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The extract, the molecular allergen or both for the *in vitro* diagnosis of peach and peanut sensitization?

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A B S T R A C T

Introduction: Identifying the target molecule in food allergies, helps to assess the risk of anaphylaxis in a patient. Lipid Transfer Protein is the most frequent cause of food allergies in the Mediterranean area. The diagnosis based on allergenic extracts, suffers from a high variability in the results because some important allergenic molecules are lacking. This study was disegned to assess whether Pru p 3 and Ara h 9 molecules are quantitative and qualitative enough present in their whole allergenic extracts.

Methods: 943 patients with a clinical history of suspected peach and/or peanut food allergies were recruited and underwent measurement of a specific serum IgE (ImmunoCAP system (Thermofisher/Phadia Diagnostics, Uppsala, Sweden) to the following allergens and molecules: peach (f95) and/or peanut (f13), Pru p 3 (f420), Pru p 1 (f419), Pru p 4 (f421), Ara h 1 (f422), Ara h 2 (f423) Ara h 3 (f424) and Ara h 9 (f427).

Results: Out of the 943 patients included in this study, 122 were positive to sIgE to peanut extract. At a cut-off point of 0.35 kIU/L, 62 patients were positive to sIgE to Ara h 9 but negative to peanut extract. Increasing the cut-off point of Ara h 9 at 10 kIU/L, 15 patients were only positive to sIgE to Ara h 9. 244 out of the 943 patients were positive to sIgE to peach extract. At a cut-off point of 0.35 kIU/L, 27 patients were negative to sIgE to Pru p 3 and positive to sIgE to peach extract, whilst 11 patients were peach extract sIgE positive and sIgE negative to Pru p 1, Pru p 3 and Pru p 4. Only 12 patients resulted positive to Pru p1 and/or Pru p 4.

Conclusion: Our data strongly suggests to include the measurement of sIgE to Ara h 9 into the diagnostic algorithm of peanut sensitization. 4.5% of the sicilian population suspected of peach sensitization were positive to peach extract and negative to all the available molecules.

1. Introduction

In recent years, component resolved diagnosis (CRD) has greatly improved diagnostic precision in the fields of respiratory and IgE-mediated food allergy [1]. The ability to of identify the target molecule involved in the allergic sensitization has opened up new horizons to approach allergic diseases. Particularly in the field of food allergy, CRD helps to improve the risk assessment of allergic patients by distinguishing between sensitization of extremely cross-reactive labile molecules (PR-10, Profilin) and highly stable allergenic molecules with an elevated number of possible cross-reacting molecules(Lipid Transfer Protein, Serum Albumin, and Parvalbumin) or molecules which are particularly stable but with a limited number of cross-reactions (Seed Storage Protein, Casein and Ovomucoid) [2]. In Europe, it has been possible to identify a geographical molecular patterns of sensitization, leading to the presence of a north-south gradient: at higher latitudes, prevails the sensitization to Profillin and PR-10 molecules, while in the south, the sensitization to LTP [3–11] is more frequent.

Recently, a sicilian study: has confirmed that sensitization to LTP was the most common cause of food allergy in the area and was frequently found as an isolated sensitization rather than associated with other panallergenic molecules [11].

Diagnosis based on allergenic extracts, particularly skin prick test extracts, suffers from a high variability, not only in the quality but also in the quantity of the allergen, between different manufacturers of the same allergenic product and between different batches of the same allergen [12–23]. In addition to the lack of standardization, it has been shown that some important allergenic molecules (such as Hev b 5, Gly m 4 and Omega-5 gliadin) are lost during the extraction process. Therefore, if the manufacturer does not artificially add the molecule into the extract, its concentration will be very low [24–30]. For example, Prolamins, which are responsible for severe allergic reactions, are not always well represented in the allergenic extracts due to their chemical characteristics [29,30]. Despite of this, the extracts must always be used for the in vitro diagnosis because contein some allergenic proteins, like Peamaclin in peach extract, that are responsabily for severe allergic reactions but at the moment are not available for daily use [31].

In a sensitized LTP population, no studies have been done to assess if the in vitro diagnostic sensitivity of peanut and peach allergenic

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extracts, is adequate. We would like to emphasized that this study was not designed to evaluate the clinical symptoms due to peach and/or peanut allergic sensitization.

2. Materials and methods

Between October 2015 and March 2016, 943 patients were consecutively recruited from the outpatient Allergy clinics of IBIM - C.N.R. and Buccheri La Ferla Hospital (Palermo, Sicily), with a suspected food allergy reaction and suggestive anamnesis of a possible sensitization due to peach or peanut fruit. The mean age was 37.8 (S.D. ± 27.4, range 3–62 ys old), 627 (66.5%) were females/316 (33.5%) were males, 67 of them were < 7 years. All individuals have reported clinical manifestations potentially due to an allergic reaction (asthma, rhinitis, conjunctivitis, urticaria/angioedema, abdominal pain, diarrhea, vomiting or anaphylaxis) after have eaten meals including one of thes fruits underwent the Skin Prick Test (SPT) with extract of peach and peanut, (ALK Abello, Spain). Furthermore, on the basis of clinical history suggestive of possible sensitization to peach or peanut, the recruited outpatients were tested for the specific serum IgE (ImmunoCAP system (Thermofisher/Phadia Diagnostics, Uppsala, Sweden). Specifically, six hundred and thirty-one outpatients having a suspected allergic reaction after a meal including peach, were tested for specific IgE (sIgE) with peach (F95), Pru p 3 (F420), Pru p 1 (F419), Pru p 4 (F421). Furthermore, 312 outpatients having a suspected allergic reaction after a meal including peanut, were tested with extract of peanut (F13), Ara h 1 (F422), Ara h 2 (F423) Ara h 3 (F424), Ara h 9 (F427), Pru p 1 (F419), Pru p 4 (F421). As a result, 569 outpatients that resulted negative to both of the previous tests, were excluded from the study. After a further depth clinical revaluation, in 32 outpatients positive to peanut and in 84 outpatients positive to peach the role of these allergens, to elicit the allergic reaction, was not confirmed. These subjects, in fact, ate peanut or peach again without reaction and then they underwent another diagnosis. 98 outpatients positive to peanut and 162 outpatients positive to peach presented a very convincing history of allergic reaction to these foods and were stratified as confirmed.

Results were expressed in kIU/L and values > 0.35 kIU/L were considered positive. Fig. 1 represents the flowchart of peanut and peach sensitization.

2.1. Data analysis

Statistical analysis was performed with MedCalc software, version. 18.2.1. Mean values with standard deviations were calculated. McNemar's test was applied to explore any statistical difference in positive/negative results in the "*in vitro*" tests. The Mann-Whitney test was used to compare the allergenic whole extract of peanut and peach by LTP. A comparison between the same groups was made using linear regression, Passing-Bablok regression and the concordance coefficient. Results were considered significant when p-value was < 0.05.

3. Results

Table 1 summarizes the positivity of outpatients with SPT, sIgE for F13, Ara h 9, F95 and Pru p 3. Fifty-six outpatients out of the 312 included in the peanut group were positive to SPT with the peanut whole extracts. If using a sIgE cut-off point of 0.35 kIU/L, the subjects positive to F13 extract numbered 60. Interestingly, with the same sIgE cut-off, 122 outpatients were positive to Ara h 9. The distribution of specific IgE levels for F13 whole extracts and Ara h 9 is represented in Fig. 2 using the Box-and-Whisker plot. The Mann-Whitney test underlined a significant difference between the F13 and Ara h 9 results (median values 0.0200 and 0.0500 kIU/L, respectively; p-value = .0009). The results of the Passing-Block regression between Ara h 9 and peanut is shown in Fig. 3. The arithmetic average and standard deviation between peanut and Ara h 9 was 0.857 ± 3.144 and 3.571 ± 11.759 kIU/L, respectively. The regression Equation was y = −0.288 + 30.318 x. The concordance coefficient between peanut and Ara h 9 was of 0.0227 with a 95% Confidence interval (CI) of −0.0759 -0.1210. Of the sensitized outpatients, 98 were symptomatic after the ingestion of peanuts, 9 with local oral symptoms and 89 with systemic symptoms (eg. urticaria and/or angioedema, anaphylaxis). In

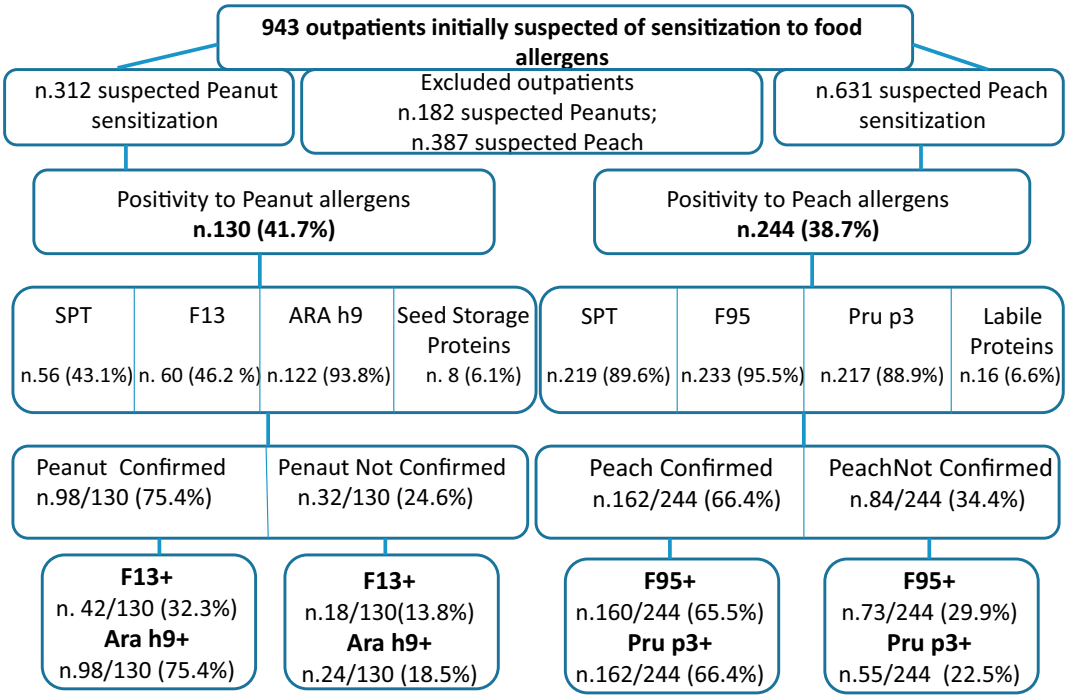

Fig. 1. Flowchart (with absolute numbers and percentages) of suspected sensitization to peanut (312) and peach (631) and test resultes. SPT = Skin Prick Test. F13 = Immunocap peanut whole extract. F95 = Immunocap Ppeach whole extract. Seed Storage proteins = Ara h 1, Ara h 2, Ara h 3. Labile proteins = Pru p 1, Pru p 4.

Table 1
Characteristics of sensitization to Peanut and Peach in 943 outpatiens studied (sIgE cut-off 0,35 kIU).

	sIgE whole extracs	sIgE LTP (Ara h9 and Pru p3)	p*	Pru p4	Prup1	Ara h1	Ara h2	Ara h3	Skin Prick test whole extracts
Peanut n.312	60/312 (19.2%)	122/312 (39.1%)	$p < 0{,}0001$	0	0	2 (0.64%)	5 (1.6%	1 (0.32%)	56 (17.9%)
Peach n.631	244/631 (38.7%)	217/631(34.4%)	$p < 0{,}0001$	12(1.9%)	4 (0.63%)				219 (34.7%)
Peanut confirmed n.98/312	42/98 (42.9%)	98/98 (100%)	$p < 0{,}0001$						39 (39.8%)
Peanut not confirmed 214/312	18/214 (19.2%)	24/214 (11.2%)	$p < .0001$						17 (7.9%)
Peach confirmed 162/631	160/162 (98.8%)	162/162 (100%)	$p = .5$						159 (98.1%)
Peach not confirmed 469	84/469 (17.9%)	55/469 (11.7%)	$p < .0001$						60 (12.8%)

* Mc Nemar test.

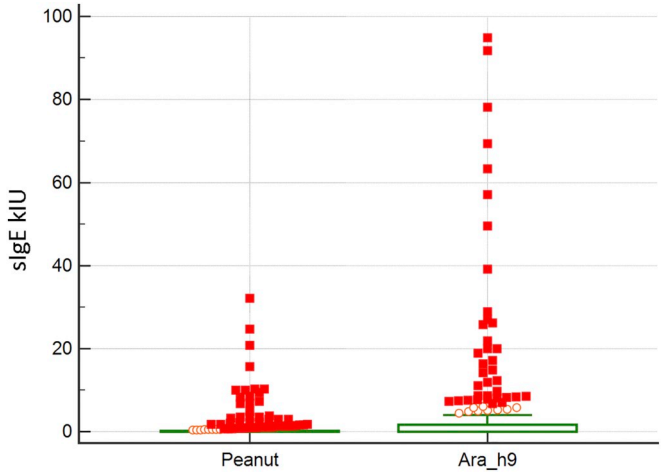

Fig. 2. Box-and-Whisker plot of distribution of specific IgE levels for F13 whole peanut extract and Ara h 9.

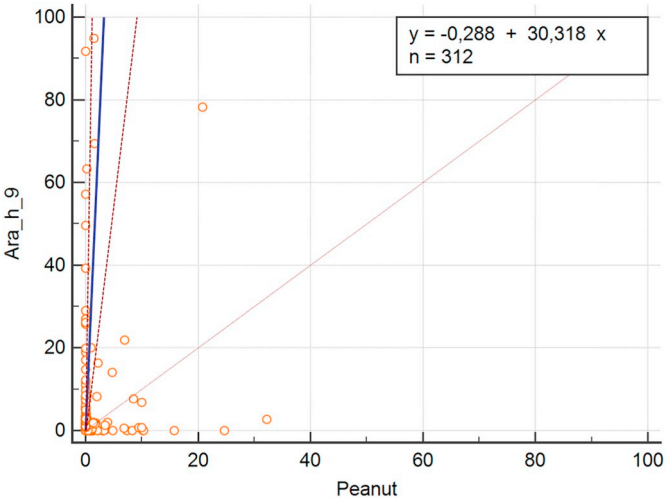

Fig. 3. Passing-Bablok regression between sIgE to Ara h 9 and sIgE to whole peanut extract.

these peanut confirmed outpatients, the Mann-Whitney test highlighted a statistically significant difference between F13 and Ara h 9 levels, with median values of 0.01000 and 3.4750 kIU/L, respectively (p-value < .0001), while in subjects not confirmed the median was of 0.0200 and 0.0050 kIU/L (p-value = .0002), respectively. Fig. 4 represents the distribution of specific IgE levels for F13 whole extracts and Ara h 9 in confirmed and not confirmed outpatients.

For peach sensitization, 219 outpatients were positive to SPT, 244 to sIgE F95, 217 with Pru p 3, 12 to Pru p 4 and 4 to Pru p 1. Fig. 5 shows the Box-and-Whisker plot of the distribution of specific IgE levels for F95 whole extracts and Pru p 3. The Mann-Whitney test didn't highlight a statistically significant difference between F95 and Pru p 3 levels (median values 0.0400 and 0.0400 kIU/L, respectively; p-value = .1138). The Passing-Bablok regression between Pru p 3 and peach is shown in Fig. 6. The arithmetic average and standard deviation between peach and Pru p 3 were 3.8379 ± 11.3103 and 4.3713 ± 13.3829 kIU/L, respectively, and the regression equation was y = 0.0038 + 1.154 x. The concordance coefficient between Pru p 3 and peach was of 0.8840 (95%CI: 0.8642–0.9985).

Interestingly, 11 of the F95-positive outpatients resulted negative to all the peach molecules available. Of the outpatients sensitized, 156 were symptomatic after the ingestion of peach, 12 with local oral symptoms and 144 with systemic symptoms (eg. urticaria and/or

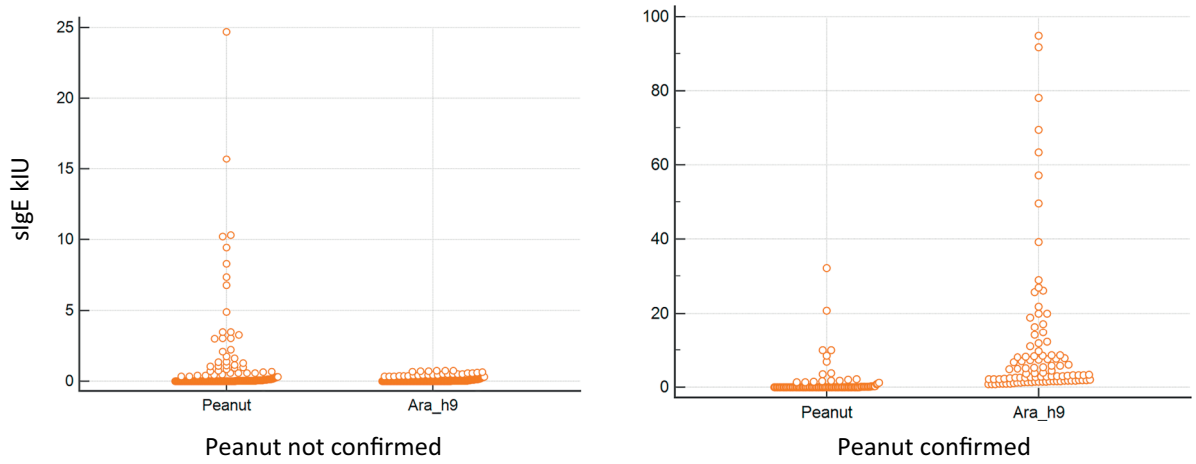

Fig. 4. Box-and-Whisker plot of distribution of specific IgE levels for F13 whole extracts and Ara h 9 in symptomatic and asymptomatic outpatients.

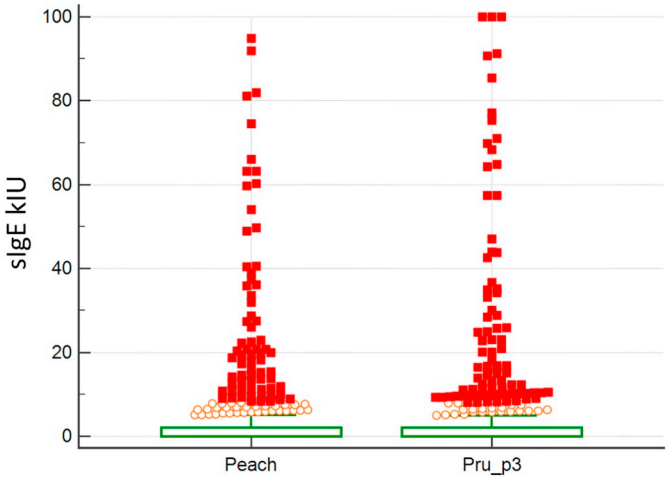

Fig. 5. Box-and-Whisker plot of distribution of specific IgE levels for whole peach extract and Pru p 3.

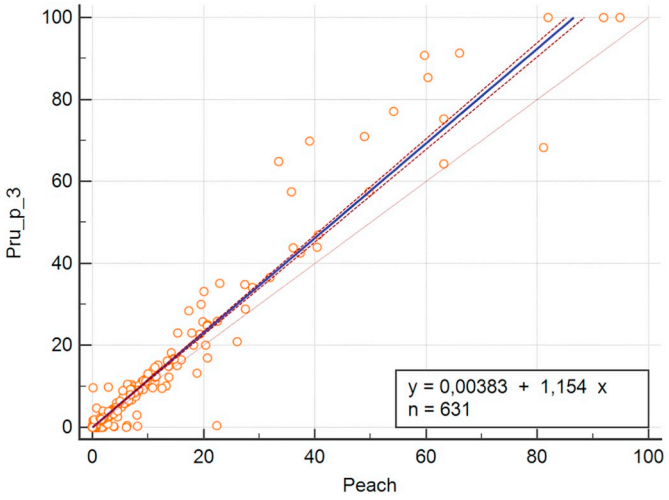

Fig. 6. Passing-Bablok regression between sIgE to Pru p 3 and sIgE to whole peach extract.

angioedema, anaphylaxis). The Mann-Whitney test was calculated both in these and in not confirmed peach sensitized outpatients, but there was no statistically significant difference between F95 and Pru p 3 both in confirmed outpatients (median values 0.02500 and 0.0300 kIU/L, respectively; p-value = .0791), while in not confirmed subjects (medians 0.0400 and 0.0400 kIU/L) the p-value was equal to 0.0235). The Mac Nemar test confirms a statistically significant difference between F95 and Pru p 3 in peach not confirmed subjects ($p < .0001$); Table 1). Fig. 7 shows the distribution of IgE levels of F95 and Pru p 3. in confirmed and not confirmed outpatients: there was no significant difference between SPT and sIgE whole extracts for peanut and peach.

4. Discussion

Peanuts are one of the main allergenic sources responsible for serious allergic reactions throughout the world. Frequently, sensitization involves the seed storage proteins, particularly Ara h 2 [32–36]. However, in some geographical regions the most frequent sensitization is not Ara h 2 but Ara h 9 [37–39].

Lauer et al. compared Mediterranean with non-Mediterranean patients allergic to peanuts and found tha,t the former had a prevalence of sensitization to Ara h 9 of 90.6% and the latter, only of 14.6% [38]. Using microarray ISAC, Goikoetxea et al. reported a sensitization of the peanut LTP of 66.6% [40].

Results from Sicilian patients sensitized to peanuts showed a high prevalence of sIgE to Ara h 9. Indeed, at a cut-off point of 0.35 kIU/L in the studied population, the sensitization was equal to 39.1%, predominant as compared with the sensitization to Seed Storage Proteins (6.1%).

It is surprising that when using the whole extract in the diagnosis the sensitivity decreased by only 19.2%.

Several studies have evaluated the sensitivity of specific IgE to peanut extract [41–44], focusing on the clinical output. A recent review highlighted that the sensitivity to the peanut extract was between 80% and 100% [45], but none of the studies were performed using a Mediterranean population. By contrast, studies from Japan, Thailand, Sweden, and Denmark have found a sensitivity of Ara h 9 between 8.6% and 26%. Our study pointed out that the sensitivity to F13 in confirmed outpatients, mainly sensitized with LTP, was of 42.9%, while the sensitivity of Ara h 9 was equal to 100%. A significant difference was shown between the results obtained with F13 and Ara h 9 both in not confirmed and in confirmed patients. Our findings documented an absence of correlation and concordance between peanut whole extract and Ara h 9. Our study is not in contrast with previous studies where the populations are different and they have different molecular patterns of allergic sensitization. Due to the allergenic importance of Ara h 9, use of peanut extract in the diagnostic algorithm of peanut sensitization in the Mediterranean populations was not considered to be suitable as a screening test, but it requires measurement of the LTP molecule. The very low prevalence of sensitization to the other peanut molecules did

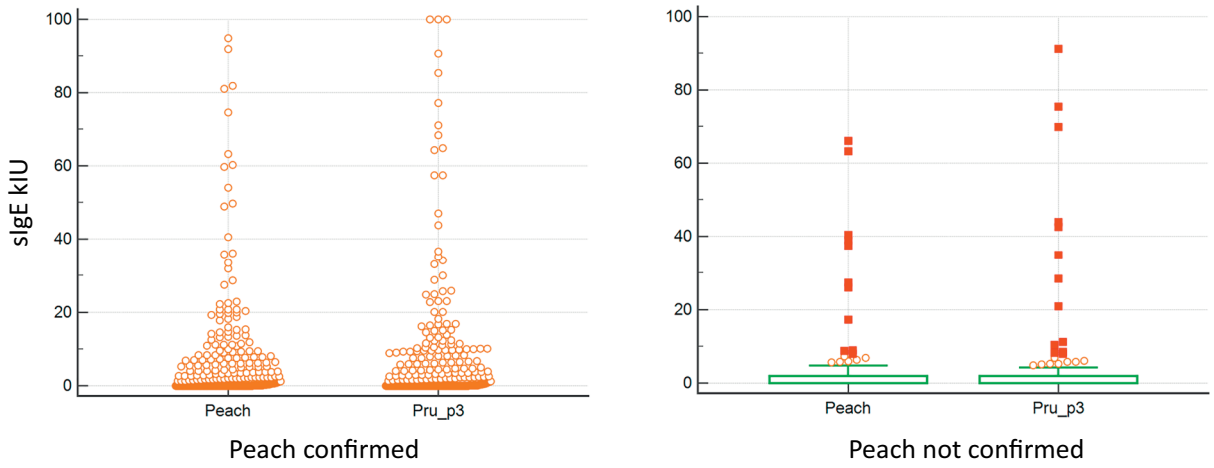

Fig. 7. Box-and-Whisker plot of distribution of specific IgE levels for F95 whole extracts and Pru- p 3 in symptomatic and asymptomatic outpatients.

not allow us to add statistically relevant results relative to the diagnostic sensitivity of peanut extract in outpatients sensitized to them.

In contrast, the measurements of the sIgE to peach extract and Pru p 3 showed a high degree of correlation between both tests, confirming the predominant sensitization of Pru p 3 in the Sicilian population [11,46]. Anyway, the Mann-Whitney test highlights a significant difference between F95 and Pru p 3 only in not confirmed subjects. This data supports the study done by Gamboa et al. [47] in a Mediterranean population. A comparison between the positivity to sIgE to peach extract and the negativity to sIgE Pru p 3 is rather interesting. Indeed, peach contains another allergen called Peamaclein (Pru p 7) that is responsible for important allergic reactions, but no specific commercial test is available at the moment [31,48,49]. This allergen is present in the pulp, while LTP is predominantly located in the skin of the fruit [50]. The sensitization to Pru p 7 could be suspected in patients who are positive to whole peach extract but negative to all other molecular peach allergens (Profilin, PR 10 and Pru p 3).

A recent study conducted in a Japanese population demonstrated the high prevalence of sensitization to Pru p 7 (13%) with a co-sensitization to Pru p 3 in 2% of patients. Interestingly, data from symptomatic peach allergic patients from France showed 78% of sensitization to Pru p 7 (cut-off point > 0.1) and 31% of sensitization in a-symptomatic patients. Sensitization to Peamaclein is clinically associated with severe symptoms [51].

This study shows that 4.5% of patients positive to peach extract were negative to Pru p 3, Profilin, and PR 10. This result was probably determined by sensitization to other molecules contained in the extract as Peamaclein or other unknown molecules. Nevertheless, only after the availability of a specific tests will it be possible to identify the target allergen.

Lastly, the findings related to Profilin and PR-10 confirm the low predominant sensitization of these molecules in patients with food allergy in Sicily as it was previously observed in a high number of patients [11,46].

5. Conclusion

This study strongly highlights the importance of including measurement of sIgE Ara h 9 in the diagnostic algorithm of peanut sensitization.

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