Meta-analysis

Association between SORL1 polymorphisms and the risk of Alzheimer's disease

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Abstract

A meta-analysis was performed to identify empirical data assessing the effects of a single nucleotide polymorphisms of sortilin-related receptor on Alzheimer's disease based on 14 studies involving 37941 cases and 49727 control studies. Analysis showed, (i) Increased risk between the single nucleotide polymorphisms (rs641120, rs1010159) and Alzheimer's disease susceptibility in Asian populations, (ii) Single nucleotide polymorphism rs689021 was associated with decreased risk in Caucasians, and (iii) Single nucleotide polymorphism rs641120 was detected as a decreased risk in both populations. Given these data, crucial evidence is provided to demonstrate that a significant relationship exists between SORL1 polymorphisms and susceptibility to Alzheimer's disease.

Keywords

Alzheimer's disease; single nucleotide polymorphisms; sortilin-related receptor; neurogenomics; susceptibility; sortilin related receptor 1

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1. Introduction

Alzheimer's disease (AD) is the most common age-dependent disease in most elderly groups [1]. It has been considered to indicate explicit memory decline followed by a loss of a wider range of cognitive functions, personality changes, and language disorders [2]. AD is a chronic and irreversible neurodegenerative disease, presumably due to the over-accumulation of beta-amyloid (Aβ) and hyperphosphorylated Tau [3]. The Aβ domain in amyloid precursor protein (APP) is located toward the C-terminal of the precursor protein [4], and is released extracellularly after cleavage by β and γ-secretase. The Aβ is a 4-kDa peptide [5] produced in neurons [6] which can evoke oxidative stress, neurotoxic Aβ aggregation leads to synaptic loss through oxidative stress and is significantly related to memory, cognitive function, and eventually neuronal cell death [7, 8]. Hyperphosphorylated Tau protein, formed Neurofibrillary tangles, can independently exacerbate mitochondrial dysfunction and reactive oxygen species production, leading to a cause of AD [9].

Gene polymorphisms have been identified as risk factors of neurodegenerative diseases with abnormal protein aggregates, such as AD [10]. Cytological and molecular biological studies have identified the sortilin related receptor 1 (SORL1) as an candidate gene for AD [11] located on human chromosome 11q24.1. It encodes a mosaic protein that consists of the vacuolar protein sorting 10 (VPS10) domain-containing receptor family and the low density lipoprotein receptor (LDLR) family. The encoded lipoprotein is proteolytically processed to generate the mature receptor, which has a significant role in endocytosis and protein sorting [12]. The gene variants may be associated with AD [13]. On the other hand, it is biologically reasonable for SORL1 to be an AD risk because of the differential sorting of the APP and regulation of Aβ production [14]. It is reported that the SORL1 gene might affect AD risk as a candidate gene [15]. SORL1 over-expression significantly decreases total cellular APP and extracellular Aβ [16]. On the contrary, increased amyloid β could be attributed to SORL1 protein expression [17].

Previously, studies have been conducted to investigate the association between SORL1 polymorphism and AD risk, however, it has to be noted that such studies had relatively a small sample size and the evidence for the role of SORL1 as a genetic marker for AD risk was unclear and controversial. Thus, a meta-analysis was carried out to provide a more convincing conclusion about the association between the six single nucleotide polymorphisms of SORL1 (rs668387, rs689021, rs3824968, rs1010159, rs641120, rs2070045) and AD susceptibility.

2. Materials and methods

A systematic search strategy of relevant studies was conducted to identify published articles on the association of AD risk with SORL1 gene polymorphisms. PubMed, Embase, Cochrane Library, China National Knowledge Infrastructure database (CNKI), and Wanfang databases (an affiliate of the Chinese Ministry of Science & Technology) were searched with the terms: SORL1 (also known as SORLA, LR11) sortilin-related receptor 1, gene polymorphisms, variant, variation. References of relative studies were searched manually to identify additional eligible studies.

Inclusion criteria included:

(1) Human case-control studies based on the six polymorphisms, rs668387, rs689021, rs3824968, rs1010159, rs641120, rs2070045 of SORL1, and AD risk.

(2) The diagnosis of AD was identified by NINCDS-ADRDA Alzheimer's Criteria (National Institute of Neurological and

Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association).
(3) The genotype distribution of controls conform to the Hardy–Weinberg equilibrium (HWE).
(4) Sufficient genotype frequency data to calculate odds ratios (ORs) and 95% confidence intervals (95% CI).

Exclusion criteria included:

(1) Reviews, meta-analysis, abstracts, case reports, comments and editorial excluded.
(2) Duplications, grey literatures, unpublished articles excluded.
(3) Studies in which data was not insufficient.

The following search terms were independently extracted from all eligible publications according to the inclusion and exclusion criteria listed above: first author, publication year, country of origin, number of cases and controls, genotype frequency, method of HWE test. Different ethnicity descents were classified as Asian, Caucasian, and mixed. Any disagreements were resolved by consensus with the third investigator's reexamination of the full text.

Association of the SORL1, rs668387, rs689021, rs3824968, rs1010159, rs641120, rs2070045 polymorphisms with the risk of Alzheimer's disease. The subgroup analysis was performed according to different the ethnicities of the subjects.

Allele, dominant, recessive, and additive models were separately evaluated for each polymorphismy. The association between SORL1 and Alzheimer's disease risk was estimated by calculation of Odds ratios (ORs) and 95% confidence intervals (CIs). Tests for Heterogeneity assumption were checked by the Cochran Q-statistic and I^2 test. When the p value of the Cochran Q-statistic was less than or equal to 0.05 or I^2 was greater than or equal to 50% ($p \leq 0.10$ or $I^2 \geq 50\%$), the random effects model was used for analysis. Otherwise, if the p value of the Cochran Q-statistic was greater than 0.05 and I^2 was less than 50% ($p > 0.10$ and $I^2 < 50\%$), the fixed-effects model was applied to pool the data. Sensitivity analyses were performed to identify individual study effects contributing to pooled results and to test the result reliability. A subgroup analysis by ethnicity (Asian, Caucasian, and Mixed) was implemented to identify whether each SNP was susceptible to AD for different populations. Publication bias was checked by Begg funnel plots and Egger publication-bias plots. When $p < 0.05$ in the test, the publication bias was considered significant. All analyses were performed using RevMan 5.3 (Review Manager) and Stata 12.0 software (StataCorp LP, College Station, Texas, USA).

3. Results

A total of 178 eligible publications were identified from the PubMed database, Embase, and Cochrane Library, of which 33 were found not relevant to SORL1 polymorphisms. 29 duplicates were excluded after initial review. Following data extraction, 102 articles did not meet the inclusion criteria. Thus, 14 case-control studies involving 37941 cases and 49727 controls (updated in January 2017) were identified and classified for inclusion in the final meta-analysis [11, 17–29]. All the compiled case-control studies were published from 2007 to 2017. Further, these studies were mostly conducted among Caucasian or Asian populations. Only one article was composed of Caucasian and Asian populations and was considered as mixed. The main characteristics of each study are listed in Table 1.

Six single nucleotide polymorphisms of SORL1 were analysed, the genotype and allele distributions are presented in Table 2. There were 11 case-control studies on SORL1 rs668387 polymorphism, 12 case-control studies on SORL1 rs689021 polymorphism, 11 case-control studies on SORL1 rs641120 polymorphism, 12 case-control studies on SORL1 rs3824968 polymorphism, 9 case-control studies on SORL1 rs1010159 polymorphism, and 8 case-control studies on SORL1 rs2070045 polymorphism; where subgroup analysis was performed and stratified by ethnicity.

SORL1 rs668387 was investigated in eleven studies including 6875 cases and 8859 controls. A fixed effect model was performed for the comparison of TT vs CC, TT + CT vs CC. Because of heterogeneity, a random-effect model was used for other comparisons. However, the rs668387 gene single nucleotide polymorphisms did not show any differences between AD patients and controls in the four genetic models tested (T vs C: OR = 0.94, 95% CI = 0.86–1.02, $p = 0.13$; $p_{\text{hete}} = 0.01$, $I^2 = 55\%$; TT + CT vs CC: OR = 0.98, 95% CI = 0.84–1.16, $p = 0.85$; $p_{\text{hete}} = 0.07$, $I^2 = 62\%$; CC + CT vs TT: OR = 0.92, 95% CI = 0.85–1.01, $p = 0.06$; $p_{\text{hete}} = 0.09$, $I^2 = 0\%$; TT vs CC: OR = 0.94, 95% CI = 0.85–1.05, $p = 0.31$; $p_{\text{hete}} = 0.28$, $I^2 = 18\%$). Meanwhile, no associations were found in the ethnicity-stratified groups. Collectively, no significant association was found between rs668387 and AD.

There were twelve case-control studies with a total of 7076 cases and 9116 controls that examined the association between rs689021 and AD. According to the study on heterogeneity, a fixed-effect model was conducted. The association between Alzheimer's disease and SORL1 rs689021 gene single nucleotide polymorphisms for different ethnicities is given in Fig. 1. As suggested, the analysis did not show any significant association between the rs689021 SNP and AD under any genetic model (A vs G: OR = 0.95, 95% CI = 0.91–1.00, $p = 0.06$; AA + AG vs GG: OR = 0.94, 95% CI = 0.86–1.03, $p = 0.19$; AA vs AG + GG: OR = 0.99, 95% CI = 0.89–1.09, $p = 0.83$; AA vs GG: OR = 0.93, 95% CI = 0.83–1.05, $p = 0.24$). No significant heterogeneity was proved by Cochran's Q-statistic and I^2 (A vs G: $p_{\text{hete}} = 0.14$, $I^2 = 31\%$; AA AG vs GG: $p_{\text{hete}} = 0.19$, $I^2 = 28\%$; AA vs AG + GG: $p_{\text{hete}} = 0.07$, $I^2 = 45\%$; AA vs GG: $p_{\text{hete}} = 0.38$, $I^2 = 7\%$). But when ethnicity-ranked analysis was performed, a decreased risk was found to be associated with the allele genotypes among Caucasians (A vs G: OR = 0.92, 95% CI = 0.86–0.98, $p = 0.01$) (Fig. 1). As highlighted in the review, results reveal that SNP rs689021 of SORL1 was only associated with a protection effect for Alzheimer's disease in Caucasians.

Twelve independent studies composed of 7019 cases and 9335 controls were investigated for any association of rs3824968 and AD. Fixed-effect models were used for analysis in the recessive model and additive model without heterogeneity, while the random-effects model was used in other models due to the presence of heterogeneity. Overall, no significant association was observed for any model (A vs T: OR = 0.99, 95% CI = 0.90–1.08, $p = 0.80$; $p_{\text{hete}} = 0.008$, $I^2 = 57\%$; AA + AT vs TT: OR = 1.03, 95% CI = 0.89–1.20, $p = 0.66$; $p_{\text{hete}} = 0.01$, $I^2 = 58\%$; AA vs AT + TT: OR = 1.00, 95% CI = 0.88–1.13, $p = 1.00$; $p_{\text{hete}} = 0.47$, $I^2 = 0\%$; AA vs TT: OR = 1.04, 95% CI = 0.91–1.19, $p = 0.57$; $p_{\text{hete}} = 0.08$, $I^2 = 44\%$). This was also the case for different ethnicity.

In summary, no significant association was detected between SORL1 rs3824968 and AD susceptibility. The association of SORL1 rs1010159 polymorphism with risk of AD was evaluated by nine studies, including 4308 case subjects and 5671 control subjects.

Table 1. Characteristics of the studies included in this meta-analysis

First author	Year	Ethnicity	Country	SNP	Case/control
Ekaterina Rogaeva [17]	2007	Caucasian	Canada	rs668387, rs689021, rs641120, rs3824968, rs1010159, rs2070045	1554/2333
Emmanuelle Cousin [11]	2011	Caucasian	France	rs668387, rs689021, rs641120, rs3824968, rs1010159	428/475
Ryo Kimura [18]	2009	Asian	Japan	rs668387, rs689021, rs3824968, rs1010159, rs2070045	437/451
Xialu Feng [19]	2014	Asian	China	rs689021	201/257
Nobuto Shibata [20]	2008	Asian	Japan	rs668387, rs689021, rs641120, rs3824968, rs1010159	180/130
Mei Ning [21]	2010	Asian	China	rs2070045, rs3824968	144/476
Giselle Izzo [22]	2013	Caucasian	Brazil	rs641120	130/71
Yanan Wen [23]	2013	Asian	Japan	rs668387, rs689021, rs641120, rs3824968, rs1010159	213/370
Ryan L. Minster [24]	2008	Mixed	USA	rs668387, rs689021, rs641120, rs3824968, rs2070045	1009/1009
Joseph H. Lee [25]	2007	Caucasian	USA	rs668387, rs689021, rs641120, rs3824968, rs1010159, rs2070045	296/428
Chandra A. Reynolds [26]	2010	Caucasian	Sweden	rs668387, rs689021, rs641120, rs2070045, rs3824968	1558/2179
Yonghong Li [27]	2008	Caucasian	Britain	rs668387, rs689021, rs641120, rs3824968, rs1010159, rs2070045	998/1033
Joseph H. Lee [28]	2008	Caucasian	USA	rs668387, rs689021, rs641120, rs3824968, rs1010159	103/93
Elena Cellini [29]	2009	Caucasian	Italy	rs668387, rs689021, rs641120, rs2070045, rs3824968, rs1010159	99/358

Table 2. Meta-analysis of association between SORL1 polymorphisms and AD susceptibility

SNP	M vs m (allele model)				MM+Mm vs mm (dominant model)				MM vs Mm+mm (recessive model)				MM vs mm (additive e model)			
	OR	95% CI	p	p_h	OR	95% CI	p	p_h	OR	95% CI	p	p_h	OR	95% CI	p	p_h
rs668387 (C > T)																
Overall	0.94	0.86–1.02	0.13	0.01	0.92	0.85–1.01	0.06	0.09	0.98	0.84–1.16	0.85	0.07	0.94	0.85–1.05	0.31	0.28
Asian	0.93	0.06–1.31	0.69	0.003	1.08	0.87–1.35	0.49	0.40	0.96	0.78–1.19	0.73	0.001	1.00	0.64–1.57	1.00	0.08
Caucasian	1.09	0.87–1.36	0.44	< 0.00001	0.92	0.84–1.01	0.09	0.61	0.95	0.85–1.07	0.44	0.33	0.89	0.78–1.02	0.11	0.59
rs689021 (G > A)																
Overall	0.95	0.91–1.00	0.06	0.14	0.94	0.86–1.03	0.19	0.19	0.99	0.89–1.09	0.83	0.07	0.93	0.83–1.05	0.24	0.38
Asian	1.06	0.94–1.19	0.37	0.33	1.15	0.95–1.39	0.17	0.19	1.17	0.87–1.58	0.30	0.09	1.08	0.85–1.37	0.51	0.34
Caucasian	**0.92**	**0.86–0.98**	**0.01***	**0.24**	0.93	0.84–1.03	0.15	0.48	0.96	0.82–1.12	0.61	0.21	0.89	0.78–1.02	0.09	0.51
rs641120 (G > A)																
Overall	**0.77**	**0.62–0.96**	**0.02***	**< 0.00001**	0.93	0.86–1.01	0.08	0.83	1.01	0.91–1.11	0.91	0.10	0.94	0.84–1.05	0.28	0.17
Asian	0.33	0.02–4.61	0.41	< 0.00001	1.07	0.79–1.44	0.67	0.69	**1.53**	**1.09–2.53**	**0.01***	**0.59**	1.46	0.99–2.16	0.06	0.50
Caucasian	0.94	0.88–1.00	0.04	0.52	0.92	0.84–1.02	0.10	0.60	0.95	0.85–1.07	0.41	0.28	0.89	0.78–1.02	0.08	0.35
rs3824968 (T > A)																
Overall	0.99	0.90–1.08	0.80	0.008	1.03	0.89–1.20	0.66	0.01	1.00	0.88–1.13	1.00	0.47	1.04	0.91–1.19	0.57	0.08
Asian	1.01	0.78–1.31	0.94	0.005	1.03	0.66–1.60	0.90	0.008	0.99	0.74–1.33	0.97	0.10	1.02	0.60–1.74	0.94	0.009
Caucasian	0.98	0.89–1.09	0.77	0.07	1.02	0.90–1.15	0.75	0.19	0.99	0.85–1.16	0.89	0.83	1.01	0.86–1.19	0.87	0.71
rs1010159 (T > C)																
Overall	1.05	0.97–1.12	0.21	0.38	1.08	0.97–1.20	0.15	0.10	1.02	0.88–1.18	0.84	0.90	1.09	0.92–1.28	0.32	0.40
Asian	1.14	1.00–1.31	0.05	0.39	**1.27**	**1.02–1.58**	**0.03***	**0.13**	1.13	0.90–1.42	0.31	0.97	**1.35**	**1.03–1.79**	**0.03***	**0.55**
Caucasian	1.01	0.93–1.10	0.79	0.49	1.03	0.91–1.16	0.69	0.30	0.95	0.78–1.14	0.56	0.84	0.97	0.79–1.18	0.74	0.74
rs2070045 (T > G)																
Overall	0.76	0.54–1.06	0.11	< 0.00001	1.06	0.91–1.23	0.46	0.009	0.92	0.73–1.15	0.45	0.05	1.00	0.74–1.34	0.98	0.008
Asian	0.29	0.07–1.22	0.09	< 0.00001	0.90	0.30–2.72	0.85	0.002	0.78	0.36–1.67	0.52	0.002	0.74	0.17–3.18	0.68	0.0002
Caucasian	1.14	0.87–1.49	0.35	< 0.00001	1.09	0.95–1.25	0.22	0.16	1.04	0.84–1.27	0.73	0.78	1.59	0.79–3.20	0.20	< 0.00001

*Statistically significant.

A fixed-effects model was applied in the absence of any apparent heterogeneity, otherwise, a random-effects model was used. The data did not provide a significant association between SORL1 rs1010159 polymorphism and AD susceptibility in the overall population. (C vs T: OR = 1.05, 95% CI = 0.97–1.12, p = 0.21; p_{hete} = 0.38, I^2 = 7%; CC + CT vs TT: OR = 1.08, 95% CI = 0.97–1.20, p = 0.15; p_{hete} = 0.10, I^2 = 43%; CC vs TT + CT: OR = 1.02, 95% CI = 0.88–1.18, p = 0.84; p_{hete} = 0.90, I^2 = 0%; CC VS TT: OR = 1.09, 95% CI = 0.92–1.28, p = 0.32; p_{hete} = 0.40, I^2 = 3%). Therefore, analysis was performed for subgroups by different ethnicity, where an increase risk was observed for the Asian population (CC vs TT: OR = 1.35, 95% CI = 1.03–1.78, p = 0.03; p_{hete} = 0.55, I^2 = 0% (Fig. 2); CC + CT vs TT: OR = 1.27, 95% CI = 1.02–1.58, p = 0.03; p_{hete} = 0.13, I^2 = 51% (Fig. 3)). According to the data, the conclusion was drawn that SORL1 rs1010159 polymorphism may contribute to an increased risk of AD in Asians.

SORL1 rs641120 polymorphism was examined in eleven studies including 6568 cases and 8479 controls. A random-effect model was specifically adopted in cases where there was heterogeneity. From the given figure, there is a significantly decreased risk of AD susceptibility in the overall population for the allele model (A vs G: OR = 0.77, 95% CI = 0.62–0.96, p = 0.02; p_{hete} < 0.00001, I^2 = 92%) (Fig. 4). But it did not show significant association under the remaining model (AA + AG vs GG: OR = 0.93, 95% CI = 0.86–1.01, p = 0.08; p_{hete} = 0.83, I^2 = 0%; AA vs AG + GG: OR = 1.01, 95% CI = 0.91–1.11, p = 0.91; p_{hete} = 0.10, I^2 = 42%; AA vs GG: OR = 0.94, 95% CI = 0.84–1.05, p = 0.28; p_{hete} = 0.17, I^2 = 32%). However, when ethnicity-stratification was performed, it was seen there was a significantly increased risk for AD for the recessive model in Asians (AA vs AG GG: OR = 1.53, 95% CI = 1.09–2.13, p = 0.01; p_{hete} = 0.59, I^2 = 0%) (Fig. 5). Pooled results revealed that SORL1 rs641120 single nucleotide polymorphisms are associated with a decreased risk in the overall population. Conversely, in a separate meta-analysis by ethnicity an increased AD susceptibility was found in Asian populations. Thus, these data support that SORL1 rs641120 polymorphism has a preventive effect among the overall

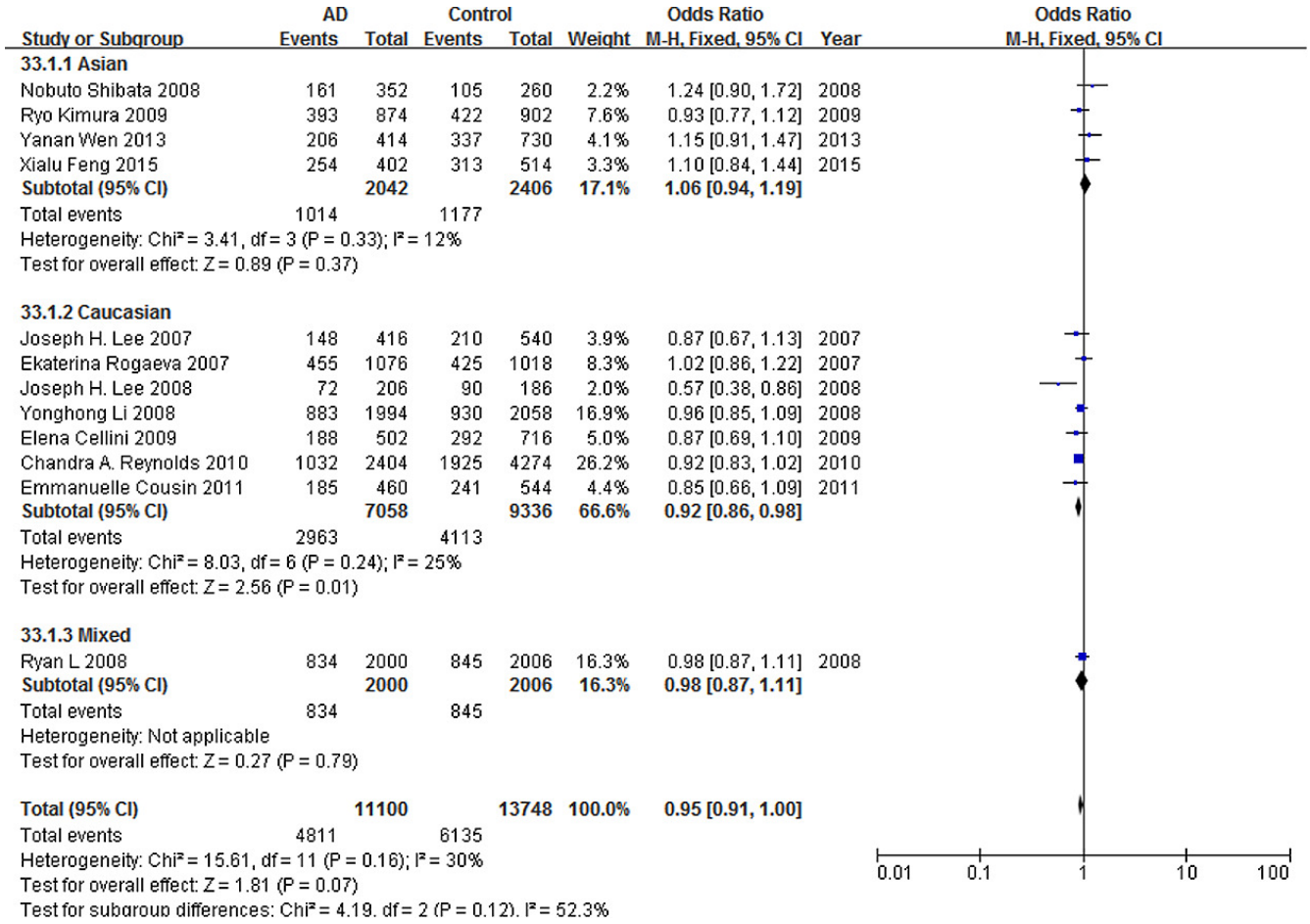

Fig. 1. Forest plot shows the association between SORL1 rs689021 and AD risk under allele model (A vs G) for different ethnicity.

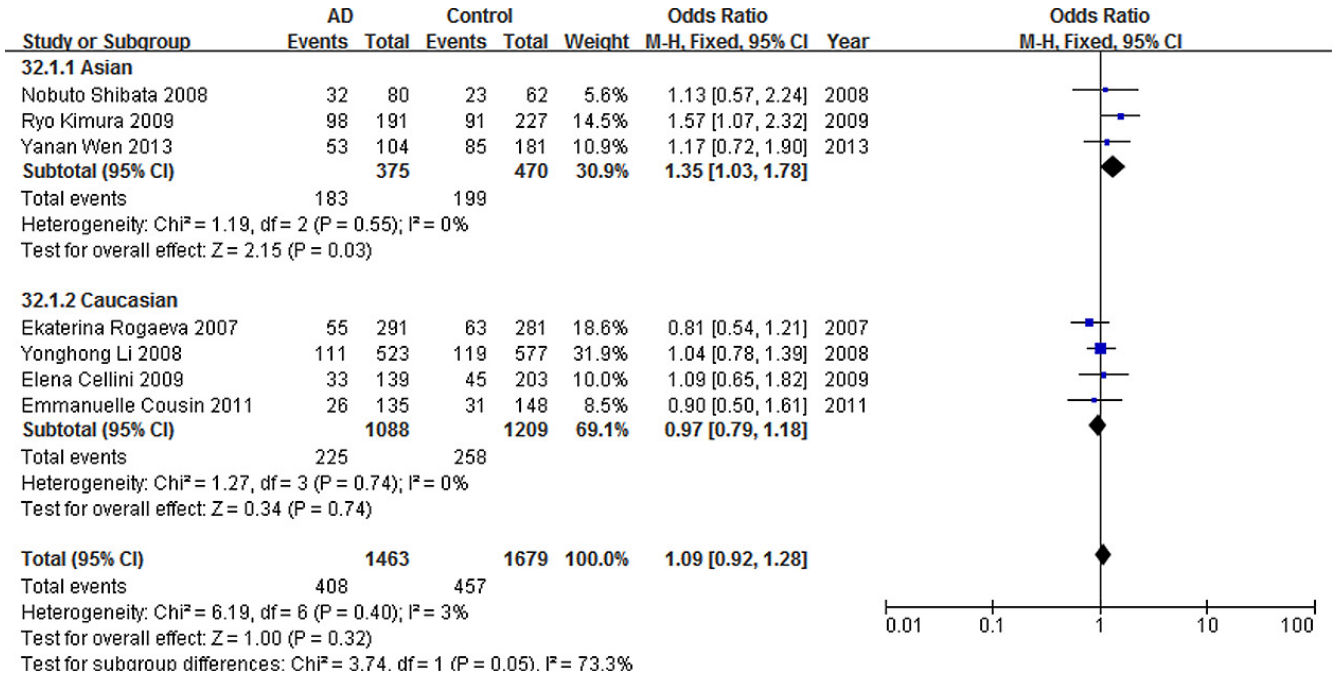

Fig. 2. Forest plot shows the association between SORL1 rs1010159 and AD risk under the additive model (CC vs TT) for different ethnicity.

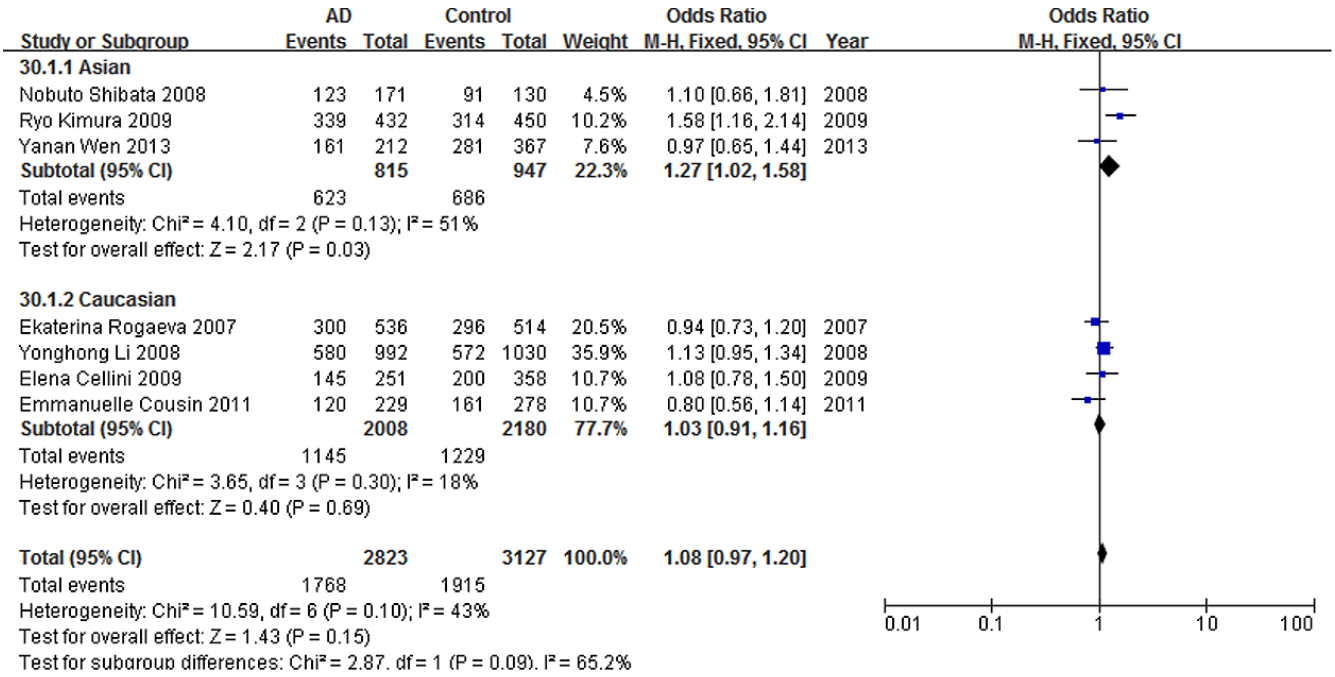

Fig. 3. Forest plot shows the association between SORL1 rs1010159 and AD risk under the dominant model (CC CT vs TT) for different ethnicity.

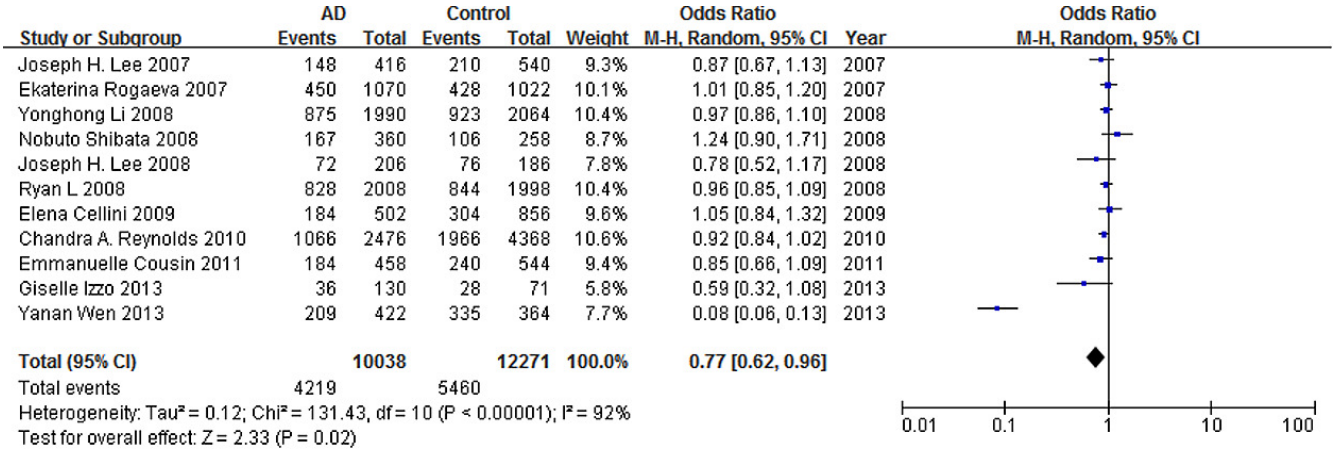

Fig. 4. Forest plot shows the association between SORL1 rs641120 and AD risk under allele model (A vs G) for the overall population.

populations, but increases risk for Asians.

The association between SORL1 rs207045 polymorphism and AD susceptibility was evaluated for eight studies with a total of 6095 case subjects and 8276 control subjects; a random-effect model was performed because of the presence of heterogeneity. There was no significant association observed, even for subgroups, for any tested model (G vs T: OR = 0.76, 95% CI = 0.54–1.06, $p = 0.11$; $p_{hete} < 0.00001$, $I^2 = 96\%$; GG + GT vs TT: OR = 1.06, 95% CI = 0.91–1.23, $p = 0.46$; $p_{hete} = 0.009$, $I^2 = 65\%$; GG vs TT: OR = 0.92, 95% CI = 0.73–1.15, $p = 0.45$; $p_{hete} = 0.05$, $I^2 = 52\%$; GG vs TT: OR = 1.00, 95% CI = 0.74–1.34, $p = 0.98$; $p_{hete} = 0.008$, $I^2 = 65\%$). Data did not provide any evidence for relationship between SORL1 rs2070045 polymorphism and AD prevalence. Sensitivity analysis was performed for each study to estimate whether any single study had an effect on the OR. When the study from Wen [23] under the allele model was excluded, heterogeneity decreased from $p < 0.00001$, $I^2 = 92\%$ to $p = 0.46$, $I^2 = 0\%$. For other studies of this meta-analysis, no individual study affected the OR qualitatively, which indicated that the studies brought into our meta-analysis were accurate. Begg's and Egger's tests were used to identify any publication bias. Funnel plots show no publication bias (Fig. 6). Egger's test did not show publication bias (rs641120: $t = 1.47$, $p = 0.175$; rs668387: $t = 1.66$, $p = 0.132$; rs3824968: $t = 0.29$, $p = 0.776$; rs689021: $t = 0.22$, $p = 0.831$; rs1010159: $t = 0.66$, $p = 0.530$; rs2070045: $t = 1.61$, $p = 0.159$). The meta-analysis indicated results were stable.

4. Discussion

It is widely accepted that SORL1 plays a significant role in AD pathogenesis [30]. The meta-analysis reported here included data from different ethnicities, thus may provide a fresh perspective into the association between SORL1 gene and AD risk. Meta-analysis can

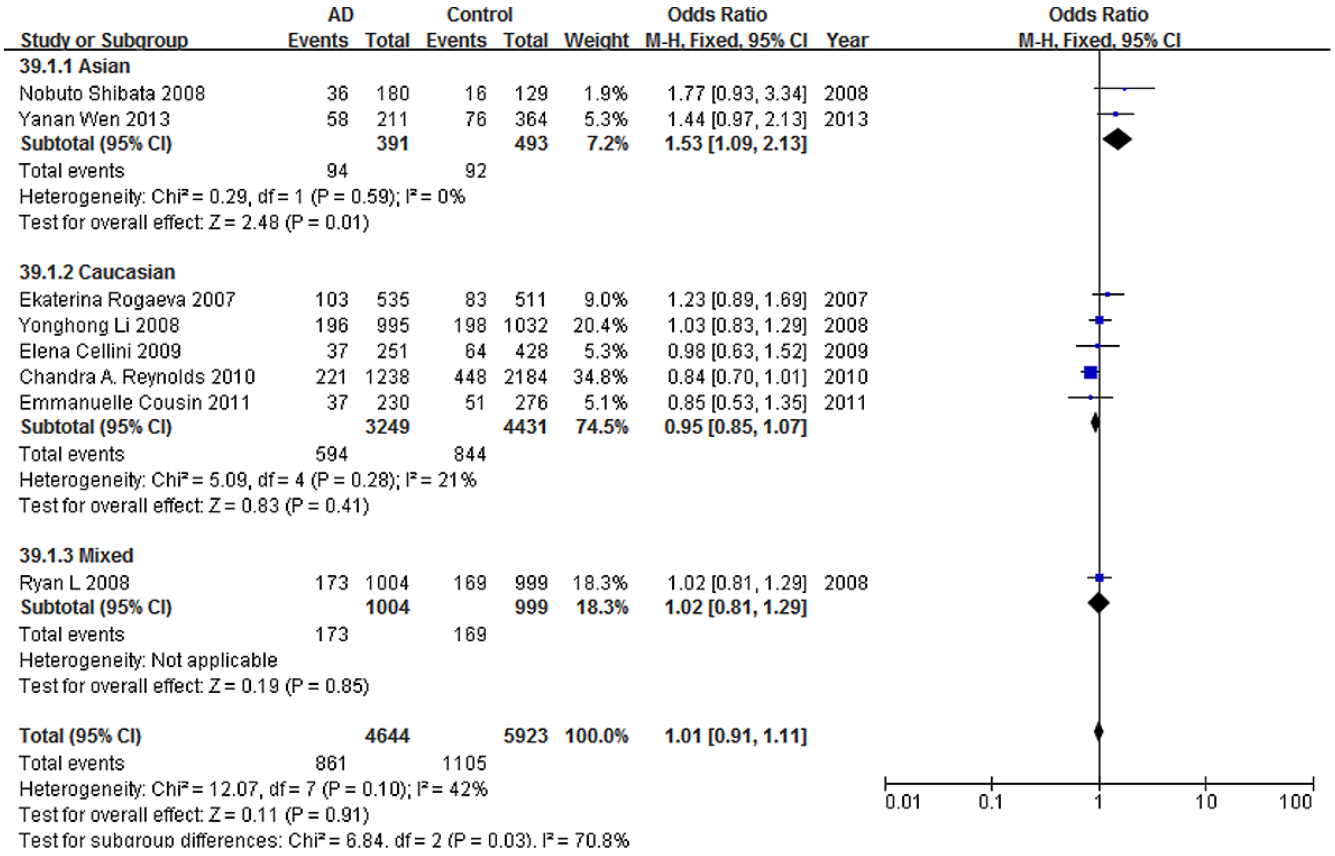

Fig. 5. Forest plot shows the association between SORL1 rs641120 and AD risk under the recessive model (AA vs AG GG) for different ethnicity.

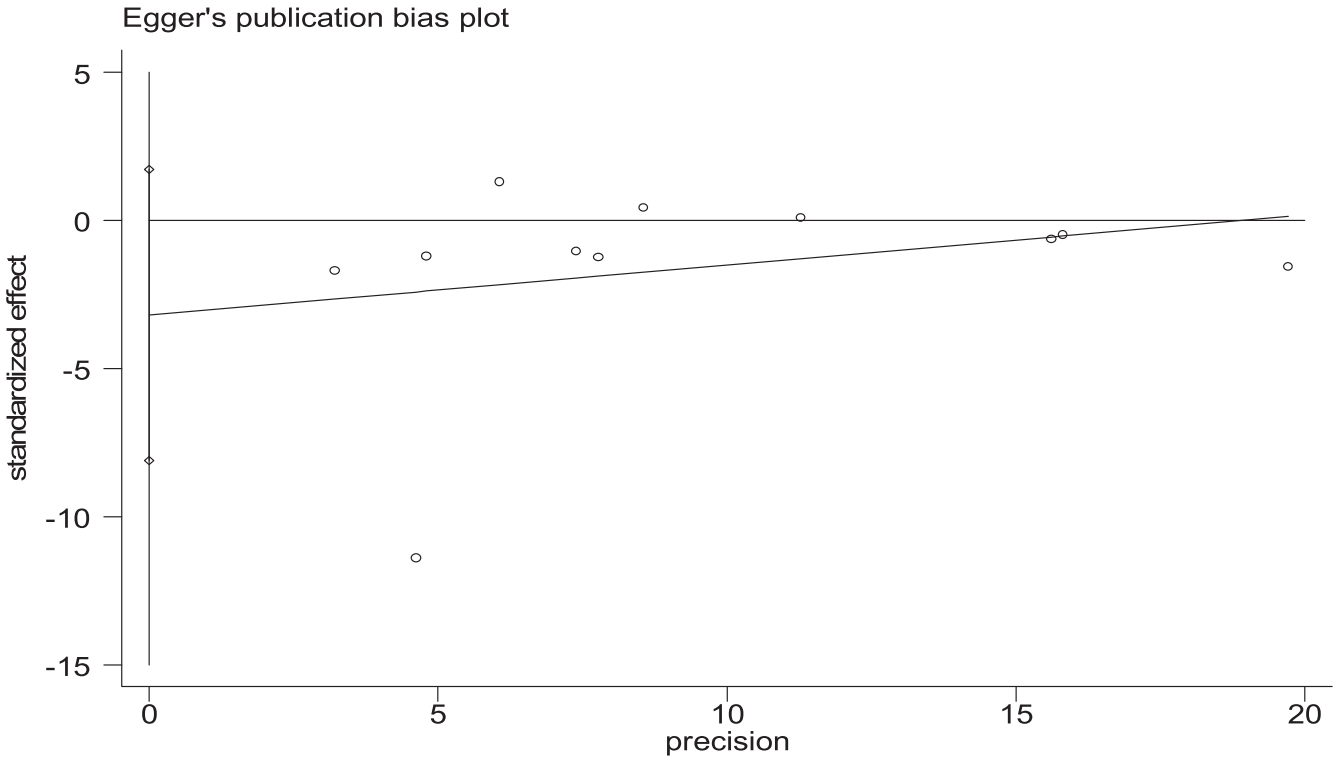

Fig. 6. Egger's publication bias plot for rs641120 and AD risk under allele model (A vs G).

enhance synthesis on a specific issue but it also contains limitations that must be considered. Firstly, only published data was included in this meta-analysis, unpublished studies were not included, which may lead to a biased conclusion. Secondly, only allele model genotype data were provided in four of the fourteen studies. Thus, it is unclear as to how each study affects the results of this meta analysis.

In this research, a meta-analysis based on data aggregated across fourteen studies was reported, based in investigation of six SNP polymorphisms in AD (rs668387, rs689021, rs3824968, rs1010159, rs641120, rs2070045). Several polymorphisms were identified as a risk factor for AD susceptibility, including: rs1010159 and rs641120 (Asian). However, rs689021 and rs641120 were associated with a preventive effect on AD, and no significant association was found between rs668387, rs2070045 and rs3824968, and AD prevalence. Subgroup analysis suggested that association between single nucleotide polymorphisms and AD could be affected by ethnicity.

Previous studies have revealed significant association between rs668387 and AD susceptibility [31–35]. Further, a meta-analysis by Wang et al. [36] based on 35 studies suggested that SNP (rs668387, rs641120) has a decreased risk on AD susceptibility. However, Olgiati et al. [37] found that there was no significant association between rs668387 and AD as was also supported by the current meta-analysis results. While analyzing the fourteen studies with a total of 37941 cases and 49727 controls, no association between rs668387 and AD was observed. It was also found that SNP rs641120 could not be described as a decreased in general populations, but when compared to Asians it was increased. Previous studies have suggested that a series of SNPs from SORL1 were associated with AD [38]. The SNP rs1010159 was one of these. It was observed that SNP rs1010159 was increased in AD prevalence among Asian populations, which is consistent with the conclusion of Liu et al. [39] that SNP rs1010159 and rs3824968 are an increased risk for AD susceptibility, but no significant association was observed between rs3824968 and AD susceptibility in this meta-analysis. The reason for this distinction may be that different data were included in this meta-analysis. A meta-analysis performed by Reynolds et al. [40] found that rs2070045 was a risk factor for AD, especially in females. In our meta-analysis, it was observed there were no significant associations between SNPs (rs2070045, rs3824968) and AD patients when stratified by ethnicity. Additionally, Kimura et al. [18], Feng et al. [19], Shibata et al. [20] and Wen et al. [23] agreed that there is no association between rs689021 and AD. However Cousin et al. [11], Ryan et al. [24], Lee et al. [25], Reynolds et al. [26], Rowland et al. [27], Lee et al. [28], Cellini et al. [29], and Chou et al. [30] found a significant association between rs689021 and AD. It was the current authors who first analyzed the association between rs689021 and AD and reported that SNP rs689021 was associated with a decreased risk to AD among Caucasians.

5. Conclusion

In conclusion, the results of this meta-analysis provide further evidence that genetic variation of SORL1 plays an important role in AD susceptibility. However, no single SNP rs668387, rs2070045 and rs3824968 of SORL1 were found to be associated with AD. It seemed that SNP rs1010159 was associated with an increased risk in AD. Altogether, the SNP rs689021 was associated with decreased risk of AD susceptibility in Caucasians, SNP rs641120 was associated with decreased risk of AD susceptibility in overall populations, whereas when subgroup analysis by ethnicity was performed, SNP rs641120 showed an increased risk of AD susceptibility in Asian populations.

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None.

Conflict of Interest

All authors declare no conflicts of interest.

References

[1] Song Y, Kim HD, Lee MK, Hong IH, Won CK, Bai HW, Lee SS, Lee S, Chung BY, Cho JH (2017) Maysin and its flavonoid derivative from Centipedegrass attenuates amyloid plaques by inducting humoral immune response with Th2 skewed cytokine response in the tg (APPswe, PS1dE9) Alzheimer's mouse model. *Plos One* **12(1)**, e0169509.

[2] Selkoe DJ (2001) Alzheimer's disease: genes, proteins, and therapy. *Physiological Reviews* **81(2)**, 741-766.

[3] Bachurin SO, Bovina EV, Ustyugov AA (2017) Drugs in clinical trials for Alzheimer's disease: the major trends. *Medicinal Research Reviews* **37(5)**, 1186-1225.

[4] Vassar R, Bennett BD, Babu-Khan S, Kahn S, Mendiaz EA, Denis P, Teplow DB, Ross S, Amarante P, Loeloff R (1999) β-Secretase cleavage of Alzheimer's amyloid precursor protein by the transmembrane aspartic protease BACE. *Science* **286(5440)**, 735-741.

[5] Glenner GG, Wong CW (1984) Alzheimer's disease: initial report of the purification and characterization of a novel cerebrovascular amyloid protein. *Biochemical and Biophysical Research Communications* **120(3)**, 885-890.

[6] Nathalie P, Jean-Noel O (2008) Processing of amyloid precursor protein and amyloid peptide neurotoxicity. *Current Alzheimer Research* **5(2)**, 92-99.

[7] Ashok BS, Ajith TA, Sivanesan S (2017) Hypoxia-inducible factors as neuroprotective agent in Alzheimer's disease. *Clinical and Experimental Pharmacology and Physiology* **44(3)**, 327-334.

[8] Guntupalli S, Widagdo J, Anggono V (2016) Amyloid-β-induced dysregulation of AMPA receptor trafficking. *Neural Plasticity* **2016**, 3204519.

[9] Tönnies E, Trushina E (2017) Oxidative stress, synaptic dysfunction, and Alzheimer's disease. *Journal of Alzheimer's Disease* **57(4)**, 1105-1121.

[10] López González I, Garcia-Esparcia P, Llorens F, Ferrer I (2016) Genetic and transcriptomic profiles of inflammation in neurodegenerative diseases: Alzheimer, Parkinson, Creutzfeldt-Jakob and tauopathies. *International Journal of Molecular Sciences* **17(2)**, 206.

[11] Cousin E, Macé S, Rocher C, Dib C, Muzard G, Hannequin D, Pradier L, Deleuze J-F, Génin E, Brice A (2011) No replication of genetic association between candidate polymorphisms and Alzheimer's disease. *Neurobiology of Aging* **32(8)**, 1443-1451.

[12] Na JY, Song K, Lee JW, Kim S, Kwon J (2017) Sortilin-related receptor 1 interacts with amyloid precursor protein and is activated by 6-shogaol, leading to inhibition of the amyloidogenic pathway. *Biochemical and Biophysical Research Communications* **484(4)**, 890-895.

[13] Piscopo P, Tosto G, Belli C, Talarico G, Galimberti D, Gasparini M, Canevelli M, Poleggi A, Crestini A, Albani D (2015) SORL1 gene is associated with the conversion from mild cognitive impairment to Alzheimer's disease. *Journal of Alzheimer's Disease* **46(3)**, 771-776.

[14] Meng Y, Lee JH, Cheng R, St George-Hyslop P, Mayeux R, Farrer LA (2007) Association between SORL1 and Alzheimer disease in a genome-wide study. *Neuroreport* **18(17)**, 1761-1764.

[15] Zhang F, Liu X, Wang B, Cheng Z, Zhao X, Zhu J, Wang D, Wang Y, Dong A, Li P (2015) An exploratory study of the association between SORL1 polymorphisms and sporadic Alzheimer's disease in the Han Chinese population. *Neuropsychiatric Disease and Treatment* **11**, 1443-1448.

[16] Offe K, Dodson SE, Shoemaker JT, Fritz JJ, Gearing M, Levey AI, Lah JJ (2006) The lipoprotein receptor LR11 regulates amyloid β production and amyloid precursor protein traffic in endosomal compartments. *Journal of Neuroscience* **26(5)**, 1596-1603.

[17] Rogaeva E, Meng Y, Lee JH, Gu Y, Kawarai T, Zou F, Katayama T, Baldwin CT, Cheng R, Hasegawa H (2007) The neuronal sortilin-related receptor SORL1 is genetically associated with Alzheimer disease. *Nature Genetics* **39(2)**, 168-177.

[18] Kimura R, Yamamoto M, Morihara T, Akatsu H, Kudo T, Kamino K, Takeda M (2009) SORL1 is genetically associated with Alzheimer disease in a Japanese population. *Neuroscience Letters* **461(2)**, 177-180.

[19] Feng X, Hou D, Deng Y, Li W, Tian M, Yu Z (2015) SORL1 gene polymorphism association with late-onset Alzheimer's disease.*Neuroscience Letters* **584**, 382-389.

[20] Shibata N, Ohnuma T, Baba H, Higashi S, Nishioka K, Arai H (2008) Genetic association between SORL1 polymorphisms and Alzheimer's disease in a Japanese population. *Dementia and Geriatric Cognitive Disorders* **26(2)**, 161-164.

[21] Ning M, Yang Y, Zhang Z, Chen Z, Zhao T, Zhang D, Zhou D, Xu J, Liu Z, Wang Y (2010) Amyloid-β-related genes SORL1 and ACE are genetically associated with risk for late-onset Alzheimer disease in the Chinese population. *Alzheimer Disease & Associated Disorders* **24(4)**, 390-396.

[22] Izzo G, Forlenza OV, Santos Bd, Bertolucci PH, Ojopi EB, Gattaz WF, Kerr DS (2013) Single-nucleotide polymorphisms of GSK3B, GAB2 and SORL1 in late-onset Alzheimer's disease: interactions with the APOE genotype. *Clinics* **68(2)**, 277-280.

[23] Wen Y, Miyashita A, Kitamura N, Tsukie T, Saito Y, Hatsuta H, Murayama S, Kakita A, Takahashi H, Akatsu H (2013) SORL1 is genetically associated with neuropathologically characterized late-onset Alzheimer's disease. *Journal of Alzheimer's Disease* **35(2)**, 387-394.

[24] Minster RL, DeKosky ST, Kamboh MI (2008) No association of SORL1 SNPs with Alzheimer's disease.*Neuroscience Letters* **440(2)**, 190-192.

[25] Lee JH, Cheng R, Schupf N, Manly J, Lantigua R, Stern Y, Rogaeva E, Wakutani Y, Farrer L, George-Hyslop PS (2007) The association between genetic variants in SORL1 and Alzheimer disease in an urban, multiethnic, community-based cohort. *Archives of Neurology* **64(4)**, 501-506.

[26] Reynolds CA, Hong MG, Eriksson UK, Blennow K, Johansson B, Malmberg B, Berg S, Gatz M, Pedersen NL, Bennet AM (2010) Sequence variation in SORL1 and dementia risk in Swedes. *Neurogenetics* **11(1)**, 139-142.

[27] Li Y, Rowland C, Catanese J, Morris J, Lovestone S, O'Donovan MC, Goate A, Owen M, Williams J, Grupe A (2008) SORL1 variants and risk of late-onset Alzheimer's disease. *Neurobiology of Disease* **29(2)**, 293-296.

[28] Lee JH, Cheng R, Honig LS, Vonsattel JG, Clark L, Mayeux R (2008) Association between genetic variants in SORL1 and autopsy-confirmed Alzheimer disease. *Neurology* **70(11)**, 887-889.

[29] Cellini E, Tedde A, Bagnoli S, Pradella S, Piacentini S, Sorbi S, Nacmias B (2009) Implication of sex and SORL1 variants in italian patients with Alzheimer disease. *Archives of Neurology* **66(10)**, 1260-1266.

[30] Chou CT, Liao YC, Lee WJ, Wang SJ, Fuh JL (2016) SORL1 gene, plasma biomarkers, and the risk of Alzheimer's disease for the Han Chinese population in Taiwan. *Alzheimer's Research & Therapy* **8(1)**, 53.

[31] Cuccaro ML, Carney RM, Zhang Y, Bohm C, Kunkle BW, Vardarajan BN, Whitehead PL, Cukier HN, Mayeux R, George-Hyslop PS (2016) SORL1 mutations in early-and late-onset Alzheimer disease. *Neurology Genetics* **2(6)**, e116.

[32] Dong HK, Gim JA, Yeo SH, Kim HS (2017) Integrated late onset Alzheimer's disease (LOAD) susceptibility genes: cholesterol metabolism and trafficking perspectives.*Gene* **597**, 10-16.

[33] Andersen OM, Rudolph IM, Willnow TE (2016) Risk factor SORL1: from genetic association to functional validation in Alzheimer's disease. *Acta Neuropathologica* **132(5)**, 653-665.

[34] Fernández MV, Black K, Carrell D, Saef B, Budde J, Deming Y, Howells B, Del-Aguila JL, Ma S, Bi C (2016) SORL1 variants across Alzheimer's disease European American cohorts. *European Journal of Human Genetics* **24(12)**, 1828-1830.

[35] Schmidt V, Schulz N, Yan X, Schürmann A, Kempa S, Kern M, Blüher M, Poy MN, Olivecrona G, Willnow TE (2016) SORLA facilitates insulin receptor signaling in adipocytes and exacerbates obesity. *The Journal of Clinical Investigation* **126(7)**, 2706-2720.

[36] Wang Z, Lei H, Zheng M, Li Y, Cui Y, Hao F (2016) Meta-analysis of the association between Alzheimer disease and variants in GAB2, PICALM, and SORL1. *Molecular Neurobiology* **53(9)**, 6501-6510.

[37] Olgiati P, Politis A, Albani D, Rodilossi S, Polito L, Ateri E, Zisaki A, Piperi C, Liappas I, Stamouli E (2012) Association of SORL1 alleles with late-onset Alzheimer's disease. findings from the GIGAS_LOAD study and mega-analysis. *Current Alzheimer Research* **9(4)**, 491-499.

[38] Young JE, Boulanger-Weill J, Williams DA, Woodruff G, Buen F, Revilla AC, Herrera C, Israel MA, Yuan SH, Edland SD (2015) Elucidating molecular phenotypes caused by the SORL1 Alzheimer's disease genetic risk factor using human induced pluripotent stem cells. *Cell Stem Cell* **16(4)**, 373-385.

[39] Liu F, Ikram MA, Janssens A, Schuur M, de Koning I, Isaacs A, Struchalin M, Uitterlinden AG, den Dunnen JT, Sleegers K (2009) A study of the SORL1 gene in Alzheimer's disease and cognitive function. *Journal of Alzheimer's Disease* **18(1)**, 51-64.

[40] Reynolds CA, Zavala C, Gatz M, Vie L, Johansson B, Malmberg B, Ingelsson E, Prince JA, Pedersen NL (2013) Sortilin receptor 1 predicts longitudinal cognitive change.*Neurobiology of Aging* **34(6)**, 1710.e11-1710.e18.