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Butyrylcholinesterase K Variant and Alzheimer's Disease Risk: A Meta-Analysis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: Although many studies have estimated the association between the butyrylcholinesterase (BCHE) K variant and Alzheimer's disease (AD) risk, the results are still controversial. We thus conducted this meta-analysis.

Material/Methods: We searched NCBI, Medline, Web of Science, and Embase databases to find all eligible studies. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of the association.

Results: We found a significant association between BCHE K variant and AD risk (OR=1.20; 95% CI 1.03–1.39; P=0.02). In the stratified analysis by ethnicity, we observed a significant association between BCHE K variant and AD risk in Asians (OR=1.32; 95% CI 1.02–1.72; P=0.04). However, no significant association between BCHE K variant and AD risk in Caucasians was found (OR=1.14; 95% CI 0.95–1.37; P=0.16). When stratified by the age of AD onset, we found that late-onset AD (LOAD) was significantly associated with BCHE K variant (OR=1.44; 95% CI 1.05–1.97; P=0.02). No significant association between BCHE K variant and early-onset AD (EOAD) risk was observed (OR=1.16; 95% CI 0.89–1.51; P=0.27). Compared with non-*APOE* ε4 and non-BCHE K carriers, no significant association between BCHE K variant and AD risk was found (OR=1.11; 95% CI 0.91–1.35; P=0.30). However, *APOE* ε4 carriers showed increased AD risk in both non-BCHE K carriers (OR=2.81; 95% CI 1.75–4.51; P=0.0001) and BCHE K carriers (OR=3.31; 95% CI 1.82–6.02; P=0.0001).

Conclusions: The results of this meta-analysis indicate that BCHE K variant might be associated with AD risk.

MeSH Keywords: Alzheimer Disease • Butyrylcholinesterase • Genetics

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Background

Alzheimer's disease (AD) is one of the most common forms of dementia. The clinical manifestations of AD include loss of memory, and behavioral and cognitive disorders [1]. The survival time for patients with AD is generally 4 to 6 years after diagnosis. Thus, AD is a major public health concern. However, the etiology and pathogenesis of AD remain unclear. Recently, accumulating evidence shows that genetic factors might be involved in the development of AD [2].

Butyrylcholinesterase (BCHE) is a hydrolytic enzyme that can catalyze the hydrolysis of excess acetylcholine neurotransmission in the synaptic space. Darreh-Shori et al. suggested that low cerebrospinal fluid (CSF) levels of BCHE might predict extensive incorporation in neuritic plaques, greater central neurodegeneration, and increased neurotoxicity [3]. They also found that BCHE levels correlated with cerebral glucose metabolism, cerebral β-amyloid load, and CSF P-tau [4]. Diamant et al. reported an association of the BChE-K variant with impaired interaction with the fibrillogenic beta-amyloid protein [5]. Shenhar-Tsarfaty also suggested that this variant could influence metabolic syndrome [6].

BCHE K variant is one of the most common polymorphism in the BCHE gene. This is an alanine-to-threonine substitution in the 539 amino acid position (Ala539Thr). This polymorphism is associated with a 30% reduction of serum BCHE activity [7]. Many studies have been conducted to evaluate the association between BCHE K variant and AD risk [8–32]. However, the results are controversial and inconsistent. Therefore, we performed a meta-analysis to assess the association between BCHE K variant and AD risk.

Material and Methods

Search for studies

We searched NCBI, Medline, Web of Science, and Embase databases to find all eligible studies. The last retrieval date was October 29, 2014. The following terms and keywords were used: ("Alzheimer's disease" or "Alzheimer disease") and ("Butyrylcholinesterase" or "BCHE"). All relevant studies were retrieved.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) the study should be case-control or a cohort design; and (2) the study should focus on the association between BCHE K variant and AD risk. The exclusion criteria were as follows: (1) animal studies; (2) reviews or abstracts; and (3) duplications.

Data extraction

According to the inclusion criteria, 2 investigators extracted the data independently. Any discrepancy was adjudicated by the third investigator. The following data was extracted from each study: first author, year, ethnicity, age and sex of patients, sample size, and genotyping results from BCHE and APOE genes.

Statistical analysis

The odds ratio (OR) and its 95% confidence interval (95% CI) were used to estimate the strength of the association between BCHE K variant and AD risk. A recessive model (KK vs. WW+WK) was applied. We estimated the heterogeneity by using the chi-square-based Q-test, which was considered significant at $P<0.10$. A fixed-effects model was used in the absence of heterogeneity; otherwise, a random-effects model was used. Subgroup analyses were performed based on ethnicity, APOE ε4 status, and the age at AD onset. We conducted sensitivity analysis by excluding every study individually and recalculating the OR and 95% CI. Potential publication bias was estimated using Egger's linear regression test and the funnel plot. All statistical analyses were conducted using STATA software version 11.0 (Stata Corporation, College Station, TX). All P values were 2-sided, with a significance level of 0.05.

Results

Study characteristics

A total of 25 eligible case-control studies (3850 cases and 3947 controls) met the inclusion criteria [8–32]. Among these 25 case-control studies, 5 studies focused on Asians and 20 focused on Caucasians. The main characteristics of the included studies investigating the association of BCHE K variant and AD risk are presented in Table 1.

Association between BCHE K variant and AD risk

We found a significant association between BCHE K variant and AD risk (OR=1.20; 95% CI 1.03–1.39; P=0.02; Figure 1). In the stratified analysis by ethnicity (Table 2), we observed a significant association between BCHE K variant and AD risk in Asians (OR=1.32; 95% CI 1.02–1.72; P=0.04), but no significant association between BCHE K variant and AD risk in Caucasians was found (OR=1.14; 95% CI 0.95–1.37; P=0.16). When stratified by age at AD onset, we found that late-onset AD (LOAD) was significantly associated with BCHE K variant (OR=1.44; 95% CI 1.05–1.97; P=0.02). No significant association between BCHE K variant and early-onset AD (EOAD) risk was observed (OR=1.16; 95% CI 0.89–1.51; P=0.27).

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

First author	Year	Ethnicity	Age	Sex	Case (n)	Control (n)	BCHE K allele frequency (%)		APOE ε4 allele frequency (%)	
							Case	Control	Case	Control
Lehmann	1997	Caucasian	>65	Mixed	74	104	13	9	41	16
Brindle	1998	Caucasian	75.4	Mixed	138	165	20.3	18.8	31.4	14
Crawford	1998	Caucasian	76.4	Mixed	391	201	17.2	14.4	75	67.4
Hiltunen	1998	Caucasian	73	Mixed	59	59	12	22	100	100
Kehoe	1998	Caucasian	NA	Mixed	181	262	21	22	56.5	28.1
Singleton	1998	Caucasian	78.3	Mixed	119	83	20	17	65.5	21.4
Yamada	1998	Asian	85.1	Mixed	48	107	31.7	31.2	NA	NA
Grubber	1999	Caucasian	NA	Mixed	169	193	18.8	23	18	25.4
Ki	1999	Asian	73	Mixed	78	74	23	16	28	7
Tilley	1999	Caucasian	81	Mixed	177	118	20	19	31	11
Wiebusch	1999	Caucasian	78	Mixed	135	70	25	16	43	18
Yamamoto	1999	Asian	68.2	Mixed	149	200	15.9	15.7	NA	NA
Lee	2000	Asian	69.1	Mixed	89	101	13.5	12.3	24.2	6.9
Mattila	2000	Caucasian	>65	Mixed	80	67	21	15	13	11
McIlroy	2000	Caucasian	77.7	Mixed	175	187	26.8	14.4	34.5	31.6
Kim	2001	Asian	71.7	Mixed	164	293	11.7	10.1	NA	NA
Prince	2001	Caucasian	NA	Mixed	204	186	20.9	20.1	NA	NA
Raygani	2004	Caucasian	75	Mixed	105	129	24.2	12	25.9	6.2
Combarros	2005	Caucasian	75	Mixed	187	172	10	15	12	8
Cook	2005	Caucasian	NA	Mixed	212	316	27	20	NA	NA
Deniz-Naranjo	2007	Caucasian	>60	Mixed	282	312	19.5	19.4	48.9	22.1
Piccardi	2007	Caucasian	76.8	Mixed	158	118	21	19	18.9	5.5
Mateo	2008	Caucasian	71.3	Mixed	231	221	12	10	NA	NA
Bizzarro	2010	Caucasian	73.3	Mixed	167	129	10.1	10.2	NA	NA
Simão-Silva	2013	Caucasian	74.5	Mixed	78	80	23	21	NA	NA

NA – not available.

Compared with non-*APOE* ε4 and non-BCHE K carriers, no significant association between BCHE K variant and AD risk was found (OR=1.11; 95% CI 0.91–1.35; *P*=0.30). However, *APOE* ε4 carriers showed increased AD risk in both non-BCHE K carriers (OR=2.81; 95%CI 1.75–4.51; P=0.0001) and BCHE K carriers (OR=3.31; 95% CI 1.82–6.02; P=0.0001). Results are listed in Table 3.

Sensitivity analysis and publication bias

In the sensitivity analysis, the impact of each study on the pooled OR was checked by repeating the meta-analysis when omitting each study. This sensitivity analysis validated the stability of the results from this meta-analysis (Figure 2). The shape of funnel plots did not show any evidence of obvious asymmetry (Figure 3). Furthermore, the Egger's test result suggested that there was no significant publication bias (*P*=0.67).
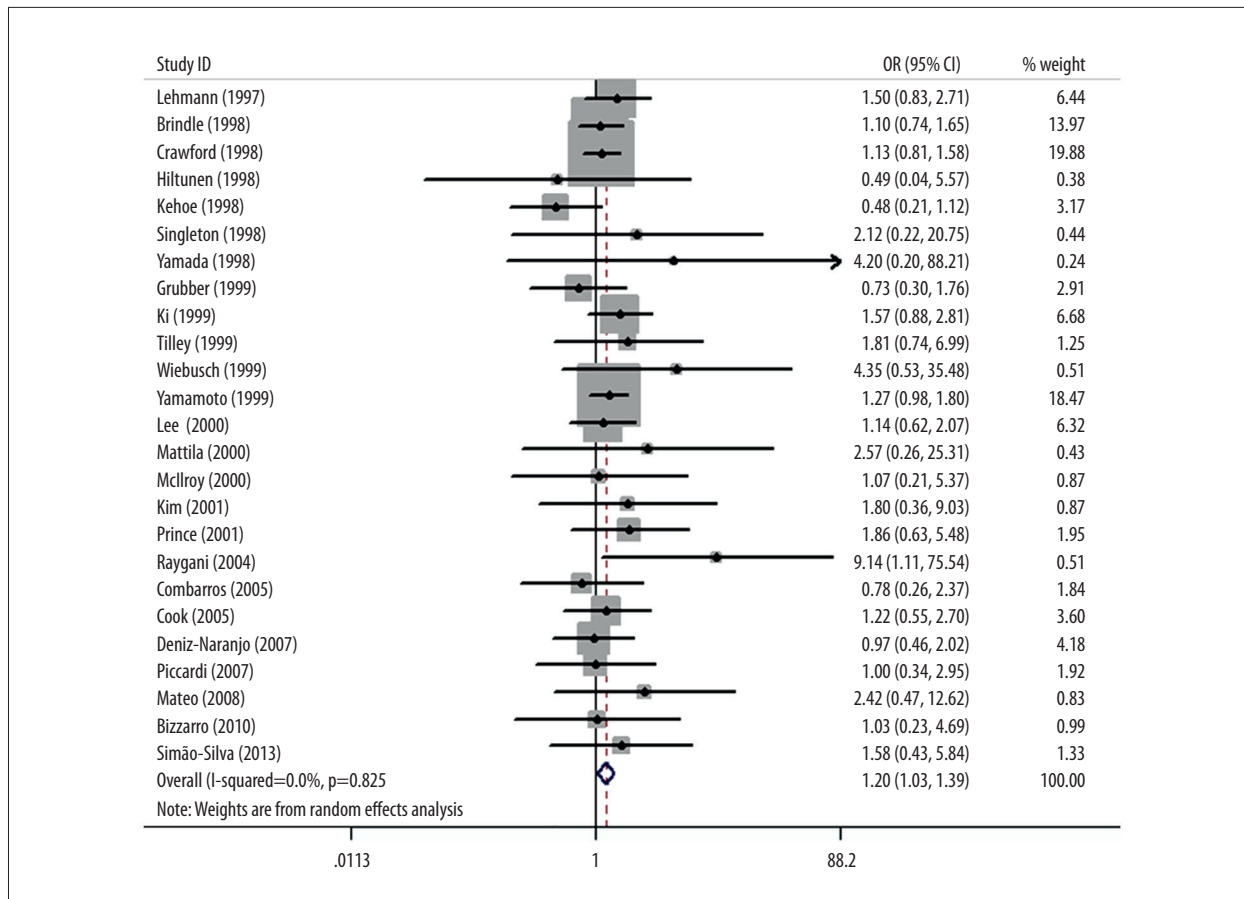
Figure 1. Meta-analysis of BCHE K variant and AD risk.

Table 2. Results from this meta-analysis.

	OR (95% CI)*	P	I² (%)
Overall	1.20 (1.03–1.39)	0.02	0
Asian	1.32 (1.02–1.72)	0.04	0
Caucasian	1.14 (0.95–1.37)	0.16	0
EOAD	1.16 (0.89–1.51)	0.27	33
LOAD	1.44 (1.05–1.97)	0.02	15

EOAD – early-onset Alzheimer's disease; LOAD – late-onset Alzheimer's disease. * OR values refer to association between BCHE K variant and AD risk.

Table 3. APOE ε4 and BCHE K variant interaction.

| APOE ε4	BCHE K	OR (95% CI)	P	I² (%)
−	−	Reference	−	−
−	+	1.11 (0.91–1.35)	0.30	45
+	−	2.81 (1.75–4.51)	0.0001	52
+	+	3.31 (1.82–6.02)	0.0001	69

Discussion

This meta-analysis with a total of 3850 cases and 3947 controls systematically evaluated the association between BCHE K variant and AD risk. Results from this meta-analysis suggested that BCHE K variant was significantly associated with AD risk. In the subgroup analysis by ethnicity, a significant association between BCHE K variant and AD risk in Asians was found, but this result was not found in Caucasians. This difference suggests that race might play a role in AD. Only 5 studies were included in our meta-analysis; thus, more studies with Asians are needed to confirm our results. In the stratified analysis by APOE ε4 status, APOE ε4 carriers, but not APOE ε4 non-carriers with BCHE K variant, showed an increased AD risk. This result suggests that gene-gene interaction also plays an important role in the development of AD. More studies should be conducted to assess the interaction between other genes and BCHE K variant. When stratified by age at AD onset, we found that the risk of LOAD, but not EOAD, was significantly associated with BCHE K variant. This information indicates that age also has a critical role in AD development.
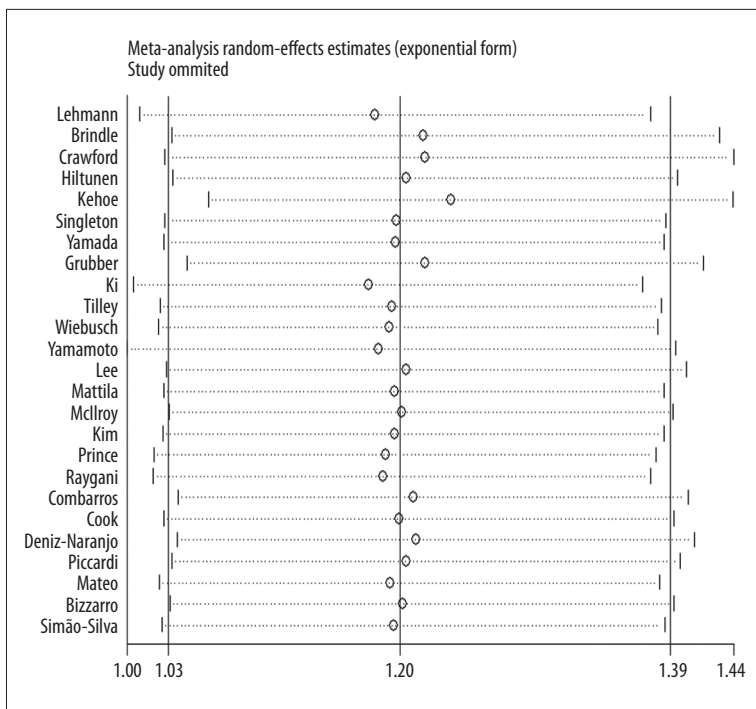
Figure 2. Sensitivity analysis of BCHE K variant and AD risk.
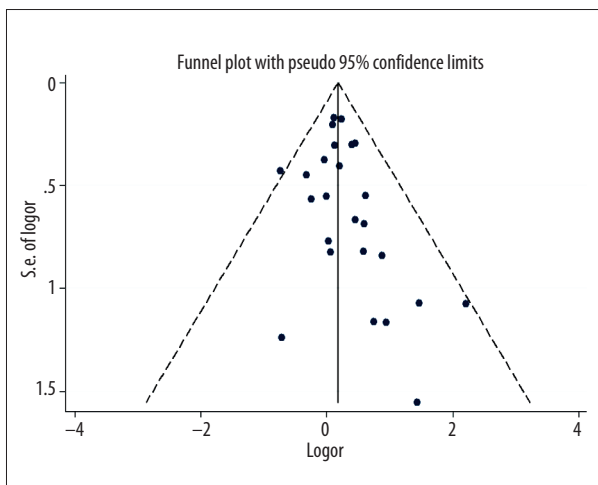
Figure 3. Funnel plot of association between BCHE K variant and AD risk.

Carson et al. found that BCHE activity was associated with the amyloid and the neuritic component in neuritic plaques [33]. Guillozet et al. also found that BCHE activity increased in the AD brain [34]. The activity of serum BCHE-K to hydrolyze butyrylthiocholine was found to be reduced by 30% relative to BCHE-U [7]. Thus, BCHE K variant might be associated with a decreased AD risk. However, Lopez et al. reported that BCHE K variant carriers were refractory to cholinesterase inhibitor therapy [35]. Additionally, Podoly et al. found that BCHE K variant had an elevated AD risk due to inefficient interference with amyloidogenic processes [36]. Furthermore,

Ballard et al. found that BuCh E may play a role in the phosphorylation of tau, relevant to therapeutic inhibition of the enzyme [37]. Alkalay et al. found no association between BChE activity and amyloid loads in the AD brain [38]. Thus, the pathological role of BCHE K variant was still controversial. Our meta-analysis confirmed that this polymorphism might be associated with AD risk. More studies are needed to investigate the mechanism by which BCHE K variant could impact the risk of AD [39,40].

This meta-analysis had several limitations. First, results of this meta-analysis were based on unadjusted OR, because not all studies offered the adjusted ORs. Second, although the number of included studies was relatively large, the sample size and statistical power was still limited. Third, we only included the published studies; thus, publication bias and selection bias might exist. Forth, lack of sufficient eligible data on BCHE K variant and AD limited our further stratified analyses.

Conclusions

In conclusion, this study shows that BCHE K variant is associated with AD risk. More well-conducted studies with larger sample size are warranted to confirm our results.

Conflicts of interest

None.

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