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ATP-binding cassette transporter A1 R219K polymorphism and ischemic stroke risk in the Chinese population: A meta-analysis

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ABSTRACT

Recently, many studies have been focused on the association between the ATP-binding cassette transporter *A1* (*ABCA1*) gene R219K polymorphism and ischemic stroke (IS). However, the study results have been inconsistent, especially in the Chinese population. Therefore, we performed a meta-analysis to better clarify the association between the *ABCA1* gene and IS. All of the relevant studies used in our meta-analysis were identified using PubMed, OVID, Cochrane Library, Chinese Wan Fang database, Chinese VIP database, China National Knowledge Infrastructure (CNKI), and China Biological Medicine Database (CBM) up to May 2013. Statistical analysis was conducted with STATA software version 11.0. Odds ratios with 95% confidence intervals were applied to evaluate the strength of the association between *ABCA1* gene R219K polymorphism and IS. Heterogeneity was evaluated using the Q-test and I^2 statistic. The funnel plots, Begg's and Egger's regression tests were used to assess the publication bias. Our meta-analysis showed the dominant genetic model (OR = 0.92, 95% CI: 0.88–0.96), the recessive genetic model (OR = 0.73, 95% CI: 0.51–1.05), the homozygote genetic model (OR = 0.64, 95% CI: 0.44–0.94), the heterozygote genetic model (OR = 0.81, 95% CI: 0.69–0.95), and the allelic genetic model (OR = 0.83, 95% CI: 0.69–0.99). For R219K in IS, there were significant associations with these genetic models, but not with the recessive genetic model. Our meta-analysis indicated that the *ABCA1* gene R219K polymorphism might be associated with IS and the K allele might be a protective factor in the Chinese population.

1. Introduction

Ischemic stroke (IS) has high morbidity and high mortality rates, and seriously affects people's health all over the world. Every year the number of those suffering from IS is approximately 15 million; a third of those die and another third of those become permanently disabled [1]. In our country, about 5 million people a year suffer from IS [2]. Many studies have found that genetic and environmental factors play important roles in the development of IS [3,4].

Atherosclerosis (AS) is the most important pathological basis for IS. Blood lipid metabolism is closely related to the development of AS. The major factor in AS resistance to high-density lipoprotein cholesterol (HDL-C) is reverse cholesterol transport (RCT) mediated by HDL-C. Many studies have shown that ABCA1, as a significant cell surface protein, is crucial in the first step of RCT [5]. Cholesterol effusion from peripheral cells regulated by the ABCA1 is the key link and the crucial rate-limiting step that affects HDL-C metabolism and RCT [6].

The *ABCA1* gene is located in 9q31, spans 149kb, and contains the 1453bp promoter, along with 50 exons and 49 introns. The *ABCA1* gene codes a 2261 amino acid long membrane protein. So far over 100 single nucleotide polymorphisms (SNPs) and mutations have been identified [7]. Mutations of the *ABCA1* gene have caused two diseases: Tangier disease (TD) [8] and familial hypoalphalipoproteinemia [9] because of heritable HDL disorder. Bochem et al. found *ABCA1* mutations displayed the mean wall thickness of arteries and atherosclerotic burden had significantly increased, HDL-C levels had significantly decreased compared with controls; so they concluded ABCA1 mutations was a higher risk for cardiovascular disease [10]. Many studies have shown that an increasing expression of ABCA1, can promote cholesterol efflux, inhibit foam cell formation and reduce formation of AS [11,12]. One study also showed a significant reduction of ABCA1 protein expression in advanced carotid atherosclerotic plaques; so the study concluded that low ABCA1 expression was an important factor in the progression of carotid atherosclerosis, which could increase the risk of IS [13]. The full function of ABCA1 will be needed to study in the protection against AS. The *ABCA1* gene SNPs with blood lipid, AS and the occurrence of IS are closely related [14–16]. R219K is a common variation in the *ABCA1* gene-coding region. Adenine (A) base substituting

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for guanine (G) base in the 1051st base of the seventh exon of the *ABCA1* gene results in arginine (R) being supplanted bylysine (K) in the 219th of the corresponding amino acid sequence. One study found that the *ABCA1* R219K polymorphism cloud modulate the association between HDL-C and age in whites [17]. Another study also found that the *ABCA1* R219K polymorphism was associated with a higher HDL-C level in Caucasians and Asians [14]. Domestically, results of the widely researched studies of *ABCA1* R219K gene polymorphism and IS are still debatable. In the Chinese population, the results also have remained controversial. Hence, the current meta-analysis was very necessary. To illustrate inconsistencies, we collected the data from the relevant published literature to quantify the *ABCA1* R219K polymorphism effect on the risk of IS in the Chinese population.

2. Materials and methods

2.1. Data sources

The relevant published literature in English or Chinese (up to May 2013) was collected from the following databases: (1) PubMed; (2) OVID; (3) Cochrane Library; (4) CNKI (China National Knowledge Infrastructure); (5) Chinese VIP database; (6) Chinese Wan Fang database and (7) China Biological Medicine Database (CBM). The following medical subject heading (MeSH) terms were used: "cerebrovascular accident," "cerebrovascular disease," "stroke," "cerebral infarct," "polymorphism,""ABCA1,""R219K"and "the Chinese population". If it was necessary, we could get in touch with the authors through e-mail for detailed information.

2.2. Selection criteria

The included studies were all selected according to the following criteria: (1) studies that related the R219K polymorphism to susceptibility to IS; (2) studies restricted to the Chinese population; (3) a clear diagnosis for IS; (4) applied case–control studies and (5) full-text articles. If one of the following was included, the literature was dropped: (1) without genotype frequency; (2) for the repeat published literature, the smaller dataset was discarded or (3) deviating from the Hardy–Weinberg equilibrium(HWE)in the studies.

2.3. Data extraction

The data of each relevant study was extracted by two of our authors independently.

Inconsistent assessments were resolved by a third author. We extracted basic information from the eligible studies: year of publication, first author's name, numbers of controls and cases, diagnostic criteria, genotyping methods, source of control groups and distributions of alleles and genotypes.

2.4. Statistical analysis

We used STATA software version 11.0 to analyze and process the data. The χ^2 test was used to check the HWE for the genotype distribution of controls. In our study, the five genetic models were selected as follows: dominant genetic model (RR vs. KK + RK), recessive model (KK vs. RR + RK), homozygote genetic model (KK vs. RR), heterozygote genetic model (RK vs. RR) and allelic genetic model (K vs. R). Odds ratios with a 95% CI were applied to evaluate the strength of the association. The Q-test and the I^2 statistic were used to evaluate heterogeneity. We used a random-effects model when significant heterogeneity ($I^2 > 50\%$, $P < 0.05$); otherwise, the fixed-effects model was adopted. The funnel plots, Begg's and Egger's regression tests were used to assess the publication bias.

3. Results

3.1. Search results

Twenty-six studies were identified in the literature search, including 10 studies that met our inclusion criteria achieved through a careful reading of the full text and strict adherence to these criteria. The flow diagram of the article selection process is shown in Fig 1. The meta-analysis included 1619 patients with IS and 1907 controls. The detailed characteristics and the distributions of genotypes are shown in Table 1 [17–26].

3.2. Meta-analysis results

The meta-analysis results were following (Table 2; Figs. 2, 3):

1. The dominant genetic model indicated a significant association between carriers of the K219 allele and the risk of IS (OR = 0.92, 95% CI: 0.88–0.96, $P = 0.000$). Heterogeneity inspection showed no obvious heterogeneity among the studies ($x^2 = 15.54$, $P = 0.08$, $I^2 = 42.1\%$);
2. The recessive genetic model (OR = 0.73, 95% CI: 0.51–1.05, $P = 0.094$) did not indicate a significant association. Heterogeneity inspection showed obvious heterogeneity among the studies ($x^2 = 31.65$, $P < 0.001$, $I^2 = 71.6\%$). Meta-regression testing can explain

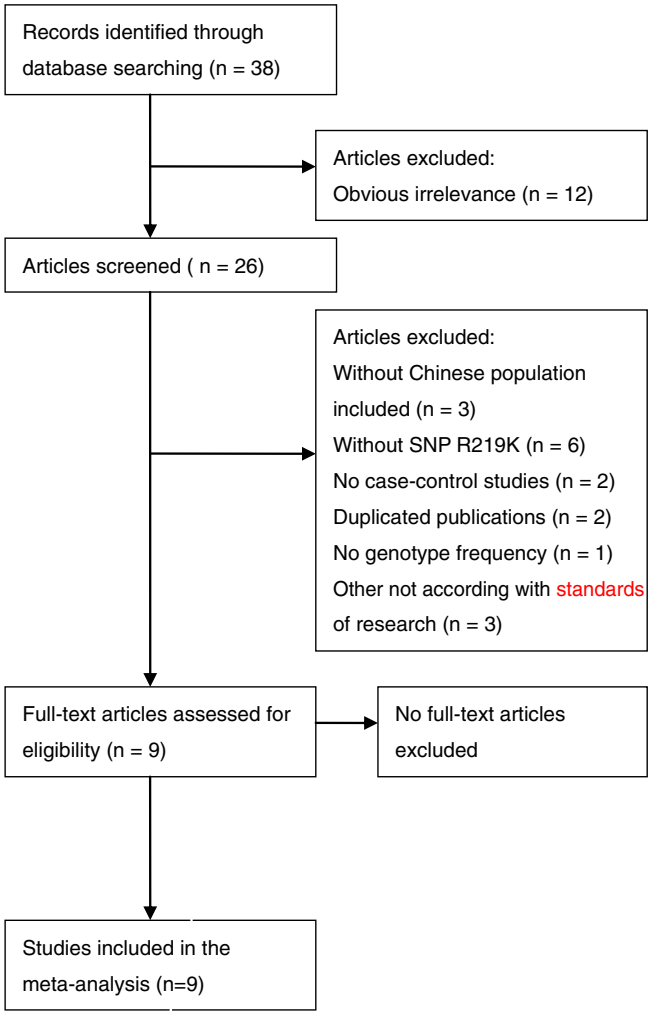

Fig. 1. The flow diagram of the article selection process.