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Rare coding variation in *PLCG2*, *ABI3* and *TREM2* associate with Alzheimer's disease.

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Introduction (150 words) = 158

We identified rare coding variants associated with Alzheimer's disease (AD) in a 3-stage case-control study of 85,133 subjects. In stage 1, 34,174 samples were genotyped using a whole-exome microarray. In stage 2, we tested associated variants ($P<1x10^{-4}$) in 35,962 independent samples using *de novo* genotyping and imputed genotypes. In stage 3, an additional 14,997 samples were used to test the most significant stage 2 associations ($P<5x10^{-8}$) using imputed genotypes. We observed 3 novel genome-wide significant (GWS) AD associated non-synonymous variants; a protective variant in *PLCG2* (rs72824905/p.P522R, $P=5.38x10^{-10}$, OR=0.68, $MAF_{cases}=0.0059$, $MAF_{controls}=0.0093$), a risk variant in *ABI3* (rs616338/p.S209F, $P=4.56x10^{-10}$, OR=1.43, $MAF_{cases}=0.011$, $MAF_{controls}=0.008$), and a novel GWS variant in *TREM2* (rs143332484/p.R62H, $P=1.55x10^{-14}$, OR=1.67, $MAF_{cases}=0.0143$, $MAF_{controls}=0.0089$), a known AD susceptibility gene. These protein-coding changes are in genes highly expressed in microglia and highlight an immune-related protein-protein interaction network enriched for previously identified AD risk genes. These genetic findings provide additional evidence that the microglia-mediated innate immune response contributes directly to AD development.

Text (1500 words) = 1624

Late-onset AD (LOAD) has a significant genetic component (h^2=58-79%[1]). Nearly 30 LOAD susceptibility loci[2–12] are known, and risk is significantly polygenic[13]. 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 AD[9–11,18–24]. Our approach to rare-variant discovery is to genotype a large sample with micro-arrays 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 3-stage design (Supplementary Figure 1) using subjects from the International Genomics of Alzheimer's Project (IGAP)(Table 1, Supplementary Tables 1 & 2). In stage 1, 16,097 LOAD cases and 18,077 cognitively normal elderly controls were genotyped 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 (minor allele frequency (MAF)≥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 METAL[30]. Rare and low frequency variants were analyzed using the score test and data combined with SeqMeta[31] (Supplementary Figure 2).

We reviewed cluster plots for variants showing association ($P<1\text{x}10^{-4}$) and identified 43 candidate variants (Supplementary Table 4) exclusive of known risk loci (Supplementary Table 5). Stage 2 tested these for association in 14,041 LOAD cases and 21,921 controls, using *de novo* and imputation derived genotypes (Online Methods). We carried forward single nucleotide variants (SNVs) with GWS 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, Supplementary Table 6).

We identified four rare coding variants with GWS association signals with LOAD ($P<5x10^{-8}$)(Table 2, Supplementary Tables 7 & 8). The first is a missense variant p.P522R ($P=5.38x10^{-10}$, OR=0.68) in *Phospholipase C Gamma 2* (*PLCG2*)(Table 2, Figure 1a, Supplementary Table 9, Supplementary Figure 3). 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 (p.P522) is conserved across several species (Supplementary Figure 4). Gene-wide analysis showed nominal evidence for association at $P=1.52x10^{-4}$ (Supplementary Tables 10 & 11) and we found no other independent association at this gene (Supplementary Figure 5).

The second novel association is a missense change p.S209F ($P=4.56x10^{-10}$, OR=1.43) in *B3 domain-containing transcription factor ABI3* (*ABI3*). The p.F209 variant shows consistent evidence for increasing LOAD risk across all stages, with a MAF of 0.011 in cases and 0.008 in controls (Table 2, Figure 1b, Supplementary Table 12, Supplementary Figure 6). The reference allele is conserved across multiple species (Supplementary Figure 7). Gene-wide analysis showed nominal evidence of association ($P=5.22x10^{-5}$)(Supplementary Tables 10 & 11). The *B4GALNT2* gene, adjacent to *ABI3,* contained an independent suggestive association (Supplementary Figure 8), but this failed to replicate in subsequent stages (P_{combined}=1.68x10^{-4})(Supplementary Table 7).

Following reports of suggestive association with LOAD[34,35], we report the first evidence for GWS association at *TREM2* coding variant p.R62H (P=1.55x10^{-14}, OR=1.67), with a MAF of 0.0143 in cases and 0.0089 in controls (Table 2, Figure 1c, Supplementary Table 13, Supplementary Figures 9 & 10). We also observed evidence for the previously reported[9,11] *TREM2* rare variant p.R47H (Table 2). These variants are not in linkage disequilibrium (Supplementary Table 14) and conditional analyses confirmed that p.R62H and p.R47H are independent risk variants (Supplementary Figure 11). Gene-wide analysis of *TREM2* showed a GWS association (P_{SKAT}=1.42x10^{-15})(Supplementary Tables 10 & 11). Removal of p.R47H and p.R62H variants from the analysis diminished the gene-wide association but the signal remains interesting ($P_{SKAT\text{-}O}$=6.3x10^{-3}, P_{Burden}=4.1x10^{-3}). No single SNV was responsible for the remaining gene-wide association (Supplementary Table 13, Supplementary Figure 11) suggesting that there are additional *TREM2* risk variants in *TREM2*. We previously reported a common variant LOAD association near *TREM2*, in a GWAS of cerebrospinal fluid tau and P-tau[36]. We also observed a different suggestive common variant signal in another LOAD case-control study (P=6.3x10^{-7})[2].

We previously identified 8 gene pathway clusters significantly enriched in AD-associated common variants[36]. 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 AD-associated pathway clusters (Online Methods, 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=8.64x10^{-3}), cholesterol transport (P=3.84x10^{-5}), hemostasis (P=2.10x10^{-3}), Clathrin/AP2 adaptor complex (P=9.20x10^{-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 analyzed[37](Supplementary Table 16).

Previous analysis of normal brain co-expression networks identified 4 gene modules that are enriched for common variants associated with LOAD risk[2,3711]. These 4 modules are enriched for immune response genes. We identified 151 genes present in 2 or more of these 4 modules and these showed a strong enrichment for LOAD-associated common variants (P=4.0x10^{-6})[36] and for rare variants described here (MAF<1%)(Supplementary Table 15, P=1.17x10^{-6}). We then used a set of high-quality protein-protein interactions[37] to construct, from these 151 genes, an interaction network containing 56 genes, including *PLCG2*, *ABI3* and *TREM2* (Figure 2)(Online Methods). This subset is strongly enriched for association signals from both the previous common variant analysis (P=5.0x10^{-6}, Supplementary Table 17) and this rare variant gene-set analysis (P=1.08x10^{-7}, Supplementary Table 15). The remaining 95 genes only have nominally-significant enrichment for either common or rare variants (Supplementary Tables 15 & 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 (Figure 2b, Supplementary Figure 12)[38]. Other known LOAD loci with the same expression pattern include *SORL1,* the *MS4A* gene cluster, and *HLA-DRB1*. *PLCG2*, *ABI3*, and *TREM2* are up-regulated in LOAD human cortex and in two APP mouse models. However, when corrected for levels of other microglia genes, these changes in expression appear to be related to microgliosis (Supplementary Tables 19 & 20).

PLCG2 (Supplementary Figure 13) encodes a transmembrane signaling enzyme (PLCɣ2) that hydrolyses the membrane phospholipid PIP2 (1-phosphatidyl-1D-myo-inositol 4,5-bisphosphate) to secondary messengers IP3 (myo-inositol 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 Ca^{2+}. 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/Ca+2 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 signalling[39].

Functional annotation (Supplementary Table 21) suggests *ABI3* (Supplementary Figure 14) plays a role in the innate immune response via interferon-mediated signaling[40]. *ABI3* is co-expressed with *INPP5D* (P=$2.2x10^{-10}$), a gene previously implicated in LOAD risk[2]. ABI3 plays a significant role in actin cytoskeleton organization through participation in the WAVE2 complex[41], a complex that regulates multiple pathways leading to T-cell activation[42].

TREM2 encodes a transmembrane receptor present in the plasma membrane of brain microglia (Supplementary Figure 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 PLCɣ2 activity[43]. In microglia, TREM2-DAP12 induces an M2-like activation[44] and participates in recognition of membrane debris and amyloid deposits resulting in microglial activation and proliferation[45–47]. When *TREM2* knockout (KO) or *TREM2* heterozygous KO 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 the loss or decrease in TREM2 function[47].

The 56-gene interaction network identified here is enriched in immune response genes and includes *TREM2*, *PLCG2*, *ABI3*, *SPI1*, *INPP5D*, *CSF1R*, *SYK* and *TYROBP* (Figure 2). *SPI1* is a central transcription factor in microglial activation state that has a significant gene-wide association with AD[5] and is in the proximity of GWS signals identified by IGAP[2]. Loss-of function mutations in *CSF1R* cause hereditary diffuse leukoencephalopathy with spheroids, a white matter disease related to microglial dysfunction[48]. Activated microglial cells surround plaques[49,50], a finding consistently observed in AD brain and AD transgenic mouse models[51]. In AD mouse model brain, synaptic pruning associates with activated microglial signalling[52]. Pharmacological targeting of CSF1R inhibits microglial proliferation and shifts the microglial inflammatory profile to an anti-inflammatory phenotype in murine models[53]. SYK regulates Aβ production and tau hyperphosphorylation[54], is affected by the INPP5D/CD2AP complex[55] encoded by two LOAD associated genes[2], and mediates phosphorylation of PLCG2[56]. Notably, the anti-hypertensive drug Nilvadipine, currently in a phase III AD clinical trial, targets *SYK* as well as *TYROBP,* a hub gene in an AD-related brain expression network[38],that encodes the TREM2 complex protein DAP12.

We identified three rare coding variants in *PLCG2, ABI3* and *TREM2* with GWS 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, PLCɣG2, as an enzyme, represents the first classically drug-able target to emerge from LOAD genetic studies. The variants described here account for a small portion of the ‘missing heritability of AD’. The remaining heritability may be due to a large number of common variants of small effect size. For rare variants, there may be additional exonic sites with lower MAF or effect size, and/or intronic and intergenic sites. Complete resolution of AD heritability will be facilitated by larger sample sizes and more comprehensive sequence data.

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

A detailed description of the Mayo Clinic RNAseq 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 (Synapse IDs: syn3157182 and syn3435792 (mouse data), and syn3163039 (human data)).

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Figure Legends

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

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 AD risk. Colours of edges refer to the type of evidence linking the corresponding proteins: red=gene fusion, dark blue = co-occurrence, black = co-expression, magenta = experiments, cyan=databases, light green = text mining, mauve = homology. *TREM2*, *PLCG2* and *ABI3* highlighted by red circles, *SYK*, *CSF1R* and *TYROBP* highlighted by blue circles, and *INPP5D*, *SPI1* and *CD33* identified as common variant risk loci[2,5–7], highlighted by black circles.

Table 1. Summary of the consortium data sets used for stages 1, 2 and stage 3. 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)(Supplement 1).

	Consortium	**N Controls**	**N Cases**	**N Total**
Stage 1	GERAD/PERADES	2974	6000	8974
	ADGC	7002	8706	15708
	CHARGE	8101	1391	9492
Total		18077	16097	**34174**
Stage 2	GERAD/PERADES genotype	5049	4049	9098
	CHARGE-genotype	1839	1434	3273
	CHARGE-*in silico*	3246	722	3968
	EADI-genotype	11787	7836	19623
Total		21921	14041	**35962**
Stage 3	ADGC-*in silico*	8345	6652	**14997**
Stage 1 + 2 + 3				
Total		**48402**	**37022**	**85133**

Table 2. Summary of stage 1, 2, 3 and combined meta-analysis results for SNVs at $P<5x10^{-8}$. Data includes p-values, 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.

SNV	rs75932628	rs143332484	rs72824905	rs616338
Chr	6	6	16	17
Position	41129252	41129207	81942028	47297297
Protein Variation	R47H	R62H	P522R	S209F
Gene	*TREM2*	*TREM2*	*PLCG2*	*ABI3*
Effect Allele	T	T	G	T
Stage 1				
P	3.02E-12	3.48E-09	1.19E-05	2.16E-05
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
N	30018	33786	33786	33786
Stage 2				
P	4.38E-08	3.66E-07	1.35E-04	8.37E-05
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
N	35831	3968	35831	35831
Stage 3				
P	1.23E-06	2.45E-03	2.48E-02	1.75E-02
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
N	14884	15288	15288	14876
Stage1, 2 and 3 Meta-Analysis				
P	5.38E-24	1.55E-14	5.38E-10	4.56E-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
N	80733	53042	84905	84493

Note: 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).

Online Methods

Genotyping and Quality Control

Stage 1

GERAD/PERADES: Genotyping was performed at Life and Brain, Bonn, Germany, with the 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 zCall[1] was used for genotype calling. Quality control (QC) filters were implemented for sample call rate excluding samples with >1% missingness, excess autosomal heterozygosity excluding outliers based on <1% and >1% minor allele frequency (MAF) separately, gender discordance, relatedness excluding one of each pair related with IBD ≥ 0.125 (the level expected for first cousins), and population outliers (i.e. non European ancestry). Variants were filtered based on call rate excluding variants with >1% missingness, genotype cluster separation excluding variants with a separation score < 0.4 and Hardy-Weinberg equilibrium (HWE) excluding variants with $P_{\mathrm{HWE}} < 1\text{x}10^{-4}$. Ten principal components (PCs) were extracted using EIGENSTRAT, including the first three PCs as covariates had the maximum impact on the genomic control inflation factor, λ[2]. After QC 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 Houston[3]. Quality control (QC) procedures for the genotype data were performed both centrally at UT Houston and at each study. The central QC procedures have been described previously[3]. Minimum QC included: 1) Concordance checking with GWAS data and removal of problematic samples, 2) Removal of individuals with low genotype completion rate (<90%), 3) Removal of variants with low genotype call rate (<95%), 4) Removal of individuals with sex-mismatches, 5) Removal of one individual from duplicate pairs, 6) Removal of first-degree relatives based on genetically calculated relatedness (IBS > 0.45), with cases retained over controls, 7) Removal of variants not called in over 5% of the individuals and those that deviated significantly form the expected Hardy-Weinberg Equilibrium proportions ($P<1\text{x}10^{-6}$).

ADGC: Genotyping was performed in subsets at four centers: NorthShore, Miami, WashU, and CHOP ("CHOP" and "ADC7" datasets) on the Illumina HumanExome BeadChip v1.0. One variant rs75932628 (p.R47H) 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 genome-wide association studies (GWAS), including excluding variants with call rates <95%, and then filtering samples with call rate <95%. Variants with MAF>0.01 were evaluated for departure from HWE and any variants for

$P_{\mathrm{HWE}}<10^{-6}$ were excluded. Population substructure within each of the five subsets (NorthShore, Miami, WashU, CHOP, and ADC7) was examined using PC analysis in EIGENSTRAT[4], and population outliers (>6 SD) were excluded from further analyses; the first three PCs were adjusted for as covariates in association testing. Prior to analysis we harmonized the alternate and reference alleles over all datasets. See Supplementary Table 3 for an overview of cohort genotype calling and quality control procedures. All sample genotyping and quality control was performed blind to participant's disease status.

Stage 2

Twenty-two variants 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 FisherTaqMan® assay 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 QC: Filters were implemented for sample call rate, excluding samples with >10% missingness, and excess autosomal heterozygosity via visual inspection. Variants were filtered based on call rate excluding variants with >10% missingness and HWE excluding variants with $P_{\mathrm{HWE}}<1\mathrm{x}10^{-5}$ in either cases or controls.

IGAP and EADI QC: Variants were genotyped in 3 different panels and QC was performed in each panel separately. Samples with more than 3 missing genotypes were excluded, as were males heterozygous for X-Chromosome variants present within the genotyped panels. Variants were excluded based on missingness >5%, HWE (in cases and controls separately) $<1\mathrm{x}10^{-5}$, and differential missingness between cases and controls $<1\mathrm{x}10^{-5}$, for each Country cohort. All variants passed quality control. PCs were determined using previously described methods[19].

Stage 3

Replication was performed using genotypes from 23 ADGC datasets as described above. Genotyping arrays used have been described in detail before for most datasets, except for the CHAP, NBB, TARCC, and WHICAP datasets. CHAP and WHICAP datasets 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[5,6], which includes 64,976 haplotypes with 39,235,157 SNPs that allows imputation down to an unprecedented MAF=0.00008.

Prior to imputation, all genotype data underwent QC procedures that have been described extensively elsewhere[7,8]. Imputation was performed on the Michigan Imputation Server (https://imputationserver.sph.umich.edu/) running MiniMac3[9,10].Genotypes from genome-wide, high-density SNP genotyping arrays for 16,175 AD cases and 17,176 cognitive-normal individuals 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 modelling for common and low frequency variants (MAF>1%) and implementing maximum likelihood estimation using the score test and 'seqMeta' package for rare variation (MAF≤1%). Analyses were conducted globally in the GERAD/PERADES consortium, and for each contributing centre in the CHARGE and ADGC consortia under two models (1) an 'unadjusted' model, which included minimal adjustment for possible population stratification, using Country of origin and the first three principal components from PCA, and (2) 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 cognitively normal controls.

Meta-analysis for common and low frequency variants were undertaken in METAL using a fixed-effects inverse variance-weighted meta-analysis. Rare variants were meta-analysed 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-analyse 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-analysed. 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 minor allele frequency 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 utilized the unadjusted model given the larger sample size this provided. See Supplementary Figure 2 for QQ 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-analysis[7], four PCs were included for the EADI1 dataset, and one in the Italian and Swedish IGAP clusters. Meta-analysis was undertaken in the SeqMeta R package.

Stage 3

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 in *PLCG2*, and 13 in *TREM2* were examined.

Pathway/Gene-set Enrichment Analysis

The eight biological pathway clusters previously identified as enriched for association in the IGAP dataset[11] were tested for enrichment in this rare variation study (Supplementary Table 15) in order 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 dataset[11]. Gene-wide SKAT-O *P*-values for the variants of interest were combined using the Fisher's combined probability test. Given the low degree of LD[12] 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 1Mb 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 also from dropping less significant genes from the analysis.

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, and closely parallel the common variant results (Supplementary Table 16).

Protein interaction Analysis

Previous analysis of normal brain co-expression networks identified 4 gene modules that were enriched for common variants associated with AD risk in the IGAP GWAS. Each of these 4 modules was also found to be enriched for immune-related genes. The 151 genes present in 2 or more of these 4 modules were particularly strongly enriched for IGAP GWAS association[41]. This set of 151 co-expressed genes thus contains genes of relevance to AD aetiology. 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 compared to the observed 56-gene network. 1000 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 association 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 ALIGATOR[13], 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 in section 11. Both the set of 151 genes (*P*=$1.17\text{x}10^{-6}$) and the subset of 56 genes (*P* =$1.08\text{x}10^{-7}$) 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*=$5.15\text{x}10^{-5}$) and the subset of 56 genes (*P*=$2.98\text{x}10^{-7}$) 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*=$1.01\text{x}10^{-13}$) among variants with MAF<1%, enrichment analyses were run omitting it. Both the set of 151 genes (*P*=$2.78\text{x}10^{-3}$) 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 labour-intensive and expensive. It is therefore important to concentrate such work on the genes that are most important to AD 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 novel genes *PLCG2* and *ABI3* in neuropathologically characterized brain post-mortem tissue (508 persons): they are expressed at low levels in the dorsolateral prefrontal cortex of subjects from two studies of aging with prospective autopsy (ranked 12,965th out of 13,484 expressed genes)[14]. However, *ABI3* and *PLCG2* were more highly expressed in purified microglia/macrophage from the cortex of 11 subjects from these cohorts (1740th and 2600th respectively out of the 11,500 expressed genes)(*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*[15]. From the same brain tissue, we examined methylation (n=714)[16] 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 (FDR < 0.05). Similarly, high TREM2 expression has been shown to correlate with increasing neuritic plaque burden[17].

AMP-AD Gene Expression Data: RNA sequencing was used to measure gene expression levels in the temporal cortex of 80 subjects with pathologically confirmed AD 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 is deposited in the Accelerating Medicines Partnership-AD (AMP-AD) knowledge portal housed in Synapse (https://www.synapse.org/#!Synapse:syn2580853/wiki/66722). After QC, our postmortem human cohort has 80 subjects with pathologically confirmed AD and 76 controls without any neurodegenerative pathologies. Assuming two samples of 100 per group, two-sample t-test, same standard deviation, we will 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 standard deviation. The human RNA sequencing data overview, QC and analytic methods are available at the following Synapse pages, respectively: syn3163039, syn6126114, syn6090802. Multivariable linear regression was used to test for association of gene expression levels with AD diagnosis (Dx) using two different models: In the Simple model, we adjust for age at death, sex, RNA integrity number (RIN), tissue source, and RNAseq flowcell. In the Comprehensive model, we adjust for all these covariates, and brain cell type markers for five cell-specific genes (*CD68* (microglia), *CD34* (endothelial), *OLIG2* (oligodendroglia), *GFAP* (astrocyte), *ENO2* (neuron)) to account for cell number changes that occur with AD neuropathology. *TREM2*, *PLCG2* and *ABI3* are significantly higher in AD temporal cortex prior to correcting for cell types (Simple model), but this significance is abolished after adjusting for cell-specific gene counts (Comprehensive model). This suggests that these elevations are likely a consequence of changes in cell types that occur with AD, most likely microgliosis given that *TREM2*, *PLCG2* and *ABI3* are microglia-enriched genes[15] (Supplementary Table 19, Supplementary Figure 12).

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

1. Sample Cohorts

GERAD/PERADES:

Stage 1: Cases and controls were recruited by the Medical Research Council (MRC) Genetic Resource for LOAD (Cardiff University; Institute of Psychiatry, London; University of Cambridge); the Alzheimer's Research UK (ARUK) Collaboration (University of Nottingham; University of Manchester; University of Southampton; University of Bristol; Queen's University Belfast); MRC PRION Unit, University College London, UK; University of Oxford, UK; Washington University, St Louis, United States; Competence Network of Dementia (CND) and Department of Psychiatry, University of Bonn, Germany; University of Halle, Germany; University Hospital, Saarland, Germany; University Medical Centre, Hamburg, Germany; University Dulsburg-Essen, Germany; Universidad Autônoma de Madrid, Spain; Universidad Autônoma de Barcelona, Spain; University of Cantabria and IDIVAL, Santander, Spain; University of Navarra, Pamplona, Spain; Santa Lucia Foundation, Rome, Italy; Aristotle University, Thessaloniki, Greece; CIBERNED, Madrid, Spain; CSIC-UAM, Madrid, Spain; Hospital Universitario Central Asturias, Oviedo, Spain.

Stage 2: Cases and controls were recruited by the MRC Genetic Resource for LOAD; MRC PRION Unit, University College London, UK; Santa Lucia Foundation, Rome, Italy; CIBERNED, Madrid, Spain; CSIC-UAM, Madrid, Spain; Hospital Universitario Central Asturias, Oviedo, Spain; ARUK collaboration; Kings College London, London, UK; University of Perugia, Perugia, Italy; Catholic University of Rome, Rome, Italy; Regional Neurogenetic Centre (CRN), ASP Catanzaro, Lamezia Terme, Italy; Memory clinic and Research Center, Institut Català de Neurociències Aplicades, Barcelona, Spain; University of Milan, Milan, Italy; University of Bonn, Bonn, Germany; Queens University, Belfast, Northern Ireland; University of Duisburg-Essen, Germany; Klinikum der Universität München, Munich, Germany and German Center for Neurodegenerative Diseases (DZNE, Munich), Munich, Germany; University of Bristol, Bristol, UK; Cardiff University, Cardiff, UK; University of Southampton, Southampton UK; University of Nottingham, Nottingham, UK; Mayo Clinic, Jacksonville, Florida, USA.

All late-onset Alzheimer's disease (LOAD) cases were aged over 60 and met criteria for either probable (NINCDS-ADRDA, DSM-IV) or definite (CERAD) AD. All elderly controls were screened for dementia using the Mini Mental State Examination (MMSE) or ADAS-cog, were determined to be free from dementia at neuropathological examination or had a Braak score of 2.5 or lower. Control samples were chosen to match case samples for age, gender, ethnicity and Country of origin. Informed consent was obtained for all research participants, and the relevant independent ethical committees approved study protocols.

CHARGE:

Stage 1:

Age Gene/Environment Susceptibility – Reykjavik study (AGES): The AGES study has been described previously[1]. The study was initiated in 2002 to examine genetic susceptibility and gene/environment interactions related to disease and disability in old age. The AGES study is comprised of 5764 individuals drawn from the Reykjavik Study, a population-based cohort comprised of individuals born between 1907 and 1935 and followed since 1967 by the Icelandic Heart Association. 3219 individuals chosen randomly among 5307 AGES individuals with 'mid-life' data available from the Reykjavik Study were genotyped on a genome-wide association (GWA) array. 2983 were further genotyped for the EC. Age was coded in years where the age of cases was the age at the visit where LOAD was first diagnosed and the age of controls was the age at the last visit individual was still free of LOAD pathology.

Diagnosis of LOAD in AGES – The Folstein MMSE and the Digit Symbol Substitution Test (DSST) were administered to all participants and persons who scored below a pre-determined threshold on these tests (≤23 on the MMSE or ≤17 on the DSST) were administered a second, diagnostic test battery. Based on performance on the Trails B and the Rey Auditory Verbal Learning test (RAVLT), a subset of these individuals with a RAVLT score ≤18 or Trails B score ≥8 (ratio of time taken for Trails B/Trails A corrected for the number correct) went on to a third step, which included a neurological examination and a structured informant interview about medical history and social, cognitive, and daily functioning. MRI was acquired as a part of the core study protocol. A panel that included a geriatrician, neurologist, neuropsychologist, and neuroradiologist reached a consensus diagnosis of dementia based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) guidelines[2]. There were 319 cases of dementia diagnosed in the first 5764 AGES participants and of these 123 also had genotyping and brain MRI. International diagnostic guidelines, including the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer Disease and Related Disorders Association (NINCDS- ADRDA) criteria for probable and possible Alzheimer Disease and the Alzheimer's Disease Diagnosis and Treatment Center's (ADDTC) State of California criteria for probable and possible vascular dementia (VaD) with or without AD, were followed. The AGES study identified 3 subtypes: possible/probable AD without VaD (included in analysis), mixed AD (cases that met criteria for both AD and VaD, included in analysis), and, possible/probable VaD or other dementia without AD (excluded from analysis). 3316 individuals participated in the follow-up visit (AGES-2) and were examined using the same protocol as used during the AGES-1 visit for diagnosis of dementia and AD. Controls were those still free of dementia and mild cognitive impairment at last assessment. Study approval – The AGES study was approved by the Icelandic National Bioethics Committee (VSN 00-063), and by the National Institute on Aging Intramural Institutional Review Board. Informed consent was obtained from all participants.

Cardiovascular Health Study (CHS): The CHS is a population-based cohort study of risk factors for coronary heart disease and stroke in adults ≥65 years conducted across four field centers[3]. The original predominantly Caucasian cohort of 5201 persons was recruited in 1989-1990 from random samples of the Medicare eligibility lists; subsequently, an additional predominantly African-American cohort of 687 persons was enrolled for a total sample of 5888. Blood samples were drawn on all participants at their baseline examination; DNA was extracted from blood from participants who donated DNA samples for storage and provided informed consent for participation in DNA studies (~95% of all CHS participants). Although CHS is a population-based sample we empirically estimated cryptic relatedness based on genotypes of a LD-pruned set of common EC variants. For this we used PLINK v1.07[4] (http://pngu.mgh.harvard.edu/purcell/plink/). We identified clusters of individuals with 'PI_HAT' > 0.15 or 'Z0' < 0.4 ('PI_HAT' is the empirical estimate of twice the kinship coefficient and Z0 is the empirical estimate of the probability of sharing zero alleles identical by decent). Among these clusters, we kept only one individual for analysis, giving preference to cases over controls. Covariates in the models were age in years, sex, and field center. Age was the age at LOAD diagnosis for cases or the age at last follow-up evaluation for controls.

Diagnosis of LOAD in CHS – The AD sample for CHS included all prevalent cases identified in 1992 and incident events identified between 1992 and December 2006. Briefly, persons were examined annually from enrolment to 1999, and the examination included a 30 minutes screening cognitive battery[5]. In 1992-94 and again, in 1997-99, participants were invited to undergo brain MRI and detailed cognitive and neurological assessment as part of the CHS Cognition Study[5]. Persons with prevalent dementia were identified, and all others were followed until 1999 for the development of incident dementia and AD. Since then, CHS participants at the Maryland and Pennsylvania centers have remained under ongoing dementia surveillance[6]. Beginning in 1988/89, all participants completed the Modified Mini-Mental State Examination (3MSE) and the DSST at their annual visits, and the Benton Visual Retention Test (BVRT) from 1994 to 1998. The Telephone Interview for Cognitive Status (TICS) was used when participants did not come to the clinic. Further information on cognition was obtained from proxies using the Informant Questionnaire for Cognitive Decline in the Elderly (IQCODE), and the dementia questionnaire (DQ). Symptoms of depression were measured with the modified version of the Center for Epidemiology Studies Depression Scale (CES-D). In 1991-94, 3608 participants had an MRI of the brain and this was repeated in 1997-98. The CHS staff also obtained information from participants and next-of-kin regarding vision and hearing, the circumstances of the illness, history of dementia, functional status, pharmaceutical drug use, and alcohol consumption. Data on instrumental activities of daily living (IADL), and activities of daily living (ADL) were also collected. Persons suspected to have cognitive impairment based on the screening tests listed above underwent a neuropsychological and a neurological evaluation. The neuropsychological battery included the following tests: the American version of the National Reading test (AMNART), Raven's Coloured Progressive Matrices, California Verbal Learning Test (CVLT), a modified Rey-Osterreith figure, the Boston Naming test, the Verbal fluency test, the Block design test, the Trails A and B tests, the Baddeley & Papagno Divided Attention Task, the Stroop, Digit Span and Grooved Pegboard Tests. The results of the neuropsychological battery were classified as normal or abnormal (>1.5 standard deviations below individuals of comparable age and education) based on normative data collected from a sample of 250 unimpaired subjects. The neurological exam included a brief mental status examination, as well as a complete examination of other systems. The examiner also completed the Unified Parkinson's Disease Rating Scale (UPDRS) and the Hachinski Ischemic Scale. After completing the neurological exam, the neurologist classified the participant as normal, having mild cognitive impairment (MCI), or dementia. International diagnostic guidelines, including the NINCDS-ADRDA criteria for probable and possible AD and the ADDTC's State of California criteria for probable and possible vascular dementia (VaD) with or without AD, were followed. CHS identified 3 subtypes: possible/probable AD without VaD (categorized as pure AD, included in analysis) and mixed AD (for cases that met criteria for both AD and VaD, included in analysis), and, possible/probable VaD without AD (excluded from current study).

Framingham Heart Study (FHS): The FHS is a three generational prospective cohort that has been described in detail previously[7–9]. Individuals were initially recruited in 1948 in Framingham, MA, USA to evaluate cardiovascular disease risk factors. The second-generation cohort (5,124 offspring of the original cohort) was recruited between 1971 and 1975. The third-generation cohort (4095 grandchildren of the original cohort) was collected between 2002 and 2005. 6946 European-American individuals were genotyped using the EC. Participants ≤60 years at the time of blood draw for DNA extraction were excluded prior to analysis. Because the statistical tests used did not account for family structure, we excluded related participants. Using genome-wide identity-by-descent, we first identified 7 pairs of related cases, and excluded the younger of the two in each pair, or the one with the most missing data. We then excluded 151 controls who were related to cases, and finally, we excluded 439 controls related to other controls, applying the same age/missing data rule as for related cases. Covariates used were age in years and sex, where age was the age at LOAD diagnosis for cases or the age at last follow-up evaluation for controls.
Diagnosis of LOAD in FHS – FHS participants were screened at each biennial examination for possible cognitive decline through a number of mechanisms, including measures of the Folstein Mini-Mental Status Examination (MMSE)[10], referral by FHS staff and physicians at regular clinic exams, by self, family or primary care physician, referral following health updates or ancillary studies by other FHS working groups, and referral from neuropsychological testing included in dedicated project. Participants “flagged” as being at risk for developing dementia underwent complete neuropsychological evaluation. If the neuropsychological testing or neurological evaluation suggested a decline in cognitive function, and other sources of data could not clarify if the person had MCI or AD, we administered a structured family interview. We then determined whether each person fulfilled criteria for a diagnosis of dementia, the probable date of onset, and type of dementia at a consensus review conducted by a panel comprising at least one behavioural neurologist and one neuropsychologist. Participants with dementia met criteria outlined in the Fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria[2], and were required to have symptoms for at least 6 months. Participants with AD met NINCDS-ADRDA criteria for definite, probable, or possible AD[11].

Rotterdam study (RS): The RS is an ongoing prospective population-based cohort study, focused on chronic disabling conditions of the elderly[12]. The study comprises an outbred ethnically homogenous population of Dutch Caucasian origin. The rationale of the study has been described in detail elsewhere[12]. In summary, 7983 men and women aged 55 years or older, living in Ommoord, a suburb of Rotterdam, the Netherlands, were invited to participate. 3163 individuals were genotyped for the EC. This cohort was extended with 3,011 participants who had become 55 years of age or had moved into the district since the start of the study (RS II).

In the RS there are some small families due to inclusion of parents as well as children living both in Ommoord. From pairs of subjects with empirical IBD>0.4 one was excluded, with a preference of keeping cases. In the stage 2 *in-silico* replication, related subjects were also excluded, with a preference to keep cases over controls. Age was coded in years for age of onset for cases and age at censoring or age at last screening for controls. Diagnosis of LOAD in RS – In the RS participants were screened for prevalent dementia at baseline using a three-stage process described in detail elsewhere[13]. Those free of dementia remained under surveillance for incident dementia, a determination made using records linkage and assessment at three subsequent re-examinations. We included all prevalent cases and all incident events up to January 1st 2014. Screening was done with the Folstein Mini-Mental Status Examination (MMSE)[10] and the Geriatric Mental Schedule (GMS)[14]organic level for all persons. Screen-positives (MMSE < 26 or GMS organic level> 0) underwent the CAMDEX[15]. Persons who were suspected of having dementia underwent more extensive neuropsychological testing. When available, imaging data were used. In addition, all participants have been continuously monitored for major events (including dementia) through automated linkage of the study database with digitized medical records from general practitioners, the Regional Institute for Outpatient Mental Health Care and the municipality. In addition physician files from nursing homes and general practitioner records of participants who moved out of the Ommoord district were reviewed twice a year. For suspected dementia events, additional information (including neuroimaging) was obtained from hospital records and research physicians discussed available information with a neurologist experienced in dementia diagnosis and research to verify all diagnoses. Dementia was diagnosed in accordance with internationally accepted criteria for dementia (Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition, DSM-III-R[16]), and AD using the NINCDS-ADRDA criteria for possible, probable and definite AD[11]. The National Institute of Neurological Disorders and Stroke–Association Internationale pour la Rechercheetl' Enseignement en Neurosciences (NINDSAIREN) criteria were used to diagnose vascular dementia. The final diagnosis was determined by a panel of a neurologist, neurophysiologist, and research physician and the diagnoses of AD and VaD were not mutually exclusive.

Study Approval – The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC and by the Ministry of Health, Welfare and Sport of the Netherlands implementing the Wet Bevolkingsonderzoek: ERGO (Population Studies Act: Rotterdam Study). All participants provided written informed consent to participate in the study and to obtain information from their treating physicians. Data can be obtained upon request. Requests should be directed towards the management team of the Rotterdam Study (secretariat.epi@erasmusmc.nl), which has a protocol for approving data requests. Because of restrictions based on privacy regulations and informed consent of the participants, data cannot be made freely available in a public repository.

Stage 2:

HRC imputed data in the Rotterdam Study: The Rotterdam Study I and Rotterdam Study II were imputed to the Haplotype Reference Consortium reference (HRC) panel[17,18]. Imputation was performed on the web-service provided by the Michigan Imputation server (date of pipeline 17-12-2015). Previously described genotype QC was performed prior to imputations[19]. In short genotypes were pre-phased with SHAPEIT2[20] and imputed using Minimac3. Imputed genotypes with low imputation quality (Rsq<0.5) were excluded. Subjects included in the stage 1 analysis were excluded from the stage 2 analysis. In the

Rotterdam Study II only controls with an age > 75 were included to decrease the case to control ratio.

Genotyped Data: An additional 3,273 case-control samples were obtained for replication from centers in Austria (1 center) and Spain (1 center). Clinical diagnoses of probable AD were all established according to the DSM-III-R and NINCDS-ADRDA criteria. Controls were defined as subjects without DMS-III-R dementia criteria and with integrity of their cognitive functions (MMS>25).

ADGC:

Stage 1: Cases and controls were taken from multiple ADGC datasets[21,22] and partitioned into five subsets for genotyping and subsequent analyses. The five subsets included:(1) 7,091 individuals selected from multiple ADGC datasets were genotyped at the Robert S. Boas Center for Genomics and Human Genetics, Feinstein Institute for Medical Research, Manhasset, New York (**NorthShore**); (2) 2,024 individuals from the ADGC "UMVUMSSM" dataset were genotyped at the John P. Hussman Institute for Human Genomics, University of Miami, Miami, Florida (**Miami**); (3) 1,374 individuals from the ADGC "WashU" dataset were genotyped at Washington University, St. Louis, Missouri (WashU); (4) 6,082 individuals from multiple Alzheimer's Disease Center (ADC) genotyping waves were genotyped at the Center for Applied Genomics, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania (**CHOP**); and (5) all 1,528 subjects in the seventh wave of ADC samples were genotyped at CHOP (**ADC7**).Per individual source studies, all subjects were recruited under protocols approved by the appropriate Institutional Review Boards. Cases living at time of recruitment were adjudicated as possible or probable AD prior to analyses according to NINCDS/ADRDA criteria[11] whereas affection status of all deceased cases was confirmed through autopsy. Samples with age-at-onset or age-at-exam less than 60 years, missing covariates, or controls with MMSE<26 were censored.

Stage 3:

*HRC-Imputed ADGC GWAS datasets: S*tage 3 replication included genotype probabilities from imputation to the Haplotype Reference Consortium (HRC) reference panels[17,18] on all ADGC samples not genotyped on the exome chip and from datasets with more than 50 samples remaining after excluding exome chip-genotyped samples. These included samples from the Adult Changes in Thought (ACT)/Electronic Medical Records and Genetics (eMERGE) study; the National Institute on Aging (NIA) Alzheimer Disease Centers (ADCs) (waves 1-3 and 6); the Alzheimer Disease Neuroimaging Initiative (ADNI) Study; the Multi-Site Collaborative Study for Genotype-Phenotype Associations in Alzheimer's Disease (GenADA) Study; the University of Miami/Vanderbilt University/Mt. Sinai School of Medicine (UM/VU/MSSM); the Multi-Institutional Research in Alzheimer's Genetic Epidemiology (MIRAGE) Study; Oregon Health and Science University (OHSU); the NCRAD/NIA-LOAD Study; the Translational Genomics Research Institute series 2 (TGEN2) dataset; the Mayo Clinic Jacksonville; the Rush University Religious Orders Study/Memory and Aging Project (ROSMAP) and Chicago Health and Aging Project (CHAP); the University of Pittsburgh (UP); Washington University (WU) in St. Louis; the Texas Alzheimer's Research and Care Consortium (TARCC); the Netherlands Brain Bank (NBB); and the Washington Heights-Inwood Columbia Aging Project (WHICAP).Detailed descriptions of the ascertainment and evaluation of subjects in the ACT/eMERGE, ADC waves, ADNI, GenADA, UM/VU/MSSM, MIRAGE, OHSU, NCRAD/NIA-LOAD, TGEN2, Mayo, ROSMAP, UP, and WU cohorts have been provided elsewhere[21,22]; brief descriptions included here note any differences between data used in this study and data used in previous studies by the ADGC and IGAP study, including short summaries of the CHAP, TARCC, NBB, and WHICAP datasets. Analyses were restricted to individuals of European ancestry due to the insufficient number of non-European samples available for imputation in HRC. All subjects were recruited under protocols approved by the appropriate Institutional Review Boards.

Chicago Health and Aging Project (CHAP): CHAP is an on-going community based study of individuals from a geographically defined community of 3 neighbourhoods in Chicago, Illinois (Morgan Park, Washington Heights, and Beverly), with 6,158 participants in the first phase of the study (78.7% overall; 80.5% of the blacks, 74.6% of the whites)[23]. Data were collected in cycles of approximately 3 years; each consisting of an in-home interview of all participants and clinical evaluation of a random, stratified sample. The baseline cycle measured disease prevalence and provided risk factor data prior to incident disease onset. A cohort of 3,838 persons free of AD was identified; 729 persons were sampled for baseline clinical evaluation. Persons in the disease-free cohort had either good cognitive function at baseline, or if cognitive function was intermediate or poor, were free from AD at the baseline clinical evaluation. This disease-free cohort was evaluated for incident disease after an average of 4.1 years. Sampling for incident clinical evaluation was based on age, sex, race, and change in cognitive function (i.e., stable or improved, small decline, or large decline). The sample set available in the ADGC for genetic analyses included 32 AD cases and 197 persons free of AD at time of last assessment (all subjects were age 65 years or older at last assessment).

Netherlands Brain Bank (NBB): The NBB is a department of the Netherlands Institute for Neuroscience, an institute of the Royal Netherlands Academy of Arts and Sciences. The NBB is a non-profit organization that collects human brain tissue from donors with a variety of neurological and psychiatric disorders and brain tissue from non-diseased donors, as well as anonymized summaries of donors' medical records to be made available for neuroscience research[24]. The sample set available in the ADGC for genetic analyses included 215 pathologically-confirmed AD cases and 85 subjects free of Alzheimer's pathology at autopsy. All cases were age 65 years or older at time of diagnosis, and all controls were age 65 years or older at time of death.

Texas Alzheimer's Research and Care Consortium (TARCC): The TARCC is a collaborative Alzheimer's research effort directed and funded by the Texas Council on Alzheimer's Disease and Related Disorders (the Council), as part of the Darrell K Royal Texas Alzheimer's Initiative. Composed of Baylor College of Medicine (BCM), Texas Tech University Health Sciences Center (TTUHSC), University of North Texas Health Science Center (UNTHSC), the UT Southwestern Medical Center at Dallas (UTSW), University of Texas Health Science Center at San Antonio (UTHSCSA), Texas A&M Health Science Center (TAMHSC), and the University of Texas at Austin (UTA), this consortium was created to establish a comprehensive research cohort of well characterized subjects to address better diagnosis, treatment, and ultimately prevention of AD[25]. The resulting prospective cohort, the Texas Harris Alzheimer's Research Study, contains clinical, neuropsychiatric, genetic, and blood biomarker data on more than 3,000 participants diagnosed with Alzheimer's disease (AD), mild cognitive impairment (MCI), and cognitively normal individuals. Longitudinal data/sample collection and follow-up on participants occurs on an annual basis. Two waves of case-control data from TARCC were examined as part of genetic analyses in the ADGC. Data from the TARCC included 323 cases and 181 controls in the first wave, with 84 cases and 115 controls in the second wave. All TARCC subjects were greater than 65 years of age at disease onset (cases) or at last disease-free exam (non-cases).

The Washington Heights- Hamilton Heights-Inwood Columbia Aging Project (WHICAP): WHICAP is a community-based longitudinal study of aging and dementia among elderly, urban-dwelling residents[26,27]. Beginning enrolment in 1989, WHICAP has followed more than 5,900 residents over 65 years of age, including white, African American, and Hispanic participants. Detailed clinical assessments were performed at approximately 24-month intervals over the 7 years of the initial study. All interviews were conducted in either English or Spanish. The choice of language was decided by the subject in order to ensure the best performance, and the majority of assessments were performed in the subject's home, which included medical, neurological, and neuropsychological evaluations. Results of the neurological, psychiatric and neuropsychological assessments were reviewed in a consensus conference comprised of neurologists, psychiatrists, and neuropsychologists. Based on this review all participants were assigned to one of three categories: dementia, cognitive impairment or normal cognitive function. The sample set available in the ADGC for genetic analyses included 73 AD cases and 570 subjects with normal cognitive function.

EADI:

Stage 2: The 2,012 AD cases were ascertained by neurologists from Bordeaux, Dijon, Lille, Montpellier, Paris, Rouen, and were identified as of European ancestry. Clinical diagnosis of probable AD was established according to the DSM-III-R and NINCDS-ADRDA criteria[21,28]. The 6,502 Controls were selected from the 3C Study[29]. This cohort is a population-based, prospective (10-years follow-up) study of the relationship between vascular factors and dementia. It has been carried out in three French cities: Bordeaux (southwest France), Montpellier (southeast France) and Dijon (central eastern France).

An additional 11,109 case-control samples were obtained for replication from centers in Belgium (1 center), Finland (1 center), Italy (8 centers), Spain (5 centers), Sweden (2 centers) and Canada (1 center). Clinical diagnoses of probable AD were all established according to the DSM-III-R and NINCDS-ADRDA criteria. Controls were defined as subjects without DMS-III-R dementia criteria and with integrity of their cognitive functions (MMS>25).

For full sample characteristics in stage 1 and stages 2+3 see Supplementary Tables 1 and 2 respectively. For details of the study design see Supplementary Figure 1.

2. Quality Control and Analyses

APOE Conditional Analyses

As expected significant evidence for association with LOAD was identified at the *APOE* locus with twenty-two variants. An intronic proxy for the rs429358 variant determining the *APOE* ε4 genotype (rs769449, OR=2.88, $P<1\text{x}10^{-500}$, r^2 with rs429358=0.82), and the exonic variant *APOE* ε2 genotypes (rs7412, OR=0.43, $P=2.7\text{x}10^{-105}$) showed the strongest associations. Performing two conditional meta-analyses, adjusting for independently determined *APOE* genotypes in all cohorts, one adjusting for *APOE* ε4 (coded 0,1,2) a second adjusting for *APOE* ε2 (coded 0,1,2), diminished all association signals identified with all the genetic variants within the *APOE* region, therefore these 22 variants were not considered further. The lead variant rs769449 reduced from $P<1\text{x}10^{-500}$ to $P=1.1\text{x}10^{-5}$, when adjusting for *APOE* ε4, and rs7412 from $P=2.7\text{x}10^{-105}$ to $P=0.07$, when adjusting for *APOE* ε2.

Additional Quality Control

Two hundred seven variants showed suggestive evidence for association ($P\leq0.0001$) in any of the four meta-analyses of the discovery dataset. One hundred and eighty-five variants, independent of *APOE* ε4 and ε2, were carried forward for additional quality control that involved a review of all study specific genotype cluster plots. Where variant genotype clusters could be improved, these were manually re-clustered. Variants whose genotype clusters were deemed too poor for accurate genotype calling were excluded from re-analysis. Re-called variants were re-analysed as previously detailed. After re-analysis twenty variants that no longer showed nominally significant association ($P>0.05$) were excluded. We also excluded seventy-one variants that had a minor allele count (MAC) of less than 4, or those variants that were observed to be polymorphic in only one analysis cohort, after recalling. Of the remaining variants 50 were common (MAF≥0.05), and the observed associations were near known genome-wide significant loci (Supplementary Table 5). Forty-three rare variants located outside of the *APOE* region were eligible for replication and considered for additional genotyping and *in silico* replication (Supplementary Table 4).

Previously Described Risk Loci

We observed association at common coding variants for a number of AD risk loci previously identified (Supplementary Table 5). Variants in *APOE*, *CLU* and *CR1* showed genome-wide significant association ($P<5\text{x}10^{-8}$) in the unadjusted analysis, while common variants near *BIN1*, *MS4A6A*, *CD33*, *HLA*-region, *ABCA7* and *INPP5D* showed suggestive association ($P<5\text{x}10^{-4}$). Previously described genes with evidence for association with AD (*TREML2*, *UNC5C*, *TTC3*, *PLXNA4*, *PLD3*, *MTHFR*, *CYP2D6*, *ADAM10*, *ZNF628*, *AKAP9*, *CD33*, *TRIP4*, *MAPT*, *SQSTM1*, *ATP5H*/*KCTD2*) or familial AD genes (*APP*, *PSEN1*, *PSEN2*) are shown in Supplementary Table 5.

Gene-wide Analysis

Variants were allocated to genes according the RefSeq database. Variants were assigned to genes if they were located within the genomic sequence lying between the start of the first and the end of the last exon of any transcript corresponding to that gene, as defined by NCBI. Gene-wide analyses were examined using the unified method implemented in SKAT-O, where the optimal linear combination of the burden and SKAT tests is implemented[36]. As in the single variant analyses, association with disease was tested for in each cohort set including the study specific covariates under both the adjusted and unadjusted models. Analyses were performed including 'ALL' variants, variants with a MAF <5% and variants with a MAF<1%. Tests were restricted to individual genes with two or more polymorphic variants. Study specific results were combined in a meta-analysis using the *seqMeta* package. Variants within genes showing statistically significant evidence for association ($P<2.5\times10^{-6}$) underwent additional cluster plot inspection and poorly performing variants were removed from the analysis.

Power Calculations

If the allele frequencies in cases is 0.003 and in controls is 0.001, then the power to detect this rare variant with 5000 cases and 2500 controls at 5% significance level is 70%. If the number of controls is 18000, then the power is increased up to 98% at α=0.05 and 28% at α=1e-6 (to account for 30,000 genes). This power calculations are performed using function power.fisher.test() in R statistical software.

Linkage Disequilibrium Calculations

Linkage disequilibrium (LD) calculations were performed using PLINK v1.9[4] and the GERAD v1.0 dataset. High *D'* values and low r^2 values were identified for all the LD pairs tested (Supplementary Table 14). This discrepancy in LD measures is to be expected when analysing rare variants. The D' calculation estimates co-presence of the minor allele at one SNV compared to a reference allele at another SNV, while r^2 is a measure of the correlation between the presence or absence of a particular allele at the first SNV and the presence or absence of a particular allele at the second SNV and is therefore affected by allele frequency. For bi-allelic markers, the most commonly used measures for LD is r^2 [37], which indicates independence of the tested SNV associations.

3. Single Variant Findings

Outside of the *APOE* region, and excluding the known common risk loci, four SNVs reached genome-wide significant evidence for association ($P<5\times10^{-8}$), under both the unadjusted and adjusted analysis models. See Supplementary Tables 7 and 8 respectively.

A forest plot of the association identified at rs72824905 in *PLCG2* is given in Supplementary Figure 3. We identified a second independent ($r^2=1.5\times10^{-5}$) suggestive signal with strong effect within *PLCG2* at synonymous SNV rs200506549 ($P_{\text{discovery}}$=5.8x10-4, OR=2.0, MAF=0.0017). However, exploration in the Stage 3 sample (*N*=12,616) did not replicate this association (*P*=0.76, OR=0.89, MAF=0.0016). All stage 1 associations tested at the *PLCG2* gene are shown in Supplementary Table 9.

A forest plot of the association identified at rs616338 in *ABI3* is given in Supplementary Figure 6. All stage 1 associations tested at the *ABI3* gene are shown in Supplementary Table 12.

A forest plot of the association identified at rs143332484 and rs75932628 in *TREM2* are given in Supplementary Figures 9 and 10 respectively. All stage 1 associations tested at the *TREM2* gene are shown in Supplementary Table 13. It should be noted that the 61% (9.6% GERAD/PERADES, 100% ADGC, 81.8% CHARGE and 33.7% EADI) of the samples utilized in this study overlaps with that of the Guerreiro *et al*.[38], and that RS stage1 plus RS1 stage 3 samples overlap with Jonsson et al.[39], in which R47H robustly associated with AD status.

An additional 3 SNVs show suggestive evidence for association ($P_{combined}$<$1x10^{-6}$) with consistent direction of effect across stages (Supplementary Tables 7 and 8).

Conditional Analyses

Conditional analyses were undertaken at the *PLCG2*, *ABI3* and *TREM2* loci using the GCTA tool[40](using the default parameters)and the stage1 unadjusted summary statistics as input. Data from the GERAD v1.0 dataset was used to calculate the background LD. The GERAD v1.0 dataset was utilised to establish LD ($N_{GERADv1.0}$=5692). We did not identify significant or suggestive association ($P<1x10^{-5}$) independent of the genome-wide significant (GWS) hits. When conditioning on rs72824905 in *PLCG2*, the top hit is rs200506549,$P=6.52x10^{-4}$ (Supplementary Figure 5). When conditioning on rs616338 in *ABI3*, the top hit is rs141826857 in *B4GALNT2*, $P=1.89x10^{-5}$(Supplementary Figure 8), this association did not replicate in the stage 2 analysis (P_{stage2}= $9.89x10^{-1}$, $P_{combined}$= $1.68x10^{-4}$). When conditioning on rs75932628 in *TREM2*, rs143332484 remains significantly associated with disease at ($P=3.38x10^{-9}$) (Supplementary Figure 11a), the opposite is observed, with rs75932628 showing significant association with disease when conditioning on rs143332484 ($P=5.12x10^{-12}$)(Supplementary Figure 11b). When conditioning on both rs143332484 and rs75932628 in *TREM2*, the top hit is rs143539514, $P=1.51x10^{-3}$, OR=1.84, MAF=0.0039 (Supplementary Figure 11c).

4. Gene-wide Findings

Outside of the *APOE* region (defined as 1MB around the *APOE* locus), in both the MAF<5% and MAF<1% unadjusted analyses, only the *TREM2* gene showed statistically significant evidence for association, with MAF<5% $P_{gene\text{-}wide}=1.42x10^{-15}$ and MAF<1% $P_{gene\text{-}wide}$ $=1.01x10^{-13}$(Supplementary Table 10). Removal of the p.R47H and p.R62H variants from the analyses diminishes the gene-wide association ($P>2.5x10^{-6}$). However, the SKAT-O test remains suggestive with $P=6.3x10^{-3}$, and if a burden test was applied $P=4.1x10^{-3}$, suggesting that more rare damaging variants increasing risk on AD may be present in *TREM2*. In the adjusted analysis a novel association with the *CBLN3* gene is identified with 2 SNVs at this locus (Supplementary Table 11). Both variants in this gene are extremely rare and this finding requires further replication.

5. Gene Expression

RNA sequencing was also used to measure gene expression levels in brains from CRND8 transgenic mouse model at 3, 6 and 12 months of age (n=12, 12 and 14, respectively); PS1APP model at age 12 months (n=11) and wild type (WT) mice at 3, 6 and 12 months of age (n=12, 12 and 10, respectively). Based on our preliminary data which showed expression changes >2-fold in innate immunity genes between Tg vs. Non-Tg mice, based on conservative estimate of variance and group sizes of 10, we have an 80% power in the RNAseq studies to detect effect sizes of 1.8, 2.2 and 2.8 at an α<0.05, 0.01 and 0.001. All mice were housed in SPF conditions in the same facility, fed standard mouse chow, and euthanized by $C0^2$ asphyxiation. Brains were dissected to remove the cerebellum and midbrain, and the "forebrains" were processed for RNA extraction and sequencing in a manner analogous to that described for the human brain samples. Transgenic animals and their non-transgenic littermates underwent RNAseq in the same batch, which included animals from both sexes and and all age groups assessed. Samples were sequenced as triplicates per lane and randomized across the flowcells by age and transgene (+ vs. -). RNAseq processing including alignment and quality control was done on all mouse samples in an automated fashion. The mouse RNA sequencing data overview and analytic methods are available at Synapse pages syn3157182 and syn3435792, respectively. Multivariable linear regression was used to test for association of gene expression levels with transgenic state (Dx). In all analyses, adjustments were made only for sex and RNA integrity number (RIN), given limited sample size. Mean normalized gene read counts and standard deviations (sd) for the transgenic (Tg) and WT groups are shown (Supplementary Table 20). The RNAseq data used in the analyses have been normalized using Conditional Quantile Normalization (CQN) via the Bioconductor package cqn ; accounting for sequencing depth, gene length, and GC content. CQN approximates log2(RPKM) except at the extremes of the expression distribution. The gene expression data shown herein have mean CQN>-1. Levels of all 3 genes increase with age but to a greater extent for Tg mice for *Trem2* and *Abi3*. All 3 genes are significantly higher in CRND8 brains at 12 months. *Trem2* and *Abi3* are also significantly higher in CRND8 mice at 6 months and PS1APP mice at 12 months.

6. Functional Annotation

To investigate the functional effect of index SNVs rs72824905 and rs616338, the surrounding sequence was analysed to identify potential cis-effects. Variants in LD (r^2>0.7) with the index SNVs were identified using HaploReg v4.1[48] using the European population from 1000 Genomes Phase 1[49] for LD calculation. Additionally, the Common Gene Haplotype Alleles feature in the University of California, Santa Cruz (UCSC) genome browser[50] (https://genome.ucsc.edu), generated from imputation of the 1000 Genomes Phase 1 data, was used to identify variants on the same haplotype background as the index SNVs. This approach identified 8 additional variants that may be tagged by the index SNVs (Supplementary Table 21). *In-silico* functional analysis of the variants was conducted using Annovar[51] and the following databases: RefSeq[52] release 69 was used to annotate variants to genes. Transcription factor binding sites computed with the Transfac Matrix Database v0.7 (http://www.gene-regulation.com/pub/databases.html) were sourced from the UCSC genome annotation tracks[53] for the Feb 2009 assembly of the human genome (http://www.ncbi.nlm.nih.gov/projects/genome/assembly/grc/). The snoRNA and miRNA track, based on the miRBase and snoRNABase release[54–58], as well as the TargetScanS[59–61]microRNAs binding site track, were sourced from the above UCSC assembly and used to identify variants overlapping microRNAs or their regulatory sites. Variants previously identified by published GWAS and collected in the Catalog of Published Genome-Wide

Association Studies at the National Human Genome Research Institute (NHGRI, accessed March 2015)[62] were flagged using data from the corresponding UCSC track.
Variants were also annotated using the dbNSFP v30a database[63,64]that compiles predictions and conservation scores from 20 sources, the CLINVAR database of variants with clinical significance[65], and functional prediction tools GWAVA[66] release 70, CADD[67] v1.0 and DANN[68].Finally, variants were investigated for their effect on gene expression using eQTL data from BRAINEAC[69], HaploReg v4.1 and those reported by Knight and co-workers[70].

PLCG2

PLCG2 encodes phospholipase Cγ2 (PLCγ2), an enzyme responsible for ligand-mediated signalling in cells of the hematopoietic system, and plays a key role in the regulation of immune responses. The p.P522R variant identified within *PLCG2* resides in a region of the protein highly conserved across human, chimp, rhesus monkey, mouse, rat, rabbit, horse, dog and elephant (Supplementary Figures 4 and 13). Functional annotation suggests that the protective variant, which encodes for an arginine residue, affects chromatin structure and potentially protein folding. As well as associating with autoimmune diseases PLAID and APLAID[71], *PLCG2* has been shown to associate with inflammatory conditions such as Inflammatory bowel disease[72].

ABI3

The function of ABI3 (previously known as NESH) is far from understood. Early studies indicated that overexpression of *ABI3* led to a reduction in cell motility and reduced metastasis in an in vivo cancer model attributed to an apparent interaction with p21 activated kinase[73]. Whilst this study did not demonstrate an impact on cell proliferation, subsequent study of both ABI3 and ABI3BP (ABI3 binding protein), reported an impact of its expression on proliferation as well as in vivo cancer cell growth[74]. These tumour suppressing roles for ABI3 are interesting in the context of observed low expression of *ABI3* in cancer cells[75]. Given the association we have made between ABI3 polymorphisms with the development of Alzheimer's disease, the key contribution of ABI3 to the aetiology of the disease and whether it is attributable to alterations in cell growth and adhesion/migration or otherwise unknown functions remains completely unknown. The risk variant p.S209F, which encodes a phenylalanine residue is predicted to be deleterious[67], the variant lies in a region of the protein highly conserved across human, chimp, rhesus monkey, mouse, rat, rabbit, dog and elephant (Supplementary Figure 7), which is thought to have a role in altering chromatin structure (Supplementary Figure 14).

TREM2

TREM2 is a Type I transmembrane receptor protein expressed on myeloid cells[76,77], in the brain, primary TREM2 expression is on microglia. TREM2 acts to control regulation of phagocytosis and suppression of inflammatory reactivity signalling pathways[78–80]. *TREM2* has shown genetic association with multiple dementias[81–85], including AD[38,39], and has also shown differential expression in Aβ plaque-associated versus Aβ plaque-free tissue from transgenic mice[86]. Both p.R47H and p.R62H are located in a Ig-like V-type domain (Supplementary Figure 15), suggesting that these variants affect ligand binding/signal transduction of TREM2.

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8. Supplementary Table Legends

Supplementary Table 1.Full description of the different stage 1 samples from the GERAD/PERADES, ADGC and CHARGE consortia.

Supplementary Table 2. Full description of the different stage 2 and stage 3 samples/datasets from the GERAD/PERADES, ADGC, CHARGE and EADI consortia.

Supplementary Table 3. Details of stage 1 calling software(s) and quality control metrics applied across the ADGC, CHARGE and GERAD/PERADES cohorts.

Supplementary Table 4. Table of 43 variants eligible to be taken forward from stage 1, meeting $P<1\text{x}10^{-4}$ before re-clustering and $P<0.05$ after re-clustering. The OR for a number of SNVs are extremely high due to a combination of the 'one-step' approximation of the effect estimate from the score-test and the rarity of the minor allele.

Supplementary Table 5. Observed associations at previously identified GWS AD risk loci. Variants in *APOE*, *CLU* and *CR1* showed genome-wide significant association ($P<5\text{x}10^{-8}$) in the unadjusted analysis, while common variants near *BIN1*, *MS4A6A*, *CD33*, *HLA*-region, *ABCA7* and *INPP5D* showed suggestive association ($P<5\text{x}10^{-4}$). Also, rare and common variation in previously described risk loci (*TREML2*, *UNC5C*, *TTC3*, *PLXNA4*, *PLD3*, *MTHFR*, *CYP2D6*, *ADAM10*, *ZNF628*, *AKAP9*, *CD33*, *TRIP4*, *MAPT*, *SQSTM1*, *ATP5H*/*KCTD2*, *APP*, *PSEN1*, *PSEN2*). Excluding *CD33* common variant rs3865444, no significant evidence for association with LOAD was identified. The OR for a number of SNVs are extremely high due to a combination of the 'one-step' approximation of the effect estimate from seqMeta and the rarity of the minor allele.

Supplementary Table 6. Concordance of alternate allele carrier genotypes for all replicated SNPs among samples with both exome chip genotyping and with GWAS imputed to HRC. For comparison, imputed genotypes were assigned if probability of a given genotype exceeded 0.9. Where percent concordance is absent, SNPs were imputed with high probability as monomorphic across all samples examined.

Supplementary Table 7. Results of unadjusted analysis of the SNVs identified as eligible for replication in stage 1. Results show p-value, odds ratio, minor allele frequency and number of individuals for each stage of the study, as well as the final combined analysis. The OR for a number of SNVs are extremely high due to a combination of the 'one-step' approximation of the effect estimate from the seqMetaand the rarity of the minor allele.

Supplementary Table 8. Results of adjusted analysis of the SNVs identified as eligible for replication in stage 1. Results show p-value, odds ratio, minor allele frequency and number of individuals for each stage of the study, as well as the final combined analysis. The OR for a number of SNVs are extremely high due to a combination of the 'one-step' approximation of the effect estimate from the seqMetaand the rarity of the minor allele.

Supplementary Table 9. Unadjusted association with single nucleotide variation within the *PLCG2* gene on chromosome 16.

Supplementary Table 10. Results of unadjusted SKAT-O gene-wide analysis of the SNVs in stage 1. Results show number of SNVs included in analysis at MAF≤0.01 and MAF≤0.05 and their respective p-values for all SNVs with $P<1\text{x}10^{-5}$ at either MAF threshold. Table also shows gene-wide analysis of *PLCG2* ($P>1\text{x}10^{-5}$).

Supplementary Table 11. Results of adjusted SKAT-O gene-wide analysis of the SNVs in stage 1. Results show number of SNVs included in analysis at MAF≤0.01 and MAF≤0.05 and their respective p-values for all SNVs with $P<1\text{x}10^{-5}$ at either MAF threshold. Table also shows gene-wide analysis of *PLCG2* and *ABI3* ($P>1\text{x}10^{-5}$).

Supplementary Table 12. Unadjusted association with single nucleotide variation within the *ABI3* gene on chromosome 17.

Supplementary Table 13. Unadjusted association with single nucleotide variation within the *TREM2* gene on chromosome 6.

Supplementary Table 14. Linkage disequilibrium calculations generated for the observed SNV associations at the *PLCG2* and *TREM2* loci.

Supplementary Table 15. Enrichment for the IGAP pathway clusters based on combining gene-wide p-values from variants with MAF<0.01 with Fisher's method. The clusters representing the immune response, cholesterol transport, hemostasis, Clathrin/AP2 adaptor complex and protein folding, survive Bonferroni for 8 tests (p<0.00625). A conservative analysis removing the *APOE* region and the more significant of any pair of genes less than 1Mb apart (to remove potential bias resulting from LD between genes) is also shown.

Supplementary Table 16. Significant pathways (FDR<0.01) from an analysis of the rare variant data (MAF<1%) on all 9,816 pathways originally analysed in the IGAP GWAS.

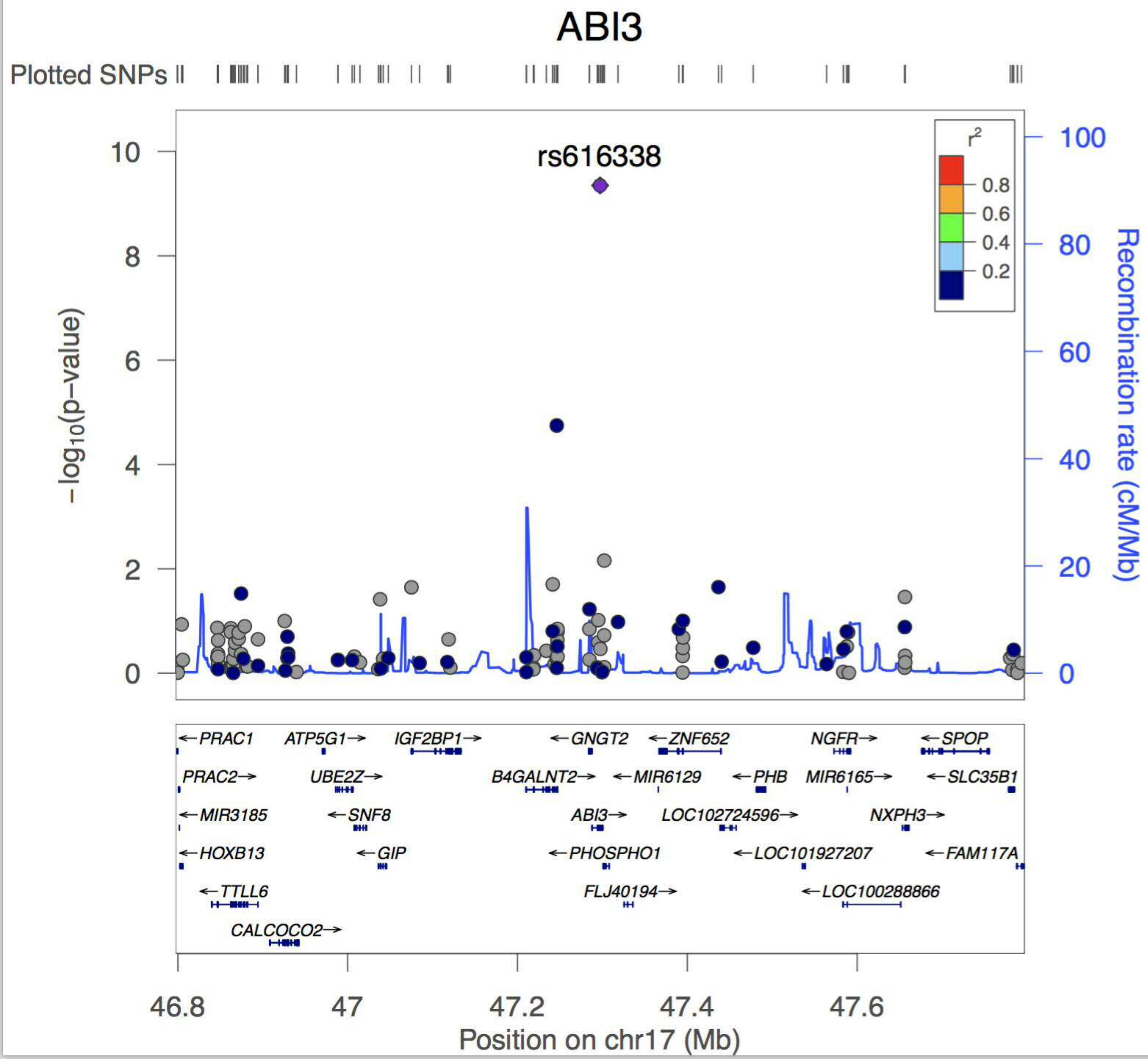
Supplementary Table 17. ALIGATOR enrichment analysis of the 151 genes in the overlap of immune-related gene expression modules in the IGAP GWAS, stratifying by membership of the protein interaction network. A range of p-value cutoffs were used to define significant SNPs (and the genes containing them). "Top 5%" refers to the top 5% of genes being counted as significant (corresponding to SNP $P<8.32\text{x}10^{-4}$) and was the primary analysis in the original pathway analysis of the IGAP data.

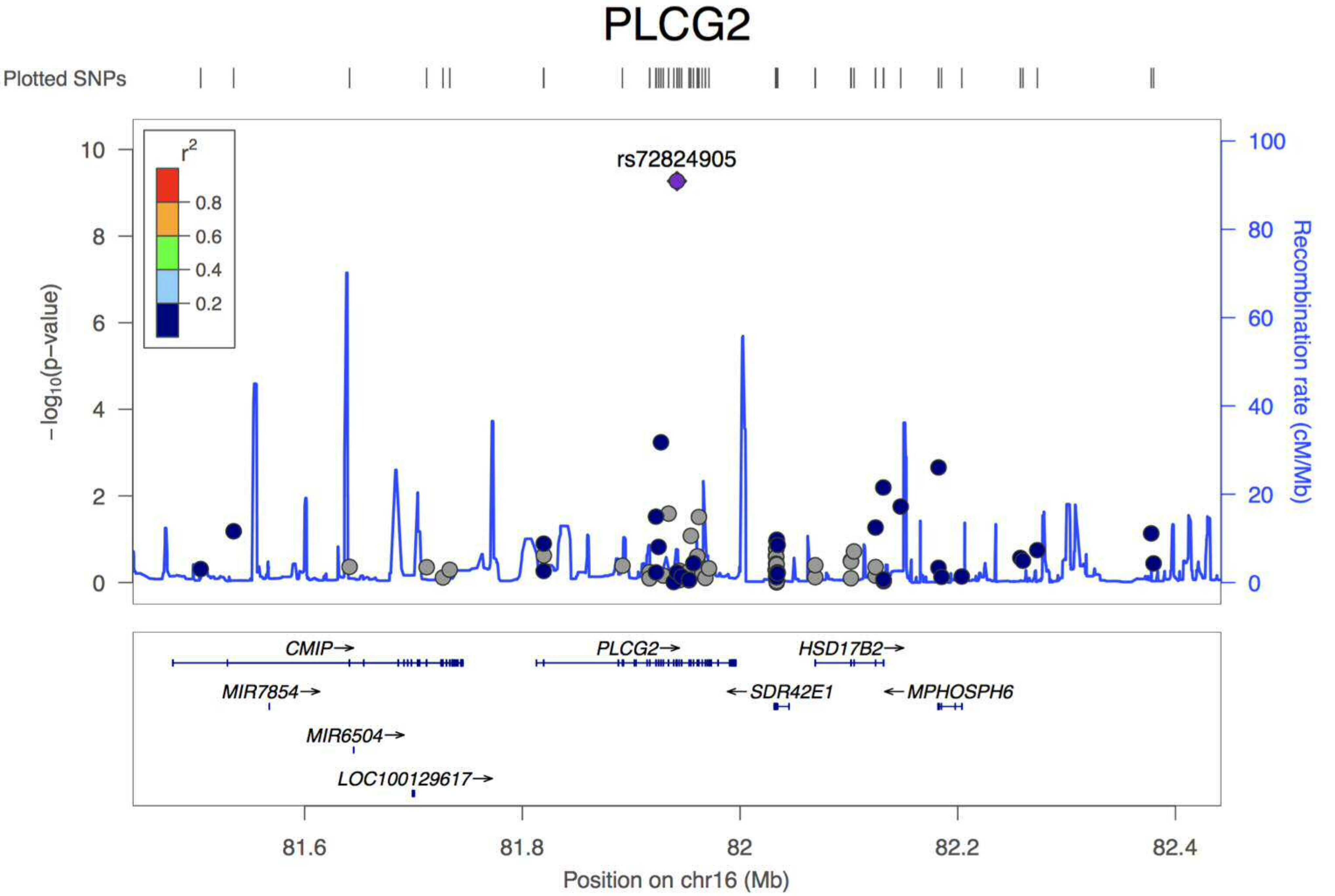
Supplementary Table 18. List of the 56 genes in the protein-protein interaction network, with gene based p-values in the IGAP common variant GWAS and in the present rare variant study (unadjusted model).

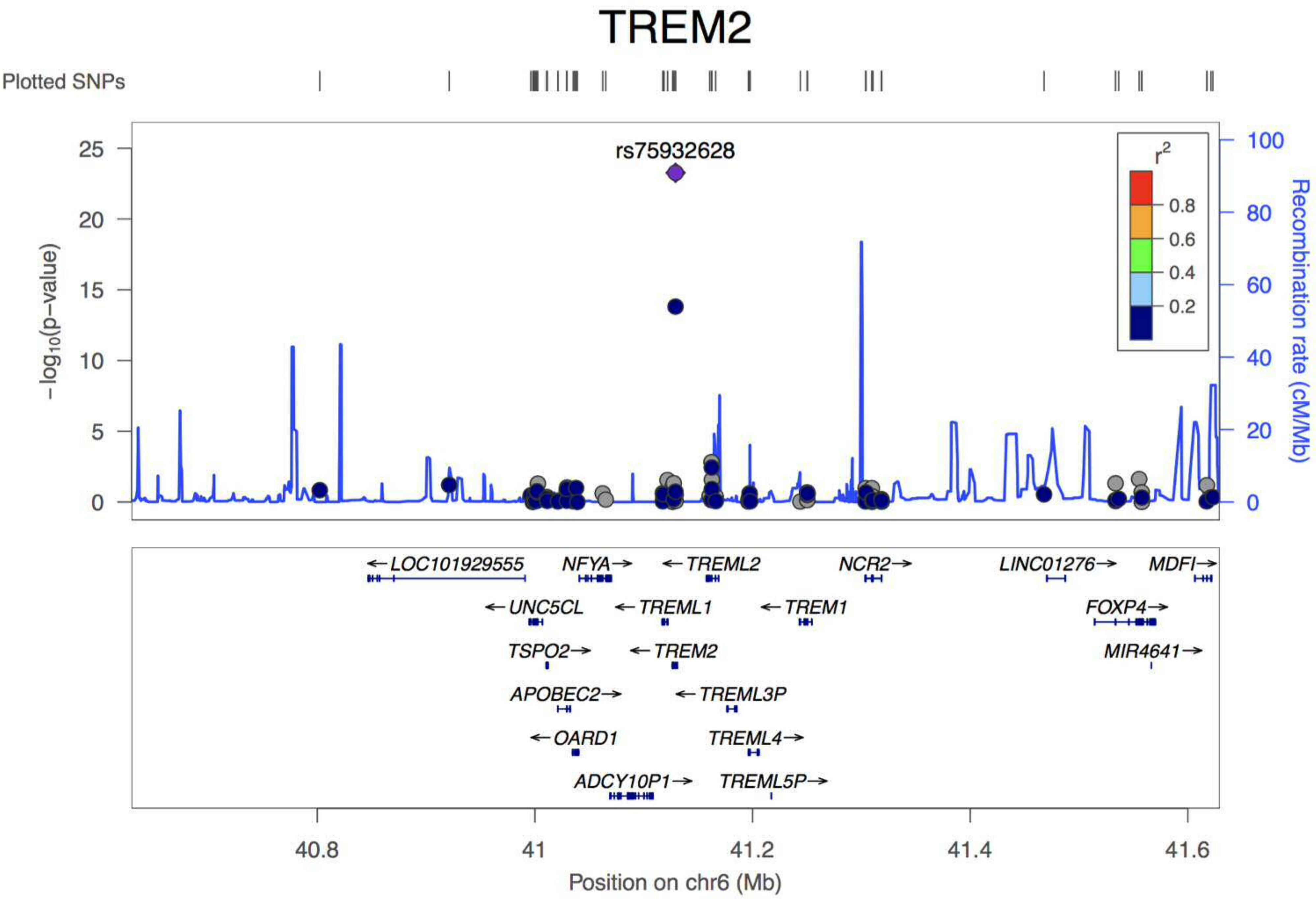
Supplementary Table 19 Differential expression of genes (DEG) in human temporal cortex. Mean normalized gene read counts and standard deviations (sd) for the AD and control (con) groups are shown. Effect of AD diagnosis (Dx.Beta, Dx.SE=standard error), significance of AD diagnosis either uncorrected, or corrected using FDR-based q values are shown. All 3 genes are significantly higher in AD temporal cortex prior to correcting for cell types (Simple model), but this significance is abolished after adjusting for cell-specific gene counts (Comprehensive model). This suggests that these elevations are likely a consequence of changes in cell types that occur with AD, most likely microgliosis given that *TREM2*, *PLCG2* and *ABI3* are microglia-enriched genes.

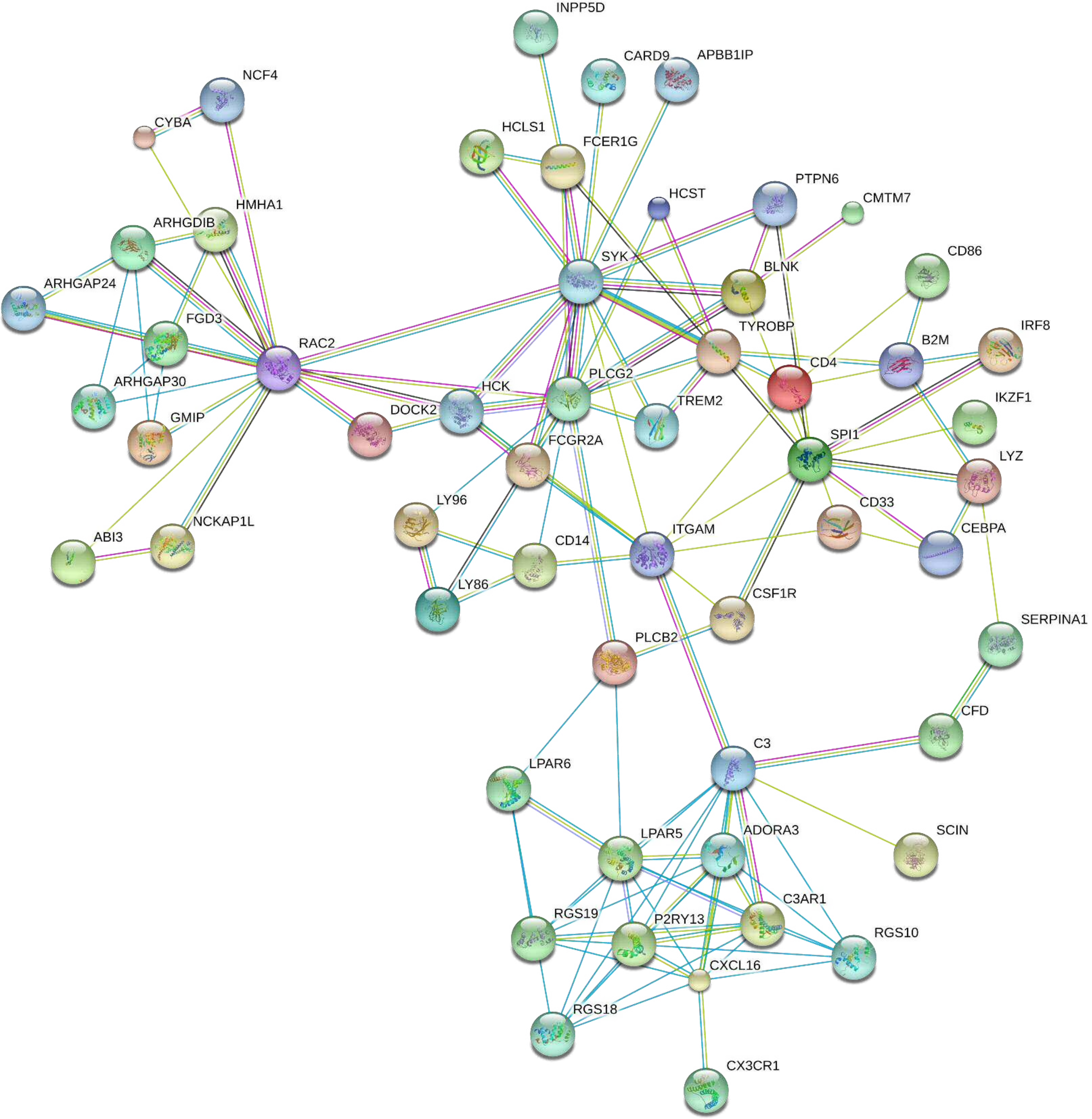
Supplementary Table 20. Differential expression of genes (DEG) in brains from CRND8 transgenic mouse model at 3, 6 and 12 months of age (n=12, 12 and 14, respectively); PS1APP model at age 12 months (n=11) and wild type (WT) mice at 3, 6 and 12 months of age (n=12, 12 and 10, respectively). Mean normalized gene read counts and standard deviations (sd) for the transgenic (Tg) and WT groups are shown. Effect of transgenic state (Dx.Beta, Dx.SE=standard error), significance of Tg state either uncorrected, or corrected using FDR-based q values are shown. Levels of all 3 genes increase with age but to a greater extent for Tg mice for Trem2 and Abi3. All 3 genes are significantly higher in CRND8 brains at 12 months. Trem2 and Abi3 are also significantly higher in CRND8 mice at 6 months and PS1APP mice at 12 months.

Supplementary Table 21. Functional annotation of the *PLCG2* and *ABI3* GWS SNVs and variants in LD (r^2>0.7). Associated SNVs are highlighted in blue. Interesting findings are highlighted in red. Interpretation of data is via the handbook of the relevant database.


ABI3
Plotted SNPs
rs616338
r2
0.8
0.6
0.4
0.2
-log10(p-value)
0
2
4
6
8
10
Recombination rate (cM/Mb)
0
20
40
60
80
100
←PRAC1
ATP5G1→
IGF2BP1→
←GNGT2
←ZNF652
NGFR→
←SPOP
PRAC2→
UBE2Z→
B4GALNT2→
←MIR6129
←PHB
MIR6165→
←SLC35B1
←MIR3185
←SNF8
ABI3→
LOC102724596→
NXPH3→
←HOXB13
←GIP
←PHOSPHO1
←LOC101927207
←FAM117A
←TTLL6
FLJ40194→
←LOC100288866
CALCOCO2→
46.8
47
47.2
47.4
47.6
Position on chr17 (Mb)


PLCG2
Plotted SNPs
r²
0.8
0.6
0.4
0.2
rs72824905
−log10(p−value)
10
8
6
4
2
0
100
80
60
40
20
0
Recombination rate (cM/Mb)
CMIP→
PLCG2→
HSD17B2→
MIR7854→
←SDR42E1
←MPHOSPH6
MIR6504→
LOC100129617→
81.6
81.8
82
82.2
82.4
Position on chr16 (Mb)


TREM2
Plotted SNPs
rs75932628
-log10(p-value)
0
5
10
15
20
25
Recombination rate (cM/Mb)
0
20
40
60
80
100
r2
0.8
0.6
0.4
0.2
←LOC101929555
NFYA→
←TREML2
NCR2→
LINC01276→
MDFI→
←UNC5CL
←TREML1
←TREM1
FOXP4→
TSPO2→
←TREM2
MIR4641→
APOBEC2→
←TREML3P
←OARD1
TREML4→
ADCY10P1→
TREML5P→
40.8
41
41.2
41.4
41.6
Position on chr6 (Mb)


INPP5D
CARD9
APBB1IP
NCF4
CYBA
HCLS1
FCER1G
HCST
PTPN6
CMTM7
HMHA1
ARHGDIB
SYK
BLNK
CD86
ARHGAP24
FGD3
TYROBP
B2M
IRF8
RAC2
CD4
PLCG2
HCK
ARHGAP30
DOCK2
TREM2
IKZF1
GMIP
FCGR2A
SPI1
LYZ
LY96
CD33
NCKAP1L
ITGAM
CEBPA
ABI3
CD14
LY86
CSF1R
SERPINA1
PLCB2
CFD
C3
LPAR6
LPAR5
ADORA3
SCIN
C3AR1
RGS19
P2RY13
RGS10
CXCL16
RGS18
CX3CR1

				Controls				Cases				
Country	**Centre**	**Consortium**	**Array**	**N**	**% Females**	**Age**	**Deviation +/-**	**N**	**% Females**	**Age at Onset**	**Deviation +/-**	**TOTAL**
Germany	Bonn	GERAD	v1.0	537	62.01	83.81	3.12	770	67.32	72.84	8.64	1307
Germany	Homborg	GERAD	v1.0	70	58.57	81.91	8.94	849	58.04	72.79	10.48	919
Germany	Munich	GERAD	v1.0	145	66.9	68.46	3.54	261	67.43	70.11	8.68	406
Iceland	AGES	CHARGE	v1.0	2374	59.00	78.90	5.00	143	59.40	82.50	4.90	2517
Italy	Rome	GERAD	v1.1	135	57.78	65.99	6.96	163	62.58	75.43	7.14	298
Netherlands	RS	CHARGE	v1.0	2416	50.79	78.22	7.71	463	68.90	83.30	6.59	2879
Spain	Barcelona	GERAD	v1.1	–	–	–	–	414	70.29	76.86	5.5	414
Spain	Madrid	GERAD	v1.1	296	62.96	72.98	14.52	219	63.93	70.04	13.79	515
Spain	Navarra	GERAD	v1.1	374	59.89	66.74	11.33	428	60.28	70.15	8.8	802
Spain	Oviedo	GERAD	v1.1	104	51.92	70.4	6.62	74	66.22	76.59	6.5	178
Spain	Santander	GERAD	v1.1	246	67.89	80.57	9.33	318	65.41	73.75	7.06	564
UK	Belfast	GERAD	v1.0	226	68.12	75.04	7.92	517	66.67	76.88	7.4	743
UK	MRC	GERAD	v1.0	475	63.37	76.82	6.37	832	71.63	75.82	6.62	1307
UK	Nottingham	GERAD	v1.0	109	40.37	–	–	173	59.87	–	–	282
UK	Prion	GERAD	v1.0	–	–	–	–	555	53.47	63.79	12.45	555
UK	Southampton	GERAD	v1.0	37	59.46	74.14	6.7	136	64.71	80	8	173
USA	ADC7	ADGC	v1.0	872	62.84	73.48	8.03	542	52.03	77.68	7.56	1414
USA	BYU	GERAD	v1.1	151	64.24	88.05	3.93	150	62	84.48	6.01	301
USA	CHOP	ADGC	v1.0	2556	56.69	80.99	6.69	2943	64.32	73.77	8.74	5499
USA	FHS	CHARGE	v1.0	1298	57.00	79.90	8.60	228	68.00	85.00	6.90	1526
USA	CHS	CHARGE	v1.0	2013	56.33	81.18	5.15	557	61.58	82.10	5.32	2570
USA	Miami	ADGC	v1.0	991	60.54	73.49	7.92	885	62.94	72.56	7.09	1876
USA	NorthShore	ADGC	v1.0	2223	63.07	77.04	9.39	3782	52.27	72.28	9.37	6005
USA	Washington	GERAD	v1.1	69	63.63	–	–	141	58.33	74.16	7.39	210
USA	WashU	ADGC	v1.0	360	61.67	74.57	8.68	554	58.3	79.78	9.71	914
			TOTAL	**18077**				**16097**				**34174**

					Controls				Cases				
Country	**Centre**	**Type**	**Analysis Dataset**	**Consortium**	**N**	**% Females**	**Age**	**Deviation +/-**	**N**	**% Females**	***Age at Onset**	**Deviation +/-**	**TOTAL**
France	EADI1	Genotyped	EADI_France	EADI	6502	60.71	79	6.93	2012	65.27	72.69	9.71	8514
Italy	Lamezia Terme	Genotyped	GERAD/PERADES	GERAD/PERADES	47	80.85	65.02	11.26	98	66.67	72.93	6.08	145
Italy	Milan (Sacred Heart)	Genotyped	GERAD/PERADES	GERAD/PERADES	85	65.88	68.06	10.91	81	70.37	76.93	7.08	166
Italy	Milan (University)	Genotyped	GERAD/PERADES	GERAD/PERADES	–	–	–	–	150	73.33	77.33	5.51	150
Italy	Perugia	Genotyped	GERAD/PERADES	GERAD/PERADES	298	63.3	77.96	8.28	531	70.06	79	7.12	829
Italy	Pisa	Genotyped	GERAD/PERADES	GERAD/PERADES	89	22.47	50.16	13.14	73	54.79	68.12	4.99	162
Italy	Rome (Sacred Heart)	Genotyped	GERAD/PERADES	GERAD/PERADES	–	–	–	–	291	68.04	75.6	10.54	291
Italy	Rome (Santa Lucia)	Genotyped	GERAD/PERADES	GERAD/PERADES	38	71.05	66.29	6.52	45	62.23	77.27	5.22	83
Spain	Navarra	Genotyped	GERAD/PERADES	GERAD/PERADES	33	51.52	69.18	11.77	92	56.52	71.84	9.23	125
Spain	Oviedo	Genotyped	GERAD/PERADES	GERAD/PERADES	96	47.92	73.07	5.44	96	73.96	77.6	6.55	192
Spain	Santander	Genotyped	GERAD/PERADES	GERAD/PERADES	–	–	–	–	15	72.73	77.5	8.48	15
UK	Cardiff	Genotyped	GERAD/PERADES	GERAD/PERADES	338	58.6	81.77	9.41	462	58.9	80.68	9.29	800
UK	London (IOP)	Genotyped	GERAD/PERADES	GERAD/PERADES	154	50.33	78.73	10.74	296	51.9	79.6	10.21	450
UK	Southampton	Genotyped	GERAD/PERADES	GERAD/PERADES	61	70.49	69.84	9.42	98	44.5	73.81	9.99	159
Austria	Graz	Genotyped	IGAP_Aus_Ger	CHARGE	–	–	–	–	210	60.95	72.47	8.07	210
Germany	Munich	Genotyped	IGAP_Aus_Ger	GERAD/PERADES	530	37.74	66.58	3.43	285	67.37	70.67	8.69	815
Germany	Bonn	Genotyped	IGAP_Aus_Ger	GERAD/PERADES	489	67.69	79.56	3.22	7	57.14	70	3.94	496
Germany	Essen	Genotyped	IGAP_Aus_Ger	GERAD/PERADES	243	60.49	76.21	5.95	132	66.67	75.98	7.00	375
Spain	ACE	Genotyped	ACE	CHARGE	1839	67.70	54.70	12.12	1224	70.60	79.11	5.96	3063
Belgium	Antwerp	Genotyped	IGAP_Bel	EADI	626	59.27	65.4	14.31	857	66.28	75.48	8.5	1483
Canada	Toronto	Genotyped	IGAP_Can	EADI	100	69	74.39	6.48	125	68	74.89	6.82	225
Finland	Kuopio	Genotyped	IGAP_Finland	EADI	503	59.84	68.95	6.31	340	69.41	71.31	7.22	843
Italy	Cagliari	Genotyped	IGAP_Italy	EADI	109	55.05	65.76	7.83	130	73.08	74.93	6.51	239
Italy	Florence	Genotyped	IGAP_Italy	EADI	77	54.55	64.04	13.08	440	60	67.07	8.53	517
Italy	Milan	Genotyped	IGAP_Italy	EADI	161	61.49	69.76	11.06	305	67.54	73.47	7.39	466
Italy	Perugia2	Genotyped	IGAP_Italy	EADI	79	51.9	74.44	6.25	124	73.39	78.85	6.76	203
Italy	Pisa	Genotyped	IGAP_Italy	EADI	7	71.43	63.29	17.18	21	76.19	72.52	9.15	28
Italy	Rome	Genotyped	IGAP_Italy	EADI	35	65.71	68.43	6.69	332	70.78	73	7.58	367
Italy	San Giovanni Rotonda	Genotyped	IGAP_Italy	EADI	63	31.75	76.6	7.02	113	64.6	79.03	6.80	176
Italy	Troina	Genotyped	IGAP_Italy	EADI	154	61.04	71.95	8.25	156	61.54	71.47	8.31	310
Spain	Barcelona	Genotyped	IGAP_Spa	EADI	1016	54.23	66.97	10.31	1173	67.95	75.03	8.65	2189
Spain	Las Palmas	Genotyped	IGAP_Spa	EADI	290	36.55	70.01	5.84	244	68.03	75.84	6.94	534
Spain	Madrid	Genotyped	IGAP_Spa	EADI	153	61.44	67.73	14.44	91	60.44	68.43	9.90	244
Spain	Oviedo	Genotyped	IGAP_Spa	EADI	165	66.06	73.12	8.04	239	63.18	78.08	6.78	404
Spain	Santander	Genotyped	IGAP_Spa	EADI	251	68.53	80.55	7.44	344	63.95	73.67	7.05	595
Sweden	Stockholm	Genotyped	IGAP_Swe	EADI	1271	62.79	69.8	8.86	513	61.4	87	5.56	1784
Sweden	Uppsala	Genotyped	IGAP_Swe	EADI	225	61.33	74.64	6.10	277	62.82	76.49	8.01	502
Greece	Thessaloniki	Genotyped	IGAP_Gre	GERAD/PERADES	227	33.48	49.24	16.48	256	63.28	69.24	8.02	483
UK	Belfast	Genotyped	IGAP_UK	GERAD/PERADES	186	69.89	74.12	9.04	177	68.36	72.66	6.73	363
UK	Bristol	Genotyped	IGAP_UK	GERAD/PERADES	7	42.86	78.57	8.44	11	54.55	71.86	8.73	18
UK	Caerphilly	Genotyped	IGAP_UK	GERAD/PERADES	451	0	71.98	3.92	29	0	74.34	4.13	480
UK	Southampton2	Genotyped	IGAP_UK	GERAD/PERADES	70	55.71	73.94	8	95	67.37	78.61	7.50	165
UK	Notthingham2	Genotyped	IGAP_UK	GERAD/PERADES	267	49.81	76.76	6.76	157	50.32	72.88	8.76	424
USA	Jacksonville	Genotyped	IGAP_USA	GERAD/PERADES	1340	54.03	79.31	6.82	572	61.89	83.46	7.56	1912
Netherlands	RS1	Imputed	RS1	CHARGE	2304	63.28	82.37	7.06	589	76.74	83.74	6.43	2893
Netherlands	RS2	Imputed	RS2	CHARGE	942	54.99	81.37	5.87	133	59.40	82.75	6.75	1075
				STAGE 2 TOTAL	**21921**				**14041**				**35962**
USA	ACT	Imputed	ACT	ADGC	549	58.83	81.19	5.76	132	57.58	81.77	6.31	681
USA	ADC1	Imputed	ADC1	ADGC	90	59.18	76.8	8.8	213	65.42	71.9	8.8	303
USA	ADC2	Imputed	ADC2	ADGC	42	66.67	77.71	7.83	50	36	72.04	7.23	92

USA	ADC3	Imputed	ADC3	ADGC	129	66.67	78.03	10.24	146	56.16	71.91	7.55	275
USA	ADNI	Imputed	ADNI	ADGC	173	40.46	78.6	5.46	268	42.16	75.3	7.15	441
USA	GSK	Imputed	GSK	ADGC	712	63.9	74.2	7.02	652	56.9	74.58	6.17	1364
USA	LOAD	Imputed	LOAD	ADGC	1121	61.64	72.67	8.3	931	63.48	73.59	6.67	2052
USA	MAYO	Imputed	MAYO	ADGC	1046	51.15	72.91	4.36	658	57.45	73.57	4.83	1704
USA	MIRAGE	Imputed	MIRAGE	ADGC	727	58.46	72.03	7.18	71	67.61	72.27	6.89	798
USA	OHSU	Imputed	OHSU	ADGC	153	54.9	83.86	7.59	132	62.12	85.89	5.74	285
USA	ROSMAP	Imputed	ROSMAP	ADGC	747	72.29	82.09	7.11	288	70.49	85.59	6.24	1035
USA	TGEN2	Imputed	TGEN2	ADGC	365	48.49	79.97	8.67	617	66.61	73.49	6.76	982
USA	UMVUMSSM_B	Imputed	UMVUMSSM_B	ADGC	93	61.29	79.62	10.56	262	71.37	78.77	8.89	355
USA	UPITT	Imputed	UPITT	ADGC	828	63.41	75.48	6.03	1160	63.02	72.91	6.41	1988
USA	WASHU	Imputed	WASHU	ADGC	64	57.81	76.94	8.27	115	55.65	74.01	7.76	179
USA	ADC6	Imputed	ADC6	ADGC	290	66.55	73.56	9.03	134	55.22	73.31	7.75	424
USA	CHAP	Imputed	CHAP	ADGC	144	52.78	81.8	6.58	27	62.96	84.81	7.65	171
USA	MTV	Imputed	MTV	ADGC	188	61.7	71.35	7.74	251	56.97	74.57	7.7	439
USA	NBB	Imputed	NBB	ADGC	48	56.25	81.52	9.41	80	71.25	74.48	7.51	128
USA	ROSMAP2	Imputed	ROSMAP2	ADGC	217	76.04	80.8	7.2	59	77.97	81.95	6.91	276
USA	TARC1	Imputed	TARC1	ADGC	181	65.19	73.87	8.18	323	61.61	74.01	7.13	504
USA	WASHU2	Imputed	WASHU2	ADGC	71	50.7	71.38	6.2	38	57.89	73.39	7.34	109
USA	WHICAP	Imputed	WHICAP	ADGC	367	60.76	81.86	6.94	45	80	83.58	7.87	412
				STAGE 3 TOTAL	**8345**	60.38	76.19	6.99	**6652**	61.46	74.84	6.69	**14997**
				REPLICATION TOTAL	**30266**				**20693**				**50959**

*Initial/Age-at-onset provided for samples where known

	ADGC	CHARGE	GERAD
Calling Software	GenomeStudio followed by manual clustering[34]	GenomeStudio followed by manual clustering[34]	Genomestudio and z Call[1]
Exclude markers	>2% missing rate	>5% missing rate	>2% missing rate
HWE check	$P<1x10^{-6}$	$P<1x10^{-6}$	$P<1x10^{-6}$
Exclude subjects with missing rate	>2%	>5% at overall calling and within individual studies	>2%
Control for relatedness	IBS > 0.125	IBS > 0.45	IBS > 0.125

Gene	ID	Chr	position	Allele 1	*P*	OR	MAF	N
TREM2	rs75932628	6	41129252	T	3.02E-12	2.46	0.0049	30018
ATP5C1	rs139967528	10	7841811	G	5.89E-10	6.12	0.0007	33811
TREM2	rs143332484	6	41129207	T	3.48E-09	1.58	0.0123	33786
AHNAK	rs11828907	11	62288978	C	1.47E-07	4.60	0.0008	33811
TECTA	rs148619105	11	121016724	A	3.42E-07	0.55	0.0058	33786
BSG	rs201850688	19	572671	G	4.80E-07	2.14	0.0034	30302
ATM	rs56009889	11	108196896	T	2.81E-06	0.33	0.0011	33786
TRAF3IP2	rs139767840	6	111896863	C	7.66E-06	2.03	0.0029	33786
SNX1	rs1802376	15	64428559	A	1.09E-05	1.30	0.0205	33786
PLCG2	rs72824905	16	81942028	G	1.19E-05	0.65	0.0089	33786
B4GALNT2	rs141826857	17	47246239	A	1.78E-05	0.31	0.0010	33786
NLRC3	rs115489359	16	3613019	T	2.09E-05	3.22	0.0010	33786
ABI3	rs616338	17	47297297	T	2.16E-05	1.42	0.0113	33786
ASTN2	rs147163004	9	119413853	T	3.42E-05	13847.97	0.0001	33786
PLEKHG4	rs80024062	16	67320811	T	3.87E-05	0.53	0.0028	33786
C2orf69	rs200098289	2	200789858	G	4.52E-05	0.10	0.0002	33786
BTNL2	rs28362679	6	32363893	A	5.05E-05	1.31	0.0173	32322
NRAP	rs11575797	10	115350366	A	5.48E-05	0.16	0.0003	33786
KBTBD6	rs139419169	13	41706233	T	5.98E-05	3.07	0.0009	33786
FAIM3	rs41304091	1	207078467	A	6.10E-05	1.37	0.0127	33786
OASL	rs201720090	12	121469316	A	6.64E-05	0.08	0.0002	33786
LAMC1	rs150421474	1	183105709	A	8.74E-05	0.33	0.0009	33786
NUDT18	rs60087873	8	21965846	C	9.15E-05	8.96	0.0002	31216
HGFAC	rs114303452	4	3449915	G	1.11E-04	1.34	0.0132	31216
TTN	rs55725279	2	179393898	A	1.22E-04	0.35	0.0009	33786
CD2AP	rs138727736	6	47563608	G	1.31E-04	0.60	0.0052	28281
DEFA6	rs45479905	8	6783479	T	1.31E-04	2.21	0.0016	33786
IFT140	rs138674110	16	1616256	T	1.75E-04	52.30	0.0001	33786
THSD4	rs201879533	15	72039251	T	2.27E-04	0.27	0.0011	15896
LAPTM4B	rs141075645	8	98828352	T	2.37E-04	0.14	0.0002	33786
RHBDF1	rs78541046	16	113027	A	3.38E-04	0.28	0.0011	15896
ISM2	rs149849326	14	77944624	C	3.47E-04	1.25	0.0189	33786
STOX1	rs201329017	10	70646130	A	4.03E-04	2.52	0.0012	30504
AMT	rs144971200	3	49455386	C	7.08E-04	0.43	0.0011	33786
MUC17	rs73712043	7	100680521	A	8.79E-04	1.29	0.0140	31188
SEC14L6	rs118116676	22	30934885	T	1.15E-03	0.81	0.0192	33786
PLVAP	rs34920409	19	17476933	T	1.18E-03	1.28	0.0141	33786
CHST6	rs139042144	16	75512546	T	1.35E-03	0.21	0.0003	33786
KIAA1324L	rs138544248	7	86554948	A	1.39E-03	425.96	0.0001	33811
SCG2	rs201824633	2	224463369	T	1.78E-03	5.83	0.0002	33786
BST1	rs141013660	4	15713513	A	4.29E-03	14.73	0.0001	33786
KIAA0415	rs201862383	7	4823883	T	1.11E-02	0.52	0.0010	33786
UTRN	rs146738862	6	144747588	G	2.52E-02	0.17	0.0001	33811

Genome wide significant

Gene	ID	chr	BP	*P*	OR	MAF	N
APOE	rs769449	19	45410002	0.00E+00	2.88	0.188	33786
APOE	rs7412	19	45412079	2.69E-105	0.43	0.059	31216
CR1	rs6656401	1	207692049	7.32E-11	1.17	0.195	23380
CLU	rs1532278	8	27466315	5.76E-10	0.89	0.376	33786
CR1	rs2296160	1	207795320	6.42E-10	1.21	0.191	14406
CLU	rs11136000	8	27464519	7.18E-10	0.90	0.383	33786
CR1	rs6701713	1	207786289	7.36E-10	1.14	0.200	33786
CR1	rs3818361	1	207784968	7.65E-10	1.14	0.200	33786
CLU	rs2279590	8	27456253	2.31E-08	0.91	0.395	33786
Suggestive							
BIN1	rs1060743	2	127826533	5.18E-08	1.11	0.31	33786
MS4A6A	rs7232	11	59940599	5.95E-07	0.91	0.37	33786
CD33	rs3865444	19	51727962	1.73E-06	0.91	0.31	33786
BIN1	rs755639	2	127860149	6.99E-06	0.92	0.40	33786
HLA-DQA1	rs1048023	6	32609150	1.59E-05	0.89	0.16	23380
ABCA7	rs3764650	19	1046520	2.87E-05	1.13	0.10	31216
INPP5D	rs1135173	2	234054873	3.81E-05	1.07	0.48	33786
Previously described risk loci							
CD33	rs3865444	19	51727962	1.73E-06	0.91	0.31	33786
CD33	rs35112940	19	51738917	5.42E-04	0.93	0.20	33786
SQSTM1	rs55793208	5	179260099	8.62E-04	1.23	0.02	29040
UNC5C	rs148691835	4	96140171	7.13E-03	0.12	0.00	33786
AKAP9	rs200034525	7	91630628	9.53E-03	0.15	0.00	33786
APP	rs2830088	21	27514740	9.90E-03	0.96	0.44	33786
MAPT	rs63750096	17	44073923	1.01E-02	1.93	0.00	33786
PLD3	rs145999145	19	40877595	3.45E-02	0.65	0.00	11352
TRIP4	rs74019250	15	64706312	4.10E-02	27.92	0.00	33786
PLXNA4	rs190791576	7	131913187	5.38E-02	0.11	0.00	33786
MTHFR	rs17367504	1	11862778	6.39E-02	1.05	0.16	33786
TTC3	rs138008526	21	38567985	6.57E-02	1.28	0.00	33786
PSEN2	rs61757781	1	227075813	7.90E-02	1.94	0.00	33786
ZNF628	rs147110934	19	55993436	8.80E-02	1.11	0.02	33786
KCTD2	rs11077773	17	73060073	9.13E-02	0.94	0.09	28281
CYP2D6	rs1135822	22	42525182	1.12E-01	0.25	0.00	20098
ATP5H	rs147284668	17	73038319	1.12E-01	0.53	0.00	33786
ADAM10	rs61751103	15	58957371	1.14E-01	0.74	0.00	33786
PSEN1	rs362373	14	73673178	3.31E-01	1.06	0.02	33786
TREML2	NA	NA	NA	NA	NA	NA	NA

SNP	Chromosome	Basepair position	Concordance (%)	Alternate Allele Carriers (Heterozygotes/Alternate Homozygotes) (n)	Subjects/Alleles (n)
rs189301790	16	81819671	86.67	27	11245/22490
rs147349332	16	81819704	--	0	11246/22492
rs61755444	16	81891928	100	9	11246/22492
rs199760975	16	81916888	66.67	10	11245/22490
rs45443101	16	81922781	88.7	871	11244/22488
rs17537869	16	81922813	98.22	1616	11246/22492
rs199636472	16	81925132	100	30	11246/22492
rs200506549	16	81927314	90	43	11246/22492
rs201654184	16	81929499	66.67	15	11245/22490
rs187956469	16	81939089	87.36	93	11244/22488
rs72824905	16	81942028	95.74	179	11243/22486
rs75472618	16	81942175	95.35	158	11245/22490
rs147396004	16	81944250	79.17	26	11244/22488
rs150833842	16	81946278	96.49	61	11246/22492
rs143195637	16	81953128	--	2	9782/19564
rs187454354	16	81953195	100	5	11246/22492
rs117077093	16	81957175	72.73	12	11245/22490
rs115583707	16	81960783	--	0	11246/22492
rs114618894	16	81962190	--	1	11245/22490
rs200677528	16	81965151	100	13	11243/22486
rs139462941	16	81968131	75	3	11246/22492
rs114262189	16	81971435	100	2	11246/22492
rs2233369	17	47293906	98.67	1139	11245/22490
rs201757928	17	47294000	--	4	11230/22460
rs142527437	17	47295162	87.5	39	11246/22492

rs137924898	17	47295165	100	3	11246/22492
rs616338	17	47297297	81.9	240	11246/22492
rs200867869	17	47297547	92	23	11246/22492
rs150100821	17	47299919	84.13	92	11246/22492
rs190840748	16	81916932	--	3	11246/22492
rs74032923	16	81954829	--	2	11242/22484
rs138355759	6	41126619	87.5	13	11246/22492
rs2234256	6	41126655	100	26	11246/22492
rs2234255	6	41127543	81.82	10	11246/22492
rs79011726	6	41127561	83.33	6	11244/22488
rs145080901	6	41129078	0	2	11246/22492
rs142232675	6	41129133	96.15	38	11246/22492
rs143332484	6	41129207	91.09	269	11244/22488
rs75932628	6	41129252	75.21	114	10825/21650
rs1800054	11	108098576	89.2	276	11242/22484
rs148590073	11	108106435	100	4	11245/22490
rs2234997	11	108106443	100	53	11239/22478
rs3218707	11	108114727	77.27	21	11241/22482
rs79075295	11	108114749	--	0	11245/22490
rs28904919	11	108117787	90.91	31	11244/22488
rs202160435	11	108117799	100	2	11246/22492
rs56128736	11	108119823	90.48	73	11239/22478
rs2235000	11	108121733	85.71	8	11246/22492
rs2227924	11	108122592	100	6	11246/22492
rs2235006	11	108122700	75	20	11239/22478
rs2227922	11	108123551	90.67	83	11245/22490
rs147934285	11	108124738	--	1	11246/22492
rs4986761	11	108124761	88.16	267	11243/22486

rs34231402	11	108128246	100	14	11235/22470
rs641252	11	108128319	--	0	11244/22488
rs3218695	11	108129778	100	4	11246/22492
rs1800056	11	108138003	92.79	313	11241/22482
rs61734354	11	108138039	100	1	11246/22492
rs139552233	11	108141988	100	15	11243/22486
rs146531614	11	108142070	92.86	16	11243/22486
rs3092857	11	108143299	80	6	11238/22476
rs1800057	11	108143456	95.99	583	11244/22488
rs2229020	11	108150316	100	2	11246/22492
rs149711770	11	108155132	100	23	11246/22492
rs3092856	11	108159732	85.71	12	11242/22484
rs1800058	11	108160350	98.44	395	11243/22486
rs201666889	11	108160416	50	9	11245/22490
rs145667735	11	108160467	--	0	11234/22468
rs138327406	11	108160480	32.69	20	10820/21640
rs34640941	11	108160516	75	20	11246/22492
rs140856217	11	108164137	66.67	19	11236/22472
rs55870064	11	108168053	--	0	11244/22488
rs1800059	11	108170506	80.77	48	11246/22492
rs1801516	11	108175462	99.54	3235	11246/22492
rs1801673	11	108175463	86.73	135	9573/19146
rs147187700	11	108180945	--	3	11245/22490
rs11212587	11	108186610	88	43	11240/22480
rs145847315	11	108186631	50	1	11245/22490
rs1800060	11	108188136	100	38	11245/22490
rs56815840	11	108190770	--	0	11244/22488
rs56009889	11	108196896	100	47	11246/22492

rs148432863	11	108198384	100	1	11245/22490
rs4988111	11	108198391	100	1	11246/22492
rs55801750	11	108201023	87.5	12	9758/19516
rs56399857	11	108201108	50	1	11242/22484
rs201958469	11	108216611	100	4	11246/22492
rs201199629	11	108236150	--	1	11246/22492

					STAGE1						STAGE2						COMBINED STAGES 1+2						STAGE3						COMBINED STAGES 1+2+3					
Gene	**ID**	**Chr**	**position**	**Allele 1**	***P***	**OR**	**L95%CI**	**U95%CI**	**MAF**	**N**	***P***	**OR**	**L95%CI**	**U95%CI**	**MAF**	**N**	***P***	**OR**	**L95%CI**	**U95%CI**	**MAF**	**N**	***P***	**OR**	**L95%CI**	**U95%CI**	**MAF**	**N**	***P***	**OR**	**L95%CI**	**U95%CI**	**MAF**	**N**
TREM2	rs75932628	6	41129252	T	3.02E-12	2.46	1.91	3.17	0.0049	30018	4.38E-08	2.37	1.74	3.22	0.00267	35831	7.56E-19	2.42	1.99	2.95	0.0037	65849	1.23E-06	2.58	1.76	3.79	0.005	14884	5.38E-24	2.46	2.06	2.92	0.00396	80733
TREM2	rs143332484	6	41129207	T	3.48E-09	1.58	1.36	1.84	0.0123	33786	3.66E-07	3.97	2.33	6.75	0.01397	3968	1.43E-12	1.70	1.47	1.97	0.0125	37754	2.45E-03	1.55	1.17	2.07	0.010	15288	1.55E-14	1.67	1.46	1.90	0.01179	53042
PLCG2	rs72824905	16	81942028	G	1.19E-05	0.65	0.54	0.79	0.0089	33786	1.35E-04	0.70	0.58	0.84	0.00800	35831	7.09E-09	0.68	0.59	0.77	0.0084	69617	2.48E-02	0.69	0.50	0.95	0.006	15288	5.38E-10	0.68	0.60	0.77	0.00804	84905
ATP5C1	rs139967528	10	7841811	G	5.89E-10	6.12	3.45	10.86	0.0007	33811	NA	NA	NA	NA	NA	NA	6.18E-01	2.13	0.11	41.34	0.0000	68084	NA	NA	NA	NA	NA	NA	5.89E-10	6.12	3.45	10.86	0.00038	65674
ABI3	rs616338	17	47297297	T	2.16E-05	1.42	1.21	1.67	0.0113	33786	8.37E-05	1.41	1.19	1.67	0.009290266	35831	7.08E-09	1.42	1.26	1.59	0.01027637	69617	1.75E-02	1.58	1.08	2.31	0.009	14876	4.56E-10	1.43	1.28	1.60	0.009991017	84493
TECTA	rs148619105	11	121016724	A	3.42E-07	0.55	0.43	0.69	0.0058	33786	9.00E-02	0.31	0.08	1.20	0.00027	16690	1.09E-07	0.54	0.43	0.68	0.0040	50476	NA	NA	NA	NA	NA	NA	1.09E-07	0.54	0.43	0.68	0.00397	50476
AHNAK	rs11828907	11	62288978	C	1.47E-07	4.60	2.60	8.13	0.0008	33811	7.09E-01	0.32	0.00	128.77	0.00001	35831	6.34E-01	1.41	0.34	5.79	0.0001	72052	NA	NA	NA	NA	NA	NA	2.02E-07	4.49	2.55	7.92	0.00037	69946
BSG	rs201850688	19	572671	G	4.80E-07	2.14	1.59	2.88	0.0034	30302	9.63E-01	0.99	0.57	1.71	0.00167	16690	1.02E-05	1.80	1.39	2.34	0.0028	46992	NA	NA	NA	NA	NA	NA	8.98E-06	1.80	1.39	2.34	0.00274	47296
PLEKHG4	rs80024062	16	67320811	T	3.87E-05	0.53	0.40	0.72	0.0028	33786	9.70E-02	0.69	0.45	1.07	0.00135	35831	1.49E-05	0.58	0.45	0.74	0.0021	69617	NA	NA	NA	NA	NA	NA	1.70E-05	0.58	0.46	0.75	0.00207	69921
OASL	rs201720090	12	121469316	A	6.64E-05	0.08	0.02	0.28	0.0002	33786	1.54E-01	0.18	0.02	1.90	0.00009	16759	2.73E-05	0.10	0.03	0.29	0.0001	50545	NA	NA	NA	NA	NA	NA	2.73E-05	0.10	0.03	0.29	0.00015	50545
ASTN2	rs147163004	9	119413853	T	3.42E-05	13847.97	152.20	1259962.23	0.0001	33786	NA	NA	NA	NA	NA	NA	3.42E-05	13847.97	152.20	1259962.23	0.0001	33786	NA	NA	NA	NA	NA	NA	3.42E-05	13847.97	152.20	1259962.23	0.00006	33786
C2orf69	rs200098289	2	200789858	G	4.52E-05	0.10	0.03	0.30	0.0002	33786	NA	NA	NA	NA	NA	NA	4.52E-05	0.10	0.03	0.30	0.0001	65649	NA	NA	NA	NA	NA	NA	4.52E-05	0.10	0.03	0.30	0.00010	65649
LAPTM4B	rs141075645	8	98828352	T	2.37E-04	0.14	0.05	0.39	0.0002	33786	7.86E-02	0.16	0.02	1.23	0.00012	16750	4.65E-05	0.14	0.06	0.36	0.0002	50536	NA	NA	NA	NA	NA	NA	4.65E-05	0.14	0.06	0.36	0.00020	50536
ATM	rs56009889	11	108196896	T	2.81E-06	0.33	0.21	0.52	0.0011	33786	9.19E-02	0.31	0.08	1.21	0.00016	31863	6.44E-07	0.33	0.21	0.51	0.0007	65649	NA	NA	NA	NA	NA	NA	6.44E-07	0.33	0.21	0.51	0.0007	65649
KBTBD6	rs139419169	13	41706233	T	5.98E-05	3.07	1.77	5.30	0.0009	33786	NA	NA	NA	NA	NA	NA	5.98E-05	3.07	1.77	5.30	0.0009	33786	NA	NA	NA	NA	NA	NA	5.98E-05	3.07	1.77	5.30	0.00089	33786
SNX1	rs1802376	15	64428559	A	1.09E-05	1.30	1.16	1.47	0.0205	33786	1.17E-01	1.09	0.98	1.21	0.02386	35831	4.43E-05	1.18	1.09	1.27	0.0222	69617	NA	NA	NA	NA	NA	NA	7.18E-05	1.17	1.08	1.27	0.02224	69921
B4GALNT2	rs141826857	17	47246239	A	1.78E-05	0.31	0.18	0.53	0.0010	33786	9.89E-01	0.99	0.38	2.61	0.00030	31863	1.68E-04	0.41	0.26	0.65	0.0006	65649	NA	NA	NA	NA	NA	NA	1.68E-04	0.41	0.26	0.65	0.00064	65953
IFT140	rs138674110	16	1616256	T	1.75E-04	52.30	6.62	413.04	0.0001	33786	NA	NA	NA	NA	NA	NA	1.75E-04	52.30	6.62	413.04	0.0001	33786	NA	NA	NA	NA	NA	NA	1.75E-04	52.30	6.62	413.04	0.00007	33786
THSD4	rs201879533	15	72039251	T	2.27E-04	0.27	0.13	0.54	0.0011	15896	NA	NA	NA	NA	NA	NA	2.27E-04	0.27	0.13	0.54	0.0011	15896	NA	NA	NA	NA	NA	NA	2.27E-04	0.27	0.13	0.54	0.00107	15896
TRAF3IP2	rs139767840	6	111896863	C	7.66E-06	2.03	1.49	2.78	0.0029	33786	4.17E-01	1.13	0.84	1.53	0.00290	35831	2.23E-04	1.50	1.21	1.86	0.0029	69617	NA	NA	NA	NA	NA	NA	2.66E-04	1.49	1.20	1.85	0.00293	69921
NLRC3	rs115489359	16	3613019	T	2.09E-05	3.22	1.88	5.51	0.0010	33786	2.59E-01	0.46	0.12	1.77	0.00014	31863	4.08E-04	2.46	1.49	4.06	0.0006	65649	NA	NA	NA	NA	NA	NA	3.22E-04	2.49	1.51	4.08	0.00057	65953
RHBDF1	rs78541046	16	113027	A	3.38E-04	0.28	0.14	0.56	0.0011	15896	NA	NA	NA	NA	NA	NA	3.38E-04	0.28	0.14	0.56	0.0011	15896	NA	NA	NA	NA	NA	NA	3.41E-04	0.28	0.14	0.56	0.00105	16200
DEFA6	rs45479905	8	6783479	T	1.31E-04	2.21	1.47	3.31	0.0016	33786	2.48E-01	1.27	0.85	1.91	0.00141	35831	4.23E-04	1.68	1.26	2.24	0.0015	69617	NA	NA	NA	NA	NA	NA	4.02E-04	1.68	1.26	2.24	0.00150	69921
AMT	rs144971200	3	49455386	C	7.08E-04	0.43	0.26	0.70	0.0011	33786	NA	NA	NA	NA	NA	NA	7.08E-04	0.43	0.26	0.70	0.0011	33786	NA	NA	NA	NA	NA	NA	7.09E-04	0.43	0.26	0.70	0.00107	34090
STOX1	rs201329017	10	70646130	A	4.03E-04	2.52	1.51	4.21	0.0012	30504	5.30E-01	0.47	0.04	4.93	0.00082	3968	8.91E-04	2.34	1.42	3.85	0.0011	34472	NA	NA	NA	NA	NA	NA	8.79E-04	2.34	1.42	3.86	0.00112	34776
NUDT18	rs60087873	8	21965846	C	9.15E-05	8.96	2.99	26.90	0.0002	31216	2.88E-01	1.64	0.66	4.05	0.00031	31863	9.31E-04	3.26	1.62	6.57	0.0003	63079	NA	NA	NA	NA	NA	NA	9.31E-04	3.26	1.62	6.57	0.00027	63079
NRAP	rs11575797	10	115350366	A	5.48E-05	0.16	0.07	0.40	0.0003	33786	7.92E-01	0.86	0.29	2.56	0.00022	31863	9.47E-04	0.32	0.16	0.63	0.0003	65649	NA	NA	NA	NA	NA	NA	9.48E-04	0.32	0.16	0.63	0.00028	65953
CD2AP	rs138727736	6	47563608	G	1.31E-04	0.60	0.46	0.78	0.0052	28281	2.40E-01	0.88	0.72	1.09	0.00601	35831	9.95E-04	0.76	0.64	0.89	0.0057	64112	NA	NA	NA	NA	NA	NA	9.55E-04	0.76	0.64	0.89	0.00566	64416
PLVAP	rs34920409	19	17476933	T	1.18E-03	1.28	1.10	1.49	0.0141	33786	8.29E-01	1.07	0.57	2.03	0.01280	3968	1.34E-03	1.27	1.10	1.47	0.0140	37754	NA	NA	NA	NA	NA	NA	1.08E-03	1.27	1.10	1.47	0.01396	38058
MUC17	rs73712043	7	100680521	A	8.79E-04	1.29	1.11	1.51	0.0140	31188	8.11E-01	1.06	0.64	1.75	0.01495	3968	1.14E-03	1.27	1.10	1.47	0.0141	35156	NA	NA	NA	NA	NA	NA	1.14E-03	1.27	1.10	1.47	0.01405	35460
SCG2	rs201824633	2	224463369	T	1.78E-03	5.83	1.93	17.63	0.0002	33786	NA	NA	NA	NA	NA	NA	1.78E-03	5.83	1.93	17.63	0.0002	33786	NA	NA	NA	NA	NA	NA	1.78E-03	5.83	1.93	17.63	0.00019	33786
LAMC1	rs150421474	1	183105709	A	8.74E-05	0.33	0.19	0.58	0.0009	33786	7.24E-01	0.90	0.51	1.60	0.00084	35831	2.11E-03	0.54	0.36	0.80	0.0009	69617	NA	NA	NA	NA	NA	NA	2.06E-03	0.53	0.36	0.80	0.00087	69921
SEC14L6	rs118116676	22	30934885	T	1.15E-03	0.81	0.71	0.92	0.0192	33786	6.93E-01	1.10	0.69	1.73	0.01734	3968	2.46E-03	0.83	0.73	0.94	0.0190	37754	NA	NA	NA	NA	NA	NA	2.47E-03	0.83	0.73	0.94	0.01910	38058
ISM2	rs149849326	14	77944624	C	3.47E-04	1.25	1.11	1.41	0.0189	33786	6.77E-01	1.03	0.89	1.20	0.01949	20658	2.29E-03	1.16	1.05	1.27	0.0191	54444	NA	NA	NA	NA	NA	NA	2.51E-03	1.16	1.05	1.27	0.01912	54748
TTN	rs55725279	2	179393898	A	1.22E-04	0.35	0.21	0.60	0.0009	33786	9.75E-01	0.99	0.51	1.91	0.00060	35831	2.58E-03	0.53	0.35	0.80	0.0008	69617	NA	NA	NA	NA	NA	NA	2.58E-03	0.53	0.35	0.80	0.00075	69921
BST1	rs141013660	4	15713513	A	4.29E-03	14.73	2.33	93.35	0.0001	33786	NA	NA	NA	NA	NA	NA	4.29E-03	14.73	2.33	93.35	0.0001	33786	NA	NA	NA	NA	NA	NA	4.29E-03	14.73	2.34	93.99	0.0001	33786
HGFAC	rs114303452	4	3449915	G	1.11E-04	1.34	1.16	1.56	0.0132	31216	6.36E-01	1.03	0.90	1.18	0.01382	35831	3.04E-03	1.16	1.05	1.29	0.0135	67047	NA	NA	NA	NA	NA	NA	4.40E-03	1.16	1.05	1.28	0.01353	67351
BTNL2	rs28362679	6	32363893	A	5.05E-05	1.31	1.15	1.49	0.0173	32322	9.25E-01	0.99	0.87	1.14	0.02858	16690	4.17E-03	1.15	1.04	1.26	0.0211	49012	NA	NA	NA	NA	NA	NA	4.47E-03	1.14	1.04	1.26	0.02114	49316
KIAA0415	rs201862383	7	4823883	T	1.11E-02	0.52	0.31	0.86	0.0010	33786	NA	NA	NA	NA	NA	NA	1.11E-02	0.52	0.31	0.86	0.0010	33786	NA	NA	NA	NA	NA	NA	1.11E-02	0.52	0.31	0.84	0.0010	33786
FAIM3	rs41304091	1	207078467	A	6.10E-05	1.37	1.18	1.60	0.0127	33786	3.16E-01	0.92	0.78	1.08	0.01026	35831	2.39E-02	1.14	1.02	1.28	0.0114	69617	NA	NA	NA	NA	NA	NA	2.20E-02	1.14	1.02	1.28	0.01143	69921
UTRN	rs146738862	6	144747588	G	2.52E-02	0.17	0.03	0.80	0.0001	33811	NA	NA	NA	NA	NA	NA	2.52E-02	0.17	0.03	0.80	0.0001	33811	NA	NA	NA	NA	NA	NA	2.52E-02	0.17	0.03	0.80	0.00012	33811
KIAA1324L	rs138544248	7	86554948	A	1.39E-03	425.96	10.41	17430.94	0.0001	33811	5.17E-01	0.24	0.00	17.75	0.00002	31863	4.60E-02	17.46	1.05	289.70	0.0000	65674	NA	NA	NA	NA	NA	NA	4.60E-02	17.46	1.05	289.70	0.00004	65674
CHST6	rs139042144	16	75512546	T	1.35E-03	0.21	0.08	0.54	0.0003	33786	1.85E-01	2.31	0.67	7.98	0.00030	20605	8.72E-02	0.51	0.24	1.10	0.0003	54391	NA	NA	NA	NA	NA	NA	8.91E-02	0.52	0.24	1.11	0.00030	54695

					STAGE1						STAGE2						COMBINED STAGES 1+2						STAGE3						COMBINED STAGES 1+2+3					
Gene	**ID**	**Chr**	**position**	**Allele 1**	***P***	**OR**	**L95%CI**	**U95%CI**	**MAF**	**N**	***P***	**OR**	**L95%CI**	**U95%CI**	**MAF**	**N**	***P***	**OR**	**L95%CI**	**U95%CI**	**MAF**	**N**	***P***	**OR**	**L95%CI**	**U95%CI**	**MAF**	**N**	***P***	**OR**	**L95%CI**	**U95%CI**	**MAF**	**N**
TREM2	rs75932628	6	41129252	T	3.95E-08	2.21	1.66	2.93	0.00511	28278	1.96E-08	2.56	1.84	3.55	0.00267	35374	4.97E-15	2.35	1.90	2.91	0.00376	63652	1.31E-06	2.65	1.79	3.94	0.005	14593	4.05E-20	2.42	2.00	2.92	0.00401	78245
TREM2	rs143332484	6	41129207	T	8.30E-07	1.52	1.28	1.79	0.01237	32046	7.27E-07	3.83	2.25	6.52	0.01397	3968	6.53E-10	1.64	1.40	1.93	0.01255	36014	3.75E-03	1.55	1.15	2.09	0.010	14997	9.42E-12	1.62	1.41	1.87	0.01179	51011
ATP5C1	rs139967528	10	7841811	G	1.58E-09	6.20	3.43	11.21	0.00074	32071	NA	NA	NA	NA	NA	NA	1.58E-09	6.20	3.43	11.21	0.00038	63477	NA	NA	NA	NA	NA	NA	1.58E-09	6.20	3.43	11.21	0.00038	63477
PLCG2	rs72824905	16	81942028	G	1.52E-04	0.68	0.55	0.83	0.00893	32046	1.09E-04	0.68	0.56	0.83	0.00801	35374	6.15E-08	0.68	0.59	0.78	0.00845	67420	3.19E-02	0.69	0.50	0.97	0.006	14997	5.80E-09	0.68	0.60	0.77	0.00806	82417
ABI3	rs616338	17	47297297	T	1.98E-04	1.40	1.17	1.67	0.01141	32046	5.29E-04	1.41	1.16	1.71	0.00851	35374	3.66E-07	1.40	1.23	1.60	0.00989	67420	1.81E-02	1.60	1.08	2.38	0.009	14585	4.86E-09	1.43	1.27	1.62	0.010004	82005
AHNAK	rs11828907	11	62288978	C	8.37E-07	4.39	2.44	7.90	0.00078	32071	7.41E-01	0.33	0.00	234.15	0.00002	35374	1.07E-06	4.30	2.39	7.72	0.00038	67445	NA	NA	NA	NA	NA	NA	1.07E-06	4.30	2.39	7.72	0.00038	67748
RHBDF1	rs78541046	16	113027	A	1.63E-06	0.16	0.08	0.34	0.00106	14156	NA	NA	NA	NA	NA	NA	1.63E-06	0.16	0.08	0.34	0.00106	14156	NA	NA	NA	NA	NA	NA	1.64E-06	0.16	0.08	0.34	0.00104	14459
THSD4	rs201879533	15	72039251	T	4.40E-06	0.18	0.08	0.37	0.00113	14156	NA	NA	NA	NA	NA	NA	4.40E-06	0.18	0.08	0.37	0.00113	14156	NA	NA	NA	NA	NA	NA	4.40E-06	0.18	0.08	0.37	0.00113	14156
UTRN	rs146738862	6	144747588	G	1.66E-05	0.00	0.00	0.00	0.00002	32071	NA	NA	NA	NA	NA	NA	1.66E-05	0.00	0.00	0.00	0.00002	32071	NA	NA	NA	NA	NA	NA	1.66E-05	0.00	0.00	0.00	0.00002	32071
IFT140	rs138674110	16	1616256	T	1.73E-05	142.43	14.83	1367.60	0.00008	32046	NA	NA	NA	NA	NA	NA	1.73E-05	142.43	14.83	1367.60	0.00008	32046	NA	NA	NA	NA	NA	NA	1.73E-05	142.43	14.83	1367.60	0.00008	32046
BSG	rs201850688	19	572671	G	1.07E-06	2.19	1.60	3.00	0.00347	28562	8.18E-01	0.94	0.53	1.65	0.00167	16690	3.23E-05	1.79	1.36	2.36	0.00280	45252	NA	NA	NA	NA	NA	NA	2.98E-05	1.80	1.37	2.37	0.00279	45555
LAPTM4B	rs141075645	8	98828352	T	9.89E-05	0.12	0.04	0.35	0.00025	32046	1.55E-01	0.21	0.02	1.81	0.00012	16750	3.82E-05	0.13	0.05	0.35	0.00021	48796	NA	NA	NA	NA	NA	NA	3.82E-05	0.13	0.05	0.35	0.00021	48796
SCG2	rs201824633	2	224463369	T	3.95E-05	12.94	3.82	43.84	0.00019	32046	NA	NA	NA	NA	NA	NA	3.95E-05	12.94	3.82	43.84	0.00019	32046	NA	NA	NA	NA	NA	NA	3.95E-05	12.94	3.82	43.84	0.00019	32046
PLEKHG4	rs80024062	16	67320811	T	4.08E-04	0.57	0.42	0.78	0.00293	32046	4.59E-02	0.63	0.40	0.99	0.00137	35374	5.30E-05	0.59	0.46	0.76	0.00211	67420	NA	NA	NA	NA	NA	NA	4.94E-05	0.59	0.46	0.76	0.00213	67723
ASTN2	rs147163004	9	119413853	T	5.03E-05	9683.92	114.56	818612.09	0.00006	32046	NA	NA	NA	NA	NA	NA	5.03E-05	9683.92	114.56	818612.09	0.00006	32046	NA	NA	NA	NA	NA	NA	5.03E-05	9683.92	114.56	818612.09	0.00006	32046
NLRC3	rs115489359	16	3613019	T	4.04E-05	3.17	1.83	5.49	0.00101	32046	9.84E-01	0.98	0.13	7.12	0.00013	31406	7.80E-05	2.91	1.71	4.95	0.00057	63452	NA	NA	NA	NA	NA	NA	6.21E-05	2.93	1.73	4.96	0.00058	63755
C2orf69	rs200098289	2	200789858	G	6.33E-05	0.10	0.03	0.31	0.00020	32046	NA	NA	NA	NA	NA	NA	6.33E-05	0.10	0.03	0.31	0.00010	63452	NA	NA	NA	NA	NA	NA	6.33E-05	0.10	0.03	0.31	0.00010	63452
AMT	rs144971200	3	49455386	C	6.60E-05	0.34	0.20	0.58	0.00103	32046	NA	NA	NA	NA	NA	NA	6.60E-05	0.34	0.20	0.58	0.00103	32046	NA	NA	NA	NA	NA	NA	6.61E-05	0.34	0.20	0.58	0.00102	32349
BST1	rs141013660	4	15713513	A	6.80E-05	99.59	10.35	958.21	0.00014	32046	NA	NA	NA	NA	NA	NA	6.80E-05	99.59	10.35	958.21	0.00014	32046	NA	NA	NA	NA	NA	NA	6.61E-05	100.32	10.43	965.14	0.00014	32349
PLVAP	rs34920409	19	17476933	T	1.27E-04	1.37	1.17	1.61	0.01424	32046	8.02E-01	1.09	0.57	2.07	0.01280	3968	1.58E-04	1.35	1.16	1.58	0.01408	36014	NA	NA	NA	NA	NA	NA	1.25E-04	1.36	1.16	1.59	0.01406	36317
ATM	rs56009889	11	108196896	T	1.13E-05	0.34	0.21	0.55	0.00120	32046	2.13E-01	0.38	0.09	1.73	0.00016	31406	5.08E-06	0.34	0.21	0.54	0.00069	63452	NA	NA	NA	NA	NA	NA	5.08E-06	0.34	0.21	0.54	0.00069	63452
OASL	rs201720090	12	121469316	A	1.05E-03	0.12	0.03	0.43	0.00017	32046	5.63E-02	0.08	0.01	1.07	0.00009	16759	1.54E-04	0.11	0.04	0.35	0.00014	48805	NA	NA	NA	NA	NA	NA	1.54E-04	0.11	0.04	0.35	0.00014	48805
MUC17	rs73712043	7	100680521	A	1.16E-04	1.39	1.17	1.63	0.01405	29448	6.93E-01	1.11	0.67	1.84	0.01495	3968	1.52E-04	1.36	1.16	1.59	0.01416	33416	NA	NA	NA	NA	NA	NA	1.59E-04	1.35	1.16	1.58	0.01409	33719
SEC14L6	rs118116676	22	30934885	T	8.05E-05	0.76	0.66	0.87	0.01943	32046	7.13E-01	1.09	0.69	1.73	0.01734	3968	2.39E-04	0.78	0.69	0.89	0.01920	36014	NA	NA	NA	NA	NA	NA	2.04E-04	0.78	0.69	0.89	0.01925	36317
DEFA6	rs45479905	8	6783479	T	5.40E-05	2.46	1.59	3.80	0.00161	32046	2.67E-01	1.30	0.82	2.05	0.00138	35374	2.24E-04	1.81	1.32	2.49	0.00149	67420	NA	NA	NA	NA	NA	NA	2.15E-04	1.82	1.32	2.49	0.00149	67723
B4GALNT2	rs141826857	17	47246239	A	5.88E-05	0.32	0.18	0.56	0.00100	32046	9.10E-01	0.94	0.32	2.77	0.00029	31406	2.94E-04	0.40	0.24	0.66	0.00065	63452	NA	NA	NA	NA	NA	NA	2.95E-04	0.40	0.24	0.66	0.00064	63755
STOX1	rs201329017	10	70646130	A	9.88E-05	3.04	1.74	5.33	0.00118	29190	4.66E-01	0.42	0.04	4.24	0.00082	3968	3.06E-04	2.73	1.58	4.70	0.00114	33158	NA	NA	NA	NA	NA	NA	2.99E-04	2.73	1.58	4.71	0.00113	33461
TECTA	rs148619105	11	121016724	A	8.64E-04	0.66	0.51	0.84	0.00568	32046	9.29E-02	0.31	0.08	1.22	0.00027	16690	3.50E-04	0.64	0.50	0.82	0.00383	48736	NA	NA	NA	NA	NA	NA	3.50E-04	0.64	0.50	0.82	0.00383	48736
TRAF3IP2	rs139767840	6	111896863	C	8.93E-05	1.95	1.40	2.73	0.00300	32046	3.21E-01	1.17	0.86	1.60	0.00291	35374	6.74E-04	1.49	1.18	1.87	0.00295	67420	NA	NA	NA	NA	NA	NA	7.34E-04	1.48	1.18	1.86	0.00298	67723
ISM2	rs149849326	14	77944624	C	2.14E-05	1.33	1.17	1.52	0.01876	32046	8.78E-01	1.01	0.87	1.18	0.01949	20658	7.95E-04	1.19	1.07	1.31	0.01904	52704	NA	NA	NA	NA	NA	NA	8.00E-04	1.19	1.07	1.31	0.01907	53007
SNX1	rs1802376	15	64428559	A	5.23E-04	1.26	1.10	1.43	0.02039	32046	1.34E-01	1.09	0.97	1.22	0.02373	35374	6.53E-04	1.16	1.06	1.26	0.02214	67420	NA	NA	NA	NA	NA	NA	1.07E-03	1.15	1.06	1.25	0.02218	67723
LAMC1	rs150421474	1	183105709	A	2.27E-05	0.28	0.15	0.50	0.00092	32046	7.27E-01	0.90	0.50	1.63	0.00085	35374	1.16E-03	0.50	0.33	0.76	0.00088	67420	NA	NA	NA	NA	NA	NA	1.13E-03	0.50	0.33	0.76	0.00088	67723
KBTBD6	rs139419169	13	41706233	T	1.17E-03	2.71	1.48	4.94	0.00087	32046	NA	NA	NA	NA	NA	NA	1.17E-03	2.71	1.48	4.94	0.00087	32046	NA	NA	NA	NA	NA	NA	1.17E-03	2.71	1.48	4.94	0.00087	32046
TTN	rs55725279	2	179393898	A	7.33E-05	0.32	0.18	0.56	0.00095	32046	7.94E-01	0.91	0.47	1.79	0.00061	35374	1.32E-03	0.49	0.32	0.76	0.00077	67420	NA	NA	NA	NA	NA	NA	1.31E-03	0.49	0.32	0.76	0.00077	67723
KIAA0415	rs201862383	7	4823883	T	2.15E-03	0.44	0.26	0.74	0.00100	32046	NA	NA	NA	NA	NA	NA	2.15E-03	0.44	0.26	0.74	0.00100	32046	NA	NA	NA	NA	NA	NA	1.70E-03	0.43	0.25	0.73	0.00100	32349
CD2AP	rs138727736	6	47563608	G	1.26E-03	0.63	0.47	0.83	0.00515	26541	2.91E-01	0.89	0.71	1.11	0.00601	35374	4.72E-03	0.78	0.65	0.92	0.00564	61915	NA	NA	NA	NA	NA	NA	4.52E-03	0.77	0.65	0.92	0.00564	62218
HGFAC	rs114303452	4	3449915	G	1.09E-03	1.31	1.11	1.54	0.01333	29476	4.04E-01	1.07	0.92	1.24	0.01385	35374	4.71E-03	1.17	1.05	1.31	0.01362	64850	NA	NA	NA	NA	NA	NA	6.46E-03	1.16	1.04	1.30	0.01363	65153
NRAP	rs11575797	10	115350366	A	1.18E-03	0.18	0.07	0.51	0.00028	32046	7.74E-01	0.85	0.27	2.65	0.00022	31406	9.11E-03	0.36	0.17	0.78	0.00025	63452	NA	NA	NA	NA	NA	NA	9.11E-03	0.36	0.17	0.78	0.00025	63755
NUDT18	rs60087873	8	21965846	C	7.75E-04	8.63	2.46	30.30	0.00022	29476	8.43E-01	1.12	0.38	3.29	0.00030	31406	1.91E-02	2.67	1.17	6.05	0.00026	60882	NA	NA	NA	NA	NA	NA	1.91E-02	2.67	1.17	6.05	0.00026	60882
KIAA1324L	rs138544248	7	86554948	A	7.10E-05	6924.36	88.26	543217.36	0.00006	32071	5.05E-01	0.24	0.00	16.56	0.00002	31406	2.17E-02	35.39	1.68	743.26	0.00004	63477	NA	NA	NA	NA	NA	NA	2.17E-02	35.39	1.68	743.26	0.00004	63477
CHST6	rs139042144	16	75512546	T	6.10E-05	0.12	0.04	0.33	0.00031	32046	2.23E-01	2.14	0.63	7.31	0.00030	20605	2.48E-02	0.40	0.18	0.89	0.00031	52651	NA	NA	NA	NA	NA	NA	2.52E-02	0.40	0.18	0.89	0.00031	52954
BTNL2	rs28362679	6	32363893	A	4.50E-03	1.23	1.07	1.41	0.01733	30582	9.02E-01	1.01	0.87	1.16	0.02858	16690	3.43E-02	1.11	1.01	1.23	0.02130	47272	NA	NA	NA	NA	NA	NA	3.76E-02	1.11	1.01	1.23	0.02129	47575
FAIM3	rs41304091	1	207078467	A	2.27E-04	1.37	1.16	1.62	0.01276	32046	2.87E-01	0.91	0.76	1.08	0.01029	35374	5.40E-02	1.13	1.00	1.27	0.01147	67420	NA	NA	NA	NA	NA	NA	5.13E-02	1.13	1.00	1.27	0.01146	67723

ID	Position	Amino Acid Change	*P*	OR	MAF	N
rs72824905	81942028	P522R	1.19E-05	0.65	0.00887	33786
rs200506549	81927314	T329T	5.78E-04	2.02	0.00176	33786
rs200137340	81934332	S437G	2.56E-02	0.23	0.00015	33786
rs45443101	81922781	H257L	3.01E-02	0.91	0.03830	33786
rs114618894	81962190	L848F	3.07E-02	0.16	0.00009	33786
rs74032923	81954829	D754D	8.35E-02	0.31	0.00016	33786
rs189301790	81819671	T26M	1.26E-01	0.64	0.00089	33786
rs199636472	81925132	A308V	1.50E-01	0.70	0.00105	33786
rs147349332	81819704	T37N	2.38E-01	0.09	0.00001	33786
rs115583707	81960783	Q838Q	2.48E-01	3.05	0.00007	33786
rs186829827	81960772	L835I	3.01E-01	0.12	0.00001	33786
rs117077093	81957175	N798S	3.58E-01	0.72	0.00056	33786
rs61755444	81891928	A133V	4.08E-01	0.68	0.00049	33786
rs370547009	81990400	R1224H	4.68E-01	0.30	0.00003	33786
rs114262189	81971435	S1042T	4.71E-01	1.62	0.00016	33786
rs200325678	81944136	R582Q	5.32E-01	4.02	0.00001	33786
rs199972098	81819605	T4M	5.41E-01	2.67	0.00003	33786
rs187454354	81953195	E721K	5.46E-01	0.69	0.00018	33786
rs199760975	81916888	P236L	5.75E-01	1.24	0.00050	33786
rs17537869	81922813	R268W	5.82E-01	0.98	0.06922	33786
rs75472618	81942175	N571S	5.87E-01	0.95	0.00804	33786
rs200677528	81965151	E877D	6.44E-01	1.26	0.00027	33786
rs201654184	81929499	Q387P	6.91E-01	0.84	0.00045	24294
rs150833842	81946278	I671V	7.27E-01	0.94	0.00259	33786
rs139462941	81968131	N946S	7.85E-01	1.22	0.00012	33786
rs190840748	81916932	I251V	7.99E-01	0.81	0.00010	33786
rs147396004	81944250	T620M	8.78E-01	0.96	0.00111	33786
rs143195637	81953128	D698D	8.90E-01	0.88	0.00009	32322
rs187956469	81939089	Y482H	9.72E-01	1.00	0.00469	33786
rs201294738	81904539	S216L	NA	NA	NA	33786
rs200824224	81927376	R350H	NA	NA	NA	33786
rs200919414	81934365	R448W	NA	NA	NA	32872
rs190001915	81954827	D754H	NA	NA	NA	33786
rs202108152	81990411	R1228W	NA	NA	NA	33786
rs201803492	81957094	Q771R	NA	NA	NA	33786

	MAF≤0.01		**MAF≤0.05**	
Gene	**N SNPs**	***P***	**N SNPs**	***P***
TREM2	12	1.01E-13	13	1.42E-15
APOE	3	2.64E-07	3	2.64E-07
BSG	9	2.25E-06	10	4.72E-06
BCAM	28	3.56E-06	32	4.69E-04
SLC16A14	4	6.14E-06	6	8.35E-04
PVR	11	9.40E-06	13	1.03E-05
ZNF775	2	1.02E-05	2	1.02E-05
ATP5C1	2	3.08E-05	2	3.08E-05
PSD2	21	5.70E-05	21	5.70E-05
TNFRSF10C	5	6.73E-05	6	6.69E-02
KBTBD6	3	9.18E-05	3	9.18E-05
BCL3	6	9.27E-05	6	9.27E-05
PLCG2	28	4.34E-04	29	1.52E-04
EXOC3L2	5	2.82E-01	6	3.77E-07
ABI3	7	6.35E-01	8	5.22E-05
SNX1	4	7.95E-01	5	2.32E-05

	MAF≤0.01		**MAF≤0.05**	
Gene	**N SNPs**	***P***	**N SNPs**	***P***
TREM2	12	1.70E-07	13	6.15E-08
SLC16A14	4	1.30E-06	6	2.64E-04
APOE	3	2.37E-06	3	2.37E-06
BSG	9	7.38E-06	10	2.00E-05
CBLN3	2	7.59E-06	2	7.59E-06
PSD2	21	1.06E-05	21	1.06E-05
SIRT5	11	2.62E-05	12	1.02E-03
TNFRSF10C	5	3.07E-05	6	3.65E-02
DHCR7	17	3.49E-05	17	3.49E-05
WDR74	9	3.67E-05	9	3.67E-05
TINAGL1	6	5.38E-05	7	8.22E-05
SCG2	6	6.73E-05	7	4.57E-01
BCAM	28	7.48E-05	32	2.14E-03
PLCG2	27	2.15E-03	28	1.68E-03
MUC17	89	3.77E-03	93	3.72E-05
PLVAP	8	9.54E-03	9	4.36E-05
ISM2	20	2.48E-01	23	3.91E-05
ABI3	7	6.23E-01	8	4.77E-04

ID	Position	Amino Acid Change	*P*	OR	MAF	N
rs616338	47297297	S209F	2.16E-05	1.42	0.01132	33786
rs142527437	47295162	Q116R	9.60E-02	1.46	0.00138	33786
rs137924898	47295165	R117Q	2.55E-01	2.64	0.00009	33786
rs200867869	47297547	G221S	3.41E-01	0.75	0.00070	33786
rs201757928	47294000	M75I	7.72E-01	0.87	0.00031	33786
rs2233369	47293906	R44Q	8.03E-01	0.99	0.05285	33786
rs201030368	47299992	R339H	8.51E-01	0.76	0.00003	33786
rs150100821	47299919	T315A	9.37E-01	1.01	0.00398	33786
rs146244763	47299454	D268D	9.60E-01	1.05	0.00009	33786
rs145120343	47299501	D284V	NA	NA	NA	33786

ID	**Position**	**Amino Acid Change**	***P***	**OR**	**MAF**	**N**
rs75932628	41129252	R47H	5.16E-12	2.56	0.00492	23380
rs143332484	41129207	R62H	3.48E-09	1.58	0.01233	33786
rs2234255	41127543	H157Y	4.63E-02	2.16	0.00044	33786
rs2234256	41126655	L211P	7.44E-02	1.45	0.00160	33786
rs150277350	41126713	A192T	1.67E-01	4.57	0.00006	33786
rs142232675	41129133	D87N	1.87E-01	1.32	0.00163	33786
rs145080901	41129078	A105V	2.14E-01	2.40	0.00016	33786
rs2234252	41129309	A28V	3.05E-01	2.56	0.00007	33786
rs139607688	41127619	D131D	3.91E-01	5.69	0.00001	33786
rs149622783	41127605	R136Q	4.60E-01	1.66	0.00016	33786
rs79011726	41127561	E151K	6.33E-01	0.79	0.00037	33786
rs200392967	41129275	D39E	8.41E-01	0.87	0.00016	30504
rs138355759	41126619	T223I	9.64E-01	1.02	0.00052	33786

Gene	**Variant 1**	**Variant 2**	**D'**	**r^2**
PLCG2	rs72824905	rs200506549	1	$1.5x10^{-5}$
TREM2	rs75932628	rs143332484	1	$4.9x10^{-5}$

Pathway	All gene-wide			APOE region removed and LD correction applied		
	P	N.Genes	P.Min (gene-wide)	*P*	N.Genes	P.Min (gene-wide)
Immune response	1.08E-04	831	2.25E-06	8.28E-01	551	4.27E-04
Endocytosis	4.38E-02	203	1.44E-03	1.11E-01	187	1.44E-03
Cholesterol transport	4.80E-06	56	2.64E-07	5.80E-03	46	3.20E-03
Hematopoietic cell lineage	1.85E-02	79	3.56E-03	6.63E-02	62	1.09E-02
Protein ubiquitination	2.10E-02	288	3.65E-03	3.65E-01	250	3.65E-03
Hemostasis	2.62E-04	420	2.25E-06	1.94E-01	334	4.27E-04
Clathrin/AP2 adaptor complex	1.15E-04	425	2.64E-07	4.83E-01	341	5.86E-04
Protein folding	2.53E-03	162	4.24E-04	6.96E-03	156	4.24E-04
151 genes in expression module overlap	1.17E-06	149	1.01E-13	5.15E-05	130	1.01E-13
56 genes in protein-protein interaction network	1.08E-07	55	1.01E-13	2.98E-07	48	1.01E-13
95 genes not in protein-protein interaction network	4.26E-02	94	3.54E-03	1.51E-01	86	1.19E-02

Pathway	#genes	*P*	FDR	Description
GO: 34384	6	4.01E-07	0.004	high-density lipoprotein particle clearance
GO: 34380	5	1.40E-06	0.004	high-density lipoprotein particle assembly
GO: 32488	4	2.06E-06	0.004	Cdc42 protein signal transduction
GO: 70326	3	2.60E-06	0.004	very-low-density lipoprotein particle receptor binding
GO: 32803	4	3.08E-06	0.004	regulation of low-density lipoprotein particle receptor catabolic process
GO: 98644	4	3.08E-06	0.004	regulation of receptor catabolic process
GO: 60228	5	3.19E-06	0.004	phosphatidylcholine-sterol O-acyltransferase activator activity
GO: 34447	3	5.02E-06	0.005	very-low-density lipoprotein particle clearance
GO: 16042	193	5.12E-06	0.005	lipid catabolic process
GO: 34382	6	5.90E-06	0.005	chylomicron remnant clearance
GO: 71830	6	5.90E-06	0.005	triglyceride-rich lipoprotein particle clearance
GO: 34363	4	6.19E-06	0.005	intermediate-density lipoprotein particle
GO: 71813	31	7.47E-06	0.005	lipoprotein particle binding
GO: 71814	31	7.47E-06	0.005	protein-lipid complex binding
GO: 33344	21	8.50E-06	0.005	cholesterol efflux
GO: 2313	5	8.54E-06	0.005	mature B cell differentiation involved in immune response
GO: 45540	10	8.86E-06	0.005	regulation of cholesterol biosynthetic process
GO: 33700	10	9.38E-06	0.005	phospholipid efflux
GO: 2335	6	9.66E-06	0.005	mature B cell differentiation
GO: 7243	360	1.27E-05	0.006	intracellular protein kinase cascade
GO: 15918	42	1.52E-05	0.007	sterol transport
GO: 42159	5	1.54E-05	0.007	lipoprotein catabolic process
GO: 14012	5	1.58E-05	0.007	peripheral nervous system axon regeneration
GO: 15248	14	1.86E-05	0.007	sterol transporter activity
GO: 42271	4	1.90E-05	0.007	susceptibility to natural killer cell mediated cytotoxicity
GO: 30301	41	2.01E-05	0.008	cholesterol transport
GO: 31965	139	2.27E-05	0.008	nuclear membrane
GO: 6200	330	2.40E-05	0.008	ATP catabolic process
GO: 16127	10	2.42E-05	0.008	sterol catabolic process
GO: 6707	10	2.42E-05	0.008	cholesterol catabolic process
GO: 34381	20	2.67E-05	0.008	plasma lipoprotein particle clearance
GO: 50865	278	2.76E-05	0.008	regulation of cell activation
GO: 45541	3	2.78E-05	0.008	negative regulation of cholesterol biosynthetic process
GO: 90206	3	2.78E-05	0.008	negative regulation of cholesterol metabolic process
GO: 16887	327	2.88E-05	0.008	ATPase activity
GO: 48156	4	3.08E-05	0.008	tau protein binding
GO: 10875	9	3.33E-05	0.009	positive regulation of cholesterol efflux

GO: 10544	6	3.54E-05	0.009	negative regulation of platelet activation
GO: 55008	33	3.66E-05	0.009	cardiac muscle tissue morphogenesis
GO: 10873	7	3.81E-05	0.009	positive regulation of cholesterol esterification
GO: 46982	231	4.12E-05	0.009	protein heterodimerization activity
GO: 2858	6	4.27E-05	0.009	regulation of natural killer cell mediated cytotoxicity directed against tumor cell target
GO: 2860	6	4.27E-05	0.009	positive regulation of natural killer cell mediated cytotoxicity directed against tumor cell target
GO: 2857	6	4.27E-05	0.009	positive regulation of natural killer cell mediated immune response to tumor cell
GO: 2855	6	4.27E-05	0.009	regulation of natural killer cell mediated immune response to tumor cell

Gene set	**#genes**	**Top 5%**	**$P<1x10^{-3}$**	**$P<1x10^{-4}$**	**$P<1x10^{-5}$**	**$P<1x10^{-6}$**
Module overlap	151	$4.0x10^{-6}$	$1.0x10^{-6}$	$1.0x10^{-5}$	$5.0x10^{-6}$	$7.5x10^{-5}$
Genes in protein network	56	$5.0x10^{-6}$	$3.1x10^{-5}$	$1.41x10^{-4}$	$1.3x10^{-5}$	$6.1x10^{-4}$
Genes outside protein network	95	0.032	0.0097	0.035	0.089	0.027

ENTREZ	Gene	Chr	Start (bp)	End (bp)	Best *P* (IGAP)	Gene-wide *P* (IGAP)	SKAT-O *P* (MAF<0.05)	SKAT-O *P* (MAF<0.01)
945	CD33	19	51728335	51743274	6.49E-08	1.95E-06	5.17E-01	4.75E-01
23526	HMHA1	19	1067174	1086627	2.37E-07	3.30E-04	6.49E-01	6.49E-01
51225	ABI3	17	47287589	47300587	9.22E-07	2.28E-03	5.22E-05	6.35E-01
6688	SPI1	11	47376409	47400127	1.99E-06	1.34E-06	1.14E-01	1.14E-01
3635	INPP5D	2	233925036	234116549	6.62E-06	3.33E-03	1.41E-01	1.41E-01
5265	SERPINA1	14	94843084	94857029	9.64E-05	8.47E-03	5.19E-01	4.92E-01
57121	LPAR5	12	6728001	6745297	1.54E-04	1.01E-01	6.58E-02	6.58E-02
112616	CMTM7	3	32433163	32496333	1.65E-04	6.75E-02	1.90E-01	2.48E-01
5336	PLCG2	16	81812930	81991899	1.69E-04	1.91E-01	1.52E-04	4.34E-04
397	ARHGDIB	12	15094950	15114562	5.69E-04	5.70E-02	6.96E-01	6.96E-01
3684	ITGAM	16	31271288	31344213	6.71E-04	5.71E-03	2.96E-01	2.96E-01
53829	P2RY13	3	151044096	151047337	7.02E-04	5.93E-02	8.44E-01	8.44E-01
5330	PLCB2	15	40580098	40600174	1.17E-03	1.11E-02	7.89E-02	7.89E-02
83478	ARHGAP24	4	86396284	86923823	1.70E-03	4.15E-01	8.34E-02	7.21E-02
54209	TREM2	6	41126246	41130922	1.82E-03	2.58E-03	1.42E-15	1.01E-13
1794	DOCK2	5	169064251	169510386	4.82E-03	3.10E-01	6.97E-01	6.97E-01
29760	BLNK	10	97951455	98031333	4.88E-03	2.20E-01	2.35E-01	2.35E-01
3059	HCLS1	3	121350246	121379791	5.08E-03	8.05E-01	7.45E-01	7.45E-01
6001	RGS10	10	121259339	121302222	6.11E-03	2.72E-01	2.16E-01	2.16E-01
9450	LY86	6	6588934	6655216	6.35E-03	7.13E-01	1.01E-01	1.01E-01
89846	FGD3	9	95709601	95798518	7.40E-03	5.85E-01	5.92E-04	9.35E-02
2207	FCER1G	1	161185087	161189038	7.68E-03	2.33E-02	4.70E-01	4.70E-01
10161	LPAR6	13	48985182	49018840	7.81E-03	1.56E-01	1.74E-02	5.77E-03
6850	SYK	9	93564012	93660842	8.19E-03	1.64E-01	4.02E-01	4.02E-01
54518	APBB1IP	10	26727266	26856732	9.33E-03	6.61E-01	7.52E-01	7.52E-01
23643	LY96	8	74903564	74941307	1.07E-02	2.02E-01	1.96E-01	8.71E-02

64407	RGS18	1	192127592	192154945	1.17E-02	5.05E-01	9.39E-01	9.39E-01
140	ADORA3	1	112025970	112106597	1.19E-02	4.82E-01	6.31E-01	5.57E-01
10320	IKZF1	7	50344378	50472798	1.28E-02	1.45E-01	1.69E-01	1.69E-01
1535	CYBA	16	88709697	88717457	1.29E-02	1.03E-01	1.57E-01	1.57E-01
1436	CSF1R	5	149432854	149492935	1.33E-02	1.76E-01	5.56E-01	2.58E-01
929	CD14	5	140011313	140013286	1.37E-02	1.72E-02	6.99E-01	6.99E-01
4689	NCF4	22	37257030	37274059	1.50E-02	1.57E-01	3.75E-01	3.75E-01
3055	HCK	20	30639991	30689657	1.99E-02	7.12E-01	4.92E-01	3.56E-01
85477	SCIN	7	12610203	12693228	2.24E-02	6.14E-01	6.42E-01	4.06E-01
2212	FCGR2A	1	161475205	161489360	2.28E-02	3.08E-01	1.24E-01	1.24E-01
5777	PTPN6	12	7055740	7070479	2.41E-02	6.39E-02	3.50E-01	3.50E-01
3071	NCKAP1L	12	54891495	54936899	2.61E-02	6.73E-01	3.61E-01	3.61E-01
257106	ARHGAP30	1	161016732	161039760	3.95E-02	2.52E-01	9.26E-01	9.12E-01
1524	CX3CR1	3	39304985	39323226	4.69E-02	5.39E-01	1.09E-01	3.38E-01
718	C3	19	6677846	6720662	4.79E-02	9.33E-01	4.74E-01	4.74E-01
920	CD4	12	6898638	6929976	4.89E-02	3.46E-01	1.00E-01	3.82E-01
64170	CARD9	9	139258408	139268133	5.15E-02	3.13E-01	5.05E-01	4.78E-01
942	CD86	3	121774209	121839988	6.81E-02	6.75E-01	1.50E-01	1.50E-01
7305	TYROBP	19	36395303	36399211	8.18E-02	3.48E-01	1.28E-01	1.28E-01
3394	IRF8	16	85932774	85956211	1.54E-01	6.79E-01	8.83E-02	8.83E-02
51291	GMIP	19	19740285	19754455	1.67E-01	9.15E-01	2.04E-02	1.83E-01
5880	RAC2	22	37621310	37640305	1.72E-01	7.32E-01	5.71E-01	5.71E-01
4069	LYZ	12	69742134	69748013	1.92E-01	7.27E-01	6.61E-01	6.61E-01
1675	CFD	19	859665	863610	2.22E-01	6.75E-01	8.33E-01	8.33E-01
10287	RGS19	20	62704535	62711324	2.53E-01	6.61E-01	6.59E-01	6.59E-01
567	B2M	15	45003685	45010357	2.82E-01	6.08E-01	N/A	N/A
719	C3AR1	12	8210919	8218955	3.26E-01	8.05E-01	1.97E-01	5.49E-01
58191	CXCL16	17	4636828	4643223	4.47E-01	8.21E-01	6.89E-01	6.89E-01

10870	HCST	19	36393382	36395173	6.25E-01	7.20E-01	1.25E-01	4.60E-01
1050	CEBPA	19	33790840	33793430	6.65E-01	8.78E-01	2.65E-01	2.65E-01

GeneID	GeneName	Chr	Start	Stop	TCX.AD.mean	TCX.AD.sd	TCX.con.mean	TCX.con.sd	Model	EffectDirection	Dx.Beta	Dx.SE	Dx.pValue	Dx.qValue
ENSG00000095970	*TREM2*	chr6	41126244	41130924	5.68	0.80	5.55	1.04	Simple	**UpInAD**	0.65	0.23	4.62E-03	**1.20E-02**
									Comprehensive	DownInAD	-0.01	0.13	9.45E-01	9.78E-01
ENSG00000197943	*PLCG2*	chr16	81772702	81991899	1.61	0.57	1.66	0.73	Simple	**UpInAD**	0.43	0.14	2.84E-03	**8.08E-03**
									Comprehensive	DownInAD	-0.12	0.10	2.06E-01	4.70E-01
ENSG00000108798	*ABI3*	chr17	47287589	47300587	3.41	0.57	3.36	0.88	Simple	**UpInAD**	0.58	0.18	1.37E-03	**4.47E-03**
									Comprehensive	UpInAD	0.05	0.10	6.42E-01	8.27E-01

Gene ID	GeneName	Model	Age	Tg-N	Tg-mean	Tg-sd	WT-N	WT-mean	WT-sd	DxBeta	DxSE	DxpValue	DxqValue
ENSMUSG00000023992	*Trem2*	control_vs_crnd8	3 months	12	2.97	0.29	12	2.77	0.19	0.21	0.10	5.33E-02	2.70E-01
		control_vs_crnd8	6 months	12	3.95	0.27	12	2.63	0.16	1.17	0.15	2.46E-07	**1.66E-03**
		control_vs_crnd8	12 months	14	4.97	0.43	10	3.12	0.17	1.82	0.13	8.86E-12	**2.40E-08**
		control_vs_ps1app	12 months	11	4.62	0.44	10	3.12	0.17	1.42	0.16	1.32E-07	**1.03E-04**
ENSMUSG00000034330	*Plcg2*	control_vs_crnd8	3 months	12	1.83	0.17	12	1.63	0.14	0.19	0.06	8.89E-03	1.30E-01
		control_vs_crnd8	6 months	12	1.81	0.21	12	1.76	0.13	0.12	0.12	3.34E-01	7.54E-01
		control_vs_crnd8	12 months	14	2.18	0.16	10	1.92	0.16	0.27	0.07	4.97E-04	**1.63E-02**
		control_vs_ps1app	12 months	11	2.11	0.15	10	1.92	0.16	0.25	0.07	2.11E-03	5.67E-02
ENSMUSG00000018381	*Abi3*	control_vs_crnd8	3 months	12	1.34	0.22	12	1.14	0.15	0.19	0.08	3.44E-02	2.24E-01
		control_vs_crnd8	6 months	12	1.53	0.17	12	1.01	0.21	0.62	0.14	1.75E-04	**4.43E-02**
		control_vs_crnd8	12 months	14	2.00	0.23	10	1.23	0.22	0.76	0.09	4.76E-08	**1.18E-05**
		control_vs_ps1app	12 months	11	1.78	0.26	10	1.23	0.22	0.51	0.12	4.65E-04	**2.62E-02**

ID	rs4586425	rs1143686	rs55711872	rs1143688	rs1143689	rs72824905	rs72824919	rs2158512	rs9896800	rs616338
Gene	PLCG2	PLCG2	PLCG2	PLCG2	PLCG2	PLCG2	PLCG2	ABI3	ABI3	ABI3
Chr	16	16	16	16	16	16	16	17	17	17
Position	81819768	81888151	81924904	81929487	81941318	81942027	81957403	47290252	47293328	47297296
Ref Allele	C	A	C	C	C	C	A	A	C	A
Functiion	syn	nonsyn	intron	nonsyn	nonsyn	nonsyn	intron	intron	intron	nonsyn
Protein Pos	p.A58A	p.L99R		p.D383V	p.A499V	p.P522A				p.F209V
TFBS_Con	889				756	830				803
SIFT_Score		0.007		0.506	0.002	0.474				0.283
SIFT_Pred		D		T	D	T				T
Polyphen2_HDIVSscore		0.303		0.988	0.842	0				0.007
Polyphen2_HDIV_Pred		B		D	P	B				B
Polyphen2_HVAR_Score		0.141		0.773	0.165	0				0.012
Polyphen2_HVAR_Pred		B		P	B	B				B
LRT_Score		0		0	0	0.427				0.271
LRT_Pred		D		D	D	N				N
MutationTaster_Score		0.998		1	1	1				1
MutationTaster_Pred		D		D	D	N				N
MutationAssessor_Score		1.7		0	1.1	0.895				0
MutationAssessor_Pred		L		N	L	L				N
FATHMM_Score		-0.12		-0.04	-0.17	-0.13				3.04
FATHMM_Pred		T		T	T	T				T
PROVEAN_Score		-3.69		1.18	-0.68	-1.47				0.44
PROVEAN_Pred		D		N	N	N				N
VEST3_Score		0.803		0.656	0.318	0.175				0.218
CADD_Raw		3.429		3.237	4.337	-0.764				1.203
CADD_Phred		**23**		**22.8**	**24**	0.052				**11.76**
DANN_Score		**0.993**		**0.9**	**0.997**	0.642				0.731
fathmm-MKL_coding_score		0.927		0.9	0.969	0.177				0.069
fathmm-MKL_coding_pred		D		D	D	N				N
MetaSVM_score		-0.682		-0.864	-0.702	-1.052				-0.95
MetaSVM_pred		T		T	T	T				T

MetaLR_score		0.226		0.176	0.17	0.114				0.012
MetaLR_pred		T		T	T	T				T
integrated_fitCons_score		0.672		0.672	0.706	0.672				0.731
integrated_confidence_val		0		0	0	0				0
GERP++_RS		5.78		4.95	5.22	0.724				3.59
phyloP7way_vertebrate		0.991		1.062	0.871	-0.064				0.673
phyloP20way_mammalian		1.061		1.199	0.935	0.852				1.061
phastCons7way_vertebrat		0.862		0.998	0.675	0.06				0.922
phastCons20way_mammal		0.46		0.612	0.055	0.005				0.926
SiPhy_29way_logOdds		15.081		14.913	18.788	3.03				10.362
GWAVA_region_score			0.38							
GWAVA_tss_score			0.42							
GWAVA_unmatched_score			182							
RegDB score	2b	7	7	3a	5	5	6	5	6	4
RegDB info	Structure, Protein_Binding		Chromatin_Structure, Pro		omatin_Struct	omatin_Struct	Motifs	Chromatin_St	Motifs	Structure, Protein_Binding
DANN(WG)		**0.993**	0.49	**0.9**	**0.997**	0.642	0.363	0.48	0.356	0.731
CADD(WG)		**2.256214,13.5**	0.629522,1.21	**.216413,9.93**	**.910481,15.7**	0.526720,1.60	0.619262,1.24	0.140501,3.31	0.723494,0.89	0.265375,2.727
BRAINEAC(p<1.10E-4)				PLCG2					PRAC-1; ZNF652	