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Association of *ABCB1* C3435T polymorphism with the susceptibility to osteonecrosis of the femoral head

A meta-analysis

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Abstract

Background and objective: The exploration for the etiology of osteonecrosis of the femoral head (ONFH) has got some promising findings, but the morbidity of ONFH is still not under control. The C3435T polymorphism of ATP-binding cassette subfamily B member 1 (*ABCB1*) gene has been reported to possess significant influence on ONFH onset, but relevant outcomes remain conflicting rather than conclusive. Therefore, a meta-analysis was useful to pool these results together for a more reliable conclusion.

Methods: The association of *ABCB1* C3435T polymorphism with ONFH susceptibility was estimated through calculated odds ratios (ORs) with their 95% confidence intervals (95% CIs). The Q-test was applied for detecting inter-study heterogeneity, whereas sensitivity analysis for identifying any study owning substantial influence on pooled results. Begg's funnel plot and Egger's test were employed to examine publication bias across included studies.

Results: *ABCB1* C3435T polymorphism significantly decreased the risk of ONFH under TT vs CC (OR = 0.26, 95% CI = 0.13–0.50), TT+CT vs CC (OR = 0.72, 95% CI = 0.52–0.99), TT vs CC+CT (OR = 0.28, 95% CI = 0.15–0.52), and T vs C (OR = 0.64, 95% CI = 0.50–0.81) contrasts.

Conclusion: The variant C3435T in the *ABCB1* gene may offer protection against the attack of ONFH, and more studies with larger sample sizes should be conducted to certify this issue.

Abbreviations: 95% CIs = 95% confidence intervals, ABCB1 = ATP-binding cassette subfamily B member 1, ALL = acute lymphoblastic leukemia, GANFH = glucocorticoid-induced avascular necrosis of the femoral head, HIV = human immunodeficiency virus, MDR1 = multidrug resistance protein 1, NOS = Newcastle–Ottawa Scale, ONFH = osteonecrosis of the femoral head, ORs = odds ratios, P-gp = P-glycoprotein 1, SCFE = slipped capital femoral epiphysis, SLE = systemic lupus erythematosus.

Keywords: ATP-binding cassette subfamily B member 1, osteonecrosis of the femoral head, polymorphism

1. Introduction

Osteonecrosis of the femoral head (ONFH) refers to bony changes caused by osteocyte death under the effects of complicated factors, which lead to the fracture and collapse of subchondral bone and the changes in shape and functions of femoral head.[1,2] ONFH is generally classified into trauma-induced ONFH and nontraumatic ONFH, and the latter, also termed as aseptic necrosis of femoral head or avascular necrosis of femoral head, contains cause-specific and idiopathic ONFH.[3,4] At the moment, blood supply insufficiency in femoral head is regarded as one of the direct, major reasons for osteocyte apoptosis.[5] It is estimated that there are more than 20 million ONFH patients all over the world, and 5 to 7.5 million cases are Chinese people.[6] As for the estimates of new ONFH cases each year, there are about 15 to 20 thousand cases in America, 2.5 to 3 thousand in Japan, and 100 to 200 thousand in China.[7–9] Moreover, the morbidity rate of ONFH has shown a rising trend in the few past years. The etiology of ONFH has been extensively researched, and the majority of nontraumatic ONFH cases are associated with hormone use and alcohol consumption.[10] Besides, potential causes of idiopathic ONFH have been proposed, containing slipped capital femoral epiphysis (SCFE), decompression disease, systemic lupus erythematosus (SLE), fat embolism syndrome, tumor chemotherapy, organ transplantation, chronic liver diseases, gout, human immunodeficiency virus (HIV) infection, and other metabolic bone diseases.[11–15]

ATP-binding cassette subfamily B member 1 (ABCB1), or multidrug resistance protein 1 (MDR1) or P-glycoprotein 1 (P-gp) which is encoded by the *ABCB1* gene, acts as an important protein pumping foreign substances out of cells, and having critical functions in drug absorption and distribution.[16] ABCB1 has become one of the most studied members in ABC family due to its production of multidrug resistance in tumor cells. ABCB1

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expresses widely and possesses momentous physiological functions, so any defect in this protein, caused by the polymorphisms in the *ABCB1* gene, may result in severe diseases or affect curative effects, such as Parkinson's disease, childhood acute lymphoblastic leukemia (ALL), ulcerative enteritis, and treatment effects on HIV.[17–19]

Certain correlations between *ABCB1* polymorphisms and ONFH risk have been proposed, and various findings have been generated. In this meta-analysis, we collected previous studies estimating the association between *ABCB1* C3435T polymorphism and ONFH susceptibility to systematically combine their results.

2. Materials and methods

2.1. Literature sources and searching strategy

This study was approved by the Ethics Committee of the Dalian University Affiliated Zhongshan Hospital.

Potentially relevant reports were identified up to September 1, 2015, from the electronic databases of PubMed, EMBASE, Wanfang, and CNKI, as well as from other sources. Searching strategy adopted the combination of key terms, including "osteonecrosis of the femoral head" or "avascular necrosis of femoral head," "ATP-binding cassette subfamily B member 1" or "ABCB1" or "multidrug resistance protein 1" or "MDR1" or "P-glycoprotein 1" or "P-gp", and "polymorphism" or "mutation" or "variant." The references of relevant reports were manually filtrated for complementary publications.

2.2. Inclusion and exclusion criteria

Indispensable criteria for every included study were formulated in advance and contained the following aspects: (1) with a case-control design; (2) applying validated genotyping methods; (3) appraising the association between *ABCB1* C3435T polymorphism and ONFH susceptibility; and (4) genotype distribution consistent with Hardy–Weinberg equilibrium in the control group. Excluded records embraced editorials, conference abstracts, review articles, and case-only studies.

2.3. Assessment of study quality

The Newcastle–Ottawa Scale (NOS) was employed to evaluate the quality of all selected studies. Based on 8 items from 3 dimensions of selection, comparability and exposure, each study could be given a score ranging from 0 to 9. In advance, we defined the quality of studies with a score between 7 and 9 as high, between 4 and 6 as medium, and between 0 and 3 as low. The grading was carried out by 2 reviewers separately, and they would finally reach consensus for each study through discussion if there were differences in study quality scores given by the 2 reviewers.

2.4. Data extraction

Two reviewers separately took charge of data extraction in accordance with the same tabulation for the main information of selected papers, and resolved all disagreements through discussion between them. The principal information drawn from eligible articles was comprised of first author's name, publication year, original country, ethnicity, numbers of cases and controls, genotype distribution in case and control groups, genotyping method, and *P* value for the Hardy–Weinberg equilibrium test in the control group.

2.5. Statistical analysis

The intensity of the association between *ABCB1* C3435T polymorphism and ONFH susceptibility was assessed by calculated odds ratios (ORs) with their corresponding 95% confidence intervals (95% CIs). In the chi-square-based *Q*-test for inter-study heterogeneity examination, $P < .05$ or $P \geq .05$ represented the presence or absence of significant heterogeneity, which ensured the choice of random- (DerSimonian–Laird method) or fixed-effects (Mantel–Haenszel method) model for ORs calculation. Sensitivity analysis was conducted through sequential omission of every included study to observe alterations in combined results. Publication bias across selected studies were detected with both Begg's funnel plot and Egger's linear regression test.[20,21]

3. Results

3.1. Study characteristics

A total of 92 potentially relevant publications were retrieved from the above databases, whereas 10 articles were identified from other sources, and 5 eligible articles were picked out through strict standards for inclusion and exclusion.[22–26] The flowchart for this meta-analysis exhibits detailed course of literature screening and particular reasons for exclusion (Fig. 1). Of the included studies, 4 had high quality whereas the other 1 had medium quality. Essential information of eligible reports is listed in Table 1.

3.2. Meta-analysis results

Corresponding results from data analyses are recorded in Table 2. A remarkable correlation of *ABCB1* C3435T polymorphism can be found with reduced susceptibility to ONFH in 4 genetic models of TT vs CC (OR = 0.26, 95% CI = 0.13–0.50) (Fig. 2), TT+CT vs CC (OR = 0.72, 95% CI = 0.52–0.99) (Fig. 3), TT vs CC+CT (OR = 0.28, 95% CI = 0.15–0.52) (Fig. 4), and T vs C (OR = 0.64, 95% CI = 0.50–0.81) (Fig. 5).

3.3. Heterogeneity test

As shown in Table 2, there was no significant heterogeneity among included studies ($P > 0.05$), so the fixed-effects model was determined for ORs calculation.

3.4. Sensitivity analysis

None of the selected studies expressed dramatic impact on pooled results during sensitivity analysis, implying statistical robustness of the results.

3.5. Publication bias examination

Begg's funnel plot provided no evidence for the existence of significant publication bias under any genetic contrast (Fig. 6), nor did Egger's test (data not shown).

4. Discussion

With the deepened exploration of ONFH etiology, it is widely believed that trauma-induced ONFH occurs due to the direct destruction of blood supply to bone, and microcirculation thrombosis and intravascular coagulation are the common

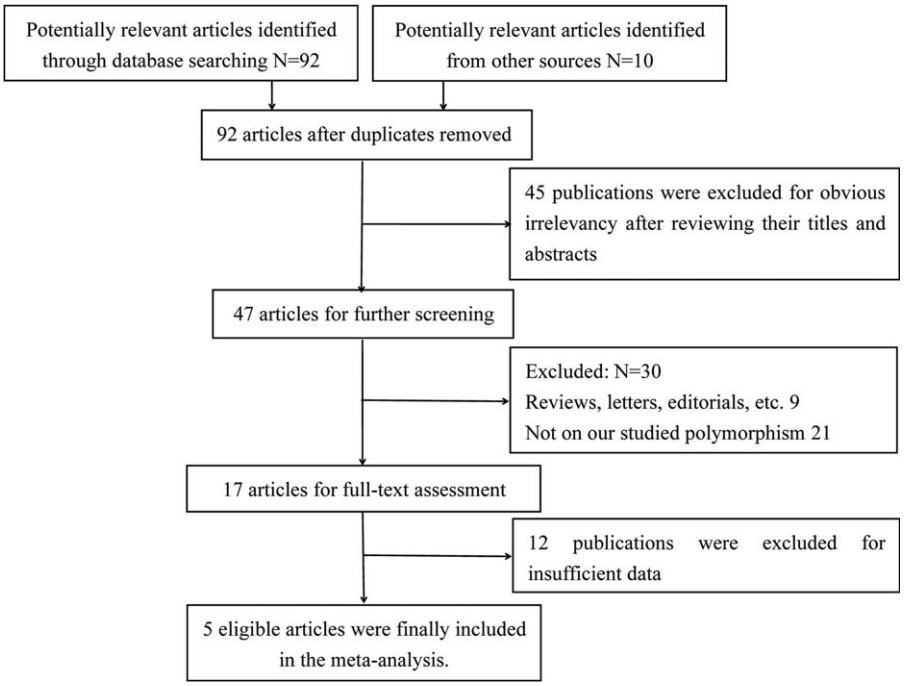

Figure 1. Flowchart for literature selection and exclusion reasons.

Table 1

Essential information of 5 eligible articles.

First author, year	Country	Ethnicity	Genotyping method	Source of control	Sample size		HWE	NOS score
					Case	Control		
Asano, 2003	Japan	Asian	PCR	Hospital-based	30	106	0.50	6
Yang, 2007	China	Asian	PCR-RFLP	Hospital-based	21	106	0.19	7
Kuribayashi, 2008	Japan	Asian	PCR	Hospital-based	30	121	0.27	8
He, 2009	China	Asian	PCR-RFLP	Hospital-based	31	17	0.69	7
Xue, 2014	China	Asian	PCR	Population-based	99	330	0.61	8

HWE = Hardy–Weinberg equilibrium, NOS = Newcastle–Ottawa Scale, PCR = polymerase chain reaction, PCR-RFLP = PCR–restriction fragment length polymorphism.

Table 2

Effects of *ABCB1* C3435T polymorphism on the ONFH risk.

Comparison	OR (95%CI)	Heterogeneity test		Model for analysis
		P_h	I^2	
TT versus CC	0.26 (0.13, 0.50)	.73	0.00%	Fixed
TT+TC versus CC	0.72 (0.52, 0.99)	.87	0.00%	Fixed
TT versus TC+CC	0.28 (0.15, 0.52)	.72	0.00%	Fixed
T versus C	0.64 (0.50, 0.81)	.72	0.00%	Fixed

95% CIs = 95% confidence intervals, ABCB1 = ATP-binding cassette subfamily B member 1, ONFH = osteonecrosis of the femoral head, ORs = odds ratios.

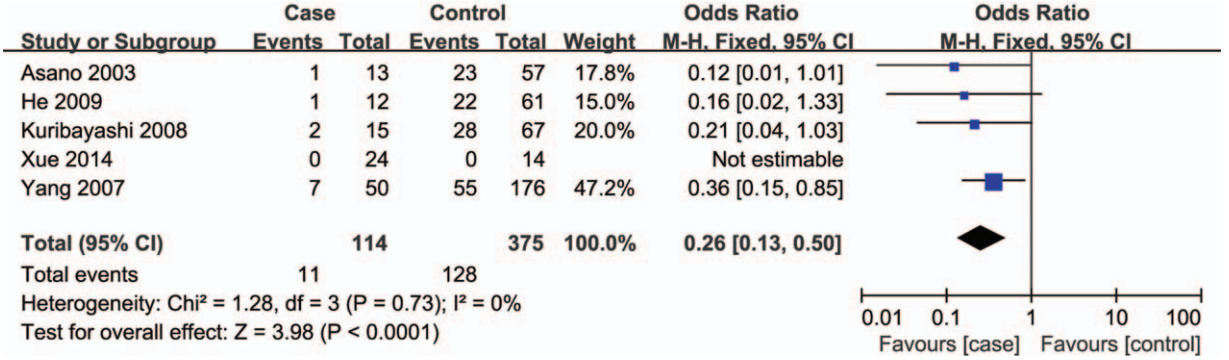

Figure 2. Forest plot for the association between ABCB1 C3435T polymorphism and ONFH susceptibility under TT vs CC contrast. ABCB1 = ATP-binding cassette subfamily B member 1, ONFH = osteonecrosis of the femoral head.

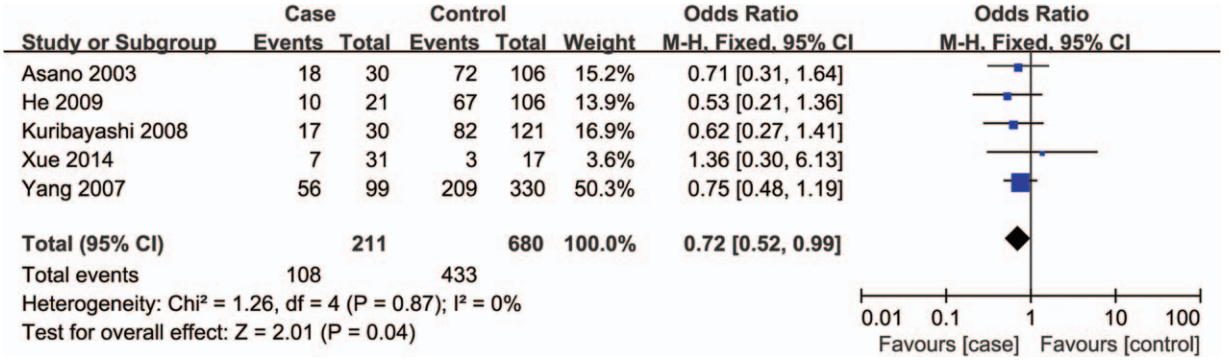

Figure 3. Forest plot for the association between ABCB1 C3435T polymorphism and ONFH susceptibility under TT+CT vs CC contrast. ABCB1 = ATP-binding cassette subfamily B member 1, ONFH = osteonecrosis of the femoral head.

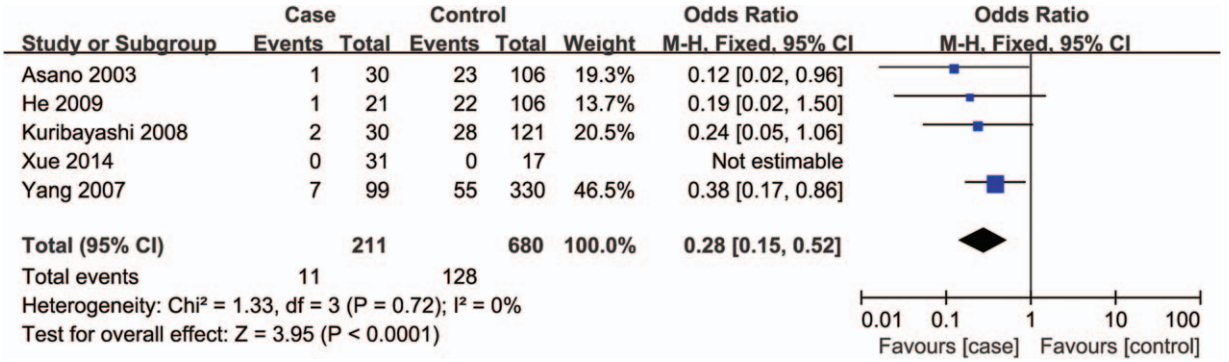

Figure 4. Forest plot for the association between ABCB1 C3435T polymorphism and ONFH susceptibility under TT vs CC+CT contrast. ABCB1 = ATP-binding cassette subfamily B member 1, ONFH = osteonecrosis of the femoral head.

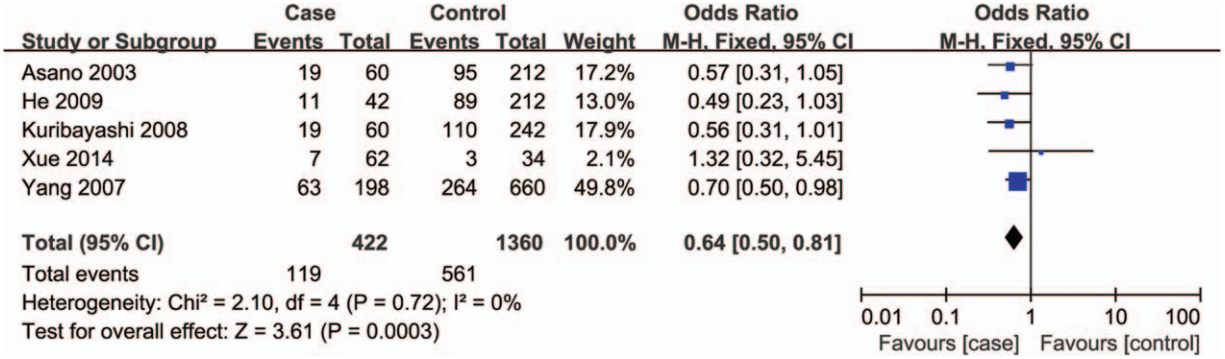

Figure 5. Forest plot for the association between ABCB1 C3435T polymorphism and ONFH susceptibility under T vs C contrast. ABCB1 = ATP-binding cassette subfamily B member 1, ONFH = osteonecrosis of the femoral head.

pathways of various causes for nontraumatic ONFH. Amidst the rapid development of molecular biotechniques, heredity is regarded as one of the possible causes for nontraumatic ONFH and leads to ONFH onset independently or together with other high-risk factors (such as like hormones and alcohol). Recent scientific findings show that ONFH attack is related to thrombophilia, decreased ability of fibrinolysis, reduced production of vasoactive substances, and the abnormalities in gene polymorphisms related to drug transporters. All these abnormal factors destroy the blood circulation in femoral head, and result in ONFH occurrence. Multiple synthetic hormones are absorbed and distributed through transportation by ABCB1, a transport protein reflecting drug resistance. There are multiple polymorphisms in the *ABCB1* gene, and the variant C3435T in exon 26 is reportedly a functional polymorphism affecting phenotypes. This polymorphism may cause changes in pharmacokinetics and metabolite for hormone,[27] so as to produce various sensitivities of people to hormone.

As for the association between *ABCB1* C3435T polymorphism and ONFH susceptibility, Asano et al[22] suggested TT genotype of the polymorphism could reduce the risk of ONFH in Japanese. Moreover, Xue et al[25] found that carriers with T allele or TT genotype had significantly lower risk of glucocorticoid-induced avascular necrosis of the femoral head (GANFH) compared with other carriers. No significant correlation was expressed between C3435T variant and ONFH risk in the research by Yang and Xu,[26] but the variant can be used for predicting the development of ONFH. A totally reverse relevance, however, was revealed in the study by He and Li,[23] that was to say, the *ABCB1* C3435T polymorphism increased the susceptibility to ONFH. With regard to discrepancies among these studies, possible reasons might be different ONFH types and genotyping methods, various criteria for the selection of cases and controls, as well as potential effects of other genetic, environmental, and demographic factors.

In our meta-analysis, *ABCB1* C3435T polymorphism was significantly related to the reduced risk of ONFH under TT vs CC, TT+CT vs CC, TT vs CC+CT and T vs C genetic models, showing its protective effects against the onset of the disease. As shown in Table 2, the risk of ONFH was reduced to less than one-third in carriers with TT genotype of C3435T polymorphism compared with wild homozygote carriers, displaying a similar tendency to the findings by Asano et al and Xue et al.[22,25] In addition, the genotype distribution of control group was consistent with Hardy–Weinberg equilibrium in every included study.

Although meta-analysis means a more powerful measure than any single study, our findings still need to be interpreted cautiously. Language and source limitations in searching strategy might miss some potent papers, and the limited number of included studies might lessen the comprehensiveness of the results. Additionally, 5 eligible studies provided data merely about Asian populations, which might produce selection bias. Meanwhile, only 1 included study was with population-based control source, and others recruited hospital-based controls, which might be deficient in representativeness for general populations. Moreover, no subgroup analysis was performed according to age, gender, ONFH type, status of alcohol consumption or other relevant respects. Furthermore, the initiation and progression of ONFH involve many aspects, but gene–gene or gene–environment interactions were not incorporated in this study, and this might sway the accuracy of our findings.

In conclusion, this analysis suggests a protective function of *ABCB1* C3435T polymorphism against ONFH occurrence. In view of restrictions in the present study, the results should be further verified via studies with more relevant researches and ethnic groups, as well as possible interactions among risk factors for ONFH.

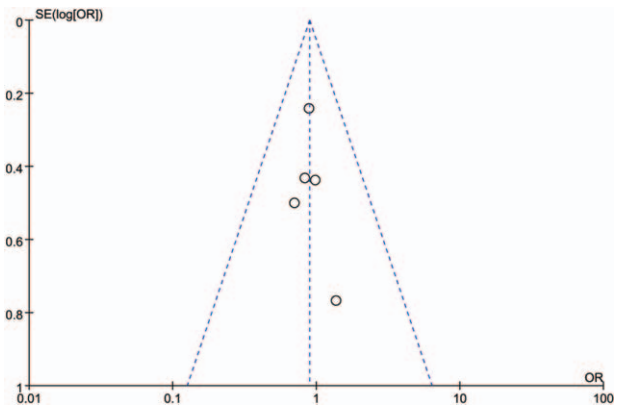

Figure 6. Funnel plot for publication bias among selected studies.

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