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Authors

Wang, Li-San
Naj, Adam C
Graham, Robert R
[et al.](#)

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Original Investigation

Rarity of the Alzheimer Disease–Protective *APP* A673T Variant in the United States

Li-San Wang, PhD; Adam C. Naj, PhD; Robert R. Graham, PhD; Paul K. Crane, MD, MPH; Brian W. Kunkle, PhD, MPH; Carlos Cruchaga, PhD; Josue D. Gonzalez Murcia, BS; Lisa Cannon-Albright, PhD; Clinton T. Baldwin, PhD; Henrik Zetterberg, MD, PhD; Kaj Blennow, MD; Walter A. Kukull, PhD; Kelley M. Faber, MS; Nicole Schupf, PhD, DrPH; Maria C. Norton, PhD; JoAnn T. Tschanz, PhD; Ronald G. Munger, MPH, PhD; Christopher D. Corcoran, PhD; Ekaterina Rogaeva, PhD; Alzheimer's Disease Genetics Consortium; Chiao-Feng Lin, PhD; Beth A. Dombroski, PhD; Laura B. Cantwell, MPH; Amanda Partch, MS; Otto Valladares, MS; Hakon Hakonarson, MD, PhD; Peter St George-Hyslop, MD, FRCP; Robert C. Green, MD, MPH; Alison M. Goate, DPhil; Tatiana M. Foroud, PhD; Regina M. Carney, MD; Eric B. Larson, MD, MPH; Timothy W. Behrens, MD; John S. K. Kauwe, PhD; Jonathan L. Haines, PhD; Lindsay A. Farrer, PhD; Margaret A. Pericak-Vance, PhD; Richard Mayeux, MD; Gerard D. Schellenberg, PhD; for the National Institute on Aging–Late-Onset Alzheimer's Disease (NIA-LOAD) Family Study

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IMPORTANCE Recently, a rare variant in the amyloid precursor protein gene (*APP*) was described in a population from Iceland. This variant, in which alanine is replaced by threonine at position 673 (A673T), appears to protect against late-onset Alzheimer disease (AD). We evaluated the frequency of this variant in AD cases and cognitively normal controls to determine whether this variant will significantly contribute to risk assessment in individuals in the United States.

OBJECTIVE To determine the frequency of the *APP* A673T variant in a large group of elderly cognitively normal controls and AD cases from the United States and in 2 case-control cohorts from Sweden.

DESIGN, SETTING, AND PARTICIPANTS Case-control association analysis of variant *APP* A673T in US and Swedish white individuals comparing AD cases with cognitively intact elderly controls. Participants were ascertained at multiple university-associated medical centers and clinics across the United States and Sweden by study-specific sampling methods. They were from case-control studies, community-based prospective cohort studies, and studies that ascertained multiplex families from multiple sources.

MAIN OUTCOMES AND MEASURES Genotypes for the *APP* A673T variant were determined using the Infinium HumanExome V1 Beadchip (Illumina, Inc) and by TaqMan genotyping (Life Technologies).

RESULTS The A673T variant genotypes were evaluated in 8943 US AD cases, 10 480 US cognitively normal controls, 862 Swedish AD cases, and 707 Swedish cognitively normal controls. We identified 3 US individuals heterozygous for A673T, including 1 AD case (age at onset, 89 years) and 2 controls (age at last examination, 82 and 77 years). The remaining US samples were homozygous for the alanine (A673) allele. In the Swedish samples, 3 controls were heterozygous for A673T and all AD cases were homozygous for the A673 allele. We also genotyped a US family previously reported to harbor the A673T variant and found a mother-daughter pair, both cognitively normal at ages 72 and 84 years, respectively, who were both heterozygous for A673T; however, all individuals with AD in the family were homozygous for A673.

CONCLUSIONS AND RELEVANCE The A673T variant is extremely rare in US cohorts and does not play a substantial role in risk for AD in this population. This variant may be primarily restricted to Icelandic and Scandinavian populations.

Author Affiliations are listed at the end of this article.

Group Information: The authors/members of the Alzheimer's Disease Genetics Consortium and the investigators for the National Institute on Aging–Late-Onset Alzheimer's Disease (NIA-LOAD) Family Study are listed at the end of this article.

Corresponding Author: Gerard D. Schellenberg, PhD, University of Pennsylvania Perelman School of Medicine, 422 Curie Blvd, Stellar Chance Laboratories, 609B, Philadelphia, PA 19104 (gerardsc@mail.med.upenn.edu).

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The amyloid precursor protein gene (*APP*; GenBank NC_011512) encodes a transmembrane protein of unknown normal function. In the normal processing of the APP protein, proteolytic cleavage yields a 39- to 43-amino acid peptide called β -amyloid ($A\beta$). Release of $A\beta$ from APP is catalyzed by the β -site APP cleaving enzyme 1 (BACE1) that cleaves APP at the N-terminal end of $A\beta$ and by the γ -secretase complex that cleaves at the C-terminal end.¹ Together, these 2 proteases generate the $A\beta$ peptide. In Alzheimer disease (AD), $A\beta$ accumulates in extracellular amyloid plaques that are characteristic of this disease. Mutations in *APP* cluster around the N-terminal and C-terminal sequences that encode $A\beta$ and cause early-onset AD. Likewise, early-onset AD is also caused by mutations in the presenilin 1 gene (*PSEN1*) and presenilin 2 gene (*PSEN2*), which encode protease subunits of the γ -secretase complex.¹ Genetic studies and a large body of functional evidence convincingly show that $A\beta$ is a toxic molecule critical to the pathogenesis of AD. As a result, multiple drug trials are in progress designed to stimulate $A\beta$ clearance using immunological approaches or to inhibit $A\beta$ production using small-molecule inhibitors of γ -secretase or BACE1.²⁻⁵

Recently, Jonsson et al⁶ reported that the *APP* coding mutation A673T, in which alanine is replaced by threonine at position 673, is protective against late-onset AD. This rare variant was enriched in Icelandic elderly controls compared with AD cases from the same population. The frequency was 0.13% in AD cases and ranged from 0.45% to 0.79% in controls, depending on age. The A673T variant was also observed in an individual with ischemic cerebrovascular disease but not AD⁷ and in a 104-year-old patient with dementia who had hippocampal sclerosis and little $A\beta$ accumulation.⁸ The A673T variant is located at position 2 of $A\beta$ and thus is immediately downstream of the BACE1 cleavage site. Ex vivo and in vitro experiments show that this variant inhibits BACE1 cleavage and results in reduced $A\beta$ production. Another mutation at this site, A673V, enhances BACE1 cleavage activity^{9,10} and is a recessive mutation causing early-onset AD. Likewise, the K670N/M671L mutation that affects the 2 amino acids immediately upstream of the BACE1 cleavage site also enhances BACE1 cleavage, increases $A\beta$ production, and causes early-onset AD.¹¹ Thus, multiple mutations in close proximity to the BACE1 cleavage site influence risk for AD and $A\beta$ production.

We genotyped a large number of AD cases and controls to determine whether the A673T mutation is an important protective variant in cognitively intact elderly US white individuals and in patients with AD from the same population. We found that this variant is extremely rare and does not have a discernible impact on AD risk in the US population.

Methods

Genotyping

We genotyped the samples listed in Table 1 using the Infinium HumanExome V1 Beadchip (Illumina, Inc). Genotyping was performed for 8410 individuals at the Robert S. Boas Center for Genomics and Human Genetics, Feinstein Institute for Medical Research, Manhasset, New York, 1990 indi-

viduals at the John P. Hussman Institute for Human Genomics, University of Miami, Miami, Florida, and 6166 individuals at the Center for Applied Genomics, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania. Genotypes were initially called using the default clustering profile from Illumina and recalled using clustering profiles generated by Genentech using data from 30 000 samples. We also genotyped the individuals listed in Table 2 for single-nucleotide polymorphism rs63750847 using the TaqMan assay C_89522366_10 (Life Technologies) and a 384-well plate format. Each plate contained samples from 2 heterozygotes from the exome array experiments. For both the exome array assay and the TaqMan assay, manual inspection of clustering indicated both were valid assays (eFigure 1 in the Supplement).

Participants

The National Institute on Aging Alzheimer's Disease Centers case-control sample, the University of Toronto/GlaxoSmithKline (also called Gen ADA) case-control sample, the Vanderbilt/Miami/Mount Sinai case-control sample, the National Institute on Aging-Late-Onset Alzheimer's Disease multiplex family-based sample, the National Cell Repository for Alzheimer's Disease multiplex family-based sample, the Multi-institutional Research in Alzheimer's Genetic Epidemiology family-based sample, and the Adult Changes in Thought (ACT) prospective cohort were described previously.^{12,13} The Genetics Differences cohort is a population-based prevalent case-control study from the same population as the ACT study.¹⁴ The Washington Heights-Inwood Columbia Aging Project sample is a multiethnic prospective cohort¹⁵; for this study, only white individuals were genotyped. The Washington University cohort is a white case-control cohort.¹³ The Miami multiplex families and the National Institute of Mental Health multiplex families were as previously described.¹⁶⁻¹⁸ The Cache County Study on Memory Health and Aging is a population-based study with 4 assessments of cognitive function since 1994.¹⁹ The Swedish cohorts are case-control studies recruited from neuropsychiatric clinics in Sweden as described previously.²⁰ For the family-based sample, we genotyped a single affected individual from each kindred. All studies were approved by institutional review boards at the respective universities involved in each study, and the overall study was approved by the University of Pennsylvania institutional review board. The participants provided written informed consent.

Analysis

The exome chip genotyping data (16 525 samples total) were first preprocessed using quality check steps adapted from Naj et al.¹³ Briefly, we excluded 881 samples and markers with a missing call rate higher than 2%, samples with genotype-imputed or reported sex mismatch, and markers significant ($P < 10^{-6}$) in either Hardy-Weinberg or informative missingness tests. We pruned 969 samples by relatedness test ($\hat{r} > 0.4$) using 15 086 linkage disequilibrium-pruned autosomal markers with a minor allele frequency >0.1) and compared samples with HapMap 3 data to exclude nonwhite individuals. We checked population substructure in 15 644 samples with good call rates using 5848 single-nucleotide polymorphisms that

Table 1. Samples Genotyped for A673T (rs63750847) With the Exome Array That Passed Quality Checking

Characteristic	Cohort											
	ADC ^a	University of Toronto/GSK ^b	Miami ^c	NIMH ^b	NIA-LOAD ^b	NCRAD ^b	MIRAGE ^b	Genetic Differences ^b	ACT ^b	WHICAP ^b	Washington University ^d	Total
Samples, No. (A673T heterozygotes, No.)												
Cases	3930 (0)	152 (0)	936 (0)	354 (0)	749 (0)	395 (0)	576 (0)	239 (0)	282 (1)	54 (0)	554 (0)	8221 (1)
Controls	2326 (0)	0	995 (0)	0	458 (0)	0	12 (0)	216 (0)	1445 (1)	322 (0)	360 (0)	6134 (1)
Total	6256 (0)	152 (0)	1931 (0)	354 (0)	1207 (0)	395 (0)	588 (0)	455 (0)	1727 (2)	376 (0)	914 (0)	14 355 (2)
Male, %	43.6	46.1	38.5	28.0	39.4	31.9	38.4	35.8	43.4	39.9	40.4	41.1
Case age at onset												
Mean (SD), y	72.4 (9.3)	77.8 (6.8)	72.6 (7.1)	71.6 (8.1)	73.8 (7.2)	71.0 (8.5)	68.6 (8.7)	76.4 (6.2)	83.7 (4.7)	84.5 (7.2)	79.8 (9.7)	73.4 (9.1)
No.	3930	152	885	354	749	393	572	239	282	54	554	6130
Control age at last examination												
Mean (SD), y	77.2 (9.3)	NA	73.5 (7.9)	NA	79.6 (8.7)	NA	76.1 (7.8)	80.8 (6.6)	81.6 (6.1)	81.0 (6.1)	74.6 (8.7)	78.0 (8.6)
No.	2326	NA	991	NA	458	NA	12	216	1445	322	360	8164
Cohort type	Case-control	Case-control	Case-control	Multiplex families	Multiplex families	Multiplex families	Multiplex families	Population-based incident cases with matched controls	Prospective cohort	Prospective cohort	Case-control	

Abbreviations: ACT, Adult Changes in Thought; ADC, Alzheimer's Disease Centers; GSK, GlaxoSmithKline; MIRAGE, Multi-institutional Research in Alzheimer's Genetic Epidemiology; NA, not applicable; NCRAD, National Cell Repository for Alzheimer's Disease; NIA-LOAD, National Institute on Aging–Late-Onset Alzheimer's Disease; NIMH, National Institute of Mental Health; WHICAP, Washington Heights–Inwood Columbia Aging Project.

^a In this cohort, 3640 cases and 2223 controls were genotyped at the Robert S. Boas Center for Genomics and Human Genetics, Feinstein Institute for Medical Research, Manhasset, New York (as 2 batches) and 282 cases and 103 controls

were genotyped at the Center for Applied Genomics, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania.

^b Genotyped at the Center for Applied Genomics, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania.

^c Genotyped at the John P. Hussman Institute for Human Genomics, University of Miami, Miami, Florida.

^d Genotyped at the Robert S. Boas Center for Genomics and Human Genetics, Feinstein Institute for Medical Research.

were present on both the exome array and in the HapMap 3 data set. Forty-nine individuals were likely to be from non-white or admixed populations. Two hundred seventy-three individuals were excluded owing to incomplete diagnosis information. In all, 14 355 individuals (8221 cases and 6134 controls) passed quality check. Five hundred eighty-five individuals were younger than 60 years at onset (512 AD cases) or at last visit (34 controls); 61 samples lacked age information.

Genotypes for rs63750847 (A673T; c.G2017>A) were ascertained via the exm1563596 marker (major/minor allele: G/A, 100% call rate after quality check). One sample with the A/A genotype was excluded owing to a very high missing call rate (20.84%). Two samples passing quality check carried the A/G genotype.

Results

A total of 8221 AD cases and 6134 elderly cognitively normal controls were genotyped using Illumina exome arrays (Table 1). These arrays have single-nucleotide polymorphism assays for more than 240 000 exonic variants that are nonsynonymous, nonsense, or splice-site variants. The exome array has an assay for rs63750847, which is the A673T variant discussed earlier (eFigure 2 in the Supplement). We identified 2 heterozygotes,

one in a sample from an AD case (minor allele frequency = 0.0061%) of Russian ancestry who had onset of AD symptoms at age 89 years and an *APOE* genotype of $\epsilon 3/\epsilon 3$ and the second in a sample from a cognitively intact 82-year-old control (minor allele frequency = 0.0082%) born in Iceland with an *APOE* genotype of $\epsilon 3/\epsilon 3$ (Table 3). Both were from the ACT study based in Seattle, Washington. Population principal components showed both to be of northern European ancestry when compared with HapMap 3 samples (eFigure 2 in the Supplement).

To validate the array genotyping results, we used a TaqMan assay to re-genotype 1610 of the same samples, including the 2 heterozygotes. We also genotyped 983 additional samples from the ACT study (Table 2). All genotypes derived from the exome array genotyping were confirmed by the TaqMan assay, including the 2 heterozygotes initially observed. All additional ACT samples were homozygous for the normal A673 allele. TaqMan genotyping was also used to survey 506 AD cases, 383 individuals with other dementias, and 3838 controls from the Cache County Study on Memory Health and Aging. All dementia cases were homozygous for the normal A673 allele. One of the 3838 individuals without dementia carried the A673T allele (Table 2). This individual was aged 77 years at last assessment, had an *APOE* genotype of $\epsilon 3/\epsilon 4$, and had ancestors from

Table 2. Samples Genotyped for A673T (rs63750847) by TaqMan Assay^a

Characteristic	Cohort					
	ACT ^b	United States		Total White Individuals	Sweden	
		Cache County Study on Memory Health and Aging			Cohort 1	Cohort 2
Samples, No. (A673T heterozygotes, No.)						
Cases	498 (1)	506 (0)	1004 (1)	298 (0)	564 (0)	862 (0)
Controls	1953 (1)	3838 (1)	5791 (2)	220 (0)	487 (3)	707 (3)
Dementia, other ^c	138 (0)	383 (0)	521 (0)	0	0	0
Total	2589 (2)	4727 (1)	7313 (3)	518 (0)	1051 (3)	1569 (3)
Male, No. (%)						
Cases	34.2	32.3		36.9	41.7	
Controls	43.5	41.7		25.0	72.1	
Age, mean (SD), y						
At onset for cases	84.1 (5.6)	82.4 (6.9)		75.7 (12.9)		
At sampling for cases					76.4 (10.7)	
At last examination for controls	81.2 (7.0)	79.8 (6.3)		98.0 (1.5)		
At sampling for controls					62.7 (10.7)	
Cohort type	Prospective cohort	Prospective cohort		Case-control	Case-control	

Abbreviation: ACT, Adult Changes in Thought.

^a Life Technologies.

^b Includes ACT samples genotyped using the exome array and an additional 364 cases, 1344 controls, and 117 other dementias. The two A673T variants are the same as in Table 1.

^c Includes vascular dementia, mixed dementias, and other rare forms of dementia.

Table 3. Heterozygotes for A673T

Cohort and Participant	Age, y ^a	APOE Genotype
ACT		
Case	89	ε3/ε3
Control	77	ε3/ε4
Cache County Study on Memory Health and Aging control	82	ε3/ε4
Swedish cohort 2		
Control 1	72	ε3/ε3
Control 2	55	ε4/ε4
Control 3	59	ε3/ε3
Family 1		
Control, mother	72	ε3/ε3
Control, daughter	84	ε3/ε3

Abbreviation: ACT, Adult Changes in Thought.

^a Age indicates age at onset for the ACT case, age at last examination for the ACT, Cache County Study on Memory Health and Aging, and family 1 controls, and age at sampling for the 3 Swedish controls.

Denmark, Ireland, Scotland, and England (Table 3). Because the minor allele of the A673T variant was observed in a Swedish sample at a frequency of 0.42%,² we also genotyped 862 AD cases and 707 cognitively normal controls from Sweden (Table 2). Three controls were heterozygous for A673T. All AD cases were homozygous for the common A673 allele.

Previous work reported that an affected individual in a small family with late-onset AD was heterozygous for A673T.²¹ Because an affected individual from the same family was genotyped using the exome array as one of the individuals from the National Institute on Aging–Late-Onset AD sample, we genotyped all other available family members for the A673T vari-

ant. This included 6 AD cases, 4 married-in spouses, and 7 blood relatives of affected individuals. We observed 1 spouse and the child of that spouse as heterozygous for A673T. The child is a blood relative of affected individuals in the family. Both the child and parent were unaffected individuals (ages at last visit, 84 and 72 years, respectively). The heterozygous individual originally reported as an AD case was actually the unaffected child described here. This family is from the United States with a Scandinavian background.

Discussion

The APP A673T variant is overrepresented in Icelandic controls when compared with Icelandic AD cases.⁶ Therefore, like the APOE ε2 allele,²² the A673T variant appears to protect against late-onset AD, defined as disease onset after age 60 years. Studies on the functional consequences of the A673T substitution showed that this amino acid substitution inhibited BACE1 cleavage of APP, potentially reducing or eliminating the production of Aβ peptide from APP encoded by this allele.⁶ That this allele appears to be protective provides additional genetic evidence that Aβ is a critical toxic molecule contributing to AD. Overproduction of Aβ (eg, from the APP K670N/M671L mutation) causes early-onset AD, and a variant associated with reduced Aβ production, A673T, protects against AD. Amino acid 673 appears to be critical for BACE1 cleavage since a different allele at the same amino acid (an alanine change to a valine, A673V) enhances Aβ production and causes recessive early-onset dementia.⁹ However, the A673T variant is exceedingly rare in the white individuals tested here (carrier frequency = 0.011% in US individuals with AD and 0.018% in cognitively normal con-

trols), so it could not have a substantial role in risk for AD in the US population. The frequency in Swedish controls tested here was somewhat higher (0.42%) and is in line with the frequency in the Icelandic population. The effect size (Fisher exact test 99% CI, 3.97– ∞) is weaker than in the Icelandic population (odds ratio = 5.29), although this observation is suggestive and a larger sample size is needed.

The protective effect of A673T against late-onset AD reported in the Icelandic study⁶ supports the hypothesis that A β not only plays a critical role in early-onset familial AD but also is important for late-onset AD. This hypothesis is also supported by earlier work showing that the APOE ϵ 4 allele not only increases risk for late-onset AD and lowers the age at onset²³ but similarly also modifies AD risk in carriers of PSEN1²⁴ and PSEN2²⁵ mutations. Mutations in PSEN1 and PSEN2 alter the C-terminal cleavage γ -secretase site and thus cause AD by an A β -related mechanism. The fact that APOE genotype influences age at onset of this A β -driven process suggests that late-onset AD and early-onset familial AD share at least 1 common mechanism. The age cutoff distinguishing early- and late-onset disease is also blurred by the observation that PSEN2 mutations occur in early- and late-onset AD cases.^{26,27}

Jonsson et al⁶ reported that in Icelandic individuals, the A673T allele frequencies were 0.13% in AD cases and 0.45% to 0.79% in controls. They also reported frequencies of 0.21%, 0.51%, and 0.42% in Norwegian, Finnish, and Swedish controls, respectively. In our Swedish cohort, we observed 3 con-

trols who were heterozygous for A673T (age at sampling, 72, 55, and 59 years). Two of these controls are too young to definitively conclude they will not develop AD in the future. In fact, 1 control (aged 55 years) has an APOE genotype of ϵ 4/ ϵ 4, suggesting increased risk for late-onset AD. In our US sample, we observed much lower frequencies in cases and controls, and 1 of our 3 carriers was born in Iceland. While our results are inconclusive regarding whether A673T is an AD-protective allele, they do indicate that this allele has little influence on risk in white individuals living in the United States. Our findings and the absence of the A673T allele in a large Chinese sample (n = 8721)²⁸ suggest the APP A673T allele may have an appreciable effect on AD risk only in Scandinavian and Icelandic populations.

Conclusions

We show that the APP A673T allele is extremely rare in US white populations and thus does not play a substantial role in risk of developing AD in this group. Our study of a Swedish cohort showed a higher carrier frequency of APP A673T, and thus this variant appears primarily present in Icelandic and Scandinavian populations. Our results are consistent with this mutation being protective because carriers in our study were mostly controls. However, because of the rarity of this mutation in our populations, we could not independently verify that APP A673T is a protective allele.

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Author Affiliations: Department of Pathology and Laboratory Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia (Wang, Lin, Dombroski, Cantwell, Partch, Valladares, Schellenberg); Department of Biostatistics and Epidemiology, University of Pennsylvania Perelman School of Medicine, Philadelphia (Naj); Department of Human Genetics, Genentech Inc, South San Francisco, California (Graham, Behrens); Department of Medicine, University of Washington, Seattle (Crane, Larson); John P. Hussman Institute for Human Genomics, University of Miami, Miami, Florida (Kunkle, Pericak-Vance); Department of Psychiatry, Washington University School of Medicine, St Louis, Missouri (Cruchaga, Goate); Hope Center Program on Protein Aggregation and Neurodegeneration, Washington University School of Medicine, St Louis, Missouri (Cruchaga, Goate); Department of Biology, Brigham Young University, Provo, Utah (Murcia, Kauwe, Farrer); Division of Genetic Epidemiology, Department of Medicine, University of Utah School of Medicine, Salt Lake City (Cannon-Albright); George E. Wahlen Department of Veterans Affairs Medical Center, Salt Lake City, Utah (Cannon-Albright); Biomedical Genetics, Department of Medicine, Boston University, Boston, Massachusetts (Baldwin); Institute of Neurology, University College London, London, England (Zetterberg); Clinical Neurochemistry Laboratory, Institute of Neuroscience and Physiology, Department of Psychiatry and Neurochemistry, Sahlgrenska

Academy at University of Gothenburg, Sahlgrenska University Hospital, Mölndal, Sweden (Zetterberg, Blennow); Department of Epidemiology, University of Washington, Seattle (Kukull); Department of Medical and Molecular Genetics, Indiana University, Indianapolis (Faber, Foroud); Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, New York (Schupf); Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Columbia University, New York, New York (Schupf, Mayeux); Gertrude H. Sergievsky Center, Columbia University, New York, New York (Schupf, Mayeux); Department of Family, Consumer, and Human Development, Utah State University, Logan (Norton); Department of Psychology, Utah State University, Logan (Norton, Tschanz); Department of Nutrition, Dietetics, and Food Sciences, Utah State University, Logan (Munger); Department of Mathematics and Statistics, Utah State University, Logan (Corcoran); Tanz Centre for Research in Neurodegenerative Disease, University of Toronto, Toronto, Ontario, Canada (Rogaeva, St George-Hyslop); Center for Applied Genomics, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania (Hakonarson); Cambridge Institute for Medical Research, Department of Clinical Neurosciences, University of Cambridge, Cambridge, England (St George-Hyslop); Division of Genetics, Department of Medicine and Partners Center for Personalized Genetic Medicine, Brigham and Women's Hospital/Harvard Medical School, Boston, Massachusetts (Green); Department of Psychiatry and Behavioral Sciences, Miller School of Medicine, University of Miami, Miami, Florida (Carney); Group Health Research Institute, Seattle, Washington (Larson); Center for Human Genetics and Research,

Department of Molecular Physiology and Biophysics, Vanderbilt University, Nashville, Tennessee (Haines); Department of Biostatistics, Boston University, Boston, Massachusetts (Farrer); Department of Ophthalmology, Boston University, Boston, Massachusetts (Farrer); Department of Neurology, Boston University, Boston, Massachusetts (Farrer); Department of Epidemiology, Boston University, Boston, Massachusetts (Farrer); Dr John T. Macdonald Foundation Department of Human Genetics, University of Miami, Miami, Florida (Pericak-Vance); Department of Neurology, Columbia University, New York, New York (Mayeux).

Authors/Members in the Alzheimer's Disease Genetics Consortium: Marilyn S. Albert, PhD; Roger L. Albin, MD; Liana G. Apostolova, MD; Steven E. Arnold, MD; Robert Barber, PhD; M. Michael Barmada, PhD; Lisa L. Barnes, PhD; Thomas G. Beach, MD, PhD; James T. Becker, PhD; Gary W. Beecham, PhD; Duane Beekly, BS; David A. Bennett, MD; Eileen H. Bigio, MD; Thomas D. Bird, MD; Deborah Blacker, MD, ScD; Bradley F. Boeve, MD; James D. Bowen, MD; Adam Boxer, MD, PhD; James R. Burke, MD, PhD; Joseph D. Buxbaum, PhD; Nigel J. Cairns, PhD; Chuanhai Cao, PhD; Chris S. Carlson; Steven L. Carroll, MD, PhD; Helena C. Chui, MD; David G. Clark, MD; David H. Cribbs, PhD; Elizabeth A. Crocco, MD; Charles DeCarli, MD; Steven T. DeKosky, MD; F. Yesim Demirci, MD; Malcolm Dick, PhD; Dennis W. Dickson, MD; Ranjan Duara, MD; Nilufer Ertekin-Taner, MD, PhD; Kenneth B. Fallon, MD; Martin R. Farlow, MD; Steven Ferris, PhD; Matthew P. Frosch, MD, PhD; Douglas R. Galasko, MD; Mary Ganguli, MD, PhD; Marla J. Gearing, PhD; Daniel H. Geschwind, MD, PhD; Bernardino Ghetti, MD; John R. Gilbert, PhD; Jonathan D. Glass, MD;

Neill R. Graff-Radford, MD; John H. Growdon, MD; Ronald L. Hamilton, MD; Kara L. Hamilton-Nelson; Lindy E. Harrell, MD, PhD; Elizabeth Head, PhD; Lawrence S. Honig, MD, PhD; Christine M. Hulette, MD; Bradley T. Hyman, MD, PhD; Gail P. Jarvik, MD, PhD; Gregory A. Jicha, MD, PhD; Lee-Way Jin, MD, PhD; Gyungah Jun, PhD; M. Ilyas Kamboh, PhD; Anna Karydas, BA; Jeffrey A. Kaye, MD; Ronald Kim, MD; Edward H. Koo, MD; Neil W. Kowall, MD; Joel H. Kramer, PhD; Patricia Kramer, PhD; Frank M. LaFerla, PhD; James J. Lah, MD, PhD; James B. Leverenz, MD; Allan I. Levey, MD, PhD; Ge Li, MD, PhD; Andrew P. Lieberman, MD, PhD; Oscar L. Lopez, MD; Kathryn L. Lunetta, PhD; Constantine G. Lyketsos, MD, MHS; Wendy J. Mack, PhD; Daniel C. Marson, JD, PhD; Eden R. Martin, PhD; Frank Martiniuk, PhD; Deborah C. Mash, PhD; Eliezer Masliah, MD; Wayne C. McCormick; Susan M. McCurry, PhD; Andrew N. McDavid, BA; Ann C. McKee, MD; M. Marsel Mesulam, MD; Bruce L. Miller, MD; Carol A. Miller, MD; Joshua W. Miller, MD; Thomas J. Montine, MD, PhD; John C. Morris, MD; Jill R. Murrell, PhD; John M. Olichney, MD; Joseph E. Parisi, MD; William Perry; Elaine Peskind, MD; Ronald C. Petersen, MD, PhD; Aimee Pierce; Wayne W. Poon, PhD; Huntington Potter, PhD; Joseph F. Quinn, MD; Ashok Raj, MD; Murray Raskind, MD; Eric M. Reiman, MD; Barry Reisberg, MD; Christiane Reitz, MD, PhD; John M. Ringman, MD, MS; Erik D. Roberson, MD, PhD; Howard J. Rosen, MD; Roger N. Rosenberg, MD; Mary Sano, PhD; Andrew J. Saykin, PsyD; Julie A. Schneider, MD; Lon S. Schneider, MD; William W. Seeley, MD; Amanda G. Smith; Joshua A. Sonnen, MD; Salvatore Spina, MD; Robert A. Stern, PhD; Rudolph E. Tanzi, PhD; Tricia A. Thornton-Wells, PhD; John Q. Trojanowski, MD, PhD; Juan C. Troncoso, MD; Debby W. Tsuang, MD; Viviana M. Van Deerlin, MD, PhD; Linda J. Van Eldik, PhD; Badri N. Vardarajan, PhD; Harry V. Vinters, MD; Jean Paul Vonsattel, MD; Sandra Weintraub, PhD; Kathleen A. Welsh-Bohmer, PhD; Jennifer Williamson, MS, MPH; Sarah Wishnek; Randall L. Woltjer, MD, PhD; Clinton B. Wright, MD, MS; Steven G. Younkin, MD, PhD; Chang-En Yu, PhD; Lei Yu, PhD.

Affiliations of Authors/Members in the Alzheimer's Disease Genetics Consortium:

Department of Neurology, Johns Hopkins University, Baltimore, Maryland (Albert); Department of Neurology, University of Michigan, Ann Arbor (Albin); Geriatric Research, Education, and Clinical Center, VA Ann Arbor Healthcare System, Ann Arbor, Michigan (Albin); Michigan Alzheimer's Disease Center, Ann Arbor (Albin); Department of Neurology, University of California, Los Angeles (Apostolova, Ringman, Vinters); Department of Psychiatry, University of Pennsylvania Perelman School of Medicine, Philadelphia (Arnold); Department of Pharmacology and Neuroscience, University of North Texas Health Science Center, Fort Worth (Barber); Department of Human Genetics, University of Pittsburgh, Pittsburgh, Pennsylvania (Barmada, Demirci, Kamboh); Department of Neurological Sciences, Rush University Medical Center, Chicago, Illinois (Barnes, Bennett, J. A. Schneider, L. Yu); Department of Behavioral Sciences, Rush University Medical Center, Chicago, Illinois (Barnes); Civin Laboratory for Neuropathology, Banner Sun Health Research Institute, Phoenix, Arizona (Beach); Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania (Becker, Ganguli); Department of Neurology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

(Becker); Department of Psychology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania (Becker); John P. Hussman Institute for Human Genomics, University of Miami, Miami, Florida (Beecham, Gilbert, Hamilton-Nelson, Martin, Perry, Wishnek); Dr John T. Macdonald Foundation Department of Human Genetics, University of Miami, Miami, Florida (Beecham, Gilbert, Martin); National Alzheimer's Coordinating Center, University of Washington, Seattle (Beekly); Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, Illinois (Bennett); Department of Pathology, Northwestern University Feinberg School of Medicine, Chicago, Illinois (Bigio); Cognitive Neurology and Alzheimer's Disease Center, Northwestern University Feinberg School of Medicine, Chicago, Illinois (Bigio, Mesulam, Weintraub); Geriatric Research, Education, and Clinical Center, VA Puget Sound Healthcare System, Seattle, Washington (Bird, Tsuang); Department of Neurology, University of Washington, Seattle (Bird); Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts (Blacker); Department of Psychiatry, Massachusetts General Hospital/Harvard Medical School, Boston (Blacker); Department of Neurology, Mayo Clinic, Rochester, Minnesota (Boeve, Petersen); Swedish Medical Center, Seattle, Washington (Bowen); Department of Neurology, University of California, San Francisco (Boxer, Karydas, B. L. Miller, Rosen, Seeley); Department of Medicine, Duke University, Durham, North Carolina (Burke, Welsh-Bohmer); Department of Neuroscience, Mount Sinai School of Medicine, New York, New York (Buxbaum); Department of Psychiatry, Mount Sinai School of Medicine, New York, New York (Buxbaum, Sano); Department of Genetics and Genomic Sciences, Mount Sinai School of Medicine, New York, New York (Buxbaum); Department of Pathology and Immunology, Washington University, St Louis, Missouri (Cairns, Morris); USF Health Byrd Alzheimer's Institute, University of South Florida, Tampa (Cao, Potter, Raj, Smith); Fred Hutchinson Cancer Research Center, Seattle, Washington (Carlson, McDavid); Department of Pathology, University of Alabama at Birmingham, Birmingham (Carroll, Fallon); Department of Neurology, University of Southern California, Los Angeles (Chui, L. S. Schneider); Department of Neurology, University of Alabama at Birmingham, Birmingham (Clark, Harrell, Marson, Roberson); Department of Neurology, University of California, Irvine (Cribbs, Pierce); Department of Psychiatry and Behavioral Sciences, Miller School of Medicine, University of Miami, Miami, Florida (Crocco); Department of Neurology, University of California, Davis, Sacramento (DeCarli, Olichney); University of Virginia School of Medicine, Charlottesville (DeKosky); now with University of Pittsburgh, Pittsburgh, Pennsylvania (DeKosky); Institute for Memory Impairments and Neurological Disorders, University of California, Irvine (Dick, Poon); Department of Neuroscience, Mayo Clinic, Jacksonville, Florida (Dickson, Ertekin-Taner, Graff-Radford, Younkin); Wien Center for Alzheimer's Disease and Memory Disorders, Mount Sinai Medical Center, Miami Beach, Florida (Duara); Department of Neurology, Mayo Clinic, Jacksonville, Florida (Ertekin-Taner, Graff-Radford); Department of Neurology, Indiana University, Indianapolis (Farlow); Department of Psychiatry, New York University, New York (Ferris, Reisberg); C. S. Kubik Laboratory for Neuropathology, Massachusetts General Hospital, Charlestown (Frosch); Department of Neurosciences,

University of California, San Diego, La Jolla (Galasko, Koo, Masliah); Department of Pathology and Laboratory Medicine, Emory University, Atlanta, Georgia (Gearing); Alzheimer's Disease Research Center, Emory University, Atlanta, Georgia (Gearing); Neurogenetics Program, University of California, Los Angeles (Geschwind); Department of Pathology and Laboratory Medicine, Indiana University, Indianapolis (Ghetti, Murrell, Spina); Department of Neurology, Emory University, Atlanta, Georgia (Glass, Lah, Levey); Department of Neurology, Massachusetts General Hospital/Harvard Medical School, Boston (Growdon, Hyman, Tanzi); Division of Neuropathology, Department of Pathology, University of Pittsburgh, Pittsburgh, Pennsylvania (Hamilton); Department of Molecular and Biomedical Pharmacology, Sanders-Brown Center on Aging, University of Kentucky, Lexington (Head); Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Columbia University, New York, New York (Honig, Reitz, Vardarajan, Vonsattel, Williamson); Department of Neurology, Columbia University, New York, New York (Honig, Reitz, Vardarajan); Department of Pathology, Duke University, Durham, North Carolina (Hulette); Department of Genome Sciences, University of Washington, Seattle (Jarvik); Division of Medical Genetics, Department of Medicine, University of Washington, Seattle (Jarvik); Department of Neurology, Sanders-Brown Center on Aging, University of Kentucky, Lexington (Jicha); Department of Pathology and Laboratory Medicine, University of California, Davis, Sacramento (Jin, J. W. Miller); Genetics Program, Department of Medicine, Boston University, Boston, Massachusetts (Jun); Department of Biostatistics, Boston University, Boston, Massachusetts (Jun, Lunetta); Department of Ophthalmology, Boston University, Boston, Massachusetts (Jun); Alzheimer Disease Research Center, University of Pittsburgh, Pittsburgh, Pennsylvania (Kamboh, Lopez); Department of Neurology, Oregon Health & Science University, Portland (Kaye, P. Kramer, Quinn); Department of Neurology, Portland Veterans Affairs Medical Center, Portland, Oregon (Kaye); Department of Pathology and Laboratory Medicine, University of California, Irvine (Kim); Department of Neurology, Boston University, Boston, Massachusetts (Kowall, McKee, Stern); Department of Pathology, Boston University, Boston, Massachusetts (Kowall, McKee); Department of Neuropsychology, University of California, San Francisco (J. H. Kramer); Department of Molecular and Medical Genetics, Oregon Health & Science University, Portland (P. Kramer); Department of Neurobiology and Behavior, University of California, Irvine (LaFerla); Department of Pathology, University of Washington, Seattle (Leverenz, Montine, Sonnen); Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Seattle (Li, Peskind, Raskind, Tsuang); Department of Pathology, University of Michigan, Ann Arbor (Lieberman); Department of Psychiatry, Johns Hopkins University, Baltimore, Maryland (Lyketsos); Department of Preventive Medicine, University of Southern California, Los Angeles (Mack); Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, New York University, New York (Martiniuk); Department of Neurology, University of Miami, Miami, Florida (Mash); Department of Pathology, University of California, San Diego, La Jolla (Masliah); Department of Medicine, University of Washington, Seattle (McCormick, C.-E. Yu); Northwest Research Group on

Aging, School of Nursing, University of Washington, Seattle (McCurry); Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, Illinois (Mesulam); Department of Pathology, University of Southern California, Los Angeles (C. A. Miller); Department of Neurology, Washington University, St Louis, Missouri (Morris); Department of Medical and Molecular Genetics, Indiana University, Indianapolis (Murrell, Saykin); Department of Anatomic Pathology, Mayo Clinic, Rochester, Minnesota (Paris); Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota (Paris); Neurogenomics Division, Translational Genomics Research Institute, Phoenix, Arizona (Reiman); Arizona Alzheimer's Consortium, Phoenix (Reiman); Banner Alzheimer's Institute, Phoenix, Arizona (Reiman); Alzheimer's Disease Center, New York University, New York (Reisberg); Gertrude H. Sergievsky Center, Columbia University, New York, New York (Reitz, Vardarajan); Department of Neurology, University of Texas Southwestern Medical Center, Dallas (Rosenberg); Department of Radiology and Imaging Sciences, Indiana University, Indianapolis (Saykin); Department of Pathology (Neuropathology), Rush University Medical Center, Chicago, Illinois (J. A. Schneider); Department of Psychiatry, University of Southern California, Los Angeles (L. S. Schneider); Center for Human Genetics and Research, Department of Molecular Physiology and Biophysics, Vanderbilt University, Nashville, Tennessee (Thornton-Wells); Department of Pathology and Laboratory Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia (Trojanowski, Van Deerlin); Department of Pathology, Johns Hopkins University, Baltimore, Maryland (Troncoso); Department of Anatomy and Neurobiology, Sanders-Brown Center on Aging, University of Kentucky, Lexington (Van Eldik); Department of Pathology and Laboratory Medicine, University of California, Los Angeles (Vinters); Department of Pathology, Columbia University, New York, New York (Vonsattel); Department of Psychiatry, Northwestern University Feinberg School of Medicine, Chicago, Illinois (Weintraub); Department of Psychiatry and Behavioral Sciences, Duke University, Durham, North Carolina (Welsh-Bohmer); Department of Pathology, Oregon Health & Science University, Portland (Woltjer); Evelyn F. McKnight Brain Institute, Department of Neurology, Miller School of Medicine, University of Miami, Miami, Florida (Wright).

Author Contributions: Drs Wang and Schellenberg had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Wang, Naj, Cruchaga, Zetterberg, Blennow, Kauwe, Haines, Farrer, Pericak-Vance, Mayeux, Schellenberg.

Acquisition, analysis, or interpretation of data: Wang, Naj, Grahams, Crane, Kunkle, Cruchaga, Gonzalez Murcia, Cannon-Albright, Baldwin, Zetterberg, Blennow, Kukull, Faber, Schupf, Norton, Tschanz, Munger, Corcoran, Rogavaeva, Albert, Albin, Apostolova, Arnold, Barber, Barnada, Barnes, Beach, Becker, Beecham, Beekly, Bennett, Bigio, Bird, Blacker, Boeve, Bowen, Boxer, Burke, Buxbaum, Cairns, Cao, Carlson, Carroll, Chui, Clark, Cribbs, Crocco, DeCarli, DeKosky, Demirci, Dick, Dickson, Duara, Ertekin-Taner, Fallon, Farlow, Ferris, Frosch, Galasko, Ganguli, Gearing, Geschwind, Ghetti, Gilbert, Glass, Graff-Radford, Growdon, Hamilton, Hamilton-Nelson, Harrell, Head, Honig, Hulette, Hyman, Jarvik, Jicha, Jin, Jun, Kamboh, Karydas,

Kaye, Kim, Koo, Kowall, J. H. Kramer, P. Kramer, LaFerla, Lah, Leverenz, Levey, Li, Lieberman, Lopez, Lunetta, Lyketsos, Mack, Marson, Martin, Martiniuk, Mash, Masliah, McCormick, McCurry, McDavid, McKee, Mesulam, B. L. Miller, C. A. Miller, J. W. Miller, Montine, Morris, Murrell, Olchney, Parisi, Perry, Peskind, Petersen, Pierce, Poon, Potter, Quinn, Raj, Raskind, Reiman, Reisberg, Reitz, Ringman, Roberson, Rosen, Rosenberg, Sano, Saykin, J. A. Schneider, L. S. Schneider, Seeley, Smith, Sonnen, Spina, Stern, Tanzi, Thornton-Wells, Trojanowski, Troncoso, Tsuang, Van Deerlin, Van Eldik, Vardarajan, Vinters, Vonsattel, Weintraub, Welsh-Bohmer, Williamson, Wisniewski, Woltjer, Wright, Younkin, C.-E. Yu, L. Yu, Lin, Dombroski, Cantwell, Partch, Valladares, Hakonarson, St George-Hyslop, Green, Goate, Foroud, Carney, Larson, Behrens, Kauwe, Pericak-Vance, Mayeux, Schellenberg.

Drafting of the manuscript: Wang, Naj, Schellenberg. **Critical revision of the manuscript for important intellectual content:** All authors.

Statistical analysis: Wang, Naj, Gonzalez Murcia, Corcoran, Carlson, Ghetti, Hamilton-Nelson, Jun, Van Deerlin, Foroud, Kauwe, Haines, Schellenberg. **Obtained funding:** Munger, Barnes, Bennett, DeKosky, Galasko, Ganguli, Ghetti, Jarvik, Kamboh, Lopez, Mesulam, Montine, Morris, Reiman, Saykin, Hakonarson, St George-Hyslop, Larson, Haines, Farrer, Mayeux, Schellenberg.

Administrative, technical, or material support: Naj, Cruchaga, Zetterberg, Blennow, Norton, Munger, Arnold, Beach, Becker, Beekly, Bennett, Boeve, Cairns, Cao, Chui, Cribbs, DeKosky, Ertekin-Taner, Ferris, Geschwind, Ghetti, Hamilton, Harrell, Hyman, Jarvik, Jin, LaFerla, Lieberman, Mash, McCormick, Parisi, Potter, Rosen, Sano, Trojanowski, Vonsattel, Larson, Behrens, Kauwe, Schellenberg.

Study supervision: Munger, Leverenz, Hakonarson, Pericak-Vance, Mayeux, Schellenberg. **Conflict of Interest Disclosures:** Drs Graham and Behrens are full-time employees of Genentech, Inc. Dr DeKosky is a consultant for AstraZeneca, Eli Lilly and Co, Merck and Co, and Rivermind and is involved in clinical trials with Baxter, Elan, Janssen, Novartis, and Pfizer. Dr Farlow receives research support from Accera, Biogen, Eisai, Eli Lilly and Co, Genentech, MedAvante/AstraZeneca, and Navidea; is the speaker's bureau at Eisai, Pfizer, Forest, Novartis, and Eli Lilly and Co; and is a consultant or advisory board member for Accera, Alltech, Avaniir, Eisai, Med Res, Hilicon, Medavante, Medivation, Merck and Co, Novartis, Pfizer, Prana Biotech, QR Pharma, Roche, Sanofi-Aventis, Schering-Plough, Toyama Pharm, Eli Lilly and Co, and UCB Pharma. Dr Ghetti has consulted for Piramal Imaging. Dr Rosenberg is the *JAMA Neurology* Editor and Dr Honig is the *JAMA Neurology* Web Editor but neither was involved in the review process or the acceptance of the manuscript. Dr Leverenz is a consultant for Boehringer-Ingelheim, Navidea Biopharmaceuticals, and Piramal Healthcare. Dr Petersen is chair for the data monitoring committee for Pfizer and Janssen Alzheimer Immunotherapy and is a consultant for GE Healthcare and Roche. Dr Wright receives royalties from UpToDate for 2 chapters; has done legal consulting for the law firms of Abali, Milne, and Faegre Baker Daniels; is a consultant for Merck and Co; and does stroke adjudication for a National Institutes of Health clinical trial. No other disclosures were reported.

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Group Information: The National Institute on Aging–Late-Onset Alzheimer's Disease (NIA-LOAD) Family Study investigators include the following: Boston University, Boston, Massachusetts: Robert C. Green, MD, MPH, Neil W. Kowall, MD, Lindsay A. Farrer, PhD; Columbia University, New York, New York: Jennifer Williamson, MS, MPH, Vincent Santana, MBA; Duke University, Durham, North Carolina: Donald Schmechel, MD, Perry Gaskell, BS, Kathleen A. Welsh-Bohmer, PhD; Indiana University, Indianapolis: Bernardino Ghetti, MD, Martin R. Farlow, MD, Kelly Horner; Massachusetts General Hospital, Boston: John H. Growdon, MD, Deborah Blacker, MD, ScD, Rudolph E. Tanzi, PhD, Bradley T. Hyman, MD, PhD; Mayo Clinic, Rochester, Minnesota: Bradley F. Boeve, MD, Karen Kuntz, RN, Lindsay Norgaard, BS, Nathan Larson, BS; Mayo Clinic, Jacksonville, Florida: Dana Kistler, BSH, Francine Parfitt, MS, Jenny Haddow, BS; Mount Sinai School of Medicine, New York, New York: Jeremy Silverman, PhD, Michal Schnaider Beeri, PhD, Mary Sano, PhD, Joy Wang, BA, Rachel Lally, BA; Northwestern University, Chicago, Illinois: Nancy Johnson, PhD, M. Marsel Mesulam, MD, Sandra Weintraub, PhD, Eileen H. Bigio, MD; Oregon Health & Science University, Portland: Jeffery A. Kaye, MD, Patricia Kramer, PhD, Jessica Payne-Murphy, BA; Rush University, Chicago, Illinois: David A. Bennett, MD, Holli Jacobs, BA, Jeen-Soo Chang, MD, Danielle Arends, RN; University of Alabama at Birmingham, Birmingham: Lindy E. Harrell, MD, PhD; University of California, Los Angeles: George Bartzokis, MD, Jeffery Cummings, MD, Po H. Lu, PsyD, Usha Toland, MS; University of Kentucky, Lexington: William Markesbery, MD, Charles Smith, MD, Alise Brickhouse, BA; University of Pennsylvania, Philadelphia: Gerard D. Schellenberg, PhD, John Q. Trojanowski, MD, PhD, Viviana M. Van Deerlin, MD, PhD, Elisabeth McCarty Wood, MS; University of

Pittsburgh, Pittsburgh, Pennsylvania: Steven T. DeKosky, MD, Robert Sweet, MD, Elise Weamer, MPH; University of Southern California, Los Angeles: Helena C. Chui, MD, Arousiak Varpetian, MD; University of Texas Southwestern Medical Center, Dallas: Ramon Diaz-Arrastia, MD, PhD, Roger N. Rosenberg, MD, Barbara Davis, MA; University of Washington, Seattle: Thomas D. Bird, MD, Malia Rumbaugh, MS, Murray Raskind, MD; Washington University, St Louis, Missouri: Alison M. Goate, DPhil, John C. Morris, MD, Joanne Norton, MSN, RN, Denise Levitch, RN, Betsy Grant, MSW, PhD, Mary Coats, MSN, RN.

Additional Contributions: Annette Lee, PhD, and Peter K. Gregersen, MD, Feinstein Institute for Medical Research, Manhasset, New York, provided genotyping services. Creighton Phelps, PhD, Stephen Snyder, PhD, and Marilyn Miller, PhD, National Institute on Aging, Bethesda, Maryland, helped in acquiring samples and data and are ex officio members of the Alzheimer's Disease Genetics Consortium. Duke University acknowledges John Ervin, BA, from the Brain Bank and Kathleen Hayden, PhD, in the Clinical Core for their respective efforts in the DNA and data pulls required. These individuals received no compensation from the funders for their contributions. We thank the contributors, including the Alzheimer's Disease Centers who collected samples used in this study, as well as the patients and their families, whose help and participation made this work possible.

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