Congenital and hereditary disease

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DEPT VET SCI
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Overlap of congenital and hereditary disease

Congenital disease

Inherited disease

Familial = suggestive of inheritance but not proven

Cerebellar hypoplasia

Genetic?  Non-genetic?
Genetic disease in people

<table>
<thead>
<tr>
<th>Phenotyped</th>
<th>Genotyped</th>
<th>Autosomal</th>
<th>X-linked</th>
<th>Y-linked</th>
<th>Mitochondrial</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>YES</td>
<td>YES</td>
<td>2,725</td>
<td>236</td>
<td>4</td>
<td>28</td>
<td>2,993</td>
</tr>
<tr>
<td>YES</td>
<td>NO</td>
<td>1,632</td>
<td>134</td>
<td>5</td>
<td>0</td>
<td>1,771</td>
</tr>
</tbody>
</table>

Inherited diseases phenotyped ± genotyped in domestic species:

-10-600/species

Phenotyping = pathologists
Genotyping = molecular geneticists

Major causes of congenital disease

- Genetic:
  - Mutations
  - Chromosomal abnormalities
  - Other – mitochondrial, repeats, other
- Non-genetic:
  - Infectious
  - Nutritional
  - Toxic
  - Secondary to conditions in dam
  - Other (neoplastic; trauma; idiopathic abnormalities of migration)
- Placental (including umbilical cord)

Genetic diseases – how common in people

Each individual carries 5 – 8 deleterious genes – most inherited, a few de novo

- ~50% of spontaneous abortions in early gestation due to detectable chromosomal errors
- 1% of newborn infants have gross chromosomal abnormalities
Congenital malformations in PEOPLE (live births)

Genetic
- Chromosomal: 10 – 15%
- Mendelian: 2 – 16%
- Multifactorial: 20 – 25%

Environmental
- Maternal infections: 2 – 3%
- Maternal diseases: 6 – 8%
- Drug and chemical: 1%
- Irradiation: 1%

Unknown: 40 – 60%

Estimated frequency of congenital disorders in cattle

1:100 – 1:500

Major genetic disorders

- Single genetic mutations with large effects:
  - Classic Mendelian inheritance
  - High penetrance = disease in high proportion of individuals
  - Exp. inbred populations
  - Important source of information about metabolic pathways

- Chromosomal disorders:
  - Structural or numerical alteration in autosomes or sex chromosomes
  - High penetrance

- Complex multigenic disorders:
  - Due to increased risk associated with specific polymorphisms
  - Low penetrance of individual genes
  - Typically: polymorphism A + B + C + D + environment = disease
Recognizing Mendelian disorders

AR
- Uniform expression
- Complete penetrance
- Early in life
- Parents normal

X-linked
- Generally recessive
- Disease in males only
- Females are carriers

AD
- Variable expression
- Incomplete penetrance
- May be later in life
- Likely to be recognized in one parent

Single gene disorders

Single-base deletion

Four base insertion in hexaminidase gene = frame-shift mutation
Single gene disorders

- Ile—Ile—Phe—Gly—Val—

**Normal DNA** ... T ATC ATC TTT GGT GTT ...

**CF DNA** ... T ATC AT— — T GGT GTT ...

- Ile—Ile—Gly—Val—

Three base deletion in CF allele with loss of amino acid at position 508 (phenylalanine)

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**What can go wrong in Mendelian disorders**

<table>
<thead>
<tr>
<th>Protein type/function</th>
<th>Example</th>
<th>Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzyme</td>
<td>Hexosaminidase</td>
<td>Storage disease</td>
</tr>
<tr>
<td>Enzyme inhibitor</td>
<td>α1-antitrypsin</td>
<td>Emphysema</td>
</tr>
<tr>
<td>Receptor</td>
<td>Low density lipoprotein receptor</td>
<td>Familial hypercholesterolemia</td>
</tr>
<tr>
<td>Transport</td>
<td>Hemoglobin</td>
<td>Sickle cell anemia</td>
</tr>
<tr>
<td>Extracellular matrix</td>
<td>Collagen</td>
<td>Ehlers-Danlos syndrome</td>
</tr>
<tr>
<td>Cell membrane</td>
<td>Dystrophin</td>
<td>Duchenne muscular dystrophy</td>
</tr>
<tr>
<td>Hemostasis</td>
<td>Factor VIII</td>
<td>Hemophilia</td>
</tr>
<tr>
<td>Growth regulation</td>
<td>Rb protein</td>
<td>Hereditary retinoblastoma</td>
</tr>
</tbody>
</table>

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![Diagram of cell and protein synthesis]
Understanding genetic location of LDL mutation is basis for classifying familial hypercholesterolemias.

Cystic fibrosis

- Disorder of ion transport
  - Abnormally viscous secretions in exocrine glands and epithelial lining of respiratory, GI, and reproductive tracts
- 1:20 carriers (Caucasians)
- 1:2,500 live births
- 1,300 disease-associated mutations in CFTR gene
- Mutations rare in nonhuman species
Cystic fibrosis

Single gene disorders with non-classic inheritance

- Expanding nucleotide repeats
- Typically guanine and cytosine
- Coding or non-coding regions:
  - Coding regions: CAG repeats = polyglutamine tracts in proteins ("polyglutamine diseases")
  - Non-coding regions: loss of function
- 40 human diseases, including fragile X syndrome and Huntington disease
- Large number of repeats = greater chance of symptoms at earlier age
- As disease passed generationally, evident at younger ages

Huntington disease

- Toxin form of huntingtin
- Loss of neurons in caudate nucleus
- Motor symptoms + motor impairment

<table>
<thead>
<tr>
<th>Repeat count</th>
<th>Classification</th>
<th>Disease status</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;28</td>
<td>Normal</td>
<td>Unaffected</td>
</tr>
<tr>
<td>28–35</td>
<td>Intermediate</td>
<td>Unaffected</td>
</tr>
<tr>
<td>36–40</td>
<td>Reduced penetrance</td>
<td>+/- Affected</td>
</tr>
<tr>
<td>&gt;40</td>
<td>Full penetrance</td>
<td>Affected</td>
</tr>
</tbody>
</table>
Chromosomal rearrangements

- Translocations
- Inversions
- Deletions
- Duplication
- Ring chromosomes

Chromosomal defects in animals

- Poorly characterized in cattle and horses
- Most commonly:
  - Translocation/deletions
  - Excessive chromosomes (e.g., trisomy)
- Less common than in people?
- Estimated at 11% of aborted and stillborn calves

Consequences of Down syndrome

- Cardiac malformations
- Atresia of bowel and esophagus
- XXS – 20 increase in leukemia risk
- Alzheimer’s >40 years
- Susceptibility to infection
Embryo and fetus are special

- The fetus is allogenic yet:
  - Immune system does not attack dam
  - Dam’s immune system does not attack fetus
- Dependence on temporary organ
  - Placenta – analogies to neoplastic tissue
- Fetus in sterile environment (no flora)
- Immunological immaturity:
  - Death, illness, malformation caused by agents with minimal effect on dam but severe effects on fetus
- Organs specialized for in utero environment
  - Lungs
  - Digestive system
  - Urinary system
  - Blood and platelets
  - Heart

Immune-mediated disease in fetus

Abortogenic infectious agents common to multiple species

- Toxoplasma gondii
- Neospora caninum
- Brucella spp.
- Campylobacter spp.
- Chlamydophila abortus
- Coxiiella burnetii
- Leptospira interrogans
- Listeria monocytogenes
- Mycoplasma/ureaplasma
- Salmonella spp.
- Herpesviruses
Some terms

- Domestic animal (ox; horse)
  - Fetal resorption: < 35 days
  - Abortion: Death before fetus viable
  - Stillbirth: Death after fetus viable

- Human
  - Fetal resorption
  - Abortion (miscarriage):
    - < 20 weeks gestation
  - Stillbirth:
    - Early: 20 – 27 weeks
    - Late: 27 – 36
    - Term: 37 – 40

Stillbirth rate: 1/100–200 live births
Unexplained stillbirth: 50%
Non-infectious causes of perinatal death

- Twinning
- Umbilical cord abnormalities:
  - Excessively long or short
  - Torsion
- Inadequate villous development:
  - Endometrial fibrosis
  - Premature placental separation

Prematurity

- ~12% of all human births
- Major causes:
  - Premature rupture of placental membranes
  - Intrauterine infections
  - Twin pregnancy
  - Abnormalities of reproductive tract