Navigating FTD

Insights into progranulin, disease progression, and clinical trial information

FTD=frontotemporal dementia.

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A closer look at frontotemporal dementia

Frontotemporal dementia (FTD) is a fatal, progressive adult-onset neurodegenerative disease affecting the frontal and temporal lobes of the brain and is characterized by declining behavioral, linguistic, and executive function.[1,2]

FTD is one of the most common causes of early-onset dementia worldwide and is estimated to affect ~60,000 patients in the US and ~110,000 patients across Europe. FTD tends to occur between the ages of 40 and 65.[3,4]

FTD may be misdiagnosed as Alzheimer's disease or a mental health issue rather than a neurological disorder. Changes in behavior occur in the early stages of the disease and may include[2]:

Loss of inhibition

Apathy

Social withdrawal

Hyperorality (mouthing of objects)

Ritualistic compulsive behaviors

FTD may progress into immobility and the inability to speak and/or understand speech.[5,6]

Survival averages 8 years following the onset of neurocognitive decline.[7]

Though there are currently no disease-modifying therapies approved for the treatment of FTD, Passage Bio is exploring the therapeutic potential of elevating progranulin (PGRN) levels for the treatment of a genetic form of FTD.[8]

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FTD can have a genetic cause

An estimated 25%-30% of FTD cases are inherited in an autosomal dominant manner. Of those, most are caused by mutations or genetic alterations in the *GRN*, *C9orf72*, or *MAPT* genes. In 5%-10% of patients with FTD, the disease is caused by an inactivating mutation in the *GRN* gene, leading to a PGRN deficiency (eg, FTD-*GRN*).[9-12]

25%-30% of all FTD cases have a known genetic cause.[9,10]

Mutations in the ***GRN***, ***C9orf72***, or ***MAPT*** genes are the most common causes of genetic FTD in inherited cases.[13]

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Progranulin may be key to neurodegenerative diseases like FTD

What is PGRN?

Progranulin (PGRN) is a protein made by the *GRN* gene which plays a critical role in safeguarding the health and survival of different types of cells.[11]

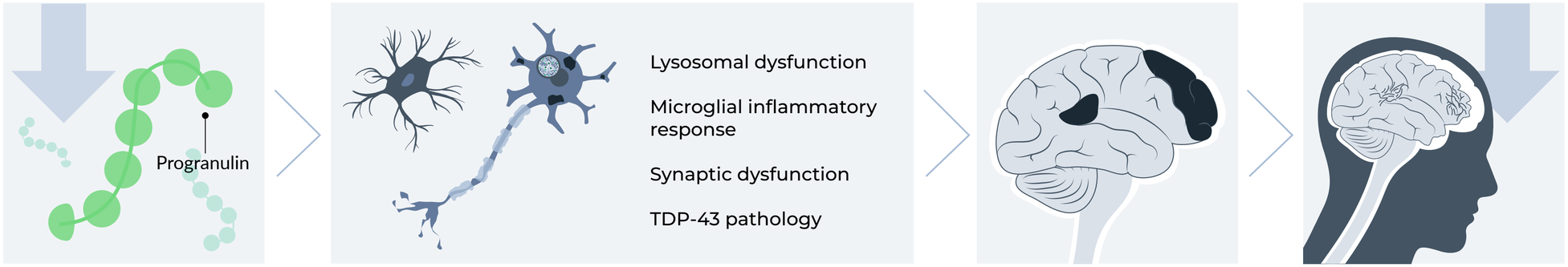
PGRN is mainly expressed by microglial cells and neurons in the central nervous system (CNS). Sufficient levels are important to help cells survive, grow, and control inflammation.[11]

Why PGRN matters

PGRN deficiency may lead to neuronal dysfunction in several ways, including[11]:

- Lysosomal dysfunction
- Activation of the microglial inflammatory response
- Synaptic disruption
- Transactive response DNA binding protein 43 kDa (TDP-43) pathology, a common hallmark in neurodegenerative conditions where PGRN levels are depleted

Reduced PGRN levels have been implicated as a risk factor for many neurodegenerative diseases, including FTD[11]:



Decrease in PGRN levels

Neuronal dysfunction, pathological changes, and inflammation

Vulnerability of neurons in affected regions

Neurodegeneration

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PGRN levels play a key role in FTD-*GRN*

FTD-*GRN* is a genetic form of FTD caused by a mutation in the *GRN* gene that leads to a deficiency of PGRN. Treatments that selectively elevate PGRN levels in people with FTD-*GRN* may slow or halt the progression of the disease.[11]

In preclinical models of neurodegeneration, elevation of PGRN levels has[14,15]:

- Restored lysosomal function
- Reduced pathology
- Reduced neuroinflammation

Achieving high PGRN levels in the CNS may improve outcomes for people with FTD-*GRN*.[14,15]

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The Passage Bio Approach to FTD-*GRN*

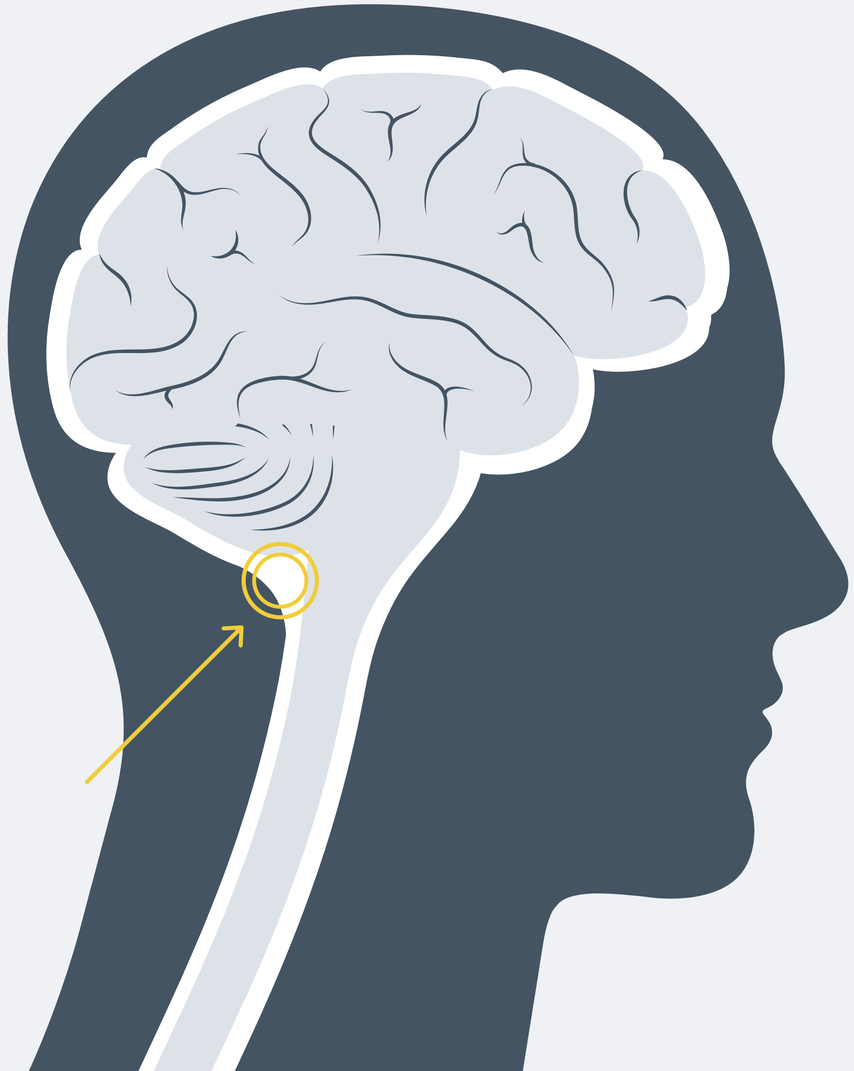
PBFT02, a potential gene therapy for FTD-*GRN*

Our investigational gene therapy candidate, PBFT02, uses an adeno-associated virus serotype 1 (AAV1) viral vector to deliver a functional *GRN* gene, encoding PGRN into a patient. The vector is delivered, with CT guidance, directly to the cerebrospinal fluid (CSF) by a one-time injection to the intracisterna magna (ICM injection). The goal of this vector and delivery approach is to provide elevated levels of PGRN directly to the CNS to overcome the PGRN deficiency seen in patients with FTD who have certain *GRN* mutations.[16-19]

Our delivery method | ICM administration

PBFT02 is delivered directly to the CSF via a single, minimally invasive injection into the cisterna magna near the base of the skull between the cerebellum and medulla. The CT-guided non-surgical procedure is brief (<60 minutes) and allows for precise delivery to the cisterna magna. This delivery method allows for direct distribution of PBFT02 throughout the CNS without disturbing brain tissue.[17,19,20]

- Direct delivery into the CSF reduces the vector doses needed for transgene expression in relevant CNS regions and lowers the potential for immune response[19]
- Neuroimaging allows for precise delivery[19]
- As with similar administration methods close to the CNS, there may be risk of bleeding, infection, or injury[21]



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Our clinical trial | upliFT-D

upliFT-D is a Phase 1/2 global, multi-center, open-label, clinical trial of PBFT02 administered by a one-time ICM injection in patients with FTD-*GRN*. This trial will assess the safety, tolerability and efficacy of PBFT02 in patients with FTD-*GRN*[16]

- The upliFT-D clinical trial will enroll up to 15 patients across 3 cohorts[20]
- Interim data from the study demonstrated that Cohort 1 achieved consistent elevation of CSF progranulin at 30 days and up to 6 months after treatment[20]

*Dose 1: 3.3e10 GC/g estimated brain weight.

● Independent Data Monitoring Committee (IDMC) review

Inclusion criteria

Aged ≥35 and ≤75 years[16]

Clinical diagnosis of FTD[16]

Documented to be a pathogenic *GRN* mutation carrier[16]

Have a reliable informant/caregiver who personally speaks with or sees the patient at least weekly[16]

Living in the community (ie, not in a nursing home); assisted living may be permitted at the discretion of the investigator[16]

upliFT-D
A Clinical Trial for Frontotemporal Dementia with Progranulin Gene Mutations

Your patients with FTD-*GRN* may be eligible to enroll in the upliFT-D clinical trial.
Visit the upliFT-D clinical trial site for more information on trial enrollment and eligibility requirements.

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Genetic testing is available at no cost

A genetic test can confirm FTD-*GRN*

Visit InformedDNA to learn more about how your US-based patients can access no-cost genetic testing and counseling†‡

InformedDNA® Genetics, Decoded

Visit PREVENTION GENETICS for more information about no-cost genetic testing in all markets‡

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†InformedDNA no-cost genetic testing and counseling is only available to US residents.
‡While the FTD testing programs are sponsored by Passage Bio, no personal identifying information of individuals participating in these genetic testing programs will be shared with the company.

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Patient discussion questions

At Passage Bio, our mission is to improve the lives of patients with neurodegenerative diseases by delivering genetic therapy that will permanently redefine the course of their conditions. We are committed to investigating gene therapies for patients with genetic CNS disorders like FTD-*GRN*. People diagnosed with or affected by FTD may find diagnostic visits difficult to approach. Below, is a sample of common questions your patients and their care partners may have. The answers provided may be used as a guide when having a discussion.

Frequently Asked Questions

How common is FTD?
FTD is the most common cause of early-onset dementia worldwide. FTD is estimated to affect ~60,000 patients in the US and ~110,000 patients across Europe and tends to occur between the ages of 40 and 65.[3,4]

Are there any approved treatments for FTD?
There are currently no approved treatments for FTD that address the underlying cause of the disease.[22]

Will my family members get this?
The cause of FTD is unknown for a majority of people with the disease. Over time, we've learned there is a strong genetic component to FTD. This means that there may be a family history of FTD. Up to 40% of people with FTD have a family history of dementia, and there is more likely a genetic cause. However, some people without a family history can also have a genetic cause.[4,8,12,23]

What is genetic testing and what does it mean for my family?
Genetic testing can identify differences in genes. It is performed using a cheek swab, saliva, or a blood sample. Genetic testing can confirm if an FTD diagnosis is caused by a genetic mutation, which may make one eligible for a clinical trial.[8,24,25]

Is genetic testing expensive?
There are no-cost genetic testing programs sponsored by Passage Bio to help you confirm FTD-*GRN*.

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Clinical Trial Questions

Am I a candidate for a clinical trial?
Passage Bio is studying a potential therapy for people with FTD caused by a genetic mutation of the *GRN* gene. A genetic test will need to be done to determine if you have a *GRN* mutation. While there are other eligibility criteria, confirming your mutation status is the first step.

What is the time commitment for upliFT-D?
upliFT-D is a two-year clinical trial with a three-year safety extension.[20]

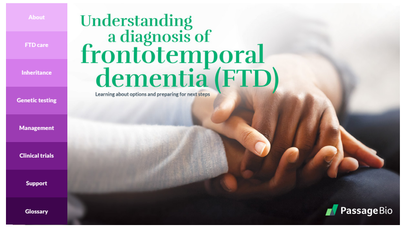
Participants in the upliFT-D trial will be asked to visit the research center several times over the duration of the study, including a stay in the hospital of at least two days for tests and observation at the time PBFT02 is administered.

It's important to note that this is a one-time treatment.

Support is available to help manage the logistics and travel even if you live far away from the study site.

What is ICM administration?
ICM administration delivers treatment directly into the cerebrospinal fluid, or CSF, the fluid that surrounds the brain and the spinal cord. This allows for direct delivery of the treatment into the central nervous system, or CNS, without disturbing brain tissue.[19]

Where can I find more information on the disease, Passage Bio clinical trial options, and the FTD patient/care partners community?



Download the FTD-*GRN* patient brochure to learn more information.

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References: 1. Riedl L, Mackenzie IR, Förstl H, Kurz A, Diehl-Schmid J. Frontotemporal lobar degeneration: current perspectives. *Neuropsychiatr Dis Treat*. 2014;10:297-310. doi:10.2147/NDT.S38706 **2.** Liu MU, Lau C, Lin CP. Precision medicine for frontotemporal dementia. *Front Psychiatry*. 2019;10:75. doi:10.3389/fpsyt.2019.00075 **3.** Galvin JE, Howard DH, Denny SS, Dickinson S, Tatton N. The social and economic burden of frontotemporal degeneration. *Neurology*. 2017;89(20):2049-2056. doi:10.1212/WNL.0000000000004614 **4.** Mayo Clinic. Frontotemporal dementia – symptoms and causes. Accessed June 20, 2024. https://www.mayoclinic.org/diseases-conditions/frontotemporal-dementia/symptoms-causes/syc-20354737?p=1 **5.** Gorno-Tempini ML, Hillis AE, Weintraub S, et al. Classification of primary progressive aphasia and its variants. *Neurology*. 2011;76(11):1006-1014. doi:10.1212/WNL.0b013e31821103e6 **6.** Neumann M, Lee EB, Mackenzie IR. FTLD-TDP pathological subtypes: clinical and mechanistic significance. *Adv Exp Med Biol*. 2021;1281:201-217. doi:10.1007/978-3-030-51140-1_13 **7.** Knopman DS, Roberts RO. Estimating the number of persons with frontotemporal lobar degeneration in the US population. *J Mol Neurosci*. 2011;45(3):330–335. doi:10.1007/s12031-011-9538-y **8.** National Institute on Aging. What are frontotemporal disorders? Causes, symptoms, and treatment. Updated July 30, 2021. Accessed June 20, 2024. https://www.nia.nih.gov/health/frontotemporal-disorders/what-are-frontotemporal-disorders-causes-symptoms-and-treatment **9.** Turner MR, Al-Chalabi A, Chio A, et al. Genetic screening in sporadic ALS and FTD. *J Neurol Neurosurg Psychiatry*. 2017;88:1042-1044. doi:10.1136/jnnp-2017-315995 **10.** Mol MO, van Rooij JGJ, Wong TH, et al. Underlying genetic variation in familial frontotemporal dementia: sequencing of 198 patients. *Neurobiol Aging*. 2021;97:148.e9-148.e16. doi:10.1016/j.neurobiolaging.2020.07.014 **11.** Rhinn H, Tatton N, McCaughey S, Kurnellas M, Rosenthal A. Progranulin as a therapeutic target in neurodegenerative diseases. *Trends Pharmacol Sci*. 2022;43(8):641-652. doi:10.1016/j.tips.2021.11.015 **12.** Greaves CV, Rohrer JD. An update on genetic frontotemporal dementia. *J Neurol*. 2019;266(8):2075-2086. doi:10.1007/s00415-019-09363-4 **13.** Moore KM, Nicholas J, Grossman M, et al. Age at symptom onset and death and disease duration in genetic frontotemporal dementia: an international retrospective cohort study. *Lancet Neurol*. 2020;19(2):145-156. doi:10.1016/S1474-4422(19)30394-1 **14.** Beel S, Herdewyn S, Fazal R, et al. Progranulin reduces insoluble TDP-43 levels, slows down axonal degeneration and prolongs survival in mutant TDP-43 mice. *Mol Neurodegener*. 2018;13(1):55. doi:10.1186/s13024-018-0288-y **15.** Arrant AE, Onyilo VC, Unger DE, Roberson ED. Progranulin gene therapy improves lysosomal dysfunction and microglial pathology associated with frontotemporal dementia and neuronal ceroid lipofuscinosis. *J Neurosci*. 2018;38(9):2341-2358.doi:10.1523/JNEUROSCI.3081-17.2018 **16.** A study of PBFT02 in patients with frontotemporal dementia and progranulin mutations (FTD-GRN) (upliFT-D). ClinicalTrials.gov identifier: NCT04747431. Updated April 18, 2024. Accessed June 20, 2024. https://clinicaltrials.gov/study/NCT04747431 **17.** Perez BA, Shutterfly A, Chan YK, Byrne BJ, Corti M. Management of neuroinflammatory responses to AAV-mediated gene therapies for neurodegenerative diseases. *Brain Sci*. 2020;10(2):119. doi:10.3390/brainsci10020119 **18.** Data on file. Passage Bio; Philadelphia, PA; 2020. **19.** Anderson KM, McNeil E, Weinstein DA, Romano G. Gene therapy for treatment of monogenic neurodegenerative diseases. *Neurology Reviews*. 2021:S1-S7(suppl). **20.** Data on file. Passage Bio; Philadelphia, PA; 2024. **21.** Data on file. Passage Bio; Philadelphia, PA; 2021. **22.** Mayo Clinic. Frontotemporal dementia – diagnosis and treatment. Accessed June 20, 2024. https://www.mayoclinic.org/diseases-conditions/frontotemporal-dementia/diagnosis-treatment/drc-20354741?p=1 **23.** Gass J, Cannon A, Mackenzie IR, et al. Mutations in progranulin are a major cause of ubiquitin-positive frontotemporal lobar degeneration. *Hum Mol Genet*. 2006;15(20):2988-3001. doi:10.1093/hmg/ddl241 **24.** MedlinePlus. What is genetic testing? Updated July 28, 2021. Accessed June 20, 2024. https://medlineplus.gov/genetics/understanding/testing/genetictesting/ **25.** MedlinePlus. How is genetic testing done? Updated July 29, 2021. Accessed June 20, 2024. https://medlineplus.gov/genetics/understanding/testing/procedure/

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