

Childhood Asthma-Predictive Phenotype

Theresa W. Guilbert, MD^a, David T. Mauger, PhD^b, and Robert F. Lemanske, Jr, MD^c Cincinnati, Ohio; Hershey, Pa; and Madison, Wis

Wheezing is a fairly common symptom in early childhood, but only some of these toddlers will experience continued wheezing symptoms in later childhood. The definition of the asthma-predictive phenotype is in children with frequent, recurrent wheezing in early life who have risk factors associated with the continuation of asthma symptoms in later life. Several asthma-predictive phenotypes were developed retrospectively based on large, longitudinal cohort studies; however, it can be difficult to differentiate these phenotypes clinically as the expression of symptoms, and risk factors can change with time. Genetic, environmental, developmental, and host factors and their interactions may contribute to the development, severity, and persistence of the asthma phenotype over time. Key characteristics that distinguish the childhood asthma-predictive phenotype include the following: male sex; a history of wheezing, with lower respiratory tract infections; history of parental

asthma; history of atopic dermatitis; eosinophilia; early sensitization to food or aeroallergens; or lower lung function in early life. © 2014 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2014;2:664-70)

Key words: Asthma risk; Wheezing; Childhood asthma; Asthma phenotypes; Asthma epidemiology childhood; Biomarkers; Genetics; Review

ASTHMA PHENOTYPES: CHILDHOOD ASTHMA-PREDICTIVE PHENOTYPE

Wheezing is a fairly common symptom in early life, but only some toddlers will experience continued wheezing symptoms in later childhood.¹ From epidemiologic data, several early childhood wheezing phenotypes were described based on the natural history and risk factors associated with each. Appropriate identification of young children at high risk to develop persistent asthma could lead to the development of effective prevention and therapeutic strategies.

DEMOGRAPHICS

Although almost 50% of children report wheeze in the first year of life, only 40% of these children will continue to wheeze in later childhood.¹ Wheezing phenotypes were defined to identify the characteristics and risk factors associated with children who experience continued wheezing in later childhood and others into adolescent and adulthood.

CLINICAL CHARACTERISTICS

Wheezing phenotypes

Several wheezing phenotypes were developed. It can be difficult to differentiate these phenotypes clinically because the expression of symptoms and risk factors can change with time.

Tucson Children's Respiratory Study classification. In this study, 4 different wheezing phenotypes were classified among 1246 newborns observed for the development of lower respiratory tract infections based on the occurrence of wheezing symptoms during the first 3 years of life and again at 6 years of life (Table 1).¹ These phenotypes included the following:

- Never wheezers (51%): healthy children without wheezing.
- Early, transient wheezers (20%): onset of wheezing before age 3 years with resolution by 6 years of age.
- Persistent wheezers (14%): onset of wheezing before age 3 years with sustained wheezing at age 6 years.
- Late-onset wheezers (15%): onset of wheezing between 3 and 6 years of age.

Thus, children in the persistent and late-onset wheezing groups may represent 2 asthma-predictive phenotypes, that is,

^aPulmonary Medicine Division, Department of Pediatrics, Cincinnati Children's Hospital, Cincinnati, Ohio

^bDepartment of Health Evaluation Sciences, Pennsylvania State University, Hershey, Pa

^cAllergy Division, Department of Pediatrics, University of Wisconsin School of Medicine and Public Health, Madison, Wis

No funding was received for this work.

Conflicts of interest: T Guilbert developed questions for the Pediatric Pulmonary board exams as a member of the American Board of Pediatrics, Pediatric Pulmonary Subboard; has received consultancy fees as an advisory board member from Teva, GlaxoSmithKline, Regeneron Pharmaceuticals; has received research support from the Center for Disease Control, DHHS, National Institutes of Health, University of Wisconsin Madison Medical and Education Research Committee, Abbott Laboratories, Array Biopharma, Teva, Mylan, Forest Research Institute, F Hoffman-LaRoche, GlaxoSmithKline and Development Limited, MedImmune, KaloBios Pharmaceuticals, Vortech Pharmaceuticals, Roxane Laboratories, CF Foundation Therapeutics, and Roche/Genentech; receives royalties from UpToDate; and has received payment for developing educational presentations from Teva. DT Mauger has received drugs for NHLBI-funded study from GlaxoSmithKline, Merck, Teva, and Boehringer Ingelheim. RF Lemanske has received research support from the NHLBI with the Program Project Grant (COAST), AsthmaNet, Lung Development Grant (RO-1); has received travel expenses for his board membership; is employed by the University of Wisconsin; has received consultancy fees from Merck, Sepracor, SA Boney and Associates, GlaxoSmithKline, American Institute of Research, Genentech, Double Helix Development, Boehringer Ingelheim, and Health Star Communications; has received a grant from Pharmaxis; has received speaker's fees from Michigan Public Health, Allegheny General Hospital, AAP, West Allegheny Health, California Chapter 4, Colorado Allergy Society, Pennsylvania Allergy Society, Howard Pilgrim Health, California Society of Allergy, NYC Allergy Society, World Allergy Organization, APAPARI, Western Society of Allergy Asthma and Immunology, Kuwait Allergy Society, Lurie Children's Hospital, Boston Children's Hospital, LA Children's Hospital, and Northwestern University; has received payment for manuscript preparation from the AAAAI; and receives royalties from Elsevier and UpToDate. Received for publication August 8, 2014; revised September 11, 2014; accepted for publication September 12, 2014.

Corresponding author: Theresa W. Guilbert, MD, Department of Pediatrics, Division of Pulmonology Medicine, Cincinnati Children's Hospital and Medical Center 3333 Burnet Ave, MLC 2021 Cincinnati, OH 45229. E-mail: Theresa.Guilbert@cchmc.org. 2213-2198

© 2014 American Academy of Allergy, Asthma & Immunology
<http://dx.doi.org/10.1016/j.jaip.2014.09.010>

Abbreviations used
API- Asthma Predictive Index
RV- Rhinovirus

those children who are most likely to experience asthma-like symptoms that persist into later childhood, adolescence, and adult life (Figure 1).

Further evaluation of the cohort led to further refinement of the persistent wheezing phenotype:

- Nonatopic persistent wheezing phenotype: the first episode of wheezing occurs in the first year of life² and the wheezing episodes become less frequent by early adolescence,³ and most outgrow their symptoms. Children with this phenotype have a lower level of prebronchodilator lung function and enhanced airway reactivity.³
- IgE-associated and/or atopic persistent wheezing phenotype: is characterized by wheezing, which usually starts in the second year of life and persists into later adolescence.⁴ It remains to be seen if this phenotype will persist into adulthood. Risk factors associated with atopic wheeze include parental asthma, male sex, atopic dermatitis, eosinophilia at 9 months, early sensitization to food or aeroallergens, and a history of wheezing with lower respiratory tract infections.^{1,5}

The Italian Studies of Respiratory Disorders in Childhood and the Environment classification. The Italian Studies of Respiratory Disorders in Childhood and the Environment was a longitudinal birth cohort of 16,333 children that identified similar phenotypes but with different frequencies, as did the Tucson study.^{1,6} The age that differentiated early transient wheezing from persistent wheezing was age 2 years rather than 3 years. In differing from the Tucson study, 83% had never wheezed, 7% had early transient wheezing, 4% had persistent wheezing, and 6% had late-onset wheezing.

Avon Longitudinal Study of Parents and Children classification. In the Avon Longitudinal Study of Parents and Children,⁷ a longitudinal birth cohort of 6265 children, the occurrence of wheeze in these children was measured by a parental report at yearly intervals from age 6 months to 7.5 years. By using a latent class analysis, the investigators identified 6 phenotypes, 4 of which had patterns similar to those identified in the Tucson study.¹ Data were collected at more time points and shorter intervals, and included lung function, which led to the identification of 2 additional subphenotypes (prolonged early wheeze and intermediate-onset wheeze):

- Never or infrequent wheeze (59%).
- Transient early wheeze (16%): wheezing at 6 to 18 months, remitting after 42 months.
- Prolonged early wheeze (9%): wheezing at 6 to 54 months, remitting after 69 months; characterized by increased airway responsiveness and lower school-aged lung function compared with the never or infrequent wheeze phenotype.
- Intermediate-onset wheeze (3%): wheezing onset between ages 18 and 42 months that persists into later childhood; these children are characterized by allergic sensitization, higher levels of airway responsiveness, and lower lung function compared with the never or infrequent wheeze phenotype.

- Late-onset wheeze (6%): infrequent wheezing from 6 to 42 months but frequent after 42 months.
- Persistent wheeze (7%): wheezing from 6 months onward.

The intermediate onset, late-onset, and persistent wheeze groups also may represent asthma-predictive phenotypes.

New Zealand classification. Risk factors that are associated with sustained wheezing from childhood (age 9 years) to adulthood were evaluated in a New Zealand longitudinal study. More than 1 in 4 children had wheezing that persisted from childhood to adulthood or who had relapsed after remission. The factors that predicted persistence or relapse were sensitization to house-dust mites, airway hyperresponsiveness, early age at onset, female sex (after puberty), and personal smoking exposure.⁸ In those with persistent asthma, lung function was decreased through childhood and adulthood in a comparatively similar pattern.

Melbourne classification. Data attained from a cohort of 378 children with asthma in Melbourne, Australia, evaluated every 7 years from age 7 years through 35 years showed a link between asthma and other atopic conditions. The presence of an atopic condition in childhood augmented the risk of severe asthma in later life, whereas severe asthma in childhood predicted an increased risk of atopic eczema or allergic rhinitis in later life.⁹ Consequently, analysis of these data indicated that children whose symptoms start in early life are at greater risk for the development of persistent chronic airflow limitation and continued severe symptoms.

Symptomatic classification. Epidemiologic phenotypes are limited by their retrospectively defined periods of wheeze. Thus, phenotypes based upon temporal patterns of wheeze were created, which can be applied prospectively and may be more practical when making treatment decisions. Other names, for example, episodic (viral) wheeze, also were proposed to describe the phenotype for children who primarily wheeze with viral infections alone. In contrast, the term multiple-trigger wheeze phenotype is used for children who wheeze when exposed to a variety of triggers rather than solely with viral infections.¹⁰ Subsequently, airway function was observed to be lower in multiple triggers than episodic wheeze, which suggests that these are distinct phenotypes.¹¹ However, some children classified into 1 of these 2 clinically based phenotypes switched into the other phenotype in the following year,¹² which suggests that these phenotypes may be inconsistent over time. A 2014 study found a high correlation between the epidemiology defined latent class analysis phenotypes and clinically defined wheeze phenotypes.¹³ Accordingly, clinical phenotypes may be useful asthma definitions for future epidemiologic studies.

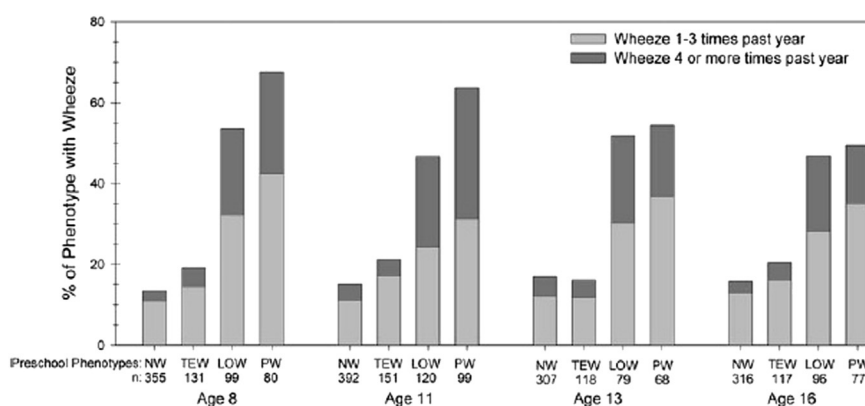
Additional perinatal and early childhood exposures associated with asthma. Genetic, environmental, developmental, and host factors and their interactions may contribute to the development, severity, and persistence of the asthma phenotype over time.^{14,15} Atopic disease,^{1,7,16-18} reduced lung function,^{1,7,17-19} viral infections,²⁰⁻²² and frequent wheeze^{1,23,24} appear to be key risk factors. Other risk factors present *in utero* and at the time of delivery associated with increasing risk of asthma include a family history of atopic disease, black race²⁵; male sex²⁶; passive tobacco smoke exposure²⁷; low birth weight; caesarean section delivery^{28,29}; and maternal consumption of milk, eggs, and wheat during pregnancy.³⁰ Factors associated with increased risk of asthma after birth and in later childhood include respiratory

TABLE I. Characteristics of wheezing phenotypes in the Tucson Children's Respiratory Study*

Wheezing phenotype†	% (no.) in each category at age 6 y (total n = 826)	Significant risk factors for each phenotype	% (no.) Diagnosed with asthma at age 6 y	% (no.) Diagnosed with bronchitis but no asthma at age 6 y	% (no. tested) that were skin test positive in each category at age 6 y
Never-wheezers	51.5 (425)	Reference group	—	—	33.8 (317)
Transient early wheezers	19.9 (164)	Maternal smoke exposure	—	—	38.4 (125)
Late-onset wheezers	15 (124)	Rhinitis apart from colds; maternal asthma; male sex	22.5 (28)	25 (31)	55.7 (97)
Persistent wheezers	13.7 (113)	Eczema; rhinitis apart from colds; maternal asthma; male sex; maternal smoke exposure	46 (52)	22.1 (25)	51.1 (90)

*From Ref 1.

†Preschool wheeze phenotypes were defined as no wheeze from birth to age 6 y (never wheeze), wheezing lower respiratory illness before age 3 y only (transient early wheeze), wheeze at age 6 y only (late-onset wheeze), and wheezing lower respiratory illness before age 3 y and wheeze at age 6 y (persistent wheeze).

**FIGURE 1.** Prevalence of infrequent and frequent wheeze by the preschool wheeze phenotypes in the Tucson Children's Respiratory Study. LOW, late-onset wheeze; NW, never wheeze; PW, persistent wheeze; TEW, transient early wheeze. Group sample sizes at each age are listed below the acronyms (from Ref 129). Reprinted with permission of the American Thoracic Society. Copyright © 2014 American Thoracic Society.

viral infections^{3,31,32} (discussed below in the Comorbidities section), early life house-dust endotoxin exposure or colonization with *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Staphylococcus aureus*^{33,34}; antibiotic and acetaminophen use³⁵⁻³⁷; obesity^{38,39}; allergen exposure^{40,41}; passive^{42,43} and active tobacco smoke^{44,45}; synthetic bedding^{46,47}; traffic-related pollutants⁴⁸⁻⁵⁰; maternal depression and familial stress⁵¹; and the development of other atopic disorders.⁵² Factors that are associated with a decreased risk of asthma in early life include larger family size and later birth order^{53,54}; day care attendance in the first 6 months of life^{55,56}; early exposure to domestic cats and dogs^{57,58}; measles and bacillus Calmette-Guérin vaccines⁵⁹⁻⁶¹; decreased maternal or child dietary intake of vegetables, fruit, zinc, vitamins (A, D, E), a Mediterranean diet, and fish⁶²⁻⁶⁶; exclusive breastfeeding for the first 6 months unless a maternal history of asthma⁶⁷⁻⁷⁰; and exposure to farm animals and related products *in utero* or during the first 6 months of life.^{71,72}

Asthma predictive risk models. Several models of risk were generated to help identify those children who will continue wheezing into school age.⁷³⁻⁸¹ These models use risk factors associated with the development of asthma in epidemiologic studies such as a parental history of allergic sensitization, recurrent wheezing history, atopic disease in the child, increased IgE levels,

decreased lung function, elevated exhaled nitric oxide, and increased T-helper-4 cytokine levels. One of the most studied, the Asthma Predictive Index (API),⁷³ was derived from the Tucson study data that includes risk factors, such as frequent wheezing, a parental history of asthma, and signs of personal atopic disease. Children with a positive index were 7 times more likely to have active asthma during the school years (sensitivity 16%, specificity 97%). The API was validated in the Leicester population-based birth cohort of 1954 children in 2011.⁸² Children with a positive API at age 3 years had an 8-fold increased risk of asthma in the school years, similar to that found in the Tucson study.^{73,82} As is typical with these risk models, the overall predictive performance was low.^{83,84} The API, however, also has a high negative predictive value when the API is negative, which enables the identification of children who are at low risk of developing asthma later.^{85,86}

The API also was modified by substituting the clinical diagnosis of allergic rhinitis with objective testing for allergic sensitization. This modified API is endorsed by the National Asthma Education Prevention Program Expert Panel Report 3^{73,87,88} and may be useful in selecting children who are more likely to respond to inhaled corticosteroids.⁸⁸ The predictive value of this modified API was determined in a cohort of children at high risk and with a family history of allergy and/or asthma. In this select population of children at high risk, the positive modified API increased future asthma probability to 90%.⁸⁹

COMORBIDITIES

Both viral and bacterial respiratory infections can cause wheezing illnesses in children of all ages and also may influence the development and the severity of asthma. Viral respiratory tract infections, particularly rhinovirus (RV) and respiratory syncytial virus, are epidemiologically associated with asthma in several ways.⁹⁰⁻⁹² Children who develop severe viral respiratory infections in the first 3 years of life are more likely to have asthma later in childhood.^{1,32,92} Several host factors, including allergic sensitization^{93,94} and virus-induced interferon responses,⁹⁵⁻⁹⁷ modify the risk of virus-induced wheezing. Viral species (human RV A and C species) also may impact the severity of wheezing illness.⁹⁸

In a cohort of children at high risk for allergic disease, respiratory syncytial virus and RV wheezing, and allergic sensitization were all predictors of asthma development at age 6. Infants with both RV wheezing and aeroallergen sensitization by age 1 year had the highest incidence (86%) of subsequent asthma.⁹² There also is evidence that increased expression and cross-linking of the FcεRI in individuals with allergy reduces type I and III interferon responses, thereby enhancing viral replication, airway inflammation, and illness severity.⁹⁹

A study by Bisgaard et al³⁴ found that neonates with bacterial colonization in the hypopharyngeal region with *S pneumoniae*, *H influenzae*, or *M catarrhalis*, or with a combination of these organisms, are at increased risk for recurrent wheeze early in life and asthma at age 5 years. Another theory for these findings may be that a person with an atopic biased immune function may have both altered host defenses that heighten susceptibility to bacterial and viral infections, and an increased risk of developing asthma.^{92,100-103}

BIOMARKERS AND/OR GENETICS

Bronchoalveolar lavage of preschool-aged children with wheeze shows a 3-fold increase in total cells, most significantly lymphocytes, polymorphonuclear cells, and macrophages and/or monocytes compared with normal children. In addition, leukotriene B₄, C₄, prostaglandin E₂, and the potentially epithelial-derived 15-hydroxy-eicosatetraenoic acid are increased.¹⁰⁴ These studies, however, were not replicated, and further investigation is needed. Bronchial biopsy specimens of infants with reversible airflow obstruction evaluated for severe wheezing or cough had no reticular basement membrane thickening or the eosinophilic inflammation characteristic of asthma in older children and adults.¹⁰⁵ However, preschool children younger than 6 years of age and with asthma demonstrate increased epithelial loss, basement membrane thickening, and eosinophilia compared with similarly ages of control subjects.¹⁰⁶

In preschool children enrolled in a birth cohort study, a higher fractional exhaled nitric oxide and inhalant allergen sensitization (specific IgE) were positively associated with asthma in later childhood, independent of the preschool clinical history.⁸¹ The combination of fractional exhaled nitric oxide, specific IgE, and clinical history enhanced the prediction of future wheezing.⁸¹ Furthermore, 2 additional studies found an association of higher fractional exhaled nitric oxide levels in preschool children with recurrent wheezing and a positive API compared with those with a negative API.^{107,108} Another study, which compared the lung function of 50 preschool children with recurrent wheezing and a positive or negative API, found that those with a positive API had significant lower lung function, maximal flow at functional residual capacity, in early life.¹⁰⁹

Asthma has a significant genetic contribution, with heritability estimates that vary between 35% and 95%.¹⁵ Several genetic polymorphisms are associated with the development of asthma in

children. The CCR5 delta32 polymorphism produces a nonfunctional chemokine receptor and is associated with decreased asthma susceptibility with children but not with adults.¹¹⁰ The CD14-159CC genotype is associated with both early onset allergic sensitization and increased airway responsiveness in childhood but not in young adults.¹¹¹ In the Melbourne asthma longitudinal study, a promoter polymorphism for IL-12b were associated with impaired lung function (FEV₁) in girls but not in boys only during childhood.¹¹² Several cross-sectional studies of genetic polymorphisms associated with asthma in children are confirmed in adult studies. Eighteen genetic polymorphisms in the IL-4, IL-4Ra, IL-13, and the STAT6 pathway are strongly associated with both asthma and allergic sensitization (IgE) when all 4 genes are considered when using stepwise statistics.¹¹³

The loss-of-function mutations in the filaggrin gene are strongly associated with atopic dermatitis and allergic phenotypes.¹¹⁴ However, the role of filaggrin in mediating asthma risk is less clear. Two studies demonstrate that the filaggrin gene null mutations are significantly associated with an increased need for medications¹¹⁵ and a greater risk of exacerbations in children with asthma¹¹⁶ compared with children without these mutations. However, it is possible that filaggrin mutation may modulate asthma severity indirectly in children with atopic dermatitis (by impairing the normal skin barrier function and resulting in increased allergen presentation). Thus, the degree to which specific genetic variations contribute to allergic sensitization, airway inflammation, and asthma remain to be determined.

Lastly, the first genome-wide association studies of asthma¹¹⁷ identified ORMDL3/GSDML as a novel asthma susceptibility locus on chromosome 17q21, which is associated with a risk for childhood onset asthma. Many studies have since replicated this association with variations of chromosome 17q21 and childhood onset asthma.¹¹⁷⁻¹¹⁹ Variation at this locus, however, is not associated with atopy.^{117,120,121} Moreover, a study of children with a parental history of atopic disease reveals significant associations between genotypes at the 17q21 asthma-susceptibility locus and asthma only in those children who had previously wheezed with RV; wheezing illness due to respiratory syncytial virus and the presence of allergic sensitization did not influence these genes by pathogen interactions.¹²²

RELATIONSHIP TO STATISTICALLY DEFINED PHENOTYPES

The Avon Longitudinal Study of Parents and Children phenotypes were validated in an independent cohort of 903 children who reported recurrent wheeze¹²³ by using latent class analyses at preschool and school age with measurements of atopic disease, lung function, and airway responsiveness. The analysis confirmed 3 of the 5 phenotypes of wheeze (early onset transient wheeze and atopic and nonatopic persistent wheeze) in the Tucson study.¹ Another birth cohort study,¹²⁴ of 1186 children, used latent class analyses by using the variables of multiple allergy skin and IgE tests, symptoms, hospitalizations, and lung function, along with airway reactivity, and found that children clustered into 5 distinct classes (multiple early, multiple late, dust mite, nonedust mite, and no atopic disease latent vulnerability). The association with asthma was stronger for the Multiple Early class compared with the other classes.¹²⁴ The National Heart Lung and Blood Institute Severe Asthma Research Program performed a cluster analysis on 161 children and identified 4 clusters, which varied according to the age of asthma onset, the degree of lung

function impairment, the presence of allergic sensitization, and the number of asthma controller medications.¹²⁵ Separate cluster analyses with European children also identified clusters of children with severe asthma defined by the degree and nature of allergic sensitization, body mass index, and airflow obstruction.^{126,127} Another cluster analysis in a pooled sample of children and adults with severe or difficult-to-treat asthma also noted separate clusters within each age stratum. Passive smoke exposure is a distinguishing variable in children, and aspirin sensitivity is a distinguishing variable in adolescents and adults.¹²⁸ A study that compared epidemiologic phenotype definitions identified by latent class analyses (similar to the Avon Longitudinal Study of Parents and Children study⁷) with those obtained by clinical phenotypes in preschool-aged children¹³ found high correlations between the latent class analysis phenotypes and clinically defined wheeze phenotypes. Altogether, these studies highlight the heterogeneity in the clinical presentation of asthma in children and the importance of age of onset of symptoms, symptom burden, atopic disease, lung function, and airway reactivity in the identification of distinct groups. These methods may be useful in the refinement of long-term outcomes and response to medications in upcoming studies.

RECOMMENDATIONS

Definition

The asthma-predictive phenotype is defined as children with frequent, recurrent wheezing in early life who have risk factors associated with the continuation of asthma symptoms in later life.

Information to be obtained to determine phenotype

Key characteristics that distinguish the childhood asthma-predictive phenotype:

- Male sex
- A history of frequent wheezing with lower respiratory tract infections, particularly RV, and other triggers
- A history of parental asthma
- A history of atopic dermatitis
- Blood eosinophilia of $\geq 4\%$ at 9 months
- Early sensitization to food or aeroallergens
- Lower lung function in early life

Research questions and future directions

1. Can environmental or immunomodulatory interventions be used with children with an asthma-predictive phenotype to prevent asthma in later life?
2. Can novel biomarkers be found that can consistently identify a childhood asthma-predictive phenotype?
3. Does exposure to specific viral pathogens in early life lead to airway disease in normal hosts or does wheezing with certain viruses identify children with preexisting abnormal host responses?
4. Do certain respiratory viral strains possess virulence factors that increase their propensity to induce both acute and chronic lower airway pathophysiologic alterations that induce the asthmatic phenotype?
5. Does the early identification of high-risk asthma genotypes permit more individualized approaches to therapy, both symptom-based and potentially preventative as well?

REFERENCES

1. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. *N Engl J Med* 1995;332:133-8.
2. Martinez F, Godfrey S. *Wheezing Disorders in the Preschool Child: Pathogenesis and Management*. New York: Martin Dunitz; 2003.
3. Stein RT, Sherrill D, Morgan WJ, Holberg CJ, Halonen M, Taussig LM, et al. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. *Lancet* 1999;354:541-5.
4. Stein RT, Holberg CJ, Morgan WJ, Wright AL, Lombardi E, Taussig L, et al. Peak flow variability, methacholine responsiveness and atopy as markers for detecting different wheezing phenotypes in childhood. *Thorax* 1997;52:946-52.
5. Guilbert TW, Morgan WJ, Zeiger RS, Bacharier LB, Boehmer SJ, Krawiec M, et al. Atopic characteristics of children with recurrent wheezing at high risk for the development of childhood asthma. *J Allergy Clin Immunol* 2004;114:1282-7.
6. Rusconi F, Galassi C, Corbo GM, Forastiere F, Biggeri A, Ciccone G, et al. Risk factors for early, persistent, and late-onset wheezing in young children. SIDRIA Collaborative Group. *Am J Respir Crit Care Med* 1999;160(Pt 1):1617-22.
7. Henderson J, Granell R, Heron J, Sherriff A, Simpson A, Woodcock A, et al. Associations of wheezing phenotypes in the first 6 years of life with atopy, lung function and airway responsiveness in mid-childhood. *Thorax* 2008;63:974-80.
8. Sears MR, Greene JM, Willan AR, Wiecek EM, Taylor DR, Flannery EM, et al. A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. *N Engl J Med* 2003;349:1414-22.
9. Wolfe R, Carlin JB, Oswald H, Olinsky A, Phelan PD, Robertson CF. Association between allergy and asthma from childhood to middle adulthood in an Australian cohort study. *Am J Respir Crit Care Med* 2000;162:2177-81.
10. Brand PL, Baraldi E, Bisgaard H, Boner AL, Castro-Rodriguez JA, Custovic A, et al. Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach. *Eur Respir J* 2008;32:1096-110.
11. Sonnappa S, Bastardo CM, Wade A, Saglani S, McKenzie SA, Bush A, et al. Symptom-pattern phenotype and pulmonary function in preschool wheezers. *J Allergy Clin Immunol* 2010;126:519-26.
12. Schultz A, Devadason SG, Savenije OE, Sly PD, Le Souef PN, Brand PL. The transient value of classifying preschool wheeze into episodic viral wheeze and multiple trigger wheeze. *Acta Paediatr* 2010;99:56-60.
13. Depner M, Fuchs O, Gennunet J, Karvonen AM, Hyvarinen A, Kaulek V, et al. Clinical and epidemiologic phenotypes of childhood asthma. *Am J Respir Crit Care Med* 2014;189:129-38.
14. Jackson DJ, Evans MD, Gangnon RE, Tisler CJ, Pappas TE, Lee WM, et al. Evidence for a causal relationship between allergic sensitization and rhinovirus wheezing in early life. *Am J Respir Crit Care Med* 2012;185:281-5.
15. Ober C, Yao TC. The genetics of asthma and allergic disease: a 21st century perspective. *Immunol Rev* 2011;242:10-30.
16. Stern DA, Morgan WJ, Halonen M, Wright AL, Martinez FD. Wheezing and bronchial hyper-responsiveness in early childhood as predictors of newly diagnosed asthma in early adulthood: a longitudinal birth-cohort study. *Lancet* 2008;372:1058-64.
17. Lowe LA, Simpson A, Woodcock A, Morris J, Murray CS, Custovic A. Wheeze phenotypes and lung function in preschool children. *Am J Respir Crit Care Med* 2005;171:231-7.
18. Kurukulaaratchy RJ, Fenn MH, Waterhouse LM, Matthews SM, Holgate ST, Arshad SH. Characterization of wheezing phenotypes in the first 10 years of life. *Clin Exp Allergy* 2003;33:573-8.
19. Oostveen E, Dom S, Desager K, Hagendorens M, De BW, Weyler J. Lung function and bronchodilator response in 4-year-old children with different wheezing phenotypes. *Eur Respir J* 2010;35:865-72.
20. Martinez FD. The connection between early life wheezing and subsequent asthma: the viral march. *Allergol Immunopathol (Madr)* 2009;37:249-51.
21. Holt PG, Sly PD. Prevention of allergic respiratory disease in infants: current aspects and future perspectives. *Curr Opin Allergy Clin Immunol* 2007;7:547-55.
22. Sly PD, Kusel M, Holt PG. Do early-life viral infections cause asthma? *J Allergy Clin Immunol* 2010;125:1202-5.
23. Lowe L, Murray CS, Martin L, Deas J, Cashin E, Poletti G, et al. Reported versus confirmed wheeze and lung function in early life. *Arch Dis Child* 2004;89:540-3.
24. Skjott N, Bonnelykke K, Bisgaard H. "To wheeze or not to wheeze": That is not the question. *J Allergy Clin Immunol* 2012;130:403-407.e405.
25. Barnes KC, Grant AV, Hansel NN, Gao P, Dunston GM. African Americans with asthma: genetic insights. *Proc Am Thorac Soc* 2007;4:58-68.
26. Ober C, Loisel DA, Gilad Y. Sex-specific genetic architecture of human disease. *Nat Rev Genet* 2008;9:911-22.
27. Gilliland FD, Li YF, Peters JM. Effects of maternal smoking during pregnancy and environmental tobacco smoke on asthma and wheezing in children. *Am J Respir Crit Care Med* 2001;163:429-36.

28. Xu B, Pekkanen J, Hartikainen AL, Jarvelin MR. Cesarean section and risk of asthma and allergy in adulthood. *J Allergy Clin Immunol* 2001;107:732-3.
29. Tollanes MC, Moster D, Daltveit AK, Irgens LM. Cesarean section and risk of severe childhood asthma: a population-based cohort study. *J Pediatr* 2008;153:112-6.
30. Gern JE, Lemanske RF Jr, Busse WW. Early life origins of asthma. *J Clin Invest* 1999;104:837-43.
31. Sigurs N, Gustafsson PM, Bjarnason R, Lundberg F, Schmidt S, Sigurgbergsson F, et al. Severe respiratory syncytial virus bronchiolitis in infancy and asthma and allergy at age 13. *Am J Respir Crit Care Med* 2005;171:137-41.
32. Jackson DJ, Gangnon RE, Evans MD, Roberg KA, Anderson EL, Pappas TE, et al. Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. *Am J Respir Crit Care Med* 2008;178:667-72.
33. Gereda JE, Leung DY, Thatayatikom A, Streib JE, Price MR, Klinnert MD, et al. Relation between house-dust endotoxin exposure, type 1 T-cell development, and allergen sensitisation in infants at high risk of asthma. *Lancet* 2000;355:1680-3.
34. Bisgaard H, Hermansen MN, Buchvald F, Loland L, Halkjaer LB, Bonnellykke K, et al. Childhood asthma after bacterial colonization of the airway in neonates. *N Engl J Med* 2007;357:1487-95.
35. Kozlyskiy AL, Ernst P, Becker AB. Increased risk of childhood asthma from antibiotic use in early life. *Chest* 2007;131:1753-9.
36. Marra F, Lynd L, Coombes M, Richardson K, Legal M, Fitzgerald JM, et al. Does antibiotic exposure during infancy lead to development of asthma? a systematic review and meta-analysis. *Chest* 2006;129:610-8.
37. Eyers S, Weatherall M, Jefferies S, Beasley R. Paracetamol in pregnancy and the risk of wheezing in offspring: a systematic review and meta-analysis. *Clin Exp Allergy* 2011;41:482-9.
38. Dixon AE, Holguin F, Sood A, Salome CM, Pratley RE, Beuther DA, et al. An official American Thoracic Society Workshop report: obesity and asthma. *Proc Am Thorac Soc* 2010;7:325-35.
39. Beuther DA. Recent insight into obesity and asthma. *Curr Opin Pulm Med* 2010;16:64-70.
40. Holt PG, Thomas WR. Sensitization to airborne environmental allergens: unresolved issues. *Nat Immunol* 2005;6:957-60.
41. Torrent M, Sunyer J, Garcia R, Harris J, Ithurriaga MV, Puig C, et al. Early-life allergen exposure and atopy, asthma, and wheeze up to 6 years of age. *Am J Respir Crit Care Med* 2007;176:446-53.
42. Gergen PJ, Fowler JA, Maurer KR, Davis WW, Overpeck MD. The burden of environmental tobacco smoke exposure on the respiratory health of children 2 months through 5 years of age in the United States: Third National Health and Nutrition Examination Survey, 1988 to 1994. *Pediatrics* 1998;101:E8.
43. Stein RT, Holberg CJ, Sherrill D, Wright AL, Morgan WJ, Taussig L, et al. Influence of parental smoking on respiratory symptoms during the first decade of life: the Tucson Children's Respiratory Study. *Am J Epidemiol* 1999;149:1030-7.
44. Gilliland FD, Islam T, Berhane K, Gauderman WJ, McConnell R, Avol E, et al. Regular smoking and asthma incidence in adolescents. *Am J Respir Crit Care Med* 2006;174:1094-100.
45. Polosa R, Knoke JD, Russo C, Piccillo G, Caponnetto P, Sarva M, et al. Cigarette smoking is associated with a greater risk of incident asthma in allergic rhinitis. *J Allergy Clin Immunol* 2008;121:1428-34.
46. Ponsonby AL, Dwyer T, Kemp A, Cochrane J, Couper D, Carmichael A. Synthetic bedding and wheeze in childhood. *Epidemiology* 2003;14:37-44.
47. Trevillian LF, Ponsonby AL, Dwyer T, Lim LL, Kemp A, Cochrane J, et al. A prospective association between cocoon use in infancy and childhood asthma. *Paediatr Perinat Epidemiol* 2004;18:281-9.
48. Bjorksten B. Risk factors in early childhood for the development of atopic diseases. *Allergy* 1994;49:400-7.
49. Brauer M, Hoek G, Smit HA, de Jongste JC, Gerritsen J, Postma DS, et al. Air pollution and development of asthma, allergy and infections in a birth cohort. *Eur Respir J* 2007;29:879-88.
50. Islam T, Gauderman WJ, Berhane K, McConnell R, Avol E, Peters JM, et al. Relationship between air pollution, lung function and asthma in adolescents. *Thorax* 2007;62:957-63.
51. Kaugars AS, Klinnert MD, Bender BG. Family influences on pediatric asthma. *J Pediatr Psychol* 2004;29:475-91.
52. Spergel JM. From atopic dermatitis to asthma: the atopic march. *Ann Allergy Asthma Immunol* 2010;105:99-106. quiz 107-9, 117.
53. Bernsen RM, de Jongste JC, van der Wouden JC. Birth order and sibship size as independent risk factors for asthma, allergy, and eczema. *Pediatr Allergy Immunol* 2003;14:464-9.
54. Goldberg S, Israeli E, Schwartz S, Shochat T, Izbicki G, Toker-Maimon O, et al. Asthma prevalence, family size, and birth order. *Chest* 2007;131:1747-52.
55. Ball TM, Castro-Rodriguez JA, Griffith KA, Holberg CJ, Martinez FD, Wright AL. Siblings, day-care attendance, and the risk of asthma and wheezing during childhood. *N Engl J Med* 2000;343:538-43.
56. Nystad W. Daycare attendance, asthma and atopy. *Ann Med* 2000;32:390-6.
57. Ownby DR, Johnson CC. Does exposure to dogs and cats in the first year of life influence the development of allergic sensitization? *Curr Opin Allergy Clin Immunol* 2003;3:517-22.
58. Simpson A, Custovic A. Pets and the development of allergic sensitization. *Curr Allergy Asthma Rep* 2005;5:212-20.
59. Hviid A, Melbye M. Measles-mumps-rubella vaccination and asthma-like disease in early childhood. *Am J Epidemiol* 2008;168:1277-83.
60. El-Zein M, Parent ME, Benedetti A, Rousseau MC. Does BCG vaccination protect against the development of childhood asthma? A systematic review and meta-analysis of epidemiological studies. *Int J Epidemiol* 2010;39:469-86.
61. Balicer RD, Grotto I, Mimouni M, Mimouni D. Is childhood vaccination associated with asthma? A meta-analysis of observational studies. *Pediatrics* 2007;120:e1269-77.
62. Devereux G, Seaton A. Diet as a risk factor for atopy and asthma. *J Allergy Clin Immunol* 2005;115:1109-17. quiz 1118.
63. Romieu U, Torrent M, Garcia-Esteban R, Ferrer C, Ribas-Fito N, Anto JM, et al. Maternal fish intake during pregnancy and atopy and asthma in infancy. *Clin Exp Allergy* 2007;37:518-25.
64. Devereux G, Turner SW, Craig LC, McNeill G, Martindale S, Harbour PJ, et al. Low maternal vitamin E intake during pregnancy is associated with asthma in 5-year-old children. *Am J Respir Crit Care Med* 2006;174:499-507.
65. Devereux G, Litonjua AA, Turner SW, Craig LC, McNeill G, Martindale S, et al. Maternal vitamin D intake during pregnancy and early childhood wheezing. *Am J Clin Nutr* 2007;85:853-9.
66. Nurmatov U, Devereux G, Sheikh A. Nutrients and foods for the primary prevention of asthma and allergy: systematic review and meta-analysis. *J Allergy Clin Immunol* 2011;127:724-733.e1-30.
67. Kull I, Almqvist C, Lilja G, Pershagen G, Wickman M. Breast-feeding reduces the risk of asthma during the first 4 years of life. *J Allergy Clin Immunol* 2004;114:755-60.
68. Gdalevich M, Mimouni D, Mimouni M. Breast-feeding and the risk of bronchial asthma in childhood: a systematic review with meta-analysis of prospective studies. *J Pediatr* 2001;139:261-6.
69. Wright AL, Holberg CJ, Taussig LM, Martinez FD. Factors influencing the relation of infant feeding to asthma and recurrent wheeze in childhood. *Thorax* 2001;56:192-7.
70. Duncan JM, Sears MR. Breastfeeding and allergies: time for a change in paradigm? *Curr Opin Allergy Clin Immunol* 2008;8:398-405.
71. Douwes J, Cheng S, Travier N, Cohet C, Niesink A, McKenzie J, et al. Farm exposure in utero may protect against asthma, hay fever and eczema. *Eur Respir J* 2008;32:603-11.
72. von Mutius E, Vercelli D. Farm living: effects on childhood asthma and allergy. *Nat Rev Immunol* 2010;10:861-8.
73. Castro-Rodriguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med* 2000;162(Pt 1):1403-6.
74. Devalapalli CS, Carlsen KC, Haland G, Munthe-Kaas MC, Pettersen M, Mowinckel P, et al. Severity of obstructive airways disease by age 2 years predicts asthma at 10 years of age. *Thorax* 2008;63:8-13.
75. Clough JB, Keeping KA, Edwards LC, Freeman WM, Warner JA, Warner JO. Can we predict which wheezy infants will continue to wheeze? *Am J Respir Crit Care Med* 1999;160(Pt 1):1473-80.
76. Kurukulaaratchy RJ, Matthews S, Holgate ST, Arshad SH. Predicting persistent disease among children who wheeze during early life. *Eur Respir J* 2003;22:767-71.
77. Vial Dupuy A, Amat F, Pereira B, Labbe A, Just J. A simple tool to identify infants at high risk of mild to severe childhood asthma: the persistent asthma predictive score. *J Asthma* 2011;48:1015-21.
78. Hafkamp-de Groen E, Lingsma HF, Caudri D, Levie D, Wijga A, Koppelman GH, et al. Predicting asthma in preschool children with asthma-like symptoms: validating and updating the PIAMA risk score. *J Allergy Clin Immunol* 2013;132:1303-10.
79. van der Mark LB, van Wonderen KE, Mohrs J, van Aalderen WM, ter Riet G, Bindels PJ. Predicting asthma in preschool children at high risk presenting in primary care: development of a clinical asthma prediction score. *Prim Care Respir J* 2014;23:52-9.
80. Caudri D, Wijga A, Schipper CM, Hoekstra M, Postma DS, Hoekstra M, et al. Predicting the long-term prognosis of children with symptoms suggestive of asthma at preschool age. *J Allergy Clin Immunol* 2009.

81. Caudri D, Wijga AH, Hoekstra MO, Kerkhof M, Koppelman GH, Brunekreef B, et al. Prediction of asthma in symptomatic preschool children using exhaled nitric oxide, Rint and specific IgE. *Thorax* 2010;65:801-7.
82. Leonardi NA, Spycher BD, Strippoli MP, Frey U, Silverman M, Kuehni CE. Validation of the Asthma Predictive Index and comparison with simpler clinical prediction rules. *J Allergy Clin Immunol* 2011;127:1466-1472.e1466.
83. Fouzas S, Brand PL. Predicting persistence of asthma in preschool wheezers: crystal balls or muddy waters? *Paediatr Respir Rev* 2013;14:46-52.
84. Savenije OE, Kerkhof M, Koppelman GH, Postma DS. Predicting who will have asthma at school age among preschool children. *J Allergy Clin Immunol* 2012;130:325-31.
85. Castro-Rodriguez JA. The Asthma Predictive Index: a very useful tool for predicting asthma in young children. *J Allergy Clin Immunol* 2010;126:212-6.
86. Castro-Rodriguez JA. The Asthma Predictive Index: early diagnosis of asthma. *Curr Opin Allergy Clin Immunol* 2011;11:157-61.
87. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. *J Allergy Clin Immunol* 2007;120(Suppl):S94-138.
88. Guilbert TW, Morgan WJ, Zeiger RS, Mauger DT, Boehmer SJ, Szeffler SJ, et al. Long-term inhaled corticosteroids in preschool children at high risk for asthma. *N Engl J Med* 2006;354:1985-97.
89. Chang TS, Lemanske RF Jr, Guilbert TW, Gern JE, Coen MH, Evans MD, et al. Evaluation of the modified asthma predictive index in high-risk preschool children. *J Allergy Clin Immunol Pract* 2013;1:152-6.
90. Gern JE. Viral respiratory infection and the link to asthma. *Pediatr Infect Dis J* 2008;27(Suppl):S97-103.
91. Gern JE, Bacharier LB, Lemanske RFJ. Infections and asthma. In: Leung DYM, Sampson HA, Geha RS, Szeffler SJ, editors. *Pediatric Allergy*. St Louis: Mosby; 2003. p. 366-78.
92. Kusel MM, de Klerk NH, Kebadze T, Vohma V, Holt PG, Johnston SL, et al. Early-life respiratory viral infections, atopic sensitization, and risk of subsequent development of persistent asthma. *J Allergy Clin Immunol* 2007;119:1105-10.
93. Green RM, Custovic A, Sanderson G, Hunter J, Johnston SL, Woodcock A. Synergism between allergens and viruses and risk of hospital admission with asthma: case-control study. *BMJ* 2002;324:763.
94. Rakes GP, Arruda E, Ingram JM, Hoover GE, Zambrano JC, Hayden FG, et al. Rhinovirus and respiratory syncytial virus in wheezing children requiring emergency care. IgE and eosinophil analyses. *Am J Respir Crit Care Med* 1999;159:785-90.
95. Copenhaver CC, Gern JE, Li Z, Shult PA, Rosenthal LA, Mikus LD, et al. Cytokine response patterns, exposure to viruses, and respiratory infections in the first year of life. *Am J Respir Crit Care Med* 2004;170:175-80.
96. Ly NP, Rifas-Shiman SL, Litonjua AA, Tzianabos AO, Schaub B, Ruiz-Perez B, et al. Cord blood cytokines and acute lower respiratory illnesses in the first year of life. *Pediatrics* 2007;119:e171-8.
97. Gern JE, Brooks GD, Meyer P, Chang A, Shen K, Evans MD, et al. Bidirectional interactions between viral respiratory illnesses and cytokine responses in the first year of life. *J Allergy Clin Immunol* 2006;117:72-8.
98. Lee WM, Lemanske RF Jr, Evans MD, Vang F, Pappas T, Gangnon R, et al. Human rhinovirus species and season of infection determine illness severity. *Am J Respir Crit Care Med* 2012;186:886-91.
99. Durrani SR, Montville DJ, Pratt AS, Sahu S, DeVries MK, Rajamanickan V, et al. Innate immune responses to rhinovirus are impaired by the high-affinity IgE receptor in allergic asthmatic children. *J Allergy Clin Immunol* 2012;130:489-95.
100. Korppi M, Kotaniemi-Syrjanen A, Waris M, Vainionpää R, Reijonen TM. Rhinovirus-associated wheezing in infancy: comparison with respiratory syncytial virus bronchiolitis. *Pediatr Infect Dis J* 2004;23:995-9.
101. Jartti T, Korppi M, Ruuskanen O. The clinical importance of rhinovirus-associated early wheezing. *Eur Respir J* 2009;33:706-7.
102. Hartert TV. Are persons with asthma at increased risk of pneumococcal infections, and can we prevent them? *J Allergy Clin Immunol* 2008;122:724-5.
103. Juhn YJ, Kita H, Yawn BP, Boyce TG, Yoo KH, McGee ME, et al. Increased risk of serious pneumococcal disease in patients with asthma. *J Allergy Clin Immunol* 2008;122:719-23.
104. Krawiec ME, Westcott JY, Chu HW, Balzar S, Trudeau JB, Schwartz LB, et al. Persistent wheezing in very young children is associated with lower respiratory inflammation. *Am J Respir Crit Care Med* 2001;163:1338-43.
105. Saglani S, Malmstrom K, Pelkonen AS, Malmberg LP, Lindahl H, Kajosaari M, et al. Airway remodeling and inflammation in symptomatic infants with reversible airflow obstruction. *Am J Respir Crit Care Med* 2005;171:722-7.
106. Saglani S, Payne DN, Zhu J, Wang Z, Nicholson AG, Bush A, et al. Early detection of airway wall remodeling and eosinophilic inflammation in preschool wheezers. *Am J Respir Crit Care Med* 2007;176:858-64.
107. Balinotti JE, Colom A, Kofman C, Teper A. Association between the Asthma Predictive Index and levels of exhaled nitric oxide in infants and toddlers with recurrent wheezing. *Arch Argent Pediatr* 2013;111:191-5.
108. Castro-Rodriguez JA, Sardon O, Perez-Yarza EG, Korta J, Aldasoro A, Corcuera P, et al. Young infants with recurrent wheezing and positive asthma predictive index have higher levels of exhaled nitric oxide. *J Asthma* 2013;50:162-5.
109. Keklikian E, Sanchez-Solis M, Bonina AJ, Meneguzzi A, Pastor-Vivero MD, Mondejar-Lopez P, et al. Do risk factors for persistent asthma modify lung function in infants and young children with recurrent wheeze? *Pediatr Pulmonol* 2010;45:914-8.
110. Hall IP, Wheatley A, Christie G, McDougall C, Hubbard R, Helms PJ. Association of CCR5 delta32 with reduced risk of asthma. *Lancet* 1999;354:1264-5.
111. O'Donnell AR, Toelle BG, Marks GB, Hayden CM, Laing IA, Peat JK, et al. Age-specific relationship between CD14 and atopy in a cohort assessed from age 8 to 25 years. *Am J Respir Crit Care Med* 2004;169:615-22.
112. Khoo SK, Hayden CM, Roberts M, Horak E, De Klerk N, Zhang G, et al. Associations of the IL12B promoter polymorphism in longitudinal data from asthmatic patients 7 to 42 years of age. *J Allergy Clin Immunol* 2004;113:475-81.
113. Kabesch M, Schedel M, Carr D, Woitsch B, Fritzsche C, Weiland SK, et al. IL-4/IL-13 pathway genetics strongly influence serum IgE levels and childhood asthma. *J Allergy Clin Immunol* 2006;117:269-74.
114. Baurecht H, Irvine AD, Novak N, Illig T, Buhler B, Ring J, et al. Toward a major risk factor for atopic eczema: meta-analysis of filaggrin polymorphism data. *J Allergy Clin Immunol* 2007;120:1406-12.
115. Palmer CN, Ismail T, Lee SP, Terron-Kwiatkowski A, Zhao Y, Liao H, et al. Filaggrin null mutations are associated with increased asthma severity in children and young adults. *J Allergy Clin Immunol* 2007;120:64-8.
116. Basu K, Palmer CN, Lipworth BJ, Irwin McLean WH, Terron-Kwiatkowski A, Zhao Y, et al. Filaggrin null mutations are associated with increased asthma exacerbations in children and young adults. *Allergy* 2008.
117. Moffatt MF, Kabesch M, Liang L, Dixon AL, Strachan D, Heath S, et al. Genetic variants regulating ORMDL3 expression contribute to the risk of childhood asthma. *Nature* 2007;448:470-3.
118. Halapi E, Gudbjartsson DF, Jonsdottir GM, Bjornsdottir US, Thorleifsson G, Helgadóttir H, et al. A sequence variant on 17q21 is associated with age at onset and severity of asthma. *Eur J Hum Genet* 2010;18:902-8.
119. Sleiman PM, Annaiah K, Imielinski M, Bradfield JP, Kim CE, Frackelton EC, et al. ORMDL3 variants associated with asthma susceptibility in North Americans of European ancestry. *J Allergy Clin Immunol* 2008;122:1225-7.
120. Bisgaard H, Bonnelykke K, Sleiman PM, Brasholt M, Chawes B, Kreiner-Moller E, et al. Chromosome 17q21 gene variants are associated with asthma and exacerbations but not atopy in early childhood. *Am J Respir Crit Care Med* 2009;179:85-9.
121. Bouzigon E, Corda E, Aschard H, Dizier MH, Boland A, Bousquet J, et al. Effect of 17q21 variants and smoking exposure in early-onset asthma. *N Engl J Med* 2008;359:1985-94.
122. Caliskan M, Bochkov YA, Kreiner-Moller E, Bonnelykke K, Stein MM, Du G, et al. Rhinovirus wheezing illness and genetic risk of childhood-onset asthma. *N Engl J Med* 2013;368:1398-407.
123. Spycher BD, Silverman M, Brooke AM, Minder CE, Kuehni CE. Distinguishing phenotypes of childhood wheeze and cough using latent class analysis. *Eur Respir J* 2008;31:974-81.
124. Simpson A, Tan VY, Winn J, Svensen M, Bishop CM, Heckerman DE, et al. Beyond atopy: multiple patterns of sensitization in relation to asthma in a birth cohort study. *Am J Respir Crit Care Med* 2010;181:1200-6.
125. Fitzpatrick AM, Teague WG, Meyers DA, Peters SP, Li X, Li H, et al. Heterogeneity of severe asthma in childhood: confirmation by cluster analysis of children in the National Institutes of Health/National Heart, Lung, and Blood Institute Severe Asthma Research Program. *J Allergy Clin Immunol* 2011;127:382-389.e1-13.
126. Just J, Saint-Pierre P, Gouvis-Echraghi R, Laoudi Y, Roufai L, Momas I, et al. Childhood allergic asthma is not a single phenotype. *J Pediatr* 2014;164:815-20.
127. Just J, Gouvis-Echraghi R, Rouve S, Wanin S, Moreau D, Annesi-Maesano I. Two novel, severe asthma phenotypes identified during childhood using a clustering approach. *Eur Respir J* 2012;40:55-60.
128. Schatz M, Hsu JW, Zeiger RS, Chen W, Dorenbaum A, Chipps BE, et al. Phenotypes determined by cluster analysis in severe or difficult-to-treat asthma. *J Allergy Clin Immunol* 2014;133:1549-56.
129. Morgan WJ, Stern DA, Sherrill DL, Guerra S, Holberg CJ, Guilbert TW, et al. Outcome of asthma and wheezing in the first 6 years of life: follow-up through adolescence. *Am J Respir Crit Care Med* 2005;172:1253-8.

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.