# The Genetics of Abstract Reasoning in Caribbean Hispanic Families with Alzheimer's Disease

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**Lay Abstract:**

Alzheimer's disease (AD) is a neurodegenerative disease that causes dementia. It has been estimated that it afflicts between 1 and 5 million people currently, and 4 million is the figure most often cited. Possibly as many as 14 million people will suffer from AD by 2050.[1] The prevalence of Alzheimer's disease has been estimated to be 3% among those 65-74, 19% among those 75-84, and 47% among those 85 and older.[2] Currently, there is no cure for Alzheimer's, and available medications can in some cases slow the progression of Alzheimer's, but neither stop nor reverse the process. In terms of annual cost in both indirect costs, such as loss of productivity, and direct costs, such as nursing care, the cost to the United States annually is between $80 and $90 billion.[3] The only definitive diagnosis for AD is brain autopsy, and early diagnosis remains difficult.

Studying the genetics of Alzheimer's disease has many advantages. It allows us to elucidate the disease pathogenesis and to develop screening and prevention. It may also provide potential targets for disease treatment and possibly provide an explanation why some patients do not respond to current medications or treatments.[4]

The Caribbean Hispanic population has an increased incidence of Alzheimer's disease (twice that of white individuals), making it highly desirable for genetic analysis.[5] My project will work within the already existing data set collected in Richard Mayeux's study of Alzheimer's in the Caribbean Hispanic population. This project studies familial Alzheimer's disease among Caribbean Hispanics, and includes over 300 families, consisting of more than 1500 individuals, half of whom are affected by Alzheimer's disease. Already, this study has found linkage on chromosomes 10q, 12 and 18q to Alzheimer's disease in this group.[6, 7] Additional studies are being done to better characterize the phenotype-genotype relations, such as age-of-onset, memory functions and Alzheimer's disease with hallucinations, etc.[8,9]

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[1] Evans, D.A., et al. Estimated Prevalence of Alzheimer's Disease in the United States. *The Milbank Quarterly*, v. 68, no. 2, 1990. P 267-289. The 4, 7 and 14 million estimates are based on a study in East Boston involving approximately 4,000 people that concluded in 1990. Estimates on the prevalence of Alzheimer's disease vary due to differing interpretations of the established research criteria, difficulty in diagnosing mild cases, impact of high refusal rates to participate in the study, the impact of an expanding aging population, and the racial/geographic characteristics of the various study groups.

[2] Evans, D.A., et al. Prevalence of Alzheimer's Disease in a Community Population of Older Persons. *Journal of the American Medical Association*, v. 262, no. 18, 1989. P. 2551-2556.

[3] Rice, D., P.J. Fox, W. Max, et al. *The Economic Burden of Alzheimer's Disease Care*. Health Affairs, v. 12, no. 2, 1993. P. 164-176.

[4] Mayeux, Richard. Mapping the new frontier: complex genetic disorders. *The Journal of Clinical Investigation*, v. 115, no. 6, June 2005. P. 1404-1407.

[5] Tang, M.-X. PhD, Cross, P Mphil, Andrews, H. PhD, et al. Incidence of AD in African-Americans, Caribbean Hispanics, and Caucasians in Northern Manhatten. *Neurology* v. 56, no. 1, Jan 2001. P. 49-56.

[6] Lee, JH, Mayeux, R, D Mayo, et al. Fine mapping of 10q and 18q for familial Alzheimer's disease in Caribbean Hispanics. *Molecular Psychiatry*, v. 9, 2004. P. 1042-1051.

[7] Mayeux, R, J.H. Lee, S.N. Romas, et al. Chromosome-12 Mapping of Late-Onset Alzheimer Disease among Caribbean Hispanics. *Am. J. Human Genetics*, v. 70, 2002. P. 237-243.

[8] Posthuma, Danielle, Michelle Luciano, Eco J. C. de Geus, et al. A Genomewide Scan for Intelligence Identifies Quantitative Trait Loci on 2q and 6p. *Am. J. Human Genet*., vol. 77, 2005. P. 318-326.

[9] Gottesman, Irving and Gould, Todd. The Endophenotype Concept in Psychiatry: Etymology and Strategic Intentions. *Am. J. Psychiatry*, v. 160, 2003. P. 636-645.

My project will look at the heritability and genetic basis of abstract reasoning, which is a neuropsychiatric measure of overall cognitive function. Alzheimer's disease has a number of criteria for diagnosis, such as memory loss and decreased function in daily activities. Diminished abstract reasoning ability is one of the first signs of Alzheimer's disease. My hypothesis has three parts: 1) Abstract reasoning is a heritable trait, 2) This trait is associated with a gene or genes. 3) Having this gene or genes predispose to Alzheimer's disease.

**A. Study Purpose and Rationale**

Over the last 8 ½ years, Dr. Mayeux's group has identified, examined and collected blood samples from over 1500 individuals from more than 300 families of Caribbean Hispanic origin with familial Alzheimer disease, and continues to process data in more families. Already a genome-wide scan was conducted of 340 markers in the first 98 families identified, and the remaining families are being genotyped. To date, approximately 200 families have been genotyped. In the initial scan, linkage was found at chromosome 18 and 12. The hypothesis of the study is that one of more susceptibility genes, in addition to APOE, increase the risk of Alzheimer's disease among Caribbean Hispanics. In particular, my study will focus on examining the endophenotype of abstract reasoning. My hypothesis is threefold: 1) Abstract reasoning is a heritable trait, 2) This trait is associated with a gene or genes. 3) Having this gene or genes predispose to Alzheimer's disease.

**B. Study Design and Statistical Analysis**

My hypotheses are that firstly, the endophenotype of abstract reasoning is a heritable trait, and secondly that there is a gene or genes linked to it, and that thirdly that these genes will help determine genetic predisposition to Alzheimer's in familial AD. Endophenotypes are based on a measurable subcomponent of a disease that is not visible, such as a biochemical, endocrinological or cognitive parameters. The concept is that "endophenotypes represent simpler clues to the genetic underpinnings than the disease syndrome itself, promoting the view that psychiatric diagnosis can be decomposed or deconstructed, which can result in more straightforward—and successful—genetic analysis." [9] Ideally, this endophenotype is heritable and associated with a quantitative trait locus, and can be used in determining relative risk for developing the disorder among those with the trait. An endophenotype of COPD, for example would be the forced vital capacity of patients (FVC). Patients with the endophenotype of low FVC would be more likely to progress to the phenotype of COPD. In the same way, I hypothesize that the endophenotype of low abstract reasoning leads to increased risk of developing Alzheimer's disease within the cohort of familial Alzheimer's disease in Caribbean Hispanics. If this is true, it would improve the statistical power and precision of the diagnosis of AD in these families.

To assess the heritability of the endophenotype of abstract reasoning in the cohort of 1500+ patients I will look at their quantitative scores of abstract reasoning. This can be measured by the "similarities" test of the WAIS (Weschler Adult Intelligence Scale) from 0-28. This data has already been collected. In order to do this analysis I must conduct data cleaning of these variables. This entails reviewing patient charts to verify that all the pertinent variables have been correctly entered into the database. Once I have ascertained that the data is "clean" I can begin my analysis.

I will use statistical methods to determine to what degree the endophenotype trait is heritable. These methods estimate the amount of genetic variance over the total phenotypic variance from members in a family. To conduct these analysis I will use the program SOLAR. I will also examine potential confounders, such as education level, gender, APOE status, AD status, etc. If it is determined that abstract reasoning is heritable, then I will conduct a genetic linkage analysis to localize genes that contribute to abstract reasoning.

For the variance component linkage analysis I will perform a two stage genome scan, using the results of two previously completed genome scans. I will conduct a first stage scan by using 400+

microsatellite markers that are 10 cM apart to cover the entire genome. Then I will focus on the regions that give best evidence for linkage (most likely location) by adding more markers to better localize the region. The variance component linkage analysis will be conducted using the computer program SOLAR.

Lastly, I will conduct an assessment of relative risk for Alzheimer's in those who have and do not have the disease.

*Below, are comments on the power of the study from Dr. Joseph Lee:*

*Power considerations*. Power in linkage study depends on a number of factors, including mode of inheritance (recessive, dominant, additive), extent of heterogeneity, gene frequency, gene effect sizes, penetrance, proportion of sporadic cases. These factors combine to determine the overall trait heritability and population prevalence. Power calculations are far too simplistic in that they presented some subset of these parameters. Our affected sibpair study includes at least two AD cases and unaffected siblings, which in some ways combine both extreme concordant and discordant approaches of quantitative trait loci.

*QLT Linkage analysis*. In our sample, we now have over 200 families in which the average sibship size of six and will continue to collect more families for the next few years. Of those, the average sibship size for living siblings (who we have genomic and neuropsychological data on) is 3.9, ranging from two to 14. Further, these siblings constitute 1,713 all possible sibling pairs (although non-independent). This number excludes families with only a pair of siblings. Of those, some 10% will not provide data, due to unwillingness to participate, death before neuropsychological examinations, etc. By the time we initiate our QTL mapping genome scan in the second year of the grant, we expect to have more than 1,700 sibling pairs, even after taking into account the number of siblings who will not provide data. Since power to detect linkage is only meaningful in the full sample for fine mapping, the power calculation reflects this.

This number of sibling pairs should provide 80% power to detect linkage at an $\alpha$ of 0.0001 (lod of 3), assuming the sibling pairs represent top 10% and bottom 30% of the memory trait distribution. This holds true for allele frequencies ranging from 0.1 to 0.5 with heritability of 0.2 or higher. When the heritability coefficient is reduced from 0.2 to 0.1, however, the sample size increases by 3-fold from 1,289 sibling pairs to 4,879 sibling pairs for allele frequency of 0.5 and for the same top 10% and the bottom 30% sibling pairs.

**C. Study Procedure**

Eligible families are recruited and once accepted all family members are asked to undergo a 45 minute neuropsychological assessment and give a blood sample. This battery is conducted by a research technician and includes:

- Selective Reminding Test
- Benton Visual Retention Test
- Orientation from Mini-Mental State Examination
- Rosen Drawing Test
- Benton Visual Retention Test, Matching
- 15-Item version of Boston-Naming Test
- WAIS-R Similarities***
- Controlled Word Association Test

The subjects repeat the exam and at yearly intervals. The study is ongoing, and will last as long as funding exists.

**D. Study Drugs**

None

**E. Medical Device**

None

**F. Study Questionnaires**

Approved.

**G. Study Subjects**

**Inclusion criteria:**

- Diagnosis of Alzheimer's disease in the proband must conform to the current standards of diagnosis. (NINCDS-ADRDA criteria for probable or definite AD)
- Eligible probands must be of the Caribbean Hispanic ethnic group.
- All probands must have an informant, either another family member or spouse, willing to provide informed consent

**Exclusion criteria for Alzheimer's disease families:**

- Failure to identify an appropriate informant
- Uncertainty of clinical diagnosis of AD
- Discovery of additional diagnosis that could account for the clinical manifestations
- Unwillingness to partipicate
- Failure to identify a living sibling with AD
- Not of Caribbean Hispanic origin

**H. Recruitment of Subjects**

The Alzheimer's probands were identified from private offices of neurologists at Columbia Presbyterian Medical Center, from word-of-mouth in the community of Washington Heights-Inwood, and by advertisements in the local Hispanic newspapers and through advertisements in the local Hispanic newspapers and through advertisements in the local community using various types of media resources. The same pattern of recruitment was used in the Dominican Republic.

**I. Confidentiality of Study Data**

Study data are recorded in paper files which are kept in the Sergievsky Center. The contents of these files are entered into a database, PROGENY, which is accessible only to research staff in the Sergievsky center with proper access.

**J. Potential Conflict of Interest**

None.

**K. Location of the study**

The locations will be New York City and the Dominican Republic. In New York City, the sites will be the Columbia Presbyterian Medical Center Neurology Clinics and in the subjects' homes in

Washington Heights-Inwood area. In the Dominican Republic visits will take place in private clinics in Santiago and Santo Domingo and in the homes of the subjects. Whether the interview happens in the office or in a house call is the choice of the subject.

**L. Potential Risks**

There are three major risks. Firstly, the neuropsychological testing may been perceived as difficult or potentially embarrassing because the questionnaires may contain questions that are difficult to answer. Secondly, some interviews regarding family history may raise issues concerning personal matters. Thirdly, there may be a concern for confidentiality.

The other risk is associated with drawing blood. This may cause pain at the site of the blood draw or bruising. However, the risk is minimal.

**M. Potential Benefits**

The benefits to the subjects is minimal. However, the benefit to society of discovering genes associated with Alzheimer's is great.

**N. Alternative Therapies**

Not applicable

**O. Compensation to subjects**

Subjects are given $20 per interview if the interview is conducted in the United States in their house, or $20 plus cab fare if they come to Columbia-Presbyterian Medical Center. The collaborators in the Dominican Republic did not wish to give $20 per interview.

**P. Costs to Subjects**

None

**Q. Minors as Research Subjects**

Not applicable.

**R. Radiation or Radioactive substances**

None.