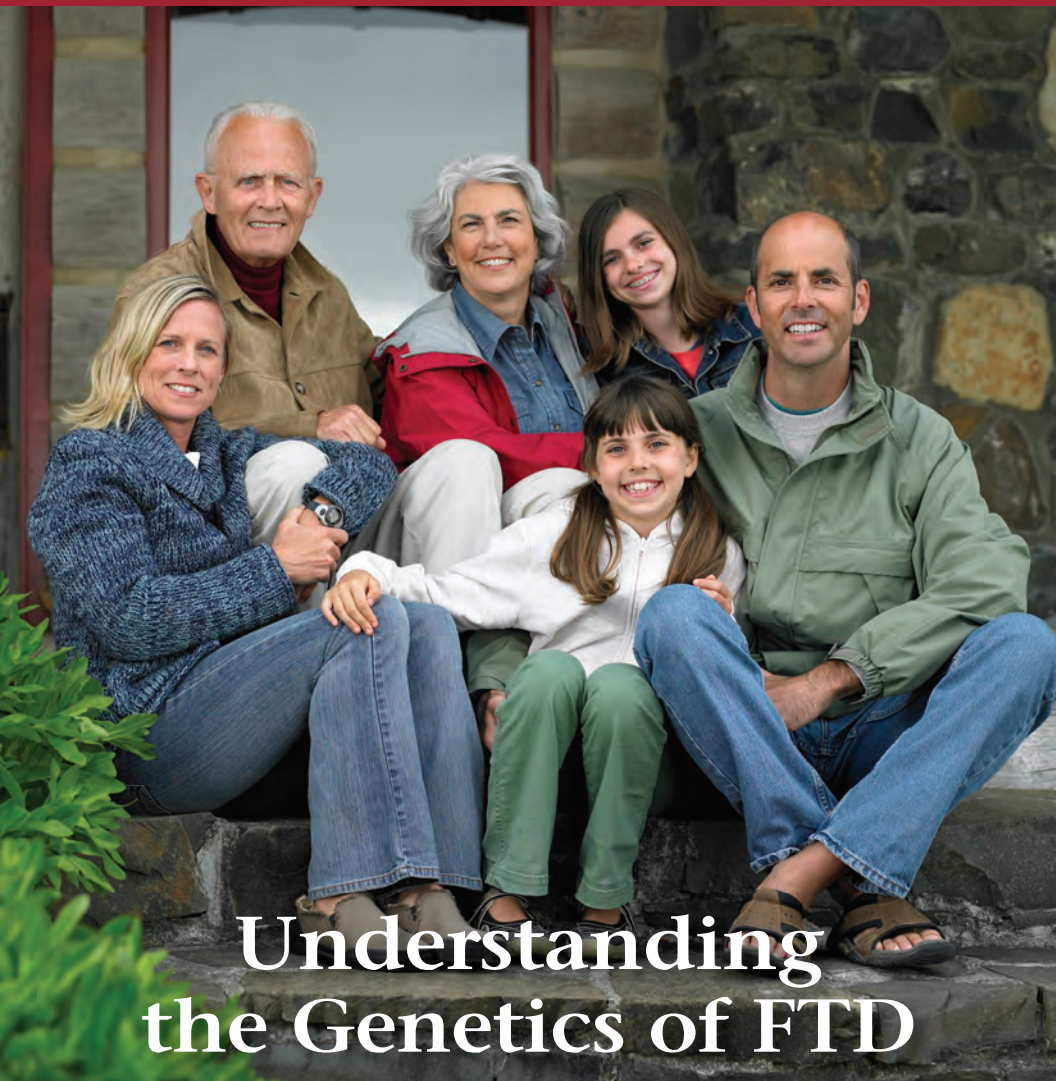




Penn Medicine



# Understanding the Genetics of FTD

*A guide for patients and their families*



The Association for  
Frontotemporal Degeneration  
Opening the gateway to help and a cure

# Acknowledgements

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# *Frontotemporal* **DEGENERATION**



*Frontotemporal degeneration (FTD) is one of the most common forms of dementia in individuals under the age of 65 years. Symptoms of FTD are caused by the progressive loss of nerve cells (neurons) in mainly the frontal and temporal regions of the brain, although other regions can be affected in some cases. The frontal lobes of the brain are involved in a number of functions, including personality, behavior, planning, reasoning, judgment, impulse control, and motor functions. The temporal lobes of the brain are involved in language, memory, and speech.*

*Despite many years of research, it is still not known what triggers the process of neurodegeneration (neuron cell death) in the brains of people who develop FTD. However, clues are gleaned from the presence of particular protein accumulations inside the diseased neurons. In a subset of patients, the root cause of those protein accumulations can be found in the individual's genetic code.*

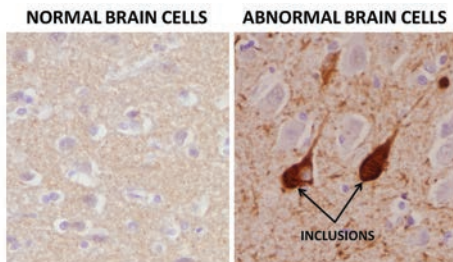
## **Symptoms**

FTD is characterized by progressive decline in behavior and/or language with an average age of onset in the mid-50s to 60s. The clinical presentations of FTD can include:

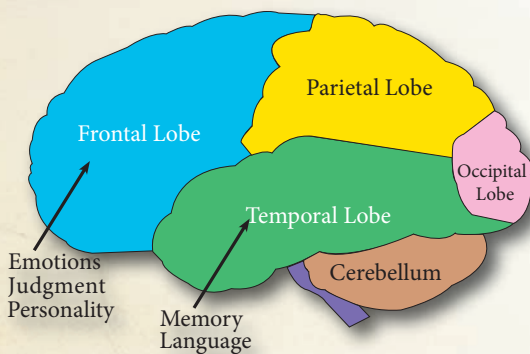
- ❖ **Behavior:** changes in personality, loss of empathy, apathy, inappropriate social behavior, and poor judgment
- ❖ **Language:** problems with expression of language or problems with word meaning

## Pathology

For any form of neurodegenerative disease, the final and definite diagnosis is made at the end of life by doing a brain autopsy. The autopsy will examine the location and severity of brain tissue loss (atrophy) as well as perform detailed microscopic examinations to detect the types of abnormal protein accumulations in the brain. In FTD, an autopsy can usually distinguish between two main types of pathology. One group is characterized by clusters of tau protein. Tau plays an important role in the structure and function of a healthy neuron, but in some forms of FTD, the tau protein begins to stick to itself and accumulates, eventually forming large clumps. These clumps are called



“inclusions.” The second group is characterized by inclusions of a protein known as TDP-43. TDP-43 is also a major disease-associated protein found at autopsy in the brains of patients with amyotrophic lateral sclerosis (ALS). A small percentage of FTD is found to have a third protein, the FUS (fused in sarcoma) protein, as the characteristic finding at autopsy. In most patients with FTD, the autopsy findings will pinpoint one of these proteins as the primary finding, but sometimes, especially in older patients, there may be an accumulation of more than one type of protein, including proteins that are associated with other neurodegenerative diseases, such as Alzheimer disease. Research is currently focused on understanding why and how these proteins accumulate, in hopes that the answer will lead to the development of FTD-specific therapies.



- ❖ **Movement:** decreased movement, muscle rigidity, parkinsonism (tremor, problems with gait and balance), or motor neuron disease/ amyotrophic lateral sclerosis (Lou Gehrig’s disease)
- ❖ **Executive:** difficulty with planning, judgment and working memory

## Treatments

Since the causes of FTD are unknown, there is no way to prevent it, slow down disease progression, or cure it. However, physicians may use medications and treatments used in similar disorders such as Alzheimer disease or psychiatric illnesses to help manage some of the symptoms.



# TYPES OF FTD

Type of FTD	Clinical Description	Description of Possible Symptoms	Type of Pathology Seen in Brain
Behavioral variant FTD (bvFTD)	Changes in personality, emotions, and/or behaviors	<ul style="list-style-type: none"> <li>✓ Hyperoral (ex. eating only sweets or a certain type of food)</li> <li>✓ Disinhibited actions (ex. making inappropriate comments)</li> <li>✓ Apathy, lack of motivation to do things</li> <li>✓ Lack of Insight (unaware of the impact of symptoms on others)</li> <li>✓ Impaired decision-making</li> </ul>	Associated with tau or AD pathology
Nonfluent or agrammatic primary progressive aphasia (PPA)	Deterioration in the ability to produce speech	<ul style="list-style-type: none"> <li>✓ Hesitant, effortful speech</li> <li>✓ Comprehension of the speech of others may be preserved in early stages</li> <li>✓ Typically lack features of bvFTD</li> </ul>	Most frequently tau protein pathology found
Semantic variant PPA	Deterioration in the ability to understand words and recognize objects.	<ul style="list-style-type: none"> <li>✓ Difficulty naming objects or recognizing the meaning of the word that names an object</li> <li>✓ May have difficulty recognizing familiar objects and faces</li> <li>✓ Fluent speech usually preserved</li> </ul>	Most frequently TDP-43 protein pathology found
Logopenic variant PPA	Deterioration in the ability to retrieve words in speech	<ul style="list-style-type: none"> <li>✓ Speech can be slow due to difficulty finding the right words</li> <li>✓ Able to understand word meaning</li> </ul>	Most often associated with Alzheimer disease (AD) pathology
Corticobasal syndrome (CBS)	Involuntary movements and/or cognitive dysfunction	<ul style="list-style-type: none"> <li>✓ Apraxia or difficulty with use of tools</li> <li>✓ Executive or social deficits</li> <li>✓ Cognitive problems such as difficulty with simple math calculations and difficulty orienting objects in space</li> </ul>	Associated with tau or AD pathology
Progressive supranuclear palsy (PSP)	Deterioration of gait and balance; eye movement abnormality	<ul style="list-style-type: none"> <li>✓ Hallmark feature is inability to move eyes up and down</li> <li>✓ May also have other features of FTD subtypes</li> </ul>	Tau protein
FTD with amyotrophic lateral sclerosis (FTD/ALS)	Same changes seen in other subtypes of FTD accompanied by deterioration of the motor neurons (also sometimes called FTD/MND)	<ul style="list-style-type: none"> <li>✓ Any symptoms associated with bvFTD or PPA</li> <li>Features of ALS can include: <ul style="list-style-type: none"> <li>✓ Muscle weakness &amp; atrophy</li> <li>✓ Muscle cramps</li> <li>✓ Difficulty swallowing</li> <li>✓ Slurred speech</li> </ul> </li> </ul>	TDP-43 protein
Pick's disease	A historic term for FTD, named for Dr. Arnold Pick	<ul style="list-style-type: none"> <li>✓ Any symptoms associated with bvFTD or PPA (see above)</li> </ul>	"Pick bodies" consisting of tau protein

# FTD & Genetics

*Genetics plays an important role in helping to better understand FTD. Even before genetic causes of FTD were first identified, doctors recognized that in some families, there was a history of multiple family members all being affected by a similar set of symptoms. These families and their participation in genetic research provided the first insights into understanding the hereditary forms of FTD. For the majority of patients with FTD, there is no family history of the disease and genetics is of little concern. However, for those individuals that do have concerns about the role that genetics plays in FTD, it is important to understand not only the specific genetic causes of FTD, but also the basic science behind why and how genes impact the risk and causes of human disease.*

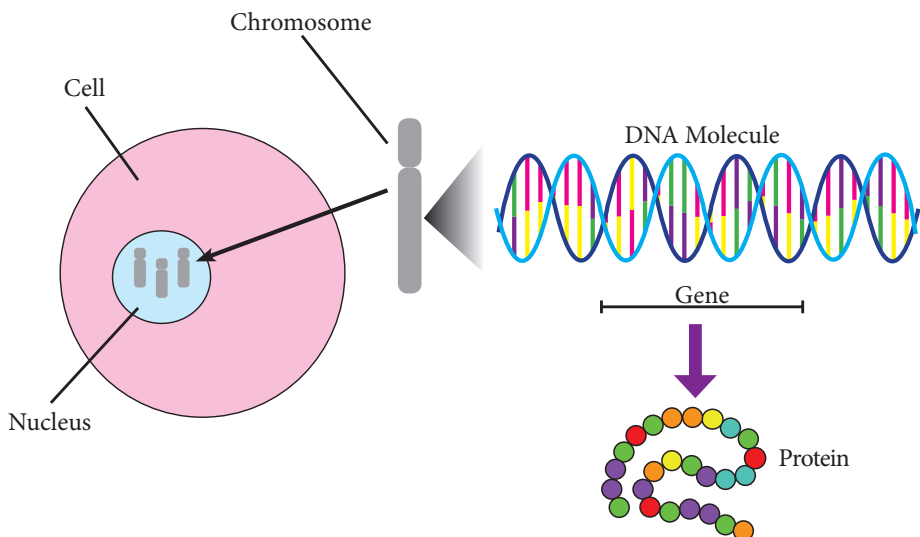
# Genetics 101

Our genetic material, DNA, is stored in every cell of our body. A DNA chain is made up of individual units called nucleotides (an alphabet of 4 letters). DNA chains are then packaged into larger units called chromosomes. Individuals have a total of 46 chromosomes. Chromosomes come in pairs, and in each pair, one chromosome comes from the father and the other from the mother. The first 22 pairs of chromosomes are the same in males and females (known as autosomes), whereas the 23rd pair determines our sex (males, XY and females, XX).

Genes are specific segments of DNA that carry the instructions for making proteins. The instructions are made up of a unique string of nucleotides that the cell knows how to read and translate into

proteins. Proteins are molecules made up of a chain of amino acid building blocks. Proteins are used by the body for maintaining its structure and function. Because our cells have two copies of every autosomal chromosome, this means we have two copies of each gene. There are many different genes present on each chromosome. Both the sequence of the DNA and the number of copies of each specific gene are important in maintaining normal function of the human body.

A mutation is a change in the DNA sequence; in other words there is a spelling mistake or typo in the instructions to make a protein. When a mutation occurs in a gene, that copy of the gene has the wrong instructions to make the protein and therefore it may



Our entire genetic code is stored in each cell of our bodies. The DNA is packaged in units called chromosomes. A gene is a specific section of DNA that contains instructions for building a protein.

make a protein that does not function correctly in the body or is not produced in sufficient quantity. There are many different types of gene mutations. For example, a mutation can occur because one or more nucleotides that encode (spell) the gene is either changed, inserted, or deleted. In some cases the insertions and deletions can be large, even involving the whole gene. In another type of mutation, a region of DNA that normally has a small number of a repeated sequence is abnormally expanded to have too many repeats, therefore affecting the function of nearby genes.

The sequence of DNA in any individual is determined using a variety of methods collectively called “molecular biology.” Not every change identified in the DNA is automatically considered to be a disease-causing mutation. Some identified DNA

changes are not harmful, they are just normal variations in the genetic code. These normal variations are called polymorphisms and they are what make each of us look and behave differently. Sometimes a variation in the DNA sequence is identified that has never been seen before so it can’t be classified as being harmful (mutation) or normal (polymorphism). There are tools and rules that researchers and doctors can use to evaluate these variations, but even so, sometimes a clear answer is not possible. In these cases the changes are “indeterminate” and are often referred to as variants of unknown significance (VOUS). When a test result is indeterminate, more work is needed to help determine whether or not that change will have a negative effect. Studying additional family members can sometimes be helpful.

# Mutations are Genetic Spelling Mistakes

When a gene is spelled correctly, the body is able to read the DNA letters in groups of three, similar to how we group letters to form words and sentences. If the gene is written correctly, the body can read the instructions.

### Correct Gene Code

Gene:     ATC  CAG  AAT  TAC  
Sentence: BUY  THE  RED  CAR

A mutation changes the type or order of DNA letters. In the example below, one of the DNA letters changed from a C to an A. This changes the word, and thus the instructions change as well.

### Incorrect Gene Code

Gene:     ATC  CAG  AAT  TAA  
Sentence: BUY  THE  RED  CAT



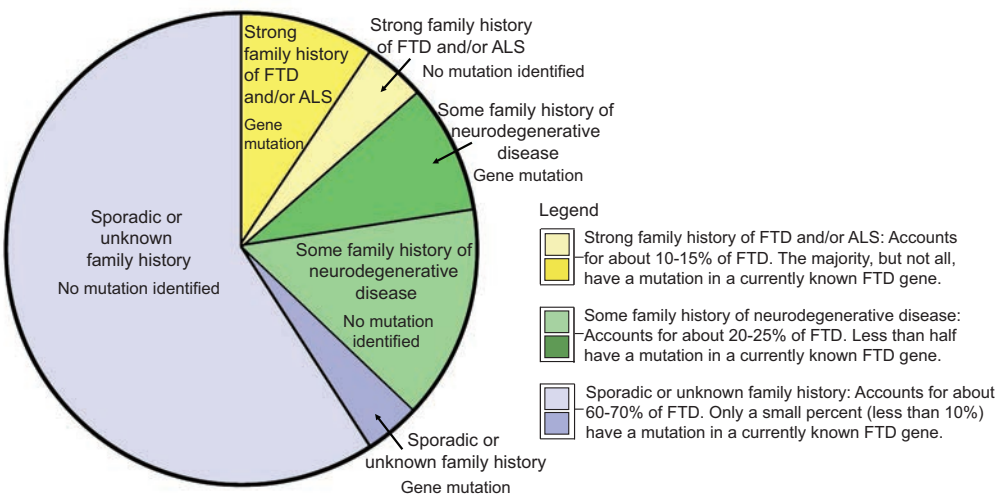
# Genes & Family History

Most cases of FTD are sporadic, meaning that there is no known family history of FTD. In some cases there is not enough information known about the neurological health of the family members to rule out a possible genetic component; this situation may be referred to as a family history of unknown significance. While a very small percentage of families that appear to be of sporadic origin or those that have family histories of unknown significance may in fact have a detectable genetic cause, the vast majority of gene mutations are found in cases with a family history of neurodegenerative disease.

Approximately 40% of individuals with FTD have a family history that includes at least one other relative who also has or had a neurodegenerative disease. In approximately 15-40% of all FTD cases, a genetic cause (e.g. a gene mutation) can be identified as the likely cause of the disease and in most cases it is an inherited mutation. The gene mutation rate can vary due to factors such as

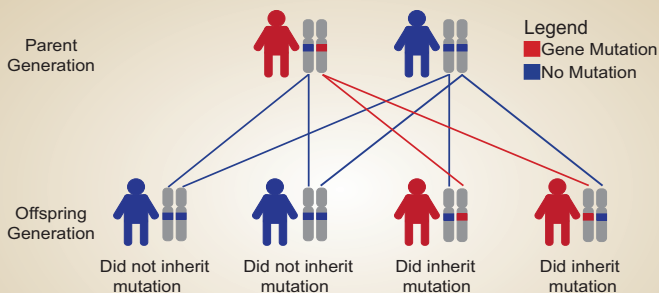
ancestry, family history, and the type of FTD (see table “Types of FTD.”) Clinically, both inherited and sporadic FTD exhibit the same symptoms, which makes evaluation of the family history the most sensitive tool for determining the likelihood of a genetic cause.

As seen in the pie chart image, families that include a history of multiple relatives with FTD and/or ALS are the most likely to have an underlying genetic cause, while cases with sporadic or unknown family histories are the least likely. There are also families that fall in the middle, meaning that there is at least one relative who has or had a related neurodegenerative disease like Alzheimer or Parkinson disease, but not a clear-cut family history of FTD or ALS in close relatives. In short, the greater the family history of FTD or an associated disease like ALS, the more likely genetics plays a role. It is important to note that not all individuals with a family history of neurodegenerative disease will have an identifiable gene mutation. This could



be because the responsible gene has not yet been identified, or because the disease is not actually due to a gene mutation. The specific genes that have been associated with FTD are discussed in detail in the next section.

## Autosomal Dominant Inheritance



This diagram shows all the possible inheritance combinations for a couple in which one parent has a gene mutation and the other parent does not. Each time the parent with the gene mutation has a child, there is a 50% chance of passing on the copy of the gene with the mutation, and a 50% chance of passing on the copy without a mutation. The chances are equal for males and females.

There are many descriptive words used in the medical setting when discussing family history. These words are often used interchangeably, making it potentially confusing to understand each term's meaning and significance. For example, the term "hereditary" indicates that a trait or disease can be directly transmitted between parent and offspring. "Familial" is a very broad term used to indicate that more than one person in a family has a trait or disease. "Familial" denotes that there is a possibility of a genetic cause due to apparent clustering of affected individuals in a family. This may occur by chance or due to a genetic mutation (hereditary cause). When a genetic counselor looks at a person's family history and draws a pedigree, they look for patterns of disease in the family and depending on the number and type of affected individuals, a "pattern of inheritance" is assigned.

A classic pattern of genetic inheritance is called autosomal dominant. "Autosomal" refers to the first 22 pairs of chromosomes, which are identical in both males and females. Therefore, both genders have an equal chance of being affected if a mutation is present on a gene in an autosomal chromosome. "Dominant"

inheritance means that only one copy of a gene has to have a mutation to cause disease. Typically, the copy of the gene with the mutation is inherited from a parent, and most individuals with an autosomal dominant condition will have a family history of the disease. A child of a person with a dominant mutation has a 50% chance of inheriting the copy of the gene with the mutation and a 50% chance of inheriting the copy of the gene without the mutation.

At this time, the only proven genetic causes of FTD fall under the pattern of autosomal dominant inheritance. It is believed that there are likely other factors, both genetic and environmental, that influence an individual's risk of developing FTD. There may be genes or specific mutations that do not directly cause FTD, but rather increase susceptibility to disease. This type of genetic finding is referred to as a risk factor. It is also likely that a combination of both genetic and environmental factors influence the risk of disease; this is often referred to as multifactorial inheritance. Research is underway to determine other risk factors that play a role in the development of FTD.

# Genes Associated with Hereditary FTD

All of the genes described in this section can cause hereditary FTD and follow the autosomal dominant pattern of inheritance (see page 9).

## **C9orf72 – Found on Chromosome 9**

- The genetic mutation on chromosome 9 was discovered in 2011, after many years of research. The function of the protein that *C9orf72* codes for is not yet understood. Individuals with the *C9orf72* mutation have abnormal accumulations of the TDP-43 protein in affected neurons.
- The *C9orf72* mutation can cause FTD, ALS, or a combination of both FTD and ALS. Research is ongoing to better understand how this mutation can lead to two different types of clinical symptoms.
- The *C9orf72* mutation is believed to be the most common genetic cause of hereditary FTD, accounting for 5-20% of all FTD cases. Most cases will have a family history of either dementia or ALS, but a small percentage of *C9orf72* cases may occur in apparently sporadic cases.
- The clinical features of patients with FTD due to *C9orf72* mutations are still being compiled, but initial reports show:
  - Average age of onset is in the 50's (range 30's to 70's)
  - Wide range of symptoms and disease progression. Patients with behavioral, language, and of course, ALS symptoms have been reported in cases of *C9orf72* mutations.
- The penetrance of *C9orf72* is not yet fully understood, but it may have reduced penetrance.
- The mutation is an expansion, or increase in size of a small section of DNA by increasing the number of

repeats. The section of DNA is referred to as a hexanucleotide repeat, which means that 6 (hexa) units of DNA (nucleotides) are repeated to such an extent as to negatively impact the gene's ability to create a functional protein.

## **Microtubule-Associated Protein Tau (*MAPT*) – Found on Chromosome 17**

- *MAPT*, discovered in 1998, was the first gene found to be associated with hereditary FTD. *MAPT* codes for the protein tau and individuals with *MAPT* mutations have abnormal accumulations of the tau protein in affected neurons.
- Mutations in *MAPT* account for 5-10% of all FTD cases. People who have FTD due to *MAPT* will typically have a family history of other relatives affected by the disease; however, family history may be unknown because of lost family members, early death, or adoption.

- Mutations in *MAPT* are associated with a wide range of FTD subtypes including bvFTD, semantic variant PPA, PSP, and CBS. The most common subtype associated with *MAPT* mutations is bvFTD.
- Average age of onset is 52 years (range: 40-60).
- Wide range of symptoms, disease progression, and age of onset both between families and within the same family.
- Most cases reported have complete penetrance.
- Mutations in the *MAPT* gene are associated with the clinical diagnosis of FTDP-17, which stands for FTD with parkinsonism on chromosome 17. The name arose because some, but not all, patients with *MAPT* mutations also developed movement symptoms, such as tremors or balance problems.

## **Progranulin (*GRN*) – Found on Chromosome 17**

- *GRN* was discovered in 2006 and codes for the protein progranulin. Individuals with *GRN* mutations have abnormal accumulations of the TDP-43 protein in affected neurons.
- Mutations in *GRN* account for 5-10% of all FTD cases. People who have FTD due to *GRN* will typically have a family history of other relatives affected by the disease; however, family history may be unknown because of lost family members, early death, or adoption.
- *GRN* mutations are associated with a wide range of FTD subtypes including bvFTD, nonfluent variant PPA, and CBS. Similar to *MAPT* mutations, bvFTD is the most common subtype associated with *GRN* mutations.
- Average age of onset is 59 years (range: 35-87 years).

- There can be a wide range of symptoms, disease progression, and age of onset both between families and within the same family.
- Reduced or age-dependent penetrance has been reported.

## **Valosin-Containing Protein (*VCP*)**

- *VCP* mutations are associated with a specific condition called inclusion body myopathy with Paget disease of the bone and FTD (IBMPFD). Inclusion body myopathy (IBM) is characterized by slowly progressive muscle weakness beginning in the teens to early adulthood. Paget disease of the bone is characterized by enlarged and misshapen bones.
- *VCP* mutations account for a very small percentage of FTD cases, but only in families with the specific constellation of symptoms as described above.
- There is a wide range of symptoms, disease progression, and age of onset both between families and among families with a *VCP* mutation. Affected individuals may develop FTD, IBM, Paget disease of the bone or any combination of the three conditions.

## **Other genes associated with rare FTD cases:**

Charged multivesicular body protein 2B (*CHMP2B*)

- Extremely rare cause of FTD, only found in a few families world-wide

TAR DNA-binding protein (*TARDBP*)

- Mutations in *TARDBP* are very rare. These mutations are more commonly associated with hereditary ALS than FTD.

Fused in sarcoma (*FUS*)

- Mutations in *FUS* are very rare. These mutations are more commonly associated with hereditary ALS than FTD.

# Genetic Testing

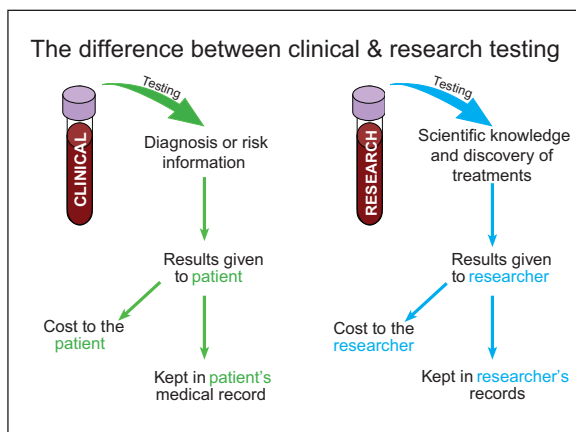


months to complete. Some insurance companies cover the costs, but policies vary regarding coverage and reimbursement for genetic testing services. Costs of clinical genetic testing can vary from a few hundred dollars to over a thousand dollars. The results of the clinical test would be reported back to the individual, as well as the doctor who ordered the test, so that the results can be recorded in the patient's medical record.

Genetic testing for FTD is performed by analyzing a DNA sample for changes in the genes known to cause FTD. This process is similar to the concept of spell-checking a document to make sure everything is correct. The DNA sample is typically obtained from blood, but sometimes other sample types, such as saliva or tissue from an autopsy can be used as the source. These sample types may be used if blood cannot be obtained, and autopsy tissue can be useful for testing a deceased affected family member.

Many FTD research centers conduct genetic research studies in which individuals can participate; however, policies vary regarding whether or not results from research tests would be returned to the individual. When participating in a genetic research study, it can be helpful to ask whether or not results are ever shared with participants. If results are shared with participants, ask when and how results might be communicated; often research testing takes much longer to conduct than clinical testing.

Clinical genetic testing is available for all of the genes associated with hereditary FTD, as well as many of the genes associated with rare FTD cases. To obtain a clinical genetic test, a doctor orders the test from a clinical laboratory that is licensed and certified to provide clinical genetic testing services. Testing of the sample by a clinical lab is usually done in 1-2 weeks, although in some cases it may take up to 1-2





If an individual definitely want the results of the genetic testing, it would be advisable to first look into clinical genetic testing, as this provides a guarantee of receiving results.

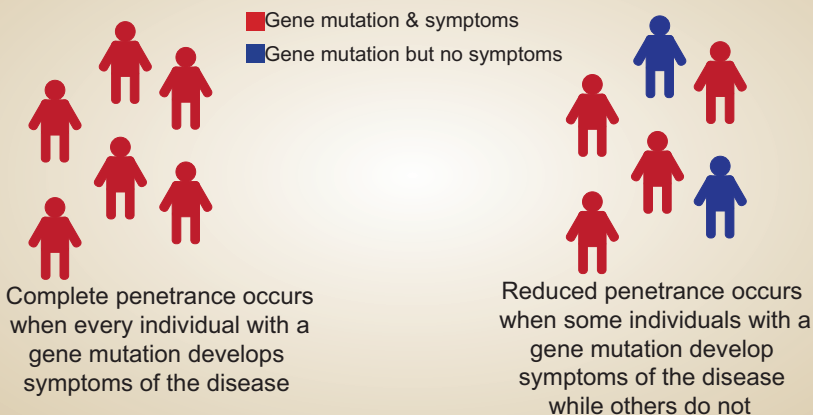
Family history provides the biggest clue as to whether genetic testing might detect a disease-causing mutation. Typically, the stronger the history of dementia and/or movement disorders in other family members, the greater the

possibility that there is a gene mutation responsible. Not every individual with a family history of disease will have a detectable mutation, but it does provide some insight regarding the possibility. There is a much lower likelihood of finding an FTD gene mutation in a sporadic family pedigree; however, sometimes mutations are found in patients that do not have a family history suggestive of hereditary disease. There

*(cont'd. on page 14)*

## The Concept of Penetrance

Penetrance refers to the proportion of individuals with a mutation in a particular gene who will actually develop symptoms of the disease.



Penetrance is an important concept to review in order to better understand the genetics of FTD. It is a term used to refer to the likelihood that a mutation in a particular gene will result in a disease. Complete penetrance occurs when every individual with a particular gene mutation develops symptoms of the disease.

Reduced penetrance occurs when some individuals with a particular gene mutation do not develop symptoms of the disease. Sometimes the term "age-dependent penetrance" is used in FTD. This means that, for an individual with a gene mutation, the likelihood of symptom onset increases with age.

are a few reasons why this may occur. Other relatives that had the mutation may have died of an unrelated cause prior to ever developing symptoms of FTD. Sometimes patients are not aware of medical information on more distant relatives that might have been affected and an assumption is made that no one else was affected. In many families, it can be difficult to get accurate medical information on aunts, uncles, and grandparents. Sometimes, it is not possible to get any family medical information because the affected individual was adopted or unsure of the identity of his or her biological father. This is why some pedigrees are classified as “unknown significance” for genetic risk assessment. Importantly, this does not mean a FTD gene mutation won’t be found, just that we don’t have enough information to assess and quantify the risk.

Any patient with FTD has the option to pursue genetic testing for the known FTD genes, although a genetic cause is more likely in those individuals who also have a family history of FTD or other neuro-degenerative diseases. For specific questions about genetic testing for FTD, it would be best to speak with a clinician familiar with genetic testing, such as a medical geneticist or genetic counselor.

## **Genetic Testing for Individuals with FTD**

If a mutation is found in a gene associated with FTD, the patient’s diagnosis would be confirmed. In some cases, it may provide insight into the progression of the disease, or even the

risk of developing other symptoms, such as symptoms of ALS in *C9orf72* mutations. The detection of a mutation would also determine the risk to other family members for inheriting the same gene mutation. At the time of this publication, there is not a specific medication or treatment that would be given to a patient based on the results of a genetic test; however, the results may prevent the patient from getting additional, unnecessary testing or prevent treating the patient for the wrong diagnosis. As the field of FTD research advances, patients with gene mutations might be candidates for new treatment options or clinical trials for the specific FTD subtype identified.

## **Genetic Testing for Family Members of Individuals with FTD**

Once a disease-causing gene mutation has been found in an individual affected by FTD, this information can be used to provide genetic testing services to other individuals in the family. Affected family members can be tested specifically for the known mutation to confirm its presence.

Unaffected family members who are at-risk of inheriting the mutation can choose to have presymptomatic genetic testing. Presymptomatic genetic testing refers to the idea of testing a currently unaffected person to determine whether or not they have inherited a known gene mutation that has been found in their family. This is also sometimes called predictive genetic testing. At this time,

*Any patient with FTD has the option to pursue genetic testing for the known FTD genes, although a genetic cause is more likely in those individuals who also have a family history of FTD or other neurodegenerative diseases.*



there are no preventative options available for FTD and therefore the decision to pursue presymptomatic genetic testing is entirely personal in nature and can be a difficult decision to make.

The purpose of the presymptomatic genetic testing process is to provide a structured, thorough, and supportive approach to the personal decision to learn one's genetic status. In order to accomplish this goal, presymptomatic genetic testing typically involves several visits. A genetic counseling session is conducted to discuss the testing decision in detail. Prior to learning one's presymptomatic testing result, it is important to consider the decision from

every possible angle, such as exploring the potential impact of the results and the risks and benefits of testing for the person being tested, their relatives, and their significant others. It is also important to explore the motivations or reasons for learning the test result, as well as the limitations of knowing this type of genetic information. Some clinics may advise that the individual have a neurology exam and/or a mental health evaluation as part of the genetic testing process.

The blood for the genetic test is drawn at a subsequent visit, allowing for a window of time during which the individual can reflect and feel absolutely sure of his or her decision to learn their genetic result.

*(cont'd. on page 16)*

The results are then disclosed during an in-person visit; not by mail or over the telephone. Most centers require the presence of a support person at this post-test visit. If the individual has not inherited the mutation, he or she is not at risk for the hereditary FTD that has affected other family members. The individual would have the same risk for neurodegenerative diseases (including FTD) as the general population. If the individual has inherited the mutation, he or she is at definite risk for developing FTD at some point in her life. It is nearly impossible to predict the exact age of onset or the type of symptoms to expect, but in some cases, the specific gene or gene mutation may provide some additional insight into the risk.

## **Genetic Testing for Family Planning Reasons**

The topic of family planning is immensely personal. For individuals with either a risk of inheriting an FTD gene mutation or individuals known to have a mutation, there may be difficult feelings and questions to face regarding starting a family of their own. Often individuals are concerned about the risk of passing the mutation on to their own children, the next generation of the family. There are reproductive technologies, such as preimplantation genetic diagnosis (PGD), that have been developed to address this concern. In PGD, the process of in vitro fertilization (IVF) is used to develop embryos. These embryos are then tested for the known family mutation, and only

embryos that did not inherit the mutation are used for implantation. PGD is only one example of available reproductive options. Other family planning options include gamete (egg or sperm) donation, adoption, natural conception, or the decision not to have children. There are clinicians, including physicians and genetic counselors, who specialize in providing pre-conception and prenatal genetic services. For individuals that desire more information and support regarding family planning, it is advisable to schedule a consultation with such a professional.



# Q & A

## FAQs for FTD Genetic Testing

The following is a guide to some of the most frequently asked questions about genetic testing for FTD.

If you have questions that are not addressed, please contact a genetic counselor or other clinician familiar with genetic testing.

### **Q: *Is there a genetic test for FTD?***

**A:** Yes, clinical genetic testing is available to look for mutations in MAPT, GRN, VCP, TARDBP, C9orf72 and FUS. A doctor or genetic counselor would be able to provide more details about the specific genetic testing options that are most appropriate based on an individual's symptoms and family history.

### **Q: *How is the genetic test done?***

**A:** Blood or saliva is collected and used to isolate a sample of DNA. This DNA sample can then be analyzed for mutations in the specific genes of interest. For individuals with an unknown genetic cause, a complete analysis for any known disease-causing genetic changes would need to be performed. However, for individuals that already know the specific gene mutation that is present in their family, the genetic test can be targeted to just check for that known family mutation.

### **Q: *Who can get genetic testing?***

**A:** Any individual with FTD who is interested in genetic testing may get tested, although a genetic cause is more likely in those individuals who also have a family history of FTD. Anyone considering genetic testing or who has a family history of FTD should seek genetic counseling prior to genetic testing. The test is most beneficial when a family member with FTD is the first person tested. Once a mutation has been identified, other members of the family may choose to be tested for the same mutation even if they don't have symptoms of the disease (presymptomatic genetic testing).

(cont'd. on page 18)





**Q: What is genetic counseling?**

**A:** The goal of genetic counseling is to help people understand more about the genetic causes of a disease and how it may affect them so they may make informed decisions. Genetic counselors can explain how genetic conditions are inherited, determine if an individual is at risk, provide options and guidance for genetic testing, and find referrals for other resources.

**Q: If I already have FTD, what would a genetic test tell me?**

**A:** Genetic testing may help define the risk of FTD for other family members. There are three possible types of genetic test results: positive, negative, and indeterminate.

**Positive:** A positive test result would mean that the individual has a disease-causing mutation. A positive test result indicates that the cause of FTD observed in the family has been found. This would further define the risk for other family members to develop FTD and allow them to pursue presymptomatic genetic testing if interested.

**Negative:** A negative test result would mean that the individual did not have a mutation in the tested gene or genes. However, a negative result would not rule out the possibility of a genetic cause entirely for the following reasons:

- Not all genes may have been tested. For example, some tests may look at only one specific gene, whereas others may test multiple genes.

- Genetic testing methods may vary. For example, some tests only look for specific mutations, whereas others look for any and all mutations in the gene.
- Not all genetic causes are known. Scientists are still working to find other genes that contribute to FTD.

**Indeterminate:** An indeterminate result means that a change was found in the genetic sequence of the gene, but the laboratory cannot yet make a clear determination as to whether it is a disease-causing mutation, a risk factor, or a normal polymorphism. Normal polymorphisms are common variations in DNA that do not cause disease. An indeterminate result is sometimes called a variant of unknown significance.

The interpretation of genetic test results can be confusing. It is recommended that anyone who has genetic testing for FTD discuss the results with a genetic counselor or another medical genetics professional.

**Q: If I have a family history of FTD, should I be tested even if I do not have symptoms?**

**A:** Testing a person who is currently not showing symptoms but who is at risk for inheriting a known family mutation is called presymptomatic (or predictive) testing. For presymptomatic testing, a mutation must have been first identified in the family so that the clinician knows the appropriate test to order and can properly interpret the results. Individuals in the same family may have differing opinions on whether or not to pursue presymp-

tomatic testing. The pursuit of pre-symptomatic testing is a very personal decision that may be confusing and emotionally difficult. Therefore, genetic counseling and psychological evaluation are usually required to help the individual throughout the testing process.

**Q: What is the difference between clinical and research genetic testing?**

**A:** The purpose of clinical genetic testing is primarily for diagnosis or prediction of disease. The testing is performed in an accredited laboratory. A report of the results is generated and will be part of the patient's official medical record. There is a charge for clinical testing, which may or may not be covered by insurance. Clinical genetic testing does not help scientists discover a cure or new treatments for FTD and the results do not affect medical management at this time (because there are no approved treatments) .

The purpose of research genetic testing is to discover and to better understand the genetic factors of FTD and how these impact the clinical presentation and pathology. In research, patient identifiers and information remain confidential and results do not become part of the patient's official medical record. There is no fee when participating in a research study, and generally results are not returned to participants. Many individuals choose to participate in research genetic testing to help advance the FTD field for the benefit of future generations. Research genetic testing may lead to a better understanding of the causes of FTD and the development of better treatments or a cure in the future.

Research testing may also identify or test for new disease-associated genes before they are available as a clinical test.

**Q: What are the risks that my child will also get FTD?**

**A:** If an individual has a mutation in one of the known FTD associated genes, there is a 50% chance of passing on the mutation and a 50% chance of NOT passing on the mutation to his/her child. This same 50/50 risk applies to every child of that individual. If the child does inherit the mutation, he or she will most likely develop symptoms of the disease at some point in adulthood, but the age of onset, severity, and type of symptoms cannot be predicted at this time.

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If an individual with FTD does not have a mutation in a known FTD gene and does not have a family history suggestive of a hereditary cause, the risk to children is much lower and is likely close to the general population risk, which is low. If an individual with FTD does not have a mutation, but does have a family history suggestive of a hereditary cause, it would be important for that family to get involved with an FTD genetic research study to try to determine whether a genetic cause or risk factor can be identified. This information would be crucial for providing accurate information to individuals possibly at-risk. As with any human disease, there may be environmental or genetic risk factors that could increase susceptibility to a disease. At this time, there are no known risk factors that could indicate a susceptibility to FTD, but ongoing research is working to better understand risk factors for FTD.

**Q: Is there protection from genetic discrimination?**

**A:** The Genetic Information Nondiscrimination Act (GINA) was signed into federal law in 2008. GINA provides legal protections against genetic discrimination in health insurance coverage and matters related to employment. GINA does not provide protections for life insurance, long-term care insurance, or disability insurance. Individuals who are considering genetic testing to determine if they are at risk for FTD are encouraged to learn more about the protections GINA does and does not provide, as well as any relevant state laws. (A guide to GINA is provided in “Helpful Links and Resources”).

**Q: If I have a genetic mutation, what can be done about it?**

**A:** At this time, we cannot change or alter an individual's genetic make-up. There are research studies looking into new technologies for treating genetic diseases, but this is currently not available as a medical treatment for FTD. Identifying a gene that causes FTD in an affected individual will not provide an answer for curing the disease, but may help prevent the patient from being treated for the wrong diagnosis. Additionally, if an unaffected person finds out that they inherited a FTD gene mutation, there is no treatment available at this time to prevent the onset of disease.

**Q: What causes a gene mutation?**

**A:** In FTD, most identified mutations are believed to have been inherited, passed from parent to child throughout many generations. There is likely an ancient ancestor who was the first person to have the mutation. In the genetics profession, this ancient ancestor is referred to as the “founder.” It can be very difficult to determine why the mutation ever occurred in the first place. Sometimes, there is a region of DNA that is less stable and prone to mistakes (i.e. mutations) being made. Our bodies have a way to detect and correct these mistakes, but sometimes not every mistake is corrected. Gene mutations due to environmental exposures can occur, but are typically restricted to the exposed person and it is unlikely that the mutation could be passed to the next generation. Gene mutations due to environmental factors have not been reported to cause FTD.

**Q:** *If I did not inherit the FTD gene mutation that has been found in my family, could it still appear in my own children?*

**A:** If an individual has been tested for a mutation that is known to affect their family, and they do not have it, they are not at risk themselves for the genetic disease and cannot pass it to their own children. Sometimes people refer to the idea of a disease “skipping a generation;” this is a common genetic myth. A truly genetic disease cannot skip through a family, as the only way to get the disease is the direct inheritance of a disease-causing mutation from parent to child. There are several reasons a genetic disease may appear to skip a generation, even though the mutation itself does not skip a generation. For example, sometimes an individual may pass away from an unrelated cause before ever developing symptoms of the disease. Also, some mutations do not always result in disease because of reduced penetrance (see page 13). In both of these scenarios, the person carrying the mutation can still pass it on to the next generation.

**Q:** *Everyone has always said that I look and act just like my mom, who has been diagnosed with FTD. Does this mean I’m more likely to also get FTD?*

**A:** Having a resemblance to a parent with FTD does not increase the risk of also developing FTD. It can be very easy to assume that if we strongly resemble one of our parents, we are destined to share many of their same fates. From a purely biological standpoint, humans are a 50/50 combination of both parents’ genes, even if a person cannot see that combination by looking in a mirror. When it comes to FTD, the only known genetic causes are inherited in an autosomal dominant manner. In this type of inheritance, there is a 50% chance of inheriting the copy of the gene with the mutation, and a 50% chance of inheriting the copy of the gene without a mutation. There is also no sex effect, in that sons are not more likely to inherit the disease from their father, nor are daughters more likely to inherit the disease from their mother.



# Glossary of FTD and Genetic Terminology

**Allele** – Another word for gene. Sometimes used when referring to different versions of a gene.

**Amino acids** - Small chemical units that link together to form a protein.

**Autosomal dominant** – A type of inheritance in which only one copy of a gene pair needs to have a mutation in order for the trait or disease to present.

**Behavioral variant FTD (bvFTD)** – The clinical term for an individual with behavioral and personality changes as the primary symptoms.

**C9orf72** – A gene of unknown function with a specific type of mutation, called a hexanucleotide repeat (a large repeat of a section of genetic material) that was recently discovered on chromosome 9. This mutation can cause hereditary FTD and/or ALS.

**CHMP2B** – A very rare cause of genetic FTD, this gene makes the charged multivesicular body protein 2b.

**Chromosome** – A unit of tightly wound and packaged DNA. Each chromosome has thousands of genes.

**Corticobasal syndrome (CBS)** – An FTD-related diagnosis that typically first presents with motor symptoms, similar to Parkinson disease. The term corticobasal degeneration (CBD) is also used, but usually is reserved for the final autopsy diagnosis of this condition.

**DNA** – Deoxyribonucleic acid. DNA is a long, double-stranded structure of genetic material.

**Frontotemporal degeneration (FTD) or Frontotemporal lobar degeneration (FTLD)** – These 2 terms are used interchangeably to refer to a spectrum of disorders that cause progressive changes in personality, behavior, and/or language.

**FUS** – The FUS gene makes the fused in sarcoma protein, which is believed to help support normal DNA functions. Mutations in this gene are a rare cause of genetic FTD.

**Gene** – A unit of DNA that carries the instructions to make a specific protein.

**Genetic testing** – The process of using laboratory techniques to analyze genetic material (DNA).

**GRN** – see Progranulin

**Microtubule-Associated Protein Tau (MAPT)** -The official name of the gene that makes the tau protein.

**Motor neuron disease** – Also known as amyotrophic lateral sclerosis (ALS) or Lou Gehrig's disease. A progressive loss of the neurons that control muscle movement. 10-15% of patients with FTD may also develop symptoms of ALS, and the two disorders have been closely linked based on results of recent research advances.

**Mutation** – A change in DNA that affects a gene's ability to make a protein. May result in disease.



**Nucleotide** – An individual chemical unit; nucleotides are the letters that make up the spelling of DNA. In DNA, the nucleotides are A, T, G, and C.

**Parkinsonism** – A term used to describe motor symptoms that are similar to those seen in Parkinson's disease, such as tremors, stiffness, and walking/balance difficulties.

**Penetrance** – The likelihood that a genetic mutation will result in disease.

**Pick's disease** – An old diagnostic term for FTD, named for the physician that first described the condition. It is also used as a pathological diagnosis for some types of FTD.

**Polymorphism** – A normal variation in the DNA code. In contrast to disease gene mutations, polymorphisms do not directly cause disease.

**Primary progressive aphasia (PPA)** – The clinical term for an individual with language difficulties as the primary symptom. There are several different types of PPA, including semantic, non-fluent/agrammatic, and logopenic.

**Progranulin** – The progranulin gene (*GRN*) makes the progranulin protein, which functions in cell growth and repair. Mutations in *GRN* cause hereditary FTD.

**Progressive supranuclear palsy (PSP)** – A rare diagnosis related to both FTD and Parkinson disease that causes both cognitive and movement difficulties, including a characteristic difficulty with eye movements.

**Protein** – A molecule that serves a specific function in the body. Proteins are made up of individual units called amino acids.

**Sequencing** – A genetic testing method in which the letters of the genetic code are read nucleotide by nucleotide and then compared to the normal sequence in humans to look for differences or misspellings.

**TARDBP** – The tar DNA-binding protein, also known as TDP-43, is made by the *TARDBP* gene. Mutations in this gene can cause genetic FTD.

**Tau** – This protein is found in about half of FTD cases at autopsy. While not all FTD cases with tau protein are genetic, there are some cases of FTD that are caused by mutations in the gene that makes the tau protein (*MAPT*).

**TDP-43** – This protein is found in about half of FTD cases and almost all cases of ALS. The function of TDP-43 in the brain and its relation to neurodegeneration is not fully understood.

**Variant of unknown significance (VOUS)** – a change in DNA that has an unknown clinical impact.

**VCP** – The valosin-containing protein is made by the *VCP* gene. Mutations in this gene cause a specific condition called inclusion body myopathy with Paget disease of the bone and FTD (IBMPFD).

## Helpful Links & Resources

### Websites

The Association for Frontotemporal Degeneration

**[www.theaftd.org](http://www.theaftd.org)**

University of Pennsylvania Center for Neurodegenerative Disease Research

**[www.med.upenn.edu/cndr](http://www.med.upenn.edu/cndr)**

National Society of Genetic Counselors

**[www.nsgc.org](http://www.nsgc.org)**

The Coalition for Genetic Fairness: A Guide to the Genetic Information Nondiscrimination Act

**[www.geneticfairness.org/ginaresource.html](http://www.geneticfairness.org/ginaresource.html)**

Genetics Home Reference

**<http://ghr.nlm.nih.gov/>**

National Institute on Aging: Frontotemporal Disorders, Information for Patients, Families and Caregivers

**[www.nia.nih.gov/alzheimers/publication/frontotemporal-disorders-information-patients-families-and-caregivers](http://www.nia.nih.gov/alzheimers/publication/frontotemporal-disorders-information-patients-families-and-caregivers)**

### Books

What if it's not Alzheimer's?  
*A Caregiver's Guide to Dementia (2008),*  
edited by Lisa Radin & Gary Radin