

Genetics

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Gene mutations

A gene mutation is a permanent change in the DNA sequence that makes up a gene. Gene mutations occur in two ways:

1. **Hereditary mutations** are inherited from a parent, are present from birth, and are passed on to the next generation.
2. **Acquired mutations** spontaneously develop during a person's lifetime, may be present at birth if it occurred prenatally, and may be passed on to the next generation only if the mutation affects the egg or sperm.

Hereditary genetic disorders

In hereditary genetic disorders, a mutated gene (one with changes in the DNA) that causes disease is passed down through generations of a family. Genes carry the instructions (DNA) to build the proteins your body needs, and changes in the genetic code can alter the proteins that are made, which can lead to disease.

There are three types of genetic disorders:

- **Single gene disorders** are caused by a mutation in a single gene. The mutation may be present on one or both chromosomes (one chromosome inherited from each parent). Sickle cell disease, cystic fibrosis and gCJD are examples of single gene disorders.
- **Chromosome disorders** are caused by an excess or deficiency of the genes that are located on chromosomes, or structural changes within chromosomes. Down syndrome, for example, is caused by an extra copy of chromosome 21, but no individual gene on the chromosome is abnormal.
- **Multifactorial inheritance disorders** are caused by a combination of small variations in genes, often in concert with environmental factors. Most genetic disorders are multifactorial inheritance disorders. Heart disease and most cancers are examples of these disorders. Both sporadic and variant CJD appear to have a multifactorial interaction of genes and environment.

Hereditary human prion disease

Approximately 10-15% of people with prion disease have a genetic form. Genetic CJD is a single gene disorder due to mutations in the prion gene (PRNP) on chromosome 20. Presently more than 20 alterations in the DNA sequence in the gene have been reported. The characteristics of the disease correlate with the different mutation types.

Several other changes in the PRNP gene (called polymorphisms) do not cause prion diseases, but may affect a person's risk of developing these diseases or alter the course of the disease.

Genetic prion disease follows an autosomal dominant inheritance pattern, meaning that the genetic mutation of the PRNP gene is generally inherited from one parent. If you inherit one abnormal PRNP gene from both parents, then you will usually develop the disease. If you inherit the gene from only one of your parents, then you have a 50:50 chance of developing the disease. You also have a 50% chance of passing it on to your children. Men and women are equally likely to inherit the mutation and to be affected. Family history typically reveals the disorder in sequential generations.

To add to the complexity, a new mutation could occur in the PRNP gene, causing a sporadic case of CJD for that individual, but then becoming a hereditary genetic disorder for the next generations.

Genetic terms used in Creutzfeldt-Jakob disease (CJD)

- **allele:** One version of a gene at a given location on a chromosome
- **amino acid:** The basic building blocks of proteins; there are 20 amino acids
- **autosomal:** Refers to any of the 22 paired chromosomes, or the genes on them, that are not the X or Y sex-determining chromosomes
- **autosomal dominant:** Describes a trait or disorder which is expressed in those who have inherited only one copy of a particular gene mutation
- **base pair:** Each base pair forms a "rung of the DNA ladder"; they are the "letters" that spell out the genetic code; the molecules connecting the complementary strands of DNA or RNA
- **carrier:** An individual who has a recessive, disease-causing gene mutation on one chromosome of a pair and a normal allele at the same spot on the other matching chromosome
- **chromosome:** Physical structure consisting of a large DNA molecule organized into genes and supported by proteins called chromatin
- **codon:** In DNA or RNA, a sequence of three nucleotides that codes for a certain amino acid or signals the termination of translation (stop or termination codon)
- **codon 129:** The human prion protein (PrP) has a common polymorphism at codon 129 of the gene PRNP; this polymorphism has a strong influence on genetic susceptibility to prion diseases
- **de novo mutation:** An alteration in a gene that is present for the first time in one family member as a result of a mutation in a germ cell (egg or sperm) of one of the parents or in the fertilized egg itself
- **diagnostic testing:** Testing designed to confirm or exclude a known or suspected genetic disorder in a symptomatic individual or, prenatally in a fetus, at risk for a certain genetic condition
- **DNA:** (deoxyribonucleic acid) The molecule that encodes the genes responsible for the structure and function of an organism and allows for transmission of genetic information from one generation to the next
- **duplication:** The presence of an extra segment of DNA, resulting in redundant copies of a portion of a gene, an entire gene, or a series of genes, usually caused by unequal crossing-over during gene replication when gametes are formed in meiosis
- **false negative result:** A test result which indicates that an individual is unaffected and/or does not have a particular gene mutation when he or she is actually affected and/or does have a gene mutation; i.e., a negative test result in an affected individual
- **false positive result:** A test result which indicates that an individual is affected and/or has a certain gene mutation when he or she is actually unaffected and/or does not have the mutation; i.e.,

a positive test result in a truly unaffected individual

- **gene therapy:** Experimental treatment of a genetic disorder by replacing, supplementing, or manipulating the expression of abnormal genes with normally functioning genes
- **genetic predisposition or susceptibility:** Increased susceptibility to a particular disease due to the presence of one or more gene mutations associated with an increased risk for the disease and/or a family history that indicates an increased risk for the disease
- **genome:** The complete DNA sequence, containing all genetic information and supporting proteins, in the chromosomes of an individual or species
- **mutation:** Any alteration in a gene from its natural state; may be disease-causing or a benign, normal variant
- **nonsense mutation:** A single base pair substitution that prematurely codes for a stop in amino acid translation (stop codon)
- **novel mutation:** A distinct gene alteration that has been newly discovered; not the same as a "new" or "de novo" mutation
- **pedigree:** A diagram of the genetic relationships and medical history of a family using standard symbols and terminology
- **phenotype:** The observable physical and/or biochemical characteristics of the expression of a gene; the clinical presentation of an individual with a particular genotype
- **polymorphism:** Natural variations in a gene, DNA sequence, protein or chromosome that do not affect the functioning of the gene or cause disease and occur with fairly high frequency in the general population; some polymorphisms can change your susceptibility or resistance to disease
- **predictive testing:** Testing offered to asymptomatic individuals with a family history of a genetic disorder and a potential risk of eventually developing the disorder
- **presymptomatic testing:** Testing of an asymptomatic individual in whom the discovery of a gene mutation indicates certain development of findings related to a specific diagnosis at some future point; a negative result excludes the diagnosis
- **RNA:** (ribonucleic acid) The molecule synthesized from the DNA template; contains the sugar ribose instead of deoxyribose, which is present in DNA; three types of RNA exist, messenger RNA (mRNA), transfer RNA (tRNA), and ribosomal RNA (rRNA)
- **transcription:** The synthesis of RNA from DNA
- **translation:** The synthesis of protein from RNA