

The National Cell Repository

is a repository for families with Alzheimer's Disease or severe 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.

**National Cell Repository
for Alzheimer's Disease**
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Imaging the Brain in AD

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with assistance from the ADNI MRI Core
and ADNI PET Core.

Introduction

The brain is made up of different structures, and some of these structures are affected earlier in the process than other brain regions in Alzheimer's Disease. We have known for some time that **Alzheimer Disease (AD)** is characterized by two main changes in the brain. The first is the accumulation of intraneuronal neurofibrillary tangles and the second is an increase in extracellular amyloid plaques. AD also involves the progressive loss of neurons that affects three areas of the brain early in the disease progression: (1) the hippocampi, (2) temporaloparietal region, and (3) the cortex. This knowledge about Alzheimer's Disease would not be possible without the contribution of brain imaging technology including structural magnetic resonance imaging (MRI), and functional imaging by positron emission tomography (PET).

In this article we will review three common ways in which the brain is imaged, and describe how each technique is contributing to our growing understanding about Alzheimer's Disease.

CAT Scans

CAT stands for Computed Axial Tomography. CAT is the process of using computers to generate a three-dimensional image from two-dimensional, or flat, X-ray pictures.



Photo Illustration

“ We have known for some time that **Alzheimer Disease (AD)** is characterized by two main changes in the brain. ”

How does CAT work?

CAT scan machines go around the area scanned in a circle: taking x-ray pictures from all sides. Each image is called a 'slice'. After all of the 'slices' have been completed, a computer puts them all together to create a 3-D image of the brain. Most CAT scanners today use highly complex programs to interpret the x-ray images taken during the scanning session.

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CAT in Alzheimer's Disease

CAT scans are used to help physicians diagnose Alzheimer's Disease. By looking at the area CT scans can show certain changes that are characteristic of Alzheimer's disease in its later stages. One of the changes CAT scans can show is a reduction in the size of the brain, called atrophy. This is common in Alzheimer's Disease because AD is associated with loss of nerve cells in the brain, and as these cells are progressively lost, the brain shrinks.

MRI Scans

MRI stands for Magnetic Resonance Imaging. MRI is a method that produces very clear pictures of your brain, without the use of X-rays or other invasive methods. MRI is an advanced medical technique that uses a large magnet, radio waves, antenna, and a computer to produce the images.

How does MRI work?

The water in your body is made up of trillions of atoms that have a magnetic moment, in other words they can act as small magnets. When placed in a magnetic field, these atoms line up with the field, much like a compass points to the North Pole. Radio waves of a specific frequency tip these tiny magnets away from the magnetic field. As they tip, they gain energy. When the radio waves are turned off, the atoms try to realign with the magnetic field, releasing the energy they gained as very weak radio signals. A special antenna picks up these signals from your brain and sends them to a computer, which reconstructs an image of your brain.

MRI in Alzheimer's Disease

MRI is beneficial in ruling out other causes of dementia, such as tumors or strokes. It also may help to show the structural and functional changes

in the brain that are associated with Alzheimer's disease. One example of this would be a longitudinal study across a certain length of time which can show the amount of brain tissue that has been lost since the individual was first scanned with MRI. By measuring one area of the brain and then again after a year, we can understand the rate of change to the brain in Alzheimer's Disease, which can be used to show a treatment's effectiveness (or lack of) on brain changes.

PET Scans

PET stands for Positron Emission Tomography. PET scanning can produce high quality pictures of different processes in your body. For brain imaging, PET can be used to take pictures of how your brain uses glucose, or sugar. Glucose is the source of energy for your brain. Scientists have learned that there are abnormal patterns of glucose use in the brains of patients with Alzheimer's disease, and in some older people.

How does PET work?

Scientists (called technologists) at the PET center make a special form of glucose that is labeled with radioactivity. This is called fluorodeoxyglucose, or FDG. The FDG is injected through a small needle into a vein in a person's arm, and the PET scanner picks up this labeled glucose. Pictures are taken every few seconds during the time that a person is in the scanner, which shows how the brain is processing glucose during that time period.

PET in Alzheimer's Disease

The information in PET scans will be analyzed to see how glucose use is different in people with memory problems, called glucose hypometabolism, and also to show how the brain with

AD is changing over time. Recent research has shown that PET scans can be used to aid physicians in diagnosing Alzheimer's Disease, and differentiating people with AD from people with other dementias. This is very important as people with non-Alzheimer's Disease dementias may require different treatment and support from people with Alzheimer's Disease.

The Alzheimer's Disease Neuroimaging Initiative

An historic study using MRI and PET imaging and funded by the National Institute of Health has begun enrolling participants this summer. The study aims to recruit 800 participants all together, 200 of which will have early-stage Alzheimer's Disease. Another 400 participants will have Mild Cognitive Impairment, and another 200 will be participants who do not have memory problems and are the same age as the other 2 groups.

In addition to periodic scanning during the 2-3 year study, information will also be collected about participants including their medical condition, medications, memory and cognition. Blood and urines samples will be collected to research the biomarkers of Alzheimer's Disease. Many of the participants will also undergo a lumbar puncture, which enables researchers to look at the cerebral spinal fluid, the fluid surrounding the brain.

For More Information

If you would like more information about this important study please go to the Alzheimer's Disease Education and Referral (ADEAR) website: <http://www.alzheimers.org/index.html> You may also call the National Referral toll-free number at: 1-800-438-4380 (8:30 a.m. to 5:00 p.m. Eastern Time, Monday - Friday)

Other Causes of Familial Dementia

By Thomas D. Bird, MD
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Thomas D. Bird, MD

Alzheimer's disease (AD) is the most common cause of dementia. For this reason, it is not unusual to see families with more than one person having a diagnosis of AD. This is often referred to as Late Onset Familial AD. Less common is Early Onset Familial AD which is often caused by mutations in one of three specific genes. Therefore, the most common cause of familial dementia is familial AD. However, there are several other less common

causes of familial dementia that are sometimes confused with AD, but are separate, distinct diseases. Four of these other diseases will be briefly discussed in this article.

One of these conditions is called frontotemporal dementia (FTD) also sometimes referred to as Pick's disease. Persons with FTD usually do not have significant memory loss in the early stages of the disease, which is quite different from AD. Rather, persons with FTD often have behavioral changes that may include lack of social inhibitions, inappropriate behavior, apathy and excessive eating with weight gain. CAT or MRI brain scans show atrophy (shrinkage of the brain) largely restricted to the frontal and temporal lobes (different from AD in which the atrophy of the brain is more widespread). FTD is not always familial. However, when it occurs several times in a family it is often caused by a mutation in the gene coding for a brain protein called tau. Interestingly, this tau protein is the same protein that accumulates in the neurofibrillary tangles (NFT) that are one of the hallmarks of AD.

Huntington's disease (HD) is a genetic disease of the brain that may also cause familial dementia. As with FTD the mental problems associated with HD are usually abnormal behavior including poor attention span, apathy, anti-social activities and poor judgment. HD is often also associated with abnormal involuntary movements of the face, trunk and limbs referred to as chorea. The onset of problems in persons with HD is

usually much younger than AD, typically in the 30's and 40's. CADASIL is another genetic disease that may cause familial dementia. The initials stand for the unfortunately cumbersome name of **Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy**. In simple language this means that CADASIL is a dominant genetic disease that produces abnormalities in small arteries in the brain that lead to strokes (infarcts) and abnormalities in the white matter (leukoencephalopathy). Persons with CADASIL often develop recurrent strokes in their 30's, 40's and 50's associated with mental deterioration. There is often also a prior history of migraine headache. MRI brain scanning is useful because it shows the white matter abnormalities that helps distinguish this disease from AD.

A rare cause of familial dementia is the genetic form of **Creutzfeldt-Jakob's disease** (CJD). CJD usually is not genetic, but there are rare families in which it is definitely a genetic disease. In this case it is caused by mutations in a gene (PRNP) which codes for a protein named prion. Abnormal prion in the brain produces progressive memory loss and intellectual decline. The disease may also be associated with

poor coordination (ataxia), muscle weakness and seizures. Abnormal prions also cause "mad cow disease", but mad cow disease is not genetic or inherited.

It is important to note that all four of these uncommon causes of familial dementia may be associated with mutations in specific genes for which there is now genetic testing. All four diseases may be autosomal dominant. This means that each child (male or female) of an affected person has a 50% risk of also inheriting the abnormal gene and developing the disease. The genetic tests are done on DNA extracted from a blood sample. The tests may be highly useful in making the correct diagnosis in the affected family member. Genetic tests can also indicate if offspring have inherited the abnormal gene prior to the development of any symptoms. This genetic testing of an asymptomatic individual should only be done in the context of formal genetic counseling by a genetics professional.

Further information about these diseases and the associated genetic testing can be found through the websites: www.genetests.org and www.nsgc.org.

The most common cause of familial dementia is familial AD. However, there are several other less common causes of familial dementia that are sometimes confused with AD, but are separate distinct diseases.

The National Institutes on Aging Alzheimer's Disease Genetics Initiative

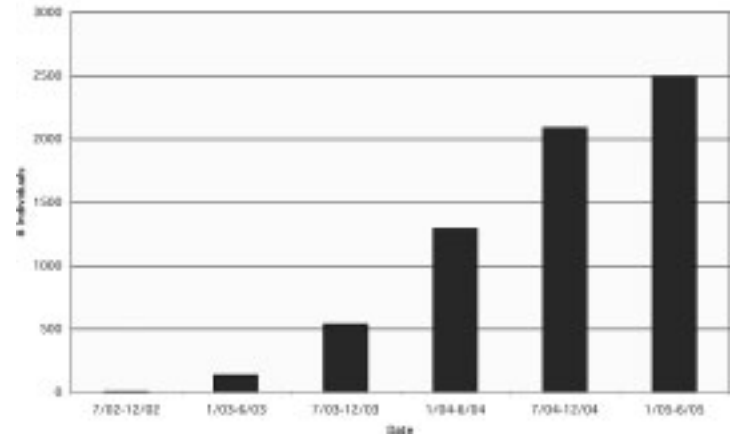
By Tatiana Foroud, Ph.D. and Michele Goodman
Indiana University School of Medicine

In March, 2002, the National Institutes on Aging brought together a number of researchers whose goal was to identify the genes that increase or decrease the risk for Alzheimer's disease (AD). The goal of the meeting was to summarize the current state of AD genetics research and identify what researchers felt were the most important things they needed in order to more rapidly identify AD susceptibility genes. The main conclusions from the meeting were that researchers felt it was essential that more families with AD participate in research studies.

Following this meeting, the National Institutes on Aging decided to establish the AD Genetics Initiative. The goal of the Initiative is to recruitment 1,000 new families with late onset AD. These families must all have at least two siblings diagnosed with AD, both of whom are still living. Alzheimer's Disease Centers located throughout the United States have been working with NCRAD staff to identify these 1,000 new families. We are delighted to report that in only three years, over 500 families have enrolled in the study. Blood samples and clinical information about Alzheimer's disease have been collected from over 2,500 individuals in these families.

AD Genetics Initiative

Individuals Enrolled July 2002-July 2005



We hope that through the generous participation of you and your family in our research studies, we will be able to help researchers to more rapidly identify the genes that increase the risk for AD. Importantly, finding these genes is only the first step. Researchers will then need to understand how these genes act to increase the risk for AD, and will work to identify medications that might alter the action of these genes.

What is the Difference Between Alzheimer's Symptoms and Normal Age-Related Memory Changes?

If someone	A person with Alzheimer's	A person with age-related memory changes
Forgets	Whole experiences	Part of an experience
Remembers later	Rarely remembers later	Often remembers later
Follows written or spoken directions	Is gradually unable	Is usually able
Uses notes	Is gradually unable	Is usually able
Cares for self	Is gradually unable	Is usually able

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Research Opportunities

Cholesterol Lowering Agent to Slow Progression (CLASP) of Alzheimer's Disease Study

- Purpose: To investigate the safety and effectiveness of simvastatin (a cholesterol lowering drug or statin) to slow the progression of AD.
- Eligibility: Ages 50+ with mild to moderate AD
- Locations: AL, AZ, CA, CT, DC, FL, GA, IL, IN, KY, MA, MI, MN, MS, MO, NY, NC, OR, PA, RI, SC, TX, VT, WA
- Contact: NCRAD staff
PH: 800-526-2839 (toll free)
E-mail: alzstudy@iupui.edu

VITAL — Vitamins to Slow Alzheimer's Disease (Homocysteine study)

- Purpose: To determine whether reduction of homocysteine levels with high-dose folic acid, B6, and B12 supplementation will slow the rate of cognitive decline in persons with AD.
- Eligibility: Ages 55+ with probable AD
- Locations: AL, AZ, CA, CT, DC, FL, GA, IL, IN, MA, MI, NV, NJ, NY, OH, OR, PA, RI, SC, TX
- Contact: NCRAD staff
PH: 800-526-2839 (toll free)
E-mail: alzstudy@iupui.edu

Huperzine A in Alzheimer's Disease

- Purpose: To evaluate the safety and efficacy of the Chinese herb huperzine A in the treatment of Alzheimer's disease (AD) in a randomized controlled trial of its effect on cognitive function.
- Eligibility: Age 55 + with probable AD, stable condition 3 months prior to screening. If interested, speak with contact about other eligibility requirements.
- Locations: AL, CA, DC, FL, GA, IL, NV, NJ, NY, NC, OR, PA, SC, TX
- Contact: Carolyn Ward, MSPH
PH: 202-784-6671
E-mail: cw2@georgetown.edu

Treatment of Agitation/Psychosis in Dementia/Parkinsonism (TAP/DAP)

- Purpose: To determine the efficacy (as well as safety, tolerability, and influence on parkinsonism) of quetiapine and donepezil, used alone or in combination, for the treatment of psychosis and/or agitation in patients with primary dementia complicated by coexistent parkinsonism.
- Eligibility: 50+, both genders, diagnosis of AD, symptoms of psychosis, agitation, parkinsonism
- Locations: AL, AZ, CA, GA, IL, MD, MA, MI, NV, NY, PA, TX, VT, WA
- Contact: Kimberly Schafer, M.S.
PH: (858) 622-5863
E-mail: kschafer@ucsd.edu

Prevention of Alzheimer's Disease by Vitamin E and Selenium (PREADVISE)

- Purpose: As a prevention trial, PREADVISE is trying to find out if taking selenium and/or Vitamin E supplements can help to prevent memory loss and dementia such as Alzheimer's disease.
- Eligibility: Ages: 60 - 90, Male. Accepts Healthy Volunteers
- Locations: AL, AK, CA, CO, DC, FL, GA, IA, KS, KY, MD, MA, MI, MN, MS, MO, MT, NE, NV, NJ, NY, OH, OK, PA, SD, TN, TX, WA, WI, CANADA, PUERTO RICO
- Contact: Cecil R. Runyons
PH: 1-859-257-1412 Ext. 235
E-mail: preadvise@lsv.uky.edu

Valproate in Dementia (VALID)

- Purpose: To demonstrate whether valproate therapy delays the emergence of agitation and/or psychosis in outpatients with probable Alzheimer's disease (AD) who have not experienced agitation and psychosis in their illness. A secondary aim is to determine whether valproate therapy delays the progression of cognitive and functional measures of illness. This trial will also assess the tolerability and safety of low-dose, long-term valproate therapy.

- Eligibility: Ages 55 - 90 with probable AD
- Locations: CA, CT, DC, FL, GA, IL, MI, MO, NV, NY, OH, PA, RI, SC, TN, TX, VT, VA
- Contact: Laura Jakimovich, RN, MS
PH: 585-760-6578
E-mail: laura_jakimovich@urmc.rochester.edu

MIRAGE: Multi-Institutional Research in Alzheimer's Genetic Epidemiology

- Purpose: In the third phase of this study, researchers continue to evaluate genetic and non-genetic risk factors for Alzheimer's disease. There is a particular emphasis on exploring whether risk factors for vascular disease are also contributing risk factors for AD.
- Eligibility: Siblings (brothers and sisters) both of whom are at least 60 years of age, one of which has been diagnosed with Alzheimer disease, willing to undergo a blood draw and a MRI scan along with answering questions regarding their family history.
- Contact: Kelly Horner
PH: 800-526-2839 (toll free)
or email: kjhorner@iupui.edu

The Safety and Efficacy of Neramexane in Patients with Moderate to Severe Alzheimer's Disease

- Purpose: To investigate the safety and effectiveness of Neramexane, a new drug that blocks the effects of excessive amounts of glutamate on nerve cells. Glutamate is a brain chemical that transmits messages from one nerve cell to another. Large amounts of glutamate can be damaging to the cell.
- Eligibility: 50+. Both genders, clinical diagnosis of moderate to severe AD, ambulatory patients welcome.
- Locations: AZ, CA, CO, CT, FL, IN, KY, LA, MI, MO, NJ, NY, NC, OH, OR, SC, TX, UT
- Contact: NCRAD Staff
PH: 800-526-2839 (toll free)
e-mail: alzstudy@iupui.edu

Sources for Information and Support

Alzheimer's Association

<http://www.alz.org>
Tel: 312-335-8700 800-272-3900

Alzheimer's Disease Education and Referral Center (ADEAR)

<http://www.alzheimers.org>
Tel: 301-495-3311 800-438-4380
‡ ADEAR lists all 29 Alzheimer Disease Centers (ADCs) and their contact information.

Depression and Related Affective Disorders Association

<http://www.med.jhu.edu/drada>
Tel: 410-955-4647

Family Caregiver Alliance

<http://www.caregiver.org>
Tel: 415-434-3388 800-445-8106

National Parkinson Foundation

<http://www.parkinson.org/>
Tel: 305-547-6666 800-327-4545

Parkinson's Disease Foundation (PDF)

<http://www.parkinsons-foundation.org>
Tel: 212-923-4700, 800-457-6676

Society for Progressive Supranuclear Palsy

<http://www.psp.org>
Tel: 410-486-3330 800-457-4777

National Organization for Rare Disorders (NORD)

<http://www.rarediseases.org>
Tel: 203-746-6518 800-999-NORD (6673)

Centers for Disease Control and Prevention (CDCP)

<http://www.cdc.gov>
Tel: 800-311-3435

Creutzfeldt-Jakob (CJD) Foundation Inc.

<http://cjd.foundation.org>
Tel: 954-704-0519 305-891-7579

10 Signs of AD

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.

If you recognize several of these warning signs in yourself or a loved one, the Alzheimer's Association recommends consulting a physician. 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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