

NCRAD Update

Newsletter of the National Cell Repository for Alzheimer's Disease

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The National Cell Repository for Alzheimer's Disease

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



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National Cell Repository for Alzheimer's Disease

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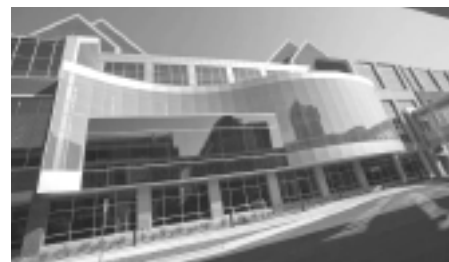
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Left: Health and Translational Sciences (HITS) Building – NCRAD Offices.

Right: Walther Hall – NCRAD Laboratory

20th ANNIVERSARY! NCRAD: Twenty Years of Progress

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The National Cell Repository for Alzheimer's Disease (NCRAD) celebrated its 20th anniversary in 2010. With the participation of the more than 900 families in NCRAD, we have significantly advanced Alzheimer's disease (AD) research. NCRAD has sent well over 50,000 biological samples to more than 90 AD researchers. Data and samples from our families have resulted in over 200 scientific publications, thirty-three of which were issued in 2010. NCRAD families have been, and continue to be, critical in many aspects of important AD research.

Critical samples and data

Families participating in NCRAD have generously provided blood samples that have been used to obtain DNA, our genetic material. From each blood sample, the laboratory staff at NCRAD is able to create immortalized cell lines, which are a type of sample that can survive indefinitely and can be a long term source of DNA for researchers. Families involved in NCRAD also provide us with important clinical information, including information about who within the family has developed symptoms of disease, medical records from physicians, and more recently, telephone evaluations that are used to assess changes in memory.

Over the past few years, NCRAD has greatly expanded its focus. First, in many of our families, the initial members with AD have passed away and we are now enrolling their children, who are entering the age of risk for AD. We encourage families to discuss the opportunities for new family members to become involved in genetic research. Researchers are particularly eager to study multiple generations in a family.

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Another initiative that NCRAD has undertaken in the past five years has been the banking of samples from control subjects. Controls are typically individuals who do not have a family history of AD (at least in their parents or siblings) and who are over the age of 60 years. Several of the studies banking samples at NCRAD have focused heavily on the recruitment of controls. The continued involvement of families with AD and control subjects is very important to NCRAD. Biological samples and data from both groups are critical for AD research.

Recent progress in AD genetics

About a decade ago, it was announced that the human genome had been sequenced. Many thought this would tell us what we needed to know about human genetics. However, this amazing scientific feat has proven to be only the first step on a long road to a better understanding of many disorders, including AD. Over the past five years, the sequencing of the human genome has led to a revolution in the tools that are available to study the genetics of AD. Scientists are now able to routinely study DNA at a very fine level, studying about 1 million different positions within the DNA sequence. Amazingly, the experiments that are used to obtain all this information are also quite rapid and data can be obtained in a matter of weeks.

With these new ways to study DNA and with the ability to study thousands of samples, researchers have made substantial progress in learning about new genes that appear to be important in the risk for Alzheimer disease. In some studies, researchers compare the DNA from individuals with AD to the DNA of individuals who are controls (individuals who do not have AD). In other studies, researchers have compared the DNA of multiple family members, some with AD and others without AD. In several journal articles as well as at the recent International Congress on Alzheimer Disease, scientists reported three new genes: clusterin, abbreviated CLU, which is also called APOEJ; the gene for phosphatidylinositol binding clathrin assembly protein (PICALM), and the gene for complement component (3b/4b) receptor 1, also called CR1. Samples from NCRAD have played an important role in confirming the role of these genes. Researchers are now focusing their efforts to understand how and why these genes are important in AD and are using samples banked at NCRAD to help do this.

Expansion of NCRAD

Over the past 5 years, NCRAD has also expanded tremendously, both in terms of the number of samples and also with regard to its space and facilities. NCRAD has expanded its role at the National Institutes on Aging, a branch of the National Institute of Health, to receive, process, and store samples from 13 different studies. As

a result, the number of samples at NCRAD has grown from about 13,000 to over 50,000! This required much more space and a year ago, NCRAD moved its laboratories to a brand new building with state-of-the-art facilities (see cover page for photo). This has ensured that the samples that NCRAD has collected can be shared more easily with far more researchers. Over the past 5 years, our autopsy program has also grown and NCRAD currently has DNA from 478 individuals who have also participated in our autopsy program.

Studies Actively Banking Samples at NCRAD

- African American Genetics Study (AA Genetics)
- Alzheimer's Disease Neuroimaging Initiative (ADNI)
- Dominantly Inherited Alzheimer Network (DIAN)
- Genetic Investigation in Frontotemporal Dementia and Alzheimer's Disease (GIFT)
- Late Onset Alzheimer's Disease (LOAD)
- Washington University Alzheimer's Disease Research Center (WU ADRC)
- University of Kentucky (UK ADC) Controls

Another area in which NCRAD has grown is in the studies of other types of dementia. NCRAD is currently banking samples from several studies of frontotemporal dementia (FTD), a less common cause of dementia. Because fewer individuals and families have this type of dementia, it is essential that NCRAD store and distribute these very valuable research samples.

The participation of families with AD is vitally important for scientific research seeking to understand why individuals develop AD. We are hopeful that any new knowledge gained from such research will help lead to preventions, treatments, and cures for this disease.

The NCRAD staff and all researchers using data and samples from NCRAD families are extremely grateful for your participation. Thank you!

• Updates to our Website

- The NCRAD staff has also created a new, updated version of our website, at www.ncrad.org.
- On the new site, we provide valuable information regarding participation in NCRAD, Alzheimer's disease and genetics, and our autopsy program. There are also a number of helpful website links and information about other studies in which our participants may be interested.
- Previous copies of NCRAD newsletters are also available on the site for viewing and downloading.

DIAN - A study opportunity for families with inherited early-onset AD



The Dominantly Inherited Alzheimer's Network (DIAN) study has been established by the National Institute

on Aging of the National Institutes of Health (US) to bring together researchers who study genetic forms of Alzheimer's disease (AD). The DIAN research volunteers are members of families in which AD is dominantly inherited, meaning that about 50% of the individuals in each generation of a family develop AD, generally before age 60. These rare forms of AD are caused by a mutation in one of 3 genes. Each child of an affected parent has a 50% chance of inheriting the mutation. If they do, they will likely develop the dementia of AD at about the same age as their parent. Siblings who do not have the mutation have no greater risk of developing AD than someone without a family history of AD and will participate in DIAN as part of a comparison group for their mutation-carrying siblings.

Individuals participating in DIAN are not required to know whether or not they carry a mutation. Should participants wish to learn their mutation status through genetic testing following genetic counseling, DIAN can assist with this process.

Research suggests that brain changes may occur years before actual Alzheimer's symptoms are detected. The major goal of DIAN is to study these changes in people who carry an AD mutation in order to determine how the disease process develops before there are any symptoms. Ultimately, knowledge gained from DIAN may lead to tests that detect people who still are normal but are at very high risk of developing dementia caused by AD. All DIAN participants will be members of families with dominantly inherited AD caused by a known mutation and may be ideal candidates to participate in possible future studies of drugs that may have the potential to halt the AD process and prevent dementia.

DIAN SITE LOCATIONS

UNITED STATES

Brown/Butler Hospital	Providence, RI
Columbia University	New York, NY
Harvard/Brigham and Women's Hospital	Boston, MA
Indiana University	Indianapolis, IN
University of California, Los Angeles	Los Angeles, CA
Washington University	St. Louis, MO

UNITED KINGDOM

Institute of Neurology, University College	London
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AUSTRALIA

Sir James McCusker AD Research Unit, Edith Cowan University	Perth
Prince of Wales Medical Research Institute	Sydney
Mental Health Research Institute, University of Melbourne	Melbourne

People from families with a known mutation causing AD are eligible to participate in DIAN and its studies of physical and mental changes that may predict future AD. These studies include:

- clinical interviews
- mental status testing
- brain scans, including magnetic resonance imaging (MRI) and positron emission tomography (PET)
- blood assays, including genetic studies
- assays of cerebrospinal fluid (CSF), obtained by lumbar puncture (spinal tap)

Presently, there are 10 DIAN study sites: 6 in the US, 1 in the United Kingdom, and 3 in Australia. Research volunteers travel to one of the sites for the studies, which are repeated every few years. It is expected that each round of DIAN studies will take about three days to complete. All DIAN assessments are for research purposes and are supported by DIAN. Reasonable costs of travel to a study site, accommodations and meals during study participation may also be covered by DIAN. Volunteers may receive payment for some study procedures; whether payment is offered and the amount will be determined by the individual study site.

DIAN participants need to:

- have a biological parent or sibling with AD caused by a known mutation
- be at least 18 years of age
- speak and read English
- have someone who knows them well and is willing to answer questions about their memory and thinking

Eligible individuals who volunteer to enroll in DIAN will contribute to this unique international effort to discover the basic causes of AD. At the same time, they must be highly committed, because DIAN asks much from these volunteers in terms of time and testing.

It is anticipated that the improved understanding of the AD process will result in better tests to detect AD and eventually lead to therapies to treat or even prevent the illness. However, there can be no guarantees of success in these areas, and almost certainly not within the next few years. DIAN volunteers who donate their valuable time to DIAN may not directly benefit themselves but hopefully will greatly help their children and grandchildren.

More information about DIAN can be found at www.dian-info.org or by calling the DIAN Global Coordinator at (314) 286-2683.

The NCRAD Autopsy Program

Autopsy can be a difficult conversation topic for many families. However, for families affected by Alzheimer's disease (AD), this discussion is very important, as the information obtained through the autopsy of individuals affected with AD can provide closure and vital family medical history. Examination of brain tissue after death is the only definitive way to confirm a degenerative neurological disorder, such as AD. Because diseases like AD may be passed on genetically to future generations, a confirmed diagnosis in a family can lead to more vigilance of symptoms and better treatment of living family members. For NCRAD, each autopsy diagnosis provides valuable data for researchers who are studying AD and related illnesses.

At NCRAD, we encourage pre-planning of autopsies for individuals affected with AD and for healthy non-affected individuals who wish to donate their brain tissue. Planning in advanced helps ensure that all of the necessary steps at the time of death are completed smoothly to avoid any undue burden to the family at a difficult time, and to facilitate the removal and processing of the brain tissue as quickly as possible. Plans may be changed or even cancelled at any time, and participation in the autopsy program is not mandatory to continue participation in NCRAD.

To begin an autopsy plan, we will need the current contact information for the donor and for their next-of-kin or legal representative who will serve as our main point of contact for the plan. It is also preferable if a funeral home has been chosen in advance, and if the funeral home staff has been notified that they are the intended funeral facility and that an autopsy is being planned. Once we receive this information, we will locate a qualified professional who will remove the brain tissue and send it for neuropathological analysis. Once the removal site has been identified, the donor's next-of-kin or legal representative must sign an authorization form that will be kept on file with NCRAD and with the removal site.

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- genetically to future generations, a confirmed
- diagnosis in a family can lead to more vigilance
- of symptoms and better treatment of living
- family members.

An autopsy planning form containing all pertinent information will then be sent to everyone involved with the autopsy plan. All family members and, if applicable, care facility personnel involved with the donor's care should be made aware of the autopsy plan so that the proper steps are taken to carry out the plan.

At the time of death, the funeral home and NCRAD should be notified of the donor's passing so that the intended plan can be carried out. The autopsy should not delay or disrupt plans for the donor's funeral, cremation, or burial, including

open-casket presentations. NCRAD will cover any autopsy costs related to the tissue removal, such as transportation to and from the removal site if necessary, the removal itself, and the analysis of the tissue.

The donor's next-of-kin or legal representative will receive a report of the autopsy results. The report will contain any and all pertinent diagnoses made based on neuropathological findings. It is not unusual for more than one diagnosis to be listed, as AD is often compounded by other neurological maladies.

Any questions or concerns regarding autopsy in general, autopsy planning, or an existing plan, may be directed to the NCRAD staff by phone at (800) 526-2839 or by e-mail at alzstudy@iupui.edu. Please do not hesitate to contact us at any time.

10 Signs of Alzheimer's Disease

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

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.

Research Opportunities

Delaying the Progression of Driving Impairment in Individuals with Mild Alzheimer's Disease

- Purpose: To determine whether the medication memantine delays the progression of driving impairment in patients with mild Alzheimer's Disease.
- Eligibility: Subjects with clinical diagnosis of mild Alzheimer's Disease over the age of 60.
- Locations: FL
- Contact: Lori Fisher, M.A.
PH: 1-561-297-0502
E-mail: lfisher8@fau.edu

Dominantly Inherited Alzheimer Network (DIAN)

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

African American Genetics Study

- Purpose: To look for risk factors for memory problems and Alzheimer's disease among older African Americans.
- Eligibility: African American men and women with or without memory problems, ages 60 years and older
- Locations: FL, NC, NY, TN
- Contact: 212-305-1893

GIFT: Genetic Investigation in Frontotemporal Dementia and Alzheimer's Disease

- Purpose: To perform DNA studies to evaluate the genetic contribution to Alzheimer's Disease (AD) and Frontotemporal Dementia (FTD). Using a microarray-based approach, 80 genes related to neurodegeneration will be resequenced in order to identify rare mutations or risk-associated genetic variants.
- Eligibility: Subjects with clinical diagnosis of AD or FTD. Healthy volunteers.
- Locations: CA, GA
- Contact: GIFT webpage <http://geschwindlab.neurology.ucla.edu/gift>

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

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

Effect of LY2062430 on the Progression of Alzheimer's Disease (EXPEDITION)

- Purpose: To determine if LY2062430 (solanezumab *USAN adopted name, INN pending, a humanized anti-A Beta peptide immunoglobulin G-1, IgG1, monoclonal antibody being developed for treatment of AD) will slow cognitive and functional decline in AD as compared with placebo. Sponsored by Eli Lilly and Company
- Eligibility: Men and women 55 years and older, diagnosed with Alzheimer's disease
- Locations: AZ, AR, CA, CO, CT, FL, GA, IN, KY, MD, MA, MI, MO, NM, NY, NC, OH, OK, OR, PA, RI, SC, SD, UT, VT, VA, CANADA (four locations)
- Contact: 1-877-CTLILLY (1-877-285-4559) or in IN: 317-615-4559

Raloxifene for Women with Alzheimer's Disease

- Purpose: To determine whether Raloxifene, a selective estrogen receptor modulator (SERM), improves cognitive function in women with Alzheimer's disease.
- Eligibility: Women 60 years and older with clinical diagnosis of AD.
- Locations: CA, IL, IN
- Contact: Narinder Bolara
PH: 1-650-721-3308
E-mail: nbolaria@stanford.edu

NCRAD Welcomes Your Ideas and Suggestions

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

• Phone 1-800-526-2839

• E-mail alzstudy@iupui.edu

• Website www.ncrad.org

Sources for Information and Support

* **Alzheimer's Association**

<http://www.alz.org>

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

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

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

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

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

Assisted Living Directory, Assisted Living Facilities Information & Senior Care

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

The Association for Frontotemporal Dementias (AFTD)

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

Tel: 866-507-7222

Family Caregiver Alliance

<http://www.caregiver.org>

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

National Parkinson Foundation

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

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

Parkinson's Disease Foundation (PDF)

www.pdf.org

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

Society for Progressive Supranuclear Palsy

<http://www.psp.org>

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

National Organization for Rare Disorders (NORD)

<http://www.rarediseases.org>

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

Center for Disease Control and Prevention (CDCP)

<http://www.cdc.gov>

Tel: 800-311-3435

Creutzfeldt- Jakob Foundation Inc. (CJD)

<http://cjdfoundation.org>

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

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

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

No phone number available

National Society of Genetic Counselors

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

Tel: 312-321-6834

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



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