

DR. CLAUDIA ALESSANDRI (Orcid ID : 0000-0003-2466-6870)

Article type : Letter to the Editor

Are peas a safe food for LTP allergic patients?

Manuscript Acceptance Date: 24-Feb-2021

Claudia Alessandri^{1,2*}, Ivana Giangrieco^{2,3*}, LisaTuppo^{2,3}, Rosetta Ferrara^{1,2}, Danila Zennaro^{1,2}, Maria Livia Bernardi¹, Michela Ciancamerla², Claudi Rafaiani², Chiara Rafaiani¹, Maurizio Tamburrini³, Adriano Mari^{1,2}, Maria Antonietta Ciardiello³.

¹*Associated Centers for Molecular Allergology (CAAM), Rome, Italy*

²*Allergy Data Laboratories s.r.l. (ADL), Latina, Italy*

³*Institute of Biosciences and BioResources (IBBR), CNR, Naples, Italy*

*These authors equally contributed to the study

Correspondence:

Claudia Alessandri

Centri Associati di Allergologia Molecolare, Rome, Italy

Tel: +39 3337637667

email: claudia.alessandri@caam-allergy.com

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/ALL.14801](https://doi.org/10.1111/ALL.14801)

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To the Editor,

Peas (*Pisum sativum*) are a popular food rich in essential amino acids and other nutrients. Besides direct ingestion, an increasing number of food companies are currently introducing on the market several products containing pea derivatives exploited for their emulsifying and gelling properties and as plant-based meat substitutes. Two main allergens were identified in peas, the vicilin Pis s 1 and the convicilin Pis s 2. Next, in 2016 pea LTP was isolated, characterized and its recognition by IgE of Pru p 3 sensitized patients was assessed.¹ Pea LTP was then registered by WHO/IUIS as Pis s 3. In the context of a globally increased abundance in pea protein in the food supply chain, this study sought to investigate the association between sensitization towards Pis s 3, revealed with the detection of specific IgE, and the clinical manifestation of allergic reactions in a random population of LTP allergic patients.

Out of 11466 sera tested for any type of suspected allergy by means of FABER[®] test, 896 resulted positive to at least one of the ten plant food LTP present on the FABER biochip (see Online Supporting Information and Figure S1). In line with the available knowledge on LTP allergy, Pru p 3 displayed the highest prevalence (93%) of sensitization, compared to LTP from other sources (Figure 1). In the randomly tested population, Pis s 3 proved to be the 9-kDa LTP showing the lowest sensitization prevalence (8.4%). This value is even lower than that obtained for tomato Sola l 6, belonging to the sub-family of the 7-kDa LTP, the components of which are known to cause sensitization with a low prevalence.³ Nevertheless, four patients sensitized to Pis s 3 were not IgE positive to Pru p 3, thus indicating that this legume LTP contains also unshared epitopes.

The clinical history was available for 189 Italian LTP sensitized patients (Male 95, average age 32 years). Most of them (154 patients, corresponding to 81%) claimed symptoms ingesting peach and/or some other LTP sources. However, all the 189 patients had the habit to eat peas without reporting any symptom, including 18 patients IgE positive to Pis s 3 (Table 1). These Pis s 3 sensitized patients were all IgE positive to Pru p 3, whereas four of them were IgE negative to Ara h 9. Therefore, despite pea and peanut belong to the same family (*Fabaceae*), whereas peach belongs to *Rosaceae*, and despite the higher sequence identity between Pis s 3 and Ara h 9,¹ Pis s 3 seems to share higher IgE co-recognition with peach LTP compared to the peanut allergen.

Out of eighteen, seven patients (39%) sensitized to several LTP, including Pru p 3 and Pis s 3, did not report symptoms when eating any plant LTP sources (Table 1). The remaining 11 patients reported a variety of allergic symptoms when eating several fresh fruits, seeds and vegetables, but peas were not included in the list of offending foods. This observation is in line with the results of a recent study reporting that in a cohort of German children peas allergy was due to seed storage proteins rather than to LTP.⁴

In conclusion, the results of this study report for the first time that a cohort of Italian LTP allergic patients can safely consume peas. This is in line with the results of a previous investigation suggesting that another legume, bean, should be regarded safe for LTP-allergic patients.⁴ However, the reported observations also raise intriguing questions concerning the relationships between protein sequence identities, IgE co-recognition, tolerance, and clinical symptoms. The prediction of possible cross-reactions is commonly based on the protein sequence identities. Nevertheless, some studies suggest that additional factors, such as the binding of different lipid ligands to LTP,^{5,6} could affect the molecule allergenicity and make its prediction more complex than expected.

CONFLICT OF INTEREST

Competing interests: CA, MLB, RF, DZ and AM as ADL stakeholder, develop, manufacture, and distribute the FABER test as a diagnostic service. LT and IG as employees of ADL contribute to develop, manufacture and perform the FABER test. MAC and MT receive funding from ADL.

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- Accepted Article
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KEYWORDS: Pis s 3, LTP, pea, multiplex testing system

Figure legend

Figure 1. Prevalence of sera IgE positive to the tested food LTP in a random population of 896 patients sensitized to at least one of the food LTP included in the FABER® biochip. Columns are labelled with the values (%) of IgE-positive patients. 9-kDa LTP are from kiwifruit (Act d 10), peanut (Ara h 9), hazelnut (Cor a 8), pea (Pis s 3), peach (Pru p 3), pomegranate (Pun g 1) and maize (Zea m 14), whereas 7-kDa LTP are from tomato (Sola l 6) and wheat (Tri a 7k-LTP).

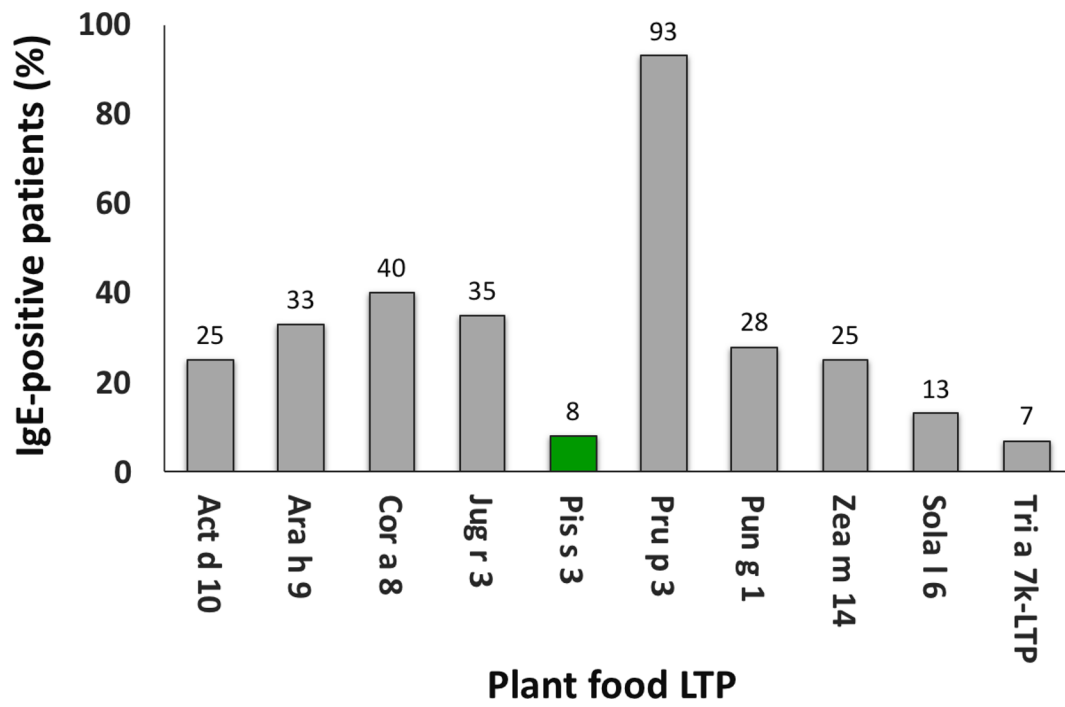
Table 1. Immunological and clinical data of 18 patients sensitized to Pis s 3. They were selected in a cohort of 189 LTP sensitized patients for which a clinical history was available.

Patient details			FABER 244 (FIU)*										Symptoms eating LTP sources [§]				Offending foods
N.	Gender	Age	Act d 10	Ara h 9	Cor a 8	Jug r 3	Pis s 3	Pru p 3	Pun g 1	Zea m 14	Sola l 6	Tri a 7k-LTP	OAS	U	G	A	Cause of symptoms [#]
1	F	54	0	0.58	0.48	0	0.39	0.97	0.39	0.39	0	0	0	1	0	0	H,P,A,B,ST
2	M	24	0.19	0.56	0.46	0	0.19	1.75	0.38	0.75	0	0	1	1	1	0	P,B
3	M	52	2.31	0.73	0	0.54	0.81	2.81	0	0	0.27	0	1	1	1	0	P,Ba,Al
4	M	11	1.2	11.56	13.07	2.56	1.49	1.8	7.95	2.39	0.9	0	0	1	0	0	W
5	F	26	0	0.23	0	0.45	0.23	2.91	0.45	0	0	0	1	0	0	0	P,H, L
6	M	45	0	3.66	0	5.24	10.95	21.95	7.36	0	7.36	0	1	0	0	0	P
7	M	15	19.62	10.98	28.39	33.82	4.41	5.49	23.41	12.01	0	0	0	1	1	0	T
8	M	25	26.22	29.97	26.19	18.22	0.71	12.11	3.5	10.56	0	0	1	0	1	0	P,RF,T,H
9	F	48	0	0.82	1.23	1.37	2.62	0.55	0.91	0	0	0	1	1	0	1	P, FJ,Wi,T
10	M	15	3.1	15.46	0.79	1.37	0.69	1.83	3.54	8.29	0.46	0	0	0	1	0	W
11	F	42	0	1.11	1.39	0.82	0.55	1.94	0	0	0.56	0	1	1	0	1	W,P,Ba,RF
12	M	16	1	0	0	2.95	3	3.92	0	0	2.94	0	0	0	0	0	0
13	M	19	2.61	24.27	31.9	20.08	13.11	2.28	22.86	4.9	0.42	0	0	0	0	0	0
14	F	40	0	0	0	0.91	8.58	7.24	7.72	1.83	0.47	0.91	0	0	0	0	0
15	M	46	0	0	0.68	1.12	0.67	1.12	3.35	1.03	0.67	0	0	0	0	0	0
16	M	38	0	0	0	0	3	1.01	0	0	0	0	0	0	0	0	0
17	F	53	7.17	14.19	6.31	8.93	6.73	4.5	4.5	9.65	9.38	6.71	0	0	0	0	0
18	M	25	2.55	2.35	8.97	1.11	0.67	1.34	4.55	0	0	0	0	0	0	0	0
Mean of all values(FIU)*			3.67	6.47	6.66	5.53	3.27	4.20	5.05	2.88	1.30	0.42					
Number of IgE-positive patients			10	14	12	16	18	18	14	10	10	2					
Mean of IgE-positive values (FIU)*			6.60	8.32	12.65	6.22	3.27	4.20	6.49	5.18	2.34	3.81					

[§]OAS, oral allergic syndrome; U, urticaria or angioedema; GI, gastrointestinal symptoms(vomiting and/or diarrhoea); A, anaphylaxis.

*FIU, FABER International Units, positive value FIU $\geq$ 0.01.

[#]H, hazelnut; P, peach; A, apricot; Al, almond; Ba, Banana; B, berries; FJ, fruit juice (peach and apricot); L, lettuce; P, peanut; RF, rosaceae fruits (peach, apricot, plum, apple); ST, string bean; T, tomato; W, walnut; Wi, wine.



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ONLINE SUPPLEMENTARY

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¹*Associated Centers for Molecular Allergology (CAAM), Rome, Italy*

²*Allergy Data Laboratories s.r.l. (ADL), Latina, Italy*

³*Institute of Biosciences and BioResources (IBBR), CNR, Naples, Italy*

*These authors equally contributed to the study

Correspondence:

Claudia Alessandri

Centri Associati di Allergologia Molecolare, Rome, Italy

Tel: +39 3337637667

email: claudia.alessandri@caam-allergy.com

METHODS

1. Specific IgE detection with the FABER® multiplex testing system

The FABER test (ADL S.r.l., Latina, Italy) is a multiplex in vitro serological test allowing the detection of specific IgE antibodies from allergic subjects.¹⁻³ This test was adopted to analyse 11466 sera of patients suffering from suspected allergy. The FABER version used to perform the present study (FABER 244-122-122) bears 244 allergenic preparations, representing 122 purified molecular allergens and 122 allergenic extracts, all conjugated to nanobeads and then spotted on a biochip. The data were obtained from a set of biochips including eight 9-kDa LTP and two 7-kDa LTP. 9-kDa LTP present on the test are the kiwi Act d 10, the peanut Ara h 9, the hazelnut Cor a 8, the pea Pis s 3, the peach Pru p 3, the pomegranate Pun g 1, the maize Zea m 14, and the 7-kDa LTP Sola l 6 from tomato and Tri a 7k-LTP from wheat.

2. Patients

Patients' demographical and clinical data, namely respiratory and ingestion-related symptoms on plant food exposure, as well as all the diagnostic data, were recorded by an allergy specialist, or transferred real time from the laboratory, into the InterAll software (version 5.0, ADL, Latina, Italy), a customized allergy electronic record for diagnostic and clinical data storing. Specific clinical informations were collected using the standard questionnaire reported in a previous study.⁴

Data from 11466 subjects consecutively tested for suspected allergy on the FABER biochip were checked and a subset of 896 patients IgE positive to at least one LTP was detected and analyzed (Figure S1). Out of 896 patients, 75 were IgE positive to Pis s 3. They were from Italy (59), Hong Kong (8), Philippines (2) Poland (2), Chile (1), Hungary (1), China (1), Paraguay (1). The clinical history was available for 18 Italian patients living in Central Southern Italy (12 from Lazio, 3 from Campania, 2 from Abruzzo, 1 from Calabria regions).

All patients gave their informed consent to the use of their clinical data for research purposes in an anonymous form. In view of the purely comparative nature of this study, along with the fact that all venous blood samplings were part of routine clinical practice and that a residual part of the routine sample was used for inhibition experiments, a formal approval by the Ethical Committee was not necessary.

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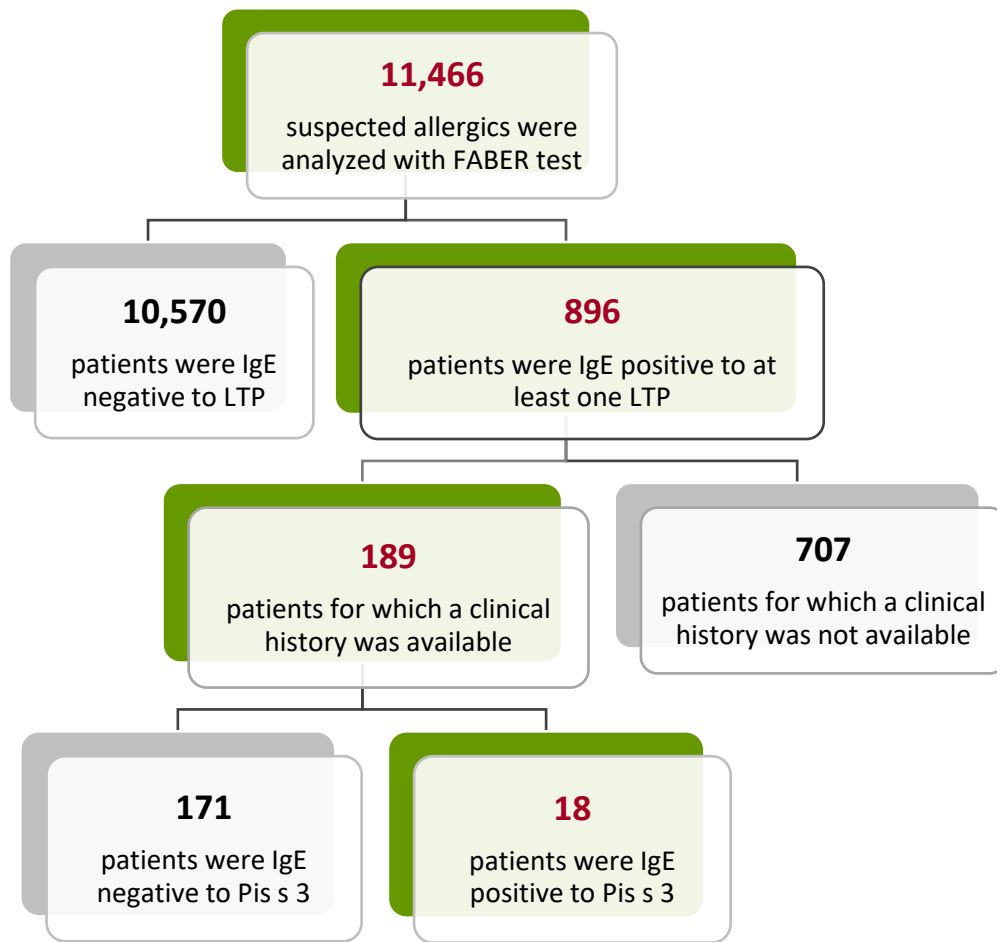


Figure S1. Flow chart showing the criteria used to obtain the grouping of patients' under investigation (from the 11,466 suspected allergics to the 18 subjects IgE positive to Pis s 3).