# Filaggrin: An Emerging Star in Atopic March

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Atopic dermatitis (AD) is a common chronic inflammatory skin disease characterized by itching and inflamed skin, showing from infancy and early childhood.[1] It affects up to 20% of children with increasing prevalence in highly industrialized countries.[1] Until recently, most pathophysiological concepts of AD have been attributed to immune system abnormalities, including Th1/Th2 imbalance and IgE-mediated sensitization.[1] However, there is growing evidence to show that heritable skin barrier defects caused by mutations in the human profilaggrin gene (*FLG*) play an important role in AD.[2]

## Filaggrin

Filaggrin, processed from profilaggrin, plays an essential role in epidermal barrier formation in the stratum corneum which forms the outermost layer of the skin, keeping skin hydrated and acting as a barrier against environmental assaults. Filaggrin aggregates keratin filaments as the keratinocytes collapse in the stratum corneum, and is subsequently disassembled into amino acids which act in retaining epidermal moisture. *FLG* resides on chromosome 1q21 and consists of three exons.[3] Exon 3 is extremely large (> 12 kb) and encodes most of the profilaggrin polypeptides with almost completely homologous 10, 11 or 12 repeats.[4] The huge size as well as high number of sequence repetitions prevent sequencing of the entire gene.

## Filaggrin Mutations Underlie Ichthyosis Vulgaris

Recently, Smith et al first identified *FLG* mutations R501X and 2282del4 as the cause of ichthyosis vulgaris.[5] Ichthyosis vulgaris is a common genetic skin disease characterized by dry and scaly skin, especially on the flexor limbs, and palmoplantar hyperlinearity. After the establishment of sequencing of the entire *FLG* gene,[6] the total number of *FLG* mutations reported in ichthyosis vulgaris is 22 to date.[7–10] In addition, these mutations are semidominant with incomplete penetrance.[10] Those who are heterozygous show a mild phenotype. Among these studies, Nomura et al revealed four *FLG* mutations among Japanese ichthyosis vulgaris patients which are unique from those found in populations of European origin.[7,8] Chen et al discovered five unique mutations and one recurrent mutation in Singaporean Chinese ichthyosis vulgaris patients.[9] These results suggest that *FLG* mutations may have regional or ethnic differences.



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## Filaggrin Mutations as Major Predisposing Factors for AD

The genome-wide linkage studies for AD revealed significant linkage to the same gene region of filaggrin.[11] In addition, ichthyosis vulgaris is known to be associated with a high incidence of AD and share some clinical features, such as dry scaly skin and keratosis pilaris. Therefore, an association between *FLG*-null mutations and AD was subsequently established.[12] Palmer et al discovered two *FLG*-null mutations (R510X and 2282del4) that were strong predisposing factors for AD (odds ratio = 13.4).[12] The further study demonstrated that these *FLG* mutations predispose for early-onset AD, which persists into adulthood.[13] Nomura et al also showed that there was statistically significant association between four Japanese *FLG* mutations and AD (odds ratio = 7.57).[7]

## Filaggrin Mutations Also Predispose to Asthma

Previous studies showed that 70% of patients with severe AD developed asthma compared with 30% of patients with mild AD and approximately 8% of the general population.[14] In addition, AD is typically the first clinical manifestation of allergic diseases, followed by the development of asthma and allergic rhinitis.[14] The process of atopic diseases is the so-called "atopic march", which suggests a common etiology among these various atopic diseases.

Recent studies hypothesized that the damage to the skin barrier caused by *FLG* mutations allows allergens to penetrate into the epidermis and subepithelial tissues and to interact with antigen presenting cells, known as Langerhans cells and dermal dendritic cells, which might further initiate Th2 immune response and lead to the development of systemic allergies, including allergic rhinitis and atopic asthma.[15] Palmer et al found that *FLG* mutations are significantly associated with the subgroup of asthmatics with AD.[12] In addition, *FLG* mutations were notably associated with greater asthma severity.[16] Thus, *FLG* mutations are responsible for mild to severe ichthyosis vulgaris and also for allergic diseases, including AD as well as asthma.

## Prospective Taiwanese Filaggrin Mutations

One recent cross-sectional study in Taiwan showed that the prevalence of AD was 1.7% among children in the southern part of Taiwan.[17] The prevalence is relatively low and has changed little over the past decade (2% in 1994) compared with Western countries and other Asian countries.[18]

Data on Taiwanese *FLG* mutations are limited. The only report showed that both the European-specific mutations R501X and 2282del4 were absent in Taiwanese psoriasis patients.[19] Data from common single-nucleotide polymorphism analysis and human leukocyte antigen haplotype analysis suggest that Taiwanese might share similar *FLG* mutations with Singaporean Chinese.[9,20,21] We believe that the analysis of *FLG* mutations in the Taiwanese population is likely to reveal the overall contribution of *FLG* mutations to the pathogenesis of atopic diseases.

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