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CHMP2B Frontotemporal Dementia

Synonyms: *CHMP2B*-FTD, Chromosome 3-Linked Frontotemporal Dementia, FTD-3

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Summary

Clinical characteristics

CHMP2B frontotemporal dementia (*CHMP2B*-FTD) has been described in a single family from Denmark, in one individual with familial FTD from Belgium, and in one individual with FTD and no family history. It typically starts between ages 46 and 65 years with subtle personality changes and slowly progressive behavioral changes, dysexecutive syndrome, dyscalculia, and language disturbances. Disinhibition or loss of initiative is the most common presenting symptom. The disease progresses over a few years into profound dementia with extrapyramidal symptoms and mutism. Several individuals have developed an asymmetric akinetic rigid syndrome with arm and gait dystonia and pyramidal signs that may be related to treatment with neuroleptic drugs. Symptoms and disease course are highly variable. Disease duration may be as short as three years or longer than 20 years.

Diagnosis/testing

The diagnosis of *CHMP2B*-FTD is established in a proband by identification of a heterozygous pathogenic (or likely pathogenic) variant in *CHMP2B* by molecular genetic testing.

Management

Treatment of manifestations: Caregivers need information and psychological support to manage the behavioral changes and the loss of insight and judgment in affected individuals. Psychosocial support is essential and

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should include occupational therapy and environmental and physical interventions. Antipsychotics and/or antidepressants may improve physical aggressiveness. Administered antipsychotics should be reevaluated at short intervals with the goal of discontinuation as soon as feasible.

Genetic counseling

CHMP2B-FTD is inherited in an autosomal dominant manner. Penetrance is age dependent and appears to be nearly complete; most individuals with *CHMP2B*-FTD have an affected parent. To date, *de novo CHMP2B* pathogenic variants have not been reported. Each child of an individual with *CHMP2B*-FTD has a 50% chance of inheriting the pathogenic variant. Once a *CHMP2B* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for *CHMP2B*-FTD are possible.

Diagnosis

Suggestive Findings

CHMP2B frontotemporal dementia (*CHMP2B*-FTD) **should be suspected** in individuals with the following:

- Frontotemporal dementia
- A neuropsychological profile of a dysexecutive syndrome, behavioral changes, lack of emotional recognition, and dyscalculia
- Generalized atrophy on neuroimaging:
  - Computed tomography (CT) or magnetic resonance imaging (MRI) show generalized cortical and central atrophy and ventricular enlargement [Gydesen et al 2002].
  - Cerebral blood flow-positron emission tomography (CBF-PET) shows a global reduction in cortical CBF with sparing of the visual cortex and basal ganglia [Gydesen et al 2002].
  - CBF-MRI shows a decreased CBF in occipital and parietal lobes in presymptomatic *CHMP2B*-FTD heterozygotes [Lunau et al 2012].
  - Fluorodeoxyglucose (FDG)-PET shows globalized hypometabolism [Johannsen et al 2016].
- Family history of frontotemporal dementia in two or more first-degree relatives consistent with an autosomal dominant mode of inheritance
- Neuropathology showing p62-positive, ubiquitin-positive, TDP-43-negative, and FUS-negative cytoplasmic intraneuronal inclusions in the hippocampal dentate granule cells and in neurons in the frontal and temporal cortex [Holm et al 2007, Holm et al 2009]

Establishing the Diagnosis

The diagnosis of *CHMP2B*-FTD **is established** in a proband by identification of a heterozygous pathogenic (or likely pathogenic) variant in *CHMP2B* by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *CHMP2B* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of *CHMP2B*-FTD is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype of familial FTD without neuropathology suggestive of *CHMP2B*-FTD are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and imaging findings suggest the diagnosis of *CHMP2B*-FTD, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *CHMP2B* to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected.

  Note: Targeted analysis for *CHMP2B* pathogenic variant c.532-1G>C can be performed first in individuals of Danish ancestry [Skibinski et al 2005].

- **A multigene panel** that includes *CHMP2B* and other genes of interest (see Differential Diagnosis) may be considered to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) Given the rarity of *CHMP2B*-FTD some panels for dementia may not include this gene. (4) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (5) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by frontotemporal dementia, **comprehensive genomic testing**, which does not require the clinician to determine which gene(s) are likely involved, is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in *CHMP2B* Frontotemporal Dementia

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
CHMP2B	Targeted analysis for c.532-1G>C	See footnote 3.
	Sequence analysis [4]	All reported [3, 5]
	Gene-targeted deletion/duplication analysis [6]	Unknown [7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. The c.532-1G>C pathogenic variant in *CHMP2B*, a change in the acceptor site of exon 6, has been identified in a single large Danish kindred with frontotemporal dementia [Gydesen et al 2002, Skibinski et al 2005, Lindquist et al 2008].
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. C-terminal truncations of *CHMP2B* appear to cause FTD [Skibinski et al 2005, Momeni et al 2006a, van der Zee et al 2008, Clayton et al 2015]. In one simplex case (i.e., a single occurrence in a family) a C-terminal truncation was reported [van der Zee et al 2008], while *CHMP2B* analysis in additional simplex cases and families with FTD evaluated for pathogenic variants [Cannon et al 2006, Rizzu et al 2006, Ghanim et al 2010] have only identified missense variants of uncertain significance [Isaacs et al 2011]. An apparently benign nonsense variant was identified in two unaffected members, but not identified in affected members of the same FTD family [Momeni et al 2006b].
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
7. No data on detection rate of gene-targeted deletion/duplication analysis are available.

Clinical Characteristics

Clinical Description

CHMP2B frontotemporal dementia (*CHMP2B*-FTD) is an early-onset dementia affecting primarily frontal lobe functions. *CHMP2B*-FTD typically starts with subtle personality changes, behavioral changes, dyscalculia, and a dysexecutive syndrome [Stokholm et al 2013].

To date, *CHMP2B*-FTD has been described in a family that originates and resides in western Jutland, Denmark. The first description of this family was by Gydesen et al [1987]. *CHMP2B*-FTD has also been described in an affected individual with familial FTD from Belgium [van der Zee et al 2008]. In addition, one individual from the United Kingdom with FTD and no clear family history was reported to have a *CHMP2B* missense variant [Skibinski et al 2005].

Symptoms usually start between ages 46 and 70 years, with an average age of onset of 57 years. Disease duration is from three to more than 20 years. The disease progresses over a few years into profound dementia with mutism [Gydesen et al 2002, Brown et al 2004].

Behavioral changes. Disinhibition or loss of initiative is the most common presenting symptom. Affected individuals lose interest in their environment and neglect personal hygiene. The manifestations may vary from very disinhibited to very apathetic. Affected individuals may show inappropriate emotional responses and a lack of empathy. Hyperorality is common including overeating sweet foods and chain smoking. Restlessness is common. Aggressiveness and hypersexuality have been described. Lack of insight into illness is common. Stereotypic speech, pacing activity, and stereotypic behavioral routines are frequent [Gydesen et al 2002, Brown et al 2004].

Psychiatric symptoms. Psychotic symptoms are unusual, but it is difficult to determine if a very disinhibited person is psychotic. Some individuals develop depressive symptoms early in the illness; they are typically mild. Manic syndromes have been observed in a few individuals.

Cognitive decline. Loss of executive function is a common early feature, as is dyscalculia and language impairment. Spontaneous speech declines, although repetition and reading from a text is relatively preserved. Perseveration, repetitive utterances, and echolalia are common. Affected individuals develop a nonfluent aphasia and then often become mute. Memory can be spared until late in the illness. Route finding and other visuospatial problems are unusual. Mini-Mental Status Examination (MMSE) scores are relatively preserved early in the disease, followed by a sharp decline with worsening aphasia [Gydesen et al 2002, Brown et al 2004, Stokholm et al 2013].

Extrapyramidal signs. Four years into the illness, several individuals have developed a striking motor syndrome that develops into an asymmetric akinetic rigid syndrome with arm and gait dystonia and pyramidal signs. This syndrome may be related to treatment with neuroleptic drugs [Gydesen et al 2002, Brown et al 2004]. Akinetic mutism has been observed in late stages of disease.

Epilepsy. Generalized tonic-clonic epileptic seizures are rare in individuals with *CHMP2B*-FTD.

Motor neuron disease. Severe motor neuron disease has not been described in individuals with *CHMP2B*-FTD; however, signs of lower motor neuron dysfunction (e.g., fasciculations) can be seen in the tongue or thigh muscles.

Neuropathology. Macroscopic examinations find severe generalized atrophy with an asymmetric and frontal preponderance; brain weight is below 1000 g [Holm et al 2007].

Microscopic analysis reveals neuronal loss, gliosis, and spongiosis in the superficial cortical layers.

Immunohistochemical analysis shows pathologic accumulation of p62-positive, ubiquitin-positive, TDP-43-negative, and FUS-negative cytoplasmic inclusions in the hippocampal dentate granule cells and in a few cortical neurons [Holm et al 2007, Holm et al 2009]. Consequently, the neuropathology is currently classified as frontotemporal lobar degeneration with inclusions positive for ubiquitin proteasome system markers [Mackenzie et al 2010, Mackenzie & Neumann 2016].

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Penetrance

Penetrance is age dependent and appears to be nearly complete in the Danish family.

Nomenclature

CHMP2B-FTD was originally described as familial nonspecific dementia. Molecular genetic studies published by Brown et al [1995] demonstrated linkage of the disease-associated gene in the Danish family to the pericentromeric region of chromosome 3, leading to the designation chromosome 3-linked frontotemporal dementia (FTD3 or FTD-3).

Following identification of a causative pathogenic variant in *CHMP2B* [Skibinski et al 2005], FTD3 is referred to as *CHMP2B*-associated frontotemporal dementia, *CHMP2B*-mediated frontotemporal dementia, or now *CHMP2B*-FTD.

Prevalence

CHMP2B-FTD has been described in one large Danish family [Gydesen et al 2002, Skibinski et al 2005], in one affected individual with familial FTD from Belgium [van der Zee et al 2008], and in one individual with FTD and no family history [Skibinski et al 2005].

Genetically Related (Allelic) Disorders

In an English cohort, three different *CHMP2B* missense variants have been found in three individuals with a lower motor neuron-predominant variant of amyotrophic lateral sclerosis (ALS) termed primary muscular atrophy (PMA) [Cox et al 2010]. However, the pathogenicity of these changes is presently unclear (see Isaacs et al [2011] for a further discussion of these missense variants).

In a Dutch cohort, four novel *CHMP2B* variants were found in one individual with PMA and three individuals with ALS. The variants were predicted to be pathogenic [van Blitterswijk et al 2012].

A rare *CHMP2B* variant has been identified in an individual from India with ALS [Narain et al 2018].

Differential Diagnosis

Pathogenic variants in *CHMP2B* have been identified in one large Danish family with frontotemporal dementia [Gydesen et al 2002, Skibinski et al 2005, Lindquist et al 2008] and in an affected individual with familial frontotemporal dementia (FTD) from Belgium [van der Zee et al 2008]. (A *CHMP2B* missense variant in one individual from the United Kingdom with FTD and no clear family history was also reported [Skibinski et al 2005]).

Pathogenic variants in *CHMP2B* are considered to be a much rarer cause of frontotemporal dementia than pathogenic variants in *MAPT* (encoding tau), *GRN* (encoding progranulin), or *C9orf72*.

Table 2. Genes of Interest in the Differential Diagnosis of *CHMP2B* Frontotemporal Dementia (*CHMP2B*-FTD)

Gene(s)	DiffDx Disorder	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/*CHMP2B*-FTD	Distinguishing from *CHMP2B*-FTD
APP *PSEN1* *PSEN2* [1]	Early-onset familial Alzheimer disease (EOFAD)	AD	• Mild behavioral changes • Prominent memory disturbance • Loss of initiative • Word-finding problems	Absence of focal frontotemporal atrophy on neuroimaging
C9orf72	*C9orf72*-ALS/FTD	AD	Adult-onset rapidly progressive features of FTD, ALS, or a combination of both	• May not be clinically distinguishable • Psychotic symptoms more common in *C9orf72*-ALS/FTD
FUS	ALS 6 w/or w/o FTD	AD	MND w/FTD	• Familial ALS w/o FTD • Onset before 5th decade • Incomplete penetrance
GBA1 (*GBA*) *SNCA* *SNCB*	Lewy body dementia (OMIM 127750)	AD	• Dementia • Extrapyramidal signs (rigidity, bradykinesia)	• REM sleep disorders • Visual hallucinations • DaT scans abnormal

Table 2. continued from previous page.

Gene(s)	DiffDx Disorder	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/*CHMP2B*-FTD	Distinguishing from *CHMP2B*-FTD
GRN	*GRN*-FTD	AD	• Adult-onset behavioral-variant FTD • Generally affects frontal & temporal cortex, → behavioral changes, executive dysfunction, & language disturbances • Parietal cortex & basal ganglia may be affected as well, resulting in parkinsonism, cortical basal syndrome, & memory impairment • Age of onset: 48-83 yrs	• Clinically indistinguishable • Metabolic changes (on FDG-PET) preceding structural changes of frontal atrophy (on MRI)
HTT	Huntington disease	AD	• Changes in personality (apathy or depression) • Cognitive decline • Dementia • Dystonia	• Chorea • Delusions • Visual hallucinations
MAPT	FTD w/parkinsonism-17	AD	• Adult-onset behavioral variant FTD • Extrapyramidal signs (rigidity, bradykinesia, supranuclear palsy, & saccadic eye movement disorders) • Symptoms usually start at ages 40-60 yrs but may occur earlier or later. • Disease progresses over few yrs to profound dementia w/mutism.	• Clinically indistinguishable • Onset before 5th decade • Metabolic changes (on FDG-PET) preceding structural changes of frontal atrophy (on MRI)
TARDBP	*TARDBP* frontotemporal lobar degeneration (See *TARDBP*-ALS-FTD.)	AD	• Adult-onset behavioral variant FTD • Generalized cerebral atrophy on MRI	• Early bulbar symptoms • Onset before 5th decade
TBK1	FTD &/or ALS 4 (OMIM 616439)	AD	• Adult-onset behavioral variant FTD • Disinhibition as presenting symptom • Generalized cerebral atrophy on MRI • Extrapyramidal features at later stage of disease	• Memory loss at early stage of disease • Incomplete penetrance
UBQLN2	ALS 15 w/or w/o FTD (OMIM 300857)	XL	• MND w/FTD • Choreic movements	• Familial ALS w/o FTD • Early spastic paralysis, dysarthria, & dysphagia • Onset before 5th decade

Table 2. continued from previous page.

Gene(s)	DiffDx Disorder	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/*CHMP2B*-FTD	Distinguishing from *CHMP2B*-FTD
VCP	Inclusion body myopathy with Paget disease of bone &/or FTD	AD	• Premature FTD • Early stages characterized by dysnomia, dyscalculia, comprehension deficits, paraphasic errors, & relative preservation of memory • Later stages characterized by inability to speak, auditory comprehension deficits for even 1-step commands, alexia, & agraphia • Mean age at FTD diagnosis: 56 yrs	• Adult-onset proximal & distal muscle weakness [2] • Muscle weakness progresses to involve other limb & respiratory muscles. • Cardiac failure & cardiomyopathy may be observed in later stages. • Early-onset PDB [3]

AD = autosomal dominant; ALS = amyotrophic lateral sclerosis; AR = autosomal recessive; DiffDx = differential diagnosis; FDG-PET = fluorodeoxyglucose-positron emission tomography; FTD = frontotemporal dementia; MND = motor neuron disease; MOI = mode of inheritance; PDB = Paget disease of bone; XL = X-linked

1. It is likely that pathogenic variants in other genes causative of EOFAD will be identified because families with autosomal dominant FAD with no known pathogenic variants in *PSEN1*, *PSEN2*, or *APP* have been described [Pasanen et al 2018].

2. Adult-onset proximal and distal muscle weakness in inclusion body myopathy associated w/Paget disease of bone and/or FTD clinically resembles a limb-girdle muscular dystrophy syndrome.

3. 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; pathologic fractures occur on occasion.

Other considerations

- Structural imaging may show a frontal preponderance of the generalized atrophy and will exclude other treatable causes of dementia (e.g., frontal meningioma, chronic subdural hematoma).
- Nongenetic acquired causes of dementia should always be considered.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *CHMP2B* frontotemporal dementia (*CHMP2B*-FTD), the following evaluations (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- A general medical history and family history
- Physical and neurologic examination
- Evaluation of the extent and profile of cognitive disturbance by neuropsychological examination
- Discussion of capabilities for job and for driving
- Consultation with a clinical geneticist and/or genetic counselor
- Discussion of advanced care planning

Treatment of Manifestations

Behavioral changes and the loss of insight and judgment in individuals with *CHMP2B*-FTD often present a considerable burden for caregivers. Information about the disease and psychological support for partners or other caregivers is essential. Caregiver support groups are valuable.

Psychosocial support is essential in the management of FTD and should include occupational therapy and environmental and physical interventions.

The behavioral and psychological symptoms should be treated as in other types of FTD. There is no consensus treatment guideline for *CHMP2B*-FTD. In clinical practice those affected individuals who present with very aggressive symptoms have proven quite difficult to treat and in some instances have been treated with high doses of antipsychotics and/or antidepressants in order to relieve the physical aggressiveness. Administered antipsychotics should be reevaluated at short intervals with the goal of discontinuation as soon as feasible.

Surveillance

Members of the Danish family with *CHMP2B*-FTD are followed in the Copenhagen Memory Disorders Clinic, a multidisciplinary clinic involving neurologic and psychiatric services, genetic counseling, molecular genetic testing, and clinical diagnostic and follow-up medical service.

Evaluation of Relatives at Risk

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

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of 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; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

CHMP2B frontotemporal dementia (*CHMP2B*-FTD) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- To date, almost all individuals diagnosed with CHMP2B-FTD have an affected parent.
- One individual with FTD and no clear family history of neurodegenerative disease was reported to have a *CHMP2B* variant [Skibinski et al 2005].
- Molecular genetic testing and neurologic examination are recommended for the parents of a proband with an apparent *de novo* pathogenic variant.
- If the *CHMP2B* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent.* Though theoretically possible, no instances of a proband inheriting a pathogenic variant from a parent with germline mosaicism have been reported.

  * Misattributed parentage can also be explored as an alternative explanation for an apparent *de novo* pathogenic variant.

- The family history of some individuals diagnosed with *CHMP2B*-FTD may appear to be negative because of failure to recognize the disorder in family members because of a milder phenotypic presentation, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has been performed on the parents of the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the *CHMP2B* pathogenic variant, the risk that sibs will be heterozygous for the pathogenic variant is 50%.
- If the *CHMP2B* pathogenic variant cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *CHMP2B* pathogenic variant but are clinically unaffected on neurologic examination, the risk to the sibs of a proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for *CHMP2B*-FTD because of the possibility of a late onset of the disease in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with *CHMP2B*-FTD has a 50% chance of inheriting the *CHM2B* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *CHMP2B* pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

Predictive testing (i.e., testing of asymptomatic at-risk individuals)

- Predictive testing for at-risk relatives is possible once the *CHMP2B* pathogenic variant has been identified in an affected family member.
- Potential consequences of such testing (including, but not limited to, socioeconomic changes and the need for long-term follow up and evaluation arrangements for individuals with a positive test result) as well as the capabilities and limitations of predictive testing should be discussed in the context of formal genetic counseling prior to testing.

Predictive testing in minors (i.e., testing of asymptomatic at-risk individuals younger than age 18 years)

- For asymptomatic minors at risk for adult-onset conditions for which early treatment would have no beneficial effect on disease morbidity and mortality, predictive genetic testing is considered inappropriate, primarily because it negates the autonomy of the child with no compelling benefit. Further, concern exists regarding the potential unhealthy adverse effects that such information may have on family dynamics, the risk of discrimination and stigmatization in the future, and the anxiety that such information may cause.
- For more information, see the National Society of Genetic Counselors position statement on genetic testing of minors for adult-onset conditions and the American Academy of Pediatrics and American College of Medical Genetics and Genomics policy statement: ethical and policy issues in genetic testing and screening of children.

In a family with an established diagnosis of *CHMP2B*-FTD, it is appropriate to consider testing of symptomatic individuals regardless of age.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic 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.

Prenatal Testing and Preimplantation Genetic Testing

Once the *CHMP2B* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Association for Frontotemporal Degeneration (AFTD)**
  Phone: 866-507-7222
  Email: info@theaftd.org
  www.theaftd.org
- **FTD Talk**
  United Kingdom
  Email: j.rohrer@ucl.ac.uk
  www.ftdtalk.org
- **National Institute of Neurological Disorders and Stroke (NINDS)**
  PO Box 5801
  Bethesda MD 20824
  Phone: 800-352-9424 (toll-free); 301-496-5751; 301-468-5981 (TTY)
  Frontotemporal Dementia Information Page
- **Rare Dementia Support**
  United Kingdom
  Email: contact@raredementiasupport.org
  www.raredementiasupport.org
- **FTD Disorders Registry**
  FTD Disorders Registry

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. CHMP2B Frontotemporal Dementia: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar

Table A. continued from previous page.

CHMP2B	3p11.2	Charged multivesicular body protein 2b	alsod/CHMP2B genetic mutations CHMP2B database	CHMP2B	CHMP2B

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for CHMP2B Frontotemporal Dementia (View All in OMIM)

600795	FRONTOTEMPORAL DEMENTIA AND/OR AMYOTROPHIC LATERAL SCLEROSIS 7; FTDALS7
609512	CHARGED MULTIVESICULAR BODY PROTEIN 2B; CHMP2B

Molecular Pathogenesis

CHMP2B encodes CHMP2B (charged multivesicular body protein 2B or chromatin modifying protein 2B), which belongs to the multiprotein *e*ndosomal *s*orting *c*omplex *r*equired for *t*ransport-III (ESCRT-III). In combination with the related complexes ESCRT-0, ESCRT-I, and ESCRT-II, ESCRTs function sequentially in the sorting of endocytosed transmembrane proteins into multivesicular bodies (MVBs), also known as late endosomes. MVBs subsequently fuse with lysosomes to enable degradation of their contents.

Mechanism of disease causation. *CHMP2B*-FTD occurs through a gain-of-function mechanism. C-terminally truncated CHMP2B protein impairs trafficking in the MVB and autophagy pathways [Filimonenko et al 2007, Lee et al 2007, Urwin et al 2010, Ghazi-Noori et al 2012]. The altered protein accumulates on the endosomal membrane. This gain-of-function effect impairs fusion of endosomes with lysosomes, resulting in lysosomal pathology [Urwin et al 2010, Nielsen et al 2012, Clayton et al 2015].

The c.532-1G>C splice site pathogenic variant leads to the formation of two aberrant transcripts that code for proteins lacking the C terminus of the protein [Skibinski et al 2005] (see Table 3). A nonsense variant, c.493C>T (p.Gln165Ter), also predicted to lead to a protein lacking the C terminus, was subsequently identified in a Belgian individual with familial frontotemporal lobar degeneration [van der Zee et al 2008].

Table 3. Notable *CHMP2B* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_014043.4 NP_054762.2	c.493C>T	p.Gln165Ter	Identified in 1 Belgian individual [van der Zee et al 2008]
NM_014043.4	c.532-1G>C	--	Founder variant in Denmark [Skibinski et al 2005]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Chapter Notes

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