

GSTM1, GSTT1, GSTP1, NAT2, CYP2E1 CYP1A1

Abstract

The Association between Pneumoconiosis and Genetic Polymorphism of GSTM1, GSTT1, GSTP1, NAT2, CYP2E1 and CYP1A1

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Objective: To investigate effects of genetic polymorphism of glutathione S-transferase M1 (GSTM1), glutathione S-transferase T1 (GSTT1), glutathione S-transferase P1 (GSTP1), N-acetyltransferase (NAT2), cytochrome P450 2E1 (CYP2E1) and cytochrome P450 1A1 (CYP1A1) on pneumoconiosis.

Methods: Eighty-five pneumoconiosis patients and 122 age and sex matched healthy controls were enrolled. Direct interview and standard questionnaire were conducted and the genotypes of GSTM1, GSTT1, GSTP1, NAT2, CYP2E1 and CYP1A1 were investigated using multiplex PCR or PCR-RFLP methods with DNA extracted from venous blood. The relationship was investigated between the severity of pneumoconiosis and the polymorphism of GSTM1, GSTT1, GSTP1, NAT2, CYP2E1 and CYP1A1, and also with various environmental factors including smoking.

Results: We observed a significantly higher rate of genetic polymorphism in pneumoconiosis patients than in normal subjects. The odds ratio (95% CI) of NAT2 was 2.09 (1.19-3.68). In addition, smoking was related significantly with pneumoconiosis (OR 2.89, 95% CI 1.40-5.95). In multiple logistic regression analyses, NAT2 and smoking were significant risk factors for the development of pneumoconiosis (OR 1.84, 95% CI 1.00-3.37; OR 2.98, 95% CI 1.40-6.35, respectively). The age of onset of the disease and smoking were significantly related with moderate or severe pneumoconiosis (OR 0.91, 95% CI 0.83-0.99; OR 6.94, 95% CI 1.54-31.30, respectively).

However there was no significant difference between the rate of genetic polymorphism of GSTM1, GSTT1, GSTP1, CYP2E1 and CYP1A1 in the two groups.

Conclusion: NAT2 genetic polymorphism was higher in pneumoconiosis patients than in normal subjects. The age of onset of the disease and smoking were significantly related with pneumoconiosis. However, the genetic polymorphism of GSTM1, GSTT1, GSTP1, CYP2E1 and CYP1A1 was not related with development or severity of pneumoconiosis.

Key Words: Pneumoconiosis, Genetic polymorphism, GSTM1, GSTT1, GSTP1, NAT2, CYP2E1, CYP1A1

가 가

가 가

가 가

1.5~3.4 (Choi et al., 1999).
2001 2003

67 (Ahn et al., 2004).

(IARC, 1997).

(pack-years)

(Harrington, 1963).
(host factor)

(Jung and Hong, 1988).
20~30

가 (Jung and Hong,
1988; Sheppard et al., 1990; Lilis, 1992).

DNA

glutathione S-transferase M1,
glutathione S-transferase T1, glutathione S-
transferase P1, N-acetyltransferase 2,
cytochrome P450 1A1 cytochrome P450 2E1

GSTM1 GSTT1

가 (Ryberg et al., 1997), GSTM1
GSTP1 PAH-DNA adduct
가 (Butkiewicz et
al., 2000). phase II NAT2
N-acetylation
, NAT2 slow-acetylator
(Hirvonen et
al., 1996). CYP1A1 polycyclic aromatic hydro-
carbons
(Romundstad et al.,
2000). CYP2E1 가
N-nitrosamine (Yamazaki
et al., 1992),
가 (Guengerich et al.,
1991).

(Kim et al., 1998; 2000)
(Nam
et al., 1999; Chung et al., 2002)

GSTM1, GSTT1,
GSTP1, NAT2, CYP2E1 CYP1A1

가

(Jung and Hong, 1988).
20~30

가 (Jung and Hong,
1988; Sheppard et al., 1990; Lilis, 1992).

DNA

1.

1)
2002 6 1

60

93

8 85

ILO (profusion) 가
 가 0/0 1/2
 mild , 2/1 3/4 moder-
 ate (com-
 plicated pneumoconiosis)
 A, B, C 3 severe

2)

2002 6 2002 10
 60 122

2.

1)

PCR -globin
 primer 5'-CAA CTT CAT CCA CGT TCA CC-3'
 3' 5'-GAA GAG CCA AGG ACA GGT AC-3'
 PCR 2% agarose gel
 band GSTM1 219 bp,
 GSTT1 410 bp band

CYP1A1

CYP1A1 primer 5'-
 CCA CCT CAG CTG TCT CCC TC-3' 5'-GAA
 AGA CCT CCC AGC GGT CA-3' PCR 94
 30 , 58 30 , 72 30 30
 180 bp PCR 2% agarose gel
 PCR 5 µl HincII
 가 37 2 digestion 2.5%
 agarose gel
 , 139 bp 48 bp band
 Ile/Ile , 139 bp, 120 bp 48 bp
 band Ile/Val , 120
 bp 48 bp band Val/Val

CYP2E1

CYP2E1 primer 5'-
 CCA GTC GAG TCT ACA TTG TCA-3' 5'-
 TTC ATT CTG TCT TCT AAC TGG CA-3'
 PCR 94 30 , 58 30 , 72 30
 30 , 2% agarose gel
 PCR 5 µl RsaI 가
 37 2 digestion , 1.8% agarose
 gel . 360 bp,
 50 bp band c1/c1 type (homozy-
 gous wild type), 410 bp, 360 bp 50 bp band
 c1/c2 type(heterozygous mutant
 type), 410 bp band c2/c2 type
 (homozygous mutant type)

GSTP1

GSTP1 Kristensen (1998)
 primer 5'-TCC
 TTC CAC GCA CAT CCT CT-3' 5'-AGC CCC
 TTT CTT TGT TCA GC-3' , 94 1 ,
 63 1 , 72 1 30
 2% agarose gel , PCR 3
 µl Alw26I 가 37 diges-
 tion , 2.5% agarose gel

(1) DNA (whole
 -70 blood) Omega Bio-tek(USA) E.N.Z.A
 blood DNA kit DNA
 (2) GSTM1 GSTT1 Chen
 GSTM1 GSTT1 PCR primers
 (1996) .
 GSTM1 5'-GAA CTC CCT GAA
 AAG CTA AAG C-3' 5'-GTT GGG CTC AAA
 TAT ACG GTG G-3' , GSTT1 5'-TTC
 CTT ACT GGT CCT CAC ATC TC-3' 5'-TCA
 CCG GAT CAT GGC CAG CA-3'
 PCR TaKaRa Taq DNA polymerase 가
 20 µl가 , 94 30 , 58 30 ,
 72 30 30 GSTM1
 GSTT1 -globin

. 294 bp band AA type, 294 bp, 234 bp 60 bp band AG type, 234 bp 60 bp band GG type . (mild, moderate severe) NAT2 CYP isoenzymes ANOVA (analysis of variance) Fisher's exact test NAT 1990 NAT HPLC Deguchi (1992) NAT 가 NAT PCR-RFLP 90% NAT isoenzymes GST subfamily, NAT2 CYP SPSS primer 5'-TGA CGG CAG GAA TTA CAT TGT C-3' 5'-ACA CAA GGG TTT ATT TTG TTC C-3' , 94 30 , 63 30 , 72 30 35 . 2μl BamHI (Promega, USA) KpnI (Promega, USA) 37 () PCR TaqI (Promega, USA) 가 64.7(5.62) 62.0(6.61) 가 , 2% agarose gel 가 가 (p=0.003). NAT2 acetylation slow, intermediate rapid . mild, moderate severe Table 1 3. () 가 64.4(5.51) 가 chi-square test GSTP1, NAT2, (p=0.02). Table 2 CYP1A1 CYP2E1 가 wild type Table 2 가 . GSTM1 ratio) 95% 가 . GSTT1 GST subfamily, 가 . GSTP1

Table 1. Distribution of age, smoking in pneumoconiosis and control

Variables	Case (%) (n=85)	Control (%) (n=122)	OR (95% CI)	P value*
Age (years)				
50 - 59	12 (14.1)	25 (20.5)	1.0	
60 - 69	58 (68.2)	79 (64.8)	1.530 (0.710-3.294)	0.276
70 -	15 (17.6)	18 (14.8)	1.736 (0.657-4.585)	0.264
Smoking status				
Never	12 (14.1)	38 (32.2)	1.0	
Former or current	73 (85.9)	80 (67.8)	2.890 (1.403-5.951)	0.003

*chi-square test

CYP isoenzymes 가 , GSTM1 가
 가 NAT2 (Adjusted OR
 2.395, 95% CI 0.462-12.411).
 (OR 2.091, 95% CI 1.189-3.676)(Table 3).
 GSTM1 GSTT1
 GSTM1 GSTT1
 CYP1A1 Val/Val C(m2/m2) (Adjusted
 OR 1.123, 95% CI 0.482-2.615). GSTM1

Table 2. Characteristics of mild, moderate and severe categories of pneumoconiosis

Variables	Category of pneumoconiosis			P value*
	Mild	Moderate	Severe	
Number of subjects (%)	23 (27.7)	36 (43.4)	24 (28.9)	
Mean age in years (SD)	66.3 (4.57)	64.0 (5.94)	63.1 (4.05)	0.085
Mean tenure in years (SD)	20.1 (7.65)	19.6 (8.70)	21.3 (10.02)	0.773
Smoking status (%)				
Never	7 (30.4)	3 (8.3)	1 (4.2)	0.020 [†]
Former or current	16 (69.6)	33 (91.7)	23 (95.8)	
Mean age of onset (SD)	53.3 (6.02)	50.2 (6.73)	49.1 (6.57)	0.073
Mean morbid duration in years (SD)	13.0 (5.65)	13.8 (4.70)	14.0 (6.27)	0.801

*ANOVA, [†]Fisher 's exact test

Table 3. Comparison of genotypes of GST subfamilies, NAT2 and CYP isoenzymes in pneumoconiosis and control

Variables	Case (%) (n=85)	Control (%) (n=122)	OR	95% CI	
GSTM1					
Present	40 (47.1)	52 (42.6)	1.0		
Null	45 (52.9)	70 (57.4)	0.836	0.479	1.459
GSTT1					
Present	42 (49.4)	56 (45.9)	1.0		
Null	43 (50.6)	66 (54.1)	0.869	0.499	1.513
GSTP1					
AA	57 (67.1)	84 (68.9)	1.0		
AG, GG	28 (32.9)	38 (31.1)	1.086	0.600	1.964
NAT2					
Rapid	39 (45.9)	78 (63.9)	1.0		
Intermediate, slow	46 (54.1)	44 (36.1)	2.091	1.189	3.676
CYP2E1					
C1C1	56 (65.9)	76 (62.3)	1.0		
C1C2, C2C2	29 (34.1)	46 (37.7)	0.856	0.480	1.526
CYP1A1					
Ile/Ile	48 (56.5)	64 (52.5)	1.0		
Ile/Val, Val/Val	37 (43.5)	58 (47.5)	0.851	0.487	1.484

GSTM1: glutathione S-transferase M1

GSTT1: glutathione S-transferase T1

GSTP1: glutathione S-transferase P1

NAT2: N-acetyltransferase 2

CYP2E1: cytochrome P450 2E1

CYP1A1: cytochrome P450 1A1

genotype NAT2 slow acetylation genotype
가
가

(Adjusted OR 0.389, 95% CI 0.088-1.721).

family, NAT2 CYP isoenzymes GST sub-
가

Table 4

GST subfamily CYP isoen-
zymes

, NAT2

(OR 1.839, 95%

CI 1.002-3.373).

(OR 2.982, 95% CI 1.401-

6.348).

가

mod-

erate severe mild GST subfamily,
GSTP1, NAT2, CYP1A1 CYP2E1

가

(OR 0.919, 95% CI

0.851-0.993)

(OR 6.125, 95% CI 1.591-

23.586)

GST subfamily, GSTP1,

NAT2

CYP isoenzymes

(Table 5).

GST subfamily, NAT2

CYP isoenzymes

(Table 6).

subfamily

CYP isoenzymes

NAT2

(OR 0.906,

95% CI 0.829-0.989)

(OR 6.942, 95%

CI 1.540-31.297)

가

(Table 1).

가

가

가

(p=0.02)(Table 2).

GSTM1,
GSTT1, GSTP1, NAT2, CYP2E1 CYP1A1

Phase II
family 가

GSTs
phase I

sub-

glutathione con-
jugates

가 (fibroblast)

(Cantin et al., 1990), Kelsey
(1997)

GSTM1

가

Kim (Kim et al., 1998)

GSTM1

61.7%

Kim

(Kim HJ et al., 2000) Kim (Kim GW et
al., 2000)

50.4%

49.1%

GSTM1

57.4%

Kim (1998)

GSTM1

Table 4. Association of pneumoconiosis and smoking, genotypes of GST subfamilies, NAT2 and CYP isoenzymes

Variables	S.E.	OR*	95% CI
Smoking (ever/never)	1.093	0.385	2.982 1.401 6.348
GSTM1 (null/present)	-0.212	0.308	0.809 0.442 1.479
GSTT1 (null/present)	-0.165	0.304	0.848 0.468 1.538
GSTP1 (AG, GG/AA)	-0.090	0.333	0.914 0.476 1.756
NAT2 (intermediate, slow/rapid)	0.609	0.310	1.839 1.002 3.373
CYP2E1 (C1C2, C2C2/C1C1)	-0.081	0.316	0.922 0.496 1.715
CYP1A1 (Ile/Val, Val/Val/Ile/Ile)	-0.062	0.312	0.940 0.511 1.732

*adjusted for the other variables including age

71.3%, 28.0% 0.7% 가
 (Table 3). (Kim et al., 2000). David (2003)
 GSTT1 GSTP1 GG 가
 가 (Brockmoller et al., GSTP1
 1996), GSTT1
 가
 Nelson (1995), Kim (1998) Kim
 (2000) 60.2%, 50% 52.5% NAT2 slow, intermediate
 54.1% Nelson (1995) GSTT1 rapid acetylator 가 10.7%,
 25.4% 63.9% . Lee (2002)
 9.6%, 46.9% 42.8%
 rapid acetylator가 Kim
 GSTT1 (2000) 65
 (Table 3). 7.6%, 34.9% 57.6% 가
 GSTP1 , NAT2 slow-acetylator
 GSTs subfamily
 (Cantlay et al., 1994). (Hirvonen et al., 1996)
 GSTP1 AA , AG GG NAT2 intermediate slow acetylator가
 68.9%, 30.3% 0.8%
 Chung (2002) - (OR: 2.091, 95% CI: 1.189-3.676)(Table 3).
 77.3%, 22.7% 0% CYP2E1

Table 5. Comparison of personal, occupational factors in moderate or severe and mild categories of pneumoconiosis

Variables	Category of pneumoconiosis		OR	95% CI	
	Moderate or severe	Mild			
Mean age of onset in years (SD)	49.8 (6.63)	53.3 (6.02)	0.919	0.851	0.993
Smoking status (%)					
Never	4 (6.7)	7 (30.4)	1.0		
Former or current	56 (93.3)	16 (69.6)	6.125	1.591	23.586
Mean tenure in years (SD)	20.3 (9.20)	20.1 (7.65)	1.002	0.948	1.059
GSTM1 (%)					
Present	28 (46.7)	10 (43.5)	1.0		
Null	32 (53.3)	13 (56.5)	0.879	0.334	2.314
GSTT1 (%)					
Present	32 (53.3)	10 (43.5)	1.0		
Null	28 (46.7)	13 (56.5)	0.879	0.256	1.772
GSTP1 (%)					
AA	39 (65.0)	17 (73.9)	1.0		
AG, GG	21 (35.0)	6 (26.1)	1.526	0.523	4.453
NAT2 (%)					
Rapid	25 (41.7)	13 (56.5)	1.0		
Intermediate, slow	35 (58.3)	10 (43.5)	1.820	0.689	4.806
CYP2E1 (%)					
C1C1	40 (66.7)	14 (60.9)	1.0		
C1C2, C2C2	20 (33.3)	9 (39.1)	0.778	0.288	2.103
CYP1A1 (%)					
Ile/Ile	33 (55.0)	14 (60.9)	1.0		
Ile/Val, Val/Val	27 (45.0)	9 (39.1)	1.273	0.478	3.390

c1/c1, c1/c2 c2/c2
 50.0%, 42.9% 7.1%,
 66.3%, 30.6% 3.1%

(Nam et al., 1999).
 CYP2E1

CYP2E1

GSTM1, GSTT1, GSTP1, NAT2,
 CYP2E1 CYP1A1

GSTM1, GSTT1, GSTP1, NAT2, CYP2E1
 CYP1A1

(Table 5).

(Table 3).

가

Xu (1996)

CYP1A1

가

Kim (1998)

CYP1A1

Ile/Ile, Ile/Val

Val/Val

A, B

C

가

(Table 6).

54.9%, 40.7%

4.5%

CYP1A1

, GST subfamily

CYP isoen-

zymes

CYP1A1

A, B C

NAT2

59.2%, 35.7%

5.1%,

52.0%, 45.9% 2.1%

(OR

(Nam et al., 1999).

CYP1A1

0.906, 95% CI 0.829-0.989)(OR 6.942, 95% CI 1.540-31.297).

56.6%, 36.1%

7.2%

GSTM1, GSTT1, GSTP1, NAT2,

52.5%, 39.3%

8.2%

CYP2E1 CYP1A1

Kim

(1998) Nam (1999)

CYP1A1

(Table 3).

가

NAT2

6가

(OR=1.839, 95% CI: 1.002-3.373),

가

(OR=2.982, 95% CI: 1.401-6.348)(Table 4).

NAT2가

Table 6. Association of personal, occupational factors and some genotypes and moderate or severe category of pneumoconiosis compared with mild category

Variables		S.E.	OR*	95% CI	
Age of onset (years)	-0.099	0.045	0.906	0.829	0.989
Smoking (ever/never)	1.938	0.768	6.942	1.540	31.297
Tenure (years)	-0.003	0.033	0.997	0.934	1.064
GSTM1 (null/present)	-0.265	0.586	0.767	0.243	2.422
GSTT1 (null/present)	-0.533	0.576	0.587	0.190	1.815
GSTP1 (AG, GG/AA)	-0.025	0.637	0.976	0.280	3.399
NAT2 (intermediate, slow/rapid)	0.308	0.563	1.361	0.451	4.105
CYP2E1 (C1C2, C2C2/C1C1)	-0.342	0.602	0.710	0.218	2.309
CYP1A1 (Ile/Val, Val/Val/Ile/Ile)	0.237	0.569	1.267	0.415	3.867

*adjusted for the other variables

: NAT2

NAT2 GSTM1, GSTT1,
GSTP1, CYP1A1 CYP2E1

가

가

가

가

85

122

glutathione S-transferase M1 (GSTM1) glutathione S-transferase T1 (GSTT1) glutathione S-transferase P1 (GSTP1), N-acetyltransferase 2 (NAT2), cytochrome P450 2E1 (CYP2E1), cytochrome P450 1A1 (CYP1A1)

: NAT2

(OR 2.09,

95% CI 1.19-3.68)

(OR 2.89, 95% CI

1.40-5.95).

NAT2

(OR 1.84, 95% CI 1.00-3.37) (OR 2.98, 95% CI 1.40-6.35)

(OR

0.91, 95% CI 0.83-0.99) (OR 6.94, 95% CI 1.54-31.30) GSTM1 GSTT1

가

GSTP1 CYP2E1

CYP1A1

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