

REVIEW ARTICLE

# What do we know about the genetics of aspirin intolerance?

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## SUMMARY

Although acetylsalicylic acid is prescribed for a broad range of diseases, it can induce a wide array of clinically recognized hypersensitivity reactions, including aspirin-intolerant asthma (AIA) with rhinitis and aspirin-intolerant urticaria (AIU) with anaphylaxis. Altered eicosanoid metabolism is the generally accepted mechanism of aspirin intolerance; the overproduction of cysteinyl leucotrienes has been suggested to play a causative role in both AIA and AIU. Genetic markers suggested for AIA include *HLA-DPBI\*0301*, *leucotriene C4 synthase (LTC4S)*, *ALOX5*, *CYSLT*, *PGE2*, *TBXA2R* and *TBX21*. Similarly, *HLA-DB1\*0609*, *ALOX5*, *FCER1A* and *HNMT* have been identified as possible genetic markers for AIU. An additional low-risk genetic marker for AIA is *MS4A2*, which encodes the beta-chain of *FCER1*. Other single and sets of two or more interacting genetic markers are currently being investigated. Analyses of the genetic backgrounds of patients with AIA and AIU will promote the development of early diagnostic and therapeutic interventions, which may reduce the incidence of AIA and AIU.

**Keywords:** aspirin-intolerant asthma, aspirin-intolerant urticaria, genetic marker, polymorphism

## BACKGROUND

Acetylsalicylic acid (ASA) is a commonly prescribed drug because of its multifunctional activity, including the prevention of stroke and myocardial infarction. Although most patients with asthma,

rhinitis and urticaria can tolerate aspirin, some report that their symptoms are exacerbated by it. Aspirin ingestion can induce a wide range of clinically recognized allergic reactions, including aspirin-intolerant asthma (AIA), aspirin-intolerant urticaria/angioedema (AIU), chronic rhinitis and anaphylaxis. The prevalence of aspirin hypersensitivity in the general population ranges from 0.6 to 2.5%. In adult asthmatics, this increases to 4.3–11% (8.8% in Finland, 4.3% in Poland and 10.5% in Australia) (1–3). In terms of pathogenesis, altered eicosanoid metabolism is thought to be responsible for aspirin intolerance, including AIA and AIU. A number of reports have suggested that the overproduction of cysteinyl leucotrienes (Cys-LTs) is a major factor in both AIA and AIU. In this review, we summarize our current understanding of the genetic mechanisms of aspirin intolerance with a particular focus on the genetic polymorphisms believed to be associated with AIA and AIU.

## CLINICAL MANIFESTATIONS OF ASPIRIN INTOLERANCE

Aspirin intolerance is divided into two general types, AIA and AIU, which are described below.

### AIA

The progression of AIA from the upper to lower respiratory tract involves a characteristic sequence of persistent asthmatic symptoms with intense eosinophilic infiltration into the upper and lower airways. Symptom severity is generally moderate to severe. AIA occurs more commonly in women (two-thirds of patients) than in men. It usually begins during adulthood, at an average age of 30 years, as persistent rhinitis with or without nasal polyposis. Most cases of AIA are non-atopic. Some patients also exhibit allergic asthma with

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sensitivity to common inhalant allergens. With respect to pathogenesis, autoimmune mechanisms (4) and close associations with infections have been suggested and the possible involvement of a specific IgE response to staphylococcal superantigens such as staphylococcal enterotoxin A (SEA), staphylococcal enterotoxin B and toxic shock syndrome toxin 1 has been proposed (5).

### AIU

The ingestion of aspirin can induce two types of AIU: aspirin-intolerant acute urticaria and aspirin-intolerant chronic urticaria (AICU). Acute and chronic urticaria may be distinguished on the basis of the severity and duration of the urticarial symptoms. Chronic urticaria is characterized by urticarial symptoms that last longer than 6 weeks and are more severe than those in patients with acute urticaria. Most patients with chronic urticaria tolerate aspirin well and, in the absence of any aetiology, may be diagnosed with chronic idiopathic urticaria. The few clinical parameters associated with AICU are atopy, a high total serum IgE value and the presence of thyroid and anti-nuclear antibodies (6).

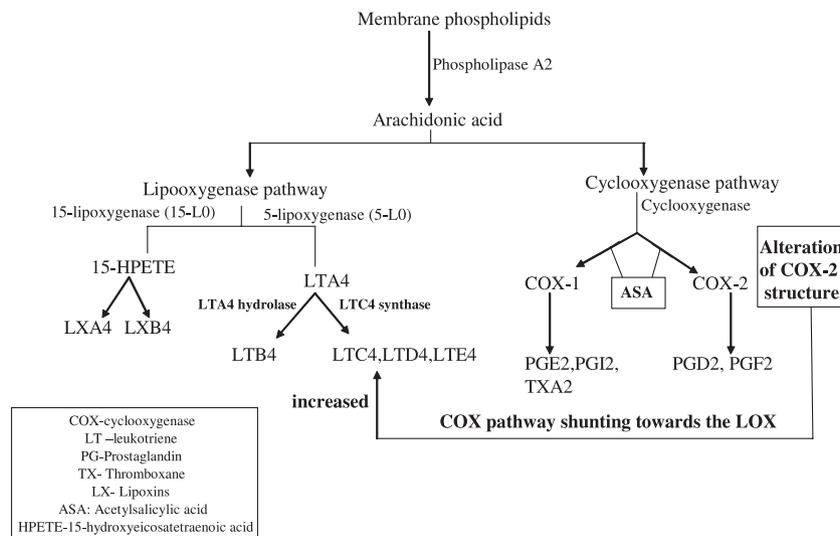
### DIAGNOSIS

A carefully controlled challenge test with aspirin is one way to confirm ASA sensitivity. An oral

challenge is common in cases of AIU because it mimics the natural route of exposure for AIU patients. In contrast, for patients with AIA, bronchoprovocation testing is widely accepted for the confirmation of ASA sensitivity, as a bronchial challenge is safer and faster than oral testing, although it is somewhat less sensitive. After lysine-ASA inhalation, a fall in the forced expiratory volume in 1 s (FEV1) of more than 20% compared with baseline is a positive result for ASA sensitivity (7). Measuring the amount of 15-hydroxyeicosatetraenoic acid (15-HETE) produced by peripheral blood cells in response to aspirin, referred to as aspirin-sensitive patient identification, has been suggested as a specific *in vitro* test (8). Another *in vitro* diagnostic test is the basophil activation test or a combined test for the evaluation of basophil activation and release of basophil sulfidoleucotrienes in response to aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) (9). However, insufficient validation is the chief problem with *in vitro* diagnostic testing. Thus, challenge tests remain the golden standard for identifying ASA sensitivity in patients with AIA or AIU.

### UPDATE ON THE PATHOGENESIS OF AIA AND AIU

Aspirin intolerance is likely to be associated with abnormalities in arachidonic acid metabolism,



**Fig. 1.** Arachidonic acid metabolic pathway via cyclooxygenase (COX) and lipoxygenase (LOX) pathway. Acetylsalicylic acid inhibits COX pathway and shunts arachidonic acid pathway towards LOX pathway and increased production of Cys-LTs such as LTC4, LTD4 and LTE4.

which include both the lipooxygenase (LOX) and cyclooxygenase (COX) pathways (Fig. 1). Under normal physiological conditions, arachidonic acid is metabolized via the COX pathway to generate prostaglandin E<sub>2</sub> (PGE<sub>2</sub>), prostacyclin I<sub>2</sub> and thromboxanes whereas inflammatory conditions lead to the production of metabolites such as prostaglandin D<sub>2</sub> (PGD<sub>2</sub>) and prostaglandin F<sub>2</sub>. In contrast, the LOX pathway produces leucotrienes A<sub>4</sub> (LTA<sub>4</sub>), B<sub>4</sub> (LTB<sub>4</sub>) and C<sub>4</sub> (LTC<sub>4</sub>) as metabolites. 15-HETE, a more stable form of hydroxyperoxyeicosatetraenoic acid is another important product, which acts as an anti-inflammatory mediator and functional antagonist of leucotrienes (10).

Aspirin-induced inhibition of the COX pathway that leads to asthmatic attacks, shunting towards the LOX pathway and enhanced Cys-LT production, has been described (11). Abnormal regulation of the LOX pathway in patients with AIA has been suggested as the cause of asthmatic attacks. It has been reported that decreased lipoxin production in AIA, compared with aspirin-tolerant asthma (ATA), correlated with increased Cys-LT action in patients with AIA (12); thus, Cys-LTs have emerged as major mediators of AIA pathogenesis. Cys-LTs exert their effects by binding to Cys-LT receptors, Cys-LTR1 and Cys-LTR2 (13, 14). Recently, third receptor, named GPR17, has also been identified for Cys-LTs (15). The overexpression of Cys-LTR1 was detected in the nasal mucosa of patients with AIA vs. those with ATA (16). Cys-LTR1 can be blocked by leucotriene receptor antagonists (LTRAs), whereas Cys-LTR2 is resistant to most LTRAs. Elevated levels of Cys-LTs are a common feature of both pathways; however, further elevation of the Cys-LT levels in the urine, sputum, peripheral blood and exhaled breath can be measured after aspirin challenge in individuals with AIA (17).

Aspirin intolerance is associated with both COX-1 and COX-2. Aspirin and NSAIDs inhibit both COX-1 and COX-2, with a greater effect on COX-1. COX-2 inhibitors are usually tolerated by patients with AIA (18). COX-2 expression was found to be downregulated in nasal polyps collected from patients with AIA (19). Decreased production of PGE<sub>2</sub> by the nasal epithelial cells in patients with AIA has also been reported (20), and decreased levels of PGE<sub>2</sub> have been reported in the peripheral blood and cultured bronchial fibroblasts of patients with ASA-intolerant rhinitis (21). Moreover,

reduced PGE<sub>2</sub> production in airway smooth muscle cells has been shown to downregulate COX-2 mRNA expression (22). In addition, eosinophil infiltration into the upper and lower airways is a key feature of AIA. The bronchial mucosa of patients with AIA also shows elevated interleukin (IL)-5 expression and enhanced local production of IL-5. Similarly, increased numbers of mast cells and eosinophils have been observed in the bronchial mucosa of AIA patients (23, 24). The PGD<sub>2</sub> concentration is significantly higher in patients with AIA than in patients with ATA.

A recent study showed that eotaxin-2 is differentially secreted in patients with asthma, according to the level of aspirin intolerance, and that secretion is not time dependent in response to aspirin-provocation testing in patients with AIA or ATA. It therefore appears that eotaxin-2 may be upregulated and may act differently in patients with ATA (25). Similarly, eicosanoid alterations have been detected in patients with AIU.

#### GENETIC MARKERS OF AIA AND AIU

##### **HLA-DPB1\*0301, a marker for AIA, and HLA-DRB1\*1302 and HLA-DB1\*0609, markers for AIU**

Most current research is focused on the genetic mechanism of aspirin intolerance in AIA and AIU. As a result, several genetic markers have been identified that may be used to distinguish AIA from AIU. The HLA allele *DPB1\*0301* was recently identified as a strong marker for AIA, as patients with this allele showed typical characteristics of AIA such as decreased FEV<sub>1</sub> levels and increased prevalence of rhinosinusitis with nasal polyps (26). Moreover, this allele is significantly associated with a greater LTRA requirement for controlling asthmatic symptoms in the long-term management of AIA (27). In comparison, the alleles *HLA-DRB1\*1302* and *HLA-DB1\*0609* are more common in patients with AIU than in patients with AIA and normal controls, suggesting an association of these two markers with AIU (28).

##### *Leucotriene-related genes*

There is clear evidence for the involvement of Cys-LTs in AIA. A previous study conducted in a Polish

population showed an association between the *LTC4S* -444A>C promoter polymorphism and AIA (29, 30); interestingly, the C allele was a risk factor for AIA in that study but was not identified as such in studies of Japanese, American and Korean populations (31, 32). In a Japanese population, patients carrying the -444A allele showed an increase in urinary leucotriene E4 after aspirin challenge (7). The overproduction of Cys-LTs was also shown to be associated with the *LTC4* -444A>C polymorphism in cases of chronic urticaria involving aspirin sensitivity; however, this was not the case in studies involving Spanish and Korean populations.

*ALOX5* is also believed to be involved in AIA. An association was previously reported between an *ALOX* gene promoter polymorphism and the transcription factor SP1; subsequently, the same polymorphism was found to be associated with airway hyperresponsiveness in a Korean population (33). Furthermore, a lack of association was noted between *ALOX5*-activating protein (*ALOX5AP* 218A>G), *COX 2* (*COX-2* -162C>G, 10T>C and 228G>A), and Cys-LTR1 (*CYS-LTR1* 927T>C) with AIA in a Korean population (8); however, an association was detected between *ALOX5* ht1 (G-C-G-A) and the development of AIA. A significant difference in genotype frequency for the -1708G>A polymorphism of *ALOX5* was detected between AIU and AIA patients; specifically, the frequency of the *ALOX5* -1708A allele was significantly lower in the AIU group than in the AIA group (34). However, no significant differences were detected for any other single nucleotide polymorphism (SNP), suggesting that *ALOX5* may be more important as a marker for AIA than AIU.

#### **Cys-LT polymorphisms and AIA: a CYS-LTR1 promoter polymorphism**

We previously reported a significant association between three SNPs (-634C>T, -475A>C and -336A>G) in the 5'-upstream region of *CYS-LTR1* and AIA in males. An *in vitro* functional study in Jurkat T cells and A549 lung epithelial cells revealed increased promoter activity in an ht2 (T-C-G) construct compared with an ht1 (C-A-A) construct (35). The increased promoter activity suggests that these polymorphisms may modulate

Cys-LTR1 expression to increase AIA susceptibility. Similarly, the mRNA expression of *CYS-LTR1* in peripheral mononuclear cells was significantly increased *in vivo* when patients with AIA were exposed to aspirin (36). The frequencies of several rare alleles of *CYS-LTR2* (-819T>G, 2078C>T and 2534A>G) were also higher in patients with AIA than in those with ATA; moreover, the former two SNPs caused a greater reduction in FEV1 following aspirin provocation.

#### **Histamine-related high-affinity IgE receptor polymorphisms in AIA and AIU**

We analysed six SNPs present in the three genes encoding FCER1 [high affinity immunoglobulin epsilon receptor gamma-subunit (*FCER1A*), high affinity immunoglobulin epsilon receptor beta subunit (*MS4A2*) and high affinity immunoglobulin epsilon receptor gamma-subunit (*FCER1G*)] and found that the frequency of the -344T allele of *FCER1A* was significantly higher in patients with aspirin tolerant chronic urticaria (-344T>C). An *in vitro* analysis revealed that the same allele showed increased promoter activity in both A549 and RBL-2H3 cells, and that Myc-associated zinc finger proteins preferentially bound the -344C promoter. In addition, AICU patients with the CT genotype showed greater anti-IgE-mediated histamine release than did those with the CC genotype (37). AICU patients with the AG/GG genotype at the *MS4A2* E237G locus and the *FCER1G* -237G allele were significantly more likely to be atopic than those with the AA genotype. The anti-IgE antibody-induced release of histamine from basophils was significantly higher in patients with AICU than in non-atopic controls and was increased in atopic patients compared with non-atopic patients. The *MS4A2* E237G and *FCER1G* -237T>G polymorphisms may be associated with the rate of atopy, which in turn could increase the release of histamine from basophils and lead to the development of AICU (38). This polymorphism was also studied in patients with AIA, and a significant difference in the genotype frequencies of *FCER1G* -237A>G was detected between AIA and ATA patients, in both co-dominant and recessive analysis models. Similarly, AIA patients carrying the homozygous AA genotype of *FCER1G* -237A>G exhibited significantly higher total serum

**Table 1.** Gene markers for aspirin intolerance

Gene	SNPs	Aspirin intolerance	Risk
<i>HLA</i>	DPB1*0301	AIA	Higher
<i>HLA</i>	DB1*0609	AIU	Higher
<i>HLA</i>	DRB1*1302	AIU	Higher
<i>LTC4S</i>	-444A>C	AIA	Higher
<i>ALOX5</i>	-1708G>A	AIA and AIU	Higher
<i>CYSLTR1</i>	-634C>T	AIA	Higher
<i>CYSLTR2</i>	-819T>C	AIA	Higher
<i>TBXA2R</i>	+795T>C	AIA	Higher
<i>FCER1A</i>	-344C>T	AICU	Higher
<i>MS4A2</i>	E237G	AIA	Higher
<i>FCER1G</i>	-237T>C	AIA and AICU	Lower
<i>HNMT</i>	939A>G	AICU	Higher

*HLA*, human leucocyte antigen; *LTC4S*, leucotriene C4 synthase; *ALOX5*, arachidonate 5-lipoxygenase; *CYSLTR1*, cysteinyl leucotriene receptor 1; *CYSLTR2*, cysteinyl leucotriene receptor 2; *TBXA2R*, thromboxane A2 receptor; *FCER1A*, high affinity immunoglobulin epsilon receptor alpha-subunit; *MS4A2*, high affinity immunoglobulin epsilon receptor beta-subunit; *FCER1G*, high affinity immunoglobulin epsilon receptor gamma-subunit; *HNMT*, histamine N-methyltransferase; AIA, aspirin-intolerant asthma; AIU, aspirin-intolerant urticaria; AICU, aspirin-intolerant chronic urticaria.

IgE levels than did those with the GG/AG genotype. Finally, AIA patients expressing the CT/TT genotype at *FCER1A* -344C>T showed a higher prevalence of serum IgE specific to SEA than did those with the CC genotype (39).

#### Histamine-related genes and AIU

A number of histamine-related genes such as those encoding histamine N-methyltransferase (*HNMT*), histamine receptor type 1 (*HRH1*) and histamine receptor type 2 (*HRH2*) were compared between patients with AIU and normal controls. No significant association was found between these genes and the AIU phenotype in a Korean population; however, the *HNMT* 939A>C polymorphism was associated with AICU through the regulation of enzymatic activity and histamine content. An *in vitro* functional study using HMC-1 cells demonstrated that the 939A allele, as compared with the 939G allele, conferred lower *HNMT* mRNA stability, *HNMT* expression and *HNMT* enzymatic activity, with increased histamine release (40).

#### Other important markers of AIA

Several other markers of AIA, including *PGE2*, *TBXA2R* and *TBX21*, have also been reported. An association was identified between a functional SNP of the gene encoding PGE2 receptor subtype 2 (*EP2*) and the risk for AIA in a Japanese population (41). A second polymorphism, *TBXA2R* +795T>C, was also shown to be associated with AIA susceptibility in a Korean population (42). Furthermore, the -1993T>C SNP in the promoter region of *TBX21* was associated with AIA in a Japanese population (43).

#### Gene-gene interaction

Recently, gene-gene interactions have also been proposed in the pathogenesis of AIA. The study showed that genetic effects of *Cys-LTR2* and *LTC4S* -444A>C synthesis increased the lower level of FEV1 after lysine-ASA inhalation (44). In addition, *TBXA2R* 795T>C polymorphism was associated with *HLA DPB1\*0301* in AIA patients compared with ATA (42).

A recent publication by Kim *et al.* has reported a significant epistatic effect with a four-locus genetic interaction in the susceptibility to aspirin intolerance in asthmatic patients. The four-locus SNP set including adrenergic, beta-2-receptor, *B2ADR* 46A>G, chemokine (C-C motif) receptor 3, *CCR3* -520T>G, *CysLTR1* -634C>T and *FCER1B* -109T>C was found to be a useful genetic marker for the AIA phenotype (45). These studies showed that further investigations are essential to determine how genes interact with each other to produce AIA pathogenesis.

#### CONCLUSIONS

Aspirin intolerance often produces a more severe phenotype in asthmatics and individuals with urticaria. The proper diagnosis of aspirin sensitivity in these patients is a challenge, despite the availability of diagnostic techniques. Various hypotheses have been put forward for aspirin intolerance, with most focussing on arachidonic acid metabolism. Suggested genetic markers for AIA include *HLA-DPB1\*0301*, leucotriene C4 synthase (*LTC4S*), *ALOX5*, *CYSLT*, *PGE2*, *TBXA2R*, *TBX21*, *MS4A2* together with the four-locus SNP

set *B2ADR* 46A>G, *CCR3* -520T>G, *CysLTR1* -634C>T and *FCER1B* -109T>C. *HLA-DB1\*0609*, *ALOX5*, *FCER1A* and *HNMT* have been identified for AIU (Table 1). Functional studies are required for the development of new diagnostic and therapeutic options. These may lead to greater emphasis on the early detection and prevention of aspirin intolerance.

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