Associations of FcεRIβ E237G polymorphism with wheezing in Taiwanese schoolchildren

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Summary

Background The β-chain of a high-affinity IgE receptor (FcεRIβ) has been proposed as a candidate gene for atopic diseases, but previous studies have come to inconsistent conclusions. Because some air pollutants would produce oxidative stress, increase serum IgE, and trigger T-helper type 2 (Th2)-type airway inflammation, the associations of FcεRIβ polymorphism with wheezing illness may vary by their exposures and variants of oxidant defence genes. The purpose of this study was to investigate the association of FcεRIβ E237G polymorphism with wheezing illness and to determine whether these associations vary with air pollution and glutathione S-transferase (GST) P1-105 and M1 genotypes.

Methods In 2001, we conducted a case–control study comprised of 214 children with any history of wheezing and 185 non-wheezing controls, all of whom were selected from 2558 fourth- to ninth-grade schoolchildren in southern Taiwan. We examined differences in associations with ambient air pollution and by GST genotypes.

Results Compared with the FcεRIβ EE genotype, children with the G allele had a significantly reduced risk of lifetime wheezing with low-ozone exposure [adjusted odds ratio (aOR) = 0.25, 95% confidence interval (CI) 0.08–0.69]. The risk was not reduced in children living in high-ozone communities (aOR = 0.98, 95% CI 0.57–1.67). This difference in genotypic effects between low- and high-pollution environments was statistically significant. The reduction of the protective effect from the G allele with higher air pollution was most marked in the GSTP1-105 Ile/Val or Val/Val and GSTM1 null groups.

Conclusion The FcεRIβ E237G allele may have a protective role in wheezing illness among Taiwanese schoolchildren, depending on airway oxidative stress levels.

Keywords children, gene–environment interaction, high-affinity IgE receptor, wheezing

Submitted 16 July 2007; revised 7 November 2007; accepted 14 November 2007

Introduction

Wheezing illness is the most common chronic childhood disease in developed nations [1]. Current studies indicate that many regions of the human genome containing susceptibility genes are associated with various wheezing/asthma phenotypes [2, 3]. Although host genetic factors may contribute to the occurrence of childhood wheezing illness, it is equally probable that environmental factors have crucial interactive roles in determining whether susceptible children develop such allergic diseases.

Some studies have reported the linkage of atopy to chromosome 11q13 [4, 5]. Although some potential candidate genes might reside in this chromosome region, we focus on the gene for the β-subunit of the high-affinity IgE receptor (FcεRIβ). FcεRI is critical in the process of induction and maintenance of an allergic response in mast cells and basophils. The β-subunit is an important modulator of the full signalling capacity of the entire FcεRI receptor, which not only amplifies the signal generated by the γ-chains but also increases the expression level of surface FcεRI [6, 7]. An amino acid change at residue 237 from glutamic acid to glycine (E237G) has been shown to
be associated with atopy and wheezing/asthma [8–12]. The studies have been inconsistent in the direction of effects, and some have found no significant association of this polymorphism [13–16]. Variation in associated phenotypes may reflect differences in the magnitude of the inflammatory response, which depends on exposures that produce oxidative stress, airway antioxidant defences, and FcεRI functions. Differences in the genetic background and environmental exposures that interact with FcεRI could also contribute to differences in results among studies.

Recent studies have revealed that outdoor air pollution may increase the risks of asthmatic symptoms [17–19], and that it is also associated with airway inflammation and bronchial hyperresponsiveness [20]. It has been suggested that some air pollutants such as ozone (O₃) and nitrogen dioxide (NO₂) could increase serum IgE, IL-4, and IL-5 levels, and recruit eosinophils and lymphocytes into the airways [21, 22]. The binding of antigen to receptor-bound IgE would induce the aggregation of the FcεRI molecule, leading to mast cell activation and degranulation [23]. The level of oxidative stress produced by air pollution drives Th2 type airway inflammation. Airway antioxidant defences are mediated in part by enzymatic antioxidants, including glutathione S-transferases (GSTs) [24]. GSTs function in antioxidant defences through reactive oxygen species metabolism, repair of reactive oxygen species damage, and detoxification of xenobiotics [25, 26]. We investigated the modifying effects of GSTM1 and GSTP1 genotypes on FcεRI–pollution associations because these genes are expressed in the respiratory tract, are involved in antioxidant defences, and have common functional alleles that result in the total absence or a marked alteration in the enzyme's activity [24, 27–31].

Although outdoor air pollution is suggested to be a risk factor for childhood asthma, only a few of the children who reside in areas with high air pollution have asthma. To further investigate the role of FcεRI in wheezing illness, we compared the genotype distribution of FcεRIβ E237G polymorphism in a case–control study nested within our previous 'International Study of Asthma and Allergies in Childhood' (ISAAC) questionnaire survey in Taiwanese schoolchildren [32]. We also examined the variation in the associations of this gene polymorphism with outcome in high and low air pollution environments and jointly with GSTP1–105 or GSTM1 genotypes.

Methods

Study design

Between February and June 2001, we conducted a national, cross-sectional, school-based survey for respiratory diseases and symptoms in middle- and elementary-schoolchildren. The study protocol has been described previously [32]. Briefly, the standard ISAAC-Chinese version questionnaire was taken home by students and answered by parents. Some information concerning basic demography, asthma risk factors, and residential exposures was also collected from the questionnaire. In June 2001, we conducted the present study focusing on the 2853 fourth- to ninth-grade schoolchildren who completed the questionnaire survey and resided in three southern Taiwan communities. The study protocol was approved by the Institutional Review Board at our university hospital, and complied with the principles outlined in the Helsinki Declaration [33].

Questionnaire and subjects selection

The definition of wheezing history was determined by a positive response to the question, 'Has your child ever had wheeze or whistling in the chest at any time in the past when he/she did not have a cold or the flu?' Non-wheezing controls were defined as those reporting not ever having dyspnoea with wheezing (from the parental questionnaire), no nocturnal dyspnoea associated with wheezing (from the video questionnaire), and without physician-diagnosed asthma. Risk factors and possible confounders were also collected in the questionnaire. After excluding questionnaires with unanswered questions, we found only 1.5% and 1.0% subjects, respectively, having in utero exposure to maternal smoking and active smoking habits in our population. Because of sample size limitation for stratification analysis, we excluded subjects with any of these two kinds of tobacco smoke exposure at study entry. Based on criteria established from questionnaire information, we randomly selected 50% of the children with lifetime wheezing and 10% of the non-wheezing controls for oral mucosa sampling and standardized pulmonary function tests [34] in the present study. Table 1 provides the demographic characteristics of the study population. Methacholine challenge tests were performed on subjects who met a few criteria (Table 2).

Air pollution data

Complete monitoring data for the criteria air pollutants are available from EPA monitoring stations beginning in 1995. The average hourly levels of each air pollutant, temperature, and humidity were measured in three communities (Sanmin, Annan, and Singang). We computed the annual average levels as the mean of the monthly averages. The ozone levels were obtained from 10:00 to 18:00 hours (the 8-h daytime average) in each community. From 1995 to 2000, the mean concentrations of community-level ozone (O₃), sulphur dioxide (SO₂), and nitrogen oxides (NOₓ) exposures are shown (Table 3). Because ozone exposures were very similar in Sanmin and Annan, they were grouped as the high-ozone
subcategory and Singang was retained as the low-ozone subcategory.

DNA collection and genotyping

The methods of oral mucosa sampling and genomic DNA extraction have been described in detail [27, 28]. The FcεRIβ E237G polymorphism fragment was amplified by a PCR. We adapted previous studies to detect the polymorphism at nucleotide 16960 by digesting the product with XmnI [11, 35]. GSTP1-105 gene variants are caused by base-pair transitions at nucleotides 1313. Previous studies were also adopted to detect the polymorphism at nucleotide 1313 by PCR and digestion of the product with Alw26I [29–31]. GSTM1 present and null genotypes were identified with allele-specific primers to exon 7 [31].

Statistical analysis

Unconditional logistic regression models were used to estimate the association of the FcεRIβ E237G polymorphisms with lifetime wheezing in schoolchildren. Genetic models were chosen based on available biological evidence from mechanistic and association studies. To investigate whether ambient air pollution modulated the association of the FcεRIβ genotype with wheezing illness, we fitted stratified models to the schoolchildren in communities with lower or higher air pollution. When...
considering the effects of GSTP1, M1 genotypes on the FcεRIβ associations, we stratified participants by GSTM1 genotype (null vs. present) or GSTP1-105 genotypes using a dominant model (Ile/Ile vs. Ile/Val or Val/Val) and assessed FcεRIβ associations in low- and high-ozone areas. Because of the reduced sample size, effect estimates in stratified models were tested using exact procedures, assuming a two-sided alternative hypothesis and a 0.05 significance level. All analyses were conducted using SAS software version 9.1 (SAS Institute, Cary, NC, USA).

**Results**

Our study finally comprised 214 participants with lifetime wheezing and 185 non-wheezing controls from three communities in southern Taiwan. All subjects were between 9 and 15 years old. Table 1 presents the demographic and residential exposure data. Participants who had genotyping data had a higher parental education level than those without genotyping data (Table 1). All the other factors showed little variation between children with and without genotyping.

We collected oral mucosa samples from 399 schoolchildren, and our DNA extraction rate was 100%. All participants had determined FcεRIβ E237G and GSTP1-105 genotypes but two had an undetermined GSTM1 genotype. The overall allele frequencies of FcεRIβ E237G polymorphisms were $G = 20.3%/E = 79.7\%$ in wheezing children and $G = 16.1%/E = 83.9\%$ in non-wheezing controls. Children with wheezing illness were likely to have a higher percentage of the FcεRIβ EE genotype than the controls (Table 4). Because the distributions of FcεRIβ EG and GG genotypes between children with wheezing illness and controls were similar, and the frequency of homozygosity at the G locus was relatively low, we combined the EG and GG genotypes as in dominant genetic models for the subsequent analyses.

We found that the protective effects of FcεRIβ G allele on wheezing illness were stronger for children living in a low-ozone community than in high-ozone communities (Table 5). Although confounders might interfere with the study results, in our population, odds ratios (ORs) did not change substantially after we controlled for age, sex, parental atopic history, parental education level, and cockroaches at home. Compared with children who had the FcεRIβ EE genotype, those with the G allele had a marked reduction of lifetime wheezing with low-ozone exposure [adjusted odds ratio (aOR) 0.25, 95% confidence

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**Table 4.** The association between FcεRIβ E237G polymorphisms and lifetime wheezing in schoolchildren

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Wheezing children</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Dominant model</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EE</td>
<td>120 (64.9)</td>
<td>153 (71.5)</td>
</tr>
<tr>
<td>EG or GG</td>
<td>65 (35.1)</td>
<td>61 (28.5)</td>
</tr>
<tr>
<td>Co-dominant model</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EE</td>
<td>120 (64.9)</td>
<td>153 (71.5)</td>
</tr>
<tr>
<td>EG</td>
<td>55 (29.7)</td>
<td>53 (24.8)</td>
</tr>
<tr>
<td>GG</td>
<td>10 (5.4)</td>
<td>8 (3.7)</td>
</tr>
<tr>
<td>Additive model</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G allele</td>
<td>(20.3)*</td>
<td>(16.1)*</td>
</tr>
</tbody>
</table>

Models are adjusted by multiple logistic regression for age, sex, parental atopic history, parental education level, and cockroaches at home. Hardy–Weinberg equilibrium tests showed insignificance ($P > 0.05$) in each case and control group.

*G allele frequency.

FcεRI, the high-affinity IgE receptor; cOR, crude odds ratio; aOR, adjusted odds ratio; CI, confidence interval.

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**Table 5.** The association of FcεRIβ E237G polymorphism with lifetime wheezing in schoolchildren by different air pollution levels

<table>
<thead>
<tr>
<th></th>
<th>Low ozone</th>
<th></th>
<th></th>
<th>High ozone</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ca/Co</td>
<td>cOR 95% CI aOR 95% CI</td>
<td>Ca/Co 95% CI aOR 95% CI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FcεRIβ polymorphism</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EE</td>
<td>38/36</td>
<td>1.00</td>
<td>1.00</td>
<td>115/84</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>EG or GG</td>
<td>11/28</td>
<td>0.37</td>
<td>0.08–0.69</td>
<td>50/37</td>
<td>0.99</td>
<td>0.57–1.67</td>
</tr>
</tbody>
</table>

$P$ for interaction 0.01

Models are adjusted by multiple logistic regression for age, sex, parental atopic history, parental education level, and cockroaches at home. FcεRI, the high-affinity IgE receptor; cOR, crude odds ratio; aOR, adjusted odds ratio; CI, confidence interval; Ca/Co, number of cases/number of controls.
interval (CI) 0.08–0.69); however, this reduction was not observed in children living in high-ozone communities (aOR 0.98, 95% CI 0.57–1.67). This difference in genotypic effects between low- and high-pollution environments was statistically significant (\(P\) for interaction = 0.01) (Table 5). Among the 214 wheezing children, 71 subjects had been diagnosed with asthma by physicians. The reduced sample size for asthma diminished the capacity of the present study to detect small effects. Restricting the analyses to children without asthma did not substantially alter the above findings (data not shown). We also checked interactions for genetic effects by sex, age, parental atopic history, or parental education level, and none were statistically significant.

In our analysis, the associations for Fc\(\epsilon\)RI\(\beta\) E237G did not differ statistically between the GSTP1-105 and GSTM1 genotypes (data now shown). To assess the roles of GSTP1 and GSTM1 genotypes in the protective effect of Fc\(\epsilon\)RI\(\beta\) E237G polymorphism on wheezing illness in a low-ozone community, we fitted models stratifying subjects by their GSTP1 and GSTM1 genotypes. We found that the difference in the Fc\(\epsilon\)RI\(\beta\) E237G effect between low and high air pollution was more marked in the GSTM1 null compared with the GSTM1 present group (Table 6). Similarly, the difference in the effect of Fc\(\epsilon\)RI\(\beta\) E237G between low and high air pollution was greater in those with the GSTP1 Ile/Val and Val/Val genotypes compared with the GSTP1 Ile/Ile genotype. Our sample size was insufficient to stratify jointly on GSTP1 and GSTM1 genotypes and to examine the interaction of the Fc\(\epsilon\)RI\(\beta\) genotype with outdoor air pollution.

### Discussion

We examined the relationships between the genotypic distribution of Fc\(\epsilon\)RI\(\beta\) E237G polymorphism, ambient air pollution, and wheezing illness among fourth- to ninth-grade schoolchildren. We found that the Fc\(\epsilon\)RI\(\beta\) G allele is protective for wheezing illness but that protection depends on outdoor air pollution in the community of residence. In addition to air pollution, two common variants in unlinked genes involved in antioxidant defences, GSTP1 and GSTM1, may affect the expression of the protective effect of the Fc\(\epsilon\)RI\(\beta\) E237G variant, as indicated by the less marked protection in high-ozone communities among groups with the GSTP1-105 Val allele or GSTM1 null groups. Our findings support a role of gene–environment interactions and genetic interactions in the occurrence of childhood wheezing illness.

Age, sex, ethnic factors, active smoking habits, in utero exposure to maternal smoking, parental atopic history, and parental education level were believed to contribute to childhood wheezing illness [32, 36–38]. We minimized interference from these confounders by recruiting lifelong non-smokers without in utero exposure to maternal smoking at study entry, and adjusting potential confounders by regression models. Because all the recruited children had the same ethnic origin, population stratification was therefore very unlikely to have influenced the findings. Cockroaches seen at home showed a positive effect on the occurrence of wheezing illness (Table 1). In our preliminary study [39], we suggested that sensitization to cockroach allergens, rather than to cat or dog

### Table 6. The association of Fc\(\epsilon\)RI\(\beta\) E237G polymorphism with lifetime wheezing in schoolchildren by air pollution levels, stratified by GSTP1-105 and GSTM1 genotypes

<table>
<thead>
<tr>
<th>Fc(\epsilon)RI(\beta) polymorphism</th>
<th>GSTP1-105 Ile/Val or Val/Val</th>
<th>GSTP1-105 Ile/Ile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low ozone</td>
<td>High ozone</td>
<td></td>
</tr>
<tr>
<td>Ca/Co</td>
<td>aOR 95% CI</td>
<td>Ca/Co</td>
</tr>
<tr>
<td>EE</td>
<td>16/9</td>
<td>24/33</td>
</tr>
<tr>
<td>EG or GG</td>
<td>6/14</td>
<td>20/11</td>
</tr>
<tr>
<td>(P) for interaction</td>
<td>0.005</td>
<td>0.05</td>
</tr>
<tr>
<td>(P) for three-way interaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GSTM1 null</td>
<td>Low ozone</td>
<td>High ozone</td>
</tr>
<tr>
<td>Ca/Co</td>
<td>aOR 95% CI</td>
<td>Ca/Co</td>
</tr>
<tr>
<td>EE</td>
<td>19/16</td>
<td>69/44</td>
</tr>
<tr>
<td>EG or GG</td>
<td>5/18</td>
<td>35/21</td>
</tr>
<tr>
<td>(P) for interaction</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>(P) for three-way interaction</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Models are adjusted by multiple logistic regression for age, sex, parental atopic history, parental education level, and cockroaches at home.

Fc\(\epsilon\)RI, the high-affinity IgE receptor; aOR, adjusted odds ratio; CI, confidence interval; Ca/Co, number of cases/number of controls; GST, glutathione S-transferase.

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dander, was associated with lower pulmonary functions in Taiwanese schoolchildren. In fact, current exposure at study entry to environmental tobacco smoke and other household environmental factors, e.g. incense burning, water damage, and visible mould on walls at home were also considered in our study. These factors showed either small or negative effects on the occurrence of wheezing illness (data not shown) because they were easily changed due to human behaviours through selection mechanisms, especially in a cross-sectional study. Adjustment for these factors individually and in combination resulted in negligible changes in the effect estimates, and therefore, these covariates were not adjusted as potential confounders in final models.

It has been known that FcεRI is essential for the induction and maintenance of an allergic response. The β-chain enhances the cell surface expression of FcεRI by association with the α-chain and amplifies the signal from an immunoreceptor tyrosine activation motif (ITAM) of the γ-chain [6, 7]. Studies have observed that the combined signalling and expression amplification resulted in an estimated 12- to 30-fold amplification of downstream events [7]. A glutamic acid to glycine substitution (E237G) in the cytoplasmic tail alters the hydrophilic nature of the C-terminus of the β-chain adjacent to ITAM. This change may alter the intracellular signalling capacity of FcεRI through the interaction of the protein tyrosin kinase Lyn with ITAM of the β-chain [40]. Our results are consistent with the studies reporting that the FcεRIβ G allele is associated with a decreased risk of atopic diseases [8, 13, 41]. However, a number of studies on the associations of this polymorphism with atopy or wheezing/asthma have reported conflicting results [9–12].

Inhalation of air pollutants such as O₃, NOₓ, and SO₂, either individually or in combination, might enhance the airway response to inhaled allergens, thereby inducing respiratory symptoms [42]. There is considerable evidence indicating that long-term exposure to ambient air pollution increases the risks of wheezing/asthma in childhood [17–19]. From our previous analysis in Taiwan, ozone and NOₓ were also found to be positively correlated with the prevalence of childhood asthma [17]. In this study, ambient air pollution was shown to modify the protective effect of FcεRIβ E237G polymorphism for wheezing illness. Because the association of FcεRIβ E237G polymorphism was similar (data not shown) and ozone levels were very close in Sanmin and Annan, we think our dichotomized exposure categorization was reasonable. In addition, we found no substantial differences in the effects of FcεRIβ E237G polymorphism in relation to exposure to other monitored air pollutants or meteorology variables such as temperature, humidity, carbon monoxide, and PM₁₀ (data not shown). Ecologic confounders like urbanization and socialization actually could exist in data analysis. However, we do not think they are really significant because our three communities are close in distance without major geographic differences. In Taiwan, the obligatory National Health Insurance has been administered since 1995 and more than 99% residents were covered. Therefore, medical practice patterns probably did not bias our results.

Although individuals may vary in genetic susceptibility to outdoor air pollution, to the best of our knowledge, there are limited epidemiological studies concerning the different effects of FcεRIβ gene polymorphisms by environmental exposures. In animal models, ozone or NO₂ exposure may shift the immune system towards a Th2 response [21, 22, 43–45]. In human studies, ozone could increase the expression of IL-1, IL-6, TNF-α, and intercellular adhesion molecule in nasal lavage fluid [46]. Increased leukotriene levels have also been found in bronchial alveolar lavage fluid after ozone exposure [47]. The increased Th2 response would result in a higher expression of FcεRI function. In the present study, we found that the risk of lifetime wheezing decreased (aOR 0.25, 95% CI 0.08–0.69) in children with the FcεRIβ G allele living in a low-ozone community. The reduction was not observed in high-ozone communities (aOR 0.98, 95% CI 0.57–1.67) (Table 5). Our results provide an important demonstration of a gene–environment interaction. Because different polymorphic forms of the FcεRIβ gene have different effects on the airway inflammatory response of an individual, it is interesting to speculate that an air pollution-induced airway injury might be different in children carrying different polymorphic forms of this gene.

The protective effect of the FcεRIβ E237G polymorphism seems to depend on the level of oxidative stress. It is believed that oxidative stress affects the intracellular glutathione redox state in airway epithelial cells, activating signals that increase the production of cytokine modulation that may influence the Th1/Th2 switching mechanism and exacerbate respiratory symptoms [48]. Although we did not measure serum IgE levels in the population, our data show that the effects of FcεRIβ E237G polymorphism on transcription are overcome by higher levels of oxidative stress. These results are consistent with studies of the effects of GSTP1, GSTM1, and antioxidant vitamins in children exposed to high levels of ozone [49]. We suggest that sequence variants that affect the expression of genes participating in inflammatory pathways may show variable penetrance in the setting of high-pollution exposure and low-antioxidant defences.

The ecologic exposure assessment had many advantages in our study. The density of elementary and middle schools in Taiwan was very high, and almost all the surveyed children attended schools within 1 km of their homes. Monitoring stations located near the schools were also likely to be near the students’ homes, and thus provided good indicators for both school and home exposure. We dichotomized exposure into high- and
low-ozone communities to account for uncertainties in indoor levels and time–activity patterns of the study participants. Although these estimates have associated measurement error, it is likely that the groups provided substantial contrasts in ambient air pollution exposure.

Our study has some limitations. We did not have genotyping data from all subjects, which made selection bias possible. However, participants with genotyping data included in this analysis did not differ from those without genotyping data on many demographic factors, but did show small differences in the proportion of parental education levels (Table 1). False-positive associations may arise due to multiple comparisons and population stratifications. Children from families with a higher education level were less likely to have moved and to be lost to follow-up. Because the differences in distribution were modest and are probably not associated with the genotypes, it is unlikely that selection of subjects biased the effect estimates in our results. Childhood wheezing illness was ascertained by parental-reported questionnaire, and so misclassification of wheezing status may have arisen from imperfect parental recall of events. Because wheezing illness was defined without knowledge of genotype, differential misclassification of wheezing by FcεRIβ E237G polymorphism is probably not a major source of bias that accounts for our results. Therefore, although there is likely to be non-differential misclassification of wheezing status, such misclassification would not account for the genetic and environmental associations we observed.

In conclusion, the protective association of FcεRIβ E237G polymorphism in children with low-ozone exposure or protective GSTP1 or GSTM1 genotypes suggests that this relatively common genetic polymorphism, or haplotype marked by this polymorphism, plays a protective role in childhood respiratory allergy depending on airway oxidative stress levels. Additional research is necessary to prove that the elimination of environmental exposures among genetically susceptible individuals could reduce rates of childhood asthma.

Acknowledgements

This study was supported by grant #NSC92-EPA-Z-006-001 and #NSC95-2314-B-006-103 from the National Science Council and grant DOH90-TD-1138 from the Department of Health in Taiwan. The authors thank the field workers, teachers, and other school staff who supported data collection, and all the parents and children who participated in this study.

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