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PATTERNS OF INHERITANCE

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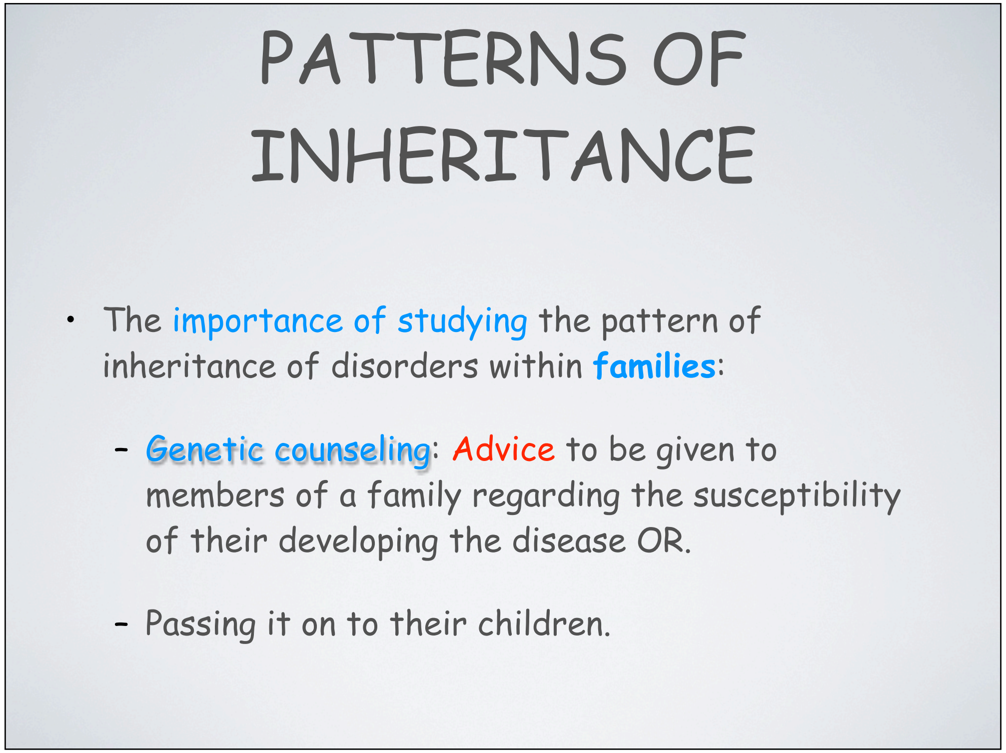
PATTERNS OF INHERITANCE

- 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.

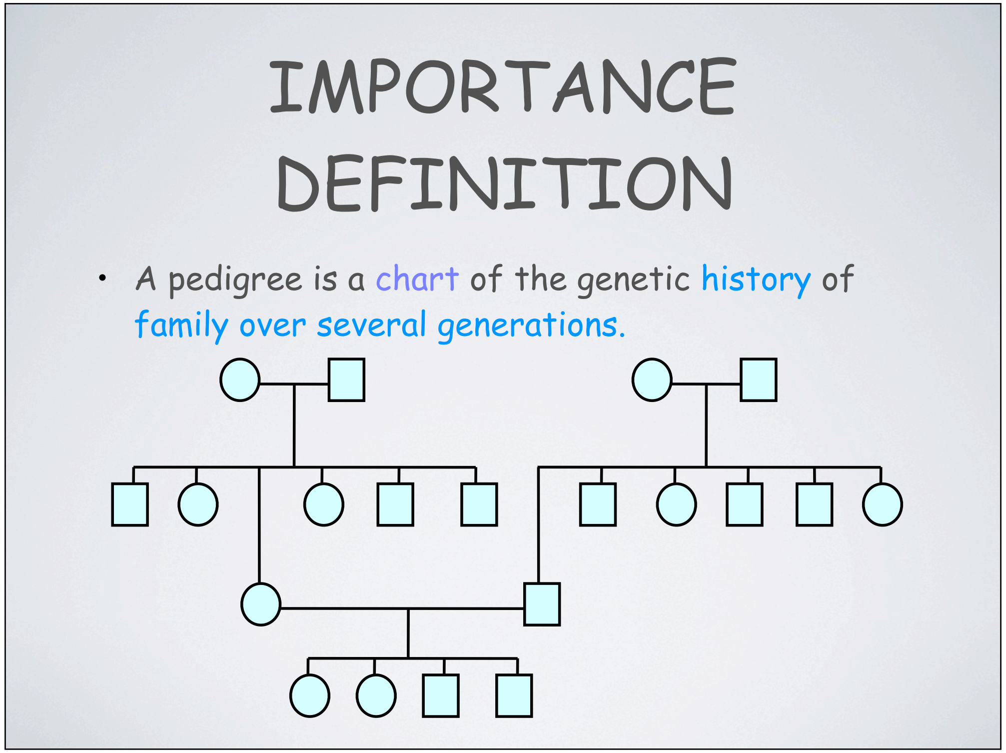
- Autosomal dominant
- autosomal recessive
- X-linked dominant
- X-linked recessive
- multifactorail,
- mitochondrial



FAMILY STUDIES

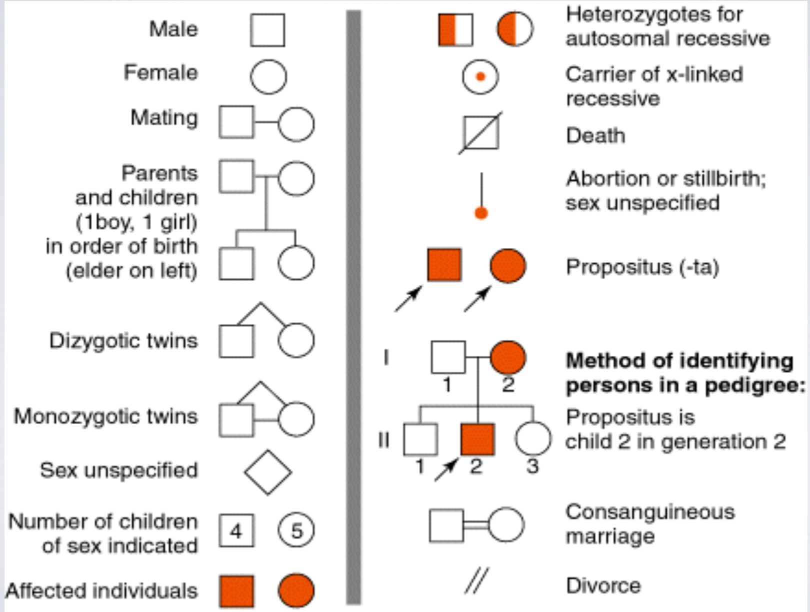
If we wish to investigate whether a particular trait or disorder in humans is genetic and hereditary, we usually have to rely either on observation of the way in which it is transmitted from one generation to another, or on study of its frequency among relatives.

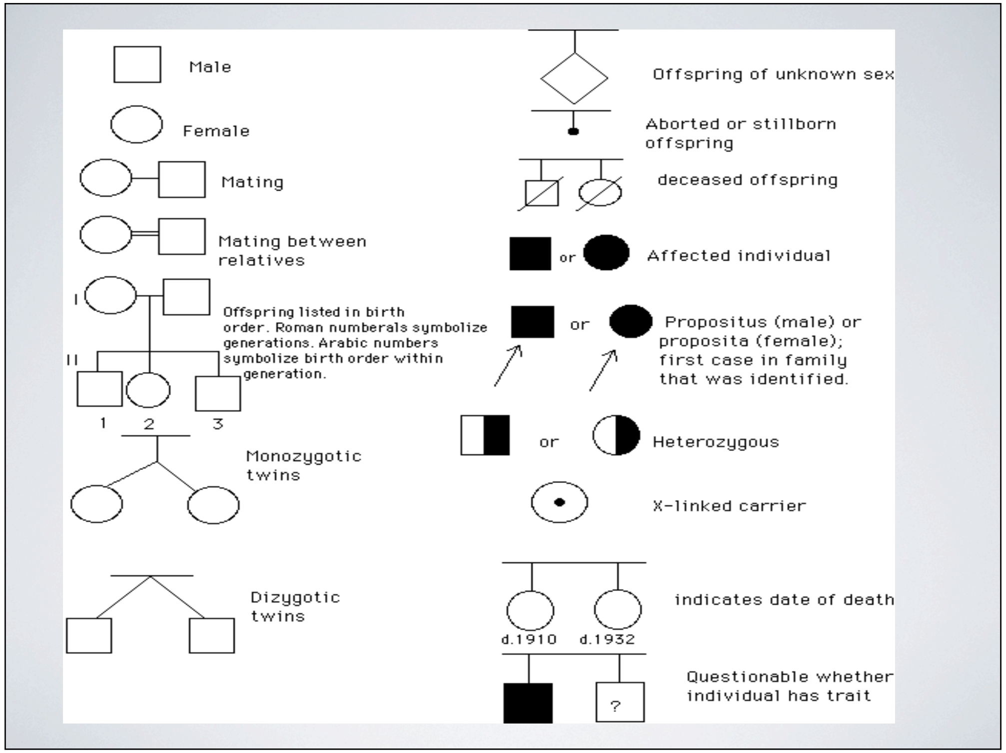
An important reason for studying the pattern of inheritance of disorders within families is to enable advice to be given to members of a family regarding the likelihood of their developing it or passing it on to their children, i.e. *genetic counseling* (Ch. 17). Taking a family history can, in itself, 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.

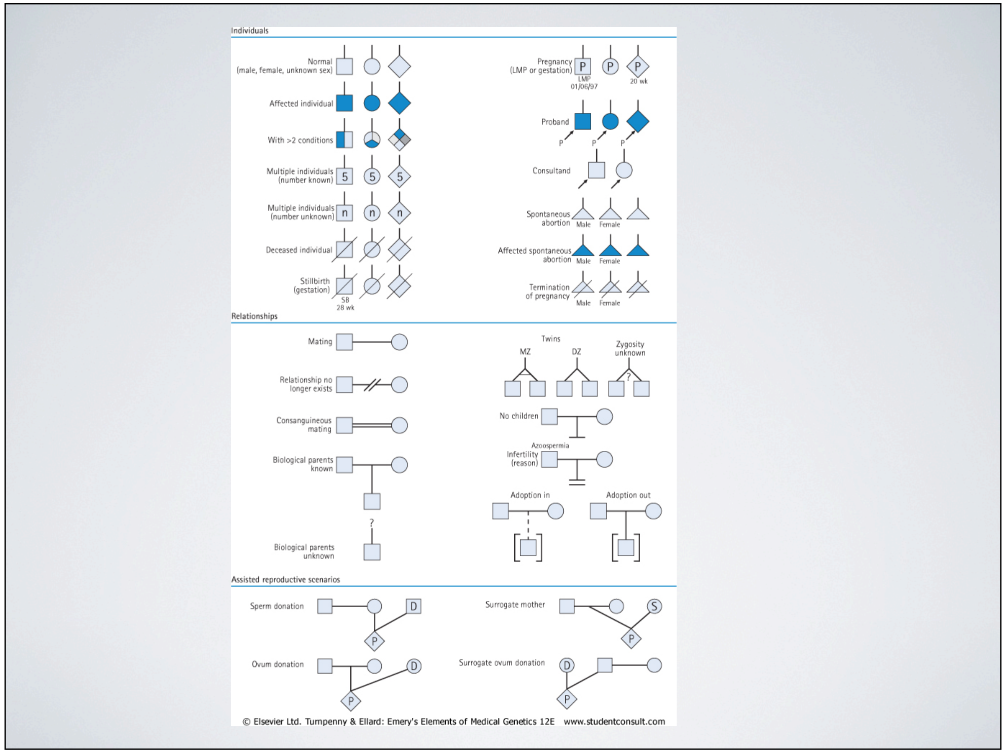


A family tree is a shorthand system of recording the pertinent information about a family.
It usually begins with the person through whom the family came to the attention of the investigator. This person is referred to as the **index case**, *proband* or *propositus*, or if female, the *proposita*. The 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
Mating between relatives
I
II
1
2
3
Offspring listed in birth order. Roman numberals symbolize generations. Arabic numbers symbolize birth order within generation.
Monozygotic twins
Dizygotic twins
Offspring of unknown sex
Aborted or stillborn offspring
deceased offspring
or
Affected individual
or
Propositus (male) or proposita (female); first case in family that was identified.
or
Heterozygous
X-linked carrier
d.1910
d.1932
indicates date of death
?
Questionable whether individual has trait



Genetic risks

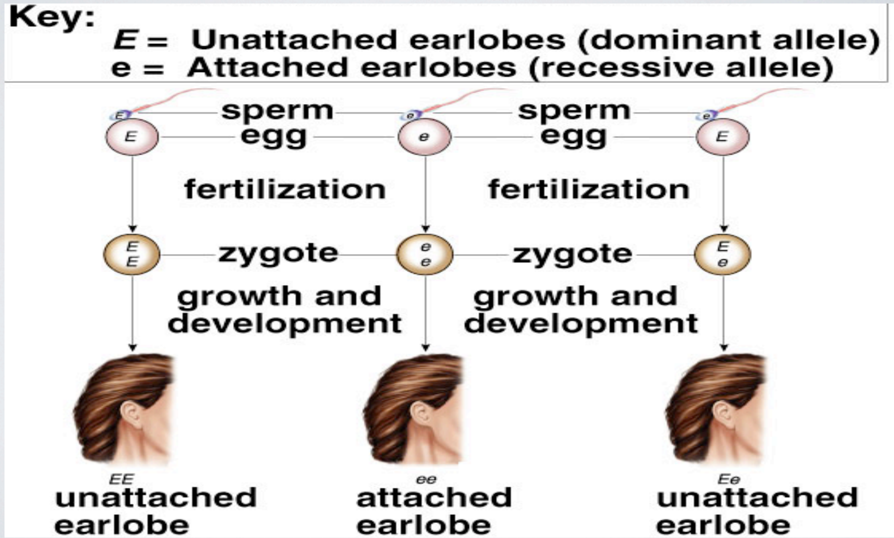
Each gamete from an individual with a dominant trait or disorder will contain either the normal allele or the mutant allele. If we represent the dominant mutant allele as 'A' and the recessive normal allele as 'a', then the various possible combinations of the gametes can be represented in a Punnett's 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.

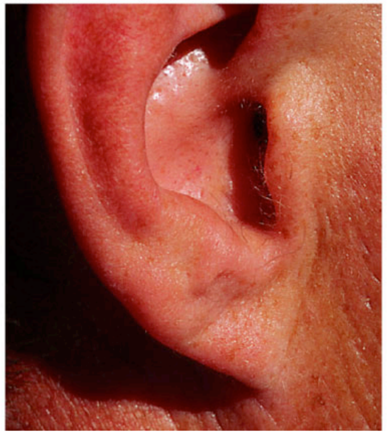
Genotype

- the gene types a person inherited

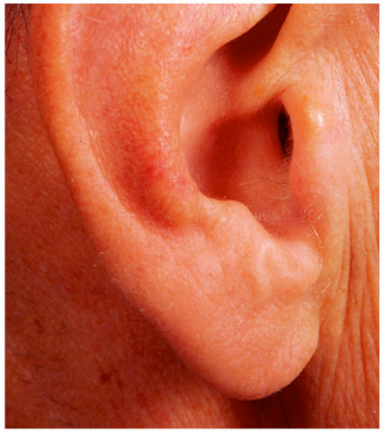


Phenotype

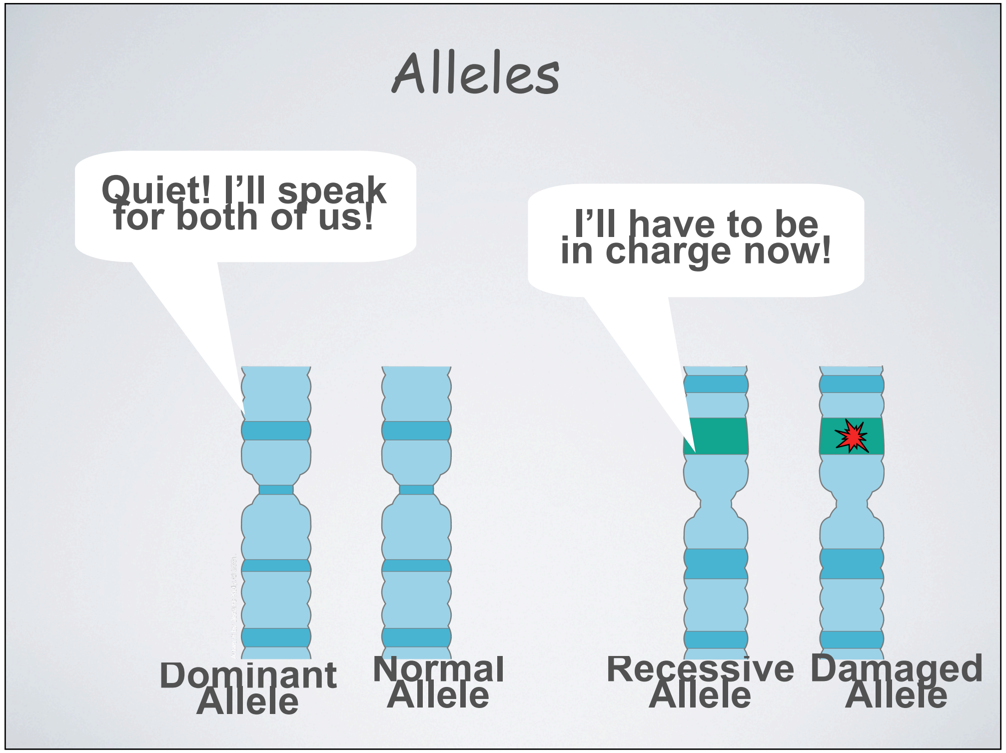
- the physical (& behavioral) characteristics an individual displays



d. **Attached earlobes: *ee***



c. **Unattached earlobes: *EE* or *Ee***



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

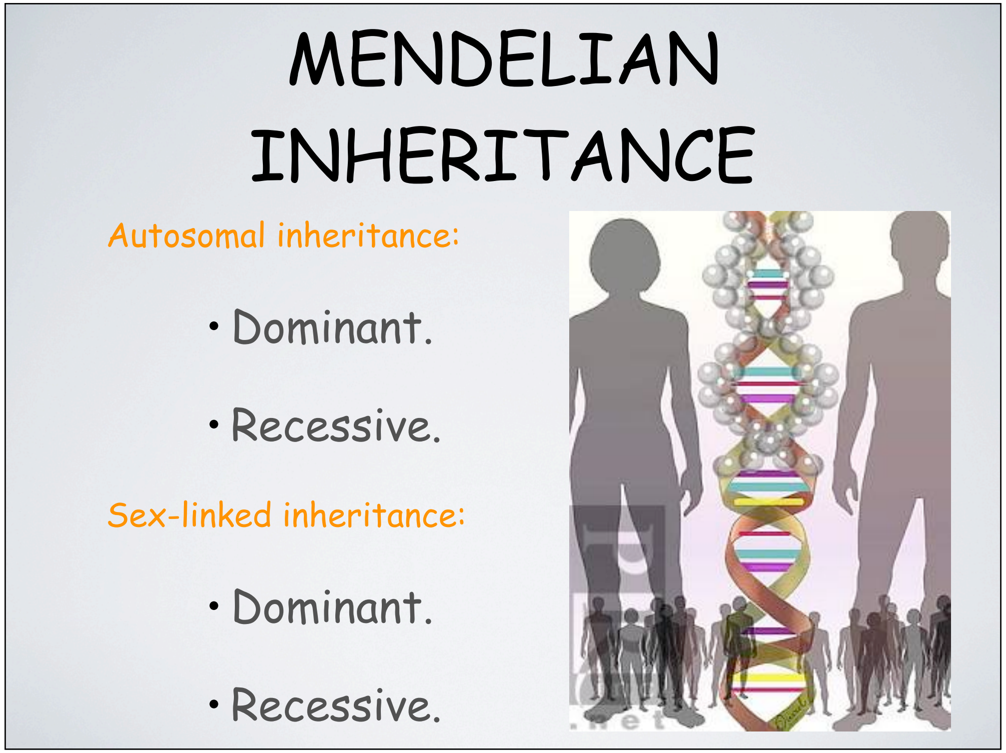
Many genes come in a number of variant forms, known as alleles.

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

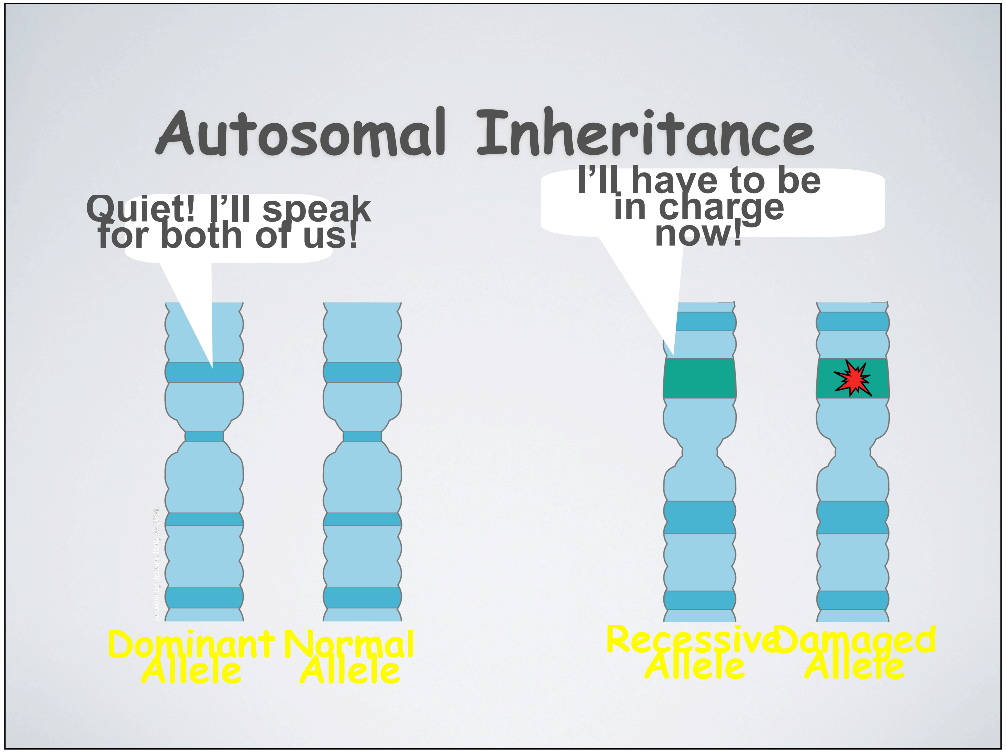
- Austrian botanist Gregor Mendel (1822-84)
- More than 11,000 Mendelian (monogenic) disorders have been revealed
- OMIM (Online Mendelian Inheritance in Man) database



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*.

Click to start



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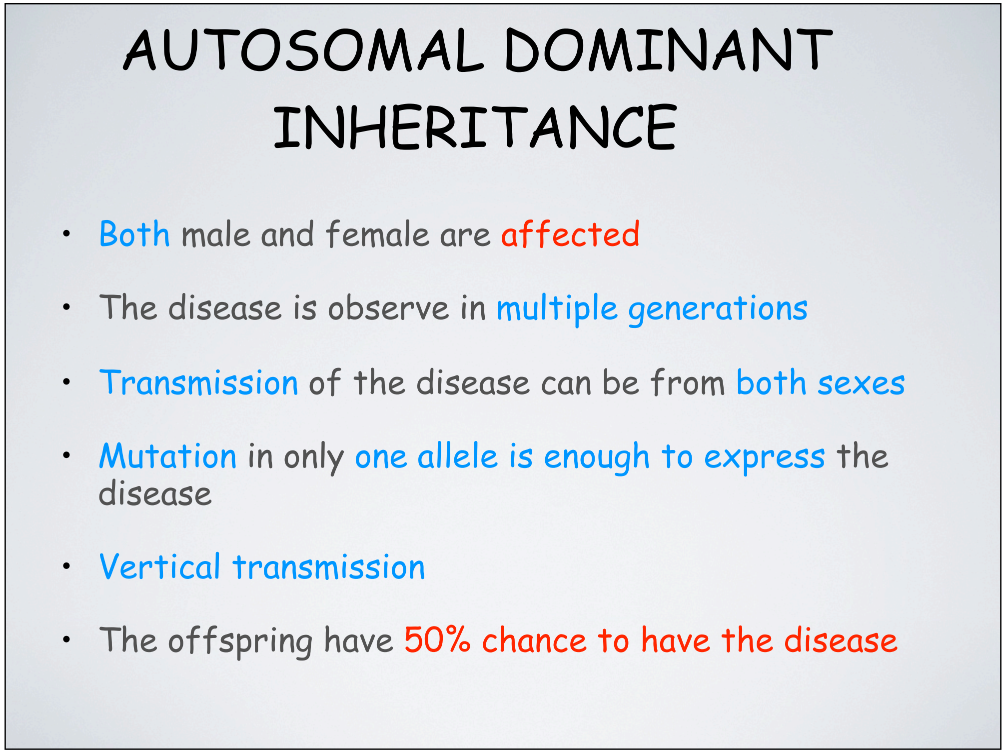
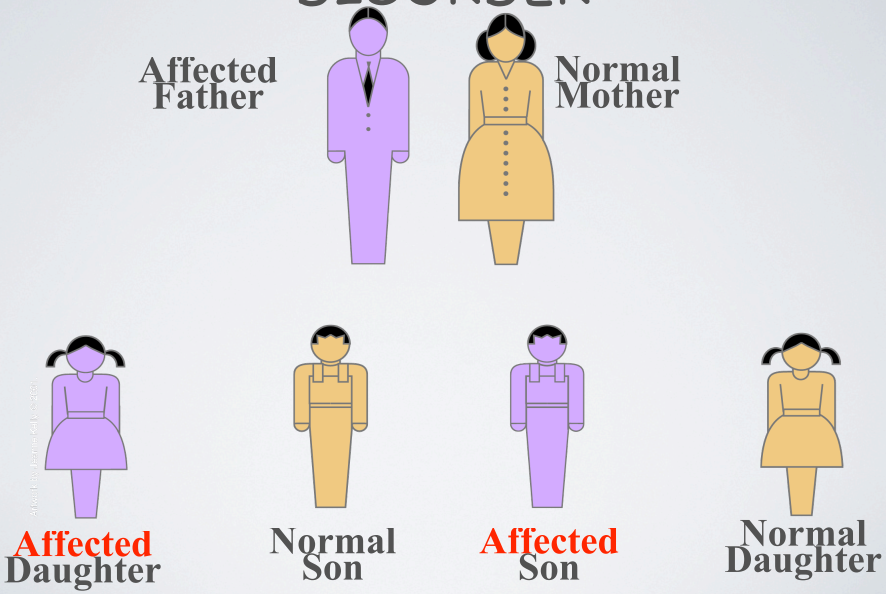


An autosomal dominant trait is one which manifests in the heterozygous state, i.e. in a person possessing both an abnormal or mutant allele and the normal allele. It is often possible to trace a dominantly inherited trait or disorder through many generations of a family (Fig. 7.2). In South Africa the 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



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

	w	w
W	W w	W w
w	w w	w w

AUTOSOMAL DOMINANT DISORDERS

- Huntington disease
- Autosomal dominant
- Gene in chromosome 4p
- Adult onset of the disease
- Choreic 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 between 35 and 44 years of age. On rare occasions, when symptoms begin before about 20 years of age, they progress faster and vary slightly, and the disease is classified as **juvenile**, **akinetic-rigid** or **Westphal variant HD**.

The Huntingtin gene normally provides the genetic code for a protein that is also called "huntingtin". The mutation of the Huntingtin gene codes for a different form of the protein, whose presence results in gradual damage to specific areas of the brain. The exact way this happens is not fully understood. Genetic testing, which has been possible since the discovery of the mutation, can be performed before the onset of symptoms in the relatives of an affected individual, as an antenatal test, and also on test-tube embryos, raising ethical debates. Genetic counseling has developed to inform and aid individuals considering genetic testing and has become a model for other genetically dominant diseases.

The exact way HD affects an individual varies and can differ even between members of the same family, but the symptoms progress predictably for most individuals. The earliest symptoms are a general lack of coordination and an unsteady gait. As the disease advances, uncoordinated, jerky body movements become more apparent, along with a decline in mental abilities and behavioral and psychiatric problems. Physical abilities are gradually impeded until coordinated movement becomes very difficult, and mental abilities generally decline into dementia. Although the disorder itself is not fatal, complications such as pneumonia, heart disease, and physical injury from falls reduce life expectancy to around twenty years after symptoms begin. There is no cure for HD, and full-time care is often required in the later stages of the disease, but there are emerging treatments to relieve some of its symptoms.

Self-help support organizations, first founded in the 1960s and increasing in number, have been working to increase public awareness, to provide support for individuals and their families, and to promote research. These organizations were instrumental in finding the gene in 1993. Since that time there have been important discoveries every few years and understanding of the disease is improving. Current research directions include determining the exact mechanism of the disease, improving animal models to expedite research, clinical trials of pharmaceuticals to treat symptoms or slow the progression of the disease, and studying procedures such as stem cell therapy with the goal of repairing damage caused by the disease.

Signs and symptoms

Symptoms of Huntington's disease commonly become noticeable between the ages of 35 and 44 years, but they can begin at any age from infancy.[1] [2] often when affected individuals have had children.[1] In the early stages, there are subtle changes in personality, cognition, or physical skills.[1] The physical symptoms are usually the first to be noticed, as cognitive and psychiatric symptoms are generally not severe enough to be recognized on their own at the earlier stages.[1] Almost everyone with Huntington's disease eventually exhibits similar physical symptoms, but the onset, progression and extent of cognitive and psychiatric symptoms vary significantly between individuals.[3][4]

The most characteristic initial physical symptoms are jerky, random, and uncontrollable movements called chorea.[1] Chorea may be initially exhibited as general restlessness, small unintentionally initiated or uncompleted motions, lack of coordination, or slowed saccadic eye movements.[1] These minor motor abnormalities usually precede more obvious signs of motor dysfunction by at least three years.[3] The clear appearance of symptoms such as rigidity, writhing motions or abnormal posturing appear as the disorder progresses.[3] These are signs that the system in the brain that is responsible for movement is affected.[5] Psychomotor functions become increasingly impaired, such that any action that requires muscle control is affected. Common consequences are physical instability, abnormal facial expression, and difficulties chewing, swallowing and speaking.[5] Eating difficulties commonly cause weight loss and may lead to malnutrition.[7][8] Sleep disturbances are also associated symptoms.[9] Juvenile HD differs from these symptoms in that it generally progresses faster and chorea is exhibited briefly, if at all, with rigidity being the dominant symptom. Seizures are also a common symptom of

Cognitive abilities are impaired progressively.[6] Especially affected are executive functions which include planning, cognitive flexibility, abstract thinking, rule acquisition, initiating appropriate actions and inhibiting inappropriate actions.[6] As the disease progresses, memory deficits tend to appear. Reported impairments range from short-term memory deficits to long-term memory difficulties, including deficits in episodic (memory of one's life), procedural (memory of the body of how to perform an activity) and working memory.[6] Cognitive problems tend to worsen over time, ultimately leading to dementia.[6] This pattern of deficits has been called a "subcortical dementia" syndrome to separate it from the typical effects of "cortical dementias" such as Alzheimer's disease.[6]

Reported neuropsychiatric manifestations are anxiety, depression, a reduced display of emotions (blunted affect), egocentrism, aggression, and compulsive behavior, the latter of which can cause or worsen addictions, including alcoholism, gambling, and hypersexuality.[10] Difficulties in recognizing other people's negative expressions have also been observed.[6] Prevalence of these symptoms is also highly variable between studies, with estimated rates for lifetime prevalence of psychiatric disorders between 33% and 76%.[10] For many sufferers and their families these symptoms are among the most distressing aspects of the disease, often affecting daily functioning and constituting reason for institutionalisation.[10] Suicidal thoughts and suicide attempts are more common than in the general population.[1]

Mutant huntingtin is expressed throughout the body and associated with abnormalities in peripheral tissues that directly caused by such expression outside the brain. These abnormalities include muscle atrophy, cardiac failure, impaired glucose tolerance, weight loss, osteoporosis and testicular atrophy.[11]

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Genetics

All humans have the Huntingtin gene (*HTT*), which provides the genetic code to produce the protein huntingtin (HTT). Part of this gene is a repeated section called a trinucleotide repeat, which varies in length between individuals and may change length between generations. When the length of this repeated section reaches a certain threshold, it produces an altered form of the protein, called mutant huntingtin protein (mHTT). The differing functions of these proteins are the cause of pathological changes which in turn cause the disease symptoms. The Huntington's disease mutation is genetically dominant, because either of a person's HTT genes being mutated causes the disease. It is not inherited according to gender, but the length of the repeated section of the gene, and hence its severity, can be influenced by the gender of the affected parent.[12]

[edit]

Genetic mutation

HD is one of several trinucleotide repeat disorders which are caused by the length of a repeated section of a gene exceeding a normal range.[13] The *HTT* gene is located on the short arm of chromosome 4[13] at 4p16.3. *HTT* contains a sequence of three DNA bases—cytosine-adenine-guanine (CAG)—repeated multiple times (i.e. ...CAGCAGCAG...), known as a trinucleotide repeat.[13] CAG is the genetic code for the amino acid glutamine, so a series of them results in the production of a chain of glutamine known as a polyglutamine tract (or polyQ tract), and the repeated part of the gene, the *PolyQ region*.[14]

Inheritance

Huntington's disease is inherited in an autosomal dominant fashion. The probability of offspring inheriting an affected gene is 50% independent of gender, and the gene does not skip generations.

Huntington's disease has autosomal dominant inheritance, meaning that an affected individual typically inherits a copy of the gene with an expanded trinucleotide repeat (the mutant allele) from an affected parent.[1] In this type of inheritance pattern, each offspring of an affected individual has a 50% chance of inheriting the mutant allele and therefore being affected with the disorder (see figure). This probability is sex-independent.[17]

Trinucleotide CAG repeats over 28 are unstable during replication and this instability increases with the number of repeats present.[15] This usually leads to new expansions as generations pass (dynamic mutations) instead of reproducing an exact copy of the trinucleotide repeat.[13] This causes the number of repeats to change in successive generations, such that an unaffected parent with an "intermediate" number of repeats (28–35), or "reduced penetrance" (36–40), may pass on a copy of the gene with an increase in the number of repeats that produces fully penetrant HD.[13] Such increases in the number of repeats (and hence earlier age of onset and severity of disease) in successive generations is known as genetic anticipation.[13] Instability is greater in spermatogenesis than oogenesis,[13] so maternally inherited alleles are usually of a similar repeat length, whereas paternally inherited ones have a higher chance of increasing in length and can exhibit the anticipation phenomenon.[13][18] It is rare for Huntington's disease to be caused by a new mutation, where neither parent have over 36 CAG repeats.[19]

Individuals with both genes affected are rare, except in large consanguineous families.[20] For some time HD was thought to be the only disease for which this did not affect the symptoms and progression of the disease,[21] but it has since been found that it can affect the phenotype and the rate of progression.[13][20] Offspring of an individual who has two affected genes will inherit one of them and therefore definitely inherit the disease. Offspring where both parents have one affected gene have a 75% chance of inheriting HD, including a 25% chance of inheriting two affected genes.[17] Identical twins, who have inherited the same affected gene, typically have differing ages of onset and symptoms.[20]

[edit]

Mechanism

The HTT protein interacts with over 100 other proteins, and appears to have multiple biological functions.[22] The behavior of mutated mHTT protein is not completely understood, but it is toxic to certain types of cells, particularly in the brain. Damage mainly occurs in the striatum, but as the disease progresses, other areas of the brain are also significantly affected. As the damage accumulates, symptoms associated with the functions of these brain areas appear. Planning and modulating movement are the main functions of the striatum, and difficulties with these are initial symptoms.[12]

[edit]

HTT function

See also: Huntingtin

HTT is expressed in all mammalian cells. The highest concentrations are found in the brain and testes, with moderate amounts in the liver, heart, and lungs.[12] The function of HTT in humans is unclear. It interacts with proteins which are involved in transcription, cell signaling and intracellular transporting.[12][23] In animals genetically modified to exhibit HD, several functions of HTT have been found.[24] In these animals, HTT is important for embryonic development, as its absence is related to embryonic death. It also acts as an anti-apoptotic agent preventing programmed cell death and controls the production of brain-derived neurotrophic factor, a protein which protects neurons and regulates their creation during neurogenesis. HTT also facilitates vesicular transport and synaptic transmission and controls neuronal gene transcription.[24] If HTT expression is increased, brain cell survival is improved and the effects of mHTT are reduced, whereas when HTT expression is reduced, the resulting characteristics are more typical of the presence of mHTT.[24] In humans the disruption of the normal gene does not cause the disease.[12] It is currently concluded that the disease is not caused by inadequate production of HTT, but by a gain of toxic function of mHTT.[12]

[edit]

Genetic

See also: Genetic testing

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 which counts the numbers of CAG repeats in each of the *HTT* alleles.[34] 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.[13]

A pre-symptomatic test is a life-changing event and a very personal decision.[13] The main reason given for choosing testing for HD is to aid in career and family decisions.[13] Over 95% of individuals at risk of inheriting HD do not proceed with testing, mostly because there is no treatment.[13] A key issue is the anxiety an individual experiences about not knowing whether they will eventually develop HD, compared to the impact of a positive result.[12] Irrespective of the result, stress levels have been found to be lower two years after being tested, but the risk of suicide is increased after a positive test result.[12] Individuals found to have not inherited the disorder may experience survivor guilt with regard to family members who are affected.[12] Other factors taken into account when considering testing include the possibility of discrimination and the implications of a positive result, which usually means a parent has an affected gene and that the individual's siblings will be at risk of inheriting it.[12] Genetic counseling in HD can provide information, advice and support for initial decision-making, and then, if chosen, throughout all stages of the testing process.[35] Counseling and guidelines on the use of genetic testing for HD have become models for other genetic disorders, such as autosomal dominant cerebellar ataxias.[36][12][37] Presymptomatic testing for HD has also influenced testing for other illnesses with genetic variants such as polycystic kidney disease, familial Alzheimer's disease and breast cancer.[38]

[edit]

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 (p. 297), dilated cardiomyopathy (p. 305), Dunnigan-type familial partial lipodystrophy (Fig. 7.6), mandibuloacral dysplasia, and the very rare condition that has always been a great curiosity- Hutchinson-Gilford progeria. These are due to heterozygous mutations, with the exception of the Charcot-Marie-Tooth disease and mandibuloacral dysplasia, which are recessive, and therefore homozygous for *LMNA* mutations. Sometimes an individual with a mutation is entirely normal. Mutations in the Filamin A gene have recently been implicated in the distinct, though overlapping, X-linked dominant dysmorphic conditions oto-palato-digital syndrome, Melnick-Needles syndrome and frontometaphyseal dysplasia. In addition, however, it would not have been foreseen that a form of X-linked dominant epilepsy in women, called periventricular nodular heterotopia, is also due to mutations in this gene.

Variable expressivity

The clinical features in autosomal dominant disorders can show striking variation from person to person, even in the same family. This difference between individuals is referred to as *variable expressivity*. In autosomal dominant polycystic kidney disease, for example, some affected individuals develop renal failure in early adulthood whilst others have just a few renal cysts that do not significantly affect renal function.

Reduced penetrance

In some individuals heterozygous for gene mutations giving rise to certain autosomal dominant disorders there may be no abnormal clinical features, representing so-called *reduced penetrance* or what is commonly referred to in lay terms as 'skipping a generation'. Reduced penetrance is thought to be the result of the modifying effects of other genes, as well as being due to interaction of the gene with environmental factors. An individual who has no features of a disorder despite being heterozygous for a particular gene mutation is said to represent *non-penetrance*.

Reduced penetrance and variable expressivity, together with the pleiotropic effects of a mutant allele, all need to be taken into account when providing genetic counseling to individuals at risk for autosomal dominantly inherited disorders.

Marfan syndrome (also called **Marfan's syndrome**) is a genetic disorder of the connective tissue.

It is sometimes inherited as a dominant trait. It is carried by a gene called FBN1, which encodes a connective protein called fibrillin-1.[1][2] People have a pair of FBN1 genes. Because it is dominant, people who have inherited one affected FBN1 gene from either parent will have Marfan's. This syndrome can run from mild to severe.

People with Marfan's are typically tall, with long limbs and long thin fingers.

The most serious complications are the defects of the heart valves and aorta. It may also affect the lungs, eyes, the dural sac surrounding the spinal cord, skeleton and the hard palate.

In addition to being a connective protein that forms the structural support for tissues outside the cell, the normal fibrillin-1 protein binds to another protein, transforming growth factor beta (TGF-β).[3] TGF-β has 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. [4]Since angiotensin II receptor blockers (ARBs) also reduce TGF-β, they have tested this by giving ARBs (losartan, etc.) to a small sample of young, severely affected Marfan syndrome patients. In some patients, the growth of the aorta was indeed reduced.[5]

It is named after Antoine Marfan,[6] the French pediatrician who first described the condition in 1896 after noticing striking features in a 5-year-old girl.[7][8] The gene linked to the disease was first identified by Francesco Ramirez at the Mount Sinai Medical Center in New York City in 1991.[9]

Although there are no unique signs or symptoms of Marfan syndrome, the constellation of long limbs, dislocated lenses, and aortic root dilation is sufficient to make the diagnosis with confidence. There are more than 30 other clinical features that are variably associated with the syndrome, most involving the skeleton, skin, and joints. There is a great deal of clinical variability even within families that carry the identical mutation.

[edit]

Skeletal system

The most readily visible signs are associated with the skeletal system. Many individuals with Marfan syndrome grow to above average height. Some have long slender limbs with long fingers and toes (arachnodactyly). This condition of elongated limbs is known as dolichostenomelia. An individual's arms may be disproportionately long, with thin, weak wrists. In addition to affecting height and limb proportions, Marfan syndrome can produce other skeletal anomalies. Abnormal curvature of the spine (scoliosis) is common, as is abnormal indentation (pectus excavatum) or protrusion (pectus carinatum) of the sternum. Other signs include abnormal joint flexibility, a high palate, malocclusions, flat feet, hammer toes, stooped shoulders, unexplained stretch marks on the skin and thin wrists. It can also cause pain in the joints, bones and muscles in some patients. Some people with Marfan have speech disorders resulting from symptomatic high palates and small jaws. Early osteoarthritis may occur.

[edit]

EyesCardiovascular system

The most serious signs and symptoms associated with Marfan syndrome involve the cardiovascular system. Undue fatigue, shortness of breath, heart palpitations, racing heartbeats, or Angina pectoris with pain radiating to the back, shoulder, or arm. Cold arms, hands and feet can also be linked to Marfan's syndrome because of inadequate circulation. A heart murmur, abnormal reading on an EKG, or symptoms of angina can indicate further investigation. The signs of regurgitation from prolapse of the mitral or aortic valves (which control the flow of blood through the heart) result from cystic medial degeneration of the valves which is commonly associated with Marfan's syndrome (see mitral valve prolapse, aortic regurgitation). However, the major sign that would lead a doctor to consider an underlying condition is a dilated aorta or an aortic aneurysm. Sometimes, no heart problems are apparent until the weakening of the connective tissue (cystic medial degeneration) in the ascending aorta causes an aortic aneurysm or aortic dissection, a medical emergency. An aortic dissection is most often fatal and presents with pain radiating down the back, giving a tearing sensation.

Because of the underlying connective tissue abnormalities that cause Marfan syndrome, there is an increased incidence of dehiscence of prosthetic mitral valve.[11] Care should be taken to attempt repair of damaged heart valves rather than replacement.

During pregnancy, even in the absence of preconceived cardiovascular abnormality, women with Marfan syndrome are at significant risk of aortic dissection, which is often fatal even when rapidly treated. For this reason, women with Marfan syndrome should receive a thorough assessment prior to conception, and echocardiography should be performed every six to ten weeks during pregnancy, to assess the aortic root diameter. For most women, safe vaginal delivery is possible.[12]

[edit]

Lungs

Marfan syndrome is a risk factor for spontaneous pneumothorax. In spontaneous unilateral pneumothorax, air escapes from a lung and occupies the pleural space between the chest wall and a lung. The lung becomes partially compressed or collapsed. This can cause pain, shortness of breath, cyanosis, and, if not treated, death. Marfan syndrome has also been associated with sleep apnea and idiopathic obstructive lung disease.

[edit]

Central nervous system

Another condition that can reduce the quality of life for an individual, though not life-threatening, is dural ectasia, the weakening of the connective tissue of the dural sac, the membrane that encases the spinal cord. Dural ectasia can be present for a long time without producing any noticeable symptoms. Symptoms that can occur are lower back pain, leg pain, abdominal pain, other neurological symptoms in the lower extremities, or headaches. Such symptoms usually diminish when the individual lies flat on his or her back. These types of symptoms might lead a doctor to order an X-ray of the lower spine. Dural ectasia is usually not visible on an X-ray in the early phases. A worsening of symptoms and the lack of finding any other cause should eventually lead a doctor to order an upright MRI of the lower spine. Dural ectasia that has progressed to the point of causing these symptoms would appear in an upright MRI image as a dilated pouch that is wearing away at the lumbar vertebrae.[10] Other spinal issues associated with Marfan include degenerative disk disease and spinal cysts. Marfan syndrome is also associated with dysautonomia.

[edit]

Pathogenesis

Marfan syndrome is caused by mutations in the *FBN1* gene on chromosome 15,[13] which encodes a glycoprotein called fibrillin-1, a component of the extracellular matrix. The Fibrillin 1 protein is essential for the proper formation of the extracellular matrix including the biogenesis and maintenance of elastic fibers. The extracellular matrix is critical for both the structural integrity of connective tissue but also serves as a reservoir for growth factors.[14] Elastin fibers are found throughout the body but are particularly abundant in the aorta, ligaments and the ciliary zonules of the eye; consequently, these areas are among the worst affected.

A transgenic mouse has been created carrying a single copy of a mutant fibrillin 1, a mutation similar to that found in the human fibrillin 1 gene that is known to cause Marfan syndrome. This mouse strain recapitulates many of the features of the human disease and promises to provide insights into the pathogenesis of the disease. Reducing the level of normal fibrillin-1 causes a Marfan-related disease in mice.[15]

Transforming growth factor beta (TGFβ) plays an important role in Marfan syndrome. Fibrillin-1 indirectly binds a latent form of TGFβ keeping it sequestered and unable to exert its biological activity. The simplest model of Marfan syndrome suggests that reduced levels of fibrillin-1 allow TGFβ levels to rise due to inadequate sequestration. Although it is not proven how elevated TGFβ levels are responsible for the specific pathology seen with the disease, an inflammatory reaction releasing proteases that slowly degrade the elastin fibers and other components of the extracellular matrix is known to occur. The importance of the TGFβ pathway was confirmed with the discovery of a similar syndrome Loeys-Dietz syndrome involving the *TGFβR2* gene on chromosome 3, a receptor protein of TGFβ.[16] Marfan syndrome has often been confused with Loeys-Dietz syndrome, because of the considerable clinical overlap between the two syndromes.[17]

[edit]

Diagnosis

Diagnostic criteria of Marfan syndrome were agreed internationally in 1996.[18] A diagnosis of Marfan syndrome is based on family history and a combination of major and minor indicators of the disorder, rare in the general population, that occur in one individual. For example: four skeletal signs with one or more signs in another body system such as ocular and cardiovascular in one individual. The following conditions may result from Marfan syndrome but may also occur in people without any known underlying disorder.

AUTOSOMAL DOMINANT DISORDER

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

Achondroplasia dwarfism (pronounced /eɪ kɒn droʊ ˈpleɪ 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, and thanatophoric dysplasia. 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[2]. However, another study at the same time found a rate of 1 per 10,000[2].

[edit]

Causes

Dwarfism is a result of autosomal dominant mutation in the fibroblast growth factor receptor gene 3 (*FGFR3*), which causes an abnormality of cartilage formation. FGFR3 normally has a negative regulatory effect on bone growth. In achondroplasia, the mutated form of the receptor is constitutively active and this leads to severely shortened bones.

People with achondroplasia have one normal copy of the fibroblast growth factor receptor 3 gene and one mutant copy. Two copies of the mutant gene are invariably fatal before, or shortly after birth. Only one copy of the gene needs to be present for the disorder to occur. Therefore, a person with achondroplasia has a 50% chance of passing on the gene to their offspring, meaning that there will be a 50% chance that each child will have achondroplasia. Since two copies (Homozygous) are fatal, if two people with achondroplasia have a child, there is a 25% chance of the child dying shortly after birth, a 50% chance the child will have achondroplasia, and a 25% chance the child will have a normal phenotype. However, in the majority of cases, people with achondroplasia are born to parents who don't have the condition. This is the result of a new mutation.[3]

New gene mutations are associated with increasing paternal age[4] (over 35 years). Studies have demonstrated that new gene mutations are exclusively inherited from the father and occur during spermatogenesis (as opposed to resulting from a gonadal mosaicism). More than 99% of achondroplasia is caused by two different mutations in the fibroblast growth factor receptor 3 (FGFR3). In about 98% of cases, a G to A point mutation at nucleotide 1138 of the FGFR3 gene causes a glycine to arginine substitution (Bellus et al. 1995, Shiang et al. 1994, Rousseau et al. 1996). About 1% of cases are caused by a G to C point mutation at nucleotide 1138.

There are two other syndromes with a genetic basis similar to achondroplasia: hypochondroplasia and thanatophoric dysplasia.

[edit]

Diagnosis

Achondroplasia can be detected before birth by the use of prenatal ultrasound. A DNA test can be performed before birth to detect homozygosity, where two copies of the mutant gene are inherited, a condition which is lethal and leads to stillbirths.

[edit]

Radiologic findings

A skeletal survey is useful to confirm the diagnosis of achondroplasia. Skull demonstrate a large skull with a narrow foramen magnum, 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,[5] with a narrow sciatic notch and horizontal acetabular roof. The tubular bones are short and thick with metaphyseal cupping and flaring and irregular growth plates. Fibular overgrowth is present. The hand is broad with short metacarpals and phalanges, and a trident configuration. The ribs are short with cupped anterior ends. If the radiographic features are not classic, a search for a different diagnosis should be entertained. Because of the extremely deformed bone structure, people with achondroplasia are often double jointed.

The diagnosis can be made by fetal ultrasound by progressive discordance between the femur length and biparietal diameter by age. The trident hand configuration can be seen if the fingers are fully extended.

[edit]

Treatment

At present, there is no treatment for achondroplasia.

Although used by those without achondroplasia to aid in growth, human growth hormone does not help people with achondroplasia. However, if desired, the controversial surgery of limb-lengthening will lengthen the legs and arms of someone with achondroplasia.[6]

[edit]

Miscellaneous

Reported by the Fox News Channel, Jyoti Amge, a 15-year-old girl from India, broke the world record for the shortest person on earth. Diagnosed with achondroplasia, she is 23 inches (58 cm) tall, and weighs 11 lbs (5 kg).[7]

The condition was present in the pre-Columbian New World (evidence from the skeletal remains), and in documentation by skeletons, wall paintings, figurines in the ancient Egypt from pre-Dynastic times (up to 30th Dynasty). The ancient Egyptian word for people affected by the condition was *nemew*. They held various offices and were regarded as highly intelligent. Several of them have been found in elaborate tombs, suggesting a status of importance and wealth. [8]

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 with the drainage many children have a surgical procedure to place tubes in their ears. Because of abnormal skull structure, overcrowding of the teeth occurs and malocclusion often results, which makes oral hygiene difficult.

Dwarfism (pronounced /ˈdwɔrfɪzəm/) is a medical disorder, the term being used to describe a person of short stature. It is sometimes defined as a person with an adult height under 4 feet 10 inches (147 cm).[1] However, this restriction is problematic since the average height of population groups differs greatly.

Dwarfism can be caused by over 200 distinct medical conditions[citation needed], and as such the symptoms and characteristics of individual dwarfs vary greatly. People who are affected by dwarfism are often referred to as "little people".[2]

Disproportionate dwarfism is characterized by one or more body parts being relatively large or small in comparison to those of a normal adult, with growth abnormalities in specific areas being apparent. In cases of *proportionate* dwarfism, the body appears normally proportioned, but is clearly abnormally small. Hypotonia, or a lack of muscle, is common in dwarfs, but intelligence and lifespan are usually normal.

Achondroplasia is a bone growth disorder responsible for 70% of dwarfism cases.[1] In cases of achondroplasia the limbs are disproportionally short compared to the trunk (abdominal area), with the head larger than normal and unique facial characteristics. Conditions in humans characterized by disproportional body parts are typically caused by one or more genetic disorders in bone or cartilage development. Extreme shortness in humans with proportional body parts usually has a hormonal cause, such as growth hormone deficiency, once known as "pituitary dwarfism".[2][3]

There is no single treatment for dwarfism. Individual abnormalities such as bone growth disorders can sometimes be treated through surgery, and some hormone disorders can be treated through medication, but in most cases it is impossible to treat all the symptoms of dwarfism. Most of the time lifestyle changes are needed to cope with the effects of dwarfism. In-home devices like specialized furniture are often needed to help people with dwarfism to function normally.[4] Many support groups exist to help sufferers of dwarfism cope with the challenges they face, and to help them develop strategies to become independent.[5]

Dwarfism is a highly visible condition that often carries negative connotations in society. Some believe[who?] people afflicted with dwarfism are intellectually challenged or have personality disorders. Due to their unusual height, people with dwarfism are often used as spectacles in entertainment or portrayed with stereotypes. In popular culture, dwarfs are frequently portrayed in roles directly related to their abnormal height. For a person with dwarfism, Heightism is a problem that can lead to ridicule as a child and discrimination as an adult.[6][7]

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.

In less striking examples other possible explanations for the 'sudden' appearance of a disorder must be considered. One of the parents might be heterozygous for the mutant allele but so mildly affected that it has not previously been detected, i.e. non-penetrance. The possibility of variable expression also needs to be considered, as well as the family relationships not being as stated, i.e. *non-paternity* (p. 269) (and occasionally *non-maternity*).

New dominant mutations, in certain instances, have been associated with an increased age of the father. It is believed that this is because of the large number of mitotic divisions that male gamete stem cells undergo during a man's reproductive lifetime (p. 46).

Codominance

Codominance is the term used for two allelic traits that are both expressed in the heterozygous state. In persons with blood group AB it is possible to demonstrate both A and B blood group substances on the red blood cells, so that the A and B blood groups are therefore codominant (p. 198).

In genetics, **dominance** describes a relationship between different forms (alleles) of a gene at a particular physical location (locus) on a chromosome. Typical plants and animals have two sets of chromosomes, one set inherited from each parent, and are described as diploid. They therefore have two alleles at each gene locus. If the two alleles at the same gene locus are identical, the individual is called a homozygote and is said to be homozygous: if instead the two alleles are different, the individual is a heterozygote and is heterozygous. The genetic makeup of an organism, either at a single locus or over all its genes collectively, is called the genotype. The genotype of an organism directly or indirectly affects its molecular, physical, behavioral, and other traits, which individually or collectively are called the phenotype. At heterozygous gene loci, the two alleles interact to produce the phenotype: the interaction can often be described as dominant or recessive.

In the simplest case, the phenotypic effect of one allele completely 'masks' the other in heterozygous combination: that is, the phenotype produced by the two alleles in heterozygous combination is identical with that produced by one of the two homozygous genotypes. The allele that masks the other is said to be **dominant** to the latter, and the alternative allele is said to be **recessive** to the former.[1]

The concept of dominance was first explained by the "father of genetics", the Moravian monk Gregor Mendel, who recognized the principle based on his work with the common garden pea *Pisum sativum*. Consider a simple trait: the shape of the edible pea seed. Peas occur in two distinct phenotypes, "round" and "wrinkled." The shape phenotype is known to be influenced by a single gene that occurs in two allelic forms, A and B. Pea plants that are homozygous AA have round seeds, and those that are homozygous BB have wrinkled seeds. Plants that are heterozygous AB have round seeds that are indistinguishable in shape from AA seeds: the A allele 'dominates' the B allele to produce the round phenotype. That is, the A allele is said to be dominant to the B allele, and the B allele is recessive to the A allele. The principle of dominance is known as Mendel's First Law.

The key concept of dominance is that the heterozygote is phenotypically identical to one of the two homozygotes, which shows which of the two alleles is designated 'dominant'. *It is critical to understand* that dominance is a *genotypic* relationship between *alleles*, as manifested in the phenotype. It is unrelated to the nature of the phenotype itself, e.g, whether it is regarded as 'normal or abnormal,' 'standard or non-standard,' 'healthy or diseased', 'stronger or weaker', or 'more or less' extreme. It is also important to distinguish between the 'round' gene locus, the 'round' allele at that locus, and the 'round' phenotype it produces. It is inaccurate to say either that 'the round gene dominates the wrinkled gene,' or that 'round peas dominate wrinkled peas.'

Co-dominance

Co-dominance occurs when both alleles contribute to the phenotype. For example, in a number of plant species, if one allele causes production of a red flower pigment and the other allele produces white pigment, the mixture of the two will be seen as a pink flower phenotype. In the ABO example, the I^A and I^B alleles are co-dominant in producing the AB blood group phenotype, in which both A- and B-type antigens are made. Another example occurs at the locus for the Beta-globin component of hemoglobin, where the three molecular phenotypes of Hb^A/Hb^A, Hb^A/Hb^S, and Hb^S/Hb^S are all equally detectable by protein electrophoresis. (The medical condition produced by the heterozygous genotype is called an incomplete dominant, see below). For most gene loci at the molecular level, both alleles are expressed co-dominantly, because both are transcribed into RNA.

Co-dominance and incomplete or semi-dominance can be difficult to distinguish. In the flower color example, pink flowers may be the product of a mixture of red and white pigments (co-dominance), or the result of one allele that produces the usual amount of red pigment and another non-functional allele that produces no pigment, so as to produce a dilute, intermediate pink color (semi-dominance). By analogy, a checkerboard of red and white squares seen at a distance is indistinguishable from a uniformly pink board.

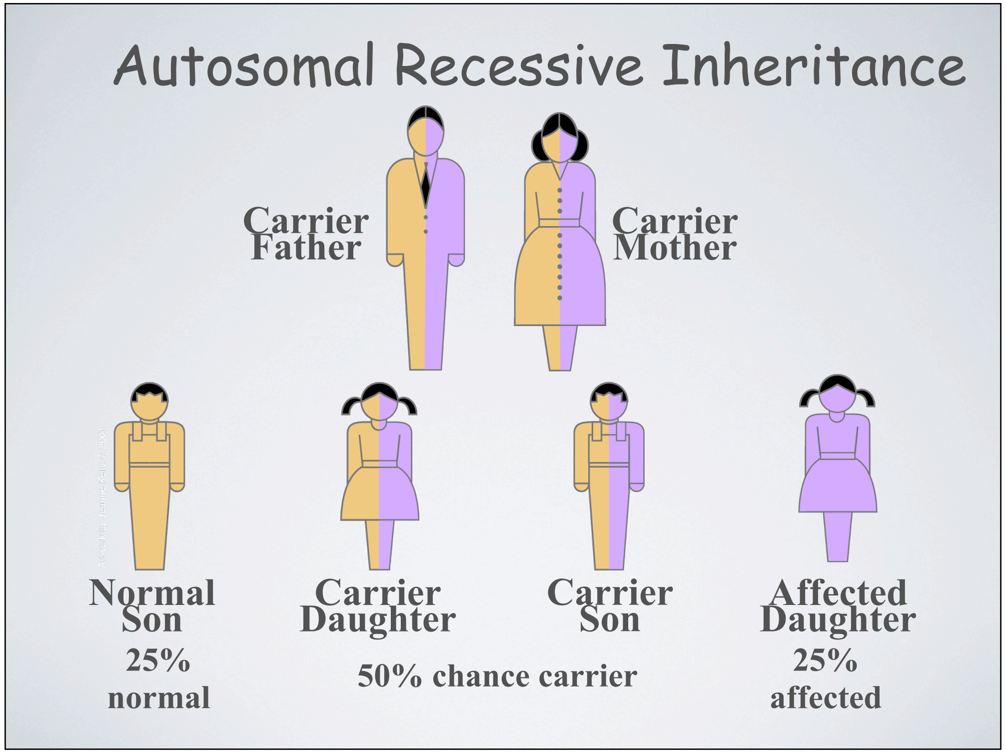
AUTOSOMAL RECESSIVE INHERITANCE

- Both male and female are affected
- The disease is observe in only single generation
- Both gene alleles 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*.

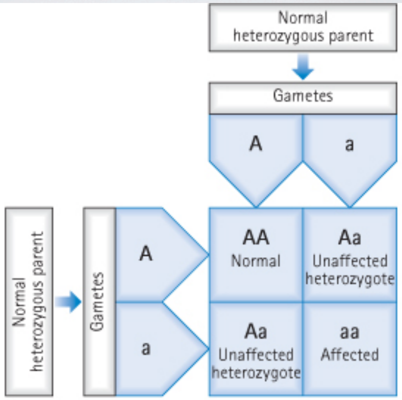
The family tree for recessive traits differs markedly from that seen in autosomal dominant traits (Fig. 7.7). It is not possible to trace an autosomal recessive trait or disorder through the family, i.e. all the affected individuals in a family are usually in a single *sibship*, i.e. brothers and sisters.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



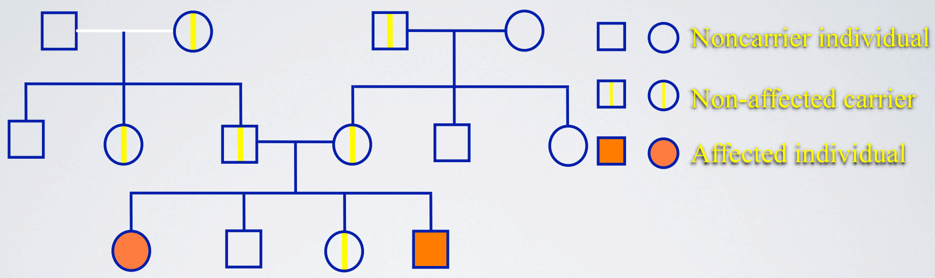
Autosomal Recessive Inheritance
Carrier Father
Carrier Mother
Normal Son
25% normal
Carrier Daughter
Carrier Son
50% chance carrier
Affected Daughter
25% affected

- Punnet`s square showing possible gamete combinations for an autosomal recessive allele

	a	A
A	Aa	AA
a	aa	aA

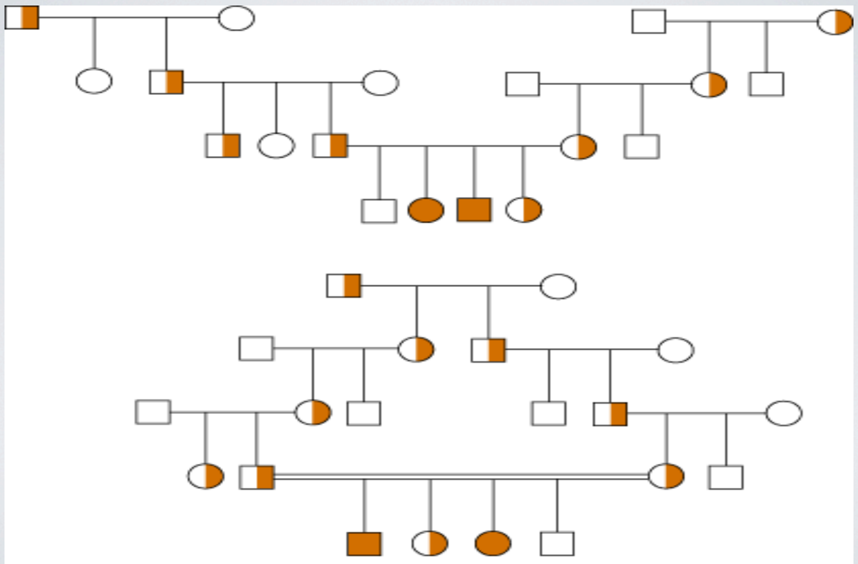

Normal heterozygous parent
Gametes
A
a
Normal heterozygous parent
Gametes
A
a
AA
Normal
Aa
Unaffected heterozygote
Aa
Unaffected heterozygote
aa
Affected

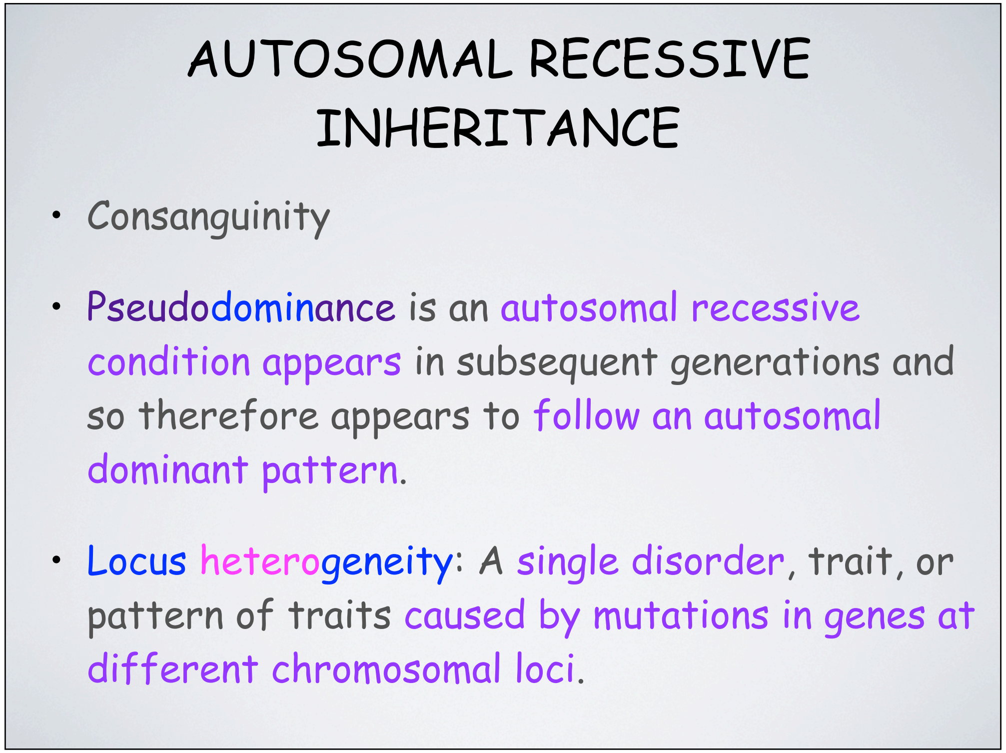
Autosomal Recessive Inheritance



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

Families with individuals expressing autosomal recessive phenotypes.





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.

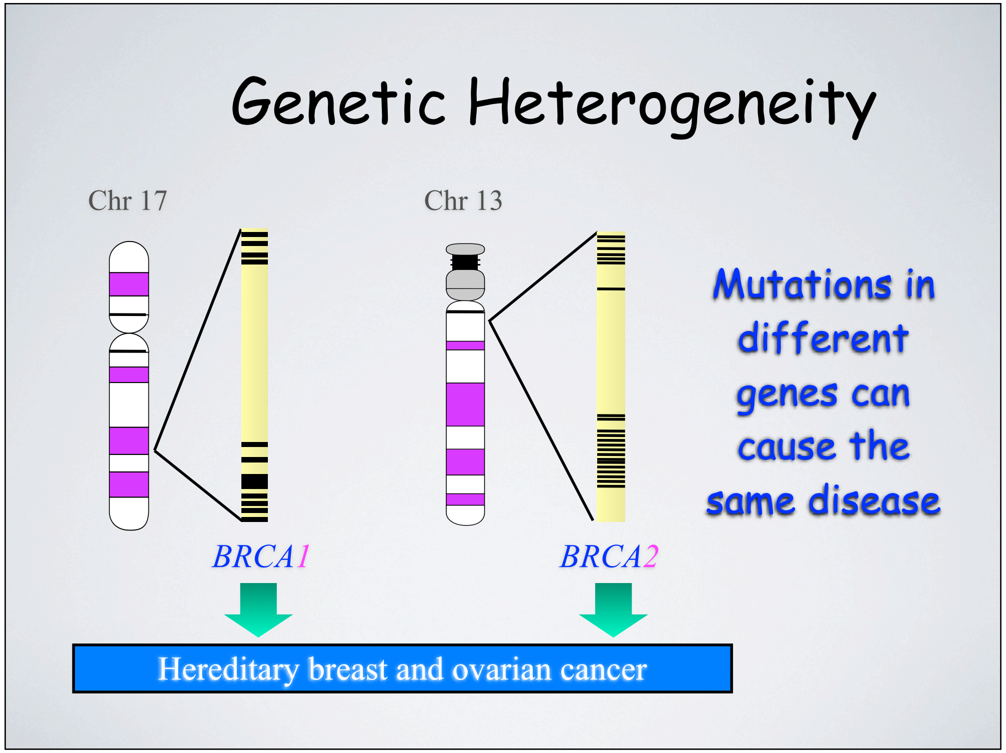
Pseudodominance also observed in autosomal recessive condition in subsequent generations .This could happen in the case of loss of genetic material from one homolog bearing the dominant allele. The heterozygous condition is therefore lost at that particular locus and the recessive phenotype is revealed.

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:

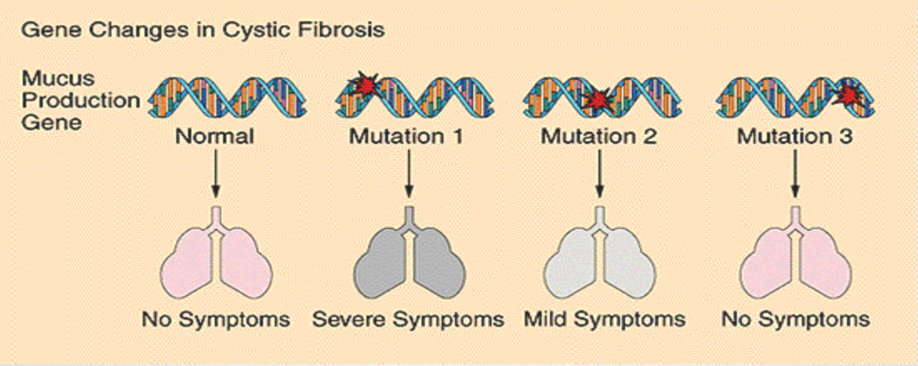
- Different FBN1 mutations causing Marfan's syndrome
- Cystic fibrosis is caused by greater than 900 different mutant alleles
- Alpha-Thalassemia or sickle cell anemia can be caused by different mutations in alpha-globin gene.



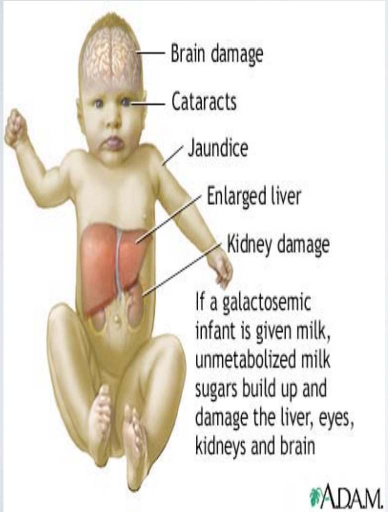
A disorder inherited in the same manner can be due to mutations in more than one gene, or what is known as *locus heterogeneity*. For example, it is recognized that sensorineural hearing impairment/deafness most commonly shows autosomal recessive inheritance. Deaf persons, by virtue of their schooling 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.

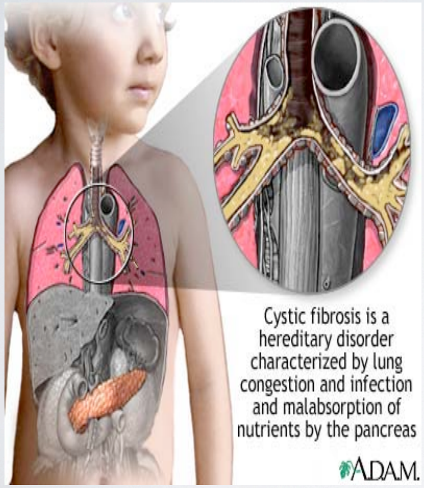


Autosomal Recessive disorder

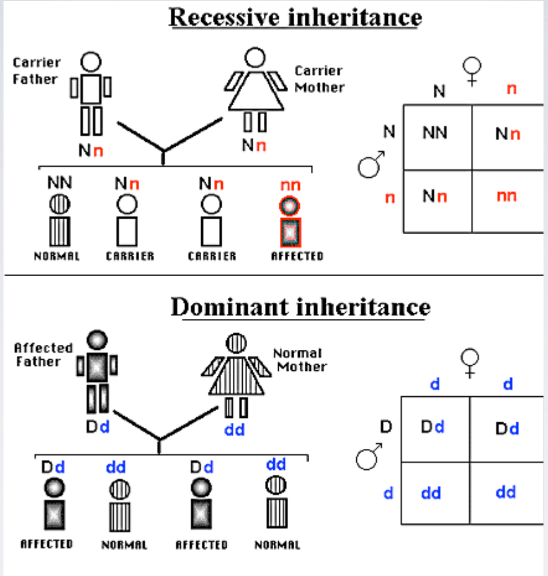


- Galactosemia
- An infant is unable to metabolize galactose
- Damage of the liver, central nervous system and various other body systems
- An infant may develop jaundice, vomiting, lethargy, irritability and convulsions

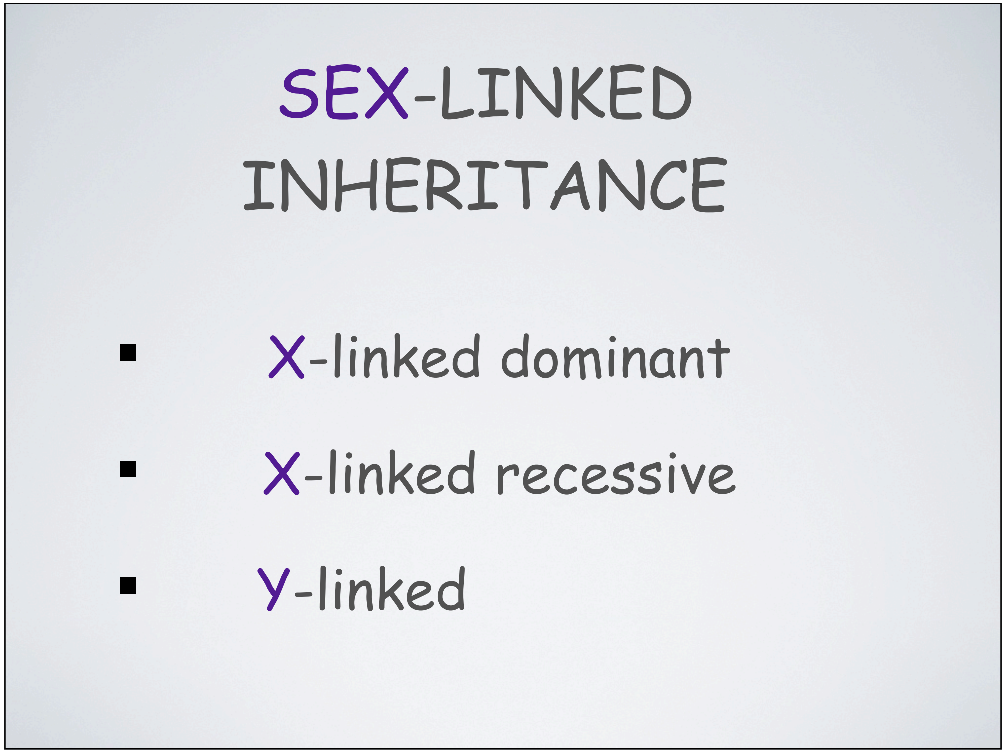
Autosomal Recessive disorder



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

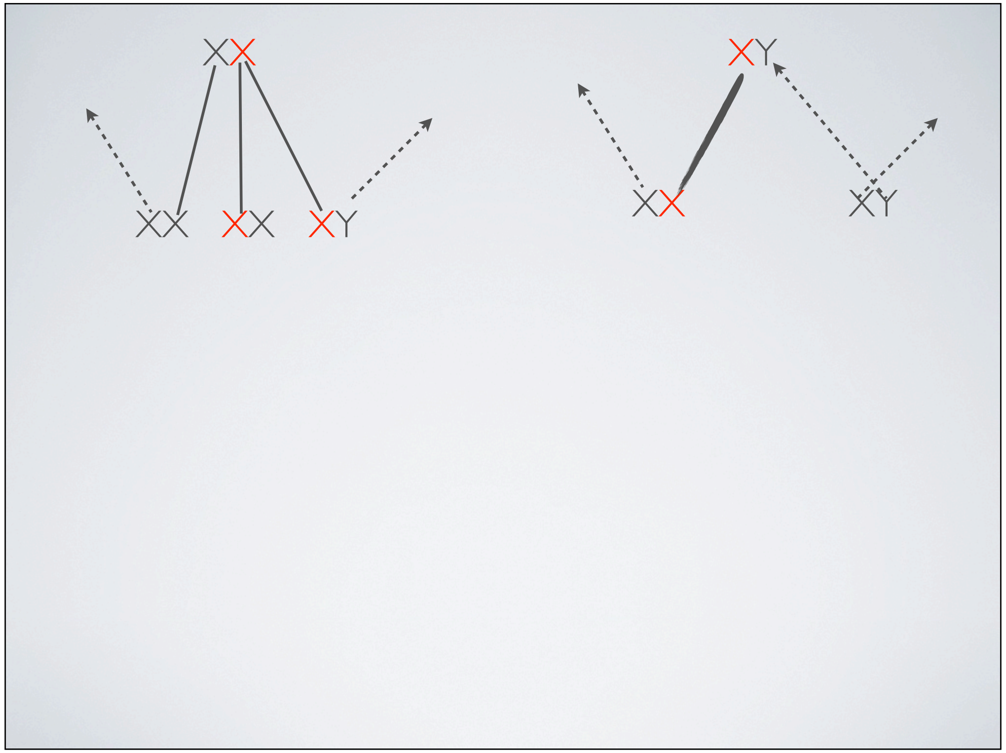


Dominant & Recessive



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*.


XX
XX
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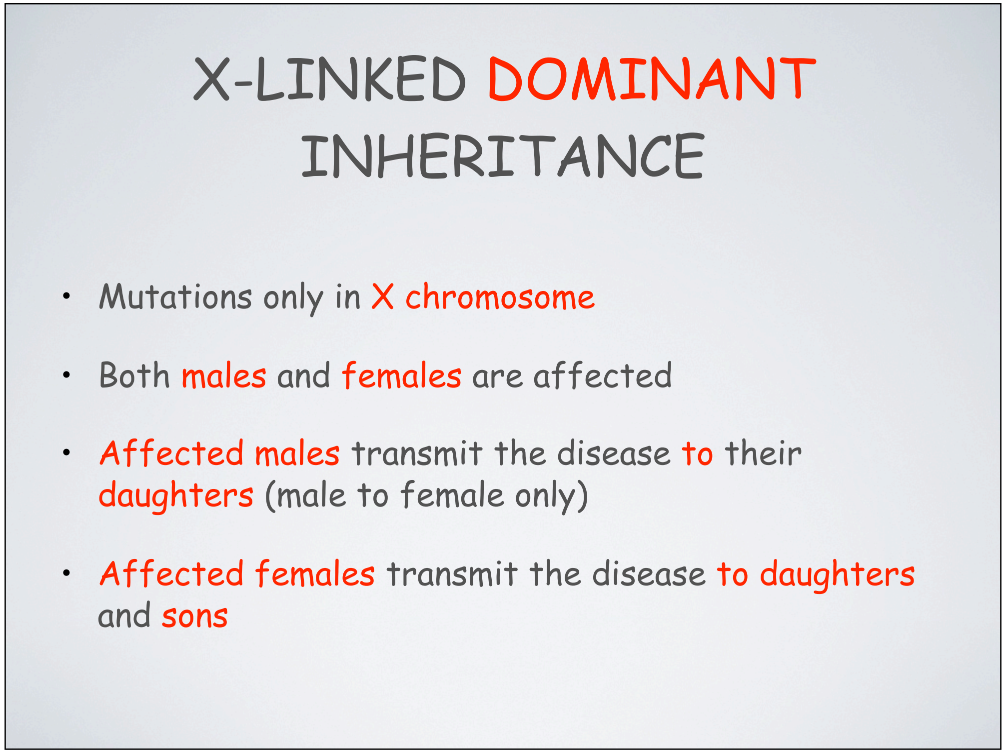
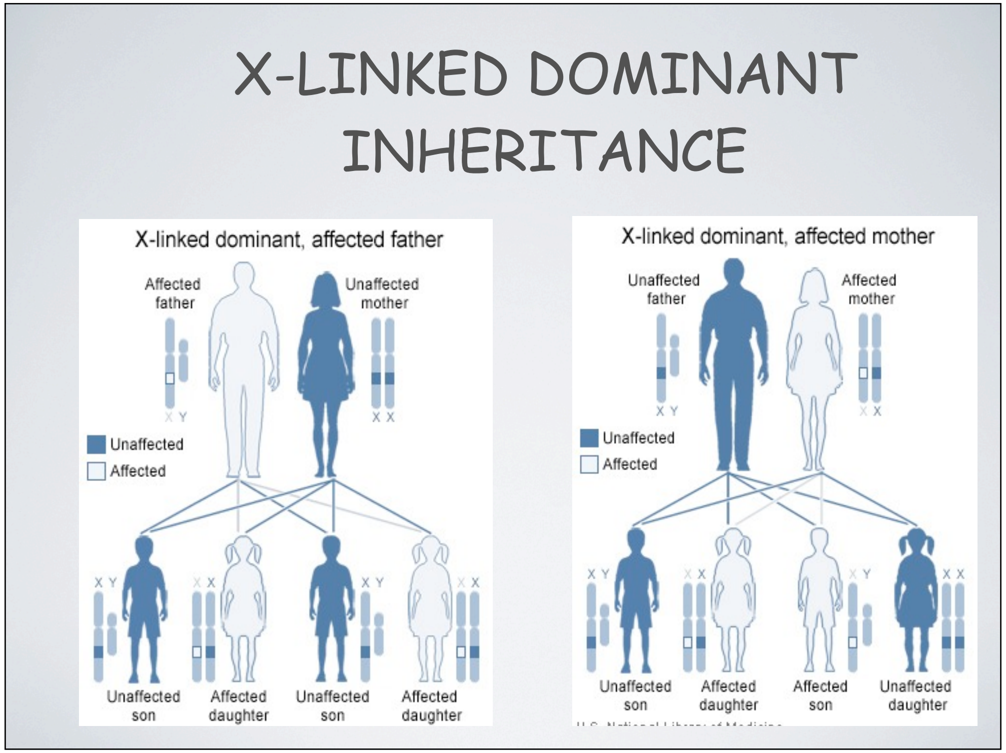


X-linked recessive inheritance

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.

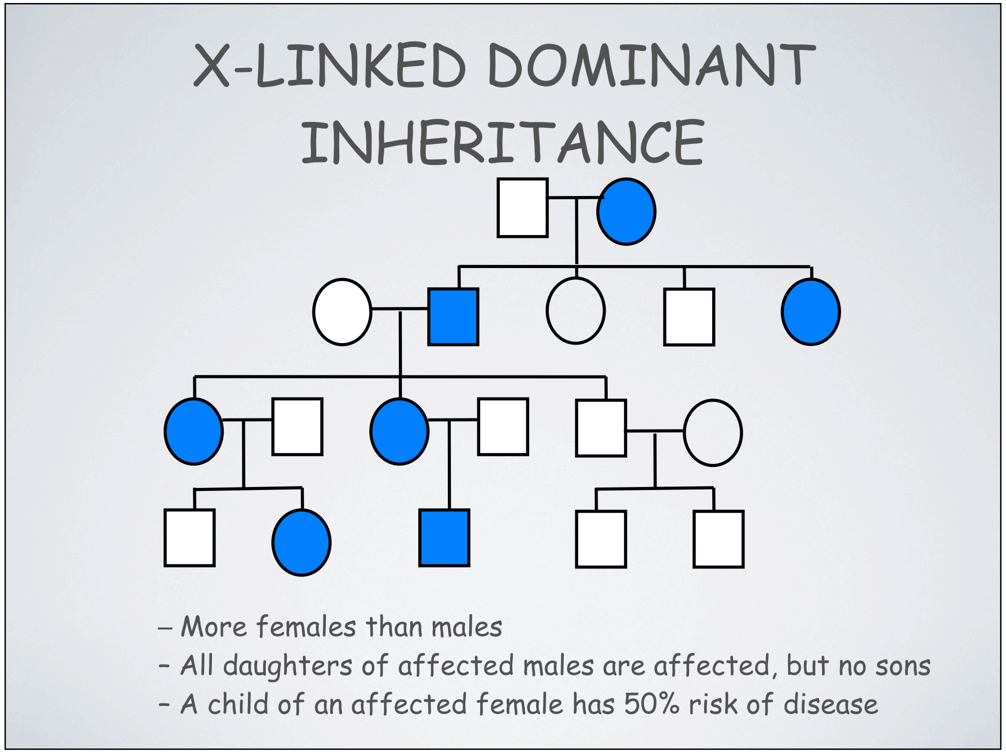


Genetic risks

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). 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).

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). Since affected boys do not usually survive to reproduce, the disease is transmitted almost entirely by healthy female carriers (Fig. 7.14).

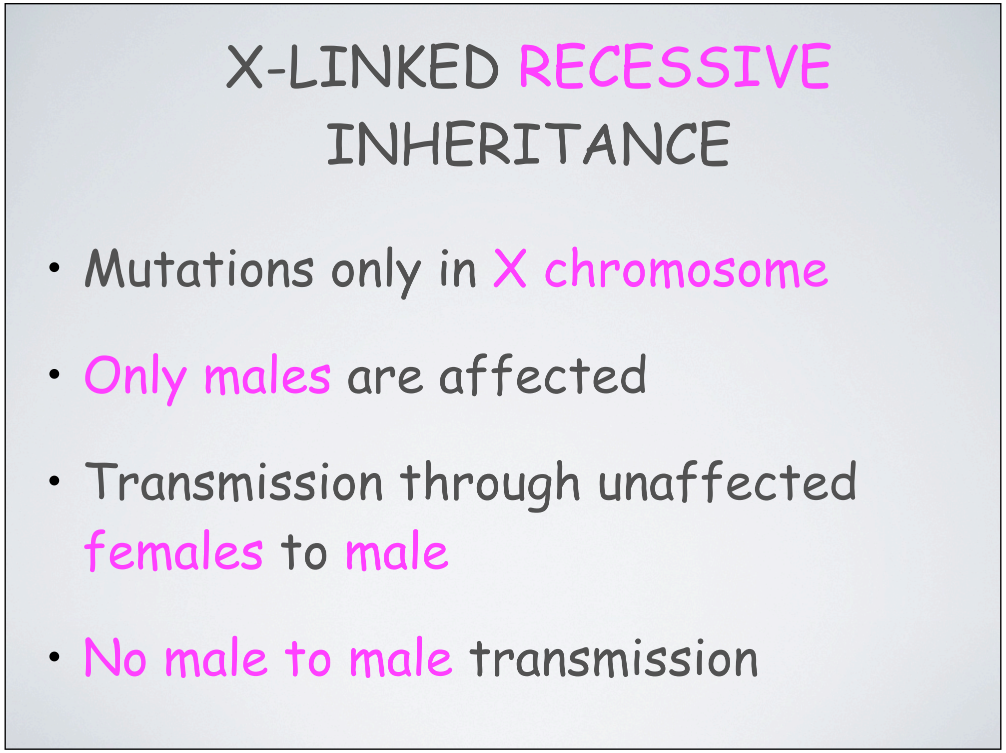


The genetics of X-linked traits is unique because **males only have one X chromosome**, whereas women have two. Therefore, men can only transmit X-linked genes to their daughters, never to their sons. The sons instead receive the Y chromosome from their fathers.

n 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).

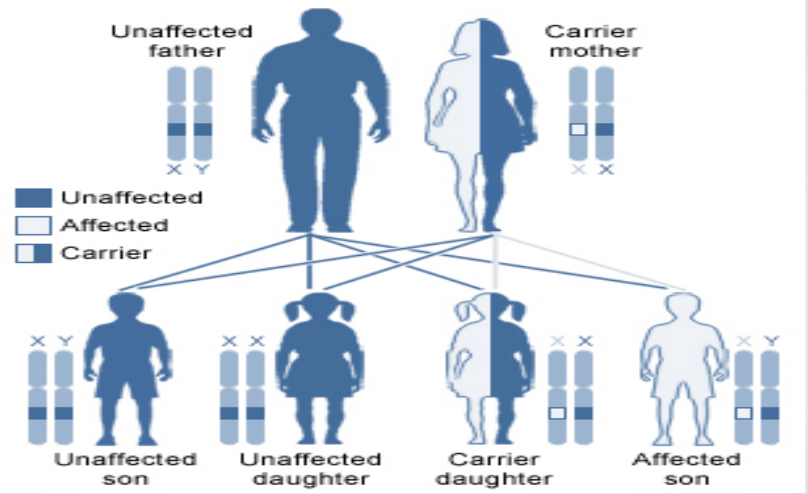
Numerical X chromosome abnormalities

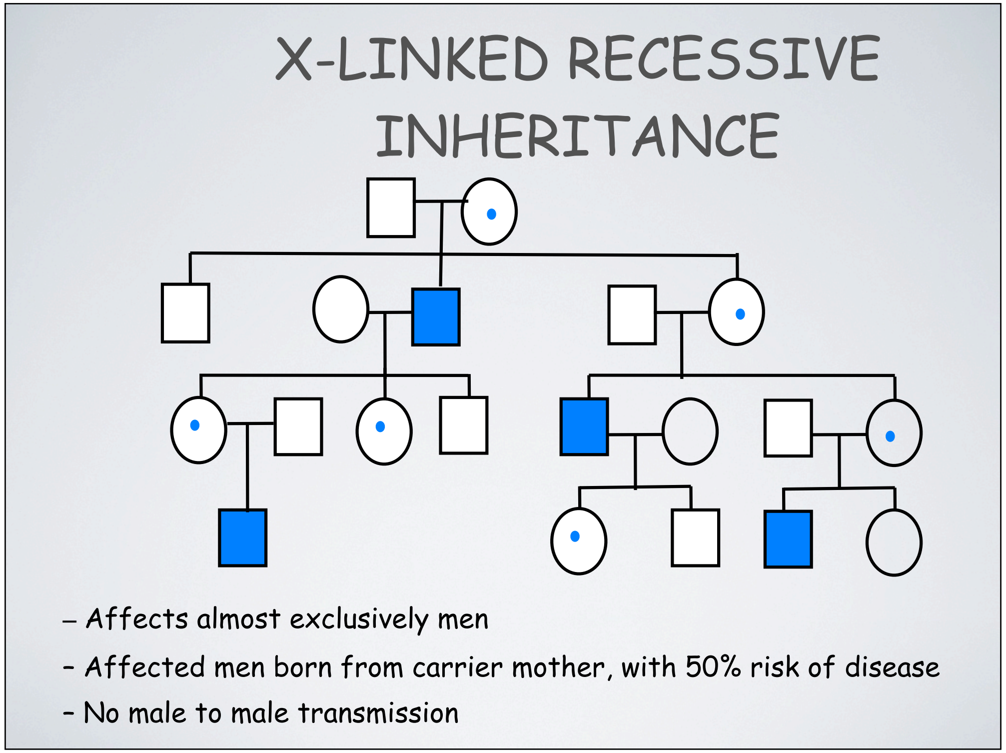
A female could manifest an X-linked recessive disorder through being a carrier of an X-linked recesssive mutation and having only a single X chromosome, i.e. Turner syndrome (p. 282). Women with Turner syndrome and hemophilia A or Duchenne muscular dystrophy have been reported.

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

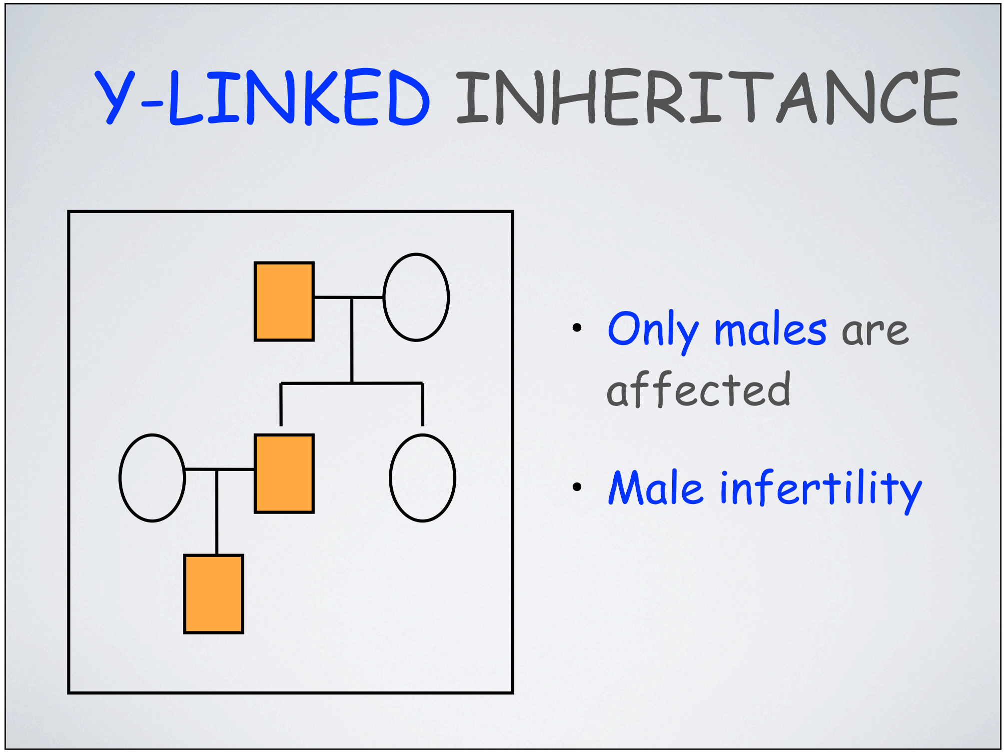




- This disease **affects almost exclusively men**, since they only have one X chromosome, and they therefore develop the disease even when they only carry one copy of the disease allele. For women, both X chromosomes must carry the affected allele before they develop the disease (in this case the father would be affected).

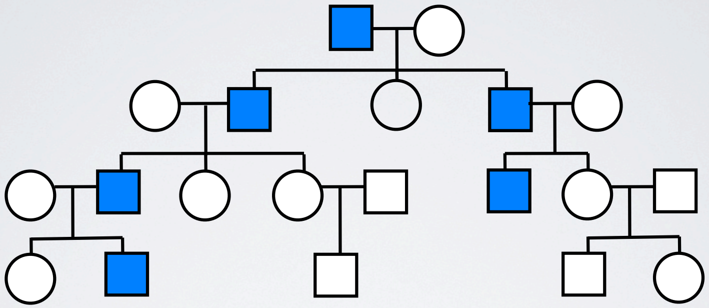
- Many women can be carriers. A boy born from a carrier mother has a **50% risk** of developing disease.

- Affected men ***can not* transmit the disease to their sons**, since they receive the Y chromosome!



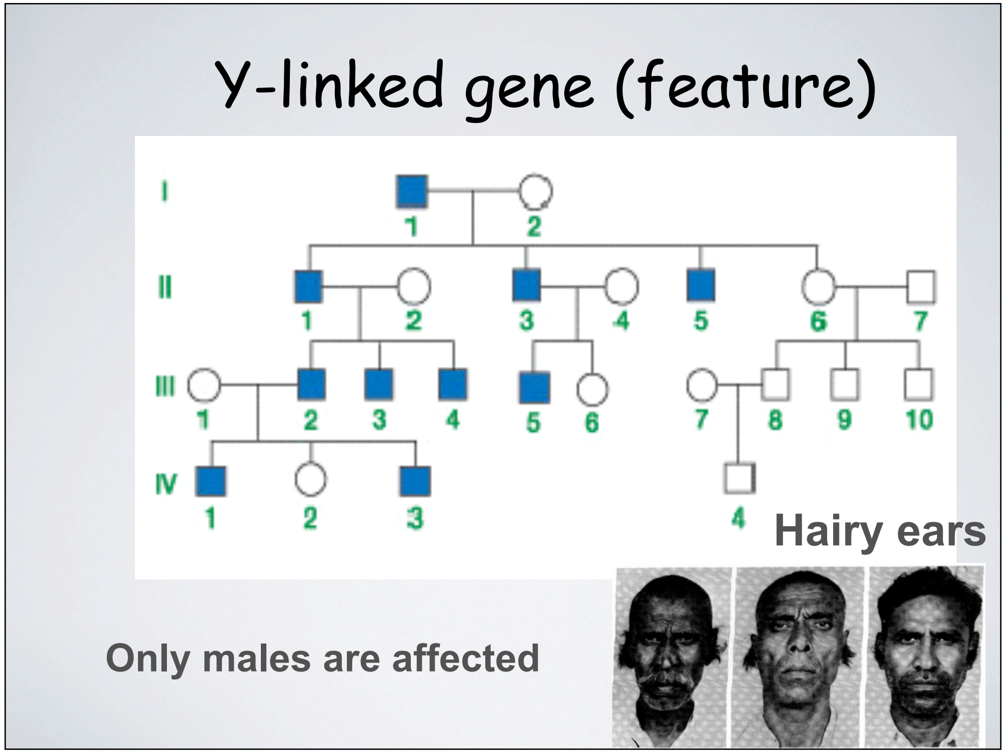
Y-linked or *holandric inheritance* implies that only males are affected. An affected male transmits Y-linked traits to all his sons but to none of his daughters. In the past it has been suggested that bizarre sounding conditions such as porcupine skin, hairy ears and webbed toes are Y-linked traits. 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!

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**.



Partial sex-linkage

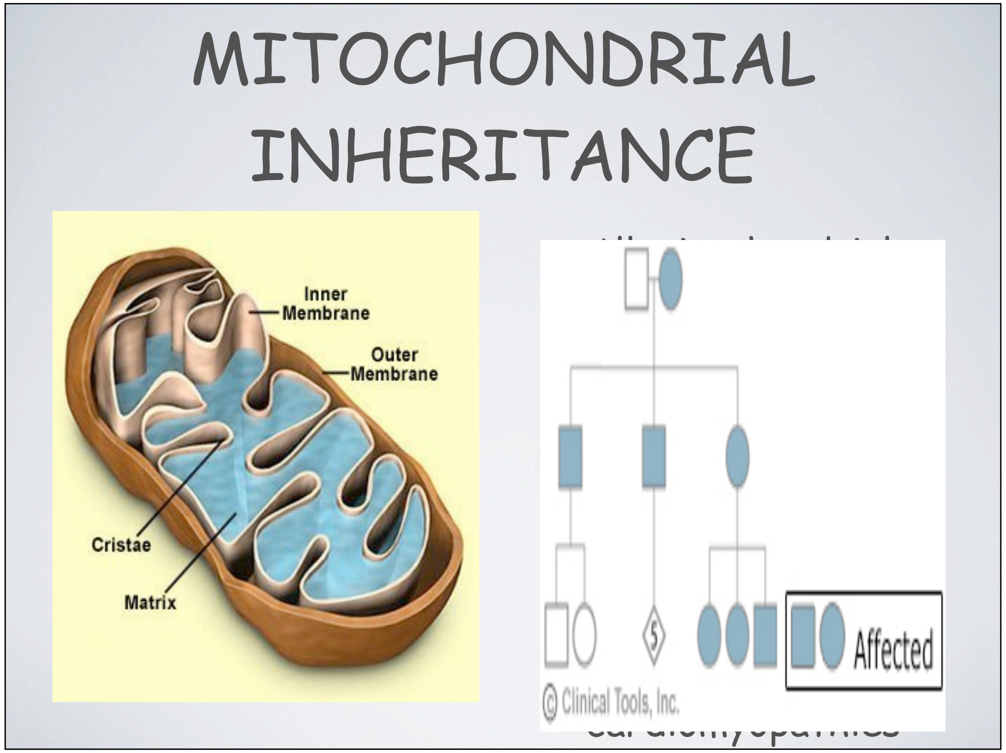
Partial sex-linkage has been used in the past for certain disorders that appear to exhibit autosomal dominant inheritance in some families and X-linked inheritance in others. This is now known to be likely to be because of genes carried on that portion of the X chromosome sharing homology with the Y 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 deletions 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).