

Endophenotypic Variations of Atopic Dermatitis by Age, Race, and Ethnicity



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Learning objectives:

1. To identify the epidemiologic differences of atopic dermatitis (AD) based on age and race/ethnicity.
2. To understand the different clinical and molecular characteristics of AD endo-phenotypes.
3. To distinguish the immune profile and genetic and barrier variations of AD in different age groups and race/ethnicities.
4. To review several current endotype-based targeted therapeutics in the pipeline for AD.

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Atopic dermatitis (AD) is a heterogeneous disease with unique clinical manifestations across age groups and race/ethnicities. Characteristic molecular mechanisms, known as endotypes, including IgE level, status of epidermal barrier genes, and

differential cytokine axes activation in the background of T_H2 upregulation, are also implicated. In adults, the T_H22, T_H17, and T_H1 pathways are involved, and a weakened epidermal barrier is characteristic. In contrast, pediatric patients exhibit

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Abbreviations used

AD- Atopic dermatitis
FLG- Filaggrin
K16- Keratin 16
LOR- Loricrin
mRNA- Messenger RNA
SCORAD- SCORing atopic dermatitis
TSLP- Thymic stromal lymphopoietin

less T_H1 activation, and defects in epidermal lipid metabolism contribute to their barrier defect. European American patients are characterized by higher differential T_H2/T_H22 activation, lower expression of the T_H1/T_H17 axes, and suppression of filaggrin (FLG) and loricrin gene expressions. Asian patients have accentuated polarity of the T_H22/T_H17 pathways, and also exhibit epidermal barrier defects despite relative maintenance of FLG and loricrin expression. African American patients do not exhibit FLG mutations and have distinct attenuation of T_H17/T_H1 axes activation. Dissecting the molecular basis of AD endotypes has provided an important framework upon which targeted therapeutics are being developed. An increased understanding of these subtypes and the alteration of biomarkers that correlate with disease can ultimately push AD treatment in an era of personalized medicine. © 2020 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;8:1840-52)

Key words: Atopic dermatitis; Phenotypes; Endotypes; Ethnicity; Race; Age; Genetics; Dupilumab; Precision medicine

INTRODUCTION

Atopic dermatitis (AD) is the most common chronic inflammatory skin disease.¹ It is increasingly recognized as a systemic condition, largely because of blood and skin transcriptomic,²⁻⁵ proteomic,⁶⁻⁸ and flow cytometry⁹⁻¹² studies. Research in recent years has dramatically improved our understanding of its complex pathophysiology and heterogeneity. Variations in phenotypes can be explained by differences in age, chronicity of disease, ethnicity, race, and genetic background, and are driven by their unique underlying pathomechanisms, or endotypes. Many endophenotypes have been described, including intrinsic versus extrinsic, pediatric versus adult, younger versus older adult, and European American versus African American and Asian AD.¹³⁻²¹

Dermatologic treatment of AD is moving toward an era of personalized medicine. Dupilumab is the first Food and Drug Administration–approved biologic for moderate to severe AD²² and its success has affirmed the pathogenesis of AD to be T-cell–driven, specifically validating the T_H2 antagonism approach. However, complete clinical clearance is achieved in only about one-third of the patients,²²⁻²⁴ because of the heterogeneous nature of the disease. T_H2 activation is an underlying theme in all patients with AD, yet differential $T_H17/T_H22/T_H1$ pathway activation perhaps defines specific AD age-related and race/ethnicity-related endotypes. This review will discuss the clinical, epidemiological, molecular, and genetic mechanisms that characterize different AD endophenotypes that have

emerged across the ages and race/ethnicities. A more precise classification of the clinical phenotypes coupled with a stronger grasp of the biomarkers that correlate with endotypes will pave the way for development of new endotype-driven disease treatment and prevention.

ENDOTYPES OF AD EVOLVE WITH AGE

Overview

AD most commonly burdens the pediatric population, with a lifetime prevalence of up to 2% to 10% among adults and 15% to 30% among children.^{25,26} Symptoms of early-onset AD may improve during adolescence, yet up to one-third of cases can persist into adulthood.²⁷ In a study, the natural course of AD was divided into subtypes by age of onset (Figure 1, A).²¹ Within each subtype, the AD course was additionally characterized, thus further illustrating the heterogeneity of this disease (Figure 1, D).²¹ Moreover, adult-onset AD is an increasingly recognized entity,²⁸ and in a study of elderly Japanese adults with AD (≥ 60 years), two-thirds of the cases began after the age of 60 years.²⁹

Manifestations of AD evolve with age. Lesions in pediatric patients exhibit an extensor predilection, whereas in adults they tend to occur in the skin folds of the elbows and knees. In elderly patients, a “reverse sign” of lichenified eczema occurs.³⁰ The distinct clinical patterns of AD seen in different age groups suggest that different endotypes drive disease manifestations. An overview of the heterogeneity by age is depicted in Figure 1. Tables I and II provide a summary of the barrier and immune genes involved in AD.

AD in children

Clinical manifestations and epidemiology of AD in children. In infantile AD (<2 years), lesions often emerge in the first few months of life, affecting the cheeks with pruritic papules and papulovesicles that form oozing plaques with crust.³¹ In addition, the scalp, neck, extensors, and trunk are implicated.^{1,32} After 1 to 2 years, lesions can still be acute; however, lichenified, chronic lesions begin to predominate with a predilection for the flexural areas.³² In addition, nummular plaques with oozing and crust on the hands and wrists can appear.³¹ One meta-analysis highlighted the differences between child-onset and adult-onset AD.²⁸ Increased facial dermatitis, conjunctivitis or eyelid dermatitis, cheilitis, pruritis after sweating, xeroderma/xerosis, hand and foot dermatitis, nipple dermatitis, and Dennie-Morgan lines were seen in children with AD.²⁸

Overall, 85% of AD cases begin before the age of 5 years.^{33,34} In industrialized countries, more than 20% of children have AD.³⁵⁻³⁹ In the United States in 2003, AD prevalence in children younger than 4 years was 13.92% of the total cases.⁴⁰ The prevalence of AD in other countries varies considerably. In Europe and Central America, the prevalence of AD in 1-year-old infants ranges from 10.6% (Spain) to 28.2% (Honduras).⁴¹ Prevalence of childhood AD ranges from 0.9% in India to 22.5% in Ecuador (age 6-7 years) and from 0.2% in China to 24.6% in Columbia (age 13-14 years).^{25,38,42}

Pediatric endotype. Because most AD cases manifest before the age of 5 years,^{33,34} the immune system in early life likely imparts susceptibility.⁴³ Indeed, the transition of naive T cells, present at birth, into memory subsets is accelerated in children with AD.⁴⁴ In addition, cord blood of neonates with AD skew

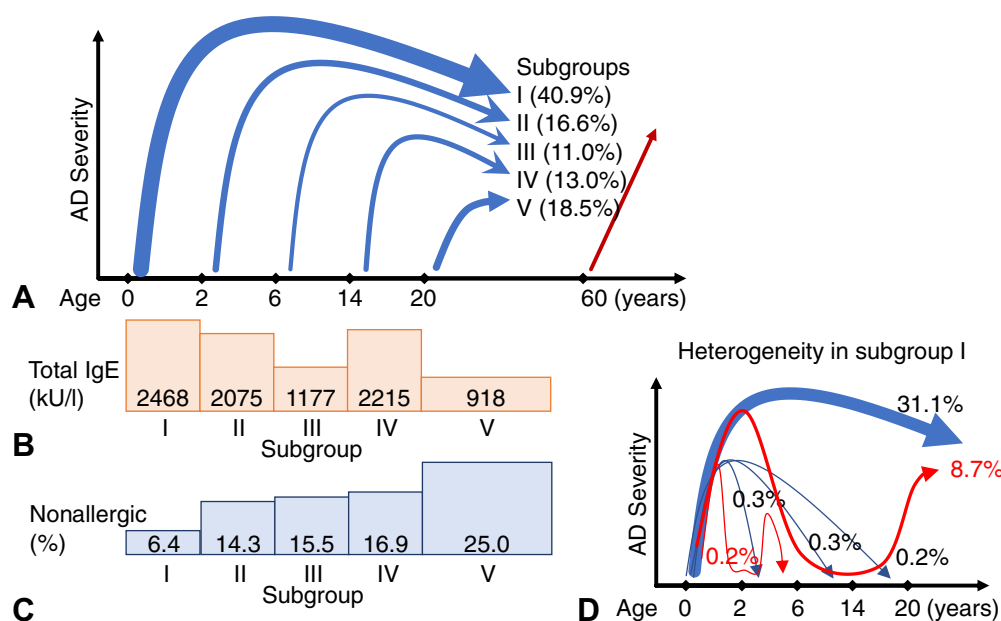


FIGURE 1. Heterogeneity and natural history of AD by age. **(A)** AD phenotypes can be stratified by age of onset. Data are based on the study by Garmhausen et al,²¹ in which a detailed clinical examination and retrospective evaluation of 607 adolescent and adult patients was performed. The natural course of AD was divided into subgroups I to V (blue arrows) on the basis of age of onset. The thickness of the blue arrows corresponds to the proportion of patients in each subset. Separately, Tanei²⁹ analyzed 60 Japanese patients with AD (41 males and 19 females [>60 years]; mean age, 77 ± 8.6 years) and found that in 40 of the patients, the age of onset was more than 60 years (red arrow). **(B)** Mean concentration of total serum IgE varies in subgroups I to V. **(C)** The proportion of the nonallergic variant of AD (defined by low serum IgE [<150 kU/l]) was the greatest in subgroup V. **(D)** An illustration of the heterogeneity in subgroup I (age of AD onset between 3 months and 2 years). Some patients have chronic persisting AD through adulthood (31.1%), others go into remission with recurrence later in life (8.7%), whereas still others experience resolution before the age of 20 years (remaining percentages). Similar heterogeneity exists in other subgroups.

toward T_H2 (IL-4) but not T_H1 (IFN- γ) cytokine production, indicating a role for the intrauterine environment in AD development.^{45–47} This immune profile may also be further induced by epigenetic factors, suggesting an environmental factor on AD susceptibility.⁴⁸ Studies of the cytokine profile in blood of infants and toddlers with AD also reflect T_H2 skewing with low or unaltered T_H1 signals.^{9,44,46,49,50} In addition, flow cytometry in blood shows suppressed and delayed skin-homing T_H1 development in children with AD compared with controls or adults with AD, whereas T_H2 frequencies in skin and systemic compartments were similarly increased in adults and children with AD.⁴⁴ However, IL-22, IL-9, and IL-17 frequencies in $CD4^+/CD8^+$ T cells were lower in children with and without AD, compared with adults.⁹ Differences regarding IL-22 may be linked to chronicity of disease,⁴⁴ and reduced counter-regulation by T_H1 cells can contribute to excess T_H2 activation in children.⁹

Recent data from blood sampling corroborated and expanded on these findings. Czarnowicki et al¹² found that unique endotypes exist for infants and toddlers (0–5 years), young children (6–11 years), and adolescents (12–17 years), when compared with adults with AD (>18 years) (Figure 2). CLA^+ (skin-homing) T_H2 cells were similarly increased in all age groups with AD, whereas CLA^- (systemic) T_H2 subsets were significantly higher in AD beginning in childhood, suggesting systemic T_H2 activation with greater chronicity. CLA^+ T_H1 cells, significantly lower in infants with AD versus all older age groups, increased

with age in patients with AD as well as controls. CLA^+ T_H17 frequencies were seen across all ages regardless of disease presence, whereas CLA^- T_H17 cells, which are relatively low in infants with and without AD, mature with time. Finally, IL-22 frequencies increased from normal levels in infants with AD to significantly higher levels in adolescents and adults with AD.¹² Notably, when comparing age-matched controls with their AD counterparts, the lack of clear clustering in controls implicates AD as the key driver of these distinct and progressive immunophenotypic changes. Thus, the data reinforce the highly varied endotypic repertoire of AD. Given the differential T_H2 activation in early-onset pediatric blood, alterations in B-cell subsets and IgE allergen sensitization to food and environmental agents are also increased with age in children with AD,¹⁰ highlighting the role of IgE and barrier integrity in early disease initiation.

Profiling of early-onset pediatric AD skin (disease duration <6 months) demonstrates profound differences when compared with adults with AD. Although T_H2 (IL-13, IL-31, CCL17) and T_H22 (IL-22 and S100A proteins) activation is as robust as in adult AD skin, measures of epidermal hyperplasia (thickness and keratin 16 [K16]) and cellular infiltrates ($CD3^+$, $CD11c^+$, $Fc\epsilon R1^+$) are comparable with or greater than those in adults with AD.⁴ Children with AD also have higher induction of T_H17 -related cytokines (IL-17A, IL-19, CCL20, LL37, PI3), T_H9 /IL-9, and antimicrobial peptides.⁴ Other studies have corroborated these results.^{4,51,52} Nonlesional, early-onset pediatric AD skin also consistently exhibits immune

TABLE 1. Dysregulated cytokines involved in AD

Cytokine	Main producers	Main targets	Function
IL-4	T _H 2 cells, mast cells	T _H 2 cells	Activation
		B cells	IgE class switch
		Nerve	Itch
		Keratinocytes	Downregulation of FLG expression
IL-13	T _H 2 cells, ILC2s	T _H 2	Activation
		Nerve	Itch
		Keratinocytes	Proliferation, downregulation of FLG expression
IL-31	T _H 2 cells	Nerve	Itch
IL-33	Keratinocytes	ILC2	Activation
		T _H 2 cells	Activation
IL-22	T _H 22 cells, T _H 17 cells	Keratinocytes	Proliferation
IL-17A	T _H 17 cells	Keratinocytes	Proliferation, induction of antimicrobial peptides
IFN- γ	T _H 1 cells	Keratinocytes	Apoptosis

ILC2s, Group 2 innate lymphoid cells.

abnormalities.^{4,51,52} Although T_H1 and regulatory responses were lower, increased T_H17/T_H22-associated mediators were seen when compared with adult disease.^{4,51} In addition, strong correlations between T_H2-associated (IL-4, IL-5, OX40L, thymic stromal lymphopoietin [TSLP] receptor) and T_H17-associated (IL-19, PI3) markers with clinical severity scores (eg, SCORing atopic dermatitis [SCORAD] and eczema area and severity index) were identified.⁴ Data from tape strips in nonlesional skin of early-onset pediatric AD also found T_H2 (IL-33, IL-4R, CCR4, CCL18) and T_H17/T_H22 (IL-23p19, IL-36G, DEFB4B, PI3, S100As) markers to be strongly correlated with AD severity scores (eg, SCORAD, eczema area and severity index, pruritis atopic dermatitis quickscore, and transepidermal water loss assessments).⁵² In addition, profiling of tape strips from children with food allergy showed differences compared with those without food allergy, perhaps indicative of the presence of additional endotypes based on allergic comorbidities.⁵³ The pediatric AD transcriptome also exhibits remarkable similarities with adult psoriasis and conversely diverges from that of healthy controls and adult AD.⁴ Taken together, these data suggest that new-onset pediatric AD and long-standing adult AD represent distinct endophenotypes.

In addition, studies have shown that filaggrin (FLG) protein and messenger RNA (mRNA) expression in the skin appear to be relatively intact in early-onset (<6 months) pediatric AD.^{4,51} In fact, in children with AD, FLG expression is similar to that in healthy controls. Instead, tight junctions and lipid barrier genes have been found to be downregulated in children with AD,^{4,51,52} possibly accounting for the compromised epidermal barrier function seen in pediatric patients with AD with preserved FLG and loricrin (LOR) levels.

AD in adults

Clinical characteristics and epidemiology. Lichenified, chronic, and dry lesions become fixed on the head, neck, and flexural surfaces in adults with AD.¹ In elderly patients, a reverse sign of lichenification—lower incidence of lichenified eczema at the elbow and knee folds—has been described.³⁰

In the United States, the 2010 and 2012 National Health Interview Survey found the 1-year prevalence of AD in adults (18–85 years) to be 10.2% and 7.2%, respectively.^{42,54–56} Internationally, studies report a prevalence ranging from 2.0%

to 17.6%.^{56–62} In adults older than 60 years, the prevalence of AD is 1% to 3% of the elderly population, with a male predominance.³⁰

Adult endotype. In adult AD, immune fingerprinting in skin has implicated the T_H2, T_H22, and T_H17/IL-23 pathways.^{13,14,18} AD endotyping by 3 age groups (18–40 years, 41–60 years, and >61 years) suggests that unique subtypes exist for younger versus older adults. Zhou et al¹⁹ described decreasing T_H2/T_H22 activation (IL-5, IL-13, CCL13, CCL18, and CCL26; IL-22) and increasing T_H1/T_H17 activation (IFN- γ , IL-12/23p40, STAT1, and CXCL2; IL-17A and IL-20) in parallel with increasing age. Adult patients with AD also exhibited normalization of epithelial abnormalities with increasing age: expression of terminal differentiation markers LOR, FLG, and S100As increased in older patients with AD, whereas measures of hyperplasia (thickness, K16, and Ki67) decreased.¹⁹ Serum trends in AD mimicked skin findings, with T_H2 downregulation (CCL26) and T_H1 upregulation (IFN- γ) with age.¹⁹ Biomarkers for disease severity (SCORAD) differed on the basis of age group as well. In the age group of 18 to 40 years, the T_H2, T_H17, and T_H1 axes correlated well with SCORAD, whereas markers of T_H17 become more dominant with age.¹⁹ Indeed, these data provide support for an “elderly” AD phenotype (>60 years), which has been proposed.^{29,30} Another study involving proteomic analyses in blood samples, using the same age group classifications, further complemented these results.²⁰ Although only a few key T_H2 chemokines (CCL13 and CCL17) were significantly upregulated in patients with AD compared with controls regardless of age, most inflammatory markers showed significant increases in the oldest patients compared with their controls and other age groups.²⁰ Similar to the skin findings, T_H1 and T_H17 pathways were significantly elevated in the oldest patients compared with their age-matched controls and other AD subsets.²⁰ Specifically, T_H1 measures (CXCL10) and T_H17/IL-17–related markers (KYNU, CCL20) uptrended with age.^{19,20} Notably, markers of cardiovascular risk and atherosclerosis were elevated in the oldest age group (>60 years) compared with younger patients and their respective controls, demonstrating high systemic inflammation in these patients who lack cardiovascular comorbidities otherwise.²⁰

TABLE II. Dysregulated barrier proteins involved in AD and other associated diseases

Protein	Function	Deficiency
FLG	Multifaceted; aggregation of keratin; maintains integrity of the epidermis as a natural moisturizing factor that preserves the acidic pH of the skin through degradation to histidine and urocanic acid	Ichthyosis vulgaris
LOR	A glycine-rich cornified envelope protein regulating normal keratinization of keratinocytes	Camisa variant of Vohwinkel syndrome (palmoplantar keratoderma with ichthyosis)
Periplakin	Cornified envelope protein	Not known

Adult-onset AD

Clinical characteristics and epidemiology. Adult-onset AD is an increasingly recognized entity.^{28,55,63} Clinically, this phenotype has a higher probability of affecting the extensors, head/neck, and hands and feet.^{28,55,64,65} In addition, atypical morphologies have been described.²⁸ Thus, it is important to rule out other cutaneous diseases in the setting of suspected adult-onset AD (Table III). In a recent meta-analysis, it was found that approximately 25% of adults with AD have adult-onset disease.^{28,63} To our knowledge, the immune mechanisms of adult-onset AD are yet to be identified.

VARIATION OF AD BY RACE AND ETHNICITY

Overview

That AD is a heterogeneous disease is further supported by the clinical, molecular, and genetic differences associated with different racial/ethnic groups. Healthy skin of individuals of European, African, and Asian descent also has differential gene expression patterns at baseline, which likely influence the inflammatory circuits of AD in each phenotype.⁶⁶ European American, African American, and Asian AD phenotypes exhibit common T_H2 activation; however, additional T-helper axes have been described in these subgroups (Figure 3).¹⁴⁻¹⁷ The clinical variability further supports the endophenotypic stratification approach by race/ethnicity.

Differences in clinical phenotype and epidemiology

In European Americans, acute AD lesions are characteristically wet and erythematous, turning lichenified, dry, and hyperpigmented in patients with chronic disease.^{1,26,27} AD in other races/ethnicities displays distinct variations. AD in Asians is clinically more demarcated than in European Americans, with increased scale and lichenification.^{14,67} In skin of color, erythema often appears more hyperpigmented and violaceous.⁶⁸ AD lesions are also more likely to exhibit extensor involvement and develop lichenification and prurigo nodularis, likely because of their greater itch.⁶⁹⁻⁷¹ Finally, AD clinical scores are less reliable in darker skin tones because of the masking of erythematous changes in skin of color that are required for accurate score assessment.

In the United States, the range of prevalence of AD in European Americans is reported to be 6.7% to 10.5%.^{40,72,73} High prevalence of AD has been reported in the Asian population as well. In the Asia Pacific region, 17.8% of children aged 6 to 7 years have been diagnosed with AD, and the prevalence ranges from 4% to 30% in other countries.²⁵ Population-based studies in the United States have identified the Asian/Pacific Islander prevalence of AD to be 9.1% to 9.7%.^{72,73} Moreover, in the United States, Asians and Pacific Islanders are 7 times more likely than whites to be diagnosed with AD at an office visit.⁷⁴ In

Africa, the prevalence of AD ranges from 4.7% to 23.0%.⁷⁵ In the United States, the prevalence in African Americans has been reported to be between 7.7% and 15.89%.^{40,72,73} In the pediatric population, African Americans are 1.7 times more likely to develop AD compared with European Americans.⁷¹ Indeed, a 2005 to 2006 National Health and Nutrition Examination Survey found the prevalence of AD in African American children (aged 1-17 years) to be 19.3% compared with 16.1% in their European American counterparts.⁷⁶ Individuals of Hispanic origin in the United States have a lower prevalence of AD (6%) compared with those of non-Hispanic origin (10.8%).⁷³ In a global study, it was found that in Latin America, the mean prevalence of flexural eczema in children aged 6 to 7 years was 11.3%, and for adolescents it was 10.6%.⁷⁷

Different races/ethnicities present with unique endotypes

European Americans. The European American AD phenotype has been the most extensively studied.^{11,13,78-80} AD is considered to be a T_H2-centered disease with a T_H22 component.^{81,82} Variations in acute versus chronic disease and intrinsic versus extrinsic disease have been described.

Intrapersonal skin profiling of acute and chronic lesions demonstrate marked differences between the 2 subtypes.¹⁸ Acute lesions show a striking increase in terminal differentiation proteins (S100As) and T_H2/T_H22-defining cytokines (IL-4, IL-13, IL-31, IL-22).¹⁸ In parallel, a lesser induction of the T_H1 axis (IFN- γ , MX1, IL-1 β , CXCL9/10/11) is detected in acute disease. Chronic lesions are even more proliferative and hyperplastic, marked by elevated K16 expression and Ki67 counts, as well as an intensification of immune activation.¹⁸ For example, strengthening of T_H2-related inflammation was paralleled by an increase in T_H1 products.¹⁸ Increases in IL-22 mRNA and its associated products (S100As, IL-32) were also detected. T_H17 induction, in contrast, was attenuated in both acute and chronic lesions.¹⁸

Intrinsic and extrinsic phenotypes have also been described in European American patients. The extrinsic phenotype accounts for 80% of AD and is characterized by a high total and environmental serum IgE, eosinophilia, family history of atopic disease, and a greater rate of FLG mutation.^{13,83,84} The intrinsic phenotype (20%) exhibits normal IgE levels, a female predominance, preserved barrier function on the basis of transepidermal water loss, and increased contact hypersensitivity to metal; however, these patients usually lack an atopic background.^{33,83,85} Studies of the immune phenotype in intrinsic and extrinsic AD skin clarify the similarities and differences.¹³ T_H2 induction was grossly similar between the 2 endotypes. However, increases in T_H1 (IFN- γ , CXCL9/10, MX1) and T_H17/T_H22 (IL-17A, CCL20, PI3, IL-22) products were more prominent in intrinsic

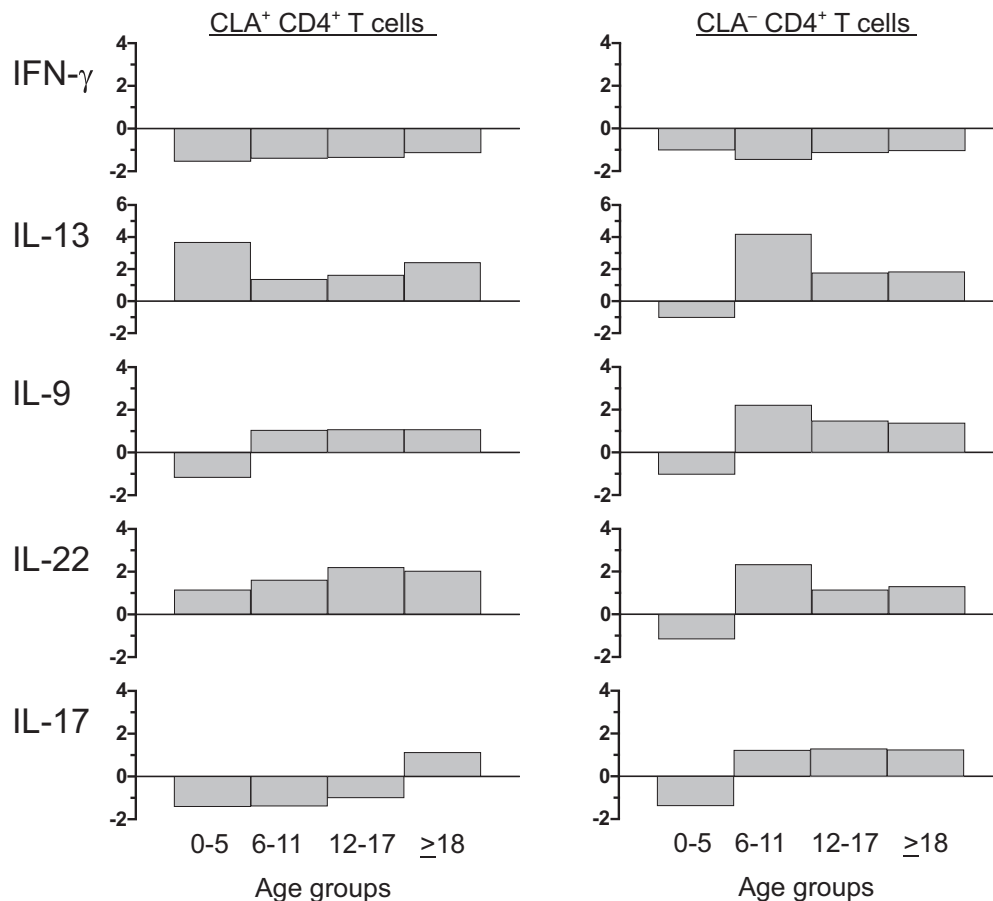


FIGURE 2. AD cytokine polarization of CLA⁺CD4⁺ and CLA⁻CD4⁺ T-cell subsets in blood. Graphical depiction of cytokine polarization of CLA⁺CD4⁺ and CLA⁻CD4⁺ T-cell subsets in AD. Data are based on a study by Czarnowski et al.¹² Horizontal axes represent different age groups, vertical axes depict fold changes of the polarized CLA⁺CD4⁺ and CLA⁻CD4⁺ T-cell subsets in peripheral blood in AD vs age-matched controls among different age groups.

AD.¹³ Consistently, S100A9/12, which are regulated by IL-17 and IL-22,⁸⁶ were increased in parallel in intrinsic AD lesions compared with extrinsic AD lesions.¹³ T_H1- and T_H17-related cytokines positively correlated with SCORAD in intrinsic AD, whereas extrinsic AD exhibited positive correlations only with T_H2 cytokines (IL-4 and IL-5). Correspondingly, in blood, IFN-γ-producing T_H1 cells were found to be significantly higher in the IgE-low AD group.⁸⁷

Asians versus European Americans. Studies in the Asian population have demonstrated an expansion of IL-17⁺ T cells in the skin and blood, suggesting that the Asian AD phenotype may exhibit distinct immune and barrier features compared with the European American AD phenotype.⁸⁸ Indeed, in contrast to other racial/ethnic populations, the skin and blood data from European American patients with extrinsic AD do not show T_H17 axis activation.^{11,13,89} Genomic profiling studies have found that the Asian immunophenotype resembles a blend of the immune dysregulation and barrier features seen in European American patients and psoriasis.^{14,16} In a study of AD in Japanese and Korean subjects from Asia, AD skin was characterized by changes in epidermal thickness reminiscent of the

psoriasiform phenotype: increased epidermal hyperplasia (as measured by thickness and Ki67 counts), more frequent parakeratosis, and focal hypogranulosis.¹⁴ Yet, the barrier protein expression (LOR and FLG) was relatively preserved as compared with European American patients with AD, possibly suggestive of more severe epidermal differentiation abnormalities in European American AD. Notably stronger induction of the T_H17 (IL-17A, IL-19, CCL20), T_H17/T_H22 (S100A12), and T_H22 (IL-22) markers and lower T_H1 activation characterized the Asian AD endotype, as compared with European American AD.¹⁴ However, T_H2 induction (IL-13, CCL17, CCL18, CCL22) was similar between the groups.¹⁴ In the serum, a T_H2/T_H17 profile with lower T_H1/IFN-γ expression mirrored the pattern found in skin.^{14,15}

Another study assessed the cutaneous immune dysregulation in Han Chinese patients with AD.¹⁶ Similar to Japanese and Korean AD, remarkable increases in epidermal hyperplasia, parakeratosis, T_H2 (IL-4, IL-4R, IL-13, IL-5, IL-10, IL-31, CCL13/17/18/22/26), T_H17/IL-23 (IL-17F, IL-19, IL-21, CCL20, PI3, DEFB4), and T_H17/T_H22-induced (IL-22, S100As) markers were demonstrated.¹⁶ SCORAD scores were also found to be well correlated with IL-31, IL-5, and IL-17A

TABLE III. Differential diagnoses of adult-onset and pediatric AD

Allergic contact dermatitis
Autoimmune blistering diseases (eg, dermatitis herpetiformis, bullous pemphigoid, and pemphigus vulgaris)
Cutaneous lupus
Cutaneous T-cell lymphoma (eg, mycosis fungoides and Sézary syndrome)
Dermatomyositis
Drug eruption
Immunodeficiency syndromes (eg, Wiskott-Aldrich syndrome and hyper-IgE syndrome)
Langerhans cell histiocytosis
Molluscum dermatitis
Nummular dermatitis
Paraneoplastic dermatitis (eg, non-Hodgkin lymphoma)
Psoriasis
Scabies
Seborrheic dermatitis
Skin infections (eg, dermatophyte infection and impetigo)
Transient acantholytic dermatosis
Vasculitides (eg, Churg-Strauss syndrome)
Zinc deficiency

expressions.¹⁶ Compared with the European American AD immunophenotype, the Chinese AD phenotype was characterized by increased T_H17 expression and lower $T_H1/IFN-\gamma$ -related marker expression.¹⁶

These data from 3 different Asian populations establish a consistent T_H17/T_H2 or blended AD-psoriasis endotype across Asian patients with AD. Future studies are needed to determine whether this phenotype is preserved in Asian Americans with AD, or whether environmental and microbiome differences manifest as a change in their AD immune profile.

African Americans versus European Americans. Global molecular profiling data in African American AD compared with European American AD also demonstrated distinct phenotypic variations between the 2 groups.¹⁷ Although they share a similar magnitude of T_H2/T_H22 upregulation (CCL17/18/26, IL-22, S100As), a few T_H2 markers were exclusively upregulated in African American AD (TSLP, IL-10, CCL13).¹⁷ In contrast to European American patients with AD, African American patients with AD have decreased expression of markers of innate immunity (TNF, IL-1 β) and T_H1 -related (IFN γ , MX1, IL-12R β 1) and T_H17 -related (IL-23p19/IL-23A, IL-36 γ , CXCL1) products.¹⁷ The increased T_H2 skewing in African Americans is also reflected by greater infiltration of the high-affinity IgE receptor (FC ϵ R1⁺) compared with European American AD, corresponding to the higher serum IgE in the African American cohort. Furthermore, there was a significant correlation between serum IgE and SCORAD found in the African American AD group but not in the European American AD group. These data are consistent with the previous observation that individuals with African ancestry exhibit higher serum IgE.⁹⁰⁻⁹² FLG was found to be exclusively downregulated in European American AD; however, LOR was downregulated in both cohorts.¹⁷

GENETIC VARIATIONS

AD pathogenesis is driven by a combination of immune dysregulation and epidermal barrier dysfunction.^{78,79,93} FLG is a key component of the epidermal differentiation complex, which is a cluster of more than 70 genes on chromosome 1q21 encoding for terminal differentiation proteins involved in the formation of the cornified envelope.⁹⁴ It is also a major protein of the stratum corneum.^{93,95} Null mutations of the FLG gene have been established and widely replicated as a risk factor for AD in adults,⁹⁵⁻⁹⁷ with an overall odds ratio of 3.12 to 4.78.^{96,98} Yet, FLG deficiency is found only in 10% to 40% of patients with AD.^{97,99-101} Furthermore, fewer than half of FLG heterozygotes develop AD (42%), and most will outgrow their disease.^{95,102}

FLG mutation status varies widely by race/ethnicity. Fifty percent of Europeans and 27% of Asians have loss-of-function mutations.¹⁰³⁻¹⁰⁷ The most frequent mutations found in 7% to 10% of populations with European ancestry^{96,105} are usually absent in individuals of Asian ancestry, who exhibit other unique FLG null mutations.^{107,108} FLG mutations are also 6 times less common in African Americans compared with European Americans,¹⁰⁹ and a US study detected FLG mutations in only 5.8% of children with AD.¹⁰⁹ Moreover, these mutations are rare in the South African and Ethiopian populations.^{100,109,110} Instead, variations in FLG2, another protein whose mutation is associated with barrier disruption, is linked with AD in African Americans.^{99,111} Indeed, studies have shown that FLG2 was significantly downregulated in both European American and African American AD, whereas FLG was downregulated only in European American AD.¹⁷ Furthermore, previous studies have not demonstrated a link with AD and FLG2 mutations in Europeans.^{112,113} Polymorphisms in additional barrier genes have been identified for specific racial/ethnic subgroups, including variants in CLDN1 (associated with early-onset AD in Ethiopians)¹¹⁴ and mutations in SPINK5 (associated with AD in Asians).¹¹⁵⁻¹¹⁸

Adult-onset AD also demonstrates distinct genetic associations. The 4 most common FLG gene mutations that were identified in early-childhood onset AD (<8 years) are not found in late-childhood onset AD (between 8 and 18 years) or adult-onset AD (>18 years).¹¹⁹ Instead, a polymorphism of CHI3L1, a known mediator of inflammation, was found to be associated with late-onset AD (>8 years).¹²⁰

In young children (<2 years) with AD, significantly higher frequencies of FLG loss-of-function mutations, compared with those who develop the disease after the age of 2 years, have been identified.¹¹⁹ SPINK5 polymorphism (Rs2303067) was also significantly associated with children who develop AD before the age of 8 years.¹²⁰

Beyond FLG mutations, mutations in innate and adaptive immunity genes are associated with AD.⁶⁹ Overall, polymorphisms of mediators of the T_H2 pathway,¹²¹⁻¹²⁶ Toll-like receptors,^{127,128} human β -defensin 1,¹²⁹ TSLP and its receptors, IFN regulatory factor 2, FC ϵ R1a, vitamin D pathway, and the IL-1 family of cytokines and receptors have all been implicated.^{78,130-134} Specifically, association of polymorphisms of T_H2 products IL-4 and IL-13/IL-13R α 1 in Asians has been established.¹³⁵⁻¹³⁸ TSLP variants are also associated with less persistent AD in European American and African American populations, whereas an IFN regulatory factor 2 polymorphism is found to be associated with increased AD risk.^{139,140} In addition,

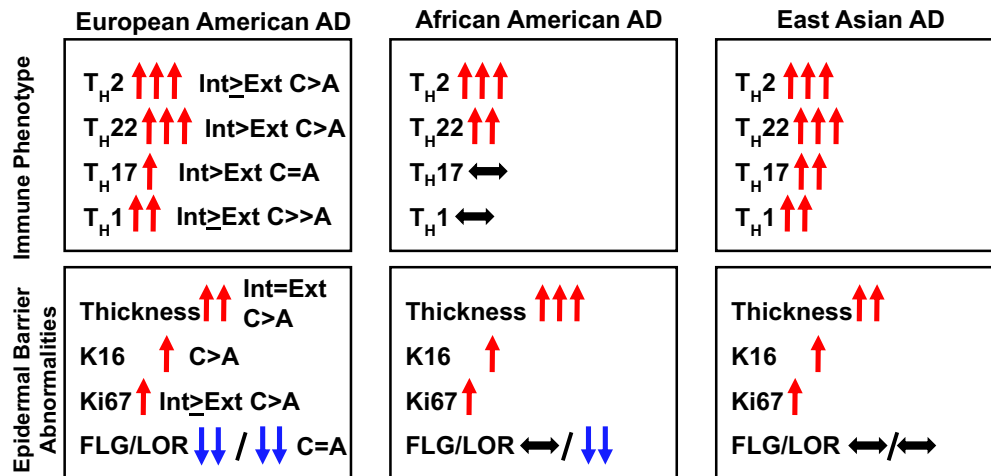


FIGURE 3. Immune and barrier changes of AD by race/ethnicity. Graphical representation and simplification of the corresponding immune and barrier changes in AD lesional skin of European Americans, African Americans, and Asian phenotypes. Red arrows indicate upregulation. Blue arrows indicate downregulation. Horizontal double-headed black arrows represent no change. Greater than (>) or less than (<) symbols are used to depict which endotype exhibits that pattern of up- or downregulation more strongly. A, Acute; C, chronic; Ext, extrinsic; Int, intrinsic.

single-nucleotide polymorphisms of the IL-12 cytokine and its receptor¹⁴¹ and mutations in β -defensin 1 were associated with increased AD risk in Korean populations.^{142,143}

ROLE OF PRECISION MEDICINE IN AD AND EMERGING TARGETED THERAPEUTICS

The therapeutic pipeline for AD is expanding.¹⁴⁴ Dupilumab is the first Food and Drug Administration–approved biologic targeting the shared receptor for IL-4 and IL-13 (IL-4R α 1) for adults with moderate to severe AD; recent data show that dupilumab is also efficacious and safe in the adolescent population,¹⁴⁵ and clinical trials (NCT02407756 and NCT03346434) in additional pediatric populations are ongoing. One post hoc analysis demonstrated similar efficacy signals in European American and Asian patients on dupilumab, whereas statistical significance was not as consistently achieved in the African American subset, albeit numeric trends always favored dupilumab.¹⁴⁶ These clinical improvements are further accompanied by normalization of immune and barrier abnormalities.^{24,147,148} This approach has cemented the notion that AD is a reversible, immune-driven disease. T_H2 antagonism is theoretically effective because it is common to all disease subtypes; however, disease heterogeneity likely accounts for the substantial proportion of patients who do not achieve complete clearance (approximately two-thirds of patients).²³ Numerous other biologics are also in clinical development, including additional T_H2 antagonists^{149–155} (anti-IL-13, anti-IL-31, anti-IL-33, anti-TSLP, anti-IL-40, anti-OSMR β) as well as T_H22 ^{156,157} (anti-IL-22) and T_H17 /IL-23^{158–160} (anti-IL-12/23p40, anti-IL-23A/IL-23p19, anti-IL-17A) targets.^{161–163} Broader agents, such as Janus kinase inhibitors, are also in early- and late-stage clinical development.^{164–168}

Talokinumab and lebrikizumab (anti-IL-13 mAbs), as well as nemolizumab (anti-IL-31R α mAb), are a few examples of additional T_H2 antagonists. Talokinumab was studied with

topical corticosteroids and a recently published study evaluated the efficacy of lebrikizumab as monotherapy.^{149,151} Both demonstrated statistically significant improvements in AD clinical scores compared with placebo. IL-31, a key itch cytokine,^{169,170} is targeted by nemolizumab. Nemolizumab was likewise successful in achieving statistically significant improvements in clinical measures as compared with placebo, although the improvement in itch was more dramatic.¹⁵³ The positive data from these trials continue to reinforce the utility of the T_H2 antagonistic approach in AD treatment.

Although T_H2 activation is a common theme to all patients with AD, the unique endophenotypes provide an important lens through which additional targeted therapeutics have been developed. In addition, targeting other immune axes may address the needs of the two-thirds of patients who do not respond to dupilumab. AD endotypes with significant T_H17 / T_H22 activation, such as patients with intrinsic AD, and pediatric, elderly, and Asian populations, may benefit from therapeutics that target the T_H17 /IL-23 (ustekinumab, risankizumab, secukinumab) or T_H22 /IL-22 (fezakinumab) axes.

Ustekinumab and risankizumab are 2 mAbs currently approved for psoriasis that target the T_H17 axis.^{171,172} Ustekinumab (anti-IL-12/23p40 mAb), however, failed to demonstrate clinical efficacy in two phase-2 studies in AD.^{158,171} Despite these results, transcriptomic-level data found that the treatment resulted in gene expression improvements of general inflammation markers as well as T_H2 products and T_H17 / T_H22 -induced S100A proteins, suggesting that ustekinumab may still harbor therapeutic potential for AD. The subtherapeutic results may in part be explained by suboptimal dosages, 45 and 90 mg, which are the currently approved dosages for psoriasis.^{158,171} Given greater immune activation in AD,¹⁷³ increased dosing may be needed for more efficacious results. Moreover, concomitant topical corticosteroids may have enhanced the placebo response. Risankizumab (an anti-IL-23A/IL-23p19 antibody) is currently in phase 2 development (NCT03706040).

Secukinumab is an anti-IL-17A mAb that has also been trialed in AD. Because of the theoretical advantage of targeting the T_H17 axis in certain endotypes, a recent study (NCT02594098) investigated the results stratified by intrinsic versus extrinsic AD. Preliminary data did not show marked numerical differences in the primary outcome of epidermal hyperplasia change, clinical outcome measures, or translational secondary end points, as measured by mRNA expression of T_H17/IL-23-related products, in either subgroup compared with placebo.¹⁶⁰ The findings suggest that anti-IL-17A monotherapy may not be an effective approach for the treatment of AD, and that increased T_H17 expression may not necessarily be a pathogenic phenomenon but rather a bystander of the larger immune dysregulation. It can also be speculated that without targeting the T_H2 pathway, which has proven to be efficacious by way of dupilumab and other T_H2 targets, successful modulation of AD does not occur.

Fezakinumab is an anti-IL-22 mAb that yielded significant clinical improvements over placebo in a phase 2 study, with the greatest benefits observed in the severe AD subgroup.¹⁵⁷ Fezakinumab also broadly demonstrated improvements in the AD genomic profile versus placebo, and, in fact, molecular improvements were seen only in the fezakinumab-treated patients with high baseline IL-22 expression.^{148,156} Moreover, IL-22 blockade resulted in suppression of numerous cytokine axes, including the T_H1, T_H2, T_H17, and T_H22 pathways. The positive data suggest that there may be additional value in investigating IL-22 antagonism in other endotypes, namely those with a blended T_H17/T_H22 phenotype (pediatric, Asian, intrinsic AD), as well as the African American AD population, which is characterized by only T_H22 upregulation.

CONCLUSIONS

AD inflicts a substantial socioeconomic burden,^{174,175} in part due to the lack of effective therapeutics that are safe for long-term use. However, recent pathogenic discoveries are beginning to narrow this gap. Genetic, immunologic, and barrier factors drive variations in endotypes that ultimately orchestrate the different phenotypes. Although T_H2 axis activation is universal across different ages and race/ethnicities, variations in their immunologic activation pathways dictate the disease manifestations. The relative contributions of each cytokine axis in driving the different endophenotypes are still being investigated, and the clinical fruits of this approach are only beginning to be uncovered. Future clinical trials may stratify each patient's endotype before treatment, which can continue to optimize therapeutic response. Moreover, a recent study compared the molecular efficacy of various broad and specific AD treatments,¹⁴⁸ and a similar analysis stratifying patients by age and race/ethnicity may be possible. Ultimately, bringing patients medicines on the basis of their unique clinical and molecular signature may help diminish the side effects and burden associated with a "one-size-fits-all" approach.

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