

PAI-1 Gene Polymorphism Was Associated with an Increased Risk of Allergic Diseases: Evidence from a Meta-Analysis of 14 Case-Control Studies

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Keywords

PAI-1 · Polymorphism · Allergic diseases · Meta-analysis

Abstract

Introduction: In recent years, many studies have focused on the association between plasminogen activator inhibitor (PAI)-1 gene 4G/5G polymorphism and risk of allergic diseases, but the results have been inconclusive. **Objective:** We conducted this meta-analysis to study the exact relationship between PAI-1 polymorphism and susceptibility to allergic diseases. **Methods:** All eligible studies were determined by an electronic literature search. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of association under all of the models. **Results:** A total of 14 studies involving 2,327 cases and 2,838 controls were included in this meta-analysis. Overall, we found a significant association between PAI-1 polymorphism and risk of allergic diseases (4G/4G + 4G/5G vs. 5G/5G: OR 1.76, 95% CI 1.39–2.22, $p < 0.00001$). In a subgroup analysis by ethnicity, we found a markedly increased risk in Asians (OR 1.62, 95% CI 1.26–2.09, $p = 0.0002$) and Caucasians (OR 1.78, 95% CI 1.26–2.52, $p = 0.001$). In addition, significant associations between PAI-1 polymorphism and risk of allergic diseases were ob-

served in both adults (OR 1.71, 95% CI 1.23–2.38, $p = 0.001$) and children (OR 1.87, 95% CI 1.42–2.46, $p < 0.00001$). In a subgroup analysis by different allergic diseases, a significantly increased risk was found for asthma (OR 1.78, 95% CI 1.33–2.39, $p = 0.001$) but not for rhinitis (OR 1.51, 95% CI 0.79–2.89, $p = 0.22$). **Conclusion:** This meta-analysis demonstrated that PAI-1 gene 4G/5G polymorphism was associated with an increased risk of allergic diseases.

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Introduction

Allergic diseases, most commonly occurring as allergic asthma, allergic rhinitis, atopic conjunctivitis, and allergic dermatitis, are considered to be multifactorial inflammatory diseases [1]. More and more evidence shows that allergic diseases are caused by the interaction of multiple genetic and environmental factors [2, 3]. To date, allergic diseases have become one of the major global health problems [4]. In recent years, many studies have focused on the association between genetic variation and risk of allergic diseases, and the plasminogen activator inhibitor (PAI)-1 gene has been extensively studied.

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Table 1. Characteristics of the 14 case-control studies included in the meta-analysis

First author [ref.]	Year	Country	Ethnicity	Adults/children	Cases, n	Controls, n	Source of controls	Disease type	Disease definition	Genotyping method
Buřková [5]	2002	Czech	Caucasians	Adults	207	186	PB	Other type	Specific IgE or skin prick test	PCR
Pampuch [7]	2006	Poland	Caucasians	Adults	127	89	PB	Asthma	GINA criteria	PCR
Hizawa [6]	2006	Japan	Asians	Adults	374	374	PB	Asthma	Clinical diagnosis	PCR
Kowal [8]	2008	Poland	Caucasians	Adults	372	160	PB	Asthma	GINA criteria	PCR
Ozbek [10]	2009	Turkey	Caucasians	Children	106	83	PB	Asthma	ATS criteria	PCR
Ozbek [10]	2009	Turkey	Caucasians	Children	99	83	PB	Rhinitis	Clinical manifestations	PCR
Cosan [9]	2009	Turkey	Caucasians	Adults	98	67	HB	Asthma	ATS criteria	PCR
Zhang [11]	2009	China	Asians	Adults	99	101	PB	Asthma	Chinese asthma diagnosis criteria	PCR
Dijkstra [12]	2011	Netherlands	Caucasians	Adults	241	1,169	PB	Asthma	Lung function, AHR and a symptom questionnaire	TaqMan
Bora [13]	2013	Turkey	Caucasians	Children	102	101	HB	Asthma	GINA criteria	PCR
Chai [14]	2016	China	Asians	Children	196	173	PB	Asthma	Chinese asthma diagnosis criteria	PCR
Li [15]	2016	China	Asians	Children	77	83	HB	Other type	Dust mites allergy test	PCR
Cao [16]	2017	China	Asians	Adults	80	80	HB	Asthma	Chinese asthma diagnosis criteria	PCR
Lampalo [17]	2018	Croatia	Caucasians	Adults	149	89	PB	Asthma	GINA criteria	TaqMan

PB, population-based controls; HB, hospital-based controls; PCR, polymerase chain reaction; GINA, Global Initiative for Asthma; ATS, American Thoracic Society; AHR, airway hyper-reactivity.

The promoter region of PAI-1 gene is located on human chromosome 7q21.3–q22, and the 4G/5G polymorphism has been confirmed to exist. The 4G/5G polymorphism is a major genetic determinant of plasma PAI-1 levels and has been studied as a potential susceptibility factor for allergic diseases. Several studies have reported that there is a link between PAI-1 gene 4G/5G polymorphism and risk of allergic diseases [5–17], but the results are not uniform. Considering inconsistent results among studies, we conducted a meta-analysis to study the exact relationship between PAI-1 gene variants and allergic diseases.

Methods

Search Strategy

A systematic search was performed in PubMed, Embase, Wanfang Database, China National Knowledge Infrastructure (CNKI) Database, and SinoMed Database to identify all the studies concerning the association between PAI-1 gene polymorphisms and susceptibility to allergic diseases. The following keywords were used: (plasminogen activator inhibitor-1 or PAI-1 or SERPINE 1) and (polymorphism or genetic polymorphism) and (asthma or allergic rhinitis or eczema or atopic dermatitis or urticaria or allergic conjunctivitis). All searched studies and references and other related publications were examined to find other eligible studies.

Inclusion and Exclusion Criteria

The included studies must meet the following requirements: (1) the study assesses the association between 4G/5G polymorphism of PAI-1 gene and risk of allergic diseases; (2) the study uses a case-control design; (3) published data are available for estimating an odds ratio (OR) and 95% confidence interval (CI); and (4) the genotype distribution of the control group must be consistent with the Hardy-Weinberg equilibrium (HWE).

Studies were excluded if one of the following criteria applied: (1) not related to PAI-1 polymorphism or allergic diseases; (2) no

control group in the study; (3) incomplete study data; and (4) reviews and meta-analyses. For overlapping studies, only the study containing the largest number of samples was selected.

Data Extraction

For each eligible study, 2 authors (L.Z. and X.L.) independently extracted the following information: first author's surname, year of publication, country, ethnicity, type of allergic disease, number of cases and controls, source of control group (hospital-based controls or population-based controls), genotyping method, and HWE. If there were any differences, these issues were discussed and evaluated with a third author (Q.S.), and a consensus was reached on each study.

Statistical Analysis

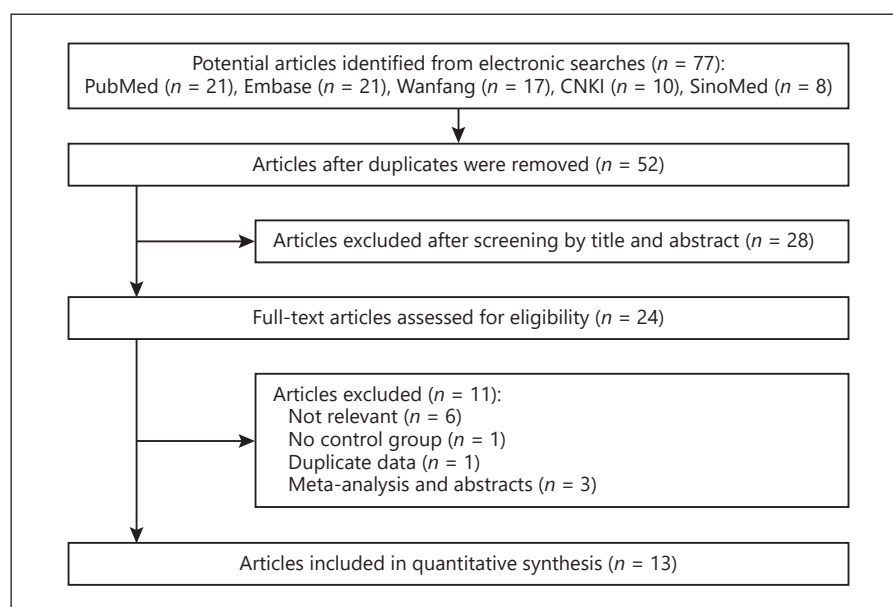
All statistical tests were performed using the Revman 5.3 software (The Nordic Cochrane Centre, Copenhagen, Denmark) and Stata 12.0 software (StataCorp LP, College Station, TX, USA). The OR and 95% CI were used to evaluate the strength of the association between 4G/5G polymorphism and risk of allergic diseases. The combined OR values were used to evaluate the following 5 models: the dominant model (4G/4G + 4G/5G vs. 5G/5G), the recessive model (4G/4G vs. 4G/5G + 5G/5G), the homozygous comparison (4G/4G vs. 5G/5G), the heterozygous comparison (4G/5G vs. 5G/5G), and the allele model (4G vs. 5G). The statistical significance of the OR value was determined by Z test and was considered statistically significant if $p < 0.05$.

The χ^2 -based Q test and I^2 statistics were used to assess the heterogeneity between studies. If $p < 0.10$ or $I^2 > 50\%$, indicating that heterogeneity existed, the calculation of the combined OR value required the random-effects model. Otherwise, the fixed-effects model was used. At the same time, a χ^2 test was used to check whether the genotype distribution of the control group was in accordance with the HWE, and $p > 0.05$ indicated that it was consistent with the HWE. In addition, subgroup analyses were conducted according to ethnicity, age, type of allergic disease, and source of control group. The evaluation of publication bias was completed by Begg's funnel plot [18] and Egger's regression method [19], and $p < 0.05$ indicated significant publication bias.

Table 2. Distribution of the PAI-1 genotype among cases and controls included in this meta-analysis

First author [ref.]	Cases			Controls			HWE <i>p</i> value
	4G/4G	4G/5G	5G/5G	4G/4G	4G/5G	5G/5G	
Bučková [5]	76	99	32	53	83	50	0.14
Pampuch [7]	61	53	13	31	36	22	0.08
Hizawa [6]	131	194	49	130	185	59	0.61
Kowal [8]	180	154	38	47	70	43	0.12
Ozbek [10]	44	39	23	15	41	27	0.93
Ozbek [10]	43	32	24	15	41	27	0.93
Cosan [9]	26	43	29	19	29	19	0.27
Zhang [11]	37	49	13	28	46	27	0.37
Dijkstra [12]	70	117	54	334	580	255	0.91
Bora [13]	24	63	15	21	43	37	0.20
Chai [14]	55	103	38	25	97	51	0.053
Li [15]	33	27	17	17	40	26	0.82
Cao [16]	33	36	11	17	41	22	0.80
Lampalo [17]	35	83	31	26	39	24	0.25

HWE, Hardy-Weinberg equilibrium.

**Fig. 1.** Flow chart of the selection procedure for eligible studies.

Result

Study Characteristics

A total of 77 articles were identified after an initial search. After removing duplicates and reading the abstracts, 53 articles were excluded for not being relevant to allergic diseases or PAI-1 polymorphism. After reading the full texts of the remaining 24 articles, 11 were excluded. One article [10] reported 2 separate case-con-

trol studies. Finally, a total of 14 case-control studies in 13 articles met our inclusion criteria, including 2,327 cases and 2,838 controls. The flow chart on the selection of the studies and the reasons for exclusion is shown in Figure 1.

In these 14 studies, there were 5 Asian studies [6, 11, 14–16] and 9 Caucasian studies [5, 7–10, 12, 13, 17]. Nine studies were conducted in adults [5–9, 11, 12, 16, 17] and 5 in children [10, 13–15]. There were 11 studies about al-

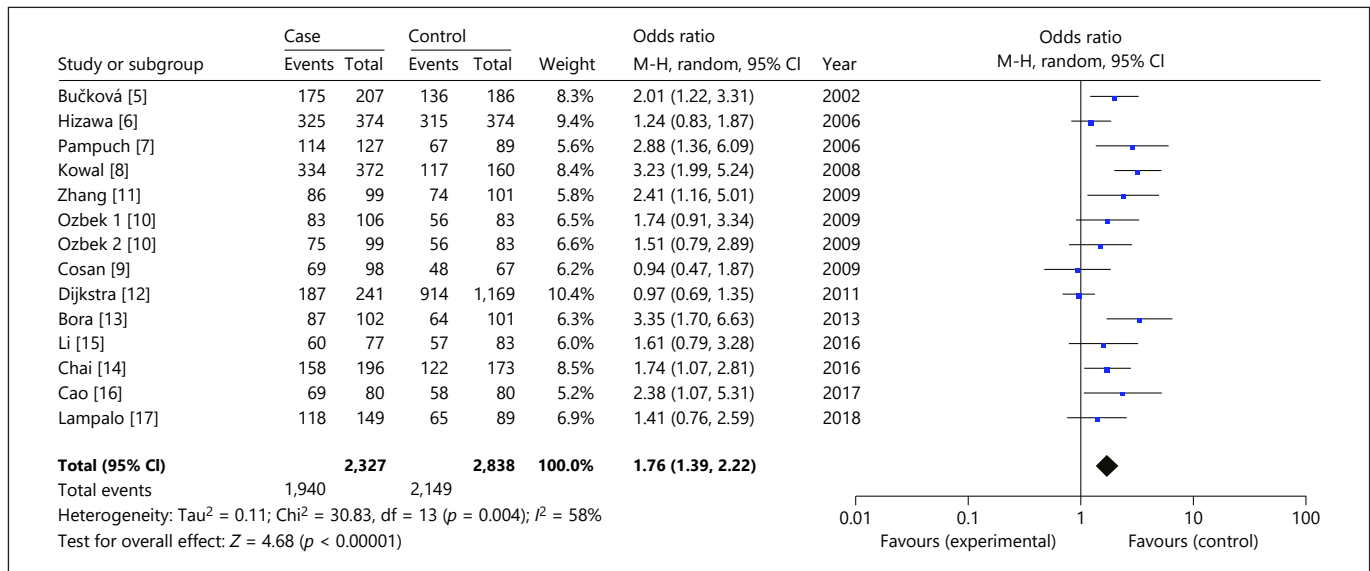


Fig. 2. Forest plot of the association between 4G/5G polymorphism and risk of allergic diseases under the dominant model (4G/4G + 4G/5G vs. 5G/5G).

lergic asthma [6–14, 16, 17], 1 study about allergic rhinitis [10], and 2 studies about other allergic diseases [5, 15] (involving allergic asthma, allergic dermatitis, allergic rhinitis, and urticaria). Regarding the source of the control group, 10 studies were population based [5–8, 10–12, 14, 17] and 4 were hospital based [9, 13, 15, 16]. The main characteristics of each study in this meta-analysis are summarized in Table 1. Genotype distribution data and HWE test results are listed in Table 2.

Quantitative Data Synthesis

Overall Analysis

A total of 2,327 cases and 2,838 controls were included in the meta-analysis. There was significant heterogeneity in the following genetic models (Table 3; dominant model: $I^2 = 58\%$; recessive model: $I^2 = 70\%$; homozygous comparison: $I^2 = 69\%$; allele model: $I^2 = 72\%$), but not in heterozygous comparison ($I^2 = 47\%$). Therefore, for heterozygous comparison, a fixed-effects model was used, and a random-effects model was used for the other genetic models to synthesize the data.

In overall analyses, the OR for the dominant model (4G/4G + 4G/5G vs. 5G/5G) was 1.76 (95% CI 1.39–2.22) and the Z test for overall effect was 4.68 ($p < 0.00001$). This result suggested that individuals who carry the 4G allele may have a 76% increased allergic diseases risk compared with 5G/5G homozygotes (Fig. 2). A significant association was also observed under other models

(4G/4G vs. 4G/5G + 5G/5G: OR 1.63, 95% CI 1.26–2.09, $p = 0.0002$; 4G/4G vs. 5G/5G: OR 2.21, 95% CI 1.60–3.05, $p < 0.00001$; 4G/5G vs. 5G/5G: OR 1.45, 95% CI 1.24–1.69, $p < 0.00001$; 4G allele vs. 5G allele: OR 1.50, 95% CI 1.27–1.77, $p < 0.00001$).

Subgroup Analyses

In subgroup analysis by ethnicity (Fig. 3), significant associations were found among Asians (OR 1.62, 95% CI 1.26–2.09, $p = 0.0002$) and Caucasians (OR 1.78, 95% CI 1.26–2.52, $p = 0.001$) in the dominant model (4G/4G + 4G/5G vs. 5G/5G). The results showed that Asians or Caucasians who carried the 4G allele (4G/4G + 4G/5G) had an increased risk of allergic diseases compared with those individuals with the 5G/5G homozygote. In a stratified analysis by age, significant associations were also found both in adults (OR 1.71, 95% CI 1.23–2.38, $p = 0.001$) and children (OR 1.87, 95% CI 1.42–2.46, $p < 0.00001$), suggesting that adult carriers of the 4G allele may have a 71% increased risk of allergic diseases, and in children, the risk may increase to 87%.

Subgroup analyses were performed by different allergic diseases (Fig. 4). A significantly increased risk was found for asthma (OR 1.78, 95% CI 1.33–2.39, $p = 0.001$) and other types of allergic diseases (OR 1.87, 95% CI 1.24–2.81, $p = 0.003$) but not for rhinitis (OR 1.51, 95% CI 0.79–2.89, $p = 0.22$). In addition, significant associations were found among population-based controls (OR

Table 3. Summary of different comparative results

Study	Sample size, <i>n</i>		Studies, <i>n</i>	Test of association			Model	Heterogeneity	
	case	control		OR (95% CI)	<i>Z</i>	<i>p</i> value		<i>p</i> value	<i>I</i> ² (%)
4G/4G + 4G/5G vs. 5G/5G									
Overall	2,327	2,838	14	1.76 (1.39–2.22)	4.68	<0.00001	R	0.004	58
Asians	826	811	5	1.62 (1.26–2.09)	3.77	0.0002	R	0.45	0
Caucasians	1,501	2,027	9	1.78 (1.26–2.52)	3.26	0.001	R	0.0007	70
Adults	1,747	2,315	9	1.71 (1.23–2.38)	3.19	0.001	R	0.001	69
Children	580	523	5	1.87 (1.42–2.46)	4.43	<0.00001	R	0.47	0
Asthma	1,944	2,486	11	1.78 (1.33–2.39)	3.84	0.001	R	0.0008	67
Rhinitis	99	83	1	1.51 (0.79–2.89)	1.24	0.22	–	–	–
Other type	284	269	2	1.87 (1.24–2.81)	3.01	0.003	R	0.62	0
PB	1,970	1,970	10	1.73 (1.32–2.26)	3.98	<0.0001	R	0.006	61
HB	357	331	4	1.85 (1.06–3.23)	2.18	0.03	R	0.07	58
4G/4G vs. 4G/5G + 5G/5G									
Overall	2,327	2,838	14	1.63 (1.26–2.09)	3.77	0.0002	R	<0.0001	70
Asians	826	811	5	1.84 (1.16–2.93)	2.59	0.010	R	0.005	73
Caucasians	1,501	2,027	9	1.53 (1.10–2.12)	2.54	0.01	R	0.0004	72
Adults	1,747	2,315	9	1.34 (1.04–1.74)	2.22	0.03	R	0.005	64
Children	580	523	5	2.43 (1.67–3.52)	4.67	<0.00001	R	0.16	40
Asthma	1,944	2,486	11	1.49 (1.13–1.96)	2.81	0.005	R	0.0008	67
Rhinitis	99	83	1	3.48 (1.75–6.91)	3.56	0.0004	–	–	–
Other type	284	269	2	1.94 (0.99–3.80)	1.94	0.05	R	0.10	64
PB	1,970	2,507	10	1.61 (1.20–2.16)	3.19	0.001	R	<0.0001	74
HB	357	331	4	1.68 (0.96–2.95)	1.81	0.07	R	0.05	62
4G/4G vs. 5G/5G									
Overall	1,235	1,467	14	2.21 (1.60–3.05)	4.83	<0.00001	R	<0.0001	69
Asians	417	402	5	2.39 (1.47–3.88)	3.50	0.0005	R	0.05	58
Caucasians	818	1,065	9	2.11 (1.35–3.29)	3.30	0.0010	R	<0.0001	75
Adults	919	1,206	9	1.88 (1.23–2.87)	2.94	0.003	R	<0.0001	76
Children	316	261	5	3.07 (2.17–4.33)	6.36	<0.00001	R	1.00	0
Asthma	1,010	1,279	11	2.10 (1.42–3.11)	3.72	0.0002	R	<0.0001	74
Rhinitis	67	42	1	3.23 (1.44–7.21)	2.85	0.004	–	–	–
Other type	158	146	2	2.44 (1.53–3.91)	3.72	0.0002	R	0.59	0
PB	1,047	1,289	10	2.19 (1.49–3.21)	4.02	<0.0001	R	<0.0001	74
HB	188	178	4	2.29 (1.20–4.36)	2.51	0.01	R	0.08	56
4G/5G vs. 5G/5G									
Overall	1,479	2,060	14	1.45 (1.24–1.69)	4.66	<0.00001	F	0.03	47
Asians	537	594	5	1.41 (1.08–1.84)	2.52	0.01	R	0.66	0
Caucasians	942	1,466	9	1.56 (1.12–2.19)	2.60	0.009	R	0.005	64
Adults	1,098	1,630	9	1.56 (1.20–2.05)	3.26	0.001	R	0.06	47
Children	381	430	5	1.40 (0.88–2.22)	1.43	0.15	R	0.05	57
Asthma	1,248	1,793	11	1.59 (1.22–2.07)	3.45	0.0006	R	0.02	53
Rhinitis	56	68	1	0.88 (0.43–1.80)	0.35	0.72	–	–	–
Other type	175	199	2	1.49 (0.85–2.61)	1.40	0.16	R	0.22	33
PB	1,238	1,803	10	1.48 (1.16–1.88)	3.19	0.001	R	0.06	44
HB	241	257	4	1.60 (0.85–3.00)	1.47	0.14	R	0.05	62
4G vs. 5G									
Overall	4,654	5,676	14	1.50 (1.27–1.77)	4.73	<0.00001	R	<0.00001	72
Asians	1,652	1,622	5	1.54 (1.18–2.00)	3.18	0.001	R	0.02	67
Caucasians	3,002	4,054	9	1.48 (1.17–1.86)	3.31	0.0009	R	<0.0001	77
Adults	3,494	4,630	9	1.37 (1.10–1.70)	2.85	0.004	R	<0.0001	77
Children	1,160	1,046	5	1.77 (1.50–2.10)	6.64	<0.00001	R	0.87	0
Asthma	3,888	4,972	11	1.44 (1.18–1.76)	3.64	0.0003	R	<0.0001	76
Rhinitis	198	166	1	1.97 (1.30–3.00)	3.18	0.001	–	–	–
Other type	568	538	2	1.60 (1.26–2.03)	3.84	0.0001	R	0.37	0
PB	3,940	5,014	10	1.48 (1.22–1.81)	3.89	0.0001	R	<0.0001	77
HB	714	662	4	1.55 (1.12–2.16)	2.62	0.009	R	0.07	57

R, random-effects model; F, fixed-effects model; PB, population based; HB, hospital based.

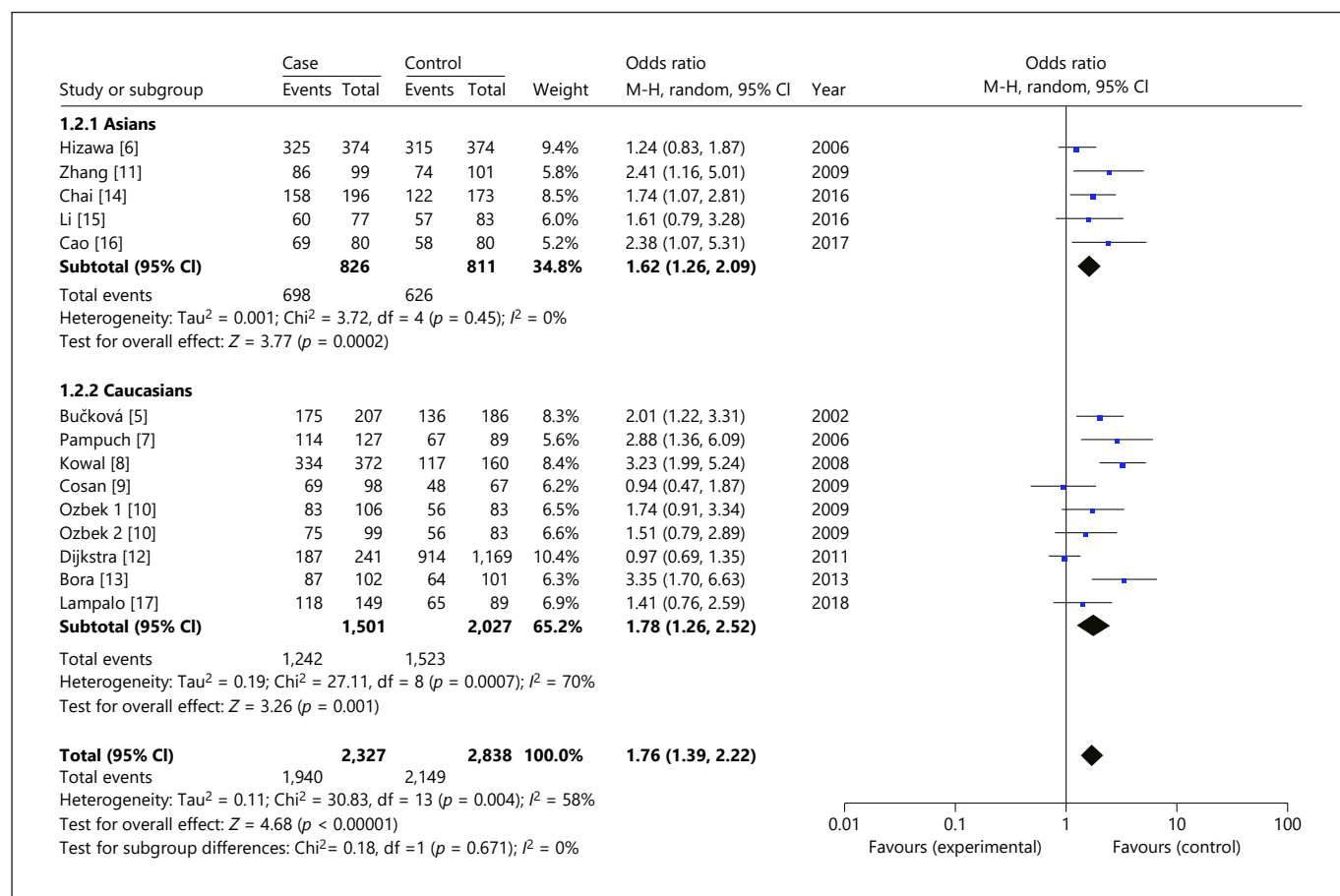


Fig. 3. Forest plot of the association between 4G/5G polymorphism and risk of allergic diseases by ethnicity stratification under the dominant model (4G/4G + 4G/5G vs. 5G/5G).

1.73, 95% CI 1.32–2.26, $p < 0.0001$) and hospital-based controls (OR 1.85, 95% CI 1.06–3.23, $p = 0.03$). It was shown that regardless of whether the source of the control group was population based or hospital based, 4G allele carriers had a markedly increased risk of allergic diseases. The results of the genetic comparisons are listed in Table 3.

Publication Bias

Potential publication bias in this meta-analysis was estimated using Begg's funnel plot and Egger's test. Under the dominant model, the shape of the funnel plot showed a slight asymmetry (Fig. 5). Therefore, an Egger's test was performed to provide statistical evidence of the asymmetry of the funnel plot. The results indicated that the current meta-analysis lacks publication bias ($t = 2.16$, $p = 0.051$).

Discussion

Allergic diseases are complex genetic diseases caused by the interaction of multiple genetic and environmental factors and are associated with increased levels of total serum immunoglobulin E levels and skin prick test reactivity [20, 21]. Due to the obvious increase in the prevalence rate in recent years, allergic diseases are gradually becoming a major global health problem, causing huge economic losses to society. Studies of common genetic variation in the human genome have highlighted the contribution of genetics to the etiology and pathogenesis of allergic diseases. Considering inconsistent results among published studies, we performed this meta-analysis by combining all eligible publications to assess the association between PAI-1 polymorphism and risk of allergic diseases.

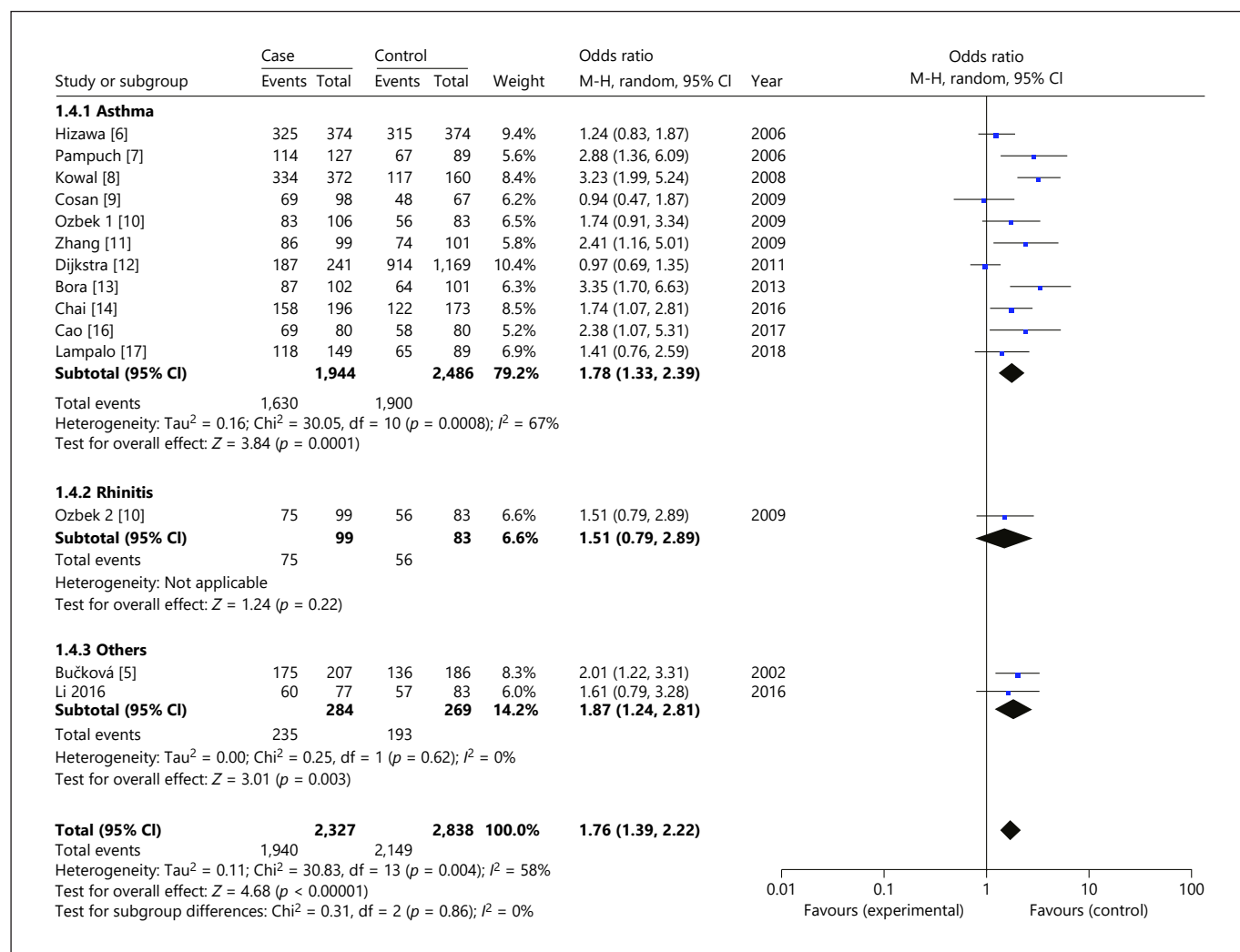


Fig. 4. Forest plot of the association between 4G/5G polymorphism and risk of allergic diseases by stratification according to allergic diseases type under the dominant model (4G/4G + 4G/5G vs. 5G/5G).

A total of 14 studies, including 2,327 cases and 2,838 controls, were enrolled in this meta-analysis to assess the association between PAI-1 gene 4G/5G polymorphism and risk of allergic diseases. The results indicate that PAI-1 gene 4G/5G polymorphism is a significant risk factor for allergic diseases in the overall study populations. In the subgroup analysis by ethnicity, carrying the 4G allele (4G/4G + 4G/5G) was associated with a markedly increased risk for allergic diseases in both Asians and Caucasians. A stratified analysis by age indicated that significant associations were found in adults and children. In addition, a significantly increased risk was found in patients with asthma but not in those with rhinitis. Since only 1 study [10] was associated with allergic rhinitis and the sam-

ple size was small, more studies are needed to reveal the correlation between the 4G allele and allergic rhinitis.

PAI-1 is a glycoprotein that belongs to the serine protease inhibitor superfamily and has a primary function in the regulation of the fibrinolytic enzyme system. The PAI-1 gene has been localized to chromosome 7(q21.3–q22), where a locus related to IgE levels has also been mapped [22], and deletion or insertion of the 4G/5G polymorphism has been found to be correlated with plasma levels of PAI-1. Sejima et al. [23] found that PAI-1 plays an important role in the immune response by changing the balance between Th2 response and Th1 response in a mouse model of allergic rhinitis. A meta-analysis by Nie et al. [24] showed that PAI-1 gene 4G/5G poly-

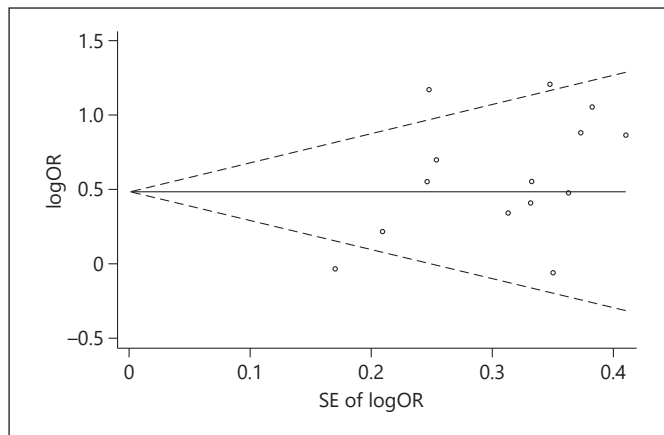


Fig. 5. Begg's funnel plot with pseudo 95% confidence limits for publication bias on an association between 4G/5G polymorphism and risk of allergic diseases under the dominant model (4G/4G + 4G/5G vs. 5G/5G).

morphism is associated with asthma susceptibility. These findings suggest a link between PAI-1 gene and allergic diseases. In recent years, there have been several reports indicating that 4G allele of the 4G/5G polymorphism in the PAI-1 gene is associated with IgE-mediated asthma and allergic diseases [5, 7, 25].

This meta-analysis had several inevitable limitations. First, the ethnicities analyzed included only Caucasians and Asians; whether Americans and Africans have 4G/5G gene is still unknown. Second, only 1 study analyzed allergic rhinitis, and the sample size was small, causing a lack of sufficient reliability in the results. More research is needed to confirm the relationship between allergic rhinitis and the 4G/5G polymorphism. Third, there was sig-

nificant heterogeneity among studies. Fourth, only published research data were included in our analysis, which may lead to publication bias.

To the best of our knowledge, this meta-analysis is the most comprehensive assessment of the relationship between PAI-1 gene 4G/5G polymorphism and susceptibility to allergic diseases. It demonstrated that the PAI-1 gene 4G/5G polymorphism may be used as a susceptibility marker for allergic diseases, providing a basis for future clinical research. However, in the future, well-designed large-scale case-control studies are needed to confirm our findings.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

None.

Author Contributions

L.Z. conceived and designed the experiments, searched the literature, and wrote the manuscript. X.L. and Q.S. searched the literature and extracted data for the meta-analysis. C.H. and B.L. prepared Tables 1–3 and Figures 1–5. X.C. prepared the manuscript and submitted it to publication. All authors read and approved the final manuscript.

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