Introduction to Fetal Medicine: Genetics and Embryology

Question: What do cancer biology, molecular biology, neurobiology, cell biology developmental biology and reproductive biology, all have in common?
Answer: BIOLOGY!
CENTRAL DOGMA

DNA $\rightarrow$ RNA $\rightarrow$ Protein

Information Flow 1950 - 1960's
Protein $\rightarrow$ function(s)

Information Flow 1970 - 1990's
DNA $\rightarrow$ RNA $\rightarrow$ Protein $\rightarrow$ function(s)

Information Flow 1990's – 2000’s
Expression arrays, Chips, Proteomics
Engineering, Automation/Robotics, Bioinformatics
“Genome News”

Surprises from the genome

So few genes!

Similarity in genome size between simple and complex organisms

“Extraneous” Sequence vs “Junk DNA”

Source and form of human Variation, SNPs & CNVs
B. Genetic controls of development
Conceptual framework

- **Programming**
- Critical windows
- Spatio-temporal specificity
Programming

Oogenesis
Fertilization
Implantation
Placentation
Organogenesis
Hyperplastic Growth
Hypertrophic Growth
Functional Maturation
Preparation for Postnatal Life
B. Genetic controls of development

Conceptual framework

- Programming
- Critical windows
- Spatio-temporal specificity
Critical Windows During Development

Adapted from: Jaenisch. Trends Genetics 1997
B. Genetic controls on development

Conceptual framework

- Programming
- Critical windows
- Spatio-temporal specificity
C. Developmental regulators

- **Specification factors:** T-Box genes and congenital heart disease

- **Transcription factors:** Foxd1 and renal anomalies; Pax3 and DiGeorge syndrome

- **Transmembrane signaling:** ET receptors and Hirschsprung’s disease; Jagged 1/Notch1 in Alagile’s syndrome and biliary atresia

- **Organizers:** Nodal, Lefty and heart disease
The Hox Gene Cluster

ANT-C
lab
pb
Dfd
Scr
Antp
Ubx
abdA
AbdB
BX-C

HOXA
a-1
a-2
a-3
a-4
a-5
a-6
a-7
a-9
a-10
a-11
a-13

HOXB
b-1
b-2
b-3
b-4
b-5
b-6
b-7
b-8
b-9

HOXC
c-4
c-5
c-6
c-8
c-9
c-10
c-11
c-12
c-13

HOXD
d-1
d-3
d-4
d-8
d-9
d-10
d-11
d-12
d-13

Early, Anterior 3'

5' Late, Posterior

Early, Anterior 3'

5' Late, Posterior
Schematic of Cardiac Morphogenesis in Humans

Migration of precardial cells

Generation of single cardiac tube

Looping and formation of cushions

Mature heart

From D. Srivastava and E. Olson, Nature 2000
D. Example: cardiac organogenesis

- Early specification: “tinman”, Nkx2.5
- Midline fusion GATA 4
- Cardiomyocyte transformation/proliferation MEF2, GATA4, p57kip2
- Looping morphogenesis SMAD2
- Segmentation and growth of cardiac chambers TBX5, RXRα
- Valvulogenesis d,eHAND, Nkx2.5
- Outflow tract septation and patterning of great vessels TBX2
D. Example: gut organogenesis

- **Midline fusion** GATA 4
- **Cardiomyocyte transformation/proliferation** MEF2, GATA4, p57kip2
- **Looping morphogenesis** SMAD2
- **Segmentation and growth of cardiac chambers** TBX5, RXRα
- **Valvulogenesis** d,eHAND, Nkx2.5
- **Outflow tract septation and patterning of great vessels** TBX2
If it is genetic, why doesn’t it look genetic?

Genetic heterogeneity

- del22q11
- NKX2.5
- Trisomy 21
- TOF
- JAG1
- ??

Reduced penetrance

Complete Penetrance

- [Diagram showing penetrance]

Reduced Penetrance (50%)

- [Diagram showing penetrance]

Variable expressivity

NKX2.5 (cardiac specific transcription factor) - mutations cause

- Atrioventricular block
- Secundum atrial septal defect
- Tetralogy of Fallot
- Ebstein’s malformation

Ventricular septal defect

- Perimembranous
- Muscular
- Swiss cheese

Table 1

<table>
<thead>
<tr>
<th>Condition</th>
<th>Linkage identified</th>
<th>1st mutation</th>
<th># genes</th>
<th># mutations</th>
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<td>Marfan syndrome</td>
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<td>~125</td>
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<td>Long QT syndrome</td>
<td>1991</td>
<td>1995</td>
<td>&gt;5</td>
<td>~200</td>
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<td>Holt Oram syndrome</td>
<td>1994</td>
<td>1997</td>
<td>1</td>
<td>10</td>
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<td>Familial CHD</td>
<td>1998</td>
<td>1998</td>
<td>1</td>
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</tbody>
</table>

Array-based SNP and CNV analysis
E. Patterns of inheritance

1. Autosomal dominant disorders
2. Autosomal recessive disorders
3. X-linked disorders
4. Chromosomal disorders
   - Deletion syndromes
   - Aneuploidy
   - Uniparental disomy
5. Mitochondrial disorders
6. Polygenetic/multifactorial disorders
7. Gene-environment interactions
   - Nutrition, oxygen, toxins
Osteogenesis Imperfecta

Type I
  - autosomal dominant
  - age at presentation: 2-6 years
Type II (congenital lethal OI)
  - autosomal recessive
  - pre or perinatal death
  - (pulmonary hypoplasia)
Type III (severe progressive OI)
  - autosomal dominant
  - marked progressive limb and spine deformity
Type IV
  - autosomal dominant
  - most mild form
  - demineralization, cortical thinning
  - multiple fractures with pseudoarthrosis
  - exuberant callus formation
  - blue sclerae
  - presenile deafness
  - dentinogenesis imperfecta
  - wide sutures + Wormian bones
E. Patterns of inheritance

1. Autosomal dominant disorders
2. **Autosomal recessive disorders**
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   - Deletion syndromes
   - Aneuploidy
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   - Nutrition, oxygen, toxins
Name 3!

Cystic Fibrosis

Sickle Cell Disease

Gaucher’s
Which present in fetal life?

Cystic fibrosis (meconium ileus)

Gaucher’s (hydrops fetalis)
E. Patterns of inheritance

1. Autosomal dominant disorders
2. Autosomal recessive disorders
3. X-linked disorders
4. Chromosomal disorders
   Aneuploidy: Trisomies 21, 18, 13
   Deletion syndromes: DiGeorge
   Uniparental disomy:
   Prader-Willi vs. Angelman
   Insertion syndromes: CTG repeat
5. Mitochondrial disorders
6. Polygenetic/multifactorial disorders
7. Gene-environment interactions
   Nutrition, oxygen, toxins
DiGeorge syndrome / Velo-cardio-facial syndrome (DGS / VCFS)

- **Etiology:** 22q11 deletions (DGCR)
- **Prevalence:** 1:4,000 live births
- **Clinical features:**
  - Cardiovascular defects
  - Craniofacial anomalies
  - Thymus gland hypoplasia
  - Learning disabilities
  - Chronic otitis media, hearing loss
- **Penetrance:** complete
- **Expressivity:** variable
E. Patterns of inheritance

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   - Aneuploidy: Trisomies 21, 18, 13
   - Deletion syndromes: DiGeorge
   - **Uniparental disomy:**
     - Prader-Willi vs. Angelman
   - Insertion syndromes: CTG repeat
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Uniparental Disomy

Angelman
Paternal Chr 15

Prader-Willi
Maternal Chr 15
E. Patterns of inheritance

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   - Deletion syndromes: DiGeorge
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**Diagnostics/Therapeutics**

SNP Genotyping
- Disease association
- Pharmacogenomics

“Biomarkers” (fingerprinting)
E. Patterns of inheritance

1. Autosomal dominant disorders
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3. X-linked disorders
4. Chromosomal disorders
   Deletion syndromes
   Aneuploidy
   Uniparental disomy
5. Mitochondrial disorders
6. Polygenetic/multifactorial disorders
7. Gene-environment interactions
   Nutrition, oxygen, toxins
   Defects/Deformations/Malformations
8. Prenatal Diagnosis
Prenatal Diagnosis / Treatment

• Amniocentesis:
• Chorionic Villous Sampling
• Preimplantation genetic diagnosis “PGD”
• Non Invasive Prenatal Testing “NIPT”
• “Tri-parenting”

Advances in embryo culturing
The New Medicine

James Spader “Stargate”

Developmental Genetics in the Post Genome Era

- Comparative Genomics
- Expression Profiling
- Genotype – Phenotype Studies
- GWAS
- Personalized Medicine
Useful Resources:

Smith’s “Patterns of Congenital Malformations”

Bianchi et al “Fetology”

OMIM  Online Mendelian Inheritance in Man