Genetic Markers for Differentiating Aspirin-Hypersensitivity

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Introduction

The ingestion of acetylsalicylic acid (ASA) can induce allergic reactions such as ASA-intolerant asthma (AIA), ASA-induced acute or chronic urticaria/angioedema (AIAU or AICU), anaphylaxis, and, in rare cases, hypersensitivity pneumonitis [1, 2]. Among these, AIA and AIU are most prevalent. Although the pathogenic mechanism of AIA is not completely understood, a chronic overproduction of cysteinyl leukotrienes (Cys-LTs) derived from cyclooxygenase (COX) inhibition has been consistently found to be associated with the condition [3, 4]. Although recent reports have suggested that an overproduction of Cys-LTs may play a role in AIU development [5, 6], knowledge about the pathogenic mechanism of AIU is limited. Here, we summarize recent data regarding the molecular genetic mechanisms that govern AIA and AIU, with the objective of identifying genetic markers that can be used to differentiate between the two conditions.

Demographic Characteristics of AIA and AIU

Acetylsalicylic acid-intolerant asthma is a clinical syndrome, characterized by eosinophilic rhinosinusitis, nasal polyposis, ASA sensitivity, and a moderate to severe degree of asthmatic symptoms [7, 8]. This condition most commonly occurs in middle-aged female asthmatic patients with chronic rhinosinusitis and/or nasal polyps [9]. The lysine-ASA bronchoprovocation test has been widely used to confirm the diagnosis of AIA in Europe and Asia [10, 11], whereas the oral provocation test has been more commonly applied in the USA.
Acetylsalicylic acid ingestion can induce swelling and aggravate wheals in patients with acute and chronic urticaria. Patients experiencing acute ASA-intolerant urticaria (AIAU) are defined as those showing urticaria and angioedema when exposed to ASA/non-steroidal anti-inflammatory drugs (NSAIDs). In chronic ASA-intolerant urticaria (AICU), chronic urticaria and/or angioedema symptoms are aggravated with exposure to ASA. AIU, which includes both AIAU and AICU, can be confirmed by an oral ASA challenge test. Chronic urticaria patients are classified into two groups: those exhibiting a positive response to oral ASA challenge (diagnosed as AICU), and those exhibiting a negative response, which is defined as ASA-tolerant chronic urticaria/angioedema (ATCU). The proportion of patients with chronic urticaria who develop exacerbation after ASA administration ranges from 20% to 30% [6]. Our recent study [12] demonstrated that AICU patients tended to be relatively young and to exhibit a high atopic rate as well as a high serum total immunoglobulin E (IgE) level. No significant differences in the prevalence of thyroid autoantibodies, the prevalence of anti-nuclear antibodies, or other clinical parameters were noted between AICU and ATCU patients.

A recent study reported that the prevalence of serum specific IgE to staphylococcal superantigens, particularly toxic shock syndrome toxin 1 (TSST-1), was significantly higher in AICU than in ATCU or normal controls, whereas the colonization rate of Staphylococcus aureus was similar between the two conditions. Moreover, patients with high specific IgE to these superantigens showed a higher serum total IgE level and atopy rate. These findings suggest that the Th2 immune response to these superantigens may be involved in the pathogenic mechanism of a subtype of AICU [13].

**Differential Contributions of Genetic Polymorphisms to ASA Hypersensitivity**

**Genetic Studies of AIA**

An association between the human leukocyte antigen (HLA) allele HLA-DPB1’0301 and AIA was first reported in a Polish population [14] and was later recognized in a Korean population [15]. The frequency of DPB1’0301 was significantly increased in AIA patients when compared with normal and asthmatic controls, suggesting that the immune recognition of an unknown antigen may be part of the pathogenesis of AIA [15]. The patients with DPB1’0301 tended to be females, having lower forced expiratory volume at 1 s (FEV1) levels, but higher prevalence of rhinosinusitis and/or nasal polyps than those lacking DPB1’0301. Interestingly, these are also the typical clinical features of AIA [15]. Furthermore, the presence of DPB1’0301 was significantly associated with a requirement for a higher dose of leukotriene receptor antagonist in the long-term management of AIA [16]. When combined, these results suggest that HLA-DPB1’0301 may be an important genetic marker for the AIA phenotype. Furthermore, a genetic interaction