

ABO/secretor genetic complex is associated with the susceptibility of childhood asthma in Taiwan

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Summary

Background Histo-blood groups, ABO, Lewis (Le) and secretor (Se) were found to be associated with lower lung function and wheezing in coal miners as well as in asthmatic children in some studies but not others, possibly reflecting the genetic heterogeneity among different ethnicities and local environmental exposure.

Objective The present study was conducted to determine the association between ABO, Lewis and secretor genetic complex with susceptibility of childhood asthma in Taiwan.

Methods We randomly selected 136 asthmatic children and 161 age-matched controls from a childhood asthma survey conducted in primary schools. ABO and Lewis blood groups were determined by red blood cell agglutination methods. Analysis of Se genotype was performed by PCR with sequence-specific primers.

Results There was a higher prevalence rate in secretor subjects (Se/Se) (odds ratio (OR) = 1.7, confidence interval (CI) = 1.022–2.938) in asthma as compared with controls. The combined effect of these three blood systems revealed that blood group O/secretor phenotype (Se/Se) (OR = 2.7, CI = 1.126–6.033), and blood group O/Le(a–b–) (OR = 3.6, CI = 1.080–11.963, $P < 0.03$) individuals were significantly associated with asthma. The Lewis Le(a–b–) recessive genotype (OR = 3.3, CI = 1.267–8.482), or the joint blood group O/Le(a–b–) phenotype (OR = 5.2, CI = 1.259–21.429, $P < 0.02$), was significantly associated with high serum IgE (> 500 IU), respectively. There was no association of these three blood systems with the sensitivity of dust mite, *Dermatophagoide pteronyssinus*, in our study population.

Conclusions We concluded that blood group O/secretors (Se/Se) and O/Le(a–b–) were associated with childhood asthma, and may act as one of the predominant factors for environmental triggers of allergy for asthmatic children in Taiwan.

Keywords ABO, childhood asthma, Lewis histo-blood group, secretor, Taiwanese

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Introduction

Although the ABO blood group was initially found in red blood cells, it is well known that tissues expressing abundant ABO antigens are the digestive and respiratory organs (ABO histo-blood group) [1]. Lewis antigens are also one of the histo-blood group substances. A major characteristic of the digestive and respiratory systems is their continuous exposure to the external environment via food and air. A normal human being inhales approximately 10 000 L of air daily, which contains particulates that include bacteria and viruses. Accordingly, the respiratory organs have developed defence mechanisms, such as mucociliary clearance of inhaled particulates and the immune system [2]. Although the exact

function of the ABO histo-blood group is not yet known, recent studies have suggested that ABO, Lewis (Le) and secretor (Se) genes control glycosyltransferases that act in concert upon common precursor chains to build up oligosaccharide structures in exocrine secretions system [3–5]. Blood group antigens are also involved in the formation of mucopolysaccharides in epithelial and mucosal secretion that may play a role in the adhesion of environmental factors, such as microorganisms, and exhausted air toxic substances to epithelial cells [6, 7]. It may also relate to the defence and inflammation of airways and pulmonary function.

One previous study identified an association between chronic obstructive pulmonary disease (COPD) and blood group A [8], and a 5-year longitudinal study showed that patients with blood group A showed a more rapid decline in lung function than patients with other blood groups [9]. However, subsequent studies failed to confirm any association between blood group and COPD or lung function in other populations [10–12]. Non-secretor status of ABO histo-

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blood group was also reported to be associated with a higher risk of COPD and a greater fall in lung function with age [13–15], but these results were not found in other studies [10, 16]. As to the association of asthma, a combined analysis of ABO blood groups and salivary secretor phenotypes was recently performed in a cohort of coal miners [17], and it showed that significantly lower lung function and higher prevalence of wheezing and asthma were found in non-secretor subjects of blood group O. From the report of Ronchetti et al. [17] group in Italy, it was also revealed that the proportion of blood group O/non-secretor in asthmatic children was higher than in controls. Therefore, the association between blood groups and disease susceptibility in the literature remains conflicting and needs further study for clarification.

The ABO and Lewis antigen profiles of epithelial surfaces are a result of complex interactions among three structural gene loci: ABO, Le and H. The Lewis phenotype of a person is determined by the epistatic interaction of the $\alpha(1,2)$ -fucosyltransferase and $\alpha(1,3/1,4)$ -fucosyltransferase encoded by the secretor (Se or FUT2) and Lewis (Le or FUT3) loci, respectively [18]. The four major Lewis phenotypes are: (a) Lewis negative secretor and non-secretor Le(a–b–), (b) Lewis positive non-secretor Le(a+b–), (c) Lewis positive secretor Le(a–b+) and (d) Lewis partial secretor Le(a+b+), which is caused by an inefficient secretor transferase because of a missense mutation of A385T mutation in the Se allele, known as Se^w [19].

The gene frequency of the above four Lewis blood groups has different prevalence rates in different ethnic populations as well as in different geographical areas. For example, the Lewis positive non-secretor genotype Le(a+b–) is rarely found in Taiwan, Japan and Korea [18, 20–22], but has a relatively high frequency in Caucasians (22%). In contrast, the phenotype Lewis weak partial secretor Le(a+b+) is virtually absent in Caucasians, but has a higher frequency in East Asians, including Taiwanese (22–25%) [23–25]. Because of these discordant results regarding the association of COPD and/or asthma with secretor, Lewis and ABO histo-blood group, and the distinguished difference in the prevalence of different Lewis histo-blood group between Caucasians and Taiwanese, the present study was intended to analyse the histo-blood groups of ABO, Lewis, secretor in a cohort of asthmatic children in Taiwan so as to confirm the association observed in other populations.

Materials and methods

Study populations

Our study population consisted of 136 asthmatic children aged between 6 and 13 years (the complete Lewis phenotype revealed after 6–7 years) and 161 aged-matched controls, who were randomly selected from an allergy and asthma questionnaire survey conducted in the primary schools in Tainan city, Taiwan. All participants or their guardians, after being well informed about the study protocol, signed the consent forms, and answered a modified 'International Study of Asthma and Allergic disease in Childhood' – Chinese version (ISAAC-C), as well as additional questions pertinent to the diagnosis and assessment of asthma [26]. The Ethical and Clinical Trial Committee of National Cheng-Kung

University Hospital has approved this study protocol. The definition of asthma has been with the inclusion of (1) a history of two or more episodes of wheezing in the last 6 months, during or without concurrent respiratory infections, (2) chronic cough for more than 1 month and diagnosed by a physician regarding the presence of wheezing episode(s) and (3) confirmation of the positive response of increased 15% of forced expiratory volume in 1 s (FEV₁) by a bronchodilator test. Age-matched controls did not have one of the above conditions in their previous physical check-up and past history. Other evaluations included skin prick tests for responsiveness to six common aeroallergens, a differential blood count (including total eosinophil count) and measures of total serum IgE, as well as IgE specific to house dust and mixed pollens using the Unicap system (Pharmacia Diagnostic, Uppsala, Sweden). A positive skin test was defined as the presence of ≥ 1 reaction with a weal diameter ≥ 5 mm. Total serum IgE was measured by a solid-phase immunoassay (Pharmacia IgE EIA; Pharmacia Diagnostics).

Sample preparation and histo-blood group typing

Fresh peripheral blood from our study population was drawn into a 15 mL ACD tube. The ABO blood group was determined by agglutination of erythrocytes with appropriate antisera (Ortho Diagnostics Systems, Raritan, NJ, USA). Lewis antigen was determined by the tube method with commercial monoclonal antibodies (BioClone 2.0 anti-Le^a and anti-Le^b reagents, BioClone, NJ, USA) or by the manual polybrene method [26].

Deoxyribose nucleic acid amplification and direct sequencing of Se allele

The coding regions of the Se genes were amplified by PCR. Genomic DNAs were prepared from buffy coats by using a DNA blood kit (VIOGEN, Mountain View, CA, USA). The PCR and pair-specific primers for the secretor DNA segment encoding the secretor $\alpha(1,2)$ -fucosyltransferase gene were used to amplify the coding region of the Se gene and Se^w gene. The sense primer 5'-ACTGGATGGAGGAGGAATACCGCCA-CA-3' located at nucleotides 358–385 relative to the Se gene, and the antisense primer 5'-GCTTCTCATGCCCGGGCACTCACTTTGAG-3', is complementary to nucleotides 1042–1070 with the 3' untranslated region [21]. The molecular basis for Se^w gene (or Se³⁸⁵) was shown to be because of a missense mutation of A385T in the Se allele, using sequencing-specific primer 5'-GACTGGATGGAGGAGG AA TACCGCC ACT-3', which has a guanine instead of thymine (underlined), and a primer design covering nucleotides 358–385 was used to detect the mutated allele. Briefly, genomic DNA was extracted from peripheral blood lymphocytes using 100 ng of sample DNA in each PCR reaction and 50 pmol of each primer (including an internal control to amplify a segment of the human growth hormone), 1 $\times$ reaction buffer (Sigma Aldrich, St Louis, MO, USA) (500 mM KCl, 15 mM MgCl₂, 100 mM Tris-HCl; pH 8.3), dNTPs (2.5 mM) and 1 U Taq DNA polymerase (AB gene, Surrey, UK) were used in a total volume of 20 μ L. Amplification was performed on a Perkin Elmer 9600 DNA thermocycler (Perkin Elmer Cetus, Norwalk, CT, USA). Double-stranded DNA was denatured initially by heating to

94 °C for 5 min, followed by 35 cycle-profile of 94 °C for 20 s, 56 °C for 30 s and 72 °C for 30 s. The last PCR cycle was followed by an additional 5 min cycle at 72 °C to ensure that the final extension step was completed. Amplified products were directly electrophoresed in 2% pre-stained agarose gels, and visualized under ultraviolet illumination. The wild type will create 713 bp PCR products using the 385A primer, and no amplicons while using the 385T primer. The Se^w will be amplified and will create 713 bp PCR products using the 385T primer. To confirm the PCR results obtained by the direct sequencing technique, the ABI prism 377 automated DNA sequencer (Applied Biosystems, Foster City, CA, USA) was used, and resulted in identical genotypes for the initial 15 samples; therefore, all other samples were subsequently genotyped by PCR with sequence-specific primers (PCR-SSP).

Statistical analysis

Data analysis was performed using the SPSS statistical package (SPSS 10.0 for windows, SPSS Inc., Chicago, IL, USA). An unmatched case-control design was used to test for association between clinical asthma status and genotype (ABO blood group, secretor and Lewis histo-blood typing). The genotype frequencies among all the subjects of asthmatic and control subjects were compared by means of χ^2 tests by two-by-two contingency tables. Linkage disequilibrium was tested for by construction of a two-by-two table of allele frequencies for the two polymorphisms and calculation of a χ^2 statistics [27]. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated as a measure of the association of each genotype with asthma. All values of $P < 0.05$ were considered to be significant. Multivariate linear regression comparison of these three genotypes in asthma with total serum IgE levels as a continuous variable was also tested. For P -value determination, the level of significance was set to 0.05.

Results

Definition of the ABO/secretor genotypes in the study population

Table 1 presents the demographic, lung function and allergen sensitization profiling of children with asthma, and controls. There is no significant difference between asthma and age-matched controls in terms of mean ages and sex ratio. The allergen sensitivity profiles of Der p for asthma and controls were 80.9% and 34.2%, respectively. The total IgE concentration was markedly different between asthmatics and controls (987.8 ± 235.5 vs. 181.3 ± 41.9 IU, $P < 0.001$). As expected, children with asthma had reduced baseline FEV₁/forced vital capacity and a lower percentage of predicted FEV₁. We found no correlation between blood group genotypes and asthma severity as assessed by FEV₁ or clinical examinations. Figure 1 shows the results of PCR-SSP for identifying Se and Se^w alleles from different study subjects. The PCR product of a 713 bp fragment was amplified with the Se/Se (385A) or Se^w/Se^w (385T), and Se/Se^w, both reactive with 385A and 385T primers (Fig. 1a). These PCR products were confirmed by direct sequencing analysis (Fig. 1b).

Table 1. Demographic characteristics of asthmatic children and controls

Categories	Asthmatics (<i>n</i> = 136)	Controls (<i>n</i> = 161)
Age (years)	8.5 ± 1.2	7.9 ± 1.6
Sex		
Boys	81 (59.6)	86 (53.4)
Girls	55 (40.4)	75 (46.6)
HDM (Der p) sensitized (%) by skin prick tests (≥ histamine positive control)	110 (80.9)	55 (34.2)
Total IgE concentration (IU)**	987.8 ± 235.5	181.3 ± 41.9
Percentage of predicted FEV ₁ (%)*	91.3 ± 11.7	103 ± 10.5
FEV ₁ /FVC (%)*	85.3 ± 9.8	92.7 ± 7.6

Results shown as mean ± SD or *n* (%).

* $P < 0.01$, ** $P < 0.001$.

HDM, house dust mite; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity.

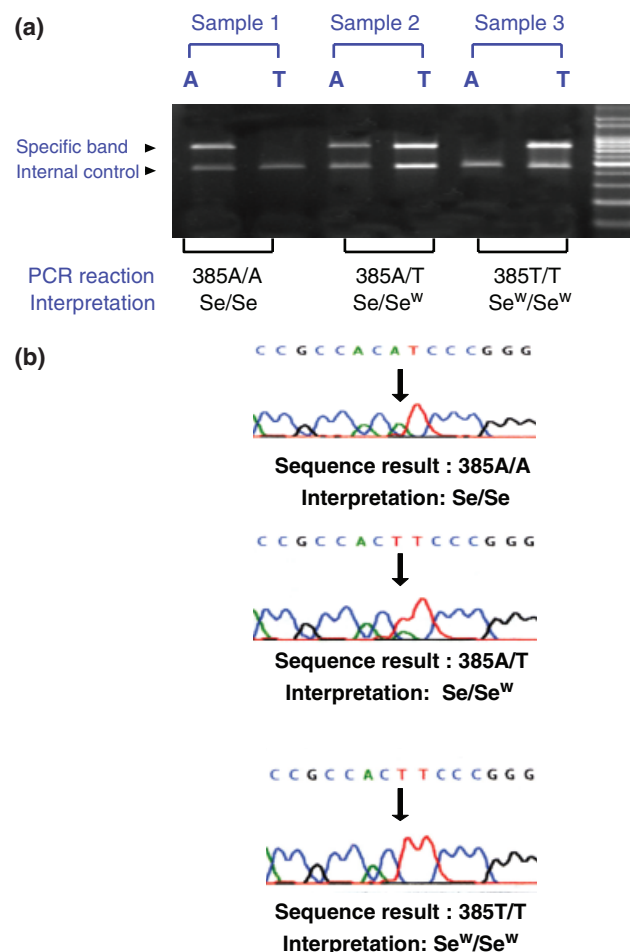


Fig 1. (a) The representative results of PCR with sequence-specific primers (PCR-SSP) analysis in three secretor genotypes (Se/Se, Se/Se^w and Se^w/Se^w). Sample 1 (Se/Se) templates generated 713 bp product only in the 385A-specific primer. Sample 2 (Se/Se^w) shows the 713 bp in both 385A- and 385T-specific primers. The Se^w/Se^w sample only reacts with the 385T primer. M denotes the 100-bp ladder marker. (b) The results of direct sequencing analysis of three secretor types (Se/Se, Se/Se^w and Se^w/Se^w). Upper sample (Se/Se) shows A/A at the codon 385, the Se/Se^w shows a T-A substitution at the codon 385 and the Se^w/Se^w sample is the T/T at the codon 385 shown in the lower panel.

Association of histo-blood phenotypes with the susceptibility of asthma

Table 2 shows the distribution of various ABO blood groups, Lewis and secretor histo-blood groups separately between asthmatic children and controls. We were unable to find any difference in the distribution of ABO blood group related to the susceptibility of asthma, although blood group O was weakly associated with asthma (OR = 1.5, CI = 0.948–2.391), but not significantly. The Lewis genotype, Le(a+b-), was not found in our study population, which has also been confirmed by others in the general survey of Taiwanese population. From the distribution of the other three genotypes of the Lewis system in asthmatic children and controls, no association of Lewis (Le) blood group with the susceptibility of asthma ($P > 0.05$) was seen. In contrast, the secretor (Se) genotype was significantly associated with asthma susceptibility in our study subjects ($\chi^2 = 6.316$, $P < 0.05$). There was a higher rate of asthma in homozygous (Se/Se) secretor subjects as compared with that of heterozygous (Se/Se^w) or homozygous (Se^w/Se^w) subjects (OR = 1.7, CI = 1.022–2.938, $P < 0.05$).

In order to study the combined effect of these three histo-blood groups on asthma susceptibility, the estimated OR of individual and combined genotypes in the association of asthma are shown in Table 3, using the two-by-two pair test method as described previously [27]. The results of association linkage between each of the two genotypes in asthma as well as in controls are also presented. There were two haplotypes, the blood group O/secretor phenotype (Se/Se)

(OR = 2.7, CI = 1.126–6.033, $P < 0.02$) and blood group O/Lewis Le(a-b-) (OR = 3.6, CI = 1.080–11.963, $P < 0.03$) individuals, which were significantly associated with asthma, respectively. There was no association linkage among blood group O, Lewis Le(a-b-) and secretor Se/Se in asthmatic children as well as controls (Table 3).

Association of histo-blood groups with serum immunoglobulin E concentrations

The association between these three histo-blood group systems and serum IgE concentration in our study population is shown in Table 4 using two-by-two pair tests. Total serum IgE levels were defined as high when they exceeded two standard deviations of the general population mean in asthmatic and non-asthmatic subjects for their respective ages. The Lewis Le(a-b-) genotype alone (OR = 3.3, CI = 1.267–8.482, $P < 0.01$), and the haplotype of blood group O/Le(a-b-) phenotype (OR = 5.2, CI = 1.259–21.429, $P < 0.02$) were significantly associated with high serum IgE (>500 IU) antibody in our study subjects, respectively. Again, there was no association linkage among blood group O, Lewis Le(a-b-) and secretor Se/Se in individuals with high total IgE levels as well as normal ones (<100 IU) (Table 4).

To confirm these results of the association of histo-blood groups with IgE levels, multivariate linear regression was used to test the variable comparisons of these three genotypes in

Table 2. Associations of blood group, Lewis and secretor gene with Asthma

	ABO blood groups					
	A	B	O	AB	χ^2	<i>P</i>
Controls	36 (22.4%)	56 (34.8%)	62 (38.5%)	7 (4.3%)	6.853	0.077
Asthmatics	36 (26.5%)	31 (22.8%)	66 (48.5%)	3 (2.2%)		
Lewis system						
	Le(a – b –)	Le(a+b+)	Le(a+b –)	Le(a – b+)	χ^2	<i>P</i>
Controls	11 (6.8%)	23 (14.3%)	0 (0%)	127 (78.9%)	2.398	0.301
Asthmatics	16 (11.8%)	21 (15.4%)	0 (0%)	99 (72.8%)		
Secretor gene						
	Se/Se	Se/Se ^w	Se ^w /Se ^w		χ^2	<i>P</i>
Controls	33 (20.5%)	108 (67.1%)	20 (12.4%)		6.316	0.043
Asthmatics	42 (30.9%)	72 (52.9%)	22 (16.2%)			

The Pearson χ^2 test was used to determine whether the distribution of different genotypes showed significant differences between groups. For *P*-value determination, Fisher's exact test was utilized, and the level of significance was set to 0.05.

Table 3. Two-by-two tests of blood group O, Le(a-b-) and secretor genes in asthmatic children and controls

Comparison		Individual association		Combined association: A, B positive vs. A, B negative	Association linkage between A and B	
Factor A	Factor B	A	B		Asthma	Controls
O	Le(a-b-)	1.5*	1.8	3.6 (0.028)*	0.9	1.9
O	Se/Se	1.5	1.7	2.7 (0.011)	0.9	0.9
Le(a-b-)	Se/Se	1.8	1.7	1.1	0.5	2.4

For *P*-value determination, Fisher's exact test was utilized, and the level of significance was set to 0.05. *Values within parentheses denote the *P*-values. OR, odds ratio.

Table 4. Two-by-two tests of blood group O, Le(a-b-) and secretor genes between children with high serum IgE ≥ 500 IU and normal IgE < 100 IU

Comparison		Individual association		Combined association: A, B positive vs. A, B negative	Association linkage between A and B	
Factor A	Factor B	A	B		IgE > 500 IU	IgE < 100 IU
O	Le(a-b-)	1.1	3.2	5.2 (0.019)*	1.9	0.8
O	Se/Se	1.1	1.5	1.5	1.3	0.8
Le(a-b-)	Se/Se	3.2	1.5	0.7	0.2	3.7

For *P*-value determination, Fisher's exact test was utilized, and the level of significance was set to 0.05. *Values within parentheses denote the *P*-values. OR, odds ratio.

Table 5. Multivariate linear regression comparison for blood group, Lewis and secretor genes between children's serum IgE level

Multivariate linear regression	<i>F</i>	<i>P</i>
Asthma	21.020	0.00001
Der p	19.016	0.00001
Der f	17.927	0.00003
Asthma and Der p, Der f	10.445	0.000002
ABO	0.364	0.457
Asthma and ABO	2.923	0.088
Secretor	0.076	0.783
Asthma and secretor	3.591	0.059
Lewis	0.119	0.703
Asthma and Lewis	0.810	0.369

For *P*-value determination, multivariate linear regression was utilized, and the level of significance was set to 0.05.

asthma, with total serum IgE levels as a continuous variable. We found that asthma and mites (Der p and Der f) sensitivity were associated with total serum IgE (Table 5). On comparing the blood group O children and non-blood group O children in terms of serum IgE, there was no significant association ($F = 0.364$, $P = 0.457$). Moreover, asthmatic children with type O blood group also showed no association with higher serum IgE ($F = 2.923$, $P = 0.088$). The Lewis Le(a-b-) system was also not associated with the serum IgE level ($F = 0.119$, $P = 0.703$); neither secretor Se/Se nor non-secretor Se/Se was associated with serum IgE ($F = 0.076$, $P = 0.783$). However, we found that asthmatic children with secretor Se/Se type were weakly associated with the serum IgE ($F = 3.591$, $P = 0.059$) in our study subjects (Table 5).

Discussion

The expression of terminal sugars in the epithelium of central airway has been associated with blood group antigens [6]. The different carbohydrate structures expressed by blood groups A, B or O determinants, and Lewis (a), Lewis (b) or secretor, form the specific oligosaccharides presented in the surface of the epithelial membrane, such as mucins, selectins, integrin receptor and endothelial growth factor receptor [28, 29]. These specific oligosaccharide epitopes are needed for the recognition of some environmental factors, such as microorganisms [30], and allergens. Recent evidences have found the importance of surface carbohydrates in the innate immunity of our body defence, such as in inflammatory cells

adhesion, and growth regulation [29]. Therefore, the presence or absence of these blood antigens might influence an individual's susceptibility to environmental pathogens, either by providing a specific receptor site or by shielding an exposed one. For example, human blood group antigen may serve as receptors for *Campylobacter jejuni* [31] and *Helicobacter pylori* [32, 33], which bind to secretor positive cells, and for uropathogenic *Escherichia coli* [34] and Norwalk virus [35], which bind to non-secretor cells.

Besides the well-known role of the reaction of microorganism lectin epitopes with specific host carbohydrates, the relationship between histo-blood group and respiratory diseases is still not clear. Previous studies based on separate analysis of the ABO and secretor system have led to discordant results [36–38], probably because of the complexity of the epistatic interactions among these genes. The full elucidation of their particular carbohydrate compositions has been hindered by the fact that these structures are not direct gene products, but rather the results of overlapping and substrate-competing functions of glycosyltransferases [39]. Moreover, the distribution of the Lewis phenotypes, especially Le(a+b+) and Le(a+b-), among ethnic populations has been noted to vary considerably. For example, the Lewis positive non-secretor Le(a+b-) phenotype has an incidence of 22% in whites [20, 40], but it is virtually absent in several Asian populations, including the Taiwanese Chinese. In contrast, the phenotype Lewis weak partial secretor Le(a+b+) is virtually absent in Caucasians, but has a higher frequency in East Asians, including Taiwanese (22–25%) [18, 20–23]. In this study, the distribution of ABO, Lewis and secretor phenotypes in our population corresponds to expected frequencies in East Asians. Our report shows that the blood group O/secretor type and group O/Le(a-b-) blood type were highly associated with the susceptibility of childhood asthma in Taiwanese, which is different from Kauffmann et al.'s [16] as well as Ronchetti et al.'s [17] reports in Caucasians adults and children. These results further confirm the ethnic difference of gene frequencies and the role of environmental effect on the susceptibility to common diseases in different parts of the world.

The development of asthma, particularly in children, is a result of interaction between genetic and environmental factors. In this study, we found that there was an association between group O/Le(a-b-) subjects and high IgE concentrations (≥ 500 IU) in schoolchildren (Tables 4), but it was only weakly associated with serum IgE levels, which was treated as a continuous variable in the multiple variable comparisons for the three histo-blood groups and serum IgE (Table 5). This discrepancy may because of the wide-ranging

concentrations of IgE in our study population, or other confounding factors, such as serum IgE level being closely related to mite sensitization and other environmental factors in young age population. Nonetheless, our results suggest that there may be different components of genetic susceptibility in histo-blood groups between allergic (high IgE levels) and non-allergic (low IgE levels) children.

Although lacking direct evidence, we presume that the expression of blood group antigens that form specific oligosaccharides in respiratory epithelium might strongly affect host response to environmental stimuli such as virus infections [4, 7, 29, 35, 36, 41], and subsequently allergen sensitization. The antigen of blood group O lacks fucosylation of its terminal sugar chains, which may expose the binding site for environmental pathogens and/or allergens, while the other blood groups, A, B and AB, have terminal oligosaccharides chains that are occupied, which decreases the epitopes for allergen to recognize. The allergen binding enhances the attachment to the surface of bronchial epithelial cells, resulting in the disruption of the tight junction of the epithelial cell through the proteolytic activity of allergen peptides, and establishing contact with submucosal dendritic cells to initiate the sensitization for IgE synthesis and/or allergen-induced bronchial inflammation [42]. The inflammation of airways and its synthesis of inflammatory cytokines, such as TNF- α , were shown to increase $\alpha(1,3)$ -fucosyltransferase activity as well as expression of FUT3 genes in the human bronchial mucosa [43]. These syntheses may be responsible for increased sialylation and expression of the sulphated Lewis x (sial-Lex) epitope on the carbohydrate chains of bronchial epithelial cells, which are specific ligands for P- and E-selectins expression on the recruited cells such as neutrophils and eosinophils during allergic inflammation [43].

Despite plenty of evidence of the association between blood groups antigens and increased susceptibility to pathogen infections, at present, there is still no report on the interaction between allergen and host expression of the different oligosaccharide determinants. Our results imply that the product of ABO and secretor genes seems to influence the development of the atopy status of children. In Ronchetti et al.'s [17] report, they compared the distribution of joint ABO/secretor phenotype in relation to age at the onset of asthma, and concluded that non-O/non-secretor individuals seemed to be more susceptible to asthma in the first years, while O/secretor individuals seemed to be protected against asthma in the first year of life and neutral in the following years. Because of the age factor in the expression of the Lewis phenotype (the complete Lewis phenotype is revealed after 6–7 years) [18], this effect may partially explain the 'Hygiene hypothesis' in the development of childhood allergy and asthma through the interaction of genetic phenotypes and their environmental exposure [45], such as virus and bacteria infections, in early infancy and subsequent influence on the maturation of the innate airway immunity.

Therefore, ABO, Lewis and secretor histo-blood groups constitute a candidate genetic complex for common diseases, such as asthma, with an important environmental aetiological influence. Moreover, the association of this complex with diseases may suggest the role of known or unknown environmental factors that trigger the development of this common disease. Further studies in the interaction between

various glycosyltransferase genetic system and environmental allergens or asthmatic-prone pathogens are needed. The results of the present study will provide a good model to investigate the interaction of genetic and environmental factors of childhood asthma.

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