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REVIEW ARTICLE

Association of family sequence similarity gene 13A gene polymorphism and interstitial lung disease susceptibility: A systematic review and meta-analysis

Yinan Hu[1,2,3,4] | **Zhen Li**[5,6] | **Yanhong Ren**[1,2,3,4] | **Huaping Dai**[1,2,3,4]

[1]National Center for Respiratory Medicine, Beijing, P.R. China

[2]National Clinical Research Center for Respiratory Diseases, Beijing, P.R. China

[3]Institute of Respiratory Medicine, Chinese Academy of Medical Sciences, Beijing, P.R. China

[4]Department of Pulmonary and Critical Care Medicine, Center of Respiratory Medicine, China-Japan Friendship Hospital, Beijing, P.R. China

[5]China-Japan Friendship Hospital, Beijing, P.R. China

[6]Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing, P.R. China

Correspondence
Yanhong Ren and Huaping Dai, National Center for Respiratory Medicine, Beijing, P.R. China.
Email: ryhong7561@sina.com and daihuaping@ccmu.edu.cn

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Abstract

Background: Among present reports, the T/G allelic variation at the rs2609255 locus of the family sequence similarity gene 13A (*FAM13A*) was considerable associated with susceptibility to interstitial lung diseases (ILDs). In this study, we summarized relevant studies and applied a meta-analysis to explore whether the polymorphism of rs2609255 site of the *FAM13A* gene can be utilized to predict susceptibility to idiopathic pulmonary fibrosis (IPF) patients or rheumatoid arthritis-associated interstitial lung disease (RA-ILD) or silicosis patients in different populations for the first time.

Methods: We compared the frequency of G allele on rs2609255 site of *FAM13A* between the control subjects and IPF or RA-ILD or silicosis patients from different races by using meta-analysis. Nine studies were involved in this meta-analysis, including five IPF studies, two RA-ILD studies, and two silicosis studies, and containing 14 subgroups. We conducted separate meta-analyses for different races.

Results: In all individuals, a substantial link between the G allele of the *FAM13A* rs2609255 polymorphism and IPF (OR: 1.47, 95% CI: 1.33–1.63, $p < 0.00001$) was indicated. After dividing by ethnicity, the G allele was illustrated to be considerable correlation with IPF in Asian (OR: 2.63, 95% CI: 1.81–3.81, $p < 0.00001$) and with RA-ILD individuals (OR: 3.27, 95% CI: 1.26–8.49, $p = 0.01$). Conversely, there was no correlation with the G allele and IPF in European individuals (OR: 1.27, 95% CI: 0.89–1.83, $p = 0.13$) or silicosis in Chinese individuals (OR: 1.20, 95% CI: 0.99–1.46, $p = 0.07$).

Conclusion: This is the first meta-analysis that provides evidence that the rs2609255 of *FAM13A* might increase susceptibility to RA-ILD, and IPF especially in Asian but not in European individuals, and not be correlated with silicosis in Chinese individuals, which indicated the differences in susceptibility to disease by race were noteworthy.

Yanhong Ren and Huaping Dai should be considered as joint senior authors.

KEYWORDS

family sequence similarity gene 13A, gene polymorphism, idiopathic pulmonary fibrosis, interstitial lung diseases, meta-analysis, rheumatoid arthritis associated interstitial lung disease, silicosis

1 | INTRODUCTION

A set of diffuse pulmonary parenchymal abnormalities known as interstitial lung diseases (ILDs) include pulmonary fibrosis and inflammation, among which idiopathic pulmonary fibrosis (IPF) characterized as a chronic disease in idiopathic interstitial pneumonia companied with a high mortality rate and rapidly undergoing. ILDs are more common in connective tissue disease-related diseases (Lederer & Martinez, 2018). Although the etiology of IPF and connective tissue disease-associated ILDs is not completely explored, a genetic component plays a role, such as in rheumatoid arthritis (RA) -associated ILDs (RA-ILDs) (Spagnolo et al., 2021; Wijsenbeek et al., 2022). Pneumoconiosis is a kind of ILD with known causes, in China, which defined as the most common occupational disease. According to China's occupational disease report, there were 23,152 increasing cases of occupational pneumoconiosis of China in 2022, accounting for 87.73% of occupational diseases, of which 34% were silicosis. Although the etiology of silicosis is relatively simple, there was heterogeneity in populations with different genetic backgrounds (Leung et al., 2012; Reynolds & Jerome, 2021). The genetic susceptibility factors for IPF and RA-ILDs and silicosis need to be explored and further summarized especially in different races.

Our comprehension of the primary risk factors for ILDs has improved with the introduction of genetic technologies notably genome-wide association studies (GWAS) and next-generation sequencing. While this is occurring, our expertise of the fundamental risk factors for ILDs, such as genetics and single nucleotide polymorphisms (SNPs), has expanded (Velagacherla et al., 2022). In a previous GWAS (Fingerlin et al., 2013) of a non-Hispanic white population comprising 1616 fibrotic idiopathic interstitial pneumonia (IIP) patients and 4683 controls and a repeat group of 876 IIP patients and 1890 controls, seven novel loci were identified that were associated with fibrosis in IIP. Among these loci, the T/G allelic variation at the rs2609255 locus of the family sequence similarity gene 13A (*FAM13A*) located in an intron of the 4q22 chromosome was considerable associated with susceptibility to IIP. In recent years, this finding has also been extended to other ILDs, such as silicosis (Baojun et al., 2018; Wang et al., 2018) and RA-ILD (Higuchi et al., 2023; Jönsson et al., 2022).

Meaningfully, we found that the polymorphism of the G allele at rs2609255 of the *FAM13A* gene has different correlations with IPF, RA-ILD, and silicosis in different populations and races for the first time. Often, the frequencies of gene allele vary considerably across populations, and therefore, race-specific correlation analyses are required to confirm genetic relationships across populations. In this study, for the first time, we summarized relevant studies and applied a meta-analysis to explore whether the polymorphism of the rs2609255 site of the *FAM13A* gene can be utilized to predict susceptibility to IPF and silicosis and RA-ILD in different populations.

2 | METHODS

2.1 | Study design

The protocol of this systematic review and meta-analysis was adopted by following the recommendations of the Preferred Reporting Items for Systematic Review and Meta-analysis Protocol (PRISMA-P) (Page et al., 2021); the details were demonstrated in the checklist (Table S1). In this meta-analysis, PICOS refers to P = the ILD patients; I = *FAM13A* rs2609255 polymorphism; C = people without ILD; O = susceptibility to ILD; and S = case–control studies.

2.2 | Study registration

We followed the Preferred Reporting Items for Systemic Reviews and Meta-Analyses 2020 statement and registered on the International Platform of Registered Systematic Review and Meta-analysis Protocols database on March 1, 2023 (INPLASY202320122). The DOI number is 10.37766/inplasy2023.2.0122.

2.3 | Search strategy

We applied a literature search on the correlation between the rs2609255 polymorphism of the *FAM13A* gene (Gene ID: 10144, Reference: GRCh38 38.1/141) and IPF or ILDs. The Web of Science, PubMed, MEDLINE, EMBASE, CNKI, VIP, and Wanfang databases were employed to search for literature on *FAM13A* gene rs2609255

in IPF or ILD patients in the past 10 years. The following search terms and corresponding medical subject headings (Mesh) were used: "family with sequence similarity 13A," "idiopathic pulmonary fibrosis," "rheumatoid arthritis associated interstitial lung disease," "silicosis," "interstitial lung disease," "connective tissue disease," "rs2609255," the details were illustrated in Table S2. The references in the cited studies were also searched, and Google Scholar was used to search again to ensure that other studies that were not included in MEDLINE or MEDLINE indexed would be covered.

2.4 | Inclusion and exclusion

No limitations on language, ethnicity, or location were placed on our search. Studies were considered whether they fulfilled the requirements: (1) published before March 2023, (2) included primary data, and (3) they supplied enough genetic information about odds ratio (OR). Disregarded if they matched the following requirements: (1) possessed overlapping data and (2) did not provide information on the numbers of mutant and wild-types.

2.5 | Data extraction

Each study's data were gathered to provide the following details: the number of cases and controls, the demographics of the patients, the frequency of genotypes and alleles, and the adherence to the Hardy–Weinberg law.

2.6 | Quality evaluation

The included studies were all nonrandomized controlled studies, and we assessed them applying the Newcastle–Ottawa Scale (NOS) (Stang, 2010), and the details were illustrated in the Table S3. The highest score was 9 stars, which included research population selection, comparability, and exposure results, and studies were assessed as high-quality studies with a score equaling or more than 6 stars. No further ethics approval or patient agreement was required since each result and analysis were based on earlier studies, which had obtained ethics approval.

2.7 | Statistical analysis

We adopted chi-square test to assess the genotype frequencies in Hardy–Weinberg equilibrium (HWE). A meta-analysis was performed employing the following *FAM13A* gene polymorphism models: (1) allelic contrast (G vs. T), (2) homozygous gene (GG vs. TT), (3) recessive gene (GG vs. TT+TG), and (4) dominant gene (GG+TG vs. TT). We performed subgroup analyses of race and disease type to assess the effect of race on disease specificity and calculated the risk rates (RRs), ORs, and 95% CIs. We adopted Cochran's Q test for variation and heterogeneity; I^2 values were adopted to quantify the effect of heterogeneity, ranging from 0% to 100%. For those with heterogeneity <50%, a fixed-effects model was adopted; for those with heterogeneity >50% and $p < 0.10$, a random-effects model was adopted. When studies are homogeneous, the two models are similar; on contrast, the fixed-effects model typically offers narrower confidence intervals than the random-effects model (Higgins et al., 2003). We employed Revman5.3 and GraphPad Prism 9.0 software for all statistical analyses and graphing, and a $p \leq 0.05$ indicated a considerable difference. We also applied funnel plots to detect heterogeneity and publication bias and adopted a sensitivity analysis.

3 | RESULTS

3.1 | Search strategy and studies included

We filtrate 19 papers for full-text review out of the 65 reports we found by computer and manual searches based on their abstract and key words. We excluded 10 studies due to lack of genotype, control number, or polymorphism data. Therefore, nine studies met the inclusion requirement. The specific retrieval process is demonstrated (Figure 1). One of the studies included information for

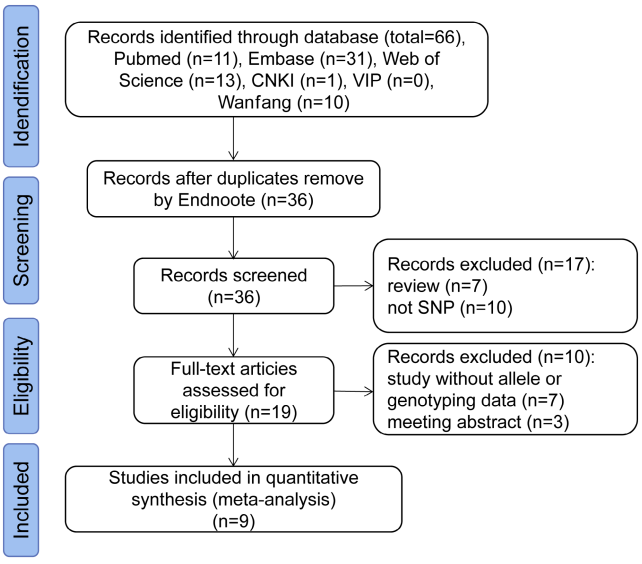

FIGURE 1 Literature screening flow chart.

individuals from four different races (Kishore et al., 2016), while another included information for individuals from two different races (Peljto et al., 2015). In addition, these studies were treated independently. There were two articles related to RA-ILD (Higuchi et al., 2023; Jönsson et al., 2022) and 2 articles related to silicosis (Baojun et al., 2018; Wang et al., 2018). The meta-analysis involved a total of 9 studies and 14 independent analyses of subgroups, including 5 IPF studies involving 7639 controls and 2848 patients and 3 other ILD studies (including 2 RA-ILD study and 2 silicosis studies) involving 1096 patients and 2542 controls. We conducted separate meta-analyses for specific race, including European, Asian, non-Hispanic populations in American and Hispanic white populations. The characteristics of studies are summarized in Table 1. A considerable correlation between the G allele and ILD was demonstrated in Figure 2 among all subjects (OR: 1.81, 95% CI: 1.39–2.34, $p < 0.00001$).

3.2 | The frequency of G allele at the rs2609255 site of the *FAM13A* gene in different ethnic control groups

Table 2 illustrates that the mean frequency was 25.75% of the G allele in the rs2609255 polymorphism in the control subjects. The G allele was highest in Asian controls (52.22%) and lowest in Hispanic white people (14.39%).

3.3 | Meta-analysis of polymorphisms at the rs2609255 site of the *FAM13A* gene and susceptibility to IPF

Figure 2 summarizes the analysis results of the correlation between the rs2609255 site of the *FAM13A* gene and IPF. Across all subjects, there was a considerable correlation between the G allele and IPF (OR: 1.47, 95% CI: 1.33–1.63, $p < 0.00001$) (Figure 3). Furthermore, analysis stratified by race illustrated that in Asians (OR: 2.63, 95% CI: 1.81–3.81, $p < 0.00001$), Hispanic white people (OR: 2.30, 95% CI: 1.42–3.72, $p = 0.0007$), and non-Hispanic white people of American (OR: 1.37, 95% CI: 1.22–1.54, $p = < 0.00001$), the G allele was significantly correlated with the incidence of IPF (Figure 4); in contrast, in Europeans (OR: 1.27, 95% CI: 0.89–1.83, $p = 0.19$), it had no considerable correlation with the incidence of IPF. Furthermore, analysis based on the dominant, recessive, and additive models revealed the similar pattern of *FAM13A* G alleles in Asians and Hispanic white people, suggesting a possible association between the G allele at the *FAM13A* locus rs2609255 and IPF (Figure 5).

3.4 | Meta-analysis of the *FAM13A* rs2609255 polymorphism and susceptibilities of silicosis and RA-ILD

There were only 2 studies related to silicosis, but also the *FAM13A* rs2609255 G allele was not correlated with the incidence of silicosis (OR: 1.20, 95% CI: 0.99–1.46, $p = 0.07$); on contrast, there was a correlation with the two studies on RA-ILD (OR: 3.27, 95% CI: 1.26–8.49, $p = 0.01$) (Figure 6).

3.5 | Heterogeneity and publication bias

A funnel plot demonstrated the correlation between the rs2609255 site of the *FAM13A* gene and ILD and the graph was basically symmetrical (Figure 7). There was no obvious heterogeneity in all of the studies, except for the study of the Korean IPF group and the Japanese group of RA-ILD, which may be related to the small number of subjects as control and the unreasonable definition or selection of the control; however, the G allele of rs2609255 at the *FAM13A* locus was significantly correlated with IPF in Asians, and we adopted a sensitivity analysis; each study was further eliminated for analysis one by one, which did not affect the analysis results (Figure S1).

4 | DISCUSSION

Genetic factor is an important pathogenic element of IPF and other ILDs. As a result, preceding research has concentrated on locating particular genes linked to the disorder. Previously, studies have involved genes related to the development of IPF, including alveolar epithelial damage, such as SFTPC, TERT, MUC5B, and epithelial-mesenchymal transition (EMT), inflammation and so on. Recently, studies have indicated that the T/G allele polymorphism at rs2609255 of the *FAM13A* gene is correlated with the prognosis and susceptibility of IPF (Hirano et al., 2017). In this review and analysis, we summarized studies on the correlation between the G allelic polymorphism at rs2609255 of the FAM13 gene and susceptibility to IPF and silicosis and RA-ILDs for the first time. There was significant correlation between the site G allele and IPF and RA-ILD. However, there was no association between IPF in European individuals and silicosis in Chinese individuals. Besides, the study of Fingerlin (Fingerlin et al., 2013) includes many more IPF patients and controls than the others studies, which may influence on the results obtained; therefore,

TABLE 1 Characteristics of individual studies involved in the meta-analysis.

Study	Year	Country	Ethnicity	Disease	Case		Control		Weight (%)	NOS
					G allele	Total	G allele	Total		
Amit Kishore (Kishore et al., 2016)	2016	UK	Czech Republic	IPF	14	41	24	96	3.90	7
Amit Kishore (Kishore et al., 2016)	2016	UK	Germany	IPF	8	33	24	96	3.10	7
Amit Kishore (Kishore et al., 2016)	2016	UK	Greece	IPF	16	51	24	96	4.30	7
Amit Kishore (Kishore et al., 2016)	2016	UK	France	IPF	48	165	24	96	6.20	7
Anna L. Peijto (Peljto et al., 2015)	2015	USA	Mexican	IPF	34	83	28	111	5.60	8
Anna L. Peijto (Peljto et al., 2015)	2015	USA	Korea	IPF	176	293	28	87	7.10	7
Chihiro Hirano (Hirano et al., 2017)	2017	Japan	Japanese	IPF	40	65	134	310	6.50	8
Ramcés Falfán-Valencia (Guzmán-Vargas et al., 2021)	2021	Mexico	Mexican	IPF	17	93	13	174	4.10	8
Tasha E. Fingerlin (replication) (Fingerlin et al., 2013)	2013	USA	non-Hispanic, white people	IPF	218	780	397	1890	13.30	9
Tasha E. Fingerlin (discovery) (Fingerlin et al., 2013)	2013	USA	non-Hispanic, white people	IPF	324	1244	983	4683	14.20	9
Solbritt Rantapaa-Dahlqvist (Jönsson et al., 2022)	2022	Sweden	Northern Sweden	RA-ILD	20	60	245	1292	6.40	8
Takashi Higuchi (Higuchi et al., 2023)	2023	Japan	Japanese	RA-ILD	201	208	353	420	3.90	6
Minjie Chu (Wang et al., 2018)	2018	China	Chinese	Silicosis	82	177	86	201	8.80	8
Baojun Yuan (Baojun et al., 2018)	2018	China	Chinese	Silicosis	299	651	259	629	12.70	8
Total					1497	3944	2622	10,181	100.00	

Abbreviations: IPF, idiopathic pulmonary fibrosis; NOS, Newcastle–Ottawa Scale; RA-ILD, rheumatoid arthritis associated interstitial lung disease; UK, United Kingdom; USA, United States of America.

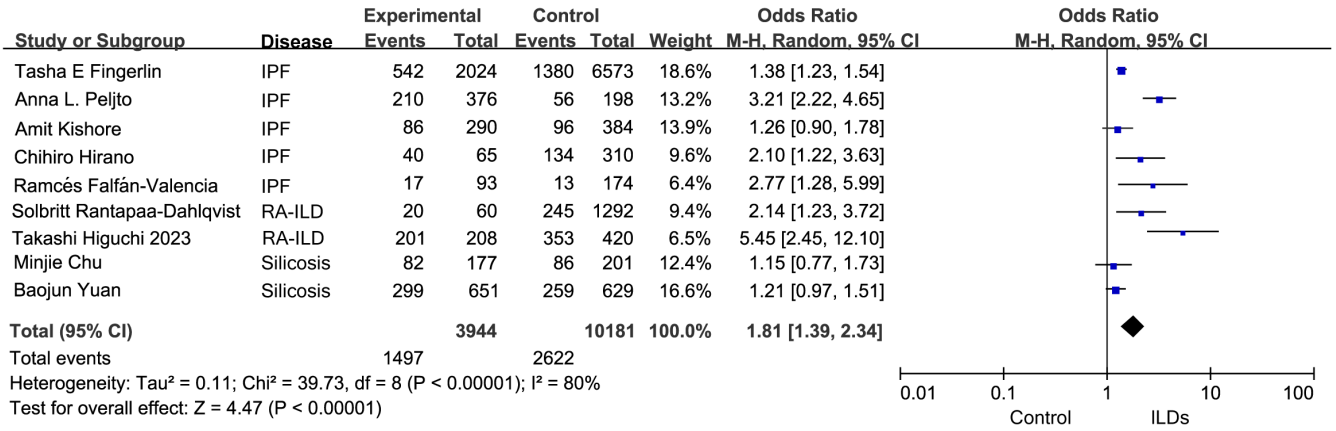

FIGURE 2 Forest plot of the correlation of the *FAM13A* rs2609255 polymorphism and the risk of ILDs with a meta-analysis (G vs. T). The figure demonstrated the studies as filled squares and the solid line as the 95% confidence interval of the difference. The diamond shape illustrated the pooled estimate and uncertainty for the combined effect. The vertical line indicates the study shows no correlation between the *FAM13A* rs2609255 polymorphism and the interstitial lung disease susceptibility (OR = 1). Furthermore, the result that confidence interval includes 1 shows no evidence of difference between the polymorphism and disease susceptibility, and if the confidence interval more than 1 indicates that there was correlation between the polymorphism and disease susceptibility.

TABLE 2 G allele prevalence of the *FAM13A* rs2609255 polymorphism.

		Numbers		G allele (%)	
Ethnicity	**Numbers**	**ILD**	**Control**	**ILD**	**Control**
European	5	350	1676	30.29	20.35
Asian	5	1394	1647	57.25	52.22
Hispanic	2	176	285	28.98	14.39
Non-Hispanic white people in America	2	2024	6573	26.78	20.99
Total	14	3944	10,181	37.96	25.75

Abbreviation: ILD, interstitial lung disease.

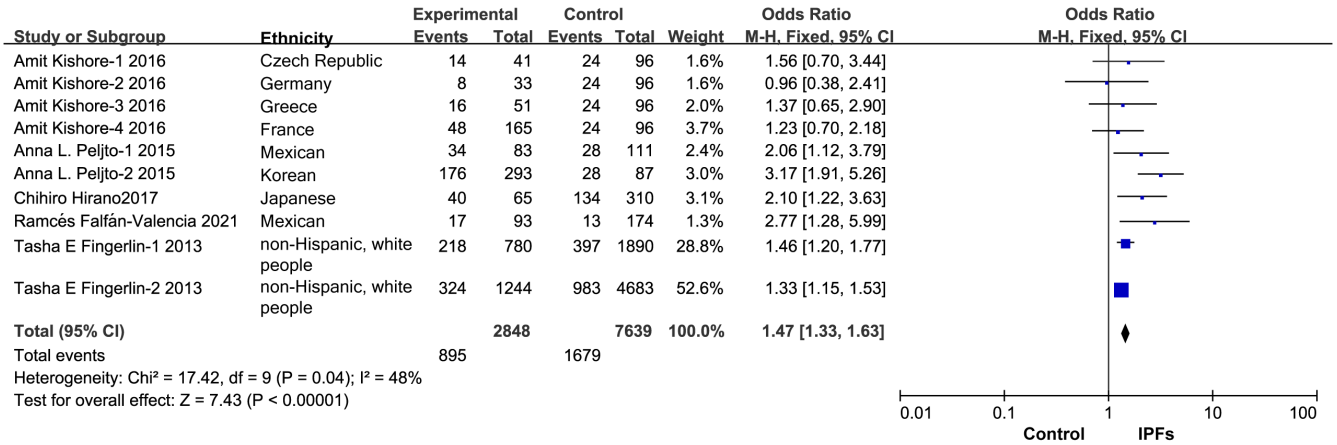

FIGURE 3 Forest plot of the correlation of the *FAM13A* rs2609255 polymorphism and the risk of IPFs with a meta-analysis (G vs. T). The figure demonstrated the studies as filled squares and the solid line as the 95% CI of the difference. The diamond shape illustrated the pooled estimate and uncertainty for the combined effect. The vertical line indicates the study shows no correlation between the *FAM13A* rs2609255 polymorphism and the IPF susceptibility (OR = 1). Furthermore, the result that confidence interval includes 1 shows no evidence of difference between the polymorphism and IPF susceptibility, and if the confidence interval more than 1 indicates that there was correlation between the polymorphism and IPF susceptibility.

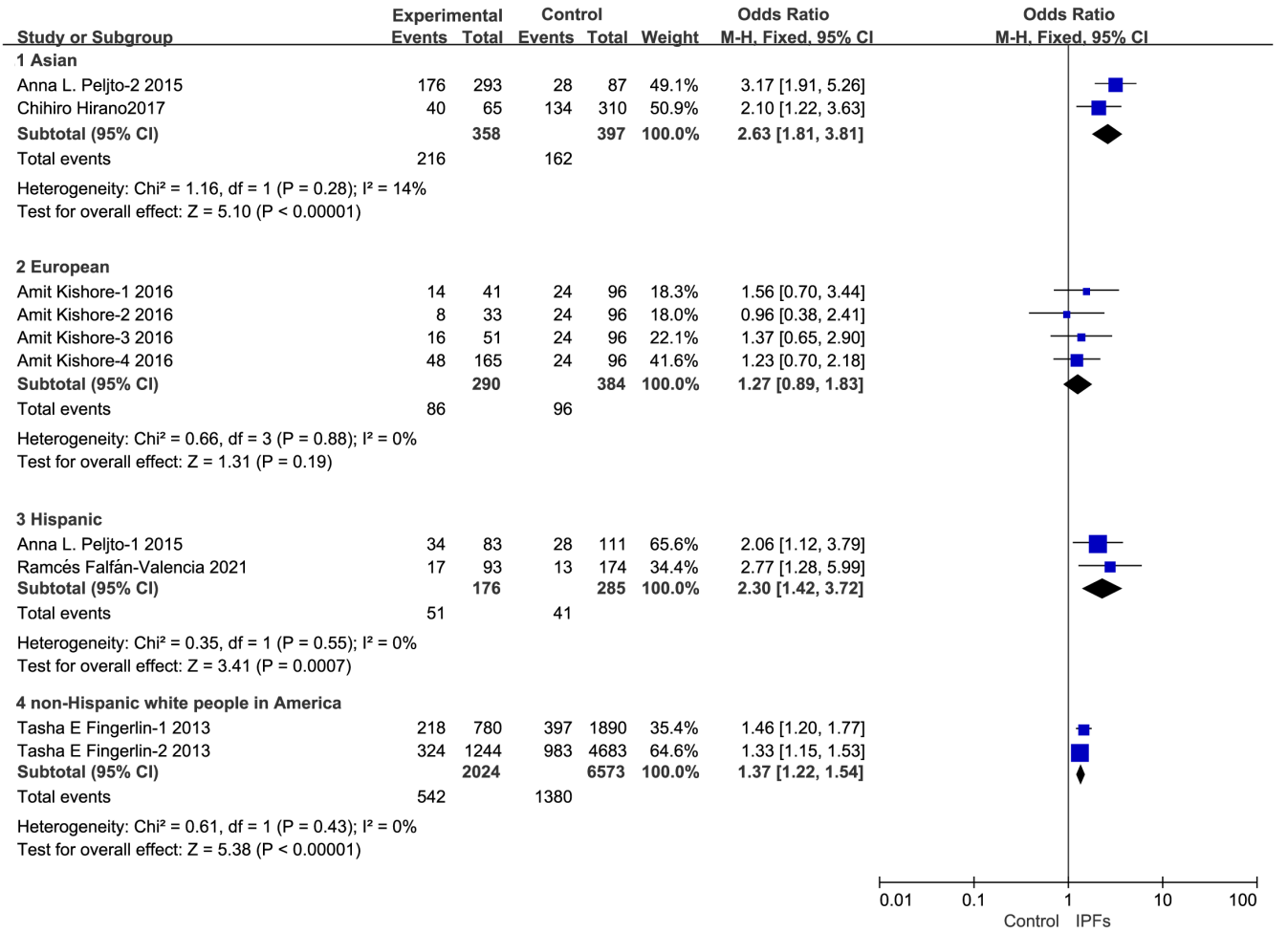

FIGURE 4 Forest plot of the correlation between the rs2609255 polymorphism at the *FAM13A* gene locus and the risk of IPFs in each ethnic group in a meta-analysis (G vs. T). The figure demonstrated the studies as filled squares and the solid line as the 95% CI of the difference. The diamond shape illustrated the pooled estimate and uncertainty for the combined effect. The vertical line indicates the study shows no correlation between the *FAM13A* rs2609255 polymorphism and the IPF susceptibility (OR = 1). Furthermore, the result that confidence interval includes 1 shows no evidence of difference between the polymorphism and IPF susceptibility, and if the confidence interval more than 1 indicates that there was correlation between the polymorphism and IPF susceptibility.

we adopted a sensitivity analysis, which did not affect the analysis results (Figure S1). Overall, we can provide some evidence that the G allele mutation at rs2609255 is possible genetic risk for IPF, especially in Asian individuals and Hispanic white people.

In agreement with our literature review, homozygosity of the G allele has been coupled to a dose-dependent increase in disease risk. The OR of GG vs. TT was higher than that of TG vs. TT (2.66 vs. 1.39). Studies have illustrated that the abnormal expression of *FAM13A* in patients with IPF may regulate alveolar EMT through the TGF-β and β-catenin (Rahardini et al., 2020). Therefore, much more mechanistic researches may be needed to confirm whether the mutation of the G site affects the expression of FAM13 and thus is related to the disease.

This study also summarized the heterogeneity in the correlation between rs2609255 and susceptibility to RA-ILD and silicosis for the first time. At present, there are few studies on RA-ILD and silicosis. Unfortunately, in this study, only two studies regarding RA-ILD and silicosis, respectively, are available; to some extent, it would be expect that the results regarding IPF will be more significant. In silicosis studies in China, the *FAM13A* polymorphism was not considerable correlated with silicosis about susceptibility. At present, only two RA-ILD studies have indicated an association with the *FAM13A* gene; the expression and the mechanism of *FAM13A* in RA-ILD have not been studied. We speculate that the susceptibility of the *FAM13A* gene may be related to the shared fibrosis mechanism of IPF and RA-ILD, often with the usual interstitial pneumonia pattern; however, the pathological pattern of silicosis is mainly that exogenous silica or silicide crystals cause a series of injuries in the lungs and form silicon nodules, which further cause pulmonary fibrosis;

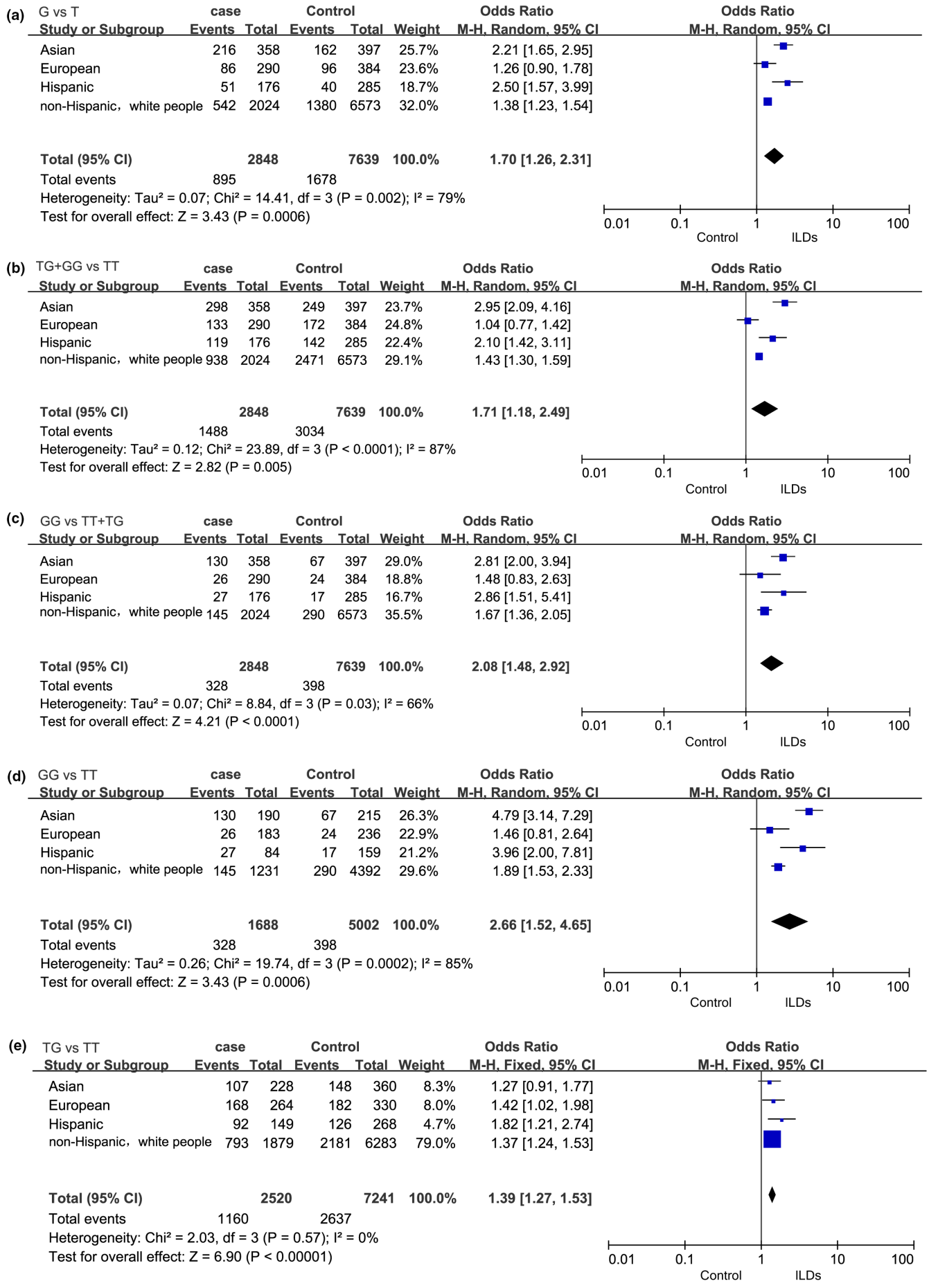
(a)
G vs T
case
Control
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Asian 216 358 162 397 25.7% 2.21 [1.65, 2.95]
European 86 290 96 384 23.6% 1.26 [0.90, 1.78]
Hispanic 51 176 40 285 18.7% 2.50 [1.57, 3.99]
non-Hispanic，white people 542 2024 1380 6573 32.0% 1.38 [1.23, 1.54]
Total (95% CI) 2848 7639 100.0% 1.70 [1.26, 2.31]
Total events 895 1678
Heterogeneity: Tau² = 0.07; Chi² = 14.41, df = 3 (P = 0.002); I² = 79%
Test for overall effect: Z = 3.43 (P = 0.0006)
0.01 0.1 1 10 100
Control ILDs
(b)
TG+GG vs TT
case
Control
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Asian 298 358 249 397 23.7% 2.95 [2.09, 4.16]
European 133 290 172 384 24.8% 1.04 [0.77, 1.42]
Hispanic 119 176 142 285 22.4% 2.10 [1.42, 3.11]
non-Hispanic，white people 938 2024 2471 6573 29.1% 1.43 [1.30, 1.59]
Total (95% CI) 2848 7639 100.0% 1.71 [1.18, 2.49]
Total events 1488 3034
Heterogeneity: Tau² = 0.12; Chi² = 23.89, df = 3 (P < 0.0001); I² = 87%
Test for overall effect: Z = 2.82 (P = 0.005)
0.01 0.1 1 10 100
Control ILDs
(c)
GG vs TT+TG
case
Control
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Asian 130 358 67 397 29.0% 2.81 [2.00, 3.94]
European 26 290 24 384 18.8% 1.48 [0.83, 2.63]
Hispanic 27 176 17 285 16.7% 2.86 [1.51, 5.41]
non-Hispanic，white people 145 2024 290 6573 35.5% 1.67 [1.36, 2.05]
Total (95% CI) 2848 7639 100.0% 2.08 [1.48, 2.92]
Total events 328 398
Heterogeneity: Tau² = 0.07; Chi² = 8.84, df = 3 (P = 0.03); I² = 66%
Test for overall effect: Z = 4.21 (P < 0.0001)
0.01 0.1 1 10 100
Control ILDs
(d)
GG vs TT
case
Control
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Asian 130 190 67 215 26.3% 4.79 [3.14, 7.29]
European 26 183 24 236 22.9% 1.46 [0.81, 2.64]
Hispanic 27 84 17 159 21.2% 3.96 [2.00, 7.81]
non-Hispanic，white people 145 1231 290 4392 29.6% 1.89 [1.53, 2.33]
Total (95% CI) 1688 5002 100.0% 2.66 [1.52, 4.65]
Total events 328 398
Heterogeneity: Tau² = 0.26; Chi² = 19.74, df = 3 (P = 0.0002); I² = 85%
Test for overall effect: Z = 3.43 (P = 0.0006)
0.01 0.1 1 10 100
Control ILDs
(e)
TG vs TT
case
Control
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Asian 107 228 148 360 8.3% 1.27 [0.91, 1.77]
European 168 264 182 330 8.0% 1.42 [1.02, 1.98]
Hispanic 92 149 126 268 4.7% 1.82 [1.21, 2.74]
non-Hispanic，white people 793 1879 2181 6283 79.0% 1.37 [1.24, 1.53]
Total (95% CI) 2520 7241 100.0% 1.39 [1.27, 1.53]
Total events 1160 2637
Heterogeneity: Chi² = 2.03, df = 3 (P = 0.57); I² = 0%
Test for overall effect: Z = 6.90 (P < 0.00001)
0.01 0.1 1 10 100
Control ILDs

FIGURE 5 Analysis of the correlation between the *FAM13A* rs2609255 T/G polymorphism and IPF. (a) G vs. T, (b) dominant model, (c) recessive model, (d) GG vs. TT, (e) additive model. The figure demonstrated the studies as filled squares and the solid line as the 95% CI of the difference. The diamond shape illustrated the pooled estimate and uncertainty for the combined effect. The vertical line indicates the study shows no correlation between the *FAM13A* rs2609255 polymorphism and the IPF susceptibility (OR = 1). Furthermore, the result that confidence interval includes 1 shows no evidence of difference between the polymorphism and IPF susceptibility, and if the confidence interval more than 1 indicates that there was correlation between the polymorphism and IPF susceptibility.

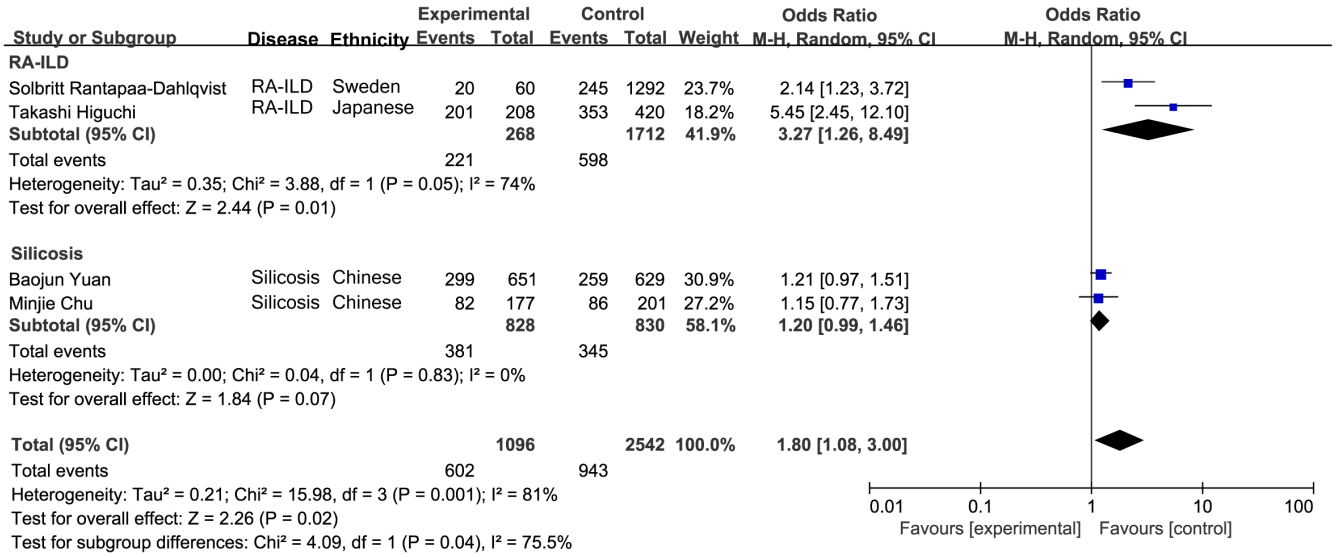

FIGURE 6 Forest plot of the correlation of the *FAM13A* gene polymorphism of rs2609255 and the risk of silicosis and RA-ILDs in a meta-analysis (G vs. T). The figure demonstrated the studies as filled squares and the solid line as the 95% CI of the difference. The diamond shape illustrated the pooled estimate and uncertainty for the combined effect. The vertical line indicates the study shows no correlation between the *FAM13A* rs2609255 polymorphism and the diseases susceptibility (OR = 1). Furthermore, the result that confidence interval includes 1 shows no evidence of difference between the polymorphism and diseases susceptibility, and if the CI more than 1 indicates that there was correlation between the polymorphism and diseases susceptibility.

thus, silicosis is different from IPF and RA-ILD. However, due to a lack of studies, it cannot be concluded that the *FAM13A* gene polymorphism is not correlated to the susceptibility to silicosis, neither the polymorphism is absolutely correlated to the susceptibility to RA-ILD.

We also demonstrated that the lower frequency of the G allele in Hispanic white individuals (14.4%) and higher in Asian individuals (41.5%). Therefore, the low level of prevalence of the G polymorphism of the *FAM13A* gene rs2609255 in Hispanic white individuals indicated that it may not be a major risk factor for IPF in this race.

In addition, in a study involving 143 Brazilian silicosis patients, the *FAM13A* gene rs2609255 was also not significantly correlation with the development of silicosis (de Castro et al., 2022), but specific data from this study were not available. Another polymorphic site of the *FAM13A* gene, rs2609260, is correlated with the incidence of hypersensitivity pneumonitis (Furusawa et al., 2021); nevertheless, it was not included in this study by lack of detailed genetic data.

FAM13A gene mutation is also considered to be a risk factor, especially in lung cancer, chronic obstructive pulmonary disease (COPD), and cystic fibrosis (Guzmán-Vargas et al., 2021); specifically, *FAM13A* gene mutation is related in regulating the invasion, migration, and proliferation of epithelial cells in lung cancer (Eisenhut et al., 2017), regulating the β-catenin involved in the development of COPD (Lin et al., 2021), and regulating the RhoA signaling pathway, which affects mesenchymal transition, in cystic fibrosis (Corvol et al., 2018). However, unfortunately, there were no researchers related to the further molecular function in ILDs, neither have performed a systematic review or a meta-analysis of *FAM13A* gene polymorphisms in ILDs, and these need more exploring.

This study also has some limitations. First, publication bias and heterogeneity can distort meta-analyses. However, most of the studies we included illustrated the same trend regarding the linkage between the *FAM13A* gene rs2609255 T/G polymorphism and IPF. Analysis after excluding one single study with high heterogeneity indicated that it was unlikely that heterogeneity and publication bias would interfere with this analysis. Second, hence, individuals who were European, Asian,

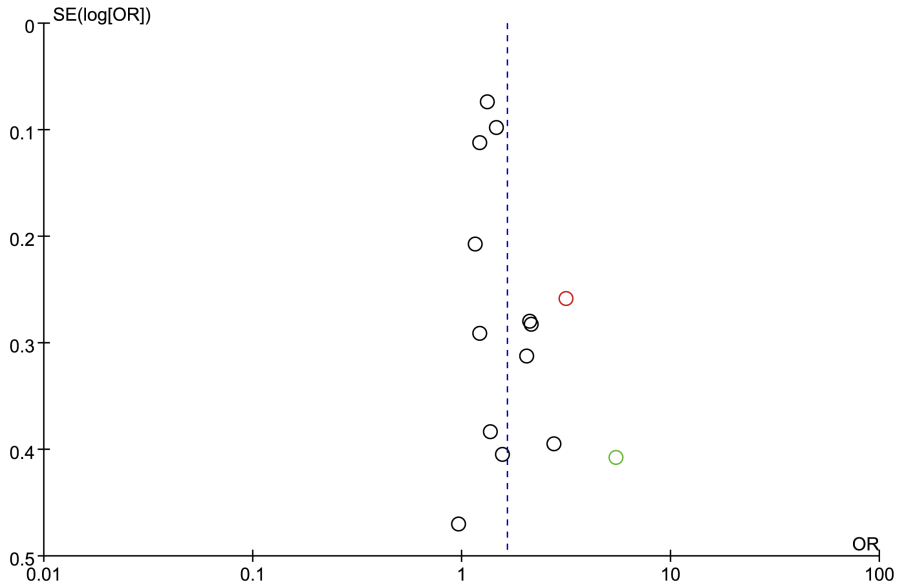

FIGURE 7 Funnel plot of the rs2609255 gene polymorphism at the *FAM13A* gene locus and risk of ILD. The red circle represents the study of the Korean IPF group (Peljto et al., 2015) and the green circle represents the Japanese group of RA-ILD (Higuchi et al., 2023). The black circles represent the other 12 studies among the total 14 subgroups in this study.

Hispanic, or non-Hispanic white American were involved in our meta-analysis; our results could not apply to other populations. Third, part of the studies was conducted in populations of non-Hispanic white ancestry, so further research in populations of other ethnicities is needed. Previous studies have indicated that the G allele at rs2609255 of the *FAM13A* gene is not only correlated with a high risk of IPF but also with the survival rate, pathological changes, and lung function of IPF. However, due to incomplete data, a complete meta-analysis could not be performed. Although the mechanism between the G allele at rs2609255 of the *FAM13A* gene and IPF is not clear, *FAM13A* is closely related to genetic risk factors.

In conclusion, this is the first meta-analysis that provides evidence that the G allele mutation at rs2609255 of the *FAM13A* gene confers different susceptibility to ILDs in different populations or disease subclassification. For IPF in Asian, non-Hispanic American, and Hispanic white individuals and RA-ILD in European individuals, there was more significant relation. However, we firstly indicated it seems that little association was demonstrated between *FAM13A* gene polymorphism and susceptibility to silicosis in China by meta-analysis. Furthermore, our findings indicated that further research is needed on the association of *FAM13A* polymorphisms with susceptibility in other populations and in ILDs other than IPF, and the differences in susceptibility to disease by race were noteworthy.

AUTHOR CONTRIBUTIONS

Yinan Hu created the research project, gathered and evaluated the data, and wrote the manuscript. Zhen Li took part in the gathering of clinical data. Yanhong Ren and Huaping Dai took part in the study's planning and revised the paper. The final manuscript was approved by all writers, who also made contributions to the work.

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CONFLICT OF INTEREST STATEMENT

The study's authors affirm that there were no financial or commercial ties that might be viewed as having a potential conflict of interest.

DATA AVAILABILITY STATEMENT

The paper contains the original contributions discussed in the study; for more information, contact the associated authors.

ETHICS STATEMENT

No further ethics approval or patient agreement was required since each result and analysis were based on earlier studies which had obtained ethics approval.

ORCID

Yinan Hu https://orcid.org/0009-0001-1583-0862

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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