Volume 3, April 2003

NCRAD Update

Newsletter of the National Cell Repository for Alzheimer's Disease

The National Cell Repository for Alzheimer's Disease (NCRAD) is a repository for families with Alzheimer's disease (AD) 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 for Alzheimer's Disease. Many family members have provided blood samples, which researchers use to study Alzheimer's disease 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

Inside this issue:

A New National Initiative to Find Genes in Alzheimer's Disease

By Jamalynne Stuck, MS
Indiana University

It is suspected that multiple genes may be involved in the development of Alzheimer's disease (AD). Several genes have been found to cause early-onset AD. Since only one genetic risk factor, a form of the ApoE gene, has been found to be associated with late-onset AD, the National Institute on Aging (NIA) has increased their effort to find other genetic risk factors for AD. They selected 10 Alzheimer Disease Centers (ADCs) to recruit 1,000 new families with late-onset AD within the next three years. The National Cell Repository for AD (NCRAD) has been selected to maintain the samples and data received from these families and provide them to qualified Alzheimer's researchers.

A microscopic picture of human chromosomes, the structures that carry our genetic information.

Dr. P. Michael Conneally, the principal investigator of NCRAD, says the NIA Genetic Initiative for AD is vital to research on the genetic risk factors for late-onset AD. Major advances have been accomplished for early-onset AD over the last 15 years, but we still know little about the cause of late-onset AD. The NIA is stressing research on the latter and are spearheading the drive to make this a very high priority in their research objectives.

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Alzheimer's Disease Form Linked to Chromosome 3

By Shirley E. Poduslo, Ph.D.
Medical College of Georgia
Institute of Molecular Medicine in Genetics

Dr. Shirley E. Podulso and her research staff have identified a form of late onset Alzheimer's disease that may be linked with markers on chromosome 3. An individual participating in research had clinical signs of AD, including loss of memory, that became progressively worse. The routine blood studies were normal, indicating that there were no thyroid or vitamin B12 problems. The CT scan showed shrinkage of the brain, but there were no signs of strokes or tumors. The patient had three siblings who were also affected. The mother who died at a young age had several siblings with severe memory problems.

The patient lived for 13 years with the disease. When the patient died, an autopsy was performed. The patient's brain in this study only had plaques, but no tangles.

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Vanderbilt University and CAP Work Together to Find AD Genes

By Jonathan Haines, Ph.D.
Vanderbilt University

The Vanderbilt University Alzheimer disease research team, headed by Dr. Jonathan Haines, has been working with the Collaborative Alzheimer Project (CAP), headed by Dr. Margaret Pericak-Vance at Duke University, to attack the genetics of Alzheimer's disease (AD) on several fronts. They have identified two DNA segments, one on chromosome 9 and another on chromosome 12, which appear to be linked to AD. These segments were identified using a large dataset of 455 families, including those families involved in the National Cell Repository for Alzheimer's Disease.

CAP along with Dr. Haines and his team are using the latest DNA technology to examine a number of genes on chromosomes 9 and 12 that might influence the risk of getting AD. On chromosome 12, they have studied several genes already proposed to be associated with AD and are

Dr. Jonathan Haines, director of Vanderbilt University's Program in Human Genetics

continuing to study others. An exciting new finding has shown that there may be genes on this chromosome that control the age at which individuals develop AD. If they can identify these genes, researchers may be able to find ways to delay onset of AD for 10-20 years, beyond an individual's natural life span. This may effectively eliminate AD. In addition, new findings also show that a gene on chromosome 10 may control onset of AD *and* Parkinson disease. The teams are working hard to identify this gene as well.

How can others get involved? For their continued studies, Dr. Haines and his research team need over 1,000 additional families. They have more than 550 enrolled and are actively seeking others. They are accepting families who have at least one family member diagnosed with AD. This can include families with multiple individuals diagnosed with Alzheimer's disease or families with no prior history of AD. Requirements for participating include providing a blood sample and family history information and performing a brief memory test called the Mini Mental Status Examination (MMSE). Families do not have to go to Vanderbilt to participate. If you are interested and not already participating in the National Cell Repository, you may call (317) 274-7360 locally or toll free at 1-800-526-2839 for details.

Alzheimer's Disease Treatment Update

Martin Rhys Farlow, MD
Indiana University School of Medicine

Alzheimer's disease (AD) is a progressive neurological disorder that causes memory and cognitive decline, impairs activities of daily living, and may eventually lead to behavioral and psychiatric symptoms. AD is the most common form of dementia in the United States, estimated to occur in 1% to 2% of the population at age 65, increasing to 33% to 50% by age 85.

Several laboratory and clinical studies have led to our increased understanding of the mechanisms of AD. As a result, better approaches to drug therapy have been identified to treat symptoms of memory and cognitive decline and to delay disease progression.

The most successful therapeutic approach to date is based on inhibiting cholinesterase, a chemical in the brain that blocks the actions of another chemical known as acetylcholine, which enables the process of memory, learning, and cognition to occur. To date, four medications have been developed that inhibit cholinesterase, allowing acetylcholine to enhance memory and cognition in AD patients. The four medications include tacrine (Cognex), donepezil (Aricept), rivastigmine (Exelon), and galantamine (Reminyl). Tacrine was the first cholinesterase inhibitor approved by the U.S. Food and Drug Administration (FDA) but is rarely used due to potential side affects, including liver toxicity. The other cholinesterase inhibitors have been shown to have fewer side effects and improve global functioning and cognition, reduce behavioral disturbances,

(Continued on page 7)

Chromosome 3 (Cont.)

As a reminder, the classical signs of Alzheimer's disease in an autopsy brain are the loss of neurons and the presence of plaques and tangles. The plaques must be of a certain number, which is dependent upon the age of the patient, in order to even make the diagnosis of Alzheimer's disease. Thus an older patient with the disease will have more plaques than a younger person will have.

The researchers were puzzled by the autopsy report. We thought that this patient might possibly have one of the frontotemporal dementias rather than Alzheimer's disease. In frontotemporal dementia, the front and side of the brain are affected first. This results in behavioral and language problems appearing before memory loss begins. Some of the frontotemporal dementias are genetically linked with markers on chromosome 17, especially with the gene called tau. Tau is a protein normally found in brain in tiny scaffolding structures called microtubules. They help the neuron to keep its shape. Abnormal tau accumulates in the tangles found in Alzheimer's brains. We analyzed 9 markers on chromosome 3 and found that the disease in this family was highly linked with several of these markers.

"A report by a group from California suggested that 30 percent of elderly Alzheimer's patients may not have tangles in their brain at autopsy."

A report by a group from California suggested that 30 percent of elderly Alzheimer's patients may not have tangles in their brain at autopsy. The plaques were present as expected in these elderly patients. The California researchers concluded that the patients without the neurofibrillary tangles also had Alzheimer's disease. They believe that the presence of tangles may be associated with a greater severity of the disease.

The family studied fits into this category of Alzheimer's disease since it has plaques, but not tangles in the brain. From our studies, this form of Alzheimer's disease with plaques, but no tangles, is linked with markers on chromosome 3. We are now looking for the gene in this area of chromosome 3 that may be mutated in this form of the disease.

Dr. Shirley Poduslo, Professor at the Medical College of Georgia in the Institute of Molecular Medicine and Genetics

The article was produced by Oleta Toliver, Volunteer Coordinator, and reprinted with permission from Dr. Shirley Poduslo. Dr. Poduslo is currently using samples from the National Cell Repository for AD in her efforts to find the gene on chromosome 3.

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 thoughts.**
7. **Misplacing things.**
8. **Changes in mood or behavior.**
9. **Changes in personality.**
10. **Loss of initiative.**

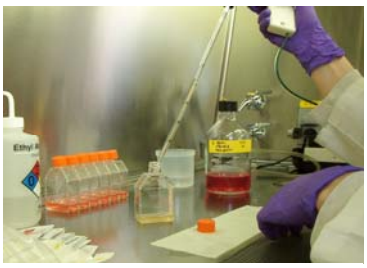
If you recognize several of these warning signs in yourself or a loved one, the Alzheimer's Association recommends consulting a physician. Early diagnosis of Alzheimer's disease or other disorders causing dementia is an important step in getting appropriate treatment, care, and support services. **For more information, call the Alzheimer's Association at (800) 272-3900.**

Banking Cells and DNA at the National Cell Repository for AD

The Banking Center for NCRAD is located at Indiana University, Department of Medical and Molecular Genetics.

Step 3

Step 4



Step 6a

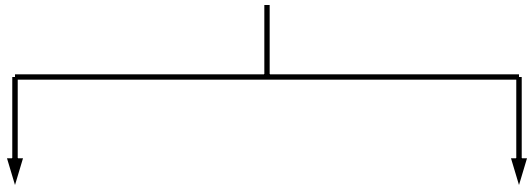
1. The main function of the National Cell Repository for Alzheimer's Disease involves collecting, storing and distributing genetic material for Alzheimer's disease research. Our goal is to provide the scientific community with a valuable resource for obtaining the genetic material needed to study families with Alzheimer's disease. Researchers from around the world may request DNA or cell lines, the materials used in genetic research.

2. The process of banking, or storing, DNA and cell lines begins when a blood sample is received from a member of a family having Alzheimer's disease or serious memory loss.

3. Each sample is assigned a unique kit number. The kit number and information about the participant is recorded in a secured database.

4. The sample is then taken to the lab and a unique bar code number is assigned to it. The bar code number is entered into a logbook along with the unique kit number. These numbers are checked by several technicians for accuracy.

5. The blood sample is then placed in a machine and spun to separate the sample into three main layers: the red blood-cell layer, the plasma layer, and the buffy coat, which contains the white-blood cells. The white-blood cells are needed to establish cell lines and obtain DNA.



6a. To establish cell lines, the white-blood cells are placed in a flask along with a solution that allows permanent cell growth. The cells are incubated at 37 °C (body temperature) anywhere from three weeks to three months.

7a. The cell-containing solution is then divided and transferred into two larger flasks for further cell growth. It takes approximately one week for the cells to divide to the desired number. The cells are checked throughout this process to ensure they are growing properly.

6b. To isolate DNA, the white-blood cells are washed and spun at a high speed, enabling the cells to cluster together.

7b. The cluster of white-blood cells are placed in a solution containing an enzyme that degrades unnecessary cell components. The solution is stored at 37°C overnight. The cells are split open during this time while the DNA stays intact.

(Continue on next page)

8a. The cells are then placed in a plastic cryo-vial along with a cryo-preservative. Each vial holds approximately 1 milliliter of solution containing $1x10^7$ (10,000,000) cells.

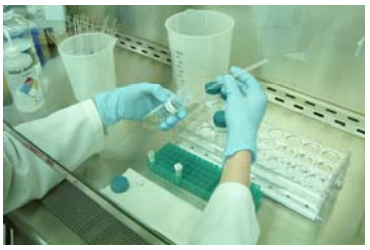
9a. The cells are gradually cooled to freezing temperatures. The slow freeze prevents damage to the cell line and takes place in a controlled-rate freezer.

10a. The frozen cells are stored in a tank filled with liquid nitrogen at –316° Fahrenheit. Cells can be preserved this way indefinitely and thawed at any time for additional cell growing. This culture and storage process is necessary for immortalizing our participant's cells for ongoing genetic research in Alzheimer's disease.

8b. Next, the DNA is separated from the cell components. This is accomplished by adding a salt solution and spinning the DNA and cell components at a high speed.

9b. The DNA is isolated and transferred to another tube, which now contains the desired DNA without the unnecessary cell components. A form of alcohol is added to the solution and interacts with the DNA. This allows the DNA to gather together and become visible.

10b. The DNA is then transferred to a small tube containing a solution that preserves the genetic material for future studies. In a freezer set at –70° Fahrenheit, the DNA is stored for future use.



Step 9b

Step 10a

Step 10b

11. Qualified researchers around the world continually request samples from the National Cell Repository for Alzheimer's Disease. A committee reviews each request and determines if the research is appropriate. After a request is approved, the samples are retrieved, thawed, and prepared for shipment. In some cases, a sample is no longer available when all the DNA has been used and the cells no longer grow. If possible, the individual who provided the original sample may be contacted again and asked to provide another blood sample.

    With each sample, researchers are given necessary information about the individual's clinical history and diagnosis. They are never provided with a participant's identification information, such as their name, in order to protect the confidentiality of the individual and their family.

    The cell lines and DNA are extremely valuable for Alzheimer's Disease research. **We greatly appreciate all the support from the families who participate in the National Cell Repository for AD.**

Step 11

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: Jami Stuck,
PH: 800-526-2839
E-mail: jastuck@iupui.edu

CATIE-Alzheimer's Disease Trial

Purpose: To determine whether three antipsychotic medications (olanzapine, quetiapine, and risperidone) help prevent behavioral and psychiatric concerns in patients with Alzheimer disease.
Eligibility: Diagnosis of Alzheimer disease, presence of psychiatric disturbances (i.e. hallucinations, delusions, agitation)
Locations: AL, CA, FL, GA, HI, IL, IA, LA, MD, MA, MO, NH, NY, NC, OH, OK, PA, SC
Contact: Karen Dagerman,
PH: (323) 442-3715,
E-mail: dagerman@hsc.usc.edu

COGNIShunt System for Alzheimer's Disease

Purpose: To determine if this surgically implanted shunt will stop or slow the progression of AD.
Eligibility: Ages 62-85 with mild to moderate AD
Locations: AZ, AK, CA, FL, GA, IN, KY, MA, MO, NY, OR, PA, RI, TN, TX, VA
Contact: Susan Cruikshank,
PH: 925-621-4100,
E-mail: info@eunoe-inc.com

Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT)

Purpose: To study the ability of naproxen and celecoxib (non-steroidal anti-inflammatory medications) to delay or prevent the onset of AD and age-related cognitive decline.
Eligibility: Healthy, ages 70+, family history of dementia (i.e. AD)
Locations: AZ, FL, MD, MA, NY, WA
Contact: Janette Negele,
PH: 206-277-6548,
E-mail: jnegele@washington.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: Jami Stuck,
PH: 800-526-2839
E-mail: jastuck@iupui.edu

Estrogen Effects on Memory Functioning in Post-Menopausal Women and Patients With Alzheimer's Disease

Purpose: To examine whether three months of estrogen administered to 1) post-menopausal women and 2) women with mild-moderate Alzheimer's disease who are concurrently treated with standard therapy (generally Aricept), will improve memory and learning.
Eligibility: Female, Between ages 45-85, normal or mild AD
Location: VT
Contact: Katie Hancur, M.S.,
PH: (802) 847-8596,
E-mail: Catherine.Hancur@vtmednet.org

Efficacy and Safety of LY451395 in Patients with Probable Alzheimer's Disease

Purpose: Study of an investigational medication for the treatment of AD in patients who are not taking Aricept, Reminyl, or Exelon.
Eligibility: Ages 50+ with clinical diagnosis of AD and not taking Aricept, Reminyl, or Exelon
Locations: CA, FL, MA, OK, TX
Contact: 1-877--285-4559

Alzheimer's Disease Prevention Trial

Purpose: To determine whether estrogen and progesterone can delay the onset of memory loss or AD in elderly women with a family history of the disease.
Eligibility: Healthy, ages 65+, family history of dementia
Locations: CA, CT, DC, FL, MD, NJ, NY, NC, OK, RI, SC, VA
Contact: Gina Garcia-Camilo,
PH: 1-877-DELAY-AD

For more information on clinical research studies, you may visit

A New National Initiative (Cont.)

(Continued from page 1)

The process of the NIA Genetic Initiative for AD, also known as Late-Onset Alzheimer's Disease (LOAD) Study, is to identify families with several members having late-onset AD who are willing to have a clinical evaluation by an expert in AD and to donate a blood sample. The clinical information would be provided to the National Cell Repository for Alzheimer's Disease without names or other identification information.

In the near future, qualified researchers interested in studying large, well-defined families with late-onset AD may contact NCRAD for the samples and clinical history information. Dr. Conneally states, "the LOAD Study will be of great help to researchers who do not have the resources to locate families, obtain blood samples and clinical information, and establish the genetic materials needed to study late-onset AD."

READER'S RESPONSE SECTION

What topics/questions would you like covered in future NCRAD Update issues?

_____

_____

What resource information would you like provided in future issues?

_____

_____

Moving? Please let us know your new address:

_____ ( ) _____

Name **Phone**

_____

Street Address

_____

City **State** **Zip**

AD Treatment Update (Cont.)

(Continued from page 2)

and delay potential nursing home placement. Patients who do not respond to one medication may respond to another.

Another form of treatment, known as memantine, has been used in Germany to treat dementia for over 10 years. Memantine appears to protect the nerves in the brain against excess amounts of glutamate, a chemical released by cells damaged by conditions like Alzheimer's disease. The presence of large amounts of glutamate increases calcium flow in cells and, as a result, may lead to cell degeneration. Forest Laboratories, Inc., is currently developing memantine in the United States.

Researchers are continuing to study other forms of AD treatment, including non-steroidal anti-inflammatory drugs (NSAIDs), hormonal treatments, vitamins and herbal supplements, and medications used to reduce cardiovascular risks.

Several large studies have suggested that the use of NSAIDs, such as asprin, by healthy elderly individuals may decrease their risk of developing AD by 30%-70%. In contrast, recent trials have not supported these results. More trials are underway to further evaluate the effectiveness of NSAIDs in preventing AD.

Another large study suggested that the use of estrogen replacement therapy by healthy elderly women may reduce their risk of developing AD by 30% to 70%. However, other studies revealed no benefits in taking estrogen to reduce the risk or delay the onset for developing AD.

Researchers have suggested that vitamins may inhibit the formation of toxic substances in the body and prevent or delay the onset of AD.

One study found that individuals who took daily doses of vitamin E had delayed nursing home placement, functional decline, and/or death by about 25% compared to those who did not take vitamin E. No prevention of cognitive decline was seen. Nevertheless, vitamin E at 2,000 units per day has been widely adopted as a standard therapy for patients with AD.

Results from recent therapeutic studies in AD are both discouraging and encouraging. The cholinesterase inhibitors appear to improve cognitive functioning and relieve behavioral symptoms in AD. Vitamin E seems to be a potential helpful therapy, especially in conjunction with other forms of treatment for AD. Recent studies with NSAIDs and estrogens are discouraging, at least in the short term. Other therapeutic approaches, such as vaccinations, are currently in trials and hoped to improve AD treatment in the future.

Resources 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

Creutzfeldt-Jakob (CJD) Foundation Inc.
http://cjdfoundation.org
Tel: 954-704-0519 305-891-7579

Parkinson's Disease Foundation (PDF)
http://www.parkinsons-foundation.org

Society for Progressive Supranuclear Palsy
http://www.psp.org
Tel: 410-486-3330 800-457-4777
Tel: 212-923-4700, 800-457-6676

National Organization for Rare Disorders (NORD)
http://www.rarediseases.org
Tel: 203-746-6518 800-999-NORD (6673)

Family Caregiver Alliance
http://www.caregiver.org
Tel: 415-434-3388 800-445-8106

We Have Changed Our Name, But Not Our Mission!

Until recently, the National Cell Repository was part of the Indiana Alzheimer's Disease Center (IADC). In July 2002, the Repository was renamed the National Cell Repository for Alzheimer's Disease (NCRAD) and is no longer a part of the IADC. This was an administration change. There has been no change in procedure, where samples are stored, or our telephone number and staff. Our goal remains to assist researchers in understanding why people develop Alzheimer's disease so that more effective treatments can be developed to stop this devastating disease.

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