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Association Between Secretoglobin Family 3A Member 2 (SCGB3A2) Gene Polymorphisms and Asthma in a Korean Population

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

ACE 1 Su Kang Kim*
AE 2 Hosik Seok*
F 1 Hae Jeong Park
F 2 Kyuup Han
D 3 Sang Wook Kang
D 3 Ju Yeon Ban
BC 4 Hee-Jae Jung
BC 4 Kwan-Il Kim
BC 4 Beom-Joon Lee
BC 5 Jinju Kim
AD 1 Joo-Ho Chung

1 Kohwang Medical Research Institute, School of Medicine, Kyung Hee University, Seoul, Republic of Korea
2 Department of Pharmacology, Graduate School, Kyung Hee University, Seoul, Republic of Korea
3 Department of Dental Pharmacology, School of Dentistry, Dankook University, Cheonan, Republic of Korea
4 Division of Allergy and Respiratory System, Department of Korean Internal Medicine, College of Korean Medicine, Kyung Hee University, Seoul, Republic of Korea
5 Department of Korean Physiology, College of Pharmacy, Kyung Hee University, Seoul, Republic of Korea

* The first 2 authors contributed equally

Corresponding Author: Joo-Ho Chung, e-mail: jhchung@khu.ac.kr

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Background: Secretoglobin family 3A member 2 (SCGB3A2) plays an important role in secreting lung surfactant protein, which is a downstream target of thyroid transcription factor.

Material/Methods: We investigated whether single-nucleotide polymorphisms (SNPs) of SCGB3A2 gene contribute to susceptibility to asthma. To explore this possible association, 2 promoter SNPs (rs6882292, 659 G/A and rs1368408, -112 G/A) and missense SNP (rs151333009, stop codon) were tested in *SCGB3A2* gene in 101 asthma patients and 377 healthy control subjects. SNPStats was used to obtain odds ratio (OR), 95% confidence intervals (CI), and P value adjusted for age and sex as covariables. Logistic regression method in each model (dominant, recessive, and log-additive) was applied to analyze genetic data.

Results: rs151333009 SNP showed a monomorphic genotype. Two promoter SNPs (rs6882292, -659 G/A and rs1368408, -112 G/A) showed significant association with asthma (rs6882292, OR=2.66, 95% CI=1.42–5.01, p=0.0033 in dominant model, OR=2.45, 95% CI=1.33–4.54, p=0.0055 in log-additive model; rs1368408, OR=1.59, 95% CI=1.02-2.49, p=0.041 in dominant model, OR=3.02, 95% CI=1.15–7.90, p=0.03 in recessive model, OR=1.63, 95% CI=1.63, 95% CI=1.12–2.37, p=0.012 in log-additive model).

Conclusions: These results suggest that the promoter SNPs (rs6882292 and rs1368408) of *SCGB3A2* gene may contribute to susceptibility to asthma in a Korean population.

MeSH Keywords: Association • Case-Control Studies • Polymorphism, Genetic • Secretoglobins

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Background

Asthma is a chronic lung disease which causes breathing difficulties because of chronic airway inflammation. It results in wheezing, shortness of breath, chest tightness, and cough. Asthma is a common health problem around the world, and its prevalence also has been increasing in Korea [1]. The pathogenesis of asthma is unknown and there are no exact biomarkers to diagnosis asthma [2]. In recent, several candidate genes for susceptibility to asthma were reported using advanced genetic technology and several genetic studies [3–6]. However, more candidate genes for asthma will be investigated in the context of personalized medicine.

Secretoglobin family 3A member 2 (SCGB3A2) gene is located on chromosome 5 (*https:/www.ncbi.nlm.nih.gov/gene/117156*). Previous studies reported that promoter polymorphisms of SCGB3A2 gene result in susceptibility to asthma [7–9]. SCGB3A2 is a small molecular weight secreted protein in airway epithelial cells [10], which is also referred to as uteroglobin-related protein 1 (UGRP1) [10,11]. It also plays an important role in anti-inflammatory activity [12]. Several studies reported that it is involved in lung development [13] and inflammatory reactions in the respiratory tract [8,14–16]. Moreover, SCGB3A2 has an anti-inflammatory function [17], and it is reported to be involved in asthma [8,18]. Development of asthma may involve a series of influences on the individual development [19–23], and the complex influences may determine SCGB3A2 levels.

Firstly, such effects may result in continued chronic inflammatory cytokine production, and SCGB3A2 secretions in airway epithelium may be affected by the cytokines [24–27]. However, SCGB3A2 not only act downstream of such inflammation modulators, but also controls the inflammatory pathways [28–30] and other hormones [31].

Secondly, SCGB3A2 production may be affected by genetic variance of its promoter region [8]. Additionally, polymorphisms in SCGB3A2 gene regions have been studied in regard to asthma or allergic diseases by many researchers [9,12,32–35].

On the basis of this background, the present study was conducted to investigate whether single-nucleotide polymorphisms (SNPs) in SCGB3A2 gene are associated with asthma in a Korean population by case-control comparison of genomic DNA.

Material and Methods

Subjects

We selected 101 asthma patients (34 males, and 67 females; mean age ± standard deviation, years, 47.2±15.2] and 377 control subjects [186 males and 191 females; 49.2±11.4]) (Table 1). The patients with asthma were recruited from among visitors at the Departments of Kyung Hee University Oriental Medical Center, Seoul, Korea. Patients with asthma were diagnosed according to a clinical history with current clinical symptoms, including episodic wheezing, chest tightness, dyspnea, and 15 or greater reversibility of forced expiratory volume at 1 second (FEV_1) spontaneously or after treatment with a nebulized $beta_2$-agonist [36]. The exclusion criteria were as follows: (1) abnormal chest X-ray; (2) patients who had tuberculosis; and (3) patients who had severe chronic obstructive pulmonary disease (FEV1/FVC <70% and FEV1<50% when using bronchodilator). Control subjects with a history of asthma and/or related lung diseases were excluded. This study was performed in accordance with the guidelines of the Helsinki Declaration and was approved by the Ethics Review Committee of the Medical Research Institute, Kyung Hee University Medical Center (IRB number: 20040915). Written informed consent was obtained from each subject.

Table 1. Demographic and clinical characteristics of asthma patients and the control subjects.

	Asthma	Control
Number of subjects	101	377
Male/female	34/67	186/191
Age (mean±SD)	47.2±15.2	49.2±11.4

N – number of subjects; SD – standard deviation.

SNP genotyping

Genomic DNA samples were extracted using peripheral blood using a commercial DNA kit (Roche, Indianapolis, IN). The 3 examined SNPs were genotyped by direct sequencing after polymerase chain reaction (PCR). PCR was performed with the primers for each SNP: rs6882292 in *SCGB3A2* gene (forward, 5'-AGGACTTCTGCTCACAAATGAAG-3'; reverse, 5'-CCCACTCACACATCTACTATGGT-3'), rs1368408 (forward, 5'-CTTTTCAATGTTCTTCCAGGAG-3'; reverse, 5'-GCAGGAAGATAGTTACCAGCTTC-3'), and rs151333009 (forward, 5'-AAAGGGCCAGAGGTAGAAGTTTT-3'; reverse, 5'-CCTGAGATTCCAGGATGTGCAA-3') (Table 2). Final PCR products were sequenced by ABI PRISM 3730XL analyzer (PE Applied Biosystems, Foster City, CA).

Statistics

To determine whether individual SNP was in equilibrium at each locus in the population, we evaluated the Hardy–Weinberg equilibrium (HWE) using SNPStats (*http://bioinfo.iconcologia.net/index.php*). SNPStats and SPSS 23.0 (SPSS Inc., Chicago, IL) programs were used to analyze genetic data. The linkage disequilibrium (LD) block was measured using Haploview

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Table 2. Primer sequences for polymerase chain reaction (PCR).

SNPs	Forward (5'-3')	Reverse (5'-3')	size (bp)
rs6882292	AGGACTTCTGCTCACAAATGAAG	CCCACTCACACATCTACTATGGT	448
rs1368408	CTTTTCAATGTTCTTCCAGGAG	GCAGGAAGATAGTTACCAGCTTC	390
rs151333009	AAAGGGCCAGAGGTAGAAGTTTT	CCTGAGATTCCAGGATGTGCAA	489

bp – base pair.

Table 3. Frequency of the genotype and alleles of tested single nucleotide polymorphisms (SNPs) of secretoglobin family 3A member 2 (*SCGB3A2*) gene in the control group and the asthma group.

SNP	Type	Control n (%)	Asthma n (%)	Model	OR (95% CI)	p
rs6882292	G/G	345 (91.5)	82 (81.2)	Dominant	2.66 (1.42–5.01)	**0.0033**
Promoter	G/A	31 (8.2)	19 (18.8)	Recessive	0.00 (0.00–NA)	0.48
-659, G/A	A/A	1 (0.3)	0 (0.0)	Log-additive	2.45 (1.33–4.54)	**0.0055**
	G	721 (95.6)	183 (90.6)		1	
	A	33 (4.4)	19 (9.4)		2.27 (1.26–4.08)	**0.006**
rs1368408	G/G	223 (59.1)	49 (48.5)	Dominant	1.59 (1.02–2.49)	**0.041**
Promoter	G/A	143 (37.9)	44 (43.6)	Recessive	3.02 (1.15–7.90)	**0.03**
-112, G/A	A/A	11 (2.9)	8 (7.9)	Log-additive	1.63 (1.12–2.37)	**0.012**
	G	589 (78.1)	142 (70.3)		1	
	A	165 (21.9)	60 (29.7)		1.51 (1.07–2.14)	**0.021**

SNP – singe nucleotide polymorphism; OR – odds ratio; CI – confidence interval; n, number of subjects. The P values were calculated using logistic regression analyses, adjusting for the sex and age. Numbers in bold font indicate significant associations.

version 4.2 (Daly Lab, Cambridge, MA). To evaluate relationships, the odds ratio (OR), 95% confidence interval (CI), and *p* value were analyzed using logistic regression method in each model [dominant (major homogenotype versus heterogenotype + minor homogenotype), recessive (major homogenotype + heterogenotype versus minor homogenotype), and log-additive (major homogenotype versus heterogenotype versus minor homogenotype) models] [37–39]. To perform multiple correction, Bonferroni' s correction was applied. A value of $p<0.05$ was considered statistically significant.

Results

The genotype and allele frequencies of 2 promoter SNPs (rs6882292, 659 G/A and rs1368408, -112 G/A) and missense SNP (rs151333009, stop codon) were selected in *SCGB3A2* in asthma patients and controls (Table 3). The genotype distributions of examined SNPs in controls were in HWE (rs6882292, $p=1.00$; rs1368408, $p=0.061$; rs151333009, $p=1.00$) (data not shown).

The genotype frequencies (G/G: G/A: A/A) of rs6882292 SNP of *SCGB3A2* gene in the control group and in the asthma group were 91.5%: 8.2%: 0.3% and 81.2%: 18.8%: 0.0%. The differences showed significance [OR=2.66, 95% CI=1.42–5.01, p=0.0033 in dominant model (G/G genotype *vs.* G/A genotype+A/A genotype); OR=2.45, 95% CI=1.33–4.54, p=0.0055 in log-additive model (G/G *vs.* G/A *vs.* A/A), respectively]. The genotype frequencies (G/G: G/A: A/A) of rs1368408 SNP of *SCGB3A2* gene in the control group and in the asthma group were 59.1%: 37.9%: 2.9% and 48.5%: 43.6%: 7.9%. The differences also showed significance [OR=1.59, 95% CI=1.02–2.49, p=0.041 in dominant model (G/G genotype *vs.* G/A genotype+A/A genotype); OR=3.02, 95% CI=1.15–7.90, p=0.03 in recessive model (G/G genotype+G/A genotype *vs.* A/A genotype); OR=1.63, 95% CI=1.63, 95% CI=1.12–2.37, p=0.012 in log-additive model (G/G *vs.* G/A *vs.* A/A), respectively].

The minor A allele frequencies rs6882292 and rs1368408 SNPs of *SCGB3A2* gene were also associated with asthma (rs6882292, p=0.006, OR=2.27, 95% CI=1.26–4.08; rs1368408,

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Table 4. Frequency of the genotype and alleles of tested single nucleotide polymorphisms (SNPs) of secretoglobin family 3A member 2 (*SCGB3A2*) gene in the control group and the asthma group according to gender.

Gender	SNP	Type	Control		Asthma		Model	OR (95 CI)		p
			n (%)		n (%)					
Male	rs6882292	G/G	172	(92.5)	25	(73.5)	Dominant	5.60	(2.07–15.15)	**0.0011**
	Promoter	G/A	14	(7.5)	9	(26.5.1)				
	-659, G/A	A/A	0	(0.0)	0	(0.0)				
		G	358	(96.2)	59	(86.8)		1		
		A	14	(3.8)	9	(13.2)		3.90	(1.62–9.42)	**0.002**
	rs1368408	G/G	107	(57.5%)	15	(44.1%)	Dominant	1.60	(0.76–3.39)	0.21
	Promoter	G/A	73	(39.2%)	14	(41.2%)	Recessive	4.61	(1.28–16.57)	**0.026**
	-112, G/A	A/A	6	(3.2%)	5	(14.7%)	Log-additive	1.82	(1.00–3.30)	0.05
		G	287	(77.2)	44	(64.7)		1		
		A	85	(22.8)	24	(35.3)		1.84	(1.06–3.20)	**0.03**
Female	rs6882292	G/G	173	(90.6%)	57	(85.1%)	Dominant	1.70	(0.74–3.90)	0.22
	Promoter	G/A	17	(8.9%)	10	(14.9%)	Recessive	0.00	(0.00–NA)	0.44
	-659, G/A	A/A	1	(0.5%)	0	(0%)	Log-additive	1.55	(0.70–3.41)	0.29
		G	363	(95.0)	124	(92.5)		1		
		A	19	(5.0)	10	(7.5)		1.54	(0.70–3.40)	0.29
	rs1368408	G/G	116	(60.7%)	34	(50.8%)	Dominant	1.52	(0.86–2.66)	0.15
	Promoter	G/A	70	(36.6%)	30	(44.8%)	Recessive	1.72	(0.40–7.45)	0.48
	-112, G/A	A/A	5	(2.6%)	3	(4.5%)	Log-additive	1.46	(0.89–2.38)	0.13
		G	302	(79.1)	98	(73.1)		1		
		A	80	(20.9)	36	(26.9)		1.39	(0.88–2.19)	0.16

SNP – singe nucleotide polymorphism; OR – odds ratio; CI – confidence interval; n, number of subjects. The P values were calculated using logistic regression analyses, adjusting for the sex and age. Numbers in bold font indicate significant associations.

p=0.021, OR=1.51, 95% CI=1.07–2.14). The A allele frequencies rs6882292 and rs1368408 SNPs of *SCGB3A2* gene were lower in the control group (rs6882292, 4.4% and rs1368408, 21.9%) than in the asthma group (rs6882292, 9.4% and rs1368408, 29.7%). These results suggest that A allele of rs6882292 and rs1368408 SNPs of *SCGB3A2* gene is a risk factor of asthma.

There were differences between males and females, such as biochemical factors and hormones. Previous studies suggested that susceptibility to asthma differs by sex [40–42].

According to sex analysis, there were significant associations between rs6882292 and rs1368408 SNPs of *SCGB3A2* gene and male asthma (Table 4). The genotypic frequency of rs6882292 and rs1368408 SNPs of *SCGB3A2* gene was associated with male asthma [rs6882292, p=0.0011, OR=5.60, 95% CI=2.07–15.15 in dominant model (G/G genotype *vs.* G/A genotype); rs1368408, p=0.026, OR=4.61, 95% CI=1.28–16.57 in a recessive model (G/G genotype and G/A genotype *vs.* A/A genotype)]. After multiple correction using Bonferroni's correction, the significant association remained (p<0.05).

LD was evaluated using Haploview version 4.2 (Daly Lab Inc., Cambridge, MA). One LD block was made between rs6882292 and rs1368408 in the *SCGB3A2* gene (D'=1.000 and r^2=0.218) (data not shown). There were 3 haplotypes in the LD block (GG haplotype frequency=0.765, GA haplotype frequency=0.181, and AA haplotype frequency=0.054). We observed differences between the control group and the asthma group in the haplotype analysis (GG haplotype, p=0.02 and AA haplotype, p=0.0051) (Table 5).

Discussion

SCGB3A2, also referred to as UGRP1, is one of the susceptibility genes for asthma. In the present study, we evaluated the

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Table 5. Frequencies of haplotypes in the control group and asthma.

Haplotype	Frequency	Control		Asthma		Chi square	p
		+	–	+	–		
GG	0.765	598.0	165.0	142.0	60.0	5.413	**0.02**
GA	0.181	132.0	622.0	41.0	161.0	0.837	0.36
AA	0.054	33.0	721.0	19.0	183.0	7.835	**0.0051**

Haplotypes of the rs6882292 and rs1368408. Numbers in bold font indicate significant correlations.

relationship between SNPs of SCGB3A2 gene and susceptibility to asthma in a Korean population. Two promoter SNPs (rs6882292, 659 G/A and rs1368408, -112 G/A) showed associations with asthma in allele, genotypic models, and haplotype. The minor allele distributions of rs6882292 and rs1368408 SNPs in the asthma group were higher compared to those of the control group, indicating the minor alleles are risk factor for asthma in a Korean population. In analysis by sex, the association with asthma only showed in the male group, not in the female group.

SCGB3A2 gene was found to be related to thyroid and lung cancer. In a previous study conducted in a Chinese Han population [43], the rs6882292 SNP haplotype was composed of rs1368408 and rs6882292 SNPs, which were reported to be correlated with Graves' disease. The rs1368408 SNP (also known as SCGB3A2, -112G>A promoter polymorphism) showed the strongest association with Graves' disease among chromosome 5q31-33 in a Chinese Han population [43]. A study of Graves' disease in the United Kingdom also showed that rs1368408 was linked to common disease variation in 5q31-33 region [44]. It is downstream-regulated by thyroid transcription factor 1 [TTF-1, also known as NK2 homeobox 1 (NKX2-1)], which also regulates the expression of other thyroid genes and lung surfactant genes [43]. Moreover, TTF-1 may be an immunohistochemical marker of primary lung cancer cells [45]. Higher immunoglobulin E levels of Graves' disease patients were associated with rs1368408 [33].

The rs1368408 SNP has been previously studied in regard to asthma in a Japanese population. Niimi et al. found that the minor A allele of rs1368408 SNP significantly affects asthma development [8]. Individuals with A allele of rs1368408 were about more 4.1 times more likely to have asthma compared to individuals with G/G genotype. Inoue et al. showed that plasma SCGB3A2 levels were associated with the G-112A SCGB3A2 gene promoter polymorphism and the severity of asthma [12]. However, Batra et al. found no association in an Indian population [7], and Rigoli reported not significant association in Sicilian children [34]. Among the SNPs not considered in the present study, Andiappan et al. reported that rs7726552 showed significant association with allergic rhinitis [32]; however, no association was observed between asthma in their study. Regarding the function between the promoter polymorphisms and asthma, A allele of rs1368408 in SCGB3A2 gene promoter decreases the affinity of a particular nuclear protein to the binding site around -112 bp [8], resulting in reduced transcriptional activity and ultimately leading to lower expression of SCGB3A2 protein [8].

Conclusions

Our results suggest that promoter SNPs (rs6882292 and rs1368408) in SCGB3A2 gene may contribute to susceptibility to asthma in a Korean population. Specially, 2 SNPs may be a risk factor for Korean male asthma. However, the present study has some limitations, including sample size and function with asthma. Our results showing an association between the promoter polymorphisms of SCGB3A2 gene and asthma need to be confirmed in studies with larger sample sizes or in other population, and functional studies are also needed.

Conflict of interest

The authors declare no conflict of interest.

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