* Syndromes & Diseases.

1] Griscelli Syndrome (GS)

- Rare Genetic
- Cause: Problem with transport (Melanosome transport & Fusion)
- MYO5A, RAB27A, MLPH.

~ Symptoms:-

1) Pigmentary dilution of skin.

2) Melanin clumps with hair shaft.

3) Silver-Grey hair.

2] Lysosomal storage diseases.

- Cause: Defective Lysosomal enzymes.

1- Glycolipidoses.

2- Oligosaccharidoses.

3- Mucopolysaccharidoses (GAGs: heparan, keratan and dermatan sulfate, chondroitin sulfate.)

~ Symptoms:-

Chronic progressively Debilitating Disorders, leading to:

1) psychomotor retardation.

2) Premature death.

3] I-Cell disease.

- Mucolipidoses IIA or Mucolipidoses II alpha/B (ML-II α/β)

- Cause: Defective targeting of lysosomal enzymes (Deficiency in tagging enzyme (phosphorylates Mannose))

~ Symptoms:-

1) Severe psychomotor retardation.

↓ Progressing

2) Death (5-8 y.o)

4] Mitochondrial diseases.

Diseases

Genetic

mitochondrial DNA

1- MERRF (Myoclonic epilepsy and ragged Redfiber)

Cause: Mutation in one mt(tRNA) genes.

2- MELAS

3- LHON.
Leber's hereditary optic Neuropathy.

Males (50%) vs. Females (10%)
↓
They transfer it

~ Symptoms:-

1) Blindness ∵ degeneration of optic nerve.

2) ↓ efficiency of OxPhos & ATP Generation

** vision loss occurs between (15-35).

4- NARP.

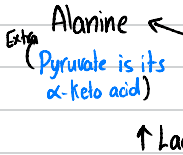
nDNA ⟶ All areas of mt metabolism will be affected.

Biochemical

1- Deficiency of Transport (into mt) - Rare

2- Deficiency of Substrate Utilization.

Ex. pyruvate Dehydrogenase Deficiency.



Pyruvate —PDH→ Acetyl-CoA

-Males are more affected.

~ Symptoms of PDH deficiency:-

1) Metabolic acidosis.

2) ↑ Lactate in blood or CSF.

3) ↑ [Alanine] & [Pyrurate]

3- Defect in Krebs cycle.

Ex. Fumarase Deficiency. (Fumarate ↓ Malate)
- reported in mt encephalopathy.

~ Symptoms:-

- ↑ [Fumarate] in urine (Large amounts)

- ↑ [Succinate] in urine (Lesser extent when compared with Fumarate.)

4- Defect of Respiratory chain.

5- Defect of oxphos.

Ex. Luft's disease (non-thyroidal hyper-metabolism.)

↑ Rate of Respiration (No ADP)
↓
No ATP Production
↓
Energy lost as Heat
↓
Causing
↙ hypermetabolism ↘ hyperthermia

5] Peroxisomal Diseases.

1- Single peroxisomal enzyme deficiencies. (Specific peroxisomal enzymes)

2- Peroxisomal biogenesis disorders. (Multiple peroxisomal enzymes; Mutations of PEX genes)

Ex. Zellwegar syndrome (at least 10 genes)

- lethal

3- X-Linked adrenoleukodystrophy. (XALD) (Defective VLCFA transport.)

- Accumulation of FAs in cells.

6] Nuclear Lamina Diseases (Laminopathies.)

1- Emery-Dreifuss muscular dystrophy)

Causes:- mutations in emerin gene (↓ x-linked) or Lamin A. (↓ autosomal Dominant)

*other Lamin A diseases.

2- Marie-charcot-tooth disease Type 2B1
3- Hutchinson-Gilford Progeria
4- Dunnigan-type partial lipodystrophy.

6] Dystrophin Deficiency.

- (X-linked)
- Inherited
- Progressive muscle diseases.

1- Duchenne muscular dystrophy. (Absent, Severe) - frameshift mutation.

2- Becker muscular dystrophy. (Defective, less severe)

7] kinesines mutations.

- Cause: Mutations in kinesines reducing the ability (of neurons) to move essential organelles from body to axon)

~ Symptoms:-

1) Neurodegeneration.

Ex.
1- amyotrophic lateral sclerosis(ALS) → loss of muscle control
2- Alzheimer's disease (dementia)
3- Marie-Charcot-Tooth disease. (lateral neuropathy)

8) Intermediate filaments diseases.

1- Skin abnormalities in mice.
2- Human epidermolysis bullosa simplex (mutation in keratin gene)
3- amyotrophic lateral sclerosis(ALS)-(Lou Gehrig's disease)

~ Symptoms:-

1) Accumulation of neurofilaments.
2) abnormal assembly of neurofilaments.

9) collagen related diseases.

1- lysyl oxidase mutation.

- Collagens are weak (Reduce Strength)
- Structures tend to tear.

2- Osteogenesis imperfecta [OI]

- Brittle bone disease.
- genetic
- 4 Types (I; mildest, II most severe, III & IV milder) ← death after birth
  - severe Crippling disease

* Mutations in COL1A1 & COL1A2 → abnormal assembly of type I collagen

3- chondrodysplasias.

Causes: mutations affecting type II collagen.

~Symptoms:-

Abnormal cartilage ⟶ bone and joint deformities.

4- Ehlers-danlos syndrome.

- mild – life-threatening.

Cause:- mutations in types I, III or V OR collagen processing enzymes)
- Procollagen N-Peptidase
- lysyl hydroxylase

~symptoms:-

1) skin fragility
2) Hyperextensibility
3) joint hypermobility.

Type 3 EDS:- (BVs are most affected)

Type 3 collagen

Symptoms are:- fragile blood vessels, stretchy skin and hypermobile joints
(major)

10] GAP Junctions mutations

Cause: Defective (mutated) Connexins.

1- Marie-Charcot-Tooth Disease

2- Cataracts

3- Deafness (can be heredity)

4- skin disorders.

11] Marfan's Syndrome.

Cause: mutated fibrillin

Symptoms:-

- Stretching too much of elasting causing Rupture (Ex. Aorta)

12] Ataxia-telangiectasia.

- loss of balance & large BV
- Defective ATM
- Defective nervous system & immune system.
- ↑ frequency of cancer.

* Ras is a Proto-oncogene (associated with colorectal cancer)

* Retinoblastoma —(associated with.)→ Uncommon eye cancer, affecting children under 5 (can affect any age also)