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Genetic variation in genes underlying diverse dementias may explain a small proportion of cases in the Alzheimer's Disease Sequencing Project

Elizabeth E. Blue, Ph.D.[1,*], **Joshua C. Bis, Ph.D.**[1], **Michael O. Dorschner, Ph.D.**[1], **Debby Tsuang, M.D.**[1,2], **Sandra M. Barral, Ph.D.**[3], **Gary Beecham, Ph.D.**[4], **Jennifer E. Below, Ph.D.**[5], **William S. Bush, Ph.D.**[6], **Mariusz Butkiewicz, Ph.D.**[6], **Carlos Cruchaga, Ph.D.**[7], **Anita DeStefano, Ph.D.**[8], **Lindsay A. Farrer, Ph.D.**[8], **Alison Goate, M.D.**[9], **Jonathan Haines, Ph.D.**[6], **Jim Jaworski, M.P.H.**[4], **Gyungah Jun, Ph.D.**[8], **Brian Kunkle, Ph.D., M.P.H.**[4], **Amanda Kuzma, Ph.D.**[10], **Jenny J. Lee, M.S.**[3], **Kathryn Lunetta, Ph.D.**[8], **Yiyi Ma, Ph.D.**[8], **Eden Martin, Ph.D.**[4], **Adam Naj, Ph.D.**[10], **Andrew Q. Nato Jr., Ph.D.**[1], **Patrick Navas, Ph.D.**[1], **Hiep Nguyen, B.S.**[1], **Christiane Reitz, M.D., Ph.D.**[3], **Dolly Reyes, B.S.**[3], **William Salerno, Ph.D.**[11], **Gerard D. Schellenberg, Ph.D.**[10], **Sudha Seshadri, M.D.**[8], **Harkirat Sohi, B.S.**[1], **Timothy A. Thornton, Ph.D.**[1], **Otto Valladares, M.S.**[10], **Cornelia van Duijn, Ph.D.**[12], **Badri N. Vardarajan, Ph.D.**[3], **Li-San Wang, Ph.D.**[10], **Eric Boerwinkle, Ph.D.**[11,13], **Joseé Dupuis, Ph.D.**[8], **Margaret A. Pericak-Vance, Ph.D.**[4], **Richard Mayeux, M.D.**[3], and **Ellen M. Wijsman, Ph.D.**[1] **on behalf of the Alzheimer's Disease Sequencing Project**

[1]University of Washington

[2]Veterans Administration Puget Sound Health Care

[3]Columbia University

[4]University of Miami

[5]Vanderbilt University Medical Center

[6]Case Western Reserve University

[7]Washington University

[8]Boston University

[9]Mount Sinai School of Medicine

[10]University of Pennsylvania

[11]Baylor College of Medicine

[12]Erasmus Medical University

[13]University of Texas Health Sciences Center at Houston

Abstract

[*]Corresponding author: 1959 NE Pacific St, BOX 357720, Seattle, WA 98195-7720, USA. (tel) 206-685-4666, em27@uw.edu.

Conflicts of Interest

All authors declare no conflicts of interest.

Background/Aims—The Alzheimer's Disease Sequencing Project (ADSP) aims to identify novel genes influencing Alzheimer's Disease (AD). Variants within genes known to cause dementias other than AD have been previously associated with AD risk. We describe evidence of co-segregation and association between variants in dementia genes and clinically-diagnosed AD within the ADSP.

Methods—We summarize the properties of known pathogenic variants within dementia genes, describe the co-segregation of variants annotated as "pathogenic" in ClinVar and new candidates observed in ADSP families, and test for association between rare variants in dementia genes in the ADSP case-control study. Participants were clinically evaluated for AD, and represent European, Caribbean Hispanic, and Dutch-isolate populations.

Results—Pathogenic variants in dementia genes were predominantly rare and conserved coding changes. Pathogenic variants within *ARSA*, *CSF1R*, and *GRN* were observed, and candidate variants in *GRN* and *CHMP2B* nominated in ADSP families. An independent case-control study provided evidence of association between variants in *TREM2*, *APOE*, *ARSA*, *CSF1R*, *PSEN1*, and *MAPT* and risk of AD. Variants in genes which cause dementing disorders may influence the clinical diagnosis of AD in a small proportion of cases within the ADSP.

Keywords

Alzheimer genetics; Alzheimer's disease; frontotemporal dementia; rare variants; candidate genes; ClinVar; pathogenicity; arylsufatase A pseudodeficiency

Introduction

Alzheimer's disease (AD; [MIM:104300]) is genetically heterogeneous, and shares phenotypic characteristics with other dementias. Autosomal dominant early-onset AD is caused by rare variants in *APP*[1], *PSEN1*[2], and *PSEN2*[3,4]. Common variants in dozens of genes are associated with late-onset AD[5–7]. The *APOE* ε4 allele has the strongest and most consistent evidence for association with increased risk of both sporadic and familial AD[6,7], and has been independently associated with cognitive function[8,9] and other dementing disorders[10,11]. Variants within genes causing other dementing disorders have also been associated with AD risk, including *MAPT*[12–14], *PRNP*[15], *GRN*[14], and *TREM2*[16,17]. Patients with variants in these genes can meet the clinical diagnostic criteria for AD, such as observed in *GRN*[18,19] and frontotemporal lobar degeneration (FTLD-TDP; [MIM: 607485])[20–22], *MAPT*[23–26] and frontotemporal dementia (FTD; [MIM: 600274])[23], and *PRNP* and prion diseases[27,28]. It can be challenging to differentiate AD from other causes of dementia using clinical criteria alone[29,30], while even the defining neuropathological features of AD may be observed in patients with other dementias and cognitively-normal controls[15,31]. These shared features suggest shared etiologies across dementing disorders.

It is possible that pathogenic variants in dementia genes may explain the genetic cause of dementia among carriers within the Alzheimer's Disease Sequencing Project (ADSP). Targeted sequencing of the early-onset AD genes, *GRN*, and *MAPT* among persons diagnosed with AD have identified known pathogenic variants in *PSEN1*[32–34],

PSEN2[35], and *GRN* [33], and candidate variants in *APP*[33,34], *PSEN1*[34–36], *PSEN2*[34,36], and both *MAPT* and *GRN*[32–34,36]. When family data is available, these candidate variants rarely explain the cause of AD throughout a given family[33], possibly due to genetic heterogeneity or incomplete penetrance. Alternatively, the candidate variants may represent neutral variation and have no relationship to AD risk.

Known pathogenic variants in dementia genes may provide useful characteristics for filtering candidate variants for AD. For Mendelian traits, it is common to prioritize rare, coding changes[37] predicted to be deleterious by a bioinformatics algorithm, such as the CADD score[38] or a measure of conservation like the GERP score[39,40]. It is not clear that the same selective pressures behind these assumptions hold for complex and late-onset traits like AD[39,41]. It would hasten the discovery of novel AD variants if bioinformatics scores could accurately predict the pathogenicity of such a variant.

We hypothesize that variants within 35 dementia-related genes (Table 1) might be associated with the risk of a clinical diagnosis of AD. We describe variants reported to be pathogenic in dementia genes and define criteria for prioritizing candidate variants. We identify these variants, and candidate variants sharing their characteristics, in families sequenced by the ADSP. Finally, we summarize the evidence of association between AD and variants within dementia genes from the ADSP case-control study. These results suggest that variants within genes causing dementias distinct from AD may yet play a role in clinically-diagnosed AD.

Materials and Methods

Subjects and samples

The Alzheimer Disease Sequencing Project (ADSP)—The ADSP has generated whole genome sequence (WGS) data from members of multiplex AD families and whole exome sequence (WES) data for a large case-control cohort[42]. Briefly, WGS data was collected on 582 individuals from 111 multiplex AD families of European or Caribbean Hispanic ancestry, favoring families with multiple cases across generations and relatively few copies of the *APOE* ε4 allele, as described elsewhere[42]. Among these 582 individuals, 498 were clinically diagnosed with probable or definite AD (~11% neuropathologically-confirmed AD) [42–44]. These genomes represent families with European-American (NC, UM, UP prefixes), Caribbean Hispanic (CU prefix), and Dutch (ERF prefix) ancestry. These families were ascertained from multiple sites, including contributors to the Alzheimer Disease Genetics Consortium (ADGC), and the neurology working group of the Cohorts for Heart and Aging Research in Genomic Epidemiology consortium (CHARGE). The WES case-control study prioritized individuals with European ancestry by their low estimated risk of AD, and neuropathologically-confirmed controls when available[42]. A balanced number of 5,107 cases (~38% neuropathologically-confirmed AD) and 4,976 controls were selected for WES. These data are available through the database of Genotypes and Phenotypes (dbGaP; Study Accession: phs000572.v7.p4). All subjects have provided informed consent, and this study was approved by the institutional review boards of participating institutions.

ADSP sequence data was generated at Baylor University, the Broad Institute, and Washington University. Sequencing, variant calling, and quality control (QC) methods are

detailed elsewhere [45]. Read data were aligned to the GRCh37-Lite reference genome using the Burrows Wheeler Aligner (BWA, v0.6.2[46]).Variants were called using both the Genome Analysis Tool Kit (GATK)-HaplotypeCaller[47–49] and Atlas V2[50] pipelines. The QC pipeline was built upon the CHARGE consortium's QC protocol[51]. Discrepancies between the GATK and Atlas V2 calls were reconciled by the ADSP QC Working Group to create the "consensus" data set. This QC protocol involved the development of scripts in the Python, Perl, and R (v2.15 and v3.1.1) languages, as well as the software programs PLINK (v1.07 and v1.9[52]) and PedCheck(v1.2[53]). *APOE* genotypes were provided by the contributing centers; the necessary genotypes did not pass QC in the WGS data set.

Single nucleotide variants (SNVs) within the canonical transcripts of the dementia genes were extracted from the consensus-called WGS data dated May 18, 2015 (Table 1)[45]. The ADSP Annotation Working group provided consistent annotation of all variants (WGS v1 annotation files [54]). The genomic context and consequence of variants was provided by the Ensembl Variant Effect Predictor tool (VEP v80[55,56]) and SeattleSeq Annotation 138 (http://snp.gs.washington.edu/SeattleSeqAnnotation138/), including allele frequencies from the Exome Sequencing Project (ESP[57]), 1000 genomes[58], and the Exome Aggregation Consortium (ExAC[59]). Variant-specific metrics of predicted pathogenicity or severity included SIFT[60], PolyPhen2[61], GERP[62], and CADD[38] scores.

Variant inclusion criteria, analysis parameters, and association test results from the ADSP WES data set is described elsewhere [63]. Subject-level QC identified unrelated samples with minimal missing genotype data and either European or Caribbean Hispanic ancestry (5,740 cases, 5,096 controls). SNVs and insertions/deletions were extracted from the Atlas V2 genotype call set, and included in association testing if they passed QC, were predicted to cause a moderate (ex., missense) or high (ex., stop-gain) impact consequence, and were rare (minor allele frequency, MAF<5%).

Center for Precision Diagnostics sample—The Center for Precision Diagnostics (CPD) at the University of Washington provided targeted sequence data for 48 neuropathologically-confirmed controls with self-reported European ancestry (50% female). The 48 controls represent cognitively-normal elderly adults enrolled in Alzheimer's Disease Centers who did not meet neuropathological criteria for AD or Parkinson's disease upon their death at age ≥ 54 years[64]. The CPD used a targeted capture approach to sequence a panel of genes known to cause neurodegenerative disorders, including the dementia panel listed in Table 1, with >99% of targeted coding regions and canonical splice sites sequenced to >20X coverage. Current information about this panel and sequencing methods are available online (http://uwcpdx.org/neurodegenerative-panel/). DNA fragments were captured using the Exome v1.0 (Integrated DNA Technologies) system, paired-end sequencing was performed using Illumina technologies, including the rapid run v2.0 chemistry and a HiSeq 2500 sequencer. Reads were aligned to the hg19 reference genome using BWA and variant calling was performed by GATK. This research was approved by the Veterans Affairs Puget Sound institutional review board (MIRB #00088).

Analysis Methods

We focus analysis on the 35 genes listed in Table 1, which represented the dementia gene panel provided by the CPD, a CLIA-certified lab for diagnostic genetic testing. Variants within these genes were downloaded from ClinVar (12/22/2015), and converted from build GRCh38 sequence positions to GRCh37 using the LiftOver tool from the UCSC Genome Browser[65,66]. We restricted analyses to "consequential" variants: those annotated as pathogenic, likely pathogenic, risk variant, or protective in ClinVar, and use their reported consequences (ex., missense). Consequential variants observed in the ADSP were evaluated by literature review on a variant-by-variant basis, including the AD & FTD Mutation Database[67] (www.molgen.ua.ac.be/admutations/), Online Mendelian Inheritance in Man[68,69] (OMIM; https://omim.org/) and AlzForum[70] (alzforum.org/mutations) databases. SNVs within the dementia genes were extracted from the 1000 genomes phase 3 data (release v1.3, cadd.gs.washington.edu) and the CPD controls using VCFtools (v0.1.14[71]). SNVs within dementia genes extracted from ClinVar, 1000 genomes, and CPD data were annotated with VEP (v84), ANNOVAR[72], and GEMINI (v0.18.0[73]). Annotation included allele frequencies in the ESP, 1000 genomes, and ExAC, and PolyPhen2 (HDIV), SIFT, GERP (++RS), and CADD (phred scaled) scores[74]. Variants with PolyPhen2 scores ≥ 0.957, SIFT scores < 0.05, or CADD scores (phred scaled) ≥15 were predicted to be deleterious/pathogenic, while GERP scores ≥3 were considered conserved[75,76].

Gene-based tests were performed using SKAT-O[77] separately for the European-ancestry and Caribbean Hispanic subjects, then meta-analyzed using skatOMeta[78,79] . Only the results of the meta-analyses under models 0 (covariates include sequencing center and population-specific principal components) and 2 (covariates include model0 plus age, sex, principal components, and dosage of *APOE* ε2 and ε4 alleles) are presented herein[63]. Results from an intermediate model, model 1, were excluded for simplicity. Summary statistics were generated in R (v 3.2.5).

Results

Characteristics of known consequential SNVs in dementia genes

Consequential SNVs in dementia genes reported in ClinVar were overwhelmingly rare missense variants with evidence of conservation and predicted pathogenicity. Although start/stop and splice site variants were represented (Figure 1), all reported consequential SNVs in nine dementia genes were missense: *EIF2B3*, *EIF2B5*, *MAPT*, *PDGFB*, *PDGFRB*, *PSEN1*, *PSEN2*, *SLC25A12*, and *VCP*. In contrast, most of the consequential SNVs in *GRN* were either start/stop or splice site variants. Most consequential SNVs reported in ClinVar were rare, with 492/496 = 99.2% of SNVs with MAF <0.001 in independent reference populations. Among the 64 consequential SNVs observed in reference data sets, 60 had MAF < 0.001. Three of the remaining four SNVs were in *APOE*: rs7412 and rs429358 define the ε2 and ε4 alleles provided by the ADSP contributors and associated with protection or risk of AD[80], while rs769455 had MAF < 1% in reference populations and was observed four times as often in European-American AD cases vs. controls[80].

Homozygotes for the remaining variant, rs5848, (MAF = 0.42 in the 1000 genomes) have increased risk of both FTD[81] and AD[82].

Most consequential SNVs reported to ClinVar within the dementia genes were predicted to be pathogenic or conserved, unlike the SNVs observed in reference or control data sets (Figure 2). Where annotation was available, the observed distribution of CADD and GERP scores better discriminate between the consequential ClinVar variants and the reference data sets (Figure 2). Most consequential SNVs had high GERP or CADD scores: 91% of consequential SNVs had GERP scores ≥3, and 84% had CADD scores (phred scaled) ≥15.

ClinVar pathogenic SNVs observed in the ADSP family WGS data

Within the ADSP family WGS data, seven SNVs within six dementia genes were annotated as pathogenic in ClinVar (Table 2). Four of the SNVs cause recessive disorders but were only observed in heterozygotes (rs28940893, rs80358257, rs113994049, rs147313927) and are therefore unlikely to cause their corresponding dementias in these heterozygotes. The remaining three SNVs in *GRN*, *CSF1R*, and *ARSA* could potentially influence the dementia phenotype in their carriers.

Dominant variants in *GRN* cause FTD (Table 1). However, the homozygous alternate genotype at *GRN* variant rs5848 is associated with both increased risk of FTD (OR = 3.18[81]) and AD (OR = 1.31[82] and 1.386[83]). Within the ADSP WGS data, 65 homozygotes (45 cases) were observed within 35 families. These cases met clinical criteria for either probable or definite AD, and are therefore not likely to have FTD, although comprehensive imaging data for these subjects are not available to formally exclude FTD pathology.

Dominant variants in *CSF1R* cause hereditary diffuse leukoencephalopathy with spheroids (HDLS; [MIM:221820]), a dementia which can mimic AD[84] (Table 1). A pathogenic[84,85] SNV in *CSF1R*, rs281860278, was observed in a member of family UM0304F diagnosed with probable AD at age 72 years. However, rs281860278 does not segregate with dementia in this family; this SNV was not observed in the carrier's sequenced relatives, including a sibling diagnosed with definite AD at age 73 years, a sibling diagnosed with probable AD at age 75 years, and a niece at-risk of AD at age 55 years. External sequence data revealed the SNV was observed in two additional siblings who were not clinically diagnosed with AD at the time of their deaths at ages 91 and 94 years.

Homozygous genotypes for each of two SNVs, rs6151429 (Table 2) and *ARSA* missense variant rs2071421[86], lead to arylsufatase A pseudodeficiency[86–89], which can cause metachromatic leukodystrophy ([MIM:250100]) if inherited with another *ARSA* missense variant[90,91]. Homozygotes for both rs6151429 and rs2071421 were observed in three ADSP families, although none carried an additional *ARSA* missense variant: CU0044F, CU0049F, and NC0205F. WGS data were available for 11 individuals diagnosed with probable AD and one individual at-risk of AD within family CU0044F. Within family CU0044F, two siblings diagnosed with probable AD at ages 71 and 86 years were homozygous for both rs6151429 and rs2071421. These two siblings are the offspring of a consanguineous marriage between avuncular relatives, suggesting they inherited both copies

of the *ARSA* SNVs identical-by-descent. External sequence data revealed that 0/3 additional at-risk members of CU0044F were homozygous for rs6151429 and rs2071421, WGS data were available for 6 individuals diagnosed with probable AD and one at-risk individual in family CU0049F. The only individual homozygous for both rs6151429 and rs2071421 from family CU0049F was the individual at-risk of developing AD at age 60 years. This at-risk individual is the offspring of parents who were diagnosed with probable AD, with no sequence data available. Within family NC0205F, WGS data were available for one individual diagnosed with definite AD, one diagnosed with probable AD, one diagnosed with possible AD, and one individual with unknown phenotype. The two homozygotes observed in family NC0205F included a subject diagnosed with definite AD at age 75 years and their sibling diagnosed with possible AD at age 80 years, but not their cousins at-risk of AD or diagnosed with possible AD at age 70 years. Most homozygotes for the two *ARSA* SNVs were clinically diagnosed with AD, but do not represent all relatives diagnosed with AD within their families. External autopsy and imaging data were unavailable for any individual homozygous for both rs6151429 and rs2071421.

Rare SNVs observed in the ADSP family WGS data that share properties with consequential ClinVar SNVs

Two SNVs in the ADSP WGS family data share characteristics with known pathogenic variants in the dementia genes: reference MAF < 0.001, CADD (phred scaled) ≥15, and GERP ≥ 3 (Table 2). The *GRN* missense SNV, rs141111290, has previously been associated with AD[34] and is observed in ADSP families CU0012F and CU0042F. Within CU0012F, rs141111290 carriers include a subject diagnosed with probable AD at age 73 years and their sibling diagnosed with possible AD at age 58 years, but not their siblings diagnosed with probable AD at ages 61 and 63 years. Within family CU0042F, the rs141111290 heterozygote was at-risk of AD as of age 69 years, but the SNV is not observed in their sequenced relatives diagnosed with either probable (age 86 and 91 years) or possible (age 73 years) AD. In contrast, the *CHMP2B* SNV rs149380040 was observed in both sequenced cases from family CU0021F, diagnosed with probable AD at ages 77 and 83 years. This SNV causes a p.Ser194Leu change in the canonical transcript of *CHMP2B* and falls outside the conserved snf7 domain containing variants thought to cause FTD[92]. Although other variants in *CHMP2B* cause FTD, the ADSP cases carrying the p.Ser194Leu variant met the clinical criteria for probable AD, and did not show clinical evidence of FTD.

Gene-based association testing in the ADSP case-control exome data

Gene-based tests of rare variants revealed evidence of association between six dementia genes and risk of AD in the ADSP case-control analysis ($p<0.05$, Table 3): *APOE*, *ARSA*, *CSF1R*, *MAPT*, *PSEN1*, and *TREM2*. *TREM2* was significantly associated with AD under model 0 after controlling for the number of dementia genes tested ($p = 1.82E-11$). For each of these genes, the frequency of carrying at least one rare variant allele with a predicted moderate or high impact was low (Table 3), suggesting that rare variants in these genes may play a small but important role in the risk of clinically-diagnosed AD.

Discussion

We provided evidence that SNVs within AD genes (*APOE*[93], *PSEN1*[2,94], *TREM2*[16,17,95]), genes causing dementias which may mimic AD (*MAPT*[12–14,23–25], *CSF1R*[96–99]), and genes causing distinct dementias (*ARSA*) possibly influence the phenotype for a small number of cases of AD in the ADSP. Detailed phenotype and pathologic data are necessary to determine what role, if any, these SNVs play in AD, which is unavailable for most carriers of these SNVs in the ADSP data set. However, a few of these SNVs have strong evidence in the literature supporting their pathogenic role in dementia, including rs5848 in *GRN*[82,83] and rs141111290 in *CHMP2B*[34] which have previously demonstrated strong statistical associations with risk of AD.

Among the genes causing non-AD dementias, pathogenic SNVs in both *ARSA* and *CSF1R* were observed in the family-based ADSP WGS data set and gene-based association testing in the large case-control cohort. *CSF1R* is differentially expressed in mouse models of AD[100,101] and surrounding Aβ plaques in human cases of AD[102]. Inhibiting *CSF1R* in mouse models of AD ameliorates memory loss and synaptic degeneration[103]. That inhibition can be done pharmacologically[103], suggesting *CSF1R* may be a promising drug candidate for AD. The connection between *ARSA* and AD is more tenuous. *ARSA* is down-regulated in sex-specific analyses of cells derived from sporadic AD patients[104]. Furthermore, the pathogenic SNV observed in the ADSP WGS data set, rs6151429, was observed in 34% of postmortem brain samples from AD cases, much higher than the frequency in related populations[105]. These findings are intriguing, though the potential relationship between *ARSA* and AD requires further study before conclusions could be drawn.

Descriptive analyses of consequential SNVs in ClinVar have revealed several patterns which may help identify novel variants driving dementing disorders in these genes. Our results suggest that coding changes in dementia genes with low (MAF<0.001) frequencies in reference populations and high CADD and/or GERP scores should be prioritized when nominating candidate variants for these disorders. Strict application of these filters to the ADSP WGS data prioritized an additional missense variant in *GRN* previously associated with AD risk[34] and a missense variant in *CHMP2B* observed in both sequenced cases diagnosed with probable AD in a single pedigree. Further analysis of each of these SNVs is required to evaluate their potential contribution to AD risk.

Variants in known dementia genes do not appear to explain the AD phenotype in the majority of the ADSP. However, rare pathogenic SNVs, or those sharing similar properties, may influence the phenotype in 1% of subjects within the ADSP family WGS data set diagnosed with either definite or probable AD; this percentage increases to 11% when the common *GRN* risk variant is included. Where observed, SNVs annotated as “pathogenic” by ClinVar in known dementia genes would explain no more than half the AD cases in a single family, consistent with the known genetic heterogeneity of AD[5,94]. This suggests that novel AD genes remain to be uncovered in the ADSP sequence data set.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Jun, PhD; M. Ilyas Kamboh, PhD; Anna Karydas, BA; Jeffrey A. Kaye, MD; C. Dirk Keene, MD PhD; Aisha Khaleeq, MD; Ronald Kim, MD; Janice Knebl, DO; David Knopman, MD; Olena Korvatska, PhD; Peter J. Koudstaal, MD PhD; Neil W Kowall, MD; Joel H. Kramer, PsyD; Walter A. Kukull, PhD; Lewis H. Kuller, MD; Brian W. Kunkle, PhD MPH; Alexander Kurz, MD; Laura J. Lacritz, PhD; Frank M. LaFerla, PhD; James J. Lah, MD PhD; Rafael Lantigua, MD; Eric B. Larson, MD MPH; W. William Lee, PhD; Allan I. Levey, MD PhD; Ge Li, MD PhD; Andrew P. Lieberman, MD PhD; Ricahrd B. Lipton, MD; Mark Logue, PhD; Oscar L. Lopez, MD; Kathryn L. Lunetta, PhD; Constantine G. Lyketsos, MD MHS; Douglas Mains, DrPH; Jennifer Manly, PhD; Daniel C. Marson, JD PhD; Eden R. Martin, PhD; Paul Massman, PhD; Richard Mayeux, MD; Wayne C. McCormick, MD MPH; Susan M. McCurry, PhD; Ann C. McKee, MD; Martin Medrano, MD; Marsel Mesulam, MD; Bruce L. Miller, MD; Carol A. Miller, MD; Abhay Moghekar, MBBS; John C. Morris, MD; Thomas H. Mosley, PhD; Shubhabrata Mukherjee, PhD; Trung Nguyen, MD/PhD; Sid O?Bryant, PhD; Thomas Obisesan, MD; John M. Olichney, MD; Marcia Ory, PhD/MPH; Ruth Ottman, PhD; Raymond Palmer, PhD; Joseph E. Parisi, MD; Henry L. Paulson, MD PhD; Valory Pavlik, PhD; David Paydarfar, MD; Victoria Perez, CRC; Margaret A. Pericak-Vance, MD PhD; Elaine Peskind, MD; Ronald C. Petersen, MD PhD; Helen Petrovitch, MD; Aimee Pierce, MD; Marsha Polk, MMEd; Wayne W. Poon, PhD; Luigi Puglielli, MD PhD; Mary Quiceno, MD; Joseph F. Quinn, MD; Ashok Raj, MD; Farid Rajabli, PhD; Gerhard Ransmayr, MD; Murray Raskind, MD; Wendy Raskind, MD PhD; Eric M. Reiman, MD; Barry Reisberg, MD; Joan S. Reisch, PhD; Christiane Reitz, MD; Dolly Reyes-Dumeyer, BS; KatieRose Richmire, BA; Robert A. Rissman, PhD; Fernando Rivadeneira, MD PhD; Erik D. Roberson, MD PhD; Monica Rodriguear, MA; Ekaterina Rogaeva, PhD; Howard J. Rosen, MD; Roger N. Rosenberg, MD; Jerome I. Rotter, MD FACP FACMG; Donald R. Royall, MD; Yasaman Saba, BSc; Marwan Sabbagh, MD; A. Dessa Sadovnick, PhD; Martin Sadowski, MD PhD; Mark A. Sager, MD; David P. Salmon, PhD; Mary Sano, PhD; Andrew J. Saykin, PsyD; Daniel Schaid, MD; Gerard D. Schellenberg PhD, PhD; Michael Schmidt, PhD; Julie A. Schneider, MD; Lon S. Schneider, MD; Nicole Schupf, PhD; Bill Scott, PhD; William W. Seeley, MD; Scott Small, MD; Amanda G. Smith, MD; Janet Smith, BS; Robert A. Stern, PhD; Yaakov Stern, PhD; Alan Stevens, PhD; Robert A Sweet, MD; Russell H. Swerdlow, MD; Rudolph E. Tanzi, PhD; Linda Teri, PhD; Jeffrey L. Tilson, PhD; Sarah E Tomaszewski Farias, PhD; Giuseppe Tosto, MD; John Q. Trojanowski, MD PhD; Juan C. Troncoso, MD; Magda Tsolaki, MD PhD; Debby W. Tsuang, MD; Andre G. Uitterlinden, PhD; Vivianna M. Van Deerlin, MD PhD; Linda J. Van Eldik, PhD; Jeffery M. Vance, MD PhD; Badri Vardarajan, PhD; Harry V. Vinters, MD; Dina Voijnovic, MD MS; Jean Paul Vonsattel, MD; Jen Chyong Wang, PhD; Sandra Weintraub, PhD; Kathleen A. Welsh-Bohmer, PhD; Shawn Westaway, PhD; Charles C. White,

PhD; April Wiechmann, PhD; Kirk C. Wilhelmsen, MD/PhD; Benjamin Williams, MD/PhD; Henrick Wilms, MD/PhD; B. Gwen Windham, MD MHS; Thomas S. Wingo, MD; Thomas Wisniewski, MD; David A. Wolk, PhD; Frank J Wolters, MD MSc; Randall L. Woltjer, MD PhD; Martin Woon, PhD; Steven G. Younkin, MD PhD; Chang-En Yu, PhD; Lei Yu, PhD.

Members of the Alzheimer's Disease Sequencing Project (ADSP) include: Shahzad Amad, PhD MSc; Najaf Amin, PhD; Lucinda Antonacci-Fulton, MS; Elizabeth Appelbaum, BA; Eric Banks, PhD; Sandra Barral, PhD; Gary Beecham, PhD; Alexa Beiser, PhD; Michelle Bellair, MS; Jennifer E. Below, PhD; David A Bennett, MD ; Joshua C. Bis, PhD; Elizabeth Blue, PhD; Eric Boerwinkle, PhD; Jan Bressler, PhD; Lisa Brown, PhD; Will Bush, PhD; Mariusz Butkiewicz, PhD; Laura Cantwell, MPH; Yuning Chen, MS; Micah Childress, AS; Seung Hoan Choi, PhD; Yi Fan Chou, MS; Jaeyoon Chung, MS; Carlos Cruchaga, PhD; Adrienne Cupples, PhD; Rebecca Cweibel, MA; Tyler Day, MS; Phillip L De Jager, MD PhD; Anita DeStefano, PhD; Huyen Dinh, BS; Harsha Doddapeneni, PhD; Michael Dorschner, PhD; Shannon Dugan-Perez, BA; Josee Dupuis, PhD; Adam English, PhD; Kelley Faber, MS; John Farrell, PhD; Lindsay Farrer, PhD; Michael Feolo, PhD; Myriam Fornage, PhD; Tatiana Foroud, PhD; Robert S. Fulton, PhD; Stacey Gabriel, PhD; Prabhakaran Gangadharan, MS; Richard A. Gibbs, PhD; Alison Goate, DPhil ; Namrata Gupta, PhD; Jonathan Haines, PhD; Kara Hamilton-Nelson, MPH; Yi Han, PhD; Andrea R Horimoto, MSc PhD; Jianhong Hu, PhD; M Afran Ikram, MD PhD; James Jaworski, MPH; Joy Jayaseelan, ; Xueqiu Jian, PhD; Divya Kalra, MS; Manav Kapoor, PhD; Ziad Khan, ; Daniel C. Koboldt, MS; Viktoriya Korchina, BS; Brian Kunkle, PhD MPH; Amanda Kuzma, PhD; Dan Lancour, BS; David E. Larson, PhD; Lenore J. Launer, PhD; Sandra Lee, PhD MSN; Yuk Yee Leung, PhD; Han-Jen Lin, MS; Honghuang Lin, PhD; Ching Ti Liu, PhD; Xiaoming Liu, PhD; Xiuping Liu, ; Yue Liu, ; Kathy Lunetta, PhD; Yiyi Ma, PhD; John Malamon, BSE; Edoardo Marcora, PhD; Eden Martin, PhD; Richard Mayeux, MD; Elisabeth Mlynarski, PhD; Thomas H. Mosley, PhD; Donna Muzny, MS; Rafael Nafikov, PhD; Adam Naj, PhD; Waleed Nasser, PhD; Alejandro Q Nato Jr., PhD; Pat Navas, PhD; Hiep Nguyen, BS; Devanshi Patel, MS; Margaret Pericak-Vance, PhD; Bruce Psaty, MD MPH PhD; Liming Qu, MS; Farid Rajabli, PhD; Christiane Reitz, MD PhD; Alan Renton, PhD; Dolly Reyes, BS; Kenneth Rice, PhD; Mohamad Saad, PhD; William Salerno, PhD; Jireh Santibanez, BS; Chloe Sarnowski, PhD; Claudia Satizabal, PhD; Gerard Schellenberg, PhD; Helena Schmidt, PhD; Michael Schmidt, PhD; Reinhold Schmidt, MD; Sudha Seshadri, MD; Evette Skinner, ; Sandra Smieszek, PhD; Harkirat Sohi, BS; Yeunjoo Song, PhD; Adam Stine, MS; Fangui Jenny Sun, PhD; Timothy Thornton, PhD; Giuseppe Tosto, MD PhD; Debby Tsuang, MD; Otto Valladares, MS; Sven van der Lee, MD; Cornelia van Duijn, PhD; Ashley Vanderspek, MSc PhD; Badri Vardarajan, PhD; Jason Waligorski, BS; Bowen Wang, MS; Weixin Wang, PhD; Li-San Wang, PhD; Simon White, MSc; Ellen Wijsman, PhD; Richard K. Wilson, PhD; Daniela Witten, PhD; Kim Worley, PhD; Li Charlie Xia, PhD; Nancy Zhang, PhD; Xiaoling Zhang, MD PhD; Yi Zhao, MS; Yiming Zhu, MS.

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References

1. Goate A, Chartier-Harlin MC, Mullan M, Brown J, Crawford F, Fidani L, Giuffra L, Haynes A, Irving N, James L, et al. Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. Nature. 1991; 349:704–706. [PubMed: 1671712]
2. Sherrington R, Rogaev EI, Liang Y, Rogaeva EA, Levesque G, Ikeda M, Chi H, Lin C, Li G, Holman K, Tsuda T, Mar L, Foncin JF, Bruni AC, Montesi MP, Sorbi S, Rainero I, Pinessi L, Nee L, Chumakov I, Pollen D, Brookes A, Sanseau P, Polinsky RJ, Wasco W, Da Silva HA, Haines JL, Perkicak-Vance MA, Tanzi RE, Roses AD, Fraser PE, Rommens JM, St George-Hyslop PH. Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. Nature. 1995; 375:754–760. [PubMed: 7596406]
3. Levy-Lahad E, Wijsman EM, Nemens E, Anderson L, Goddard KA, Weber JL, Bird TD, Schellenberg GD. A familial Alzheimer's disease locus on chromosome 1. Science. 1995; 269:970–973. [PubMed: 7638621]
4. Levy-Lahad E, Wasco W, Poorkaj P, Romano DM, Oshima J, Pettingell WH, Yu CE, Jondro PD, Schmidt SD, Wang K, et al. Candidate gene for the chromosome 1 familial Alzheimer's disease locus. Science. 1995; 269:973–977. [PubMed: 7638622]
5. Lambert JC, Ibrahim-Verbaas CA, Harold D, Naj AC, Sims R, Bellenguez C, DeStafano AL, Bis JC, Beecham GW, Grenier-Boley B, Russo G, Thorton-Wells TA, Jones N, Smith AV, Chouraki V, Thomas C, Ikram MA, Zelenika D, Vardarajan BN, Kamatani Y, Lin CF, Gerrish A, Schmidt H, Kunkle B, Dunstan ML, Ruiz A, Bihoreau MT, Choi SH, Reitz C, Pasquier F, Cruchaga C, Craig D, Amin N, Berr C, Lopez OL, De Jager PL, Deramecourt V, Johnston JA, Evans D, Lovestone S, Letenneur L, Moron FJ, Rubinsztein DC, Eiriksdottir G, Sleegers K, Goate AM, Fievet N, Huentelman MW, Gill M, Brown K, Kamboh MI, Keller L, Barberger-Gateau P, McGuiness B, Larson EB, Green R, Myers AJ, Dufouil C, Todd S, Wallon D, Love S, Rogaeva E, Gallacher J, St George-Hyslop P, Clarimon J, Lleo A, Bayer A, Tsuang DW, Yu L, Tsolaki M, Bossu P, Spalletta G, Proitsi P, Collinge J, Sorbi S, Sanchez-Garcia F, Fox NC, Hardy J, Deniz Naranjo MC, Bosco P, Clarke R, Brayne C, Galimberti D, Mancuso M, Matthews F, European Alzheimer's Disease I, Genetic, Environmental Risk in Alzheimer's D, Alzheimer's isease Genetic C, Cohorts for H Aging Research in Genomic E. Moebus S, Mecocci P, Del Zompo M, Maier W, Hampel H, Pilotto A,

Bullido M, Panza F, Caffarra P, Nacmias B, Gilbert JR, Mayhaus M, Lannefelt L, Hakonarson H, Pichler S, Carrasquillo MM, Ingelsson M, Beekly D, Alvarez V, Zou F, Valladares O, Younkin SG, Coto E, Hamilton-Nelson KL, Gu W, Razquin C, Pastor P, Mateo I, Owen MJ, Faber KM, Jonsson PV, Combarros O, O'Donovan MC, Cantwell LB, Soininen H, Blacker D, Mead S, Mosley TH Jr, Bennett DA, Harris TB, Fratiglioni L, Holmes C, de Bruijn RF, Passmore P, Montine TJ, Bettens K, Rotter JI, Brice A, Morgan K, Foroud TM, Kukull WA, Hannequin D, Powell JF, Nalls MA, Ritchie K, Lunetta KL, Kauwe JS, Boerwinkle E, Riemenschneider M, Boada M, Hiltuenen M, Martin ER, Schmidt R, Rujescu D, Wang LS, Dartigues JF, Mayeux R, Tzourio C, Hofman A, Nothen MM, Graff C, Psaty BM, Jones L, Haines JL, Holmans PA, Lathrop M, Pericak-Vance MA, Launer LJ, Farrer LA, van Duijn CM, Van Broeckhoven C, Moskvina V, Seshadri S, Williams J, Schellenberg GD, Amouyel P. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. Nat Genet. 2013; 45:1452–1458. [PubMed: 24162737]

6. Naj AC, Schellenberg GD. Genomic variants, genes, and pathways of Alzheimer's Disease Genetics C: Genomic variants, genes, and pathways of Alzheimer's disease: An overview. Am J Med Genet B Neuropsychiatr Genet. 2017; 174:5–26. [PubMed: 27943641]
7. Lane CA, Hardy J, Schott JM. Alzheimer's disease. Eur J Neurol. 2017
8. Bojar I, Stasiak M, Cyniak-Magierska A, Raczkiewicz D, Lewinski A. Cognitive Function, APOE Gene Polymorphisms, and Thyroid Status Associations in Postmenopausal Women in Poland. Dement Geriatr Cogn Disord. 2016; 42:169–185. [PubMed: 27649316]
9. Perna L, Mons U, Rujescu D, Kliegel M, Brenner H. Apolipoprotein E e4 and Cognitive Function: A Modifiable Association Results from Two Independent Cohort Studies. Dement Geriatr Cogn Disord. 2016; 41:35–45. [PubMed: 26495840]
10. Ji Y, Liu M, Huo YR, Liu S, Shi Z, Liu S, Wisniewski T, Wang J. Apolipoprotein Epsilon epsilon4 frequency is increased among Chinese patients with frontotemporal dementia and Alzheimer's disease. Dement Geriatr Cogn Disord. 2013; 36:163–170. [PubMed: 23887281]
11. Liu B, Shen Y, Cen L, Tang Y. Apolipoprotein E gene polymorphism in a Chinese population with vascular dementia: a meta-analysis. Dement Geriatr Cogn Disord. 2012; 33:96–103. [PubMed: 22433749]
12. Allen M, Kachadoorian M, Quicksall Z, Zou F, Chai HS, Younkin C, Crook JE, Pankratz VS, Carrasquillo MM, Krishnan S, Nguyen T, Ma L, Malphrus K, Lincoln S, Bisceglio G, Kolbert CP, Jen J, Mukherjee S, Kauwe JK, Crane PK, Haines JL, Mayeux R, Pericak-Vance MA, Farrer LA, Schellenberg GD, Parisi JE, Petersen RC, Graff-Radford NR, Dickson DW, Younkin SG, Ertekin-Taner N. Association of MAPT haplotypes with Alzheimer's disease risk and MAPT brain gene expression levels. Alzheimers Res Ther. 2014; 6:39. [PubMed: 25324900]
13. Bullido MJ, Aldudo J, Frank A, Coria F, Avila J, Valdivieso F. A polymorphism in the tau gene associated with risk for Alzheimer's disease. Neurosci Lett. 2000; 278:49–52. [PubMed: 10643798]
14. Wojtas A, Heggeli KA, Finch N, Baker M, Dejesus-Hernandez M, Younkin SG, Dickson DW, Graff-Radford NR, Rademakers R. C9ORF72 repeat expansions and other FTD gene mutations in a clinical AD patient series from Mayo Clinic. Am J Neurodegener Dis. 2012; 1:107–118. [PubMed: 23383383]
15. Mann DM, Jones D. Deposition of amyloid (A4) protein within the brains of persons with dementing disorders other than Alzheimer's disease and Down's syndrome. Neurosci Lett. 1990; 109:68–75. [PubMed: 2138261]
16. Jonsson T, Stefansson H, Steinberg S, Jonsdottir I, Jonsson PV, Snaedal J, Bjornsson S, Huttenlocher J, Levey AI, Lah JJ, Rujescu D, Hampel H, Giegling I, Andreassen OA, Engedal K, Ulstein I, Djurovic S, Ibrahim-Verbaas C, Hofman A, Ikram MA, van Duijn CM, Thorsteinsdottir U, Kong A, Stefansson K. Variant of TREM2 associated with the risk of Alzheimer's disease. N Engl J Med. 2013; 368:107–116. [PubMed: 23150908]
17. Pottier C, Wallon D, Rousseau S, Rovelet-Lecrux A, Richard AC, Rollin-Sillaire A, Frebourg T, Campion D, Hannequin D. TREM2 R47H variant as a risk factor for early-onset Alzheimer's disease. J Alzheimers Dis. 2013; 35:45–49. [PubMed: 23380991]
18. Nho K, Saykin AJ, Alzheimer's Disease Neuroimaging I. Nelson PT. Hippocampal Sclerosis of Aging, a Common Alzheimer's Disease 'Mimic' Risk Genotypes are Associated with Brain Atrophy Outside the Temporal Lobe. J Alzheimers Dis. 2016; 52:373–383. [PubMed: 27003218]

19. Brouwers N, Nuytemans K, van der Zee J, Gijselinck I, Engelborghs S, Theuns J, Kumar-Singh S, Pickut BA, Pals P, Dermaut B, Bogaerts V, De Pooter T, Serneels S, Van den Broeck M, Cuijt I, Mattheijssens M, Peeters K, Sciot R, Martin JJ, Cras P, Santens P, Vandenberghe R, De Deyn PP, Cruts M, Van Broeckhoven C, Sleegers K. Alzheimer and Parkinson diagnoses in progranulin null mutation carriers in an extended founder family. Arch Neurol. 2007; 64:1436–1446. [PubMed: 17923627]

20. Baker M, Mackenzie IR, Pickering-Brown SM, Gass J, Rademakers R, Lindholm C, Snowden J, Adamson J, Sadovnick AD, Rollinson S, Cannon A, Dwosh E, Neary D, Melquist S, Richardson A, Dickson D, Berger Z, Eriksen J, Robinson T, Zehr C, Dickey CA, Crook R, McGowan E, Mann D, Boeve B, Feldman H, Hutton M. Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17. Nature. 2006; 442:916–919. [PubMed: 16862116]

21. Cruts M, Gijselinck I, van der Zee J, Engelborghs S, Wils H, Pirici D, Rademakers R, Vandenberghe R, Dermaut B, Martin JJ, van Duijn C, Peeters K, Sciot R, Santens P, De Pooter T, Mattheijssens M, Van den Broeck M, Cuijt I, Vennekens K, De Deyn PP, Kumar-Singh S, Van Broeckhoven C. Null mutations in progranulin cause ubiquitin-positive frontotemporal dementia linked to chromosome 17q21. Nature. 2006; 442:920–924. [PubMed: 16862115]

22. Mackenzie IR, Baker M, West G, Woulfe J, Qadi N, Gass J, Cannon A, Adamson J, Feldman H, Lindholm C, Melquist S, Pettman R, Sadovnick AD, Dwosh E, Whiteheart SW, Hutton M, Pickering-Brown SM. A family with tau-negative frontotemporal dementia and neuronal intranuclear inclusions linked to chromosome 17. Brain. 2006; 129:853–867. [PubMed: 16401619]

23. Dermaut B, Kumar-Singh S, Rademakers R, Theuns J, Cruts M, Van Broeckhoven C. Tau is central in the genetic Alzheimer-frontotemporal dementia spectrum. Trends Genet. 2005; 21:664–672. [PubMed: 16221505]

24. Lindquist SG, Holm IE, Schwartz M, Law I, Stokholm J, Batbayli M, Waldemar G, Nielsen JE. Alzheimer disease-like clinical phenotype in a family with FTDP-17 caused by a MAPT R406W mutation. Eur J Neurol. 2008; 15:377–385. [PubMed: 18284428]

25. Rademakers R, Dermaut B, Peeters K, Cruts M, Heutink P, Goate A, Van Broeckhoven C. Tau (MAPT) mutation Arg406Trp presenting clinically with Alzheimer disease does not share a common founder in Western Europe. Hum Mutat. 2003; 22:409–411. [PubMed: 14517953]

26. Reed LA, Grabowski TJ, Schmidt ML, Morris JC, Goate A, Solodkin A, Van Hoesen GW, Schelper RL, Talbot CJ, Wragg MA, Trojanowski JQ. Autosomal dominant dementia with widespread neurofibrillary tangles. Ann Neurol. 1997; 42:564–572. [PubMed: 9382467]

27. Jayadev S, Nochlin D, Poorkaj P, Steinbart EJ, Mastrianni JA, Montine TJ, Ghetti B, Schellenberg GD, Bird TD, Leverenz JB. Familial prion disease with Alzheimer disease-like tau pathology and clinical phenotype. Ann Neurol. 2011; 69:712–720. [PubMed: 21416485]

28. Perry RT, Go RC, Harrell LE, Acton RT. SSCP analysis and sequencing of the human prion protein gene (PRNP) detects two different 24 bp deletions in an atypical Alzheimer's disease family. Am J Med Genet. 1995; 60:12–18. [PubMed: 7485229]

29. Ramirez-Gomez L, Zheng L, Reed B, Kramer J, Mungas D, Zarow C, Vinters H, Ringman JM, Chui H. Neuropsychological Profiles Differentiate Alzheimer Disease from Subcortical Ischemic Vascular Dementia in an Autopsy-Defined Cohort. Dement Geriatr Cogn Disord. 2017; 44:1–11. [PubMed: 28595184]

30. Matias-Guiu JA, Valles-Salgado M, Rognoni T, Hamre-Gil F, Moreno-Ramos T, Matias-Guiu J. Comparative Diagnostic Accuracy of the ACE-III, MIS, MMSE, MoCA, and RUDAS for Screening of Alzheimer Disease. Dement Geriatr Cogn Disord. 2017; 43:237–246. [PubMed: 28384640]

31. Uchikado H, DelleDonne A, Ahmed Z, Dickson DW. Lewy bodies in progressive supranuclear palsy represent an independent disease process. J Neuropathol Exp Neurol. 2006; 65:387–395. [PubMed: 16691119]

32. Jin SC, Pastor P, Cooper B, Cervantes S, Benitez BA, Razquin C, Goate A. Ibero-American Alzheimer Disease Genetics Group R, Cruchaga C. Pooled-DNA sequencing identifies novel causative variants in PSEN1, GRN and MAPT in a clinical early-onset and familial Alzheimer's disease Ibero-American cohort. Alzheimers Res Ther. 2012; 4:34. [PubMed: 22906081]

33. Cruchaga C, Haller G, Chakraverty S, Mayo K, Vallania FL, Mitra RD, Faber K, Williamson J, Bird T, Diaz-Arrastia R, Foroud TM, Boeve BF, Graff-Radford NR, St Jean P, Lawson M, Ehm

MG, Mayeux R, Goate AM, Consortium N-LNFS. Rare variants in APP, PSEN1 and PSEN2 increase risk for AD in late-onset Alzheimer's disease families. PLoS One. 2012; 7:e31039. [PubMed: 22312439]

34. Lee JH, Kahn A, Cheng R, Reitz C, Vardarajan B, Lantigua R, Medrano M, Jimenez-Velazquez IZ, Williamson J, Nagy P, Mayeux R. Disease-related mutations among Caribbean Hispanics with familial dementia. Mol Genet Genomic Med. 2014; 2:430–437. [PubMed: 25333068]
35. Nicolas G, Wallon D, Charbonnier C, Quenez O, Rousseau S, Richard AC, Rovelet-Lecrux A, Coutant S, Le Guennec K, Bacq D, Garnier JG, Olaso R, Boland A, Meyer V, Deleuze JF, Munter HM, Bourque G, Auld D, Montpetit A, Lathrop M, Guyant-Marechal L, Martinaud O, Pariente J, Rollin-Sillaire A, Pasquier F, Le Ber I, Sarazin M, Croisile B, Boutoleau-Bretonniere C, Thomas-Anterion C, Paquet C, Sauvee M, Moreaud O, Gabelle A, Sellal F, Ceccaldi M, Chamard L, Blanc F, Frebourg T, Campion D, Hannequin D, et al. Screening of dementia genes by whole-exome sequencing in early-onszheimer disease input and lessons. Eur J Hum Genet. 2016; 24:710–716. [PubMed: 26242991]
36. Sassi C, Guerreiro R, Gibbs R, Ding J, Lupton MK, Troakes C, Al-Sarraj S, Niblock M, Gallo JM, Adnan J, Killick R, Brown KS, Medway C, Lord J, Turton J, Bras J, Alzheimer's Research UKC. Morgan K, Powell JF, Singleton A, Hardy J. Investigating the role of rare coding variability in Mendelian dementia genes (APP, PSEN1, PSEN2, GRN, MAPT, and PRNP) in late-onset Alzheimer's disease. Neurobiol Aging. 2014; 35:881. e2881–2886.
37. Chong JX, Buckingham KJ, Jhangiani SN, Boehm C, Sobreira N, Smith JD, Harrell TM, McMillin MJ, Wiszniewski W, Gambin T, Coban Akdemir ZH, Doheny K, Scott AF, Avramopoulos D, Chakravarti A, Hoover-Fong J, Mathews D, Witmer PD, Ling H, Hetrick K, Watkins L, Patterson KE, Reinier F, Blue E, Muzny D, Kircher M, Bilguvar K, Lopez-Giraldez F, Sutton VR, Tabor HK, Leal SM, Gunel M, Mane S, Gibbs RA, Boerwinkle E, Hamosh A, Shendure J, Lupski JR, Lifton RP, Valle D, Nickerson DA, Centers for Mendelian G. Bamshad MJ. The Genetic Basis of Mendelian Phenotypes: Discoveries, Challenges, and Opportunities. Am J Hum Genet. 2015; 97:199–215. [PubMed: 26166479]
38. Kircher M, Witten DM, Jain P, O'Roak BJ, Cooper GM, Shendure J. A general framework for estimating the relative pathogenicity of human genetic variants. Nat Genet. 2014; 46:310–315. [PubMed: 24487276]
39. Thomas PD, Kejariwal A. Coding single-nucleotide polymorphisms associated with complex vs. Mendelian disease: evolutionary evidence for differences in molecular effects. Proc Natl Acad Sci U S A. 2004; 101:15398–15403. [PubMed: 15492219]
40. Cooper GM, Stone EA, Asimenos G, Program NCS, Green ED, Batzoglou S, Sidow A. Distribution and intensity of constraint in mammalian genomic sequence. Genome Res. 2005; 15:901–913. [PubMed: 15965027]
41. Kryukov GV, Pennacchio LA, Sunyaev SR. Most rare missense alleles are deleterious in humans: implications for complex disease and association studies. Am J Hum Genet. 2007; 80:727–739. [PubMed: 17357078]
42. Beecham GW, Naj A, Martin ER, Haines JL, Farrer L, Mayeux R, Pericak-Vance MA, Schellenberg G, DeStefano A, Bis JC, Choi SH, van Duijn C, Fornage M, Boerwinkle E, Goate A, Foroud T. Seshadri STADSPDaSS. The Alzheimer Disease Sequencing Project: study design and sample selection. Neurology: Genetics. 2017; 5:e194.
43. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R, Mohs RC, Morris JC, Rossor MN, Scheltens P, Carrillo MC, Thies B, Weintraub S, Phelps CH. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011; 7:263–269. [PubMed: 21514250]
44. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology. 1984; 34:939–944. [PubMed: 6610841]

45. Naj AC, Lin H, Martin ER, DeStefano AL. Quality Control (QC) and Multi-Pipeline Genotype Consensus Calling Strategies for 578 whole genomes in the Alzheimer's Disease Sequencing Project (ADSP). in preparation.
46. Li H, Durbin R. Fast and accurate long-read alignment with Burrows-Wheeler transform. Bioinformatics. 2010; 26:589–595. [PubMed: 20080505]
47. McKenna A, Hanna M, Banks E, Sivachenko A, Cibulskis K, Kernytsky A, Garimella K, Altshuler D, Gabriel S, Daly M, DePristo MA. The Genome Analysis Toolkit: a MapReduce framework for analyzing next-generation DNA sequencing data. Genome Res. 2010; 20:1297–1303. [PubMed: 20644199]
48. DePristo MA, Banks E, Poplin R, Garimella KV, Maguire JR, Hartl C, Philippakis AA, del Angel G, Rivas MA, Hanna M, McKenna A, Fennell TJ, Kernytsky AM, Sivachenko AY, Cibulskis K, Gabriel SB, Altshuler D, Daly MJ. A framework for variation discovery and genotyping using next-generation DNA sequencing data. Nat Genet. 2011; 43:491–498. [PubMed: 21478889]
49. Van der Auwera GA, Carneiro MO, Hartl C, Poplin R, Del Angel G, Levy-Moonshine A, Jordan T, Shakir K, Roazen D, Thibault J, Banks E, Garimella KV, Altshuler D, Gabriel S, DePristo MA. From FastQ data to high confidence variant calls: the Genome Analysis Toolkit best practices pipeline. Curr Protoc Bioinformatics. 2013; 43:11. 10 11–33. [PubMed: 25431634]
50. Challis D, Yu J, Evani US, Jackson AR, Paithankar S, Coarfa C, Milosavljevic A, Gibbs RA, Yu F. An integrative variant analysis suite for whole exome next-generation sequencing data. BMC Bioinformatics. 2012; 13:8. [PubMed: 22239737]
51. Morrison AC, Voorman A, Johnson AD, Liu X, Yu J, Li A, Muzny D, Yu F, Rice K, Zhu C, Bis J, Heiss G, O'Donnell CJ, Psaty BM, Cupples LA, Gibbs R, Boerwinkle E. Cohorts for H, Aging Research in Genetic Epidemiology C. Whole-genome sequence-based analysis of high-density lipoprotein cholesterol. Nat Genet. 2013; 45:899–901. [PubMed: 23770607]
52. Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA, Bender D, Maller J, Sklar P, de Bakker PI, Daly MJ, Sham PC. PLINK: a tool set for whole-genome association and population-based linkage analyses. Am J Hum Genet. 2007; 81:559–575. [PubMed: 17701901]
53. O'Connell JR, Weeks DE. PedCheck: a program for identification of genotype incompatibilities in linkage analysis. Am J Hum Genet. 1998; 63:259–266. [PubMed: 9634505]
54. Butkiewicz M, Blue E, Leung YY, Jian X, Marcora E, Renton A, Partch A, Wang L-S, Koboldt D, Haines JL, Bush W. Functional Annotation of genomic variants in studies of Late-Onset Alzheimer's Disease. Bioinformatics under revision.
55. McLaren W, Gil L, Hunt SE, Riat HS, Ritchie GR, Thormann A, Flicek P, Cunningham F. The Ensembl Variant Effect Predictor. Genome Biol. 2016; 17:122. [PubMed: 27268795]
56. McLaren W, Pritchard B, Rios D, Chen Y, Flicek P, Cunningham F. Deriving the consequences of genomic variants with the Ensembl API and SNP Effect Predictor. Bioinformatics. 2010; 26:2069–2070. [PubMed: 20562413]
57. Tennessen JA, Bigham AW, O'Connor TD, Fu W, Kenny EE, Gravel S, McGee S, Do R, Liu X, Jun G, Kang HM, Jordan D, Leal SM, Gabriel S, Rieder MJ, Abecasis G, Altshuler D, Nickerson DA, Boerwinkle E, Sunyaev S, Bustamante CD, Bamshad MJ, Akey JM, Broad GO, Seattle GO, Project NES. Evolution and functional impact of rare coding variation from deep sequencing of human exomes. Science. 2012; 337:64–69. [PubMed: 22604720]
58. Genomes Project C. Auton A, Brooks LD, Durbin RM, Garrison EP, Kang HM, Korbel JO, Marchini JL, McCarthy S, McVean GA, Abecasis GR. A global reference for human genetic variation. Nature. 2015; 526:68–74. [PubMed: 26432245]
59. Lek M, Karczewski KJ, Minikel EV, Samocha KE, Banks E, Fennell T, O'Donnell-Luria AH, Ware JS, Hill AJ, Cummings BB, Tukiainen T, Birnbaum DP, Kosmicki JA, Duncan LE, Estrada K, Zhao F, Zou J, Pierce-Hoffman E, Berghout J, Cooper DN, Deflaux N, DePristo M, Do R, Flannick J, Fromer M, Gauthier L, Goldstein J, Gupta N, Howrigan D, Kiezun A, Kurki MI, Moonshine AL, Natarajan P, Orozco L, Peloso GM, Poplin R, Rivas MA, Ruano-Rubio V, Rose SA, Ruderfer DM, Shakir K, Stenson PD, Stevens C, Thomas BP, Tiao G, Tusie-Luna MT, Weisburd B, Won HH, Yu D, Altshuler DM, Ardissino D, Boehnke M, Danesh J, Donnelly S, Elosua R, Florez JC, Gabriel SB, Getz G, Glatt SJ, Hultman CM, Kathiresan S, Laakso M, McCarroll S, McCarthy MI, McGovern D, McPherson R, Neale BM, Palotie A, Purcell SM, Saleheen D, Scharf JM, Sklar P, Sullivan PF, Tuomilehto J, Tsuang MT, Watkins HC, Wilson JG,

Daly MJ, MacArthur DG. Exome Aggregation C. Analysis of protein-coding genetic variation in 60,706 humans. Nature. 2016; 536:285–291. [PubMed: 27535533]

60. Ng PC, Henikoff S. SIFT: Predicting amino acid changes that affect protein function. Nucleic Acids Res. 2003; 31:3812–3814. [PubMed: 12824425]
61. Adzhubei I, Jordan DM, Sunyaev SR. Predicting functional effect of human missense mutations using PolyPhen-2. Curr Protoc Hum Genet. 2013 Chapter 7:Unit7 20.
62. Davydov EV, Goode DL, Sirota M, Cooper GM, Sidow A, Batzoglou S. Identifying a high fraction of the human genome to be under selective constraint using GERP++ PLoS Comput Biol. 2010; 6:e1001025. [PubMed: 21152010]
63. Bis, JC., Naj, AC., Beecham, GW., Dupuis, J., Below, JE., Hamilton-Nelson, KL., Lin, H., Ma, Y., Gupta, N., Salerno, W., Chen, Y., Chouraki, V., Cupples, LA., Cruchaga, C., Jun, G., Kunkle, B., Partch, A., Koester, R., Schmidt, M., Vardarajan, B., Wijsman, E., Goate, A., Haines, J., Van Der Lee, SJ., Van Duijn, C., Seshadri, S., DeStefano, A., Martin, E., Fornage, M., Farrer, L. Group AsDSPC-CW. The Alzheimer's Disease Sequencing Project Discovery Phase: Case-Control Study Design, Progress, and Preliminary Results; Annual meeting of the American Society for Human Genetics; 2015.
64. Tsuang D, Leverenz JB, Lopez OL, Hamilton RL, Bennett DA, Schneider JA, Buchman AS, Larson EB, Crane PK, Kaye JA, Kramer P, Woltjer R, Trojanowski JQ, Weintraub D, Chen-Plotkin AS, Irwin DJ, Rick J, Schellenberg GD, Watson GS, Kukull W, Nelson PT, Jicha GA, Neltner JH, Galasko D, Masliah E, Quinn JF, Chung KA, Yearout D, Mata IF, Wan JY, Edwards KL, Montine TJ, Zabetian CP. APOE epsilon4 increases risk for dementia in pure synucleinopathies. JAMA Neurol. 2013; 70:223–228. [PubMed: 23407718]
65. Kent WJ, Baertsch R, Hinrichs A, Miller W, Haussler D. Evolution's cauldron duplication, deletion, and rearrangement in the mouse and human genomes. Proc Natl Acad Sci U S A. 2003; 100:11484–11489. [PubMed: 14500911]
66. Speir ML, Zweig AS, Rosenbloom KR, Raney BJ, Paten B, Nejad P, Lee BT, Learned K, Karolchik D, Hinrichs AS, Heitner S, Harte RA, Haeussler M, Guruvadoo L, Fujita PA, Eisenhart C, Diekhans M, Clawson H, Casper J, Barber GP, Haussler D, Kuhn RM, Kent WJ. The UCSC Genome Browser database: 2016 update. Nucleic Acids Res. 2016; 44:D717–725. [PubMed: 26590259]
67. Horaitis O, Talbot CC Jr, Phommarinh M, Phillips KM, Cotton RG. A database of locus-specific databases. Nat Genet. 2007; 39:425. [PubMed: 17392794]
68. Hamosh A, Scott AF, Amberger J, Valle D, McKusick VA. Online Mendelian Inheritance in Man (OMIM). Hum Mutat. 2000; 15:57–61. [PubMed: 10612823]
69. Amberger JS, Bocchini CA, Schiettecatte F, Scott AF, Hamosh A. OMIM.org: Online Mendelian Inheritance in Man (OMIM(R)), an online catalog of human genes and genetic disorders. Nucleic Acids Res. 2015; 43:D789–798. [PubMed: 25428349]
70. Kinoshita J, Clark T. Alzforum. Methods Mol Biol. 2007; 401:365–381. [PubMed: 18368375]
71. Danecek P, Auton A, Abecasis G, Albers CA, Banks E, DePristo MA, Handsaker RE, Lunter G, Marth GT, Sherry ST, McVean G, Durbin R. Genomes Project Analysis G. The variant call format and VCFtools. Bioinformatics. 2011; 27:2156–2158. [PubMed: 21653522]
72. Wang K, Li M, Hakonarson H. ANNOVAR: functional annotation of genetic variants from high-throughput sequencing data. Nucleic Acids Res. 2010; 38:e164. [PubMed: 20601685]
73. Paila U, Chapman BA, Kirchner R, Quinlan AR. GEMINI: integrative exploration of genetic variation and genome annotations. PLoS Comput Biol. 2013; 9:e1003153. [PubMed: 23874191]
74. Dong C, Wei P, Jian X, Gibbs R, Boerwinkle E, Wang K, Liu X. Comparison and integration of deleteriousness prediction methods for nonsynonymous SNVs in whole exome sequencing studies. Hum Mol Genet. 2015; 24:2125–2137. [PubMed: 25552646]
75. Jha P, Lu D, Xu S. Natural Selection and Functional Potentials of Human Noncoding Elements Revealed by Analysis of Next Generation Sequencing Data. PLoS One. 2015; 10:e0129023. [PubMed: 26053627]
76. Liu X, Jian X, Boerwinkle E. dbNSFP v2.0: a database of human non-synonymous SNVs and their functional predictions and annotations. Hum Mutat. 2013; 34:E2393–2402. [PubMed: 23843252]

77. Lee S, Emond MJ, Bamshad MJ, Barnes KC, Rieder MJ, Nickerson DA, Team NGESP-ELP. Christiani DC, Wurfel MM, Lin X. Optimal unified approach for rare-variant association testing with application to small-sample case-control whole-exome sequencing studies. Am J Hum Genet. 2012; 91:224–237. [PubMed: 22863193]

78. Wu MC, Lee S, Cai T, Li Y, Boehnke M, Lin X. Rare-variant association testing for sequencing data with the sequence kernel association test. Am J Hum Genet. 2011; 89:82–93. [PubMed: 21737059]

79. Lee S, Wu MC, Lin X. Optimal tests for rare variant effects in sequencing association studies. Biostatistics. 2012; 13:762–775. [PubMed: 22699862]

80. Medway CW, Abdul-Hay S, Mims T, Ma L, Bisceglio G, Zou F, Pankratz S, Sando SB, Aasly JO, Barcikowska M, Siuda J, Wszolek ZK, Ross OA, Carrasquillo M, Dickson DW, Graff-Radford N, Petersen RC, Ertekin-Taner N, Morgan K, Bu G, Younkin SG. ApoE variant p.V236E is associated with markedly reduced risk of Alzheimer's disease. Mol Neurodegener. 2014; 9:11. [PubMed: 24607147]

81. Rademakers R, Eriksen JL, Baker M, Robinson T, Ahmed Z, Lincoln SJ, Finch N, Rutherford NJ, Crook RJ, Josephs KA, Boeve BF, Knopman DS, Petersen RC, Parisi JE, Caselli RJ, Wszolek ZK, Uitti RJ, Feldman H, Hutton ML, Mackenzie IR, Graff-Radford NR, Dickson DW. Common variation in the miR-659 binding-site of GRN is a major risk factor for TDP43-positive frontotemporal dementia. Hum Mol Genet. 2008; 17:3631–3642. [PubMed: 18723524]

82. Sheng J, Su L, Xu Z, Chen G. Progranulin polymorphism rs5848 is associated with increased risk of Alzheimer's disease. Gene. 2014; 542:141–145. [PubMed: 24680777]

83. Xu HM, Tan L, Wan Y, Tan MS, Zhang W, Zheng ZJ, Kong LL, Wang ZX, Jiang T, Tan L, Yu JT, et al. PGRN Is Associated with Late-Onszheimer's Disease a Case-Control Replication Study and Meta-analysis. Mol Neurobiol. 2017; 54:1187–1195. [PubMed: 26820675]

84. Rademakers R, Baker M, Nicholson AM, Rutherford NJ, Finch N, Soto-Ortolaza A, Lash J, Wider C, Wojtas A, DeJesus-Hernandez M, Adamson J, Kouri N, Sundal C, Shuster EA, Aasly J, MacKenzie J, Roeber S, Kretzschmar HA, Boeve BF, Knopman DS, Petersen RC, Cairns NJ, Ghetti B, Spina S, Garbern J, Tselis AC, Uitti R, Das P, Van Gerpen JA, Meschia JF, Levy S, Broderick DF, Graff-Radford N, Ross OA, Miller BB, Swerdlow RH, Dickson DW, Wszolek ZK. Mutations in the colony stimulating factor 1 receptor (CSF1R) gene cause hereditary diffuse leukoencephalopathy with spheroids. Nat Genet. 2011; 44:200–205. [PubMed: 22197934]

85. Sundal, C., Wszolek, Z. Adult-Onset Leukoencephalopathy with Axonal Spheroids and Pigmented Glia. In: Pagon, RA.Adam, MP.Ardinger, HH.Wallace, SE.Amemiya, A.Bean, LJH.Bird, TD.Ledbetter, N.Mefford, HC.Smith, RJH., Stephens, K., editors. GeneReviews(R). Seattle (WA): 1993.

86. Harvey JS, Carey WF, Morris CP. Importance of the glycosylation and polyadenylation variants in metachromatic leukodystrophy pseudodeficiency phenotype. Hum Mol Genet. 1998; 7:1215–1219. [PubMed: 9668161]

87. Gieselmann V, Polten A, Kreysing J, von Figura K. Arylsulfatase A pseudodeficiency: loss of a polyadenylylation signal and N-glycosylation site. Proc Natl Acad Sci U S A. 1989; 86:9436–9440. [PubMed: 2574462]

88. Serre D, Gurd S, Ge B, Sladek R, Sinnett D, Harmsen E, Bibikova M, Chudin E, Barker DL, Dickinson T, Fan JB, Hudson TJ. Differential allelic expression in the human genome: a robust approach to identify genetic and epigenetic cis-acting mechanisms regulating gene expression. PLoS Genet. 2008; 4:e1000006. [PubMed: 18454203]

89. Alsmadi O, John SE, Thareja G, Hebbar P, Antony D, Behbehani K, Thanaraj TA. Genome at juncture of early human migration: a systematic analysis of two whole genomes and thirteen exomes from Kuwaiti population subgroup of inferred Saudi Arabian tribe ancestry. PLoS One. 2014; 9:e99069. [PubMed: 24896259]

90. Regis S, Corsolini F, Stroppiano M, Cusano R, Filocamo M. Contribution of arylsulfatase A mutations located on the same allele to enzyme activity reduction and metachromatic leukodystrophy severity. Hum Genet. 2002; 110:351–355. [PubMed: 11941485]

91. Gieselmann V, Fluharty AL, Tonnesen T, Von Figura K. Mutations in the arylsulfatase A pseudodeficiency allele causing metachromatic leukodystrophy. Am J Hum Genet. 1991; 49:407–413. [PubMed: 1678251]

92. Skibinski G, Parkinson NJ, Brown JM, Chakrabarti L, Lloyd SL, Hummerich H, Nielsen JE, Hodges JR, Spillantini MG, Thusgaard T, Brandner S, Brun A, Rossor MN, Gade A, Johannsen P, Sorensen SA, Gydesen S, Fisher EM, Collinge J. Mutations in the endosomal ESCRTIII-complex subunit CHMP2B in frontotemporal dementia. Nat Genet. 2005; 37:806–808. [PubMed: 16041373]

93. Huynh TV, Davis AA, Ulrich JD, Holtzman DM. Apolipoprotein E and Alzheimer Disease: The influence of apoE on amyloid-beta and other amyloidogenic proteins. J Lipid Res. 2017

94. Cacace R, Sleegers K, Van Broeckhoven C. Molecular genetics of early-onset Alzheimer's disease revisited. Alzheimers Dement. 2016; 12:733–748. [PubMed: 27016693]

95. Colonna M, Wang Y. TREM2 variants: new keys to decipher Alzheimer disease pathogenesis. Nat Rev Neurosci. 2016; 17:201–207. [PubMed: 26911435]

96. Ahmed R, Guerreiro R, Rohrer JD, Guven G, Rossor MN, Hardy J, Fox NC. A novel A781V mutation in the CSF1R gene causes hereditary diffuse leucoencephalopathy with axonal spheroids. J Neurol Sci. 2013; 332:141–144. [PubMed: 23816250]

97. Mitsui J, Matsukawa T, Ishiura H, Higasa K, Yoshimura J, Saito TL, Ahsan B, Takahashi Y, Goto J, Iwata A, Niimi Y, Riku Y, Goto Y, Mano K, Yoshida M, Morishita S, Tsuji S. CSF1R mutations identified in three families with autosomal dominantly inherited leukoencephalopathy. Am J Med Genet B Neuropsychiatr Genet. 2012; 159B:951–957. [PubMed: 23038421]

98. Terada S, Ishizu H, Yokota O, Ishihara T, Nakashima H, Kugo A, Tanaka Y, Nakashima T, Nakashima Y, Kuroda S. An autopsy case of hereditary diffuse leukoencephalopathy with spheroids, clinically suspected of Alzheimer's disease. Acta Neuropathol. 2004; 108:538–545. [PubMed: 15365727]

99. Wider C, Van Gerpen JA, DeArmond S, Shuster EA, Dickson DW, Wszolek ZK. Leukoencephalopathy with spheroids (HDLS) and pigmentary leukodystrophy (POLD): a single entity? Neurology. 2009; 72:1953–1959. [PubMed: 19487654]

100. Murphy GM Jr, Zhao F, Yang L, Cordell B. Expression of macrophage colony-stimulating factor receptor is increased in the AbetaPP(V717F) transgenic mouse model of Alzheimer's disease. Am J Pathol. 2000; 157:895–904. [PubMed: 10980129]

101. Lopez-Gonzalez I, Schluter A, Aso E, Garcia-Esparcia P, Ansoleaga B, F LL, Carmona M, Moreno J, Fuso A, Portero-Otin M, Pamplona R, Pujol A, Ferrer I. Neuroinflammatory signals in Alzheimer disease and APP/PS1 transgenic mice: correlations with plaques, tangles, and oligomeric species. J Neuropathol Exp Neurol. 2015; 74:319–344. [PubMed: 25756590]

102. Mitrasinovic OM, Grattan A, Robinson CC, Lapustea NB, Poon C, Ryan H, Phong C, Murphy GM Jr. Microglia overexpressing the macrophage colony-stimulating factor receptor are neuroprotective in a microglial-hippocampal organotypic coculture system. J Neurosci. 2005; 25:4442–4451. [PubMed: 15858070]

103. Olmos-Alonso A, Schetters ST, Sri S, Askew K, Mancuso R, Vargas-Caballero M, Holscher C, Perry VH, Gomez-Nicola D. Pharmacological targeting of CSF1R inhibits microglial proliferation and prevents the progression of Alzheimer's-like pathology. Brain. 2016; 139:891–907. [PubMed: 26747862]

104. Maes OC, Xu S, Yu B, Chertkow HM, Wang E, Schipper HM. Transcriptional profiling of Alzheimer blood mononuclear cells by microarray. Neurobiol Aging. 2007; 28:1795–1809. [PubMed: 16979800]

105. Philpot M, Lewis K, Pereria ML, Ward C, Holmes C, Lovestone S, Fensom A, Seller M. Arylsulphatase A pseudodeficiency in vascular dementia and Alzheimer's disease. Neuroreport. 1997; 8:2613–2616. [PubMed: 9261837]

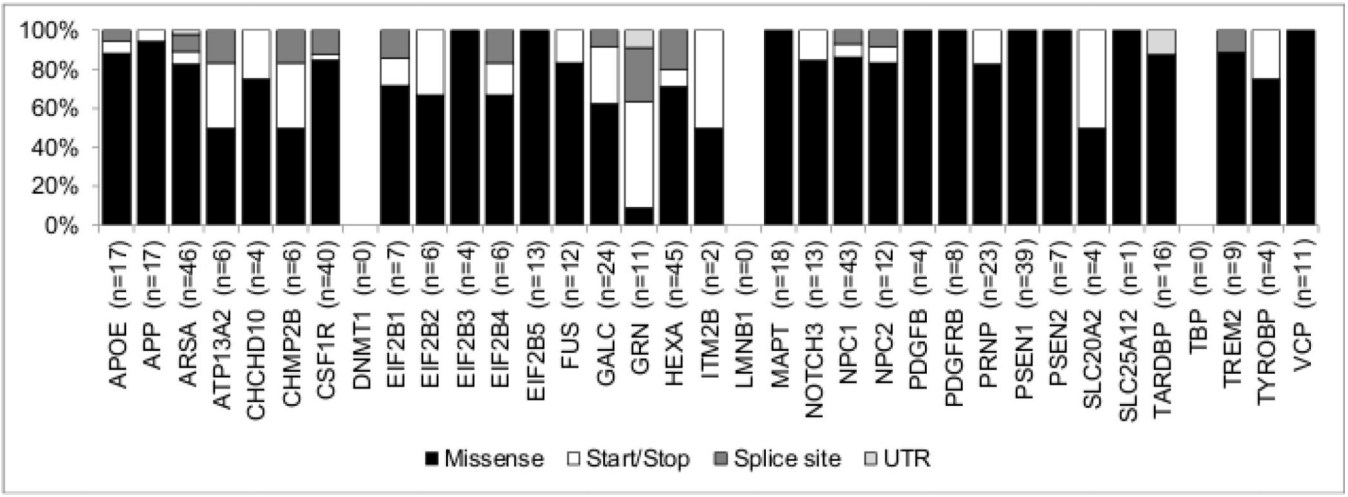

Figure 1. Distribution of consequential ClinVar SNVs across dementia genes

Y axis = number of pathogenic/likely pathogenic/risk variant/protective variants meeting inclusion criteria. Black: missense variants, white: start or stop gain or loss or frameshift, dark grey: splice donor/acceptor/region variant, light grey: 3'UTR variant.

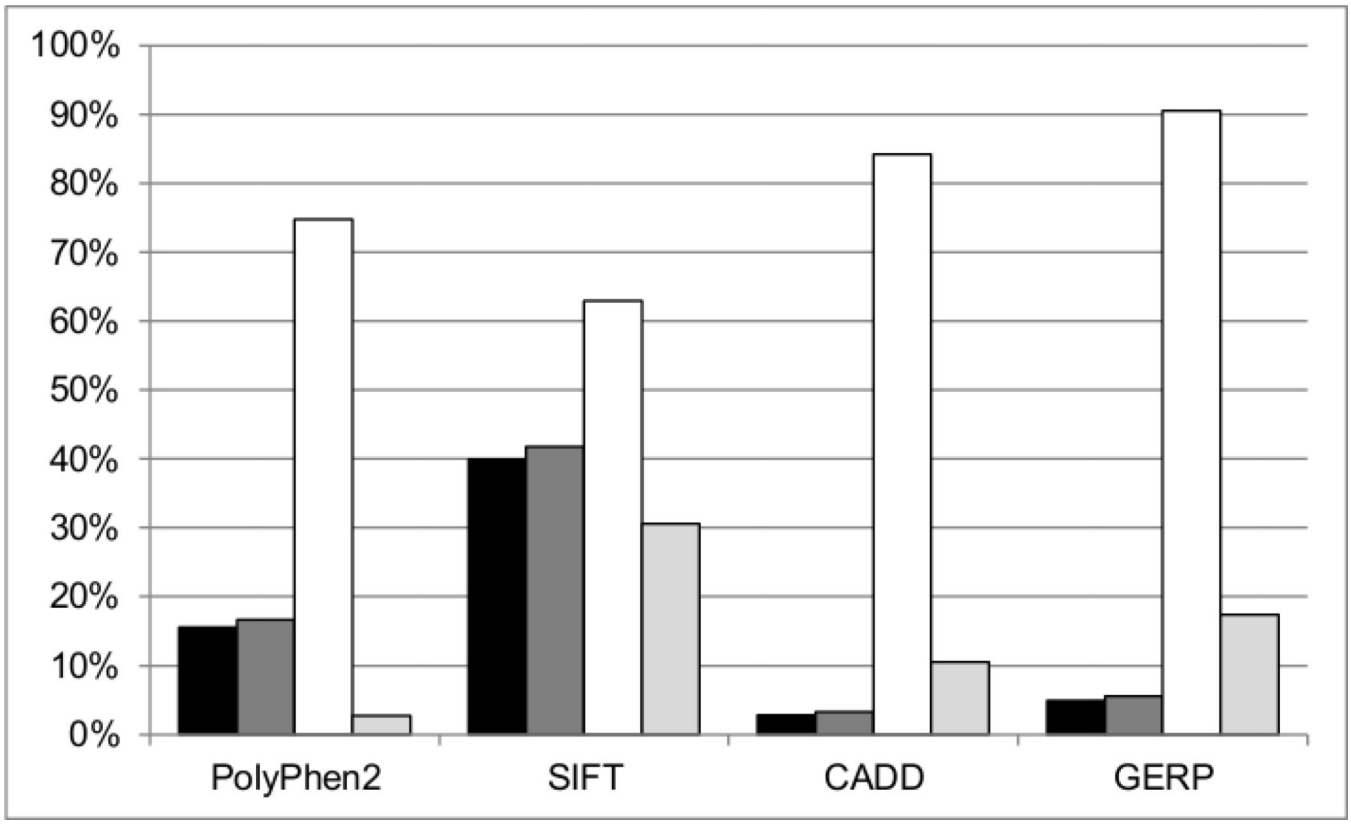

Figure 2. Percent of SNVs passing pathogenic/deleterious/conserved thresholds across SNV data sets

PolyPhen2: 143/496 SNVs were missing data, SIFT scores: 116/496 SNVs were missing data, phred-scaled CADD scores: 85/496 were missing data, GERP scores: 85/496 SNVs are missing data. Black: All consequential variants in 1000 genomes, dark grey = consequential variants in 1000 genomes with minor allele frequency < 0.001 in 1000 Genomes, Exome Sequencing Project, and Exome Aggregation Consortium data sets, white: consequential variants reported in ClinVar, light grey: consequential variants in CPD controls.

Table 1

Genes whose variants cause dementing disorders.

CHR	START	END	GENE	MIM
1	11072679	11085549	*TARDBP*	612069
1	17312453	17338423	*ATP13A2*	606693
1	45316194	45452394	*EIF2B3*	603896
1	227058273	227083804	*PSEN2*	606889
2	27587219	27592919	*EIF2B4*	603896
2	172639915	172750816	*SLC25A12*	612949
3	87276413	87304698	*CHMP2B*	600795
3	183852810	183863099	*EIF2B5*	603896
5	126112315	126172712	*LMNB1*	169500
5	149432854	149492935	*CSF1R*	221820
5	149493402	149535422	*PDGFRB*	615007
6	41126244	41130924	*TREM2*	221770
6	170863421	170881958	*TBP*	607136
8	42273980	42396655	*SLC20A2*	213600
9	35056065	35072739	*VCP*	613954, 167320
12	124105570	124118323	*EIF2B1*	603896
13	48807274	48836232	*ITM2B*	176500, 117300
14	73603143	73690399	*PSEN1*	607822, 600274
14	74946643	74960084	*NPC2*	607625
14	75469612	75476294	*EIF2B2*	603896
14	88399358	88459615	*GALC*	245200
15	72635778	72668520	*HEXA*	272800
16	31191431	31206192	*FUS*	608030
17	42422491	42430470	*GRN*	607485
17	43971748	44105699	*MAPT*	600274
18	21111463	21166581	*NPC1*	257220
19	10244022	10305755	*DNMT1*	604121
19	15270444	15311792	*NOTCH3*	125310
19	36395303	36399211	*TYROBP*	221770
19	45409039	45412650	*APOE*	104310
20	4667157	4682234	*PRNP*	137440, 123400
21	27252861	27543138	*APP*	104300, 605714
22	24108021	24110141	*CHCHD10*	615911
22	39619685	39640957	*PDGFB*	615483
22	51061182	51066601	*ARSA*	250100

CHR: chromosome, START: gene start position in build hg19/GRCh37 coordinates, END: gene end position in build hg19/GRCh37 coordinates, MIM: Mendelian Inheritance in Man identifier.

Table 2

Pathogenic and candidate SNVs observed in the ADSP family WGS data.

								Alternate Allele Frequency				ADSP carrier counts		
TIER	**rsID**	**ALT**	**GENE**	**CADD**	**GERP**	**PolyPhen2**	**SIFT**	**$ADSP_{WGS}$**	**1KG**	**ESP**	**ExAC**	**N_{cases}**	**$N_{unaffected}$**	**$N_{families}$**
ClinVar	rs6151429	C	*ARSA*	10.14	2.27	NA	NA	0.0803	0.0499	-	-	63	23	34
ClinVar	rs28940893	A	*ARSA*	33	5.57	1	0	0.0009	-	0.0005	0.0004	0	1	1
ClinVar	rs281860278	C	*CSF1R*	27.9	5.04	0.8	0	0.0009	-	-	4.94E-05	1	0	1
ClinVar	rs113994049	A	*EIF2B5*	22.8	1.51	0.003	0.15	0.0035	-	0.0005	0.0002	2	2	1
ClinVar	rs186547381	T	*FUS*	23.6	3.57	0.999	0.01	0.0026	0.0004	0.0001	0.0001	1	2	1
ClinVar	rs147313927	C	*GALC*	23	5.39	0.997	0	0.0026	0.0010	0.0026	0.0026	2	1	2
ClinVar	rs5848	T	*GRN*	9.012	2.11	NA	NA	0.3195	0.4245	-	-	203	81	86
ClinVar	rs80358257	C	*NPC1*	27.7	5.37	0.962	0	0.0009	0.0002	0.0002	0.0001	0	1	1
Candidate	rs149380040	T	*CHMP2B*	23.4	5.85	0.085	0.02	0.0017	-	0.0002	0.0005	2	0	1
Candidate	rs141111290	A	*GRN*	26.1	4.28	0.986	0	0.0026	0.0002	0.0001	0.0001	1	2	2

TIER: Variant annotated as consequential in ClinVar or a new candidate variant, ALT: alternate allele, and CADD: phred-scaled CADD score. Alternate allele frequencies are provided for the entire Alzheimer's Disease Sequencing Project whole genome sequence data ($ADSP_{WGS}$), the 1000 Genomes reference data set (1KG), the NHLBI GO Exome Sequencing Project (ESP), and for the Exome Aggregation Consortium (ExAC). Alternate allele carrier counts are provided for those in the $ADSP_{WGS}$ by affectation status (cases = probable or possible AD, un = unaffected or at-risk of AD), and the number of families carrying the alternate allele. Variants with PolyPhen2 scores ≥ 0.957, SIFT scores < 0.05, or phred-scaled CADD scores ≥15 were predicted to be deleterious/pathogenic, while GERP scores ≥3 were considered conserved.

Table 3

Gene-based analysis of rare SNVs in the ADSP exome data

		cumulative MAF			p–value	
Gene	**N**	**average**	**EUR**	**HISPANIC**	**model 0**	**model 2**
TREM2	50	0.0286	0.0252	0.0127	1.82E-11	0.0013
APOE	24	0.0103	0.0048	0.0150	0.0069	0.2009
ARSA	61	0.0285	0.0278	0.0795	0.0261	0.0170
CSF1R	87	0.0348	0.0328	0.0880	0.0214	0.0790
PSEN1	37	0.0232	0.0223	0.0139	0.0223	0.0665
MAPT	66	0.0704	0.0677	0.0874	0.0192	0.0303

Cumulative MAF: frequency of an individual carrying at least one variant allele matching the study inclusion criteria, EUR: samples with European ancestry, HISPANIC: samples with Hispanic ancestry, model 0: covariates include sequencing center and population-specific principal components, model 2: covariates include model 0 plus age, sex, principal components, and dosage of *APOE* ε2 and ε4 alleles.