PATTERNS OF INHERITANCE

- Definition
- Family Studies
- Pedigree drawing and Terminology
- Mendelian inheritance
- Non-Mendelian inheritance
- Mitochondrial inheritance
PATTERNS OF INHERITANCE: DEFINITION

• It's 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,
  • multifactorial, and
  • mitochondrial inheritance.
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 sclerae would suggest the diagnosis of osteogenesis imperfecta. In the absence of a positive family history other diagnoses would have to be considered.
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.

- Male
- Female
- Mating
- Parents and children (1 boy, 1 girl) in order of birth (elder on left)
- Dizygotic twins
- Monozygotic twins
- Sex unspecified
- Number of children of sex indicated
- Affected individuals
- Heterozygotes for autosomal recessive
- Carrier of x-linked recessive
- Death
- Abortion or stillbirth; sex unspecified
- Propositus (+ta)
- Method of identifying persons in a pedigree:
  - Propositus is child 2 in generation 2
- Consanguinous marriage
- Divorce
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 gameetes 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 forms 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

Key:

E = Unattached earlobes (dominant allele)
e = Attached earlobes (recessive allele)

1. **sperm**
2. **egg**
3. **fertilization**
4. **zygote**
5. **growth and development**

- **E E** unattached earlobe
- **ee** attached earlobe
- **E e** unattached earlobe
Phenotype

- the physical (& behavioral) characteristics an individual displays
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
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.
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.
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 excretion of urine that becomes 'port wine' colored on standing as a result of the presence of porphyrins (p. 175) (Fig. 7.3). This pattern of inheritance is sometimes referred to as 'vertical' transmission and is confirmed when male-male (i.e. father to son) transmission is observed.
AUTOSOMAL DOMINANT DISORDER

Affected Father

Normal Mother

Affected Daughter

Normal Son

Affected Son

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

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Because HD is dominant, there is a strong motivation for individuals who are at risk of inheriting it to seek a diagnosis. The genetic test for HD consists of a blood test that looks for the presence of a particular DNA sequence. Over 95% of individuals at risk of inheriting HD do not proceed with testing, mostly because there is no treatment. A positive result is not considered a diagnosis, since it may be obtained decades before the symptoms begin. However, a negative test means that the individual does not carry the expanded copy of the gene and will not develop HD.

Huntington's disease has an autosomal dominant pattern of inheritance, meaning that an affected individual typically inherits a copy of the gene with an expanded trinucleotide repeat (the mutant allele) from one parent. This causes the number of repeats to change in successive generations, such that an unaffected parent with an expanded copy of the gene will have a 50% chance of passing it on to a child, and, if they do, there is a 50% chance that that child will also inherit the expanded copy of the gene. The expansion is unstable during meiosis, and especially affected are the offspring of pre-symptomatic individuals (36–40), who, in the absence of symptoms in the parent, are likely to inherit a copy of the gene with an increase in the number of repeats that produces fully penetrant HD.

For some time HD was thought to be the only disease for which this did not affect the symptoms and progression of the disease, but it is now known that children born to parents with HD can have subtle changes in personality, egocentrism, aggression, compulsive behavior, abstract thinking, difficulty with rule acquisition, initiating appropriate actions and inhibiting inappropriate actions, short-term memory, procedural memory, and controls the production of glutamine. So a series of them results in the production of a chain of glutamine known as a poly-Q region (CAGCAGCAG...) that is expanded in HD.

In these animals, HTT is important for embryonic development, as its absence is related to embryonic death. It also acts as an anti-apoptotic protein and controls the production of glutamine. The function of HTT in humans is unclear. It interacts with proteins which are involved in cell signaling, neurotransmitter transport, vesicular transport, synaptic transmission, neurogenesis, and synaptic plasticity.
Diagnostic criteria of Marfan syndrome were agreed internationally in 1996. A diagnosis of Marfan syndrome is based on family history and a combination of major and minor indicators of the disorder. A major indicator is the presence of at least one of the following conditions: (1) severe aortic root dilatation, (2) idiopathic scoliosis, (3) mitral valve prolapse, (4) ectopia lentis, (5) joint hyperlaxity, or (6) pectus excavatum. Minor indicators include a positive family history of Marfan syndrome, Marfan syndrome in a first-degree relative, and aortic root dilatation. These indicators are used to support the diagnosis, which is often confirmed by genetic testing.

The most serious signs and symptoms associated with Marfan syndrome involve the cardiovascular system. Undue fatigue, shortness of breath, racing heartbeats, and abnormal indentation on an EKG can indicate further investigation. The signs of regurgitation from aortic, ocular and dural aneurysms may result from Marfan syndrome but may also occur in people without any known underlying disorder. Reducing the level of normal fibrillin-1 causes a Marfan-related disease in mice. It may also affect the elastic fibers of the lungs, heart valves, and aorta, and this weakens the tissues and causes the features of Marfan syndrome.

Secondary to mutated fibrillin there is excessive TGF-β, which encodes a connective protein called fibrillin-1 protein. The normal fibrillin-1 protein binds to another protein, keeping it sequestered and unable to exert its biological activity. The simplest model of Marfan syndrome suggests that reduced levels of fibrillin-1 allows TGF-β to have deleterious effects on vascular smooth muscle development and the integrity of the extracellular matrix. Researchers now believe that secondary to mutated fibrillin there is excessive TGF-β at the lungs, heart valves, and aorta, and this weakens the tissues and causes the features of Marfan syndrome.

Autosomal dominant traits may involve only one organ or part of the body, for example the eye in congenital cataracts. It is possible that a particular gene present in the population will have no effect in some people, while others may present with either learning difficulties, epilepsy, or a facial rash known as adenoma sebaceum. Reduced penetrance is thought to be the result of a variety of factors: environmental, genetic, or stochastic. The same gene mutation in different individuals can present with quite different clinical outcomes.

Review the text to gain a better understanding of Marfan syndrome. Notice how the different signs and symptoms are directly related to the connective tissue abnormalities. Many of the signs and symptoms associated with Marfan syndrome are the result of secondary effects of the underlying connective tissue abnormalities. The lack of one specific gene may result in a wide array of symptoms, as seen in the case of X-linked dominant polycystic kidney disease and X-linked dominant epilepsy in women, called periventricular nodular heterotopia, is also due to mutations in this gene. Sometimes an individual with a mutation is entirely normal. Mutations in the Filamin A gene have recently been discovered in patients with X-linked dominant polycystic kidney disease and X-linked dominant epilepsy in women, called periventricular nodular heterotopia, is also due to mutations in this gene. The extracellular matrix is critical for both the structural integrity of connective tissue but also serves as a reservoir for growth factors. It is thought that secondary to mutated fibrillin there is excessive TGF-β, which encodes a connective protein called fibrillin-1 protein. The normal fibrillin-1 protein binds to another protein, keeping it sequestered and unable to exert its biological activity. The simplest model of Marfan syndrome suggests that reduced levels of fibrillin-1 allows TGF-β to have deleterious effects on vascular smooth muscle development and the integrity of the extracellular matrix. Researchers now believe that secondary to mutated fibrillin there is excessive TGF-β at the lungs, heart valves, and aorta, and this weakens the tissues and causes the features of Marfan syndrome.
Dwarfism is a highly visible condition that often carries negative connotations in society. Some believe there is no single treatment for dwarfism. Individual abnormalities such as bone growth disorders can sometimes be managed medically, while others require more significant interventions.

Dwarfism can be caused by over 200 distinct medical conditions, with many genetic in nature. Achondroplasia, the most common form, affects about 1 in 10,000 births. It is characterized by slow motor movement, low muscle tone, and a distinctive body proportion where legs are shorter than the upper body. Jyoti Amge, from India, is the world's tallest living woman suffering from achondroplasia. At 156 cm (4 feet, 1/2 inches) tall, she weighs 11 lbs (5 kg).

The diagnosis can be made by fetal ultrasound. A skeletal survey is useful to confirm the diagnosis of achondroplasia. Skull demonstrate a large skull with a narrow metopic suture and relatively small skull base. The vertebral bodies are short and flattened with relatively large intervertebral disk height, and there is congenitally narrowed spinal canal. The iliac wings are small and squared, with a narrow sciatic notch and horizontal acetabular roof. The tubular bones are short and thick with metaphyseal flaring. This makes estimates of prevalence difficult, with changing and subjective diagnostic criteria over time. One detailed and long-running study in the Netherlands found that the prevalence determined at birth was only 1.3 per 100,000 live births.

Achondroplasia is autosomal dominant genetic disorder that is a common cause of dwarfism. Other indicators of achondroplasia include slow motor movement and low muscle tone (hypotonia). One result of low muscle tone is that walking does not occur until between 24 and 36 months. Because of short stature, obesity is often associated with the condition. Children often have middle ear infections (otitis media) because of abnormal drainage of the tube from the middle ear to the throat due to the abnormal skull structure. To help children with achondroplasia, they can have ear tubes 

**Fibular Hemimelia:**
- Causes: This is a congenital anomaly where the fibula (one of the two bones in the lower leg) is missing or incompletely formed. Affected individuals are missing part of the fibula bone, which is one of the two bones in the lower leg. The condition is thought to be caused by a genetic error occurring early in development. Fibular hemimelia is not hereditary and is not linked to other medical conditions. However, it can be inherited in rare cases. Fibular hemimelia is a congenital anomaly where the fibula (one of the two bones in the lower leg) is missing or incompletely formed. Affected individuals are missing part of the fibula bone, which is one of the two bones in the lower leg. The condition is thought to be caused by a genetic error occurring early in development. Fibular hemimelia is not hereditary and is not linked to other medical conditions. However, it can be inherited in rare cases.

**Genetic Counseling:**
- Genetic counselors help families understand the risks and benefits of genetic testing and counseling. They can provide information about the chances of passing on a genetic disorder to future generations. Genetic counselors can also help families make informed decisions about treatment options. Genetic counseling is an important part of genetic testing. It helps families understand the results of their tests and make informed decisions about their health. Genetic counselors can provide information about the chances of passing on a genetic disorder to future generations. They can also help families make informed decisions about treatment options. Genetic counseling is an important part of genetic testing. It helps families understand the results of their tests and make informed decisions about their health.

**Conclusion:** Dwarfism is a complex condition with varied causes and presentations. While there is no cure, management can help improve quality of life and reduce complications.
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)

Codominance

Codominance refers to the condition in which both alleles contribute to the phenotype. For example, in a case of plant breeding studies, where both alleles produce a particular trait, the heterozygous plant will show both traits. This is due to the fact that both alleles are present in the same organism, hence both are expressed. In case of blood groups, the ABO system, the expression of alleles is codominant. The presence of both alleles results in the production of both antigens, which are responsible for the ABO blood groups.

In autosomal disorders, the dominant allele is represented by a gene at a particular physical location (locus) on a chromosome. Heterozygous individuals have two alleles at each gene locus, one of which is the dominant allele and the other is the recessive allele. The phenotype produced by the dominant allele masks the phenotype produced by the recessive allele.

In blood groups, the ABO system is a classic example of codominance. The ABO system is based on two alleles, A and B. An individual with the genotype A/B will produce both A and B antigens in their red blood cells. This is because both alleles are expressed, and the phenotype produced is a combination of the two alleles.

In genetics, codominance is a term used to describe the situation where both alleles contribute to the phenotype. This is in contrast to dominance, where only one allele is expressed. Codominance is important in understanding the expression of alleles in genetic disorders and in the development of blood groups.

Co-dominance occurs in cases where both alleles are present, and neither allele completely masks the other. However, in some cases, one allele may be expressed more strongly than the other, leading to incomplete dominance or over-dominance. This can be observed in cases where the phenotype of one allele is dominant over the other, and the other allele is recessive.

In the context of genetics, it is important to note that codominance is distinct from dominance and recessivity. Dominance refers to the situation where one allele masks the other, while recessiveness refers to the situation where the allele is masked by a dominant allele. Codominance, on the other hand, refers to the situation where both alleles are expressed, and the phenotype produced is a combination of the two alleles.

In summary, codominance is a genetic phenomenon where both alleles contribute to the phenotype. It is an important concept in understanding the expression of alleles in genetic disorders and in the development of blood groups.
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

Carrier Father
Carrier Mother

Normal Son
25% normal

Carrier Daughter
50% chance carrier

Carrier Son

Affected Daughter
25% affected
• Punnet's square showing possible gamete combinations for an autosomal recessive allele
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 recessive phenotype is revealed.

**Heterogeneous** is an adjective used to describe an object or system consisting of multiple items having a large number of structural variations. It is the opposite of homogeneous, which means that an object or system consists of multiple identical items. The term is often used in a scientific (such as a kind of catalyst), mathematical, sociological or statistical context.

In genetics, heterogeneity refers to multiple origins causing the same disorder in different individuals. If a number of different mutations occurring the same gene produce disorders, it is said to manifest **allelic heterogeneity.** This term has been used when a number of different alleles cause a similar phenotype or different phenotypes.

**Example diseases:**

- Different FBN1 mutations causing Marfan's syndrome
- Cystic fibrosis is caused by greater than 900 different mutant alleles
- Alpha-Thalassemia or sickle cell anemia can be caused by different mutations in alpha-globin gene.
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 loci for primary autosomal recessive microcephaly.

Disorders with the same phenotype due to different genetic loci are known as genocopies, while the same phenotype being the result of environmental causes is known as a phenocop.
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.
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
Recessive inheritance

Dominant inheritance

Dominant & Recessive
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 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 normal females was appreciated by the Jews nearly 2000 years ago. They excused from circumcision the sons of all the sisters of a mother who had sons with the 'bleeding disease', in other words, hemophilia (p. 310). The sons of the father's siblings were not excused. Queen Victoria was a carrier of hemophilia and her carrier daughters, who were perfectly healthy, introduced the gene into the Russian and Spanish royal families. Fortunately for the British royal family, Queen Victoria's son, Edward VII, did not inherit the gene, and so could not transmit it to his descendants.
**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](#fig711)). 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](#fig712)).

Some X-linked disorders are not compatible with survival to reproductive age and are not, therefore, transmitted by affected males. Duchenne muscular dystrophy is the commonest muscular dystrophy and is a severe disease (p. 308). The first signs are a waddling gait, difficulty in climbing stairs unaided, and a tendency to fall over easily. By about the age of 10 years affected boys usually need to use a wheelchair. The muscle weakness gradually progresses and affected males ultimately become confined to bed and will often die in their late teenage years or early 20s ([Fig. 7.13](#fig713)). Since affected boys do not usually survive to reproduce, the disease is transmitted almost entirely by healthy female carriers ([Fig. 7.14](#fig714)).
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**

Although uncommon, there are disorders that are manifest in the heterozygous female as well as in the male who has the mutant allele on his single X chromosome. This is known as X-linked dominant inheritance *(Fig. 7.16)*. X-linked dominant inheritance superficially resembles that of an autosomal dominant trait because both the daughters and sons of an affected female have a 1 in 2 (50%) chance of being affected. There is, however, an important difference. With an X-linked dominant trait an affected male transmits the trait to all his daughters but to none of his sons. Therefore, in families with an X-linked dominant disorder there is an excess of affected females and direct male-to-male transmission cannot occur.
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. Therefore, a female can be affected with an X-linked recessive disorder as a result of homozygosity for an X-linked allele but the rarity of most X-linked conditions means that the phenomenon is uncommon. A female could also be homozygous if her father was affected and her mother was normal but a new mutation occurred on the X chromosome transmitted to the daughter; or alternatively if her mother was a carrier and her father was normal but a new mutation occurred on the X chromosome he transmitted to his daughter - but these scenarios are rare.

Skewed X-inactivation

The process of X-inactivation usually occurs randomly, there being an equal chance of either of the two X chromosomes in a heterozygous female being inactivated in any one cell. Following X-inactivation in embryogenesis, therefore, in roughly half the cells one of the X chromosomes is active, whilst in the other half it is the other X which is active. Sometimes this process is not random, allowing for the possibility that the active X chromosome in most of the cells of a heterozygous female carrier is the one bearing the mutant allele. If this happens, a carrier female would exhibit some of the symptoms and signs of the disease and be a so-called manifesting heterozygote or carrier. This has been reported in a number of X-linked disorders, including Duchenne muscular dystrophy and hemophilia A (p. 312). In addition, there are reports of several X-linked disorders in which there are several manifesting carriers in the same family, consistent with the coincidental inheritance of an abnormality of X-inactivation (p. 99).

Numerical X chromosome abnormalities

A female could manifest an X-linked recessive disorder through being a carrier of an X-linked recessive mutation and having only a single X chromosome, i.e. Turner syndrome (p. 282). Women with Turner syndrome and hemophilia A or Duchenne muscular dystrophy have been reported.

X-autosome translocations

Females with a translocation involving one of the X chromosomes and an autosome can be affected with an X-linked recessive disorder. If the break-point of the translocation disrupts a gene on the X chromosome, then a female can be affected. This is because the X chromosome involved in the translocation survives preferentially so as to maintain functional disomy of the autosomal genes (Fig. 7.15). The observation of females affected with Duchenne muscular dystrophy with X-autosome translocations involving the same region of the short arm of the X chromosome helped to map the Duchenne muscular dystrophy gene (p. 309). This type of observation has been vital in the positional cloning of a number of genes in humans (p. 78).
X-LINKED RECESSIVE INHERITANCE
- 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!
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!
- 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**.

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

**Y-LINKED INHERITANCE (Y)**
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 dominant and X-linked inheritance. The disorder has been shown to be due to deleotions of, or mutations in, the short stature homeobox (SHOX) gene (p. 282), which is located in the pseudoautosomal region.

Sex influence

Some autosomal traits are expressed more frequently in one sex than another, so-called sex influence. Gout and presenile baldness are examples of sex-influenced autosomal dominant traits, males being predominantly affected in both cases. The influence of sex in these two examples is probably through the effect of male hormones. Gout, for example, is very rare in women before the menopause but the frequency increases in later life. Baldness does not occur in males who have been castrated. In hemochromatosis (p. 242), the most common autosomal recessive disorder in Western society, homozygous females are much less likely than homozygous males to develop iron overload and associated symptoms; the explanation usually given is that women have a form of natural blood loss through menstruation.

Sex limitation

Sex limitation refers to the appearance of certain features in individuals of only one sex. Examples include virilization of female infants affected with the autosomal recessive endocrine disorder, congenital adrenal hyperplasia (p. 168).
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).

A number of rare disorders with unusual combinations of neurological and myopathic features, sometimes occurring in association with other conditions such as cardiomyopathy and conduction defects, diabetes or deafness, have been characterized as being due to mutations in mitochondrial genes (p. 178). As mitochondria have an important role in cellular metabolism through oxidative phosphorylation, it is not surprising that the organs most susceptible to mitochondrial mutations are the central nervous system, skeletal muscle and heart.

In most persons the mitochondrial DNA from different mitochondria is identical, or shows what is termed homoplasmy. If a mutation occurs in the mitochondrial DNA of an individual, initially there will be two populations of mitochondrial DNA, so-called heteroplasmy. The proportion of mitochondria with a mutation in their DNA varies between cells and tissues and this, together with mutational heterogeneity, is a possible explanation for the range of phenotypic severity seen in persons affected with mitochondrially inherited disorders (Fig. 7.25).

Whilst matrilineal inheritance applies to disorders that are directly due to mutations in mitochondrial DNA, it is also very important to be aware that mitochondrial proteins are mainly encoded by nuclear genes. Mutations in these genes can have a devastating impact on respiratory chain functions within mitochondria. Examples include genes encoding proteins within the cytochrome-c (COX) system, which follow autosomal recessive inheritance, and the G4.5 (TAZ) gene that is X-linked and causes Barth syndrome (endocardial fibroelastosis) in males (p. 179). There is even a mitochondrial myopathy following autosomal dominant inheritance where multiple mitochondrial DNA deletions can be detected, though the gene(s) mutated in this condition are as yet unknown. Further space is devoted to mitochondrial disorders in Chapter 11 (p. 178).