Correlation Between the *TERT* rs2736100 A/C Polymorphism and Susceptibility to Interstitial Lung Diseases: An Ethnicity-Based Meta-Analysis Study

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Research Article

Keywords: TERT, Rs2736100, Interstitial lung disease, Connective tissue disease, Idiopathic pulmonary fibrosis

Posted Date: March 8th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1414064/v1

Abstract

Objective: This meta-analysis aimed to investigate the correlation between the *TERT* rs2736100 A/C polymorphism and susceptibility to interstitial lung diseases (ILD).

Methods: The systematic review was registered in PROSPERO. OVID MEDLINE, OVID EMBASE, and Web of Science electronic databases were searched. The meta-analysis effect size was estimated using either incidence with 95% confidence intervals (CIs) or odds ratio (OR). A funnel plot was used to assess the risk of publication bias.

Results: A total of 12 eligible studies were finally analyzed, involving 5272 cases and 14767 controls. The frequency of rs2736100_C was lower in patients with ILD (38.4% vs 47.3%). Asian population had a lower rs2736100_C frequency than European population (32.8% vs 40%). A significant association between rs2736100_A and ILD was identified (p<0.00001, OR 1.36, 95% CI 1.24-1.48). The incidence of ILD increased with rs2736100_A in both European population (p<0.00001, OR 1.34, 95% CI 1.27-1.41) and Asian population (p=0.008, OR 1.42, 95% CI 1.10-1.85). Among six idiopathic pulmonary fibrosis (IPF) studies, rs2736100_A was associated with the incidence of IPF (p<0.00001, OR 1.53, 95% CI 1.27-1.85). All genetic models, including recessive, dominant, and additive models, showed increased risk of IPF was associated with rs2736100_A. Rs2736100_A was not associated with the incidence ofconnective tissue disease associated ILD (CTD-ILD) (p=0.75, OR 1.07, 95% CI 0.71-1.61).

Conclusion: This study demonstrated the frequency of rs2736100_A was lower in Asian population. We confirmed the *TERT* rs2736100 A/C polymorphism was a strong risk factor for IPF, but not for CTD-ILD. Whether the incidence of CTD-ILD increases with the TERT rs2736100 A/C polymorphism needs to be evaluated in the future.

Introduction

Interstitial lung disease (ILD) is characterized by fibrosis and inflammation in the pulmonary parenchyma. ILD encompasses a large, heterogeneous group of entities, such as idiopathic interstitial pneumonias (IIP), environmental exposure-related ILD, connective tissue disease associated ILD (CTD-ILD), pulmonary sarcoidosis and smoking-related ILD [1]. Of note, a progressive fibrosing phenotype that represented by idiopathic pulmonary fibrosis (IPF) leads to aggressive fibrosing, decline in lung function, worsening symptoms and poor prognosis [2]. Besides of IPF, this phenotype can also be observed in CTD-ILD, fibrotic non-specific interstitial pneumonia, chronic hypersensitivity pneumonitis (HP) and asbestos-induced lung fibrosis [3-4].

Emerging evidences suggest that the incidence of ILD increases with telomere abnormalities and mutations in telomere related genes (TRGs), including telomerase reverse transcriptase (TERT) catalytic subunit and the telomerase RNA component (TERC), poly(A)-specific ribonuclease (PARN), regulator of telomere elongation helicase 1(RTEL1), and TERTF1 interacting nuclear factor 2 (TINF2) (Diaz de Leon, et al. 2010; Newton et al., 2016; Borie et al. 2019). So far, *TERT* mutations have been pointed to be associated with familial IPF, sporadic IPF, NSIP, desquamative interstitial pneumonia, CTD-ILD, and chronic hypersensitivity pneumonitis [5-7].

Rationale

Rs2736100 polymorphism, an important single nucleotide polymorphism in the intron region of TERT, has been associated with ILD in several genome wide association studies (GWAS), but the results of these studies were conflicting. Some of studies found significant associations between rs2736100 polymorphism and IIP patients, whereas others did not [8-11]. The rs2736100 risk allele was associated with shorter telomere length in IPF patients, but not in non-IPF patients [6,12]. Furthermore, the role of the *TERT* rs2736100 polymorphism seems to differ substantially between populations [11].

Objectives

Therefore, we conducted this meta-analysis to investigate the incidence and risk of the *TERT* rs2736100 polymorphism in patients with ILD and to better illuminate the relation between the *TERT* rs2736100 polymorphism and ILD.

Materials And Methods

Ethical compliance

This study does not involve with ethics as it is a systematic review and meta-analysis.

Study registration

The systematic review was registered in PROSPERO (CRD42022303887). We followed the Preferred Reporting Items for Systemic Reviews and Meta-Analyses 2009 statement.

Search Strategy

To perform systematic retrieval, we searched the electronic databases OVID MEDLINE, OVID EMBASE, and Web of Science using a Medical Subject Headings term and a keyword on Jan 30, 2022. The terms used in searching were as follow: The search terms were “interstitial lung diseases”, “ILD”, “Genetic Variation”, “variant”, “gene polymorphism”, “TERT”, “telomerase reverse transcriptase” . The detailed search strategy is provided in the supplemental file. The duplication were removed. The references of retrieved publications were manually filtered for potentially relevant articles.

Inclusion criteria and exclusion criteria

Inclusion criteria were as follow: (a) contained original data; (b) provide adequate data to calculate odds ratios (ORs) and 95% confidence intervals (CIs). Exclusion criteria were as follow: (a) contained overlapping data; (b) family member had been studied because the analyses were based on linkage considerations. (c) English texts were not available. (d) abstracts, reviews, comments and conference presentations.

Data extraction and quality assessment

Retrieved studies were filtered by titles and abstracts based on our study selection criteria. The full texts of the remaining studies from the first screening were downloaded for further screening based on the study eligibility criteria. Two authors independently screened the studies, and any disagreement was resolved via discussion or adjudication by a third reviewer, if necessary.

Two authors independently collected data on the first author’s family name, year of publication, country, study design, ethnicity, the number of participants, classification of ILD, alleles frequency, genotypic distribution of rs2736100. If a study contained several independent groups, the groups would be listed respectively.

The methodological quality assessment of included studies was conducted using the Newcastle–Ottawa quality assessment scale (NOS). A total of three domains — selection, comparability, and exposure — with eight numbered items yielded the highest total score of 9. For selection and exposure, each of seven numbered items was scored as 1 if the answer was yes, while for comparability, a maximum score of 2 was given for a numbered item. Studies with a score ≥6 were considered high-quality studies. Two authors performed the methodological quality assessment, and any disagreement was resolved via discussion or adjudication by a third reviewer, if necessary.

Statistical analysis

We performed data analyses using RevMan software (version 5.4). The probability value (p value) of Hardy–Weinberg equilibrium (HWE) was calculated. (https://ihg.gsf.de/cgi-bin/hw/hwa1.pl). Meta-analyses were performed using 4 models, including allelic contrast, additive, recessive and dominant. Subgroup analysis was performed according to ethnicity and classification of ILD.

The effect size of the meta-analysis was estimated by incidence with 95% confidence intervals (CIs) and odds ratio (OR). We assessed clinical diversity across studies through statistical heterogeneity using I^2 and p-values. I^2 values of 25%, 50%, and 75% represented low, moderate, and high heterogeneity, respectively. Fixed-effect models (FEMs) were used for synthetic analyses. A random effect model was applied when heterogeneity was over 50% or $P<0.05$. Sensitivity analysis was performed by excluding studies one by one to identify the potential source of heterogeneity. We assessed the risk of publication bias via funnel plot. The power of each study on assessing the association between rs2736100 and ILD was conducted via G*Power (convention $w = 0.1$, http://www.gpower.hhu.de/).

Results

Literature Search and Study Characterisitc

A total of 831 studies were retrieved via electronic and manual searching, with 17 selected articles for further evaluation based on title and abstract details. Seven articles were excluded due to incomplete data. Among the 10 included articles, two studies contained complete data from two independent groups, so we listed them respectively. A total of 12 eligible studies were finally analyzed, involving 5272 cases and 14767 controls. The details are shown in Fig. 1.

A total of 12 eligible studies were finally analyzed, involving 5272 cases and 14767 controls. The studies included 5 IPF studies, 2 CTD-ILD studies, 1 environment-exposured ILD study, 3 IIP studies (one study contains specific data of IPF and non-IPF groups), 1 familial ILD study. All of the 12 eligible studies were case-control studies. Seven studies involved European populations, whereas five studies involved Asian population. The characteristics of eligible studies are shown in Table 1. The power of eligible studies varies from 37.2–99.9%.

Table 1
Characterisitics of individual studies included in the mata-analysis

References	Year	Country	Ethnicity	Disease	Numbers		Minor alleles (%)		Allele association				Power(%)*
					Case	Control	Case	Control	OR	95% CI		p value	
Guzmán-Vargas[20]	2021	Mexico	European	IPF	93	174	25	38.9	0.52	0.34	0.8	0.0028	37.2
Jonsson[10]	2021	Sweden	European	RA-ILD	60	2350	39.2	45.9	0.76	0.52	1.1	0.1447	99.8
Arimura-Omori[21]	2020	Japan	Asian	IPF	155	379	28.7	41.3	0.57	0.43	0.76	0.0001	63.7
Kawasaki[16]	2020	Japan	Asian	AAV-ILD	176	216	34.7	31.6	1.15	0.8	1.66	0.4468	50.8
Yuan[22]	2020	China	Asian	CWP	645	626	38.4	42.7	0.84	0.72	0.98	0.031	94.6
Mathai[23]	2019	USA	European	PF	77	417	44.8	45	0.99	0.7	1.4	0.971	60.3
Dressen[12]	2018	USA	European	IPF	1510	1874	42.7	49	0.78	0.7	0.86	< 0.00001	99.9
Wei[14]	2014	USA	European	ILD	277	689	43.8	50.1	0.78	0.63	0.96	0.0198	87.5
Fingerlin – 1[8]	2013	USA	European	IIP	1616	4683	43	51.1	0.72	0.66	0.78	< 0.00001	99.9
Fingerlin – 2[8]	2013	USA	European	IIP	876	1890	42.9	50.1	0.75	0.67	0.84	< 0.00001	99.9
Mushiroda – 1[9]	2008	Japan	Asian	IPF	159	934	27	40.9	0.54	0.41	0.7	< 0.00001	91.1
Mushiroda – 2[9]	2008	Japan	Asian	IPF	83	535	28.9	41	0.58	0.41	0.84	0.0032	70.1

OR, odds ratio; CI, confidence interval; IPF, idiopathic pulmonary fibrosis; RA, rheumatoid arthritis;AAV, ANCA-associated vasculitis;CWP, coal workers' pneumoconiosis; PF, pulmonary fibrosis;ILD, interstitial lung diseases; IIP, idiopathic interstitial pneumonia; *: Convention w = 0.1 at a 0.05 significance level;

Methodological quality

Of the ten studies, 8 studies had a NOS score of ≥ 6, indicating high study quality, while 2 studies were rated as being of low quality (NOS score < 6). The NOS scores are shown in **supplemental tables S1**.

Allele frequency of the *TERT* rs2736100 A/C polymorphism

Compared with controls, the frequency of rs2736100_C was lower in patients with ILD (38.4% vs 47.3%). Asian population had a lower rs2736100_C frequency than European population (32.8% vs 40%). The details are shown in Table 2.

Table 2
MAF of the TERT rs2736100 polymorphism

Population	No. of studies	Numbers		MAF	
		ILD	Control	ILD	Control
European	7	4509	12077	0.40	0.49
Asian	5	1218	2690	0.34	0.4
Total	12	5727	14767	0.38	0.47

MAF, minor allele frequency; ILD, interstitial lung diseases.

Meta-analysis of the *TERT* rs2736100 A/C polymorphism and susceptibility to ILD

A significant association between rs2736100_A and ILD was identified (p < 0.00001, OR 1.36, 95% CI 1.24–1.48). Ethnicity-specific meta-analysis demonstrated the incidence of ILD increased with rs2736100_A in both European population (p < 0.00001, OR 1.34, 95% CI 1.27–1.41) and Asian

population (p = 0.008, OR 1.42, 95% CI 1.10–1.85). All genetic models, including recessive, dominant, and additive models, showed increased ILD risk was associated with rs2736100_A in both European population and Asian population. The details are shown in Table 3 and Fig. 2.

Table 3
Analysis of the association between the TERT rs2736100 polymorphism and ILD

Polymorphism	Population	No. of studies	Test of association			Test of heterogeneity		
			OR	95%CI	p value	Model	p value	I^2(%)
A vs. C allele	Overall	12	1.36	1.24–1.48	< 0.00001	RE	0.008	57
	European	7	1.34	1.27–1.41	< 0.00001	FE	0.35	11
	Asian	5	1.42	1.10–1.85	0.008	RE	0.001	78
AA + AC vs. CC (dominant)	Overall	9	1.42	1.31–1.54	< 0.00001	FE	0.06	47
	European	5	1.41	1.29–1.53	< 0.00001	FE	0.1	49
	Asian	4	1.65	1.10–2.48	0.02	RE	0.07	58
AA vs. AC + CC (recessive)	Overall	9	0.65	0.57–0.74	< 0.00001	RE	0.004	64
	European	5	0.7	0.60–0.82	< 0.00001	RE	0.01	68
	Asian	4	0.56	0.43–0.73	< 0.00001	RE	0.06	59
AA vs. CC (additive)	Overall	9	1.77	1.51–2.07	< 0.00001	RE	0.04	50
	European	5	1.63	1.47–1.80	< 0.00001	FE	0.21	32
	Asian	4	2.2	135 – 3.59	< 0.00001	RE	0.03	68
AC vs. CC (additive)	Overall	9	1.25	1.14–1.36	< 0.00001	FE	0.10	40
	European	5	1.33	1.12–1.58	< 0.00001	RE	0.04	59
	Asian	4	1.19	0.94–1.51	0.16	FE	0.34	10

OR, odds ratio; CI, confidence interval; RE, R random effects model; FE, F fixed effects model; ILD, interstitial lung diseases.

Meta-analysis of the *TERT* rs2736100 A/C polymorphism and susceptibility to IPF

Among all of six IPF studies, rs2736100_A was associated with the incidence of IPF (p < 0.00001, OR 1.53, 95% CI 1.27–1.85). Significant increase of IPF risk was found for rs2736100_A in both European population (p = 0.02, OR 1.33, 95% CI 1.06–1.67) and Asian population (p < 0.00001, OR 1.79, 95% CI 1.51–2.12). All genetic models, including recessive, dominant, and additive models, showed increased IPF risk was associated with rs2736100_A in both European population and Asian population. The details are shown in Table 4 and Fig. 2.

Table 4
Analysis of the association between the TERT rs2736100 polymorphism and IPF

Polymorphism	Population	No. of studies	Test of association			Test of heterogeneity		
			OR	95%CI	p value	Model	p value	I^2(%)
A vs. C allele	Overall	6	1.53	1.27–1.85	< 0.00001	RE	0.010	67
	European	3	1.33	1.06–1.67	0.02	RE	0.11	55
	Asian	3	1.79	1.51–2.12	< 0.00001	FE	0.91	0
AA + AC vs. CC (dominant)	Overall	6	1.41	1.24–1.61	< 0.00001	FE	0.09	48
	European	3	1.32	1.15–1.52	< 0.00001	FE	0.15	47
	Asian	3	2.09	1.45-3.00	< 0.00001	FE	0.72	0
AA vs. AC + CC (recessive)	Overall	6	0.61	0.47–0.80	0.0004	RE	0.004	71
	European	3	0.78	0.69–0.87	< 0.00001	FE	0.19	40
	Asian	3	0.48	0.39–0.60	< 0.00001	FE	0.95	0
AA vs. CC (additive)	Overall	6	2.12	1.43–3.12	0.0002	RE	0.01	65
	European	3	1.61	1.02–2.54	0.04	RE	0.13	51
	Asian	3	2.85	1.95–4.16	< 0.00001	FE	0.83	0
AC vs. CC (additive)	Overall	6	1.26	1.10–1.45	0.0009	FE	0.46	0
	European	3	1.23	1.06–1.42	0.007	FE	0.22	34
	Asian	3	1.52	1.04–2.24	0.03	FE	0.73	0

OR, odds ratio; CI, confidence interval; RE, R random effects model; FE, F fixed effects model; IPF, idiopathic interstitial pneumonia.

The *TERT* rs2736100 A/C polymorphism and susceptibility to other ILD

For meta-analysis of the *TERT* rs2736100 A/C polymorphism and susceptibility to other ILD, we analyzed 2 CTD-ILD studies, 1 other ILD study and 1 CWP study.The association between rs2736100_A and ILD patients with other ILD was identified (p = 0.002, OR 1.21, 95% CI 1.07–1.36). Rs2736100_A was not associated with the incidence of CTD-ILD (p = 0.75, OR 1.07, 95% CI 0.71–1.61). The details are shown in Table 5 and Fig. 2.

Table 5
Analysis of the association between the TERT rs2736100 polymorphism and other ILD

Polymorphism	Population	No. of studies	Numbers		Test of association			Test of heterogeneity		
			Case	Control	OR	95%CI	p value	Model	p value	I^2(%)
A vs. C allele	Overall	4	318	3183	1.2	0.89–1.62	0.23	RE	0.08	60
	CTD-ILD	2	175	2497	1.07	0.71–1.61	0.75	RE	0.12	59

OR, odds ratio; CI, confidence interval; RE, R random effects model; FE, F fixed effects model; CTD-ILD, connective tissue disease associated interstitial lung diseases.

Publication bias

Publication bias were evaluated with Funnel plots. The funnel plots of any comparisons were symmetrical (**Supplementa fig S1-3**). Therefore, publication bias was considered unlikely.

Heterogeneity source and sensitivity analysis

Heterogeneity was observed in the incidence of ILD. Nevertheless, subgroup analyses by ethnicity and classification of ILD reduced the heterogeneity (Table 2–4). Sensitivity analysis performed by excluding studies one by one did not reveal any apparent possible heterogeneity source (data not shown).

Discussion

To our knowledge, this is the first meta-analysis of the *TERT* rs2736100 polymorphism and susceptibility to ILD. We found rs2736100_A was significantly associated with ILD in both European and Asian population. The TERT rs2736100 minor allele, rs2736100_C, was lower frequent in Asian population. Subgroup analysis stratified by classification of ILD revealed that the *TERT* rs2736100 A/C polymorphism was genetic risk factor for IPF, but not for CTD-ILD.

Previous studies demonstrated genes involved in the host-defense, cell-cell adhesion, DNA repair were associated with the incidence of ILD. According to GWAS studies, identified genetic risk foci include *MUC5B* (rs35705950), *TERT* (rs2736100), *TOLLIP* (rs111521887, rs5743894, rs2743890), *IL1RN* (rs408392, rs419598), *DSP* (rs2076295), *FAM13A* (rs2609255), *IL8* (rs4073, rs2227307) and so on [5–7]. The *MUC5B* rs35705950 has been consider as a common and strong genetic risk factor for ILD in general population [13].

Our study confirmed the *TERT* rs2736100 polymorphism was a strong risk factor for IPF, while no association was observed in patients with CTD-ILD. OR for AA vs. CC was higher than that for AC vs. CC (1.77 vs 1.25). In a previous study, the *TERT* rs2736100 polymorphism was associated with other ILD but not IPF [14]. In a Chinese population study, no significant difference of the *TERT* rs2736100 polymorphism was found between IPF and controls [15]. Of note, the sample sizes were small in these two studies.

Ethnic differences of the *TERT* rs2736100 polymorphism have been analyzed in our study. In a SNP association study in cohorts of Mexican and Korean patients with IPF, after adjusted for MUC5B rs35705950, the *TERT* rs2736100 polymorphism was associated with IPF in Mexican patients, but not in Korean patients [11]. We found Asian patients had a lower rs2736100_C frequency. For A vs C, AA vs CC, AA + AC vs CC genetic models, OR of Asian ILD patients was higher than that of European group.

In this study, no association of the *TERT* rs2736100 polymorphism was observed in patients with CTD-ILD. Two studies, involving rheumatoid arthritis (RA) patients and anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV) patients, have been included in this meta-analysis [10, 16]. We noticed that control groups of these studies were patients with CTD. These results might suggest *TERT* may also participate in pathogenesis of RA or AAV patients without ILD.

The mechanism of the *TERT* rs2736100 polymorphism in ILD remains unclear. Emerging evidences suggest the incidence of ILD increases with telomere abnormalities. Shorter telomere lengths (TLs) had more frequency in IPF and other ILD (e.g. CTD-ILD and HP). According to previous studies, TLs in AT2 cells of IPF lung were shorter than controls and were associated with total collagen of patients [17]. Shorter blood leukocyte TL was also observed in patients with IIP [18]. The shorten changes of telomere can be induced by mutations in the *TERT* rs2736100 polymorphism. IPF homozygous for rs2736100_C had longer telomeres than patients homozygous for rs2736100_A [13]. Hence, we suppose the role of the *TERT* rs2736100 polymorphism in the occurrence and development of ILD might be a result from its effects on telomere length. Furthermore, a luciferase assay study on pulmonary epithelial cells showed the enhancer activity of rs2736100_A was lower than that of rs2736100_C, and was also related with decreased expression of TERT mRNA [19]. Further studies are warranted to clarify the role of the *TERT* rs2736100 polymorphism in ILD.

This study has several limitations. High heterogeneity existed among the studies. Subgroup analysis according to ethnicity and classification of ILD did not completely reduce heterogeneity, which could be explained by the diverse study design. ILD could be effected by multiple factors, such as age, gender and smoking, so characteristics of study subjects will increase the heterogeneity of our study. The selection of control groups may also influence the heterogeneity. Some studies used healthy people as control groups, while other studies chose patients without ILD, such as asthma or RA. Furthermore, the number of included CTD-ILD studies was small and genotype distribution of rs2736100 was not available. Therefore, meta-analysis of genetic models could not be performed.

Conclusion

In conclusion, this study demonstrated the frequency of rs2736100_A was lower in Asian population. We confirmed the *TERT* rs2736100 A/C polymorphism was a strong risk factor for IPF, but not for CTD-ILD. Whether the incidence of CTD-ILD increases with the *TERT* rs2736100 A/C polymorphism needs to be evaluated in the future.

Declarations

Ethics approval and consent to participate

This study does not involve with ethics as it is a systematic review and meta-analysis.

Consent for publication

No patient involved.

Availability of data and materials

The datasets generated during and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

All authors do not have any conflicts of interest to disclose.

Funding

This study is supported by Sichuan Science and Technology Program (2021JDRC0045, 2021YFS0164, 2021YJ0472, 2021JDRC0169), and Clinical Research Incubation Project of West China Hospital, Sichuan University (2019HXFH038).

Authors' contributions

Xie, Yin and Cui conceived the study, Chen and Cui designed the study forms, and Yin and Xie guided this study. Cui searched the literature; Chen and Ma screened the studies for inclusion and extracted data; Chen and Cui assessed methodological quality; Chen and Cui organized data. All authors drafted and revised the manuscript.

Acknowledgements

Not applicable

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Figures

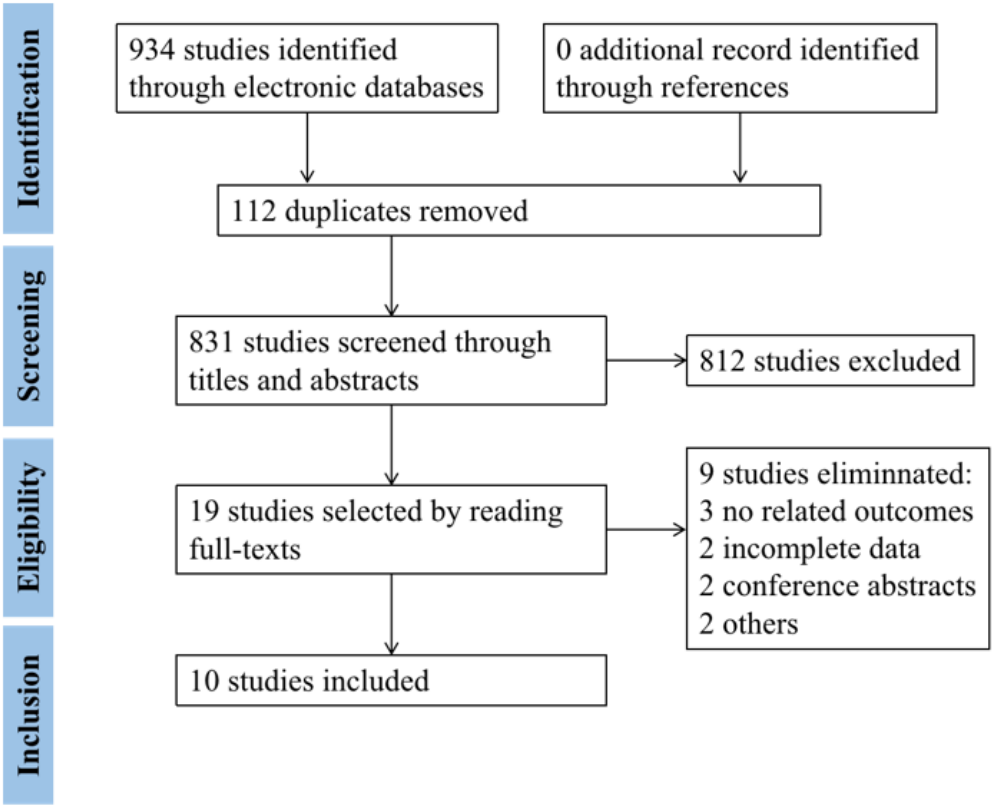

Figure 1

Study selection flowchart.

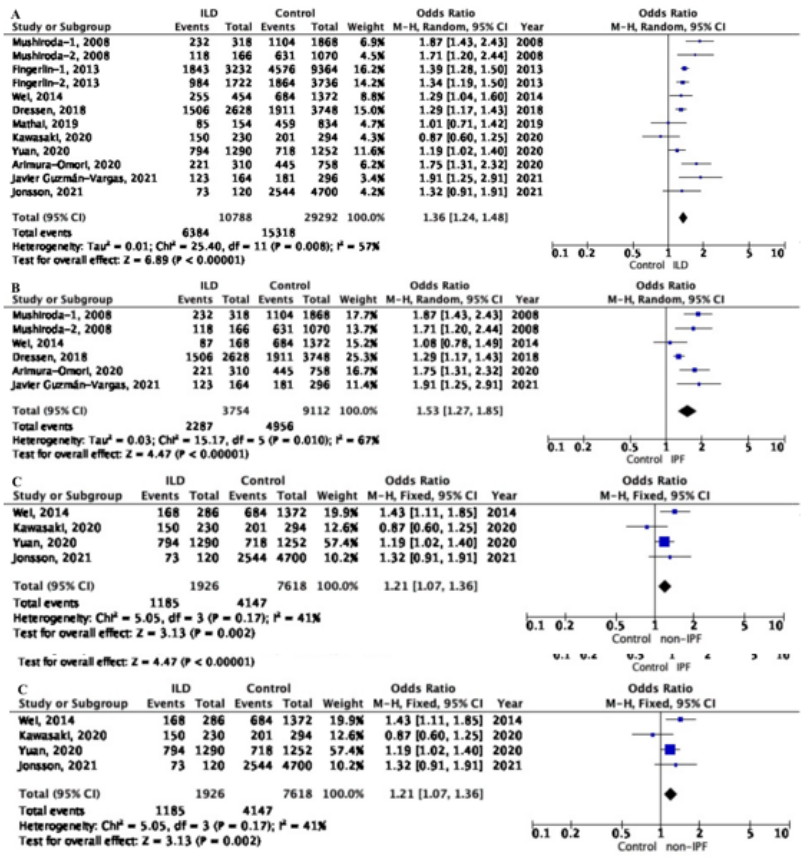

Figure 2

Odds ratios and 95 % confidence intervals from individual studies and pooled data, for association between rs2736100_A and ILD (A), IPF (B) and other ILD (C).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementaltable1Themethodologicalqualityas.docx
- ildfunnelplot.png
- ipfFunnelplot.png
- nonipfFunnelplot.png