

Common Filaggrin Null Alleles Are Not Associated with Hymenoptera Venom Allergy in Europeans

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Key Words

Hymenoptera allergy · Atopic dermatitis · Filaggrin · Gene

Abstract

The association of filaggrin mutations with atopic eczema (atopic dermatitis, AD) is well established and it is thought that filaggrin dysfunction impairs the skin's barrier function allowing allergen penetration and subsequent cutaneous sensitisation and inflammation. However, as most forms of barrier dysfunction are not associated with allergic sensitisation to common allergens, the possibility that filaggrin itself is involved in Th1/Th2 polarisation remains. We tested the hypothesis that allergen delivered to the skin independently of the stratum corneum is not associated with filaggrin mutations. Wasp stings bypass the stratum corneum and deliver antigen to the dermis. We found that European individuals with AD (n = 32) have an increased frequency of the 2 commonest filaggrin null mutations (R501X and 2282del4) compared to those with vespid allergy (n = 56) and healthy controls (n = 30). Thus, filaggrin does not appear to have a downstream effect on the development of allergic disease, and it is indeed filaggrin's role in the epithelial function that is likely to determine the link between filaggrin mutations and allergic sensitisation.

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Introduction

Null mutations in filaggrin are associated with atopic eczema (atopic dermatitis, AD) and with asthma when present with AD [1]. The two most common mutations in Europeans, R501X and 2282del4, confer susceptibility to AD with a reported OR of 3.52 from a recent meta-analysis [1] and account for 11% of the susceptibility to AD [2]. However, the presence of heterozygous filaggrin null mutations carries a variable clinical phenotype from normal through to severe disease. Other modifying factors are therefore involved, which are likely to include the innate and adaptive immune responses [3–5]. The prevailing disease model is that filaggrin insufficiency results in barrier dysfunction of the skin, which predisposes to allergen penetration, sensitisation and cutaneous inflammation. This results in further barrier dysfunction [3, 6]. However, whilst this is a plausible model, most forms of barrier dysfunction do not lead to sensitisation to common allergens. Thus, it remains possible that filaggrin itself is involved directly in Th1/Th2 polarization. We sought to test the hypothesis that sensitisation to an allergen delivered to the skin, independent of the stratum corneum, is not associated with common filaggrin null mutations.

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Table 1. Characteristics of patients with atopic dermatitis and vespid allergy and healthy controls

	Vespid allergy	Atopic dermatitis	Healthy controls
Sex			
Male	35 (64.8%)	17 (53.1%)	17 (57%)
Female	19 (35.2%)	15 (46.9%)	13 (43%)
Age, years (mean $\pm$ SD)	54 $\pm$ 11.04	50 $\pm$ 16.34	42 $\pm$ 13.09
History of atopic dermatitis, hay fever or asthma	16 (30%)	32 (100%)	8 (27%)
History of atopic dermatitis	4 (7%)	32 (100%)	0
History of hay fever	10 (19%)	16 (50%)	5 (25%)
History of asthma	6 (11%)	20 (63%)	2 (6.7%)

Table 2. Filaggrin mutations in atopic dermatitis, vespid allergy and healthy control groups

	R501X and 2282del4 mutations absent		R501X or 2282del4 mutations present	
	count	row n, %	count	row n, %
Vespid allergy	56	100.0	0	0
Atopic dermatitis	25	78.1	7	21.9
Healthy control	30	100.0	0	0

Individuals with atopic dermatitis have an increased frequency of filaggrin mutations (R501X or 2282del4) compared to those with vespid allergy and healthy controls.

Wasp stings typically bypass the stratum corneum and deliver antigen into the dermis with an average sting length of 1 mm [7]. Wasp venom-allergic patients therefore represent an excellent group to potentially dissect the relative contributions of barrier dysfunction and systemic Th2 susceptibility in developing sensitisation.

Materials and Methods

Fifty-six adult wasp-allergic European individuals with a history of systemic reactions to wasp venom and with elevated wasp venom-specific IgE and positive skin prick tests were recruited. Thirty-two adult European patients with moderate-severe atopic eczema were recruited with clinical features that satisfied the UK refinements of the Hanifin and Rajka diagnostic criteria [8]. Thirty healthy adult European controls without a history of eczema or wasp venom reactivity were also recruited. The common filaggrin null mutations identified in European populations, R501X and 2282del4, were detected by restriction fragment length polymorphism after PCR from genomic DNA as previ-

ously described [9]. Fisher's exact test was used to determine the significance of the association between the different groups and filaggrin mutations and was calculated using SPSSv16 statistical software.

Results

Patient characteristics are detailed in table 1 and show that the groups are similar for age and sex. The prevalence of hay fever and asthma was determined by history alone and was similar in the vespid-allergic group and the healthy controls. We observed that 7% of the vespid-allergic patients gave a history of mild eczema, 19% a history of hay fever and 11% a history of asthma. The AD population had a higher frequency of hay fever and asthma, 50 and 63%, respectively. 25% of the controls had a history of hay fever and 6.7% had asthma.

Seven of the 32 AD patients had filaggrin mutations: 2 were heterozygous for the 2282del4 mutation and 2 heterozygous for the R501X mutation; 2 had homozygous R501X mutations, and there was 1 compound heterozygote to give an overall prevalence of 21.9% (table 2). Interestingly, we were unable to detect any individuals with either of the two mutations in vespid-allergic patients or healthy controls. The AD patients therefore had an increased frequency of filaggrin mutations when compared to the wasp-allergic patients and the healthy controls ($p = 0.001$ and $p = 0.035$, respectively, using Fisher's exact test; table 2). Although hay fever and asthma were found in all 3 study groups, filaggrin mutations were only found in the AD group, which is consistent with previous reports showing that the association of filaggrin mutations with asthma and hay fever only occurs in the context of eczema [1, 10].

Our inability to detect any individuals with filaggrin mutations in our control group contrasts a prevalence of 6–11% for filaggrin loss of function mutations in unselected adult populations [11, 12]. It is possible that the lack of filaggrin mutations in our control group reflects our exclusion of individuals with eczema from this group. However, it is more likely that the lack of filaggrin mutations in both the control and vespid allergy groups is due to the relatively small sample sizes, even though our 56 patients with vespid venom allergy represent recruitment over at least 5 years through a regional venom allergy clinic and are one of the larger cohorts of vespid-allergic patients within the medical literature.

Discussion

It is now firmly established that null mutations in filaggrin predispose individuals to AD. Yet, less is known about the mechanisms underlying the link between filaggrin mutations and clinical phenotype. These are clearly important questions for identifying future approaches to treatment. Furthermore, most forms of barrier dysfunction, such as psoriasis, trauma, burns, and most inherited disorders of keratinization (except ichthyosis vulgaris and Netherton's syndrome) do not typically associate with elevated IgE. This suggests that it is the nature of defects associated with filaggrin mutations that particularly promotes allergic sensitisation. In the current study,

we were able to exclude one possible explanation for this, namely that filaggrin does not appear to have a downstream effect on the development of allergic disease, and that it is indeed filaggrin's role in the epithelial function (e.g. keratin cross-linking, keratinocyte differentiation, hydration) that is likely to determine the link between filaggrin mutations and allergic sensitisation.

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