International Archives of Occupational and Environmental Health (2023) 96:45–56
https://doi.org/10.1007/s00420-022-01893-1

REVIEW ARTICLE

Genetic susceptibility in pneumoconiosis in China: a systematic review

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Received: 13 March 2022 / Accepted: 23 May 2022 / Published online: 29 July 2022

Abstract

Objective Pneumoconiosis, encompassing coal workers' pneumoconiosis (CWP), silicosis and asbestosis, is one of the most common occupational diseases in China. Previous studies revealed significant associations between genetic variations and pneumoconiosis risk among individuals in different countries. With the known variability of genetic makeup between ethnicities, susceptibility to pneumoconiosis due to genetic differences is likely to be ethnicity-specific. The present review aimed at providing a comprehensive overview on the association between genetic polymorphisms and susceptibility of pneumoconiosis, specifically among people in China.

Methods The literature search was performed in seven English and Chinese databases using keywords related to the review aim. An appraisal of the methodological quality of the included studies was conducted using the assessment tool derived from the Strengthening the Reporting of Genetic Association Studies (STREGA) statement.

Results Forty-five studies were included in this review. Genotypes of specific genes which are associated with the risk of CWP, silicosis and asbestosis were reported. Our findings showed that genes encoding inflammatory cytokines have been examined extensively, and they demonstrated an association between these genes and pneumoconiosis risk. Gene–environment interactions in pneumoconiosis susceptibility were also reported by a number of studies.

Conclusions This review summarised the evidence demonstrating the association between genetic polymorphisms and pneumoconiosis susceptibility among people in China, and that various genotypes could modify their risk to develop pneumoconiosis. The findings prompt that identification of individuals at high pneumoconiosis risk through genetic screening and strategies limiting their exposure to dust could be a potential strategy for the control of this occupational disease in China.

Keywords Single nucleotide polymorphism · Genotype · Coal workers' pneumoconiosis, silicosis · Asbestosis

Introduction

Pneumoconiosis is a group of interstitial lung diseases caused by chronic inhalation of dust particles that induce inflammation of the alveoli and eventually result in irreversible lung damage and even death (Cullinan and Reid 2013). Pneumoconiosis appears in different forms depending on the type of dust inhaled, such as coal dust, silica and asbestos. China is among the countries that contribute to an alarming number of diagnosed pneumoconiosis cases around the world (Han et al. 2015a). In 2016, 27,992 new pneumoconiosis cases were reported in China, of which 16,658 (59.5%) had coal workers' pneumoconiosis (CWP) and 10,072 (36%) had silicosis (Han et al. 2018). New cases of lung diseases caused by coal dust made up 44.83% of all occupational diseases (Han et al. 2018). By the end of 2018, the cumulative reports of occupational pneumoconiosis had been around 870,000 cases (Data available at http://www.gov.cn/zhengce/2019-05/14/content_5391271.htm), of which 193 cases (0.69%) had asbestosis (Chen et al. 2020). For the data of coal dust exposure, it was estimated that the maximum concentration of coal dust was between 198–3420 mg/m^3, which was 49.5–855 times that of the standard of occupational exposure limit (Han et al. 2018).

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In addition to its high prevalence, pneumoconiosis is also difficult to diagnose and treat. Difficult diagnosis is due to complicated assessment procedures and the need for highly-trained medical personnel. In general, patients are diagnosed with pneumoconiosis at later disease stages, when their conditions are often too serious for treatment to have any positive effect. There is no effective treatment that can reverse lung damage caused by coal dust, although certain interventions can help to slow down disease progression, relieve symptoms and improve patients' quality of life (Ochmann et al. 2012).

Many studies had explored the contribution of genetic factors to the susceptibility to develop pneumoconiosis, and they demonstrated the combined influence of genotypes and genetic polymorphisms in risk alleles to such susceptibility. Nevertheless, with genetic makeup known to be different among individuals between ethnicities (Huang et al. 2015), it is likely that the genetic variations that contribute to susceptibility to pneumoconiosis among individuals would also likely be different between ethnicities. Also, given the different characteristics of the population and the environment of the coal mines alike in different countries, it is likely that the findings on the identified genetic variations associated with pneumoconiosis risk among individuals, reported by studies in different countries may not necessarily apply to China (Li et al. 2007), the country with the highest coal production, the highest number of coal miners and the highest prevalence of CWP in the world (Han et al. 2018). To date, many genetic association studies were conducted in China, uncovering the contribution of genetic background in susceptibility of pneumoconiosis in Chinese populations. Given the complex and ethnic-group-dependent interplay between genetic and environmental factors imposes a challenge for us to understand the aetiology of the complex diseases, a review on the identified association between genetic polymorphism and pneumoconiosis, specifically in China, is needed. This review aims to provide a systematic overview of evidence for the association between genetic polymorphisms and different types of pneumoconiosis in China.

Methods

Search strategy

We performed a literature search according to the criteria outlined in the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guideline (Moher et al. 2009). No registration for the protocol was made. Literature search was conducted in December 2021 and repeated in May 2022, using seven databases including PubMed, Ovid Medline, Ovid Nursing, Embase and CINAHL, as well as Chinese databases of Wanfang and CNKI using the search strategy shown in Table 1. We also performed manual searches by screening the reference section of the included studies.

Eligibility criteria

Studies were eligible for inclusion if they were written in English or Chinese, reporting cohort or case–control studies comparing the genetic variations between control subjects and pneumoconiosis patients in China. Studies were excluded if they are reviews, study protocols, conference abstracts or original articles reporting animal- or cell-based studies. Studies with outcomes not measuring pneumoconiosis susceptibility or the study population not on Chinese were also excluded.

Data extraction

Using the Covidence software (available at www.covidence.org), duplicated articles retrieved during the literature search were first removed. The titles and abstracts of the retrieved articles were then screened, and articles reporting studies irrelevant to the review aim were removed. Examination of the full-text of the remaining articles was performed independently by two authors to confirm their eligibility for inclusion. For each included study, one author completed data extraction in full, and the second author verified all the data extracted to ensure their accuracy. Extracted data included study centre, study design, study population, cohort size, concerned gene polymorphism, statistical measures of outcome and confounders such as smoking status, age, dust exposure year. Conflicts were discussed between the two authors and a third author was consulted in case a consensus could not be reached. We anticipated a high degree of heterogeneity among the included studies in terms of the gene polymorphisms and the type of pneumoconiosis examined, resulting in an insufficient number of studies examining the association between a particular gene polymorphism and a particular type of pneumoconiosis for a meta-analysis. The conduction of a meta-analysis of the extracted data was

Table 1 Search strategy

"Pneumoconiosis" **OR** "Anthracosis" **OR** "Anthracosilicosis" **OR** "Silicosis" **OR** "Silica" **OR** "Asbestosis" **OR** "Asbestos" **OR** "Aluminosis" **OR** "Aluminium" **OR** "Potter's Pneumoconiosis"
AND
"Polymorphism" **OR** "Polymorphic" **OR** "SNP" **OR** "SNPs" **OR** "Genotype" **OR** "Genetic Variant" **OR** "Genomic Variant" **OR** "Genetic Variation" **OR** "Genomic Variation" **OR** "GWAS" **OR** "Genome-Wide Association Study"
AND
"Chinese" **OR** "China" **OR** "Han"

therefore not planned. The findings of the included studies were presented in a narrative and tabular manner.

Quality assessment

All included studies were subjected to methodological quality assessment based on a 9-item quality checklist, with assessment items taken from the Strengthening the Reporting of Genetic Association Studies (STREGA) Statement that provides recommendations on the reporting of genetic association studies (Little et al. 2009). The quality assessment evaluates whether the included studies have provided an adequate description of the following: (1) The method and centre for genotyping; (2) Number of genotyped samples and successful rate; (3) Methods on determine genotypes, haplotypes and population stratification; (4) Statement on Hardy–Weinberg equilibrium and novelty of genetic association. A total quality score for each study was calculated by adding all the corresponding quality item scores (range: 0–9), with higher scores indicating higher overall quality. The quality item score was then expressed as a percentage, and studies were categorised as high quality, moderate quality or low quality based on this percentage score, as done previously (Andric et al. 2021). Studies achieving a percentage score of over 80% were considered high quality. Those with a percentage score of 50–80% were considered moderate quality, and those having a percentage score lower than 50% were of low quality. In addition to STREGA that evaluate the genotyping methods, we have considered other confounders such as smoking status and dust exposure time which have given importance of gene-environment interactions.

Results

Search results

We retrieved 681 studies during the literature search. After excluding 77 duplicated articles and a further 518 studies owing to their inability to fit the eligibility criteria, we examined the full-text of the remaining 86 articles. Forty-four of these studies were excluded as they were either reporting irrelevant outcomes (not measuring susceptibility of pneumoconiosis, $N=40$), irrelevant study design (not original research study, $N=3$) or inappropriate study population (not Chinese population, $N=1$). Three additional articles were sourced through reference list, resulting in the inclusion of 45 studies in this review. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram depicting the search results is shown in Fig. 1.

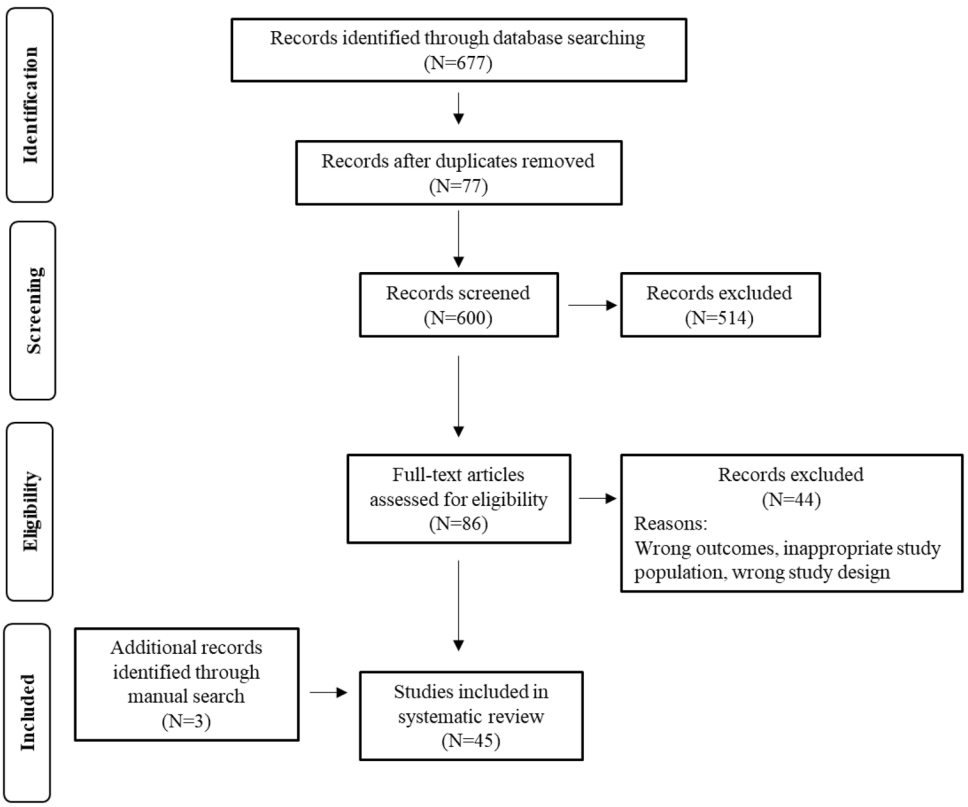

Fig. 1 The PRISMA flow diagram

Quality of included studies

The quality score for each included study, as assessed using the 9-item checklist, is shown in Table 2. Among the included studies, their quality scores range between 22.2% and 66.7%. Nine studies scored as low quality and thirty-six studies as moderate quality. Most of the studies reported well on the genotyping methods (98%), number of genotypes samples (96%) and Hardy–Weinberg equilibrium consideration (89%). However, none of the studies provided a hint on whether the genotyping was done in one single batch or a few smaller batches. In addition, only one of the studies described the centre at which the genotyping was performed (2%) and few studies described any methods on determining genotypes or haplotypes (16%). About half of the studies (45%) indicated that the study was the first to show the association between gene polymorphism concerned and pneumoconiosis. Other confounding factors concerning gene-environment interactions was listed in the Supplementary Table.

Characteristics of included studies

The characteristics of the included studies are listed in the Supplementary Table. All included studies are case–control studies. These studies were published between 2001 and 2021 (Bian et al. 2014; Chen et al. 2014, 2015; Chu et al. 2014; Dang et al. 2012; Fan et al. 2021; Fang et al. 2011; Han et al. 2015b; Ji et al. 2012, 2014, 2015, 2017; Jin et al. 2012; Liu et al. 2017; Ni et al. 2007, 2009; Qian et al. 2010; Qu et al. 2007; Tang et al. 2020; Wang et al. 2011, 2012a, b, 2013, 2014, 2018a, b, c; Weng et al. 2015; Wu et al. 2008a, b, 2014, 2016; Xu et al. 2006, 2010; Yang et al. 2009, 2015, 2020; Yu et al. 2009; Yuan et al. 2017, 2018a, b, 2020; Zhai et al. 2001, 2002; Zhang et al. 2011). All investigated the association between genetic polymorphism and pneumoconiosis in the Chinese population. Among the included studies, 34 studies involved subjects with CWP (Bian et al. 2014; Chen et al. 2015; Chu et al. 2014; Dang et al. 2012; Han et al. 2015b; Ji et al. 2012, 2014, 2015, 2017; Jin et al. 2012; Liu et al. 2017; Ni et al. 2007, 2009; Qian et al. 2010; Tang et al. 2020; Wang et al. 2011, 2012b, 2013, 2014, 2018a; Wu et al. 2014, 2016; Xu et al. 2010; Yang et al. 2009, 2015, 2020; Yu et al. 2009; Yuan et al. 2017, 2018a, b, 2020; Zhai et al. 2001, 2002; Zhang et al. 2011) while ten other studies involved subjects with silicosis (Chen et al. 2014; Fan et al. 2021; Fang et al. 2011; Qu et al. 2007; Wang et al. 2012a; Wang et al. 2018b, c; Weng et al. 2015; Wu et al. 2008a, b). One additional study had subjects with asbestosis (Xu et al. 2006). Many of the included studies involved examination of genetic polymorphisms of cytokine genes including IL-1 (Dang et al. 2012; Ji et al. 2012; Weng et al. 2015; Wu et al. 2008b), IL-4 (Fang et al. 2011; Wang et al. 2011), IL-6 (Zhai et al. 2001), IL-10 (Wu et al. 2008a), IL-13 (Wang et al. 2011), IL-17 (Chen et al. 2014; Han et al. 2015b), IL-18 (Ji et al. 2012), TNF-α (Qu et al. 2007; Wang et al. 2012a; Wu et al. 2008a; Xu et al. 2006; Yang et al. 2009; Yu et al. 2009), IFN-γ (Wu et al. 2008a). The genes and genotypes associated with pneumoconiosis risk were summarized in Table 3.

Genetic susceptibility of pneumoconiosis in China

Association of cytokine genes with pneumoconiosis

Pneumoconiosis results from the accumulation of fine inhaled particles. As the inhaled particles enter the lung, alveolar macrophages take up the particles via phagocytosis and the resulting release of inflammatory cytokines is the first and most important step in pneumoconiosis. Therefore, the association between cytokine gene polymorphisms and pneumoconiosis was analysed.

In the included studies of this review, TNF-α genotype -308G/A was reported to be significantly associated with increased risk of CWP, silicosis and asbestosis (Wang et al. 2012a; Xu et al. 2006; Yang et al. 2009). The multivariate unconditional logistic regression model presented by Wang et al. (Wang et al. 2012a) showed that the association between 3 SNPs (TNF-α -308, TNF-α -238 and IL-1RA + 2018) and silicosis was statistically significant, where all three SNPs led to increased silicosis risk among the subjects. Consistent with this, Xu et al. (Xu et al. 2006) reported that TNF-α -308G/A genotype was associated with an increased risk of asbestosis (OR = 4.44, 95% CI 1.27–15.54, $p = 0.014$) (Xu et al. 2006), while Yang et al. (Yang et al. 2009) reported an increased risk of CWP among individuals carrying the minor allele of TNF-α -308G/A genotype ($p < 0.05$) (Yang et al. 2009). However, conflicting results were reported by Wu et al. (Wu et al. 2008a), where the authors showed no association between TNF-α -308 genotypes and the risk of silicosis (Wu et al. 2008a).

For IL-1β, four studies included in this review reported negative association of IL-1β genotype with the risk of CWP (Dang et al. 2012; Ji et al. 2012) and silicosis (Weng et al. 2015; Wu et al. 2008b). Nevertheless, Weng et al. (2015) reported no significant association between IL-1 genotype and silicosis risk when the data were stratified before analysis (Weng et al. 2015). Furthermore, Wu et al. (2008b) did not report any association between a number of cytokine genes (IL-1A, IL-1B and IL-1RN) and risk of silicosis (Wu et al. 2008b).

Two included studies demonstrated the protective effect of IL-4 genotypic variants on CWP and silicosis (Fang et al. 2011; Wang et al. 2011). Wang et al. (2011) reported that individuals bearing the minor C allele of IL-4 -590 showed were at lower risk of CWP when compared to those bearing the T allele (OR = 0.80, 95% CI 0.65–0.98,

Table 2 Reporting quality of the included studies

Study	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Score (% Score)
Bian et al. 2014	Y	N	N	N	Y	N	N	Y	N	3 (33.3%)
Chen et al. 2014	Y	N	N	N	Y	N	Y	Y	Y	5 (55.6%)
Chen et al. 2015	Y	N	N	N	Y	N	N	Y	N	3 (33.3%)
Chu et al. 2014	N	N	N	N	Y	Y	N	Y	Y	4 (44.4%)
Dang et al. 2012	Y	N	Y	N	Y	N	N	Y	N	4 (44.4%)
Fan et al. 2021	Y	N	N	N	Y	N	N	N	Y	3 (33.3%)
Fang et al. 2011	Y	N	N	N	Y	N	Y	N	N	3 (33.3%)
Han et al. 2015b	Y	N	N	N	Y	Y	N	Y	Y	5 (55.6%)
Ji et al. 2012	Y	N	N	N	Y	Y	N	Y	Y	5 (55.6%)
Ji et al. 2014	Y	N	N	N	N	Y	N	Y	Y	4 (44.4%)
Ji et al. 2015	Y	N	N	N	N	Y	N	Y	Y	4 (44.4%)
Ji et al. 2017	Y	N	N	N	Y	Y	N	Y	N	4 (44.4%)
Jin et al. 2012	Y	N	N	N	Y	Y	N	Y	Y	5 (55.6%)
Liu et al. 2017	Y	N	N	N	Y	Y	N	Y	Y	5 (55.6%)
Ni et al. 2007	Y	N	N	N	Y	N	N	Y	N	3 (33.3%)
Ni et al. 2009	Y	N	N	N	Y	Y	N	Y	Y	5 (55.6%)
Qian et al. 2010	Y	N	N	N	Y	Y	N	Y	N	4 (44.4%)
Qu et al. 2007	Y	N	N	N	Y	Y	Y	Y	Y	6 (66.7%)
Tang et al. 2020	Y	N	N	N	Y	N	Y	Y	N	4 (44.4%)
Wang et al. 2011	Y	N	N	N	Y	Y	N	Y	N	4 (44.4%)
Wang et al. 2012a	Y	N	N	N	Y	N	Y	Y	N	4 (44.4%)
Wang et al. 2012b	Y	N	N	N	Y	N	N	Y	N	3 (33.3%)
Wang et al. 2013	Y	N	N	N	Y	Y	N	Y	N	4 (44.4%)
Wang et al. 2014	Y	N	N	N	Y	Y	N	Y	Y	5 (55.6%)
Wang et al. 2018a	Y	N	N	N	Y	N	N	Y	Y	4 (44.4%)
Wang et al. 2018b	Y	N	N	N	Y	Y	N	Y	Y	5 (55.6%)
Wang et al. 2018c	N	N	N	N	Y	Y	N	Y	Y	4 (44.4%)
Weng et al. 2015	Y	N	N	N	Y	Y	N	N	N	3 (33.3%)
Wu et al. 2008a	Y	N	N	N	Y	N	Y	Y	N	4 (44.4%)
Wu et al. 2008b	Y	N	N	N	Y	N	Y	Y	N	4 (44.4%)
Wu et al. 2014	Y	N	N	N	Y	N	N	Y	Y	4 (44.4%)
Wu et al. 2016	Y	N	N	N	Y	N	N	Y	N	3 (33.3%)
Xu et al. 2006	Y	N	N	N	Y	N	N	Y	N	3 (33.3%)
Xu et al. 2010	Y	N	N	N	Y	N	N	Y	N	3 (33.3%)
Yang et al. 2009	Y	N	N	N	Y	N	N	Y	N	3 (33.3%)
Yang et al. 2015	Y	N	N	N	Y	N	N	Y	Y	4 (44.4%)
Yang et al. 2020	Y	N	N	N	Y	N	N	Y	N	3 (33.3%)
Yu et al. 2009	Y	N	N	N	Y	N	N	Y	N	3 (33.3%)
Yuan et al. 2017	Y	N	N	N	Y	N	N	Y	N	3 (33.3%)
Yuan et al. 2018a	Y	N	N	N	Y	N	N	Y	N	3 (33.3%)
Yuan et al. 2018b	Y	N	N	N	Y	N	N	Y	Y	4 (44.4%)
Yuan et al. 2020	Y	N	N	N	Y	N	N	Y	Y	4 (44.4%)
Zhai et al. 2001	Y	N	N	N	Y	N	N	N	N	2 (22.2%)
Zhai et al. 2002	Y	N	N	N	Y	N	N	N	N	2 (22.2%)
Zhang et al. 2011	Y	N	N	N	Y	N	N	Y	Y	4 (44.4%)

Description of items: Item 1. Describe laboratory methods, including source and storage of DNA, genotyping methods and platforms; Item 2: Describe the error rate and call rate; Item 3: Describe the centre at which the genotyping was performed; Item 4: Provide a hint on whether the genotyping was done in one single batch or a few smaller batches; Item 5: Report the number of individual participants' samples were genotyped and how many of these samples were successfully genotyped; Item 6: Describe how to assess the level of and/or control for population stratification; Item 7: Describe any methods on determining (inferring) genotypes or haplotypes; Item 8: Stated that the Hardy–Weinberg equilibrium is considered; Item 9: Stated whether this is the first report to report such genetic association or was it a replicated effort of a previous study, or both

Table 3 List of genes and genotypes associated with pneumoconiosis risk

Gene	SNPs reported	Patient type	Effect of SNPs on disease risk	Reference
AnnexinA5	-1C/T	CWP	Decreased	Wang et al. 2012b
Autophagy related gene (ATG)	rs26538	CWP	Decreased	Yuan et al. 2017
	rs1864182	CWP	Decreased	
	rs510432	CWP	Decreased	
Caspase-1 (CASP1)	rs1042743	Silicosis	Increased	Weng et al. 2015
Caspase-8 (CASP8)	rs3834129	CWP	Increased	Ni et al. 2009
Cyclo-oxygenase 2 (COX-2)	rs689466	CWP	Decreased	Bian et al. 2014
	rs20417	CWP	Decreased	
Cytochrome b-245α polypeptide (CYBA)	rs7195830	CWP	Increased	Yuan et al. 2018b
Desmoplakin (DSP)	rs2076304	Silicosis	Increased	Wang et al. 2018c
Epoxide Hydrolase 1 (EPHX1)	rs2234922	CWP	Decreased	Chen et al. 2015
E-selectin (SELE)	rs5368	CWP	Increased	Wang et al. 2013
Family with sequence similarity 13, member A (FAM13A)	rs2609255	Silicosis	Increased	Wang et al. 2018b
FAS Ligand (FASL)	844 T/C	CWP	Increased	Ni et al. 2007
Glucocorticoid-induced tumour necrosis factor receptor-related protein (GITR)	rs3753348	CWP	Increased	Wu et al. 2014
H19	rs2067051	CWP	Decreased	Wu et al. 2016
Heat shock protein 70 (HSP70)	rs1061581	CWP	Decreased	Zhang et al. 2011
	rs2227956	CWP	Increased	
High-mobility group box 1 (HMGB1)	rs1360485	CWP	Increased	Tang et al. 2020
Inducible nitric oxide synthase (iNOS)	Ser608Leu	Silicosis	Decreased	Qu et al. 2007
Interleukin-1 receptor antagonist (IL-1RA)	+2018 T/C	Silicosis	Increased	Wang et al. 2012a
Interleukin-4 (IL-4)	− 33C/T	Silicosis	Decreased	Fang et al. 2011
	− 590 T/C	CWP	Decreased	Wang et al. 2011
Interleukin-17A (IL-17A)	rs3748067	CWP	Decreased	Han et al. 2015b
	rs8193036	CWP	Decreased	
Interleukin-17F (IL-17F)	7488A/G	Silicosis	Decreased	Chen et al. 2014
Laminin beta 1 (LAMB1)	rs4320486	CWP	Decreased	Ji et al. 2017
Lipopolysaccharide-responsive beige-like anchor protein (LRBA)	rs2290846	CWP	Decreased	Liu et al. 2017
Macrophage migration inhibitory factor (MIF)	rs755622	CWP	Decreased	Jin et al. 2012
Matrix metalloproteinase 3 (MMP3)	rs522616	CWP	Decreased	Ji et al. 2015
Matrix metalloproteinase-7 (MMP-7)	rs10502001	CWP	Increased	Yang et al. 2015
Mucin 5B (MUC5B)	rs2672794	CWP	Increased	Ji et al. 2014
NLR family pyrin domain containing 3 (NLRP3)	rs1539019	CWP	Increased	Ji et al. 2012
	rs34298354	Silicosis	Increased	Weng et al. 2015
Nuclear Assembly Factor 1 (NAF1)	rs4691896	CWP	Increased	Yuan et al. 2020
Nuclear factor kappa B (NF-kB)	94 ins/del	Silicosis	Decreased	Wu et al. 2008b
Osteonectin (SPARC)	rs1059279	CWP	Increased	Wang et al. 2014
	rs1059829	CWP	Increased	
	rs1053411	CWP	Increased	
Osteopontin (OPN)	rs1126772	CWP	Increased	Yang et al. 2015
	rs11728697	CWP	Increased	
SMAD4	rs10502913	CWP	Increased	Xu et al. 2010
	rs9304407	CWP	Decreased	
Transforming growth factor-β1 (TGF-β1)	rs1800470	CWP	Decreased	Qian et al. 2010
	rs11466345	CWP	Increased	

Table 3 (continued)

Gene	SNPs reported	Patient type	Effect of SNPs on disease risk	Reference
Tumour necrosis factor-α (TNF-α)	− 308G/A	Silicosis	Increased	Wang et al. 2012a
	− 238G/A	Silicosis	Increased	
	− 308G/A	Asbestosis	Increased	Xu et al. 2006
	− 308G/A	CWP	Increased	Yang et al. 2009
Vitamin D receptor (VDR)	rs7975232	CWP	Increased	Yang et al. 2020
	rs731236	CWP	Decreased	
Unknown gene	rs73329476	CWP	Increased	Chu et al. 2014
Unknown gene	rs4320486	CWP	Decreased	Chu et al. 2014
Unknown gene	rs117626015	CWP	Increased	Chu et al. 2014
Unknown gene	rs10797062	CWP	Increased	Wang et al. 2018a
Unknown gene	rs2540438	CWP	Increased	Wang et al. 2018a
Unknown gene	rs2274554	CWP	Increased	Wang et al. 2018a
Unknown gene	rs1667614	CWP	Decreased	Wang et al. 2018a

$p = 0.034$). Individuals with CT/CC genotype also had lower risk of CWP than those having the TT genotype (OR = 0.73, 95% CI .57–0.94, $p = 0.016$). In addition, combined polymorphism analysis of IL-4 and IL-13 demonstrated a dose-dependent increase in silicosis risk with increasing numbers of risk variant alleles ($P_{trend} = 0.023$). A protective effect of IL-4 CT/CC genotype on silicosis was also reported by Fang et al. ($p < 0.05$) (Fang et al. 2011).

Zhai et al. (2001) investigated the prevalence of IL-6 -174G/C SNP in CWP patients and found that this IL-6 polymorphism at -174 is extremely rare in the study population and is unlikely to be associated with CWP susceptibility.

As shown by Han et al. (Han et al. 2015b), individuals bearing the AA genotype of the rs3748067 SNP of IL-17A were at significantly reduced risk of CWP compared to those having the GG genotype (OR: 0.43; 95% CI 0.23 – 0.83; $p = 0.011$), while those having the CC genotype of rs8193036 SNP of IL-17A were at significantly lower CWP risk when compared with those having the TT genotype (OR: 0.59; 95% CI 0.40 – 0.86; $p = 0.006$) (Han et al. 2015b). Further, Chen et al. reported the protective effect of genetic polymorphisms in another member of IL-17. They showed that GA genotype of IL17F of the 7488A/G SNP conferred a decreased risk of silicosis (OR: 0.374; 95% CI 0.198 – 0.705; $p = 0.002$).

No association was found between the examined SNPs of IL-10 (Wu et al. 2008a), IL-13 (Wang et al. 2011), IL-18 (Ji et al. 2012) and IFN-γ (Wu et al. 2008a) and the risk of pneumoconiosis.

Gene-environment interaction

Stratification analyses in some of the included studies revealed that the associations between gene polymorphisms and pneumoconiosis risk could be affected by environmental factors. For example, the association between SNPs of the potential pneumoconiosis susceptibility genes and CWP risk was demonstrated to be significantly modified under certain environmental conditions, including duration of dust exposure (Ji et al. 2012, 2015; Ni et al. 2007; Qian et al. 2010; Wang et al. 2012a, 2018a; Wu et al. 2016; Yang et al. 2020; Yuan et al. 2018a), smoking (Ji et al. 2012, 2014, 2015; Jin et al. 2012; Liu et al. 2017; Ni et al. 2007; Qu et al. 2007; Wang et al. 2014; Wu et al. 2016; Xu et al. 2006; Yang et al. 2020; Yuan et al. 2018a), age (Ji et al. 2012; Jin et al. 2012; Qian et al. 2010; Wang et al. 2012a, 2014; Yuan et al. 2018a) and pneumoconiosis stage (Ji et al. 2012, 2014; Jin et al. 2012; Qu et al. 2007; Wang et al. 2012a, 2018a; Weng et al. 2015; Wu et al. 2016; Xu et al. 2006; Yuan et al. 2018a). Nevertheless, findings on the effect of these environmental factors on such association appear inconsistent between studies. Association between genotypic variations and decreased risk of pneumoconiosis was reported in shorter dust exposure time (Liu et al. 2017; Yuan et al. 2017) and in longer dust exposure time (Han et al. 2015b; Wang et al. 2011), in smokers (Han et al. 2015b; Ji et al. 2017; Jin et al. 2012; Yuan et al. 2017) and non-smokers (Liu et al. 2017; Qian et al. 2010; Wu et al. 2016), in younger age (Han et al. 2015b; Ji et al. 2017; Wang et al. 2011; Yuan et al. 2017) and older age (Ji et al. 2017), as well as in different stages of CWP or silicosis (Stage I (Han et al. 2015b; Ji et al. 2017; Wang et al. 2011; Wu et al. 2016; Yuan et al. 2017), Stage II (Yuan et al. 2017). On the other hand, association between genotypic variations and increased risk of

pneumoconiosis was reported in shorter dust exposure time (Ji et al. 2014; Yang et al. 2015) or in longer dust exposure time (Ni et al.2009; Wang et al.2014; Wu et al.2014; Yang et al.2015), in smoker (Ji et al. 2012, 2014) or non-smoker (Qian et al. 2010; Wang et al. 2013; Wu et al. 2014; Yang et al. 2015), in younger age (Ni et al. 2009) or older age (Wang et al. 2013), as well as in different stages of CWP or silicosis Stage I (Ji et al. 2012; Qian et al. 2010), Stage II/III (Qian et al. 2010; Wang et al. 2011, 2014, 2018c; Wu et al. 2014).

Three included studies reported the interaction of genotypes and different environmental factors using multifactor dimensionality reduction (MDR) analysis. Yang et al. (2020) and Tang et al. (2020) demonstrated that the strongest interaction in CWP was detected between genotypes and dust exposure time. Another study found that the number of cigarettes smoked was the strongest factor for predicting CWP risk (Wang et al. 2013).

Discussion

China, the United States and Australia were among the top three coal-producing countries in the world in 2017. However, the prevalence of CWP in China (6.02%) has been comparatively higher than that in the United States (1.88%) and Australia (<0.5%) (Mo et al. 2014; Laney et al. 2010; Joy et al. 2012). The high prevalence of pneumoconiosis in China therefore raised a concern on the local population's health. In the past decades, it is recognised that genetic variations may contribute greatly to the development of pneumoconiosis and such variations are influenced by environmental factors. In addition, genetic variations are also different among ethnic groups. For these reasons, we conducted a comprehensive review to summarize the findings in China exclusively. Our findings demonstrated that genes of cytokines and inflammasomes have strong association with the risk of pneumoconiosis. In addition, the interaction between gene polymorphisms and environmental factors is also critical on pneumoconiosis susceptibility.

Cytokines have been shown to play important roles in the pathogenesis of dust particle-induced pulmonary inflammatory reactions and chronic inflammatory diseases (Rimal et al. 2005; Wynn et al. 2004; Wilson et al. 2009). In the included studies, cytokines such as IL-1 (Dang et al. 2012; Ji et al. 2012; Weng et al. 2015; Wu et al. 2008b), IL-4 (Fang et al. 2011; Wang et al. 2011), IL-6 (Zhai et al. 2001), IL-17 (Chen et al. 2014; Han et al. 2015b), TNF-α (Qu et al. 2007; Wang et al. 2012a; Wu et al. 2008a; Xu et al. 2006; Yang et al. 2009; Yu et al. 2009) were reported to be associated with the risk of CWP and silicosis among people in China. Wang et al. (2012a) showed that the TNF-α (-308), TNF-α (-238) and IL-1RA (+2018) SNPs were significantly associated with silicosis. Similar findings were also reported by studies in other countries. For example, Yucesoy et al. (2001) examined the association between TNF-α and IL-1 polymorphisms and silicosis in a case–control study with 489 Caucasian in the United States (Yucesoy et al. 2001). Carriers of the minor variants of the TNF-α (-308) and IL-1RA (+2018) SNPs showed an increased risk for both moderate and severe disease groups. Carriers of the minor variant of the TNF-α (-238) SNP were also shown to be at markedly higher risk for severe silicosis (OR = 4.0), although they would be at 50% lower risk for moderate silicosis (OR = 0.52). No significant differences in the distribution of the IL-1α (+4845) or IL-1β (+3953) variants with respect to disease severity (Yucesoy et al. 2001).

Pneumoconiosis is a disease which is characterized by chronic inflammation and formation of fibrotic nodular lesions, leading to progressive fibrosis in the lungs (McCunney et al. 2009). Inflammasomes have been demonstrated to play a crucial role in the host response to silica and asbestos. Indeed, the Nalp3 inflammasome is an important innate immune receptor involved in the recognition of silica and asbestos by macrophages. Stimulation of macrophages with silica results in the activation of caspase-1 in a Nalp3-dependent manner (Cassel et al. 2008; Dostert et al. 2008). Macrophages deficient in components of the Nalp3 inflammasome were incapable of secreting the proinflammatory cytokines IL-1β in response to silica. Therefore, the impact of genetic polymorphisms of Nalp3, caspase-1 and IL-1β on pneumoconiosis may be crucial for pneumoconiosis susceptibility (Cassel et al. 2008; Dostert et al. 2008). One of the included studies in this review (Weng et al. 2015) reported the association between Nalp3, caspase-1 and IL-1β polymorphisms and the risk of silicosis among people in China. Subjects with the CT genotype of Ex4-849C > T in Nalp3 and the GA genotype of Ex2 + 37G > A in caspase-1 had increased risks of silicosis. Moreover, the association of genetic polymorphisms with silicosis risk may be affected by age, dust exposure or smoking status (Weng et al. 2015). The polymorphisms of another gene COX-2, which is also important for the synthesis of inflammatory mediator prostaglandin E2, was demonstrated to be associated with the risk of CWP in Chinese coal miners (Bian et al. 2014). Two COX-2 SNPs (rs689466 and rs20417) were found to be significant risk factors in decreasing the risk of CWP, providing further evidence for a role of inflammatory pathway in the pathogenesis of pneumoconiosis.

Reactive oxygen species (ROS) are key mediators of inflammation. Studies have suggested that exposure to mineral dust particles generate ROS, which are implicated directly in the pathogenesis of pneumoconiosis (Mastruzzo et al. 2002; Wallaert 1990; Schins et al. 1999). Therefore, the inhibitory effects of antioxidants on pneumoconiosis are of value to be further explored. Antioxidant gene

polymorphisms were investigated in one of the included studies by Zhai et al. (2002). However, no association between MnSOD, GSTM1, GSTT1 or OGG1 genetic polymorphisms and CWP was found in Chinese coal miners. In the United States, a matched case–control study was conducted to determine the influence of the GSTP1, GSTT1 and MnSOD polymorphisms on the susceptibility to progressive massive fibrosis (PMF), a severe form of CWP (Yucesoy et al. 2005). Their findings were similar to those observed by Zhai et al. (2002). The allele frequencies for GSTP1, GSTT1 and MnSOD in the control population were similar to those determined in other studies involving Caucasian participants. No significant differences were found in the genotype frequencies or the allelic frequencies between PMF cases and controls for the GSTT1, GSTP1 or MnSOD. In addition, no significant gene–gene interactions were detected (Yucesoy et al. 2005). This may imply that polymorphisms of antioxidant genes are not associated with susceptibility of pneumoconiosis, and suggests that ROS may not be directly involved in the pathogenesis of pneumoconiosis.

The occurrence of pneumoconiosis is multifactorial. These factors include dust exposure time, smoking status, patients' age and genetic makeup. Dust levels exposed to the patients are of most importance. Age and dust exposure time are directly accounted for the dust levels exposed, while smoking status and genetic makeup are modifiers of pneumoconiosis susceptibility. An early study in 1975 had demonstrated the effect of dust exposures time and smoking habits on the attack rate of pneumoconiosis among coal miners (Jacobsen et al. 1975). Few studies provided quantitative data to ascertain the relationships between occupational dust exposure, cigarette smoking, and emphysema severity (Ruckley et al. 1984; Leigh et al. 1994). Among the included studies of this review, 15 studies reported the effect of smoking status on the genotypic association with pneumoconiosis risk (Han et al. 2015b; Ji et al. 2012; Ji et al. 2015; Ji et al. 2017; Jin et al. 2012; Liu et al. 2017; Wang et al. 2013; Wang et al. 2014; Weng et al. 2015; Wu et al. 2014; Wu et al. 2016; Xu et al. 2006; Xu et al. 2010; Yang 2009; Yang et al. 2015) while nine studies reported the effect of dust exposure time on such association (Ji et al. 2014; Ni et al. 2009; Qu et al. 2007; Wang et al. 2011; Wang et al. 2012b, 2018b, c; Wu et al. 2016; Yang et al. 2015). Although smoking status and dust exposure time were found to be crucial factors in pneumoconiosis (Leung et al. 2012; Fan et al. 2020), the influence of these factors on genetic susceptibility in pneumoconiosis were not consistent among the included studies. Similarly, the effects of disease stage on risk of pneumoconiosis were inconsistently reported among the included studies and other studies conducted in other countries. However, in this review, more studies reported the association between genotypes and pneumoconiosis risk among individuals with stage I CWP/silicosis on such association (Han et al. 2015b; Ji et al. 2012, 2015, 2017; Liu et al. 2017; Ni et al. 2007, 2009; Qian et al. 2010; Wang et al. 2011; Wu et al. 2016) while fewer reported such association among individuals at stage II/III (Wang et al. 2013, 2018b, c; Wu et al. 2014). The results are more consistent among the studies reporting the effect of patients' age of such association, where increased risk of CWP and silicosis with specific genotypes was more evident at higher age (Ji et al. 2017; Ni et al. 2009; Wang et al. 2011; Weng et al. 2015). Globally, the largest number of CWP cases was shifting to higher age groups, from aged 35–39 in 1990 to aged 50–54 in 2019 (Wang et al. 2021). However, statistical data are lacking in China to confirm if the increased pneumoconiosis risk is directly related to age.

The effect of environmental factors on genetic susceptibility of pneumoconiosis were found to be controversial. A possible reason for this may be the small sample sizes used in the studies, thereby generating a higher risk of bias in study findings that may contribute to inconsistencies of findings between studies. Moreover, the effect of the aforementioned environmental factors on the association of the genotype of a particular susceptibility gene and pneumoconiosis risk was understudied, with such effect reported by one single trial only. Therefore, more studies are needed to consolidate the findings related to the environmental effects on the association between genotypes and pneumoconiosis risks, which may shed light on the future planning of occupational disease control in China.

Limitations

There are some limitations of this review that need to be acknowledged as follows: (1) Due to the heterogeneity of various genetic polymorphisms examined in the studies, pooled effects using a meta-analysis was not feasible, limiting our ability to visualise the variations in the level of the association between the examined genotypes and pneumoconiosis risk; (2) Most of the genetic polymorphisms examined for a particular gene were only reported by one case–control study. More studies are required to consolidate the findings; (3) Given some studies of low quality rating, we should be cautious in interpreting the review findings; (4) The findings regarding the association between the reported genotypes and pneumoconiosis risks may not apply to populations in other countries because this review only include the studies conducted in China.

Conclusion

Identifying the factors affecting the susceptibility of pneumoconiosis may offer clues to the development of strategies to prevent or monitor the disease. As pneumoconiosis is a complicated and multifactorial disease without any effective treatment, and that the prevalence of this disease is

high in China, it is of value to provide an overview on the potential factors affecting pneumoconiosis susceptibility in China. Genetic polymorphisms may explain the differences in outcomes of pneumoconiosis resulting from similar working conditions or exposure history. In this review, different genotypes were found to influence the pneumoconiosis susceptibility in patients in China, in particular the genes involved in the inflammatory pathway such as cytokines and inflammasomes. We also found that such associations were affected by various environmental factors, including duration of dust exposure, age, pneumoconiosis stage and smoking habits, although there were inconsistencies on such findings between studies. Given the effects of genetic variations on pneumoconiosis risks, genetic testing could potentially serve as a tool for the identification of individuals with increased genetic susceptibility to the disease especially in countries with high numbers of coal mine workers such as China if the conflicting results can be verified by more studies conducted on the issue.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00420-022-01893-1.

Declarations

Conflict of interest None declared.

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