NCRAD Update

Newsletter of the National Cell Repository for Alzheimer's Disease Volume 4 ■ January 2004

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.

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Inside this Issue...

Gene That Influences Age of Onset of Alzheimer's Disease May Have Been Identified

Tatiana Foroud, Ph.D. Associate Professor, Department of Medical and Molecular Genetics, Indiana University School of Medicine

Researchers have recently reported that they may have identified a gene that helps determine when an individual develops symptoms of Alzheimer's disease [AD]. Scientists at Duke University and Vanderbilt University studied a number of families whose members developed symptoms of AD at an average age of 71. These scientists also studied families with Parkinson's disease.

A critical part of this research was the careful study of the brain tissue from individuals with varying ages of onset of Parkinson's disease and AD. These analyses allowed the scientists to identify a small number of genes that appeared to be making either more or less of their normal gene product. This led the scientists to more carefully study the gene called glutathione S-transferase, omega-1 [GSTO1, pronounced gusto]. From their studies,

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Meet the New NCRAD Staff

Recently, the National Cell Repository for Alzheimer's disease said goodbye to our wonderful study coordinator, **Jamalynne (Jami) Stuck**. Jami got married June, 2003 and moved to northern Minnesota with her new husband. We wish Jami the best and will miss her tremendously!

With the renewed focus on studies to better understand the genetics of Alzheimer's Disease we have expanded the NCRAD staff. We now have three study coordinators who are managing the many aspects of NCRAD: Michele Goodman, Jessica Leatherland, and Valerie Parks.

Michele Goodman is originally from Bloomington, Indiana and joined NCRAD in July 2003. Her primary focus at NCRAD is to coordinate efforts for the new AD Genetics Family study which is supported by the National Institute of Aging and the Alzheimer's Association. Michele is working with new families who meet criteria for this study and is referring individuals whenever possible to one of the 29 Alzheimer's Disease Centers located through the United States.

Jessica (Jessie) Leatherland has been at Indiana University since 2002. She initially was a research coordinator in the Indiana Alzheimer Disease Center but joined NCRAD in July 2003. Jessie has been working closely with the families who have participated in NCRAD over the past few years. She also coordinates the NCRAD newsletter and is working with researchers interested in using NCRAD samples.

Valerie Parks recently moved to Indiana and joined NCRAD in August, 2003. She is also working closely with the families who have participated in NCRAD over the past decade. Her role also includes maintaining contact with families to ensure that accurate and current information is on file. Valerie brings three years of clinical research experience to the National Cell Repository for AD.

Members of the NCRAD staff
From left to right - Front row: Jessie Leatherland, Michele Goodman, Dr. P. Michael Conneally. **Back row**: Dr. Tatiana Foroud, Valerie Parks

During the past 13 years, **Dr. P. Michael Conneally**, Distinguished Professor of Medical and Molecular Genetics and Neurology has been the leader of the National Cell Repository for Alzheimer's Disease. Dr. Conneally has been instrumental in the identification of a number of different genes leading to neurodegenerative disorders including Alzheimer's disease and Huntington's disease. **Dr. Tatiana Foroud**, Associate Professor of Medical and Molecular Genetics and Psychiatry, who has worked closely with Dr. Conneally over the past decade, will be assuming the leadership of NCRAD. Dr. Conneally will continue to be instrumental in NCRAD.

Gene Identified

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it appears that this gene may influence the age of onset of AD or Parkinson's disease. Interestingly, there was no evidence that this gene determines whether an individual will develop AD or Parkinson's disease.

How GSTO1 might influence when an individual develops a neurodegenerative disorder like AD or Parkinson's disease is still unclear. GSTO1, and other genes with a similar DNA sequence, are believed to be important in clearing certain compounds, such as drugs or carcinogens, from the body. There was a recent report that this gene may be involved in the body's inflammatory responses.

The results of this study must be replicated by others. However, this is an exciting new research finding that may help us to better understand when an individual will develop these devastating disorders. This study also highlights the critical role that brain tissue plays in research designed to identify genes. It was only through the careful comparison of brain tissue from individuals with AD and Parkinson's disease that the GSTO1 gene was identified.

NIA Launched a New Alzheimer's Disease Family Genetics Study

The National Institute of Aging (NIA) a branch of the National Institute of Health (NIH), has recently launched a new effort to help researchers identify the genes that play a role in the development of Alzheimer's disease. This national effort seeks to recruit 1,000 families with two or more living brothers or sisters who have been diagnosed with Alzheimer's disease. Through the participation of these families, scientific researchers will be able to obtain the critical information they need to help them identify the genes that increase the risk for Alzheimer's disease.

Family members will be seen at one of the 29 Alzheimer's Disease Centers located throughout the United States. In some cases, an Alzheimer's disease researcher will come to see a family member. Blood samples from participating individuals will be mailed to the National Cell Repository for Alzheimer's Disease (NCRAD) and stored with those samples from families who have already participated in genetic family studies.

We have had calls from many of you about this new initiative! We are so pleased to hear how committed you are to research that will help us to better understand Alzheimer's disease. Families already participating in NCRAD are not eligible to enroll in the new NIA genetics efforts. The reason for this is that we have already obtained the valuable blood samples from your family. It is not necessary for us to obtain another blood sample. We have already obtained DNA (genetic material) and an immortalized cell line, which is a replenishable source of DNA.

NIA seeks to recruit 1,000 families with two or more living brothers or sisters who have been diagnosed with Alzheimer's disease.

In the coming months, we will be asking all families participating in genetic family studies to help us obtain the most complete information possible so that researchers can find the genes that increase and decrease the risk for AD. We are making an effort to obtain newer medical records in some families. We will also be asking some family members if they would be willing to complete a telephone questionnaire with a NCRAD staff member. As always, we will ask families to consider brain donation, which provides important information for AD research.

We thank you for your past participation in NCRAD and look forward to hearing from you!

Authorization for the Release of Health Information for Research

The Health Insurance Portability and Accountability Act (HIPAA) of 1996 is a healthcare regulation that most health providers have to comply with that protects the privacy, security, and confidentiality of a patient or research subject's health information. The HIPAA Privacy Rule of 1996 for the first time created national standards to protect the medical records and other personal health information of individuals. For patients, it means being able to make informed choices when seeking care and reimbursement for care based on how personal health information may be used.

It is now required that individuals involved in the National Cell Repository for Alzheimer's Disease sign an Authorization for the Release of Health Information for Research form. NCRAD is in the process of updating all family files and will be contacting individuals who have not signed an Authorization form with us.

If you have questions concerning this form, please feel free to contact the NCRAD staff at 1-800-526-2839 or email at alzstudy@iupui.edu.

Why is Genetics an Important Area of AD Research

Tatiana Foroud, Ph.D. Associate Professor, Department of Medical and Molecular Genetics, Indiana University School of Medicine

During the past decade, many scientists have been carefully examining the role of genes in Alzheimer's disease [AD]. Through the careful comparison of the genetic material (deoxyribonucleic acid, DNA) inherited by family members who develop AD and those who do not, researchers have been able to identify three genes which are important in AD. Changes in the DNA sequence of any of these three genes, presenilin 1 (PS1), presenilin 2 (PS2) and amyloid precursor protein (APP), can result in AD. Most individuals with an altered DNA sequence in these genes will develop AD at an earlier age, typically before the age of 60 years. Since most people develop AD at an older age, only 5% of individuals with AD have a mutation, or DNA sequence change, in one of these three genes.

A fourth gene, Apolipoprotein E (APOE), has been found to be a gene important in later onset AD. The DNA sequence of the APOE gene has been carefully studied and it has been shown that there are three relatively common forms or sequences of this gene. These have been termed APOE2, APOE3 and APOE4. Studies from many different researchers have shown that individuals who have inherited at least one copy of the APOE4 sequence are at higher risk of developing AD as compared to individuals who have only the APOE3 sequence, which is the most common. Individuals who have inherited at least one copy of the APOE2 sequence are at lower risk of developing AD as compared with those having inherited only the APOE3 sequence. Individuals who have inherited an APOE4 sequence are at higher risk of developing AD; however, unlike the DNA sequences in the PS1, PS2 and APP gene which can cause AD, the APOE4 sequence is considered a risk factor rather than a cause of AD. Thus, there are individuals who have inherited the APOE4 sequence who do not develop AD.

The search for genes that increase or decrease the risk for AD is an important area of scientific research. It is hoped that through the identification of these genes, researchers will be able to develop drugs that can counteract the negative effects of these genes. Some researchers are pursuing alternate approaches to develop treatments that might delay or improve the symptoms of research. Some have attempted to use stem cell research. This is a very different type of research from that which seeks to identify genes that increase the risk of AD. The goal of stem cell research is to potentially replace the cells in the brain that have been altered and died. The promise of stem cell replacement as a treatment for AD is likely to be decades away.

Unfortunately, the media has called the search for genes and the use of stem cells as 'genetic research'. Some have used the terms stem cell research and cloning interchangeably. Few, if any, researchers have proposed to clone individuals as a means of treatment for AD. We must wait to see whether stem cell research will prove a useful therapy in AD. In the meantime, the identification of genes has been an immediate focus for many researchers who hope that this might more rapidly lead to better treatments for AD.

GENETIC DEFINITIONS

The following definitions were obtained from the Alzheimer Association (www.alz.org).

Amyloid precursor protein (APP)
A protein found in the brain, heart, kidneys, lungs, spleen, and intestines. The normal function of APP in the body is unknown. In Alzheimer's disease, APP is abnormally processed and converted to beta amyloid protein. Beta amyloid is the protein deposited in amyloid plaques.

Apolipoprotein E
A protein whose main function is to transport cholesterol. The gene for this protein is on chromosome 19 and is referred to as APOE. There are three forms of APOE: e2, e3, and e4. APOE-e4 is associated with about 60 percent of late-onset Alzheimer's cases and is considered a risk factor for the disease.

DNA (deoxyribonucleic acid)
A chain of nucleotides (cytosine, guanine, adenine, or thymine) linked with ribose sugar molecules that form the basis of genetic material. Specific patterns of nucleotides represent particular genes.

Gene
The basic unit of heredity; a section of DNA coding for a particular trait.

Presenilins
Proteins that may be linked to early-onset Alzheimer's disease. Genes that code for presenilin 1 and presenilin 2 have been found on chromosomes 14 and 1, respectively, and are linked to early-onset familial Alzheimer's disease.

Autopsy: An Important Part of Our Research

Jessica Leatherland, Clinical Research Specialist, Department of Medical and Molecular Genetics, Indiana University School of Medicine

The word "autopsy" is derived from the Greek word autopsia, which means to see with one's own eyes. An autopsy is the examination of brain tissue by a pathologist with special training in the area of neurological disorders, such as Alzheimer's disease. The pathologist looks for changes in brain tissue that would only occur in an individual with Alzheimer's disease.

While it is often difficult to decide to pursue an autopsy of a family member, there are several important reasons to consider this option. First, a post-mortem examination of the brain is the only way to definitively diagnose Alzheimer's disease. Second, information obtained through an autopsy may provide family members with essential information, particularly in the case of hereditary diseases. Third, the autopsy procedure provides additional tissue samples for research into the causes and mechanisms of the disease.

While it is often difficult to decide to pursue an autopsy of a family member, there are several important reasons to consider this option.

Many families are reluctant to discuss an autopsy and wait until the last moment to do so. The time when a family member passes away is filled with many emotions as well as the need to carry out any arrangements and notify the necessary individuals. By having the autopsy planned well in advance, this time will not have the added stress of deciding whether or not to have an autopsy done, contacting all of the individuals needed to make the decision, and alerting the appropriate physicians.

Coping with a degenerative illness affecting a family member is emotionally difficult as is the decision to prearrange an autopsy; however, it is important for both the family and the community. We will pay all costs associated with the autopsy such as transportation of the body, brain tissue removal, and neuropathological examination of the tissue. Additionally, family members will receive an autopsy report generated by the neuropathologist who examined the brain tissue.

The National Cell Repository for Alzheimer's Disease staff members can discuss autopsy with you and answer any questions that you might have. We can work together to plan the autopsy and ensure that the opportunity to gain this valuable family medical information is not lost.

For further information, please contact the NCRAD coordinator's at 1-800-526-2839.

Did You Know?

- 485 autopsies have been performed on NCRAD participants
- 82 autopsies are currently planned
- We have planned autopsies in 40 different states
- We have even planned autopsies for individuals as far away as Alaska and Hawaii

Thank You!

Thank you to all the families who have expressed interest or pursued an autopsy. This is the ultimate gift to research and can provide valuable information for the family.

Your generous contribution towards Alzheimer's research is greatly appreciated and respected.

For questions or additional information about the autopsy program, please contact a NCRAD coordinator at 1-800-526-2839 or e-mail at alzstudy@iupui.edu.

Memantine - A New Treatment for Alzheimer's Disease

Ann Marie Hake, M.D., Clinical Assistant Professor, Department of Neurology, Indiana University School of Medicine

For the past 11 years, Alzheimer's disease has been treated with cholinesterase inhibitors - tacrine (Cognex), donepezil (Aricept), rivastigmine (Exelon), and galantamine (Reminyl) - a group of medications that help memory by increasing the amounts of the brain chemical acetylcholine. 2004 will mark the beginning of a new era in the treatment of AD when a new drug becomes available in January. Approved by the FDA for the treatment of moderate to severe-stage Alzheimer's in October 2003, memantine works by keeping excessive calcium from flowing into nerve cells in the brain while the nerve cells are at rest. When it is time for the nerve cell to be activated, memantine moves aside and allows the calcium to enter the cell. By allowing calcium into the nerve cell only during cell activation, memantine essentially reduces "background noise" in the brain and allows nerve cell signals to be transmitted more clearly.

Memantine has been available for several years in Europe under the brand names "Ebixa", "Axura", and "Akatinol". Forest Pharmaceuticals will market memantine in the United States under the brand name "Namenda". In clinical trials, patients with moderate to severe-stage Alzheimer's who were taking memantine declined at a slower rate than the patients on placebo (sugar pill). The most common side effects seen with memantine were dizziness, headache, confusion, and constipation, although most patients tolerated the medication without any problems. Taking memantine at the same time as a cholinesterase inhibitor did not decrease the effectiveness of either drug or cause any drug interactions, and it is expected that most people will take memantine in addition to the Alzheimer's medications they are already taking. The starting dose for memantine is 5 mg daily; it is increased by 5 mg each week up to the target dose of 10 mg twice a day.

For more information, please contact your physician and/or pharmacist.

What is a Clinical Trial?

Kathleen Miller, C.O. and Jessica Leatherland, Clinical Research Specialist, Department of Medical and Molecular Genetics, Indiana University School of Medicine

Many clinical trials are being conducted across the country to identify better means to treat and prevent Alzheimer's disease and memory loss. Participation in a clinical trial offers many opportunities to learn more about possible treatments for Alzheimer's disease and also provides a means to have a more active role in health care. However, it is essential to understand what a clinical trial is as well as the risks and benefits of participating in one.

Before a new drug is made widely available to treat patients with a disease, it must undergo a lengthy process to determine whether or not the drug is safe, what doses of the drug should be used and what kinds of side effects should be expected. A series of steps are usually followed in order to learn this information in a way that is safe and limits the risks to patients. The steps are typically called Phases.

In the first stage, **Phase I**, a drug is given to a small group of healthy people (typically 20 to 80) for the very first time, to determine and establish **safety** and **tolerance** of the drug in humans. In **Phase II**, the drug is given to a larger group (typically 100 to 200) of individuals with the disease, to further determine an appropriate range of doses and to learn more about the drug **safety** and also drug **effectiveness**. In **Phase III**, the clinical trial tries to expand on the effectiveness and safety of what is known regarding the drug along with selected dosing amounts of the drug (i.e. number of tablets per day or milligrams given to the subject). Sometimes the study protocol is further analyzed to understand the effects of sex, race, ethnic background, age or other indicators on drug **effectiveness**. **Phase IV** trials are any studies done after a drug is approved. This involves a very large group (typically thousands) of subjects to continue to monitor **safety** in larger, broader, populations.

If you are interested in participating in a clinical trial, please see "Research Opportunities" on page 7 for a list of current ongoing studies.

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

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

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

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-CTLILLY (1-877-285-4559) (toll free)

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 probably 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

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://cjdfoundation.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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