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ORIGINAL RESEARCH

# Associations of SMAD4 rs10502913 and NLRP3 rs1539019 Polymorphisms with Risk of Coal Workers' Pneumoconiosis Susceptibility in Chinese Han Population

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**Purpose:** CWP is an untreatable but preventable fibrotic lung disease caused by the chronic inhalation of coal dust. Genetic factors such as polymorphisms play an important role in the development of CWP. The present study investigated the association between the polymorphisms of SMAD4 and NLRP3 and CWP risk in a Chinese Han population.

**Patients and Methods:** SMAD4 rs10502913 and NLRP3rs1539019 polymorphisms were examined in 292 CWP subjects and 315 coal dust-exposed controls. The genotypes were analyzed using direct sequencing. The allele and genotype proportion between the cases and controls were compared using the chi-square test.

**Results:** The AG and GG genotypes of SMAD4 rs10502913 were not associated with altered CWP risk compared with AA genotype (adjusted OR = 1.535 and 1.426, 95% CI = 0.785–3.000 and 0.732–2.781, $p$ = 0.210 and 0.297, respectively). Also, the NLRP3 rs1539019 heterozygous and homozygous variants CA and CC genotypes were not associated with the risk of CWP compared with the AA genotype (adjusted OR = 0.985 and 1.127, 95% CI = 0.652–1.489 and 0.713–1.782, $p$ = 0.944 and 0.608, respectively). In addition, there was no interaction between SMAD4 rs10502913 and NLRP3 rs1539019 genotypes and smoking status on CWP risk in the stratified analyses.

**Conclusion:** In this present study, SMAD4 rs10502913 and NLRP3 rs1539019 genotypes were not associated with altered CWP risk in the Chinese Han population. Large sample sizes and multicenter studies are needed to elucidate these results in the future.

**Keywords:** CWP, polymorphisms, SMAD4 rs10502913, NLRP3 rs1539019

## Introduction

Coal workers' pneumoconiosis (CWP), also known as "black lung disease", is characterized by a specific pathological change in the lungs, including inflammation and massive fibrosis caused by long-term exposure and inhalation of coal dust from occupational activities.[1–3] CWP and silicosis accounted for 95.5% of the newly reported cases of occupational pneumoconiosis in China in 2016. Significantly, CWP accounts for almost 60% of all new pneumoconiosis cases.[4] At present, there have been few effective drugs to slow down the progression of CWP, which is an irreversible disease.[5] As the disease progresses, patients with CWP will gradually feel dyspnea, fatigue and eventually lead to respiratory failure.[6] Moreover, the disease may continue to worsen even if exposure factors are removed.[5,7] Although the incidence and mortality of CWP were increasing, only a part of individuals had been developed CWP, compared to the majority of people exposed to dust,[8] which suggests that genetic factors play an important role in the development of CWP besides

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environmental factors. Therefore, the identification of new genetic factors of CWP will be beneficial to the study of the pathogenesis of this disease and provide a theoretical basis for the early diagnosis and prevention.

Similar to mother against decapentaplegic 4 (SMAD4) was first identified in pancreatic ductal adenocarcinoma and has been identified as a tumor suppressor gene in the homozygous deletion region of human chromosome 18q21.1.[9] SMAD4, a member of the Smad family, is an indispensable mediator of the canonical TGF-β signaling pathway. It plays an important role in the biological processes of disease pathogenesis, such as migration and proliferation of smooth muscle cells (SMCs) and extracellular matrix degradation.[10] The signals from TGF-β family members are transmitted via cell surface receptors to the SMAD proteins, which act as signal transducers to transmit signals to the nucleus, ultimately activating transcription of target genes.[11] Also, the role of the SMAD gene in fibrotic diseases has been well documented.[12] SMADs genes are highly polymorphic, and mutations in these genes are frequently present in numerous diseases.

When pathogens invade the body, NOD-like receptor, pyrin domain-containing 3 (NLRP3), effector cysteine protease caspase 1 and adapter protein apoptosis-associated speck-like protein rapidly form a cytoplasmic complex, which has been shown to play a central role in regulating the maturation and secretion of pro-inflammatory cytokines IL-1β and IL-18.[13] NLRP3 recognizes not only pathogen-associated molecular patterns (PAMPs) but also damage-related molecular patterns (DAMPs) in the cytoplasm, which are endogenous ligands produced after tissue injury or cell death.[14] Activation of NLRP3 inflammasome leads to the recruitment of fibroblasts and inflammatory cells, which play a key role in fibrogenesis.[15] Increasing evidence indicates that genetic variation in the NLRP3 gene may be an important determinant of immune inflammatory response, affecting susceptibility to numerous diseases.[16]

Therefore, based on the association between fibrosis and genes, our study was designed to investigate whether SMAD4 rs10502913 and NLRP3rs1539019 are associated with CWP development.

# Materials and Methods

## Patients and Methods

We enrolled 607 male Chinese Han patients including 292 CWP patients and 315 coal dust-exposed controls in the study from November 2018 to February 2021. All enrolled patients worked for different coal mines at Datong Coal Mine Group Co. Ltd. The high kilovolt chest X-ray and physical examinations were performed for reconfirming the diagnoses according to the China National Diagnostic Criteria for Pneumoconiosis (GBZ70-2009), which is the same as the 1980 International Labour Organization (ILO) Classification of Pneumoconiosis for judgment of opacity profusion. CWP patients were divided into stage I, stage II, and stage III according to the size, number, and distribution of the opacity profusion on the high kilovolt chest X-ray. The chest X-rays were assessed by three national certified independent physicians; agreement between at least two independent physicians was required. The inclusion criteria for CWP include: 1) Male miners with a history of coal dust exposure who are diagnosed with CWP; 2) Aged between 40 and 80 years. The exclusion criteria for CWP patients were as follows: 1) The patient who had other significant respiratory diseases such as interstitial lung disease, lung cancer, tuberculosis, and cystic fibrosis. 2) The patient who had other serious diseases such as congestive heart failure, diseases associated with the rheumatic system, liver fibrosis, renal fibrosis and other related fibrotic diseases. 3) The patients had a previous history of chemotherapy, radiotherapy or other cancers. The inclusion criteria for controls include: 1) Male miners with a history of coal dust exposure who are not diagnosed with CWP. 2) Aged between 40 and 80 years. The exclusion criteria are consistent with the CWP. Interviews were conducted by experienced interviewers using structured questionnaires. Questionnaires include personal characteristics (age, height, weight, education level, family history), occupational history (type of work, duration of dust exposure and personal protection), occupational diseases (CWP stage, date of the first diagnosis, disease progression), and lifestyle (alcohol consumption and smoking). After the interview, approximately 5–6 mL of venous blood were obtained from each participant. All participants in this study signed informed consent and agreed to use their biological samples for research purposes. This study was approved by the Ethics Committee of Sinopharm Tomei General Hospital. The study was in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration.

## Genotyping

Genomic DNA was extracted from venous blood by the conventional phenol-chloroform method. The ABI 7900HT PCR system and the TaqMan method were used for genotyping based on the manufacturer's instructions (Applied Biosystems, Foster City, CA, USA). In order to better control the quality of the experiment and the authenticity of the data, 15% of the case and control samples were randomly genotyped twice with 100% repeatability. The primers of SMAD4 rs10502913 used were 5'-CTT TGT CAG TCT AAT TTC TGA GCG A-3' (forward) and 5'-GGC ATC TGA AAG TCT TGT GG GA-3' (reverse). The primers of NLRP3 rs1539019 used were 5'-CAC TTT CCC TGT ATC ACC TGC TC-3' (forward) and 5'-GAG AGC CAG ATG AAG AAG CCC TG-3' (reverse).

## Statistical Analysis

All tests were performed using the SPSS 26.0 software (IBM, New York, USA) and Microsoft Excel. Pearson's $\chi^2$ test was used for categorical variables, and Student's *t*-test was used for continuous variables. The frequency of CWP cases and coal dust-exposed control genotypes were assessed for Hardy-Weinberg equilibrium using a goodness-of-fit $\chi^2$ test. Differences in demographic characteristics and selected variables between CWP cases and controls were calculated by Student's *t*-test or $\chi^2$ test. 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 $p < 0.05$.

# Results

## Characteristics of the Study Population

A total of 292 CWP cases and 315 coal dust-exposed controls were included in this study. The frequency distribution characteristics and general information about clinical subjects are shown in Table 1. The mean age of 292 CWP patients is 71.4 years, and the mean coal dust exposure time is 27.2 years. Compared with the coal dust-exposed group, the CWP group has significantly older ages ($p= 0.001$), longer coal dust exposure time ($p< 0.001$). There was not a significant difference in smoking years between CWP group and the coal dust-exposed group ($p= 0.625$). However, there was a significant difference in smoking status between the cases and controls ($p= 0.002$), with more former smokers and fewer current smokers in the CWP groups (63.2% and 27.1%, respectively) than in the control groups (48.3% and 38.7%,

**Table 1** Demographic and Selected Variables of the CWP Cases and Control Subjects

| Variables | CWP (N = 292) | | Controls (315) | | P |
|---|---|---|---|---|---|
| | N | % | N | % | |
| Age, year (mean ±SD) | 71.4±10.2 | | 68.4±10.8 | | 0.001 |
| Exposure years (mean ±SD) | 27.2±6.2 | | 23.8±8.3 | | <0.001 |
| Smoking status | | | | | 0.002 |
| Never | 31 | 10.6 | 41 | 13.0 | |
| Current | 79 | 27.1 | 122 | 38.7 | |
| Former | 182 | 62.3 | 152 | 48.3 | |
| Smoking years | | | | | 0.625 |
| 0 | 31 | 10.6 | 41 | 13.0 | |
| 1–20 | 43 | 14.7 | 49 | 15.6 | |
| 21–40 | 127 | 43.5 | 122 | 38.7 | |
| >40 | 91 | 31.2 | 103 | 32.7 | |
| Stage | | | | | |
| I | 190 | 65.1 | | | |
| II | 37 | 12.7 | | | |
| III | 65 | 22.2 | | | |

**Note**: Significant difference in comparison with the study group, P < 0.05.
**Abbreviations**: CWP, coal workers' pneumoconiosis; SD, standard deviation; N, number of patient.

respectively). Furthermore, there were 190 patients with stage I (65.1%), 37 with stage II (12.7%), 65 with stage III (22.2%).

## Allelic Frequencies and Genotype Distributions of Two Gene Polymorphisms

The primary information and allele frequencies are listed in Table 2. The distribution of all genotypes in the control groups was consistent with what would be expected from the Hardy-Weinberg equilibrium. The minor allele frequency of the two SNPs matched that reported in the HapMap database.

## Association Analysis Between Polymorphisms and CWP Risk

As shown in Table 3, the genotypes of SMAD4 rs10502913 were not differently distributed between CWP groups and control groups ($p = 0.534$). In addition, when compared with AA genotype, AG and GG genotypes were not associated with altered CWP risk (adjusted OR = 1.535 and 1.426, 95% CI = 0.785–3.000 and 0.732–2.781, $p = 0.210$ and 0.297, respectively). Also, the genotype frequency of NLRP3 rs1539019 polymorphism was not significantly different between the CWP and controls ($p = 0.800$). The NLRP3 rs1539019 heterozygous and homozygous variant CA and CC genotypes were not associated with the risk of CWP compared with the AA genotype (adjusted OR = 0.985 and 1.127, 95% CI = 0.652–1.489 and 0.713–1.782, $p = 0.944$ and 0.608, respectively).

To confirm the above findings, the allele frequency distributions of SMAD4 rs10502913 and NLRP3 rs1539019 were also analyzed, as shown in Table 4. The results supported that SMAD4 rs10502913 and NLRP3 rs1539019 genotypes were not associated with CWP risk. The G allele of SMAD4 rs10502913 was not significantly associated with CWP risk compared with A allele (OR = 1.027, 95% CI = 0.803–1.315, $p= 0.831$). Similarly, the C allele of NLRP3 rs1539019 was not significantly associated with CWP risk compared with A allele (OR = 1.006, 95% CI = 0.803–1.260, $p= 0.962$).

## Interaction Between Genotypes and Behavioral Factors on CWP Risk

From an epidemiological point of view, smoking may be the cause of accelerating CWP in coal miners. Therefore, we were interested in evaluating the interaction between SMAD4 rs10502913 and NLRP3 rs1539019 polymorphisms and

**Table 2** Primary Information on Genotyped SNPs

| Gene | SNP | Chromosomal Position | Base | MAF | | HWE P |
|---|---|---|---|---|---|---|
| | | | | Cases | Controls | |
| SMAD4 | rs10502913 | chr18:51041901 | G>A | 0.293 | 0.298 | 0.929 |
| NLRP3 | rs1539019 | chr1:247436999 | A>C | 0.481 | 0.483 | 0.923 |

**Note**: HWE P value in the control group.
**Abbreviations**: HWE, Hardy-Weinberg equilibrium; SNP, single nucleotide polymorphism.

**Table 3** Distributions of the Genotypes of Different Genes and Their Associations with CWP Risk

| Variables | CWP (N = 292) | | Controls (N = 315) | | Univariate Analysis | | Multivariable Analysis | |
|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | OR (95% CI) | P value | OR (95% CI) | P value |
| SMAD4 rs10502913 | | | | | | | | |
| AA | 18 | 6.2 | 26 | 8.3 | 1.00 (ref) | 0.534 | 1.00 (ref) | 0.454 |
| AG | 135 | 46.2 | 136 | 43.2 | 1.434 (0.751–2.737) | 0.275 | 1.535 (0.785–3.000) | 0.210 |
| GG | 139 | 47.6 | 153 | 48.5 | 1.312 (0.690–2.497) | 0.408 | 1.426 (0.732–2.781) | 0.297 |
| NLRP3 rs1539019 | | | | | | | | |
| AA | 74 | 25.3 | 76 | 24.1 | 1.00 (ref) | 0.800 | 1.00 (ref) | 0.788 |
| CA | 133 | 45.6 | 152 | 48.3 | 1.003 (0.648–1.555) | 0.988 | 0.985 (0.652–1.489) | 0.944 |
| CC | 85 | 29.1 | 87 | 27.6 | 0.899 (0.605–1.335) | 0.597 | 1.127 (0.713–1.782) | 0.608 |

**Note**: All variables in the table were included in the multivariate model, while adjusting for age, coal dust exposure time and smoking status.
**Abbreviations**: CWP, coal workers' pneumoconiosis; OR, odds ratio; CI, confidence interval; N, number of patients.

**Table 4** Distributions of the Genotypes of Different Alleles and Their Associations with CWP Risk

| Variables | CWP (N = 292) | | Controls (N = 315) | | P | OR | 95% CI |
|---|---|---|---|---|---|---|---|
| | N | % | N | % | | | |
| SMAD4 rs10502913 | | | | | | | |
| A allele | 171 | 29.3 | 188 | 29.8 | 0.831 | 1.00 | ref |
| G allele | 413 | 70.7 | 442 | 70.2 | | 1.027 | 0.803–1.315 |
| NLRP3 rs1539019 | | | | | | | |
| A allele | 281 | 48.1 | 304 | 48.3 | 0.962 | 1.00 | ref |
| C allele | 303 | 51.9 | 326 | 51.7 | | 1.006 | 0.803–1.260 |

**Abbreviations**: CWP, coal workers' pneumoconiosis; OR, odds ratio; CI, confidence interval; N, number of patients.

smoking. As shown in Table 5, among the smokers, when compared with AA genotype of SMAD4 rs10502913, AG and GG genotypes were not increased the risk of CWP (adjusted OR = 1.591 and 1.502, 95% CI = 0.786–3.220 and 0.743–3.038, $p$= 0.197 and 0.257, respectively). The CA and CC genotypes of NLRP3 rs1539019 were not associated with CWP risk compared with the AA genotype (adjusted OR = 0.998 and 1.164, 95% CI = 0.654–1.544 and 0.711–1.905, $p$= 0.993 and 0.547, respectively). Similarly, a non-significant effect was observed among the non-smokers.

## Discussion

CWP is an untreatable but preventable fibrotic lung disease caused by the chronic inhalation of coal dust. Coal consists mainly of pure carbon, which is essentially inert. However, the composition of processed coal is more complex and includes organic and inorganic contaminants known as pro-inflammatory, such as silica, cadmium, pyrite, and polycyclic aromatic hydrocarbons.[17] The physical properties of carbon particles and the chemical composition of these contaminants have a significant impact on the risk of pneumoconiosis.[18] Long-term exposure to coal dust leads to activation of pro-inflammatory and pro-fibrotic pathways in the lungs, followed by tissue repair processes that result in the development of CWP.[19] The activation of fibrotic pathways is due to the cytotoxicity of coal dust particles and the release of pro-inflammatory and pro-fibrotic mediators by cells responding to the particles.[19] Essentially, coal particles produce a large number of reactive oxygen species and induce oxidative stress.[20]

Although it has been well established that coal dust exposure is the main pathogenic factor of CWP, only a proportion of coal miners exposed to dust eventually develop CWP, suggesting that genetic factors such as polymorphisms play a role in the pathogenesis of this disease. A recent study demonstrated that vitamin D receptor (VDR) gene ApaI T allele significantly increased the risk of CWP, and also the genotypes ApaI GT and TT were associated with an increased risk of CWP in the Chinese Han population.[21] A case–control study showed an association between the gene nuclear assembly factor 1 (NAF1) rs4691896 and CWP in the Chinese Han population.[4] Another case–control study reported that a significant association between cytochrome b-245α polypeptide gene b alpha (CYBA) rs7195830 and CWP using an additive model in which the minor allele increases CWP risk. In addition, the AA and AG genotypes significantly increased the risk of CWP compared to GG genotype using the dominant model.[2] Furthermore, the lipopolysaccharide (LPS)-responsive beige-like anchor protein (LRBA) rs2290846 AA was associated with decreased risk of CWP.[22] Our present study focused on the association between SMAD4 and NLRP3 polymorphisms and CWP.

SMAD family genes mediate cellular responses and play an important role in downstream transduction of TGF-β signaling pathway. When SMAD4 expression is lost, the thymus epithelial cell function is altered, and the number of early T-line progenitor cells is significantly reduced.[23] Studies have shown that SMAD4 loss is a common feature of numerous malignancies and is associated with cancer progression.[24] Therefore, many studies have indicated that SMAD4 mutation is closely related to pancreatic cancer,[25] cholangiocarcinoma,[26] colorectal cancer,[27] gastric carcinoma,[24] and other tumors since its discovery in 1996. It has been shown that different SNPs of SMAD4 have different effects on the same disease, the SMAD4 rs17663887 TC genotype and the rs12456284 GG genotype significantly decreased gastric cancer risk compared with the wild-type genotype, but SMAD4 rs10502913 was not associated with the risk of gastric cancer.[28] Another study demonstrated no significant association between the SMAD4 rs10502913 and the risk of

**Table 5** Odds Ratios for Association of Genotypes with CWP After Stratification by Smoking Status

| Variables | Smokers, n | | Univariate Analysis | | Multivariable Analysis | | Non-Smokers, n | | Univariate Analysis | | Multivariable Analysis | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | CWP | Controls | OR (95% CI) | P | OR (95% CI) | P | CWP | Controls | OR (95% CI) | P | OR (95% CI) | P |
| SMAD4 rs10502913 | 261 | 274 | | | | | 31 | 41 | | | | |
| AA | 16 | 23 | 1.00 (ref) | 0.568 | 1.00 (ref) | 0.435 | 2 | 3 | 1.00 (ref) | 0.898 | 1.00 (ref) | 0.969 |
| AG | 122 | 121 | 1.360(0.686–2.659) | 0.378 | 1.591(0.786–3.220) | 0.197 | 13 | 15 | 1.300(0.187–9.021) | 0.791 | 0.971(0.127–7.432) | 0.977 |
| GG | 123 | 130 | 1.449(0.730–2.878) | 0.289 | 1.502(0.743–3.038) | 0.257 | 16 | 23 | 1.043(0.156–6.974) | 0.965 | 0.862(0.118–6.304) | 0.884 |
| NLRP3 rs1539019 | | | | | | | | | | | | |
| AA | 65 | 66 | 1.00 (ref) | 0.789 | 1.00 (ref) | 0.752 | 9 | 10 | 1.00 (ref) | 0.887 | 1.00 (ref) | 0.691 |
| CA | 123 | 137 | 0.912(0.599–1.388) | 0.666 | 0.998(0.654–1.544) | 0.993 | 10 | 15 | 0.741(0.222–2.471) | 0.625 | 0.796(0.223–2.844) | 0.725 |
| CC | 73 | 71 | 1.044(0.650–1.767) | 0.859 | 1.164(0.711–1.905) | 0.547 | 12 | 16 | 0.833(0.258–2.688) | 0.760 | 0.578(0.173–2.045) | 0.395 |

**Note**: All variables in the table were included in the multivariate model, while adjusting for age, coal dust exposure time and smoking status.
**Abbreviations**: CWP, coal workers' pneumoconiosis; OR, odds ratio; CI, confidence interval; N, number of patients.

developing colorectal cancer.[29] A previous study examined the association between different SNPs in SMAD4 and the risk of CWP, suggesting that only SMAD4 rs10502913 AA genotype increased the risk of CWP, while other SNPs (rs12958604, rs8084630, rs17663887, rs12456284) were not associated with CWP risk.[30] Therefore, the present study is interested in the association between SMAD4 rs10502913 polymorphisms and CWP.

In this study, we revealed that the AG or GG genotypes at SMAD4 rs10502913 were not significantly associated with CWP risk in the Chinese Han population. Also, there was no association between the G allele of SMAD4 rs10502913 and CWP risk. Furthermore, we analyzed the interaction of SMAD4 rs10502913 genotypes with risk behaviors such as smoking. And the results showed that there was no interaction among SMAD4 rs10502913 genotypes and cigarette smoking on determining the personal susceptibility of CWP. Interestingly, a previous study indicated that SMAD4 rs10502913 AA genotype was significantly increased CWP risk and this result was more evident among subgroups of smokers and subjects with stage I,[30] which was inconsistent with our results. The exact reason for the inconsistency is unclear, but one reason might be differences in the regions where samples are collected. The role of SMAD4 rs10502913 polymorphism in disease development of CWP needs further research.

NLRP3 belongs to the NLR protein family and is composed of leucine-rich repeat domains and nucleotide-binding domains.[13] NLRP3 inflammasome plays a crucial role in inflammation and is a key signal node controlling the maturation of pro-inflammatory cytokines IL-1β and IL-18.[31] It has been shown that the C allele of NLRP3 rs1539019 significantly increased the risk of renal cell carcinoma, and the genotype of CC was associated with increased renal cell carcinoma risk compared with AA genotype.[32] Previous studies suggested that the CC genotype of NLRP3 rs1539019 was not associated with altered major blunt trauma risk[33] and coronary heart disease risk.[34] In our study, we demonstrated that the CC genotypes at NLRP3 rs1539019 were not associated with CWP risk in the Chinese Han population. Also, there was no association between the C allele of NLRP3 rs1539019 and CWP risk compared with A allele. In addition, we analyzed the interaction of NLRP3 rs1539019 genotypes with smoking status. The results indicated that there was no interaction among NLRP3 rs1539019 genotypes and smoking in determining the susceptibility of CWP. More intriguingly, a previous study reported that the NLRP3 rs1539019 TT genotype was significantly increased CWP risk compared with the GG/GT genotype, in particular among smokers. In addition, the increased risk was more pronounced in the CWP patients with stage I.[35] This inconsistency may require further confirmation by large samples.

There are several limitations of this study. First, it is a case–control study, so the possibility of subject selection bias cannot be ruled out. Second, this study is a single medical center-based study and the number of recruited participants is moderate, which may render other differences between groups. Third, our study did not include female patients, because there are almost no female workers underground in the coal mines of Datong city, China. Fourth, there was a poor age match between the two groups. Therefore, further large sample sizes and multicenter studies are needed to elucidate these results.

## Conclusion

In the present study, SMAD4 rs10502913 and NLRP3 rs1539019 genotypes were not associated with altered risk for CWP in a Chinese Han population. In addition, in the stratified analyses, there was no interaction between SMAD4 rs10502913 and NLRP3 rs1539019 genotypes and smoking status on CWP risk. Our results showed that those polymorphisms were not significantly associated with the CWP risk. Thus, we thought that SMAD4 rs10502913 and NLRP3 rs1539019 genotypes cannot be potential candidate biomarkers for predicting CWP development.

## Ethics Approval

This study was approved by the Ethics Committee of the Sinopharm Tongmei General Hospital (NO.201902).

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## Disclosure

The authors report no conflicts of interest in this work.

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