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Filaggrin gene mutations may influence the persistence of food allergies in Japanese primary school children

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Short title: FLG mutations and food allergies in Japanese pupils

Conflicts of interest: None to declare

Key words:
(1) atopic dermatitis, (2) food allergy, (3) genetics, (4) filaggrin, (5) FLG

Mutations in FLG are the underlying cause of ichthyosis vulgaris and are an important predisposing factor for atopic dermatitis (AD). In 2011, FLG mutations were reported to increase the risk of peanut allergy, and they have been proven to increase the risk of other food sensitizations and allergies. In this study, we comprehensively screened 411 children in Japan for 10 Japanese-population-specific FLG mutations and suggested that FLG mutations influence the persistence of food allergies (FAs).
To investigate the association of FLG mutations with allergies, particularly FAs, in a general pediatric population, we studied pupils at a primary school in Japan. Of the 411 pupils, 410 pupils were measured for total IgE and 6 antigen-specific IgEs. Of these 410 pupils, the present study covers the 375 pupils who answered our questionnaire only one time each. We used a portion of the questionnaire survey data (Supplementary Table 1, all supplementary data is available on direct request to the corresponding author) and IgE data to survey the allergic conditions of elementary school-age children. The FA, AD, asthma and allergic rhinitis outcomes were parent-reported, physician-diagnosed ones. Details of samples and methods are described in the supplementary information. The local institutional review boards approved this study, and all guardians of the subjects provided written informed consent.

In the present FLG mutation screening, we studied the 10 FLG mutations specific to the Japanese population (Supplementary Table 3). All are loss-of-function mutations. Genotyping of the FLG mutations was performed with the TaqMan probe genotyping assay as our previous study.
Of the 375 participants with outcome data available, 28 individuals (7.5%) were heterozygous for 1 of the 10 FLG mutations. The genotypes are detailed in the supplementary information. According to the present data obtained from the 374 pupils through the clinical questionnaire, 14 individuals reported current FAs (3.7%). Among the total of 374 pupils, 4 out of the 28 individuals with FLG mutations (14.3%) were current FA patients and 10 out of the 346 individuals without FLG mutations (2.9%) were current FA patients. Thus, FLG mutations were significantly associated with current FAs (odds ratio=5.60 [95% CI: 1.64-19.18, p=0.0023]) (Table 1). Furthermore, FLG mutations were significantly associated with current FAs that occurred in combination with current/past atopic dermatitis (odds ratio=5.96 [95% CI: 1.43-24.81, p=0.0059]) (Table 1). In contrast, the association of FLG mutations with current and past FAs was not significant (odds ratio=1.69 [95% CI: 0.55-5.20, p=0.352]).

The past FA group consisted of primary school students who had a history of FAs but who reported having no current FAs in the present study. All the participants answered the questionnaire only once, and positive past FA means that a participant answered that he or she had once FA at any time point prior to his or her participation in the present study (Table 1). We had 21 participants in the past FA group. Interestingly, none of them had any FLG mutations. From this fact, we speculate that FLG mutation carriers with past FAs rarely grow.
out of their FAs. If this speculation is true, the present results might suggest that FLG
mutations are associated with the persistence of FA from the infantile period to the primary
school years, although this speculation is not based on a statistically significant sample. The
reason there were no FLG mutation-carrying individuals with past FAs is probably because it
takes time for the children to grow out of their FAs, and for nuts/peanuts, they usually do not.

In other words, FA patients transiently seen in the infantile period without FLG mutations tend
to remit spontaneously. As the patients with FLG mutation have continuous incidences of
percutaneous sensitization, FAs in the individuals with FLG mutations remain at primary
school age. Thus, FLG mutations might be associated with the persistence of FAs. Indeed, FLG
mutations were reported to have a significant effect on the risk of FA in later childhood (age
10) but an insignificant effect at the ages of 1, 2 and 4. It has been reported that FLG mutation
is associated with IgE sensitization to peanuts, but not to other food allergens.

We investigated the association between FLG mutations and allergy to each allergen.
However, children allergic to each allergen were too few to be significant (Supplementary
Information).
In conclusion, the present study suggests that FLG mutations are a significant predisposing factor for FAs in primary school students and may influence the persistence of FAs from infancy to the primary school years. In a future study, the association between FA and FLG mutations needs to be determined in FA patients who are diagnosed by food-challenge tests.

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References


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Table 1. Prevalence of allergic disease among the total participants (n=375) and the sub-groups of participants with the combined genotype (one or more FLG mutations) (n=28) and without the combined genotype (no FLG mutations) (n=346)

<table>
<thead>
<tr>
<th>History*</th>
<th>All individuals % (n)</th>
<th>Individuals with FLG mutations % (n)</th>
<th>Individuals without FLG mutations % (n)</th>
<th>OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current food allergy</td>
<td>3.7% (14/374)</td>
<td>14.3 % (4/28)</td>
<td>2.9 % (10/346)</td>
<td>5.60</td>
<td>1.64-19.18</td>
<td>0.00225</td>
</tr>
<tr>
<td>Past food allergy</td>
<td>5.6% (21/374)</td>
<td>0% (0/28)</td>
<td>6.1% (21/346)</td>
<td>N.A.</td>
<td>N.A.</td>
<td>N.A.</td>
</tr>
<tr>
<td>Current food allergy with current/past atopic dermatitis</td>
<td>2.7% (10/374)</td>
<td>10.7 % (3/28)</td>
<td>2.0% (7/346)</td>
<td>5.96</td>
<td>1.43-24.81</td>
<td>0.00586</td>
</tr>
<tr>
<td>Current food allergy without current/past atopic dermatitis</td>
<td>1.1% (4/374)</td>
<td>3.6% (1/28)</td>
<td>0.9% (3/346)</td>
<td>4.23</td>
<td>0.43-40.10</td>
<td>0.181</td>
</tr>
<tr>
<td>Current and past food allergy</td>
<td>9.4 % (35/374)</td>
<td>14.3 % (4/28)</td>
<td>9.0 % (31/346)</td>
<td>1.69</td>
<td>0.55-5.20</td>
<td>0.352</td>
</tr>
<tr>
<td>Current atopic dermatitis</td>
<td>10.1 % (38/375)</td>
<td>14.3 % (4/28)</td>
<td>9.8 % (34/347)</td>
<td>1.53</td>
<td>0.50-4.68</td>
<td>0.449</td>
</tr>
<tr>
<td>Current allergic rhinitis</td>
<td>38.1 % (143/375)</td>
<td>35.7 % (10/28)</td>
<td>38.3 % (133/347)</td>
<td>0.89</td>
<td>0.40-2.00</td>
<td>0.784</td>
</tr>
<tr>
<td>Current asthma</td>
<td>9.7 % (37/375)</td>
<td>10.7 % (3/28)</td>
<td>9.8 % (34/347)</td>
<td>1.10</td>
<td>0.32-3.85</td>
<td>0.876</td>
</tr>
</tbody>
</table>
*Both current allergy and past allergy history are from answers to the questionnaire obtained at only one time point for each participant. In addition, past FA mean positive history of FA at any time in the past and the participants with past FA did not have uniform time frame for their allergy history. The intervals from the past FA to current absence of FA are different among participants in the past FA group.