

CME Article

Update on in vitro allergy diagnostics

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Individual IgE profiles and allergen patterns allow for closer examinations of cross-reactions, molecules of risk and prognostically significant sensitizations.

Summary

Component-resolved diagnostics (CRD) have become of growing importance in clinical investigation of IgE-mediated allergies. This review updates the current use of CRD in respiratory allergies (e. g. to pollen, animal dander, mites, latex), as well as in allergies to hymenoptera venom or in food allergies to plants (e. g. Bet v 1 homologues, lipid transfer proteins, storage proteins) or to animal-derived food allergens (e. g. milk, meat, fish). CRD may help to elucidate the clinical relevance of an allergic sensitization. In some cases, CRD may also be useful in predicting either severity of clinical reactions or the therapeutic effect of specific immunotherapy.

Introduction

Clinical allergology profits from the rapid advance in precise molecular biological methods. Molecular characteristics of individual components in allergen extracts and their targeted use in diagnostics allows for detection of specific IgE antibodies (sIgE) and thus for component-resolved diagnostics (CRD; Table 1) [1–3]. The following internet data banks provide an overview of the allergens identified to date: www.allergome.org, www.allergen.org, www.meduniwien.ac.at/allergens/allfam.

For sIgE diagnostics purified (natural) or recombinant allergens manufactured by gene technology are employed. Knowledge of allergen nomenclature simplifies understanding. For example in the major birch pollen allergen “rBet v 1”, the “r” stands for recombinant, “Bet” for the first three letters of the genus (*Betula*), “v” for the first letter of the species (*verrucosa*) and the number “1” for the numbering of the allergen (usually in the order of reporting).

In the individual determination of sIgE quantitative results are measured that are reported in kU/l and in classes (e. g. 6 classes in the CAP system, Phadia, Sweden). Recently the increasing availability of continually more allergen components has led to test systems that make possible by use of modern biochip technology the simultaneous determination of sIgE towards more than 100 allergen components using only a very small quantity of serum (about 10 µl) (ImmunoCAP ISAC®, Phadia). The test results are semi-quantitative [4, 5]. The sensitivity of this test system appears, on the basis of own observation, to be somewhat lower than the sensitivity of individual allergen diagnostics at present with respect to many allergens.

An ever increasing number of allergens have found their way into routine diagnostics in recent years and individual IgE profiles and allergen patterns (allergograms) allow for closer examinations of cross-reactions, molecules of risk and prognostically significant sensitizations.

Table 1: Special features of component-resolved diagnostics.

- Standardization of allergen extracts by use of individual allergens
- Increase of analytic sensitivity by replacement/ supplementation of relevant individual allergens in the test extract
- Detection of cross-reactions
- Determination of individual sensitization profiles
- No cross-reacting carbohydrate chains (CCD)

Table 2: Pollen and food Bet v 1 homologues.

Pollen	Pomaceous and stone fruit, nuts	Vegetables/ legumes
Aln g 1 (alder)	Act c 8 (gold kiwi)	rApi g 1 (celery)
rBet v 1 (birch)	Act d 8 (kiwi)	rAra h 8 (peanut)
Car b 1 (hornbeam)	Cas s 1 (sweet chestnut)	Aspa o 17kD (asparagus)
Cas s 1 (sweet chestnut)	rCor a 1 (hazelnut)	Dau c 1 (carrot)
rCor a 1 (hazel)	Fra a 1 (strawberry)	rGly m 4 (soy)
Fag s 1 (beech)	Mal d 1 (apple)	Pet c 1 (parsley)
Que a 1 (oak)	Pru ar 1 (apricot)	Vig r 1 (mungbean)
	Pru av 1 (cherry)	
	rPru p 1 (peach)	
	Pyr c 1 (pear)	
	Rub i 1 (raspberry)	

Not everything that is diagnostically possible is sensible for use in routine diagnostics.

We present an overview of current developments in IgE diagnostics of frequent allergens. Diagnostic tests already commercially available today are characterized by bold type. At the onset it is important to stress that not everything that is diagnostically possible at present is sensible for use in routine diagnostics [2, 3].

Aeroallergens

Birch/Bet v 1 homologues

When there is a history suggesting a birch pollen-associated food allergy, sIgE against **rBet v 1** should be determined.

Treatment success of SIT can be quite variable depending on the sensitization pattern present.

Sensitizations to the major birch pollen allergen Bet v 1 is found in over 90 % of patients with birch pollen allergy, with the sensitization rate in Central Europe being between 5 and 15 %. Bet v 1 belongs to the family of thermo- and acid-labile pathogenesis-related (PR)-10 proteins, whose actual physiological function is still unclear. Cross-reactive allergens (Bet v 1 homologues) are found in a series of allergens from pollen, fruits and nuts as well as in vegetables and legumes (Table 2). When there is a history suggesting a birch pollen-associated food allergy, sIgE against **rBet v 1** should be determined [2, 3].

Treatment success of specific immunotherapy (SIT) against birch pollen can be quite variable depending on the sensitization pattern present. It has been shown that a sensitization solely to the major birch pollen allergen Bet v 1 is associated with a good response to SIT. In contrast, when patients are additionally or exclusively sensitized to minor allergens, such as **rBet v 2** (profilin) or **rBet v 4**, it appears that only little or even no response can be expected (sIgE can also be determined in a fixed combination of both allergens **rBet v 2/4**).

Grass pollen

sIgE using the recombinant allergens **rPhl p 1** and **rPhl p 5** is positive in practically all patients with grass pollen allergy, with seasonal fluctuations based on amount of pollen release. Specific IgE against **rPhl p 12** (profilin) and **rPhl p 7** (polcalcin) are

also being positive in about 75 % of those affected, but these are considered to be cross-reacting allergens without clinical relevance.

When a sensitization to Phl p 1 and Phl p 5b is present, the chances of alleviating symptoms through SIT are good. In accompanying or exclusive sensitizations to Phl p 7 and Phl p 12 the chances of a successful SIT decline [6]. To simplify diagnostics, sIgE can be tested in fixed combinations (sIgE **rPhp p 1/5b** and **rPHI p 7/12**). Altogether, routine molecular diagnostics before initiating SIT are sensible in both birch as well as grass pollen sensitization in order to evaluate therapy chances [6].

In birch as well as grass pollen sensitization molecular allergy diagnostics before initiating SIT are sensible in order to evaluate therapy chances.

Weed pollen

In the examination of patients with mugwort allergy, 79 % of sera contains sIgE to **rArt v 1**, 39 % to rArt v r and 14 % to **nAmb a 1**, a major allergen in Ambrosia (ragweed). The prevalence of sIgE reactivity to rArt v 1 and nArt v 3 (LTP) appears to be higher in Northern Europe than in North America, while sIgE to Amb a 1 is more common in North America.

Molds

In sensitizations to *Alternaria alternata* sIgE to the major allergen **rAlt a 1** is usually found. Determination of allergens of *Aspergillus fumigatus* (**rAsp f 1–4** and **6**) are usually performed to differentiate between asthma and allergic bronchopulmonary aspergillosis (ABPA). Both in simple Aspergillus allergy as well as in ABPA sIgE to Asp f 1 and Asp f 3 could be detected; only in ABPA, in contrast, sensitizations to the allergens Asp f 4 and Asp f 6 are also found [6].

Animal dander

Fel d 1 is the major allergen of the cat. Molecular diagnostics can be sensible in cat allergy to test patients before SIT (sIgE to **rFel d 1**) or in possible cross-reaction in the cat-pork syndrome (**nFel d 2** or Fel d 5) (see 5.3.3). The same holds true for the dog for sIgE to **rCan f 1** and **rCan f 2** (major allergens) before SIT or for sIgE to **nCan f 3** (serum albumin) in a possible cross-reaction in meat allergy [7].

Fel d 1 is the major allergen of the cat.

House dust mites

In sensitizations towards house dust mites sIgE to the major allergens of *Dermatophagoides pteronyssinus* **nDer p 1** and **rDer p 2** can frequently be found. Patients with sIgE to the tropomyosin **rDer p 10** are supposed to react to a series of other mite allergens. Cross-reactions exist between antibodies to Der p 10 of mites and **rPen a 1** from shrimps as well as with Ani s 2 and Ani s 3 from roundworms (*Ascaris*). The p 10-negative patients, on the other hand, primarily possess sIgE to nDer p 1 and/or rDer p 2. This can be important for evaluating the prospects of success of SIT [8].

Latex

It is unclear if a clinically relevant sensitization is present when only sIgE to latex is detected; when this sensitization is due to the profilin (**Hev b 8**) in latex, clinical symptoms are unlikely. On the other hand, sIgEs to other latex allergens such as **Hev b 1**, **Hev b 3**, **Hev b 5** and **Hev b 6** are highly likely to be associated with allergic symptoms. Sensitizations to Hev b 2 (not yet commercially available) and **Hev b 11** have been connected with the latex-fruit syndrome (e. g. to banana, avocado, sweet chestnut) [2].

It is unclear if a clinically relevant sensitization is present when only sIgE to latex is detected.

Cross-reacting carbohydrate determinants (CCD)

The carbohydrate-containing epitopes of glycoproteins are termed cross-reacting carbohydrate determinants (CCD) [1, 2, 4, 7]. Two types of CCD are differentiated: the MUX type and the α -galactose type (Table 3).

Two types of CCD are differentiated: MUX type and α -galactose type.

CCD of the MUX type

CCD of the MUX type are found in almost all plants and invertebrate animals and can induce the production of highly cross-reacting IgE antibodies. These CCD antibodies are thus a potential source of interferences in in vitro tests in the sense of unspecific positive findings [2, 3].

CCD of the MUX type are a cause of false-positive in vitro tests.

Table 3: Characteristics of both types of cross-reacting carbohydrate determinants.

	MUX type	α-galactose-type
Sensitization via	Among others, pollen, insect venom	Tick bites, parasites?
Diagnostics	sIgE against MUXF3 , among others	Expected to be possible routinely soon (e. g. Phadia)
Clinical relevance	Being discussed, probably not	Delayed anaphylaxis caused by red meat, anaphylaxis caused by cetuximab

Usually IgE antibodies of the MUX type possess no clinical relevance.

An association exists with exposition to glycoproteins from pollen or insect venoms. About 20 % of atopic individuals are sensitized to CCD of the MUX type. Also in patients with increased alcohol consumption elevated IgE levels are thought to be associated with sensitization to these CCD. The detection of anti-CCD IgE antibodies of the MUX type is possible with a series of commercially available kits: In addition to detection of sIgE to **MUXF3** (bromelin), other carbohydrate determinants are also used, e. g. bromelin from pineapple (**nAna c 2**), horseradish peroxidase from horseradish/MMSF, ascorbate oxidase from zucchini/MMXF).

Clinically, in α-Gal sensitized patients delayed immediate-type reactions to red meat (beef, pork) can occur. Cetuximab administration can result in severe anaphylactic reactions in patients sensitized to α-Gal.

Specific IgE antibodies to α-galactose (galactose-α-1,3-galactose)

The α-galactose epitope (in short: α-Gal) is a ubiquitous sugar structure on glycoproteins and glycolipids of all mammals; immunoglobulins as responsible glycoproteins carrying α-Gal possibly play an important role here. It was also identified as an important IgE epitope on secreted IgA of the cat. α-Gal is highly immunogenic for humans. In the meantime it is assumed that sensitization to α-Gal can be induced by tick bites (see 5.3.3.3) or certain parasite infections. A sensitization to α-Gal is found particularly often in the southern states of the USA [4]. Clinically, in α-Gal sensitized patients delayed immediate-type reactions to red meat (beef, pork) can occur. No plausible explanation exists at present for the delayed onset of symptoms. The relevance of α-Gal sensitization was first noticed after the administration of the chimeric antibody cetuximab which resulted in severe anaphylactic reactions in the sensitized; this was brought into connection with preformed IgE antibodies to α-Gal on the murine portion of the antibody.

A test for specific IgE antibodies to α-Gal should be available for routine diagnostics shortly. Routine tests before administration of cetuximab should be considered.

The sensitivity of IgE diagnostics can be increased from 88 % to 96 % by the combined determination of rVes v 1 and rVes v 5 in comparison to the sole determination of rVes v 5.

Hymenoptera venom allergy

The most important hymenoptera venom allergens are listed in Table 4. The determination of individual allergens with CRD allows for the discrimination between true double sensitizations and cross-reactivity [8]. Currently, sIgE antibodies to the following allergens are available: **rApi m 1**, **Ves v 1**, **Ves v 5** and **rPol d 5**. It can be expected that this spectrum will soon be expanded. It is known from studies that in wasp venom allergy the sensitivity of IgE diagnostics can be increased from 88 % to 96 % by the combined determination of rVes v 1 and rVes v 5 in comparison to the sole determination of rVes v 5.

In patients with bee venom allergy the determination of sIgE to **rApi m 1** has a sensitivity of only 69–79 %. The sensitization rates to other major allergens are reported as follows: Api m 2: 47 %, Api m 3: 58 %, Api m 5: 65 %, Api m 10: 55 %. Api m 10 appears to be a major allergen in bee venom allergic patients, that cannot yet routinely be determined with molecular IgE diagnostics. The combined determination of sIgE to Api m 1–3, 5 and 10 leads to a sensitivity of 91 % according to recent congress reports.

Most hymenoptera venom allergens possess carbohydrate side chains (CCD) that are responsible for a portion of the IgE cross-reactivity between bee and wasp venom. This CCD reactivity can also develop primarily through sensitization to plant allergens with CCD and may explain why so many atopic individuals have high antibody levels against hymenoptera venom allergens.

Due to CCD cross-reactivity many atopic individuals have high antibody levels against hymenoptera venom allergens.

Table 4: Molecular allergens in hymenoptera venom allergy.

Molecular allergen	Name	CCD
Bee venom allergens		
rApi m 1	Phospholipase A2	+
Api m 2	Hyaluronidase	++
Api m 3	Acid phosphatase	++
Api m 4	Mellitin	–
Api m 5	Dipeptidylpeptidase IV homologue	++
Api m 10	Icarapin	++
Wasp venom allergens		
rVes v 1	Phospholipase A1	+
Ves v 2	Hyaluronidase	++
Ves v 3	Dipeptidylpeptidase IV homologue	++
Ves v 4	Protease	–
rVes v 5	Antigen 5	++

Table 5: Frequently sensitizing plant allergen families.

Family	Characteristics	Examples of allergens (sIgE already available commercially)
Bet v 1 homologue	Major allergen of birch <i>Betula verrucosa</i> . Similar proteins are termed Bet v 1 homologues.	rApi g 1 – Celery rAra h 8 – Peanut rCor a 1 – Hazel rGly m 4 – Soy
Lipid transfer proteins	Sensitizations usually in Southern Europe, severe reactions, gastrointestinal sensitization	rAra h 9 – Peanut rPru p 3 – Peach rCor a 8 – Hazel
Profilins	Little clinical relevance, often responsible for cross-reactions	rBet v 2 – Birch rPhl p 12 – Grass
Storage proteins	Stable proteins, represent a large proportion of proteins in nuts, seeds, legumes and cereals	rAra h 2 u. 3 – Peanut rGly m 5 u. 6 – Soy rTri a 19 – Wheat

The cross-reactivity can, however, also be based on common protein epitopes, when allergens of bee and wasp venom display a high degree of sequence homology (e. g. hyaluronidases Api m 2 and Ves v 2 and the dipeptidyl-peptidases Api m 5 and Ves v 3).

Food allergies

Plant food allergens

The important plant food allergens belong to a few protein families, the most well-known of which are the Bet v 1 homologues (Table 1), lipid transfer proteins (LTP), profilins and storage proteins (Table 5) [2, 3, 9].

Lipid transfer proteins

Sensitization to LTP is observed particularly in the Mediterranean region and probably develops by eating peaches via the gastrointestinal tract.

The peach LTP **rPru p 3** has structural similarities to LTP from other fruits and vegetables. Further clinically significant LTP are: **rCor a 8** (hazelnut), **rAra h 9** (peanut), **rJug r 3** (walnut) [3, 11].

Sensitization to LTP is observed particularly in the Mediterranean region.

Profilins

Profilins are responsible for sensitizations to pollen and food in a smaller proportion of patients (minor allergens). Extensive cross-reactivity among profilins of different sources (e. g. **rBet v 2** from birch pollen, **rPhl p 12/** grass, **rHev b 8/** latex; **rPru b 4/** peach, **Mal d 4 /** apple, **Ara h 5/** peanut) exists, which can lead to unspecific reactions in sIgE diagnostics [3].

Storage proteins

Sensitizations to storage proteins are associated with a high risk of systemic symptoms.

The term storage proteins denotes a large number of structurally related, usually stable and thus often clinically significant food allergens. As they usually survive passage through the stomach unaltered, they are associated with a high risk of systemic symptoms. The allergens are found in many plant allergen sources, for example in nuts, seeds, legumes (including peanut, soy, lupin) and cereal. Numerous cross-reactions are known [3].

Examples of molecular diagnostics for selected plant foods

Peanut

Sensitization to the allergens Ara h 1, Ara h 2, Ara h 3 or Ara h 9 is associated with the occurrence of severe immediate-type reactions.

About 1–2 % of children in Germany are sensitized to peanut allergens. Studies show that molecular allergy diagnostics allow for differentiation, if the patients must expect severe or milder reactions when eating peanuts. It was observed that a sensitization to the storage proteins **rAra h 1**, **rAra h 2** and **rAra h 3**, which are also resistant to heat and digestion, is associated with severe immediate-type reactions. The same is true for a sensitization to the LTP **rAra h 9**, which may be associated with an allergy to peaches (**rPru p 3**).

Sensitizations to **rAra h 8**, a heat- and acid-labile PR-10 protein (Bet v 1 homologue) usually results in local reactions in the sense of an oral allergy syndrome (OAS) [2, 3].

Hazelnut

Sensitizations to **rCor a 8** (LTP), Cor a 9 and Cor a 11 are associated with severe immediate-type reactions, while a sensitization to the Bet v 1 homologue **rCor a 1** more likely leads to mild symptoms of an OAS [2, 3].

Soy

In a Bet v 1 sensitization a cross-reaction to the soy allergen Gly m 4 can occur.

Birch pollen allergic patients with a Bet v 1 sensitization can typically demonstrate a cross-reaction to the Bet v 1 homologue soy allergen **rGly m 4**. With the increasing consumption of food stuffs containing soy (e. g. drinks, diet powder) especially in recent years, there have been increasing reports of the clinical relevance. Sensitizations to the storage proteins **nGly m 5** and **nGly m 6** are associated with severe anaphylactic reactions [2, 3].

Peach

In the Mediterranean region 80 % of peach allergic patients are sensitized to the LTP rPru p 3.

In the Mediterranean region peach allergies are among the most common food allergies with 80 % of the patients there sensitized to the LTP **rPru p 3**. This sensitization can lead to cross-reactions to LTP from other fruits and vegetables. **rPru p 1** (Bet v 1 homologue) and rPru p 4 (profilin) are pollen-associated allergens [2, 3].

Celery

In celery allergy sensitizations are found to rApi g 1 (Bet v 1 homologue) as well as to rApi g 4 (profilin) and Api g 5 – both not yet routinely testable [2, 3, 11]. To date no marker for severe reactions has been identified.

Kiwi

The prevalence of kiwi allergies appears to be increasing. Sensitizations to Act d 1 are seen in mono-sensitizations, while sIgE to **rAct d 8** and Act d 9 occur in pollen-associated allergies. Sensitizations to Act d 1 and Act d 3 are associated with the occurrence of severe reactions [3, 11].

Wheat

In wheat-dependent exercise-induced anaphylaxis sIgE to Tri a 19 should be determined.

Wheat proteins contain 80 % gluten (to one-half each the storage proteins gliadin and glutenin), 15 % albumin and 5 % globulins. A sensitization to the storage protein **rTri a 19** (ω -5-gliadin) is observed in wheat-dependent exercise-induced anaphylaxis (WDEIA) [6].

Animal food allergens

Cow's milk and cow's milk products

Milk from the cow (*Bos domesticus*) is found in a multitude of food stuffs. Cheese is produced by fermentation and coagulation of milk. In coagulation the insoluble (quark) and soluble (whey) proteins are separated. Quark contains primarily casein (**nBos d 8**, heat-stable); in the whey serum proteins such as α -lactalbumin (**nBos d 4**, somewhat heat-stable), β -lactoglobulin (**nBos d 5**, not heat-stable), bovine serum albumin (**nBos d 6**) and immunoglobulin (Bos d 7) are found. Studies to date have not been able to establish which sensitization patterns are associated with a clinically relevant allergy, so that provocation testing remains the gold standard for evaluating a cow's milk allergy [12].

Studies have not been able to establish which sensitization patterns are associated with a clinically relevant allergy.

Hen's egg

Allergic reactions to proteins in hen's egg (*Gallus domesticus*) are among the most common food allergies in childhood [11]. Hen's egg contains allergens in the egg white (greater allergenic potential) and in the egg yolk. The most important allergen in the egg white is the very thermostable ovomucoid (**nGal d 1**) followed by the less heat-stable allergens ovalbumin (**nGal d 2**), ovotransferrin (**nGal d 3**) and lysozyme (**nGal d 4**). These four major allergens are contained in the sIgE to egg white that is well-suited for the in vitro test in practice and for a multiallergen screening test. Clinical reactions to hen's egg are associated with the detection of sIgE to hen's egg white and ovomucoid (nGal d 1), to which 70 % of patients are sensitized. Patients with a persistent hen's egg allergy had higher sIgE levels to ovomucoid (nGal d 1) and ovalbumin (nGal d 2) in studies than children who develop tolerance [13].

Clinical reactions to hen's egg are associated with the detection of sIgE to hen's egg white and ovomucoid (nGal d 1).

Meat allergies

Meat allergies are rare in relation to the widespread consumption; most frequent are sensitizations to red meat, especially beef, with prevalences of up to 20 % in children with milk allergy being reported. Further reactions have, among others, been reported for pork and lamb, white meat (chicken, turkey) as well as for a multitude of exotic meat varieties (kangaroo, whale, frog etc.). Clinical reactions range from local contact reactions up to anaphylaxis. Sensitization can develop primarily and secondarily, e. g. as cross-reactions in inhalative allergies, in allergies to other food stuffs (milk) or in case of α -Gal sensitization. Altogether, routine diagnostics of meat allergy is at present still predominantly based on poorly standardized extracts with in part unsatisfactory sensitivity and specificity [4, 9].

Primary meat allergy

The most important allergens in beef, which is reported as the most common cause of allergies to red meat, are bovine serum albumins (**nBos d 6**) and immunoglobulins (Bos d 7). Nevertheless, only in a small proportion of those sensitized does a clinical relevance exist. Relevant triggers of meat allergies can also be innards (especially kidneys), that obviously have a high allergen content. In most patients allergy tests reveal sensitization to several varieties of meat, with the association between beef, lamb and game being particularly strong. Possibly both the sensitization as well as the cross-reactivity are due to serum albumins (e. g. to **nBos d 6**), with sensitization occurring in addition to meat consumption also as a secondary meat allergy via milk consumption. For Bos d 7, cross-reactivity was observed between beef, lamb and venison as well as cow's milk [9].

The most important allergens in beef are bovine serum albumin (**nBos d 6**) and immunoglobulins (Bos d 7).

Secondary meat allergy in inhalative sensitization

An example of cross-reactions in primary inhalative sensitization is the cat-pork syndrome, where patients develop a sensitization to cat serum albumin (**nFel d 2**) and due to cross-reactivity with the serum albumin in pork can experience anaphylactic symptoms after eating pork. This sensitization can also be induced by the serum albumins of other furry animals (e. g. dog/ **nCan f 3**). IgE antibodies to Fel d 2 were found in 14–23 % of patients with a cat allergy, while only a small proportion demonstrated clinical relevance in the sense of a pork allergy. IgE antibodies to cat immunoglobulins (Fel d 5, Fel d 6) can also be induced. Here it is predominantly IgE against the sugar side chain galactose- α -1,3-galactose (α -Gal) (see 5.3.3.3) [4, 9].

cat-pork syndrome

bird-egg syndrome

In the bird-egg syndrome bird contact leads to an inhalative sensitization to bird serum albumin resulting in clinical symptoms after eating eggs due to cross-reactions to hen's serum albumin in the egg yolk (Gal d 5, not commercially available) [3].

Delayed anaphylaxis to red meat in α -Gal sensitization

In a sensitization to the α -galactose epitope (in short: α -Gal, routine diagnostics for sIgE are not yet possible, see 3.2.), clinically a delayed immediate-type reaction can occur after red meat (beef, pork). This reaction has been reported particularly frequently in regions of the USA with a high prevalence of the tick *Amblyomma americanum* (vector for Rocky Mountain spotted fever) [4].

Fish

Particularly Gad c 1 homologue allergens are responsible for the highly variable cross-reactions between the fish.

Fish are among the most frequent causes of food allergies. The decisive allergens are located in muscle. Both species-specific as well as cross-reacting allergens have been reported. Sensitizations to cod (*Gadus callaris*) are found most often, with the major allergen being a member of the parvalbumin family, the relatively stable **Gad c 1**. Particularly Gad c 1 homologue allergens are responsible for the highly variable cross-reactions between the fish, e. g. in Atlantic cod (Gad m 1), salmon (Sal s 1), carp (**Cyp c 1**) and in mackerel species (Sco j 1, Sco a 1, Sco c 1) [3].

Crustaceans

Crustaceans (prawn, shrimps, lobster, crayfish, edible crabs) represent an important source of allergens. The following sensitizations to major allergens have been reported: shrimp: Met e 1 and **rPen a 1**, lobster: Hom a 1, crab: Cha f 1. They correspond to tropomyosin, an important muscle structure protein of all arthropods and other animals, explaining the cross-reactivities (e. g. also to **rDer p 10** or Ani s 1–3) [2].

Allergic anisakiasis

Anisakis simplex, a parasite worm, can enter the human body after eating insufficiently cooked fish, which serves as an intermediate host. *Anisakis simplex* larvae contain several thermostable and robust allergens (Ani s 1, Ani s 2, Ani s 3/ tropomyosin) to which sensitization may develop. In certain regions sensitization to anisakis is supposed to be more common than true fish allergies. Cross-reactions of Ani s 2 and Ani s 3 with ascaris (roundworms), house dust mites (**rDer p 10**/ tropomyosin/k) and crustaceans (**Pen a 1**, **Pen m 1** and **Pen I 1**) are reported [2, 8].

Conclusions

Component-resolved allergy diagnostics (CRD) are increasingly entering routine care. It demands new knowledge on the part of the physician involved with allergology, uncovers molecularly comprehensible cross-reactivities and often allows for better understanding of the disease. In pollen allergies with determination of the respective major allergens (e. g. Bet v 1: birch, Phl p 1/5: grass) clinically relevant sensitizations can be differentiated from those to cross-reacting, clinically less relevant panallergens such as profilins (e. g. Bet v 2/4, Phl p 7/12). These diagnostics allow for establishing a more precise indication for specific immunotherapy with tree and grass pollen. In food allergies sensitizations to storage (e. g. Ara h 2/ peanut, Gly m 5 and 6/ soy) or lipid transfer proteins (e. g. peach allergen Pru p 3 and wheat gliadin Tri a 19) signal a high risk of anaphylaxis, while sensitizations to Bet v 1 homologues (e. g. Ara h 8) are usually associated with milder symptoms in the sense of an oral allergy syndrome. Sensitizations to profilins (e. g. to Hev b 8 in latex) that are also considered as cross-reacting panallergens are rarely associated with clinical symptoms. By determination of the major allergens Api m 1 (bee) and Ves v 1 and Ves v 5 (wasp) double sensitizations can already today be better differentiated from cross-reactivities in hymenoptera venom allergies than previously. Further promising improvements in diagnostics are expected from additional, not yet commercially available molecules of risk. It should not be forgotten, that even today the detection of specific IgE only demonstrates a sensitization and the clinical relevance of every in vitro finding must be evaluated critically, perhaps even including organ-specific provocation testing. <<<

Conflicts of interest

None.

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