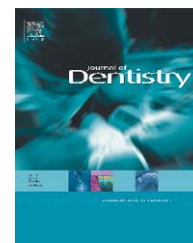


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Latex allergy and filaggrin null mutations

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ABSTRACT

Objectives: Natural rubber latex (NRL) contains over 200 proteins of which 13 have been identified as allergens and the cause of type I latex allergy. Health care workers share a high occupational risk for developing latex allergy. Filaggrin null mutations increase the risk of type I sensitizations to aeroallergens and it is possible that filaggrin null mutations also increase the risk of latex allergy. The aim of this paper was to examine the association between filaggrin null mutations and type I latex allergy.

Methods: Twenty latex allergic and 24 non-latex allergic dentists and dental assistants, occupationally exposed to latex, were genotyped for filaggrin null mutations R501X and 2282del4. Latex allergy was determined by a positive reaction or a historical positive reaction to a skin prick test with NRL.

Results: 41 individuals were successfully genotyped. Three individuals were filaggrin mutation carriers. One (2.4%) was a 2282del4 heterozygote and two (4.9%) were R501X heterozygote. No homozygote or compound heterozygote carriers were detected. No association between filaggrin null mutations and type I latex allergy was found ($p = 0.24$). Patients with type I latex allergy more often reported contact dermatitis.

Conclusions: This is the first study to examine a highly plausible association between filaggrin null mutations and type I latex allergy. The study subjects were occupationally exposed to latex but no association between latex allergy and filaggrin mutations were detected. Sensitization to latex in the cases in this study may not have occurred through direct skin contact but through the respiratory organs via latex proteins that are absorbed in glove powder and aerosolized.

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1. Introduction

Natural rubber latex (NRL) is a significant allergen capable of causing a wide spectrum of allergic responses ranging from contact dermatitis to allergic contact urticaria to a poten-

tially life-threatening hypersensitivity.¹ Type I latex hypersensitivity ("latex allergy") is an IgE antibody-mediated reaction to the protein antigens inherent in NRL. The user is exposed to these proteins through direct skin contact or from airborne powdering agents found in some NRL

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products such as gloves, masks and eyewear.² This systemic reaction may also be known as an immediate hypersensitivity, and can involve the skin, respiratory tract, gastrointestinal tract, and the cardiovascular system. Reactions can include rash, coughing, wheezing, chest tightness, and dyspnoea. Type IV hypersensitivity is an acquired immune reaction mediated by skin-localized T cells. Also known as delayed hypersensitivity, it is often caused by the processing chemicals found in natural and synthetic rubber products.

Health care workers in dentistry and medicine share a high occupational risk for developing both delayed and/or immediate hypersensitivity. Studies estimate the prevalence of immediate NRL hypersensitivity in healthcare workers to range between 3% and 17.9% depending on the population studied, the definition of sensitization used, and the selection criteria for inclusion of subjects in the study.^{3–7} Data regarding the general population indicate that the prevalence of type I latex allergy in the general population was between 1% and 4%.^{7,8}

Filaggrin is a skin protein which plays an essential role in establishing the cornified envelope in the uppermost part of the epidermis.⁹ The cornified envelope constitutes the skin barrier providing protection against exogenous noxious agents and microbes. Null mutations in the filaggrin gene result in lack of production of filaggrin.⁹ Filaggrin-deficient skin is dysfunctional with increased transepidermal water loss and increased penetration of protein allergens.¹⁰ It is known, that filaggrin null mutations increase the risk of allergic type I sensitization to aeroallergens, allergic rhinitis, and asthma in combination with atopic dermatitis.¹¹ Filaggrin is not expressed in the conjunctiva, respiratory epithelium, bronchial or esophageal mucosa.^{12–14} Therefore, it has been proposed that the allergic diseases develop because of penetration of protein allergens through the skin. The possible association between latex allergy and filaggrin mutations has to our knowledge not yet been examined.

The objective of this study was to examine whether filaggrin null mutations increase the risk of type I latex allergy. Twenty type I latex allergic subjects, as assessed by medical history and outcome of skin prick testing, and 24 non-type I latex allergic individuals were genotyped for filaggrin null mutations R501X and 2282del4. The current study is of relevance as filaggrin null mutations are prevalent in the general population^{15,16} and an association with latex allergy could have great implications for the counselling of individuals with filaggrin null mutations including health care workers.

2. Materials and methods

The study population consisted of 20 subjects with latex allergy and 24 controls without latex allergy recruited from an American population of dentists and dental assistants. For this study a latex allergy is defined as a type I hypersensitivity as determined by (1) a positive skin prick test with NRL (Stallergenes latex eluant®) or (2) had a medical history with a positive reaction to skin prick test with NRL at the time of the blood draw. The controls all had a negative skin prick test to

NRL at the time of the blood draw. Thirty eight out of the 44 individuals had answered a health screening questionnaire related to their occupational and allergic history including latex exposure.

Filaggrin mutation R501X is represented in the Caucasian and Asian race¹⁷. 2282del4 is represented in the Caucasian race¹⁷. Three individuals were not of Asian or Caucasian ethnicity and were therefore excluded from further analysis.

Venous blood samples were collected from each participant and genotyped for the filaggrin null mutations R501X and 2282del4. The genotyping assay was based on polymerase chain reaction (PCR) followed by typing through hybridization to mutation and wildtype specific microbeads (Luminex, Austin, TX, USA) and analysed on a BioPlex 200 (Biorad, Hercules, CA, USA). For each individual, two blood samples were examined. Genotyping results based on blood samples from the same individual matched for all participants. Genotyping was performed at Department of Clinical Biochemistry, Copenhagen University Hospital Gentofte, Denmark.

Association between filaggrin null mutations and latex allergy was estimated using the chi square test and Fisher exact test when appropriate. Comparison of characteristics for, respectively, latex-allergic and non-latex allergic individuals, and filaggrin null mutation carriers and wildtype individuals, were also performed with chi square tests. Comparison of mean years in dental practises was examined by independent samples T tests. Assumptions of normality were checked by Kolmogorov–Smirnov tests and assumption of equal variances by Levenés test. A *p* value of 0.05 was regarded as significant.

3. Results

Forty-one individuals were successfully genotyped. Three (7.3%) individuals were filaggrin null mutation carriers. One (2.4%) was a 2282del4 heterozygote and two (4.9%) were R501X heterozygote. No homozygote or compound heterozygote carriers were detected.

Characteristics for cases and controls are represented in Table 1 and for filaggrin mutation and wildtype genotypes in Table 2. A significantly higher proportion of individuals with latex allergy reported allergic reactions to gloves and reported itching, swelling and burning as symptoms of latex sensitivity (Table 1). Individuals with latex allergy had been practising for the same amount of time in dental practice as non-latex allergic individuals. Twenty-nine percent of latex allergic individuals still used latex gloves in comparison to 90% of non-latex allergic individuals (*p* < 0.001). Latex allergic individuals more often reported contact dermatitis.

None of the three individuals with a filaggrin null mutation had latex allergy. Two were dentists: one was a dental assistant. They did not report contact dermatitis or eczema. Eczema in this study refers to dermatitis without specification. The total number of years in a dental practice was the same for mutation carriers and wildtype individuals. Two mutation carriers reported using latex gloves. No information on glove use was available for the third mutation carrier.

Table 1 – Characteristics of latex-allergic individuals and non-latex allergic individuals.

	Presence of latex allergy n = 18	Absence of latex allergy n = 23	Chi square test p value
Male sex	9/15 (60.0%)	13/19 (68.4%)	0.61
Occupation			
Dentist	14/18 (77.8%)	20/23 (87.0%)	0.68
Dental assistant	4/18 (22.2%)	3/23 (13.0%)	
Years in dental practice			
Mean ± SD	26.1 ± 11.0 years	26.7 ± 10.3 years	0.83*
Ethnicity			
Asian	1/18 (5.6%)	4/23 (17.4%)	
Caucasian	12/18 (66.7%)	14/23 (60.9%)	
Missing information	5/18 (27.8%)	5/23 (21.7%)	
Contact dermatitis	8/15 (53.3%)	3/17 (17.6%)	0.03
Eczema ^a	2/15 (13.3%)	2/17 (11.8%)	1.00
Self-reported allergic reaction to gloves	10/15 (66.7%)	4/18 (22.2%)	0.01
Symptoms of latex sensitivity			
Itching	11/15 (73.3%)	5/18 (27.8%)	0.009
Swelling	7/14 (50.0%)	2/18 (11.1%)	0.02
Cracking	8/15 (53.3%)	4/18 (22.2%)	0.06
Burning sensation	7/15 (46.7%)	1/18 (5.6%)	0.01
Rash	8/15 (53.3%)	5/18 (27.8%)	0.14
Hives	4/15 (26.7%)	1/18 (5.6%)	0.15
Rhinoconjunctivitis	5/15 (33.3%)	1/18 (5.6%)	0.07
Bronchospasm	1/15 (6.7%)	0/18	0.46
Hypotension	1/15 (6.7%)	0/18	0.46
Anaphylaxis	1/15 (6.7%)	0/18	0.46
Current use of gloves			
Latex	4/14 (28.6%)	17/19 (89.5%)	<0.001
Filaggrin null mutation status			
R501X/2282del4 combined	0/18 (0%)	3/23 (13.0%)	0.24

^a Eczema refers to dermatitis without specification.
* T-test, equal variances assumed.

Table 2 – Characteristics of R501X/2282del4 mutation carriers and wildtype individuals.

	R501X/2282del4 n = 3	Wildtype n = 38	p value
Male sex ^a	1/2 (50%)	21/32 (65.6%)	1.00
Occupation			
Dentist	2/3 (66.7%)	32/38 (84.2%)	0.44
Dental assistant	1/3 (33.3%)	6/38 (15.8%)	
Years in dental practice ^a			
Mean ± SD (years)	28 ± 2.8 years	26.4 ± 10.8 years	0.84*
Self-reported reaction to gloves ^a	0/2	14/31 (45.2%)	0.50
Contact dermatitis ^a	0/2	11/30 (36.7%)	0.53
Eczema ^a	0/2	4/30 (13.3%)	1.00
Gloves ^a			
Latex	2/2 (100%)	19/31 (61.3%)	0.52

^a Information on sex, years in dental practice, self-reported reaction to gloves, contact dermatitis, eczema and glove use was no available for one mutation carrier.
* T-test, equal variances assumed.

4. Discussion

Surprisingly, none of the individuals with filaggrin null mutations had a type I latex allergy. Natural rubber latex consists of over 200 proteins of which 13 have been identified as allergens and the cause of type I (immediate) latex allergy.¹ Protein allergens have been shown to penetrate filaggrin-deficient skin resulting in both localized and systemic

inflammatory responses.¹⁰ It has also been shown that type I sensitization to aeroallergens is positively associated with filaggrin null mutations¹¹ despite the fact that filaggrin is not expressed in conjunctiva, respiratory epithelium, or bronchial mucosa.^{12–14} Theoretically, type I latex allergy might also be associated with filaggrin mutations due to the direct skin exposure via gloves and the defect skin barrier because of lack of filaggrin with decreased resistance to exogenous noxious

agents. Despite the theoretical plausibility, we were not able to detect any association between filaggrin null mutations and type I latex allergy. The subjects in this study may not have been sensitized to latex through skin exposure but alternatively through the respiratory organs from airborne protein-containing glove powder.

Individuals with a filaggrin null mutation were all heterozygote for either R501X or 2282del4 that means that they carry one “healthy” gene and therefore still have some production of filaggrin, albeit reduced. Additionally, given that even filaggrin-deficient skin still provides a substantial barrier to infection and other insults, it may be that under the conditions of NRL glove use for these heterozygote individuals, the skin barrier was simply not enough affected for an increased risk of type I latex allergy to appear.

Individuals with type I latex allergy reported classic symptoms of latex allergy, increasing the relevance of the skin prick results. All allergic subjects and controls were dentists or dental assistants; occupations with the potential for great exposure to latex protein antigens via glove use. All filaggrin mutation carriers reported use of latex gloves which excluded lack of exposure as a possible explanation for no association. Additionally, the years of potential exposure to latex, measured as years in dental practice did not deviate between individuals with or without filaggrin mutations.

Filaggrin mutations increase the risk of the dermatological disease atopic dermatitis and possibly also the risk of two other dermatological diseases irritant and allergic contact dermatitis^{11,18,19}; however, none of the filaggrin mutation carriers reported eczema or contact dermatitis. Previous events of dermatitis could have resulted in behavioural changes with a tendency towards choosing gloves with reduced protein or powder content or increased frequency of hand washing following glove use. This did not seem to be the case for the individuals with filaggrin mutations who still used latex gloves.

Both filaggrin null mutation carriers and wildtype individuals had on average practised dentistry for more than 20 years. Individuals who experienced skin problems may have stopped working at an earlier stage, and this “healthy worker” effect might also explain why no association was found.

Individuals with type I latex allergy diagnosed by skin prick test more often reported contact dermatitis. It is well known that NRL can cause both type I and type IV hypersensitivity¹ and these data might reflect that patients with type I allergy are also prone to develop simultaneous type IV allergy. However, contact dermatitis covers both irritant contact dermatitis where no hypersensitivity reaction is involved and allergic contact dermatitis where the underlying pathogenesis is a type IV hypersensitivity. The study subjects were not patch tested with NRL and therefore a distinction between irritant and allergic contact dermatitis cannot be made. Filaggrin mutations have, however, been associated with both irritant as well as allergic contact dermatitis,^{18,19} albeit not examined in relation to latex-specific type IV hypersensitivity. The increased prevalence of contact dermatitis amongst patients with type I latex allergy could therefore have biased the results if a positive relation had been found. On the other hand, skin damage in relation to contact dermatitis caused by environmental risk factors such as long-lasting glove use

might have increased the possibility of a type I allergy in itself and outbalanced any possibility of detecting genetic predisposing factors as risk factors for type I latex allergy.

5. Conclusions

This is the first study to examine a highly plausible association between the presence of filaggrin null mutations and latex allergy. The study subjects were dentists and dental assistants occupationally exposed to latex but no association was detected between type I latex allergy and the filaggrin null mutations tested for. Due to the small study size, the results need to be confirmed in larger study populations.

Conflict of interest

Curt Hamann is an owner of SmartPractice which distributes latex and synthetic gloves; there is no economic benefit however, from this study.

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