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LETTER TO THE EDITOR

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Mutations in *FLG*, the gene-coding profilaggrin/filaggrin, are associated with putative hay fever in patients with atopic dermatitis

Dear Editor,

Filaggrin is a major structural protein in the stratum corneum (SC) of the epidermis and plays a key role in the barrier function of the skin.[1] The disruption of the barrier function causes xerosis associated with atopic dermatitis (AD). Mutations in the gene encoding profilaggrin/filaggrin, *FLG*, are a predisposing factor for AD.[2]

Thymus and activation-regulated chemokine/ C-C motif chemokine ligand 17 (TARC/CCL17), constitutively expressed in the thymus and produced by dendritic cells, endothelial cells, keratinocytes and fibroblasts, is a designated Th2 type chemokine binding to C-C chemokine receptor 4.[3] TARC, along with immunoglobulin (Ig) E, are considered reliable serum markers of Th2-dominant inflammation and, thus, indirectly of AD.

We performed analyses of association between *FLG* mutation status and the serum levels of IgE, TARC, and past history in patients with AD.

This study was approved by the Ethics Review Committee of Nagoya University Graduate School of Medicine, Aichi, Japan. Twenty-eight patients (14 males, 14 females; age range 3-45 years) with AD, who visited the outpatient clinic of dermatology, Hirosaki University Hospital, were included. *FLG* mutations were comprehensively screened using real-time PCR with TaqMan probe genotyping assay as previously reported.[2] In total, 10 *FLG* mutations previously reported to account for all *FLG* mutations in the Japanese population were examined.[2] Patients with hay fever were defined as individuals who reported to have had frequent episodes of all three symptoms of watery eyes, running nose, and sneezing. Patients with asthma were defined as individuals who reported to have a history of asthma diagnosed by a physician.

Of the 28 AD patients, 5 were carriers of one of 10 *FLG* mutations (Table 1). Thus, the incidence rate was 17.9%. *FLG* mutations were associated with putative hay fever (odds ratio = 10 [95% CI: 1.15-86.89]), however, and were not associated with asthma (odds ratio = 5.5 [95% CI: 0.28-107.16]). [4,5]

In AD patients, there was a positive correlation between the serine protease activity in the SC and the total serum IgE.[1] Although the IgE of patients with *FLG* mutations exceeded the reference values, there is not the statistical significant difference between IgE, TARC, and *FLG* mutations. However, the 3 *FLG* mutation carriers with high serum TARC level also had severe xerosis and eczematous eruptions. This finding consisted with that serum TARC levels sharply reflect the disease activity of AD.[3]

Consistent with the previous study,[2,4,5] we also found an association between *FLG* mutation positivity and putative hay fever in AD patients. Contrasting reports also suggest that the significant association observed between *FLG* mutations and hay fever may be due to the close association between *FLG* mutations and the co-occurrence of hay fever and eczema.[5]

Our study is limited by the small sample size; nevertheless, the findings show a significant association between *FLG* mutations and hay fever and provide strong evidence for the role of *FLG* mutations in the pathogenesis of hay fever.

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DECLARATIONS

Approval of the research protocol: The Hirosaki University Internal Review Board approved the research.

INFORMED CONSENT

The Ethics Review Committee of Nagoya University Graduate School of Medicine, Aichi, Japan, provided the informed consent.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

TABLE 1 Detailed clinical and laboratory data of the AD patients involved in the present study

Patient	Sex	Age (year)	Family history	DNA Sequence Variant	IgE (IU/mL)	TARC (pg/mL)	Past history
1	F	9	+	c.5368C > T	469	247	Hay fever, pityriasis simplex faciei
2	M	42	–	c.7661C > G	8981	1709	Hay fever
3	M	12	+	c.8666_7CC > GA	11 588	877	Asthma, hay fever, chronic tonsillitis, Kawasaki disease.
4	M	21	–	c.8666_7CC > GA	2385	27 700	Postoperative cataract surgery
5	F	44	–	c.8666_7CC > GA	535	293	Asthma, herpes simplex
6	F	3	–	Not detected	1430	706	Food allergy (egg)
7	F	7	–	Not detected	144	1997	Molluscum contagiosum
8	F	8	+	Not detected	46	720	
)9	M	10	+	Not detected	270	1900	
10	F	12	+	Not detected	370	622	Alopecia areata
11	M	14	–	Not detected	16 903	7190	Hay fever
12	F	16	+	Not detected	1124	438	Food allergy(peach)
13	M	17	+	Not detected	5077	564	Asthma
14	M	17	–	Not detected	16 476	707	
15	M	20	–	Not detected	5737	1020	
16	F	23	+	Not detected	17	250	Food allergy (egg, tomato)
17	M	29	+	Not detected	1896	1759	
18	M	29	–	Not detected	225	382	Epidermal cyst (axilla)
19	M	35	–	Not detected	959	574	Cellulitis (right lower thigh)
20	F	38	–	Not detected	32	13 790	Anemia, herpes simplex, Takayasu arteritis
21	F	39	–	Not detected	295	1096	Postoperative breast cancer, schizophrenia
22	M	41	–	Not detected	4104	717	Postoperative cataract surgery
23	F	41	–	Not detected	993	6945	Nephrotic syndrome
24	F	41	–	Not detected	14 349	547	Herpes simplex, Hypertension, hyperthyroidism, lipoma
26	M	44	–	Not detected	992	136	Alopecia areata
26	F	44	–	Not detected	460	1939	Alopecia areata
27	M	44	+	Not detected	439	846	Hay fever
28	F	45	+	Not detected	284	632	Alopecia areata, hay fever

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REFERENCES

1. Nomura H, Suganuma M, Takeichi T, Kono M, Isokane Y, Sunagawa KO, et al. Multifaceted analyses of epidermal serine protease activity in patients with atopic dermatitis. Int J Mol Sci. 2020;21(3):E913.
2. Kono M, Nomura T, Ohguchi Y, Mizuno O, Suzuki S, Tsujiuchi H, et al. Comprehensive screening for a complete set of Japanese-populationspecific filaggrin gene mutations. Allergy. 2014;69(4):537–40.
3. Saeki H, Tamaki K. Thymus and activation regulated chemokine (TARC)/CCL17 and skin diseases. J Dermatol Sci. 2006;43(2):75–84.
4. Osawa R, Konno S, Akiyama M, Nemoto-Hasebe I, Nomura T, Nomura Y, et al. Japanese-specific filaggrin gene mutations in Japanese patients suffering from atopic eczema and asthma. J Invest Dermatol. 2010;130(12):2834–6.
5. Schuttelaar MLA, Kerkhof M, Jonkman MF, Koppelman GH, Brunekreef B, de Jongste JC, et al. Filaggrin mutations in the onset of eczema, sensitization, asthma, hay fever and the interaction with cat exposure. Allergy. 2009;64(12):1758–65.