INTRODUCTION

Since its introduction to medicine more than 110 years ago, aspirin has been the most commonly prescribed medication for control of pain and prevention of various vascular diseases. Aspirin (acetylsalicylic acid, ASA)-hypersensitivity refers to development of bronchoconstriction, nasal symptoms (aspirin-exacerbated respiratory diseases, AERD), and ocular and skin manifestations in asthmatics following ingestion of aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs).\(^1\) Recently, aspirin hypersensitivity has attracted a great deal of attention because of its association with severe asthma, it remains widely under-diagnosed in the asthmatic population. Oral aspirin challenge is the best method of diagnosing AERD, but this is a time-consuming procedure with serious complications in some cases. Thus, development of non-invasive methods for easy diagnosis is necessary to prevent unexpected complications of aspirin use in susceptible patients. For the past decade, many studies have attempted to elucidate the genetic variants responsible for risk of AERD. Several approaches have been applied in these genetic studies. To date, a limited number of biologically plausible candidate genes in the arachidonate and immune and inflammatory pathways have been studied. Recently, a genome-wide association study was performed. In this review, the results of these studies are summarized, and their limitations discussed. In addition to the genetic variants, changes in methylation patterns on CpG sites have recently been identified in a target tissue of aspirin hypersensitivity. Finally, perspectives on application of new genomic technologies are introduced; these will aid our understanding of the genetic pathogenesis of aspirin hypersensitivity in asthma.

Key Words: Aspirin; hypersensitivity; asthma; single nucleotide polymorphism; genome-wide association study; methylation
ated with development of AERD. Some results have not been replicated due to small sample sizes or ethnic differences between study populations. In the present review, the genetic variants showing association with AERD are discussed.

**HERITABILITY OF AERD AND A WHOLE-GENOME LINKAGE STUDY**

Asthma is a genetically complex disease that is associated with the family syndrome of atopy and increased levels of total serum IgE, bronchial hyperreactivity (BHR), and elevated blood eosinophil count. These intermediate phenotypes are themselves highly heritable and are the subject of much research into the genetics of asthma. They cluster in families, indicating that a genetic component is likely to be operating. Linkage-based methods have been used in individual families where members are affected by the disease in an attempt to demonstrate linkage between the occurrence of disease and genetic markers in a chromosomal region. This approach has been successfully used to map and clone genes causing monogenic disorders with simple Mendelian inheritance such as cystic fibrosis.\(^6\) Using this approach, at least 5 asthma genes including a disintegrin and metalloprotease 33 (ADAM33) on 20p13, dipeptidylpeptidase 10 on 2q14.1, plant homeodomain zinc finger protein 11 on 13q14.2, G protein-coupled receptor for asthma susceptibility on 7p15-p14, and prostaglandin 2 receptor on 14q 24 have been identified as being associated with a high risk of asthma.

An intermediate genetic background may be present in aspirin hypersensitivity. The European Network on Aspirin-induced Asthma found that 6% of AERD patients had a family history of aspirin hypersensitivity.\(^7\) However, the low incidence of familial aggregation is a serious limitation to application of the whole-genome linkage study approach in AERD. Besides, the growing recognition of the limitations of linkage analysis in complex human diseases has shifted emphasis toward single nucleotide polymorphisms (SNPs) genotyping and association and haplotype analyses. Thus, further application of linkage analysis may not be expected.

**CANDIDATE GENE ASSOCIATION STUDY USING SNPS OF ARACHIDONATE PATHWAY GENES**

Association studies with AERD began with biologically plausible genes responsible for over- or under-production of critical modulators in the metabolism of arachidonic acids. Of these, a two-compartment model has been proposed in which both augmentation of cysteinyl leukotriene (CysLT) production and overexpression of CysLT receptors on inflammatory cells occur within the respiratory tract.\(^7\) In addition, lipoxins, thromboxanes, and prostaglandins contribute to adverse reactions to aspirin.

Cysteinyl leukotrienes and their receptors

CysLTs are important inflammatory mediators in the development of asthma, as they mediate bronchoconstriction, mucus oversecretion, and vascular permeability, as well as cell trafficking and innate immune responses. CysLTs are overproduced in the airways and circulation of asthmatics who are intolerant to aspirin.\(^6\) Aspirin challenge induces increased concentrations of leukotriene E4 in the urine and airways of those with aspirin-intolerant asthma (AIA) compared with patients with aspirin-tolerant asthma (ATA). The CysLTs are synthesized by the 5-lipoxygenase (ALOX5) from arachidonic acid. The ALOX5 pathway contains several distinct enzymes, including cytosolic phospholipase A2, ALOX5, ALOX5-activating protein, and leukotriene C4 synthase (LTC4S), which is the terminal enzyme for CysLTs production. LTC4S is highly expressed in the bronchial mucosa of AIA compared with ATA patients, and this increase is significantly correlated with bronchial hyperresponsiveness to inhaled lysine aspirin.\(^8\)

**LEUKOTRIENE C4 SYNTHASE (LTC4S on 5q35, MIM#246530):** LTC4S rs730012 (-444A>C) on the promoter was associated with the risk of AIA in a Polish population (Table 1).\(^10\) This allele is a transcription-factor-binding site for histone H4 transcription factor-2, binding of which results in increased transcription. However, other studies have found no significant association between LTC4S polymorphism and AIA in other ethnic groups.\(^11,12\) In a study of the Korean population,\(^13\) the frequency of the LTC4S -444C allele in AIA was similar to that in a Japanese population, which was one-half the frequency of that in Polish and American populations, suggesting that ethnic differences in LTC4S gene polymorphism contribute to AIA (Table 1 and Fig. 1C).

**ARACHIDONATE 5-LIPOXYGENASE (ALOX5 on 10q11.2, MIM#152390):** The initial enzymatic step in leukotriene (LT) production is the oxidation of arachidonic acid by ALOX5 to LTA4. A variable number of tandem repeats (VNTR), other than 5 in the Sp1-binding motif GGCGCG in the promoter region, diminishes ALOX5 gene expression.\(^14\) However, VNTR was not related to the AIA phenotype in a study of a Japanese population.\(^11\) In a Korean population,\(^13\) the frequency of the ALOX5-ht1/G-C-G-A/haplotype was significantly higher in the AIA than in the ATA group (Table 1 and Fig. 1), suggesting possible involvement of ALOX5 gene polymorphisms in AIA.

**N-ACETYLTRANSFERASE 2 (NAT2 on 8p22, MIM#612182):** The CysLTs, comprising LTC4, LTD4, and LTE4, are eliminated from the bloodstream by the liver and kidneys. The CysLTs can be inactivated by N-acetylation, and their β-carboxyl backbone is subject to carboxylation and β-elimination. The o-carboxy-N-acetyl-LTE4 is degraded exclusively in peroxisomes. The CysLTs are inactivated by acetylated coenzyme A-dependent NAT2.\(^15\) Thus, functional alterations in the NAT gene may contribute to the risk of AIA. Of six common SNPs of the NAT2 gene in a Korean population, minor allele frequencies of NAT2 -9246G>C and
haplotype 2 (TCACGG) were significantly higher in the AIA than in the ATA group (Table 1 and Fig. 1C), suggesting that the genetic variant of NAT2 gene may be associated with aspirin hypersensitivity via the different degradation of CysLTs. CYSTEINYL LEUKOTRIENE RECEPTOR 1 (CYSLT1R on Xq13.2-q21.1, MIM#30020) and CYSLT2R (on 13q14.2-21.1, MIM#605666): CysLTs exert their biological actions by binding two types of G-protein-coupled seven-transmembrane receptors: CysLTR1 and CysLTR2. CysLTs bind to CysLTR1, which is antagonized selectively by leukotriene modifiers such as montelukast, pranlukast, and zafirlukast. The main role of CysLTR2 mRNA is abundantly expressed in eosinophils, the main effector cells in asthma and AERD, CysLTR2 may have an important physiological role in CYSLT2R gene polymorphisms associated with the risk of asthma development in Caucasian and Japanese populations. Because CYSLT2 is located close to a chromosomal locus for increased risk of asthma in various populations. Because CYSLT2 mRNA is abundantly expressed in eosinophils, the main effector cells in asthma and AERD, CysLTR2 may have an important physiological role in CYSLT2R gene polymorphisms associated with the risk of asthma development in Caucasian and Japanese populations.
nounced bronchospasm by aspirin provocation than did those who carried common alleles (Table 1 and Fig. 1C). This suggests that CYSLTR2 polymorphisms may induce AERD by increasing mRNA levels via affecting their stability.  

Prostaglandins and their receptors

Prostaglandin E receptors (PTGERs): PGE2 modulates airway tone by inhibiting acetylcholine release by cholinergic nerve endings and histamine release from mast cells, and by directly suppressing aspirin-induced CysLTs synthesis from eosinophils and mast cells infiltrating the bronchial mucosa. These effects may be exerted via prostaglandin E receptors on airway leukocytes. At least four subtypes of PTGERs have been identified to differ in their tissue distribution, ligand-binding affinity, and coupling to intracellular signaling pathways. An extensive association study of the 370 SNPs mainly on the arachidonate pathway demonstrated that SNPs in the promoter region of the PTGER2 gene (-12813 G→A) and promoter -1220 A→C differ in their tissue distribution, ligand-binding affinity, and coupling to intracellular signaling pathways. An extensive association study of the 370 SNPs mainly on the arachidonate pathway demonstrated that SNPs in the promoter region of the PTGER2 gene (-12813 G→A) and promoter -1220 A→C.

Fig. 1. Summary of AERD associated single nucleotide polymorphisms in the genes of immune response and arachidonate pathway. OR, odds ratio; Ref, reference. (A) HLA DQ, Major histocompatibility complex, class II, DQ, HLA-DPB1, Major histocompatibility complex, class II, DP beta 1; IL4, INTERLEUKIN 4; IL13, INTERLEUKIN 13, IL-10, Interleukin 10, TGF-beta 1, transforming growth factor, beta 1. (B) MS4A2, MEMBRANE-SPANNING 4-DOMAINS, SUBFAMILY A, MEMBER 7; FCER1, Fc fragment of IgE, high affinity I, receptor for; gamma polypeptide; FCER1B, FC fragment of IgE, high affinity II, receptor for; alpha polypeptide. (C) TLR4, TOLL-LIKE RECEPTOR 4; TLR3, TOLL-LIKE RECEPTOR 3; NLRP3, NOD-LIKE RECEPTOR PYRAMIDAL DOMIAN-CONTAINING 3; PPARG, Peroxisome proliferator-activated receptor-gamma; ADAM33, A disintegrin and metalloproteinase domain 33; F3, Fibrinogen alpha 1; EMID2, EF-hand calcium-binding protein 2; SLC6A12, Solute carrier family 6 (neurotransmitter transporter, betaine/gaba), member 12; SLC22A2, Solute carrier family 22 (organic cation transporter), member 2; KIF3A, Kinesin family member 3A; ADORA1, adenosine A1 receptor; ADORA2A, adenosine A2a receptor; GPR44, G protein-coupled receptor 44; PTGER2, Prostaglandin E Receptor 2; PTGER3, Prostaglandin E Receptor 3; PTGER4, Prostaglandin E Receptor 4; PTGIR, Prostaglandin I2 receptor; TBXAS1, Thromboxane A synthase 1; TBXAS2, Thromboxane A2 receptor; RGS7BP, Regulator of G protein signaling 7-binding protein.
most significantly associated SNP, -12813 G/A, is located in the regulatory region of the PTGER2 gene in which a STATs binding consensus sequence is present. In Korean populations (Table 2 and Fig. 1F), several SNPs on PTGER2, 3, and 4 showed a good association with aspirin hypersensitivity in asthma. Of seven SNPs on PTGER2, the minor allele frequency of -616 C>G was significantly lower in AIA than in ATA patients, whereas AIA patients had a significantly higher frequency of GG homozygotes of -166 G>A (Table 2 and Fig. 1F). One PTGER3 polymorphism in the promoter region (-1709 T>A) exhibited a different genotype distribution in Korean AIA and ATA patients. The minor allele frequency was higher in AIA than in ATA patients (Table 2 and Fig. 1F). Another Korean study revealed that rs7543182 G was positive association between TBXA2R polymorphisms and the frequency of the minor allele +141931 T>A (rs6962291) in intron 9 was significantly lower in the AIA than the ATA groups. AA carriers of +141931 T>A had significantly lower plasma TXB2 levels than TT carriers. The mRNA levels of the full-length wild-type and an exon 12-deleted splice variant were significantly higher in the TT than in the AA homozygotes of +141931 T>A. Based on these data, it appears that the minor allele of rs6962291 may protect against aspirin hypersensitivity via a lower catalytic activity of the TBXAS1 gene, itself attributed to an increased nonfunctioning isoform of TBXAS1 (Table 2 and Fig. 1F). TXA2 exerts its effects by interacting with the G protein-coupled TXA2R. Genetic association studies have identified a positive association between TXA2R polymorphisms and the risk of asthma, atopy, and atopic dermatitis. The minor C allele frequency of TXA2R rs11085026 (+795 T>C) on exon 3 was significantly higher in AIA than in ATA (Table 2 and Fig. 1F). The association was validated in another Korean AIA population. The three SNPs rs4807491 (-4684 C>T), +795 T>C, and R343Q of TBXA2R, one SNP in the promoter area (-4684 C>T) and one non-synonymous coding SNP in exon 3 (+795 T>C) were significantly associated with the AIA phenotype. The fre-
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MAJOR HISTOCOMPATIBILITY COMPLEX, CLASS II (MHC on chromosome 6p21.3): HLA-DQ (DQ) is a cell-surface receptor found on antigen-presenting cells. DQ is a αβ heterodimer of the MHC Class II type. The α and β chains are encoded by HLA-DQA1 and HLA-DQB1, respectively, and vary greatly. Different DQ isoforms bind to and present different antigens to T-cells. T-cells are then stimulated to grow and can signal B-cells to produce antibodies. In addition to foreign antigens, DQ is involved in recognizing common self-antigens and presenting those antigens to the immune system to develop tolerance. HLA-DP is a protein/peptide-antigen receptor composed of two subunits, DPα and DPβ, which are encoded by two loci, HLA-DPA1 and HLA-DPB1. Amino acids located at key positions along the α-helical portions of these HLA heterodimers dictate which peptide antigens can bind. Even single amino acid substitutions in these regions may alter the shape of the HLA-peptide binding pocket sufficiently to change its specificity.41 In a limited number of Caucasian patients, a significant increase in HLA-DQw2 was associated with AIA (Table 3 and Fig. 1A).42 In British and German populations, the incidence of DPB1*0401 was lower in AIA compared with AIA (Table 3 and Fig. 1A).43 DPB1*0401 was more frequently present in a polish population, where the DPB1*0301 frequency was increased fourfold in AIA compared with ATA patients (Table 3 and Fig. 1A).44 These findings suggest that AIA represents a disease entity that involves different immune responses than other forms of asthma.

INTERLEUKIN 4 (IL4 on 5q31.1, MIM#147780): Given that IL-4 plays a central role in the development of allergic asthma and atopy, genetic variation of IL-4 may alter its transcription and translation and influence the pathogenesis of allergic diseases. The possible associations of -589C>T (rs2243250) with asthma and airway obstruction in asthmatics have been investigated.45,46 As one of the important biochemical pathways regulating inflammatory cells, ASA inhibits nuclear factor κ-light-chain-enhancer of activated B cells activation, and interleukin-4 (IL-4) and IL-13-induced STAT6 activation.47 In a Korean population, of 15 SNPs tested, the frequency of rare allele rs2243250 (-589T>C) was higher in the AIA than the ATA group (Table 3 and Fig. 1A).48 Functional characterization of this SNP indicates that CCAAT-enhancer-binding proteins β and nuclear factor of activated T-cells are their transcription factors and that their binding is augmented by aspirin. These data indicate that aspirin may regulate IL4 expression in an allele-specific manner by altering the availability of transcription factors to the key regulatory elements in the IL4 promoter, thus leading to aspirin hypersensitivity.

INTERLEUKIN 13 (IL13 on 5q31, MIM#147683): IL-13 is a key cytokine involved in allergic inflammation by inducing airway eosinophilia and bronchial hyper-reactivity. AIA is characterized by chronic rhinosinusitis and nasal polyposis due to persistent upper and lower airway inflammation with marked eosinophilia. In a Korean population, AIA patients with the AA genotype rs1881457 (-1510A>C) and CC genotype rs1800925 (-1055C>T) on the promoter had a significantly higher fre-
Table 3. AERD associated single nucleotide polymorphisms in the genes of immune response

| Immunity Pathway | Gene | Locus | rs number | Genotype | AA change | Race | N (AIA/ATA) | MAF (AIA/ATA) | P value | OR (95% CI) | Yr | First author | Ref. |
|------------------|------|-------|-----------|----------|-----------|------|-------------|--------------|---------|-------------|----|--------------|-----|
| Adaptive Th1 and Th2 immune response | HLA DQ | - | w2 | - | Caucasian | 26/22 | - | 0.001 | - | 1996 | Mullarkay MF | 54 |
| | HLA DPB1 | Exon 2 | 0401 | - | British, German Polish | 19/21, 21/18 | 0.007, 0.008 | Pc=0.08 | 0.48 (0.28-0.83) | 1993 | Lympnay PA | 55 |
| | | | 0301 | - | - | 59/57 | 0.288/0.456 | - | 0.176/0.201 | 0.018 | 1997 | Dekker JW | 56 |
| IL4 | Promoter | rs2243250 | -589 T>C | - | Korean | 103/270 | 0.316/0.220 | Pc=0.018 | 1.89 (1.30-2.75) | 2010 | Kim BS | 61 |
| IL13 | Promoter | rs18811457 | -1510 A>C | - | Korean | 162/301 | 0.287/0.290 | 0.012 | - | 2010 | Paliike NS | 62 |
| | | rs1800925 | -1055 C>T | - | Japanese | 72/640 | 0.257/0.146 | Pc=0.004 | <0.001 | 2.15 (1.26-3.64) | 2005 | Akahoshi M | 63 |
| T-BET | Promoter | -193 T>C | - | - | Japanese | 72/640 | 0.257/0.146 | Pc=0.004 | <0.001 | 2.15 (1.26-3.64) | 2005 | Akahoshi M | 63 |
| IgE regulation and high affinity receptors for IgE | MS4A2 (FcrRh1β) | Promoter | rs1441586 | -109 T>C | - | Korean | 164/144 | 0.284/0.289 | 0.012 | 7.723 (1.327-39.860) | 2006 | Kim SH | 65 |
| | FcER1γ | Promoter | rs11587323 | -237 A>G | - | Korean | 126/177 | 0.060/0.119 | 0.012 | - | 2008 | Paliike NS | 66 |
| | FcER1α | Promoter | rs2427827 | -344 C>T | - | Japanese | 79/470 | 0.71/0.61 | 0.018 | 1.55 (1.08-2.24) | 2009 | Hitomi Y | 73 |

A.A, amino acid; AIA, Aspirin-induced asthma; ATA, Aspirin-tolerance asthma; MAF, Minor allele frequency; OR, odds ratio; CI, confidence interval; Yr, year; Ref, reference; HLA DQ, Major histocompatibility complex, class II, DQ; HLA-DPB1, Major histocompatibility complex, class II, DP beta 1; IL4, INTERLEUKIN 4; IL13, INTERLEUKIN 13; T-BET, T-BOX EXPRESSED IN T CELLS; MS4A2, MEMBRANE-SPANNING 4-DOMAINS, SUBFAMILY A, MEMBER 7; FcER1γ, Fc fragment of IgE, high affinity I, receptor for; FcER1α, Fc fragment of IgE, high affinity I, receptor for; alpha polypeptide; TLR3, TOLL-LIKE RECEPTOR 3; NLRP3, NLR FAMILY, PYRIN DOMAIN-CONTAINING 3.

frequency of rhinosinusitis compared with those with the minor alleles of these two SNPs (Table 3 and Fig. 1A), suggesting participation of IL-13 gene polymorphisms in AERD upper airway remodeling.

T-BOX EXPRESSED IN T CELLS (TBET or T-BOX 21 on 17q21.32, MIM#604895): A Th1-specific transcription factor of the T-box family controls INF-γ production by T helper cells. Of the 24 known SNPs, a promoter -1993T>C SNP was significantly associated with a risk of AIA. This allele is in linkage disequilibrium with a synonymous coding +390A>G SNP in exon 1. This association has also been confirmed in additional independent samples of asthma with nasal polyposis. On functional characterization, the -1993T>C substitution increased the affinity of a particular nuclear protein to the binding site of TBX21 covering the -1993 position (Table 3 and Fig. 1A). These data indicate that increased T-beta and subsequent change of IFN-γ production in human airways of individuals with the -1993T>C polymorphism may contribute to the development of AIA.

IgE regulation and high affinity receptors for IgE

MEMBRANE-SPANNING 4-DOMAINS, SUBFAMILY A, MEMBER 7 (MS4A7 on 11q13, CD20/FCER1B FAMILY MEMBER 4, MIM#606502): The beta chain of the high-affinity receptor for IgE is linked to atopy and asthma. The β-chain of FcEpR1 enhances receptor maturation and signal transduction capacity, leading to the release of pro-inflammatory mediators such as prostaglandins, leukotrienes, and cytokines such as IL-4, IL-5, IL-13, TNF-α and chemokines including IL-8, and monocyte chemotactic protein 1 (MCP-1), macrophage inflammatory protein-1α (MIP-1α), MIP-1β from mast cells, and basophils. In a Korean population, two genetic polymorphisms of the FcεR1β gene [FcεR1 β rs1441586 (-109T>C) and FcεR1β E237G] were associated with AIA. FcεR1β -109T>C polymorphism was significantly associated with the presence of IgE to
staphylococcal enterotoxin B (SEB), with higher MS4A2 promoter activity in cell lines (Table 3 and Fig. 1B).31

Of the two SNPs of FcεR1α [rs2427827 (-344C>T) and rs2251746 (-95T>C)], two SNPs of FcεR1β [MS4A2 rs1441586 (-109T>C) and MS4A2 E237G], and two SNPs of FcεR1γ [FcεR1γ rs11567213 (-237A>G) and FcεR1γ-54G>T], the genotype frequencies of FcεR1γ-237A>G differed significantly between AIA and ATA patients. Additionally, AIA patients carrying the homozygous AA genotype of FcεR1γ-237A>G had significantly higher total serum IgE levels than those with the GG/AG genotype. AIA patients expressing the CT/TT genotype at FcεR1α-344C>T had a higher prevalence of serum IgE specific to staphylococcal enterotoxin A than did those with the CC genotype (Table 3 and Fig. 1B),32 suggesting that the FcεR1γ-237A>G and FcεR1α-344C>T polymorphisms may contribute to development of AIA via regulation of IgE production.

TOLL-LIKE RECEPTOR 3 (TLR3 on 4q35, MIM#603029): Because eosinophils activated via TLR3, one of the virus-recognition TLRs, recruit leukocytes to sites of inflammation, eosinophils may function as a link between viral infection and exacerbation of allergic disease. Viral respiratory infections contribute to allergic sensitization and the development of asthma and exacerbation in subjects with already established asthma. Aspirin hypersensitivity is diminished in some AERD patients during acyclovir treatment of herpes simplex infection.33 In a Korean population, AERD patients had a significantly higher frequency of missense variants ‘A’ allele of rs3775291 (+293391G>A, Leu412Phe) than did the ATA group (Table 3 and Fig. 1D).34 The amino acid change from Leu to Phe results in functional deterioration of TLR3 and predisposes individuals to increased susceptibility to the innate immune response, which may be a cause of viral-induced AERD.

NLR FAMILY, PYRIN DOMAIN-CONTAINING 3 (NLRC3 on 1q44, MIM#606416): A member of the nucleotide-binding domain, leucine-rich repeat-containing (NLR) family controls the activity of inflammatory caspase-1 by forming inflammasomes. Tight collaboration between pathogen-associated molecular patterns and their receptors initiates an innate immune response, and NLRC3 inflammasomes are activated by pathogen-associated molecular patterns including microbial toxins, live bacteria, and viruses.35 After being activated, NLRC3 recruits apoptosis-associated speck-like proteins containing pro-caspase-1, leading to activation of caspase-1. Activated caspase-1 cleaves the procytokines IL-1b and IL-18 into their active forms. Of 15 tag SNPs of NLRC3 in a large population, one (rs4612666) was significantly associated with AIA. The risk allele of rs4612666 increases the enhancer activity of NLRC3 expression and NLRC3 mRNA stability (Table 3 and Fig. 1E),36 indicating that the NLRC3 SNP might play an important role in the development of AIA in a gain-of-function manner.

Airway remodeling and fibrosis genes

A DISINTEGRIN AND METALLOPROTEINASE DOMAIN 33 (ADAM33 on 20q13, MIM#607114): ADAM33 is expressed strongly in smooth muscle layers and basement membrane in more than 80% of subjects with asthma but not in normal control subjects, indicating that ADAM33 may be involved in airway remodeling in asthma.37 A genome-wide screen revealed ADAM33 to be a novel asthma-susceptibility gene that plays a role in AHR.38 ADAM33 polymorphisms are associated with asthma susceptibility and airway hyperreactivity in several ethnicities, including the Korean population.39 In a Japanese population, of 10 polymorphic sites (ST+4, ST+7, T1, T2, T+1, V-3, V-2, V-1, V4, V5), the ST+7, V-1, and V5 sites in the AIA group were significantly different from those in the ATA group. Haplotypes of three sites (ST+7, V-1, and V5) were significantly different in frequency between the AIA and ATA groups, indicating that the ADAM33 sequence variations are likely to correlate with susceptibility to AIA (Table 4 and Fig. 1E).40

FIBROUS SHEATH-INTERACTING PROTEIN 1 (FSIP1, HSD10): With its primary function in protein binding, the FSIP1 gene is expressed in the airway epithelium. FSIP1 is regulated by amyloid beta precursor protein (APP).41 APP is an integral membrane protein expressed in many tissues, particularly in the synapses of neurons. APP is cleaved by ADAM33. Of 66 SNPs in the FSIP1 gene, one (rs7179742) was associated with AIA in a Korean population (Table 4 and Fig. 1E).42 In Asian populations from the International HapMap Project (http://hapmap.ncbi.nlm.nih.gov/), the FSIP1 gene is in LD with the thrombospondin-1 (THBS1 or TSP-1) gene. The THBS1 gene has been implicated in a network underlying the pulmonary response to oxidative stress in asthma.43 Aspirin leads to a reduction in THBS1 levels.44 These data suggest that FSIP1 affects aspirin hypersensitivity in asthma associated with the nearby THBS1 gene.

EMILIN/MULTIMERIN DOMAIN-CONTAINING PROTEIN 2 (EMID2 on 7q22.1, MIM#608927): Airway remodeling is the dominant physiological event that leads to the reversible clinical symptoms in asthma such as airway hyperresponsiveness and airflow obstruction. Airway remodeling may not be entirely reversible, and subepithelial fibrosis has been highlighted as an integral component of the remodeling response. Accumulation of extracellular matrix (ECM) components such as fibronectin and types I, III, and V collagens in the basement membrane results in thickening of the subepithelial space.45 Emilin is a component of elastic fibers located at the elastin-microfibril interface. Pathological studies have observed an abnormal deposition of elastic fibers in both large and small asthmatic airways. Additionally, EMID2 is a glycosylated protein that is secreted and deposited in the ECM, serving a variety of structural and functional roles.46 In Korean subjects, five of 49 SNPs and the BL2 ht2 haplotype (unique to the minor alleles of rs4727494 and rs13233066) were significantly associated with AIA, indi-
cating that EMID2 polymorphisms could cause meaningful deficits in the upper and lower airways of AIA patients (Table 4 and Fig. 1E).66

Airway inflammation and eosinophil activation

Angiotensin 1-converting enzyme (ACE on 17q23, MIM #106180) is a membrane-bound peptidase expressed by epithelial and endothelial cells. ACE inactivates a wide range of peptides, including kinins and substance P, which are overproduced in the lungs of asthmatics.67 The inhibition of ACE is linked to suppression of kinase II activity, resulting in the accumulation of kinins, substance P, and prostaglandins in the airways and consequent stimulation of vagal afferents, which in turn leads to bronchial hyper-reactivity and airway inflammation, especially eosinophilic inflammation, in asthmatics.68 Of four SNPs [rs4292 (-262A>T) and rs4292 (-115T>C) in the 5'-flanking region and +5467T>C [Pro450Pro] and +11860A>G [Thr776Thr] in the coding region] and one ins/del (+21288 CT), the frequency of the minor alleles of -262A>T and -115T>C was higher in subjects with AIA than in subjects with ATA in a Korean asthma cohort. ACE promoters containing the minor -262A>T allele possessed lower promoter activity than did the common allele, indicating that the minor allele may confer aspirin hypersensitivity via down-regulation of ACE expression (Table 4 and Fig. 1E).69

ADENINE DEAMINASE (ADA on 20q13, MIM #608958): Adenosine is endogenous in human tissues at low concentrations but increases markedly in the extracellular space during inflammation. Inhalation of adenosine induces acute bronchoconstriction in those with asthma through interactions with four GPCRs for adenosine.70 In subjects with asthma, lysine as

### Table 4. AERD associated single nucleotide polymorphisms in the genes of airway inflammation and remodeling

| Pathway                  | Gene | Locus | rs number | Genotype         | A.A change |Race  | N (AIA/ATA) | MAF (AIA/ATA) | Pvalue | OR (95% CI) | Yr    | First author | Ref.  |
|--------------------------|------|-------|-----------|------------------|------------|------|------------|---------------|--------|-------------|-------|---------------|------|
| Airway remodeling and fibrosis genes | ADAM33 | Intron 19 | - | ST+7G>A | - | Japanese  | 102/282 | 0.059/0.134 | 0.004 | - | 2006 | Sakagami T | 77   |
| | ADAM33 | Intron 21 | - | V-1C>A | - | - | 0.091/0.151 | 0.034 | | | | | |
| | ADAM33 | Intron 22 | - | V5A>G | - | - | 0.071/0.152 | 0.004 | | | | | |
| | FSIPI | Intron 2 | rs719742 | - | BL2_h2 | - | Korean | 163/429 | 0.358/0.262 | Pc=0.03 | 1.63 (1.23-2.16) | 2010 | Kim JY | 79   |
| | EMID2 | Intron 2 | - | - | - | Korean | 163/429 | 0.288/0.331 | Pc=0.02 | 0.64 (0.44-0.93) | 2011 | Pasaje CF | 86   |
| Airway inflammation and eosinophil activation | ACE | Promoter | rs4291 | -262A>T | - | Korean | 81/231 | 0.5/0.375 | 0.003 | 2.08 (1.28-3.38) | 2008 | Kim TH | 93   |
| | ADORA1 | 3'-UTR | rs16651030 | 1405C>T | - | Korean | 136/181 | 0.376/0.300 | 0.001 | 3.22 (1.50-6.92) | 2009 | Kim SH | 99   |
| | ADORA2A | Exon 5 | rs10920568 | T>G | A102A | - | Korean | 136/181 | 0.376/0.300 | 0.001 | 3.22 (1.50-6.92) | 2009 | Kim SH | 99   |
| | ADORA2A | - | - | - | - | - | - | - | - | - | - | - | - |
| | GPR44 | Promoter | - | -466T>C | - | Korean | 107/115 | 0.259/0.339 | 0.037 | - | 2010 | Palikehe NS | 103  |
| | PPARG | Exon 10 | rs3856808 | +82466C>T | H449H | Korean | 60/343 | 0.15/0.145 | 0.04 | 3.97 (1.08-14.53) | 2009 | Oh SH | 108  |
| Vesicle trafficking, solute transfer and ion channel | KIF3A | Intron 9 | rs3738130 | +30966A>G | - | Korean | 103/288 | 0.304/0.226 | Pc=0.01 | 3.75 (1.67-8.43) | 2011 | Kim JH | 112  |
| | SMCOC2 | Intron 2 | rs2882510 | C>T | - | Korean | 163/429 | 0.253/0.332 | Pc=0.004 | 0.24 (0.09-0.62) | 2010 | Kim JY | 119  |
| | ADORA1 | Intron 6 | rs2294752 | T>G | - | Korean | 163/429 | 0.253/0.334 | Pc=0.004 | 0.24 (0.09-0.62) | 2010 | Kim JY | 119  |
| | ADORA2 | Intron 9 | rs446738 | T>A | - | Korean | 163/429 | 0.349/0.409 | Pc=0.03 | 0.44 (0.24-0.80) | 2010 | Pasaje CF | 123  |
| | SLC6A12 | Exon 4 | rs499368 | A>T | - | Korean | 163/429 | 0.399/0.321 | Pc=0.03 | 1.49 (1.13-1.98) | 2010 | Pasaje CF | 123  |
| | CACNG6 | Intron 5 | rs316021 | A>G | - | Korean | 163/429 | 0.172/0.245 | Pc=0.05 | 0.6 (0.43-0.85) | 2011 | Park TJ | 129  |
| | CACNG6 | Intron 6 | rs192808 | C>T | - | Korean | 102/249 | 0.103/0.045 | P=0.0029 | 2.88 (1.60-5.17) | 2010 | Lee JS | 134  |
| | CACNG6 | - | - | BL1_h6 | - | Korean | 102/249 | 0.103/0.045 | P=0.0029 | 2.88 (1.60-5.17) | 2010 | Lee JS | 134  |

A.A, amino acid; AIA, Aspirin-induced asthma; ATA, Aspirin-tolerance asthma; MAF, Minor allele frequency; OR, odds ratio; CI, confidence interval; Yr, year; Ref, reference; ADAM33, A disintegrin and metalloproteinase domain 33; FSIPI, Fibrous sheath interacting protein 1; EMID2, Emilin/multimerin domain-containing protein 2; ACE, Angiotensin 1-converting enzyme; ADORA1, adenosine A1 receptor; ADORA2A, adenosine A2a receptor; GPR44, G protein-coupled receptor 44; PPARG, Peroxisome proliferator-activated receptor-gamma; KIF3A, Kinesin family member 3A; SMCOC2, Sparc-related modular calcium-binding protein 2; SLC6A12, Solute carrier family 6 (neurotransmitter transporter, betaine/gaba), member 12; SLC22A2, Solute carreier family Y 22 (organic cation transporter), member 2; CACNG6, Calcium channel, voltage-dependent gamma-6 subunit.
animal model of asthma and adenosine receptor-deficient mice exhibited enhanced AHR and airway inflammation. Of 13 SNPs in adenosine deaminase (ADA) and the four adenosine receptors (ADOR1A, ADOR2A, ADOR2B, and ADOR3), significant differences were detected between patients with AIA and those with ATA. ADOR1A SNPs [rs16851030 (1465C>T)], rs10920568 (A102A)] and haplotypes (ht[A-C-G] in ADOR1 and ht[A-T] in ADOR2) are significantly associated with AIA, suggesting that adenosine may play a crucial role in the development of AIA through interactions with the A(1) and A(2A) receptors (Table 4 and Fig. 1F).

G PROTEIN-COUPLED RECEPTOR 44 (GPR44, CRTH2, on 11q12-q13.3, MIM#604837): PGD2, a major prostaglandin produced by allergen-activated mast cells, is an important mediator in the pathogenesis of eosinophilic airway inflammation via its receptor, a chemoattractant receptor molecule expressed on Th2 cells (CRTH2). The human CRTH2 gene is also expressed in other allergy-related cells such as eosinophils, basophils, and monocytes and mediates chemotaxis of these cells toward PGD2. Genetic alteration of CRTH2 is related to allergic asthma in African-Americans. In Korean subjects, two polymorphisms (-466T>C and -129C>A) were significantly different between AIA and ATA patients. The -466T allele exhibits higher eotaxin-2 production in human lung epithelial cells, indicating that this polymorphism increases serum and cellular eotaxin-2 production in AERD patients through lowered GRP44 expression, leading to eosinophilic infiltration (Table 4 and Fig. 1F).

PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR-GAMMA (PPARG on 3p25, MIM#601487). PPARs are transcription factors activated by ligands of the nuclear hormone receptor superfamily. Three different PPAR subtypes have been identified: PPARα (PPARA), PPARγ (PPARG), and PPARδ (PPARD), which is also called PPARβ. A variety of natural substances, including arachidonate pathway metabolites such as 15-hydroxyeicosatetraenoic acid (15-HETE), strongly promote PPARγ expression. Stimulation of the PPARγ ligand significantly inhibited the downregulation of eosiinophil function. PPARγ expression is associated with the inflammatory and remodeling responses in the asthmatic airway. Additionally, levels of proinflammatory, immune cytokines and chemokines, including IL-2, IL-3, IL-4, IL-5, IL-13, GM-CSF, and eotaxin are increased in the airways and systemic circulation in AIA. The production of these molecules is regulated by various transcription factors, including PPARγ. PPARγ gene polymorphisms are associated with risk of asthma exacerbation in Caucasian populations. In Korean subjects, rs3856806 (+82466C>T, His449His) and haplotype 1 (CC) (+34C>G [Pro12Ala] were associated with development of aspirin hypersensitivity in asthmatics. The frequency of the minor allele of +82466C>T was two times higher in AIA than in ATA patients. Additionally, the frequency of PPARG haplotype 1 was significantly lower in AIA than in ATA patients, indicating that the +82466C>T polymorphism and haplotype 1 of the PPARG gene may be linked to an increased risk of aspirin hypersensitivity in asthma (Table 4 and Fig. 1E).

Genetic Basis of Aspirin Hypersensitivity Asthma

 Vesicle trafficking, solute transfer, and ion channels

KINESIN FAMILY MEMBER 3A (KIF3A on 5q31-33, MIM# 604683): KIF3A encodes a motor subunit of kinesin-2, an important component for cilia formation, and plays a crucial role in the generation and functioning of cilia. In the case of Bardet-Biedl syndrome, which includes an increased incidence of asthma (25%), abnormal functions of cilia have been discovered. Differential expression of KIF3A is present in nasal epithelial cells of exacerbated asthmatics and normal controls, and KIF3A polymorphisms are significantly associated with asthma. KIF3A mRNA level is increased in aspirin-induced bronchial epithelial cells and protein expression is also up-regulated in nasal polyp epithelia in AIA patients. CysLT1, a key mediator in AIA, can affect ciliary activity and orientation. Interestingly, the IL-4 gene has a strong LD with KIF3A in the same LD block. Aspirin also regulates IL-4 expression in an allele-specific manner by altering the availability of transcription factors to the key regulatory elements in the IL-4 promoter, leading to aspirin hypersensitivity. Another explanation for the association between KIF3A and aspirin hypersensitivity in asthma may be over-production of CysLTs by cyclooxygenase (COX) inhibition through constrained β-catenin-dependent Wnt signaling derived from a KIF3A abnormality. This stabilization of β-catenin may lead to NF-κB activation, which also plays a crucial role in immune responses, resulting in the activation of target effectors, such as COX-2. Of a total of 22 SNPs in introns and five haplotypes, several SNPs were significantly associated with AIA. The KIF3A h3 haplotype, which is unique to most of the minor alleles, showed the most significant association with AIA. Several KIF3A isoforms derived from alternative splicing events in intron 9 have been observed; thus, it is possible that the rs3798130 in intron 9 may produce dysfunctional products in respiratory epithelia, resulting in increased expression of KIF3A (Table 4 and Fig. 1E).

SPARC-RELATED MODULAR CALCIUM-BINDING PROTEIN 2 (SMOC2 on 6q27, MIM#607223): A number of intracellular signaling proteins are implicated in various aspects of the inflammatory processes that regulate asthma pathogenesis. Pulmonary surfactant synthesis is decreased in experimentally induced asthma when the intracellular storage capacity and its physical activity are hindered. Alveolar type II cells synthesize pulmonary surfactant, which is a surface-active lipoprotein complex. SMOC2 is involved in the recycling of lamellar bodies-associated proteins or in surfactant uptake from the extracellular space. SMOC2 exhibits GTPase activity and interacts with clathrin and EpsinR on the early endosome/trans-Golgi network, thus affecting vesicle trafficking. In Korean subjects, of 19 SNPs, rs2982510, rs2294752, and rs446738 were associated with the increased susceptibility to AIA (Table 4 and Fig. 1E).
SOLUTE CARRIER FAMILY 6 (NEUROTRANSMITTER TRANSPORTER, BETAINE/GABA), MEMBER 12 (SLC6A12 on 12p13, MIM#603080): Although the SLC6A12 gene, also referred to as sodium and chloride-dependent betaine/GABA transporter-1, is widely expressed in the proximal tubules of the kidney and cells of the central nervous system, an excitatory GABAergic system was described recently in the airway epithelium. γ-aminobutyric acid (GABA) signaling in the airway epithelium plays a critical role in asthma development through its ability to enhance mucus production. Aspirin is involved in the detoxification of GABA-lytic picrotoxin (PT), an antagonist of GABA-receptor chloride channels. The inhibition of picrotoxin by aspirin restores GABA activity. In Korean subjects, of eight SNPs, two polymorphisms (rs499368 and rs557881 [non-synonymous C10R]) and the BL1 h1 haplotype were significantly associated with AIA (Table 4 and Fig. 1E). A non-synonymous variant translates to an amino acid (C10R) change from T to C in the rs557881 polymorphism. Modification of cysteine by introduction of either a methyl or t-butyl group on the free sulfhydryl group and replacement of the guanidine group with a urea linkage in the side chain of arginine may be a risk factor for AIA.

SOLUTE CARRIER FAMILY 22 (ORGANIC CATION TRANSPORTER), MEMBER 2 (SLC22A2 on 6q26, MIM#602608): SLC22A2 is a member of the solute carrier family 22 superfamily of organic cation transporters and mediates the transport of prostaglandins in the basolateral membrane of the proximal tubule. Polyspecific organic cation transporters are involved in transportation of acetylcholine as a novel regulator of airway remodeling. Release of acetylcholine from bronchial epithelial cells mediates bronchoconstriction following the release of serotonin from mast cells. Additionally, airway epithelial cells possess various muscarinic receptors that serve as potential targets of locally released acetylcholine, and dysregulation of these receptors in airway epithelial cells is a major cause of asthma. Overexpression of SLC22A2 variants (Thr199Ileu, Thr201Met, and Ala270Ser) decreases uptake of [3H]methyl-4-phenylpyridinium acetate and [14C]tetraethylammonium (TEA) compared with wild-type SLC22A2-expressing cells. These data suggest that the three SLC22A2 SNPs are involved in development of asthma via a reduced vital capacity, itself caused by a decrease in the transport of TEA because TEA plays a role in increased vital capacity among asthmatic patients. In Korean subjects, of 18 variants, a SNP in intron 5 (rs316021) was significantly associated with susceptibility to AIA. The minor allele frequency of rs316021 in the AIA group was significantly lower than that in the ATA controls, suggesting that SLC22A2 may be associated with susceptibility to aspirin intolerance in asthmatics (Table 4 and Fig. 1E).

CALCIUM CHANNEL, VOLTAGE-DEPENDENT; GAMMA-6 SUBUNIT (CACNG6 on 19q13.4, MIM#606898): Among the remarkable signaling molecules released by mast cells, LTC4 is secreted following Ca^{2+} influx through store-operated calcium-release-activated calcium (CRAC) channels. Airway smooth muscle cell contraction is regulated by changes in intracellular Ca^{2+} concentration and airway bronchodilation. Novel effects of NSAIDs on vascular ion channels, including L-type calcium channels, have also been suggested. L-type calcium channels are composed of five subunits. The CACNG6 gene encodes one of these, specifically the gamma subunit protein, which was first identified in muscle cells. Recent studies have revealed negative associations of CACNG6 gene expression with chronic obstructive pulmonary disease and responses of the human airway epithelium to injury. In Korean subjects, of eight variants, a SNP (rs192808C>T) in the intron and a haplotype unique to this variant (CACNG6 BL1 h66) were significantly associated with risk of AIA, suggesting an association with risk of AIA (Table 4 and Fig. 1C).

GENOME-WIDE ASSOCIATION STUDY

In addition to the genes of the arachidonate pathway, variants of several genes in the immune response and inflammatory pathways are also associated with aspirin hypersensitivity in asthmatics. These data suggest that genetic variations in other pathways may be more relevant to the development of aspirin hypersensitivity in asthmatics than has previously been thought. The International Hap-Map Consortium has revealed nearly 4,000,000 SNPs and demonstrated that individual SNPs predict adjacent SNPs, suggesting that genotyping of 500,000 SNPs may allow a nearly complete survey of all common genetic variations. Based on this concept, whole-genome SNP genotyping arrays were developed and have for the past 5 years been applied to studies of the genetic background underlying multifactorial complex diseases. Recently, genome-wide association studies (GWAS) of asthma and related phenotypes have reported several susceptibility-associated genes, including ORMDL3, PDE4D, and IL1RL1. A GWAS of 109,365 SNPs was undertaken in a Korean AIA cohort using aspirin-tolerant asthma subjects as controls. Results suggested 11 candidate genes with the greatest differences in frequency between AIA and ATA (Table 5). The second stage of fine mapping of 150 common SNPs from the 11 candidate genes showed that SNPs of CEP68 had the most significant association with aspirin intolerance. Seven such SNPs and a CEP68 h4 haplotype (T-G-A-A-A-C-G) exhibited a highly significant association with aspirin intolerance. Moreover, the non-synonymous CEP68 rs7572857G>A variant, in which glycine is replaced with serine, shows greater aspirin-provocation-induced bronchospasm than other variants, implying that CEP68 may be associated with susceptibility to aspirin intolerance in asthmatics. This study also confirmed the association of several other genes (TNF, TGF, HLA-DPB1, ALOX5, and IL-10) with AIA. There has been a debate concerning whether GWAS can successfully detect variants that are associ-
**Table 5.** AERD associated single nucleotide polymorphisms in the genes of Korean Genome-Wide Association Study (modified from Ref. 103)

| Gene-Gene | Locus | rs number | Genotype | AA change | N (AIA/ATA) | MAF (AIA/ATA) | P value | OR (95% CI) | Yr | First author | Ref. |
|-----------|-------|-----------|----------|-----------|-------------|---------------|--------|-------------|----|--------------|------|
| ALOX5AP_G and LTA4H_T | Intron 4 | rs1053744 | C>T | 173/260 | 0.05/0.365 | 3.0×10^-7 | - | 2.17 (1.41-3.32) | 2008 | Holloway | 142 |
| LTA4S -444 A>C and CysLTR2 | 3'UTR | Novel | 2078 C>T | 2534 A>G | Korean 66/134 | 0.152/0.338 | 0.007 | 0.153/0.419 | 0.003 | Park JS | 32 |
| HLA DPB1*0301(-) and TNF-α | Promoter | -1031 T>C | -863 C>A | Korean 163/197 | - | 0.001 | 5.182 | 0.001 | 5.092 | <0.001 | 5.014 | Kim SH | 147 |
| IL-10 -1082 AG or Gs and TGF-β1 -509 CT or TT | Promoter | - | - | Korean 173/260 | - | 0.024 | 2.664 (1.230-5.468) | 2009 | Kim SH | 154 |

**Table 6.** AERD associated single nucleotide polymorphisms in gene to gene interaction

| Gene | Locus | rs number | Genotype | AA change | Race | N (AIA/ATA) | MAF (AIA/ATA) | P value | OR (95% CI) | Yr | First author | Ref. |
|------|-------|-----------|----------|-----------|------|-------------|---------------|--------|-------------|----|--------------|------|
| ALOX5AP and LTA4H | Intron 1 | rs3213729 | C>G | T1853T | - | 0.465/0.290 | 3.0×10^-4 | - | 0.200/0.365 | 1.0×10^-1 | - | - |
| ALOX5AP and LTA4H | Intron 1 | rs9132523 | T>C | I262I | - | 0.195/0.365 | 2.0×10^-4 | - | 0.230/0.100 | 1.0×10^-1 | - | - |
| ALOX5AP and LTA4H | Intron 4 | rs6498124 | G>T | - | - | 0.350/0.535 | 4.0×10^-4 | - | 0.535/0.390 | 5.0×10^-4 | - | - |
| ALOX5AP and LTA4H | Intron 6 | rs4867084 | G>A | - | - | 0.090/0.215 | 3.0×10^-4 | - | 0.090/0.215 | 5.0×10^-4 | - | - |

**GENE–GENE INTERACTIONS**

ALOX5AP and LTA4H genes: In a Korean population study,13 the frequency of the ALOX5-ht1[G-C-G-A]-containing genotype in the AIA group was significantly higher than in the ATA group. Individual odds ratios for risk alleles were 1.78 for SG13S41(G) on ALOX5AP and 1.22 for rs1978331(T) on LTA4H. Gene-gene interactions between these two demonstrated that asthmatics carrying both risk alleles of ALOX5AP and LTA4H (G allele in SG13S41/Intron4 and a T allele in rs1978331/Intron11, respectively) had a twofold increased risk of aspirin hypersensitivity (Table 6).106

CYSLTR2 and LTC4S genes: The association of CYSLTR2 2078 C>T and LTC4S rs912278 (2534 A>G) with decreased FEV1 following aspirin challenge became more pronounced when paired analysis was performed with LTC4S -444 A>C and a T allele in rs1987331/Intron11, respectively) had a twofold increased risk of aspirin hypersensitivity (Table 6).106

The association of CYSLTR2 2078 C>T and LTC4S rs912278 (2534 A>G) with decreased FEV1 following aspirin challenge became more pronounced when paired analysis was performed with LTC4S -444 A>C and a T allele in rs1987331/Intron11, respectively) had a twofold increased risk of aspirin hypersensitivity (Table 6).106

**A.A., amino acid; AIA, Aspirin-induced asthma; ATA, Aspirin-tolerance asthma; MAF, Minor allele frequency; Ref, reference; SBF1, SET binding factor 1; DCBLD2, Discoidin, CUB and LCLL domain containing 2; WOR21A, DDB1 and CUL4 associated factor 4; FILIP1, Filamin A interacting protein 1; PDZK3, PDZ domain containing 2; LRRC43, Leucine rich repeat containing 43; CIITA, Class II, major histocompatibility complex, transactivator; DAF, CD55 molecule, decay accelerating factor for complement; ENPP5, Ectonucleotide pyrophosphatase/phosphodiesterase 5; CEP68, Centrosomal protein 68 kDa; C6, Complement; ENPP5, Ectonucleotide pyrophosphatase/phosphodiesterase 5; CEP68, Centrosomal protein 68 kDa; C6, Complement; ENPP5, Ectonucleotide pyrophosphatase/phosphodiesterase 5; CEP68, Centrosomal protein 68 kDa; C6, Complement.**
responsiveness (AHR) and the phenotype of severe asthma. The TNF-α gene and HLA DPB1 lie adjacent to each other within the class III region of the MHC on chromosome 6p21, so gene-to-gene interaction between TNF-α and the HLA subtype may contribute to the development of AIA. Three SNPs of TNF-α gene (-1031T>C, -863C>A, and -857C>T) polymorphisms are in significant LD with HLA B and HLA DRB1 allele. 109 TNF-α -308G>A was significantly associated with atopic asthma in a Korean adult and child asthma cohort. 106,109 Gene-to-gene interaction between TNF-α -1031T>C (or -863C>A or -857C>A) and HLA DPB1*0301 significantly increased susceptibility to AIA (Table 6). 110

IL-10 and TGF-β1: AIA is characterized by excessive proliferation of target tissues such as eosinophilic rhinosinusitis and nasal polypsis. The TGF-β1 -509 C>T polymorphism on the promoter is associated with rhinosinusitis in AIA patients. 111 The regulatory function of TGF-β1 is interrelated with IL-10. 112 A gene-gene interaction between TGF-β1 and IL-10 polymorphisms has also been implicated in allergy and asthma. 113 The IL-10 haplotype (-1082A, -819T, and -592A) is considered to be a risk haplotype in atopic asthmatics in North India. 114 The IL-10 ATA haplotype was associated with reduced IL-10 production observed in severe asthma. 115 Furthermore, the -1082A>G of IL-10 was significantly associated with the AIA phenotype. Moreover, a synergistic effect between TGF-β1 -509 C>T and IL-10 -1082 A>G has been observed in the AIA phenotype. The frequency of minor alleles (the CT or TT genotype of TGF-β1-509 C>T and AG or GG genotype of IL-10-1082 A>G) was three times higher in patients with AIA than in those with ATA (Table 6 and Fig. 1A). 116

PHARMACOGENETICS

Both augmentation of CysLTs production and overexpression of CysLT receptors on inflammatory cells occur within the respiratory tract in patients with AIA. 7,117 The CysLT receptor is selectively antagonized by several currently available leukotriene modifiers, including montelukast, pranlukast, and zafirlukast. However, clinical studies have demonstrated that the response to these medications is incomplete. 118,119 Individual differences in the response to leukotriene antagonists may be genetically determined by genes involved in either arachidonate metabolism or extra-arachidonate pathways. The HLA allele DPB1*0301 may represent the AERD phenotype. Furthermore, higher doses of leukotriene receptor antagonists are required to control asthma symptoms in patients with AERD. 120 Of the arachidonate pathway genes, the CysLTR1 promoter polymorphism -634C>T is strongly associated with the mean montelukast dose required to maintain asthma control. 111 Of the extra-arachidonate pathway genes, angiotensinogen is associated with individual differences in the effect of montelukast on bronchospasm protection following aspirin challenge. 122 The angiotensinogen gene enhances the effect of several bronchoconstrictors and produces angiotensin in the airways of asthmatics. Of 38 SNPs in the AGT gene, two (+2401C>G and +2476C>T) in the AGT intron were significantly associated with modification of a long-term leukotriene-receptor antagonist effect. However, these data are preliminary, and a larger-scale study is warranted.

STRUCTURAL VARIATION AND EPIGENESIS IN AERD GENETICS

Previous epidemiologic studies have demonstrated that SNPs are not responsible for all differences in phenotype. Because monozygotic twins are genetically identical, asthma develops almost concurrently. However, a twin cohort study showed one fifth of concordance rate of self-reported asthma in monozygotic twin pairs. 123 A possible explanation for this is epigenesis. Epigenetics is the study of heritable changes in DNA structure that do not alter the underlying sequence; well-known examples are DNA methylation and histone modification. These changes may remain through cell divisions for the remainder of the cell’s life and may also last for multiple generations. For example, human epidemiologic studies have shown that the mother’s diet affects her offspring’s risk of allergic asthma. 124 It is not known whether exposure to environmental agents induces epigenetic changes in aspirin hypersensitivity. In nasal polyps from subjects with AERD and ATAs, the methylation pattern of 27,168 DNA CpG sites was assessed using a whole-genome methylation analysis. 125 Methylation patterns were significantly different in nasal polyps, but not so different in buffy coats. A volcano plot showed differential methylation levels in AERD and ATA: 332 CpG sites on 296 genes were hypomethylated, and 158 sites on 141 genes were hypermethylated (Fig. 2). CpG-site methylation in nasal polyps were not correlated with those of buffy coats, indicating that the difference in methylation pattern is nasal-tissue specific. Of the genes in the arachidonate pathway, prostaglandin E synthase was hypermethylated, whereas prostaglandin D synthase, arachidonate 5-lipoxygenase activating protein, leukotriene B4 receptor, and lipoxygenase homology domain1 were hypomethylated, indicating that this may be responsible for the existence of specific phenotypes, such as AERD, in asthma.

PERSPECTIVES

The GWAS and fine-mapping studies will increase the number of candidate genes associated with a well-defined sub-phenotype AERD. However, the genetic impact will improve only when sample sizes are more increased and the role of environmental contributors, such as the extent of aspirin exposure, are considered. Furthermore, much of the speculation about missing heritability from GWAS has focused on the possible contribution of rare variants [low minor-allele frequency [MAF]
<0.5%). Because GWAS chips to date have been capable of analyzing common variants (>5% MAF), identification of rare variants is problematic, even though these rare alleles confer a substantial risk of disease. Sequencing of individual genomes has begun and should provide more information on these rare variants.

In addition to SNPs, genomic variability can take many other forms, including variable numbers of tandem repeats (VNTRs), presence/absence of transposable elements (e.g., alu elements), and structural alterations (e.g., deletions, duplications, and inversions). Until recently, SNPs were thought to be the predominant form of genomic variation and to account for much normal phenotypic variation. However, the widespread presence of copy-number variation was recently reported in normal individuals. Contrary to our previous beliefs, identical twins are not genetically identical. A study of 19 pairs of monozygotic, identical twins found differences in copy-number variation and found that this was associated with Parkinson’s disease. A genome-wide association study of CNV in 16,000 cases of eight common diseases, including types 1 and 2 diabetes, rheumatoid arthritis, and Crohn’s disease, revealed that some CNV are strongly associated with the risk of disease development. It seems much more likely, however, that most genetic control is due to rarer variants, either single-site or structural, that are not represented in current studies and that have considerably larger effects than common variants. Therefore, integration of several-omics may be the solution to the search for the genetic background and mechanism underlying aspirin hypersensitivity in asthma.

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