Review



# Pathophysiology of Atopic Dermatitis in Different Ethnic Groups

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*Review*

# Pathophysiology of Atopic Dermatitis in Different Ethnic Groups

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**Abstract:** Atopic dermatitis (AD) is a common chronic inflammatory skin disease with high prevalence worldwide, including countries from Asia, Africa and Latin America, and in different ethnic groups. In recent years, more attention on AD heterogeneity associated on multiple factors, including patient's ethnic background, has been posed, resulting in an increasing body of clinical, genetic, epidemiologic, and immune-phenotypic evidence that delineate differences among racial groups with AD. Filaggrin (FLG) mutations, the strongest genetic risk factor for the development of AD, are detected in up to 50% of European and 27% of Asian AD patients, while very rarely in Africans. Th2 hyperactivation is a common attribute of all ethnic groups, though the Asian endotype of AD is also characterized by an increased Th17-mediated signal whereas African Americans own a strong Th2/Th22 signature and the absence of Th1/Th17 skewing. In addition, the ethnic heterogeneity may own important therapeutic implications as the genetic predisposition may affect treatment response and, thereby, a tailored strategy that better targets the dominant immunologic pathways in each ethnic subgroup may be envisaged. Nevertheless, white patients with AD represent the largest ethnicity enrolled and tested in clinical trials and the most treated in a real-world setting, limiting the investigation about safety and efficacy across different ethnicities. The purpose of this review is to describe the heterogeneity of pathophysiology across ethnicities and its potential therapeutic implications.

**Keywords:** atopic eczema; dermatitis; allergy; itch; skin disease; treatment; prevention; epidemiology; ethnic differences; cellular; molecular; immunological; physiological therapeutic

## 1. Introduction

Atopic dermatitis (AD) is among the most common immune-mediated skin disorder, with a chronic-relapsing course and a multifactorial pathogenesis [1]. Prevalence of AD is very high worldwide, including countries from Asia, Africa and Latin America, in different ethnic groups, as well as in different ages [2].

The disease is clinically characterized by itchy eczematous lesions primarily involving flexural areas, face, neck, and distal extremities, and it might precede other non-cutaneous atopic manifestations, such as asthma and allergic rhinitis (AR), priming the so-called "atopic march"[3].

Unlike other inflammatory skin diseases, AD shows a certain degree of clinical heterogeneity, leading to consider this condition as a spectrum instead of a single entity. For this reason, in recent years, several efforts have been made to characterize disease subtype according to different parameters, such as phenotypes, skin barrier status, IgE levels, age, gender, and ethnicity [4]. Moreover, different endotypes across different age groups and ethnicities and according to IgE levels and filaggrin mutation status have been identified through specific molecular signatures [5].

Depending on the patient's racial background, AD seems to show different clinical, genetic and immunopathogenic features [6]. Nevertheless, Caucasian patients with AD still represent the most

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studied ethnic group, leading to uncertainity in fully defining differences and similarities in disease pathophysiology across different ethnicities.

This review aimed to explore the current insights on AD heterogeneity depending on patient ethnicity and to analyze the possible therapeutic implications of these pathophysiologic differences.

## 2. Clinical features

Several AD phenotypes have been described according to lesion distribution (e.g., flexural, head and neck, periorificial) or the predominant clinical feature, such as nummular eczema, prurigo nodularis, lichenified dermatitis, follicular/papular dermatitis [7].Interestingly, some differences in the clinical manifestations of AD exist among ethnic groups, which may pose diagnostic challenges. The clinical heterogeneity of AD is oftentimes the result of differences in distribution and pigmentation of the lesions [8].Asian individuals typically present lesions with more defined borders, sometimes closely resembling psoriasis plaques, as well as more scaling and lichenification, in comparison to white AD patients [9,10]. Conversely, African AD patients presents with a predominant extensor involvement [11] and sometimes with perifollicular accentuation and distinct papules on the extensor surfaces and on the trunk [12,13]. Furthermore, in darker skin types exclusively, a lichen-planus like presentation of AD has been described [14].

Because of the almost complete absence of erythema in dark skin types, oedema, warmth of the skin or overlying scale, may help dermatologists in identifying the presence of erythema. Furthermore, many scoring system in clinical practice, such as the eczema area and severity index (EASI) [15] or the scoring AD (SCORAD) [16], rely on erythema to assess the disease's severity and thus have the tendency to underestimate the severity of AD in darker skin types [17]. In addition, patients with darker skin types, more frequently than whites, exhibit xerosis, hyperlinearity of the palms, Dennie-Morgan lines, periorbital darkening, lichenification and prurigo nodularis [11].

Finally, the risk of developing post-inflammatory hyper- or hypo-pigmentation is more common in dark skin [18].

## 3. Genetic variability across ethnic groups

Similarly to other chronic inflammatory dermatoses, a genetic predisposition based on a polygenic background is associated with development of AD. Certain genes have been implicated in AD predisposition, in particular, those related to the skin barrier function, those involved in Th2 immune responses and those implicated in the vitamin D metabolism and synthesis of its receptors [19].

An attempt to study ethnic differences in AD from a genetic perspective, seeking to identify ethnic-specific genes, have been recently conducted in African, Asian and Hispanic populations through genome wide association studies (GWAS) [20–26].

Loss-of-function mutations (LOF) of the structural protein filaggrin represent the strongest genetic risk factor for the development of AD and are detected in up to 50% of European and 27% of Asian AD patients [27–29]. The filaggrin precursor pro-filaggrin is encoded by the *FLG* gene, located in the epidermal differentiation complex (EDC) on chromosome 1q23.3. Filaggrin deficiency is a major determinant of defective barrier function [30], and it is associated with: *(i)* a disrupted keratinocyte differentiation, *(ii)* an impaired corneocyte integrity and cohesion, *(iii)* an altered tight junction formation, *(iv)* a decreased water retention, *(v) an* abnormal lipid formation as well as *(vi)* an enhanced susceptibility to cutaneous infection [31]. Patients carrying LOF mutations in the *FLG* gene exhibit a more severe phenotype of AD, with a more persistent course, a higher risk of skin infections and allergic sensitization, as well as a major impairment of the immune system compared to patients with wild-type *FLG* [32,33].

Interestingly, filaggrin LOF mutations show a certain population specificity. The first two characterized mutations, R501X and 2282del4 [34], as well as S3247X and R2447X have been extensively studied and are present in 7-10% of the white European population, whereas they are absent in Asians having a different spectrum of *FLG* variants [27]. Conversely, studies failed to detect common *FLG* LOF mutations in people of African ancestry with AD, although decreased levels of

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filaggrin have been reported in the skin of these patients [35,36]. Interestingly, no association between *FLG* LOF and AD have been found in African populations (Ethiopia) so far [37], whereas a relationship has been described in African Americans, probably due to genetic admixture [33,38]. Overall, *FLG* LOF mutations are six-time less common in subjects of African descent than in people of European and Asian descent, suggesting a minor contribution to AD development [33].

The absence of *FLG* gene mutations in African people has prompted further genetic investigations in this ethnicity. Results from whole exome sequencing (WES) analysis in Ethiopian AD patients revealed an association between LOF mutations in the *FLG2* gene and the persistence of AD [39]. The *FLG2* gene is located, within the EDC, sharing with *FLG* a similar molecular structure and biological functions [40,41]. Similarly, another study based on the whole exome analysis demonstrated that *FLG2* mutations were associated with a more persistent AD in an African American cohort [42]. On the contrary, studies conducted in European subjects did not reveal any association between the *FLG2* missense variant (rs16833974) and AD [43,44].

Beyond the EDC, variants in genes encoding for proteins involved in maintaining the epidermal homeostasis have been described in specific ethnicities. For example, mutations in claudin 1 (*CLDN1*) gene, encoding for a structural protein of the tight junctions, have been related to the early onset of AD in Ethiopian patients and it may be involved in the susceptibility of AD in this population [45]. In addition, some studies detected an association between LOF mutations in *SPINK5*, encoding for a serine-protease inhibitor involved in epidermis homeostasis and classically associated with both an autosomal recessive congenital ichthyosis and AD in East Asian populations [46–49].

The second class of genes implicated in AD susceptibility are related to the innate and adaptive immunity, and, in particular, to the Th2 pathway, that is central to AD pathogenesis.

Several studies described a correlation between polymorphisms in *IL-4, IL-13, IL-31, IL-4RA* and *IL-31RA1* genes, all belonging to the Th2 pathway, and an increased risk of developing AD [50–55].Similar to those involved in epidermal function, genes related to the immune response characterizing AD showed some differences across ethnic groups.

In detail, polymorphisms of *IL-4, IL13/IL-13RA1* have been associated with an AD predisposition in Japanese, Koreans and Chinese populations [52,54,56,57], while AD susceptibility was significantly associated with *IL4RA* and *STAT6* polymorphisms in Egyptian children [54]. One specific polymorphism (Q576R) of the *IL4R* gene has been found to be overrepresented in the African American population [58].

Moreover, many other genes encoding molecules that contribute to AD pathogenesis at different levels, such as *STAT6*, thymic stromal lympopoietin (*TSLP*), *IL7R, TSLPR*, interferon regulatory factor 2 (*IRF2*), toll-like receptor 2 (*TLR2*), FcεRIα (*FCER1A)* and β-Defensin (*DEFB1*), have been found to been implicated in AD susceptibility in different ethnic groups [59–61]. For example, polymorphisms in the *IRF2* gene were associated with AD in European Americans (rs793814 and rs3756094) and in African Americans (rs3775572) [62] and a specific *TSLP* variant (rs1898671) has been related to less persistent AD in white and African Americans [63].

In Japan, a *TLR2* variant has been proposed as a genetic predictor of AD severity while *FCER1A* polymorphisms have been related to significantly higher IgE serum levels in AD patients [64,65].

Variants in the *DEFB1* gene, encoding a small antimicrobial peptide mainly expressed in

The epidermis and promoting host defense against pathogens, has been related to an increased risk of AD in Brazilian, Mexican and Korean populations [66–68]. Notably, variants in genes encoding IL-12 and its receptor, has been reported as susceptibility genes in Korean AD patients [69].

## 4. Pathogenesis

The pathogenesis of AD is characterized by a complex interplay between genetic and environmental factors contributing to epidermal barrier disruption, commensal skin microbiota dysbiosis and alterations in immune responses, causing disease occurrence and/or exacerbation [3]. The current pathogenic model is centered on the activation of type 2 immune cells such as T helper (h)2, T follicular helper (Tfh) cells, innate lymphoid cells 2 (ILC2), T cytotoxic (c)2 cells, eosinophils,

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mast cells, and basophils, with the contribution, at different extent, of other pathways that include Th/Tc22, Th9, Th1, Th/Tc21, and Th17 [69–71].

During the initial phases of the pathogenic cascade, keratinocytes are activated by the excessive exposure to allergens, irritants and microbial antigens due to an epidermal barrier disruption, causing the release of chemokines such as thymus and activation-regulated chemokine [70], macrophage-derived chemokine (MDC or CCL22)[71,72] , and innate immune cytokines, such as IL-1β, IL-33 and thymic stromal lymphopoietin (TSLP), with subsequent activation of ILC2s and Th2 cell-mediated immune responses [73]. Particularly, TSLP-activated dendritic cells express OX40 ligand (OX40L) which, upon binding to its receptor OX40, induce Th2 differentiation of naïve T cells, resulting in the production of Th2 cytokines (IL-4, IL-5, IL-13 and IL-31) [74]. Also, ILC2s represent a relevant source of IL-5 and IL-13, thus contributing to create a type 2 inflammatory cytokine milieu [75].

While the type 2 signal dominates acute and chronic phases of the disease and results to be constantly elevated in all AD ethnic groups, an upregulation of other immune pathways can occur differently across ethinicities [76,77].

The Asian endotype of AD is typically characterized by a strong Th17 signature, as well as by peculiar clinical and histological features [78]. Comparing the gene expression profile of European American, Japanese and Koreans AD patients, and including as control groups patients with psoriasis and healthy controls, the presence of a strong Th2 activation was detected in both Asian and European American AD patients but not in psoriasis patients. Conversely, a significantly higher expression of Th17 and Th22 (IL17A, IL19, S100A12, IL-22) and lower of Th1 genes (CXCL9, CXCL10, IFNG) was found in Asian AD patients [10]. In addition, Asian AD skin showed greater acanthosis, higher Ki67 counts, and frequent parakeratosis, prompting the conclusion that AD Asian endotype presents overlap features of European AD and psoriasis [10].

Another study investigating the molecular profile of AD has been conducted on Chinese AD patients in comparison with European Americans, psoriatic patients, and ethnic-matched healthy controls. The gene expression analysis showed similar results in Chinese AD patients compared with those observed in Japanese and Korean patients, suggesting a consistent Th17/Th2 or blended AD-psoriasis endotype across all Asian AD patients [79].

Along these lines, an upregulation of the serum Th2 markers was found in both Asian and European Americans AD patients, together with a lower expression of Th1 markers (IFNγ, CCL2, CCL3, CCL4) and increased Th22 activation in Asian patients, compared with European American. In contrast to the gene expression signature detected in the skin, serum levels of Th17 markers were not increased in Asian patients [80]. Similarly, a characterization of the immunophenotype of AD in African Americans was recently carried out through gene expression analysis. The results from this study revealed a strong Th2/Th22-skewing in African American AD patients, with both Th2 and Th22 markers correlating significantly with disease severity, and, concomitantly, an attenuation of Th1 and Th17 axes compared to European Americans was observed. In addition, the skin of African American AD patients had peculiar barrier changes such as a lower filaggrin decrease but greater loricrin reduction that differed from Europeans AD subjects [81].

## 5. Therapeutic implications

Currently, therapeutic approaches and recommendations for AD treatment do not differ across the diverse ethnic groups, nor they are taken under consideration in current Eurpean or American guidelines or recommendations [82–84]. Indeed, limited investigation on the effects of AD therapeutic agents in different ethnic groups has been performed so far.

From daily clinical practice, it can be inferred that topical steroids are overall effective in all skin type. However, they should be used with caution as they frequently induce or worsen hypopigmentation in darker skin types [85].

A study on the use of pimecrolimus cream 1% of AD patients of different origins showed that ethnicity had no impact on treatment outcomes [86]. Also, a pooled data analysis about efficacy and

safety data of tacrolimus ointment compared outcomes obtained in eight Asian countries with those in the United States, Europe, and Japan, reporting similar results [87].

For moderate-to-severe AD, phototherapy is a possible therapeutic option, especially narrow band UVB (NB-UVB). In one study conducted in Singapore both NB-UVB and UVA/NB-UVB based phototherapy resulted effective for the treatment of AD in Asian children [88]. Noteworthy, the use of phototherapy in darker skin types requires some special considerations: NB-UVB has been shown to require higher doses in darker skin [89,90], while UVA1 phototherapy seems to be equally effective in Fitzpatrick I-V skin phototypes without any dose adjustment [91].

About systemic therapies, differences in terms of efficacy and safety profile across ethnicities may depend on several factors, such as a different metabolism of the drug, which may ultimately affect its bioavailability. For example, black individuals have a 20–50% lower bioavailability of cyclosporine than white individuals, thus requiring higher doses of the drug [92]. The use of methotrexate, an antifolate metabolite acting as a immunosuppressive agent, has been associated with a higher risk of alopecia in black patients [92]. Furthermore, azathioprine, another immunosuppressive agent that requires the activity of the enzyme thiopurine methyltransferase (TPMT) for its metabolism, may cause severe toxicity in black patients at normal dosages, since deficiency of TPMT is prevalent in this population [92].

Dupilumab, a fully human monoclonal antibody blocking the shared IL4R$\alpha$ subunit, binding to both IL-13 and IL-4, was the first biologic agent approved for the treatment of moderate-to-severe AD [93]. Phase III trials testing dupilumab included 20%-27% Asian and 5%-7% Black patients,and suggested a comparable efficacy in diverse populations [94–96]. Recently, a post-hoc analysis from three phase III trials (LIBERTY AD SOLO 1, SOLO 2 and CHRONOS) assessed the efficacy and safety of dupilumab vs placebo across racial subgroups (White, Asian, Black/African American) and demonstrated that, independently from ethnicity, dupilumab resulted effective in improving AD and safe, with a favorable benefit-risk profile [97].

Furthermore, a cross-sectional study assessing the patient burden and the impact on quality of life impact of AD in the U.S. population has shown that the effectiveness of dupilumab in improving the quality of patients with AD was similar amongst various racial groups (white, Asian, Black/African Americans) [85].

Novel biologic agents and small molecules, such as tralokinumab [98], upadacitinib [99] baricitinib [98], and abrocitinib [100], have been recently approved and many others are currently under investigation for the treatment of moderate-to severe AD.

Tralokinumab is a first-in-class, IgG4 monoclonal antibody, that specifically binds with high affinity to IL-13. Results from phase III clinical trials have demonstrated a substantial improvement in severity and symptoms of AD after tralokinumab administration [101,102]. Recently, a sub-analysis of tralokinumab phase III trials (ECZTRA 1, 2, and 3) was conducted to evaluate its efficacy and safety in a North American population vs. a non-North American population. Of note, approximately 30–52% of patients in the North American population had skin of color, versus 5–25% in the non-North American population. The results of this post-hoc analysis of three large phase III displayed safety and efficacy of tralokinumab regardless of the ethnicity [103].

## 6. Discussion

In recent years, a great interest to decipher the clinical and molecular heterogeneity of AD across ethnicities has prompted the development of clinical, genetic, epidemiologic and molecular studies analyzing AD in different ethnic groups, in an attempt of characterizing disease´s subtypes. Although similarities among different ethnic groups are by far larger then differences in all disease aspects, a growing body of evidence suggests race-specific alterations in the epidermal structure as well as differences in the magnitude of upregulation related to certain immune pathways. In general, healthy skin from European, African and Asian populations might exhibit significant molecular differences. For instance, the higher rate of *FLG* mutations in European populations could be attributed to evolutionary pressures as *FLG* deficiency may have provided enhanced immunity against infections, and therefore protection during European pandemics in the past centuries [104], and it may have

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ensured greater vitamin D synthesis in the skin, conferring an evolutionary advantage at high latitudes [105].

Interestingly, even the atopic march, which encompasses food allergy, asthma, allergic rhinitis and conjunctivitis after AD, and may show a certain racial variability [106]. A longitudinal study indicated wide differences in allergic comorbid trajectories between black and white children with AD. Black children had higher asthma risk and lower risk of allergic rhinitis and food allergy, while white children were most likely to progress to allergic rhinitis and food allergy, despite a lower asthma risk. These differences may be partly explained by ancestral genetic variabilities but also by different exposure to various race-specific environmental risk factor [107]. Overall, the presence of extracutaneous atopic manifestations suggest a prominent role of the type 2 inflammation in all ethnic groups. However, the contribution of other immune pathways led to the identification of endotypes corresponding to specific phenotypes that, so far, has been poorly defined as demonstrated by the relatively high upregulation of the Th17 signal in Asian AD compared with European AD skin, that could explain the predominance of well-demarcated, psoriasiform lesions in Asians compared to Europeans but it cannot explain why the inhibition of IL-17A failed to demonstrate clinical, histopathological and transcriptomic benefits (Figure 1) [105].

On the contrary, the efficacy of dupilumab first, and tralokinumab lately, across ethnicities, confirmed the central role of type 2 inflammation in all AD ethnic groups. Notably, transcriptomic studies revealed broader effects of dupilumab in suppressing directly the type 2 inflammatory signal, and indirectly the down-regulation of the Th17/Th22-related signals, partially explaining its efficacy in treating patients belonging to different ethnicities, even in those ones characterized by a lessened type 2 inflammatory signature [108]. African AD patients show a strong Th2 skewing with a high correlation between disease severity and Th2/Th22-related markers as well as IgE serum levels [81]. Therefore, those patients may reasonably benefit the most from the neutralization of IL-22 (by fezakinumab, an anti-IL-22 monoclonal antibody) or a Th2-targeting agent.

Beyond selected cytokine antagonists, novel classes of drugs targeting Janus kinases (JAK) with different selectivity, having a “broader” range of action demonstrated high efficacy in treating AD. The JAK inhibitors, targeting one or more members of the JAK family, can simultaneously inhibit several downstream pathogenic pathways in AD [109]. Their broad suppressive activity may be promising and appealing in order to provide therapeutic benefit across all ethnicities. No data are currently available on the safety and efficacy profile of JAK inhibitors across all ethnicity because non-white patients are still underrepresented in AD clinical trials (18% of all patients included are black, 6,9% Asian and 2% Hispanic), estimating that only 59% of AD clinical trials performed between 2000 and 2009, included race and ethnicity as a baseline demographic characteristic and this is a limitation for data interpretation through race [110–112].

## 7. Conclusion

Differences amongst various ethnicities in terms of clinical phenotypes and their corresponding immune endotypes exist, though not fully elucidated.

However, this ethnic heterogeneity of AD may hold important therapeutic implications.

The "one-size-fits-all" therapeutic approach offers results that are not always satisfactory and may not be ideal. Therefore, future investigations could hopefully stratify AD populations more precisely by ethnicity and pave the way for the development of a personalized and tailored approach that better targets the immunologic pathways involved in each ethnic subgroup.

Unfortunately, ethnicity data on most new agents for AD are largely not available, and the inclusion of different ethnic groups in randomized clinical trials, as well as sub-analyses by race, are of great importance and should be strongly encouraged.

**Conflicts of Interest:** Dr. Maurelli and Dr Calabrese declares no conflict of interest. Prof. Girolomoni has received personal fees from AbbVie, Abiogen, Almirall, Amgen, Biogen, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli-Lilly, Leo Pharma, Merck Serono, Novartis, Pfizer, Samsung and Sanofi. Prof. Ketty Peris has served on advisory board, received honoraria for lectures and/or research grants for Abbvie, Almirall, Lilly, Galderma,

Leo Pharma, Pierre Fabre, Novartis, Sanofi, Sun Pharma, Janssen. Prof. Andrea Chiricozzi has served as advisory board member and consultant and has received fees and speaker's honoraria or has participated in clinical trials for AbbVie, Almirall, Bristol Myers Squibb, Leo Pharma, Lilly, Janssen, Novartis, Pfizer and Sanofi Genzyme.

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**Figure 1. Main genetic, clinical, and immunological features in AD patients across ethnicities.** Predominant genetic features of each subgroup, immune-polarization and potential therapeutic implications are shown. FLG: Filaggrin; LOF: Loss-of-function; IL: Interleukin; TSLP: Thymic stromal lymphopoietin; IRF2: Interferon regulatory factor 2; TLR2: Toll-like receptor 2; FCER1A: Fcε Receptor1α; DEFB1: B -Defensin 1; SPINK5: Serine Peptidase Inhibitor Kazal Type 5; TCHH: Trichohyalin; TCHHL1: Trichohyalin like 1; CRNN: Cornulin; HRNR: Hornerin; CLDN1: Claudin 1; Th: T helper; JAKi: JAK inhibitors. This figure was created with BioRender.com.