NCRAD Update

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Basic Genetics

Tatiana Foroud, Ph.D., P. Michael Conneally Professor of Medical and Molecular Genetics and Director, Hereditary Genomics, Indiana University School of Medicine

The human genome is the entire set of genetic instructions found within a cell. In humans, there are 23 pairs of chromosomes which contain about 3 billion base pairs and 20,000 genes. One member of each chromosome pair comes from each biological parent. Genes are found on chromosomes and contain the information needed to specify traits. Genes are arranged on a long DNA (deoxyribonucleic acid) molecule that consists of two strands. Each strand has a backbone made of alternating sugar (deoxyribose) and phosphate groups. Attached to each sugar is one of four bases: adenine (A), thymine (T), cytosine (C), and guanine (G). Adenine (A) always bonds with thymine (T) and cytosine (C) always bonds with guanine (G). These bonds hold the two strands together to form a double helix. Along the length of the DNA are segments that are called genes. Genes are often described as beads along a string. However, not all parts of DNA are genes. Genes are important because they provide the code or blueprint for proteins. Proteins are made in all of our cells and perform important functions like the digestion of food. When a protein does not function correctly or not enough of the protein is made, it may result in a specific disease.

Mutations and Proteins

The order of the bases in a gene is important because it provides the information a cell needs to make proteins. Importantly for Alzheimer disease, proteins are necessary for the cell to properly process certain products. For example, changes in key proteins lead to the production of amyloid plaques and neurofibrillary tangles, which result in Alzheimer disease.

Changes in the order of the bases (A, T, G, and C) can be introduced sporadically along the DNA strand. This change can cause one base to be exchanged for another, it can insert an additional base or it can remove a base entirely. It is also possible for groups of bases to be added or removed. Often, the change in the order of the bases has no effect. However, in some instances the change in the order can have major effects and result in a protein that is made incorrectly and does not work properly. When a change in the bases results in a known protein effect, we call this change in the DNA, a mutation.

DNA Sequencing

Researchers have been studying the order of the bases, or DNA sequence, for many decades. This has led to the identification of several genes which we know are important in Alzheimer disease because some families have mutations in these genes that result in key proteins working incorrectly. In the past few years, new instruments and techniques allow scientists to sequence genes and even the entire genome much faster and for far less cost. Researchers can choose to limit the sequencing to just genes. Genes are broken up into smaller pieces, called exons – which are used to code for a protein. When the sequencing is just limited to the exons of genes, the process is called whole exome sequencing. Researchers

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The National Cell Repository for Alzheimer's Disease (NCRAD) is a data and specimen collection source for families with Alzheimer's 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 for AD. Many family members have provided blood samples, which researchers use to study 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
SCHOOL OF MEDICINE

National Cell Repository for Alzheimer's Disease
Hereditary Genomics Division
Health Information and Translational Sciences Building
410 West 10th Street, HS 4000
Indianapolis, IN 46202-3002

Phone: 1-800-526-2839
e-mail: alzstudy@iupui.edu
Website: www.ncrad.org

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can also sequence the entire genome of an individual, which is called whole genome sequencing (see Figure 1). These two new types of sequencing have changed the scope of research that can be done and are leading to new discoveries for many. Currently, Alzheimer disease researchers are focusing their efforts on studying the genome of thousands of individuals who do have Alzheimer disease. The goal is to identify genes in which many individuals have a change in the order of DNA bases. To be sure that the changes in the DNA are really a possible factor in Alzheimer disease, the researchers will also study the genome of thousands of individuals who are older and have not developed Alzheimer disease. We would expect that the DNA changes we find in those who have Alzheimer disease will not be found in those who do not have Alzheimer disease. These studies are ongoing and we believe they will be an important source of new information on the genetics of Alzheimer disease.

Single Nucleotide Polymorphisms

A change in the sequence of a gene that codes for a protein can have a dramatic effect on the risk for Alzheimer disease. However, we also know that smaller changes in DNA, particularly in regions between genes, may also increase or decrease the risk of disease. When there is a change in the base found at a particular position along the DNA sequence, we call this a single nucleotide polymorphism (SNP) (see Figure 2). Some SNPs are also mutations – that is they can change the function of a protein. However, many SNPs do not have such a dramatic effect. Researchers believe that such changes in the DNA sequence might affect how much of a protein is made, or have other effects that could still make it more or less likely that an individual will develop Alzheimer disease.

There are millions of SNPs throughout the genome and Alzheimer disease researchers have been studying their possible effect on disease risk. They have studied tens of thousands of individuals with Alzheimer disease (called cases) and a similar number of individuals who are older and remain free of Alzheimer disease (called controls). When investigators study millions of SNPs in a single study, they are typically using a special laboratory instrument that can run an array (see Figure 3). An array is like a codebook that allows the instrument to test millions of SNPs at once. This type of study is often called a Genome Wide Association Study (GWAS). A GWAS tests SNPs throughout the genome and uses a statistical test called an association test. Association simply means that at a SNP, one of the bases that can be seen at this position on the DNA, is more common in cases than it is in controls. Genome Wide Association Studies have led to the identification of new genetic factors that appear to increase or decrease the risk of Alzheimer disease. ■

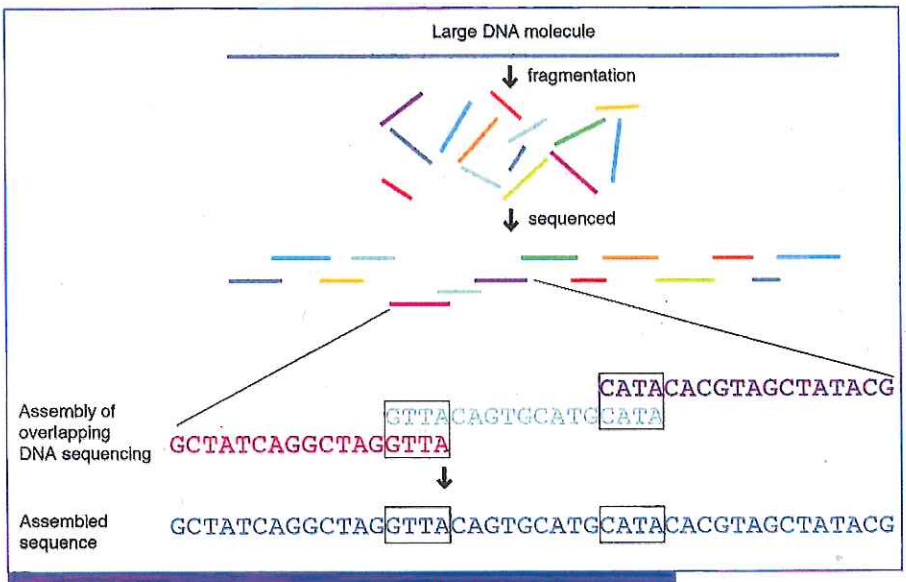

FIGURE 1: *Whole Genome Sequencing-Illustration from NHGRI*

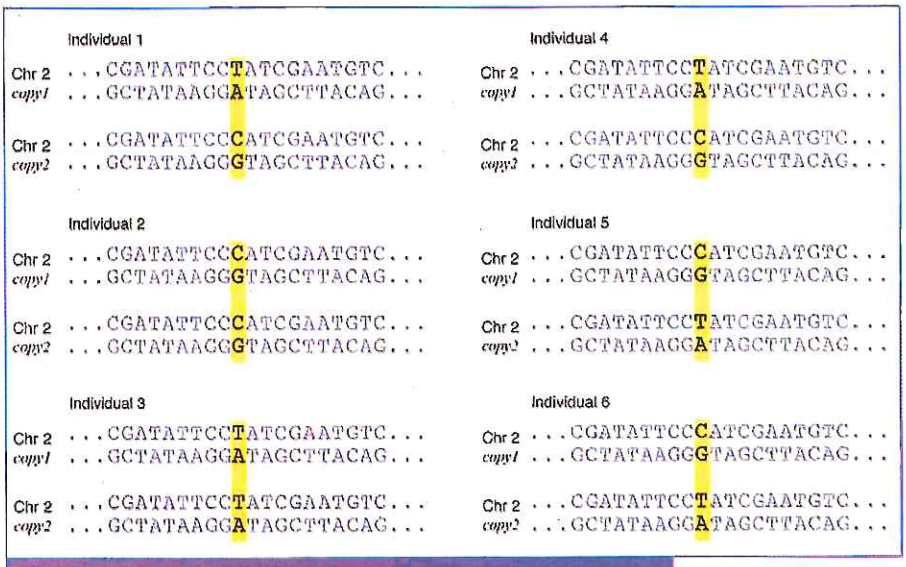

FIGURE 2: *Illustration of SNP from NHGRI*

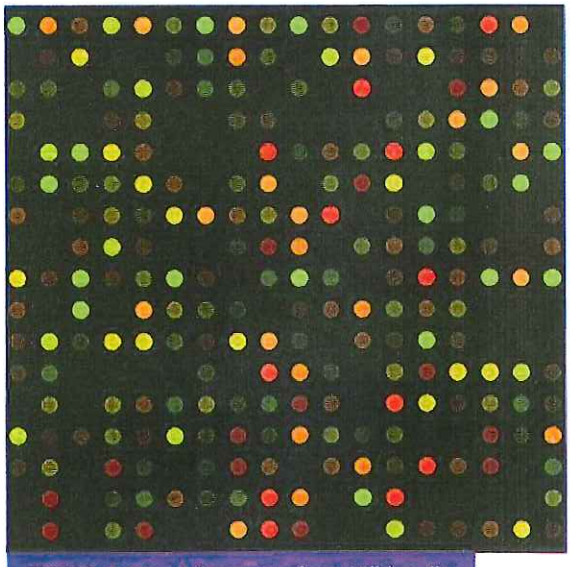

FIGURE 3: *DNA Microarray from Wikipedia*

Studies Identify New Genes Important in Alzheimer Disease

Tatiana Foroud, Ph.D., P. Michael Conneally Professor of Medical and Molecular Genetics and Director, Hereditary Genomics, Indiana University School of Medicine and Laura Cantwell, MPH, ADGC Project Manager, University of Pennsylvania

There are many new laboratory methods that have been developed recently which have made it possible to identify new genes that are important in Alzheimer disease. The Alzheimer's Disease Genetics Consortium (ADGC) was established in 2009 to allow many groups studying Alzheimer disease to work together to better understand the genetics of Alzheimer disease. The ADGC has brought together Alzheimer disease researchers from over 35 institutions.

This group of Alzheimer disease researchers has worked collaboratively to study clinical information and DNA samples from more than 22,000 Alzheimer disease subjects and 28,000 healthy older controls. Much of the needed clinical data and DNA samples were collected by the 31 Alzheimer's Disease Centers supported by the National Institutes of Health (NIH). The DNA samples are stored at the National Cell Repository for Alzheimer's Disease (NCRAD).

Researchers analyzed the samples and data using a study design called a Genome Wide Association Study (GWAS; see previous article). From this analysis, they identified three new genes that are important in determining the risk for Alzheimer disease.

More recently, the researchers in the United States have partnered with other Alzheimer disease researchers around the world. Together, they have formed the International Genomics Alzheimer Project (IGAP). This international group has worked together to gather even more clinical data and DNA samples. In the most recent study, data from 74,046 individuals was analyzed. Studying so much data has allowed the researchers to identify 11 more genes that are important in Alzheimer disease.

The Alzheimer disease research community is working together again to use DNA sequence studies to identify more genes important in Alzheimer disease. APOE has been known for nearly ten decades and has the strongest effect on disease risk. The remaining genes each explain a much smaller proportion of disease risk – perhaps 3-6% each. This means that if we study only one of these genes, we still cannot accurately predict if an individual will develop Alzheimer disease. Even if we study several of these genes together, it is still very difficult to predict if the individual will develop Alzheimer disease. The importance of the discovery of these genes is primarily in what we have learned about what factors are important in Alzheimer's risk. Our hope that this knowledge will help us identify better treatments in the future. ■

References: Naj, A.C., et al., Common variants at MS4A4/MS4A6E, CD2AP, CD33 and EPHA1 are associated with late-onset Alzheimer's disease. Nat Genet, 2011. 43(5): p. 436-41.

Lambert, J. C., et al., Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. [Letter]. Nature Genetics, Advanced Online Publication, 2013. 1-9.

Thank you to the ADGC

Research Opportunities:

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 55 to 80 years, diagnosis of mild to moderate Alzheimer's disease, good general health and medically able to undergo neurosurgery.
- Locations: USA - CA, IN, MA, MO, NY, RI; United Kingdom; Australia
- Contact: PH: 314-286-2683 or DIAN webpage http://www.dian-info.org

Neuroimaging in Frontotemporal Dementia (NIFD)

- Purpose: To identify the best methods for imaging and analysis for tracking frontotemporal lobar degeneration (FTLD) over time.
- Eligibility: Individuals between the ages of 45 and 90 who meet the criteria for behavioral variant frontotemporal dementia (bvFTD), semantic dementia (SD), progressive nonfluent aphasia (PNFA), or healthy aging. A study partner who has frequent contact with the volunteer and can provide information about them and accompany them to study visits is also required. All volunteers must be willing and able to undergo testing procedures and agree to follow-up.
- Locations: CA, MN, MA
- Contact: Aly Caplan, PH: 415-476-0670, e-mail: acaplan@ucsf.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 email or by phone.

Phone: 1-800-526-2839 **Email:** alzstudy@iupui.edu **Website:** www.ncrad.org

Meet the NCRAD Staff

Since our last staff update in 2010 NCRAD has had staff changes. We would like to take this opportunity to introduce our new staff and to update you on what our staff has been working on.

Dr. Tatiana Foroud is the 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.

Pictured from left to right: Ashley Bozell, Kelly Horner, Kelley Faber, and Tatiana Foroud

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 studies banked in the repository. She also works closely with the investigators requesting samples for their research.

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.

Ashley Bozell, MPH, is a newcomer to the Department of Medical and Molecular Genetics. She began working with NCRAD in July, 2013 and has been with the IU School of Medicine since 2012. Ashley serves as a research coordinator and her duties include: family follow up mailings, data validation, and publication tracking. She also helps complete annual chart reviews.

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 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.theaftd.org
Tel: 267-514-7221 or 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/

Research Match is a free service that pairs volunteers interested in participating in research opportunities from surveys to clinical trials with researchers. Open to all, including healthy volunteers.
http://www.researchmatch.org

National Society of Genetic Counselors
http://www.nsgc.org/
Tel: 312-321-6834

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 personality
9. Changes in mood or behavior
10. Loss of initiative

For more information, call the Alzheimer's Association at (800) 272-3900

National Cell Repository for Alzheimer's Disease Hereditary Genomics Division
Health Information and Translational Sciences Building
410 West 10th Street • HS 4000
Indianapolis, IN 46202-3002

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SCHOOL OF MEDICINE

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E-mail: alzstudy@iupui.edu
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