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CME Review

# Diversity of atopic dermatitis and selection of immune targets

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**Key Messages**

- Atopic dermatitis (AD) is a complex and heterogeneous immune-mediated skin condition, characterized by various phenotypes, each exhibiting distinct molecular variations.
- Despite significant progress in AD treatment options, achieving complete clinical clearance remains a challenge.
- Recent studies have revealed unique AD signatures across age, ethnicity/race, disease chronicity, IgE levels, filaggrin mutation status, and other atopic comorbidities.
- The future of personalized and tailored treatment, based on individual patient molecular profiles, holds significant potential for optimizing management.

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ABSTRACT

Atopic dermatitis (AD) is a heterogeneous immune-mediated skin disorder affecting people of all ages and ethnicities. Despite the development of targeted therapeutics such as biologics and Janus kinase inhibitors, attaining complete clinical efficacy remains difficult. This therapeutic challenge may be attributed to the complex pathogenesis of AD. Although the $T_H2$ axis has been extensively studied, recent advancements have started to reveal the involvement of additional immune pathways including $T_H1$, $T_H17$, and $T_H22$. Understanding the interplay of these immune axes may contribute to a more personalized therapeutic approach based on patients' molecular profile, with the prospect of improving clinical outcome. This review will discuss studies exploring the molecular profile of AD in both skin and blood across age, ethnicity/race, disease chronicity, IgE levels, filaggrin mutation status, and AD association with other atopic conditions. Moreover, it will explore the potential of personalized treatment strategies based on a patient's distinct immune signature.


## Introduction

Atopic dermatitis (AD) is a chronic, immune-mediated skin disorder that affects individuals of various ages and ethnicities.[1-3] It is characterized by dysregulation in the immune system, epidermal barrier, and skin microbiome, influenced by both environmental and genetic factors.[4-7] Although the $T_H2$ pathway and its related cytokines (eg, interleukin [IL]-4, IL-13) have been extensively studied and play a central role in AD, recent research has unveiled other unique immune pathways or endotypes across age, IgE levels, ethnicity/race, filaggrin (FLG) mutation status, and disease chronicity.[8-16]

In-depth exploration of immune axes, including $T_H1$, $T_H2$, $T_H17$, and $T_H22$, along with the integration of objective measures such as skin and blood biomarkers, has provided valuable insights into the pathophysiology of AD.[7,17-19] These biomarkers could reflect the underlying mechanisms involved, aid in monitoring treatment response, and have been crucial in the development of targeted therapies specifically biologics and Janus kinase (JAK) inhibitors.[19,20]

Although these treatments have greatly improved management, they are not without limitations. In contrast to psoriasis, where the

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

- Summarize the molecular profile characterizing diverse atopic dermatitis phenotypes.
- Distinguish which therapeutic demonstrated clinical improvement in patients with high IL-22 levels.

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Physicians involved in providing patient care in the field of allergy/asthma/immunology.

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rates of near complete clearance are reaching 80%, targeted cytokine inhibition for patients with AD has not demonstrated comparable efficacy.[21-23] This disparity could be due to the heterogeneous nature of AD, which encompasses a wide range of phenotypes and endotypes.[16,17,24] Consequently, a personalized approach that matches the patients' characteristics may be necessary to achieve similar therapeutic success.[25]

This review will focus on the molecular profiles associated with these distinct AD phenotypes and will explore the potential of personalized treatment approaches, paving the way for more targeted and effective therapeutic interventions.

## Acute vs Chronic

A common phenotypic classification of AD includes acute (within 72 hours) or chronic lesions. Acute lesions typically present as bright erythematous patches with oozing, whereas chronic lesions are lichenoid and dry,[26] though these archetypes exist more on a gradient. Transcriptomic analysis revealed that acute and chronic lesions exhibited hyperplasia, marked by increased epidermal thickness and expression of proliferative markers K16 and Ki67, with chronic lesions exhibiting a more significant up-regulation.[10] Both acute and chronic AD shared similarities with up-regulation of most immune pathways and markers, including T-cells, dendritic cells (DCs), the S100 genes, and $T_H1$, $T_H2$, and $T_H22$ axes. However, although chronic AD lesions had significantly higher expression levels of these pathways, $T_H17$ activation did not significantly differ between lesions (Fig 1A). When evaluating specific markers within the $T_H2$ pathway, the pivotal IL-4 and its receptor IL-4R were found to have greater expression in acute lesions, although IL-13 increases further in chronic lesions.[10]

A recent study corroborated these findings and further observed that chronic AD, compared with acute AD, had greater expression of inflammatory marker IL-36, $T_H2$ marker TSLP, and potential negative regulator FOXK1, significant dysregulation of genes involved in wound healing and barrier repair/maintenance, and negative regulation of T-cells.[11]

## Intrinsic vs Extrinsic

AD can also present as 2 distinct phenotypes: extrinsic and intrinsic. The identification of IgE played a pivotal role in establishing these 2 phenotypes. The term extrinsic has historically classified AD with elevated total serum IgE levels and specific IgE for environmental and food allergens, whereas intrinsic (nonallergic AD) is defined by normal total IgE values without specific IgE.[12] However, in recent years, extrinsic AD has come to be also characterized by early onset, a family history of atopy, and is more prevalent in men and adults, whereas intrinsic AD features a later onset, the absence of a family history of atopy, and is more prevalent among females and infants.[12,27,28] Mutations in FLG, an epidermal differentiation marker strongly implicated in AD, has been found more prevalent in extrinsic AD compared with intrinsic AD.[12,29]

In patients with moderate-to-severe AD, both groups exhibited T-cell and DC infiltration and epidermal barrier dysregulation.[9] Intrinsic AD had more pronounced overall immune activation than extrinsic AD, revealing heightened $T_H17$ and $T_H22$ pathway activation and greater (or comparable) $T_H2$ and $T_H1$ responses.[9] In mild AD, both had comparable increased expression of epidermal proliferation markers such as KRT16, the general inflammatory marker MMP12, and markers associated with the $T_H2$ (IL-13 and CCL18) or $T_H1$

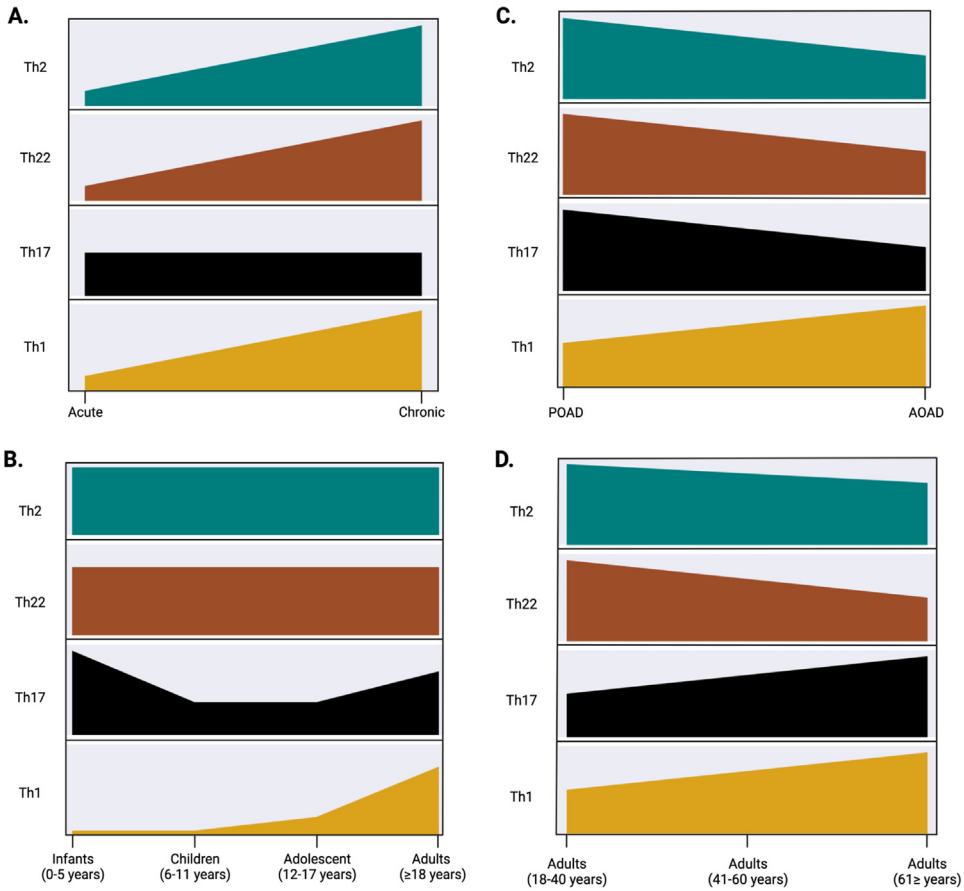


**Figure 1.** T helper activity among atopic dermatitis (AD) phenotypes based on transcriptomic data. A) acute AD vs chronic AD. B) Pediatric Onset AD vs Adult onset AD. C) Changes T helper axes across ages, from infancy to adulthood AD. D) Changes in T helper axes across different age groups in adults with AD.

response (CXCL10).[30] Mild intrinsic AD had an immune activation pattern similar to severe intrinsic AD, with higher expression of $T_H22$ and $T_H17$ pathway markers, including IL-22, S100A8, S100A9, and S100A12 compared with mild extrinsic AD.[30] However, mild AD did not exhibit the down-regulation of genes implicated in skin barrier formation as observed in the severe phenotype.

A recent study investigated the transcriptomic variances in the skin between Han Chinese patients with extrinsic and intrinsic AD.[31] The findings revealed that patients with extrinsic AD displayed up-regulation of the $T_H17$ pathway, particularly evidenced by the increased expression of IL-17A, which correlated with total IgE levels and disease severity. These findings further highlight that AD classification is more complex and spreads across multiple characteristics.

## Age-Related Differences

### *Infants*

AD typically begins in infancy and early childhood, with a significant proportion of cases (45%) emerging within the first 6 months of life, which further increases to 60% within the first year, and to 85% by the age of 5 years.[32] During infancy, the clinical presentation of AD is marked by involvement of the facial, scalp, and extensor areas; elevated transepidermal water loss (TEWL) on the cheeks at birth has been associated with increased risk of AD (Fig 1B).[17,33]

Blood levels at birth in infants who develop AD within the first year of life exhibit a notable decrease in interferon gamma (IFN-γ), suggesting a potential causal role rather than an effect of the disease.[34,35] Moreover, in the first 6 months, their serum is characterized by a distinct $T_H2$ molecular fingerprint with elevated levels of IL-4, IL-5, and IL-13 followed by an increase in IL-13 expression, suggesting early involvement of the $T_H2$ pathway in AD development.[36] This is accompanied by decreased levels of the anti-inflammatory cytokine IL-10 and reduced expression of IFN-γ, contributing to disease progression.[36]

A recent study compared the blood molecular profile across different age groups.[37] Increased expression of skin-homing memory cells was noted, potentially contributing to AD development. Moreover, $CD4^+CLA^{+/-}$ ICOS expression was up-regulated, whereas $CD8^+$ activation was reduced. Infants had low levels of IL-17 and IL-22 in their serum, with levels increasing with aging.

Skin biopsy studies have also contributed valuable insights into the pediatric AD phenotype.[38] In children under 5 years old with AD lasting less than 6 months, skin biopsies exhibited pronounced epidermal hyperplasia and cellular infiltrates comparable with (or more severe than) those in adults with long-lasting AD. Infants' skin had evidence of barrier disruption through elevated TEWL, although FLG expression remained normal. Their molecular profiles revealed an up-regulation of $T_H2$ pathway markers (IL-13, IL-31, and CCL17), $T_H22$-related markers (IL-22 and S100As), $T_H17$-related cytokines, antimicrobial markers, $T_H9$ marker IL-9, and innate marker IL-8. However, the activation of the $T_H1$ pathway was less prominent compared with adults.

A recent study expanded the molecular profile of infant AD by evaluating additional immune and barrier markers compared with adult AD in the skin.[39] The study confirmed the activation of the $T_H2$ pathway and up-regulation of the $T_H9$, $T_H17$, and $T_H22$ pathways, without $T_H1$ up-regulation. Although minimal down-regulation of FLG expression and epidermal differentiation factors was observed, lipid and protein abnormalities were present, potentially contributing to increased TEWL. Notably, a specific $T_H17$ cytokine, IL-26, exhibited a significant correlation with TEWL, implicating the involvement of $T_H17$ in barrier disruption found in infants.

When compared with skin biopsies of other age groups, infants and toddlers with AD exhibited the highest up-regulation of $T_H17$-related markers in addition to significant up-regulation of innate immunity markers and $T_H2$-related markers.[40] In particular, this cohort exhibited even greater up-regulation of IL-17A, CXCL1, CCL20, and IL-19 compared with older children.

An analysis of blood transcriptomics was conducted in early onset pediatric AD, comparing it with both healthy controls and skin samples.[41] The findings unveiled a distinct profile in the blood and skin, with only a limited number of shared markers. Blood samples exhibited increased expression of $T_H2$/eosinophil markers and low $T_H1$ activation. Up-regulation of $T_H2$-related marker CCL18, $T_H17$-related markers, and $T_H17$/$T_H22$-related markers was observed only in the skin. In this study, the overlap between differentially expressed genes (DEGs) in the blood and skin was limited to a few genes including desmocollin 2 (DSC2), indoleamine-pyrrole-2.3-dioxygenase (IDO)-1, and sphingomyelin phosphodiesterase 3 (SMPD3). However, combining skin and blood biomarkers may provide a complementary approach, providing a bigger picture of the molecular profile that characterizes infant AD.

A separate study aimed to investigate inflammatory and cardiovascular risk proteins in early onset pediatric patients with AD, comparing them with adult patients with AD.[42] Consistent with the findings in the skin, this proteomic study revealed a distinct $T_H2$ and $T_H17$ immune polarization, accompanied by a lack of $T_H1$ up-regulation. Moreover, notable up-regulation was observed in inflammatory markers associated with endothelial cell activation (eg, SELE), tissue remodeling (eg, MMP3 and MMP9), and lipid metabolism (eg, FAB4). These findings provide evidence of systemic inflammation during the initial stages of pediatric AD onset, underscoring the importance of early intervention.

### *Children*

AD diagnosed during childhood (6-11 years old) exhibits unique molecular characteristics in the blood, distinguishing it from other age groups, including infants (0-5 years), adolescents (12-17 years), and adults (18 years and older).[37] In childhood AD, specific changes are observed, such as increased activation of skin-homing Tregs, central memory T-cells (Tcm), and effector memory T-cells (Tem), along with decreased expression of IFN-γ compared with healthy controls, despite higher levels compared with infancy. In addition, the immune marker IL-9 and $T_H22$ pathway are up-regulated in this cohort. It has been postulated that this unique profile may be linked to disease clearance or noncutaneous symptoms such as allergic rhinitis or food allergies that occur during this period.[37]

Regarding immune and barrier changes in the skin, children diagnosed with having AD exhibit a common molecular profile similar to other age groups regarding T-cell activation and negative regulators.[40] However, what distinguishes children with AD is the significantly diminished expression of $T_H17$-related genes and lower CCL17 levels compared with both younger and older cohorts.

### *Adolescents*

In the blood, adolescents diagnosed with having AD, akin to other age groups, exhibited a similar immune profile.[37] In this age group, including in adults, there was a substantial up-regulation of the $T_H22$ marker IL-22, a marker of disease chronicity, and an elevated presence of skin-homing $T_H22$/Tc22 cells—emphasizing their importance within the later stages of disease. In addition to the shared up-

regulation of immune biomarkers,[40] up-regulation of IL-16 and CXCL12, which are implicated in T-cell activation and recruitment, was noted in this cohort (12-17 years old). Adolescents exhibited increased expression of $T_H2$ and $T_H22$ markers, with relatively lower up-regulation of $T_H17$-related markers.

*Adults*

In adults with AD, lesions are primarily located on flexural surfaces.[43] The molecular blood profile of adults with AD, compared with younger age groups, exhibits notable features including heightened $CD8^+$ activation and elevated expression of IFN-γ.[37] Furthermore, alongside the observed $T_H2/T_H22$ immune polarization across all age groups, there was a noteworthy up-regulation of $T_H17$ cells in the adult population.[40] The adult group also exhibited distinct $T_H1$ up-regulation, marked by significant expression of CXCL9/CXCL10/CXCL11. Another distinctive characteristic observed was the substantial reduction in FLG and loricrin (LOR).

Age-related changes in blood and skin immune responses and barrier function were investigated across different age groups in adulthood: 18 to 40, 41 to 60, and above or equal to 61 years.[44] Skin analyses revealed a progressive decrease in DC infiltrates with advancing age. $T_H2$-related markers declined, whereas a negative correlation was observed between serum IgE levels and eosinophil counts with age. The $T_H22$ marker IL-22 also consistently decreased across age groups. Conversely, $T_H1$-related and $T_H17$-related markers exhibited increased expression with age (Fig 1D). Similar trends were observed in the serum, with down-regulation of $T_H2$ markers and up-regulation of $T_H1$ markers, suggesting the presence of systemic inflammation.

Distinct associations were observed among immune markers and AD severity. In the youngest age group (18-40 years), markers of $T_H2$, $T_H17$, and $T_H1$ pathways positively correlated with AD severity as measured by Scoring Atopic Dermatitis. However, in older patients, disease severity revealed a closer association with $T_H17$ markers, suggesting a shift in the immunologic drivers of AD as individuals age. Notably, in the oldest age group (≥61 years), the $T_H2$ pathway exhibited a significant correlation with Scoring Atopic Dermatitis, whereas $T_H1$ markers displayed an inverse correlation. In addition, in the serum, elderly patients had systemic inflammation characterized by elevated expression of markers associated with atherosclerosis (such as CCL4 and CCL7), cardiovascular risk (including GDF15 and MPO), cell adhesion (CDH3), and apoptosis (FAS), when compared with the younger cohorts.[45]

Regarding the skin barrier, with increasing age, there were increased levels of LOR, suggesting an improvement in the epidermal abnormalities associated with AD. Conversely, S100As and epidermal hyperplasia markers decreased, suggesting age-related alterations in skin barrier components.

## Children With Atopic Dermatitis and Food Allergy vs Children Only With Atopic Dermatitis

Children diagnosed with having AD can also experience comorbid food allergies.[46,47] In a tape-strip study involving children aged 4 to 17 years, comparisons of nonlesional skin between those with AD and food allergies (AD FA+) and those with AD but without food allergies (AD FA−) revealed molecular differences.[47] Although $T_H2$ activity was found in both cohorts, AD FA+ group had greater up-regulation of $T_H2$-related receptors such as IL-4R, CCR8, and CRLF2 (TSLP receptor).

In addition, in nonlesional skin, AD FA+ children displayed a disrupted skin barrier characterized by higher TEWL, lower FLG, and decreased lipid content (EOS CER, ω-esterified fatty acid sphingosine ceramide) compared with both AD FA− and controls. These findings suggest that the nonlesional skin of AD FA+ patients has stronger $T_H2$ activity and an impaired skin barrier.

## Adult-Onset Atopic Dermatitis vs Pediatric-Onset Atopic Dermatitis

Significant differences were observed in the molecular profiles of adult-onset AD (AOAD, symptoms presenting during adulthood) and adults with pediatric-onset AD (POAD, symptoms beginning during childhood) in skin and blood samples.[48] In the skin, AOAD and POAD had an up-regulation of $T_H1$, $T_H2$, and $T_H22$ immune responses. However, POAD had a higher level of inflammation with increased expression of $T_H2$, $T_H17$, and $T_H22$-related markers compared with AOAD. Conversely, AOAD displayed greater up-regulation of the $T_H1$ pathway, which was significantly correlated in both skin and blood samples (Fig 1C).

Regarding the skin barrier, POAD presented a more disrupted barrier with increased hyperplasia, down-regulation of FLG and LOR, and decreased levels of lipids and cell adhesion products.

Adult POAD shared some similarities with pediatric AD, including greater $T_H2$ skewing in the skin and serum and up-regulation of $T_H17$ markers. Furthermore, the barrier defect in POAD more closely resembled the barrier disruption observed in pediatric AD. POAD also exhibited increased cellular infiltration, including $CD3^+$, $CD8^+$ T-cells, and $FcER1^+$ DCs, which is consistent with the infiltration observed in pediatric AD when compared with adults.

## Ethnicity/Race

European Americans have been thoroughly studied in the context of AD, with studies now starting to focus on other ethnicities and races.[3] Across studies, all races share a predominant $T_H2$ and $T_H22$ involvement, with a varied activation of the other immune axes (Fig 2A).[13,14,49]

*Asian*

Asian patients with AD often exhibit distinct demarcation of lesions characterized by notable scaling and lichenification.[13] A recent study shed light on the unique immunologic and barrier characteristics of extrinsic AD in the skin of Asian patients (Japanese and Korean) compared with that of European American (EA) patients.[13] In both cohorts, as expected, a predominant $T_H2$ immune response was observed. However, differences were identified between Asian patients and EAs. Asian patients exhibited increased expression of key $T_H17$-related markers, such as IL-17A, IL-19, and the $T_H17/T_H22$ marker S100A12, along with elevated levels of the $T_H22$ cytokine IL-22. Conversely, there was reduced activation of the $T_H1$ pathway, as indicated by lower expression levels of CXCL9 and CXCL10, when compared with EA patients (Fig 2B and C).

The barrier function in Japanese and Korean patients displayed distinct features, including greater epidermal hyperplasia characterized by increased epidermal thickness and expression levels of Ki67. Although comparable infiltration of T-cells and Langerhans cell (LC) counts was found in both groups, FcεRI+ DCs exhibited higher expression levels in Asian patients.

Another study comparing serum and skin biomarkers in the same Japanese, Korean, and EA patients revealed important insights.[50] The Asian and EA groups had comparable expression of serum $T_H2$ markers (IL-13, CCL13, CCL17), consistent with their respective skin molecular profiles. However, EA patients exhibited greater expression of $T_H1$-related markers (IFN-γ, CCL2, CCL3) compared with these Asian AD patients, aligning with the observed skin findings. Serum IL-17 levels were comparable between both groups, contrasting with skin findings where IL-17 levels were significantly up-regulated. This discrepancy could potentially be explained by a higher influx of IL-17 to the skin in Asian patients and has been postulated to suppress the

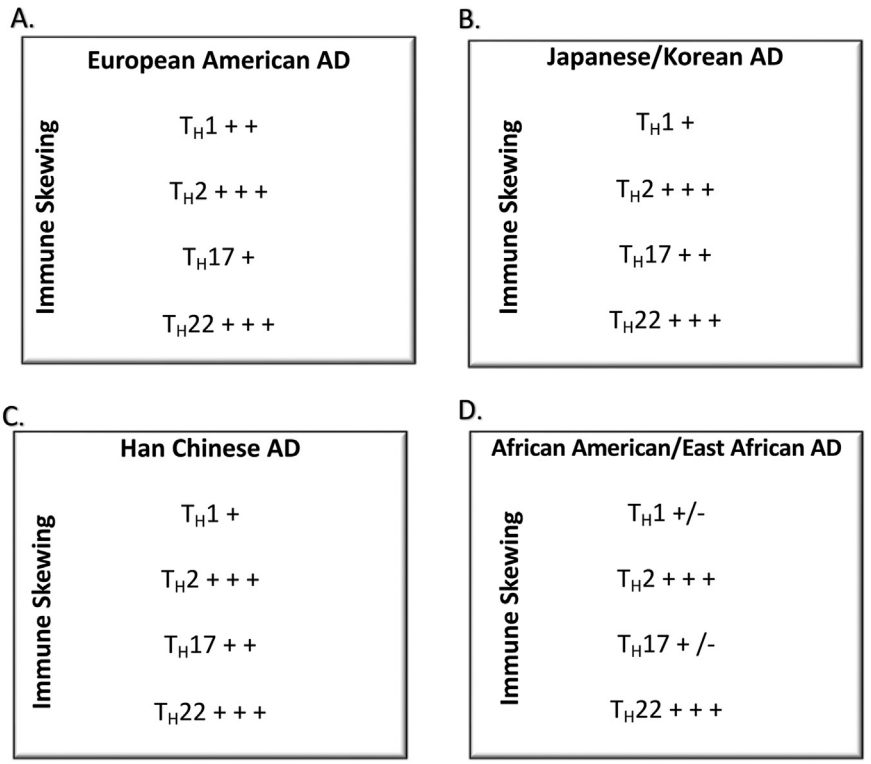


**Figure 2.** Molecular skin profiles of atopic dermatitis (AD) across select ethnicities/races. A) Molecular skin profile of European American patients with AD. B) Molecular skin profile of Japanese and Korean patients with AD. C) Molecular skin profile of Han Chinese patients with AD. D) Molecular skin profile of African American and East African patients with AD.

$T_H1$ axis.[50] Furthermore, the serum $T_H22$-related cytokine IL-22 had greater expression in these Asian patients compared with EA patients, which mirrors the findings observed in their skin.

When comparing skin samples of Han Chinese patients with AD to EA patents with AD, notable differences were observed as well.[49] Han Chinese patients with AD exhibited increased neutrophil infiltration and greater expression of $T_H17$ markers (IL-17F and IL-12p40), whereas $T_H1$ expression was reduced.

### *African Americans and East Africans*

In African American (AA) patients, AD lesions exhibit a lichenified phenotype.[17,51] A recent study revealed that the skin of AA patients with AD displayed a distinctive molecular fingerprint that partially overlapped with the immune profile observed in East African patients.[52] Both AA and East African patients exhibited increased expression of markers associated with the $T_H2$ and $T_H22$ signatures. However, in AA patients, there was a down-regulation of genes related to innate immunity, $T_H1$ axis, and $T_H17$ axis, and elevated expression of DCs, including FcεR1+, in comparison to East African patients. Notably, the reduction in FLG was exclusive to East African patients, whereas both cohorts had decreased expression of LOR (Fig 2D).

In the case of East African patients with AD, particularly those from Tanzania, a comparable molecular profile in the skin to AA patients was observed.[53] They exhibited up-regulation of the $T_H2$ (eg, IL-13, IL-10) and $T_H22$ immune pathways (eg, IL-22), along with a lesser up-regulation of $T_H17$ and $T_H1$ markers. In addition, there was a noticeable presence of the MMP12 and T-cell and DC immune activation. Interestingly, there was no significant increase in the expression of innate immunity-related markers or down-regulation of epidermal differentiation factors. However, the expression of lipid metabolism genes was suppressed.

Another study compared the immune and barrier skin profiles of East African, AA, and EA patients with AD.[54] Across all cohorts, there was an increase in the expression of T-cell activation, $T_H2$-, and $T_H22$-related markers. $T_H1$ activation, however, was not up-regulated in East African patients. Regarding the barrier function, all groups had a decrease in the expression of barrier lipid genes, with the most significant decrease observed in East African and AA patients. In addition, EA patients had reduced expression of epidermal differentiation markers, including FLG and LOR. Overall, these studies underscore the molecular variability of East African and AA patients with AD. However, environmental, sociologic, and socioeconomical differences may also play a role in the disease burden and severity.[55] A study revealed that AA patients had lower incomes and less education compared with non-Hispanic Whites.[55] Moreover, a qualitative study in South Africa revealed that parents of children with AD faced financial constraints for medications and had limited disease education.[56] These factors could serve as barriers to seeking early stage care or accessing medications and, thus, contribute to greater disease severity and morbidity often observed in these populations.

### *Latin Americans*

The clinical phenotype of AD in Latin Americans exhibits broad clinical features, posing challenges for accurate diagnosis. Nevertheless, a frequently reported clinical feature includes marked lichenification.[57] In a study conducted in Brazil, elevated expression of IL-22 was observed in AD dermal lesions.[58] Another study revealed increased levels of IL-17 in both serum and skin, along with an increase in CD4/CD8 T cells in AD lesional skin.[59] A cohort study in Brazil is currently assessing the expression of skin barrier proteins and the activation of the $T_H17$ and $T_H22$ axes across ethnic/racial variations. Preliminary findings suggest distinct immune profiles across ethnoracial categories, characterized by varied decreased expression

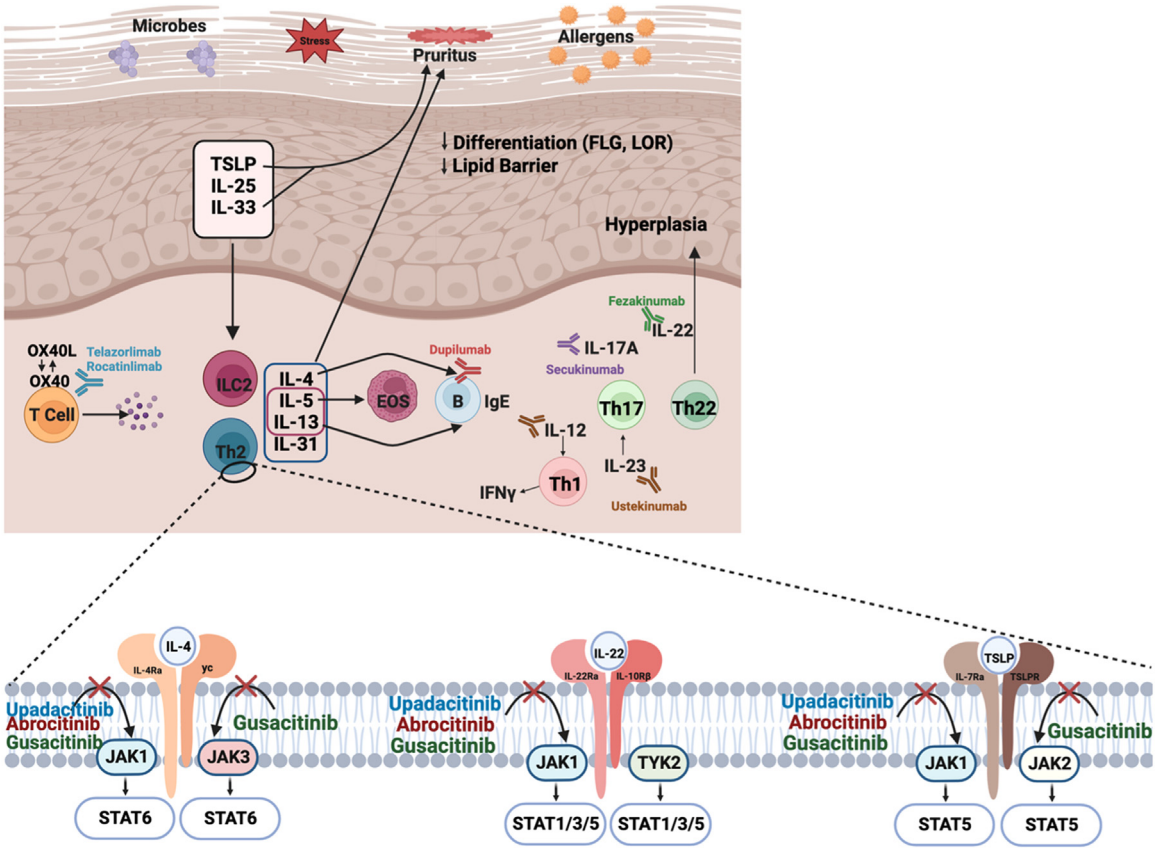


**Figure 3.** An illustrative overview of the pathogenesis of atopic dermatitis, featuring the associated biologics and JAK inhibitors. The Figure was created with BioRender.com.

of FLG, CLDN-1, and CLDN-4 and increased expression of IL-17 and IL-22.[57]

Currently, there are limited studies evaluating the immune profiles of Latin Americans, which may be attributed to racial/ethnic diversity and varied geographic locations. More research is needed to better elucidate the immunologic ethnoracial differences within this population.

## Filaggrin Status

The FLG serves as a critical structural component of the cornified envelope, functioning as an epidermal terminal differentiation factor.[60] Among the genetic factors associated with AD, FLG mutations have emerged as the strongest risk factor[16,61,62] and are linked to a greater lifetime prevalence of hand and foot dermatitis, a higher susceptibility of herpes virus skin infections, and increased prevalence of severe alopecia areata.[63,64] Patients with FLG loss-of-function (LOF) mutations, which result in the complete absence of protein expression, exhibit a unique phenotype,[17,61] with palmar hyperlinearity and a persistent course, including an increased risk of eczema herpeticum, asthma, and allergic sensitization.[61,65-67]

The 4 most common FLG null mutations (R501X, 2282del4, R2447X, S3247X) were more prevalent in early onset AD (≤2 years) compared with later-onset cases.[68] Another study revealed that tape strips were more effective in detecting FLG mutations compared with biopsies and found that children with FLG mutations had elevated expression of $T_H2$ markers such as CCL17/TARC and increased levels of innate inflammatory markers, including IL-1β and IL-8.[69] Moreover, FLG LOF mutations have been linked to an increased susceptibility to developing early onset AD continuing into adulthood.[70]

Adult-onset AD (>18 years) did not exhibit these 4 FLG mutations.[68] However, a polymorphism in CHI3L1, which is associated with immune system regulation, was observed in individuals who developed AD after 8 years of age.[71]

FLG mutations also correlate differently among ethnicities/races. Studies have reported approximately 50% prevalence of LOF FLG mutations in Europeans, whereas Asians have a lower frequency of approximately 27%.[1,16,72-74] In addition, there are distinct mutations observed in these groups. For instance, certain FLG LOF mutations such as R501X and 2282del4 have a higher occurrence among Europeans but are not found in Asians,[75] and within different Asian populations (eg, Japanese, Korean, Chinese), FLG mutations vary.[76] In African Americans, FLG mutations are much less prevalent compared with European Americans[77]; nevertheless, a recent longitudinal study discovered FLG LOF variants in AA children that are linked to a more persistent disease course.[78]

## Selection of Immune Targets

The understanding that $T_H2$-related mechanisms predominate in AD has driven the development of biologics targeting this pathway, leading to significant clinical improvements with parallel molecular changes in the skin and blood.[79-85] One such biologic is dupilumab, an IL-4 receptor alpha chain (IL-4Rα) inhibitor, which was the first Food and Drug Administration–approved biologic treatment for moderate-to-severe AD, in patients aged 6 months and older.[24,86] Dupilumab, in addition to its clinical efficacy, has also demonstrated its effect by improving serum and skin transcriptomic profiles, downregulating inflammatory pathways beyond the $T_H2$ pathway, including $T_H1$, $T_H17$, and $T_H22$, while also enhancing the epidermal barrier (Fig 3).[80,87,88]

In addition to dupilumab, other biologics targeting the $T_H2$ pathway have also been found to improve clinical outcomes and have led to significant molecular changes, including tralokinumab (an IL-13 inhibitor), GBR830/telazorlimab, and rocatinlimab (OX40

inhibitors).[82,84,85,89] These findings further highlight the therapeutic potential of targeting the $T_H2$ pathway in AD.

However, despite the ability of these medications to modulate $T_H2$-related biomarkers (and others), achieving complete clinical clearance in AD remains a challenge. Hence, exploring therapeutic options with broader effects, such as JAK inhibitors, may be warranted. JAK inhibitors, which are small molecules targeting the JAK/STAT pathway, have demonstrated significant efficacy in treating AD and other inflammatory conditions.[90-93] For example, gusacitinib/ASN002, a JAK/Spleen Tyrosine Kinase (SYK) inhibitor, significantly down-regulated key immune pathways ($T_H1$, $T_H2$, $T_H17$, and $T_H22$) in the skin and serum and substantially improved the skin's barrier.[94,95] In addition, other JAK inhibitors, such as the Food and Drug Administration–approved JAK1 inhibitors abrocitinib and upadacitinib, have demonstrated similar positive results.[96-98] Although JAK inhibitors hinder multiple downstream cytokines simultaneously, head-to-head comparisons with biologics are still needed to determine whether they are more clinically effective and have higher clearance rates.

Another approach that holds promise is the shift toward personalized management, which considers the individual patient's molecular profile to optimize treatment. An illustrative example of this approach is the use of fezakinumab, an IL-22 antagonist, which revealed significant clinical improvement compared with placebo, specifically in patients with higher IL-22 levels.[99] The efficacy of fezakinumab is further supported by its ability to modulate the transcriptome, leading to the down-regulation of $T_H1$, $T_H2$, and $T_H17$-related biomarkers. This highlights the potential benefits of targeted drugs in molecularly differentiated patient cohorts. Exploring the effects of fezakinumab on patients with elevated IL-22 levels, such as those with intrinsic AD, pediatric patients, Asian patients, and African American patients, reveals great promise for further improving therapeutic outcomes.[17] Future studies with IL-22 antagonists such as the novel treatment that antagonizes IL-22R[100] will be able to clarify the contribution of this pathway to various AD phenotypes.

Certain patient groups who exhibit up-regulation of the $T_H17$/$T_H22$ pathway (intrinsic AD, infants, elderly individuals, Asians, and Africans) may have a more favorable response to biologics that target this pathway. Although previous studies with secukinumab (an IL-17A inhibitor) or ustekinumab (an IL-12/IL-23 p40 antagonist) did not reveal significant clinical improvement, the latter did exhibit substantial improvement in the molecular profile by affecting $T_H1$, $T_H2$, $T_H17$, and $T_H22$.[101,102] Therefore, although these medications might not suffice as monotherapies, combining them with other biologics might have a synergistic effect.

## Conclusion

The emergence of targeted therapeutics based on patients' molecular profiles holds great promise for managing AD. Fezakinumab serves as a prime example of a drug that reveals how biomarker stratification can lead to meaningful clinical improvement, highlighting the potential of personalized medicine in this field. By identifying specific molecular markers across ethnicity/race, age, disease duration, and FLG status, clinicians will be able to customize treatment approaches to optimize efficacy and minimize adverse effects. Thus, as our knowledge deepens and more targeted therapeutics are developed, we can anticipate improved patient clinical outcomes and quality of life. In the years to come, we believe that this paradigm shift toward precision medicine will pave the way for more comprehensive and patient-centered management.

## Disclosures

Dr Guttman-Yassky has served as a consultant to AbbVie, Almirall, Amgen, Aslan Pharmaceuticals, AstraZeneca, Biolojic Design, Boehringer-Ingelheim, Bristol-Myers Squibb, Cara Therapeutics, Connect Pharma, DBV Technologies, Eli Lilly, EMD Serono, Evidera, Galderma, Gate Bio, Genentech, Incyte, Inmagene, Janssen Biotech, Kyowa Kirin, Leo Pharma, Merck, Pfizer, Q32 Bio, RAPT, Regeneron, Sanofi, SATO, Siolta, Target, UCB, and Ventyx; and has had research grants paid to her institution from the following: Boehringer-Ingelheim, Leo Pharma, Pfizer, Cara Therapeutics, UCB, Kyowa Kirin, RAPT, Amgen, GlaxoSmithKline, Incyte, Sanofi, Bristol-Myers Squibb, Aslan, Regeneron, Anaptysbio, Concert, and Janssen. All other authors disclose no conflict of interest.

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