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The National Institute on Aging Late Onset Alzheimer's Disease Family Based Study: A Resource for Genetic Discovery

Dolly Reyes-Dumeyer¹, Kelley Faber², Badri Vardarajan¹, Alison Goate³, Alan Renton³, Michael Chao³, Brad Boeve⁴, Carlos Cruchaga⁵, Margaret Pericak-Vance⁶, Jonathan L. Haines⁷, Roger Rosenberg⁸, Debby Tsuang⁹, Robert A. Sweet¹⁰, David A. Bennett¹¹, Robert S. Wilson¹¹, Tatiana Foroud², Richard Mayeux¹

¹Department of Neurology, Taub Institute for Research on Alzheimer's Disease and the Aging Brain and the Gertrude H. Sergievsky Center, Columbia University in the City of New York, NY, USA.

²Department of Medical and Molecular Genetics, National Centralized Repository for Alzheimer's Disease and Related Dementias (NCRAD), Indiana University School of Medicine, Indianapolis, IN, USA.

³Department of Genetics & Genomic Sciences, Ronald M. Loeb Center for Alzheimer's disease, Icahn School of Medicine at Mount Sinai, New York, NY, USA

⁴Department of Neurology, Mayo Clinic, Rochester, MN, USA.

⁵Department of Psychiatry, Washington University in St. Louis, St. Louis, MO, USA.

⁶John P Hussman Institute for Human Genomics, Dr. John T Macdonald Foundation Department of Human Genetics, University of Miami Miller School of Medicine, Miami, FL, USA

⁷Department of Population & Quantitative Health Sciences and Cleveland Institute for Computational Biology. Case Western Reserve University, Cleveland, OH, USA.

⁸Department of Neurology, University of Texas Southwestern Medical Center at Dallas, TX, USA.

⁹GRECC VA Puget Sound, Department of Psychiatry and Behavioral Sciences, University of Washington Seattle, WA, USA

¹⁰Departments of Psychiatry and Neurology, University of Pittsburgh, Pittsburgh, PA, USA.

¹¹Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, IL, USA.

Abstract

INTRODUCTION: The National Institute on Aging Late-Onset Alzheimer's Disease Family Based Study (NIA-LOAD FBS) was established to study the genetic etiology of Alzheimer's disease (AD).

METHODS: Recruitment focused on families with two living affected siblings and a third first degree relative similar in age with or without dementia. Uniform assessments were completed,

DNA was obtained as was neuropathology, when possible. *APOE* genotypes, genome-wide SNP arrays and sequencing was completed in most families.

RESULTS: *APOE* genotype modified the age-at-onset in many large families. Novel variants and known variants associated with early- and late-onset AD and frontotemporal dementia were identified supporting an international effort to solve AD genetics.

DISCUSSION: The NIA-LOAD FBS is the largest collection of familial AD worldwide, and data or samples have been included in 123 publications addressing the genetic etiology of AD. Genetic heterogeneity and variability in the age-at-onset provides opportunities to investigate the complexity of familial AD.

1. Introduction

In 2020, 5.8 million Americans were living with Alzheimer's disease (AD). By 2050 this number is projected to grow to 13.9 million people, nearly 3.3% of the US population¹. The etiology of AD remains unclear, but there is substantial evidence that AD is a highly heritable disorder. The National Institute on Aging Late-Onset Alzheimer's Disease Family Based Study (NIA-LOAD FBS) is the largest collection of multiplex AD families recruited and longitudinally assessed worldwide. Since 2003, the central goal of this cohort was to broadly support genetic research by making clinical and genomic data and biological samples rapidly available to the AD research community to support the development of therapies to treat or prevent AD. The use of multiplex families to understand genetic susceptibility to AD began with early onset forms. These studies led to the discovery of rare and highly-penetrant mutations in autosomal dominant AD: *APP*², *PSEN1*^{3,4} and *PSEN2*^{5,6}. Nearly 60% of individuals with early onset AD have other affected family members,⁷ and of these, approximately 13% inherit the mutations in an autosomal dominant manner⁸. While variants in these genes have explained only a small proportion of the occurrence of familial, early-onset AD, they formed the basis for the development of novel therapies now being investigated in AD regardless of age at onset of disease⁹.

Genetic research on the more common late onset form of AD was transformed by the work of Pericak-Vance and her colleagues¹⁰ using a novel linkage strategy in multiply affected families with late-onset AD. They were the first to identify a locus on chromosome 19¹⁰. This led to the discovery of the association between the *APOE* $\epsilon 4$ allele and the increased risk of AD as well as the reduced risk of AD with the *APOE* $\epsilon 2$ allele^{11,12}. The association was later confirmed in almost all ethnic groups, but with slightly weaker effects among those of African ancestry¹³. Overall, the population attributable risk of the *APOE*- $\epsilon 4$ allele has been estimated at 20%¹⁴. Nonetheless, the accumulating evidence indicates that late-onset AD is multifactorial with high heritability, 70% or higher, implying that other genes and risk factors also contribute to its etiology.

Genetic investigations typically require time and effort to ascertain samples for genetic studies. While it was presumed that recruitment of unrelated patients and controls would be a faster and more efficient way to find risk alleles than families, there are many scientific and practical advantages for recruiting families for genetic research. The observed incidence rates for AD are estimated to be three to five times higher in multiplex families¹⁵.

Multiplex families may be enriched in disease causing genetic variants, allowing penetrance to be studied while minimizing the effects of population stratification. Familial enrichment is particularly valuable for rare variants (minor allele frequency [MAF]<0.01), where population-level studies have little power. Family members are generally eager to participate in such research and often have shared environments and parents of origin. Moreover, they also provide the opportunity to assess interaction between alleles at the same locus and to detect epistasis due to the high penetrance.

The NIA-LOAD FBS has contributed to nearly every genetic study of AD over the past two decades and with the advent of novel strategies to understand how genetic variation leads to this disease, it will continue to do so. Here we describe the cohort, the variable range of age-at-onset across and within families, the effects of *APOE* on the risk of AD across ethnic groups, the genetic heterogeneity and highlight the broad availability of clinical and genetic data and biological samples.

2. Methods

2.1 Participant recruitment.

Families assumed to be multiply affected by AD by history or autopsy were recruited from sites across the United States (supplemental figure 1). The criteria for study entry included two living affected siblings, 60 years of age or older, and a third living relative, similar in age, with or without dementia. We also included families with deceased affected siblings, as long as frozen brain tissue was available for affected members. Families in which participants were symptomatic, but did not meet criteria for AD, were still included with the commitment for follow-up. Healthy controls without a family history of AD in a 1st degree relative, who were 55 years of age or older were also recruited. Participants demonstrated the full range of cognitive function including normal cognition and dementia (table 1). The clinical diagnosis of AD was required to meet established research criteria¹⁶.

Families were enrolled and consented at individual study sites and completed the following protocols either by in person or telephone interview and assessments. The study protocol included: a family pedigree, standardized cognitive and psychiatric assessments, as well as a review of AD and cardiovascular risk factors (table 1). Regular follow-up visits were used to update the family history and obtain additional clinical information on new family members that had not previously participated. All study data were stored at the Columbia University, the Coordinating Center.

2.2 Cognitive assessment.

Standardized cognitive assessments began in 2006, and over 75% of the cohort has been assessed^{17,18}. The 15-minute cognitive battery consisted of seven brief tests that were administered in person or by telephone and assessed: Working memory - Digit Span Forward and Backward and Digit Ordering; Episodic memory - Immediate and Delayed Recall of story "A" from the Wechsler Memory Scale and Semantic memory - asked persons to name members of two semantic categories (Animals, Vegetables) in separate 1-minute trials. From these measures, a factor analysis of the seven tests summarizing measures

of working memory, declarative memory, episodic memory, semantic memory, and global cognition was developed and is regularly updated. Interviews using different methods, in-person or by telephone, had little effect on performance and provided operational flexibility and a means of reducing costs and missing data¹⁷.

2.3 Psychiatric Interview.

The assessment of psychiatric manifestations was added in 2010 and was designed to be completed in an interview with a knowledgeable informant and could be conducted after the participant's death. This approach captured psychotic symptoms that occurred in the prior month, identifying the month during which each symptom was most persistent and recording the frequency of symptoms¹⁹. The Neuropsychiatric Inventory (NPI-Q)^{19,20}, a widely used, validated informant-based interview that is used to evaluate neuropsychiatric symptoms in patients with dementia was selected. The NPI-Q has good interrater reliability and concurrent validity compared with more structured interviews^{21,22}.

2.4 Antecedent risk factors.

A structured interview was used to collect putative risk and protective factors associated with AD, at baseline and follow-up to incorporate any changes. The primary focus was on modifying factors such as hypertension, heart diseases (myocardial infarction, congestive heart failure, or other type of heart disease) and diabetes²³. A stroke assessment captured the number of stroke events. antecedent (risk or protective) factors was also used in follow-up by telephone. For participants unable to be interviewed, the person who best knew the patient provided the information. Other factors to be ascertained included history of head injury, smoking, alcohol use, physical activities and leisure activities. Current medications were queried. In addition, for each medical condition or risk factor endorsed, the age at onset, duration, treatment history and whether there had been any change in the condition since the prior assessment was ascertained.

2.5 Biological Resources Collection.

Initially, blood, saliva or frozen brain tissue collected at baseline and at subsequent visits. All such biological materials sent to the National Centralized Repository for Alzheimer's Disease and Related Dementias (NCRAD) which extracted and stored DNA. As shown in supplemental table 1, we collected DNA from 7,925 participants. In 2018, we expanded blood collection to also obtain peripheral blood mononuclear cells (PBMCs) at follow-up visits.

2.6 Genotyping and sequencing.

Supplemental table 1 summarizes available genetic data. Genome wide SNP array (GWAS) data were obtained in 1,340 families (76.3%) in the cohort, which included 7,012 (72.4%) of their family members. Whole exome (WES) or whole genome sequencing (WGS) was conducted in 1,340 (76.3%) of the families. *APOE* genotyping was performed in 1,260 families (71.8%). The results of all genetic studies have been stored at the National Institute on Aging Genetics of Alzheimer's Disease Storage Site (NIAGADS).

2.7 Neuropathological confirmation of diagnosis.

At the inception of the study, NIA-LOAD FBS began preplanning brain donation with all family members to maximize the likelihood that neuropathology would be performed after death. This resulted in a robust brain donation program in which autopsy reports or brain tissue was successfully obtained in 836 individuals (table 2). In the event an autopsy was performed, and no tissue was available, the autopsy report was requested. Brain autopsy was performed at Columbia University or at one of the study sites, with diagnoses based on the 2012 NIA-Alzheimer's Association Working Group guidelines²⁴. Brain tissue, frozen and fixed, were sent to NCRAD to share with the research community. In 2019 we expanded the use of brain tissue to serve, not only as a means of confirming the diagnosis, but also to support functional studies including transcriptomics and DNA methylation studies.

2.8 Accessible biological samples, clinical and genetic data.

As shown in figure 1, qualifying families (A) were recruited by the NIA-LOAD FBS investigators (B). Blood was sent to NCRAD (C), which in turn, supplied biological samples (D) to the Alzheimer's Disease Sequencing Projects (ADSP) and to other qualified individual investigators (D) along with phenotype data from the Columbia University Coordinating Center for the NIA-LOAD FBS. Any new data that were generated by these investigators was required to be shared by sending it to NIAGADS (E) where other investigators could request clinical and genetic results from these studies (F).

3. Results

3.1 Recruitment and Demographics.

We recruited 1,756 families and acquired data from 9,682 family members. The families were diverse: 181 (10.3%) African American, 425 (24.2%) Caribbean Hispanic, 138 (7.8%) self-reporting as "other or mixed" and 1,012 white, non-Hispanic (supplemental table 2). Among the affected and unaffected family members, 63% were women, a percentage that differed significantly by ethnic group (72% among African Americans and 66% among Hispanics, 62% among white non-Hispanics and 57% the other group, $p=0.009$). Among the 1,756 families, 451 (25.7%) had three or more affected family members. Another 31.5% had two affected individuals while 598 (34%) families consisted of only a single affected individual or a single individual who, after clinical evaluation, did not meet criteria for dementia or AD but had cognitive impairment. The proportions of affected to unaffected individuals was similar across the ethnic groups (supplemental table 2). Ultimately, 1,343 families with two or more affected individuals meeting research criteria for AD were recruited. Of those, 569 (42.4%) families represented a single generation; 683 (50.8%) were represented by two generations and 91 (6.8%) of families were represented by three generations. Ascertainment of other family members continues for remaining 413 families.

3.2 Data collection.

In the family cohort, 8,610 (77.7%) individuals had detailed clinical information including multiple cognitive assessments. The other 22.3% were either too impaired for cognitive testing or were recruited before the clinical assessments were standardized in 2006. Tables

1 and 3 summarize the data collected and the resulting clinical diagnoses. Telephone interviews was initiated early on to make it easier for family members to participate. We conducted in-person interviews in 7,412 (68.5%) and follow-up interviews in 3,349 (30.9%). Because we had alternatives to in-person assessment in place prior to the pandemic, we were able to continue to follow family members; however, our ability to recruit new families was limited. Since the inception of the study in 2003, 15.1% of the cohort has been lost to follow-up without leaving a forwarding address or telephone number, and 2,878 (26.6%) died.

Below we present some of the published and unpublished results from this data collection.

3.3 Age-at-onset.

The average age of onset in affected family members differed slightly, but significantly, across all ethnic groups ranging from 72 years in Caribbean Hispanics to 74 years in African Americans and white non-Hispanics ($p < 0.0001$). The average age at last visit among unaffected family members differed significantly by ethnic group (66.2 yrs, African American, 63.9 yrs, Hispanic vs. 68.7 yrs, white non-Hispanic; $p < 0.0001$). In general, we observed a very wide range of age-at-onset among families especially those with three or more affected members. Individuals with later ages-at-onset were significantly less likely to carry an *APOE-ε4* allele (non-*ε4* 44.9% vs. *ε4* 60.5%) and more likely to carry an *APOE-ε3* allele (*ε3* 47.1% vs. *ε4* 33.3%) supplemental figures 2a and 2b). *APOE-ε4* had the stronger effects in white, non-Hispanic families when the genotype was homozygous or heterozygous. However, among Caribbean Hispanics and African Americans the genotypic effects were limited to *APOE-ε4* homozygotes (supplemental figures 3a–d) indicating that although *APOE* is a robust risk factor for sporadic AD, but also has a role in familial AD.

3.4 Conversion rate to dementia.

The annual incidence, or conversion rate to dementia in the NIA-LOAD FBS participants ranged from 3% per year between ages 65 to 74 years; 7% per year in those aged 75 to 84 years and 8% in those 85 years or older. Contrasting these results with the population-based estimates, the incidence was increased by 3-fold for NIA-LOAD FBS (standardized annual incidence ratio, 3.44)²⁵.

3.5 Genome-wide SNP Array.

Using data from 992 families, investigators confirmed results seen among unrelated individuals in *BINI*, *CLU*, *CR1* and *APOE* and identified a novel gene *CUGBP2* among *APOE-ε4* carriers²⁶. The variants in these families were not statistically significant due to the small sample size but found nominal significance in several *CD2AP* and *EPHA1* and contributed to several large AD meta-analyses (figure 2)^{27–29}. Investigators also created a polygenic risk scores constructed from summary statistics from sporadic AD that demonstrated the enrichment of genetic risk variants in these families^{23,30}.

3.6 Variant analyses.

In this group of families, we also found variants in *APP*, *PSEN1* and *PSEN2* usually associated with familial early onset forms of AD and *MAPT*, *GRN* and *C9orf72* usually

associated with frontotemporal dementia (FTD) ^{31–35}. The most frequent variants were found were *PSEN1 p.A79V* (0.46% of the families) and the *C9orf72* expansion (0.48% of the families). Among the probands, 1.82% carried pathogenic variants in *APP*, *PSEN1*, and *PSEN2*, and 1.94% had pathogenic variants in *MAPT*, *GRN*, or *C9orf72*. This suggests that modifying factors may exist, either genetic or environmental, that delay the onset of dementia in these families.

Although autopsies were not available for all the individuals with FTD pathogenic variants, the neuropathology in some individuals, was compatible with a diagnosis of AD with mixed pathologies³⁶. *C9orf72* expansion has also been associated with several clinical presentations (FTD and ALS). The NIA-LOAD FBS extends these data to other genes and diseases, supporting the previous finding of pathogenic variants in FTD genes among individuals with AD pathology³⁷.

The NIA-LOAD FBS dataset was also instrumental in the identification of novel risk variants, and confirmed the large Alzheimer's Disease Genetic Consortium Case-Control study and in a study using whole genome sequencing^{26,31}. Beecham et al³⁸ identified rare, damaging variants segregating with disease in the non-Hispanic white families using whole exome sequencing data that included: *NOS1AP*, *RP11-433J8*, *ABCA1*, and *FISP2*. A rare-variant association study identified two known AD genes: *FERMT2* and *SLC24A4*, and a similar approach was used to identify rare variants in the 67 families of Hispanic ancestry³⁵. Lambert JC et al²⁷ conducted a meta-analysis that identified 11 novel gene regions, most notably *HLA-DRB5*, *HLA-DRB1*, *PTK2B*, *SORL1*, *SLC24A4*, *RIN3* and *DSG2*. Kunkle BW et al²⁸, identified new risk regions that implicated disorders of amyloid, tau, immunity and lipid processing. Using a slightly different approach, investigators found genes that are strongly expressed in immune-related tissues and cell types (e.g. microglia), and gene-set analyses indicated biological mechanisms involving lipid-related processes and degradation of amyloid precursor proteins²⁹. Using a whole exome meta-analysis, Bis et al³⁹ confirmed associations with common and rare variants in several previously established AD genes: *ABCA7*, *APOE*, *HLA-DPA1*, *MS4A6A*, *PILRA*, *SORL1* and *TREM2* and nominated variants in two new genes: *IGHG3* and *ZNF655*.

3.7 New methods developed for family-based analyses.

Leal and her colleagues⁴⁰ used the NIA-LOAD FBS to develop a rare variant extension of the generalized disequilibrium test (GDT) to analyze sequence data obtained from nuclear and extended families. The GDT utilizes genotype differences of all discordant relative pairs to assess associations within a family and combines the single-variant GDT statistic over a genomic region of interest. The also develop rare variant, non-parametric linkage methods to analyze data from whole genome sequencing studies⁴¹, and subsequently extended the analytic method to include quantitative non-parametric methods to evaluate sharing of minor alleles⁴². Fernandez and Cruchaga⁴³ examined the performance of several collapsing, variance-component, and transmission disequilibrium tests across eight different software packages and 22 models utilizing the NIA-LOAD FBS cohort and developed a method using gene-based and variant-based approaches.

3.8 Neuropathological confirmation of diagnosis.

In 492 (82%) participants, neuropathology confirmed the diagnosis of AD. Other diagnoses accounted for the remaining 163 with and without dementia (table 2). Brain tissue is available by request to NCRAD.

4. Discussion

The success of the NIA-LOAD FBS can be measured by the broad use of the data and samples (table 4). Over 67,000 biological samples collected as part of the NIA-LOAD FBS have been distributed to approved investigators. These samples have been analyzed, and the resulting data briefly described above are available through NIAGADS. In total, over 830 national and international investigators have requested data from the NIA-LOAD FBS, including the Alzheimer's Disease Genetics Consortium, the Alzheimer's Disease Sequencing Project, the Consortium for Alzheimer's Disease Research, the NIA-sponsored Alzheimer's Disease Research Centers and the National Alzheimer's Coordinating Center. Investigators have generated 123 publications from the data and samples (Supplement 4) that include not only genotyping but methods development and assessments of risk to family members.

Multiplex families are more difficult to recruit for research studies, sometimes taking several years to identify all of the affected relatives in a single family and complete their phenotyping. Large multiplex families are often thought to be too rare to be relevant. However, such families may be much more common than assumed, and there are families in isolated geographical regions where very large sibships occur.⁴⁴⁻⁴⁶ Families with multiple affected members can more easily be found and ascertained for such studies. With the increased use of virtual visits, the ability to longitudinally follow these families is becoming easier. These large multiplex families may hold the key to survival without dementia despite carrying a disease-causing variant.

The ultimate goals of genetic studies of complex diseases, such as AD, are to identify causal biological pathways that might provide targets for therapeutic development. However, diseases such as AD are multigenic and it is likely that there are multiple strategies to accomplish this difficult task. A significant proportion of the heritability remains unexplained but may be due to rare, inherited, moderately penetrant variants unique to individual families.

When the NIA-LOAD FBS began in 2003, a goal was set to collect as many as 1,000 families or more including all appropriate members in existing families and complete follow-up assessments. Blood samples from the sent to NCRAD for DNA extraction and storage allowed samples to be broadly available to the research community. Initially, clinical data regarding the diagnoses was limited to the criteria used by each Alzheimer's Disease Center, but a more standardized approach was used to collect clinical information in 2006. Clinical data stored centrally at the Columbia University Coordinating Center, was immediately shared along with genetic data with the AD research community. Nineteen dataset accession numbers contain genetic data from the NIA-LOAD FBS (table 4).

The ADSP Discovery Extension Study (2015–2018) included whole genome sequencing (WGS) on individuals from multiply affected families provided by the NIA-LOAD FBS. The ADSP Follow-Up Phase (2018–2023) relies heavily on resources from the NIA-LOAD FBS and depends on continued longitudinal follow up of families and the further collection of 500 families from under-represented populations. Thus, over the past two decades, the NIA-LOAD FBS has acted as the key source of biological materials, genetic and longitudinal clinical data on large multiply affected AD families from ethnically diverse populations.

Phenotypic variation among family members with dementia, including differences in the age of onset and the effects of *APOE* or the presence of sleep behavior disorder, psychosis and parkinsonism may be due to interactions with other genes or epigenetic effects. Thus, we began brain transcriptomics and DNA methylation may help to clarify the origin of these differences. Moreover, because vascular risk factors clearly contribute to the pathogenesis of AD²³, the effect of cerebrovascular pathology continues to be investigated.

The NIA-LOAD FBS remains a critical component of the overall strategy to tackle AD genetics in the United States that includes the Alzheimer's Disease Genetics Consortium, the Alzheimer's Disease Sequencing Project, the NCRAD and NIAGADS. Together these groups have created a large collaborative international effort to combine data worldwide in pursuit of uncovering the relevant genetic risk factors for AD with the hope that patterns may emerge that ultimately will uncover biologic pathways underlying the illness.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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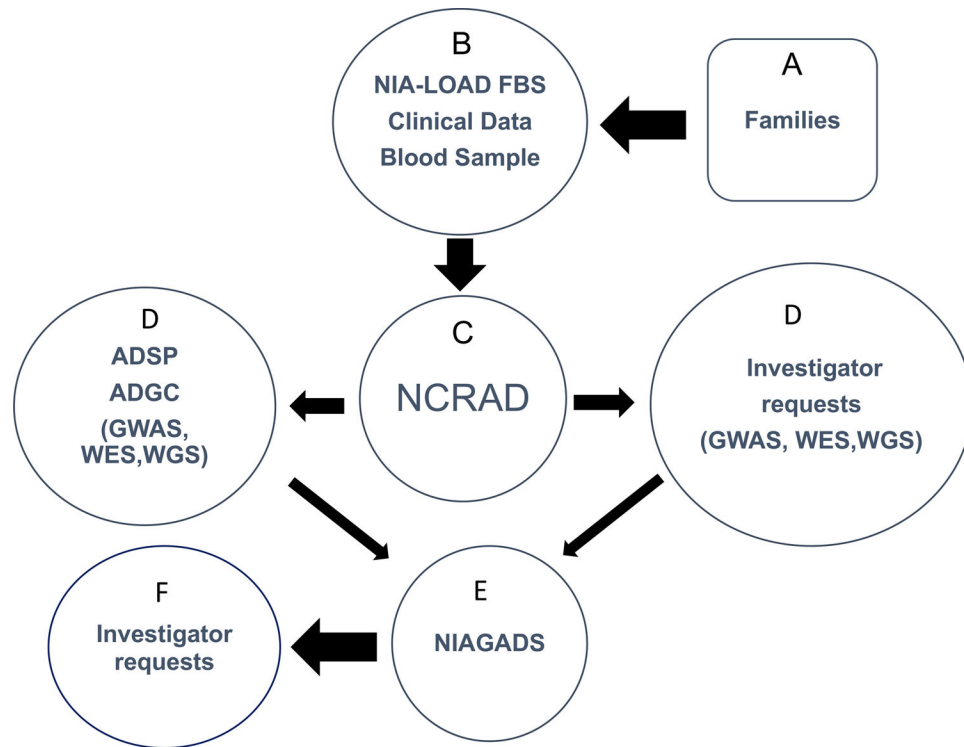


Figure 1. Potentially qualifying families (A) were recruited by the NIA-LOAD FBS investigators (B). Blood was sent to NCRAD (C). NCRAD supplied biological samples to the Alzheimer’s Disease Sequencing Projects (ADSP) (D) and to other qualified individual investigators (D) along with phenotype data from the Columbia University Coordinating Center. Any new data generated by investigators was required to be shared by sending it to NIAGADS (E) where other investigators could request clinical and genetic results from these studies (F).

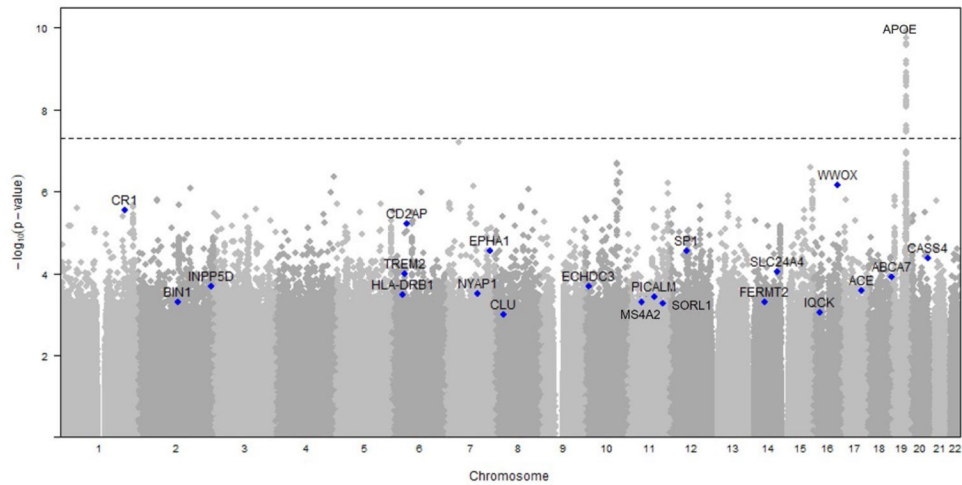


Figure 2. Results of genome-wide array in the NIA-LOAD FBS. The APOE locus reached genome-wide significance in associated with AD. However, a number of other loci, labeled on the Manhattan plot below were nominally significant. Many of these loci supported several large meta-analyses that included other cohorts^{27–29}.

Table 1.

NIA-LOAD Family Based Study: Clinical Data and Diagnoses

Clinical diagnoses ¹⁶	N
Probable AD	2,672 (27.6%)
Possible AD	395 (4.1%)
Other dementias *	160 (1.7%)
Dementia by family report only	227 (2.3%)
Unaffected family members	4,587 (47.4%)
Assessments	N
Cognitive	8,610 (89%)
NPI-Q	3,187 (33%)
Cardiovascular and other risk factor questionnaire	6,553 (68%)

Percentages are based on the total number of family members 9,682 individuals.

* Table 3 shows the diagnoses of other dementias.

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Table 2.

NIA-LOAD Family Based Study Neuropathology Data

Autopsy	N (%)
Total neuropathology/autopsy information	836
Neuropathology/autopsy reports provided by family	181 (21.6%)
Autopsy by Columbia or study site	655 (78.3%)
Definite AD ²⁴	492 (58.9%)
Non-AD dementia	47 (5.6%)
No dementia	116 (13.9%)

Percentages are based on the total number of individuals with neuropathology or autopsy information.

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Table 3.

Other forms of dementia

Clinical Diagnosis	N (%)
Frontotemporal degeneration	21 (13%)
Parkinson's disease with dementia	9 (5.6%)
Progressive supranuclear palsy	5 (3.1%)
Corticobasal degeneration	1 (0.6%)
Communicating, obstructive, or normal pressure hydrocephalus	1 (0.6%)
Cerebrovascular disease with dementia	32 (20%)
Dementia with Lewy bodies	28 (17.5%)
Primary progressive aphasia	2 (1.2%)
Posterior cortical atrophy	1 (0.6%)
Dementia associated with multiple non-Alzheimer's etiologies	28 (17.5%)
Dementia of unknown cause	32 (20%)
Total	160

Percentages are based on the 160 individuals with a clinical diagnosis of dementia other than Alzheimer's disease.

Table 4.

Summary of Biological Sample and Data Requests for NIA-LOAD Family Based Study

Sample Requests	N
Number of researchers approved for specimens from NCRAD	56
Number of DNA samples distributed from NCRAD	67,626
Inclusion in Independent Efforts	
DNA samples in the ADSP white, non-Hispanic	27 families; 142 individuals
DNA samples in the ADSP Caribbean Hispanic	31 families; 186 individuals
Independently approved researchers for sequencing (WES or WGS)	421 families; 1,655 individuals
Approved Data Requests	
dbGaP-phs000160.v1.p1 (NIA-LOAD linkage)	228
dbGaP-phs000168.v2.p2 (NIA-LOAD GWAS)	321
dbGaP-phs000372.v1.p1 (ADGC & NIA-LOAD GWAS)	101
dbGaP-phs0001572.v7.p4 (ADSP & NIA-LOAD WGS/WES)	166
dbGaP-phs000126.v1.p1 (controls for PD case-control)	268
Special analysis group data requests to the ADGC & NIA-LOAD	145
NIA Genetics of Alzheimer's Disease Data Storage Site (NIAGADS) (NG00032, NG00020, NG00033, NG00039, NG00027, NG00015, NG00081, NG00062, NG00036, NG00041, NG00048, NG00058, NG00065, NG00075, NG00076, NG00078, NG00100, NG00067, NG00091)	111

A summary of the results published and not published is presented on pages 8 to 10.