GENETIC TESTING AND MOLECULAR BIOMARKERS
Volume 15, Number 12, 2011

Pp. 841–847
DOI: 10.1089/gtmb.2011.0002

JAK-1 rs2780895 C-Related Genotype and Allele but Not JAK-1 rs10789166, rs4916008, rs2780885, rs17127114, and rs3806277 Are Associated with Higher Susceptibility to Asthma

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Background: Asthma, one major respiratory consequence, might be caused by a complex interaction between multiple candidate genes and environmental factors. Herein, we aimed to investigate whether Janus kinase (JAK)-1 gene polymorphisms are associated with asthma susceptibility. *Materials and Methods:* Patients were divided into two groups: (1) asthma ($n=117$) and (2) nonasthma ($n=60$). The JAK-1 polymorphisms (rs2780895, rs10789166, rs4916008, rs2780885, rs17127114, and rs3806277) were amplified by polymerase chain reaction and detected by electrophoresis after restriction enzyme (*Hpy*CH4IV, *Tsp*45I, *Hpa*II, *Xmn*I, *Msp*I, and *Hpa*II) digestions. Genotypes, allelic frequencies, and association of haplotypes in both groups were compared. *Results:* JAK-1 rs2780895 gene polymorphism is associated with susceptibility to asthma. Distributions of JAK-1 rs2780895*CC/CT/TT and C/T allele in both groups are: (1) 80/4/16% and 82/18%; (2) 48/45/7% and 71/29%. Other 5 JAK-1 SNPs (rs10789166, rs4916008, rs2780885, rs17127114, and rs3806277) are not associated with asthma susceptibilities. Distributions of JAK-1 rs10789166*AA/AG/GG, rs4916008*CC/CT/TT, rs2780885*CC/CT/TT, rs17127114*AA/AG/GG, rs3806277*AA/AG/GG in both groups are: (1) 50/40/10%, 42/49/9%, 50/40/10%, 9/37/54%, 8/35/57%; (2) 43/50/7%, 40/50/10%, 50/43/7%, 7/48/45%, 6/42/52%. Haplotype analyses for JAK-1 gene polymorphisms (rs2780895-rs10789166-rs4916008-rs2780885-rs17127114-rs3806277) revealed that JAK-1 haplotypes are not associated with asthma susceptibilities. *Conclusions:* JAK-1 rs2780895 C-related genotype and allele are associated with higher susceptibility to asthma. JAK-1 rs10789166, rs4916008, rs2780885, rs17127114, and rs3806277 single-nucleotide polymorphisms are not associated with asthma development. Some JAK-related genetic variations might be associated with asthma pathogenesis, which deserve further surveys.

Introduction

Asthma, a major respiratory illness, has 6%–9% prevalence in the general population (Moorman *et al.*, 2007). The incidence of asthma increased during the past decade (Woolcock and Peat, 1997). Asthma is caused by a complex interaction between multiple candidate genes and environmental factors. The increased incidence of asthma has been attributed to increased environment contamination and overusage of antibiotics as well as constitutional and genetic factors. Genetic studies suggested the functional role of some cytokines upon airway infection and hyperstimulation. However, the related molecular basis for this upper airway disorder remains unclear. The mechanistic roles of these cytokine-associated single-nucleotide polymorphisms (SNPs) have to be yet elucidated, especially in the context of the pathophysiology of asthma. Further, a basis for predicting asthma susceptibilities remains obscure.

The Janus kinase (JAK)/signal transducers and activators of transcription (STAT) cascade is essential for cytokines, growth factors, G-proteins, and hormones (Buslei *et al.*, 2006). The STA of JAK-STAT pathway controls signal transduction

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between cell surface receptors and the nucleus (Ferguson *et al.*, 2010). JAK constitutes a protein family that plays a pivotal role in signaling a large number of cytokine receptors (Bartunek *et al.*, 1999). The JAK family with four members (JAK1, JAK2, JAK3, and TYK2) plays an essential role in the signal transduction pathway from noncatalytic cytokine receptors to the nucleus (Cools *et al.*, 1999). Some JAK genetic variations were associated with significantly enhanced susceptibility to DNA damage (Ferguson *et al.*, 2010).

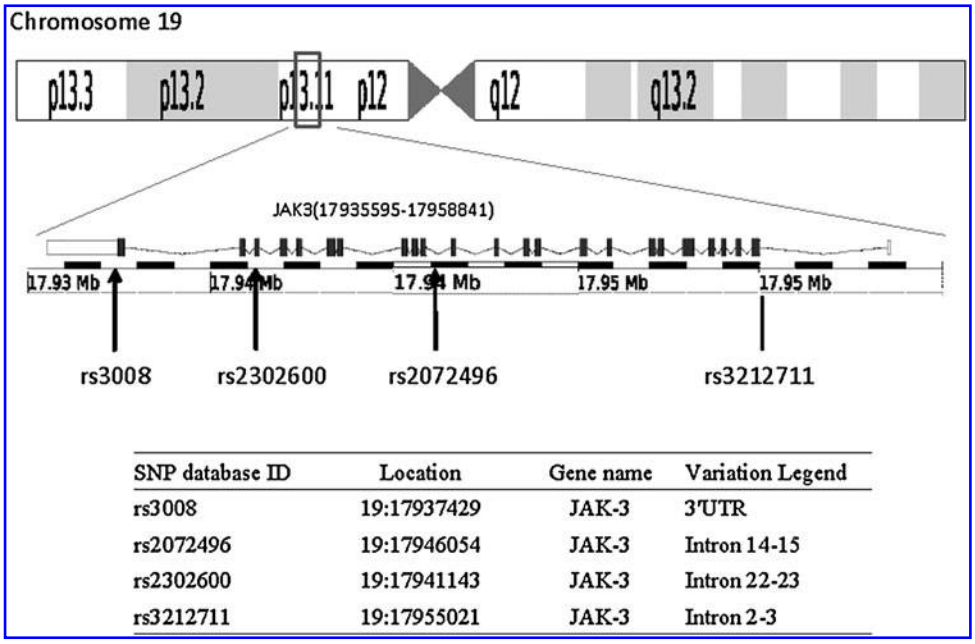
JAK is a tyrosine kinase that participates in the signaling of several cytokines and the development of allergic airway disease (Kudlacz *et al.*, 2008). Bronchial epithelial cell changes in asthma are induced by activation of the JAK/STAT pathway (Hu *et al.*, 2006). Malaviya *et al.* (2010) have demonstrated that JAK-dependent inflammatory responses are associated with allergic asthma. Morales *et al.* (2010) found that the JAK-STAT pathway influences mast cell homeostasis and the allergic process of asthma. Some cytokines, such as tumor necrosis factor and interferon, might induce asthma development by activating the STAT through the JAK pathways (Qi *et al.*, 2009). The compromised JAK-STAT pathway might interfere with the cytokine network and T-cell function as well as the development of allergic airway disease (Fukuyama *et al.*, 2009). Some suppressors of cytokine proteins have been shown to regulate the JAK-STAT pathway and the development of asthma (Inoue *et al.*, 2007). Some medication might be used to improve airway allergy and asthma through regulation of JAK1-STAT6 signal pathway (Chen *et al.*, 2007). Therefore, it is logical to suspect that some JAK genetic variations might play important roles in the complex pathogenesis of asthma.

Reviewing the MEDLINE database, the functional consequences of JAK variants upon asthma have not been previously demonstrated. Some investigators demonstrated the correlation of JAK-2 or 3 and asthma or other disorders (Cools *et al.*, 1999; Vaclavicek *et al.*, 2007; Kudlacz *et al.*, 2008; Sperati *et al.*, 2009; Ferguson *et al.*, 2010; Zhong *et al.*, 2010). However, few investigators demonstrated the correlation of JAK-1 gene polymorphisms with asthma. In our previous report, we observed the relationship between the JAK polymorphisms and hepatoma (Wan *et al.*, 2008). Based on the previous experience, we tried to evaluate whether the JAK-1 polymorphisms are useful markers for predicting the susceptibility to asthma. We aimed to evaluate whether JAK-1 gene polymorphisms are useful markers for predicting susceptibility to asthma. We also performed linkage and association analysis in these candidate regions. To the best of our knowledge, this is the first survey in this aspect.

Patients and Methods

Taiwanese children with asthma at China Medical University Hospital were recruited. All patients were divided into two groups: (1) asthma ($n = 117$) and (2) nonasthma groups ($n = 60$). All individuals accepted the peripheral blood sampling for genotype analyses. The experiment was approved by the Ethical Committee and Institutional Review Board of China Medical University Hospital. Informed consents were obtained from all study participants. A questionnaire was designed for collecting information regarding gender, age, and age at diagnosis of asthma.

The genomic DNA was prepared from peripheral blood leukocytes by use of a genomic DNA isolation kit (Blossom, Taipei, Taiwan). A total of 50 ng genomic DNA was mixed with 20 pmol of each polymerase chain reaction (PCR) primer in a total volume of 25 μL containing 10 mM Tris-HCL (pH 8.3), 50 mM potassium chloride, 2.0 mM magnesium chloride, 0.2 mM each deoxyribonucleotide triphosphate, and 1 U DNA polymerase (Amplitag; Perkin-Elmer, Foster City, CA). The PCR amplification was performed in a programmable thermal cycler GenAmp PCR system 2400 (Perkin Elmer Applied Biosystems, Foster City, CA). JAK-1 genetic mapping, PCR primer sequences, and conditions are listed in Figure 1 and Table 1.



SNP database ID	Location	Gene name	Variation Legend
rs3008	19:17937429	JAK-3	3'UTR
rs2072496	19:17946054	JAK-3	Intron 14-15
rs2302600	19:17941143	JAK-3	Intron 22-23
rs3212711	19:17955021	JAK-3	Intron 2-3

FIG. 1. Map of JAK 1 (rs2780895, rs10789166, rs4916008, rs2780885, rs17127114, rs3806277) located within chromosome 1p31.1 region (65298912–65432187).

Table 1. Gene Positions, PCR Primers, and Restriction Enzymes for *JAK*-1 Polymorphisms (rs2780895, rs10789166, rs4916008, rs2780885, rs17127114, and rs3806277)

Gene (rs number)	*Primer pairs (5′→3′)*	*Alleles*	*Enzyme*	*Genotype: length of DNA fragment (bp)*		*Annealing temperature (°C)*
JAK-1 (rs2780895)	F: ATTTGCAGGGCTCTTAGGGT R: TATAGAGTGACAGGCATGCA	C/T	*Hpy*CH4IV	TT:286	CC: 184 + 102	58
JAK-1 (rs10789166)	F: TGGCAGGGATGTGAGGTTTA R: AAACGAAAGCCCAGAGGAGT	A/G	*Tsp*45I	GG:262	AA:202 + 60	58
JAK-1 (rs4916008)	F: ACATGGCACCAGGGTTAACA R: AGAACCCTGATGATACAGGA	C/T	*Hpa*II	TT: 254	CC:154 + 100	60
JAK-1 (rs2780885)	F: TTTTGTGTCGCATGAGCCCT R: ACAGCAAGACACTGTCTCAA	C/T	*Xmn*I	CC: 300	TT: 189 + 111	58
JAK-1 (rs17127114)	F: ATTGCTGTTTCCCTAGCACCT R: AGGTGCACAGCATTCTAAGA	A/G	*Msp*I	AA: 342	GG:227 + 115	58
JAK-1 (rs3806277)	5′-TGAGCAGAAGCAAGGCATTA-3′ 5′-AGGATGTTGTTAGCTCTGGT-3′	A/G	*Hpa*II	AA:304	GG:205 + 100	60

After PCR amplification, the JAK-1 polymorphisms (rs2780895, rs10789166, rs4916008, rs2780885, rs17127114, and rs3806277) were analyzed by restriction digestion with restriction enzymes (*Hpy*CH4IV, *Tsp*45I, *Hpa*II, *Xmn*I, *Msp*I, and *Hpa*II; New England Biolabs, Inc., Beverly, MA). The JAK-1 polymorphisms were determined by the different sizes of PCR products following electrophoresis. Electrophoresis of the PCR products was performed on a 3% agarose gel, which was stained with ethidium bromide to visualize the amplified DNA bands (Fig. 2). The individual PCR conditions following electrophoresis and base pairs for their wild and SNP types are listed in Table 1.

Genotypes and allelic frequencies for JAK-1 rs2780895, rs10789166, rs4916008, rs2780885, rs17127114, and rs3806277 polymorphisms in both groups were compared. Correlations of these gene polymorphisms and asthma were evaluated. Allelic frequencies are expressed as a percentage of the total number of alleles. The SAS package (Version 8.1; SAS Institute, Inc., Cary, NC) with χ^2 and Fisher's exact tests were utilized for statistical analyses. A p-value of <0.05 was considered statistically significant.

Results

JAK-1 rs2780895 gene polymorphisms are associated with susceptibility to asthma (Table 2). Distributions of JAK-1 rs2780895*CC/CT/TT and C/T allele in both groups were (1) 80/4/16% and 82/18% and (2) 48/45/7% and 71/29%, respectively ($p<0.05$). JAK-1 rs2780895*C-related genotype and allele are associated with higher susceptibility to asthma. In contrast, genotype proportions of the other five JAK-1 SNPs (rs10789166, rs4916008, rs2780885, rs17127114, and rs3806277) in both groups were not significantly different (Table 2). Distributions of JAK-1 rs10789166*AA/AG/GG-A/G, JAK-1 rs4916008*CC/CT/TT-C/T, and JAK-1 rs2780885*CC/CT/TT-C/T in both groups are (1) 50/40/10%–70/30%, 42/49/9%–66/34%, and 50/40/10%–70/30% and (2) 43/50/7%–68/32%, 40/50/10%–65/35%, and 50/43/7%–72/28%, respectively (nondifference). Proportions of JAK-1 rs17127114*AA/AG/GG-A/G and JAK-1 rs3806277*AA/AG/GG-A/G in both groups are (1) 9/37/54%–27/73% and 8/35/57%–25/75% and (2) 7/48/45%–31/69% and 6/42/52%–28/72%, respectively (nondifference).

There were 11 haplotypes in both groups. Haplotype analyses for JAK-1 gene polymorphisms (rs2780895-rs10789166-rs4916008-rs2780885-rs17127114-rs3806277) demonstrated the nonsignificantly different distributions between both groups. JAK-1 haplotypes were not associated with asthma susceptibilities (Fig. 3). Proportions of JAK-1 haplotype in both groups are presented in Table 3.

Discussion

Bronchial asthma is a chronic airway disorder characterized by reversible bronchial hyperresponsiveness and airway inflammation. Asthma is a multifactorial disease influenced by genetic and environmental factors. Cytokines are major immune system regulators and key components of inflammation, which are essential for asthma pathogenesis. Variation in genes encoding inflammatory responses might influence asthma risk through interaction with chronic infections and proinflammatory environmental risk factors, such as sedentary conditions, lifestyle, and air pollutions. However, the mechanism for asthma is complex. The precise physiological stimulus mediating asthma presentation remains obscure.

Cytokines are proteins that play important roles in the communication link between the immunological system and air way. Cytokines also reach the circulation and act locally as paracrine or endocrine signals. Growing evidence suggests that asthma is a multistep process of genetic alterations. Some possible factors have been implicated with asthma, including cytokines, signal ligands, and defense factors (Nadel, 2007; Aumeunier *et al.*, 2010; Brochu-Bourque *et al.*, 2011). Genetic surveys for asthma might provide insight into related pathophysiology and mechanisms. During the past several decades, some loci and genes have been found to be associated with the disorder. Numerous genetic factors might interfere with the inflammatory capacity of leukocytes, thus altering whole-body allergy and asthma events. Some patients with different clinical phenotypes display variable susceptibilities toward asthma.

JAK has a wide variety of immunosuppressive activities. The JAK-STAT mediates the signals of a wide range of cytokines, growth factors, and hormones. The JAK is the gatekeeper in the JAK-STAT pathway, which is a major

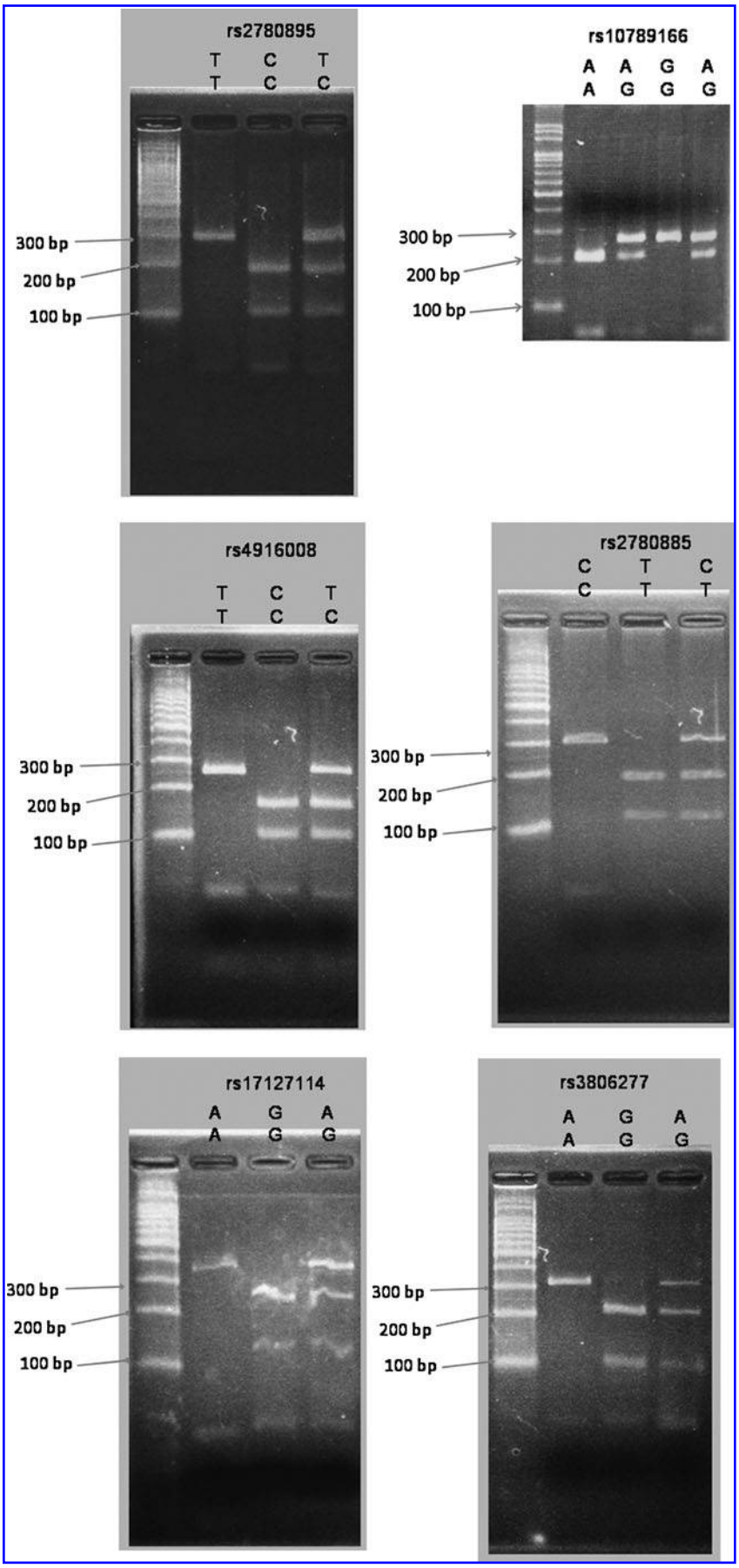


FIG. 2. Electrophoresis of PCR products for rs2780895, rs10789166, rs4916008, rs2780885, rs17127114, and rs3806277.

Table 2. Genotype and Allele Distributions of JAK-1 Polymorphisms in Controls and Asthma Patients

Gene name (SNP database ID)	*Genotype/ allele*	*Asthma (n = 117)*	*Controls (n = 60)*	p-*Values*	*Odds ratio*	*95% Confidence interval*
JAK-1 rs2780895	CC	93 (0.80)	29 (0.48)	< 0.05	0.68	0.19–2.42
	CT	5 (0.04)	27 (0.45)		0.04	0.01–0.21
	TT	19 (0.16)	4 (0.07)		1.00	
	Allele C	191 (0.82)	85 (0.71)	< 0.05	1.83	1.02–3.28
	Allele T	43 (0.18)	35 (0.29)		1.00	
JAK-1 rs10789166	AA	58 (0.50)	26 (0.43)	0.41	0.74	0.39–1.43
	AG	47 (0.40)	30 (0.50)		0.52	0.15–1.77
	GG	12 (0.10)	4 (0.07)		1.00	
	Allele A	163 (0.70)	82 (0.68)	0.80	1.06	0.66–1.71
	Allele G	71 (0.30)	38 (0.32)		1.00	
JAK-1 rs4916008	CC	49 (0.42)	24 (0.40)	0.97	1.11	0.58–2.15
	CT	57 (0.49)	30 (0.50)		1.04	0.35–3.08
	TT	11 (0.09)	6 (0.10)		1.00	
	Allele C	155 (0.66)	78 (0.65)	0.82	1.06	0.67–1.68
	Allele T	79 (0.34)	42 (0.35)		1.00	
JAK-1 rs2780885	CC	58 (0.50)	30 (0.50)	0.72	0.64	0.34–1.24
	CT	47 (0.40)	26 (0.43)		0.60	0.18–2.06
	TT	12 (0.10)	4 (0.07)		1.00	
	Allele C	163 (0.70)	86 (0.72)	0.70	0.91	0.56–1.47
	Allele T	71 (0.30)	34 (0.28)		1.00	
JAK-1 rs17127114	AA	10 (0.09)	4 (0.07)	0.39	1.07	0.31–3.74
	AG	44 (0.37)	29 (0.48)		0.65	0.34–1.25
	GG	63 (0.54)	27 (0.45)		1.00	
	Allele A	64 (0.27)	37 (0.31)	0.49	0.84	0.52–1.37
	Allele G	170 (0.73)	83 (0.69)		1.00	
JAK-1 rs3806277	AA	9 (0.08)	4 (0.06)	0.69	1.04	0.29–3.74
	AG	41 (0.35)	25 (0.42)		0.76	0.39–1.46
	GG	67 (0.57)	31 (0.52)		1.00	
	Allele A	59 (0.25)	33 (0.28)	0.64	0.89	0.54–1.46
	Allele G	175 (0.75)	87 (0.72)		1.00	

SNP, single-nucleotide polymorphism.
Numbers in parentheses indicate percentages of the genotype or allele frequency.

suppressor of some cytokines during cell-signaling process. The JAK/STAT pathway is active in human malignancies (Zhong *et al.*, 2010). Aberrant activation of the JAK/STAT pathway may predispose to malignancy because of deregulation of proliferation, differentiation, or apoptosis (Vaclavicek *et al.*, 2007). Some JAK genetic variants also strongly enhanced the risk of ileal/stricturing behavior and ileocolonic disease (Ferguson *et al.*, 2010).

The JAK-1 gene, which is located on chromosome 1p31.1, has a highly polymorphic flanking region. JAK gene polymorphisms were related with the susceptibility to disease activities for individual diseases. JAK mutations or SNPs are associated with leukemia (Zhong *et al.*, 2010). The JAK SNP is part of a haplotype associated with enhanced susceptibility to myeloproliferative neoplasms. The JAK2 A830G might be an important marker for therapeutic outcomes of patients with acute myeloid leukemia (Zhong *et al.*, 2010). JAK genetic variations are associated with the risk of Crohn's disease (Ferguson *et al.*, 2010). The JAK expression levels might be regulated by DNA methylation (Buslei *et al.*, 2006).

Some genetic variations in the JAK/STAT signaling pathway might increase the risk of cardiovascular events in dialysis patients (Sperati *et al.*, 2009). JAK3 rs3212780 and rs3213409 might be associated with cardiovascular diseases (Sperati *et al.*, 2009). Functional studies of the JAK2R683G mutation showed growth factor independence and constitutive activation of the JAK/STAT signaling pathway (Kearney *et al.*, 2009). JAK2 SNPs (rs7046736, rs10815148, and rs12342421) are associated with polycythemia vera (Pardanani *et al.*, 2008). Several genes from JAK/STAT signaling pathway have been demonstrated to be associated with fertility traits (Khatib *et al.*, 2009).

SNP results from a base substitution mutation. SNPs in protein-coding regions might result in a synonymous mutation (same polypeptide sequence) or nonsynonymous mutations with a change of amino acids (missense change) or termination codon (nonsense change). In addition, SNPs in promoter regions can result in reduced or increased gene expression, whereas SNPs in introns can result in defective splicing or a change in transcription rate if a regulatory element is mutated. SNPs occur on average every 1.9 kb in the genome, where 1.42 million SNPs have been mapped with over 60,000 being represented within exons and untranslated regions (Marth *et al.*, 2001). However, literature results on the genetic association of JAK-1 upon asthma are inconsistent.

In this study, we first observed some association between asthma susceptibility and JAK-1-related genotype and allelic distributions. JAK-1 rs2780895 C-related genotype and allele

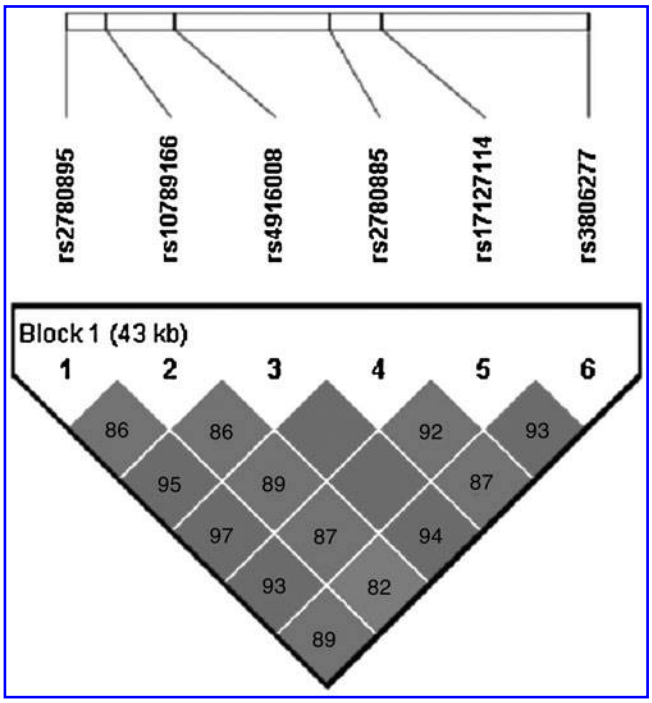


FIG. 3. Haplotype blocks of rs2780895, rs10789166, rs4916008, rs2780885, rs17127114, and rs3806277 for asthma, constructed according to the confidence interval approach using Haploview software. Dark gray indicates linkage disequilibrium; white indicates evidence of recombination.

but not JAK-1 rs10789166, rs4916008, rs2780885, rs17127114, and rs3806277 are associated with higher susceptibility to asthma.

It suggests that JAK-1 rs2780895 gene might be a susceptibility gene for asthma. JAK-1 rs2780895 genetic variation might influence the mRNA translations for innate immune events. Based on this association and linkage surveys, we speculate that alterations in this gene could be responsible for the aberrant immune response that characterizes asthma. These findings suggested that some genetic variations within the JAK-1 might be associated with the genetic presentation, such as transcription and translations as well as asthma phenotypes and susceptibilities. These findings highlighted the potential role of JAK-1–related genes upon the future surveys of asthma. Some JAK polymorphisms might have a potential influence upon the expression of this repair protein.

In contrast, we observed the nonassociation of another five JAK-1 genetic variation with asthma susceptibility. The JAK-1 haplotypes rs2780895-rs10789166-rs4916008-rs2780885-rs17127114-rs3806277 are not associated with the susceptibility and contribution for asthma. Although these JAK genetic variations might result in some nonsynonymous coding change, these SNPs might interfere, modify, or influence the JAK-1–related cytokines pathways as well as the following pathogenesis of asthma. There is biological plausibility for an association between the JAK-1 polymorphisms in the exon or promoter regions and asthma risk. It also provides a valuable insight into the pathogenesis of asthma. The differences of JAK-1 genetic variations might exist between different illness classification and racial and disease variations. Our study should permit a more precise evaluation of the risks associated with individual susceptibility genes and a better insight into asthma pathogenesis. This intervening sequence located on an mRNA untranslated region might not influence the amino acid coding, mRNA production, genetic expression, and illness susceptibilities.

In conclusion, JAK-1 rs2780895 polymorphism is associated with asthma susceptibility. Some of the JAK-1 genes might play a role to confer a risk of asthma. JAK-1 rs2780895 polymorphisms might become potential markers for the prediction of asthma susceptibility. It also provides a valuable insight into the pathogenesis of asthma. Other JAK-1 genes (rs10789166, rs4916008, rs2780885, rs17127114, and rs3806277) and related haplotypes are not associated with asthma development. The real roles and relationships of these genetic traits upon asthma remain complex to be clarified, especially concerning the effects of other cytokine additions. Additional *in vitro* or *in vivo* researches are requested, including functional studies correlating genotype and phenotype for other JAK-1 alleles within asthma tissue. After the clarification of these issues, some JAK genetic variations might become useful markers to predict the future development of asthma as well as the modulating or interfering factors of related pathogeneses.

Table 3. Haplotype Distributions of JAK-1 Gene in Asthma Patients and Controls

Haplotype	*rs2780895*	*rs10789166*	*rs4916008*	*rs2780885*	*rs17127114*	*rs3806277*	*Asthma*	*Controls*	p-*Values*	*Odds ratio (95% CI)*
Ht 1	C	A	C	C	G	G	0.334	0.304	0.568	1.15 (0.71–1.85)
Ht 2	C	A	T	C	G	G	0.297	0.337	0.441	0.83 (0.52–1.33)
Ht 3	T	G	C	T	A	A	0.223	0.25	0.569	0.86 (0.51–1.44)
Ht 4	T	G	C	T	A	G	0.028	0.025	0.869	1.12 (0.28–4.49)
Ht 5	T	G	C	T	G	G	0.021	—	0.110	
Ht 6	C	G	T	C	G	G	0.018	—	0.139	
Ht 7	T	A	C	T	A	A	0.013	—	0.210	
Ht 8	T	A	T	C	G	G	0.011	—	0.249	
Ht 9	T	A	C	C	G	G	0.011	—	0.249	
Ht 10	C	G	C	C	G	G	—	0.034	0.005	
Ht 11	C	A	C	C	A	A	—	0.017	0.045	

Disclosure Statement

No competing financial interests exist.

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