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Research Article

Association between the Promoter -675 4G/5G Polymorphism of the Plasminogen *Activator Inhibitor-1* Gene and Asthma: An Update of Meta-Analysis

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Abstract

Background and Objectives: Several studies have explored the association between the promoter -675 4G/5G polymorphism of the ***Plasminogen Activator Inhibitor-1 (PAI-1)*** gene and asthma risk; however the results are inconsistent. The purpose of this study was to evaluate the genetic risk of this polymorphism for asthma using the method of meta-analysis.

Methods: Systemic electronic literature search was conducted on *PAI-1* polymorphism and asthma risk in several databases. The data were pooled employing the meta-analysis method.

Results: Eight case-control studies involving 1551 asthmatics and 2339 healthy controls were included in this meta-analysis. In the overall population, our results showed that the *PAI-1* -675 4G/5G polymorphism was significantly associated with elevated asthma risk in a dominant genetic model [odds ratio (OR)=1.716, 95% confidence interval (CI)=1.190-2.474]. Stratified analyses were conducted based on ethnicity, age and atopic status of asthmatic patients. We observed that the *PAI-1* -675 4G allele carriers have increased risk of asthma in both Caucasian and Asian populations (OR=1.749, 95% CI=1.084-2.823 and OR=1.456, 95% CI=1.019-2.081, respectively). Increased risk of asthma was also seen in adult and children populations of the *PAI-1* -675 4G allele carriers (OR=1.558, 95% CI=1.028-2.360 and OR=2.380, 95% CI=1.486-3.811, respectively). In the case of atopic asthma and non-atopic asthma, the *PAI-1* 4G/5G polymorphism was significantly associated with atopic asthma susceptibility (OR=2.436, 95% CI=1.783-3.328 for 4G4G+4G5G *vs.* 5G5G).

Conclusion: Data indicated that the *PAI-1* -675 4G/5G polymorphism was associated with increased asthma risk. Recommendations for further studies include pooling of individual data to facilitate assessment of gene-gene and gene-environment interactions in asthma susceptibility.

Keywords: Asthma; Meta-analysis; Plasminogen activator inhibitor-1; Polymorphism

Abbreviations

BHR: Bronchial Hyperresponsiveness; PAI: Plasminogen Activator Inhibitor; OR: Odds Ratio; CI: Confidence Interval; CNKI: Chinese National Knowledge Infrastructure; HWE: Hardy-Weinberg Equilibrium

Introduction

Asthma is a common chronic inflammatory respiratory disease, which is characterized by chronic airway inflammation, Bronchial Hyperresponsiveness (BHR) and airway remodeling. The prevalence of asthma is high in developed countries and there is a concern that its prevalence is still rising in both developed and developing countries [1]. It is widely accepted that asthma is a complex polygenic disease whose pathogenesis involves complex interactions of environmental and genetic factors [2,3]. In the past decades, much effort has been made to explore the susceptible genes of asthma.

The Plasminogen Activator Inhibitor *(PAI)-1*, a 50 kD glycoprotein, belongs to the SERPIN family, which is abbreviated from the serine protease inhibitor. *PAI-1* is the key inhibitor of the fibrinolytic system by hindering the activation of plasminogen and is known to play an essential role in tissue remodeling [4]. *PAI-1* might play an important role in the pathogenesis of asthma [4]. For instance, Kowal, et al. and Xiao, et al. have reported that there are elevated *PAI-1* levels in the induced sputum or plasma of patients with asthma in comparison with that of healthy controls [5,6], and the plasma *PAI-1* levels of asthmatics were pronouncedly up-regulated during allergen challenge [6]. A large number of mast cells, a predominant effector cell of asthma, expressing high level of *PAI-1* were found in the lung tissue of severe asthmatics [7].

A polymorphism at position -675 in the 5' terminal promoter region of the *PAI-1* gene, consisting of two alleles 4G and 5G (*PAI-1* -675 4G/5G, rs1799889), has been described to regulate transcription of the *PAI-1* gene. For example, Dawson, et al. and Kowal, et al. have reported that the plasma levels of *PAI-1* are higher in individuals with

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the 4G4G genotype than in those with the 5G5G genotype, whereas the 4G5G genotype has intermediate values [6,8]. Since Cho, et al. demonstrated that the *PAI-1* 4G allele is preferentially transmitted to asthmatic children based on the transmission disequilibrium test in nuclear families from the UK [9], several case-control studies have investigated the association between the *PAI-1* 4G/5G polymorphism and asthma risk [10-18]. However, the results of these studies were inconsistent and inconclusive. Because a single study may have low power to detect the effect of polymorphism, it is necessary to carry out a meta-analysis to summarize the effect size of *PAI-1* 4G/5G polymorphism on asthma risk. To date, one meta-analysis of association of this polymorphism with asthma risk has been reported [19], however, the results needed further evaluation for the following reasons: firstly, the included studies were not strictly checked in accordance with their inclusion criteria and some overlapped studies were included into the meta-analysis more than once; secondly, the previous meta-analysis was performed using a classical meta-analysis method. Considering a meta-analysis of genetic polymorphism association studies involving multiple comparisons with a classical method, this might increase the risk of type I error. Thirdly, one new case-control study concerning this polymorphism and asthma risk has been reported since the meta-analysis was published.

Based on above analysis, an updated meta-analysis was performed to summarize reported case-control studies concerning the *PAI-1* -675 4G/5G polymorphism and asthma risk in all ethnic populations according to the framework for conducting a meta-analysis of molecular association studies [20]. To overcome the limitation of the classical meta-analysis involving multiple comparisons in genetic association studies, a logistic-regression based meta-analysis of genetic association case-control studies was applied to calculate the Odds Ratio (OR) and 95% Confidence Interval (CI) for *PAI-1* -675 4G4G versus (*vs.*) 5G5G ($OR_{4G4G\ vs.\ 5G5G}$) and 4G5G *vs.* 5G5G ($OR_{4G5G\ vs.\ 5G5G}$) and to decipher the most plausible genetic action model [21].

Methods

Search strategy and inclusion criteria

A systematic literature search was carried out in Medline, Embase, Wanfang, Weipu and Chinese National Knowledge Infrastructure (CNKI) to indentify studies concerning the association between the *PAI-1* polymorphism and asthma susceptibility. The following search terms were used: "asthma or asthmatic" in combination with "plasminogen activator inhitor-1 or *PAI-1* or SERPIN-1". We reviewed all related studies published before October 1, 2016.

The studies which meet the following criteria were incorporated into this meta-analysis: (1) the paper should include asthma risk and *PAI-1* 4G/5G polymorphism; (2) the article should be published in English or Chinese; (3) only case-control or cohort studies were considered, however, the study design should not be a family-based association or sibling pairs; (4) the study should clearly report the frequencies of each genotype; (5) when there were multiple publications from the same group, only the most recent or the publication with more complete information was included in the analysis.

Data extraction

The following information was extracted from each study: the name of the first author, publication year, country of origin, ethnicity and age of subjects, sample size and asthma definition and frequencies of each genotype.

Statistical analysis

The effect size of the *PAI-1* -675 4G/5G polymorphism on asthma risk was evaluated using OR with corresponding 95% CI. Firstly, the 4G and 5G alleles of *PAI-1* 4G/5G promoter polymorphism were compared. Then the risks of a dominant model (4G4G+4G5G *vs.* 5G5G) and a recessive model (4G4G *vs.* 4G5G+5G5G) were estimated. Data were pooled using a fixed-effect model when there was no significant heterogeneity, otherwise a random-effect model (DerSimonian and Laird method) was used [22]. The statistical significance of summary ORs was analyzed by the Z test. A chi-square-based Cochran's Q statistic and index of inconsistency (I^2) were employed to assess heterogeneity among studies [23].

To calculate ORs for 4G4G *vs.* 5G5G genotypes and 4G5G *vs.* 5G5G genotypes, which involve multiple comparisons if using the classical meta-analysis method, a novel logistic-regression based meta-analysis of case-control genetic association studies was adopted [21]. It was reported that this methodology could avoid multiple comparisons and give the most plausible genetic model based on statistical results rather than empirical observations. The estimation algorisms are as follows: $OR_{4G4G\ vs.\ 5G5G}$ (OR1) and $OR_{4G5G\ vs.\ 5G5G}$ (OR2) are calculated using the logic-regression-based method and then compared, if OR1=OR2=1, no statistically significant association was indicated; if OR1>1 and OR2=1 (the difference between OR1 and OR2 are statistically significant), then a recessive genetic model is proposed; if OR1>OR2>1 (statistically significantly), then a co-dominant model is suggested; if OR1=OR2>1, then a dominant model is indicated.

Deviations from Hardy-Weinberg Equilibrium (HWE) of the genotype distribution of each control group were assessed by Pearson's chi-squared test. Publication bias was examined using Egger's regression test and Begg's rank correlation method [24,25]. All statistical analyses were performed using STATA of version 10.1 (STATA Corporation, College Station, Texas, USA). All tests were two-sided, and a *P* value of less than 0.05 was considered to be statistically significant, with the exception of heterogeneity tests where a *P* value less than 0.10 and I^2 value of more than 50.0% were used.

Results

Characteristics of studies included in the meta-analysis

A total of 57 articles were identified after the initial search, including 46 papers written in English and 11 in Chinese. Based on the abstract of each article, 11 studies were enrolled for full-text review. After reading the full texts, three studies were excluded from the meta-analysis for the following reasons: one for repeated publication [12], one for a family-based association study design [9] and one for being unrelated to asthma risk and *PAI-1* 4G/5G polymorphism [26]. Accordingly, eight case-control studies were summarized in this meta-analysis, including 1551 asthmatics and 2339 controls [10,11,13-18]. Among all studies, 6 were conducted in Caucasians [10,13-15,17,18] and 2 were performed in Asians [11,16]. Six studies were conducted in adults [10,11,13,14,16,17] and

Table 1: Characteristics of the eight case-control studies included in the meta-analysis.

First author	Year	Country	Ethnicity	Case age (year)	Control age (year)	Asthmatic category	Asthma definition
Buckova D [10]	2002	Czech	Caucasian	26.9±12.8	32.6±10.4	Atopic	Questionnaire with physician diagnosed asthma
Hizawa N [11]	2006	Japan	Asian	45 (16-81)	32 (18-72)	Mixed	Asthma diagnosed by a physician
Kowal K [13]	2008	Poland	Caucasian	25 (23-26)	24 (23-26)	Atopic	Guidelines of the Global Initiative for Asthma
Cosan D [14]	2009	Turkey	Caucasian	42.8±1.05	41.8±1.90	Mixed	American Thoracic Society
Ozbek OY [15]	2009	Turkey	Caucasian	9.47±2.79	10.80±3.30	NA	American Thoracic Society
Zhang XY [16]	2009	China	Asian	50±15	47±15	NA	Chinese asthma diagnosis criteria (2003)
Dijkstra A [17]	2011	Holland	Caucasian	50 (35-75)	52 (35–79)	NA	Published algorithm [35]
Bora E [18]	2012	Turkey	Caucasian	9.24±2.92	10.84±3.15	Mixed	Guidelines of the Global Initiative for Asthma

Table 2: *PAI-1* -675 4G/5G polymorphism genotype and allele frequencies among asthmatics and controls.

Studies	Case				Control				Case		Control		HWE	
	No.	5G5G	5G4G	4G4G	No.	5G5G	5G4G	4G4G	5G	4G	5G	4G	χ^2	*P*
Overall														
Buckova D [10]	159	27	75	57	186	50	83	53	129	189	183	189	2.414	0.143
Hizawa N [11]	374	49	194	131	374	59	185	130	292	456	303	445	0.259	0.611
Kowal K [13]	372	38	154	180	160	43	70	47	230	514	156	164	2.478	0.115
Cosan D [14]	98	29	43	26	67	19	29	19	101	95	67	67	1.209	0.272
Ozbek Y [15]	106	23	39	44	83	27	41	15	85	127	95	71	0.007	0.934
Zhang XY [16]	99	13	49	37	101	27	46	28	75	123	100	102	0.800	0.371
Dijkstra A [17]	241	54	117	70	1267	275	627	365	225	257	1177	1357	0.035	0.852
Bora E [18]	102	15	63	24	101	37	43	21	93	111	117	85	1.619	0.203
Total	1551	248	734	569	2339	537	1124	678	1230	1872	2198	2480	2.931	0.087
Atopic asthma														
BuckovaD [10]	159	27	75	57	186	50	83	53	129	189	183	189	2.414	0.143
Kowal K [13]	372	38	154	180	160	43	70	47	230	514	156	164	2.478	0.115
Cosan D [14]	19	5	9	5	67	19	29	19	19	19	67	67	1.209	0.272
Bora E [18]	67	10	40	17	101	37	43	21	60	74	117	85	1.619	0.203
Total	617	70	278	259	514	149	225	140	438	796	523	505	7.935	0.005
Non-atopic asthma														
Cosan D [14]	79	24	34	21	67	19	29	19	72	76	67	67	1.209	0.272
Bora E [18]	35	5	23	7	101	37	43	21	33	37	117	85	1.619	0.203
Total	114	29	57	28	168	56	72	40	105	113	184	152	3.062	0.080

HWE: Hardy-Weinberg Equilibrium

2 were performed in children [15,18]. Four studies involved atopic asthmatics [10,13,14,18] and 2 studies clearly reported non-atopic asthmatics [14,18]. The characteristics of the included studies are listed in (Table 1) and the detailed allele and genotype frequencies of the 4G/5G polymorphism of *PAI-1* in each study are shown in (Table 2). The genotype frequency distributions of control groups were all in consistent with HWE (Table 2).

Heterogeneity test

(Table 3) shows the relationship between the *PAI-1* -675 4G/5G polymorphism and asthma risk. The heterogeneity of *PAI-1* 4G/5G polymorphism: 4G versus 5G (allele), 4G4G+4G5G *vs.* 5G5G (dominant model), and 4G4G *vs.* 4G5G+5G5G (recessive model), were analyzed in eight case-control studies. The results indicate that both the dominant and recessive comparisons in Asians, all comparisons in atopic asthmatics, allele and recessive model comparisons in non-atopic asthmatics and allele and dominant model comparisons in childhood asthmatics had no significant heterogeneity, therefore those ORs were calculated with a fixed-effect model. A Random-effect model was used to examine the other ORs.

Genetic model decipherment

Table 4 shows the ORs for *PAI-1* -675 4G4G *vs.* 5G5G and 4G5G *vs.* 5G5G based on a logistic-regression method and genetic model decipherment results. The heterogeneity of genetic effect *i.e.* OR and genetic model *i.e.* the inferred dominant, co-dominant or recessive model is also listed in (Table 4). Our results indicated that the *PAI-1* 675 4G/5G polymorphism was associated with asthma

Table 3: Summary odds ratios of the association between *PAI-1* -675 4G/5G polymorphism and asthma risk.

Comparisons	Sample size	No. of studies	Hypothesis test		Heterogeneity test		Publication bias test (*P*)	
	Case/control		OR (95% CI)	*P*	χ^2 (df)	*P*	Begg' test	Egger'test
Overall								
4G *vs.* 5G	3102/4678	8	1.396 (1.108-1.760)	0.005	32.97 (7)	<0.001	0.368	0.279
4G4G *vs.* 4G5G+5G5G	1551/2339	8	1.394 (1.047-1.856)	0.023	21.07 (7)	0.004	0.368	0.252
4G4G+4G5G *vs.* 5G5G	1551/2339	8	1.716 (1.190-2.474)	0.004	26.78 (7)	<0.001	0.548	0.291
Caucasians								
4G *vs.* 5G	2156/3728	6	1.445 (1.068-1.954)	0.017	27.75 (5)	<0.001	1.000	0.559
4G4G *vs.* 4G5G+5G5G	1078/1864	6	1.479 (1.015-2.156)	0.041	17.44 (5)	0.004	1.000	0.524
4G4G+4G5G *vs.* 5G5G	1078/1864	6	1.749 (1.084-2.823)	0.078	24.25 (5)	<0.001	0.806	0.552
Asians								
4G *vs.* 5G	946/950	2	1.261 (0.846-1.879)	0.255	3.26 (1)	0.071	1.000	NA
4G4G *vs.* 4G5G+5G5G	473/475	2	1.104 (0.844-1.444)	0.470	1.59 (1)	0.207	1.000	NA
4G4G+4G5G *vs.* 5G5G	473/475	2	1.456 (1.019-2.081)	0.039	2.41 (1)	0.120	1.000	NA
Atopic asthma								
4G *vs.* 5G	1234/1028	4	1.705 (1.428-2.035)	<0.001	6.12 (3)	0.106	0.308	0.342
4G4G *vs.* 4G5G+5G5G	617/514	4	1.685 (1.288-2.204)	<0.001	4.33 (3)	0.228	0.308	0.236
4G4G+4G5G *vs.* 5G5G	617/514	4	2.436 (1.783-3.328)	<0.001	4.96 (3)	0.175	0.734	0.569
Non-atopic asthma								
4G *vs.* 5G	228/336	2	1.252 (0.880-1.780)	0.211	0.96 (1)	0.326	1.000	NA
4G4G *vs.* 4G5G+5G5G	114/168	2	0.928 (0.520-1.658)	0.802	<0.01 (1)	0.948	1.000	NA
4G4G+4G5G *vs.* 5G5G	114/168	2	1.682 (0.454-6.235)	0.437	4.40 (1)	0.036	1.000	NA
Adulthood asthma								
4G *vs.* 5G	2686/4310	6	1.297 (0.998-1.686)	0.052	26.56 (5)	<0.001	0.452	0.476
4G4G *vs.* 4G5G+5G5G	1343/2155	6	1.289 (0.967-1.716)	0.083	13.80 (5)	0.017	0.452	0.574
4G4G+4G5G *vs.* 5G5G	1343/2155	6	1.558 (1.028-2.360)	0.037	21.01 (5)	0.001	0.452	0.351
Childhood asthma								
4G *vs.* 5G	416/368	2	1.804 (1.357-2.396)	<0.001	0.46 (1)	0.499	1.000	NA
4G4G *vs.* 4G5G+5G5G	208/184	2	1.937 (0.720-5.209)	0.190	4.34 (1)	0.037	1.000	NA
4G4G+4G5G *vs.* 5G5G	208/184	2	2.380 (1.486-3.811)	<0.001	1.86 (1)	0.172	1.000	NA

OR: Odds Ratio; CI: Confidence Interval; df: degree of freedom

risk in the overall population in a dominant genetic model. When stratified analyses based on ethnicity, age and atopic status, the data suggested that the *PAI-1* -675 4G/5G polymorphism might be linked with asthma in a co-dominant model in Caucasians and atopic populations; the polymorphism might be complicated in asthma risk in a dominant model in Asian, children and adult populations. Our results also indicated that the *PAI-1* 4G/5G polymorphism might not be associated with non-atopic asthma risk.

Quantitative data synthesis

Table 3 lists the summary ORs of the *PAI-1* 4G/5G polymorphism in the form of allele (4G *vs.* 5G), recessive (4G4G *vs.* 4G5G+5G5G) and dominant (4G4G+5G5G *vs.* 5G5G) genetic model in overall and various stratified populations. Our results revealed that the *PAI-1* -675 4G4G or 4G5G carriers have 71.6% increased risk of asthma compared with 5G5G homozygote in the overall population [OR (95% CI)=1.716 (1.190-2.474)]. As illustrated in (Figure 1), the 4G variant was associated with elevated risk of asthma in both Caucasians and Asians, with OR (95% CI)=1.749 (1.084-2.823) and 1.456 (1.019-2.081), respectively. When stratified analysis was conducted by atopic status of asthmatic patients, we observed that the 4G allele was correlated with increased risk of atopic asthma with OR (95% CI) = 2.436 (1.783-3.328). Our data also indicated that the *PAI-1* -675 4G variant was involved in increased risk of asthma in populations of both children and adults, as shown in (Figure 2) and (Table 4).

Publication bias diagnosis

Publication bias in this study was assessed by Begg's rank correlation test and Egger's regression method. As shown in (Table 4), the results of these two tests both indicated that publication bias in the current meta-analysis was not statistically significant (P>0.05).

Discussion

Due to the important role of *PAI-1* in the pathogenesis of asthma, many studies have investigated the association between polymorphisms in the *PAI-1* gene and asthma risk. To address

Table 4: Summary Odds ratios of 4G4G *vs.* 5G5G and 4G5G *vs.* 5G5G comparisons and genetic model decipherment results.

Group Sample size (case/control)	OR	Logistic-regression		Heterogeneity test						Genetic model test		Genetic model selection
				Genetic effect			Genetic model					
		OR(95% CI)	*P*	χ^2 (df)	*P*	I^2	χ^2 (df)	*P*		χ^2	*P*	
Overall 1551/2339	OR1	1.888 (1.337-2.666)	<0.001	39.987(14)	<0.001	0.650	13.866(7)	<0.001		3.544	0.060	Dominant
	OR2	1.520 (1.196-1.932)	0.001									
Asians 473/475	OR1	1.475 (0.996-2.185)	0.052	2.909(2)	0.233	0.313	0.499(1)	0.480		0.006	0.941	Dominant
	OR2	1.459 (1.004-2.120)	0.047									
Caucasians 1078/1864	OR1	1.986 (1.311-3.009)	0.001	35.528(10)	<0.001	0.719	11.957(5)	0.035		4.187	0.041	Co-dominant
	OR2	1.527 (1.137-2.050)	0.005									
Atopic 617/514	OR1	2.911 (2.038-4.159)	<0.001	8.161(6)	0.227	0.265	3.393(3)	0.335		3.893	0.049	Co-dominant
	OR2	2.187 (1.560-3.066)	<0.001									
Non-atopic 114/168	OR1	1.248 (0.628-2.484)	0.527	4.654(2)	0.570	0.098	0.427(1)	0.513		0.692	0.405	No association
	OR2	1.628 (0.899-2.905)	0.101									
Adulthood 1343/2155	OR1	1.669 (1.119-2.490)	0.012	25.930(10)	0.004	0.614	5.687(5)	0.338		1.777	0.183	Dominant
	OR2	1.420 (1.080-1.868)	0.012									
Childhood 208/184	OR1	3.097 (1.627-5.893)	0.001	9.253(2)	0.010	0.784	7.054(4)	0.008		0.705	0.401	Dominant
	OR2	2.018 (0.939-4.336)	0.072									

OR: Odds Ratio; OR1: Odds Ratio for 4G4G versus 5G5G comparison; OR2: Odds Ratio for 4G5G versus 5G5G comparison; df: degree of freedom.

the inconsistent results among those studies, a meta-analysis was conducted using a standard procedure of meta-analysis of genetic association studies advocated by Thakkinstian, et al. [20]. Our results indicated that the *PAI-1* -675 4G/5G polymorphism was associated with increased asthma risk in the overall population in a dominant genetic model. When stratified analysis was performed based on ethnicity, age and atopic status of asthmatic patients, we observed that the *PAI-1* -675 4G/5G polymorphism was associated with elevated asthma risk in both Asians and Caucasians. However, the genetic model in these two types of populations might be different, and a co-dominant genetic model in Caucasians and a dominant genetic model in Asians were indicated, respectively. Our results also suggested that the *PAI-1* -675 4G/5G polymorphism was associated with enhanced atopic asthma risk in a co-dominant genetic model, with OR (95% CI) for 4G4G *vs.* 5G5G and 4G5G *vs.* 5G5G being equal to 2.911 (2.038-4.159) and 2.187 (1.560-3.066), respectively, using logistic-regression-based meta-analysis method. The difference between the two ORs was statistically significant, indicating a dose-response relationship effect of the *PAI-1* -675 4G/5G polymorphism on atopic asthma risk. With respect to the stratified analysis by age of asthmatic patients, our results showed that the *PAI-1* -675 4G/5G polymorphism was associated with increased risk of asthma in populations of both children and adults in a dominant genetic model.

In general, the findings of our study were similar to that of Nie, et al. [19] although several discrepancies also occur. Firstly, we observed that the *PAI-1* -675 4G/5G polymorphism is associated with increased asthma risk in Caucasians which was not found in the study of Nie, et al. This might be due to a different ethnic classification. In our study, we define Turkish subjects as Caucasian referring to other well-conducted meta-analyses [27,28]. Secondly, significant associations of the *PAI-1* 4G/5G polymorphism with elevated asthma risk were seen in both adolescent and adult populations; however Nie, et al. reported no significant association of this polymorphism with adolescent asthma risk [19]. Our analysis showed several advantages compared to the previous meta-analysis [19]: (1) excluding overlapped studies from the analysis; (2) including new publications; (3) overcoming the limitation of classical meta-analysis of molecular genetic studies involving multiple comparisons, reducing the risk of

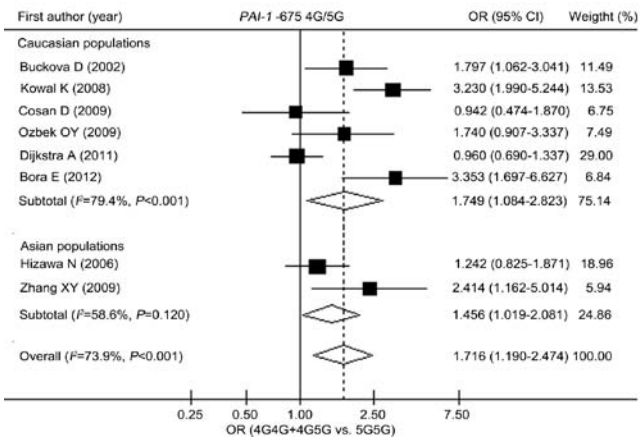

Figure 1: Overall odds ratios from the meta-analysis and odds ratios from individual studies for the association between PAI-1 -675 4G/5G polymorphism and risk of asthma (stratified by ethnicity). 95% CI: 95% Confidence Interval; OR: Odds Ratio.

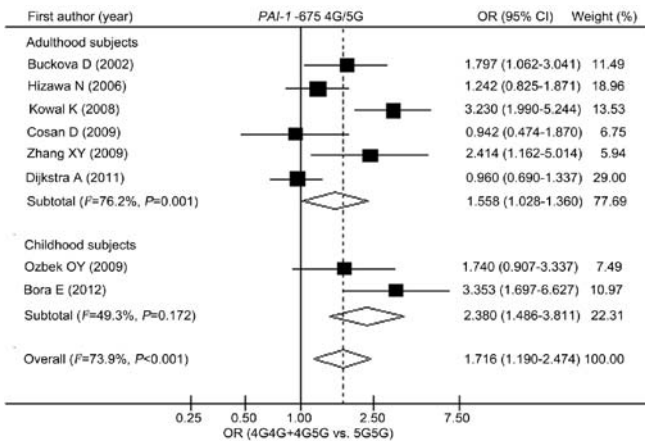

Figure 2: Overall odds ratios from the meta-analysis and odds ratios from individual studies for the association between PAI-1 -675 4G/5G polymorphism and risk of asthma (stratified by age). 95% CI: 95% Confidence Interval; OR: Odds Ratio.

type I error; (4) giving the most plausible genetic model based on statistical analysis rather than empirical observation. Thus the result of our meta-analysis is more reliable and comprehensive compared with the previous one.

There are several lines of evidence suggesting the involvement of the *PAI-1* -675 4G/5G polymorphism in the pathogenesis of asthma. For instance, in the stimulated human MC line, Ma, et al. demonstrated that the *PAI-1* -675 4G allele has higher promoter activity by binding to the upstream stimulatory factor 1 with greater affinity compared with the 5G allele [29]. Kowal, et al. reported that in allergic asthma patients the *PAI-1* gene -675 4G allele corresponded to higher increase in plasma *PAI-1* levels and strongly correlated with BHR compared with the 5G allele [6]. The findings of our meta-analysis lend supports to the experimental evidence that the *PAI-1* gene -675 4G allele is associated with higher expression levels of *PAI-1* protein [6,29] and the coagulation system such as fibrin was involved in the pathogenesis of asthma [30,31].

It has been reported that IL-13 promotes the deposition of coagulation proteins such as fibrinogen and fibrin on the airway surface [31]. Inflammatory cytokines, in particular TNF-alpha and TGF-beta1, activate the *PAI-1* gene transcription [4]. Our previous and other meta-analyses indicated that certain polymorphisms in those genes were associated with susceptibility to asthma [32-34]. In combination with the results of our present study, future studies to clarify the gene-gene interaction among these genes would be of great significance.

There were several limitations, which should be taken into account when interpreting the results of our meta-analysis. Firstly, summary ORs were derived from heterogeneous individual studies, albeit a random-effect model was used to combine data. Subgroup analysis according to ethnicity, heterogeneity was absent in Asians, indicating that ethnicity is a source of heterogeneity. Secondly, all incorporated studies were published in Chinese and English from selected databases, thus some related studies written in other languages or unpublished data might be missing. Thirdly, all existing studies were performed in Caucasians and Asians. No studies were conducted in Africans, thus the results might not apply to Africans. Fourthly, other stratified factors, such us severity of asthma patients, were not considered in this meta-analysis, because most of the included case-control studies did not provide information on category severity.

Conclusion

This meta-analysis revealed that the *PAI-1* -675 4G/5G polymorphism is associated with increased asthma risk. Further studies should be conducted to ascertain whether the association applies to African populations and to clarify the potential gene-gene interaction such as with *IL13* and *TGF-beta1* or gene-environment interaction in the susceptibility to asthma.

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