Chapter 2
Atopic Dermatitis: Disease Background and Risk Factors

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Abstract Multiple risk factors have been associated with the development of atopic dermatitis (AD). Recent advances in understanding the role of genetics in this disease have been made, with discovery of the filaggrin (FLG) gene as the most notable so far. In addition to FLG gene mutations as a risk factor for AD, a positive family history of atopic or allergic disease in either parent, has been shown to confer a greater risk of developing AD. Atopic dermatitis usually presents early in life and is thought to represent the initial-step in the *"atopic march"* which is characterized by the development of other atopic diseases later in life such as asthma, allergic rhinitis and/or rhinoconjunctivitis, food allergies and hay fever. Other comorbid diseases that have been associated with AD include increase risk of viral and bacterial skin infections, neuropsychiatric diseases such as attention-deficit hyperactivity disorders (ADHD) and autistic spectrum disorder (ASD). Patients with AD, have also been found to have worse sleep quality overall compared to patients without AD. In this chapter, we will discuss the risk factors associated with development of atopic dermatitis as well as the most commonly reported comorbidities in patients with this disease.

Keywords Atopic dermatitis • Disease background • Risk factors • Comorbidities

2.1 Genetics of Atopic Dermatitis

Recent advances in understanding the role of genetics in atopic dermatitis have been made, with discovery of the filaggrin (FLG) gene as the most notable so far [1, 2]. Identification of the FLG gene, which codes for filaggrin, an important structural component of the epidermis, as the cause of ichthyosis vulgaris resulted in a significant breakthrough in increasing our understanding of the pathogenesis of atopic

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dermatitis (AD) [3]. Filaggrin is an integral part of the Epidermal Differentiation Complex (EDC), a group of proteins responsible for maintaining skin barrier function [4]. The EDC is located on chromosome 1 and consists of a series of genes which code for: (1) proteins of the cornified envelope (i.e., *loricrin, involucrin and 'late, cornified envelope proteins'*); (2) calcium-binding proteins (*S100 proteins*); and (3) 'fused gene proteins' (i.e., *filaggrin, filaggrin-2, trichohyalin, trichohyalin-like protein, hornerin, repetin, and cornulin*) [4].

Mutations in the FLG gene have been associated with skin barrier impairment and the *"outside-in-hypothesis"* [5]. In this hypothesis, a defect in the epidermal barrier results in increased transepidermal water loss, or TEWL, which explains the associated dryness or xerosis seen in patients with AD, as well as allows greater penetration of allergens, irritants, and skin colonizing organisms that can result in infection [5–7]. Defects in skin barrier function can also result in an increased Th-2 inflammatory response with increased production of pro-inflammatory cytokines such as IL-4 and IL-13 thus perpetuating the inflammatory cycle seen in AD [6].

The FLG gene codes for profilaggrin the main component of keratohyalin granules. The profilaggrin molecule is composed of an N-terminal domain, followed by multiple filaggrin repeats with keratin-binding properties, and a C-terminal domain [3]. As keratinocytes differentiate in the epidermis, profilaggrin is cleaved into filaggrin proteins, which then aggregate in the keratin cytoskeleton to form a dense protein-lipid matrix and results in a fully differentiated epidermal barrier [8]. Filaggrin is then further degraded into a group of proteins or amino acids known as natural moisturizing factors, which have an important role in maintaining skin hydration and barrier function [8]. The main breakdown products of filaggrin are *trans*-urocanic acid and pyrrolidone-5-carboxylic acid. These organic compounds are responsible for maintaining a physiologic, acidic pH and have also been shown to have an inhibitory effect on the growth of *Staphylococcus aureus* on the skin [3, 9]. Conversion of *trans*-urocanic acid to *cis*-urocanic acid, a molecule with an action spectrum of 280–310 nm, has been suggested to have a possible photoprotective role [10, 11].

Loss-of function (LOF) mutations in the FLG gene are considered the strongest known genetic risk factor for AD and the presence of 2 homozygous mutations has been associated with more persistent disease [12, 13]. The FLG gene mutations most strongly associated with an increased risk for AD include R501x and 2282del4, both located on exon 3, with one study showing a higher risk for R501x compared to 2282del4 [14]. The prevalence of FLG gene mutations varies widely. It is estimated that approximately 20–50% of patients with AD and 8–10% of the normal population carry a FLG mutation [15, 16]. Filaggrin mutations have been more frequently described in Caucasian populations particularly those of Eastern Europe as well as various Asian populations [3]. However, although R501x and 2282del4 are frequently identified in populations of European descent, these have not been consistently observed in Asian and African populations [17–19]. While other LOF mutations in the FLG gene have been identified in Asian populations [20], these have not been observed in those of African ancestry. On the contrary, mutations in filaggrin-2 (FLG2), which is has been shown to have a similar skin barrier function as FLG, have been found to be more prevalent in AD patients of African ancestry and have also been associated with more persistent disease in this population [21, 22].

While specific mutations in the FLG gene have been well established as a risk factor for a subset of patients with AD, it has also been shown that down-regulation of filaggrin gene expression can be induced by active inflammation independent of the presence or absence of FLG gene mutations [3, 23, 24].

2.2 Familial and Environmental Risk Factors in Atopic Dermatitis

In addition to FLG gene mutations as a risk factor for atopic dermatitis, a positive family history of atopic or allergic disease in either parent has been shown to be a strong risk factor for the development of AD. It is estimated that approximately 70% of patients with AD have a positive family history for AD [25]. Children of one or two affected parents with AD are thought to have a two to threefold, or three to sixfold increased odds of developing atopic dermatitis, respectively [25–28]. Children whose mothers had atopic dermatitis are also thought to be at an increased risk for developing AD [27, 28]. One study showed having a mother with a FLG-mutation was associated with a 1.5-fold increased risk of developing AD independent from the patient's carrier status [29].

Populations at higher risk for developing AD include those with a strong family history of atopic diseases as well as the presence of FLG gene mutations in certain populations, particularly caucasians of Eastern European descent and Asian populations. There is increasing evidence to suggest that the prevalence of AD may be higher in populations who identify as black or of African ancestry compared to Caucasians [30–32]. Other factors including daycare exposure [33], level of parental education [34], socioeconomic status [35], place of residence (i.e., rural vs. urban setting) [36], smoking [37, 38], type of delivery during childbirth (i.e., vaginal vs. cesarean section) [25, 39], weight at birth [40], breast-feeding [28, 41], being overweight [42], exposure to hard water [43], pets [44–47] and/or dust mites [48], may influence the risk of developing AD, but the data is varied and inconclusive. Because the microbiota of patients with and without AD are known to be different, it has been suggested that exposure to antibiotics early in life leads to alteration in colonizing organisms, resulting in an increased risk of developing AD. Current data is insufficient to determine if early exposure to antibiotics is associated with an increased risk of developing AD [41].

2.3 The Role of Diet Atopic Dermatitis Development

The relationship between dietary intake and risk for developing atopic dermatitis is not fully understood. It is unclear if maternal dietary restriction, breastfeeding or timing of food introduction affects the risk of developing AD [25]. A systematic review of sixty studies confirmed the association between AD, food sensitization

and food allergies (FA), with increased AD severity and duration of AD being more strongly associated with FA [49]. This study also found that the onset of AD usually preceded that of FA, thus suggesting a positive causal relationship [49]. Another study found evidence that dysfunction in the skin barrier as measured by increased TEWL during the neonatal period was a positive predictor for the development of FA at 2 years of age, thus supporting the role of transcutaneous sensitization in AD [50]. Care must be taken when considering strict elimination diets in these patients as there is evidence to support that avoidance may increase the likelihood of developing new, immediate, food reactions in the future [51].

2.4 Atopic Dermatitis: Comorbidities

Atopic dermatitis usually presents early in life and is thought to represent the initial-step in the *"atopic march"* which is characterized by the development of other atopic diseases later in life [52, 53]. Skin barrier defects in AD lead to the introduction of foreign antigens through the epidermis resulting in activation of the innate immune system and promotion of a Th2 inflammatory response which can lead to the development of other atopic diseases [52].

In patients with AD, the most commonly reported comorbidities include other *atopic diseases* such as asthma, allergic rhinitis and/or rhinoconjunctivitis, food allergies and hay fever [54]. The prevalence of these diseases varies by age [55]. In the case of asthma, a systematic review found the prevalence of asthma in AD varied between 20–45% [55, 56]. The prevalence of allergic rhinitis and food allergies varies between 33–45% and 13–47%, respectively. [57, 58] The occurrence of asthma, food allergies and allergic rhinitis in patients with AD can persist for several years, and in some cases resolve with increasing age [59]. The estimated prevalence of hay fever in patients with AD is approximately 30–47% [56]. Other atopic diseases that have been reported include contact dermatitis and hand dermatitis [60, 61].

Patients with AD are at an increased risk for infections, in particular skin infections with *Staphylococcus aureus*, eczema herpeticum, eczema vaccinatum, and eczema cocksackium [62]. It is estimated that *S. aureus* is present in nearly 90% of AD lesions and that MRSA colonization occurs in approximately 12% of patients with AD [62, 63]. *Streptococcus pyogenes* is also frequently identified in patients with AD [64]. Eczema herpeticum occurs as a result of herpes virus infection and is more frequently seen in patients with more severe atopic disease [65]. Eczema cocksackium is considered a newer recognized complication of AD and is oftentimes confused with eczema herpeticum [54, 66]. Eczema vaccinatum is a potentially life-threatening infection in AD which occurs as a result of vaccination with the smallpox vaccine in susceptible patients [62]. Warts and infection with molluscum contagiosum have also been reported as more prevalent in children with AD compared to children without atopic disease [67]. Other infectious diseases associated with AD include sinus infections, recurrent ear infections, strep throat, influenza, pneumonia, varicella zoster and urinary tract infections [67].

Higher rates of neuropsychiatric diseases have been reported in patients with AD including attention-deficit hyperactivity disorders (ADHD) and autistic spectrum disorder (ASD), depression, anxiety and somatization disorder [68–71]. A large population-based, longitudinal study found that children with early-onset AD had a greater risk of developing ADHD and ASD compared to children without AD. The risk was fourfold higher in those patients who also had other allergic diseases including asthma and allergic rhinitis [68].

Atopic dermatitis has also been demonstrated to have a negative impact on sleep, including decreased sleep duration and worse quality of sleep [72–74]. AD does not only impact sleep in patients but has also been shown to have a negative impact in patient's caregivers. Caregivers of patients with AD often report poorer quality of sleep, increased symptoms of insomnia and chronic sleep deprivation [75]. The mechanism of sleep disturbance in patients with AD is unclear and it is though that pruritus alone is not the sole cause [76]. Alterations in the circadian rhythm, immune dysregulation and increased TEWL are also thought to play a role [76].

Other diseases that have been reported to be more prevalent in adult patients with AD include cardiovascular disease (CVD). A study in the US adult population showed that patients with AD had higher odds of CVD, including coronary artery disease, myocardial infarction, and peripheral vascular disease [77]. Other studies have found marginal or no association between AD and CVD after adjustment for risk factors [78–80]. It is unclear if the association between AD and CVD is due to the chronic inflammatory state seen in patients with AD or if it is due to the presence of poor health behaviors (e.g., smoking, obesity) that are more prevalent in this population [38, 81].

The relationship between AD and cancer is complex [82] and remains to be clearly defined. Prior studies have shown inconsistent results and are difficult to interpret due to dissimilarities in study design, small sample sizes, and varying case definitions for AD [82–84]. Most studies failed to examine the impact of AD severity on cancer risk and did not control for confounding factors such as smoking. The risk of acute lymphoblastic leukemia, meningioma, and glioma have been shown to be lower in pediatric patients with a history of atopy [83]. [85] Legendre et al. [86] showed a slightly increased risk of lymphoma, particularly cutaneous T-cell lymphoma (CTCL), compared to an inverse or null association with solid-organ malignancies. Other studies show increased risk of non-melanoma skin cancer, however results are not consistent [83, 85, 87]. It is unclear if the increased risk for cancer seen in some studies is due to disease misclassification, persistent systemic inflammation, and/or exposure to multiple immune suppressive medications.

References

1. Palmer CN, Irvine AD, Terron-Kwiatkowski A, et al. 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.
2. Fallon PG, Sasaki T, Sandilands A, et al. A homozygous frameshift mutation in the mouse Flg gene facilitates enhanced percutaneous allergen priming. Nat Genet. 2009;41:602–8.

3. Brown SJ, McLean WH. One remarkable molecule: filaggrin. J Invest Dermatol. 2012;132:751–62.
4. Kypriotou M, Huber M, Hohl D. The human epidermal differentiation complex: cornified envelope precursors, S100 proteins and the 'fused genes' family. Exp Dermatol. 2012;21:643–9.
5. Wang D, Beck LA. Immunologic targets in atopic dermatitis and emerging therapies: an update. Am J Clin Dermatol. 2016;17:425–43.
6. Elias PM, Steinhoff M. "outside-to-inside" (and now back to "outside") pathogenic mechanisms in atopic dermatitis. J Invest Dermatol. 2008;128:1067–70.
7. Proksch E, Folster-Holst R, Jensen JM. Skin barrier function, epidermal proliferation and differentiation in eczema. J Dermatol Sci. 2006;43:159–69.
8. McLean WH. Filaggrin failure—from ichthyosis vulgaris to atopic eczema and beyond. Br J Dermatol. 2016;175(Suppl 2):4–7.
9. Miajlovic H, Fallon PG, Irvine AD, Foster TJ. Effect of filaggrin breakdown products on growth of and protein expression by Staphylococcus aureus. J Allergy Clin Immunol. 2010;126:1184–1190.e3.
10. McLoone P, Simics E, Barton A, Norval M, Gibbs NK. An action spectrum for the production of cis-urocanic acid in human skin in vivo. J Invest Dermatol. 2005;124:1071–4.
11. Barresi C, Stremnitzer C, Mlitz V, et al. Increased sensitivity of histidinemic mice to UVB radiation suggests a crucial role of endogenous urocanic acid in photoprotection. J Invest Dermatol. 2011;131:188–94.
12. Irvine AD, McLean WH. Breaking the (un)sound barrier: filaggrin is a major gene for atopic dermatitis. J Invest Dermatol. 2006;126:1200–2.
13. Margolis DJ, Apter AJ, Gupta J, et al. The persistence of atopic dermatitis and filaggrin (FLG) mutations in a US longitudinal cohort. J Allergy Clin Immunol. 2012;130:912–7.
14. Rodriguez E, Baurecht H, Herberich E, et al. Meta-analysis of filaggrin polymorphisms in eczema and asthma: robust risk factors in atopic disease. J Allergy Clin Immunol. 2009;123:1361–1370.e7.
15. Visser MJ, Landeck L, Campbell LE, et al. Impact of atopic dermatitis and loss-of-function mutations in the filaggrin gene on the development of occupational irritant contact dermatitis. Br J Dermatol. 2013;168:326–32.
16. O'Regan GM, Irvine AD. The role of filaggrin in the atopic diathesis. Clin Exp Allergy. 2010;40:965–72.
17. Winge MC, Bilcha KD, Lieden A, et al. Novel filaggrin mutation but no other loss-of-function variants found in Ethiopian patients with atopic dermatitis. Br J Dermatol. 2011;165:1074–80.
18. Margolis DJ, Gupta J, Apter AJ, et al. Exome sequencing of filaggrin and related genes in African-American children with atopic dermatitis. J Invest Dermatol. 2014;134:2272–4.
19. Sun LD, Xiao FL, Li Y, et al. Genome-wide association study identifies two new susceptibility loci for atopic dermatitis in the Chinese Han population. Nat Genet. 2011;43:690–4.
20. Hsu CK, Akiyama M, Nemoto-Hasebe I, et al. Analysis of Taiwanese ichthyosis vulgaris families further demonstrates differences in FLG mutations between European and Asian populations. Br J Dermatol. 2009;161:448–51.
21. Makino T, Mizawa M, Yamakoshi T, Takaishi M, Shimizu T. Expression of filaggrin-2 protein in the epidermis of human skin diseases: a comparative analysis with filaggrin. Biochem Biophys Res Commun. 2014;449:100–6.
22. Margolis DJ, Gupta J, Apter AJ, et al. Filaggrin-2 variation is associated with more persistent atopic dermatitis in African American subjects. J Allergy Clin Immunol. 2014;133:784–9.
23. Pellerin L, Henry J, Hsu CY, et al. Defects of filaggrin-like proteins in both lesional and nonlesional atopic skin. J Allergy Clin Immunol. 2013;131:1094–102.
24. Thawer-Esmail F, Jakasa I, Todd G, et al. South African amaXhosa patients with atopic dermatitis have decreased levels of filaggrin breakdown products but no loss-of-function mutations in filaggrin. J Allergy Clin Immunol. 2014;133:280–282.e2.
25. Eichenfield LF, Tom WL, Chamlin SL, et al. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. J Am Acad Dermatol. 2014;70:338–51.

26. Schmitz R, Atzpodien K, Schlaud M. Prevalence and risk factors of atopic diseases in German children and adolescents. Pediatr Allergy Immunol. 2012;23:716–23.
27. Lee YL, Li CW, Sung FC, Yu HS, Sheu HM, Guo YL. Environmental factors, parental atopy and atopic eczema in primary-school children: a cross-sectional study in Taiwan. Br J Dermatol. 2007;157:1217–24.
28. Purvis DJ, Thompson JM, Clark PM, et al. Risk factors for atopic dermatitis in New Zealand children at 3.5 years of age. Br J Dermatol. 2005;152:742–9.
29. Esparza-Gordillo J, Matanovic A, Marenholz I, et al. Maternal filaggrin mutations increase the risk of atopic dermatitis in children: an effect independent of mutation inheritance. PLoS Genet. 2015;11:e1005076.
30. Shaw TE, Currie GP, Koudelka CW, Simpson EL. Eczema prevalence in the United States: data from the 2003 National Survey of Children's health. J Invest Dermatol. 2011;131:67–73.
31. Williams HC, Pembroke AC, Forsdyke H, Boodoo G, Hay RJ, Burney PG. London-born black Caribbean children are at increased risk of atopic dermatitis. J Am Acad Dermatol. 1995;32:212–7.
32. Wegienka G, Havstad S, Joseph CL, et al. Racial disparities in allergic outcomes in African Americans emerge as early as age 2 years. Clin Exp Allergy. 2012;42:909–17.
33. de Meer G, Janssen NA, Brunekreef B. Early childhood environment related to microbial exposure and the occurrence of atopic disease at school age. Allergy. 2005;60:619–25.
34. Wen HJ, Chen PC, Chiang TL, Lin SJ, Chuang YL, Guo YL. Predicting risk for early infantile atopic dermatitis by hereditary and environmental factors. Br J Dermatol. 2009;161:1166–72.
35. Uphoff E, Cabieses B, Pinart M, Valdes M, Anto JM, Wright J. A systematic review of socioeconomic position in relation to asthma and allergic diseases. Eur Respir J. 2015;46:364–74.
36. Xu F, Yan S, Zheng Q, et al. Residential risk factors for atopic dermatitis in 3- to 6-year old children: a cross-sectional study in shanghai, China. Int J Environ Res Public Health. 2016;13(6):537.
37. Bohme M, Kull I, Bergstrom A, et al. Parental smoking increases the risk for eczema with sensitization in 4-year-old children. J Allergy Clin Immunol. 2010;125:941–3.
38. Kantor R, Kim A, Thyssen JP, Silverberg JI. Association of atopic dermatitis with smoking: a systematic review and meta-analysis. J Am Acad Dermatol. 2016;75:1119–1125.e1.
39. Papathoma E, Triga M, Fouzas S, Dimitriou G. Cesarean section delivery and development of food allergy and atopic dermatitis in early childhood. Pediatr Allergy Immunol. 2016;27:419–24.
40. Panduru M, Salavastru CM, Panduru NM, Tiplica GS. Birth weight and atopic dermatitis: systematic review and meta-analyis. Acta Dermatovenerol Croat. 2014;22:91–6.
41. Taylor-Robinson DC, Williams H, Pearce A, Law C, Hope S. Do early-life exposures explain why more advantaged children get eczema? Findings from the U.K. millennium cohort study. Br J Dermatol. 2016;174:569–78.
42. Sybilski AJ, Raciborski F, Lipiec A, et al. Obesity—a risk factor for asthma, but not for atopic dermatitis, allergic rhinitis and sensitization. Public Health Nutr. 2015;18:530–6.
43. Perkin MR, Craven J, Logan K, et al. Association between domestic water hardness, chlorine, and atopic dermatitis risk in early life: a population-based cross-sectional study. J Allergy Clin Immunol. 2016;138:509–16.
44. Pelucchi C, Galeone C, Bach JF, La Vecchia C, Chatenoud L. Pet exposure and risk of atopic dermatitis at the pediatric age: a meta-analysis of birth cohort studies. J Allergy Clin Immunol. 2013;132:616–622.e7.
45. Zirngibl A, Franke K, Gehring U, et al. Exposure to pets and atopic dermatitis during the first two years of life. A cohort study. Pediatr Allergy Immunol. 2002;13:394–401.
46. Epstein TG, Bernstein DI, Levin L, et al. Opposing effects of cat and dog ownership and allergic sensitization on eczema in an atopic birth cohort. J Pediatr. 2011;158:265–271.e5.
47. Schuttelaar ML, Kerkhof M, Jonkman MF, et al. Filaggrin mutations in the onset of eczema, sensitization, asthma, hay fever and the interaction with cat exposure. Allergy. 2009;64:1758–65.
48. Ricci G, Patrizi A, Bellini F, Medri M. Use of textiles in atopic dermatitis: care of atopic dermatitis. Curr Probl Dermatol. 2006;33:127–43.

49. Tsakok T, Marrs T, Mohsin M, et al. Does atopic dermatitis cause food allergy? A systematic review. J Allergy Clin Immunol. 2016;137:1071–8.
50. Kelleher MM, Dunn-Galvin A, Gray C, et al. Skin barrier impairment at birth predicts food allergy at 2 years of age. J Allergy Clin Immunol. 2016;137:1111–1116.e8.
51. Chang A, Robison R, Cai M, Singh AM. Natural history of food-triggered atopic dermatitis and development of immediate reactions in children. J Allergy Clinical Immunol Pract. 2016;4:229–236.e1.
52. Egawa G, Kabashima K. Multifactorial skin barrier deficiency and atopic dermatitis: essential topics to prevent the atopic march. J Allergy Clin Immunol. 2016;138:350–358.e1.
53. Spergel JM, Paller AS. Atopic dermatitis and the atopic march. J Allergy Clin Immunol. 2003;112:S118–27.
54. Brunner PM, Silverberg JI, Guttman-Yassky E, et al. Increasing comorbidities suggest that atopic dermatitis is a systemic disorder. J Invest Dermatol. 2017;137:18–25.
55. 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.
56. Silverberg JI, Simpson EL. Association between severe eczema in children and multiple comorbid conditions and increased healthcare utilization. Pediatr Allergy Immunol. 2013;24:476–86.
57. Gustafsson D, Sjoberg 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.
58. 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.
59. Spergel JM. Epidemiology of atopic dermatitis and atopic march in children. Immunol Allergy Clin North Am. 2010;30:269–80.
60. Gittler JK, Krueger JG, Guttman-Yassky E. Atopic dermatitis results in intrinsic barrier and immune abnormalities: implications for contact dermatitis. J Allergy Clin Immunol. 2013;131:300–13.
61. Thyssen JP, McFadden JP, Kimber I. The multiple factors affecting the association between atopic dermatitis and contact sensitization. Allergy. 2014;69:28–36.
62. Ong PY, Leung DY. Bacterial and viral infections in atopic dermatitis: a comprehensive review. Clin Rev Allergy Immunol. 2016;51:329–37.
63. Leyden JJ, Marples RR, Kligman AM. Staphylococcus Aureus in the lesions of atopic dermatitis. Br J Dermatol. 1974;90:525–30.
64. Hayakawa K, Hirahara K, Fukuda T, Okazaki M, Shiohara T. Risk factors for severe impetiginized atopic dermatitis in Japan and assessment of its microbiological features. Clin Exp Dermatol. 2009;34:e63–5.
65. Beck LA, Boguniewicz M, Hata T, et al. Phenotype of atopic dermatitis subjects with a history of eczema herpeticum. J Allergy Clin Immunol. 2009;124:260–269.e7. 9.e1–7
66. Mathes EF, Oza V, Frieden IJ, et al. "eczema coxsackium" and unusual cutaneous findings in an enterovirus outbreak. Pediatrics. 2013;132:e149–57.
67. Silverberg JI, Silverberg NB. Childhood atopic dermatitis and warts are associated with increased risk of infection: a US population-based study. J Allergy Clin Immunol. 2014;133:1041–7.
68. Lee CY, Chen MH, Jeng MJ, et al. Longitudinal association between early atopic dermatitis and subsequent attention-deficit or autistic disorder: a population-based case-control study. Medicine. 2016;95:e5005.
69. Kim SH, Hur J, Jang JY, et al. Psychological distress in young adult males with atopic dermatitis: a cross-sectional study. Medicine. 2015;94:e949.
70. Liao TC, Lien YT, Wang S, Huang SL, Chen CY. Comorbidity of atopic disorders with autism spectrum disorder and attention deficit/hyperactivity disorder. J Pediatr. 2016;171:248–55.
71. Strom MA, Fishbein AB, Paller AS, Silverberg JI. Association between atopic dermatitis and attention deficit hyperactivity disorder in U.S. children and adults. Br J Dermatol. 2016;175:920–9.

72. Yu SH, Attarian H, Zee P, Silverberg JI. Burden of sleep and fatigue in US adults with atopic dermatitis. Dermatitis. 2016;27:50–8.
73. Choi JH, Nam GE, Kim DH, Lee JY, Han KD, Cho JH. Association between sleep duration and the prevalence of atopic dermatitis and asthma in young adults. Asian Pacific J Allergy Immunol. 2016;34:265. doi:10.12932/AP0772.
74. Kong TS, Han TY, Lee JH, Son SJ. Correlation between severity of atopic dermatitis and sleep quality in children and adults. Ann Dermatol. 2016;28:321–6.
75. Meltzer LJ, Booster GD. Sleep disturbance in caregivers of children with respiratory and atopic disease. J Pediatr Psychol. 2016;41:643–50.
76. Chang YS, Chiang BL. Mechanism of sleep disturbance in children with atopic dermatitis and the role of the circadian rhythm and melatonin. Int J Mol Sci. 2016;17:462.
77. Silverberg JI. Association between adult atopic dermatitis, cardiovascular disease, and increased heart attacks in three population-based studies. Allergy. 2015;70:1300–8.
78. Drucker AM, Li WQ, Cho E, et al. Atopic dermatitis is not independently associated with nonfatal myocardial infarction or stroke among US women. Allergy. 2016;71:1496–500.
79. Standl M, Tesch F, Baurecht H, et al. Association of atopic dermatitis with cardiovascular risk factors and diseases. J Invest Dermatol. 2017;137:1074–81.
80. Egeberg A, Andersen YM, Gislason GH, Skov L, Thyssen JP. Prevalence of comorbidity and associated risk factors in adults with atopic dermatitis. Allergy. 2017;72(5):783–91.
81. Silverberg JI, Becker L, Kwasny M, Menter A, Cordoro KM, Paller AS. Central obesity and high blood pressure in pediatric patients with atopic dermatitis. JAMA Dermatol. 2015;151:144–52.
82. Wang H, Rothenbacher D, Low M, Stegmaier C, Brenner H, Diepgen TL. Atopic diseases, immunoglobulin E and risk of cancer of the prostate, breast, lung and colorectum. Int J Cancer. 2006;119:695–701.
83. Wang H, Diepgen TL. Is atopy a protective or a risk factor for cancer? A review of epidemiological studies. Allergy. 2005;60:1098–111.
84. Wang H, Diepgen TL. Atopic dermatitis and cancer risk. Br J Dermatol. 2006;154:205–10.
85. Deckert S, Kopkow C, Schmitt J. Nonallergic comorbidities of atopic eczema: an overview of systematic reviews. Allergy. 2014;69:37–45.
86. Legendre L, Barnetche T, Mazereeuw-Hautier J, Meyer N, Murrell D, Paul C. Risk of lymphoma in patients with atopic dermatitis and the role of topical treatment: a systematic review and meta-analysis. J Am Acad Dermatol. 2015;72:992–1002.
87. Margolis DJ, Abuabara K, Hoffstad OJ, Wan J, Raimondo D, Bilker WB. Association between malignancy and topical use of pimecrolimus. JAMA Dermatol. 2015;151:594–9.