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Common variants in ABCA7, MS4A6A/MS4A4E, EPHA1, CD33 and CD2AP are associated with Alzheimer's disease

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Abstract

We sought to identify new susceptibility loci for Alzheimer's disease (AD) through a staged association study (GERAD+) and by testing suggestive loci reported by the Alzheimer's Disease Genetic Consortium (ADGC). First, we undertook a combined analysis of four genome-wide association datasets (Stage 1) and identified 10 novel variants with $P \leq 1\times10^{-5}$. These were tested for association in an independent sample (Stage 2). Three SNPs at two loci replicated and showed evidence for association in a further sample (Stage 3). Meta-analyses of all data provide compelling evidence that *ABCA7* (meta-P 4.5×10^{-17}; including ADGC meta-P=5.0×10^{-21}) and the *MS4A* gene cluster (rs610932, meta-P=1.8×10^{-14}; including ADGC meta-P=1.2×10^{-16}; rs670139, meta-P=1.4×10^{-9}; including ADGC meta-P=1.1×10^{-10}) are novel susceptibility loci for AD. Second, we observed independent evidence for association for three suggestive loci reported by the ADGC GWAS, which when combined shows genome-wide significance: *CD2AP* (GERAD + P=8.0×10^{-4}; including ADGC meta-P=8.6×10^{-9}), *CD33* (GERAD+ P=2.2×10^{-4}; including ADGC meta-P=1.6×10^{-9}) and *EPHA1* (GERAD+ P=3.4×10^{-4}; including ADGC meta-P=6.0×10^{-10}). These findings support five novel susceptibility genes for AD.

Alzheimer's disease (AD) is the most common form of dementia, with both environmental and genetic factors contributing to risk. AD is genetically complex and shows heritability up to 79%[1]. Rare variants in three genes (*APP, PSEN1 & PSEN2*)[1] cause disease in a minority of cases, but until recently the Apolipoprotein E gene (*APOE*), was the only gene known to increase disease risk for the common form of AD with late-onset[2]. In 2009 we published a genome-wide association study (GWAS) of AD in a sample designated GERAD1 (Genetic and Environmental Risk in AD Consortium 1), which identified two new genome-wide significant susceptibility loci: clusterin (CLU: $P=8.5\times10^{-10}$) and phosphatidylinositol-binding clathrin assembly protein gene (*PICALM:* $P=1.3\times10^{-9}$). We also observed more variants with *P*-values$<1\times10^{-5}$ than were expected by chance ($P=7.5\times10^{-6}$)[3]. These included variants in the complement receptor 1 (*CR1*) gene, the bridging integrator 1 (*BIN1*) gene and the membrane-spanning 4A gene cluster (*MS4A* gene cluster). A second independent AD GWAS by Lambert and colleagues[4] using the EADI1 sample (European Alzheimer's Disease Initiative 1) showed genome-wide significant evidence for association with *CLU* ($P=7.5\times10^{-9}$) and *CR1* ($P=3.7\times10^{-9}$), and support for *PICALM* ($P=3\times10^{-3}$). Combined analysis of the GERAD1 and EADI1 data yield highly significant support for all three loci (*CLU* meta-$P=6.7\times10^{-16}$, *PICALM* meta-$P=6.3\times10^{-9}$, *CR1* meta-$P=3.2\times10^{-12}$). The associations in *CLU, PICALM* and *CRI* have since been replicated in several independent datasets[5-8], shown trends in another[9] and relationships with neurodegenerative processes underlying disease[10]. In addition, members of this consortium have since reported genome-wide significant association for *BIN1* ($P=1.6\times10^{-11}$) and support for ephrin receptor A1 (*EPHA1;* $P=1.7\times10^{-6}$)[11]..

This study sought to identify new common susceptibility variants for AD by first undertaking a three-stage association study based upon predominantly European samples (GERAD+, see Figure 1) and second, by testing these samples for loci showing suggestive evidence for association in the American Alzheimer's Disease Genetics Consortium (ADGC) GWAS[12].

The first stage of this study comprised a meta-analysis of four AD GWAS datasets (6688 cases, 13685 controls), including: GERAD1[3], EADI1[4], Translational Genomics Research Institute (TGEN1)[13] and Alzheimer's Disease Neuroimaging Initiative (ADNI)[14]. Single nucleotide polymorphisms (SNPs) which remained significant at $P\leq1\times10^{-5}$ were then tested for replication in the second stage of this study, comprising 4896 cases and 4903 controls including genotyping of the GERAD2 sample and *in silico* replication in the deCODE and German Alzheimer's disease Integrated Genome Research Network (AD-IG) GWAS datasets. In Stage 3, novel SNPs showing significant evidence of replication in Stage 2 were then tested for association in a sample comprising 8286 cases and 21258 controls, which included new genotyping in the EADI2[4] and Mayo2 samples, and *in silico* replication in the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) sample[11]. Sample descriptions and characteristics can be found in the Supplementary Note and Supplementary Table 1.

In Stage 1 we identified 61 SNPs associated with AD at $P\leq1\times10^{-5}$ following meta-analysis of 496763 SNPs in the GERAD1, TGEN1, ADNI and EADI1 (see Supplementary Table 2 and the Supplementary Note). Ten SNPs at novel loci and two at previously identified susceptibility loci that surpassed the $P\leq1\times10^{-5}$ threshold, were selected for further analysis (see below). One SNP, rs610932 (Stage 1 $P=1.8\times10^{-8}$) at the *MS4A* (membrane spanning 4A) gene cluster, surpassed the threshold ($P<5.0\times10^{-8}$)[15] for genome-wide significance. We also observed strong evidence for association at *ABCA7* (ATP-binding cassette, sub-family A, member 7; rs3764650; Stage 1 $P=2.6\times10^{-7}$).

When selecting SNPs for testing in Stage 2, we excluded known susceptibility loci that had previously been tested in GERAD2 and limited analysis of *BIN1* and *CR1*, which had not been tested in GERAD2, to the most significant SNPs at each locus (See Supplementary Table 2). Following pruning for linkage disequilibrium, twelve SNPs were taken forward for replication in Stage 2 (10 excluding *BIN1* and *CR1*).

Five of the twelve SNPs tested in Stage 2 showed significant evidence for replication using a Bonferroni adjusted threshold for significance of $P=4.2\times10^{-3}$ (see Table 1 and Supplementary Table 3). In addition to SNPs at *BIN1* and *CR1*, one SNP within ABCA7 (rs3764650, Stage 2 $P=1.9\times10^{-5}$) and two SNPS at the *MS4A* gene cluster (rs610932, stage 2 $P=1.6\times10^{-3}$; rs670139 Stage 2 $P=1.1\times10^{-3}$) showed evidence of replication in Stage 2. The three SNPs implicating novel risk loci were tested for association in the Stage 3 sample and showed further evidence of replication (rs3764650, Stage 3 $P=2.9\times10^{-7}$; rs610932, Stage 3 $P=2.1\times10^{-5}$; rs670139, Stage 3 $P=3.2\times10^{-3}$; see Table 1 and Supplementary Table 3).

We conducted an inverse variance weighted meta-analysis of data from Stages 1, 2 and 3 (See Table 1 and Supplementary Table 3). This provided strong evidence for association with rs3764650 at *ABCA7* (meta-$P=4.5\times10^{-17}$) and two SNPs at the *MS4A* gene cluster: rs610932 (meta-$P=1.8\times10^{-14}$) and rs670139 (meta-$P=1.4\times10^{-9}$). When combining GERAD + and ADGC results (after removing overlapping samples) ABCA7 has a *P*-value of 5.0×10^{-21} (OR=1.22). The two SNPs at the *MS4A* gene cluster, rs610932 and rs670139, showed *P*-values of 1.2×10^{-16} (OR=0.91) and 1.1×10^{-10} (OR=1.08), respectively, in the combined analysis of GERAD+ and ADGC results. It is noteworthy that the most significant ADGC SNP at the MS4A locus is in LD with our top SNP (rs4938933 with rs610932 $r^2=0.62$, D'=0.86), thus both datasets may be detecting the same underlying signal.

This study also provides additional independent support for association with CR1 (Stage 2 $P=1.4\times10^{-3}$) and BIN1 (Stage 2 $P=3.8\times10^{-5}$; see Table 1 for meta-analysis.) We did not observe interaction between *APOE* and the novel variants identified in this study, indeed we did not find evidence of epistasis between any of the genome-wide significant variants identified to date (*ABCA7, MS4A, BIN1, CR1, PICALM, CLU* or *APOE*) (see Supplementary Table 4a). Likewise, adjusting for the presence of at least one *APOE* ε4 allele had little effect on the results of analysis of the three novel variants (see Supplementary Table 4b). We also found no evidence for association between these loci and age at onset of AD (rs3764650: $P=0.17$; rs670139: $P=0.38$; rs610932: $P=0.95$; rs744373: $P=0.87$; rs3818361: $P=0.58$).

This study therefore shows strong statistical support for two novel AD risk loci, which replicate over a number of independent case-control samples. The first of these is the ATP-binding cassette, sub-family A, member 7 (*ABCA7*) locus (Figure 2A). The associated marker is rs3764650, which is located in intron 13. This SNP was the only variant in the gene that passed our Stage 1 criterion, which is not unexpected given the low levels of linkage disequilibrium (LD) between this SNP and others included in the GWAS. However, in a preliminary attempt to identify an associated functional variant at the *ABCA7* locus, we genotyped the GERAD2 sample for rs3752246, a non-synonymous SNP in exon 32 of the gene, which showed the highest LD with rs3764650 out of all HapMap *ABCA7* coding variants based on r^2 ($r^2=0.36$, D'=0.89). This variant (which was not genotyped in Stage 1) was also associated with AD (GERAD2 $P=1\times10^{-3}$, OR=1.17). Rs3752246 encodes a glycine to alanine substitution at position 1527 of the protein (accession number NP_061985.2) which is predicted to be a benign change[16], and is unlikely to be the relevant functional variant. We used data from two published expression quantitative trait loci (eQTL) datasets (derived from lymphoblastoid cell lines[17] and brain[18]) to determine if

rs3764650 is associated with the expression of *ABCA7*. However, no association was observed (see Supplementary Table 5). Further work will be required to identify the causal variant(s) at this locus.

Second, we implicate the membrane-spanning 4A (*MS4A*) gene cluster (Figure 2B). The association spans an LD block of 293 kb (chr11: 59,814,28760,107,105) and includes 6 of 16 known genes comprising the membrane-spanning 4-domains, subfamily A (*MS4A*). These are *MS4A2, MS4A3, MS4A4A, MS4A4E, MS4A6A* and *MS4A6E*. The associated SNPs are found in the 3′ UTR of MS4A6A (rs610932) and the intergenic region between *MS4A4E* and *MS4A6A* (rs670139). rs610932 shows nominally significant association with expression levels of *MS4A6A* in cerebellum and temporal cortex ($0.01<P<0.05$; see Supplementary Table 5), but not in frontal cortex, pons, or lymphoblastoid cell lines. The non-synonymous SNP that is most strongly associated with the genome-wide significant variants is rs2304933. This SNP was analyzed in Stage 1 but showed weaker evidence for association ($P=0.006$) than the genome-wide significant variant at this locus in the same sample.

We also sought to follow up four additional loci showing suggestive evidence for association with AD ($1\times10^{-6}>=P>5\times10^{-8}$) from the ADGC GWAS[12]. These loci included *CD33, EPHA1, CD2AP* and *ARID5B*. It should be noted that evidence for suggestive association with *EPHA1* and *CD33* has been reported previously. Members of this collaboration were the first to report *EPHA1* as showing suggestive evidence of association with AD (rs11771145, $P=1.7\times10^{-6}$; LD with ADGC SNP rs11767557: $r^2 = 0.28$, D'=0.75)[11], which included GERAD1 and EADI1 samples reported on here. Similarly, Bertram and colleagues were the first to show suggestive evidence for *CD33* (rs3826656, $P=4.0\times10^{-6}$; LD with ADGC SNP rs3865444: $r^2 = 0.13$, D'=1.0)[19].

We combined data from the GERAD+ dataset comprising GERAD1, EADI1, deCODE and AD-IG GWAS datasets (up to 6992 cases and 13472 controls) using inverse variance meta-analysis. The TGEN1, ADNI and Mayo1 datasets were included in the ADGC discovery set and were thus excluded from these particular analyses. We observed support for association with *CD2AP* (rs9349407, $P=8.0\times10^{-4}$, OR=1.11), *CD33* (rs3865444, $P=2.2\times10^{-4}$, OR=0.89) and *EPHA1* (rs11767557, $P=3.4\times10^{-4}$, OR=0.90).

When these data were combined with ADGC we observed genome-wide evidence for association with AD (rs9349407, GERAD+ & ADGC meta-$P=8.6\times10^{-9}$, OR=1.11; rs3865444, GERAD+ & ADGC meta-$P=1.6\times10^{-9}$, OR=0.91; rs11767557, GERAD+ & ADGC meta-$P=6.0\times10^{-10}$, OR=0.90). We observed nominally significant evidence of association with *ARID5B* (rs2588969, $P=3.3\times10^{-2}$, OR=1.06), however the direction of effect was opposite to that reported by ADGC[12], and was not significant overall (GERAD+ & ADGC meta-$P=3.6\times10^{-1}$, OR=0.99). See Table 2 for results and Supplementary Table 6 for results of additional SNPs at these loci.

Taken together, these results show compelling evidence for an additional five novel AD susceptibility loci. *ABCA7* encodes an ATP-binding cassette (ABC) transporter. The ABC transporter superfamily has roles in transporting a wide range of substrates across cell membranes[20] *ABCA7* is highly expressed in brain, particularly in hippocampal CA1 neurons[21] and in microglia[22]. ABCA7 is involved in the efflux of lipids from cells to lipoprotein particles. Notably, the main lipoproteins in brain are APOE followed by CLU. Although no evidence for epistasitic interactions between the three genetic loci was observed (see Supplementary Table 4a), however, this is not a prerequisite for biological interaction between these molecules. In addition, ABCA7 has been shown to regulate APP processing and inhibit β-amyloid secretion in cultured cells overexpressing APP[23]. *ABCA7*

also modulates phagocytosis of apoptotic cells by macrophages mediated through the C1q complement receptor protein on the apoptotic cell surface[23]. *ABCA7* is an orthologue of *C. elegans ced-7*, the product of which is known to clear apoptotic cells and the high levels of expression of *ABCA7* in microglia are consistent with such a role.

The genes in the *MS4A* cluster on chromosome 11 have a common genomic structure with all other members of the family, including transmembrane domains indicating that they are likely to be part of a family of cell surface proteins[24]. *MS4A2* encodes the beta subunit of high affinity IgE receptors[25]. The remaining genes in the LD block have no known specific functions. *CD33* is a member of the sialic-acid-binding immunoglobulin-like lectins (Siglec) family which are thought to promote cell-cell interactions and regulate functions of cells in the innate and adaptive immune systems[26]. Most members of the Siglec family, including *CD33*, act as endocytic receptors, mediating endocytosis through a mechanism independent of clathrin[27]. *CD2AP* (CD2-associated protein) is a scaffold/adaptor protein[28] which associates with cortactin, a protein also involved in the regulation of receptor mediated endocytosis[29]. It is striking that these two new susceptibility genes for AD, and the recently established susceptibility genes *PICALM* and *BIN1* are all implicated in cell-cell communication and transduction of molecules across the membrane. *EPHA1* is a member of the ephrin receptor subfamily. Ephrins and Eph receptors are membrane bound proteins which play roles in cell and axon guidance[30] and in synaptic development and plasticity[31]. However EphA1 is expressed mainly in epithelial tissues[32] where it regulates cell morphology and motility[33]. Additional roles in apoptosis[34] and inflammation[35] have also been proposed.

Our study has generated strong statistical evidence that variants at *ABCA7* and the *MS4A* gene cluster confer susceptibility to AD, which replicates over a number of independent case control samples. We also provide independent support for three loci showing suggestive evidence in a companion paper[12], *CD33, CD2AP* and *EPHA1*,which when the data are combined show genome-wide levels of significance. Finally, we provide further evidence for *BIN1* and *CR1* loci as susceptibility loci. What is striking about our findings is the emerging consistency in putative function of the genes identified. Five of the recently identified AD susceptibility loci *CLU, CR1, ABCA7, CD33* and *EPHA1* have putative functions in the immune system; *PICALM, BIN1, CD33, CD2AP* are involved in processes at the cell membrane, including endocytosis and *APOE, CLU* and *ABCA7* in lipid processing. It is conceivable that these processes would play strong roles in neurodegeneration and Aβ clearance from the brain. These findings therefore provide new impetus for focused studies aimed at understanding the pathogenesis of AD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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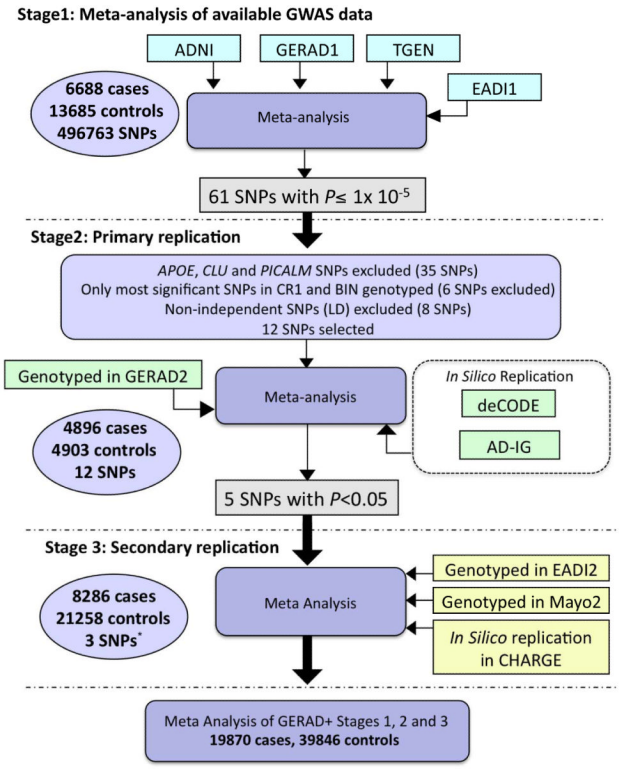

Figure 1.

GERAD+ study design.

* Data for rs744373 and rs3818361 in the CHARGE consortium have been presented elsewhere[15], as has data for rs381861 in the EADI2 samples[4], as such these SNPs were not included in Stage 3.

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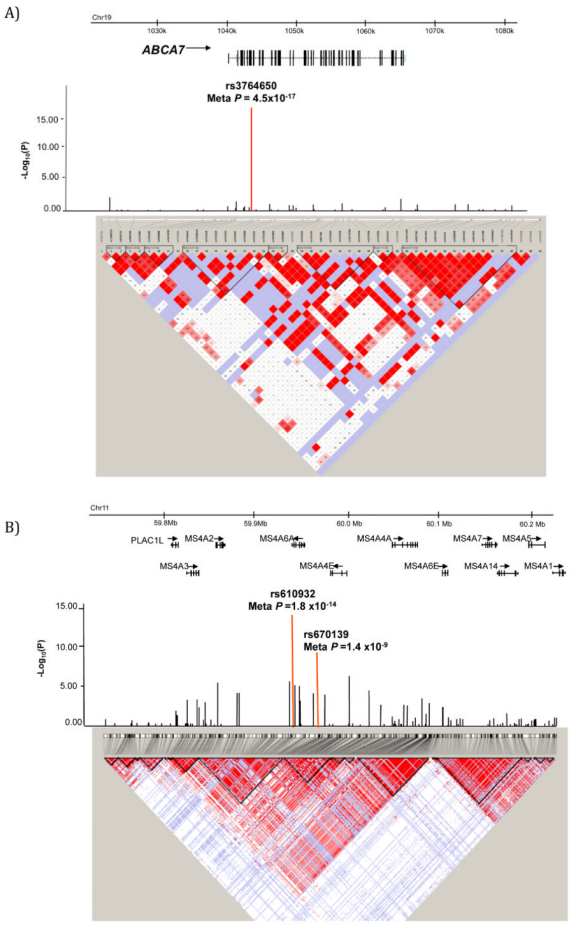

Figure 2.

Schematic of the associated variants reported in reference to (A) the ABCA7 gene and (B) chromosomal region chr11:59.81Mb-60.1Mb harboring members of the *MS4A* gene cluster. Chromosome positions are shown at the top of the schematics (UCSC Feb 2009). Gene schematic: horizontal arrows indicate directions of transcription, black boxes indicate gene exons/UTR. The $-\text{Log}_{10}(P)$ of the SNPs analyzed in Stage 1 are shown in chart graph. The GERAD+ Stage 1, 2 and 3meta-analysis *P*-values for SNPs rs3764650 (*ABCA7*), rs610932 (*MS4A6A*) and rs670139 (*MS4A4E*) are indicated by the red lines. The D' LD block structure of the *ABCA7* gene plus surrounding region, and chr11:59.81Mb-60.1Mb according to the CEPH HapMap data, are provided at the bottom of each schematic with lines indicating where each SNP genotyped on the Illumina 610-quad chip is represented.

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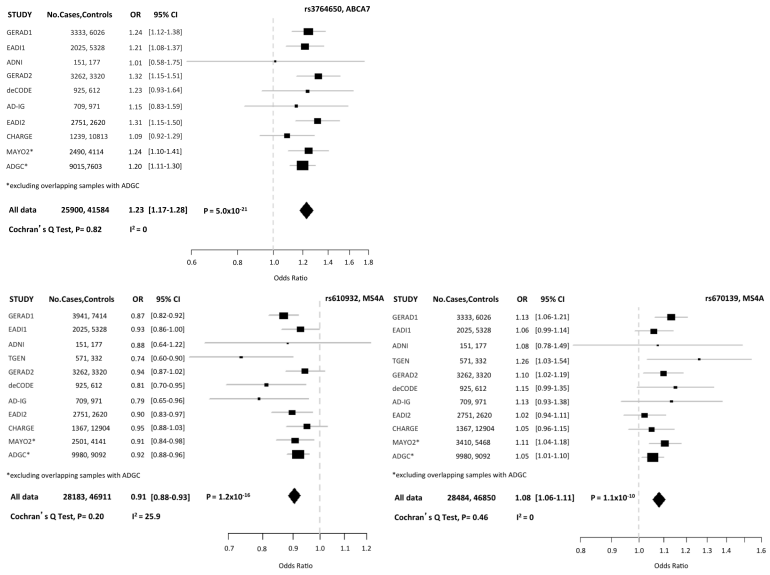

Figure 3.
Forest plots showing association in the different datasets for SNPs at the *ABCA7* (rs3764650) and *MS4A* (rs610932 & rs670139) loci.

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Table 1

Results of the GERAD+ study.

SNP	Closest Gene	CHR	MAF	Stage 1*			Stage 2†			Stage 3 ‡			Meta-analysis of GERAD+ Stage 1, 2 and 3 §			Meta-analysis of GERAD+ & ADGC		
				P	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P	OR	95% CI
rs3764650	*ABCA7*	19	0.10	2.6×10^{-7}	1.22	1.13-1.32	1.9×10^{-5}	1.28	1.14-1.44	2.9×10^{-7}	1.22	1.13-1.32	4.5×10^{-17}	1.23	1.18-1.30	5.0×10^{-21}	1.23	1.17-1.28
rs610932	*MS4A6A*	11	0.42	1.8×10^{-8}	0.88	0.85-0.92	1.6×10^{-3}	0.90	0.84-0.96	2.1×10^{-5}	0.91	0.87-0.95	1.8×10^{-14}	0.90	0.87-0.92	1.2×10^{-16}	0.91	0.88-0.93
rs670139	*MS4A4E*	11	0.41	1.0×10^{-5}	1.11	1.06-1.16	1.1×10^{-3}	1.11	1.04-1.19	3.2×10^{-3}	1.06	1.02-1.11	1.4×10^{-9}	1.09	1.06-1.12	1.1×10^{-10}	1.08	1.06-1.11
rs3818361	*CR1*	1	0.19	3.2×10^{-12}	1.21	1.14-1.27	1.4×10^{-3}	1.14	1.05-1.23	NA	NA	NA	3.7×10^{-14}	1.18	1.13-1.24	NA	NA	NA
rs744373	*BIN1*	2	0.29	1.5×10^{-10}	1.17	1.11-1.22	3.8×10^{-5}	1.17	1.08-1.25	NA	NA	NA	2.6×10^{-14}	1.17	1.12-1.21	NA	NA	NA

CHR=Chromosome, MAF=Minor Allele Frequency in cases and controls.

*GERAD1, EADI1, ADNI, & TGEN1 <6688 Cases, 13685 Controls.

†GERAD2, deCODE, AD-IG: 4896 AD Cases, 4903 Controls.

‡EADI2, CHARGE, Mayo2 <8286 AD Cases, 21258 Controls,

§GERAD1&2, EADI1&2, ADNI, TGEN1, Decode, AD-IG, CHARGE, Mayo2 <19870 AD Cases and 39846 Controls

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Table 2

Results of the combined analysis of the ADGC and GERAD+ consortia.

SNP	Closest Gene	CHR	MAF	Linkage Disequilibrium with the top ADGC SNP at each loci		GERAD+ Consortia *					GERAD+ & ADGC Metaanalysis		
				r^2	D'	Cases	Controls	P	OR	95% CI	P	OR	95% CI
rs9349407†	*CD2AP*	6	0.29	N/A	N/A	6283	7165	8.0×10^{-4}	1.11	1.04-1.18	8.6×10^{-9}	1.11	1.07-1.15
rs9296559‡	*CD2AP*	6	0.29	0.71	0.95	6283	7165	1.5×10^{-3}	1.10	1.04-1.17	NA	NA	NA
rs11767557	*EPHA1*	7	0.21	N/A	N/A	6283	12935	3.4×10^{-4}	0.90	0.85-0.95	6.0×10^{-10}	0.90	0.86-0.93
rs2588969†	*ARID5B*	10	0.40	N/A	N/A	6283	7165	3.3×10^{-2}	1.06‡	1.01-1.13	3.6×10^{-1}	0.99	0.95-1.02
rs4948288	*ARID5B*	10	0.26	0.55	0.78	6992	13472	3.6×10^{-3}	1.07‡	1.03-1.15	NA	NA	NA
rs3865444§	*CD33*	19	0.31	N/A	N/A	6283	7165	2.2×10^{-4}	0.89	0.84-0.95	1.6×10^{-9}	0.91	0.88-0.93

CHR=Chromosome, MAF=Minor Allele Frequency in cases and controls.

*GERAD1, EADI1, deCODE, AD-IG.

†results generated from imputed data. The results from the top genotyped SNP are also shown. See Supplementary Table 6 for full details.

‡opposite direction of effect to that reported by Naj et al.

§data imputed in the deCODE dataset.