The Ontology of Craniofacial Development and Malformation

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Goals

• Create an ontology for use by FaceBase
• Standardized terms
  – for annotation
  – retrieval by keyword search
• Relations
  – representation of knowledge
  – to allow intelligent integration
FaceBase

Genomic studies

Gene expression profiles

Medical imaging

Clinical studies and findings
Importing Other Ontologies

OCMM

Model organisms

Gene expression profiles

Clinical studies and findings

Medical ontologies

Gene expression profiles

Medical imaging

Genomic studies
OCDM as part of the infrastructure
Principles of the OCDM

- Based on human anatomy and development
  - Foundational Model of Anatomy (FMA)
- Utilize existing ontologies as much as possible
- Modular
- Ontology best practices
FaceBase 1

• Use Case
  – Cleft lip and/or palate
• Species
  – Mouse, human
• Developed an overall framework
• Anatomy
  – Mouth and nose
  – Additional anatomy “for free”
Topics

• Overall Framework
• FaceBase 2 content to-date
• Milestones for future content
• Conversion to OWL 2
• Workflow and access
Overall Framework of the OCDM

http://purl.org/sig/ocdm/viewer
• Filling in the framework created in FaceBase 1
• Use Cases
  – Craniosynostosis
  – Midface hypoplasia
  – Interactive atlas of normal skull development
  – Mandible development
  – 3-D craniofacial morphometrics
• Species: human, mouse, zebrafish
• Anatomy: Musculoskeletal system of head, additional “for free”
Content enhancement: Musculoskeletal system of head

Foundational Model of Anatomy Ontology (FMA)
Enhanced spatio-structural relationships between bones and joints
Extract Craniofacial Human Ontology (CHO) from the FMA

1. Enhance FMA
2. Extract craniofacial anatomy view of FMA
3. Create OCDM based on CHO and other ontologies
Craniofacial Human Ontology (CHO)
Create CMO from CHO

Human: CHO

Mouse: CMO

Class hierarchy:

```
- Thing
  - 'Anatomical entity'
    - 'Non-physical anatomical entity'
    - 'Physical anatomical entity'
      - 'Immaterial anatomical entity'
    - 'Material anatomical entity'
      - 'Anatomical set'
    - 'Anatomical structure'
      - 'Developmental structure'
      - 'Postnatal anatomical structure'
        - 'Acellular anatomical structure'
        - 'Anatomical cluster'
        - 'Biological macromolecule'
      - Body
        - 'Cardinal body part'
        - 'Cardinal cell part'
        - 'Cardinal organ part'
        - 'Cardinal tissue part'
      - Cell
        - Organ
          - 'Organ system'
          - 'Organ system subdivision'
          - 'Portion of tissue'
          - 'Subdivision of cardinal body part'
          - 'Vestigial embryonic structure'
        - 'Portion of body substance'
```
Update CMO content

- remove anatomical entities (classes) not related to the mouse
- add anatomical entities (classes) missing from CHO
- verify existence of mouse anatomical entities
  - map to Mouse Adult Gross Anatomy (MA)
  - PubMed literature
  - domain experts (Cox, Cunningham)
Not in mouse:

canine teeth
premolar teeth
mental protuberance
Examples of classes missing from CHO

Hyoid apparatus
Levator auris longus
Intermolar eminence
Levator nasolabialis
Mandible petrous part
Supraoccipital bone
Squamosal bone
Septal organ of Masera
Septal organ of Gruneberg
CMO-MA mapping

Total craniofacial mappings = 725
Verify existence of entity in mouse

Publications

- Faucial pillar (Mus musculus)
- Hard palate (Mus musculus)
- Internal nose (Mus musculus)
- Internal table of calvaria (Mus musculus)
- Jaw (Mus musculus)

Verified

Verified By

http://www.ncbi.nlm.nih.gov/pubmed/?term=%28%22hard+palate%22+AND+(mouse+OR+mice+OR+"Mouse"[MeSH]))
Verify existence of entity in mouse

Verified by domain expert

<table>
<thead>
<tr>
<th>Region of internal nose (Mus musculus)</th>
<th>FMA Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Region of soft palate (Mus musculus)</td>
<td>59852</td>
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<tr>
<td>Anterior part of soft palate (Mus musculus)</td>
<td></td>
</tr>
<tr>
<td>Posterior part of soft palate (Mus musculus)</td>
<td></td>
</tr>
<tr>
<td>Soft palate proper (Mus musculus)</td>
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<tr>
<td>Uvula (Mus musculus)</td>
<td></td>
</tr>
<tr>
<td>Right side of lower jaw (Mus musculus)</td>
<td></td>
</tr>
<tr>
<td>Right side of nasal septum (Mus musculus)</td>
<td></td>
</tr>
<tr>
<td>Right side of suspensory (Mus musculus)</td>
<td></td>
</tr>
</tbody>
</table>

Verified By: T. Cox
Update CMO with FaceBase terms

Normal anatomy at E18.5

1. Anterior point of maxilla
2. Lateral point of premaxillary-maxillary suture
3. Tip of sphenoid process of maxilla
4. Anterior-medial point to sphenoid process
5. Posterior point of maxilla
6. Posterior-lateral point of palatal process of maxilla
7. Posterior-medial point of palatal process of maxilla
8. Most anterior-medial point of palatal process of maxilla
9. Anterior-lateral point of palatal process of maxilla
10. Medial point of premaxillary-maxillary suture
Correlate different sources
Correlate different sources
# Content Milestones

<table>
<thead>
<tr>
<th>Task</th>
<th>Date</th>
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<tbody>
<tr>
<td>Canonical musculoskeletal system (MS) of head</td>
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</tr>
<tr>
<td>a. CHO (Human)</td>
<td>May 1, 2014 – Aug. 31, 2014</td>
</tr>
<tr>
<td>b. CMO (Mouse)</td>
<td>Sept 1, 2014 – Dec, 31, 2014</td>
</tr>
<tr>
<td>c. CZO (Zebrafish)</td>
<td>Jan 1, 2015 – March 31, 2015</td>
</tr>
<tr>
<td>Embryonic development of MS of head</td>
<td></td>
</tr>
<tr>
<td>a. CHDO (Human)</td>
<td>April 1, 2015 – July 31, 2015</td>
</tr>
<tr>
<td>b. CMDO (Mouse)</td>
<td>Aug 1, 2015 – Nov. 30, 2015</td>
</tr>
<tr>
<td>Anatomy mappings</td>
<td></td>
</tr>
<tr>
<td>a. CHO with CMO</td>
<td>April 1, 2016 – Sept 30, 2016</td>
</tr>
<tr>
<td>Craniofacial malformation (facial and cranial vault dysmorphology)</td>
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</tr>
<tr>
<td>a. CHMO (Human)</td>
<td>Feb 1, 2017 – June 30, 2017</td>
</tr>
<tr>
<td>b. CMMO (Mouse)</td>
<td>July 1, 2017 – Nov. 30, 2017</td>
</tr>
<tr>
<td>c. CZMO (Zebrafish)</td>
<td>Dec. 1, 2017 – March 30, 2018</td>
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## Content Milestones

<table>
<thead>
<tr>
<th>Task</th>
<th>Date</th>
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</thead>
<tbody>
<tr>
<td>Malformation mappings</td>
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<tr>
<td>a. CHMO with CMMO</td>
<td>April 1, 2018 – August 30, 2018</td>
</tr>
<tr>
<td>b. CHMO with CZMO</td>
<td>Sept 1, 2018 – Dec 31. 2018</td>
</tr>
<tr>
<td>Connect all species structure to molecular level</td>
<td>Jan 1, 2019 – April 30, 2019</td>
</tr>
</tbody>
</table>
Conversion to OWL 2

- FMA and OCDM originally in Protégé Frames
- Most ontology development now in OWL2
- Converted both FMA and OCDM to OWL2
  - Custom program using configuration files
  - Potential use for any Frame-based ontology
- Now all development is in OWL2
Workflow 1: FMA to CHO

- FMA Editor
- Protégé
- Working Copy
- SVN Repository
- CHO Extractor
- CHO
Workflow 2: CHO to OCDM

OCDM Editor → Protégé → Working Copy → SVN Repository → Official Release

https://www.facebase.org/content/ocdm

http://purl.org/sig/ont/ocdm
Workflow 3: OCDM toQueryable Resource

- OCDM Working Copy
- Punning Generator
- Triple Store Builder
- RDF Store
Potential Access and Applications

- RDF Store
- Query Integrator
- Data

Create and save queries

Create 3-D scenes

View the OCDM

Annotate Data
Personnel

• Onard Mejino
• Todd Detwiler
• Tim Cox
• Michael Cunningham
• Linda Shapiro

• Trond Nilsen
• Melissa Clarkson
References

• Overview of OCDM

• OCDM Viewer

• Foundational Model Browser
| Ontology metrics: |  |
|---|---|---|
| No of classes | No. of properties | No. of spatio-structural relationships |
| CHO | 14911 | 169 | 38857 |
| CMO | 12672 | 161 | 30657 |
Craniofacial Human Ontology (CHO)
Craniofacial
Human
Developmental
Ontology
(CHDO)
Mouse canonical anatomy

Head (Mus musculus)
  R Face (Mus musculus)
    R Left eye (Mus musculus)
    R Left pharyngotympanic tube (Mus musculus)
    R Left temple (Mus musculus)
  R Mouth (Mus musculus)
    R External part of mouth (Mus musculus)
      R External mandibular part of mouth (Mus musculus)
      R Labial part of mouth (Mus musculus)
        R Lower lip (Mus musculus)
      R Upper lip (Mus musculus)
        R Left side of upper lip (Mus musculus)
        R Philtrum (Mus musculus)
        R Right side of upper lip (Mus musculus)
    C Integument of upper lip (Mus musculus)
    C Mucosa of upper lip (Mus musculus)
    C Superior zone of orbicularis oris (Mus musculus)
  C Integument of labial part of mouth (Mus musculus)
    C Mucosa of labial part of mouth (Mus musculus)
    C Orbicularis oris (Mus musculus)

Upper lip (Mus musculus)

is regional part of:
Labial part of mouth Mus musculus

has regional part:
Left side of upper lip Mus musculus
Philtrum Mus musculus
Right side of upper lip Mus musculus

is constitutional part of:

has constitutional part:
Superior zone of orbicularis oris Mus musculus
Integument of upper lip Mus musculus
Mucosa of upper lip Mus musculus
Craniofacial Human Mouse Mappings Ontology (CHMMO)

Upper Lip maps to Upper Lip (Mus Musculus)
Craniofacial Mouse Developmental Ontology (CMDO)

- Region of embryonic palatal epithelium (Mus musculus)
  - Embryonic nasal palatal epithelium (Mus musculus)
  - Embryonic oral palatal epithelium (Mus musculus)
  - Epithelium of embryonic hard palate (Mus musculus)
  - Epithelium of embryonic secondary palate (Mus musculus)
  - Epithelium of embryonic soft palate (Mus musculus)
- Epithelium of palatal shelf (Mus musculus)
  - TS19 epithelium of palatal shelf (Mus musculus)
  - TS20 epithelium of palatal shelf (Mus musculus)
  - TS21 epithelium of palatal shelf (Mus musculus)
  - TS22 epithelium of palatal shelf (Mus musculus)
  - TS23 epithelium of palatal shelf (Mus musculus)
- Medial edge epithelium of palatal shelf (Mus musculus)
- Region of epithelium of palatal shelf (Mus musculus)
Beta-catenin gene expression

Description: Beta-catenin is expressed in the palatal epithelium along the AP axis throughout development, including the oral and nasal epithelia and in the MEE at E14.5.

**Beta-catenin gene expression**

Description: **Beta-catenin** is expressed in the palatal epithelium along the AP axis throughout development, including the oral and nasal epithelia and in the MEE at E14.5.

USC Craniofacial Central:

*Beta-catenin expression in E14.5 palatal epithelium*

**OCDM CMDO**

- Epithelium of embryonic hard palate (Mus musculus)
- Epithelium of embryonic secondary palate (Mus musculus)
- Epithelium of embryonic soft palate (Mus musculus)
- Epithelium of palatal shelf (Mus musculus)
- TS19 epithelium of palatal shelf (Mus musculus)
- TS20 epithelium of palatal shelf (Mus musculus)
- TS21 epithelium of palatal shelf (Mus musculus)
- TS22 epithelium of palatal shelf (Mus musculus)
- TS23 epithelium of palatal shelf (Mus musculus)
- Medial edge epithelium of palatal shelf (Mus musculus)
- Region of epithelium of palatal shelf (Mus musculus)

**Genes detected in palatal shelf epithelium, TS23**

Example: Krt 16
Craniofacial Human Malformations Ontology (CHMO)
**Davis and Ritchie**

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clefts of the lip: (a) unilateral (incomplete and complete), (b) bilateral (incomplete and complete) cleft of the palate may be associated with this group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clefts of the palate: (a) soft palate, (b) hard palate cleft of the lip may be associated with this group</td>
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<td></td>
</tr>
<tr>
<td>Clefts of the alveolus: (a) unilateral (incomplete and complete), (b) bilateral (incomplete and complete) clefts of the lip and palate are usually associated with this group</td>
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</table>

**Key**

- **cleft must be present**
- **cleft present at some location**

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**Veau**

<table>
<thead>
<tr>
<th>Type I</th>
<th>Type II</th>
<th>Type III</th>
<th>Type IV</th>
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</thead>
<tbody>
<tr>
<td>Clefts of the soft palate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clefts of the soft and hard palate, posterior to the incisive foramen</td>
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<tr>
<td>Complete unilateral cleft alveolus and cleft palate</td>
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<td></td>
<td></td>
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<tr>
<td>Complete bilateral cleft with complete isolation of the median tubercle</td>
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</table>

**Pruzansky**

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clefts of the lip (and alveolus)</td>
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<td></td>
<td></td>
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<tr>
<td>Clefts of the lip and palate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clefts of the palate (includes clefts of both the soft palate and hard palate, but not the hard palate alone)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Congenital insufficiency of the palate (includes submucous clefts and deficient palatal development)</td>
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</table>

**Ross and Johnston**

<table>
<thead>
<tr>
<th>CL</th>
<th>CLP</th>
<th>CP</th>
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</thead>
<tbody>
<tr>
<td>Clefts involving the lip (and alveolus)</td>
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<td></td>
</tr>
<tr>
<td>Clefts involving the lip and palate</td>
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<td></td>
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<tr>
<td>Clefts involving the lip with or without cleft palate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clefts involving the hard and soft palate only</td>
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<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary palatal defects</td>
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<tr>
<td>CL</td>
<td>Clefts involving the lip (and alveolus)</td>
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<tr>
<td>CLP</td>
<td>Clefts involving the lip and palate</td>
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<tr>
<td>CL(P)</td>
<td>Clefts involving the lip with or without cleft palate</td>
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**Iowa system**

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cleft of the lip only</td>
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<td></td>
</tr>
<tr>
<td>Secondary palatal clefts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clefts of the lip, alveolus, and palate (complete cleft lip and palate)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary cleft palate and lip</td>
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</table>

**ICPR**

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clefts of the primary palate: (a) lip, (b) alveolus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clefts of the primary and secondary palate: (a) lip, (b) alveolus, (c) hard palate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clefts of the secondary palate: (a) hard palate, (b) soft palate</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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*Interpretation of this system was based on secondary descriptions (Mooney 2008)*
Phenotypic Abnormality (part of CHMO)
Clinical Classification (part of CHMO)

Clinical CL/P class type

- Davis-Ritchie cleft type
  - Davies-Ritchie group 1
    - Davies-Ritchie group 1 bilateral
      - Davies-Ritchie group 1 bilateral complete
      - Davies-Ritchie group 1 bilateral incomplete
    - Davies-Ritchie group 1 midline
    - Davies-Ritchie group 1 unilateral
      - Davies-Ritchie group 1 unilateral complete
      - Davies-Ritchie group 1 unilateral incomplete
  - Davies-Ritchie group 2
  - Davies-Ritchie group 3

- Expression system cleft type
  - Fogh-Andersen cleft type
  - Friedman cleft type
  - ICD-10 cleft lip and palate
Clinical Classification

Phenotypic Abnormality

Clinical C/L/P class type
- Davis-Ritchie cleft type
  - Davies-Ritchie group 1
    - Davies-Ritchie group 1 bilateral
      - Davies-Ritchie group 1 bilateral complete
    - Davies-Ritchie group 1 bilateral incomplete
    - Davies-Ritchie group 1 midline
  - Davies-Ritchie group 1 unilateral
    - Davies-Ritchie group 1 unilateral complete
    - Davies-Ritchie group 1 unilateral incomplete
  - Davies-Ritchie group 2
  - Davies-Ritchie group 3
  - Expression system cleft type
  - Fogh-Andersen cleft type
  - Friedman cleft type
  - ICD-10 cleft lip and palate

Abnormality of lip
- Abnormality of lower lip
- Abnormality of upper lip
  - Cleft of upper lip
    - Microform cleft of upper lip
    - Overt cleft of upper lip
    - Lateral cleft of upper lip
    - Bilateral cleft of upper lip
      - Complete bilateral cleft of upper lip
      - Incomplete bilateral cleft of upper lip
      - Unilateral cleft of upper lip
        - Complete unilateral cleft of upper lip
          - Left complete unilateral cleft of upper lip
          - Right complete unilateral cleft of upper lip
        - Incomplete unilateral cleft of upper lip
          - Upper lip pit
          - Midline cleft of upper lip

Abnormality of palate

has phenotype abnormality:

Davies-Ritchie group 1 bilateral complete

Complete bilateral cleft of upper lip
Types of anatomical entities needed to be represented in the OCDM based on abstracts

<table>
<thead>
<tr>
<th>Data and techniques</th>
<th>Anatomical and developmental entities</th>
</tr>
</thead>
</table>
| Volumetric images of tissues of mouse embryos | • Tissue and cell types  
• Craniofacial regions  
• Developmental stages |
| Volumetric images of adult and child heads, plus genetic analysis | • Craniofacial landmarks |
| Volumetric images of tissues of mouse strains with different craniofacial morphologies, plus genetic analysis | • Craniofacial regions  
• Craniofacial landmarks  
• Malformation phenotypes  
• Developmental stages |
| Data on human malformation phenotypes and environmental exposure, plus genetic analysis | • Craniofacial landmarks  
• Malformation phenotypes |
| Regions of craniofacial tissue dissected from mouse embryos for analysis by CHiP-seq | • Tissue types  
• Craniofacial regions  
• Developmental stages |
| Regions of craniofacial tissue dissected from mouse embryos for gene expression analysis | • Tissue types  
• Craniofacial regions  
• Developmental stages |
| Regions of craniofacial tissue dissected from zebralish or mouse embryos for miRNA analysis | • Tissue types  
• Craniofacial regions  
• Developmental stages |
Content extension:

- zebrafish ontology (primary source – Zfin)
- anatomical representation of musculoskeletal system of head
- development of skeletal system of head
- anatomical landmarks
- abnormalities of the musculoskeletal system of head
- cross-species correlation