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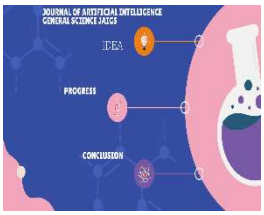

Understanding Atopic Dermatitis Across Ethnicities

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ABSTRACT

Atopic dermatitis (AD) is a prevalent chronic inflammatory skin disease affecting diverse populations worldwide, including those in Asia, Africa, and Latin America. Recent research has highlighted the heterogeneity of AD, influenced by multiple factors such as ethnic background. This has led to a growing body of clinical, genetic, epidemiological, and immunophenotypic evidence illustrating differences in AD among racial groups. Filaggrin (FLG) mutations, the strongest genetic risk factor for AD, are found in up to 50% of European and 27% of Asian AD patients, but are very rare in Africans. Th2 hyperactivation is a common feature across all ethnic groups, though the Asian endotype of AD is also marked by increased Th17-mediated signaling. In contrast, African Americans display a strong Th2/Th22 signature without Th1/Th17 skewing. The ethnic heterogeneity of AD has important therapeutic implications, as genetic predispositions may affect treatment responses. This suggests the need for tailored strategies that better target the dominant immunologic pathways in each ethnic subgroup. However, white patients with AD constitute the majority in clinical trials and real-world treatments, limiting data on safety and efficacy across different ethnicities. This review aims to describe the heterogeneity in AD pathophysiology across ethnicities and explore its potential therapeutic implications.

Introduction:

Atopic dermatitis (AD) is one of the most common immune-mediated skin disorders, characterized by a chronic-relapsing course and multifactorial pathogenesis . The prevalence of AD is very high worldwide, affecting individuals in Asia, Africa, and Latin America, across different ethnic groups and ages .

Clinically, AD is marked by itchy eczematous lesions that primarily involve the flexural areas, face, neck, and distal extremities. The condition can precede other non-cutaneous atopic manifestations, such as asthma and allergic rhinitis (AR), leading to the so-called “atopic march” .

Unlike other inflammatory skin diseases, AD exhibits significant clinical heterogeneity, prompting researchers to consider it a spectrum rather than a single entity. Consequently, recent efforts have focused on characterizing disease subtypes based on various parameters, including phenotypes, skin barrier status, IgE levels, age, gender, and ethnicity . Specific molecular signatures have identified different endotypes across age groups and ethnicities, as well as variations according to IgE levels and filaggrin mutation status .

Depending on the patient’s racial background, AD presents distinct clinical, genetic, and immunopathogenic features . However, Caucasian patients with AD remain the most studied ethnic group, resulting in incomplete understanding of the differences and similarities in disease pathophysiology across various ethnicities.

This review aims to explore the current insights into AD heterogeneity based on patient ethnicity and to analyze the potential therapeutic implications of these pathophysiologic differences.

Clinical Features

Atopic dermatitis (AD) manifests in several phenotypes based on lesion distribution (e.g., flexural, head and neck, periorificial) or predominant clinical features, such as nummular eczema, prurigo nodularis, lichenified dermatitis, or follicular/papular dermatitis . The clinical presentation of AD can differ among ethnic groups, posing diagnostic challenges due to variations in lesion distribution and pigmentation .

Asian individuals with AD often present with lesions that have more defined borders, resembling psoriasis plaques, along with increased scaling and lichenification compared to white AD patients . In contrast, African AD patients typically exhibit predominant extensor involvement, with perifollicular accentuation and distinct papules on the extensor surfaces and trunk . Additionally, a lichen-planus-like presentation of AD has been observed exclusively in darker skin types .

Due to the almost complete absence of erythema in dark skin types, dermatologists may need to rely on other indicators such as edema, skin warmth, or overlying scale to identify the presence of erythema. Many clinical scoring systems, such as the Eczema Area and Severity Index (EASI) and the SCORing Atopic Dermatitis (SCORAD) index, depend on erythema to assess disease severity, potentially underestimating AD in darker skin types . Moreover, patients with darker skin more frequently exhibit xerosis, hyperlinearity of the palms, Dennie–Morgan lines, periorbital darkening, lichenification, and prurigo nodularis compared to white patients .

Finally, darker skin types have a higher risk of developing post-inflammatory hyperpigmentation or hypopigmentation .

Genetic Variability Across Ethnic Groups

Similar to other chronic inflammatory dermatoses, atopic dermatitis (AD) has a genetic predisposition based on a polygenic background. Certain genes, especially those related to skin barrier function, Th2 immune responses, and vitamin D metabolism, have been implicated in the predisposition to AD .

Recent genome-wide association studies (GWAS) have aimed to identify ethnic-specific genes in African, Asian, and Hispanic populations . Loss-of-function (LOF) mutations in the structural protein filaggrin (encoded by the FLG gene) represent the strongest genetic risk factor for AD. These mutations are found in up to 50% of European and 27% of Asian AD patients but are very rare in African populations . Filaggrin deficiency leads to defective barrier function, disrupted keratinocyte differentiation, impaired corneocyte integrity and cohesion, altered tight junction formation, decreased water retention, abnormal lipid formation, and increased susceptibility to skin infections . Patients with FLG LOF mutations exhibit more severe AD phenotypes, with a more persistent course, higher risk of skin infections and allergic sensitization, and greater immune system impairment compared to those with wild-type FLG .

Filaggrin LOF mutations show population specificity. The first characterized mutations, R501X and 2282del4, as well as S3247X and R2447X, are present in 7-10% of the white European population but are absent in Asian populations, which have different FLG variants . Common FLG LOF mutations are not detected in people of African ancestry with AD, although decreased filaggrin levels have been reported in their skin . No association between FLG LOF mutations and AD has been found in African populations (e.g., Ethiopians), but a relationship has been described in African Americans, likely due to genetic admixture . Overall, FLG LOF mutations are six times less common in subjects of African descent than in those of European and Asian descent, suggesting a minor role in AD development in African populations .

The absence of FLG gene mutations in African populations has prompted further genetic investigations. Whole-exome sequencing (WES) in Ethiopian AD patients revealed an association between LOF mutations in the FLG2 gene and persistent AD . The FLG2 gene, located within the epidermal differentiation complex (EDC), shares molecular structure and biological functions with FLG . Similar findings have been observed in African American cohorts, whereas no association has been found between FLG2 mutations and AD in European subjects .

Beyond the EDC, mutations in genes encoding proteins involved in maintaining epidermal homeostasis have been identified in specific ethnicities. For instance, claudin-1 (CLDN1) gene mutations, associated with early-onset AD in Ethiopian patients, may play a role in AD susceptibility in this population . Additionally, LOF mutations in the SPINK5 gene, encoding a serine protease inhibitor involved in epidermal homeostasis, have been associated with AD in East Asian populations .

The second class of genes implicated in AD susceptibility involves the innate and adaptive immunity, particularly the Th2 pathway central to AD pathogenesis. Polymorphisms in IL-4, IL-13, IL-31, IL-4RA, and IL-31RA1 genes, all part of the Th2 pathway, have been correlated with an increased risk of developing AD . These immune response genes show ethnic-specific differences. For example, IL-4 and IL-13/IL-13RA1 polymorphisms are associated with AD in Japanese, Korean, and Chinese populations, while IL-4RA and STAT6 polymorphisms are linked to AD in Egyptian children . A specific polymorphism (Q576R) of the IL4Rα gene, associated with AD severity in murine models, is over-represented in the African American population .

Other genes contributing to AD pathogenesis, such as STAT6, thymic stromal lymphopoietin (TSLP), IL7R, TSLPR, interferon regulatory factor 2 (IRF2), toll-like receptor 2 (TLR2), FcεRIα (FCER1A), and β-defensin (DEFB1), have been implicated in AD susceptibility across different ethnic groups . For example, IRF2 gene polymorphisms are associated with AD in European Americans and African Americans, while a TSLP variant (rs1898671) is linked to less persistent AD in white and African Americans . In Japan, a TLR2 variant is a genetic predictor of AD severity, and FCER1A polymorphisms are associated with higher IgE serum levels in AD patients . Variants in the DEFB1 gene, encoding an antimicrobial peptide in the epidermis, are linked to increased AD risk in Brazilian, Mexican, and Korean populations . Additionally, IL-12 and its receptor gene variants have been reported as susceptibility genes in Korean AD patients .

Pathogenesis

The pathogenesis of atopic dermatitis (AD) involves a complex interplay of genetic and environmental factors, leading to epidermal barrier disruption, commensal skin microbiota dysbiosis, and immune response alterations. These factors contribute to both the occurrence and exacerbation of the disease.

The role of skin microbiota in AD is well-established. Over 90% of AD patients have skin lesions colonized by *Staphylococcus aureus*, with the density of this bacterium correlating with AD severity. During flares, AD skin exhibits reduced microbiota diversity, favoring *S. aureus* dominance. Notably, *S. aureus* colonization in infancy often precedes an AD diagnosis, suggesting it may trigger the disease. Differences in *S. aureus* colonization and the prevalence of specific bacterial virulence factors among ethnic groups may partly explain the molecular and phenotypic heterogeneity of AD across ethnicities, contributing to a mixed immune dysregulation involving Th2, Th22, and Th17 cells. Environmental factors such as tobacco smoking, sun exposure, and psychosocial stressors can also impact disease onset or severity, with significant variations across ethnicities. For instance, racial and ethnic disparities exist in tobacco use, sun exposure habits, and the psychosocial impact of racism, discrimination, and acculturative stress, particularly among ethnic minorities.

Immune Mechanisms Involved in AD Pathogenesis

The current model of AD pathogenesis centers on the activation of type 2 immune cells, such as T helper (Th)2 cells, T follicular helper (Tfh) cells, innate lymphoid cells 2 (ILC2), T cytotoxic (Tc)2 cells, eosinophils, mast cells, and basophils, with additional contributions from other pathways, including Th/Tc22, Th9, Th1, Th/Tc21, and Th17. In the initial phases of the pathogenic cascade, keratinocytes are activated by excessive exposure to allergens, irritants, and microbial antigens due to an epidermal barrier disruption. This activation leads to the release of chemokines such as thymus and activation-regulated chemokine (TARC/CCL17), macrophage-derived chemokines (MDC/CCL22), and innate immune cytokines like IL-1β, IL-33, and thymic stromal lymphopoietin (TSLP). These cytokines activate ILC2s and Th2 cell-mediated immune responses. Specifically, TSLP-activated dendritic cells express OX40 ligand (OX40L), which binds to its receptor OX40 on naive T cells, inducing Th2 differentiation and production of Th2 cytokines (IL-4, IL-5, IL-13, and IL-31). ILC2s also contribute to the type 2 inflammatory cytokine milieu by producing IL-5 and IL-13.

While the type 2 signal dominates both acute and chronic phases of AD and is consistently elevated across all ethnic groups, upregulation of other immune pathways varies among ethnicities. The Asian endotype of AD is characterized by a strong Th17 signature and specific clinical and histological features. Gene expression profiles of European American, Japanese, and Korean AD patients reveal strong Th2 activation in both Asian and European American patients, but not in psoriasis patients. Asian AD patients show higher expression of Th17 and Th22 markers (IL17A, IL19, S100A12, IL-22) and lower expression of Th1 genes (CXCL9, CXCL10, IFNG), with greater acanthosis, higher Ki67 counts, and frequent parakeratosis, suggesting overlapping features with both European AD and psoriasis.

Further studies on Chinese AD patients have shown similar Th17/Th2 or blended AD–psoriasis endotypes across all Asian AD patients. Both Asian and European American AD patients exhibit upregulated serum Th2 markers, but Asian patients have lower Th1 marker expression (IFNγ, CCL2, CCL3, CCL4) and increased Th22 activation. However, serum levels of Th17 markers are not elevated in Asian patients.

In African American AD patients, gene expression analysis reveals a strong Th2/Th22-skewing, with significant correlations between Th2 and Th22 markers and disease severity. Additionally, African American patients show attenuation of the Th1 and Th17 axes compared to European Americans. Their skin also exhibits distinct barrier changes, such as a lower decrease in filaggrin but greater reduction in loricrin, differentiating them from European AD subjects.

Therapeutic Implications in Different Ethnic Subgroups

Currently, therapeutic approaches and recommendations for treating atopic dermatitis (AD) do not vary across ethnic groups, and ethnicity is not a consideration in current European or American guidelines and recommendations . Research into the effects of therapeutic agents on AD across different ethnicities has been limited.

In daily clinical practice, topical steroids are generally effective for all skin types. However, they should be used cautiously as they can frequently induce or worsen hypopigmentation in darker skin types .

A study on the use of 1% pimecrolimus cream in AD patients of different ethnicities showed that treatment outcomes were not influenced by ethnicity . Similarly, a pooled data analysis comparing the efficacy and safety of tacrolimus ointment across eight Asian countries, the United States, Europe, and Japan reported consistent results across these regions .

For moderate-to-severe AD, phototherapy, particularly narrowband UVB (NB-UVB), is a viable option. A study in Singapore found both NB-UVB and UVA/NB-UVB-based phototherapy effective in treating AD in Asian children . However, special considerations are necessary for darker skin types: NB-UVB may require higher doses , while UVA1 phototherapy is equally effective across Fitzpatrick skin types I-V without dose adjustment .

Systemic therapies may exhibit different efficacy and safety profiles across ethnicities, influenced by variations in drug metabolism and bioavailability. For example, black individuals have 20–50% lower bioavailability of cyclosporine compared to white individuals, necessitating higher doses . Methotrexate use is associated with a higher risk of alopecia in black patients . Azathioprine can cause severe toxicity in black patients at standard dosages due to a higher prevalence of thiopurine methyltransferase (TPMT) deficiency in this population .

Dupilumab, a fully human monoclonal antibody targeting the shared IL4Rα subunit of IL-13 and IL-4, was the first biologic agent approved for moderate-to-severe AD treatment . Phase III trials of dupilumab included 20–27% Asian and 5–7% Black patients, demonstrating comparable efficacy across diverse

populations . A post-hoc analysis from three phase III trials (LIBERTY AD SOLO 1, SOLO 2, and CHRONOS) confirmed the efficacy and safety of dupilumab across racial subgroups (White, Asian, Black/African American), highlighting its favorable benefit–risk profile . The identification of a specific IL4Rα gene polymorphism (Q576R) prevalent in the African American population further supports dupilumab's efficacy in this subgroup . Additionally, a cross-sectional study in the U.S. found dupilumab equally effective in improving quality of life among white, Asian, and Black/African American patients .

New biologic agents and small molecules, including tralokinumab , upadacitinib , baricitinib , and abrocitinib , have recently been approved for moderate-to-severe AD treatment, with many others under investigation. Tralokinumab, an IgG4 monoclonal antibody that binds with high affinity to IL-13, has shown substantial improvement in AD severity and symptoms in phase III trials . A sub-analysis of tralokinumab phase III trials (ECZTRA 1, 2, and 3) evaluated its efficacy and safety in North American versus non-North American populations. The North American cohort included 30–52% patients with skin of color, compared to 5–25% in the non-North American cohort. The post-hoc analysis confirmed tralokinumab's safety and efficacy regardless of ethnicity .

Discussion

Recent years have witnessed a surge of interest in understanding the clinical and molecular diversity of atopic dermatitis (AD) across different ethnicities. This interest has spurred the development of clinical, genetic, epidemiological, and molecular studies aimed at characterizing the disease's subtypes. While similarities among ethnic groups outweigh differences in all disease aspects, accumulating evidence suggests race-specific variations in epidermal structure and the magnitude of upregulation related to certain immune pathways.

Healthy skin from European, African, and Asian populations may exhibit significant molecular distinctions. For example, the higher prevalence of filaggrin (FLG) mutations in European populations could be attributed to evolutionary pressures, providing enhanced immunity against infections and possibly ensuring greater vitamin D synthesis in the skin, conferring an evolutionary advantage at high latitudes.

Interestingly, even the atopic march, which involves the progression from food allergy, asthma, allergic rhinitis, to conjunctivitis after AD, may demonstrate racial variability. Longitudinal studies have revealed wide differences in allergic comorbidity trajectories between black and white children with AD. Black children exhibit a higher risk of asthma but a lower risk of allergic rhinitis and food allergy compared to white children. These differences may stem from ancestral genetic variabilities and exposure to various race-specific environmental risk factors.

Overall, the presence of extracutaneous atopic manifestations underscores the prominent role of type 2 inflammation in all ethnic groups. However, the contribution of other immune pathways has led to the identification of endotypes corresponding to specific phenotypes. For instance, the relatively high upregulation of the Th17 signal in Asian AD compared to European AD skin could explain the predominance of well-demarcated, psoriasiform lesions in Asian patients. Still, it cannot entirely account for why the inhibition of IL-17A failed to demonstrate clinical, histopathological, and transcriptomic benefits.

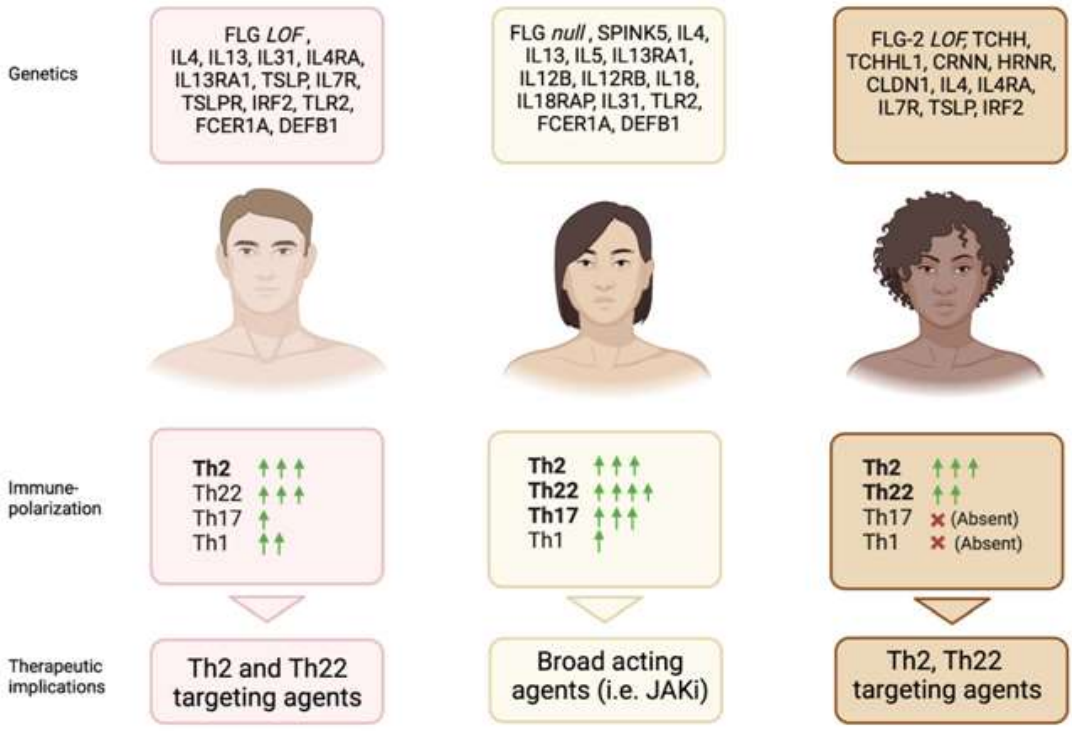

Figure 1: Main Genetic, Clinical, and Immunological Features in AD Patients Across Ethnicities

This figure illustrates the predominant genetic, clinical, and immunological features observed in atopic dermatitis (AD) patients across different ethnicities, along with potential therapeutic implications.

Key Features:

FLG: Filaggrin

LOF: Loss-of-function

IL: Interleukin

TSLP: Thymic Stromal Lymphopoietin

IRF2: Interferon Regulatory Factor 2

TLR2: Toll-like Receptor 2

FCER1A: Fcε Receptor 1α

DEFB1: β-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 visual representation highlights the genetic predispositions, immune polarization, and potential therapeutic implications across various ethnic subgroups affected by AD. It emphasizes the role of specific genetic mutations, cytokine profiles, and novel drug targets in understanding and treating AD within diverse populations.

Conclusions

While differences in clinical phenotypes and immune endotypes across various ethnicities in atopic dermatitis (AD) are evident, they remain incompletely understood.

However, recognizing this ethnic heterogeneity holds significant therapeutic implications. The current "one-size-fits-all" therapeutic approach may not always yield satisfactory outcomes and may not be optimal. Thus, future investigations should aim to stratify AD populations more precisely by ethnicity, paving the way for the development of personalized and tailored treatment approaches that better target the specific immunologic pathways involved in each ethnic subgroup.

Regrettably, data regarding ethnicity are largely unavailable for most new agents for AD. Therefore, it is crucial to advocate for the inclusion of diverse ethnic groups in randomized clinical trials and to conduct sub-analyses by race, as these efforts are essential for advancing our understanding and improving treatment outcomes for all affected individuals.

References List:

[1]. Prakash, S., Malaiyappan, J. N. A., Thirunavukkarasu, K., & Devan, M. (2024). Achieving Regulatory Compliance in Cloud Computing through ML. AIJMR-Advanced International Journal of Multidisciplinary Research, 2(2).

[2]. Malaiyappan, J. N. A., Prakash, S., Bayani, S. V., & Devan, M. (2024). Enhancing Cloud Compliance: A Machine Learning Approach. AIJMR-Advanced International Journal of Multidisciplinary Research, 2(2).

[3]. Devan, M., Prakash, S., & Jangoan, S. (2023). Predictive Maintenance in Banking: Leveraging AI for Real-Time Data Analytics. Journal of Knowledge Learning and Science Technology ISSN: 2959-6386 (online), 2(2), 483-490.

[4]. Eswaran, P. K., Prakash, S., Ferguson, D. D., & Naasz, K. (2003). Leveraging Ip For Business Success. International Journal of Information Technology & Decision Making, 2(04), 641-650.

[5]. Prakash, S., Malaiyappan, J. N. A., Thirunavukkarasu, K., & Devan, M. (2024). Achieving Regulatory Compliance in Cloud Computing through ML. AIJMR-Advanced International Journal of Multidisciplinary Research, 2(2).

[6]. Malaiyappan, J. N. A., Prakash, S., Bayani, S. V., & Devan, M. (2024). Enhancing Cloud Compliance: A Machine Learning Approach. AIJMR-Advanced International Journal of Multidisciplinary Research, 2(2).

[7]. Talati, D. (2023). Telemedicine and AI in Remote Patient Monitoring. Journal of Knowledge Learning and Science Technology ISSN: 2959-6386 (online), 2(3), 254-255.

[8]. Talati, D. (2023). Artificial Intelligence (Ai) In Mental Health Diagnosis and Treatment. Journal of Knowledge Learning and Science Technology ISSN: 2959-6386 (online), 2(3), 251-253.

[9]. Talati, D. (2023). AI in healthcare domain. Journal of Knowledge Learning and Science Technology ISSN: 2959-6386 (online), 2(3), 256-262.

[10]. Talati, D. (2024). AI (Artificial Intelligence) in Daily Life. Authorea Preprints.

[11]. Fan, K. (2024). Implications of Large Language Models in Medical Education. https://doi.org/10.62594/brmo4385

[12]. Ferdinand, J. (2024). Recognising Clinical Signs and Symptoms on Black, Asian and Minority Ethnic (BAME) Skin Types. https://doi.org/10.62594/ovfn5405