Effects of Glutathione *S*-Transferase *P1*, *M1*, and *T1* on Acute Respiratory Illness in School Children

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The relationships between glutathione *S*-transferase (GST) M1, GSTT1, and GSTP1 genotypes and acute respiratory illness were investigated in a cohort of fourth grade school children aged 9–11 years who resided in 12 southern California communities. We used respiratory illness–related absences as a measure of respiratory illness occurrence. We ascertained respiratory illness–related school absences using an active surveillance system from January 1996 through June 1996. Genotypes for *GSTM1* (null versus present), *GSTT1* (null versus present), and *GSTP1* (Ile105Val) were determined using genomic DNA from buccal cell specimens. The effects of *GST* genotypes on respiratory illness were assessed using stratified absence incidence rates and Poisson regression models. *GSTP1* genotype was associated with risk for respiratory illness severe enough to result in a school absence. Children who were homozygous for the Val105 variant allele had lower incidence rates of upper and lower respiratory illnesses than did children who were homozygous for the Val105 allele. Children inheriting at least one Val105 allele were protected from respiratory illnesses (relative risk, 0.80; 95% confidence interval, 0.65–0.99). *GSTM1* and *T1* genotypes were not associated with respiratory illness. We conclude that *GSTP1* genotype influences the risk or severity of respiratory infections in school-aged children.

Keywords: *GSTM1*; *GSTT1*; *GSTP1*; respiratory illnesses; school absenteeism

Acute respiratory illnesses are an important cause of childhood morbidity (1, 2). Although the etiology of acute respiratory illnesses has been extensively documented, few studies have investigated the role of genetics on acute respiratory illness occurrence during childhood (2–4). A better understanding of the genetic determinants may allow the establishment of environmental factors in the etiology and provide new directions for therapy and prevention of these common conditions.

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One approach to identifying genetic factors for respiratory illness occurrence involves candidate gene association studies. In the candidate gene approach, pathways involved in illness pathogenesis are defined and genes with functional polymorphic variants that operate in the pathways are identified (5). With regard to acute respiratory illnesses among school-aged children, viral infections are responsible for the majority of acute respiratory illnesses and exacerbations of chronic illnesses such as asthma, and genes involved in the pathobiology of viral infections may modulate the frequency and severity of respiratory illnesses (2, 6–9). Evolving evidence supports an important pathophysiologic role for oxidative stress in viral infections and pulmonary immune responses (10, 11). A number of pathways are involved in protection and repair of damage from excessive oxidative stress, including enzymatic antioxidants and hydroperoxide detoxification enzymes (5, 12–14). Several members of the glutathione *S*-transferase (GST) superfamily, notably *GSTM1*, *GSTT1*, and *GSTP1*, are expressed in the respiratory tract and function as enzymatic antioxidants and hydroperoxidases (14–16). Each gene has a common functional variant (*GSTM1* null, *GSTT1* null, and *GSTP1* A105G or Ile105Val), supporting the hypothesis that *GSTM1*, *GSTT1*, and *GSTP1* are candidate genes for acute respiratory illness.

The Children's Health Study (CHS) offers an opportunity to investigate the associations of GST genotypes with respiratory illness (17, 18). The CHS is a cohort study that includes approximately 6,000 school children residing in 12 communities within a 200-mile radius of Los Angeles. We conducted a substudy within the CHS cohort and collected incidences of respiratory illness–related absences ascertained by an active surveillance system to investigate acute respiratory illness occurrence. We sought to determine whether associations exist between *GSTM1*, *GSTT1*, and *GSTP1* genotypes with respiratory illness–related absences for a cohort of fourth grade school children aged 9–11 years who attended schools in the 12 CHS study communities during January 1996 through June 1996 (19).

METHODS

Details on the design, site selection, subject recruitment, and assessment of health effects for the CHS cohort have been reported previously (17, 19). In this report, we focus on respiratory illnesses that led to school absences among 1,932 children in fourth grade who participated in a substudy of the CHS, the Air Pollution and Absence Study, during the first 6 months of 1996. The study protocols were approved by the University of Southern California's Institutional Review Board for human studies, and informed written consent was obtained from the children's parents.

Participant Characteristics

Sociodemographic information, indoor exposures, and medical histories were obtained from questionnaires completed by parents or guardians at study entry in 1993. The subset of participants with asthma was defined using parent-reported history of physician-diagnosed asthma. "Severe asthma" included children with two or more asthma illnesses in the year before entry or one or more asthma illnesses and any med-

ication use, overnight hospital stay, or episodes of asthma-interrupted sleep. "Children with wheezing" were those with a history of wheezing in the 12 months before study entry. "Parental educational attainment" was assigned using the highest level of the parent or guardian who completed the questionnaire. Information was collected about the current and past household smoking status of each participant's mother, father, other adult household members, and regular household visitors.

Respiratory Illness Surveillance

Incident respiratory illnesses were ascertained by monitoring school absences (19). We collected school absence reports from the 27 elementary schools attended by the newly recruited fourth grade children for the period January 1, 1996, to June 30, 1996. Daily absence information was collected using methods described previously (19). An absence was defined as a day or an adjacent series of school days in which a participant did not attend school when the school was in session.

We established an active surveillance system using telephone interviews to collect information about the reasons for absences, and we categorized absences as illness-related and non–illness-related (including injuries) and classified illness-related absences into gastrointestinal (GI) and respiratory categories. To ensure adequate parental recall of events associated with the absence of interest, interviews were conducted only for absences that were reported within 4 weeks of occurrence. Parents were contacted after each absence that was reported within 4 weeks to inquire whether the absence was illness-related and if so, what the symptoms were. Each illness-related absence was classified as respiratory or nonrespiratory, on the basis of the reported symptoms. A respiratory illness was defined as an illness that included one or more of the following symptoms: runny nose/sneezing, sore throat, cough (any—wet or dry), earache, wheezing, or asthma attack. Respiratory absences were further classified into non–mutually exclusive categories of upper respiratory illness and/or one of two types of lower respiratory illness: lower respiratory illness with wet cough and that with wet cough/wheeze/asthma. An upper respiratory illness was defined as a respiratory illness with one or more of the following symptoms: runny nose/sneezing, sore throat, and earache. GI-related illnesses included illnesses that had "stomach problems" such as vomiting and diarrhea as one of the reported symptoms.

On the basis of data collected by the active surveillance system, absences were divided into three mutually exclusive outcomes: non–illness-related absences, illness-related absences, and absences of unknown type (due to failure to obtain necessary classification information). Because some absences were of unknown type, the type-specific absence incidence rates were adjusted for ascertainment failure. To adjust the type-specific incident absence rates, a smoothed daily community-specific information success ratio was calculated, which was defined as the daily proportion of timely absence reports in each community for which sufficient information was obtained to identify the absence as illness or non–illness-related. A symptom-specific incidence rate corrected for ascertainment is of the form (number of incident cases)/(number at risk $\times$ smoothed success ratio).

Laboratory Methods

Buccal cells were collected from participants as a source of genomic DNA for genotyping assays. Details of buccal cell processing and genotyping assays are provided in an online data supplement. In brief, DNA was extracted using a PUREGENE DNA isolation kit (cat #D-5000; GENTRA, Minneapolis, MN). Genotypes for *GSTM1* were determined using two methods. The first 380 samples were analyzed by enzymatic amplification of the polymorphic *GSTM1* locus. Polymerase chain reaction products were visualized by electrophoresis on 2.5% agarose gel. The remaining *GSTM1* samples and all of the *GSTT1* and *GSTP1* genotypes were determined using real-time polymerase chain reaction using a TaqMan 7700 (Applied Biosystems, Foster City, CA). The presence or absence of a fluorescent amplification signal was used as an indication of whether the *GSTM1* and *GSTT1* alleles were present or absent in a particular genomic DNA sample. Samples showing no signal or late cycle number for start of amplification were repeated and further analyzed with primers and probes for the actin gene to verify the presence of amplifiable DNA. Analysis of the single nucleotide polymorphism at codon 105 in the *GSTP1* gene was performed using allele-specific probes.

Statistical Analysis

The daily number of incident absences in each community and the corresponding daily number of children at risk for an absence in each community were used to calculate average daily incident absence rates. Stratified rates (e.g., by genotype) were calculated by identifying the number of absences and number of students at risk within each stratum and calculating average rates as described in the online data supplement.

Poisson regression models that accounted for overdispersion were used to estimate associations between GST genotypes and respiratory illness–related school absences adjusted for potential confounding covariates (20) (additional detail is provided in the online data supplement). Models were fitted to estimate the relative risk of absences associated with each locus using codominant, dominant, recessive, and additive genetic models for the variant alleles. Additive genetic models were assessed using significance of linear terms for the number of variant alleles at each locus. We compared the goodness of model fit values to determine which nested model best described the data by testing differences in model deviances. Model Akaike's Information Criterion was used to compare fits of models that were not nested. On the basis of the study design and *a priori* consideration of potential confounders, all models included terms for age, sex, ethnicity, and community. If estimates of the genetic effects changed by 10% or more when a covariate was included in the base model, the covariate was included in the final model. Modification of the effects of genotypes by environmental tobacco smoke or asthma status was assessed using nested models and a likelihood ratio test. All analyses were conducted using the GENMOD procedure in the SAS software (21).

RESULTS

Of the 2,081 fourth grade participants, 1,183 (57.2%) provided buccal cells for genotyping assays. The primary reasons for nonparticipation were declines of our invitation to participate in the genotyping study (10.0%) and failure to locate or collect specimens from children who moved or graduated (32.8%). Most participants were 9 years old and reported that they were non-Hispanic or were of Hispanic white ethnicity (Table 1). Histories of wheezing (33.1%) and asthma (15.6%) were common among participants. At study entry, more than 16.6% of the children were exposed to household smokers. Participants with genotyping were generally similar to those without genotyping; however, more non-Hispanic whites were included in the group with genotyping (60%) than in the group without genotyping (50%). The null genotype for *GSTM1* and *GSTT1* was present in 43.0% and 22.1% of participants, respectively. The frequency of the homozygous *GSTP1* Val105 variant was 13.7%. The allele frequencies are consistent with those reported in other studies (22).

The children had a median of two incident school absences over the 6-month study period, the number ranging from zero (18.2%) to 14. Forty-two percent reported that they had at least one illness-related absence during the study period, and 29% had at least one respiratory illness–related absence. Incidence rates for types of absences varied by ethnicity, educational attainment of a parent or guardian, history of asthma and wheezing, and environmental tobacco smoke exposure (Table 2). Incidence rates for respiratory illness–related absence (0.98/100 children-days) were relatively low but accounted for approximately two-thirds of illnesses resulting in school absences. GI illness accounted for almost all the remaining illness-related absences. Respiratory illness rates varied among children with different *GSTP1* codon 105 genotypes. The homozygous *GSTP1* variant (Val105) genotype was associated with an approximately 40% decrease in respiratory illness rates, compared with either the homozygous

TABLE 1. SELECTED CHARACTERISTICS OF PARTICIPANTS WITH GENOTYPE IN THE AIR POLLUTION AND ABSENCE STUDY, JANUARY–JUNE 1996

	n	%
All	1,183	100.0
Age at entry, yr		
8	12	1.0
9	921	77.9
10	247	20.9
11	3	0.3
Ethnicity		
Missing	3	0.3
Non-Hispanic white	649	54.9
Hispanic	367	31.0
Black	52	4.4
Asian	53	4.5
Other	59	5.0
Sex		
F	605	51.1
M	578	48.9
Wheeze*		
Missing	51	4.3
No	740	62.6
Yes	392	33.1
Asthma†		
Missing	20	1.7
No	979	82.8
Yes	184	15.6
Serious asthma‡		
Missing	28	2.4
No	1,051	88.8
Yes	104	8.8
Any ETS		
Missing	28	2.4
No	959	81.1
Yes	196	16.6
GSTT1		
Missing	4	0.3
Present	918	77.6
Null	261	22.1
GSTM1		
Missing	4	0.3
Present	670	56.6
Null	509	43.0
GSTP1 (Ile105Val)		
Missing	25	2.1
Ile/Ile	461	39.0
Ile/Val	535	45.2
Val/Val	162	13.7

Definition of abbreviations: ETS = household environmental tobacco smoke; GST = glutathione *S*-transferase.

GSTP1 codon 105 A allele codes for isoleucine; codon 105 G allelic variant codes for valine.

* Lifetime history.

† Physician-diagnosed asthma.

‡ Two or more asthma illnesses in the year before entry, or least one asthma illness and any medication use, overnight hospital stay, or episodes of asthma interrupted sleep.

Val105 genotype or heterozygous Val105 genotype (Table 3). There were no large differences in rates between *GSTM1* and *GSTT1* genotypes; however, children with the *GSTM1* null genotype had slightly higher rates of respiratory illness than did those with the *GSTM1* present genotype. Rates for GI illnesses did not vary substantially within any of the genotypes.

The *GSTP1* Val105 variant was protective against acute respiratory illnesses, as manifested by school absences (Table 4). After adjustment for the 12 communities, ethnicity, sex, and age, children who were homozygous for the *GSTP1* Val105 variant allele had significantly lower risk for respiratory illness-related absences than did subjects homozygous for the common Val105 allele. Both the recessive and the additive models for the protective effect of the Val105 variant allele fit the data significantly better that did the codominant model. Based on the Akaike's Information Criterion, the additive model for the number of Val105 variant alleles provided the best model fit. Adjustment for additional covariates including environmental tobacco smoke exposure, asthma, and wheezing did not substantially change the association between *GSTP1* genotype and respiratory illness–related absences. There was little evidence that environmental tobacco smoke exposure or asthma status modified the protective effects of the *GSTP1* Val105 variant allele. *GSTM1* and *GSTT1* were not significantly associated with acute respiratory illness risk. The effects of the *GSTP1* Val105 variant allele remained a significant protective factor in models that included all three genes, and we found no statistically significant gene–gene interactions among the three loci.

DISCUSSION

The relationship between genetics and acute respiratory illness has received little research attention. We focused our investigation on three related candidate genes with functional polymorphisms (*GSTM1*, *GSTT1*, and *GSTP1*). Each of the candidate genes is involved in oxidative stress response pathways that are important in the pathobiology of viral respiratory infections, which are the most common cause of respiratory illnesses among children (10, 11, 23). We found that fourth grade children who inherited *GSTP1* Val105 variant alleles had a 40% lower risk for respiratory illnesses severe enough to result in a school absence than did children who had a *GSTP1* Val105 allele. The protective effect increased as the number of Val105 variant alleles increased and was not explained by the effects of environmental tobacco smoke exposure or asthma status. Because the Val105 allele is a common polymorphism and respiratory illnesses are frequent events, our findings may have important clinical and public health implications that warrant further investigation.

The mechanism for the protective effects of *GSTP1* on respiratory illnesses may involve pathways that affect the amount of and responses to oxidative stress (5, 12, 14). GSTs contribute to protection against oxidative stress by using glutathione to detoxify a variety of electrophilic compounds, including oxidized lipid, DNA, and catechol products generated by reactive oxygen species–induced damage to intracellular molecules (12, 14). Because *GSTP1* is strongly expressed in the respiratory epithelium and is the dominant GST in the lung, variation in *GSTP1* function may have larger effects on respiratory health outcomes than do other members of the GST superfamily. The Val105 allele of *GSTP1*, which causes a substitution of valine for isoleucine in the catalytic domain of the enzyme product, changes the kinetics of the enzyme in a complex manner. The Val105 allele is threefold less active in conjugating 1-chloro-2,4-dinitrobenzene; however, it is sevenfold more active in metabolizing some polycyclic aromatic hydrocarbons but is less active for others (24–26). Polymorphic alleles in *GSTP1* may contribute to variation in pulmonary response to oxidative stress. The protective role of *GSTP1* in removing reactive oxygen species and their secondary products may be related to the risk of respiratory infection because oxidative stress plays a central role in the pathophysiology of acute respiratory infections (10, 11, 23). Viral infection of the respiratory epithelium produces oxidative stress that mediates the production of inflammatory cytokines including interleukin-8, tumor necrosis factor-α, and regulated upon activation normal T cell expressed and presumably secreted (RANTES), and adhesion molecules such as ICAM-1 via nuclear factor

TABLE 2. INCIDENCE RATES OF ABSENCES PER 100 CHILDREN-DAYS BY SELECTED PARTICIPANT CHARACTERISTICS, AIR POLLUTION AND ABSENCE STUDY, JANUARY–JUNE 1996, GENOTYPED SUBJECTS ONLY

	Type of Illness-related Absence*					
	Illness	Respiratory	Upper Respiratory	Lower Respiratory	Lower Respiratory With Wheeze	Gastrointestinal Symptoms
Sex						
F	1.65	0.99	0.93	0.16	0.26	0.64
M	1.52	0.97	0.86	0.17	0.25	0.56
Ethnicity/race						
Non-Hispanic white	1.60	0.93	0.86	0.15	0.24	0.68
Hispanic	1.58	1.03	0.95	0.14	0.19	0.49
African American	1.14	1.03	0.97	0.09	0.41	0.13
Asian/Pacific isle	1.34	1.10	0.84	0.17	0.27	0.21
Other	2.57	1.37	1.31	0.44	0.48	1.04
Education†						
< 12th grade	1.77	1.21	1.08	0.04	0.31	0.56
12th grade	2.18	1.29	1.14	0.25	0.36	0.69
Some coll/tech	1.50	0.93	0.83	0.16	0.25	0.57
Four-year college	1.28	0.88	0.80	0.16	0.25	0.45
Post-grad	1.27	0.81	0.81	0.16	0.17	0.60
Diagnosed asthma						
No	1.49	0.90	0.85	0.15	0.17	0.58
Yes	1.95	1.34	1.10	0.23	0.73	0.64
Serious asthma						
No	1.50	0.92	0.86	0.16	0.19	0.56
Yes	2.25	1.51	1.16	0.15	0.90	0.93
Wheezing						
No	1.47	0.83	0.78	0.11	0.13	0.62
Yes	1.88	1.34	1.18	0.26	0.52	0.57
Environmental tobacco smoke						
No	1.54	0.99	0.90	0.17	0.25	0.55
Yes	2.00	1.08	1.02	0.16	0.31	0.72

* Absence types are: illness, respiratory illness, upper respiratory illness, lower respiratory illness, lower respiratory illness with wheeze, and gastrointestinal symptoms.
† Educational attainment of participant's parent or guardian.

kappa B and activator protein-1 (AP1) pathways (10, 23, 27, 28). The cytokines and chemokines recruit and activate immune cells, which results in increased neutrophils, macrophages, eosinophils, and lymphocytes in secretions and respiratory epithelium (29, 30). The intensity of the inflammatory response is related to the severity of symptoms. It follows that risk for and response to viral infection are influenced by level of oxidant defenses. The proposition that oxidant defenses modulate respiratory infections is supported by a study showing that antioxidants can block rhinovirus-induced interleukin-8 secretions in cell systems. Thus, antioxidant enzymes such as *GSTP1* may have a role in modulating the severity of respiratory symptoms from viral infection (23). Furthermore, the effect of *GSTP1* on respiratory illness–related absences might be magnified among children with chronic respiratory conditions because infections are the most common cause of

TABLE 3. INCIDENCE RATES OF SCHOOL ABSENCES PER 100 CHILDREN-DAYS BY PARTICIPANT *GSTM1*, *T1*, AND *P1* GENOTYPE, AIR POLLUTION AND ABSENCE STUDY, JANUARY–JUNE 1996

	Type of Illness-related Absence*					
	Illness	Respiratory Illness	Upper Respiratory Illness	Lower Respiratory Illness	Lower Respiratory Illness With Wheeze	Gastrointestinal Symptoms
All	1.58	0.98	0.89	0.16	0.26	0.59
Gene/genotype						
GSTM1						
Present	1.56	0.94	0.88	0.14	0.22	0.59
Null	1.62	1.05	0.93	0.20	0.32	0.60
GSTT1						
Present	1.59	0.98	0.89	0.16	0.27	0.57
Null	1.47	0.96	0.89	0.16	0.19	0.65
GSTP1 (A105G)†						
Ile/Ile	1.69	1.05	0.96	0.16	0.28	0.65
Ile/Val	1.57	1.00	0.92	0.19	0.26	0.58
Val/Val	1.30	0.62	0.53	0.08	0.18	0.58

* Absence types are: illness, respiratory illness, upper respiratory illness, lower respiratory illness, lower respiratory illness with wheeze, and gastrointestinal symptoms.
† *GSTP1* codon 105 A allele codes for isoleucine; codon 105 G allelic variant codes for valine.

TABLE 4. ASSOCIATION OF *GSTP1*, *M1*, *T1* GENOTYPE ON RISK OF SCHOOL ABSENCES, RELATIVE RISK AND 95% CI*

		Illness-related Absences RR (95% CI)	Respiratory Illness-related Absences RR (95% CI)	Nonrespiratory Illness-related Absences RR (95% CI)
Genetic model†				
GSTM1				
Recessive	Present	1	1	1
	Null	1.06 (0.9, 1.25)	1.10 (0.89, 1.35)	1.00 (0.76, 1.27)
GSTT1				
Recessive	Present	1	1	1
	Null	0.94 (0.77, 1.16)	0.96 (0.74, 1.24)	0.92 (0.68, 1.25)
GSTP1 (A105G)‡				
Codominant	Ile/Ile	1	1	1
	Val/Ile	0.90 (0.75, 1.07)	0.87 (0.70, 1.08)	0.95 (0.73, 1.23)
	Val/Val	0.71 (0.54, 0.93)	0.60 (0.42, 0.86)	0.91 (0.62, 1.33)
Dominant	Ile/Ile	1	1	1
	Ile/Val or Val/Val	0.85 (0.72, 1.01)	0.80 (0.65, 0.99)	0.94 (0.73, 1.20)
Recessive	Ile/Ile or Ile/Val	1	1	1
	Val/Val	0.75 (0.59, 0.97)	0.65 (0.46, 0.91)	0.94 (0.66, 1.33)
Additive	0,1,2 Val alleles	0.86 (0.76, 0.97)	0.80 (0.69, 0.94)	0.95 (0.80, 1.14)

Definition of abbreviations: CI = confidence interval; GST = glutathione *S*-transferase; RR = relative risk.
* All analyses are adjusted for 12 communities, ethnicity, sex, and age.
† Models refer to effect of variant Val105 allele.
‡ *GSTP1* codon 105 A allele codes for isoleucine; codon 105 G allelic variant codes for valine.

exacerbation of asthma and airway hyperresponsiveness in this age group. On the basis of the central role of oxidant stress defenses in each of these inter-related conditions, the effects of the *GSTP1* Val105 variant may be mediated through multiple inter-related pathways.

The effects of *GSTP1* on respiratory illnesses may also involve exposure to ambient air pollution (5). We have reported that daily variations in O_3 as well as chronic exposure to environmental tobacco smoke were directly associated with respiratory illness–related school absenteeism, indicating that O_3 and environmental tobacco smoke increase the risk or severity of respiratory infections (19). The increased risk of respiratory infections from exposure to environmental tobacco smoke and ambient air pollution may be mediated by oxidative stress. Oxidants in environmental tobacco smoke and ambient air pollution produce oxidative stress in respiratory epithelial cells and macrophages that are likely to increase the risk of infection. Macrophage function is adversely affected, reducing the ability to inactivate viruses. The oxidative stress from air pollution may add to the elevated levels of oxidative stress from viral infections to increase the severity of illness. Individuals with *GSTP1* Val105 alleles may be better equipped to defend against the adverse effect of excess oxidative stress. Taken together, the pathophysiology indicates that individuals who have *GSTP1* Val105 alleles may be at lower risk for respiratory infections, symptomatic respiratory illnesses, and school absences.

Our active surveillance system for acute respiratory illnesses had some limitations. We used the incidence of respiratory illness–related absences as our measure of acute respiratory disease occurrence. We did not test for viral infections and therefore could not distinguish infections from exacerbations of asthma; however, exacerbations of asthma are primarily induced by viral infections. Clearly, some mild respiratory illnesses were not ascertained because mild illnesses may not lead to an absence event. We cannot exclude the possibility that the *GSTP1* genotype is associated with increased acute respiratory illness severity but does not influence the incidence of illnesses. However, illnesses of greater severity may be of greater clinical and public health importance. To reduce recall bias, we restricted interviews to absences that occurred within 4 weeks of ascertainment. We do not have data to assess how successful we were in minimizing errors in recall. To aid in recall, we asked parents about a list of symptoms, diagnoses, and treatments for each absence and then used the reported symptoms to assign illness type categories. Some errors in recall are likely to occur but are unlikely to be differential by genotype, suggesting that any misclassification is likely to be nondifferential and reduce the effect toward the null. Therefore, our effect estimates may be low. The restriction of absences to those reported within 1 month of occurrence may have resulted in incomplete ascertainment of the type of absence that may have introduced bias into our study. We believed it was necessary to adopt this restriction to minimize any recall bias of absence events by parents. On the basis of the distributions of the study population in the full and restricted samples of absence days, we found little evidence of any selection bias from the restriction (19). To account for the effects of incomplete ascertainment, the denominator of the rates and the offset in the Poisson models were adjusted for the proportion of absences with information on absence type. We did not have genotyping data from all subjects, making selection bias possible; however, we found no substantial differences in the characteristics of those with genotypes compared with those without genotypes, indicating that any bias from selection by availability of DNA is likely to be small.

We conclude that fourth grade school children who inherited a *GSTP1* Val105 variant allele have a decreased risk of respiratory illness–related school absence, indicating that *GSTP1* genotype influences the risk and/or severity of acute respiratory infections in school-aged children. Our findings demonstrate that genes involved in oxidative stress response pathways may be determinants of acute respiratory illness occurrence in children. The protective Val105 allele may have clinical and public health importance for therapeutic and prevention research because the variant is common in many populations and acute respiratory illnesses are frequent causes of morbidity. Further investigation of the relationship between *GSTP1* genotype and risk of respiratory illness is warranted.

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