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NAF1 rs4691896 Is Significantly Associated with Coal Workers' Pneumoconiosis in a Chinese Han Population: A Case-Control Study

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

AG 1 Baojun Yuan
BCDEF 2 Xiaoting Wen
CDE 2 Liubing Li
AG 2 Yongzhe Li
BF 1 Chao Li
BF 1 Baolin Li
BF 3 Wei Yuan
BF 3 Liufu Cui

1 Department of Clinical Laboratory, Kai Luan General Hospital, Tangshan, Hebei, P.R. China
2 Department of Clinical Laboratory, Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing, P.R. China
3 Department of Rheumatology and Clinical Immunology, Kai Luan General Hospital, Tangshan, Hebei, P.R. China

* Baojun Yuan, Xiaoting Wen and Liubing Li are equal contributors

Corresponding Authors: Baojun Yuan, e-mail: ybj25999@163.com, Yongzhe Li, e-mail: yongzhelipumch@126.com
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Background: Previous studies have demonstrated the important role of genetic predisposition in coal workers' pneumoconiosis (CWP) in addition to environmental factors. The pathogenesis of pulmonary fibrosis disease is related to telomere activity. We performed this study to assess the association between genetic variants of telomere-related genes and the risk of CWP.

Material/Methods: We enrolled 652 CWP Chinese Han patients and 648 dust-exposed controls in this case-control design study, genotyping 8 single-nucleotide polymorphisms (SNPs) including *TERT* (rs2736100), *TERC* (rs10936599 and rs12696304), and *NAF1* (rs7675998, rs3822304, rs12331717, rs936562 and rs4691896) using the Sequenom MassARRAY system.

Results: We identified a significant allele association between *NAF1* rs4691896 and CWP by comparing patients with controls (22.0% *vs.* 13.0%, odds ratio [OR]: 1.89, 95% confidence interval [CI]: 1.54–2.33, $Pc=1.14\times10^{-8}$). The genotype frequency of rs4691896 differed significantly between the patients and controls ($Pc=1.49\times10^{-8}$). In addition, rs4691896 was correlated with CWP in an additive genetic model (OR: 1.96, 95% CI: 1.58–2.44, $Pc=8.96\times10^{-9}$) and a dominant model (OR: 2.15, 95% CI: 1.70–2.73, $Pc=2.39\times10^{-9}$).

Conclusions: Our study for the first time demonstrates an association between a telomere-related gene (*NAF1*) and CWP in a Chinese Han population, and provides valuable insight to further understand the possible pathogenetic mechanism of fibrosis in CWP.

MeSH Keywords: Anthracosis • Genetic Predisposition to Disease • Polymorphism, Single Nucleotide

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Background

Coal workers' pneumoconiosis (CWP), an irreversible fibrotic lung disorder, is associated with absorbing excessive coal dust particulates. CWP and silicosis are the predominant pneumoconioses, accounting for 95.5% of newly reported cases of occupational pneumoconiosis in 2016 in China. Notably, CWP accounted for nearly 60% of all new pneumoconiosis cases [1]. A systematic analysis in China reported a far higher prevalence of CWP in local government-owned mines compared with state-owned mines due to the different types of protection measures employed [2], highlighting again the vital importance of various coal dust exposures to CWP.

Free crystalline silica-containing coal dust accumulates in the lung, triggering inflammation, lung fibrosis, and chronic obstructive pulmonary disease. Such exposure activates resident macrophages to release pro-inflammatory cytokines, resulting in the promotion of dense collagen fiber formation in the lung and eventually the development of pulmonary fibrosis and focal emphysema. Additionally, a comparison of antioxidant enzymes between patients and controls [3,4] revealed a possible role of oxidant injury in lung damage based on some oxidant markers.

As for many other occupational diseases, few of the people exposed to inorganic dust particulates develop CWP. Therefore, in addition to exposure factors, a genetic susceptibility has also been illustrated in the pathogenesis of CWP. Previous studies suggested relationships of single-nucleotide polymorphisms (SNPs) in *MUC5B*, *NLRP3,* and *TICAM1* genes with pneumoconiosis, providing new insights into CWP pathogenesis [5–7]. Because CWP is characterized by lung fibrosis, we wondered whether pulmonary fibrosis is correlated with genetic variations in the context of CWP predisposition. Previously, studies showed that another fibrotic lung disorder, idiopathic pulmonary fibrosis (IPF), is associated with telomerase RNA component (*TERC*) and telomerase reverse transcriptase (*TERT*) genes [8]. These 2 genes are telomere-related genes with the function of regulating telomere length. Additionally, gene nuclear assembly factor 1 (*NAF1*) can affect telomere activity through the association of NAF1 protein with other proteins such as TERT to form the telomerase enzyme. These findings indicate that pulmonary fibrosis-emphysema patients have frameshift mutations in *NAF1* [9]. Based on the association between lung fibrosis and telomere-related genes, the present study aimed to investigate the correlation between mutations in *TERC*, *TERT,* and *NAF1* and CWP susceptibility in a Chinese Han population.

Material and Methods

Study population

We enrolled 652 male Han Chinese patients with CWP in the study from February 2011 to December 2015. CWP was diagnosed for pneumoconiosis according to the China National Diagnostic Criteria (GBZ70-2009). A total of 648 unrelated male dust-exposed controls were recruited from the Kailuan mining area from March to June 2015. The controls were subjected to X-ray and physical examinations to exclude CWP. The case subjects were divided into 2 groups exposed to either coal dust or rock dust. The coal dust group included 303 cases and 321 controls, whereas the rock dust group included 349 cases and 327 controls. Both groups consisted of heading drivers, coal diggers, and workers who performed both jobs. The present study was approved by the Ethics Committee of Kailuan General Hospital.

SNPs selection

As shown in Table 1, we genotyped 8 SNPs. Among them, rs10936599 from *TERC* and rs2736100 from *TERT* are associated with pulmonary fibrosis [8], whereas rs12696304 is near *TERC* and rs7675998 of *NAF1* is related to mean telomere length. Additionally, 4 variants (rs3822304, rs12331717, rs936562, and rs4691896) on the untranslated region (UTR) and exon region of *NAF1* were also analyzed (Table 1).

DNA extraction and genotyping

Genomic DNA from each participant was extracted from peripheral blood using genomic DNA kits (Tiangen, Beijing, China). The genotyping of the SNPs of 3 candidate genes was conducted using the Agena MassARRAY system (San Diego, CA, USA) through matrix-assisted laser desorption ionization-time-of-flight mass spectrometry (MALDI-TOF MS). The subsequent products were dispensed onto a 384-element Spectro CHIP array for analysis with MassARRAY Typer v4.0.

Statistical analysis

Eight SNPs were genotyped in controls, and the Hardy-Weinberg equilibrium (HWE) of SNPs was analyzed using the χ^2 test. We performed association analyses using PLINK 1.07 software (Shaun Purcell, Boston, MA). Associations were analyzed by comparing the frequencies of each allele in cases and controls, and odds ratios (ORs) were calculated. $Pc<0.05$ after Bonferroni correction was considered indicative of a statistically significant difference. Additionally, genetic models for the variants were assessed. Linkage disequilibrium (LD) analysis was conducted using Haploview v4.2.

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Table 1. HWE test of 8 SNPs.

Gene	SNP	Minor allele/ major allele	Position	Function	*P*	*Pc* for HWE
TERC	rs10936599	C/T	Chr3: 169774313	9.3 kB upstream of TERC	0.52	NS
TERC	rs12696304	C/G	Chr3: 169763483	1.5 kB downstream of TERC	0.85	NS
TERT	rs2736100	C/A	Chr5: 1286401	Intron variant	0.93	NS
NAF1	rs7675998	A/G	Chr4: 163086668	80 kB downstream of TERC	0.89	NS
NAF1	rs3822304	G/C	Chr4: 163166899	Upstream variant 2 kB, UTR variant 5 prime	>0.99	NS
NAF1	rs12331717	T/C	Chr4: 163166907	Upstream variant 2 kB, UTR variant 5 prime	0.19	NS
NAF1	rs936562	A/T	Chr4: 163166802	UTR variant 5 prime	0.72	NS
NAF1	rs4691896	T/C	Chr4: 163164273	Missense variant, exon variant	>0.99	NS

HWE – Hardy-Weinberg equilibrium; SNPs – single-nucleotide polymorphisms; *Pc* – p value corrected by Bonferroni method; NS – not significant.

Results

Population characteristics

The study included 652 patients with CWP (mean age±standard deviation [SD]: 62.7±5.9) and 648 controls (mean age±SD: 60.9±7.3). The average durations of exposure to dust in the patients and controls were 25.8±4.4 years and 23.6±4.1 years, respectively. The smoking rates in cases and controls were 55.2% (360/652) and 51.5% (334/648), respectively. The basic characteristics of age, smoking rate, and exposure duration were all comparable between the patient and control groups ($P>0.05$).

SNP allele and genotype analysis between cases and controls

The genotype frequencies of 8 SNPs in 3 genes in the control group were all distributed according to HWE criteria ($Pc>0.05$, Table 1). The genotyping of the quality control sample was completely consistent, and the call rate for each SNP was greater than 97%.

As shown in Table 2, the minor allele T frequencies of rs4691896 in *NAF1* in CWP cases and in controls were 22.0% and 13.0%, respectively. The G allele frequencies of genetic variant rs3822304 of *NAF1* in CWP cases and in controls were 3.3% and 1.7%, respectively. The results showed that both rs4691896-T (OR: 1.89, 95% CI: 1.54–2.33, $Pc=1.14\times10^{-8}$) and rs3822304-G (OR: 1.96, 95% CI: 1.17–3.30, $P=0.01$) were more common in patients than in healthy subjects. The C allele of rs2736100 from *TERT* showed a lower allele frequency in the patients with CWP than in the healthy subjects (38.4% *vs.* 42.7%, OR: 0.84, 95% CI: 0.72–0.98, $P=0.04$). There was no significant association of rs3822304 and rs2736100 with CWP after Bonferroni correction.

As shown in Table 3, the genotype frequency of rs4691896 in *NAF1* differed significantly between the cases and controls ($Pc=1.49\times10^{-8}$). Seven SNPs (rs10936599 and rs12696304 from *TERC*, rs2736100 of *TERT* and rs7675998, rs3822304, rs12331717, and rs936562 from *NAF1*) were found to be negatively associated with CWP.

Genetic model analysis of candidate genes

As shown in Table 4, among the 8 SNPs, only rs4691896 of *NAF1* was significantly correlated with CWP in the additive genetic model (OR: 1.96, 95% CI: 1.58–2.44, $Pc=8.96\times10^{-9}$) and dominant model (OR: 2.15, 95% CI: 1.70–2.73, $Pc=2.39\times10^{-9}$), whereas the other 7 SNPs showed no significant association with CWP in any genetic model ($Pc>0.05$).

LD analysis of *NAF1*

The outcomes of LD analysis are shown in Figures 1 and 2, and the data show that rs7675998, rs4691896, and rs936562 of NAF1 were in strong LD (D' >0.7, r^2 >0.3).

Discussion

Our study showed that *NAF1*, a telomere length maintenance gene, was associated with CWP, which suggests that CWP has susceptibility genes in common with pulmonary fibrosis, providing a clue to the pathogenesis of CWP.

Telomeres located at linear chromosome ends are protective structures, playing a role in preventing genome instability. Telomere shortening accelerates the process of aging during

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Table 2. Allele distribution of case-control association analysis.

Gene	SNP	Minor allele/ major allele	CWP group, n (%)		Exposed control group, n (%)		OR (95%CI)	*P*	*Pc*
			Minor allele	Major allele	Minor allele	Major allele			
TERC	rs10936599	C/T	579 (44.7%)	715 (55.3%)	576 (45.1%)	702 (54.9%)	0.99 (0.85–1.15)	0.89	NS
TERC	rs12696304	C/G	412 (31.7%)	886 (68.3%)	395 (30.8%)	887 (69.2%)	1.04 (0.88–1.23)	0.62	NS
TERT	rs2736100	C/A	496 (38.4%)	794 (61.6%)	534 (42.7%)	718 (57.3%)	0.84 (0.72–0.98)	0.04	NS
NAF1	rs7675998	A/G	234 (18.0%)	1064 (82.05)	213 (16.5%)	1077 (83.5%)	1.11 (0.91–1.36)	0.31	NS
NAF1	rs3822304	G/C	43 (3.3%)	1259 (96.7%)	22 (1.7%)	1264 (98.2%)	1.96 (1.17–3.30)	0.01	NS
NAF1	rs12331717	T/C	64 (4.9%)	1234 (95.1%)	63 (4.9%)	1233 (95.1%)	1.02 (0.71–1.45)	0.94	NS
NAF1	rs936562	A/T	287 (22.2%)	1007 (77.8%)	273 (21.3%)	1007 (78.7%)	1.05 (0.87–1.27)	0.60	NS
NAF1	rs4691896	T/C	287 (22.0%)	1017 (78.0%)	168 (13.0%)	1126 (87.0%)	1.89 (1.54–2.33)	1.43×10^{-9}	1.14×10^{-8}

SNP – single-nucleotide polymorphism; CWP – coal workers' pneumoconiosis; OR – odds ratio; CI – confidence interval; *Pc* – p value corrected by Bonferroni method; NS – not significant.

Table 3. Genotype distribution of candidate genes in CWP cases and dust-exposed controls.

Gene	SNP	Minor allele/ major allele	CWP group, n (%)			Exposed control group, n (%)			χ^2	*P*	*Pc*
			AA	AB	BB	AA	AB	BB			
TERC	rs10936599	C/T	137 (21.2%)	305 (47.1%)	205 (31.7%)	134 (21.0%)	308 (48.2%)	197 (30.8%)	0.16	0.92	NS
TERC	rs12696304	C/G	74 (11.4%)	264 (40.7%)	311 (47.9%)	62 (9.7%)	271 (42.3%)	308 (48.0%)	1.12	0.57	NS
TERT	rs2736100	A/C	105 (16.3%)	286 (44.3%)	254 (39.4%)	113 (18.1%)	308 (49.2%)	205 (32.7%)	6.06	0.05	NS
NAF1	rs7675998	A/G	14 (2.2%)	206 (31.7%)	429 (66.1%)	18 (2.8%)	177 (27.4%)	450 (69.8%)	3.19	0.20	NS
NAF1	rs3822304	C/G	1 (0.2%)	41 (6.2%)	609 (93.5%)	0 (0%)	22 (3.4%)	621 (96.6%)	6.80	0.03	NS
NAF1	rs12331717	C/T	4 (0.6%)	56 (8.6%)	589 (90.8%)	3 (0.5%)	57 (8.8%)	588 (90.7%)	0.15	0.93	NS
NAF1	rs936562	A/T	23 (3.6%)	241 (37.2%)	383 (59.2%)	27 (4.2%)	219 (34.2%)	394 (61.6%)	1.49	0.48	NS
NAF1	rs4691896	C/T	21 (3.2%)	245 (37.6%)	386 (59.2%)	11 (1.7%)	146 (22.65)	490 (75.7%)	40.52	1.86×10^{-9}	1.49×10^{-8}

CWP – coal workers' pneumoconiosis; SNP – single-nucleotide polymorphism; *Pc* – p value corrected by Bonferroni method.

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Table 4. Analysis of candidate SNPs based on 3 genetic models with logistic regression analysis.

Gene	SNP	Additive model			Dominant model			Recessive model		
		OR (95% CI)	*P*	*Pc*	OR (95% CI)	*P*	*Pc*	OR (95% CI)	*P*	*Pc*
TERC	rs10936599	0.99 (0.85–1.15)	0.87	NS	0.96 (0.76–1.22)	0.74	NS	1.01 (0.77–1.32)	0.93	NS
TERC	rs12696304	1.04 (0.89–1.23)	0.62	NS	1.01 (0.81–1.25)	0.96	NS	1.20 (0.84–1.72)	0.31	NS
TERT	rs2736100	0.84 (0.72–0.99)	0.03	NS	0.75 (0.60–0.94)	0.01	NS	0.88 (0.66–1.18)	0.40	NS
NAF1	rs7675998	1.12 (0.91–1.37)	0.30	NS	1.18 (0.94–1.50)	0.16	NS	0.77 (0.38–1.56)	0.46	NS
NAF1	rs3822304	1.96 (1.16–3.30)	0.01	NS	1.95 (1.15–3.30)	0.01	NS	NA	1.00	NS
NAF1	rs12331717	1.01 (0.72–1.43)	0.94	NS	1.00 (0.69–1.45)	0.99	NS	1.33 (0.30–5.98)	0.71	NS
NAF1	rs936562	1.05 (0.87–1.28)	0.59	NS	1.10 (0.88–1.38)	0.39	NS	0.84 (0.48–1.48)	0.54	NS
NAF1	rs4691896	1.96 (1.58–2.44)	1.12×10^{-9}	8.96×10^{-9}	2.15 (1.70–2.73)	2.99×10^{-10}	2.39×10^{-9}	1.92 (0.92–4.02)	0.82	NS

SNPs – single-nucleotide polymorphisms; OR – odds ratio; CI – confidence interval; *Pc* – p value corrected by Bonferroni method; NS – not significant.

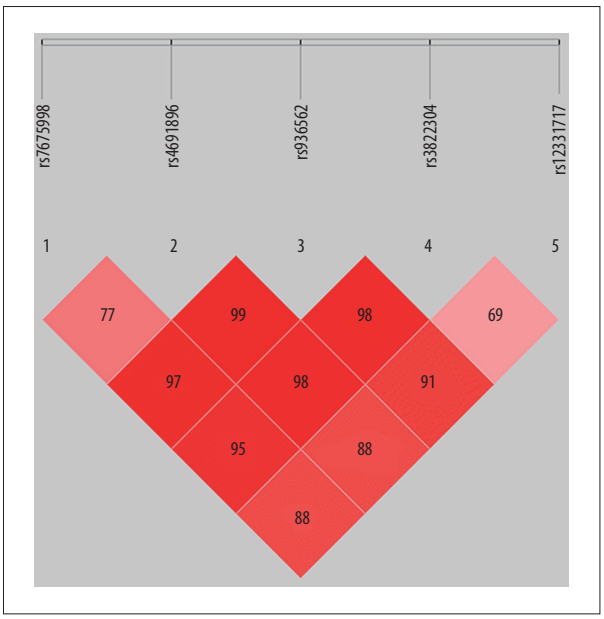

Figure 1. D' values map of linkage disequilibrium analysis of NAF1 gene.

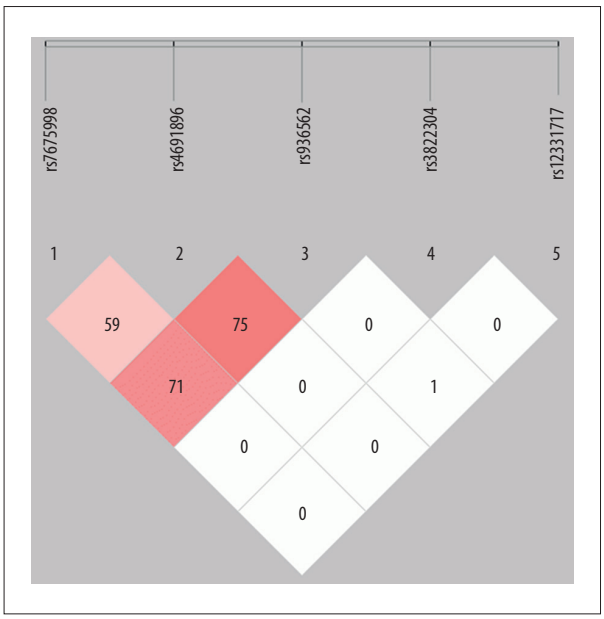

Figure 2. r^2 values map of linkage disequilibrium analysis of NAF1 gene.

cell division. Mutations in genes needed for telomere maintenance generate a spectrum of diseases such as telomeropathies, including pulmonary fibrosis and liver fibrosis, in addition to aplastic anemia [8,10]. Many studies have shown that telomere dysfunction is involved in the etiologies of IPF, familial pulmonary fibrosis, and pulmonary fibrosis-emphysema [11–14]. Moreover, IPF patients with shorter telomeres have shorter survival times than those with longer telomeres [14,15]. Telomere length less than the 10th percentile was shown to be associated with poor prognosis in IPF patients [16]. Interestingly, telomere length was proven to be related to fibrotic joint conditions, such as hip stiffness, knee stiffness, and frozen shoulder [17].

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The evidence described suggests that telomere deficiency is a shared mechanistic pathway for fibrotic disorders.

NAF1 is an essential protein required for the biogenesis of H/ACA box small nucleolar RNAs, which are abundant non-coding RNAs, and thus has important functions in telomeric DNA synthesis [18]. Frameshift mutations in pulmonary fibrosis-emphysema patients result in short telomere length and low telomerase RNA levels. SNP rs4691896 in the second exon of *NAF1* is a missense variant (c.484A>G) that causes replacement of isoleucine (Ile) with valine (Val) (Ile162Val). The rs4691896-coded amino acid is located outside of the globular domain Naf1 RNA-binding region, without effect on the proper function of *NAF1* by PolyPhen [19]. Prediction using the web-based software MUpro v1.0 confirmed that the Val162 variant can decrease the stability of the protein structure of *NAF1* [20]. Thus, the evidence suggests that SNP rs4691896 is related to pulmonary fibrosis in pneumoconiosis via an effect on *NAF1* stability, but this must be validated further.

Our study has several limitations. Although the duration of dust exposure and the smoking rate were matched in CWP patients and healthy controls, we did not consider their levels. We also need to validate the genetic variant in independent CWP cohorts to ensure the positive association.

Conclusions

In conclusion, this case-control study demonstrates for the first time that a genetic variation of *NAF1* can increase susceptibility to CWP and provides valuable information for better understanding the pathogenesis of this disease. Further studies are required to validate the relationship of telomerase level and telomere length with pulmonary fibrosis in CWP.

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Conflicts of interest

None.

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