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An ontology of human developmental anatomy

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Abstract

Human developmental anatomy has been organized as structured lists of the major constituent tissues present during each of Carnegie stages 1–20 (E1–E50, ~8500 anatomically defined tissue items). For each of these stages, the tissues have been organized as a hierarchy in which an individual tissue is catalogued as part of a larger tissue. Such a formal representation of knowledge is known as an ontology and this anatomical ontology can be used in databases to store, organize and search for data associated with the tissues present at each developmental stage. The anatomical data for compiling these hierarchies comes from the literature, from observations on embryos in the Patten Collection (Ann Arbor, MI, USA) and from comparisons with mouse tissues at similar stages of development. The ontology is available in three versions. The first gives hierarchies of the named tissues present at each Carnegie stage (http://www.ana.ed.ac.uk/anatomy/database/humat/) and is intended to help analyse both normal and abnormal human embryos; it carries hyperlinked notes on some ambiguities in the literature that have been clarified through analysing sectioned material. The second contains many additional subsidiary tissue domains and is intended for handling tissue-associated data (e.g. gene-expression) in a database. This version is available at the humat site and at http://genex.hgu.mrc.ac.uk/Resources/intro.html/), and has been designed to be interoperable with the ontology for mouse developmental anatomy, also available at the genex site. The third gives the second version in GO ontology syntax (with standard IDs for each tissue) and can be downloaded from both the genex and the Open Biological Ontology sites (http://obo.sourceforge.net/)

Introduction

Although the developmental anatomy of the human embryo has been studied for well over a hundred years, principally through the analysis of serially sectioned embryos, no comprehensive overview of the tissue constituents of the developing embryo has yet been published. The classic work of Streeter in the 1940s and 1950s made a start here by defining horizons (Streeter, 1942, 1945, 1948, 1951), whereas the more recent publication of O'Rahilly & Müller (1987) built on these to give the Carnegie Staging (CS) system of human development that extends to about 8 weeks (CS23), the end of the embryonic period. These overviews do, however, focus mainly on the key features of embryogenesis such as heart formation, primitive streak, renal development and the early stages of brain formation, and do not attempt to record systematically the gradual development of the embryo as a whole. Here, we report the production of an ontology of human developmental anatomy comprising a detailed set of anatomical hierarchies covering Carnegie stages 1–20 in which the tissues are linked by a 'part-of' rule. Together, these hierarchies comprise an anatomical ontology or computer-comprehensible domain of knowledge (Bard & Winter, 2002). Such ontologies are becoming increasingly important, following the introduction of the Gene Ontology (GO) that links knowledge about genes to a database of genes (Ashburner et al. 2000).

Until recently, such a detailed analysis of human development was not necessary, but the need to investigate the genetic control of human development has made it clear that standard anatomy lists for staged embryos are now required, and for two obvious reasons. First,

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the regulatory basis of congenital disorders can only really be understood in the context of a normal human developmental anatomy that includes detailed information on exactly when tissues are first apparent, and, second, storage of human gene-expression and other tissue-associated data requires that the database be linked to an ontology of human developmental anatomy. Such databases are already in place for the mouse (e.g. Ringwald et al. 1997) and other model organisms, see the Open Biological Ontology site, OBO*-* refers to a website; the URLs for these are listed at the end of the reference list).

This paper details the production of such an ontology of human developmental anatomy and the associated websites provide the tissue hierarchies in three formats. The first lists the standard tissues present in each Carnegie stage during the first seven or so weeks of development (up to Carnegie stage 20, about 50–51 days of development), when most of the major tissues are in place. The second, detailed version provides the input, storage and access terminology for databases of human gene-expression and other tissue-associated data (this version includes many minor cell domains associated with defined tissues – see below). The third provides the data in a format appropriate for ontology editors. This paper also considers the anatomical implications of the data collected and, through the notes associated with the ontology, clarifies some aspects of human developmental anatomy.

Materials and methods

The anatomical data

Three sources of anatomical data were used for compiling the anatomical lists: published descriptions of human developmental anatomy, analyses of serially sectioned human embryos and comparisons with datasets already in place for approximately equivalent stages in mouse development (Bard et al. 1998). The literature search involved some 350 papers and monographs (~160 key publications are linked to the website), with baseline information coming from the summaries compiled by O'Rahilly & Müller (1987). Analysis of serially sectioned material also had to be undertaken because, in a relatively few cases, ambiguities in the human literature could not be clarified from the mouse data. Some 10 serially sectioned embryos from the Patten collection (Ann Arbor, MI, USA) were therefore analysed to establish, for example, detailed information on the early vascular, muscular and skeletal systems that were not well documented in the literature. The ontology ceases at CS20 partly because of time and funding limitations and partly because it becomes difficult to explore the details of neurological development in later sectioned embryos that are only haematoxylin and eosin stained.

The mouse developmental anatomy ontology (Bard et al. 1998; available at the genex* site) was used as a template for constructing the human ontology because the formal structures and developmental pathways of mouse and human embryos are similar and there is a degree of similarity between human and mouse developmental stages (see, for example, Kaufman, 1994). The hierarchical and logical style of the mouse embryo ontology could therefore be used as a basis for constructing the human embryo lists, with the additional advantage that the resulting similarities in format would facilitate interoperability between the two databases (this term describes the ability of one database to interrogate another).

The existing mouse ontology was also very useful in providing a guide to tissues whose developmental timing had not been extensively discussed in the literature. These included:

1 the tissues within embryos of Carnegie stages 1–6, particularly the primitive streak and the extra-embryonic membranes, for which few well-fixed embryos have been available for serial sectioning and detailed analysis;
2 the temporal and anatomical origins of the early extra-embryonic blood and intra-embryonic vascular system, and the primordial germ cells;
3 early musculoskeletal development (this is still based on only a few embryos, e.g. Lewis, 1902);
4 placode development in the head ectoderm.

Informatics

The standard anatomical ontology format

The named anatomical tissues for each Carnegie stage were integrated in hierarchies based on 'part of' relationships, and these were embedded in a simple database (humat) using the file system on the web server as the core of the database schema. These data in humat were integrated with a website (to the user, the two are seamless) holding the links to the notes and literature using a small custom database program (written in C) from which all lists and tissue searches are generated

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de novo from the data each time a search request is made. Further user facilities include an ability to search for tissues and to show first and last occurrences of specific tissues in specific locations, as well as links to the pages for mouse and human staging systems and to other web pages of related interest.

This original version, which has now been available for some years, is only accessible at the humat* site.

The detailed gene-expression nomenclature format

This format is directly comparable with that used in the mouse ontology, with both nomenclature and hierarchical structures being conserved as far as possible. The detailed ontology includes, for example, entries for unnamed tissues such as the domains of mesenchyme and surface ectoderm in the interdigital regions of the handplate. As this version excludes the links to the notes and the literature, it is portable and can be downloaded from the humat site. In addition, the data are also held in a database at the genex* site where there is a Java viewer that allows the user to analyse the ontology branch by branch.

The ontology format

The ontology has been transformed into GO syntax*: here, each node and leaf (higher- and lower-level tissue terms) within the ontology is displayed with its unique ID. This version of the ontology can be downloaded from the genex* and has been submitted to the OBO* and GOBO* sites, but its inspection requires an ontology editor such as Dag-Edit*. This format is only likely be of use to database bioinformaticians.

The data and their structure

The standard anatomical ontology

The ontology presents the human embryo at each Carnegie stage up to CS20 (~E50) as a hierarchical list of its standard, anatomically defined tissues. Each tissue in a hierarchy is generally to be found as a part of a tissue that is both local and larger. The radius is thus chosen to be part of the arm rather than part of the skeleton, a less localized tissue (only including a tissue once, avoids some techical complexities). This ideal is not met in two types of cases. First, some tissues that would be intuitively grouped have no local neighbourhood: the prime example here is the set of glands. Second, high levels in the hierarchy are grouped by function rather than by location: thus central nervous system is a part of the nervous system which is, in turn, a part of organ systems. Where there were choices in how to link tissues, we have chosen the option that seemed likely to be intuitive to someone with an anatomical background.

The criterion for defining when a tissue is first present is, in principle at least, that an experienced embryologist can recognize it in a standard histological section stained with haematoxylin and eosin (ideally, by its boundary rather than its midpoint). It should, however, be emphasized that the identification of the great majority of the tissues in the ontology comes from the literature, some have come from direct observation of sections and a few have been extrapolated from our knowledge of mouse development. Tissue ontogeny is, we hope, always logical and sensible, but, because of the vast amount of information integrated into the ontology, we cannot vouch for its complete accuracy (see Discussion).

The tissues in the basic lists are expressed as a hierarchy that extends up to about eight levels deep. In the earlier embryos (up to about CS9), the major categories are the extra-embryonic tissues (placental details are omitted from the extra-embryonic component, mainly because so little early sectioned material exists), the three germ layers and their early derivatives, and the various body cavities. In the later stages, as the embryo matures (> CS10), less attention is paid to the extra-embryonic membranes, and the lists are organized around the major organ systems (brain, cardiovascular, reproductive, etc.). Table 1 details the named tissues present in the CS9 (E20) embryo, the stage at which organogenesis is first apparent.

Hierarchies typically give all subordinate tissues, but symmetric tissues are only mentioned once, unless they have different structures or fates (e.g. left and right dorsal aortae). The constituent cell types within a tissue are only given when such detail seems appropriate, e.g. the epithelium of the otic placode and the associated mesenchyme are both included at CS9 as they have separate fates. The total number of tissue items in each Carnegie stage is detailed in Table 2 and shown graphically in Fig. 1. The number of tissues for each stage should be viewed as indicative rather than precise, as the figures include all levels of the hierarchy, e.g. the listings for the CS20 heart include 68 component parts in an eight-level hierarchy; there are thus several high-level 'umbrella' terms (e.g. atrium) in the list. Nevertheless,

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Table 1 Anatomical components of the Carnegie stage 9 human embryo

CS09
embryo
  cavities and their linings
    intra-embryonic coelom
      future pleuropericardial cavity
        cavity
        mesothelium
  cloacal membrane
  ectoderm
    neural ectoderm
      future brain
        future mesencephalon (midbrain)
          floor plate
          neural folds
            neural crest
        future prosencephalon (forebrain)
          floor plate
          neural folds
      future rhombencephalon (hindbrain)
          pro-rhombomere a
            floor plate
            neural folds
              neural crest
          pro-rhombomere b
            floor plate
            neural folds
              neural crest
          pro-rhombomere c
            floor plate
            neural folds
              neural crest
          pro-rhombomere d
            floor plate
            neural folds
              neural crest
      future spinal cord
        neural plate
          neural folds
          neural groove
    surface ectoderm
  mesenchyme
    head mesenchyme
      mesenchyme derived from head mesoderm
      mesenchyme derived from neural crest
        mesencephalic neural crest
        rhombencephalic neural crest
      paraxial mesenchyme
        somite
          somite 01
          somite 02
          somite 03
        unsegmented mesenchyme
      prechordal plate
    trunk mesenchyme
      caudal eminence
      lateral plate mesenchyme
        somatopleure
        splanchnopleure
          cardiogenic
      paraxial mesenchyme
        unsegemented mesenchyme
      septum transversum
    neurenteric canal
    notochordal plate

Table 1 *Continued*

organ system
cardiovascular system
  arterial system
    head and neck
      branchial arch artery
        1st arch artery
      internal carotid artery
    trunk
      dorsal aorta
        left
        right
      umbilical artery
        left
        right
      vitelline arterial plexus
  heart
    cardiogenic (myocardial) plate (early stage)
    early primitive heart tube
      cardiac jelly
      endocardial tube
      myocardium
    mesentery
      dorsal mesocardium
    primitive heart tube
      bulbus cordis
        caudal half (future right ventricle)
        cardiac jelly
        endocardial tissue
        myocardium
      rostral half (proximal outflow tract)
        cardiac jelly
        endocardial tissue
        myocardium
      common atrial chamber
        cardiac jelly
        endocardial tissue
        myocardium
      outflow tract
        cardiac jelly
        endocardial tissue
        myocardium
      primitive ventricle (future left ventricle)
        cardiac jelly
        endocardial tissue
        myocardium
    sinus venosus
      left horn
      right horn
  primitive blood cells
  venous system
    umbilical vein
      left
      right
    vitelline vein
      left
      right
sensory organ
  ear
    otic placode
      epithelium
      associated mesenchyme
visceral organ
  alimentary system
    allantoenteric diverticulum
    gut

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Table 1 *Continued*

- **foregut**
  - ***associated mesenchyme***
  - ***endoderm***
- **foregut-midgut junction**
  - **associated mesenchyme**
  - **endoderm**
- ***rest of endoderm***
- **mouth-foregut junction**
  - **buccopharyngeal membrane**
    - ***ectoderm***
    - **endoderm**
  - **oral region**
    - **stomatodaeum**
- primitive streak
  - primitive groove
  - primitive node
  - primitive pit

extraembryonic component

- amnion
  - ectoderm
    - mesoderm
- **cardiovascular system**
  - **arterial system**
  - **umbilical arteries (L+R)**
  - **primitive blood cells**
  - **venous system**
    - ***venous plexus (umbilical vein primordia)***
- **vitelline capillary plexus**
- cavities
  - amniotic cavity
    - *amniotic duct*
  - secondary yolk sac cavity
- connecting stalk
  - ***allantoenteric diverticulum***
  - mesenchyme
  - mesothelium
  - secondary yolk sac
- **blood islands**
- *endoderm*
- mesenchyme
  - primordial germ cells
- mesothelium

Bold, new tissue. *Italic*, last mention of tissue ***B/I***, only mention. Underlined, associated note.

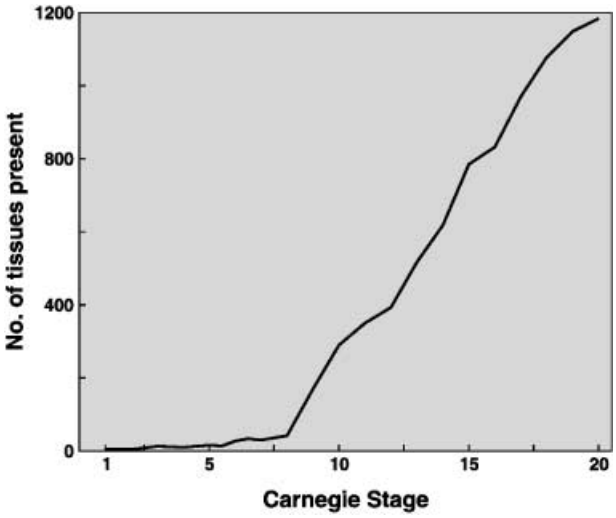

Fig. 1 This graph of the data in Table 1 shows that the generation of anatomical complexity starts at about CS8 (E8) and is slowing by CS20 (E50).

the figures show clearly that anatomical complexity is initiated at about CS8 (E18) with the number of named tissues (42) quadrupling over the next 2 days and then increasing more slowly until about CS18 (E44) before the rate tails off and growth takes over as the embryo becomes a fetus.

Associated notes

Compiling these lists has in some cases forced us to examine the literature of human embryogenesis in more detail than can be found in textbooks (e.g. Larsen, 2001). Ambiguities in the literature have, in a few cases, required us to re-examine histological material (from

Table 2 The number of tissues included in the ontology for each Carnegie stage (CS) and days of embryonic age (E)

Stage	No. of tissues	Stage	No. of tissues	Stage	No. of tissues	Stage	No. of tissues
CS1	4	CS5c	14	CS10	290	CS16	832
E1		E11–12		E22		E37	
CS2	4	CS6a	27	CS11	350	CS17	970
E2–3		E13–14		E24		E41	
CS3	13	CS6b	34	CS12	393	CS18	1078
E4		E14–15		E26		E44	
CS4	10	CS7	30	CS13	517	CS19	1149
E5–6		E16		E28		E47	
CS5a	13	CS8	42	CS14	618	CS20	1184
E7–8		E18		E32		E50	
CS5b	16	CS9	170	CS15	785		
E9–10		E20		E33			

Note that these figures include high-level tissues (cardiovascular system) as well as individual tissues (the atrial septum) and thus really only provide a qualitative indication of the increasing complexity of the embryo as it develops.

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the Patten collection). The results of this work are incorporated in about 90 notes* hypertext-linked both to the tissues and to references (Table 3). These notes allow readers to establish the grounds upon which a tissue is deemed 'present' as opposed to 'not present' by reference to the literature, histological observations from the Patten collection and by comparison with the database of mouse developmental anatomy.

A typical example is the note on the amnion: this considers the development of the amnion, amniotic cavity and amniotic duct at CS5, 6, 7, 9, 13, 14 and 16, citing eight relevant papers and linking these papers to an associated topic, the umbilical cord. This note also summarizes the development of the cord from CS8 to CS16, and the webpage is additionally linked to further pages on the umbilical arteries, the umbilical veins and future umbilical cord, which is linked to the vessels and midgut herniation (i.e. the 'physiological' umbilical hernia), which is in turn linked to further pages of notes. The standard lists, which are intended for embryologists and developmental anatomists, include all the normally named tissues together with references and notes and are available at the humat* website.

Table 3 Tissues discussed in the anatomical notes of the ontology (http://www.ana.ed.ac.uk/anatomy/database/humat/notes)

Embryonic tissue	Pre-implantation stages
Abducens nerve (VI)	Primitive blood cells
Accessory nerve (XI)	Primitive streak
Anal region	Primordial germ cells
Arterial system	Prosencephalon
Basal ganglia	Renal system
Branchial arches	Reproductive system
Caudal eminence	Respiratory system
Cerebral cortex	Rhombencephalon
Cerebellum	Septum (telencephalon)
Chiasmatic plate	Skeleton
Cloacal membrane	Skin
Cranial nerve ganglia	Somites
Diaphragm	Spinal cord
Diencephalon	Spinal nerve plexi
Dorsal thalamus	Spinal nerves and ganglia
Ear	Spleen
Eye	Subthalamus
Epithalamus	Sympathetic nervous division
Facial nerve (VII)	Telencephalic structures (miscellaneous)
Glossopharyngeal nerve (IX)	Telencephalon
Gut	Thymus
Heart	Thyroid
Hypoglossal nerve (XII)	Trigeminal nerve (V)
Hypothalamus	Trochlear nerve (IV)
Intra-embryonic coelom	Urinary system
Limbic system	Vagus nerve (X)
Limbs	Venous system
Liver and biliary system	Ventral thalamus
Meninges	Ventricles (brain)
Mesencephalon	Vestibulocochlear nerve (VIII)
Mesenchyme	
Muscle	**Extra-embryonic tissue**
Neural crest	Allantois
Neural plate	Amnion, amniotic cavity and amniotic duct
Neurenteric canal	Blastocyst cavity
Nose	Mesoderm, reticulum & endoderm
Notochord	Normal umbilical hernia
Oculomotor nerve (III)	Trophectoderm and syncytio/cytotrophoblast
Olfactory area of telencephalon	Umbilical arteries
Olfactory nerve (I)	Umbilical cord and connecting stalk
Optic nerve	Umbilical veins
Oral region	Umbilical vessels
Parasympathetic nervous division	Vitelline arteries
Peritoneal cavity	Vitelline veins
Pituitary gland	Vitelline vessels
Pleural cavity	Yolksac
Prechordal plate	Zona pellucida and polar bodies

The detailed anatomy ontology

This version of the ontology is designed for databases holding tissue-associated properties and is more elaborate than that just described as the lists include the subordinate domains of named tissues. The CS20 footplate demonstrates this precision: it has 40 geographically distinct domains, many of them small volumes of mesenchyme that have no formal name. This finer resolution allows tissue properties such as gene expression to be mapped more accurately than is possible using the standard version of the anatomy. In this context, it should also be pointed out that a 'part of' ontology has the property that, if a low-level tissue has some association, e.g. the femur expresses a particular gene, then this association is carried upwards so that the superior node (the leg) incorporates this information (although of course with lower degree of geographical precision).

This detailed version of the ontology is available at the humat* site in list format. However, people using these data will probably want to use the version that can be examined branch-by-branch using the downloadable Java-based viewer accessible at the genex* site.

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The GO format

Because the detailed ontology is designed for database work and we can envisage the possibility that human databases will soon be interoperable (can communicate) with other databases, we have given each tissue (named and un-named) a formal ID with an EHDA tag (Edinburgh Human Developmental Anatomy). These IDs are accessible in the Java viewers from the genex* site and in the version of the ontology that is written in GO syntax* viewable using editors such as Dag-Edit*.

This GO syntax version of the ontology has again been produced in two rather different formats. The first gives a hierarchy of all the tissues present at each stage of development and is essentially the same as the detailed ontology discussed above. Such a format is useful for searching databases, but clumsy for archiving data, which may be associated with a tissue for as long as it exists during embryogenesis (perhaps 15 stages). To simplify the archiving of such data, the detailed ontology has also been written in a time-independent format, known as 'the abstract human embryo': here, the ontology simply contains a hierarchy of all the tissues that are ever present during human embryogenesis, independent of the Carnegie stages at which they are present. Tissues in the abstract human ontology carry an EHDAA ID. Here, the criterion for two tissues being different is that they have different paths in the hierarchy, and this can sometimes lead to repetitions when an early tissue is re-positioned. Thus, for example, the common atrial chamber is given three times: first, as part of the primitive heart tube (present at CS9), then as part of the primitive heart (CS10) and finally as part of the atrium (CS11). Such cases are, however, rare. Both versions of the ontology in GO format are available at genex* and have been submitted to OBO*, the Open Biological Ontology site and public ontology archive.

Discussion

Limitations on the data

This paper reports the production of a web-accessible ontology of early human developmental anatomy that can be used for analysing congenital abnormalities as well as for archiving tissue-associated data in databases and other bioinformatics tasks. We consider first the standard ontology that incorporates all the named tissues.

The essential test of usefulness of this ontology is the accuracy of the incorporated anatomical data and there are several caveats about these data lists that should immediately be mentioned. First, they are mainly based on publications; this means that the correction of any inconsistencies or faults in the literature has depended on our ability to identify them (and these are discussed in the notes on the webpage). Second, the completeness of the data is subjective: we have tried to include all the major anatomically defined tissues of the embryo at each Carnegie stage, but there are certainly tissues that we may just have missed or that experts on particular tissues might have wished to include. One reason for excluding, for example, most tendons and ligaments is that they are essentially made of extracellular matrix and unlikely to be major sites of gene expression (it is for this reason that the zonule of Zinn has been excluded); another is that few of them are named and it seemed unbalanced to include just the named subset.

In addition, the number of embryos at each Carnegie stage that have been reported in any detail is relatively few and the ontology thus pays no regard to the natural variation in tissue timing that exists among developing humans of the same apparent stage of development. Readers should therefore accept that the time at which a tissue is first apparent in any given embryo may not mesh exactly to that in the ontology, but the presence or absence of these features should not be out by more than a single stage.

The detailed version of the ontology

This version of the developmental anatomy was designed with two purposes in mind. The first was to provide the nomenclature of human developmental anatomy at a resolution appropriate for storing gene-expression and other tissue-associated data, and the ontology therefore partitions named tissues into many minor anatomical domains. The second was to allow for the possibility that, in the future, three-dimensional voxel models of human embryos would be made to match those of the mouse embryo (Davidson et al. 1997, and genex*), and the ontology is intended for naming all recognizable spatial domains and, indeed, for providing a full spatial description of each Carnegie stage.

It might seem to the user that the way in which the hierarchies are organized within the ontology is unreasonably subjective, but, given the prior production of the mouse developmental anatomy, we had little choice:

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it was of key importance to design the human ontology around the mouse template (Bard et al. 1998) to facilitate future communication between databases for the mouse (e.g. Davidson et al. 1997; Ringwald et al. 1997) and human. Although the use of the mouse ontology, which has been part of the mouse gene expression database GXD* for several years, seems to have posed few problems to users, we accept that a simple, hierarchical structure generally based on geographical proximity has limitations. In the case of the mouse anatomical ontology, we are currently considering the implementation of alternative hierarchies based on groups of similar tissues (e.g. the muscles, the skeleton, etc.). In more formal terms, we will turn the current simple hierarchy into a directed acyclic graph (DAG) where a tissue can have more than one parent. Once these changes have been implemented for the mouse, we plan to upgrade the human ontology.

In a perfect world, there should be easy interoperability between the mouse and human tissues, but there are two difficulties here. First, because early human embryogenesis is rather different from that of the mouse: tissues develop at slightly different rates in the two embryos, so their staging systems are inevitably different and exact mappings between the two species cannot be made. Second, the anatomical terminologies differ, albeit in minor ways, e.g. the mouse forelimb is the human upper limb. We are currently examining whether it is possible to incorporate such terminological differences within a system that would allow a user to move transparently from one species to the other.

The website and database

The websites at both humat* and genex* are intended to be self explanatory and their most complex part, the databases in which the ontology is stored, are hidden: the user interrogates them through a web interface and the server then outputs to the browser a list of the tissues present at each Carnegie stage, which a user may copy or use to explore the links. One aspect of the humat* database design should be mentioned again here: the output displays first and last occurrences of tissues, and these are created *de novo* each time the database is accessed. Should any changes be made to the database in the light of new histological data, the remarking of first and last occurrences will be made automatically.

This design feature is only incorporated in the humat* version of the detailed anatomy. The other versions of this ontology are replicates of the data in humat* but, although the browsing interface lacks the ability to display first and last occurrences, they do have other advantages. The genex* site, for example, hosts a Java viewer that provides the user with a version of the ontology in which specific branches of the ontology tree can be opened and shut as required. This version is certainly the easiest to use in practice. In addition, this interface provides a search dialogue that allows queries by name, by ID and by the stage range of any tissue. The accession numbers (IDs) of each tissue are also provided by the interface.

The versions of the ontology in GO format will be the least intuitive for anatomists (their viewing requires the downloading of an ontology editor such as DAG-edit*), but they will probably be of greatest use to the bioinformatics community. This is because this format, which includes IDs for each tissue, is already readily understood by a number of bioinformatics resources and will therefore be easy to implement for interoperability purposes along the following lines. If one database contained information about human congenital abnormality data linked to anatomical IDs, it could

Websites (marked with * in the text)

Dag-Edit	http://www.geneontology.org/#dagedit
Digital anatomist	http://sig.biostr.washington.edu/projects/fm/aboutfm.html
Galen	http://www.openclinical.org/dld_galen.html
gene ontology	http://www.geneontology.org
genex	http://genex.hgu.mrc.ac.uk/Resources/intro.html
GO syntax	http://www.geneontology.org/doc/GO.doc.html#datarep
GXD:	http://www.informatics.jax.org/menus/expression_menu.shtml
humat	http://www.ana.ed.ac.uk/anatomy/database/humat/
notes	http://www.ana.ed.ac.uk/anatomy/database/humat/notes
OBO:	http://obo.sf.net
Ontologies (GOBO)	http://www.geneontology.org/doc/gobo.html
Physiome	http://www.bioeng.aukland.ac.nz/physiome/physiome.php

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query a second database containing human embryo gene-expression data that was also linked to anatomy IDs merely by incorporating the appropriate tissue ID in the query. This is how the Edinburgh Mouse Atlas interfaces at genex* are made interoperable with the Jackson Laboratory GXD* database.

All versions of the ontology currently work well, being housed in stable servers, and it is envisaged that they will be upgraded as new data and formats become available. We also plan to expand the ontology and so make it a more useful resource for those interested in early human developmental anatomy. These plans include adding pictures of early embryos, details of more recent literature and links to other relevant sites as they become available.

Finally, we emphasize that this ontology of human developmental anatomy is intended to be a community resource that supplements the existing adult anatomy ontologies (Digital Anatomist*, Galen* and Physiome*) and hope that, not only will it be used, but that anyone in the field who has comments, criticisms or corrections will contact the database curator (j.bard@ed.ac.uk).

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