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Filaggrin gene mutations in relation to contact allergy and hand eczema in adolescence

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Abstract

Background: Filaggrin is an important protein for structure and function of the skin barrier. Filaggrin gene (*FLG*) mutations are known to result in dry skin, impaired skin barrier, and increased risk for atopic dermatitis. However, it is not clear whether these mutations are associated with contact allergy or hand eczema in adolescence.

Objectives: The purpose of this study was to investigate whether *FLG* mutations are associated with contact allergy, self-reported hand eczema, or dry skin in adolescence.

Methods: We used data from the 16-year follow-up in the BAMSE cohort, information obtained from a Web-based questionnaire including questions on hand eczema and dry skin, from *FLG* mutation analysis (R501X, R2447X, 2282del4), and patch testing ($n = 1822$).

Results: Logistic regression analyses showed no statistically significant associations between *FLG* mutations and contact allergy (any contact allergy, nickel allergy, or fragrance allergy) according to patch test, or self-reported hand eczema at 16 years, or hand eczema ever. However, *FLG* mutations were associated with self-reported dry skin at 16 years.

Conclusions: *FLG* mutations are associated with self-reported dry skin at 16 years. However, in this study no consistent associations were found between *FLG* mutations and contact allergy or hand eczema at 16.

KEYWORDS

adolescent, contact allergy, dry skin, epidemiology, filaggrin, fragrance, hand eczema, nickel

1 | INTRODUCTION

Filaggrin is an epidermal protein that is important for the skin structure and the barrier function of stratum corneum. Loss-of-function mutations in the filaggrin gene (*FLG*) result in dry skin, impaired skin barrier function, and increased risk for atopic dermatitis (AD).^{1–3} However, the role of *FLG* mutations in relation to contact allergy in adolescence needs further exploration.

Results from our Swedish birth cohort show that approximately 5% of adolescents suffer from hand eczema and that there is an association between AD and hand eczema in adolescence.^{4,5} In addition, an association between hand eczema and contact allergy has been reported among Danish adolescents and there is a well-known association between hand eczema and contact allergy among adults.^{6,7} Several studies have reported that *FLG* mutations are associated with dry skin among children and young adults.^{8–11} It has also been suggested

that the association between skin dryness, AD, hand eczema, and contact allergy is independent of *FLG* mutations.¹² Thus, the role of *FLG* mutations in relation to adolescent hand eczema remains unclear. The hypothesis of this study was that *FLG* mutations increase the risk for contact allergy, hand eczema, and dry skin in adolescence and the aim was to study whether *FLG* mutations are associated with contact allergy according to patch test, self-reported hand eczema, or self-reported dry skin in adolescence.

2 | MATERIALS AND METHODS

2.1 | Questionnaire and patch testing

We used information from a population-based birth cohort (BAMSE) in which children recruited in early infancy ($n = 4089$) have been followed up to 16 years of age with repeated questionnaires and clinical examinations.¹³ At age 16 years, the participants answered a Web-based questionnaire including questions on hand eczema, AD, and dry skin. AD at 16 years was defined as self-reported dry skin and itchy rash for >2 weeks with rash in specific locations (face or arm/leg extension surfaces or arm/leg flexures or wrist/ankles or neck) in the last 12 months. The participants were patch tested using the TRUE test (Mekos Laboratories, Hillerød, Denmark) containing three panels of prepared test material (30 substances, including common contact allergens). The test procedure and test substances have been described in detail in a previous publication.¹⁴

2.2 | Filaggrin genotyping

DNA was isolated from blood drawn from patch-tested adolescents and genotyped for the three most common *FLG* mutations in Northern Europe (R501X, R2447X, and 2282del4).¹¹ For all three mutations, TaqMan SNP genotyping assays (Applied Biosystems, Foster City, California) were used. Genotyping was performed in 384-well microtiter plates containing a minimum of 10 ng DNA and TaqMan Master Mix (Applied Biosystems).¹⁵ Thermal cycling conditions were set according to the manufacturer's protocol. Triplicates of all samples were analyzed. Sample genotypes were analyzed using the QuantStudio 6 and 7 Flex Real-Time PCR System software v1.0 (Applied Biosystems).

2.3 | Study population

The study population consisted of all participants who had completed questions regarding symptoms of hand eczema in the 16-year follow-up, had been patch tested, and analyzed for *FLG* mutations ($n = 1822$; Figure 1, Tables 1 and 2). This study was approved by the Regional Ethical Review Board in Stockholm, Sweden (93:189, 2010/1474–31/3). The Declaration of Helsinki principles were followed. All parents and adolescents gave written informed consent to participate in the clinical examinations.

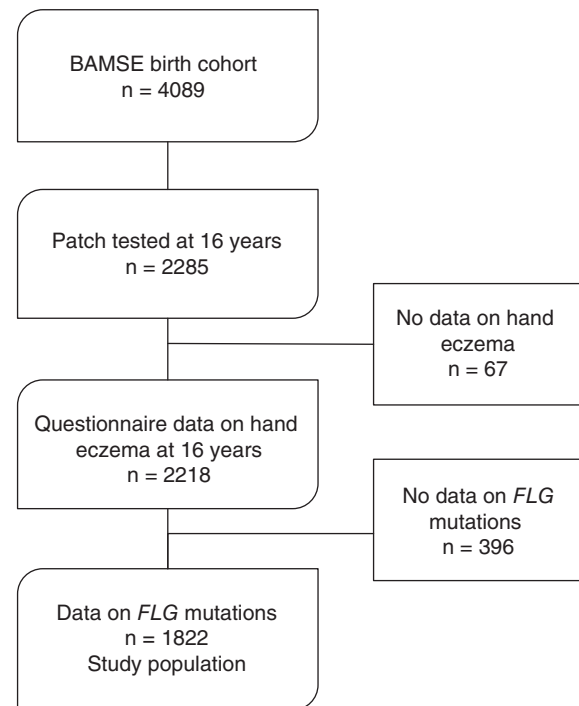


FIGURE 1 Flowchart showing the BAMSE birth cohort (original cohort) and the final study population

2.4 | Statistical analysis

The study population was compared with the original cohort on a number of background characteristics by calculation of proportions with 95% confidence intervals (95%CI). Differences in background characteristics between patch-tested adolescents with and without *FLG* mutations were displayed and calculated with the chi-square test. Differences were considered statistically significant at $P < .05$. Logistic regression analysis was used to assess association between the *FLG* mutations and contact allergy, hand eczema, or dry skin at age 16 years. For assessment of contact allergy, we used three categorizing variables for contact allergy in separate analyses: (i) any contact allergy (contact allergy to one or more of the 30 tested substances), (ii) contact allergy to nickel (the most common contact allergy), and (iii) contact allergy to fragrance mix I (the second most common contact allergy).¹⁴ Hand eczema and dry skin were defined based on self-reports in the Web-based questionnaire at age 16 years. The variables analyzed were 1-year prevalence of hand eczema at 16 years of age, lifetime prevalence of hand eczema, and 1-year prevalence of dry skin at 16 years of age (defined in Table 3). Crude analyses were performed and, in addition, analyses with adjustment for potential confounders that changed the odds ratio (OR) estimate >5% (parental atopic disease, parental smoking, and parental migration) were performed. Results are presented as OR with 95%CI. As a sensitivity analysis, we investigated the interaction between *FLG* mutations and self-reported AD at 16 years or self-reported dry skin at 16 years. In addition, we performed analyses of *FLG* mutations and any contact allergy stratified by AD or dry skin at 16 years. All analyses were performed with STATA statistical software (release 13, Stata-Corp, College Station, Texas).

TABLE 1 Comparison between the original cohort and the study population

Background factors	Original cohort (n = 4089)	Study population (n = 1822)	
	n (%)	n (%)	95%CI
Male sex	2065/4089 (50.5)	855/1822 (46.9)	44.6-49.2
Parental atopic disease ^a	1746/4045 (43.2)	815/1803 (45.2)	42.9-47.5
Parental smoking ^b	855/4067 (21.0)	349/1811 (19.3)	17.5-21.1
Socioeconomic status ^c : white-collar worker	3323/4018 (82.7)	1524/1793 (85.0)	83.3-86.7
Young mother ^d	319/4088 (7.8)	127/1822 (7.0)	5.8-8.1
Parental migration status ^e	543/3398 (16.0)	279/1736 (16.1)	14.3-17.8
Exclusive breastfeeding ≥4 months	3116/3919 (79.5)	1448/1786 (81.1)	79.3-82.9

Note: Statistically significant differences are in bold.

Abbreviation: CI, confidence interval.

^aSelf-reported doctor's diagnosis of asthma and asthma medication and/or doctor's diagnosis of hay fever in combination with furred pets and/or pollen allergy and/or doctor's diagnosis of atopic dermatitis at baseline in any parent.

^bMother or father smoked at least one cigarette daily.

^cWhite-collar worker parent in household at baseline, socioeconomic groups according to Statistics Sweden based on occupation: manual workers (blue collar), non-manual employees (white collar), and employers.

^dMother's age below 25 years at birth of the child.

^eAny parent born outside Sweden, Norway, Denmark, or Finland.

TABLE 2 Selected background factors and outcomes in patch-tested adolescents with or without filaggrin gene (FLG) mutations

	No FLG mutations (n = 1695)		FLG mutations (n = 127)		P-value
	n	%	n	%	
Background factors ^a					
Male sex	802/1695	47.3	53/127	41.7	.22
Parental atopic disease ^b	750/1678	44.7	65/125	52.0	.11
Parental smoking ^c	325/1685	19.3	24/126	19.0	.95
Socioeconomic status ^d : white-collar worker	1414/1666	84.9	110/127	86.6	.60
Parental migration status ^e	269/1615	16.7	10/121	8.3	.015
Exclusive breastfeeding ≥4 months	1340/1660	80.7	108/126	85.7	.17
Young mother ^f	123/1695	7.3	4/127	3.1	.08
Atopic dermatitis at 16 years ^g	132/1674	7.9	15/125	12	.11
Outcomes					
Any contact allergy at 16 years ^h	253/1695	14.9	21/127	16.5	.63
1-Year prevalence of hand eczema ^g	96/1695	5.7	8/127	6.3	.77
Lifetime prevalence of hand eczema at 16 years ^g	178/1695	10.5	11/127	8.7	.51
1-Year prevalence of dry skin at 16 years ^g	646/1687	38.3	62/127	48.8	.02

Note: P-values obtained from the chi-square test; Statistically significant differences in bold.

^aValues for 0%-5% of the background factors were missing.

^bSelf-reported doctor's diagnosis of asthma and asthma medication and/or doctor's diagnosis of hay fever in combination with furred pets and/or pollen allergy and/or doctor's diagnosis of atopic dermatitis at baseline in any parent.

^cMother or father smoked at least one cigarette daily.

^dWhite-collar worker parent in household at baseline, socioeconomic groups according to Statistics Sweden based on occupation: manual workers (blue collar), non-manual employees (white collar), and employers.

^eAny parent born outside Sweden, Norway, Denmark or Finland.

^fMother <25 years at birth of child.

^gSelf-reported by adolescent at 16 years in questionnaire.

^hAccording to patch test at 16 years.

	FLG mutation			
	No (n = 1695) ^a		Yes (n = 127) ^a	
	n	Adjusted OR (95% CI)	n	Adjusted OR (95% CI)
Contact allergy at 16 years ^b				
Any contact allergy	253	1.00 (ref.)	21	1.05 (0.62-1.76)
Nickel allergy	122	1.00 (ref.)	8	0.82 (0.37-1.80)
Fragrance allergy ^c	33	1.00 (ref.)	4	1.77 (0.61-5.14)
Hand eczema ^d				
1-year prevalence at 16 years ^d	96	1.00 (ref.)	8	1.06 (0.48-2.34)
Lifetime prevalence ^e	178	1.00 (ref.)	11	0.80 (0.41-1.56)
Dry skin ^f (N = 1814) ^a	No (n = 1687) ^a		Yes (n = 127) ^a	
1-year prevalence at 16 years	646	1.00 (ref.)	62	1.50 (1.02-2.15)

Note: Adjusted for parental atopic disease, parental smoking, and parental migration changing OR > 5%. Results from crude logistic regression analysis are shown in Table S1. Statistically significant result is presented in bold.

Abbreviations: CI, confidence interval; FLG, filaggrin gene; OR, odds ratio; ref., reference.

^aN and n for dry skin at 16 years are corrected due to missing values in the analysis.

^bAccording to patch test at 16 years.

^cFragrance mix I.

^dAn affirmative answer to the question, "Have you had hand eczema on any occasion during the past 12 months?"⁵

^eAn affirmative answer to the question, "Have you ever had hand eczema (itching eruption, vesicles or itching rash)?"⁵

^fAccording to questionnaire at 16 years, an affirmative answer to the question, "Have you in the past 12 months had problems with dry skin?"

TABLE 3 Results from adjusted logistic regression analysis of association between filaggrin gene (FLG) mutations and contact allergy at 16 years of age, FLG mutations and hand eczema at 16 years or ever, and FLG mutations and dry skin at 16 years

3 | RESULTS

The study population (n = 1822, 44.6% of the original cohort) was comparable with the original cohort (N = 4089) in terms of background characteristics. Small, but statistically significant differences were found for sex and socioeconomic status (Table 1).

The overall prevalence of the assessed FLG mutations was 7.0% (n = 127). Comparisons of background characteristics in relation to these mutations showed that having a parent born outside Sweden, Norway, Denmark, or Finland was more common among participants without FLG mutations than among those with FLG mutations (16.7% vs 8.3%, $P = .015$). No other statistically significant differences were found (Table 2). All individuals with FLG mutations included in this study were heterozygous for these mutations.

3.1 | FLG mutations and contact allergy, hand eczema, or dry skin at 16 years of age

The prevalence of contact allergy and hand eczema among individuals with FLG mutations was comparable with that among individuals without FLG mutations. In contrast, the prevalence of dry skin was somewhat higher among individuals with FLG mutations (Table 2). Adjusted logistic regression analysis showed no significant association between FLG mutations and any contact allergy, nickel allergy, or fragrance mix I allergy at 16 years of age (Table 3). Furthermore, FLG mutations

were not associated with 1-year prevalence of hand eczema at 16 years of age or with ever having hand eczema, but FLG mutations were associated with an increased OR for dry skin at 16 years of age (Table 3). Corresponding results from crude logistic regression analysis are presented in Table S1.

Adjusted logistic regression analysis restricted to participants with both parents born in Sweden, Norway, Denmark, or Finland (n = 1457) was also performed. These results indicate lower ORs for nickel allergy and lifetime prevalence of hand eczema, and higher OR for fragrance allergy. No ORs were statistically significant due to the limited number of events. Details are presented in Table S2. Among the remaining participants who reportedly had any parent born outside Sweden, Norway, Denmark, or Finland, 37% (n = 102) had both parents born in other European countries and 63% (n = 177) had any parent born outside Europe (ie, a considerable majority of the adolescents had both parents born in Europe).

3.2 | Sensitivity analyses

When the analysis of FLG mutations and any contact allergy was stratified for AD at 16 years, we observed a tendency toward an increased OR for contact allergy among adolescents with AD (adjusted OR 2.84, 95% CI 0.87-9.21); however, the analysis was based on the small number of adolescents who had both contact allergy and FLG mutations (n = 6). In contrast, no apparent association was observed among

adolescents without AD (adjusted OR 0.79, 95% CI 0.43-1.48). The *P*-value for interaction between AD and *FLG* mutation was .07.

In a similar manner, we stratified the analyses for dry skin at 16 years. There was no significant difference between the observed ORs among adolescents with or without dry skin (adjusted OR 1.46, 95% CI 0.72-2.95 and adjusted OR 0.69, 95% CI 0.31-1.56, respectively, *P*-value for interaction = .11). This stratified analysis is also based on a limited number of events.

4 | DISCUSSION

Our results from a population-based cohort showed an association between *FLG* mutation and self-reported dry skin at 16 years. However, the results did not indicate any consistent associations between *FLG* mutation and contact allergy or hand eczema in adolescence.

AD is known to be one of the most important risk factors for hand eczema in the general population.^{7,16} The association has also been shown among adolescents and a strong association was found in the BAMSE cohort at the 16-year follow-up.^{4,17} Other well-known risk factors for hand eczema in adulthood are contact allergy and wet work. These factors may have great impact on the occurrence of hand eczema in adulthood, when occupational and non-occupational exposure to contact allergens as well as to water and other skin irritants may be massive.^{18,19} We suggest that adolescence may be a poorly suited time for assessment of a possible association between *FLG* mutation and expected lifetime contact allergy, because contact allergy in adolescence reflects skin exposures during childhood and adolescence only. Even though skin exposures related to adornment behaviors may be substantial in adolescence, occupational and non-occupational exposure to contact allergens and skin irritants is limited at that age, and the exposures have lasted for a relatively short period compared with exposure of adults.^{18,20-22} In a previous study within the BAMSE cohort, no statistically significant exposure differences were found concerning self-reported water exposure to the hands among adolescents in relation to AD or hand eczema.²²

Despite the strength of having a large study with 1822 patch-tested adolescents, we have not been able to show associations between *FLG* mutation and contact allergy or hand eczema. However, *FLG* mutations may be a risk factor for contact allergy and/or hand eczema owing to the impaired skin barrier and thus a higher risk of use of moisturizers, topical drugs, and rubber gloves that often contain contact allergens.²³⁻²⁵ Based on human and animal studies, it is also well-known that an impaired skin barrier facilitates penetration of substances, and that skin sensitization is enhanced by exposure of inflamed skin (eg, dermatitis) and occluded skin (eg, by diapers and gloves).^{26,27}

The higher occurrence of having a parent born outside Sweden, Norway, Denmark, or Finland among participants without the assessed *FLG* mutations in our study may be explained by the fact that other types of *FLG* mutations are prevalent outside Europe, while our study assessed the mutations most common here.²⁸

Association between *FLG* mutation and nickel allergy among adults in the general population has been studied with conflicting

results; two studies based on selected participants (an enriched sample with atopic diseases in Germany, and a small subsample of non-pierced individuals in Denmark, respectively) indicated an association.^{29,30} No association between *FLG* mutation and nickel allergy, however, was indicated when all participants (regardless of piercing) were included.³⁰ Our study among unselected adolescents is thus not directly comparable with these studies.

We observed a tendency toward an association between *FLG* mutation and an increased OR for any contact allergy among adolescents with AD at 16 years. Our finding is in line with the findings from another study of the aforementioned Danish population, which indicated that *FLG* mutations were associated with contact allergy to substances other than nickel among adults with self-reported AD.³¹

Moreover, results from a 5-year follow-up of the aforementioned Danish population indicate that *FLG* mutations are associated with persistent, but not incident, hand eczema among individuals with a history of AD.³² In the TOACS cohort in Denmark the most common location of AD was the hands among participants with persistent AD and 60% of these participants had the onset of hand eczema after 18 years of age.³³ Individuals with AD have an impaired skin barrier and they may have high exposure to topical treatments. A previous study from our cohort indicated a possible association between AD at preschool age and contact allergy to fragrance substances in adolescence.³⁴ The interplay between *FLG* mutations, contact allergy, and hand eczema is complex and influenced by age and several other cofactors such as presence or absence of AD.³⁵ In contrast, the association between *FLG* mutation and dry skin has been consistently described in children as well as in adults in various populations.^{2,8,11}

In conclusion, the results from our study show that *FLG* mutation is associated with dry skin at 16 years. The results do not indicate that *FLG* mutations are associated with contact allergy or hand eczema at 16 years, which might be explained by the participants' relatively low age and limited skin exposure to contact allergens and skin irritants.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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Supporting Information

Filaggrin gene mutations in relation to contact allergy and hand eczema in adolescence

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Table S1. Results from crude logistic regression analysis of association between filaggrin gene (*FLG*) mutations and contact allergy at 16 years of age, *FLG* mutations and hand eczema at 16 years or ever, and *FLG* mutations and dry skin at 16 years

	<i>FLG</i> mutation			
	No (n = 1695) ^a		Yes (n = 127) ^a	
	n	Crude OR (95%CI)	n	Crude OR (95%CI)
Contact allergy at 16 years^b				
Any contact allergy	253	1.00 (ref.)	21	1.13 (0.69-1.84)
Nickel allergy	122	1.00 (ref.)	8	0.87 (0.41-1.82)
Fragrance allergy ^c	33	1.00 (ref.)	4	1.64 (0.57-4.70)
Hand eczema^d				
1-year prevalence at 16 years ^e	96	1.00 (ref.)	8	1.12 (0.53-2.36)
Lifetime prevalence ^f	178	1.00 (ref.)	11	0.81 (0.43-1.53)
Dry skin^g (N = 1814)^a				
	No (n = 1687) ^a		Yes (n = 127) ^a	
1-year prevalence at 16 years	646	1.00 (ref.)	62	1.54 (1.07-2.21)

Abbreviations: *FLG*: filaggrin gene; OR: odds ratio; CI: confidence interval.

^aN and n for dry skin at 16 years are corrected due to missing values in the analysis.

^bAccording to patch test at 16 years.

^cFragrance mix I.

^dAccording to questionnaire at 16 years.

^eAn affirmative answer to the question, 'Have you had hand eczema on any occasion during the past 12 months?'⁵.

^fAn affirmative answer to the question, 'Have you ever had hand eczema (itching eruption, vesicles or itching rash)?'⁵.

^gAccording to questionnaire at 16 years, an affirmative answer to the question, 'Have you in the past 12 months had problems with dry skin?'

Statistically significant results in bold.

Table S2. Results from adjusted logistic regression analysis of association between filaggrin gene (*FLG*) mutations and contact allergy at 16 years of age, *FLG* mutations and hand eczema at 16 years or ever, and *FLG* mutations and dry skin at 16 years. Analysis restricted to participants with both parents born in Sweden, Norway, Denmark or Finland

	<i>FLG</i> mutation			
	No (n = 1346) ^a		Yes (n = 111) ^a	
	n	Adjusted OR (95%CI)	n	Adjusted OR (95%CI)
Contact allergy at 16 years^b				
Any contact allergy	188	1.00 (ref.)	16	0.97 (0.55-1.70)
Nickel allergy	92	1.00 (ref.)	6	0.65 (0.26-1.62)
Fragrance allergy ^c	25	1.00 (ref.)	4	1.96 (0.67-5.75)
Hand eczema^d				
1-year prevalence at 16 ^e	73	1.00 (ref.)	8	1.16 (0.52-2.58)
Lifetime prevalence ^f	135	1.00 (ref.)	9	0.70 (0.33-1.46)
Dry skin^g (N = 1453)^a				
	No (n = 1342) ^a		Yes (n = 111) ^a	
1-year prevalence at 16	506	1.00 (ref.)	52	1.41 (0.95-2.08)

Abbreviations: *FLG*: filaggrin gene; OR: odds ratio; CI: confidence interval.

Adjusted for parental atopic disease and parental smoking changing OR > 5%.

^aN and n for dry skin at 16 years are corrected due to missing values in the analysis.

^bAccording to patch test at 16 years.

^cFragrance mix I.

^dAccording to questionnaire at 16 years.

^eAn affirmative answer to the question, 'Have you had hand eczema on any occasion during the past 12 months?'⁵.

^fAn affirmative answer to the question, 'Have you ever had hand eczema (itching eruption, vesicles or itching rash)?'⁵.

^gAccording to questionnaire at 16 years, an affirmative answer to the question, 'Have you in the past 12 months had problems with dry skin?'