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ATP binding cassette subfamily A member 7 rs3764650 polymorphism and the risk of Alzheimer's disease

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We did a meta-analysis to assess the association between ABCA7 rs3764650 polymorphism and the risk of Alzheimer's Disease (AD). A total of 10 eligible studies with 20511 patients and 40503 controls met the inclusion criteria. ABCA7 rs3764650 polymorphism was significantly associated with AD risk (OR=1.21, 95% CI 1.16–1.26, P<0.00001; I^2=5%). In the subgroup analysis by race, statistically significant associations were found in Asians (OR=1.09, 95% CI 1.01–1.18, P =0.03; I^2=0%) and in Caucasians (OR=1.25, 95% CI 1.19–1.31, P<0.00001; I^2=0%). In conclusion, this meta-analysis suggested that ABCA7 rs3764650 polymorphism is significantly associated with AD risk.

1. Introduction

Alzheimer's disease (AD) is characterized by gradual memory loss and a progressive learning disability and inability to carry out daily tasks. Research suggests that genetic changes are a driving force, rather than a consequence, of the aging process and AD pathogenesis (Ross et al. 2013).

ATP binding cassette subfamily A member 7 (ABCA7) encodes a highly conserved protein belonging to the ABCB family of ATP-binding cassette (ABC) transporters (Savary et al. 1997). Members of the ABC superfamily are transmembrane proteins that use the hydrolysis of ATP to facilitate transport of a range of substrates across membranes. Yu et al. (2015) found that RNA expression of transcripts of ABCA7 was associated with paired helical filament tau tangle density. Vasquez et al. (2013) found that ABCA7 expression is increased in AD individuals. In addition, they reported that the rs3764650T allele was associated with increased ABCA7 expression. Recently, some studies investigated the association between ABCA7 rs3764650 polymorphism and the risk of AD (Lambert et al. 2010; Harold et al. 2009; Hollingworth et al. 2011; Tan et al. 2013; Chung et al. 2013; Miyashita et al. 2013; Carrasquillo et al. 2011; Liu et al. 2014; Omoumi et al. 2014; Cuyvers et al. 2015; Chan et al. 2008). However, the results were controversial. Therefore, we did a meta-analysis to assess the association between ABCA7 rs3764650 polymorphism and the risk of AD.

2. Investigations and results

2.1. Study characteristics

In this current study, a total of 10 eligible studies with 20511 patients and 40503 controls met the inclusion criteria. The duration of studies ranged from 2009 to 2015. Four studies were performed in Asians and 5 studies were did in Caucasians. The case numbers ranged from 44 to 855. All studies reported the data of OS. The characteristics of the studies included in this meta-analysis are presented in the Table.

2.2. Quantitative synthesis

ABCA7 rs3764650 polymorphism was significantly associated with AD risk (OR = 1.21, 95% CI 1.16 – 1.26, P <0.00001; I^2=5%; Fig. 1). In the subgroup analysis by race, statistically significant associations were found in Asians (OR = 1.09, 95% CI 1.01 – 1.18, P =0.03; I^2=0%) and in Caucasians (OR = 1.25, 95% CI 1.19 – 1.31, P <0.00001; I^2=0%).

As shown in Fig. 3, the shape of the funnel plot showed symmetry. Egger's test found no evidence of publication bias (P=0.445)

3. Discussion

The present meta-analysis, including 20511 patients and 40503 controls, explored the association of ABCA7 rs3764650 polymorphism and AD risk. We demonstrated that ABCA7 rs3764650 polymorphism was significantly associated with AD risk. In the subgroup analysis by race, statistically significant associations were found in Asians and in Caucasians. These results suggested that ABCA7 rs3764650 polymorphism may play an important role in the prognosis of AD.

ABCA7 gene, located on chromosome 19p13.3, spans 1,040,102–1,065,570 base pairs (bp) and encodes 47 exons. Chan et al. (2012) reported that ABCA7 could have the capacity to regulate APP processing, which may further result in an inhibition of Aβ deposition. Recently, a study aiming at investigating the role of ABCA7 in cognition and behaviors by using homozygous ABCA7 knockout

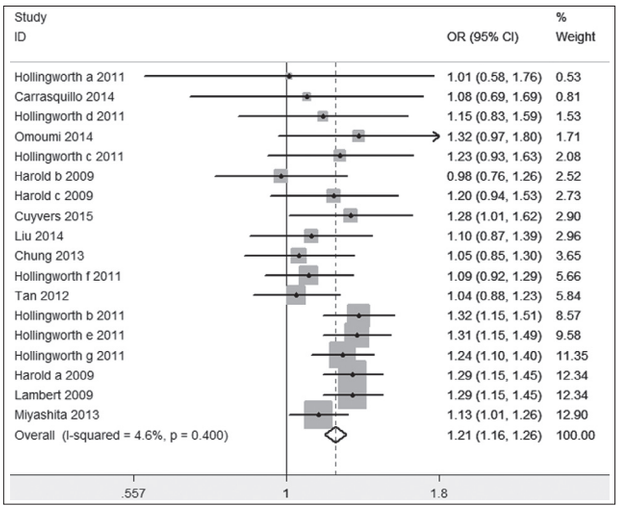

Fig. 1: Meta-analysis for the association between ABCA7 rs3764650 polymorphism and AD risk

Table: Characteristics of included studies

First Author	Year	Race	Age	Gender	No. of cases	No. of controls	Hardy-Weinberg equilibrium
Lambert	2009	Caucasian	Adult	Mixed	2025	5328	Yes
Harold a	2009	Caucasian	Adult	Mixed	2226	4704	Yes
Harold b	2009	Caucasian	Adult	Mixed	555	824	Yes
Harold c	2009	Caucasian	Adult	Mixed	551	960	Yes
Hollingworth a	2011	Caucasian	Adult	Mixed	151	177	Yes
Hollingworth b	2011	Caucasian	Adult	Mixed	3262	3320	Yes
Hollingworth c	2011	Caucasian	Adult	Mixed	925	612	Yes
Hollingworth d	2011	Caucasian	Adult	Mixed	709	971	Yes
Hollingworth e	2011	Caucasian	Adult	Mixed	2751	2620	Yes
Hollingworth f	2011	Caucasian	Adult	Mixed	1239	10813	Yes
Hollingworth g	2011	Caucasian	Adult	Mixed	2490	4114	Yes
Tan	2012	Asian	Adult	Mixed	612	612	Yes
Chung	2013	Asian	Adult	Mixed	290	554	Yes
Miyashita	2013	Asian	Adult	Mixed	891	844	Yes
Carrasquillo	2014	Caucasian	Adult	Mixed	132	2486	Yes
Liu	2014	Asian	Adult	Mixed	350	283	Yes
Omoumi	2014	Caucasian	Adult	Mixed	580	524	Yes
Cuyvers	2015	Caucasian	Adult	Mixed	772	757	Yes

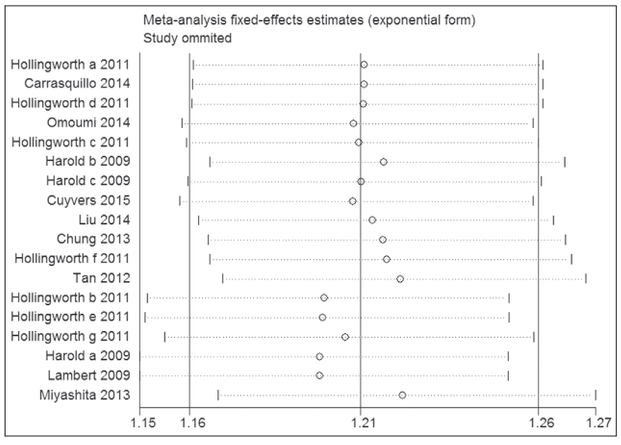

Fig. 2: Sensitivity analysis for the association between ABCA7 rs3764650 polymorphism and AD risk

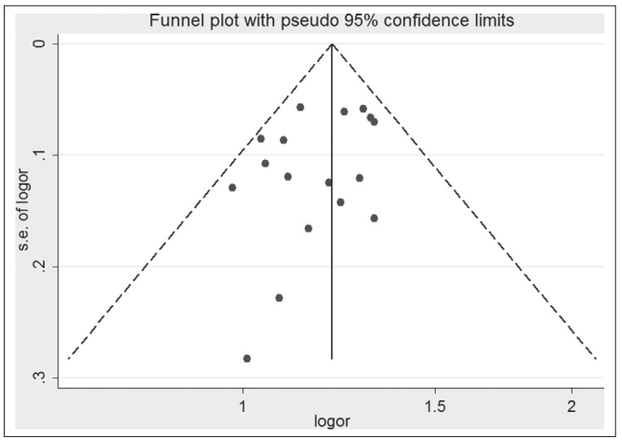

Fig. 3: Funnel plot for the association between Meta-analysis for the association between ABCA7 rs3764650 polymorphism and AD risk

mice has demonstrated that male knockout mice exhibit significantly impaired novel object recognition memory and female mice exhibit impaired spatial reference memory, compared with the control mice (Karch et al. 2012). Additionally, emerging evidence has implied that higher ABCA7 expression levels are correlated with more advanced cognitive decline, later age at onset, and shorter disease duration. There are also some limitations of our study. First, lacking of the original data of the eligible studies limited the evaluation of the subgroup analyses by gender, age, and other factors. Second, publication bias may have occurred, even though the statistical test did not show it. Third, almost all the studies were conducted in Asians and Caucasians, no study from other races was included. In conclusion, this meta-analysis suggested that ABCA7 rs3764650 polymorphism was significantly associated with AD risk.

4. Experimental

4.1. Publication search

PUBMED, EMBASE, COCHRANE, and WEB OF SCIENCE databases were retrieved for the association studies focused on the relationship between ABCA7 rs3764650 polymorphism and AD risk. The key words and subject terms used were as follows: "ATP binding cassette subfamily A member 7 or ABCA7"; "Alzheimer's disease"; and "polymorphism or variant". The research was limited to English-language journals, and the additional studies were identified by a manual search of the reference list from the retrieved studies.

4.2. Inclusion and exclusion criteria

For the selection of eligible studies in this meta-analysis should meet all of the following criteria: (a) estimation the association between ABCA7 rs3764650 polymorphism and AD risk; (b) the study should be designed as a cohort or case-control study; (c) sufficient original data. Additionally, studies were excluded if they did not include sufficient data.

4.3. Data extraction

Two investigators independently reviewed and extracted data from all the eligible publications. The following data were extracted: name, year of publication, race, age, gender, number of cases and controls, and Hardy-Weinberg equilibrium (HWE).

4.4. Statistical analysis

Statistical analysis was conducted by using STATA statistical package (version 11, STATA, College Station, TX). The association of ABCA7 rs3764650 polymorphism

and AD risk by OR with 95% CI. The heterogeneity was tested by the Q-statistics with P-values < 0.1. Dependent on the results of heterogeneity test among individual studies, the fixed effect model (Mantel–Haenszel) or random effect model (DerSimonian and Laird) was selected to summarize the combined OR and their 95% CI. The significance of the pooled OR was determined by the Z test. Subgroup analyses were carried out by race. Publication bias was investigated with Egger's linear regression test. All the P values were two sided. P value less than 0.05 was considered statistically significant.

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Conflicts of interest: None reported.

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