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***Short title*:** *FLG* mutations and food allergies in Japanese pupils

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(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).[1] In 2011, *FLG* mutations were reported to increase the risk of peanut allergy[2], and they have been proven to increase the risk of other food sensitizations and allergies.[3,4] 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.[5] Of these 410 pupils, the present study covers the 375 pupils who answered our questionnaire[5] 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.[6]

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.[3] It has been reported that *FLG* mutation is associated with IgE sensitization to peanuts, but not to other food allergens.[7]

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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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)

History*	All individuals % (n)	Individuals with *FLG* mutations % (n)	Individuals without *FLG* mutations % (n)	OR	95% CI	*P*-value
Current food allergy	3.7% (14/374)	14.3 % (4/28)	2.9 % (10/346)	5.60	1.64-19.18	0.00225
Past food allergy	5.6% (21/374)	0% (0/28)	6.1% (21/346)	N.A.	N.A.	N.A.
Current food allergy with current/past atopic dermatitis	2.7% (10/374)	10.7 % (3/28)	2.0% (7/346)	5.96	1.43-24.81	0.00586
Current food allergy without current/past atopic dermatitis	1.1% (4/374)	3.6% (1/28)	0.9% (3/346)	4.23	0.43-40.10	0.181
Current and past food allergy	9.4 % (35/374)	14.3 % (4/28)	9.0 % (31/346)	1.69	0.55-5.20	0.352
Current atopic dermatitis	10.1 % (38/375)	14.3 % (4/28)	9.8 % (34/347)	1.53	0.50-4.68	0.449
Current allergic rhinitis	38.1 % (143/375)	35.7 % (10/28)	38.3 % (133/347)	0.89	0.40-2.00	0.784
Current asthma	9.7 % (37/375)	10.7 % (3/28)	9.8 % (34/347)	1.10	0.32-3.85	0.876

*Both current allergy and past allergy history are from answeres to the questionnaire obtained at only one time point for each participants. In addition, past FA measn 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.