Why is it important to recognize congenital anomalies during the neonatal period?

- 2-3% all live births have at least one congenital anomaly.
- Congenital disorders contribute to 2/3 admissions to children’s hospitals
- Early identification helps focus resources for providing better care
- 0.6% of newborns have chromosomal anomalies and 66% not picked up on physical exam at birth.
- Genetic counseling for future children
Some Basics...

Congenital: present at birth
Genetic: determined by genes
Anomaly: structural defect, deviation from the norm

**Major anomaly:** requires surgical or cosmetic intervention
* 2-3% of neonates

**Minor anomaly:** no significant surgical or cosmetic importance
* 13% of newborns with 1 minor malformation
* 0.8% with 2 minor malformations

Normal Morphogenesis:

- Proper cell migration
- Control over cellular mitotic rate
- Appropriate interaction between adjacent tissues
- Aggregation of similar cell types
- Controlled cell death
- Normal hormonal influence
- Appropriate mechanical factors
Useful Approach to Etiology of Congenital Anomaly:

• **Malformation**: Primary structural defect in tissue formation, usually due to abnormal development (Morphogenesis)
  - Renal agenesis, micrognathia, cleft palate

• **Deformation**: abnormal mechanical forces, usually due intrauterine constraint, acting on normally developing tissues. Late gestation and often reversible.
  - Clubbed feet, altered head shape, Crainiosynostosis

• **Disruption**: interruption of development in intrinsically normal tissue, usually affects a body part rather than an organ.
  - Vascular occlusion/interruption (Cocaine exposure) and amniotic bands.

• **Dysplasia**: Abnormal organization of cellular formation into tissue; deregulation.
  - Hemangiomas, ectodermal dysplasia

Epidemiology and Etiology

• **Unknown**: (Most common) 40-45%
• **Environmental**
• **Genetic**:
  - Mitochondrial
  - Single gene
  - Chromosomal abnormalities
  - 86% congenital malformations isolated and multifactorial inheritance. (i.e.: CHD, Neural tube defects, cleft lip/palate, clubfoot and congenital hip dysplasia)
• **Multifactorial**: (Both Genetic and Environmental)
Sequences, Syndromes and Associations...Huh?

- **Isolated disruptions** = malformations that are sporadic, but can predispose to other deformations
  - Renal agenesis and neural tube defects

- **Sequence**: Pattern of multiple anomalies derived from single known cause.
  - Oligohydramnios sequence = Potter syndrome (limb deformations, simple ears, beaked nose, infraorbital creases and pulmonary hypoplasia).

- **Association**: non-random occurrence of multiple malformations for which no specific or common etiology has been identified. VACTERL

- **Syndrome**: A group of symptoms or signs of disordered function related to one another by means of some anatomic, physiologic or biochemical peculiarity.

Teratogens:

- Anything external to fetus that causes a structural or functional disability postnatally.
- Can be drugs, chemicals, altered metabolism of mother, infectious agents, mechanical forces.
- Only 5 to 10% of congenital anomalies
- Patterns due to exposure at developmental phase 2-12 weeks gestation
- Not all exposed infants affected, but genetic susceptibility also plays role.
  - Alcohol
  - IDM
  - Anticonvulsants
  - TORCH
Genetic Etiologies

- 0.2% of newborns have a chromosomal disorder
- 10% of newborns with major malformation have chromosomal disorder

Mendelian (single gene)
- Responsible for 20% major malformations (0.4% newborns).
- Mostly autosomal dominant, minority are recessive and rarely are x-linked.
- Variation in inheritance pattern due to new mutations, mosiacism, reduced penetrance, variable expression, genomic imprinting, expansion of trinucleotide repeats

Genetic Etiologies

- Chromosomal maldistribution:
  - Error in assortment, usually due to nondisjunction
  - Aneuploidy (abnormal #), polyploidy (extra) or monosomy (decreased).
- Chromosomal rearrangements
  - Deletions/Microdeletions (DiGeorge, Prader Willi)
  - Duplication
  - Mutation (Point mutation in CF)
  - Translocation: balanced, Robersonian (lost short arm of chromosome 13, 14, 15, 21, 22), inversion, isochromosome (two long arms or two short arms) and ring chromosome (monosomy)
What are the most prevalent chromosomal syndromes?

Down syndrome
Followed by Trisomy 13 and 18
Klinefelter syndrome
(1:1000 male births)
Turner syndrome
(1:5000 female birth)

What is Mendelian Genetics again?

- **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
Mendelian Inheritance Patterns

Trait carried on the autosome

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

Mendelian Inheritance Patterns

• Disease carried on the sex chromosome (allosome)
• **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
Fetal Screening:

**Alpha-Fetoprotein (AFP)**

- AFP produced by fetal yolk sac in early gestation, then later by liver and GI.
- AFP passes from fetal serum to fetal urine to amniotic fluid, catabolized by the GI tract.
- AFP can cross the placenta into maternal circulation.
- AFP requires precise GA of fetus at time of measurement.

**AFP Test results...**

- **High AFP (>2-2.5)**
  - Neurologic: Neural tube defects
  - GI: Liver necrosis, Esophageal or intestinal obstruction, gastroschisis, omphalocele.
  - Renal: Urinary obstruction, PKD, renal aplasia, cloacal extrophy.
  - Masses: Pilonidal cyst, cystic hygroma, sacrococcygeal teratoma.
  - Other: IUGR, oligohydramnios, multiple gestation, wrong EGA, OI, placental chorioangioma.

- **Low AFP (<0.6)**
  - Genetic trisomies
  - Fetal death, increased maternal weight, overestimated GA, gestational trophoblastic disease.
The “Triple Screen”

- Performed 15-20 weeks (16 weeks optimal)
  - AFP: least sensitive
  - Unconjugated estriol (uE₃): produced by placenta from precursors provided by fetal adrenal glands and liver
  - β-hCG: most sensitive for trisomy 21
  - Inhibin A: 4th serum marker. Heterodimeric glycoprotein secreted mainly from the corpus luteum and placenta that is elevated in pregnancies affected with Down Syndrome

Trisomy 21: Low AFP, high β-hCG, low uE₃
  - Triple screen detection rate 60%
  - High false-positive (5%) that increases with maternal age

Trisomy 18: low AFP, low β-hCG, low uE₃

Trisomy 13: Not helpful

Genetic Testing

- Amniocentesis: Routine cytogenetics
- CVS
- PUBS
- Not all deletions detectable by routine cytogenetics
  - FISH (Fluorescence in Situ Hybridization uses fluorescently labeled DNA probes) to detect microdeletions
    - Prader-Willi (Long arm 15), Miller Dieker (Short arm 17), Williams (Long arm 7) and Velocardiofacial/DiGeorge (Long arm 22)
First Trimester Screening

- Pregnancy-associated plasma protein (PAPP-A), free hCG and ultrasound for nuchal translucency
  - Combine detection rate 85%
  - False positive rate 3.5%
- PAPP-A decreases by ½ in Trisomy 21
- Free hCG doubled in Down Syndrome
- Nuchal translucency thickness at 10-13 weeks identifies 75% of Trisomy 21 cases.

Amniocentesis vs. CVS

<table>
<thead>
<tr>
<th>Amniocentesis</th>
<th>Chorionic Villus Sampling (CVS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 15-20 weeks gestation,</td>
<td>• 10-13 weeks gestation</td>
</tr>
<tr>
<td>• Modified early amniocentesis at 11-14 weeks</td>
<td>• Biopsy of chorionic villi with US guidance</td>
</tr>
<tr>
<td>• 20-30 cc amniotic fluid using 20-22 gauge spinal needle</td>
<td>• transcervical</td>
</tr>
<tr>
<td>• Chromosomal analysis of desquamated fetal cells</td>
<td>• transabdominal</td>
</tr>
<tr>
<td>• Fetal loss rate 0.5% above baseline (1/200)</td>
<td>• Chromosomal analysis of trophoblast cells</td>
</tr>
<tr>
<td></td>
<td>• Fetal loss rate 1 % above amniocentesis</td>
</tr>
<tr>
<td></td>
<td>• high if transcervical</td>
</tr>
</tbody>
</table>
Amniocentesis vs. CVS

<table>
<thead>
<tr>
<th>Amniocentesis</th>
<th>Chorionic Villus Sampling (CVS)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages:</strong></td>
<td><strong>Advantages:</strong></td>
</tr>
<tr>
<td>• Safer than CVS</td>
<td>• Earliest prenatal diagnosis desirable if termination being considered</td>
</tr>
<tr>
<td>• Less likelihood of severe fetal injury</td>
<td></td>
</tr>
<tr>
<td>• Less expensive, more available</td>
<td>• Increased risk for infection</td>
</tr>
<tr>
<td>• Measures AFP in amniotic fluid</td>
<td>• Increased risk of PROM and placental disruption</td>
</tr>
<tr>
<td>• Acetylcholinesterase (high in neural tube defects)</td>
<td>• Increased risk of limb abnormalities or oromandibular malformations if done &lt; 9 weeks</td>
</tr>
<tr>
<td><strong>Disadvantages:</strong></td>
<td>• Greater contamination of maternal cells</td>
</tr>
<tr>
<td>• 1-2 weeks for chromosomal analysis</td>
<td>• Increased risk of Rh sensitization</td>
</tr>
<tr>
<td>• Increased risk with Rh sensitization</td>
<td>• Doesn’t detect neural tube defects</td>
</tr>
<tr>
<td>• Obtained late in gestation</td>
<td></td>
</tr>
<tr>
<td>• Increased incidence of chorioamnionitis, positional foot deformities and ROM</td>
<td></td>
</tr>
<tr>
<td>• 1-2% have spotting or leakage</td>
<td></td>
</tr>
</tbody>
</table>

New Testing Technology: NIPT

- Maternal blood sample taken to test for free fetal DNA from placenta
- NIPT is most often used to look for chromosomal disorders that are caused by the presence of an extra or missing copy (aneuploidy) of a chromosome
- Primarily used to screen for trisomies (21, 18, 13) and extra or missing copies of the X and Y chromosome
- May inadvertently pick up maternal mutations
The Dreaded... Advanced Maternal and Paternal Age

**Advanced Maternal Age:**
- Klinefelter syndrome
- Trisomy 13
- Trisomy 18
- Trisomy 21

**Advanced Paternal Age:**
- Achondroplasia
- Apert syndrome
- Marfan syndrome
- Treacher Collins Syndrome
- Osteogenesis Imperfecta
- Waardenburg Syndrome

Recurrence Risk

- **Cardiac Defect:**
  - 1 child → 3-4% risk to next child
  - 2 or more kids → 10% risk to next child

- **Cleft lip:**
  - 1 child/normal parents → 4-5% risk
  - 1 child/1 parent → 10% risk

- **Cleft Palate:**
  - 1 child → 2-6% risk to siblings

- **Congenital Hip Dysplasia:**
  - 1 child → 0.5% if next child male, 6.3% if female

- **Club feet:**
  - 1 child/normal parents → 2-5% risk (low if first child male)
  - 1 child/1 parent → 25% risk

- **Neural tube:**
  - 1 child → 3-5% to next child

- **Hirschsprung:**
  - 1 child → 3-5% to next child

- **Pyloric stenosis:**
  - If mother w/ PS → 19% for son, 7% for daughter
  - If father w/ PS → 5.5% for son, 2.4% for daughter
  - If one child w/ PS → 4% if next child male, 2.4% if female

- **Trisomy 21**
  - If mother has balanced translocation → 10-15%
  - If father has balanced translocation → 5%
  - 1 child/no translocation → 1% until risk higher (age 37)
What is her story?

Trisomy 21: Down Syndrome

- 1 in 800 live births
- Majority due to extra maternal chromosome
- 94% complete trisomy
- 3-5% Robertsonian

- Risk at 20 years 1:1667
- Risk at 30 years 1:952
- Risk at 35 years 1:385
- Risk at 40 years 1:106
- Risk at 45 years 1:30
Down Syndrome PE

Facial:
- Upslanting palpebral fissures,
- Small posterior rotated ears,
- Flat facies, brushfield spots,
- Inner epicanthal folds,
- Large tongue,
- Flat maxillary region
- Short neck,
- Redundant posterior folds
- Flat occiput

Cardiac (40-50%) AV canal>VSD>PDA

GI: Duodenal atresia, hirschsprung disease

GU: hypogonadal

Endocrine: hypothyroid

Extremities: Transverse palmar crease
- 5th finger hypoplastic middle phalanx
- Clinodactyly
- Wide gap 1st toe
- Hyperflexible joints
- Broad and short limbs

Neurology: hypotonia, microcephaly

Brushfields spots

(a) (b) (c) (d) (e)

Brushfield spots
Is there a racial difference?

What race are these malformations more common:

1. Mongolian Spots, polydactyly, Umbilical hernias
2. Hypospadius, clubfeet, anencephaly, myelomeningocele
3. Cleft lip and palate

1. African Americans
2. Caucasians
3. Asian

What is wrong?
Trisomy 13: Patau Syndrome

- 1 in 5-10,000 births
- > 90% die within first year
- PE:
  - Midline abnormalities, holoprosencephaly
  - Aplasia Cutis, microcephaly
  - Cleft lip/palate, small eyes/hypotelorism, colobomas (iris), low set malformed ears
  - Cardiac (80-90%): VSD > PDA
  - Umbilical hernia, inguinal hernia
  - Cryptorchidism
  - Polydactyly, transverse palmar crease, hypoconvex narrow fingernails
  - Seizures, hypotonia or hypertonia
What is the differential for this?

Genetic differential for Hypotonia...

- Metabolic: hypothyroidism, Lowe syndrome, canavan disease
- Myotonic distrophy
  - Associated with polyhydramnios, maternal h/o spontaneous abortions, decreased fetal movements, delays in second stage labor, retained placenta
- Trisomy 18, Trisomy 21
- Prader Willi Syndrome
- Angelman Syndrome
- Cri du Chat
- Smith Lemli-Opitz (hypertonia later infancy)
- Menkes syndrome (Kinky hair syndrome)
Prader-Willi and Angelman Syndrome
Similarities: 15q11-13 deletion

**Angelman Syndrome:**
- 20-30% maternal point mutation
- Findings:
  - Protruding tongue, blond hair, deep set eyes, midface hypoplasia
  - Bursts of laughter
  - Severe MR
  - Seizures
  - Hypotonia

**Prader-Willi Syndrome:**
- Always paternal origin deletion
- Variable features based on age
- Neonatal Findings:
  - Small hands and feet
  - Almond shaped palpebral fissures
  - Thin upper lip
  - Hypotonia
  - Failure to thrive
  - Hypogenitalia, undescended testes

---

**Differential Diagnosis?**

What work-up might you anticipate?

*Medical illustrations depicted in the image.*
Noonan Syndrome

- Sporatic in etiology
- Autosomal Dominant with wide variable expression
- Abnormality 12q22
- Turner-like syndrome
- Exam Findings:
  - Short web neck, low posterior hairline, epicanthal folds, hypertelorism, ptosis, lowset ears, low nasal bridge, downslanting palpebral fissures
  - Cardiac (>50%) dysplastic pulmonary valve, ASD, cardiomyopathy
  - Pectus Excavatum, Joint Laxity
  - Cryptorchidism, small penis
  - Increased incidence cystic hygroma, lymphedema, prominent pads of fingers and toes
  - Von Willebrand disease, thrombocytopenia, coagulopathy

Turner Syndrome and Noonan Syndrome

Similarities: Short stature, web neck, cardiac defects, low posterior hairline, broad chest, wide-spaced nipples, edema of the dorsum of hands and feet, cubitus valgus

- Turner Syndrome
  - Females only (45,X)
  - Near-normal IQ
  - Coarctation most common cardiac defect
  - Amenorrhea and sterility

- Noonan Syndrome
  - Both female and male
  - Normal chromosomes
  - Autosomal recessive inheritance
  - Mental deficiency
  - Pulmonary Stenosis most common cardiac defect
  - Normal menstrual cycle in females
Fetal Alcohol Syndrome

Dysmorphic Features of FAS:

• Microcephaly – HC < 5thile
• Small palpebral fissures
• Flat nasal bridge
• Smooth or indistinct philtrum
• Thinned upper lip
• Flattening of mid-face
• Epicanthal folds
• Low set or mildly malformed ears

• Skeletal deformities: deformed ribs and sternum; curved spine; hip dislocations; bent, fused, webbed, or missing fingers or toes; limited movement of joints; small head.

• Organ deformities: heart defects; heart murmurs; genital malformations; kidney and urinary defects.

Fetal Alcohol Syndrome

Possible FAS Symptoms:

• Growth deficiencies: small body size and weight, slower than normal development and failure to catch up.

• Nearsightedness; failure of eyes to move in same direction;

Central nervous system handicaps:

• Small brain; faulty arrangement of brain cells and connective tissue

• Mental retardation – usually mild to moderate but occasionally severe

• Learning disabilities

• Short attention span; irritability in infancy; hyperactivity in childhood

• Poor body, hand, and finger coordination.
Pop Quiz

• Most common inherited form of mental retardation?

• Most common non-inherited form of mental retardation?

• What is the chance that a newborn with a single transverse palmar crease has Trisomy 21?

Answers:

• Most common inherited form of mental retardation?
  • Fragile X

• Most common non-inherited form of mental retardation?
  • Fetal Alcohol Syndrome

• What is the chance that a newborn with a single transverse palmar crease has Trisomy 21?
  • 1 in 60. 4% normal newborns have single crease, 1% have bilateral.
Name this syndrome...

cryochidism
Rocker-bottom feet

Microcephaly, IUGR
Micrognathia
Small mouth
Small eyes

Clenched hand
Hypoplastic nails
Hypertonia

Short sternum
Hypertonia
Low-set ears

corneal opacity
Trisomy 18: Edward Syndrome

- 1 in 6000 births
- 90% mortality in first year
- Females > males (3:1)
- 1/3 premature, 1/3 post dates

Physical Findings:
- Microcephaly, IUGR
- Micrognathia (Pierre-Robin) small mouth, small eyes, corneal opacity, low-set ears, occipital prominence
- Cardiac (95-99%) VSD, PDA > PS, CoA
- Short sternum
- 2VC, cryptorchidism, polycystic kidneys
- Clenched hand, hypoplastic nails, rocker-bottom feet
- Hypertonia

Trisomy 18 / Edwards Syndrome

- Small mouth, small jaw, short neck
- Shield chest, or short and prominent sternum, and wide-set nipples
- Cleft lip or palate
- Hypertonia
Which film is his? What is the diagnosis?

Radiology clues...

- Metaphyseal flaring
- Proximal long bones short (femoral neck)
- Telephone receiver femurs
- U-shaped or cuboidal vertebral bodies
- Punctate calcifications
- Fractures,
- Deformation of limbs,
- Crumpled tibias
- Short ribs
- Undermineralization.
Achondroplasia

• Autosomal Dominant
  • 80-90% new mutations
  • Mutation in transmembrane domain of the fibroblast growth factor receptor 3 gene (4p16.3 locus)

• Radiology:
  • Metaphyseal flaring
  • Proximal long bones short (femoral neck)
  • Telephone receiver femurs
  • U-shaped or cuboidal vertebral bodies
  • Punctate calcifications
  • Cloverleaf skull
  • Thoracic findings help with subtype

Achondroplasia

• Clinical
  • Facial:
    • Depressed nasal bridge
    • Prominent mandible
    • Frontal bossing
  • Neurology:
    • Megaloocephaly
    • Mild hypotonia
    • Small foramen magnum (possible hydrocephalus)
    • Caudal narrowing of spinal cord
  • Endocrine: Relative glucose intolerance
  • Increased risk with increased paternal age
  • Extremities: Trident hands, short limbs
Osteogenesis Imperfecta

- Autosomal dominant
- Defect in type I collagen
- 4 types (overlap types II and III)

Radiographic Findings:
Fractures, Deformation of limbs, Crumpled tibias Warmian bones, Undermineralization, Flat vertebrae, short ribs Triangular head

Name the syndrome...
Goldenhar Syndrome

Oculo-auriculo-vertebral spectrum  
Unknown Etiology  
1 in 3000 to 5000  
Due to 1st and 2nd brachial arch abnormalities

Findings:
- Malar, maxillary or mandibular hypoplasia  
- Lateral extension of mouth  
- Malformed ears, ear tags and pits  
- Cardiac: VSD>PDA>TOF> CoArc  
- Cervical hemivertebrae or hypoplasia

Clinical: Deafness, MR (13% with IQ<85)

This baby is hypoglycemic...

What other things might he have?
Beckwith Wiedemann Syndrome

Grooves in ear lobes
Hemi-hypertrophy
Risk for Wilms tumor
Hepatoma

What malformations are present?
CHARGE syndrome

Unknown etiology
1 in 10,000 births, sporadic, recurrence rate of 1-2%

Clinical Findings:
- Coloboma (80%, retinal)
- Heart Disease (TOF, DORV, VSD, ASD, PDA, right sided arch)
- Atresia of Choanae (60%)
- Retarded growth (90% post natal)
- Genital hypoplasia (males 75%)
- Ear anomalies/Deafness (90%)
- Other: mild MR (94%), micrognathia, cleft lip/palate, renal anomalies, TE fistula

Associated with DiGeorge sequence, hypocalcemia

Amniotic band syndrome

Malformations associated with multiple stands of amnion that have separated from the chorion → entangle normally developing limbs of fetus.

Sporadic, not genetic

Associated With:
- Simian Creases
- Cleft lip/palate
- Gastrochisis
- Omphalocele
What is the diagnosis?

Pentalogy of Cantrell

**Definition:**

- Two major defects: 
  - *Ectopia cordis* and an *abdominal wall defect*
  - Most commonly an omphalocele
  - Gastrochisis can also be present

- Three other defects:
  - Disruption of the interposing structures:
    - The distal sternum
    - Anterior diaphragm
    - Diaphragmatic pericardium

**Prevalence:** Very rare.
What is the diagnosis?

**Etiology:** Unknown.

**Pathogenesis:** Postulated developmental failure of a segment of the mesoderm between 14 and 18 days after conception.

**Associated anomalies:** Intracardiac anomalies (i.e., tetralogy of Fallot) are the rule.

Others include:
- Cranial and facial anomalies
- Chromosomal abnormalities
- Clubfeet
- Malrotation of the colon
- Hydrocephalus
- Anencephaly

---

**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 11 deletion  
D. Cornelia de Lange
Chromosomal Anomalies

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. Velocardiofacial Syndrome

Chromosomal Anomalies

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
**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 time-consuming, 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 hybridization

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 from a metaphase cell
FISH - Fluorescence in situ hybridisation

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 aneuploïdies like triploïdies, 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.
Di/Di

Split within 3-4 days after fertilization:
When the fertilized egg divides before 3-4 days after fertilization then the twins are dichorionic/diamniotic.
That is the membrane configuration as if the twins were dizygotic except that monozygotic twins have the same genetic composition (DNA), while dizygotic twins share only 50% of DNA.

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.

TTTS / TAPS

TTTS
- Large central artery-to-vein connections

TAPS
- Tiny peripheral artery-to-vein connections
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.

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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