

# Genetic mechanism of aspirin-induced urticaria/angioedema

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## Purpose of review

Aspirin-induced urticaria/angioedema is a major aspirin-related hypersensitivity often associated with aspirin-intolerant asthma. Genetic studies on aspirin-intolerant asthma have shown chronic overproduction of cysteinyl leukotrienes. The genetic analysis of aspirin-induced urticaria/angioedema is limited, however.

## Recent findings

A recent study on HLA genotypes has suggested that the HLA alleles *DRB1*\*1302 and *DQB1*\*0609 may be genetic markers for aspirin-induced urticaria/angioedema. A polymorphism study that examined nine single-nucleotide polymorphisms of five leukotriene-related genes [*ALOX5* (encoding 5-lipoxygenase), *ALOX5AP* (5-lipoxygenase-activating protein), *PTGS2* (cyclooxygenase 2), *LTC4S* (leukotriene C4 synthase), and *CYSLTR1* (cysteinyl leukotriene receptor 1)] found that promoter polymorphisms of *ALOX5* (−1708A>G) and *CYSLTR1* (−634C>T) were significantly different between aspirin-intolerant asthma and aspirin-induced urticaria/angioedema, suggesting different contributions to the lipoxygenase pathway. A second polymorphism study, conducted on histamine-related genes, did not find any significant associations with aspirin-induced urticaria/angioedema for the genes *HNMT* (encoding histamine N-methyltransferase), *HRH1* or *HRH2* (encoding histamine receptor types 1 and 2 respectively), or the gene encoding high-affinity IgE receptor *Iβ* (*FcεRIβ*); however, the *FcεRIα* gene promoter polymorphism was significantly associated with aspirin-induced urticaria/angioedema. This finding has been supported by *in vitro* functional studies.

## Summary

The HLA alleles *DRB1*\*1302 and *DQB1*\*0609, and the *ALOX5* and *FcεRIα* promoter polymorphisms, may contribute to the pathogenesis of aspirin-induced urticaria/angioedema. Further investigation to identify candidate genetic markers would help to elucidate the pathogenic mechanism of this condition.

## Keywords

aspirin-induced urticaria, gene polymorphism, histamine, HLA marker, leukotriene-related genes

## Abbreviations

|                |                                                 |
|----------------|-------------------------------------------------|
| <b>AIA</b>     | aspirin-intolerant asthma                       |
| <b>AIU</b>     | aspirin-induced urticaria/angioedema            |
| <b>AICU</b>    | aspirin-intolerant chronic urticaria/angioedema |
| <b>ALOX5</b>   | 5-lipoxygenase                                  |
| <b>ALOX5AP</b> | 5-lipoxygenase-activating protein               |
| <b>CYSLTR1</b> | cysteinyl leukotriene receptor 1                |
| <b>FcεR1</b>   | high-affinity IgE receptor                      |
| <b>HNMT</b>    | histamine N-methyltransferase                   |
| <b>HRH1</b>    | histamine receptor type 1                       |
| <b>HRH2</b>    | histamine receptor type 2                       |
| <b>LTC4S</b>   | leukotriene C4 synthase                         |
| <b>PTGS2</b>   | cyclooxygenase 2                                |
| <b>SNP</b>     | single-nucleotide polymorphism                  |

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1528-4050

## Introduction

Aspirin ingestion can induce several allergic reactions, such as aspirin-intolerant asthma (AIA), aspirin-induced urticaria/angioedema (AIU), anaphylaxis and, rarely, hypersensitivity pneumonitis [1,2]. Among these, AIU is the most prevalent. Although the pathogenic mechanism of AIA is not completely understood, chronic overproduction of cysteinyl leukotrienes derived from cyclooxygenase inhibition is a consistent finding [3–6,7<sup>\*</sup>]. Recent studies have shown an increased number of cells expressing cysteinyl leukotriene receptor 1 (*CYSLTR1*) in the nasal mucosa, especially in AIA patients [8], and have identified a promoter polymorphism of the *CYSLTR1* gene related to increased expression [9]. In contrast with AIA, knowledge about the pathogenic mechanism of AIU is limited; however, recent reports [10–12] have suggested that overproduction of cysteinyl leukotrienes may be involved. In this review, we summarize recent findings on the molecular genetic mechanisms of AIU.

## Clinical phenotype of aspirin-induced urticaria/angioedema

Aspirin ingestion can induce acute and chronic urticaria with angioedema, with chronic urticaria defined as patients suffering from daily urticaria symptoms for more than 6 weeks [1,2,10]. AIU can be confirmed by an oral aspirin challenge test [11,12]. Based on oral aspirin challenge test results, chronic urticaria patients were classified into two groups: aspirin-intolerant chronic urticaria (AICU), and chronic urticaria with a negative response to aspirin (chronic idiopathic urticaria, CIU). In our recent study [13], AICU patients were younger and had a higher atopy rate, higher total serum IgE, and a greater association with a history of asthma. No significant differences were noted in the prevalence of thyroid auto-antibodies, anti-nuclear

Curr Opin Allergy Clin Immunol 6:266–270. © 2006 Lippincott Williams & Wilkins.

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Current Opinion in Allergy and Clinical Immunology 2006, 6:266–270

antibody, or other clinical parameters between AIU and CIU patients.

### Genetic approach to aspirin-induced urticaria/angioedema

Current studies to investigate the genetic mechanism of aspirin-induced urticaria/angioedema have been performed using two approaches. The first is to identify HLA gene markers for aspirin-induced urticaria/angioedema, and the second is to identify genetic polymorphisms that increase or decrease the susceptibility of this phenotype.

#### HLA gene markers for patients with aspirin-induced urticaria/angioedema

We have demonstrated an association between HLA genotype and AIU by using a high-resolution analysis technique, confirming a strong positive association between the HLA *DRB1*\*1302 and HLA *DQB1*\*0609 alleles in AIU [14<sup>••</sup>]; allelic frequencies of HLA *DRB1*\*1302 and HLA *DQB1*\*0609 were significantly higher in AIU patients than in AIA patients or in normal control subjects (Table 1). When clinical parameters were analyzed according to the presence of these two alleles, the patients carrying HLA *DRB1*\*1302 or HLA *DQB1*\*0609 ( $28.2 \pm 7.0$  and  $29.0 \pm 6.9$  years respectively) were significantly younger (by 10 years) than those without either allele ( $38.0 \pm 13.6$  and  $36.4 \pm 13.4$  years respectively), indicating that patients with these alleles develop AIU at an earlier age. No significant differences were found in the other clinical parameters, including atopy and total serum IgE, between the two groups. It has

been reported that AIU has been associated with various auto-antibodies [13,15]. When we analyzed any associations between HLA *DRB1*\*1302 and *DQB1*\*0609 on the one hand, and the prevalence of serum anti-nuclear antibody, thyroid auto-antibodies and IgG to *Helicobacter pylori* on the other, no associations were found between them. These findings suggested that the HLA alleles *DRB1*\*1302–*DQB1*\*0609–*DPB1*\*0201 may be a strong genetic marker for determining AIU phenotype [14<sup>••</sup>]. Further studies will be needed to explore the genetic interactions between these HLA alleles and immunologic markers and gene polymorphisms.

#### Leukotriene-related gene polymorphisms in aspirin-induced urticaria/angioedema

Although there is no clear evidence for the involvement of cysteinyl leukotrienes in AIU, it has been proposed that they may participate in the pathogenesis of AIU, as in AIA [10–12]. Immunopharmacological studies have demonstrated that mast cells and basophils are activated to a greater extent in patients with AIU [16]. Mastalerz *et al.* [17] demonstrated the overproduction of cysteinyl leukotrienes in association with a polymorphism of the leukotriene C4 synthase gene (*LTC4S*), –444 A>C, in patients with chronic urticaria with aspirin sensitivity; the frequency of subjects carrying the C allele of *LTC4S* –444A>C was significantly higher among chronic urticaria patients with positive aspirin challenge than among patients who did not react to aspirin. Moreover, AIU was shown to be aggregated in families inheriting the *LTC4S* –444C allele [18<sup>•</sup>]; the frequency of the –444C allele

**Table 1 Allele frequencies of HLA *DRB1* and *DQB1* in study subjects**

| HLA                 | AIU ( <i>n</i> = 188) | AIA ( <i>n</i> = 152) | NC ( <i>n</i> = 370) | <i>P</i> value (OR) |              |
|---------------------|-----------------------|-----------------------|----------------------|---------------------|--------------|
|                     |                       |                       |                      | AIU vs AIA          | AIU vs NC    |
| <i>DRB1</i> alleles |                       |                       |                      |                     |              |
| <i>DRB1</i> *0101   | 7 (3.7%)              | 3 (2.0%)              | 25 (6.8%)            | 0.0040 (0.4)        |              |
| <i>DRB1</i> *0405   | 17 (9.0%)             | 10 (6.6%)             | 29 (7.8%)            |                     |              |
| <i>DRB1</i> *0701   | 13 (6.9%)             | 8 (5.3%)              | 28 (7.6%)            |                     |              |
| <i>DRB1</i> *0803   | 14 (7.4%)             | 11 (7.2%)             | 29 (7.8%)            |                     |              |
| <i>DRB1</i> *0901   | 15 (8.0%)             | 28 (18.4%)            | 38 (10.3%)           |                     |              |
| <i>DRB1</i> *1101   | 14 (7.4%)             | 9 (5.9%)              | 19 (5.1%)            | 0.0004 (4.0)        | 0.0005 (2.5) |
| <i>DRB1</i> *1201   | 7 (3.7%)              | 5 (3.3%)              | 16 (4.3%)            |                     |              |
| <i>DRB1</i> *1202   | 7 (3.7%)              | 2 (1.3%)              | 18 (4.9%)            |                     |              |
| <i>DRB1</i> *1302   | 34 (18.1%)            | 8 (5.3%)              | 30 (8.1%)            |                     |              |
| <i>DRB1</i> *1501   | 7 (3.7%)              | 11 (7.2%)             | 26 (7.0%)            |                     |              |
| <i>DQB1</i> alleles |                       |                       |                      |                     |              |
| <i>DQB1</i> *0501   | 10 (5.3%)             | 5 (3.3%)              | 30 (8.1%)            | 0.0139 (4.3)        |              |
| <i>DQB1</i> *0503   | 9 (4.8%)              | 6 (3.9%)              | 15 (4.1%)            |                     |              |
| <i>DQB1</i> *0601   | 16 (8.5%)             | 13 (8.6%)             | 34 (9.2%)            |                     |              |
| <i>DQB1</i> *0604   | 15 (8.0%)             | 3 (2.0%)              | 18 (4.9%)            |                     |              |
| <i>DQB1</i> *0609   | 19 (10.1%)            | 3 (2.0%)              | 12 (3.2%)            |                     |              |
| <i>DQB1</i> *02     | 15 (8.0%)             | 16 (10.5%)            | 34 (9.2%)            | 0.0024 (5.6)        | 0.0008 (3.4) |
| <i>DQB1</i> *0301   | 31 (16.5%)            | 20 (13.2%)            | 56 (15.1%)           |                     |              |
| <i>DQB1</i> *0302   | 14 (7.4%)             | 21 (13.8%)            | 44 (11.9%)           |                     |              |
| <i>DQB1</i> *0303   | 19 (10.1%)            | 29 (19.1%)            | 45 (12.2%)           |                     |              |
| <i>DQB1</i> *0401   | 16 (8.5%)             | 10 (6.6%)             | 28 (7.6%)            |                     |              |

Ten frequent alleles in the aspirin-induced urticaria group are listed. AIA, aspirin-intolerant asthma; AIU, aspirin-induced urticaria/angioedema; NC, normal control; OR, odds ratio.

**Table 2** Allele and genotype frequencies of single-nucleotide polymorphisms in the candidate genes

| Gene           | Locus        | Genotype | AIU ( <i>n</i> = 101) | AIA ( <i>n</i> = 95) | NC ( <i>n</i> = 123) | <i>P</i> value |           |
|----------------|--------------|----------|-----------------------|----------------------|----------------------|----------------|-----------|
|                |              |          |                       |                      |                      | AIU vs AIA     | AIU vs NC |
| <i>ALOX5</i>   | −1708G>A     | GG       | 57 (56.4%)            | 48 (64.9%)           | 76 (67.9%)           | 0.04           | NS        |
|                |              | AG       | 33 (32.7%)            | 25 (33.8%)           | 30 (26.8%)           | 0.01           | NS        |
|                |              | AA       | 11 (10.9%)            | 1 (1.4%)             | 6 (5.4%)             | NS             | NS        |
|                |              | <i>q</i> | 0.272                 | 0.182                | 0.188                | 0.06           | 0.04      |
|                | 270G>A       | GG       | 92 (91.1%)            | 72 (90.0%)           | 98 (85.2%)           | NS             | NS        |
|                |              | AG       | 9 (8.9%)              | 8 (10.0%)            | 16 (13.9%)           | NS             | NS        |
|                |              | AA       | 0                     | 0                    | 1 (0.9%)             | NS             | NS        |
|                |              | <i>q</i> | 0.045                 | 0.05                 | 0.078                | NS             | NS        |
|                | 1728A>G      | AA       | 80 (81.6%)            | 71 (92.21%)          | 98 (86.0%)           | NS             | NS        |
|                |              | AG       | 17 (17.3%)            | 6 (7.8%)             | 16 (14.0%)           | NS             | NS        |
| <i>ALOX5AP</i> | 218A>G       | GG       | 1 (1.0%)              | 0                    | 0                    | 0.05           | NS        |
|                |              | <i>q</i> | 0.097                 | 0.039                | 0.07                 | 0.04           | NS        |
|                | 218A>G       | AA       | 99 (98.0%)            | 90 (98.9%)           | 119 (98.3%)          | NS             | NS        |
|                |              | AG       | 2 (2.0%)              | 1 (1.1%)             | 2 (1.7%)             | NS             | NS        |
|                |              | GG       | 0                     | 0                    | 0                    | NS             | NS        |
|                |              | <i>q</i> | 0.01                  | 0.005                | 0.008                | NS             | NS        |
| <i>PTGS2</i>   | −162C>G      | CC       | 95 (96.9%)            | 86 (98.9%)           | 114 (96.6%)          | NS             | NS        |
|                |              | CG       | 3 (3.1%)              | 1 (1.1%)             | 4 (3.4%)             | NS             | NS        |
|                |              | GG       | 0                     | 0                    | 0                    | NS             | NS        |
|                |              | <i>q</i> | 0.015                 | 0.006                | 0.017                | NS             | NS        |
|                | 10T>G        | TT       | 96 (97.0%)            | 89 (98.9%)           | 120 (98.4%)          | NS             | NS        |
|                |              | GT       | 3 (3.0%)              | 1 (1.1%)             | 2 (1.6%)             | NS             | NS        |
|                |              | GG       | 0                     | 0                    | 0                    | NS             | NS        |
|                |              | <i>q</i> | 0.015                 | 0.006                | 0.008                | NS             | NS        |
|                | R228H* (G>A) | GG       | 97 (97.0%)            | 84 (98.8%)           | 114 (96.6%)          | NS             | NS        |
|                |              | AG       | 3 (3.0%)              | 1 (1.2%)             | 4 (3.4%)             | NS             | NS        |
| <i>LTC4S</i>   | −444A>C      | AA       | 0                     | 0                    | 0                    | NS             | NS        |
|                |              | <i>q</i> | 0.015                 | 0.006                | 0.017                | NS             | NS        |
|                | −444A>C      | AA       | 72 (72.0%)            | 64 (71.9%)           | 85 (72.6%)           | NS             | NS        |
|                |              | AC       | 24 (24.0%)            | 23 (25.8%)           | 25 (21.4%)           | NS             | NS        |
|                |              | CC       | 4 (4.0%)              | 2 (2.2%)             | 7 (6.0%)             | NS             | NS        |
|                |              | <i>q</i> | 0.16                  | 0.156                | 0.167                | NS             | NS        |
| <i>CYSLTR1</i> | −634C>T      | CC       | 60 (59.4%)            | 68 (42.2%)           | 137 (53.1%)          | 0.024          | NS        |
|                |              | CT       | 20 (19.8%)            | 49 (30.4%)           | 64 (24.8%)           | NS             | NS        |
|                |              | TT       | 21 (20.8%)            | 44 (27.3%)           | 57 (22.1%)           | 0.08           | NS        |
|                |              | <i>q</i> | 0.307                 | 0.425                | 0.345                | 0.007          | NS        |

*ALOX5*, 5-lipoxygenase gene; *ALOX5AP*, 5-lipoxygenase-activating protein gene; *PTGS2*, cyclooxygenase 2 gene; *LTC4S*, leukotriene C4 synthase gene; *CYSLTR1*, cysteinyl leukotriene receptor 1 gene; AIA, aspirin-intolerant asthma; AIU, aspirin-intolerant urticaria; NC, normal controls; *n*, number of patients; *q*, minor allele frequency; R, arginine; H, histidine; NS, not significant. Each *P* value was calculated with co-dominant, dominant and recessive models.

was significantly higher in patients who were sensitive to aspirin than in those who were not sensitive. No association was found, however, between the *LTC4S* −444A>C polymorphism with the phenotype of non-steroidal anti-inflammatory drug (NSAID)-induced isolated periorbital angioedema in a Spanish population [19] or a Korean population [20\*].

We also investigated the genetic polymorphisms of candidate genes encoding enzymes involved in leukotriene synthesis in a Korean population [20\*]. We examined nine single-nucleotide polymorphisms (SNPs) of four leukotriene-related genes: 5-lipoxygenase (*ALOX5*; −1708G>A, 270G>A and 1728G>A), 5-lipoxygenase-activating protein (*ALOX5AP*; 218A>G), cyclooxygenase 2 (*PTGS2*; −162C>G, 10T>G and 228G>A), *LTC4S* (−444A>C), and *CYSLTR1* (−634C>T). We found that the polymorphisms of *ALOX5* (−1708G>A) and *CYSLTR1* (−634C>T) showed significant differences

in genotype frequency between AIU and AIA patients; the frequency of the *ALOX5* −1708A allele was significantly higher in the AIU group than in the normal control group, whereas the frequency of the *CYSLTR1* −634T allele was significantly lower in the AIU group than in the AIA group (Table 2). These results suggest that *ALOX5* and *CYSLTR1* make different contributions to two major aspirin-related conditions, AIU and AIA, in the Korean population.

#### Histamine-related genes in chronic urticaria with aspirin sensitivity

Considering the pathogenic mechanism of AIU, we can speculate that polymorphisms of candidate genes involved in the release and metabolism of histamine and of histamine receptor genes may be associated with the AIU phenotype. We analyzed 11 known SNPs of the genes encoding high-affinity IgE receptor I (*FcεRIβ*), histamine *N*-methyltransferase (*HNMT*), histamine receptor type 1

**Table 3 Allele and genotype frequencies of the single-nucleotide polymorphisms in histamine-related genes**

| Gene         | Locus                | Genotype | AIU ( <i>n</i> = 110) | DA ( <i>n</i> = 53) | NC ( <i>n</i> = 99) | <i>P</i> value |           |
|--------------|----------------------|----------|-----------------------|---------------------|---------------------|----------------|-----------|
|              |                      |          |                       |                     |                     | AIU vs DA      | AIU vs NC |
| <i>MS4A2</i> | -109T>C              | TT       | 53 (48.6%)            | 23 (43.4%)          | 46 (46.5%)          | NS             | NS        |
|              |                      | CT       | 46 (42.2%)            | 24 (45.3%)          | 43 (43.4%)          | NS             | NS        |
|              |                      | CC       | 10 (9.2%)             | 6 (11.3%)           | 10 (10.1%)          | NS             | NS        |
|              | <i>Rsa</i> I_in2 G>A | <i>q</i> | 0.3                   | 0.34                | 0.32                | 0.278          | 0.673     |
|              |                      | GG       | 73 (66.4%)            | 35 (66.0%)          | 69 (70.4%)          | NS             | NS        |
|              |                      | GA       | 32 (29.1%)            | 13 (24.5%)          | 26 (26.5%)          | NS             | NS        |
|              | E237G* (A>G)         | AA       | 5 (4.5%)              | 5 (9.4%)            | 3 (3.1%)            | NS             | NS        |
|              |                      | <i>q</i> | 0.19                  | 0.22                | 0.16                | 0.482          | 0.466     |
|              |                      | AA       | 86 (78.2%)            | 40 (75.5%)          | 70 (70.7%)          | NS             | NS        |
|              | <i>Rsa</i> I_ex7 T>C | GA       | 23 (20.9%)            | 12 (22.6%)          | 27 (27.3%)          | NS             | NS        |
|              |                      | GG       | 1 (0.9%)              | 1 (1.9%)            | 2 (2.0%)            | NS             | NS        |
|              |                      | <i>q</i> | 0.11                  | 0.13                | 0.16                | 0.386          | 0.162     |
| <i>HNMT</i>  | T105I* (C>T)         | TT       | 99 (90.0%)            | 44 (84.6%)          | 89 (90.8%)          | NS             | NS        |
|              |                      | CT       | 9 (8.2%)              | 8 (15.4%)           | 8 (8.2%)            | NS             | NS        |
|              |                      | CC       | 2 (1.8%)              | 0                   | 1 (1.0%)            | NS             | NS        |
|              | 939A>G               | <i>q</i> | 0.06                  | 0.08                | 0.05                | 0.354          | 0.678     |
|              |                      | CC       | 100 (90.9%)           | 50 (94.3%)          | 89 (89.9%)          | NS             | NS        |
|              |                      | CT       | 10 (9.1%)             | 3 (5.7%)            | 10 (10.1%)          | NS             | NS        |
|              |                      | TT       | 0                     | 0                   | 0                   | NS             | NS        |
|              |                      | <i>q</i> | 0.05                  | 0.03                | 0.05                | 0.453          | 0.857     |
|              |                      | AA       | 61 (56.0%)            | 26 (50.0%)          | 48 (49.0%)          | NS             | NS        |
|              |                      | AG       | 41 (37.6%)            | 21 (40.4%)          | 39 (39.8%)          | NS             | NS        |
|              |                      | GG       | 7 (6.4%)              | 5 (9.6%)            | 11 (11.2%)          | NS             | NS        |
|              |                      | <i>q</i> | 0.25                  | 0.3                 | 0.31                | 0.54           | 0.196     |
| <i>HRH1</i>  | -17C>T               | CC       | 97 (89.8%)            | 47 (92.2%)          | 89 (90.8%)          | NS             | NS        |
|              |                      | CT       | 11 (10.2%)            | 4 (7.8%)            | 9 (9.2%)            | NS             | NS        |
|              |                      | TT       | 0                     | 0                   | 0                   | NS             | NS        |
|              |                      | <i>q</i> | 0.05                  | 0.04                | 0.05                | 0.714          | 0.858     |
| <i>HRH2</i>  | 543G>A               | GG       | 100 (91.7%)           | 48 (92.3%)          | 83 (83.8%)          | NS             | NS        |
|              |                      | AG       | 9 (8.3%)              | 4 (7.7%)            | 16 (16.2%)          | NS             | NS        |
|              |                      | AA       | 0                     | 0                   | 0                   | NS             | NS        |
|              |                      | <i>q</i> | 0.04                  | 0.04                | 0.08                | 0.824          | 0.098     |

FcεR1, high-affinity IgE receptor; *HNMT*, histamine *N*-methyltransferase gene; *HRH1*, histamine receptor type 1 gene; *HRH2*, histamine receptor type 2 gene; E, glutamate; G, glycine; T, threonine, I, isoleucine; AIU, aspirin-induced urticaria/angioedema; DA, other drug allergy; NC, normal controls; *q*, minor allele frequency; NS, not significant. Each *P* value was calculated with co-dominant, dominant, and recessive models. Logistic regression analysis was applied to control for age, sex, and atopy as co-variables.

(*HRH1*) and histamine receptor type 2 (*HRH2*) and their haplotypes in AIU patients, and compared the frequencies with those in patients exhibiting other drug allergies and in normal controls. No significant differences were observed in allele or genotype frequencies, and haplotype frequencies of all the SNPs of the FcεRIβ gene, *HNMT*, *HRH1* and *HRH2* were noted among the three groups, suggesting that the polymorphisms of the FcεRIβ

gene and the three histamine-related genes might not contribute to the development of the AIU phenotype in the Korean population (Table 3) [21\*].

Furthermore, we analyzed genetic polymorphisms of the FcεRIα gene and found a significant association of two promoter polymorphisms (-344C>T and -95 T>C) with AICU (Table 4) [22]. In particular, the genotype

**Table 4 Genotype and allele frequencies for the human high-affinity IgE receptor α chain (FcεRIα)**

| Locus   | Genotype | AICU ( <i>n</i> = 105) | ATCU ( <i>n</i> = 154) | NC ( <i>n</i> = 222) | <i>P</i> value |            |
|---------|----------|------------------------|------------------------|----------------------|----------------|------------|
|         |          |                        |                        |                      | AICU vs ATCU   | AICU vs NC |
| -344C>T | CC       | 59 (56.2%)             | 108 (70.1%)            | 148 (66.7%)          | 0.007          | 0.028      |
|         | CT       | 39 (37.1%)             | 45 (29.2%)             | 69 (31.1%)           | 0.039          | 0.062      |
|         | TT       | 7 (6.7%)               | 1 (0.6%)               | 5 (2.3%)             | 0.028          | 0.071      |
|         | <i>q</i> | 0.252                  | 0.153                  | 0.178                | 0.008          | 0.03       |
| -95T>C  | TT       | 92 (87.6%)             | 149 (96.8%)            | 200 (90.1%)          | 0.014          | 0.512      |
|         | CT       | 13 (12.4%)             | 5 (3.2%)               | 22 (9.9%)            | NA             | NA         |
|         | CC       | 0                      | 0                      | 0                    | 0.014          | 0.512      |
|         | <i>q</i> | 0.062                  | 0.016                  | 0.05                 | 0.016          | 0.524      |

AICU, aspirin-intolerant chronic urticaria; ATCU, aspirin-tolerant chronic urticaria; NC, normal healthy control; *q*, minor allele frequency; NA, not applicable. Each *P* value was calculated for co-dominant, dominant, and recessive models. Logistic regression analysis was applied to control for age and sex as co-variables.

**Table 5 Summary of genetic study for aspirin-induced urticaria/angioedema in a Korean cohort**

| Gene           | Locus | SNP               | Phenotype | Risk   | n       |
|----------------|-------|-------------------|-----------|--------|---------|
| HLA            | 6     | <i>DRB1</i> *1302 | AIU       | Higher | 188 AIU |
|                |       | <i>DQB1</i> *0609 | AIU       | Higher | 188 AIU |
| <i>ALOX5</i>   | 10q11 | −1708G>A          | AIU       | Higher | 101 AIU |
| <i>CYSLTR1</i> |       | −634C>T           | AIU       | Lower  |         |
| <i>FcεR1α</i>  | 1q23  | −344C>T           | AICU      | Higher | 95 AICU |

*ALOX5*, 5-lipoxygenase gene; *CYSLTR1*, cysteinyl leukotriene receptor 1 gene; *FcεR1α*, high-affinity IgE receptor; SNP, single-nucleotide polymorphism; AICU, aspirin-intolerant chronic urticaria/angioedema; AIU, aspirin-induced urticaria/angioedema.

and allele containing −344T occurred with a significantly higher frequency in AICU patients than in control groups (aspirin-tolerant chronic urticaria/angioedema and normal controls), whereas no significant differences were noted in the genotype and allele frequencies of the −95T>C polymorphism between the AICU and normal control groups. In addition, the genetic variants of *FcεR1α* −344C>T were shown to increase promoter activity in both the human A549 and rat RBL-2H3 cell lines. These findings suggest that the *FcεR1α* −335C>T polymorphism may contribute to the development of AICU by increasing promoter activity. Further investigation is needed to elucidate whether this genetic variant can increase histamine release and/or augment mast cell signaling, which could lead to the release of pro-inflammatory mediators.

Table 5 summarizes the genes representing the phenotype of AIU.

## Conclusion

Further information on the genetic polymorphisms of candidate genes with supporting functional studies will make it possible to elucidate the molecular mechanism of AIU and to identify the candidate genetic markers for differentiating AIU from other aspirin-related allergic conditions, possibly leading to the development of new diagnostic markers and additional therapeutic targets.

## Acknowledgements

This study was supported by a grant from the Korean Health 21 R&D Project, Ministry of Health and Welfare, Republic of Korea (03-PJ10-PG13-GD01-0002 and A050571).

## References and recommended reading

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 303).

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