

The hands in health and disease of individuals with filaggrin loss-of-function mutations: clinical reflections on the hand eczema phenotype

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Summary

During the last 2 years, we have performed filaggrin genotyping in patients with eczema seen in our hand eczema clinic. We present pictures of healthy and diseased hands from individuals with filaggrin gene (*FLG*) mutations to describe a clinical entity of hand eczema. We show that xerosis and hyperkeratosis on the dorsal aspects of the hands and fingers, as well as palmar hyperlinearity, should alert the clinician about a possible inherited barrier abnormality of the skin resulting from *FLG* mutations. The series of photographs range from the hands of an individual with *FLG* mutations but no history of eczema, to the hands of individuals with typical and atypical filaggrin hand eczema, and finally to the hands of an individual with *FLG* mutations and hand eczema caused by exposure to irritants and allergens. We briefly discuss this possible subtype of hand eczema, present pathomechanisms, and indicate the signs that should alert the clinicians about a possible inherited skin barrier defect.

Key words: classification; filaggrin; hand eczema; loss-of-function mutations; phenotype.

Approximately 9–10% of individuals of European descent with lightly pigmented skin are heterozygous carriers of loss-of-function mutations in the filaggrin gene (*FLG*) (1, 2). Mutations result in structural alterations of the skin, for example poor stratum corneum cohesion and abnormal lamellar bilayer organization, and functional alterations, for example increased pH levels in the stratum corneum and decreased skin hydration (1, 3). The *FLG* mutations cause ichthyosis vulgaris, which is characterized by xerosis, scales, hyperkeratosis, keratosis pilaris, and palmar hyperlinearity (4). A strongly increased risk of atopic eczema in *FLG* mutation carriers has been established, emphasizing the crucial role of the skin barrier for the development of eczema (1). Although several studies

have investigated whether *FLG* mutations also increase the risk of hand eczema, the results have been conflicting (5–7). It seems plausible that an already impaired skin barrier might be more vulnerable to irritants and allergens, resulting in hand eczema. In line with this, a German case–control study showed that *FLG* mutations were associated with a subtype of chronic hand eczema characterized by combined allergic and irritant dermatitis (5), and a Danish general population study showed that *FLG* mutations increased the risk of hand eczema in subjects with atopic eczema and that mutations were associated with early onset and persistence of hand eczema into adulthood (2). Moreover, a decreased threshold level for the development of allergic and irritant contact dermatitis was shown in mice (3, 4), and increased penetration of chemicals across human and animal epidermis was observed. Whether *FLG* mutation carriers, because of their inherited skin barrier abnormality, tend to avoid occupational exposure to irritants and allergens has not yet been determined, but is likely.

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Fig. 1. *FLG* Mutation in a Healthy Child: A 9-year old girl and her mother are both heterozygous carriers of the R501X *FLG* mutation. Morphological findings: Hyperkeratosis and xerosis on the dorsal aspects of the fingers and palmar hyperlinearity were found. The hyperkeratosis was worse during periods of dry and cold weather.

Medical history: The 9-year-old female patient was referred because of hyperkeratosis on the palms. There was no past history of atopic dermatitis or other eczemas.

Message: The picture shows that the *FLG* mutation affects the skin on the dorsal aspect of the hands and fingers, as well as the palmar aspects. Palmar hyperkeratosis was judged to be post-traumatic, and was not caused by hand eczema.



Fig. 2. *FLG* Mutation in a Healthy Adult: A 36-year-old male is a heterozygous carrier of the R501X *FLG* mutation.

Morphological findings: Hyperkeratosis and xerosis on the dorsal aspects of the fingers and palmar hyperlinearity were found. The hyperkeratosis was worse during periods of dry and cold weather.

Medical history: There was no past history of atopic eczema or other eczema. There were complaints of annoying friction when soft fabrics such as silk were touched or handled. During times of low humidity, painful skin fissures (chapping) appeared on the fingertips, and the skin on the dorsal aspects of the fingers became hyperkeratotic. This individual was not a patient.

Message: The picture illustrates that the *FLG* mutations affect skin hydration on the backs of the hands and fingers, and not only the skin on the palms. Hence, the hyperkeratosis caused by the mutations leads to folded skin, expressed as hyperlinearity in the palms, and as accentuated skin folding on the knuckles and dorsal aspects.

For almost 2 years, *FLG* mutation analyses for the two most common loss-of-function mutations, R501X and 2282del4, have constituted a part of the routine analysis of patients referred to our hand eczema clinic (8). From our early clinical experience, we have published a case series of 8 patients with generalized atopic eczema and hand eczema who were *FLG* mutation carriers (6). They all suffered from a distinct and similar type of hand eczema, in which the skin on the dorsal aspects of the hands and fingers was affected by hyperkeratosis and

dermatitis, and palmar involvement was sparse or not present at all. This observation is in line with studies on atopic hand eczema conducted prior to the *FLG* genotyping era, where subgroups of patients with atopic eczema had a distinct and similar subtype of hand eczema (9, 10). We suspect that the group of patients with dorsal hand eczema in these studies mainly consisted of *FLG* mutation carriers, although a small proportion of these individuals could have had severe inflammation resulting in deficient filaggrin protein expression (3).



Fig. 3. *FLG* Mutation Carrier through Disease 1—Typical Presentation of Hand Eczema: A 30-year-old female is a heterozygous carrier of the 2282del4 *FLG* mutation.

Morphological findings: Hyperkeratosis on the dorsal aspects of the fingers, erythema indicating mild inflammation, skin fissures on the fingertips and Beau's lines were found. There was almost no palmar eczema.

Medical history: The patient had a past history of atopic eczema. She recently began working as a hairdresser, and rapidly developed hand eczema. She was referred and treated in our hand eczema clinic. Patch testing showed no positive reactions. Because of chronic hand eczema, she was re-trained as a medical secretary.

Message: *FLG* mutations may result in chronic hand eczema, typically located on the dorsal aspects of the fingers and hands, and with only sparse involvement of palmar aspects. Skin fissures (chapping) are a frequently accompanying complaint. Causative exposures include mainly dry and cold weather, typically in combination with exposure to water and/or irritants. Inflammation is often mild to moderate.



Fig. 4. *FLG* Mutation Carrier through Disease 2—a Typical Presentation of Hand Eczema: A 64-year-old female is a compound heterozygous carrier of the R501X and 2282del4 *FLG* mutations (compound heterozygous carrier status is equal to homozygous carrier status presenting with complete absence of *FLG* expression).

Morphological findings: A universal distribution of eczema on the hands, scaling, fissures and postinflammatory hypopigmentation were found. Palmar hyperlinearity was present.

Medical history: The patient has suffered from severe atopic eczema since early childhood. When we saw the patient, she also had severe dermatitis on the hands. She was treated with emollients and topical corticosteroids. She was not able to tolerate azathioprine or ultraviolet light therapy. Patch testing showed positive reactions to fragrance mixes I and II, which were considered to be of current clinical relevance, as well as a positive reaction to nickel sulfate, which was considered to be of past clinical relevance. Prick testing showed multiple positive reactions to mould, house dust mites, grass, mugwort, horse dander, dog dander, wheat, egg white, cats, cow's milk, and rye flour.

Message: This patient suffered from very severe hand eczema, resulting in gross inflammation. No clinical suspicion would have raised regarding the barrier abnormality being caused by *FLG* mutations if it had not been for palmar hyperlinearity, concomitant severe atopic eczema, and the presentation of very severe inflammation and course of disease.

Hand eczema can, to a certain degree, be regarded as a rather homogeneous disease dominated by eczema in different temporal stages (i.e. acute dermatitis defined by erythema and vesicles, and chronic dermatitis defined by dry and fissured skin with scales) but with multiple trigger factors, including irritants, proteins, and allergens (11, 12).

Although it is sometimes possible to establish the causal mechanism of hand eczema on the basis of the clinical expression and medical history alone, we often find it difficult to do so, because there may be mixed exposure to irritants and allergens, as well as different genetic predispositions interacting with each other. In general, hand



Fig. 5. *FLG* Mutation Carrier through Disease 3—Multiple Exposures to Allergens and Irritants: (a) A 30-year-old female is a heterozygous carrier of the R501X *FLG* mutation.

Medical history: The patient had no history of atopic eczema; however, she had, since childhood, suffered from xerosis with dorsal hyperkeratosis and palmar hyperlinearity. She worked as a hairdresser, and developed hand eczema. Patch testing showed positive reactions to thiuram mix, mercapto mix, mercaptobenzothiazole, fragrance mix I and methylchoroisothiazolinone/methylisothiazolinone of past relevance, and weak positive reactions to ammonium persulfate, 2-nitro-*p*-phenylenediamine and chloroacetamide of current relevance. Morphological findings after intense occupational exposure: The right hand had sparse palmar involvement of dermatitis with some vesicles, whereas the palmar aspect of the left hand had much more severe dermatitis, with multiple vesicles, some scaling, and fissures. The same difference was observed on the dorsal aspects of the hands and fingers. The patient explained this asymmetry by the way in which she would typically hold and use the scissors with her right hand, and hold the wet and coloured hair with her left hand, resulting in asymmetrical irritant exposure and dermatitis.

(b) Morphological findings in the same patient as in Fig. 5a after topical therapy with corticosteroids: The dorsal aspects showed hyperkeratosis, erythema, and skin fissures on the fingertips (chapping). The palmar aspects showed vesicles and lichenification. The nails showed Beau's lines and had a shiny appearance.

Message: *FLG* mutation carriers may also develop severe inflammatory dermatitis when exposed to irritants and/or allergens in high concentrations. Hand eczema is characterized in its acute form by vesicles, but once the acute inflammation is controlled or in regress, the chronic hand eczema becomes more 'typical', with the dorsal effects as described in Fig. 2.

eczema caused by allergen exposure may be characterized by the presence of erythema and vesicles (12), whereas irritant hand eczema may be characterized by interdigital dermatitis, as well as dry and fissured skin. Additionally, a subgroup of patients with atopic eczema suffer from recurrent vesicular palmo-plantar eczema (13). Identification of 'filaggrin hand eczema' may therefore be of value to clinicians in their clinical analysis of patients, as this could help to further subcategorize hand eczema.

In this review, we present pictures (Figs. 1–5) of healthy and diseased hands from individuals with *FLG* mutations, in an attempt to demonstrate a distinct clinical entity of hand eczema. The series of pictures range from the hands of an individual with *FLG* mutations but no history of eczema, to the hands of individuals with typical and atypical 'filaggrin hand eczema', and finally the hands of an individual with *FLG* mutations and hand eczema caused by exposure to irritants and allergens.

Discussion

The hands of individuals with *FLG* mutations have a distinct phenotype (Cases 1–5). Because of hyperkeratosis, they display palmar hyperlinearity, as well as thickened and folded skin on the dorsal aspects of the fingers. Also, they have intermittent skin fissures (chapping) (14, 15), which typically develop during the winter, when skin hydration decreases because of a drop in the relative humidity. If the hands are affected by chronic eczema, it is mainly located on the dorsal aspects of the hands and fingers (and even the wrists), whereas the palms are less frequently affected. Eczema is characterized by erythema, hyperkeratosis, and skin fissures, rather than by vesicles. Exposure to irritants and allergens may result in the same acute expression of dermatitis as observed in non-mutation carriers, and may, to some degree, 'cover' the clinical features of 'filaggrin hand eczema'.

The dorsal location of hyperkeratosis and eczema is caused by the more intense cutaneous exposure to drying and irritant factors, such as water, ultraviolet light, wind, changes in temperature, and radiation from indoor heating. With an inherently abnormal skin barrier, individuals with *FLG* mutations who are exposed to environmental influences are likely to experience a chronic homeostatic response aimed at restoring barrier function. This initially results in epidermal thickening (hyperkeratosis), and ultimately in dermatitis, if internal and external stimuli are sustained. In support of this interpretation is a study showing that filaggrin-deficient flaky-tail mice bred in cages with contact with the environment experienced a higher level of dermatitis and skin inflammation than mice bred in cages with no environmental contact (16). Also, note that filaggrin molecules are hydrolysed in a humidity-sensitive fashion to carboxylic acids, referred to as 'natural moisturizing factor' (17), a process that begins as environmental humidity declines below 80%, and continues with a further decline in humidity. This control mechanism works to protect the skin from dehydration, as osmolites are being produced when needed. Many of our patients have spontaneously reported a sudden improvement, and the even disappearance, of hand eczema when escaping the cold Danish winter by travelling to places with a high humidity. They typically experience a rapid recurrence of hand eczema following their return to Denmark. In a similar way, the transfer of mice from a humid environment to a dry environment resulted in a delayed increase in proliferation that might also contribute to the barrier abnormality (16). Moreover, exposure to low humidity increased epidermal DNA synthesis and resulted in marked epidermal hyperplasia (18). This is a second mechanism, besides increased lipid synthesis, by which the epidermis repairs defects in barrier

function (19). Taken together, the above observations explain the hyperkeratosis noted on the dorsal aspects of the fingers and hands in *FLG* mutation carriers during the winter in temperate climates, even in individuals without dermatitis.

It is important to note that skin inflammation, probably independently of cause, may result in functional *FLG* deficiency (18). *FLG* mutations can therefore not be considered to be a specific sign of 'filaggrin hand eczema'. However, the *FLG* mutations, in contrast to most acquired inflammatory skin diseases of the hands, including atopic eczema, have an impact on the entire epidermis. Hyperkeratosis causes hyperlinearity in the palms, as well as accentuated skin folding on the knuckles and the interphalangeal joints. However, skin folding caused by chronic eczema, including atopic eczema, can be the result of a functional *FLG* deficit. At present, we are not able to provide the definite criteria for differentiation between acquired *FLG* deficiency caused by skin inflammation and inherited *FLG* deficiency caused by *FLG* mutations. One sign that indicates the difference, however, is the universal distribution of the changes on the hands in those with the *FLG* genotype (hyperlinearity in palms and skin folding dorsally), which stands in contrast to the more localized distribution in acquired *FLG* deficiency, where only dorsal thickening and folding may be present. A future goal would be to provide accurate specificity and sensitivity of these characteristics in clinical populations. A recent general population study showed that the positive and negative predictive values for palmar hyperlinearity in *FLG* mutation carriers were 71% and 90%, respectively (20).

We have demonstrated that the combination of hyperkeratosis on the dorsal aspects of the hands and fingers and palmar hyperlinearity should alert the clinician to a possible genetic barrier defect caused by *FLG* mutations. A recent study on 2 patients with congenital hemidysplasia with ichthyosiform erythroderma and limb defects (CHILD) syndrome showed that pathogenesis-based therapy for cutaneous manifestations of disorders of lipid metabolism may hold promise (19). The phenotype in CHILD syndrome reflects both cholesterol deficiency and accumulation of toxic sterol metabolites. Topical application of cholesterol and lovastatin (but not of cholesterol alone) normalized the skin within 6 months in both patients, and long-term follow-up showed good results. However, another study indicated that even short-term exposure to potent corticosteroids may exert profound negative effects on cutaneous structure and function (21), because: (i) the production and secretion of lamellar bodies were profoundly decreased in topical corticosteroid-treated mice, resulting in decreased

extracellular lamellar bilayers; and (ii) only 3 days of topical treatment in humans with clobetasol produced a deterioration in barrier homeostasis, characterized by delayed barrier recovery and abnormal stratum corneum integrity and stratum corneum cohesion. With our present knowledge, dermatologists should, when possible, limit the use of topical corticosteroid therapy in patients with *FLG*

mutations, as they already have an impaired skin barrier, and rather provide lipid-containing topical products that will restore the disorganized lipid bilayers embedding the corneocytes.

We invite others to further explore the association between *FLG* mutations and hand eczema, as this could provide major prognostic advances for our patients.

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