

Medical Genetics



Marrow ss
Paediatrics 2024

Medical Genetics

CLINICAL 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

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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.

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- Advanced parental age.
 - Maternal age ≥ 35 yr.
 - Paternal age ≥ 40 yr.
- 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.

Ethical principles

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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.

E-Emotions :

m : meetings.

P : Patients perspective.

A : Adequate language.

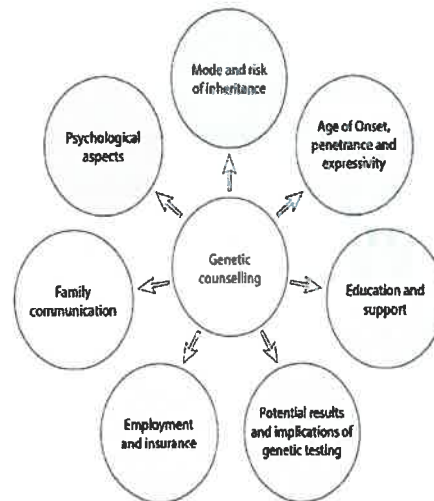
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TH : Truth & Hope.

Y : Yes for patient empowerment.

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 :

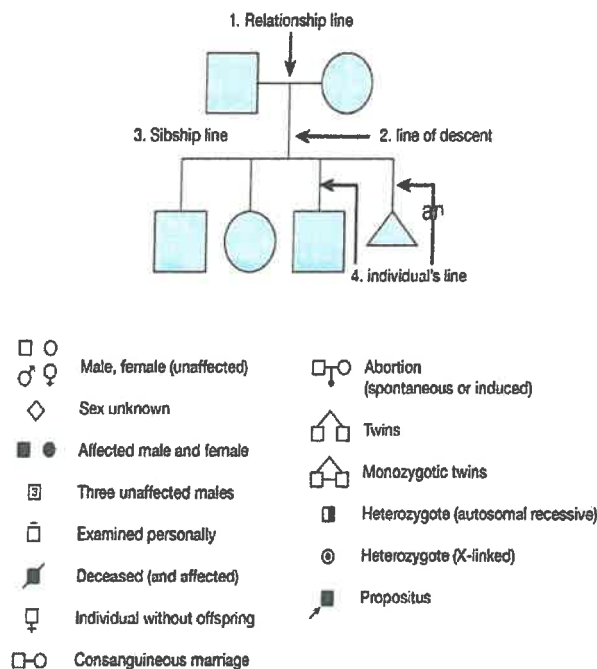
- Diagnostic Tests.
- Disease condition.
- Knowledge about the disease.

Communication & decision making :

- Natural History.
- Genetic aspects.
- Prenatal diagnosis.

Support groups.

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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
- 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.

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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 diseases.
- 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.

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

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Chromosomal disorders :

- Course of the disorders and outcome.
- De novo aneuploidy ROR ~ <1 %.
- Parents karyotyping – only in structural abnormalities.
- Prenatal diagnosis/ USG & Biochemical screening/NIIPS counseling.
- Advanced maternal age.

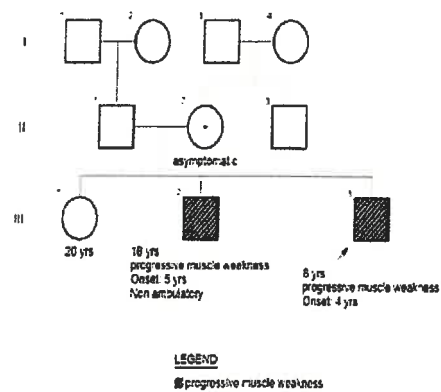
Single gene disorders :

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

Case I :

History and Examination :

- 8 year-old male child with progressive proximal weakness of lower^{5e} limbs since 4 years of age.
- Gower sign +.
- Calf hypertrophy +.
- Diminished deep tendon reflexes.
- CVS/Respiratory/ Abdomen- unremarkable.



Investigations :

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

Family tree.

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.

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Treatment :

Supportive (pulmonology and cardiology follow up, immunisation, physiotherapy) and eligibility for newer therapeutics like Eteplersen (this mutation is amenable to Exon 51 skipping ASO) should be discussed with cost issues and nonavailability through government health care system. Though the long term outcomes of treated patients is still awaited.

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 (IIa).

Option for at risk members and prenatal diagnosis :

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

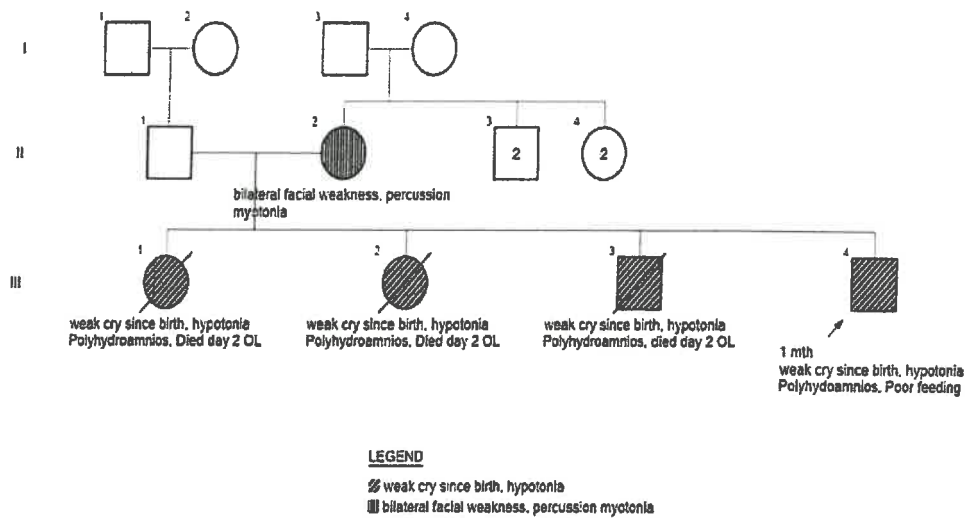
Case 2 :**History and examination :**

- One month-old male baby presented with poor cry and feeding since birth.
- B/I 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 (revving engine sound) detected in muscles of left upper extremity.
- -TP-PCR- expansion, short PCR- shows expansion of CTG repeats in one allele beyond the threshold level of MDI.

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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 :

DMI is inherited in an autosomal dominant manner. Since mother is affected though with mild manifestations, there is 50% chance of transmitting the DMI 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.

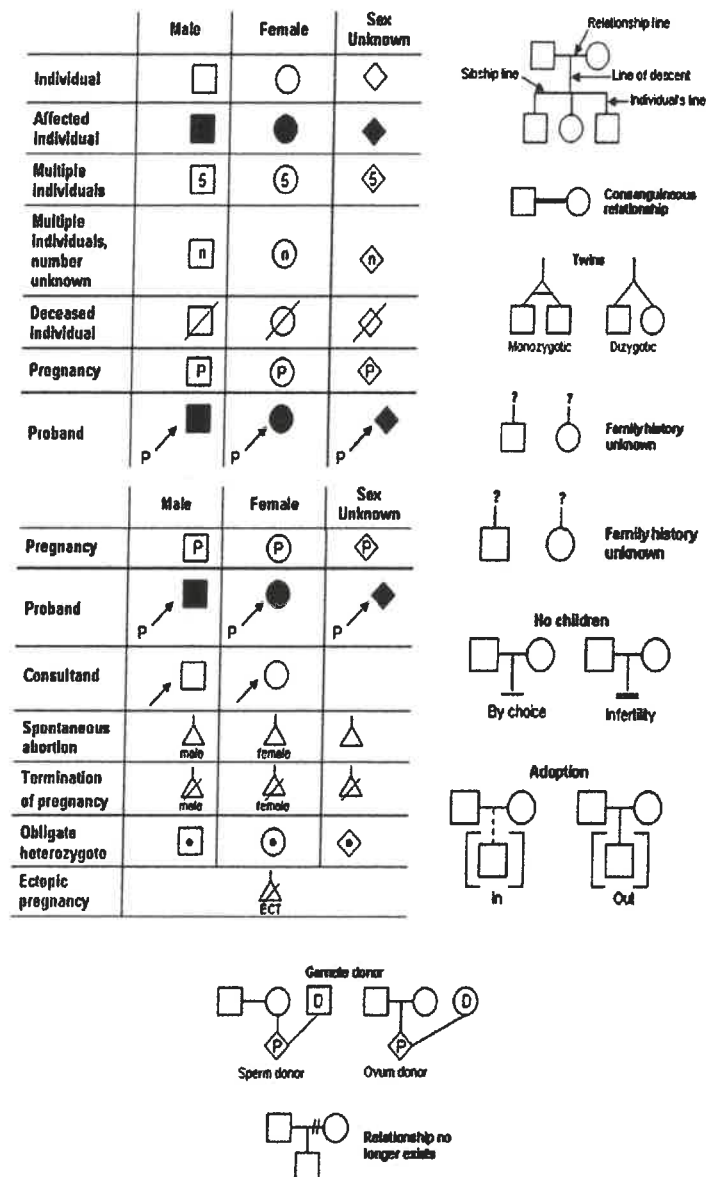
PATTERNS OF INHERITANCE

Introduction

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Pedigree chart :

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



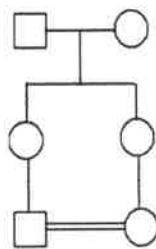
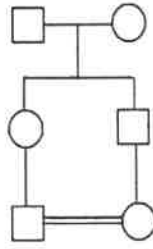
Consanguinity :

- Refers to the union between blood relatives.
- The couple are descendants of a common ancestor.
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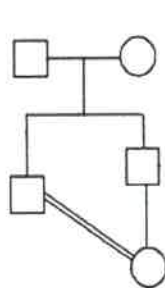
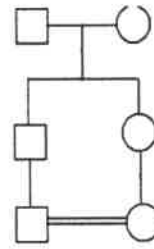
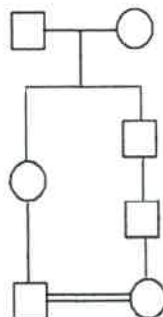
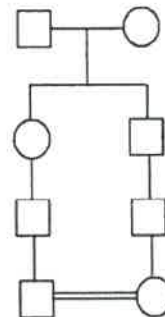
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- Common types of consanguinity :
 - 2nd degree : A woman marrying her maternal uncle.
 - 3rd degree : marriage between first cousins.
- Increased risk of autosomal recessive (AR) disorders, since couple tend to be carriers for the same mutation.
- 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 %.

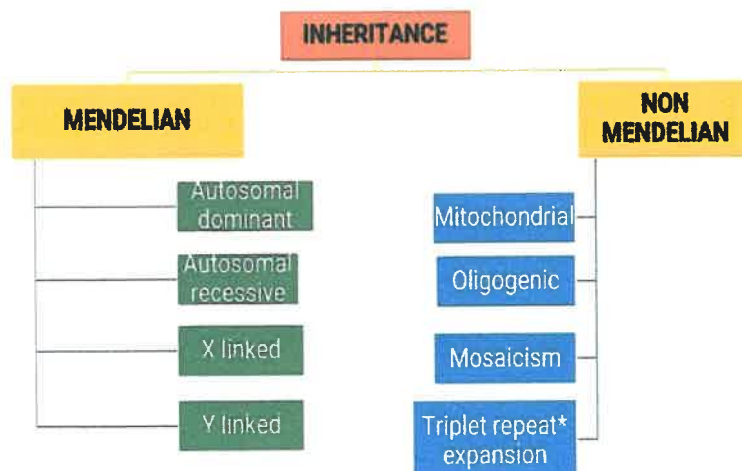
Consanguinity types :

maternal first cousins :
3rd degree.

Cross first cousins : 3rd degree.

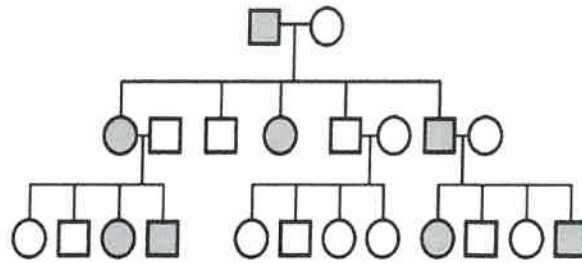
Uncle niece :
2nd degree.First cousins
once removed :
4th degree.Second cousins :
5th degree.

Types of inheritance :

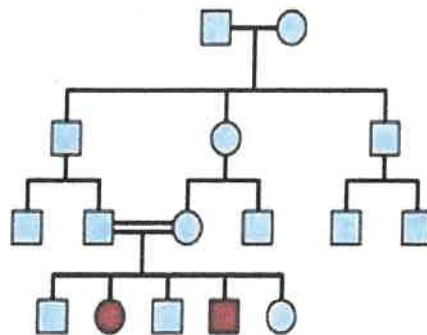


Autosomal dominant (AD) :

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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.

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).



Angioma.

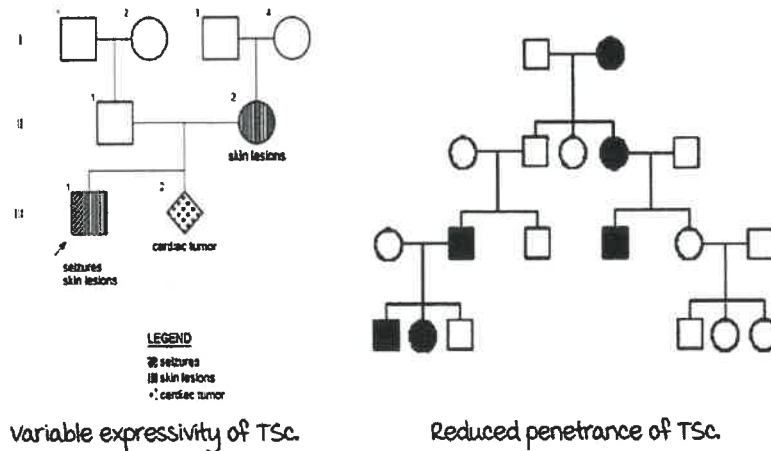


Hypopigmented macules.



Shagreen patch.

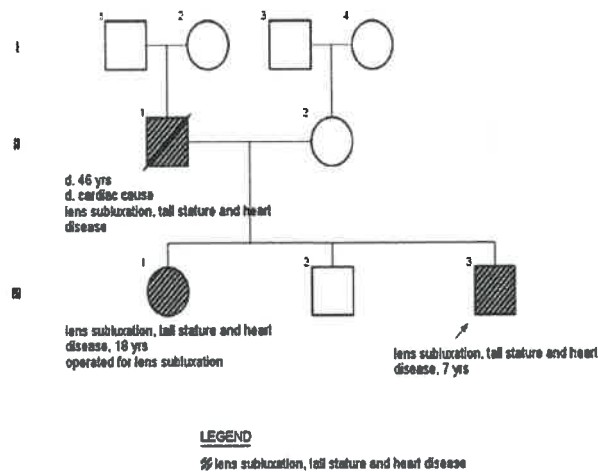
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Variable expressivity of TSC.

Reduced penetrance of TSC.

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

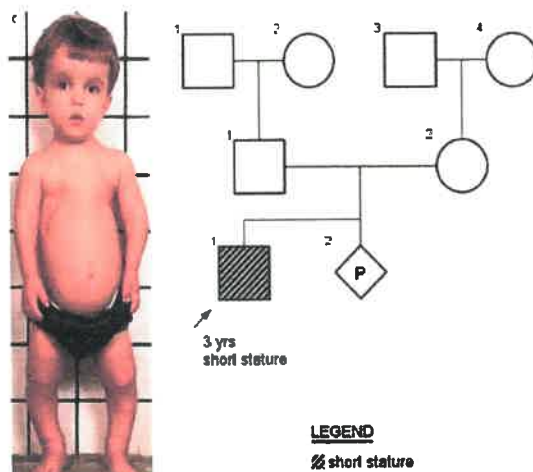


Case 3 : Achondroplasia

3-year-old boy.

Predominant motor delay and short stature since birth.

Family history insignificant.
 relative macrocephaly,
 rhizomelia, trident hand
 • D/t gonadal mosaicism
 and baby also born with
 achondroplasia.



Achondroplasia.

Note :

Reduced penetrance :

An individual with no features of disorder despite being heterozygous for a

particular gene.

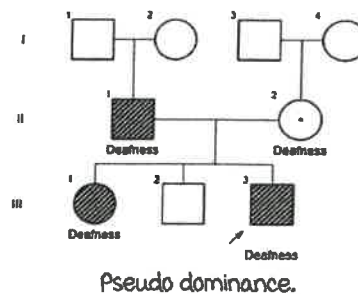
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Variable expressivity :

If a trait that is seen in all individuals carrying the mutant gene but is expressed differently among individuals.

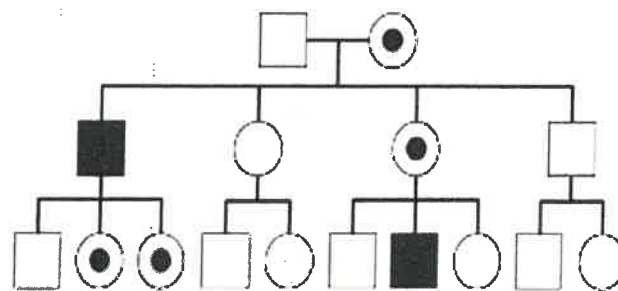
Pseudodominance :

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



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.

Examples :

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

Note :

manifesting carrier : Female affected in X linked recessive disease.

Obligate carrier : Female with both sibling & offspring affected.

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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.

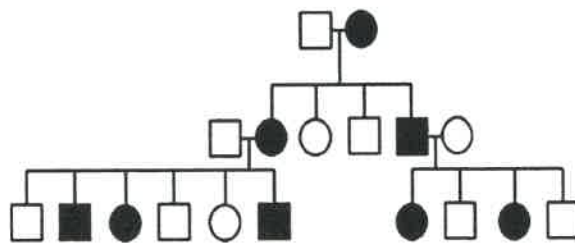
X linked Dominant :

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 :

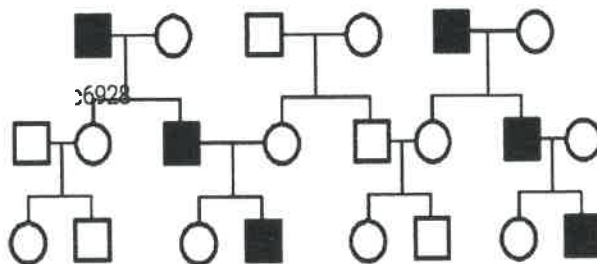
- vit D resistant rickets.
- Ornithine transcarbamylase deficiency.

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.