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Heterozygous Ins/Del genotype of the *CASP8* rs3834129 polymorphism significantly decreases the risk of coal workers' pneumoconiosis in a Chinese Han population: a case-control study

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Abstract. – OBJECTIVE: Coal workers' pneumoconiosis (CWP) is a chronic inflammatory and fibrotic pulmonary disease that involves a complex interaction of multiple environmental and genetic factors. Polymorphism, as a genetic factor, may affect the onset of the disease in susceptible populations. The present study investigated the association between the polymorphisms of six genes and CWP risk in a Chinese Han population.

PATIENTS AND METHODS: Six polymorphisms (*CASP8* rs3834129, *IL1A* rs1800587, *IL6* rs1800796, *IL4* rs2070874, *TNFA* rs361525, and *NLRP3* rs1539019) were examined in 222 CWP subjects and 247 dust-exposed control subjects.

RESULTS: The *CASP8* rs3834129 Ins/Del genotype significantly decreased CWP risk (p=0.040; adjusted odds ratio [OR] = 0.586; 95% confidence interval [CI] 0.367–0.935) compared with the Ins/Ins genotype. Stratification analyses revealed a significant interaction between the heterozygous Ins/Del genotype and age. Compared with the Ins/Ins + Del/Del genotype, this was particularly evident among subjects aged 41–60 (p<0.001; adjusted OR = 0.054; 95% CI 0.007–0.420) and those with an exposure time of 20–29 years (p=0.014; adjusted OR = 0.392; 95% CI 0.183–0.842). This decreased risk was also found in the group with former smokers (p=0.012; adjusted OR = 0.448; 95% CI 0.238–0.844). Findings revealed that the heterozygous Ins/Del genotype of *CASP8* rs3834129 was related to a significantly decreased risk of stage I CWP (p=0.045; adjusted OR = 0.592; 95% CI 0.353–0.992), but not stage II or III CWP.

CONCLUSIONS: Our study indicated that the heterozygous Ins/Del genotype of *CASP8* rs3834129 significantly decreased CWP risk in a Chinese Han population.

Key Words:
Coal workers' pneumoconiosis, Polymorphism, CASP8 rs3834129.

Introduction

Pneumoconiosis is the most common occupational disease among coal miners and remains the most serious occupational disease worldwide, including China[1,2]. More than 95% of the newly reported cases of occupational pneumoconiosis in China in 2016 were coal workers' pneumoconiosis (CWP) and silicosis. Notably, CWP accounts for nearly 60% of all new pneumoconiosis cases[3]. Progression of the disease leads to a gradual loss of ability to work, a reduced quality of life, and even death. The pathogenesis of pneumoconiosis may include oxidative stress in the early stage, inflammatory response, and extensive fibrosis in the late stage, but the specific mechanism remains unclear[4]. Interestingly, the disease may progress even if factors causing exposure are removed[4-6]. At present, only few effective drugs are available to slow down CWP progression[5,6]. Therefore, early CWP diagnosis and prevention remain the fo-

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cus of occupational health interventions. Due to insufficient occupational health awareness and management, the incidence of CWP is on the rise in China[7]. To improve patients' quality of life, early CWP diagnosis is of vital importance. Both environmental factors and genetic variations contribute to CWP[8]. Therefore, identifying new genetic factors associated with CWP will help aid early diagnosis, identify effective preventive interventions, and prolong the life of patients.

It is particularly interesting to note that caspase-8 has different functions in various inflammatory processes. It plays an important role in regulating inflammation, such as inflammasome activation, interleukin-1 (IL-1) processing, and cytokine induction[9,10]. In particular, caspase-8 is critical for the induction, synthesis, and processing of IL-1β through both atypical and canonical pathways[11]. Single nucleotide polymorphisms (SNPs) on *CASP8* are associated with the risk of various diseases. *CASP8* rs3834129 Del allele and Del/Del genotype are significantly associated with a decreased risk and delayed age of onset of epithelial ovarian cancer[12]. Available literature has confirmed that genetic variations in the promoter of *CASP8*, especially rs3834129, may be risk factors for breast cancer in the Iranian population[13]. Genetic variations in the underlying apoptotic pathway associated with *CASP8* rs3834129 polymorphism may be decisive factors in predicting the risk of oropharyngeal squamous cell carcinoma and tumor cell differentiation[14]. However, the functionality of *CASP8* rs3834129 SNPs in CWP has not been fully elucidated.

Other polymorphisms have also been linked to inflammation. *IL1A* rs1800587 polymorphisms are significantly associated with chronic periodontitis, rheumatoid arthritis, and the severity of lumbar disc degeneration[15-17]. The *IL6* rs1800796 polymorphism is related to the risk of ulcerative colitis, chronic Hepatitis B Virus infection, and rheumatoid arthritis in the Chinese Han population[18-20]. The susceptibility to multiple sclerosis and the severity of recurrent viral-induced wheeze may be associated with *IL4* rs2070874 polymorphism[21,22]. A significant correlation of *TNFA* rs361525 polymorphisms with oral pre-cancer in the North Indian population and with reproductive tract infections in women has been reported[23,24]. While the TT allele of *NLRP3* rs1539019 significantly increases CWP risk, the CC allele of *NLRP3* rs1539019 may be related to a lower risk of chronic Hepatitis C Virus infection[25,26]. Therefore, based on the association between inflammation and a set of six genes, our study was designed to investigate whether the polymorphic features of six SNPs, *CASP8* rs3834129, *IL1A* rs1800587, *IL6* rs1800796, *IL4* rs2070874, *TNFA* rs361525, and *NLRP3* rs1539019, are associated with CWP progression.

Patients and Methods

Study Population

We recruited 222 male Chinese Han patients with CWP and 247 dust-exposed control subjects from November 2018 to December 2020. The dust-exposed controls were subjected to imaging and physical examinations to rule out CWP. A total of 469 persons, who worked in different mining areas for the Sinopharm Tongmei General Hospital, were enrolled. In accordance with the China National Diagnostic Criteria for Pneumoconiosis (GBZ70-2009), high kilovolt chest X-rays and physical examinations were used to confirm the diagnoses. The diagnostic criteria were the same as the evaluation criteria for opacity profusion, in accordance with the classification of pneumoconiosis of the International Labor Organization[27]. Subjects were categorized as having stage I, II, or III CWP based on the size, number, and distribution of the opacity profusion on high kilovolt chest X-rays. The chest X-rays were assessed by three national certified independent physicians; agreement between at least of two independent physicians was required. The dust-exposed control subjects came from the same coal mines, and were matched for age, dust exposure time, and type of work. Experienced interviewers conducted face-to-face interviews with the subjects using structured questionnaires, and participants' case or control status was blinded. Questionnaires included personal demographics (height, age, weight, and education level), occupational diseases (date of the first diagnosis, disease stage and disease progression), occupational history (duration of dust exposure, type of work, and personal protection), and lifestyle (alcohol consumption and smoking). After the interview, approximately 5–10 ml of venous blood was drawn from all participants. All participants in this study signed informed consent and agreed to the use of their biological samples for research purposes. This study was approved by the Ethics Committee of the Sinopharm Tongmei General Hospital (NO. 201902).

Genotyping

Genomic DNA was extracted from venous blood by the conventional phenol-chloroform method. All isolated DNA samples from case and control groups were randomly segmented into 96-well plates. Based on the manufacturer's instructions (Applied Biosystem, Foster City, CA, USA), the ABI 7900HT PCR system and the TaqMan method were used for genotyping. To better control the experimental quality and the authenticity of the data, a total of 15% of the case and control random samples were genotyped twice and the repeatability was 100%.

Statistical Analysis

The frequency of CWP cases and dust-exposed control genotypes was assessed for Hardy-Weinberg equilibrium using the Chi-square test (χ^2 test). Categorical variables between cases and controls were tested using Pearson's χ^2 test, while the continuous variables were tested using Student's *t*-test. Either the *t*-test or the χ^2 test was used to analyze differences in the distribution of demographic characteristics and selection variables, as well as allele and genotype frequency between CWP and controls. Crude odds ratios (ORs), adjusted ORs, and 95% confidence intervals (CI) between CWP and genotypes were obtained using a logistic regression model. The significance of all statistical tests was two-tailed and set at $p<0.05$. All tests were performed using the SPSS 26.0 software (IBM, Armonk, NY, USA).

Results

Population Characteristics

A total of 222 CWP cases and 247 dust-exposed control subjects were included in the present trial. Table I shows the frequency distribution characteristics and general information about clinical cases. There were no significant differences in age (p=0.648), years of exposure (p=0.622), and duration of smoking (p=0.791) between CWP cases and controls. The frequency distribution and general features between CWP and controls were well matched. There was a statistically significant difference in smoking status between the cases and controls (p=0.005), with more former smokers and fewer current smokers in the case groups (64.0 and 25.6%, respectively) than in the control groups (49.0 and 37.6%, respectively). In addition, there were 151 patients with stage I (68.0%), 23 with stage II (10.4%), and 48 with stage III (21.6%) CWP.

Allelic Frequencies and Genotype Distributions of Six Gene Polymorphisms

The allele frequencies and related information of six SNPs are shown in Table II. The minor allele frequency for six SNPs was matched to the ones recorded in the HapMap database. The distribution of all genotypes in both CWP cases and control subjects was consistent with Hardy-Weinberg equilibrium.

Table I. Demographic and selected variables of the CWP cases and control subjects.

Variables	CWP (N=222)		Controls (247)		*p*
	N	%	N	%	
Age, year (mean ± SD)	71.2±10.2		68.2±10.6		0.648
Exposure years (mean ± SD)	27.4±6.3		26.5±6.2		0.622
Smoking status					0.005
Never	23	10.4	33	13.4	
Former	142	64.0	121	49.0	
Current	57	25.6	93	37.6	
Pack-years smoked					0.791
0	23	10.4	33	13.4	
1-20	37	16.7	40	16.2	
21-40	96	43.2	105	42.5	
>40	66	29.7	69	27.9	
Stage					
I	151	68.0			
II	23	10.4			
III	48	21.6			

Significant difference in comparison with the study group, $p<0.05$; CWP: coal workers' pneumoconiosis; SD: standard deviation; N: number of patients.

Table II. Primary information on genotyped SNP.

Gene	SNP	Chromosomal position	Base	MAF		HWE P
				Cases	Controls	
CASP8	rs3834129	chr2:201232809-201232814	Ins>Del	0.153	0.170	0.492
NLRP3	rs1539019	chr1:247436999	C>A	0.489	0.494	0.885
IL1A	rs1800587	chr2:112785383	G>A	0.117	0.097	0.993
IL6	rs1800796	chr7:22726627	G>C	0.345	0.306	0.704
IL4	rs2070874	chr5:132674018	C>T	0.230	0.217	0.948
TNF	rs361525	chr6:31575324	G>A	0.070	0.053	0.455

HWE: Hardy-Weinberg equilibrium; SNP: Single nucleotide polymorphism; HWE *p*-value in the control group.

The Relationship Between CASP8 rs3834129 Polymorphism and CWP Risk

As observed in Table III, the genotype frequency of *CASP8* rs3834129 polymorphism was significantly different between the CWP and control subjects (p=0.040). There was no significant difference between Del and Ins alleles (p=0.484). When compared with the Ins/Ins genotype, the *CASP8* rs3834129 Ins/Del genotype significantly decreased CWP risk (adjusted OR = 0.586; 95% CI 0.367–0.935), while the *CASP8* rs3834129 Del/Del showed no significant CWP predisposition (adjusted OR = 1.373; 95% CI 0.615–3.067). Therefore, it was found that *CASP8* rs3834129 Ins/Del polymorphism affected susceptibility to CWP. However, other polymorphisms (*NLRP3* rs1539019, *IL1A* rs1800587, *IL6* rs1800796, *IL4* rs2070874, *TNFA* rs361525) detected in this study were not significantly associated with the development of CWP.

Further Analyses of the Heterozygous Ins/Del Genotype and its Relationship with CWP Risk

Further stratification analyses of the *CASP8* rs3834129 polymorphism are shown in Table IV. When the homozygous Ins/Ins + Del/Del genotype was used as a reference, heterozygous Ins/Del genotype was related to a decreased risk of CWP (adjusted OR = 0.578; 95% CI 0.365–0.913). There was a significant interaction between heterozygous Ins/Del genotype and age (p<0.001). Subjects aged 41–60 who had the Ins/Del genotype showed an OR of 0.054 (95% CI 0.007–0.420). Furthermore, there was a relationship between coal exposure time and the Ins/Del genotype, which significantly decreased the risk of CWP in subjects with an exposure time of 20–29 years (p=0.014; adjusted OR = 0.392; 95% CI 0.183–0.842). The decreased risk was also more pronounced in the group with former smokers (p=0.012; adjusted OR = 0.448; 95% CI 0.238–0.844). Moreover, a significantly decreased risk for stage I CWP was found for the heterozygous Ins/Del genotype of *CASP8* rs3834129 (p=0.045; adjusted OR = 0.592; 95% CI 0.353–0.992), but not for stage II or III.

Discussion

To understand the factors that affect CWP risk in the Chinese Han population, we investigated genetic polymorphisms related to six inflammatory processes. We found that the heterozygous Ins/Del genotype of *CASP8* rs3834129 was related to a decreased risk of CWP. This relationship was more evident in former smokers and younger workers with an exposure history of 20–29 years. In addition, a significant relationship between the Ins/Del genotype and stage I CWP was observed.

CWP is a chronic inflammatory and fibrotic pulmonary disease that involves a complex interaction between multiple environmental and genetic factors, but its pathogenesis is not fully understood. Polymorphisms may affect the onset of the disease in susceptible populations. Previous studies have found that many genetic factors are involved in CWP development[28-30]. The *NLRP3* rs1539019 TT genotype is related to a significantly increased risk of CWP[25], while the *IL4* CT/CC genotype significantly decreases the risk of CWP[27]. *NAF1* rs4691896 is significantly related to CWP in a Chinese Han population[3]. Although *CASP8* is involved in many inflammatory responses, there are relatively few studies on the role of *CASP8* polymorphism in CWP.

In this study, a more striking finding was a relationship between *CASP8* rs3834129 and CWP risk. The heterozygous Ins/Del genotype

Table III. Distributions of the genotypes of different genes and their associations with CWP risk.

Variables	CWP (N=222)		Controls (247)		P[a]	OR (95%CI)	OR (95% CI)[b]
	N	%	N	%			
CASP8 rs3834129							
Ins/Ins (II)	170	76.6	174	70.4	0.040	1.00	1.00
Ins/Del (ID)	36	16.2	62	25.1		0.594 (0.374-0.943)	0.586 (0.367-0.935)
Del/Del (DD)	16	7.2	11	4.5		1.489 (0.671-3.301)	1.373 (0.615-3.067)
Ins allele	376	84.7	410	83.0	0.484	1.00	
Del allele	68	15.3	84	17.0		0.883 (0.623-1.251)	
NLRP3 rs1539019							
AA	60	27.0	63	25.5	0.670	1.00	1.00
CA	97	43.7	118	47.8		0.863 (0.554-1.346)	0.917 (0.584-1.439)
CC	65	29.3	66	26.7		1.034 (0.632-1.692)	1.123 (0.681-1.854)
A allele	217	48.9	244	49.4	0.874	1.00	
C allele	227	51.1	250	50.6		1.021 (0.790-1.319)	
IL1A rs1800587							
GG	175	78.8	202	81.8	0.582	1.00	1.00
GA	42	18.9	42	17.0		1.154 (0.719-1.853)	1.091 (0.674-1.767)
AA	5	2.3	3	1.2		1.924 (0.453-8.165)	1.500 (0.334-6.742)
G allele	392	88.3	446	90.3	0.324	1.00	
A allele	52	11.7	48	9.7		1.233 (0.814-1.867)	
IL6 rs1800796							
GG	29	13.1	27	10.9	0.457	1.00	1.00
GC	95	42.8	97	39.3		0.912 (0.503-1.654)	0.975 (0.531-1.789)
CC	98	44.1	123	49.8		0.742 (0.412-1.335)	0.775 (0.426-1.410)
G allele	153	34.5	151	30.6	0.204	1.00	
C allele	291	65.5	343	69.4		0.837 (0.637-1.101)	
IL4 rs2070874							
CC	8	3.6	13	5.3	0.328	1.00	1.00
CT	86	38.7	81	32.8		1.725 (0.680-0.546)	1.766 (0.688-4.536)
TT	128	57.7	153	61.9		1.359 (0.546-3.382)	1.403 (0.558-3.527)
C allele	102	23.0	107	21.7	0.629	1.00	
T allele	342	77.0	387	78.3		0.927 (0.681-1.261)	
TNF rs361525							
GG	196	88.3	224	90.7	0.595	1.00	1.00
GA	21	9.5	20	8.1		1.200 (0.632-2.280)	1.214 (0.635-2.320)
AA	5	2.3	3	1.2		1.905 (0.449-8.073)	1.807 (0.418-7.818)
G allele	413	93.0	468	94.7	0.273	1.00	
A allele	31	7.0	26	5.3		1.351 (0.789-2.313)	

CWP: coal workers' pneumoconiosis; OR: odds ratio; CI: confidence interval; N number of patients, [a]Two-sided χ^2 test; [b]Adjusted for age, exposure years, smoking status, and duration of smoking.

Table IV. Stratification analyses between the genotypes of CASP8 rs3834129 polymorphism and CWP risk.

Variables	Controls cases	Genotypes (controls/cases)				*p*	OR (95% CI)[a]
		II+DD		DI			
		N	%	N	%		
Total	247/222	185/186	74.9/83.8	62/36	25.1/16.2	0.018	0.578 (0.365-0.913)
Age							
41-60	62/40	42/39	67.7/97.5	20/1	32.3/2.5	<0.001	0.054 (0.007-0.420)
61-80	152/134	118/107	77.6/79.9	34/27	22.4/20.1	0.648	0.876 (0.496-1.547)
>80	33/48	25/40	75.8/83.3	8/8	24.2/16.7	0.400	0.625 (0.208-1.878)
Exposure years							
10-19	20/17	13/15	65.0/88.2	7/2	35.0/11.8	0.137	0.248 (0.044-1.408)
20-29	106/82	76/71	71.7/88.6	30/11	28.3/13.4	0.014	0.392 (0.183-0.842)
30-39	117/116	93/95	79.5/81.9	24/21	20.5/18.1	0.641	0.857 (0.446-1.644)
>40	4/7	3/5	75.0/71.4	1/2	25.0/28.6	0.898	1.200 (0.073-19.631)
Smoking status							
Never	33/23	25/15	75.8/65.2	8/8	24.2/34.8	0.390	1.667 (0.517-5.373)
Former	121/142	90/123	74.4/86.6	31/19	25.6/13.4	0.012	0.448 (0.238-0.844)
Current	93/57	70/48	75.3/84.2	23/9	24.7/15.8	0.194	0.571 (0.243-1.340)
Stage							
I	247/151	185/126	74.9/83.4	62/25	25.1/16.6	0.045	0.592 (0.353-0.992)
II	247/23	185/20	74.9/87.0	62/3	25.1/13.0	0.196	0.448 (0.129-1.558)
III	247/48	185/40	74.9/83.3	62/8	25.1/16.7	0.209	0.597 (0.265-1.344)

CWP: coal workers' pneumoconiosis; OR: odds ratio; CI: confidence interval; N number of patients; II: ins/ins; DD: del/del; DI: del/ins; [a]Adjusted for age, exposure years, smoking status, and duration of smoking.

of *CASP8* rs3834129 significantly decreased the risk of CWP development determined using genotype analysis. However, there was no significant difference between the Ins/Ins and the Del/Del genotypes. Interestingly, these results were not consistent with those reported by Ni et al[31]. The specific reasons for this inconsistency are unknown but could be ascribed to differences in the regions where the samples were collected. As already mentioned, the association of the heterozygous Ins/Del genotype and CWP was more evident in stage I CWP, suggesting that *CASP8* rs3834129 might participate in CWP development in the Chinese Han population. One possible explanation is that the *CASP8* rs3834129 polymorphism may contribute to the early onset and late progression of CWP. Interestingly, even though the risk of reduction effects of the heterozygous Ins/Del were pronounced in younger patients with an exposure history of 20–29 years, there was no significant difference in subjects exposed for less than 20 years or more than 29 years. Although the exact underlying molecular mechanism is not clear, one reason may be that patients in these subgroups are likely to be less exposed to risk factors associated with CWP pathophysiology[32]. The second possible reason is that the duration of exposure was 20–29 years, which is likely to be a period of significant inflammatory and fibrotic response reaction. However, the relevant response is weak when the exposure time is less than 20 years, and immune tolerance will be induced after more than 30 years of exposure. Further mechanism studies are needed to validate our hypothesis. Studies have shown that the long-term effects of silica dust are more pronounced in smokers than in non-smokers[33]. A previous meta-analysis revealed that smoking is significantly related to a risk of developing silicosis[34]. Several studies have revealed a superimposed effect of smoking and silicosis on lung damage[33]. Interestingly, our results show that the group with former smokers also displayed a lower risk of developing CWP.

Our study presents several limitations. First of all, it is a case-controlled study, so the possibility of subject selection bias cannot be ruled out. Second, although this study revealed that *CASP8* rs3834129 polymorphism significantly decreases CWP risk, functional experiments and more studies on its physiological mechanism are need-

ed to explain this result. Third, the sample size of this experiment is moderate, which may lead to other differences between the groups that cannot be reflected. Therefore, further multicenter and multi-ethnic studies with a larger sample size are needed to better clarify these results.

Conclusions

The present study revealed that the heterozygous Ins/Del genotype of *CASP8* rs3834129 significantly decreases CWP risk in a Chinese Han population, which may provide evidence for the susceptibility and genetic polymorphism of CWP.

Author Contribution

ZH; Conception of study design, literature search, participation in sample and data collection and analysis, and drafting of full text. HW; Analysis the data; SJ, DK, HZ, YG, JM, JW; Collection of sample and data. The manuscript was revised by YG, XM. Each author contributed to the article and participated in the review of the final manuscript.

Conflict of Interest

All authors declare that they have no conflict of interest.

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