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Title: Atopic Dermatitis in Diverse Racial and Ethnic Groups – Variations in Epidemiology, Genetics, Clinical Presentation, and Treatment

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Abstract:

Atopic dermatitis (AD) is a chronic inflammatory skin condition that affects diverse ethnic groups with varying prevalence. Despite a predominance of studies in individuals of European ancestry, AD has been found to occur more frequently in Asian and black individuals than whites. Therefore, an understanding of the unique clinical features of AD in diverse ethnic groups, as well as the differences in genetic polymorphisms that influence

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susceptibility to AD and response to current therapies, is paramount for management of an increasingly diverse patient population. In this article, we review key nuances in the epidemiology, pathophysiology, clinical presentation, and treatment of AD in non-white ethnic groups, which are largely under-appreciated in the literature. We highlight the need for studies evaluating the tissue molecular and cellular phenotypes of AD in non-white patients, as well as greater inclusion of minority groups in clinical trials, in order to develop targeted treatments for a multi-ethnic population.

1. Introduction

Atopic dermatitis(AD) is a common, chronic inflammatory skin condition that classically develops during infancy and early childhood. AD occurs worldwide with varying prevalence depending on country and ethnic origin. However, limited data exists on the epidemiology, clinical features, different pathogenic pathways and respective differences in treatment of AD across different racial/ethnic groups.

2. Epidemiology of Atopic Dermatitis in Diverse Racial and Ethnic Groups

The prevalence of AD varies by country and has been increasing in recent years.[1] The International Study of Asthma and Allergies in Childhood(ISAAC) studied 385,853 participants in 60 countries from 1999-2004 and demonstrated a prevalence of eczema ranging from 0.2% to 24.6%.[2] In general, countries in Africa and Oceania have a higher rate of eczema and countries in the Indian subcontinent and Northern/Eastern Europe have a lower rate.[2] In Africa, the eczema prevalence ranges from 4.7% to 23.0%; however, there is wide variation between neighboring countries and even amongst cities within the same country.[3] In the Asia-Pacific region, 17.8% of children ages 6 to 7 years have been

diagnosed with AD, with prevalence ranging from 4% to 30% in different countries.[2]

Clinic-based investigations similarly demonstrate high variability in the reported prevalence of AD.[4]

The inconsistent estimates of AD prevalence within and between countries make it difficult to extrapolate the effect of ethnicity on the risk of developing AD. Nonetheless, population-based studies in the US have demonstrated a higher prevalence of AD in African American(AA) children than European American(EA) children.[5-9] The 2005-2006 National Health and Nutrition Examination Survey, which estimated a prevalence of AD of 15.6%, reported that eczema disproportionately affects AA (19.3%) compared to EA (16.1%) and Hispanics (7.8%).[7] Overall, AA children are 1.7 times more likely to develop AD than their EA counterparts, even when adjusting for household income, parental education level, metropolitan versus rural environment, and health insurance coverage status.[5] Consequently, children of African descent are three times more likely than white children to attend a dermatology visit during which AD is diagnosed, even though they are significantly less likely to seek dermatological care. An analysis of dermatology clinic visits from 1990-1998 found that, while AA only comprised 8.2% of visits, they received 20.1% of AD diagnoses, more than double the number per capita.[10]

A similarly disproportionate prevalence of AD in black children has been observed in Europe. A UK study demonstrated that, based on dermatologist examination, 16.3% of London-born black Caribbean children versus 8.7% of white children had AD.[11] The increased risk in black children persisted after adjusting for potential cofounders.[11] A clinic-based study in south-east London found AD to be the most frequently diagnosed dermatologic condition in black children, affecting 36.5% of those seen.[12]

The disproportionate number of AD cases in blacks compared to whites may reflect decreased health care utilization in black communities leading to more advanced disease at presentation.[10,13] The masking of erythema in skin of color may also contribute to diagnosis at a later stage or referral to dermatology for more severe disease.[14] A recent 2 year longitudinal cohort study found that, while blacks were less likely to report attending an office visit for eczema, those black patients who sought medical attention attended more office visits, received more prescriptions, and were more likely to see a dermatologist for their skin condition than whites.[13]

Similarly, Asians and Pacific Islanders are seven times more likely than whites to be diagnosed with AD at an office visit.[10] Nevertheless, large-scale population studies to corroborate this are limited.[10,15,16] The increased prevalence of AD in Asians (versus whites) may in part be due to differences in molecular phenotype, including stronger Th17/Th22 polarization and an overall phenotype that combines features of psoriasis and AD.[17] Interestingly, in both African and Asian countries, where AD seems more prevalent than in Europe or the US, there is a very low prevalence of psoriasis of below 0.5%, unlike its 2-3% prevalence in the US and Europe.[18-22]

3. Etiology and Genetics of Atopic Dermatitis in Non-European Populations

Atopic dermatitis is a complex disease that involves an interplay of genetic predisposition, immune dysregulation, skin barrier dysfunction, and environmental factors.[3-6,23-28]

Although initial genetics studies in AD focused on families of European ancestry, more recent genome-wide association studies(GWAS) in Asian, Hispanic, and African populations and growing collaborations amongst researchers worldwide have allowed for the identification of genes associated with the development of AD in diverse ethnic groups.[28-34] Paternoster et al. recently published the largest GWAS to date in European, Japanese, African, and Hispanic populations and found 15 million genetic variants in 31 AD risk loci, many of which varied between ethnic groups.[30]

Among the genes implicated in the pathogenesis of AD are those involved in immune regulation (innate host defenses, T-cell function, and autoimmunity) and epithelial barrier function (Table 1). Given the complexity of AD, it is unlikely that individual gene polymorphisms contribute significantly to the development of AD. Rather, AD likely results from the synergistic effect of multiple genes on cellular signaling, immune activation, and epidermal membrane structure.[28]

3.1 Skin Barrier Genes

Filaggrin (FLG) loss-of-function mutations are the most widely studied genetic link to AD across ethnic groups.[31,35-48] The FLG gene, located on chromosome 1q12 within the epidermal differentiation complex (EDC), encodes filaggrin, a major structural protein in the stratum corneum. Filaggrin deficiency contributes to inherent barrier defects in atopic skin that, in combination with the effects of inflammatory cytokines and environmental factors, results in the development of AD.[28,32,49-52] Studies in Europeans and Asians have consistently demonstrated that loss-of-function mutations in the FLG gene, present in up to 50% of European and 27% of Asian AD cases, are a major predisposing factor for the development of AD.[21,41,49,53] Patients with FLG mutations exhibit earlier onset of AD, more severe disease, a higher rate of eczema herpeticum, and a greater incidence of other atopic diseases as compared to those with wild-type FLG.[35,42,43,49,54,55] The most common FLG loss-of-function mutations (R501X, 2282del4, S3247X, R2447X) are present in 7-10% of white Europeans.[35,49] These mutations are rare in Asian populations, who all exhibit FLG null mutations unique to their ethnic groups.[41,56]

The association between FLG mutations and AD is less clear in people of African ancestry, and several investigators have failed to find any association at all (Table 2).[43-47,50,57-59] Research in Ethiopia has found no relationship between FLG null mutations or

copy number variations and the development of AD.[58,59] Several studies in the US have demonstrated an association between FLG null mutations and AD in AA individuals, likely due to the effect of genetic admixture in this population.[43,44,60] Overall, studies suggest that FLG mutations are about 6 times less common in AA than EA.[43] The four most common FLG null mutations occur in less than 5.8% of AA versus 27.5% of EA.[42-44] The prevalence appears to be higher in AA with both AD and ichthyosis vulgaris, with one study demonstrating FLG null mutations in 22.2% of individuals with both diagnoses.[60] Like in whites, low intragenic copy number variation in AA is associated with severe AD, and each additional FLG monomer decreases the odds of developing AD by 0.88.[46]

Evolutionary pressures may explain the higher rate of FLG mutation in Europeans and relative paucity in non-European ethnic groups. The increased skin barrier permeability in filaggrin-deficient skin may enhance immunity to infections, conferring an evolutionary advantage that selected for individuals with FLG mutations during European pandemics.[61,62] Additionally, FLG may have an evolutionary advantage in higher latitudes (i.e. Northern Europe) through its role in increasing vitamin D biosynthesis.[63,64] Vitamin D₃ levels are 10% higher in German and Danish individuals with FLG mutations, which is thought to be due to FLG's downregulation of an endogenous UVB filter in the skin.[63]

Given the paucity of FLG mutations in certain ethnic groups, and the fact that immune-mediated skin inflammation is similar in individuals with and without FLG mutations, there are likely other genes responsible for epidermal dysfunction in AD.[58,65,66] Upregulation of Th2 cytokines IL-4 and IL-13 has been shown to downregulate FLG expression, resulting in acquired filaggrin deficiency and impaired epidermal barrier function irrespective of FLG mutation status.[50,67] Release of IL-22 and IL-25 has also been associated with decreased filaggrin expression in the skin.[51,52]

Dysregulation of other genes within the EDC, including upregulation of loricrin and downregulation of involucrin, has been implicated in both non-lesional and lesional AD skin.[28,48,68-71] Recently, whole exome analyses of AA and Ethiopian patients with AD revealed an association with loss-of-function mutations in filaggrin-2(FLG-2), which encodes a protein closely related to filaggrin.[44,59,72] AA children with a FLG-2 loss-of-function mutation or non-synonymous variant were 50% more likely to have persistent AD, but there was no effect on incidence, age of onset, or disease severity.[72] These results are consistent with a recent study demonstrating a correlation between decreased FLG-2 expression in the skin and active skin inflammation due to AD.[73] Interestingly, initial studies in Europeans failed to identify an association between FLG-2 and AD, which is consistent with known differences in gene expression patterns between European, African, and Asian skin.[74-76]

Variants in claudin 1(CLDN1), a tight junction gene, have been associated with early onset AD (younger than 5 years of age) in an Ethiopian cohort.[77] In East Asia, AD has been linked to loss-of-function mutations in SPINK5, a serine protease inhibitor that plays a key role in epidermis homeostasis.[32,78-81]

3.2 Immune-Related Genes

Polymorphisms in genes involved in innate and adaptive immunity, particularly those involved in Th2 signaling pathways, also have been implicated in the pathogenesis of AD and appear to differ amongst ethnic groups.[66] Polymorphisms of Th2-related genes IL-4, IL-13, and IL-31 and their receptors (IL-4RA, IL13RA1) are associated with increased risk of AD due to alternations in signal transduction pathways.[28,30,48,67,82-91] Upregulation of IL-4 and IL-13 also has been shown to downregulate FLG expression, resulting in epidermal barrier dysfunction in the absence of FLG mutations.[50,67] In Egyptians, there is an association between IL-4/IL-4R α polymorphisms

and susceptibility to AD.[89] Research has also found associations between AD and polymorphisms in IL-4 and IL-13/IL-13R α 1 in Japanese, Chinese, and Koreans.[86,89,92,93]

Other immune-related genes that have been implicated in the pathogenesis of AD in specific ethnic groups include STAT6, thymic stromal lymphopoietin(TSLP) and its receptors(IL-7R and TSLPR), interferon regulatory factor 2(IRF2), toll-like receptor 2(TLR2), Fc ϵ silonRIalpha gene(FCER1A), and B-Defensin 1(DEFB1).[34,89,94-96] TSLP variant rs1898671 has been associated with less persistent AD in both blacks and whites, whereas genetic variants in IRF2 have been associated with an increased risk of AD in both ethnic groups.[97,98] TLR2 and FCER1A, a marker associated with atopic dendritic cells, have been implicated in Japanese populations.[99-102] Mutations in DEFB1, an anti-microbial peptide, have also been associated with increased risk of AD in Mexican, Korean, and Brazilian populations.[103-105]

3.3 Environmental Triggers

Gene-environment interactions play a key role in the pathophysiology of AD and may help explain differences in prevalence and severity between different ethnic groups and/or geographic regions.[28,106] Most studies have shown that living in a metropolitan area is associated with a higher risk of AD, likely due to differences in environmental pollution, contact with tobacco smoke, hygiene practices, diet, rates of breastfeeding, and exposure to infectious disease.[3-5] Differences in skin *Staphylococcal aureus* colonization, including variability in the prevalence of specific bacterial virulence factors, between ethnic groups may partially explain differences in disease severity.[107] Higher latitude and lower annual outdoor temperature also are associated with greater rates of AD, whereas subtropical climates (high temperature and humidity) appear to be protective.[6,108] Use of topical emollients during the neonatal period has been shown to decrease the risk of AD in Japanese infants.[109] Allergy to dust mites, intra-natal exposure to a newly renovated or decorated house, and high levels of household mold may

play a role in Chinese children and adults.[110,111] In Taiwan, people born in October through December are more likely to develop AD.[53]

4. Presentation of Atopic Dermatitis in Skin of Color

The presentation of AD is considered to be similar amongst ethnic groups. Important nuances in the visual appearance of AD, which are largely underappreciated in the literature, are predominantly due to differences in pigmentation and distribution of the lesions.

Classically in AD, pruritic, erythematous plaques with fine overlying scale develop on the flexor surfaces, particularly the posterior neck and antecubital and popliteal fossae. Asian individuals tend to have more well-demarcated lesions and increased scaling and lichenification when compared to whites.[17,112] Patients of African descent less commonly develop flexural dermatitis, but rather present with extensor involvement as a more prominent feature(Fig.1).[113] Perifollicular accentuation and scattered distinct papules on the extensors and trunk are also more common in dark-skinned individuals, affecting up to 54.1% of patients in one Nigerian study(Figs.2-3).[114-116] A lichen planus-like presentation of AD has been observed exclusively in dark-skinned individuals.[117] This variant usually presents on extensor surfaces, lacks lichenification, and responds more rapidly to treatment.

Even in patients with a typical distribution and morphology of lesions, the appearance of AD varies based on skin color. Erythema in darker skin is more likely to appear violaceous or may be missed completely(Fig.4A,B). The presence of edema, skin warmth, or scale may help patients and providers perceive underlying erythema. Nonetheless, the use of common scoring systems that rely on skin erythema, including SCORAD, SASSAD, NESS, and EASI,

dramatically underestimate the severity of AD in darker skin types.[14,113] After adjusting for erythema score, black children have a six times higher risk of severe AD than their white counterparts.[14]

Other classic findings more commonly seen in darker skin types include diffuse xerosis, Dennie-Morgan lines, and hyperlinearity of the palms.[114] Black patients are also more likely to develop periorbital dark circles, lichenification, and prurigo nodularis than whites(Fig.5).[113,114] This may be due to greater pruritus and consequent increased rubbing and scratching in black patients with AD.[118,119]

Patients with darker skin types are also at higher risk for developing post-inflammatory dyspigmentation(Fig.6A,B).[120,121] Hypopigmented skin is often more noticeable in skin of color due to the contrast with normal skin.[12,122] Oftentimes the resulting dyspigmentation may be more distressing than the skin findings of AD itself. Fortunately, alterations in skin pigmentation may return to normal within weeks to months. Chronic excoriation associated with severe eczema, however, may result in permanent depigmentation in darker skinned patients(Fig.7).

Beyond differences in clinical appearance, AD may appear molecularly and histologically distinct in ethnic skin. This may in part be due to differences in epidermal gene expression between white, Asian, and black individuals with AD, with resulting race-specific alterations in epidermal structure.[43,44,56,57,76,123] In a study comparing white and Asian AD patients from Korea and Japan, Asians showed increased epidermal hyperplasia (increased epidermal thickness and Ki67 counts) and frequent parakeratosis, which often characterizes psoriasis and is infrequent in white patients with AD.[17,48,124-126] These histological changes were accompanied by similar Th2 activation but significantly increased gene expressions of Th17 and Th22-related markers.[17] This is particularly significant given that 26 of the 27 Asians studied had extrinsic AD (high IgE levels), which tends to be

associated with lower Th17 expression than intrinsic AD.[17,127] Th17-polarized cells have also been shown to be increased in the peripheral blood, where the percentage of Th17 cells positively correlates with the severity of AD.[128] Overall, the Asian AD phenotype resembles a mixture of European AD and European psoriasis profiles on a cellular and molecular level.[17,100,125,126,129] This data has important therapeutic relevance as, in addition to Th2 targeting therapies, approaches targeting the Th17/IL-23 axis may also provide benefit in Asian AD patients.[17,48,126,130]

A recent study in European patients using *in vivo* confocal Raman microspectroscopy to evaluate alterations in the molecular structure of atopic skin demonstrated a decrease in total water content, decreased lipid content, differences in lipid matrix conformation and organization, and changes in epidermal protein structure.[123] Given the apparent race-specific genetic polymorphisms associated with AD, particularly with regard to FLG mutations, there are likely differences in epidermal structure between ethnic groups that have yet to be studied.[17,43,44,56,57,76,123] This may explain the difference in transepithelial water loss (TEWL) between EA and AA with AD, with recent research suggesting a lower rate of TEWL in AA despite an overall greater severity of disease.[131-133] Future research should aim to evaluate differences in epidermal structure in AD between European, Asian, African, and Hispanic populations that may help direct therapy in diverse ethnic groups.

5. Treatment of Atopic Dermatitis

Despite the high prevalence of AD in skin of color populations, there is little data on the efficacy of common therapies for AD in non-white ethnic groups. This is, at least in part, due to underrepresentation of some races in clinic trials as well as lack of subset analyses by race.[134-136] Of AD clinical trials published between 2000-2009, only 59.5% of studies included race and ethnicity as baseline demographic information.[134]

The majority of patients included were white (62.1%), followed by 18.0% black, 6.9% Asian, and 2.0% Hispanic. Only 10.3% of studies commented on race or ethnicity in the interpretation of results, making it difficult to extrapolate the results to other ethnic groups.[134]

The current recommendations for treatment of AD are similar across ethnic groups, with minor nuances due to differences in skin phototype, genetics, and cultural practices. The first-line therapy for AD is topical anti-inflammatory agents, either corticosteroids or calcineurin inhibitors. A new topical phosphodiesterase 4 inhibitor, crisaborole, is also approved for the treatment of mild-to-moderate AD, and several other topical therapies are in development (NCT03351777, NCT03011892, NCT02925793). A study of pimecrolimus cream 1% in whites, blacks, Asians, and Hispanics showed no difference in treatment outcome amongst ethnic groups.[137] Pooled data on the efficacy of tacrolimus ointment in eight Asian countries demonstrated an 80% success rate in the treatment of AD, which is on par with studies in Europe, the US and Japan.[138] Clinical trials of tacrolimus in the US included black patients but did not stratify treatment response by ethnicity.[139,140] Phase III studies of crisaborole enrolled almost 40% non-whites, the majority of whom (27.9%) were black, and demonstrated a statistically significant improvement in psoriasis severity and quality of life measures in the black and Hispanic subgroups.[141,142] Numeric improvement was seen in Asian/Pacific Islanders and American Indians, but did not reach statistical significance due to the small number of participants in these subgroups.[142] Clinical experience also suggests that topical steroids are highly effective in different skin types, although this has not been proven in the literature. There is some concern that use of topical corticosteroids in darker skin types may worsen hypopigmentation; however, hypopigmentation is more likely related to post-inflammatory changes than a medication effect.[113]

For recalcitrant AD, alternative treatment options include phototherapy, immunosuppressive agents (cyclosporine, mycophenolate, azathioprine, methotrexate), intravenous immunoglobulin (IVIG), IFN- γ , and biologics.[143-145] Studies in Asian

populations have suggested that narrowband(NB)-UVB and UVA/NB-UVB are effective in the treatment of moderate to severe AD.[146] NB-UVB, which is generally preferred in the treatment of AD, requires higher doses in more pigmented skin types.[143,147,148] UVA1 is thought to be faster and more efficacious for treating acute AD, and is equally effective in skin types I-V without requiring dose adjustments.[146,149]

There is little data comparing the efficacy of systemic therapies between ethnic groups; however, differences in drug pharmacokinetics and skin and blood phenotypes of different ethnic groups may affect treatment outcomes.[17,25,48,124,136,150] Certain enzymatic deficiencies, polymorphisms in CYP450 genes, or variations in oral bioavailability may affect the optimal dose and side effect profile of medications in certain populations.[113] The true impact of differences in drug pharmacokinetics, cytokine profiles, and epidermal membrane structure on treatment response has yet to be elucidated.

Recent research has focused on biologics and small molecules targeting Th2, Th22, and Th17/IL-23 pathways.[48,124,130,151,152] Phase II and III trials of dupilumab, a fully human monoclonal antibody targeting the shared α -subunit of the IL-4 and IL-13 receptors, have demonstrated substantial improvement in severity and symptoms of AD, improvements in Th2 pathways, and normalization of the epidermal barrier.[153-157] Phase III trials of dupilumab included 20-27% Asians and 5-7% blacks, suggesting efficacy in diverse ethnic groups.[155-158] A subsequent pooled sub-analysis by race demonstrated numerically comparable results between white, black, and Asian individuals.[156,158] These results were limited by the small number of black subjects.[158]

Currently monoclonal antibodies directed against IL-13 (NCT02340234, NCT03363854, NCT03160885, NCT03131648), IL-22 (NCT01941537), and IL-31 (NCT01986933, NCT03100344), as well as oral Janus kinase (JAK) inhibitors (NCT03334435, NCT03334422, NCT03334396) and compounds that antagonize the chemoattractant receptor homologous molecule expressed on Th2 cells (CRTH2) (NCT01785602, NCT02002208) are being studied in clinical trials.[48,152,158]

Inclusion of diverse ethnic groups and subset analysis by race will be important as we assess novel therapies, both in terms of differences in treatment and placebo responses and changes in the molecular phenotype in skin and blood of patients. Further, future studies must seek specific and potentially unique molecular targets in blacks, Asians, and Hispanics that may allow for the development of targeted treatments for these populations in-need.[5,10,134,137,158]

6. Cultural Considerations in the Management of AD

Recognition of common cultural practices and traditional herbal remedies used for the treatment of AD is paramount. In African, Asian, and Hispanic cultures, patients often use herbal remedies for skin ailments prior to (and while) seeking dermatological care, which may have significant implications on treatment outcome.[159,160] While some cultural remedies have been shown to be beneficial in AD, the associated risks are largely unknown.

In Chinese, Korean, and Southeast Asian cultures, oral herbal preparations, bath therapy, and topical treatments (oils, ointments, plasters, poultices) are commonly used for skin conditions.[161] Interestingly, ingestion of Chinese Herbal Medicine(CHM) and Japanese Kampo medicines may improve erythema and inflammation in patients with AD, and may have additive benefits when combined with Western medicine.[162-166] A meta-analysis of nine randomized controlled trials showed that a combination of CHM and Western medicine is superior to Western medicine alone, and that, when compared to placebo, CHM significantly improves erythema, surface damage, pruritus, sleep scores, and quality of life.[165] Several adverse events have been reported with the use of CHM, including liver enzyme elevations, gastrointestinal upset, rashes, dizziness, and headache.[165,166] Therefore, providers should thoroughly review the risk/benefit profile with any patient who uses or plans to use CHM.

Alternative medicine practices are also common in Africa, Mexico, and Central America. A clinic-based study in Lagos, Nigeria showed that 65% of patients applied an herbal remedy prior to seeking dermatological treatment, including several herbs shown to be beneficial in AD: *Adansonia digitata*, *Azadirachta indica*, *Jatropha gossypifolia*, and *Ocimum gratissimum*.^[159] Unfortunately there is limited data on the safety of these products. In some Mexican and Central American cultures, where illness is thought to be an imbalance between hot and cold states, patients may treat “hot” skin eruptions with “cold” remedies including oatmeal, cornstarch, amica, lubricating lotions, and skin rubs containing alcohol, lemon juice, or watermelon peel. While oatmeal and lubricating lotions are beneficial, harsh rubs and excessive bathing may worsen skin inflammation.^[167]

7. Conclusion

A thorough understanding of the unique genetic, clinical, and molecular features of AD across a broad range of racial/ethnic AD subtypes is critical as we care for an increasingly multi-national patient population. Variability in the frequency and type of mutations in genes involved in skin barrier function (i.e. FLG, FLG-2, SPINK5) and innate/adaptive immunity (i.e. IL-4, IL-13, DEFB1) likely impacts the incidence and severity of AD in certain populations.^[37,44,46,54,55,67,72,78,88,104,105] The differential expression of inflammatory cytokines helps explain the predominance of more lichenified, well-demarcated and scaly lesions in Asians compared to whites.^[17,127] Further characterization of genetic and molecular features of AD in other non-white populations may help explain the unique features seen in these groups.

Genetic variability between ethnic groups likely also has important implications on the treatment of AD. Further studies looking at differences in treatment response and safety profiles in black, Asian, and Hispanic individuals are needed. Following on recent research

using Th17-targeting approaches in Asians, future studies should aim to develop personalized medicine approaches for AD patients across different races and in different parts of the world.[17,48,130,168]

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Figure Legends:

Figure 1: Lichenified, hyperpigmented plaques due to AD on the extensor surface of the right forearm in a black female.

Figure 2: Atopic dermatitis with severe lichenification and follicular accentuation on the anterior leg and dorsal foot in a black female.

Figure 3: Papular predominance in a Filipino woman with AD.

Figure 4A,B: Violaceous hue of AD in type 5 skin due to background constitutive pigmentation.

Figure 5: Lichen simplex chronicus with hyperpigmentation in black skin.

Figure 6A,B: AD with post-inflammatory hyperpigmentation in a black male (A) and perioral AD with post-inflammatory hypopigmentation in a 4 year old black girl (B).

Figure 7: Permanent depigmentation of the anterior legs resulting from chronic excoriation in a black female with severe AD.

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Author Contribution

All authors contributed to the original concept and defined the scope of the review article. BPK prepared the first draft. AFA and EGY provided critical draft reviews, feedback, and revisions on the manuscript. All authors approved submission to the journal.

Conflicts of Interest:

AFA is a member of the advisory board for Pfizer, Galderma, and Sanofi-Genzyme/Regeneron; has been an investigator for Galderma- and LEO-sponsored clinical trials. EGY is a member of the advisory board for Sanofi-Aventis, Regeneron, Stiefel/GlaxoSmithKline, MedImmune, Celgene, Anacor, and LEO; has received consultancy fees from Regeneron, Sanofi-Aventis, MedImmune, Celgene, Stiefel/GlaxoSmithKline, Celsus, Bristol-Myers Squibb, Amgen, and Drais; and has received research support from Regeneron, Celgene, Bristol-Myers Squibb and Janssen. BPK has received consultancy fees from Sanofi-Genzyme/Regeneron.

Table 1: Genetic Susceptibility to Atopic Dermatitis in Diverse, Non-European Ethnic Groups

Gene Symbol	Gene Name	Locus	Mutation or Allele Repeat	Susceptibility	Level of Association with AD in Non-Europeans	Ethnicity	Ref.
Epidermal Differentiation Complex							
FLG	Filaggrin	1q21	R501X Q507X R3409X S3707X 2282del4 R2447X S3247X 632del2 rs12730241	Increased	Strong association A strong relationship between FLG and AD has been demonstrated through large GWAS, genetic sequencing in case-control and prospective cohort studies, and meta-analyses of GWAS (24 to 21,399 subjects with AD).	African American	[30,42-44,47]
			rs2065956	Decreased		Chinese	[31,34,36,37]
			P478S 441delA 1249insG Q2417 E2422 7945delA R4307 3321delA K4671X	Increased			
			3321delA S1695 Q1701 S2554X S2889X S3296X K4022 Lys4021X	Increased		Japanese	[28,30,31,33,38-40]
			306delAAAGCACAG 3321delA S1515 R1891 W1947 E3070 S3296 K4022	Increased		Korean	[41]
FLG-2	Filaggrin-2	1q21	S2377X S2392X	Increased	Weak association The MAF of FLG-2 in AD has been shown to be similar to that of the overall population (based on 1000 Genomes Consortium and HapMap).	African American	[44,59]
			S2377X	Increased		Ethiopian	[59]

SPINK5	Serine protease inhibitor, kazal-type, 5	5q31	rs2303070T	Increased	Moderate association Based on several small to medium sized genetic studies (90-124 subjects with AD). A single study suggests that SPINK5 mutations are unlikely to be associated with AD given the high prevalence in the general population.[59]	Taiwanese	[80]
			1258G > A IV12-26C > T IVS12-10A > G IVS14 + 19 G > A IVS 13-50 G > A 1103A > G 1156 G > A 1188T > C 1258G > A His396His	Increased		Japanese	[28,78,79]
			1258 G > A 2475 G > T	Associated		Chinese	[81]
			rs2303067 rs34393923 rs111662216	Associated		Ethiopian	[59]
TCHH	Trichohyalin	1q21.3	E207X	Associated	Weak association Based on one small genetics study (22 subjects).	Ethiopian	[59]
TCHHL1	Trichohyalin like 1	1q21.3	Q294X	Associated	Weak association Based on small genetics studies (22-60 subjects with AD) showing low MAF.	Ethiopian	[59]
			Q294X	Associated		African American	[44]
CRNN	Comulin	1q21.3	R59H	Associated	Weak association Based on one small genetics study (22 subjects).	Ethiopian	[59]
HRNR	Homerin	1q21.3	Q761H R896C P1360S Q500H S522T	Associated	Weak association Based on one small genetics study (22 subjects).	Ethiopian	[59]
Innate and Adaptive Immunity							
DEFB1	Human β -Defensin 1	8p23	692GG 668CC 1654AA	Increased	Moderate association Based on multiple small and large genetic studies (59-631 subjects with AD). The smallest study failed to	Mexican Mestizo	[28,103]
			2266TC 1241TG	Increased		Korean	[28,104]
			52GA*	Increased*		Brazilian	[105]

					achieve statistical significance.		
IL-4	Interleukin 4	5q31.1	590 C/T	Increased	Moderate association Based on multiple small to medium sized genetic studies (46-201 subjects with AD). A larger study (631 subjects) in Koreans failed to find an association.[88]	Egyptian	[89]
			rs2265753 rs2254672 rs2265753 rs2254672 rs2254672 590C/T C3112T T1803C C327A A326C G186A	Associated		Japanese	[28,92,169]
			rs2265753 rs2254672 589C/T 590C/T	Associated		Chinese	[86]
IL-4R α IL-4R	Interleukin 4 receptor	16p12.1-p11.2	I50V Q576R	Increased	Moderate association Based on multiple small to medium sized genetic studies (27-106 subjects with AD).	Egyptian	[89]
			Glu551Arg C703T G186A A326C C327A T1803C C3112T	Associated		Japanese	[28,87,169]
			I50V	Associated		Saudi Arabian	[89]
IL-5	Interleukin 5	5q31.1	rs2522411	Associated	Moderate association with allergic-type AD Based on one large genetic study (676 subjects with AD).	Korean	[170]
IL-7R	Interleukin 7 receptor	5p13.2	rs12516866 rs10213865 rs1389832 rs10058453	Decreased	Weak association Based on a single medium-sized genetic study (187 AA subjects with AD).	African American	[94]
			rs1053496	Increased			
IL-12B	Interleukin 12, beta	5q31.1-q33.1	rs582504 rs582054 rs2243151 rs438421 rs375947 rs1870063	Increased	Moderate association Based on multiple medium-to-large genetic studies (164	Korean	[171]

			A1188C	Increased	and 631 subjects with AD, respectively).	Japanese	[28,172]
<i>IL-12RB</i>	Interleukin 12 receptor, beta	19p13.1	rs438421 rs2066446	Increased	Moderate association Based on multiple medium-to-large genetic studies (382 and 631 subjects with AD, respectively).	Korean	[171]
			-111A/T -2C/T	Increased		Japanese	[28,173]
IL-13	Interleukin 13	5q31	rs3091307 rs20541 (R144Q)	Associated	Strong association Based on meta-analysis of GWAS and medium-to-large genetic studies (185-21,399 subjects with AD).	Korean	[88]
			G4257A rs12188917 rs848	Increased		Japanese	[28,30,31,91]
			rs848 rs2158177	Increased		Chinese	[31,93]
IL-13R α 1	Interleukin 13 receptor alpha 1	Xq24	rs2265753 rs2254672 rs2265753 rs2254672 rs2265753 rs2254672	Associated	Moderate association Based on one large genetic study (631 subjects with AD).	Korean	[88]
IL-18	Interleukin 18	11q22.2-q22.3	rs187238	Decreased*	Moderate association Based on a large meta-analysis (5331 subjects with allergic disease) and large genetic study (646 subjects with AD). NB: an association between AD and IL-18 was seen in the entire cohort, but not when stratified by Asian versus Caucasian ethnicity.	Chinese	[174]
			rs795437	Associated		Korean	[28,175]
IL-1RL1 IL-18R1 IL-18RAP	Interleukin 18 receptor	2q12.1	rs6419573	Associated	Strong association Based on large meta-analyses of GWAS (3328 to 21,399 subjects with AD).	Japanese	[30,31,33]
				Associated		African American	[30]
IL-31	Interleukin 31	12q24.3	rs7977932	Increased	Weak association Based on a small genetic study (90	Taiwanese	[80]

					subjects with AD).		
FCER1A	Fc fragment of IgE receptor 1a	1q23.2	rs2251746 rs2427827	Increased	Weak association Based on a single medium-sized genetic study (129 subjects with AD).	Japanese	[102]
TSLP	Thymic stromal lymphopoietin	5q22.1	rs10043985 rs2289276	Decreased Increased	Moderate association with allergic type AD Based on a single medium-sized genetic study (187 AA subjects with AD).	African American	[94]
STAT6	Signal transducer and activator of transcription 6	12q13	G2964	Increased	Moderate association Based on a medium-sized cohort study (491 with AD) and small case-control studies (26-50 subjects with AD).	Saudi Arabian	[90]
			rs324011	Increased		Taiwanese	[96]
Other Mutations							
ORAI1	ORAI calcium release-activated calcium modulator 1	12q24.31	rs3741596	Increased	Weak association Based on a single medium-sized genetic study (209 subjects with AD).	Japanese	[176]
			rs3741595	Increased		Taiwanese	[176]
OVOL1	Ovo like transcriptional repressor 1	11q13.1	rs479844	Decreased	Strong association Based on a large meta-analyses of GWAS and a medium-sized (235 subjects with AD) genetic study.	Chinese	[177]
			rs10791824	Associated		Japanese	[30]
KIF3A	Kinesin family member 3A	5q31.1	rs2897442	Increased	Weak association Based on a single medium-sized genetic study (235 subjects with AD).	Chinese	[177]
ADAM33	ADAM	20p13	rs2853209	Decreased	Weak association	Japanese	[28,17]

	metallopeptidase domain 33				Based on a single medium-sized genetic study (140 subjects with AD).		[8]
BDNF	<i>Brain-derived neurotrophic factor</i>	11p14.1	C270T	Increased	Moderate association Based on a single medium-sized genetic study (160 subjects with AD).	Chinese	[28,179]
CMA1	Mast cell chymase	14q11.2	BstXI	Increased	Moderate association Based on several medium-sized genetic studies (100-169 subjects with AD).	Japanese	[28,180-182]
RANTES (CCL5)	Chemokine (C-Cmotif) ligand 5	17q11.2-q12	-401A	Associated	Moderate association Based on several small- to medium-sized genetic studies (100-169 subjects with AD).	Japanese	[28,183,184]
SMPD SMPD2	Sphingomyelin phosphodiesterase (2)	6q21	—	Associated	Moderate association Based on a single large-sized genetic study (535 subjects with AD).	Korean	[28,185]
TIM1	T cell immunoglobulin and mucin domain 1	5q33.2	5383_5397del	Associated	Weak association Based on a single medium-sized genetic study (112 subjects with AD).	Korean	[28,186]
TNFRSF6B	TNF receptor superfamily member 6b	20q13.3	—	Increased	Moderate Association Based on a large GWAS (1012 subjects with AD).	Han Chinese	[34]
CYP2R1	Cytochrome P450 2R1	11p15.2	rs1076619 rs1553006 rs16930609	Increased	Moderate Association	Chinese	[187]

			rs11819875		Based on a single large genetic study (1442 subjects with AD).		
CYP27A1	Cytochrome P450 27A1	2q35	rs4674343	Decreased		Chinese	[187]
VDR	Vitamin D receptor	12q13.11	AT	Decreased		Chinese	[187]
GC	GC, vitamin-D binding protein	4q13.3	rs222020 rs2298849	Increased		Chinese	[187]
C11orf30/LRRC32	—	11q13.5	—	Increased	Moderate Association Based on multiple large GWAS (1012 to 21,399 subjects with AD).	Japanese	[30,31]
				Increased		Chinese	[31,188]
				Increased		African American	[30]
TMEM232, SLC25A46	—	5q22.1	—	Increased		Chinese	[34]
CCDC80/CDC200R1L	—	3q13.2	—	Increased		Chinese	[188]
				Increased		Japanese	[30,31,33]
OR10A3/NLRP10	—	11p15.4	—	Increased		Chinese	[188]
ADAMTS10/ACTL9	—	19p13.2	—	Increased		Japanese	[30,31]
CLEC16A	—	16p13.13	—	Increased		Japanese	[30,31]
				Increased		Chinese	[31]
ZNF652	—	17q21.32	—	Increased		Japanese	[30,31]
				Increased		Chinese	[31]
RTEL1-TNFRSF6B	—	20q13.33	—	Associated		Japanese	[30,31]
				Associated		Chinese	[31]
HLA-DRB1/HLA-DQA1	—	6p21.32	—	Associated		Japanese	[30,31]
ZNF365	—	10q21.2	—	Decreased		Japanese	[30,31]
				Increased		Japanese	[33]
MICB	—	6p21.33	—	Associated		Japanese	[30,31]
OR10A3/NLRP10	—	11p15.4	—	Decreased		Japanese	[30,31]
				Increased		Japanese	[33]
PRR5L	—	11p13	—	Associated		Japanese	[30,31]
—/ETS1	—	11q24.3	—	Associated		Japanese	[30,31]
MIR5708/ZBTB10	—	8q21.13	—	Associated		Japanese	[30,31]
CD207/VAX2	—	2p13.3	—	Associated		Japanese	[30,31]
GLB1	—	3p21.33	—	Increased		Japanese	[31,33]
MHC	—	6p21.3	—	Increased		Japanese	[31,33]
CARD11	—	7p22	—	Increased		Japanese	[31,33]
CYP24A1/PFDN4	—	20q13	—	Increased		Japanese	[31,33]

MAF = mean allele frequency, NB= nota bene
* Not statistically significant

Study sizes were defined in the following way: small (<100 subjects), medium (100-499 subjects), large (500 or more subjects). The strength of association for each gene was characterized as “weak,” “moderate,” or “strong.” Weak association was defined as a gene only identified in a single small or medium-sized genetic study. Moderate association was defined a gene that was identified in multiple studies (small, medium, or large), a gene implicated in a single large genetic study, or a gene identified in several large studies with conflicting results (i.e. association seen in entire population does not hold up when stratified by race). Strong association was defined as a gene that was identified in multiple large studies or a large meta-analysis of genetic studies without conflicting results.

Table 2: Filaggrin Null Mutations in Individuals of African Ancestry

Race	Number studied	% with R501X	% with 2282del4	% with R2447X	% with S3247X	New (% affected)	Ethnic group	Ref.
Black	370 AD	3.2%	0.5%	0.7%	1.5%	N/A	African American	[43]
White	433 AD	13.8%	12.0%	1.4%	2.8%	N/A		
Black	60 AD	0	0	0	0	Q507X (1.7%) R3409X (1.7%) S3707X (1.7%)	African American	[44]
Black	187 AD/ADEH	3.2% Aa	3.2% Aa*	N/A	N/A	None	African American	[42]
	152 C	0	1.3%					
White	278 AD/ADEH	14% Aa, 1.4% aa	13.9% Aa, 1.8% aa					
	157 C	2.6% Aa	3.2% Aa					
Black	18 AD + IV	5.6%	11.1%	N/A	N/A	R826X (5.6%)	African American	[60]
	17 C	0	0			R826X (5.6%)		
Black	12 AD	0	0	N/A	N/A	None	African American	[50]
	11 C							
White	17 AD	0	8.8% Aa					
	27 C							
Black	69 AD	0	0	0	0	N/A	South African amaXhosa	[45]
Black	103 AD 7 IV	0	0	0	0	632del2 (.009%)	Ethiopian	[47]
	103 C					0		

* Not statistically significant association

AD = atopic dermatitis, ADEH = atopic dermatitis, eczema herpeticum, IV = ichthyosis vulgaris,
C= control

















