Research Article

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The R219K polymorphism of the ATP binding cassette subfamily A member 1 gene and susceptibility to ischemic stroke in Chinese population

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Abstract: Stroke is the major cause of death and disability worldwide. ABCA1 R219K has been suggested as a risk factor for ischemic stroke, but the results remain inconclusive in the Chinese population. This study aimed to assess the association between ABCA1 R219K and ischemic stroke using meta-analysis. A systematic literature search was conducted to select eligible studies and the pooled odds ratio (OR) with 95% confidence interval (CI) was used to evaluate the strength of association. Fourteen studies containing 2865 cases and 3227 controls were included in the meta-analysis and the results suggested that there is a strong association between ABCA1 R219K and the ischemic stroke risks (K vs. R: OR = 0.837, 95% CI: 0.735-0.954, p=0.008; KK vs. RR: OR = 0.689, 95% CI: 0.520-0.912, p=0.009; KK+RK vs. RR: OR = 0.782, 95% CI: 0.691-0.885, p<0.001). Subgroup analysis revealed that significant association was found for the 4 genetic models (p<0.05) in the Southern population, while in the northern population significant association was only found under the dominant model (KK+RK vs. RR: OR = 0.744, 95% CI: 0.583-0.949, p<0.017). This meta-analysis suggested that ABCA1 R219K polymorphism might be a protective factor against developing IS, indicating this SNP may contribute to the pathogenesis of ischemic stroke and might be potentially used as a biomarker to predict the susceptibility to ischemic stroke.

Keywords: ABCA1, Ischemic stroke, R219K, meta-analysis

1 Introduction

Stroke is a common but serious cerebral vascular condition, and it is estimated to cause 5% of disability and 10% of deaths worldwide [1]. The lifetime risk of stroke is now 25% from the age of 25 years globally. Ischemic stroke (IS) is the main type of stroke, which accounts for more than 70% of the stroke [2]. In particular, the highest estimated lifetime risk of stroke is found in East Asia and it has become the leading cause of mortality in China [3]. Although both the environmental and genetic factors contribute to the pathogenesis of IS, the precise etiology of IS has not been completely elucidated yet [4]. Several genome-wide association studies (GWAS) and large collaborative efforts have been devoted to explore the genetic risk factors of IS, and many genetic variants such as PITX2 and ZFHX3 have been identified [5]. However, these genes only account for a portion of the overall genetic risk and the genetic risk factors may vary among populations. More studies on the genetic factors of IS, in particular, in individual populations are still required.

It is well accepted that the serum high-density lipoprotein cholesterol (HDL-C) level is an independent risk factor of vascular disease with the increased HDL-C providing a protective effect against vascular disease incidence. ATP binding cassette subfamily A member 1 (ABCA1) is a key regulator of cholesterol efflux and plays...
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2 Methods

2.1 Literature search and inclusion criteria

The relevant literature, published before August 2019, was searched across the electronic database of Pubmed, WangFang and China National Knowledge Infrastructure (CNKI) in English or Chinese. The following key terms were used for the literature searching: “ischemic stroke”, “cerebrovascular accident”, “cerebrovascular disease”, “cerebral infarction”, “polymorphism”, “gene mutation” and “ABCA1”. A manual search was also carried out on the references of the literature to identify additional eligible studies.

The following criteria was used to select eligible studies for the meta-analysis: (1) studies evaluating the association between ABCA1 and ischemic stroke; (2) studies containing data from the Chinese population; (3) Clear diagnosis of ischemic stroke patients; (4) R219K polymorphism was genotyped and detailed frequency data available. Accordingly, studies that did not meet the above criteria were excluded. If there was more than one case-control study reported, they were treated independently.

2.2 Data extraction

Two authors performed the data extraction independently and any disagreements were resolved by discussion with a third author. Following information was extracted from the included studies: the surname of the first author, year of publication, region of the study (South or North China), numbers of controls and cases, genotype methods and distribution of alleles and genotypes. Additionally, P values of Hardy-Weinberg equilibrium (HWE) test for the controls were also extracted or calculated based on the genotype data.

2.3 Statistical analysis

The meta-analysis was performed as previously reported [19]. The analysis was carried out using STATA statistical software (Version 12.0; Stata Corporation, College Station, TX, USA). The pooled odds ratios (ORs) with 95% confidence intervals (CIs) were employed to estimate the association between R219K and ischemic stroke risk. During the ORs calculation, four genetic models were used: additive model (K vs. R), recessive model (KK vs. RK+RR),
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Although data, and not case control studies (n=2). Subsequently, full texts readings were performed on the 15 studies and 1 study was further excluded due to duplicated data. Finally, 14 studies, containing 2865 cases and 3227 controls, investigating the PD-L1 R219K C>G and the risks of ischemic stroke were included in the present meta-analysis (Fig. 1) [14–18, 20–28]. As shown in Table 1, the publication year varied from 2014 to 2015, and the genotype distributions in the controls were in agreement with Hardy–Weinberg equilibrium (HWE) except for one study.

3 Results

3.1 Characteristics of included studies

Through literature searching, 68 publications relevant to ABCA1 gene and ischemic stroke were identified. Follow-up title and/or abstract reading excluded 42 studies as they were irrelevant to the meta-analysis. After further abstract reading, 11 studies were excluded because there was no data from Chinese population (n=3), no R219K data, and not case control studies (n=2). Subsequently, full texts readings were performed on the 15 studies and 1 study was further excluded due to duplicated data. Finally, 14 studies, containing 2865 cases and 3227 controls, investigating the PD-L1 R219K C>G and the risks of ischemic stroke were included in the present meta-analysis (Fig. 1) [14–18, 20–28]. As shown in Table 1, the publication year varied from 2014 to 2015, and the genotype distributions in the controls were in agreement with HWE except for one study.

3.2 Meta-analysis and heterogeneity test

As shown in Table 2, ABCA1 R219K was significantly associated with ischemic stroke for the allelic model (K vs. R: OR = 0.837, 95% CI: 0.735-0.954, p=0.008), the homozygotic model (KK vs. RR: OR = 0.689, 95% CI: 0.520-0.912, p=0.009) and the dominant model (KK+RK vs. RR: OR = 0.782, 95% CI: 0.691-0.885, p<0.001) (Fig. 2), but not the recessive model (KK vs. RK+RR: OR = 0.772, 95% CI: 0.594-1.003, p=0.053). As the control population of one study deviated from HWE, this study was omitted in the further analysis but there was still significant association between ABCA1 R219K with ischemic stroke for 3 genetic models (p<005). P values from I2 test were used to detect

![Figure 1: The flow diagram of the selection process for the meta-analysis](image)
the potential heterogeneity in the meta-analysis. Heterogeneity were found for the allelic model, the homozygotic model and the recessive model (p<0.001) but not for the dominant model (p<0.294). These results indicate that allele K might be a protective factor for ischemic stroke, but heterogeneity exist in the included populations.

By considering that genetic background between Southern and Northern Chinese population might be different, stratified analysis was conducted based on the region of the study. In the Southern population, significant association was found for the 4 genetic models (p<0.05); in the northern population, significant association was found under the dominant model (KK+RK vs. RR: OR = 0.744, 95% CI: 0.583-0.949, p<0.017), but not under the allelic model, homozygotic model and recessive model (p>0.05). However, heterogeneity were still found in the allelic model, the homozygotic model and the recessive model (p<0.05) in both Southern and Northern populations. Taking together, the meta-analysis revealed that ABCA1 KK+RK carriers might have decreased risk of ischemic stroke in Chinese populations.

3.3 Publication bias

Begg’s funnel plots and Egger’s tests were employed to evaluate the potential publication bias. The results of Begg’s and Egger’s tests are shown in Table 2 and a funnel plot under the dominant model (Fig. 3). Studies in the funnel plots were symmetrically distributed in the overall meta-analysis under all genetic models (p>0.05), suggesting the absence of publication bias for the meta-analysis of ischemic stroke risks.

3.4 Sensitivity Analysis

Sensitivity analysis was performed by replicating the analysis after omitting one study at a time to evaluate the effect of quality of studies on the final findings. A representative picture for the dominant model is shown in Fig. 4. The results found that the meta-analysis of the correlation between the ABCA1 R219K and ischemic stroke susceptibility remained unchanged in all genetic models.
This study included 1619 IS cases and 1907 controls of 9 publications. The results showed that ABCA1 R219K was associated with IS in all genetic models except the recessive genetic model. However, five years have passed and more studies on the Chinese populations have been published. Through the literature search, 5 new publications were identified [22, 24–27]. The numbers of cases and controls increased to 2865 and 3227 respectively in the present meta-analysis. We also found that the allele K of ABCA1 R219K might be a protective factor for IS and, particularly, the KK+RK carriers might have decreased risk of ischemic stroke in Chinese populations. Our results provided more convincing evidence for a protective role of ABCA1 R219K in IS in a larger Chinese population.

More recently, a meta-analysis was carried out in the Asian and Caucasian populations and have found that homozygous RR of R219K was significantly associated with increased IS risk (OR = 1.31, 95% CI: 1.16-1.48; p<0.001) [30], which is consistent with our finding that ABCA1 KK+RK carriers might have decreased risk of ischemic stroke. However, the subgroup analysis revealed that such association was presented in Asian populations, but not in Caucasian populations, suggesting the
heterogeneity among the populations may affect the association between ABCA1 gene polymorphism and IS. In the present meta-analysis, a modest difference was found between the Southern and the Northern Chinese population, indicating the potential heterogeneity may also existed in Asian groups. In addition, only two Caucasian studies were identified and included in the meta-analysis of Au and colleagues, such lack of association between ABCA1 R219K and IS may also be due to the limited study numbers. More studies are needed to clarify whether there is an association between ABCA1 R219K and IS in Caucasians.

Another question is how to explain the protective role of ABCA1 R219K in IS risk in the Chinese population. It is generally accepted that HDL-C is a protective factor against vascular disease. As a kind of cerebral vascular condition, increased serum HDL-C has been linked to decreased IS risk. Recent studies found that ABCA1 gene polymorphisms are associated with elevated blood lipid levels, in particular, the serum HDL-C levels. Considering the important regulatory role of ABCA1 in cholesterol homeostasis, it is likely that the protective role of ABCA1 R219K in IS is due to the elevated HDL-C. However, how the R219K variation affects the function of ABCA1 protein is unclear, and requires much more investigation in the future.

The present meta-analysis should be interpreted with caution due to several limitations. First, we only focused on R219K variation in the ABCA1 gene, while not evaluating other genes or environmental factors. It is possible that the potential roles of ABCA1 R219K are diluted or masked by other gene-gene or gene-environment interactions. Second, we only conducted the meta-analysis in the Chinese population, and so far only 2 studies have been published in Caucasians populations. Whether there is such association in Caucasian populations merits further investigations. The last but not the least, heterogeneity still exists even if we perform subgroup analysis based on the region of the Chinese populations. The association between ABCA1 R219K and IS should considered with caution when applied to a specific population.

Table 2: Meta-analysis on the association between ABCA1 R219K and ischemic stroke

| Population | Genetic model | Pooled OR (95% CI) | P | Heterogeneity (P) | Publication bias (P) |
|------------|---------------|--------------------|---|-------------------|---------------------|
|            |               |                    |   |                   | Begg’s    | Egger’s   |
| Overall    | K vs. R       | 0.837 (0.735, 0.954) | 0.008 | 0.000 | 0.784 | 0.495 |
|            | KK vs. RK+RR  | 0.772 (0.594, 1.003) | 0.053 | 0.000 | 0.784 | 0.915 |
|            | KK vs. RR     | 0.689 (0.520, 0.912) | 0.009 | 0.000 | 0.927 | 0.724 |
|            | KK+RK vs. RR  | 0.782 (0.691, 0.885) | 0.000 | 0.294 | 0.649 | 0.170 |
| South      | K vs. R       | 0.838 (0.734, 0.957) | 0.009 | 0.031 | 0.297 | 0.839 |
|            | KK vs. RK+RR  | 0.786 (0.619, 0.996) | 0.046 | 0.025 | 1.000 | 0.797 |
|            | KK vs. RR     | 0.718 (0.544, 0.949) | 0.020 | 0.021 | 0.532 | 0.754 |
|            | KK+RK vs. RR  | 0.803 (0.693, 0.932) | 0.004 | 0.304 | 1.000 | 0.640 |
| North      | K vs. R       | 0.856 (0.632, 1.158) | 0.313 | 0.000 | 0.188 | 0.304 |
|            | KK vs. RK+RR  | 0.773 (0.396, 1.510) | 0.451 | 0.000 | 0.573 | 0.614 |
|            | KK vs. RR     | 0.666 (0.342, 1.296) | 0.232 | 0.000 | 0.348 | 0.423 |
|            | KK+RK vs. RR  | 0.744 (0.583, 0.949) | 0.017 | 0.287 | 0.348 | 0.258 |
| HWE        | K vs. R       | 0.833 (0.725, 0.957) | 0.010 | 0.000 | 0.288 | 0.220 |
|            | KK vs. RK+RR  | 0.767 (0.578, 1.017) | 0.066 | 0.000 | 0.757 | 0.884 |
|            | KK vs. RR     | 0.677 (0.500, 0.915) | 0.011 | 0.000 | 0.918 | 0.686 |
|            | KK+RK vs. RR  | 0.771 (0.677, 0.878) | 0.000 | 0.280 | 0.757 | 0.193 |
5 Conclusion

This meta-analysis suggests that ABCA1 R219K polymorphism might be a protective factor against developing IS. However, the strength of association might vary among populations, and larger and well-designed studies are warranted to validate our findings.

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