

Rare coding variants in *PLCG2*, *ABI3*, and *TREM2* implicate microglial-mediated innate immunity in Alzheimer's disease

We identified rare coding variants associated with Alzheimer's disease in a three-stage case-control study of 85,133 subjects. In stage 1, we genotyped 34,174 samples using a whole-exome microarray. In stage 2, we tested associated variants ($P < 1 \times 10^{-4}$) in 35,962 independent samples using *de novo* genotyping and imputed genotypes. In stage 3, we used an additional 14,997 samples to test the most significant stage 2 associations ($P < 5 \times 10^{-8}$) using imputed genotypes. We observed three new genome-wide significant nonsynonymous variants associated with Alzheimer's disease: a protective variant in *PLCG2* (rs72824905: p.Pro522Arg, $P = 5.38 \times 10^{-10}$, odds ratio (OR) = 0.68, minor allele frequency (MAF)_{cases} = 0.0059, MAF_{controls} = 0.0093), a risk variant in *ABI3* (rs616338: p.Ser209Phe, $P = 4.56 \times 10^{-10}$, OR = 1.43, MAF_{cases} = 0.011, MAF_{controls} = 0.008), and a new genome-wide significant variant in *TREM2* (rs143332484: p.Arg62His, $P = 1.55 \times 10^{-14}$, OR = 1.67, MAF_{cases} = 0.0143, MAF_{controls} = 0.0089), a known susceptibility gene for Alzheimer's disease. These protein-altering changes are in genes highly expressed in microglia and highlight an immune-related protein-protein interaction network enriched for previously identified risk genes in Alzheimer's disease. These genetic findings provide additional evidence that the microglia-mediated innate immune response contributes directly to the development of Alzheimer's disease.

Late-onset Alzheimer's disease (LOAD) has a substantial genetic component ($h^2 = 58\text{--}79\%$)¹. Nearly 30 LOAD susceptibility loci^{2–12} are known, and risk is highly polygenic¹³. However, these loci explain only a proportion of disease heritability. Rare variants also contribute to disease risk^{14–17}. Recent sequencing studies identified a number of genes that have rare variants associated with Alzheimer's disease^{9–11,18–24}. Our approach to rare variant discovery is to genotype a large sample with microarrays targeting known exome variants with follow-up using genotyping and imputed genotypes in a large independent sample. This is a cost-effective alternative to *de novo* sequencing^{25–29}.

We applied a three-stage design (Supplementary Fig. 1) using subjects from the International Genomics of Alzheimer's Project (IGAP) (Table 1 and Supplementary Tables 1 and 2). In stage 1, we genotyped 16,097 LOAD cases and 18,077 cognitively normal elderly

controls using the Illumina HumanExome microarray. Data from multiple consortia were combined in a single-variant meta-analysis (Online Methods) assuming an additive model. In total, 241,551 variants passed quality control (Supplementary Table 3). Of these, 203,902 were polymorphic, 26,947 were common (MAF $\geq 5\%$), and 176,955 were low frequency or rare (MAF $< 5\%$). We analyzed common variants using a logistic regression model in each sample cohort and combined data using METAL³⁰. Rare and low-frequency variants were analyzed using the score test and data were combined with SeqMeta³¹ (Supplementary Fig. 2).

We reviewed cluster plots for variants showing association ($P < 1 \times 10^{-4}$) and identified 43 candidate variants (Supplementary Table 4), excluding known risk loci (Supplementary Table 5). In stage 2, we tested these for association in 14,041 LOAD cases and 21,921 controls, using genotypes derived from *de novo* genotyping and imputation (Online Methods). We carried forward single-nucleotide variants (SNVs) with genome-wide significant associations and consistent directions of effect to stage 3 where genotypes for 6,652 independent cases and 8,345 controls were imputed using the Haplotype Reference Consortium resource^{32,33} (Online Methods and Supplementary Table 6).

We identified four rare coding variants with genome-wide significant association signals with LOAD ($P < 5 \times 10^{-8}$) (Table 2 and Supplementary Tables 7 and 8). The first is a missense variant p.Pro522Arg ($P = 5.38 \times 10^{-10}$, OR = 0.68) in *PLCG2* (phospholipase C $\gamma 2$) (Fig. 1a, Table 2, Supplementary Fig. 3, and Supplementary Table 9). This variant is associated with decreased risk of LOAD, showing a MAF of 0.0059 in cases and 0.0093 in controls. The reference allele (Pro522) is conserved across several species (Supplementary Fig. 4). Gene-wide analysis showed nominal evidence for association at $P = 1.52 \times 10^{-4}$ (Supplementary Tables 10 and 11), and we found no other independent association at this gene (Supplementary Fig. 5).

The second new association is a missense change p.Ser209Phe ($P = 4.56 \times 10^{-10}$, OR = 1.43) in *ABI3* (B3-domain-containing transcription factor ABI3). The Phe209 allele showed consistent evidence for increasing LOAD risk across all stages, with a MAF of 0.011 in cases and 0.008 in controls (Fig. 1b, Table 2, Supplementary Fig. 6, and Supplementary Table 12). The reference allele is conserved across multiple species (Supplementary Fig. 7). Gene-wide analysis showed nominal evidence of association ($P = 5.22 \times 10^{-5}$) (Supplementary

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Table 1 Summary of the consortium data sets used for stages 1–3

	Consortium	<i>n</i> controls	<i>n</i> cases	<i>n</i> total
Stage 1	GERAD/PERADES	2,974	6,000	8,974
	ADGC	7,002	8,706	15,708
	CHARGE	8,101	1,391	9,492
	Total	18,077	16,097	34,174
Stage 2	GERAD/PERADES genotype	5,049	4,049	9,098
	CHARGE, genotype	1,839	1,434	3,273
	CHARGE, <i>in silico</i>	3,246	722	3,968
	EADI, genotype	11,787	7,836	19,623
Total		21,921	14,041	35,962
Stage 3	ADGC, <i>in silico</i>	8,345	6,652	14,997
Stage 1–3 total		48,402	37,022	85,133

Data are from the Genetic and Environmental Risk for Alzheimer’s Disease (GERAD)/Defining Genetic, Polygenic and Environmental Risk for Alzheimer’s Disease (PERADES) Consortium, the Alzheimer’s Disease Genetic Consortium (ADGC), the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE), and the European Alzheimer’s disease Initiative (EADI) (**Supplementary Note**).

Tables 10 and **11**). The *B4GALNT2* gene, adjacent to *ABI3*, contained an independent suggestive association (**Supplementary Fig. 8**), but this failed to replicate in subsequent stages ($P_{\text{combined}} = 1.68 \times 10^{-4}$) (**Supplementary Table 7**).

Following reports of suggestive association with LOAD^{34,35}, we report the first evidence for genome-wide significant association at *TREM2* coding variant p.Arg62His ($P = 1.55 \times 10^{-14}$, OR = 1.67), with a MAF of 0.0143 in cases and 0.0089 in controls (**Fig. 1c**, **Table 2**, **Supplementary Figs. 9** and **10**, and **Supplementary Table 13**). We also observed evidence of association for the previously reported^{9,11} *TREM2* rare variant p.Arg47His (**Table 2**). These variants are not in linkage disequilibrium (**Supplementary Table 14**), and conditional analyses confirmed that p.Arg62His and p.Arg47His are independent risk variants (**Supplementary Fig. 11**). Gene-wide analysis of *TREM2* showed a genome-wide significant association ($P_{\text{SKAT}} = 1.42 \times 10^{-5}$) (**Supplementary Tables 10** and **11**). Removal of p.Arg47His and the p.Arg62His variants from the analysis diminished the gene-wide association, but the signal remained interesting ($P_{\text{SKAT-O}} = 6.3 \times 10^{-3}$, $P_{\text{Burden}} = 4.1 \times 10^{-3}$). No single SNV was responsible for the remaining gene-wide association (**Supplementary Fig. 11** and **Supplementary Table 13**), suggesting that there are additional risk

variants in *TREM2*. We previously reported a common variant association with LOAD near *TREM2*, in a genome-wide association study (GWAS) of cerebrospinal fluid tau and phosphorylated tau (P-tau)³⁶. We also observed a different suggestive common variant signal in another LOAD case–control study ($P = 6.3 \times 10^{-7}$)².

We previously identified eight gene pathway clusters significantly enriched in common variants associated with Alzheimer’s disease³⁶. To test whether biological enrichments observed in common variants are also present in rare variants, we used the rare variant data (MAF < 1%) to reanalyze these eight Alzheimer’s disease–associated pathway clusters (Online Methods and **Supplementary Table 15**). We used Fisher’s method to combine gene-wide *P* values for all genes in each cluster. After correction for multiple testing, we observed enrichment for immune response ($P = 8.64 \times 10^{-3}$), cholesterol transport ($P = 3.84 \times 10^{-3}$), hemostasis ($P = 2.10 \times 10^{-3}$), clathrin–AP2 adaptor complex ($P = 9.20 \times 10^{-4}$), and protein folding ($P = 0.02$). We also performed pathway analyses on the rare variant data presented here using all 9,816 pathways used previously. The top pathways are related to lipoprotein particles, cholesterol efflux, B cell differentiation and immune response, areas of biology also enriched when common variants are analyzed³⁷ (**Supplementary Table 16**).

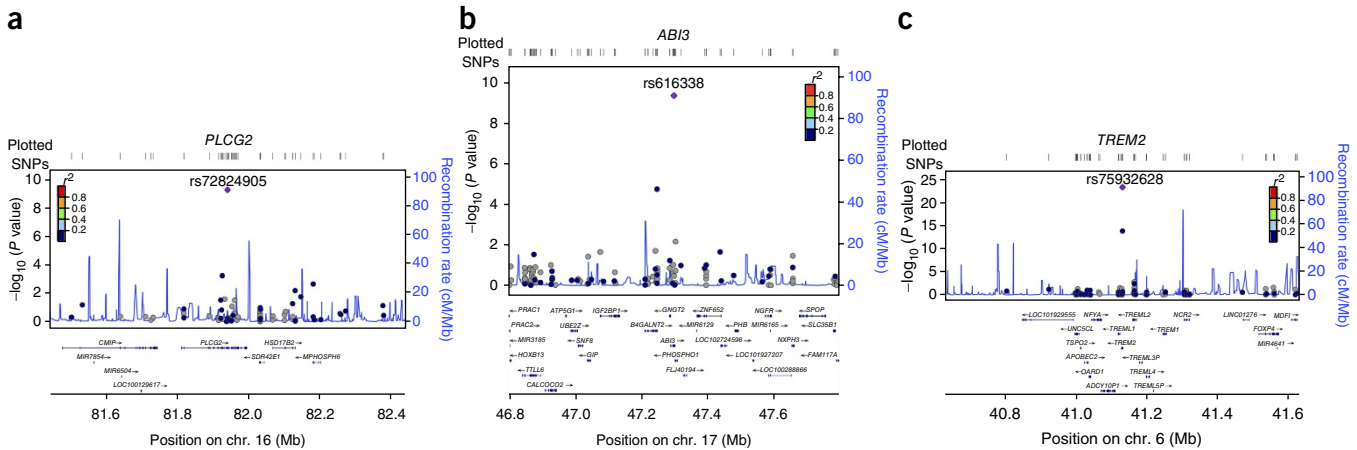


Figure 1 Association plots of *PLCG2*, *ABI3*, and *TREM2*. **(a)** Regional plot of identified association at the *PLCG2* locus. Top hit rs72824905 is indicated in purple. Data presented for rs72824905 include data from stage 1, stage 2, and stage 3 ($n = 84,905$). **(b)** Regional plot of identified association at the *ABI3* locus. Top hit rs616338 is indicated in purple. Data presented for rs616338 include data from stage 1, stage 2, and stage 3 ($n = 84,493$). **(c)** Regional plot of identified association at the *TREM2* locus. Top hit rs75932628 is indicated in purple. Data presented for rs75932628 and rs143332484 include data from stage 1, stage 2, and stage 3 ($n = 80,733$ and $53,042$, respectively). SNVs with missing LD information are shown in gray.

Table 2 Summary of stages 1, 2 and 3 and combined meta-analysis results for SNVs at $P < 5 \times 10^{-8}$

SNV	rs75932628	rs143332484	rs72824905	rs616338
Chr.	6	6	16	17
Position (bp)	41,129,252	41,129,207	81,942,028	47,297,297
Protein variation	Arg47His	Arg62His	Pro522Arg	Ser209Phe
Gene	<i>TREM2</i>	<i>TREM2</i>	<i>PLCG2</i>	<i>ABI3</i>
Effect allele	T	T	G	T
Stage 1				
<i>P</i>	3.02×10^{-12}	3.48×10^{-9}	1.19×10^{-5}	2.16×10^{-5}
OR	2.46	1.58	0.65	1.42
MAF _{cases}	0.003	0.015	0.006	0.013
MAF _{controls}	0.001	0.010	0.011	0.010
<i>N</i>	30,018	33,786	33,786	33,786
Stage 2				
<i>P</i>	4.38×10^{-8}	3.66×10^{-7}	1.35×10^{-4}	8.37×10^{-5}
OR	2.37	3.97	0.70	1.41
MAF _{cases}	0.004	0.014	0.006	0.010
MAF _{controls}	0.002	0.006	0.008	0.008
<i>N</i>	35,831	3,968	35,831	35,831
Stage 3				
<i>P</i>	1.23×10^{-6}	2.45×10^{-3}	2.48×10^{-2}	1.75×10^{-2}
OR	2.58	1.55	0.69	1.58
MAF _{cases}	0.006	0.012	0.006	0.010
MAF _{controls}	0.003	0.008	0.007	0.008
<i>N</i>	14,884	15,288	15,288	14,876
Stage 1–3 meta-analysis				
<i>P</i>	5.38×10^{-24}	1.55×10^{-14}	5.38×10^{-10}	4.56×10^{-10}
OR	2.46	1.67	0.68	1.43
MAF _{cases}	0.004	0.014	0.006	0.011
MAF _{controls}	0.002	0.009	0.009	0.008
<i>N</i>	80,733	53,042	84,905	84,493

Data include *P* value, odds ratios (OR), minor allele frequency (MAF) in cases and controls, and number of subjects included in each analytical stage. For OR 95% confidence intervals, see **Supplementary Table 7**. Concordance for alternate allele carrier genotypes between imputed versus called SNPs in stage 3 was 75.2% for rs75932628, 91.1% for rs143332484, 95.7% for rs72824905, and 81.9% for rs616338 (Online Methods and **Supplementary Table 6**). Chr., chromosome.

Previous analysis of normal brain coexpression networks identified four gene modules that are enriched for common variants associated with LOAD risk^{2,3711}. These four modules are enriched for immune-response genes. We identified 151 genes present in two or more of these four modules, and these showed a strong enrichment for LOAD-associated common variants ($P = 4.0 \times 10^{-6}$)³⁶ and for rare variants described here (MAF < 1%) ($P = 1.17 \times 10^{-6}$; **Supplementary Table 15**). We then used a set of high-quality protein-protein interactions³⁷ to construct, from these 151 genes, an interaction network containing 56 genes, including *PLCG2*, *ABI3*, and *TREM2* (**Fig. 2** and Online Methods). This subset is strongly enriched for association signals from both the previous common variant analysis ($P = 5.0 \times 10^{-6}$; **Supplementary Table 17**) and this rare variant gene set analysis ($P = 1.08 \times 10^{-7}$; **Supplementary Table 15**). The remaining 95 genes only have nominally significant enrichment for either common or rare variants (**Supplementary Tables 15 and 17**), suggesting that the 56-gene (**Supplementary Table 18**) network is driving the enrichment.

TREM2, *ABI3*, and *PLCG2* have a common expression pattern in human brain cortex, with high expression in microglia cells and limited expression in neurons, oligodendrocytes, astrocytes, and endothelial cells (**Supplementary Fig. 12**)³⁸. Other known LOAD-associated loci with the same expression pattern included *SORL1*, the *MS4A* gene cluster, and *HLA-DRB1*. *PLCG2*, *ABI3*, and *TREM2* are upregulated in LOAD human cortex and in two amyloid precursor protein (APP) mouse models. However, when corrected for levels of

other microglial genes, these changes in expression appeared to be related to microgliosis (**Supplementary Tables 19 and 20**).

PLCG2 (**Supplementary Fig. 13**) encodes a transmembrane signaling enzyme (PLCγ2) that hydrolyzes the membrane phospholipid PIP₂ (1-phosphatidyl-1D-myoinositol 4,5-bisphosphate) to secondary messengers IP₃ (myoinositol 1,4,5-trisphosphate) and DAG (diacylglycerol). IP₃ is released into the cytosol and acts at the endoplasmic reticulum where it binds to ligand-gated ion channels to increase cytoplasmic Ca²⁺. DAG remains bound to the plasma membrane where it activates two major signaling molecules, protein kinase C (PKC) and Ras guanyl-nucleotide-releasing proteins (RasGRPs), which initiate the NF-κB and mitogen-activated protein kinase (MAPK) pathways. While the IP₃–DAG–Ca²⁺ signaling pathway is active in many cells and tissues, in brain *PLCG2* is primarily expressed in microglial cells. *PLCG2* variants also cause antibody deficiency and immune dysregulation (PLAID) and autoinflammation and PLAID (APLAID)³⁹. Genomic deletions (PLAID) and missense mutations (APLAID) affect the cSH2 autoinhibitory regulatory region. The result is a complex mix of loss and gain of function in cellular signaling³⁹.

Functional annotation (**Supplementary Table 21**) suggests that *ABI3* (**Supplementary Fig. 14**) has a role in the innate immune response via interferon-mediated signaling⁴⁰. *ABI3* is coexpressed with *INPP5D* ($P = 2.2 \times 10^{-10}$), a gene previously implicated in LOAD risk². *ABI3* has an important role in actin cytoskeleton organization through participation in the WAVE2 complex⁴¹, a complex that regulates multiple pathways leading to T cell activation⁴².

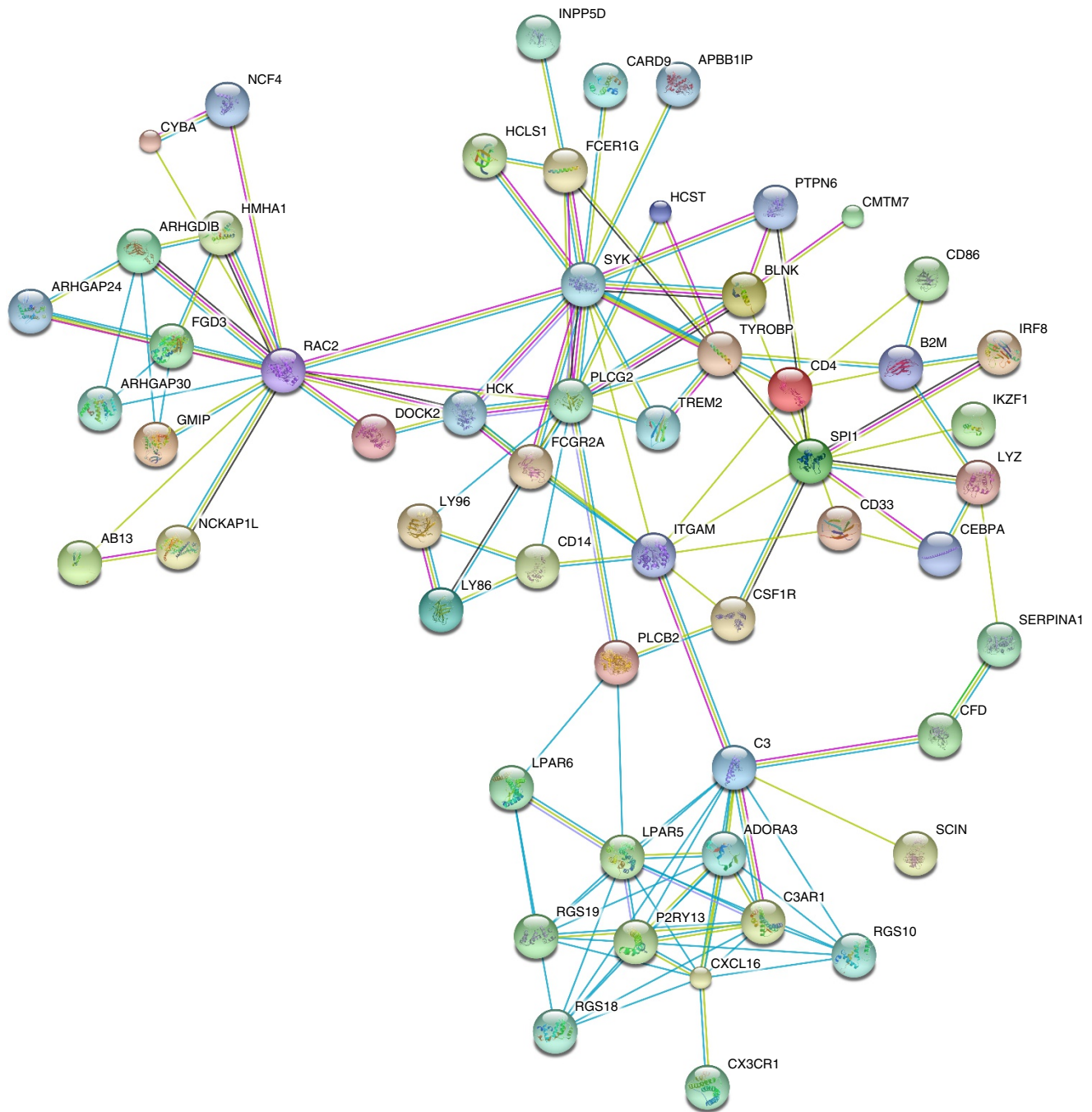


Figure 2 Protein–protein interaction network (using high-confidence human interactions from the STRING database) of 56 genes enriched for both common and rare variants associated with Alzheimer’s disease risk. Colors of edges refer to the type of evidence linking the corresponding proteins: red, gene fusion; dark blue, co-occurrence; black, coexpression; magenta, experiments; cyan, databases; light green, text mining; mauve, homology. *TREM2*, *PLCG2*, and *AB13* are highlighted by red circles, *SYK*, *CSF1R*, and *TYROBP* are highlighted by blue circles, and *INPP5D*, *SPI1*, and *CD33* identified as common variant risk loci^{2,5–7} are highlighted by black circles.

TREM2 encodes a transmembrane receptor present in the plasma membrane of brain microglia (Supplementary Fig. 15). *TREM2* protein forms an immune-receptor-signaling complex with DAP12. Receptor activation results in activation of Syk and ZAP70 signaling, which in turn activates PI3K activity and influences PLCγ2 activity⁴³. In microglia, *TREM2*–DAP12 induces M2-like activation⁴⁴ and participates in recognition of membrane debris and amyloid deposits, resulting in microglial activation and proliferation^{45–47}. When *Trem2*-homozygous-knockout or *Trem2*-heterozygous-knockout

mice are crossed with *APP* transgenics that develop plaques, the size and number of microglia associated with plaques are markedly reduced^{46,47}. *TREM2* risk variants are located within exon 2, which is predicted to encode the conserved ligand-binding extracellular region of the protein. Any disruption in this region may attenuate or abolish *TREM2* signaling, resulting in loss or decrease in *TREM2* function⁴⁷.

The 56-gene interaction network identified here is enriched in immune-response genes and includes *TREM2*, *PLCG2*, *AB13*, *SPI1*,

INPP5D, *CSF1R*, *SYK*, and *TYROBP* (Fig. 2). *SPI1* is a central transcription factor in microglial activation state that has a significant gene-wide association with Alzheimer's disease⁵ and is in the proximity of genome-wide significant signals identified by IGAP². Loss-of-function mutations in *CSF1R* cause hereditary diffuse leukoencephalopathy with spheroids, a white matter disease related to microglial dysfunction⁴⁸. Activated microglial cells surround plaques^{49,50}, a finding consistently observed in Alzheimer's disease brain in humans and transgenic mouse models of Alzheimer's disease⁵¹. In the brains of mouse models of Alzheimer's disease, synaptic pruning associates with activated microglial signaling⁵². Pharmacological targeting of *CSF1R* inhibits microglial proliferation and shifts the microglial inflammatory profile to an anti-inflammatory phenotype in mouse models⁵³. *SYK* regulates amyloid- β production and tau hyperphosphorylation⁵⁴, is affected by the *INPP5D*-*CD2AP* complex⁵⁵ encoded by two *LOAD*-associated genes², and mediates phosphorylation of *PLC γ 2* (ref. 56). Notably, the antihypertensive drug nilvadipine, currently in a phase 3 Alzheimer's disease clinical trial, targets *SYK* as well as *TYROBP*, a hub gene in an Alzheimer's disease-related brain expression network³⁸ that encodes the *TREM2* complex protein *DAPI2*.

We identified three rare coding variants in *PLCG2*, *ABI3*, and *TREM2* with genome-wide significant associations with *LOAD* that are part of a common innate immune response. This work provides additional evidence that the microglial response in *LOAD* is directly part of a causal pathway leading to disease and is not simply a downstream consequence of neurodegeneration^{46,47,57,58}. Our network analysis supports this conclusion. In addition, *PLC γ 2*, as an enzyme, represents the first classically druggable target, to our knowledge, to emerge from *LOAD* genetic studies. The variants described here account for a small portion of the 'missing heritability' of Alzheimer's disease. The remaining heritability may be due to a large number of common variants of small effect. For rare variants, there may be additional exonic sites with lower MAF or effect size, and/or intronic and intergenic sites. Complete resolution of the heritability for Alzheimer's disease will be facilitated by larger sample sizes and more comprehensive sequence data.

METHODS

Methods, including statements of data availability and any associated accession codes and references, are available in the [online version of the paper](#).

Note: Any Supplementary Information and Source Data files are available in the online version of the paper.

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ONLINE METHODS

Genotyping and quality control. Stage 1. GERAD/PERADES. Genotyping was performed at Life and Brain, Bonn, Germany, with Illumina HumanExome BeadChip v1.0 ($n = 247,870$ variants) or v1.1 ($n = 242,901$ variants). Illumina's GenTrain version 2.0 clustering algorithm in GenomeStudio or zCall⁵⁹ was used for genotype calling. Quality control filters were implemented for sample call rate excluding samples with >1% missingness, excess autosomal heterozygosity excluding outliers based on <1% and >1% MAF separately, sex discordance, relatedness excluding one of each pair related with identity by descent (IBD) ≥ 0.125 (the level expected for first cousins), and population outliers (non-European ancestry). Variants were filtered on the basis of call rate excluding variants with >1% missingness, genotype cluster separation excluding variants with a separation score <0.4, and Hardy–Weinberg equilibrium excluding variants with $P_{HWE} < 1 \times 10^{-4}$. Ten principal components were extracted using EIGENSTRAT, including the first three principal components as covariates had the maximum impact on the genomic control inflation factor, λ (ref. 60). After quality control, 6,000 LOAD cases and 2,974 elderly controls (version 1.0, 4,093 LOAD cases and 1,599 controls; version 1.1, 1,907 LOAD cases and 1,375 controls) remained. The version 1.0 array had 244,412 variants available for analysis and 239,814 remained for the version 1.1 array.

CHARGE. All four CHARGE cohorts were genotyped for the Illumina HumanExome BeadChip v1.0. To increase the quality of the rare variant genotype calls, the genotypes for all four studies were jointly called with 62,266 samples from 11 studies at the University of Texas HSC at Houston⁶¹. Quality control procedures for the genotype data were performed both centrally at UT Houston and at each study. The central quality control procedures have been described previously⁶¹. Minimum quality control included (i) concordance checking with GWAS data and removal of problematic samples; (ii) removal of individuals with low genotype completion rate (<90%); (iii) removal of variants with low genotype call rate (<95%); (iv) removal of individuals with sex mismatches; (v) removal of one individual from duplicate pairs; (vi) removal of first-degree relatives on the basis of genetically calculated relatedness (identity by state (IBS) > 0.45), with cases retained over controls; and (vii) removal of variants not called in over 5% of the individuals and those that deviated significantly from the expected Hardy–Weinberg equilibrium proportions ($P < 1 \times 10^{-6}$).

ADGC. Genotyping was performed in subsets at four centers: NorthShore, Miami, WashU, and CHOP (CHOP and ADC7 data sets) on the Illumina HumanExome BeadChip v1.0. One variant, rs75932628 (p.Arg47His) in *TREM2*, clustered poorly across all ADGC cohorts and was therefore re-genotyped using a TaqMan assay. Data on all samples underwent standard quality control procedures applied to GWAS, including exclusion of variants with call rates <95% and filtering out of samples with call rate <95%. Variants with MAF >0.01 were evaluated for departure from Hardy–Weinberg equilibrium and any variants with $P_{HWE} < 10^{-6}$ were excluded. Population substructure within each of the five subsets (NorthShore, Miami, WashU, CHOP, and ADC7) was examined using principal-component analysis in EIGENSTRAT⁶², and population outliers (>6 s.d. from the mean) were excluded from further analyses; the first three principal components were adjusted for as covariates in association testing. Prior to analysis, we harmonized the alternate and reference alleles over all data sets. See **Supplementary Table 3** for an overview of cohort genotype calling and quality control procedures. All sample genotyping and quality control were performed with blinding to participants' disease status.

Stage 2. Twenty-two variants were successfully designed for replication genotyping on the Agena Bioscience MassARRAY platform. Genotyping was performed at Life and Brain, Bonn, Germany, and the Centre National de Génotypage (CNG), Paris, France. Twenty-one variants were successfully genotyped, with one variant (rs147163004 in *ASTN2*) failing visual cluster plot inspection. An additional nine variants were successfully genotyped using the Agena Bioscience MassARRAY platform or Thermo Fisher TaqMan assays at the CNG, Paris, France, in a subset of the replication samples, $n = 16,850$ (7,755 cases, 9,095 controls).

GERAD/PERADES and ACE quality control. Filters were implemented for sample call rate, excluding samples with >10% missingness and excess autosomal heterozygosity via visual inspection. Variants were filtered on the basis of call rate, excluding variants with >10% missingness, and

Hardy–Weinberg equilibrium, excluding variants with $P_{HWE} < 1 \times 10^{-5}$ in either cases or controls.

IGAP and EADI QC. Variants were genotyped in three different panels, and quality control was performed in each panel separately. Samples with more than three missing genotypes were excluded, as were males heterozygous for X chromosome variants present within the genotyped panels. Variants were excluded on the basis of missingness >5%, Hardy–Weinberg equilibrium (in cases and controls separately) $< 1 \times 10^{-5}$, and differential missingness between cases and controls $< 1 \times 10^{-5}$, for each country cohort. All variants passed quality control. Principal components were determined using previously described methods.

Stage 3. Replication was performed using genotypes from 23 ADGC data sets as described above. The genotyping arrays used have been described in detail before for most data sets, except for the CHAP, NBB, TARCC, and WHICAP data sets. CHAP and WHICAP data sets were genotyped on the Illumina OmniExpress-24 array, while NBB was genotyped on the Illumina 1M platform. TARCC first-wave subjects were genotyped using the Affymetrix 6.0 microarray chip, while subjects in the second wave (172 cases and 74 controls) were genotyped using the Illumina HumanOmniExpress-24 BeadChip. Second-wave TARCC subjects (TARCC2) were genotyped together with 84 cases and 115 controls from second-wave samples ascertained at the University of Miami and Vanderbilt University. All samples used in stage 3 were imputed to the HRC haplotype reference panel^{32,33}, which includes 64,976 haplotypes with 39,235,157 SNPs that allows imputation down to an unprecedented MAF of 0.00008.

Prior to imputation, all genotype data underwent quality control procedures that have been described extensively elsewhere^{2,7}. Imputation was performed on the Michigan Imputation Server (<https://imputationserver.sph.umich.edu/>) running Minimac3^{63,64}. Genotypes from genome-wide, high-density SNP genotyping arrays for 16,175 Alzheimer's disease cases and 17,176 individuals with normal cognition were imputed. Across all samples, 39,235,157 SNPs were imputed, with the actual number of SNPs imputed for each individual varying based on the regional density of array genotypes available. As a subset of these samples had also been genotyped as part of stage 1, we examined the imputation quality for critical variants by comparing imputed genotypes to those directly genotyped by the exome array; overall concordance was >99%, while concordance among alternate allele genotypes (heterozygotes and alternate allele homozygotes) was >88.5% on average ($n = 13,000$ samples). Concordance between stage 3 imputed genotypes and exome chip genotypes for replicated SNPs is reported in **Supplementary Table 6**.

Analysis. Stage 1. We tested association with LOAD using logistic regression modeling for common and low-frequency variants (MAF > 1%) and implementing maximum-likelihood estimation using the score test and seqMeta package for rare variation (MAF $\leq 1\%$). Analyses were conducted globally in the GERAD/PERADES consortium and for each contributing center in the CHARGE and ADGC consortia under two models: (i) an 'unadjusted' model, which included minimal adjustment for possible population stratification, using country of origin and the first three principal components from principal-component analysis, and (ii) an 'adjusted' model, which included covariates for age and sex, as well as country of origin and the first three principal components. Age was defined as the age at onset of clinical symptoms for cases and the age at last interview for controls with normal cognition.

Meta-analysis for common and low-frequency variants was undertaken in METAL using a fixed-effects inverse-variance-weighted meta-analysis. Rare variants were meta-analyzed in the SeqMeta R package. In the SeqMeta pipeline, cohort-level analyses generated score statistics through the function 'prepScores()', which were captured in *.Rdata objects. These *.Rdata objects contain the necessary information to meta-analyze SKAT analyses: the individual SNP scores, MAF, and a covariance matrix for each unit of aggregation. Using the 'singlesnpMeta()' and 'skatOmeta()' functions of SeqMeta, the *.Rdata objects for individual studies were meta-analyzed. The seqMeta coefficients and standard errors can be interpreted as a 'one-step' approximation to the maximum-likelihood estimates. Monomorphic variants in individual studies were not excluded as they contribute to the MAF information. Three independent analysts confirmed the meta-analysis results.

In the GERAD/PERADES consortium, 1,740 participants (888 LOAD cases and 852 controls) did not have age information available and were excluded from the adjusted analyses. Therefore, 16,160 cases and 17,967 controls were included in the unadjusted analyses, and 15,272 cases and 17,115 controls were included in the adjusted analyses. The primary analysis used the unadjusted model given the larger sample size this provided. See **Supplementary Figure 2** for quantile–quantile plots of unadjusted and adjusted analyses.

Stage 2. We tested association with LOAD using the score test and seqMeta package. Analyses were conducted under the two models described above, in the analysis groups indicated in **Supplementary Table 2**. Analyses were undertaken globally in the GERAD/PERADES cohort and by country in the IGAP cohorts, with the EADI1 cohort only including French participants and the ACE cohort including only Spanish participants. Following the format of the IGAP mega meta-analysis², four principal components were included for the EADI1 data set and one was included in the Italian and Swedish IGAP clusters. Meta-analysis was undertaken in the SeqMeta R package.

Stage 3. The association analyses performed followed stage 1 and stage 2 analytical procedures described below, and only variants in *ABI3*, *PLCG2*, and *TREM2* were examined. For gene-based testing, 10 variants in *ABI3*, 35 variants in *PLCG2*, and 13 variants in *TREM2* were examined.

Pathway and gene set enrichment analysis. The eight biological pathway clusters previously identified as enriched for association in the IGAP data set³⁷ were tested for enrichment in this rare variation study (**Supplementary Table 15**) to test whether the biological enrichments observed in common variants also apply to rare variants. Genes were defined without surrounding genomic sequence, as this yielded the most significant excess of enriched pathways in the common variation data set³⁷. Gene-wide SKAT-O *P* values for the variants of interest were combined using Fisher's combined probability test. Given the low degree of LD⁶⁵ between rare variants, our primary analyses did not control for LD between pathway genes. However, as a secondary analysis, the *APOE* region was removed and, for each pair of pathway genes within 1 Mb of each other, the gene with the more significant SKAT-O *P* value was removed. This highly conservative procedure removes any potential bias in the enrichment test both from LD between the genes and dropping less significant genes from the analysis.

We also performed pathway analyses on the rare variant data presented using all 9,816 pathways used previously. The top pathways are related to lipoprotein particles, cholesterol efflux, B cell differentiation, and immune response, and they closely parallel the common variant results (**Supplementary Table 16**).

Protein interaction analysis. Previous analysis of normal brain co-expression networks identified four gene modules that were enriched for common variants associated with Alzheimer's disease risk in the IGAP GWAS. Each of these four modules was also found to be enriched for immune-related genes. The 151 genes present in two or more of these four modules were particularly strongly enriched for IGAP GWAS association. This set of 151 co-expressed genes thus contains genes of relevance to Alzheimer's disease etiology. To identify these genes and clarify biological relationships between them for future study, protein interaction analysis was performed. First, a list of high-confidence (confidence score > 0.7) human protein–protein interactions was downloaded from the latest version (v10) of the STRING database (<http://string-db.org/>). Then, protein interaction networks were generated as follows:

1. Choose a gene to start the network (the 'seed' gene).
2. For each remaining gene in the set of 151 genes, add it to the network if its corresponding protein shows a high-confidence protein interaction with a protein corresponding to any gene already in the network.
3. Repeat step 2 until no more genes can be added.
4. Note the number of genes in the network.
5. Repeat, choosing each of the 151 genes in turn as the seed gene.

The largest protein interaction network resulting from this procedure resulted in a network of 56 genes connected by high-confidence protein interactions. To test whether this network was larger than expected by chance, given the total number of protein–protein interactions for each gene, random sets of 151 genes were generated, with each gene chosen to have the same total number

of protein–protein interactions as the corresponding gene in the actual data. Protein networks were generated for each gene as described above, and the size of the largest such network was compared to the observed 56-gene network. 1,000 random gene sets were generated, and none of them yielded a protein interaction network as large as 56 genes. Note that the procedure for generating the protein interaction network relies only on protein interaction data and is agnostic to the strength of GWAS or rare variant associations for each gene. Thus, the strength of genetic association in the set of 56 network genes can be tested relative to that in the original set of 151 genes without bias.

Gene set enrichment analysis of the protein network. The set of 56 network genes was tested for association enrichment in the IGAP GWAS using ALIGATOR⁶⁶, as was done in the original pathway analysis, using a range of *P*-value thresholds for defining significant SNPs (and thus the genes containing those SNPs). The same analysis was also performed on the 95 genes in the module overlap but not the protein interaction network (**Supplementary Table 17**). It can be seen that the 56 network genes account for most of the enrichment signal observed in the set of 151 module overlap genes.

The set of 56 network genes, the set of 151 module overlap genes, and the set of 95 genes in the module overlap but not the network were tested for enrichment of association signal in variants with MAF <1% using the gene set enrichment method described above. Both the set of 151 genes ($P = 1.17 \times 10^{-6}$) and the subset of 56 genes ($P = 1.08 \times 10^{-7}$) show highly significant enrichment for association in the rare variants with MAF <1%. It can be seen that the 56 network genes account for most of the enrichment signal observed in the set of 151 module overlap genes (**Supplementary Table 17**). Again, the subset of 56 genes accounts for most of the enrichment signal observed in the set of 151 genes, as the remaining 95 genes have only nominally significant enrichment ($P = 0.043$). Both the set of 151 genes ($P = 5.15 \times 10^{-5}$) and the subset of 56 genes ($P = 2.98 \times 10^{-7}$) show significant enrichment under a conservative analysis excluding the *APOE* region and correcting for possible LD between the genes (**Supplementary Table 17**). Thus, the rare variants show convincing replication of the biological signal observed in the common variant GWAS, and, furthermore, the protein network analysis has refined this signal to a set of 56 interacting genes. Given that *TREM2* has a highly significant gene-wide *P* value ($P = 1.01 \times 10^{-13}$) among variants with MAF <1%, enrichment analyses were run omitting it. Both the set of 151 genes ($P = 2.78 \times 10^{-3}$) and the subset of 56 genes ($P = 0.010$) (**Supplementary Table 18**) still showed significant enrichment of signal, suggesting that the contribution of rare variants to disease susceptibility in these networks is not restricted to *TREM2*. Biological follow-up of genetic results is labor intensive and expensive. It is therefore important to concentrate such work on the genes that are most important to Alzheimer's disease susceptibility. Thus, the rationale for reducing the gene set is that it defines a network of genes that are not only related through co-expression and protein interaction, but also show enrichment for genetic association signal. These genes are therefore strong candidates for future biological study.

Gene expression. We examined mRNA expression of the newly associated genes *PLCG2* and *ABI3* in post-mortem brain tissue from neuropathologically characterized individuals (508 persons): these genes are expressed at low levels in the dorsolateral prefrontal cortex of subjects from two studies of aging with prospective autopsy (ranked 12,965 out of 13,484 expressed genes)⁶⁷. However, *ABI3* and *PLCG2* were more highly expressed in purified microglia/macrophages from the cortex of 11 subjects from these cohorts (ranked 1,740 and 2,600, respectively, out of the 11,500 expressed genes) (P.L.D.J., D.A.B. and C.C.W., unpublished data). These findings are consistent with the high levels of expression of both *PLCG2* and *ABI3* in peripheral monocytes, spleen, and whole blood reported by the ROADmap project and in microglia as reported by Zhang *et al.*³⁸. From the same brain tissue, we examined methylation ($n = 714$)⁶⁸ and H3K9ac acetylation ($n = 676$) data and found differential methylation at four CpG sites and lower acetylation at two H3K9ac sites adjacent to *PLCG2* and *ABI3* in relation to increased global neuritic plaque and tangle burden (false discovery rate (FDR) < 0.05). Similarly, high *TREM2* expression has been shown to correlate with increasing neuritic plaque burden⁶⁹.

AMP-AD gene expression data. RNA sequencing was used to measure gene expression levels in the temporal cortex of 80 subjects with pathologically

confirmed Alzheimer's disease and 76 controls without any neurodegenerative pathologies obtained from the Mayo Clinic Brain Bank and the Banner Sun Health Institute. The human RNA sequencing data are deposited in the Accelerating Medicines Partnership-AD (AMP-AD) knowledge portal housed in Synapse (<https://www.synapse.org/#!Synapse:syn2580853/wiki/66722>). After quality control, our post-mortem human cohort had 80 subjects with pathologically confirmed Alzheimer's disease and 76 controls without any neurodegenerative pathologies. Assuming two samples of 100 per group, two-sample *t* test, same s.d., we would have 80% power to detect effect sizes of 0.40, 0.49, and 0.59 at $P < 0.05$, 0.01, and 0.001, respectively, where effect size is the difference in means between two groups divided by the within-group s.d. The human RNA sequencing data overview, quality control, and analytic methods are available at the following Synapse pages, respectively: syn3163039, syn6126114, and syn6090802. Multivariable linear regression was used to test for association of gene expression levels with Alzheimer's disease diagnosis using two different models. In the simple model, we adjust for age at death, sex, RNA integrity number (RIN), tissue source, and RNA-seq flow cell. In the comprehensive model, we adjust for all these covariates, and brain cell type markers for five cell-type-specific genes (*CD68* (microglia), *CD34* (endothelial), *OLIG2* (oligodendroglia), *GFAP* (astrocyte), *ENO2* (neuron)) to account for cell number changes that occur with Alzheimer's disease neuropathology. *TREM2*, *PLCG2*, and *ABI3* expression is significantly higher in Alzheimer's disease temporal cortex before correcting for cell type (simple model), but this significance is abolished after adjusting for cell-type-specific gene counts (comprehensive model). This suggests that these elevations are likely a consequence of changes in cell types that occur with Alzheimer's disease, most likely microgliosis, given that *TREM2*, *PLCG2*, and *ABI3* are microglia-enriched genes¹⁵ (Supplementary Fig. 12 and Supplementary Table 19).

Data availability. Summary statistics for the 43 genetic associations identified are provided in Supplementary Table 6.

Stage 1 data (individual level) for the GERAD exome chip cohort can be accessed by applying directly to Cardiff University. Stage 1 ADGC data are

deposited in a NIAGADS- and NIA/NIH-sanctioned qualified-access data repository. Stage 1 CHARGE data are accessible by applying to dbGaP for all US cohorts and to Erasmus University for Rotterdam data. AGES primary data are not available owing to Icelandic laws. Stage 2 and stage 3 primary data are available upon request.

A detailed description of the Mayo Clinic RNA-seq data is available to all qualified investigators through the Accelerating Medicines Partnership in Alzheimer's Disease (AMP-AD) knowledge portal that is hosted in the Synapse software platform from Sage Bionetworks under Synapse IDs syn3157182 and syn3435792 (mouse data) and syn3163039 (human data).

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