found no association between nasal ORMDL3 gene expression and 17q21 genotype. Nevertheless, these findings should inform further studies on the regulation and role of SPT subunits in asthma.

Overall, this study lends evidence supporting the concept that genetically altered sphingolipid metabolism in children who carry 17q21 asthma-risk genotypes may lead to functional consequences on airway resistance, acting as a predisposing factor for the development of asthma. Although the manifestations of classic inborn disorders of sphingolipid metabolism mainly result from the accumulation of toxic products affecting the nervous system and skin, decreased synthesis of bioactive lipids such as sphinganine-1-phosphate and sphingosine-1-phosphate may also have specific functional consequences (10). We may also learn from other manifestations of decreased SPT activity, such as in hereditary sensory autonomic neuropathy caused by a loss of function mutation of the SPT subunit Sptlc2, which has recently been shown to have relevant consequences on immune cell function (11). Although the exact role of sphingolipids in asthma remains enigmatic, Rago and colleagues have opened the door a little further, providing another glimpse of how this class of lipids is involved in the complex pathogenesis of childhood asthma. ■

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# Understanding How Asthma Starts: Longitudinal Patterns of Wheeze and the Chromosome 17q Locus

Most childhood asthma starts in the preschool years. Symptoms such as wheeze, cough, and dyspnea are not specific to asthma and can also represent transient symptoms due to viral respiratory tract infections. Triggers of preschool wheeze can change over time (1) and therefore are not reliable predictors of asthma. No valid, reproducible diagnostic or predictive test of preschool asthma is currently available (2). This inability to diagnose preschool asthma has seriously impeded better understanding of childhood-onset asthma and the ability to design targeted, early-life interventions.

In this issue of the *Journal,* Hallmark and colleagues (pp. 864–870) combine two strategies to better understand the development of childhood wheeze: the description of longitudinal patterns of wheeze in seven U.S. birth cohorts participating in the Children's Respiratory Research and Environment Workgroup, and the investigation of the association of these longitudinal wheezing phenotypes with the 17q12-21 locus ("17q") (3). 17q is the most replicated childhood-onset asthma locus (4). Using data from birth until age 11 years, their latent class modeling revealed four classes of wheeze: infrequent (no or low presence of wheeze;



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estimated prevalence 62% based on *post hoc* assignment to most probable class), transient (wheeze in the first years of life, but absent at school age; 17%), late-onset (10%), and persistent (wheeze persisting from preschool to school age; 11%). These patterns were similar in children of European American (EA) and African American (AA) descent. Notably, AA children had higher probability to be assigned to the persistent wheeze group, indicating a higher burden of wheeze in these children. This clearly calls for further research to better understand this higher burden in AA children.

Are four wheezing patterns all there are? Whereas many longitudinal birth cohorts have identified these four patterns (5, 6), two additional wheezing patterns have been described by latent class analysis of UK and Dutch birth cohorts, with an additional transient wheeze group (prolonged early wheeze) and an additional late-onset group, the intermediate-onset wheeze group, which is strongly associated with atopy (7). This illustrates the strength but also the limitation of data-driven methods: the ability to define wheezing phenotypes is indeed strongly driven by the data, such as the number of assessments of wheeze and number of children studied.

How does the description of longitudinal wheezing phenotypes advance our understanding of asthma development? No wheezing pattern was uniquely predictive of asthma; in fact, all wheezing patterns were associated with a higher chance of ever developing asthma (3). Interpretation of this analysis may be complicated by the fact that a doctor's diagnosis of asthma at any age was taken as an outcome, as many children obtained their asthma diagnosis in the first 3 years of life. However, other studies also indicate that there is no wheezing pattern that uniquely leads to asthma, defined by asthma at school age, reduced lung function, or airway hyperresponsiveness (7). Thus, the pattern itself has limited ability to predict asthma, and the fact that these wheezing patterns can only be defined retrospectively limits their clinical use.

Do the longitudinal wheezing phenotypes represent unique pathophysiological mechanisms and thus represent endotypes of asthma (8)? Genetic studies may reveal this, and Hallmark and coworkers chose to investigate SNPs at the 17q locus. Recent analysis has shown that this locus is strongly related to the age of onset of asthma but not to the onset of eczema or hay fever (9). 17q SNPs were associated with any of the three wheezing phenotypes in both AA and EA children, suggesting that these phenotypes have a shared genetic origin and, thus, that differences may actually be influenced by other factors, such as the environment. Fine mapping of this locus has been challenging because of extensive linkage disequilibrium (LD). By investigating associations between wheezing phenotypes and 17q SNPs in both EA and AA children, in whom the LD blocks extend over shorter distances, they aimed to pinpoint potential causal variants. The same technique recently allowed Ober and coworkers (10) to narrow down the association between 17q SNPs and childhood-onset asthma (<6 yr) in AA children to two SNPs: rs2305480 and rs8076131. In a subsequent expression quantitative trait loci analysis, rs2305480, an SNP in the coding region for *GSDMB* (gasdermin B), was strongly associated with expression of *GSDMB* in airway epithelial cells. Similarly, Gui and coworkers (11) used next-generation DNA sequencing data from AA individuals in three cohorts to evaluate the association between 17q and childhood-onset asthma (<5 yr). The lead association from their meta-analysis, rs11078928, is located in a 4-kb haplotype block containing four potentially functional polymorphisms in very strong LD, including rs2305480. rs11078928 affects splicing of *GSDMB* transcripts, and expression levels of these transcript isoforms in whole blood RNA sequencing were associated with asthma status, making this a likely causal candidate mechanism of childhood-onset asthma (12).

The authors propose that the 17q locus may be considered a "wheezing locus" instead of an "asthma locus." However, this statement may need support from future studies. For most of the tested SNPs, the odd ratios are higher in wheezing classes with higher proportions of children with doctor-diagnosed asthma. These results are in line with previous observations by Granell and coworkers (13) who describe a strong association of 17q SNPs, including rs2305480, with persistent and intermediate-onset childhood wheezing phenotypes, but a much weaker association with transient wheeze. Similarly, Sordillo and coworkers (14) observed an increased odds for persistent wheeze, but no association with transient or late-onset wheeze, for the 17q SNP rs12603332. In fact, in one of the first studies to assess the association between rs2305480 and preschool wheeze, the association was strongest for children wheezing in the third and fourth year of life (likely indicating persistent wheeze) and nonsignificant for wheeze in the first year of life (with the highest prevalence of the transient wheezing phenotype) (15).

Hallmark and coworkers (3) have shown that it is possible to harmonize and jointly analyze multiple birth cohorts. Investigating the genetics of longitudinal wheezing phenotypes, in the future at a genome-wide basis, may help to disentangle mechanisms of early life wheeze and subsequent asthma development. ■

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# Oral Corticosteroids Tapering in Severe Asthma

First marketed 70 years ago, corticosteroids transformed the life of patients suffering from asthma and quickly became the mainstay of treatment for this condition. Despite major developments in therapeutic options since, particularly with the use of inhaled corticosteroids more than 40 years ago, the powerful antiinflammatory effects of oral corticosteroids (OCS) are as of yet impossible to replace completely, explaining their persistent use in asthma management. Most of the time, they are prescribed intermittently to treat severe exacerbations, although some patients require them chronically to achieve asthma control (1). However, OCS are associated with well-recognized long-term side effects and an increase in mortality (2, 3). Recent evidence suggests that this risk is related to the cumulative lifetime exposure to OCS (4, 5), implying that even repeated short courses may have a significant impact on their associated morbidity.

More recently, monoclonal antibodies brought the first real long-term alternative to OCS in severe asthma since the 1950s. They are powerful antiinflammatory agents targeting T-helper cell type 2 (Th2) inflammation with minimal side effects and with corticosteroid-sparing properties (6–9). Their availability provoked a change in OCS perception in severe asthma, from a necessary evil to an increasingly avoidable one. With the increasing use of biologics, tapering and cessation of maintenance OCS has become much more common and feasible, but specific guidance on how to proceed is lacking.

Numerous studies exploring steroid-sparing drugs have reported their OCS weaning protocols. The OCS tapering regimens used were quite variable, as were the assessments of asthma control, biomarker use, and screening for adrenal insufficiency, thus making generalization difficult. Many of them also lacked the details needed to be efficiently implemented in clinical practice. An exception would be the ongoing PONENTE trial, investigating the safety and efficacy of OCS tapering after initiation of benralizumab. Although not evidenced-based, it provides a detailed OCS reduction algorithm with systematic assessment of adrenal insufficiency that could be used by clinicians.

Research and guidelines have recognized the need to reach the minimal effective dose when OCS are needed for long-term treatment of severe asthma. To achieve this, their focus and advice has been to optimize asthma control strategies and use of OCS-sparing drugs without clear guidance on how to actually proceed with weaning. Hence, there are currently no standardized guidelines on how and when to safely perform OCS tapering. A recent review identified this lack of clear recommendations as a clinical barrier to reduce OCS exposure in severe asthma (10).

In this issue of the *Journal*, Suehs and colleagues (pp. 871–881) provide an expert consensus report on the important topic of OCS use and tapering in patients with asthma, including statements on less frequent conditions such as eosinophilic granulomatosis with polyangiitis and allergic bronchopulmonary aspergillosis (11). A modified Delphi method was used to develop a consensus (>70% agreement) among 131 experts from different specialties, mostly pulmonologists (73%) and allergists (18%), in addition to patient advocacy organization representatives. Although opinions sometimes differed, some general principles for use and reduction of OCS were agreed on.

This study is a first major attempt to provide clinicians with guidelines based on expert opinion specifically on OCS use for



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