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GENETIC AND ENVIRONMENTAL FACTORS IN ATOPIC DERMATITIS

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ABSTRACT

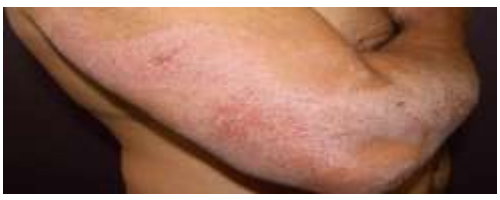
Atopic dermatitis (AD) is one of the most common skin conditions in humans.AD affects up to 20% of children worldwide and results in morbidity for both patient and their caregivers. The basis of AD is an interplay between genetics and the environment characterized by immune deregulation. Atopic dermatitis (AD) is a chronic inflammatory skin disorder that affects a substantial number of children and has a significant negative impact on affected patients and their families, which leading to cause of global burden from skin disease. Atopic dermatitis is associated with increased risk of multiple comorbidities, including food allergy, asthma, allergic rhinitis, and mental health disorders. A myriad of mutation that compromise the skin barrier and /or immune function have been linked to AD. Of these filaggrin gene (FLG) mutation are the most evidenced. Many other mutations have been implicated in isolated studies that are often un-replicated, creating an archive of genes with potential but uncomfortable relevance to AD. Harnessing a big data, polygenic risk scores (PRSs) and genome –wide association studies (GWAS) may provide a more practical strategy for identifying the signature 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 pathogenic stains 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, Genome-Wide Association Studies.

I. INTRODUCTION

AD is one of the most common skin conditions, affecting up to 20% of children worldwide. 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. AD results in significant impact on children's quality of life due to itching, scratching, emotional distress, and sleep disturbance. The median annual out of-pockets expenses 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

Children with AD may suffer a wide ranges of allergic, psychology, 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. However, while atopic diseases do commonly co-occur, most do not follow this temporality. The childhood origin of asthma study, a high-risk birth cohort study, has shown that the early/recurrent phenotype of AD (present 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. Notably atopic comorbidity may be a feature of pediatric AD and less common in adult-onset AD. Besides allergic comorbidities, children with AD show increased risk of having anxiety and attention-deficit hypersensitivity disorder as well as certain bacterial and viral infections. The consequences of AD extend to caregivers, who suffer mental and physical health effects tied to the quality of life these children.



AD is a disease of defective genetics in an unfavorable environment. Its underlying mechanisms 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. Regarding immune deregulation, pediatric AD shows the highest skin eosinophil and neutrophil counts and greater

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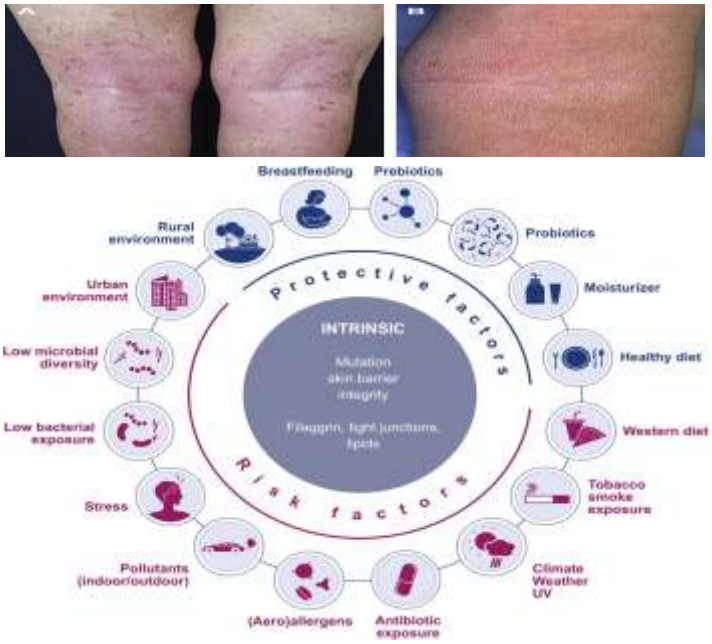
induction of T-helper (Th) 2, Th9, Th17, interleukin (IL) 31, IL33, and innate immune markers; meanwhile, adult AD is skewed towards Th1 activation. In both children and adults, AD skin is likely predisposed to pathogen colonization which may contribute to disease progression.



1. Environmental Factors

1. Climate
2. Urban *vs.* Rural life
3. Diet
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4) Pets
5) Bacterial Endotoxins
6) Helminthes
7) Antibiotics

1.1 Climate:

Climate, a factor that potentially could explain the differences in prevalence between different populations, has received scant attention in relation to AD. Data on association with prevalence AD and temperature are conflicting. From an ISAAC phase one study, where the variables latitude, altitude, average outside temperature, and relative outside humidity were factored in, it became apparent that symptoms of AD correlate positively with latitude and negatively with annual outside temperature. These results are confirmed by other similar studies in Spain, Taiwan, and the USA. UV light has a well-known immunosuppressive effect, in part related to the fact that it facilitates the conversion of trance-urogenic acid with immunosuppressive effect. Also, because exposure to the sun/UVB increases serum level in vitamin D, it can logically be assumed that the clinical improvement of AD through sun exposure can be mediated at the molecular level by the same vitamin. This data point is supported by the observation that vitamin D deficiency is associated with the severe AD

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manifestation in skin areas not exposed to light, which demonstrates a protective local effect of vitamin D. Low outside temperature, especially in combination with skin irritants, are responsible for an aggravation of eczema.

1.2 Urban and Rural Life:

It is known that in population of the same ethnicity and genetic background the risk of AD is higher in cities than the countryside. This contrast between city and country life is supported by the systematic review of 2 studies. Environmental risk factors, which needs to be considered relevant are urbanization, differences in hygiene, microbial infections, vaccination, and use of antibiotics, environmental pollution, and exposure to allergens, and diet. Further studies are needed in order to identify the risk factors of urban living in development of AD.

1.3 Diet:

Given the fact that AD is still not very common in developing countries, we can ask if a "Western diet" (i.e., high intake of refined cereals, red and preserved meats, and saturated and unsaturated fatty acids)is a possible contributor to the increase in the disease. One ISAAC phase Three study showed a significant protective effect of the frequent intake of fresh fruit (1-2x/weeks) and an aggravating effect of fast-food intake (>3x/week). Another ISAAC study came similar conclusion, highlighting an inverse association between the prevalence of AD and the per capita intake of vegetables, cereal proteins, and fresh and frozen fish. This is confirmed in other studies, which show that a high intake of fish during pregnancy lowers the risk of AD in the first 5 years of life by 25-43%. A similar risk reduction was also reported in children with high intake of fish during late childhood. The protective effect of fish can be attributed to its high content in n-3 polyunsaturated fatty acids (n-3PUFA), which is correlated with anti-inflammatory activity. The western diet of the last decades is poor in n-3 PUFA, while pro-inflammatory n-6PUFA, such as linoleic acids, is increased.

1.4 Breastfeeding and Weaning:

It is common belief that breastfeeding prevent allergies, including AD. The World Health Organization (WHO), in fact, recommends exclusive breastfeeding for at least 4 months, to prevent allergies. However ISAAC phase two studies conducted both in developed and in developing countries including 51.119 school-age children show only modest support for this thesis. Systematic research on various populations also did not show a statistically significant benefit of exclusive breastfeeding. Further studies are necessary to determine the role of breastfeeding in childhood AD and the relation between breastfeeding and introducing solid foods.

1.5 Obesity and Physical Exercise:

A growing number of children in affluent societies are overweight. Various research suggests both an association and a dissociation between spent in front of television (> 5hours) has a positive association with the risk of AD, the same being stronger in obese vs. overweight vs. underweight / normal children with respect to time of exposure and response. It remains to be established whether these positive associations are casual, e. g, linked to inflammation of adipokines (molecule synthesized and secreted by adipose tissue), such as leptin and adiponectins, or related to dietary factors, that may encourage the development of AD through oxidative stress, since diet that exclude antioxidant foods, such as fruits and vegetables, are related to an increase in obesity and AD.

1.6 Air pollution:

Air pollution is the source of a wide variety of substances derived from industrial and non-industrial processes. In normal conditions, air pollution usually excludes derivatives of natural phenomena such as volcanic eruptions and smoke of spontaneous forest fires, or radioactive material from military tests, and batteries. Mold and spores, however, are sometimes included because of the allergological damage they cause in a large population segment. Air pollutant can originate from indoor and outdoor environments and can penetrate the skin, binding to the stratum corneum, entering the systemic circulation. Long-term study conducted with sufferers of AD in early childhood (from 3 months to 8 years) which took in to account of variety of daily parameters (NO_2, particulate matter, volatile organic compounds such as benzene, toluene, xylene, and styrene, temperature, and relative humidity), showed a significant SCORAD deterioration in the presence of high concentration of particulate matter, toluene, and other volatile organic compounds. In particular AD got worse

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in spring with high level of styrene, in autumn with high level of volatile organic compounds, and in winter with high levels of fine particulate, in summer with high levels of toluene and NO2. These data were confirm by other researches.

Confirming the "outdoors" observations above, a move "indoors" into a clean house and a hospital significantly improves the SCOARD of AD sufferers. A Swedish study showed a dose-dependent association between AD and lower ventilation in the houses, in particular, in the child's bedrooms. A German study found association between indoor renovation activities, (painting, floor covering, and new furniture) before the birth and the first year of life and lifetime prevalence of AD, likely in connection with high level of organic compounds (VOCs). Cleanliness that needs to take in to consideration chemical, physical, and biotic (dust, mites, microorganisms, particulates, volatile organic compounds, temperature and relative humidity) parameter should be observed not only in the home and in hospitals, but also in kindergarten and schools

1.7 Tobacco Smoke:

A controlled case study (83 patients/142 control subjects) showed a direct relationship between the cumulative number of cigarettes and the onset and / or worsening of AD in adults. The same significant relationship between environmental tobacco smoke and AD onset was also highlighted in nonsmokers. It is known that AD in character such as prurigo, involving especially the face and hands, and associated with high values of IgE, asthma, and allergic rhinitis. From various studies it emerges that AD is significantly associated with active and passive smoking also in adolescents. Under an immunological profile, tobacco smoke increases the level of pro-inflammatory cytokines; it causes oxidative damage, decreases skin barrier function and has an irritant effect on skin.

1.8 Ozone:

Measured daily for about 2 years from 10 am to 6 pm, an excess of ozone (formed by the action of UV rays on the oxygen of the air) aggravates various skin condition, thus requiring a greater number of visits to the doctor. After 7 days of increased ozone levels there is a significant increase of 3,84% of visits for AD, of 2,86% for contact dermatitis, and of 0.8% for urticarial. Ozone is a highly unstable and therefore very reactive oxidant; it reacts with the biomolecules of the skin and forms ozonides and free radicals. Low nontoxic doses of ozone increase the production of antioxidants, while high doses act as a pro-inflammatory cytokine.

1.9 Skin Barrier and Allergic Sensitization:

Recently, the strong association between genetic mutation of FLG in the epidermal barrier and might play in the development of AD and sensitization. The current hypothesis is that in subject without skin barrier defects the epidermis is in a state of integrity with resulting normal "trans-epidermal water loss" (TEWL) and adequate protection from microorganisms and environmental allergens. Genetic mutation of FLG increase TEWL and are associated with sensitization, which therefore becomes predominantly "secondary phenomenon" in AD and a significant cause of aggravation and chronicity of the same.

1.10 Microbial Exposure:

In two recent literature reviews, the relationship between microbial exposure and the risk of AD has been studied. The argument of the risk of disease inversely related to hygiene has been widely studied in response to observations in different scenarios since the end of the 1980.

1.10.1hygiene:

Many studies concerning the risk factors in AD regard the "hygiene hypothesis". One study conducted on a very large cohort (>10,000) of infants, which took in to account the level of hygiene at 15 months (frequency of washing, use of household detergents, and baby wipes, showed a proportional increase in the risk of disease between the age of 2.5 and 3.5 years with an increased level of hygiene. One Japanese study, on the contrary, on a cohort of 865 subjects, has found an inverse relationship between daily baths or showers vs. less frequent ones.

1.10.2 Daycare Centers:

The stay in nurseries seems to be associated with increased microbial exposure, in particular with respiratory infections, and some authors have reported a reduction in risk of AD in children attending daycare in the first year of life. However, have found the opposite effect.

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1.10.3 Animal and Farm Life:

Various studies conducted in this area did not show a convincing protective effect of this lifestyle. It is very interesting fact that the consumption of unpasteurized farm milk during the first 2 years of life is an independent protective factor against the development of AD, even in families not living in the countryside. This inverse relationship is also independent from a family history of allergies. With boiling, cow's milk loses its protective effect. The mechanism of this protective effect remains uncertain and could be related to microbial contamination or other constituents of non-processed milk. It has also been shown that direct contact with farm animals reduces the risk of AD in the first year of life, in particular where the mother have regular contact with farm animals during pregnancy; this protective effect appears even more pronounced in those exposed during their prenatal life rather than post-natally, confirming that innate immune may have a particular importance. This is the casual for the well-known argument about the contrast between "country children" compared to "city child".

1.10.4 Pets:

Many studies have been conducted on this subject. They all found dogs to have a protective effect, especially in the first year of the life. The role of cats is not clear. Where the mutation, suggesting that cat sensitization may be favored by a compromised skin barrier, which is turn contributes to the risk of AD.

1.10.5 Bacterial Endotoxins:

Risk reduction through the exposure to farm animals and dogs, in particular during pregnancy, is attributed to endotoxins (lipopolysaccharides on the surface of Gram-negative bacteria), also because they are known to induce IL-10 and INF-gram. Cohort studies have shown a risk of AD up to 50% with exposure to bacterial endotoxins, with the effect limited to high levels of exposure and/or the first year of life.

1.10.6 Helminthes:

The protective effect of helminthes infections (Ascaris lumbricoids) on AD risk was demonstrated in double-blind randomized controlled study with antiparasitic therapy conducted on more than 2500 pregnant women in an endemic helminthes area in Uganda during the last trimester of pregnancy: the AD risk up to first year of life is increased two times in the treated group. It was observed that lack of exposure to helminthes seems to have no effect in subsequent years of life, confirming that the innate immune system protects from the risk of AD.

1.10.7 Antibiotics:

The antibiotics used in respiratory, gastrointestinal, and aural infections, rather than the infections themselves, are casually responsible for the risk of AD development. The same risk is increased by 41% in those receiving at least one cycle of antibiotics in the first year of life. There are also a significant dose-related association with an increased risk of 7% for each additional cycle of antibiotics with a particular strong effect of broad spectrum antibiotics.

II. GENETIC FACTORS

1. Skin Barrier Defects
2. Immune System Defects and Deregulation
3. Genetic Disorders with AD-Like lesions
4. Polygenic Risk Scores and Genome-Wide Association Studies

2.1 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 (ceramides, cholesterol, fatty acid). Compared to healthy skin, AD skin shows reduced hydration and increased water loss as measured by Tran's epidermal water loss (TEWL). This holds true even when AD skin normal appearing. Supporting to the role of a defective skin barrier in AD, TEWL is positively correlated with AD severity and may predict AD development. 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. The EDC also controls epithelial tissue development and

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repair by regulating the terminal differentiation program of KC. The EDC includes three gene families including the cornfield envelop precursor family, the S100 protein family, and the S100 fused type proteins (SFTP).

Potential Genetic Factors Contribute to AD:

Skin Barrier	Epidermal differentiation complex SP and SP inhibition Desmosome component Epigenetics	*FLG, FLG2, HRNR, LCE2C, LCE5A, LCE4A, RPTN, S100A3, S100A7, S1OOA8,S100A16, SPRR3, SPRR4, TCHH,TCHHL1, CLDN1, Tmem79/matt, LELP1* *SERPINB7, KLK7* *DSC1* *KIF3A* methylation, *PPAR* up regulation.
Immune system	Innate immunity Antigen receptor signaling Cytokine-related Leukotriene- related Epigenetics	*TLR2, TLR4, TLR9, NOD2, NOD1, IRF2, SIDT2,RBBP8NL* *CARD14, LRRC32* *IL4/4R, IL5, IL7R, IL9, IL10, IL12, IL13, IL18, IL31, TSLP, STAT6* *CYSLTR1* *AHR* up regulation, reduced *IL*13methylation, reduced *AcH3K9* acetylation.

2.2 Immune System Defects and Deregulation:

Regarding the innate immune system, stimulated KCs from AD patients produced diminished levels of antimicrobial peptides (AMPs) versus healthy subjects and those with psoriasis, another chronic 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. TLR2 is a key PRR for S. aureus, and TLR2 polymorphism are linked to severe AD with recurrent skin infections. Overall, AD patient show diminished response upon TLR2 stimulation including reduced IL6, IL8, CCL20, and MMP9 production, which may pre-dose to infections. Human beta defensins provide antimicrobial and immunomodulary benefits and are relevant to the genetics of AD. It produced at low level in lesion skin of patient with AD relative to patient with psoriasis.

Classically, AD lesion are characterized by an increased expression of Th2 cytokines, which have been implicated in tissue repair. Indeed cytokine related genes represents a sizeable group of potential offender genes whose variant have been associated with AD. As result of inherent barrier defects such as FLG mutation or lipid deficiencies, there is an overproduction of Th2 cytokine in the skin lesion of pre-disposed individuals.

Epigenetics may modulate the immune response of AD. There are significant differences in the DNA methylation levels between the skin-homing CD+CLA+T cells of AD patients are associated with an increased expression of IL13 mRNA in these cells.

2.3 Genetic Disorders with AD-like Lesion:

There are a number of genetic disorders including immunodeficiency, autoimmunity, and non-immune abnormalities that feature AD-like lesion. These condition and there known culprit gene include hyper IgE syndrome, CARMIL2 deficiency, Omen syndrome. Recently GoF STAT6 variant have been associated with a novel autosomal dominant allergic disorder featuring early onset allergic immune deregulation with widespread refractory AD, hyper eosinophilia with eosinophilia esophagitis, high serum IgF, food allergies, and brain anomalies.

Genetic Disorder with AD-Like Lesion:

Wiskott-aldrich syndrome	Actin polymerization	WAS
ADA-SCID	Antigen receptor signaling	ADA
IPEX syndrome	Cytokine related	FOXP3
CADINS disease	Antigen receptor signaling	CARD11
Congenital disorder of glycosylation	Cellular metabolism	PGM3

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2.4 Polygenic Risk Scores and Genome-Wide Association Studies:

While 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 comprise 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 deregulated 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.

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