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The relation between the sensitization to molecular components of inhalant allergens and food reactions in patients suffering from atopic dermatitis

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ABSTRACT

To evaluate the relation between the sensitization to molecular components of inhalant allergens and the occurrence of food reactions in atopic dermatitis patients. Another aim is to evaluate the semi-quantification results of the ISAC Multiplex testing to reveal the relevance of the leading allergens. The complete dermatological and allergological examination including the examination of the sensitization to molecular components with Multiplex ISAC testing was performed. The food reactions to examined food allergens were confirmed in the open exposure test (history). Altogether 100 atopic dermatitis patients were examined – 48 men, 52 women, the average age 40.9 years. The leading molecular components are cysteine protease (Der f 1, Der p 1), NPC2 protease (Der f 2, Der p 2), Acidic glycoprotein (Alt a 1), PR 10 proteins (Bet v 1, Mal d 1, Aln g 1 and Cor 1.04), lipocalins (Can f 1, Fel d 4, Mus m 1, Equ c 1), uteroglobulin (Fel d 1), Kallikrein (Can f 5) and molecular components of Timothy and Bermuda grass (glycoprotein). The significantly higher occurrence of sensitization to molecular components Aln g 1, Bet v 1, Phl p 1, 2, 4, 5, 6, 11 was confirmed in patients suffering from reactions to peanuts, hazelnuts, celery, apple and peach.

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atopic dermatitis; molecular components; food allergy; ISAC multiplex testing

Introduction

Multiple IgE sensitization to allergens is present in the majority of patients with atopic dermatitis (AD) and there are only few rare forms of atopic dermatitis such as intrinsic atopic dermatitis in which no disease-eliciting exogenous allergens have been identified (Anto et al., 2017; Heratizadeh, 2016; Navarrete-Dechent et al., 2016; Reginald et al., 2011a, 2011b; Valenta et al., 2009; Weidinger & Novak, 2016; Werfel et al., 2016; Wollenberg et al., 2016). Adult atopic dermatitis patients show much higher rates of food sensitization than controls, particularly to food proteins that are cross-reactive with airborne allergens

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(Anto et al., 2017; Heratizadeh, 2016; Weidinger & Novak, 2016; Werfel et al., 2016; Wollenberg et al., 2016). Food hypersensitivity reactions (FH reaction) are a common finding in AD patients; the term FH reaction represents the umbrella term for food allergy (IgE-, cellular-, and mixed IgE- and cell-mediated disorders) and for food intolerance (non-allergic FH) (Bindslev-Jensen et al., 2004). Food intolerance is a non-allergic hypersensitivity to food that does not include the immune system even though the symptoms are similar to those of IgE-mediated allergic reactions. An impaired histamine degradation based on reduced diaminoxidase activity and the resulting histamine excess may cause numerous symptoms mimicking an allergic reaction (Bindslev-Jensen et al., 2004). Many birch pollen-allergic patients show allergic reactions to various fruits and vegetables, which are caused by IgE cross-reactivity between Bet v 1 and homologous allergens from plant foods. Most Bet v 1-related food allergens have been found in members of certain plant families: Rosaceae (apple, pear, stone fruits), Apiaceae (celery, carrot), and Fabaceae (soybean, peanut) (Matricardi et al., 2016; Roerdink et al., 2016). Pathogenesis-related protein group 10 (PR-10 proteins, i.e. Bet v 1 and homologous allergens) (Breiteneder et al., 1988; Niederberger et al., 1998) are the major allergens in Fagales pollen and are recognized by virtually all allergic patients, thus representing the major cause of clinical allergy. In addition to PR-10 proteins, several other allergens have been described. Profilins (e.g. Bet v 2 from birch pollen or Cor a 2 from hazel pollen) (Valenta et al., 1992) are plant panallergens present in the whole plant kingdom. Profilins are recognized by 10–20% of patients primarily sensitized to birch pollen, but this proportion is higher in areas where grass pollen represents the primary sensitizer (Asero et al., 2010). Profilins may cause secondary plant-food allergy to various fruits and vegetables. Polcalcin-like proteins (calcium-binding proteins; e.g. Bet v 3 and Bet v 4 from birch, and Aln g 4 from alder) are pollen panallergens, which generally sensitize <10% of pollen allergic individuals. The clinical relevance is variable and often limited (Asero et al., 2010; Karamloo et al., 1999; Mahler et al., 2001). Olive pollen allergy is caused by Ole e 1 in the majority of cases; the Ole e 1-like protein family comprises several other allergenic glycosylated proteins from tree pollen (Rodríguez et al., 2001). Besides Ole e 1, several other molecules have been identified and a biologic function can be associated with most of these molecules, such as lipid transfer protein (Ole e 7). Olive tree Ole e 7, shares <20% of amino acid sequence with Pru p 3 (Rodríguez et al., 2001; Scala et al., 2016). The most important allergen from London plane tree (*Platanus acerifolia*) pollen is Pla a 1 (Asturias et al., 2002); the plane tree Pla a 3 belongs to the family of non-specific lipid transfer proteins, showing 58.3% sequence identity with the nsLTP Pru p 3 from peach (Scala et al., 2015). Clinical entities due to IgE sensitization to cross-reactive aero-allergen and food allergen components are described for many sources of plant origin (pollen-food syndromes and associations, such as birch-apple, cypress-peach and celery-mugwort-spice syndromes, and mugwort-peach, mugwort-chamomile, mugwort-mustard, ragweed-melon-banana, goosefoot-melon associations), fungal origin (*Alternaria*-spinach syndrome), and invertebrate, mammalian or avian origin (mite-shrimp, cat-pork, and bird-egg syndromes), (Matricardi et al., 2016). In some of these patients, the positive results of specific IgE to food allergens (components) without clinical symptoms of food reactions to this allergens are confirmed also (= sensitization) (Matricardi et al., 2016). Molecular allergy diagnosis using singleplex allergens or multiplex allergen microarrays are typical methods of precision medicine (Anto et al., 2017; Matricardi et al., 2016; Wollenberg et al., 2016). These methods can be applied in polysensitized respiratory allergies, in

food allergies and atopic dermatitis and may even reveal unexplained anaphylaxis (Matricardi et al., 2016). ImmunoCAP ISAC is a solid-phase multiple immunoassay (Phadia AB, Uppsala, Sweden). It is a predefined allergen panel of 112 allergen components derived from 51 common allergen sources including food, inhalation allergens, latex, and venoms (Melioli et al., 2011; van Hage et al., 2017). The finding might explain broad cross-reactivities to other allergen sources, if the candidate belongs to a protein family with many members of similar structure and a high degree of cross-reactive IgE recognition. In adult patients with AD, studies investigating the co-prevalence of AD and food allergy are still scarce (Matricardi et al., 2016). In our previous studies in patients suffering from AD we evaluated the occurrence of sensitization to food and inhalant allergens according to the results of examinations sIgE, skin prick tests and atopy patch tests and challenge test with suspected food allergens (Čelakovská et al., 2015a, 2015b). In this study, we evaluate the occurrence food reactions in relation to the results of specific IgE to molecular components of inhalant allergens and we evaluate the semi-quantification results of the ISAC Multiplex testing to reveal the relevance of the leading allergens that cause the atopic dermatitis.

Aim

- (1) The aim of our study is to evaluate in atopic dermatitis patients, if there is the significant relation between the sensitization to molecular components of inhalant allergens and the occurrence of food reactions to peanuts, walnuts, hazelnuts, wheat, soy, celery, apple, peach and kiwi.
- (2) To evaluate the semi-quantification results of the ISAC Multiplex testing to reveal the relevance of the leading allergens that cause the atopic dermatitis.

Method

Patients and methods

In the period 2018–2019, 100 patients suffering from atopic dermatitis at the age of 14 years and older were examined in the Department of Dermatology, Faculty Hospital Hradec Králové, Charles University, Czech Republic. The diagnosis of atopic dermatitis was made with the Hanifin-Rajka criteria, the severity of atopic dermatitis was evaluated with SCORAD system (Hanifin & Rajka, 1980). Exclusion criteria were systemic therapy (cyclosporin, systemic corticoids, biological therapy), pregnancy, breastfeeding. Patients with atopic dermatitis having other systemic diseases were excluded from the study as well. Complete dermatological and allergological examination was performed in patients included in the study. This study was approved by Ethics committee of Faculty Hospital Hradec Králové, Charles University of Prague, Czech Republic.

Examination of specific IgE to molecular components

In 100 atopic dermatitis patients, the serum level of the sIgE was measured by the component-resolved diagnosis microarray-based sIgE detection assay ImmunoCAP ISAC (Phadia, Thermo Fisher Scientific, Uppsala, Sweden). ImmunoCAP ISAC is a solid-

phase multiple immunoassay which enables to determine 112 different components from 51 allergen sources (Melioli et al., 2011; van Hage et al., 2017). The allergens are applied in triplicates to ensure the test reproducibility. The specific IgE values are presented in arbitrary units called ISAC Standardized Units (measuring range of 0.3–100 ISU-E). The level of specific IgE higher than 0.3 ISU-E was assessed as positive. The level of molecular components in ISU-E was evaluated: <0.3 – negative, 0.3–0.9 low positivity, 0.9–15 moderate positivity, above 15 ISU-E very high positivity (Melioli et al., 2011; van Hage et al., 2017).

Confirmation of food reactions

The reaction to examined food was confirmed in these cases:

- (1) In patients with the positive result in the open exposure test (early and/or late reactions) with examined food allergens.
- (2) In patients with the repeated reactions after the ingestion of examined food in their history; the open exposure test was not performed in these patients because of anaphylactic reaction danger. The food reaction to peanuts was confirmed in this way.

Open exposure test with suspected food allergens, the diagnostic hypoallergenic diet, the elimination diet

In patients suffering from moderate and severe form of AD and with suspicion to food allergy according to the ISAC Multiplex testing we recommended the diagnostic hypoallergenic diet. In patients with mild form of AD, we recommended the elimination diet with the elimination of suspected food allergens according to the ISAC Multiplex testing (Čelakovská et al., 2015a, 2015b).

Diagnostic hypoallergenic diet: In the period of four weeks we recommended these foods: gluten-free foods, potatoes, rice, meat – beef, pork, vegetable, and fruits only after thermal modification, but parsley, celery, and seasoning were not allowed. The patients are allowed to drink only drinking water, mineral water, or black tea (Čelakovská et al., 2015a, 2015b).

Open exposure test: Open exposure test was performed after this diet in intervals without symptoms or during a consistent period with regard to atopic dermatitis (not in pollen season in patients with pollen allergy). In general, the open exposure test (OET) was performed with three doses of examined foods given during two days. One dose of examined food was given in incremental dosages in 10 min intervals during one hour. The food challenge results were scored as positive if one or more of the following objective and subjective clinical reactions were noted: itching, rash, urticaria, angioedema, vomiting, wheezing, abdominal pain, diarrhoea, pruritus, or worsening of atopic dermatitis. Early reactions were defined as clinical symptoms within 2 h after the ingestion of food and late symptoms if occurring after more than 2 h. In the case the physician or the patient recorded worsening of the atopic dermatitis or some other reactions during the open exposure test, the patient continued in the elimination of suspected food and the severity of atopic dermatitis was evaluated every 3 month during 1 year. If the open exposure test was negative, the patient introduced this food in the diet regimen. The

severity of atopic dermatitis was evaluated during the ingestion of food over a period of 3 months during 1 year. If there is a suspicion to food allergy to more than one food, the next open exposure test was performed in 2–3 weeks after the first exposure test (Čelakovská et al., 2015a, 2015b).

Statistical analysis

- (1) We evaluated if there is a significant relation between the occurrence of food reactions to peanuts, walnuts, hazelnuts, wheat, soy, celery, apple, peach and kiwi and sensitization to molecular components of inhalant allergens such as:
 - a Aln g 1, Bet v 1, Art v 1, Alta a 1, Asp f 6, Ole e 1 and Ol e e 9
 - b molecular components of timothy Phl p 1, 2, 4, 5, 6, 11
 - c pollen-derived panallergens (Lipid transfer proteins – LTPs – Ole e 7, Pla a 3, Art v 3, Profilins – Bet v 2, Phl p 12, Mer a 1, and Polcalcins – Phl p 7, Bet v 4).

Pairs of these categories were enrolled in the contingency tables and the Chi-square independence test was performed. The significance level was set to 5%. The *p*-value is displayed in the right hand column. Unfortunately, zeroes appeared in some of the tables and one has to be careful in making conclusions.

- (2) We evaluated the semi-quantification results of the ISAC Multiplex testing to reveal the relevance of the leading allergens that cause the atopic dermatitis. For this evaluation, we used the method Total Unduplicated Reach and Frequency Analysis, in Programme IBM SPSS Statistics v. 26.

Results

Patients

One hundred patients suffering from atopic dermatitis were included in the study – 48 men and 52 women with an average age 40.9 years and with the average SCORAD 39, s.d.13.1 points. The mild form of AD was recorded in 14 patients (14%), moderate form in 58 patients (58%), severe form in 28 patients (28%), 55 patients (55%) suffer from asthma bronchial and 78 patients (78%) suffer from rhinitis. The characteristics of patients are shown in Table 1. The laboratory examination with the use of ISAC Multiplex examination was performed in all included patients. The highest observed

Table 1. The characteristic of patients with atopic dermatitis.

– 100 patients examined – 48 men, 52 women, the average age 40.9 years
– the average SCORAD 39 s.d. 13.1 points
– the positive results in sensitization to molecular components – 93 patients (93%)
– mild form of AD patients 14 (14%)
– moderate form of AD patients 58 (58%)
– severe form of AD patients 28 (28%)
– number of patients with asthma bronchial – 55 (55%)
– number of patients with allergic rhinitis – 78 (78%)

sensitization rate was 61.0% to grass specific molecule Phl p 1, the second most frequent sensitization was 57.0% to Betulaceae-specific molecule Bet v 1. Frequently observed sensitizations were those to PR-10 proteins, NPC2 proteins family, Uteroglobulin and Lipocalin.

We evaluated the semi-quantification results of the ISAC Multiplex testing to reveal the relevance of the leading molecular components. According to our results, in 64.3% of patients suffering from atopic dermatitis we recorded positive results to one or more of 21 molecular components with high level of specific IgE (above 15 ISU-E very high positivity). These molecular components were found as leading components: House dust mite – Der f 1, Der p 1 (Cysteine protease), Der f 2, Der p 2 (NPC2 protease), *Alternaria* Alt a 1 (Acidic glycoprotein), birch Bet v 1 (PR 10 protein), apple Mal d 1 (PR 10 protein), alder Aln g 1, hazelnuts Cor a 1.04 (PR 10 protein), dog Can f 1 (Lipocalin), cat Fel d 4 (Lipocalin), mouse Mus m 1 (Lipocalin), Fel d 1 (Uteroglobulin), Timothy grass Phl p 1 (Beta expansin), Phl p 2, Timothy grass Phl p 4 (Berberine – bridge enzyme) Phl p 5 (Grass group 5 ribonuclease), Phl p 6 (Grass group 6) Bermuda grass Cyn d 1 (Glycoprotein) (Table 2).

The results of the open exposure test (history) with the examined food allergens are shown in Table 3. The food reaction to peanuts was confirmed in 49 patients (49%), to walnuts in 50 patients (50%), to hazelnuts in 47 patients (47%), to soy in 13 patients (13%), to wheat in 14 patients (14%), to celery in 24 patients (24%), to apple in 23 patients (23%), to peach in 19 patients (19%) and to kiwi in 16 patients (16%).

We evaluated the relation between the occurrence of food reaction to examined food allergens and the sensitization to molecular components of inhalant allergens, Tables 4–13. The significantly higher occurrence of sensitization (p -value <0.05) to molecular components Aln g 1 (Alder, PR 10 Protein), Bet v 1 (Birch, PR 10 Protein), to molecular

Table 2. The leading molecular components with very high level of specific IgE (above 15 ISU-E) found in 64.3% patients suffering from AD.

Molecular components with very high level of specific IgE found in 64.3% of patients		
Molecular components	Protein family	Allergen
Der f 1	Cysteine protease	House dust mite
Der p 1	Cysteine protease	
Der f 2	NPC2 protease	
Der p 2	NPC2 protease	
Alt a 1	Acidic glycoprotein	<i>Alternaria</i>
Bet v 1	PR 10 protein	Birch
Mal d 1	PR 10 protein	Apple
Aln g 1	PR 10 protein	Alder
Cor a 1.04	PR 10 protein	Hazelnut
Can f 1	Lipocalin	Dog
Can f 5	Kallikrein	
Fel d 4	Lipocalin	Cat
Fel d 1	Uteroglobulin	
Mus m 1	Lipocalin	Mouse
Equ c 1	Lipocalin	Horse
Phl p 1	Beta expansin	Timothy grass
Phl p 2	Grass group 2	
Phl p 4	Berberine bridge enzyme	
Phl p 5	Grass group 5 ribonuclease	
Phl p 6	Grass group 6	
Cyn d 1	Glycoprotein	Bermuda grass

Table 3. The results of open exposure test (or history) with the symptoms of food reaction (OAS – oral allergy syndrome, pruritus, GIT – gastrointestinal symptoms, worsening of atopic dermatitis, urticaria, worsening of asthma) in 100 patients (= 100%).

Food allergens	Number of patients with confirmed FA	Clinical symptoms of food reaction in the whole group of patients					
		OAS	Pruritus	GIT symptoms	Worsening of eczema	Urticaria	Worsening of breathing
Peanuts	49 (49%)	40%	15%	8%	10%	2%	1%
Walnuts	50 (50%)	40%	20%	9%	12%	3%	1%
Hazelnuts	47 (47%)	38%	22%	5%	10%	2%	1%
Soy	13 (13%)	5%	10%	2%	10%	0	0
Wheat	14 (14%)	0	12%	3%	10%	0	0
Celery	24 (24%)	20%	9%	2%	12%	2%	1%
Apple	23 (23%)	17%	10%	10%	11%	0	1%
Peach	19 (19%)	12%	8%	2%	8%	2%	2%
Kiwi	16 (16%)	10%	7%	2%	9%	0	2%

Table 4. Food reaction to peanuts.

Molecular components, number of patients with positive results in the whole group of patients	Number of patients with positive results to molecular components		
	Reaction to peanuts no 51 patients = 100%	Reaction to peanuts yes 49 patients = 100%	p-value
Aln g 1 (Ballmer-Weber & Hoffmann-Sommergruber, 2011)	16(31.4%)	27(55.1%)	0.017*
Bet v 1 (Herrera-Mozo et al., 2006)	22(43.1%)	35(71.4%)	0.004*
Art v 1 (Mari et al., 2011)	13(25.5%)	16(32.7%)	0.43
Alt a 1 (Mari et al., 2011)	11(21.6%)	18(36.7%)	0.095
Asp f 6 (Asturias et al., 2002)	8(15.7%)	13(26.5%)	0.183
Ole e 9 (Karamloo et al., 1999)	5(9.8%)	12(24.5%)	0.051
Ole e 1 (Breiteneder et al., 1988)	5(9.8%)	9(18.4%)	0.217
Phl p 1 (Czarnowicki et al., 2017 Jun)	25(49.0%)	36(73.5%)	0.012*
Phl p 2 (Rodríguez et al., 2007)	14(27.5%)	25(51.0%)	0.016*
Phl p 4 (Custovic et al., 2015a)	19(37.3%)	33(67.3%)	0.003*
Phl p 5 (Ballmer-Weber & Hoffmann-Sommergruber, 2011)	17(33.3%)	26(53.1%)	0.046*
Phl p 6 (Ballmer-Weber et al., 2000)	15(29.4%)	27(55.1%)	0.009*
Phl p 11 (Scala et al., 2016)	7(13.7%)	13(26.5%)	0.11
Ole e 7 (Heratizadeh, 2016)	1(2.0%)	0(0.0%)	0.325
Pla a 3 (Anto et al., 2017)	1(2.0%)	4(8.2%)	0.155
Art v 3 (Anto et al., 2017)	1(2.0%)	4(8.2%)	0.155
Bet v 2 (Navarrete-Dechent et al., 2016)	2(3.9%)	7(14.3%)	0.07
Phl p 12 (Weidinger & Novak, 2016)	0(0.0%)	3(6.1%)	0.073
Mer a 1 (Niederberger et al., 1998)	3(5.9%)	10(20.4%)	0.031*
Phl p 7 (Reginald et al., 2011a)	1(2.0%)	6(12.2%)	0.044*
Bet v 4 (Wollenberg et al., 2016)	1(2.0%)	3(6.1%)	0.288

Notes: In patients suffering from food reaction to peanuts (49 patients), the significant relation was confirmed to sensitization to molecular components Aln g1 (Alder, PR 10 Protein), Bet v 1 (Birch), Phl p1, 2, 4, 5, 6, 7 (Timothy) and Mer a 1 (Annual Mercury). The significant relation of sensitization to molecular components of inhalant allergens is marked extra bold.*

components of Timothy Phl p 1, 2 (grass group 1, 2) Phl p 4 (Berberine bridge enzyme) Phl p 5, 6 (grass group 5, 6), Phl p 7 (Polcalcin) and Mer a 1 (Annual Mercury, profilin) was confirmed in patients suffering from food reaction to peanuts (49 patients), Table 4. In patients suffering from food reaction to hazelnuts (47 patients), the significant relation (p -value <0.05) was confirmed to sensitization to molecular components Aln g1 (Alder, PR – 10 Protein), Bet v 1 (Birch, PR – 10 Proteins), Ole e 1 (Olive pollen, common olive

Table 5. Food reaction to Hazelnuts.

Molecular components, number of patients with positive results in the whole group of patients	Number of patients with positive results to molecular components		<i>p</i> – value
	reaction to hazelnuts no 53 patients = 100%	reaction to hazelnuts yes 47 patients = 100%	
Aln g 1 (Ballmer-Weber & Hoffmann- Sommergruber, 2011)	17(32.1%)	25(53.2%)	0.033*
Bet v 1 (Herrera-Mozo et al., 2006)	24(45.3%)	33(70.2%)	0.012*
Art v 1 (Mari et al., 2011)	13(24.5%)	16(34.0%)	0.295
Alt a 1 (Mari et al., 2011)	13(24.5%)	16(34.0%)	0.295
Asp f 6 (Asturias et al., 2002)	9(17.0%)	12(25.5%)	0.295
Ole e 9 (Karamloo et al., 1999)	7(13.2%)	12(25.5%)	0.117
Ole e 1 (Breiteneder et al., 1988)	4(7.5%)	10(21.3%)	0.048*
Phl p 1 (Czarnowicki et al., 2017 Jun)	27(50.9%)	34(72.3%)	0.029*
Phl p 2 (Rodríguez et al., 2007)	13(24.5%)	26(55.3%)	0.002*
Phl p 4 (Custovic et al., 2015a)	19(35.8%)	33(70.2%)	0.001*
Phl p 5 (Ballmer-Weber & Hoffmann- Sommergruber, 2011)	21(39.6%)	22(46.8%)	0.469
Phl p 6 (Ballmer-Weber et al., 2000)	18(34.0%)	24(51.1%)	0.084
Phl p 11 (Scala et al., 2016)	10(18.9%)	10(21.3%)	0.764
Ole e 7 (Heratizadeh, 2016)	1(1.9%)	0(0.0%)	0.344
Pla a 3 (Anto et al., 2017)	2(3.8%)	3(6.4%)	0.55
Art v 3 (Anto et al., 2017)	2(3.8%)	3(6.4%)	0.55
Bet v 2 (Navarrete-Dechent et al., 2016)	2(3.8%)	7(14.9%)	0.052
Phl p 12 (Weidinger & Novak, 2016)	0(0.0%)	3(6.4%)	0.062
Mer a 1 (Niederberger et al., 1998)	4(7.5%)	9(19.1%)	0.085
Phl p 7 (Reginald et al., 2011a)	2(3.8%)	5(10.6%)	0.179
Bet v 4 (Wollenberg et al., 2016)	2(3.8%)	2(4.3%)	0.902

Notes: In patients suffering from food reaction to hazelnuts (47 patients), the significant relation was confirmed to sensitization to molecular components Aln g1 (Alder), Bet v 1 (Birch), Ole e 1 (Olive pollen), Phl p1, 2, 4 (Timothy). The significant relation of sensitization to molecular components of inhalant allergens is marked extra bold.*

Table 6. Food reaction to Walnuts.

Molecular components, number of patients with positive results in the whole group of patients	Number of patients with positive results to molecular components		<i>p</i> -value
	reaction to walnuts no 50 patients = 100%	reaction to walnuts yes 50 patients = 100%	
Aln g 1 (Ballmer-Weber & Hoffmann- Sommergruber, 2011)	17(34.0%)	26(52.0%)	0.069
Bet v 1 (Herrera-Mozo et al., 2006)	23(46.0%)	34(68.0%)	0.026*
Art v 1 (Mari et al., 2011)	11(22.0%)	18(36.0%)	0.123
Alt a 1 (Mari et al., 2011)	9(18.0%)	20(40.0%)	0.015*
Asp f 6 (Asturias et al., 2002)	7(14.0%)	14(28.0%)	0.086
Ole e 9 (Karamloo et al., 1999)	4(8.0%)	13(26.0%)	0.017*
Ole e 1 (Breiteneder et al., 1988)	4(8.0%)	10(20.0%)	0.084
Phl p 1 (Czarnowicki et al., 2017 Jun)	21(42.0%)	39(78.0%)	0.000*
Phl p 2 (Rodríguez et al., 2007)	11(22.0%)	28(56.0%)	0.000*
Phl p 4 (Custovic et al., 2015a)	16(32.0%)	36(72.0%)	0.000*
Phl p 5 (Ballmer-Weber & Hoffmann- Sommergruber, 2011)	16(32.0%)	27(54.0%)	0.026*
Phl p 6 (Ballmer-Weber et al., 2000)	13(26.0%)	29(58.0%)	0.001*
Phl p 11 (Scala et al., 2016)	8(16.0%)	12(24.0%)	0.317
Ole e 7 (Heratizadeh, 2016)	1(2.0%)	0(0.0%)	0.315
Pla a 3 (Anto et al., 2017)	1(2.0%)	4(8.0%)	0.169
Art v 3 (Anto et al., 2017)	1(2.0%)	4(8.0%)	0.169
Bet v 2 (Navarrete-Dechent et al., 2016)	2(4.0%)	7(14.0%)	0.081
Phl p 12 (Weidinger & Novak, 2016)	0(0.0%)	3(6.0%)	0.079
Mer a 1 (Niederberger et al., 1998)	3(6.0%)	10(20.0%)	0.037*
Phl p 7 (Reginald et al., 2011a)	2(4.0%)	5(10.0%)	0.24
Bet v 4 (Wollenberg et al., 2016)	1(2.0%)	3(6.0%)	0.307

Notes: In patients suffering from food reaction to walnuts (50 patients), the significant relation was confirmed to sensitization to molecular components Bet v 1 (Birch), Alt a 1 (Alternaria), Ole e 9 (Olive pollen), Phl p1, 2, 4, 5, 6 (Timothy) and Mer a 1 (Annual Mercury). The significant relation of sensitization to molecular components of inhalant allergens is marked extra bold.*

Table 7. Food reaction to Soy.

Molecular components, number of patients with positive results in the whole group of patients	Number of patients with positive results to molecular components		
	reaction to soy no	reaction to soy yes	p-value
	87 patients = 100%	13 patients = 100%	
Aln g 1 (Ballmer-Weber & Hoffmann- Sommergruber, 2011)	37(42.5%)	7(53.8%)	0.443
Bet v 1 (Herrera-Mozo et al., 2006)	47(54.0%)	10(76.9%)	0.120
Art v 1 (Mari et al., 2011)	22(25.3%)	6(46.2%)	0.118
Alt a 1 (Mari et al., 2011)	25(28.7%)	4(30.8%)	0.880
Asp f 6 (Asturias et al., 2002)	18(20.7%)	3(23.1%)	0.844
Ole e 9 (Karamloo et al., 1999)	15(17.2%)	2(15.4%)	0.868
Ole e 1 (Breiteneder et al., 1988)	13(14.9%)	1(7.7%)	0.482
Phl p 1 (Czarnowicki et al., 2017 Jun)	53(60.9%)	8(61.5%)	0.966
Phl p 2 (Rodríguez et al., 2007)	32(36.8%)	7(53.8%)	0.239
Phl p 4 (Custovic et al., 2015a)	46(52.9%)	6(46.2%)	0.651
Phl p 5 (Ballmer-Weber & Hoffmann- Sommergruber, 2011)	40(46.0%)	3(23.1%)	0.120
Phl p 6 (Ballmer-Weber et al., 2000)	38(43.7%)	4(30.8%)	0.379
Phl p 11 (Scala et al., 2016)	18(20.7%)	2(15.4%)	0.656
Ole e 7 (Heratizadeh, 2016)	1(1.1%)	0(0.0%)	0.698
Pla a 3 (Anto et al., 2017)	5(5.7%)	0(0.0%)	0.375
Art v 3 (Anto et al., 2017)	5(5.7%)	0(0.0%)	0.375
Bet v 2 (Navarrete-Dechent et al., 2016)	8(9.2%)	1(7.7%)	0.860
Phl p 12 (Weidinger & Novak, 2016)	2(2.3%)	1(7.7%)	0.288
Mer a 1 (Niederberger et al., 1998)	12(13.8%)	1(7.7%)	0.542
Phl p 7 (Reginald et al., 2011a)	6(6.9%)	1(7.7%)	0.916
Bet v 4 (Wollenberg et al., 2016)	4(4.6%)	0(0.0%)	0.430

Note: In patients suffering from food reactions to soy (13 patients), the significant relation to sensitization to molecular components was not confirmed.

Table 8. Food reaction to wheat.

Molecular components, number of patients with positive results in the whole group of patients	Number of patients with positive results to molecular components		
	reaction to wheat no	reaction to wheat yes	p-value
	86 patients = 100%	14 patients = 100%	
Alng 1 (Ballmer-Weber & Hoffmann- Sommergruber, 2011)	40(46.5%)	3(21.4%)	0.079
Betv 1 (Herrera-Mozo et al., 2006)	49(57.0%)	8(57.1%)	0.991
Artv 1 (Mari et al., 2011)	25(29.1%)	4(28.6%)	0.970
Alt a 1 (Mari et al., 2011)	25(29.1%)	4(28.6%)	0.970
Asp f 6 (Asturias et al., 2002)	19(22.1%)	2(14.3%)	0.506
Olee 9 (Karamloo et al., 1999)	16(18.6%)	1(7.1%)	0.290
Ole e 1 (Breiteneder et al., 1988)	11(12.8%)	3(21.4%)	0.388
Phl p 1 (Czarnowicki et al., 2017 Jun)	50(58.1%)	11(78.6%)	0.146
Phl p 2 (Rodríguez et al., 2007)	31(36.0%)	8(57.1%)	0.133
Phl p 4 (Custovic et al., 2015a)	44(51.2%)	8(57.1%)	0.678
Phl p 5 (Ballmer-Weber & Hoffmann- Sommergruber, 2011)	37(43.0%)	6(42.9%)	0.991
Phl p 6 (Ballmer-Weber et al., 2000)	36(41.9%)	6(42.9%)	0.944
Phl p 11 (Scala et al., 2016)	18(20.9%)	2(14.3%)	0.564
Ole e 7 (Heratizadeh, 2016)	0(0.0%)	1(7.1%)	0.013*
Pla a 3 (Anto et al., 2017)	4(4.7%)	1(7.1%)	0.692
Art v 3 (Anto et al., 2017)	4(4.7%)	1(7.1%)	0.692
Bet v 2 (Navarrete-Dechent et al., 2016)	8(9.3%)	1(7.1%)	0.793
Phl p 12 (Weidinger & Novak, 2016)	2(2.3%)	0(0.0%)	0.564
Mer a 1 (Niederberger et al., 1998)	12(14.0%)	1(7.1%)	0.482
Phl p 7 (Reginald et al., 2011a)	6(7.0%)	1(7.1%)	0.982
Bet v 4 (Wollenberg et al., 2016)	3(3.5%)	1(7.1%)	0.518

Notes: In patients suffering from food reaction to wheat (14 patients), the significant relation was confirmed to sensitization to molecular component Ole e 7. Unfortunately, zeroes appeared in this table tables and one has to be careful in making conclusions. The significant relation of sensitization to molecular components of inhalant allergens is marked extra bold.*

Table 9. Food reaction to Celery.

Molecular components, number of patients with positive results in the whole group of patients	Number of patients with positive results to molecular components		p-value
	reaction to celery no 76 patients = 100%	reaction to celery yes 24 patients = 100%	
Aln g 1 (Ballmer-Weber & Hoffmann- Sommergruber, 2011)	28(36.8%)	15(62.5%)	0.027*
Bet v 1 (Herrera-Mozo et al., 2006)	40(52.6%)	17(70.8%)	0.116
Art v 1 (Mari et al., 2011)	19(25.0%)	10(41.7%)	0.117
Alt a 1 (Mari et al., 2011)	22(28.9%)	7(29.2%)	0.984
Asp f 6 (Asturias et al., 2002)	13(17.1%)	8(33.3%)	0.089
Ole e 9 (Karamloo et al., 1999)	11(14.5%)	6(25.0%)	0.231
Ole e 1 (Breiteneder et al., 1988)	9(11.8%)	5(20.8%)	0.268
Phl p 1 (Czarnowicki et al., 2017 Jun)	43(56.6%)	18(75.0%)	0.107
Phl p 2 (Rodríguez et al., 2007)	27(35.5%)	12(50.0%)	0.205
Phl p 4 (Custovic et al., 2015a)	34(44.7%)	18(75.0%)	0.010*
Phl p 5 (Ballmer-Weber & Hoffmann- Sommergruber, 2011)	34(44.7%)	9(37.5%)	0.532
Phl p 6 (Ballmer-Weber et al., 2000)	33(43.4%)	9(37.5%)	0.608
Phl p 11 (Scala et al., 2016)	16(21.1%)	4(16.7%)	0.640
Ole e 7 (Heratizadeh, 2016)	1(1.3%)	0(0.0%)	0.572
Pla a 3 (Anto et al., 2017)	2(2.6%)	3(12.5%)	0.053
Art v 3 (Anto et al., 2017)	3(3.9%)	2(8.3%)	0.390
Bet v 2 (Navarrete-Dechent et al., 2016)	6(7.9%)	3(12.5%)	0.492
Phl p 12 (Weidinger & Novak, 2016)	1(1.3%)	2(8.3%)	0.079
Mer a 1 (Niederberger et al., 1998)	9(11.8%)	4(16.7%)	0.540
Phl p 7 (Reginald et al., 2011a)	6(7.9%)	1(4.2%)	0.533
Bet v 4 (Wollenberg et al., 2016)	3(3.9%)	1(4.2%)	0.962

Notes: In patients suffering from food reaction to celery (24 patients), the significant relation was confirmed to sensitization to molecular components Aln g1 (Alder) and Phl p 4 (Timothy). The significant relation of sensitization to molecular components of inhalant allergens is marked extra bold.*

Table 10. Food reactivity to Apple.

Molecular components, number of patients with positive results in the whole group of patients	Number of patients with positive results to molecular components		p-value
	reaction to apple no 77 patients = 100%	reaction to apple yes 23 patients = 100%	
Aln g 1 (Ballmer-Weber & Hoffmann- Sommergruber, 2011)	28(36.4%)	15(65.2%)	0.014*
Bet v 1 (Herrera-Mozo et al., 2006)	38(49.4%)	19(82.6%)	0.005*
Art v 1 (Mari et al., 2011)	19(24.7%)	10(43.5%)	0.081
Alt a 1 (Mari et al., 2011)	21(27.3%)	8(34.8%)	0.486
Asp f 6 (Asturias et al., 2002)	18(23.4%)	3(13.0%)	0.286
Ole e 9 (Karamloo et al., 1999)	10(13.0%)	7(30.4%)	0.051
Ole e 1 (Breiteneder et al., 1988)	10(13.0%)	4(17.4%)	0.593
Phl p 1 (Czarnowicki et al., 2017 Jun)	45(58.4%)	16(69.6%)	0.337
Phl p 2 (Rodríguez et al., 2007)	28(36.4%)	11(47.8%)	0.323
Phl p 4 (Custovic et al., 2015a)	38(49.4%)	14(60.9%)	0.332
Phl p 5 (Ballmer-Weber & Hoffmann- Sommergruber, 2011)	30(39.0%)	13(56.5%)	0.136
Phl p 6 (Ballmer-Weber et al., 2000)	30(39.0%)	12(52.2%)	0.260
Phl p 11 (Scala et al., 2016)	12(15.6%)	8(34.8%)	0.043*
Ole e 7 (Heratizadeh, 2016)	1(1.3%)	0(0.0%)	0.583
Pla a 3 (Anto et al., 2017)	5(6.5%)	0(0.0%)	0.210
Art v 3 (Anto et al., 2017)	4(5.2%)	1(4.3%)	0.870
rBet v 2 (Navarrete-Dechent et al., 2016)	7(9.1%)	2(8.7%)	0.954
Phl p 12 (Weidinger & Novak, 2016)	2(2.6%)	1(4.3%)	0.666
Mer a 1 (Niederberger et al., 1998)	10(13.0%)	3(13.0%)	0.994
Phl p 7 (Reginald et al., 2011a)	6(7.8%)	1(4.3%)	0.570
Bet v 4 (Wollenberg et al., 2016)	3(3.9%)	0(0.0%)	0.336

Notes: In patients suffering from food reaction to apple (23 patients), the significant relation was confirmed to sensitization to molecular components Aln g1 (Alder), Bet v 1 (Birch), Phl p 11 (Timothy). The significant relation of sensitization to molecular components of inhalant allergens is marked extra bold.*

Table 11. Food reaction to peach.

Molecular components, number of patients with positive results in the whole group of patients	Number of patients with positive results to molecular components		p-value
	reaction to peach no 81 patients = 100%	reaction to peach yes 19 patients = 100%	
Aln g 1 (Ballmer-Weber & Hoffmann- Sommergruber, 2011)	31(38.3%)	12(63.2%)	0.049*
Bet v 1 (Herrera-Mozo et al., 2006)	42(51.9%)	15(78.9%)	0.032*
Art v 1 (Mari et al., 2011)	23(28.4%)	6(31.6%)	0.783
Alt a 1 (Mari et al., 2011)	21(25.9%)	8(42.1%)	0.162
Asp f 6 (Asturias et al., 2002)	16(19.8%)	5(26.3%)	0.527
Ole e 9 (Karamloo et al., 1999)	10(12.3%)	7(36.8%)	0.011*
Ole e 1 (Breiteneder et al., 1988)	11(13.6%)	3(15.8%)	0.803
Phl p 1 (Czarnowicki et al., 2017 Jun)	47(58.0%)	14(73.7%)	0.208
Phl p 2 (Rodríguez et al., 2007)	29(35.8%)	10(52.6%)	0.176
Phl p 4 (Custovic et al., 2015a)	40(49.4%)	12(63.2%)	0.279
Phl p 5 (Ballmer-Weber & Hoffmann- Sommergruber, 2011)	31(38.3%)	12(63.2%)	0.049*
Phl p 6 (Ballmer-Weber et al., 2000)	30(37.0%)	12(63.2%)	0.038
Phl p 11 (Scala et al., 2016)	13(16.0%)	7(36.8%)	0.041*
Ole e 7 (Heratizadeh, 2016)	1(1.2%)	0(0.0%)	0.626
Pla a 3 (Anto et al., 2017)	3(3.7%)	2(10.5%)	0.219
Art v 3 (Anto et al., 2017)	4(4.9%)	1(5.3%)	0.953
Bet v 2 (Navarrete-Dechent et al., 2016)	7(8.6%)	2(10.5%)	0.796
Phl p 12 (Weidinger & Novak, 2016)	1(1.2%)	2(10.5%)	0.033*
Mer a 1 (Niederberger et al., 1998)	9(11.1%)	4(21.1%)	0.246
Phl p 7 (Reginald et al., 2011a)	8(9.9%)	1(5.3%)	0.527
Bet v 4 (Wollenberg et al., 2016)	3(3.7%)	1(5.3%)	0.755

Notes: In patients suffering from food reaction to peach (19 patients), the significant relation was confirmed to sensitization to molecular components Aln g 1 (Alder), Bet v 1 (Birch), Phl p 5, 11, 12 (Timothy). The significant relation of sensitization to molecular components of inhalant allergens is marked extra bold.*

Table 12. Food reaction to kiwi.

Molecular components, number of patients with positive results in the whole group of patients	Number of patients with positive results to molecular components		p-value
	reaction to kiwi no 84 patients = 100%	reaction to kiwi yes 16 patients = 100%	
Aln g 1 (Ballmer-Weber & Hoffmann- Sommergruber, 2011)	35(41.7%)	8(50.0%)	0.537
Bet v 1 (Herrera-Mozo et al., 2006)	47(56.0%)	10(62.5%)	0.628
Art v 1 (Mari et al., 2011)	25(29.8%)	4(25.0%)	0.700
Alt a 1 (Mari et al., 2011)	21(25.0%)	8(50.0%)	0.043*
Asp f 6 (Asturias et al., 2002)	17(20.2%)	4(25.0%)	0.668
Ole e 9 (Karamloo et al., 1999)	15(17.9%)	2(12.5%)	0.601
Ole e 1 (Breiteneder et al., 1988)	11(13.1%)	3(18.8%)	0.550
Phl p 1 (Czarnowicki et al., 2017 Jun)	49(58.3%)	12(75.0%)	0.210
Phl p 2 (Rodríguez et al., 2007)	32(38.1%)	7(43.8%)	0.671
Phl p 4 (Custovic et al., 2015a)	42(50.0%)	10(62.5%)	0.359
Phl p 5 (Ballmer-Weber & Hoffmann- Sommergruber, 2011)	34(40.5%)	9(56.2%)	0.243
Phl p 6 (Ballmer-Weber et al., 2000)	33(39.3%)	9(56.2%)	0.208
Phl p 11 (Scala et al., 2016)	16(19.0%)	4(25.0%)	0.585
Ole e 7 (Heratizadeh, 2016)	1(1.2%)	0(0.0%)	0.661
Pla a 3 (Anto et al., 2017)	5(6.0%)	1(6.2%)	0.963
Art v 3 (Anto et al., 2017)	4(4.8%)	1(6.2%)	0.802
Bet v 2 (Navarrete-Dechent et al., 2016)	7(8.3%)	2(12.5%)	0.594
Phl p 12 (Weidinger & Novak, 2016)	3(3.6%)	0(0.0%)	0.443
Mer a 1 (Niederberger et al., 1998)	12(14.3%)	1(6.2%)	0.381
Phl p 7 (Reginald et al., 2011a)	6(7.1%)	1(6.2%)	0.898
Bet v 4 (Wollenberg et al., 2016)	3(3.6%)	1(6.2%)	0.616

Notes: In patients suffering from food reaction to kiwi (16 patients), the significant relation was confirmed to sensitization to molecular component Alt a 1 (Alternaria). The significant relation of sensitization to molecular components of inhalant allergens is marked extra bold.*

Table 13. Summary table – the list of food allergens with the significantly higher occurrence of sensitization to molecular components.

Allergen	Molecular component	Protein family	Food allergens with the significantly higher occurrence of sensitization to molecular components.
Alder	Aln g 1	PR 10 protein	Peanuts, hazelnuts, celery, apple, peach
Birch	Bet v 1	PR 10 protein	Peanuts, hazelnuts, walnuts, apple, peach
Mugwort	Art v 1	Defensin like protein	0
Alternaria	Alt a 1	Acidic glycoprotein	Walnuts, kiwi
Aspergillus	Asp f 6	Peroxisomal protein	0
Olive pollen	Ole e 9	Beta-1,3-glucanase	Walnuts, peach
Olive pollen	Ole e 1	Common olive group 1	Hazelnuts
Timothy	Phl p 1	Grass group 1	Peanuts, hazelnuts, walnuts
	Phl p 2	Grass group 2	Peanuts, hazelnuts, walnuts
	Phl p 4	Berberine bridge enzyme	Peanuts, hazelnuts, walnuts, celery
	Phl p 5	Grass group 5	Peanuts, walnuts, peach
	Phl p 6	Grass group 6	Peanuts, walnuts
	Phl p 11	Ole e 1-related protein	Apple, peach
Olive pollen	Ole e 7	Lipid transfer protein (nsLTP)	Wheat
Plane tree	Pla a 3	Lipid transfer protein (nsLTP)	0
Mugwort	Art v 3	Lipid transfer protein (nsLTP)	0
Birch	Bet v 2	Profilin	0
Timothy	Phl p 12	Profilin	Peach
Annual mercury	Mer a 1	Profilin	Peanuts
Timothy	Phl p 7	Polcalcin	Peanuts
Birch	Bet v 4	Polcalcin	0

group 1), Phl p 1, 2 (grass group 1, 2), Phl p 4 (Berberine bridge enzyme), [Table 5](#). The significantly higher occurrence of sensitization (p -value <0.05) to molecular components Bet v 1 (Birch, PR 10 protein), Alt a 1 (Alternaria, Acidic glycoprotein), Ole e 9 (Olive pollen, Beta-1,3-glucanase), Phl p 1, 2, 5, 6 (Grass group 1, 2, 5, 6), Phl p 4 (Timothy, Berberine bridge enzyme) and Mer a 1 (Annual Mercury, profilin) was confirmed in patients suffering from food reaction to walnuts (50 patients), [Table 6](#). In patients suffering from food reaction to soy (13 patients), we did not confirm the significant relation to sensitization to examined molecular components, [Table 7](#). In patients suffering from food reaction to wheat (14 patients), the significant relation (p -value <0.05) was confirmed to sensitization to molecular component Ole e 7 (Olive pollen, lipid transfer protein) – unfortunately, zeroes appeared in this table and one has to be careful in making conclusions ([Table 8](#)). In patients suffering from food reaction to celery (24 patients), the significantly (p -value <0.05) higher occurrence of sensitization to molecular components Aln g1 (Alder, PR 10 protein) and Phl p 4 (Timothy, Berberine bridge enzyme) was confirmed, [Table 9](#). In patients suffering from food reaction to apple (23 patients), the significantly (p -value <0.05) higher occurrence of sensitization to molecular components Aln g1 (Alder, PR 10 protein), Bet v 1 (Birch, PR 10 protein), Phl p 11 (Timothy, Ole e related protein) was confirmed, [Table 10](#). In patients suffering from food reaction to peach (19 patients), the significant relation (p -value <0.05) was confirmed to sensitization to molecular components Aln g1 (Alder, PR 10 protein), Bet v 1 (Birch, PR 10 protein), Phl p 5 (grass group 5), Phl p 11 (Ole e related protein), Phl p 12 (Timothy,

profilin), Table 11. In patients suffering from food reaction to kiwi (16 patients), the significant relation (p -value <0.05) was confirmed to sensitization to molecular component Alt a 1 (*Alternaria*, Acidic glycoprotein), Table 12. The molecular components with the significantly higher occurrence of sensitization (p -value <0.05) in patients suffering from food reaction to examined food allergens are recorded in the Summary Table 13.

Discussion

The purpose of our study was to show the relationship between the sensitization to molecular components of inhalant allergens and the occurrence of clinical reactions to peanuts, walnuts, hazelnuts, wheat, soy, celery, apple, peach and kiwi in atopic dermatitis patients. We evaluated also the semi-quantification results of the ISAC Multiplex testing to reveal the relevance of the leading allergens that cause the atopic dermatitis. Molecular components such as Cysteine protease (Der f 1, Der p 1), NPC2 protease (Der f 2, Der p 2), Acidic glycoprotein (Alt a 1), PR 10 proteins (Bet v 1, Mal d 1, Aln g 1 and Cor 1.04), Lipocalins (Can f 1, Fel d 4, Mus m 1, Equ c 1), Uteroglobulin (Fel d 1), Kallikrein (Can f 5) and molecular components of Timothy grass are the leading molecular components with high level of specific IgE. The molecular component Cyn d 1 from Bermuda grass was found as the leading component also. As Bermuda grass pollen is not present in our region, possible cross-reactivity with β -expansins from other grasses could be the explanation for the results with high sensitization to Cyn d 1 in our study. Regarding the patients suffering from food reactions to examined food allergens, we confirmed the significantly higher occurrence of sensitization to molecular components Bet v 1, Aln g 1, Alt a 1 and to molecular components of Timothy; these molecular components are consistent with components of leading inhalant allergens. In addition, the significantly higher sensitization to molecular components of Olive pollen (Ole e 1 – common olive group 1, Ole e 9 – Beta 1,3 glucanase, Ole e 7 – Lipid transfer protein) was recorded in patients suffering from a food reaction to walnuts, hazelnuts, peach and wheat. Ole e 9 (glucanase) is the main olive allergen that usually causes sensitization in geographical areas exposed to high levels of olive pollen. Ole e 9 shares some common epitopes with glucanases from birch, tomato, potato, pepper, banana and latex pollen, so it may be the explanation for the higher sensitization rate in patients with AD in our study.

According to literature, the usefulness of broad testing (such as in ISAC Multiplex testing) was underlined by microarray data showing that patients with AD were frequently sensitized to allergens not routinely included in currently established sIgE screening panels, such as *Staphylococcus aureus* exotoxins, *Alternaria alternata* and hazelnut allergens (Mari et al., 2011; Ott et al., 2014). The ISAC platform combines biochip technology and purified natural and recombinant allergen components in a miniaturized assay and gives semiquantitative results. Customized biochips with additional components have been produced for special purposes, for example the MeDALL biochip (Lupinek et al., 2014; Westman et al., 2015). Although the broad panel of allergen components on the ISAC chip has the potential to reveal unanticipated sensitizations, this technique is less sensitive than ImmunoCAP method (Canonica et al., 2013).

Component – resolved diagnosis permits the diagnosis of the allergen sensitization profile. Some authors observed the underlying sensitizations to plant-derived foods,

mainly vegetables and cereals (Asero, 2012; Cardona et al., 2012; Pascal et al., 2012; Romano et al., 2012). In Europe, the prevalence of positive skin prick test to birch pollen allergens ranges from 5% in The Netherlands to 54% in Switzerland, while Scandinavian countries have the highest number of patients with exclusive sensitization to Bet v 1 (Custovic et al., 2015a; Kinaciyan et al., 2007). Ole e 1 is the most common sensitizing molecule in olive pollen. In areas with heavy olive pollen exposure, Ole e 7 and Ole e 9 should be tested to identify patients with a more severe allergic phenotype (Rodríguez et al., 2001; Scala et al., 2016). Pla a 1 and Pla a 2 may serve as a marker of primary sensitization to plane tree pollen, while the nsLTP Pla a 3 has been linked with sensitization to plant-food LTPs (Rodríguez et al., 2007).

Our study confirms the important role of PR 10 proteins in atopic dermatitis patients. The PR-10 proteins are actually one of the 11 subfamilies of the Bet v 1 family. PR-10 proteins are expressed in high concentrations in reproductive tissues such as pollen, seeds, and fruits. Oral allergy syndrome (OAS) is the most common clinical representation of pollen–food syndrome; it is defined by the occurrence of itching and tingling of the lips, mouth, and throat immediately after eating some fruits and vegetables, as it was observed in our study. The most frequent OAS occurs in Bet v 1-sensitized patients when eating fruits from the *Rosaceae* family, mainly apple. Apple OAS depends on the molecular homology between Bet v 1 and the Bet v 1-homologous Mal d 1, the major allergen of apple belonging to PR-10 family (Ballmer-Weber et al., 2000; Ballmer-Weber & Hoffmann- Sommergruber, 2011; Boyano-Martínez et al., 2013; Fernández-Rivas et al., 2006).

According to our results, patients suffering from the sensitization to Phl p 1, Phl p 2, Phl p 4, Phl p 5, Phl p 6 and Phl p 7 suffer significantly more often from food reaction to peanuts, the sensitization to Phl p 11 and Phl p 12 is in significant relation to food reaction to peach. Phl p 1 shares epitopes with group 1 allergens from other grasses and shows IgE cross-reactivity to most other group 1 allergens from grasses, corns, and monocots (Bousquet et al., 2007; Devanaboyina et al., 2014; Focke et al., 2001; Hatzler et al., 2012; Laffer et al., 1994; Suphioglu & Singh, 1995). Phl p 5 is another major pollen allergen of temperate grasses with a lower sensitization prevalence, but often with high IgE levels. Phl p 5 is a cytoplasmatic ribonuclease, important in the enzymatic degradation of RNA. It shows broad IgE cross reactivity with other group 5 allergens from the Pooideae subfamily of temperate grasses. Phl p 4 is a tryptase-resistant glycoprotein, berberine bridge enzyme, involved in the synthesis of alkaloids. It can be classified as a major allergen. It shows IgE cross-reactivity with other group 4 grass pollen allergens, including with Cyn 4 to some extent (Focke et al., 2001; Suphioglu & Singh, 1995). Natural Phl p 4 contains CCD, which may lead to IgE crossreactivity with a wide range of plants and plant products. Phl p 11 belongs to the Ole e 1 related proteins and hence exhibits a broad range of cross-reactivities to pollen from different plants such as olive, ash, privet, saffron crocus, thistle, plantain, and corn. It is an acidic polypeptide with homology to the tryptase inhibitor of soybean. Profilin and polcalcin represent the major causes of cross reactivity due to their highly conserved structure and ubiquitous distribution (Scala et al., 2016). Profilin or polcalcin reactors score positive to all tree pollen after an extract-based diagnostic testing (Custovic et al., 2015a; Lombardero et al., 2004; Magler et al., 2010; Matricardi, 2014; Tripodi et al., 2012). Phl p 7 (polcalcin) and Phl p 12 (profilin) are minor allergens, representing

panallergens from the plant world. Phl p 7 is a calcium-binding protein present in many different pollens, hence representing a broad cross-reacting allergen: birch, alder, juniper, ragweed, mugwort, olive, goosefoot, etc. Phl p 7 sensitization can be used as a marker for a more general pollen sensitization. Phl p 12 is a member of the profilin family, an actin-binding protein that is present throughout the whole plant world. As profilins are ubiquitous in plant cells, profilin sensitization gives rise to a long range of cross-reacting plants and plant products as birch, soybean, corn, latex, and plant foods (Custovic et al., 2015a; Lombardero et al., 2004; Magler et al., 2010; Matricardi, 2014; Tripodi et al., 2012;). In our study, only the significant relation between the sensitization to Phl p 7 and the food reactions to peanuts was confirmed. Interestingly, the food reactions to walnuts and kiwi are higher in patients with sensitization to Alt a 1 (*Alternaria*, acidic glycoprotein). *Alternaria* and *Cladosporium* species are considered to be important outdoor allergens, and sensitization and exposure to species of these genera are related to the development of asthma and rhinitis, as well as epidemics of asthma exacerbation, including life-threatening asthma exacerbation; however, *Alternaria* and other allergenic fungi can colonize in indoor environments and thereby increase the fungal aeroallergen exposure levels. In our previous publications we confirmed that patients suffering from sensitization to outdoor fungi suffer significantly more from food allergy to peanuts and walnuts (Čelakovská et al., 2018). The *Alternaria*-spinach syndrome, in which Alt a 1 is mentioned as an involved allergen component was recently recognized (Herrera-Mozo et al., 2006), this cross-reactivity between aeroallergens from fungi imperfecti and allergens from spinach and mushroom *Agaricus bisporus* was described (Herrera-Mozo et al., 2006). Surprisingly, no significant relation was confirmed in patients with food reaction to soy and the sensitization to molecular inhalant components. In Central Europe, soy is a clinically relevant birch pollen-related allergenic food. Crossreaction is mediated by a Bet v 1 homologous protein, Gly m 4. Additionally, birch pollen allergic patients might acquire through Bet v 1 sensitization allergies to mungbean or peanut, in which Vig r 1 and Ara h 8 are the main cross-reactive allergens (Mittag et al., 2004). According to the literature, the sera of 29 patients who suffered from pollen-related food hypersensitivities and complained of allergic reactions to kiwi fruit and other tropical fruits were tested for specific IgE antibodies against kiwi fruit, apple, carrot, celery and birch pollen using an enzyme allergosorbent test (EAST). In 20 sera, specific IgE antibodies were detected against all five extracts. Sodium dodecyl sulphate polyacrylamide gel electrophoresis/ immunoblot of kiwi fruit extract revealed two major allergens with molecular weights of approximately 43 and 67 kDa. In EAST inhibition assays, cross-reactivities between kiwi fruit, apple, birch pollen and, to a lesser degree, carrot and celery were demonstrated. The cross-reactivities seen between kiwi fruit, birch pollen and apple were not caused by the major allergen of birch pollen (Bet v 1). Allergens with molecular weights of approximately 68 kDa in birch pollen and 67 kDa in apple cross-reacted with the allergens of kiwi fruit, as demonstrated by immunoblot inhibition. Profilins, which are known plant panallergens, do not seem to be relevant allergens in kiwi fruit (Möller et al., 1997). To obtain data on the antibody binding epitopes of Mal d 1 and to gain insights into the structures responsible for its B-cell cross-reactivity to Bet v 1, the binding characteristics were studied with 3 monoclonal antibodies (MAbs) raised against Mal d 1 and with patients' IgE directed against Mal d 1 and Bet v 1 by immunoblotting and ELISA. The different binding characteristics

of these three MAbs indicated that the MAbs 1D6, 2B2 and 3F8 recognized different epitopes on the major apple allergen. MAb 2B2 cross-reacted with Bet v 1 on immunoblots, whereas 1D6 and 3F8 did not. Since 1D6 and 2B2 (but not 3F8) always competed with IgE from the same apple-allergic patients, 1D6 may be a useful tool for Mal d 1 epitope studies and 2B2 for an epitope that cross-reacts with IgE specific for Bet v 1 (Son et al., 2001).

On the other hand, our study shows, that molecular components from house dust mites (cysteine protease, NPC2 protease) and animals (lipocalins, uteroglobulins, kallikreins) and from *Alternaria* (Acydic glycoprotein) are the leading allergens with very high levels of specific IgE also. These results may demonstrate the significance of disturbed epidermal barrier, resulting in increased transepidermal water loss and permeation of allergens, irritants, and microbes. It is evident that the direct contact of skin with allergens could trigger signals to initiate Th2 allergic response. Emerging data now suggest that epithelial cell-derived cytokines such as TSLP, IL-33, and IL-25 may drive the progression from atopic dermatitis to bronchial asthma and food allergy (Czarnowicki et al., 2017; Paller et al., 2019).

In our previous study, we confirmed the occurrence of food allergy to fish in 13% of patients, and the food allergy to shrimps in 6% of patients suffering from AD. In patients with allergy to fish, the significantly higher occurrence of sensitization to Asp f 1, Der f 1, Der f 2, Der p 1, Der p 2, Lep d 2 and Blo t 5 was confirmed; in patients with food allergy to shrimps the significantly higher occurrence of sensitization to Cla h 8, Bla g 1 and Bla g 5 was confirmed also (Čelakovská et al., 2020).

The evaluation of the relation between the results of the open exposure test (history) to examined food allergens and specific IgE to molecular components of peanuts (Ara h 1, Ara h 2, Ara h 3, Ara h 6, Ara h 8 and Ara h 9), walnuts (Jug r 2, Jug r 3), hazelnuts (Cor a 1.0401, Cor a 8, Cor a 9), wheat (Tri a 14, Tri a 19.0101, Tri a aA-TI), soy (Gly m 4, Gly m 5, Gly m 6), celery (Api g 1), apple (Mal d 1), peach (Pru p 1, Pru p 3) and kiwi (Act d 1, Act d 2, Act d 5, Act d 8) is the topic for our other publications.

The knowledge of significant syndromes and associations related to cross-reactive allergen components and the impact of relevant cross-reactivities between aeroallergens and food allergens are of great importance for the allergy specialist. Allergen cross-reactivity may be an underestimated problem in clinical practice (Pfißner et al., 2010). Moreover, molecular-based allergy diagnosis is essential for an accurate allergy evaluation of cross-reactions, sometimes with impact on the therapeutic strategy. Patients with reactions to certain food allergens and inhaled allergens should be carefully instructed about cross-reactions to other food allergens (Muraro et al., 2014). Dietary avoidance of foods that are related and have potentially cross-reactive proteins should be individualized according to the risk of clinical cross-reactivity (Sampson et al., 2014).

Conclusion

The leading inhalant allergens in atopic dermatitis patients are molecular components of cysteine protease (Der f 1, Der p 1), NPC2 protease (Der f 2, Der p 2), Acydic glycoprotein (Alt a 1), PR 10 proteins (Bet v 1, Mal d 1, Aln g 1 and Cor 1.04), lipocalins (Can f 1, Fel d 4, Mus m 1, Equ c 1), uteroglobulin (Fel d 1), Kallikrein (Can f 5) and molecular components of Timothy and Bermuda grass (glycoprotein). In patients with

food reactions to peanuts, hazelnuts, walnuts, celery, apple, peach and kiwi we recorded the leading molecular components such as Bet v 1, Aln g 1, Alt a 1 and molecular components of Timothy. In addition, in patients suffering from food reactions to walnuts, hazelnuts, peach and wheat, we recorded the significant relation to molecular components of Olive pollen (Ole e 1 – common olive group 1, Ole e 9 – Beta 1,3 glucanase, Ole e 7 – Lipid transfer protein).

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