

Peach Tree Pollen and *Prunus persica* 9 Sensitisation and Allergy in Children and Adolescents

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Keywords

Peach tree pollen · *Prunus persica* 9 · Sensitisation · Allergy · Children · Adolescents

respiratory symptoms in children and adolescents. This allergen should be evaluated in children living in regions of peach tree cultivars.

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Abstract

Background: Although plant and fruit pollens are entomophilous and relevant in exposed workers, we have shown a high frequency of sensitisation and symptoms induction of peach tree pollen (PTP) and *Prunus persica* 9 (Pru p 9) in adults from areas of peach cultivars. **Methods:** We studied the sensitisation and clinical relevance of PTP and Pru p 9 in a large group of children and adolescents aged 3–19 years. A detailed questionnaire plus skin prick testing to prevalent allergens, PTP, and Pru p 9 were carried out. The clinical relevance was established by nasal provocation test (NPT) and symptom score index. **Results:** We evaluated 685 children (mean age 8.75 ± 3.3 years, median 9 years), 52% of them female. Sensitisation to PTP occurred in 20% of the cases following olive tree (33%) and *Phleum pratense* (26%). In a randomly selected subgroup of subjects sensitised to PTP, 30% were skin prick test-positive to Pru p 9. Most cases had rhinitis or rhinoconjunctivitis. NPT showed the relevance of PTP and Pru p 9 in the induction of symptoms. **Conclusion:** PTP and Pru p 9 are relevant in the induction of sensitisation and

Introduction

Pollens are one of the main sensitisers in the general population, including children and adolescents [1, 2]. Although allergy develops to anemophilous pollens [3, 4], allergic reactions have also been reported to entomophilous pollens [3–8]. These occur mainly in subjects occupationally exposed on big farms or closed spaces, but usually do not affect children and adolescents [9–12]. A study by Yabuhara et al. [13] found that rice pollen can induce seasonal asthma and allergic rhinoconjunctivitis in children living close to rice fields.

Allergy to peach is relevant mostly in Mediterranean countries, where this fruit is extensively consumed by persons of all ages [14]. Sensitisation to peach tree that includes lipid transfer protein or other components present

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in branches, leaves, or pollen has been shown in exposed workers, though mainly isolated cases [15, 16]. A recent study by Pérez-Calderón et al. [9] showed sensitisation to allergens present in peach tree leaves and branches in workers, who developed asthma after exposure.

A recent study carried out by our group in a large population exposed to peach tree pollen (PTP) showed that sensitisation to this pollen in the general population was third overall in frequency (20%), after olive tree and grass [17]. We identified and registered a protein of 18 kDa named *Prunus persica* 9 (Pru p 9) [18, 19], with 40% of adults sensitised to PTP [20] also being sensitised to this allergen. These subjects developed symptoms after nasal provocation test (NPT) with PTP and Pru p 9. In fact, these subjects had symptoms during the period of peach tree flowering even if they did not visit peach tree farms or orchards.

We have also reported a small series of children who were sensitised to PTP, some of whom were also positive to Pru p 9 [21]. These data were surprising since some children visited farms during the flowering season (directly exposed) whilst others did not, though they developed symptoms after contact with clothes of people working in peach tree cultivars or other circumstances (indirectly exposed).

Given this background, we wished to determine the situation regarding sensitisation in children living in the same region where the study in adults was undertaken. Accordingly, we examined a large group of children and adolescents in the same area in order to verify the sensitisation and the clinical relevance of both PTP and the new allergen named Pru p 9. Since peach tree cultivars are extensive in Europe and other regions of the world, we believe that our results can be extrapolated to other countries and are relevant in the study of induction of allergy in children and adolescents.

Methods

Study Design

We carried out a cross-sectional study in a large population of children and adolescents living in Blanca, Murcia region, south-east Spain. In order to provide information to the parents, grandparents, or caregivers responsible for the children, formal oral presentations were given in primary and secondary schools. In addition, information leaflets were provided and talks given to paediatricians, general practitioners, and teachers.

Cases

All subjects aged 3–19 years were included. Since attending primary and secondary school is compulsory, we decided to give the questionnaire and perform the skin prick test (SPT) in the schools. In those children and adolescents who volunteered after

their parents had signed written informed consent, we implemented a clinical questionnaire plus SPT and blood sample collection. In all cases the parents were also interviewed to complete the questionnaire.

Questionnaire Implementation

For each case we gave a personal interview and completed a questionnaire that included demographic, environmental, and clinical data such as birth place and date, nationality, type of delivery, school, pets, tobacco exposure, exercise, visits to farms or vegetable gardens, working on farms/vegetable gardens in the case of adolescents, and family history of atopy. Other variables included were related with socioeconomic factors: family educational status and income, work of parents, and others. We used a previously validated population-adapted questionnaire [22–24] given by two trained allergists.

Atopy Signature

Atopy was considered when subjects were SPT-positive to at least one allergen. The criteria used to establish the clinical entities like rhinitis, conjunctivitis, and asthma were as described in Johansson et al. [25].

Skin Prick Testing with Common Environmental Allergens

Skin prick testing was done with *Phleum pratense*, *Cupressus arizonica*, *Olea europaea*, *Platanus acerifolia*, *Parietaria judaica*, *Artemisia vulgaris*, and *Salsola kali* pollens (ALK-Abello®, Madrid, Spain).

Group Classification

According to the response to SPT, subjects were classified into two groups: group A, positive to at least one pollen and also positive to PTP, and group B, positive to at least one pollen but negative to PTP.

Pru p 9 Purification

Pru p 9 was purified from PTP (Iberpolen®, Spain). Briefly, Pru p 9 was purified from defatted mixture and extracted with PBS buffer (0.1 mM sodium phosphate pH 7.4, 1.5 M NaCl; 1:5 [w/v]; 1 h at 4 °C). The extract was dialysed against H₂O, freeze-dried, and fractionated by anion exchange chromatography on a Waters AccellTM Plus QMA Sep-PakR cartridge (Waters Corp., Milford, MA, USA). Elution was carried out with 20 mM ethanolamine, pH 9.0, and the retained material was then eluted with 0.75 mM NaCl in the same buffer (1 mL/min). Purified Pru p 9 was quantified by means of the commercial bicinchoninic acid test (Pierce, Cheshire, UK), and purity was measured by SDS-PAGE, mass spectrophotometric analysis with a Biflex III Spectrometer (Bruker-Franzen Analytik, Bremen, Germany), and fingerprinting after tryptic digestion, using standard methods.

Skin Prick Testing with PTP and Pru p 9

PTP extract was also made by ALK-Abello®. Optimal concentrations for SPT with PTP and Pru p 9 were established by titration curves.

NPTs with PTP and Pru p 9

Nasal provocation testing was performed with PTP and Pru p 9 as described [26]. Two groups of subjects were tested: one group of subjects who were SPT-positive to PTP and Pru p 9, and an-

Fig. 1. Frequency of pollen sensitisation. PTP, peach tree pollen.

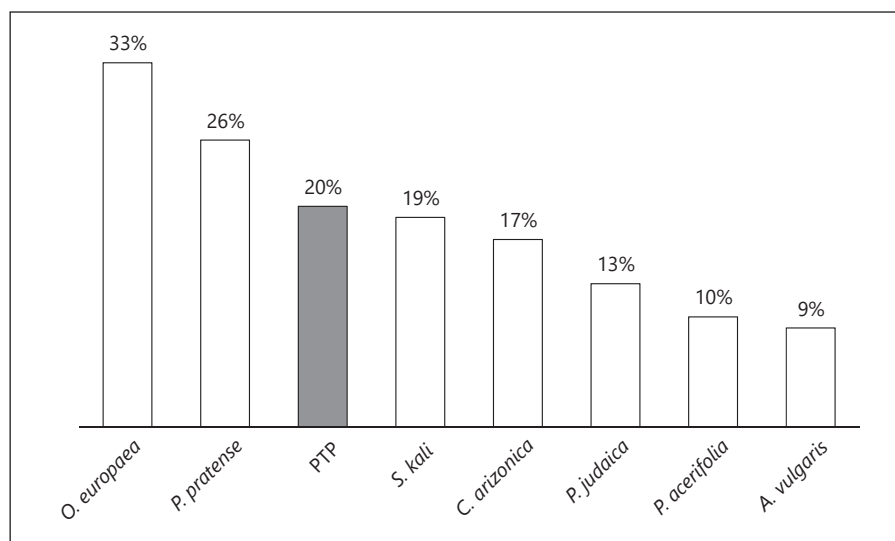
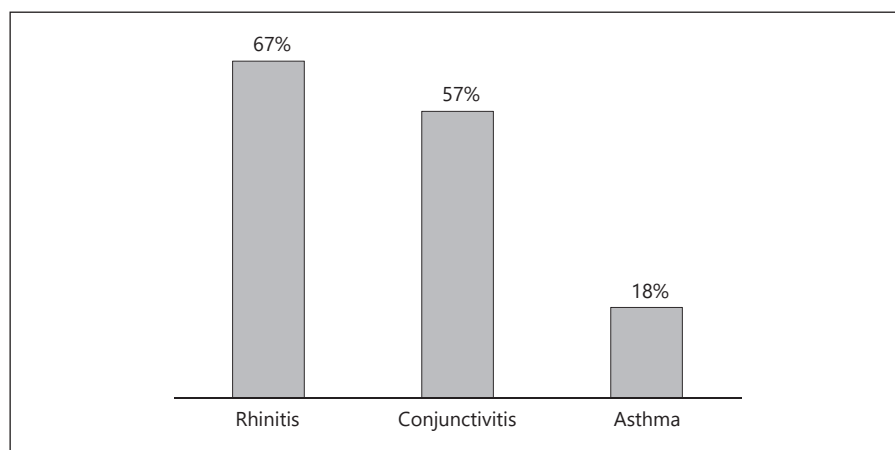


Fig. 2. Clinical entities of the study cases.



other group of subjects who were SPT-positive to PTP but negative to Pru p 9. In order to verify the specificity of the nasal response, a group of 6 subjects who were SPT-negative to both PTP and Pru p 9 was also challenged.

Statistical Analysis

For categorical variables we used the χ^2 test and for quantitative variables Student's *t* test. The association between PTP and Pru p 9 SPT wheal size expressed as the percentage of histamine area was made by Pearson's correlation coefficient. These tests were done using the statistical package SPSS 21.

Results

A total of 685 children (52% female) were evaluated, with a mean age of 8.75 ± 3.3 and a median of 9 years; 63% were younger than 10 years. When we stratified gender

into 3-year age intervals, the percentage of males in each interval was as follows: 51% in the interval 3–6 years, 48% in the interval 7–10 years, 47.5% in the interval 11–14 years, and 43.8% in the interval 15–19 years, with no significant differences.

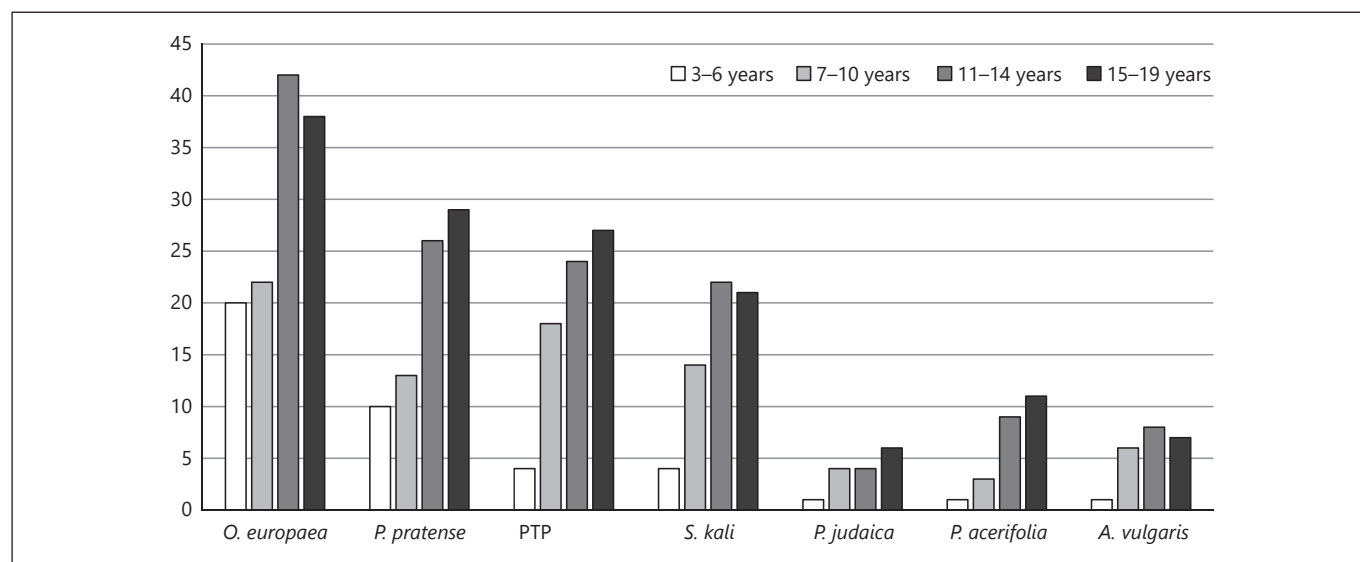
A total of 267 subjects (39%) were sensitised to at least one pollen, with the following frequency: 33% to *O. europaea*, 26% to *P. pratense*, 20% to PTP, 19% to *S. kali*, 17% to *C. arizonica*, 13% to *P. acerifolia*, and 9% to *A. vulgaris* (Fig. 1). Regarding clinical entities, 67% reported rhinitis, 57% conjunctivitis, and 18% asthma (Fig. 2).

Group A included 123 cases and group B 115 cases (Table 1). Comparison between the groups showed the following information. Sensitisation to pollen was: *O. europaea*, 74 vs. 68%, non-significant (ns); *P. pratense*, 50 vs. 57%, ns; *S. kali*, 56 vs. 21%, $p < 0.0001$; *C. arizonica*, 38

Table 1. Comparison of cases sensitised to pollen who were positive (group A) or negative (group B) to PTP

	Group A (PTP+)	Group B (PTP-)	Significance (<i>p</i> value)
Number of subjects	123	115	
Age, years	13±4	12±5	ns
Male gender	47.5%	52.5%	ns
Number of pollens +	3±1.6	2±0.9	<0.0001
Cases with symptoms in March	50.4%	26.1%	<0.001
<i>Phleum pratense</i>	50%	57%	ns
<i>Olea europaea</i>	74%	68%	ns
<i>Cupressus arizonica</i>	38%	18%	<0.02
<i>Salsola kali</i>	56%	21%	<0.0001
<i>Platanus acerifolia</i>	29%	6%	<0.001
<i>Artemisia vulgaris</i>	21%	5%	<0.02
<i>Parietaria judaica</i>	15%	7%	ns
Conjunctivitis	48.4%	51.3%	ns
Rhinitis	56.2%	62.1%	ns
Asthma	19%	18%	ns

Values are presented as *n*, mean ± SD, or percentage. ns, non-significant; PTP, peach tree pollen.

**Fig. 3.** Frequency of sensitisation stratified in 3-year periods from 3 to 19 years. PTP, peach tree pollen.

vs. 18%, $p < 0.02$; *P. acerifolia*, 29 vs. 6%, $p < 0.001$; *A. vulgaris*, 21 vs. 5%, $p < 0.02$; and *P. judaica*, 15 vs. 7%, ns. According to the questionnaire the symptoms reported were within the following clinical entities: rhinitis in 56.2 vs. 62.1%, followed by conjunctivitis in 48.4 vs. 51.3% and asthma in 19 vs. 18%. These differences were not significant (Table 1). The number of subjects with symptoms in March was 50.4 vs. 26.1%, $p = 0.001$ (Table 1).

Fourteen cases (11%) were sensitised only to PTP and therefore not included in either group A or B. Of these, 6 were male and the median age was 13 ± 1.8 years. Regarding the clinical entities, 6 cases reported symptoms compatible with rhinitis, 4 symptoms compatible with conjunctivitis, and 1 asthma.

When we analysed the frequency of sensitisation stratifying by 3-year intervals from 3 to 19 years of age (Fig. 3),

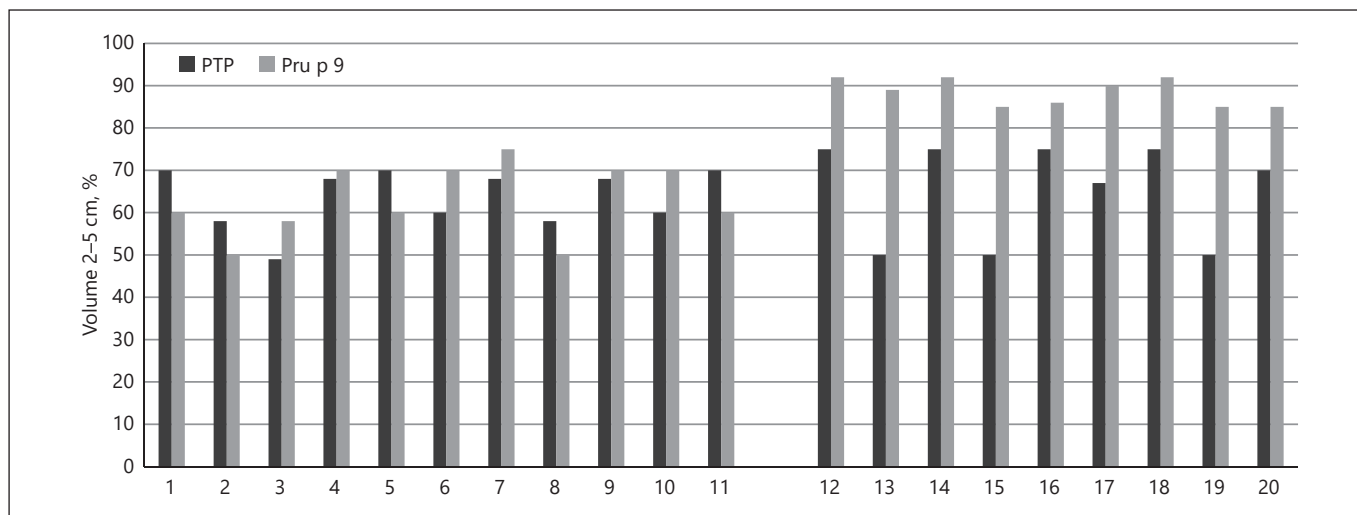


Fig. 4. PTP and Pru p 9 NPTs. Volume decrease after NPT with PTP and Pru p 9. Cases 1–11: positive NPT with PTP and positive NPT with Pru p 9. Cases 12–20: positive NPT with PTP and negative NPT with Pru p 9. NPT, nasal provocation test; Pru p 9, *Prunus persica* 9; PTP, peach tree pollen.

an increase in sensitisation was observed with all the pollens tested, including PTP, until the age of 19. The sensitisation to *O. europaea* varied from 20 to 42% between the first and the third strata. The same happened with *P. pratense* (from 10 to 26%). In the case of PTP the values increased from 4 to 24%. A similar increase occurred with *S. kali* (from 4 to 22%).

Regarding SPT with Pru p 9, the optimal concentration found for the challenge was 25 µg/mL; this did not induce a false-positive response in any of the negative control subjects. With this concentration, as shown above in this section, 30% of the cases sensitised to PTP were also SPT-positive to Pru p 9 (group A), but none in group B.

The Pearson's correlation coefficient comparison of cases that were SPT-positive to both PTP and Pru p 9 showed a low non-significant correlation ($r = 0.09$).

We performed NPT in 20 randomly selected cases positive to PTP, 11 also sensitised to Pru p 9, and 9 not sensitised (Fig. 4). In all cases a positive response appeared within the first 10–15 min after challenge with PTP, which normalised at 60 min, except for cases 2 and 8 that persisted for 24 h. The symptom scores are shown in Table 2. All cases developed a clear positive response, with a score index of ≥ 8 . On demand we administered oxymetazoline to cases 2, 3, 8, 9, 10, 13, 15, and 19. Regarding NPT with Pru p 9, the 11 cases that were skin test-positive to Pru p 9 showed a positive NPT response, but none of the 9 who were SPT-negative had a positive NPT

to Pru p 9 (Fig. 4). In cases 1, 2, 5, 8, and 11 the response was more intense and in cases 3, 4, 6, 7, 9, and 10 less intense than the response after PTP challenge; these corresponded with a larger or smaller Pru p 9 SPT wheal size (Fig. 4; Table 2).

Discussion and Conclusion

The results of our study showed that an important proportion of children and adolescents (1 in 5) were sensitised to PTP and developed symptoms, mainly in the period when flowering occurred. This frequency of sensitisation is similar to that found in adults [17]. If we consider sensitisation to common inhalant pollens, most cases sensitised to PTP were allergic to more than one pollen, implying that these children behave like they were atopic and become sensitised after encountering it in the natural habitat, even before going to farms or orchards. The importance of other indoor environmental allergens in this population was rather low, so children first became sensitised to pollens. This is in line with results from the study by Kulig et al. [27] in which sensitisation to outdoor allergens was higher than that to indoor allergens in children aged up to 6 years.

When we divided the group into 3-year age periods from 3 to 19 years, we found a striking increase in fre-

Table 2. Symptom development after NPT with PTP and Pru p 9

Case no.	Symptoms of NPT with PTP	Index score	Symptoms of NPT with Pru p 9	Index score
1	Nasal and ocular itching, rhinorrhoea, sneezing, and nasal obstruction	9	Nasal and ocular itching, rhinorrhoea, sneezing, and nasal obstruction	11
2	Nasal itching with obstruction, followed by rhinorrhoea and itching in the eyes appearing 15 min after challenge and normalised at 24 h after the challenge; oxymetazoline administration was required	11	Nasal itching with rhinorrhoea, sneezing, and nasal obstruction followed by eye redness; oxymetazoline administration was required	12
3	Nasal itching with rhinorrhoea, sneezing, and nasal obstruction followed by eye redness and cough; oxymetazoline administration was required	12	Nasal itching with obstruction, followed by rhinorrhoea and itching in the eyes appearing 15 min after challenge	9
4	Nasal and ocular itching, rhinorrhoea, sneezing, and nasal obstruction	9	Nasal itching with rhinorrhoea, sneezing, and nasal obstruction followed by eye redness	8
5	Nasal itching with obstruction, followed by rhinorrhoea and itching in the eyes appearing 15 min after challenge	10	Nasal and ocular itching, rhinorrhoea, sneezing, and nasal obstruction	11
6	Nasal itching with obstruction, followed by rhinorrhoea and itching in the eyes	10	Nasal itching with rhinorrhoea, sneezing, and nasal obstruction	9
7	Nasal and ocular itching, rhinorrhoea, sneezing, and nasal obstruction	9	Nasal and ocular itching, rhinorrhoea, sneezing, and nasal obstruction	9
8	Nasal itching with obstruction, rhinorrhoea, and itching in the eyes appearing 15 min after challenge and normalised at 24 h after the challenge; oxymetazoline administration was required	11	Nasal itching with rhinorrhoea, sneezing, and nasal obstruction with eye redness; oxymetazoline administration was required	12
9	Nasal and ocular itching, rhinorrhoea, sneezing, and nasal obstruction	9	Nasal itching with rhinorrhoea, sneezing, and nasal obstruction followed by eye redness	8
10	Nasal itching with obstruction, followed by rhinorrhoea and itching in the eyes	10	Nasal itching with rhinorrhoea, sneezing, and nasal obstruction; oxymetazoline administration was required	10
11	Nasal itching with obstruction, followed by rhinorrhoea and itching in the eyes appearing 15 min after challenge	10	Nasal and ocular itching, rhinorrhoea, sneezing, and nasal obstruction	11
12	Nasal itching, rhinorrhoea, sneezing, and nasal obstruction	9	None	0
13	Nasal and ocular itching, rhinorrhoea, sneezing, nasal obstruction, and cough; oxymetazoline administration was required	12	None	0
14	Nasal itching with rhinorrhoea, sneezing, and nasal obstruction followed by eye redness	8	None	0
15	Nasal itching, rhinorrhoea, sneezing, and nasal obstruction; oxymetazoline administration was required	11	None	0
16	Nasal itching with obstruction, followed by rhinorrhoea and itching in the eyes appearing 15 min after challenge	9	None	0
17	Nasal and pharyngeal itching followed by rhinorrhoea, sneezing, and obstruction 10 min after challenge	10	None	0
18	Nasal itching, rhinorrhoea, sneezing, and nasal obstruction	9	None	0
19	Nasal itching, rhinorrhoea, sneezing, and nasal obstruction; oxymetazoline administration was required	11	None	0
20	Nasal itching with obstruction, followed by rhinorrhoea and itching in the eyes appearing 15 min after challenge	10	None	0

NPT, nasal provocation test; Pru p 9, *Prunus persica* 9; PTP, peach tree pollen.

quency of sensitisation to PTP as age increased, with more than four times the value in the fourth stratum compared to the first (Fig. 3). This contrasts with the situation with olive tree and *P. pratense*, in which these differences were not so great, showing that sensitisation to olive tree starts earlier in life, but by the age of 7–10 years sensitisation to PTP becomes higher than that to grass pollen. At the first age period only 4% were sensitised to PTP, whereas in the period of 15–19 years 27% were sensitised. In this stratum almost one-third of all adolescents evaluated were sensitised to PTP. The pattern of PTP sensitisation was similar to that of the other pollens.

The sensitisation in our children to the main allergen so far identified, Pru p 9 [18, 19], was 30%, quite similar to that in adults from the same area [20]. This has been identified as a pathogenesis-related protein of the family PR-1, with a molecular weight of 18 kDa. These proteins can be induced by stress, such as infections. Two allergens of the same family present in pollens have been identified in *A. vulgaris* (Art v 2) and *Cynodon dactylon* (Cyn d 24) [28, 29] as well as in melon (Cuc m 3) [30]. The lack of a correlation between SPT to PTP and Pru p 9 suggests that other allergens could be involved. We have shown that at least three more allergens are possibly involved, with molecular weights of 25, 40, and 55 kDa [20].

The clinical entities reported were rhinitis followed by conjunctivitis and asthma. These entities, particularly rhinitis, are commonly reported in children, with an increase in incidence over the years. Regarding gender, stratified in 3-year intervals, no differences were found although there was an increase in the percentage of females with age.

Eleven percent of subjects were monosensitised to PTP, and the clinical entities involved were similar to those in children who were also sensitised to other pollens. We do not know at present whether these cases will remain monosensitised or whether they will become sensitised to more pollens in their allergic march. PTP-monosensitised cases have also been observed in adults from the same area (data not published).

Comparison between group A (SPT-positive to peach tree and other pollen) and group B (SPT-negative to PTP but positive to other pollens) showed that group A subjects were sensitised to a higher number of pollens ($p < 0.0001$) as well as to *C. arizonica*, *S. kali*, *P. acerifolia*, and *A. vulgaris*. Further studies are needed to determine whether this is due to the existence of cross-reactivity or pan-allergens, especially with *C. dactylon* and *A. vulgaris*,

as previously noted. Regarding the clinical entities, no differences were found.

The clinical relevance of PTP and Pru p 9 was shown by challenge in those cases that were previously tested with Pru p 9. In 11 cases sensitised to PTP and Pru p 9, the NPT was positive with both, but in the cases that were SPT-positive to that pollen but negative to Pru p 9, a positive nasal response only appeared with PTP, showing the selectivity of the response to Pru p 9.

Since most of the children were sensitised and exposed to several inhalant allergens, particularly olive tree, grass, and *Salsola* pollens, the question was to verify how each of these pollens could contribute to allergy. At the time of the year when the children developed symptoms, the more relevant allergens were olive tree and grass pollen. Although the former is most prevalent in sensitisation, this does not seem to contribute to symptoms for two reasons: the low load of olive tree pollen and the months of the year when the subjects report symptoms. The presence of olive tree pollen in the air occurs during the second to third week of May and the maximum levels detected are $< 400 \text{ g/m}^3$. However, according to the clinical history the months when these cases were more affected were from early March to the end of June, which is the period when peach tree flowering occurs, with a peak of symptoms in March. In fact, significantly more subjects sensitised to PTP (group A) reported symptoms in March compared to group B. Regarding the levels of *P. pratense* pollen in this area, although it is the second most important pollen in inducing sensitisation, the load is $< 40 \text{ g/m}^3$ and low, as is the case for olive tree pollen [31].

A limitation of this study is that we did not monitor the presence of PTP in the air and the distance to which this pollen can travel. Usually entomophilous pollens are considered to travel only short distances (50 m), although one study showed that they can be found at a distance of up to 15 km. The other possibility is that submicronic particles can transport pollen allergens and children become sensitised even if they are not directly exposed. It is known that trees produce massive amounts of pollens compared to weeds.

We present here for the first time the relevance of PTP and the new allergen Pru p 9 in sensitisation and induction of symptoms in children and adolescents, including those not directly exposed. Since Pru p 9 seems to be a species-specific allergen, this must be considered in cases sensitised to that pollen. The contribution of other allergens in those who had positive SPT only to PTP is being

evaluated. As peach orchards are extensive in Europe (Italy, Spain, Greece, France, and Portugal) as well as in other countries from the Mediterranean region, South America, China, the USA, and South Africa, populations all over the world may develop symptoms induced by PTP.

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Statement of Ethics

The study was approved by the institutional ethics committee. Informed consent was obtained from all individual participants (or their parents or guardians) included in the study.

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Disclosure Statement

The authors declare that they have no conflict of interest.

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Author Contributions

L. Victorio Puche: recruitment of cases, evaluation of cases, sample processing, and manuscript elaboration. M.L. Somoza: evaluation of cases, undertaking of the nasal provocation tests, statistical analysis, and manuscript elaboration. J.D. López-Sánchez: recruitment of cases, evaluation of cases, sample processing, and manuscript elaboration. M. Garrido-Arandia: allergen extract preparation, purification of allergens, and manuscript elaboration. A. Díaz-Perales: allergen extract preparation, purification of allergens, and manuscript elaboration. M. Blanca: patient recruitment and evaluation, skin testing for molecular allergens, data management, and manuscript elaboration.

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