

Genetics

DNA, chromosomes and genes

Every cell in your body contains DNA (deoxyribonucleic acid). DNA, the genetic code for your body, exists as two long, paired strands spiraled into a double helix called a chromosome. DNA is like a blueprint that tells your body how to grow and develop.

Each cell contains two copies of each chromosome, one copy inherited from your mother through the egg and one from your father through the sperm. Each cell has a total of 46 chromosomes including a pair of sex chromosome that determines if you are male or female. Girls inherit two X-chromosomes. Boys inherit an X-chromosome and a Y-chromosome.

Genes are segments of DNA on a chromosome. Each gene is made up of a sequence of four different chemical bases (adenine, thymine, cytosine and guanine). The specific sequence determines which protein the cell will build, much as the specific sequence of letters determines words and sentences. Each gene contains specific instructions which help to build, regulate and maintain your body. Since you have two copies of each chromosome, you also have two copies of each gene. The two versions of the same gene are called "alleles." Sometimes the two alleles are the same, other times they are different. Changes in one or both alleles can sometimes cause the gene to not work properly.

Genetic disorders

Sometimes a change occurs on a gene that causes it to stop working properly. This change is called a mutation. Such changes in the genetic sequence can

1. Inactivate the gene and result in a loss of function,
2. Cause the gene to create abnormal forms of the normal protein or
3. Result in increased production of the normal protein.

Genetic disorders can be caused by disease-causing mutations in a single gene or changes in a number of genes combined with environmental and lifestyle factors. Genetic mutations can be acquired during your lifetime (through exposure to radiation, certain chemicals, etc.) or can be inherited from one or both of your parents.

Diseases that are caused by a change in a single gene can be inherited in one of several ways, including:

- **Autosomal dominant:** This means the condition is caused by a genetic change in just one copy of the gene. Each child of a parent with an autosomal dominant condition has a 50 percent chance of inheriting the change and also developing the condition. Huntington's disease is an example of this type of inheritance.
- **Autosomal recessive:** In contrast to autosomal dominant inheritance, conditions that are autosomal recessive are due to a change in both copies of a gene. People who have a change in just one copy of the gene are called carriers and are not themselves affected. If two people who are carriers decide to have children together, each of their children would have a 25 percent chance of being affected with the condition. In order to be affected with the condition, a child would need to inherit the genetic change from both parents. Cystic fibrosis and sickle cell anemia are examples of this type of inheritance.
- **Susceptibility gene:** Some genes predispose to a condition but do not invariably lead to the disease. Apolipoprotein E4 represents an example of a susceptibility gene for Alzheimer's disease. Susceptibility genes for frontotemporal dementia are being sought.

Some genetic disorders that "run in families" are due to multifactorial inheritance, meaning they are associated with a combination of both genetic and environmental factors. Although complex disorders such as diabetes and heart disease 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 developing the condition in the future.

Hereditary FTD

Approximately 20-50% of individuals with frontotemporal dementia (FTD) have an affected first-degree-relative. Conversely, 50-80% of individuals appear to be the first person with FTD in the family, also called sporadic or nonfamilial FTD. In these cases, other individuals in the family do not

appear to be at increased risk for developing the condition.

Familial FTD is suspected when more than one family member is affected, often in two or more generations. The underlying reason for FTD within the family is not always known. Although there does appear to be an increased chance for other family members to develop FTD, the exact risk is often difficult to assess. In these cases, it can be helpful to meet with a genetic counselor to review the family history and discuss possible implications for other family members.

Among individuals with FTD, approximately 10% have a change in a single gene (also called a mutation). Single gene causes for FTD are inherited in an autosomal dominant manner, meaning each child of an affected parent has a 50% chance of inheriting the change and also developing the condition. Currently, changes in five genes have been associated with autosomal dominant FTD. It is possible additional genes will be identified in the future. Therefore, not finding a change in one of these genes does not reduce the risk for family members to zero. At this time, changes in the following five genes have been identified:

1. **MAPT gene** on chromosome 17 that makes the protein tau,
2. **GRN gene** , also called the *PGRN* gene, on chromosome 17 that makes progranulin protein,
3. **TARDBP gene** on chromosome 1 that produces trans-active response DNA-binding protein of 43-kDa molecular weight (TDP-43),
4. **VCP gene** on chromosome 9 that codes for valosin-containing protein and
5. **CHMP2B gene** on chromosome 3 that expresses charged multivesicular body protein 2B (also known as chromatin modifying protein 2B).

Mutations in the *MAPT* and *GRN* genes on chromosome 17 are the most common genetic causes of FTD. Clinical genetic testing for *MAPT* , *GRN* and *VCP* is available. Genetic testing is usually coordinated through a genetic counselor or other genetics professional following a genetic counseling appointment and detailed three-generation pedigree.

Mutations in the MAPT gene cause the normal tau protein to clump abnormally in brain cells and the nervous system. Normally, tau helps maintain the structure of neurons and move nutrients move up and down the cell. Tau mutations can reduce the effectiveness of tau or increase the quantity of it, either of which can lead to disease. More than 50 different mutations on the tau gene have been associated with hereditary FTD. Genetic changes in the gene that codes for *GSK3B*, an enzyme that regulates tau, may explain some of the cases where people have FTD and tau inclusions but no *MAPT* mutations. *MAPT* mutations are associated with FTD, Pick's disease and frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17).

GRN mutations cause reduced progranulin production (haploinsufficiency) and increased neuronal inclusions made of TDP-43 and ubiquitin. Progranulin assists cell growth while ubiquitin helps to clear out cellular waste products and TDP-43 regulates the process of creating proteins from DNA (expression). *GRN* mutations are associated with bvFTD, PNFA and movement disorders, although people with the *GRN* mutation rarely develop [amyotrophic lateral sclerosis \(ALS\)](#). *GRN* mutations are responsible for 5-10% of all cases of FTLD and 13-25% of familial cases.

TARDBP mutations lead to accumulated inclusions consisting of ubiquitin and TDP-43 in cells of the brain and nervous system. TDP-43 is normally only found in the nucleus of a cell, but in its abnormal form is found in the working area of the cell outside the nucleus. *TARDBP* mutations have been identified in individuals with sporadic and familial ALS. Genetic testing to look for changes in the *TARDBP* gene is available on a research basis only.

Mutations in the VCP gene cause neuronal inclusions made of ubiquitin but not tau and only rarely TDP-43 or VCP. VCP is a structural protein that has a wide variety of functions, particularly in cleaning up the cell. Scientists think that perhaps the *VCP* mutation disrupts the pathway that uses ubiquitin to clean up cells. *VCP* mutations are associated with an autosomal dominant condition called inclusion body myopathy associated with Paget disease of bone (PDB) and/or FTD (IBMPFD). Approximately 80% of individuals have a family history of the condition with 20% appearing to be the first affected individual in the family. Among individuals who meet diagnostic criteria for IBMPFD, nearly 100% have an identified mutation in the *VCP* gene. No other conditions are known to be associated with changes in the *VCP* gene.

CHMP2B mutations are a rare cause of familial FTLD and may be specific to a single Danish family. *CHMP2B* encodes a protein that recycles or destroys old receptors on the cell surface. It is unclear at this point whether the mutation increases or decreases function, but it does lead to

inclusions made of ubiquitin but not TDP-43 in brain cells. *CHMP2B* mutations are associated with FTD, FTD-ALS and ALS. Currently, testing for *CHMP2B* mutations is available on a research basis only.

Because of the variability in how these diseases present, a careful analysis of family, medical and social history can help clarify whether an affected person has a sporadic or genetic form of FTD. Even when there appears to be an autosomal dominant pattern of FTD within a family, the exact genetic cause may not be known. Genetic counseling and testing is appropriate if you have concerns about your family history.