

Review Article

Classification of atopic hand eczema and the filaggrin mutations

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Hand eczema is a common disease with various risk factors of which atopic dermatitis is known to be one of the most important. Recently, two mutations in the gene coding for filaggrin, a protein important for the skin barrier, have repeatedly been shown to be associated with atopic dermatitis. Moreover, one study point towards an association between the filaggrin null alleles and the subgroup of patients having both hand eczema and atopic dermatitis. For the remainder of hand eczema patients, still unknown genetic risk factors exist. We propose that in future, classification of atopic hand eczema should distinguish between patients with and without the filaggrin null alleles and to further differentiate between associations with type I allergy, type IV allergy and exposure to irritants, respectively. Furthermore, we suggest future studies of atopic hand eczema to analyse for the filaggrin mutations. We believe this will increase the possibility of subgrouping this otherwise heterogeneous disease and thereby enable a better phenotype–genotype characterization of hand eczema. This could improve the preventive initiatives, secure better information of patients about the prognosis for their disease, and possibly enable targeted treatment.

Key words: atopic dermatitis; classification; contact allergy; filaggrin mutation; hand eczema.
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Filaggrin is a protein essential for aggregating keratin filaments, which lead to keratinocyte compaction and formation of the stratum corneum. Profilaggrin, the precursor of filaggrin, is located in the keratohyalin granules in the granular layer of the epidermis. The formation of the cornified cell envelope is crucial for the skin barrier function as it prevents epidermal water loss and penetration of infectious agents, toxic chemicals, and allergens (1).

Two polymorphisms in the filaggrin gene, R501X and 2282del4, both result in a loss of function of the filaggrin protein. Homozygotes or compound heterozygotes for the genetic variants have a total loss of filaggrin products and therefore a dry, scaly skin (ichthyosis vulgaris), whereas heterozygotes present with a milder form or without symptoms at all (2). The two loss-of-function genetic variants in the filaggrin gene were recently identified as major predisposing factors for atopic eczema (3), an association confirmed by several studies (4–6). No genetic markers for hand eczema have yet been identified and only a few studies published so far have investigated a possible rela-

tionship between the filaggrin loss-of-function mutations and the development of hand eczema and/or contact allergy (7–9).

Hand eczema is a common disease often known to have a chronic relapsing course. Risk factors include atopic dermatitis and exposure to allergens and irritants (10, 11). A twin study has shown that genetic factors influence the risk of developing hand eczema (12).

There is no universally accepted classification of hand eczema. Traditionally classification is based on aetiological factors (irritant, allergic, and atopic disease), the localization of the eczema (dorsum, palmar, fingers, and wrist), or morphological features (vesicular, hyperkeratotic, lichenification, and recurrent vesicular hand dermatitis). It is generally believed that this classification system is insufficient, which makes comparison of studies and therapeutic strategies difficult, and hampers the possibilities for better understanding and treating the disease (13, 14). It seems likely that hand eczema is a common phenotype expressing a variety of underlying diseases.

We propose a revised classification for the subgroup of patients having atopic hand eczema based on concurrent atopic dermatitis and filaggrin loss-of-function mutations.

Risk Factors for Hand Eczema

During the last three decades, research has, as mentioned above, shown atopic dermatitis, contact allergy, and irritants, e.g. wet work, to be the most important risk factors for the development of hand eczema.

Atopic dermatitis

Most studies agree that the frequency of atopic dermatitis is increased in patients with hand eczema (10, 15–18). The explanation is an atopic skin diathesis, an endogenous risk factor not well understood. The risk of developing hand eczema can be predicted by means of a scoring system of atopic dermatitis (19, 20).

Contact allergy

The development of contact allergy requires a combination of genetic susceptibility and environmental exposure (21). Contact allergy is an independent risk factor for developing hand eczema as the hands are the prime site for exposure to allergens, occupational as well as domestic (17, 18, 22).

Wet work

Several studies have verified wet work as a major external risk factor for the development of hand eczema, probably because water decreases the protectiveness of the skin and occlusion increases its irritant effect (23, 24). Bryld et al. (17) did not find wet work to be an independent risk factor in their twin study. Instead, the authors suggest that wet work is a risk factor only for a subgroup of the population, in accordance with the general observation that only some people develop hand eczema although many more are heavily exposed.

Genetic Studies

Based on a twin study, Bryld et al. (17) found that genetics influence the risk of acquiring hand eczema. Furthermore, they concluded that an unknown genetic risk factor independent of atopic dermatitis and contact allergy is important for developing hand eczema. In a follow-up study on the same twin population, Lerbaek et al. (25) found that genetic risk factors explain 41% of the variance in liability to develop hand eczema and

monozygotic twins to have a doubled risk for developing hand eczema if their co-twin have had hand eczema compared with a dizygotic twin individual having a co-twin with hand eczema, and further document this risk factor to be independent of atopic dermatitis.

Filaggrin Mutations and Atopic Dermatitis

In 2006, Palmer et al. (3) documented for the first time the two filaggrin mutations, R501X and 2282del4, to be associated with the development of atopic dermatitis. Several studies have confirmed this finding, and the mutations are currently the most strongly associated genetic factors known to confer susceptibility to atopic dermatitis in European populations (6, 26). Odds ratios vary between 3.73 and 7.1 (4, 27). No negative or equivocal studies have been reported.

The two mutations, R501X and 2282del4, are carried by 16.7–56 % of all individuals with atopic dermatitis (6) and are inherited in a semidominant mode (2). The high frequencies of filaggrin mutations are seen in studies investigating adults with both persisting and early onset of atopic dermatitis. The mutations are associated with asthma and allergy as well as early onset of atopic dermatitis and persistence into adulthood as well as certain phenotypic characteristics, e.g. hyperlinearity of the hands (3, 4, 28). Other mutations in or nearby the filaggrin gene have been documented. In one population, a third mutation, R2447X, was as strongly and independently associated with atopic dermatitis as the mutations R501X and 2282del4 (29). Besides R2447X, two other mutations, S3247X and 3702delG as well as other lesser frequent mutations, have recently been shown to be associated with atopic dermatitis. These mutations are qualitatively different from the previously reported mutations with some residual function, as demonstrated by a significantly lower penetrance of eczema. Generally, these new mutations reported are neither as prevalent nor as strongly associated with atopic dermatitis (29, 30).

Filaggrin Mutations and Hand Eczema

Lerbaek et al. investigated a possible association between the filaggrin mutations and atopic hand eczema (7). They found a borderline statistical significance pointing towards an association between the subgroup of patients with hand eczema, atopic dermatitis, and the filaggrin mutations. All individuals having hand eczema and atopic dermatitis also had the filaggrin mutations, but the group only included 26 individuals and there was no comparable control group with atopic dermatitis,

but without hand eczema. No association between the filaggrin mutations and hand eczema in general or contact allergy was found, but this might be because of lack of statistical power and a possible association could not be excluded. A recent study by de Jongh et al. has confirmed these findings but is hampered by the same problem of statistical power (9).

A single study of the filaggrin mutations and nickel allergy has been published. Novak et al. (8) confirm earlier findings of an association between the filaggrin mutations and atopic dermatitis. They observed an association between contact sensitization to nickel and contact sensitization to nickel combined with intolerance to fashion jewellery. The positive association between the filaggrin null alleles and contact sensitization to nickel could be explained in different ways. One possibility is that because the mutations induce a skin barrier dysfunction, nickel could act as an irritant instead of an allergen and thus result in false-positive patch results, which in particular would apply to the atopic individuals. But, in the population investigated by Novak et al. (8), nickel allergy occurs with the same frequency in both atopic and non-atopic individuals. Another explanation could be nickel accumulation in the skin of filaggrin mutation-positive individuals because of increased ability to bind to the filaggrin-mutated epidermis.

Further studies, including twin studies and population studies, are needed to investigate whether contact sensitization to nickel itself is associated with the filaggrin mutations or the observed association is biased because of the above-mentioned explanations.

Discussion

So far, only two studies have been published concerning filaggrin mutations and atopic hand eczema. The tendency towards an association between atopic hand eczema and the allele variants is plausible because atopic dermatitis is the most frequent risk factor for developing hand eczema, and previous work has suggested that atopic dermatitis is the core phenotype associated with the filaggrin mutations. Further studies with more statistical power are needed to better investigate this topic.

The gene for filaggrin is probably not the only responsible carrier of barrier-deficiency. According to Bryld et al. (12, 17) and Lerbaek et al. (7, 18, 25), genetic risk factors independent of atopic dermatitis and contact allergy exists. Twin studies document that genes account for up to 82% of the individual susceptibility to develop atopic

dermatitis (31–33) but only 16.7–56% of individuals with atopic dermatitis carry the filaggrin mutations. Obviously other genes must be of relevance, which might be genes coding for other important substances in the epidermal skin barrier, both proteins and lipids. Further studies are needed, including extended genetic studies.

The possible association between the atopic hand eczema and the filaggrin mutations is interesting as it raises the possibility of subgrouping this otherwise heterogenic disease and thereby enables a better phenotype–genotype characterization of atopic hand eczema. This could improve the preventive initiatives, secure better information of patients about the prognosis for their disease, and possibly enable targeted treatment. Also, as it seems that the filaggrin mutations are associated with both a prolonged course of atopic dermatitis and hand eczema, being able to screen for the mutations could help to better inform the patients about the prognosis for their disease including carrier guidance.

In a future classification of hand eczema, we suggest subgrouping patients having atopic hand eczema. We propose a distinction between patients with and without the filaggrin loss-of-function polymorphisms and a further differentiation between associations with type I allergy, type IV allergy and exposure to irritants, respectively. Furthermore, we suggest future studies of hand eczema to analyse for inherited barrier deficiencies such as the filaggrin mutations.

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