

## 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.



INDIANA UNIVERSITY  
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### National Cell Repository for Alzheimer's Disease

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# NCRAD Update

Newsletter of the National Cell Repository for Alzheimer's Disease

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## Silver Alert System Keeping Persons with AD Safe



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A growing number of states are adopting Silver Alert programs, an alert system that helps locate seniors with Alzheimer's disease (AD) or other dementias who become lost. Modeled on the Amber Alert system, which is used to locate lost or abducted children, the Silver Alert system is activated when someone with AD or another form of dementia goes missing. Alerts are sent out to local law enforcement, as well as radio and television stations, providing the name, license plate number, a photo, physical attributes and other vital identification information.

It is common for some people with dementia to wander or drive off and become lost. Quickly locating the missing person is critical, since it is estimated that half of those who are not found in the first 24 hours will suffer serious injury or death. If someone with dementia is reported missing, Silver Alerts are broadcast various ways. In addition to radio, TV, and the Internet, electronic highway signs that normally convey traffic conditions can give the make and license plate number of the car that the person may be driving. Or, thousands of automated phone calls may go out to homes in the area where the person with dementia went missing. Approximately 95 percent of people with AD who wander are found within a quarter-mile of their home or the last location seen.



While the Amber Alert system is now active in all 50 states, the Silver Alert program is just now gaining traction. Colorado was the first state to initiate the program, in 2006. Since then, Georgia, Illinois, Indiana, Kentucky, Michigan, North Carolina, Oklahoma, Ohio, Texas, Virginia and Florida are among the states that have followed suit. There are currently two more states that have legislation pending. The U.S. House of Representatives passed the National Silver Alert Act (H.R. 6064) in February 2009 but the Senate has not yet considered the bill. The bill, supported by the Alzheimer's Association, directs the Department of Justice to develop voluntary state guidelines for the development of Silver Alert plans, establish minimum standards for the issuance of alerts through the network, and make training and educational programs and materials available to states, local governments, law enforcement and other agencies.

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# Meet the NCRAD Staff

Since our last staff update in 2006 NCRAD, has had staff changes. We would like to take this opportunity to introduce our current staff and to update you on what each of us has been working on.

**Dr. Tatiana Foroud, PhD** is the principal 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 use 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.

**Kelley Faber, MS, CCRC** has been with NCRAD since June 2006 and serves as the research manager for the repository. Kelley monitors clinical data and biological specimens for all Alzheimer's Disease studies banked in the repository. She also works closely with the investigators requesting samples for their research.

**Danielle (Champagne) Smith** has been with NCRAD since August 2008 and the Department of Medical and Molecular Genetics since 2005. Danielle serves as a research coordinator and her roles include annual chart reviews, following up with



From left to right - Kelly Horner, Kelley Faber, Danielle (Champagne) Smith, Dr. Tatiana Foroud

families and collecting medical history data from subjects. In addition, she works to verify existing family data.

**Kelly Horner** has been with NCRAD since 2002 and the Department of Medical and Molecular Genetics since 1990. Kelly serves as a research coordinator for the repository and her roles include autopsy planning, cognitive testing and maintaining contact with NCRAD participants. She also performs annual chart reviews and organizes the newsletter.

## Silver Alert > continued from page 1

To date, the system has helped reconnect many lost dementia patients with family and friends.

While Silver Alert also increases awareness about wandering and can alert families to the possibility of future problems or the need for additional assistance if they have had to use the system, it is important for people to understand that the Silver Alert program is a system that coordinates law enforcement activities after a person with dementia is missing. Preventing or reducing the risk of wandering and getting lost is better yet. A number of technologies are available now that can help people with AD and their caregivers minimize the chances of getting lost. A good place to start to decide which technology or program might be most useful for you is at the Alzheimer's Association's website ([www.alz.org](http://www.alz.org)) where you can check out a new program called Comfort Zone. Comfort Zone and other services, like Safe Return, provide options for care partners and are part of a larger care plan for people with AD. Comfort Zone proactively communicates the location of the person with AD - either when that person cannot be located, or if there is a wandering incident and emergency assistance is needed. It prevents the sole reliance upon emergency responders to help families locate a missing person with AD or dementia.

Silver Alert and Comfort Zone address wandering issues through separate but related concepts. Basically, Silver Alert helps police mount a search for a missing person with AD or dementia, and Comfort Zone is intended to help families find the location of a missing person with AD more quickly - within two to 30 minutes, based on the family's selected plan - and with fewer calls to law enforcement.

The Alzheimer's Association also provides families and caregivers education on how to decrease the likelihood of wandering, as well as modifications that can be made in the home. Comfort Zone is one tool that, in combination with education and support, may reduce the incidence of wandering.

In addition, the Alzheimer's Association has emergency responder training material to help educate and build relationships with local law enforcement agencies in an effort to maintain safety for people with Alzheimer's disease and their families.

To find out more about Comfort Zone and keeping persons with AD safe, check out [www.alz.org](http://www.alz.org) or call 1-800-272-3900.

# New Risk Factors for Late-Onset Alzheimer's Disease Identified

by Carlos Cruchaga, Ph.D. and Alison Goate, Ph.D., Washington University School of Medicine, St. Louis, MO

**A**lzheimer's disease (AD) is a neurodegenerative disease that manifests as memory loss, cognitive decline and loss of autonomy. Neuropathologically, AD is characterized by the presence of intracellular deposits of hyperphosphorylated tau protein (tangles) and extracellular deposits of the  $\beta$ -amyloid protein (A $\beta$ ) as plaques. Mutations in the genes that code for the  $\beta$ -amyloid protein (APP: amyloid beta precursor protein) and enzymes that cleave APP (PSEN1 and 2: presenilin 1 and 2) cause rare (<1% of all AD cases), Mendelian (familial) forms of the disease, usually with an early age at onset<sup>1</sup>.

The more common form of AD presents with a late age at onset. Mutations in APP, PSEN1 and PSEN2 are rarely found in families with a late age at onset. However, genetic studies in late-onset AD (LOAD) suggest that genes play a role in more than 60% of cases<sup>1</sup>. Genetic studies have provided significant insights into the molecular basis of AD, and therefore identifying new genes implicated in AD will help us to better understand the disease and help in identifying new targets for drug therapies.

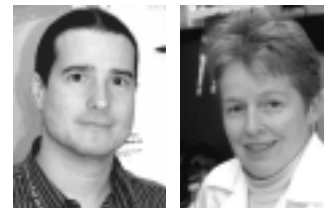
In 1993, it was reported that the frequency of the E4 allele (a genetic variant) of the APOE gene, is increased in AD patients compared to non-demented elderly individuals (E4 frequency 60.4% in LOAD cases vs 26.5% in healthy elderly controls)<sup>2</sup>.

However the association of APOE with LOAD does not explain all of the genetic risk for AD, and therefore researchers have been trying to identify new genetic risk factors. Since then, many genes have been proposed as candidates for LOAD susceptibility, but none of them were confirmed in independent studies<sup>3</sup>. These results indicated that LOAD is complex with many underlying risk

factors, each with small effect. To detect genes, which have a small effect on risk, it is necessary to perform large studies involving thousands of samples. This is only feasible through large collaborative and international efforts. In 2009, 16 years after the identification of APOE as a risk factor for LOAD, two different groups published in the same issue of the journal *Nature Genetics*, two articles describing three new candidate genes that showed consistent and compelling evidence for association with risk for LOAD<sup>4,5</sup>. These three new genes are Clusterin (CLU, also called APOEJ; chromosome 8), the gene for the phosphatidylinositol binding clathrin assembly protein (PICALM; chromosome 11) and the gene for complement component (3b/4b) receptor 1 (CR1; chromosome 1).

Because pathogenic mutations in APP, PSEN1 and PSEN2 directly affect the processing of  $\beta$ -amyloid and isoforms of APOE could also increase risk for AD by modifying A $\beta$  aggregation and clearance, researchers have tried to find evidence that link CLU, PICALM and CR1 with A $\beta$ . It has been proposed that CLU could affect risk for AD by promoting the pathogenic form of A $\beta$ . PICALM, is involved in the intracellular trafficking of proteins and lipids, and could influence A $\beta$  levels by affecting trafficking of APP or the enzymes that cleave APP. Finally, several observations suggest that pathways involving C3b and CR1 are involved in the Alzheimer's disease process, particularly in A $\beta$  clearance.

However, it is important to note that CLU, PICALM and CR1 participate in other processes not related to A $\beta$  fibrillogenesis, processing or clearance, and therefore studies of the role of these proteins in the brain may reveal evidence for additional disease mechanisms, which go beyond A $\beta$  accumulation. For example, two of the identified AD susceptibility genes (CLU, CR1) have known functions in the immune system, suggesting a possible role for the immune system in the risk



From left to right - Carlos Cruchaga, Ph.D. and Alison Goate, Ph.D.

for AD. It is hoped that these new genes lead to a better understanding of the pathological processes implicated in AD, leading to new drug targets and new and more efficient therapies.

The proportion of AD cases associated with these risk genes has been calculated to be approximately 25.5% for APOE, 8.9% for CLU, 5.8% for PICALM and 3.8% for CR1. Although these are only crude estimates it is very likely that other genetic risk factors remain to be identified. The identification of such factors may be possible by combining the results from previous studies (meta-analyses) or by the collaboration of several research groups and consortiums in order to carry out a bigger study. The participation of subjects with Alzheimer's disease and control subjects in research projects has played a critical role in these studies.

1. Avramopoulos, D. Genetics of Alzheimer's disease: recent advances. *Genome Med* 1, 34 (2009).
2. Corder, E.H. et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* 261, 921-3 (1993).
3. Bertram, L., McQueen, M., Mullin, K., Blacker, D. & Tanzi, R. The AlzGene Database. Alzheimer Research Forum. Available at: <http://www.alzgene.org>.
4. Harold, D. et al. Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. *Nat Genet* 41, 1088-93 (2009).
5. Lambert, J.C. et al. Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease. *Nat Genet* 41, 1094-9 (2009).

See page 4 for Genetic Definitions

# Genetic Definitions

## 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.

## Beta amyloid protein ( $\beta$ -amyloid)

A specific type of amyloid normally found in humans and animals. In Alzheimer's disease, beta amyloid is abnormally processed by nerve cells and becomes deposited in amyloid plaques in the brains of persons with the disease.

## 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.

## 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.**

## We Welcome 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 email or give us a call.

**Phone:** 1-800-526-2839

**E-mail:** [alzstudy@iupui.edu](mailto:alzstudy@iupui.edu)

**Website:** [www.ncrad.org](http://www.ncrad.org)

# 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

## The Genetics of Late Alzheimer's Disease (LOAD)

- Purpose: To identify families with multiple members diagnosed with late-onset Alzheimer's Disease. Families will be characterized clinically and blood samples will be collected to establish cell lines. If a blood sample is not available, autopsy samples will be collected for DNA extraction and storage. Our goal is to recruit 1,000 families over the course of the study. Clinical and demographic data from these families will be collected at the local site and coded data, without identifiers, will be sent and included in a national database of families with Alzheimer's Disease. This database, along with the biological samples, will be housed at the National Cell Repository for Alzheimer's Disease (NCRAD) at Indiana University.
- Eligibility: Two siblings (brothers or sisters) who developed AD after the age of 60 and another family member over 50 who may have memory loss or a family member over 60 who does not have any memory loss. Participants can live anywhere in the U.S. and can be of any racial or ethnic background.
- Locations: (sites in following states, but participation is open to subjects all over the United States)  
FL, IL, IN, MN, MO, NY, PA, TX, WA
- Contact: 1-800-526-2839  
E-mail: alzstudy@iupui.edu

## 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

## We Need Your Help Untangle the Mystery Of Alzheimer's

Autopsy is still the only way to definitively diagnose the specific kind of dementia affecting an individual. Please contact us if you are interested in pursuing an autopsy for a family member with dementia.

We appreciate your support in helping us unravel the mystery of devastating diseases, like Alzheimer's.



For more information  
call **1-800-526-2839**  
or email [alzstudy@iupui.edu](mailto:alzstudy@iupui.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.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/>

### **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](http://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.**

<http://cjd.foundation.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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