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INVESTIGATIVE REPORT

Xerosis is Associated with Atopic Dermatitis, Hand Eczema and Contact Sensitization Independent of Filaggrin Gene Mutations

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Atopic dermatitis, hand eczema and contact sensitization are prevalent disorders, and may, in many cases, be secondary to skin barrier abnormality. The aim of this study was to investigate the association between self-reported generalized xerosis, atopic dermatitis, hand eczema and contact sensitization, taking filaggrin gene mutations into account. Questionnaire data were collected from a cross-sectional study performed in a general population in Copenhagen. A total of 3,460 18–69-year-olds were patch-tested and 3,335 were genotyped for the 2282del4 and R501X mutations in the *filaggrin* gene. Atopic dermatitis and hand eczema were significantly associated with generalized xerosis, whereas contact sensitization (not nickel) showed only a borderline significant association. These results suggest that generalized xerosis may increase the risk of common skin disorders.
Key words: xerosis; atopic dermatitis; hand eczema; contact sensitization; general population; epidemiology.

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Xerosis is characterized by skin that is dehydrated, displays slight-to-severe flaking and scaling, has fine lines and cracks, and which may show redness. The prevalence of self-reported xerosis was 6.2% in 30–76-year-old Norwegians (1). In a mixed population of Chinese controls (n=312) and patients with coronary heart disease (n=224), mean ages 56 and 69 years, respectively, xerosis was observed in 46–47%. Futhermore, generalized xerosis was found in 19.2% and 7.6%, respectively, with a mean of 14% (2). Causes of xerosis include environmental exposures (e.g. ultraviolet (UV) light, cold climate, indoor heating, excessive bathing, and use of soaps), non-cutaneous disease (e.g. thyroid and haematological disorders), drug use (e.g. cimetidine and hypocholesterol agents), skin inflammation and genetic predisposition (e.g. common filaggrin gene (*FLG*) mutations) (3, 4). In elderly patients, risk factors include increasing age, female gender, treatments that can potentially cause xerosis, sweating, and history of atopic dermatitis (AD) (5).

AD, hand eczema and contact sensitization are characterized by complexity and a multi-factorial pathogenesis. A strong association was recently identified between AD and mutations in the *FLG* (6, 7), whereas a moderate association was found with genetic variations in the claudin 1 gene (encoding epidermal tight junctions) in mainly African Americans (8), supporting the notion that skin inflammation is often secondary to skin barrier abnormality (9). Although genetic risk factors for hand eczema and contact sensitization are not yet well-characterized, and are expected to play a more modest role for the pathogenesis, they include *FLG* mutations and polymorphisms in detoxification systems and immunological pathways (4, 10–12). Whether xerotic skin increases the risk of hand eczema and contact sensitization has been little-investigated, whereas the association between AD and xerosis is well-established. We hypothesize that generalized xerosis, whether acquired or inherited, may increase the risk of common skin disorders, including AD, hand eczema and contact sensitization. We present here, for the first time, association estimates between generalized xerosis and common skin disorders adjusted for common *FLG* mutations.

MATERIALS AND METHODS

Study population

During 2006–2008, a cross-sectional study was performed in the general population in Copenhagen. Of 7,931 randomly invited adult Danes born in Denmark and aged 18–69 years, 3,471 (43.7%) participated in a general health examination, and 3,335 (96.1%) were successfully *FLG* genotyped for R501X and 2282del4. For study details, please refer to previous publications (13). The ethics committee of Copenhagen County approved the study (KA-20060011). A written informed consent form was obtained from all participants prior to the beginning of the study.

Questionnaire

Participants were asked about general health, lifestyle, and socioeconomic factors.

Before the questions on eczema, a description was provided: "Eczema is an itching skin disorder showing redness, dryness, and possibly vesicles and exudation. Eczema is present at the same area for some time". Participants were asked: "Have you

ever had hand eczema?". Participants who gave an affirmative answer were further asked: "Have you had hand eczema within the past 12 months?", "At what age did you have hand eczema on the first occurrence?" (<6, 6–14, 15–18, and >18 years), "How often have you suffered from hand eczema?" (only 1 time (<2 weeks), only 1 time (>2 weeks), several times, nearly all the time). Participants were also asked: "Has your doctor ever told you that you suffered from AD?", "Have you ever had dry skin all over your body?" and "Have you ever had dry skin all over your body within the past 12 months?". An affirmative answer was used to create the variable "generalized xerosis ever" and "generalized xerosis within past 12 months".

Filaggrin genotyping

Regions covering the mutations R501X and 2282del4 of the *FLG* were amplified from genomic DNA by PCR, and the DNA fragments obtained were hybridized to both mutation-specific and wild-type-specific DNA-probes attached to microbeads. Hybridization was detected in a Bio-Plex 200 device and genotypes derived from detection data. The genotyping method was recently described in detail (14).

Patch-tests

Patch-testing was performed by using the panel 1 and 2 of the standardized ready to apply TRUE-test (Mekos Laboratories, Hillerød, Denmark). Patch-test readings were carried out on day 2. For details please refer to our previous publication (15). Since nickel exposure is often associated with skin penetration, e.g. ear and body-piercing, we used a contact sensitization variable without nickel allergy to prevent potential confounding by exposures where the skin compartments had been by-passed (16).

Measurement of immunoglobulin E antibodies

Venous blood was taken on the day of examination. Serum was collected after centrifugation at 3,000 r.p.m. for 10 min and stored frozen until analysis for IgE specific to birch, grass (timothy), cat, and mite (*Dermatophagoides pteronyssinus*) with the ADVIA Centaur IgE antibody assay system (Siemens, Deerfield, IL, USA) (17). The analysis was judged to be positive if the measurement exceeded 0.35 kU/l for at least one of the 4 allergens tested.

Statistical analysis

Characteristics of participants were compared using the χ^2 test. Logistic regression models were used for association testing. In these models, tests for interactions were performed by using a log-likelihood ratio test. *FLG* mutation status was defined as subjects who were heterozygote, compound heterozygote or homozygote for the mutations R501X or 2282del4. Data analyses were performed using the Statistical Products and Service Solutions package (SPSS Inc., Chicago, IL, USA) for Windows (release 15.0). Odds ratios (OR) and 95% confidence intervals (CI) were given.

Table I. *The prevalence of universal xerotic skin at some point in life stratified by population characteristics*

	Total % (n/n_{total})	Generalized xerosis ever % (n/n_{total})	Crude odds ratio (95% confidence interval)	*p*-value
Sex				
Men	44.7 (1,491/3,335)	9.4 (137/1,462)	1 (ref)	0.001
Women	55.3 (1,844/3,335)	19.4 (350/1,803)	2.33 (1.88–2.87)	
Age				
18–35 years	18.7 (624/3,335)	16.2 (99/612)	1 (ref)	0.59
36–55 years	48.4 (1,615/3,335)	14.8 (234/1,582)	0.90 (0.69–1.16)	
56–69 years	32.9 (1,096/3,335)	14.4 (154/1,071)	0.87 (0.66–1.15)	
Atopic dermatitis[a]				
No	–	13.0 (392/3,018)	1 (ref)	0.001
Yes	5.5 (178/3,240)	45.7 (80/175)	5.64 (4.11–7.73)	
Filaggrin gene mutation (*FLG*)				
No	–	13.0 (389/3,001)	1 (ref)	0.001
Yes	8.1 (269/3,335)	37.1 (98/264)	3.96 (3.02–5.20)	
Contact sensitization (not nickel)				
No	–	14.5 (452/3,114)	1 (ref)	0.004
Yes	4.6 (154/3,335)	23.2 (35/151)	1.77 (1.20–2.62)	
Hand eczema ever[b]				
No	–	11.8 (301/2,542)	1 (ref)	0.001
Yes	21.5 (716/3,295)	26.2 (184/703)	2.64 (2.15–3.25)	
Hand eczema within past 12 months				
No	–	25.5 (96/377)	1 (ref)	0.67
Yes	9.9 (329/3,295)	26.9 (87/324)	1.07 (0.76–1.51)	
Age at first onset of hand eczema				
<6 years	1.2 (39/715)	51.3 (20/39)	1 (ref)	0.001
6–14 years	2.5 (82/715)	35.8 (29/81)	0.53 (0.24–1.15)	
15–18 years	2.6 (88/715)	34.5 (30/87)	0.50 (0.23–1.08)	
>18 years	15.2 (506/715)	20.8 (103/495)	0.25 (0.13–0.49)	
Hand eczema persistence				
One time only (<2 weeks duration)	1.9 (63/703)	25.6 (44/172)	1 (ref)	
One time only (>2 weeks)	11.8 (393/703)	21.7 (15/69)	0.81 (0.42–1.57)	0.86
Several times	2.2 (72/703)	27.1 (105/388)	1.08 (0.72–1.63)	
Nearly all the time	5.2 (175/703)	27.9 (17/61)	1.13 (0.58–2.16)	

[a]An affirmative answer to the question, "Has a doctor ever informed you that you suffered from atopic dermatitis?".
[b]An affirmative answer to the question, "Have you ever had hand eczema?".

RESULTS

The overall prevalence of AD was 5.5% (177/3,040). In individuals with positive or negative specific IgE, the prevalence of AD was 9.4% (70/678) and 4.3% (107/2,362), respectively ($p < 0.001$), supporting the validity of self-reported AD in this cohort. We also found that AD and "hand eczema ever" were strongly associated. Hence, the prevalence of hand eczema was 53.4% (93/174) and 19.8% (603/3,046) in individuals with and without AD ($p < 0.001$), respectively.

The overall prevalence of self-reported generalized xerosis at "some point in life" and "within the past 12 months" were 14.6% (487/3,265) and 10.4% (338/3,265), respectively. Study population characteristics stratified by generalized xerosis are shown in Table I. Crude data analysis showed that xerosis was significantly associated with female gender, AD, *FLG* mutations, "hand eczema ever", and contact sensitization.

The R501X and 2282del4 mutations were successfully genotyped for 99.4% and 99.5% of the participants. The observed genotype frequencies of the 2 *FLG* polymorphisms did not deviate significantly from the expected frequencies under assumption of Hardy-Weinberg equilibrium in any of the study populations ($p > 0.05$).The prevalence of *FLG* mutations in different subgroups is presented in Table II. The overall prevalence was 8.1% (269/3,335). In crude data analysis, *FLG* mutations were strongly associated with AD and "xerosis ever" and moderately associated with hand eczema and contact sensitization.

In individuals with "generalized xerosis at some point", the strongest association was found with hand eczema within the past 12 months, whereas non-significant associations were found with AD and contact sensitization.

The attributable risks (AR) of reporting generalized xerosis for the diagnosis of AD, hand eczema and contact sensitization (not nickel) were 13%, 19% and 3%, respectively.

In adjusted logistic regression analyses, hand eczema and AD were significantly associated with generalized xerosis (Table III). A regression analysis restricted to individuals without AD, and with "hand eczema ever" as the dependent variable and the explanatory variables as described in Table III, showed a similar positive and significant association with generalized xerosis (the OR was 2.21; 95% CI 1.74–2.81). Moreover, a borderline-significant association with contact sensitization was found, the OR being 1.46 (95% CI 0.96–2.23). Subgroup analysis restricted to individuals without self-reported AD did not change the association estimate (the OR was 1.41; 95% CI 0.88–2.26). Further analysis showed that the association with contact senstization was driven mainly by chemicals used in topical products (data not shown). "Hand eczema within the past 12 months" was also positively associated with generalized xerosis within the past 12 months (adjusted OR 1.66; 95% CI 1.18–2.32). While the association estimates between xerosis and hand eczema and contact sensitization, respectively, were similar in *FLG* mutation and non-mutation carriers, a slightly stronger association was observed between "xerosis past 12 months" and "hand eczema within the past 12 months" among *FLG* mutation carriers (OR 2.67; 95% CI 1.26–5.68 vs. OR 1.47; 95% CI 1.00–2.16). Also, a slightly stronger association was observed between AD and xerosis among *FLG* mutation carriers (OR 7.27; 95% CI 3.11–16.94 vs. OR 4.45; 95% CI 3.08–6.44); however, the interaction term was non-significant (p 0.48). In a similar adjusted logistic regression analysis with generalized xerosis as the dependent variable, an association with onset of hand eczema before 6 years (OR 2.23; 95% CI 1.05–4.74), at age 6–14 years (OR 1.78; 95% CI 1.03–3.09), and at age 15–18 years (OR 1.55; 95% CI 0.90–2.66) was shown. No significant relationship was however shown between

Table II. *Prevalence of filaggrin gene mutations in different sub groups*

	FLG mutations % (n/n_{total})	Crude OR (95% CI)	p-value
All	8.1 (269/3,335)		
Atopic dermatitis[a]			
No	7.4 (228/3,062)	1	0.001
Yes	19.7 (35/178)	3.04 (2.05–4.51)	
Contact sensitization			
No	7.8 (249/3,181)	1	0.02
Yes	13.0 (20/154)	1.76 (1.08–2.86)	
Hand eczema ever[b]			
No	7.5 (193/2,579)	1	0.03
Yes	9.9 (71/716)	1.36 (1.02–1.81)	
Hand eczema within past 12 months			
No	8.1 (31/385)	1	0.07
Yes	12.2 (40/329)	1.58 (0.96–2.59)	
Generalized xerosis ever			
No	6.0 (166/2,778)	1	0.001
Yes	20.1 (98/487)	3.96 (3.02–5.20)	
Generalized xerosis within past 12 months			
No	12.7 (20/157)	1	0.001
Yes	22.5 (76/338)	1.99 (1.17–3.39)	
All individuals with generalized xerosis			
Atopic dermatitis[a]			
No	17.6 (46/262)	1	0.11
Yes	23.6 (49/208)	1.44 (0.92–2.27)	
Contact sensitization			
No	19.2 (87/452)	1	0.08
Yes	31.4 (11/35)	1.92 (0.91–4.08)	
Hand eczema ever[b]			
No	19.3 (58/301)	1	0.61
Yes	21.2 (39/184)	1.13 (0.72–1.78)	
Hand eczema within past 12 months			
No	13.5 (13/96)	1	
Yes	29.9 (26/87)	2.72 (1.29–5.72)	0.007
Generalized xerosis within past 12 months			
No	13.7 (18/131)	1	
Yes	22.8 (76/333)	1.86 (1.06–3.25)	0.03

[a]An affirmative answer to the question, "Has a doctor ever informed you that you suffered from atopic dermatitis?".
[b]An affirmative answer to the question, "Have you ever had hand eczema?".
OR: odds ratio; CI: confidence interval.

Table III. *Logistic regression analyses showing the association between atopic dermatitis, hand eczema, and contact sensitization, respectively, and dry skin*

Explanatory variables	Atopic dermatitis[a] *n* = 3,193 Adjusted OR (95% CI[c])	Hand eczema ever[b] *n* = 3,174 Adjusted OR (95% CI[c])	Contact sensitization (not nickel) *n* = 3,193 Adjusted OR (95% CI[c])
Generalized xerosis ever			
No	1 (ref)	1 (ref)	1 (ref)
Yes	4.82 (3.45–6.74)	2.12 (1.69–2.65)	1.46 (0.96–2.23)
Sex			
Male	1 (ref)	1 (ref)	1 (ref)
Female	1.28 (0.91–1.80)	1.44 (1.20–1.72)	1.25 (0.88–1.77)
Age			
18–35 years	1 (ref)	1 (ref)	1 (ref)
36–55 years	0.75 (0.52–1.07)	1.22 (0.97–1.56)	1.06 (0.68–1.67)
56–69 years	0.25 (0.15–0.42)	1.05 (0.82–1.37)	1.01 (0.62–1.65)
Filaggrin mutations			
No	1 (ref)	1 (ref)	1 (ref)
Yes	1.91 (1.24–2.92)	0.92 (0.67–1.26)	1.51 (0.90–2.51)
Contact sensitization (not nickel)			
No	1 (ref)	1 (ref)	–
Yes	2.02 (1.16–3.52)	1.52 (1.05–2.22)	
Atopic dermatitis			
No	–	1 (ref)	1 (ref)
Yes		3.48 (2.50–4.84)	2.04 (1.17–3.53)

[a]An affirmative answer to the question, "Has a doctor ever informed you that you suffered from atopic dermatitis?". [b]An affirmative answer to the question, "Have you ever had hand eczema?". [c]Logistic regression analysis mutually adjusted for shown variables.
OR: odds ratio; CI: confidence interval

"generalized xerosis" and "hand eczema persistence", albeit the relationship was positive. Finally, "xerosis within the past 12 months" was positively associated with these variables (data not shown). No differences were observed when stratification by sex was performed.

DISCUSSION

Generalized xerosis was positively associated with AD, hand eczema and contact sensitization in an adult general population. While it is possible that xerosis followed primary skin inflammation, we find it more likely that xerosis came first as, for example, axillary allergic contact dermatitis to fragrances, mild AD in the elbow flexures, and hand eczema are localized conditions and therefore unlikely to cause generalized xerosis. Also, previous studies have suggested that xerosis is a risk factor for hand eczema, at least in individuals with AD (18, 19). The association with contact sensitization could be caused by frequent application of topical products containing contact allergens, e.g. to treat xerotic or inflamed skin as indicated by a recent study (16). However, it should be acknowledged that the association with contact sensitization was only borderline significant in crude and adjusted analyses and that it could be a result of random error. Although *FLG* mutations are associated with xerosis (3, 4), AD, hand eczema, and contact sensitization (4, 11, 20), xerosis remained positively associated with these disorder despite adjustment for *FLG* mutations. The *FLG* shows intragenic copy number variation with alleles encoding 10, 11 or 12 filaggrin monomers (21). Since a low copy number has been associated with AD independently of *FLG* mutations and is probably due to lower levels of filaggrin metabolites (the natural moisturizing factor) (21), it is possible that *FLG* copy number variation also may affect the risk of developing hand eczema and contact sensitization. Taken together, our results support the hypothesis that xerotic skin may be an independent risk factor for common eczematous skin disorders.

Study weaknesses include a low participation rate, possibly resulting in selection bias. However, the study was a 2-hour general health examination with a broad focus on health where no skin examination was provided besides patch testing. Hence, we do not expect that we selected individuals with skin diseases in particular for this study. The question on hand eczema within the past 12 months has been validated, showing a high specificity (22). While none of the remaining questions have been validated, the positive association between AD and specific IgE supports its use in this study. Since we only performed genotyping for the 2 most common mutations in the *FLG* covering about 80% of known mutations (23), misclassification may have affected our results. Also, our study was restricted to Danes born in Denmark and the results can therefore not be generalized.

We are not aware of any published studies that have investigated genetic risk factors for xerosis besides the *FLG* mutations. Genetic discovery studies are warranted to identify mutations that are associated with xerosis. Ultimately, these may also increase the risk of AD, hand eczema and contact sensitization. It is acknowledged that a proportion of the genetic contribution to these common skin diseases has not yet been identified, making such

an attempt worthwhile. For hand eczema, the genetic influence is moderate, and it was recently shown that the heritability was not explained by co-morbidity with AD (24). For contact sensitization, the heritability is suspected to be moderate to low (12, 25), although twin studies have focused mainly on nickel sensitization. For AD, the estimated heritability is high, at 71–84% (26). Studies are currently investigating whether the use of moisturizers can prevent the development of AD and atopic disorders. While we are awaiting the outcome of these studies, it should be emphasized that low-allergenic formulations used to treat xerosis should be recommended to avoid contact sensitization.

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