



Childhood asthma: recent developments and update

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Purpose of review

The purpose of this review is to provide an update on childhood asthma specifically related to the underlying genetic background and pathophysiology of asthma and their interaction with environmental stimuli. We will also discuss emerging data in the field of disease phenotyping.

Recent findings

The field of genetics is continuously evolving to expand our knowledge on the cause of disease. Childhood onset asthma has been related to atopy and exposure to early-life infections. More recently, phenotypes have been used to classify asthma as transient and persistent, but the association of each phenotype with the genetic origin of asthma is not clearly understood.

Summary

This review covers the topics of genetics, epigenetics, pathophysiology, phenotypes and treatment as they relate to childhood asthma. Overall, it provides a basis for the future of asthma treatment through description of the current research.

Keywords

asthma phenotypes, atopy, childhood asthma, epigenetics, genetics

INTRODUCTION

In this review, we will discuss recent findings about childhood asthma specifically those related to genetics, epigenetics, phenotyping and treatment approaches. Aspects of childhood onset asthma will be discussed in association with atopy as well as infection.

GENETICS

Asthma is genetically heterogeneous. Genome-wide association studies (GWAS) have provided more insight into the unique genetic origins of childhood-onset asthma.

GWAS have recently identified a locus on chromosome 17q21 (encoding *ORMDL3* and *GSDMB*) to be strongly associated with childhood-onset asthma [1] and specific to wheezing phenotypes. The strongest evidence for phenotypic association was seen for persistent wheezing phenotype (rs8076131, near *ORMDL3*), whereas less association was seen for intermediate-onset wheezing [2[■]]. Chromosome 17q21 was associated with two-fold increased risk of recurrent wheeze, asthma exacerbations and bronchial hyperresponsiveness, but it was not related to the risk of eczema, rhinitis or allergic sensitization [3]. The above associations are not explained by atopy [2[■]], confirming the 17q21 locus as an important risk factor of childhood-onset nonatopic asthma [3].

The genes controlling IgE level have surprisingly little overlap with the genes mediating asthma susceptibility. *FCER1A*, the gene encoding a ligand-binding subunit of the high-affinity IgE receptor, is a major susceptibility locus for serum IgE level. However, *FCER1A* polymorphisms influence IgE level not only in asthma patients but also in nonasthmatic populations [4[■]].

Other than persistent wheezing, childhood asthma phenotypes have been associated with several single nucleotide polymorphisms (SNPs). Severe childhood and nonatopic childhood asthma phenotypes have been associated with an MYB binding site in the *PDCD4* gene [5[■]], and polymorphisms of protocadherin-1 (*PCHDH1*) [6] (Table 1) [1,2[■],3,4[■],5[■],6,7,8[■],9,10].

Forno *et al.* [8[■]] conducted the first GWAS of the onset of childhood asthma among participants in the Childhood Asthma Management Program (CAMP) using three independent cohorts for replication. They identified two SNPs (rs9815663, rs7927044) associated with earlier childhood

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KEY POINTS

- Epigenetic mechanisms allow for research into the heritability of asthma.
- Airway epithelial cells express genes that encode proteins directly related to asthma.
- Respiratory infections early in life are not always protective over asthma.
- It appears that atopy genes are not necessarily directly related to childhood asthma.
- Early identification of persistent wheezing phenotype reinforced by family history of asthma, and early tailored treatment may allow for optimal lung function and disease control, and decreased burden.

asthma onset. Thus far, SNPs in several genes have been associated with asthma risk, linked to asthma or to bronchial hyperresponsiveness or atopy, or a combination of both [2[■]].

Spycher *et al.* [11] reported that some pathways are specific to wheezing syndromes whereas others are shared with atopy and bronchial hyperresponsiveness. Two SNPs are specifically associated with persistent wheezing phenotype and less associated to intermediate wheezing. However, these polymorphisms are not associated with early-onset wheezing, atopy or nonasthma phenotypes.

In addition to chromosome 17q21, other loci associated with asthma risk include *DENND1B* [9], the locus containing *IL1RL1* and *IL18R1* on chromosome 2q12.1, *HLA-DQ*, *IL33*, *IL2RB* and *SMAD3* [9], and a SNP rs4950928 on the promoter region of

CHI3L1 expression in the airway epithelium [10] (Table 1).

Maternal asthma and child's sex are significant risk factors for asthma development. Thompson *et al.* [12[■]] hypothesized that some of the observed risks for asthma may be because of different rates of transmission or persistence of maternal cells to children of asthmatic mothers (maternal microchimerism), compared with children of nonasthmatic mothers, or sons compared with daughters. They further hypothesized that rates of maternal microchimerism differ between children with and without asthma, suggesting that maternal microchimerism may protect against the development of asthma.

Two completed meta-analyses of asthma GWAS, the European GABRIEL Consortium and the US EVE Consortium [9,13], point to the epithelium as a primary player in asthmatic susceptibility. It is possible that the observed airway inflammation is a result of events rather than the cause. The epithelial damage may communicate to the adaptive immune system, leading to airway inflammation [9] of recurrent severity.

The genomic results to date are exciting. Chromosome 17q21 gene variants are predominantly associated with childhood-onset asthma and exacerbations but not atopy. These findings suggest that atopy is a secondary rather than a primary driver to asthma. Atopy genes do not explain early-onset asthma.

EPIGENETICS–INFECTIONS–HYGIENE HYPOTHESIS

The cause of asthma is complex with strong genetic and environmental components. Environmental

Table 1. Genes/single nucleotide polymorphisms associated with childhood-onset asthma

Chromosome	Gene/variant SNP	Relation to asthma
17q21	<i>ORMDL3/GSDMB</i>	Childhood-onset asthma; asthma exacerbation; bronchial hyperresponsiveness [1,2 [■] ,3]
1q31.3	<i>DENND1B</i>	Increased asthma risk [7]
1q23	<i>FCER1A</i>	IgE levels in asthmatic and nonasthmatic children [4 [■]]
Chromosome 10	<i>PDCD4</i>	Severe childhood asthma [5 [■]]
Chromosome 13	<i>PCHDH1</i>	Nonatopic childhood asthma [6]
3p26	rs9815663	Earlier childhood-onset asthma [8 [■]]
11q24	rs7927044	Earlier childhood-onset asthma [8 [■]]
Chromosome 2	<i>IL1RL1/IL18R1</i>	Increased asthma risk [9]
Chromosome 6	<i>HLA-DQ</i>	Increased asthma risk [9]
Chromosome 9	<i>IL-33</i>	Increased asthma risk [9]
Chromosome 22	<i>IL2RB</i>	Increased asthma risk [9]
Chromosome 15	<i>SMAD3</i>	Increased asthma risk [9]
Chromosome 1	<i>CHI3L1/rs49250928</i>	Increased asthma risk [10]

exposures associated with asthma risk such as maternal smoking, ambient air pollution, diet and microbial exposure during pregnancy have been associated with DNA methylation at several CpG sites [14].

Previous reports have associated the development of asthma with early-life respiratory syncytial virus (RSV) infections [15,16]. Similarly, asthma is correlated with early-life human rhinovirus infections [17]. Human rhinovirus infections have also been related to maternal atopic predisposition [18] and to decreased lung function at age 8 years in the high-risk birth cohort [19], both conditions indirectly linked with asthma development. The above studies contradict previous ones showing that episodic viral wheezing in early life, facilitated by either other siblings at home or day care attendance, protects from later development of asthma [20]. However, a recent study following children who had experienced an early severe episodic viral wheeze up to age 5–10 years showed an increased risk of asthma development at age 5–10 years [21].

Genetic variation at the 17q21 locus and virus-induced respiratory wheezing illnesses are associated with the development of asthma. Caliskan *et al.* [22²²] investigated the variants at the 17q21 locus in association with asthma in children with human rhinovirus wheezing illnesses and found that the expression levels of two genes, *ORMDL3* and *GSDMB*, increased in response to human rhinovirus stimulation. In regards to bacterial infections, Ege *et al.* [23] described seven bands of bacteria to be inversely associated with childhood asthma.

According to the hygiene hypothesis, decreased early-life contact with infectious agents could explain the increase in prevalence of asthma. Children living on farms are exposed to a variety of microbes, which explains a substantial fraction of the inverse relation between asthma and the farm environment [24]. Varraso *et al.* [25] investigated the farming/hygiene hypothesis and confirmed the protective role of contact with livestock and farming lifestyle on asthma. Paradoxically, in developing countries, the protective role of early-life exposure to farm animals on asthma symptoms does not exist. The International Study of Asthma and Allergies in Childhood (ISAAC) phase III study showed that maternal exposure to farm animals during pregnancy and infants' exposure to farms in the first year of life were associated with the increased symptoms of asthma in 6–7-year-old children living in nonaffluent but not in affluent countries [26²⁶]. Michel *et al.* [27²⁷] used the Protection Against Allergy: Study in Rural Environments (PASTURE) birth cohort to investigate the effect of farm exposure on epigenetic patterns in asthma

candidate genes, the change of status throughout the first year of life, and the possible contribution of these changes to the development of asthma. Their results demonstrated that the farming environment decreases DNA methylation at specific asthma-related genes, and the timing of DNA collection for epigenetic analysis is crucial.

Exposure to endotoxin is associated with the decreased risk of asthma. A meta-analysis of studies examining the association of endotoxin exposure with wheeze and asthma in children showed that endotoxin is a risk factor for wheeze in younger children, but a protective factor for asthma in older children [28] through an unknown mechanism.

Lower exposure to microbes does not always result in atopic/responsive phenotype. Figueiredo *et al.* [29²⁹] studied whether the hygiene hypothesis operates in urban Latin America and identified three phenotypes labeled under-responsive, intermediate, and responsive. Children living in improved environmental conditions, with little exposure to infection, were significantly more likely to have the atopic/responsive phenotype. A subgroup of 31 759 children from the ISAAC phase I population was tested through skin prick test to common allergens based on questionnaire response. Pertussis and measles vaccination was not significantly associated with any of the allergy outcomes or skin prick test positivity, and although both were associated with higher prevalence of wheeze and eczema, these associations were unlikely to be IgE mediated [30]. Finally, 1128 Latin American children aged 4–11 years were tested for infection by eight pathogens in serum and stool, specific (s)IgE (RAST) and skin prick test reactivity for common local allergens. Children with fewer infection markers had a higher prevalence of sIgE (RAST) and skin prick test reactivity compared to those with four or more infection markers. Isolated infections or pathogen burden were not associated with the prevalence of atopic or nonatopic wheeze, suggesting that the hygiene hypothesis applies with regards to the atopic status but not to asthma symptoms [31³¹].

PATHOPHYSIOLOGY

The key pathophysiological features of asthma are airway hyperresponsiveness and airway inflammation [32]. Recent data imply that airway remodeling [33], characterized as structural changes such as epithelial injury, thickening of reticular basement membrane, airway smooth muscle and goblet cell hypertrophy, hyperplasia, and angiogenesis can occur early in childhood, not necessarily subsequent to but rather in parallel with airway inflammation [34].

Several birth cohort and follow-up studies in symptomatic infants and toddlers examined the significance of early airway responsiveness to subsequent outcomes of lung function and symptoms. The Copenhagen Prospective Study of Asthma in Childhood (COPSAC) cohort study involved 362 neonates at 1 month of age and assessed them annually for asthma until age 7 years [35]. The investigators found that neonatal airway responsiveness was significantly associated with the development of asthma by age 7 and it was a stronger predictor of asthma than neonatal lung function. Airway responsiveness may be more strongly associated with asthma in infancy and early childhood than in school age and adolescence.

In order to define whether early abnormal airway responsiveness is a determining factor for childhood asthma development or if airway responsiveness is connected to other asthmatic pathophysiological pathways, more birth cohort studies on the development of lung function and airway responsiveness combined with bronchial biopsy data may be required. Two recent studies including bronchial biopsies in asthmatic children investigated airway remodeling in children suffering from noneosinophilic asthma. They demonstrated that in asthma patients, airway remodeling early in life could be promoted by other mechanisms apart from eosinophilic inflammation [36]. O'Reilly *et al.* [37] demonstrated for the first time that airway smooth muscle is increased in preschool children with severe wheeze who will later develop asthma at school age.

PHENOTYPES

Asthma can be classified into phenotypes based on several characteristics. These characteristics include onset of disease, persistence, atopy, triggers, duration, symptoms and more. Below, we will review the most recent phenotype classifications.

Asthmatic symptoms in young children reflect a heterogeneous group of diseases that vary in clinical presentation, severity and response to treatment. The heterogeneity of wheezing phenotypes may account for different responses to treatment and outcomes.

For almost 20 years, population-based studies have followed children from birth or early childhood into adulthood. Epidemiologic phenotyping classifies patterns of recurrent wheezing in young children. The Avon Longitudinal Study of Parents and Children (ASLPAC) and the Dutch Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort studies followed children up to 8 years of age and used latent class analysis to propose six phenotypes of wheezing, never/infrequent,

transient early, prolonged early, intermediate onset, late onset, persistent in ASLPAC, and five phenotypes in PIAMA. With the exception of the 'prolonged early wheezing' phenotype, these phenotypes were identical in both cohorts [38] (Table 2) [38,39,40[■],41[■],42[■],43,44[■],45].

Latent class analysis of data from the ISAAC phase II study in Spanish children 8–12 years old identified seven classes of phenotypes based on respiratory symptoms collected from a questionnaire. Three of these phenotypes were related to wheeze, three to congestion and coughed-up phlegm, and one included nonsymptomatic children [39] (Table 2).

Phenotypes of recurrent wheezing have been identified in early life. Grad and Morgan [46] reviewed longitudinal cohorts which indicated that early-life wheezing that continues into the school years generally persists into childhood. They noted that allergic sensitization, rhinovirus infection or bacteria colonization early in life has been associated with the increased risk of persistent wheeze and that deficits in lung function in childhood can persist into adulthood and may be associated with the risk for later development of chronic obstructive pulmonary disease.

Recently, Zedan *et al.* [40[■]] classified asthmatic children based on symptomatology into three phenotypes: shortness of breath, cough and wheeze (Table 2). The shortness of breath group was of older age, had longer disease duration, high sIgE and responded better to fluticasone alone. The cough group was of a younger age, had a high eosinophil count, and responded to montelukast alone. The wheeze group showed mixed patterns and responded to both medications. Symptom-based asthma phenotypes triggered by viruses or multiple factors resulting in exacerbations of asthma are classified according to the European Respiratory Society Task Force on Preschool Wheeze as episodic viral wheeze and multiple trigger wheeze. Additionally, Just *et al.* [41[■]] identified different phenotypes of recurrent wheezing in children using cluster analysis. Boys more frequently had atopic multiple-trigger wheezing, whereas girls had non-atopic uncontrolled wheezing associated with infectious agents. Skytt *et al.* [47] reported that a quantitative assessment of troublesome respiratory symptoms in the first 3 years of life is a better predictor of asthma than the assessment of wheeze alone, which may lead to undertreatment.

The Childhood Asthma Prevention Study (CAPS) high-risk cohort outlined atopic phenotypes characterized by their pattern of sensitization and change over time into four groups: late mixed inhalant, mixed food and inhalant, house dust mite monosensitized and nonatopic. All atopic

Table 2. Pediatric asthma phenotypes described by longitudinal cohort or cross sectional studies

Phenotype classification	Studies	
Onset and persistence of symptoms	Birth cohort to 7 years ($n = 5760$), ALSPAC [38] Transient early wheezing Intermediate-onset wheezing Persistent wheezing Prolonged early wheezing Late-onset wheezing Never/infrequent wheezing	Birth cohort to 8 years ($n = 2810$), PIAMA [38] Transient early wheezing Intermediate wheezing Persistent wheezing Late wheezing Never/infrequent wheezing
Type of symptoms	ISAAC phase II cross sectional study 8–12 years ($n = 3890$) [39] Cough during colds Chronic cough and phlegm Wheeze only with colds Wheeze only without colds Wheeze without colds, with cough Nocturnal breathlessness No respiratory symptoms	Cross sectional study; asthmatic children 8–14 years ($n = 203$) [40 [■]] Shortness of breath phenotype Cough phenotype Wheeze phenotype
Triggers	Cluster analysis of 20 variables in children younger than 36 months ($n = 551$) [41 [■]] Wheeze atopic with multiple triggers (more common in boys) Wheeze with infectious agents (more common in girls)	
Sensitization/atopy	Birth cohort to 8 years, high risk for allergies ($n = 616$), CAPS [42 [■]] Late mixed inhalant Mixed food and inhalant House-dust mite mono-sensitized Nonatopic	Infant cohort, PARIS At age 18 months ($n = 1831$) [43] Intermittent mild wheeze Severe atopic wheezing Severe nonatopic wheezing At age 4 years ($n = 2522$) [44 [■]] Transient wheeze phenotype Persistent (atopic) cough/rhinitis phenotype
Cytokines of bronchoalveolar lavage fluid	53 asthmatic children; 31 of them had severe asthma [45] Moderate asthma phenotype Severe asthma phenotype (IL-12, interferon γ , IL-10, CXCL1, CCL5 in lavage fluid)	
Other criteria ^a		

ALSPAC, Avon Longitudinal Study of Parents and Children; CAPS, Childhood Asthma Prevention Study; IL, interleukin; ISAAC, International Study of Asthma and Allergies in Childhood; PARIS, Pollution and Asthma Risk: an Infant Study; PIAMA, Prevention and Incidence of Asthma and Mite Allergy.

^aSeverity of symptoms, viral infections, lung function, bronchial hyperactivity and pathogenetic mechanisms.

phenotypes were related to asthma, rhinitis and eczema, but the mixed food and inhalant phenotype had the strongest correlation with asthma suggesting that food sensitization in early life may imply subsequent asthma risk [42[■]]. Herr *et al.* [43] evaluated children at 18 months old and determined three phenotypes using latent class analysis: one mild group (intermittent mild wheeze), and

two severe phenotypes (atopic: wheezing, high prevalence of atopy and atopic dermatitis; non-atopic: recurrent wheezing). This study concluded that atopy should be recognized during the evaluation of severe exacerbation and that infants with atopy should be protected against respiratory irritants, molds and weight gain. Another study evaluated children from the Pollution and Asthma

Risk (PARIS) cohort followed annually from birth until the age of 4 years [44^{***}]. The researchers classified four different phenotypes: two transient (rhinitis, wheeze) and two persistent (cough/rhinitis, dermatitis). Bisgaard *et al.* [35] reported that children with asthma by the age of 7 years have increased bronchial responsiveness and lung function deficits as neonates. Furthermore, they indicated that the lung deficit seems to progress to age 7 years. Research into the origins of asthma should consider early life before and after birth.

Savenije *et al.* [48] reviewed the use of clinical prediction rules in assessing children who will have asthma at school age among preschool children. The researchers concluded that prediction can be improved by more precise definitions and measures and, ultimately, by more knowledge on pathophysiologic mechanisms of asthma.

Severe asthma has been proposed to separate into three groups including untreated severe asthma, difficult-to-treat severe asthma and treatment-resistant severe asthma [49]. Furthermore, the phenotypes of severe asthma have been classified in various ways ranging from clinical and pathological findings to age subphenotypes such as patterns of symptoms, inflammatory cells in induced sputum or a combination of factors (e.g. patterns of symptoms, sputum cellularity and airway function). Fitzpatrick *et al.* [45] studied bronchoalveolar lavage fluid and alveolar macrophage lysate to discriminate between moderate and severe asthma in children using linear discriminate analysis. The analysis showed a complete separation of the moderate and severe asthmatic groups, and correlations between the alveolar macrophage and bronchoalveolar lavage fluid analytes measured. The main discriminator between controls and asthma patients was interleukin (IL)-6 from the alveolar macrophage lysate, and GRO (growth-related oncogene; CXCL1), RANTES (regulated upon activation normal T cell expressed and secreted; CCL5), IL-12, interferon γ and IL-10 were the best discriminators of the severe asthma phenotype.

In an effort to identify the immunopathology that distinguishes phenotypes or identifies a target population for specific therapy, Wenzel [50] proposed classifying asthma by endotypes. An asthma endotype classifies phenotypes based on their cause or pathogenic mechanism. Currently, treatment guidelines assume that asthma is a unified disorder with a common inflammatory mechanism and the nature of this inflammation is responsive to corticosteroids. Lotvall *et al.* [51] differentiated between endotypes using seven different parameters: clinical characteristics, biomarkers, lung function, genetics, histopathology, epidemiology and response to

treatment. Correlation with at least five of the above parameters is adequate to confirm endotype status. Thus far, six endotypes have been proposed.

TREATMENT

Different guidelines address the management of childhood asthma. Diagnosis of asthma, particularly in children younger than 5 years, is difficult. Fewer scientific publications for this age group and the near absence of biopsy data make this group particularly challenging.

Treatment of preschool children

Evidence in the preschool children (0–5 years) cohort is limited, causing this age group to be the most difficult to diagnose. However, the recognizable patterns of illness are recurrent exacerbations of cough and wheeze typically triggered by viral respiratory tract infections. Diagnosis is usually based on symptom patterns, risk factor and therapeutic response. Thomas *et al.* [52] suggested three set regimens. The first set is used for persistent, prolonged period of time and an overall increase in medication, known as ‘step-up long-term’. The second set, ‘step-up short-term,’ is used during a temporary loss of acceptable control. This set of therapy is terminated within 3–10 days, once asthma is in control. The third set, ‘step-up intermittent’ approach is used to treat symptoms related to the variability of asthma on a daily basis.

Zeiger *et al.* [53] compared a daily low dose of budesonide therapy to an intermittent 7 days therapy of high dose budesonide in 278 children between the ages of 12 and 53 months – without a control group. The authors concluded that a daily low-dose regimen of budesonide was not superior to an intermittent high-dose regimen in reducing asthma exacerbations and reducing the frequency of treatment for respiratory illness.

As the efficacy of oral corticosteroids in preschool-aged children has not been adequately supported, a study was performed through replication analyses in two outpatient cohorts of 214 1–5-year-old children with episodic wheezing by comparing symptom scores during respiratory tract infection of patients who were or were not treated with oral corticosteroids. A total of 798 acute respiratory tract infections did not have different total symptom scores with regards to the use of oral corticosteroids. Although these findings need to be further confirmed, the study suggests that during outpatient care of acute respiratory tract infections, the addition of oral corticosteroids does not reduce episode severity [54^{***}].

In addition, inhaled corticosteroid treatment on wheezing infants and preschoolers with either multiple trigger wheeze or episodic viral wheeze ultimately showed that therapy with high doses of inhaled corticosteroids had significant beneficial effects [55].

A meta-analysis was completed using data from 185 trials comparing the efficacy of daily versus intermittent inhaled corticosteroid among preschoolers, children, and adults with persistent wheezing and mild-to-moderate stable persistent asthma. Data from five of those studies (two with toddlers) showed no statistically significant difference in asthma exacerbation frequency among patient groups receiving daily versus intermittent inhaled corticosteroid. However, the daily inhaled corticosteroid treatment was superior to the intermittent inhaled corticosteroid treatment in fields such as asthma free days, rescue beta-2-agonist use and exhaled nitric oxide. However, there is still the need to have further evidence for a conclusion to be made [56].

Treatment of school-aged children

Daily inhaled corticosteroids remain the recommended treatment in children with persistent asthma. The efficacy and safety of four doses of once-daily fluticasone furoate, a novel inhaled corticosteroid with maintained activity for 24 h, administered using a dry powder inhaler, was investigated in patients older than 12 years with uncontrolled moderate asthma. Six hundred twenty-two patients were randomized to one of six treatments: fluticasone furoate (100, 200, 300 or 400 µg) once daily in the evening, fluticasone propionate 250 µg twice daily (active control), or placebo for 8 weeks. Although the study included high withdrawal rate and 8-week duration, it also showed that all doses of once-daily fluticasone furoate caused significant improvement from baseline the evening before treatment, compare with placebo [57].

In a randomized, double blind placebo-controlled (TREXA) study of 843 children and adolescents assigned to three treatment groups, daily, combined, rescue, and placebo, differing in their daily beclomethasone, rescue beclomethasone and placebo dosages. The frequencies of exacerbation that required oral corticosteroids were highest in the placebo group (49%) and lowest in the daily group (28%). The treatment failure frequency was highest in the placebo group (23%), followed by the rescue group (8.5%). Because the daily group had the lowest treatment failure frequency and the lowest exacerbation frequency, daily inhaled corticosteroids remain the treatment of choice for exacerbation prevention [58].

A systematic review of 65 randomized trials in children and adults compared the safety and efficacy of antileukotrienes with inhaled corticosteroids as monotherapy in patients with asthma older than 2 years. The conclusion was that monotherapy with inhaled corticosteroids displays superior efficacy to antileukotrienes in children and adults with persistent asthma [59].

It was previously thought that the daily treatment of inhaled corticosteroids caused a temporary reduction in growth velocity in children. The CAMP followed 943 participants during the trial period of 4–6 years. The adjusted mean adult height was 1.2 cm lower in the group receiving budesonide than in the placebo group, and, the effect was greater for women. Additionally, it was found that a larger daily dose was associated with a lower adult height, concluding that the reduction of growth seen during the initial administration of inhaled glucocorticoids in prepubertal children persists as lowered adult height [60].

CONCLUSION

Recent genetic advancements have determined that chromosome 17q21 is the main gene locus for childhood-onset asthma. Phenotypic classifications have allowed for further understanding of the heterogeneity of disease in association with its origin. Furthermore, research in different types of childhood asthma classified by age, sex, atopy and response to treatment might add significant information about the pathogenesis of childhood asthma.

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Conflicts of interest

There are no conflicts of interest.

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- of outstanding interest

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