

Interleukin (IL)-13, IL-17A, and Mast Cell Chymase Gene Polymorphisms in Bronchial Asthma and Chronic Obstructive Pulmonary Disease - A Pilot Study in a Japanese Population

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) and bronchial asthma might have common genetic factors. Interleukin 13 (IL-13) gene polymorphism has been suggested to be one of the candidates; however inconsistent results have been reported. Studies of the gene polymorphisms in IL-17A gene and mast cell chymase gene (CMA1) in COPD and bronchial asthma have not been reported.

Methods: The single nucleotide polymorphisms in IL-13 -1111C>T, IL-13 Arg130Gln, IL-17A -737C>T, and CMA1 -1903G>A genes were examined in 100 COPD patients, 250 asthmatics and 100 normal control. All patients were Japanese who were in a stable condition.

Results: The frequency of TT/CT genotype of the IL-13 -1111C>T was higher than that of CC genotype in COPD patients compared with asthmatics. Subgroup analyses with gender showed that in female COPD patients the frequency of TT/CT genotype of the IL-13 -1111C>T was higher than that of CC genotype compared with female asthmatics. The frequency of TT/CT genotype of the IL-17A -737C>T was lower than that of CC genotype in COPD patients compared with asthmatics. Subgroup analyses with gender showed that in male COPD patients the frequency of TT/CT genotype of the IL-17A -737C>T was lower than that of CC genotype compared with male asthmatics. The frequency of AA/GA and GG genotypes of the CMA1 -1903G>A in COPD patients did not differ from that of asthmatics. Asthmatics with CC genotype of the IL-13 Arg130Gln showed higher levels of total serum IgE than that of the patients with TT/CT genotype.

Conclusion: This study suggested the IL-13 -1111C>T and IL-17A -737C>T gene sequence variations might have a role in COPD and asthma in a Japanese population.

Keywords: IL-13; IL-17A; Mast cell chymase; CMA1; Gene polymorphism; Bronchial asthma; COPD

Introduction

Bronchial asthma and chronic obstructive pulmonary disease (COPD) are common respiratory diseases that are caused by the interaction of genetic susceptibility with environmental factors [1,2]. In 1961 Orie and colleagues postulated the Dutch hypothesis [3], and they suggested asthma and COPD have genetic and environmental risk factors in common [4]. Latter investigations have led to the evaluation of interleukin 13 (IL-13) as a possible common candidate gene for bronchial asthma and COPD [5].

The IL-13 gene is located on chromosome 5q31-q33, a region frequently linked to asthma [6,7]. Two of the most characterized single nucleotide polymorphisms (SNPs) in IL-13 include a promoter SNP (-1111C>T) and a coding SNP in exon 4 (Arg130Gln). The IL-13 Arg130Gln polymorphism is associated with elevated eosinophil count and high total serum IgE levels [8,9]. The case-control studies in two separate Dutch populations have shown that the promoter polymorphism -1111 in the IL-13 gene was found to be associated with bronchial asthma [10,11].

The involvement of IL-13 genetic variants in COPD is lesser clear. In a Dutch study, the IL-13 -1111C>T polymorphisms has been reported to be associated with COPD patients compared with healthy control subjects [12]. This association was confirmed in Taiwanese [13]. However, these data are inconsistent, and another case-control study with Japanese and Egyptian subjects did not show the association [14].

Few investigations about involvement of common candidate genes including IL-17 in bronchial asthma and COPD have been reported. The IL-17 family is composed by six members designated IL-17A through F, but CD4+ T helper (Th) 17 lymphocytes particularly produce IL-17A and IL-17F [15]. Accumulation of IL-17A and IL-17F mRNA has been shown in the bronchial sub mucosa of moderate to severe asthma [16]. Elevation of plasma IL-17A level has been reported to be associated with asthma severity [17], and airway hyper responsiveness positively correlated with IL-17A levels in the sputum from asthma patients [18]. Human Th17 lymphocyte, like mice [19], has been demonstrated to express IL-13 receptor $\alpha 1$ and that IL-13 attenuated IL-17A production [20].

Hizawa and his colleagues reported that the IL-17F gene could be another gene in a common pathway mediating the development of bronchial asthma and COPD in a Japanese population [21,22].

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Received October 12, 2014; **Accepted** November 17, 2015; **Published** November 24, 2015

Citation: Kurosawa M, Sutoh E, Sutoh Y (2015) Interleukin (IL)-13, IL-17A, and Mast Cell Chymase Gene Polymorphisms in Bronchial Asthma and Chronic Obstructive Pulmonary Disease - A Pilot Study in a Japanese Population. J Allergy Ther 6: 224. doi:[10.4172/2155-6121.1000224](http://dx.doi.org/10.4172/2155-6121.1000224)

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However, to our knowledge, there has been no published paper reported on the association of IL-17A gene polymorphisms with COPD. The IL-17A gene is located on chromosome 6p12.1, the genomic region associated with different types of asthma [23-25]. The association between asthma susceptibility and IL-17A gene polymorphisms in a Taiwanese population has been reported, which showed among nine SNPs investigated only one SNP -737C>T was associated with asthma, and the risk genotype of the SNP was CC genotype [26].

Mast cell chymase is a chymotrypsin-like protease stored in high amounts within the secretory granules of mast cells found in asthmatic airway [27], and it is an important mediator of inflammation and remodeling in the asthmatic lung [28]. Some studies have demonstrated higher numbers of mast cells in patients with COPD than in control [29,30]. Theoretically, mast cells could play a role in the pathogenesis of COPD by inducing fibroblast proliferation as reported from our laboratory [31]. In fact, histological characterization of mast cell chymase in patients with COPD has been reported [32,33].

The gene for mast cell chymase (CMA1) is located within a cluster of genes for cellular proteases on chromosome 14q11.2 [34]. Various studies have examined the association between the CMA1 promoter region (-1903 G>A) SNP and bronchial asthma, but inconsistent results have been obtained [35-37]. To our knowledge, no comparative studies have evaluated the association of CMA1 gene polymorphisms with bronchial asthma and COPD.

Based on the contradictory results among the studies of the involvement of IL-13 gene polymorphisms in COPD, we sought to partly replicate the association previously described between IL-13 gene polymorphisms and COPD patients in a Japanese population. In addition, we examined the association between the gene polymorphisms in IL-17A and CMA1 and COPD patients and asthmatics. Taking all into account, we selected the gene polymorphism of IL-13 -1111C>T, IL-13 Arg130Gln, IL-17A -737 C>T, and CMA1 -1903G>A as representative SNPs of the genes for the analyses in the present study. Although similar studies of IL-13 gene polymorphisms in the respiratory diseases have been conducted in different cohort of patients, we first performed a pilot study of IL-17A and CMA1 gene polymorphisms in Japanese patients with COPD and bronchial asthma.

Materials and Methods

Subjects and clinical assessment

This study was performed with the approval of the Institutional Ethics Committee of Gunma Institute for Allergy and Asthma, Gunma, Japan, and written informed consent was obtained from each individual before the study commenced.

All patients were Japanese, and were recruited from the outpatient clinic at Department of Allergy and Respiratory Medicine, Sutoh Hospital, Gunma, Japan. All patients with bronchial asthma and COPD were diagnosed by experienced pulmonologists. In this pilot study the patients consisted of 100 patients with COPD and 250 patients with bronchial asthma as shown in Table 1. All of the patients were in a stable clinical condition. Diagnosis of bronchial asthma was confirmed using the criteria of the Global Initiative for Asthma guidelines [38], and all patients with bronchial asthma were non-smoking. All patients showed clinical symptoms that met the criteria for asthma, such as cough, wheeze and shortness of breath. Forced expiratory volume in one second (FEV1) was measured with a spirometer, and airway reversibility was defined as a >12% and >200 mL increase in volume in the first second of forced expiration from baseline after inhalation

	COPD	BA	NC
Number of subjects	100	250	100
Age (years) ^b	68.1 ± 10.4 ^b	50.8 ± 16.0 ^b	47.1 ± 13.6
Gender (male) ^c	72 (72.0%) ^c	78 (31.2%) ^c	34 (34.0%)
FEV1 (% predicted)	70.3 ± 21.5	72.9 ± 25.5	NA
Total serum IgE (IU/ml) ^d	123.4 ± 145.8 ^d	262.8 ± 327.6 ^d	NA
Eosinophil (cells/μl) ^e	221.5 ± 264.4 ^e	441.1 ± 408.8 ^e	NA

COPD: Chronic Obstructive Pulmonary Disease; BA: Bronchial Asthma; FEV1: Forced Expiratory Volume in One Second; NC: Normal Control; NA: Not Applicable

^aData are presented as means ± SD or numbers (%).

^{b,d,e}P < 0.01 for COPD patients versus BA patients by the Welch's t-test

^cP < 0.01 for COPD patients versus BA patients by the Chi-square test

Table 1: Clinical characteristics of the subjects in the study^a.

of short-acting β2-adrenergic bronchodilators. COPD was diagnosed according to the criteria of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [39,40]. The entry criteria for COPD patients were post-bronchodilator FEV1 <80% predicted and FEV1/forced vital capacity <0.7. All patients with COPD were current smokers and had a history of 10 pack-year cigarette smoking. A total of 100 non-smoking subjects with no history of bronchial asthma, COPD or other respiratory symptoms were selected from healthy volunteers who visited our clinic for annual routine physical examinations which did not include FEV1 measurement, and comprised normal control. Following laboratory tests were performed in the patients. Serum levels of total immunoglobulin E (IgE) were measured by the Phadia ImmunoCAP[®] system (Phadia, Uppsala, Sweden). The total eosinophil count was measured in peripheral blood using a flow cytometer (Coulter Maxm; Beckman-Coulter Inc., Fullerton, CA, USA). Characteristics of the study population are shown in Table 1.

Genotyping of IL-13, IL-17A and CMA1 polymorphisms

DNA in the specimens obtained by rubbing buccal mucosa by a cotton swab was extracted by using QIAamp 96 DNA blood kits (Qiagen, Hilden, Germany). The target DNA sequence of the IL-13 -1111C>T was amplified using a set of primers (forward: 5'-TGGGGGTTTCTG-GAGGAC-3', reverse: 5'-GCAGAATGAGTGCTGTGGAG-3') and that of Arg110Gln was amplified using a set of primers (forward: 5'-GGTC-CTGT-CTCTGCAAATAATG-3', reverse: 5'-GTTTTCCAGCTTG-CATGTCC-3'). The target DNA sequence of the IL-17A -737C>T was amplified using a set of primers (forward: 5'-CCCCCATCATGTCTC-CTCTCC-3' reverse: 5'-CCAAGCAACTTGGTGTTTTG-AGG-3'). The target of DNA sequence of the CMA1 -1903G>A was amplified using a set of primers (forward: 5'-GAGCAGATAGTGCAGTC-CTCGTTTC-3', reverse: 5'-CTCCACAGCATCAAGATTCA-GATCC-3'). Allelic discrimination assay for SNPs relating to the expressions of IL-13 -1111C>T, IL-13 Arg110Gln, IL-17A -737C>T and CMA1 -1903G>A (rs1800925, rs20541, rs8193036 and rs1800875, respectively) was carried out by a SNPs detective system as described [41-44]. All subjects and investigators remained unaware of the genotype until the final analysis.

Statistical analysis

Data are presented as means ± SD or numbers (%) of observations, unless stated otherwise. Differences in the mean value of the phenotypic characteristics within the groups were compared using either ANOVA test or t-test, and qualitative data were compared by the Chi-square test. Allele frequencies were estimated by gene counting method. Significant departures of genotype frequency from the Hardy-Weinberg equilibrium at each SNP were tested by the Chi-square analysis. Differences in

minor allele frequencies of IL-13 -1111C>T, IL-13 Arg110Gln, IL-17A -737C>T and CAM1-1903G>A in the patients with bronchial asthma were compared with those in COPD patients and control subjects by the Chi-square test. Logistic regression analysis was used to estimate odds ratio (OR) and 95% confidence interval (CI). Each gene polymorphism related to bronchial asthma and COPD was examined by multivariable logistic regression models with adjustment for covariates, namely with the chronic respiratory disease phenotype as dependent variable and independent variables including age (continuous value), gender (male=0, female=1), two alternatives genotype models that were either combined TT/CT and CC or combined AA/GA and GG. In addition, subgroup analyses with gender of the multivariable logistic regression analysis were performed. Statistical analyses were undertaken using SPSS for Windows version 17 (SPSS Inc, Chicago, IL, USA). P-values of <0.05 were considered to be significant.

Results

The clinical characteristics of the subjects are summarized in Table 1. There was significant difference between COPD patients and asthma patients in terms of age and gender except FEV1 (% predicted). Namely, the age of the patients with COPD was significantly higher than that of the patients with bronchial asthma (P<0.01), and the number of male

patients with COPD was significantly higher than that of bronchial asthma (P<0.01). The levels of total serum IgE in COPD patients were lower than those in asthma patients (P=0.01). Asthma patients had a higher peripheral total eosinophil count compared with COPD patients (P<0.01).

OR: Odds Ratio; CI: Confidence Interval. Multivariable logistic regression analysis was applied for age and sex (A) and age (B) as covariables. Values in bold indicate significant P-Value.

Table 2 indicates the frequencies of the IL-13 -1111C>T and Arg130Gln genotype, and the T minor allele in each group. The genotype distribution fulfills the Hardy-Weinberg equilibrium in each group. The frequencies of the T allele of the IL-13 -1111C>T genotype in COPD patients (frequency of allele [q]=0.240) and normal control (q=0.175) did not differ between them, whereas the frequency in the patients with bronchial asthma was decreased (q=0.116). Namely, the frequencies of the T allele in COPD patients and normal control were higher than that in the patients with bronchial asthma (P<0.001 in COPD patients and P=0.038 in normal control, respectively). On the other hand, the frequencies of the T allele of the IL-13 Arg130Gln genotype did not differ among the three groups.

SNPs loci	Genotype			Allele Frequency	P-value	HWE P-Value
	CC	CT	TT			
-1111C>T						
COPD	57	38	5	0.24	<0.001	0.109
(n=100)	(57.0%)	(38.0%)	(5.0%)			
BA	196	50	4			
(n=250)	(78.4%)	(20.0%)	(1.6%)	0.116	-	0.038
NC	68	29	3	0.175	0.038	-
(n=100)	(68.0%)	(29.0%)	(3.0%)			
Arg130Gln						
COPD	67	31	2	0.175	0.824	0.698
(n=100)	(67.0%)	(31.0%)	(2.0%)			
BA	172	72	6			
(n=250)	(68.8%)	(28.8%)	(2.4%)	0.168	-	0.488
NC	66	30	4	0.19	0.488	-
(n=100)	(66.0%)	(30.0%)	(4.0%)			

COPD: Chronic Obstructive Pulmonary Disease; BA: Bronchial Asthma; NC: Normal Control; HWE: Hardy-Weinberg Equilibrium. Minor alleles in patients with COPD and control subjects were compared with that in patients with bronchial asthma by means of the Chi-square test. Values in bold indicate significant P-values.

Table 2: Genotype and allele frequencies of the IL-13 gene in each group.

(A)			
SNPs loci	Genotype	OR (95%CI)	P-value
-1111C>T	CC	1	<0.001
	TT/CT	2.397 (1.316-4.366)	
Arg130Gln	CC	1	0.856
	TT/CT	1.057 (0.584-1.913)	
(B)			
SNPs loci	Male		Female
Genotype	OR (95% CI), P-value		OR (95%CI), P-value
-1111C>T			
CC	1.000		1.000
TT/CT	1.363 (0.617-3.010), 0.444		4.752 (1.921-11.753), 0.001
Arg130Gln			
CC	1.000		1.000
TT/CT	1.406 (0.621-3.181), 0.414		0.760 (0.300-1.924), 0.269

Table 3: Multivariable logistic regression analysis (A) and the subgroup analysis with gender (B) of genotype of the IL-13 gene in Japanese COPD patients compared with those in the patients with bronchial asthma.

Frequencies of the IL-17A -737C>T genotype and the T minor allele, and those of CMA1 -1903G>A genotype and the A minor allele in each group are given in Table 5-(A) and Table 5-(B). The genotype distribution of each gene fulfills the Hardy-Weinberg equilibrium in each group. There were no differences between the minor allele frequencies among the three groups in each gene.

Table 3-(A) presents the results of multivariable logistic regression analysis of the IL-13 -1111C>T and Arg130Gln genotype controlling age and gender in COPD compared with those with bronchial asthma. Frequencies of combined homozygous TT and heterozygous CT genotype group of the IL-13 -1111C>T were higher than those of homozygous CC genotype in COPD compared with those with bronchial asthma ($P<0.001$), and the OR of COPD compared with bronchial asthma associated with the combined TT and CT genotype group to those with CC genotype was 2.397 (95% CI=1.316-4.366).

COPD: Chronic Obstructive Pulmonary Disease; BA: Bronchial Asthma; NC: Normal Control; HWE: Hardy-Weinberg Equilibrium Minor alleles in patients with COPD and control subjects were compared with that in patients with bronchial asthma by means of the Chi-square test.

Frequencies of combined TT and CT genotype group of the IL-13 Arg130Gln were not different from those of CC genotype in COPD compared with bronchial asthma. Subgroup analyses with gender

showed the positive association between the respiratory disease phenotype and the IL-13 -1111C>T genotype in female, but not in male, and in female patients with COPD the frequencies of combined TT and CT genotype group were higher than those of CC genotype compared with female patients with bronchial asthma ($P=0.001$, OR=4.752, 95% CI=1.921-11.753) as shown in Table 3-(B).

OR: Odds Ratio; CI: Confidence Interval. Multivariable logistic regression analysis was applied for age and sex (A) and age (B) as covariables. Values in bold indicate significant P-Value.

Table 4 presents the comparison of the clinical characteristics in the patients with COPD and bronchial asthma according to the IL-13 gene polymorphisms. The levels of total serum IgE and the count of peripheral total eosinophil were not different between the IL-13 gene polymorphisms in COPD patients. The patients with bronchial asthma with the combined TT and CT genotype group of the IL-13 Arg130Gln showed higher levels of total serum IgE than that in the patients with CC genotype ($P=0.025$).

Table 6-(A) presents the results of multivariable logistic regression analysis of the IL-17A -737C>T and CMA1 -1903G>A genotype controlling age and gender in COPD compared with those with bronchial asthma. Frequencies of combined homozygous TT and heterozygous CT genotype group of the IL-17A -737CT were lower than those of homozygous CC genotype in COPD compared with those

SNPs loci Genotype	COPD		Bronchial Asthma		Normal Control	
	Total IgE (IU/ml)	Eosinopil (cells/ μ l)	Total IgE (IU/ml)	Eosinopil (cells/ μ l)	Total IgE (IU/ml)	Eosinopil (cells/ μ l)
IL-13 -1111C>T						
CC	139.7 \pm 164.4	248.4 \pm 325.5	246.5 \pm 277.2	427.8 \pm 389.2	NA	NA
TT/CT	103.3 \pm 117.8	185.8 \pm 146.1	322.5 \pm 467.1	488.3 \pm 472.8	NA	NA
P-value	0.225	0.26	0.142	0.338	-	-
IL-13 Arg130Gln						
CC	132.6 \pm 154.5	215.6 \pm 284.0	206.6 \pm 183.4	400.8 \pm 413.1	NA	NA
TT/CT	104.0 \pm 125.8	234.5 \pm 219.2	288.1 \pm 372.7	459.5 \pm 406.7	NA	NA
P-value	0.977	0.565	0.025	0.298	-	-

Table 4: Comparison of the clinical characteristics according to IL-13 gene polymorphisms in the patients with COPD and bronchial asthma^a.

(A)							
IL-17A -737C>T	Genotype			Allele Frequency	P-value		HWE P-Value
	CC	CT	TT				
COPD	47	43	10	0.315	0.169	0.172	0.971
(n=100)	(47.0%)	(43.0%)	(10.0%)				
BA	97	121	32	0.37	-	0.805	0.546
(n=250)	(38.8%)	(48.4%)	(12.8%)				
NC	35	54	11	0.38	0.805	-	0.144
(n=100)	(35.0%)	(54.0%)	(11.0%)				
(B)							
CMA1-1903G>A	Genotype			Allele Frequency	P-value		HWE P-Value
	GG	GA	AA				
COPD	66	32	2	0.18	0.089	0.896	0.401
(n=100)	(66.0%)	(32.0%)	(2.0%)				
BA	187	61	2	0.13	-	0.124	0.213
(n=250)	(74.8%)	(24.4%)	(0.8%)				
NC	68	29	3	0.175	0.124	-	0.965
(n=100)	(68.0%)	(29.0%)	(3.0%)				

Table 5: Genotype and allele frequencies of the IL-17A -737C>T (A) and the CMA1 -1903G>A (B) gene in each group.

(A)				
SNPs loci	Genotype	OR (95%CI)		P-value
IL-17A-737C>T	CC	1		0.041
	TT/CT	0.550 (0.310 – 0.967)		
CMA1-1903G>A	GG	1		0.326
	AA/GA	1.355 (0.739 – 2.483)		
(B)				
SNPs loci	Male		Female	
Genotype	OR (95%CI)	P-value	OR (95%CI)	P-value
IL-17A -737C>T				
CC	1		1	
TT/CT	0.422 (0.190-0.973)	0.034	0.727 (0.308-1.717)	0.467
CMA1 -1903G>A				
GG	1		1	
AA/GA	1.535 (0.666-3.537)	0.315	1.198 (0.479-2.996)	0.699

Table 6: Multivariable logistic regression analysis (A) and the subgroup analysis with gender (B) of genotype of the IL-17A and CMA1 gene in Japanese COPD patients compared with those in the patients with bronchial asthma.

with bronchial asthma (P=0.041), and the OR of COPD compared with bronchial asthma associated with the combined TT and CT genotype group to those with CC genotype was 0.550 (95% CI=0.310–0.967). Frequencies of combined AA and GA genotype group of the CMA1 -1903G>A were not different from those of GG genotype in COPD compared with bronchial asthma. Subgroup analyses with gender showed the positive association between the respiratory disease phenotype and the IL-17A -737C>T genotype in male, but not in female, and in male patients with COPD the frequencies of combined TT and CT genotype group were lower than those of CC genotype compared with male patients with bronchial asthma (P=0.034, OR=0.422, 95% CI=0.190-0.973) as shown in Table 6-(B). The relation between the genotyping of either IL-17A -737C>T or CMA1-1903G>A gene and the clinical characteristics investigated was not present both in COPD patients and asthma patients (data not shown).

Discussion

First, we investigated the frequencies of the IL-13 -1111C>T and Arg130Gln genotype in the three groups (COPD patients, asthma patients and normal healthy control). The genotype distribution fulfills the Hardy-Weinberg equilibrium in each group. The frequency of T allele of the IL-13 -1111C>T genotype in COPD patients was higher than that in asthma patients, but not that of the IL-13 Arg130Gln genotype. Frequencies of combined TT and CT genotype group of the IL-13 -1111C>T were higher than those of CC genotype in COPD patients compared with asthma patients. In female patients with COPD, but not in male, frequencies of combined TT and CT genotype group of the IL-13 -1111C>T were higher than those of CC genotype compared with female asthma patients.

Two case-control studies in a Dutch population have shown that the promoter polymorphism -1111 in the IL-13 gene was found to be associated with asthma [10,11]. Also functional studies support a regulatory role associated with allergic inflammation in asthma for the -1111C>T variant [9,45]. In this study, the frequency of the T allele of the IL-13 -1111C>T genotype in the patients with asthma (q=0.116) was decreased compared with that in normal control (q=0.175). This finding correspond to the results of our previous assessment performed in 300 asthmatics and 100 normal control, none of the subjects were involved in the present study, which showed q=0.12 in asthma patients and q=0.165 in normal control, respectively [46]. Although, local adaptation and population differentiation at the IL-13 gen has been

evaluated [47], these were relatively small sample size studies, and larger statistically more powerful studies may show a different result.

The IL-13 promoter polymorphism has also been reported to be associated with COPD compared with healthy control subjects [12,13]. The frequency of the IL-13 Arg130Gln polymorphism was not different between COPD patients and healthy control, indicating the specificity of the association of COPD with the IL-13 -1111T allele [12]. However, the association of the IL-13 promoter polymorphism with COPD was not confirmed in another case-control study with Japanese and Egyptian subjects [14], which may not correspond to our results. In this study, we showed the frequency of T allele of the IL-13 -1111C>T genotype in COPD patients was significantly higher than that in asthmatics. Jiang and colleagues reported that the TT genotype of -1112C>T was not an independent risk factor for COPD but increased the risk for smokers of developing COPD in Chinese Han residents of Beijing [48]. In fact, the IL-13 promoter polymorphism -1112C>T has been reported to modulate the adverse effect of smoking on lung function [49]. This study showed the frequencies of combined TT and CT genotype group of the IL-13 -1111C>T were higher than those of CC genotype in COPD patients, who were current smokers and had a history of 10 pack-year cigarette smoking, compared with non-smoking asthma patients.

An IL-13 Arg130Gln polymorphism in exon 4 has been shown to be associated with high total serum IgE levels [50,51] and bronchial asthma [52]. We showed the association between the levels of serum total IgE and the IL-13 Arg130Gln gene polymorphism in asthma patients, but not in COPD patients, which may correspond to the reports [50-52].

In experimental studies, pulmonary expression of transgenic IL-13 in adult murine lungs resulted in a COPD phenotype with inflammation, mucus metaplasia and matrix-metalloproteinase- and cathepsin-dependent emphysema [53], indicating the prominent and unique role of IL-13 in asthma as well as COPD. Overproduction of pulmonary mucus secretion was a key feature of IL-13-induced COPD in mice [53], which may correspond to a feature in COPD patients [54]. The capacity of IL-13 to induce the COPD phenotype in mice combined with our findings that COPD is specifically associated with the minor T allele of the IL-13 -1111C>T genotype, but not with the IL-13 Arg130Gln gene polymorphism, may suggest that the IL-13 promoter polymorphism itself might responsible for the risk of develop COPD. It is important to note that, while both asthma/atopy and COPD

analyses highlighted a role for IL-13 SNPs in the diseases mechanisms, asthma/atopy associations involve the promoter SNP (-1111C>T) and the coding SNP in exon 4 (Arg130Gln) regions, whereas COPD signal might be localized to the promoter region. These findings may in part explain the lack of correlation between COPD and IL-13 expression [55] clearly observed in asthma and atopy [56].

Next, we compared the polymorphisms of the IL-17A -737C>T between COPD patients and asthma patients. Frequencies of combined homozygous TT and heterozygous CT genotype group of the IL-17A -737C>T were lower than those of homozygous CC genotype in COPD compared with those with bronchial asthma. In male patients with COPD, but not in female, frequencies of CC genotype of the IL-17A -737C>T were higher than those of combined TT and CT genotype group compared with male asthma patients. This is the first pilot study suggesting the association between the IL-17A gene polymorphisms and COPD.

This work did not describe the linkage between the IL-17A genotype and the clinical markers neither in COPD patients nor in asthma patients as far as we investigated. However, COPD is well known to be less atopic than bronchial asthma, and it has been demonstrated that human Th17 cells express IL-13 receptor $\alpha 1$ and that IL-13 attenuates IL-17A production [20]. So, we might hypothesize that the interaction between IL-13 -1111C>T and IL-17A -737C>T gene sequence variations might be involved in the process to induce non-allergic inflammation in COPD. Further investigations are required.

Finally, we compared the polymorphisms of the CMA1 -1903G>A between COPD patients and asthma patients. The frequencies of combined AA and GA genotype group of the CMA1 -1903G>A were not different from those of GG genotype in COPD compared with bronchial asthma, suggesting the polymorphisms of CMA1 gene won't be associated with the susceptibility to COPD. This is a pilot study with a limited number of the subjects. The larger population, the more one can generalize the results. Further studies are required including replication studies in another population, and it is obvious that generalizing is necessary for forming coherent interpretations in different situations.

In conclusion, although similar studies about IL-13 gene polymorphisms in COPD and bronchial asthma have been conducted in different cohort of patients, we first analyzed the IL-17A and CMA1 gene polymorphisms in COPD patients and asthmatics in a Japanese population, suggesting IL-13 -1111C>T and IL-17A -737C>T gene sequence variations might have a role in COPD and bronchial asthma.

Authors' Contributions

MK designed the research study, collected samples and analyzed data. MK, YS and ES drafted the manuscript. All authors read and approved the final manuscript.

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Citation: Kurosawa M, Sutoh E, Sutoh Y (2015) Interleukin (IL)-13, IL-17A, and Mast Cell Chymase Gene Polymorphisms in Bronchial Asthma and Chronic Obstructive Pulmonary Disease - A Pilot Study in a Japanese Population. *J Allergy Ther* 6: 224. doi:10.4172/2155-6121.1000224

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