Medical Genetics

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GENETIC COUNSELLING

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Definition :

Process of helping people understand and adapt to the medical, psychological, and familial implications of genetic contributions to disease.

This process integrates the following :

- Interpretation of family and medical histories to assess the chance of disease occurrence or recurrence.
- Education about inheritance, testing, management, prevention, resources, and research.
- Counseling to promote informed choices and adaptation to the risk or condition.

Models of genetic counselling :

Eugenics : To improve or impair racial qualities of future generations.

Medical/preventive :

- Preventing genetic disorders.
- Offer information, sympathy, & the option to avoid childbearing.

Decision making : Exploring decisions about reproduction, testing, management.

Psychosocial : Exploring experiences, emotional responses, goals, beliefs, resources, family dynamics, and coping styles.

Indications of genetic counselling 00:04:24

Indications are :

- Prior to whole genome or exome sequencing.
- Adult-onset genetic disease (Presymptomatic testing).
  - Cancer.
  - Huntington disease.
- Pharmacogenomics.
- Heterozygote screening based on ethnic risk.
  - Sickle cell anemia.
  - Thalassemias.
- Advanced parental age.
  - Maternal age ≥35 yr.
  - Paternal age ≥40 yr.

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- Antenatal screening.
  - Positive Maternal Dual, triple or quad screen.
  - Fetal ultrasonography.
  - Noninvasive prenatal testing (NIPT).
- Consanguinity.
- Teratogen exposure.
- Unexplained stillbirth with or without malformations.
- Previous child with or family history of :
  i. Congenital abnormality.
  ii. Dysmorphology.
  iii. Intellectual disability.
  iv. Isolated birth defect.
  v. Metabolic disorder.
  vi. Chromosome abnormality.
  vii. Single-gene disorder.
- Prior to preimplantation genetic testing.
- Follow-up to abnormal neonatal genetic testing (NBS).
- Congenital malformations.
- Developmental delay/intellectual disability.
- Neurodegenerative diseases.
- Myopathy, neuropathy.
- Ambiguous genitalia.
- Hypogonadism.
- Short stature : Proportionate or disproportionate.
- Acutely sick infant , neonate : Inborn error of metabolism.
- Known genetic disease : Wilson disease, Down syndrome, mucopolysaccharidosis, etc.

Various factors to be explained during genetic counselling :

Autosomal dominant :

- Variable Expressivity.
- Reduced penetrance.
- New mutations.
- Homozygosity.
- Germ line mosaicism.

Autosomal recessive :

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- Consanguinity.
- Heterogeneity.
- Compound heterozygotes.
- Pseudodominant.

X linked inheritance :

- Expression in heterozygous females.
- Isolated case --> Carrier status.
- Problems of a female carrier (Can manifest as cardiomyopathy, mild bleeding in hemophilia).

Ethical principles

00:15:27

Terminologies :

- Autonomy : Free of coercion with protection of their privacy.
- Beneficence : Intent of doing good.
- Non-maleficence : First, do no harm.
- Justice : Burdens and benefits of care must be distributed equally over society.

Counselling essentials :

SPIKES :

S : Setting.

P : Perception.

I : Invitation.

K : Knowledge.

E : Empathy, Emotions.

S : Summary & Strategy.

EMPATHY :

E : Emotions.

M : Meetings.

P : Patients perspective.

A : Adequate language.

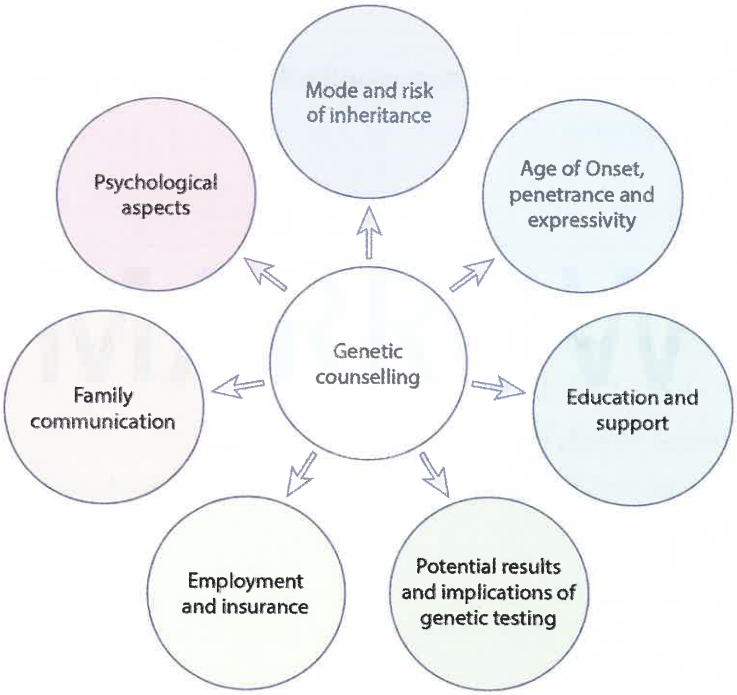
TH : Truth & Hope.

Y : Yes for patient empowerment.

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Main elements of genetic counselling :

- Listening to concerns.
- Building an empathic relationship.
- Considering diagnostic and clinical aspects.
- Inheritance patterns and risk estimation.
- Communicating information.
- Providing support.



Components of genetic counselling

Steps of genetic counselling

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Steps of genetic counselling :

Collecting the information :

- History & family history.
- Physical examination of affected patient.
- Examination of the family members.

Risk estimation :

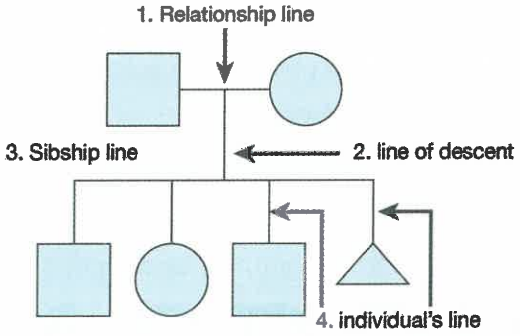
- Diagnostic tests.
- Disease condition.
- Knowledge about the disease.

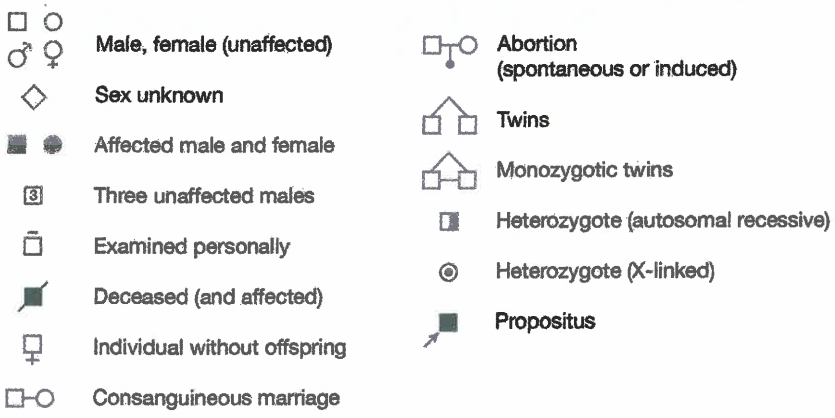
Communication & decision making :

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- Natural history.
- Genetic aspects.
- Prenatal diagnosis.

Support groups :





Family tree

Concept of high and low risk :

- Risk acceptable : Perception of the patient.
- Previous affected child : Experience of disease.
- Nature & severity : Burden of disease.
- For eg. Previous child with DS : 1% risk unacceptable.
- Bad Obstetric history : DS risk of 1 in 50 acceptable.

Genetic risk estimation :

- Empirical risks
- Mendelian risks.
- Modified genetic risks.
- Risk estimates from independent evidence.
- Estimate based on observed data

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- Most of the more common non-Mendelian or chromosomal disorders.
- Clear basis of single gene inheritance recognised.
- Phenotype may vary if : Incomplete penetrance or age dependent.
- Prior genetic risk, modified by 'conditional' information.
- Other information such as lab tests help to modify risk.

Risk of abnormalities in the normal population :

Risk of a child being born with some congenital abnormality	1 in 30
Risk of child being born with a serious physical or mental impairment or disability	1 in 50
Risk of a recognised pregnancy ending in a spontaneous abortion	1 in 8
Risk that a couple will be infertile	1 in 10

Communication of information :

- Disease condition.
- Knowledge about the disease.
- Natural History.
- Genetic aspects.
- Prevention & prenatal diagnosis.
- Therapies and intervention.

Non directive counselling :

- Choices left to the family : Decide what is right for them.
- The role of the counselor : Provide information in understandable terms and outline the range of options.
- Consultants not counselors, live with the decision.

Practical aspects of communication of information :

- Probabilities and odds refer to the future, not the past.
- Each conception is an independent event, so that 'chance has no memory'.
- Present risk information in multiple ways to avoid framing bias and directiveness.

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Support groups :

- Community and online lay support groups.
- Provide information and fund research.
- An important part of genetic counseling is to give information about these groups to patients and to suggest a contact person for the families.

Case scenarios 00:28:48

Chromosomal disorders :

- Course of the disorders and outcome.
- De novo aneuploidy ROR : <1 %.
- Parents Karyotyping : Only in structural abnormalities.
- Prenatal diagnosis/ USG & Biochemical screening/NIPS counseling.
- Advanced maternal age.

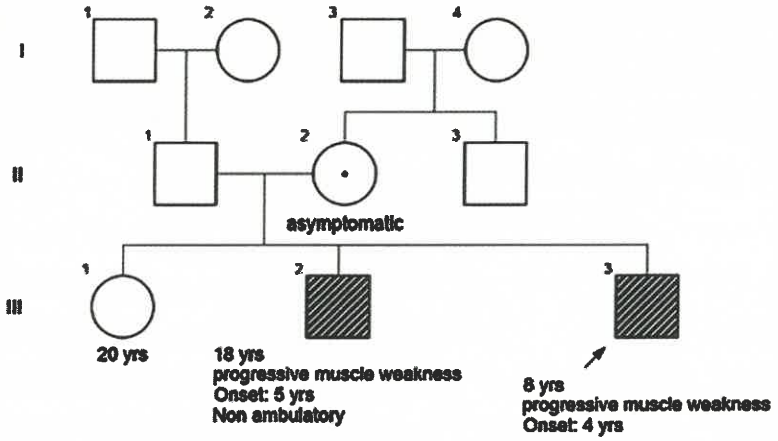
Single gene disorders :

- About the disorder.
- Recurrence risk depends upon the inheritance pattern.
- Confirmation of diagnosis by molecular studies.
- PND if desired.

Case 1 :

History and Examination :

- 8 year-old male child with progressive proximal weakness of lower limbs since 4 years of age.
- Gower sign +
- Calf hypertrophy +
- Diminished deep tendon reflexes.
- CVS/Respiratory/ Abdomen : Unremarkable.



Family tree

Investigations :

- Serum CPK : 4800 IU/l (Raised).
- MLPA for DMD : Deletion of exons 49-50 in Dystrophin gene consistent with dystrophinopathy.

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Counselling :

Nature and prognosis :

Affected children become wheelchair dependent by late teens, if untreated.

Cardiomyopathy can occur in individuals with DMD after age 10 years.

Treatment :

- Supportive : Pulmonology and cardiology follow up, immunisation, physiotherapy.
- Eligibility for newer therapeutics like Eteplersin (This mutation is amenable to Exon 51 skipping ASO).
  - Cost issues and nonavailability through government health care system to be considered.

Inheritance and ROR :

- The dystrophinopathies are inherited in an X-linked manner.
- Since mother is obligate carrier, there is 50% chance of transmitting the DMD pathogenic variant in each pregnancy.
- Sons who inherit the pathogenic variant will be affected; daughters who inherit the pathogenic variant are carriers and may or may not develop cardiomyopathy (1|2).

Option for at risk members and prenatal diagnosis :

Carrier testing for at-risk females (1|1|1) and prenatal testing for pregnancies at increased risk are possible as pathogenic variant is known.

Case 2 :

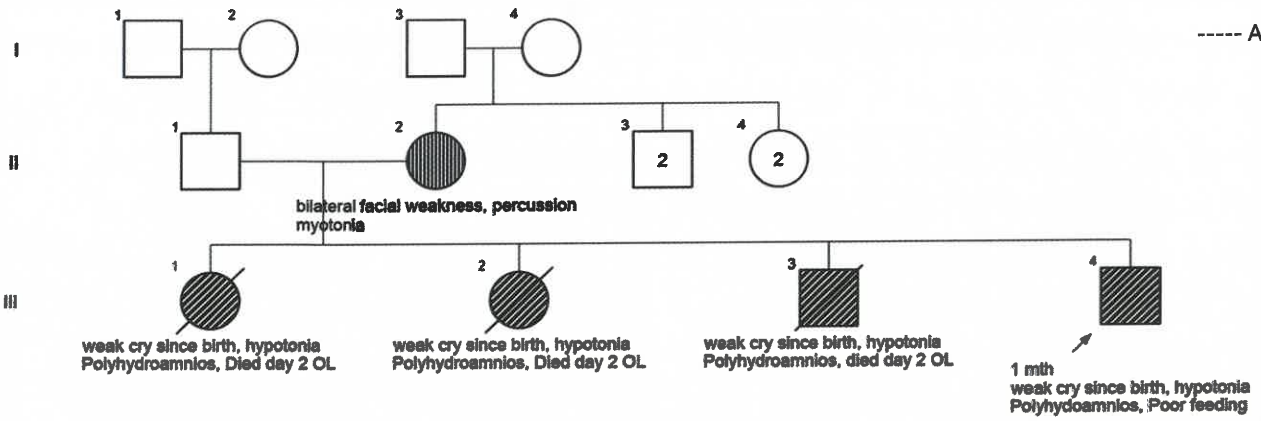
History and examination :

- One month-old male baby presented with poor cry and feeding since birth.
- B/l facial weakness, inverted V Shape lips, retrognathia, flat philtrum, low set ears.
- Generalised hypotonia.
- Moro's incomplete, grasp and suck reflex weak .

Investigations :

- S.CPK : 142 U/L. (N : 39-308).
- NCS : Normal. Needle EMG : Abnormal spontaneous activity s/o myotonic discharges (Reviving engine sound) detected in muscles of left upper extremity.
- TP-PCR- expansion, short PCR show expansion of CTG repeats in one allele beyond the threshold level of MDI.

----- Active space -----



Family tree

Counselling :

Nature and prognosis :

- It is a multisystem disorder that affects skeletal and smooth muscle as well as the eye, heart, endocrine system, and central nervous system.
- The clinical findings can range from mild to severe.

Treatment :

Supportive (monitoring for heart rhythm abnormalities, diabetes, sleep disturbances and cataract).

Inheritance and ROR :

- DM1 is inherited in an autosomal dominant manner.
- Since mother is affected though with mild manifestations, there is 50% chance of transmitting the DM1 pathogenic variant in each pregnancy.
- more severe manifestations when the disease is transmitted through the mother is due to anticipation and the increase in the number of CTG repeats.

Option for at risk members and prenatal diagnosis :

Testing for at-risk members after detailed examination, as symptoms may be subtle, and prenatal testing for pregnancies at increased risk are possible as pathogenic variant is known.

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Empirical risk of common chromosomal disorders :

Malformation	Frequency per 1000 births	Recurrence for normal parents of one affected child
Anencephaly Spina bifida	4 – 5	5%
Cardiac malformation	6 – 8	3 – 4%
Cleft lip and cleft palate	2	4 – 5%
Cleft palate alone	0.5	2 – 6%
Pyloric stenosis	2 – 3	3%
Talipes equinovarus	3 – 4	2 – 8%
Dislocation of hip	3 – 4	3 – 4%
Hirschsprung disease	0.1	6%

Presymptomatic testing :

- Predictive testing refers to genetic testing in a healthy high-risk relative for a specific later onset monogenic disorder and the mutation in the family leads to the disease or a considerably high risk for the disease.
- Some use "presymptomatic testing" as a synonym for "predictive testing".
- Pre and post-test genetic counselling.
- Psychosocial evaluation and support.

PATTERNS OF INHERITANCE

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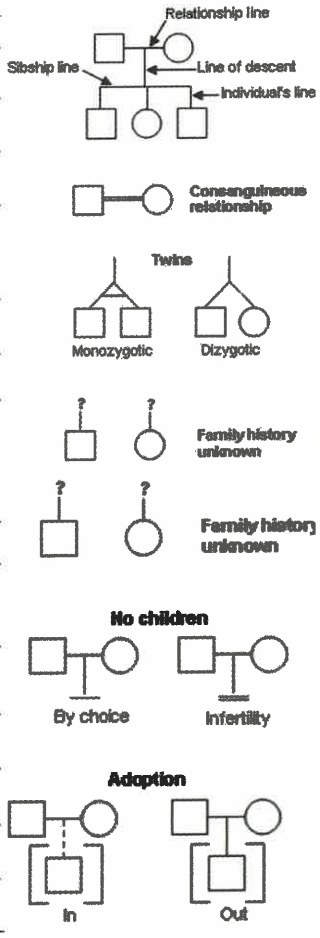
Introduction

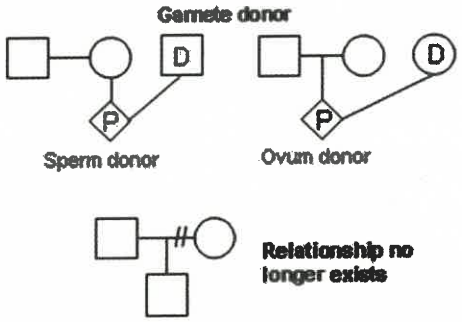
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Pedigree chart :

A diagram depicting a family, relationships & the distribution of phenotypes in them, using standardized symbols.

	Male	Female	Sex Unknown
Individual	□	○	◇
Affected individual	■	●	◆
Multiple individuals	5	5	5
Multiple individuals, number unknown	n	n	n
Deceased individual	⊘	⊘	⊘
Pregnancy	P	P	P
Proband	P Male	P Female	P Sex Unknown
Pregnancy	P	P	P
Proband	P	P	P
Consultand			
Spontaneous abortion	male	female	
Termination of pregnancy	male	female	
Obligate heterozygote	⊙	⊙	◈
Ectopic pregnancy		ECT	





Consanguinity :

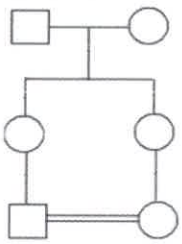
- Refers to the union between blood relatives.
- The couple are descendants of a common ancestor.

Common types of consanguinity :

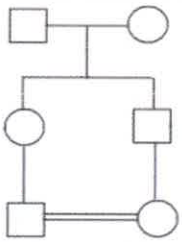
- 2nd degree : A woman marrying her maternal uncle.
- 3rd degree : marriage between first cousins.
- Increased risk of autosomal recessive (AR) disorders, since couple tend to be carriers for the same mutation.
- There is a doubling of risk (4 to 6 %) for AR disorders among consanguineous couples, compared to the general population risk of 2 to 3 %.

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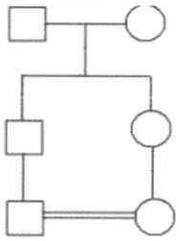
Consanguinity types :

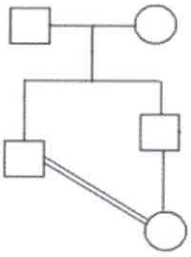


maternal first cousins : 3rd degree

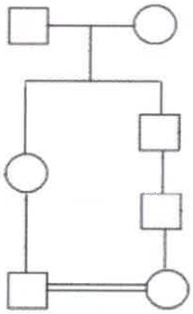


Cross first cousins : 3rd degree

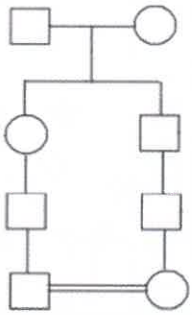




Uncle niece : 2nd degree

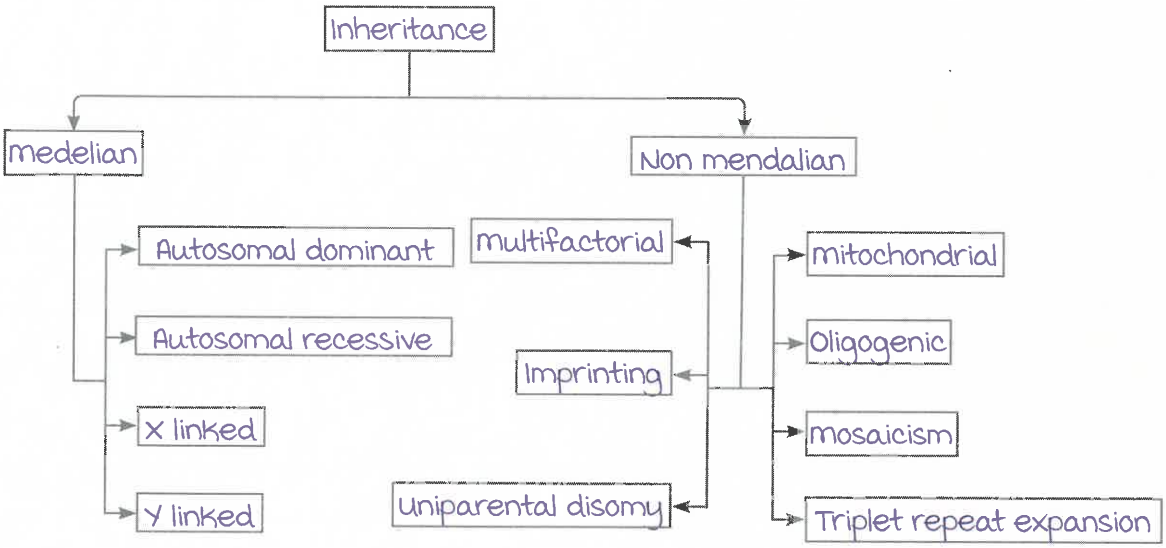


First cousins once removed : 4th degree

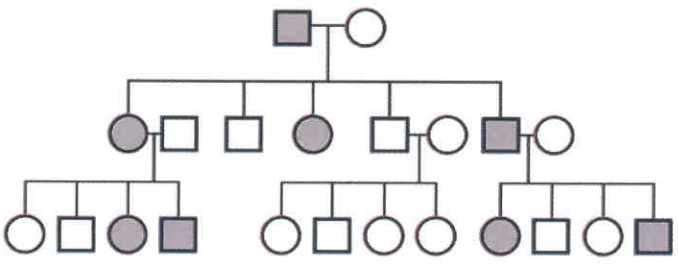


Second cousins : 5th degree

Types of inheritance :



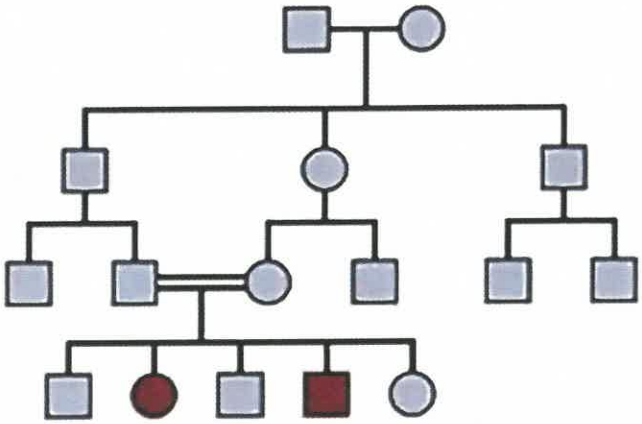
Autosomal dominant (AD) :



AD

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- Phenotype manifests with one mutant allele.
- Vertical transmission from parent to offspring.
- may also occur de-novo.
- Both genders are equally affected.
- Recurrence risk is 50 % if inherited.
- Recurrence risk low, if de novo.



AR

Autosomal recessive (AR) :

- Two mutant alleles must be present for phenotype.
- Horizontal transmission.
- Both parents are carriers for the disease.
- Carriers usually do not manifest.
- Both genders are equally affected.
- Recurrence risk is 25 %.

Case discussion :

Case 1 : Tuberous sclerosis(TSc : AD inheritance).



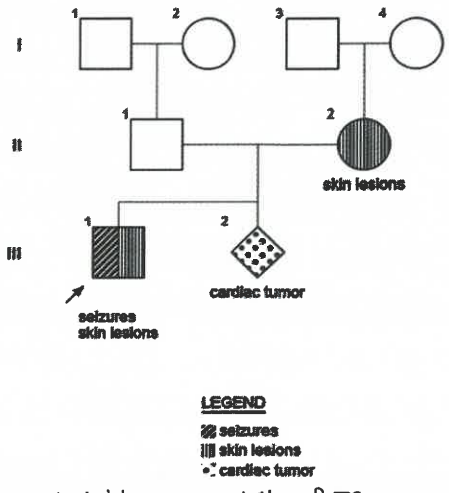
Angiofibroma



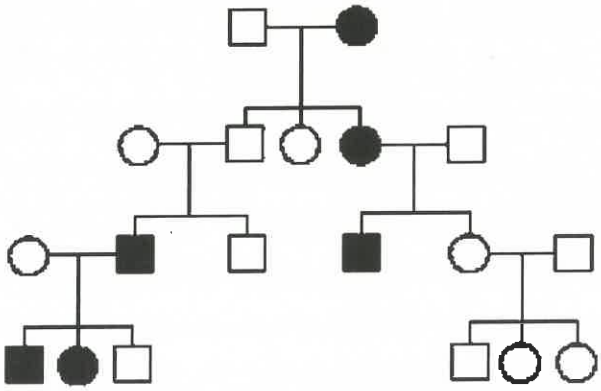
Hypopigmented macule



Shagreen patch



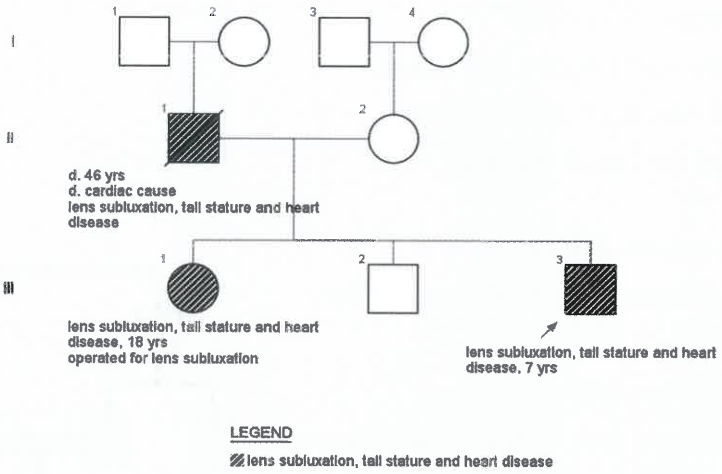
Variable expressivity of TSc



Reduced penetrance of TSc

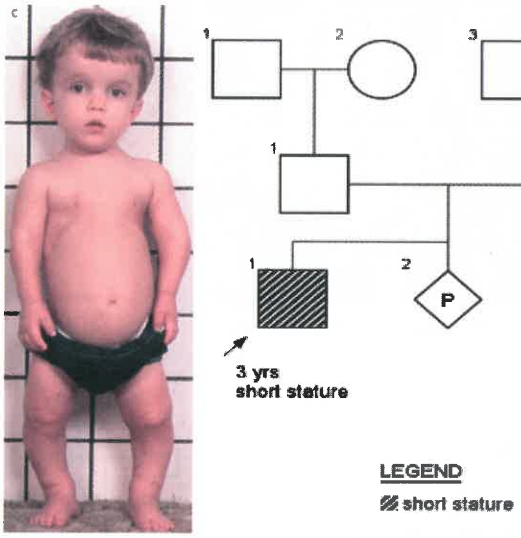
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Case 2 : marfan's syndrome (AD) with vertical transmission.



Case 3 : Achondroplasia

3-year-old boy with predominant motor delay and short stature since birth.
Family history insignificant, relative macrocephaly, rhizomelia, trident hand.
D/t gonadal mosaicism, 2nd baby also born with achondroplasia.



Achondroplasia

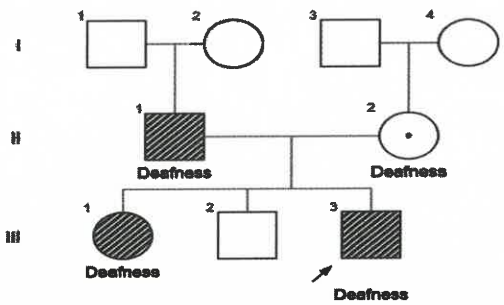
Note :

- Reduced penetrance :
  - An individual with no features of disorder despite being heterozygous for a particular gene.
- Variable expressivity :
  - If a trait that is seen in all individuals carrying the mutant gene but is expressed differently among individuals.

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Pseudodominance :

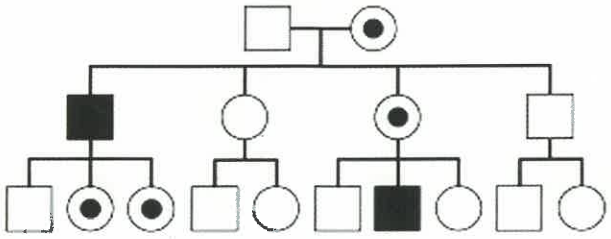
- A condition where a recessive allele mimics the pattern of dominant allele.
- Implications in genetic counselling.
- Here 50 % affected & 50% will be carrier.



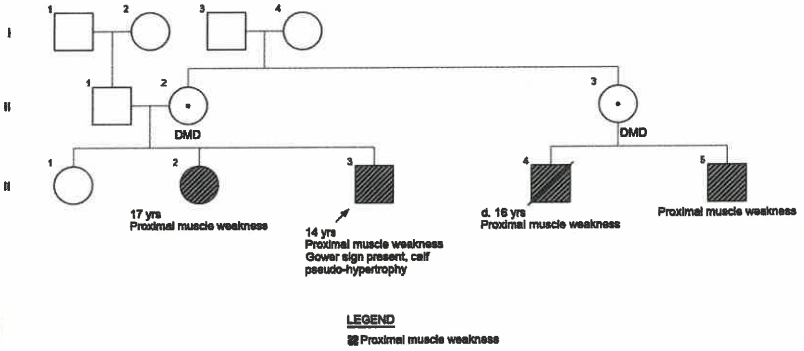
Pseudo dominance

X linked recessive :

- Mutation is present on a single X chromosome.
- Diagonal transmission (Knight's move) from carrier mothers to sons.
- Women passing on the trait are termed obligate carriers & may express nil or mild symptoms (DMD, hemophilia).
- Recurrence risk of disease is 50 % among sons and 50 % daughters are carriers, if mother is a carrier.
- Affected male will have all carrier daughters.
- Can occur de novo (Risk of recurrence is low).



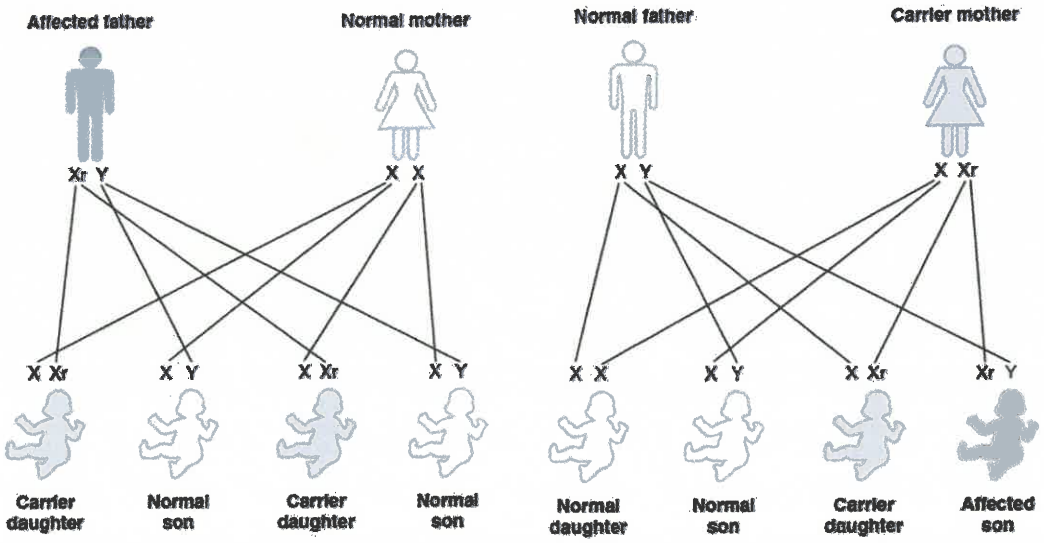
X linked recessive



Manifesting carrier

Examples :

- Duchenne muscular dystrophy.
- Hemophilia A & B.
- Colour blindness.
- G6PD.



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Note :

- Manifesting carrier : Female affected in X linked recessive disease.
- Obligate carrier : Female with both sibling & offspring affected.

Causes of manifesting carrier :

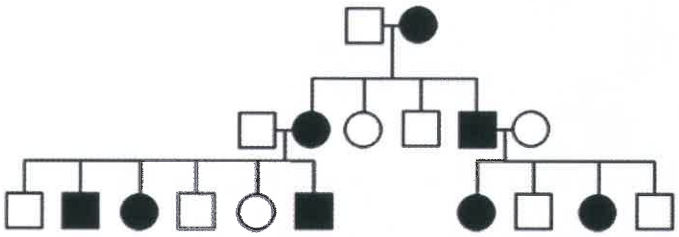
- Skewed X inactivation (m/c).
- Numerical X chromosome abnormality.
- X autosome translocation.
- X autosome translocation.
- Homozygosity for X linked disorder.
- UPD maternal X chromosome.

X linked Dominant :

- Mutation is present on a single X chromosome & dominant in nature.
- Affected mother can transmit disease to both sons & daughters.
- Affected male transmit the disease to all daughters.
- Recurrence risk of disease is 50 % from an affected mother.

Example :

- Vit D resistant rickets.
- Ornithine transcarbamylase deficiency.

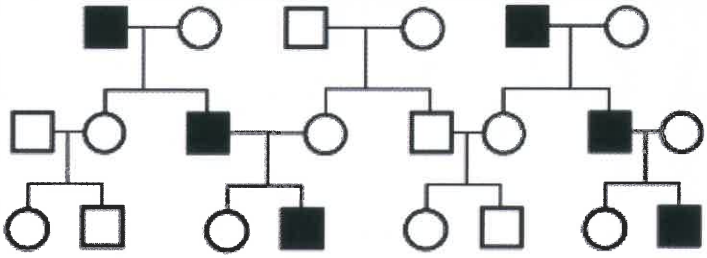


Y linked :

- Mutation is present on Y chromosome.
- Only male to male transmission is observed.
- All sons are affected & all daughters are normal.

Example :

- Azoospermia.
- Swyer syndrome.



Examples of mendelian disorders :

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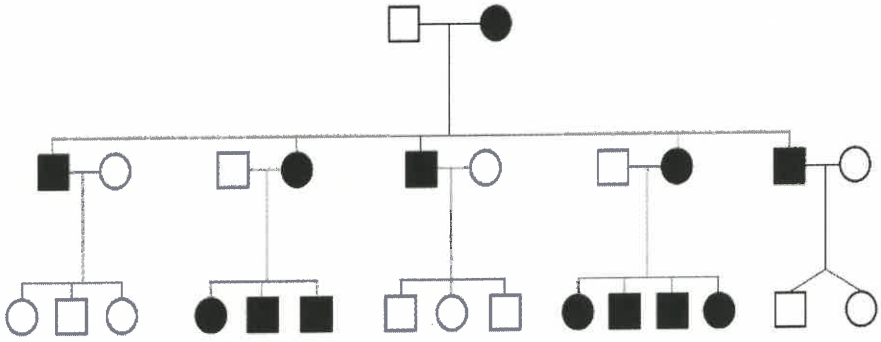
AD	AR	X linked recessive	X linked dominant	Y linked
Achondroplasia	Thalassemia	Duchenne muscular dystrophy	Vit D resistant rickets	Y chromosome infertility
Marfan syndrome	Spinal muscular atrophy	Hemophilia A	Ornithine transcarbamylase deficiency	Swyer syndrome
Familial hypercholesterolemia	Cystic fibrosis	Glucose 6 phosphate dehydrogenase deficiency (G6pD)		
Neurofibromatosis	Inborn errors of metabolism			

Non mendelian inheritance

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Case : 4

12 years old developmentally normal boyGradually progressive loss of vision for past 7 daysFundus- disc pallorMRI brain and orbit- normal, thinning of left optic nerve in the retrobulbar segment likely optic atrophy.



Mitochondrial inheritance

Mitochondrial inheritance :

- Transmission through mitochondrial DNA, which is inherited only from the mother.
- Maternal Inheritance : Mother can transmit the disease to all her children.
- Affected father will not transmit the disease.
- Multisystem.
- Variability in presentation.
- Mostly progressive.

Examples :

- Leber hereditary optic neuropathy.
- Kearns Sayre syndrome.

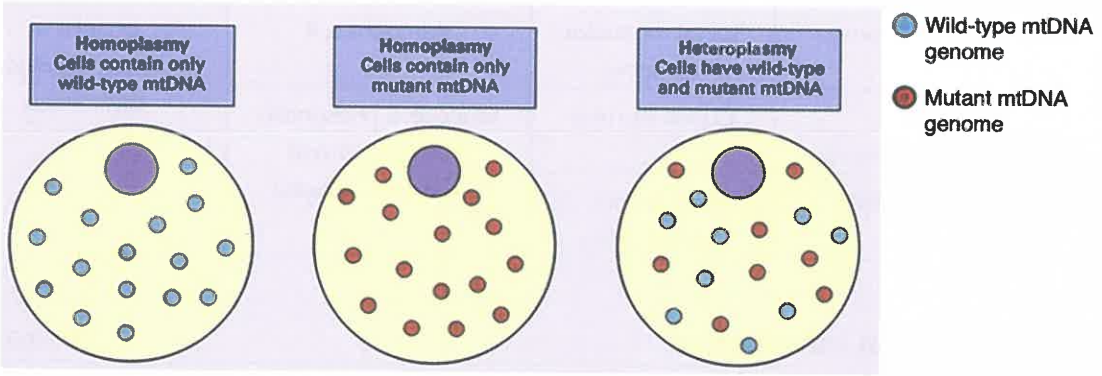
Homoplasmy :

- Refers to the presence of one type of mitochondria only.
- Either wild type or mutant type.

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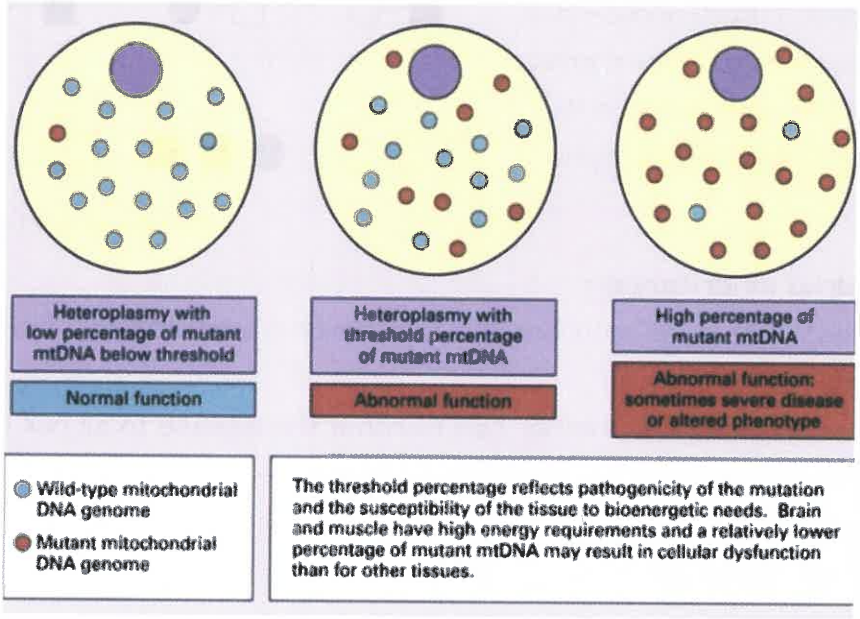
Heteroplasmy :

- Refers to the presence of both wild & mutant types of alleles.
- The phenotype depends on the mutation burden in mitochondria.
- Greater number of mutant alleles gives rise to severe phenotype.



Threshold effect :

- Upto particular percentage of mutant mitochondrial DNA , body can cope up.
- Beyond that result in cellular dysfunction.

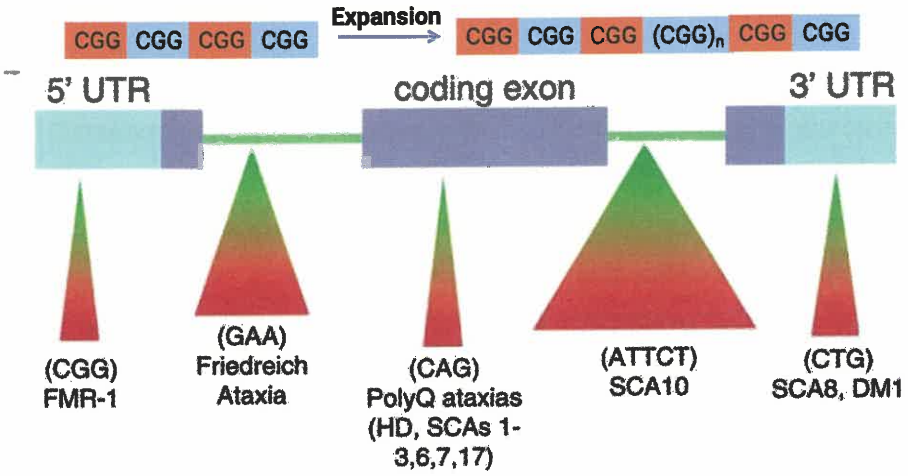


Triple repeat disorders :

- Trinucleotide repeats : Extragenic DNA belonging to the family of microsatellites, polymorphic in general population.
- Repeats are dynamic in nature (Unstable when expands in size).
- 2 subclasses based on location : Exonic repeats, Intronic repeats.

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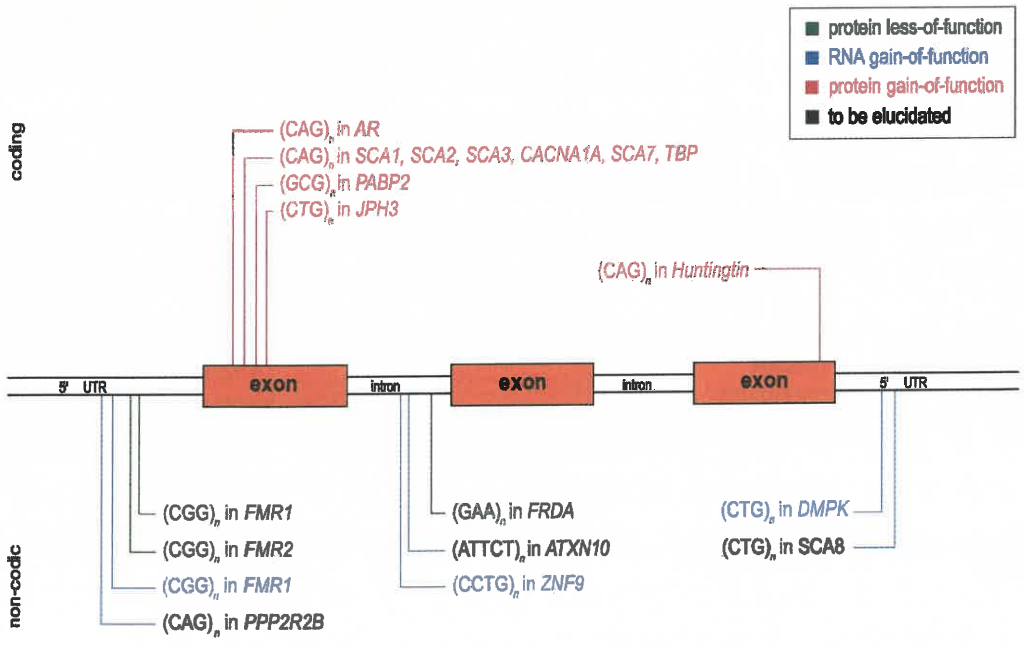
Examples	Sequence	Normal repeats	Pathogenic repeats
Huntington disease	CAG	6 to 29	38 to 180
myotonic dystrophy	CTG	<30	50
Friedrich ataxia	GAA	5 to 30	70 to 1000
Fragile x syndrome	CGG	6 to 50	200 to 4000
Spinocerebellar ataxia	CAG	6 to 39	41 to 83



Trinucleotide repeat disorders

Diseases causing mechanisms :

- Protein loss of function.
- RNA gain of function in non coding region.
- Protein gain of function mutation in coding region.



Genetic location of trinucleotide repeat disorders

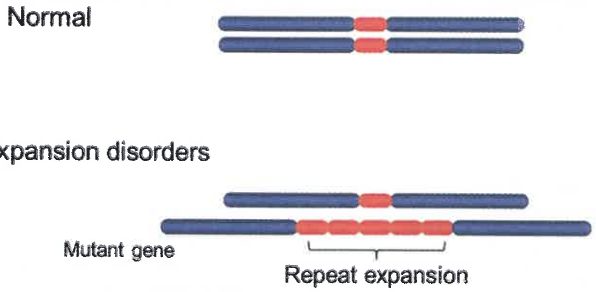
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Note :

- Only triple prime repeat PCR can detect the triple nucleotide repeat disorders.
- Full mutation : Loss of function.
- Premutation :
  - Toxic RNA gain of function.
  - Eg : In CGG repeats (55-200) : Primary ovarian insufficiency & Fragile x associated ataxia syndromes.

Repeat expansion disorders

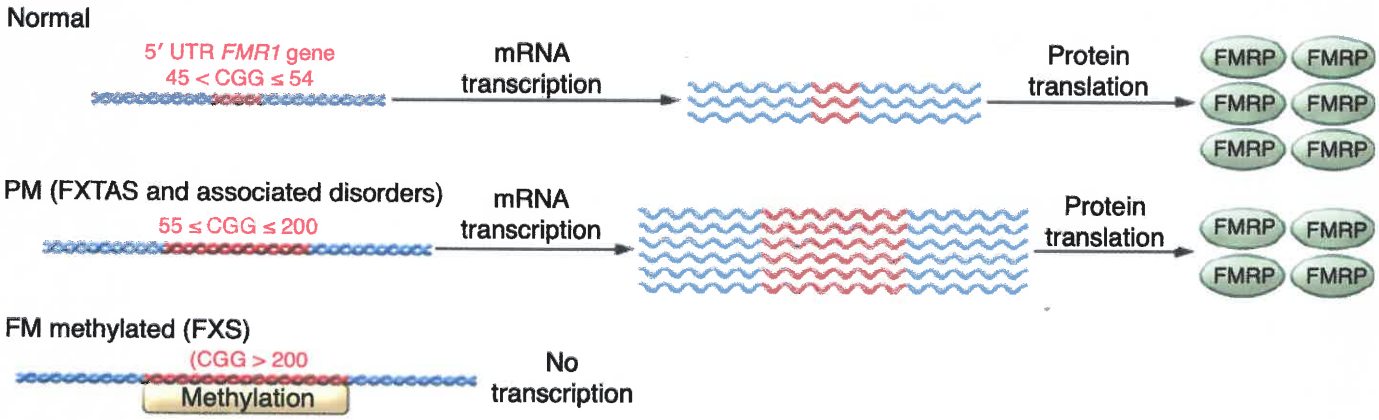
- Genetic conditions resulting from the expansion of the repeats (Triplet/ tetra/hexa) within a gene.
- Repeat expansion can result in reduced protein expansion, accumulation of toxic inclusions or alter the gene expression.
- This is a dynamic unstable mutation since the repeats can rapidly expand over successive generation.
- Triple prime repeat PCR is performed to detect fragile X syndrome.





Fragile x syndrome

Molecular mechanism :



- Full mutation : Loss of function.
- Premutation : Toxic RNA gain of function.

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Friedrich ataxia :

- most frequent inherited ataxia.
- AR inheritance.
- GAA expansions in 1st intron of frataxin gene on chromosome 9.
- Normal allele : 5 to 33 GAA repeats.
- mutable allele : 34 to 65 GAA repeats.
- Disease allele : 67 to 1000 GAA repeats.

Pathophysiology :

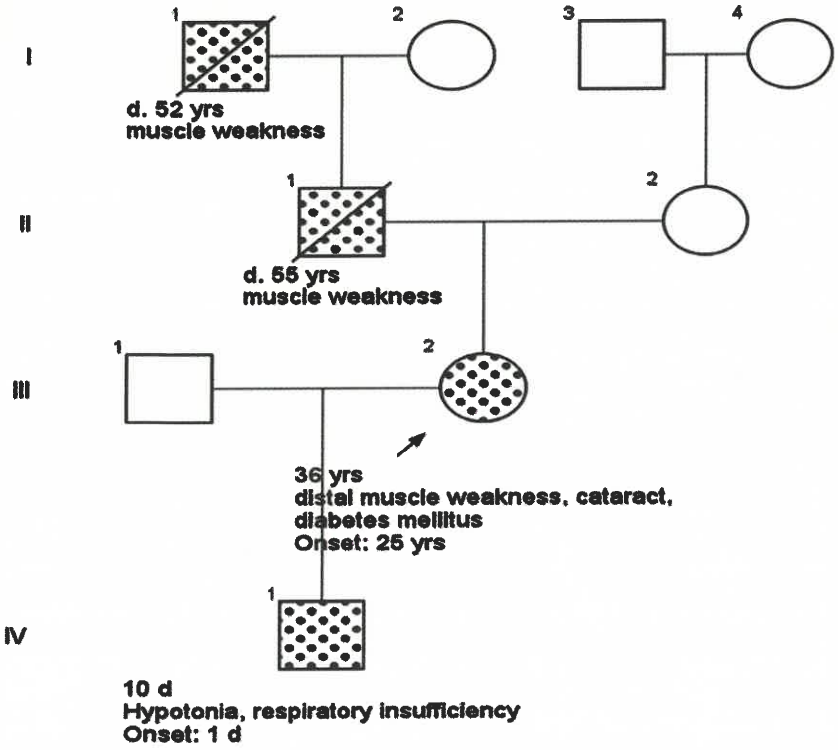
- Frataxin is an iron binding protein.
- Decreased levels of frataxin :
  - Mitochondrial iron overload.
  - Decreased oxidative phosphorylation.
  - Formation of reactive oxygen species.

Anticipation :

With each generation

- Repeat increases.
- Severity increases.
- Onset decreases.

Case : 5



Anticipation in myotonic dystrophy