

## SHORT REPORT

# Individuals who are homozygous for the 2282del4 and R501X filaggrin null mutations do not always develop dermatitis and complete long-term remission is possible

JP Thyssen,<sup>†,\*</sup> BC Carlsen,<sup>†</sup> H Bisgaard,<sup>‡</sup> C Giwercman,<sup>‡</sup> JD Johansen,<sup>†</sup> A Linneberg,<sup>§</sup> M Meldgaard,<sup>¶</sup> PB Szecsi,<sup>¶</sup> S Stender,<sup>¶</sup> T Menne<sup>†</sup>

<sup>†</sup>National Allergy Research Centre, Department of Dermato-Allergology, Gentofte Hospital, University of Copenhagen, Denmark,

<sup>‡</sup>Danish Pediatric Asthma Center, Gentofte Hospital, University of Copenhagen, Denmark, <sup>§</sup>Research Centre for Prevention and

Health, Glostrup Hospital, University of Copenhagen, Denmark, and <sup>¶</sup>Department of Clinical Biochemistry, Gentofte Hospital,

University of Copenhagen, Denmark

\*Correspondence: JP Thyssen. E-mail: jacpth01@geh.regionh.dk

## Abstract

**Background** About 8–10% of the general population in Europe carry a null mutation in the filaggrin gene which is associated with early onset of atopic dermatitis as well as persistence into adulthood. No studies have investigated whether individuals with the homozygous filaggrin null genotype always develop dermatitis.

**Objectives** The aim of this study was to describe the natural history of individuals with no filaggrin expression.

**Materials** Three study populations were included: (i) a random sample of 3335 subjects aged 18–69 years from the general population in Copenhagen who underwent general health examination; (ii) a total of 499 patients seen in our dermatitis clinic since 2009 and who were filaggrin genotyped as a part of the routine diagnostic work up; and (iii) a prospective, longitudinal, birth cohort study of 411 children born to mothers with a history of asthma. Filaggrin genotyping was performed for the 2282del4 and R501X mutations.

**Results** Filaggrin homozygous/compound heterozygous individuals accounted for 0.3% of adults, 3% of dermatitis patients and 0.7% of children. Respectively, one of nine adults and one of three children never experienced dermatitis until now. All hospital patients had atopic dermatitis with onset during (early) childhood. Year-long complete remission was observed in half of patients.

**Conclusions** The natural history of individuals with the filaggrin null genotype is fairly good in the sense that they may not develop dermatitis at all, and if they do, they may experience complete remission.

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## Conflict of interests

The authors have no conflict of interest to disclose.

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## Introduction

About 8–10% of the general population in Europe carry a null mutation in the filaggrin gene<sup>1,2</sup> which is associated with ichthyosis vulgaris, early onset of atopic dermatitis as well as persistence of atopic dermatitis into adulthood.<sup>3–6</sup> Early onset and persistence of atopic dermatitis might be expected as individuals carrying one or more filaggrin null alleles have impaired barrier formation from

birth.<sup>3</sup> One study including unselected children showed that individuals with the infrequently encountered homozygous filaggrin null genotype developed dermatitis more frequently than heterozygous filaggrin null genotype.<sup>7</sup> However, no studies have so far investigated the natural course of dermatitis in homozygous adults. One would expect individuals with no filaggrin expression at all, to develop atopic dermatitis at a very early age and maintain severe chronic disease during life. We attempted to describe the natural history of individuals with no filaggrin expression by using clinical data from children of mothers with asthma and dermatitis

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patients from a tertiary clinic as well as questionnaire data from adults Danes from the general population.

### Materials and methods

Three study populations were included. They were all genotyped for the 2282del4 and R501X filaggrin null mutations. For a detailed method description, please refer to our previous studies.<sup>2,8–11</sup> During 2006–2008, a random sample of 7931 subjects aged 18–69 years from the general population in Copenhagen were invited to participate in a general health examination. A total of 3335 were filaggrin genotyped. Participants completed a questionnaire on health, lifestyle and socioeconomic factors. The questionnaire had a description of eczema. The exact questions used can be seen in Table 1. Atopic dermatitis was defined by the U.K. Working Party's diagnostic criteria for atopic dermatitis as a history of an itchy skin condition plus a minimum of two of four minor criteria.<sup>12</sup> No clinical examination for dermatitis was performed. Serum samples were analysed for IgE specific to birch, grass (timothy), cat and mite (*Dermatophagoides pteronyssinus*) with the ADVIA Centaur (Siemens, Deerfield, IL, USA). Specific

IgE positivity was defined as a positive test to at least one of the four allergens tested. A total of 499 patients seen in our dermatitis clinic since 2009 were filaggrin genotyped as a part of the routine diagnostic work up. Atopic dermatitis and hand dermatitis was diagnosed by dermatologists. Medical charts were reviewed retrospectively. The Copenhagen Prospective Study on Asthma in Childhood (COPSAC) cohort is a prospective, longitudinal, birth cohort study of 411 children born to mothers with a history of asthma, followed up for 11 years with scheduled visits every 6 months as well as visits for acute exacerbations of eczema. The diagnosis of eczema was based on the criteria of Hanifin and Rajka.<sup>13</sup> Of the 411 children, 392 were filaggrin genotyped. IgE antibody levels were determined using the ImmunoCAP assay against a panel of common inhalant and food allergens (Phadia AB, Uppsala, Sweden).<sup>14</sup>

### Results

In the general population, 260 (7.8%) were heterozygous and 9 (0.3%) individuals aged respectively, 19, 33, 42, 44, 49, 57, 58, 65 and 65 years were homozygous/compound heterozygous for the

**Table 1** Characteristics of individuals from the general population with different filaggrin null genotypes (R501X and 2282del4 mutations)

	Wild-type filaggrin n = 3066 % (n)	Heterozygotic filaggrin n = 260 % (n)	Homozygotic filaggrin n = 9 % (n)
Female gender	55.0 (1687)	58.5 (152)	55.6 (5)
Median age (years, range)	48 (18–69)	48 (18–69)	44 (19–65)
Atopic dermatitis*	9.1 (268)	20.2 (50)	66.7 (6)
Specific IgE†	24.0 (737)	21.9 (57)	44.4 (4)
<i>Self-reported:</i>			
Rhinitis	18.0 (542)	17.8 (45)	33.2 (3)
Asthma	10.6 (321)	12.6 (32)	33.3 (3)
Food allergy	4.9 (147)	6.3 (16)	22.2 (2)
Self-reported hand eczema ever	21.3 (645)	25.5 (65)	66.7 (6)
<i>Among subjects with hand eczema:</i>			
Hand eczema within past 12 months	55.2 (354)	41.5 (27)	66.7 (4)
<i>Age at first onset of hand eczema:‡</i>			
<6 years	3.9 (25)	15.6 (10)	66.7 (4)
6–14 years	11.7 (75)	10.9 (7)	0
15–18 years	11.8 (76)	15.6 (10)	33.3 (2)
>18 years	72.6 (467)	57.8 (37)	0
<i>Hand eczema persistence:‡</i>			
One time only (<2 weeks duration)	25.8 (163)	17.5 (11)	20.0 (1)
One time only (>2 weeks)	10.3 (65)	11.1 (7)	0
Several times	56.2 (356)	50.8 (32)	60.0 (3)
Nearly all the time	7.7 (49)	20.6 (13)	20.0 (1)

\*Atopic dermatitis was defined by the U.K. Working Party's diagnostic criteria for atopic dermatitis as a history of an itchy skin condition plus a minimum of two of four minor criteria.<sup>12</sup>

†Analysis for IgE specific to birch, grass (timothy), cat, and mite (*Dermatophagoides pteronyssinus*). The analysis was judged to be positive if the measurement was in excess of 0.35 kU/L.

‡A few subjects who gave an affirmative answer to the question about ever having experienced hand eczema did not respond to the questions about first onset and persistence of hand eczema. This explains the missing data.

filaggrin null genotype (Table 1). Homozygous individuals tended to have the highest prevalence of self-reported atopic dermatitis, asthma, rhinitis, food allergy, hand eczema and early onset of hand eczema as well as persistence of hand eczema. Of particular interest, 3 (age 19, 49 and 58 years) of 9 homozygous individuals never reported atopic dermatitis and 3 (age 33, 49 and 65 years) never reported hand eczema. Thus, one of nine individuals never experienced dermatitis until now.

Among hospital dermatitis patients, a total of 15 (3.0%) aged 3–72 years were homozygous for the filaggrin null genotype whereas 92 (20.1%) were heterozygous (Table 2). All patients had atopic dermatitis with onset during (early) childhood. Only one male patient aged 35 years had never experienced hand eczema. Most had generalized dermatitis, four of 15 patients received systemic immune therapy at some point whereas nine of 15 had complete remission for years. One patient (case 14) was hospitalized for 6 months as toddler for the purpose of topical tar therapy and one patient had received cyclosporine and azathioprine already at the age of 8 years. Several patients had complete remission for decades but then redeveloped dermatitis.

One patient (case 14) developed palmar hand eczema following accidental exposure to wet cement at age 70 years after 60 years of complete remission. Therapy with topical corticosteroids and UV-therapy led to complete remission after 1 year. Two patients, case 8 and 9, had complete remission for many years but were then occupationally exposed to irritants and developed hand eczema

(negative patch testing was performed in both) due to work as respectively, a mechanic and a cleaner. Change of work and topical therapy resulted in complete remission.

Three (0.7%) of the COPSAC children were homozygous/compound heterozygous for the null mutations. They all had dry skin/ichthyosis vulgaris, but only two of them developed dermatitis (at age 5 and 7 months respectively). The child without dermatitis developed dry skin much later than the other two (3.1 years vs. since birth). Both children with dermatitis had hand eczema at some point. One of the children had complete remission at age 3.9 years, the other still had dermatitis at age 11 years. The child with persisting dermatitis was also the only one with elevated specific IgE measurements. None of the children had other atopic diseases including rhinitis, asthma and allergy.

## Discussion

This study is the first to investigate whether individuals with the homozygous/compound heterozygous filaggrin null genotype develop dermatitis and offers important findings. Despite total absence of filaggrin in the epidermis, one of nine adults from the general population and one of three COPSAC children did not report dermatitis at any point in life and occurrence of dermatitis came earlier in homozygous than in heterozygous individuals. In dermatitis patients from a tertiary referral centre, who expectedly had early onset and persistence of dermatitis, year-long complete remission was observed in half of patients. Finally, nearly all atopic dermatitis patients suffered from hand dermatitis at some

**Table 2** Characteristics of 15 dermatitis patients who were homozygous for the filaggrin null genotypes R501X and 2282del4

Case	Gender	Current age (years)	Predisposition†	AD	Ichthyosis/dry skin since early childhood (<1 years of age)	Hand Eczema	Generalized Dermatitis	Year-long remission at some point	Systemic immune therapy at some point‡
1	M	2	+	+	+	+*	+	+	–
2	F	3	+	+	+	+*	+	+	–
3	M	14	+	+	+	+*	+	–	–
4	M	15	+	+	+	+*	+	–	+
5	F	15	+	+	+	+*	–	–	–
6	F	34	+	+	+	+*	–	–	–
7	M	35	+	+	+	–	+	+	–
8	F	36	Unknown	+	+	+*	+	+	+
9	M	36	+	+	+§	+¶	–	+	–
10	F	42	+	+	+§	+¶	–	+	–
11	M	49	+	+	+	+*	+	–	–
12	F	54	+	+	+	+*	+	–	+
13	F	63	+	+	+	+*	+	+	+
14	M	70	+	+	+	+*	–	+	–
15	M	72	Unknown	+	+	+	+	+	–

\*Dorsal location of fissured dermatitis.

†AD, asthma or rhinitis in first degree relative(s).

‡Prednisolone, azathioprine, cyclosporine, mycophenolate.

§Onset as a child, age not specified in medical chart.

¶Hand eczema, morphology not specified in medical chart.

point, probably an indicator of skin vulnerability and disease severity.

Study weaknesses include a low participation rate in the general population study, a retrospective design of the patient based part of the study, restriction to R501X and 2282del4 filaggrin mutation status and few homozygous individuals in the COPSAC prospective birth cohort. However, the study leads to the conclusions that (i) other barrier proteins are important for skin function; (ii) total filaggrin deficiency does not automatically result in chronic dermatitis (suggesting that gene-environmental interaction is also important for this subgroup); and (iii) filaggrin genotyping may be useful in the clinic to inform patients on their prognosis. The natural history of individuals with the filaggrin null genotype is fairly good in the sense that they may not develop dermatitis at all, and if they do, they may experience complete remission.

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