

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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NCRAD Update

Newsletter of the National Cell Repository for Alzheimer's Disease

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ACHIEVING A BALANCE

Can You Take Care of Yourself and Them Too?



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Caring for a loved one with a demanding disorder is stressful at the best of times. When the caregiver is an adult child of the patient, with a family of their own, a busy job, actively involved in their community and so on, the caregiving role can become very demanding and burdensome. Can you effectively care for your family member and still take care for yourself and all of your other responsibilities? The answer is yes you can, but not all at the same time. With appropriate planning and allowing time to care for yourself, most family members can provide excellent care to an older adult in times of need. The following coping strategies have been found to be very helpful when caring for someone with dementia or any chronic disorder.

Be realistic. Consider if you can realistically do everything you are planning, thinking or willing to do. Many caregivers react to situations emotionally first, then think later. Think through the ramifications of your decisions first, and then react. If you are thinking about moving a frail or cognitively impaired parent in with you, answer the following questions first:

- Does your parent or older family member want to move in with you and your family?
- Do you have enough space in your home for another person?



- Do you have enough time to provide the care or supervision necessary to keep them safe?
- Will providing care impact your budget in any way? If so, can your budget handle the additional costs?
- Have you discussed this with your spouse and any children who might still be living at home?
- Have you considered other options or services available in your community that can help you provide care and supervision allowing the older adult to remain in their own home longer?

Once you have thought through a particular issue and all of the options then adjust your expectations accordingly. For example, if you do decide to move your parent in with your family, do not expect that things will go smoothly from the very beginning. Give everyone time to adjust to the changes in living arrangements, the changes in your time and so on. If you are feeling overwhelmed, ask yourself:

- In the bigger scheme of things, how important is this?
- Does the bath have to happen now or can it wait a few hours or a day?

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If the issue is bathing or changing clothes, and the older person is resistant, it is usually not life threatening, **let it go**. Remember it is easier to change the subject, walk away, take a deep breath and count to 10 than it is to reason or rationalize with a person who has dementia or cognitive impairment.

Be good to yourself; reward yourself. Remember that you cannot take care of anyone else if you do not first take care of yourself. Take time for your own needs and special interests. Caregivers must try not to feel guilty about taking a bit of time for themselves. When caregivers finally do so, many of them report how much better they feel and are actually able to provide care longer. Do not give up everything important to you in order to assume caregiving duties. Eventually these duties will end or change, therefore keeping yourself connected to others is vital for your own long term well-being. **Do not ignore your own physical health.** Take time to go to your doctor, if you are on medications, take them as prescribed. Eat right, exercise and get enough sleep. Make sure your older adult is eating, drinking and staying as active as possible.

Plan...plan...plan... Then plan some more. You can never be overly prepared! The more contingencies you are prepared for, the fewer stressors and surprises you will encounter. It is much easier to make tough decisions when you are not in a crisis. For example, find out about services available in your community, visit day care centers, long term care facilities, and talk to an elder law attorney long before you really **need** to. You can make better decisions and remain more objective if you are not in a crisis situation. A wise caregiver once said, be prepared for the worst but pray for the best. This is good advice for everyone regardless of whether or not you are a caregiver. Once your plans are in place, take one day at a time.

Communicate with everyone! Try to include all family members in planning meetings and discussions. You can avoid

“ **Focus** on all things you do well and **forgive** yourself and others for mistakes. **Learn** from mistakes and **move on**. ”

or avert potential family conflicts if everyone is kept informed. Many tough decisions are made around the kitchen table. Remember though, that everyone, siblings, parents, and children come to the kitchen table with their own history, perspective and expectations. Have everyone share their perspective but try not to point fingers or lay blame. Try to encourage a sharing of ideas for working together to provide the best care for your family member with dementia.

Maximize the older person's independence (and everyone else's too!) Do not try to do everything for your loved one with dementia; allow them to maintain as much independence for as long as possible. Too often caregivers increase dependence by trying to do too much for the patient. Do not worry about their clothes matching or perfectly applied makeup if it means an argument or frustration for both of you. If the person can still dress, feed, and toilet him or herself, let them do so for as long as possible. Celebrate the fact that they can still participate in their own care—do not focus on what they can't do. Ask your spouse and children to help out as well. Ask for help and encourage everyone to pitch in with chores.

You may need to adjust your own expectations and standards of housekeeping. If your spouse or children help with dinner, laundry or other chores, try not to criticize their efforts or feel that you could have done a better job yourself. Remember, if it is not life threatening, **let it go**.

Keep your sense of humor. Look for the joy in life and try to laugh a little every day. There is always a bright side to things, even when everything appears to be quite glum. Try to focus on at least one positive, joyful thing every day.

It can be as simple as appreciating the sunshine, a child's giggles, or birds singing. A positive attitude has been shown to have beneficial effects on one's coping ability and overall quality of life.

Positive self-talk. Focus on all things you do well and forgive yourself and others for mistakes. Learn from mistakes and move on. Apologize to your older adult if you lose your patience or your temper. It happens to everyone. Try telling yourself... *I am a good person. I am doing the best I can. Everyone makes mistakes now and then. I'm sorry and I will do better tomorrow.*

Ask for help when you need it. Do not be a martyr! Asking for help is not a sign of weakness but a sign of strength. Try to be very specific about what kind of help you need and you will be more likely to receive it. For example, if someone offers to lend a hand, ask them to pick up the dry cleaning, the groceries, or to spend a couple of hours with your older adult while you run errands, go to the hairdresser, or play a round of golf. A great idea about asking for help came from one family caregiver who kept a jar full of chore cards. If someone offered to help, she simply had him or her pick a card.

Join a support group. Support groups have been found to be a very beneficial source of support for some caregivers. Many caregivers report that they get the best caregiving help from support group members who have had similar experiences and therefore understand what they are feeling. Some caregivers report that it is nice to know that they are not alone or going crazy.

If you are interested in finding a support group in your area, call the Alzheimer's Association at 1-800-272-3900.

Putting Alzheimer's case-control studies to the test by using NCRAD families



By Lars Bertram, MD
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Genetically, Alzheimer's disease (AD) is heterogenous and complex, displaying no single or simple mode of inheritance. Rare, early-onset autosomal dominant forms of the disease are caused by mutations in three genes (APP, PSEN1, PSEN2), which are all related to an altered production of the amyloid- β peptide (A β), which accumulates in the brains of patients and eventually leads to nerve cell death and dementia. In contrast, susceptibility for late-onset AD, which shows a less obvious familial aggregation (and is therefore sometimes – albeit incorrectly – called “sporadic AD”), is likely governed by a multitude of different risk factors across a number of different genes that probably affect a variety of biochemical processes. In the quest for uncovering the underlying and largely unknown collection of AD risk (or susceptibility) genes, a vast body of evidence has been accrued in the scientific literature over the past 20 years, represented by well over 1,000 studies genetically implicating or excluding certain genes as risk factors for AD. However, with the exception of one single gene-locus, the apolipoprotein E gene (APOE) on chromosome 19q13, none of these putative AD genes has been unequivocally proven to consistently influence disease risk or onset age in more than a handful of samples. Due to the exceedingly large

number of studies published (in 2005 and 2006 approximately ten different AD genetic association studies were published each month), it has virtually become impossible – even for the specialist – to systematically follow, evaluate, and much less interpret these findings.

In an attempt to alleviate this situation, my laboratory has recently created a publicly available database, “AlzGene” (<http://www.alzgene.org>), that systematically collects, summarizes and meta-analyzes all genetic association studies published in the field of AD (Bertram, 2007). After thorough (and still ongoing) searches of the available scientific literature, all studies published in peer-reviewed journals and available in English are included. Key variables (such as sample size, onset age, gender ratio, genetic information etc.) are extracted from the original publications and summarized on the AlzGene website. Furthermore, polymorphisms with published genetic data in at least four independent case-control studies are systematically subjected to meta-analyses, a statistical procedure that allows results from independent studies from different laboratories to be combined in order to judge whether any single genetic factor significantly increases or decreases risk for AD. On the AlzGene website, a section entitled “Top Results” provides an up-to-date list of the most promising findings (“hits”) across the entire body of genetic literature in AD.

The vast majority of studies published on the genetics of late-onset AD (and thus those included in AlzGene) are using a case-control design. This means that the presence (or prevalence) of a certain genetic risk factor is measured in a sample of individuals affected by AD (“cases”) and then compared to a sample of unrelated individuals not affected by the disease (“controls”). If there is a difference in the occurrence of the risk factor under scrutiny across these two groups, the gene is said to be “associated” with the disease. This popular but rather simple research

design has many advantages, but also some pitfalls, which can be overcome by the study of related individuals (i.e. families), rather than unrelated cases and controls. The National Cell Repository for Alzheimer's Disease (NCRAD) is the single largest collection of AD families currently available to the genetics research community. As such it gives scientists the unique opportunity to study genetic factors of AD in individuals for whom the disease “runs in the family”, an intuitive and obvious way to assess the genetics of any heritable condition.

A little over a year ago, my laboratory at Massachusetts General Hospital received a large collection of DNA samples from NCRAD (2,250 DNAs from nearly 800 independent families) through grant2 from the Extencicare Foundation and the NIH, for the study of genetic factors in AD. The first project that these and additional family samples from other collections like the NIMH and CAG were used for was for the assessment of “Top Results” of the AlzGene database, i.e. those potential AD genetic risk factors that were identified via the systematic meta-analysis of case-control studies. The importance of this project was afforded by the fact that the vast majority of AlzGene “hits” had never actually been tested in AD families. In a first round of analyses, which were spearheaded by Brit-Maren Schjeide in my lab, we tested 13 genes that were found to show significant association in our original AlzGene analyses (Schjeide, 2007). Besides the well-known risk factor APOE, at least three other genes showed statistically significant effects in these families, namely ACE (an enzyme possibly responsible for the removal of the toxic A β protein), CHRN2 (a receptor of acetylcholine, one of the molecular transmitters in the brain involved in memory and other cognitive processes), and TF (an iron transport protein that may mediate nerve cell death through a processes called 'oxidative stress'). The fact that all three of these genes were implicated

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Recent Gene Discovery in Non-Alzheimer's Syndrome



By Jennifer Adamson
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Frontotemporal Lobar Degeneration (FTLD)
Alzheimer's disease is the most common form of dementia, but there are many other forms.

Frontotemporal Lobar Degeneration (FTLD) or Frontotemporal Dementia (FTD) is a neurodegenerative syndrome that usually features behavioral/personality changes, or language disorders with an initial preservation of memory. Most patients have an age of onset before the age of 65. FTLD can overlap with other degenerative diseases and therefore may be more common than once thought, especially in patients over the age of 65. Until recently, the only major gene found to be associated with FTLD was Microtubule-Associated Protein Tau (MAPT also called Tau). Approximately 5% of FTLD patients carry a mutation in the Tau gene. However, up to 40% of FTLD patients have a family history of the disease, suggesting there are other genes yet to be identified. Focusing on these families, researchers continued the search for other gene mutations responsible for FTLD.

Identification of the Gene: Progranulin

In spring of 2006, researchers at the Mayo Clinic found mutations in a new gene called Progranulin (PGRN). These mutations cause FTLD. The mutations in PGRN were confirmed by Belgian collaborators at the University of Antwerp and the results were published in the July 2006 issue of the journal *Nature*. Although PGRN has a newly-described role in FTLD, it was previously identified as a gene of interest in cancer research where it was known to be associated with inflammation and wound repair. To date there are 49 different pathogenic (disease-causing) PGRN mutations (FTD mutation database: www.molgen.ua.ac.be/FTDmutations). Mutations in PGRN result in a depletion of the normal protein production by half.

Clinical Features of PGRN Patients

Presenting symptoms often include behavioral changes or aphasia (language problems) sometimes followed by parkinsonism. Interestingly, related patients can differ greatly in their disease presentation, and the age of onset can also vary widely among family members. Characterization of the brain pathology upon autopsy has led to better understanding and diagnosis criteria of disease. Hallmark

features of the disease seen at autopsy are "cat-eye" inclusions found inside the nuclei of some neurons. Recently the protein contained in these inclusions was identified and also found in brain tissue from Alzheimer's disease, Amyotrophic Lateral Sclerosis, and Lewy Body disease patients. This finding suggests that different disease processes may indeed be shared by some forms of neurodegenerative diseases.

Implications for Patients and their Families

Approximately 5% of FTLD patients have a PGRN mutation; this number will probably increase as deletions of the whole or part of the gene are identified. If patients have a family history of FTLD then the chance of carrying a PGRN mutation can be as high as 20%. Patients with PGRN mutations can have a broad range of symptoms; no distinct pattern has been seen. The average age of onset is approximately 59 years old, with a range of 32 to 83 years old. The duration of disease can range from 3 to 12 years. The mutation is not completely penetrant; that is, it is predicted that 90% of mutation carriers will have the disease by age 70. The mutation carrier's without symptoms of the disease may have other genes modifying PGRN, or be influenced by environmental exposures such as diet which could cause the disease manifestation to be delayed.

While genetic mutation screening for PGRN is available, it is only warranted in patients where there is a known family history of FTLD. Asymptomatic first degree relatives (parents, children, siblings) of identified PGRN patients should also be offered genetic counseling and testing. All first degree relatives of known mutation carriers have a 50% chance of inheriting the mutation, as it is inherited in an autosomal dominant fashion.

There are medications available to treat some symptoms of FTLD, but there is currently no cure for the disease. The identification of genes involved in the disease provides the foundation for more accurate diagnosis, better understanding of the disease process, and assists in the exploration into new therapies for patients. These discoveries also provide insights into other over-lapping syndromes and related neurodegenerative diseases.

For further information on FTLD and other related syndromes, visit the Association for Frontotemporal Dementias website at: www.ftd-picks.org

Putting Alzheimer's case-control studies to the test > continued from page 3

via systematic meta-analysis of the existing case-control literature and by direct analysis of families of the NCRAD and other collections, strongly suggests that these genes actually have an important role in contributing to AD risk in the general population, rather

than merely reflecting statistical artifacts and/or genes of irrelevant effect on a population-wide level, like essentially all of the AD risk factors proposed to date. While the actual disease pre-disposing role of these (and other) potential AD genes needs

to be further investigated and established, the knowledge gained from this and similar studies will lead to a better understanding of the causes of AD, ultimately enabling researchers and clinicians to more reliably predict and treat this devastating disease.

Research Opportunities

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

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>

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.
- Contact: Lori Fisher, M.A.
PH: 1-561-297-0502
E-mail: lfisher8@fau.edu

Depression in Alzheimer's Disease

- Purpose: To demonstrate whether the medication sertraline (Zoloft®) helps people with Alzheimer's disease. Through this study we hope to find out if treating depression can 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: 1-410-614-4605
E-mail: amorris7@jhmi.edu

Raloxifene for Women with Alzheimer's Disease

- 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

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

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.

For more information call **1-800-526-2839** or email alzstudy@iupui.edu
We appreciate your support to help us unravel the mystery of devastating diseases, like Alzheimer's Disease.



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.

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.

<http://cjd.foundation.org>

* **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

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

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.

Expanding the information being collected by NCRAD

A Note from Tatiana Foroud, Ph.D. and the NCRAD Coordinators

Over the past 17 years, we have been working to try to help understand the genetics of Alzheimer disease (AD). Through the involvement of families, we have been able to provide researchers worldwide with the biological samples and clinical information they needed to perform studies to help us tease apart this mystery.

However, we've learned that what we have been collecting may not be enough. Researchers have learned that there are many biological, environmental and genetic links between diseases such as Alzheimer disease, Parkinson disease, stroke, head injury, etc. As a result, we have been asked with growing frequency about other diseases or diagnoses that our NCRAD families and subjects might have.

Over the coming year, we will be asking many of you to help us learn more about the diseases, diagnoses and risk factors

in your family. We will be sending along a brief questionnaire to NCRAD participants and their family members. We'll be asking specific questions about particular disease and diagnoses and we'll often ask how the diagnosis was made (by a doctor, through blood tests, etc). As always, we appreciate any information that you can provide us.

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.