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The association between sixteen genome-wide association studies-related allergic diseases loci and childhood allergic rhinitis in a Chinese Han population

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ABSTRACT

Background: Allergic rhinitis (AR) is one of the most common respiratory diseases in children. It is caused by a combination of genetic and environmental factors. Moderate-to-severe AR decreases the quality of life and social performance in children.

Objective: To investigate whether polymorphisms in previously published genome-wide association studies (GWAS) allergic disease loci are associated with childhood AR and the severity of AR symptoms in a Chinese Han population.

Methods: A case-control study was conducted in 503 pediatric patients with AR and 393 control Chinese school-aged subjects. AR severity was classified as mild or moderate-to-severe according to the AR and its Impact on Asthma (ARIA) guidelines. Overall, 16 tagged single-nucleotide polymorphisms (tSNPs) of published GWAS associations with allergic diseases were selected. All subjects were genotyped and analyzed for the 16 selected tSNPs using the improved multiplex ligation detection reaction (iMLDR) technique.

Results: Both rs7130588_AG and rs7927894_CT genotypes in *EMSY* region were associated with a significantly increased risk of AR (1.75-fold and 1.50-fold) compared to the AA and CC genotypes, respectively, specific to moderate-to-severe AR. The difference of rs7130588 genotypes in cases vs. controls was still statistically significant under the additive model after multiple test correction to adjust the false discovery rate (FDR) with an adjusted odds ratio of 1.818 and 95% confidence interval (CI) of 1.240–2.664 (P_{FDR} = 0.0349). The rs7130588_G allele was only associated with a high risk of moderate-to-severe AR (1.85-fold, $P_{age\ and\ gender\_adjustment}$ = 0.003). The rs2227284_TG genotype at the *IL4* locus was significantly associated with a 0.65-fold decreased risk of AR compared to the TT genotype. The protective effect of the rs2227284_G allele was also found in different severity of AR. Haplotype analysis showed a significantly increased AR risk associated with the haplotype G-T-T (rs7130588-rs2155219-rs7927894) and a protective effect with the haplotype C-G-C (rs2243250-rs2227284-s2243290).

Conclusions: The loci in *EMSY* and *IL4* can be considered as a hereditary marker for childhood AR. The rs7130588_G allele seems to predispose only to moderate-to-severe AR, though other mechanisms are also likely to be involved.

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1. Introduction

The prevalence of allergic diseases, including allergic rhinitis (AR), in children, appears to have increased since industrial revolution commenced. AR, a chronic inflammatory disease of the upper airway, is not only one of the most common chronic diseases in children, but also a global health problem [1]. The reported prevalence of AR varies widely, ranging from 7.83 to 48% in China, resulted from sampling strategy, the definition of AR, the ages of the children and the study results across cities with the different gross domestic product and health-system coverage [2–4]. In 2015, Li et al. [5] reported that the prevalence of AR was 12.9% of school-aged children in Shanghai, China. Besides presenting recognized common symptoms of AR such as sneezing, rhinorrhea, nasal obstruction, and compromised respiratory function, children suffering from AR also have additional impairments such as decreased school performance, sleep disturbance, and emotional and other psychosocial problems [6]. The severity of AR can therefore be classified as “mild” or “moderate-to-severe” according to the World Health Organization (WHO) guidelines entitled Allergic Rhinitis and its Impact on Asthma (ARIA) [1].

AR is typically a multifactorial disease caused by the interplay of genetic and environmental factors. Genetic variations are components of genetic factors. Genome-wide association studies (GWAS) have revealed allergic disease susceptibility loci in an unbiased and hypothesis-free manner. Many candidate genes in susceptibility loci suggest roles for innate immunity and immunoregulation including type 2 T helper (TH2) cell differentiation and effectors’ functions, epithelial barrier functions, *IL1* family signaling, and regulatory T cells in the pathogenesis of allergic diseases. The first GWAS on allergic sensitization identified putative susceptibility loci including 11q13.5 near *EMSY* (previously known as *C11orf30*) and the HLA region at 6p21.32 in individuals of European origins with AR only sensitization to a single allergen (grass), [7] which was previously associated with atopic dermatitis(AD) [8] and asthma [9]. Polymorphisms in *IL-18* and *IL18RAP* in the IL-1 family signaling were reported to be associated with AD in a Japanese population [10]. The association of *IL-13* SNP rs20541 with AR was found in an Asian population of ethnic Chinese in Singapore [11]. Polymorphisms in *IL-4* have been associated with increased total serum IgE levels [12], and asthma [13] in some populations but not associated with AR in the Asian populations [14]. Rs2897422 in *KIF3A* encoding a component of the kinesin complex involved in the assembly of cilia, met genome-wide significance in AD cases and controls of European descent [15]. Independent replication of genotype-phenotype associations in distinct populations is generally thought to provide the most convincing evidence for the identification of a true disease susceptibility gene [16].

In view of the existing evidence, we conducted a study to test whether genetic loci associated with allergic diseases including (*EMSY)* and leucine rich repeat containing 32 (*LRRC32*) at 11q13.5, the HLA region at 6p21.32, *IL18R1* and *IL18RAP* at 2q12.1, and *IL13, IL4*, and *KIF3A* at 5q31.1 [11] are associated with AR risk and the severity of AR in a Chinese Han population. Confirming the association will strengthen the evidence for a causal relationship and elucidate the common genetic basis of AR and other allergic diseases.

2. Methods

2.1. Study subjects

We used a population-based case-control association study design to assess the risk of AR in Chinese children. Five hundred and three patients suffering from AR were recruited from the outpatient clinic of Otolaryngology Department at Shanghai Children's Medical Center from January 2015 to December 2015. Their ages ranged from 4 to 14 years. Age and gender matched controls were healthy children undergoing regular physical examination in our hospital. All subjects were ethnic Han Chinese, who had lived in the Shanghai region, China, since birth. The study approved by the ethics committee of Shanghai Children's Medical Center, and written informed consent was obtained from the parents or legal guardians. Of them, 156 patients with AR and 173 matched controls were enrolled in the preliminary study.

2.2. Clinical evaluation

We clinically diagnosed 503 patients with AR according to ARIA 2008 guidelines [1], with the recurrence of symptoms over a year; i.e., two or more persistent symptoms of water-like tears, nasal itching, congestion, or sneezing lasting for more than 1 h every day. One or more serum IgE species (SIgE) were found positive ($\geq$0.35 kU/ml) by Western blotting using AllergyScreen™ human serum specific IgE allergen

Table 1
Clinical and demographic characteristics of the study subjects.

Demographic index	AR						Control
	Mild n = 254	p^a	Moderate-to-severe n = 249	p^b	Total n = 503	p^c	n = 393
Gender, n (%)							
Male	164(64.8)	0.100	147(59.0)	0.806	311(61.8)	0.271	228(58.0)
Female	90(35.4)		102(41.0)		192(38.1)		165(41.9)
Age(years), SD	6.1(2.6)	0.114	5.82(2.9)	0.569	5.9(2.7)	0.156	5.61(1.8)
Weight(kg), SD	25.1(9.2)	0.100	24.2(11.2)	0.447	24.7(9.6)	0.113	23.1(7.5)
Height(cm), SD	120.3(19.1)	0.224	118.9(18.6)	0.522	119.6(18.8)	0.205	117.1(12.6)
Allergen category, n (%)							
House dust mite	180(70.87)		179(71.89)		359(71.37)		n
Cat/dog hair	97(38.19)		80(31.50)		177(35.19)		n
Molds	61(24.02)		47(18.88)		108(21.47)		n
Seasonal grass/tree pollens	25(9.84)		22(8.84)		47(9.34)		n
Cockroaches	17(6.69)		19(7.63)		36(7.16)		n
ragweed	16(6.30)		17(6.82)		31(6.16)		n
Artemisia argyi	14(5.51)		13(5.22)		27(5.37)		n
Penicillium notatum	14(5.51)		16(6.42)		30(5.96)		n
Aspergillus fumigatus	12(4.72)		11(4.41)		23(4.57)		n

[a] *P* value for the comparison between mild and controls calculated by $\chi 2$ test for categorical variables or *t*-test for continuous variables.
[b] *P* value for the comparison between moderate/severe AR and controls calculated by $\chi 2$ test for categorical variables or *t*-test for continuous variables.
[c] *P* value for the comparison between AR and controls calculated by $\chi 2$ test for categorical variables or *t*-test for continuous variables.