

Myeloperoxidase (*MPO*) Gene Polymorphisms are not Associated with Japanese Patients with COPD

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Background: The pathogenesis of chronic obstructive pulmonary disease (COPD) is suggested to be involved with systemic inflammation and influenced by genetic factors. Myeloperoxidase (MPO) is secreted by activated polymorphonuclear neutrophils and plays a crucial role in the inflammation response. This study attempts to examine the associations of the genetic variants of the *MPO* gene with susceptibility to COPD in Japanese patients.

Methods: Six single nucleotide polymorphisms (SNPs) within the *MPO* were genotyped, including rs2107545 (A/G) and rs2243828 (A/G, variants of expression quantitative trait loci: eQTL) in the promotor region, rs7208693 (C/A, Val53Phe) in exon 2, rs35921530 (C/A, eQTL) in intron 7, rs35670089 (C/T, Arg604Cys) in exon 11, and rs2071409 (T/G, eQTL) in intron 11, in 260 patients with COPD and 129 non-COPD smokers. These 6 SNPs were able to capture at least more than 50 SNPs throughout the length of *MPO* gene. In addition, the plasma MPO concentrations were measured in both groups.

Results: There were no significant differences of allele frequencies of the six SNPs between the COPD and non-COPD groups. In addition, the plasma MPO concentration was not significantly different between the two groups.

Conclusion: The genetic variants of *MPO* were not associated with the susceptibility to COPD in the Japanese population. The MPO biomolecule is not involved with the pathogenesis of COPD. *Shinshu Med J* 68 : 41–48, 2020

(Received for publication July 30, 2019 ; accepted in revised form October 15, 2019)

Key words: COPD, myeloperoxidase, gene, single nucleotide polymorphism (SNP), inflammation

I Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by an abnormal persistent inflammatory response to noxious environmental stimuli, most commonly cigarette smoke¹. Inflammation is suggested to be one of the mechanisms in the pathogenesis of COPD, for example, the recruitment and regulation of neutrophils potentially activate polymorphonuclear neutrophils (PMNs) that release myeloperoxidase (MPO) and other intracellular prod-

ucts, resulting in lung parenchymal destruction and airway remodeling². MPO is a mediator for tissue damage and it affects neutrophil functions including cytokine production³. Meanwhile, it is also a major enzymatic source of endogenous acrolein⁴. The irritant acrolein is a pathological reactive aldehyde in the airway with toxicity directly affecting the development of COPD^{5,6}. Thus, we hypothesize that MPO plays an important role in the pathogenesis of COPD.

It has been well demonstrated that the development of COPD is influenced by ethnicity, gender, and environmental factors as well as genetic factors⁷. The marked variability in lung function and risk of COPD in people with similar cigarette smoking histories, together with studies of familial aggregation, support an important role for genetics in COPD^{7,8}.

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The *MPO* gene contains 12 exons and spans about 13 kb locating in chromosome 17q22⁹⁾. The genetic variants of *MPO* were reported to be associated with susceptibility to diseases involved with inflammation, such as vascular diseases¹⁰⁾. Thus, we performed this study in order to observe associations of the genetic variants of *MPO* with susceptibility to COPD in Japanese patients.

II Subjects and Methods

A Subjects

This study was approved by the Ethics Committee of Shinshu University. The study protocols were performed in accordance with the principles outlined in the Declaration of Helsinki of the World Medical Association. We obtained written informed consent from all subjects of cases and controls. Patients with COPD were recruited from the Department of Respiriology and Infectious Disease and Allergology in Shinshu University Hospital (Matsumoto, Japan). All participants were Japanese. COPD was diagnosed by smoking history (99.2 % of the patients had over 10 pack-years in smoking history), chronic respiratory symptoms (cough, sputum, breathlessness), and spirometric measurements that indicated an irreversible airflow limitation according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD)¹⁾. Spirometry measurements were performed with a pulmonary function test system (Chestac-55 V, Chest Co. Ltd., Tokyo, Japan). An airflow limitation was defined as the ratio of forced expiratory volume in 1 second (FEV₁) to forced vital capacity (FVC) less than 70 % (FEV₁/FVC < 70 %) and the percentage of the predicted value for FEV₁ less than 80 % (%FEV₁ < 80 %) (I). The severity of the airflow limitation was determined according to spirometric classifications of GOLD¹⁾.

The patients with COPD present two phenotypes, one is termed as small airway disease (obstructive bronchiolitis) and the other is parenchymal destruction (emphysema) based on the images on high-resolution computed tomography (HRCT)¹¹⁾. Low attenuation areas (LAA) were visually evaluated in three bilateral lung fields according to the method of Goddard et

al.¹²⁾. We defined the emphysema phenotype as a total score ≥ 7 in lung fields.

Subjects with the following disorders were excluded from the study: late sequelae of pulmonary tuberculosis, diffuse panbronchiolitis, sinobronchitis, bronchiectasis, bronchiolitis obliterans due to autoimmune disease, and bronchial asthma.

B Controls

Controls were non-COPD smokers and they were recruited from people for health screening at our affiliated hospitals (Misayama Hospital and Shinmachi Hospital, Japan). The selection criteria for non-COPD smokers included former or current smokers (all the controls had over 10 pack-years in smoking history), Japanese ethnicity, 50 years old or older, and FEV₁/FVC ≥ 71 % and %FEV₁ > 81 %. Generally, they were healthy Japanese individuals.

C Genotyping

DNA was extracted from whole blood with the QuickGene-800 kit (FUJIFILM, Tokyo, Japan). Genomic DNA was prepared at concentrations of 5–15 ng/ μ l for the TaqMan SNP genotyping assay. Six single nucleotide polymorphisms (SNPs) within *MPO* were genotyped, including rs2107545 (A/G) and rs2243828 (A/G) in the promotor region, rs7208693 (C/A) in exon 2, rs35921530 (C/A) in intron 7, rs35670089 (C/T) in exon 11, and rs2071409 (T/G) in intron 11. These SNPs covered a length of 11.888 kb of *MPO* with minor allele frequency > 5 % in the Japanese population according to the National Center for Biotechnology Information SNP database (**Table 1**). Among them, rs7208693 (Val53Phe) and rs35670089 (Arg604Cys) are SNPs of nonsynonymous substitutions in *MPO*; the rs2243828, rs35921530 and rs2071409 are variants of the expression quantitative trait loci (eQTL). These (eQTLs) are genomic loci that explain all or a fraction of variations in the expression levels of mRNA¹³⁾¹⁴⁾. In addition, setting the threshold of correction coefficient (r^2) at 0.8, these 6 SNPs served as tag SNPs and were able to capture at least more than 50 SNPs in the *MPO* gene in the Japanese population according to the 1000 Genomes data in Ensembl (http://grch37.ensembl.org/Homo_sapiens/Info/Index) (**Table 2**). The tag SNPs act as direct

Table 1 The genetic information of the SNPs of *MPO* in the study

rs number	Major/Minor alleles	Position	Genomic Region	Character of Variant	Function
rs2107545	A/G	Chr17 : 58282757	Promotor	Intergenic	
rs2243828	A/G	Chr17 : 58281523	Promotor	Intergenic	eQTL
rs7208693	C/A	Chr17 : 58280457	Exon 2	Missense	Val53Phe
rs35921530	C/A	Chr17 : 58276230	Intron 7	Intron	eQTL
rs35670089	C/T	Chr17 : 58271875	Exon 11	Missense	Arg604Cys
rs2071409	T/G	Chr17 : 58270869	Intron 11	Intron	eQTL

Abbreviations : Chr, chromosome ; eQTL, expression quantitative trait loci ; MPO, myeloperoxidase ; SNP, single nucleotide polymorphism.

Table 2 Tagging efficiency of SNPs of rs2107545, rs2243828, rs7208693, rs35921530, rs35670089, rs2071409 in *MPO* in JTP population

Test SNP	Alleles captured*
rs2107545 (eQTL) in the promotor region	rs79720816, rs4401102, rs2243828, rs2333227, rs71365871, rs59377187, rs62083750, rs73993644, rs16942914, rs12938133, rs11079344, rs77472986, rs569425179, rs9908667, rs115013689, rs11649901, rs2240261, rs72839983, rs3744102
rs2243828 (eQTL) in the promotor region	rs2333227, rs2107545, rs79720816, rs4401102, rs71365871, rs59377187, rs62083750, rs73993644, rs16942914, rs12938133, rs11079344, rs77472986, rs569425179, rs9908667, rs115013689, rs11649901, rs2240261, rs72839983, rs3744102
rs7208693 (Val53Phe) in exon 2	rs62083752, rs62084578, rs3744099, rs62084580, rs34212101, rs11575868, rs8178377, rs11656836, rs11652686, rs8178340, rs8178307, rs7219860, rs8178290, rs11654568, rs62083746, rs62083745, rs11337012, rs8178409, rs62084581
rs35921530 (eQTL) in intron 7	rs2071409, rs8178392, rs8178375, rs60650460, rs2301869, rs2301870, rs8178350, rs11871239, rs8178348, rs8178345, rs540966028, rs12942443, rs148318946, rs12953025, rs79822084, rs10853005, rs12944679, rs79706658, rs76781940, rs8178326, rs2240262
rs35670089 (Arg604Cys) in exon 11	Not available
rs2071409 (eQTL) in intron 11	Not available

Abbreviations : eQTL, expression quantitative trait loci ; MPO, myeloperoxidase ; SNPs, single nucleotide polymorphisms ; JPT, Japanese population in Tokyo.

*tag SNPs ($r^2 > 0.8$) based on the 1000 Genomes data in Ensembl http://grch37.ensembl.org/Homo_sapiens/Info/Index with JPT.

proxies for all other untyped SNPs because they are highly correlated with one another by means of pairwise tagging in the capture of the untyped SNPs perfectly and efficiently¹⁵).

The SNP genotyping was performed using the TaqMan[®] SNP Genotyping Assay Mix with the Applied Biosystems 7500 Fast Real-time PCR System (Applied Biosystems Inc. Foster City, CA, USA) following the manufacturer's instructions. After thermal cycling, genotype data were automatically ana-

lyzed using sequence detection software (SDS v1.3.1 ; Applied Biosystems, Inc.).

D Measurement of plasma MPO concentrations

The plasma MPO concentrations were measured using enzyme-linked immunosorbent assay (ELISA) kit specific for humans according to the manufacturer's instructions (IDK[®] MPO ELISA, Immundiagnostik AG, Germany).

E Statistical analysis

Continuous data are expressed as mean \pm standard

Table 3 Phenotypes of patients with COPD and non-COPD smokers

Phenotypes	Patients with COPD	Non-COPD smokers
Number	260	129
Male/Female	255/5	125/4
Age (years)	71.0 ± 7.7*	62.7 ± 9.5
Smoking history (pack years)	59.4 ± 29.6*	38.7 ± 18.3
FEV ₁ (Liter)	1.6 ± 0.7*	2.6 ± 0.5
FEV ₁ (% pred)	58.9 ± 21.8*	88.1 ± 12.8
FEV ₁ /FVC (%)	51.9 ± 11.3*	80.4 ± 6.8
Plasma MPO level (ng/ml)	21.4 ± 23.2	21.3 ± 25.5

Data are expressed as mean ± SD.

Abbreviations : FEV₁, forced expiratory volume in 1 second ; % pred, percent of the predicted value ; FVC, forced vital capacity

* $p < 0.01$ versus non-COPD group by the Mann-Whitney U test

deviation (SD). The differences in the continuous data between the two groups were analyzed by student's *t* test, and the differences in the categorical data were analyzed by a contingency table (2 × 2). Allele frequencies were calculated by allele counting and were expressed as decimals. The Hardy-Weinberg equilibrium (HWE) was calculated individually for each SNP in the two groups using the Genepop software package¹⁶. The inherited effects of the major alleles, assuming dominant mode or recessive mode in the COPD groups, were analyzed by Chi-squared test. The odds ratio (OR) was estimated with the approximate 95 % confidence interval (CI). A P value of less than 0.05 was considered significant.

III Results

A Characteristics of study subjects

Table 3 shows the characteristics, spirometry data and plasma MPO concentrations of the study subjects. The study subjects consisted of 260 patients with COPD (255 males and 5 females) and 129 non-COPD smokers (125 males and 4 females). The gender ratio was matched between the two groups ($p = 0.48$), however, the age and smoking history were significantly higher in patients with COPD compared to non-COPD smokers ($p < 0.01$). In agreement with the selection criteria for the COPD group and non-COPD group, the FEV₁/FVC and %FEV₁ were significantly different between the two groups ($p < 0.01$). Among the patients with COPD, 87 patients were in GOLD stage

III & IV and 103 patients presented the emphysema phenotype on HRCT. The plasma MPO concentration was 21.4 ± 23.2 ng/ml in the COPD group and 21.3 ± 25.5 ng/ml in the non-COPD groups. There was no significant difference of the plasma MPO levels between the two groups.

The genotype distributions of the six SNPs in the COPD and non-COPD groups were in HWE ($p > 0.2$). There were no significant differences of allele frequencies of the SNPs between the COPD and non-COPD groups (**Table 4**). The major alleles did not show any dominant mode or recessive mode of inheritance on the COPD group (**Table 4**). Further analyses showed that there were no significant associations regarding the SNPs of *MPO* with patients with severe COPD in Stage III & IV as well as with the emphysema phenotype of COPD (**Table 5**). Moreover, these SNPs also did not show any associations with the circulating MPO concentrations in both COPD and non-COPD groups (data not shown).

IV Discussion

The current study did not reveal associations of the six SNPs of *MPO* with susceptibility to COPD in Japanese patients. The SNPs of the eQTL loci and nonsynonymous substitutions were not associated with airflow limitations in Japanese patients with COPD either. Moreover, these six SNPs did not show any associations with the severe airflow limitation as well as the emphysema phenotype. Furthermore, the

Table 4 Genotype distribution and allele frequencies of the six SNPs in *MPO* in the COPD group versus non-COPD group

SNPs	COPD group (n = 260)				non-COPD group (n = 129)				P value	OR (95 % CI)	P value	P value
	Genotype (freq)		Allele (freq)		Genotype (freq)		Allele (freq)					
	11	12	22	1	11	12	22	1				
rs2107545 (A/G)	0.78	0.21	0.01	0.89	0.77	0.23	0	0.88	0.82	1.06 (0.66–1.68)	0.67	0.31
rs2243828(A/G) ^a	0.78	0.21	0.01	0.89	0.77	0.23	0	0.88	0.82	1.06 (0.66–1.68)	0.67	0.31
rs7208693 (C/A) ^b	0.73	0.25	0.02	0.86	0.74	0.23	0.03	0.85	0.84	1.04 (0.69–1.59)	0.99	0.49
rs35921530 (C/A) ^a	0.82	0.18	0	0.91	0.83	0.16	0.01	0.91	0.81	0.94 (0.56–1.58)	0.66	0.16
rs35670089 (C/T) ^c	0.99	0.01	0	0.99	0.98	0.02	0	0.98	0.21	2.98 (0.49–17.93)	0.21	0.21
rs2071409 (T/G) ^a	0.83	0.17	0	0.92	0.84	0.15	0.01	0.92	0.95	0.98 (0.58–1.68)	0.79	0.16

Abbreviations: freq, frequency; *MPO*, the gene encoding myeloperoxidase; SNP, single nucleotide polymorphism; OR, odds ratio; 95 % CI, 95 % confidence interval.

1 is for major allele and 2 is for minor allele, and the SNP variant is shown as the rs number (major allele/minor allele).

^a Expression quantitative trait loci (eQTLs), the genomic loci contribute to variations in the mRNA expression levels of the *MPO*.

^b The nonsynonymous substitution Val53Phe in the *MPO*.

^c The nonsynonymous substitution Arg604Cys in the *MPO*.

P values were calculated using the chi-square test (2×2 contingency table).

^d 2×2 contingency table assuming the dominant mode with major allele (11/12 + 22) of inheritance in COPD group.

^e 2×2 contingency table assuming the recessive mode with major allele (11 + 12/22) of inheritance in COPD group.

plasma *MPO* concentrations did not differ between the patients with COPD and non-COPD smokers.

COPD is a multifactorial disease and many factors, including genetic and environmental, interact to involve with the pathogenesis and development of COPD. The pathophysiology of COPD is characterized by a mixed pathology with phenotypes of small airway disease (chronic bronchiolitis) and parenchymal destruction (emphysema), the relative contributions of which vary from person to person¹¹. Most patients with COPD have a combination of both phenotypes. The genetic variants are believed to contribute to the pathogenesis of COPD and related traits, including disease severity, extent of emphysema, exacerbations of COPD, lung function decline, and drug effects¹⁷. By understanding that *MPO* is highly involved with the inflammation through activating PMNs, the genetic case-control studies concerning the associations of the genetic variants of *MPO* with inflammation-related diseases, such as COPD, cardiovascular disease, and coronary artery disease, have been performed worldwide elsewhere^{10,18,19}. However, most of the results were conflicting and remain generally in-

conclusive, despite meta-analysis attempts to clarify these controversies^{10,19}. Korytina and colleagues hypothesized that the *MPO*-derived oxidants pathogenically promote inflammation and cause tissue damage in the pathogenesis of COPD; however, the case-control study with 425 patients of COPD and 457 control subjects did not find any association of genetic variants in *MPO* with COPD²⁰. Similarly, the present study did not detect any associations of the SNPs of *MPO* with COPD, the severity of airway limitation of COPD and the emphysema phenotype in Japanese patients. Moreover, more than 50 SNPs captured by the six tag SNPs were found to have no association with COPD in the Japanese population. Thus, it seems that the *MPO* gene and the *MPO* biomolecule are not likely to be involved with the pathogenesis and development of COPD. Further prospective confirmatory studies beyond initial association studies would evaluate the true facts concerning this issue.

The circulating *MPO* levels did not show a significant difference between the COPD and non-COPD smokers and the SNPs of *MPO* were not significantly associated with the circulating level in either the

Table 5 Associations of the six SNPs in the *MPO* gene with the severity of COPD as well as with the emphysema phenotype.

SNPs	Stage III & IV in COPD n = 87	Non-COPD smokers n = 129	P Value*
	Major/Minor alleles (freq)	Major/Minor alleles (freq)	
rs2107545 (A/G)	0.88/0.12	0.88/0.12	0.94
rs2243828 (A/G) ^a	0.88/0.12	0.88/0.12	0.94
rs7208693 (C/A) ^b	0.83/0.17	0.85/0.15	0.59
rs35921530 (C/A) ^a	0.91/0.09	0.91/0.09	0.97
rs35670089 (C/T) ^c	0.99/0.01	0.99/0.01	0.54
rs2071409 (T/G) ^a	0.92/0.08	0.92/0.08	0.91

SNPs	Emphysema in COPD n = 103	Non-COPD smokers n = 129	P Value*
	Major/Minor alleles (freq)	Major/Minor alleles (freq)	
rs2107545 (A/G)	0.87/0.13	0.88/0.12	0.77
rs2243828 (A/G) ^a	0.87/0.13	0.88/0.12	0.77
rs7208693 (C/A) ^b	0.84/0.16	0.85/0.15	0.82
rs35921530 (C/A) ^a	0.89/0.11	0.91/0.09	0.58
rs35670089 (C/T) ^c	0.99/0.01	0.99/0.01	0.86
rs2071409 (T/G) ^a	0.91/0.09	0.92/0.08	0.73

Abbreviations: freq, frequency; *MPO*, the gene encoding myeloperoxidase; SNP, single nucleotide polymorphism.

^a Expression quantitative trait loci (eQTLs), the genomic loci contribute to variations in the mRNA expression levels of *MPO*.

^b The nonsynonymous substitution Val53Phe in *MPO*.

^c The nonsynonymous substitution Arg604Cys in *MPO*.

P values were calculated using the chi-square test (2×2 contingency table).

COPD group or non-COPD smokers. The *MPO* levels were measured in the sputum in COPD²¹⁾, in the serum in healthy smokers and smokers with COPD²²⁾, and in the serum in patients with exacerbations of COPD²³⁾. The circulating level of *MPO* was suggested as a potential systemic neutrophilic inflammation biomarker in patients with COPD. However, the importance of the circulating *MPO* level in COPD was not verified

in the present study. *MPO* activity may need to be measured to confirm the present results.

Several potential limitations of this study have been considered. The sample size was small with unmatched age and smoking history in the case and control groups. The logistic regression statistical analysis was not applied to the adjustments of age and smoking history for the two study groups

because the results showed no significance and the sample size was less than 500. Regardless, the odds ratio was very close to 1, which provided a negative hint that these SNPs were not associated with COPD. Another limitation was that the MPO measurements lacked precision with large variability of measurements, and the MPO activity may need to be

measured to confirm this result.

V Conclusion

The genetic variants of the *MPO* gene were not associated with susceptibility to COPD in the Japanese population. The MPO biomolecule is not involved with the pathogenesis of COPD.

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(2019. 7. 30 received ; 2019. 10. 15 accepted)
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