

SINGLE GENE DISORDERS

Presented by
Dr. Sophy.R.Da
Dept of P M

Autosomal recessive inheritance

Disorders manifesting only when both the chromosomes carry the mutated gene.

Parents are unaffected healthy carriers

No family history, though the defective gene is passed from generation to generation.

If carriers marry, the offspring have

1 in 4 chance of being homozygous & affected

1 in 2 chance of being a carrier

1 in 4 chances of being genetically normal.

Autosomal recessive disorders

- Phenylketonuria
- Albinism
- Tay-Sachs disease
- Alkaptonuria
- Cystic fibrosis
- Galactosemia
- Haemoglobinopathies
- Maple syrup urine disease
- Homocystinuria
- Wilsons disease
- Glycogen storage disease

Phenylketonuria

- Cause: Deficiency of enzyme phenylalanine hydroxylase which catalyzes conversion of phenylalanine to tyrosine.
- C/F: Mental & growth retardation; eczema & pigment dilution; seizures, tremor, muscular hypertonicity, microcephaly, enamel hypoplasia & decalcification of long bones.
- Diagnosis: Serum phenylalanine raised (>1.2 mmol /l) with raised phenylacetic acid & phenyl pyruvic acid

Tay – sach's disease

- Disorder caused by total hexosaminidase A deficiency
- Infantile form is a fatal neuro degenerative disease with macrocephaly, loss of motor skills, increased startle reaction & macular cherry red spot.
- Juvenile onset form presents with ataxia & dementia.
- The adult onset disorder is characterised by clumsiness in childhood, progressive motor weakness in adolescence & additional spino cerebellar LMN symptoms, and dysarthria in adulthood.
- Intelligence declines slowly & psychosis is common.

Maple syrup disease

- Disorder of aminoacid metabolism with defect in enzyme branched chain ketoacid dehydrogenase.
- Valine, isoleucine & their derivatives are excreted in urine.
- Failure to thrive, fits, neonatal acidosis & severe cerebral degeneration.

Homocystinuria

- Disorder of methionine metabolism caused by deficiency of the enzyme cystathionine synthase.
- Cardinal signs include ocular lense dislocation , mental retardation, skeletal abnormalities, & thromboembolic complications.

Glycogen storage disease

- Characterized by abnormal tissue concentration (> 70 mg /gm of liver or >15 mg/gm of muscle) and/ an abnormal structure of glycogen molecule.
- Types
- Von- Gierkes disease:
- Forbe's disease
- Anderson's disease
- Her's disease
- Pompe's disease
- Mc Ardle's disease

ALKAPTONURIA

- Caused by the lack of enzymes homogentisic acid oxidase.
- Affected person excrete dark coloured urine due to the presence of homogentisic acid.

ALBINISM

Complete depigmentation of skin due to deficiency of tyrosinase.

Cystic fibrosis

- It is a condition where the mucus secretion become unusually thick & the accumulated secretion produces obstruction of the duct system
- Most commonly affected organs are lungs & pancreas
- CF locus has been marked on chromosome 7q31
- The product of CF gene known as Cystic fibrosis transmembrane regulator is involved in chloride transport & mucin secretion through the cell membrane.
- There is elevated levels of Na & Cl in the sweat

WILSONS DISEASE

- Rare inborn error of metabolism that results in copper deposits in various organs.
- c/f: abnormal involuntary movements- tremor & dystonia, cirrhosis of liver, Kayser-Fleischer ring.
- Low serum ceruloplasmin (<20mg/dl), high urinary cu excretion (>200mcg/24hrs)

Galactosemia

- Disorder due to deficiency of enzyme galactose-1-phosphate uridyl transferase resulting in accumulation of galactose-1-phosphatase in blood.
- C/F: Failure to thrive, vomiting, jaundice & hepatomegaly. Cataracts, diabetes & developmental delay.

X-linked recessive inheritance

- These disorders present in males & present only in homozygous females.
- Transmitted by healthy female carriers or affected males.
- Of the offspring from a carrier female & a normal male:
 - 50% of girls will be carriers & 50% of girls will be normal.
 - 50% of the boys will have disease & 50% of the boys will be normal.

X-linked recessive disorders

- Haemophilia type A & B
- Duchenne type of muscular dystrophy
- Colour blindness
- G6 P D deficiency
- Retinitis pigmentosa
- Fabry's disease
- Menkes syndrome
- Lesch-Nyhan syndrome

Glucose 6 phosphate dehydrogenase deficiency

- The gene for G6PD is localised to chromosome Xq28.
- Manifested by haemolytic anaemia when treated with analgesics, anti malarials, sulfonamides & acetyl salycilic acid

Lesch-Nyhan syndrome

- X linked disorder of purine metabolism in which there is deficiency of the enzyme hypoxanthine guanine phosphoribosyl transferase.
- There is accumulation of excessive amount of uric acid which produce adverse effect on the CNS.
- Affected male exhibits periodic uncontrolled movements, spasticity, mental retardation & compulsive self mutilation

Duchenne type of muscular dystrophy

- DMD gene is located at Xp 21
- There is deficiency of dystrophin.
- It is characterised by progressive muscular weakness affecting the boys bwn ages 3 and 5 yrs. Manifested by awkward gait, inability to walk & difficulty in climbing stairs.
- During the early stages calf muscles show pseudo hypertrophy.
- Progressive deterioration of muscle leads to respiratory failure & death.

Menkes kinky hair syndrome

- Condition caused by malabsorption of copper.
- The Menkes disease gene encodes a copper transporting ATPase & has a homology to the gene in Wilsons disease.
- C/F: Growth failure, mental retardation, bone lesions & brittle hair.
- Anaemia & neutropenia

RETINITIS PIGMENTOSA

- Slowly progressive degenerative disease of the retina characterised by night blindness & deposition of melanine pigment in the retina.

Fabry's disease

- Condition due to a deficiency of the lysosomal hydrolase alpha galactosidase causing an accumulation of gluco sphingo lipids in the lysosomes of various tissues.
- Characterised by telangiectatic skin lesions, hypo hydrosis, corneal & lenticular opacities, acroparasthesias & vascular disease of the kidney, heart & / or brain.

X-linked dominant inheritance

- Heterozygous females & males who have the mutant gene on their x chromosome will manifest the disease.
- Half the male or female offspring of an affected mother & all the female offspring of an affected man will have the disease.

X-linked dominant disorders

- Vitamin D resistant rickets
- Pseudohypoparathyroidism

VIT D RESISTANT RICKETS (FAMILIAL HYPOPHOSPHATAEMIC RICKETS)

- Due to defective tubular re absorption, there is excessive urinary loss of phosphates
- Other tubular functions are preserved, hence there is no acidosis, hypocalcemia, glycosuria or amino aciduria
- Defective bone growth & body deformities

Pseudohypoparathyroidism

- Syndrome of end organ resistance to parathyroid hormone owing to a mutation in the G α protein which is coupled to the PTH receptor.
- Associated with short stature, short metacarpals, subcutaneous calcification & intellectual impairment.