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Letter to the Editor

Pen a 1-specific IgE does not improve the accuracy of a shrimp allergy diagnosis among Japanese children due to cross-reactivity with Der p 10

Dear Editor,

Tropomyosin, a major allergen component of shrimp, is a highly conserved protein found in all vertebrates and invertebrates.¹ A Spanish report² found specific IgE (sIgE) to shrimp tropomyosin (Pen a 1) to be a better predictor of shrimp allergy than sIgE to crude shrimp extract. However, regional differences should be considered, as the sensitization rate to *Dermatophagoides pteronyssinus* (Der p) tropomyosin (Der p 10) reportedly differs among regions,³ which might influence sensitization to Pen a 1 as a result of their high cross-reactivity.¹ To our knowledge, few reports have assessed the diagnostic utility of sIgE to Pen a 1 in Japan, where the rate of sensitization to house dust mite (HDM) is extremely high. We therefore investigated the diagnostic accuracy of sIgE to Pen a 1 and evaluated the correlation between sIgE to Pen a 1 and Der p 10 in Japanese children.

Forty-three shrimp-sensitized Japanese children (≤ 15 years old) were enrolled. Twenty-two were diagnosed with shrimp allergy (SA) based on a positive oral food challenge (OFC) ($n = 17$) or a definitive history ($n = 5$). The remaining 21 children, defined as the non-shrimp allergy (NSA) group, were able to ingest shrimp without any symptoms, as diagnosed by a negative OFC ($n = 8$) or a history of daily consumption ($n = 13$) (Table 1). OFCs were conducted in accordance with the Japanese guidelines for food allergy 2012 under written informed consent. *Penaeus monodon* was used for OFCs. OFCs were considered positive when objective symptoms or subjective symptoms of sufficient severity that patients could not continue OFCs were observed. sIgE to Der p, Pen a 1 and Der p 10 were measured using ImmunoCAP® at Thermo Fisher Diagnostics (Tokyo, Japan). Ethical approval was obtained through the institutional review board at Aichi Children's Health and Medical Center (2017037). All statistical analyses were performed using the EZR software program (Saitama Medical Center, Jichi Medical University, Saitama, Japan). A non-parametric Mann–Whitney U test and Spearman's Rank Sum test were used. P values of <0.05 were considered to indicate statistical significance.

Among the 43 subjects recruited, 38 (88%) had sIgE to Pen a 1 exceeding $0.1 \text{ U}_A/\text{mL}$, which did not significantly correlate with sIgE to crude shrimp extract ($r = 0.11$, $p = 0.49$, Table 1). The sIgE levels to Pen a 1 showed no significant difference between the SA (median $5.4 \text{ U}_A/\text{mL}$) and NSA ($1.5 \text{ U}_A/\text{mL}$) groups, similar to those to crude shrimp extract (median $8.9 \text{ U}_A/\text{mL}$ in SA, $4.0 \text{ U}_A/\text{mL}$ in

NSA) (Supplementary Fig. 1). In the receiver operating characteristics (ROC) analysis, the areas under the curve (AUCs) of sIgE levels to crude shrimp extract and Pen a 1 were 0.62 and 0.56, respectively ($p = 0.11$) (Supplementary Fig. 2). Among the 43 patients, 41 (95.3%) had positive sIgE to Der p, and 35 (81.3%) had positive sIgE to Der p 10. However, there was no significant correlation between sIgE to Der p and those to Der p 10 ($r = 0.008$, $p = 0.96$). Notably, the sIgE levels to Pen a 1 and Der p 10 showed a significantly strong correlation in both the SA and NSA groups (SA: $R_s = 0.95$, $p < 0.001$, NSA: $R_s = 0.98$, $p < 0.001$) (Fig. 1).

To our knowledge, this is the first study to show a strong correlation between Pen a 1 and Der p 10 among Japanese children. Sensitization to Pen a 1 through HDM exposure has been reported by several groups.^{3–6} Pen a 1 (Genbank #AAZ76743.1) and Der p 10 (Genbank #AAB69424.1) show 81% amino acid identity and 91% homology (Supplementary Fig. 3). Furthermore, Ayuso *et al.* reported 88%–100% amino-acid identities to Der p 10 in 7 of 8 IgE-binding epitopes of Pen a 1.⁷ These findings support the presence of strong cross-reactivity between them.

Tuano *et al.* reported that Pen a 1 showed better diagnostic accuracy in patients without HDM sensitization (AUC = 0.80 in an ROC analysis) than in those who were sensitized to HDM (AUC = 0.66),⁸ and our study showed an even lower AUC (0.56) than the latter value. This may be due to differences in the rate of sensitization to Der p 10 in HDM-sensitized patients. Resch *et al.* from Austria reported a rate of 15.2%.⁹ In our study, however, 85% of the Der p-sensitized patients (35/41, Table 1) were sensitized to Der p 10. This high frequency of Der p 10 sensitization might be why the diagnostic accuracy of Pen a 1 for shrimp allergy in Japanese children was lower than the values reported in other countries. Regarding cross-reactivity with other tropomyosin-related food allergens, 27% of SA patients reacted to mollusks, which is consistent with a previous Japanese report.¹⁰

Several limitations warrant mention. First, we selected only shrimp-sensitized children. This was because the sensitivity of sIgE to crude shrimp extract was 100% in the OFC-proven SA patients in our institute, except for patients with shrimp-dependent exercise-induced anaphylaxis. Second, the provoked symptoms in some SA patients were mild and subjective. Furthermore, even the NSA patients sometimes reported feeling mild oral symptoms in their daily consumption of shrimp. However, the main difference between these two patient groups in the present study was that SA patients avoided eating shrimp altogether due to the strong sensation of discomfort. Third, we did not prove the allergenic activity of

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Table 1
Clinical background of the subjects.

No.	Sex	Age	Allergic history	OFC conducted	Symptoms	Specific IgE (UA/mL)			
						shrimp	Der p	Pen a 1	Der p 10
SA1	F	3	BA, AR	—	runny nose, systemic hives	100.0	100.0	0.5	0.3
SA2	M	6.3	AD	+	oral or pharyngeal itch	92.7	100.0	7.3	7.5
SA3	M	8.7	AD	—	oral or pharyngeal itch, swelling of lip	41.3	100.0	6.2	4.7
SA4	M	2.5	AD	—	abdominal pain, loss of activity, cyanosis	37.3	100.0	5.3	4.8
SA5	M	10	AD, BA, AR	+	oral or pharyngeal itch, sneeze, runny nose	32.2	9.9	28.4	25.0
SA6	F	5.2	AD, BA	+	abdominal pain	25.1	100.0	2.8	3.3
SA7	M	4.6	AD, BA, AR	+	oral or pharyngeal itch	17.7	40.9	14.6	6.4
SA8	M	9.4	AD	+	systemic hives, swelling of lip	17.3	25.7	4.8	3.1
SA9	M	5.9	AD, BA	+	oral or pharyngeal itch	12.1	6.6	0.4	0.4
SA10	F	10.4	AD, BA	+	systemic hives	10.1	100.0	9.2	9.7
SA11	M	15.4	AD	+	oral or pharyngeal itch	9.0	100.0	33.9	22.2
SA12	M	13	AD, AR	+	oral or pharyngeal itch	8.8	100.0	13.9	10.1
SA13	M	9.2	AD	+	oral or pharyngeal itch, abdominal pain, vomiting	6.8	100.0	0.1	0.1
SA14	M	7.5	AR	+	oral or pharyngeal itch	4.9	100.0	5.4	4.5
SA15	M	6.3	AR	+	oral or pharyngeal itch, laryngeal discomfort	3.1	81.7	0.1	0.1
SA16	M	7.7	AR	+	oral or pharyngeal itch	3.1	65.7	4.0	4.2
SA17	M	2.9	AD	—	systemic hives	2.6	1.1	27.9	22.7
SA18	F	4	AD	+	oral or pharyngeal itch, abdominal pain, local erythema	2.4	16.2	61.3	47.2
SA19	F	3.4	AD	+	local erythema, abdominal pain	1.9	0.1	0.5	0.2
SA20	M	7.9	AD	+	oral or pharyngeal itch	1.0	100.0	6.3	2.3
SA21	F	14	AD	+	local hives	0.9	100.0	0.1	0.1
SA22	M	11.2	AD, AR	—	oral or pharyngeal itch	0.8	100.0	0.4	0.6
NSA1	F	3.9	—	—	—	48.3	40.8	0.1	0.1
NSA2	M	8.3	AD, AR	+	—	37.8	100.0	1.3	1.2
NSA3	M	7	AD	—	—	34.2	100.0	0.6	0.6
NSA4	M	14.4	AD	—	—	16.6	100.0	0.7	0.5
NSA5	F	2.4	AD	+	—	16.3	4.6	18.3	15.1
NSA6	F	5.6	AD	—	—	14.5	100.0	55.8	57.6
NSA7	M	1.5	—	—	—	6.7	0.9	4.0	4.2
NSA8	M	1.1	AD	—	—	5.9	0.4	66.8	43.6
NSA9	F	6.1	AR	+	—	5.0	5.4	2.1	2.1
NSA10	M	4.4	AD	—	—	4.3	33.2	2.1	2.1
NSA11	M	8.9	AD, AR	+	—	4.0	68.8	0.1	0.1
NSA12	M	5.9	AD	+	—	2.6	96.3	1.1	1.1
NSA13	M	2.8	AD, BA, AR	—	—	2.4	100.0	1.4	0.7
NSA14	F	7.5	AD	+	—	2.3	40.8	0.7	0.8
NSA15	M	4.5	AD, BA	—	—	1.9	100.0	12.4	6.6
NSA16	M	3.6	AD	—	—	1.8	100.0	5.1	3.7
NSA17	M	10	AD	—	—	1.4	0.1	0.5	0.2
NSA18	F	3.7	AD	+	—	1.3	54.4	1.5	1.2
NSA19	F	6.8	AD, BA	—	—	1.2	61.1	3.6	4.3
NSA20	M	7.2	AD	+	—	1.1	30.0	0.8	0.7
NSA21	M	5.1	AR	—	—	0.7	100.0	30.0	26.4

SA, shrimp allergy; NSA, non-shrimp allergy; M, male; F, female.
AD, atopic dermatitis; BA, bronchial asthma; AR, allergic rhinitis.

- Shrimp allergy patients
Rs=0.95 (p<0.001)
- Non-shrimp allergy patients
Rs=0.98 (p<0.001)

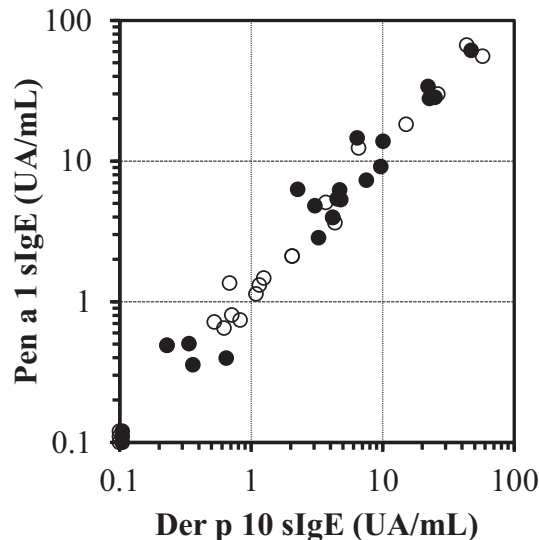


Fig. 1. A scatterplot of specific IgE to Pen a 1 and Der p 10. Closed and open circles represent shrimp allergy (SA) and non-shrimp allergy (NSA) patients, respectively. The correlation coefficient was calculated using Spearman's rank sum test.

Pen a 1 or Der p 10 directly. However, recombinant Der p 10 is reported to show low allergenic activity detected by the degranulation of passively sensitized rat basophil leukemia cells transfected with human FcεR 1.⁹ Wong *et al.* suggested that sensitization to shrimp tropomyosin would induce mild oral symptoms after the ingestion of shrimp,⁶ but sIgE to Pen a 1 did not differentiate shrimp oral allergy syndrome in the present study (Supplementary Fig. 4). Finally, we did not directly prove a causal relationship between sIgE to Pen a 1 and Der p 10. Further studies including non-HDM-sensitized children or inhibition analyses are needed.

In conclusion, we showed that Pen a 1 is a cross-reactive allergen to Der p 10 and might not contribute to the occurrence of shrimp allergy. A more comprehensive approach of component-resolved diagnostics may be needed to improve the diagnostic power of shrimp allergy.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.alit.2019.10.002>.

Conflict of interest

The authors have no conflict of interest to declare.

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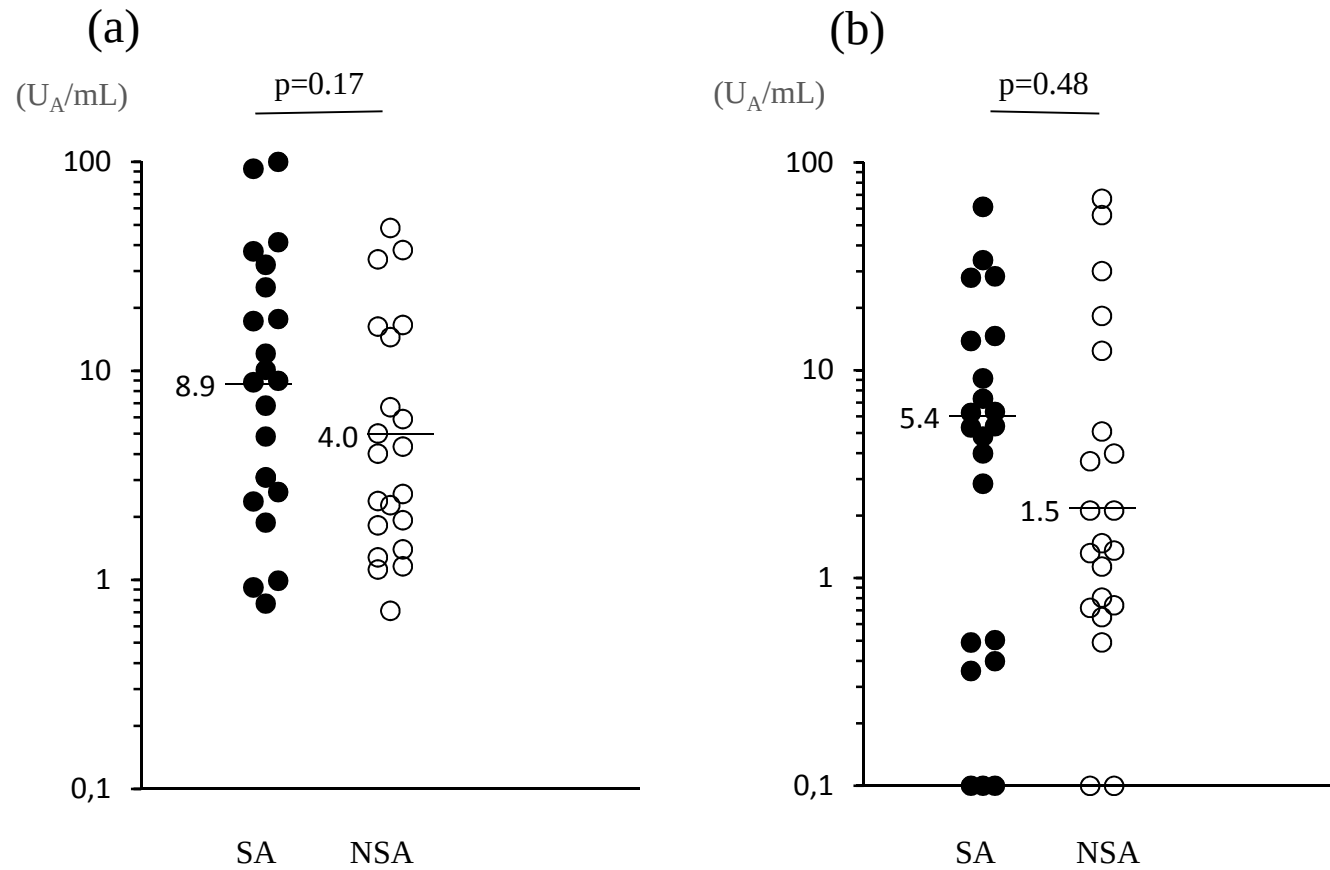
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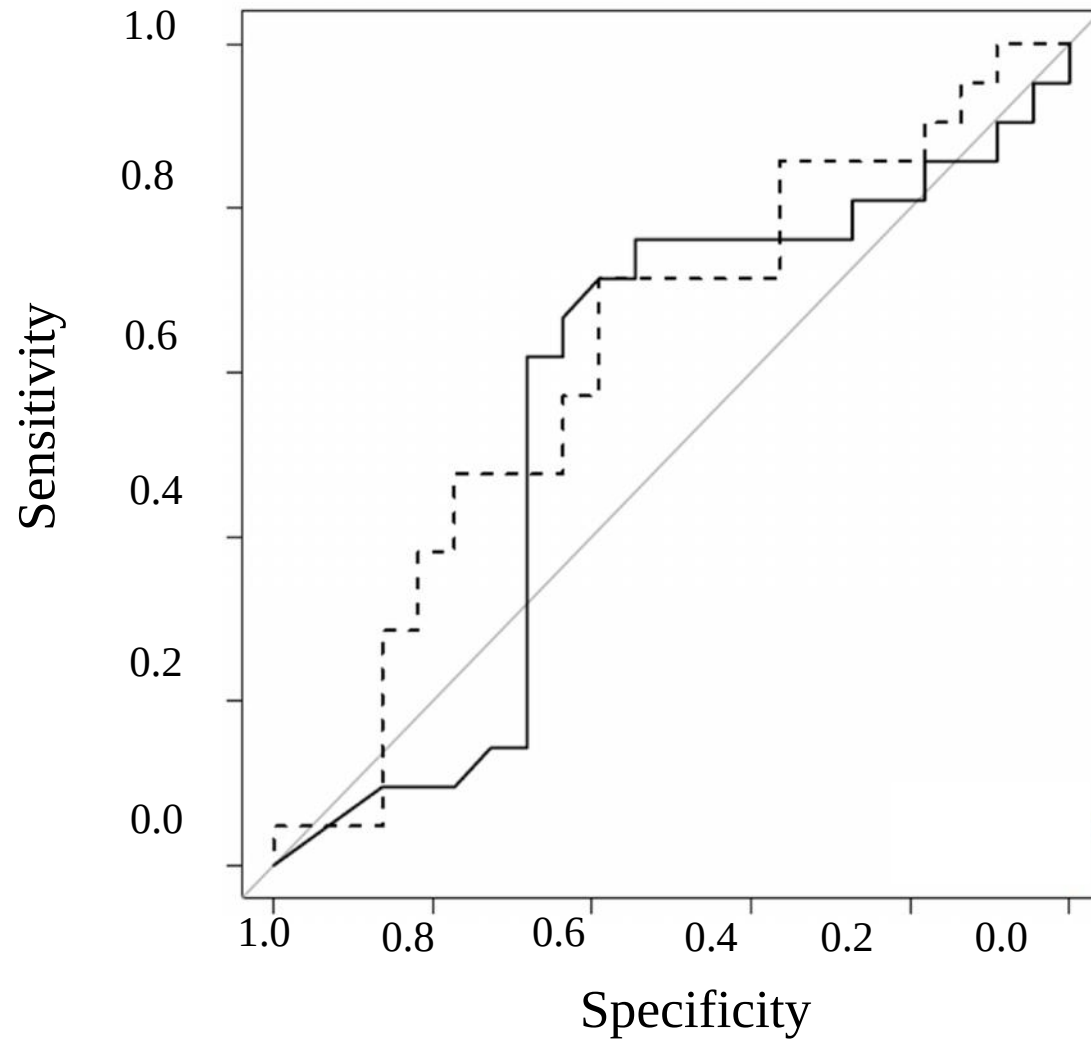
Supplementary Figures

Pen a 1-specific IgE does not improve the accuracy of a shrimp allergy diagnosis among Japanese children due to cross-reactivity with Der p 10.



Supplementary Figure 1. Specific IgE levels to crude shrimp extract and Pen a 1.

Individual sIgE levels to crude shrimp extract (a) and Pen a 1 (b) are plotted in shrimp allergy (SA) and non-shrimp allergy (NSA) children. The lines represent the median level of each group. The Mann-Whitney U test was used to compare the significance of differences between the study groups.



Supplementary Figure 2. ROC analysis of specific IgE to Pen a 1 and shrimp extract.

sIgE to Pen a 1 (solid line, AUC = 0.56; 95% confidence interval 0.38-0.75) did not improve the diagnostic accuracy of sIgE to crude shrimp extract (dashed line, AUC = 0.62; 95% confidence interval 0.45-0.79)

Pen a 1	(Genbank #AAZ76743.1)
Der p 10	(Genbank #AAB69424.1)

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Pen a 1  M D A I K K K M Q A M K L E K D N A M D R A D T L E Q Q N K E A N N R A E K S E E E V H N L Q K R M Q Q L E N D L D Q V
          M + A I K K K M Q A M K L E K D N A + D R A +   E Q + + +   A N   R A E K S E E E V   L Q K + + Q Q + E N + I D Q V
Der p 10 M E A I K K K M Q A M K L E K D N A I D R A E I A E Q K A R D A N L R A E K S E E E V R A L Q K K I Q Q I E N E L D Q V

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Pen a 1  Q E S L L K A N I Q L V E K D K A L S N A E G E V A A L N R R I Q L L E E D L E R S E E R L N T A T T K L A E A S Q A A
          Q E   L   A N   + L   E K + K A L   A E G + V A A L N R R I Q L + E E D L E R S E E R L   A T   K L E A   S Q + A
Der p 10 Q E Q L S A A N T K L E E K E K A L Q T A E G D V A A L N R R I Q L I E E D L E R S E E R L K I A T A K L E E A S Q S A

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Pen a 1  D E S E R M R K V L E N R S L S D E E R M D A L E N Q L K E A R F L A E E A D R K Y D E V A R K L A M V E A D L E R A E
          D E S E R M R K + L E + R S + + D E E R M +   L E N Q L K E A R +   A E + A D R K Y D E V A R K L A M V E A D L E R A E
Der p 10 D E S E R M R K M L E H R S I T D E E R M E G L E N Q L K E A R M M A E D A D R K Y D E V A R K L A M V E A D L E R A E

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Pen a 1  E R A E T G E S K I V E L E E E L R V V G N N L K S L E V S E E K A N Q R E E A Y K E Q I K T L T N K L K A A E A R A E
          E R A E T G E S K I V E L E E E L R V V G N N L K S L E V S E E K A   Q R E E A + + + Q I +   + T   K L K   A E A R A E
Der p 10 E R A E T G E S K I V E L E E E L R V V G N N L K S L E V S E E K A Q Q R E E A H E Q Q I R I M T T K L K E A E A R A E

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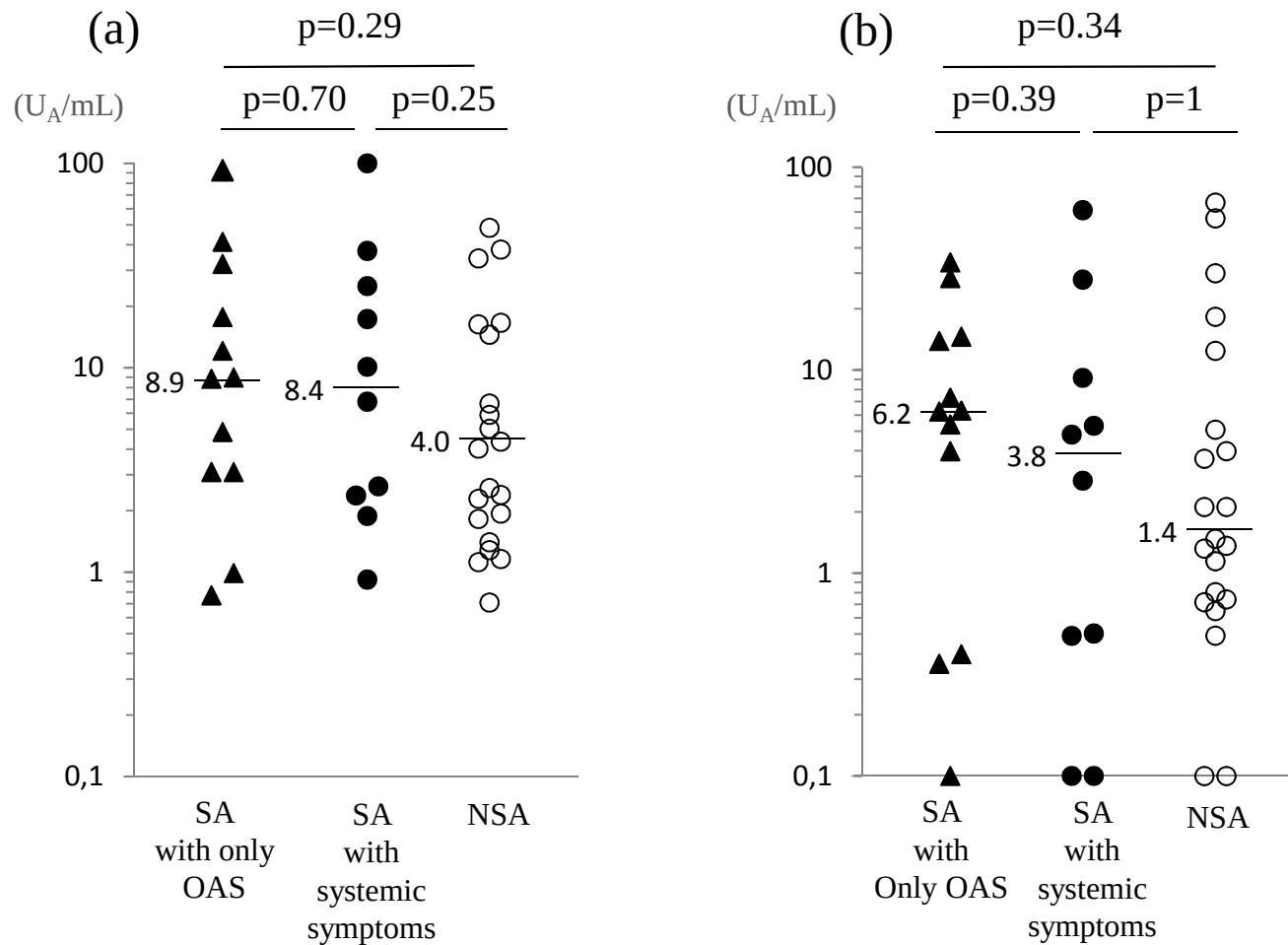
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Pen a 1  F A E R S V Q K L Q K E V D R L E D E L V N E K E K Y K S I T D E L D Q T F S E L S G Y
          F A E R S V Q K L Q K E V D R L E D E L V + E K E K Y K S I + D E L D Q T F + E L + G Y
Der p 10 F A E R S V Q K L Q K E V D R L E D E L V H E K E K Y K S I S D E L D Q T F A E L T G Y

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Supplementary Figure 3. Alignment of the amino acid sequences of Pen a 1 and Der p 10.

Pen a 1 (Genbank #AAZ76743.1) and Der p 10 (Genbank #AAB69424.1) show 81% amino acid identity and 91% homology according to a Basic Local Alignment Search Tool (BLAST) analysis.



Supplementary Figure 4. Specific IgE levels to crude shrimp extract and Pen a 1 between SA patients with only oral allergy syndrome (OAS), SA patients with systemic symptoms and NSA patients.

Individual sIgE levels to crude shrimp extract (a) and Pen a 1 (b) are plotted in SA children with only oral allergy syndrome (OAS), SA children with systemic symptoms and non-shrimp allergy (NSA) children. The lines represent the median level of each group. The Mann-Whitney U test was used to compare the significance of differences between each of the study groups.