary cavity of long bone](#), [Trabecular bone of long bone](#), [Epiphysis](#), [Diaphysis](#), [Periosteum of long bone](#)

Annotation Table

PUB	Genotype	Entity	Quality	Add'l Entity	Genetic Context	Abnormal	Description
PMID:10951468	OMIM:608160.0006	Long bone	curvature			normal	absence of curvature - characteristic of
PMID:10951468	OMIM:608160.0006	Long bone	deformed			abnormal	angulation of long bones
PMID:10951468	OMIM:608160.0006	Skeletal system	deformed			abnormal	together with other skeletal and extrask
PMID:10951468	OMIM:608160.0006	development of secondary female sexual	present		penetrance_incomple	abnormal	two-thirds of affected XY individuals ma
PMID:10951468	OMIM:608160.0006	development of primary female sexual characteristics	present		penetrance_incomple	abnormal	two-thirds of affected XY individuals ma
PMID:10951468	OMIM:608160.0006	Genital system	decreased functionality		penetrance_incomple	abnormal	Up to two-thirds of affected XY individu
PMID:10951468	OMIM:608160.0006	Respiratory system	decreased functionality			abnormal	severe respiratory distress
PMID:10951468	OMIM:608160.0006	Renal pelvis	dilated			abnormal	renal pelvis dilation
PMID:10951468	OMIM:608160.0006	Nasal bone	flat			abnormal	flattened nasal bridge
PMID:10951468	OMIM:608160.0006	Lower jaw	decreased size			abnormal	micrognathia - abnormally small lower j
PMID:10951468	OMIM:608160.0006	Palate	cleft			abnormal	midline cleft palate
PMID:10951468	OMIM:608160.0006	Philtrum	deep			abnormal	long deep philtrum
PMID:10951468	OMIM:608160.0006	Mouth	decreased size			abnormal	small mouth
PMID:10951468	OMIM:608160.0006	Face	round			abnormal	round face
PMID:10951468	OMIM:608160.0006	External genitalia	deformed			abnormal	ambiguous external genitalia
PMID:10951468	OMIM:608160.0006	Scrotum	bifid			abnormal	bifid scrotum
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NCBI Browser (SOAP plug-in)

Phenote Editor

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Genetic Context

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Add'l Entity ALL Comp

Abnormal abnormal

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PMID:10951468	OMIM:608160.0006	development of secondary female sexual	present	
PMID:10951468	OMIM:608160.0006	development of primary female sexual characteristics	present	
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Graph DAC Viewer

Ancestor views: Long bone

All parents

Graphical Viewer

OBD: phenotype annotation DB

- OBD model - currently one DB
- Distribution is the key
- Need software that can pull from several resources (think napster)
- Data can be accessed through a RESTful API.
 - Very unstable test server: <http://yuri.lbl.gov:8182/>
 - Examples:
 - All statements ABOUT a node
 - /html/nodes/CL:0000148/statements
 - All statements concerning a node in some way, optionally filtered by relation
 - /html/nodes/CL:0000148/statements/about/OBO_REL:is_a
 - Composite description (class expression, post-composition)
 - /html/nodes/MP:0004176/description
 - /html/nodes/PATO:0000963^OBO_REL:inheres_in(FMA:58238)/description
- Integrate into tools (itunes-esque) in Phenote

OMIM annotation: a “triple-blind” experiment

- Three curators independently curate 5 OMIM-gene records
- Compare style
- Compare granularity
- Determine/refine annotation protocol

An OMIM Record

[*601653](#)

GeneTests, Links

EYES ABSENT 1; EYA1

Alternative titles; symbols

EYES ABSENT, DROSOPHILA, HOMOLOG OF, 1

Gene map locus [8q13.3](#)

TEXT

CLONING

By positional cloning in the 8q13.3 region where the branchiootorenal dysplasia syndrome (BOR; [113650](#)) maps, [Abdelhak et al. \(1997\)](#) identified a gene that they showed to be responsible for the disorder. The gene is a human homolog of the Drosophila 'eyes absent' gene (Eya) and was therefore called EYA1. The gene encodes a deduced 559-amino acid polypeptide with a predicted molecular mass of 61.2 kD. [Abdelhak et al. \(1997\)](#) also found a highly conserved 271-amino acid C-terminal region in the products of 2 other human genes, which were subsequently called EYA2 ([601654](#)) and EYA3 ([601655](#)), demonstrating the existence of a novel gene family. 

GENE FUNCTION

[Abdelhak et al. \(1997\)](#) studied the expression pattern of the mouse EYA1 ortholog and obtained results suggesting a role in the development of all components of the inner ear, from the emergence of the otic placode. In the developing kidney, the expression pattern indicated a role for Eya1 in the metanephric cells surrounding the 'just-divided' ureteric branches. 

ALLELIC VARIANTS

[\(selected examples\)](#)

.0001 BRANCHIOOTORENAL SYNDROME 1 [EYA1, ARG275TER]

In a familial case of BOR syndrome ([113650](#)), [Abdelhak et al. \(1997\)](#) demonstrated a C-to-T transition of nucleotide 823 in exon z, resulting in a change of codon 275 from arginine to stop.

.0002 BRANCHIOOTORENAL SYNDROME 1 [EYA1, 1-BP DEL AND 2-BP INS, 1251T-CC]

In a familial case of BOR syndrome ([113650](#)), [Abdelhak et al. \(1997\)](#) demonstrated substitution of 1251T with CC in exon D, resulting in a frameshift and premature termination of transcription.

.0003 BRANCHOOTIC SYNDROME 1 [EYA1, 2-BP INS, 870GT]

In a kindred in which 8 members in 3 generations had the branchiootic syndrome ([602588](#)) (without renal anomalies), [Vincent et al. \(1997\)](#) demonstrated linkage to the same region of chromosome 8 where the EYA1 gene is located. Furthermore, they demonstrated a 2-bp (GT) insertion in exon A, at position 870. 

An OMIM Record

[*601653](#)

EYES ABSENT 1; EYA1

GeneTests, Links

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branches. 

[ALLELIC VARIATION](#)
[\(selected examples\)](#)

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branches.

Branchiootorenal syndrome is an autosomal dominant disorder characterized by sensorineural, conductive, or mixed hearing loss, structural defects of the outer, middle, and inner ear, branchial fistulas or cysts, and renal abnormalities ranging from mild hypoplasia to complete absence. Reduced penetrance and variable expressivity has been observed ([Fraser et al., 1978](#)).

Melnick et al. ([1975](#), [1976](#)) described a family in which the father and 3 of 6 living children (a son and 2 daughters) had mixed hearing loss associated with a Mondini-type cochlear malformation (hypoplasia of cochlear apex shown by tomography) and stapes fixation, cup-shaped, anteverted pinnae, bilateral prehelical pits, bilateral branchial cleft fistulas, and bilateral renal dysplasia with anomalies of the collecting system. The father and affected son also had aplasia of the lacrimal ducts. A fourth child, who died at 5 months of age, was said to have had branchial cleft fistulas and bilateral polycystic kidneys. Conditions in the same nosoembryologic community were discussed. [Fitch and Srolovitz \(1976\)](#) reported a woman with preauricular pits, cervical fistulae, and partial deafness who gave birth to 2 children with preauricular pits and severe renal dysgenesis.

An OMIM Record

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In a 4-year-old Japanese girl with congenital cataracts and ocular anterior segment anomalies, [Azuma et al. \(2000\)](#) found an A-to-G transition at position 1688 of the cDNA corresponding to the EYA1 gene, expected to result in an arg514-to-gly amino acid substitution. Ocular examinations revealed central corneal opacity, adhesion to the iris (Peters anomaly), and slight cataracts in both eyes, whereas the fundus was normal. Her mother, aged 32, had nuclear-type congenital cataracts. The patient and her mother were otherwise normal in appearance, intelligence, and karyotype. No clinical findings suggesting BOR syndrome were detected except for a slight elevation of the auditory brainstem response (ABR) threshold in hearing. 

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Ontologies needed

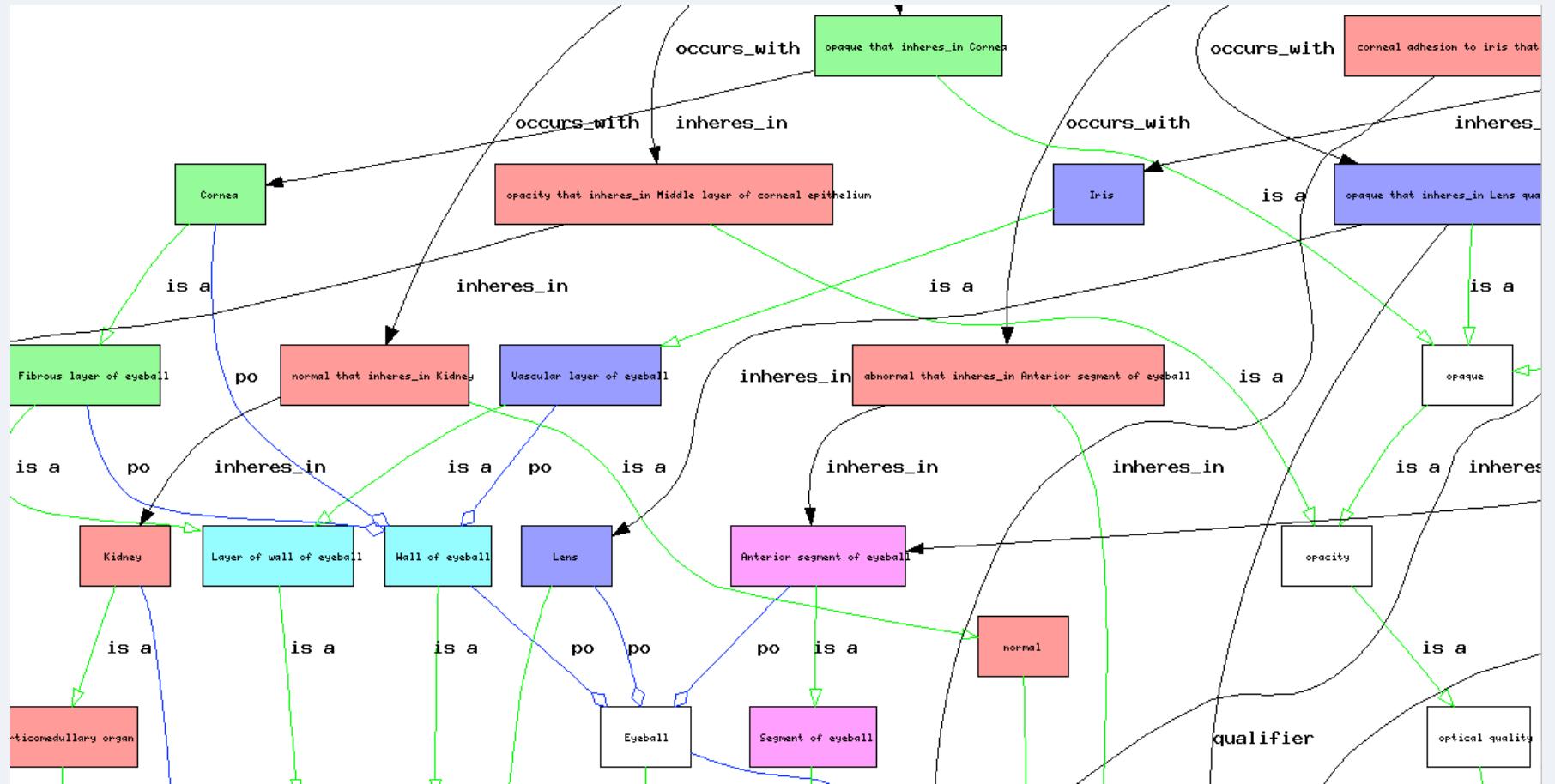
- Human Anatomy (FMA)
- Qualities (PATO)
- Biological Processes (GO)
- Cell types (CL)
- Chemicals (CHEBI)

Comparing curator annotation similarities (PAX2)

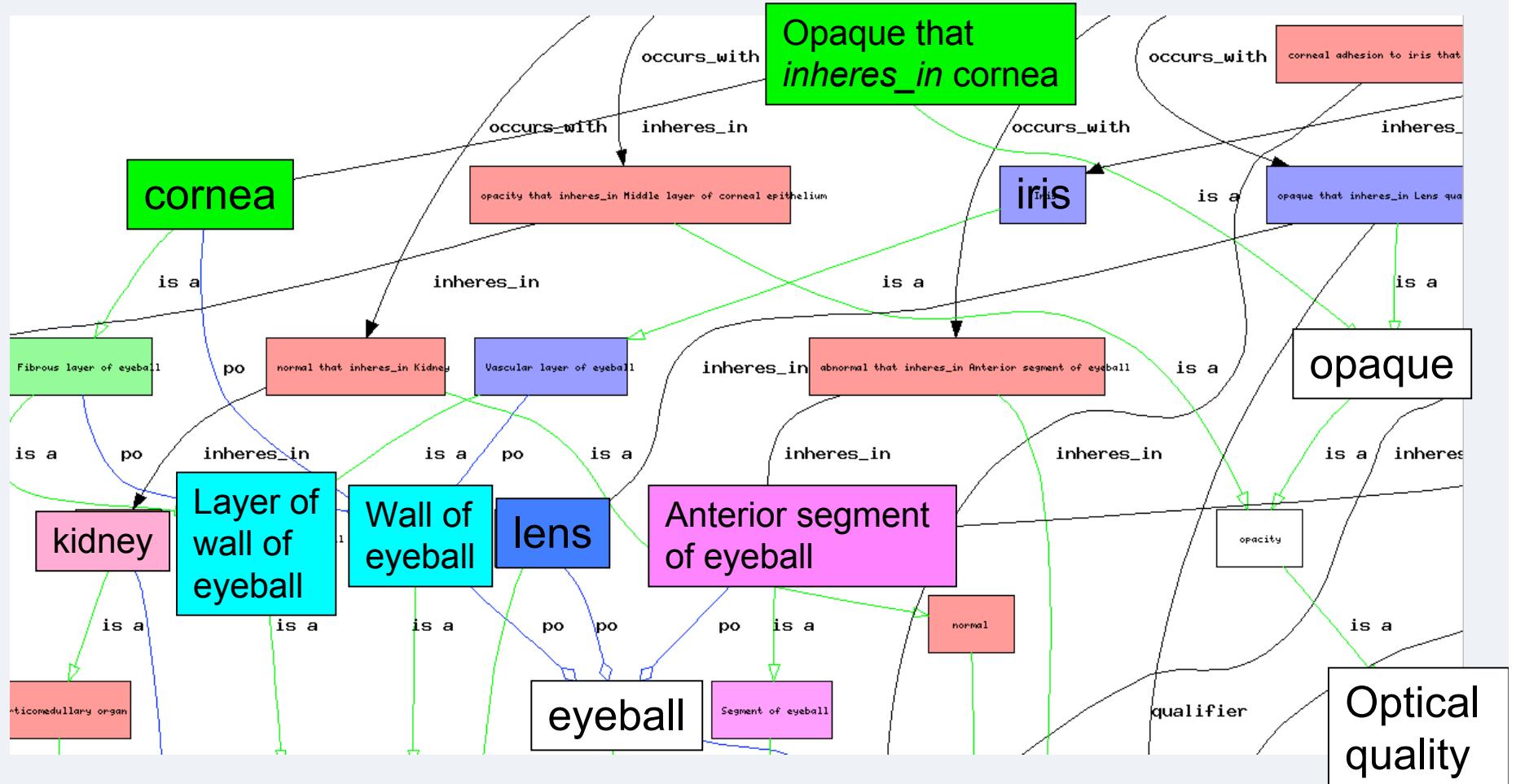
	curator 1	curator 2	curator 3
anatomy			
optic nerve	+	-	+
kidney	+	+	+
urine	+	-	-
quality			
hypoplastic	+	+	+
functionality impairment	+	-	+
	-	+	-

optic nerve	colomba	-	structure, malformed in
kidney	hypoplastic	hypoplastic	hypoplastic
kidney	functional failure	impaired	non-functional
urine	increased protein concentration	-	-

Overlap observed at different levels of granularity (EYA1)



Overlap observed at different levels of granularity (EYA1)



Summary: OMIM annotation

Summary curator OMIM annotations (#genotypes/similarity)

curator	1	2	3	overall %
1	24/22%	34/45%	33.5	
2	24/73%	25/71%	72	
3	34/63%	25/39%	51	
overall %	68	30.5	58	

OMIM Annotation Standards

- Basics
 - Utilize the same configuration in Phenote. This will use the latest ontologies.
 - Use standard notation to describe zygosity
 - OMIM:1234567.0001/OMIM:1234567.0001; homozygous
 - OMIM:1234567.0001/+; heterozygous
 - OMIM:1234567.0001 listed without indicated second allele; unknown zygosity
 - Dates that annotations are created will be set automatically in the background by Phenote
- Ontologies
 - Human Anatomy (FMA), Gene Ontology (GO), Cell type (CL), Qualities (PATO)
 - No use of Mammalian Phenotype (MP) ontology, though it can be used to look for cross-products
 - Annotate only to non-obsoleted terms

OMIM Annotation Standards (con't)

- Annotation best practices
 - Annotate to both general omim id, as well as the alleles.
 - If its known that a process is affected (usually when there is more than one time point), **annotate to the process in addition to the anatomy**.
 - When a PATO term is missing, always **annotate to the next most specific term**. If a branch is missing, annotate to the general term "quality".
 - no postcomposition using GO:Biological_Process with a continuant
 - limit the post-comp relation to ***part_of***
 - indicate dominance/recessiveness in the **Genetic Context** box.
 - mark annotations as '**abnormal**', except in the case of 'remarkable normality'.
 - be sure to indicate **incomplete_penetrance** in the cases where multiple family members are described with the same genotype but different phenotypes.

General Annotation Issues

- Remarkable normality
- Absence
- Relative qualities (what does “small” mean?)
- rates/frequencies (does it inhere in the heart or a process?)-
- homeotic transformation-
- phenotypes specific to a stage or temporal duration

Cross-species comparison

- Comparing phenotype across species (fly, fish, human)
 - Gene homology (BLAST)
 - Phenotype homology
 - Anatomical homology
- How would different searches produce same/different results?
 - Do we want the same results?
 - Should they complement or be identical

Requirements for linking human and model phenotypes

- Linking together diverse anatomies
 - CARO - a common anatomy reference ontology
 - Different types of links - by function, by developmental path, etc.
- Informative algorithms for comparison of phenotypes - the “BLAST” for phenotypes
 - Information Content: (how surprising is the average annotation)
 - $IC(node) = -\log_2(p(node))$
 - $p(node)$ is the probability of that node being annotated
 - Semantic similarity?
 - Other ontology-based statistical methods

Progress on phenotype annotations

(November 26, 2007)

	Genotypes	Annotations	Distinct terms used
OMIM (Human)	138	1106	974
ZFIN (Zebrafish)	4196	14141	2460
FB (Fly)	219	422	108
MGI (Mouse)	61	452	285

Disease genes in common: EYA1, PAX2, SOX9

Summary

- EQ annotation model using ontologies
- Pilot annotation study shows ...
 - Triple-blind
 - Cross-species
- Annotation standards
- Improvements to PATO
- Two software tools (Phenote, OBD)

Future Directions

- Production annotation of OMIM records
- Recruitment of MODs for phenotype annotation
- Collaboration with BIRN group
- Expanding the Phenote Tool - plugins (phenomap, protocol editor, region editor, PDF markup)
- Linking existing anatomies to CARO
- New analysis algorithms

Issues still to address

- Ontologies change, what happens to annotations?
- New ontology content
- Linking diverse resources
- CARO - how to properly apply/annotate “homologous_to” relation for different items: genes, anatomical parts, processes?

Promise & Peril

- Promise
 - New ways to look at data
- Peril
 - Wow, there's so much data... how to analyze?

Acknowledgements

- BBOP group
 - PI, Suzanna Lewis
 - Chris Mungall (Phenote, OBD)
 - Mark Gibson (Phenote)
 - Seth Carbon (ORB)
 - John Day-Richter (alumni)



- Annotations
 - Melissa Haendel, Amy Singer, Yvonne Bradford (Zfin)
 - Michael Ashburner, David Sutherland (FB)
 - Georgios V. Gkoutos (FB)
 - Karen Yook (WB)

- NCBO, NIH



fin

Abstract

- Title: Promise and Peril of Phenotype Annotation using Ontologies to link Human Diseases to Animal Models
- Abstract: The path to disease gene discovery in humans is often a lengthy one, but can be significantly shortened if links between human and model organism *phenotypes* are readily available. Collecting and storing these descriptions in a common resource, recorded with ontologies, as well as developing the tools for annotation, access, and analysis are among the goals of the National Center for Biomedical Ontology. We have developed the *EQ annotation model*, which uses ontology terms to label and link together *entities*, such as anatomical structures, with the *qualities* describing them. Together with the model organism databases Zfin and Flybase, we will use this model in the Phenote Annotation Tool to record the mutant phenotypes of 200 genes known to cause human disease (from OMIM records) that have corresponding fly and zebrafish mutant phenotypes. I will discuss our initial annotation effort of four genes from each organism, which has lead to refinement of the PATO (quality) ontology, development of annotation standards, and a glimpse at the promise of this technique for information discovery. Comparison of annotations across species has reinforced the need for a common anatomy reference ontology (CARO), to which all anatomy ontologies need to be linked. All annotations are available in the NCBO Open Biomedical Database (OBD), which has the same underlying *annotation* data model, and can currently be accessed via a computational (REST) interface.