NCRAD Update

Newsletter of the National Cell Repository for Alzheimer's Disease Volume 8 ▪ March 2006

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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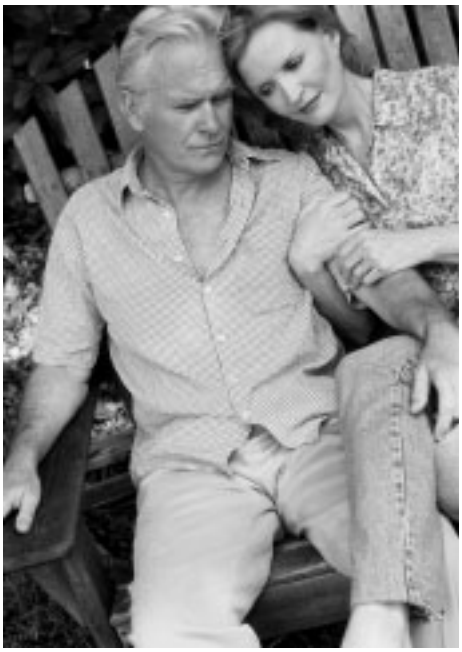
USE OF BLOOD SAMPLES AND DATA COLLECTED AT NCRAD

By Tatiana Foroud, Ph.D.
and Teresa Evans
Indiana University School of Medicine

NCRAD began in 1991 at Indiana University. The goal of NCRAD is to involve families with dementia in research. The blood collected from NCRAD study participants are used to obtain DNA and to establish an immortalized cell line. This is a special kind of cell that continues to grow and can be used as a source of DNA. Families and individuals participating in NCRAD also provide information about their family's history of dementia and Alzheimer's disease. Individuals are also often asked to help NCRAD staff obtain medical records to document Alzheimer's disease or dementia.

Since 1991, NCRAD has collected 6,392 samples from individuals and families. These samples and the clinical and family history information from these individuals have been used by researchers to understand the genetics of Alzheimer's disease. Over the past 15 years, over 15,174 samples have been distributed to researchers studying AD. All samples are sent to researchers without any identifying information, such as name. Researchers do not know the identity of any of the samples they are studying.

Nearly 50 different investigators from around the world have requested samples from NCRAD. These researchers have published 119 different papers about Alzheimer's disease and dementia.



> "Through the continuing participation of NCRAD study families, we hope to identify the genes that increase and decrease an individual's risk for dementia."

These papers have helped to better understand the genetics of early onset Alzheimer's disease, late onset Alzheimer's disease and other types of dementia. Through the continuing participation of NCRAD study families, we hope to identify the genes that increase and decrease an individual's risk for dementia.

See related graph on page 4

BRAIN AUTOPSY: QUESTIONS AND ANSWERS

By Teresa Evans
NCRAD Coordinator IU School of Medicine

Q. Why is a brain autopsy important?

A. Examination of brain tissue after death is currently the only definitive way to diagnose the specific neurodegenerative disorder of an individual. The information obtained through autopsy has provided family members with invaluable family medical history information. Many neurodegenerative disorders are passed through families from one generation to the next. There are several different types of these disorders that require different types of treatments. Once a specific neurodegenerative disorder is known to be common in the family, physicians can better treat the surviving family members. In addition, a confirmed diagnosis is a valued asset to researchers working hard to unlock mysteries of these debilitating illnesses.

Q. How expensive is a brain autopsy?

A. Because the information gained through a brain autopsy is a very valuable resource for research and family members, NCRAD will cover the costs involved for study participants. Currently, NCRAD is only accepting plans for individuals showing signs of dementia. Most autopsy expenses stem from transportation, removal of brain tissue and the neuropathological examination.

Q. Who is involved in planning a brain autopsy?

A. NCRAD staff will assist study participants in planning for a brain tissue autopsy for those showing signs of dementia. We will need the current contact information for the brain tissue donor, next-of-kin or legal representative, as well as information about the funeral home chosen for the donor. After we receive this information, NCRAD will locate a professional who will remove the brain tissue and send it to a qualified neuropathologist for the autopsy.

Once a professional for the removal is located, an authorization to perform the autopsy must be signed by the next-of-kin or legal representative. Next, a detailed Autopsy Planning form is sent to all individuals involved.

Q. Who is notified about the planned autopsy?

A. At the time of death, all tissue rapidly begins to degrade or be destroyed. In order to ensure the greatest research and diagnostic value for the brain tissue, it is essential that it is removed as quickly after death as possible. Therefore, we suggest that all persons involved with the care of the donor be made aware of the planned autopsy. These individuals need to know who to contact at the time of death so that the appropriate steps are taken to ensure rapid removal of brain tissue.

Q. Who is contacted at the time of death?

A. Who to contact at the time of death is dependant upon the specific plans in place. Usually, the family notifies the funeral home staff and the staff notifies the remaining individuals involved. They should also contact NCRAD at 1-800-526-2839.

Q. Will funeral or burial plans be affected?

A. Autopsy will not delay or complicate plans for a funeral, cremation, or burial. Neither will it interfere with an open casket. In most cases the funeral home is very helpful in assisting with brain tissue removal.

Q. Who receives the autopsy results?

A. The next-of-kin or legal representative assisting with the arrangements will receive information regarding the diagnosis. This usually takes 9 to 12 months after the time of death.

Q. Why plan ahead?

A. Planning for an autopsy should be done well ahead of time, because of the steps involved. Some autopsies are planned several years in advance. However, if the donor passes away before any plans have been made, NCRAD staff will do all they can to assist the family with a brain autopsy.

Q. May the plans be cancelled?

A. Plans may be cancelled at any time by notifying the NCRAD staff.

Q. How is the NCRAD staff contacted?

A. NCRAD staff may be contacted toll-free by phone at **800-526-2839** or by e-mail at **alzstudy@iupui.edu**. Please do not hesitate to contact us with any concerns or questions.

Researcher's Corner: Rodney Go, Ph.D. **Familial Alzheimer's Disease Research at UAB**

By Ryan Dickson, MS

The biological processes initiating or accelerating the development of Alzheimer's Disease (AD) are complex and not completely understood, and the disease has been observed to cluster within families. Thus, studying the genetics of AD can help to improve our understanding of AD pathology. That is why Rodney Go, Ph.D. and his research team at The University of Alabama at Birmingham (UAB) in the Department of Epidemiology and International Health are committed to identifying genetic risk factors for AD. Dr. Go is a genetic epidemiologist with experience in the genetic analyses of complex diseases and traits. Included in his research team are Rodney Perry, Ph.D., Associate Director of the group's Familial AD Molecular Genetics Laboratory; Howard Wiener, Ph.D., a genetic statistician; three research assistants, Muktar Aliyu, Zuomin Chen and Micah Simmons; a research technician Wenzhu Hao; and three graduate students; Jian Li, Ryan Dickson, and Dora Adobe.

Most cases of AD are late onset (age at onset is at least 65 years), of complex origin and probably caused by a combination of environmental and genetic factors and their interactions. Specifically, Dr. Go and his research team have been part of several collaborative efforts with researchers from many universities that apply methods in molecular genetics and statistics to identify regions of the genome shared by affected family members in order to isolate genes involved in late onset AD. Included within the studiedfamilies used are several large late onset AD families that are also part of the NCRAD family resource. The group focuses primarily on genes in biochemical pathways that appear to be involved with the pathogenesis of AD, such as inflammation, oxidative stress, cholesterol metabolism, neurological function, and beta amyloid processing. Additionally, since AD and cardiovascular disease (CVD), share common risk factors, the genes involved in CVD are a new target for the group for future research.

The research aims are accomplished using clinical and genotype data from different patient populations. The first population is a large group of families collected as part of the National Institute of Mental Health (NIMH) AD Genetics Initiative. A second population, identified at UAB, consists of a group of African American AD subjects and unrelated, age and race matched controls. The third group is samples from families that participated in the National Cell Repository for Alzheimer's Disease.

Left to Right Standing- Zuomin Chen, Micah Simmons, Howard Wiener, Wenzhu Hao, Rodeny Go, Rodney Perry, and Sitting- Dora Adoboe, and Ryan Dickson.

Using these families, the laboratory reported an AD associated genomic region near the Tumor Necrosis Factor (TNF) gene on 6p. TNF is an important proinflammatory protein that is upregulated in AD patients. TNF co-localizes to AD affected areas of the brain with particularly high expression near the pathological features that are found in the AD brain, neuritic plaques and neurofibrillary tangles (NFTs), but is absent or minimal in unaffected regions of the AD brain. Inflammatory mediators such as TNF could cause neuronal damage by overstimulating the immune system resulting in a chronic inflammatory state, which is supported by animal studies where induced brain inflammation in rats causes neurodegeneration and memory loss. Our lab has found a significant association of a promoter polymorphism in TNF, that may increase TNF protein levels, with AD. Also, we have shown that genomic regions harboring TNF receptor genes (TNFR1+TNFR2), which mediate the biological effects of TNF, to be associated with AD. These results provide solid evidence for the involvement of TNF in the pathogenesis of AD.

Transforming Growth Factor-B___TGFB1_ and Superoxide Dismutase 2 (SOD2) are two other genes with which we have found significant associations with AD in both study populations. TGFB1_is another protein involved in inflammation and, in particular is a key regulator of the brain's responses to injury. SOD2 is an antioxidant enzyme that is responsible for repairing oxidative damage to cells. Our results support possible roles for TGFB1 and SOD2 in AD pathogenesis.

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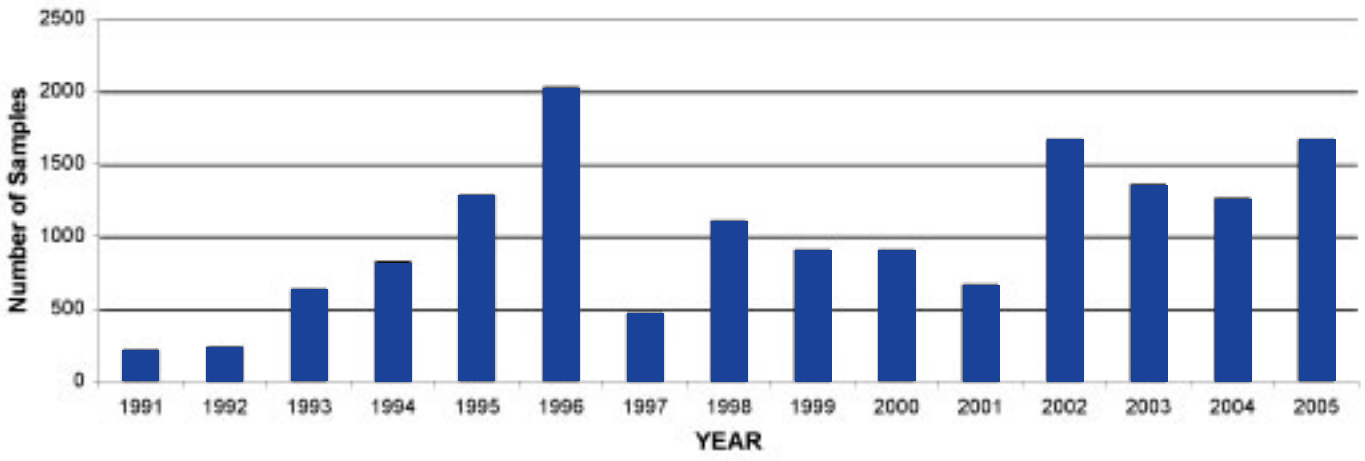
TOTAL SAMPLES SENT PER YEAR



Over the past 15 years, over 15,174 samples have been distributed to researchers studying AD.

NCRAD Staff

Since our last staff update in 2004 NCRAD has had several staff changes. We would like to take this opportunity to introduce our new staff and to update you on what our staff has been working on.

Dr. Tatiana Foroud is the principle investigator for the NCRAD study. She works closely with the NIH to ensure that the specific aims and goals of the NCRAD project are met. She is responsible for the oversight of the NCRAD study from the participation of families all the way to the used of samples by researchers throughout the United States. Dr. Foroud is the P. Michael Conneally Professor of Medical and Molecular Genetics and the Director of the Division of Hereditary Genomics at Indiana University.

Michele Goodman has been with NCRAD since July 2003 and continues to serve as a primary coordinator for the AD Genetics Initiative supported by the National Institute on Aging. Michele recruits new families and monitors clinical data and biological specimens collected by participating Alzheimer Disease Centers.

Teresa Evans is a Clinical Research Specialist at NCRAD, joining, the team in May 2005. Teresa has been with the IU School of Medicine since 1999 and brings several years of clinical research to the team. Her primary role is to maintain contact with NCRAD participants and families. She also performs annual chart reviews, verifying existing family data and updating the files as new information becomes available.

Kate Kreiner recently moved to Indiana in February of 2006. Kate is a Clinical Research Specialist with NCRAD. She is responsible for coordinating brain autopsies for NCRAD patients. She works closely with NCRAD families and everyone involved in autopsy planning including funeral homes, hospitals, and laboratories. Kate is also responsible for organizing the NCRAD Newsletter.

Researcher's Corner: Rodney Go, Ph.D. continued from page 3

Results of studies utilizing genomic data from the family sample that includes NCRAD families have shown chromosome 9 to be a region of interest for AD risk. Genes of interest in this region are currently being investigated for contribution to AD.

Dr. Go's group at UAB continues to search for candidate genes identified in these genomic scans while focusing on relevant physiological pathways. The fundamental benefit of the research is that genes found to be associated with disease help us better understand disease pathology and ultimately allow the identification of new targets for the development of novel treatments and interventions for AD. For questions please contact, Dr. Rodney Go, at rgo@uab.edu.

Research Opportunities

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. It is hoped that by obtaining data from 1000 families, these associations can be better understood.
- 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: 1-800-526-2839
  or email: kjhorner@iupui.edu

Alzheimer's Disease Neuroimaging Initiative

- Purpose: to examine how brain imaging technology can be used with other tests to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). This information will aid future clinical trials by providing a standard assessment tool to measure the effects of treatments being studied.
- Eligibility: Minimum Age 50 Maximum Age 90, Both Genders, Disease stages: Pre-Clinical, Early, and Middle. Participants will be classified as either MCI patients, AD patients, or healthy controls
- Locations: AL, AZ, CA, CT, DC, FL, GA, IL, IN, KS, KY, MD, MO, NV, NH, NY, NC, OH, OR, PA, SC, TX, VT, WI
- Contact: Laura Jakimovich, RN, MS
  PH: 585-760-6578
  E-mail:
  laura_jakimovich@urmc.rochester.edu

Depression in Alzheimer's Disease

- Purpose: To demonstrate whether the medication sertraline (Zoloft®) helps people with Alzheimer's disease and depression their families and caregivers. Through this study we hope to find out if treating depressioncan slow the progression of Alzheimer's disease.
- Eligibility: People who suffer from memory loss, Alzheimer's disease, and symptoms of depression. Participants must also be accompanied by their caregiver.
- Locations: CA, MD, NY, PA, SC
- Contact: Ann Morrison, PhD, RN
  PH: 410-614-4605
  E-mail: amorris7@jhmi.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

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

Anti-Oxidant Treatment of Alzheimer's Disease

- Purpose: To examine the safety and effectiveness of two anti-oxidant treatment regimens in patients with mild to moderate Alzheimer's disease. The anti-oxidant treatments include vitamin E+ C+ alpha –lipoic acid, and Coenzyme Q (CoQ).
- Eligibility: Ages 60-85, Both Genders, Diagnosis of probably Alzheimer's Disease
- Locations: AL, AZ, CA, FL, NY, OH, OR, PA, SC, WA
- Contact: ADCS Anti-Oxidant Study webpage http://adcs.ucsd.edu/Anti-Oxidant_protocol.htm or Linda Mandelco E-mail: linda.mandelco@med.va.gov

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

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.alzheimers.org
Tel: 301-495-3311 or 800-438-4380
** ADEAR lists all 29 Alzheimer Disease Centers (ADCs) and their contact information.

Depression and Related Affective Disorders Association (DRADA)
www.drada.org
Tel:703-610-9026

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- Jacob (CDJ) Foundation Inc.
http://cjdfoundation.org

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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SCHOOL OF MEDICINE

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