Clinical Conditions Summary

Topic 1:

- Osteogenesis Imperfecta: brittle bone disease, is a disorder caused by defects in the formation of bone, leading to fragile bones that break easily.

Genetic Defect	Pathophysiology	Mode of Inheritance
- Mutations in the genes that encode **type I collagen**, which is crucial for bone strength. - 90% of cases are due to mutations in: COL1A1 (on chromosome 17) and COL1A2 (on chromosome 7). These genes encode the pro-α1(I) and pro-α2(I) chains that form the triple helix of type I collagen. **- Mutations often involve:** **1. Missense mutations** replacing glycine with another amino acid in the center of the triple helix structure of type I collagen, causing instability and poorly formed fibrils. **(the most common mutation).** **2. Post-translational modification defects** (e.g. issues with hydroxylation or glycosylation of proline/lysine residues result in unstable collagen fibrils). **3. In rarer types (e.g., type VII, VIII),** mutations affect collagen processing enzymes, not the collagen genes themselves.	- Type I collagen is a structural protein in bone, acting like rebar in concrete. - Mutated collagen leads to: Improper helix formation → weak or unstable collagen fibers → abnormal or insufficient bone matrix → bone fragility. ➢ **Clinical Effects**: **1. Bone Fragility:** Frequent fractures, deformities (e.g., scoliosis), short stature. **2. Extra skeletal Manifestations:** Blue/gray sclerae, dentinogenesis imperfecta, hearing loss. - Severity depends on the type of mutation: Glycine substitution → severe Reduced collagen production → milder. - Type I is mild but Type II is very severe and lethal.	- **Types I – IV**: Mostly **autosomal dominant.** Recurrence Risk: 50% if one parent is affected. - **Types VII – VIII** and other rare types: **Autosomal recessive**. Recurrence Risk: 25% if both parents are carriers.

Topic 2:

- Xeroderma Pigmentosum: A Disease of Faulty DNA Repair

Genetic Defect	Pathophysiology	Mode of Inheritance
- Mutations in any of **the 7 genes** involved in the nucleotide excision repair (NER) pathway, which normally repairs UV-induced DNA damage (e.g., pyrimidine dimers). **- Affected Proteins:** Helicases (unwind DNA), endonucleases (cut damaged DNA), exonucleases (remove damaged bases), polymerases (fill gaps), and ligases (rejoin DNA). - Expression of XP requires inherited germline and somatic mutations.	- Normally, NER fixes UV-induced DNA damage, but in XP, the DNA repair system (nucleotide excision repair (NER)) is broken due to genetic mutations. - Inevitable consequence of UV exposure → DNA damage (pyrimidine dimers) → because of defective NER → Damage isn't repaired → Mutations accumulate → Skin cells turn cancerous. ➢ **Clinical Effects:** **1. Skin Manifestations:** Dry, scaly skin (xeroderma), freckling, abnormal skin pigmentation (pigmentosum), and 1000-fold increased risk of skin cancers by age 10. Primarily in sun-exposed parts of the body. Patients are advised to avoid sources of UV light (e.g., sunlight). **2. Neurological Symptoms** (30% of cases): Neurodegeneration due to unrepaired. **3. Severe, potentially lethal malignancies** can occur before 20 years of age. **4. Cataract.**	**Autosomal Recessive** (meaning both copies of the gene must be defective for the disease to manifest). **- Recurrence risk if both parents are carriers (heterozygous):** 25% affected 50% chance the child will be a carrier 25% chance the child will be unaffected/non-carrier.

Topic 3:

1. Cystic Fibrosis (CF): the most common single-gene disorder in North America.

Genetic Defect	Pathophysiology	Mode of Inheritance
- Caused by **mutations in the CFTR gene.** - Over 2,000 mutations identified; most common is F508del (3-base deletion → loss of phenylalanine). **- Mutations are classified into 6 classes** (e.g., no protein synthesis, defective trafficking, reduced function). **Mutation Class** / **Molecular Defect** **Class I** — No protein synthesis (nonsense/stop mutations) **Class II** — Misfolded protein degraded in proteasomes **Class III** — Channel reaches surface but fails to open **Class IV** — Reduced Cl^- conductance **Class V** — Splicing/promoter defects reduce CFTR mRNA **Class VI** — Accelerated turnover at cell surface	- Normally CFTR encodes cyclic AMP-regulated chloride ion channels that span the membranes of specialized epithelial cells, such as those that line the bowel and lung. In addition, CFTR is involved in regulating the transport of sodium ions across epithelial cell membranes. - Mutations in the CFTR gene → defective ion transport → thick mucus in lungs/pancreas → obstruction, infections (e.g., Pseudomonas), pancreatic insufficiency, and high sweat chloride. ➢ **Clinical effects:** **1. Lungs:** Thick, dehydrated mucus → chronic infections (Pseudomonas, S. aureus) → inflammation → fibrosis and airwy obstruction. **2. Pancreas:** Obstructed ducts → pancreatic insufficiency (malabsorption, diabetes). **3. Sweat Glands:** Cl^- cannot be reabsorbed → salty sweat (diagnostic hallmark). **4. Reproductive Tract:** Absent vas deferens (CBAVD) in males → sterile. **5. Meconium ileus:** thickened obstructive intestinal matter (in 15%-20% of newborns).	**Autosomal recessive** 25% risk of affected child if both parents are carriers.

- The combination of airway obstruction, inflammation, and infection leads to destruction of the airways and lung tissue, resulting eventually in death from pulmonary disease in more than 90% of CSF patients.

- Severe Mutations (e.g., F508del): complete lack of chloride ion channel production or in channels that cannot migrate to the cell membrane. Patients homozygous for these mutations nearly always have pancreatic insufficiency.

- Other mutations (e.g., R117H, a missense mutation) result in ion channels that do proceed to the cell membrane but respond poorly to cyclic AMP and consequently do not remain open as long as they should. The phenotype is thus milder, and patients who have this mutation are less likely to have pancreatic insufficiency.

2. Retinoblastoma: the most common childhood eye tumor.

Genetic Defect	Pathophysiology	Mode of Inheritance
- Mutations in the **RB1** tumor suppressor gene. - "Two-hit" hypothesis: Inherited mutation (1st hit) + somatic mutation (2nd hit) in retinal cells → tumor.	- Normally the RB1 gene produces the pRb protein, a critical regulator of cell division. In its active state, pRb binds to and blocks E2F transcription factors, preventing cells from progressing from G1 to S phase in the cell cycle - essentially acting as a "brake" on cell growth. When cell division is needed, cyclin-dependent kinases phosphorylate pRb, causing it to release E2F and allow controlled cell proliferation. - However, mutations that disable RB1 create a dangerous situation: without functional pRb to restrain E2F, cells lose this vital brake and can divide uncontrollably. This **unchecked cell division in retinal cells leads to tumor formation,** specifically retinoblastoma. - They are also susceptible to other types of cancer later in life. In particular, about 15% of those who inherit an RB1 mutation later develop osteosarcomas (malignant bone tumors). Other common second cancers include soft tissue sarcomas and cutaneous melanomas.	**- 60% sporadic** (somatic mutations only, not transmitted to the affected individual's offsprings). **- 40% inherited (autosomal dominant):** 30% are caused by new mutations, usually from the father and 10% are inherited from a parent who has the mutation. - Offspring risk: 50% if a parent carries RB1 mutation.

TABLE 3-2 **Examples of Diseases That Are Caused by a Defect in DNA Repair**

DISEASE	FEATURES	TYPE OF REPAIR DEFECT
Xeroderma pigmentosum	Skin tumors, photosensitivity, cataracts, neurological abnormalities	Nucleotide excision repair defects, including mutations in helicase and endonuclease genes
Cockayne syndrome	Reduced stature, skeletal abnormalities, optic atrophy, deafness, photosensitivity, mental retardation	Defective repair of UV-induced damage in transcriptionally active DNA; considerable etiological and symptomatic overlap with xeroderma pigmentosum and trichothiodystrophy
Fanconi anemia	Anemia; leukemia susceptibility; limb, kidney, and heart malformations; chromosome instability	As many as eight different genes may be involved, but their exact role in DNA repair is not yet known
Bloom syndrome	Growth deficiency, immunodeficiency, chromosome instability, increased cancer incidence	Mutations in the reqQ helicase family
Werner syndrome	Cataracts, osteoporosis, atherosclerosis, loss of skin elasticity, short stature, diabetes, increased cancer incidence; sometimes described as "premature aging"	Mutations in the reqQ helicase family
Ataxia-telangiectasia	Cerebellar ataxia, telangiectases,* immune deficiency, increased cancer incidence, chromosome instability	Normal gene product is likely to be involved in halting the cell cycle after DNA damage occurs
Hereditary nonpolyposis colorectal cancer	Proximal bowel tumors, increased susceptibility to several other types of cancer	Mutations in any of six DNA mismatch-repair genes

*Telangiectases are vascular lesions caused by the dilatation of small blood vessels. This typically produces discoloration of the skin.

3. Huntington Disease (HD):

Genetic Defect	Pathophysiology	Mode of Inheritance
- CAG repeat expansion located on exon 1 in HTT gene (≥36 repeats = pathogenic). Normal: ≤26 repeats Intermediate: 27-35 Reduced penetrance: 36-39 Full penetrance: ≥40	- Huntington disease is caused by an abnormal CAG trinucleotide repeat expansion in the HTT gene, which encodes the huntingtin protein. - The expanded CAG repeats result in an abnormally long polyglutamine tract in the huntingtin protein. This altered protein forms toxic aggregates inside neurons, particularly in the striatum (a brain region critical for movement control). ➢ **Clinical effects:** **1. Progressive loss of motor control** and **Psychiatric disorders**. **2. Substantial loss of neurons** in the brain, which is detectable by (MRI). **3. Decreased glucose uptake in the brain**, an early sign of the disorder, can be detected by positron-emission tomography (PET). **4. In some patients, the disease leads to a loss of 25% or more of total brain weight.** **5. Patients with HD experience difficulties in swallowing; aspiration pneumonia** is the most common cause of death. **6. Cardiorespiratory failure and subdural hematoma** (due to head trauma) are other frequent causes of death. 7. The suicide rate among HD patients is 5 to 10 times higher than in the general population.	**- Autosomal dominant (50% risk).** - Anticipation (earlier onset in next generations, especially paternal transmission).

4. Marfan Syndrome:

Genetic Defect	Pathophysiology	Mode of Inheritance
1. Mutations **in FBN1 (fibrillin-1).** - **Most are missense mutations** (dominant-negative effect: the abnormal fibrillin proteins bind to and disable many of the normal fibrillin proteins produced by the normal allele). **- Some are frameshift/nonsense mutations** (truncated protein). 2. Rarely, **mutations in TGFBR2** (transforming growth factor β receptor 2) can mimic Marfan syndrome.	- Normally Fibrillin-1 is critical for elastic fiber formation in connective tissues. - Fibrillin-1 Dysfunction→ Mutations disrupt tissue integrity → aortic weakness (risk of dissection), lens dislocation, and bone overgrowth. - Mutant fibrillin fails to bind TGF-β → excessive TGF-β activity → contributes to aortic dilatation and skeletal abnormalities. ➢ **Clinical Effects (Pleiotropy):** **1. Ocular:** Myopia, ectopia lentis (lens dislocation). **2. Skeletal:** Long limbs (dolichostenomelia), arachnodactyly, scoliosis, chest deformities (pectus excavatum ("hollow chest"), pectus carinatum ("pigeon chest")). **3. Cardiovascular:** Aortic root dilatation (life-threatening dissection risk), mitral valve prolapses (cusps of the mitral valve protrude upward into the left atrium during systole).	**- Autosomal Dominant:** One mutated FBN1 allele is sufficient to cause the disorder. - Risk to Offspring: 50% chance of inheriting the mutation if one parent is affected.

Note: FBN2 gene are associated with a related but distinct disorder called Congenital Contractural Arachnodactyly (share arachnodactyly and some skeletal features but lacks the life-threatening cardiovascular and ocular complications of Marfan syndrome).

Topic 4:

1. Hemophilia A: the most common of the severe bleeding disorders.

Genetic Defect	Pathophysiology	Mode of Inheritance
- Gene: **F8** encoding factor VIII. **Mutation Types:** 1. **Chromosome inversion** (45% of severe cases). 2. **Nonsense/frameshift** (severe hemophilia, truncated protein). 3. **Missense** (mild/moderate hemophilia, partially functional protein). **- Many of the point mutations take place at methylated CG sequences, which are hot spots.**	- Deficient factor VIII → impaired clotting cascade → Fibrin formation is affected, resulting in prolonged and often severe bleeding from wounds and hemorrhages in the joints and muscles. ➢ **Clinical effects:** 1. **Bruising is often seen.** 2. **Hemarthroses** (bleeding into the joints) are common in the ankles, knees, hips, and elbows. 3. **These events are often painful, and repeated episodes can lead to destruction of synovium and diminished joint function.** 4. **Intracranial hemorrhages** can occur and are a leading cause of death. 5. **Platelet activity is normal in hemophiliacs**, so minor lacerations and abrasions do not usually lead to excessive bleeding. - <1% activity → Severe → Spontaneous bleeding. - 1-5% → moderate → generally have bleeding episodes only after mild trauma and typically experience one to several episodes per year. - 5% to 30% → mild and usually experience bleeding episodes only after surgery or relatively severe trauma.	- **X-linked recessive**: Males affected and females carriers. - 50% risk for carrier mothers to pass to **sons**. - Manifesting heterozygotes: 10% of female carriers show mild symptoms.

- Hemophilia B (Christmas disease) is also an **X-linked recessive** disorder and is caused by a deficiency of **clotting factor IX**.

- Von Willebrand disease autosomal dominant disorder that is highly variable in expression. The von Willebrand factor, encoded by a gene on chromosome 12, serves as a carrier protein for factor VIII. Additionally, it binds to platelets and damaged blood vessel endothelium, facilitating platelet adhesion to injured vessel walls

2. Duchenne Muscular Dystrophy: progressive weakness and loss of muscle.

Genetic Defect	Pathophysiology	Mode of Inheritance
- Mutation in DMD gene encoding dystrophin protein. - **Mutation Types:** **Deletions** (65% of cases)/**duplications** (6%-7% of cases) → producing frameshift mutations → no dystrophin. - Large gene size (79 exons) → high mutation rate.	- Normally the amino terminus of dystrophin binds to F-actin, an essential cytoskeletal protein, while its carboxyl terminus attaches to a glycoprotein complex called the **dystroglycan–sarcoglycan complex.** This complex spans the cell membrane and connects to extracellular proteins. By linking these two cellular components, **dystrophin plays a critical role in preserving the structural stability of muscle cells.** - Absent dystrophin → muscle membrane instability → progressive muscle cell death. ➢ **Clinical Effects:** 1. Early onset (before age 5). 2. Wheelchair-bound by ~11 years; death by ~25 (cardiorespiratory failure). 3. Pseudohypertrophy (infiltration of the muscle by fat and connective tissue). 4. Cardiomyopathy and respiratory failure. 5. Creatine kinase (CK) is released into the bloodstream. The serum CK levels are at least 20 times higher than the upper limit of the normal range.	**- X-linked recessive:** - Males affected; females usually carriers (8–10% show mild weakness).

3. Becker Muscular Dystrophy (BMD)

- **Genetic Defect:** Same gene as DMD, but **in-frame mutations** (partial dystrophin).
- **Pathophysiology:** Reduced/shortened dystrophin → slower muscle degeneration.
- **Inheritance: X-linked recessive (like DMD).**
- **Clinical Effects:** Milder than DMD: Onset ~11 years, slower progression, some retain mobility and Wheelchair-bound after 12 years.

4. Color Vision Deficiency (Red-Green Colorblindness)

هاد المرض فيه كثير تفاصيل بس حاولت احط اهم النقاط

Genetic Defect	Pathophysiology	Mode of Inheritance
- Mutations in: OPN1LW (long-wavelength/red opsin). OPN1MW (medium-wavelength/green opsin). **-** Both genes are on the X chromosome (distal long arm). - Defects usually due to **unequal crossover during meiosis**, not typical point mutations. - Protanopia (loss of red opsin gene). - Deuteranopia (loss of green opsin gene). **-** Protanomaly and deuteranomaly: hybrid genes produce abnormal opsins with shifted sensitivity.	- The cone cells (red, green, blue) each contain a specific opsin protein. - Opsin defects alter how cones respond to light → Loss of red or green cones → inability to distinguish those colors properly. - Hybrid opsin genes → cones respond abnormally to wavelengths.	**- X-linked recessive** **-** Much more common in males (~8% of European males). - Females can be carriers and rarely show mild symptoms. - Female carriers have a 50% chance of passing the defective gene to sons (who will be affected) and daughters (who may become carriers).

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