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Review Article

The Association between MUC5B Rs35705950 and Risks of Idiopathic Interstitial Pneumonia, Systemic Sclerosis Interstitial Lung Disease, and Familial Interstitial Pneumonia: A Meta-Analysis

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Abstract

Background: Interstitial lung disease (ILD) is a category of chronic lung diseases with more than 200 subtypes. Idiopathic interstitial pneumonia (IIP), systemic sclerosis (SSc) ILD, and familial interstitial pneumonia (FIP) are three major groups of lung diseases with different causes or with unknown causes. Mucin5B (MUC5B) belongs to the mucin family, which contribute to the lubricating and viscoelastic properties of the whole saliva, normal lung mucus, and cervical mucus. The association between MUC5B rs35705950 and ILDs risks has been widely studied. However, the results were inconclusive and inconsistent.

Methods: In the present meta-analysis, the database PubMed, Embase, Cochrane Central Register of Controlled Trials, CNKI and Chinese Biomedical Literature Database were searched till Aug 20th, 2018. Overall 16 publications with 28 studies, 76345 cases and 18402 controls were included.

Results: The results indicated a significant increase of overall IIP risk for TT genotype and T allele of the rs35705950 in all genetic models (TT vs GG, OR=9.11; TT vs GT+TT, OR=5.80; GT+TT vs GG, OR=4.34; T vs G, OR=4.03. *P*<0.0001). Subgroup analysis by subtypes of IIP revealed higher risks of TT genotype and T allele for IPF and iNSIP (*P*<0.05). A significant increase of FIP risk was also found for the TT genotype and T allele of the rs35705950 (TT vs GG, OR=17.08; GT+TT vs GG, OR=6.02; T vs G, OR=1.64.*P*<0.05).

Conclusion: No significant relations existed between the rs35705950 and SSc-ILD risks. MUC5B rs35705950 might be a predictor for the susceptibility of IIP and FIP.

Keywords: Idiopathic interstitial pneumonia; Familial interstitial pneumonia; Polymorphism; Meta-analysis

Introduction

Interstitial lung disease (ILD) is a category of chronic lung diseases characterized by the scarring and/or inflammation of the lungs. ILD includes over 200 disorders (1, 2). Among them, idiopathic interstitial pneumonia (IIP) is a group of diffuse parenchymal lung diseases of unknown cause. IIP is characterized by cellular infiltration of the interstitial compartment of the lung and

with various patterns of inflammation and fibrosis. According to the 2013 American Thoracic Society/European Respiratory Society Statement, the IIPs were divided into major IIP, rare IIP and Unclassifiable IIP (3). The major IIP included idiopathic pulmonary fibrosis (IPF), idiopathic nonspecific interstitial pneumonia (iNSIP), respiratory bronchiolitis–interstitial lung disease (RB-ILD), desquamative interstitial pneumonia (DIP), cryptogenic organizing pneumonia (COP), and acute interstitial pneumonia (AIP). Rare idiopathic interstitial pneumoniaincludes idiopathic lymphoid interstitial pneumonia (ILP), and idiopathic pleuroparenchymal fibroelastosis (PPFE) (3). Systemic sclerosis ILD (SSc-ILD) is a lung disease caused by systemic sclerosis (SSc). As reported previously, 40% of the SSc patients were present ILD. ILD has been the major cause of death during SSc (4). Familial interstitial pneumonia (FIP) is an inherited lung disease, in which at least two or more primary biological family members have a clinical classification of IPF (3). Many evidence indicated that IIP, SSc-ILD, FIP have a genetic basis.

Mucin 5B (MUC5B) belongs to the mucin family of proteins, which contribute to the lubricating and viscoelastic properties of the whole saliva, normal lung mucus and cervical mucus. Rs35705950 is an important mutation on the MUC5B promoter. The association between MUC5B mutations and IIP, FIP, SSc-ILD risks have been widely studied (5-8). However, the results were inconclusive and inconsistent. A comprehensive meta-analysis of the published studies was needed to give a more precise estimation of the association between MUC5B rs35705950 and IIP, SSc-ILD, FIP.

In the present meta-analysis, a comprehensive analysis was performed to reveal whether rs35705950 is related to IIP, SSc-ILD, and FIP.

Methods

Search methods and inclusion criteria

In order to include all the related literature, a comprehensive search was conducted via the electronic databases Pubmed, Cochrane Central Register of Controlled Trials (CENTRAL), Embase, Chinese National Knowledge Infrastructure (CNKI) and Chinese Biomedical Literature Database (CBM). The terms used in the present searching were ("MUC5B" or "mucin5b") and ("idiopathic interstitial pneumonias" or "idiopathic pulmonary fibrosis" or "idiopathic nonspecific interstitial pneumonia" or "respiratory bronchiolitis–interstitial lung disease" or "desquamative interstitial pneumonia" or "cryptogenic organizing pneumonia" and "acute interstitial pneumonia" or "idiopathic lymphoid interstitial pneumonia", or "idiopathic pleuroparenchymal fibroelastosis" or "familial interstitial pneumonia" or "systemic sclerosis interstitial lung disease") and ("polymorphism" or "mutation" or "single nucleotide polymorphism"). The deadline for publication search was Oct 20, 2018. For the retrieved results, the duplications were removed first. The title and abstract were screened secondly to determine whether they met the inclusion criteria. Then, the full text was retrieved if the title and abstract met the requirements. Also, the references of included studies were checked for potentially relevant studies.

The included studies should meet the following criteria: case-control studies, studies demonstrated the association of MUC5B polymorphism and IIP, SSc-ILD or FIP. If the studies are abstracts, dissertations, letter to the editor, reviews or not meet the inclusion criteria, they will be excluded.

Data extraction

All the data from each included studies were extracted manually by two independent investigators. If discrepancies happened during data extraction, a consensus was conducted by the third author to solve it. The information extracted from each involved study are first author, published year, country, ethnicity, genotype method, subjects number, age, gender, odds ratio (OR) and confidence interval (CI).

Statistical Methods

Meta-analysis, sensitivity analysis, publication bias, heterogeneity were conducted on the STATA 12.0 software (StataCorp, College Station, TX, USA).

The pooled OR and 95% CI were used to evaluate the association between MUC5B rs35705950 and IIP, SSc-ILD, FIP. Subtypes of IIP, including IPF, iNSIP were analyzed. The *Z* test was used to evaluate the statistical significance of the association, with $P<0.05$ considered to be statically significant. Genetic models such as additive model (TT vs GG), recessive model (TT vs GT+GG), dominant model (TT+TG vs GG) and allelic model (T vs G) were analyzed.

The heterogeneity of included studies was determined by the I^2 test.$I^2>50\%$ was considered to be with obvious heterogeneity, while $I^2<50\%$ not. When $I^2>50\%$, the random-effects model (the DerSimonian and Laird method) was used for the meta-analysis, otherwise the fixed-effect model (the Mantel-Haenszel method) was used.

The publication bias was evaluated by Begg's funnel plot and Egger's linear regression method.

The influence of each individual study on pooled ORs and 95% CIs were performed by omitting one study at one time using STATA 12.0 software in the sensitivity analysis.

Results

Literature search and characteristics of included studies

After a comprehensive searching of relevant studies, totally 80 studies were found without duplications. Among them, 19 were irrelevant, 25 were reviews, 9 were not case-control studies, 10 were abstract, and 1 with other mutation. At last, 16 publications with 28 studies, 76345 cases and 18402 controls were included. The PRISMA flowchartwas shown in Fig. 1, and the detailed information of the included studies was presented in Table 1.

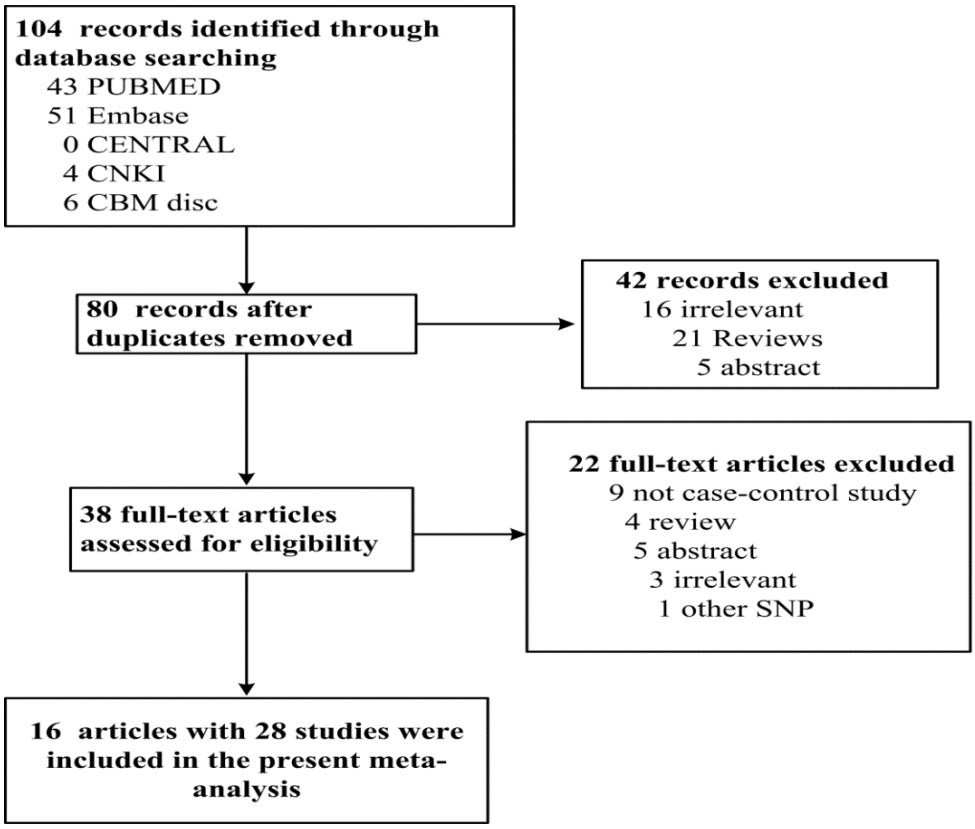

Fig. 1: PRISMA flow chart for the association between MUC5B rs35705950 and IIP, SSc-ILD, and FIP

Table 1: Characteristics of eligible studies included in the meta-analysis

Author	*Year*	*Country*	*Ethnicity*	*Disease*	*Genotyping Methods*	*Sample Size (Case/Control)*	*Odds Ratio*	*LCI*	*UCI*	*HWE of Control*
Borie R [1](9)	2013	France	Caucasian	IPF	Taqman	142/1383	5.22	3.99	6.81	0.284
Coghlan MA(10)	2014	USA	Caucasian	IPF	Taqman	132/192	2.68	1.78	4.01	N.A.
Fingerlin TA(11)	2013	UK/TX/etc	Non-hispanic White	IPF	Taqman	2492/6573	4.51	3.91	5.21	N.A.
Helling BA(12)	2017	USA	Caucasian	IPF	Taqman	202/139	3.11	2.03	4.77	0.125
Horimasu Y [1](13)	2015	Germany	Caucasian	IPF	Taqman	71/35	11.05	3.3	36.99	0.791
Horimasu Y [2](13)	2015	Japan	Asian	IPF	Taqman	44/310	4.34	1.02	18.49	0.886
Jiang H(14)	2015	China	Asian	IPF	Taqman	187/250	1.93	1.32	2.82	0.01
Kishore A [1](15)	2016	Czech	Caucasian	IPF	Taqman	41/96	3.77	1.9	7.47	N.A.
Kishore A [2](15)	2016	Germany	Caucasian	IPF	Taqman	33/96	4.83	2.39	9.79	N.A.
Kishore A [3](15)	2016	Greek	Caucasian	IPF	Taqman	40/96	5.46	2.76	10.82	N.A.
Kishore A [4](15)	2016	France	Caucasian	IPF	Taqman	51/96	6.77	3.62	12.65	N.A.
Noth I et al(16)	2013	USA	Caucasian	IPF	Taqman	1410/1931	2.43	2.13	2.77	N.A.
Seibold MA [1](5)	2011	USA	Caucasian	IPF	Taqman	492/322	8.3	5.8	11.9	N.A.
Stock CJ [1](17)	2013	UK	Caucasian	IPF	Taqman	110/416	4.9	3.42	7.03	N.A.
van der Vis JJ[1](18)	2015	Holland	Caucasian	IPF	Taqman	115/249	3.63	2.38	5.55	0.426
Wang C [1](19)	2014	China	Asian	IPF	Taqman	165/1013	4.33	1.99	9.42	0.800
Wei R [1](20)	2014	USA	Caucasian	IPF	Taqman	84/689	3.2	2.21	4.63	0.556
Zhang Y, et al(21)	2011	USA	Caucasian	IPF	Taqman	341/802	4.18	3.35	5.22	0.447
Borie R [2](9)	2013	France	Caucasian	Ssc-ILD	Taqman	346/1383	1.05	0.8	1.37	0.284
Borie R [3](9)	2013	Italy	Caucasian	Ssc-ILD	Taqman	207/494	1.18	0.84	1.66	0.342
Peljto A (22)	2012	USA	Caucasian	Ssc-ILD	Taqman	109/122	1.02	0.55	1.91	N.A.
Stock CJ [2](17)	2013	UK	Caucasian	Ssc-ILD	Taqman	229/416	1.24	0.86	1.79	N.A.
Horimasu Y [3](13)	2015	Germany	Caucasian	NSIP	Taqman	31/35	8.44	2.34	30.47	0.791
Horimasu Y [4](13)	2015	Japan	Asian	NSIP	Taqman	30/310	2.08	0.24	18.14	0.886
van der Vis JJ [3](18)	2015	Holland	Caucasian	NSIP	Taqman	43/249	2.85	1.58	5.17	0.426
Seibold MA [2](5)	2011	USA	Caucasian	FIP	Taqman	83/322	6.2	3.7	10.4	N.A.
van der Vis JJ [2](18)	2015	Holland	Caucasian	FIP	Taqman	55/249	4.31	2.59	7.18	0.426
Johnson C [2](23)	2017	USA	Caucasian	IIP	Taqman	60/134	4.1	2.17	7.74	N.A.

IPF: idiopathic pulmonary fibrosis; ssc-ILD: systemic sclerosis-interstitial lung diseases; iNSIP: idiopathic nonspecific interstitial pneumonia; FIP: Familial interstitial pneumonia; IIP: idiopathic interstitial pneumonia; LCI: low confidence interval; UCI: upper confidence interval; HWE: Hardy-Weinberg equilibrium

Results of meta-analysis

As shown in Table 2 and Fig. 2-4, a total of 28 studies, with 76345 cases and 18402 controls, were included in the allelic models (T vs G). Overall 16 studies were involved in additive (TT vs GG), recessive (TT vs TG+GG) and dominant model (TT+TG vs GG) respectively. Significant increase of overall IIP risks were found for TT genotype or T allele of rs35705950 in all genetic models (TT vs GG, OR=9.11, 95% CI=6.06-13.70, *P*<0.0001; TT vs GT+TT, OR=5.80, 95% CI=3.95-8.52, *P*<0.0001; GT+TT vs GG, OR=4.34, 95% CI=3.22-5.84, *P*<0.0001; T vs G, OR=4.03, 95% CI= 3.34-4.86, *P*<0.0001). Subgroup analysis by ethnicity demonstrated significant increases of IIP risks for TT genotype and T allele of rs35705950 in both Asians and Caucasians (Asians: TT vs GG, OR = 4.09, 95% CI=1.67-10.00, *P*=0.002; TT vs GT+TT, OR=3.93, 95% CI=1.61-9.55, *P*=0.003; GT+TT vs GG, OR=4.95, 95% CI=3.85-6.35, *P*<0.0001; T vs G, OR=2.64, 95% CI= 1.60-4.34, *P*<0.0001.

Table 2: Pooled ORs and 95% CIs of the association between MUC5B promoter mutation (rs35705950) and interstitial lung diseases

Genetic model	*Subgroup*	*N*	*Model*	*OR*	*P value*	*I² %*
TT vs GG	Overall IIP	13	F	9.11 [6.06, 13.70]	<0.0001	18%
	Asian	4	F	4.09 [1.67, 10.00]	0.002	N.A.
	Caucasian	9	F	11.72 [7.46, 18.41]	<0.0001	0%
	IPF	10	F	9.00 [5.93, 13.64]	<0.0001	35%
	iNSIP	3	F	12.29 [1.61, 93.86]	0.02	0%
	Ssc-ILD	2	F	0.94 [0.43, 2.08]	0.88	0
	FIP	1	N.A.	17.08 [1.49, 195.49]	0.02	N.A.
TT vs	Overall IIP	13	F	5.80 [3.95, 8.52]	<0.0001	0
GT+ GG	Asian	4	F	3.93 [1.61, 9.55]	0.003	N.A
	Caucasian	9	F	6.42 [4.20, 9.82]	<0.0001	0
	IPF	10	F	5.71 [3.86, 8.46]	<0.0001	0
	iNSIP	3	F	8.41 [1.11, 63.80]	0.04	0
	Ssc-ILD	2	F	0.92 [0.42, 2.02]	0.83	0
	FIP	1	N.A.	9.36 [0.83, 105.11]	0.07	N.A.
GT+TT	Overall IIP	13	R	4.34 [3.22, 5.84]	<0.0001	69%
vs GG	Asian	4	F	2.09 [1.44, 3.05]	0.0001	46%
	Caucasian	9	R	4.95 [3.85, 6.35]	<0.0001	52%
	IPF	10	R	4.39 [3.17, 6.10]	<0.0001	75%
	iNSIP	3	F	3.96 [2.23, 7.03]	<0.0001	23%
	Ssc-ILD	2	F	1.11 [0.90, 1.38]	0.34	0
	FIP	1	N.A.	6.02 [3.22, 11.24]	<0.0001	N.A.
T vs G	Overall IIP	22	R	4.03 [3.34-4.86]	<0.0001	79.4%
	Asian	4	F	2.64 [1.60-4.34]	<0.0001	26.9%
	Caucasian	18	R	4.22 [3.47-5.14]	<0.0001	81.2%
	IPF	18	R	4.06 [3.31-4.97]	<0.0001	82.9%
	iNSIP	3	F	3.35 [1.99-5.65]	<0.0001	18.8%
	Ssc-ILD	4	F	1.12 [0.94-1.34]	0.197	0.0%
	FIP	2	F	1.64 [1.28-2.00]	<0.0001	0.0%

PF: idiopathic pulmonary fibrosis; ssc-ILD: systemic sclerosis-interstitial lung diseases; iNSIP: idiopathic nonspecific interstitial pneumonia; FIP: Familial interstitial pneumonia; IIP: idiopathic interstitial pneumonia; LCI: low confidence interval; UCI: upper confidence interval; HWE: Hardy-Weinberg equilibrium; F: Fixed model; R: random model

Caucasians: TT vs GG, OR=11.72, 95% CI=7.46-18.41, *P*<0.0001; TT vs GT+TT, OR=6.42, 95% CI= 4.20-9.82, *P*<0.0001; GT+TT vs GG, OR=2.68, 95% CI=1.39-5.16, *P*=0.0001; T vs G, OR=4.22, 95% CI= 3.47-5.14, *P*<0.0001). When analyzed by subtypes of IIP, higher risk of IPF and NSIP was found for the TT genotype or T allele of rs35705950 in all genetic models (IPF: TT vs GG, OR=9.00, 95% CI=5.93-13.64, *P*<0.0001; TT vs GT+TT, OR=5.71, 95% CI=3.86-8.46, *P*<0.0001; GT+TT vs GG, OR=4.39, 95% CI=3.17-6.10, *P*<0.0001; T vs G, OR=4.06, 95% CI= 3.31-4.97, *P*<0.0001; iNSIP: TT vs GG, OR=2.29, 95% CI=1.61-93.86, *P=0.02*; TT vs GT+TT, OR=8.41, 95% CI=1.11-63.80, *P=0.04*; GT+TT vs GG, OR=3.96, 95% CI=2.23-7.03, *P*<0.0001; T vs G, OR=3.35, 95% CI=1.99-5.65, *P*<0.0001).Dramatic increase of FIP risks were found for the TT genotype and T allele of rs35705950 in additive, dominant, and allelic model (TT vs GG, OR=17.08, 95% CI=1.49-195.49, *P* = 0.02; GT+TT vs GG, OR=6.02, 95% CI=3.22-11.24, *P*<0.0001; T vs G, OR=1.64, 95% CI= 1.28-2.00, *P*<0.0001).No significant relations existed between rs35705950 and ssc-ILD risks (TT vs GG, OR=0.94, 95% CI=0.43-2.08, *P* = 0.88; TT vs GT+TT, OR=0.92, 95% CI = 0.42-2.02, *P* =0.83; GT+TT vs GG, OR=1.11, 95% CI=0.90-1.38, *P*=0.34; T vs G, OR=1.12, 95% CI= 0.94-1.34, *P*=0.34).

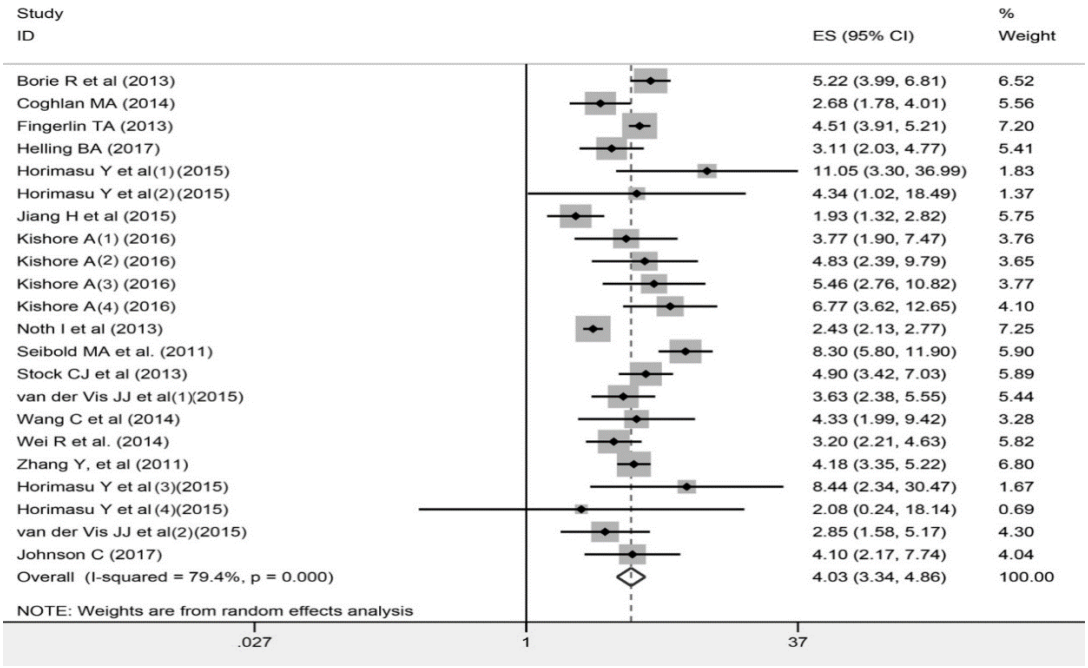

Fig. 2: Forest plot of ORs for the association between rs35705950 and overall IIP in the allelic model (T vs G)

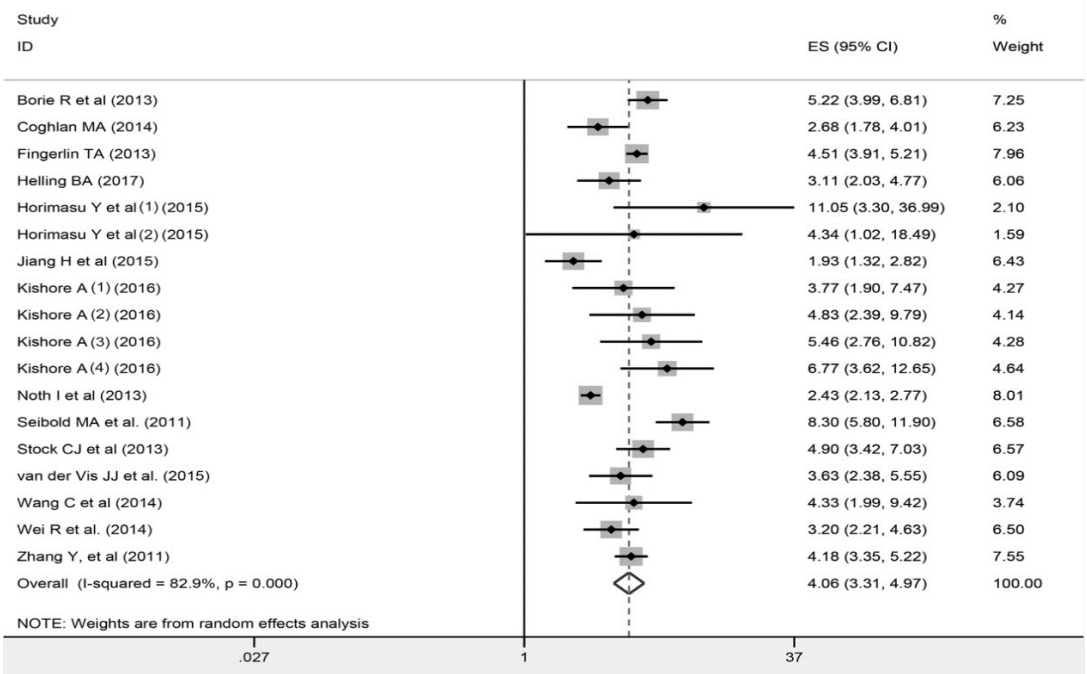

Fig. 3: Forest plot of ORs for the association between rs35705950 and IPF in the allelic model (T vs G)

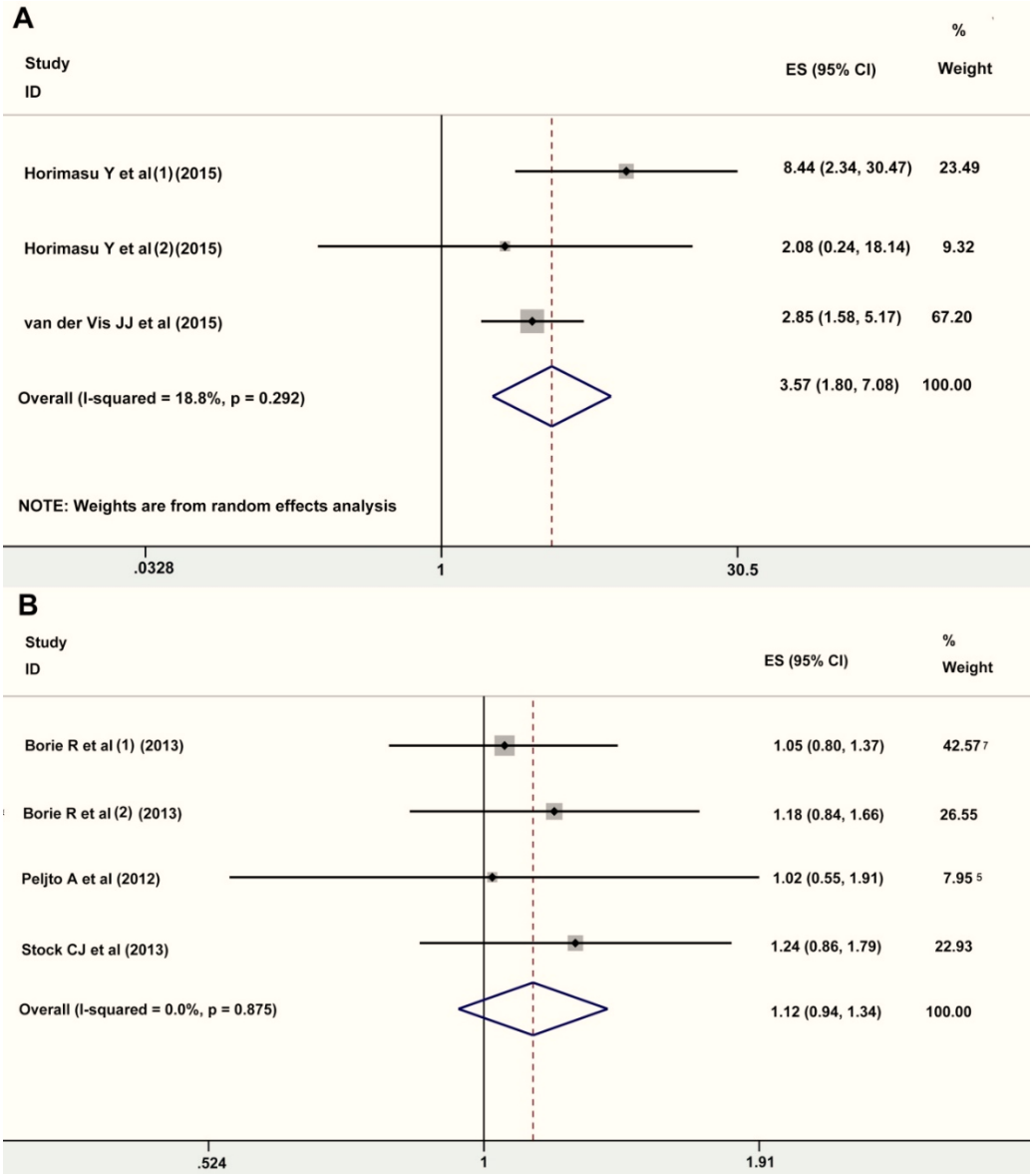

Fig. 4: Forest plot of ORs for the association between rs35705950 and iNSIP and ssc-ILD in the allelic model (T vs G). A, iNSIP; B, ssc-ILD

Publication Bias

To assess the publication bias, funnel plots with the Egger's and Begg's tests were used in the present meta-analysis. As shown in Table 3, Egger's and Begg's tests did not find any significant bias either.

Table 3: *P*-value of publication bias tests of included studies

Test	*IIP*	*IPF*	*NSIP*	*SSc-ILD*	*FIP*
Begg's	0.218	0.880	1.000	0.734	1.000
Egger's	0.910	0.211	0.773	0.931	N.A

Sensitivity analysis

The sensitivity analysis was performed by evaluating the influence of each individual study on pooled ORs and 95% CIs. The STATA software was used to omit each individual study at one time and evaluate the influences. The results showed no obvious influence on pooled ORs by each individual study.

Source of heterogeneity

Obvious heterogeneity was found between the studies involved for IIP in the dominant model (GT+TT vs GG) and the allelic model (T vs G)(69.0% and 79.4% respectively). To identify the sources of the heterogeneity, subgroup analysis by disease subtypes (iNSIP and IPF) and ethnicity were conducted. The results showed no significant heterogeneity existed between studies involved for iNSIP, but a high heterogeneity between studies involved for IPF, indicating the disease subtype partly responsible for the heterogeneity. Further subgroup analysis by ethnicity found a relatively high heterogeneity existed in both Asians and Caucasians in the dominant model, and high heterogeneity in Caucasians in the allelic model, indicating the ethnicity may not be the source.

After checking each individual study carefully, we found one study deviated from HWE (14), and one was with relative high influence on overall pooled ORs (16). After adjustment by excluding these two studies, the obvious heterogeneity was removed (Table 4).

Table 4: Comparison of pooled ORs and heterogeneity after adjustment

Genetic model	*Subgroup*	*N*	*OR*	*P value*	*I²%*	*OR adjusted**	*P-value adjusted**	*I²% adjusted**
GT+TT vs GG	Overall IIP	13	4.34 [3.22, 5.84]	<0.0001	69%	5.13[4.41,5.97]	<0.0001	37%
	Asian	4	2.09 [1.44, 3.05]	<0.0001	46%	4.13[2.15,7.95]	<0.0001	0%
	Caucasian	9	4.95 [3.85, 6.35]	<0.0001	52%	4.95 [3.85, 6.35]	<0.0001	52%
	IPF	10	4.39 [3.17, 6.10]	<0.0001	75%	5.22[4.46, 8.10]	<0.0001	42%
T vs G	Overall IIP	22	4.03 [3.34-4.86]	<0.0001	79%	4.38[3.82,5.03]	<0.0001	34%
	Asian	4	2.64 [1.60-4.34]	<0.0001	27%	4.05[2.11, 7.78]	<0.0001	0.40
	Caucasian	18	4.22 [3.47-5.14]	<0.0001	81%	4.43[4.07, 4.83]	<0.0001	33.89
	IPF	18	4.06 [3.31-4.97]	<0.0001	83%	4.47[4.10, 4.87]	<0.0001	30.71

Note: * adjusted by removing the data of Jiang H et al. and Noth I et al

Discussion

In the present meta-analysis, significant increases risks of overall IIP, and IIP subtypes, IPF and NSIP, were found for TT genotype and T allele of rs35705950 in all genetic models (Table 2 and Fig. 2, 3). A significant increase of FIP risk also existed for the TT genotype and T allele of rs35705950 in additive, dominant, and allelic model (Table 2). No significant relation between the rs35705950 and SSc-ILD risks.

ILDs were a group of diseases with a high death rate and low survival expectancy. Studies have shown MUC5B played important roles in the pathogenesis of ILD. MUC5B was a gene encodes a protein named mucin 5B, a member of the mucin family. Mucin was a family of high glycosylated macromolecular proteins, which was a major component of mucus secretion. Their gel-forming characteristics made them essential for the functions of lubrication, cell signal transduction and chemical barrier (24). Mucin5bwas a principle mucin secreted by submucosal glands and epithelial secretory cells on airway (25). The function of mucin5b in the airway was responsible for the clearance of inhaled particles (26). Loss of mucin5b may lead to the overwhelming of inhaled particles over normal clearance mechanisms. However, the mutation on the MUC5B promoter, rs35705950, actually increased the ex-

pression of mucin5b (5). And this overexpression of mucin5b mainly presented in terminal bronchioles, where normally didn't express mucin5b. The increased mucin5b in distal airway cells led to the increase of cell turnover and repaire of mesenchymal cell proliferation and fibrosis, which was partly responsible for the ILD (27). The associations between rs35705950 and ILDs, such as IPF, NISP, and FIP have been identified by several reports (5, 18). Our meta-analysis confirmed the increased risks of IIP and FIP for TT genotype or T allele of MUC5B.

However, we didn't find any associations between rs35705950 and SSc-ILD. SSc-ILD is a disease-specific phenotype of systemic sclerosis. It is a lung disease with different pathological process compared to IIP (28). Other SSc related factors, such as IRF5 rs20046640, STAT4 rs7574865 may contribute to SSc-ILD (29).

Obvious heterogeneity existed in the present meta-analysis in dominant model (GT+TT vs GG) and allelic model (T vs G) for overall IIP. Subgroup analysis by IIP subtypespartly illustrated the source of this heterogeneity. However, we found two studies may responsible for this heterogeneity, one deviated from HWE and another had a high influence on pooled ORs (14, 16). After adjustment by excluding these two studies, the obvious heterogeneity has been removed.

The present meta-analysis should be interpreted with caution because of the following limitations: First, most of the studies were conducted in Caucasians. We included 28 studies, and only 4 studies were conducted in Asians. Second, the heterogeneity between included studies in dominant and allelic models was significant. Third, more subtypes of IIP were not studied yet. The ILDs included more than 130 subtypes, our meta-analysis only studied IIP, FIP and SSc-ILD because of lacking information from original studies. Fourth, ILDs were influenced by both environmental and genetic factors. However, most of the included studies were without the information on environmental exposure and multiple SNPs in haplotypes.

Conclusion

The current meta-analysis suggested a significantly higher risk of overall IIP, IIP subtypes (IPF and NSIP), and FIP in TT genotype and T allele of MUC5B rs35705950. No associations were found between rs35705950 and SSc-ILD. However, the results of the present meta-analysis should be interpreted with caution because of the ethnicity and heterogeneity. Further studies in Asians, and with environmental exposure were required.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that there is no conflict of interest.

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