

# Phenotype annotation

**Jim Balhoff**

**NESCent Informatics, Phenoscape**



# Annotation

- ✱ “Applying” ontologies to data
- ✱ Tagging
- ✱ Modeling — Knowledge Representation



# What is annotated

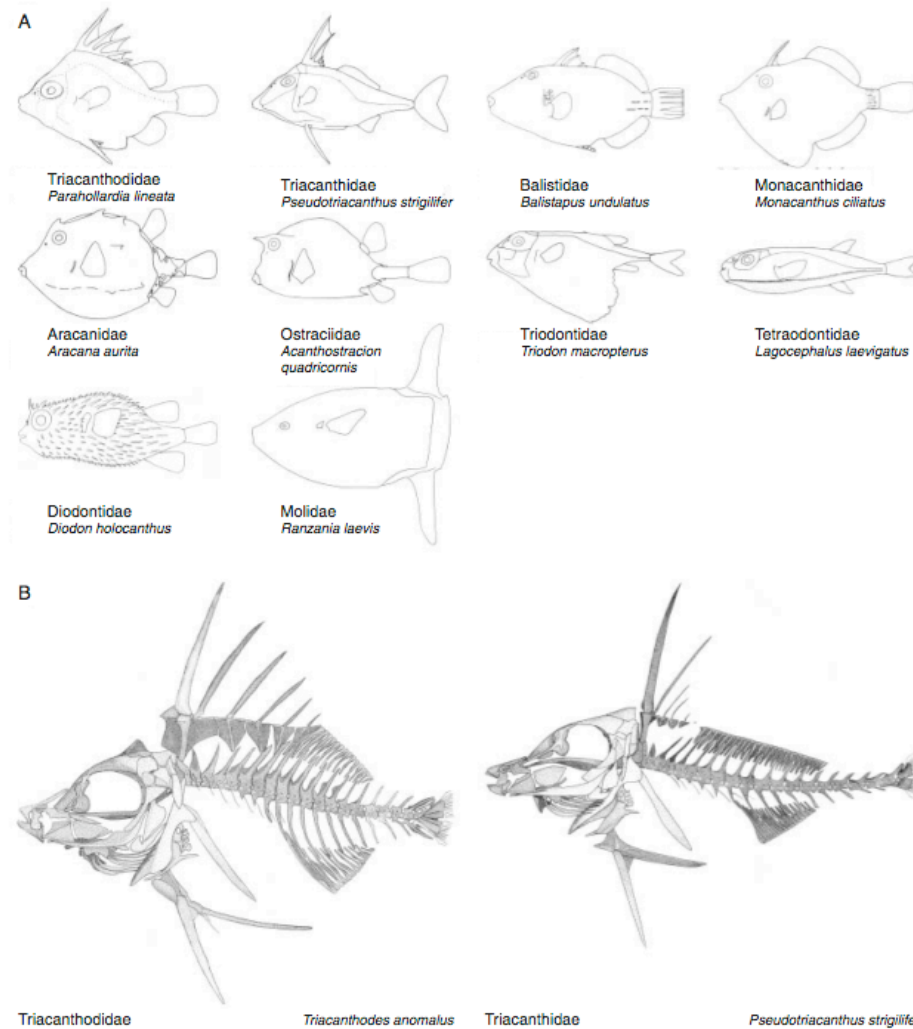
- ✱ Gene function/cellular location/process
- ✱ Gene expression patterns (anatomy)
- ✱ Phenotype (mutant, comparative, descriptive)



# Phenotypic data



# Phenotypic data

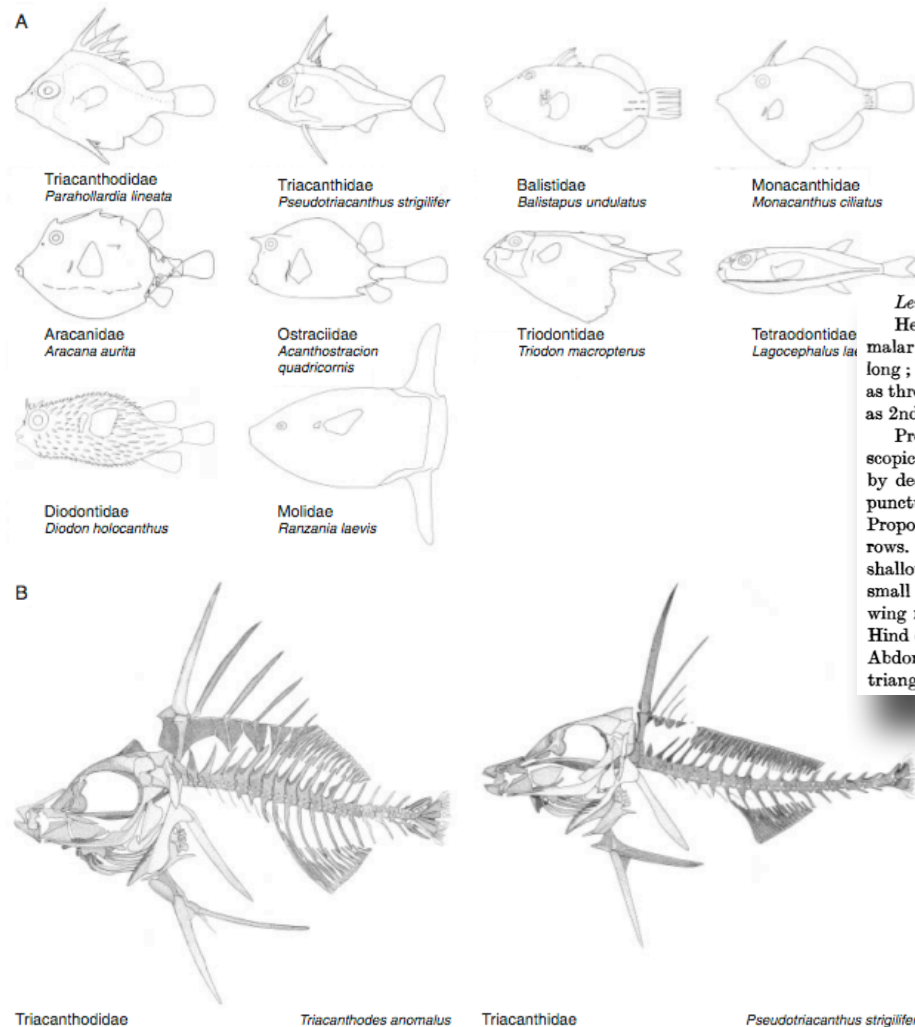


**Figure 1.** Illustrations of the skeletal anatomy and body shape of a generalized representative for each of the ten extant tetraodontiform families. Lateral views of (A) ten species, one from each extant family, and (B–F) of the skeletons of a representative species for each family, as follows: (B) triacanthodid *Triacanthodes anomalus* and triacanthid *Pseudotriacanthus strigilifer*; (C) balistid *Balistapus undulatus* and monacanthid *Monacanthus ciliatus*; (D) aracanid *Kentrocapros aculeatus* and ostraciid *Acanthostracion quadricornis*; (E) triodontid *Triodon macropterus* and tetraodontid *Lagocephalus laevigatus*; (F) diodontid *Diodon holocanthus* and molid *Ranzania laevis*.



# Phenotypic data

566 F. SANTINI and J. C. TYLER



**Figure 1.** Illustrations of the skeletal anatomy and body shape of a generalized representative for each of the ten extant tetraodontiform families. Lateral views of (A) ten species, one from each extant family, and (B–F) of the skeletons of a representative species for each family, as follows: (B) triacanthodid *Triacanthodes anomalus* and triacanthid *Pseudotriacanthus strigilifer*; (C) balistid *Balistapus undulatus* and monacanthid *Monacanthus ciliatus*; (D) aracanid *Kentrocapros aculeatus* and ostraciid *Acanthostracion quadricornis*; (E) triodontid *Triodon macropterus* and tetraodontid *Lagocephalus laevis*; (F) diodontid *Diodon holocanthus* and molid *Ranzania laevis*.

*Length.*—8 mm. Entirely black.

Head shining, microscopically finely punctured, without furrows below antennae; malar area large, equal to half the length of eye; mandible with two teeth. Scape very long; in male a little longer than two following segments together, in female nearly as long as three following together; 3rd segment four times as long as 2nd, 4th three times as long as 2nd, in male; 3rd three times and 4th twice as long as 2nd in female.

Prothorax very short; mesonotum shining, almost smooth, except for diffuse microscopic puncturation and one or two larger punctures; prescutum separated from scutum by deep lateral grooves; parapsidal furrows distinct; scutellum with scattered shallow punctures; mesopleura almost smooth; metapleura strongly and closely punctured. Propodeum with large shallow reticulate punctures with a tendency to lie in transverse rows. Boundary of propodeum with metapleuron marked by a regular horizontal row of shallow dorsoventrally elongated depressions. Fore wings with one recurrent nervure, one small closed submarginal cell, very large 1st discoidal cell, and 3rd discoidal cell open to wing margin; each wing with large pointed anal lobe; hind wings each with 10 hamuli. Hind coxae with a few scattered punctures, and hind legs nearly twice as long as the body. Abdomen shining, “club” sometimes reddish ventrally, strongly compressed laterally, triangular or almost ovate. Ovipositor not exerted.

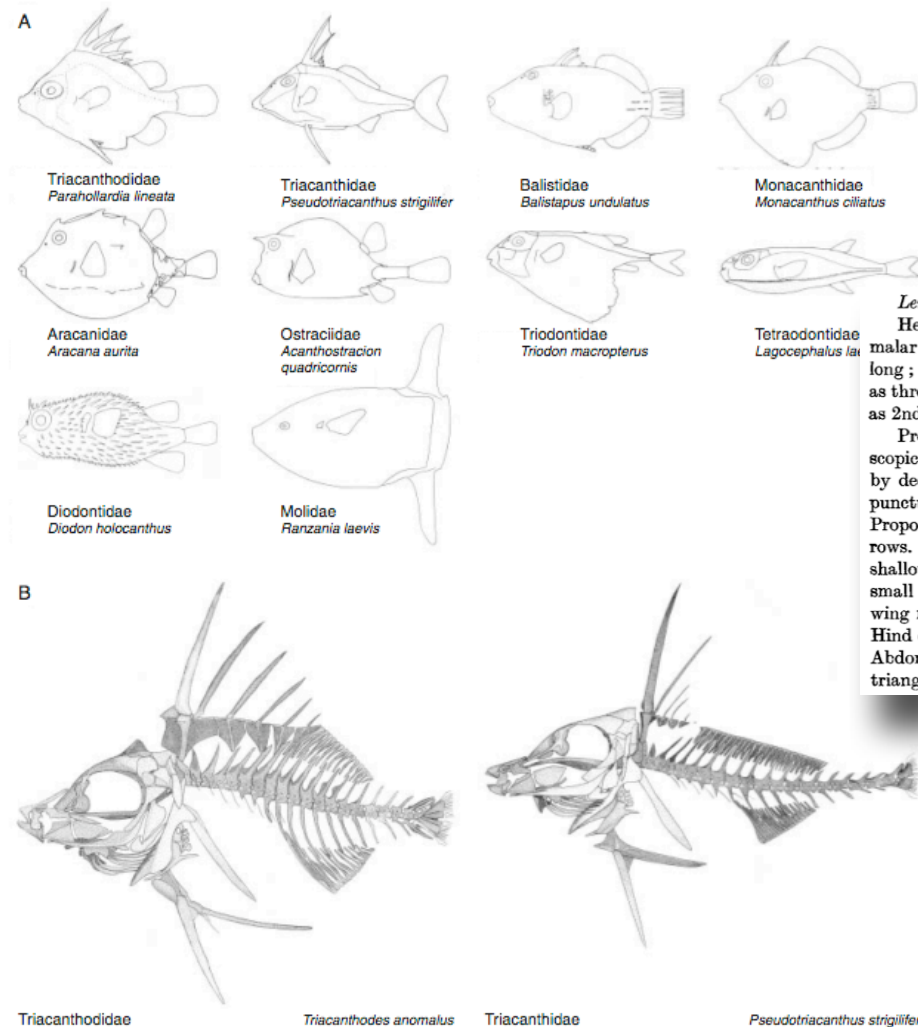


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# Phenotypic data

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**Figure 1.** Illustrations of the skeletal anatomy and body shape of a generalized representative for each of the ten extant tetraodontiform families. Lateral views of (A) ten species, one from each extant family, and (B–F) of the skeletons of a representative species for each family, as follows: (B) triacanthodid *Triacanthodes anomalus* and triacanthid *Pseudotriacanthus strigilifer*; (C) balistid *Balistapus undulatus* and monacanthid *Monacanthus ciliatus*; (D) aracanid *Kentrocapros aculeatus* and ostraciid *Acanthostracion quadricornis*; (E) triodontid *Triodon macropterus* and tetraodontid *Lagocephalus laevis*; (F) diodontid *Diodon holocanthus* and molid *Ranzania laevis*.

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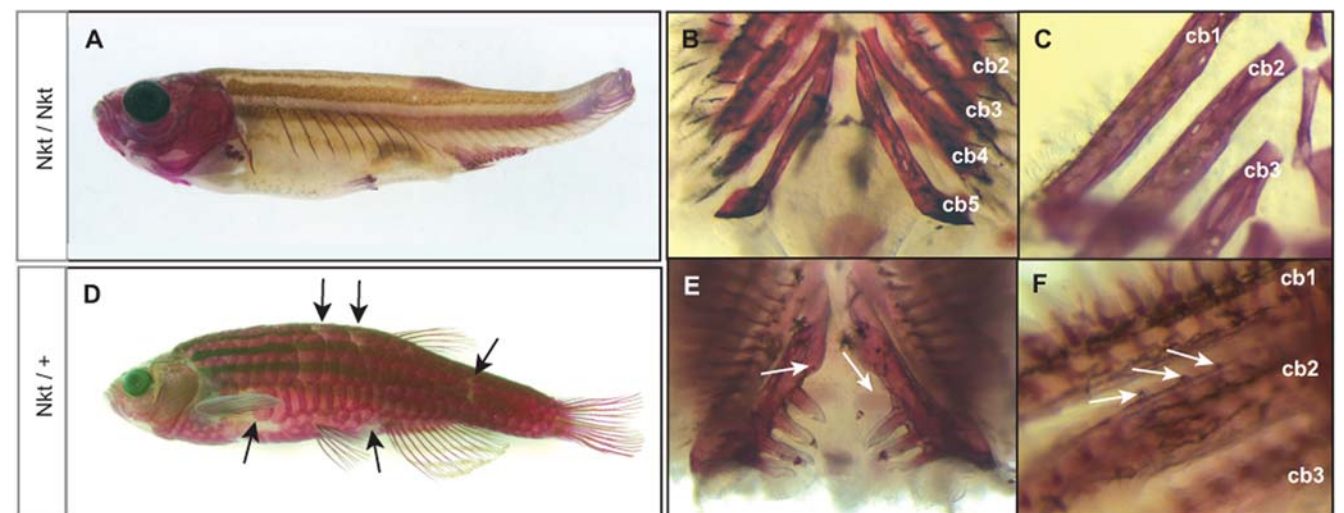
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**Figure 2.** The dominant gene *Nkt* is phenotypically similar, however complements *fls* mutants. *Nkt* homozygotes show complete loss of scales, teeth and gill rakers resembling the *fls* phenotype (A–C). Heterozygous *Nkt* zebrafish show an intermediate phenotype of scale loss and patterning defect (arrows) while no effect on fin development is seen (D). Heterozygous *Nkt* also show a dominant effect on the number of teeth (arrows, E) and gill rakers (F), showing deficiencies along the posterior branchial arches and formation of rudimentary rakers along ceratobranchial 1 and 2 (arrows, F). *Cb1–5*, ceratobranchial bones.

doi:10.1371/journal.pgen.1000206.g002



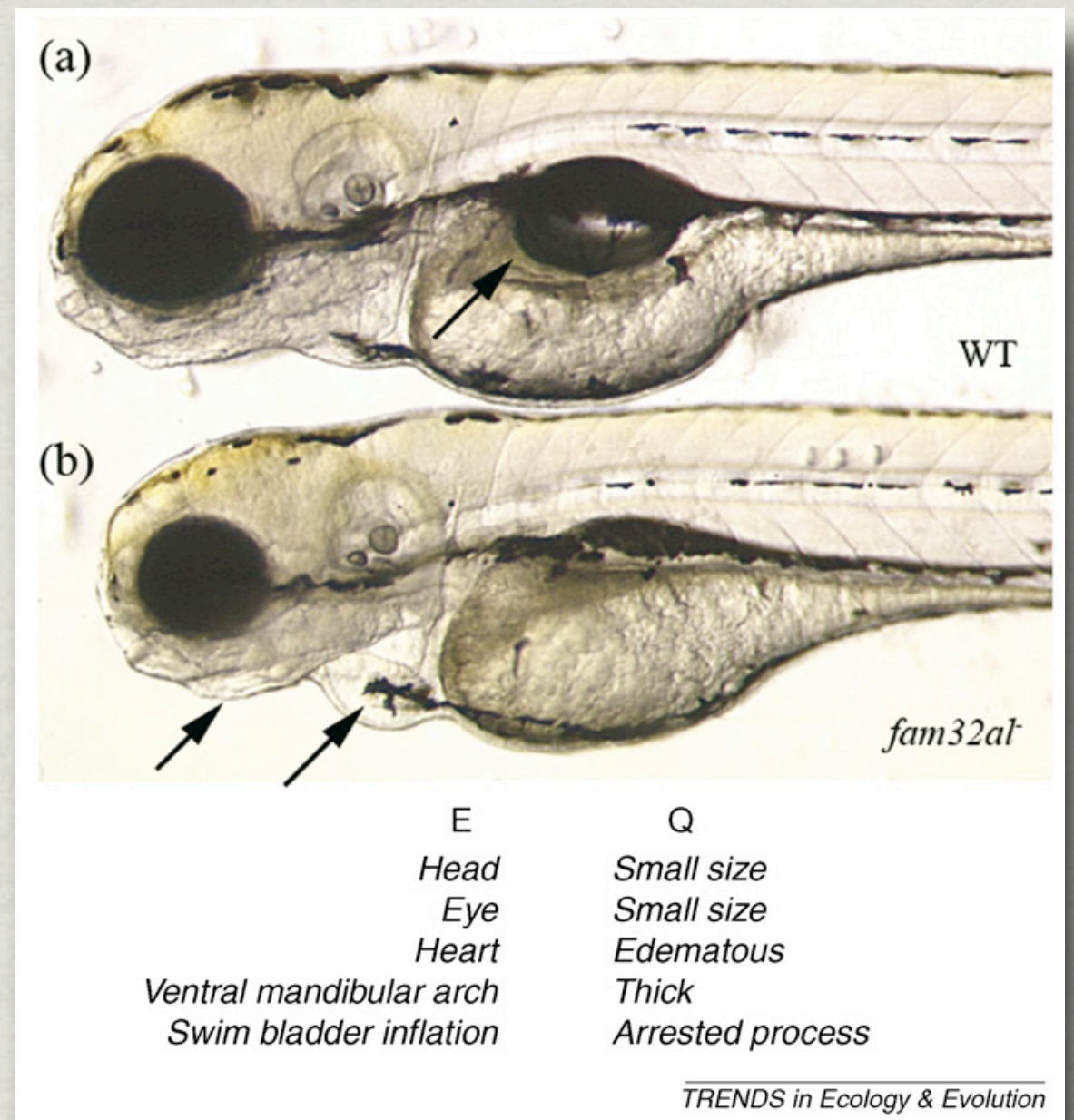
# Phenotype annotation

- ✱ Ontology of phenotypes?
  - ✱ Can be done, but could become unwieldy
- ✱ Compositional approach: Entity–Quality



# Entity–Quality model

- ✱ Organism-specific anatomy **entity** terms are associated with more general phenotypic **quality** terms
- ✱ Compositional approach allowing any number of features to be described for a given entity





# *Brachyplatystoma capapretum*: a New Species of Goliath Catfish from the Amazon Basin, with a Reclassification of Allied Catfishes (Siluriformes: Pimelodidae) from Lundberg & Akama 2005

TABLE 1. CHARACTER STATE MATRIX USED FOR PHYLOGENETIC ANALYSIS OF THE PLACEMENT OF *B. capapretum* WITHIN PIMELODIDAE AND *Brachyplatystoma*. Character states described in Appendix 1 and text.

	12345	1 67890	11111 12345	11112 67890	22222 12345	22223 67890	33333 12345
<i>Steindachnerdion</i>	11110	00000	00000	21000	00000	00000	00011
<i>Phractocephalus-Leiarius</i> group	11110	00000	00000	00000	00000	00000	00001
<i>Pimelodus</i> group	11111	11111	00000	00000	00000	00000	00000
<i>Calophysus</i> group	11111	11111	00000	00000	01110	00000	01201
<i>Zungaro</i>	11111	10000	00000	01001	20000	00000	00010
<i>Sorubim</i> group	11111	10000	00000	20001	20000	00000	00011
<i>Platynematichthys</i>	11111	10000	11000	00000	00000	00000	00000
<i>Brachyplatystoma vaillantii</i>	11111	10000	11111	11000	00000	00000	00000
<i>B. tigrinum</i>	11111	10000	11121	00111	11000	00000	10010
<i>B. platynemum</i>	11111	10000	11120	11111	11110	00000	11100
<i>B. filamentosum</i>	11111	10000	11111	11111	21101	11111	01101
<i>B. capapretum</i>	11111	10000	11111	11111	21101	11111	01101
<i>B. rousseauxii</i>	11111	10000	11111	11111	21101	11100	01101
Heptapteridae	00000	00000	00000	00001	00000	00000	00001
Pseudopimelodidae	00000	00000	00000	00000	01000	00000	10010
Bagridae	00100	00000	00000	01000	00000	00000	00000
Ictaluridae	00000	00000	00000	00001	00000	00000	00000

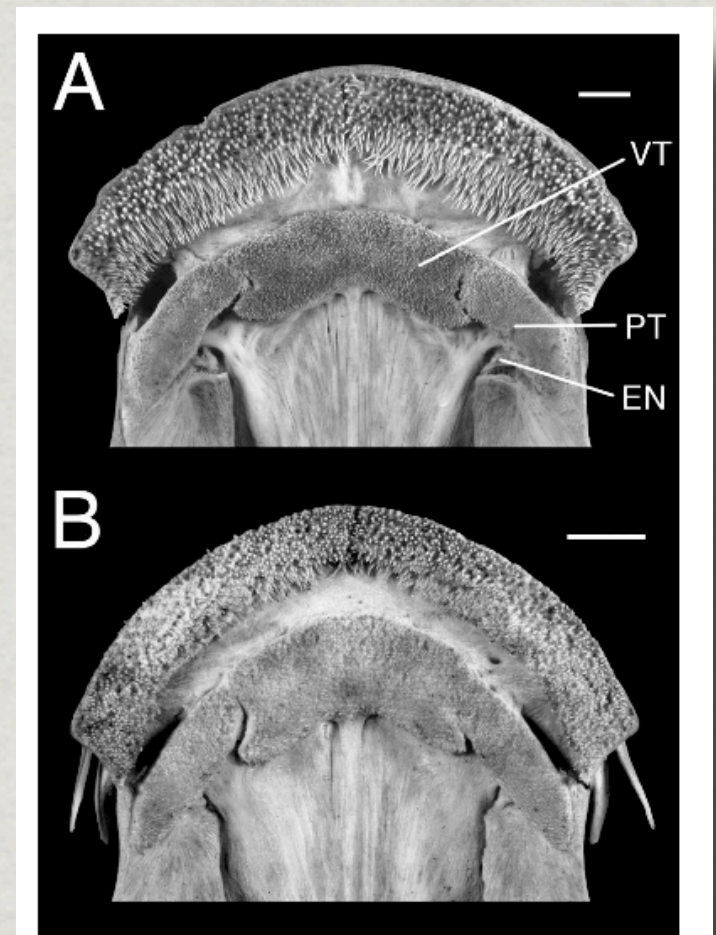
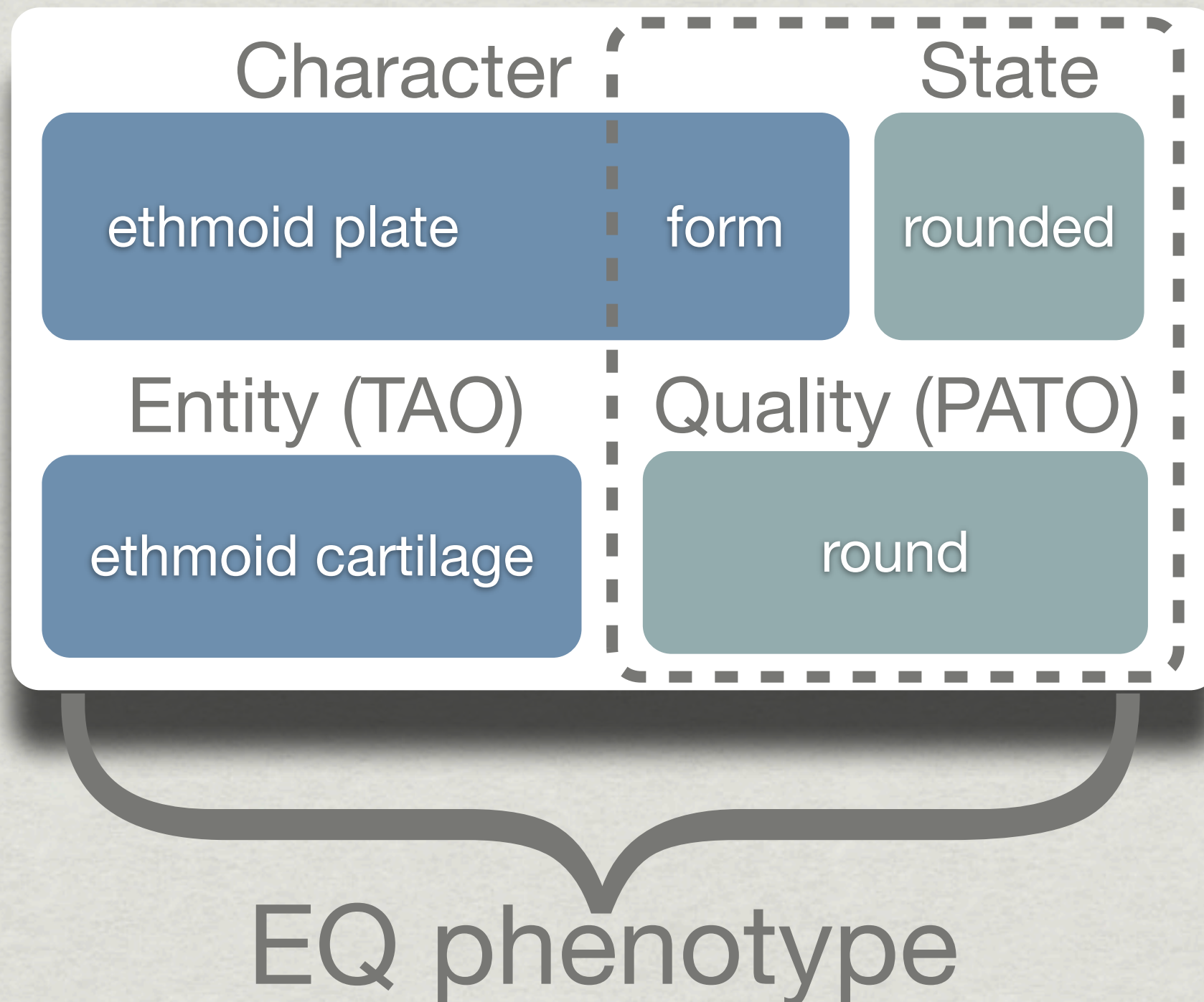


Fig. 7. Dentition of premaxilla and palate in ventral view of (A) *Brachyplatystoma filamentosum*, DU F1052; (B) *Brachyplatystoma capapretum*, MZUSP 53262. Scale bars = 1 cm. PT = pterygoid tooth plate, EN = endopterygoid, VT = vomerine teeth.

7. Ethmoid plate form: rounded [0]; quadrangular [1] (Lundberg et al., 1991b). Within Pimelodidae a uniquely derived and unreversed synapomorphy of *Pimelodus* group plus *Calophysus* group.

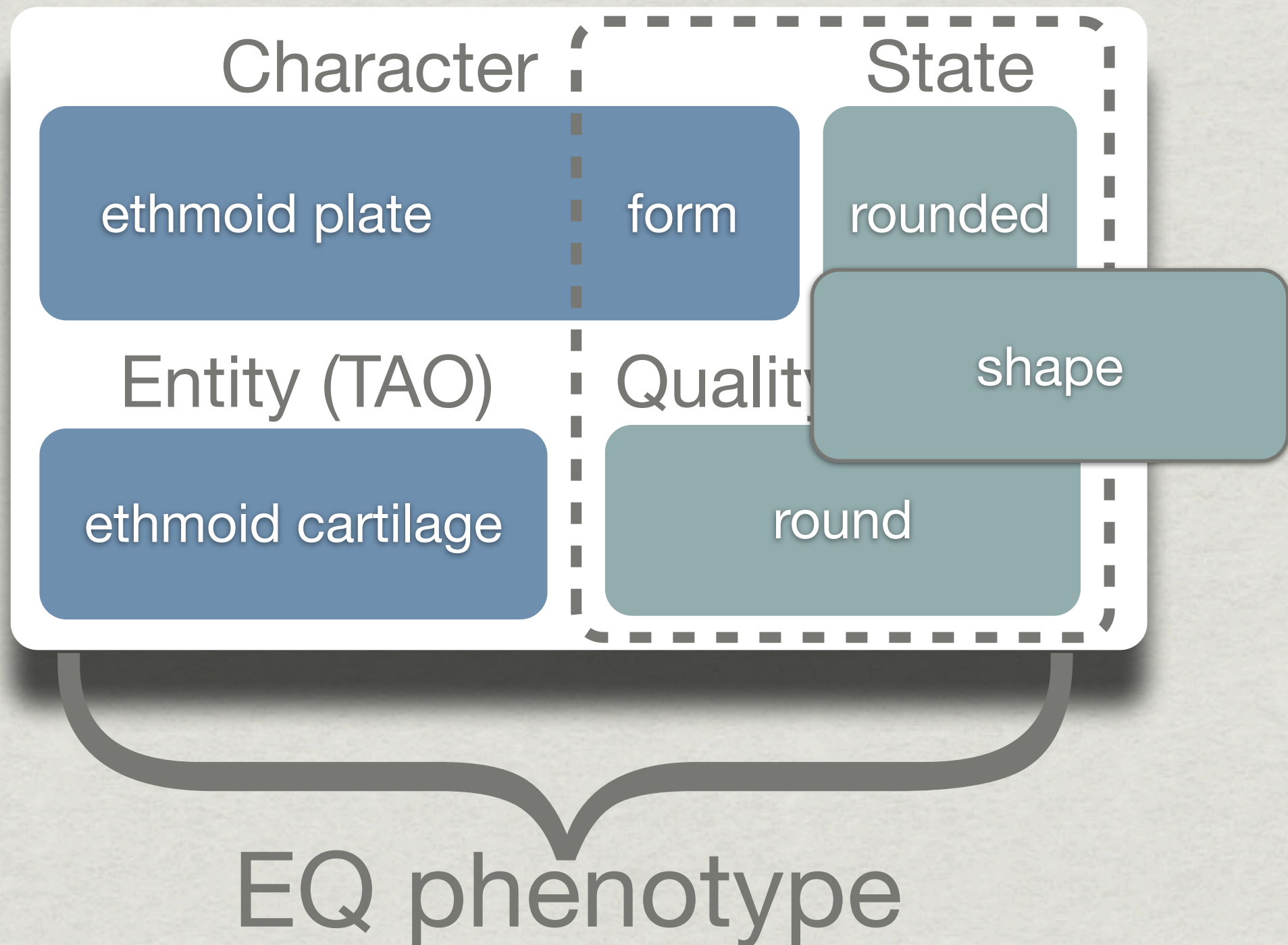


# Entity-Quality Model for Evolutionary Phenotypes



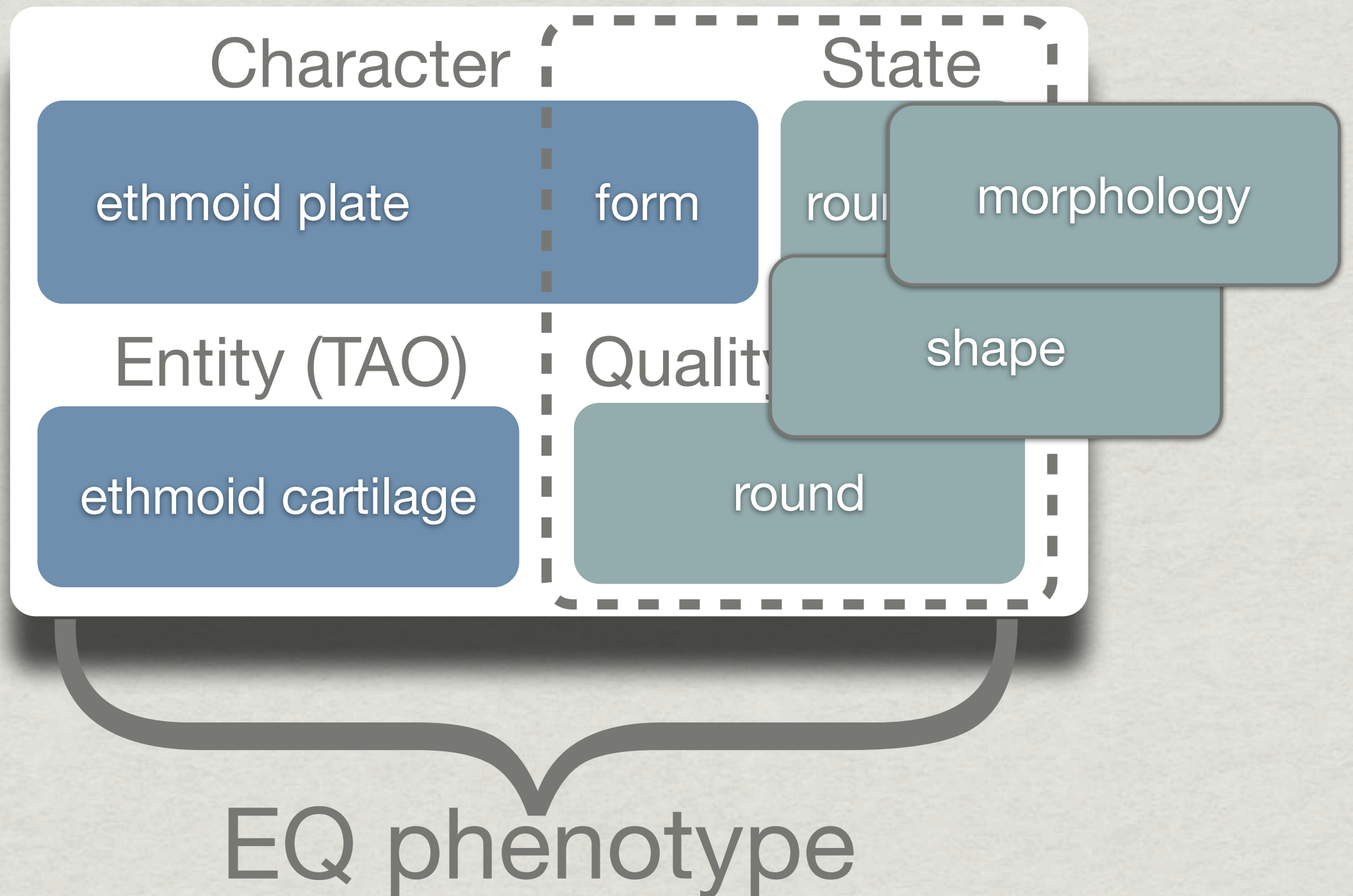


# Entity-Quality Model for Evolutionary Phenotypes





# Entity-Quality Model for Evolutionary Phenotypes





# PATO gotchas

- ✱ Deviation from “normal” (“increased size”)
- ✱ Relational/dependent qualities (“sensitivity toward”)

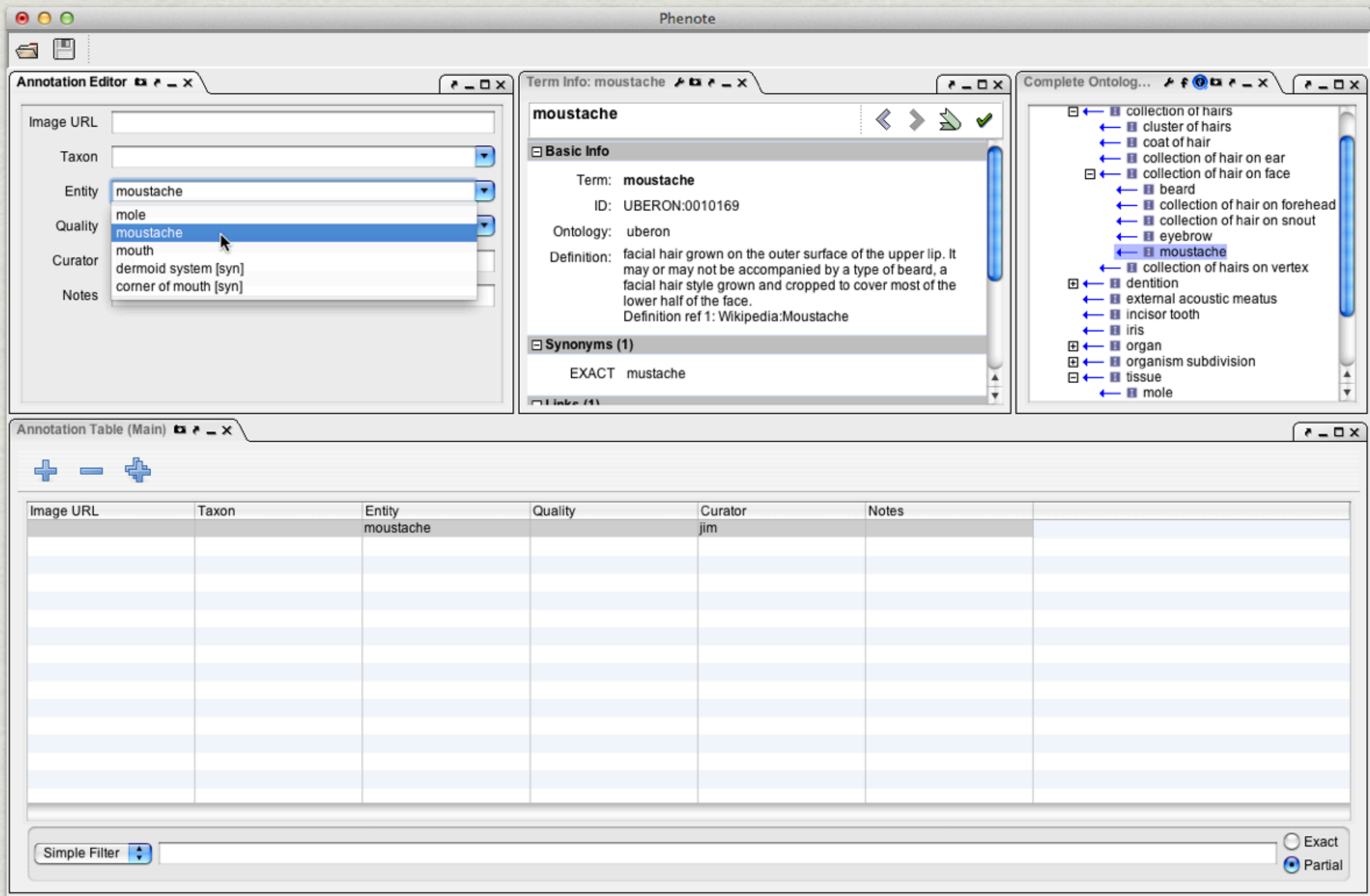


# Creating annotations

- \* **Phenote** — generic, configurable table editor
  - \* loads ontologies, provides term autocomplete
- \* **Phenex** — specialized for character matrix annotation
- \* Custom web interfaces
- \* **Protégé** OWL editor



# Phenote

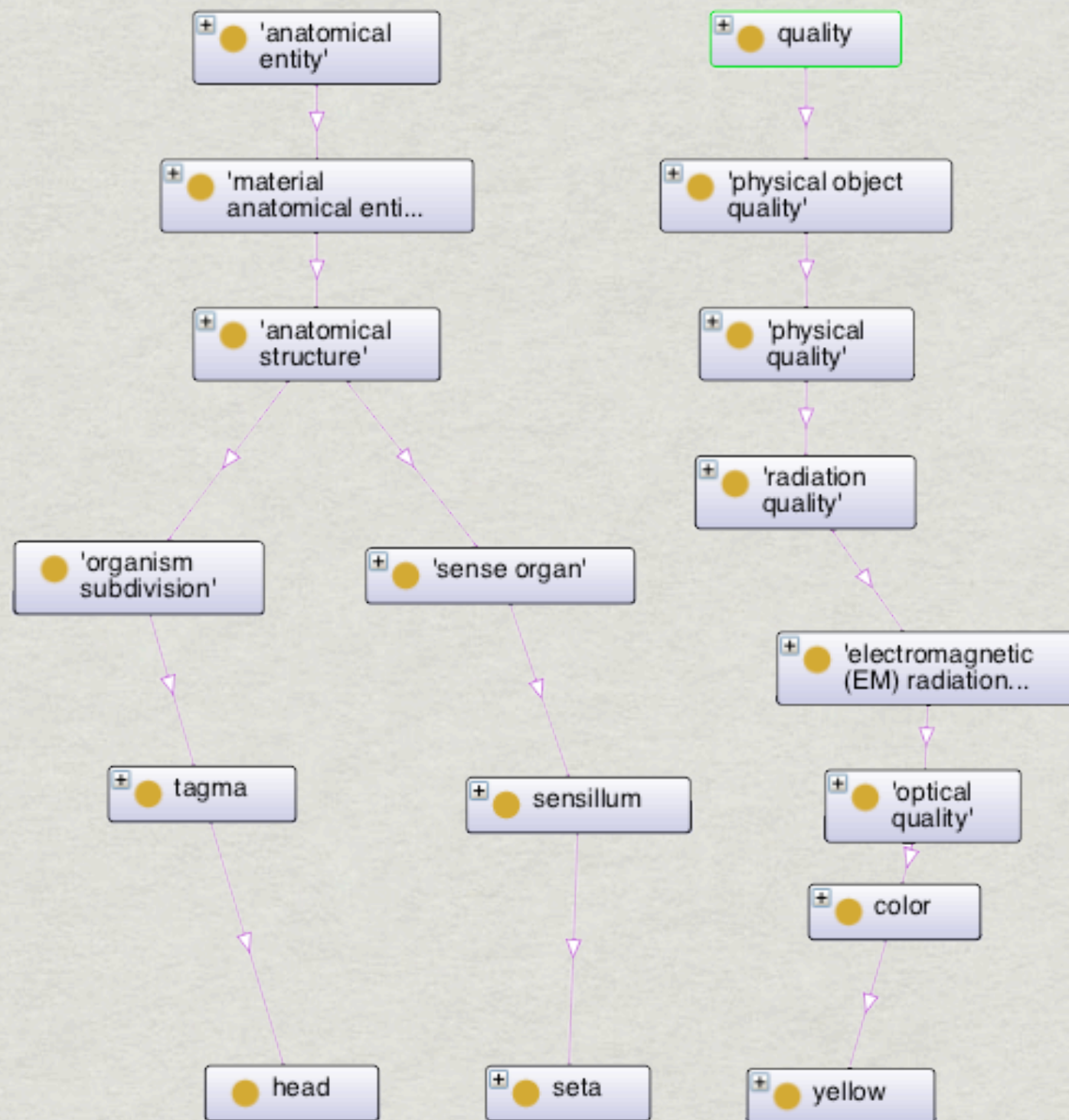




# Using annotations

- \* Tagging/keyword — provide search for data using ontology hierarchy
- \* “Yellow bristles apparent on head”
- \* ***tags:** PATO:yellow, HAO:seta, HAO:head*





- ✳ Can expand keyword query using hierarchy-aware middleware (e.g. -ontop- OBDA)



# Using annotations

“Yellow bristles apparent on head”

- \* **E** and **Q** are not always sufficient
- \* **Post-composition**: E = “bristle which is part of head”
- \* **L** — locator (“head”)
- \* **RE**: Related/Dependent Entity — needed for some PATO qualities (“sensitivity toward”)



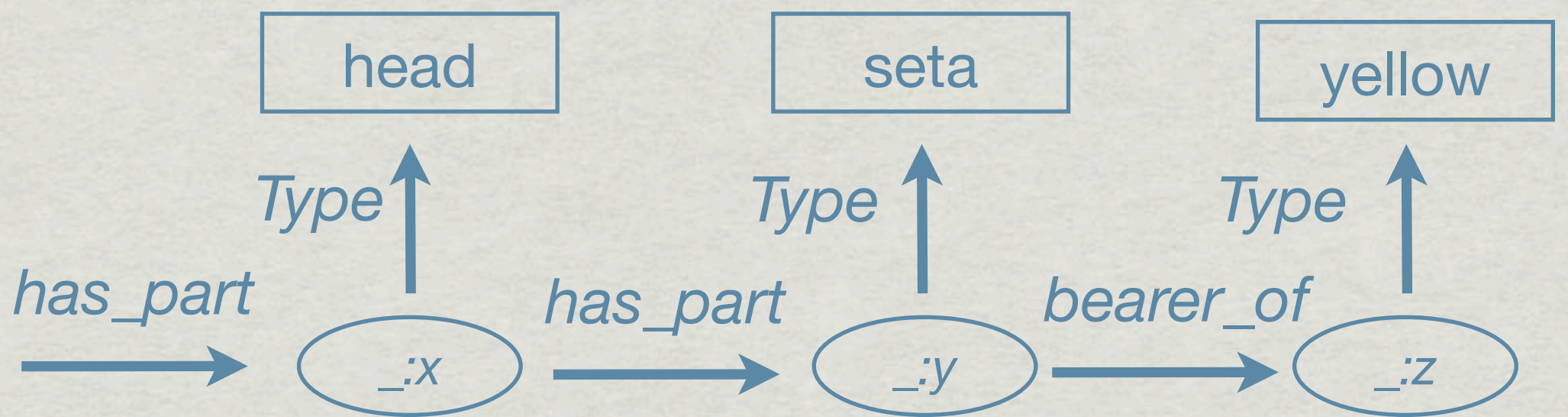
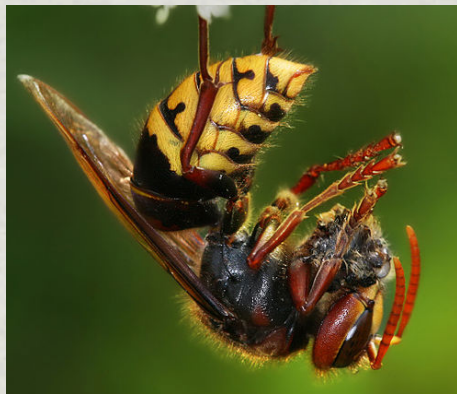
# Using annotations

- \* Knowledge representation
  - \* Construct semantic model using EQ components
  - \* “Extend” ontology
  - \* Describe class of organisms or structures using a logical definition



# Using annotations

- \* “Yellow bristles apparent on head”
- \* OWL class expression
  - \* *has\_part* some (**head** and *has\_part* some (**seta** and *bearer\_of* some **yellow**))





# Limitations

- \* Difficult to adequately represent certain kinds of statements
  - \* “antennae absent” ← (works but complicates reasoning)
  - \* “antenna is longer than eye”
  - \* “increased count of antennae”
- \* Reasoning software does not scale well
- \* *But, keep “tagging” utility in mind*

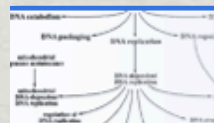


# Available annotations

- ✱ GO annotations
- ✱ Model organism phenotypes: ZFIN, MGI
- ✱ Virtual Fly Brain
- ✱ Phenoscape Knowledgebase
- ✱ Raw data available from most (all?)



# Gene Ontology


the Gene Ontology
AmiGO

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☒ terms
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 ☐ exact match

## mRNA transcription

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### Gene Product Associations to mRNA transcription ; GO:0009299 and children

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▼ Filter associations displayed ?

Filter by Gene Product

Gene Product Type	Data source	Species
<input type="text" value="All"/> complex gene gene product	<input type="text" value="All"/> ASAP AspGD CGD	<input type="text" value="All"/> Arabidopsis thaliana Aspergillus fumig... Aspergillus niger

Filter by Association

Evidence Code
<input type="text" value="All"/> IBA IKR IRD

View associations

☒ All
 ☐ Direct associations


1 2 [View all results](#)

[mRNA transcription ; GO:0009299](#) [\[show def\]](#) [\[view in tree\]](#)

	Symbol, full name	Information	Qualifier	Evidence	Reference	Assigned by
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<input type="checkbox"/>	<a href="#">ceh-37</a> 11 associations <a href="#">BLAST</a>	gene from <i>Caenorhabditis elegans</i>		ISS	PMID:12711598	Wormbase
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# ZFIN



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General Information

ZIRC

Site Search:

ZFIN ID: ZDB-GENO-080925-13

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















**Genotype:** *brpf1*<sup>t20002/t20002</sup>  
**Background:** Unspecified  
**Affected Gene:** *brpf1*  
**Current Source:** No data available

**GENOTYPE COMPOSITION**

Genomic Feature	Zygosity	Parental Genotype	Lab of Origin	Construct
t20002	homozygous	♀ +/- ♂ +/-	Nüsslein-Volhard Lab	

**GENE EXPRESSION** ⓘ











Gene expression in *brpf1*<sup>t20002/t20002</sup>

Expressed Gene	Structure	Conditions	Figures
<i>egr2b</i>	rhombomere 3  , rhombomere 5 	standard or control	Fig. S4  from Laue <i>et al.</i> , 2008
<i>hoxa2b</i>	(not) pharyngeal arch 2  , pharyngeal arch 3-7   , (not) rhombomere 2  (all 6) ▶	standard or control	3 figures  from Laue <i>et al.</i> , 2008
	pharyngeal arch 2  , pharyngeal arch 3-7  , rhombomere 2  (all 6) ▶	chemical	Fig. 4  from Laue <i>et al.</i> , 2008
<i>hoxb1a</i>	rhombomere 4 	standard or control	3 figures  from Laue <i>et al.</i> , 2008
	rhombomere 4 	chemical	Fig. S6  from Laue <i>et al.</i> , 2008

Show all 7 expressed genes

**PHENOTYPE** ⓘ


Phenotype in *brpf1*<sup>t20002/t20002</sup>


Phenotype	Conditions	Figures
basihyal bone aplastic, abnormal 	standard or control	Fig. S1  , Fig. S6  , Fig. T1 from Laue <i>et al.</i> , 2008
basihyal bone aplastic, abnormal 	MO3-kat6a	Fig. S6  from Laue <i>et al.</i> , 2008
basihyal bone decreased size, abnormal 	standard or control	Fig. T1 from Laue <i>et al.</i> , 2008
(normal or recovered) basihyal bone present 	chemical	Fig. S6  from Laue <i>et al.</i> , 2008
basihyal cartilage aplastic, abnormal 	standard or control	Fig. 1  from Laue <i>et al.</i> , 2008

Show all 30 phenotype statements



# MGI



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**Mssq16<sup>KK/TaJcl</sup>**  
QTL Variant Detail

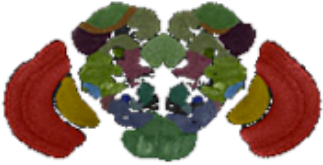
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[Nomenclature](#)
[Variant origin](#)
[Variant description](#)
[Phenotype summary](#)
[Phenotypes by genotype](#)
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Nomenclature	<b>QTL variant:</b> <b>Mssq16<sup>KK/TaJcl</sup></b> <b>Name:</b> mandible size and shape QTL 16; KK/TaJcl <b>MGI ID:</b> MGI:3832921 <b>QTL:</b> <a href="#">Mssq16</a> <i>Location:</i> unknown <i>Genetic Position:</i> Chr18, cM position of peak correlated region/allele: Syntenic																																				
Variant origin	<b>Strain of Specimen:</b> KK.Cg-A <sup>Y</sup> /TaJcl																																				
Variant description	<b>Allele Type:</b> QTL <b>Mutation:</b> Undefined This allele confers increased mandible size compared to C57BL/6Jcl. ( <i>J:143893</i> )																																				
Phenotype summary	<div> <b>Phenotype Summary by Mammalian Phenotype terms</b> Key: <table border="1"> <tr> <td>hm</td><td>homozygous</td> <td>ht</td><td>heterozygous</td> </tr> <tr> <td>cn</td><td>conditional genotype</td> <td>cx</td><td>complex: &gt; 1 genome feature</td> </tr> <tr> <td>tg</td><td>involves transgenes</td> <td>ot</td><td>other: hemizygous, indeterminate,...</td> </tr> <tr> <td>N</td><td>normal phenotype</td> <td>⊗</td><td>expected model not found</td> </tr> </table> </div> <div> (show or hide all annotated terms)  Genotypes are listed in the next section. </div> <div> <b>Affected Systems</b> <table border="1"> <thead> <tr> <th></th> <th>Genotypes:</th> <th>cx1</th> <th>cx2</th> </tr> </thead> <tbody> <tr> <td><b>craniofacial</b></td> <td></td> <td>✓</td> <td>✓</td> </tr> <tr> <td>abnormal mandible morphology</td> <td></td> <td>✓</td> <td>✓</td> </tr> <tr> <td><b>skeleton</b></td> <td></td> <td>✓</td> <td>✓</td> </tr> <tr> <td>abnormal mandible morphology</td> <td></td> <td>✓</td> <td>✓</td> </tr> </tbody> </table> </div>	hm	homozygous	ht	heterozygous	cn	conditional genotype	cx	complex: > 1 genome feature	tg	involves transgenes	ot	other: hemizygous, indeterminate,...	N	normal phenotype	⊗	expected model not found		Genotypes:	cx1	cx2	<b>craniofacial</b>		✓	✓	abnormal mandible morphology		✓	✓	<b>skeleton</b>		✓	✓	abnormal mandible morphology		✓	✓
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Phenotypic data by genotype	<b>Phenotypic Data by Genotype</b> (show or hide all phenotypic details) <table border="1"> <thead> <tr> <th>Genotype</th> <th>Allelic Composition</th> <th>Genetic Background</th> </tr> </thead> <tbody> <tr> <td>cx1</td> <td>a/a Mssq16<sup>KK/TaJcl</sup>/?</td> <td>Involves: C57BL/6Jcl * KK/TaJcl</td> </tr> <tr> <td>cx2</td> <td>A<sup>Y</sup>/a Mssq16<sup>KK/TaJcl</sup>/?</td> <td>Involves: C57BL/6Jcl * KK/TaJcl</td> </tr> </tbody> </table>	Genotype	Allelic Composition	Genetic Background	cx1	a/a Mssq16 <sup>KK/TaJcl</sup> /?	Involves: C57BL/6Jcl * KK/TaJcl	cx2	A <sup>Y</sup> /a Mssq16 <sup>KK/TaJcl</sup> /?	Involves: C57BL/6Jcl * KK/TaJcl																											
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# Virtual Fly Brain



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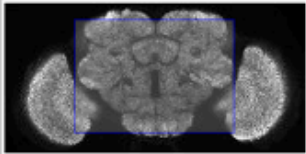
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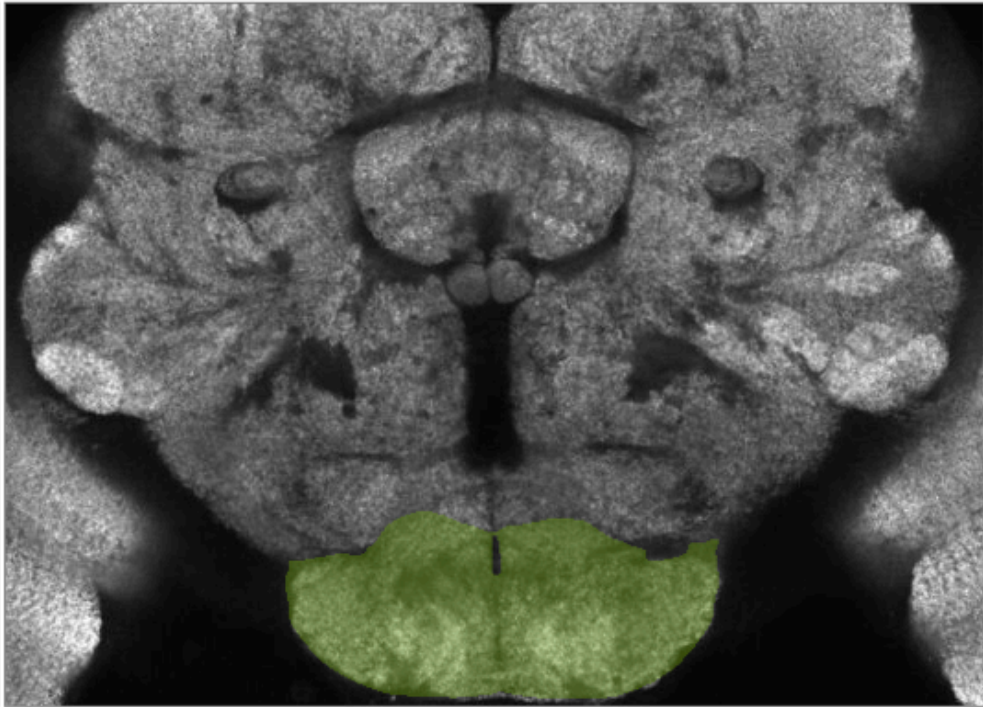
Front Horiz Sagit Fx Pt

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Focus term: adult subesophageal ganglion

optoc glomerulus of the PLP

Clear all Selections

- ☐ adult brain centre
- ☒ adult subesophageal ganglion centre
- ☐ supraesophageal ganglion centre
- ☐ adult antennal lobe centre
- ☐ adult central complex centre
- ☐ adult mushroom body centre
- ☐ inferior neuropils centre
- ☐ lateral complex centre
- ☐ lateral horn centre
- ☐ optic lobe centre
- ☐ periesophageal neuropils centre
- ☐ superior neuropils centre
- ☐ ventrolateral neuropils centre
- ☐ optic glomerulus
  - ☐ optic glomerulus of the PLP
- ☐ optic tubercle centre
- ☐ posterior lateral protocerebrum centre
- ☐ ventrolateral protocerebrum centre
- ☐ ventromedial neuropils centre

### adult subesophageal ganglion

Definition: Region of the adult brain beneath the esophagus, consisting of the fused gnathal segments.

Synonyms:

- \* SOG
- \* subesophageal ganglion

Parent classes:

- \* subesophageal ganglion

[Sitemap](#) | [Virtual Fly Brain](#)

Right/ctrl click for queries

- Neurons with:
  - . some part here
  - . . synaptic terminals here
  - . . . presynaptic terminals here
  - . . . postsynaptic terminals here
- Tracts/nerves innervating here
- Transgenes expressed here
- Genes expressed here
- Phenotypes here
- Cancel



# Phenoscape KB



Site search:

Enter entity terms (e.g. basihyal bone), phenotypic qualities (e.g. shape, size), taxonomic names (e.g. Ictaluridae), gene names or symbols (e.g. cadherin 6, cdh6), or publications.

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## Query for:

Taxa

Taxon is:

Any

and

Phenotype is ☐ any ☒ all:

fin • shape [broaden/refine]

☐ including parts

and

head • length [broaden/refine]

☐ including parts

and

Publication is ☒ any ☐ all:

Any

☐ Apply higher taxon annotations to all included species

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<input type="button" value="+"/> <input type="button" value="i"/>	Order ↓	Family	Taxon
	Siluriformes	Heptapteridae	<i>Brachyrhamdia heteropleura</i>
	Siluriformes	Heptapteridae	<i>Genus 6 sp. (Bockmann 1998)</i>
	Siluriformes	Heptapteridae	<i>Phenacorhamdia unifasciata</i>
	Siluriformes	Heptapteridae	<i>Nemuroglanis pauciradiatus</i>
	Siluriformes	Heptapteridae	<i>Cetopsorhamdia molinae</i>
	Siluriformes	Heptapteridae	<i>Pimelodella sp. B (Bockmann 1998)</i>
	Siluriformes	Heptapteridae	<i>Chasmocranus chimantanus</i>
	Siluriformes	Heptapteridae	<i>Brachyrhamdia imitator</i>
	Siluriformes	Heptapteridae	<i>Mastiglanis asopos</i>
	Siluriformes	Heptapteridae	<i>Brachyrhamdia marthae</i>
	Siluriformes	Heptapteridae	<i>Brachyrhamdia meesi</i>
	Siluriformes	Heptapteridae	<i>Imparfinis guttatus</i>
	Siluriformes	Heptapteridae	<i>Horiomyzon retropinnatus</i>
	Siluriformes	Heptapteridae	<i>Phenacorhamdia sp. C (Bockmann 1998)</i>
	Siluriformes	Heptapteridae	<i>Pimelodella sp. A (Bockmann 1998)</i>