

Clinical course of occupational irritant contact dermatitis of the hands in relation to filaggrin genotype status and atopy

L. Landeck,¹ M. Visser,² C. Skudlik,¹ R. Brans,¹ S. Kezic² and S.M. John¹

¹Department of Dermatology, Environmental Medicine and Health Theory, University of Osnabrück, Osnabrück, Germany

²Coronel Institute of Occupational Health, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands

Summary

Correspondence

Lilla Landeck.

E-mail: llandeck@uos.de

Accepted for publication

24 August 2012

Funding sources

None.

Conflicts of interest

None to declare.

S.K. and S.M.J. contributed equally to this manuscript.

DOI 10.1111/bjd.12035

Background Filaggrin loss-of-function mutations and atopy may alter the clinical course of irritant contact dermatitis (ICD).

Objective To investigate the clinical course of patients with occupational ICD according to loss-of-function mutations in the filaggrin gene (FLG) and atopy.

Methods In a prospective cohort study, the clinical course, use of topical corticosteroids, sick leave, recovery rate and job continuation were investigated in 459 inpatients treated for occupational ICD of the hands. Patients were genotyped for four FLG mutations, examined for atopy and followed for up to 3 years after discharge.

Results Our study included 327 (71.2%) atopic individuals and 132 nonatopic individuals. Overall, 68 patients showed a mutation in the FLG alleles R501X, R2447X, S3247X and 2282del4 (60 atopic and eight nonatopic). Nonatopic patients with ICD responded well to therapeutic approaches, while atopy status made subjects more resistant to therapy, resulting in lower rates of recovery and job continuation and higher use of topical corticosteroids. Carriage of FLG loss-of-function mutations in combination with atopy worsened the course. The risk of abandoning one's profession in this group was significantly increased when compared with 'pure' ICD (odds ratio 3.1) after 3 years.

Conclusions Patients with atopy are a special risk population for ICD. In the presence of atopy, FLG mutations seem to be a modifier of the severity of the clinical course in ICD. Early-stage identification of this subgroup may result in additional emphasis to these patients regarding the importance of adherence to specific therapeutic interventions.

Irritant contact dermatitis (ICD) occurs with repetitive skin exposure to exogenous substances, such as acids, alkalis, and soaps, leading to a stepwise progression of skin barrier damage resulting in an eczematous skin reaction. Because the hands are the body site most commonly exposed to irritants in occupational settings, they are most frequently affected by occupational ICD.

Besides exogenous factors, genetic features contribute to the complex interplay leading to the development of ICD. For a long time it has been recognized that with similar exposures, some individuals are more prone to ICD than others. Atopy, in particular atopic dermatitis, has been identified in numerous epidemiological investigations as the major risk factor. Furthermore, the studies revealed that if atopic individuals developed ICD, they had a poorer prognosis regarding improvement of the skin disease than nonatopic individuals.^{1,2}

Loss-of-function mutations in the gene encoding epidermal structural protein filaggrin (FLG) have convincingly been shown to be a crucial risk factor for atopic dermatitis. As replicated in numerous case-control and population-based studies, between 14% and 56% of individuals suffering from atopic dermatitis are carriers of at least one FLG mutation.³ Forty-nine loss-of-function mutations within the FLG gene have been reported recently with five loss-of-function mutations being highly prevalent among European caucasians, giving a combined null allele frequency of 0.09.^{4,5}

Filaggrin aggregates keratin filaments in the stratum corneum and is responsible for the mechanical strength of the principal barrier of the skin. Moreover, filaggrin is the main source of hygroscopic constituents of the natural moisturizing factor which has a central role in maintaining the hydration of

the stratum corneum. It is proposed that one of the filaggrin breakdown products, urocanic acid, plays a significant role in the maintenance of the pH gradient of the skin, cutaneous antimicrobial defence and regulation of key enzymatic events in the stratum corneum. As a potent scavenger of free radicals, the epidermal chromophore urocanic acid is important in protecting the skin against oxidative stress when exposed to ultraviolet radiation and skin irritants.^{5,6}

Considering the important role of filaggrin for stratum corneum function, it can be hypothesized that a constitutionally altered skin barrier in carriers of the FLG mutation will facilitate the penetration of skin irritants. It is likely that individuals with reduced levels of filaggrin will have an altered skin barrier leaving them more susceptible to ICD. Once contact dermatitis has developed, an intrinsically altered skin barrier and aberrant inflammatory response might play a role in the repair processes influencing individual recovery. In a previous case-control study we found that the carriers of FLG mutations have an enhanced risk of acquiring occupational ICD.⁷ Recently, we demonstrated that carriers of FLG mutations have reduced amounts of natural moisturizing factor in the stratum corneum, an impaired skin barrier function and higher levels of proinflammatory interleukin 1 cytokines in the stratum corneum.^{8,9} This finding is consistent with data obtained in filaggrin-deficient mice suggesting that FLG deficiency alone can provoke a barrier abnormality in the epidermis and an elevated inflammatory response when exposed to skin irritants.^{10,11}

Although carriers of filaggrin deficiency were shown to have a significant role in the individual susceptibility to ICD, the influence of FLG genotype status on the course of the disease is not known. In this article, we present results of a study investigating the clinical course of patients referred to our clinic for treatment of chronic occupational ICD of the hands in relation to their FLG genotype and atopy status. Special attention was given to the clinical course of skin symptoms, the use of topical corticosteroids, total length of sick time taken and the percentage of those who recovered and were able to return to the same occupation over a period of up to 3 years.

Methods

Study population

After obtaining approval by the ethics committee of the University of Osnabrück, a cohort of 712 patients who were hospitalized at our clinic for treatment of long-lasting chronic occupational hand eczema were asked to participate in the study conducted in accordance with the Declaration of Helsinki. Forty-seven patients (6.6%) chose not to enrol. After obtaining informed consent, patients' genotype was determined for mutations in genes coding for FLG, 2282del4, R501X, R2447X and S3247X, between November 2005 and March 2011. Patients were consecutively included into this study if they met the following inclusion criteria: Caucasian,

age ≥ 18 years, primary diagnosis of ICD of the hands, and no history of a secondary chronic inflammatory disorder (e.g. rheumatoid arthritis, psoriasis). Two hundred and six patients (31%) were excluded because of a primary diagnosis of allergic contact dermatitis or atopic eczema, or because of failure of filaggrin determination, leaving a total number of 459 patients for analysis. The diagnosis of ICD was based on a patient's history, exposure to irritants, clinical distribution, presence of skin lesions and exclusion of other dermatological entities, and if patients had no clinically relevant type-IV sensitization. Patients were patch tested to an extended range of allergens, including standardized and customized substances. Patients were at least tested to the European standard tray, and tests were conducted and read according to international guidelines.¹²

For each patient, an experienced dermatologist performed a full examination of the skin and a detailed medical history was recorded using a standardized questionnaire. The criteria to establish a diagnosis of skin atopic diathesis vary with investigators¹³ but in this study we made a diagnosis of 'atopy' according to ongoing or past flexural eczema and/or if at least 10 points on the Erlangen atopy score were reached.¹⁴ The Erlangen score is based on anamnestic and clinical atopic features as well as laboratory investigations (IgE).

Schedule of investigation

The rehabilitation programme developed by our department for cases of occupational dermatoses, in whom outpatient prevention measures are not sufficient, comprised a standardized diagnostic and therapy-based programme, which included a 3-week inpatient component (Fig. 1).¹⁵ After hospital discharge, to ensure a complete restoration of skin barrier function, patients remained on sick leave and were closely monitored for an additional 3 weeks in an outpatient setting. At the end of this 6-week period, patients were re-evaluated in the department in Osnabrück with ongoing monitoring for 4 weeks after resuming work. Patients were invited to our department again at the end of the first and third year after participating in the programme. At each visit, a dermatologist examined the patient and documented the disease severity score of the hand eczema based on the evaluation of erythema, scaling, papules, vesicles, induration and fissures, and the extent of the hand eczema as described earlier.¹⁶ Moreover, therapeutic interventions (e.g. use of topical corticosteroids), sick leave days and job loss/retraining were recorded.

Filaggrin genotyping

DNA material was obtained from buccal mucosa cells with buccal swabs (Medispo, Oud-Beijerland, the Netherlands). For each subject, two swabs were obtained and 2 mL of lysis buffer (Puregene[®] Cell Lysis Solution; Gentra Systems, Minneapolis, MN, U.S.A.) was added to each swab to disrupt the cells and stabilize the DNA. Extraction and genotyping for the mutations R501X, R2447X and S3247X were performed by KBioscience (Hoddesdon, U.K.). Mutations were genotyped

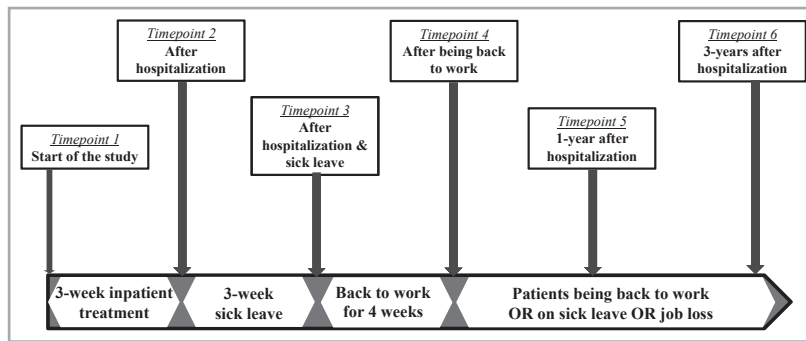


Fig 1. Schedule for the investigation.

using the KASP genotyping system, a homogeneous fluorescent resonance energy transfer-based system, coupled with competitive allele specific polymerase chain reaction. Blind duplicates and Hardy–Weinberg equilibrium tests were used as quality control tests. R501X was genotyped using the primer pair GAATGCCTGGAGCTGTCTCG (C-allele) and CTGAATGCCTGGAGCTGTCTCA (T-allele) with the common allele primer GCACTGGAGGAAGACAAGGATCG. R2447X was genotyped using the primer pair GAGTGCCTGGAGCTGTCTCG (C-allele) and GAGTGCCTGGAGCTGTCTCA (T-allele) with the common allele primer GAGGAAGACAAGGATCCACCACA. S3247X was genotyped using the primer pair GTGTCTGGAGCCGTGCCTTG (C-allele) and GGTGTCTGGAGCCGTGCCTTT (A-allele) with the common primer CTTCCAGAAACCATCGTGGATCTGT. Genotyping for 2282del4 was performed as described previously.¹⁷

Data analyses and statistics

For additional analysis, the total study population was further classified according to FLG and atopy status into: (i) 'pure' ICD (no atopy or FLG loss-of-function mutations); (ii) ICD and FLG loss-of-function mutation(s) (combined loss-of-function genotype, grouping together individuals with one or more of any of the filaggrin mutations); (iii) ICD and atopy;

and (iv) ICD and atopy and FLG loss-of-function mutations [see explanation in (ii)]. Our reference group was patients with ICD without atopy or FLG. All other subgroups were contrasted to this peer group.

The observed genotype frequencies were compared with the expected Hardy–Weinberg distribution using the chi-square test. To estimate the risk of a clinical feature conferred by a particular genotype, we calculated the odds ratios (ORs) with 95% confidence intervals (CIs) between the subgroups. We used mid-P exact (<http://www.openepi.com>) to calculate CIs for proportions. Patients with incidental missing data were excluded from the statistical analysis of that specific variable. The statistical analyses were performed using SPSS software version 16.0 (SPSS Inc., Chicago, IL, U.S.A.).

Results

A total number of 432 patients completed the 1-year evaluation, and 204 of these were also evaluated at the 3-year follow-up, at the time of drafting this manuscript. The remaining 255 patients are still under observation and will finish the 3-year follow-up within the next 2 years. More than half of our study population originated from the subgroup of ICD and atopy (58.2%), representing therefore the largest of the four subgroups, followed by ICD (27%) as shown in Table 1.

Table 1 General epidemiological data of the four subgroups

	ICD (n = 124, 27%) (reference)	ICD and atopy (n = 267, 58.2%)	ICD and FLG loss-of-function mutations (n = 8, 1.7%)	ICD, atopy and FLG loss-of-function mutations (n = 60, 13.1%)
Female (%)	37.7	72.9 P < 0.05	42.9 n.s.	55.0 P < 0.05
Age (years), median (min–max)	46 (19–66)	42 (18–67) P < 0.05	49 (33–59) n.s.	40 (19–62) P < 0.05
Age at onset of hand eczema (years), median (min–max)	41 (16–58)	28 (15–60) P < 0.05	43 (29–52) n.s.	29 (16–57) P < 0.05
Years of exposure at onset of hand eczema, median (min–max)	16 (1–52)	14 (0–53) P < 0.05	17 (9–42) n.s.	11 (1–44) P < 0.05
Duration of hand eczema (months), median (min–max)	48 (5–360)	48 (5–480) n.s.	24 (8–180) n.s.	60 (6–370) n.s.

ICD, irritant contact dermatitis; n.s. not significant.

General characteristics

Table 1 shows a summary of the general epidemiological data of the subgroups.

Atopy and FLG carriers

Our study included 327 (71.2%) atopic individuals and 132 nonatopic individuals. Overall, 63 patients showed a heterozygous mutation, and five individuals a compound heterozygous mutation, in the FLG alleles R501X, R2447X, S3247X and 2282del4. No homozygote carriers were detected. Among the atopic individuals, 60 out of the 327 (18.3%, 95% CI 14.4–22.8) were carriers of a FLG loss-of-function mutation and in nonatopic individuals eight of the 132 (6.1%, 95% CI 2.9–11.2) were carriers. Atopic patients (with and without FLG loss-of-function mutations) were not only the youngest in our study but were also the patients who were youngest at the onset of hand eczema. This finding was significant when compared with the group with ICD ($P < 0.05$). At the same time, they displayed a significantly lower number of years of exposure to irritants when developing hand eczema compared with the subjects with 'pure' ICD.

Clinical course: disease severity score revealed highest values for atopic individuals and FLG carriers

A summary of hand eczema scores is shown in Table 2 for each of the four subgroups. Patients with ICD and FLG loss-of-function mutations, and those with ICD, atopy and FLG loss-of-function mutations had the highest scores.

Subgroup analysis for possible differences between compound heterozygous and heterozygous patients did not reveal significant differences in the disease severity hand eczema score at the different points of time (T1–T6).

Under the assumption that women might be exposed to wet work to a higher degree than men (e.g. due to house-keeping), we also performed subgroup analyses for sex. No significant differences in the clinical course between female and male individuals were observed (detailed results are not shown).

Use of topical corticosteroids

The percentage of patients reporting the need for topical glucocorticosteroid use is displayed in Table 3. After 3 years, the use of topical corticosteroids was significantly increased in patients with ICD and atopy compared with those with ICD alone (50% vs. 30.9%, $P < 0.05$).

Sick leave and job loss

Higher numbers of patients with ICD and atopy were on sick leave and experienced a job loss because of the hand eczema when contrasted to our comparison subgroup. Additional FLG mutation seemed to worsen both findings. Results revealed that 13.1% and 19.6% of discharged patients with ICD could not return to their occupations after 1 and 3 years, respectively. The risk of abandoning their occupation was significantly increased in the subgroup with atopy and positive FLG mutation carrier status: after 1 year the risk was more than doubled (OR 2.3), with a threefold increase after 3 years (OR 3.1). Further details are summarized in Tables 4 and 5.

Discussion

Our study investigated the clinical course of a large cohort of a well-defined patient population with occupational ICD of the hands with respect to the clinical course in relation

Table 2 Disease severity and eczema score¹⁶ in the course of observation^a

	ICD (n = 124)	ICD and atopy (n = 267)	ICD and FLG loss-of-function mutations (n = 8)	ICD, atopy and FLG loss-of-function mutations (n = 60)
Start of study, median (IQR)	5 (0–14)	6 (0–18)	5 (3–11)	7 (1–13)
Total number	124	267	8	60
After hospitalization, median (IQR)	2 (0–11)	3 (0–11)	3 (1–6)	3 (0–7)
Total number	124	267	8	60
After sick leave, median (IQR)	2 (0–14)	2 (0–14)	2.5 (0–9)	3 (0–11)
Total number	124	260	8	57
Back to work, median (IQR)	2 (0–12)	3 (0–17)	3 (0–8)	3 (0–16)
Total number	112	243	8	54
After 1 year, median (IQR)	2 (0–16)	3 (0–15)	4 (1–12)	3 (0–16)
Total number	122	248	8	54
After 3 years, median (IQR)	2 (0–13)	2 (0–15)	6 (2–7)	2 (0–7)
Total number	56	124	3	21
Total score	15	19	23.5	21

ICD, Irritant contact dermatitis; IQR, interquartile range.

^aHand eczema score, range 1–18. Grading of the hand eczema: mild, 1–3; moderate, 4–6; severe, 7–18.

Table 3 Number and percentage of patients using topical corticosteroids at least once a month since the last visit in the office

	ICD (reference)	ICD and atopy	ICD and FLG loss-of-function mutations	ICD, atopy, and FLG loss-of-function mutations
Start of study, n (%)	101 (81.5)	232 (86.9)	6 (75)	50 (83.3)
Total number	124	267	8	60
		n.s.	n.s.	n.s.
Back to work, n (%)	15 (13.4)	46 (18.9)	1 (12.5)	12 (22.2)
Total number	112	243	8	54
After 1 year, n (%)	44 (36.1)	115 (46.4)	2 (25)	24 (44.4)
Total number	122	248	8	54
		n.s.	n.s.	n.s.
After 3 years, n (%)	17 (30.9)	61 (50)	1 (50)	8 (40)
Total number	55	122	2	20
		P < 0.05, OR 2.2 (95% CI 1.1–4.4)	n.s.	n.s.

ICD, irritant contact dermatitis; n.s. not significant; OR, odds ratio; CI, confidence interval.

	ICD	ICD and atopy	ICD and FLG loss-of-function mutations	ICD, atopy, and FLG loss-of-function mutations
Start of study, n (%)	30 (24.2)	56 (21)	0 (0)	12 (20)
Total number	124	267	8	60
After 1 year, n (%)	8 (6.6)	17 (6.9)	0 (0)	5 (9.3)
Total number	122	248	8	54
After 3 years, n (%)	1 (1.8)	6 (4.8)	0 (0)	1 (4.8)
Total number	56	124	3	21

No significant findings between the groups at all time points.

Table 4 Number and percentage of patients on sick leave at the start of the study and after 1 and 3 years

	ICD (reference)	ICD and atopy	ICD and FLG loss-of-function mutations	ICD, atopy and FLG loss-of-function mutations
After 1 year, n (%)	16 (13.1)	46 (18.5)	0 (0)	14 (25.9)
Total number	122	248	8	54
		n.s.	n.s.	P < 0.05, OR 2.3 (95% CI 1.1–5.2)
After 3 years, n (%)	11 (19.6)	36 (29.0)	1 (33.3)	9 (42.9)
Total number	56	124	3	21
		n.s.	n.s.	P < 0.05, OR 3.1 (95% CI 1.1–9.1)

Table 5 Number and percentage abandoning job after 1 and 3 years

to atopy and FLG status. The best clinical outcome was observed in patients with ICD without atopy and FLG loss-of-function mutations, exemplified by the highest decrease in eczema scores, sick leave times and use of topical corticosteroids. This subgroup also had the lowest rate of individuals who had to abandon their job because of the irritant hand eczema. Thus, this cohort had the greatest chance of going on to prolonged remission if appropriate treatment

and preventive measures were taken. Patients with ICD and atopy were the youngest at first hospitalization and youngest at the initial occurrence of hand eczema. In accordance with the literature, significantly more women were seen among this subgroup compared with those with pure ICD.¹⁸ Subjects with ICD and atopy showed decreases in eczema scores, but also included the highest number of patients with ongoing topical corticosteroid treatment. Moreover, this group

represented a high percentage of patients with recurrent sick time events.

In accordance with other studies, the general epidemiological characteristics of patients with ICD, atopy and FLG loss-of-function mutations resembled the ICD and atopy subgroup, for whom significantly younger age at onset of hand eczema and presentation with more persistent disease with longer median duration have been reported.^{19–22}

The ICD–FLG subgroup was the smallest, with a total of only eight subjects. The low number of cases with FLG mutations in this special cohort probably reduced the power of statistical analysis and we cannot exclude that FLG mutation itself may play a role in the course of the disease. In patients with allergic contact dermatitis, FLG loss-of-function mutations have been associated with an earlier onset of eczema and a tendency towards a longer duration.²³

In our study, after 1 and 3 years, the risk of abandoning an occupation was increased in patients with atopy-related ICD compared with ICD. FLG loss-of-function mutation status in patients with ICD and atopy increased the risk significantly (1 year: OR 2.3, 95% CI 1.1–5.2, $P < 0.05$; 3 years: OR 3.1, 95% CI 1.1–9.1, $P < 0.05$), suggesting a worsening effect of the FLG mutation carrier status in the presence of atopy. Thyssen *et al.* similarly studied the impact of FLG mutations on the risk for persistence of hand eczema in the general population.²⁴ Results revealed significant associations (OR 2.98, 95% CI 1.27–7.01) between hand eczema within the past 12 months and FLG loss-of-function mutation status in participants with a history of atopic dermatitis, but not in subjects without atopic dermatitis (OR 0.82, 95% CI 0.41–1.67). Presence of both atopic dermatitis and FLG loss-of-function mutations revealed an OR of 3.23 (95% CI 1.51–6.91) for hand eczema. Furthermore, this group demonstrated that patients with atopic dermatitis and FLG loss-of-function mutation status had an earlier onset as well as higher persistence of their hand eczema compared with wild-type subjects and nonatopics.²⁴

The prevalence of FLG mutations within European populations was reported to be between 7% and 10%.¹⁹ Mutations in the FLG gene were associated with atopic dermatitis,^{19,25} and the presence of atopic dermatitis increased the risk of development of ICD.²⁶ FLG mutation in our study was strongly related to atopy: 18.3% of patients with ICD and atopy (95% CI 14.4–22.8) carried at least one FLG loss-of-function mutation compared with 6.1% (95% CI 2.9–11.2) of ICD subjects without atopy. This supports the firmly established association of FLG loss-of-function mutations with atopy, particularly with atopic dermatitis. Previous studies have reported combined FLG carrier frequencies of up to 22.9% for the four most common loss-of-function mutations in adult patients with atopic dermatitis.^{27,28} In an earlier case–control study by our group investigating the prevalence of FLG loss-of-function mutations R501X and 2282del4 in patients with ICD, heterozygote carriers for the FLG loss-of-function alleles R501X and 2282del4 were found in 12.5% of patients and in 6.9% of the controls.⁷

The exact nature of the skin barrier defect associated with FLG deficiency and the mechanisms through which FLG mutations contribute to atopic dermatitis risk are not yet fully understood. The question arises as to whether, independent of atopic dermatitis, FLG mutations may be a risk factor or modifier for the course of ICD. FLG is a multifunctional protein that can alter the skin barrier function and inflammatory response by different mechanisms. In an *in vivo* animal model, Kawasaki *et al.* investigated the effect of filaggrin loss on skin barrier function and percutaneous immune responses. For this, the authors generated Flg^{−/−} mice.²⁹ Complete filaggrin deficiency was shown to alter barrier integrity and enhance sensitization. Scharschmidt *et al.* described exclusive FLG deficiency provoking a paracellular barrier abnormality in mice reducing inflammatory thresholds to topical irritants.¹¹ Flohr and colleagues investigated 88 infants and found that FLG mutation carriers were significantly more likely to have dry skin, even in the absence of eczema (OR 8.5). The same applied to the median transepidermal water loss (TEWL), which was significantly increased in FLG loss-of-function mutation carriers, independently of eczema.²⁰

In contrast, others did not find clear evidence that FLG mutations alone are able to provoke barrier abnormalities that may lead to ICD. Jungersted *et al.* found a higher TEWL in FLG carriers. Regarding skin hydration, a trend toward lower values in atopic dermatitis, particularly in those with FLG mutation was described. However, comparing atopic dermatitis with and without FLG, there was no significant difference.³⁰ Further studies by Hubiche *et al.* and Jakasa *et al.* on patients with atopic dermatitis did not show significant differences in the level of barrier function defects between FLG-positive and -negative atopic dermatitis.^{31,32} The authors concluded that there probably exists a variety of mechanisms that modulate barrier integrity other than the filaggrin system.³²

The following limitations to this study need to be recognized. Our study sample was drawn from patients who were referred to a tertiary referral centre with a long-lasting chronic ICD; as such, patients with atopy, and particularly atopic dermatitis may be over-represented and results may not be characteristic of the general population. Secondly, patch testing was conducted to an individual choice of allergens. Thus, we might have overlooked some allergens and several patients may have been misclassified as ICD.

In conclusion, patients with atopy, particularly atopic dermatitis are a special risk population for ICD. In the presence of atopy FLG loss-of-function mutation carrier status seems to be a worsening modifier of the severity of the clinical presentation of irritant hand eczema.

Thus, early-stage identification of individuals with ICD related to atopy and FLG loss-of-function mutations may result in additional emphasis to these patients of the importance of adherence to therapeutic interventions and preventive measures to achieve the goal of dermatological rehabilitation. The impact of exclusive FLG mutation without atopy in ICD is yet not fully understood and larger studies are needed to draw statistically representative conclusions.

What's already known about this topic?

- Exogenous and genetic factors contribute to the development of irritant contact dermatitis (ICD).
- Atopy, particularly atopic dermatitis has been identified as the major risk factor for the development of ICD and for a poorer prognosis.
- No long-term data exist on the influence of FLG on the course of ICD.

What does this study add?

- In the presence of atopy, FLG loss-of-function mutations seem to be a modifier of the severity of the clinical course in ICD.

Acknowledgement

We acknowledge the support of the EU COST Action BM 0903 (Skin Barrier in Atopic Diseases, 'SKINBAD').

References

- Cahill J, Keegel T, Nixon R. The prognosis of occupational contact dermatitis in 2004. *Contact Dermatitis* 2004; **51**:219–26.
- Lee A, Nixon R. Occupational skin disease in hairdressers. *Australas J Dermatol* 2001; **42**:1–6.
- Brown SJ, McLean WH. Eczema genetics: current state of knowledge and future goals. *J Invest Dermatol* 2009; **129**:543–52.
- Brown SJ, Irvine AD. Atopic eczema and the filaggrin story. *Semin Cutan Med Surg* 2008; **27**:128–37.
- Irvine AD, McLean WH, Leung DY. Filaggrin mutations associated with skin and allergic diseases. *N Engl J Med* 2011; **365**:1315–27.
- Gibbs NK, Tye J, Norval M. Recent advances in urocanic acid photochemistry, photobiology and photoimmunology. *Photochem Photobiol Sci* 2008; **7**:655–67.
- de Jongh CM, Khrenova L, Verberk M *et al.* Loss-of-function polymorphisms in the filaggrin gene increase susceptibility to chronic irritant contact dermatitis. *Br J Dermatol* 2008; **159**:621–7.
- Kezic S, Kemperman PM, Koster ES *et al.* Loss-of-function mutations in the filaggrin gene lead to reduced level of natural moisturizing factor in the stratum corneum. *J Invest Dermatol* 2008; **128**:2117–9.
- Kezic S, O'Regan GM, Lutter R *et al.* Filaggrin loss-of-function mutations are associated with enhanced expression of IL-1 cytokines in the stratum corneum of patients with atopic dermatitis and in a murine model of filaggrin deficiency. *J Allergy Clin Immunol* 2012; **129**:1031–9.
- Presland RB, Boggess D, Lewis SP *et al.* Loss of normal profilaggrin and filaggrin in flaky tail (ft/ft) mice: an animal model for the filaggrin-deficient skin disease ichthyosis vulgaris. *J Invest Dermatol* 2000; **115**:1072–81.
- Scharschmidt TC, Man MQ, Hatano Y *et al.* Filaggrin deficiency confers a paracellular barrier abnormality that reduces inflammatory thresholds to irritants and haptens. *J Allergy Clin Immunol* 2009; **124**:496–506.
- Lindberg M, Matura M. Patch testing. In: *Textbook of Contact Dermatitis* (Johansen JD, Frosch PJ, Leppitvein JP, eds). Berlin: Springer, 2011; 439–64.
- Uter W, Schwanitz HJ, Pfahlberg A, Gefeller O. Atopic signs and symptoms: assessing the 'atopy score' concept. *Dermatology* 2001; **202**:4–8.
- Diepgen TL, Sauerbrei W, Fartasch M. Development and validation of diagnostic scores for atopic dermatitis incorporating criteria of data quality and practical usefulness. *J Clin Epidemiol* 1996; **49**:1031–8.
- Skudlik C, Wulfhorst B, Gediga G *et al.* Tertiary individual prevention of occupational skin diseases: a decade's experience with recalcitrant occupational dermatitis. *Int Arch Occup Environ Health* 2008; **81**:1059–64.
- Skudlik C, Dulon M, Pohrt U *et al.* Osnabrück hand eczema severity index – a study of the interobserver reliability of a scoring system assessing skin diseases of the hands. *Contact Dermatitis* 2006; **55**:42–7.
- Palmer CN, Irvine AD, Terron-Kwiatkowski A *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**:441–6.
- Thyssen JP, Ross-Hansen K, Johansen JD *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**:46–53.
- Brown SJ, McLean WH. One remarkable molecule: filaggrin. *J Invest Dermatol* 2012; **132**:751–62.
- Flohr C, England K, Radulovic S *et al.* Filaggrin loss-of-function mutations are associated with early-onset eczema, eczema severity and transepidermal water loss at 3 months of age. *Br J Dermatol* 2010; **163**:1333–6.
- Henderson J, Northstone K, Lee SP *et al.* The burden of disease associated with filaggrin mutations: a population-based, longitudinal birth cohort study. *J Allergy Clin Immunol* 2008; **121**:872–7.
- Brown SJ, Sandilands A, Zhao Y *et al.* Prevalent and low-frequency null mutations in the filaggrin gene are associated with early-onset and persistent atopic eczema. *J Invest Dermatol* 2008; **128**:1591–4.
- Carlsen BC, Johansen JD, Menné T *et al.* Filaggrin null mutations and association with contact allergy and allergic contact dermatitis: results from a tertiary dermatology clinic. *Contact Dermatitis* 2010; **63**:89–95.
- Thyssen JP, Carlsen BC, Menné T *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**:115–20.
- O'Regan GM, Irvine AD. The role of filaggrin in the atopic diathesis. *Clin Exp Allergy* 2010; **40**:965–72.
- Thyssen JP, Johansen JD, Linneberg A, Menné T. The epidemiology of hand eczema in the general population – prevalence and main findings. *Contact Dermatitis* 2010; **62**:75–87.
- Weidinger S, Rodríguez E, Stahl C *et al.* Filaggrin mutations strongly predispose to early-onset and extrinsic atopic dermatitis. *J Invest Dermatol* 2007; **127**:724–6.
- Greisenegger E, Novak N, Maintz L *et al.* Analysis of four prevalent filaggrin mutations (R501X, 2282del4, R2447X and S3247X) in Austrian and German patients with atopic dermatitis. *J Eur Acad Dermatol Venereol* 2010; **24**:607–10.
- Kawasaki H, Nagao K, Kubo A *et al.* Altered stratum corneum barrier and enhanced percutaneous immune responses in filaggrin-null mice. *J Allergy Clin Immunol* 2012; **129**:1538–46.

- 30 Jungersted JM, Scheer H, Mempel M *et al.* Stratum corneum lipids, skin barrier function and filaggrin mutations in patients with atopic eczema. *Allergy* 2010; **65**:911–8.
- 31 Hubiche T, Ged C, Benard A *et al.* Analysis of SPINK 5, KLK 7 and FLG genotypes in a French atopic dermatitis cohort. *Acta Derm Venereol* 2007; **87**:499–505.
- 32 Jakasa I, Koster ES, Calkoen F *et al.* Skin barrier function in healthy subjects and patients with atopic dermatitis in relation to filaggrin loss-of-function mutations. *J Invest Dermatol* 2011; **131**:540–2.