

# The *MIF* –173G/C polymorphism and risk of coal workers' pneumoconiosis in a Chinese population

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**Objective:** To investigate the possible relationship between macrophage migration inhibitory factor (*MIF*) –173 polymorphism (rs755622) and susceptibility to coal workers' pneumoconiosis (CWP) in a Chinese population.

**Methods:** A total of 699 patients with CWP and 677 controls were genotyped for the polymorphism by TaqMan method.

**Results:** Our results showed that the *MIF* –173CC genotype was associated with a significantly decreased risk of CWP (adjusted odds ratio = 0.44, 95% confidence interval = 0.22–0.85), compared with the GG/GC genotype, particularly among smokers.

**Conclusion:** Our results indicate that the functional *MIF* –173G/C polymorphism is involved in the etiology of CWP and susceptibility to this disease. Further studies are warranted to validate our findings.

**Keywords:** *MIF*, polymorphism, coal workers' pneumoconiosis, molecular epidemiology

## Introduction

Macrophage migration inhibitory factor (*MIF*) is a key proinflammatory cytokine and chemokine-like function cytokine that is rapidly released from various immune cells, endothelial cells, tissue macrophages, and certain parenchymal cells upon inflammatory and stress stimulation.<sup>1</sup> It has been generally acknowledged that *MIF* plays a pivotal role in the pathogenesis of acute and chronic inflammatory diseases such as septic shock, rheumatoid arthritis, inflammatory lung disease, and atherosclerosis by promoting and amplifying involved inflammatory reactions such as monocyte/macrophage survival, MAPK signaling, or inflammatory cytokine release.<sup>1–4</sup> More and more evidence shows that *MIF* also plays an essential and crucial role in cell proliferation and cell cycles,<sup>5,6</sup> which together with *MIF* properties of cytokine and chemokine are implicated in fibrotic diseases and cancers, such as cystic fibrosis,<sup>7</sup> liver fibrosis,<sup>4</sup> idiopathic pulmonary fibrosis,<sup>8</sup> and pancreatic cancer.<sup>9</sup>

Coalworkers' pneumoconiosis (CWP) is one of the most widespread occupational lung diseases in China. It is a kind of lung fibrosis without effective treatment, produced by prolonged and extensive exposure to coal and silica dust, which is characterized by lung chronic inflammation and fibrotic nodular lesions that usually lead to progressive fibrosis. Ingestion of coal dust or silica by alveolar macrophages leads to cell death and release of intracellular dust, which is then taken up by other macrophages. This recurring cycle of macrophage phagocytosis and cell death perpetuates the inflammatory process.<sup>10</sup> During this inflammatory process, macrophages become activated and release inflammatory mediators, such as chemokines and cytokines, which attract

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neutrophilic granulocytes, upregulate alveolitis, damage the alveolar epithelial cells, and induce the formation of gaps in the epithelial basement membranes. The migration of fibroblasts through these gaps into the alveolar space leads to intra-alveolar fibrosis.<sup>11,12</sup>

The extent of fibrosis varies greatly among individuals who have been exposed to similar levels of mineral dust, indicating a prominent role for host genetic factors that influence the fibrogenic tissue response.<sup>13,14</sup> Therefore, understanding genetic polymorphism and the interaction between genetic variation and dust exposure may aid in the identification of high-risk individuals and prevent them from developing CWP. Recent studies have reported that *MIF* is capable of regulating the expression of cytokines such as tumor necrosis factor- $\alpha$ , interleukin (IL)-1 $\beta$ , IL-6, and IL-8, some of which play a critical role in the pathogenesis of CWP.<sup>15</sup> *MIF* can also induce macrophage production of cytokines and promote T-lymphocyte proliferation.<sup>1</sup> In lung tissues, *MIF* is expressed in alveolar macrophages, alveolar endothelium, and bronchial epithelial cells.<sup>16</sup> The *MIF* -173G/C (rs755622) polymorphism located in the 5'-flanking region of the *MIF* gene has been shown to be functionally relevant in vitro and in vivo.<sup>17-19</sup>

Although research has focused on the association between the *MIF* polymorphisms and the susceptibility to diseases,<sup>20-22</sup> to date no data exist on their roles in CWP. Therefore, the purpose of the present research was to investigate the association between the *MIF* -173G/C polymorphism and the risk of CWP in a Chinese population.

## Materials and methods

### Study subjects

This study, including 699 CWP patients and 677 controls, has been described previously.<sup>23</sup> All subjects were recruited in an ongoing study from five coal mines of Xuzhou Mining Business Group Co, Ltd, People's Republic of China, between January 2006 and December 2010. A high kilovolt chest X-ray and physical examinations were performed to reconfirm the diagnoses based on the China National Diagnostic Criteria for Pneumoconiosis (GBZ70-2002), which is the same as the 1980 International Labor Organization classification of pneumoconiosis in the judgment of opacity profusion.<sup>24</sup> The CWP patients were classified into stage I, stage II, or stage III according to the size, profusion, and distribution range of opacities on chest X-ray. The controls were selected from the same coal mines and were matched for age (within 5 years), dust exposure period, and job type. Subjects were excluded if

they had clinical evidence of autoimmunity diseases or had immunosuppressive or immunostimulating therapy or radiotherapy. To obtain individual information including age, dust exposure period, job types, smoking status, and others, an epidemiological survey was done by face-to-face interviewers in order. The questionnaire was blinded regarding the case or control status of participants. A blood sample of 5 mL was obtained from all subjects and used for routine lab tests. The written informed consent was obtained from all subjects and the research protocol was specifically approved by the Institutional Review Board of Nanjing Medical University.

### Genotyping

Genomic DNA was isolated from peripheral blood lymphocytes using the conventional phenol-chloroform method. The *MIF* -173G/C polymorphism was genotyped using the TaqMan method with the ABI 7900HT real-time polymerase chain reaction system according to the manufacturer's instructions (Applied Biosystem, Foster City, CA). The sequences of primer and probe for each single nucleotide polymorphism are available on request. More than 10% of the samples were randomly selected for repeated genotyping for confirmation, and the results were 100% concordant. Genotyping was conducted by two researchers independently in a blinded fashion.

### Statistical analyses

Differences in the distributions of demographic characteristics, selected variables, and frequencies of genotypes of *MIF* -173G/C polymorphism between the CWP cases and controls were evaluated by using the Student's *t*-test or  $\chi^2$  test. Hardy-Weinberg equilibrium was tested using a goodness-of-fit  $\chi^2$  test. The associations between genotypes and CWP were estimated by computing odds ratios (ORs) and their 95% confidence intervals (CIs) from unconditional logistic regression analysis with the adjustment for possible confounders. The statistical power was calculated using the PS software (<http://biostat.mc.vanderbilt.edu/twiki/bin/view/Main/PowerSampleSize>). We have 80% power at 0.05 significance level to detect an OR of 1.43 or higher and 0.67 or lower with an exposure frequency of 20% under the current sample size. In this study, the dust exposure cutoff used for the stratified analysis accorded with the median of dust exposure years of the recruited patients and controls. All statistical tests were two-sided at a significance level of 0.05 and were analyzed using SAS software (version 9.1; SAS Institute, Inc, Cary, NC).

## Results

### Characteristics of the study population

The frequency distributions of the selected characteristics of the cases and controls are presented in Table 1. There was no significant difference in the distribution of age ( $P = 0.091$ ), exposure years ( $P = 0.085$ ), and work types ( $P = 0.404$ ) between the cases and the controls. The smoking status of CWP was similar to the controls ( $P = 0.356$ ), but the pack-years smoked in CWP cases were significantly less than those of controls ( $P < 0.001$ ). The frequency distributions and means of the selected characteristics were matched adequately between cases and controls. In addition, of the 699 CWP cases, 421 (60.2%) were stage I, 214 (30.6%) were stage II, and the remaining 64 (9.2%) were stage III.

### Genotype distributions of *MIF* polymorphism among the cases and controls

The observed *MIF* -173G/C genotypes among the control subjects conform to the Hardy-Weinberg equilibrium ( $\chi^2 = 0.046$ ,  $P = 0.229$ ). The genotypes and allele frequencies of the *MIF* -173G/C polymorphism and their associations with risk of CWP are shown in Table 2. The *MIF* genotype

frequencies differ significantly between cases and control subjects ( $P = 0.009$ ). When the GG genotype was used as reference, multivariate logistic regression analysis indicated that the homozygous CC carriers had a statistically significantly decreased effect of CWP ( $P = 0.019$ , adjusted OR = 0.47, 95% CI = 0.24–0.91), but the heterozygous GC carriers had no statistical difference in risk of CWP ( $P = 0.108$ , adjusted OR = 1.21, 95% CI = 0.96–1.53).

### Association and stratification analysis between *MIF* polymorphism and CWP risk

Next, because the presentation of two C alleles causes the protective effect of CWP, we use the recessive model to illustrate the association between *MIF* polymorphism and CWP risk in the association and stratification analysis (Table 3). The recessive model revealed that the CC carriers had a statistically significantly decreased effect of CWP ( $P = 0.015$ , adjusted OR = 0.44, 95% CI = 0.22–0.85), compared with the combined GG/GC genotype. In the stratification analysis, we found that the risk decrease of the CC carriers was more pronounced among the subgroup of smokers ( $P = 0.016$ , adjusted OR = 0.31, 95% CI = 0.12–0.81).

## Discussion

In this present study, we investigated the associations between the *MIF* -173G/C polymorphism and the risk of CWP in a Chinese population. As the two C alleles play the protective part in CWP and the GC genotype had no significant difference with CWP, we selected the recessive model to observe the association between the *MIF* polymorphism and CWP risk. Then, we found that when the combined GG/GC genotype was used as reference, the homozygous CC carriers had a statistically significantly decreased effect of CWP, which was more evident among smokers.

Although the pathophysiology has not been fully understood, CWP and silicosis involve complex interactions among multiple genes and dust exposure. Some evidence has suggested that the alveolar macrophages play a prominent role in lung inflammation and fibrosis via the production of a large panel of mediators including cytokines, reactive oxygen species, enzymes, and arachidonic acid metabolites.<sup>25,26</sup> Polymorphisms in cytokine genes have been reported to contribute to the recognized stable interindividual variation in the level of cytokine production rates.<sup>26–28</sup> Cytokines play a critical role in the prevalence of inflammatory diseases that relate to the functional T-cell

**Table 1** Demographic and selected variables among the coal workers' pneumoconiosis (CWP) cases and control subjects

Variables	CWP (n = 699)		Controls (n = 677)		P
	N	%	N	%	
Age, year (mean $\pm$ SD)	67.8 $\pm$ 11.0		66.9 $\pm$ 8.2		0.091
Exposure years (mean $\pm$ SD)	26.6 $\pm$ 9.0		27.4 $\pm$ 8.0		0.085
<b>Smoking status</b>					0.356
Never	345	49.4	351	51.8	
Ever	354	50.6	326	48.2	
Former	158	22.6	84	12.4	
Current	196	28.0	242	35.8	
<b>Pack-years smoked</b>					<0.001
0	345	49.4	351	51.8	
0–20	223	31.9	133	19.7	
>20	131	18.7	193	28.5	
<b>Work type</b>					0.404
Tunnel and coal mining	663	94.9	632	93.4	
Transport	12	1.7	12	1.8	
Others	24	3.4	33	4.8	
<b>Stage</b>					
I	421	60.2			
II	214	30.6			
III	64	9.2			

**Abbreviation:** SD, standard deviation.

**Table 2** Distributions of genotypes of *MIF* –173G/C associations with risk of coal workers' pneumoconiosis (CWP)

Variables (Genotypes)	CWP cases (n = 699)		Controls (n = 677)		P <sup>a</sup>	OR (95% CI)	OR (95% CI) <sup>a</sup>
	N	%	N	%			
GG	448	64.1	450	66.5	0.009	1.00	1.00
GC	238	34.0	198	29.2		1.21 (0.96–1.52)	1.21 (0.96–1.53)
CC	13	1.9	29	4.3	0.019	0.45 (0.23–0.88)	0.47 (0.24–0.91)

**Note:** <sup>a</sup>Adjusted for age, exposure years, and pack-years of smoking in logistic regression model.

**Abbreviations:** CI, confidence interval; OR, odds ratio.

subsets known as T helper 1 and T helper 2.<sup>29</sup> As a proinflammatory cytokine released from T cells and macrophages, *MIF* plays an important role in inflammatory response.<sup>30,31</sup> It has been involved in the pathogenesis of immune and inflammatory diseases, including rheumatoid arthritis, pneumonia, ulcerative colitis, pancreatitis, and oligoarticular juvenile idiopathic arthritis.<sup>19,20,32–34</sup> Thus, the functional variation in *MIF* may play a role in the etiology of CWP. Although how the *MIF* –173G/C polymorphism affects the inflammatory reactions remains unclear, some studies have suggested that the polymorphism may influence the protein functions. The G to C transition at *MIF* polymorphism creates a potential transcription factor-binding site for activator protein-4, suggesting that polymorphism could functionally alter *MIF* production.<sup>18</sup> Kaznowska et al<sup>35</sup> reported that the polymorphism of *MIF* was associated with increased production of *MIF* and has been found to confer increased risk of susceptibility to chronic inflammatory diseases. Gomez et al<sup>36</sup> found that *MIF* –173G/C polymorphism influenced the risk of developing human tuberculosis in a well-defined Latin-American population. The subjects with the –173GC genotype had significantly increased risk, compared with the GG homozygous genotype in tuberculosis. Prencipe et al<sup>37</sup>

indicated that the *MIF* expression was increased in the lung and serum of preterm infants and suggested that the high-producing *MIF* –173C allele was a protective factor for bronchopulmonary dysplasia from a case-control study of 25 bronchopulmonary dysplasia patients and 66 controls. In the present study, carriers of the CC genotype had a decreased risk of CWP compared with the GG/GC genotypes. One possible explanation is that the C allele may result in increased anti-inflammatory cytokine production or a profibrogenic factor favoring the fibrotic nodular lesions of the lung. An interesting thing is that there was no CC genotype in stage III, which may suggest that the polymorphism plays a part in the development of CWP rather than the subsequent progression of CWP. It has been posed that different stages of CWP have different etiology involving different genetic defects.<sup>38</sup>

To our knowledge, this is the first study to investigate the role of genetic polymorphism in *MIF* in the development of CWP. Our present study indicates that the functional *MIF* –173G/C polymorphism is associated with the increased risk of CWP in the Chinese population. Further validated studies with diverse populations are warranted to confirm our findings.

**Table 3** Stratification analyses between the genotypes of *MIF* –173G/C and coal workers' pneumoconiosis risk

Variables	Cases/controls	Genotypes (cases/controls)				P <sup>a</sup>	OR (95% CI) <sup>a</sup>
		GG/GC		CC			
		n	%	n	%		
Total	699/677	686/648	98.1/95.7	13/29	1.9/4.3	0.015	0.44 (0.22–0.85)
Exposure years							
<27	278/260	274/249	98.6/95.8	4/11	1.4/4.2	0.078	0.32 (0.10–1.01)
≥27	421/417	412/399	97.9/95.7	9/18	2.1/4.3	0.112	0.52 (0.23–1.17)
Smoking status							
Never	345/351	338/339	98.0/96.6	7/12	2.0/3.4	0.364	0.64 (0.25–1.67)
Ever	354/326	348/309	98.3/94.8	6/17	1.7/5.2	0.016	0.31 (0.12–0.81)
Stage							
I	421/677	411/648	97.6/95.7	10/29	1.5/4.3		
II	214/677	211/648	98.6/95.7	3/29	1.4/4.3		
III	64/677	64/648	100.0/95.7	0/29	0.0/4.3		

**Note:** <sup>a</sup>Adjusted for age, exposure years, and pack-years of smoking in logistic regression model.

**Abbreviations:** CI, confidence interval; OR, odds ratio.



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## Disclosure

The authors declare no conflicts of interest in this work.

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