



Pharmacogenetics of aspirin-intolerant asthma

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Leukotriene overproduction is the major characteristic of aspirin-intolerant asthma (AIA). Most studies examining the molecular genetic mechanisms of AIA have focused on leukotriene-related genes, including *ALOX5*, *LTC4S*, *TXA2R* and prostanoid-receptor genes. One study suggested that the human leukocyte antigen (HLA) allele *DPB1*0301* may be a genetic marker for the AIA phenotype in European and Asian populations, and *HLA-DPB1*0301* has been suggested as a useful genetic marker for predicting more favorable responders to leukotriene-receptor antagonists for long-term management of AIA. Although several reports have indicated possible associations between genetic polymorphisms and variable responses to leukotriene modifiers in nonaspirin sensitive asthmatic patients, few have suggested relationships between such genetic polymorphisms and variable responses to asthma drugs in AIA patients.

Recent studies have demonstrated that genetic polymorphisms of the receptor for leukotriene-receptor antagonist (LTRA), cysteinyl leukotriene receptor type 1 (*CysLTR1*; -634C>T), could be associated with the aspirin-intolerant asthma (AIA) phenotype. Leukotriene-related gene polymorphisms, including those of leukotriene C4 synthase (*LTC4S*), arachidonate 5-lipoxygenase (*ALOX5*), thromboxane A2 receptor (*TXA2R*), prostaglandin endoperoxide synthase 2 (*COX2*) and *CysLTR1*, were screened for associations with LTRA responses in long-term management of AIA patients; patients carrying the T allele of the *CysLTR1* promoter polymorphism, -634C>T, were shown to require significantly higher doses of LTRA to control asthmatic symptoms, whereas no significant associations were found with the other leukotriene-related gene polymorphisms, including those of *ALOX5* and *LTC4S*. These results suggest that the *CysLTR1* promoter polymorphism at -634C>T may be a useful gene marker for predicting more favorable responders to LTRA for long-term management of chronic AIA patients. Further molecular genetic studies identifying susceptible genetic markers for AIA would help elucidate potential molecular targets for predicting drug-response variability in AIA patients.

Clinical features of aspirin-intolerant asthma

The majority of AIA patients experience moderate-to-severe persistent asthmatic symptoms combined with chronic rhinosinusitis [1,2] and,

therefore, require daily medication to control their symptoms [3]. Given the pathogenic mechanisms of AIA, a LTRA has been recommended as the first-line drug for long-term management of the disease including the recent Global Initiative for Asthma (GINA) guideline [4–6]. Lipworth *et al.* demonstrated that LTRAs, such as zafirlukast and montelukast, improve lung function, as measured by the forced expiratory volume in 1 s (FEV1) and peak expiratory flow (PEF) in 55% of asthmatics in a randomized, open, crossover trial of 167 patients [7].

The pathogenic mechanism of AIA is not completely understood; however, the chronic overproduction of cysteinyl leukotrienes (CysLTs) derived from cyclooxygenase (COX) inhibition is a major consistent finding among AIA patients [8–10]. CysLT promotes persistent inflammation by inducing bronchoconstriction, eosinophil migration and mucus secretion [11,12]. A recent study has demonstrated the deficiency of COX transcripts in cultured primary bronchial epithelial cells of aspirin-sensitive asthmatics [13]. Therefore, their symptoms may result from the abnormal regulation of arachidonate-related genes.

Diagnostic tests for AIA include the lysine–aspirin bronchoprovocation test, which has been widely applied in Europe and Asia, and the oral provocation test, which is more common in the USA.

The therapeutic efficiency of LTRA in the management of AIA symptoms (by reducing the persistent production of CysLT), genetic polymorphisms of genes in the arachidonic acid

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cascade and CysLT receptors could be the first targets identified for determining drug-response variability to LTRAs.

Here we review recent reports of molecular genetic mechanisms and pharmacogenetic data to identify potential molecular targets associated with variable responses to LTRAs in AIA patients.

Molecular genetic mechanisms & pharmacogenetics of AIA

*The HLA allele HLA-DPB1*0301 as a genetic marker*

The association of the HLA allele *HLA-DPB1*0301* with the AIA phenotype was first reported in a Polish population [14] and later in a Korean population [15]. In the Korean population, the frequency of *DPB1*0301* was significantly increased in AIA patients compared with normal (OR = 8.3) and asthmatic controls (OR = 5.2) [15], suggesting that immune recognition of an unknown antigen may be part of the pathogenesis of AIA. Carriers of *DPB1*0301* tended to be female and exhibited typical clinical features of AIA, such as a lower FEV1 and a higher prevalence of rhinosinusitis and/or nasal polyps [15]. Furthermore, the presence of *DPB1*0301* was significantly associated with a higher dose requirement for LTRAs in a 1-year study of AIA patients [16]. An interaction between *DPB1*0301* and a *TNF-α* promoter polymorphism (-1031T>C, -863C>A or -857C>A) synergistically increased susceptibility to AIA, indicating that a *TNF-α* promoter polymorphism may genetically interact with *DPB1*0301* to significantly increase susceptibility to AIA independently, not derived from linkage disequilibrium [17]. These results suggest that *DPB1*0301* may be a potential genetic marker for the AIA phenotype and may, therefore, be useful for predicting good responders to LTRAs from among AIA patients.

LTC4S, ALOX5 & drug response variability to LTRAs

It has been suggested that *LTC4S*, which encodes a key enzyme for CysLT synthesis, may be genetically associated with AIA pathogenesis. Of the two recognized promoter polymorphisms, -1072G>A and -444A>C, the latter has been reported to be positively associated with the AIA phenotype in a Polish population [18]. However, this association has not been replicated in other cohorts, including Japanese, American and Korean populations [19–21]. In

some aspects, the lack of replication might be derived from the different ethnicity and, hence, a different definition of the phenotype of AIA.

All pharmacogenetic studies examining associations between the *LTC4S* gene polymorphism (-444A>C) and the variability in responses to LTRAs, have been conducted in patients with aspirin-tolerant asthma (ATA) not in AIA patients. Although there has been one study demonstrating no significant differences in the clinical response to the montelukast treatment between AIA and ATA patients [22], several other groups demonstrated that the individuals carrying the variant genotype (C allele) showed a more favorable response to LTRAs compared with those carrying the more common A allele [23–26]. However, a negative association was also found between this promoter polymorphism and drug responses to LTRAs [27,28]. Our recent study examining the LTRA dose required to control asthmatic symptoms in AIA patients over a 1-year study period demonstrated no significant associations between the two *LTC4S* promoter polymorphisms at -1072 G>A and -444 A>C and LTRA requirements [29].

The Drazen group was the first to report an association between a promoter polymorphism of *ALOX5*, consisting of a variable number of tandem repeats of GC-rich motifs, and the binding of Sp1 transcription factors [30]. ATA patients with the wild-type genotype (five repeats) exhibited a significantly higher capacity to produce CysLTs compared with those carrying a mutant genotype (three, four or six repeats). Some reports have suggested the possible involvement of this *ALOX5* polymorphism in AIA patients. Indeed, a significant association between the *ALOX5* promoter polymorphism and the severity of airway hyper-responsiveness was reported in a Korean population [31]. Specifically, AIA patients carrying a mutant *ALOX5* allele (> or < five repeats) showed increased airway hyper-responsiveness compared with AIA patients with the wild-type genotype. We screened for ten SNPs of genes for key enzymes involved in arachidonate metabolism, *ALOX5* (-1708G>A, 21C>T, 270G>A and 1728G>A), *ALOX5*-activating protein (*ALOX5AP*; 218A>G), *COX-2*; (-162C>G, 10T>G and 228G>A), *LTC4S* (-444A>C) and *CysLTR1* (927T>C), in a Korean population and found no significant relationships between these *ALOX5AP*, *COX-2* and *CysLTR1* polymorphisms and the AIA phenotype [21]. However, possible associations were suggested between the development of AIA and the *ALOX5* haplotype (G-C-G-A), as well as some

ALOX5 polymorphisms (-1708G>A, 21C>T, 270G>A and 1728G>A). The haplotype of *ALOX5* was in order of -1708G>A, -21C>T, -270G>A and -1728A>G.

To date, all pharmacogenetic studies examining *ALOX5* gene polymorphisms and responses to leukotriene modifiers have been conducted in ATA patients rather than AIA patients. One study demonstrated a positive relationship between various genotypes of the *ALOX5* promoter polymorphism and decreased bronchodilator response to the *ALOX5* enzyme inhibitor ABT-761 in mild-to-moderate asthma patients [30]. Another study suggested that the genetic variant of the *ALOX5* tandem repeat was associated with a reduced risk for exacerbation in patients receiving the LTRA montelukast [26]. However, no association has been identified between the *ALOX5* tandem repeat polymorphism and bronchodilator response to adenosine 5'-monophosphate (AMP) following treatment with an LTRA [32]. An additional report indicated that two SNPs of the *ALOX5* gene (rs 4987105 and rs 4986832) were associated with variable responses (percentage increase of peak expiratory flow rate [PEFR]) to a leukotriene modifier in ATA patients [28]. In our recent study, we did not identify any associations among four SNPs of *ALOX5* (-1708G>A, 21C>T, 270G>A and 1728A>G) and the LTRA dose required to control asthmatic symptoms in a 1-year study conducted in 89 AIA patients [29].

Most studies focusing on the relationship between *ALOX5* and *LTC4S* gene polymorphisms and leukotriene modifier responses have been conducted in ATA patients. The polymorphisms of these two genes had inconsistent pharmacogenetic effects on LTRA responses among the populations examined; the inconsistencies may result from differences among the studies with regard to study design, number of patients and genotype frequencies. Given that these two genes are key players in the leukotriene synthesis pathway, further studies may identify novel SNPs associated with the AIA phenotype as well as with pharmacogenetic effects in AIA patients.

CysLTR1, CysLTR2 polymorphisms & pharmacogenetic studies in AIA patients

CysLTs exert their biological actions by binding to two types of receptors, CysLTR1 and CysLTR2. Two studies have examined the genetic associations between these genes and AIA [33,34]. The first report indicated that three SNPs (*CysLTR1* -634C>T, -475A>C and

-336A>G) in the 5' upstream region of *CysLTR1* [33] are significantly associated with the AIA phenotype, particularly in males. These polymorphisms were related to increased promoter activity, suggesting that they may modulate *CysLTR1* expression to increase AIA susceptibility. The second study demonstrated that the mRNA level of *CysLTR1* from peripheral mononuclear cells was significantly increased *in vivo* when AIA patients were exposed to aspirin [35].

Three *CysLTR2* SNPs (c.-819T>G, c.2078C>T and c.2534A>G) were found to be significantly associated with the AIA phenotype, with the rare alleles occurring more frequently in subjects with AIA than in subjects with ATA [34]. Patients exhibiting the rare SNP alleles showed a greater percentage decrease in FEV1 after aspirin provocation than those carrying the more common alleles. Few studies have evaluated the pharmacogenetic effects of the two receptor genes in asthmatics with respect to responses to leukotriene modifiers [28,29], although one study demonstrated that two *CysLTR2* SNPs (rs 912277 and rs 912278) were associated with variable responses (increase of percentage PEFR predicted) to a leukotriene modifier in ATA patients [28].

We evaluated the associations between the clinical requirements for LTRA therapy and genetic polymorphisms of genes in the arachidonic acid cascade in 89 AIA patients [29]. Asthma control status with maintenance medications of inhaled corticosteroids and LTRA was monitored for 1 year. AIA patients were classified into three groups according to the mean montelukast dose required per month (mg/month) to maintain asthma control for 1 year: group I (≥ 200 ; n = 37), group II (5–150; n = 25) and group III (< 5 ; n = 27). Polymorphisms were genotyped using a single-base extension method. We found a significant association between the LTRA requirement and a single *CysLTR1* promoter polymorphism (-634C>T) but no significant associations with polymorphisms of the other genes examined, including 14 SNPs of *ALOX5* (-1708G>A, Sp1 tandem repeat, 21C>T, 270G>A and 1728A>G), *ALOX5AP* (poly-A tandem repeat and 218A>G), *LTC4S* (-1072G>A and -444A>C), *TXA2R* (795T>C and 924T>C) and *COX2* (-162C>G, 10T>G and 228G>A) [29]. Furthermore, the promoter construct carrying the -634 T allele of the *CysLTR1* -634C>T polymorphism exhibited increased *in vitro* promoter activity compared with the promoter

carrying the -634 C allele [33]. Patients carrying the variant genotype of the *CysLTR1* -634C>T polymorphism showed a trend toward higher *CysLTR1* mRNA levels compared with wild-type patients [35].

Given these findings, we suggest that patients with a variant genotype of the *CysLTR1* -634C>T polymorphism exhibit persistent overexpression of CysLT1 receptors, which may exacerbate asthma symptoms, especially in AIA patients with persistently high production of CysLTs. Thus, this polymorphism could be a useful genetic marker for predicting the usefulness of LTRAs to control asthmatic symptoms in AIA patients.

Other possible candidate genes for pharmacogenetic studies in AIA patients

A case-control study of 63 candidate genes identified an association between a functional SNP of the prostaglandin E (PGE)₂ receptor subtype 2 gene and increased risk for AIA in a Japanese population [36]. This may be attributable to a reduction in the PGE₂ braking mechanism of inflammation. Although a novel promoter polymorphism of *COX-2* (-765G>C) was not associated with the AIA phenotype, the CC homozygote of this promoter polymorphism was associated with increased PGE₂ production by creating an E2F transcription factor binding motif [37]. We

recently screened AIA patients for genetic variations in the prostanoid receptor genes (*PTGER1*, *PTGER2*, *PTGER3*, *PTGER4*, *PTGDR*, *PTGIR* and *PTGFR*) and in *TXA2R*, using 32 tagging SNPs [38]. We identified significant associations between the AIA phenotype and polymorphisms of *PTGER2* (-616C>G and -166G>A), *PTGER3* (-1709T>A), *PTGER4* (-1254A>G) and *PTGIR* (1915T>C). Furthermore, the frequencies of the *TXA2R* polymorphisms -4684C>T and 795T>C differed significantly between AIA and ATA patients. These findings suggest that genetic polymorphisms of *PTGER2*, *PTGER3*, *PTGER4*, *PTGIR* and *TXA2R* may participate in the pathogenesis of AIA. Therefore, these genes could be considered as targets for future pharmacogenetic studies in AIA patients.

TXA2R is a receptor for a potent bronchoconstrictor, thromboxane A₂, and the *TXA2R* 795T>C polymorphism could augment the bronchoconstrictive response to inhaled aspirin, which could in turn contribute to AIA development [39]. Although a *TXA2R* antagonist is available in some Asian countries, there are no pharmacogenetic studies describing this gene polymorphism and drug responses to LTRAs or the *TXA2R* antagonist in either AIA or ATA patients. In our recent study examining AIA patients, we did not find any associations between

Table 1. The summary of candidate genes associated with variable responses to leukotriene modifiers in asthmatic patients.

Gene	Name	Loci	Polymorphism
<i>HLA</i>	Human leukocyte antigen	6p21.3	<i>DPB1</i> *0301
<i>ADRB2</i>	Adrenergic, β_2 -, receptor, surface	5q32	rs1042714 and rs1042711
<i>ALOX5</i>	Arachidonate 5-lipoxygenase	10q11.21	rs4987105, rs4986832, Sp1 motif and rs2115819
<i>ALOX5AP</i>	Arachidonate 5-lipoxygenase-activating protein	13q12.3	218A>G
<i>LTA4H</i>	LTA4 hydrolase	12q22	rs2660845
<i>LTC4S</i>	Leukotriene C4 synthase	5q35.3	-1072G>A and -444A>C
<i>CysLTR1</i>	Cysteinyl leukotriene receptor 1	Xq21.1	-634C>T and 927T>C
<i>CysLTR2</i>	Cysteinyl leukotriene receptor 2	13q14.2	rs912277 and rs912278
<i>MRP1</i>	Multidrug resistance protein 1	16p13.1	rs119774
<i>NR3C1</i>	Glucocorticoid receptor	5q31.3	rs6188 and rs6196
<i>PTGER2</i>	Prostaglandin E receptor 2	14q22.1	-616C.G and -166G>A
<i>PTGER3</i>	Prostaglandin E receptor 3	1p31.1	-1709T>A
<i>PTGER4</i>	Prostaglandin E receptor 4	5p13.1	-1254A>G
<i>PTGIR</i>	Prostaglandin I ₂ (prostacyclin) receptor	19q13.32	1915T>C
<i>PTGS2</i>	Prostaglandin-endoperoxide synthase 2 (COX2)	1q25.2-q25.3	-765G>C, -162C>G, 10T>G and 228G>A
<i>TXA2R</i>	Thromboxane A ₂ receptor	19p13.3	-4684C>T, 795T>C and 924T>C
<i>TNFA</i>	TNF- α	6p21.3	rs1799964, 1800630 and 1799724
<i>TBX21</i>	T-box expressed in T cells	17q21.32	-1993T>C

Table 2. Genetic polymorphisms associated with variable responses to leukotriene modifiers in asthmatic patients.

Study	Gene	Polymorphism	Pharmacogenetic effect <i>in vivo</i> *	Nation	Ref.
Park <i>et al.</i> (2004) [‡]	HLA	DPB1*0301	LTRA requirement	Korea	[16]
Kim <i>et al.</i> (2007) [‡]	CysLTR1	-634C>T	LTRA requirement	Korea	[29]
Drazen <i>et al.</i> (1999)	ALOX5	Sp1/Egr1	FEV1	USA	[30]
Sampson <i>et al.</i> (2006)	LTC4S	-444A>C	FEV1, FVC	UK	[23]
Asano <i>et al.</i> (2002)	LTC4S	-444A>C	FEV1	Japan	[24]
Lima <i>et al.</i> (2006)	ALOX5	rs2115819	FEV1	USA	[26]
	MRP1	rs119774	FEV1	USA	
	ALOX5	Sp1 motif	Asthma exacerbation	USA	
	LTA4H	rs2660845	Asthma exacerbation	USA	
	LTC4S	rs730012	Asthma exacerbation	USA	
Klotsman <i>et al.</i> (2007)	ADRB2	rs1042714 and rs1042711	FEV1	USA	[28]
	NR3C1	rs6188 and rs6196	FEV1	USA	
	ALOX5	rs4987105, rs4986832 and Sp1 motif	AM PEF	USA	
	CysLTR2	rs912277 and rs912278	AM PEF	USA	

*LTRA requirement: mean montelukast dose required per month (mg/month) to maintain asthma control for one year, .

[‡]These studies were done for aspirin-intolerant asthmatic patients.

AM PEF: Weakly mean morning peak expiratory flow; FEV1: Forced expiratory volume in 1 s; FVC: Forced vital capacity;

LTRA: Leukotriene-receptor antagonist.

two *TXA2R* polymorphisms (795T>C and 924T>C) and LTRA dose requirements for controlling asthma symptoms [29].

T-box expressed in T cells (*TBX21*) encodes the transcription factor T-bet, which controls the T-box and ultimately influences naive T-lymphocyte development. *TBX21* has been implicated in asthma pathogenesis. The -1993T>C SNP of the *TBX21* promoter was recently shown to be significantly associated with increased risk for AIA in a Japanese population [40], although this association has not been reported in other populations. No published data exist regarding pharmacogenetics of this gene related to drug responses to leukotriene modifiers in either ATA or AIA patients.

All the candidate genes associated with variable responses to leukotriene modifiers in asthmatic patients, including AIA patients, are summarized in Table 1 and the pharmacogenetic effects of each gene in response to leukotriene modifiers is summarized in Table 2, in which the first two studies were performed in AIA patients.

Future perspective

Most genetic and pharmacogenetic studies in AIA patients have focused on leukotriene-related genes and drug responses to leukotriene modifiers. The *CysLTR1* gene polymorphism and *HLA-DPB1*0301* allele may be useful genetic

markers for determining AIA susceptibility and for independently predicting LTRA requirements for long-term management of AIA symptoms. However, these studies are largely preliminary, and further studies in patients exhibiting the same degree of asthma severity and in larger cohorts of AIA patients from a variety of populations are needed to confirm these hypotheses.

ALOX5, LTC4S, PTGER2, *TXA2R* and LTC4S are viable future targets for pharmacogenetic studies in AIA patients. Their pharmacogenetic effects on other asthma drugs, including long-acting β_2 agonists and corticosteroids, should be evaluated in larger cohorts of AIA patients. Additional molecular genetic studies, including whole-genome association studies in order to identify susceptible genetic markers for AIA would provide potential molecular markers for predicting drug-response variability among AIA patients.

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Executive summary**Clinical features of aspirin-intolerant asthma**

- Chronic overproduction of cysteinyl leukotriene is a common characteristic of aspirin-intolerant asthma (AIA).
- A leukotriene-receptor antagonist (LTRA) has been recommended as the first-line drug in the long-term management of AIA patients.

Molecular genetic mechanisms and pharmacogenetics of AIA

- *HLA-DPB1*0301* and *CysLTR1* promoter polymorphism may be potential genetic markers for the AIA phenotype and could be used independently for predicting favorable responses to LTRA.
- *PTGER2*, *TXA2R*, *TBX21* and unknown sites of *LTC4S* and *CysLTR2* gene polymorphisms may be candidate genes for the pharmacogenetic study of leukotriene modifiers for AIA patients.

Conclusion

- *ALOX5*, *LTC4S*, *PTGER2*, *TXA2R* and *LTC4S* are viable future targets for pharmacogenetic studies in AIA patients.
- Molecular genetic studies identifying susceptible genetic markers for AIA would help elucidate potential molecular targets for predicting drug-response variability in AIA patients.

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