TOPIC 10: GENETIC AND PAEDIATRIC DISEASES

Syllabus Scope: *Cytogenetic abnormalities, Single gene mutations (PKU, CF), and Pediatric Tumors (Wilms, Neuroblastoma).*

I. COMMON CYTOGENETIC ABNORMALITIES

Cytogenetic disorders involve alterations in the number or structure of chromosomes. They may be Autosomal or Sex chromosomal.

A. Down Syndrome (Trisomy 21)

The most common chromosomal disorder and cause of mental retardation.

Pathogenesis (Karyotype):

1. **Meiotic Nondisjunction (95%):** Trisomy 21 (47, XX, +21). Strong association with **Maternal Age** (>45 years). Nondisjunction usually occurs in Meiosis I of the ovum.
2. **Robertsonian Translocation (4%):** Translocation of long arm of Chr 21 to Chr 14 or 22. (Familial Down Syndrome).
3. **Mosaicism (1%):** Mixture of normal and trisomic cells (46,XX / 47,XX,+21). Mild symptoms.

Clinical Features:

- **Face:** Flat facial profile, Oblique palpebral fissures, Epicanthic folds.
- **Hands:** Simian crease (Single transverse palmar crease), short broad hands.
- **Mental Retardation:** IQ 25–50.
- **Congenital Heart Disease:** 40% cases. Most common is Endocardial Cushion Defect (**Ostium Primum ASD**, VSD).
- **Risk of Malignancy:** 10-20x increased risk of Acute Leukemia (ALL and Megakaryocytic AML).
- **Neurology:** Early onset Alzheimer's Disease (>40 years).

B. Klinefelter Syndrome (47, XXY)

- **Definition:** Male hypogonadism occurring when there are two or more X chromosomes and one or more Y chromosomes.
- **Karyotype:** Classical **47, XXY** (82%). Caused by nondisjunction during gametogenesis (maternal or paternal).

- **Clinical Features:**
  - **Hypogonadism:** Small, atrophic testes; Azoospermia (Infertility); Failure of male secondary sexual characteristics.
  - **Hormones:** Low Testosterone, **High FSH and LH**, High Estradiol.
  - **Physical:** Tall stature (eunuchoid habitus), **Gynecomastia** (risk of breast cancer), reduced facial hair.
  - **Mental:** Slight reduction in IQ.

C. Turner Syndrome (45, X)

- **Definition:** Complete or partial monosomy of the X chromosome in a phenotypic female.
- **Karyotype:** **45, X** (57%). (Most common cause of primary amenorrhea).
- **Clinical Features:**
  - **Short stature** (Shortest females).
  - **Neck:** Webbing of neck (`Cystic Hygroma` remnants).
  - **Chest:** Shield-like chest with widely spaced nipples.
  - **Genitalia:** "Streak Ovaries" (fibrous stroma, no follicles) → Primary Amenorrhea & Infertility.
  - **Cardiovascular:** **Coarctation of Aorta** (Preductal).

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2. MUTATIONS IN CHILDHOOD (SINGLE GENE DISORDERS)

Common Mendelian disorders manifesting in childhood.

A. Phenylketonuria (PKU)

- **Genetics:** Autosomal Recessive. Deficiency of hepatic enzyme **Phenylalanine Hydroxylase (PAH)**.
- **Pathogenesis:** Inability to convert Phenylalanine (Phe) to Tyrosine.
  → Accumulation of Phenylalanine (neurotoxic) and Phenylpyruvic acid (excreted in urine/sweat).
  → Lack of Tyrosine leads to reduced Melanin.

- **Clinical Features:**
  - Severe **Mental Retardation** (if untreated).
  - Seizures.
  - **Pigmentation:** Fair skin, blond hair, blue eyes (hypopigmentation).
  - **Odor:** "Mousy" or "Musty" odor of urine/sweat.
- **Treatment:** Phenylalanine-free diet restricted early in life.

B. Cystic Fibrosis (Mucoviscidosis)

- **Genetics:** Autosomal Recessive. Mutation in **CFTR Gene** (Chr 7q31). Most common mutation: **ΔF508**.
- **Pathogenesis:** Defective Cl^- channel protein → Impermeable to Chloride → Na^+ and H_2O reabsorption increases → Dehydrated, thick, viscous mucus secretions.
- **Morphology & Effects:**
  - **Lungs:** Thick mucus blocks airways → Recurrent infections (*Pseudomonas*), Bronchiectasis, Lung abscess.
  - **Pancreas:** Plugged ducts → Atrophy & fibrosis → Malabsorption (Steatorrhea) and Vitamin deficiency.
  - **Sweat Glands:** High Salt content in sweat (**Salty baby syndrome**).
  - **Gut:** Meconium Ileus in newborns.

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3. TUMOR AND TUMOR-LIKE CONDITIONS

A. Tumor-Like Lesions (Benign)

1. **Hamartoma:** A focal, disorganized overgrowth of tissue elements *indigenous* (native) to the site.
   - *Example:* Pulmonary Hamartoma (cartilage + bronchial epithelium in lung).
2. **Choristoma (Heterotopia):** Mass of histologically normal tissue in an *abnormal* location.
   - *Example:* Pancreatic tissue rest in stomach wall or Meckel's diverticulum.

3. **Hemangioma:** Most common tumor of infancy.
    - *Capillary Hemangioma:* "Strawberry Nevus". Appears at birth, grows rapidly, then regresses spontaneously (fades by age 7).
    - *Cavernous Hemangioma:* Large, deep vascular channels. Associated with von Hippel-Lindau disease.
4. **Lymphangioma:** Benign lymphatic tumor.
    - *Cystic Hygroma:* Large cystic mass in neck/axilla of infants. Associated with Turner syndrome.

B. Malignant Tumors of Childhood

Characterized by "Small Round Blue Cells" (Blastemal origin).

1. Wilms Tumor (Nephroblastoma)

Most common primary renal tumor in children (2-5 years).

Pathogenesis:
Mutation in **WT1 gene** (Chr 11p13). Arises from Nephrogenic Rests (persistent blastema).
Associated Syndromes:

- **WAGR Syndrome:** **W**ilms, **A**niridia (no iris), **G**enital anomaly, **R**etardation (Mental).
- **Denys-Drash Syndrome:** Gonadal dysgenesis + Nephropathy.
- **Beckwith-Wiedemann Syndrome:** Hemihypertrophy + Macroglossia (WT2 gene).

Morphology (Triphasic Histology):

1. **Blastemal:** Sheets of small round blue cells.
2. **Epithelial:** Abortive tubules or glomeruli (rosettes).
3. **Stromal:** Fibrocystic or myxoid stroma (sometimes muscle/cartilage).

Clinical: Large palpable abdominal mass (does not cross midline), Hematuria, Hypertension. Excellent prognosis.

2. Neuroblastoma

Most common extracranial solid tumor of childhood. Arises from Neural Crest cells (Adrenal Medulla or Sympathetic Chain).

Pathogenesis:
N-MYC amplification (Chr 2) correlates with poor prognosis.
Partial deletion of Chr 1p.

Morphology:

- **Gross:** Large, soft, hemorrhagic mass in adrenal gland.
- **Microscopy:** Small round blue cells. Homer-Wright Rosettes (cells surrounding a central meshwork of neuropil/fibrils).

Clinical:

- Abdominal mass (crosses midline).
- Metastasis to skin ("Blueberry Muffin Baby") and bones.
- Secretes Catecholamines (VMA/HVA elevated in urine).

3. Retinoblastoma

Most common intraocular tumor in children.

Pathogenesis: Mutation in **RB1 Gene** (Chr 13q14) - Tumor suppressor gene. Follows "Knudson's Two-Hit Hypothesis" (Familial cases are bilateral; Sporadic are unilateral).

Morphology: Flexner-Wintersteiner Rosettes (cells surrounding a true central lumen).

Clinical: **Leukocoria** (White pupillary reflex / Cat's eye reflex).

IMPORTANT UNIVERSITY QUESTIONS

Q1: Classify chromosomal disorders. Describe the clinical features and karyotype of Down Syndrome.

Introduction: Chromosomal disorders are alterations in the number or structure of chromosomes, leading to genetic syndromes. Down syndrome is the most common autosomal trisomy.

Body:
Classification:

- Numerical (Aneuploidy): Trisomy (21, 18, 13), Monosomy (Turner).
- Structural: Translocation, Deletion (Cri-du-chat), Inversion.

Down Syndrome (Trisomy 21):
Karyotype: 47, XX, +21 (95% due to meiotic nondisjunction).
Clinical Features: Flat facial profile, oblique palpebral fissures, epicanthic folds, simian crease, mental retardation, and congenital heart defects (ASD/VSD).

Conclusion: It is strongly associated with advanced maternal age and carries an increased risk of acute leukemia.

Q2: Describe the pathogenesis and morphology of Wilms Tumor.

Introduction: Wilms tumor (Nephroblastoma) is the most common primary malignant renal tumor in children, derived from primitive nephrogenic blastema.

Body:
Pathogenesis: Linked to mutations in the **WT1 gene** on Chromosome 11p13. It is associated with WAGR syndrome (Wilms, Aniridia, Genital anomalies, Retardation) and Denys-Drash syndrome. It arises from nephrogenic rests.
Morphology:

- Gross: Large, solitary, well-circumscribed mass. Cut surface is grey-white and fleshy.

- *Microscopy: Classical **Triphasic pattern** consisting of:*
  1. *Blastema (small round blue cells).*
  2. *Epithelium (abortive tubules/glomeruli).*
  3. *Stroma (fibrous/myxoid spindle cells).*

***Conclusion:** Prognosis is generally excellent with nephrectomy and chemotherapy.*

Q3: Differentiate between Neuroblastoma and Wilms Tumor.

***Introduction:** Both are common pediatric abdominal malignant tumors presenting as masses.*

Body:

Feature	Wilms Tumor	Neuroblastoma
Origin	Kidney (Nephrogenic blastema)	Adrenal Medulla (Neural crest)
Gene	WT1 (Chr 11)	N-MYC (Chr 2)
Microscopy	Triphasic histology	Homer-Wright Rosettes (Neuropil)
Abdominal Mass	Does **not** cross midline	Often **crosses** midline
Urine markers	Hematuria	VMA / HVA elevated (Catecholamines)

***Conclusion:** Differentiation is crucial as Neuroblastoma generally has a worse prognosis if N-MYC amplified.*