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Geographical differences in food allergy

Introduction

Food allergy is an IgE-mediated reaction to a food, usually during the 2 hours following its intake. It represents a health problem that can lead to life-threatening reactions and can even impair quality of life [1]. Any food can potentially trigger an allergic response; in fact, more than 170 foods have been identified as being potentially allergenic, but only a minority of them causes the majority of reactions. The classical “eight groups of foods” more frequently involved in allergic reactions around the world are: cow's milk, egg, wheat, soy, peanut, tree nuts, fish and shellfish [2]. Despite relevant advances in the knowledge of food allergy during the last two decades, gaps in epidemiology in this area are evident. Recent reviews of the literature have provided very heterogeneous results regarding food allergy and its epidemiology because they have not been undertaken following standard diagnostic methods, and very few of them have used oral challenge procedures (either open or double-blind, placebo controlled food challenge (DBPCFC)) to confirm diagnosis [3, 4]. The prevalence of food allergies may have a different geographical distribution depending on several factors: a) dietary habits or practices (for example, peanut allergy has increased as a consequence of the widespread use of peanuts in the USA [5]), b) the cooking method used (as an example, roasted or emulsified peanut products in the United States have raised the allergenicity to peanuts) [6], c) the age of weaning (it has been demonstrated

that earlier consumption of peanut proteins may reduce the prevalence of peanut allergy) [7], d) exposure to aeroallergens, which determines the pattern of food allergy in each region [8] and e) other factors, such as genetic factors (genetic variants in the HLA-DR and HLA-DQ seem to be a risk factor for peanut allergy in children of European ancestry) [9].

In the first part of this article we will review the geographical distribution of the most common food allergies based on the most recent systematic review and meta-analysis of the prevalence of common food allergies in Europe and on the EuroPrevall project [10–12], which is the first study designed to evaluate food allergies using cohort studies, questionnaires, and also standard diagnostic methods, such as oral food challenges and serological data in patients across major climatic and cultural regions in Europe.

Each allergen source (which is a tissue, particle, food or organism inducing allergy) contains different allergenic molecules (allergen components), which can be identified by specific IgE (sIgE) antibodies [13]. IgE mediated food allergies can be caused by a primary genuine sensitisation to a food allergen, but most of them (60 %) are due to a cross-reacting allergenic structure shared by inhalants and foods. Cross-reaction is a consequence of the binding of an IgE antibody to homologous allergen structures called epitopes (which can be linear or conformational) of panallergens belonging to different protein families [13]. Patients who are allergic to the same food source can show different molecular/allergenic

patterns, depending on the geographical area they live in. The objective of the second part of the review is to describe the different molecular patterns in each main food source allergy, and to link them with the predominant aeroallergens of the different geographical areas.

The most common food allergies – geographical distribution

The incidence of food allergy ranges between 3 and 35 % in self-reported studies, being lower (2–5 %) when assessing for sensitization and symptoms to food [14]. The prevalence is even lower when performing oral challenges, but few studies have used the gold-standard tool (DBPCFC) to confirm the diagnosis of food allergy [15]. The systematic review and meta-analysis published by Nwaru et al. is general population based and provides the prevalence of the eight most common food allergies across different regions in Europe. It integrates studies published in Europe from January 1, 2000 to September 30, 2012, identified from databases [10]. Prevalences were stratified by age and geographical region of Europe (east, west, south, and north). Some of the studies evaluated the prevalence of food allergy confirmed by DBPCFC in German and Danish populations involving children, adolescents and adults [16–18]. The food allergies assessed were: cow's milk, egg, wheat, soy, peanut, tree nuts, fish and shellfish. Allergy to cow's milk, egg, wheat, tree nut, fish and shellfish were more preva-

Tab. 1 The prevalence and distribution of food sensitization in European adults

Food	Zurich	Madrid	Utrecht	Lodz	Sofia	Reykjavik	All
Hazelnut	17.79	6.00	11.95	6.54	6.27	1.27	9.26
Peach	13.43	11.29	9.74	5.77	3.58	2.31	7.93
Apple	10.75	8.94	8.15	4.83	3.58	1.56	6.53
Carrot	10.18	9.53	5.69	4.51	6.27	1.34	5.96
Celery	11.66	8.24	6.86	4.51	4.48	1.27	6.25
Kiwi	9.35	10.35	4.67	4.88	1.79	2.38	5.20
Tomato	8.07	9.29	3.85	4.33	5.38	1.71	4.91
Wheat	8.55	10.47	3.03	4.14	4.48	0.67	4.50
Sesame	7.61	10.24	3.24	4.26	4.48	1.27	4.50
Shrimp	6.89	5.29	3.94	4.93	6.27	2.76	4.79
Banana	5.90	8.94	2.27	4.83	2.69	2.16	3.79
Corn	6.41	8.00	1.93	2.72	3.58	1.19	3.38
Sunflower	5.81	8.24	1.86	3.49	2.69	0.75	3.17
Poppy	5.44	7.77	1.38	3.12	3.58	0.97	3.03
Melon	6.55	7.88	1.79	3.05	2.69	0.15	3.10
Buckwheat	6.18	7.06	0.89	3.05	3.58	0.74	2.90
Walnut	5.59	7.65	1.86	3.57	2.69	0.07	2.98
Lentils	5.07	6.71	1.24	2.87	4.48	0.74	2.88
Peanut	5.04	7.18	1.58	3.12	1.79	0.45	2.65
Soya	4.61	6.47	1.45	2.35	1.79	0.15	2.33
Mustard	3.59	2.71	0.41	1.71	2.69	0.37	1.60
Egg	1.31	0.59	0.69	1.07	0.90	0.67	0.86
Milk	0.74	1.65	0.84	0.69	0	1.20	0.82
Fish	0.17	1.18	0.20	0	0	0.12	0.22
Any food	23.63	19.53	17.56	13.99	12.54	6.55	15.81

lent in Northern Europe than in the rest of Europe, while the prevalence of soy allergy and peanut allergy was higher in Western Europe than in other regions.

Some important limitations when analysing the differences in the geographical distribution pattern regarding the studies in this systematic review and meta-analysis were that only few studies were undertaken in Eastern Europe and Southern Europe, compared with studies from Western and Northern Europe. Moreover, different diagnostic methods were undertaken (based on self-reported questionnaires, skin prick test results, sIgE results and oral challenge studies). Further, there were different rates of participation between different studies and between geographical areas, which led to a wide heterogeneity between studies and represent a weak point on reliability.

The prevalence and distribution of food sensitization in the European population

EuroPrevall is an EU-funded multidisciplinary project including 62 institutions from different countries (19 European countries representing different geographical areas and major climatic and cultural regions in Europe, including Alpine, Mediterranean, Central, and Nordic regions, and maritime areas), with collaborating centres in USA, Australia, New Zealand, as well as Ghana, India, China and Russia.

A standardized diagnostic protocol is being used in EuroPrevall to obtain good estimated prevalence and distribution of food allergies in infants, children, adolescents, and adults, basically in Europe, but also in other mentioned regions in the world [19–22]. Three complementary epidemiological studies are being conducted in EuroPrevall: a birth co-

hort study with standardized questionnaires, a general population survey in schoolchildren and adults and a cross-sectional study reflecting different climatic and cultural regions.

A panel of 24 foods using serum IgE measurements and skin prick test were tested (hen's egg, cow's milk, fish, shrimp, peanut, hazelnut, apple, peach, celery, kiwi, mustard, sesame, soy, walnut, wheat, sunflower, buckwheat, banana, carrot, corn, lentil, melon, poppy seed and tomato) [11]. The prevalence of participants reporting reactions to one of the priority foods ranged from <1 % in Vilnius to 19 % in Madrid. IgE analysis by Immuno-CAP for the 24 foods evaluated was performed in all participants.

The prevalence of IgE sensitization to the different foods evaluated varies between different geographical regions, ranging from 24 % in Zurich to 7 % in Reykjavik, but IgE sensitization to all food allergens was globally distributed in approximately the same relative prevalence or ratio in the different geographical areas. The most frequent global sensitizations were hazelnut, peach, apple, celery and carrot. Soya, mustard, egg, milk and fish were the foods with less prevalence sensitizations (■ Tab. 1). The fact that IgE sensitization shows a wide variation between different geographical sites could be due to true differences between populations. The sites in the study were selected to represent variations across Europe, but were not intended to represent the European population. Given the fact there is such a wide variation between different areas, the overall prevalence of IgE sensitization to foods across Europe cannot be estimated as a whole.

On the other hand, the same distribution of the relative prevalence of IgE sensitization to each food suggests that the exposure to different foods is not the cause determining the IgE sensitization to a particular food.

Although this is the most extensive analysis of IgE sensitization to food allergens, other studies that perform DBPCFC are needed to go one step forward and help us to better understand the distribution of clinical relevant sensitizations in food allergy.

As an example of the analysis of not only the IgE sensitization, but also the clinical relevant distribution pattern in food allergy across Europe, we analyzed a cow's milk allergy (CMA) study in European children within the EuroPrevall birth cohort [12].

Most studies analyzing prevalence of milk allergy are performed using anamnesis and evidence of allergic sensitization or open food challenges [23, 24].

The EuroPrevall birth cohort is the largest longitudinal observational population-based study and the first to provide reliable and internationally comparable incidence data on IgE and non-IgE-associated confirmed CMA, using DBPCFC [12].

A cohort of EuroPrevall was followed and analyzed to define the global and centre-specific incidence and natural history of CMA in children up to 2 years of age in 9 European countries. Participants underwent clinical evaluation with cow's milk-specific IgE antibodies (sIgE), a skin prick test and DBPCFC to milk.

The aims were to define cumulative incidence, prevalence patterns and natural history of food allergy in early childhood across Europe. CMA was suspected in 358 children and it was confirmed in 55, resulting in global incidence of confirmed CMA of 0.54 % (0.41–0.70 %) during the first 2 years of life. Adjusted incidences of challenged-proven CMA ranged from 0 to 1.3 %. The incidences in different countries were similar, except for south-eastern Europe (Greece and Italy), which had the lowest rates.

Molecular pattern of food allergy – geographical distribution

Food allergy due to cross-reactivity to inhalant allergens

An allergen or allergenic molecule/component is a molecule derived from a given allergen source that is identified by specific IgE (sIgE) and may lead to an IgE-mediated reaction [13].

The number of allergic individuals who are mono-sensitized to a single allergenic source is very limited. In fact, most patients seem to display adverse re-

Bundesgesundheitsbl 2016 · 59:755–763 DOI 10.1007/s00103-016-2357-0
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Abstract

Background. Food allergy represents a health problem worldwide and leads to life-threatening reactions and even impairs quality of life. Epidemiological data during the past decades is very heterogeneous because of the use of different diagnostic procedures, and most studies have only been performed in specific geographical areas.

Objectives. The aim of this article is to review the available data on the geographical distribution of food allergies at the food source and molecular level and to link food allergy patterns to the aeroallergen influence in each area.

Methods. Systematic reviews, meta-analysis, studies performed within the EuroPrevall

Project and EAACI position papers regarding food allergy were analysed.

Conclusions. The prevalence of food allergy sensitization differs between geographical areas, probably as a consequence of differences among populations, their habits and the influence of the cross-reactivity of aeroallergens and other sources of allergens. Geographical differences in food allergy are clearly evident at the allergenic molecular level, which seems to be directly influenced by the aeroallergens of each region and associated with specific clinical patterns.

Keywords

Food allergy · Geographical differences · Prevalence · Aeroallergens · Molecular pattern

Geographische Unterschiede bei Nahrungsmittelallergien

Zusammenfassung

Hintergrund. Nahrungsmittelallergien stellen ein weltweites Gesundheitsproblem dar, sie führen zu lebensbedrohlichen Reaktionen und selbst zur Beeinträchtigung der Lebensqualität. Die epidemiologischen Daten aus den vergangenen Jahrzehnten sind wegen des Einsatzes unterschiedlicher diagnostischer Verfahren sehr heterogen, außerdem sind die meisten Studien nur in spezifischen geographischen Regionen durchgeführt worden.

Ziel. Ziel des vorliegenden Beitrags ist es, einen Überblick über die verfügbaren Daten zur geographischen Verteilung von Nahrungsmittelallergien auf der Ebene der Nahrungsquellen und auf molekularer Ebene zu geben und Muster von Nahrungsmittelallergien mit dem Einfluss von Aeroallergenen in der jeweiligen Region zu verknüpfen.

Methoden. Systematische Übersichtsarbeiten, Metaanalysen, innerhalb des EuroPrevall-Projekts durchgeführte Studien und Positionspapiere der EAACI (Europäische Akademie

für Allergologie und klinische Immunologie) in Bezug auf Nahrungsmittelallergien wurden ausgewertet.

Schlussfolgerung. Die Prävalenz der Sensibilisierung bei Nahrungsmittelallergie ist zwischen geographischen Regionen unterschiedlich, wahrscheinlich als Folge von Unterschieden zwischen den jeweiligen Bevölkerungsgruppen, ihren Gewohnheiten und dem Einfluss der Kreuzreaktivität von Aeroallergenen und anderen Allergenquellen. Auf molekularer Ebene der Allergene sind geographische Unterschiede bei Nahrungsmittelallergien deutlich nachweisbar; dies scheint unmittelbar durch Aeroallergene der jeweiligen Region beeinflusst und mit spezifischen klinischen Mustern verknüpft zu sein.

Schlüsselwörter

Nahrungsmittelallergie · Geographische Unterschiede · Prävalenz · Aeroallergene · Molekulare Muster

actions against multiple allergen sources. This might be simply due to poly-sensitization to different allergenic sources, or the cause could be IgE cross-reactivity, in which IgE antibodies originally raised against a given allergen can bind homologous molecules from a different allergen source, including aeroallergens.

In other words, IgE-mediated reactions to foods can occur as a primary sensitization to a food or as a cross-reactive phenomenon by primary sensitization to aeroallergens, such as pollens, or to other food allergens [25].

Cross-reactivity in plant food allergy is mediated to panallergens, which

Tab. 2 PR-10 (Bet v 1 homologues) allergens from pollen and plant food

PR-10 (Bet v 1 homologues)					
Pollen		Plant food			
Species	Allergen	Species	Allergen	Species	Allergen
<i>Alnus glutinosa</i> (alder)	Aln g 1	<i>Actinidia chinensis</i> (gold kiwi fruit)	Act c 8	<i>Malus domestica</i> (apple)	Mal d 1
<i>Betula verrucosa</i> (European white birch)	Bet v 1	<i>Actinidia deliciosa</i> (kiwi fruit)	Act d 8	<i>Prunus armeniaca</i> (apricot)	Pru ar 1
<i>Carpinus betulus</i> (hornbeam)	Car b 1	<i>Apium graveolens</i> (celery)	Api g 1	<i>Prunus avium</i> (sweet cherry)	Pru av 1
<i>Castanea sativa</i> (chestnut)	Cas s 1	<i>Arachis hypogaea</i> (peanut)	Ara h 8	<i>Prunus persica</i> (peach)	Pru p 1
<i>Fagus sylvatica</i> (European beech)	Fag s 1	<i>Corylus avellana</i> (hazel)	Cor a 1	<i>Pyrus communis</i> (pear)	Pyr c 1
<i>Ostrya carpinifolia</i> (European hophornbeam)	Ost c 1	<i>Daucus carota</i> (carrot)	Dau c 1	<i>Rubus idaeus</i> (red raspberry)	Rub i 1
		<i>Fragaria ananassa</i> (strawberry)	Fra a 1	<i>Solanum lycopersicum</i> (tomato)	Sola l 4
		<i>Glycine max</i> (soybean)	Gly m 4	<i>Vigna radiata</i> (mung bean)	Vig r 1

are cross-reactive allergens, belonging to a protein family, well preserved throughout any widely different species, able to trigger IgE antibody binding of different allergy sources from pollen or other plant food [13].

In fact, in the analysis of the geographical distribution of sensitization to pollen and foods undertaken within the EuroPrevall project, it was demonstrated that pollen sensitization is the most dominant factor in determining sensitization to plant foods [11].

Geographical differences in pollen exposure across Europe have already been demonstrated in analyses performed by monitoring pollen of *Betulaceae*, *Oleaceae*, *Poaceae* and *Asteraceae* from 13 different sites close to the EuroPrevall survey centres. *Betula* was the most dominant pollen exposure, followed by *Poaceae*, *Oleaceae* and *Asteraceae*. Only in Reykjavik (Iceland), Madrid (Spain) and Derby (United Kingdom) was *Poaceae* the dominant pollen, as was *Oleaceae* in Thessaloniki (Greece) [26].

These differences in pollen distribution would explain the geographical differences in food allergy [11]. Microarray

data was analyzed in this same EuroPrevall study [11]. IgE sensitization to the following allergens was evaluated: birch allergens Bet v 1 (PR-10) or Bet v 2 (profilin), plant food allergens cross-reacting with pollens (either PR-10 allergens (Api g 1.01, Ara h 8, Cor a 1, Dau c 1, Gly m 4, Mal d 1, Pru p 1) or profilin (Cor a 2, Dau c 4, Hel a 2, Hev b 8, Mal d 4, Tri a 12)), and “true” non-cross-reacting plant food allergens (Act d 1, Ara h 1, Ara h 2/Ara h 6, Ara h 3.01/Ara h 3.02, Cor a 8, Cor a 9, Cor a 11, Gly m 5, Hel a 3, Jug r 2, Jug r 4, Lyc e 3, Mal d 2, Mal d 3, Pru p 3, Ses i 1, Ses i 2, Ses i 3, Sin a 1, Tri a 19, Tri a Gliadin) [11]. This study concluded that IgE sensitization to whole plant food extracts is strongly associated with the IgE sensitization to birch pollen allergens Bet v 1 (PR-10), and Bet v 2 (profilin), and this can be partially explained because most plant foods contain allergens that cross-react with pollens. The microarray data also showed that true-plant allergen sensitizations are rare and seem differently distributed (with low prevalence in Utrecht, and high prevalence in Sofia).

Main allergens involved in pollen – plant food allergy

In older children and adults, most plant food allergy reactions are due to a cross-reactivity phenomenon to an inhalant allergen, most of the time, a pollen [8]. The main allergens responsible for pollen-plant food IgE cross-reactivity are PR-10 proteins (Bet v 1 homologues) and profilins. Meanwhile, non-specific lipid transfer proteins (nsLTP), and thaumatin-like proteins (TLP) have also been described in some pollens and plant food, but cross-reactivity has not been well established ([5, 27, 28]; ■ Tab. 2, 3, 4, 5).

PR-10/Bet v 1 homologues

The PR-10 is one of the most important families of proteins in pollen-plant food syndrome. These proteins are widespread throughout the plant kingdom and are highly conserved [29]. They are intracellular proteins with enzymatic activity (■ Tab. 2).

These proteins are sensitive to heat and digestion, which usually leads to mild symptoms, restricted to the oral cavity allergy syndrome. Nevertheless, systemic reactions have also been described in birch pollen-mediated soy allergy and other fruits like sharon fruit and jack fruit [29].

Bet v 1, a PR-10 protein, is the birch major allergen, birch pollen being the most prevalent in Northern and Central Europe [26].

This would explain that plant food allergy in Northern and Central Europe follows a pollen-food cross-reactivity phenomenon due to a PR-10 sensitization pattern [26].

Lipid transfer proteins

Lipid transfer proteins (LTP) are members of the prolamin superfamily and have a low molecular weight and a conserved pattern structure. They are highly resistant to proteolytic digestion and heat, which allows the allergen to reach the intestinal immune system without modifications, which would explain the high incidence of severe systemic reactions. They are classically considered to be non-pollen-related “true” food allergens [30]. The cross-reactivity between LTP from

Tab. 3 Non-specific lipid transfer protein (ns-LTP) allergens from pollen and plant food					
Lipid transfer proteins					
Pollen		Plant food			
Species	Allergen	Species	Allergen	Species	Allergen
<i>Ambrosia artemisiifolia</i> (Short ragweed)	Amb a 6	<i>Apium graveolens</i> (celery)	Api g 2	<i>Morus nigra</i> (mulberry)	Mor n 3
<i>Artemisia vulgaris</i> (Mugwort)	Art v 3		Api g 6	<i>Musa acuminata</i> (banana)	Mus a 3
<i>Cannabis sativa</i> (Indian hemp)	Can s 3	<i>Arachis hypogaea</i> (peanut)	Ara h 9	<i>Phaseolus vulgaris</i> (Green bean, French bean)	Pha v 3
<i>Olea europea</i> (Olive)	Ole e 7		Ara h 16	<i>Prunus armeniaca</i> (Apricot)	Pru ar 3
<i>Parietaria judaica</i> (Pellitory-of-the-Wall)	Par j 1		Ara h 17	<i>Prunus avium</i> (sweet cherry)	Pru av 3
	Par j 2	<i>Asparagus officinalis</i> (asparagus)	Aspa o 1	<i>Prunus domestica</i> (European plum)	Pru d 3
<i>Parietaria officinalis</i> (Pellitory)	Par o 1	<i>Brassica oleracea</i> (cabbage and others)	Bra o 3	<i>Prunus dulcis</i> (almond)	Pru du 3
<i>Platanus acerifolia</i> (London plane tree)	Pla a 3	<i>Castanea sativa</i> (chestnut)	Cas s 8	<i>Prunus persica</i> (peach)	Pru p 3
		<i>Citrus limón</i> (lemon)	Cit l 3	<i>Punica granatum</i> (pomegranate)	Pun g 1
		<i>Citrus reticulata</i> (tangerine)	Cit r 3	<i>Pyrus communis</i> (pear)	Pyr c 3
		<i>Citrus sinensis</i> (sweet orange)	Cit s 3	<i>Rubus idaeus</i> (red raspberry)	Rub i 3
		<i>Corylus avellana</i> (hazel)	Cor a 8	<i>Sinapis alba</i> (yellow mustard)	Sin a 3
		<i>Fragaria ananassa</i> (strawberry)	Fra a 3	<i>Solanum lycopersicum</i> (tomato)	Sola l 3
		<i>Helianthus annuus</i> (sunflower)	Hel a 3		Sola l 6
		<i>Juglans regia</i> (English walnut)	Jug r 3	<i>Triticum aestivum</i> (wheat)	Tri a 14
		<i>Lactuca sativa</i> (cultivated lettuce)	Lac s 1	<i>Vitis vinifera</i> (grape)	Vit v 1
		<i>Lens culinaris</i> (lentil)	Len c 3	<i>Zea mays</i> (maize)	Zea m 14
		<i>Malus domestica</i> (apple)	Mal d 3		Zea m 14

pollen and plant food has been already reported and could explain a LTP pollen sensitization leading to plant food allergy. Lombardero et al. showed that Art v 3 (*artemisia* LTP) acts as a primary sensitizer in some patients sensitized to Pru p 3 (peach LTP) [31].

Regarding the geographical distribution, LTP are the dominant allergens in the south of Europe and the Mediterranean area and are hardly ever reported in Central or Northern Europe.

In a study focused on cherry allergy, 186 patients from Central Europe and Spain were tested with three purified cherry allergens, Pru av 1 (PR-10), Pru av 3 (LTP) and Pru av 4 (profilin) [32]. A significantly higher rate of Pru av 3 (cherry LTP) sensitization was found in the Spanish patients, compared with those from Central Europe.

These geographical differences could be partially explained by different exposure to pollens containing allergenic LTPs: olive, plane tree, wall pellitory and cypress [33–35]. Other factors could be the differences in plant food consumption and exposure to nsLTPs from other sources [26–28].

The allergenic LTPs described in pollen and plant food are represented in **Tab. 3**.

Profilins

Profilin is an actin-binding protein present in all eukaryotic cells. It was first identified as a pollen allergen. Plant profilins are widespread throughout the plant kingdom and they are highly conserved, which explains multiple positive IgE responses in sensitized patients, as they are considered a ubiquitous cross-reactive plant allergen between inhalant and plant food allergen sources or latex ([36]; **Tab. 4**).

Patients who are sensitized to pollen profilins, react to a broad range of pollen allergens (from trees, grasses, and weeds). Profilins are recognized by 20 % of pollen-allergic patients [37]. As profilins are sensitive to heat denaturation and gastric digestion, their consumption leads to reactions that are usually restricted to the oral cavity [38]. Nonetheless, they may lead to severe reactions in areas with a

Tab. 4 Profilin allergens from pollen and plant food

Profilins			
Pollen		Plant food	
Species	Allergen	Species	Allergen
<i>Acacia farnesiana</i> (Needle bush)	Aca f 2	<i>Actinidia deliciosa</i> (kiwi fruit)	Act d 9
<i>Amaranthus retroflexus</i> (redroot pigweed)	Ama r 2	<i>Ananas comosus</i> (pineapple)	Ana c 1
<i>Ambrosia artemisiifolia</i> (short ragweed)	Amb a 8	<i>Apium graveolens</i> (celery)	Api g 4
<i>Artemisia vulgaris</i> (mugwort)	Art v 4	<i>Arachis hypogaea</i> (peanut)	Ara h 5
<i>Beta vulgaris</i> (sugar beet)	Beta v 2	<i>Capsicum annuum</i> (bell pepper)	Cap a 2
<i>Betula verrucosa</i> (European white birch)	Bet v 2	<i>Citrus sinensis</i> (sweet orange)	Cit s 2
<i>Chenopodium album</i> (lambsquarters)	Che a 2	<i>Corylus avellana</i> (hazel)	Cor a 2
<i>Crocus sativus</i> (saffron crocus)	Cro s 2	<i>Cucumis melo</i> (muskmelon)	Cuc m 2
<i>Cynodon dactylon</i> (bermuda grass)	Cyn d 12	<i>Daucus carota</i> (carrot)	Dau c 4
<i>Helianthus annuus</i> (sunflower)	Hel a 2	<i>Fragaria ananassa</i> (strawberry)	Fra a 4
<i>Kochia scoparia</i> (burning bush)	Koc s 2	<i>Glycine max</i> (soybean)	Gly m 3
<i>Mercurialis annua</i> (Annual mercury)	Mer a 1	<i>Hordeum vulgare</i> (barley)	Hor v 12
<i>Olea europea</i> (olive)	Ole e 2	<i>Litchi chinensis</i> (litchi)	Lit c 1
<i>Parietaria judaica</i> (pellitory-of-the-Wall)	Par j 3	<i>Malus domestica</i> (apple)	Mal d 4
<i>Phleum pratense</i> (timothy)	Phl p 12	<i>Musa acuminata</i> (banana)	Mus a 1
<i>Phoenix dactylifera</i> (date palm)	Pho d 2	<i>Oryza sativa</i> (rice)	Ory s 12
<i>Prosopis juliflora</i> (mesquite)	Pro j 2	<i>Prunus avium</i> (sweet cherry)	Pru av 4
<i>Salsola kali</i> (Russian thistle)	Sal k 4	<i>Prunus dulcis</i> (almond)	Pru du 4
<i>Zea mays</i> (maize)	Zea m 12	<i>Prunus persica</i> (peach)	Pru p 4
		<i>Pyrus communis</i> (pear)	Pyr c 4
		<i>Sinapis alba</i> (yellow mustard)	Sin a 4
		<i>Solanum lycopersicum</i> (tomato)	Sola l 1
		<i>Triticum aestivum</i> (wheat)	Tri a 12

high concentration of pollens containing profilins [39].

The first allergenic profilin was described in birch pollen and was named Bet v 2 [40].

Shortly after the identification of Bet v 2, IgE cross-reactive profilins were found in the pollen of grasses and weeds [36–41].

Furthermore, profilins from hazelnut, strawberry, apple, cherry, almond, peach, pear, celery and carrots cross-react with grass and birch profilins [42].

As an example, in the mugwort-celery-spice syndrome, patients sensitized to mugwort profilin, cross-react to profilins in celery and spices of the *Apiaceae* or *Umbelliferae* family (carrots, caraway

seeds, parsley, coriander, aniseed or fennel seeds) [43].

In recent molecular epidemiological studies it was demonstrated that the prevalence of profilin sensitization grew as the grass pollen gradients grew, and it is not statistically associated with other pollens or total pollen counts [44].

In summary, plant food allergy due to profilin keeps a geographical distribution depending on the exposition to pollens containing profilins, such as grass and weeds pollen.

Thaumatins-like proteins

Thaumatins-like proteins (TLP) are proteins with molecular masses of 20–30 kDa, with a very stable three-dimensional structure, which makes them resistant to proteases and acid pH or heat. They are plant defence proteins (PR-5) against pathogens, especially fungal ones [27].

TLP can have a role as allergens in a wide panel of plant food and several pollens, although there is still little evidence on its cross-reactivity between foods and pollens ([45]; ■ Tab. 5).

In the Palacin et al. multicentre study [46], a large number of plant food allergic patients from seven different geographical and climatic Spanish regions were selected, and a TLPs microarray panel to pollens and food was tested to evaluate food TLP sensitization and check its association with pollinosis. Globally, a geographical distribution was observed regarding the frequency of TLP food sensitization and an association with plane tree pollen TLP was found. Thus, according to the results of this study, TLP recognition patterns seem to be related to the different geographical sites, as a result of a possible influence of local pollen.

Molecular sensitization pattern and geographical distribution

The existence of a geographical distribution of food allergy regarding the molecular sensitization pattern and its relationship with aeroallergens (mostly pollens) has been demonstrated in several studies which evaluated the allergenic molecular pattern of some foods in different geographical regions.

Tab. 5 Thaumatin like-protein (TLP) allergens from pollen and plant food

Thaumatins-like proteins			
Pollen		Plant food	
Species	Allergen	Species	Allergen
<i>Cupressus sempervirens</i> (common cypress)	Cup s 3	<i>Actinidia deliciosa</i> (kiwi fruit)	Act d 2
<i>Juniperus ashei</i> (Mountain cedar)	Jun a 3	<i>Capsicum annuum</i> (bell pepper)	Cap a 1
<i>Juniperus virginiana</i> (eastern red cedar)	Jun v 3	<i>Malus domestica</i> (apple)	Mal d 2
		<i>Musa acuminata</i> (banana)	Mus a 4
		<i>Prunus avium</i> (sweet cherry)	Pru av 2
		<i>Prunus persica</i> (peach)	Pru p 2

One study focused on apple allergy across Europe evaluated the primary sensitizers, the individual allergens involved, and whether these differences determine the clinical presentation [47]. 389 apple-allergic patients from four different countries (Spain, Italy, Austria and The Netherlands) were clinically evaluated. Skin prick tests and sIgE to a panel of pollens and plant foods, as well as to sIgE Bet v 1 and the apple allergens Mal d 1 (PR-10), Mal d 2 (TLP), Mal d 3 (LTP) and Mal d 4 (profilin) were performed. Regarding the molecular pattern, only Mal d 1 and Mal d 3 were associated to the clinical presentation of apple allergy. Apple allergy was related to birch pollinosis and sensitization to Bet v 1 and to Mal d 1 in The Netherlands, Austria and Italy, causing mild symptoms. Mal d 3 was the dominant apple allergen in Spain, causing more than 35 % of severe reactions and was related to peach LTP (Pru p 3) sensitization. The authors consequently hypothesized that exposure to peach and mugwort or plane tree pollen, as LTP sources, at a young age, with a lack of exposure to birch pollen, could lead to the development of LTP allergy in Spain.

Another similar study was focused on peanut allergy, involving 115 peanut-allergic patients from Madrid (Spain), New York (USA), and Gothenburg and Stockholm (Sweden) [48]. Regarding the specific peanut allergen pattern, most of the American patients were sensitized to Ara h 1 to 3 (seed storage proteins), had the lowest sensitization rate to birch and grass pollen and its specific allergens, and frequently presented severe symptoms. The

Spanish patients were more often sensitized to Ara h 9 (LTP) and developed peanut allergy after becoming allergic to other plant foods. The Swedish patients had the highest sensitization rate to Ara h 8 (PR-10) and to Bet v 1 and grass pollen and its specific grass pollen allergens, and were more frequently sensitized to Ara h 1 to 3 than the Spanish patients. The authors concluded that peanut allergy follows a different clinical and immunologic pattern in different geographical regions, possibly because of the different pollen exposures and cooking traditions within the different populations.

Hazelnut and kiwifruit are other foods that were evaluated at the molecular level in the context of the EuroPrevall project [49, 50]. The four European geographical regions were represented with different centres in 12 cities: Madrid (Spain), Sofia, (Bulgaria), Reykjavik (Iceland), Athens (Greece), Prague (Czech Republic), Lodz (Poland), Utrecht (The Netherlands), Strasbourg (France), Manchester (United Kingdom), Milan (Italy), Zurich (Switzerland), and Vilnius (Lithuania), where a panel of 48 foods was evaluated.

The study focused on 731 hazelnut evaluated subjects who had reported any reaction to hazelnut in the EuroPrevall community surveys [49]. The authors concluded that in adulthood, the importance of hazelnut sensitization to storage proteins (Cor a 9, 11, 14), oleosin (Cor a 12) and Cor a 8 (LTP) is diluted by the increased role of birch pollen cross-reactivity with Cor a 1 (PR-10). Birch pollen exposure drives the hazelnut allergy in Central and Northeastern Europe, with

Cor a 1 being the dominant allergen. Sensitization to hazelnut storage proteins (Cor a 9, Cor a 11, Cor a 14) is observed across Europe, decreasing with age, as the role of pollen cross-reactivity increases. Hazelnut oleosin (Cor a 12) sensitization is prevalent across Europe; however, clinical relevance still remains unclear. And in the Mediterranean (Spain, Italy and Greece) hazelnut allergy is an LTP-driven phenomenon (Cor a 8) directly associated with peach and walnut and to a lesser extent with pollen sensitizations (chenopodium, plane tree, mugwort).

In the study of kiwifruit allergy, 311 patients with a suggestive history of kiwifruit allergy were included [50]. The aim of the study was to investigate geographical differences regarding clinical and molecular patterns to the kiwifruit allergens Act d 1, Act d 2, Act d 5, Act d 8, Act d 9 and Act d 10. Kiwifruit allergen sensitization patterns differ across Europe. Patients from Iceland were mainly sensitized to Act d 1 (TLP), those from Western/Central and Eastern Europe were mainly sensitized to Act d 8 (PR-10) in the context of birch pollinosis, and those from Southern Europe were mainly sensitized to Act d 9 (profilin) and Act d 10 (nsLTP) in the context of grass sensitization. Sensitization to Act d 1 and living in Iceland are strong risk factors for severe kiwifruit allergy.

The influence of aeroallergens on the molecular and clinical pattern of food allergy can not only be explained by pollens involved in cross-reactivity syndromes with plant food, but also by proteins of animal origin, which can also elicit allergic reactions to food after an initial sensitization to the aeroallergen. One example of this would be shellfish allergy as a cross-reactivity to tropomyosin, which is the major allergen in shellfish and shows a high degree of similarity to tropomyosins from house dust mites [51]. Thus, we could extrapolate that in geographical areas where house dust mites are frequent, we would expect to find a higher prevalence of shellfish allergy, although this statement still remains unclear, as complete data concerning this issue is lacking.

Another example of cross-reactivity reactions with animal origin allergens

would be the delayed anaphylaxis to red meat due to allergy to galactose- α -1,3-galactose (α -Gal) [52]. IgE antibodies against α -Gal were first identified in patients who developed severe anaphylactic reactions 3–6 hours after the intake of red meat, who had had tick bites and, usually within the previous weeks, as α -Gal epitope is present in the gastrointestinal tract of the tick and it involves host exposure to α -Gal during a tick bite. The first published cases were initially reported about patients from the same region in the southeast of the United States, which could lead to the suggestion that the cross-reactivity originating from locally occurring tick bites would explain why the incidence of α -Gal allergy is higher in rural areas where tick bites are more feasible.

In conclusion, when answering the question as to whether there are any geographical differences in food allergies, we can state that, in global terms, the prevalence of food allergy sensitization differs among geographical areas, and these differences are more evident at the allergenic molecular level, which seems to be partially, but directly influenced by the aeroallergens of each region, leading to a specific clinical pattern and providing valuable information about the risks of inducing mild or severe food allergy reactions.

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Compliance with ethical guidelines

Conflict of interest. J. Bartra, A. García-Moral and E. Enrique state that there are no conflicts of interest.

The accompanying manuscript does not include studies on humans or animals.

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