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REVIEW

Genetic/Environmental Contributions and Immune Dysregulation in Children with Atopic Dermatitis

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Abstract: Atopic dermatitis (AD) is one of the most common skin conditions in humans. AD affects up to 20% of children worldwide and results in morbidity for both patients and their caregivers. The basis of AD is an interplay between genetics and the environment characterized by immune dysregulation. A myriad of mutations that compromise the skin barrier and/or immune function have been linked to AD. Of these, filaggrin gene (*FLG*) mutations are the most evidenced. Many other mutations have been implicated in isolated studies that are often unreplicated, creating an archive of genes with potential but unconfirmed relevance to AD. Harnessing big data, polygenic risk scores (PRSs) and genome-wide association studies (GWAS) may provide a more practical strategy for identifying the genetic signatures of AD. Epigenetics may also play a role. *Staphylococcus aureus* is the most evidenced microbial contributor to AD. Cutaneous dysbiosis may result in over-colonization by pathogenic strains and aberrant skin immunity and inflammation. Aeroallergens, air pollution, and climate are other key environmental contributors to AD. The right climate and/or commensals may improve AD for some patients.

Keywords: atopic dermatitis, genetics, environment, pollution

Introduction

AD is one of the most common skin conditions, affecting up to 20% of children worldwide.[1] It is characterized by a chronic relapsing pruritic rash appearing in an age-dependent distribution and is often associated with elevated immunoglobulin (Ig)E, peripheral eosinophilia, and other allergic diseases.[2] AD results in significant impact on children's quality of life due to itching, scratching, emotional distress, and sleep disturbance.[3] The median annual out-of-pocket expense for AD in the United States (US) is 600 US dollars (USD) and may be 1000 USD or greater for over 40% of patients and families.[4]

Children with AD may suffer a wide range of allergic, psychological, and infectious comorbidities. Classically, AD has been linked to asthma and allergic rhinitis (AR) in the "atopic march", a hypothesized progression of diseases from AD to respiratory allergies.[5] However, while atopic diseases do commonly co-occur, most do not follow this temporality.[5,6] The Childhood Origin of ASThma study, a high-risk birth cohort study, has shown that the early/recurrent phenotype of AD (presents early and persists through childhood) is associated with food allergy and both the early/recurrent phenotype and late–onset phenotype (AD starting at four- to six-years-old) are associated with asthma in children.[7] Notably, atopic comorbidity may be a feature of pediatric AD and less common in adult-onset AD.[8,9] Besides allergic comorbidities, children with AD show increased risks of having anxiety and attention-deficit hyperactivity disorder as well as certain bacterial and viral infections.[10,11] The consequences of AD extend to caregivers, who suffer mental and physical health effects tied to the quality of life of these children.[3,12,13]

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AD is a disease of defective genetics in an unfavorable environment. Its underlying mechanisms are largely based in immune dysregulation. Notably, there may be pathophysiological differences between AD in children and adults. Regarding the skin barrier, pediatric AD has more *FLG* loss-of-function (LoF) variants and lipid-barrier defects, while adult AD shows more epidermal differentiation and cornification defects.[6] Regarding immune dysregulation, pediatric AD shows the highest skin eosinophil and neutrophil counts and greater induction of T-helper (Th)2, Th9, Th17, interleukin (IL)31, IL33, and innate immune markers; meanwhile, adult AD is skewed towards Th1 activation.[6,9,14,15] In both children and adults, AD skin is likely predisposed to pathogen colonization, which may contribute to disease progression.[16] Pediatric AD not only predisposes to skin infections but also increases allergen sensitization, including to food and aeroallergens.[17] Taken together, in pediatric AD, microbes, aeroallergens, and pollutants may penetrate the inherently defective skin barrier to trigger dysregulation of the immune system (which may itself be predisposed by genetic defects), causing further skin damage, chronic inflammation, and itch; notably, the right climate and/or commensals may improve some AD[18,19] [Figure 1]. This paper summarizes the current understanding of how genetics, environment, and immune system dysregulation drive AD in children.

Genetic Contributions

Skin Barrier Defects

AD skin shows decreased keratinocyte (KC) differentiation in the epidermis and is deficient in stratum corneum components including proteins (filaggrin, loricrin, involucrin, claudins) and lipids (ceramide, cholesterol, fatty acids).[20] Compared to healthy skin, AD skin shows reduced hydration and increased water loss as measured by trans-epidermal water loss (TEWL)[21] [Figure 1]. This holds true even when AD skin is normal-appearing. Supporting the role of a defective skin barrier in AD, TEWL is positively correlated with AD severity and may predict AD development.[22,23] The epidermal differentiation complex (EDC) is a 2 Mb region of human chromosome 1q21 that is the site of key genes for establishing the skin barrier (ie, *FLG*).[24] The EDC also controls epithelial tissue development and repair by regulating the terminal differentiation program of KC.[25] The EDC includes three gene families including the cornified envelope precursor family, the S100 protein family, and the S100 fused type proteins (SFTP).[26]

FLG is the most studied and implicated gene in AD and is a member of the SFTP family on the EDC. A *FLG* LoF mutation reduces skin hydration[12] [Figure 1]. Given that TEWL is increased in unaffected *FLG* mutation carriers, skin barrier impairment likely precedes clinical eczema.[27] *FLG* mutations occur in up to 50% of children with moderate to

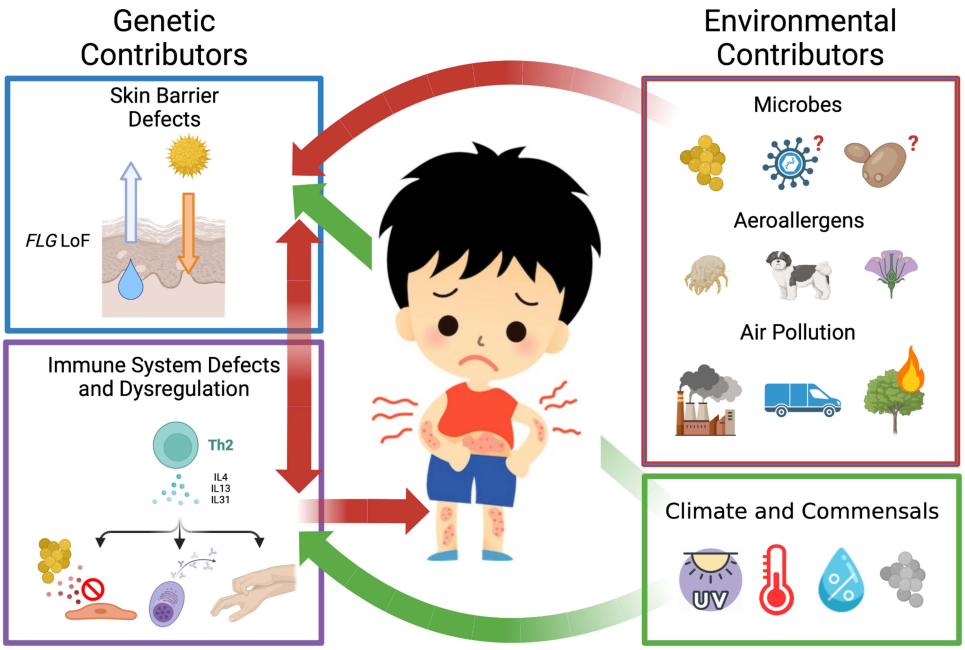

Figure 1 The interplay of genetic and environmental contributors in modulating the immune dysregulation of AD.

severe eczema, and the presence of *FLG* LoF variants in AD is significantly greater than in healthy controls.[26,28] The genetic configuration is likely a combination of common variants and rare LoF variants.[28] *FLG* LoF status appears to control the disease course of AD. Carrying a *FLG* LoF variant is associated with earlier disease onset among AD patients and increases the odds of onset before age 5- and 20-years-old by 7.8 and 8.9 times, respectively.[26] Certain *FLG* LoF mutations are associated with AD patients with a history of recurrent skin infections.[29] *FLG* mutations cause both barrier defects as well as altered hydration and pH of the stratum corneum, which may modulate the growth of *S. aureus*.[20,30] The *FLG* LoF mutation may also predispose to increased allergic sensitization[31] due to increased ability of allergens to penetrate into deeper skin layers. In addition to direct *FLG* mutations, Th2 cytokines IL4, IL13, and IL31 can suppress *FLG* expression and/or interfere with KC differentiation.[32–35]

While *FLG* has received the most attention, other EDC genes may be relevant in AD [Table 1]. A whole genome sequencing study showed enrichment of rare LoF variants of *FLG2, HRNR, LCE2C, LCE4A, LCE5A, RPTN, S100A3, S100A16, SPRR3, SPRR4, TCHH*, and *TCHHL1* in AD patients.[26] Expression of *FLG2* and *HRNR* are significantly reduced in both lesional and non-lesional skin of patients with AD compared with healthy subjects.[36] Upregulation of *S100A7* and *S100A8* and downregulation of *FLG* and the loricrin gene (*LOR*) has also been observed in AD and may represent abnormal epidermal differentiation and defective defenses favoring the alternative keratinization pathway.[37] Single nucleotide polymorphisms (SNPs) in *CLDN1* in AD may compromise tight junctions.[38] In fact, *CLDN1* is involved in the susceptibility to AD in the Ethiopian population.[39] Missense mutations in the Transmembrane Protein 79 (or Mattrin) gene (*Tmem79/matt*) may also predispose humans to AD.[40] In mice, mutations in the gene produce a dermatitis phenotype likely by disrupting the lamellar granule secretory system and altering stratum corneum barrier function.[41] *Tmem79/matt* has limited sequence homology to microsomal glutathione transferases and protects against reactive oxygen species.[29] Interestingly, mice with specific *Tmem79/matt* mutations developed IL17A-dependent

Table 1 Potential Genetic Contributors to AD

Skin Barrier		
	Epidermal differentiation complex	*FLG, FLG2, HRNR, LCE2C, LCE4A, LCE5A, RPTN, S100A3, S100A7, S100A8, S100A16, SPRR3, SPRR4, TCHH, TCHHL1, CLDN1, Tmem79/matt, LELP1*
	SP and SP inhibition	*SERPINB7, KLK7*
	Desmosome component	*DSC1*
	Epigenetics	*KIF3A* methylation, *PPARδ* upregulation, *EMSY* upregulation
Immune System		
	Innate immunity	*TLR2, TLR4, TLR9, NOD1, NOD2, DEFβ1, IFNγ, IFNγR, IRF2, SIDT2, RBBP8NL*
	Cytokine-related	*IL4/4R, IL5, IL7R, IL9, IL10, IL12, IL13, IL18, IL31, TSLP, STAT6*
	Antigen receptor signaling	*CARD14, LRRC32*
	IgE-related	*FcεRIβ, ADAMTSL4*
	Leukotriene-related	*CYSLTR1*
	Epigenetics	*AHR* upregulation, reduced *IL13* methylation, reduced *AcH3K9* acetylation

Note: Gene names are italicized.

dermatitis and were refractory to *S. aureus* infection.[42] Certain genetic variants of *LELP1* have been associated with elevated IgE levels, early-onset, house dust mite (HDM) sensitization, and disease severity in AD.[43]

Beyond the EDC, aberrant epidermal serum protease (SP) activity and desmosome instability may contribute to the skin barrier defects of AD [Table 1]. *SERPINB7* and *DSC1* code for a SP inhibitor and desmosome component, respectively, and missense mutations of these genes have been linked to AD via GWAS.[44] Meanwhile, AACC insertion in the SP gene *KLK7* has also been associated with AD,[45] introducing the potential relevance of direct SP mutations.

Epigenetics may contribute to the defective skin barrier of AD [Table 1]. For example, highly methylated *KIF3A* SNPs are associated with a decreased expression of KIF3A barrier protein in epithelial cells, leading to an increase in TEWL and risk of AD.[46] Meanwhile, transcription factor PPARδ, which regulates inflammation and promotes KC proliferation and differentiation, is upregulated in lesional AD skin versus non-lesional skin.[45,47,48] FABP5, a fatty acid-binding protein expressed in the epidermis, delivers ligands to PPARδ in keratocyte nuclei to enhance transcription.[49] Supporting this mechanism, *PPARδ* and *FABP5* expressions parallel each other in AD.[45,50] Recently, GWAS has implicated *EMSY*, a transcriptional regulator supporting skin barrier formation.[51]

Immune System Defects and Dysregulation

Regarding the innate immune system, stimulated KCs from AD patients produce diminished levels of antimicrobial peptides (AMPs) versus healthy subjects and those with psoriasis,[52] another chronic skin condition with barrier defects. Pattern recognition receptor (PRR) defects may mediate this phenomenon. For example, genetic polymorphisms in toll-like-receptors (TLRs) make AD skin vulnerable to infections.[35] TLR2 is a key PRR for *S. aureus*, and *TLR2* polymorphisms are linked to severe AD with recurrent skin infections.[53,54] Overall, AD patients show diminished responses upon TLR2 stimulation including reduced IL6, IL8, CCL20 and MMP9 production, which may predispose to infections.[55] However, monocytes with *TLR2* heterozygous R753Q polymorphism showed higher production of IL6 and IL12 versus those with non-mutated *TLR2*. This mutation is found more frequently in Italian children with severe AD but not in Turkish AD children.[55–57] *TLR2* mutations are especially interesting, as TLR2 may mediate transformation of acute to chronic AD via IL4-mediated suppression of IL10.[58] Other PRR mutations have also been linked to AD. The *TLR4* 896G mutation may be associated with a severe AD course, while *TLR9* promoter polymorphisms have been associated with impaired immunity in some cases of AD.[59,60] *NOD1* and *NOD2* encode PRRs for sensing viral/parasitic infections and perceiving perturbations of cellular processes such as regulation of the actin cytoskeleton and maintenance of endoplasmic reticulum homeostasis;[61] variants in these genes have been associated with AD.[62,63]

Besides PRRs, other components of innate immunity may be involved[45,64] [Table 1]. Human beta defensins (hβDs) provide antimicrobial and immunomodulatory benefits and are relevant to the genetics of AD.[65] hβD2 and hβD3 are produced at low levels in lesional skin of patients with AD relative to patients with psoriasis.[66,67] Furthermore, patients with AD complicated by eczema herpeticum (EH) have reduced hβD2 and hβD3 in lesional skin relative to patients with AD or psoriasis.[68] *DEFβ1* SNPs are significantly associated with susceptibility to AD in Koreans.[69] However, they are not associated with AD in children and adolescents from northeast Brazil.[70] *IFN* and IFN receptor gene (*IFNR*) variants are associated with AD patients with a history of EH; transcripts for *IFNγ* and *IFNRs* (α, β, ω, γ) are downregulated in these patients.[20,71,72] Specifically, mutations in *IFNγ* and the *IFNγR* may occur in AD patients with EH history versus those without EH history.[20] IRF2 blocks the IFNγ-mediated pathway, and different variants of *IRF2* are associated with Caucasian American and African American AD patients with a history of EH.[73] Recently, whole genome sequencing has identified *SIDT2* and *RBBP8NL* variants in AD; these genes participate in defense against herpes simplex virus (HSV)1.[74]

Classically, AD lesions are characterized by an increased expression of Th2 cytokines, which have been implicated in tissue repair.[75] Indeed, cytokine-related genes represent a sizeable group of potential offender genes whose variants have been associated with AD[35,64,76,77] [Table 1]. As a result of inherent barrier defects such as *FLG* mutations or lipid deficiencies, there is an overproduction of Th2 cytokines (classically IL4, IL13, and IL31) in the skin lesions of predisposed individuals [Figure 1]. IL4 activation of signal transducers and activators of transcription (STAT)6 results in Th2-deviated T cell differentiation, IgE production in B cells, and the production of Th2 chemokines such as CCL17 and CCL22 by dendritic cells (DCs). Th2 cytokines may in turn downregulate *FLG, LOR*, and involucrin gene (*IVL*) expression and reduce AMP production, further compromising the skin barrier and increasing susceptibility to pathogens.[78] 590T and 589T alleles of *IL4* may be associated with high serum IL4 levels, which appear to increase the risk of AD in children.[79] *IL13* Arg130Gln polymorphism and haplotypes consisting of *IL13*

Arg130Gln and *IL4* −589C/T are linked to development of atopy and AD.[80] IL31 causes pruritus, and *IL31* variants are associated with AD and its severity.[81,82] Janus kinase (JAK)1 and JAK2 are tyrosine kinases involved in the JAK-STAT pathway that direct inflammation via cytokines (including IL4, IL13, IL31) and IFN signal transduction.[76,83] Thymic stromal lymphopoietin (TSLP) activates dermal DCs to recruit Th2 cells that release IL4 and IL13.[84–87] TSLP also activates type 2 innate lymphoid cells, which express IL4, IL5, and IL13. Furthermore, TSLP may cause pruritus by activating cutaneous sensory neurons. SNPs in *TSLP* and its receptor component *IL7R* may modulate AD persistence.[88,89] *TSLP* SNPs are also associated with EH.[90] Interestingly, while *STAT6* mediates IL4/IL13 activation of Type 2 inflammation,[91] it may also work with another transcription factor T-bet to suppress skin inflammation by inhibiting TSLP-dependent IL9 production in CD4+ T cells of mice.[92] *STAT6* genetic variants are associated with AD patients with a history of EH and are known to increase viral replication in the skin of these patients.[93]

Several other categories of immune genes have been implicated in AD including antigen receptor signaling (*CARD14, LRRC32*), IgE-related (*FcεRIβ, ADAMTSL4*), and leukotriene-related (*CYSLTR1*) genes[76,94,95] [Table 1]. *CARD14* mediates production of proinflammatory genes and AMPs via activation of the nuclear factor-κB (NF-κB) pathway.[96,97] Interestingly, while a dominant gain-of-function (GoF) mutation in *CARD14* occurs in psoriasis, a LoF mutation in this gene accompanies severe AD.[98] *LRRC32* (also known as *GARP*) encodes GARP, a cell surface receptor on Treg cells, platelets, and certain cancer cells.[99] GARP may inhibit Treg immunosuppressive activity.[100] Recently, polymorphisms in *LRRC32* have also been linked to AR.[101] IgE-mediated inflammation may also contribute to AD.[102] *FcεRIβ* encodes a subunit of the high-affinity IgE receptor FcεRI and mediates trafficking and signaling of this receptor.[103] Meanwhile, *ADAMTSL4* encodes a potential IgE-binding self-antigen in AD and has been linked to eosinophil counts, which are known to be elevated in AD.[104–106] Finally, *CYSLTR1* encodes a receptor for cysteinyl leukotrienes; variants may predispose children to asthma and AD.[107]

Epigenetics may modulate the immune response of AD [Table 1]. There are significant differences in the DNA methylation levels between the skin-homing CD4+CLA+ T cells of AD patients compared to healthy controls.[108] Reduced methylation levels in the *IL13* gene in CD4+CLA+ T cells of AD patients are associated with an increased expression of IL13 mRNA in these cells.[108] The transcription factor aryl hydrocarbon receptor gene (*AHR*) is upregulated in AD lesional skin versus normal skin in healthy controls.[109] Chronic AHR activation is immunotoxic[110] and results in expression of neurotrophic factor artemin, alloknesis, epidermal hyper-innervation, and inflammation.[111] In mice, constitutive activation of AHR increases artemin and produces an AD phenotype including erosive facial and back eczema with frequent scratching.[110–112] AD epigenetics may also be modulated by microbial metabolites including butyric acid (BA), a fermentation product of *Staphylococcus epidermidis* that inhibits *S. aureus* growth.[113,114] In response to BA derivative BA–NH–NH–BA, human KCs increase acetylation of *AcH3K9*, which is accompanied by reduced *S. aureus*-induced production of proinflammatory IL6 and *S. aureus* colonization in murine skin,[115] suggesting modulation of *S. aureus* pathogenicity through epigenetic mechanisms.

Genetic Disorders with AD-Like Lesions

There are a number of genetic disorders including immunodeficiency, autoimmunity, and non-immune abnormalities that feature AD-like lesions. These conditions and their known culprit genes include Hyper IgE syndrome (*STAT3, DOCK8*), CARMIL2 deficiency (*CARMIL2*), Omenn syndrome (*RAG1, RAG2*), Netherton syndrome (*SPINK5*), Wiskott-Aldrich syndrome (*WAS*), adenosine deaminase severe combined immunodeficiency (ADA-SCID) (*ADA*), immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome (*FOXP3*), CARD11-associated atopy with dominant interference of NF-κB signaling (CADINS) disease (*CARD11*), congenital disorders of glycosylation (*PGM3*), prolidase deficiency (*PEPD*), severe dermatitis, multiple allergies, and metabolic wasting (SAM) syndrome (*DSG1, DSP*), and growth hormone insensitivity (GHI) syndrome with immunodeficiency (*STAT5B*).[116–129] Recently, GoF *STAT6* variants have been associated with a novel autosomal dominant allergic disorder featuring early-onset allergic immune dysregulation with widespread refractory AD, hypereosinophilia with eosinophilic esophagitis, high serum IgE, food allergies, and brain vascular anomalies.[130] Although rare, these genetic disorders should be considered in the differential diagnosis of AD, especially in patients where the constellation of findings exceeds atopy. These findings include unresponsiveness to conventional AD treatments, unusual opportunistic infections, or symptoms of autoimmunity.[131] Understanding the basis of these genetic disorders may also provide insights into the mechanisms of AD.

The culprit genes for such conditions fall under several categories: cytokine-related (*STAT3, STAT5B, STAT6, FOXP3*), antigen receptor signaling (*CARD11, CARMIL2, ADA, RAG1, RAG2*), actin polymerization (*DOCK8, WAS,*

CARMIL2), cellular metabolism (*PGM3*), collagen metabolism (*PEPD*), SP inhibition (*SPINK5*), and desmosome components (*DSG1, DSP*) [Table 2]. STAT3 participates in Th2 differentiation[132] and KC STAT3 may mediate histaminergic itch.[133] STAT5B and STAT6 also mediate Type 2 inflammation and STAT5B additionally mediates growth hormone signaling.[91,134] FOXP3 suppresses the immune system through its influence on transcription factors including

Table 2 Genetic Disorders with AD-Like Lesions and Their Implicated Genes

Hyper-IgE syndrome		
	Cytokine-related	*STAT3*
	Actin polymerization	*DOCK8*
CARMIL2 deficiency		
	Antigen receptor signaling, actin polymerization	*CARMIL2*
Omenn syndrome		
	Antigen receptor signaling	*RAG1, RAG2*
Netherton syndrome		
	SP inhibition	*SPINK5*
Wiskott-Aldrich syndrome		
	Actin polymerization	*WAS*
ADA-SCID		
	Antigen receptor signaling	*ADA*
IPEX syndrome		
	Cytokine-related	*FOXP3*
CADINS disease		
	Antigen receptor signaling	*CARD11*
Congenital disorders of glycosylation		
	Cellular metabolism	*PGM3*
Prolidase deficiency		
	Collagen metabolism	*PEPD*
SAM syndrome		
	Desmosome components	*DSG1, DSP*
GHI syndrome with immunodeficiency		
	Cytokine-related	*STAT5B*
Novel autosomal dominant allergic disorder		
	Cytokine-related	*STAT6*

Note: Gene names are italicized.

NF-κB.[135] CARMIL2 mediates NF-κB signaling and regulates actin polymerization in T cells; besides immunodeficiency, genetic variants have also been associated with inflammatory bowel disease in children.[136] ADA is part of the purine salvage pathway and plays a key role in B and T cell development; defects may cause mild AD.[137,138] RAG1 and RAG2 enable V(D)J recombination to produce diverse T and B cell receptors.[139] DOCK8 controls lymphocyte migration, survival, and effector functions through CDC42-mediated actin polymerization.[140,141] DOCK8 deficiency may cause Th2 polarization away from the Th1 and Th17 types, resulting in atopic disease and compromised immunity against viruses and fungi; the AA genotype of DOCK8 is linked to elevated total IgE levels.[98,142] WAS mediates actin cytoskeleton remodeling to enable immune functions including signal transduction, adhesion, movement, proliferation, and phagocytosis.[143] PGM3 is a phosphoglucomutase that metabolizes glycans, and deficiencies may impair cell–cell recognition and immune signaling.[144] *PEPD* encodes prolidase, which metabolizes proline-containing proteins including collagen.[124] *SPINK5* encodes the SP inhibitor LEKTI, thereby modulating skin desquamation.[145,146] Finally, *DSG1* and *DSP* encode desmosome components that contribute to epidermal structure and integrity.[147]

Polygenic Risk Scores and Genome-Wide Association Studies

While a genetic basis to AD is clear, confirming the clinical relevance of specific genes in AD has proven challenging. The *FLG* LoF mutation is a special case, where mutations in a specific gene are known to compromise the AD skin barrier. The tendency is for studies to highlight one gene or another without reproduction in most cases. For example, no particular gene has been confirmed in the dysregulated immune response of AD. To bridge the gap between research and clinical utility, PRSs have been introduced and show promise for predicting AD. The PRS is a prediction of an individual's phenotype based on the individual's particular genetic variants weighted by their disease-specific effect sizes; disease-specific effect sizes are determined from external, independent GWAS. Recently, Arehart et al showed that AD PRSs track phenotypic outcome and correlate with AD severity.[148] Furthermore, incorporating genetic determinants across atopic phenotypes and *FLG* LoF variants into PRSs increased their predictive capacity, and this model was able to distinguish individuals with severe AD from control subjects with an odds ratio of 3.86 (95% CI, 2.77–5.36). The predictive potential of PRSs is expected to increase with larger, higher-quality GWAS databases and inclusion of non-genetic covariates into these models, as the environment is a key driver of AD.[149]

GWAS has identified two highly significant loci for AD representing the EDC (chromosome 1q21.3) and a region including *IL4* and *IL13* (chromosome 5q13.1).[150] Chromosome 11q13.5 is another locus that has been strongly linked to AD in GWAS among different ethnicities and suggests *LRRC32* and *EMSY* as possible players in AD.[51,150] Among Caucasian patients, Sliz et al identified 30 AD-associated loci including five novel loci.[44] Missense variants in *DSC1* and *SERPINB7* were identified at two of these new loci; these genes have key roles in epidermal strength and stability.[44] Recently, a GWAS meta-analysis identified 271 AD-associated genes including seven with strong evidence of association (*ADAMTSL4, FKBPL, SIPA1, PPT2, C1orf68, SLC2ARG*, and *TDRKH*).[151] Notably, AD has polygenic architecture and shares biology with asthma.[44,151] GWAS may also be used to identify relationships between AD and other diseases or lifestyle factors via comparative analysis or Mendelian randomization.[150,151] For example, opposing genetic mechanisms have been identified in AD versus psoriasis[152] and BMI has been shown to have a small causal effect on AD.[153] Current GWAS only account for less than 20% of AD heritability.[154] Future GWAS should include greater ethnic diversity and functional assessment of candidate genes.[154] Furthermore, gene-environment interaction studies for AD are currently scant.[155]

Environmental Contributions

Bacteria

Bacteria have a role in modulating AD and the evidence implicating *S. aureus* is strongest [Figure 1, Table 3]. In a meta-analysis of 95 observational studies, Totte et al found that *S. aureus* is present on 70% of AD lesions compared to statistically lower presence on non-lesional or healthy control skin.[156] The authors also noted that in lesional skin, disease severity is associated with increased prevalence of *S. aureus*. Meanwhile, Tauber et al showed an association between *S. aureus* density and AD presence and disease course severity in lesional and non-lesional skin.[157] Biofilm-generating

Table 3 Potential Environmental Contributors to AD

Microbes		
	Bacteria	*S. aureus*
	Viruses	Herpes simplex virus, molluscum contagiosum virus, coxsackie virus, vaccinia virus
	Fungi	*Malassezia spp.*
Aeroallergens		
	Indoor allergens	House dust mite, pet dander, fur, cockroach, mold
	Outdoor allergens	Tree pollens, grass pollens, weed pollens
Air Pollution		
	Particulate matter	PM2.5, PM10
	Gaseous pollutants	Sulfur dioxide, nitrogen dioxide, carbon monoxide
Climate		
	Humidity	Low or very high humidity
	UV index	Low UV index
	Temperature	Low or very high temperature, high indoor heating days
	Precipitation	High precipitation
Food		
	Rare occurrence	Cow's milk, hen's egg
	Birch pollen-related	Apple, carrot, celery, hazelnut

Note: Bacterial and fungal genera and species are italicized.

S. aureus strains from anterior nares and lesional skin in AD patients have been associated with more severe AD and extent of biofilm formation positively correlates with lesional intensity.[158–160] Allen et al reported that biofilm formation plays a major role in the occlusion of eccrine sweat ducts, which leads to inflammation and pruritus. Patients with severe AD were colonized by strong biofilm producing *S. aureus* strains.[161] Biofilms enhance bacterial adhesion, providing immune evasion and protection from competitor microbial species.[161,162] MRSA may colonize 18.3–25% of pediatric AD patients and is more prevalent in moderate to severe AD versus mild AD.[163–165] Colonization of AD skin with MRSA predisposes to increased skin and soft tissue infections (SSTIs) compared to colonization with MSSA.[166]

Staphylococcal enterotoxins (superantigens) are the most-studied bacterial virulence factors in AD. They include classical (SEA, SEB, SEB, SED, TSST-1) and non-classical (SEE, SEG, SEQ) superantigens.[20] More than 80% *S. aureus* in AD produce these superantigens.[167] Superantigen-activated DCs stimulate Th2 cells to produce IL4, IL5, IL13, and IL31, leading to skin barrier disruption including decreased FLG production, suppressed AMP production, impaired KC differentiation, and pruritus.[168,169] Moreover, specific IgE (sIgE) directed at superantigens leads to basophil histamine release.[6] MRSA produces more superantigen than MSSA[170] and superantigens may cause corticosteroid resistance in AD flares associated with MRSA skin infections.[171] *S. aureus* also produces alpha toxin that causes KC cytotoxicity, lymphocyte apoptosis, and alters E-cadherin integrity.[168,172,173] FLG deficiency and expression of *IL4* and *IL13* in AD enhance cytotoxicity of alpha toxin to KCs.[174,175] Delta toxin increases mast cell degranulation via MRGPRX2; notably, MRGPRX2 is also found on KCs.[176,177] Staphylococcal protein A blocks formation of IgG hexamers and downstream

activation of complement.[178] Finally, lipoteichoic acid (LTA) is a staphylococcal virulence factor that may activate TLR2 to convert acute AD into chronic AD.[58]

Cutaneous dysbiosis may be a key driver of AD. Microbiome diversity decreases in lesional AD skin with specific reduction in *Streptococcus, Corynebacterium, Propionibacterium*, and favoring *Staphylococcus*.[114] The microbiome composition returns to normal diversity after treatment, suggesting that treating AD supports the re-establishment of a normal microbiome. Commensals may counter *S. aureus* and support a healthy skin barrier and immunity [Figure 1]. For example, coagulase-negative Staphylococci (CoNS) (*S. epidermidis, S. hominis*, and *S. lugdunensis*) can produce AMPs that inhibit *S. aureus* growth.[179–181] CoNS strains with antimicrobial activity are deficient in AD versus healthy skin and reintroducing these strains may decrease *S. aureus* burden.[180] Indeed, *S. hominis* transplantation may improve local eczema severity by killing *S. aureus*.[19] Other commensals such as *Roseomonas, Corynebacterium*, and *Propionibacterium* have also been shown to affect *S. aureus* growth and virulence.[182–185] Normal microflora may promote healthy skin in diverse ways. *S. epidermidis* may shape cutaneous T cell populations to promote tolerance of commensals, immunogenicity against pathogens, and cutaneous wound repair.[186,187] Independent of T cells, LTA in the *S. epidermidis* cell wall may temper inflammatory responses to injury via TLR2.[188] Finally, *S. epidermidis* may curb skin inflammation through BA-mediated epigenetic mechanisms.[115,189]

Viruses

Viral diseases including EH, molluscum contagiosum (MC), eczema coxsackium (EC), and eczema vaccinatum (EV) may afflict AD patients, yet whether viral infections lead to worsening of AD requires further study [Figure 1, Table 3]. AD patients are at increased risk of EH, which is caused by HSV.[11] Nearly a third of pediatric hospitalizations for AD infectious complications are related to EH.[190] Interestingly, EH is associated with AD flares and is more often a reactivation of HSV as opposed to a primary infection.[191,192] In AD patients, a history of skin infections with *S. aureus* is a risk factor for development of EH, and alpha toxin increases HSV load in KCs.[72,193] Meanwhile, downregulation of IFNs and their receptors also contribute to EH susceptibility as discussed previously. MC spreads by autoinoculation in AD patients due to scratching. *FLG* mutations have been linked to increased risk of sustained MC skin infection.[194] Furthermore, a history of AD has been reported in over a third of cases of MC in pediatric dermatology and appears to intensify the course of MC.[195] EC may appear similar to EH, and a lesional polymerase chain reaction for enterovirus may help differentiate between the two etiologies. Unlike EH, EC is not typically life-threatening and can be managed with skin hydration, moisturization, and topical corticosteroids (TCS).[196] EV is caused by vaccinia virus (VV) in smallpox vaccines and presents as a rapidly developing, generalized vesiculopustular rash that is life-threatening.[197] Given the recent monkeypox outbreaks across the globe, smallpox vaccines have seen renewed use as they provide some cross-protection for monkeypox.[198,199] Susceptibility to EV may be mediated by defects in IFNγ or its receptor and increases in IL4, IL13, and IL17.[200–202] Clinicians should be advised that the ACAM2000 (replication-competent VV) is contraindicated in AD patients due to the risk of EV, but the Jynneos (replication-deficient Modified vaccinia Ankara) vaccine is safe for AD patients including those with human immunodeficiency virus.[203]

Fungi

Further research is needed to evaluate fungi as potential contributors to AD [Figure 1]. *Malassezia spp*. are common commensals on human skin that may contribute to AD [Table 3]. While not life-threatening, *Malassezia spp*. are thought to enhance AD skin inflammation by eliciting IgE production and activating auto-reactive T cells.[204] The relative cutaneous abundance of *Malassezia spp*. differ by AD severity; for example, *M. restricta* predominates over *M. globosa* in mild or moderate AD while these species are more equally represented in severe disease.[205,206] AD appears to increase sensitization to *Malassezia spp*., yet sensitization occurs preferentially in adults.[204] Specifically, *Malassezia spp*. sIgE are found in 5–27% of pediatric and 29–65% of adult AD patients,[204] although testing for *Malassezia spp*. sIgE is not standard practice. Interestingly, non-*Malassezia* yeast are more diverse in AD patients versus healthy individuals.[207] While topical ketoconazole has been observed to improve head and neck AD in some patients, a placebo-controlled trial found no difference between topical miconazole-hydrocortisone cream and ketoconazole shampoo versus hydrocortisone alone for head and neck AD.[208]

Aeroallergens

Aeroallergens are recently established triggers of AD and produce cutaneous reactions likely through direct skin contact[209,210] [Figure 1]. Triggers include indoor aeroallergens (ie, HDM, pet dander, fur, cockroach, and mold) and outdoor aeroallergens (ie, tree, grass, and weed pollens) [Table 3]. Sensitization to HDM is particularly common in pediatric AD patients (48.9%) and children with a strong skin prick test (SPT) reaction to HDM have greater AD severity.[211] Upon penetrating the defective skin barrier, allergens may be presented in an IgE-facilitated or IgE-independent manner to T cells with subsequent release of Th2 cytokines IL4, IL13, and IL31 and downstream effects of B cell maturation to plasma cells and pruritus.[210] Alternatively, allergens may directly trigger neurons to release substance P and degranulate skin mast cells via the MRGPRX2 receptor.[212,213] Recently, propyl-paraben exposure has been linked with aeroallergen sensitization and AD severity.[214] Notably, sensitization to specific aeroallergens such as birch pollen may mediate late eczematous reactions to related foods.[215] A late reaction to melons in ragweed pollen sensitization has also been observed.[216]

Epicutaneous skin testing (ie, SPT) or serum sIgE testing may diagnose aeroallergen sensitivities. sIgE testing is an option for patients with dermatographia or widespread AD. While guidelines do not recommend routine testing for aeroallergens in AD, testing should be considered in patients in whom aeroallergen triggers are suspected.[217] Currently, management centers on avoidance and maintenance of the skin barrier.[210] Avoidance includes removing pets or keeping them in another room, implementing dust mite-proof pillow or mattress encasings, and wearing occlusive clothing outdoors. Skin moisturization and TCS for flares are recommended to restore and maintain the skin barrier. Subcutaneous immunotherapy (SCIT) has been shown to improve AD in patients sensitized to HDM and decreases the need for topical corticosteroids.[218] Meanwhile, sublingual immunotherapy (SLIT) to HDM has been shown to improve mild, moderate, and severe AD.[219,220] While SCIT and SLIT have shown promise, they are not yet indicated for the management of AD at this time.

Air Pollution

Air pollution is an increasingly recognized contributor to AD [Figure 1, Table 3]. A recent study found that short-term exposure to air pollution secondary to a California wildfire was associated with increased health-care use for patients with AD and itch.[221] Increases were seen in pediatric appointments for both AD and itch. Specifically, a 10-μg/m3 increase in weekly mean particulate matter ≤2.5 μm in diameter (PM2.5) concentration was associated with a 7.7% increase in weekly pediatric itch clinic visits. Meanwhile, long-term exposure to air pollutants has been shown to increase the development of AD.[222] These pollutants include PM2.5, particulate matter ≤10 μm in diameter (PM10), sulfur dioxide, nitrogen dioxide, and carbon monoxide. Notably, younger AD patients (age zero- to seven-years-old) may be most susceptible to air pollutants.[223] In a systematic review and meta-analysis, pediatric AD was also associated with active and passive smoking, with odds ratios of 2.19 (1.34–3.57) and 1.15 (1.01–1.30), respectively.[224] However, smoke exposure may not trigger AD since cohort studies showed a lack of association between AD and passive smoking or maternal smoking during pregnancy.[224] Regarding a mechanism for air pollution-induced AD, PM contains polycyclic hydrocarbons (PAHs) that may activate AHR.[225] In fact, treatment of human skin equivalents and murine skin with PM2.5 inhibits FLG protein expression via PM2.5-induced TNF-α and is AHR-dependent.[226] As discussed above, AHR activation may also increase artemin expression and itch. Finally, PM10 exposure has been shown to induce/aggravate dermatitis in an AD mouse-model via the differential expression of genes controlling skin barrier integrity and the immune response.[227]

Climate

Climate including humidity, UV index, temperature, and precipitation influences the prevalence of pediatric AD [Table 3]. Higher humidity, UV index, and temperature are associated with decreased AD prevalence.[228] However, overly high humidity or temperatures can cause perspiration, which may trigger AD in some patients.[229] Higher indoor heating days (a measure of the coldness of weather experienced) and precipitation are associated with increased AD prevalence.[228] Humidity may improve AD by compensating for increased TEWL.[229] Meanwhile, sub-thermogenic UV

light has been shown to reduce skin inflammation and may also reduce pruritus by direct or indirect effects on cutaneous sensory nerve fibers.[230] It is possible that a subset of mild AD patients may benefit from the right amount of humidity and UV exposure at the right (moderate) temperature [Figure 1]. While cohort studies of children in Europe have observed *FLG* LoF mutation frequencies of 15.1–20.9% and 5.8–13.0% in AD and non-AD groups, respectively,[231–236] Sasaki et al found no difference in *FLG* LoF mutation frequency between children with and without AD on a subtropical Ishigaki Island where humidity (monthly average, 60.8–78.7%) and temperature (monthly average, 18.5–29.4 °C) are elevated throughout the year.[18] While this is an interesting suggestion that a genetic predisposition to AD may be abrogated by a beneficial environment in some patients, future randomized controlled trials are required to further assess the potential benefits of climate on AD.

Food

Ingestion of certain foods may exacerbate AD in select patients. Although rarely the cause, cow's milk and hen's egg are the most reported food triggers for AD in younger children.[217] Pollen-related food allergies may be considered in older children and adults.[215,217] Notably, avoidance of food is not indicated in management of most AD.[237] It is not uncommon that patients or providers incorrectly suspect diet as the cause of AD and inaccurately assign food allergies; this not only results in inappropriate testing and dietary changes but may also result in neglect of established AD treatments and possibly even development of IgE-mediated food allergy.[237,238] However, it is important for clinicians to be aware that the prevalence of food allergy is significantly higher in children with AD, as compared to healthy children. Therefore, timely prevention and proper diagnosis of food allergy in this population is warranted. While breastfeeding undoubtedly confers multiple physiological and psychological benefits to both mothers and children, the protective effect of breastfeeding against development of AD remains uncertain.[239]

Conclusion

The pathogenesis of AD involves genetic and environmental triggers and is marked by immune dysregulation. From a genetics standpoint, mutations result in skin barrier defects (ie, EDC, SP/SP inhibition, desmosome component variants) and immune system defects (ie, innate immunity, cytokine-related, antigen receptor signaling, IgE-related, and leukotriene-related variants) and dysregulation. Epigenetics may modulate the immune disarray. As the vast complexity of AD genetics is now apparent, we look to PRSs and GWAS for more comprehensive genetic signatures of AD. From an environmental standpoint, microbes (ie, *S. aureus*), aeroallergens (ie, HDM and pollens), air pollution (ie, PM2.5), and climate (ie, humidity, temperature, UV index, precipitation) are key contributors. Cutaneous dysbiosis may modulate AD by increasing susceptibility to *S. aureus* and fostering abnormal skin immunity and inflammation. Meanwhile, the right climate and/or commensals may improve AD for some patients. While food may trigger AD in a small subset of patients, we caution against excessive dietary avoidance and recommend prioritization of AD management fundamentals.

Identification of AD offender genes and research into the dysregulated immune pathways has enabled the rapid expansion of precision medicine-based therapies.[77] Dupilumab is an anti-IL4 receptor antibody that interferes with IL4 and IL13 signaling and is approved for AD.[240] It may also improve AD related to *IL4/4R, IL13, DOCK8, CARD11, STAT3, SPINK5, ERBB2IP*, and *ZNF341* dysregulation.[241–248] Tralokinumab targets IL13 and is approved for moderate to severe AD in adults.[77] Topical ruxolitinib and oral upadacitinib, abrocitinib, and baricitinib (approved in Europe and Japan) are JAK inhibitors indicated for AD.[249,250] Topical PDE4 inhibitor crisaborole is also approved for AD patients down to three months of age.[76] Other biologics under study in the US include lebrikizumab, nemolizumab, and tezepelumab, which block IL13, IL31 receptor, and TSLP, respectively.[76,251–253] At the epigenetic level, topical tapinarof is approved for psoriasis and is being studied for use in AD. Tapinarof may outcompete toxigenic ligands for AHR binding, resulting in downregulation of proinflammatory cytokines and normalization of the skin barrier.[225,254,255] Meanwhile, increasing recognition of the role of the microbiome in AD may lead to new therapies to re-balance pathogens and commensals on the skin. Cutaneous microbial transplantation and vaccines against *S. aureus* are two nascent strategies.[256,257] Randomized controlled trials are also needed to evaluate climate as a modulator of AD.

Explaining the genetic basis of AD to patients and families may improve compliance with moisturizers and topical anti-inflammatory medications based on their understanding that AD patients are inherently predisposed to skin barrier defects and cutaneous inflammation. Meanwhile, minimizing environmental triggers may lead to optimization of topical anti-inflammatory treatments and prevent the need for systemic therapy. Further studies in genetics and environmental triggers may lead to better AD treatments and possibly prevention of AD.

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All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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