

See related article on pg 98

Profilaggrin, Dry Skin, and Atopic Dermatitis Risk: Size Matters

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Mutations in the *FLG* gene, which encodes profilaggrin, are known to be a major risk factor for atopic dermatitis as well as other atopic diseases and systemic allergies. New research, however, shows that intragenic copy number variation within *FLG* also represents an independent risk factor for atopic dermatitis. The new findings indicate that upregulating FLG protein levels by 5–10% may have clinical utility in improving the management of many patients with dry skin and atopy.

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The major component of keratohyalin granules within the granular layer is profilaggrin, an ~500-kDa, highly phosphorylated, histidine-rich polypeptide that is encoded by the *FLG* gene. During posttranslational processing, individual filaggrin (FLG) polypeptides, each ~35 kDa (324 amino acids), is released proteolytically. In the stratum corneum, FLG is degraded further to generate hygroscopic amino acids that contribute to skin natural moisturizing factor and the formation of an intact skin barrier. The fundamental importance of profilaggrin to skin barrier integrity was realized in 2006 with the discovery of loss-of-function mutations in the *FLG* gene in patients with the semidominant condition ichthyosis vulgaris (Smith *et al.*, 2006). *FLG* mutations were then also shown to be a major risk factor for atopic dermatitis (Palmer *et al.*, 2006). Notably, the presence of one *FLG* mutation has been found to increase the risk of atopic dermatitis 6-fold, and two mutations increase the risk 150-fold. *FLG* mutations have also been associated with increased susceptibility to atopic asthma, the atopic march, systemic allergies, contact dermatitis, and peanut allergy (Marenholz *et al.*, 2006; Weidinger *et al.*, 2006; Palmer *et al.*, 2007; Brown *et al.*, 2011; Carlsen *et al.*, 2011).

The significance of FLG in the pathophysiology of atopic dermatitis has also

been suggested in cases lacking specific mutations in the *FLG* gene. Notably, skin inflammation in atopic dermatitis is associated typically with increased expression of cytokines, such as IL-4 and -13, both of which have been shown to reduce *FLG* gene and protein expression in keratinocytes (Howell *et al.*, 2007). The cytokine IL-22 has also been shown to reduce *FLG* expression (Gutowska-Owsiak *et al.*, 2011). Moreover, polymorphisms in the genes encoding IL-10 and -13 can affect *FLG* expression (Lesiak *et al.*, 2011). Reduced FLG levels, either from a primary gene mutation or from a secondary reduction in protein expression, can also influence innate immune responses via Toll-like-receptor stimuli and thus contribute to skin inflammation (Lee *et al.*, 2011).

Consequently, although mutations in the *FLG* gene represent the most significant genetic risk factor for atopic dermatitis identified thus far, it is evident that *FLG* gene and protein expression can be influenced by several other factors.

In addition to mutations, the *FLG* gene demonstrates intragenic copy number variation. *FLG* encodes 10 highly homologous and only slightly genetically different FLG units, but the exact number encoded can vary, with individuals harboring 10, 11, or 12 monomers. The differences are attributable to possible repeats of subunits 8 or 10 or both. It has

been suggested that the number of FLG repeats can relate to a dry skin phenotype; i.e., fewer repeats may lead to less FLG protein expression and drier skin (Ginger *et al.*, 2005). What is currently not known, however, is whether there is a relationship between the intragenic copy number variation in *FLG* and the risk of atopic dermatitis.

In this issue, Brown *et al.* (2012) compare *FLG* intragenic copy number variation in a cohort of Irish pediatric atopic dermatitis patients and controls. In the combined Irish population (~1,800 subjects tested), the 11-monomer repeat variant was most common (51.5%), followed by the 10-repeat allele (33.9%), with the 12-repeat allele being the least frequent (14.6%). After common *FLG* mutations were excluded, however, the control group was shown to have a higher number of repeats than did the cases. Moreover, copy number variation was shown to correlate with urocanic acid levels (derived from FLG proteolysis) in the stratum corneum. The findings indicate that copy number variation in the *FLG* gene affects the composition of the stratum corneum and makes a significant dose-dependent contribution to atopic dermatitis risk.

The findings by Brown *et al.* (2012) prompt the question of how *FLG* intragenic copy number variation and atopic dermatitis risk compare with the same risk associated with *FLG* gene mutations. To date, loss-of-function mutations in *FLG* represent the strongest and most important single genetic factor in the etiology of atopic dermatitis, with an odds ratio from meta-analysis estimated to be 3.12 (Baurecht *et al.*, 2007). In Brown and colleagues' current report, the comparable odds ratio for the effect of copy number variation is much lower, 1.14. Nevertheless, when comparing individuals with 10 FLG repeats on both alleles with subjects who have 12 repeats on both alleles (i.e., 20 vs. 24 FLG polypeptides), the increased odds ratio for atopic dermatitis in the former is 1.67.

As clinicians are aware, the severity and behavior of atopic dermatitis can vary enormously among individuals, and the precise or relative influence of intragenic copy number variation in *FLG* on disease parameters such as time of disease onset, extent and pattern of

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dermatitis, optimal emollient use, and response (or lack thereof) to topical therapies remains to be seen. However, Brown *et al.* (2012) identify an important therapeutic consideration, namely, that a 5–10% increase in FLG in the skin could be clinically useful. Current work to identify drugs, small molecules, and compounds with the capacity to upregulate FLG expression is therefore expected to be of considerable value in improving the management of atopic dermatitis and other skin and systemic disorders in which a primary or secondary reduction in FLG expression contributes to disease pathophysiology.

A 5–10% increase in filaggrin may be clinically useful.

In pursuit of this therapeutic target, a number of compounds have already been shown to increase FLG expression in keratinocytes. For example, oleanolic acid and ursolic acid—pentacyclic triterpenoids that occur naturally in many medicinal herbs and plants—have both been shown to improve skin barrier function by increasing FLG expression (Lin *et al.*, 2007), and many more compounds with similar, or perhaps superior, FLG-promoting properties are likely to be discovered soon. A therapeutic future that can be extrapolated from the report by Brown *et al.* (2012) is one in which increasing FLG expression in individuals with lower intragenic copy number *FLG* allele variants has the potential to improve skin barrier integrity and reduce disease burden for several disorders. There is a clear translational route to follow, one that is likely to have huge clinical impact in the not too distant future. Size, when it comes to *FLG* intragenic copy number variation, really does matter.

CONFLICT OF INTEREST

The author states no conflict of interest.

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See related article on pg 76

Dermatology Life Quality Index: Time to Move Forward

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Since its introduction in 1994, the Dermatology Life Questionnaire Index (DLQI) has played an important role in assessing dermatology-specific health-related quality of life (HRQoL) and has affected several medical decision-making processes. However, the psychometric requirements for instruments have evolved over the years, and the DLQI is failing these new standards. Therefore, it is time to move forward and use valuable alternatives because the DLQI's scientific limitations outweigh the practicalities of its use.

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The Dermatology Life Questionnaire Index (DLQI) (Finlay and Kahn, 1994), the first dermatology-specific health-related quality-of-life (HRQoL) instrument, has helped enormously to introduce and assess HRQoL in

dermatology. Studies have shown that the DLQI captures specific information that is missed by generic HRQoL instruments such as the SF-36, illustrating the need for dermatology-specific questionnaires. Although the DLQI was

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