Genetic Disorders

• Chromosomes are thread-like structures located inside the nucleus of animal and plant cells.

• Each chromosome is made of protein and a single molecule of deoxyribonucleic acid (DNA).

• Passed from parents to offspring, DNA contains the specific instructions that make each type of living creature unique.

What is a karyotype?

A. A karyotype is the functional unit of heredity
B. A karyotype is the gene’s observable characteristic in an individual
C. A karyotype is the degree to which an inherited trait is expressed in an individual
D. A karyotype is a picture of an individual’s chromosomes that can be used to look for specific traits or abnormalities
Mendelian Inheritance Patterns

Trait carried on the autosome

**Autosomal recessive** - 2 changed copies of a gene are inherited
- Both parents are carriers
- Not seen in every generation
- Disease examples: Tay-Sachs, sickle-cell, cystic fibrosis, PKU

- If both parents are carriers
  - Each child has a 1 in 4 chance of inheriting the 2 changed genes
  - Each child has a 1 in 2 chance of inheriting 1 a changed gene
  - Each child has a 1 in 4 chance of inheriting 2 normal genes

- If only one parent is a carrier there is a 1 in 2 chance of that child becoming a carrier

**Autosomal dominant** – 1 copy of the gene
- One parent is affected
- Seen in every generation
- Disease examples: achondroplasia, neurofibromatosis

**Disease carried on the sex chromosome**

**X-linked recessive**
- Males more affected
- One appears in every generation: females as carriers, males affected**
- Examples: Hemophilia A, Duchenne’s Muscular Dystrophy

**X-linked dominant (rare)**
- Females may be more affected
- Can have affected males and females in same generation
- Examples: hypophosphatemic rickets
Mendelian Inheritance Patterns

A baby has been diagnosed with a genetic disorder. The mother does not have the disorder but her brother does. What should the mother know about this disorder?

A. This is an x-linked recessive disorder  
B. This is an x-linked dominant disorder  
C. This is an autosomal recessive disorder  
D. This is an autosomal dominant disorder

Which of the following is true of an autosomal recessive disorder?

A. There is a 25% chance of offspring having the disorder  
B. There is a 50% chance of offspring having the disorder  
C. Only male offspring are affected  
D. Only female offspring are affected

Chromosomal Anomalies

This disorder is characterized by triangular face, ptosis, low set malformed ears, prominent occiput, overlapping fingers and rocker bottom feet

A. Trisomy 13  
B. Trisomy 18  
C. 22q deletion  
D. Cornelia de Lange
You are admitting a baby with the following features: macroglossia, omphalocele, and hypoglycemia. What is the likely diagnosis?

A. VATER syndrome  
B. Turner syndrome  
C. Beckwith-Wiedemann syndrome  
D. Cardio Velo facial syndrome

Which of the following is NOT a feature of Trisomy 21?

A. Brushfield's spots  
B. Rocker bottom feet  
C. Hypotonia  
D. Upslanted palpebral fissures
Brushfields spots

Chromosomal Anomalies:
22q11 Deletion Syndrome (DiGeorge, Velocardiofacial Syndrome)
- Caused by missing segment on long arm of chromosome 22
- CHD (Tet, VSD, IAA)
- Cleft lip or palate
- Hypocalcemia due to hypoparathyroidism
- Microcephaly, hooded eyelids, small mouth and chin
- Small or absent thymus = recurrent infections
- Developmental delay

Chromosomal Anomalies: Turner’s Syndrome
- Missing arm or complete deletion of X chromosome (45X)
- CHD (CoAo and bicuspid aortic valve)
- Shield chest, wide spaced nipples
- Webbed neck
- Edema hands and feet
- Short 4th and 5th metacarpals and metatarsals
- Increased incidence of hip dysplasia
Chromosomal Anomalies

Blue sclera are one of the physical findings in this genetic disorder
A. Trisomy 21
B. Trisomy 13
C. Osteogenesis imperfecta
D. Prader-Willi syndrome

DNA is the chemical information database that carries the complete set of instructions for the cell as to the nature of the proteins produced by it, its life span, maturity, function and death.

Genes are the working subunits of DNA. Each gene contains a particular set of instructions, usually coding for a particular protein or for a particular function.

Karyotype

The benefits of karyotyping are:
1. It can view the entire genome.
2. It can visualize individual cells and individual chromosomes.

The limits of karyotyping are:
1. Resolution limited to around 5 Mb.
2. An actively growing source of cells is required. It is important to note that classic karyotyping is timeconsuming, with the preparation of cells for examination taking several days. In addition, live lymphocytes are required so blood samples need to arrive at the laboratory within a maximum of 48 hours after sampling, preferably sooner.
FISH - Fluorescence in situ hybridisation

The benefits of FISH are:
1. It can turn almost any DNA into a probe.
2. A much higher resolution compared to G-banding for identifying deletions, insertions, and translocation breakpoints.
3. It can use cells in any stage of the cell cycle as well as archived tissue.
4. It can analyze results on a cell-by-cell basis.
5. Shorter turnaround times, as tissue does not need to be cultured for metaphase cell.

SNP - Single nucleotide polymorphism array

A single nucleotide polymorphism (SNP), a variation at a single site in DNA, is the most frequent type of variation in the genome.

The chief advantages of SNP array is:
1. It can determine both CNVs and LOH (loss of heterozygosity i.e.: loss of genetic material of one of the two parents)
2. It can detect aneuploidies like triploidies, which represent approximately 5% of chromosomal abnormalities responsible for miscarriages.

CNVs – Copy number variations
LOH – Loss of heterozygosity
SNP - Single nucleotide polymorphism array

Diagnostic yield

- A Karyotype is like looking at a book
- A FISH is like looking a chapter in that book
- A SNP Array is like looking at a sentence in that chapter

Understanding Twins

- Di/Di
- Mono/Di
- Mono/Mono
Twins

- About 1 in 90 spontaneous human births (1.1%) result from a twin pregnancy.
- Twins account for about 1% of all spontaneous pregnancies, but up to 35% of IVF pregnancies are twins.
- The incidence of spontaneous twin pregnancies depends on the mother’s ethnicity.
- With fertility treatments and IVF, the number of twin births can increase significantly as high as 1 in 3 pregnancies. 1 in 50 people is a fraternal twin in the USA, and 1 in 150 is an identical twin. 1/3 of all twins born in the United States are identical, but in Japan, the figure rises to 2/3.

Dizygotic Twins

- Monozygotic Twins (dichorionic or monochorionic)
- Polar Body Twins

Dizygotic twins - Fraternal

- Result from the fertilization of two different eggs with two different sperms.
- They are genetically like siblings, sharing about 50% of the genes.
- Each fetus lies within its own two membranes (chorion and amnion) and they do not share blood vessels.
- All dizygotic twins have two membranes each (dichorionic-dizygotic) and two placentas, though occasionally the placentas attach.
Monozygotic twins - Identical

- Result from the fertilization of one egg and one sperm.
- The fertilized embryo then splits within days after fertilization resulting in two individuals which usually share the same chromosomes.
- They are genetically identical sharing about 100% of the genes. Depending on when the fertilized egg splits, you can have either different sacs (dichorionic/diamniotic), the same outer sac and two inner sacs (monochorionic/diamniotic), or they are within the same 2 sacs (monochorionic/monoamniotic).

Mono/Di

- Split between 3-8 days after fertilization:
  - If the cells divide between 3 and 8 days they are monochorionic/diamniotic.
  - This can be dangerous because they share a placenta and blood vessels.
**Mono/Mono**

**Split between 8-13 days after fertilization:**

- When the cells divide between 8 and 13 days, they are in one sac monochorionic/monoamniotic.
- This is dangerous because cords can become entangled.

**Mono/Mono**

- Split after 13 days after fertilization:
  - If the division happens after day 13, they are all in the same sacs and conjoined twins can happen.
Polar Body
• Result from one egg fertilized by two different sperm.
• This is very rare
• Polar body twinning would result in "half-identical" twins.

Morula cleavage before 3-4 days
Blastocyst cleavage 4-8 days
Implanted blastocyst cleavage 8-13 days
Formed embryonic disc cleavage 13 – 15 days

Twin Gestations
Metabolic/Endocrine

Calcium
It's job: maintains cell membrane permeability, muscle contraction; nerve conduction; clotting; skeletal development. Regulated by parathyroid hormone.
- Total Ca 8.5-10.2 mg/dL
- Ionized Ca greater than 1.2 mg/dL
- Hypocalcemia
  - Why? Inadequate stores/intake, inability to mobilize, stress, IDM, asphyxia
  - Sx: none, jitteriness, twitching, severe: neonatal tetany is rare
  - Tx: usually resolves, if not calcium boluses/infusions
- Hypercalcemia
  - Why? Over tx; excessive maternal VitD, SQFN, hyperparathyroidism
  - Sx: hypotonia, weakness, bradycardia, constipation,
  - Tx: hydration, restrict Ca and Vit D, increase phosphorus

Magnesium
It's job: cellular enzymatic activity, muscle contraction, CHO metabolism
- Normal levels: 1.5-2.5 mg/dL
- Hypomagnesemia
  - Why? Decreased supply, increased losses, neo-hypoparathyroidism, mat hyperparathyroidism
  - Sx: tremors, irritability, hyperreflexia; seizures
  - Tx: administration of magnesium sulfate
- Hypermagnesemia
  - Why? Excessive load (maternal Mg), inadequate secretion
  - Sx: respiratory depression, apnea, lethargy, GI hypomotility
  - Tx: Prepare to resuscitate baby exposed to Mg, increase hydration, usually self resolves
Phosphorus

It's job:
• Normal levels: 6-11 mg/dL
• Hypophosphatemia
  • Why? Hyperglycemia, alkalosis, hypercalcemia, hypophosphatemia
  • Sx: rickets, fractures
  • Tx: supplements in PN and enteral feeds (HMF)
• Hyperphosphatemia
  • Why?
  • Sx: rare, renal failure
  • Tx: stop supplementation

Metabolic Bone Disease

Why?
• Prematurity greatest factor
• Inadequate Ca and P intake
• Unsupplemented human milk
• Fluid restriction with diuretic use (BPD patients)
Sx: asymptomatic, bone fx on xrays, late onset resp distress, pain
Tx: maintain Ca and P ratios, use supplementation for MBM, use preterm formulas, gentle handling

Glucose

It's job: Cellular metabolism/energy
• Normal levels 70-100 mg dL
• Hypoglycemia
  • Why? Inadequate stores, hyperinsulinemia, increased utilization, inborn errors
  • Sx: none, jitteriness, tremors, apnea, seizures
  • Tx: identify babies at risk, screen, feed, gel, IV infusion, hormonal therapy
• Hyperglycemia >120-150 mg/dL
  • Why? Low birth weight, excessive glucose load, med side effects, stress
  • Sx: glycosuria, dehydration; weight loss, fever, ketosis
  • Tx: screen, decrease load, enteral feeds, insulin for ELBW
Glucose Homeostasis

- **Fetal**
  - Fetus sees 70-80% of maternal glucose levels
  - Fetal pancreas starts secreting insulin around 9 weeks gestation
  - Fetus begins to store glucose mostly toward end of 3rd trimester
  - Capable of gluconeogenesis

- **Neonatal**
  - Nadir at 1-2 hours after birth
  - Utilizes lactate after delivery for brain energy
  - Mobilizes glucose from tissues using catecholamines and glucagon

Hypoglycemia

**High risk groups**
- Inadequate glycogen stores and decreased glucose production
- Hyperinsulinemia
- ALL sick babies
  - Metabolic acidosis/increased energy demands
  - ↑ work of breathing, thermal regulation, etc
  - Lack of excess oxygen for conversion

Signs and Symptoms of Hypoglycemia

- Abnormal cry
- Apnea
- Cyanosis
- Feeding Difficulty
- Grunting, Tachypnea
- Hypothermia
- Hypotonia
- Irritability
- Jitteriness, tremors
- Lethargy
- Seizures
- Diaphoresis
- Tachycardia
- NO SYMPTOMS
Infant of the Diabetic Mother

Effects of Maternal Hyperglycemia on the Fetus

Barnes-Powell, 2007

Fetal Hyperinsulinemic State

Barnes-Powell, 2007
Metabolic Disorders: Amino Acid Metabolism

- PKU
  - Autosomal recessive trait
  - Why? Inborn error of amino acid metabolism, deficient phenylalanine hydroxylase, cannot convert phenylalanine to tyrosine.
  - Sx: vomiting, poor feeding, irritability
  - Tx: Lifelong low protein diet, phenylalanine free formula

Metabolic Disorders: Amino Acid Metabolism

- Maple syrup urine disease
  - Autosomal recessive trait
  - Why? Distinctive sweet odor of affected infants' urine
  - Why? branched-chain ketoacid dehydrogenase deficiency resulting in branched-chain ketoaciduria
  - Sx: poor feeding, vomiting, lack of energy (lethargy), abnormal movements, and delayed development. If untreated, maple syrup urine disease can lead to seizures, coma, and death.
  - Tx: a specialized diet. However, even with treatment, both affected children and adults are at high risk for developing episodes of acute illness (metabolic crises) often triggered by infection, injury, failure to eat (fasting), or psychological stress. During these episodes there is a rapid, sudden spike in amino acid levels necessitating immediate medical intervention.
Metabolic Disorders: Errors of Carbohydrate Metabolism

• Galactosemia
• Why?
  - Deficiency of GALT (galactose 1-phosphate uridyltransferase)
  - Galactose metabolic pathway responsible for breaking down galactose to glucose
  - Babies unable to metabolize lactose
  - Autosomal recessive
• Sx: vomiting, diarrhea, FTT, hepatomegaly, hypoglycemia, jaundice; speech delay, developmental delay
• Tx: lactose-free diet for life

Fluids and Electrolytes

Fluid Changes After Delivery

Total body water (TBW)
• Term baby 75%
• Preterm baby 90%

Diuresis after birth
• Term babies should lose 5-10% of birthweight
• Preterm babies lose 10-15% of birthweight
Urine Output: Neonatal Period

- UOP 1-4 mL/kg/hr
- Highest in fluid recovery phase

Sensible and Insensible Water Loss

**Sensible water loss** (can be measured):
- Urine, stool, gastric contents, chest drain etc

**Insensible water loss** (IWL) (cannot be accurately measured):
- Loss via skin = 2/3
- Loss via respiratory tract = 1/3

Factors that increase IWL: prematurity, radiant warmers, fever, photokx, abdominal wall or neural tube defects, low humidity

Potassium

**Normal levels**

<table>
<thead>
<tr>
<th></th>
<th>Premature</th>
<th>Newborn</th>
<th>Infant</th>
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<tr>
<td>mEq/L</td>
<td>4.0-4.5</td>
<td>3.7-5.5</td>
<td>4.1-5.3</td>
</tr>
<tr>
<td>mmol/L</td>
<td>4.0-4.5</td>
<td>3.7-5.5</td>
<td>4.1-5.3</td>
</tr>
</tbody>
</table>

**Job**: Chief intracellular cation; nerve, muscle and BP function; electrolyte function

- **Hypokalemia**
  - How? Chronic diuretic use (Lasix); GI losses
  - Sx: arrhythmias; ileus; lethargy
  - Tx: switch to potassium sparing diuretics (Aldactone); K replacement

- **Hyperkalemia**
  - How? Hemolyzed sample; excessive supplementation; transcellular shift; decreased K secretion by kidneys; metabolic acidosis; old PRBCs
  - Sx: arrhythmias; wide QRS; peaked T waves
  - Tx: decrease/stop supplementation; Kayexalate; insulin gtt; correct acidosis
Sodium
- Normal 130-145 mEq/L
- Job: Chief extracellular cation
- Hyponatremia
  - How?: Diuretic use; fluid overload; excessive sodium losses; methylxanthines
  - Sx: Twitching; irritability; seizures; apnea; no symptoms
  - Tx: fluid restriction; increase supplemental sodium DOL 2
- Hypernatremia
  - How?: Excessive losses without adequate intake (dehydration); IWL esp preterm via skin and resp tract; poor feeding; too much in fluids
  - Sx: Lethargy; hyperreflexia; seizures; ICH
  - Tx: Improve enteral intake; increase total fluids; humidity

Quiz
Name four ways to reduce TEWL in the ELBW baby:
1. 
2. 
3. 
4. 

Dehydration
Causes
- Insensible water loss extreme prematurity
- Acute blood loss
- Diarrhea; GI losses
- DI
- Open surgery; open defects (gastrochisis, myelomingocele)
- Inadequate enteral intake
- Meds causing fluid loss (caffeine, theophylline)
Overhydration

Causes
• Too much fluid
• Edema secondary to low oncotic pressure and illness
• Paralysis
• SIADH
• Asphyxia; sepsis

Symptoms
• Weight gain
• Edema
• Symptomatic PDA

Nutrition and Feeding: for self-study

• Nutritional requirements
  • Calories
  • Carbohydrates
  • Fat
  • Minerals
  • Protein
  • Vitamins

Nutrition and Feeding: for Self-Study

Enteral feedings
• Gut stim/minimal enteral feeds
• Breastfeeding
• Bottle feeding
• Dietary supplements
Parenteral therapy
• TPN