

# PEDIATRICS

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Lecture: No.1

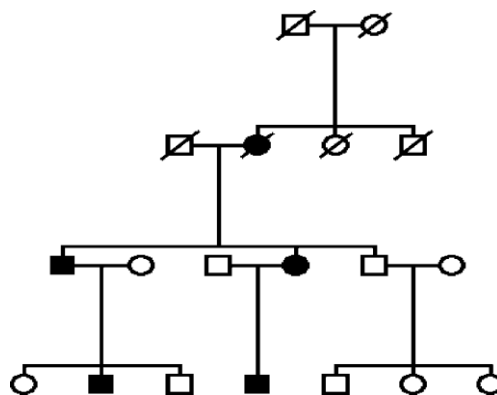
## MODES OF INHERITANCE

### Autosomal Dominant Inheritance

An autosomal dominant disorder is a condition in which the disease state is expressed when a mutation is present in one copy of the gene pair. The condition can equally affect both males and females and can be transmitted from parent to child. The risk that an affected individual can have a child with the same disorder is 50% with each pregnancy.

In some autosomal dominant conditions, if an individual has mutations in both gene copies for the disorder, the phenotype is more severe.

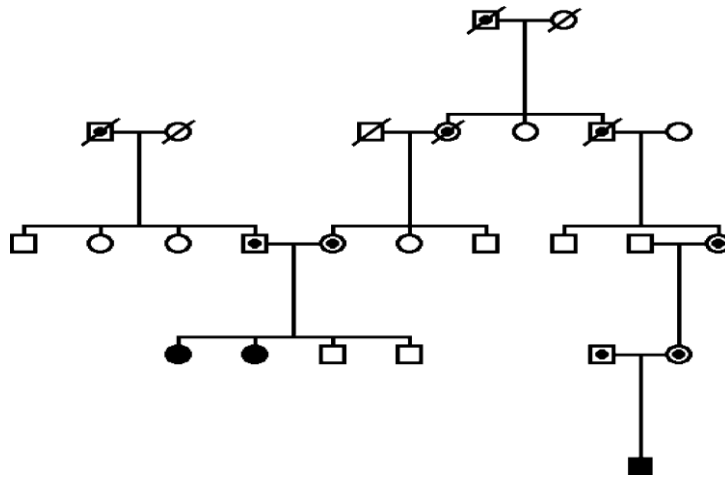
In achondroplasia, if both parents have the condition, there is a 25% risk with each pregnancy that the infant will inherit FGFR3 mutations from both parents. In the majority of autosomal dominant conditions, unaffected parents of a child with a de novo autosomal dominant condition will rarely have a second affected child. The risk of recurrence is generally estimated at  $\leq 1\%$ . In some autosomal dominant disorders, however, the risk of recurrence can be increased due to observance of germline mosaicism. Germline mosaicism is defined as an individual having the presence of two or more genetically different types of germline cells, resulting from mutation during the proliferation and differentiation of the germline. Osteogenesis imperfecta (OI) type II, a perinatal lethal form of a group of autosomal dominant type I collagen disorders, is one of the first disorders in which the occurrence of germline mosaicism was demonstrated



A typical pedigree of an autosomal dominant condition.

## Autosomal Recessive Inheritance

Autosomal recessive disorders are defined as conditions in which the disease state is expressed in the family until the first affected child is born. With each pregnancy, carrier couples have a 25% risk of having an affected child, 50% risk of having a child who is a carrier, and a 25% risk of having a child who is not a carrier and not affected with the disorder. Parents who are consanguineous have an increased risk of having a child with an autosomal recessive disorder and first cousin unions have an overall 1.7–2.8% increased risk above the general population risk to have a child with a major congenital anomaly

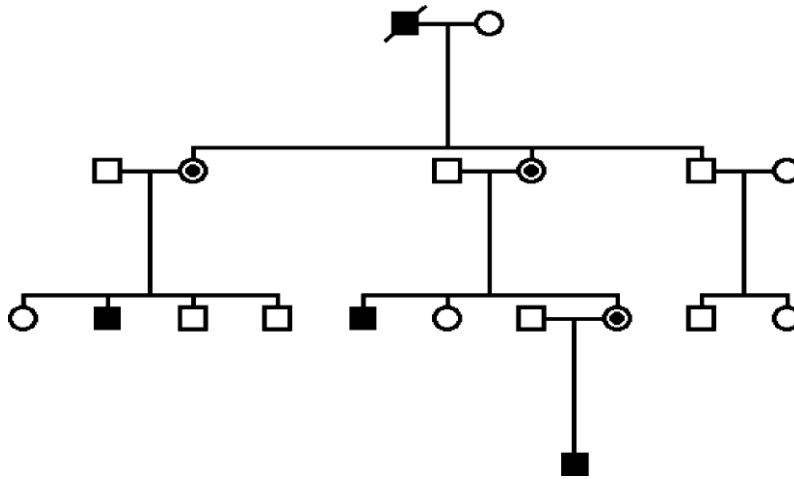


**A typical pedigree of an autosomal recessive condition.**

## Sex-Linked Conditions

Disorders that involve mutations in genes located on the X sex chromosome are referred to as X-linked disorders. They can be either dominant or recessive. Pedigrees of families with X-linked conditions can be distinguished from autosomal dominant or recessive conditions because transmission of the condition differs between males and females. Because normal males have one copy of the X chromosome and females have two copies, females undergo inactivation of one of their X chromosomes to maintain equal gene dosage between the sexes. The principle of X inactivation is referred to as the Lyon hypothesis.

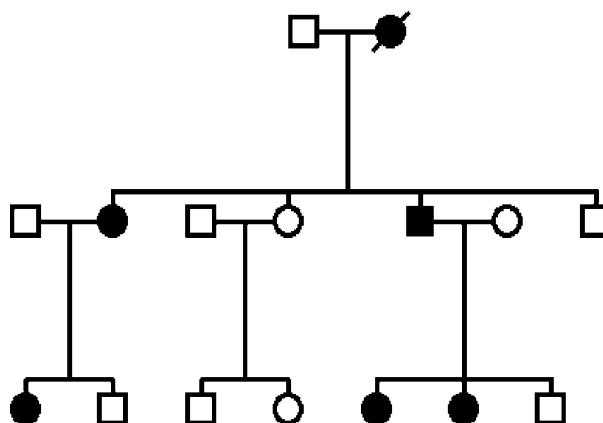
Inactivation of one of the X sex chromosomes occurs early in embryogenesis, generally randomly determined, and permanent, with all subsequent cells derived from the original cell having the same X sex chromosome inactivated



**A typical pedigree of an X-linked recessive condition.**

There are areas of the X sex chromosome, however, that never become inactivated, and these segment Only a few disorders are inherited in an X-linked dominant pattern. In disorders like X-linked hypophosphatemic rickets, both males and females express the disease state if a gene mutation is present. The risk of transmitting the disorder, however, differs based on the sex of the individual . Affected males cannot transmit the condition to their sons but all of their daughters will be affected. Affected females have a 50% risk with each pregnancy of having an affected child, regardless of whether the child is male or female. In conditions like incontinentia pigmenti type 2 and X-linked chondrodysplasia punctata, the condition is generally considered lethal in males and therefore, only affected females may be observed in the family . With each pregnancy, affected females have a 25% risk of having an affected daughter, 25% risk of having an unaffected daughter, 25% risk of having an unaffected son, and 25% risk of having an affected son. The affected male infant may be miscarried, stillborn, or expire shortly after birth.

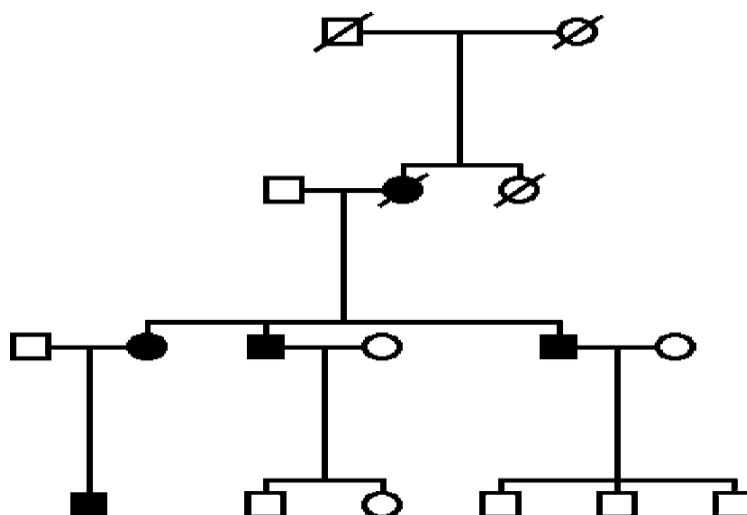
In X-linked recessive disorders, males who have a gene mutation express the disease state but females who have one gene mutation are generally carriers and may not manifest features of the disorder. Females who have mutations in both gene copies will be affected.



**A typical pedigree of an X-linked dominant condition.**

## Mitochondrial Disorders

The mitochondria are unique organelles in the human cell because it has its own genome and a single cell generally has >1000 copies of the mitochondrial genome dispersed in >100 mitochondria. Mitochondrial DNA (mtDNA) disorders are unique in that they are associated with maternal inheritance only. A mature oocyte is felt to have >100,000 copies of the mitochondrial genome while sperm contain very few. A child, therefore, inherits the mitochondrial genome from the mother and not from the father. A typical pedigree is characterized by the presence of both affected males and females but no transmission of the disorder through affected males.



### A typical pedigree of an mt DNA disorder.

Complex Disorders Disorders in which a combination of genetic and environmental factors is involved in the manifestation of the disease state are referred to as complex or multifactorial disorders. Multifactorial disorders, such as isolated congenital heart defects, isolated cleft lip and/or palate, diabetes mellitus, and hypertension, can be observed to aggregate in a family but not follow a clear mendelian mode of inheritance.

## GENETIC SCREENING AND PRENATAL DIAGNOSIS

The prevalence of some genetic disorders varies by ethnic group and populations due to factors such as the founder effect and genetic drift. Current practices of standard care recommend screening for carrier status of certain genetic disorders given a person's ethnicity.

Screening for Genetic Disorders in the Fetus Assessing risk for certain genetic conditions has become a routine aspect of prenatal care. These methods of screening are designed to adjust the person's baseline risk and are not considered diagnostic tools. Positive screen results should lead to referrals for genetic counseling and consideration or prenatal diagnostic testing. Since the 1970s, maternal serum screening in the second trimester has been utilized as an effective tool to assess risks for open neural tube defect (ONTD), Down syndrome,

trisomy 18, and Turner syndrome. The traditional maternal serum screen (also referred to as the triple screen) involves assessment of maternal  $\alpha$ -fetoprotein (AFP), human chorionic gonadotropin (hCG), and unconjugated estriol (uE3) between 15 and 20 weeks gestation, with optimal time of screening at 16–18 weeks gestation.

## **Methods of Prenatal Diagnosis**

Amniocentesis and chorionic villus sampling (CVS) are two methods of prenatal diagnosis that are being routinely offered to couples. Both methods can be used to detect chromosome abnormalities and single gene disorders with equal sensitivity and accuracy of results (>99%). Chromosome analysis is generally performed on cultured amniocytes or villi with a 1.5–2 week turnaround time for results. Amniocentesis has been available since the 1970s for the detection of chromosome abnormalities. Traditionally, ultrasound-guided amniocentesis is performed after 15 weeks gestation and the risk of fetal loss is 0.5–1.0%.

Early amniocentesis is performed between 13 and 15 weeks gestation but associated with a higher risk of fetal loss and leakage of amniotic fluid. A significant increased risk for talipes equinovarus (club foot) has also been observed with early amniocentesis, especially if leakage of amniotic fluid is present.

Chorionic villus sampling has been readily available since the mid 1980s as a method of detecting chromosome abnormalities and single gene disorders in the fetus. The majority of cases are performed transcervically with the use of ultrasound guidance and a catheter between 10 and 12 weeks gestation. The risk of CVS-associated limb defects appears to be small but real and is estimated to be 1 in 3000.

Since the 1980s, fetal blood sampling or cordocentesis has been an available method of prenatal diagnosis and a vehicle for fetal therapy. Fetal blood sampling is performed after 18 weeks gestation using ultrasound guidance to insert a needle into the umbilical vein or artery.

Fetal blood sampling can be offered for rapid chromosome analysis, diagnosis of blood disorders when direct gene testing is not available, and for fetal infections. Fetal blood sampling can also be used for treatments such as transfusion of blood components or direct delivery of medications to the fetus. The risk of miscarriage is higher than CVS or amniocentesis and is estimated at 1–2%.