

The National Cell Repository for Alzheimer's Disease

(NCRAD) is a data and specimen collection source for families with Alzheimer disease (AD) or serious memory loss. Families having two or more living individuals with memory loss are encouraged to participate. We would like to thank the hundreds of families nationwide who are already participating in the National Cell Repository. Many family members have provided blood samples, which researchers use to study Alzheimer's disease (AD) and other related diseases. Our hope is that, through the efforts of our participants, we will one day unravel the mystery of devastating diseases, like AD. We are always eager to accept new families to help us move toward this goal.



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SCHOOL OF MEDICINE

National Cell Repository for Alzheimer's Disease

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NCRAD Update

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Single Gene Implicated in FTD/ALS

UCSF Memory and Aging Center, San Francisco, California

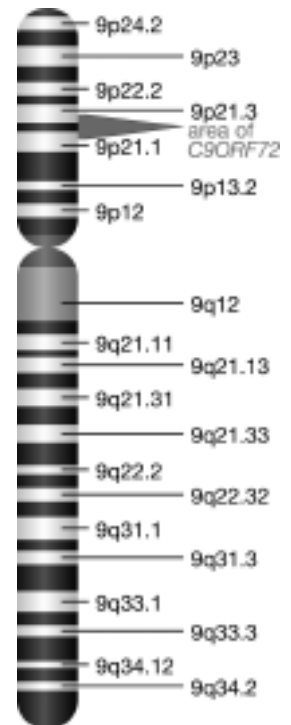
Researchers have recently found a single gene cause for two neurodegenerative conditions that are distinct but related, frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS).

In an online issue of the scientific journal *Neuron*, researchers at Mayo Clinic in Florida, in collaboration with the UCSF Memory and Aging Center and others, report that the newly discovered genetic abnormality is responsible for a significant proportion of families with both FTD and ALS (FTD/ALS) and many families where the dominant syndrome is either familial FTD or familial ALS. Less commonly, it is associated with sporadic FTD or sporadic ALS, meaning occurrences of FTD or ALS without a family history.

Identification of the genetic abnormality marks the culmination of many years of investigation. This discovery has been highly anticipated since researchers began in 2006 to publish evidence that a region on chromosome 9 was responsible for the pattern of disease in families with FTD and ALS.

This collaborative group has now narrowed down the region on chromosome 9 to a single gene called C9ORF72. The abnormality or mutation within the C9ORF72 gene is called an expanded repeat, which describes a short DNA sequence that is abnormally repeated hundreds to thousands of times, one sequence right after another, resulting in a long abnormal stretch of DNA that is not observed in individuals without disease. How this expanded repeat mutation leads to FTD, ALS, or both, however, remains a mystery. The function of the gene on chromosome 9 is not known, and its exact role in disease has yet to be identified.

The C9ORF72 gene is one of the few that have been implicated in the co-occurrence of FTD and ALS, but the expanded repeat mutation does not explain all cases of FTD/ALS, familial FTD, or familial ALS. In addition, the vast majority of sporadic FTD or sporadic ALS occurs for reasons we still do not completely understand. The finding offers great potential to improve our understanding of FTD/ALS. We are hopeful that it will lead to future advances in disease-specific management or even treatment, and we are indebted to our research participants whose generosity of time and support have been invaluable to this recent discovery.



An expanded repeat in gene C9ORF72 on chromosome 9 has been linked to frontotemporal dementia and amyotrophic lateral sclerosis.

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A Primer on Frontotemporal Degeneration

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Frontotemporal degeneration (FTD) is a distinct type of dementia that is distinguished from Alzheimer's Disease (AD). Unlike AD, which is more often seen in individuals in their 70s or 80s, FTD most commonly affects individuals before the age of 65. In fact, in patients younger than 65 years, FTD and AD occur at similar rates. Memory problems are typically considered to be the hallmark symptom of AD, while in FTD, memory loss is not the primary symptom. There are two major types of FTD. One form is characterized by changes in the patient's behavior and/or personality. In the other major form of FTD, language is affected such that the individual experiences a change in language ability or difficulty speaking or understanding language. Sometimes a patient with FTD will have only one type, but often there is a combination of symptoms. The manner in which the brain is affected is the primary explanation for the different disease presentations. In FTD, the atrophy (shrinking) of the brain occurs primarily in the frontal and/or temporal lobes of the brain. An individual's personality and behaviors are primarily controlled by the frontal lobes of the brain, while language is controlled by the temporal lobes. A patient with FTD could also have symptoms of a movement disorder, similar to Parkinson disease (PD), or symptoms of muscle weakness, such as amyotrophic lateral sclerosis (ALS; Lou Gehrig's disease). As with any dementia diagnosis, a thorough evaluation including a neurologic examination, brain imaging, neuropsychological testing, blood work, and cerebrospinal fluid testing should be completed to help establish or exclude a clinical diagnosis of FTD.

For both FTD and AD, the final and definite diagnosis is made at the end of life by doing a brain autopsy. In AD, there are two proteins that occur together in the brain: tau (tangles) and beta-amyloid (plaques). However, for FTD, there are actually two different categories to describe the findings of a brain autopsy. One group is characterized by clusters of tau, the same protein that is also seen in brains affected by AD. 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. The second group is characterized by clusters 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 ALS. Research is currently focused on understanding why and how the tau and TDP-43 proteins accumulate, in hopes that the answer will lead to the development of FTD-specific therapies.

Similar to AD, the exact reason why FTD occurs is unknown. While the majority of FTD is not genetic and is unlikely to be inherited, FTD does have significant genetic contributions.

While almost one-half of individuals with FTD have a family history that includes some form of neurodegenerative disease, an inherited gene mutation can be found in only 15-30% of all FTD cases. There are three genes that cause the majority of hereditary FTD: MAPT (tau protein), GRN (progranulin), and C9ORF72. The C9ORF72 gene mutation has also been found to cause hereditary ALS. Having a family history of neurodegenerative disease, especially relatives that had FTD or ALS, is the main indicator that there may be a genetic cause for an individual's disease; however, not all individuals with a family history of neurodegenerative disease will have a gene mutation.

Mutations that cause FTD are inherited in an autosomal dominant manner, meaning that there is a 50% risk of passing the mutation from a parent to a child. There are other genes that in rare cases cause FTD and researchers believe that there are still more FTD genetic factors to be discovered. Genetic testing for some FTD genes is available. Genetic testing can be used to help to confirm the diagnosis of hereditary FTD in an affected patient, as well as for predictive, or presymptomatic, genetic testing in a healthy individual with a known risk for inheriting a FTD gene mutation. Patients with concerns about a family history of FTD-associated symptoms may want to consult with a clinician that specializes in the genetic basis of disease, such as a genetic counselor. A genetic counselor can be found by going to the website of the National Society of Genetic Counselors (www.nsgc.org).

There is no cure or preventative treatment for FTD. Management of the condition focuses on the treatment of a patient's symptoms. Often the medications used in the management of FTD are similar to those used to treat other neurodegenerative diseases, such as AD and PD. There are also non-medication management strategies for FTD, such as using slow and simple speech when speaking to a patient with language difficulties or removing items from the home that can trigger behavioral symptoms.

Research of many kinds is vital to gain a better understanding of FTD. There are many centers around the country that have expertise in FTD and perform research studies. Active areas of investigation include examination of clinical features, brain imaging, biomarkers (molecules and proteins found in spinal fluid and blood), brain pathology at autopsy, and genetic risk factors. The Center for Neurodegenerative Disease Research and the Penn FTD Center at the University of Pennsylvania are at the forefront of neurodegenerative disease research with

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4RTNI & NIFD

At the Forefront of Neuroimaging in Tauopathies and Frontotemporal Lobar Degeneration

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Neuroimaging in Frontotemporal Dementia (NIFD) and the 4-Repeat Tauopathy Neuroimaging Initiative (4RTNI) are NIH-funded neuroimaging studies based at the University of California, San Francisco (UCSF) that receive additional support from the Tau consortium and National Institute of Neurological Disorders and Stroke (NINDS). NIFD and 4RTNI aim to identify the most precise biomarkers and clinical assessments for tracking disease progression of frontotemporal lobar degeneration (FTLD), progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) with the hope that this information will increase efficacy and power in future clinical trials. Concurrent enrollment of healthy control subjects will enable analyses with age-matched comparison. These are the first and largest rigorous observational neuroimaging studies of FTLD, CBD or PSP.

Frontotemporal lobar degeneration (also known as frontotemporal dementia/FTD) characterized by neurodegeneration in the frontal and anterior temporal lobes, is associated with multiple biological mechanisms and distinct clinical syndromes including: behavioral variant frontotemporal dementia (bvFTD), semantic dementia (SD), and progressive nonfluent aphasia (PNFA), all of which are studied in NIFD. After Alzheimer's disease (AD), FTLD is the second most common form of dementia, and is as prevalent as AD among populations under age 65. Therefore, therapeutic agents and biomarker data to reliably measure treatment effects are much needed.

Progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD), rare neurodegenerative movement disorders, are symptomatically reminiscent of Parkinson's disease, but biologically more similar to Alzheimer's disease (AD). Dementia, language impairment and social-emotional changes often appear in patients with CBD and PSP, and are supportive diagnostic features. AD is related to toxic accumulation of both tau and beta amyloid proteins in the brain, and often includes other co-pathologies such as vascular disease, whereas CBD and PSP are pure tauopathies, meaning that tau is the principle neurodegenerative protein. It is thought that clinical trials in pure tauopathies will allow for more direct evaluation of the effectiveness of tau-directed drugs before they are tested in AD patients since there are fewer co-pathologies that can mask the effectiveness of a drug. For this reason, 4RTNI aims to enroll participants who closely meet diagnostic criteria for PSP and CBD, suggestive of pure tau pathology.

NIFD and 4RTNI have been carefully designed to mirror the data collection standards and protocols of the Alzheimer's Disease Neuroimaging Initiative (ADNI) so that brain images, blood and cerebrospinal fluid biomarkers, and clinical assessments can be compared across all three projects. Furthermore, neuroimaging and clinical data are uploaded to the same central databases to allow for increased collaboration.

4RTNI and NIFD enrollees undergo comprehensive longitudinal neuroimaging assessments every six months. Magnetic resonance imaging (MRI) of the brain and brainstem includes structural, resting state, blood flow perfusion, and white matter tract imaging. NIFD and healthy control participants also undergo positron emission tomography (PET) scans using Pittsburgh compound B (PiB) which measures buildup of amyloid, and FDG, which measures glucose metabolism.

Longitudinal clinical assessments utilize various standardized rating scales, which are included as part of the physical and neurological exam, neuropsychological evaluation and family member interviews. All clinical evaluations are accompanied by an extensive evaluation of social and medical history and standardized eye movement testing. The clinical assessments serve two roles in the research: first, to hone in on the clinical diagnosis; and second, to reveal specific clinical changes that may be correlated with imaging and fluid biomarkers.

NIFD began enrolling in 2010, followed by 4RTNI in 2011. Both studies are funded for at least five years and are well on track to meet their combined total enrollment objective of over 200 patients with diagnoses of CBD, PSP, FTD, SD, and PNFA. Between the two studies, 4 sites in the United States and Canada are currently enrolling subjects, with the addition of more sites on the horizon. Given current successes in enrollment and in preliminary analyses, NIFD and 4RTNI hope to continue enrolling beyond the initial 5-year funding period.

Extensive collaboration with other projects in the UCSF Memory and Aging Center means that many patients are co-enrolled in the UCSF autopsy program, further strengthening the benefit of the research.

NIFD and 4RTNI are recruiting. To learn more or to find out if you or someone you know is eligible to participate, visit <http://memory.ucsf.edu/ftd/research/clinical/nifd/single> or <http://memory.ucsf.edu/research/studies/4rtni>. You may also contact the study coordinator at lVoltarelli@memory.ucsf.edu, 415-476-9578.

Guide to FTD Terminology

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.

Pick's disease

An old diagnostic term for FTD, named for the physician that first described the condition.

Behavioral variant FTD (bvFTD)

The clinical term for an individual with behavioral and personality changes as the primary symptoms.

Primary progressive aphasia (PPA)

The clinical term for an individual with language difficulties as the primary symptom. There are many different types of PPA, including semantic, non-fluent/agrammatic, and logopenic.

Corticobasal syndrome (CBS)

A 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.

Progressive supranuclear palsy (PSP)

A rare diagnosis related to both FTD and PD that causes both cognitive and movement difficulties, including difficulty with eye movements.

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.

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.

Microtubule-Associated Protein Tau (MAPT)

The official name of the gene that makes the tau protein. Mutations in MAPT cause hereditary FTD.

Progranulin

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

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.

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.

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.

NCRAD Welcomes Your Ideas and Suggestions

We hope that you and your family find the NCRAD Newsletter informative. We would welcome suggestions on future topics for articles, questions you would like to ask the NCRAD doctors or anything you would like shared with our readers about your family's experience with Alzheimer disease. Please send us your ideas by e-mail or by phone.

• **Phone** 1-800-526-2839

• **E-mail** alzstudy@iupui.edu

• **Website** www.ncrad.org

Research Opportunities

Dominantly Inherited Alzheimer Network (DIAN)

- Purpose: To study brain changes in people who carry an AD mutation in order to determine how the disease process develops before the onset of symptoms.
- Eligibility: Men and women ages 18 and older with a biological parent or sibling with AD caused by a known mutation. All participants must be able to speak and read English, and must provide contact information for someone who knows them well and would be willing to answer questions about their memory and thinking.
- Locations: USA - CA, IN, MA, MO, NY, RI; United Kingdom; Australia
- Contact: PH: 314-286-2683 or the DIAN website, <http://www.dian-info.org>

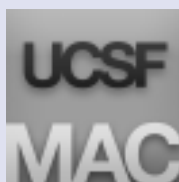
Randomized, Controlled Study Evaluating CERE-110 in Subjects with Mild to Moderate Alzheimer's Disease

- Purpose: To evaluate the potential benefits of CERE-100 in the treatment of Alzheimer's disease. CERE-110 is an experimental drug that is designed to help the nerve cells in the brain function better. CERE-110 uses a virus to transfer a gene that makes Nerve Growth Factor (NGF, a protein that may make nerve cells in the brain healthier and protect them from dying. The virus used in CERE-110 does not cause disease in people; it has been carefully studied in laboratory animals and is in the early stages of being tested in people.
- Eligibility: Men and women ages 55 to 80 years of age, a diagnosis of mild to moderate Alzheimer's disease, a study partner who can attend all study visits, good general health and medically able to undergo neurosurgery.
- Locations: AL, AZ, CA, DC, GA, NY, NC OH, SC, UT
- Contact: PH: 858-622-5863 or 858-458-8853

A randomized, clinical trial of Vitamin E and Memantine in Alzheimer's Disease (TEAM-AD)

- Purpose: The primary study hypothesis is that compared with placebo, alpha-tocopherol, memantine (Namenda), or the combination will significantly delay clinical progression in mild to moderately demented patients with AD.
- Eligibility: Men and women 40 years of age and older with a clinical diagnosis of AD.
- Locations: FL, IA, MA, MD, MI, MN, OH, SC, TX, WI, and Puerto Rico
- Contact: Susan Love, PH: 612-467-3342, e-mail: lovex008@tc.umn.edu, or Julie Tomaska, PH: 612-467-1563, e-mail: julie.tomaska@va.gov

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We are pleased to share with you this promising breakthrough in neurodegenerative disease research and are optimistic about the discovery's potential clinical significance. Presently, genetic testing for the C9ORF72 abnormality is not

yet clinically available, because laboratories that intend to provide testing must further refine the test and obtain FDA approval (called CLIA-certification) before it can be offered to the public. Please feel free to contact us by email for more information: genetics@memory.ucsf.edu.

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a special interest in FTD. While it is clear that FTD is a separate and distinct clinical diagnosis, it overlaps and shares important features with other conditions, as evidenced by the disease proteins FTD shares in common with AD (tau) and ALS (TDP-43). Therefore, research on FTD will not only improve its diagnosis and treatment, but also may provide breakthroughs important in the fight against all neurodegenerative diseases.

For more information on FTD research opportunities, please contact the Center for Neurodegenerative Disease Research at the University of Pennsylvania: www.med.upenn.edu/cndr.

For more information on FTD, contact The Association for Frontotemporal Degeneration: www.theaftd.org.

Sources for Information and Support

* **Alzheimer's Association**

<http://www.alz.org>

Tel: 312-335-8700 or 800-272-3900

* **Alzheimer's Disease Education and Referral Center (ADEAR)**

<http://www.nia.nih.gov/Alzheimers>

Tel: 301-495-3311 or 800-438-4380

ADEAR lists all 29 Alzheimer's Disease Centers (ADCs) and their contact information.

Assisted Living Directory, Assisted Living Facilities Information & Senior Care

<http://www.assisted-living-directory.com/>

The Association for Frontotemporal Dementias (AFTD)

<http://www.ftd-picks.org/>

Tel: 866-507-7222

Family Caregiver Alliance

<http://www.caregiver.org>

Tel: 415-434-3388 or 800-445-8106

National Parkinson Foundation

<http://www.parkinson.org/>

Tel: 305-547-6666 or 800-327-4545

Parkinson's Disease Foundation (PDF)

www.pdf.org

Tel: 212-923-4700 or 800-457-6676

Society for Progressive Supranuclear Palsy

<http://www.psp.org>

Tel: 410-486-3330 or 800-457-4777

National Organization for Rare Disorders (NORD)

<http://www.rarediseases.org>

Tel: 203-746-6518 or 800-999-NORD (6673)

Center for Disease Control and Prevention (CDCP)

<http://www.cdc.gov>

Tel: 800-311-3435

Creutzfeldt- Jakob Foundation Inc. (CJD)

<http://cjd.foundation.org>

Tel: 954-704-0519 or 305-891-7579

National Society of Genetic Counselors

<http://www.nsgc.org/>

Tel: 312-321-6834

* **Research Match** is a free service that pairs volunteers interested in participating in research opportunities from surveys to clinical trials with researchers. Open to all, including healthy volunteers.

<http://www.researchmatch.org>

* **ClinicalTrials.gov** is a registry of federally and privately supported clinical trials conducted in the United States and around the world. ClinicalTrials.gov gives you information about a trial's purpose, who may participate, locations, and phone numbers for more details. This information should be used in conjunction with advice from health care professionals.

<http://www.clinicaltrials.gov/>

* These are good sources for research opportunities in your area.

10 Signs of Alzheimer's Disease

1. Memory loss.
2. Difficulty performing familiar tasks.
3. Problems with language.
4. Disorientation to time and place.
5. Poor or decreased judgment
6. Problems with abstract thinking.
7. Misplacing things.
8. Changes in mood or behavior.
9. Changes in personality.
10. Loss of initiative.

Early diagnosis of Alzheimer's disease or other disorders causing dementia is an important step in getting appropriate treatment, care, and support services.

For more information, call the Alzheimer's Association at (800) 272-3900.



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