Eczema in Early Life: Genetics, the Skin Barrier, and Lessons Learned from Birth Cohort Studies

Jocelyn M. Biagini Myers, PhD and Gurjit K. Khurana Hershey, MD, PhD

Eczema is a chronic inflammatory disorder of the skin that affects as much as 30% of children. It often afflicts infants in the first few months of life and can be the first indicator of the atopic march. Recent results from birth cohort studies have uncovered novel information about genetic and environmental factors that promote the development of eczema. Birth cohort studies provide an optimal study design to elucidate these associations and prospectively track longitudinal data including exposure assessment and health outcomes from birth into early life and childhood. This is especially relevant for eczema because of the age-specific emergence of this disease. In this review, we will provide a general overview of pediatric eczema and discuss the important findings in the literature for genetics and environmental exposures, highlighting those derived from birth cohort studies. Additionally, we will review how these relate to the atopic march, the hygiene hypothesis, and the integrity of the skin barrier.

AhR	Aryl-hydrocarbon Receptor
ALSPAC	Avon Longitudinal Study of Parents and Children
BAMSE	Children, Allergy, Environment Stockholm Epidemiology
CCAAPS	Cincinnati Childhood Allergy and Air Pollution Study
CMA1	Mast cell chymase 1
COAST	Childhood Origins of Asthma
ECA	Environment and Childhood Asthma
EDC	Epidermal differentiation complex
eNO	Exhaled nitric oxide
ETS	Environmental tobacco smoke
FLG	Filaggrin
GINI	German Infant Nutritional Intervention Study
GMAS	German Multicenter Allergy Study
Ig	Immunoglobulin
IL	Interleukin
IL4Rα	Interleukin 4 receptor alpha
ISAAC	International Study of Asthma and Allergies in Childhood
LEKTI	Lymphoepithelial Kazal-type inhibitor
LISA	Lifestyle-related factors in the Immune System/Development of Allergies in Children
LPS	Lipopolysaccharide
PAH	Polycyclic aromatic hydrocarbons
PIAMA	Prevention and Incidence of Asthma and Mite Allergy
SEATON	Study of Eczema/Asthma to Observe Influence on Nutrition
SNP	Single nucleotide polymorphism
SPINK5	Serine peptidase inhibitor Kazal-type 5
SPT	Skin prick test
SSCE	Stratum corneum chymotryptic enzyme
TEWL	Transepidermal water loss
Th2	T-helper cell 2
TNFα	Tumor necrosis factor alpha
URECA	Urban Environment and Childhood Asthma

Eczema Definition, Prevalence, and Epidemiology

Eczema is a multi-factorial inflammatory skin disease, arising from the interplay of both genetic pre-disposition and environmental exposures. It a form of dermatitis, which constitutes local inflammation of the skin characterized by itching and redness. This chronic skin disorder is often associated with cutaneous hyper-reactivity and other atopic disorders such as allergic rhinitis and asthma.[1,2] Also known as atopic dermatitis, eczema is the preferred term for skin inflammation associated with itchiness and rash according to the World Allergy Organization, because not all eczema is associated with immunoglobulin (Ig)E-mediated sensitivity to allergens.[3]

The prevalence of eczema differs between developing and industrialized nations.[4] In the last 3 decades, prevalence rates in industrialized nations have increased to as much as 15% to 30% of children and 2% to 10% of adults.[1] As part of the International Study of Asthma and Allergies in Childhood (ISAAC), data on eczema prevalence was collected during phase 1 (1994-1995) and phase 3 (5-10 years after phase 1) in 56 countries.[5] These data revealed that although 58% of participating centers reported an increase in eczema prevalence in older children (13-14 years), it has since seemed to plateau or decrease in nations with historically high eczema prevalence, such as Northwest Europe and New Zealand.[5,6] Large increases in eczema prevalence, however, are now observed in developing countries such as Mexico, Chile, Kenya, and southeast Asia in this age group.[5] However, in younger children (6-7 years), 84% of participating centers reported increased prevalence of eczema, with the highest increases seen in Western Europe, Canada, South America, Australasia, and the Far East.[5] These substantial differences argue that environmental factors and genetic predisposition are key players for eczema development worldwide.[5] Further, the recent plateau in eczema prevalence in countries with historically high rates suggests there may be a finite number of persons susceptible to eczema development.[5,7]

From the Division of Asthma Research (J.B.M. G.K.H.) and Division of Allergy and Immunology (G.K.H.), Cincinnati Children's Hospital Medical Center, Cincinnati, OH

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Pathology, Clinical Features, and Immune Function in Eczema

The development of eczema has been described in 3 distinct stages defined by age of onset (infancy, childhood, and adolescence/adulthood). Sixty percent of all eczema cases will appear during the first year of life (infantile eczema).[1] A total of 45% of all eczema develops in infants 2 to 6 months of age with itching, redness, and small bumps on the cheeks, forehead, or scalp that may later spread to the trunk.[1,8] The childhood phase of eczema eruption commonly occurs between the ages of 4 and 10 and is characterized by raised, itchy, scaly bumps on the face, trunk, or both and also accompanied by dryness and thickening of the skin.[8] The adolescent/adult phase appears at or after the time of puberty and is distinguished by itchy, dry, scaly skin that may continue into adulthood.[8] Despite the life stage, pruritic erythematous papules and plaques with secondary skin peeling are common to all stages.

In individuals with eczema, there is considerable evidence for immune dysregulation, including increased serum IgE and allergen sensitization, increased T-helper cell 2 (Th2) cytokine expression in eczematous lesions, increased T-cells expressing cutaneous lymphocyte-associated antigen, increased Fcε receptor 1 on Langerhans cells and inflammatory dendritic epidermal cells, and decreased expression of antimicrobial peptides.[9-12] Atopic keratinocytes have a reduced ability to synthesize antimicrobial peptides, contributing to an increased susceptibility to bacterial and viral infection.[9] Although there are many unanswered questions about the interplay of skin barrier dysfunction, immune dysregulation, and susceptibility to microbial colonization in eczema, genetic pre-disposition is known to play a central role the pathophysiology of eczema.[10,13]

Genetics of Eczema

Strong evidence exists in the literature to support a genetic predisposition to eczema. The risk of childhood eczema is two to three times higher in children with a maternal or paternal history, irrespective of parent sex or body region affected.[14,15] Twin studies show high concordance rates for eczema in monozygotic twins, ranging from 72% to 86%.[16,17]

Genome wide scans have identified several possible eczema-related loci on chromosomes 1q21, 3q21, 16q, 17q25, and 3p26, most notably 1q21, which harbors a family of epithelium-related genes called the epidermal differentiation complex (EDC).[1,18-21] Genes in the EDC have been reported to have significantly altered expression in the skin of patients with eczema.[20,22] Recent research has highlighted the importance of the skin barrier and genes related to barrier dysfunction in the pathogenesis of skin disorders.[1,23-27]

The single most replicated gene in eczema studies is filaggrin (FLG), reported in 21 independent studies.[27,28] FLG is a keratinocyte protein that is a key component in the granular cell layer of the skin.[29,30] The FLG gene was first cloned in 1989 and hypothesized to have an important role in disorders of keratinazation because of its key role in the terminal differentiation of the epidermis.[27,31,32] Smith et al were the first group to identify two mutations in FLG (R501X and 2282del4) in patients with ichthyosis vulgaris.[33] Data from 8 pedigrees of families with ichthyosis vulgaris strongly supported that FLG null alleles predispose to eczema,[34] and these results have been confirmed many times in multiple ethnic populations, including Caucasians from multiple European countries and the Japanese.[27] FLG null alleles have also been shown to predispose to early-onset eczema that persists into adulthood.[35] It has been estimated that 50% of all eczema cases can be explained by the presence of one FLG null allele.[29]

In individuals with eczema, studies suggest that the FLG null alleles predispose them to asthma,[34,36-40] allergic rhinitis,[36,39] and allergen sensitization.[38] Thus, the FLG null alleles may predispose to the sequential eruption of allergic rhinitis and asthma, supporting the atopic march theory.[36] Skin inflammation associated with eczema is typically associated with increased cytokine expression, mainly interleukin (IL)-4 and IL-13, which reduces FLG function and expression.[41]

During formation of the cornified cell envelope, profilaggrin is dephosphorylated and cleaved by serine proteases ending in the release of functional FLG.[42] A series of inhibitors control the protease activity, and serine peptidase inhibitor Kazal-type 5 (SPINK5) is the best characterized of these inhibitors.[42] Genetic variation in SPINK5 has also been associated with eczema in multiple studies,[43-45] although its physiological functions are not completely understood. Therefore, immune and skin barrier related genetic variations may work synergistically to increase susceptibility to eczema.

Indeed, there are two predominant groups of genes that have been associated with eczema: genes that encode epidermal or epithelial structural proteins, such as FLG and SPINK5, and genes that encode for major elements in the immune system, such as IL-4, IL-5, and IL-13, which promote allergic inflammation.[1] The most replicated immune genes associated with eczema are IL-4, IL-4 receptor alpha (IL4Rα), IL-13, mast cell chymase 1 (CMA1), and CD14.[36,46-49] IL-4 promotes the development of Th2 cells in allergic inflammation and decreases gene expression in the EDC that contribute to barrier function and innate immune defense.[41,50-52] IL-13 promotes tissue inflammation and is up-regulated in eczematous skin lesions.[9,50] Multiple SNPs in IL-13 have been significantly associated with eczema in Canadian, Japanese, Dutch, and German populations.[53] Furthermore, IL-13 haplotypes have been associated with eczema in Caucasian infants during the first year of life.[49,54-57] IL-4 and IL-13 also share a common receptor subunit, IL4Rα,[58] and SNPs in IL4Rα have also been identified in subjects with eczema.[46,49,59-64]

Mast cell chymase has numerous activities that contribute to inflammation including activation of interstitial pro-collagenase,[65] process pro-collagen into collagen,[66] and release of transforming-growth-factor beta 1 (TGF-β1) from the