Review
Allergy Asthma Immunol Res. 2011 April;3(2):67-73.
doi: 10.4168/aair.2011.3.2.67
pISSN 2092-7355 • eISSN 2092-7363

The Atopic March: Progression from Atopic Dermatitis to Allergic Rhinitis and Asthma

Tao Zheng,[1]* Jinho Yu,[2] Min Hee Oh,[1] Zhou Zhu[1]

[1]Division of Allergy and Clinical Immunology, Johns Hopkins University School of Medicine, Baltimore, MD, USA
[2]Division of Pediatric Allergy and Pulmonology, Asan Medical Center, Ulsan University College of Medicine, Seoul, Korea

Atopic dermatitis (AD) is an inflammatory disease characterized by pruritic skin lesions. The pathogenesis of AD may include disrupted epidermal barrier function, immunodysregulation, and IgE-mediated sensitization to food and environmental allergens. AD is also part of a process called the atopic march, a progression from AD to allergic rhinitis and asthma. This has been supported by multiple cross-sectional and longitudinal studies and experimental data. Research on the mechanisms of AD has been centered on the adaptive immune system with an emphasis on the T-helper 1 (Th1)-Th2 paradigm. Recently, the conceptual focus has largely shifted to include a primary defect in the epithelial barrier as an initial event in AD providing a significant insight into the disease initiation and pointing to a complex secondary interplay of environmental and immunological sequelae with barrier disruption. Further understanding of AD will help the development of more effective treatment for AD and ultimately, preventative algorithms for the atopic march. In this review we highlight recent advances in our understanding of the pathogenesis of AD and the atopic march.

Key Words: Eczema; atopic dermatitis; allergic rhinitis; asthma; atopic march

INTRODUCTION

Atopic diseases, including atopic dermatitis (also known as eczema), allergic rhinitis and asthma, have increased in frequency in recent decades and now affect approximately 20% of the population in the developed countries. The concept of the atopic march was developed to describe the progression of atopic disorders from atopic dermatitis (AD) in infants to allergic rhinitis and asthma in children.[1] Patients with AD may develop a typical sequence of AD and allergic rhinitis and asthma, which develop at certain ages; some may persist for several years, whereas others may resolve with increasing age.[2] Atopy is defined as a personal and/or familial propensity to produce IgE antibodies and sensitization in response to environmental triggers.[3] Underlying atopy has been considered to be critical in linking AD, allergic rhinitis and asthma.[1,4] The risk of developing all atopic diseases is complex and the temporal pattern described in the atopic march may not be a simple progression and the development of these diseases is strongly influenced by both genetic and environmental factors. These disorders, while sharing genetic and environmental risk factors, can be unrelated disorders that may develop sequentially along an atopic pathway or there may be a causal link between eczema and these later-onset atopic respiratory disorders. However, the concept of the atopic march has been supported by cross-sectional and longitudinal studies,[5-14] and is confirmed when examining data on the prevalence of each atopic disease across the lifespan as well as by experimental evidence of mouse models.

THE FIRST STEP OF THE ATOPIC MARCH: ATOPIC DERMATITIS

Many studies have referred specifically to AD, and in this review the terms atopic dermatitis and eczema are considered interchangeable. AD is a common chronic pruritic skin disease seen in infants and children. In the International Study of Asthma and Allergies in Childhood (ISAAC), among the 56 countries, the prevalence of AD in children varied significantly from 0.3% to 20.5% but shows consistent trends in increasing disease prevalence over time.[15,16] In a population based study in the US, the prevalence of AD among children 5 to 9 years old is estimat-

Correspondence to: Tao Zheng, MD, Division of Allergy and Clinical Immunology, Johns Hopkins University School of Medicine, 5501 Bayview circle, 1A-38, Baltimore, MD 21224, USA.
Tel: +1-410-550-1990; Fax: +1-410-550-2527; E-mail: tzheng@jhmi.edu
Received: November 28, 2010; Accepted: December 9, 2010
• There are no financial or other issues that might lead to conflict of interest.

ed at 17.2%.[17] AD starts early in the first few years in life. Of the affected children, 45% of them had the condition during the first 6 months of life, 60% during the first year of life and up to 85% suffered AD before 5 years of age.[4,18] Less than half of the patients with AD have complete resolution by 7 years of age and only 60% of them have resolution by adulthood, indicating the chronic nature of AD.[1,4,19]

AD is a major risk factor for the development of asthma, with an increased odds ratio in children with AD in several longitudinal studies compared with children without AD. Patients with eczema with specific IgE antibodies to common environmental allergens (extrinsic AD), present by the age of 2 to 4 years, are at a higher risk for progressing in the atopic march to allergic rhinitis and asthma than those with eczema without IgE sensitization (intrinsic AD).[9,20] Thus, extrinsic AD appears to more precisely define the initial step and risk factor for the subsequent development of other atopic diseases. The main risk factors for progression and persistence of asthma are early onset, IgE sensitization, and severity of AD. Approximate 70% of patients with severe AD develop asthma compared with 20-30% of patients with mild AD and approximately 8% in the general population. Only children with the mildest AD did not develop either asthma or allergic rhinitis. Similarly the severity of AD correlated with the risk of developing rhinitis and with elevated levels of total and specific IgE antibodies.[8] Of note, an important aspect of the natural history of AD is the number and percentage of patients who will outgrow their disease.[5] The mechanisms of the "outgrow" of AD remain largely unknown and this could be influenced by both genetic and environmental factors.

THE END POINTS (PROGRESSION) OF THE ATOPIC MARCH: ALLERGIC RHINITIS AND ASTHMA

The atopic march is supported by many cross-sectional and longitudinal studies highlighting AD as a possible first step of this process. van der Hulst et al.[12] examined the risk of developing asthma in young children with extrinsic AD from 13 prospective cohort studies including 4 representing birth cohort studies and 9 representing eczema cohort studies. In the birth cohort studies, the odds ratio for the risk of asthma in subjects with AD, compared with children without AD was 2.14. The prevalence of asthma at the age of 6 years in AD cohort studies was about 30%. There was an increased risk of developing asthma after AD in early childhood and 1 in every 3 children with eczema developed asthma during later childhood. Kapoor et al.[13] examined the prevalence of allergic rhinitis and asthma in 2,270 children with physician-confirmed AD and found that by 3 years of age, nearly 66% of the subjects reported to have allergic rhinitis or asthma or both and the presence of these diseases correlates with poor AD control. The Tucson Children's Respiratory Study found that eczema during the first year of life is an independent risk factor for persistent wheezing and 18% of children with wheezing at 6 years of age had eczema before 2 years of age.[6,21] The cohort study followed the subjects who reached 22 years of age and fund that childhood asthma is strongly associated with eczema, whereas adult-onset asthma is not.[20] A prospective study examined development of allergies and asthma in infants with AD, follow-up to 7 years of age, showed that the eczema improved in 82 of the 94 children, but 43% developed asthma and 45% allergic rhinitis.[8] The risk of developing asthma was higher in children with eczema, and an early onset of eczema was associated with an increased risk of sensitization to inhalant allergens. The studies indicate that IgE sensitization to environmental allergens in patients with eczema is an important contributing factor to progression into an allergic phenotype of asthma. In a German Multicenter Atopy Study, 1,314 newborns were recruited and analyzed and in this group, 499 infants were at increased risk of atopic disease. Their results showed that disease severity and atopic sensitization are major determinants of increased risk of subsequent wheeze or bronchial hyperreactivity; in contrast, early AD without these cofactors constituted no increased risk of subsequent wheeze.[22] The Tasmanian Longitudinal Health Study investigated the influence of eczema on the development of asthma from childhood to adult life and found that childhood eczema was significantly associated with new-onset asthma in three separate life stages: pre-adolescence (hazard ratio 1.70; 95% confidence interval [CI] 1.05–2.75), adolescence (2.14; 1.33–3.46), and adult life (1.63; 1.28–2.09) as well as over the life-span from the ages of 8 to 44 years (1.73; 1.42–2.12).[23] This study strongly suggests that the atopic march progresses well past childhood. It is still unclear why some of the infants with AD outgrow the disease with increasing age, whereas others will "march" to develop other atopic conditions such as allergic rhinitis and/or asthma in later stages.

Epidemiologic studies have consistently demonstrated strong associations between rhinitis and asthma.[24-28] Recent clinical and basic science evidence indicated that the two diseases share anatomical, physiological, immunopathological, and therapeutical factors.[29] Allergic rhinitis is an inflammatory condition affecting nasal mucosal membranes. In sensitized individuals, allergens such as pollens, molds, and animal dander provoke this allergic response. Although allergic rhinitis is often trivialized, it has a significant impact on quality of life and substantial socioeconomic consequences, and it is associated with multiple comorbidities, including asthma. Cardinal features of asthma include airway inflammation and airway hyperreactivity to allergens associated with structural remodeling. Studies on the prevalence of asthma in patients with rhinitis varies considerably, but has been reported to be as high as 80%.[29] Many patients with allergic rhinitis have lower airway hyperreactivity or bronchial hyperresponsiveness. Allergic rhinitis as a risk factor for developing asthma has been supported by several studies.[4,30] Ciprandi et al.[30] showed that nasal symptoms, airflow

and markers of inflammation (eosinophils, Th2 cytokine levels) directly correlated with lower airway markers including forced expiratory volume in 1 second (FEV1). Leynaert et al.[24] found that approximate 75% of subjects with asthma reported rhinitis; patients with rhinitis have increased risk for asthma and lower airway reactivity compared with patients without rhinitis; and the risk for asthma increased from 2.0% in subjects without rhinitis to 18.8% in subjects with allergic rhinitis either when exposed to pollen or to animal dander. These studies suggested that allergic rhinitis is considered as a risk factor for asthma and can precede asthma in the atopic march.

ROLE OF FOOD ALLERGY IN THE ATOPIC MARCH

Over the past decade, a significant increase in the prevalence of food allergy-related anaphylaxis[31,32] indicates that there is a rise in food allergy. AD and food allergy commonly co-exist, particularly in those with early onset, severe and persistent atopic eczema. Food allergy is a known provoking cause of AD and the prevalence of IgE-mediated food allergy among children with AD is about 35% of affected children.[33] Whether children with IgE-mediated food allergy are at increased risk of developing subsequent other allergic manifestations (asthma and allergic rhinitis) is unclear. In a most recent study, investigators prospectively followed 118 children with cow's milk allergy (CMA) at baseline and assessed whether challenge-proven CMA in infancy predisposes children to bronchial hyperresponsiveness at school age. They found that children with a history of IgE-positive CMA diagnosed at a mean age of 7 months, not IgE-negative CMA, exhibited increased airway inflammation and higher bronchial responsiveness to histamine at 8 years of age.[34,35] It is unclear whether the progression from IgE-mediated food allergy to asthma in subjects without eczema is causal or a result of shared environment and/or shared genetics. Because eczema and food allergy can co-exist in infants, hence, also unclear whether the observed association is related to co-manifestation of other allergic conditions such as eczema and allergic rhinitis that predict asthma or is a consequence of CMA itself. It is important to have large population-based prospective cohorts to include food allergy as a baseline outcome to further investigate whether food allergy truly represents an initial step of the atopic march in infants with shared environmental and genetic determinants or whether it is an independent predictor.

ANIMAL MODELS SUPPORTING THE ATOPIC MARCH

Environmental and genetic studies provide evidence that a defect in epithelial barrier integrity may contribute to the onset of AD and progression of the atopic march. Many studies in animal models demonstrate that epidermal barrier dysfunction can be caused by repeated sensitization to allergens to the skin, which leads to phenotypes of AD and systemic sensitization and increased risk of allergic rhinitis and lung inflammation and airway hyperresponsiveness.[36,37] A study in a mouse model showed that epicutaneous aeroallergen exposure induces systemic Th2 immunity that predisposes to allergic nasal responses, suggesting that the skin is a potent site for antigen sensitization in the development of experimental allergic rhinitis.[38] In addition, the progression from AD to asthma in mice is supported by the data that epicutaneous sensitization with ovalbumin induces localized AD and airway hyperresponsiveness to methacholine after challenge with aerosolized ovalbumin.[36] In deed, murine models have shown that epicutaneous exposure to ovalbumin and peanut after the removal of the stratum corneum induces a strong systemic Th2 immune responses characterized by elevated IL-4 secretion by T cells from draining lymph nodes and high levels of allergen specific IgE and IgG1.[33,39] Thymic stromal lymphopoietin (TSLP) in the pathogenesis in human AD has been well documented, and TSLP is shown to be highly increased in human AD skin as well as in the blood of patients with AD.[40,41] However, its role in the atopic march in humans remains to be defined. We and other show that the expression of TSLP is strongly increased by keratinocytes of AD skin in IL-13 transgenic mouse of AD by IHC and ELISA[42] and that topical application of vitamin D3 induces TSLP expression in mouse keratinocytes and triggers AD.[43] TSLP, when overexpressed by skin keratinocytes, is a systemic driver of bronchial hyperresponsiveness and its deletion prevents the atopic march from occurring suggesting that keratinocyte-produced TSLP may be involved in the link of AD to asthma.[44] A possible role of IL-17 in the atopic march is supported by a recent study showing that ovalbumin inhalation by epicutaneously-sensitized mice induced expression of IL-17 and bronchial hyperreactivity, which are reversed by IL-17 blockade.[37]

POTENTIAL MECHANISMS AND SPECULATIONS UNDERLYING THE ATOPIC MARCH

Previous approaches to understanding AD have centered on mechanisms in the adaptive immune system, often with an emphasis on the Th1–Th2 paradigm. Recently, the conceptual focus has increasingly shifted to including a primary defect in the epithelial barrier as a threshold event in AD. The epidermis provides an essential attribute to the integrity of occlusive interface barrier, restricting both water loss from the body and ingress of pathogens. This barrier is formed after complex and integrated biochemical events. Epithelial keratinocytes replace their plasma membrane with a tough, insoluble layer termed the cornified envelope to achieve and maintain this barrier to prevent infectious agents and allergens from gaining access to the body. Although it has become evident that the mechanisms by which allergen exposure through the impaired skin barriers can initiate systemic allergy and predispose individuals to AD,

allergic rhinitis, and asthma, the cause of AD remains incompletely understood, and the mechanisms of the atopic march is largely unknown.

SKIN BARRIER DEFECTS IN AD AND THE ATOPIC MARCH

The epidermis functions as a primary defense and biosensor to the external environment. Skin barrier defect promotes easy entry for pathogens, and allergens and other environmental insults (toxins, irritants, pollutants) and is now considered as a primary mechanism of development of AD.[45] The skin barrier function is impaired in AD as a consequence of multiple abnormalities responsible for the barrier defect including reduced lipids (ceramide and sphingosine), abnormal keratinization due to dysfunctional filaggrin, a critical component in the cornified envelope formation.[22,46-50] Clinically the disrupted skin barrier is supported by the increased transepidermal water loss (TEWL) observed in both lesional and nonlesional skin.[45,51,52] Increased TEWL correlates with increased AD severity.[53] AD keratinocytes have an aberrant response to environmental triggers and are able to produce a unique profile of cytokines including IL-13, TSLP, and chemokines that promote Th2 predominant inflammatory responses in acute AD lesions followed by chronic AD characterized by prominent Th1 inflammation.[54] The mechanism of the switch from Th2 inflammation in acute AD to Th1 inflammation in chronic AD is not well understood. In addition, the impaired skin barrier can be further compromised by chronic heavy colonization of *Staphylococcus aureus*, which occurs in 90% of AD patients.[55] Superantigens secreted from *S. aureus* in AD skin further stimulate keratinocytes to produce TSLP and induces polyclonal activation of T cells via binding directly to the common variable β (vβ) chains of T-cell receptors,[56-58] which results in exaggerated Th2 inflammatory responses leading to worsening AD and may promote systemic Th2 responses and respiratory allergy. When allergens are captured and processed by the Langerhans cells, the antigen-presenting cells of the epidermis, they migrate to draining lymph nodes and interact with naïve T cells to promote Th2 immunity leading to systemic allergies.[46]

ROLE OF FILAGGRIN MUTATION IN AD AND IN THE ATOPIC MARCH

Many of the key structural proteins in the outermost layer of the epidermis involved in cornification are encoded for in a locus on chromosome 1q21, which is termed the epidermal differentiation complex (EDC).[59] Genes found within this locus encode for filaggrin, a key member of the EDC, in addition to other proteins such as loricrin, involucrin, small proline-rich proteins, late envelope proteins, and the S100 calcium-binding proteins. Discovery of both independent loss-of-function genetic variants (R510X and 2282del4) in the gene encoding filaggrin, whose product is a key structural protein in the outermost layer of the epidermis in up to 50% of patients with AD, provides a genetic basis for the skin barrier defect in AD.[60] These recent genetic studies lend strong support to the role of filaggrin in the pathogenesis of AD and in the subsequent progression in the atopic march.[61] The filaggrin mutations are currently considered as a major risk factor for AD, particularly in patients who have onset of AD at 2 years or younger.[62] A recent study showed a significant association of two filaggrin gene mutations with asthma and allergic rhinitis, but this association is only seen in subjects with the co-existence of AD and the association is not apparent without the co-existence of AD.[48] In addition, filaggrin has currently not been found to be expressed in the human bronchial epithelium[63,64]; hence, filaggrin mutations appear not to exert effects in the upper airway suggesting that the association of filaggrin mutations with other atopic disorders is likely due to the common feature of allergen sensitization through the skin. Moreover, the fact that asthma is found only in a subset of filaggrin mutation carriers with AD supports the hypotheses that asthma is secondary to allergic sensitization that occurs after epidermal skin barrier impairment. Filaggrin mutations seem likely to play a role in chronicity of the disease and IgE sensitization in patients with AD. Recent studies show that patients with early-onset AD and filaggrin mutations have a tendency to have persistent disease into adulthood.[65] AD patients carrying filaggrin mutations are significantly associated with the extrinsic form of the disease (IgE-mediated sensitization to inhalant or food allergens), and the development of allergic rhinitis and asthma.[61,66,67] The filaggrin mutations predisposing to asthma, allergic rhinitis, and allergic sensitization only in the presence of AD strongly support the role of filaggrin in the pathogenesis of AD and in the subsequent progression along the atopic march. Expression of filaggrin gene is down-regulated in AD skin by Th2 cytokines (IL-4 and IL-13)[68] and normal human keratinocytes by sphingosylphosphorylcholine, a proinflammatory and proprurigenic in AD[69,70] suggesting that filaggrin defects can develop as an acquired and/or genetic defect. Reduced expression of loricrin and involucrin, two cornified-envelope proteins, have been shown in the lesional skin of AD patients, which contributes to the skin barrier defects in AD[71,72] and their expression were also down-regulated by Th2 cytokines.[73]

Experimental evidence for the hypothesis that antigens enter through an impaired epidermal barrier inducing systemic allergen-specific IgE responses is supported in mouse with filaggrin frameshift mutation, analogous to human filaggrin mutation. Epicutaneous application of allergen to these mice resulted in cutaneous inflammatory infiltrates and enhanced cutaneous allergen priming with development of IgE antibody responses.[74] Although genetic studies on filaggrin mutation indicates that defective barrier function plays an initial key role in the pathogenesis of AD in many patients, much is still unknown

about the sequence of biologic and regulatory events that constitute the transition from an inherited barrier defect to clinical manifestations of eczematous dermatitis and susceptibility to related atopic disorders. The filaggrin gene mutation leads to an epithelial barrier defect and reduced mechanic defense mechanisms that allows easy entry for pathogens, allergens and other environmental insults (toxins, irritants, pollutants) followed by polarized Th2 lymphocyte responses with resultant chronic inflammation. However, approximately 40% of carriers of filaggrin gene mutations do not develop AD.[75] Patients with ichthyosis vulgaris, an inherited dry, scaly skin disorder who have filaggrin mutations[76] do not have apparent skin inflammation or infection, which are cardinal features of human AD. Therefore, additional factors may directly and or indirectly interact with filaggrin in the pathogenesis of AD.

CONCLUSION

Multiple lines of evidence (clinical, genetic and experimental studies) suggest that previous expression of AD is a prerequisite for the development of allergic rhinitis and asthma and specific sensitization highlighting the importance of the epidermal barrier in the pathogenesis of these disorders. Whether AD in the march is necessary for progression to other atopic disorders remains to be defined. To establish a causal relationship from AD to airway allergic diseases, evidence of immunological mechanisms accounting for the association and randomized controlled trials demonstrating an effective intervention for AD with reduced subsequent asthma incidence are necessitated. It also is important to identify infants at risk for developing lifelong chronic atopic diseases to provide a critical window of opportunity early in life for therapeutic intervention. Therapy targeting the maintenance and repair of the epidermal barrier in infants with AD may prevent the subsequent development of asthma.

ACKNOWLEDGMENTS

This work was supported by NIH grants R01AI075025 to Dr. T. Zheng and R01HL079349 to Dr. Z. Zhu. Dr. JH Yu was supported by a fellowship grant from Asan Medical Center.

REFERENCES

1. Spergel JM, Paller AS. Atopic dermatitis and the atopic march. J Allergy Clin Immunol 2003;112:S118-27.
2. Spergel JM. Epidemiology of atopic dermatitis and atopic march in children. Immunol Allergy Clin North Am 2010;30:269-80.
3. Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, Motala C, Ortega Martell JA, Platts-Mills TA, Ring J, Thien F, Van Cauwenberge P, Williams HC. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. J Allergy Clin Immunol 2004;113:832-6.
4. Spergel JM. Atopic march: link to upper airways. Curr Opin Allergy Clin Immunol 2005;5:17-21.
5. Ricci G, Patrizi A, Baldi E, Menna G, Tabanelli M, Masi M. Long-term follow-up of atopic dermatitis: retrospective analysis of related risk factors and association with concomitant allergic diseases. J Am Acad Dermatol 2006;55:765-71.
6. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. N Engl J Med 1995;332:133-8.
7. Kulig M, Bergmann R, Klettke U, Wahn V, Tacke U, Wahn U. Natural course of sensitization to food and inhalant allergens during the first 6 years of life. J Allergy Clin Immunol 1999;103:1173-9.
8. Gustafsson D, Sjöberg O, Foucard T. Development of allergies and asthma in infants and young children with atopic dermatitis--a prospective follow-up to 7 years of age. Allergy 2000;55:240-5.
9. Novembre E, Cianferoni A, Lombardi E, Bernardini R, Pucci N, Vierucci A. Natural history of "intrinsic" atopic dermatitis. Allergy 2001;56:452-3.
10. Ohshima Y, Yamada A, Hiraoka M, Katamura K, Ito S, Hirao T, Akutagawa H, Kondo N, Morikawa A, Mayumi M. Early sensitization to house dust mite is a major risk factor for subsequent development of bronchial asthma in Japanese infants with atopic dermatitis: results of a 4-year followup study. Ann Allergy Asthma Immunol 2002;89:265-70.
11. Wüthrich B, Schmid-Grendelmeier P. The atopic eczema/dermatitis syndrome. Epidemiology, natural course, and immunology of the IgE-associated ("extrinsic") and the nonallergic ("intrinsic") AEDS. J Investig Allergol Clin Immunol 2003;13:1-5.
12. van der Hulst AE, Klip H, Brand PL. Risk of developing asthma in young children with atopic eczema: a systematic review. J Allergy Clin Immunol 2007;120:565-9.
13. Kapoor R, Menon C, Hoffstad O, Bilker W, Leclerc P, Margolis DJ. The prevalence of atopic triad in children with physician-confirmed atopic dermatitis. J Am Acad Dermatol 2008;58:68-73.
14. Guilbert TW, Morgan WJ, Zeiger RS, Bacharier LB, Boehmer SJ, Krawiec M, Larsen G, Lemanske RF, Liu A, Mauger DT, Sorkness C, Szefler SJ, Strunk RC, Taussig LM, Martinez FD. Atopic characteristics of children with recurrent wheezing at high risk for the development of childhood asthma. J Allergy Clin Immunol 2004;114:1282-7.
15. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Lancet 1998;351:1225-32.
16. Asher MI, Montefort S, Björkstén B, Lai CK, Strachan DP, Weiland SK, Williams H. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. Lancet 2006;368:733-43.
17. Laughter D, Istvan JA, Tofte SJ, Hanifin JM. The prevalence of atopic dermatitis in Oregon schoolchildren. J Am Acad Dermatol 2000;43:649-55.
18. Kay J, Gawkrodger DJ, Mortimer MJ, Jaron AG. The prevalence of childhood atopic eczema in a general population. J Am Acad Dermatol 1994;30:35-9.
19. Spergel JM. From atopic dermatitis to asthma: the atopic march. Ann Allergy Asthma Immunol 2010;105:99-106; quiz 107-9, 117.
20. Wuthrich B, Schmid-Grendelmeier P. Natural course of AEDS. Allergy 2002;57:267-8.

21. 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.
22. Illi S, von Mutius E, Lau S, Nickel R, Gruber C, Niggemann B, Wahn U. The natural course of atopic dermatitis from birth to age 7 years and the association with asthma. J Allergy Clin Immunol 2004;113:925-31.
23. Burgess JA, Dharmage SC, Byrnes GB, Matheson MC, Gurrin LC, Wharton CL, Johns DP, Abramson MJ, Hopper JL, Walters EH. Childhood eczema and asthma incidence and persistence: a cohort study from childhood to middle age. J Allergy Clin Immunol 2008;122:280-5.
24. Leynaert B, Neukirch C, Kony S, Guénégou A, Bousquet J, Aubier M, Neukirch F. Association between asthma and rhinitis according to atopic sensitization in a population-based study. J Allergy Clin Immunol 2004;113:86-93.
25. Burgess JA, Walters EH, Byrnes GB, Matheson MC, Jenkins MA, Wharton CL, Johns DP, Abramson MJ, Hopper JL, Dharmage SC. Childhood allergic rhinitis predicts asthma incidence and persistence to middle age: a longitudinal study. J Allergy Clin Immunol 2007;120:863-9.
26. Shaaban R, Zureik M, Soussan D, Neukirch C, Heinrich J, Sunyer J, Wjst M, Cerveri I, Pin I, Bousquet J, Jarvis D, Burney PG, Neukirch F, Leynaert B. Rhinitis and onset of asthma: a longitudinal population-based study. Lancet 2008;372:1049-57.
27. Bugiani M, Carosso A, Migliore E, Piccioni P, Corsico A, Olivieri M, Ferrari M, Pirina P, de Marco R. Allergic rhinitis and asthma comorbidity in a survey of young adults in Italy. Allergy 2005;60:165-70.
28. Guerra S, Sherrill DL, Martinez FD, Barbee RA. Rhinitis as an independent risk factor for adult-onset asthma. J Allergy Clin Immunol 2002;109:419-25.
29. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, Zuberbier T, Baena-Cagnani CE, Canonica GW, van Weel C, Agache I, Aït-Khaled N, Bachert C, Blaiss MS, Bonini S, Boulet LP, Bousquet PJ, Camargos P, Carlsen KH, Chen Y, Custovic A, Dahl R, Demoly P, Douagui H, Durham SR, van Wijk RG, Kalayci O, Kaliner MA, Kim YY, Kowalski ML, Kuna P, Le LT, Lemiere C, Li J, Lockey RF, Mavale-Manuel S, Meltzer EO, Mohammad Y, Mullol J, Naclerio R, O'Hehir RE, Ohta K, Ouedraogo S, Palkonen S, Papadopoulos N, Passalacqua G, Pawankar R, Popov TA, Rabe KF, Rosado-Pinto J, Scadding GK, Simons FE, Toskala E, Valovirta E, van Cauwenberge P, Wang DY, Wickman M, Yawn BP, Yorgancioglu A, Yusuf OM, Zar H, Annesi-Maesano I, Bateman ED, Ben Kheder A, Boakye DA, Bouchard J, Burney P, Busse WW, Chan-Yeung M, Chavannes NH, Chuchalin A, Dolen WK, Emuzyte R, Grouse L, Humbert M, Jackson C, Johnston SL, Keith PK, Kemp JP, Klossek JM, Larenas-Linnemann D, Lipworth B, Malo JL, Marshall GD, Naspitz C, Nekam K, Niggemann B, Nizankowska-Mogilnicka E, Okamoto Y, Orru MP, Potter P, Price D, Stoloff SW, Vandenplas O, Viegi G, Williams D. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). Allergy 2008;63 Suppl 86:8-160.
30. Ciprandi G, Cirillo I, Vizzaccaro A, Milanese M, Tosca MA. Airway function and nasal inflammation in seasonal allergic rhinitis and asthma. Clin Exp Allergy 2004;34:891-6.
31. Liew WK, Williamson E, Tang ML. Anaphylaxis fatalities and admissions in Australia. J Allergy Clin Immunol 2009;123:434-42.
32. Poulos LM, Waters AM, Correll PK, Loblay RH, Marks GB. Trends in hospitalizations for anaphylaxis, angioedema, and urticaria in Australia, 1993-1994 to 2004-2005. J Allergy Clin Immunol 2007;120:878-84.
33. Eigenmann PA, Sicherer SH, Borkowski TA, Cohen BA, Sampson HA. Prevalence of IgE-mediated food allergy among children with atopic dermatitis. Pediatrics 1998;101:E8.
34. Malmberg LP, Saarinen KM, Pelkonen AS, Savilahti E, Mäkelä MJ. Cow's milk allergy as a predictor of bronchial hyperresponsiveness and airway inflammation at school age. Clin Exp Allergy 2010;40:1491-7.
35. Saarinen KM, Pelkonen AS, Mäkelä MJ, Savilahti E. Clinical course and prognosis of cow's milk allergy are dependent on milk-specific IgE status. J Allergy Clin Immunol 2005;116:869-75.
36. Spergel JM, Mizoguchi E, Brewer JP, Martin TR, Bhan AK, Geha RS. Epicutaneous sensitization with protein antigen induces localized allergic dermatitis and hyperresponsiveness to methacholine after single exposure to aerosolized antigen in mice. J Clin Invest 1998;101:1614-22.
37. He R, Kim HY, Yoon J, Oyoshi MK, MacGinnitie A, Goya S, Freyschmidt EJ, Bryce P, McKenzie AN, Umetsu DT, Oettgen HC, Geha RS. Exaggerated IL-17 response to epicutaneous sensitization mediates airway inflammation in the absence of IL-4 and IL-13. J Allergy Clin Immunol 2009;124:761-70.e1.
38. Akei HS, Brandt EB, Mishra A, Strait RT, Finkelman FD, Warrier MR, Hershey GK, Blanchard C, Rothenberg ME. Epicutaneous aeroallergen exposure induces systemic TH2 immunity that predisposes to allergic nasal responses. J Allergy Clin Immunol 2006;118:62-9.
39. Strid J, Hourihane J, Kimber I, Callard R, Strobel S. Disruption of the stratum corneum allows potent epicutaneous immunization with protein antigens resulting in a dominant systemic Th2 response. Eur J Immunol 2004;34:2100-9.
40. Liu YJ. Thymic stromal lymphopoietin: master switch for allergic inflammation. J Exp Med 2006;203:269-73.
41. Lee EB, Kim KW, Hong JY, Jee HM, Sohn MH, Kim KE. Increased serum thymic stromal lymphopoietin in children with atopic dermatitis. Pediatr Allergy Immunol 2010;21:e457-60.
42. Zheng T, Oh MH, Oh SY, Schroeder JT, Glick AB, Zhu Z. Transgenic expression of interleukin-13 in the skin induces a pruritic dermatitis and skin remodeling. J Invest Dermatol 2009;129:742-51.
43. Li M, Hener P, Zhang Z, Kato S, Metzger D, Chambon P. Topical vitamin D3 and low-calcemic analogs induce thymic stromal lymphopoietin in mouse keratinocytes and trigger an atopic dermatitis. Proc Natl Acad Sci U S A 2006;103:11736-41.
44. Demehri S, Morimoto M, Holtzman MJ, Kopan R. Skin-derived TSLP triggers progression from epidermal-barrier defects to asthma. PLoS Biol 2009;7:e1000067.
45. Cork MJ, Robinson DA, Vasilopoulos Y, Ferguson A, Moustafa M, MacGowan A, Duff GW, Ward SJ, Tazi-Ahnini R. New perspectives on epidermal barrier dysfunction in atopic dermatitis: gene-environment interactions. J Allergy Clin Immunol 2006;118:3-21; quiz 22-3.
46. McGrath JA, Uitto J. The filaggrin story: novel insights into skin-barrier function and disease. Trends Mol Med 2008;14:20-7.
47. Kissling S, Wuthrich B. Follow-up of atopic dermatitis after early childhood. Hautarzt 1993;44:569-73.
48. Palmer CN, Irvine AD, Terron-Kwiatkowski A, Zhao Y, Liao H, Lee SP, Goudie DR, Sandilands A, Campbell LE, Smith FJ, O'Regan GM, Watson RM, Cecil JE, Bale SJ, Compton JG, DiGiovanna JJ, Fleck-

man P, Lewis-Jones S, Arseculeratne G, Sergeant A, Munro CS, El Houate B, McElreavey K, Halkjaer LB, Bisgaard H, Mukhopadhyay S, McLean WH. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. Nat Genet 2006;38:441-6.
49. Arikawa J, Ishibashi M, Kawashima M, Takagi Y, Ichikawa Y, Imokawa G. Decreased levels of sphingosine, a natural antimicrobial agent, may be associated with vulnerability of the stratum corneum from patients with atopic dermatitis to colonization by *Staphylococcus aureus*. J Invest Dermatol 2002;119:433-9.
50. Werner Y, Lindberg M. Transepidermal water loss in dry and clinically normal skin in patients with atopic dermatitis. Acta Derm Venereol 1985;65:102-5.
51. Grice K, Sattar H, Baker H, Sharratt M. The relationship of transepidermal water loss to skin temperature in psoriasis and eczema. J Invest Dermatol 1975;64:313-5.
52. Seidenari S, Giusti G. Objective assessment of the skin of children affected by atopic dermatitis: a study of pH, capacitance and TEWL in eczematous and clinically uninvolved skin. Acta Derm Venereol 1995;75:429-33.
53. Gupta J, Grube E, Ericksen MB, Stevenson MD, Lucky AW, Sheth AP, Assa'ad AH, Khurana Hershey GK. Intrinsically defective skin barrier function in children with atopic dermatitis correlates with disease severity. J Allergy Clin Immunol 2008;121:725-30.e2.
54. Leung DY, Boguniewicz M, Howell MD, Nomura I, Hamid QA. New insights into atopic dermatitis. J Clin Invest 2004;113:651-7.
55. Leyden JJ, Marples RR, Kligman AM. *Staphylococcus aureus* in the lesions of atopic dermatitis. Br J Dermatol 1974;90:525-30.
56. Nomura I, Tanaka K, Tomita H, Katsunuma T, Ohya Y, Ikeda N, Takeda T, Saito H, Akasawa A. Evaluation of the staphylococcal exotoxins and their specific IgE in childhood atopic dermatitis. J Allergy Clin Immunol 1999;104:441-6.
57. Allakhverdi Z, Comeau MR, Jessup HK, Yoon BR, Brewer A, Chartier S, Paquette N, Ziegler SF, Sarfati M, Delespesse G. Thymic stromal lymphopoietin is released by human epithelial cells in response to microbes, trauma, or inflammation and potently activates mast cells. J Exp Med 2007;204:253-8.
58. Bunikowski R, Mielke ME, Skarabis H, Worm M, Anagnostopoulos I, Kolde G, Wahn U, Renz H. Evidence for a disease-promoting effect of *Staphylococcus aureus*-derived exotoxins in atopic dermatitis. J Allergy Clin Immunol 2000;105:814-9.
59. Mischke D, Korge BP, Marenholz I, Volz A, Ziegler A. Genes encoding structural proteins of epidermal cornification and S100 calcium-binding proteins form a gene complex ("epidermal differentiation complex") on human chromosome 1q21. J Invest Dermatol 1996;106:989-92.
60. O'Regan GM, Sandilands A, McLean WH, Irvine AD. Filaggrin in atopic dermatitis. J Allergy Clin Immunol 2009;124:R2-6.
61. Marenholz I, Nickel R, Rüschendorf F, Schulz F, Esparza-Gordillo J, Kerscher T, Grüber C, Lau S, Worm M, Keil T, Kurek M, Zaluga E, Wahn U, Lee YA. Filaggrin loss-of-function mutations predispose to phenotypes involved in the atopic march. J Allergy Clin Immunol 2006;118:866-71.
62. Stemmler S, Parwez Q, Petrasch-Parwez E, Epplen JT, Hoffjan S. Two common loss-of-function mutations within the filaggrin gene predispose for early onset of atopic dermatitis. J Invest Dermatol 2007;127:722-4.
63. Ying S, Meng Q, Corrigan CJ, Lee TH. Lack of filaggrin expression in the human bronchial mucosa. J Allergy Clin Immunol 2006;118:1386-8.
64. Morar N, Cookson WO, Harper JI, Moffatt MF. Filaggrin mutations in children with severe atopic dermatitis. J Invest Dermatol 2007;127:1667-72.
65. Barker JN, Palmer CN, Zhao Y, Liao H, Hull PR, Lee SP, Allen MH, Meggitt SJ, Reynolds NJ, Trembath RC, McLean WH. Null mutations in the filaggrin gene (FLG) determine major susceptibility to early-onset atopic dermatitis that persists into adulthood. J Invest Dermatol 2007;127:564-7.
66. Weidinger S, Rodríguez E, Stahl C, Wagenpfeil S, Klopp N, Illig T, Novak N. Filaggrin mutations strongly predispose to early-onset and extrinsic atopic dermatitis. J Invest Dermatol 2007;127:724-6.
67. Weidinger S, Illig T, Baurecht H, Irvine AD, Rodriguez E, Diaz-Lacava A, Klopp N, Wagenpfeil S, Zhao Y, Liao H, Lee SP, Palmer CN, Jenneck C, Maintz L, Hagemann T, Behrendt H, Ring J, Nothen MM, McLean WH, Novak N. Loss-of-function variations within the filaggrin gene predispose for atopic dermatitis with allergic sensitizations. J Allergy Clin Immunol 2006;118:214-9.
68. Howell MD, Kim BE, Gao P, Grant AV, Boguniewicz M, Debenedetto A, Schneider L, Beck LA, Barnes KC, Leung DY. Cytokine modulation of atopic dermatitis filaggrin skin expression. J Allergy Clin Immunol 2007;120:150-5.
69. Choi H, Kim S, Kim HJ, Kim KM, Lee CH, Shin JH, Noh M. Sphingosylphosphorylcholine down-regulates filaggrin gene transcription through NOX5-based NADPH oxidase and cyclooxygenase-2 in human keratinocytes. Biochem Pharmacol 2010;80:95-103.
70. Andoh T, Saito A, Kuraishi Y. Leukotriene B(4) mediates sphingosylphosphorylcholine-induced itch-associated responses in mouse skin. J Invest Dermatol 2009;129:2854-60.
71. De Benedetto A, Agnihothri R, McGirt LY, Bankova LG, Beck LA. Atopic dermatitis: a disease caused by innate immune defects? J Invest Dermatol 2009;129:14-30.
72. Sugiura H, Ebise H, Tazawa T, Tanaka K, Sugiura Y, Uehara M, Kikuchi K, Kimura T. Large-scale DNA microarray analysis of atopic skin lesions shows overexpression of an epidermal differentiation gene cluster in the alternative pathway and lack of protective gene expression in the cornified envelope. Br J Dermatol 2005;152:146-9.
73. Kim BE, Leung DY, Boguniewicz M, Howell MD. Loricrin and involucrin expression is down-regulated by Th2 cytokines through STAT-6. Clin Immunol 2008;126:332-7.
74. Fallon PG, Sasaki T, Sandilands A, Campbell LE, Saunders SP, Mangan NE, Callanan JJ, Kawasaki H, Shiohama A, Kubo A, Sundberg JP, Presland RB, Fleckman P, Shimizu N, Kudoh J, Irvine AD, Amagai M, McLean WH. A homozygous frameshift mutation in the mouse Flg gene facilitates enhanced percutaneous allergen priming. Nat Genet 2009;41:602-8.
75. Henderson J, Northstone K, Lee SP, Liao H, Zhao Y, Pembrey M, Mukhopadhyay S, Smith GD, Palmer CN, McLean WH, Irvine AD. The burden of disease associated with filaggrin mutations: a population-based, longitudinal birth cohort study. J Allergy Clin Immunol 2008;121:872-7.e9.
76. Smith FJ, Irvine AD, Terron-Kwiatkowski A, Sandilands A, Campbell LE, Zhao Y, Liao H, Evans AT, Goudie DR, Lewis-Jones S, Arseculeratne G, Munro CS, Sergeant A, O'Regan G, Bale SJ, Compton JG, DiGiovanna JJ, Presland RB, Fleckman P, McLean WH. Loss-of-function mutations in the gene encoding filaggrin cause ichthyosis vulgaris. Nat Genet 2006;38:337-42.