

Pharmacogenetics of asthma in children

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Allergic diseases such as bronchial asthma and atopic dermatitis develop by a combination of genetic and environmental factors. Several candidate causative genes of asthma and atopy have been reported as the genetic factors. The clinical features of patients and causes of diseases vary. Therefore, personalized medicine (tailor-made medicine) is necessary for the improvement of quality of life (QOL) and for asthma cure. Pharmacogenetics is very important for personalized medicine. Here, we present the genetics and pharmacogenetics of asthma in children. Finally, we show the guideline for personalized medicine for asthma, particularly in childhood, including the pharmacogenetics of anti-asthmatic drugs, preliminarily produced by the authors.

Key Words: Pharmacogenetics; asthma; individualized medicine

INTRODUCTION

Allergic diseases such as bronchial asthma and atopic dermatitis develop as a result of a combination of genetic and environmental factors. Several candidate causative genes of asthma and atopy have been reported as the genetic factors.

Recently treatment/management guidelines on bronchial asthma and many other disorders have been published, and they are used in clinical practice. However, the clinical features of patients and causes of diseases vary. Therefore, personalized medicine (tailor-made medicine) is necessary for the improvement of quality of life (QOL) and for asthma cure. Pharmacogenetics is very important for personalized medicine.

Here, we present the genetics and pharmacogenetics of asthma in children.

GENETIC PREDISPOSITION TO DEVELOPMENT OF ASTHMA AND ATOPY

There is sufficient evidence to indicate that asthma is hereditary. A number of studies have shown an increased prevalence of asthma and the phenotype associated with asthma among the offspring of subjects with asthma compared with the offspring of subjects without asthma.

Many studies have shown that there is a genetic accumulation in the development of asthma and allergic disorders. Therefore, the development of asthma and allergic disorders is correlated

with some genes. We consider that multiple causative genes are involved, and not a single gene, because there are multiple pathogenesises of asthma and allergic reactions.

GENES RELATED TO DEVELOPMENT OF ASTHMA AND ATOPY

Many candidate genes related to the development of asthma and atopy have been identified, and different genes may be involved in different ethnic groups.¹ Among more than 100 genes determined from candidate gene association studies, 79 genes are associated with an asthma- or atopy-related phenotype in 2 or more independent study samples.²

Next, we focus on the several genes related to the development of asthma and atopy, in accordance with the various stages of allergic reaction and development of asthma and atopy.

HLA genes and asthma

HLA genes have been reported to be associated with bronchial asthma.³ Moreover, a relationship between the severity of childhood asthma and HLA type has been reported.⁴

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Received: September 3, 2009; Accepted: September 14, 2009.

• There are no financial or other issues that might lead to conflict of interest.

Genetic variation of cytokine signaling in atopy, and enhanced IgE production

IgE production is upregulated by Th2 cytokines, particularly interleukin-4 (IL-4), and is downregulated by Th1 cytokines, particularly interferon- γ (IFN- γ). Interleukin-12 (IL-12) and interleukin-18 (IL-18) are the cytokines that induce IFN- γ and downregulate IgE production.⁵ We review the genetic variation of the cytokine signaling in atopy, and enhanced IgE production.

This item is divided into two parts, (i) "*Genes related to upregulation of IgE production in asthma and atopy*" and (ii) "*Genes related to downregulation of IgE production in asthma and atopy*."

Genes related to upregulation of IgE production in asthma and atopy

Several linkage analyses and mutations of candidate genes of atopy (i.e., enhanced IgE production) have been reported. In 1989, Cookson et al.⁶ reported a linkage between IgE responses underlying asthma and rhinitis and chromosome 11q. Moreover, Shirakawa et al.⁷ reported that a common variant of Fc ϵ R1 β on chromosome 11, Ile181Leu within the 4th transmembrane domain, shows significant association with positive IgE responses. Several associations have been noted between atopy and genes on the chromosome 5 cytokine cluster, including IL-4.

An Ile50Val (numbering for mature peptide) variant of human IL-4R α has been identified. In 1998, Mitsuyasu et al.⁸ reported that the Ile50Val variant of the IL-4R α chain upregulates IgE synthesis and is associated with atopic asthma. Ile50 is associated with atopic asthma but not with nonatopic asthma; Ile50 is specifically and significantly associated with increased total serum IgE levels and mite-specific IgE. The association with atopy was particularly strong in children.⁸ The data from both mouse and human cell lines strongly suggest that the Ile50 variant of IL-4R α significantly upregulates receptor response to IL-4, with a resultant increased activation of Stat6, and hence, increased cell proliferation and increased IgE production. Moreover, Shirakawa et al.⁹ noted genetic variants of IL-13.

Genes related to downregulation of IgE production in asthma and atopy

The genetic defects in the downregulation (brake) of IgE production, particularly in terms of IL-12 and IL-18 signalings, are discussed. We found that the reduced IFN- γ production by peripheral blood mononuclear cells (PBMCs) following stimulation with IL-12 or IL-18 is associated with heterozygous IL-12 receptor β 2 (IL-12R β 2) chain gene mutations (2496 del 91, 1577 A to G (Arg 313 Gly), 2799 A to G (His 720 Arg) or IL-18 receptor α (IL-18R α) chain gene mutation (del 950 CAG) in atopic subjects.^{10,11}

We identified a novel heterozygous single-nucleotide substitution 1400 T to C (Leu 467 Pro), in the seventh exon of the IFN- γ receptor 1 (IFN- γ R1) chain gene.¹² This substitution was detected in six of 89 allergic patients (including asthma), but not

in 72 nonallergic subjects. There was a difference in the Leu 467 Pro frequency between allergic and nonallergic subjects ($P < 0.05$). The serum IgE levels of the allergic patients with the Leu 467 Pro substitution were higher than those of the nonallergic subjects ($P < 0.001$). These results suggest that Leu 467 Pro in the IFN- γ R1 chain gene is one of the candidate susceptibility genes for asthma or atopic diseases.

Genetic variation of mediators and other molecules in asthma and atopy

LTC4S and asthma

The locus of leukotriene C4 synthase (LTC4S) is on chromosome 5q35 and has been associated with allergic diseases on the basis of a genomewide search. Cysteinyl leukotrienes (cysLTs) play important roles in asthma and can mediate bronchial smooth muscle constriction and increase mucous secretion, vascular permeability, and cellular infiltration.¹³ LTC4S converts LTA4 to LTC4 by conjugation to reduced glutathione. A single-nucleotide promoter polymorphism (A-444C) in LTC4S has been associated with aspirin-sensitive asthma,^{14,15} although recent studies have found no association between this promoter polymorphism and aspirin-sensitive asthma.¹⁶

Very recently, we have reported that a novel single-nucleotide substitution 10G>A (Glu 4 Lys) in LTC4S is associated with asthma.¹⁷

nNOS and asthma

Nitric oxide (NO) is produced by a group of enzymes referred to as nitric oxide synthase: endothelial (eNOS), neuronal (nNOS), and inducible NOS (iNOS). The association of some nNOS markers with asthma or related phenotypes has been reported.¹⁸

Genetic defects in target organs in asthma and atopy

ADR β 2 and asthma

There was no relationship between β 2-adrenergic receptor (ADR β 2) polymorphisms and asthma prevalence, but the Gly-16 variant was apparently associated with a more severe form of asthma.¹⁹ Subsequently, Turki et al.²⁰ found that the Gly-16 allele is more frequent among subjects with nocturnal asthma than among nonnocturnal asthmatics.

ADAM33 and asthma

Van Eerdewegh and Holgate et al.²¹ performed a genomewide scan on 460 Caucasian families and identified a locus on chromosome 20p13 that is linked to asthma (Log₁₀ of the likelihood ratio LOD, 2.94) and bronchial hyperresponsiveness (LOD, 3.93). A survey of 135 polymorphisms in 23 genes identified the ADAM33 gene as being significantly associated with asthma using case control, transmission disequilibrium and haplotype analyses ($P = 0.04-0.000003$). ADAM proteins are membrane-anchored metalloproteases with diverse functions, which include the shedding of cell-surface proteins such as cytokines

and cytokine receptors. The identification and characterization of ADAM33, a putative asthma susceptibility gene identified by positional cloning in an outbred population, should provide insights into the pathogenesis and natural history of this common disease.

GENETIC CLASSIFICATION OF ATOPY AND ASTHMA

On the basis of many reports and our results, we present a new genetic classification of atopy and asthma in Fig. 1.²² There are four categories of genes that control the expression of allergic disorders, which include (i) antigen recognition, (ii) IgE production (downregulation=brake, and upregulation), (iii) production and release of mediators, and (iv) events on target organs. This genetic classification will facilitate the development of pharmacogenetics and personalized medicine.

PHARMACOGENETICS OF ASTHMA

The response of an individual patient to any given drug depends on several factors such as pathogenesis of disease, compliance, disease severity, and genetic background.²³ The great hope in pharmacogenetics is that it will help predict either treatment response (efficacy) or the risk of adverse drug reactions in the general population and that it will prove cost-effective to genotype individuals before treatment,²³ that is, for personalized medicine (tailor-made medicine). Here, we review the pharmacogenetics of anti-asthmatic drugs.

Pharmacogenetics of β 2-agonists

Beta2-agonists act via binding to the β 2-adrenergic receptor (ADR β 2), that is, a cell surface G-protein-coupled receptor. The β 2-adrenergic receptor has several polymorphisms in the coding region, such as Arg 16 Gly, Gln 27 Glu, and Thr 164 Ile. The

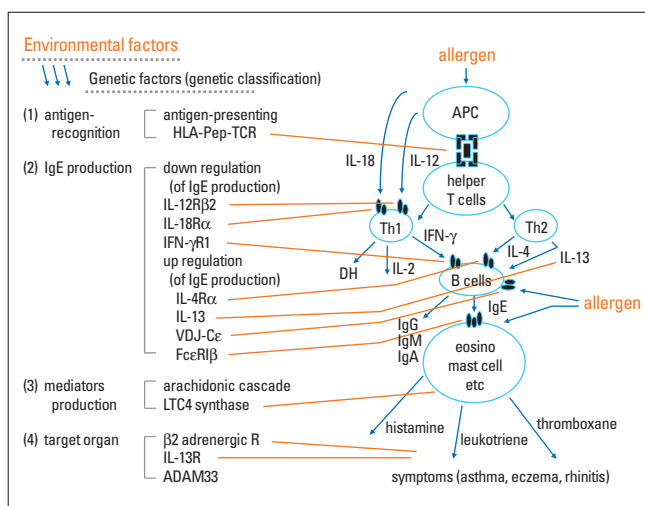


Fig. 1. A new genetic classification of asthma and atopy.

Arg 16 Gly and Gln 27 Glu are functionally important. Patients with homozygous for Arg 16 did worse clinically in terms of the major end points and showed adverse effects, rather than homozygous for Gly 16.²⁴⁻²⁶

Pharmacogenetics of leukotriene antagonists

Leukotrienes are very important mediators in asthma in children as well as in adults. Leukotrienes are released by eosinophils, mast cells, and alveolar macrophages. In the production of leukotrienes, several enzymes such as 5-lipoxygenase (ALOX5) and leukotriene C4 synthase (LTC4S) are important. LTC4S is a membrane-bound glutathione transferase, and synthesizes cysteinyl-leukotrienes, converting LTA4 to LTC4.

In the treatment with zafirlukast (one of the leukotriene receptor antagonists), patients with the homozygous for A-444 showed a lower FEV1 response than those with the A/C or C/C genotype.²⁷

Moreover, treatment with leukotriene receptor antagonists (montelukast or pranlukast) was more effective on adult or pediatric patients with the A/C or C/C genotype at position-444 (LTC4S-444) than on those with the A/A genotype.^{28,29}

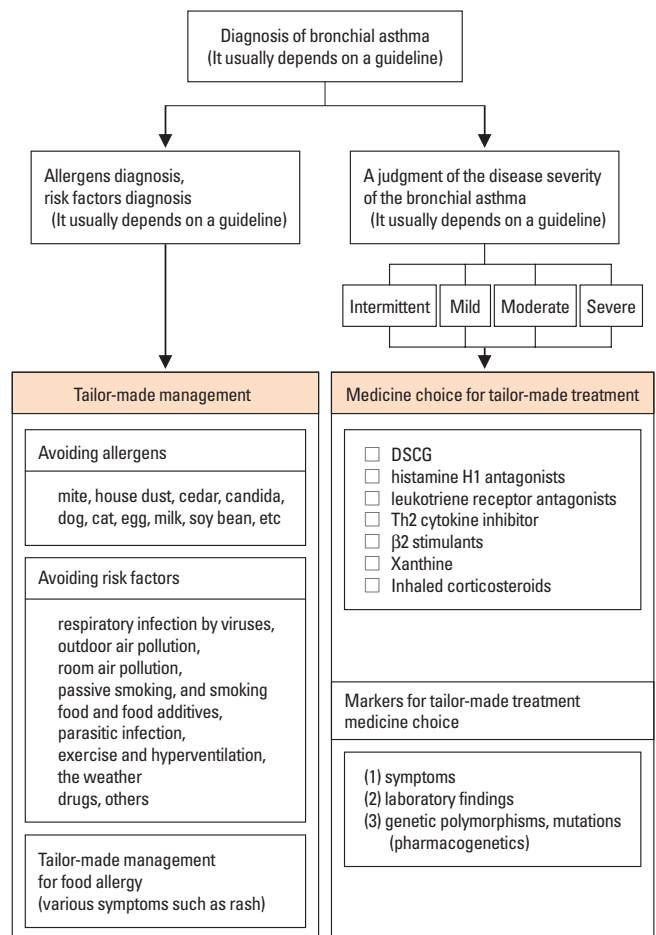


Fig. 2. Management of personalized medicine (tailor-made medicine) for asthma.

Pharmacogenetics of a Th2 cytokine inhibitor

Suplatast tosilate is a Th2 cytokine inhibitor.³⁰ In our recent study, treatment with suplatast tosilate was more effective in children without the -444 A/C polymorphism of the LTC4S gene, and in children without the IL-13 variant Arg 110 Gln. In children who responded well, IFN- γ production was significantly increased after treatment.

Pharmacogenetics of corticosteroids

Inhaled corticosteroids (ICS) are very effective for asthma in children as well as adults. However, there are patients with severe asthma who show no response to treatment with ICS. There are reports concerning the pharmacogenetics of corticosteroids. The IL-4 589T allele (589 C/T SNP) was found to be associated with ICS-resistant asthma.^{31,32} The TBX21 (T-bet) gene

(His 33 Gln) and the corticotropin-releasing hormone receptor 1 (CRHR1) gene are important for the pharmacogenetics of ICS.³³ Particularly in Caucasian children, the heterozygous TBX21 33 His/Gln individuals demonstrated a marked improvement in airway hyperresponsiveness compared with 33 His/His homozygotes on ICS therapy.^{33,34}

PERSONALIZED MEDICINE (TAILOR-MADE MEDICINE) FOR ASTHMA IN CHILDHOOD

The clinical features of patients and causes of diseases vary. Therefore, personalized medicine is necessary for the improvement of QOL and for asthma cure. Pharmacogenetics is very important for personalized medicine. Here, we show the guideline for personalized medicine for asthma, particularly in chil-

	DSCG	H1-antagonists	LTRA	Th2 cytokine inhibitor	long-acting theophylline	β 2 agonists		ICS
	effective	effective	effective	effective	(side effect)	effective	(non-effective)	effective
(1) Symptoms and clinical findings								
viral infection			○					
exercise induced asthma	○		○			○		
aspirin induced asthma	○		○					
complicated with allergic rhinitis			○					
complicated with atopic dermatitis		○						
(2) Laboratory findings								
reduced No. of eosinophil or basophil in peripheral blood				○				
reduced production of IFN- γ				○				
increased LT level in urine			○					
reduced expression of CysLT1R in eosinophil (less than 60%)			○					
(3) Gene polymorphisms and mutations (Pharmacogenetics)								
LTC4S A-444C (AA)				○				
LTC4S A-444C (AC or CC)			○					
IL-13 R110Q (R)				○				
ALOX5 (rs2115819 GG)			○					
MRP1 (rs119774 CT)			○					
CYP1A2 -3594(GT)					○			
ADRB2 R16G (R)							(○)	
TBX21 (T-bet) H33Q (H/Q or Q/Q)								○
CRHR1 (rs1876828)								○

Fig. 3. Medicine choice for personalized medicine based on the symptoms, laboratory findings and pharmacogenetics.

○ : positive markers; (○) : possible markers.

DSCG, disodium cromoglycate; H1-antagonists, histamine H1-receptor antagonists; LTRA, leukotriene receptor antagonists; ICS, inhaled corticosteroids; LT, leukotriene; LTC4S, leukotriene C4 synthase; ALOX5, 5-lipoxygenase; MRP1, Multidrug resistance-associated protein 1; ADR β 2, β 2-aderenergic receptor; CRHR1, corticotropin-receptor 1 releasing hormone; R, Arginine; G, Glycine; H, Histidine; Q, Glutamine.

dren, including the pharmacogenetics of anti-asthmatic drugs, preliminarily produced by the authors (Figs. 2, 3).

Asthma develops by a combination of genetic and environmental factors. There are many environmental factors such as allergens (house dust, mites, foods, and pets so on), viral infections, exercise, passive smoking, and air pollution. The environmental factors are different for each patient. Therefore, it is very important to first eliminate each environmental factor for each patient and to take preventive measures against each environmental factor (Fig. 2), that is, the personalized preventive measures. The preliminary guideline for personalized medicine (tailor-made medicine) for asthma has been published, on the basis of various clinical symptoms, various laboratory findings, as well as pharmacogenetics of anti-asthmatic drugs.

Figure 3 shows the guideline for personalized medicine. For example, as one of the markers of symptoms, for viral-induced asthma, leukotriene receptor antagonists are effective. For exercise induced asthma, disodium cromoglycate (DSCG), leukotriene receptor antagonists, or β_2 -agonists are effective. As one of the laboratory findings, in the patients with poor IFN- γ production, Th2 cytokine inhibitor is effective. As one of the gene markers, in LTC4S-444 A/A type, Th2 cytokine inhibitor is effective, and in LTC4S-444 A/C or C/C type, leukotriene receptor antagonists are effective. In TBX21 (T-bet) 33 His/Gln or Gln/Gln, ICS is effective.

In the near future, the guidelines for the personalized medicine (tailor-made medicine) for asthma will become more available. For personalized medicine, it is necessary for us to obtain both the approval of an ethical committee and informed consent.

ACKNOWLEDGMENTS

This study was supported by Health and Labour Science Research Grants from the Ministry of Health, Labour and Welfare for Research on Allergic Disease and Immunology.

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