HUGEN 2051: Inborn Errors of Development (2 credits)
Graduate School of Public Health
Spring 2015
Mondays and Wednesdays, 5:00-6:00 PM
Crabtree Hall A312

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Office hours: Friday, 9-11 AM
Classroom: Crabtree Hall A312

Catalogue Description
This course focuses on the connections between human development and inherited disease. The course will include core principles of development of the body plan and signaling pathways involved in development and differentiation. These biological processes will be used to categorize inherited human diseases, understand disease mechanisms, and the current efforts to develop targeted treatments.

Course Rationale
Recent discoveries in developmental biology and human genetics have been rapid and synergistic. The use of animal models of development identified genes that were subsequently found to be causing congenital malformations in human individuals. Conversely, discovery of human disease genes using the tools developed by the human genome project and the understanding of genotype-phenotype correlations uncovered key molecular pathways of development. Traditionally, human genetics and developmental biology are taught as separate courses. This course is intended to explore the interdisciplinary overlap between these subjects.

Objectives
By the end of this course, each student will be able to:
• Understand the development of major organ systems
• Describe the main molecular signaling pathways directing human development
• Identify and classify inherited developmental diseases using molecular information
• Search the literature based on citations and impact factor.
• Organize, and summarize research data in writing and speech.

Prerequisites
No prerequisites are required, but students will find the course easier if they had some prior undergraduate or graduate coursework on Developmental Biology or Molecular Biology. Taking HUGEN 2034 and 2040 prior to this course is recommended. For English as a Second Language students, a general academic writing course is also recommended.
Teaching Philosophy
This course is intended for upper level graduate students and places an emphasis on active participation. The classes will consist of short presentations by students and lectures. The assignments are designed to improve your scientific writing and presentation skills. I value your ability to think independently and critically and to see connections between seemingly disparate research findings.

Ground Rules: Please be on time and turn off your cell phone. The use of laptops is permitted. Please switch sound effects off. No texting or online chatting during class.

Academic Integrity
All students are expected to adhere to the school’s standards of academic honesty. Any work submitted by a student for evaluation must represent his/her own intellectual contribution and efforts. The GSPH policy on academic integrity, which is based on the University policy, is available online at http://www.publichealth.pitt.edu/interior.php?pageID=126. The policy includes obligations for faculty and students, procedures for adjudicating violations, and other critical information. Please take the time to read this policy.

Students committing acts of academic dishonesty, including plagiarism, unauthorized collaboration on assignments, cheating on exams, misrepresentation of data, and facilitating dishonesty by others, will receive sanctions appropriate to the violation(s) committed. Sanctions include, but are not limited to, reduction of a grade for an assignment or a course, failure of a course, and dismissal from GSPH. All student violations of academic integrity must be documented by the appropriate faculty member; this documentation will be kept in a confidential student file maintained by the GSPH Office of Student Affairs. If a sanction for a violation is agreed upon by the student and instructor, the record of this agreement will be expunged from the student file upon the student’s graduation. If the case is referred to the GSPH Academic Integrity Hearing Board, a record will remain in the student’s permanent file. Repeat violations automatically will be referred to the Hearing Board.

Disability
If you have a disability for which you are or may be requesting an accommodation, please contact me as soon as possible. Additionally, you should contact the Office of Disability Resources and Services, 216 Pitt Union, (412) 648-7890 or (412) 383-7355 (TTY) as early as possible in the semester. DRS will verify your disability and assist with determining reasonable accommodations for this course.

Course Website
All readings and course material will be found on the Blackboard site for this class. The website for Blackboard is http://courseweb.pitt.edu. To login, you must have a Pitt account. Your login ID is the same as your login ID for your Pitt account and your password is the same as for your Pitt account. To access the site for this class, double click on the course title, 2154_HUGEN_2051_SEC1060. The site will contain all readings, power point presentations, assignments, and additional information. The PowerPoint presentations and required readings for each class will be found under the course documents main menu option. Have an electronic or hard copy of the PowerPoint with you for taking notes.

Books:
Course Requirements

The final grade is based on sum of the following graded items:

- Attendance and participation: max 10 points
- Article commentary: max 20 points
- Short presentation: max 20 points
- Mini review: max 30 points
- Final exam: max 20 points

Attendance and participation: max 10 points
You may miss three classes without penalty. You may make up missed classes by submitting a 1-page summary of a research article related to the topic of the class no later then 1 month after the class or no later than the end of semester, whichever the earlier. The summary may not be copied from the abstract or the article text.

Written article commentary: 20 points
You will need to select a list of 5 articles related to development and human disease. The articles need to be recent (not older than 1 year), must not have been published by University of Pittsburgh researchers, and each must be published in a journal with an impact factor of 6 or higher. For each article, list all review articles that cited it. This list is due on the 4th class (January 14) and counts for 5 points of the assignment. The subject of the commentary will be selected from this list of 5 articles (one of the 5 articles). The commentary should be in the “Perspectives” format of Science magazine (900-1100 words, 5-15 references) and should provide a context to the article within a scientific field and discuss its interdisciplinary significance. Rather than a simple summary of the article, the commentary should give a new dimension to the research study. Also point out the limitations of the study. An article has been the main focus of prior reviews and commentaries may not be used for this assignment. The commentary is due on February 11. Grading guide: article list (5 points), accuracy of summary (5 points), discussion of context and significance (5 points), new dimension to research (3 points), accuracy and relevance of references (2 points).

Short presentation: 20 points
Prepare and present 15-minute powerpoint presentation of a recent high impact publication related to one of the lecture topics listed in the class schedule. The topic should be selected at the end of the first lecture and the publication by the 4th class (January 14). The publication should not be the same as the subject of your commentary or a subject of a previous Human Genetics Journal Club meeting. Your presentation should briefly introduce the research field and the question addressed by the publication. Summarize the results of the study and describe the conclusions. Your final 1-2 slides should include a criticism of the paper (Do the results support the conclusions? Are the methods appropriate? Are there any limitations?) As a general guideline, count 1 minute per slide. Images used in the presentation should be properly referenced. Grading guide: clarity and accuracy of the presentation (5 points), quality of visuals (5 points), critical evaluation (5 points), on-time delivery (5 points). The presentation is to be given on the date of lecture on the same topic.
**Mini-review: 30 points**
Select a recent, well-focused topic in the area of developmental genetics and write a 2000-3000 word mini review about the topic with 20-50 references. Choose a topic that you find exciting, important or particularly interesting. In the introduction discuss previous reviews of the topic and state how your review is new or different from the previous ones. The mini-review is due on March 30. Grading guide: impact and importance of the topic (5 points), discussion of prior reviews and novelty of this review (5 points), logical structure (5 points), clear, engaging style (5 points), accuracy and relevance of references (5 points), discussion of future research directions and opportunities (5 points).

**Final exam: 20 points**
The exam will consist of short questions focusing on the main ideas covered in the course and research scenarios.

**Late assignments**
Late assignments will be penalized by a 5 percentage point reduction of the assignment grade per week.

**Grade Scale**

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January 5  Introduction, animal models of development

By the end of this class each student will be able to:
• Find the impact factor of journals, compare journals by impact factor, rank publications by citations
• Identify different types of citing articles
• Explain the utility of animal models in understanding the developmental basis of human disease.

Class activities:
• Introduction, review of the syllabus, explanation and timeline of assignments
• Tutorial on the use of the Journal Citation Reports, Web of Science and other online resources
• Lecture on commonly used animal models of development and their genetic manipulation

Readings:
• Epstein pp. 25-48, Model organisms

January 7  Fertilization

By the end of this class each student will be able to:
• Describe the mechanisms of fertilization and initiation of embryonic development

Class activities:
• Lecture on fertilization.

Readings:
• Gilbert pp. 118-151, Rules of evidence, Internal fertilization in mammals

January 12  Early development and implantation

By the end of this class, each student will be able to:
• Understand the early stages of embryonic development and specialized developmental innovations in placental animals

Class activities:
• Lecture on early development

Readings:
• Gilbert pp. 298-309, Early mammalian development

January 14  Axis determination and HOX genes

List of articles related to the commentary assignment due!
Article selection for short presentation due!
By the end of this class each student will be able to:
• Understand how the embryonic axes are defined
• Recognize disorders of the limbs and axial skeleton caused by homeobox gene mutations
• Describe the molecular pathways impaired in heterotaxy

Class activities:
• Lecture on axis determination, heterotaxy and homeobox gene-related disorders

Readings:
- Gilbert pp. 309-318, Mammalian axis formation
- Epstein pp. 373-381, Visceral heterotaxy
- Epstein pp. 653-696, HOX genes and related diseases

January 19 MLK day – no class

January 21 Development of the nervous system and related diseases

By the end of this class each student will be able to:
• Describe the main stages of neural development
• Recognize disorders of neuronal migration
• Understand key components of the hedgehog signaling pathway
• Recognize the Smith-Lemli-Opitz and holoprosencephaly syndromes

Class activities:
• Lecture on neural development

Readings:
- Gilbert pp. 333-359, Ectodermal and CNS development
- Epstein pp. 79-93, Development of the nervous system
- Epstein pp. 263-300, Sonic hedgehog signaling pathway, and related diseases
- Epstein pp. 697-709, EMX2, HSEX1, type 1 schizencephaly, septo-optic dysplasia
- Epstein pp. 1103-1107, ZIC1, ZIC4 and Dandy-Walker malformation
- Epstein pp. 1309-1312, GPR56, bilateral frontoparietal polymicrogyria

January 26 Neural crest and craniofacial development

By the end of this class each student will be able to:
• Identify neural crest derivatives and their development
• Recognize disorders of the neural crest craniofacial development

Class activities:
• Lecture on neural crest development and related disorders
Readings:
- Gilbert pp. 375-414, Neural crest and axonal specificity
- Epstein pp. 69-78, Neural crest and craniofacial development
- Epstein pp. 803-808, PAX3 and Waardenburg syndrome type 1
- Epstein pp. 1038-1041, MITF and Waardenburg syndrome type 2
- Epstein pp. 521-535, Endothelin signaling and Shah-Waardenburg syndrome
- Epstein pp. 499-520, Glial cell-derived neurotrphic factor signaling and Hirschsprung disease
- Epstein pp. 1069-1072, Non-syndromic cleft lip and palate
- Epstein pp. 1476-1482 EFNB1 and EFNA4 craniofrontonasal syndrome and craniosynostosis

January 28   Development of the eye and related disorders

By the end of this class each student will be able to:
- Identify the key steps of eye development
- Recognize disorders of eye development

Class activities:
- Lecture on eye development and related disorders

Readings:
- Gilbert pp. 359-367, Development of the vertebrate eye
- Epstein pp. 94-106, Development of the eye
- Epstein pp. 787-795 Paired-box genes
- Epstein pp. 809-817, PAX6 and aniridia
- Epstein pp. 826-833, Forkhead gene family
- Epstein pp. 834-840, FOXC1, FOXL2, disorders of the anterior segment and eyelids
- Epstein pp. 1483-1489, GJA1 (connexin 43) oculodentodigital syndrome

February 2   Development of the ear and related disorders

By the end of this class each student will be able to:
- Describe the main stages of ear development
- Recognize disorders of hearing

Class activities:
- Lecture on ear development and disorders of hearing

Readings:
- Epstein pp. 107-123, Development of the ear
- Epstein pp. 747-756, EYA1 and the brachio-oto-renal syndrome
- Epstein pp. 1024-1047, POU3F4, mixed deafness with temporal bone defect (DFN3)
- Epstein pp. 1055-1060, Hypoparathyroidism, deafness and renal disease

December 17, 2014
February 4  
**Cardiac development and congenital heart diseases – Dr. Beth Roman**

By the end of this class each student will be able to:
- Articulate key processes of heart formation and septation
- Recognize the contribution of the neural crest to cardiovascular structures
- Understand the genetic causes of cardiac malformations

Class activities:
- Lecture on cardiac development

Readings:
- Gilbert pp. 388-389, 445-455, Heart development
- Epstein pp. 124-129, Molecular regulation of cardiogenesis
- Epstein pp. 768-777, NKX2-5 and congenital heart disease
- Epstein pp. 605-614, The RAS pathway
- Epstein pp. 620-631, RAS signaling and Noonan syndrome
- Epstein pp. 632-637, HRAS and Costello syndrome
- Epstein pp. 639-646, RAS/MAPK pathway and cardio-facio-cutaneous syndrome
- Epstein pp. 1048-1054, TFAP2B and the Char syndrome
- Epstein pp. 1061-1068, FOG2/ZFPM2, GATA4, congenital heart disease and diaphragmatic hernia

February 9  
**Vascular and blood development – Dr. Beth Roman**

By the end of this class each student will be able to:
- Describe the molecular mechanisms of developmental vasculogenesis, angiogenesis, arterial, venous and lymphatic specification
- Understand the genetic causes of vascular malformations

Class activities:
- Lecture on vascular development

Readings:
- Gilbert pp. 432, 456-466, Formation of blood vessels
- Epstein pp. 130-149, Development of the vascular system
- Gilbert pp. 466-471, Hematopoiesis
- Epstein pp. 358-368, TGFβ-related signaling
- Epstein pp. 388-389, ENG, ACVRL1 and SMAD4 and hereditary hemorrhagic telangiectasia
- Epstein pp. 491-494, TEK/TIE2 and cutaneous venous malformation
- Epstein pp. 417-422, TGFBR1, TGFBR2 Loeys-Dietz syndrome
- Epstein pp. 647-650, RASA1, capillary and arterio-venous malformation
- Epstein pp. 495-498, 841-845, 913-915, lymphedema syndromes
- Gilbert pp. 648-649, Anti-angiogenic therapies
February 11  Somite and muscle development

Perspectives assignment due!

By the end of this class each student will be able to:
• Understand the formation and segmentation of the somites
• Describe the developmental fates of the somites
• Recognize steps of muscle differentiation and fiber formation
• Identify disorders of segmentation and muscle development

Class activities:
• Lecture on muscle and somite development

Readings:
- Gilbert pp. 413-428, The somites and their derivatives
- Epstein pp. 150-161, Muscle and somite development
- Epstein pp. 536-551, NOTCH signaling
- Epstein pp. 560-572, DLL3, MESP2, LFNG and spondylocostal dysostosis
- Epstein pp. 552-559, JAG1, NOTCH2 and the Alagille syndrome

February 16  Development of the cartilage and bone

By the end of this class each student will be able to:
• Identify the mechanisms necessary bone formation
• Recognize the developmental abnormalities of chondrogenesis and osteogenesis

Class activities:
• Lecture on bone and cartilage development

Readings:
- Gilbert pp. 428-432, Osteogenesis
- Epstein pp. 162-181, The development of bone and cartilage
- Epstein pp. 449-460, FGF signaling
- Epstein pp. 461-470, FGF receptor mutations, bone dysplasia and craniosynostosis syndromes

February 18  Limb development and malformations

By the end of this class each student will be able to:
• Identify the mechanisms necessary for limb development
• Recognize the developmental limb malformations

Class activities:
• Lecture on limb development and malformations

Readings:
- Gilbert pp. 489-518, development of the tetrapod limb
- Epstein pp. 182-202, development of the limbs
- Epstein pp. 1507-1512, LMBR1. acheiropodia and preaxial polydactily

February 23  Development of the kidney - Dr. Sunder Sims-Lucas

By the end of this class each student will be able to:
- Understand development of the kidney
- Connect diseases of the kidney to development

Class activities:
- Lecture on kidney development

Readings:
- Gilbert pp. 434-444, Intermediate mesoderm, the urogenital system
- Epstein pp. 212-228, Development of the kidney
- Epstein pp. 796-802, PAX2 renal-coloboma syndrome

February 25  Development of the endodermal derivatives

By the end of this class each student will be able to:
- Understand development of the lungs the gastrointestinal tract
- Recognize inherited forms of diabetes and pancreatic agenesis
- Understand the principles of reciprocal epidermal/mesenchymal signaling

Class activities:
- Lecture on lung and gastrointestinal development

Readings:
- Gilbert pp. 471-483, Endoderm
- Epstein pp. 229-244, Development of the endodermal derivatives
- Epstein pp. 846-851 FOXE2 and thyroid agenesis
- Epstein pp. 710-716, PDX1, pancreatic agenesis, and type 2 diabetes
- Epstein pp. 1073-1077, PTF1A, pancreas and celebellar agenesis
- Epstein pp. 1096-1102, TCF2, MODY5 and urogenital malformations

March 2  Development of the skin and epidermal appendages

By the end of this class each student will be able to:
- Understand the mechanisms of skin and appendage development
- Identify developmental diseases of the skin

Class activities:
- Lecture on epidermal development
Readings:
- Gilbert pp. 365-372, The epidermis and its appendages
- Epstein pp. 245-259, Development of teeth and hair
- Epstein pp. 442-448 Ectodysplasin pathway and hypohydrotic ectodermal dysplasia
- Epstein pp. 717-729 MSX1 partial anodontia, Witkop syndrome
- Epstein pp. 818-825 PAX9 and hypodontia

March 4  
Sex determination, production of gametes – Dr. Alexander Yatsenko

By the end of this class each student will be able to:
• Describe the main stages of sex determination
• Recognize disorders affecting fertility

Class activities:
• Lecture on sex organ development

Readings:
- Gilbert pp. 510-528, Sex determination
- Epstein pp. 203-211, The sex determination pathway
- Epstein pp. 1513-1523, NR0B1 (DAX1) and X-linked adrenal hypoplasia congenital and XY sex reversal
- Epstein pp. 1531-1539, P450 oxidoreductase and Antley-Bixler syndrome

March 9  
No class: Spring Break

March 11  
No class: Spring Break

March 16  
Cell cycle and apoptosis in development

By the end of this class each student will be able to:
• Identify key signaling pathways of cell proliferation important for development
• Describe malformations caused by impaired cell proliferation

Class activities:
• Lecture on cell cycle in development

Readings:
- Epstein pp. 1201-1211, Mechanisms of cell cycle regulation and apoptosis
- Epstein pp. 1212-1218, MYCN and Feingold syndrome
- Epstein pp. 1230-1236, Fanconi anemia
- Epstein pp. 1237-1245, RECQL4, Rothmund-Thomson and related syndromes
- Epstein pp. 1246-1257, TP63, ectrodactily and related syndromes
March 18  Cancer and development

By the end of this class each student will be able to:

• Identify the shared signaling pathways involved in development and carcinogenesis

Class activities:

• Lecture on cancer and development

Readings:

■ Gilbert pp. 643-646, Cancer as a disease of development
■ Epstein pp. 306-312, PTCH and Gorlin/basal cell nevus syndrome
■ Epstein pp. 615-619, NF1, Neurofibromatosis

March 23  Transcriptional regulation and chromatin structure in development

By the end of this class each student will be able to:

• Understand the role of chromatin modifications and transcriptional regulation in development
• Recognize inherited diseases associated with chromatin or transcriptional abnormalities

Class activities:

• Lecture on transcriptional and chromatin regulation

Readings:

■ Gilbert pp. 31-52, Developmental genetics
■ Epstein pp. 919-924, Mechanisms of regulated gene expression
■ Epstein pp. 925-942, CBP and the Rubinstein-Taybi syndrome
■ Epstein pp. 955-964, Beckwith-Wiedeman Syndrome
■ Epstein pp. pp. 965-973, 1161-1167, Prader-Willi syndrome and Angelman syndrome

March 25  RNA processing in development

By the end of this class each student will be able to:

• Identify the mechanism by which RNA processing regulates development
• Recognize disorders caused by abnormal RNA processing

Class activities:

• Lecture on RNA processing

Readings:

■ Gilbert pp. 53-66, Differential RNA processing
■ Epstein pp. 1108-1125, Nuclear RNA processing
■ Epstein pp. 1126-1132, FMR1 and the Fragile X syndrome
March 30  

**Protein processing**

Mini-review due!

By the end of this class each student will be able to:
- Understand the mechanisms of posttranslational regulation
- Describe the molecular machinery responsible for ubiquitin modification and protein degradation
- Identify the diseases caused by dysfunction of proteosomal degradation

Class activities:
- Lecture on protein processing

Readings:
- Epstein pp. 1148-1160, Ubiquitin-mediated proteolysis
- Epstein pp. 1168-1172, VHL and von Hippel-Lindau disease
- Epstein pp. 1190-1194, UBR1 and the Johanson-Blizzard syndrome
- Epstein pp. 1195-1200, CUL7 and the 3M syndrome
- Epstein pp. 1173-1176, MKKS McKusick-Kaufmann and Bardet-Biedl syndrome
- Epstein pp. 1186-1189, TBCE, hypoparathyroidism-retardation-dysmorphism syndrome

April 1  

**Cilia and cytoskeleton in development**

By the end of this class each student will be able to:
- Understand the role of cilia in development
- Recognize inherited diseases associated with mutations in cytoskeletal genes

Class activities:
- Lecture on cilia and cytoskeleton in development

Readings:
- Epstein pp. 1313-1321, Microtubule motors
- Epstein pp. 1322-1333, LIS1, DCX1, and lissencephaly
- Epstein pp. 1334-1337, RELN, lissencephaly with cerebellar hypoplasia
- Epstein pp. 1338-1349, DNAH5, primary ciliary dyskinesia
- Epstein pp. 1371-1378, Bardet-Biedl syndromes
- Epstein pp. 1379-1386, Oral-facial-digital type 1 syndrome
- Epstein pp. 1387-1391, MKS genes and Meckel syndrome
- Epstein pp. 1350-1360, FLNA, FLNB filaminopathies

April 6  

**Vesicular trafficking in development**
By the end of this class each student will be able to:
• Understand the molecular regulation of vesicular trafficking
• Recognize developmental disorders caused by impaired vesicular transport

Class activities:
• Lecture on vesicular transport

Readings:
■ Epstein pp. 1392-1399, Inborn defects of membrane trafficking
■ Epstein pp. 1400-1406, VPS13B, Cohen syndrome
■ Epstein pp. 1410-1415, VPS33B, arthrogryposis renal dysfunction and cholestasis syndrome
■ Epstein pp. 1407-1409, SNAP29, cerebral dysgenesis, neuropathy ichthyosis, palmoplantar keratoderma
■ Epstein pp. 1416-1423, SEC23A, cranio-lenticulo-sutural dysplasia

April 8  Extracellular matrix and development

By the end of this class each student will be able to:
• Describe mechanism by which the extracellular matrix regulates development
• Identify developmental disorders of the extracellular matrix

Class activities:
• Lecture on the extracellular matrix

Readings:
■ Epstein pp. 1424-1429, Extracellular matrix signaling in development
■ Epstein pp. 1430-1434, GPC3, Simpson-Golabi-Behmel syndrome
■ Epstein pp. 1435-1442, HSPG2 (perlecan), Schwartz-Jampel syndrome
■ Epstein pp. 1443-1446, L1CAM, X-linked hydrocephalus
■ Epstein pp. 1447-1452, COMP, pseudoachondroplasia
■ Epstein pp. 1453-1462, MMP2, multicentric osteolysis, nodulosis and arthropathy
■ Epstein pp. 1463-1465, ADAMTS10, Weill-Marchesani syndrome

April 13  Developmental basis of aging and disease

By the end of this class each student will be able to:
• Identify theories of aging and the underlying molecular mechanisms
• Describe examples of age-related disease and developmental risk factors

Class activities:
• Lecture on development and aging

Readings:
■ Gilbert pp. 571-579, Aging: the biology of senescence
- Gilbert pp. 646-648, The embryonic origins of adult-onset diseases
- Epstein pp. 1219-1229, LMNA and LBR: Hutchinson-Gilford Progeria syndrome

**April 15    Stem cells and regeneration – Dr. Beth Roman**

By the end of this class each student will be able to:
- Understand the definition of stem cells
- Describe the location and potency of embryonic and adult stem cells
- Articulate methods to derive induced pluripotent stem cells
- Recognize the utility and limitations of stem cells in the therapy of genetic and acquired disorders

Class activities:
- Student short presentation
- Lecture on stem cells

Readings:
- Gilbert pp. 323-331, the stem cell concept
- Gilbert pp. 649-655, stem cells and tissue regeneration

**April 20    Final exam**

**April 22    Environmental disruptors of development – Dr. Beth Roman**

By the end of this class each student will be able to:
- Describe the mechanisms of developmental defects caused by cyclopamine and ethanol exposure
- Identify the teratogenic mechanism of pharmaceuticals including thalidomide, isotretinoin and statins

Class activities:
- Lecture on teratogens

Readings:
- Gilbert pp. 628-643, Teratogenesis