



CME review

Racial differences in atopic dermatitis

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Key Messages

- Atopic dermatitis (AD) is a heterogeneous disease, with differences in prevalence, genetic background, and immune activation patterns, depending on the racial group.
- All patients with AD had strong T_H2 activation, with T_H17/T_H22 strongly upregulated in Asian patients with AD and higher IgE serum levels (and absent T_H17/Th1 activation) in African American patients with AD.
- These differences necessitate further evaluations of parallel responses in clinical trials with targeted treatments for AD to optimize AD therapeutics that account for these differences.
- To fully resolve the AD phenotype across its ethnic and other variants, multiple cytokine axes might need to be targeted.

ARTICLE INFO

Article history:

Received for publication October 2, 2018.

Received in revised form November 4, 2018.

Accepted for publication November 12, 2018.

ABSTRACT

Objective: To summarize studies investigating ethnical and racial differences in atopic dermatitis (AD) epidemiology, clinical features, and skin and blood phenotypes.

Data Sources: PubMed literature review (years 2000–2018).

Study Selections: Articles discussing primarily human disease.

Results: Higher overall rates of AD were found in Africa and Oceania as opposed to India and Northern and Eastern Europe. In the United States, AD prevalence was found to be higher in African American (19.3%) compared with European American (16.1%) children. Although several studies have consistently found *FLG* loss-of-function mutations in up to 50% of European and 27% of Asian patients with AD, *FLG* mutations were 6 times less common in African American than in European American patients, even in patients with severe AD. Thus, *FLG* mutations seem to play less a pathogenic role in patients of African origin than in individuals of European or Asian ancestry. The immune phenotype of all ethnic groups was characterized by strong T_H2 activation, but important differences in immune polarization exist among the different ethnicities. Asian patients with AD had stronger T_H17/T_H22 activation than African American and European American patients with AD, whereas African American patients had the highest serum IgE levels among all groups, while largely lacking T_H1 and T_H17 activation.

Conclusion: AD is a heterogeneous disease that has differences among various ethnic and racial groups, which might be important for the development of future, targeted treatments and for personalized medicine approaches.

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Disclosures: Dr Brunner received personal fees from LEO Pharma, Pfizer, Lilly, and Sanofi. Dr Guttman-Yassky is an employee of Mount Sinai and has received research funds (grants paid to the institution) from: Abbvie, Celgene, Eli Lilly, Janssen,

Medimmune/AstraZeneca, Novartis, Pfizer, Regeneron, Vitae, Glenmark, Galderma, Asana, Innovaderm, Dermira, UCB. EGY is also a consultant for Sanofi Aventis, Regeneron, Stiefel/GlaxoSmithKline, MedImmune, Celgene, Anacor, AnaptysBio, Dermira, Galderma, Glenmark, Novartis, Pfizer, Vitae, Leo Pharma, Abbvie, Eli Lilly, Kyowa, Mitsubishi Tanabe, Asana Biosciences, and Promius.

Funding: None.

<https://doi.org/10.1016/j.anai.2018.11.015>

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Learning Objectives

At the conclusion of this activity, participants should be able to:

- Identify racial differences in the presentation of atopic dermatitis (AD).
- Identify differing immune and molecular phenotypes of AD in different ethnic groups with AD.

Release Date: May 1, 2019

Expiration Date: April 30, 2021

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Introduction

Atopic dermatitis (AD), the most common chronic inflammatory skin disease,¹ usually starts in early infancy and can develop into a lifelong therapeutic challenge, especially in its moderate to severe form.² The origin of this complex disease remains only partly understood, but it is most likely based on a complex interplay of genetic predisposition, skin barrier dysfunction, and environmental factors.³ AD is now understood to be an immune-mediated disease with contributions of multiple inflammatory pathways, particularly type 2 associated inflammation.^{1,3} However, unlike psoriasis,^{4,5} AD is a rather heterogeneous disease. Although some patients outgrow their disease before reaching adolescence or early adulthood, others have chronic lifelong disease.^{6,7} Other aspects of disease heterogeneity are intrinsic vs extrinsic disease, allergic comorbidities, such as asthma or rhinitis, and the presence or absence of *FLG* mutations.¹ Only recently it became clear that AD has disease heterogeneity that also depends on the patient's racial background, a yet understudied aspect of immune-mediated disease, which is now getting more attention across several atopic diseases.^{8–11} Clinically, AD in East Asian populations has been described as more demarcated than European American populations, consistent with some molecular features of psoriasis in this patient population.¹² African Americans, by contrast, are more likely to have extensor involvement and less frequent flexural involvement compared with European American patients.¹¹ Diffuse xerosis, Dennie-Morgan lines, and hyperlinearity of the palms are also more common in darker skin types.¹³ In black patients, lichenification and prurigo nodularis are more frequently seen than in white patients, potentially because of greater pruritus and consequently increased rubbing and scratching,^{11,14,15} and postinflammatory dyspigmentation is of great concern.¹⁶ Importantly, the use of common scores that depend on erythema (eg, Eczema Area and Severity Index [EASI], Scoring Atopic Dermatitis [SCORAD], and others) can strongly underestimate the severity of AD in darker skin types.^{11,17}

Despite the fact that AD is highly prevalent in patients with skin of color, who also often present with more treatment-resistant AD, few data exist on the efficacy of AD therapies in these patients, which have traditionally been studied in white ethnic groups. White patients still represent most patients studied in clinical therapeutic trials (eg, 62.1% in AD clinical trials published between 2000 and 2009),¹⁸ and only 10.3% of studies interpreted their results considering race or ethnicity. In this review, we explore the current understanding of differences in the AD epidemiology and pathogenesis based on the racial and ethnic backgrounds of patients to raise awareness of these contributing factors to disease phenotype and possibly also to varying therapeutic responses in clinical trials.

Epidemiology of AD

The prevalence of AD shows large differences worldwide, ranging from 0.2% to 24.6% in certain locations,¹⁹ as revealed by the International Study of Asthma and Allergies in Childhood, which studied more than 350,000 participants in 60 countries from 1999 to 2004. In general, higher rates of eczema were found in Africa and Oceania, as opposed to India and Northern and Eastern Europe, which had lower rates.¹⁹ Even within Africa, disease prevalence rates had a wide range, depending on the study center, of 4.7% to 23%. Similarly, the AD prevalence in the Asia-Pacific region is 4% to 30% in various study centers.¹⁹ The mean eczema prevalence per country is given in Figure 1, and the mean prevalence of severe eczema is displayed in Figure 2, showing many high prevalence countries to be located in Africa.

In the United States, AD prevalence is higher in African American children compared with European American children.¹¹

African American children are 1.7 times more likely to develop AD compared with European American children, even after adjustment for various factors, such as health insurance coverage, metropolitan vs rural environment, or household income.^{11,20} This difference is also reflected by a 3-fold higher likelihood of African American children to be diagnosed with AD during a dermatologist visit, despite the fact that they are significantly less likely to seek dermatologic care.¹¹ Similarly, Asians and Pacific Islanders are 7 times more likely compared with whites to be diagnosed with AD at a dermatologic office visit.^{11,21} Overall, eczema remains a top concern in dermatologic visits in various different US populations with skin of color.^{22–24}

Genetic Differences

AD is thought to have a considerable genetic component, although it is not a classic monogenetic disease. More recently, genome-wide association studies (GWASs) are now also focusing on African, Hispanic, and Asian populations in addition to only white populations.¹¹ The largest GWAS to date identified 31 AD risk loci, with variations among ethnic groups for many of these markers.²⁵ Genes potentially involved in the pathogenesis of AD are genes of immune regulation and epithelial barrier function.¹¹

FLG loss-of-function mutations are currently the best studied genetic risk factors for the development of AD, and harboring *FLG* mutations is the strongest risk factor for AD.^{26–28} This mutation results in a defective expression of the epidermal barrier protein filaggrin, which is a central component of the skin barrier function and of epidermal terminal differentiation, including the regulation of skin pH and epidermal hydration.²⁹ *FLG* loss-of-function mutations are associated with more severe and persistent AD, a higher degree of immune dysregulation, and increased rates of skin infections and allergic sensitization.^{30–38} Several studies have consistently found loss-of-function mutations in up to 50% of European and 27% of Asian patients with AD.^{39,40} The most frequent *FLG* loss-of-function mutations (R501X, 2282del4, S3247X, R2447X) have been found in 7% to 10% of white Europeans,^{40,41} but these mutations are usually absent in Asian individuals, who exhibit *FLG* null mutations that are unique to their respective ethnic groups.^{39,42} In contrast, *FLG* mutations are 6 times less common in African American than in European American patients,³⁸ and data from Ethiopia failed to find an association between *FLG* null mutations or copy number variations and the development of AD.^{43,44} Overall, *FLG* mutations seem to be much less frequent in patients of African descent than European or Asian descent, despite the fact that they have increased frequencies of AD. Thus, *FLG* mutations seem to play a less pathogenic role in patients of African origin than in individuals of European or Asian ancestry. Higher numbers of *FLG* mutations in (Northern) Europeans might be explained by genetic pressure because *FLG* deficiency (and thus a decreased skin barrier) might enhance immunity to infections and has a role in increasing vitamin D biosynthesis, which could be relevant for especially higher latitudes.^{11,45}

Because of the strong difference in *FLG* mutation frequencies and in light of the fact that skin inflammation is present in patients with AD with and without *FLG* mutations, other genes are likely involved in the origin of AD. Whole exome sequencing analyses of Ethiopian and African American individuals with AD found associations with loss-of-function mutations of *FLG2*, encoding a protein that is closely related to filaggrin.^{44–47} In one study, African American children with an *FLG2* mutation were more than 50% more likely to develop persistent AD compared with those without these variants.⁴⁶ Consistently, *FLG2* expression levels in skin showed an inverse correlation with active skin inflammation attributable to AD.⁴⁸ Importantly, associations of AD with *FLG2* have not been found in Europeans.^{49,50} Other variants in barrier genes

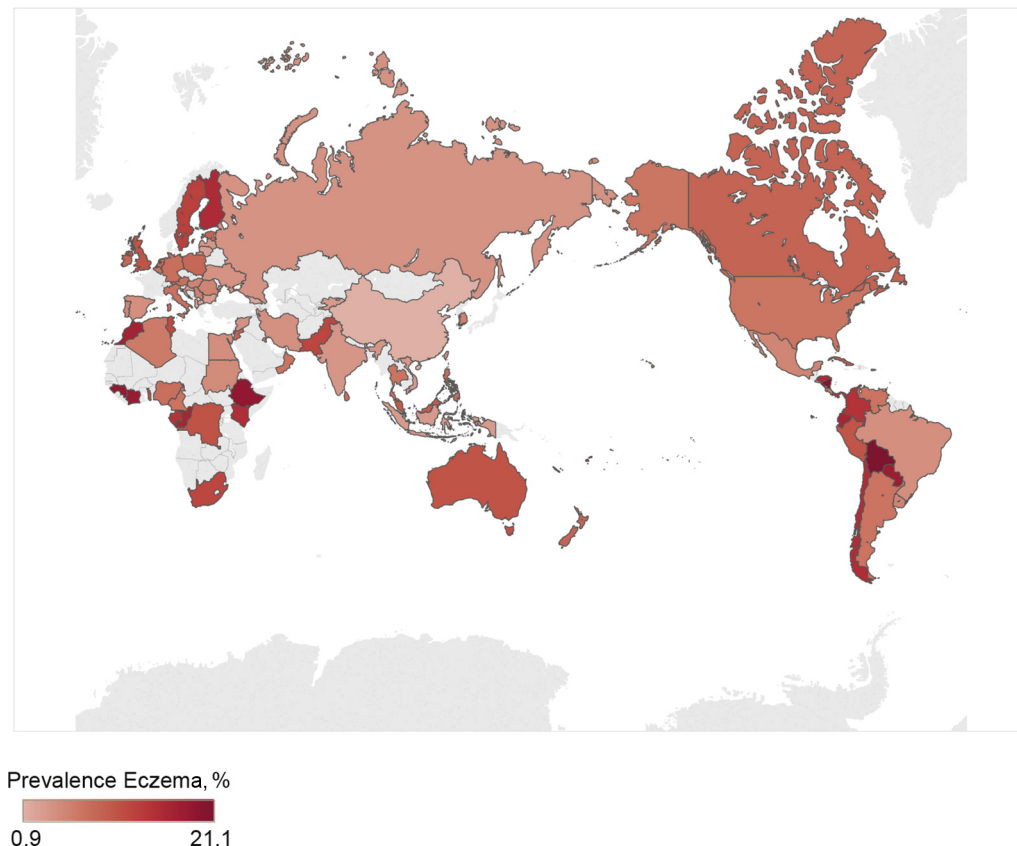


Figure 1. World map of eczema prevalence. Cross-sectional data on eczema symptoms defined as an itchy flexural rash in the past 12 months in the age group of 13 to 14 years. Data are based on 663,256 participants from 230 centers in 96 countries. The mean prevalence per country is depicted. Data are modified from Odhiambo et al²⁰ with permission.

that have been associated with AD are *CLDN1* in Ethiopians (early-onset AD)⁵¹ and *SPINK5*, a serine protease inhibitor involved in epidermal homeostasis, in AD of East Asian patients.^{52–56}

Differences among ethnic groups have also been described for polymorphisms of genes involved in innate and adaptive immunity, especially T_H2 signaling pathways.⁵⁷ Coding genetic polymorphisms of the interleukin (IL) 4 receptor α (IL-4R α) have been implicated in susceptibility to both atopy and asthma.⁵⁸ An association between IL-4/IL-4R α polymorphisms and susceptibility of AD has been described in Egyptians⁵⁹ and for IL-4 and IL-13/IL-13R $\alpha1$ in Korean, Japanese, and Chinese populations.^{59–62} One polymorphism (Q576R), showing augmented IL-4R α -dependent signaling in a mouse model,⁵⁸ is especially associated with severe asthma and increased allergen sensitization in the context of maternal smoking⁶³ and is overrepresented in African Americans (70% allele frequency vs only 20% in whites).^{58,64} Another study describes a potential role for IL-4R α single-nucleotide polymorphisms in baseline lung function among African American patients with asthma.⁶⁵

A *TSLP* variant has been associated with less persistent AD in white and black populations, and in interferon regulatory factor 2 polymorphisms were associated with increased AD risks in these 2 groups.^{66,67} high-affinity IgE receptor 1A and Toll-like receptor 2, both markers found on atopic dendritic cells, were characterized in Japanese populations.^{68,69} In Mexican and Korean populations, mutations in β -defensin 1, an antimicrobial peptide, were associated with elevated AD risks.^{70,71} Single-nucleotide polymorphisms of the T_H1 lead cytokine IL-12 and its receptor have also been described in Koreans with AD.⁷²

Differences in the AD Immune Phenotype

Even healthy skin from European, African, and Asian populations have certain differences in gene expression patterns,⁷³ conceivably influencing immune circuits of AD in different populations. The fact that AD is primarily a T-cell-driven disease^{74,75} has initially been reported with T-cell-targeting therapeutics, such as alefacept, efalizumab, and cyclosporine.^{76–78} The T_H2 axis is central to disease pathogenesis, as demonstrated by the clinical efficacy of the IL-4R α blocker dupilumab.⁷⁹ Importantly, T_H2 activation has been described across all races and ethnicities investigated.^{12,80–82} However, immune activation patterns of AD lesions are more complex and heterogeneous than just T_H2 -centric inflammation. Although EASI-75 responses were obtained in roughly half of patients receiving dupilumab in several phase 3 studies, the other patients did not reach this end point,⁷⁹ but the causes remain to be elucidated. Besides T_H2 activation in European American, African American, Japanese/Korean, and Chinese individuals,^{12,80–82} additional T_H cell axes were also described at different expression levels in these AD populations (Table 1), and their individual roles will need further investigations in with specific targeted therapeutics. T_H1 activation is present in chronic AD of European Americans, with lower levels found in infants with early-onset disease.^{83,84} Patients of Asian origin (Japanese, Korean) with AD had additional, strong T_H17 activation, overlapping clinically and molecularly with some hallmarks of psoriasis.¹² An ongoing clinical trial ([clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02594098) Identifier: NCT02594098) will elucidate the contribution of the T_H17 immune axis to AD, whether it is proinflammatory or protective, and whether different

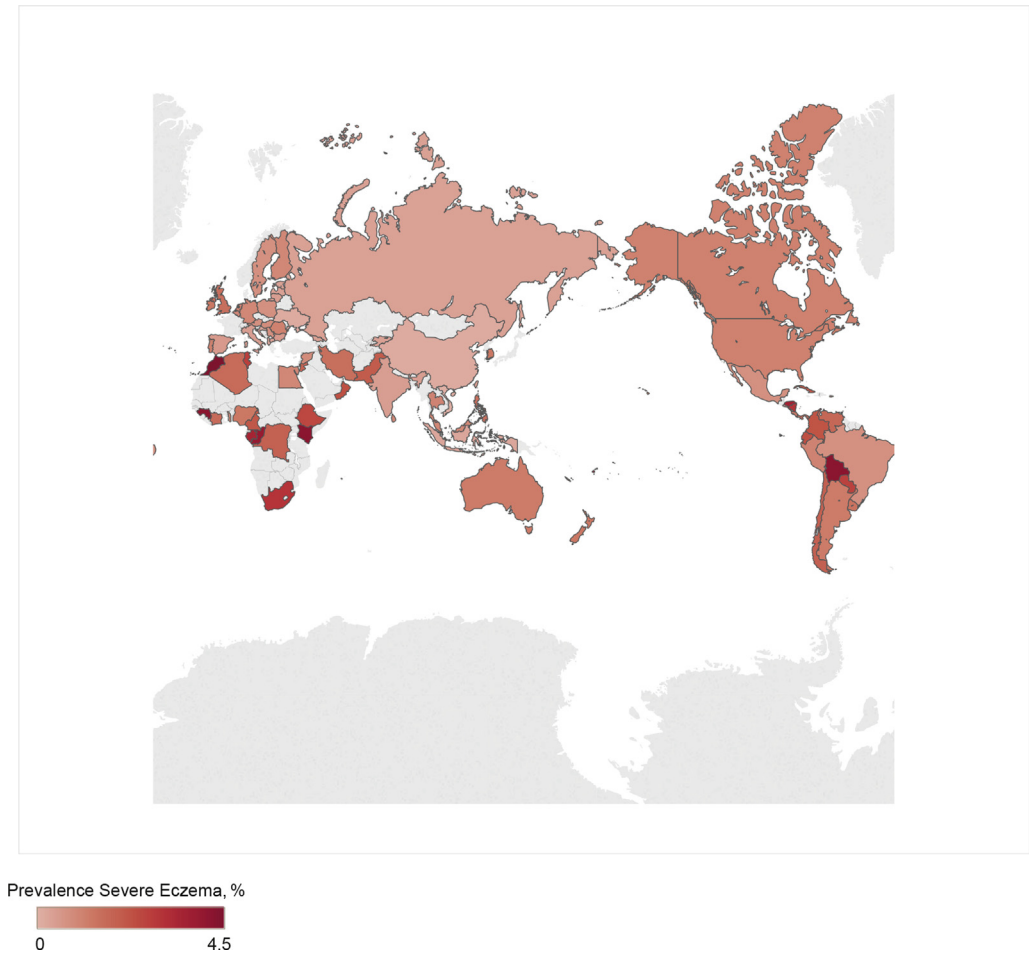


Figure 2. World map of severe eczema prevalence. Cross-sectional data on eczema symptoms defined as an itchy flexural rash in the past 12 months in the age group of 13 to 14 years. Data are based on 663,256 participants from 230 centers in 96 countries. The mean prevalence per country is depicted. Data are modified from Odhiambo et al²⁰ with permission.

expression levels in European American vs Asian individuals affects clinical efficacy of the IL-17 secukinumab.

Asian patients also had greater T_H22 and lower T_H1 skewing than European Americans but comparable T_H2 activation.¹² Peripheral blood from these Asian patients further showed decreased T_H1 (interferon γ , CCL2, CCL3, CCL4) related measures than European Americans, but both groups had mutual upregulation of T_H2 measures (IL-13, CCL13, CCL17, CCL22), with further increases in CCL26 in Asian individuals.⁸¹ The increases in T_H17 mediators as seen in the skin of Asians with AD¹² were not seen in the peripheral blood of the same patients, but IL-22 levels were higher in AD serum samples from Asian patients than samples from European American patients,⁸¹ which is consistent with increases in the skin of Asians with AD.¹²

A study of biopsy specimens from patients with AD of Han Chinese descent found increased T_H17 skewing with decreased T_H1 activation compared with European Americans with AD,⁸² similar to Japanese/Korean patients.⁸² However, samples from Han Chinese patients also had increases in neutrophil counts compared to European American patients with AD.⁸² In addition, these Chinese samples had even stronger T_H2 activation than EA samples. Similar to their Japanese and Korean Asian counterparts, the Chinese patients' samples also had prominent parakeratosis,^{12,82} which was less frequently found in European American patients with AD.¹² Overall, East Asian (Japanese, Korean, Han Chinese) AD seems to be characterized by increased T_H17 levels and some psoriasiform

features,^{12,82} even in patients with much higher IgE levels than the European American AD group that served for comparisons. In general, African American patients with AD had highly elevated serum IgE levels (higher than European American and Asian patients with AD),⁸¹ similar to what has been seen in other atopic diseases, where African American patients had the highest IgE

Table 1
Molecular Differences in Atopic Dermatitis Skin Biopsy Specimens, Depending on Racial Background

Race/Ethnicity	Immune Skewing	Other Features
European American	T_H1 ↑↑	IgE ↑↑
	T_H2 ↑↑↑	Filaggrin ↓↓
	T_H17 ↑	Loricrin ↓↓
	T_H22 ↑↑↑	Neutrophils ↑
African American	T_H1 (↑)	IgE ↑↑↑
	T_H2 ↑↑↑	Filaggrin (↓)
	T_H17 (↑)	Loricrin ↓↓
	T_H22 ↑↑↑	Neutrophils ↑↑
Japanese/Korean	T_H1 ↑	IgE ↑↑
	T_H2 ↑↑↑	Filaggrin ↓↓
	T_H17 ↑↑	Loricrin ↓↓
	T_H22 ↑↑↑	Neutrophils ↑↑
Han Chinese	T_H1 ↑	IgE ↑↑
	T_H2 ↑↑↑	Filaggrin ↓
	T_H17 ↑↑	Loricrin ↓↓
	T_H22 ↑↑↑	Neutrophils ↑↑

Upward arrows indicate increase; downward arrows, decrease.

levels.^{85–87} The overrepresentation of polymorphisms augmenting IL-4R α -dependent signaling^{58,63,64} might play a key role in this regard because enhanced IL-4R α signaling is associated with increased IgE production.⁶⁴ African American patients furthermore had the higher numbers of high-affinity IgE receptor 1-positive dendritic cells, in addition to increases in IgE levels.⁸⁰ The strong T_H2 and allergic skewing in African American patients is further emphasized by the high correlation seen between disease severity (SCORAD) and IgE only in African American but not European American patients with AD, as well as the correlations between IL-13 expressions in lesional and nonlesional skin with SCORAD in this population.⁸⁰ Importantly, T_H17 (IL-23p19, IL-36G, CXCL1) and T_H1 (interferon γ , MX1, IL-12RB1) activation were largely absent in African American skin as opposed to European American skin with AD.⁸⁰ In addition, expression of innate immune (tumor necrosis factor, IL-1 β) mediators was lower than in European American patients, but strong T_H2/T_H22 skewing was common to both the African American and European American groups.⁸⁰ Filaggrin downregulation was less in African American patients than in European American patients, but loricrin downregulation was stronger than in European American patients.⁸⁰

Therapeutic Implications

The emerging clinical, epidemiologic, and molecular differences among various ethnic phenotypes holds important therapeutic implications. It is crucial to understand how the differences in phenotypes may affect therapeutic responses and ultimately influence selection of therapeutics. Although novel treatments approved (dupilumab) or being tested for patients with AD (anti-IL-22, anti-IL-17C, anti-IL-33) show great promise in AD, it is likely that a one-size-fits-all approach is not going to be applicable to this heterogeneous disease because EASI-90 treatment responses are often seen in less than 50% of patients.⁶ Thus, personalized medicine strategies that will be able to identify the responders to a particular drug at baseline, as recently reported in a study with IL-22, may be warranted.^{88,89} It may be that to be able to fully resolve the AD phenotype across its ethnic and other variants, several cytokine axes may need to be targeted via bispecific antibodies or through oral drugs that target more than one axis, such as the JAK inhibitors.⁹⁰

Conclusion

There is an increasing bulk of clinical, epidemiologic, and molecular data outlining differences among various ethnic AD patient populations. These differences mandate further evaluations of parallel responses in clinical trials with various treatments for AD to optimize AD therapeutics that account for these differences.

References

- Weidinger S, Novak N. Atopic dermatitis. *Lancet*. 2016;387:1109–1122.
- Silverberg JL. Public health burden and epidemiology of atopic dermatitis. *Dermatol Clin*. 2017;35:283–289.
- Leung DY, Guttman-Yassky E. Deciphering the complexities of atopic dermatitis: shifting paradigms in treatment approaches. *J Allergy Clin Immunol*. 2014;134:769–779.
- Guttman-Yassky E, Krueger JG. Atopic dermatitis and psoriasis: two different immune diseases or one spectrum? *Curr Opin Immunol*. 2017;48:68–73.
- Guttman-Yassky E, Krueger JG, Lebwohl MG. Systemic immune mechanisms in atopic dermatitis and psoriasis with implications for treatment. *Exp Dermatol*. 2018;27:409–417.
- Brunner PM, Guttman-Yassky E, Leung DY. The immunology of atopic dermatitis and its reversibility with broad-spectrum and targeted therapies. *J Allergy Clin Immunol*. 2017;139:S65–S76.
- Czarnowicki T, Krueger JG, Guttman-Yassky E. Novel concepts of prevention and treatment of atopic dermatitis through barrier and immune manipulations with implications for the atopic march. *J Allergy Clin Immunol*. 2017;139:1723–1734.
- Wang D, Wang Y, Liang H, David JE, Bray CL. Race and ethnicity have significant influence on fractional exhaled nitric oxide. *Ann Allergy Asthma Immunol*. 2018;120:272–277, e1.
- Gupta J, Johansson E, Bernstein JA, et al. Resolving the etiology of atopic disorders by using genetic analysis of racial ancestry. *J Allergy Clin Immunol*. 2016;138:676–699.
- Dunlop JH, Keet CA. Epidemiology of food allergy. *Immunol Allergy Clin North Am*. 2018;38:13–25.
- Kaufman BP, Guttman-Yassky E, Alexis AF. Atopic dermatitis in diverse racial and ethnic groups: variations in epidemiology, genetics, clinical presentation and treatment. *Exp Dermatol*. 2018;27:340–357.
- Noda S, Suarez-Farinas M, Ungar B, et al. The Asian atopic dermatitis phenotype combines features of atopic dermatitis and psoriasis with increased TH17 polarization. *J Allergy Clin Immunol*. 2015;136:1254–1264.
- Vachiramon V, Tey HL, Thompson AE, Yosipovitch G. Atopic dermatitis in African American children: addressing unmet needs of a common disease. *Pediatr Dermatol*. 2012;29:395–402.
- Oh CC, Li H, Lee W, Tey HL. Biopsychosocial factors associated with prurigo nodularis in endogenous eczema. *Indian J Dermatol*. 2015;60:525.
- Shaw FM, Luk KMH, Chen KH, Wrenn C, Chen SC. Racial disparities in the impact of chronic pruritus: a cross-sectional study on quality of life and resource utilization in United States veterans. *J Am Acad Dermatol*. 2017;77:63–69.
- Alexis AF, Blackcloud P. Psoriasis in skin of color: epidemiology, genetics, clinical presentation, and treatment nuances. *J Clin Aesthet Dermatol*. 2014;7:16–24.
- Ben-Gashir MA, Hay RJ. Reliance on erythema scores may mask severe atopic dermatitis in black children compared with their white counterparts. *Br J Dermatol*. 2002;147:920–925.
- Hirano SA, Murray SB, Harvey VM. Reporting, representation, and subgroup analysis of race and ethnicity in published clinical trials of atopic dermatitis in the United States between 2000 and 2009. *Pediatr Dermatol*. 2012;29:749–755.
- Odhiamblo JA, Williams HC, Clayton TO, Robertson CF, Asher MI, Group IPTS. Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three. *J Allergy Clin Immunol*. 2009;124:1251–1258.e23.
- 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.
- Janumpally SR, Feldman SR, Gupta AK, Fleischer AB Jr. In the United States, blacks and Asian/Pacific Islanders are more likely than whites to seek medical care for atopic dermatitis. *Arch Dermatol*. 2002;138:634–637.
- Davis SA, Narahari S, Feldman SR, Huang W, Pichardo-Geisinger RO, McMichael AJ. Top dermatologic conditions in patients of color: an analysis of nationally representative data. *J Drugs Dermatol*. 2012;11:466–473.
- El-Essawi D, Musial JL, Hammad A, Lim HW. A survey of skin disease and skin-related issues in Arab Americans. *J Am Acad Dermatol*. 2007;56:933–938.
- Shah SK, Bhanusali DG, Sachdev A, Geria AN, Alexis AF. A survey of skin conditions and concerns in South Asian Americans: a community-based study. *J Drugs Dermatol*. 2011;10:524–528.
- Paternoster L, Standl M, Waage J, et al. Multi-ancestry genome-wide association study of 21,000 cases and 95,000 controls identifies new risk loci for atopic dermatitis. *Nat Genet*. 2015;47:1449–1556.
- Palmer CN, Irvine AD, Tarron-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;38:441–446.
- van den Oord RA, Sheikh A. Filaggrin gene defects and risk of developing allergic sensitisation and allergic disorders: systematic review and meta-analysis. *BMJ*. 2009;339:b2433.
- Chen H, Compton JE, Haines RL, et al. Wide spectrum of filaggrin-null mutations in atopic dermatitis highlights differences between Singaporean Chinese and European populations. *Br J Dermatol*. 2011;165:106–114.
- Sandilands A, Sutherland C, Irvine AD, McLean WH. Filaggrin in the frontline: role in skin barrier function and disease. *J Cell Sci*. 2009;122:1285–1294.
- Oliva M, Renert-Yuval Y, Guttman-Yassky E. The 'omics' revolution: redefining the understanding and treatment of allergic skin diseases. *Curr Opin Allergy Clin Immunol*. 2016;16:469–476.
- Cole C, Kroboth K, Schurch NJ, et al. Filaggrin-stratified transcriptomic analysis of pediatric skin identifies mechanistic pathways in patients with atopic dermatitis. *J Allergy Clin Immunol*. 2014;134:82–91.
- Czarnowicki T, Krueger JG, Guttman-Yassky E. Skin barrier and immune dysregulation in atopic dermatitis: an evolving story with important clinical implications. *J Allergy Clin Immunol Pract*. 2014;2:371–379. quiz 80–81.
- Gutowska-Owsiak D, Schaupp AL, Salimi M, et al. IL-17 downregulates filaggrin and affects keratinocyte expression of genes associated with cellular adhesion. *Exp Dermatol*. 2012;21:104–110.
- Malajian D, Guttman-Yassky E. New pathogenic and therapeutic paradigms in atopic dermatitis. *Cytokine*. 2015;73:311–318.
- Kezic S, O'Regan GM, Lutter R, et al. Filaggrin loss-of-function mutations are associated with enhanced expression of IL-1 cytokines in the stratum corneum of patients with atopic dermatitis and in a murine model of filaggrin deficiency. *J Allergy Clin Immunol*. 2012;129:1031–1039.e1.
- Irvine AD, McLean WH, Leung DY. Filaggrin mutations associated with skin and allergic diseases. *N Engl J Med*. 2011;365:1315–1327.
- Kono M, Nomura T, Ohguchi Y, et al. Comprehensive screening for a complete set of Japanese-population-specific filaggrin gene mutations. *Allergy*. 2014;69:537–540.

38. 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;130:912–917.
39. Park J, Jekarl DW, Kim Y, Kim J, Kim M, Park YM. Novel FLG null mutations in Korean patients with atopic dermatitis and comparison of the mutational spectra in Asian populations. *J Dermatol*. 2015;42:867–873.
40. Brown SJ, McLean WH. One remarkable molecule: filaggrin. *J Invest Dermatol*. 2012;132:751–762.
41. 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.
42. Li K, Oh WJ, Park KY, Kim KH, Seo SJ. FLG mutations in the East Asian atopic dermatitis patients: genetic and clinical implication. *Exp Dermatol*. 2016;25:816–818.
43. Fernandez K, Asad S, Taylan F, et al. Intragenic copy number variation in the filaggrin gene in Ethiopian patients with atopic dermatitis. *Pediatr Dermatol*. 2017;34:e140–e141.
44. Taylan F, Nilsson D, Asad S, et al. Whole-exome sequencing of Ethiopian patients with ichthyosis vulgaris and atopic dermatitis. *J Allergy Clin Immunol*. 2015;136:507–509.e19.
45. Thyssen JP, Thuesen B, Huth C, et al. Skin barrier abnormality caused by filaggrin (FLG) mutations is associated with increased serum 25-hydroxyvitamin D concentrations. *J Allergy Clin Immunol*. 2012;130:1204–1207.e2.
46. 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;133:784–789.
47. 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;134:2272–2274.
48. Seykora J, Dentschev T, Margolis DJ. Filaggrin-2 barrier protein inversely varies with skin inflammation. *Exp Dermatol*. 2015;24:720–722.
49. Marenholz I, Rivera VA, Esparza-Gordillo J, et al. Association screening in the Epidermal Differentiation Complex (EDC) identifies an SPRR3 repeat number variant as a risk factor for eczema. *J Invest Dermatol*. 2011;131:1644–1649.
50. 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;131:1094–1102.
51. Asad S, Winge MC, Wahlgren CF, et al. The tight junction gene Claudin-1 is associated with atopic dermatitis among Ethiopians. *J Eur Acad Dermatol Venereol*. 2016;30:1939–1941.
52. Liang Y, Chang C, Lu Q. The genetics and epigenetics of atopic dermatitis: filaggrin and other polymorphisms. *Clin Rev Allergy Immunol*. 2016;51:315–328.
53. Kato A, Fukai K, Oiso N, Hosomi N, Murakami T, Ishii M. Association of SPINK5 gene polymorphisms with atopic dermatitis in the Japanese population. *Br J Dermatol*. 2003;148:665–669.
54. Nishio Y, Noguchi E, Shibasaki M, et al. Association between polymorphisms in the SPINK5 gene and atopic dermatitis in the Japanese. *Genes Immun*. 2003;4:515–517.
55. Lan CC, Tu HP, Wu CS, et al. Distinct SPINK5 and IL-31 polymorphisms are associated with atopic eczema and non-atopic hand dermatitis in Taiwanese nursing population. *Exp Dermatol*. 2011;20:975–979.
56. Zhao LP, Di Z, Zhang L, et al. Association of SPINK5 gene polymorphisms with atopic dermatitis in Northeast China. *J Eur Acad Dermatol Venereol*. 2012;26:572–577.
57. Al-Shobaili HA, Ahmed AA, Alnomair N, Alobead ZA, Rasheed Z. Molecular genetic of atopic dermatitis: an update. *Int J Health Sci (Qassim)*. 2016;10:96–120.
58. Tachdjian R, Mathias C, Al Khatib S, et al. Pathogenicity of a disease-associated human IL-4 receptor allele in experimental asthma. *J Exp Med*. 2009;206:2191–2204.
59. Hussein YM, Shalaby SM, Nassar A, Alzahrani SS, Alharbi AS, Nouh M. Association between genes encoding components of the IL-4/IL-4 receptor pathway and dermatitis in children. *Gene*. 2014;545:276–281.
60. Shang H, Cao XL, Wan YJ, Meng J, Guo LH. IL-4 gene polymorphism may contribute to an increased risk of atopic dermatitis in children. *Dis Markers*. 2016;2016:1021942.
61. Kawashima T, Noguchi E, Arinami T, et al. Linkage and association of an interleukin 4 gene polymorphism with atopic dermatitis in Japanese families. *J Med Genet*. 1998;35:502–504.
62. Jiang XY, Zhao JH, Yu CX, et al. Association analyses identify two susceptibility loci 5q31 and 5q22.1 for atopic dermatitis in Chinese Han population. *Asian Pac J Allergy Immunol*. 2017;35:196–202.
63. Liu X, Beaty TH, Deindl P, et al. Associations between total serum IgE levels and the 6 potentially functional variants within the genes IL4, IL13, and IL4RA in German children: the German Multicenter Atopy Study. *J Allergy Clin Immunol*. 2003;112:382–388.
64. Caggana M, Walker K, Reilly AA, Conroy JM, Duva S, Walsh AC. Population-based studies reveal differences in the allelic frequencies of two functionally significant human interleukin-4 receptor polymorphisms in several ethnic groups. *Genet Med*. 1999;1:267–271.
65. Battle NC, Choudhry S, Tsai HJ, et al. Ethnicity-specific gene-gene interaction between IL-13 and IL-4Ralpha among African Americans with asthma. *Am J Respir Crit Care Med*. 2007;175:881–887.
66. Margolis DJ, Kim B, Apter AJ, et al. Thymic stromal lymphopoietin variation, filaggrin loss of function, and the persistence of atopic dermatitis. *JAMA Dermatol*. 2014;150:254–259.
67. Gao PS, Leung DY, Rafaels NM, et al. Genetic variants in interferon regulatory factor 2 (IRF2) are associated with atopic dermatitis and eczema herpeticum. *J Invest Dermatol*. 2012;132:650–657.
68. Potaczek DP, Nastalek M, Okumura K, Wojas-Pelc A, Undas A, Nishiyama C. An association of TLR2-16934A >T polymorphism and severity/phenotype of atopic dermatitis. *J Eur Acad Dermatol Venereol*. 2011;25:715–721.
69. Niwa Y, Potaczek DP, Kanada S, et al. FcεR1α gene (FCER1A) promoter polymorphisms and total serum IgE levels in Japanese atopic dermatitis patients. *Int J Immunogenet*. 2010;37:139–141.
70. Prado-Montes de Oca E, Garcia-Vargas A, Lozano-Inocencio R, et al. Association of beta-defensin 1 single nucleotide polymorphisms with atopic dermatitis. *Int Arch Allergy Immunol*. 2007;142:211–218.
71. Kim E, Lee JE, Namkung JH, et al. Single nucleotide polymorphisms and the haplotype in the DEFB1 gene are associated with atopic dermatitis in a Korean population. *J Dermatol Sci*. 2009;54:25–30.
72. Namkung JH, Lee JE, Kim E, et al. Association of single nucleotide polymorphisms in the IL-12 (IL-12A and B) and IL-12 receptor (IL-12Rβ1 and β2) genes and gene-gene interactions with atopic dermatitis in Koreans. *J Dermatol Sci*. 2010;57:199–206.
73. Yin L, Coelho SG, Ebsen D, et al. Epidermal gene expression and ethnic pigmentation variations among individuals of Asian, European and African ancestry. *Exp Dermatol*. 2014;23:731–735.
74. Werfel T, Allam JP, Biedermann T, et al. Cellular and molecular immunologic mechanisms in patients with atopic dermatitis. *J Allergy Clin Immunol*. 2016;138:336–349.
75. Biedermann T, Skabytska Y, Kaesler S, Volz T. Regulation of T cell immunity in atopic dermatitis by microbes: the yin and yang of cutaneous inflammation. *Front Immunol*. 2015;6:353.
76. Simon D, Wittwer J, Kostylina G, Buettiker U, Simon HU, Yawalkar N. Alefacept (lymphocyte function-associated molecule 3/IgG fusion protein) treatment for atopic eczema. *J Allergy Clin Immunol*. 2008;122:423–424.
77. Harper EG, Simpson EL, Takiguchi RH, et al. Efalizumab therapy for atopic dermatitis causes marked increases in circulating effector memory CD4+ T cells that express cutaneous lymphocyte antigen. *J Invest Dermatol*. 2008;128:1173–1181.
78. Hijnen DJ, ten Berge O, Timmer-de Mik L, Bruijnzeel-Koomen CA, de Bruin-Weller MS. Efficacy and safety of long-term treatment with cyclosporin A for atopic dermatitis. *J Eur Acad Dermatol Venereol*. 2007;21:85–89.
79. Simpson EL, Bieber T, Guttman-Yassky E, et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. *N Engl J Med*. 2016;375:2335–2348.
80. Sanyal RD, Pavel AB, Glickman J, et al. Atopic dermatitis in African American patients is TH2/TH22-skewed with TH1/TH17 attenuation [published online September 14, 2018]. *Ann Allergy Asthma Immunol*. <https://doi.org/10.1016/j.anai.2018.08.024>.
81. Wen HC, Czarnowicki T, Noda S, et al. Serum from Asian patients with atopic dermatitis is characterized by TH2/TH22 activation, which is highly correlated with nonlesional skin measures. *J Allergy Clin Immunol*. 2018;142:324–328.e11.
82. Chan TC, Sanyal RD, Pavel AB, et al. Atopic dermatitis in Chinese patients shows TH2/TH17 skewing with psoriasiform features. *J Allergy Clin Immunol*. 2018;142:1013–1017.
83. Esaki H, Brunner PM, Renert-Yuval Y, et al. Early-onset pediatric atopic dermatitis is TH2 but also TH17 polarized in skin. *J Allergy Clin Immunol*. 2016;138:1639–1651.
84. Gittler JK, Shemer A, Suarez-Farinas M, et al. Progressive activation of T(H)2/T(H)22 cytokines and selective epidermal proteins characterizes acute and chronic atopic dermatitis. *J Allergy Clin Immunol*. 2012;130:1344–1354.
85. Grundbacher FJ, Massie FS. Levels of immunoglobulin G, M, A, and E at various ages in allergic and nonallergic black and white individuals. *J Allergy Clin Immunol*. 1985;75:651–658.
86. Haus M, Heese HD, Weinberg EG, Potter PC, Hall JM, Malherbe D. The influence of ethnicity, an atopic family history, and maternal ascariasis on cord blood serum IgE concentrations. *J Allergy Clin Immunol*. 1988;82:179–189.
87. Vergara C, Murray T, Rafaels N, et al. African ancestry is a risk factor for asthma and high total IgE levels in African admixed populations. *Genet Epidemiol*. 2013;37:393–401.
88. Brunner PM, Pavel AB, Khattri S, et al. Baseline IL-22 expression in patients with atopic dermatitis stratifies tissue responses to fezakinumab [published online April 17, 2018]. *J Allergy Clin Immunol*. <https://doi.org/10.1016/j.jaci.2018.07.028>.
89. Guttman-Yassky E, Brunner PM, Neumann AU, et al. Efficacy and safety of fezakinumab (an IL-22 monoclonal antibody) in adults with moderate-to-severe atopic dermatitis inadequately controlled by conventional treatments: a randomized, double-blind, phase 2a trial. *J Am Acad Dermatol*. 2018;78:872–881.e6.
90. Howell MD, Fitzsimons C, Smith PA. JAK/STAT inhibitors and other small molecule cytokine antagonists for the treatment of allergic disease. *Ann Allergy Asthma Immunol*. 2018;120:367–375.