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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

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Abstract

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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; arylsulfatase 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* $\epsilon 4$ 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* $\epsilon 2$ and $\epsilon 4$ 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 $\epsilon 2$ and $\epsilon 4$ 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 arylsulfatase 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 A β 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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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	<i>TARDBP</i>	612069
1	17312453	17338423	<i>ATP13A2</i>	606693
1	45316194	45452394	<i>EIF2B3</i>	603896
1	227058273	227083804	<i>PSEN2</i>	606889
2	27587219	27592919	<i>EIF2B4</i>	603896
2	172639915	172750816	<i>SLC25A12</i>	612949
3	87276413	87304698	<i>CHMP2B</i>	600795
3	183852810	183863099	<i>EIF2B5</i>	603896
5	126112315	126172712	<i>LMNB1</i>	169500
5	149432854	149492935	<i>CSF1R</i>	221820
5	149493402	149535422	<i>PDGFRB</i>	615007
6	41126244	41130924	<i>TREM2</i>	221770
6	170863421	170881958	<i>TBP</i>	607136
8	42273980	42396655	<i>SLC20A2</i>	213600
9	35056065	35072739	<i>VCP</i>	613954, 167320
12	124105570	124118323	<i>EIF2B1</i>	603896
13	48807274	48836232	<i>ITM2B</i>	176500, 117300
14	73603143	73690399	<i>PSEN1</i>	607822, 600274
14	74946643	74960084	<i>NPC2</i>	607625
14	75469612	75476294	<i>EIF2B2</i>	603896
14	88399358	88459615	<i>GALC</i>	245200
15	72635778	72668520	<i>HEXA</i>	272800
16	31191431	31206192	<i>FUS</i>	608030
17	42422491	42430470	<i>GRN</i>	607485
17	43971748	44105699	<i>MAPT</i>	600274
18	21111463	21166581	<i>NPC1</i>	257220
19	10244022	10305755	<i>DNMT1</i>	604121
19	15270444	15311792	<i>NOTCH3</i>	125310
19	36395303	36399211	<i>TYROBP</i>	221770
19	45409039	45412650	<i>APOE</i>	104310
20	4667157	4682234	<i>PRNP</i>	137440, 123400
21	27252861	27543138	<i>APP</i>	104300, 605714
22	24108021	24110141	<i>CHCHD10</i>	615911
22	39619685	39640957	<i>PDGFB</i>	615483
22	51061182	51066601	<i>ARSA</i>	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.

TIER	rsID	ALT	GENE	CADD	GERP	PolyPhen2	SIFT	Alternate Allele Frequency				ADSP carrier counts		
								ADSPWGS	IKG	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	NPCI	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 (ADSPWGS), 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 ADSPWGS by affection 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

Gene	N	average	cumulative MAF			p-value	
			EUR	HISPANIC	model 0	model 2	
<i>TREM2</i>	50	0.0286	0.0252	0.0127	1.82E-11	0.0013	
<i>APOE</i>	24	0.0103	0.0048	0.0150	0.0069	0.2009	
<i>ARSA</i>	61	0.0285	0.0278	0.0795	0.0261	0.0170	
<i>CSF1R</i>	87	0.0348	0.0328	0.0880	0.0214	0.0790	
<i>PSEN1</i>	37	0.0232	0.0223	0.0139	0.0223	0.0665	
<i>MAPT</i>	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* e2 and e4 alleles.