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Association of interleukin 1 receptor-like 1 gene polymorphisms with eosinophilic phenotype in Japanese adults with asthma ☆

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ABSTRACT

Background: IL1RL1 (ST2) is involved in Th2 inflammation including eosinophil activation. Single nucleotide polymorphisms (SNPs) of the *IL1RL1* gene are associated with asthma development and increased peripheral blood eosinophil counts. However, the association between *IL1RL1* SNPs and eosinophilic phenotype among adults with asthma remains unexplored.

Methods: In a primary cohort of 110 adult Japanese patients with stable asthma, we examined the associations between *IL1RL1* SNPs and clinical measurements including forced expiratory volume (FEV_1), airway reversibility of FEV_1, exhaled nitric oxide (FeNO), serum soluble-ST2 (sST2) levels, peripheral blood eosinophil differentials and serum total IgE level. The findings in the primary cohort were confirmed in a validation cohort of 126 adult Japanese patients with stable asthma.

List of abbreviations: FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in one second; GWAS, genome-wide association study; ICS, inhaled corticosteroids; IL1RL1, interleukin 1 receptor-like 1; LD, linkage disequilibrium; SNP, single nucleotide polymorphism; Th2, T helper cell type 2

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SNP
ST2

Results: Patients with minor alleles in 3 SNPs (rs17026974, rs1420101, and rs1921622) had high FeNO, blood eosinophil differentials, and reversibility of FEV_1, but low levels of serum sST2 and FEV_1. Minor alleles of rs1041973 were associated with low serum sST2 levels alone. In the validation cohort, minor alleles of rs1420101 were associated with high FeNO and blood eosinophil differentials, whereas minor alleles of rs17026974 and rs1921622 were associated with high blood eosinophil differentials and FeNO, respectively. Multivariate analyses revealed that the minor allele of rs1420101 additively contributed to the FeNO, blood eosinophil differentials, and reversibility of FEV_1.

Conclusions: The minor alleles of *IL1RL1* SNPs were associated with high FeNO and peripheral blood eosinophilia among adult Japanese patients with stable asthma. *IL1RL1* SNPs may characterize the eosinophilic phenotype with greater eosinophilic inflammation in the Japanese asthma cohort.

1. Introduction

Chronic airway inflammation, reversibility, and hyperresponsiveness are the characteristic pathophysiological features of asthma. T helper cell type 2 (Th2) immunity, mediated by eosinophils, basophils, macrophages, and lymphocytes, has been shown to be involved in the development and persistence of airway inflammation in asthma pathogenesis [1]. Evidences indicate that interleukin 1 receptor-like 1 (IL1RL1), also known as suppression of tumorigenicity 2 (ST2), is a key molecule in the Th2-mediated allergic inflammation process [2]. IL1RL1 is a member of the Toll-like/IL-1 family, and includes 4 isoforms: a longer membrane-anchored form (ST2L), a shorter soluble form (sST2), and two variant forms (ST2V and ST2LV) [3,4]. ST2L is a transmembrane receptor for IL-33, and is expressed on Th2 lymphocytes [2], mast cells [5], eosinophils [6,7], basophils [8], and airway epithelial cells [9]. The binding of IL-33 to ST2L induces Th2-associated functions, such as mast cell maturation and degranulation [5,10,11], eosinophil adhesion [7], and IL-5/IL-13 production from Th2 lymphocytes [3,8,12]. Recent evidence shows that type 2 innate lymphoid cells (ILC2s) are important drivers for eosinophilic inflammation through the IL-33-IL1RL1 axis [13,14]. The release of Th2 cytokines (such as IL-4, IL-5, and IL-13) contributes to the exacerbation of airway inflammation and hyperresponsiveness [15]. In contrast, sST2 inhibits Th2 immunity by acting as a decoy receptor for IL-33 [16,17].

The genetic associations between *IL1RL1* and asthma susceptibility have been repeatedly demonstrated in recently published articles [18–22]. In a genome-wide association study (GWAS), single nucleotide polymorphisms (SNPs) of *IL1RL1* and *IL-33* were found to be significantly associated with the development of asthma and the number of peripheral blood eosinophils [18]. A SNP in the distal promoter region of *IL1RL1*, -26999G/A, has been reported to be associated with childhood asthma severity [19]. In addition to asthma, *IL1RL1* SNPs have also been reported to be associated with the onset of atopic dermatitis [23,24]. A recent study revealed that multiple SNPs in *IL1RL1* were associated with IL1RL1 expression in airway epithelial cells and severe asthma with a Th2-like phenotype [20]. Apart from these genetic associations, the serum level of sST2 is considered to be an inflammatory marker, with elevated levels observed in asthma exacerbation [19,25], noncardiac dyspnea [26], sepsis [27], and ischemic heart disease [28].

Eosinophilic inflammation, as a downstream effect of Th2 immunity, is one of the common features of asthma, and a cluster analysis of asthmatic populations has identified eosinophilic asthma as a distinct clinical phenotype [29]. As the aforementioned reports have described the possibility of IL1RL1 being a key molecule responsible for eosinophilic inflammation in the pathogenesis of asthma, we hypothesized that *IL1RL1* genotype may affect the eosinophilic phenotype among Japanese asthmatic patients. In this study, we examined the associations between *IL1RL1* SNPs and clinical measurements of eosinophilic phenotype including serum sST2 levels in Japanese adult patients with stable asthma.

2. Methods

2.1. Patients and study design

Study patients of the primary cohort ($n=110$) were recruited consecutively from our outpatient clinic between January 2009 and July 2010. As a second (validation) cohort, we used pooled whole blood samples ($n=126$) collected from consecutive patients between June 2003 and December 2008 at our outpatient clinic. Furthermore, we also collected their clinical data retrospectively, except serum sST2 levels due to the lack of stored serum samples. Patients were diagnosed as having asthma according to the criteria proposed by the American Thoracic Society (ATS) [30]. Each patient was found to have at least one of the following criteria: airway reversibility with 200 ml and 12% increase in forced expiratory volume in one second (FEV_1) after bronchodilator use, airway hyperresponsiveness to methacholine, or typical asthma symptoms including wheeze, dyspnea, or cough with treatment responses to β_2-adrenergic receptor agonists or inhaled corticosteroids (ICS). Asthma severity was defined according to the 2010 Global Initiative for Asthma guidelines [31]. Patients were included in the study if they had stable asthma without any history of respiratory infection or asthma exacerbation requiring oral or intravenous corticosteroid treatment, for at

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