



Umm AL Qura University

PATTERNS OF INHERITANCE

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PATTERNS OF INHERITANCE

- Definition
- Family Studies
- Pedigree drawing and Terminology
- Mendelian inheritance
- Non-Mendelian inheritance
- Mitochondrial inheritance

PATTERNS OF INHERITANCE: DEFINITION

- Its the manner in which a particular genetic trait or disorder is passed from one generation to the next.
- Examples:
 - Autosomal dominant,
 - autosomal recessive,
 - X-linked dominant,
 - X-linked recessive,
 - multifactorail, and
 - mitochondrial inheritance.

- Autosomal dominant
- autosomal recessive
- X-linked dominant
- X-linked recessive
- multifactorail,
- mitochondrial

PATTERNS OF INHERITANCE

- The importance of studying the pattern of inheritance of disorders within families:
 - Genetic counseling: Advice to be given to members of a family regarding the susceptibility of their developing the disease OR.
 - Passing it on to their children.

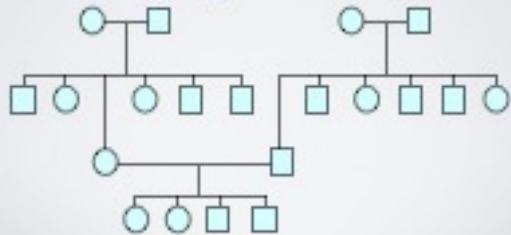
FAMILY STUDIES

If we wish to investigate whether a particular trait or disorder in humans is genetic and hereditary, we usually have to rely either on observation of the way in which it is transmitted from one generation to another, or on study of its frequency among relatives.

An important reason for studying the pattern of inheritance of disorders within families is to enable advice to be given to members of a family regarding the likelihood of their developing it or passing it on to their children, i.e. *genetic counseling* (Ch. 17). Taking a family history can, in itself, provide a diagnosis. For example, a child could come to the attention of a doctor having a fracture after a seemingly trivial injury. A family history of relatives with a similar tendency to fracture and blue

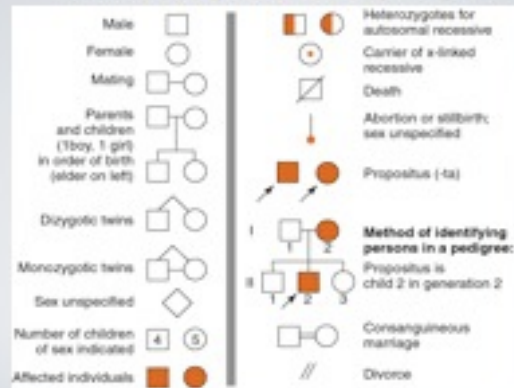
IMPORTANCE DEFINITION

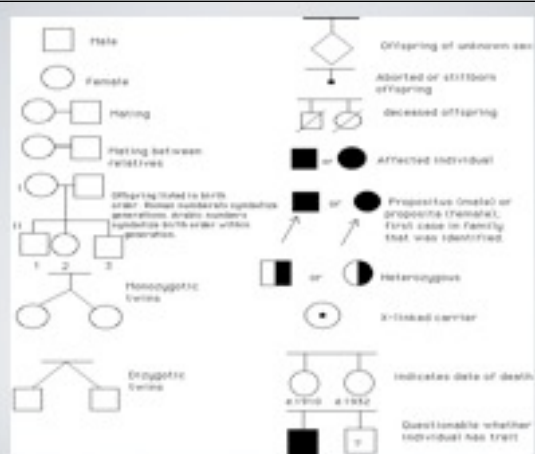
- A pedigree is a chart of the genetic history of family over several generations.



A family tree is a shorthand system of recording the pertinent information about a family. It usually begins with the person through whom the family came to the attention of the investigator. This person is referred to as the **index case**, *proband* or *propositus*, or if female, the *proposita*. The position of the proband in the family tree is indicated by an arrow. Information about the health of the rest of the family is obtained by asking direct questions about brothers, sisters, parents and maternal and paternal relatives, with the relevant information about the sex of the individual, affection status and relationship to other individuals being carefully recorded in the pedigree chart (Fig. 7.1). Attention to detail can be crucial because patients do not always appreciate the important difference between siblings and *half*-siblings, or might overlook the fact, for example, that the child of a brother who is at risk of Huntington disease is actually a *step*-child and not a biological relative.

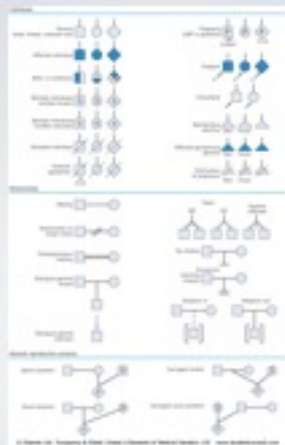
Standard symbols for pedigrees.





Genetic risks

Each gamete from an individual with a dominant trait or disorder will contain either the normal allele or the mutant allele. If we represent the dominant mutant allele as 'A' and the recessive normal allele as 'a', then the various possible combinations of the gametes can be represented in a Punnett's square ([Fig. 7.4](#)). Any child born to a person affected with a dominant trait or disorder has a 1 in 2 (50%) chance of inheriting it and being similarly affected.



IMPORTANCE DEFINITION

- **Locus:** The position of a gene on a chromosome.
- **Allele:** one of several alternative form of a gene at a given gene locus.
- **Genotype:** refers to an individual's genes.
- **Phenotype:** refers to an individual's physical appearance.
- **Heterozygous:** having two different alleles at a given gene locus.
- **Homozygous:** having identical alleles at a given gene locus.

Genotype

- the gene types a person inherited



Phenotype

- the physical (& behavioral) characteristics an individual displays



Alleles

Quiet! I'll speak for both of us!

I'll have to be in charge now!



Genes come in pairs, with one copy inherited from each parent.

Many genes come in a number of variant forms, known as alleles.

A dominant allele prevails over a normal allele.

A recessive allele prevails if its counterpart allele on the other chromosome becomes inactivated or lost.

MENDELIAN DISORDERS

- Austrian botanist Gregor Mendel (1822-84)
- More than 11,000 Mendelian (monogenic) disorders have been revealed
- OMIM (Online Mendelian Inheritance in Man) database



MENDELIAN INHERITANCE

Autosomal inheritance:

- Dominant.
- Recessive.

Sex-linked inheritance:

- Dominant.
- Recessive.



Over 11000 traits or disorders in humans exhibit single gene *unifactorial* or *Mendelian inheritance*. However, characteristics such as height, and many common familial disorders, such as diabetes, hypertension, etc., do not usually follow a simple pattern of Mendelian inheritance ([Ch. 9](#)).

A trait or disorder that is determined by a gene on an autosome is said to show *autosomal inheritance*, whereas a trait or disorder determined by a gene on one of the sex chromosomes is said to show *sex-linked inheritance*.

Autosomal Inheritance

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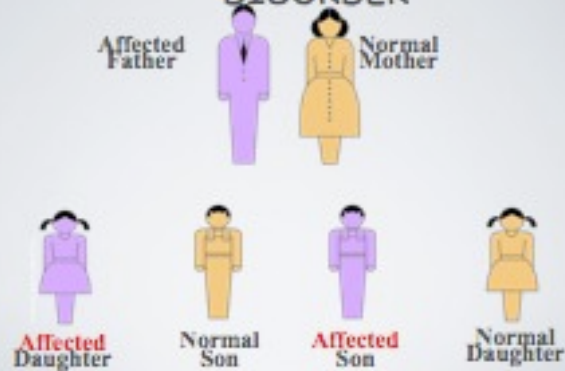
A recessive allele prevails if its counterpart allele on the other chromosome becomes inactivated or lost.

AUTOSOMAL DOMINANT INHERITANCE

- Both male and female are **affected**
- The disease is observed in **multiple generations**
- Transmission of the disease can be from **both sexes**
- Mutation in only **one allele** is enough to express the disease
- Vertical transmission
- The offspring have **50% chance to have the disease**

An autosomal dominant trait is one which manifests in the heterozygous state, i.e. in a person possessing both an abnormal or mutant allele and the normal allele. It is often possible to trace a dominantly inherited trait or disorder through many generations of a family ([Fig. 7.2](#)). In South Africa the vast majority of cases of porphyria variegata can be traced back to one couple in the late seventeenth century. This is a metabolic disorder characterized by skin blistering through increased sensitivity to sunlight and the

AUTOSOMAL DOMINANT DISORDER



- Punnett's square showing possible gamete combinations for an autosomal dominant allele

	W	w
W	WW	Ww
w	Ww	ww

AUTOSOMAL DOMINANT DISORDERS



- Huntington disease
- Autosomal dominant
- Gene in chromosome 4p
- Adult onset of the disease
- Chorea movement disorder
- Mood disturbance
- Progressive loss of mental activity

Huntington's disease, chorea, or disorder (HD), is an incurable [neurodegenerative genetic disorder](#) that affects muscle coordination and some [cognitive](#) functions, typically becoming noticeable in middle age. It is the most common genetic cause of abnormal involuntary writhing movements called [chorea](#). It is much more common in people of Western Europe descent than in those from Asia or Africa. The disease is caused by a [dominant mutation](#) on either of the two copies of a specific [gene](#), located on an [autosomal chromosome](#). Any child of an affected parent has a 50% chance of inheriting the disease. In rare situations where both parents have an affected gene, or either parent has two affected copies, this chance is greatly increased. Physical symptoms of Huntington's disease can begin at any age from infancy to old age, but usually begin

AUTOSOMAL DOMINANT DISORDER



- Marfan Syndrome
- Autosomal dominant
- Gene in chromosome 15q (Fibrillin)
- Connective tissue disorder with characteristic skeletal, dermatological, cardiac, aortic, ocular and dural malformations.

Autosomal dominant traits may involve only one organ or part of the body, for example the eye in congenital cataracts. It is common, however, for autosomal dominant disorders to manifest in different systems of the body in a variety of ways. This is pleiotropy - a single gene that may give rise to two or more apparently unrelated effects. In tuberous sclerosis affected individuals can present with either learning difficulties, epilepsy, or a facial rash known as adenoma sebaceum ([Fig. 7.5](#)) (histologically composed of blood vessels and fibrous tissue known as angiokeratoma); some affected individuals have all features (see also [p. 318](#)). Recently, our conceptual understanding of the term *pleiotropy* has been challenged by the remarkably diverse syndromes that can result from different mutations in the same gene, for example the *LMNA* gene (which encodes Lamin A/C) and the X-linked Filamin A gene. Mutations in *LMNA* may cause Emery-Dreifuss muscular dystrophy, a form of limb girdle muscular dystrophy, a form of Charcot - Marie-Tooth disease ([n 297](#)) dilated cardiomyopathy ([n 305](#)) Dunnigan-type familial partial

AUTOSOMAL DOMINANT DISORDER



Achondroplasia is autosomal dominant genetic disorder that is a common cause of **dwarfism**

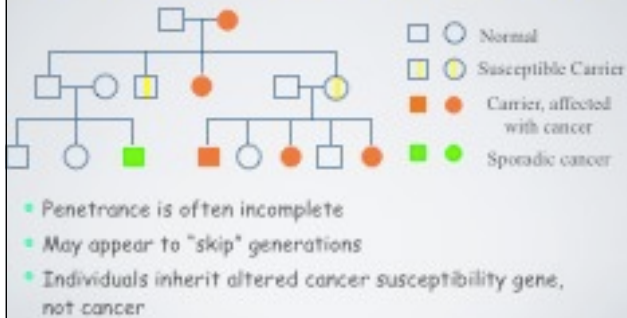
Achondroplasia dwarfism (pronounced [/eɪ kən drou 'pleɪ ziː ʌ/](#)) is a type of [autosomal dominant genetic disorder](#) that is a common cause of [dwarfism](#). Achondroplastic dwarfs have [short stature](#), with an average adult height of 131 [cm](#) (4 [feet](#), 3-1/2 inches) for males and 123 cm (4 feet, 1/2 inches) for females.

The prevalence is approximately 1 in 25,000.[\[1\]](#)

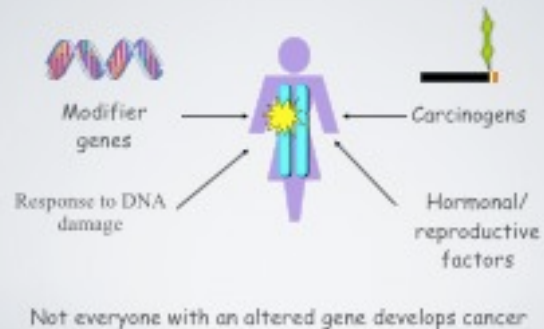
Epidemiology

Achondroplasia is one of several [congenital conditions](#) with similar presentations, such as [osteogenesis imperfecta](#), multiple epiphyseal dysplasia tarda, [achondrogenesis](#), [osteopetrosis](#),

Most Cancer Susceptibility Genes Are Dominant With Incomplete Penetrance



Factors Affecting Penetrance



AUTOSOMAL DOMINANT DISORDERS

- **Variable expressivity:** some individuals show more aggressive form of the disease while other showed a milder form of the disease.
- **Reduced penetrance:** is term used to indicate that the disease some time to presenting no abnormal clinical feature
- **New mutation**
- **Codominance:** the presence of two alleles in heterozygous state (e.g. AB blood group)

New mutations

In autosomal dominant disorders an affected person will usually have an affected parent. However, this is not always the case and it is not unusual for a trait to appear in an individual when there is no family history of the disorder. A striking example is achondroplasia, a form of short-limbed dwarfism ([p. 92](#)), in which the parents usually have normal stature. The sudden unexpected appearance of a condition arising as a result of a mistake occurring in the transmission of a gene is called a *new mutation*. The dominant mode of inheritance of achondroplasia could only be confirmed by the observation that the offspring of persons with achondroplasia had a 50% chance of having achondroplasia or being of normal stature.

AUTOSOMAL RECESSIVE INHERITANCE

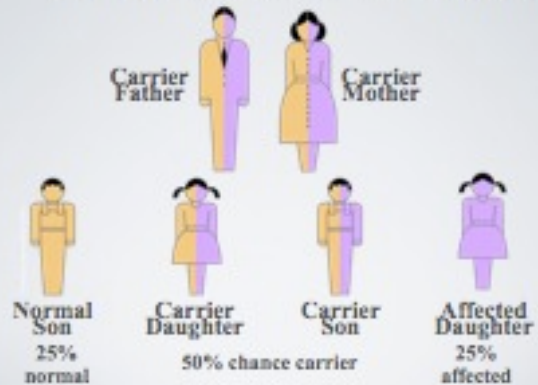
- Both male and female are **affected**
- The disease is observed in only **single generation**
- Both gene alleles (**Heterozygous**) need to be affected in order to **express the disease**

Recessive traits and disorders are only manifest when the mutant allele is present in a double dose, i.e. **homozygosity**.

Individuals heterozygous for such mutant alleles show no features of the disorder and are perfectly healthy, i.e. they are *carriers*.

The family tree for recessive traits differs markedly from that seen in autosomal dominant traits ([Fig. 7.7](#)). It is not possible to trace an autosomal recessive trait or disorder through the family, i.e. all the affected individuals in a family are usually in a single *sibship*, i.e. brothers and sisters. This is sometimes referred to as 'horizontal' transmission (an inappropriate and misleading term)

Autosomal Recessive Inheritance



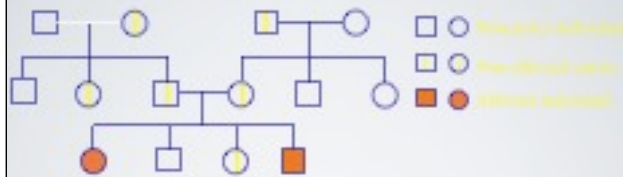
- Punnett's square showing possible gamete combinations for an autosomal recessive allele

	a	A
A	Aa	AA
a	aa	aA



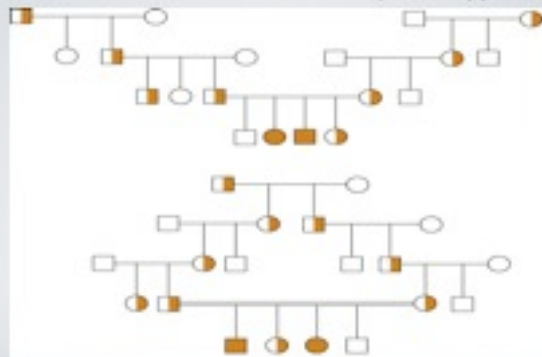
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Autosomal Recessive Inheritance



- Two germline mutations (one from each parent) to develop disease
- Equally transmitted by men and women

Families with individuals expressing autosomal recessive phenotypes



AUTOSOMAL RECESSIVE INHERITANCE

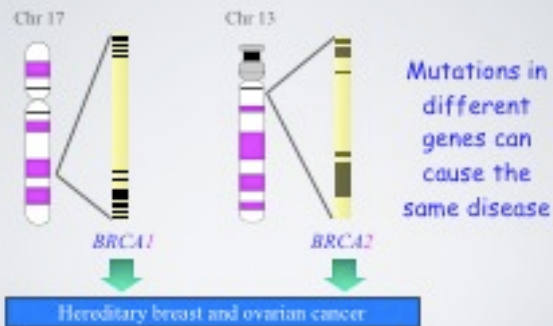
- Consanguinity
- Pseudodominance is an autosomal recessive condition appears in subsequent generations and so therefore appears to follow an autosomal dominant pattern.
- Locus heterogeneity: A single disorder, trait, or pattern of traits caused by mutations in genes at different chromosomal loci.

Pseudodominance is situation where the inheritance of an [autosomal recessive](#) trait mimics an [autosomal dominant](#) pattern.[1]

The pattern of inheritance in which the recessive allele could give its expression in absence of its dominant allele is known as pseudodominance. Haemophilia and colour blindness are the genetic disease due to X linked recessive allele giving their expression in human male is pseudodominance and in human female is dominance.

Pseudodominance also observed in autosomal recessive condition in subsequent generations .This could happen in the case of loss of genetic material from one homolog bearing the dominant allele. The heterozygous condition is therefore lost at that particular locus and the

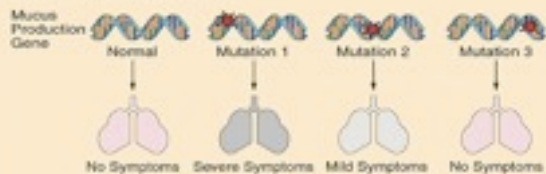
Genetic Heterogeneity



A disorder inherited in the same manner can be due to mutations in more than one gene, or what is known as *locus heterogeneity*. For example, it is recognized that sensorineural hearing impairment/deafness most commonly shows autosomal recessive inheritance. Deaf persons, by virtue of their schooling and involvement in the deaf community, often choose to have children with another deaf person. It would be expected that if two deaf persons were homozygous for the same recessive gene, all of their children would be similarly affected. Families have been described in which all the children born to parents deaf due to autosomal recessive genes have had perfectly normal hearing and are what is known as *double heterozygotes*. The explanation for this must be that the parents were homozygous for mutant alleles at different loci, i.e. that a number of different genes can cause autosomal recessive sensorineural deafness. In fact, over the past 10-15 years, 20 genes and a further 15 loci have been shown to be involved! A very similar story applies to autosomal recessive retinitis pigmentosa and there are now six distinct

- Different mutations in the same gene can produce a wide range of effects. In *cystic fibrosis*, for instance, the gene that controls mucus production can have more than 300 different mutations; some cause severe symptoms; some, mild symptoms; and some, no symptoms at all.

Gene Changes in Cystic Fibrosis

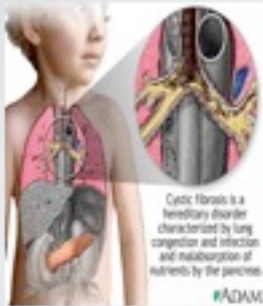


Autosomal Recessive disorder



- **Galactosemia**
- An infant is unable to metabolize galactose
- Damage of the liver, central nervous system and various other body systems
- An infant may develop jaundice, vomiting, lethargy, irritability and convulsions

Autosomal Recessive disorder



- **Cystic fibrosis (CF)**
- Gene localized at chromosome 7q
- Affected children have chronic respiratory infection, and malabsorption

SEX-LINKED INHERITANCE

- X-linked dominant
- X-linked recessive
- Y-linked

SEX-LINKED INHERITANCE

Sex-linked inheritance refers to the pattern of inheritance shown by genes that are located on either of the sex chromosomes. Genes carried on the X chromosome are referred to as being X-linked, while genes carried on the Y chromosome are referred to as exhibiting *Y-linked* or *holandric inheritance*.

X-LINKED DOMINANT INHERITANCE

- Mutations only in **X chromosome**
- Both **males** and **females** are affected
- **Affected males** transmit the disease to their **daughters** (male to female only)
- **Affected females** transmit the disease to **daughters and sons**

X-linked recessive inheritance

An X-linked recessive trait is one determined by a gene carried on the X chromosome and usually only manifests in males. A male with a mutant allele on his single X chromosome is said to be hemizygous for that allele. Diseases inherited in an X-linked manner are transmitted by healthy heterozygous female carriers to affected males, as well as by affected males to their obligate carrier daughters, with a consequent risk to male grandchildren through these daughters ([Fig. 7.10](#)). This type of pedigree is sometimes said to show 'diagonal' or a 'knight's move' pattern of transmission.

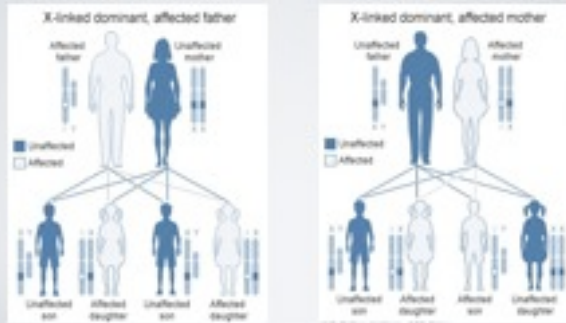
The mode of inheritance whereby only males are affected by a disease that is transmitted by

Genetic risks

A male transmits his X chromosome to each of his daughters and his Y chromosome to each of his sons. If a male affected with hemophilia has children with a normal female, then all his daughters will be *obligate carriers* but none of his sons will be affected ([Fig. 7.11](#)). A male cannot transmit an X-linked trait to his son, with the very rare exception of uniparental heterodisomy ([p. 117](#)).

For a carrier female of an X-linked recessive disorder having children with a normal male, each son has a 1 in 2 (50%) chance of being affected and each daughter has a 1 in 2 (50%) chance of being a carrier ([Fig. 7.12](#)).

X-LINKED DOMINANT INHERITANCE



X-LINKED DOMINANT INHERITANCE



- More females than males
- All daughters of affected males are affected, but no sons
- A child of an affected female has 50% risk of disease

The genetics of X-linked traits is unique because **males only have one X chromosome**, whereas women have two. Therefore, men can only transmit X-linked genes to their daughters, never to their sons. The sons instead receive the Y chromosome from their fathers.

In humans, several X-linked disorders are known in which heterozygous females have a mosaic phenotype with a mixture of features of the normal and mutant alleles. In X-linked ocular albinism the iris and ocular fundus of affected males lack pigment. Careful examination of the ocular fundus in females heterozygous for ocular albinism reveals a mosaic pattern of pigmentation ([Fig. 6.21, p. 100](#)). This mosaic pattern of involvement can be explained through the random process of X-inactivation ([p. 99](#)). In the pigmented areas the normal gene is on the active X chromosome while in the depigmented areas the mutant allele is on the active X chromosome.

X-linked dominant inheritance

X-LINKED RECESSIVE INHERITANCE

- Mutations only in **X chromosome**
- **Only males** are affected
- Transmission through unaffected **females to male**
- **No male to male** transmission

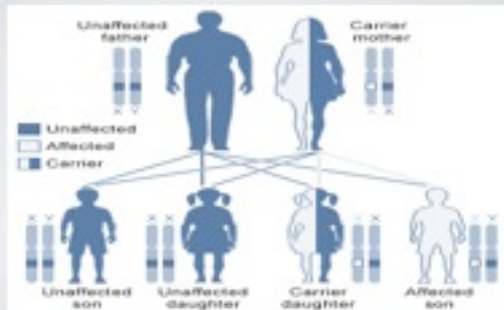
Females affected with X-linked recessive disorders

Occasionally a woman might manifest features of an X-linked recessive trait. There are several explanations for how this can happen.

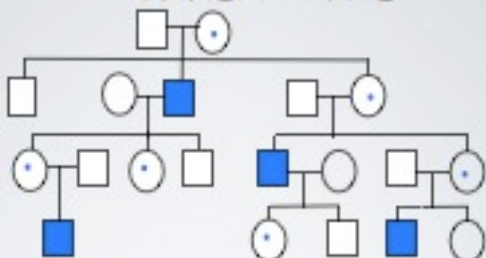
Homozygosity for X-linked recessive disorders

A common X-linked recessive trait is red-green color blindness - the inability to distinguish between the colors red and green. About 8% of males are red-green color blind and, although it is unusual, because of the high frequency of this allele in the population, about 1 in 150 women are red-green colour blind by virtue of both parents having the allele on the X chromosome.

X-LINKED RECESSIVE INHERITANCE



X-LINKED RECESSIVE INHERITANCE



- Affects almost exclusively men
- Affected men born from carrier mother, with 50% risk of disease
- No male to male transmission

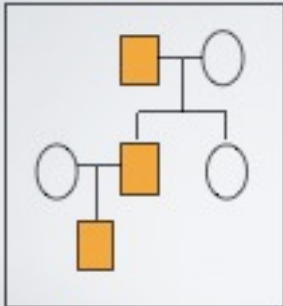
- This disease **affects almost exclusively men**, since they only have one X chromosome, and they therefore develop the disease even when they only carry one copy of the disease allele. For women, both X chromosomes must carry the affected allele before they develop the disease (in this case the father would be affected).
- Many women can be carriers. A boy born from a carrier mother has a **50% risk** of developing disease.
- Affected men **can not transmit the disease to their sons**, since they receive the Y chromosome!

X-LINKED RECESSIVE DISORDER



- Duchenne muscular dystrophy (DMD)
- Affected gene on chromosome Xp21
- Progressive weakness and muscle wasting

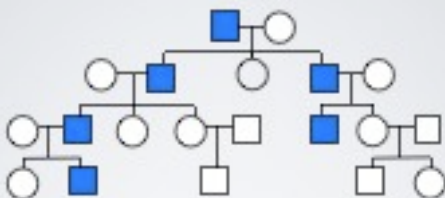
Y-LINKED INHERITANCE



- Only males are affected
- Male infertility

Y-linked or *holandric inheritance* implies that only males are affected. An affected male transmits Y-linked traits to all his sons but to none of his daughters. In the past it has been suggested that bizarre sounding conditions such as porcupine skin, hairy ears and webbed toes are Y-linked traits. With the possible exception of hairy ears, these claims of holandric inheritance have not stood up to more careful study. Evidence clearly indicates, however, that the H-Y histocompatibility antigen ([p. 194](#)) and genes involved in spermatogenesis are carried on the Y chromosome and, therefore, manifest holandric inheritance. The latter, if deleted, lead to infertility due to azoospermia (absence of the sperm in semen) in males. The recent advent of techniques of assisted reproduction, particularly the technique of intracytoplasmic sperm injection (ICSI), means that if a pregnancy with a male conceptus results after the use of this technique, the child will also necessarily be infertile!

Y-LINKED INHERITANCE (Y)

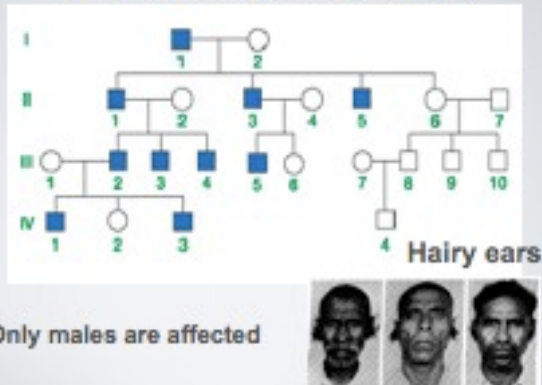


- Affects only males
- Affected males always have affected fathers
- All sons of an affected male are affected

- **No Y-linked diseases** are known, only characters. Y-linked diseases are unlikely because the existence of a disease gene usually means that there is a normal gene as well, carrying out some important function. But females are perfectly normal without any Y-linked genes.

- Defects in Y-linked genes are thus unlikely to cause diseases apart from **male infertility**.

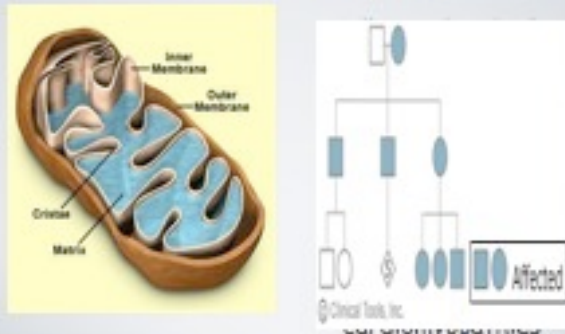
Y-linked gene (feature)



Partial sex-linkage

Partial sex-linkage has been used in the past for certain disorders that appear to exhibit autosomal dominant inheritance in some families and X-linked inheritance in others. This is now known to be likely to be because of genes carried on that portion of the X chromosome sharing homology with the Y chromosome, and which escapes X-inactivation. During meiosis pairing occurs between the homologous distal parts of the short arms of the X and Y chromosomes, the so-called *pseudoautosomal region*. As a result of a cross-over, a gene could be transferred from the X to the Y chromosome, or vice versa, allowing the possibility of male-to-male transmission. The latter instances would be consistent with autosomal dominant inheritance. A rare skeletal dysplasia Leri-Weil dyschondrosteosis, in which affected individuals have short stature and a characteristic wrist deformity (Madelung deformity), has been reported to show both autosomal

MITOCHONDRIAL INHERITANCE



MITOCHONDRIAL INHERITANCE

Each cell contains thousands of copies of mitochondrial DNA with more being found in cells that have high energy requirements, such as brain and muscle. Mitochondria, and therefore their DNA, are inherited almost exclusively from the mother through the oocyte ([p. 19](#)). Mitochondrial DNA has a higher rate of spontaneous mutation than nuclear DNA and the accumulation of mutations in mitochondrial DNA has been proposed as being responsible for some of the somatic effects seen with aging.

In humans, *cytoplasmic* or *mitochondrial inheritance* has been proposed as a possible explanation for the pattern of inheritance observed in some rare disorders that affect both males and females but are transmitted only through females, so-called maternal or matrilineal inheritance ([Fig. 7.24](#)).