UNIVERSITY of WASHINGTON TACOMA

Interplay of Environmental and Genetic Factors in the Prevalence of Atopic Dermatitis

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Background

- Atopic dermatitis, also known as atopic eczema, continues to increase in prevalence throughout children and adults.
- Developing in infancy and progressing through adulthood, it affects at least 20% of children and 5% of adults.
- Atopic dermatitis is commonly found in arms, hands and neck but also in other areas such as around the eyelids, and creases of elbows, knees and wrists.
- Physical appearance consists of red patches of cracked skin that blister, crust, scale, and thicken causing discomfort and severe itchiness.
- Physical symptoms of atopic dermatitis impact one's quality of life, sleep quality and overall self esteem.
- In the United States alone, child-onset atopic dermatitis increased from 8% to 12% back in 2011 and only continues to increase.
- United States holds the highest quantity of adult-onset cases at 53% compared to other countries.
- Family history and genetics are the biggest risk factor in the development of atopic dermatitis.
- A child's susceptibility to develop atopic dermatitis is 1.5-fold when one parent has any atopic disease and three to five-fold when one or both parents have a history of atopic dermatitis.

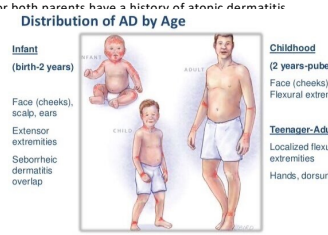

Figure 1. A visual representation of distribution of atopic dermatitis commonly found by age (Sugerman 2014).

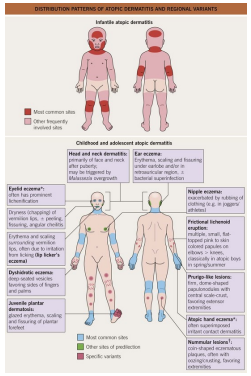

Figure 2. A comparison of the distribution of atopic dermatitis found on infants, children and adolescents (Themes 2016 Apr 22).

Methods

- Extensive research of primary and peer reviewed articles regarding atopic dermatitis and it's genetic and environmental factors was conducted to complete this literature review.
- Total of 25 primary articles reviewed were gathered from multiple databases such as PubMed, NCBI, and Science Direct.

Genetic Factors:

- *FLG* gene located in the epidermal differentiation complex and null mutations cause a reduced expression of the epidermal protein filaggrin.
- FLG is a keratinocyte protein that is the main component in the granular cell layer of the skin.
- FLG mutations are the primary cause for ichthyosis vulgaris (IV), a skin disordered that triggers an abnormal keratinocyte differentiation causing dry, scaley and thickened skin.
  - A homozygous mutation R501X and heterozygous mutation 2282del4
  - Result of these two mutations in a premature termination codon occurs within filaggrin repeat 1, causing lack of processed filaggrin in the epidermis.
- An impaired skin barrier no longer protects the skin from significant water loss nor blocks entry of foreign substances from the external environment.
- Interleukin (IL)-4 immune gene functions in stimulating the production of Th2 cells in allergic inflammation and decreasing gene expression in epidermal differentiation complex (ECD), which is important to barrier function and immune defense.
- IL-13 gene promotes tissue inflammation and is found to be upregulated in atopic dermatitis skin lesions.
- The epidermal Th2 cellular expression and Th2 cytokines suppressing the production of antimicrobial peptide (AMP) and epidermal differentiation causes the skin phenotype of atopic dermatitis.

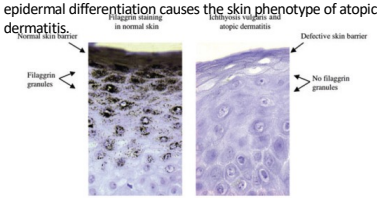

Figure 3. FLG mutations lead to complete loss-of-function filaggrin expression in ichthyosis vulgaris and atopic dermatitis, causing a defective skin barrier (Irvine and McLean 2006).

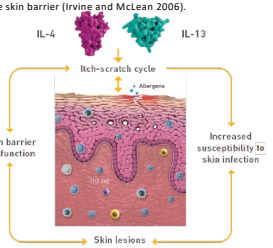

Figure 4. Increased IL-4 and IL-13 immune signaling leads to dysregulated immune system, resulting in the itch-scratch cycle. IL-4 contributes to skin barrier dysfunction and increases susceptibility to skin infection and IL-13 is found in atopic dermatitis skin lesions and promotes tissue inflammation (DUPIXENT® (dupilumab) Mechanism of Action).

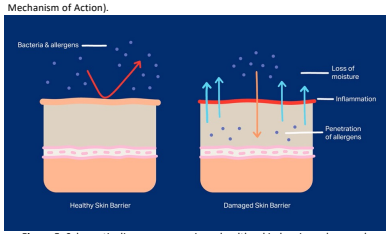

Figure 5. Schematic diagram comparing a healthy skin barrier a damaged skin barrier. Where bacteria and allergens are more susceptible to penetrate the skin when the skin barrier is damaged (Nelson 2023 Mar 1).

Exposome:

Air pollution:

- Outdoor air pollutants: both natural or man-made
  - Natural air pollutants: wildfires, volcanoes, and duct storms
  - Man-made air pollutants: motor vehicles, power plants, biomass burning, and combustion of gaseous products
- Exposure of outdoor air pollution from traffic emissions can induce atopic dermatitis in children in French communities.
- Indoor air pollutants from at home stoves of low ventilation and indoor renovating activities can trigger or aggravate childhood atopic dermatitis.
- An increase in medical visits and prescribed medications treating pediatric and adult patients with atopic dermatitis due to exposure from high concentrations of particulate matter and smoke plume from California wildfires.

Aeroallergens:

- Indoor aeroallergens: house dust mite (HDM), pet dander, and fur
- Outdoor aeroallergens: cockroach, mold, tree, grass, and weed pollens
- House dust mite is most common allergen among atopic dermatitis patients and those with a strong skin prick test (SPT) against house dust mite have greater severity of atopic dermatitis
- Patients with atopic dermatitis with known Immunoglobulin E (IgE) sensitization to grass allergen were challenged with grass pollen allergen using environmental challenge chamber (ECC) had worsen air-exposed eczematous skin lesions than skin areas that were covered.

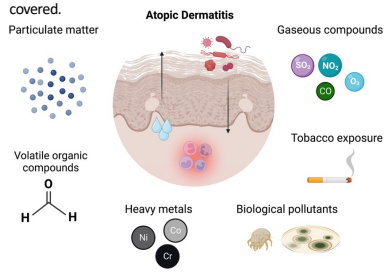

Figure 6. Air pollution subtypes associated with atopic dermatitis. Exposure to these air pollutants can trigger an immune response that drives an allergic reaction thus contributing to the severity of atopic dermatitis (Lai et al. 2023).

UV Exposure:

- UV exposure has been tested to be beneficial in improving atopic dermatitis.
- Temporarily relocating children with atopic dermatitis from colder climates and minimal sun exposure to warmer, more humid and UV exposure improved severity of atopic dermatitis.
- Exposure to sub-erythemal (low dose) ultraviolet B (UVB) by irradiation from fluorescent lamps in mice increased β-defensins and cathelin-related antimicrobial peptide (CRAMP) while amplifying barrier recovery and reinforcing permeability barrier function.

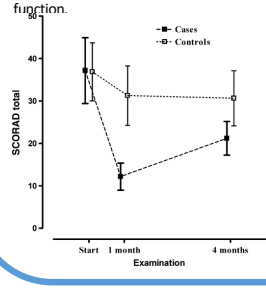

Figure 7. Results of scoring atopic dermatitis in patients temporarily moving from subarctic climate to sunny subtropical climate. A standardized scoring system (SCORAD) was used to measure the distribution and intensity of atopic dermatitis. Total SCOARD scores after baseline, 1 month in a subtropical climate, and after follow up for 3 months (4 months from baseline) displayed improvement for index groups and slight improvement for control groups (Byremo et al. 2006).

Conclusions

- Atopic dermatitis is a common skin disease that begins in infancy and progresses through adulthood.
- The itchy, dry, and red skin patches of atopic dermatitis were reported most burdensome and impact one's overall quality of life and self esteem.
- Loss of function mutations in *FLG* gene reduces the expression of the epidermal protein filaggrin.
- Without proper expression of filaggrin, the skin barrier is compromised.
- Immune system dysregulation triggers allergic inflammation and impacts the skin barrier function and immune defense by decreasing gene expression in the epidermal differentiation complex.
- Gene to environment interactions, such as polycyclic aromatic hydrocarbons (PAH) from cigarette smoke and car exhaust affecting keratinocytes and dust mite allergen inducing miR-155 expression and identifying the immune suppressor cytotoxic T lymphocyte-associated antigen 4 (*CTLA-4)* as its target gene, can further be studied in providing treatments and prevention mechanisms for atopic dermatitis.

Future Directions

- Testing on irradiating skin with fluorescent lamps to increase expression of antimicrobial peptides and human β-defensins promoting an immune response to protect the skin.
- Future research on temporarily relocating patients living in colder climates with atopic dermatitis to areas with higher temperatures, humidity and more exposure to UV radiation to relieve and improve symptoms.
- Application of vitamin D supplements in therapeutics for improving severity of atopic dermatitis and quality of life to pediatric and adult patients
- Increased prevention strategies for patients with atopic dermatitis such as using dust mite-proof pillowcases and bed sheets and wearing occlusive out clothing when outdoors.
- Further studies on targeting gene expression and immune system changes correlated to age to provide research in the similarities and differences of atopic dermatitis at various times of onset.

References

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