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Original Article

Relation between osteonecrosis of the femoral head and PAI-1 4G/5G gene polymorphism: a meta-analysis

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Abstract: Objective: The aim of this study was to investigate the association of plasminogen activator inhibitor-1 (PAI-1) 4G/5G gene polymorphism and osteonecrosis of the femoral head (ONFH). Methods: The pooled relative risk ratio (RR) and 95% confidence intervals (95% CI) were calculated using the the RevMan 5.0 software. Results: The present study included 969 patients with ONFH and 419 healthy controls. The Meta analysis results showed: There is association between PAI-1 gene 4G/5G polymorphism and the increasing risk of ONFH (allele model: RR = 1.24, 95% CI = 1.16 ~ 1.33; dominant genetic model: RR = 1.12, 95% CI = 1.05 ~ 1.18). It was found that the association between PAI-1 gene 4 G/5 G polymorphism and the susceptibility of ONFH ($P < 0.05$) through the comparison of Caucasian population and Asian people according to the analysis of different races. Conclusions: There is association between PAI-1 gene 4 G/5 G polymorphism and the increasing of the susceptibility of ONFH.

Keywords: Plasminogen activator inhibitor-1, osteonecrosis of the femoral head, meta-analysis

Introduction

Osteonecrosis of the femoral head (ONFH) is a kind of ischemic damage of femoral head, and ONFH can cause the necrosis of the cartilage hip joint and the collapse and degeneration of the femoral head [1, 2]. The age of onset of ONFH is early in the field of orthopedics [3, 4], and the incidence of ONFH increased recent year. The main symptoms of ONFH are limitation of activity, limping, and pain etc. The early diagnosis of ONFH is difficult, and it always was found in moderate and advanced stage. It can leads to the occurrence of the disorder of the hip joint, lower limb disability if the patients had not be treated in time.

The etiology and pathogenesis of ONFH is still not entirely explicit, there are some statements that the etiology and pathogenesis of ONFH is associated with the factors such as long-term hormone therapy [5], trauma [6], alcoholism [7], and inheritance [8] etc. In recent years, it was proved that the genetic polymorphisms of plasminogen activator inhibitor-I (PAI-1) gene [9-14], apolipoprotein A1 (apoA 1) gene [15], and apoA5 gene [16] were associated with ONFH. The susceptibility of vascular endothelial growth factor (VEGF) gene and other genes can also leads to the ONFH [17, 18]; there are more reports about PAI-1 gene 4G/5G polymorphism and ONFH susceptibility [9-14]. PAI-1 gene, which regulates the fibrinolysis system, is composed of 379 amino acids and locates in human chromosome 7q21.3-q22 [19]. The primary function is to reduce the fibrin degradation of protein aggregation, maintain the normal dynamic balance of coagulation and fibrinolysis system in the natural blood circulation [20]. It is reported that hypercoagulation is the main factor which can lead to ONFH, disseminated intravascular coagulation (DIC) is the pathway of ONFH and it can lead to the formation of thromboses in femoral head; at the same time, secondary fibrinolysis can lead to the bleeding inside the bone marrow, cause nontraumatic osteonecrosis [21]. In recent years, more and more studies have confirmed that PAI-1 gene 4G/5G polymorphism is closely correlated with the susceptibility of ONFH [9-14]. However, the conclusion is still debated because of the difference between the case group and control group in these studies. The aim of this study is to collect the reports about the association between

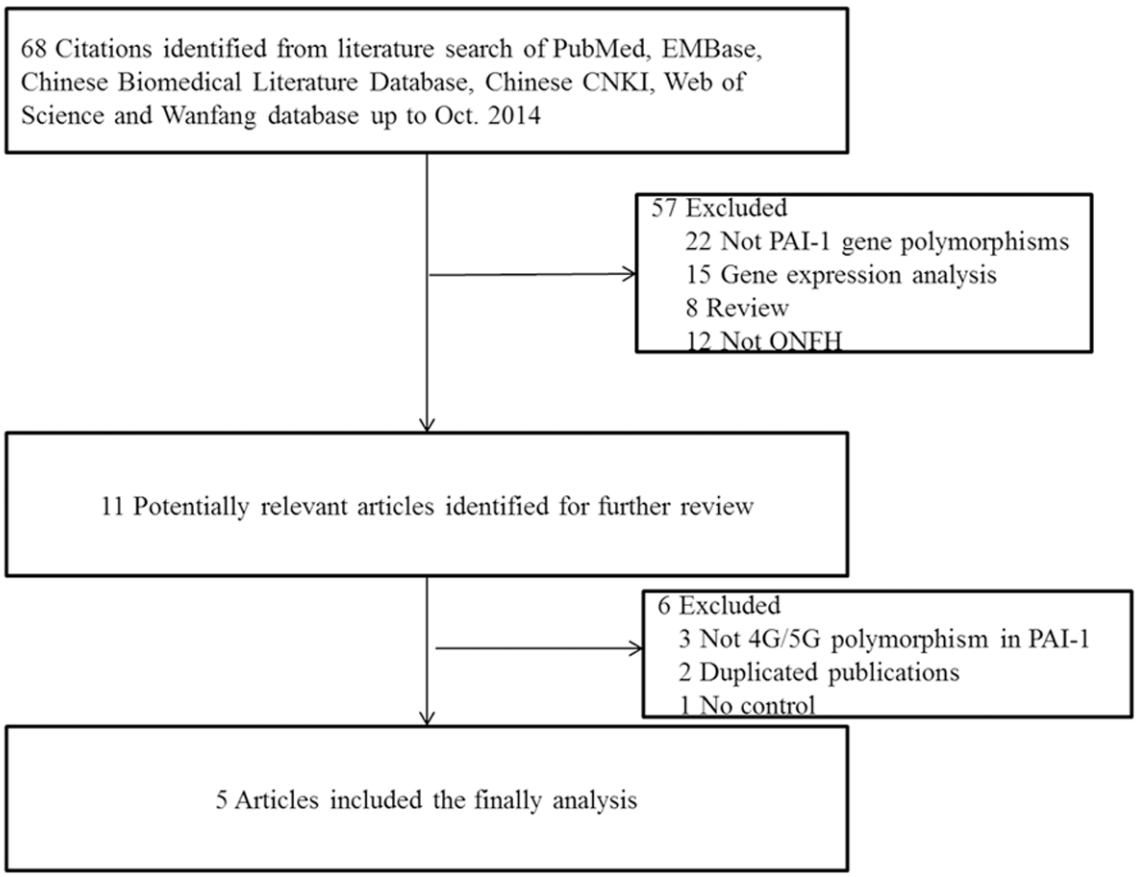

Figure 1. Flow chart of literatures identification.

Table 1. Characteristic of included studies

First author	Publication Year	Country	Ethnicity	Genotyping methods	Sample Size (Case/Control)	Genotype distribution and allele frequency									
						Case					Control				
						4G4G	4G5G	5G5G	4G	5G	4G4G	4G5G	5G5G	4G	5G
Kim	2011	Korea	Asian	PCR	206/251	82	95	29	0.63	0.37	75	130	46	0.56	0.44
Glueck	2001	USA	Caucasian	PCR	95/234	36	44	15	0.61	0.39	47	103	84	0.42	0.58
Ferrari	2002	Switzerland	Caucasian	PCR	26/326	16	8	2	0.77	0.23	67	166	93	0.46	0.54
Asano	2004	Japan	Asian	PCR	31/106	16	11	4	0.69	0.31	36	56	14	0.6	0.4
Sun	2008	China	Asian	PCR	61/52	23	22	16	0.56	0.44	13	27	12	0.51	0.49

PAI-1 gene polymorphism and ONFH susceptibility, and to provide the reference for the clinical diagnosis and treatment of ONFH.

Materials and methods

Search strategy

We retrieved the database Pub Med, EM Base, Chinese Biomedical Literature Database, Chinese CNKI, Web of Science and Wanfang database up to Oct. 2014. The search terms including PAI-1, plasminogen activator inhibitor-1, polymorphism, ONFH, osteonecrosis of the femoral head, ONFH, avascular necrosis of the femoral head, ANFH.

Inclusion criteria

The included studies should be meet to the following criteria: 1) The case-control study about the correlation between PAI-1 gene 4G/5G polymorphism and the susceptibility of ONFH; 2) The data which were provided by the refer-

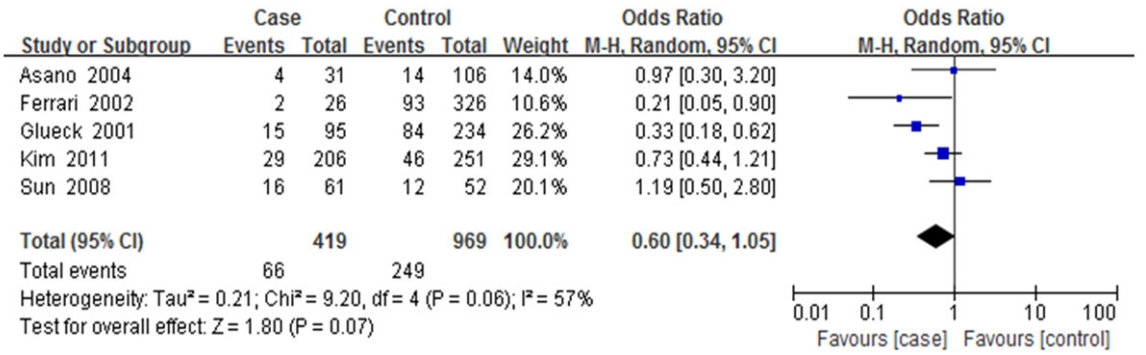

Figure 2. Forest plot of ONFH risk associated with PAI-1 polymorphism in dominant model [5G5G vs. (4G5G + 4G4G)]. The squares and horizontal lines correspond to the study-specific OR and 95% CI, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of OR and 95% CI.

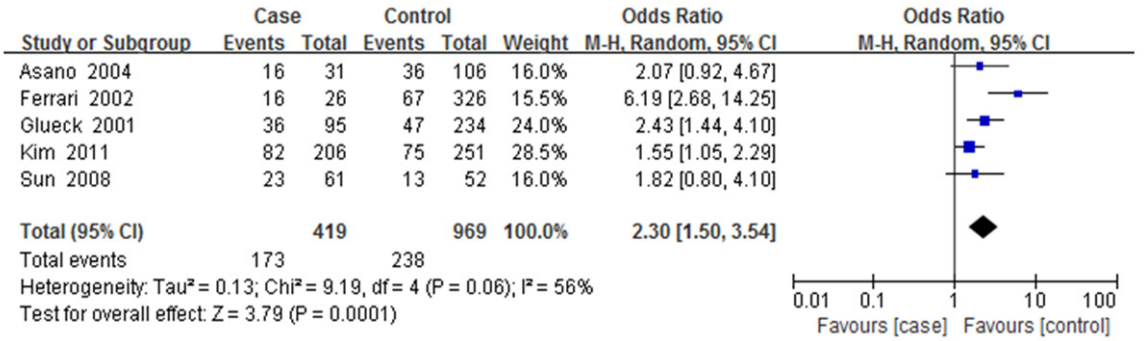

Figure 3. Forest plot of ONFH risk associated with PAI-1 polymorphism in recessive model [4G4G vs. (4G5G + 5G5G)]. The squares and horizontal lines correspond to the study-specific OR and 95% CI, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of OR and 95% CI.

ences such as clinical data, allele and genotype frequencies etc; 3) The genotypes in control group are all compatible with Hardy-Weinberg equilibrium (HWE).

Exclusion criteria

The exclusion criteria were as follows: (1) a review, case report, editorial, or comment; (2) a duplicated study; (3) preliminary results that do not include PA-1 4G/5G polymorphisms or outcome; and (4) animal models researchers.

Data extraction

The collection schedule with the unified data was used in data extraction, the main data information include: the first author, the publish date, country, language, race, study design, the source of control group (people in the hospital or the general population), sample size, the test method of SNP, genotypes or allele frequency, and Hardy-Weinberg equilibrium (HWE).

Statistical analysis

Fixed effect model or random effect model was used according to heterogeneity testing results in the meta-analysis of the correlation evaluation between PAI-1 gene 4G/5G polymorphism and the susceptibility. Three different genetic models, including allele model (4G vs. 5G), dominance genetic model (4G4G + 4G5G vs. 5G5G), and recessive genetic model (4G4G vs. 4G5G + 5G5G) were carried out in the present study.

Results

Assessment of baseline characteristics

As shown in **Figure 1**, we retrieved 68 pertinent literatures, and excluded 63 literatures for duplicated publication and other reason. There are 5 literatures [9-13] were selected to perform meta-analysis finally. These 5 randomized

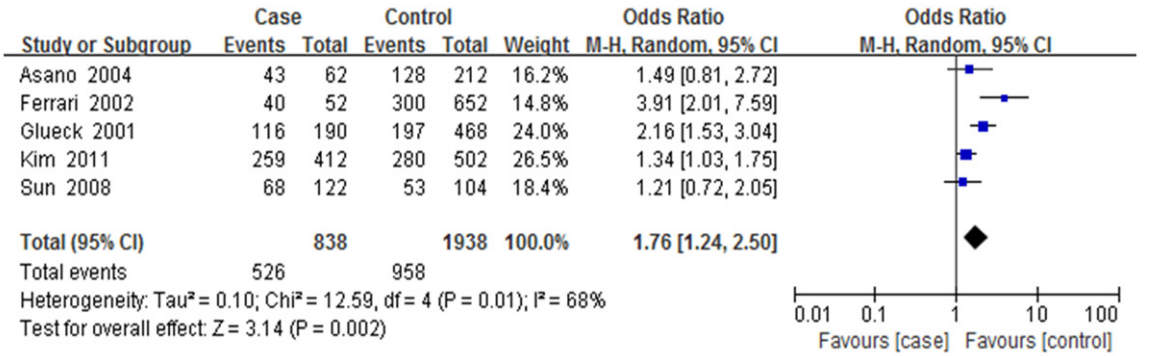

Figure 4. Forest plot of ONFH risk associated with PAI-1 polymorphism in allelic model (4G vs. 5G). The squares and horizontal lines correspond to the study-specific OR and 95% CI, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of OR and 95% CI.

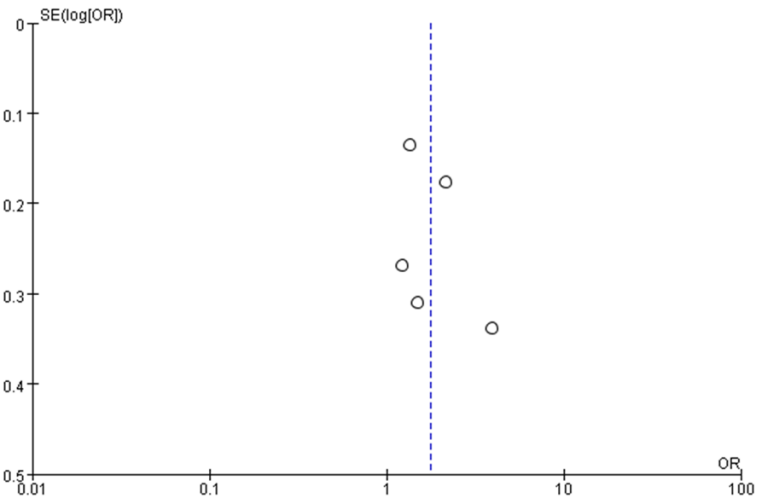

Figure 5. Funnel plot of publication bias test.

controlled trials included 419 ONFH patients and 969 healthy controls, all the patients were consistent to the diagnostic criteria of ONFH. Peripheral-blood specimens were used during the investigations of polymorphism in all the studies. All the genotypes distributions were in line with Hardy -Weinberg equilibrium (HWE). The characteristics of included studies were shown in **Table 1**.

Meta-analysis

The results of the meta-analysis and heterogeneity test were shown in **Figures 2**-**4**. We found significant heterogeneity for all five studies. Therefore, the random effect model was used to merge the OR values. We found significant association of PAI-1 genetic polymorphism 4G/5G with ONFH in a dominant model (OR = 2.30; 95% CI: 1.50-3.54) and allelic comparison (OR = 1.76, 95% CI: 1.24-2.50). We did not find association of PAI-1 genetic polymorphism 4G/5G with ONFH in a recessive model (OR = 0.60; 95% CI: 0.34-1.05).

Publication bias

We strengthened the confidence level in the results by conducting a publication bias analysis. Publication bias was detected on the comparison of 4G5G + 4G4G vs. 5G5G. The shape of the funnel plots was symmetrical, suggesting no evidence of publication bias among the studies (**Figure 5**). The Egger's test, performed to provide statistical evidence of funnel plot asymmetry, indicated a lack of publication bias in the current meta-analysis (P = 0.453).

Sensitivity analysis

Sensitivity analysis was used in this study. The statistical results show that there is no single study can significantly influence the results of the existing analysis

Discussion

ONFH is a kind of orthopedic diseases which can lead to the femoral head collapse and it is caused by the degeneration and necrosis of notochordal cell and cartilage cell which are

caused by the disruption and hypoxia of blood supply of femoral head. The present study suggested that PAI-1 4G/5G polymorphism was associated with ONFH. The subjects with 4G allele have 1.76-fold risk for ONFH compared to subjects with 5G allele.

PAI-1 is a kind of main regulatory factors of the fibrinolytic system which involved in the combination of the fibrinolytic activator and the balance of the fibrinolytic system; it plays an important role in the process of ONFH. From a biological standpoint, the increasing of the risk of ONFH has association with the genetic variation of PAI-1 gene. The previous studies showed that, PAI-1 gene promoter 4G/5G polymorphism played an important role in the occurrence and the development of ONFH, but the available evidence remains controversial [9-14].

The results of Meta-analysis showed that PAI-1 gene 4G/5G polymorphism located -675 locus can increase the susceptibility of ONFH. Though there is no definitive mechanism of action, PAI-1 is the mainly regulatory factor of the fibrinolytic system, which can influence the balance between the blood coagulation and the fibrinolytic system directly. Overall, the results of this study are consistent with the results of the previous studies, which confirmed that PAI-1 gene 4G/5G polymorphism was an important biomarker in the prediction of ONFH.

Nevertheless, there are several disadvantages and limitations existing in the analysis. On the one hand, the lack of the comprehensive evolution of PAI-l gene polymorphism and ONFH susceptibility during the clinical actual research, therefore need the larger sample to continue the further research. On the other hand, the possible target or offset was analyzed in this study, but other indicators, such as age, gender and other factors did not be evaluated.

In addition, the present study is an analysis about the PAI-1 gene polymorphism and ONFH susceptibility, which still has important clinical value for ONFH mechanism. In conclusion, PAI-1 gene 4G/5G polymorphism was associated with the risk of ONFH. However, our conclusion needs further confirmation in other ethnic populations with large sample studies.

Disclosure of conflict of interest

None.

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