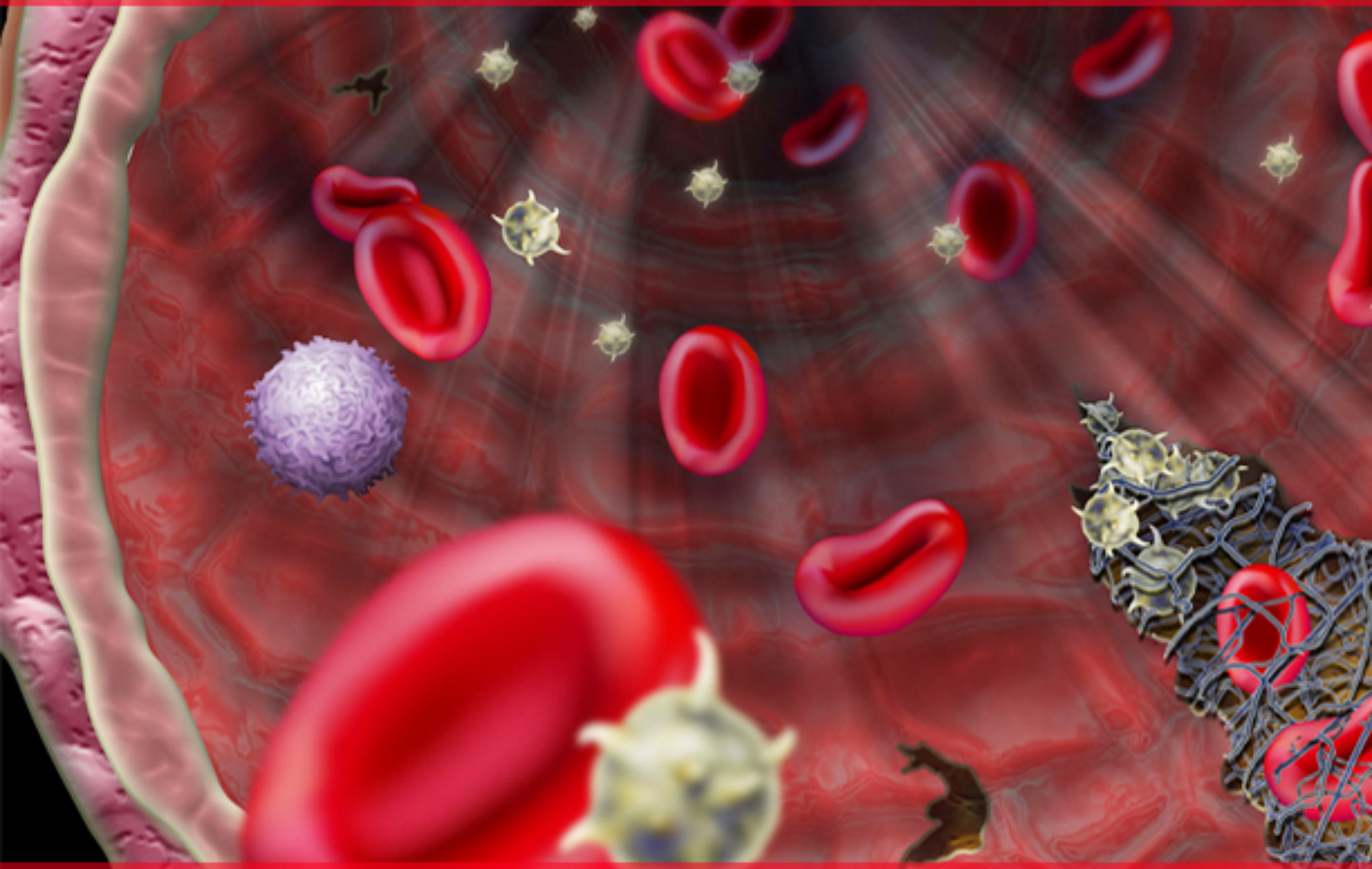
Human Genetic Engineering



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Introduction

Human genetic engineering is the alteration of an individual's genotype with the aim of choosing the phenotype of a newborn or changing the existing phenotype of a child or adult. It holds the promise of curing genetic diseases like cystic fibrosis, and increasing the immunity of people to viruses. It is speculated that genetic engineering could be used to change physical appearance, metabolism, and even improve mental faculties like memory and intelligence, although for now these uses seem to be of lower priority to researchers and are therefore limited to science fiction.

History

The first gene therapy trials on humans began in 1990 on patients with Severe Combined Immunodeficiency (SCID). In 2000, the first gene therapy "success" resulted in SCID patients with a functional immune system. These trials were stopped when it was discovered that two of ten patients in one trial had developed leukemia resulting from the insertion of the gene-carrying retrovirus near an oncogene. In 2007, four of the ten patients had developed leukemia . Work is now focusing on correcting the gene without triggering an oncogene.

Trial treatments of SCID have been gene therapy's only success; since 1999, gene therapy has restored the immune systems of at least 17 children with two forms (ADA-SCID and X-SCID) of the disorder.

Human genetic engineering is already being used on a small scale to allow infertile women with genetic defects in their mitochondria to have children. Healthy human eggs from a second mother are used. The child produced this way has genetic information from two mothers and one father. The changes made are germline changes and will likely be passed down from generation to generation, and, thus, are a permanent change to the human genome.

Other forms of human genetic engineering are still theoretical. Recombinant DNA research is usually performed to study gene expression and various human diseases. Some drastic demonstrations of gene modification have been made with mice and other

animals, however, testing on humans is generally considered off-limits. In some instances changes are usually brought about by removing genetic material from one organism and transferring them into another species.

Methods

Somatic

Somatic genetic engineering involves adding genes to cells other than egg or sperm cells. For example, if a person had a disease caused by a defective gene, a healthy gene could be added to the affected cells to treat the disorder. As of now, this is likely to take the form of gene therapy. The distinguishing characteristic of somatic engineering is that it is non-inheritable, i.e. the new gene would not be passed to the recipient's offspring.

There are two techniques researchers are currently experimenting with:

- Viruses are good at injecting their DNA payload into human cells and reproducing it. By adding the desired DNA to the DNA of non-pathogenic virus, a small amount of virus will reproduce the desired DNA and spread it all over the body.
- Manufacture large quantities of DNA, and somehow package it to induce the target cells to accept it, either as an addition to one of the original 23 chromosomes, or as an independent 24th human artificial chromosome.

Germline

Germline engineering involves changing genes in eggs, sperm, or very early embryos. This type of engineering is inheritable, meaning that the modified genes would appear not only in offspring that resulted from the procedure, but also in subsequent generations.

Uses

Two motivators of human genetic engineering are referred to as "negative" and "positive". The former aims to remove genetic disorders and the latter aims to alter phenotypic expression to result in an enhanced being.

Negative genetic engineering (cures and treatments)

When treating problems that arise from genetic disorder, one solution is gene therapy, also known as negative genetic engineering. A genetic disorder is a condition caused by the genetic code of the individual, such as spina bifida or autism. When this happens, genes may be expressed in unfavorable ways or not at all, and this generally leads to further complications.

The idea of gene therapy is that a non-pathogenic virus or other delivery systems can be used to insert into DNA—a good copy of the gene—into cells of the living individual.

The modified cells would divide as normal and each division would produce cells that express the desired trait. The result would be that he/she would then have the ability to express the trait that was previously absent, at least partially. This form of genetic engineering could help alleviate many problems, such as diabetes, cystic fibrosis, or other genetic diseases.

Positive genetic engineering (enhancement)

The potential of genetic engineering to cure medical conditions opens the question of exactly what such a condition is. Some view aging and death as medical conditions and therefore potential targets for engineering solutions. They see human genetic engineering potentially as a key tool in this. The difference between cure and enhancement from this perspective is merely one of degree. Theoretically genetic engineering could be used to drastically change people's genomes, which could enable people to regrow limbs and other organs, perhaps even extremely complex ones such as the spine.

It could also be used to make people smarter, stronger, or to increase the capacity of the lungs, among other things. If a gene exists in nature, perhaps it could be changed into a human cell. In this view, there is no qualitative difference (only a quantitative one) between, for instance, a genetic intervention to cure muscular atrophy, and a genetic intervention to improve muscle function even when those muscles are functioning at or below the human average (since there is also an average muscle function for those with a particular type of dystrophy, which the treatment would improve upon).

Others feel, there is an important distinction between using genetic technologies to treat those who are suffering, and to make those who are already healthy seem more superior to the average person. Though theory and speculation suggest, that genetic engineering could be used to make people stronger, faster, smarter, or to increase lung capacity. The AAAS report finds that there is little evidence to support this theory. Can this currently be done without very unsafe and therefore unethical human experiments. Because different cells have different tasks, changing one cell to do a function differently, will not only affect that one task, but it can affect many other tasks as well.

Controversy

Ethics

The genetic engineering of humans has raised many controversial ethical issues. While negative genetic engineering (gene therapy) does indeed raise a debate, the use of genetic engineering for human enhancement arouses the strongest feelings on both sides.

Genetic engineering is tested on animals, often including primates. Some animal rights activists find this inhumane.

Genetic engineering must be used to cure peoples with diabetes. It is possible to extract genes from cells which are called beta cells and then to insert the insulin producing genes

into a bacterium. Then the bacterium will start producing insulin. Genetic modification of embryos can pose an ethical question about the rights of the baby. One belief is that every fetus should be free to not be genetically modified. Others believe that parents hold the rights to change their unborn children. Still others believe that every child should have the right to be born free from preventable diseases.

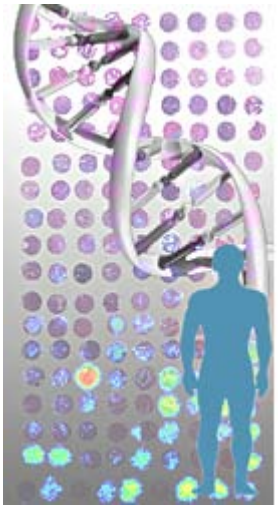
Molecular Biologist Lee M. Silver believes that unlike Aldous Huxley's Brave New World, where a totalitarian government controls all of the genetic enhancements (they actually use eugenics instead of direct genetic modification) in society, the use of gene therapy to design children will be spread through what he calls "free market eugenics" (Silver 315). Wealthy families will opt to design their child with genetic advantages because other families are doing so, and everybody wants to provide their newborn child with the best opportunities in life, with a leg up on the competition.

The greatest fear for Silver is that we will design so many children with germline gene therapy, that the families wealthy enough to design their children, will pass down these enhanced traits to future generations. This gene therapy will obviously cost money, and the less wealthy families will be left to procreate naturally, and introduce their children into the world disadvantaged from their first breath.

The impact on society will be a new alignment of classes, no longer will we separate people by their ethnic differences, the new division will be between what Silver calls 'the naturals' and 'the GenRich', or genetically enhanced. The major worry here is that the 'genetic gulf' between these two classes will become so wide that humans will become separate species (Silver 313).

Chapter 1

Human Genetics



A small piece of human DNA

Human genetics describes the study of inheritance as it occurs in human beings. Human genetics encompasses a variety of overlapping fields including: classical genetics, cytogenetics, molecular genetics, biochemical genetics, genomics, population genetics, developmental genetics, clinical genetics, and genetic counseling. Genes can be the common factor of the qualities of most human-inherited traits. Study of human genetics can be useful as it can answer questions about human nature, understand the diseases and development of effective disease treatment, and understand genetics of human life.

Genetic differences and inheritance patterns

Inheritance of giant woods for black humans are based upon Gregor Mendel's model of inheritance. Mendel deduced that inheritance depends upon discrete units of inheritance, called factors or genes.

Autosomal dominant inheritance

Autosomal traits are associated with a single gene on an autosome (non-sex chromosome)—they are called "dominant" because a single copy—inherited from either parent—is enough to cause this trait to appear. This often means that one of the parents must also have the same trait, unless it has arisen due to a new mutation. Examples of autosomal dominant traits and disorders are Huntington's disease, and achondroplasia.

Autosomal recessive inheritance

Autosomal recessive traits is one pattern of inheritance for a trait, disease, or disorder to be passed on through families. For a recessive trait or disease to be displayed two copies of the trait or disorder needs to be presented. The trait or gene will be located on a non-sex chromosome. Because it takes two copies of a trait to display a trait, many people can unknowingly be carriers of a disease. From an evolutionary perspective, a recessive disease or trait can remain hidden for several generations before displaying the phenotype. Examples of autosomal recessive disorders are albinism, Cystic Fibrosis, Tay-Sachs disease.

X-linked and Y-linked inheritance

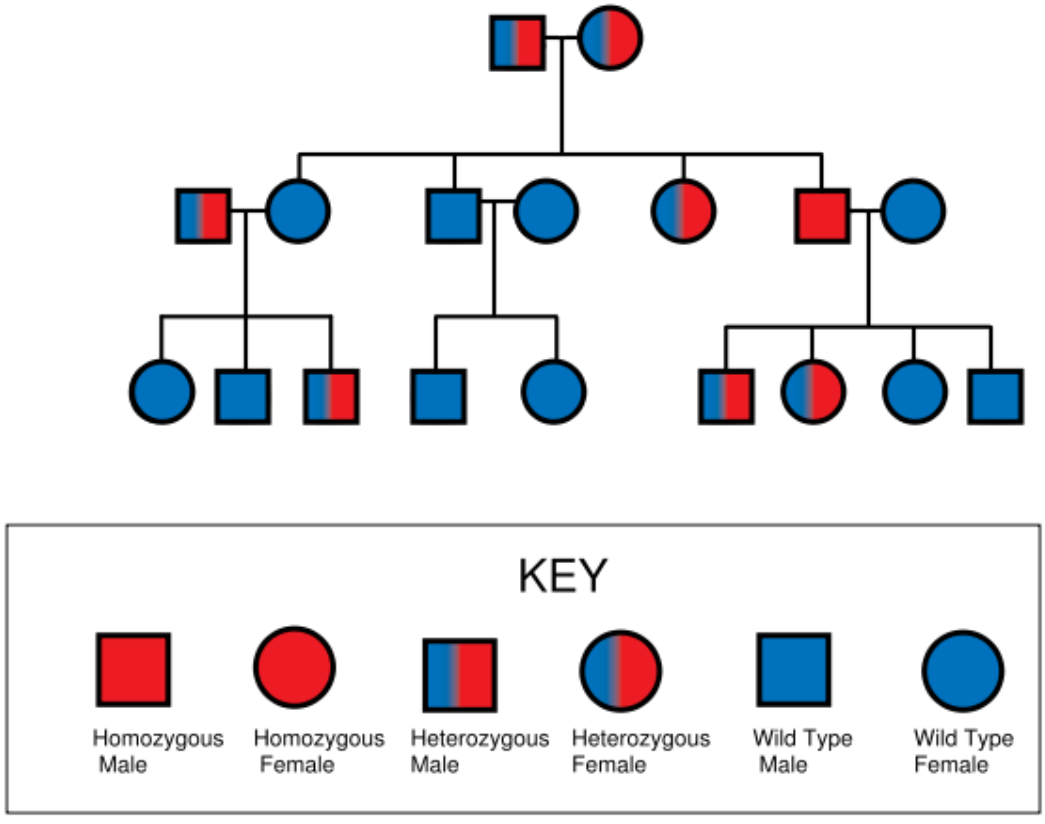
X-linked genes are found on the sex X chromosome. X-linked genes just like autosomal genes have both dominant and recessive types. Recessive X-linked disorders are rarely seen in females and usually only affect males. This is because males inherit their X chromosome and all X-linked genes will be inherited from the maternal side. Fathers only pass on their Y chromosome to their sons, so no X-linked traits will be inherited from father to son. Females express X-linked disorders when they are homozygous for the disorder and become carriers when they are heterozygous. X-linked dominant inheritance will show the same phenotype as a heterozygote and homozygote. Just like X-linked inheritance, there will be a lack of male-to-male inheritance, which makes it distinguishable from autosomal traits. One example of a X-linked trait is Coffin-Lowry syndrome, which is caused by a mutation in ribosomal protein gene. This mutation results in skeletal, craniofacial abnormalities, mental retardation, and short stature.

X chromosomes in females undergo a process known as X inactivation. X inactivation is when one of the two X chromosomes in females is almost completely inactivated. It is important that this process occurs otherwise a woman would produce twice the amount of normal X chromosome proteins. The mechanism for X inactivation will occur during the embryonic stage. For people with disorders like trisomy X, where the genotype has three X chromosomes, X-inactivation will inactivate all X chromosomes until there is only one

X chromosome active. X inactivation is not only limited to females, males with Klinefelter syndrome, who have an extra X chromosome, will also undergo X inactivation to have only one completely active X chromosome.

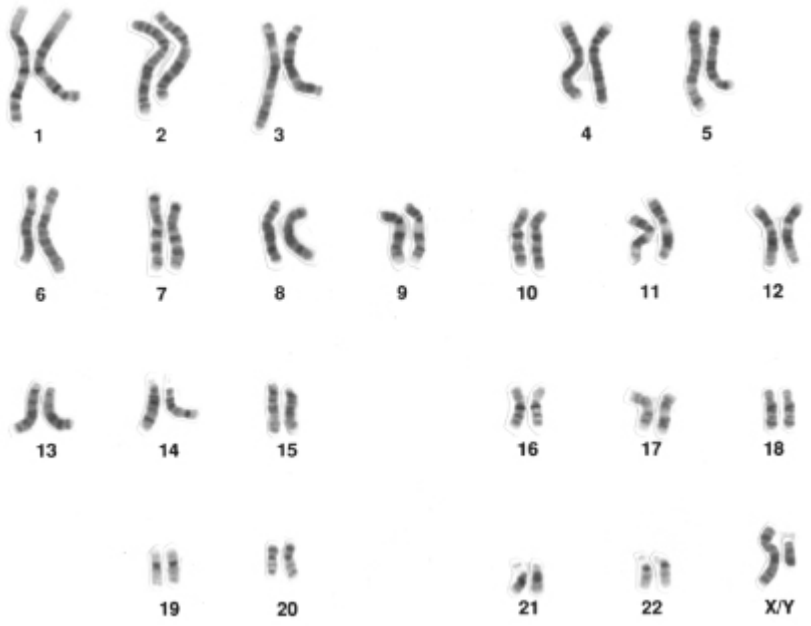
Y-linked inheritance occurs when a gene, trait, or disorder is transferred through the Y chromosome. Since Y chromosomes can only be found in males, Y linked traits are only passed on from father to son. The testis determining factor, which is located on the Y chromosome, determines the maleness of individuals. Besides the maleness inherited in the Y-chromosome there are no other found Y-linked characteristics.

Pedigrees



An example of a family pedigree displaying an autosomal recessive trait

A pedigree is a diagram showing the ancestral relationships and transmission of genetic traits over several generations in a family. Pedigrees are used to help detect many different genetic diseases. A pedigree can also be used to help determine the chances for a parent to produce an offspring with a specific trait. Four different traits can be identified by pedigree chart analysis: autosomal dominant, autosomal recessive, x-linked, or y-linked. Partial penetrance can be shown and calculated form pedigrees. Penetrance is the percentage expressed frequency with which individuals of a given genotype manifest at least some degree of a specific mutant phenotype associated with a trait. Inbreeding, the mating between closely related organisms of traits can clearly be seen on pedigree charts. Pedigree charts of royal families have a high degree of inbreeding, because it was customary and preferable for royalty to marry another member of royalty. Genetic councilors commonly use pedigrees to help couple determine if the parents will be able to produce healthy children.



A karyotype of a human male, showing 46 chromosomes including XY sex chromosomes.

Karyotype

A karyotype is a very useful tool in cytogenetics. A karyotype is picture of all the chromosomes in the metaphase stage arranged according to length and centromere position. A karyotype can also be useful in clinical genetics, due to its ability to diagnose genetic disorders. On a normal karyotype, aneuploidy can be detected by clearly being able to observe any missing or extra chromosomes. Giemsa banding, g-banding, of the karyotype can be used to detect deletions, insertions, duplications, inversions, and translocations. G-banding will stain the chromosomes with light and dark bands unique to each chromosome. A FISH, fluorescent in situ hybridization, can be used to observe

deletions, insertions, and translocations. FISH uses fluorescent probes to bind to specific sequences of the chromosomes that will cause the chromosomes to fluoresce a unique color.

Genomics

Genomics refers to the field of genetics concerned with structural and functional studies of the genome. A genome is all the DNA contained within an organism or a cell including nuclear and mitochondrial DNA. The human genome is the total collection of genes in a human being contained in the human chromosome, composed of over three billion nucleotides. In April 2003, the Human Genome Project was able to sequence all the DNA in the human genome, to discover the human genome was composed around 20,000 protein coding genes.

Population genetics

Population genetics is the branch of evolutionary biology responsible for investigating processes that cause changes in allele and genotype frequencies in populations based upon Mendelian inheritance. Four different forces can influence the frequencies: natural selection, mutation, gene flow (migration), and genetic drift. A population can be defined as a group of interbreeding individuals and their offspring. For human genetics the populations will consist only of the human species. The Hardy-Weinberg principle is a widely used principle to determine allelic and genotype frequencies.

Hardy-Weinberg principle

The Hardy-Weinberg principle states that when no evolution occurs in a population the allele and genotype frequencies do not change from one generation to the next. No evolution refers to no mutation, no gene flow, no natural selection, and no genetic drift. To be in equilibrium two more assumptions need to be made that random mating occurs and there are discrete, non-overlapping generations.

Mitochondrial DNA

In addition to nuclear DNA, humans (like almost all eukaryotes) have mitochondrial DNA. Mitochondria, the "power houses" of a cell, have their own DNA because they are descended from a proteobacterium that merged with eukaryotic cells over 2 billion years ago—an assertion known as the endosymbiotic hypothesis. Mitochondria are inherited from one's mother, and its DNA is frequently used to trace maternal lines of descent. Mitochondrial DNA is only 16kb in length and encodes for 62 genes.

Genes and human characteristics

Genes are a fundamental unit of inheritance. Genes can be defined as a sequence of DNA in the genome that is required for production of a functional product. Genes have both

minor and major effects on human characteristics. Human genes have become prominent in the nature versus nurture debate.

Genes and behavior

Genes have a strong influence on human behavior. IQ is largely heritable. However, this has been questioned. The stance that humans inherit substantial behavioral characteristics is called psychological nativism, compared to the stance that human behavior and culture are virtually entirely constructed (tabula rasa).

In the early 20th century, eugenics was policy in parts of the United States and Europe. The goal was to reduce or eliminate traits that were considered undesirable. One form of eugenics was compulsory sterilization of people deemed mentally unfit. Hitler's eugenics programs turned social consciousness against the practice, and psychological nativism became associated with racism and sexism.

Genes and gender

Evolutionary psychology

Evolutionary psychology explains many human behaviors as more or less moderated by genes that evolved in the hunter-gatherer stage of human cultural development.

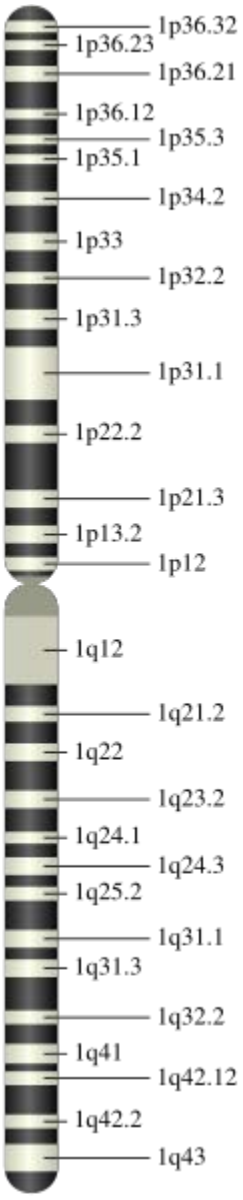
Human traits with simple inheritance patterns

Dominant	Recessive
Widow's peak	No Widow's peak
Facial Dimples	No Facial Dimples
Able to taste PTC	Unable to taste PTC
Unattached earlobe	Attached earlobe
Cleft chin	No Cleft chin
Brunette iris (anatomy)	Blue Iris (anatomy)
Color Vision	Color blindness
Brown Hair	Blonde Hair
normal	turned up nose
Ability to roll tongue (Able to hold tongue in a U shape)	No ability to roll tongue
Normal Pinkies	Crooked Pinkies
Normal Thumb	Hitchhiker's Thumb
Freckles	No Freckles
Wet-type earwax	Dry-type earwax
Curly Hair	Straight Hair

Chapter 2

Human Chromosomes

Chromosome 1 (Human)



Map of Chromosome 1

Chromosome 1 is the designation for the largest human chromosome. Humans have two copies of chromosome 1, as they do with all of the autosomes, which are the non-sex chromosomes. Chromosome 1 spans about 247 million nucleotide base pairs, which are the basic units of information for DNA. It represents about 8% of the total DNA in human cells.

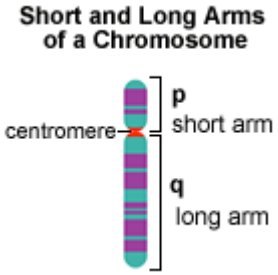
Identifying genes on each chromosome is an active area of genetic research. Chromosome 1 is currently believed to have 4,220 genes, exceeding previous predictions based on its size. It was the last completed chromosome, sequenced two decades after the beginning of the Human Genome Project.

The number of single nucleotide polymorphisms (SNPs) is about 740,000.

Genes

The following are some of the genes located on chromosome 1:

p-arm



Short and long arms

- ACADM: acyl-Coenzyme A dehydrogenase, C-4 to C-12 straight chain
- COL11A1: collagen, type XI, alpha 1
- CPT2: carnitine palmitoyltransferase II
- DBT: dihydrolipoamide branched chain transacylase E2
- DIRAS3: DIRAS family, GTP-binding RAS-like 3
- ESPN: espin (autosomal recessive deafness 36)
- GALE: UDP-galactose-4-epimerase
- GJB3: gap junction protein, beta 3, 31kDa (connexin 31)
- HMGCL: 3-hydroxymethyl-3-methylglutaryl-Coenzyme A lyase (hydroxymethylglutaricaciduria)
- KCNQ4: potassium voltage-gated channel, KQT-like subfamily, member 4
- KIF1B: kinesin family member 1B
- MFN2: mitofusin 2
- MTHFR: 5,10-methylenetetrahydrofolate reductase (NADPH)
- MUTYH: mutY homolog (E. coli)
- NGF: Nerve Growth Factor
- PARK7: Parkinson disease (autosomal recessive, early onset) 7

- PINK1: PTEN induced putative kinase 1
- PLOD1: procollagen-lysine 1, 2-oxoglutarate 5-dioxygenase 1
- TSHB: thyroid stimulating hormone, beta
- UROD: uroporphyrinogen decarboxylase (the gene for porphyria cutanea tarda)

q-arm

- ASPM: a brain size determinant
- F5: coagulation factor V (proaccelerin, labile factor)
- FMO3: flavin containing monooxygenase 3
- GBA: glucosidase, beta; acid (includes glucosylceramidase) (gene for Gaucher disease)
- GLC1A: gene for glaucoma
- HFE2: hemochromatosis type 2 (juvenile)
- HPC1: gene for prostate cancer
- IRF6: gene for connective tissue formation
- LMNA: lamin A/C
- MPZ: myelin protein zero (Charcot-Marie-Tooth neuropathy 1B)
- MTR: 5-methyltetrahydrofolate-homocysteine methyltransferase
- PPOX: protoporphyrinogen oxidase
- PSEN2: presenilin 2 (Alzheimer disease 4)
- SDHB: succinate dehydrogenase complex subunit B
- TNNT2: cardiac troponin T2
- USH2A: Usher syndrome 2A (autosomal recessive, mild)

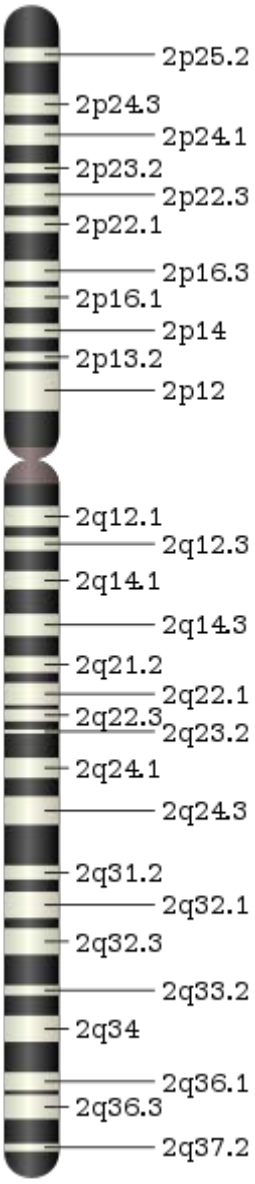
Diseases & disorders

There are 890 known diseases related to this chromosome. Some of these diseases are deafness, Alzheimer disease, glaucoma and breast cancer. Rearrangements and mutations of chromosome 1 are prevalent in cancer and many other diseases. Patterns of sequence variation reveal signals of recent selection in specific genes that may contribute to human fitness, and also in regions where no function is evident. The following diseases are some of those related to genes on chromosome 1 (which contains the most known genetic diseases of any human chromosome):

- 1q21.1 deletion syndrome
- 1q21.1 duplication syndrome
- Alzheimer disease
- Alzheimer disease, type 4
- Breast cancer
- Brooke Greenberg Disease (Syndrome X)
- Carnitine palmitoyltransferase II deficiency
- Charcot-Marie-Tooth disease
- Charcot-Marie-Tooth disease, type 1
- Charcot-Marie-Tooth disease, type 2
- collagenopathy, types II and XI

- congenital hypothyroidism
- Deafness, autosomal recessive deafness 36
- Ehlers-Danlos syndrome
- Ehlers-Danlos syndrome, kyphoscoliosis type
- Factor V Leiden thrombophilia
- Familial adenomatous polyposis
- galactosemia
- Gaucher disease
- Gaucher disease type 1
- Gaucher disease type 2
- Gaucher disease type 3
- Gaucher-like disease
- Gelatinous drop-like corneal dystrophy
- Glaucoma
- Hemochromatosis
- Hemochromatosis, type 2
- Hepatoerythropoietic porphyria
- Homocystinuria
- Hutchinson Gilford Progeria Syndrome
- 3-hydroxy-3-methylglutaryl-CoA lyase deficiency
- Hypertrophic cardiomyopathy, autosomal dominant mutations of TNNT2; hypertrophy usually mild; restrictive phenotype may be present; may carry high risk of sudden cardiac death
- maple syrup urine disease
- medium-chain acyl-coenzyme A dehydrogenase deficiency
- Microcephaly
- Muckle-Wells Syndrome
- Nonsyndromic deafness
- Nonsyndromic deafness, autosomal dominant
- Nonsyndromic deafness, autosomal recessive
- Oligodendroglioma
- Parkinson disease
- Pheochromocytoma
- porphyria
- porphyria cutanea tarda
- popliteal pterygium syndrome
- prostate cancer
- Stickler syndrome
- Stickler syndrome, COL11A1
- trimethylaminuria
- Usher syndrome
- Usher syndrome type II
- Van der Woude syndrome
- Variegate porphyria

Chromosome 2 (Human)



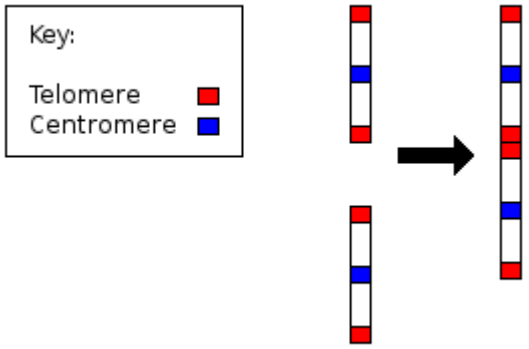
Chromosome 2 is one of the 23 pairs of chromosomes in humans. People normally have two copies of this chromosome. Chromosome 2 is the second largest human chromosome, spanning more than 237 million base pairs (the building material of DNA) and representing almost 8% of the total DNA in cells.

Identifying genes on each chromosome is an active area of genetic research. Because researchers use different approaches to predict the number of genes on each chromosome,

the estimated number of genes varies. Chromosome 2 likely contains 1,491 genes, including those of the HOXD homeobox gene cluster.

Evolution

All members of Hominidae except humans have 24 pairs of chromosomes. Humans have only 23 pairs of chromosomes. Human chromosome 2 is widely accepted to be a result of an end-to-end fusion of two ancestral chromosomes.



Fusion of ancestral chromosomes left distinctive remnants of telomeres, and a vestigial centromere

The evidence for this includes:

- The correspondence of chromosome 2 to two ape chromosomes. The closest human relative, the chimpanzee, has near-identical DNA sequences to human chromosome 2, but they are found in two separate chromosomes. The same is true of the more distant gorilla and orangutan.
- The presence of a vestigial centromere. Normally a chromosome has just one centromere, but in chromosome 2 there are remnants of a second centromere.
- The presence of vestigial telomeres. These are normally found only at the ends of a chromosome, but in chromosome 2 there are additional telomere sequences in the middle.

Some argue that chromosome 2 presents very strong evidence in favour of the common descent of humans and other apes. According to researcher J. W. IJdo, "We conclude that the locus cloned in cosmids c8.1 and c29B is the relic of an ancient telomere-telomere fusion and marks the point at which two ancestral ape chromosomes fused to give rise to human chromosome 2."

Genes

The following genes are located on chromosome 2:

- ABCA12: ATP-binding cassette, sub-family A (ABC1), member 12
- ABCG5 and ABCG8: ATP-binding cassette, subfamily A, members 5 and 8

- AGXT: alanine-glyoxylate aminotransferase (oxalosis I; hyperoxaluria I; glycolicaciduria; serine-pyruvate aminotransferase)
- ALMS1: Alstrom syndrome 1
- ALS2: amyotrophic lateral sclerosis 2 (juvenile)
- BMPR2: bone morphogenetic protein receptor, type II (serine/threonine kinase)
- COL3A1: collagen, type III, alpha 1 (Ehlers-Danlos syndrome type IV, autosomal dominant)
- COL4A3: collagen, type IV, alpha 3 (Goodpasture antigen)
- COL4A4: collagen, type IV, alpha 4
- COL5A2: collagen, type V, alpha 2
- HADHA: hydroxyacyl-Coenzyme A dehydrogenase/3-ketoacyl-Coenzyme A thiolase/enoyl-Coenzyme A hydratase (trifunctional protein), alpha subunit
- HADHB: hydroxyacyl-Coenzyme A dehydrogenase/3-ketoacyl-Coenzyme A thiolase/enoyl-Coenzyme A hydratase (trifunctional protein), beta subunit
- MSH2: mutS homolog 2, colon cancer, nonpolyposis type 1 (E. coli)
- MSH6: mutS homolog 6 (E. coli)
- NR4A2: nuclear receptor subfamily 4, group A, member 2
- OTOF: otoferlin
- PAX3: paired box gene 3 (Waardenburg syndrome 1)
- PAX8: paired box gene 8
- PELI1: Ubiquitin ligase
- SLC40A1: solute carrier family 40 (iron-regulated transporter), member 1
- TPO: thyroid peroxidase
- TBR1: T-box, brain, 1

Related diseases & disorders

The following diseases are related to genes located on chromosome 2:

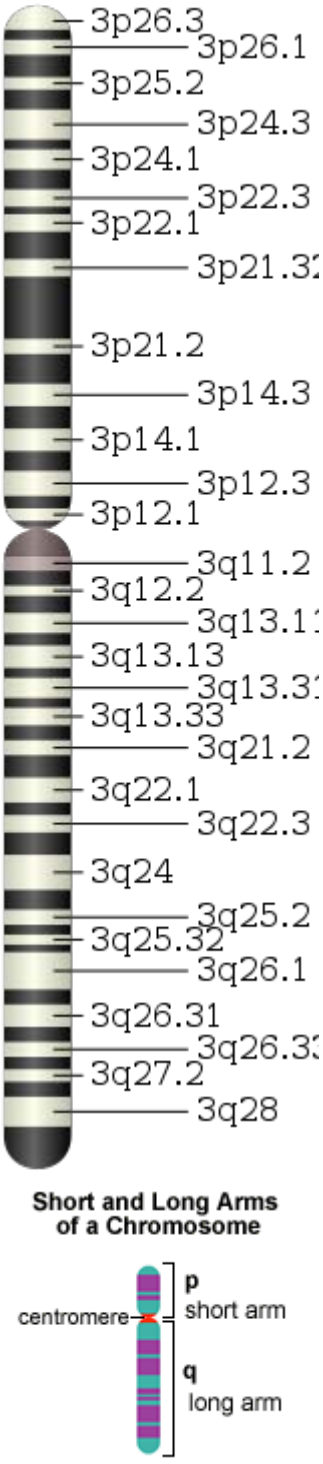
- Autism
- Alport syndrome
- Alström syndrome
- Amyotrophic lateral sclerosis
- Amyotrophic lateral sclerosis, type 2
- Congenital hypothyroidism
- Ehlers-Danlos syndrome
- Ehlers-Danlos syndrome, classical type
- Ehlers-Danlos syndrome, vascular type
- Fibrodysplasia ossificans progressiva
- Harlequin type ichthyosis
- Hemochromatosis
- Hemochromatosis, type 4
- Hereditary nonpolyposis colorectal cancer
- Infantile-onset ascending hereditary spastic paralysis
- Juvenile primary lateral sclerosis
- Long-chain 3-hydroxyacyl-coenzyme A dehydrogenase deficiency

- Maturity onset diabetes of the young type 6
- Mitochondrial trifunctional protein deficiency
- Nonsyndromic deafness
- Nonsyndromic deafness, autosomal recessive
- Primary hyperoxaluria
- Primary pulmonary hypertension
- Sitosterolemia (knockout of either ABCG5 or ABCG8)
- Synesthesia
- Waardenburg syndrome

Intelligence

Recent studies suggest that genes on chromosome 2 may play an important role in human intelligence.

Chromosome 3 (Human)



Short and long arms

Chromosome 3 is one of the 23 pairs of chromosomes in humans. People normally have two copies of this chromosome. Chromosome 3 spans almost 200 million base pairs (the building material of DNA) and represents about 6.5 percent of the total DNA in cells.

Identifying genes on each chromosome is an active area of genetic research. Because researchers use different approaches to predict the number of genes on each chromosome, the estimated number of genes varies. Chromosome 3 likely contains between 1,100 and 1,500 genes.

Genes

The following are some of the genes located on chromosome 3:

p-arm

- ALAS1: aminolevulinate, delta-, synthase 1
- BTD: biotinidase
- CCR5: chemokine (C-C motif) receptor 5
- CNTN4: Contactin 4
- COL7A1: Collagen, type VII, alpha 1 (epidermolysis bullosa, dystrophic, dominant and recessive)
- MITF: microphthalmia-associated transcription factor
- MLH1: mutL homolog 1, colon cancer, nonpolyposis type 2 (E. coli)
- OXTR: oxytocin receptor
- PTHR1: parathyroid hormone receptor 1
- SCN5A: sodium channel, voltage-gated, type V, alpha (long QT syndrome 3)
- SLC25A20: solute carrier family 25 (carnitine/acylcarnitine translocase), member 20
- TMIE: transmembrane inner ear
- VHL: von Hippel-Lindau tumor suppressor

q-arm

- CPOX: coproporphyrinogen oxidase (coproporphyria, harderoporphyria)
- HGD: homogentisate 1,2-dioxygenase (homogentisate oxidase)
- MCCC1: methylcrotonoyl-Coenzyme A carboxylase 1 (alpha)
- PCCB: propionyl Coenzyme A carboxylase, beta polypeptide
- PDCD10: programmed cell death 10
- PIK3CA: phosphoinositide-3-kinase, catalytic, alpha polypeptide
- RAB7: RAB7, member RAS oncogene family
- RHO: rhodopsin visual pigment
- SOX2: transcription factor
- USH3A: Usher syndrome 3A
- ZNF9: zinc finger protein 9 (a cellular retroviral nucleic acid binding protein)

Diseases & disorders

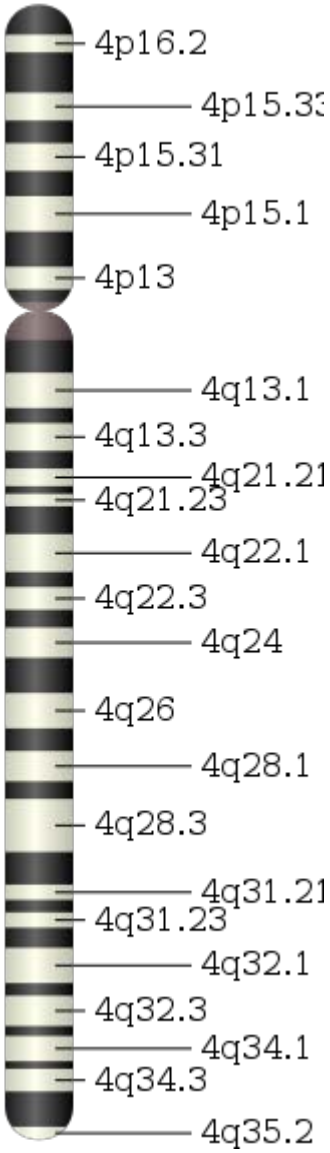
This list is incomplete; you can help by expanding it.

The following diseases are some of those related to genes on chromosome 3:

- 3-methylcrotonyl-CoA carboxylase deficiency
- 3q29 microdeletion syndrome
- Alkaptonuria
- Arrhythmogenic right ventricular dysplasia
- Atransferrinemia
- Autism
- Biotinidase deficiency
- Blepharophimosis, epicanthus inversus and ptosis type 1
- Breast/colon/lung/pancreatic cancer
- Brugada syndrome
- Carnitine-acylcarnitine translocase deficiency
- Cataracts
- Cerebral cavernous malformation
- Charcot-Marie-Tooth disease, type 2
- Charcot-Marie-Tooth disease
- Chromosome 3q duplication syndrome
- Coproporphyria
- Deafness
- Diabetes
- Dopamine receptor
- Dystrophic epidermolysis bullosa
- Endplate acetlycholinesterase deficiency
- Essential tremors
- Glaucoma, primary open angle
- Glycogen storage disease
- Hailey-Hailey disease
- Harderoporphyrinuria
- Heart block, progressive/nonprogressive
- Hereditary coproporphyria
- Hereditary nonpolyposis colorectal cancer
- HIV infection, susceptibility/resistance to
- Hypobetalipoproteinemia, familial
- Leukoencephalopathy with vanishing white matter
- Long QT syndrome
- Lymphomas
- Malignant hyperthermia susceptibility
- Metaphyseal chondrodysplasia, Murk Jansen type
- Moebius syndrome
- Moyamoya disease
- Mucopolysaccharidosis
- Muir-Torre family cancer syndrome

- Myotonic dystrophy, type 2
- Myotonic dystrophy
- Neuropathy, hereditary motor and sensory, Okinawa type
- Night blindness
- Nonsyndromic deafness, autosomal recessive
- Nonsyndromic deafness
- Ovarian cancer
- Porphyria
- Propionic acidemia
- Protein S deficiency
- Pseudo-Zellweger syndrome
- Retinitis pigmentosa
- Romano-Ward syndrome
- Septo-optic dysplasia
- Short stature
- Spinocerebellar ataxia
- Sucrose intolerance
- T-cell leukemia translocation altered gene
- Usher syndrome type III
- Usher syndrome (Finland)
- Usher syndrome
- von Hippel-Lindau syndrome
- Waardenburg syndrome
- Xeroderma pigmentosum, complementation group c

Chromosome 4 (Human)



Chromosome 4 is one of the 23 pairs of chromosomes in humans. People normally have two copies of this chromosome. Chromosome 4 spans more than 186 million base pairs (the building material of DNA) and represents between 6 and 6.5 percent of the total DNA in cells.

Identifying genes on each chromosome is an active area of genetic research. Because researchers use different approaches to predict the number of genes on each chromosome, the estimated number of genes varies. Chromosome 4 likely contains between 700 and 1,100 genes.

Genes

The following are some of the genes located on chromosome 4:

- ANK2: ankyrin 2, neuronal
- CRMP1: Collapsin response mediator protein 1, a member of CRMP family
- CXCL1: chemokine (C-X-C motif) ligand 1, *scyb1*
- CXCL2: chemokine (C-X-C motif) ligand 2, *scyb2*
- CXCL3: chemokine (C-X-C motif) ligand 3, *scyb3*
- CXCL4: chemokine (C-X-C motif) ligand 4, Platelet factor-4, PF-4, *scyb4*
- CXCL5: chemokine (C-X-C motif) ligand 5, *scyb5*
- CXCL6: chemokine (C-X-C motif) ligand 6, *scyb6*
- CXCL7: chemokine (C-X-C motif) ligand 7, PPBP, *scyb7*
- CXCL8: chemokine (C-X-C motif) ligand 8, interleukin 8 (IL-8), *scyb8*
- CXCL9: chemokine (C-X-C motif) ligand 9, *scyb9*
- CXCL10: chemokine (C-X-C motif) ligand 10, *scyb10*
- CXCL11: chemokine (C-X-C motif) ligand 11, *scyb11*
- CXCL13: chemokine (C-X-C motif) ligand 13, *scyb13*
- DUX4: Thought to be inactive but 2010 research shows a key role in FSHD
- EVC: Ellis van Creveld syndrome
- EVC2: Ellis van Creveld syndrome 2 (limbin)
- FGFR3: fibroblast growth factor receptor 3 (achondroplasia, thanatophoric dwarfism, bladder cancer)
- FGFRL1: fibroblast growth factor receptor-like 1
- Complement Factor I: Complement Factor I
- HTT (Huntingtin): huntingtin protein (Huntington's disease)
- MMAA: methylmalonic aciduria (cobalamin deficiency) cblA type
- PHOX2B: codes for a homeodomain transcription factor
- PKD2: polycystic kidney disease 2 (autosomal dominant)
- PLK4
- QDPR: quinoid dihydropteridine reductase
- SNCA: synuclein, alpha (non A4 component of amyloid precursor)
- UCHL1: ubiquitin carboxyl-terminal esterase L1 (ubiquitin thiolesterase)
- WFS1: Wolfram syndrome 1 (wolframin)
- FGF2: Fibroblast growth factor 2 (basic fibroblast growth factor)
- KDR: Kinase insert domain receptor (Vascular endothelial growth factor receptor 2)
- IGJ: linker protein for immunoglobulin alpha and mu polypeptides
- HCL2 (also called RHA or RHC): related to red hair

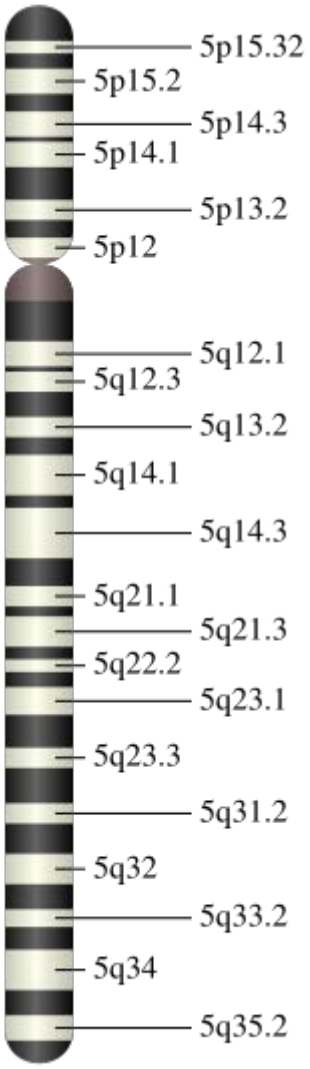
Diseases & disorders

The following are some of the diseases related to genes located on chromosome 4:

- achondroplasia
- bladder cancer

- Crouzonodermoskeletal syndrome
- Chronic Lymphocytic Leukemia
- Ellis-van Creveld syndrome
- Facioscapulohumeral muscular dystrophy
- Fibrodysplasia ossificans progessiva FOP
- Hemophilia C
- Huntington's disease
- Hemolytic Uremic Syndrome
- Hirschprung's disease
- hypochondroplasia
- methylmalonic acidemia
- Muenke syndrome
- nonsyndromic deafness
- nonsyndromic deafness, autosomal dominant
- Ondine's Curse
- Parkinsons disease
- polycystic kidney disease
- Romano-Ward syndrome
- SADDAN
- tetrahydrobiopterin deficiency
- thanatophoric dysplasia
- thanatophoric dysplasia, type 1
- thanatophoric dysplasia, type 2
- Wolfram syndrome

Chromosome 5 (Human)



Chromosome 5 is one of the 23 pairs of chromosomes in humans. People normally have two copies of this chromosome. Chromosome 5 spans about 181 million base pairs (the building blocks of DNA) and represents almost 6% of the total DNA in cells. **Chromosome 5** is one of the largest human chromosomes, yet has one of the lowest gene densities. This is partially explained by numerous gene-poor regions that display a remarkable degree of non-coding and syntenic conservation with non-mammalian vertebrates, suggesting they are functionally constrained.

Identifying genes on each chromosome is an active area of genetic research. Because researchers use different approaches to predict the number of genes on each chromosome, the estimated number of genes varies. Chromosome 5 likely contains between 900 and 1,300 genes.

Genes

The following are some of the genes located on chromosome 5:

- ADAMTS2: ADAM metallopeptidase with thrombospondin type 1 motif, 2
- APC: adenomatosis polyposis coli
- EGR1: early growth response protein 1
- DTDST: diastrophic dysplasia sulfate transporter
- ERCC8: excision repair cross-complementing rodent repair deficiency, complementation group 8
- FGFR4: fibroblast growth factor receptor 4
- GM2A: GM2 ganglioside activator
- HEXB: hexosaminidase B (beta polypeptide)
- MASS1: monogenic, audiogenic seizure susceptibility 1 homolog (mouse)
- MCCC2: methylcrotonoyl-Coenzyme A carboxylase 2 (beta)
- MTRR: 5-methyltetrahydrofolate-homocysteine methyltransferase reductase
- NIPBL: Nipped-B homolog (Drosophila)
- NSD1: Transcription coregulator protein
- Pikachurin: Responsible for the functioning of the ribbon synapses; allows the eye to track moving objects
- SLC22A5: solute carrier family 22 (organic cation transporter), member 5
- SLC26A2: solute carrier family 26 (sulfate transporter), member 2
- SMN1: survival motor neuron 1, telomeric
- SMN2: survival motor neuron 2, centromeric
- SNCAIP: synuclein, alpha interacting protein (synphilin)
- TGFBI: keratoepithelin
- TCOF1: Treacher Collins-Franceschetti syndrome 1
- FGF1: fibroblast growth factor 1 (acidic fibroblast growth factor)

Diseases & disorders

The following are some of the diseases related to genes located on chromosome 5:

- Achondrogenesis type 1B
- Atelosteogenesis, type II
- Cockayne syndrome
- Cornelia de Lange syndrome
- Corneal dystrophy of Bowman layer, type I
- Corneal dystrophy of Bowman layer, type II
- Cri du Chat
- Diastrophic dysplasia
- Ehlers-Danlos syndrome
- Ehlers-Danlos syndrome, dermatosparaxis type
- Familial adenomatous polyposis
- Granular corneal dystrophy type I
- Granular corneal dystrophy type II

- GM2-gangliosidosis, AB variant
- Homocystinuria
- 3-Methylcrotonyl-CoA carboxylase deficiency
- Nicotine dependency
- Parkinson's disease
- Primary carnitine deficiency
- Recessive multiple epiphyseal dysplasia
- Sandhoff disease
- Spinal muscular atrophy
- Sotos Syndrome
- Survival motor neuron spinal muscular atrophy
- Treacher Collins syndrome
- Usher syndrome
- Usher syndrome type II

Chromosomal conditions

The following conditions are caused by changes in the structure or number of copies of chromosome 5:

- Cri-du-chat syndrome is caused by a deletion of the end of the short (p) arm of chromosome 5. This chromosomal change is written as 5p-. The signs and symptoms of cri-du-chat syndrome are probably related to the loss of multiple genes in this region. Researchers have not identified all of these genes or determined how their loss leads to the features of the disorder. They have discovered, however, that a larger deletion tends to result in more severe mental retardation and developmental delays in people with cri-du-chat syndrome.

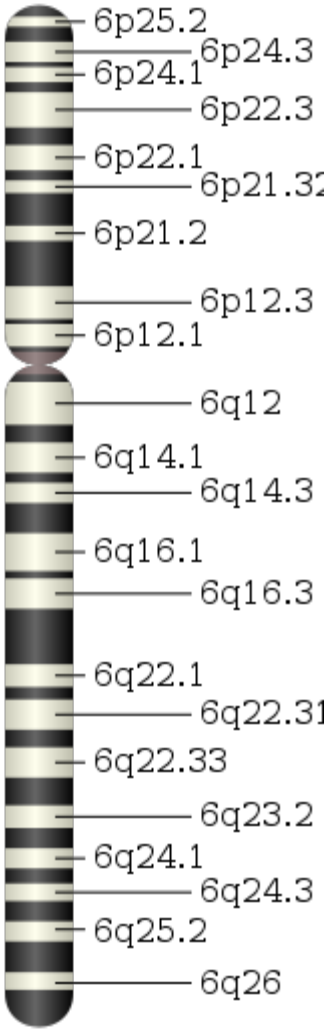
  Researchers have defined narrow regions of the short arm of chromosome 5 that are associated with particular features of cri-du-chat syndrome. A specific region designated 5p15.3 is associated with a cat-like cry, and a nearby region called 5p15.2 is associated with mental retardation, small head size (microcephaly), and distinctive facial features.

- Familial Adenomatous Polyposis is caused by a deletion of the APC tumor suppressor gene on the long (q) arm of chromosome 5. This chromosomal change results in thousands of colonic polyps which gives the patient a 100% risk of colon cancer if total colectomy is not done.

- Other changes in the number or structure of chromosome 5 can have a variety of effects, including delayed growth and development, distinctive facial features, birth defects, and other medical problems. Changes to chromosome 5 include an extra segment of the short (p) or long (q) arm of the chromosome in each cell (partial trisomy 5p or 5q), a missing segment of the long arm of the chromosome in each cell (partial monosomy 5q), and a circular structure called ring

chromosome 5. A ring chromosome occurs when both ends of a broken chromosome are reunited.

Chromosome 6 (Human)



Chromosome 6 is one of the 23 pairs of chromosomes in humans. People normally have two copies of this chromosome. Chromosome 6 spans more than 170 million base pairs (the building material of DNA) and represents between 5.5 and 6% of the total DNA in cells. It contains the Major Histocompatibility Complex, which contains over 100 genes related to the immune response, and plays a vital role in organ transplantation.

Identifying genes on each chromosome is an active area of genetic research. Because researchers use different approaches to predict the number of genes on each chromosome,

the estimated number of genes varies. Chromosome 6 likely contains between 1,100 and 1,600 genes.

Genes

The following are some of the genes located on chromosome 6:

- BCKDHB: branched chain keto acid dehydrogenase E1, beta polypeptide (maple syrup urine disease)
- CNR1: cannabinoid 1 receptor
- COL11A2: collagen, type XI, alpha 2
- CYP21A2: cytochrome P450, family 21, subfamily A, polypeptide 2
- DSP: Desmoplakin gene linked to cardiomyopathy
- EYA4: eyes absent homolog 4 (Drosophila)
- HFE: hemochromatosis
- HLA-A, HLA-B, HLA-C: major histocompatibility complex (MHC), class I, A, B, and C loci.
- HLA-DQA1 and HLA-DQB1 form HLA-DQ heterodimer MHC class II, DQ: Celiac1, IDDM
- HLA-DRA, HLA-DRB1, HLA-DRB3, HLA-DRB4, HLA-DRB5 forms HLA-DR, heterodimer MHC class II, DR
- HLA-DPA1 and HLA-DPB1 forms HLA-DR, MHC class II, DP
- MUT: methylmalonyl Coenzyme A mutase
- MYO6: myosin VI
- PARK2: Parkinson disease (autosomal recessive, juvenile) 2, parkin
- PKHD1: polycystic kidney and hepatic disease 1 (autosomal recessive)
- TNXB: tenascin XB
- VEGF: vascular endothelial growth factor A (angiogenic growth factor)
- IGF2R: insulin-like growth factor 2 receptor
- HLA-Cw*0602: gene variation related to psoriasis
- PLG: plasminogen (6q26)

BGHS

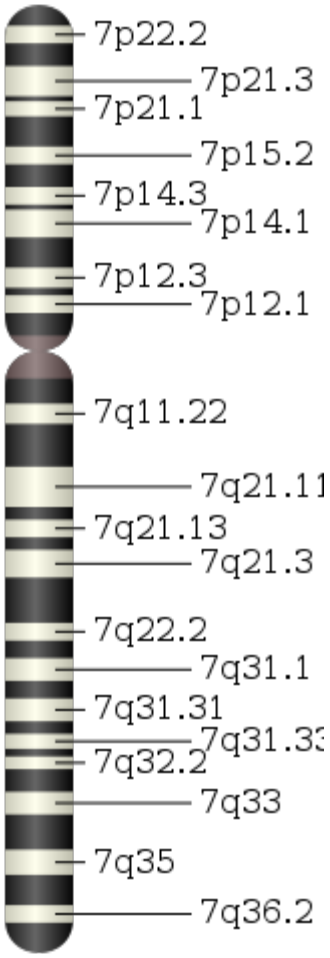
Diseases & disorders

The following diseases are some of those related to genes on chromosome 6:

- ankylosing spondylitis, HLA-B
- collagenopathy, types II and XI
- Coeliac disease, HLA-DQA1 & DQB1
- Ehlers-Danlos syndrome, classical, hypermobility, and Tenascin-X types
- Hashimoto's thyroiditis
- hemochromatosis
- Hemochromatosis type 1
- 21-hydroxylase deficiency

- maple syrup urine disease
- methylmalonic acidemia
- Autosomal nonsyndromic deafness
- otospondylomegaepiphyseal dysplasia
- Parkinson disease
- polycystic kidney disease
- porphyria
- porphyria cutanea tarda
- Rheumatoid arthritis, HLA-DR
- Stickler syndrome, COL11A2
- Systemic lupus erythematosus
- Diabetes mellitus type 1, HLA-DR, DQA1 & DQB1
- X-linked sideroblastic anemia
- Epilepsy

Chromosome 7 (Human)



Chromosome 7 is one of the 23 pairs of chromosomes in humans. People normally have two copies of this chromosome. Chromosome 7 spans more than 158 million base pairs (the building material of DNA) and represents between 5 and 5.5 percent of the total DNA in cells.

Identifying genes on each chromosome is an active area of genetic research. Because researchers use different approaches to predict the number of genes on each chromosome, the estimated number of genes varies. Chromosome 7 is likely to contain between 1,000 and 1,400 genes. It also contains the Homeobox A gene cluster.

Diseases & disorders

The following diseases are some of those related to genes on chromosome 7:

- argininosuccinic aciduria
- cerebral cavernous malformation
- Charcot-Marie-Tooth disease
- Charcot-Marie-Tooth disease, type 2
- citrullinemia
- congenital bilateral absence of vas deferens
- cystic fibrosis
- distal spinal muscular atrophy, type V
- Ehlers-Danlos syndrome
- Ehlers-Danlos syndrome, arthrochalasia type
- Ehlers-Danlos syndrome, classical type
- hemochromatosis
- hemochromatosis, type 3
- hereditary nonpolyposis colorectal cancer
- lissencephaly
- maple syrup urine disease
- maturity onset diabetes of the young type 2
- mucopolysaccharidosis type VII or Sly syndrome
- myelodysplastic syndrome
- nonsyndromic deafness
- nonsyndromic deafness, autosomal dominant
- nonsyndromic deafness, autosomal recessive
- osteogenesis imperfecta
- osteogenesis imperfecta, type I
- osteogenesis imperfecta, type II
- osteogenesis imperfecta, type III
- osteogenesis imperfecta, type IV
- p47-phox-deficient chronic granulomatous disease
- Pendred syndrome
- Romano-Ward syndrome
- Shwachman-Diamond syndrome
- Schizophrenia
- Tritanopia or tritanomaly color blindness
- Williams syndrome

Chromosomal disorders

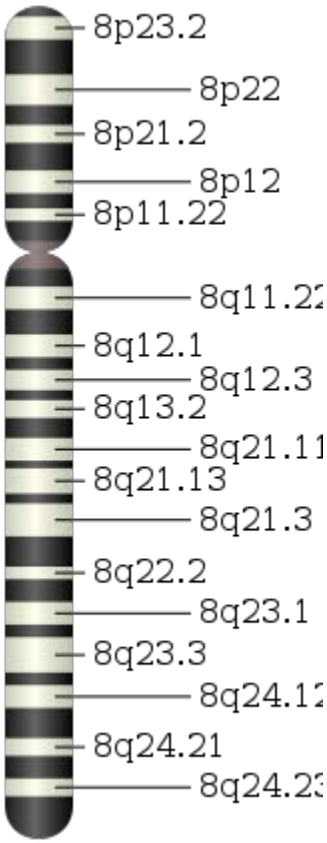
The following conditions are caused by changes in the structure or number of copies of chromosome 7:

- Williams syndrome is caused by the deletion of genetic material from a portion of the long (q) arm of chromosome 7. The deleted region, which is located at position 11.23 (written as 7q11.23), is designated as the Williams syndrome critical region. This region includes more than 20 genes, and researchers believe that the characteristic features of Williams syndrome are probably related to the loss of multiple genes in this region.

While a few of the specific genes related to Williams syndrome have been identified, the relationship between most of the genes in the deleted region and the signs and symptoms of Williams syndrome is unknown.

- Other changes in the number or structure of chromosome 7 can cause delayed growth and development, mental retardation, characteristic facial features, skeletal abnormalities, delayed speech, and other medical problems. These changes include an extra copy of part of chromosome 7 in each cell (partial trisomy 7) or a missing segment of the chromosome in each cell (partial monosomy 7). In some cases, several DNA building blocks (nucleotides) are deleted or duplicated in part of chromosome 7. A circular structure called ring chromosome 7 is also possible. A ring chromosome occurs when both ends of a broken chromosome are reunited.

Chromosome 8 (Human)



Chromosome 8 is one of the 23 pairs of chromosomes in humans. People normally have two copies of this chromosome. Chromosome 8 spans about 145 million base pairs (the building material of DNA) and represents between 4.5 and 5.0% of the total DNA in cells.

The chromosome has two arms, 8p and 8q. The short arm, 8p, has about 45 million base pairs, about 1.5% of the genome, and includes 484 genes and 110 pseudogenes; about 8% of its genes are involved in brain development and function, and about 16% are involved in cancer. A unique feature of 8p is a big region of about 15 megabases that appears to have a high mutation rate, and which shows an immense divergence between human and chimpanzee, suggesting that its high mutation rates have contributed to the evolution of the human brain.

Identifying genes on each chromosome is an active area of genetic research. Because researchers use different approaches to predict the number of genes on each chromosome, the estimated number of genes varies. Chromosome 8 is likely to contain between 700 and 1,000 genes.

Genes

The following are some of the genes located on chromosome 8:

- AEG1 : Astrocyte Elevated Gene (linked to hepatocellular carcinoma and neuroblastoma)
- Arc/Arg3.1
- FGFR1: fibroblast growth factor receptor 1 (fms-related tyrosine kinase 2, Pfeiffer syndrome)
- GDAP1: ganglioside-induced differentiation-associated protein 1
- LPL: lipoprotein lipase
- MCPH1: microcephaly, primary autosomal recessive 1
- NDRG1: N-myc downstream regulated gene 1
- NEF3: neurofilament 3 (150kDa medium)
- NEFL: neurofilament, light polypeptide 68kDa
- SNAI2: snail homolog 2 (Drosophila)
- TG: thyroglobulin
- TPA: tissue plasminogen activator
- VMAT1: vesicular monoamine transporter protein
- WRN: Werner syndrome
- GULOP pseudogene: responsible for human inability to produce our own Vitamin C

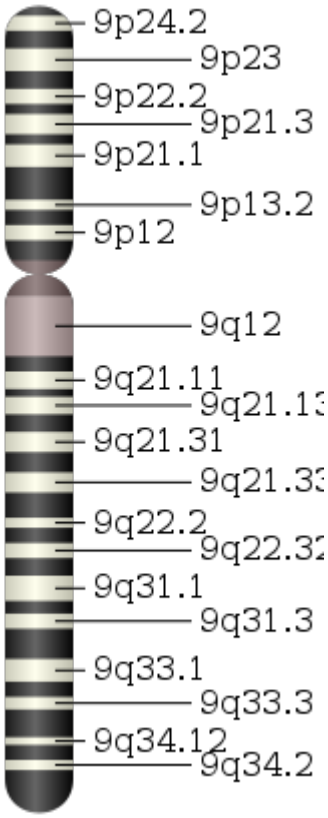
Diseases & disorders

The following diseases are some of those related to genes on chromosome 8:

- 8p23.1 duplication syndrome
- Burkitt's lymphoma
- Charcot-Marie-Tooth disease
- Charcot-Marie-Tooth disease, type 2
- Charcot-Marie-Tooth disease, type 4
- Cleft lip and palate

- Congenital hypothyroidism
- Lipoprotein lipase deficiency, familial
- Primary microcephaly
- Hereditary Multiple Exostoses
- Pfeiffer syndrome
- Rothmund-Thomson syndrome, or poikiloderma congenitale
- Schizophrenia, associated with 8p21-22 locus
- Waardenburg syndrome
- Werner syndrome
- Pingelapese blindness
- Langer-Giedion syndrome
- Roberts Syndrome

Chromosome 9 (Human)



Chromosome 9 is one of the 23 pairs of chromosomes in humans. People normally have two copies of this chromosome, as they normally do with all chromosomes. Chromosome 9 spans about 145 million base pairs of nucleic acids (the building blocks of DNA) and represents between 4 and 4.5 percent of the total DNA in cells.

Identifying genes on each chromosome is an active area of genetic research. Because researchers use different approaches to predict the number of genes on each chromosome, the estimated number of genes varies. Chromosome 9 likely contains between 800 and 1,200 genes.

Genes

The following are some of the genes located on chromosome 9:

- ABO: ABO histo-blood group glycosyltransferases
- ADAMTS13: ADAM metallopeptidase with thrombospondin type 1 motif, 13
- ALAD: aminolevulinate, delta-, dehydratase
- ALS4: amyotrophic lateral sclerosis 4
- ASS: argininosuccinate synthetase
- CCL21: chemokine (C-C motif) ligand 21, SCYA21
- CCL27: chemokine (C-C motif) ligand 27, SCYA27
- COL5A1: collagen, type V, alpha 1
- ENG: endoglin (Osler-Rendu-Weber syndrome 1)
- FXN: frataxin
- GALT: galactose-1-phosphate uridylyltransferase
- GLE1L: Nucleoporin GLE1
- GRHPR: glyoxylate redasductase/hydroxypyruvate reductase
- IKBKAP: inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein
- TGFBR1: transforming growth factor beta, receptor type I
- TMC1: transmembrane channel-like 1
- TSC1: t

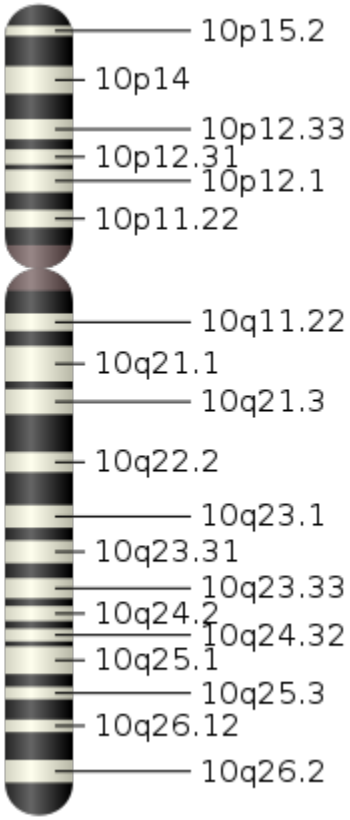
Diseases & disorders

The following diseases are some of those related to genes on chromosome 9:

- acytosiosis
- ALA-D deficiency porphyria
- citrullinemia
- Ehlers-Danlos syndrome
- Ehlers-Danlos syndrome, classical type
- familial dysautonomia
- Friedreich ataxia
- galactosemia
- Gorlin syndrome or Nevoid Basal Cell Carcinoma syndrome
- hereditary hemorrhagic telangiectasia
- lethal congenital contracture syndrome
- Nail-patella syndrome (NPS)
- nonsyndromic deafness
- nonsyndromic deafness, autosomal dominant

- nonsyndromic deafness, autosomal recessive
- porphyria
- primary hyperoxaluria
- Tangier's disease
- tetrasomy 9p
- thrombotic thrombocytopenic purpura
- trisomy 9
- tuberous sclerosis
- VLDLR-associated cerebellar hypoplasia

Chromosome 10 (Human)



Chromosome 10 is one of the 23 pairs of chromosomes in humans. People normally have two copies of this chromosome. Chromosome 10 spans about 135 million base pairs (the building material of DNA) and represents between 4 and 4.5 percent of the total DNA in cells.

Identifying genes on each chromosome is an active area of genetic research. Because researchers use different approaches to predict the number of genes on each chromosome, the estimated number of genes varies. Chromosome 10 likely contains between 800 and 1,200 genes.

Genes

The following are some of the genes located on chromosome 10:

- ALOX5: Arachidonate 5-Lipoxygenase (processes essential fatty acids to leukotrienes, which are important agents in the inflammatory response; also facilitates development and maintenance of cancer stem cells, slow-dividing cells thought to give rise to a variety of cancers, including leukemia);
- CDH23: cadherin-like 23
- CXCL12: chemokine (C-X-C motif) ligand 12, SDF-1, *scyb12*
- EGR2: early growth response 2 (Krox-20 homolog, Drosophila)
- ERCC6: excision repair cross-complementing rodent repair deficiency, complementation group 6
- FGFR2: fibroblast growth factor receptor 2 (bacteria-expressed kinase, keratinocyte growth factor receptor, craniofacial dysostosis 1, Crouzon syndrome, Pfeiffer syndrome, Jackson-Weiss syndrome)
- PCBD1: 6-pyruvoyl-tetrahydropterin synthase/dimerization cofactor of hepatocyte nuclear factor 1 alpha (TCF1)
- PCDH15: protocadherin 15
- PTEN gene: phosphatase and tensin homolog (mutated in multiple advanced cancers 1)
- RET: ret proto-oncogene (multiple endocrine neoplasia and medullary thyroid carcinoma 1, Hirschsprung disease)
- UROS: uroporphyrinogen III synthase (congenital erythropoietic porphyria)

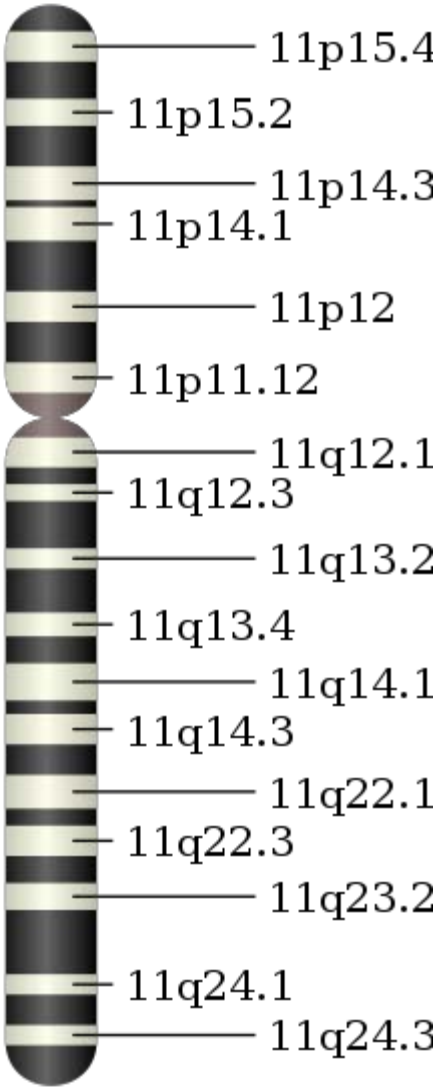
Diseases & disorders

The following diseases are some of those related to genes on chromosome 10:

- Apert syndrome
- Beare-Stevenson cutis gyrata syndrome
- Charcot-Marie-Tooth disease
- Charcot-Marie-Tooth disease, type 1
- Charcot-Marie-Tooth disease, type 4
- Cockayne syndrome
- congenital erythropoietic porphyria
- Cowden syndrome
- Crouzon syndrome
- Hirschprung disease
- Jackson-Weiss syndrome
- multiple endocrine neoplasia type 2

- nonsyndromic deafness
- nonsyndromic deafness, autosomal recessive
- Pfeiffer syndrome
- porphyria
- tetrahydrobiopterin deficiency
- Thiel-Behnke corneal dystrophy
- Usher syndrome
- Usher syndrome type I
- Wolman syndrome

Chromosome 11 (Human)



Chromosome 11 Chart

Chromosome 11 is one of the 23 pairs of chromosomes in humans. Humans normally have two copies of this chromosome. Chromosome 11 spans about 134.5 million base pairs (the building material of DNA) and represents between 4 and 4.5 percent of the total DNA in cells. It is one of the most gene- and disease-rich chromosomes in the human genome.

Identifying genes on each chromosome is an active area of genetic research. Because researchers use different approaches to predict the number of genes on each chromosome,

the estimated number of genes varies. Chromosome 11 likely contains between 1,300 and 1,700 genes.

A recent study shows that 11.6 genes per megabase, including 1,524 protein-coding genes and 765 pseudogenes can be found on chromosome 11.

More than 40% of the 856 olfactory receptor genes in the human genome are located in 28 single- and multi-gene clusters along this chromosome.

Genes

The following are some of the genes located on chromosome 11:

- ACAT1: acetyl-Coenzyme A acetyltransferase 1 (acetoacetyl Coenzyme A thiolase)
- APOA4: apolipoprotein A-IV
- ATM: ataxia telangiectasia mutated (includes complementation groups A, C and D)
- CD81
- WT1
- C11orf1
- CPT1A: carnitine palmitoyltransferase 1A (liver)
- DHCR7: 7-dehydrocholesterol reductase
- HBB: hemoglobin, beta
- HMBS: hydroxymethylbilane VIIA
- PAX6
- PTS: 6-pyruvoyltetrahydropterin synthase
- SAA1: serum amyloid A1
- SBF2: SET binding factor 2
- SMPD1: sphingomyelin phosphodiesterase 1, acid lysosomal (acid sphingomyelinase)
- TECTA: tectorin alpha (nonsyndromic deafness)
- TH: tyrosine hydroxylase
- USH1C: Usher syndrome 1C (autosomal recessive, severe)

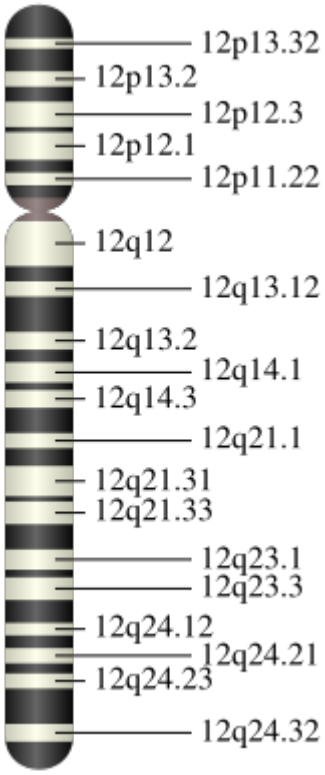
Diseases & disorders

The following diseases are some of those related to genes on chromosome 11:

- autism (neurexin 1)
- aniridia
- acute intermittent porphyria
- albinism
- ataxia-telangiectasia
- Beckwith-Wiedemann syndrome
- Best's disease

- beta-ketothiolase deficiency
- beta thalassemia
- bladder cancer
- breast cancer
- carnitine palmitoyltransferase I deficiency
- Charcot-Marie-Tooth disease
- Charcot-Marie-Tooth disease, type 4
- Denys-Drash syndrome
- familial Mediterranean fever
- Hereditary angioedema OMIM: 106100
- Jacobsen syndrome
- Jervell and Lange-Nielsen syndrome
- Meckel syndrome
- methemoglobinemia, beta-globin type
- Mixed Lineage Leukemia
- multiple endocrine neoplasia type 1
- Hereditary Multiple Exostoses
- Niemann-Pick disease
- nonsyndromic deafness
- nonsyndromic deafness, autosomal dominant
- nonsyndromic deafness, autosomal recessive
- porphyria
- Romano-Ward syndrome
- sickle cell anemia
- Smith-Lemli-Opitz syndrome
- tetrahydrobiopterin deficiency
- Usher syndrome
- Usher syndrome type I
- WAGR syndrome

Chromosome 12 (Human)



Chromosome 12 is one of the 23 pairs of chromosomes in humans. People normally have two copies of this chromosome. Chromosome 12 spans about 143 million base pairs (the building material of DNA) and represents between 4 and 4.5 percent of the total DNA in cells.

Identifying genes on each chromosome is an active area of genetic research. Because researchers use different approaches to predict the number of genes on each chromosome, the estimated number of genes varies. Chromosome 12 likely contains between 1,000 and 1,300 genes. It also contains the Homeobox C gene cluster.

Genes

The following are some of the genes located on chromosome 12:Obed M. Ha

- ACVRL1: activin A receptor type II-like 1
- CBX5: chromobox homolog 5
- COL2A1: collagen, type II, alpha 1 (primary osteoarthritis, spondyloepiphyseal dysplasia, congenital)
- HPD: 4-hydroxyphenylpyruvate dioxygenase

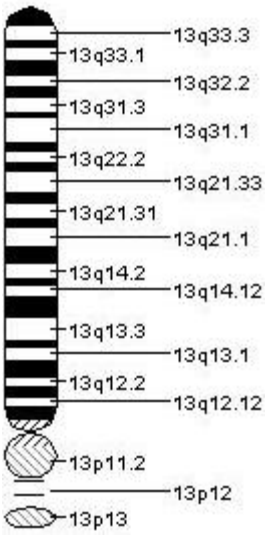
- KERA: keratocan
- LRRK2: leucine-rich repeat kinase 2
- MMAB: methylmalonic aciduria (cobalamin dewrong ficiency) cblB type
- MYO1A: myosin IA
- NANOG: NK-2 type homeodomain gene
- PAH: phenylalanine hydroxylase
- PPP1R12A: protein phosphatase 1, regulatory (inhibitor) subungfdit 12A
- PTPN11: protein tyrosine phosphatase, non-receptor type 11 (Noonan syndrome 1)
- KRAS: V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog

Diseases & disorders

The following diseases are some of those related to genes on chromosome 12:

- achondrogenesis type 2
- collagenopathy, types II and XI
- cornea plana 2
- hereditary hemorrhagic telangiectasia
- hypochondrogenesis
- ichthyosis bullosa of Siemens
- Kniest dysplasia
- maturity onset diabetes of the young type 3
- methylmalonic acidemia
- narcolepsy
- nonsyndromic deafness
- nonsyndromic deafness, autosomal dominant
- Noonan syndrome
- Parkinson disease
- Pallister-Killian syndrome (tetrasomy 12p)
- phenylketonuria
- spondyloepimetaphyseal dysplasia, Strudwick type
- spondyloepiphyseal dysplasia congenita
- spondyloperipheral dysplasia
- Stickler syndrome
- Stickler syndrome, COL2A1
- Stuttering
- Triose Phosphate Isomerase deficiency
- tyrosinemia
- Von Willebrand Disease

Chromosome 13 (Human)



Chromosome 13 is one of the 23 pairs of chromosomes in humans. People normally have two copies of this chromosome. Chromosome 13 spans about 114 million base pairs (the building material of DNA) and represents between 3.5 and 4 % of the total DNA in cells.

Identifying genes on each chromosome is an active area of genetic research. Because researchers use different approaches to predict the number of genes on each chromosome, the estimated number of genes varies. Chromosome 13 likely contains between 300 and 700 genes.

Genes

The following are some of the genes located on chromosome 13:

- ATP7B: ATPase, Cu++ transporting, beta polypeptide (Wilson disease)
- BRCA2: breast cancer 2, early onset
- CARKD: Carbohydrate Kinase Domain Containing Protein (Unknown Function)
- EDNRB: endothelin receptor type B
- GJB2: gap junction protein, beta 2, 26kDa (connexin 26)
- GJB6: gap junction protein, beta 6 (connexin 30)
- HTR2A: 5-HT_{2A} receptor
- PCCA: propionyl Coenzyme A carboxylase, alpha polypeptide
- RB1: retinoblastoma 1 (including osteosarcoma)
- FLT1: Fms related tyrosine kinase 1 (Vascular endothelial growth factor receptor 1)
- SLITRK1: mutation in this gene causes some (although very few) cases of Tourette syndrome and trichotillomania

- SOX21: Transcription factor SOX-21 is a protein that in humans is encoded by the SOX21; its disruption can lead to types of alopecia in mice.

Diseases and disorders

The following diseases are some of those related to genes on chromosome 13:

- Bladder cancer
- Breast cancer
- Heterochromia
- Hirschsprung's disease
- Maturity onset diabetes of the young type 4
- Nonsyndromic deafness
- Nonsyndromic deafness, autosomal dominant
- Nonsyndromic deafness, autosomal recessive
- Propionic acidemia
- Retinoblastoma
- Waardenburg syndrome
- Wilson disease
- Patau syndrome

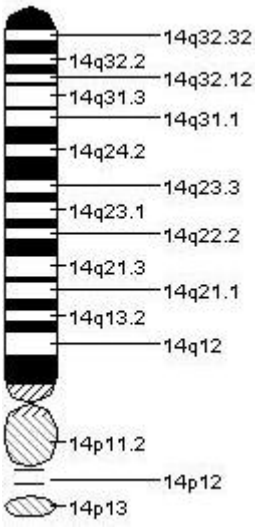
Chromosomal conditions

The following conditions are caused by changes in the structure or number of copies of chromosome 13:

- Retinoblastoma: A small percentage of retinoblastoma cases are caused by deletions in the region of chromosome 13 (13q14) containing the RB1 gene. Children with these chromosomal deletions may also have mental retardation, slow growth, and characteristic facial features (such as prominent eyebrows, a broad nasal bridge, a short nose, and ear abnormalities). Researchers have not determined which other genes are located in the deleted region, but a loss of several genes is likely responsible for these developmental problems.
- Trisomy 13: Trisomy 13 occurs when each cell in the body has three copies of chromosome 13 instead of the usual two copies. Trisomy 13 can also result from an extra copy of chromosome 13 in only some of the body's cells (mosaic trisomy 13). In a small percentage of cases, trisomy 13 is caused by a rearrangement of chromosomal material between chromosome 13 and another chromosome. As a result, a person has the two usual copies of chromosome 13, plus extra material from chromosome 13 attached to another chromosome. These cases are called translocation trisomy 13. Extra material from chromosome 13 disrupts the course of normal development, causing the characteristic signs and symptoms of trisomy 13. Researchers are not yet certain how this extra genetic material leads to the features of the disorder, which include severely abnormal cerebral functions, a small cranium, retardation, non functional eyes and heart defects.

- Other chromosomal conditions: Partial monosomy 13q is a rare chromosomal disorder that results when a piece of the long arm (q) of chromosome 13 is missing (monosomic). Infants born with partial monosomy 13q may exhibit low birth weight, malformations of the head and face (craniofacial region), skeletal abnormalities (especially of the hands and feet), and other physical abnormalities. Mental retardation is characteristic of this condition. The mortality rate during infancy is high among individuals born with this disorder. Almost all cases of partial monosomy 13q occur randomly for no apparent reason (sporadic).

Chromosome 14 (Human)



Chromosome14 is one of the 23 pairs of chromosomes in humans. People normally have two copies of this chromosome. Chromosome 14 spans about 109 million base pairs (the building material of DNA) and represents between 3 and 3.5% of the total DNA in cells.

Identifying genes on each chromosome is an active area of genetic research. Because researchers use different approaches to predict the number of genes on each chromosome, the estimated number of genes varies. Chromosome 14 likely contains between 700 and 1,300 genes.

Genes

The following are some of the genes located on chromosome 14:

- COCH: coagulation factor C homolog, cochlin (Limulus polyphemus)
- GALC: galactosylceramidase (Krabbe disease)
- GCH1: GTP cyclohydrolase 1 (dopa-responsive dystonia)

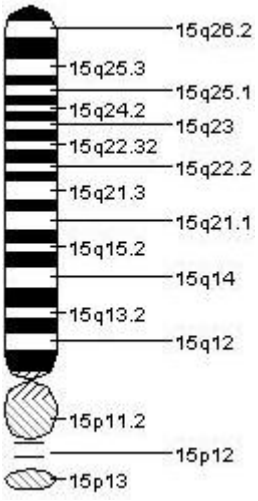
- IGH@: immunoglobulin heavy chain locus
- NPC2: Niemann-Pick disease, type C2
- PSEN1: presenilin 1 (Alzheimer disease 3)
- SERPINA1: serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 1
- TSHR: thyroid stimulating hormone receptor

Diseases & disorders

The following diseases are some of those related to genes on chromosome 14:

- alpha-1 antitrypsin deficiency
- Alzheimer disease
- Alzheimer disease, type 3
- congenital hypothyroidism
- dopamine-responsive dystonia
- Krabbe disease
- Machado-Joseph disease
- multiple myeloma
- Niemann-Pick disease
- nonsyndromic deafness
- nonsyndromic deafness, autosomal dominant
- tetrahydrobiopterin deficiency
- Uniparental disomy (UPD) 14

Chromosome 15 (Human)



Human chromosome 15

Chromosome 15 is one of the 23 pairs of chromosomes in humans. People normally have two copies of this chromosome. Chromosome 15 spans about 106 million base pairs (the building material of DNA) and represents between 3% and 3.5% of the total DNA in cells.

Identifying genes on each chromosome is an active area of genetic research. Because researchers use different approaches to predict the number of genes on each chromosome, the estimated number of genes varies. Chromosome 15 likely contains between 700 and 900 genes.

Genes

The following are some of the genes located on chromosome 15:

- CAPN3: Calpain 3 (limb-girdle muscular dystrophy type 2A)
- CHP: Calcium binding protein P22
- FAH: fumarylacetoacetate hydrolase (fumarylacetoacetase)
- FBN1: fibrillin 1 (Marfan syndrome)
- HEXA: hexosaminidase A (alpha polypeptide)
- IVD: isovaleryl Coenzyme A dehydrogenase
- MCPH4: microcephaly, primary autosomal recessive 4
- OCA2: oculocutsexous albinism II (pink-eye dilution homolog, mouse)
- RAD51: RAD51 homolog (RecA homolog, E. coli) (S. cerevisiae)
- STRC: stereocilin
- UBE3A: ubiquitin protein ligase E3A (human papilloma virus E6-associated protein, Angelman syndrome)
- PML: promyelocytic leukemia protein (involved in t(15,17) with RARalpha, predominant cause of acute promyelocytic leukemia.
- SLC24A5: the gene responsible for at least 1/3 of the skin color differences between races, expressed in the brain and the nervous system
- EYCL3 Eye color 3, BROWN - location: 15q11-q15 (note eye colour is a polygenic trait)
- EYCL2 Eye color 2,Determines the positionning of melanocytes on the iris (note eye colour is a polygenic trait)

Chromosomal conditions

The following conditions are caused by mutations in chromosome 15. Two of the conditions (Angelman syndrome and Prader-Willi syndrome) involve a loss of gene activity in the same part of chromosome 15, the 15q11-q13 region. This discovery provided the first evidence in humans that something beyond genes could determine how the genes are expressed.

Angelman syndrome

Angelman syndrome results from a loss of gene activity in a specific part of chromosome 15, the 15q11-q13 region. This region contains a gene called UBE3A that, when mutated or absent, likely causes the characteristic features of this condition. People normally have two copies of the UBE3A gene, one from each parent. Both copies of this gene are active in many of the body's tissues. In the brain, however, only the copy inherited from a person's mother (the maternal copy) is active. If the maternal copy is lost because of a chromosomal change or a gene mutation, a person will have no working copies of the UBE3A gene in the brain.

In most cases (about 70%), people with Angelman syndrome have a deletion in the maternal copy of chromosome 15. This chromosomal change deletes the region of chromosome 15 that includes the UBE3A gene. Because the copy of the UBE3A gene inherited from a person's father (the paternal copy) is normally inactive in the brain, a deletion in the maternal chromosome 15 results in no active copies of the UBE3A gene in the brain.

In 3% to 7% of cases, Angelman syndrome occurs when a person has two copies of the paternal chromosome 15 instead of one copy from each parent. This phenomenon is called paternal uniparental disomy (UPD). People with paternal UPD for chromosome 15 have two copies of the UBE3A gene, but they are both inherited from the father and are therefore inactive in the brain.

About 10% of Angelman syndrome cases are caused by a mutation in the UBE3A gene, and another 3% result from a defect in the DNA region that controls the activation of the UBE3A gene and other genes on the maternal copy of chromosome 15. In a small percentage of cases, Angelman syndrome may be caused by a chromosomal rearrangement called a translocation or by a mutation in a gene other than UBE3A. These genetic changes can abnormally inactivate the UBE3A gene.

Prader-Willi syndrome

Prader-Willi syndrome is caused by the loss of active genes in a specific part of chromosome 15, the 15q11-q13 region. People normally have two copies of this chromosome in each cell, one copy from each parent. Prader-Willi syndrome occurs when the paternal copy is partly or entirely missing. Researchers are working to identify genes on chromosome 15 that are responsible for the characteristic features of Prader-Willi syndrome.

In about 70% of cases, Prader-Willi syndrome occurs when the 15q11-q13 region of the paternal chromosome 15 is deleted. The genes in this region are normally active on the paternal copy of the chromosome and are inactive on the maternal copy. Therefore, a person with a deletion in the paternal chromosome 15 will have no active genes in this region.

In about 25% of cases, a person with Prader-Willi syndrome has two maternal copies of chromosome 15 in each cell instead of one copy from each parent. This phenomenon is called maternal uniparental disomy. Because some genes are normally active only on the paternal copy of this chromosome, a person with two maternal copies of chromosome 15 will have no active copies of these genes.

In a small percentage of cases, Prader-Willi syndrome is caused by a chromosomal rearrangement called a translocation. Rarely, the condition is caused by an abnormality in the DNA region that controls the activity of genes on the paternal chromosome 15.Prader Willi Syndrome is hereditary.

Isodicentric chromosome 15

A specific chromosomal change called an isodicentric chromosome 15 (previously called an inverted duplication 15) can affect growth and development. The patient possesses an "extra" or "marker" chromosome. This small extra chromosome is made up of genetic material from chromosome 15 that has been abnormally duplicated (copied) and attached end-to-end. In some cases, the extra chromosome is very small and has no effect on a person's health. A larger isodicentric chromosome 15 can result in weak muscle tone (hypotonia), mental retardation, seizures, and behavioral problems. Signs and symptoms of autism (a developmental disorder that affects communication and social interaction) have also been associated with the presence of an isodicentric chromosome 15.

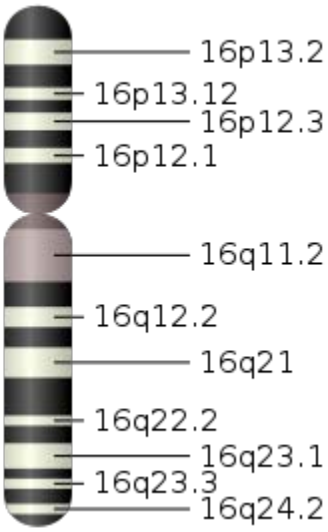
Other chromosomal conditions

Other changes in the number or structure of chromosome 15 can cause mental retardation, delayed growth and development, hypotonia, and characteristic facial features. These changes include an extra copy of part of chromosome 15 in each cell (partial trisomy 15) or a missing segment of the chromosome in each cell (partial monosomy 15). In some cases, several of the chromosome's DNA building blocks (nucleotides) are deleted or duplicated.

The following diseases are some of those related to genes on chromosome 15:

- Bloom syndrome
- Breast cancer
- Isovaleric acidemia
- Marfan syndrome
- Nonsyndromic deafness
- Tay-Sachs disease
- Tyrosinemia

Chromosome 16 (Human)



Chromosome 16 is one of the 23 pairs of chromosomes in humans. People normally have two copies of this chromosome. Chromosome 16 spans about 90 million base pairs (the building material of DNA) and represents just under 3 % of the total DNA in cells.

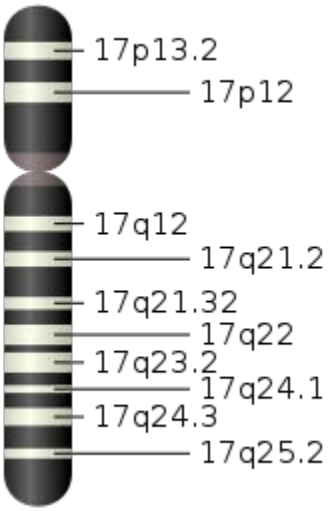
Identifying genes on each chromosome is an active area of genetic research. Because researchers use different approaches to predict the number of genes on each chromosome, the estimated number of genes varies. Chromosome 16 probably contains between 850 and 1,200 genes.

In February 2010, a new cause of obesity due to a microdeletion on chromosome 16 was announced. It may explain about 1% of obesity cases. This research was carried out by Professor Froguel, a CNRS researcher, in Lille, and others at Imperial College in London and Vaudois University and was published in *Nature* on February 4, 2010. This defect was identified using DNA microarrays and it leads to the suppression of about thirty genes in one region of chromosome 16. Research showed that this microdeletion is relatively common in obese people but lacking in most non-obese people.

Diseases and Disorders

- Trisomy 16
- Familial Mediterranean fever (FMF)
- Crohn's disease
- Thalassemia

Chromosome 17 (Human)



Chromosome 17 is one of the 23 pairs of chromosomes in humans. People normally have two copies of this chromosome. Chromosome 17 spans more than 81 million base pairs (the building material of DNA) and represents between 2.5 and 3 % of the total DNA in cells.

Identifying genes on each chromosome is an active area of genetic research. Because researchers use different approaches to predict the number of genes on each chromosome, the estimated number of genes varies. Chromosome 17 likely contains between 1,200 and 1,500 genes. It also contains the Homeobox B gene cluster.

Genes

The following are some of the genes located on chromosome 17:

- ACADVL: acyl-coenzyme A dehydrogenase, very long chain
- ACTG1: actin, gamma 1
- ASPA: aspartoacylase (Canavan disease)
- BRCA1: breast cancer 1, early onset
- CBX1: chromobox homolog 1
- COL1A1: collagen, type I, alpha 1
- CTNS: cystinosin, the lysosomal cystine transporter
- ERBB2 loca leukemia viral oncogene homolog 2, neuro/glioblastoma derived oncogene homolog (avian)
- FLCN: folliculin
- GALK1: galactokinase 1
- GFAP: glial fibrillary acidic protein

- KCNJ2: potassium inwardly-rectifying channel, subfamily J, member 2
- MYO15A: myosin XVA
- NF1: neurofibromin 1 (neurofibromatosis, von Recklinghausen disease, Watson disease)
- PMP22: peripheral myelin protein 22
- SHBG: Sex hormone binding globulin
- SLC6A4: Serotonin transporter
- TMC6 and TMC8: Transmembrane channel-like 6 and 8 (epidermodysplasia verruciformis)
- TP53: tumor suppressor protein p53 (Li-Fraumeni syndrome), tumor suppressor gene
- USH1G: Usher syndrome 1G (autosomal recessive)
- RAI1: retinoic acid induced 1
- RAR-alpha: Retinoic acid receptor Alpha (involved in t(15,17) with PML)
- GRB7: Growth factor Receptor-Bound protein 7
- Several CC chemokines: CCL1, CCL2, CCL3, CCL4, CCL5, CCL7, CCL8, CCL11, CCL13, CCL14, CCL15, CCL16, CCL18, and CCL23

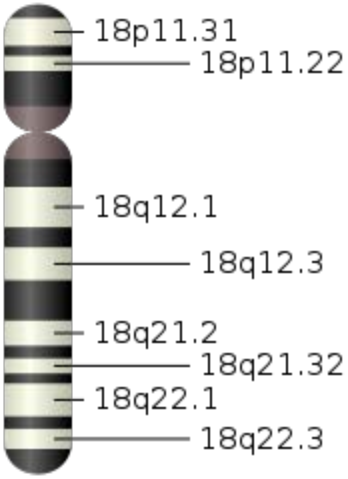
Diseases & disorders

The following diseases are related to genes on chromosome 17:

- Alexander disease
- Andersen-Tawil syndrome
- Birt-Hogg-Dubé syndrome
- Bladder cancer
- Breast cancer
- Camptomelic dysplasia
- Canavan disease
- Charcot-Marie-Tooth disease
- Charcot-Marie-Tooth disease, type 1
- Corticobasal degeneration
- Cystinosis
- Ehlers-Danlos syndrome
- Ehlers-Danlos syndrome, arthrochalasia type
- Ehlers-Danlos syndrome, classical type
- Epidermodysplasia verruciformis
- Galactosemia
- Hereditary neuropathy with liability to pressure palsies
- Li-Fraumeni syndrome
- Maturity onset diabetes of the young type 5
- Miller-Dieker syndrome
- Neurofibromatosis type I
- Nonsyndromic deafness
- Nonsyndromic deafness, autosomal dominant
- Nonsyndromic deafness, autosomal recessive

- Osteogenesis imperfecta
- Osteogenesis Imperfecta, Type I
- Osteogenesis Imperfecta, Type II
- Osteogenesis Imperfecta, Type III
- Osteogenesis Imperfecta, Type IV
- Smith-Magenis syndrome
- Usher syndrome
- Usher syndrome type I
- Very long-chain acyl-coenzyme A dehydrogenase deficiency

Chromosome 18 (Human)



Chromosome 18 is one of the 23 pairs of chromosomes in humans. People normally have two copies of this chromosome. Chromosome 18 spans about 76 million base pairs (the building material of DNA) and represents about 2.5 percent of the total DNA in cells.

Identifying genes on each chromosome is an active area of genetic research. Because researchers use different approaches to predict the number of genes on each chromosome, the estimated number of genes varies. Chromosome 18 likely contains between 300 and 400 genes.

Genes

The following are some of the genes located on chromosome 18:

- FECH: ferrochelatase (protoporphyria)

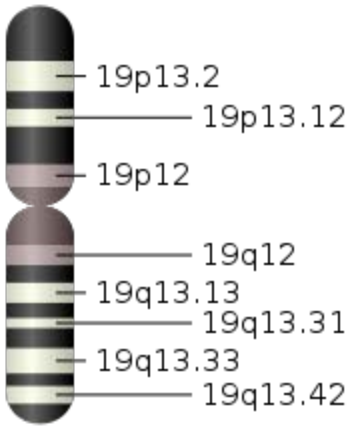
- NPC1: Niemann-Pick disease, type C1
- SMAD4: SMAD, mothers against DPP homolog 4 (Drosophila)
- KC6: Keratoconus gene 6, discovery reported in 2005;

Diseases & disorders

The following diseases are some of those related to genes on chromosome 18:

- erythropoietic protoporphyria
- hereditary hemorrhagic telangiectasia
- Niemann-Pick disease Type C
- porphyria
- Selective Mutism
- Edwards syndrome (Trisomy 18)
- Tetrasomy 18p
- Monosomy 18p
- Pitt Hopkins Syndrome 18q21

Chromosome 19 (Human)



Chromosome 19 is one of the 23 pairs of chromosomes in humans. People normally have two copies of this chromosome. Chromosome 19 spans more than 63 million base pairs (the building material of DNA) and represents between 2 and 2.5 percent of the total DNA in cells.

Identifying genes on each chromosome is an active area of genetic research. Because researchers use different approaches to predict the number of genes on each chromosome,

the estimated number of genes varies. Chromosome 19 likely contains between 1,300 and 1,700 genes.

Genes

The following are some of the genes located on chromosome 19:

- A1BG: Plasma glycoprotein, unknown function. Gene map locus 19q13.43
- APOE: Apolipoprotein E, gene associated with Alzheimer's disease
- BCKDHA: Branched chain keto acid dehydrogenase E1, alpha polypeptide (maple syrup urine disease)
- CACNA1A: Calcium channel, voltage-dependent, P/Q type, alpha 1A subunit, mutations of which are associated with Familial hemiplegic migraine Type I
- DMPK: Dystrophia myotonica-protein kinase
- EYCL1: EYE COLOR 1; EYE COLOR, GREEN/BLUE; GEY. Gene map locus 19p13.1-q13.11 OMIM: 227240
- GCDH: Glutaryl-Coenzyme A dehydrogenase
- HAMP: Hepcidin antimicrobial peptide
- HCL1: HAIR COLOR 1; BROWN HAIR COLOR; BRHC. Gene map locus 19p13.1-q13.11 OMIM: 113750
- MCPH2: microcephaly, primary autosomal recessive 2
- NOTCH3: Notch homolog 3 (Drosophila)
- NRTN: Neurturin, associated with Hirschsprung's disease
- NWD1: NACHT and WD repeat domain containing 1.
- PEX11G: peroxisomal biogenesis factor 11 gamma
- PRX: Periaxin
- SLC5A5: Solute carrier family 5 (sodium iodide symporter), member 5
- STK11: Serine/threonine kinase 11 (Peutz-Jeghers syndrome)

Diseases & disorders

The following diseases are some of those related to genes on chromosome 19:

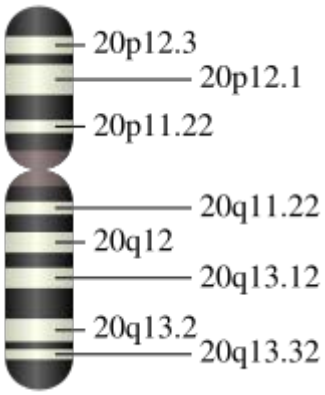
- Alzheimer's disease
- CADASIL
- Centronuclear myopathy autosomal dominant form
- Charcot-Marie-Tooth disease
- Congenital hypothyroidism
- Familial hemiplegic migraine
- Glutaric acidemia type 1
- Hemochromatosis
- Leber's Congenital Amaurosis
- Maple syrup urine disease
- Myotonic dystrophy
- Myotubular myopathy autosomal dominant form
- Marfan Syndrome

- Oligodendroglioma
- Peutz-Jeghers syndrome
- Spinocerebellar ataxia type-6
- X-linked agammaglobulinemia or Bruton's Disease

Proteins

The Human Proteome Project (HPP) has been initiated by Human Proteome Organization (HUPO) aims to sequence the entire human proteome based on the advances in mass spectrometry and will build a global protein capture knowledge base with open sharing of proteome datasets. The proteome sequencing has been initiated with a chromosome centric and gene centric approach. Sequencing of chromosome 19 proteome will be coordinated by Prof. György Marko-Varga, Clinical Protein Science & Imaging Group, Lund University, Sweden.

Chromosome 20 (Human)



Chromosome 20 is one of the 23 pairs of chromosomes in humans. People normally have two copies of this chromosome. Chromosome 20 spans around 63 million base pairs (the building material of DNA) and represents between 2 and 2.5 percent of the total DNA in cells. Chromosome 20 was fully sequenced in 2001 and contained 59,187,298 base pairs representing 99.4% of the euchromatic DNA.

Identifying genes on each chromosome is an active area of genetic research. Because researchers use different approaches to predict the number of genes on each chromosome, the estimated number of genes varies. Chromosome 20 contains over 900 genes. New discoveries have recently linked this chromosome to the increasing susceptibility to male-pattern baldness.

Genes

The following are some of the genes located on chromosome 20:

- EDN3: endothelin 3
- JAG1: jagged 1 (Alagille syndrome)
- PANK2: pantothenate kinase 2 (Hallervorden-Spatz syndrome)
- PRNP: prion protein (p27-30) (Creutzfeld-Jakob disease, Gerstmann-Strausler-Scheinker syndrome, fatal familial insomnia)
- tTG:tissue transglutaminase (Celiac disease)
- AHCY: S-adenosylhomocysteine hydrolase
- ARFGEF2: ADP-ribosylation factor guanine nucleotide-exchange factor 2 (brefeldin A-inhibited)
- GSS: glutathione synthetase
- SALL4: sal-like 4 (Drosophila)
- VAPB: VAMP (vesicle-associated membrane protein)-associated protein B and C
- BMP2: Bone Morphogenetic Protein 2 (osteoblast differentiation)
- GNAS1: Gs alpha subunit (membrane G-protein)

Diseases & disorders

The following diseases are some of those related to genes on chromosome 20:

- Arterial tortuosity syndrome
- Adenosine deaminase deficiency
- Alagille syndrome
- Celiac disease
- Galactosialidosis - CTSA
- Maturity onset diabetes of the young type 1
- Pantothenate kinase-associated neurodegeneration
- Transmissible spongiform encephalopathy (prion diseases)
- Waardenburg syndrome

Chromosome 21 (Human)

Chromosome 21 is one of the 23 pairs of chromosomes in humans. People normally have two copies of this chromosome. The trisomy of the 21st chromosome causes Down's Syndrome. Chromosome 21 is the smallest human chromosome, spanning 47 million nucleotides (the building material of DNA) and representing about 1.5 percent of the total DNA in cells.

In 2000, researchers working on the Human Genome Project announced that they had determined the sequence of base pairs that make up this chromosome. Chromosome 21 was the second human chromosome to be fully sequenced.

Identifying genes on each chromosome is an active area of genetic research. Because researchers use different approaches to predict the number of genes on each chromosome, the estimated number of genes varies. Chromosome 21 likely contains between 300 and 400 genes.

Genes

The following are some of the genes located on chromosome 21:

- APP: amyloid beta (A4) precursor protein (peptidase nexin-II, Alzheimer disease)
- CBS: cystathionine-beta-synthase
- CLDN14: claudin 14
- HLCS: holocarboxylase synthetase (biotin-(proprionyl-Coenzyme A-carboxylase (ATP-hydrolysing)) ligase)
- KCNE1: potassium voltage-gated channel, Isk-related family, member 1
- KCNE2: potassium voltage-gated channel, Isk-related family, member 2
- LAD: leukocyte adhesion deficiency (symbols are ITGB2, CD18, LCAMB)
- SOD1: superoxide dismutase 1, soluble (amyotrophic lateral sclerosis 1 (adult))
- TMPRSS3: transmembrane protease, serine 3
- PCNT: centrosomal pericentrin
- DSCR1: Down Syndrome critical region 1
- DYRK1A: dual specificity tyrosine-(Y)-phosphorylation regulated kinase 1A
- RRP1B: ribosomal RNA processing 1 homolog B
- s100B: calcium binding protein

Diseases & disorders

The following diseases are some of those related to genes on chromosome 21:

- Alzheimer's disease
  - Alzheimer's disease type 1
- Amyotrophic lateral sclerosis
  - Amyotrophic lateral sclerosis type 1
- Down syndrome
- Erondu-Cymet Syndrome
- Holocarboxylase synthetase deficiency
- Homocystinuria
- Jervell and Lange-Nielsen syndrome
- Leukocyte adhesion deficiency
- Majewski osteodysplastic primordial dwarfism type II (MOPD II, or MOPD2)
- Nonsyndromic deafness
  - Nonsyndromic deafness, autosomal recessive

- Romano-Ward syndrome

Chromosomal conditions

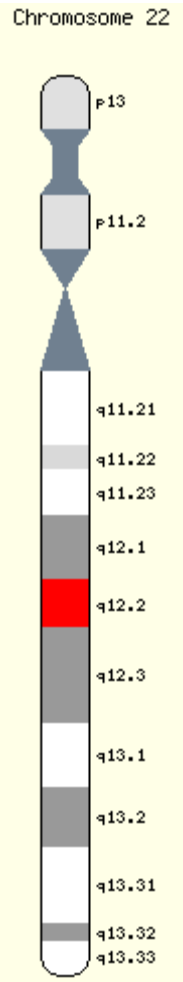
The following conditions are caused by changes in the structure or number of copies of chromosome 21:

- Cancers: Rearrangements (translocations) of genetic material between chromosome 21 and other chromosomes have been associated with several types of cancer. For example, acute lymphoblastic leukemia (a type of blood cancer most often diagnosed in childhood) has been associated with a translocation between chromosomes 12 and 21. Another form of leukemia, acute myeloid leukemia, has been associated with a translocation between chromosomes 8 and 21.

In a small percentage of cases, Down syndrome is caused by a rearrangement of chromosomal material between chromosome 21 and another chromosome. As a result, a person has the usual two copies of chromosome 21, plus extra material from chromosome 21 attached to another chromosome. These cases are called translocation Down syndrome. Researchers believe that extra copies of genes on chromosome 21 disrupt the course of normal development, causing the characteristic features of Down syndrome and the increased risk of medical problems associated with this disorder.

- Other changes in the number or structure of chromosome 21 can have a variety of effects, including mental retardation, delayed development, and characteristic facial features. In some cases, the signs and symptoms are similar to those of Down syndrome. Changes to chromosome 21 include a missing segment of the chromosome in each cell (partial monosomy 21) and a circular structure called ring chromosome 21. A ring chromosome occurs when both ends of a broken chromosome are reunited.
- Duplication in Amyloid precursor protein (APP) locus (duplicated segment varies in length but includes APP) on Chromosome 21 was found to cause early onset familial Alzheimer's disease in a French family set (Rovelet-Lecrux et al.) and a Dutch family set (Sleegers et al.). Compared to Alzheimer's caused by missense mutations in APP, the frequency of the Alzheimer's caused by APP duplications is significant. All patients that have an extra copy of APP gene due to the locus duplication show Alzheimer's with severe Cerebral amyloid angiopathy.

Chromosome 22 (Human)



Chromosome 22 is one of the 23 pairs of chromosomes in humans. Humans normally have two copies of Chromosome 22. Chromosome 22 is the second smallest human chromosome, spanning about 49 million base pairs (the building material of DNA) and representing between 1.5 and 2 % of the total DNA in cells.

In 1999, researchers working on the Human Genome Project announced they had determined the sequence of base pairs that make up this chromosome. Chromosome 22 was the first human chromosome to be fully sequenced.

Identifying genes on each chromosome is an active area of genetic research. Because researchers use different approaches to predict the number of genes on each chromosome, the estimated number of genes varies. Chromosome 22 contains about 693 genes.

Chromosome 22 was originally identified as the smallest chromosome, but after extensive research, researchers concluded that it was indeed chromosome 21. The chromosomes weren't renamed because of the popularity of chromosome 21 (being known as the chromosome that can lead to Down's Syndrome). For this reason, researchers did not rearrange the numbers on these chromosomes.

Genes

The following are some of the genes located on chromosome 22:

Locus	Gene	Description	Condition
22q11.1-q11.2	IGL@	immunoglobulin lambda locus - contains genes for the light chains of antibodies	
22q11.21	TBX1	T-box 1	
22q11	RTN4R	Reticulon 4 receptor	Schizophrenia
22q11.21-q11.23	COMT	catechol-O-methyltransferase gene	
22q12.1-q13.1	NEFH	neurofilament, heavy polypeptide 200kDa	
22q12.1	CHEK2	CHK2 checkpoint homolog (S. pombe)	
22q12.2	NF2	neurofibromin 2	bilateral acoustic neuroma
22q13	SOX10	SRY (sex determining region Y)-box 10	
22q13.2	EP300	E1A binding protein p300	
22q13.3	WNT7B	Wingless-type MMTV integration site family, member 7B	
22q13.3	SHANK3	SH3 and multiple ankyrin repeat domains 3	22q13 deletion syndrome

Diseases & disorders

The following diseases are some of those related to genes on chromosome 22:

- Amyotrophic lateral sclerosis
- Breast cancer
- Desmoplastic small round cell tumor
- 22q11.2 deletion syndrome
- 22q13 deletion syndrome or Phelan-McDermid syndrome
- Li-Fraumeni syndrome
- Neurofibromatosis type 2
- Rubinstein-Taybi syndrome
- Waardenburg syndrome
- Cat eye syndrome

- Methemoglobinemia
- Schizophrenia

Chromosomal conditions

The following conditions are caused by changes in the structure or number of copies of chromosome 22:

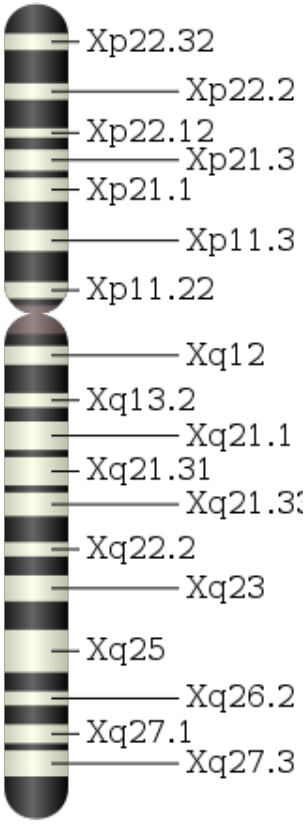
- 22q11.2 deletion syndrome: Most people with 22q11.2 deletion syndrome are missing about 3 million base pairs on one copy of chromosome 22 in each cell. The deletion occurs near the middle of the chromosome at a location designated as q11.2. This region contains about 30 genes, but many of these genes have not been well characterized. A small percentage of affected individuals have shorter deletions in the same region.
  The loss of one particular gene, TBX1, is thought to be responsible for many of the characteristic features of 22q11.2 deletion syndrome, such as heart defects, an opening in the roof of the mouth (a cleft palate), distinctive facial features, and low calcium levels. A loss of this gene does not appear to cause learning disabilities, however. Other genes in the deleted region are also likely to contribute to the signs and symptoms of 22q11.2 deletion syndrome.
- 22q13 deletion syndrome (Phelan-McDermid syndrome): The deletion of the distal tip of the chromosome 22 is related to moderate to severe developmental delay and mental retardation. This region includes the Shank3 gene, thought to be responsible for the neurological deficits of the syndrome (Wilson et al., 2003). Almost all children affected by the 22q13 deletion have absent or severely delayed speech; minor facial dysmorphism; thin, flaky toenails; large, fleshy hands; large feet; prominent, poorly formed ears and other characteristics which are not visually apparent: hypotonia (97%); normal to accelerated growth (95%); increased tolerance to pain (86%); seizures (unknown percentage) .
- Other chromosomal conditions: Other changes in the number or structure of chromosome 22 can have a variety of effects, including mental retardation, delayed development, physical abnormalities, and other medical problems. These changes include an extra piece of chromosome 22 in each cell (partial trisomy), a missing segment of the chromosome in each cell (partial monosomy), and a circular structure called ring chromosome 22 that is caused by the breakage and reattachment of both ends of the chromosome.
- Cat-eye syndrome is a rare disorder most often caused by a chromosomal change called an inverted duplicated 22. A small extra chromosome is made up of genetic material from chromosome 22 that has been abnormally duplicated (copied). The extra genetic material causes the characteristic signs and symptoms of cat-eye syndrome, including an eye abnormality called ocular iris coloboma (a gap or split in the colored part of the eye), small skin tags or pits in front of the ear, heart defects, kidney problems, and, in some cases, delayed development.
- A rearrangement (translocation) of genetic material between chromosomes 9 and 22 is associated with several types of blood cancer (leukemia). This chromosomal abnormality, which is commonly called the Philadelphia chromosome, is found

only in cancer cells. The Philadelphia chromosome has been identified in most cases of a slowly progressing form of blood cancer called chronic myeloid leukemia, or CML. It also has been found in some cases of more rapidly progressing blood cancers (acute leukemias). The presence of the Philadelphia chromosome can help predict how the cancer will progress and provides a target for molecular therapies.

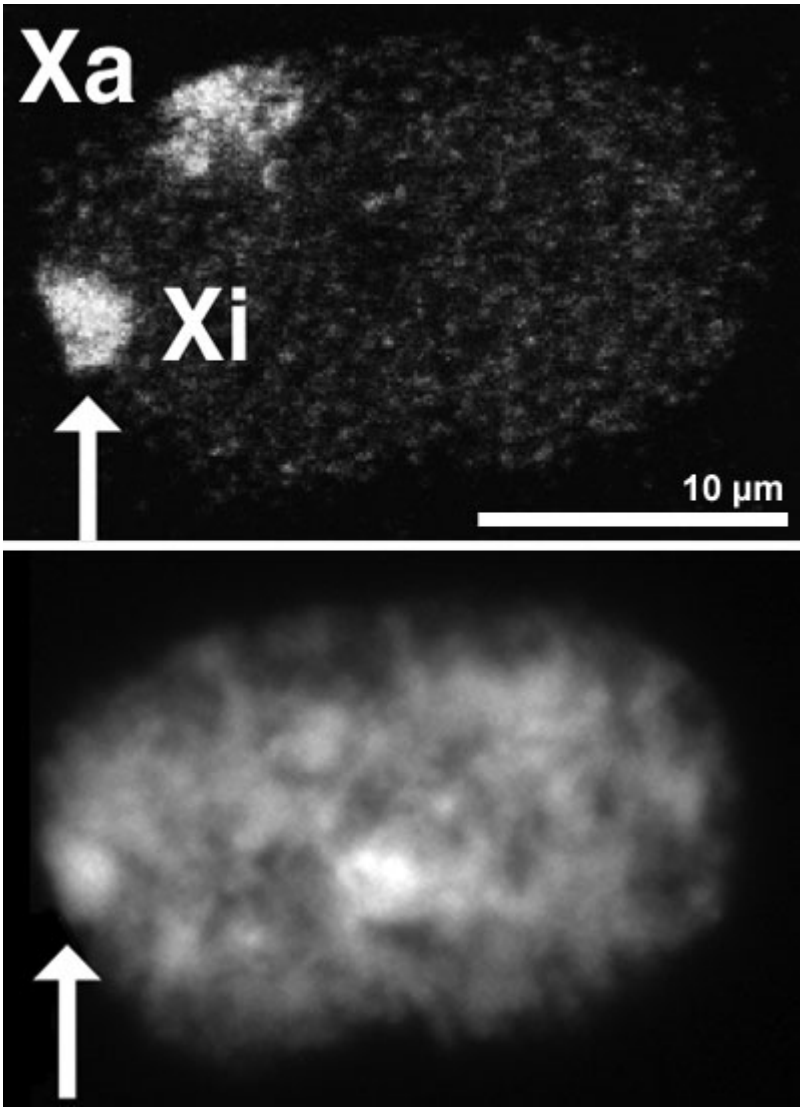
Chapter 3

X Chromosome & Y Chromosome

X Chromosome



Scheme of the X chromatid



Nucleus of a female amniotic fluid cell. Top: Both X-chromosome territories are detected by FISH. Shown is a single optical section made with a confocal microscope. Bottom: Same nucleus stained with DAPI and recorded with a CCD camera. The Barr body is indicated by the arrow, it identifies the inactive X (Xi).

The **X chromosome** is one of the two sex-determining chromosomes in many animal species, including mammals (the other is the Y chromosome). It is a part of the XY sex-determination system and X0 sex-determination system. The **X** chromosome was named for its unique properties by early researchers, which resulted in the naming of its counterpart **Y** chromosome, for the next letter in the alphabet, after it was discovered later.

In humans

Function

The sex chromosomes X X are one of the 23 homologous pairs of chromosomes in a female. The X chromosome spans more than 153 million base pairs (the building material of DNA) and represents about 5% of the total DNA in women's cells, 2.5% in men's.

Each person normally has one pair of sex chromosomes in each cell. Females have two X chromosomes, whereas males have one X and one Y chromosome. Both males and females retain one of their mother's X chromosomes, and females retain their second X chromosome from their father. Since the father retains his X chromosome from his mother, a human female has one X chromosome from her paternal grandmother (father's side), and one X chromosome from her mother.

Identifying genes on each chromosome is an active area of genetic research. Because researchers use different approaches to predict the number of genes on each chromosome, the estimated number of genes varies. The X chromosome contains about 2000 genes compared to the Y chromosome containing 78 genes, out of the estimated 20,000 to 25,000 total genes in the human genome. Genetic disorders that are due to mutations in genes on the X chromosome are described as **X linked**.

The X chromosome carries a couple of thousand genes but few, if any, of these have anything to do directly with sex determination. Early in embryonic development in females, one of the two X chromosomes is randomly and permanently inactivated in nearly all somatic cells (cells other than egg and sperm cells). This phenomenon is called X-inactivation or Lyonization, and creates a Barr body. X-inactivation ensures that females, like males, have one functional copy of the X chromosome in each body cell. It was previously assumed that only one copy is actively used. However, recent research suggests that the Barr body may be more biologically active than was previously supposed.

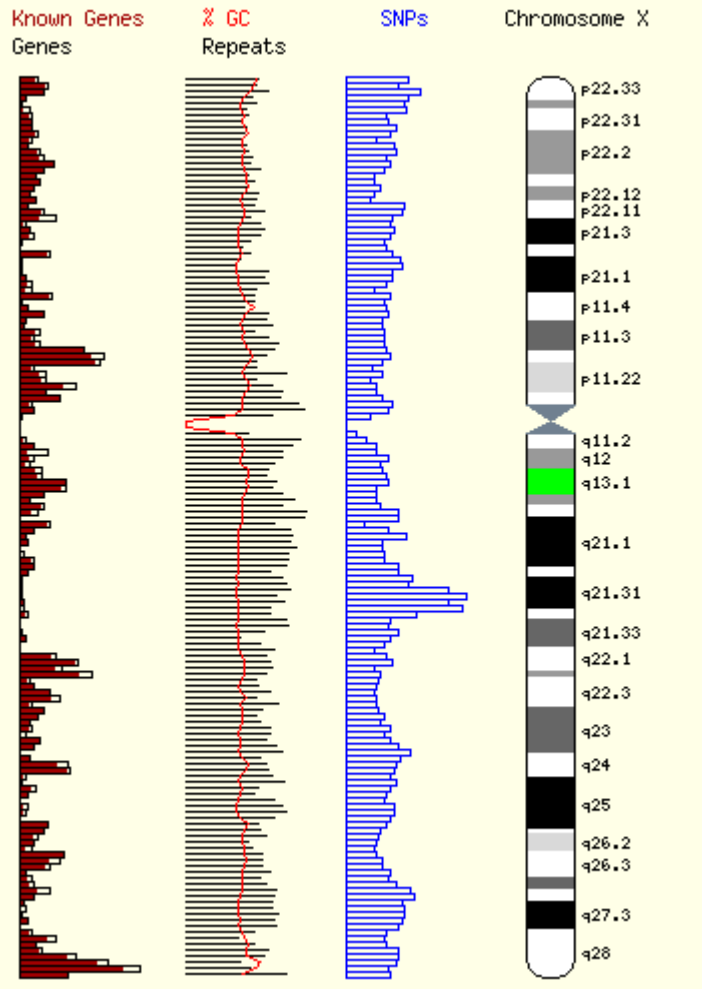
Structure

It is theorized by Ross et al. 2005 and Ohno 1967 that the X-chromosome is at least partially derived from the autosomal (non-sex-related) genome of other mammals evidenced from interspecies genomic sequence alignments.

The X-chromosome is notably larger and has a more active euchromatin region than its Y-chromosome counterpart. Further comparison of the X and Y reveal regions of homology between the two. However, the corresponding region in the Y appears far shorter and lacks regions that are conserved in the X throughout primate species, implying a genetic degeneration for Y in that region. Because males have only one X-chromosome, they are more likely to have an X chromosome-related disease.

It is estimated that about 10% of the genes encoded by the X-chromosome are associated with a family of "CT" genes, so named because they encode for markers found in both tumor cells (in **C**ancer patients) as well as in the human testis (in healthy patients).

Role in diseases



Numerical abnormalities

Klinefelter's syndrome:

- Klinefelter's syndrome is caused by the presence of one or more extra copies of the X chromosome in a male's cells. Extra genetic material from the X chromosome interferes with male sexual development, preventing the testicles from functioning normally and reducing the levels of testosterone.
- Males with Klinefelter's syndrome typically have one extra copy of the X chromosome in each cell, for a total of two X chromosomes and one Y chromosome (47,XXY). It is less common for affected males to have two or three extra X chromosomes (48,XXXY or 49,XXXXY) or extra copies of both the X and Y chromosomes (48,XXYY) in each cell. The extra genetic material may lead

to tall stature, learning and reading disabilities, and other medical problems. The average IQ in Klinefelter syndrome is in the normal range. When additional X and/or Y chromosomes are present in 48,XXXY, 48,XXYY, or 49,XXXXY, developmental delays and cognitive difficulties can be more severe and mild intellectual disability may be present.
- Klinefelter's syndrome can also result from an extra X chromosome in only some of the body's cells. These cases are called mosaic 46,XY/47,XXY.

Triple X syndrome (also called 47,XXX or trisomy X):

- This syndrome results from an extra copy of the X chromosome in each of a female's cells. Females with trisomy X have three X chromosomes, for a total of 47 chromosomes per cell. The average IQ of females with this syndrome is 90, while the average IQ of their normal siblings is 100 . Their stature on average is taller than normal females. They are fertile and their children do not inherit the condition.

- Females with more than one extra copy of the X chromosome (48, XXXX syndrome or 49, XXXXX syndrome) have been identified, but these conditions are rare.

Turner syndrome:

- This results when each of a female's cells has one normal X chromosome and the other sex chromosome is missing or altered. The missing genetic material affects development and causes the features of the condition, including short stature and infertility.
- About half of individuals with Turner syndrome have monosomy X (45,X), which means each cell in a woman's body has only one copy of the X chromosome instead of the usual two copies. Turner syndrome can also occur if one of the sex chromosomes is partially missing or rearranged rather than completely missing. Some women with Turner syndrome have a chromosomal change in only some of their cells. These cases are called Turner syndrome mosaics (45,X/46,XX).

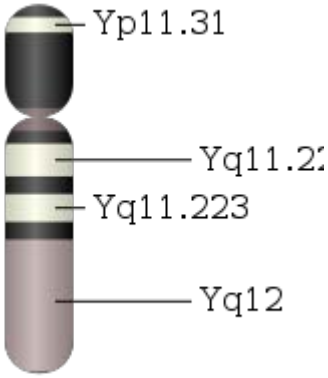
Other disorders

XX male syndrome is a rare disorder, where the SRY region of the Y chromosome has recombined to be located on one of the X chromosomes. As a result, the XX combination after fertilization has the same effect as a XY combination, resulting in a male. However, the other genes of the X chromosome cause feminization as well.

X-linked endothelial corneal dystrophy is an extremely rare disease of cornea associated with Xq25 region. Lisch epithelial corneal dystrophy is associated with Xp22.3.

Megalocornea 1 is associated with Xq21.3-q22

Y Chromosome



Human Y-chromatid

The **Y chromosome** is one of the two sex-determining chromosomes in most mammals, including humans. In mammals, it contains the gene SRY, which triggers testis development if present. The human Y chromosome is composed of about 60 million base pairs. DNA in the Y chromosome is passed from father to son, and Y-DNA analysis may thus be used in genealogy research.

Overview

Most mammals have one pair of sex chromosomes in each cell. Males have one Y chromosome and one X chromosome, while females have two X chromosomes. In mammals, the Y chromosome contains a gene, SRY, which triggers embryonic development as a male. The Y chromosomes of humans and other mammals also contain other genes needed for normal sperm production.

There are exceptions, however. For example, the platypus relies on an XY sex-determination system based on five pairs of chromosomes . Platypus sex chromosomes in fact appear to bear a much stronger homology (similarity) with the avian Z chromosome, and the SRY gene so central to sex-determination in most other mammals is apparently not involved in platypus sex-determination. Among humans, some men have two Xs and a Y, or one X and two Ys, and some women have three Xs or a single X instead of a double X. There are other exceptions in which SRY is damaged (leading to an XY female), or copied to the X (leading to an XX male).

Origins and evolution

Before Y-chromosome

Many ectothermic vertebrates have no sex chromosomes. If they have different sexes, sex is determined environmentally rather than genetically. For some of them, especially reptiles, sex depends on the incubation temperature; others are hermaphroditic (meaning they contain both male and female gametes in the same individual).

Origin

The X and Y chromosomes are thought to have evolved from a pair of identical chromosomes, termed autosomes, when an ancestral mammal developed an allelic variation, a so-called 'sex locus' - simply possessing this allele caused the organism to be male. The chromosome with this allele became the Y chromosome, while the other member of the pair became the X chromosome. Over time, genes which were beneficial for males and harmful to (or had no effect on) females either developed on the Y chromosome, or were acquired through the process of translocation..

Until recently, the X and Y chromosomes were thought to have diverged around 300 million years ago. However recent research, particularly that stemming from the sequencing of the platypus genome, has suggested that the XY sex-determination system wouldn't have been present more than 166 million years ago, at the split of the monotremes from other mammals. This reestimation of the age of the therian XY system is based on the finding that sequences that are on the X chromosomes of marsupials and eutherian mammals are present on the autosomes of platypus and birds. The older estimate was based on erroneous reports that the platypus X chromosomes contained these sequences .

Recombination inhibition

Recombination between the X and Y chromosomes proved harmful - it resulted in males without necessary genes formerly found on the Y chromosome, and females with unnecessary or even harmful genes previously only found on the Y chromosome. As a result, genes beneficial to males accumulated near the sex-determining genes, and recombination in this region was suppressed in order to preserve this male specific region. Over time, the Y chromosome changed in such a way as to inhibit the areas around the sex determining genes from recombining at all with the X chromosome. As a result of this process 95% of the human Y chromosome is unable to recombine.

Shrinking

The human Y chromosome has lost 1,393 of its 1,438 original genes over the course of its existence. With a rate of genetic loss of 4.6 genes per million years, the Y chromosome may potentially lose complete function within the next 10 million years. Comparative genomic analysis, however, reveals that many mammalian species are experiencing a

similar loss of function in their heterozygous sex chromosome. Degeneration may simply be the fate of all nonrecombining sex chromosomes due to three common evolutionary forces: high mutation rate, inefficient selection and genetic drift. On the other hand, recent comparisons of the human and chimpanzee Y chromosomes show that the human Y chromosome has not lost any genes since the divergence of humans and chimpanzees between 6-7 million years ago, providing direct evidence that the linear extrapolation model may be flawed.

High mutation rate

The human Y chromosome is particularly exposed to high mutation rates due to the environment in which it is housed. The Y chromosome is passed exclusively through sperm, which undergo multiple cell divisions during gametogenesis. Each cellular division provides further opportunity to accumulate base pair mutations. Additionally, sperm are stored in the highly oxidative environment of the testis, which encourages further mutation. These two conditions combined put the Y chromosome at a risk of mutation 4.8 times greater than the rest of the genome.

Inefficient selection

Without the ability to recombine during meiosis, the Y chromosome is unable to expose individual alleles to natural selection. Deleterious alleles are allowed to "hitchhike" with beneficial neighbors, thus propagating maladapted alleles in to the next generation. Conversely, advantageous alleles may be selected against if they are surrounded by harmful alleles (background selection). This inability to sort through its gene content, the Y chromosome is particularly prone to the accumulation of "junk" DNA. Massive accumulations of retrotransposable elements are scattered throughout the Y. The random insertion of DNA segments often disrupt encoded gene sequences and render them nonfunctional. However, the Y chromosome has no way of weeding out these "jumping genes". Without the ability to isolate alleles, selection cannot effectively act upon them.

A clear, quantitative indication of this inefficiency is the entropy rate of the Y chromosome. Whereas all other chromosomes in the human genome have entropy rates of 1.5-1.9 bits per nucleotide (compared to the theoretical maximum of exactly 2 for no redundancy), the Y chromosome's entropy rate is only 0.84. This means the Y chromosome has a much lower information content relative to its overall length; it is more redundant.

Genetic drift

Even if a well adapted Y chromosome manages to maintain genetic activity by avoiding mutation accumulation, there is no guarantee it will be passed down to the next generation. The population size of the Y chromosome is inherently limited to 1/4 that of autosomes: diploid organisms contain two copies of autosomal chromosomes while only half the population contains 1 Y chromosome. Thus, genetic drift is an exceptionally strong force acting upon the Y chromosome. Through sheer random assortment, an adult

male may never pass on his Y chromosome if he only has female offspring. Thus, although a male may have a well adapted Y chromosome free of excessive mutation, it may never make it in to the next gene pool. The repeat random loss of well-adapted Y chromosomes, coupled with the tendency of the Y chromosome to evolve to have more deleterious mutations rather than less for reasons described above, contributes to the species-wide degeneration of Y chromosomes through Muller's ratchet.

Gene conversion

In 2003, researchers from MIT discovered a process which may slow down the process of degradation. They found that human Y chromosome is able to "recombine" with itself, using palindrome base pair sequences. Such a "recombination" is called gene conversion or *recombinational loss of heterozygosity* (RecLOH).

In the case of the Y chromosomes, the palindromes are not noncoding DNA; these strings of bases contain functioning genes important for male fertility. Most of the sequence pairs are greater than 99.97% identical. The extensive use of gene conversion may play a role in the ability of the Y chromosome to edit out genetic mistakes and maintain the integrity of the relatively few genes it carries. In other words, since the Y chromosome is single, it has duplicates of its genes on itself instead of having a second, homologous, chromosome. When errors occur, it can use other parts of itself as a template to correct them.

Findings were confirmed by comparing similar regions of the Y chromosome in humans to the Y chromosomes of chimpanzees, bonobos and gorillas. The comparison demonstrated that the same phenomenon of gene conversion appeared to be at work more than 5 million years ago, when humans and the non-human primates diverged from each other.

Future evolution

In the terminal stages of the degeneration of the Y chromosome, other chromosomes increasingly take over genes and functions formerly associated with it. Finally, the Y chromosome disappears entirely, and a new sex-determining system arises. Several species of rodent in the sister families Muridae and Cricetidae have reached these stages, in the following ways:

- The Transcaucasian mole vole, *Ellobius lutescens*, the Zaisan mole vole, *Ellobius tancrei*, and the Japanese spinous country rats *Tokudaia osimensis* and *Tokudaia muenninki*, have lost the Y chromosome and SRY entirely. *Tokudaia* spp. have relocated some other genes ancestrally present on the Y chromosome to the X chromosome. Both genders of *Tokudaia* spp. and *Ellobius lutescens* have an XO genotype, whereas all *Ellobius tancrei* possess an XX genotype. The new sex-determining system for these rodents remains unclear.
- The wood lemming *Myopus schisticolor*, the arctic lemming, *Dicrostonyx torquatus*, and multiple species in the grass mouse genus *Akodon* have evolved

fertile females who possess the genotype generally coding for males, XY, in addition to the ancestral XX female, through a variety of modifications to the X and Y chromosomes.
- In the creeping vole, *Microtus oregoni*, the females, with just one X chromosome each, produce X gametes only, and the males, XY, produce Y gametes, or gametes devoid of any sex chromosome, through nondisjunction.

Outside of the rodent family, the black muntjac, *Muntiacus crinifrons*, evolved new X and Y chromosomes through fusions of the ancestral sex chromosomes and autosomes. Primate Y chromosomes, including in humans, have degenerated so much that primates will also evolve new sex determination systems relatively soon, in about 14 million years in humans.

Human Y chromosome

In humans, the Y chromosome spans about 58 million base pairs (the building blocks of DNA) and represents approximately 2% of the total DNA in a male cell. The human Y chromosome contains 86 genes, which code for only 23 distinct proteins. Traits that are inherited via the Y chromosome are called holandric traits.

The human Y chromosome is unable to recombine with the X chromosome, except for small pieces of pseudoautosomal regions at the telomeres (which comprise about 5% of the chromosome's length). These regions are relics of ancient homology between the X and Y chromosomes. The bulk of the Y chromosome which does not recombine is called the "NRY" or non-recombining region of the Y chromosome. It is the SNPs in this region which are used for tracing direct paternal ancestral lines.

Genes

Not including pseudoautosomal genes, genes include:

- NRY, with corresponding gene on X chromosome
  - AMELY/AMELX (amelogenin)
  - RPS4Y1/RPS4Y2/RPS4X (Ribosomal protein S4)

- NRY, other
  - AZF1 (azoospermia factor 1)
  - BPY2 (basic protein on the Y chromosome)
  - DAZ1 (deleted in azoospermia)
  - DAZ2
  - PRKY (protein kinase, Y-linked)
  - RBMY1A1
  - SRY (sex-determining region)
  - TSPY (testis-specific protein)
  - USP9Y
  - UTY (ubiquitously transcribed TPR gene on Y chromosome)

- ZFY (zinc finger protein)

Y-chromosome-linked diseases

Y-chromosome-linked diseases can be of more common types, or very rare ones. Yet, the rare ones still have importance in understanding the function of the Y-chromosome in the normal case.

More common

No vital genes reside only on the Y chromosome, since roughly half of humans (females) do not have Y chromosomes. The only well-defined human disease linked to a defect on the Y chromosome is defective testicular development (due to deletion or deleterious mutation of *SRY*). However, having two X-chromosomes and one Y-chromosome has similar effects. On the other hand, having Y-chromosome polysomy has other effects than masculinization.

Defective Y-chromosome

This results in the person presenting a female phenotype even though that person possesses an XY karyotype (i.e., is born with female-like genitalia). The lack of the second X results in infertility. In other words, viewed from opposite direction, the person goes through defeminization but fails to complete masculinization.

The cause can be seen as an incomplete Y chromosome: the usual karyotype in these cases is 44X, plus a fragment of Y. This usually results in defective testicular development, such that the infant may or may not have fully formed male genitalia internally or externally. The full range of ambiguity of structure may occur, especially if mosaicism is present. When the Y fragment is minimal and nonfunctional, the child usually is a girl with the features of Turner syndrome or mixed gonadal dysgenesis.

XXY

Klinefelter's syndrome (47, XXY) is not an aneuploidy of the Y chromosome, but a condition of having an extra X chromosome, which usually results in defective postnatal testicular function. The mechanism is not fully understood; the extra X does not seem to be due to direct interference with expression of Y genes.

XYY

47,XYY syndrome is caused by the presence of a single extra copy of the Y chromosome in each of a male's cells. 47, XYY males have one X chromosome and two Y chromosomes, for a total of 47 chromosomes per cell. Researchers have found that an extra copy of the Y chromosome is associated with increased stature and an increased incidence of learning problems in some boys and men, but the effects are variable, often minimal, and the vast majority do not know their karyotype. When chromosome surveys were done in the mid-1960s in British secure hospitals for the developmentally disabled,

a higher than expected number of patients were found to have an extra Y chromosome. The patients were mischaracterized as aggressive and criminal, so that for a while an extra Y chromosome was believed to predispose a boy to antisocial behavior (and was dubbed the "criminal karyotype"). Subsequently, in 1968 in Scotland the only ever comprehensive nationwide chromosome survey of prisons found no overrepresentation of 47,XYY men, and later studies found 47,XYY boys and men had the same rate of criminal convictions as 46,XY boys and men of equal intelligence. Thus, the "criminal karyotype" concept is inaccurate and obsolete.

Rare

The following Y-Chromosome-linked diseases are rare, but notable because of their elucidating of the nature of the Y-chromosome.

More than two Y chromosomes

Greater degrees of Y chromosome polysomy (having more than one extra copy of the Y chromosome in every cell, e.g., XYYYY) are rare. The extra genetic material in these cases can lead to skeletal abnormalities, decreased IQ, and delayed development, but the severity features of these conditions are variable.

XX male syndrome

XX male syndrome occurs when there has been a recombination in the formation of the male gametes, causing the SRY-portion of the Y chromosome to move to the X chromosome. When such an X chromosome contributes to the child, the development will lead to a male, because of the SRY gene.

Genetic genealogy

In human genetic genealogy (the application of genetics to traditional genealogy) use of the information contained in the Y chromosome is of particular interest since, unlike other genes, the Y chromosome is passed exclusively from father to son. Mitochondrial DNA, maternally inherited, is used in an analogous way to trace the maternal line.

Non-mammal Y-chromosome

Many groups of organisms in addition to mammals have Y chromosomes, but these Y chromosomes do not share common ancestry with mammalian Y chromosomes. Such groups include Drosophila, some other insects, some fish, some reptiles, and some plants. In Drosophila melanogaster, the Y chromosome does not trigger male development. Instead, sex is determined by the number of X chromosomes. The *D. melanogaster* Y chromosome does contain genes necessary for male fertility. So XXY *D. melanogaster* are female, and *D. melanogaster* with a single X (X0), are male but sterile. There are some species of Drosophila in which X0 males are both viable and fertile.

ZW-chromosomes

Other organisms have mirror image sex chromosomes: the female is "XY" and the male is "XX", but by convention biologists call a "female Y" a W chromosome and the other a Z chromosome. For example, female birds, snakes, and butterflies have ZW sex chromosomes, and males have ZZ sex chromosomes.

Chapter 4

Introduction to Genetics

Genetics is the study of genes, and tries to explain what they are and how they work. Genes are how living organisms inherit features from their ancestors; for example, children usually look like their parents because they have inherited their parents' genes. Genetics tries to identify which features are inherited, and explain how these features are passed from generation to generation.

In genetics, a feature of a living thing is called a "trait". Some traits are part of an organism's physical appearance; such as a person's eye-color, height or weight. Other sorts of traits are not easily seen and include blood types or resistance to diseases. Some traits are inherited through our genes, so tall and thin people tend to have tall and thin children. Other traits come from interactions between our genes and the environment, so a child might inherit the tendency to be tall, but if they are poorly nourished, they will still be short. The way our genes and environment interact to produce a trait can be complicated. For example, the chances of somebody dying of cancer or heart disease seems to depend on both their genes and their lifestyle.

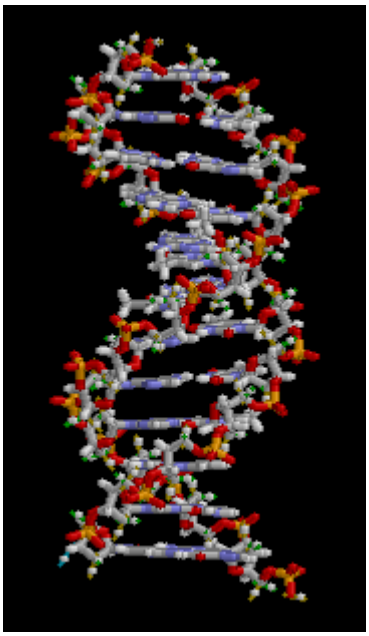
Genes are made from a long molecule called DNA, which is copied and inherited across generations. DNA is made of simple units that line up in a particular order within this large molecule. The order of these units carries genetic information, similar to how the order of letters on a page carry information. The language used by DNA is called the genetic code, which lets organisms read the information in the genes. This information is the instructions for constructing and operating a living organism.

The information within a particular gene is not always exactly the same between one organism and another, so different copies of a gene do not always give exactly the same instructions. Each unique form of a single gene is called an allele. As an example, one allele for the gene for hair color could instruct the body to produce a lot of pigment, producing black hair, while a different allele of the same gene might give garbled instructions that fail to produce any pigment, giving white hair. Mutations are random changes in genes, and can create new alleles. Mutations can also produce new traits, such

as when mutations to an allele for black hair produce a new allele for white hair. This appearance of new traits is important in evolution.

Inheritance in biology

Genes and inheritance



A section of DNA; the sequence of the plate-like units (nucleotides) in the center carries information.

Red hair is a recessive trait.

Genes are inherited as units, with two parents dividing out copies of their genes to their offspring. You can think of this process like mixing two hands of cards, shuffling them, and then dealing them out again. Humans have two copies of each of their genes and when people reproduce they make copies of their genes and put them into eggs or sperm, but only put in one copy of each type of gene. When an egg joins with a sperm, this gives a child a complete set of genes. This child will have the same number of genes as its parents, but for any gene one of their two copies will come from their father, and one from their mother.

The effects of this mixing depends on the types (the alleles) of the gene you are interested in. If the father has two copies for an allele for red hair, and the mother has two copies for brown hair, all their children will get the two alleles that give different instructions, one for red hair and one for brown. The hair color of these children depends on how these alleles work together. If one allele overrides the instructions from another, it is called the *dominant* allele, and the allele that is overridden is called the *recessive* allele. In the case of a daughter with alleles for both red and brown hair, brown is dominant and she ends up with brown hair.

Although the red color allele is still there in this brown hair girl, it doesn't show. This is a difference between what you see on the surface (the traits of an organism, called its phenotype) and the genes within the organism (its genotype). In this example you can call the allele for brown "B" and the allele for red "b". (It is normal to write dominant alleles

with capital letters and recessive ones with lower-case letters.) The brown hair daughter has the "brown hair phenotype" but her genotype is Bb, with one copy of the B allele, and one of the b allele.

Now imagine that this woman grows up and has children with a brown hair man who also has a Bb genotype. Her eggs will be a mixture of two types, one sort containing the B allele, and one sort the b allele. Similarly, her partner will produce a mix of two types of sperm containing one or the other of these two alleles. Now, when the transmitted genes are joined up in their offspring, these children have a chance of getting either brown or red hair, since they could get a genotype of BB = brown hair, Bb = brown hair or bb = red hair. In this generation, there is therefore a chance of the recessive allele showing itself in the phenotype of the children - some of them may have red hair like their grandfather.

Many traits are inherited in a more complicated way than the example above. This can happen when there are several genes involved, each contributing a small part to the end result. Tall people tend to have tall children because their children get a package of many alleles that each contribute a bit to how much they grow. However, there are not clear groups of "short people" and "tall people", like there are groups of people with brown or red hair. This is because of the large number of genes involved; this makes the trait very variable and people are of many different heights. Unlike common belief, the green/blue eye traits are also inherited in this complex inheritance model. Inheritance can also be complicated when the trait depends on the interaction between genetics and the environment. This is quite common, for example, if a child does not eat enough nutritious food this will not change traits like eye color, but it could stunt their growth.

Inherited diseases

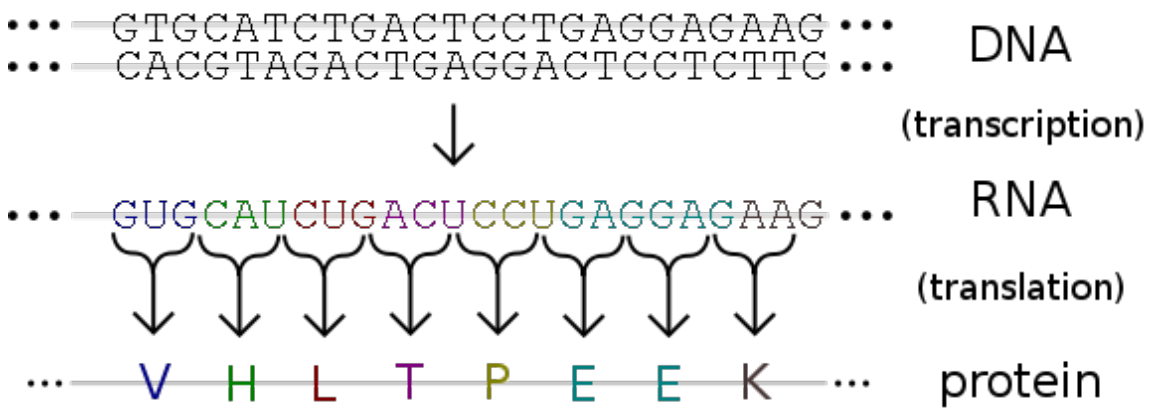
Some diseases are hereditary and run in families; others, such as infectious diseases, are caused by the environment. Other diseases come from a combination of genes and the environment. Genetic disorders are diseases that are caused by a single allele of a gene and are inherited in families. These include Huntington's disease, Cystic fibrosis or Duchenne muscular dystrophy. Cystic fibrosis, for example, is caused by mutations in a single gene called *CFTR* and is inherited as a recessive trait.

Other diseases are influenced by genetics, but the genes a person gets from their parents only change their risk of getting a disease. Most of these diseases are inherited in a complex way, with either multiple genes involved, or coming from both genes and the environment. As an example, the risk of breast cancer is 50 times higher in the families most at risk, compared to the families least at risk. This variation is probably due to a large number of alleles, each changing the risk a little bit. Several of the genes have been identified, such as *BRCA1* and *BRCA2*, but not all of them. However, although some of the risk is genetic, the risk of this cancer is also increased by being overweight, drinking a lot of alcohol and not exercising. A woman's risk of breast cancer therefore comes from a large number of alleles interacting with her environment, so it is very hard to predict.

How genes work

Genes make proteins

The function of genes is to provide the information needed to make molecules called proteins in cells. Cells are the smallest independent parts of organisms: the human body contains about 100 trillion cells, while very small organisms like bacteria are just one single cell. A cell is like a miniature and very complex factory that can make all the parts needed to produce a copy of itself, which happens when cells divide. There is a simple division of labor in cells - genes give instructions and proteins carry out these instructions, tasks like building a new copy of a cell, or repairing damage. Each type of protein is a specialist that only does one job, so if a cell needs to do something new, it must make a new protein to do this job. Similarly, if a cell needs to do something faster or slower than before, it makes more or less of the protein responsible. Genes tell cells what to do by telling them which proteins to make and in what amounts.

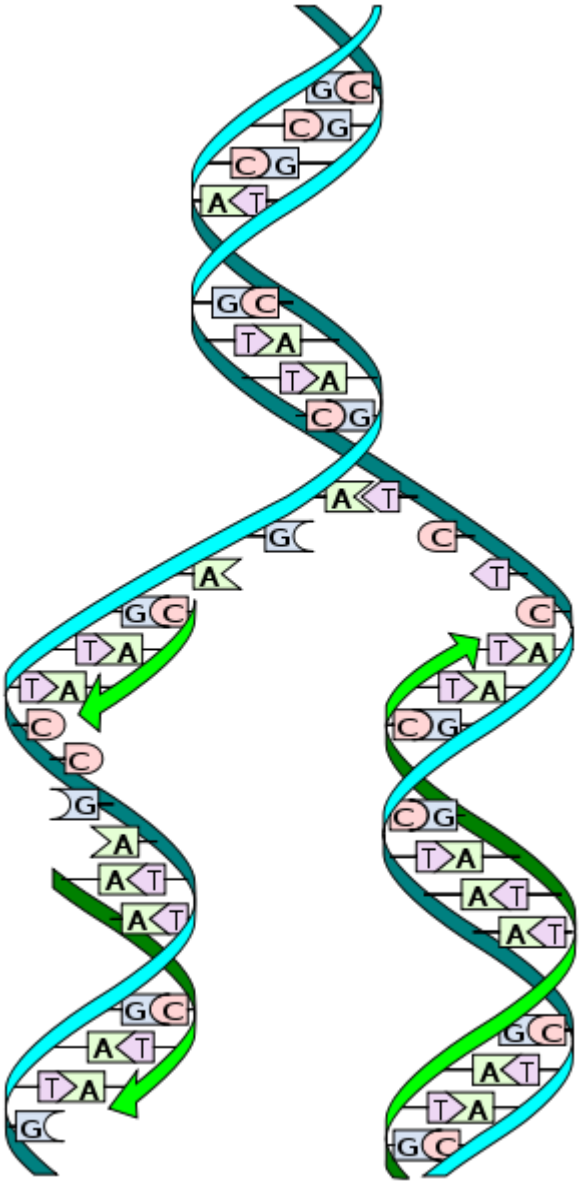


Genes are expressed by being transcribed into RNA, and this RNA then translated into protein.

Proteins are made of a chain of 20 different types of amino acid molecules. This chain folds up into a compact shape, rather like an untidy ball of string. The shape of the protein is determined by the sequence of amino acids along its chain and it is this shape that, in turn, determines what the protein will do. For example, some proteins have parts of their surface that perfectly match the shape of another molecule, allowing the protein to bind to this molecule very tightly. Other proteins are enzymes, which are like tiny machines that alter other molecules.

The information in DNA is held in the sequence of the repeating units along the DNA chain. These units are four types of nucleotides (A,T,G and C) and the sequence of nucleotides stores information in an alphabet called the genetic code. When a gene is read by a cell the DNA sequence is copied into a very similar molecule called RNA (this process is called transcription). Transcription is controlled by other DNA sequences (such as promoters), which show a cell where genes are, and control how often they are copied.

The RNA copy made from a gene is then fed through a structure called a ribosome, which translates the sequence of nucleotides in the RNA into the correct sequence of amino acids and joins these amino acids together to make a complete protein chain. The new protein then folds up into its active form. The process of moving information from the language of DNA into the language of amino acids is called translation.



DNA replication. DNA is unwound and nucleotides are matched to make two new strands.

If the sequence of the nucleotides in a gene changes, the sequence of the amino acids in the protein it produces may also change - if part of a gene is deleted, the protein produced will be shorter and may not work any more. This is the reason why different alleles of a gene can have different effects in an organism. As an example, hair color depends on

how much of a dark substance called melanin is put into the hair as it grows. If a person has a normal set of the genes involved in making melanin, they make all the proteins needed and they grow dark hair. However, if the alleles for a particular protein have different sequences and produce proteins that can't do their jobs, no melanin will be produced and the hair will be white. This condition is called albinism and the person with this condition is called an albino.

Genes are copied

Genes are copied each time a cell divides into two new cells. The process that copies DNA is called DNA replication. It is through a similar process that a child inherits genes from its parents, when a copy from the mother is mixed with a copy from the father.

DNA can be copied very easily and accurately because each piece of DNA can direct the creation of a new copy of its information. This is because DNA is made of two strands that pair together like the two sides of a zipper. The nucleotides are in the center, like the teeth in the zipper, and pair up to hold the two strands together. Importantly, the four different sorts of nucleotides are different shapes, so in order for the strands to close up properly, an **A** nucleotide must go opposite a **T** nucleotide, and a **G** opposite a **C**. This exact pairing is called base pairing.

When DNA is copied, the two strands of the old DNA are pulled apart by enzymes which move along each of the two single strands pairing up new nucleotide units and then zipping the strands closed. This produces two new pieces of DNA, each containing one strand from the old DNA and one newly made strand. This process isn't perfect and sometimes the proteins will make mistakes and put the wrong nucleotide into the strand they are building. This causes a change in the sequence of that gene. These changes in DNA sequence are called mutations. Mutations produce new alleles of genes. Sometimes these changes stop the gene from working properly, like the melanin genes discussed above. In other cases these mutations can change what the gene does or even let it do its job a little better than before. These mutations and their effects on the traits of organisms are one of the causes of evolution.

Genes and evolution

Mice with different coat colors.

A population of organisms evolves when an inherited trait becomes more common or less common over time. For instance, all the mice living on an island would be a single population of mice. If over a few generations, white mice went from being rare, to being a large part of this population, then the coat color of these mice would be evolving. In

terms of genetics, this is called a change in allele frequency—such as an increase in the frequency of the allele for white fur.

Alleles become more or less common either just by chance (in a process called genetic drift), or through natural selection. In natural selection, if an allele makes it more likely that an organism will survive and reproduce, then over time this allele will become more common. But if an allele is harmful, natural selection will make it less common. For example, if the island was getting colder each year and was covered with snow for much of the time, then the allele for white fur would become useful for the mice, since it would make them harder to see against the snow. Fewer of the white mice would be eaten by predators, so over time white mice would out-compete mice with dark fur. White fur alleles would become more common, and dark fur alleles would become more rare.

Mutations create new alleles. These alleles have new DNA sequences and can produce proteins with new properties. So if an island was populated entirely by black mice, mutations could happen creating alleles for white fur. The combination of mutations creating new alleles at random, and natural selection picking out those which are useful, causes adaptation. This is when organisms change in ways that help them to survive and reproduce.

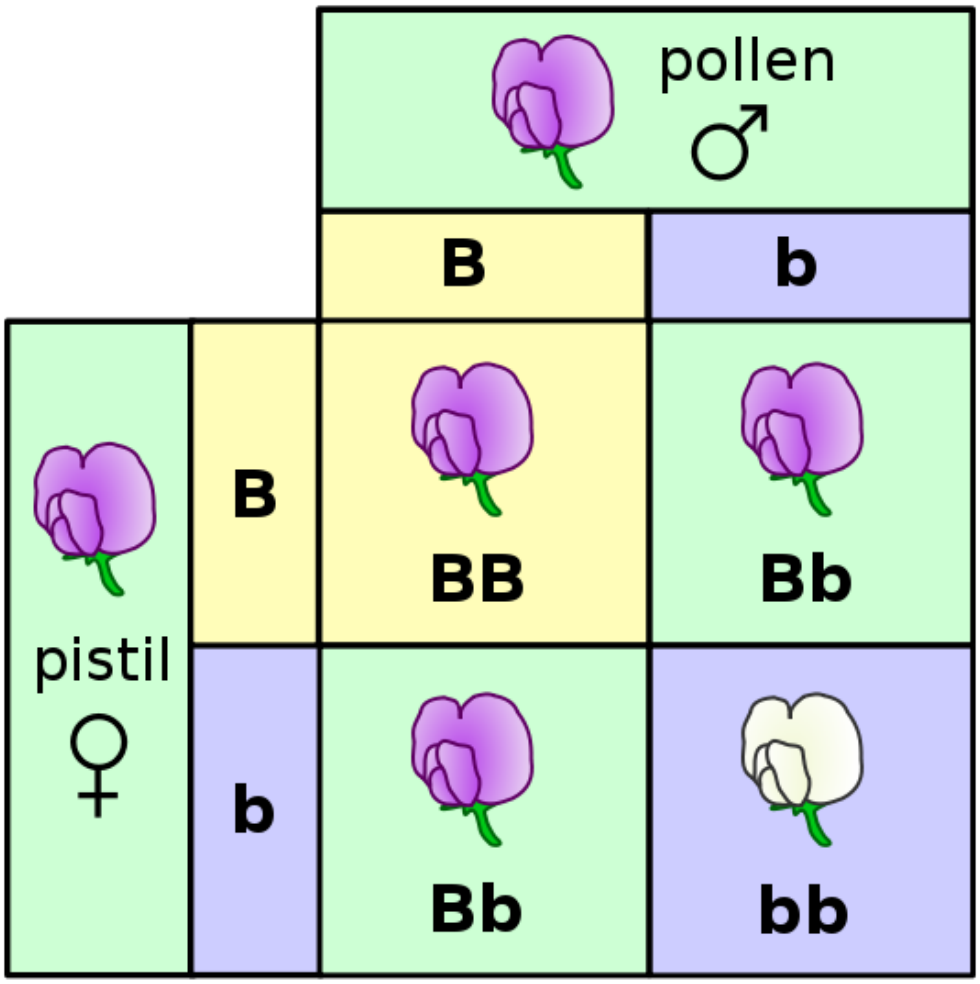
Genetic engineering

Since traits come from the genes in a cell, putting a new piece of DNA into a cell can produce a new trait. This is how genetic engineering works. For example, crop plants can be given a gene from an Arctic fish, so they produce an antifreeze protein in their leaves. This can help prevent frost damage. Other genes that can be put into crops include a natural insecticide from the bacteria *Bacillus thuringiensis*. The insecticide kills insects that eat the plants, but is harmless to people. In these plants the new genes are put into the plant before it is grown, so the genes will be in every part of the plant, including its seeds. The plant's offspring will then inherit the new genes, something which has led to concern about the spread of new traits into wild plants.

The kind of technology used in genetic engineering is also being developed to treat people with genetic disorders in an experimental medical technique called gene therapy. However, here the new gene is put in after the person has grown up and become ill, so any new gene will not be inherited by their children. Gene therapy works by trying to replace the allele that causes the disease with an allele that will work properly.

Chapter 5

Genotype



Here the relation between genotype and phenotype is illustrated, using a Punnett square, for the character of petal colour in pea. The letters B and b represent genes for colour and the pictures show the resultant flowers.

The **genotype** is the genetic makeup of a cell, an organism, or an individual (i.e. the specific allele makeup of the individual) usually with reference to a specific character under consideration. For instance, the human CFTR gene, which encodes a protein that transports chloride ions across cell membranes, can be dominant (A) as the normal version of the gene, or recessive (a) as a mutated version of the gene. It is receiving two recessive alleles that individuals will be diagnosed with cystic fibrosis. It is generally accepted that inherited genotype, transmitted epigenetic factors, and non-hereditary environmental variation contribute to the phenotype of an individual.

Non-hereditary DNA mutations are not classically understood as representing the individual's genotype. Hence, scientists and physicians sometimes talk for example about the (geno)type of a particular cancer, that is the genotype of the disease as distinct from the diseased.

Genotype and genomic sequence

One's genotype differs subtly from one's genomic sequence. A sequence is an absolute measure of base composition of an individual, or a representative of a species or group; a genotype typically implies a measurement of how an individual *differs* or is specialized within a group of individuals or a species. So typically, one refers to an individual's genotype with regard to a particular gene of interest and, in polyploid individuals, it refers to what combination of alleles the individual carries. The genetic constitution of an organism is referred to as its genotype. Such as the letters Bb.

Genotype and Mendelian inheritance

The distinction between genotype and phenotype is commonly experienced when studying family patterns for certain hereditary diseases or conditions, for example, haemophilia. Due to the diploidy of humans (and most animals), there are two alleles for any given gene. These alleles can be the same (homozygous) or different (heterozygous), depending on the individual. With a dominant allele, the offspring is guaranteed to inherit the trait in question irrespective of the second allele.

In the case of an albino with a recessive allele (aa), the phenotype depends upon the other allele (Aa, aA or AA). An affected person mating with a heterozygous individual (Aa or aA, also **carrier**) there is a 50-50 chance the offspring will be albino's (phenotype. If a heterozygote mates with another heterozygote, there is 75% chance passing the gene on and only a 25% chance that the gene will be displayed. A homozygous dominant (AA) individual has a normal phenotype and no risk of abnormal offspring. A homozygous recessive individual has an abnormal phenotype and is guaranteed to pass the abnormal gene onto offspring.

In the case of haemophilia, it is sex linked thus only carried on the X chromosome. Only females can be a **carrier** in which the abnormality is not displayed. This woman has a normal phenotype, but runs a 50-50 chance, with an unaffected partner, of passing her

abnormal gene on to her offspring. If she mated with a man with hemophilia (another carrier) there would be a 75% chance of passing on the gene.

Genotype and mathematics

Inspired by the biological concept and usefulness of genotypes, computer science employs simulated phenotypes in genetic programming and evolutionary algorithms. Such techniques can help evolve mathematical solutions to certain types of otherwise difficult problems.

Determining Genotype

Genotyping is the process of elucidating the genotype of an individual with a biological assay. Also known as a *genotypic assay*, techniques include PCR, DNA fragment analysis, allele specific oligonucleotide (ASO) probes, DNA sequencing, and nucleic acid hybridization to DNA microarrays or beads. Several common genotyping techniques include restriction fragment length polymorphism (*RFLP*), terminal restriction fragment length polymorphism (*t-RFLP*), amplified fragment length polymorphism (*AFLP*), and multiplex ligation-dependent probe amplification (*MLPA*).

DNA fragment analysis can also be used to determine such disease causing genetics aberrations as microsatellite instability (*MSI*), *trisomy* or aneuploidy, and loss of heterozygosity (*LOH*). MSI and LOH in particular have been associated with cancer cell genotypes for colon, breast and cervical cancer.

The most common chromosomal aneuploidy is a trisomy of chromosome 21 which manifests itself as Down syndrome. Current technological limitations typically allow only a fraction of an individual's genotype to be determined efficiently.

Chapter 6

Genetic Disorder

A **genetic disorder** is an illness caused by abnormalities in genes or chromosomes. While some diseases, such as cancer, are due in part to genetic disorders, they can also be caused by environmental factors. Most disorders are quite rare and affect one person in every several thousands or millions. Some types of recessive gene disorders confer an advantage in the heterozygous state in certain environments.

Single gene disorder

Prevalence of some single gene disorders

Disorder	Prevalence (approximate)
Autosomal dominant	
Familial hypercholesterolemia	1 in 500
Polycystic kidney disease	1 in 1250
Hereditary spherocytosis	1 in 5,000
Marfan syndrome	1 in 4,000
Huntington's disease	1 in 15,000
Autosomal recessive	
Sickle cell anemia	1 in 625 (African Americans)
Cystic fibrosis	1 in 2,000 (Caucasians)
Tay-Sachs disease	1 in 3,000 (American Jews)
Phenylketonuria	1 in 12,000
Mucopolysaccharidoses	1 in 25,000
Glycogen storage diseases	1 in 50,000

Galactosemia	1 in 57,000
X-linked	
Duchenne muscular dystrophy	1 in 7,000
Hemophilia	1 in 10,000

A **single gene disorder** is the result of a single mutated gene. There are estimated to be over 4000 human diseases caused by single gene defects. Single gene disorders can be passed on to subsequent generations in several ways. Genomic imprinting and uniparental disomy, however, may affect inheritance patterns. The divisions between recessive and dominant types are not "hard and fast" although the divisions between autosomal and X-linked types are (since the latter types are distinguished purely based on the chromosomal location of the gene). For example, achondroplasia is typically considered a dominant disorder, but children with two genes for achondroplasia have a severe skeletal disorder that achondroplasics could be viewed as carriers of. Sickle-cell anemia is also considered a recessive condition, but heterozygous carriers have increased resistance to malaria in early childhood, which could be described as a related dominant condition. When a couple where one partner or both are sufferers or carriers of a single gene disorder and wish to have a child they can do so through IVF which means they can then have PGD (pre-implantation genetic diagnosis) to check whether the fertilised egg has had the genetic disorder passed on.

Autosomal dominant

Only one mutated copy of the gene will be necessary for a person to be affected by an autosomal dominant disorder. Each affected person usually has one affected parent. There is a 50% chance that a child will inherit the mutated gene. Conditions that are autosomal dominant sometimes have reduced penetrance, which means that although only one mutated copy is needed, not all individuals who inherit that mutation go on to develop the disease. Examples of this type of disorder are Huntington's disease, neurofibromatosis type 1, Marfan syndrome, hereditary nonpolyposis colorectal cancer, and hereditary multiple exostoses, which is a highly penetrant autosomal dominant disorder. Birth defects are also called congenital anomalies.

Autosomal recessive

Two copies of the gene must be mutated for a person to be affected by an autosomal recessive disorder. An affected person usually has unaffected parents who each carry a single copy of the mutated gene (and are referred to as carriers). Two unaffected people who each carry one copy of the mutated gene have a 25% chance with each pregnancy of having a child affected by the disorder. Examples of this type of disorder are cystic fibrosis, sickle-cell disease, Tay-Sachs disease, Niemann-Pick disease, spinal muscular atrophy, and Roberts syndrome. Certain other phenotypes, such as wet versus dry earwax, are also determined in an autosomal recessive fashion.

X-linked dominant

X-linked dominant disorders are caused by mutations in genes on the X chromosome. Only a few disorders have this inheritance pattern, with a prime example being X-linked hypophosphatemic rickets. Males and females are both affected in these disorders, with males typically being more severely affected than females. Some X-linked dominant conditions such as Rett syndrome, incontinentia pigmenti type 2 and Aicardi syndrome are usually fatal in males either in utero or shortly after birth, and are therefore predominantly seen in females. Exceptions to this finding are extremely rare cases in which boys with Klinefelter syndrome (47,XXY) also inherit an X-linked dominant condition and exhibit symptoms more similar to those of a female in terms of disease severity. The chance of passing on an X-linked dominant disorder differs between men and women. The sons of a man with an X-linked dominant disorder will all be unaffected (since they receive their father's Y chromosome), and his daughters will all inherit the condition. A woman with an X-linked dominant disorder has a 50% chance of having an affected fetus with each pregnancy, although it should be noted that in cases such as incontinentia pigmenti only female offspring are generally viable. In addition, although these conditions do not alter fertility per se, individuals with Rett syndrome or Aicardi syndrome rarely reproduce.

X-linked recessive

X-linked recessive conditions are also caused by mutations in genes on the X chromosome. Males are more frequently affected than females, and the chance of passing on the disorder differs between men and women. The sons of a man with an X-linked recessive disorder will not be affected, and his daughters will carry one copy of the mutated gene. A woman who is a carrier of an X-linked recessive disorder (X^RX^r) has a 50% chance of having sons who are affected and a 50% chance of having daughters who carry one copy of the mutated gene and are therefore carriers. X-linked recessive conditions include the serious diseases Hemophilia A, Duchenne muscular dystrophy, and Lesch-Nyhan syndrome as well as common and less serious conditions such as male pattern baldness and red-green color blindness. X-linked recessive conditions can sometimes manifest in females due to skewed X-inactivation or monosomy X (Turner syndrome).

Y-linked

Y-linked disorders are caused by mutations on the Y chromosome. Because males inherit a Y chromosome from their fathers, *every* son of an affected father will be affected. Because females inherit an X chromosome from their fathers, female offspring of affected fathers are *never* affected.

Since the Y chromosome is relatively small and contains very few genes, there are relatively few Y-linked disorders. Often the symptoms include infertility, which may be circumvented with the help of some fertility treatments. Examples are male infertility and hypertrichosis pinnae.

Mitochondrial

This type of inheritance, also known as maternal inheritance, applies to genes in mitochondrial DNA. Because only egg cells contribute mitochondria to the developing embryo, only mothers can pass on mitochondrial conditions to their children. An example of this type of disorder is Leber's hereditary optic neuropathy.

Multifactorial and polygenic (complex) disorders

Genetic disorders may also be complex, multifactorial, or polygenic, meaning that they are likely associated with the effects of multiple genes in combination with lifestyle and environmental factors. Multifactorial disorders include heart disease and diabetes. Although complex disorders often cluster in families, they do not have a clear-cut pattern of inheritance. This makes it difficult to determine a person's risk of inheriting or passing on these disorders. Complex disorders are also difficult to study and treat because the specific factors that cause most of these disorders have not yet been identified.

On a pedigree, polygenic diseases do tend to "run in families", but the inheritance does not fit simple patterns as with Mendelian diseases. But this does not mean that the genes cannot eventually be located and studied. There is also a strong environmental component to many of them (e.g., blood pressure).

- asthma
- autoimmune diseases such as multiple sclerosis
- cancers
- ciliopathies
- cleft palate
- diabetes
- heart disease
- hypertension
- inflammatory bowel disease
- mental retardation
- mood disorder
- obesity
- refractive error
- infertility

Prognosis and treatment of genetic disorders

Genetic disorders rarely have effective treatments, though gene therapy is being tested as a possible treatment for some genetic diseases, including some forms of retinitis pigmentosa

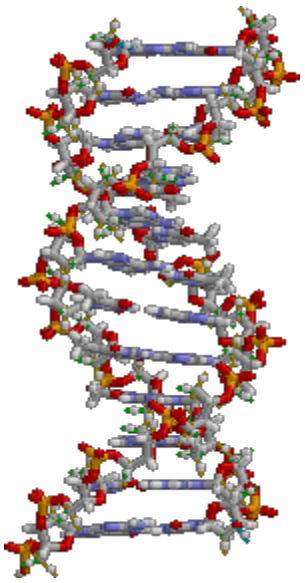
- Gauchers disease is a genetic disease affecting metabolism. It is more treatable then most other genetic diseases, and can be treated with enzyme replacement therapy, medication miglustat, and bone marrow transplantion.

Chapter 7

Heredity

Heredity is the passing of traits to offspring (from its parent or ancestors). This is the process by which an offspring cell or organism acquires or becomes predisposed to the characteristics of its parent cell or organism. Through heredity, variations exhibited by individuals can accumulate and cause some species to evolve. The study of heredity in biology is called genetics, which includes the field of epigenetics.

Overview



DNA structure. Bases are in the centre, surrounded by phosphate–sugar chains in a double helix.

In humans, eye color is an inherited characteristic and an individual might inherit the "brown-eye trait" from one of the parents. Inherited traits are controlled by genes and the complete set of genes within an organism's genome is called its genotype.

The complete set of observable traits that make up the structure and behaviour of an organism is called its phenotype. These traits come from the interaction of its genotype with the environment. As a result, many aspects of an organism's phenotype are not inherited. For example, suntanned skin comes from the interaction between a person's genotype and sunlight; thus, suntans are not passed on to people's children. However, some people tan more easily than others, due to differences in their genotype; a striking example are people with the inherited trait of albinism, who do not tan at all and are very sensitive to sunburn.

Heritable traits are known to be passed from one generation to the next via DNA, a molecule that encodes genetic information. DNA is a long polymer composed of four types of bases. The sequence of bases along a particular DNA molecule specify the genetic information, in a manner similar to a sequence of letters spelling out a sentence. Before a cell divides, the DNA is copied, so that each of the resulting two cells will inherit the DNA sequence. Portions of a DNA molecule that specify a single functional unit are called genes; different genes have different sequences of bases. Within cells, the long strands of DNA form condensed structures called chromosomes. The specific location of a DNA sequence within a chromosome is known as a locus. If the DNA sequence at a locus varies between individuals, the different forms of this sequence are called alleles. DNA sequences can change through mutations, producing new alleles. If a mutation occurs within a gene, the new allele may affect the trait that the gene controls, altering the phenotype of the organism.

However, while this simple correspondence between an allele and a trait works in some cases, most traits are more complex and are controlled by multiple interacting genes within and among organisms. Developmental biologists suggest that complex interactions in genetic networks and communication among cells can lead to heritable variations that may underlay some of the mechanics in developmental plasticity and canalization.

Recent findings have confirmed important examples of heritable changes that cannot be explained by direct agency of the DNA molecule. These phenomena are classed as epigenetic inheritance systems that are causally or independently evolving over genes. Research into modes and mechanisms of epigenetic inheritance is still in its scientific infancy, however, this area of research has attracted much recent activity as it broadens the scope of heritability and evolutionary biology in general. DNA methylation marking chromatin, self-sustaining metabolic loops, gene silencing by RNA interference, and the three dimensional conformation of proteins (such as prions) are areas where epigenetic inheritance systems have been discovered at the organismic level. Heritability may also occur at even larger scales. For example, ecological inheritance through the process of niche construction is defined by the regular and repeated activities of organisms in their environment. This generates a legacy of effect that modifies and feeds back into the selection regime of subsequent generations. Descendants inherit genes plus environmental characteristics generated by the ecological actions of ancestors. Other examples of heritability in evolution that are not under the direct control of genes include the inheritance of cultural traits, group heritability, and symbiogenesis. These examples of heritability that operate above the gene are covered broadly under the title of

multilevel or hierarchical selection, which has been a subject of intense debate in the history of evolutionary science.

Relation to theory of evolution

When Charles Darwin proposed his theory of evolution in 1859, one of its major problems was the lack of an underlying mechanism for heredity. Darwin believed in a mix of blending inheritance and the inheritance of acquired traits (pangenesis). Blending inheritance would lead to uniformity across populations in only a few generations and thus would remove variation from a population on which natural selection could act. This led to Darwin adopting some Lamarckian ideas in later editions of *On the Origin of Species* and his later biological works. Darwin's primary approach to heredity was to outline how it appeared to work (noticing that traits could be inherited which were not expressed explicitly in the parent at the time of reproduction, that certain traits could be sex-linked, etc.) rather than suggesting mechanisms.

Darwin's initial model of heredity was adopted by, and then heavily modified by, his cousin Francis Galton, who laid the framework for the biometric school of heredity. Galton rejected the aspects of Darwin's pangenesis model which relied on acquired traits.

The inheritance of acquired traits was shown to have little basis in the 1880s when August Weismann cut the tails off many generations of mice and found that their offspring continued to develop tails.

History

The ancients had a variety of ideas about heredity: Theophrastus proposed that male flowers caused female flowers to ripen; Hippocrates speculated that "seeds" were produced by various body parts and transmitted to offspring at the time of conception, and Aristotle thought that male and female semen mixed at conception. Aeschylus, in 458 BC, proposed the male as the parent, with the female as a "nurse for the young life sown within her."

Various hereditary mechanisms were envisaged without being properly tested or quantified. These included blending inheritance and the inheritance of acquired traits. Nevertheless, people were able to develop domestic breeds of animals as well as crops through artificial selection. The inheritance of acquired traits also formed a part of early Lamarckian ideas on evolution.

In the 9th century AD, the Afro-Arab writer Al-Jahiz considered the effects of the environment on the likelihood of an animal to survive, and first described the struggle for existence. His ideas on the struggle for existence in the *Book of Animals* have been summarized as follows:

Animals engage in a struggle for existence; for resources, to avoid being eaten and to breed. Environmental factors influence organisms to develop new characteristics to

ensure survival, thus transforming into new species. Animals that survive to breed can pass on their successful characteristics to offspring.

In 1000 AD, the Arab physician, Abu al-Qasim al-Zahrawi (known as Albucasis in the West), wrote the first clear description of haemophilia, a hereditary genetic disorder, in his *Al-Tasrif*. In this work, he wrote of an Andalusian family whose males died of bleeding after minor injuries.

During the 18th century, Dutch microscopist Antonie van Leeuwenhoek (1632–1723) discovered "animalcules" in the sperm of humans and other animals. Some scientists speculated they saw a "little man" (homunculus) inside each sperm. These scientists formed a school of thought known as the "spermists." They contended the only contributions of the female to the next generation were the womb in which the homunculus grew, and prenatal influences of the womb. An opposing school of thought, the ovists, believed that the future human was in the egg, and that sperm merely stimulated the growth of the egg. Ovists thought women carried eggs containing boy and girl children, and that the gender of the offspring was determined well before conception.

Gregor Mendel: father of modern genetics

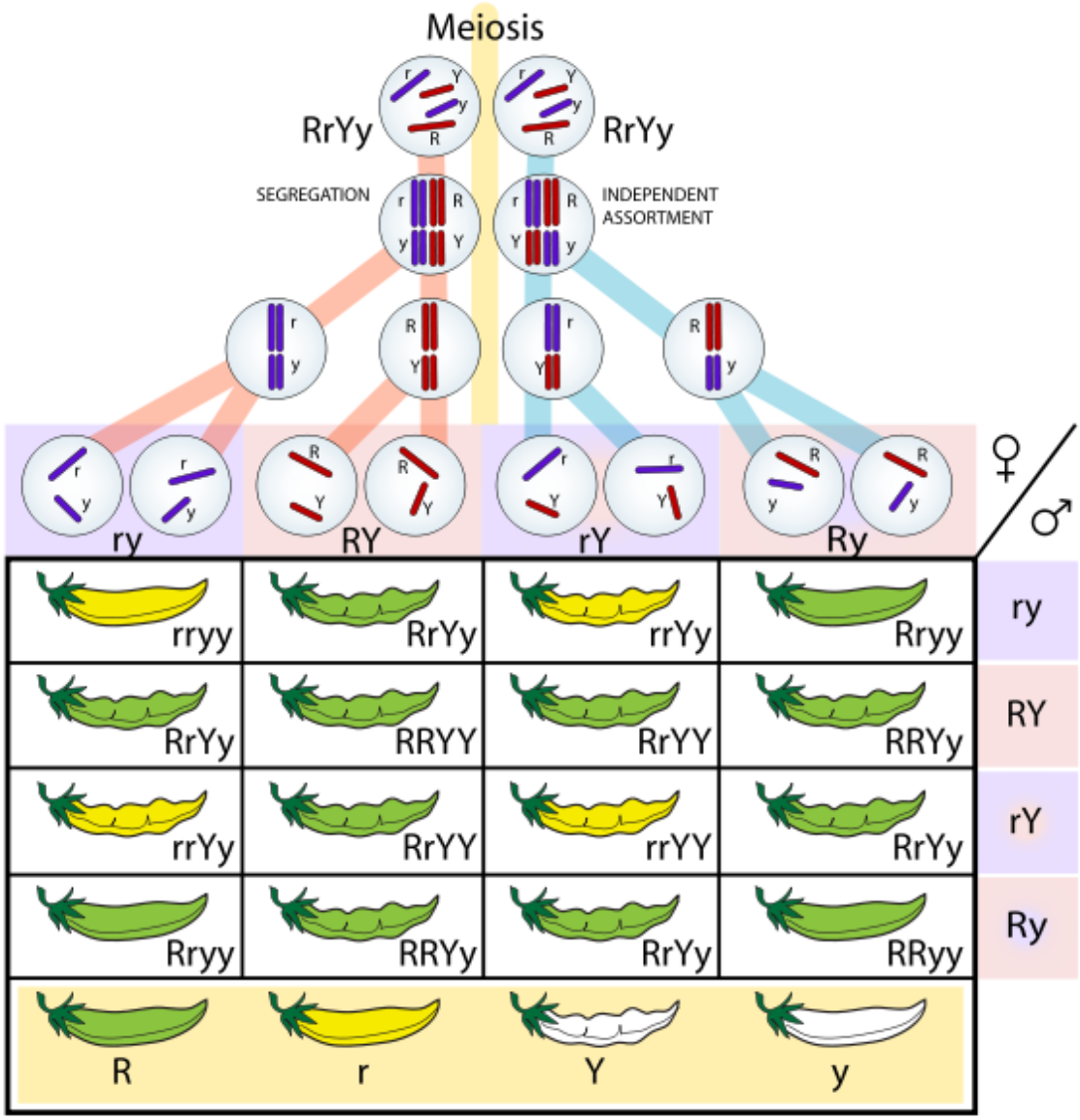


Table showing how the genes exchange according to segregation or independent assortment during meiosis and how this translates into Mendel's laws

The idea of particulate inheritance of genes can be attributed to the Moravian monk Gregor Mendel who published his work on pea plants in 1865. However, his work was not widely known and was rediscovered in 1901. It was initially assumed the Mendelian inheritance only accounted for large (qualitative) differences, such as those seen by Mendel in his pea plants—and the idea of additive effect of (quantitative) genes was not realised until R.A. Fisher's (1918) paper, "The Correlation Between Relatives on the Supposition of Mendelian Inheritance."

Modern development of genetics and heredity

In the 1930s, work by Fisher and others resulted in a combination of Mendelian and biometric schools into the modern evolutionary synthesis. The modern synthesis bridged the gap between experimental geneticists and naturalists; and between both and palaeontologists, stating that:

1. All evolutionary phenomena can be explained in a way consistent with known genetic mechanisms and the observational evidence of naturalists.
2. Evolution is gradual: small genetic changes, recombination ordered by natural selection. Discontinuities amongst species (or other taxa) are explained as originating gradually through geographical separation and extinction (not saltation).
3. Selection is overwhelmingly the main mechanism of change; even slight advantages are important when continued. The object of selection is the phenotype in its surrounding environment. The role of genetic drift is equivocal; though strongly supported initially by Dobzhansky, it was downgraded later as results from ecological genetics were obtained.
4. The primacy of population thinking: the genetic diversity carried in natural populations is a key factor in evolution. The strength of natural selection in the wild was greater than expected; the effect of ecological factors such as niche occupation and the significance of barriers to gene flow are all important.
5. In palaeontology, the ability to explain historical observations by extrapolation from micro to macro-evolution is proposed. Historical contingency means explanations at different levels may exist. Gradualism does not mean constant rate of change.

The idea that speciation occurs after populations are reproductively isolated has been much debated. In plants, polyploidy must be included in any view of speciation. Formulations such as 'evolution consists primarily of changes in the frequencies of alleles between one generation and another' were proposed rather later. The traditional view is that developmental biology ('evo-devo') played little part in the synthesis, but an account of Gavin de Beer's work by Stephen Jay Gould suggests he may be an exception.

Almost all aspects of the synthesis have been challenged at times, with varying degrees of success. There is no doubt, however, that the synthesis was a great landmark in evolutionary biology. It cleared up many confusions, and was directly responsible for stimulating a great deal of research in the post-World War II era.

Trofim Lysenko however caused a backlash of what is now called Lysenkoism in the Soviet Union when he emphasised Lamarckian ideas on the inheritance of acquired traits. This movement affected agricultural research and led to food shortages in the 1960s and seriously affected the USSR.

Types of heredity

Dominant and recessive

An allele is said to be dominant if it is always expressed in the appearance of an organism (phenotype). For example, in peas the allele for green pods, G, is dominant to that for yellow pods, g. Since the allele for green pods is dominant, pea plants with the pair of alleles GG (homozygote) or Gg (heterozygote) will have green pods. The allele for yellow pods is recessive. The effects of this allele are only seen when it is present in both chromosomes, gg (homozygote).

The description of a mode of biological inheritance consists of three main categories:

1. Number of involved loci

- Monogenetic (also called "simple") – one locus
- Oligogenetic – few loci
- Polygenetic – many loci

2. Involved chromosomes

- Autosomal – loci are not situated on a sex chromosome
- Gonosomal – loci are situated on a sex chromosome
    - X-chromosomal – loci are situated on the X chromosome (the more common case)
    - Y-chromosomal – loci are situated on the Y chromosome
- Mitochondrial – loci are situated on the mitochondrial DNA

3. Correlation genotype–phenotype

- Dominant
- Intermediate (also called "codominant")
- Recessive

These three categories are part of every exact description of a mode of inheritance in the above order. Additionally, more specifications may be added as follows:

4. Coincidental and environmental interactions

- Penetrance
    - Complete
    - Incomplete (percentual number)
- Expressivity
    - Invariable
    - Variable

- Heritability (in polygenetic and sometimes also in oligogenetic modes of inheritance)
- Maternal or paternal imprinting phenomena

5. Sex-linked interactions

- Sex-linked inheritance (gonosomal loci)
- Sex-limited phenotype expression (e.g., cryptorchism)
- Inheritance through the maternal line (in case of mitochondrial DNA loci)
- Inheritance through the paternal line (in case of Y-chromosomal loci)

6. Locus–locus interactions

- Epistasis with other loci (e.g., overdominance)
- Gene coupling with other loci
- Homozygotous lethal factors
- Semi-lethal factors

Determination and description of a mode of inheritance is primarily achieved through statistical analysis of pedigree data. In case the involved loci are known, methods of molecular genetics can also be employed.