Principles of Inheritance

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OVERVIEW

- Introduction
- Types of Genetic diseases
- Genetic Assessment
- Drawing Pedigree
- Single gene diseases
- Chromosomal diseases
- Polygenic diseases

Introduction

- Genetic disorders place considerable health and economic burdens NOT only on affected individuals and their families but also on the community.

Introduction

Despite a general fall in the perinatal mortality rate, the incidence of lethal malformations in newborn infants remains constant.

Between 2 and 5% of all live born infants have genetic disorders or congenital malformations.

Prevalence of genetic disease

Type of genetic disease	Estimated prevalence per 1000 population
❖ **Single gene**	
Autosomal dominant	**2 – 10**
Autosomal recessive	**2**
X linked recessive	**1 – 2**
❖ **Chromosomal abnormalities**	**6–7**
❖ **Common disorders with appreciable genetic component**	**7–10**
❖ **Congenital malformations**	**20**
Total	**38–51**

Types of genetic diseases

1. Single gene (mendelian)

- Numerous though individually rare
- Clear pattern of inheritance
- High risk to relatives

2. Multifactorial

- Common disorders
- No clear pattern of inheritance
- Low or moderate risk to relatives

Type of genetic disease

3. Chromosomal

- Mostly rare
- No clear pattern of inheritance
- Usually low risk to relatives

Common reasons for cytogenetic analysis

- **Postnatal**
  - Newborn infants with birth defect
  - Children with learning disability
  - Children with dysmorphic features
  - Infertility
  - Recurrent miscarriages

Common reasons for cytogenetic analysis

- **Prenatal**

- Abnormalities on ultrasound scan
- Increased risk of Down syndrome (maternal age or biochemical screening)
- Previous child with a chromosomal abnormality
- One parent carries a structural chromosomal abnormality

- **Consanguinity** is an important issue to identify in genetic assessment because of the **increased risk of autosomal recessive disorders** occurring in the offspring of consanguineous couples.

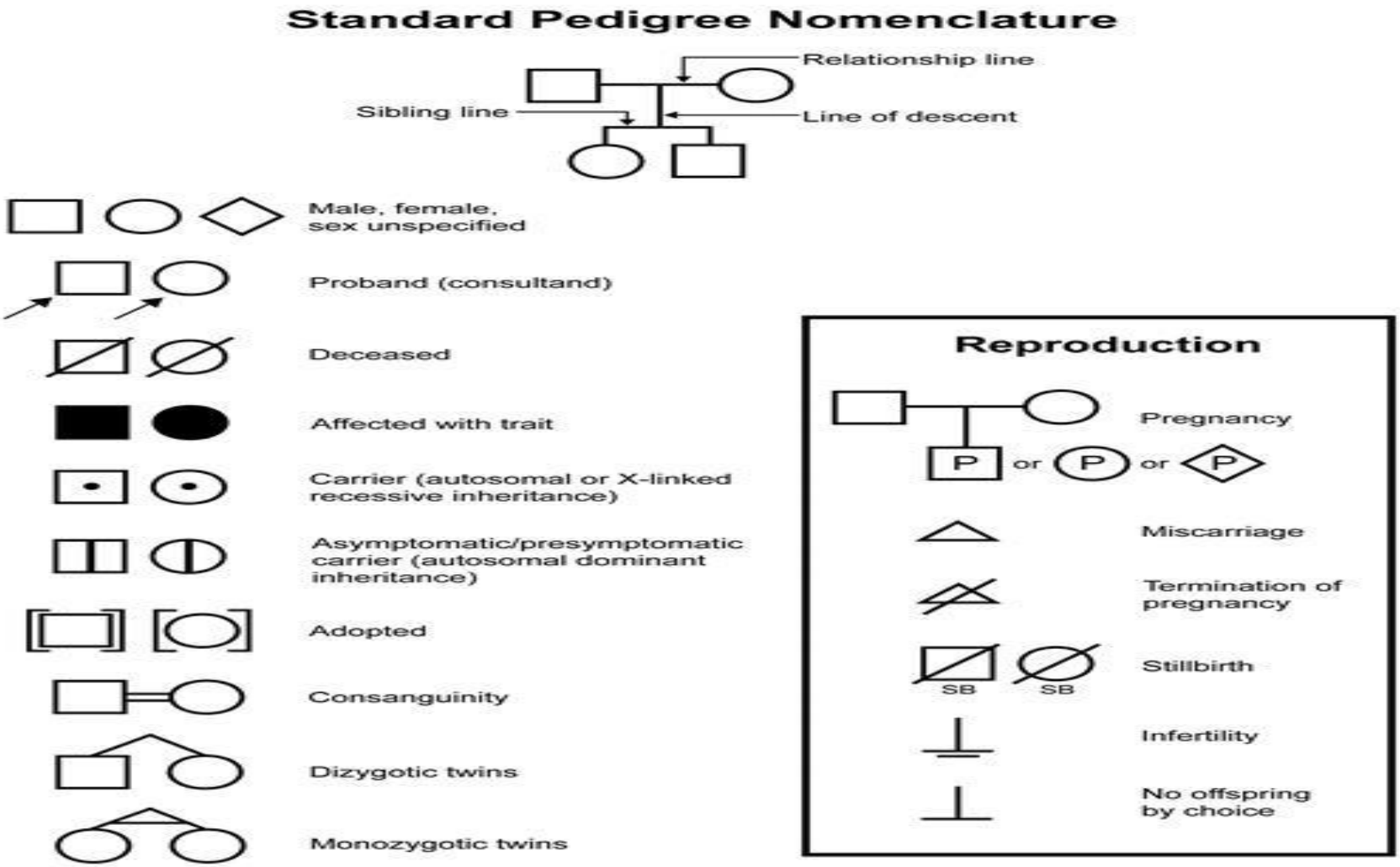
Genetic assessment

- Genetic diagnosis
- History
- Examination
- Investigation

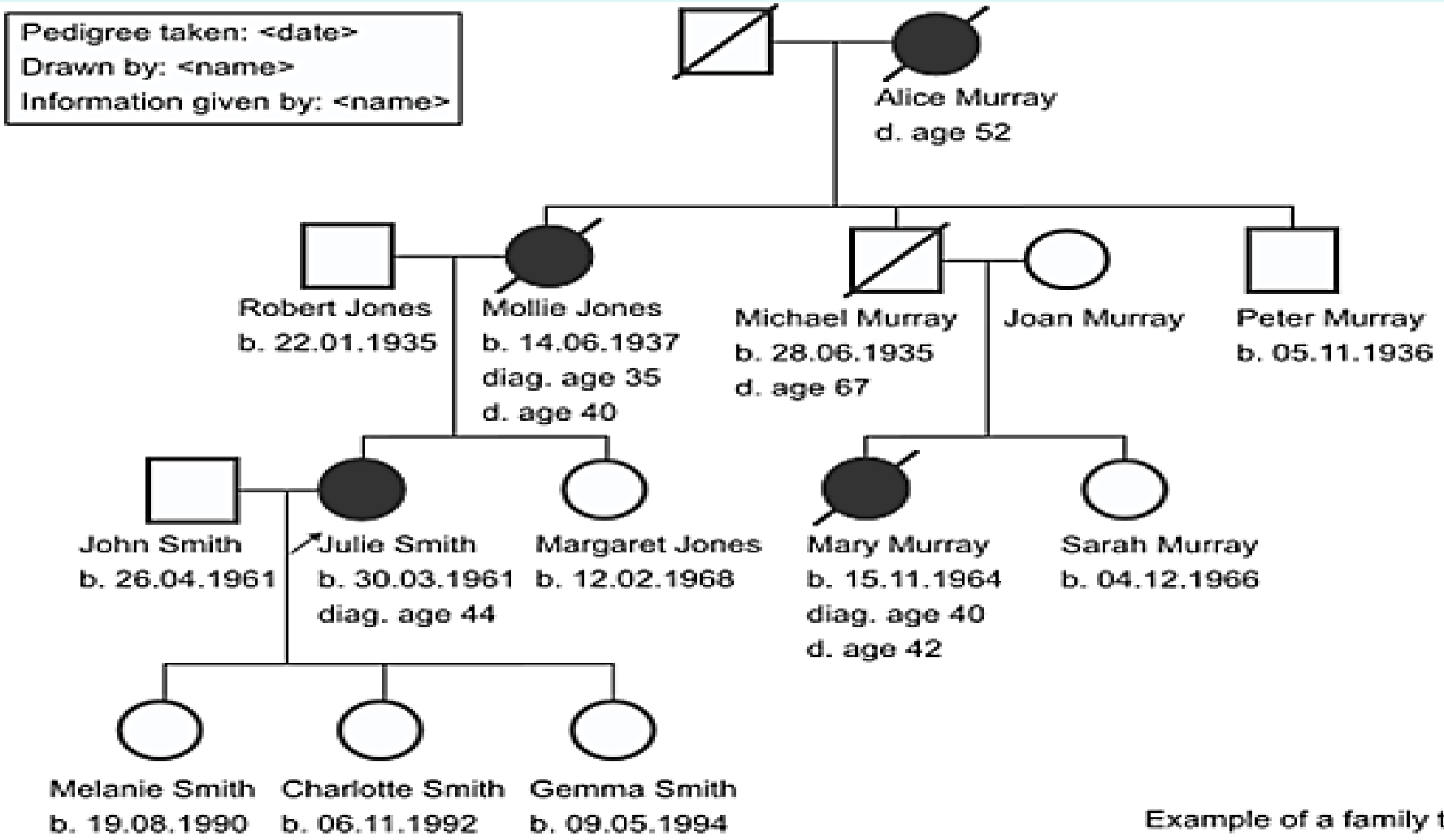
Genetic testing defined:

- **Diagnostic** – confirms a clinical diagnosis in a symptomatic individual
- **Presymptomatic** (“predictive”) – confirms that an individual will develop the condition later in life
- **Susceptibility** – identifies an individual at increased risk of developing the condition later in life
- **Carrier** – identifies a healthy individual at risk of having children affected by the condition
- **Prenatal** – diagnoses an affected fetus

Drawing a pedigree



Drawing a pedigree



Example of a family tree

Autosomal Dominant

- One parent is affected
- Manifested (occurs) in heterozygous state (the presence of 1 abnormal gene on one of the autosomes)
- Males and females are equally affected.
- 50% chance of children getting affected.
- New mutation
- Incomplete penetrance or non penetrance
- Variable expression

Examples of Autosomal Dominant Disorders

- Achondroplasia
- Marfan syndrome
- Neurofibromatosis
- Tuberous sclerosis.
- Ehlers–Danlos syndrome
- Huntington disease
- Myotonic dystrophy
- Noonan syndrome
- Osteogenesis imperfecta
- Otosclerosis
- Polyposis coli
- Familial hypercholesterolaemia

Autosomal Dominant inheritance

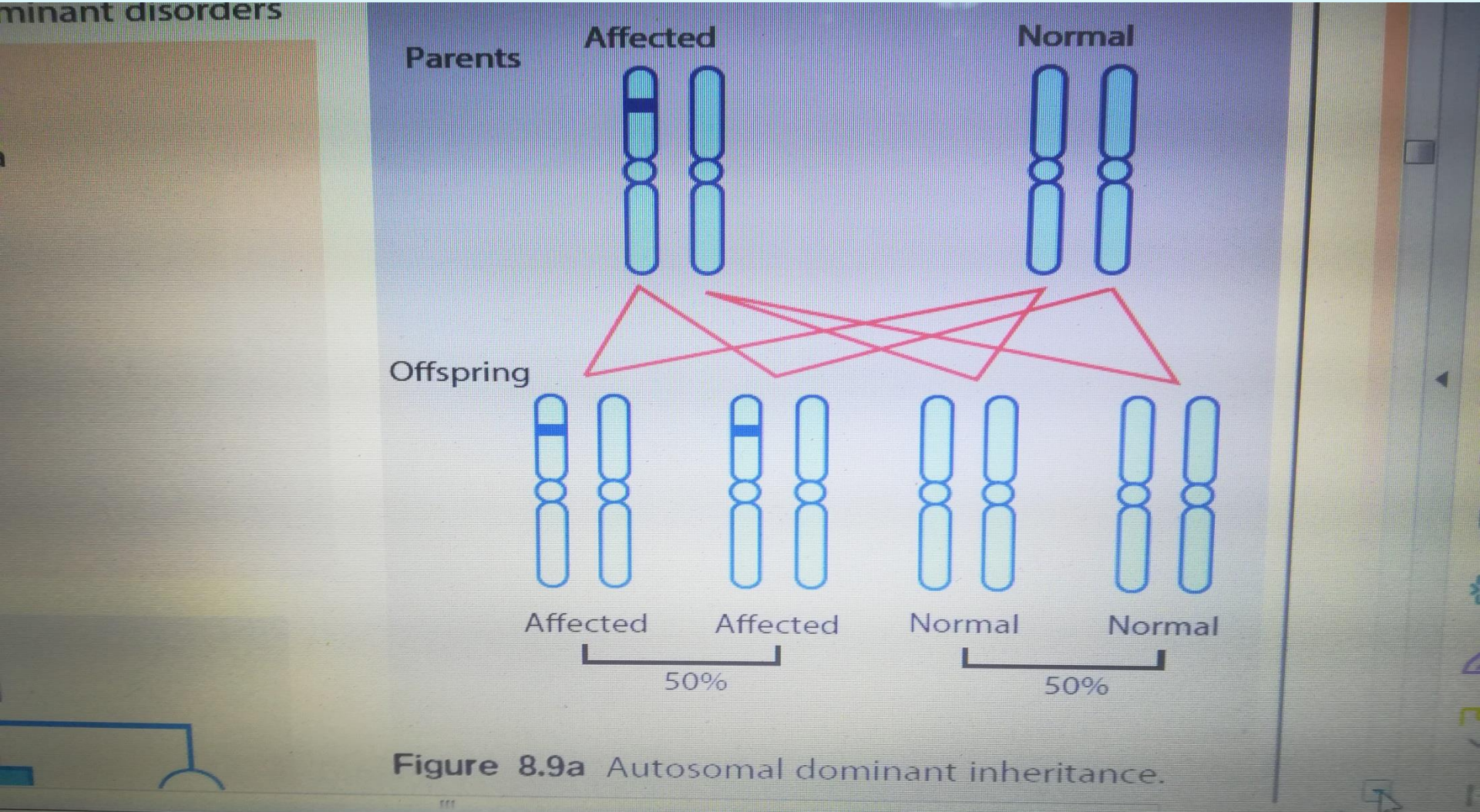
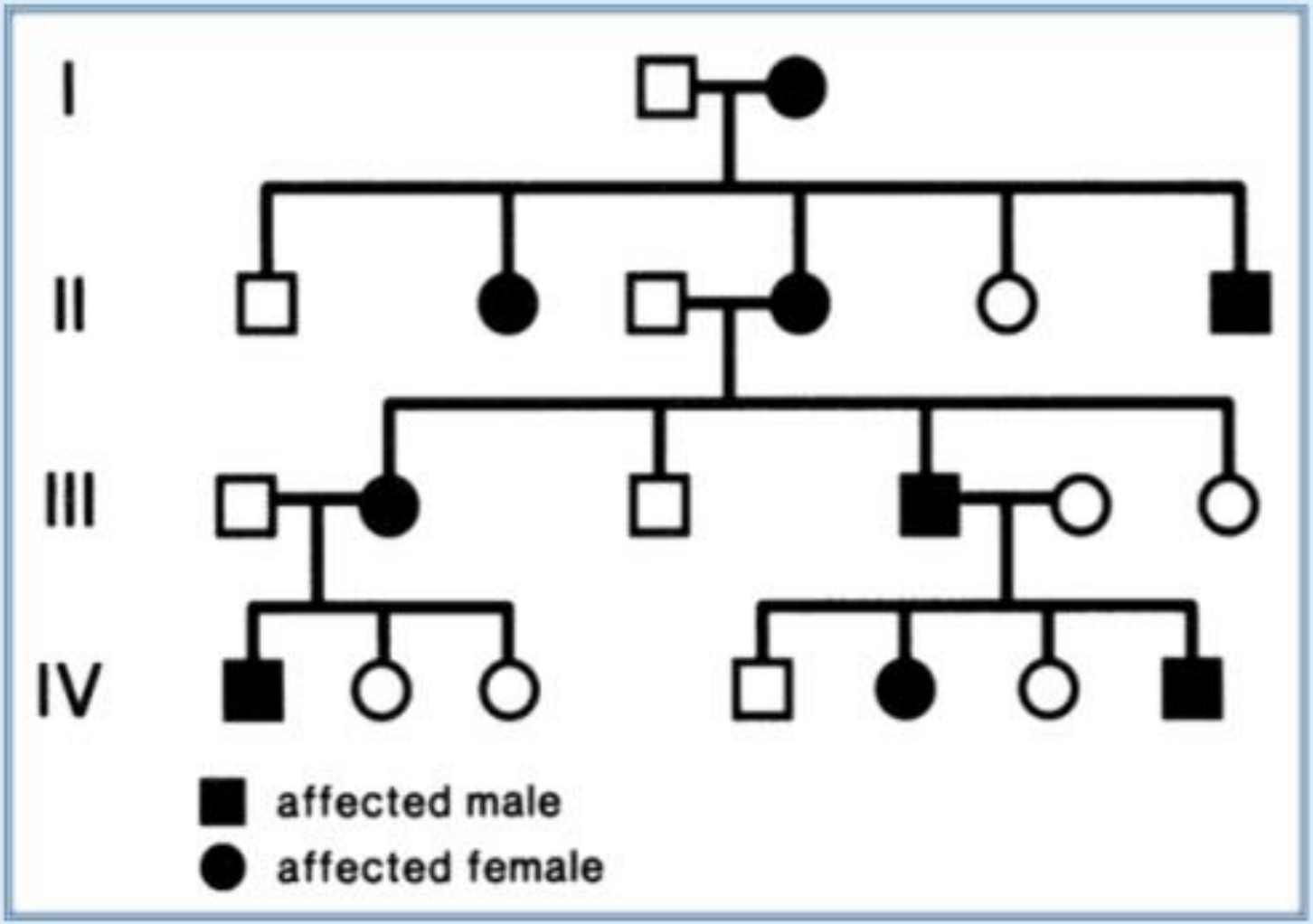


Figure 8.9a Autosomal dominant inheritance.

Autosomal Dominant



Autosomal Recessive

- Affected individuals are homozygous for the abnormal gene.
- Each unaffected parent will be a **heterozygous carrier (Healthy carriers)**
- Two carrier parents have a 1 in 4 risk of having an affected child
- Risk of these disorders is **increased by consanguinity**
- Autosomal recessive disorders often **affect metabolic pathways**, whereas autosomal dominant disorders often **affect structural proteins.**

Examples of Autosomal Recessive Disorders

- Congenital adrenal hyperplasia
- Cystic fibrosis
- Friedreich ataxia
- Galactosaemia
- Glycogen storage diseases
- Hurler syndrome
- Maple syrup urine disease
- Oculocutaneous albinism
- Phenylketonuria
- Sickle cell disease
- Tay –Sachs disease
- Thalassemia
- Werdnig–Hoffmann disease (SMA I).

Autosomal recessive inheritance

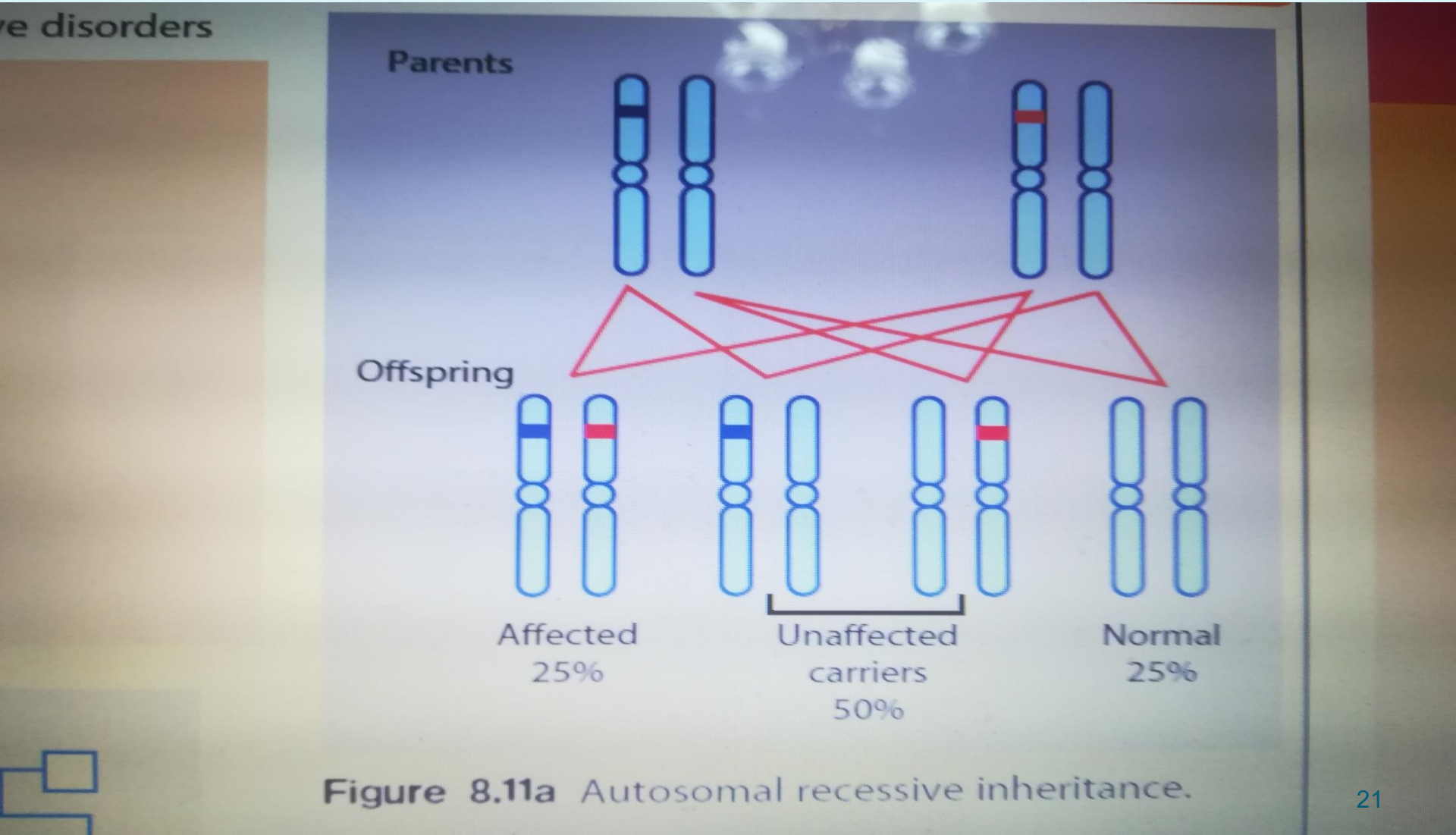


Figure 8.11a Autosomal recessive inheritance.

Autosomal Dominant

Autosomal Recessive

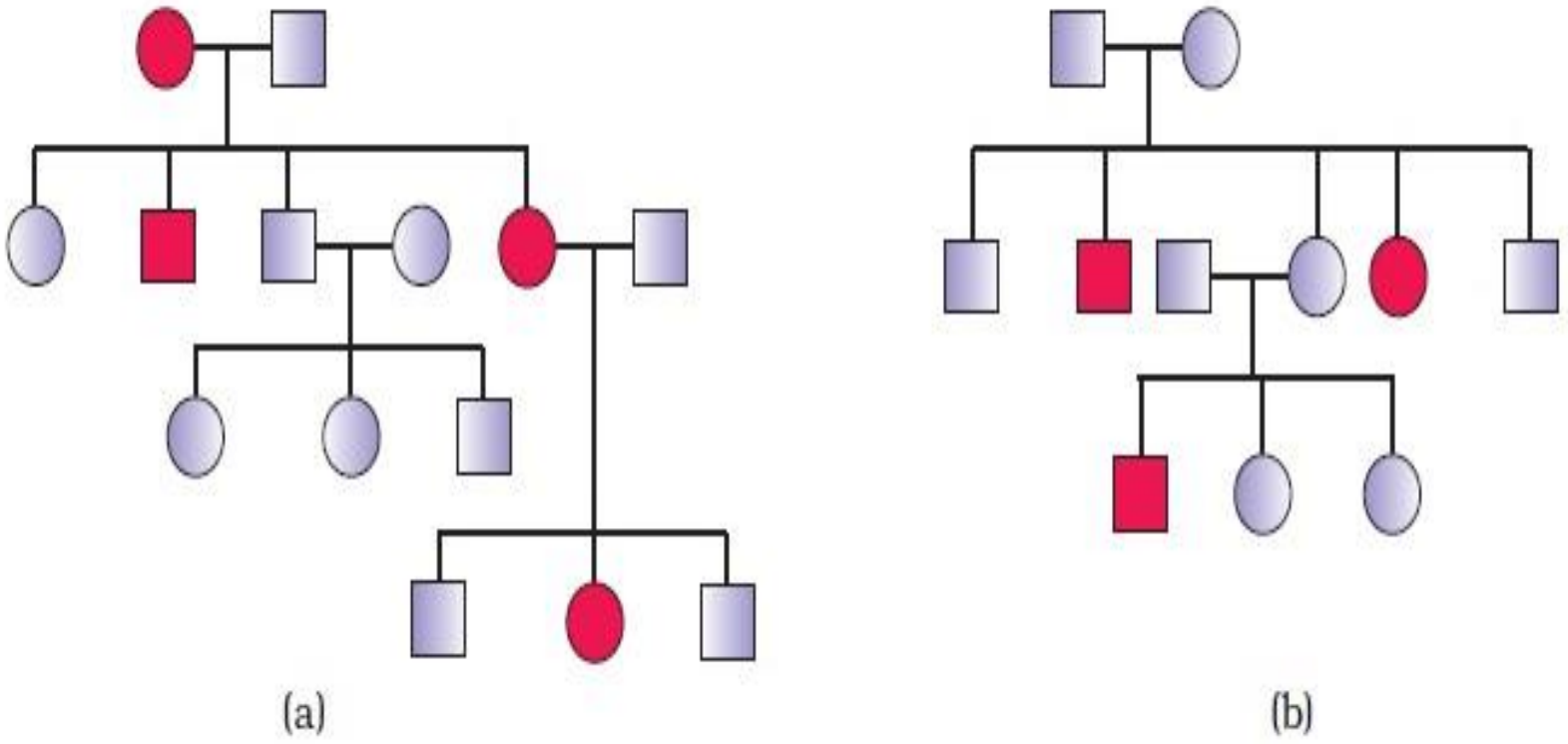


Figure 5.14 Representative pedigree analysis of (a) Autosomal dominant trait (for example: Myotonic dystrophy) (b) Autosomal recessive trait (for example: Sickle-cell anaemia)

X-Linked Recessive Inheritance

- Males are more commonly and more severely affected than females.
- Female carriers are **generally** unaffected, or if affected, they are affected more mildly than males.
- Female carriers have a 25% risk for having an affected son, a 25% risk for a carrier daughter, and a 50% chance of having a child that does not inherit the mutated X-linked gene.
- Affected males will have only carrier daughters.

X-Linked Recessive Inheritance

- Each son of a female carrier has a 1 in 2 (50%) risk of being affected
- Each daughter of a female carrier has a 1 in 2 (50%) risk of being a carrier

X-linked recessive inheritance

ve disorders

dystrophies

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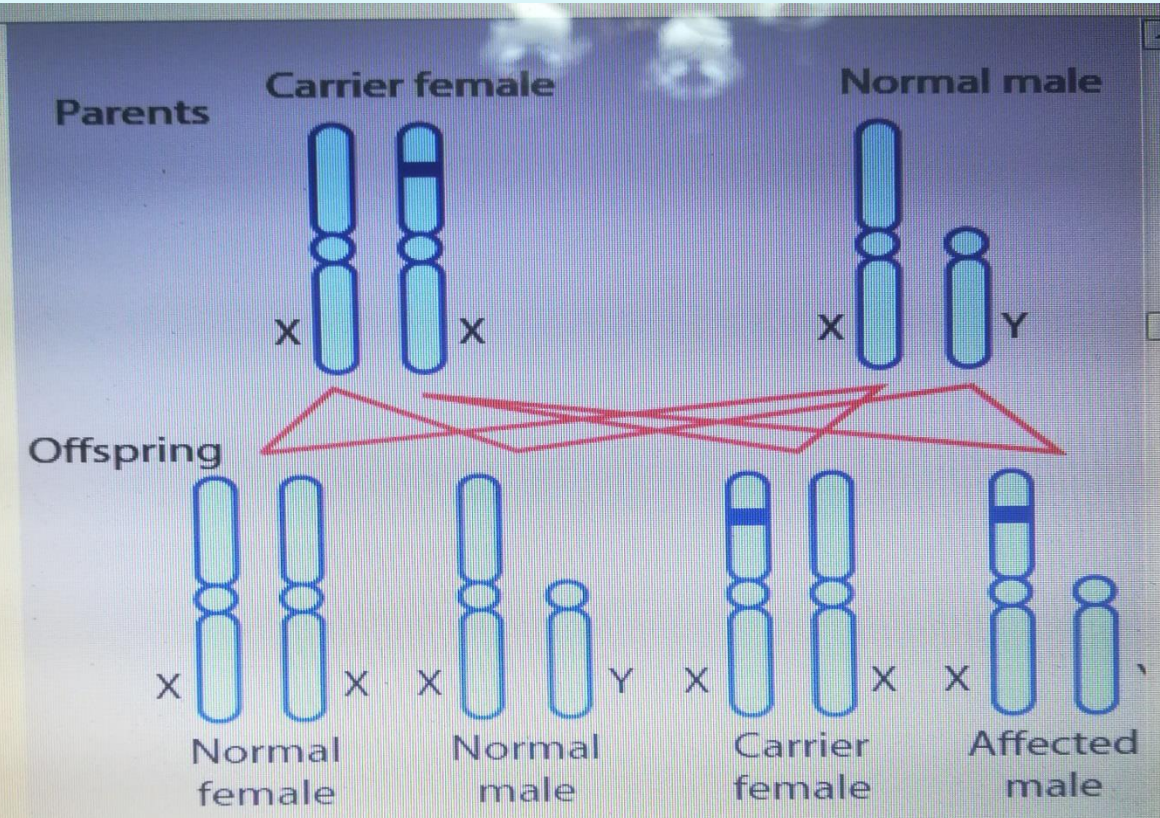


Figure 8.12a X-linked recessive inheritance.

Examples of X-Linked Recessive Disorders

- Colour blindness (red–green)
- Duchenne and Becker muscular dystrophies
- Fragile X syndrome
- Glucose-6-phosphate dehydrogenase (G6PD) deficiency
- Haemophilia A and B
- Hunter syndrome (Mucopolysaccharidosis II).

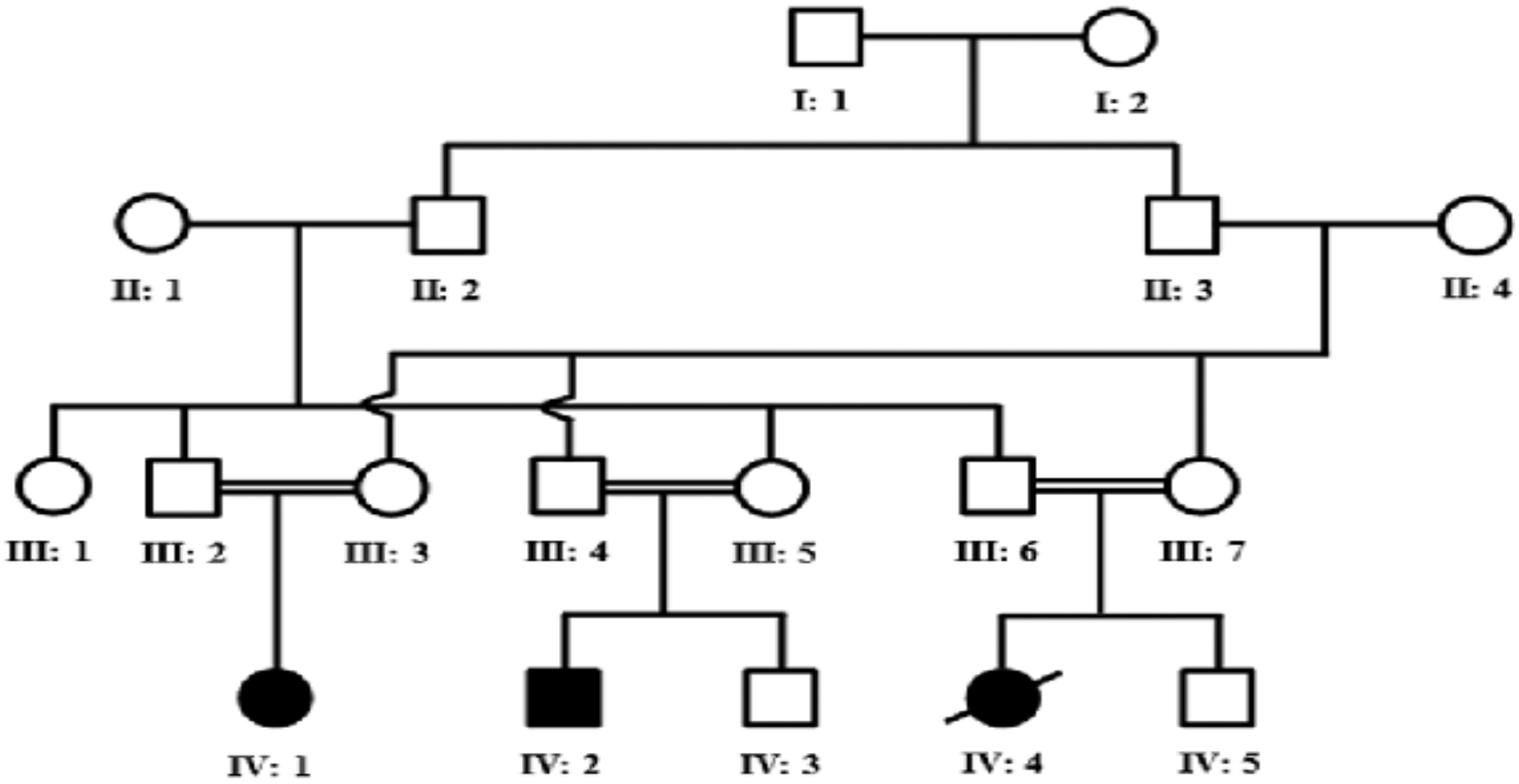
X-linked dominant

- Female carriers typically manifest abnormal findings.**(= Males &females affected)**
- An affected man will have only affected daughters and unaffected sons.
- Half of the offspring of an affected woman will be affected
- X-linked dominant conditions are lethal in a high percentage of males e.g…….

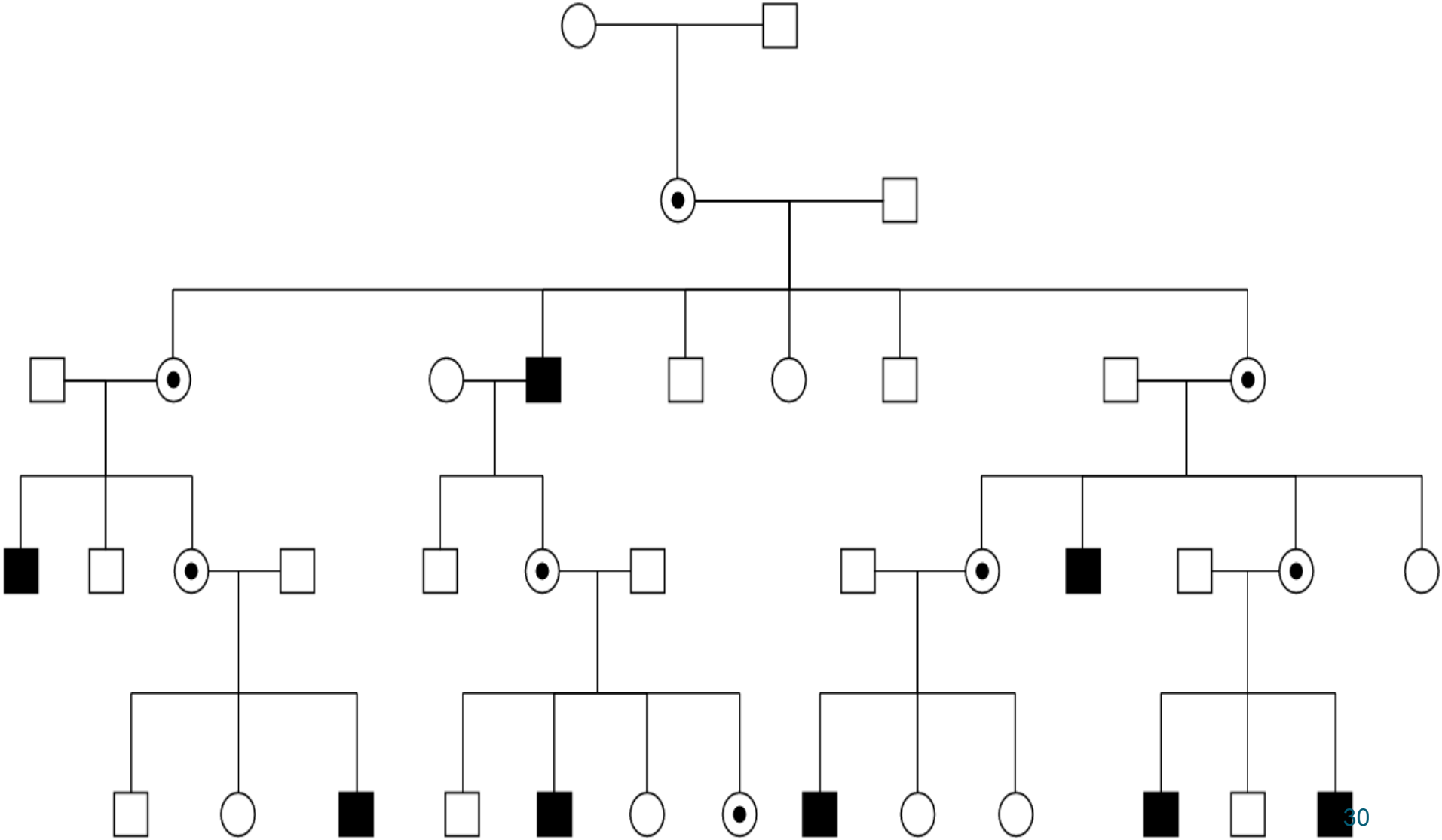
Examples of X-Linked Dominant Disorders

- Hypophosphatemic Rickets (Vit. D Resistant Rickets)
- Rett Syndrome
- Incontinentia pigmenti.

Autosomal ……..?


I: 1
I: 2
II: 1
II: 2
II: 3
II: 4
III: 1
III: 2
III: 3
III: 4
III: 5
III: 6
III: 7
IV: 1
IV: 2
IV: 3
IV: 4
IV: 5

X-LINKED ……???



Chromosomal abnormalities

- Chromosomal abnormalities are either **numerical** or **structural**.
- 20% of all conceptions are estimated to be lost spontaneously, and about half of these are associated with a chromosomal abnormality, mainly autosomal trisomy.
- Cytogenetic studies of gametes have shown that 10% of spermatozoa and 25% of mature oocytes are chromosomally abnormal

Down syndrome

- The most common autosomal trisomy and the **most common genetic cause** of **severe learning difficulties**.
- Risk of having a child with trisomy 21 increases with maternal age.
- The risk of recurrence after the birth of a child with trisomy 21 is increased by

  about 1% above the population age related risk.

Cytogenetics

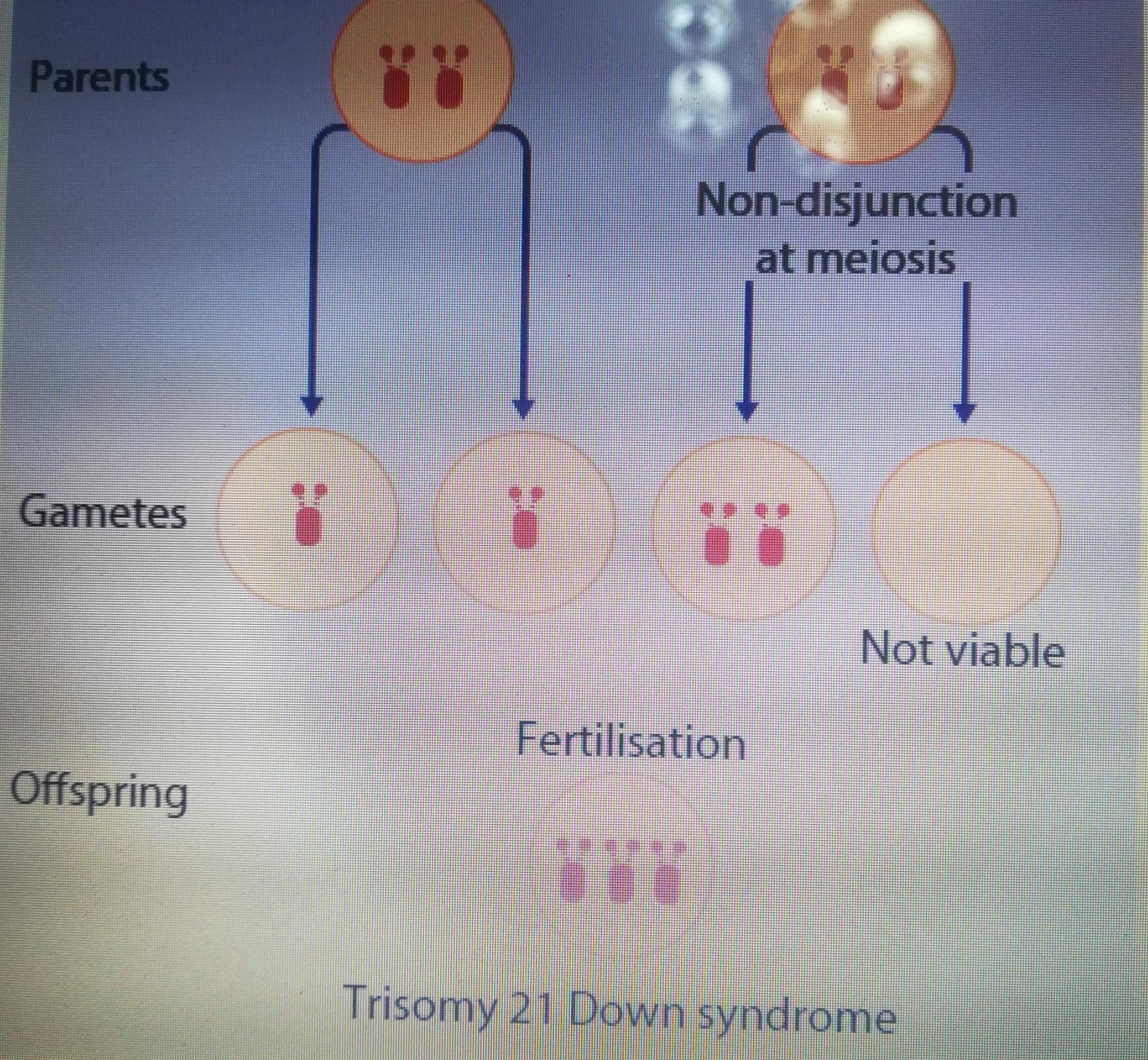
- The extra chromosome 21 may result from
- **Meiotic non-disjunction (94%)**
- **Translocation (5%)**
- **Mosaicism (1%)**

Incidence : All ages 1: 650 – 800

increase w. increase maternal age to

1:100 by 40 years old

1: 40 by 44 years old


Parents
Non-disjunction
at meiosis
Gametes
Not viable
Fertilisation
Offspring
Trisomy 21 Down syndrome

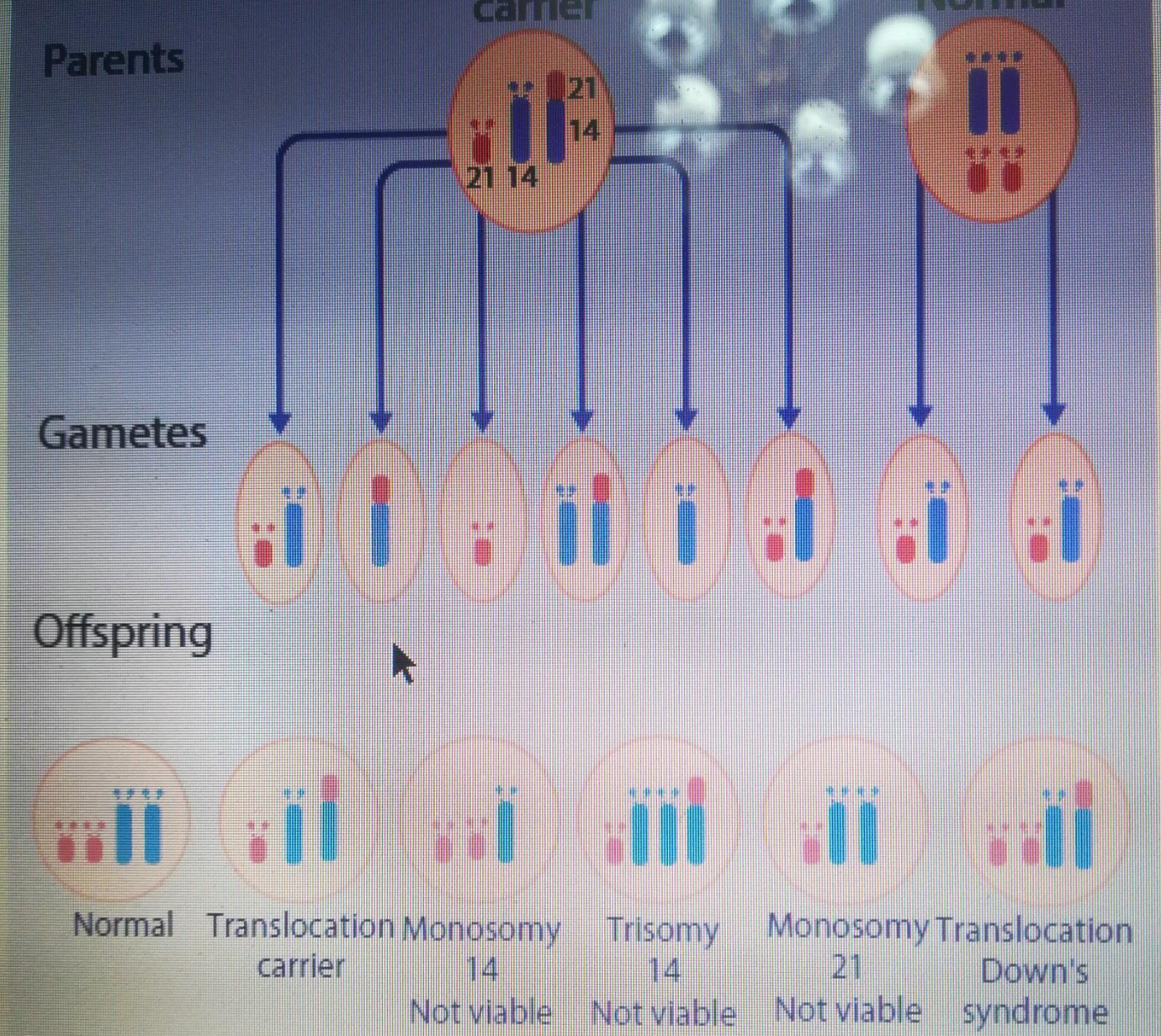
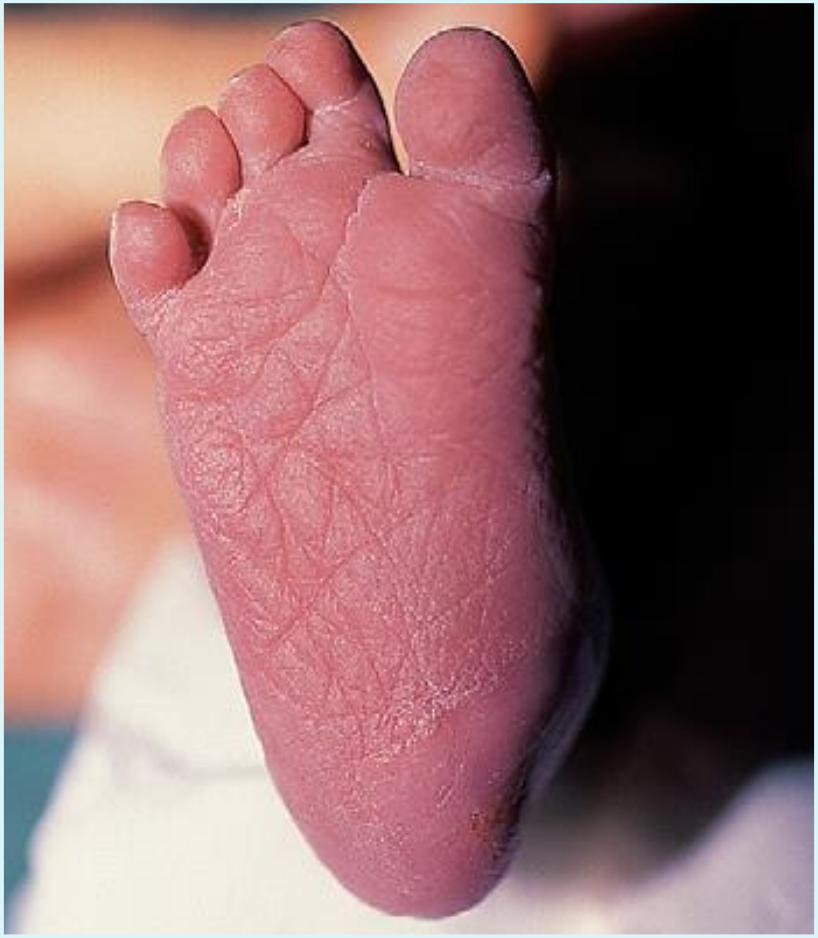
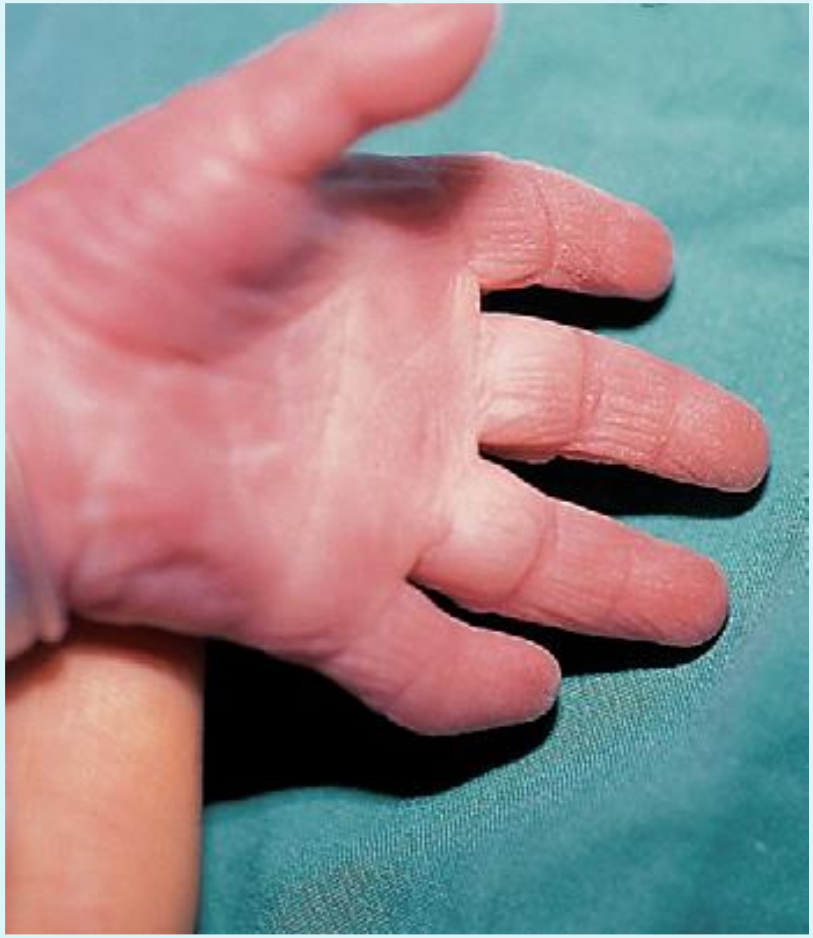


Figure 8.4 Translocation Down syndrome.
There is a Robertsonian translocation involving

Typical craniofacial appearance

- Round face and flat nasal bridge
- Lateral Upslanted palpebral fissures
- Epicanthic folds (a fold of skin running across the inner edge of the palpebral fissure)
- Brushfield spots in iris (pigmented spots)
- Small mouth and protruding tongue
- Small ears
- Flat occiput and third fontanelle





- Short neck
- Single palmar creases, incurved fifth finger and
- wide ‘sandal’ gap between toes
- Hypotonia
- **Congenital heart defects (40%)**]
- **Duodenal atresia**]
- **Hirschsprung disease**]

Imm. Med. problem

Later medical problems

- Delayed motor milestones
- Moderate to severe learning difficulties
- Small stature
- Increased risk of hypothyroidism and coeliac disease
- Epilepsy
- Alzheimer’s disease.

Later medical problems

- Increased susceptibility to infections
- Hearing impairment from secretory otitis media
- Visual impairment from cataracts, squints, myopia
- Increased risk of leukaemia and solid tumours
- Risk of atlanto-axial instability

Turner syndrome (45, X)

- The incidence is about 1 in 2500 live- born females
- The incidence does not increase with maternal age and risk of recurrence is very low.

Treatment is with:

- Growth hormone therapy
- Estrogen replacement for development of secondary sexual characteristics at the time of puberty (but infertility persists).

Clinical features of Turner

- Lymphedema of hands and feet in neonate,
- Spoon-shaped nails
- Short stature – a cardinal feature
- Neck webbing or thick neck
- Wide carrying angle (cubitus valgus)
- Widely spaced nipples
- Congenital heart defects (particularly coarctation of the aorta)

Clinical features of Turner

- Delayed puberty
- Ovarian dysgenesis resulting in infertility, although
- Hypothyroidism
- Renal anomalies
- Pigmented moles
- Recurrent otitis media
- Normal intellectual function in most


LADY
LUCK

Polygenic or multifactorial inheritance

- **Congenital malformations**
  - Neural tube defects (anencephaly and spina bifida)
  - Congenital heart disease
  - Cleft lip and palate
  - Pyloric stenosis
  - Congenital dislocation of the hip
  - Talipes equinovarus
  - Hypospadias