

INPLASY PROTOCOL

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

Association of FAM13A gene polymorphism and interstitial lung disease susceptibility: A meta-analysis

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Review question / Objective: The FAM13A rs2609255 T/G polymorphism with IPF patients or other ILDs, including rheumatoid arthritis associated interstitial lung disease (RA-ILD) and silicosis, were investigated using a meta-analysis, in which, we also employed different allele models. Eight studies were involved in this meta-analysis, in which, there were 7639 controls and 2848 patients in five IPF studies, one RA-ILD study involving 1292 controls and 60 patients, and two silicosis studies containing 830 controls and 828 patients. We compared the frequency of G allele on rs2609255 site of FAM13A between the control subjects and IPFs or RA-ILD, silicosis from different races to indicate whether the susceptibility of IPF and other ILDs is associated with the FAM13A rs2609255 polymorphism in different races.

Eligibility criteria: No limitations on language, ethnicity, or location were placed on our search. Studies were considered whether they fulfilled the requirements: (1) published before November 2022; (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.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 28 February 2023 and was last updated on 28 February 2023 (registration number INPLASY202320122).

INTRODUCTION

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lung disease (RA-ILD) and silicosis, were investigated using a meta-analysis, in which, we also employed different allele models. Eight studies were involved in this meta-analysis, in which, there were 7639 controls and 2848 patients in five IPF

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Condition being studied: 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 accompanied with a high mortality rate and rapidly undergoing. ILDs are more common in connective tissue-related diseases. 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). 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, genetic susceptibility factors for silicosis need to be explored.

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. In a previous GWAS 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 considerably associated with susceptibility to IIP. In recent years, this finding has also been extended to other ILDs, such as silicosis and RA-ILD. 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 other ILDs in different populations.

METHODS

Participant or population: Eight studies met the inclusion requirement. One of the studies included information for individuals from four different races, while the other included information for individuals from two different races. In addition, these studies were treated independently. There was 1 article related to RA-ILD and 2 articles related to silicosis. The meta-analysis involved a total of 8 studies and 13 independent analyses of subgroups, including 5 IPF studies involving 7639 controls and 2848 patients and 3 other ILD studies (including 1 RA-ILD study and 2 silicosis studies) involving 888 patients and 2122 controls. We conducted separate meta-analyses for specific race, including European, Asian, non-Hispanic American and Hispanic white populations.

Intervention: The frequency of G allele on rs2609255 site of FAM13A of idiopathic pulmonary fibrosis (IPF) patients or rheumatoid arthritis associated interstitial

lung disease (RA-ILD), silicosis from different race.

Comparator: The frequency of G allele on rs2609255 site of FAM13A of healthy subjects with different races, including European, Asian, non-Hispanic American and Hispanic white populations.

Study designs to be included: These studies were treated independently. 8 studies and 13 independent analyses of subgroups, including 5 IPF studies involving 7639 controls and 2848 patients and 3 other ILD studies (including 1 RA-ILD study and 2 silicosis studies) involving 888 patients and 2122 controls. We conducted separate meta-analyses for specific race.

Eligibility criteria: No limitations on language, ethnicity, or location were placed on our search. Studies were considered whether they fulfilled the requirements: (1) published before November 2022; (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.

Information sources: The Web of Science, PubMed, MEDLINE, EMBASE, CNKI, VIP, and Wanfang databases. 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.

Main outcome(s): This is the first meta-analysis which 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 were 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.

Quality assessment / Risk of bias analysis: The included studies were all nonrandomized controlled studies, and we assessed them applying the Newcastle-Ottawa Scale (NOS). The highest score was 9 points, 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. No further ethics approval or patient agreement was required since each result and analysis were based on earlier studies which had obtained ethics approval.

A funnel plot demonstrated that the correlation between the rs2609255 site of the FAM13A gene and ILD, and the graph was basically symmetrical.

Strategy of data synthesis: 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); (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% confidence intervals (CIs). We adopted Cochran's Q test for variation and heterogeneity; I² values were adopted to quantify the effect of heterogeneity, ranging from 0 to 100%. For those with heterogeneity less than 50%, a fixed-effects model was adopted; for those with heterogeneity greater than 50% and p less than 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. We employed Revman5.3 software for all statistical analyses and graphing, and a p value of ≤ 0.05 indicated a considerable

difference. We also applied funnel plots to detect heterogeneity and publication bias.

Subgroup analysis: There were 13 independent analyses of subgroups, including 5 IPF studies involving 10 races respectively, we also put them into 4 subgroup for 4 categories, and 3 other ILD studies, including 1 RA-ILD study and 2 silicosis studies, we analyzed the data respectively, as the number of study was small.

Sensitivity analysis: There was no obvious heterogeneity in all of the studies, except for the study of the Korean IPF group, which may be related to the small number of subjects as 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.

Country(ies) involved: China.

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

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