Filaggrin Gene Mutations: A Clinician's Perspective

29

David Bregnbak, Claus O.C. Zachariae, and Torkil Menné

Contents

D. Bregnbak, MD (✉)
C.O.C. Zachariae, MD, DMSci
Department of Dermato-Allergology,
Copenhagen University, Gentofte Hospital,
Niels Andersens Vej 65, Hellerup
DK-2900, Denmark
e-mail: david.kaspar.bregnbak@regionh.dk;
claus.zachariae@regionh.dk

T. Menné, MD
Department of Dermatology KA-1502,
Gentofte Hospital, University of Copenhagen,
Niels Andersensvej 65, Hellerup 2900 Denmark
e-mail: torkil.menne@regionh.dk

29.1 Introduction

Filaggrin gene (*FLG*) mutations have a significant association with a number of common diseases such as atopic dermatitis (AD), asthma, and hand eczema [1, 2]. The primary effect of the *FLG* mutations is through the effects on the skin barrier leading to xerosis [3].

29.2 Atopic Dermatitis

Historically, AD was first described as an entity in the early 1930s. Nexmand, in his thesis from 1948 [4], noted an increase in the number of AD patients hospitalized in the Copenhagen Dermatology Departments during 1930–1946 (Fig. 29.1).

Later, population-based studies at the end of the twentieth century illustrated a significant increase in the prevalence of AD [5, 6].

Recently, the question was raised whether AD was associated with *FLG* mutations and as a specific variant of the disease. We analyzed this question in a retrospective cohort and found that the frequency of AD increased slightly more in those with the *FLG* mutations, arguing in favor of a disease modified by gene-environment interaction [7].

J.P. Thyssen, H. Maibach (eds.), *Filaggrin*,
DOI 10.1007/978-3-642-54379-1_29,

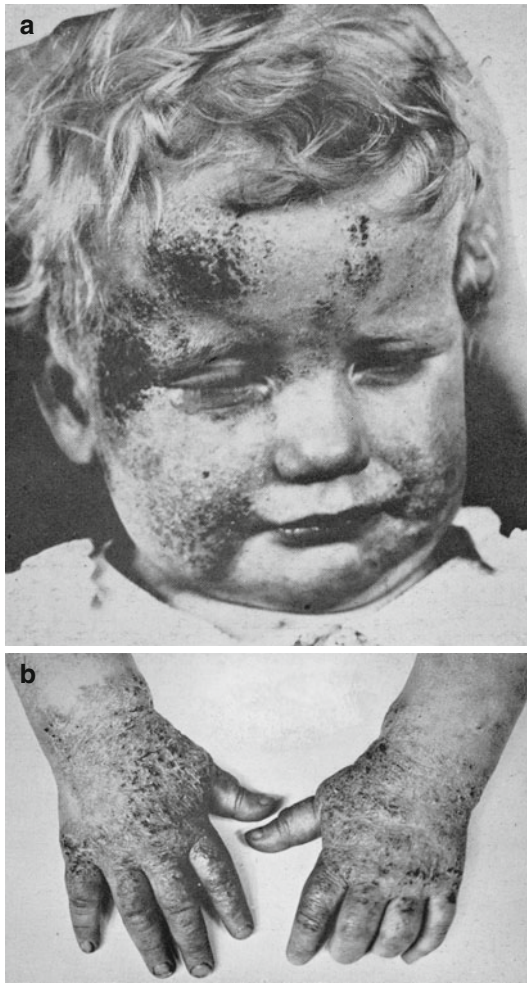

Fig. 29.1 (**a**, **b**) Historical pictures from Nexmand's thesis of severe AD in a child 2 years of age

29.3 The Primary Clinical Effects of the Filaggrin Gene Mutation, Xerosis, and Early Onset of Atopic Dermatitis

In a prospective study on children born by mothers with asthma, we found that the *FLG* mutations were associated with a specific endotype of AD with a dominance of dermatitis on the cheeks and the dorsal part of the hands. Interestingly, this is the part of the skin that is mainly in prolonged contact with the climate (leading to aggravation of xerosis) and endures friction from clothes and bed linen [8]. These early signs of dermatitis may be the first step to a lifelong disease with AD, asthma, rhinitis, food allergy, and irritant allergic contact dermatitis (Fig. 29.2).

AD is today one of the most frequent childhood diseases, often continuing into adult life. AD, particularly combined with hand eczema in childhood, is also the most significant risk factor for hand eczema in adults [9]. Females are at particular risk due to both domestic and occupational irritant exposures, leading to onset of hand eczema in the early twenties that often persists as a chronic disease [10, 11]. Adult-onset hand eczema may provoke the first outbreak of AD in patients without AD in childhood [12, 13].

Even if AD is common and in some cases difficult to treat, the historical perspective tells a different story. The individuals with the *FLG* mutations represent a special subgroup that often requires more intensive treatment and closer follow-ups, particularly the homozygotic, which constitutes 0.3 % of the population [14], with the tendency to early-onset AD and more severe and prolonged problems.

AD in patients with *FLG* mutations still represents a major challenge to clinicians who treat patients with chronic widespread dermatitis and severe fissures, particularly on the hands and feet (Fig. 29.3).

29.4 Allergic Hand Eczema

Contact allergy is more common in individuals with both dermatitis and the *FLG* mutations compared to individuals without the mutation [15]. This has been known for nickel allergy for some years but seems to be a general trend [16, 17]. Probably because of the high histidine content in filaggrin and its degradation products, it is functioning as a specific skin barrier for nickel and probably other divalent metal ions [18, 19]. The *FLG* mutations not only increase the risk of contact allergy but also seem to modify the cause of the clinical disease. We recently reported a young female who developed severe vesicular bullous acute dermatitis on the hands, imitating rubber glove dermatitis. She had been contact sensitized to sorbitan sesquioleate and had applied a steroid ointment containing this emulsifier and had worn a pair of rubber gloves for housekeeping, at the same time. The point is that a weak contact allergen can simulate a reaction to a more potent allergen in individuals with *FLG* mutations [20].

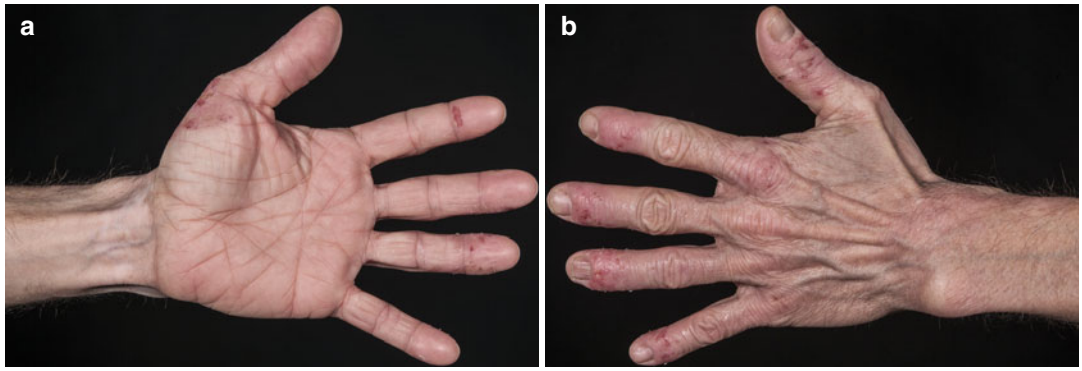

Fig. 29.2 (**a**, **b**) A 51-year-old male patient who was a homozygous *FLG* mutation carrier with a lifelong history of AD. As long as he remembered, he had prominent skin folds on the palmar and dorsal parts of the hands and fingers independent of his AD. This symptom is a sign seen in many individuals with AD with the *FLG* mutation starting early in life and probably a sign of subclinical inflammation due to a defect skin barrier. The patients often tell us that they have been teased during childhood for having "elephant fingers"

Figure 29.4 depicts a patient with an *FLG* mutation and contact allergy to thiurams who has been exposed to rubber gloves. It is our clinical impression that the patients with allergic contact dermatitis and the *FLG* mutation more frequently have problems with long-lasting dermatitis and fissures.

Figure 29.5 depicts a 66-year-old female who is heterozygotic for *FLG* mutation; she has had xerotic skin and slight ichthyosis on her lower legs all her life, but she never had AD or hand eczema in childhood. At 40 years of age, she developed acute vesicular hand eczema due to contact allergy to thiuram and exposure to rubber gloves. The vesicular component of the hand eczema disappeared gradually, and then the dermatitis transformed into lichenified, slightly hyperkeratotic hand eczema located on both the dorsal and the volar part of the hands. Her ichthyosis on the lower legs at the same time changed into a lichenified chronic dermatitis. Most dermatologists, including us, would until a few years ago have called such a case "adult-onset AD," but these types of cases [12] are probably not uncommon in individuals with an inborn defect of the skin barrier who, because of environmental skin exposures to allergens and irritants, develop chronic skin inflammation that leads to degeneration of an already weak skin barrier [21].

The progress in the understanding of disease mechanisms will improve treatment and classification of such cases.

29.5 Protein Contact Dermatitis

Protein contact dermatitis is an inflammatory skin disease that can be a result of the protein exposure acting either as an allergen or as an irritant. An increased risk of type I sensitization to food items has been described in individuals with the *FLG* mutations, specifically for peanuts [22] and more generally in a large population-based study [23].

We have recently described a heterozygous carrier of an *FLG* mutation who most likely developed primary occupational type I skin allergy to salmon [24]. She later developed asthma and anaphylaxis when she was working in a room where salmon were handled. Protein contact dermatitis is a difficult condition to classify. In the future, further subclassifications by genomic studies might be possible in those cases that have a skin barrier defect and thereby are exposed to the protein through the skin.

29.6 Irritant Contact Dermatitis

Irritant contact dermatitis (ICD) depends on the interplay between the quality of the skin barrier and the magnitude of the irritant exposure. Irritant exposure qualifying for *occupational* ICD is today defined as 2 h of wet work or 2 h of glove use daily [25]. The definition probably only holds true for a fraction of individuals. In individuals with a defect in the skin barrier, the trauma

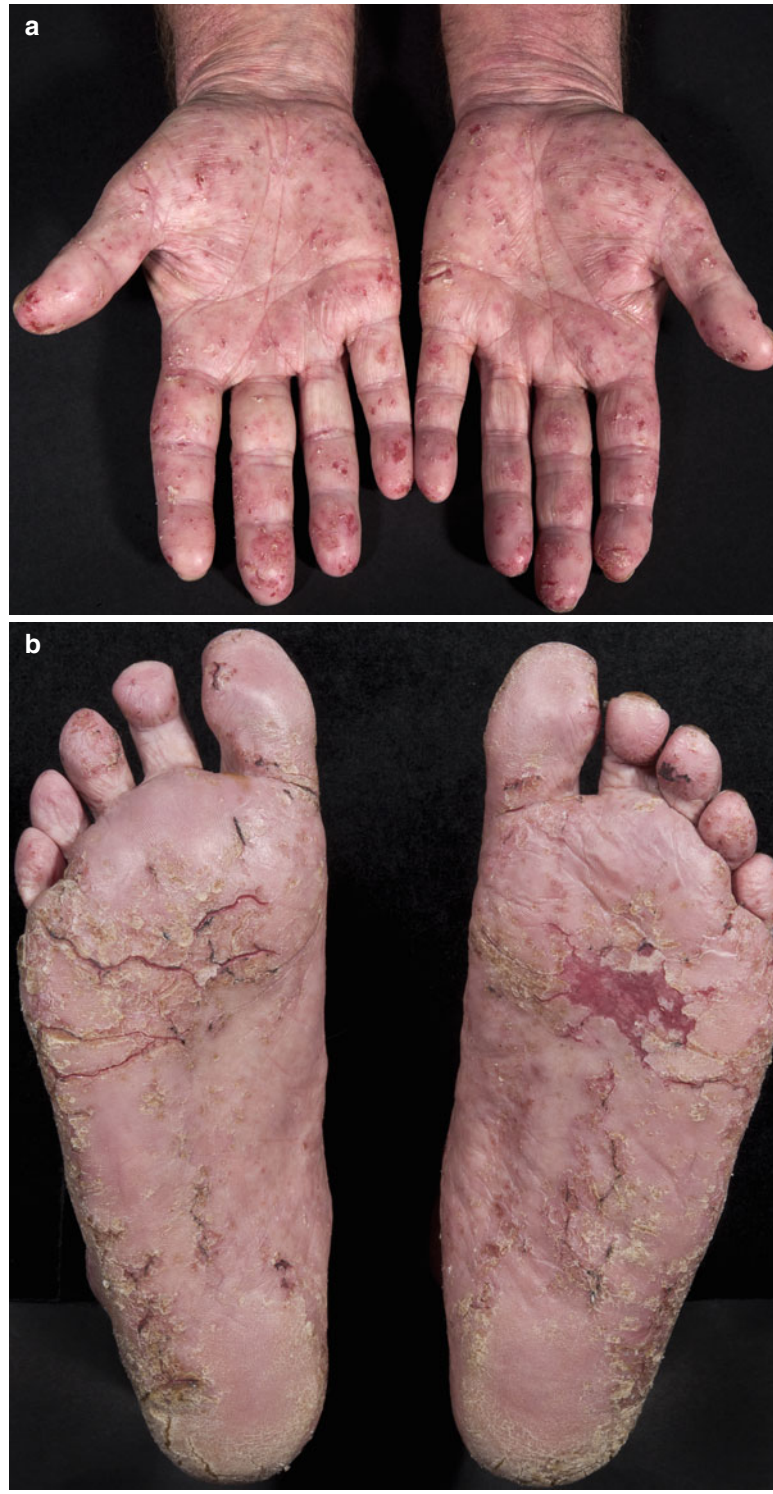

Fig. 29.3 (**a**, **b**) Severe fissured hands and feet on a 45-year-old male patient with generalized AD since early childhood and an *FLG* mutation

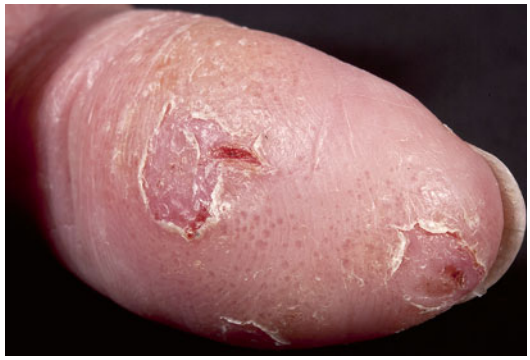

Fig. 29.4 A 48-year-old female's thumb of the right hand, with allergic contact dermatitis to thiurams from rubber gloves. She was heterozygous to a common *FLG* mutation. Note the vesicular inflammation with secondary fissures

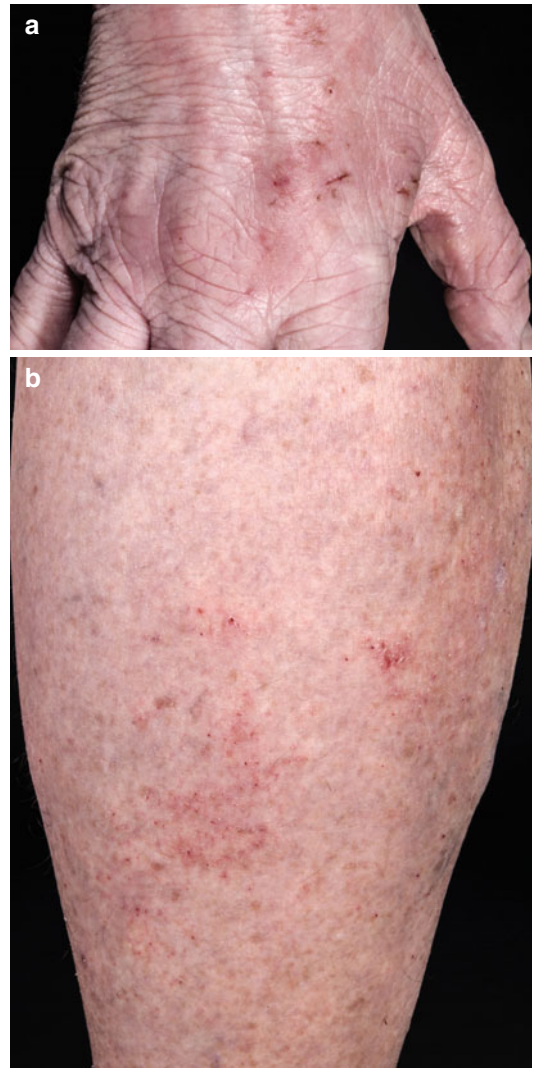

Fig. 29.5 (**a**, **b**) A 66-year-old female patient heterozygous for an *FLG* mutation. She has never had AD. She developed lasting skin changes similar to AD after an acute episode of allergic contact dermatitis due to thiurams. Such a patient should not be classified as having AD but as sequela from allergic contact dermatitis in a patient with the *FLG* mutation. This may have significant medicolegal consequences

required to make an irritant skin exposure is much less, and in another group of individuals, much larger. Individuals with *FLG* mutations have a risk of developing dorsal hand eczema within the first few months of life simply from exposure to air and friction from clothes [8]. We have recently shown that individuals with the *FLG* mutations, AD, and hand eczema in childhood to a large extent avoid wet work and occupational irritant exposure in adulthood [26]. These types of jobs account for 40 % of all available jobs. This observation is in agreement with the fact that individuals with AD are underrepresented among hairdresser trainees/apprentices [27]. Early-onset occupational ICD has been a repeated observation, particularly in young females with childhood AD and with or without childhood hand eczema [10, 11].

Notwithstanding this observation, it is clear from the epidemiological studies that a large group of individuals with the *FLG* mutations and only dry skin in childhood and teenage years, but without AD and hand eczema, will enter into wet work jobs. In a recent study based on selected occupational ICD, it was clearly shown that *FLG* mutations were individual risk factors for this disease independent of AD and childhood eczema [28]. In this context, it needs to be remembered that in large population studies the *FLG* mutation only acts as a risk factor for hand eczema in conjunction with AD and individuals with only the *FLG* mutation and no AD have a risk for hand

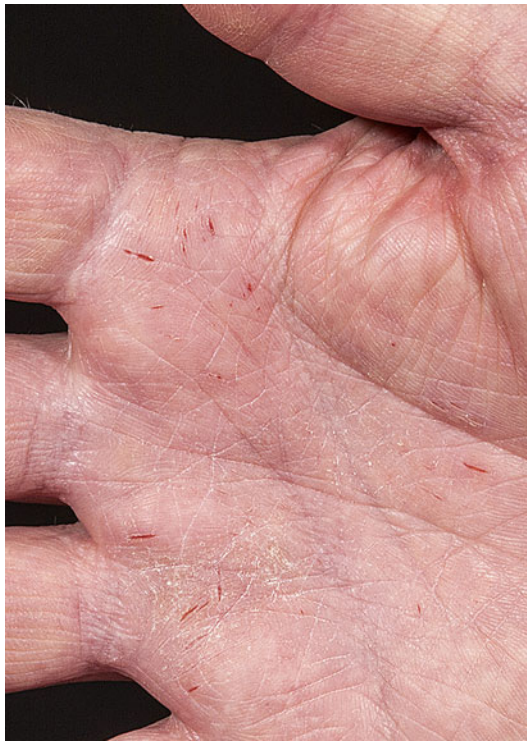

Fig. 29.6 A moderate case of a steatotic ICD based on professional oil contact in a patient with the *FLG* mutation. The case is notable because of the multiple knifelike cut fissures following the fine lines in the palms. The patients have many expressions for the vulnerability of their hands. One patient expressed to us "when the winter comes with its dry air, my hands sing like crystal and then they crack"

eczema in the same magnitude as the population in general [29]. So this is an area still open to further research to understand and identify the group at particular risk. First of all, the *FLG* mutation gives more severe and persistent disease, and painful skin fissures are a typical symptom [29, 30] (Fig. 29.6).

Conclusion

The discovery of the association between xerosis, AD, and the *FLG* mutations [1, 3] has been an eye opener for the clinical dermatologists who work with eczema disease. In our clinic, we have used this knowledge for the last 5 years. Even though information about whether a patient has a mutation may not result in immediate help for the patient, it is a major step in their understanding of the disease and of their whole family history.

It is our impression that this information and understanding lead to more focus on the rationale for using emollients and anti-inflammatory topical drugs. It also leads to less speculation on all other reasons for the background of their illness. The understanding of the *FLG* mutation for the skin barrier has opened up a completely new area for understanding the eczema mechanism and prognosis and, further, for development of specific topical and systemic treatments.

References

1. McLean WH, Irvine AD. Heritable filaggrin disorders: the paradigm of atopic dermatitis. J Invest Dermatol. 2012;132(E1):E20–1.
2. Palmer CN, Irvine AD, Terron-Kwiatkowski A, Zhao Y, Liao H, Lee SP, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. Nat Genet. 2006;38(4):441–6.
3. Thyssen JP, Johansen JD, Zachariae C, Menne T, Linneberg A. Xerosis is associated with atopic dermatitis, hand eczema and contact sensitization independent of filaggrin gene mutations. Acta Derm Venereol. 2013;93(4):406–10.
4. Nexmand P-H. Clinical studies of Besnier's prurigo. Thesis, Faculty of Health and Medical Science. Copenhagen: Roskilde and Bagger Publishers; 1948.
5. Asher MI, Montefort S, Bjorksten B, Lai CK, Strachan DP, Weiland SK, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. Lancet. 2006;368(9537):733–43.
6. Taylor B, Wadsworth J, Wadsworth M, Peckham C. Changes in the reported prevalence of childhood eczema since the 1939-45 war. Lancet. 1984;2(8414):1255–7.
7. Thyssen JP, Johansen JD, Linneberg A, Menne T, Engkilde K. The association between contact sensitization and atopic disease by linkage of a clinical database and a nationwide patient registry. Allergy. 2012;67(9):1157–64.
8. Carson CG, Rasmussen MA, Thyssen JP, Menne T, Bisgaard H. Clinical presentation of atopic dermatitis by filaggrin gene mutation status during the first 7 years of life in a prospective cohort study. PLoS One. 2012;7(11):e48678.
9. Rystedt I. Factors influencing the occurrence of hand eczema in adults with a history of atopic dermatitis in childhood. Contact Dermatitis. 1985;12(4):185–91.

10. Dickel H, Bruckner TM, Schmidt A, Diepgen TL. Impact of atopic skin diathesis on occupational skin disease incidence in a working population. J Invest Dermatol. 2003;121(1):37–40.
11. Schwensen JF, Friis UF, Menne T, Johansen JD. One thousand cases of severe occupational contact dermatitis. Contact Dermatitis. 2013;68(5):259–68.
12. McFadden JP, White JM, Basketter DA, Kimber I. Does hapten exposure predispose to atopic disease? The hapten-atopy hypothesis. Trends Immunol. 2009;30(2):67–74.
13. Puangpet P, Lai-Cheong J, McFadden JP. Chemical atopy. Contact Dermatitis. 2013;68(4):208–13.
14. Thyssen JP, Carlsen BC, Bisgaard H, Giwercman C, Johansen JD, Linneberg A, et al. Individuals who are homozygous for the 2282del4 and R501X filaggrin null mutations do not always develop dermatitis and complete long-term remission is possible. J Eur Acad Dermatol Venereol. 2012;26(3):386–9.
15. Thyssen JP, Linneberg A, Ross-Hansen K, Carlsen BC, Meldgaard M, Szecsi PB, et al. Filaggrin mutations are strongly associated with contact sensitization in individuals with dermatitis. Contact Dermatitis. 2013;68(5):273–6.
16. Novak N, Baurecht H, Schafer T, Rodriguez E, Wagenpfeil S, Klopp N, et al. Loss-of-function mutations in the filaggrin gene and allergic contact sensitization to nickel. J Invest Dermatol. 2008;128(6):1430–5.
17. Weidinger S, Illig T, Baurecht H, Irvine AD, Rodriguez E, Diaz-Lacava A, et al. Loss-of-function variations within the filaggrin gene predispose for atopic dermatitis with allergic sensitizations. J Allergy Clin Immunol. 2006;118(1):214–9.
18. Ross-Hansen K, Menne T, Johansen JD, Carlsen BC, Linneberg A, Nielsen NH, et al. Nickel reactivity and filaggrin null mutations–evaluation of the filaggrin bypass theory in a general population. Contact Dermatitis. 2011;64(1):24–31.
19. Ross-Hansen K, Østergaard O, Tanassi JT, Thyssen JP, Johansen JD, Menne T, et al. Filaggrin is a predominant member of the nickel binding proteome of human epidermis. J Invest Dermatol. 2013. doi:10.1038/jid.2013.445.
20. Hald M, Menne T, Johansen JD, Zachariae C. Allergic contact dermatitis to sorbitan sesquioleate imitating severe glove dermatitis in a patient with filaggrin mutation. Contact Dermatitis. 2013;69(5):313–5.
21. Irvine AD, McLean WH, Leung DY. Filaggrin mutations associated with skin and allergic diseases. N Engl J Med. 2011;365(14):1315–27.
22. Brown SJ, Asai Y, Cordell HJ, Campbell LE, Zhao Y, Liao H, et al. Loss-of-function variants in the filaggrin gene are a significant risk factor for peanut allergy. J Allergy Clin Immunol. 2011;127(3):661–7.
23. Linneberg A, Fenger RV, Husemoen L, Carlsen BC, Johansen JD, Menne T, et al. Association between loss-of-function mutations in the filaggrin gene and self-reported food allergy and alcohol sensitivity. Int Arch Allergy Immunol. 2013;161(3):234–42.
24. Kaae J, Menne T, Thyssen JP. Severe occupational protein contact dermatitis caused by fish in 2 patients with filaggrin mutations. Contact Dermatitis. 2013; 68(5):319–20.
25. Uter W, Pfahlberg A, Gefeller O, Schwanitz HJ. Hand dermatitis in a prospectively-followed cohort of hairdressing apprentices: final results of the POSH study. Prevention of occupational skin disease in hairdressers. Contact Dermatitis. 1999;41(5):280–6.
26. Bandier J, Ross-Hansen K, Carlsen BC, Menne T, Linneberg A, Stender S, et al. Carriers of filaggrin gene (FLG) mutations avoid professional exposure to irritants in adulthood. Contact Dermatitis. 2013;69(6):355–62.
27. Bregnhoj A, Sosted H, Menne T, Johansen JD. Validation of self-reporting of hand eczema among Danish hairdressing apprentices. Contact Dermatitis. 2011;65(3):146–50.
28. Landeck L, Visser M, Skudlik C, Brans R, Kezic S, John SM. Clinical course of occupational ICD of the hands in relation to filaggrin genotype status and atopy. Br J Dermatol. 2012;167(6):1302–9.
29. Thyssen JP, Carlsen BC, Menne T, Linneberg A, Nielsen NH, Meldgaard M, et al. Filaggrin null mutations increase the risk and persistence of hand eczema in subjects with atopic dermatitis: results from a general population study. Br J Dermatol. 2010;163(1):115–20.
30. Thyssen JP, Ross-Hansen K, Johansen JD, Zachariae C, Carlsen BC, Linneberg A, et al. Filaggrin loss-of-function mutation R501X and 2282del4 carrier status is associated with fissured skin on the hands: results from a cross-sectional population study. Br J Dermatol. 2012;166(1):46–53.