GENEReviews

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GRN-Related Frontotemporal Dementia

Ging-Yuek Robin Hsiung, MD, MHSc, FRCPC
Assistant Professor, Division of Neurology
Faculty of Medicine
University of British Columbia and Providence Health Care
Vancouver BC, Canada

Howard H Feldman, MD, CM, FRCPC
Professor and Head, Division of Neurology
Faculty of Medicine
University of British Columbia
Vancouver BC, Canada

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Summary

Disease characteristics. The spectrum of frontotemporal dementia associated with *GRN* (also known as *PGRN*) mutations (FTD-GRN or FTD-PGRN) includes the behavioral variant (FTD-bv), primary progressive aphasia (PPA; also known as progressive non-fluent aphasia, or PNFA), and movement disorders with extrapyramidal features such as parkinsonism and corticobasal syndrome. A broad range of clinical features both within and across families is observed. The age of onset ranges from 35 to 87 years. Behavioral disturbances are the most common early feature, followed by progressive aphasia. Impairment in executive function manifests as loss of judgment and insight. In early stages, PPA often manifests as deficits in naming, word finding, or word comprehension. In late stages, affected individuals often become mute and lose their ability to communicate. Early findings of parkinsonism include rigidity, bradykinesia or akinesia (slowing or absence of movements), limb dystonia, apraxia (loss of ability to carry out learned purposeful movements), and disequilibrium. Late motor findings may include myoclonus, dysarthria, and dysphagia. Most affected individuals eventually lose the ability to walk. Disease duration is three to 12 years.

Diagnosis/testing. Diagnosis is based on clinical findings, neuropathologic findings, and molecular genetic testing of *GRN*, the only gene associated with FTD-GRN. Molecular genetic testing is available on a clinical basis.

Management. *Treatment of manifestations:* Behavioral symptoms such as apathy, impulsivity, and compulsiveness may respond to selective serotonin reuptake inhibitors. Roaming, delusions, and hallucinations may respond to antipsychotic medications. Reports have suggested potential benefits with certain pharmacotherapy on management of FTD in general; however, evidence from randomized controlled trials is limited to the following: trazodone for treating irritability, agitation, depression, and eating disorders; galantamine for treating primary progressive aphasia; methylphenidate for treating risk-taking behavior. *Therapies under investigation:* Clinical trials are investigating efficacy of a variety of medications for treatment of FTD in general.

Genetic counseling. FTD-GRN is inherited in an autosomal dominant manner. About 95% of individuals diagnosed with FTD-GRN have an affected parent. The proportion of cases caused by *de novo* mutations is unknown but would be estimated at 5% or less. Each child of an individual with FTD-GRN has a 50% chance of inheriting the mutation. Prenatal diagnosis

for pregnancies at increased risk is possible if the disease-causing mutation in a family is known.

Diagnosis

Clinical Diagnosis

The spectrum of frontotemporal dementia associated with *GRN* (also known as *PGRN*) mutations (FTD-GRN or FTD-PGRN) includes the behavioral variant (FTD-bv), primary progressive aphasia (PPA; also known as progressive non-fluent aphasia, or PNFA), and movement disorders with extrapyramidal features such as parkinsonism and corticobasal syndrome.

The diagnostic criteria for FTD are still evolving; proposed versions have aimed at improving research classification [The Lund and Manchester Groups 1994, Neary et al 1998, McKhann et al 2001]. Strict adhesion to these criteria in the clinical setting tends to provide high specificity for the diagnosis of FTD, while generally yielding a rather low sensitivity.

Behavioral variant of frontotemporal dementia (FTD-bv). Clinical diagnostic features:

- Early progressive decline in social interpersonal conduct
- Emotional blunting
- Loss of insight

Supportive features:

- Mental rigidity
- Inflexibility
- Distractibility
- Hyperorality
- Decline in personal grooming and hygiene

Primary progressive aphasia (PPA; also known as progressive non-fluent aphasia, or PNFA). Clinical diagnostic features:

- Gradual decline in spontaneous speech associated with:
  - Anomia
  - Agrammatism
  - Phonemic paraphasias
- Loss of verbal fluency

Parkinsonism. Clinical diagnostic features:

- Bradykinesia
- Rigidity
- Gait instability
- Resting tremor

Corticobasal syndrome Clinical diagnostic features [Boeve et al 2003]:

- Progressive asymmetric rigidity

- Apraxia
- Alien-limb phenomenon
- Cortical sensory loss
- Focal dystonia
- Myoclonus
- Dementia

Testing

Neuroimaging

- **Computed tomography (CT) or magnetic resonance imaging (MRI)** may show focal, often asymmetrical, atrophy in the frontal and/or temporal regions [Neary et al 2005]. A study comparing the pattern of cerebral atrophy in persons with FTD using voxel-based morphometry suggests that those with *GRN* mutations have a more widespread and severe pattern of gray matter loss in the frontal, temporal, and parietal lobes than those who do not have a *GRN* mutation [Whitwell et al 2007].
- **Single photon emission computed tomography (SPECT)** may reveal decreased perfusion in the frontal and temporal lobes [Pasquier et al 2003].
- **Positron emission tomography (PET)** may also demonstrate decreased glucose metabolism in the frontotemporal region, often before structural changes can be appreciated [Pasquier et al 2003].

Neuropathology. The neuropathology of FTD-GRN is characterized by the following [Mackenzie et al 2006]:

- Tau-negative alpha-synuclein-negative ubiquitin-positive "cat-eye" or lentiform-shaped neuronal intranuclear inclusions (NII), often found in the neocortex and striatum
- Superficial laminar spongiosis with ubiquitin-positive neurites and neuronal cytoplasmic inclusions (NCI) in the neocortex
- Granular appearance of the ubiquitin-immunoreactive (ub-ir) neurites in the striatum and the NCI in the hippocampus

The major protein component of these ubiquitin inclusions is a TAR DNA-binding protein of 43 kd (TDP 43). TDP 43 is a nuclear factor involved in regulating transcription and alternative splicing, although its role in the pathogenesis of neurodegenerative diseases remains to be determined [Arai et al 2006, Neumann et al 2006].

It is now recognized that pathologically, FTD-GRN is a major subtype of frontotemporal lobar degeneration (FTLD). The neuropathologic diagnostic criteria for FTLD have recently been updated based on current molecular understanding of the disease [Cairns et al 2007].

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Gene. The gene *GRN* encoding the protein granulin is the only gene known to be associated with frontotemporal dementia with ub-ir NII pathology [Baker et al 2006; Cruts, Gijselinck et al 2006]. *GRN* is also known as *PGRN*, encoding progranulin.

Clinical testing. In a series of 378 individuals with frontotemporal lobar degeneration, 23% of those with a positive family history had a *GRN* mutation identified using sequence analysis of the entire gene including the promoter region, whereas 4.8% of simplex cases (i.e., a single occurrence in a family) had an identifiable *GRN* mutation [Gass et al 2006].

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in *GRN*-Related Frontotemporal Dementia

Test Method	Mutations Detected	Mutation Detection Frequency [1]	Test Availability
Sequence analysis	*GRN* sequence variants	5% [2]	Clinical Testing

1. Proportion of affected individuals with a mutation(s) as classified by test method
2. In a series of 167 individuals with FTLD referred to Alzheimer Disease Research Centers (ADRC) (population sample), 5% were found to have *GRN* mutations. The *GRN* mutations were as common as mutations in the tau gene *(MAPT*), associated with frontotemporal dementia with parkinsonism-17 (FTDP-17) [Gass et al 2006].

Testing Strategy

The algorithm for diagnosis of FTD begins with detailed clinical assessment and consideration of the consensus clinical criteria [The Lund and Manchester Groups 1994, Neary et al 1998, McKhann et al 2001].

Because FTD-GRN has distinct neuropathologic findings, one approach is to determine if other relatives with dementia had an autopsy demonstrating the characteristic neuropathologic findings [Mackenzie et al 2006].

For those individuals with a family history of FTD and at least one relative with the characteristic NII pathologic findings, molecular genetic testing of *GRN* would be warranted.

Genetically Related (Allelic) Disorders

No phenotypes other than FTD-GRN are associated with mutations in *GRN*.

Clinical Description

Natural History

Frontotemporal dementia associated with *GRN* mutations (FTD-GRN) generally affects the frontal and temporal cortex leading to behavioral changes, executive dysfunction, and language disturbances. In FTD-GRN, the parietal cortex and basal ganglia may be affected as well, resulting in parkinsonism, cortical basal syndrome, and memory impairment [Baker et al 2006, Masellis et al 2006, Mukherjee et al 2006, Behrens et al 2007, Josephs et al 2007, Mesulam et al 2007, Spina et al 2007].

Age of onset. The age of onset of FTD-GRN ranges from 35 to 87 years with a mean of 59 ±7 years [Bruni et al 2007].

Neurocognitive symptoms. Neuropsychological testing may demonstrate early symptoms of impairment on frontal lobe tasks or specific language dysfunction prior to the onset of frank dementia.

Behavioral disturbances are the most common early feature, followed by progressive aphasia [Gass et al 2006, Josephs et al 2007]. This is usually an insidious but profound change in personality and conduct, characterized by distractibility, loss of initiative, apathy and loss of interest in their environment, often accompanied by neglect in personal hygiene and social disinhibition. Some affected individuals demonstrate impulsiveness or compulsiveness and may alter their eating habits with food fads and food craving.

With impairment in executive function, there is loss of judgment and insight, which may manifest early in the disease as making poor financial decisions, quitting jobs abruptly, or becoming unduly forward or rude to strangers. Alternatively, persons with predominant apathy symptoms may lose all interest and initiative with usual activities, appear socially withdrawn, ignore all previous interests and hobbies, and be unable to complete tasks due to lack of persistence. Early in the course of the illness, affected individuals may be misdiagnosed as having psychiatric conditions such as depression, mania, or psychosis because of the unusual and bizarre nature of their behavior. Psychometric testing may demonstrate impairment on frontal executive tasks including the Trail-Making Test, proverb interpretation, descriptions of similarities, categorical naming, and abstract pattern recognition (e.g., Wisconsin Card Sort Test).

To date, the clinical FTD subtype semantic dementia has not been reported with *GRN* mutations. Semantic dementia is characterized by impaired naming and comprehension, semantic paraphasias, and impaired recognition of familiar faces or objects.

Language deficits. Primary progressive aphasia (PPA, or PNFA) can be another presentation of FTD-GRN [Mesulam et al 2007]. In early stages, PPA often manifests as deficits in naming, word finding, or word comprehension. Although behavioral manifestations tend to be more common than language deficits as the initial presentation of FTD-GRN, in one series 82% of affected individuals eventually developed language problems [Josephs et al 2007].

In late stages, affected individuals often become mute and lose their ability to communicate.

Movement disorders. In several families with FTD-GRN parkinsonism is prominent, and in some the initial clinical diagnosis was corticobasal syndrome [Gass et al 2006, Masellis et al 2006]. Early findings include rigidity, bradykinesia or akinesia (slowing or absence of movements), limb dystonia, apraxia (loss of ability to carry out learned purposeful movements), and disequilibrium. Late motor findings may include myoclonus, dysarthria, and dysphagia. Most affected individuals eventually lose the ability to walk.

Motor neuron disease. Although the histopathologic findings of ubiquitin-positive inclusions were initially associated with motor neuron disease, it seems to occur only rarely if at all in families with *GRN* mutations [Schymick et al 2007].

Disease course. The mean age at death is 65±8 years. The disease duration ranges from three to 12 years [Gass et al 2006].

Genotype-Phenotype Correlations

No obvious correlations between age of onset, disease duration, or clinical phenotype and specific *GRN* mutations have been identified. Variability is high among persons who have the same mutation.

If the final cellular effect of all mutations is the same, i.e., haploinsufficiency for granulin, then one could anticipate some uniformity of clinical features. However, a broad range of clinical features both within and across families is observed. The heterogeneity in clinical presentation

likely reflects the different anatomical distribution of the lesions in each individual, while the variation in age of onset and disease duration suggests that other modifying genetic or environmental factors are involved.

Penetrance

Penetrance is about 90% by age 75 years, but apparent incomplete penetrance has also been observed in a few cases [Cruts, Gijselinck et al 2006; Gass et al 2006]. More reports will be needed before the penetrance can be more accurately established.

Anticipation

No well-documented evidence of genetic anticipation has been reported to date.

Nomenclature

The use of the term frontotemporal dementia (FTD) has been inconsistent and is still evolving. In this *GeneReview* the term FTD refers to the clinical presentation of the dementing illness, and frontotemporal lobar degeneration (FTLD) to denote the pathologic diagnosis of the disease.

FTDP-17 has been used to denote individuals with FTD with or without parkinsonism associated with mutations in *MAPT*, the gene encoding the tau protein. This syndrome includes persons diagnosed with Pick's disease.

The term FTD-GRN has been used in this *GeneReview* to designate FTD associated with *GRN* gene mutations. Note that the alternative term FTD-PGRN with *PGRN* mutations is often used in the literature as well.

Prior to the identification of *GRN* as the gene responsible for this form of FTD, a number of terms were used to describe this disorder.

- **FTDU-17.** Analogous to FTDP-17, the term FTDU-17 has been used because the pathologic characteristics of this condition are associated with **ubiquitinated inclusions** and the genetic locus was also located on chromosome 17.
- **HDDD1 and HDDD2.** Other kindreds with familial dementia with similar clinical presentations were descriptively named as hereditary dysphasic disinhibition dementia (HDDD1 and HDDD2). It has now been shown that mutations in *GRN (PGRN*) are also responsible for these families, and therefore these are basically the same disease [Mukherjee et al 2006, Behrens et al 2007].

Prevalence

FTD is a progressive neurodegenerative disease accounting for 5%-10% of all individuals with dementia and 10%-20% of individuals with dementia with onset before age 65 years [Bird et al 2003, Neary et al 2005].

FTD-GRN represents about 5% of all FTD, and 20% of FTD in which the family history is positive. FTD-GRN is at least as common as FTDP-17.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Neuroimaging can evaluate for other conditions that mimic frontotemporal dementia (FTD), such as white matter diseases and frontotemporal focal lesions, such as frontal lobe tumors and cerebrovascular disease.

The clinical manifestations of FTD associated with *GRN* gene mutations (FTD-GRN) significantly overlap with those of other inherited conditions such as FTDP-17, familial Parkinson disease (see Parkinson Disease Overview) and Alzheimer disease (see Alzheimer Disease Overview), as well as sporadically occurring disorders such as Pick's disease, frontotemporal dementia, corticobasal degeneration, other Parkinsonian syndromes, and Creutzfeldt-Jacob disease (see Prion Diseases). This clinical overlap makes it difficult to predict which family has a *GRN* mutation by clinical presentation alone.

Up to 50% of individuals with FTD have a positive family history of dementia, usually with autosomal dominant inheritance [Chow et al 1999, Rosso et al 2003].

Frontotemporal dementia with parkinsonism-17 (FTDP-17) is a presenile dementia affecting the frontal and temporal cortex and some subcortical nuclei. Clinical presentation is variable. Individuals may present with slowly progressive behavioral changes, language disturbances, and/or extrapyramidal signs. Onset is usually between ages 40 and 60 years, but may occur earlier or later. The disease progresses over a few years into profound dementia with mutism. Disease duration is usually between five and ten years, but occasionally may be up to 20-30 years. *MAPT*, the gene encoding microtubule-associated protein tau, is the only gene associated with FTDP-17. Between 25% and 40% of families with autosomal dominant frontotemporal dementia show mutations in *MAPT*.

At autopsy, all persons with FTDP-17 consistently show tau-positive inclusion pathology, whereas all persons with FTD-GRN show ub-ir neuronal intranuclear inclusions [Ghetti et al 2003, Mackenzie 2007].

Inclusion body myopathy with Paget disease of the bone (PDB) and frontotemporal dementia (IBMPFD) is characterized by adult-onset proximal and distal muscle weakness (clinically resembling a limb-girdle muscular dystrophy syndrome), early-onset PDB, and premature frontotemporal dementia (FTD). Muscle weakness progresses to involve other limb and respiratory muscles. Cardiac failure and cardiomyopathy have been observed in later stages. PDB involves focal areas of increased bone turnover that typically lead to spine and/or hip pain and localized enlargement and deformity of the long bones. Early stages of FTD are characterized by dysnomia, dyscalculia, comprehension deficits, paraphasic errors, and relative preservation of memory, and later stages by inability to speak, auditory comprehension deficits for even one-step commands, alexia, and agraphia. Mean age at diagnosis for muscle disease and PDB is 42 years; for FTD, 55 years. *VCP* is the only gene known to be associated with IBMPFD.

Other. Mutations in *CHMP2B*, the gene encoding the chromatin-modifying protein 2B, have been identified in individuals with autosomal dominant FTD [Skibinski et al 2005, Momeni et al 2006, Parkinson et al 2006] (see *CHMP2B*-Related Frontotemporal Dementia).

The disorder FTD-associated motor neuron disease (FTD-MND) has been mapped to chromosome 9q21-q22; the causative gene is unknown [Morita et al 2006, Vance et al 2006].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with *GRN*-related frontotemporal dementia (FTD-GRN), the following evaluations are recommended:

- Detailed general, neurologic, and family history
- Physical, neurologic, and cognitive examination

When clinical cognitive assessments are not informative enough, a neuropsychologic assessment may be performed to provide a more comprehensive and objective view of a patient's cognitive function. Formal neuropsychologic assessment requires comparison of the patient's raw score on a specific test to a large general population normative sample which is usually drawn from a population comparable to the person being examined. This allows for the patient's performance to be compared to a suitable control group, adjusted for age, gender, level of education, and/or ethnicity. While much more sensitive than bedside clinical cognitive examination, such assessment is resource intensive and time consuming.

Treatment of Manifestations

There is currently no known treatment for FTD-GRN or FTD in general. However, some behavioral symptoms such as apathy, impulsivity, and compulsiveness may respond to selective serotonin reuptake inhibitors.

Symptoms of roaming, delusions, and hallucinations, may respond to antipsychotic medications.

Although reports have suggested potential benefits with certain pharmacotherapy on management of FTD in general, evidence from randomized controlled trials is limited [Freedman 2007]. All of the following findings require confirmation with larger clinical trials.

- One double-blind placebo-controlled cross-over trial suggests that trazodone, a serotonergic agent, may be beneficial in treating the symptoms of irritability, agitation, depression, and eating disorders in FTD [Lebert et al 2004].
- While an open-label study suggested some benefits on behavioral symptoms with paroxetine, a double-blind placebo-controlled trial of ten subjects found worsening of performance on paired associates learning, reversal learning, and delayed pattern recognition [Moretti et al 2003, Deakin et al 2004].
- A study of galantamine in FTD-bv and primary progressive aphasia (PPA) found significant benefits in subjects with PPA but not in those with FTD-bv [Kertesz et al 2005].
- A double-blind placebo-controlled cross-over study of methylphenidate found attenuation of risk-taking behavior but worsening of spatial span [Rahman et al 2006].

Testing of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

For treatment of behavioral symptoms in FTD in general, a phase II clinical trial is examining the efficacy of a stimulant (dextroamphetamine) and an atypical antipsychotic (quetiapine).

Other trials are investigating efficacy of amantadine and citalopram.

A clinical trial is assessing in FTD the efficacy and tolerability of memantine (anti-excitotoxic, neuroprotective treatment currently used in Alzheimer disease).

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

Genetics clinics, staffed by genetics professionals, provide information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section may include disease-specific and/or umbrella support organizations.

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Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Frontotemporal dementia associated with *GRN* gene mutations (FTD-GRN) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most (95%) individuals diagnosed with FTD-GRN have an affected parent [Gass et al 2006].
- A proband with FTD-GRN may have the disorder as the result of a new gene mutation. The proportion of cases caused by *de novo* mutations is unknown but would be estimated at 5% or less.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* mutation include a neurologic assessment and molecular genetic testing of *GRN*. Evaluation of parents may determine that one is affected but has escaped previous diagnosis because of failure by health care professionals to recognize the syndrome and/or a milder phenotypic presentation. Therefore, an apparently negative family history cannot be confirmed until appropriate evaluations have been performed.

Note: Although most individuals diagnosed with FTD-GRN have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members, such as early death of the parent before the onset of symptoms or late onset of the disease in the affected parent.

Sibs of a proband

- The risk to the sibs of the proband depends upon the genetic status of the proband's parents.
- If a parent of the proband is affected, the risk to the sibs is 50%.
- If the disease-causing mutation found in the proband cannot be detected in the DNA of either parent, the risk to sibs is low but greater than that of the general population because of the possibility of germline mosaicism.

Offspring of a proband. Each child of an individual with FTD-GRN has a 50% chance of inheriting the mutation.

Other family members of a proband. The risk to other family members depends upon the status of the proband's parents. If a parent is found to be affected, his or her family members may also be at risk.

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has the disease-causing mutation or clinical evidence of the disorder, it is likely that the proband has a *de novo* mutation. However, possible non-medical explanations including alternate paternity or undisclosed adoption could also be explored.

Family planning. The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy. It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk of being affected.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about ten to 12 weeks' gestation. The disease-causing allele of an affected family member must be identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Requests for prenatal testing for adult-onset conditions such as *GRN*-related frontotemporal dementia are not common. Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most

centers would consider decisions about prenatal testing to be the choice of the parents, careful discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of GRN-Related Frontotemporal Dementia

Gene Symbol	Chromosomal Locus	Protein Name
GRN	17q21.3	Granulins

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for GRN-Related Frontotemporal Dementia

138945	GRANULIN; GRN
607485	FRONTOTEMPORAL DEMENTIA, UBIQUITIN-POSITIVE

Table C. Genomic Databases for GRN-Related Frontotemporal Dementia

Gene Symbol	Entrez Gene	HGMD
GRN	138945	GRN

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Molecular Genetic Pathogenesis

To date, evidence suggests that all *GRN* mutations exert their pathogenic effect through reduced progranulin protein levels by (1) loss of transcript (nonsense or frameshift mutations), (2) reduced transcription (promoter mutations), (3) loss of translation (mutation of initiating methionine), or (4) loss of protein function (missense mutations) [Baker et al 2006; Cruts, Gijselinck et al 2006; Gass et al 2006; van der Zee et al 2007].

Normal allelic variants: A number of normal variants as well as other variants of unknown significance in *GRN* have been identified.

Pathologic allelic variants: Over 80 genetic variations in *GRN* have been identified, of which 44 have been shown to be pathogenic (Table 3) (pdf) [Baker et al 2006; Benussi et al 2006; Boeve et al 2006; Cruts, Kumar-Singh et al 2006; Gass et al 2006; Huey et al 2006; Masellis et al 2006; Mukherjee et al 2006; Pickering-Brown et al 2006; Bronner et al 2007; Le Ber et al 2007; Leverenz et al 2007; Mesulam et al 2007; Spina et al 2007; van der Zee et al 2007].

The Flanders Interuniversity Institute for Biotechnology in Belgium keeps an up-to-date tally of all mutations associated with FTD (see database). Also see Genomic Databases table.

Current known mutations are listed in Table 3 (pdf). To date, the most frequently found mutation is g.3240C>T (p.Arg493X) (Table 2). Haplotype analyses suggest that it may result from a founder effect [Gass et al 2006,Bronner et al 2007,van der Zee et al 2007].

The majority of the mutations are nonsense, frameshift, and splice-site mutations that cause premature termination of the coding sequence and degradation of the mutant RNA by nonsense-mediated decay [Baker et al 2006, Gass et al 2006]. Other unusual mutations include the following [Gass et al 2006, Bronner et al 2007, van der Zee et al 2007]:

- A splice-site in exon 1 5' splice site that leads to loss of the Kozac sequence
- A missense mutation in the hydrophobic core of the granulin signal peptide
- Missense mutations predicted *in silico* to affect protein folding
- Sequence variations in the 5' regulatory region that may affect GRN transcriptional activity

All of these mutations are expected to result in loss of a functional *GRN* transcript and consequent haploinsufficiency.

Table 2. *GRN* Allelic Variants Discussed in the *GeneReview*

Class of Variant Allele	DNA Nucleotide Change (Aliases [1])	Protein Amino Acid Change	Reference Sequence [2]
Pathologic	c.1477C>T (g.3240C>T)	p.Arg493X	NM_002087 NP_002078

See Quick Reference for an explanation of nomenclature. *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org).

1. Variant designations that do not conform to current naming conventions
2. Reference sequence (www.ncbi.nlm.nih.gov/Genbank/index.html)

Normal gene product: The granulins are a family of cysteine-rich polypeptides, some of which have growth-modulating activity. All four known human granulin-like peptides are encoded in a single precursor, progranulin, a 593-amino acid glycoprotein with a highly conserved 12-cysteine backbone defining a consensus sequence that is repeated seven times [Bateman & Bennett 1998].

Progranulin, also known as PC-cell-derived growth factor, proepithelin, granulin-epithelin, or acrogranin, is a high molecular weight secreted mitogen. Progranulin mRNA is widely expressed in rapidly cycling epithelial cells, in the immune system, and in neurons such as cerebellar Purkinje cells, suggesting an important function in these tissues. Progranulin is involved in multiple physiologic processes such as cellular proliferation and survival as well as tissue repair, and pathologic processes including tumorigenesis [He & Bateman 2003]. Transcriptome analyses show that the progranulin gene is induced in numerous situations varying from obesity to the transcriptional response of cells to antineoplastic drugs [Ong & Bateman 2003]. The role of progranulin and granulins in the central nervous system are still unclear, but progranulin is expressed normally by a subset of pyramidal neurons. It is up-regulated in activated microglia in many neurodegenerative diseases including Creutzfeldt-Jakob disease, motor neuron disease, Alzheimer disease, and FTD [Daniel et al 2000].

The progranulin gene comprises a total of 13 exons, including a non-coding exon 0 and 12 protein-coding exons covering about 3,700 bp [Cruts, Gijselinck et al 2006]. Each tandem granulin repeat is encoded by two nonequivalent exons, a configuration unique to the granulins that would permit the formation of hybrid granulin-like proteins by alternate splicing [Bhandari & Bateman 1992].

Abnormal gene product: Although *GRN* mutations have been identified as a cause of autosomal dominant FTD, the ubiquitin-positive inclusions are not stained by progranulin immunostaining, suggesting that most mutations do not result in production of abnormal progranulin. In fact, most mutations lead to abnormal mRNAs that are degraded by nonsense-mediated decay (i.e., null mutations). This progranulin haploinsufficiency likely leads to

neurodegeneration from reduced progranulin-mediated neuronal survival [Baker et al 2006; Cruts, Kumar-Singh et al 2006].

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

The Association for Frontotemporal Dementias
100 North 17th Street Suite 600
Philadelphia PA 19103
Phone: 866-507-7222; 267-514-7221
Email: info@ftd-picks.org
www.ftd-picks.org

National Institute of Neurologic Disorders and Stroke
NINDS Frontotemporal Dementia Information Page

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

Literature Cited

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Chapter Notes

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