

Palmar hyperlinearity in early childhood atopic dermatitis is associated with filaggrin mutation and sensitization to egg

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Abstract

Background/Objectives: Palmar hyperlinearity is a typical clinical feature of *Filaggrin* gene (*FLG*) null mutations. There are reports of *FLG* mutations and allergic sensitization; however, reports on the relationship between palmar hyperlinearity to sensitization are limited. This study aimed to examine the association between palmar hyperlinearity and sensitization in atopic dermatitis (AD) children.

Methods: This cross-sectional, case-control study included children < 6 years old with moderate-severe AD whose parents consented for mutation analysis and photographic documentation. Each child underwent genotyping to detect the eight most prevalent *FLG* mutations in the Japanese population: R501X, 3321delA, S1695X, Q1701X, S2554X, S2889X, S3296X, and K4022X. Clinical features and parameters including egg-specific IgE were examined, and palm photographs were evaluated by 12 trained dermatologists blinded to genotyping results.

Results: Of the 57 patients (age range, 2 months to 5 years; median, 22 months), 16 were heterozygotes and three were compound heterozygotes. Palmar hyperlinearity, as recognized by more than two-thirds of dermatologists, was significantly associated with *FLG* mutation ($P = 0.002$, OR = 6.98, 95% CI = 2.1–23.7), and this association was observed especially in children over 2 years. Cross-shaped crease of the thenar eminence, as known in previous reports, also demonstrated significant correlation with *FLG* mutation. When the children were divided according to the presence or absence of palmar hyperlinearity, the egg white-specific IgE was significantly higher in the hyperlinearity group (55.9 vs 18.3 IU/mL, $P < 0.05$).

Conclusions: Palmar hyperlinearity indicates possible inherited barrier abnormalities of the skin in early childhood. Its identification may help to predict a more accurate prognosis, such as sensitization.

KEYWORDS

atopic dermatitis, atopic march, filaggrin gene mutation, immunoglobulin E, palmar hyperlinearity

1 | INTRODUCTION

Palmar hyperlinearity is one of the typical clinical features of ichthyosis vulgaris (IV).¹ Recently, *filaggrin* gene (*FLG*) null mutations, which are

causative genes of IV, have been reported to remarkably relate to palmar hyperlinearity.² Moreover, palmar hyperlinearity is also known as one of the minor diagnostic criteria of atopic dermatitis (AD),³ and palmar hyperlinearity has been reported to be present at school age.⁴

Filaggrin (filament aggregating protein) is a multifunctional epidermal protein involved in the hydration of the stratum corneum and is essential for the formation of a normal, intact, and protective skin barrier.⁵⁻⁷ Impaired epidermal barrier function is a crucial factor in allergic sensitization; however, in the case of *FLG* loss-of-function mutations, it has been considered a strong risk factor for allergic diathesis called the atopic march.^{8,9} Approximately 30 loss-of-function mutations have been identified so far,¹⁰ and roughly 10% of individuals with European ancestry carry a single null mutation in *FLG*, and patients with AD associated with *FLG* mutations are present in 20%-50% of the European population.¹¹ The mutation is present in about 27% of Japanese patients with AD with the mutations of eight genes, namely, R501X, 3321delA, S1695X, Q1701X, S2554X, S2889X, S3296X, and K4022X.¹²

The recent discovery of the common loss-of-function variants in the *FLG* gene and the strong association with atopic disease have led to a heightened interest in the role of skin barrier impairment in the development of AD and allergic sensitization.^{13,14} An animal study suggests that antigen-presenting cells in the superficial epidermis can make contact with not only environmental allergens, such as house dust mites, but also food protein, leading to sensitization, which may be also an important precursor of food and respiratory allergies.¹⁵

In a study of adults with AD examined for the frequency of palmar hyperlinearity with *FLG* null mutation, palmar hyperlinearity was confirmed higher (79%) in adult patients with AD with *FLG* null mutation than those without the mutation (24%).¹⁶ In children, Brown et al reported that patterns of palmar hyperlinearity were examined in 484 patients aged 7-9 years. Most children have very smooth palmar skin, and palmar hyperlinearity was confirmed in 74.5% of children with *FLG* null heterozygotes, and the majority showed cross-shaped crease patterns.⁴ The palmar skin features of patients with *FLG* null mutations show several characteristic patterns of linear markings, a crosshatched pattern, and a running horizontal pattern to the thenar eminence and have numerous deep creases on the entire palm and fingers.¹⁷

Thus, having palmar hyperlinearity was hypothesized to associate with increased risk of allergic sensitization and elevation of serum IgE levels. However, since this association has not been sufficiently reported, this study aimed to examine the relationship between palmar hyperlinearity and sensitization in young children with AD who were examined for *FLG* null mutations.

2 | MATERIALS AND METHODS

2.1 | Patients

This study involved children age 5 years or younger with moderate-to-severe AD, as defined by the scoring system of the Scoring Atopic Dermatitis (SCORAD) index,¹⁸ who visited the Department of Pediatrics and Dermatology, Hamamatsu University School of Medicine, from January 2014 to July 2014 and whose parents gave written informed consent for the mutation analysis and photographic

documentation. The ethics committee of the university reviewed the protocol and granted approval before study initiation (No. 24-283) in accordance with the ethical principles described in the Declaration of Helsinki.

2.2 | Genotyping

All children underwent genotyping to detect the eight most prevalent *FLG* null mutations in the Japanese population using measurement methods as previously reported.¹¹

2.3 | Skin examination

Each child's palm was examined for features associated with the phenotypes of linearity. Photographs of palms were examined by 12 trained dermatologists blinded to the genotyping results. There has not been a validated score system for digitizing palmar hyperlinearity so far. With reference to our own criteria (Figure 1), the photographs of each palm were evaluated by all dermatologists as follows: (a) Is there a palmar hyperlinearity at first glance? (yes/no) (b) How deep is this palm linearity? (0-10 points) (c) How many wrinkles are there in this palm? (0-10 points) (d) Is there a cross-type marking of the thenar eminence? (yes/no) Regarding the depth (b) or the wrinkles (c) of the palms, the average of the points answered by all dermatologists was used.

2.4 | Clinical parameters and biomarkers

We evaluated the following typical clinical markers of allergic diseases: blood eosinophil count, serum total IgE, thymus and activation-regulated chemokine/CCL17, sensitization to specific allergens (house dust mite, egg white) based on ImmunoCAP (Thermo Fisher Scientific, Uppsala, Sweden), and SCORAD index at first visit.

2.5 | Statistical analysis

We examined the phenotype of palmar linearity in groups with or without *FLG* null mutation, and we investigated the relationship between palmar hyperlinearity and clinical features. For a comparison of these groups, we assessed group means using Mann-Whitney test and proportions with Fisher's exact test. All tests were two-sided with a significance level of 5%. All statistical analyses were performed using JMP® software (version 12.0.1, SAS Institute Inc., Cary, NC, USA).

3 | RESULTS

Of the 86 children below age 6 years who underwent *FLG* genotyping during the study period, 57 children (age range, 2 months to 5 years old, median 22 months), whose parents consented to photographic documentation of the palms, were included, while the remaining 29 whose parents did not consent were excluded. Among

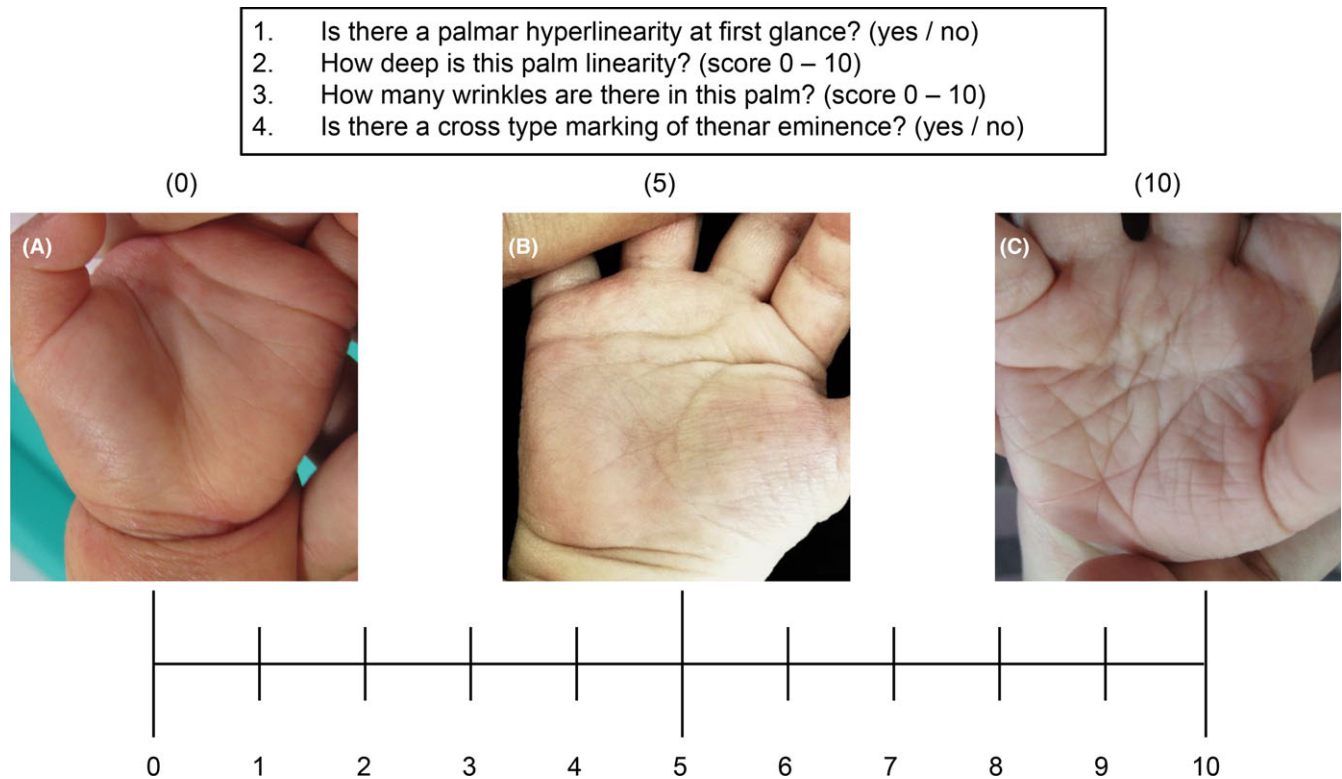


FIGURE 1 Palmar hyperlinearity photographic scale. When the blinded dermatologists evaluated the palmar linearity of each palm photograph, the answers were made with reference to this scale. A, *FLG* mutation-negative AD children with a smooth palm, B, AD children with suspected palmar hyperlinearity, C, *FLG* mutation-positive AD children with apparent palmar hyperlinearity

the 57 children, 19 (33.3%) had *FLG* null mutations, including 16 heterozygotes and three compound heterozygous mutations (Table 1). The children were divided into *FLG* null heterozygotes (19 children) and *FLG* wild-type homozygotes (38 children).

The background characteristics at first visit of these 57 children are shown in Table 2. Serum total IgE and allergen-specific IgE levels tended to be higher in the group with *FLG* null mutations, but no significant difference was observed between the two groups.

Table 3 shows the association of skin features of the 57 children. In children with *FLG* null mutations, there was a significant difference in “judged to have hyperlinearity at a glance” by blinded investigators compared to children without the mutations ($P = 0.002$, OR: 6.98, 95% CI: 2.1–23.7). When stratifying them into two groups under or over the age of 2 years, this tendency was observed especially in the group aged 2 years and over ($P < 0.001$, OR: 54.0, 95% CI: 4.1–707). In the group aged under 2 years, palmar hyperlinearity had a tendency to correlate with positive *FLG* mutation; however, there was no statistically significance difference ($P = 0.45$, OR: 2.4,

95% CI: 0.5–11.1). Among children aged 2 years and older, the positive predictive value of *FLG* mutation in the case with palmar hyperlinearity was 85.7%, and the negative predictive value in the case without palmar hyperlinearity was 90.0%.

When the scores for the depth of linearity and the number of wrinkles were high (score > 6), there was also a significant correlation with *FLG* null mutations. When wrinkles were oriented vertically and horizontally cross the thenar eminence, a *FLG* null mutation was confirmed with an odds ratio (OR) of 4.80 (95% CI: 1.3–17.8). However, among 22 children judged to have hyperlinearity, nine children did not have *FLG* null mutations. On the contrary, in two cases, two-thirds or more of the dermatologists answered “that does not have hyperlinearity” on the palms of children with *FLG* null mutations, and both cases were K4022X heterozygotes. Of the 19 patients with *FLG* null mutations, those with the S2889X, S2554X, S3296X, and combined mutations appeared to display a cross-shaped crease at the thenar eminence. In contrast, patients with the K4022X mutation appeared to have smooth palmar skin (data not shown).

TABLE 1 Number (%) of children with *FLG* genotype ($n = 57$)

	R501X	3321delA	S1695X	Q1701X	S2554X	S2889X	S3296X	K4022X	Compound
Wild-type <i>FLG</i>	57 (100%)	51 (89.5%)	57 (100%)	57 (100%)	52 (91.2%)	51 (89.5%)	55 (96.5%)	54 (94.7%)	
<i>FLG</i> null mutation	0 (0%)	6 (10.5%)	0 (0%)	0 (0%)	5 (8.8%)	6 (10.5%)	2 (3.5%)	3 (5.3%)	3 (5.3%) ^a

FLG, *filaggrin* gene.

^aThis includes (3321delA/S2554X), (3321delA/S2889X), and (S2889X/S3296X).

TABLE 2 Baseline characteristics at first visit (n = 57)

	FLG null mutation (–), (n = 38)	FLG null mutation ^a (+), (n = 19)	P Value
Male:Female	19:19	13:6	0.260
Median age at first visit, months (range)	8 (2-62)	11 (2-42)	0.716
Median age of AD onset, months (range)	3 (1-8)	2 (1-5)	0.253
Any parents with AD history (%)	20 (%)	12 (%)	0.574
Any parents with allergic diseases (%)	30 (83.3%)	16 (84.2%)	1.000
SCORAD, median (IQR)	62.4 (45.0-77.3)	55.7 (42.8-74.7)	0.503
TARC, median (IQR)	3711 (2176-5348)	2878 (1161-8950)	0.593
Eosinophil count, median (IQR)	884 (299-1578)	1343 (439-1774)	0.374
Total IgE, IU/mL, mean (95% CI)	623.9 (265.4-982.4)	1124.8 (181.2-2068.3)	0.594
HDM-specific IgE, UA/mL, mean (95% CI)	12.8 (2.6-22.9)	14.4 (–1.7-30.5)	0.808
Egg white-specific IgE, UA/mL, mean (95% CI)	21.7 (11.5-31.9)	55.1 (15.4-94.8)	0.066

AD, atopic dermatitis; CI, confidence interval; FLG, *filaggrin* gene; HDM, house dust mite; IQR, interquartile range; SCORAD, scoring atopic dermatitis; TARC, thymus and activation-regulated chemokine.

^aThere were no mutant allele homozygotes for any allele tested.

TABLE 3 Association of skin features with FLG null alleles (n = 57)

(At taking photographs)	FLG null mutation (–), (n = 38)	FLG null mutation (+), (n = 19)	OR (95% CI)	P Value
Median age, months (range)	23 (2-62)	21 (2-58)		0.741
Palmar hyperlinearity at a glance ^a	9 (23.7%)	13 (68.4%)	6.98 (2.1-23.7)	0.002
No palmar hyperlinearity at a glance ^a	20 (52.6%)	2 (10.5%)	0.11 (0.02-0.52)	0.003
Deepness of linearity, ^b Score > 6	3 (7.9%)	6 (31.6%)	5.38 (1.2-24.8)	0.048
Amount of wrinkles, ^b Score > 6	4 (10.5%)	7 (36.8%)	4.96 (1.2-20.0)	0.031
Cross-type marks of thenar eminence	5 (13.2%)	8 (42.1%)	4.80 (1.3-17.8)	0.021
Hand eczema (%)	15 (39.5%)	6 (31.6%)	0.71 (0.2-2.3)	0.772

CI, confidence interval; FLG, *filaggrin* gene; OR, odds ratio.

^aTwo-thirds or more blinded investigators answered.

^bThe average score is higher than 6.

TABLE 4 Association of palmar hyperlinearity with biomarkers (n = 57)

(At first visit)	Hyperlinearity (–), (n = 36)	Hyperlinearity (+), (n = 21)	P Value
Median age, months (range)	7.9 (3-62)	9.9 (2-42)	0.987
Hand eczema (%)	15 (41.7%)	6 (28.6%)	0.272
SCORAD, median (IQR)	61.0 (43.7-77.1)	61.1 (44.3-75.1)	0.831
TARC, median (IQR)	3080 (1739-5138)	4734 (1765-8905)	0.263
Total IgE, IU/mL, mean (95% CI)	624.5 (239.8-1009.3)	1055.5 (240.1-1870.8)	0.486
HDM-specific IgE, UA/mL, mean (95% CI)	16.3 (4.5-28.0)	8.4 (–3.2-19.9)	0.422
Egg white-specific IgE, UA/mL, mean (95% CI)	18.3 (9.4-27.2)	55.9 (21.4-90.2)	0.024

CI, confidence interval; FLG, *filaggrin* gene; HDM, house dust mite; IQR, interquartile range; SCORAD, scoring atopic dermatitis; TARC, thymus and activation-regulated chemokine.

When the children were divided according to the presence or absence of hyperlinearity without considering FLG null mutation, there was no difference between the two groups in terms of age and SCORAD at the first visit, but the serum total IgE tended to be higher. The egg white-specific IgE was significantly higher in the group with palmar hyperlinearity (Table 4), and this association was also confirmed by examination of the non-egg-tolerant children (n = 47; data not shown).

4 | DISCUSSION

This study is the first to evaluate the association between palmar hyperlinearity, which is a typical clinical feature of FLG null mutations, on sensitization of young children with AD. In the present study, as in the adult reports,^{1,2} there was a significant correlation between palmar hyperlinearity and FLG null mutations, especially over age 2 years. On the contrary, we found that the degree of

sensitization to egg at first visit was higher in children with palmar hyperlinearity than those without it.

Meanwhile, of the 22 children with AD who were judged to have hyperlinearity, nine children (40.9%) do not have *FLG* null mutations. Even by investigating for the same eight gene mutations in Japanese adult AD patients, the reported proportion was 24%.¹⁹ With regard to the mechanism that hyperlinearity is still exhibited even if *FLG* null mutation is negative, the possibility of having a European-type mutation or having an abnormality in an involved enzyme or maturation, such as profilaggrin processing, exists.²⁰ In addition, abnormalities may be present in molecules such as Hornerin and filaggrin 2, which play an important role in epidermal barrier function other than *FLG*.²¹ Not only those genetic mutations or single-nucleotide polymorphisms but also factors that influence the environment in which protease works (such as pH) affect the production of filaggrin monomers.²²

Importantly, in all cases, physical examination findings of palmar hyperlinearity are indicative of clinical phenotype given the above-mentioned results. The clinical features means that the child may have an atopic tendency, even without genetic tests. Even if having an *FLG* null mutation, a study reported that there is no increased risk of developing asthma without eczema.¹³ In other words, early intervention and maintenance therapy by repairing the skin barrier using emollients^{23,24} and topical corticosteroids²⁵ may be important for young children, even with *FLG* null mutations, to prevent progression to asthma and rhinitis.

The present study confirmed that sensitization tended to intensify in the group with hyperlinearity compared with the group without hyperlinearity, although there was no difference in the severity of eczema at the first visit. For this reason, these simple diagnostic findings may be an indicator for clinicians who routinely examine children to predict subsequent sensitization. Given that the present study found that palmar hyperlinearity was associated with sensitization risk from early childhood, for physicians responsible for the treatment of eczema in childhood, identification of high-risk children and early treatment of impaired epidermal barriers may be therapeutic strategies to improve the disease prognosis of the child.

The present study has a few limitations. First, the subjects of this study were children with AD only; hence, the sensitization status of children with hyperlinearity without AD was unknown. In addition, there were some cases in which the levels of egg-specific IgE extremely fluctuate in infantile AD. In this study, we only investigated sensitization to egg, which is the most common food allergen in Japan; however, clinical egg allergy remains to be evaluated. Second, we did not investigate foods other than egg, such as cow's milk or peanut, because of insufficient inquiries detail intake situations, which affect its tolerance and sensitization levels. Third, there are no validated objective criteria of evaluation or scoring system of the severity of hyperlinearity, so we used the visual analog scale shown in Figure 1 as well as the overall clinical judgment (yes/no) of specially trained senior dermatologists. However, the "judgment at first glance" by dermatologists was the most

accurate method for prediction of *FLG* null mutation in this study. Although the visual analog scale scores correlated significantly with *FLG* null mutations, they did not perform as well as when a dermatologists stated, "Oh, I think this palm has hyperlinearity." Briefly, clinical experience of a specialist is proved to be the most reliable method for assessment, though, in the future, we would like to evaluate image analysis technology as an identification method on a birth cohort population.

In conclusion, palmar hyperlinearity is associated with the possibility of an inherited barrier abnormality of the skin since early childhood. Identification of palmar hyperlinearity may help pediatric clinicians in predicting a more accurate prognosis, such as risks of sensitization and the atopic march.

ACKNOWLEDGMENTS

We thank the study investigators Dr. Ito, Dr. Tatsuno, Dr. Kasuya, Dr. Fukuchi, Dr. Kuriyama, Dr. Suzuki, Dr. Kaneko, Dr. Aoshima, and Dr. Sakabe.

ETHICAL APPROVAL

The ethics committee of the university reviewed the protocol and granted approval before study initiation (No. 24-283) in accordance with the ethical principles described in the Declaration of Helsinki.

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How to cite this article: Fukui T, Yasuoka R, Fujiyama T, Sakabe J, Taguchi T, Tokura Y. Palmar hyperlinearity in early childhood atopic dermatitis is associated with filaggrin mutation and sensitization to egg. *Pediatr Dermatol*. 2019;00:1–6. <https://doi.org/10.1111/pde.13752>