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Letter to the Editor

Angiotensin-converting enzyme genotype is a risk factor for wheat-dependent exercise-induced anaphylaxis sensitized with hydrolyzed wheat protein

Dear Editor,

In Japan, substantial interest has recently focused on wheat-dependent exercise-induced anaphylaxis (WDEIA) caused by percutaneous and/or rhino-conjunctival sensitization of hydrolyzed wheat protein (HWP), Glupearl 19S®, which was used as ingredient of popular facial soap of which 46 million units had been sold. To date, more than 2000 people in Japan have been diagnosed with HWP-sensitized WDEIA (HWP-WDEIA).[1–3] Apart from the sensitization pathway, patients with HWP-WDEIA manifest variable levels of immediate-type response following natural wheat product ingestion and exercise, which is quite similar to conventional WDEIA.[1–3] Although some genetic factors may be responsible for the manifestation of WDEIA, its pathomechanism remains largely unknown. WDEIA is a rare disease in our country but we have encountered some patients with near-fatal anaphylactic reactions. Therefore this mechanism and genetic factors associated with the risk for WDEIA should be investigated.

It has been reported that the angiotensin-converting enzyme (ACE) genotype was associated with cardiovascular, thrombotic and metabolic disorders.[4–6] Very recently, the ACE genotype was implicated in the manifestation of anaphylactic reactions to food, venom, and drugs.[7] The ACE gene, located at chromosome 17q23.3, has two allelic forms, with the presence (I) or absence (D) of a 287-base-pair intron. The II and ID genotypes are significantly more common than DD in patients with anaphylaxis, with odds ratios (ORs) of 44 and 5.6, respectively.[7] DD genotypes has been reported as a risk factor of coronary heart disease and an effect modifier of its therapeutic effect.[4–6]

In the present study, we examined the ACE genotypes of 47 HWP-WDEIA patients with a median age of 46.3 (range 16–75). The allergologic data of the patients are shown in Table 1. We isolated DNA from the patients' oral mucosa with the DNeasy Blood &Tissue Kit® (Qiagen KK, Tokyo, Japan), and amplified it by PCR. Samples were genotyped using the quenching probe method for a single-nucleotide polymorphism (rs4341). Allele frequency of the cases with WDEIA followed the Hardy–Weinberg equilibrium ($p = 0.88$). The genotypes for WDEIA patients are shown in Table 2, along with the previously published data in a prospective population-based cohort study for 2125 subjects aged 40 or older Japanese living in the town of Hisayama, a suburban community in Fukuoka prefecture, and participating in periodic health check-ups.[4] We examined the association between the genotypes and the risk of having WDEIA using this general population as a control group. Logistic regression analysis with a statistical software, STATA, revealed an increased risk for HWP-WDEIA in individuals with the ID genotype (OR = 1.71, 95% confidence interval (CI) = 0.50–5.88) and in those with the II genotype (OR = 2.75, 95% CI = 0.83–9.12), compared with those with DD (p for trend = 0.04). Persons with more I allele had a greater risk than those with less I allele although the two point estimates of the risk were not significant.

Table 1
Distribution of the 40 cases with HWP-WDEIA by sex, age, serum total IgE, and RAST score for wheat, gluten and ω-5gliadin.

Characteristics		N
Sex	Female	44
	Male	3
Age (years)	<20	1
	21–30	3
	31–39	11
	41–49	11
	51–60	11
	>60	10
Serum total IgE (IU/mL)	≦170	35
	170–500	8
	501–1000	2
	≧1000	2
RAST score	Class	Wheat
	0–1	32
	2–3	11
	≧4	1
	Missing	1
	Class	Gluten
	0–1	28
	2–3	18
	≧4	1
	Missing	0
	Class	ω-5gliadin
	0–1	42
	2–3	2
	≧4	2
	Missing	2

RAST, radioallergosorbent test.

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Table 2
Genotypes of the ACE gene in cases with WDEIA and the general population.

	HWP-WDEIA	General population[†]
II-ACE	27 (57.4%)	918 (43.2%)
ID-ACE	17 (36.2%)	927 (43.6%)
DD-ACE	3 (6.4%)	280 (13.2%)
Total	47	2125

HWP, hydrolyzed wheat protein; WDEIA, wheat-dependent exercise-induced anaphylaxis.
[†] Quoted from a published study.[4]

To the best of our knowledge, no previous studies have examined possible association between ACE genotypes and the risk of HWP-WDEIA. ACE plays a key role in the circulating renin–angiotensin system through converting angiotensin I to angiotensin II. Another important action of ACE is to degrade bradykinin to inactive peptides.[7] Bradykinin induces endothelial nitric oxide (NO) production and has been implicated in the development of anaphylaxis, such as hypotension and mucosal swelling. Findings have suggested that bradykinin and NO are involved in angioedema, which is mediated by ACE inhibitors.[7–9] Since aerobic exercise increases the interstitial concentration of bradykinin and neuronal NO release, exercise may enhance the onset of WDEIA. As the production of ACE is up-regulated in the DD genotype compared with that in the ID and II genotypes,[10] the degradation of bradykinin tends to be accelerated in individuals with the DD genotype.[7–9] These findings may explain why individuals with the II or ID genotype are more susceptible to HWP-WDEIA. There are large differences in the reported I/D frequencies between studies and countries.[11] Those different allele frequencies might be related to the different prevalence of WDEIA between countries. Because the present study were small in size, it should be desirable to extend the present analysis in collaboration with other institutes in order to have more reliable estimates of the risk due to the genetic polymorphism based on a larger data set. Furthermore a comprehensive genetic examination by use of genome-wide association studies for other polymorphisms may identify other candidate genes.

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Conflict of interest
The authors have no conflict of interest to declare.

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