including obesity and both asthma and diabetes. The association between type 2 diabetes and asthma is not surprising as a high proportion of youth were overweight or obese (90.6%) and the linkage between asthma and increased BMI is well described in many studies. It is interesting to note that children whose asthma was treated with leukotriene modifiers, alone or in combination with inhaled corticosteroids or rescue inhalers, had the lowest prevalence of poor glycemic control; in fact, 72% had good glycemic control. The authors speculate that this could be because leukotriene synthesis or receptor blockers may help reduce the systemic inflammation present in both obesity and diabetes as well the direct effect on ameliorating airway inflammation.

CONCLUSIONS. DNA hypomethylation was associated with increased risk for persistent wheezing in both studies, although only 1 of the 2 was statistically significant (Menorca: odds ratio 1.13, 95% confidence interval 0.99–1.29, P = .077; Sabadell: odds ratio 1.16, 95% confidence interval 1.03–1.37, P = .017). Higher levels of dichlorodiphenyldichloethene were associated with persistent wheezing in both studies. It is interesting to note that children whose asthma was treated with leukotriene modifiers, alone or in combination with inhaled corticosteroids or rescue inhalers, had the lowest prevalence of poor glycemic control; in fact, 72% had good glycemic control. The authors speculate that this could be because leukotriene synthesis or receptor blockers may help reduce the systemic inflammation present in both obesity and diabetes as well the direct effect on ameliorating airway inflammation.

REVIEWER COMMENTS. This study adds to the knowledge that genes and the environment combine to influence asthma phenotype. In this case, ALOX12, a gene associated with airway inflammation, appears to exhibit variation in methylation, not based on genotype alone, but possibly on environmental factors, including prenatal pollutant exposure. Therefore, the degree of methylation at certain CpG sites on this gene may be an early biomarker that helps to predict wheezing phenotype.

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DNA Hypomethylation at ALOX12 Is Associated With Persistent Wheezing in Childhood

PURPOSE OF THE STUDY. To determine if epigenetic changes play a role in asthma phenotypes.

STUDY POPULATION. There were 2 groups studied, both involved children enrolled from pregnancy cohorts. The first group (Menorca cohort) was 122 children with data available through age 6 years. The second group (Sabadell cohort) was 236 children with available DNA extracted from whole cord blood.

METHODS. Children were assigned wheezing phenotypes at age 4 to 6 years based on validated questionnaires (never, transient, late-onset, or persistent wheezing). Prenatal exposure data were collected through questionnaire and by measuring for presence of a specific pollutant, dichlorodiphenyldichloethene, in cord blood.

RESULTS. DNA hypomethylation was associated with increased risk for persistent wheezing in both studies, although only 1 of the 2 was statistically significant (Menorca: odds ratio 1.13, 95% confidence interval 0.99–1.29, P = .077; Sabadell: odds ratio 1.16, 95% confidence interval 1.03–1.37, P = .017). Higher levels of dichlorodiphenyldichloethene were associated with hypomethylation of ALOX12 in the Menorca study (P = .033), but not the Sabadell study (P = .377). Level of methylation at ALOX12 was strongly influenced by polymorphisms in the gene.

CONCLUSIONS. DNA hypomethylation at ALOX12 was associated with a higher risk of persistent wheezing. This may be an epigenetic biomarker that predicts increased likelihood of persistent wheezing in childhood.

Identification of IL6R and Chromosome 11q13.5 as Risk Loci for Asthma

PURPOSE OF THE STUDY. To identify novel genetic variations imputing asthma risk.

STUDY POPULATION. Pediatric and adult Australians of European descent consisting of 2669 asthmatic subjects (28% diagnosed by clinical examination, 54% childhood onset, 59% atopic) and 4528 controls (40% with unknown asthma status) produced candidate asthma genetic variations. Meta-analysis of 12 475 physician-diagnosed asthmatic subjects and 19 967 controls provided a prioritization cohort. Four additional individual cohorts totaling 3322 asthmatic subjects and 22 036 controls provided replication.

METHODS. Microarray-derived genotypes of Australian asthmatic subjects and controls underwent a genome-wide association study to produce asthma candidate loci. Meta-analysis using unique adult Australian and previously published GABRIEL genotypes prioritized candidate novel genetic loci. The prioritized, novel genetic loci endured replication analysis via 4 individual cohorts and a combined meta-analysis. A genomic phenotype prediction model for asthma was produced and subsequently tested. Secondary analysis considered asthma and other immune disease associations.

RESULTS. Two novel loci were significantly associated with asthma risk. The interleukin-6 receptor (IL6R) locus on chromosome 1q21.3 associated more significantly (odds ratio [OR] = 1.09, P = .0033) than the indeterminate locus (rs7130588) at chromosome 11q13.5 (OR = 1.07, P = .328) in the replication cohorts. However, when considering all available data, 1q21.3 and 11q13.5 both demonstrated very significant asthma association (OR = 1.09, P = 2.3 × 10−8 and OR = 1.09, P = 1.8 × 10−8, respectively). Secondary analyses of 11q13.5 revealed an association with atopy and no asthma risk association.
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