

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.

National Cell Repository for Alzheimer's Disease Hereditary Genomics

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NCRAD Update

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GENETIC RESEARCH ADVANCES IN ALZHEIMER'S DISEASE

By Susan Conova, Science Writer
Columbia University Medical Center
and Jennifer Williamson Catania, MS, CGC

Adapted from an article published in the Jan/Feb 2007 issue of *In Vivo*, Columbia University



Dr. Mayeux

A team of researchers from Columbia University Medical Center, University of Toronto, Boston University and the Mayo Clinic recently published a paper in *Nature Genetics* (February 2007) announcing another gene involved in Alzheimer's disease (AD) risk. The gene, called SORL1, may provide insight into new ways to treat the disease because it identifies a previously unknown pathway within cells by which toxic amyloid beta peptides can build up in the brain. This research was conducted by studying families with AD. Richard Mayeux of Columbia University led the study with Peter St. George-Hyslop of Toronto and Lindsay Farrer of Boston University.

While many genetic studies have published possible genetic risk factors for AD, few have been able to replicate (repeat) the results with the same findings. "Many genes have been linked to Alzheimer's in the past 15 years but those findings have not been replicated," Dr. Mayeux says. "We think SORL1 is different because we built several replicates into the study, and those replicates include different ethnic groups. But even with the replication we have, we all want to see this finding repeated by other researchers before

we accept it completely." Replicates refer to the ability to repeat the study in a variety of independent study groups (containing different individuals of various ethnic origins) and obtain the same results.

The new gene, SORL1 was discovered by comparing the DNA of individuals with AD to the DNA of unaffected people. All participants in this study were from the Dominican Republic. Certain DNA sequence variations within the SORL1 gene were more frequent in AD than in unaffected people. These same patterns were found in four other separate groups of subjects: two groups of Americans of European descent, one group of African Americans, and one group of Israeli Arabs. In total, more than 6,000 people participated in the study.

A prominent theory regarding the cause of AD is attributed to a build-up of amyloid beta peptides, which are released when a protein called APP is cut into pieces. However, the genetic and environmental factors that determine how much amyloid beta peptide accumulates in the brain have been difficult to determine and remain largely unknown. The new study shows that certain forms of the SORL1 gene increase the risk of developing AD because of the effect they have on APP. Identifying genes that raise the risk of AD is very important because it can help researchers find different mechanisms for treating the disease.

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Anger and what to do with it

By Malia Rumbaugh, MS, CGC

NIA-LOAD Genetics Study Coordinator, Seattle, WA



Rumbaugh, MS, CGC

I just got off the phone with Grace¹, whose husband's family is enrolled in our research study. She and others in the family spent most of the night at the bedside of her brother-in-law during his last hours. A sister in this family also died of Alzheimer's just a few weeks ago and Grace's husband is

in the moderate stages of the disease. So why was she calling me? While regular updates are very helpful, it is amazing that amidst the devastation of this disease, people reach out to participate in research.

But why? In our genetic studies, we can't promise any direct benefit to our participants. Why add to the tremendous burden of this disease? Of course, the reasons are as individual as our participants. For some, the drive to help others is as natural as breathing. For others it is the fear

that catches in the throat; that this might happen to their children or their grandchildren. There is also the desire for a redemption of sorts, to see something good come out of something bad.

Lately though, I've been thinking about anger. Anger gets a bad rap and can certainly be destructive. Most of us were raised to be polite, well mannered and considerate people. Some of us even are that way most of the time. Yet how can we not be angry at this disease? As we watch it erode thoughts, memories, personality and so much of what we hold dear in each other, I think anger is a reasonable response. The key is what we do with it.

Mahatma Gandhi is probably not the first person to come to mind when you think of anger, but he knew it well. As he said: "I have learned through bitter experience the one supreme lesson to conserve my anger, and as heat conserved is transmuted into energy, even so our anger controlled can be transmuted into a power which can move the world."²

I think this is what I see sometimes in our research

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Genetic Testing Highlight: The REVEAL Study

By Susan Hiraki, M.S.

The REVEAL Study (Risk Evaluation and Education for Alzheimer's Disease) is a multi-center NIH-funded study based at Boston University School of Medicine. REVEAL provides healthy adults with genetic testing and information about the risk of developing Alzheimer's disease (AD). The purpose of the study is to evaluate the psychological and behavioral impact of genetic risk assessment with APOE disclosure for Alzheimer's disease.

The REVEAL Study has been funded by the National Human Genome Research Institute at the National Institute of Health (NIH) since 1999. In the first funding cycle of REVEAL, the study demonstrated that genetic risk assessment with APOE disclosure, can be offered to first-degree relatives

of people with Alzheimer's disease in a safe and effective way. In the second funding cycle of REVEAL, results have shown that such information can be safely disseminated in a condensed, more clinically feasible protocol. In the third funding cycle of REVEAL, it is continuing to provide genetic risk assessment for Alzheimer's disease in a condensed protocol along with information on other complex diseases.

The study involves a telephone interview and mailed survey followed by an in-person visit in which family and medical history are elicited and blood is drawn for genetic testing. Genetic test results and risk assessment are provided 3-4 weeks later either in-person or over the telephone. Follow-up for the study involves a phone call after 1 week, 2 in-person visits at 6 weeks and 6 months post-disclosure, and a mailed survey after 12 months. As with the first

2 phases, this phase of the REVEAL study is being conducted at 4 study sites: Boston University, Case Western Reserve University (Cleveland, OH), Howard University (Washington, D.C.), and the University of Michigan (Ann Arbor, MI).

The REVEAL Study can serve as a prototype for the design of genetic risk assessment protocols for other adult-onset diseases. Through our research, we hope to learn how to best provide this information to people in a safe, supportive, and effective way.

To find out more about this study please contact:

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Genetic Counselor Q&A

Collaborative Effort by Kelley Faber, MS, CCRC, Jennifer Williamson Catania, MS, CGC and Kate Kreiner, BS

Q. Who are genetic counselors?

A. The American Board of Genetic Counseling (www.abgc.net) describes the genetic counselor as "a health professional who is academically and clinically prepared to provide genetic services to individuals and families seeking information about the occurrence, or risk of occurrence, of a genetic condition or birth defect. The genetic counselor practices as part of a genetic services delivery team. The genetic counselor communicates genetic, medical and technical information in a comprehensive, understandable, non-directive manner." Further information on genetic counseling is available from the National Society of Genetic Counselors at (610) 872-7608 or www.nsgc.org.

Q. What qualifications do genetic counselors have?

A. Certified genetic counselors hold a Master's degree from an accredited U.S. graduate program. Students in these programs study genetics, psychosocial theory, ethics, and counseling. They also participate in clinical training. Certification is obtained through the American Board of Genetic Counseling's examination and successful completion of documented clinical experience. For more information please visit www.abgc.net.

Q. What is the difference between genetic testing and genetic counseling?

A. Genetic testing is the process whereby an individual's DNA is analyzed to look for a variation in the DNA sequence that may indicate an increased risk for developing a specific disease or disorder.

Genetic counseling is the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease. This process integrates:

- Interpretation of family and medical histories to assess the chance of disease occurrence or recurrence.
- Education about inheritance, testing, management, prevention, resources and research.
- Counseling to promote informed choices and adaptation to the risk or condition.

National Society of Genetic Counselors, 2005

Q. Is genetic counseling necessary before and after genetic testing?

A. Yes. Before testing, the genetic counselor's job is to ensure that:

- the person has the ability to make a truly "informed" consent to the testing process
- the person is psychologically prepared to cope with the possibility of a positive or negative test result. If the person decides to proceed with testing, counselors and physicians

help the individual and family understand and adjust to the test results, and plan for future care as appropriate to the disorder.

Q. What do we know about genetics and Alzheimer's disease?

A. There are three known genes involved in early-onset (symptoms beginning prior to age 60), familial Alzheimer's disease (AD) - presenilin 1 (PS1), presenilin 2 (PS2) and amyloid precursor protein (APP). A change in the DNA sequence (called a mutation) of any of these three genes can result in early-onset Alzheimer's disease. An individual who has inherited the mutation will typically develop Alzheimer's disease if they live long enough. In addition, the mutation can be passed to individuals in the next generation. Each child of a person who has early-onset AD and a known mutation has a 50% chance of inheriting the disease causing mutation. Importantly, mutations in these three genes are a rare cause of Alzheimer's disease. Early-onset, familial Alzheimer's disease accounts for less than 5% of all Alzheimer's cases. Genetic testing is available for families who have an early-onset of the disease with several generations of affected family members. It may be possible to test these families for changes in one of the three known genes associated with early-onset Alzheimer's disease.

The gene APOE has been shown to be an important risk factor for AD, particularly the more typical late onset form. The APOE gene occurs in three forms or alleles: APOE-e2, APOE-e3 and APOE-e4. People can inherit any combination of two of the APOE forms. For example, a person can inherit the APOE-e4 allele from one parent and the APOE-e3 allele from the other parent.

The increased risk for late-onset Alzheimer's disease is associated with inheriting the APOE-e4 allele from one or both parents. However, the exact role of the APOE-e4 is uncertain. A person without the APOE-e4 allele can still develop AD and some people with the APOE-e4 allele never get the disease.

Having one or two copies of APOE-e4 is not enough to cause Alzheimer's disease. Therefore, we consider APOE a risk factor for AD.

Q. Is genetic testing for PS1, PS2, APP or APOE recommended?

A. According to the Alzheimer's Association, "with regard to late-onset sporadic Alzheimer's disease, consensus statements by professional groups-medical, genetic and others-agree that APOE testing is not appropriate for individuals with no symptoms of dementia. Testing positive for APOE-e4, even among individuals with a family history of Alzheimer's disease, does not provide any useful information. People who possess

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Genetic Counselor Q&A

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APOE-e4 may or may not develop Alzheimer's disease. Similarly, people who do not inherit APOE-e4 may still develop the disease. There are also multiple medical, legal, social and ethical issues involved in receiving such tests. Testing positive may cause problems in getting a job or insurance and may also create a psychological burden."

"For individuals with symptoms of dementia, testing for APOE status is of limited value. The information may be helpful to a clinician trying to determine the underlying cause of dementia, but the test results should be interpreted in the context of a complete diagnosis. In a thorough assessment without APOE testing, Alzheimer's disease can be diagnosed with approximately 90% accuracy. Therefore, the accuracy of the diagnosis can only be slightly improved with APOE testing. And the test results can provide perhaps unwanted information for the children of the patient about their own genetic makeup."

"Genetic testing can be very important, however, in a research setting. Such testing can be done so that the results are kept confidential and not revealed to study participants"

Genes and Alzheimer's Disease, Alzheimer's Association 2006 (www.alz.org)

Q. Will insurance cover genetic counseling/testing for Alzheimer's disease?

A. Individuals will need to contact their health insurance company to find out if genetic counseling and testing is covered.

Q. Will having genetic testing performed for Alzheimer's disease affect one's insurance (health, life, long-term and disability)? If so, how?

A. At this time, there is no real definitive answer. While federal and state governments are working on legislation regarding genetic information discrimination, and some states have laws prohibiting genetic discrimination, there is still a lot of work to be done. The National Conference of State Legislatures provides a listing of current legislation regarding genetic information and health insurance. It can be found at:

(<http://www.ncsl.org/programs/health/genetics/ndishlth.htm>)
For more information please also visit:
http://www.ornl.gov/sci/techresources/Human_Genome/home.shtml.

Q. Where can one find more information on genetic counseling and testing for Alzheimer's disease?

A. Often major hospitals and universities will have information on genetic counseling and testing. However, here are a few national organizations:

National Society of Genetic Counselors

401 North Michigan Ave., Chicago, IL 60611

Phone: 312-321-6834

www.nsgc.org

E-mail: nsgc@nscg.org

GeneTests

9725 Third Ave. NE, Suite 602, Seattle, WA 98115

Phone: 206-616-4089

www.geneclinics.org

Alzheimer Research Forum

<http://www.alzforum.org>

Genetic Research Advances > continued from page 1

The announcement of this new gene involved in AD raises the question of risk for unaffected individuals. While the discovery of SORL1 may prove to be important in calculating each individual's risk of developing the disease, researchers do not know how much SORL1 increases the chances of getting AD. "In the future, there may be prognostic value in knowing your SORL1 status, just as now there is prognostic value in knowing your cholesterol levels," Dr. Mayeux says. "We hope to have preventative treatments we can give to people with the greatest risk of developing the disease, much the same way we now give statins to prevent cardiovascular disease."

The collaboration that occurred between academic institutions studying AD is an important aspect of this work. In order to have a sufficient number of families to study, researchers need to share their resources. The National Cell Repository for Alzheimer's Disease (NCRAD) helps facilitate collaborative research to understand AD. In fact, many of the researchers involved in the SORL1 finding are also actively participating in the National Institutes on Aging Late Onset Alzheimer's Disease Family Study (NIA-LOAD Family Study) coordinated by Tatiana Foroud, PhD at NCRAD and Richard Mayeux, MD, MSc at Columbia University. This research study has organized researchers around the country to identify families with

multiple members diagnosed with late-onset Alzheimer's disease with the goal of recruiting 1,000 families over the course of the study. Clinical data and a blood sample for DNA is included in a national database of families with Alzheimer's disease housed at NCRAD. The biological samples and data from these families provide a wealth of information for qualified researchers studying AD. Collaborative studies such as the NIA-LOAD Family Study will lead to a better understanding of the factors involved in AD.

For full article please visit:
www.cumc.columbia.edu/news/in-vivo/january_february_2007

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>

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 probable 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

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's disease, willing to undergo a blood draw and a MRI scan along with answering questions regarding their family history.
- Contact: Contact: Michael Wake
E-mail: mirage@bu.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: 410-614-4605
E-mail: amorris7@jhmi.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) AL, CA, FL, IL, IN, KY, MA, MN, MO, NC, NY, OR, PA, TX, WA
- Contact: 1-800-526-2839

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.

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- Jakob Foundation Inc.

<http://cjd.foundation.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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participants and their families. It's that glint in their eyes, that steely note in their voice. It hints at a determination to beat this disease even if they themselves may not know the victory. And whatever your reasons for participating, it is because of people like you that we will find a cure.

1. Not her real name.
2. *Gandhi the Man*, by Eknath Easwaran, Nilgiri Press.

“ I have learned through bitter experience the one supreme lesson to conserve my anger, and as heat conserved is transmuted into energy, even so our anger controlled can be transmuted into a power which can move the world. ”

- Gandhi



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