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Original Article

Meta-analysis of association between the genetic polymorphisms on chromosome 11q and Alzheimer's disease susceptibility

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Abstract: Alzheimer's disease (AD) is a neurodegenerative disease mostly occurred in the elderly. Genetic mutation is one of well-established risk factors for AD. Several polymorphisms on chromosome 11q were reported to be associated with AD susceptibility. Hence we performed a meta-analysis to systematically assess the association between the most-reported polymorphisms on chromosome 11q (rs10793294, rs7115850, rs7101429, rs4945261, rs2373115, rs670142, rs610932, rs541458 and rs3851179) and AD risk. A comprehensive literature search in the electronic databases was performed to identify all eligible studies. The pooled odds ratios (OR) and 95% confidence intervals (95% CI) were calculated to evaluate the association between 11q variants and AD risk by using the allelic model. Sensitivity analysis was carried out to analyze the influence of single study on the overall results. Begg's funnel plots and Egger's test were used to assess the publication biases among studies. All the statistical analyses were conducted by using STATA 12.0 Software (Stata Corp, College Station, TX, USA). A total of 35 eligible articles were included in our meta-analysis. Our data showed that the polymorphism of rs610932 were significantly associated with lower AD risk with a pooled OR of 0.88 (95% CI: 0.84-0.92, *P*=0.005). The other SNPs of rs494526 (OR=0.83, 95% CI: 0.65-1.00, *P*<0.001), rs2373115 (OR=0.85, 95% CI: 0.75-0.95, *P*<0.001) and rs670139 (OR=1.09, 95% CI: 1.05-1.12, *P*=0.554) were shown to be correlated with lower AD risk. Subgroup analysis revealed a similar result in Caucasians. But only the rs610932 polymorphism was found to be associated with lower AD risk in Asians. The polymorphism of rs610932 was shown to be a risk factor for AD while the other three genetic variants (rs494526, rs2373115 and rs610932) may act as protective factors against AD.

Keywords: Meta-analysis, Alzheimer's diseases, single nucleotide polymorphisms, GRB2, MS4A, PICALM

Introduction

Alzheimer's disease (AD) is a neurodegenerative disease characterized by progressive memory loss and cognitive impairment, accounting for approximately 60% to 80% of dementia cases in the elderly [1]. The disease seriously affects the patient's ability to carry out daily tasks and activities and imposes a severe burden on their caregivers. The main pathological hallmarks of Alzheimer's disease are the accumulation of beta-amyloid plaques outside the neurons and the presence of neurofibrillary tangles inside the neurons [2]. However, the genetic mechanism and etiology of the disease is not fully understood. To date, there's no treatment or intervention available for the cure or prevention of Alzheimer's disease. Most of the current approaches in treatment or medication lie in helping patients maintain the mental function and delay the symptoms of the disease [3]. A number of factors are likely to contribute to the increased risk of Alzheimer's disease, including age, diet, lifestyle, environment, genetics, etc. Among them, age and genetic factors are the two unequivocally established risk factors for Alzheimer's disease [4]. Most of the AD patients are diagnosed at age 65 or older. The incidence of Alzheimer's disease doubles every 5 years after age 65 [5]. Growing evidences have indicated that genetic mutations also play important role in the development of Alzheimer's disease. Several risk genes have been identified to be associated with AD. One of the most studied AD-related genes is *Apolipoprotein E* (*APOE*) and previous studies confirmed that *APOE ε4* increase the risk of developing the disease [6].

The *APOE4* gene, located on chromosome 19, encodes the apolipoprotein E, which is one of major component of very low-density lipoproteins (VLDLs) responsible for transporting the cholesterol to bloodstream and further delivering it to the liver for further processing [7]. Therefore, apolipoprotein E is essential for maintaining the homeostasis of cholesterol in the body and thereby preventing the cardiovascular diseases such as stroke and heart attack [8]. So far, at least three different alleles of *APOE* gene are identified as follows: *ε2*, *ε3*, and *ε4*. The *ε3* is the most common allele in the general population and over half of the general population is found to carry *ε3* allele [9]. The *ε4* allele is associated with increased risk of late-onset Alzheimer's disease [10]. But it's important to note that not all of the AD cases were found to be *ε4* carriers and not all of *ε4* carriers will surely develop the disease.

In addition to *APOE4*, several genome-wide association studies (GWAS) have been performed to identify the additional risk genes for AD. Evidences show that the loci on chromosome 11q are likely to be associated with the increased risk of AD, in which most reported AD-associated polymorphisms are rs1079-3294, rs7115850, rs7101429, rs4945261, and rs2373115 located in the *GRB2 associated binding protein 2* (*GRB2*), rs670142 and rs610932 in *Membrane-spanning 4-domains subfamily A* (*MS4A*), as well as rs541458 and rs3851179 in the *Phosphatidylinositol binding clathrin assembly protein* (*PICALM*) [11-14]. Hence, it's of great value to investigate the association between AD susceptibility and single nucleotide polymorphisms (SNP) on chromosome 11q. Moreover, a number of studies have examined the association between the common susceptible variants on chromosome 11q and AD risk. But no conclusive finding was reported due to inconsistent results among existing studies. Therefore, we conducted a meta-analysis to systematically evaluate the association between the 11q variants and AD susceptibility.

Materials and methods

Selection of studies

The meta-analysis was performed under the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA). We searched the electronic database such as PubMed/Medline, EMBASE, the Cochrane Library and Chinese National Knowledge Infrastructure (CNKI) to identify all relevant articles published between January 2009 and November 2014 without language limitation. The following search terms "Alzheimer's disease", "Polymorphism", "SNP", "Genetic variants", "Chromosome 11q", "GAB2", "MS4A6A", "MS4A4E", "PICALM" were used in the literature retrieval. Additionally, we also reviewed the reference list in the retrieved articles to manually search the additional relevant articles.

Inclusion and exclusion of studies

Two reviewers independently screened the retrieved publications. Studies qualified for inclusion in the meta-analysis have to meet the following criteria: 1) they are case-control studies focused on the association between the genetic variants of GAB2 (rs10793294, rs7115850, rs7101429, rs4945261, rs2373115), MS4A (rs670142, rs610932), PICALM (rs541458, rs3851179) on chromosome 11q and AD susceptibility; 2) the diagnosis of AD patients was confirmed by histopathological examination; 3) studies provided the data of odds ratios (OR) and their 95% confidence interval (CI); 4) the genotype frequencies are consistent with the Hardy Weinberg Equilibrium. Studies were excluded if 1) they were not case-control studies; 2) they were irrelevant to the research topic; 3) they were duplicated publication; 4) relevant data was unavailable.

Data extraction

Two reviewers independently extracted the information and data from all eligible publications. Disagreement between the two reviewers was resolved by third reviewer. The following characteristics of each study was documented: first author's surname, publication year, ethnicity of subjects, genotyping methods, studied SNP, number of total AD cases and healthy controls, number of AD cases and healthy controls for each genotype.

Statistical analyses

The Chi-square test was used to examine whether the genotype distribution in healthy controls was consistent with Hardy Weinberg equilibrium. The pooled OR and its corresponding 95% CI were calculated to assess the association between the common SNPs on chromo-

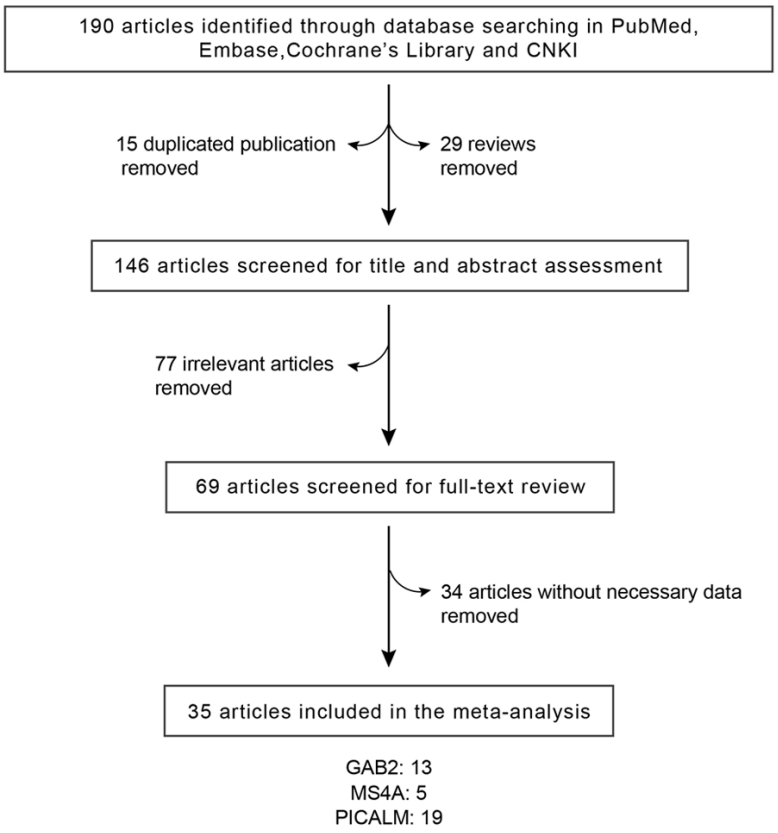

Figure 1. Flow chart of literature search and study selection.

some 11q and AD under allele model. Z test was carried out to determine the statistical significance of OR, which $P<0.05$ was considered as statically significant. Cochran's Q and Higgin's I^2 test was used to assess the level of heterogeneity among studies. If the result showed $P>0.05$ and $I^2<0.5$, the pooled OR should be calculated with fixed effect model (Mantel Haenszel method). Otherwise, random model (DerSimonian and Laird method) should be applied. Sensitivity analyses were performed to evaluate the impact of each study on the overall result of meta-analysis. Publication bias was assessed by Begg's funnel plot and Egger's regression. STATA 12.0 Software (Stata Corp, College Station, TX, USA) was used to perform all the statistical analyses.

Results

Study characteristics

The flow chart of study selection is presented in **Figure 1**. Firstly, we retrieved a total of 190 articles from electronic database and manual search. According to the inclusion and exclusion criteria, 15 duplicated publications and 29 reviews were removed in the preliminary screening. After reviewing the titles and abstracts, 77 irrelevant articles were further excluded. The remaining articles were subjected to full-text review by two independent investigators. 34 articles were removed since they failed to provide data needed to construct 2×2 table for meta-analysis. Finally, 35 eligible articles were included in this meta-analysis, in which the articles focused on the GAB2, MS4A and PICALM variants were 13, 5 and 19, respectively [12-46]. Besides, 23 of 35 identified articles study on the Caucasians while the other 23 studies on the Asians. The articles such as Hollingworth et al., Harold et al., Lambert et al., Reiman et al., and Miyashita et al. contained several independent case-control studies performed in different samples or in different stages. In this case, we divided the entire study into several independent studies in this meta-analysis. The detailed characteristics of studies were presented in the Supplementary Table 1. The whole study subjects were mostly Caucasians and Asians recruited from Europe, North America and East Asia. This meta-analysis includes 45,674 cases and 79,218 controls in total. Several studies have further carried out the subgroup analyses based on APOE *ε4* status.

Meta-analysis of association between 11q variants and AD risk

The overall results of meta-analysis for the association between 11q variants and AD risk were summarized in **Figure 2** and Supplementary Tables 2, 3 and 4. Under the allele model, polymorphisms of rs610932 (G>T) on *MS4A6A* were significantly associated with lower AD risk with a pooled OR of 0.88 (95% CI: 0.84-0.92, $P=0.005$). Similarly, the genetic variants of rs2373115 (G>T) on *GAB2* were shown to significantly decrease the risk of developing AD

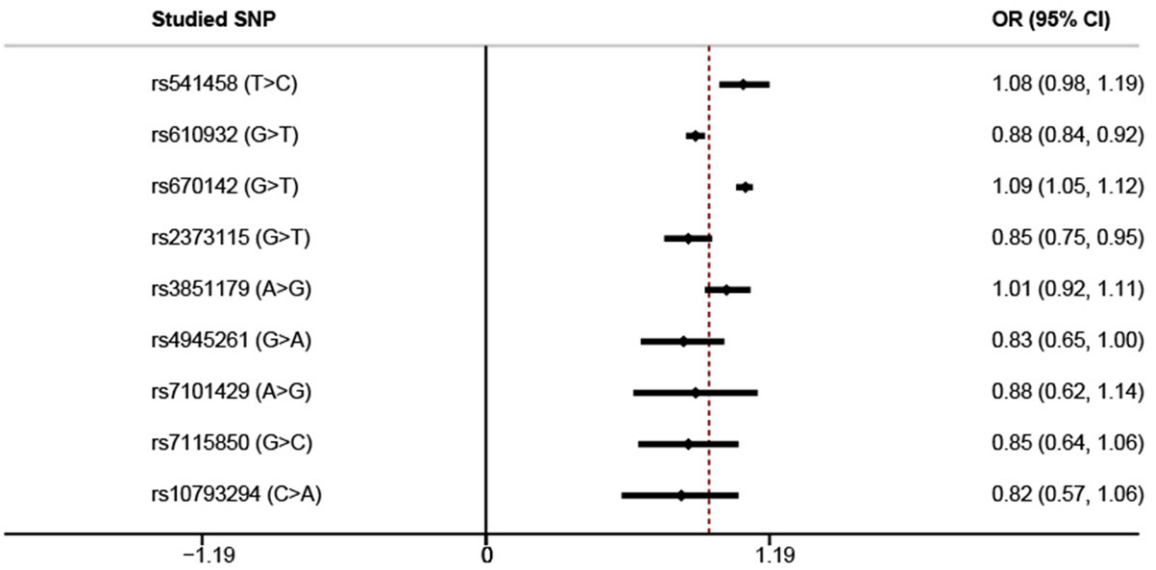

Figure 2. Summary of forest plots with ORs and 95% CI for all studied SNPs on chromosome 11q.

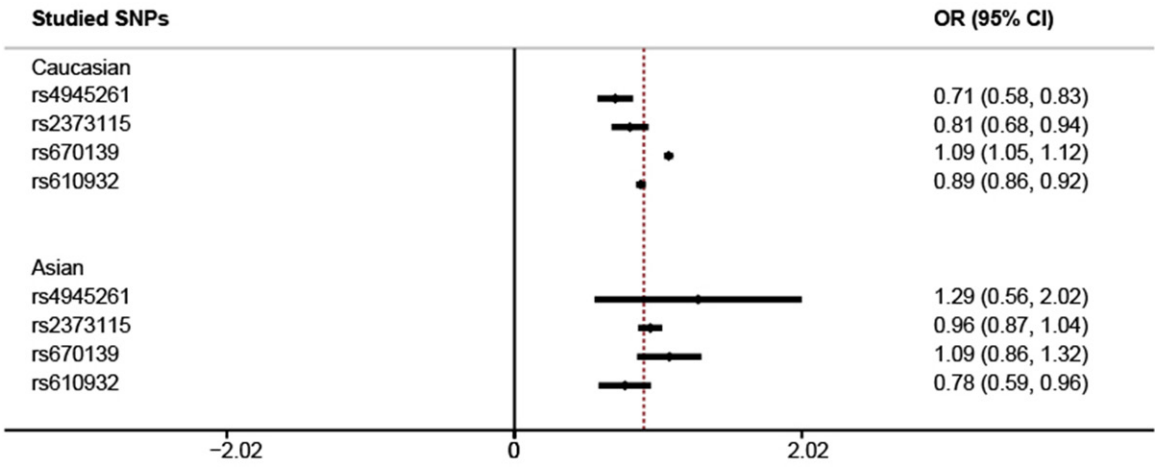

Figure 3. Summary of forest plots with ORs and 95% CI stratified by ethnicity for SNP.

(OR=0.85, 95% CI: 0.75-0.95, *P*<0.001). Besides, the polymorphism of rs4945261 (G>A) was also found to associate with lower AD risk (OR=0.83, 95% CI: 0.65-1.00, *P*<0.001). On the contrary, rs670139 (G>T) risk-allele carriers appear to show a higher risk of developing AD compared with non risk-allele carriers (OR=1.09, 95% CI: 1.05-1.12, *P*=0.554). There was no evidence of association between the rs10793294, rs7101429, rs7115850, rs3851179, rs541458 polymorphisms and AD susceptibility.

Subgroup analysis

We further conducted a subgroup analysis stratified by ethnicity (**Figure 3**). The polymorphism of rs670139 conferred an increased risk for AD (OR=1.09, 95% CI: 1.05-1.12, *P*=0.618) in Caucasians while the other three SNPs, rs4945261 (OR=0.71, 95% CI: 0.58-0.83, *P*=0.15), rs2373115 (OR=0.81, 95% CI: 0.68-0.94, P<0.001) and rs610932 (OR=0.89, 95% CI: 0.86-0.92, *P*=0.148), were associated with lower risk of AD. Nonetheless, only the rs610932 variant was shown to be associated with a lower risk of AD in Asians (OR=0.78, 95% CI: 0.59-0.96, *P*=0.035).

Publication bias and sensitivity analysis

Begg's funnel plots and Egger's test were performed to assess the publication biases among

Table 1. Meta-analysis of association between 11q variants and AD risk

Studied SNPs	Gene	OR	95% CI	I-squared	P_h	Z	P*	Model	Pr
rs541458	PICALM	1.08	0.98-1.19	82.3%	<0.001	19.72	<0.001	Random	0.33
rs610932	MS4A6A	0.87	0.83-0.91	54.6%	<0.001	42.12	0.007	Random	0.85
rs670142	MS4A6E	1.09	1.06-1.12	0.0%	0.55	70.67	<0.001	Random	0.88
rs2373115	GAB2	0.85	0.75-0.95	65.9%	<0.001	16.77	<0.001	Random	0.11
rs3851179	PICALM	1.01	0.92-1.11	84.7%	<0.001	20.7	<0.001	Random	0.29
rs4945261	GAB2	0.83	0.65-1.00	81.4%	<0.001	9.16	<0.001	Random	0.29
rs7101429	GAB2	0.88	0.62-1.14	87.7%	<0.001	6.7	<0.001	Random	0.70
rs7115850	GAB2	0.85	0.64-1.06	82.4%	<0.001	8.03	<0.001	Random	0.46
rs10793294	GAB2	0.82	0.57-1.06	90.7%	<0.001	6.55	<0.001	Random	0.16

Note: P_h=*P*-value for heterogeneity; *P**=*P*-value for Q test; *Pr*=*P*-value for publication bias.

studies. There was no obvious asymmetry in the shape of Begg's funnel plots. And the result of Egger's test showed no evidence of statistically significant asymmetry in the Begg's funnel plots (**Table 1**), and indicated no publication bias in this meta-analysis. The impact of each study on the overall OR was evaluated by using sensitivity analysis. The result of sensitivity analysis revealed no significant variation in the pooled OR when any one of single study was removed (data not shown), which suggested the overall results in this meta-analysis were robust and reliable.

Discussion

In this meta-analysis, we performed a comprehensive literature search to identify all eligible articles. According to the inclusion and exclusion criteria, a total of 35 articles were included in this meta-analysis. Our results showed that the four SNPs (rs4945261, rs670139, rs2373115 and rs610932) were significantly associated with AD risk. Among which, the rs670142 variant carriers were likely to have a higher risk of developing AD. However, the other three SNPs (rs494526, rs2373115 and rs610932) were shown to act as protective factors against AD. Stratified by ethnicity, subgroup analysis also revealed a similar result in Caucasians. Only the rs610932 variant was significantly associated with lower AD in Asians. Collectively, the meta-analysis showed that the four polymorphisms on chromosome 11q have significant association with AD risk.

GAB2 is a member of highly conserved human adaptor protein Gab/DOS subfamily, which ubiquitously expressed in white blood cells, posterior cingulated cortex and hypothalamus [47]. Gab/DOS subfamily play important role in various differentiation and proliferation pathways. The transduction and amplification of signals from growth factors, cell adhesion molecules, and cytokines was mediated by Gab/DOS proteins [48]. GAB proteins usually act as the downstream effector in response to the signal triggered by tyrosine kinase in the upstream pathway. Phosphorylated GAB proteins may mainly lead to the recruitment and activation of various signaling molecules, such as PI3K, CrK, SHP2, etc, which are critical for cell proliferation, survival, differentiation and apoptosis [49]. In addition, evidences showed that GAB2 may suppress the glycogen synthase kinase-3 (Gsk3)-dependent phosphorylation of AD-related tau tangles [50]. Hyperphosphorylated tau is unable to stimulate microtubule assembly, which disrupts the maintenance of microtubule network and promotes the tau aggregation [51]. Reiman et al. performed a GAB2 knock-down assay by using small-interfering RNA (siRNA). And it showed a marked increase of tau formation and aggregation in the neurons in absence of GAB2 [14]. Hence, the abnormal hyperphophorylated tau may contribute to the development of neurodegenerative disease, especially AD. Alternatively, mutations in GAB2 may facilitate the phosphorylation of tau and thereby result in the formation of neurofibrillary tangles. Moreover, GAB2 is also reported to interact with other potential AD-related genes, but the underlying mechanism is still not elucidated. Collectively, it can be hypothesized that GAB2 play a protective role against AD. In this meta-analysis, two polymorphisms of GAB2 (rs2373115 and rs4945261) were identified as protective factors against AD.

MS4A cluster consist of at least 16 paralogues including MS4A6A and MS4A6E on chromosome 11q in humans. MS4A cluster encodes a variety of cell membrane proteins with N- and C-terminal cytoplasmic domains and extracellular and intracellular loops. MS4A genes encode proteins with sequence homology and they are likely to share similar functional properties [52]. Although functional properties of most MS4A genes still remain unexplored, they have been shown to play important role in immunity. Several SNPs within MS4A has been reported to be correlated with atopic allergic diseases. MS4A1 may result in the activation and differentiation of B cells through interacting with activated B cell antigen receptor complex (BCR) [53]. MS4A4B appear to involve in the survival and apoptosis of T cells [54, 55]. Low expression of MS4A4B promotes the apoptosis of T-cells while high level of MS4A4B inhibits the apoptosis of T-cells. MS4A genes were previously identified to regulate the intracellular calcium homeostasis as well [56]. The release or uptake of Ca^{2+} is an important intracellular signal that regulates a wide range of physiological functions. The function of intracellular Ca^{2+} varies across the diverse cell types. La Ferla et al. revealed that high level of intracellular Ca^{2+} is likely to facilitate the formation of amyloid plaque, hyperphophorylation of tau, and neuronal cell death, subsequently leading to the pathogenesis of neurodegenerative disease [57]. The study of Berridge et al. also revealed the dysregulation of Ca^{2+} signaling may affect the memory formation and consolidation followed by cognition decline and dementia [58]. The genetic variants of rs610932 in MS4A6A were significantly associated with increased AD risk, but the other polymorphisms of rs670142 were found to be correlated with lower AD risk.

PICALM encodes a phosphatidylinositol-binding clathrin assembly protein, which is predominately expressed in the endothelial cells [59]. PICALM is reported to be involved in the modulation of APP uptake, trafficking and processing. Inhibition of endocytosis or PICALM expression has been found to result in the reduced APP internalization and diminished AB release [60]. The APP needs to be internalized through endocytosis prior to the proteolysis of APP. The formation of amyloid beta peptides requires the proteolysis of APP. Therefore, overexpression of PICALM may contribute to increase the level of amyloid beta peptides. Contradictorily, PICALM also participate in the elimination of amyloid beta peptides. The transportation of amyloid beta peptides across the blood-brain barrier into blood circulation is the main pathway to eliminate the amyloid beta peptide in brain [61]. The abundance of PICALM in endothelial cells is thought to facilitate the clearance process [59]. Altered expression of PICALM modulate the APP metabolism through various mechanism, thereby further researches are needed to illuminate the role of PICALM in the pathogenesis of AD. In this meta-analysis, no evidence was found for the association between PICALM variants and AD risk.

This is a first report investigating the correlation between aforementioned SNPs in the same chromosome region and AD susceptibility. On the other hand, there're still some limitations that should be acknowledged. We only used the allele model to estimate the odds ratio in this meta-analysis since some studies only report the allele frequencies. In addition, AD is a multifactorial disease resulting from a combination of environmental factors and genetic factors. Due to the different ethnicity and limited data available, it is unlikely to adjust the estimate of AD risk with different environmental factors, which may lead to a part of between-study heterogeneity. Hence, we only focused on the unadjusted OR and *P*-value in the meta-analysis.

In conclusion, our results revealed a significant association between four SNPs on chromosome 11q and AD risk. The polymorphism of rs610932 were shown to be a risk factor for AD while the other three genetic variants (rs494526, rs2373115 and rs610932) may act as protective factors against AD.

Disclosure of conflict of interest

None.

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References

[1] Alzheimer's Association. 2014 Alzheimer's disease facts and figures. Alzheimers Dement 2014; 10: e47-e92.

[2] Oddo S, Caccamo A, Shepherd JD, Murphy MP, Golde TE, Kayed R, Metherate R, Mattson MP, Akbari Y and LaFerla FM. Triple-transgenic

model of Alzheimer's disease with plaques and tangles: intracellular Aβ and synaptic dysfunction. Neuron 2003; 39: 409-421.

[3] Cummings JL, Vinters HV, Cole GM and Khachaturian ZS. Alzheimer's disease Etiologies, pathophysiology, cognitive reserve, and treatment opportunities. Neurology 1998; 51: S2-S17.

[4] Kalaria RN, Maestre GE, Arizaga R, Friedland RP, Galasko D, Hall K, Luchsinger JA, Ogunniyi A, Perry EK and Potocnik F. Alzheimer's disease and vascular dementia in developing countries: prevalence, management, and risk factors. Lancet Neurol 2008; 7: 812-826.

[5] Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M, Hall K, Hasegawa K, Hendrie H and Huang Y. Global prevalence of dementia: a Delphi consensus study. Lancet 2006; 366: 2112-2117.

[6] Raber J, Huang Y and Ashford JW. ApoE genotype accounts for the vast majority of AD risk and AD pathology. Neurobiol Aging 2004; 25: 641-650.

[7] Puglielli L, Tanzi RE and Kovacs DM. Alzheimer's disease: the cholesterol connection. Nat Neurosci 2003; 6: 345-351.

[8] Martins IJ, Hone E, Foster JK, Sünram-Lea SI, Gnjec A, Fuller SJ, Nolan D, Gandy SE, Martins RN. Apolipoprotein E, cholesterol metabolism, diabetes, and the convergence of risk factors for Alzheimer's disease and cardiovascular disease. Mol Psychiatry 2006; 11: 721-736.

[9] Ashford JW. APOE genotype effects on Alzheimer's disease onset and epidemiology. J Mol Neurosci 2004; 23: 157-165.

[10] Saunders A, Strittmatter W, Schmechel D, George-Hyslop PS, Pericak-Vance M, Joo S, Rosi B, Gusella J, Crapper-MacLachlan D and Alberts M. Association of apolipoprotein E allele ε4 with late-onset familial and sporadic Alzheimer's disease. Neurology 1993; 43: 1467-1467.

[11] Naj AC, Jun G, Beecham GW, Wang LS, Vardarajan BN, Buros J, Gallins PJ, Buxbaum JD, Jarvik GP and Crane PK. Common variants at MS4A4/MS4A6E, CD2AP, CD33 and EPHA1 are associated with late-onset Alzheimer's disease. Nat Genet 2011; 43: 436-441.

[12] Harold D, Abraham R, Hollingworth P, Sims R, Gerrish A, Hamshere ML, Pahwa JS, Moskvina V, Dowzell K, Williams A, Jones N, Thomas C, Stretton A, Morgan AR, Lovestone S, Powell J, Proitsi P, Lupton MK, Brayne C, Rubinsztein DC, Gill M, Lawlor B, Lynch A, Morgan K, Brown KS, Passmore PA, Craig D, McGuinness B, Todd S, Holmes C, Mann D, Smith AD, Love S, Kehoe PG, Hardy J, Mead S, Fox N, Rossor M, Collinge J, Maier W, Jessen F, Schurmann B, Heun R, van den Bussche H, Heuser I, Kornhuber J, Wiltfang J, Dichgans M, Frolich L, Hampel H, Hull M, Rujescu D, Goate AM, Kauwe JS, Cruchaga C, Nowotny P, Morris JC, Mayo K, Sleegers K, Bettens K, Engelborghs S, De Deyn PP, Van Broeckhoven C, Livingston G, Bass NJ, Gurling H, McQuillin A, Gwilliam R, Deloukas P, Al-Chalabi A, Shaw CE, Tsolaki M, Singleton AB, Guerreiro R, Muhleisen TW, Nothen MM, Moebus S, Jockel KH, Klopp N, Wichmann HE, Carrasquillo MM, Pankratz VS, Younkin SG, Holmans PA, O'Donovan M, Owen MJ and Williams J. Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. Nat Genet 2009; 41: 1088-1093.

[13] Hollingworth P, Harold D, Sims R, Gerrish A, Lambert JC, Carrasquillo MM, Abraham R, Hamshere ML, Pahwa JS, Moskvina V, Dowzell K, Jones N, Stretton A, Thomas C, Richards A, Ivanov D, Widdowson C, Chapman J, Lovestone S, Powell J, Proitsi P, Lupton MK, Brayne C, Rubinsztein DC, Gill M, Lawlor B, Lynch A, Brown KS, Passmore PA, Craig D, McGuinness B, Todd S, Holmes C, Mann D, Smith AD, Beaumont H, Warden D, Wilcock G, Love S, Kehoe PG, Hooper NM, Vardy ER, Hardy J, Mead S, Fox NC, Rossor M, Collinge J, Maier W, Jessen F, Ruther E, Schurmann B, Heun R, Kolsch H, van den Bussche H, Heuser I, Kornhuber J, Wiltfang J, Dichgans M, Frolich L, Hampel H, Gallacher J, Hull M, Rujescu D, Giegling I, Goate AM, Kauwe JS, Cruchaga C, Nowotny P, Morris JC, Mayo K, Sleegers K, Bettens K, Engelborghs S, De Deyn PP, Van Broeckhoven C, Livingston G, Bass NJ, Gurling H, McQuillin A, Gwilliam R, Deloukas P, Al-Chalabi A, Shaw CE, Tsolaki M, Singleton AB, Guerreiro R, Muhleisen TW, Nothen MM, Moebus S, Jockel KH, Klopp N, Wichmann HE, Pankratz VS, Sando SB, Aasly JO, Barcikowska M, Wszolek ZK, Dickson DW, Graff-Radford NR, Petersen RC, van Duijn CM, Breteler MM, Ikram MA, DeStefano AL, Fitzpatrick AL, Lopez O, Launer LJ, Seshadri S, Berr C, Campion D, Epelbaum J, Dartigues JF, Tzourio C, Alperovitch A, Lathrop M, Feulner TM, Friedrich P, Riehle C, Krawczak M, Schreiber S, Mayhaus M, Nicolhaus S, Wagenpfeil S, Steinberg S, Stefansson H, Stefansson K, Snaedal J, Bjornsson S, Jonsson PV, Chouraki V, Genier-Boley B, Hiltunen M, Soininen H, Combarros O, Zelenika D, Delepine M, Bullido MJ, Pasquier F, Mateo I, Frank-Garcia A, Porcellini E, Hanon O, Coto E, Alvarez V, Bosco P, Siciliano G, Mancuso M, Panza F, Solfrizzi V, Nacmias B, Sorbi S, Bossu P, Piccardi P, Arosio B, Annoni G, Seripa D, Pilotto A, Scarpini E, Galimberti D, Brice A, Hannequin D, Licastro F, Jones L, Holmans PA, Jonsson T, Riemenschneider M, Morgan K,

Younkin SG, Owen MJ, O'Donovan M, Amouyel P and Williams J. Common variants at ABCA7, MS4A6A/MS4A4E, EPHA1, CD33 and CD2AP are associated with Alzheimer's disease. Nat Genet 2011; 43: 429-435.

[14] Reiman EM, Webster JA, Myers AJ, Hardy J, Dunckley T, Zismann VL, Joshipura KD, Pearson JV, Hu-Lince D, Huentelman MJ, Craig DW, Coon KD, Liang WS, Herbert RH, Beach T, Rohrer KC, Zhao AS, Leung D, Bryden L, Marlowe L, Kaleem M, Mastroeni D, Grover A, Heward CB, Ravid R, Rogers J, Hutton ML, Melquist S, Petersen RC, Alexander GE, Caselli RJ, Kukull W, Papassotiropoulos A and Stephan DA. GAB2 alleles modify Alzheimer's risk in APOE epsilon4 carriers. Neuron 2007; 54: 713-720.

[15] Chapuis J, Hannequin D, Pasquier F, Bentham P, Brice A, Leber I, Frebourg T, Deleuze JF, Cousin E, Thaker U, Amouyel P, Mann D, Lendon C, Campion D and Lambert JC. Association study of the GAB2 gene with the risk of developing Alzheimer's disease. Neurobiol Dis 2008; 30: 103-106.

[16] Ikram MA, Liu F, Oostra BA, Hofman A, van Duijn CM and Breteler MM. The GAB2 gene and the risk of Alzheimer's disease: replication and meta-analysis. Biol Psychiatry 2009; 65: 995-999.

[17] Miyashita A, Arai H, Asada T, Imagawa M, Shoji M, Higuchi S, Urakami K, Toyabe S, Akazawa K, Kanazawa I, Ihara Y and Kuwano R. GAB2 is not associated with late-onset Alzheimer's disease in Japanese. Eur J Hum Genet 2009; 17: 682-686.

[18] Nacmias B, Tedde A, Bagnoli S, Cellini E, Guarnieri BM, Piacentini S and Sorbi S. Implication of GAB2 gene polymorphism in Italian patients with Alzheimer's disease. J Alzheimers Dis 2009; 16: 513-515.

[19] Ramirez-Lorca R, Boada M, Saez ME, Hernandez I, Mauleon A, Rosende-Roca M, Martinez-Lage P, Gutierrez M, Real LM, Lopez-Arrieta J, Gayan J, Antunez C, Gonzalez-Perez A, Tarraga L and Ruiz A. GAB2 gene does not modify the risk of Alzheimer's disease in Spanish APOE 4 carriers. J Nutr Health Aging 2009; 13: 214-219.

[20] Sleegers K, Bettens K, Brouwers N, Engelborghs S, van Miegroet H, De Deyn PP and Van Broeckhoven C. Common variation in GRB-associated Binding Protein 2 (GAB2) and increased risk for Alzheimer dementia. Hum Mutat 2009; 30: E338-344.

[21] Biffi A, Anderson CD, Desikan RS, Sabuncu M, Cortellini L, Schmansky N, Salat D and Rosand J. Genetic variation and neuroimaging measures in Alzheimer disease. Arch Neurol 2010; 67: 677-685.

[22] Carrasquillo MM, Belbin O, Hunter TA, Ma L, Bisceglio GD, Zou F, Crook JE, Pankratz VS, Dickson DW, Graff-Radford NR, Petersen RC, Morgan K and Younkin SG. Replication of CLU, CR1, and PICALM associations with alzheimer disease. Arch Neurol 2010; 67: 961-964.

[23] Corneveaux JJ, Myers AJ, Allen AN, Pruzin JJ, Ramirez M, Engel A, Nalls MA, Chen K, Lee W, Chewning K, Villa SE, Meechoovet HB, Gerber JD, Frost D, Benson HL, O'Reilly S, Chibnik LB, Shulman JM, Singleton AB, Craig DW, Van Keuren-Jensen KR, Dunckley T, Bennett DA, De Jager PL, Heward C, Hardy J, Reiman EM and Huentelman MJ. Association of CR1, CLU and PICALM with Alzheimer's disease in a cohort of clinically characterized and neuropathologically verified individuals. Hum Mol Genet 2010; 19: 3295-3301.

[24] Lin K, Tang M, Han H, Guo Y, Lin Y and Ma C. GAB2 is not associated with late-onset Alzheimer's disease in Chinese Han. Neurol Sci 2010; 31: 277-281.

[25] Seshadri S, Fitzpatrick AL, Ikram MA, DeStefano AL, Gudnason V, Boada M, Bis JC, Smith AV, Carassquillo MM, Lambert JC, Harold D, Schrijvers EM, Ramirez-Lorca R, Debette S, Longstreth WT Jr, Janssens AC, Pankratz VS, Dartigues JF, Hollingworth P, Aspelund T, Hernandez I, Beiser A, Kuller LH, Koudstaal PJ, Dickson DW, Tzourio C, Abraham R, Antunez C, Du Y, Rotter JI, Aulchenko YS, Harris TB, Petersen RC, Berr C, Owen MJ, Lopez-Arrieta J, Varadarajan BN, Becker JT, Rivadeneira F, Nalls MA, Graff-Radford NR, Campion D, Auerbach S, Rice K, Hofman A, Jonsson PV, Schmidt H, Lathrop M, Mosley TH, Au R, Psaty BM, Uitterlinden AG, Farrer LA, Lumley T, Ruiz A, Williams J, Amouyel P, Younkin SG, Wolf PA, Launer LJ, Lopez OL, van Duijn CM and Breteler MM. Genome-wide analysis of genetic loci associated with Alzheimer disease. JAMA 2010; 303: 1832-1840.

[26] Zhou S, Huriletemuer, Wang J, Wang B, Zhao S, Wang de S, Zhang C and Ma X. Association analysis between polymorphism rs2373115 of gene GRB-associated binding protein 2 and Mongolian Alzheimer patients. Neurosci Lett 2010; 480: 4-6.

[27] Lambert JC, Zelenika D, Hiltunen M, Chouraki V, Combarros O, Bullido MJ, Tognoni G, Fievet N, Boland A, Arosio B, Coto E, Del Zompo M, Mateo I, Frank-Garcia A, Helisalmi S, Porcellini E, Pilotto A, Forti P, Ferri R, Delepine M, Scarpini E, Siciliano G, Solfrizzi V, Sorbi S, Spalletta G, Ravaglia G, Valdivieso F, Alvarez V, Bosco P, Mancuso M, Panza F, Nacmias B, Bossu P, Piccardi P, Annoni G, Seripa D, Galimberti D, Licastro F, Lathrop M, Soininen H and Amouyel P. Evidence of the association of BIN1 and

PICALM with the AD risk in contrasting European populations. Neurobiol Aging 2011; 32: 756, e711-755.
[28] Li HL, Shi SS, Guo QH, Ni W, Dong Y, Liu Y, Sun YM, Bei W, Lu SJ, Hong Z and Wu ZY. PICALM and CR1 variants are not associated with sporadic Alzheimer's disease in Chinese patients. J Alzheimers Dis 2011; 25: 111-117.
[29] Wang G, Pan XL, Cui PJ, Wang Y, Ma JF, Ren RJ, Deng YL, Xu W, Tang HD and Chen SD. Association study of the GAB2 gene with the risk of Alzheimer disease in the chinese population. Alzheimer Dis Assoc Disord 2011; 25: 283-285.
[30] Yu JT, Song JH, Ma T, Zhang W, Yu NN, Xuan SY and Tan L. Genetic association of PICALM polymorphisms with Alzheimer's disease in Han Chinese. J Neurol Sci 2011; 300: 78-80.
[31] Zhong XL, Yu JT, Hou GY, Xing YY, Jiang H, Li Y and Tan L. Common variant in GAB2 is associated with late-onset Alzheimer's disease in Han Chinese. Clin Chim Acta 2011; 412: 446-449.
[32] Chen LH, Kao PY, Fan YH, Ho DT, Chan CS, Yik PY, Ha JC, Chu LW and Song YQ. Polymorphisms of CR1, CLU and PICALM confer susceptibility of Alzheimer's disease in a southern Chinese population. Neurobiol Aging 2012; 33: 210, e211-217.
[33] Deng YL, Liu LH, Wang Y, Tang HD, Ren RJ, Xu W, Ma JF, Wang LL, Zhuang JP, Wang G and Chen SD. The prevalence of CD33 and MS4A6A variant in Chinese Han population with Alzheimer's disease. Hum Genet 2012; 131: 1245-1249.
[34] Kamboh MI, Minster RL, Demirci FY, Ganguli M, Dekosky ST, Lopez OL and Barmada MM. Association of CLU and PICALM variants with Alzheimer's disease. Neurobiol Aging 2012; 33: 518-521.
[35] Nizamutdinov II, Andreeva TV, Stepanov VA, Marusin AV, Rogaev EI, Zasedatelev AS and Nasedkina TV. Biochip for determination of genetic markers of sporadic Alzheimer's disease risk in the Russian Slavic population. Mol Biol 2013; 47: 827-835.
[36] Ohara T, Ninomiya T, Hirakawa Y, Ashikawa K, Monji A, Kiyohara Y, Kanba S and Kubo M. Association study of susceptibility genes for late-onset Alzheimer's disease in the Japanese population. Psychiatr Genet 2012; 22: 290-293.
[37] Schott JM. Using CSF biomarkers to replicate genetic associations in Alzheimer's disease. Neurobiol Aging 2012; 33: 1486, e1489-1415.
[38] Izzo G, Forlenza OV, Santos B, Bertolucci PH, Ojopi EB, Gattaz WF and Kerr DS. Single-nucleotide polymorphisms of GSK3B, GAB2 and SORL1 in late-onset Alzheimer's disease: interactions with the APOE genotype. Clinics 2013; 68: 277-280.
[39] Kohannim O, Hua X, Rajagopalan P, Hibar DP, Jahanshad N, Grill JD, Apostolova LG, Toga AW, Jack CR Jr, Weiner MW and Thompson PM. Multilocus genetic profiling to empower drug trials and predict brain atrophy. Neuroimage Clin 2013; 2: 827-835.
[40] Miyashita A, Koike A, Jun G, Wang LS, Takahashi S, Matsubara E, Kawarabayashi T, Shoji M, Tomita N, Arai H, Asada T, Harigaya Y, Ikeda M, Amari M, Hanyu H, Higuchi S, Ikeuchi T, Nishizawa M, Suga M, Kawase Y, Akatsu H, Kosaka K, Yamamoto T, Imagawa M, Hamaguchi T, Yamada M, Morihara T, Takeda M, Takao T, Nakata K, Fujisawa Y, Sasaki K, Watanabe K, Nakashima K, Urakami K, Ooya T, Takahashi M, Yuzuriha T, Serikawa K, Yoshimoto S, Nakagawa R, Kim JW, Ki CS, Won HH, Na DL, Seo SW, Mook-Jung I, St George-Hyslop P, Mayeux R, Haines JL, Pericak-Vance MA, Yoshida M, Nishida N, Tokunaga K, Yamamoto K, Tsuji S, Kanazawa I, Ihara Y, Schellenberg GD, Farrer LA and Kuwano R. SORL1 is genetically associated with late-onset Alzheimer's disease in Japanese, Koreans and Caucasians. PLoS One 2013; 8: e58618.
[41] Tan L, Yu JT, Zhang W, Wu ZC, Zhang Q, Liu QY, Wang W, Wang HF, Ma XY and Cui WZ. Association of GWAS-linked loci with late-onset Alzheimer's disease in a northern Han Chinese population. Alzheimers Dement 2013; 9: 546-553.
[42] Belcavello L, Camporez D, Almeida LD, Morelato RL, Batitucci MC and de Paula F. Association of MTHFR and PICALM polymorphisms with Alzheimer's disease. Mol Biol Rep 2015; 42: 611-6.
[43] Carrasquillo MM, Khan Q, Murray ME, Krishnan S, Aakre J, Pankratz VS, Nguyen T, Ma L, Bisceglio G, Petersen RC, Younkin SG, Dickson DW, Boeve BF, Graff-Radford NR and Ertekin-Taner N. Late-onset Alzheimer disease genetic variants in posterior cortical atrophy and posterior AD. Neurology 2014; 82: 1455-1462.
[44] Gharesouran J, Rezazadeh M, Khorrami A, Ghojazadeh M and Talebi M. Genetic Evidence for the Involvement of Variants at APOE, BIN1, CR1, and PICALM Loci in Risk of Late-Onset Alzheimer's Disease and Evaluation for Interactions with APOE Genotypes. J Mol Neurosci 2014; 54: 780-786.
[45] Proitsi P, Lee SH, Lunnon K, Keohane A, Powell J, Troakes C, Al-Sarraj S, Furney S, Soininen H, Kloszewska I, Mecocci P, Tsolaki M, Vellas B, Lovestone S and Hodges A. Alzheimer's disease susceptibility variants in the MS4A6A gene are associated with altered levels of

MS4A6A expression in blood. Neurobiol Aging 2014; 35: 279-290.
[46] Wang HZ, Bi R, Hu QX, Xiang Q, Zhang C, Zhang DF, Zhang W, Ma X, Guo W, Deng W, Zhao L, Ni P, Li M, Fang Y, Li T and Yao YG. Validating GWAS-Identified Risk Loci for Alzheimer's Disease in Han Chinese Populations. Mol Neurobiol 2014; [Epub ahead of print].
[47] Gu H, Botelho RJ, Yu M, Grinstein S and Neel BG. Critical role for scaffolding adapter Gab2 in FcγR-mediated phagocytosis. J Cell Biol 2003; 161: 1151-1161.
[48] Wohrle F, Daly RJ and Brummer T. Function, regulation and pathological roles of the Gab/DOS docking proteins. Cell Commun Signal 2009; 7: 22.
[49] Adams SJ, Aydin IT and Celebi JT. GAB2-a scaffolding protein in cancer. Mol Cancer Res 2012; 10: 1265-1270.
[50] Hooper C, Killick R and Lovestone S. The GSK3 hypothesis of Alzheimer's disease. J Neurochem 2008; 104: 1433-1439.
[51] Iqbal K, Alonso Adel C, Chen S, Chohan MO, El-Akkad E, Gong CX, Khatoon S, Li B, Liu F, Rahman A, Tanimukai H, Grundke-Iqbal I. Tau pathology in Alzheimer disease and other tauopathies. Biochim Biophys Acta 2005; 1739: 198-210.
[52] Liang Y, Buckley TR, Tu L, Langdon SD and Tedder TF. Structural organization of the human MS4A gene cluster on Chromosome 11q12. Immunogenetics 2001; 53: 357-368.
[53] Polyak MJ, Li H, Shariat N and Deans JP. CD20 homo-oligomers physically associate with the B cell antigen receptor. Dissociation upon receptor engagement and recruitment of phosphoproteins and calmodulin-binding proteins. J Biol Chem 2008; 283: 18545-18552.
[54] Yan Y, Li Z, Zhang GX, Williams MS, Carey GB, Zhang J, Rostami A and Xu H. Anti-MS4a4B treatment abrogates MS4a4B-mediated protection in T cells and ameliorates experimental autoimmune encephalomyelitis. Apoptosis 2013; 18: 1106-1119.
[55] Xu H, Yan Y, Williams MS, Carey GB, Yang J, Li H, Zhang GX and Rostami A. MS4a4B, a CD20 homologue in T cells, inhibits T cell propagation by modulation of cell cycle. PLoS One 2010; 5: e13780.
[56] Parolini D, Cassinelli L, Razini P, Sitzia C, Tonna N, Erratico S, Colleoni F, Angeloni V, Maffioli E and Farini A. Expression of CD20 reveals a new store-operated calcium entry modulator in skeletal muscle. Int J Biochem Cell Biol 2012; 44: 2095-2105.
[57] LaFerla FM. Calcium dyshomeostasis and intracellular signalling in Alzheimer's disease. Nat Rev Neurosci 2002; 3: 862-872.
[58] Berridge MJ. Calcium regulation of neural rhythms, memory and Alzheimer's disease. J Physiol 2014; 592: 281-293.
[59] Baig S, Joseph SA, Tayler H, Abraham R, Owen MJ, Williams J, Kehoe PG and Love S. Distribution and Expression of Picalm in Alzheimer Disease. J Neuropathol Exp Neurol 2010; 69: 1071-7.
[60] Xiao Q, Gil SC, Yan P, Wang Y, Han S, Gonzales E, Perez R, Cirrito JR and Lee JM. Role of phosphatidylinositol clathrin assembly lymphoid-myeloid leukemia (PICALM) in intracellular amyloid precursor protein (APP) processing and amyloid plaque pathogenesis. J Biol Chem 2012; 287: 21279-21289.
[61] Deane R, Bell R, Sagare A and Zlokovic B. Clearance of amyloid-β peptide across the blood-brain barrier: implication for therapies in Alzheimer's disease. CNS Neurol Disord Drug Targets 2009; 8: 16.

Supplementary Table 1. Characteristics of included studies

First author	Country	Ethnicity	Year	Case	Control	Studied SNPs	Ref.
Reiman	USA	Caucasian	2007	861	551	rs10793294; rs2373115; rs4945261; rs7101429; rs7115850	[14]
Chapuis	France & UK	Caucasian	2008	1759	1406	rs2373115	[15]
Harold	Multi-nations	Caucasian	2009	3941	7848	rs3851179; rs541458	[12]
Ikram	Netherland	Caucasian	2009	443	5064	rs4945261	[16]
Miyashita	JAPAN	Asian	2009	1656	1656	rs10793294; rs2373115; rs4945261; rs7101429; rs7115850	[17]
Nacmiasa	Italy	Caucasian	2009	241	338	rs2373115	[18]
Ramirez-Lorca	Spain	Caucasian	2009	521	476	rs2373115	[19]
Sleegers	Belgium	Caucasian	2009	508	601	rs10793294; rs2373115; rs4945261; rs7101429; rs7115850	[20]
Biffi	USA	Caucasian	2010	168	205	rs3851179	[21]
Carrasquillo	USA	Caucasian	2010	1829	2576	rs3851179	[22]
Corneveaux	USA	Caucasian	2010	1019	591	rs541458	[23]
Lin	China	Asian	2010	292	227	rs2373115	[24]
Sheshadri	USA	Caucasian	2010	1140	1209	rs541458	[25]
Zhou	Mongolia	Asian	2010	107	100	rs2373115	[26]
Hollingworth	Multi-nations	Caucasian	2011	18897	39846	rs610932; rs670139	[13]
Lambert	Multi-nations	Caucasian	2011	2744	2597	rs541458	[27]
Li	China	Asian	2011	474	591	rs3851179	[28]
Wang	China	Asian	2011	159	151	rs2373115; rs4945261; rs7101429; rs7115850	[29]
Yu	China	Asian	2011	266	343	rs3851179	[30]
Zhong	China	Asian	2011	358	366	rs10793294	[31]
Chen	Hong Kong	Asian	2012	462	350	rs3851179; rs541458	[32]
Deng	China	Asian	2012	190	193	rs610932	[33]
Kamboh	USA	Caucasian	2012	1348	1359	rs3851179; rs541458	[34]
Nizamutdinova	Russia	Caucasian	2012	166	128	rs3851179; rs2373115	[35]
Ohara	Japan	Asian	2012	825	2934	rs3851179	[36]
Schott	UK	Caucasian	2012	102	114	rs3851179; rs541458	[37]
Izzo	Brazil	Caucasian	2013	130	71	rs2373115	[38]
Kohannim	USA	Caucasian	2013	106	160	rs3851179	[39]
Miyashita	Japan	Asian	2013	1224	2114	rs3851179; rs541458	[40]
Tan	China	Asian	2013	612	612	rs610932; rs670139	[41]
Belcavello	Brazil	Caucasian	2014	82	161	rs3851179	[42]
Carrasquillo	USA	Caucasian	2014	135	2422	rs3851179	[43]
Gharesouran	Turkey	Caucasian	2014	160	163	rs3851179	[44]
Proitsi	UK	Caucasian	2014	411	399	rs610932	[45]
Wang	China	Asian	2014	1082	1094	rs610932; rs670139	[46]

Supplementary Table 2. Odds ratio and corresponding *P*-value in the included studies investigating the GAB2 variants

Studied SNP	Study	Ethnicity	Sample Size		Sub-group	OR (95% CI)	*P*-value
			Case	Control			
rs10793294 (C>A)	Reiman et al. (Discovery), 2007, USA	Caucasian	446	290	-	0.55 (0.43, 0.70)	9.49E-07
	Reiman et al. (Neuropathology Replication), 2007, USA	Caucasian	197	114	-	0.61 (0.41, 0.90)	1.26E-02
	Reiman et al. (Clinical Replication), 2007, USA	Caucasian	218	146	-	0.51 (0.36, 0.72)	8.23E-05
	Miyashita et al., 2009, Japan	Asian	1616	1631	APOE e4	1.08 (0.96, 1.22)	2.03E-01
	Sleegers et al., 2009, Belgium	Caucasian	528	601	APOE e4	0.91 (0.74, 1.12)	3.86E-01
	Zhong et al., 2011, China	Asian	358	366	APOE e4	1.33 (1.03, 1.72)	2.58E-02
rs2373115 (G>T)	Reiman et al. (Discovery), 2007, USA	Caucasian	446	290	APOE e4	0.53 (0.40, 0.70)	7.04E-06
	Reiman et al. (Neuropathology Replication), 2007, USA	Caucasian	197	114	APOE e4	0.86 (0.55, 1.32)	4.85E-01
	Reiman et al. (Clinical Replication), 2007, USA	Caucasian	218	146	APOE e4	0.60 (0.39, 0.91)	1.68E-02
	Chapuis et al., 2008, France & UK	Caucasian	1759	1406	APOE e4	0.92 (0.81, 1.05)	2.16E-01
	Miyashita et al., 2009, Japan	Asian	1627	1645	APOE e4	0.96 (0.87, 1.06)	4.36E-01
	Sleegers et al., 2009, Belgium	Caucasian	527	601	APOE e4	0.92 (0.73, 1.15)	4.64E-01
	Nacmiasa et al., 2009, Italy	Caucasian	241	338	APOE e4	0.65 (0.48, 0.88)	5.32E-03
	Ramirez-Lorca et al., 2009, Spain	Caucasian	521	476	APOE e4	1.02 (0.81, 1.28)	8.83E-01
	Zhou et al., 2010, Mongolia	Asian	107	100	APOE e4	1.10 (0.74, 1.63)	6.49E-01
	Lin et al., 2010, China	Asian	292	227	APOE e4	0.91 (0.71, 1.16)	4.38E-01
	Wang et al., 2011, China	Asian	129	109	-	0.92 (0.64, 1.33)	6.65E-01
	Ikram et al., 2009, Netherlands	Caucasian	443	5064	APOE e4	1.00 (0.83, 1.21)	9.92E-01
	Izzo et al., 2013, Brazail	Caucasian	130	71	-	0.73 (0.44, 1.22)	2.27E-01
	Nizamutdinova et al., 2013, Russia	Caucasian	166	128	-	1.00 (0.60, 1.66)	9.92E-01
rs4945261 (G>A)	Reiman et al. (Discovery), 2007, USA	Caucasian	446	290	-	0.54 (0.40, 0.72)	1.81E-05
	Reiman et al. (Clinical Replication), 2007, USA	Caucasian	218	146	-	0.70 (0.46, 1.06)	1.13E-01
	Reiman et al. (Neuropathology Replication), 2007, USA	Caucasian	197	114	-	0.70 (0.46, 1.06)	9.05E-02
	Ikram et al., 2009, Netherlands	Caucasian	443	5064	APOE e4	0.78 (0.63, 0.97)	9.92E-01
	Miyashita et al., 2009, Japan	Asian	1630	1631	APOE e4	0.97 (0.88, 1.07)	4.98E-01
	Sleegers et al., 2009, Belgium	Caucasian	528	597	APOE e4	0.85 (0.67, 1.08)	1.76E-01
	Wang et al., 2011, China	Asian	159	151	-	1.72 (1.24, 2.36)	9.30E-04
rs7101429 (A>G)	Reiman et al. (Discovery), 2007, USA	Caucasian	446	290	-	0.66 (0.49, 0.90)	6.87E-03
	Reiman et al. (Clinical Replication), 2007, USA	Caucasian	218	146	-	1.02 (0.67, 1.55)	9.29E-01
	Reiman et al. (Neuropathology Replication), 2007, USA	Caucasian	197	114	-	0.41 (0.26, 0.65)	1.11E-04
	Miyashita et al., 2009, Japan	Asian	1634	1644	APOE e4	0.98 (0.89, 1.09)	7.60E-01
	Sleegers et al., 2009, Belgium	Caucasian	525	595	APOE e4	0.86 (0.68, 1.08)	1.98E-01
	Wang et al., 2011, China	Asian	159	151	-	2.01 (1.44, 2.82)	4.44E-05
rs7115850 (G>C)	Reiman et al. (Discovery), 2007, USA	Caucasian	446	290	-	0.57 (0.43, 0.75)	5.25E-05
	Reiman et al. (Clinical Replication), 2007, USA	Caucasian	218	146	-	0.61 (0.40, 0.92)	1.91E-02
	Reiman et al. (Neuropathology Replication), 2007, USA	Caucasian	197	114	-	0.78 (0.50, 1.20)	2.56E-01
	Miyashita et al., 2009, Japan	Asian	1649	1652	APOE e4	0.97 (0.88, 1.07)	5.61E-01
	Sleegers et al., 2009, Belgium	Caucasian	527	599	APOE e4	0.95 (0.76, 1.19)	6.57E-01
	Wang et al., 2011, China	Asian	159	151	-	1.55 (1.10, 2.18)	1.24E-02

Supplementary Table 3. Odds ratio and corresponding *P*-value in the included studies investigating the MS4A6A, MS4A6E variants

Studied SNP	Study	Ethnicity	Sample Size		Subgroup	OR (95% CI)	*P*-value
			Cases	Controls			
rs610932 (G>T) (MS4A6A)	Hollingworth et al. (Stage 1, GERAD1), 2011, Europe & USA	Caucasian	3941	7848		0.87 (0.82, 0.92)	1.49E-06
	Hollingworth et al. (Stage 1, EADI1), 2011, Europe & USA	Caucasian	2025	5328		0.93 (0.86, 1)	4.60E-02
	Hollingworth et al. (Stage 1, ADNI), 2011, Europe & USA	Caucasian	151	177		0.88 (0.64, 1.22)	4.48E-01
	Hollingworth et al. (Stage 1, TGEN1), 2011, Europe & USA	Caucasian	571	332		0.74 (0.6, 0.9)	2.79E-03
	Hollingworth et al. (Stage 2, GERAD2), 2011, Europe & USA	Caucasian	3262	3320		0.94 (0.87, 1.02)	1.40E-01
	Hollingworth et al. (Stage 2, AD-IG), 2011, Europe & USA	Caucasian	709	971		0.79 (0.65, 0.96)	2.00E-02
	Hollingworth et al. (Stage 2, deCODE), 2011, Europe & USA	Caucasian	925	612		0.81 (0.7, 0.95)	9.00E-03
	Hollingworth et al. (Stage 3, EADI2), 2011, Europe & USA	Caucasian	2751	2620		0.9 (0.83, 0.97)	7.70E-03
	Hollingworth et al. (Stage 3, Mayo2), 2011, Europe & USA	Caucasian	4168	5734		0.89 (0.83, 0.95)	8.80E-04
	Hollingworth et al. (Stage 3, CHARGE), 2011, Europe & USA	Caucasian	394	12904		0.95 (0.88, 1.03)	2.17E-01
	Deng et al., 2012, China	Asian	190	193	APOE e4	0.62 (0.47, 0.83)	1.08E-03
	Tan et al., 2013, China	Asian	612	612		0.75 (0.64, 0.89)	9.45E-04
	Proitsi et al., 2014, UK	Caucasian	411	399		0.77 (0.6, 0.99)	4.30E-02
	Wang et al., 2014, China	Asian	333	334		1 (0.8, 1.25)	1.00E+00
rs670139 (G>T) (MS4A6E)	Hollingworth et al. (Stage 1, GERAD1), 2011, Europe & USA	Caucasian	3941	7848		1.13 (1.06, 1.21)	8.66E-05
	Hollingworth et al. (Stage 1, EADI1), 2011, Europe & USA	Caucasian	2025	5328		1.06 (0.99, 1.14)	1.20E-01
	Hollingworth et al. (Stage 1, ADNI), 2011, Europe & USA	Caucasian	151	177		1.08 (0.78, 1.49)	6.62E-01
	Hollingworth et al. (Stage 1, TGEN1), 2011, Europe & USA	Caucasian	571	332		1.26 (1.03, 1.54)	2.25E-02
	Hollingworth et al. (Stage 2, GERAD2), 2011, Europe & USA	Caucasian	3262	3320		1.1 (1.02, 1.19)	1.44E-02
	Hollingworth et al. (Stage 2, AD-IG), 2011, Europe & USA	Caucasian	709	971		1.13 (0.93, 1.38)	2.10E-01
	Hollingworth et al. (Stage 2, deCODE), 2011, Europe & USA	Caucasian	925	612		1.15 (0.99, 1.35)	7.50E-02
	Hollingworth et al. (Stage 3, EADI2), 2011, Europe & USA	Caucasian	2751	2620		1.02 (0.94, 1.11)	5.85E-01
	Hollingworth et al. (Stage 3, Mayo2), 2011, Europe & USA	Caucasian	4168	5734		1.09 (1.03, 1.16)	2.50E-03
	Hollingworth et al. (Stage 3, CHARGE), 2011, Europe & USA	Caucasian	394	12904		1.05 (0.96, 1.15)	2.69E-01
	Tan et al., 2013, China	Asian	612	612		1.2 (1.02, 1.4)	2.80E-02
	Wang et al., 2014, China	Asian	333	334		0.97 (0.78, 1.2)	7.67E-01

Supplementary Table 4. Odds ratio and corresponding *P*-value in the included studies investigating the GAB2 variants

Studied SNP	Study	Ethnicity	Sample Size		Subgroup	OR (95% CI)	*P*-Value
			Case	Control			
rs3851179 (A>G)	Harold et al. (USA), 2009, USA, UK, Ireland & Germany	Caucasian	1159	2188	-	1.14 (1.03, 1.27)	1.37E-02
	Harold et al. (Germany), 2009, USA, UK, Ireland & Germany	Caucasian	555	824	-	1.10 (0.94, 1.30)	2.23E-01
	Harold et al. (UK & Ireland), 2009, USA, UK, Ireland & Germany	Caucasian	2227	4836	-	1.22 (1.13, 1.31)	1.83E-07
	Biffi et al., 2010, USA	Caucasian	168	205	-	0.99 (0.81, 1.20)	8.80E-01
	Carrasquillo et al., 2010, USA	Caucasian	1829	2576	-	0.80 (0.73, 0.89)	1.30E-05
	Li et al., 2011, China	Asian	474	591	APOE e4	1.04 (0.87, 1.24)	6.86E-01
	Yu et al., 2011, China	Asian	266	343	APOE e4	1.15 (0.91, 1.46)	2.35E-01
	Chen et al., 2012, Hong Kong	Asian	457	341	-	1.02 (0.83, 1.25)	8.41E-01
	Kamboh et al., 2012, USA	Caucasian	1328	1337	-	1.12 (1.00, 1.25)	5.53E-02
	Ohara et al., 2012, Japan	Asian	825	2934	-	1.13 (1.01, 1.27)	2.88E-02
	Schott et al., 2012, UK	Caucasian	102	114	-	0.82 (0.58, 1.18)	2.90E-01
	Nizamutdinov et al., 2012, Russia	Caucasian	166	128	-	0.75 (0.53, 1.05)	9.64E-02
	Kohannim et al., 2013, USA	Caucasian	106	160	-	1.15 (0.80, 1.65)	4.51E-01
	Miyashita et al. (Japan), 2013, Japan	Asian	885	985	-	0.80 (0.73, 0.89)	1.71E-05
	Miyashita et al. (South Korea), 2013, Japan	Asian	339	1129	-	0.79 (0.66, 0.96)	1.99E-02
	Belcavello et al., 2014, Brazil	Caucasian/African	82	161	-	1.40 (0.93, 2.10)	1.03E-01
	Carrasquillo et al., 2014, USA	Caucasian	135	2422	-	0.82 (0.64, 1.05)	1.12E-01
	Gharesouran et al., 2014, Turkey	Caucasian	160	163	APOE e4	4.85 (3.16, 7.43)	1.95E-14
	Wang et al., 2014, China	Asian	749	760		1.12 (0.97, 1.3)	1.28E-01
rs541458 (T>C)	Harold et al. (USA), 2009, USA, UK, Ireland & Germany	Caucasian	1159	2188	-	1.13 (1.01, 1.26)	3.00E-02
	Harold et al. (Germany), 2009, USA, UK, Ireland & Germany	Caucasian	555	824	-	1.05 (0.89, 1.23)	5.72E-01
	Harold et al. (UK & Ireland), 2009, USA, UK, Ireland & Germany	Caucasian	2227	4836	-	1.21 (1.12, 1.31)	1.45E-06
	Corneveaux et al., 2010, USA	Caucasian	1019	591	-	1.25 (1.07, 1.46)	5.75E-03
	Sheshadri et al., 2010, USA	Caucasian	1140	1209	-	1.20 (1.06, 1.36)	3.32E-03
	Lambert et al. (Finland), 2011, Finland, Italy & Spain	Caucasian	561	521	-	1.19 (1.00, 1.42)	5.26E-02
	Lambert et al. (Italy), 2011, Finland, Italy & Spain	Caucasian	1460	1257	-	0.82 (0.73, 0.92)	1.08E-03
	Lambert et al. (Spain), 2011, Finland, Italy & Spain	Caucasian	723	819	-	1.22 (1.04, 1.43)	1.37E-02
	Chen et al., 2012, Hong Kong	Asian	449	340	-	0.97 (0.79, 1.18)	7.47E-01
	Schott et al., 2012, UK	Caucasian	102	114	-	0.68 (0.47, 0.98)	4.00E-02
	Kamboh et al., 2012, USA	Caucasian	1322	1338	-	1.14 (1.01, 1.28)	3.21E-02