EAACI
EUROPEAN ACADEMY OF ALLERGY AND CLINICAL IMMUNOLOGY

Molecular Allergology

Pocket Guide

Published by the European Academy of Allergy and Clinical Immunology

2024

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The European Academy of Allergy and Clinical Immunology, EAACI, is a non-profit organisation active in the field of allergic and immunologic diseases such as asthma, rhinitis, eczema, occupational allergy, food and drug allergy and anaphylaxis. It includes over 13.000 members from 124 countries as well as 77 national and international societies.

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Introduction Note

Why this pocket guide? The Molecular Allergology User's Guide (MAUG) 2.0 was published as an e-book in July 2022 and as a hardcover book in June 2023. It is the most comprehensive and most recent book on Molecular Allergology. Its size and volume, however, are not ideal for daily clinical practice. Therefore, a new EAACI Task Force (TF) was created to provide essential information and clinical algorithms in a condensed format.

The new TF, coordinated by Christiane Hilger and supported by the MAUG 2.0 editorial team (Karin Hoffmann-Sommergruber, Alexandra Santos, Leticia de la Vecillas, and Stephanie Dramburg), EAACI junior members (Mattia Giovannini and Riccardo Castagnoli) and members of the Interest Group of Allergy Diagnosis & Systems Medicine (IGADSM) (Alma Villaseñor, Simon Blank, and Annette Kuehn), created a pocket guide version of MAUG 2.0, compiling key information in a practical and easy-to-use format.

The pocket guide contains all B chapters (Clinical practice) and C chapters (Cross-reactive molecules) of MAUG 2.0. All chapters follow the same structure: key information, tips for molecular diagnosis, a table of available allergens, and a diagnostic algorithm. The pocket guide is not meant to be a substitute for the book, and readers are invited to read the corresponding chapters in MAUG 2.0 for comprehensive background information. Allergen tables are limited to the currently available molecules, and not all might yet be available in all countries. The layout of the pocket guide is similar to MAUG 2.0, and all chapters have been validated by the authors of the original chapters and have undergone a final review. All authors and reviewers are listed and acknowledged at the end of the guide.

We would like to express our special thanks to all authors of MAUG 2.0 for their collaboration and to EAACI for supporting the TF. We hope readers will enjoy the pocket edition of MAUG 2.0 and find it helpful in their daily clinical practice.

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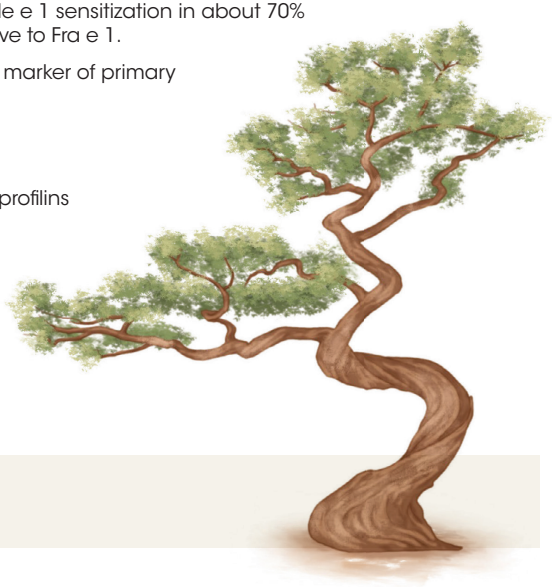
Alexandra Santos, Leticia de la Vecillas,
Stephanie Dramburg,
Simon Blank, Annette Kuehn,
Mattia Giovannini, Riccardo Castagnoli

B01 Tree Pollen Allergy

Key points:

- PR-10 molecules (Bet v 1-like) are the major allergens in Fagales pollen often associated with an oral allergy syndrome.
- Cup a 1 reactivity is the specific marker for a sensitization to the Cupressaceae family.
- Olive pollen allergy is caused by Ole e 1 sensitization in about 70% of cases. Ole e 1 is fully cross-reactive to Fra e 1.
- Pla a 1 and Pla a 2 may serve as a marker of primary sensitization to plane tree pollen.



Tips for molecular diagnosis

- Important panallergen groups are: profilins (Bet v 2), polcalcins (Bet v 4), nsLTP (Ole e 7 and Pla a 3), and gibberellin-regulated proteins (Cry j 7, Cup s 7, and Jun a 7).
- In case of IgE to multiple tree pollen, rule out a possible cross-reactive carbohydrate determinants (CCD)-reactivity.

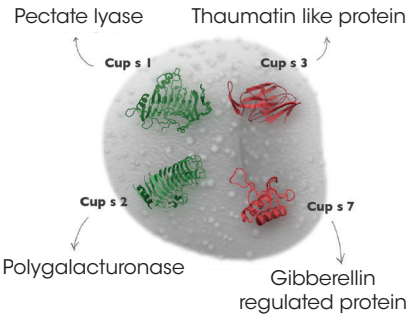
Table of available components for IgE-diagnosis:

Allergen source	Component
(European white) Birch, *Betula verrucosa*	Bet v 1, Bet v 2, Bet v 4, Bet v 6
Alder, *Alnus glutinosa*	Aln g 1, Aln g 4
Hazel, *Corylus avellana*	Cor a 1 and isoallergens Cor a 1.0101, Cor a 1.0103, Cor a 1.0104
(Arizona) Cypress, *Cupressus arizonica*	Cup a 1
Olive, *Olea Europaea*	Ole e 1, Ole e 7, Ole e 9
Ash, *Fraxinus excelsior*	Fra e 1
Beech, *Fagus sylvatica*	Fag s 1
Date palm, *Phoenix dactylifera*	Pho d 2
London plane tree, *Platanus acerifolia*	Pla a 1, Pla a 2, Pla a 3
Sugi, *Cryptomeria japonica*	Cry j 1

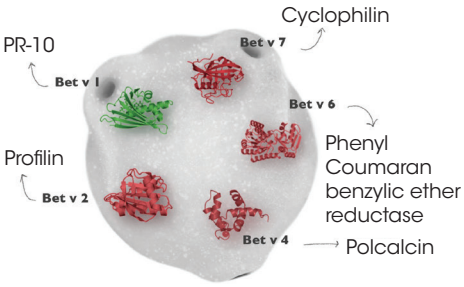
Tree Pollen Allergy B01

Overview of the clinically most relevant marker molecules of genuine sensitisation (green) and panallergens (red)

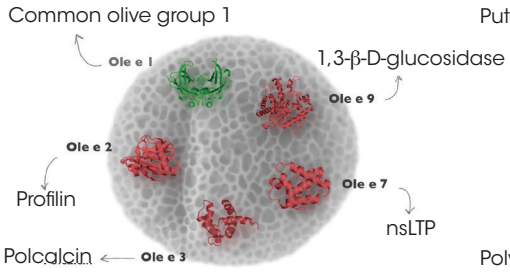
Cupressaceae



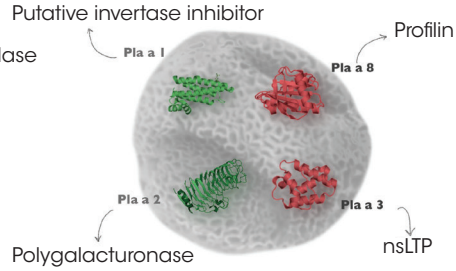
Betulaceae

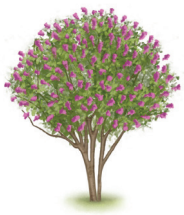


Oleaceae



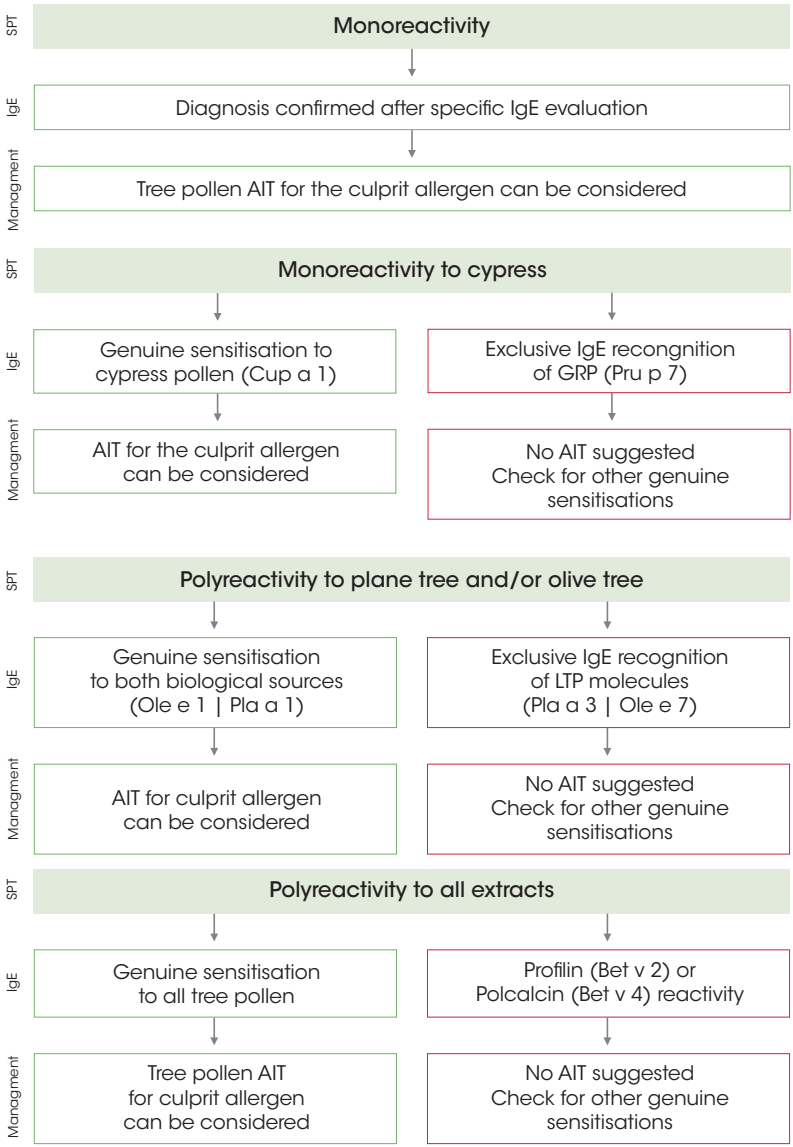
Platanaceae





B01 Tree Pollen Allergy

Diagnostic algorithms for suspected tree pollen allergy:



Note: GRP: gibberelin-regulated AIT: allergen immunotherapy.

Grass Pollen Allergy B02

Key points:

- IgE to group 1 allergens (e.g. Phl p 1) is a marker of true grass pollen sensitization.
- Group 1 allergens of subtropical grass pollens (Pas n 1, Sor h 1 and Cyn d 1) are relevant allergens for patients in subtropical regions.
- In temperate climates, patient serum IgE shows broad cross-reactivity between similar allergen components from different temperate grass pollens.

Tips for molecular diagnosis:

- IgE to other major grass pollen allergens is infrequently observed in the absence of IgE to Phl p 1.
- IgE to Phl p 5 or Phl p 2 can also serve as a markers of true grass pollen sensitization.
- Phl p 12 (profilin) and Phl p 7 (polcalcin) are minor panallergens; IgE to these allergens alone are not sufficient to indicate grass pollen allergy.
- Natural Phl p 4, Cyn d 1, and Cyn d 4, contain CCD, which may lead to a clinically irrelevant IgE cross-reactivity with a wide range of plants and plant products.

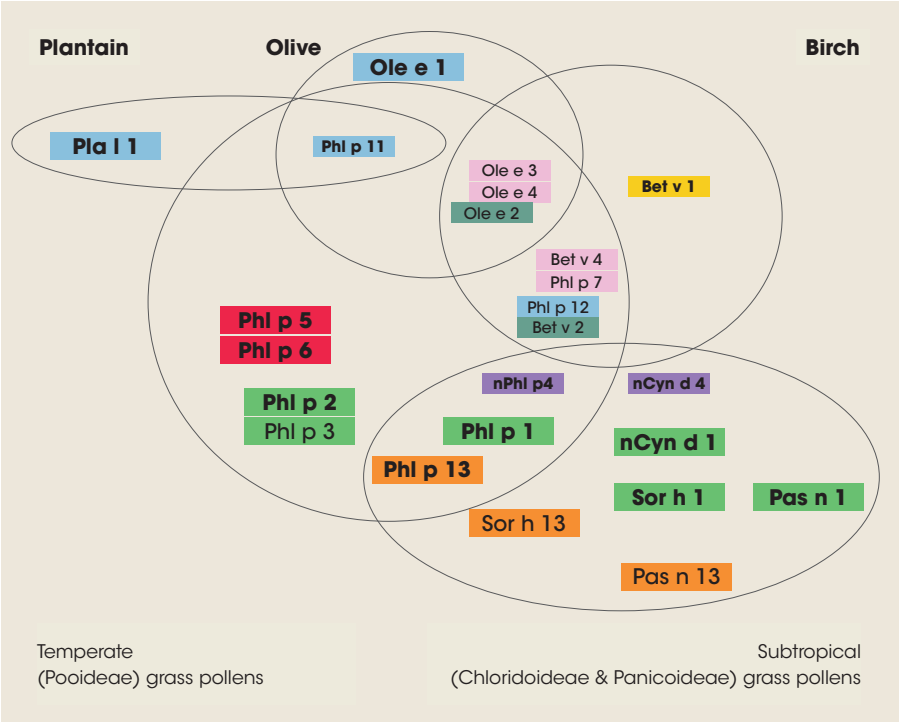
Table of available components for for IgE-diagnosis:

Allergen	Significance
Timothy grass, *Phleum pratense*	
Phl p 1	Is often the initiator molecule in grass pollen allergy Marker for true grass pollen allergy
Phl p 2	Confirms true sensitization to grass pollen
Phl p 4	Native form contains CCD
Phl p 5	Marker for true grass pollen allergy
Phl p 6	Cross-reactive to Phl p 5 – does not add any further information
Phl p 7	Highly cross-reactive polcalcin
Phl p 11	Ole e 1-related protein
Phl p 12	Highly cross-reactive profilin
Bermuda grass, *Cynodon dactylon*	
Cyn d 1	Major allergen of Bermuda grass; native form contains CCD
Cyn d 4	Major allergen of Bermuda grass; native form contains CCD
Perennial ryegrass, *Lolium perenne*	
Lol p 1	Major allergen of Perennial ryegrass

B02 Grass Pollen Allergy

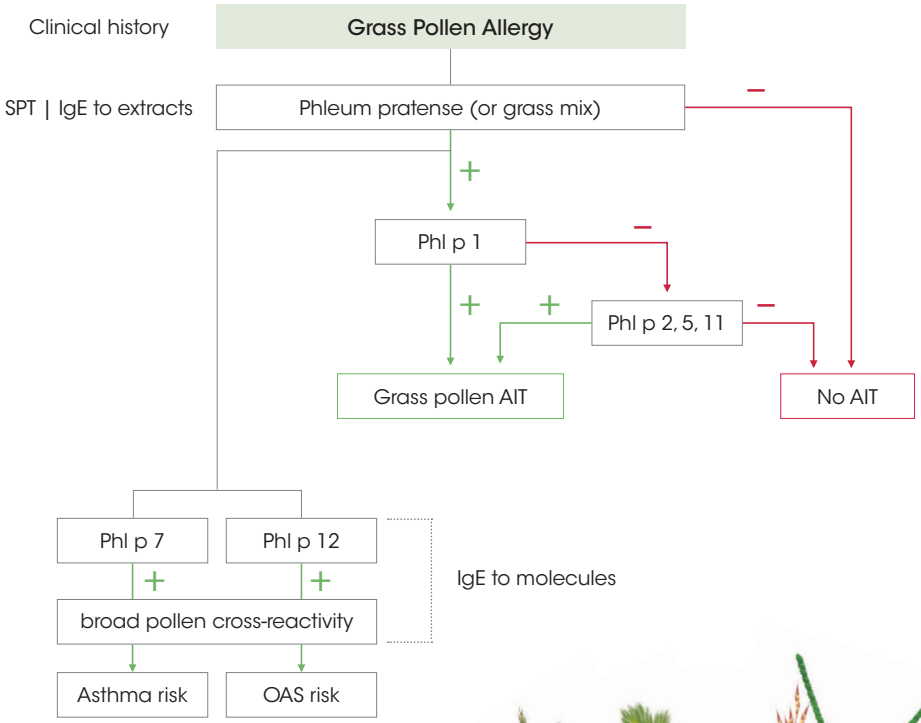
Venn diagram showing allergens of different sources that are similar to temperate and/or subtropical grass pollen allergens.

Major allergens are in bold. Allergens of the same biochemical family are shown in boxes of the same color. Panallergens are in small font. NOTE: native allergens indicated by 'n' (e.g. nPhl p 4 contain CCD, which may lead to clinically irrelevant cross-reactivity).



Grass Pollen Allergy B02

Diagnostic algorithms for suspected grass pollen allergy:



Note: OAS: Oral allergy syndrome, AIT: Allergen immunotherapy

B03 Weed Pollen Allergy

Key points:

- Common weeds like ragweed, mugwort, Russian thistle and English plantain, are important allergen sources typically flowering in summer through to autumn.
- The biogeographical range and pollination periods of allergenic weeds can overlap confounding accurate allergy diagnosis.
- The habitat and flowering period of English plantain coincide with grass and IgE to Pla l 1 should be consequently tested if symptoms persist for some weeks after the grass pollen season.

Tips for molecular diagnosis

- Art v 3 reactivity frequently indicates LTP sensitization and may be associated with oral allergy syndrome.
- Specific IgE to Amb a 1 is a useful marker for ragweed sensitization but shows cross-reactivity with Art v 6 from mugwort and Hel a 6 from sunflower.
- Specific IgE to Art v 1 is a marker for mugwort sensitization, but shows partial cross-reactivity with ragweed Amb a 4.
- Par j 2 and Pla l 1 are highly specific markers for sensitization towards pellitory and English plantain, respectively.
- Sal k 1 is a specific marker of *Salsola kali* sensitization and is a dominant allergen in dry desertified areas.

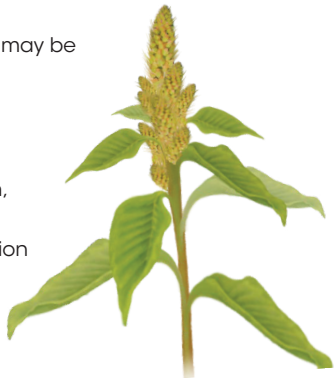


Table of available components for IgE-diagnosis:

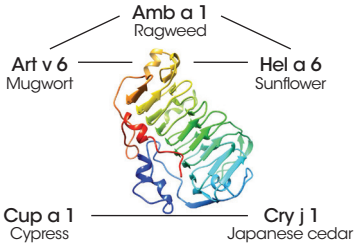
Allergen source	Component
Ragweed, *Ambrosia artemisiifolia*	Amb a 1, Amb a 4
Mugwort, *Artemisia vulgaris*	Art v 1, Art v 3
Wall pellitory, *Parietaria judaica*	Par j 2
Russian thistle, *Salsola kali*	Sal k 1
English plantain, *Plantago lanceolata*	Pla l 1
Annual mercury, *Mercurialis annua*	Mer a 1
Goosefoot, *Chenopodium album*	Che a 1
Hemp, *Cannabis sativa*	Can s 3

Weed Pollen Allergy

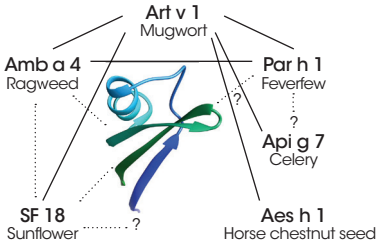
B03

Overview of cross-reactive weed allergens. Lines represent documented IgE cross-reactivity, dotted lines represent potential IgE cross-reactivity based on high sequence identity. Lack of lines indicates absent IgE cross-reactivity.

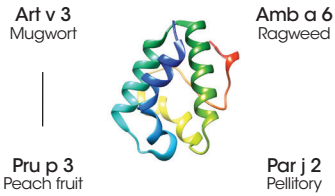
A - Pectate lyases



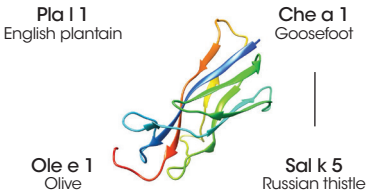
B - Defensin-like proteins



C - Lipid transfer proteins



D - Ole e 1 like-proteins



B03 Weed Pollen Allergy

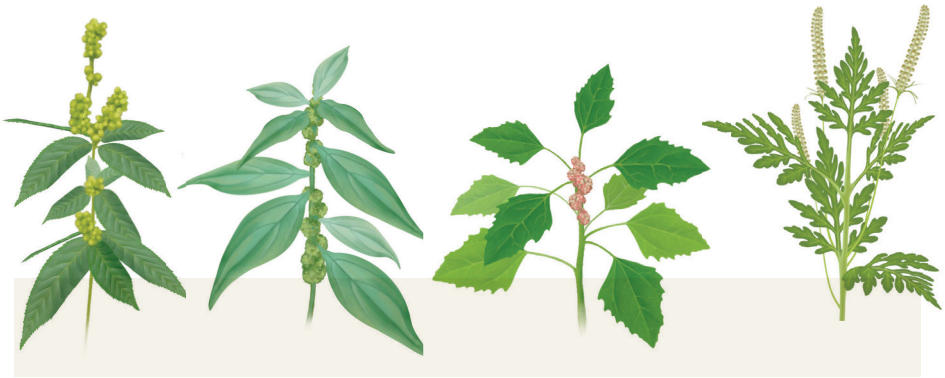
Diagnostic algorithms for suspected weed pollen allergy:

A – Ragweed and mugwort

Case History: pollen-related rhinoconjunctival and/or asthmatic symptoms from late summer to autumn

Skin prick test using ragweed and mugwort pollen extract

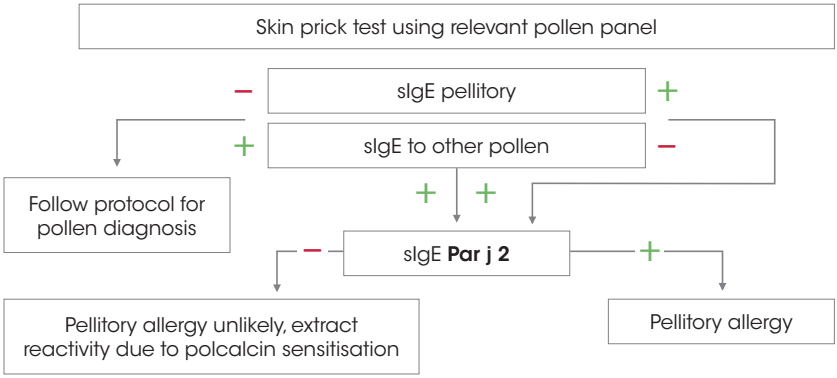
–	sIgE ragweed	+
+	sIgE mugwort	–
+ +		
(+) –	sIgE **Amb a 1**	+
+	sIgE **Art v 1**	–
+	sIgE **Art v 6**	– (+)
+ + +		
Primary mugwort pollen allergy	Ragweed and mugwort co-sensitisation	Primary ragweed pollen allergy



Weed Pollen Allergy B03

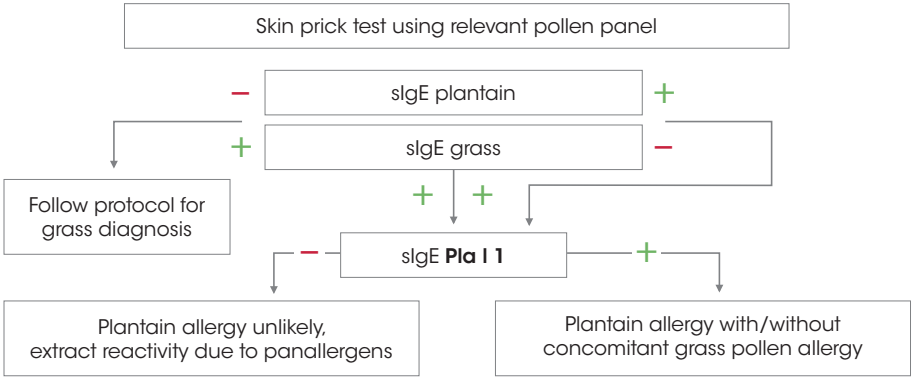
B – Pellitory

Case History: pollen-related rhinitis and/or conjunctivitis in the Mediterranean area during pellitory flowering season



C – English plantain

Case History: pollen-related rhinitis and/or conjunctivitis from late summer to autumn



B04 House Dust Mite Allergy

Key points:

- House dust mite (HDM) sensitization is an important risk factor for allergic rhinitis (AR) and asthma (AA).
- Most recognized house dust mites are *Dermatophagoides pteronyssinus, Dermatophagoides farinae* and *Blomia tropicalis*.
- In the majority of cases, a skin test with HDM extracts is able to detect sensitization and define the specificity of immunotherapy in patients suffering from AR/AA.

Tips for molecular diagnosis

- Cross-reactivity between *D. pteronyssinus* and *D. farinae* extracts is high but it is low between *Dermatophagoides* and *B. tropicalis*. Species-specific component testing becomes relevant in places like the tropics, where co-exposure to both genera is common.
- Tropomyosin (Der p/Der f/Blo t 10) is the main cause of cross-reactivity among mites, cockroaches, shellfish and helminths.

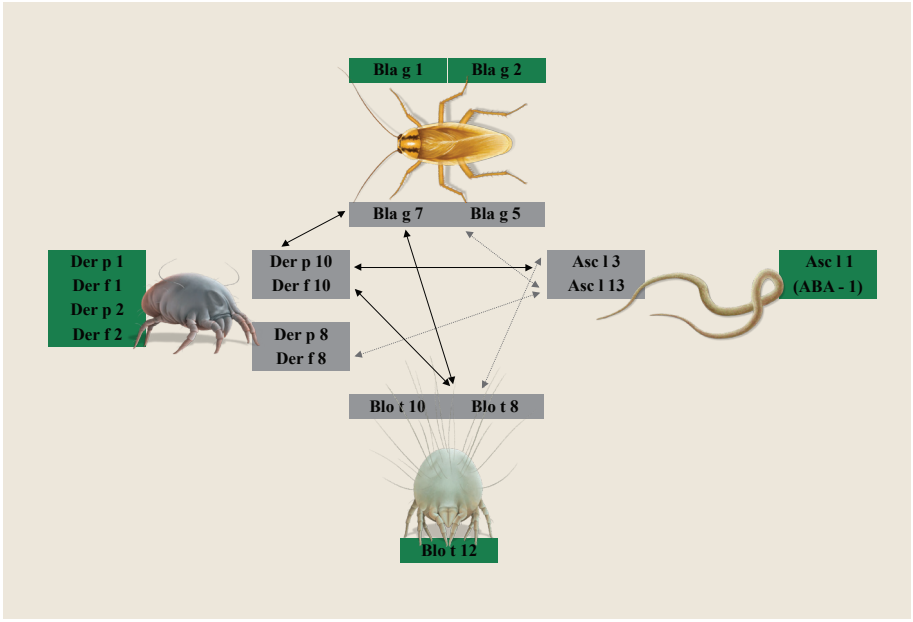
Table of available components for IgE-diagnosis:

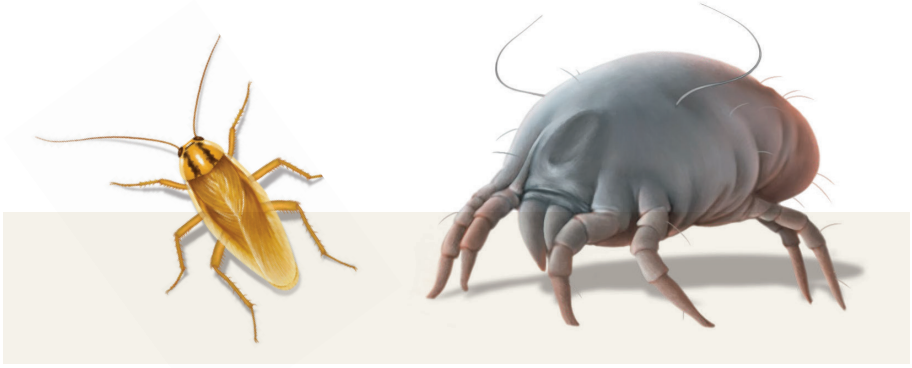
Allergen source	Component
European house dust mite, *Dermatophagoides pteronyssinus*	Der p 1, Der p 2, Der p 5, Der p 7, Der p 10, Der p 11, Der p 20, Der p 21, Der p 23
American house dust mite, *Dermatophagoides farinae*	Der f 1, Der f 2
Storage mite, *Blomia tropicalis*	Blo t 5, Blo t 10, Blo t 21
Storage mite, *Lepidoglyphus destructor*	Lep d 2
Storage mite, *Glycyphagus domesticus*	Gly d 2
Mold mite, *Tyrophagus putrescentiae*	Tyr p 2

House Dust Mite Allergy

B04

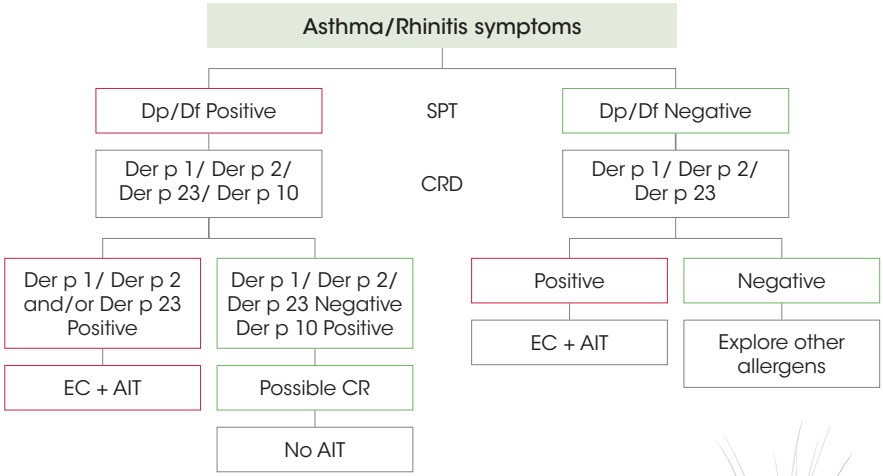
Clinically relevant cross-reactivity of mite allergens.
Species-specific components are shown in green.





B04 House Dust Mite Allergy

Diagnostic algorithms for suspected house dust mite allergy in temperate (A) and tropical (B) countries:



Note: SPT: Skin Prick Test. CRD: Component Resolved Diagnosis. CR: Cross-reactivity. EC: Environmental Control. AIT: Allergen Immunotherapy. Dp: *Dermatophagoides pteronyssinus extract.* Df: *Dermatophagoides farinae extract.*

Cockroach Allergy B05

Key points:

- Cockroach allergens are strong inducers of IgE sensitization and asthma.
- Clinically important species are American and German cockroaches, although Oriental, Asian, brown-banded and smoky-brown cockroaches have also been reported to be associated with induction of cockroach allergies.
- In some places co-exposure to cockroach and mite allergens occurs.

Tips for molecular diagnosis

- In case of sensitization to both cockroach and mite extract, molecular IgE testing can help to distinguish sensitization to mite or cockroach using species-specific allergens such as Bla g 2, which are not present in mites.
- Bla g 2 and Bla g 5 were originally reported to induce the highest frequency of IgE sensitization among cockroach allergens. Recently, additional allergens (e.g. Bla g 9) were also found to induce high levels of sensitization.
- There are important differences in IgE sensitization profiles to nine allergens among individual patients and populations, and no immunodominant allergens are present at the population level.

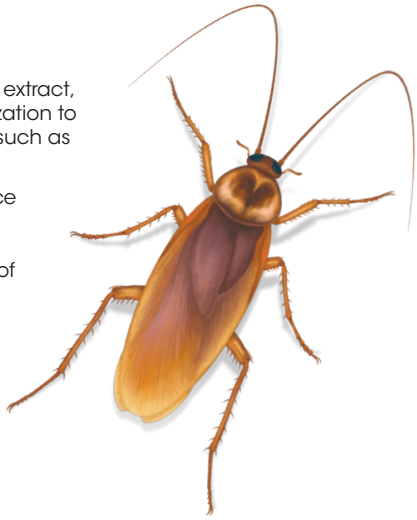
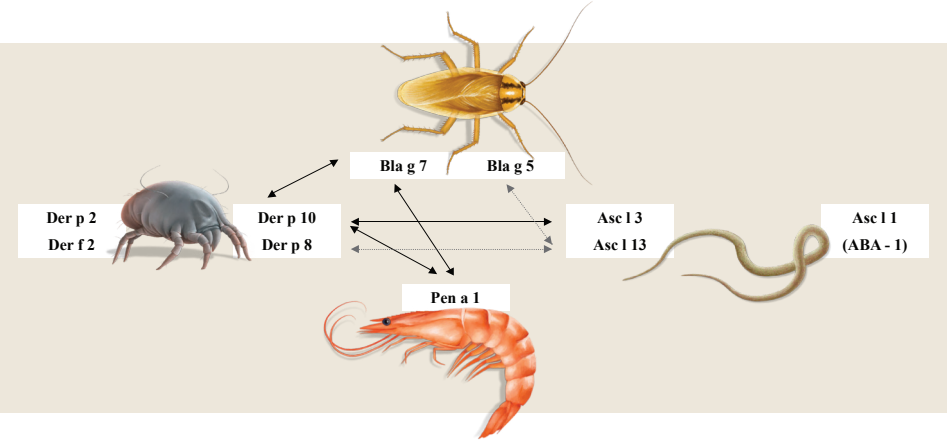


Table of commercially available components for IgE-diagnosis:

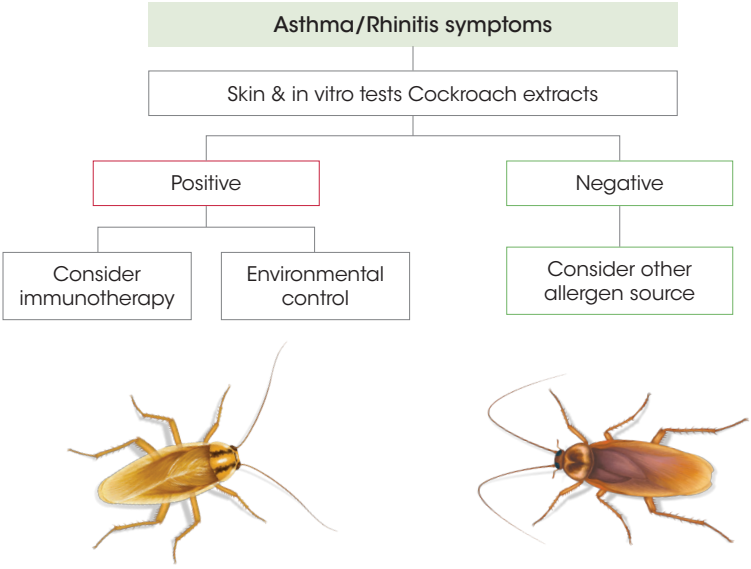
Allergen source	Component
German cockroach, *Blatella germanica*	Bla g 1, Bla g 2, Bla g 4, Bla g 5, Bla g 9
American cockroach, *Periplaneta americana*	Per a 7

B05 Cockroach Allergy

Clinically relevant cross-reactivity of cockroach allergens



Diagnostic algorithm for suspected cockroach allergy:



Furry animals B06

Key points:

- Important indoor allergen source.
- Marker allergens allow determination of primary sensitization source.
- High risk of cross-reactivity between serum albumins from furry animals, contained in dander, milk and meat (→milk and meat chapters: B10 and B14).

Tips for molecular diagnosis

- IgE to Fel d 1 is as good as IgE to cat extract for diagnosing cat allergy.
- Sensitisation to major cat/dog/horse allergens (e.g. Fel d 1 /Can f 1-Can f 5/Equ c 1) are specific markers of cat/dog/horse sensitisation.
- Multisensitisation to dog allergen molecules is associated with dog allergy.

Table of available components for IgE-diagnosis of allergy to animal dander

Allergen source	Component
Cat	Fel d 1, Fel d 2, Fel d 4, Fel d 7
Cattle	Respiratory: Bos d 2 (dander) Food: Bos d 4, Bos d 5, Bos d 6, Bos d 8 (milk); Bos d 6 (meat)
Dog	Can f 1, Can f 2, Can f 3, Can f 4, Can f 5, Can f 6
Guinea-pig	Cav p 1
Hamster	Phod s 1 (Siberian/Djungarian hamster); Mes a 1 (Golden hamster)
Horse	Equ c 1, Equ c 3, Equ c 4
Mouse	Mus m 1
Pig	Sus s 1
Rat	No components available
Rabbit	Ory c 1, Ory c 2, Ory c 3

Table of available components for occupational exposure to bovine products

Allergen	Main source	Protein	Exposed workers
Bos d 2	Dander	Lipocalin	Dairy farmers
Bos d 4	Milk	α-Lactalbumin	Candy and pastry workers
Bos d 6	Milk	Serum albumin	Lab workers
Bos d 8	Serum	Casein	Leather tanning

B06 Furry animals

1. Diagnostic algorithm for cat.

Suspected allergic reaction to cat

History and SPT or sIgE to cat

Diagnosis unclear or questions regarding severity or potential cross-reactivity with other furry animals

Diagnosis certain

Molecular allergy diagnostics to available molecules (Fel d 1, Fel d 2, Fel d 4, Fel d 7)

sIgE to Fel d 1 indicates primary sensitisation to cat; sIgE to Fel d 1, Fel d 2, Fel d 4 is associated with increased likelihood of developing rhinits and asthma, and increased bronchial hyperresponsiveness

sIgE only to Fel d 2 and/or to Fel d 4 suggests cross-reactivity with other furry animals

2. Diagnostic algorithm for dog.

Suspected allergic reaction to dog

History and SPT or sIgE to dog

Diagnosis unclear or questions regarding severity, potential cross-reactivity with other furry animals or tolerance to female dogs

Diagnosis certain

Molecular allergy diagnostics to available molecules (Can f 1- Can f 6)

sIgE to Can f 1, Can f 2, Can f 5 indicates primary sensitisation to dog; sIgE to an increasing number of dog components, particularly lipocalins, is associated with increased likelihood for dog allergy and asthma severity

sIgE only to Can f 5 indicates tolerance to female dogs

sIgE only to albumin Can f 3 and/or Can f 6, suggests cross-reactivity with other furry animals

3. Diagnostic algorithm for horse.

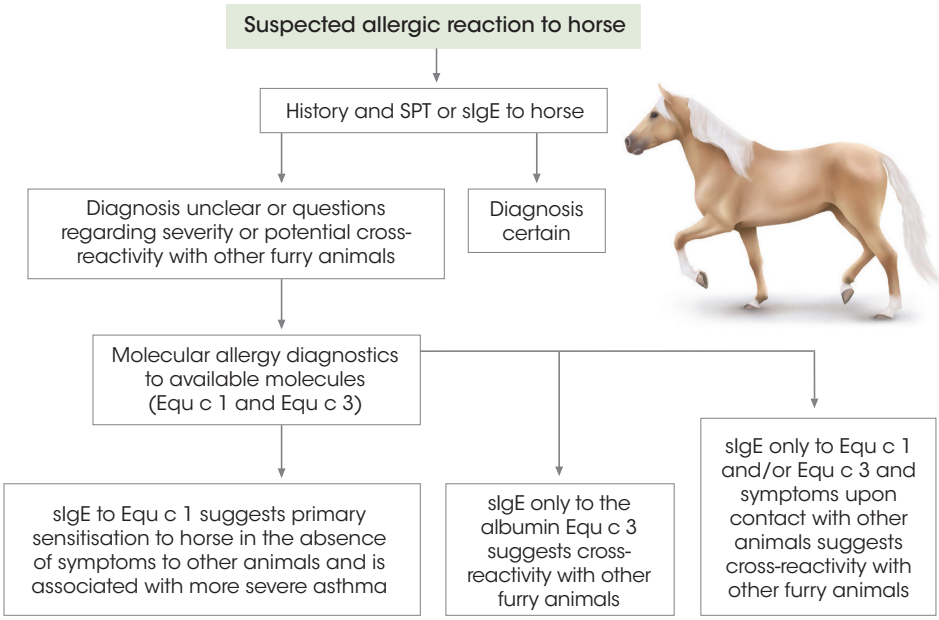


Table of cross-reactive allergens from furry animals

Allergen	Protein	Degree of cross-reactivity
Can f 1, Fel d 7	Lipocalin	moderate risk of cross-reactivity
Can f 3, Fel d 2, Equ c 3, Sus s 1	Serum albumin	high risk of cross-reactivity with other serum albumins
Can f 6, Fel d 4, Equ c 1, Cav p 6, Mus m 1	Lipocalin	moderate risk of cross-reactivity with some lipocalins
Can f 8, Fel d 3	Cystatin	moderate risk of cross-reactivity
Equ c 6, Equ a 6	Lysozyme	high risk of cross-reactivity

Furry animal dander extract contains cross-reactive molecules such as serum albumins, some of the lipocalins as well as other cross-reactive molecules (e.g. cystatin). Thus, it is important to define the primary allergenic source, especially if a specific immunotherapy is intended.

B07 Allergy to Moulds

Key points:

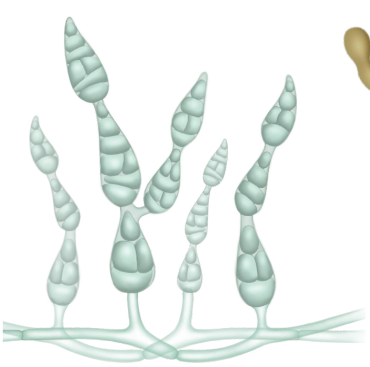
- Moulds are ubiquitous, but although exposure to spores in the air is frequent, the sensitization rate to mould spores in the general population is relatively low.
- Mould sensitization is more common in asthmatics and should be considered in the diagnosis.
- Of the huge variety of moulds worldwide, only few species can be used in allergy testing.
- Due to the difficult production and standardisation of mould allergen extracts, it can be helpful to improve mould allergy diagnosis using single allergen components.
- The mould species with the greatest clinical relevance are: *Alternaria alternata* and *Cladosporium herbarum* (outdoor); *Aspergillus fumigatus* and *Penicillium chrysogenum* (indoor).

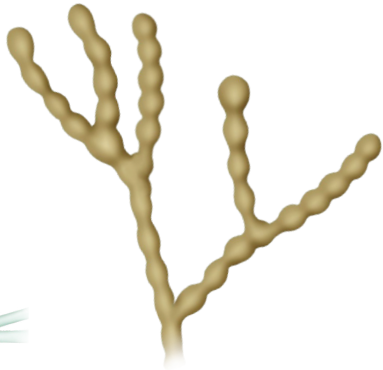
Tips for molecular diagnosis

- Component-resolved diagnosis is useful to verify allergic bronchopulmonary aspergillosis (ABPA) in patients with sensitization to *Aspergillus fumigatus* as shown in the decision algorithm.
- In patients sensitized to *Alternaria alternata* testing to Alt a 1 is recommended before starting specific immunotherapy (SIT).

Table of available components for IgE-diagnosis (see also B08 for *Malassezia sympodialis*):

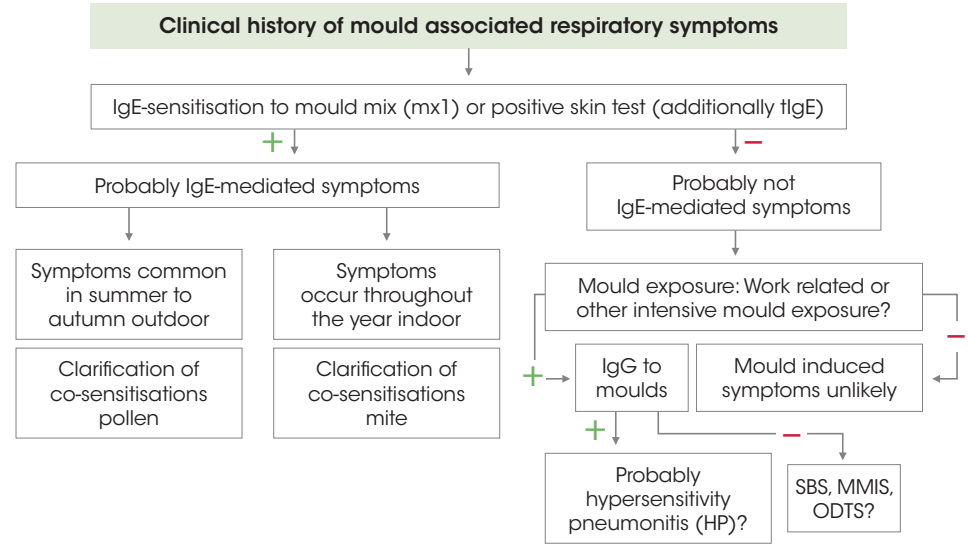
Allergen source	Component
Aspergillus fumigatus	Asp f 1, Asp f 3, Asp f 4, Asp f 6
Alternaria alternata	Alt a 1, Alt a 6
Cladosporium herbarum	Cla h 8

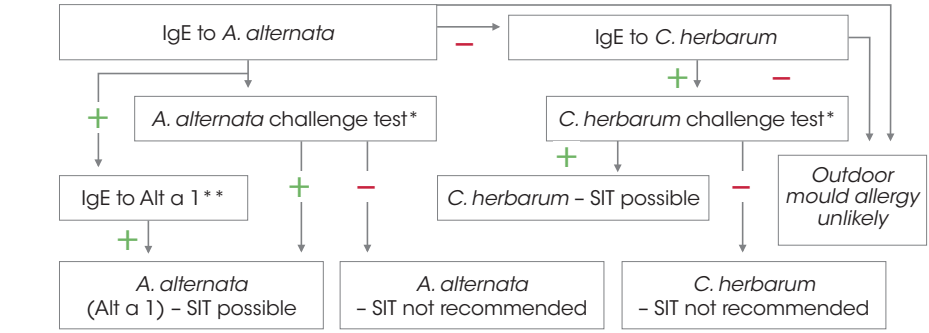


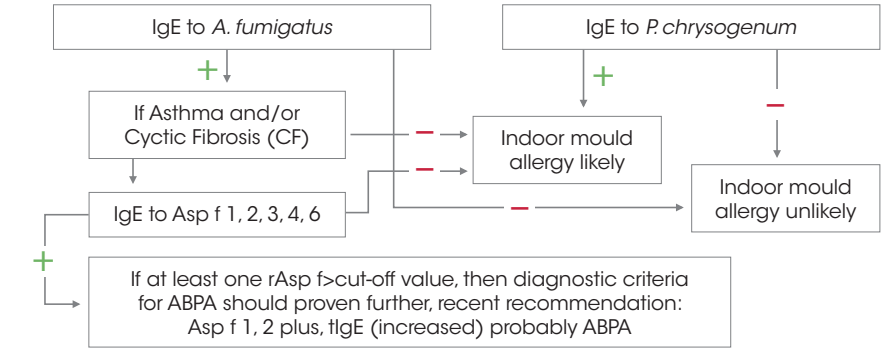


Allergy to Moulds

B07







Mould mix (mx1): *Aspergillus fumigatus, Penicillium chrysogenum, Cladosporium herbarum, Alternaria alternata;* SBS: sick building syndrome; MMIS: mucous-membrane irritation syndrome, ODTS: organic dust toxic syndrome (endotoxin, mycotoxin)

B08 Microbial allergens in atopic dermatitis and beyond

Key points:

- Yeast-like Malassezia species are commensals of the normal skin flora and are part of the skin microbiome.
- A sensitization to allergens of Malassezia species can frequently be found in the head and neck type of atopic dermatitis.
- The skin microbiome, especially Malassezia spp and Staphylococcus aureus, can be a target in atopic dermatitis therapy.

Tips for molecular diagnosis

- Fourteen allergens from 3 Malassezia species have been characterized to date.
- Three single allergens are available for allergy diagnosis.
- Mala s 11 is cross-reactive to Asp f 6, an allergen from *Aspergillus fumigatus*.

Table of available components for IgE-diagnosis of Malassezia allergy in atopic dermatitis

Common name (Species)	Allergenic molecule	Biochemical name
Malassezia (*Malassezia sympodialis*)	Mala s 5	unknown
	Mala s 6	cyclophilin
	Mala s 11	Mn superoxide-dismutase

Clinical algorithms:

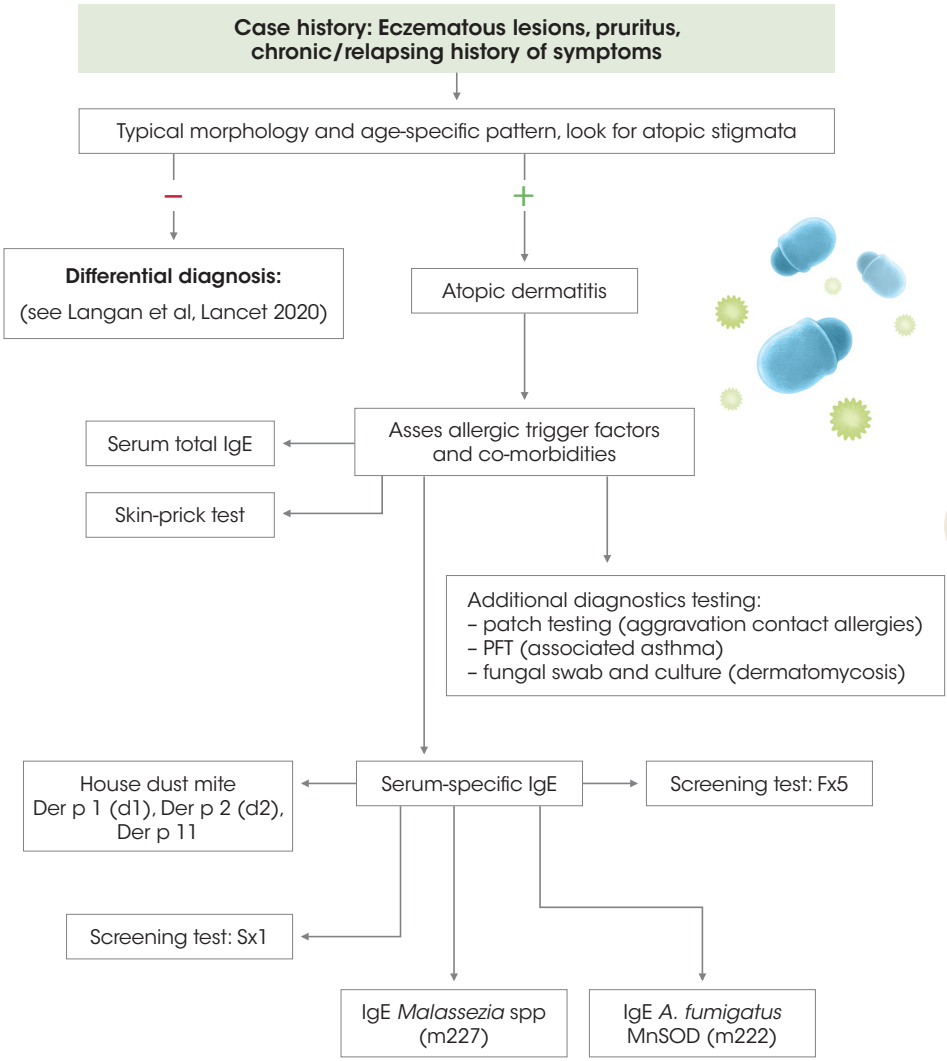
The diagnosis of Malassezia-associated atopic dermatitis (AD) is based on the clinical picture. It may be supported by a positive type I allergic reaction to Malassezia spp, measured by a positive skin prick test, or by measuring Malassezia-specific serum IgE with a commercially available standardized assay (ImmunoCAP® m227) based upon extract of three different Malassezia species. Furthermore, a recently developed multiplex IgE-macroassay (MacroArray Diagnostics GmbH, Vienna, Austria) is available, including the allergens Mala s 5, 6, and 11. Based on its sequence homology, Asp f 6 shows high cross-reactivity with Mala s 11 and can be measured additionally. Total IgE measurements can allow one to determine the sensitization attributable to the whole extract, e.g. specific IgE can be expressed as a ratio or percentage of total IgE; it also indicates a reduced sensitivity of specific IgE in very low amounts of total IgE (< 25kU/l). Atopy patch testing has shown varying results. Some studies have shown no correlation between specific IgE and atopy patch test for Malassezia. In contrast, others have found a positive atopy patch test in 41% of patients with head and neck dermatitis and 30% in AD patients without head and neck involvement.

The benefit of topical or systemic antifungal treatment for clinical improvement of AD is controversial. Azole antifungals are the most commonly prescribed class of antifungals for AD patients. Azole antifungals show inhibitory effects against Malassezia spp *in vitro*. However, the relevance of systemic antifungal treatment (e.g. keto/itraconazole) to routine clinical practice remains to be demonstrated.

In the flow scheme of Figure 1, the diagnostic algorithm in suspected atopic dermatitis and suggested serological investigations in patients with confirmed atopic eczema is represented.

Microbial allergens in atopic dermatitis and beyond

B08



[Figure 1] Diagnostic algorithm in suspected atopic dermatitis and suggested serological investigations in patients with confirmed atopic eczema

Abbreviations: Fx5, ImmunoCAP food allergy screening mix of egg white, milk, fish, wheat, peanut, soybean; PFT, Pulmonary Function Test; Sx1, ImmunoCAP respiratory allergy screening test *Dermatophtagoides pteronyssinus*, cat dander, dog dander, timothy grass pollen, ryegrass pollen, *Cladosporium herbarum*, birch, mugwort.

B09 Edible insects

Key points:

- Clinically relevant cross-reactivity between mealworm and shrimp has been found.
- Primary sensitisation to insects (mealworms) is possible.
- Currently good diagnostic tools for insect food allergy are missing.
- In case of unclear clinical history and serology, food challenges are necessary to confirm the diagnosis.

Tips for molecular diagnosis

- Important allergenic proteins are tropomyosin and arginine kinase (cross-reactivity).
- Tropomyosin and arginine kinase may be responsible for clinical cross-reactivity among crustaceans, molluscs, insects, and mites.
- In primary allergy, other allergens than tropomyosin and arginine kinase might be responsible such as Larval cuticle protein.
- Patients with shrimp allergy will most likely react to all insects, while primary allergy to a particular insect does not have to include allergies to other edible insects.

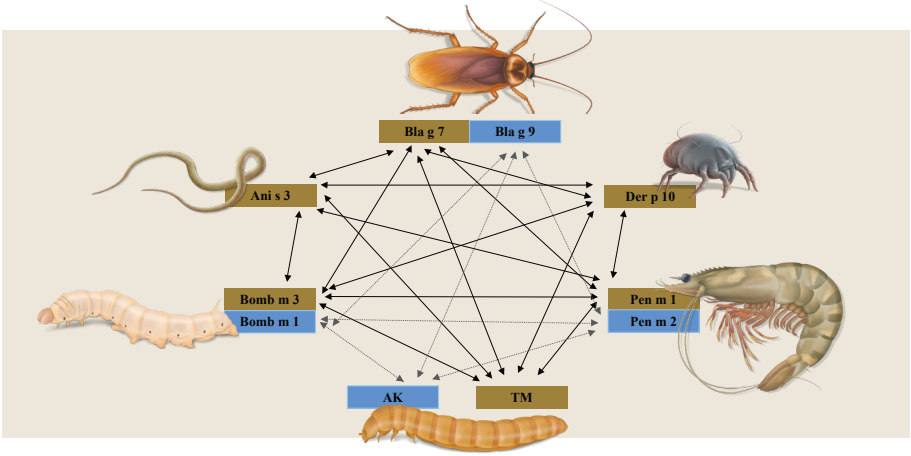
Allergen components from silkworm and mealworm.

Species	Allergenic molecule	Protein family	Frequency of IgE	MW (kDa)
Silkworm *Bombyx mori*	Bomb m 1	Arginine Kinase	100% (n=10)	42
	Bomb m 3	Tropomyosin	53.3% (n=15)	38
Mealworm *Tenebrio melitor*	NA	Arginine Kinase	23.1% (n=13)*	27
	NA	Tropomyosin	76.9% (n=13)*	34
	NA	LCP AIA	100% (n=2)	18

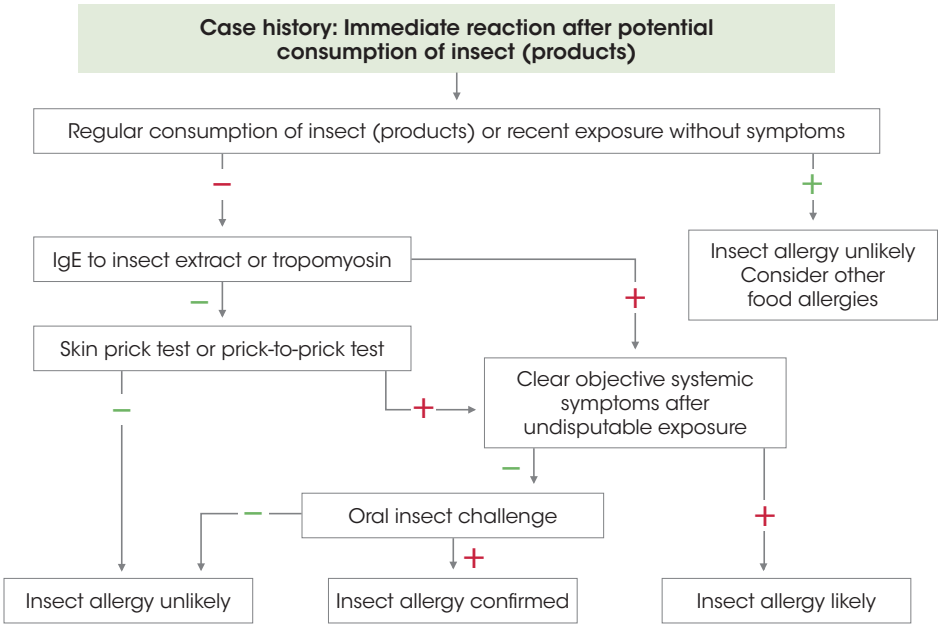
*Unpublished data.

Edible insects B09

Cross-reactivity of tropomyosin (TM) and arginine kinase (AK) between different allergenic sources



Diagnostic algorithm for insect food allergy



B10 Cow's milk allergy

Key points:

- Allergies to cow's milk are the most common in the world, but they are often outgrown.

Tips for molecular diagnosis

- The utility of IgE to allergen components does not exceed that of IgE to cow's milk extract to support the diagnosis of cow's milk allergy.
- Sensitisation to heat-resistant proteins (e.g., ovomucoid) and sequential epitopes have been associated with reactivity to baked milk and persistent milk allergy.

Allergens in Cow's Milk (CM), sensitisation and cross-reactivity patterns

Allergen name	Allergenicity	Sensitisation rate % among those reactive to CM	Laboratory cross-reactivity	Clinical cross-reactivity
Curd (coagulum) - Casein family				
Caseins (Bos d 8)	Major	63	>85% with sheep and goat milk caseins	>90%
Alpha sl-casein (Bos d 9)	Major	98*		
Alpha s2-casein (Bos d 10)	Major	94*		
Beta-casein (Bos d 11)	Major	91*		
Kappa-casein (Bos d 12)	Major	91*		
Whey (lactoserum)				
Alpha lactalbumin (Bos d 4)	Major	51		
Beta lactalbumin (Bos d 5)	Major	61		
Bovine serum albumin (Bos d 6)	Minor	43	80% with beef	15-20% with raw beef
Immunoglobulins (Bos d 7)	Minor	36		
Lactoferrin	Minor	35		

* Percentage of those sensitised to casein Bos d 8

Cow's milk allergy B10

Proposed specific IgE diagnostic decision points for CM allergy diagnosis derived from studies in children, the majority of whom had atopic dermatitis.

	CM-sIgE [kUA/L]	OFC to unheated milk
>95% PPV	>15; >5 if less than 1 year old	Defer
>50% to <95% PPV	5-15	Consider the OFC based on the clinician and patient's/ family preference, social and nutritional importance of dairy, history of recent reactions and type of symptoms
<50% PPV	<5	Perform
	CM skin prick test mean wheal diameter, mm	
>95% PPV	> 8 Casein-sIgE [KU/L]	Defer **OFC to baked milk**
>95% PPV	> 10	Defer
>50% to <95% PPV	5-10	Consider the OFC based on the clinician and patient's/ family preference, social, and nutritional importance of dairy, history of recent reactions and type of symptoms
<50% PPV	<5	Perform
	CM skin prick test mean wheal diameter, mm	
>90 NPV	<12	Perform
	Casein skin prick test mean wheal diameter, mm	
>90% NPV	<9	Perform

Note: OFC: Oral food challenge, PPV: positive predictive value, NPV: negative predictive value.

B11 Egg Allergy

Key points:

- Egg allergy is one of the most frequent food allergies in children.
- The result of an IgE test can confirm the diagnosis of egg allergy in the case of a clear clinical history of reaction; in equivocal cases, an oral food challenge to egg may be needed to clarify the diagnosis.

Tips for molecular diagnosis

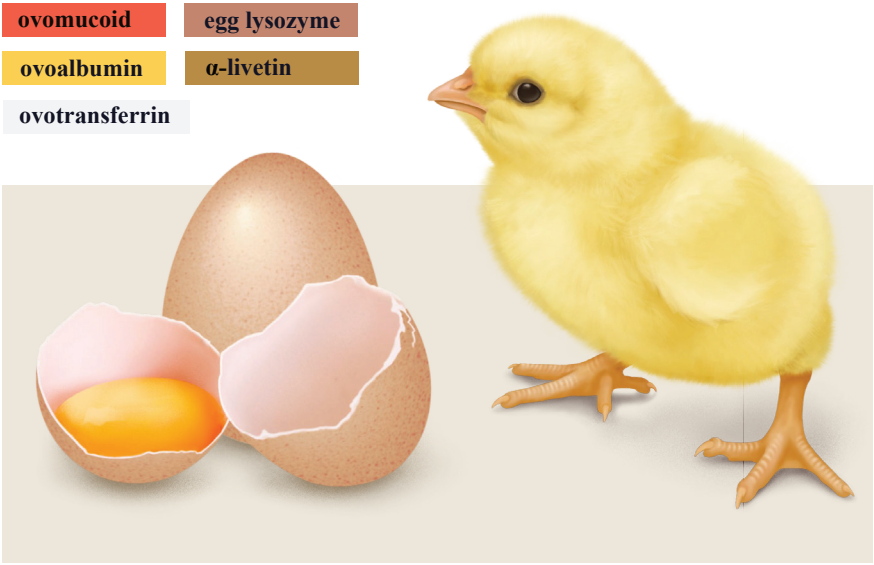
- The use of egg white components can help distinguishing between allergy to baked, cooked, and raw egg.
- The use of egg white components is clinically helpful for distinguishing between transient and persistent allergy to egg.

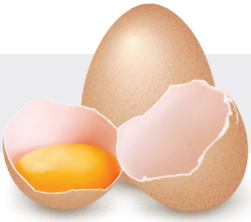
Major egg allergens:

ovomucoid | **egg lysozyme**

ovoalbumin | **α-livetin**

ovotransferrin





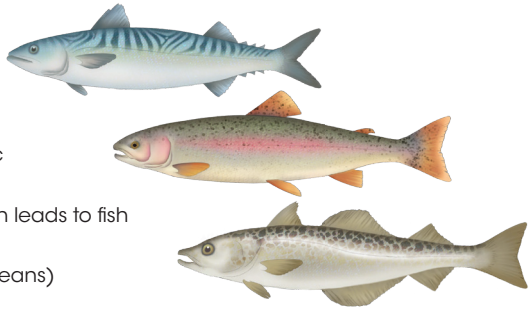
Egg Allergy

B11

Table of allergenic molecules of hen's egg and clinical relevance of specific proteins.

Protein name	MW (kDa)	Protein Family	Biological function(s)	Resistance to heating and chemical denaturation	Clinical relevance
Egg White Proteins					
Ovomucoid (Gal d 1)	28	Kazal-type serine protease inhibitor	serine protease inhibition activity antibacterial activity	high	Heat-stable and highly allergenic. Risk for reaction to all forms of egg. High levels of specific IgE might indicate sustained egg allergy.
Ovalbumin (Gal d 2)	45	serine protease inhibitor	storage protein?	low	Heat-labile. Most abundant egg white protein. Risk for clinical reaction to raw or slightly heated egg.
Ovotransferrin or conalbumin (Gal d 3)	76-77	transferrin	iron-binding capacity with antimicrobial activity	low	Heat-Labile. Risk for clinical reaction to raw or slightly heated egg.
Egg lysozyme (Gal d 4)	14.3	glycoside hydrolase family 22	antibacterial activity	moderate	Risk for clinical reaction to raw or slightly heated egg.
Ovomucin	165	contains trypsin inhibitor-like-domains	heavily glycosylated protein with potent antiviral activities	n.a.	
Egg Yolk Proteins					
Phosvitin	35	transferase?	Metal-chelating agent	n.a.	
α-livetin (Gal d 5)	65-70	serum albumin	bind ions, fatty acids, hormones in physiological conditions	n.a.	
Apovitellenins I	9.5	very low-desity lipo protein	potent lipoprotein lipase inhibitor	n.a.	
Apovitellenins VI (orapoprotein B)	170	unknown	lipid-binding activity	n.a.	

B12 Allergy to fish and *Anisakis simplex*



Key points:

- Fish and *Anisakis* are important food allergen sources.
- Fish species may differ by their allergenic potency.
- Ingestion of *Anisakis* in contaminated fish leads to fish allergy as well.
- Allergens from fish, shellfish (e.g., crustaceans) and *Anisakis* are not the same.

Tips for molecular diagnosis

- Parvalbumin is the major fish allergen and specific marker for fish allergy.
- Sensitization to multiple fish allergens is associated with fish allergy.
- Ani s 1 is a clinically relevant allergen for the diagnosis of *Anisakis* allergy.

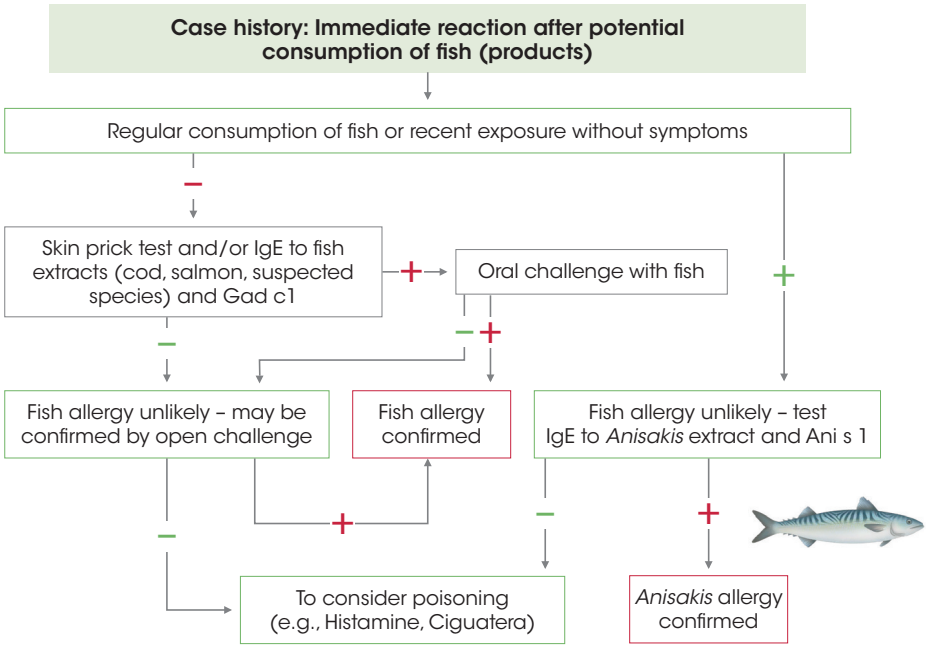
Table of available components for IgE-diagnosis of allergy to fishes and fish parasite

English name (Species)	Allergenic molecule	Biochemical name
FISHES		
Herring (*Clupea harengus*)	Clu h 1	β-parvalbumin
Carp (*Cyprinus carpio*)	Cyp c 1	β-parvalbumin
Atlantic cod (*Gadus callarias*)	Gad c 1	β-parvalbumin
Atlantic cod (*Gadus morhua*)	Gad m 1	β-parvalbumin
	Gad m 2	enolase
	Gad m 3	aldolase
Tuna (*Thunnus albacares*)	Thu a 1	β-parvalbumin
Atlantic mackerel (*Scomber scombrus*)	Sco s 1	β-parvalbumin
Swordfish (*Xiphias gladius*)	Xip g 1	β-parvalbumin
Salmon (*Salmo salar*)	Sal s 1	β-parvalbumin
Thornback ray (*Raja clavata*)	Raj c PV	α-parvalbumin
ANISAKIS		
Herring worm (*Anisakis simplex*)	Ani s 1	protease inhibitor
	Ani s 3	tropomyosin

Allergy to fish and *Anisakis simplex* B12

Clinical algorithms:
When fish allergy is initially suspected (algorithm below), the question need to be asked is how "sensitive" is the patient. This is based first and foremost on the clinical history (e.g. severe reaction after ingestion of very small quantities) and can also be deduced from titrated challenge with the suspected fish. Severity might also be determined by the oral provocation test. It should be noted that the algorithm diagram below reflects a complete workflow, rather than a temporal sequence. Results of skin testing are sometimes available before the results of biological analyses. Challenge tests are not recommended in cases of suspected severe reaction. This problem is sometimes circumvented by challenging a supposedly less reactive fish first. As mentioned in the "Parvalbumins" section, some patients allergic to fish may develop cross-reactivity to chicken meat due to cross-reactivity between parvalbumins. Depending on the patient's history, it may be advisable to carry out prick-to-prick tests to chicken meat, as well as serum IgE measurements to chicken meat, especially in the case of reactivity to alpha-parvalbumins. During the diagnostic procedure (diagnostic algorithm below), it is important to rule out an anaphylaxis to *Anisakis simplex*, especially if no sensitization to fish is found, and in the case that raw fish has been consumed or not properly 'frozen' (-20°C for at least 24 hours or -35°C for at least 15 hours). It is important to bear in mind that measurement of IgE to *Anisakis* extract can produce false-positive results due to molecular cross-reactivity, such as to shellfish or arthropod allergens (e.g., house dust mite or cockroach tropomyosins).

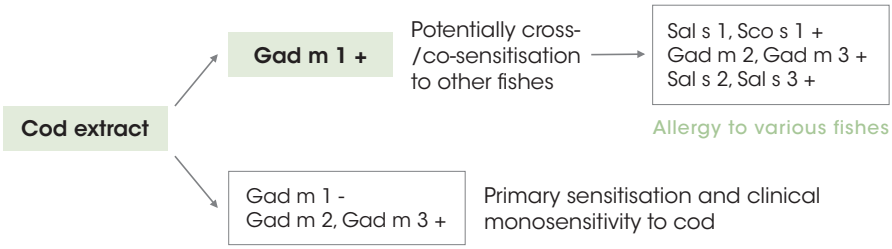
Diagnostic algorithm in patients with suspected fish allergy.

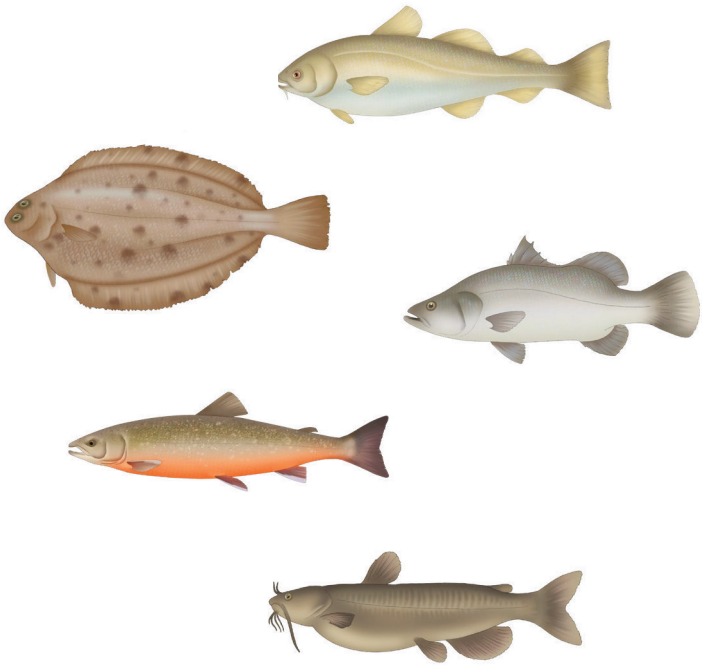


B12 Allergy to fish and Anisakis simplex

In the flow scheme below, the clinical cross-reactivity to unspecific fishes was confirmed by the detection of specific IgE to a broad panel of fish allergens, including parvalbumins, enolases, and aldolases.

Diagnostic procedure. Orange text box = established diagnosis.





Allergy to crustaceans and molluscs B13

Key points:

- Some shellfish allergens can sensitise via the oral and inhalation route (tropomyosin, arginine kinase, triosephosphate isomerase, hemocyanin).
- It is important to consider that the symptoms elicited upon shellfish exposure may have been not directly related to the shellfish, such as *Anisakis simplex* allergy through fish, or in the case of mussels and oysters, paralytic shellfish /diarrhoetic shellfish poisoning which are caused by molluscs contaminated with algae producing toxins.

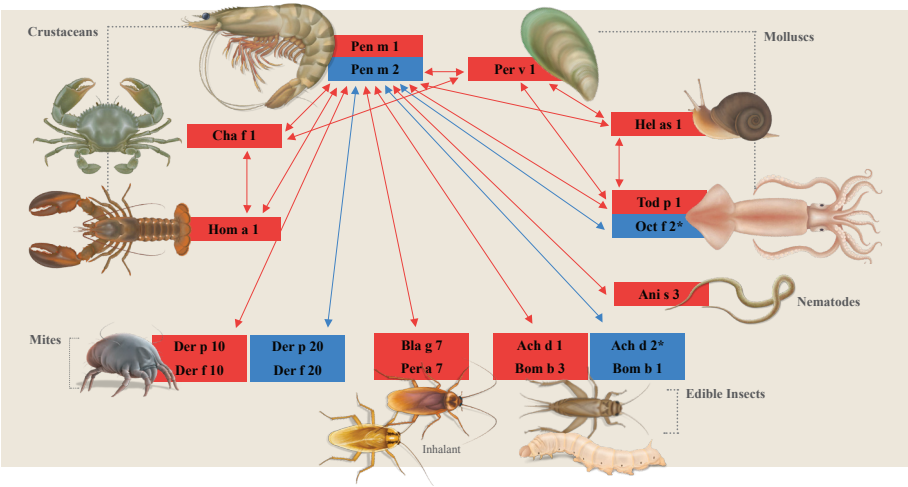
Tips for molecular diagnosis

- Tropomyosin and arginine kinase are highly cross-reactive allergens and are responsible for clinical cross-reactivity among crustaceans, molluscs, insects, and mites. Tropomyosin is heat-stable, while arginine kinase is heat-labile.
- Co-sensitization to tropomyosin (Pen m 1) and sarcoplasmic calcium binding protein (Pen m 4) may be a better predictor of clinical reactivity to shrimps.

Table of available components for IgE-diagnosis of allergy to crustacean or molluscs

Allergen source	Component
Prawns, shrimp	Pen a 1, Pen m 1; tropomyosin Pen m 2; arginine kinase Pen m 3; myosin light chain Pen m 4; sarcoplasmic calcium- binding protein Cra c 6; troponin C
Crabs	No components, only extracts available
Lobsters	No components, only extracts available
Bivalves	No components, only extracts available
Gastropods	No components, only extracts available
Cephalopods	No components, only extracts available

B13 Allergy to crustaceans and molluscs

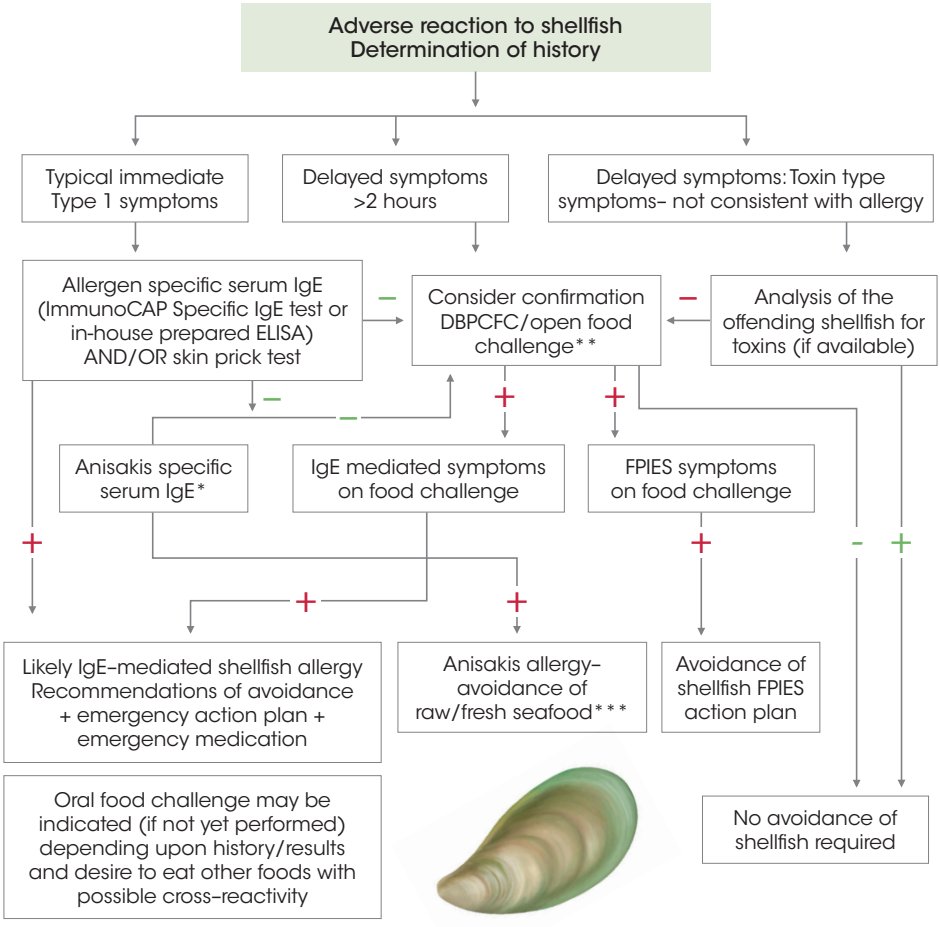


[Figure 1] – Clinically relevant cross-reactivities between shellfish (crustacean and mollusc) and invertebrate (mite, insect, and nematode) allergens. Cross-reactivity due to different allergen families is depicted in red (tropomyosin) or blue (arginine kinase) arrows. *indicates allergens that are not currently registered in the WHO-IUIS Allergen nomenclature database.

Allergy to crustaceans and molluscs

B13

Diagnostic algorithm for component-resolved diagnosis of shellfish allergy:



* More common in fish/mollusk than crustaceans.

** Consider exercice food challenge if history is suggestive of exercice related reaction and tolerance in other settings.

*** Cooking at temperatures above 60°C or storage in industrial freezers for 2 days is required to kill the parasite.

Note: FPIES: food protein enterocolitis syndrome, DBPCFC: double-blind placebo controlled food challenge

B14 Allergy to mammalian meat

Key points:

- Sensitisation to meat can be acquired through different routes (inhaled, oral, skin).
- New forms of allergic reactions to meat have been recognized (pork-cat and red meat).
- IgE immunoassays including meat allergen sources and components will help identifying the patients.
- Patients should be informed about the eliciting meat sources and about the avoidance regimen.
- Patients with alpha-gal syndrome (AGS) should avoid tick bites.
- Sensitisation to alpha-gal is also a major risk factor for immediate reactions to Cetuximab.

Tips for molecular diagnosis

- IgE to pork and cat albumin are markers of pork-cat syndrome.
- IgE to alpha-gal (galactose alpha-1,3-galactose) is a marker of mammalian meat allergy (AGS).

Table of allergens available for diagnosis for different forms of mammalian meat allergy.

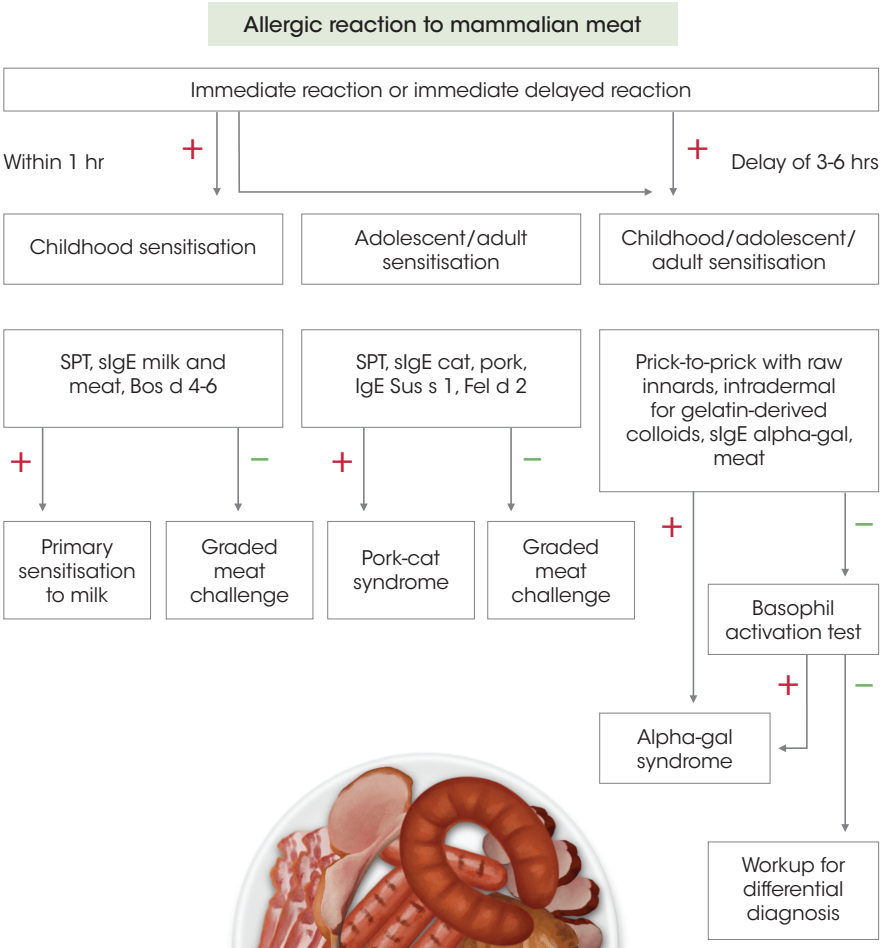
Clinical syndrome	Component	Available allergens components
Pork-cat syndrome	serum albumins	Fel d 2, Can f 3, Sus s 1, Bos d 6
Alpha-gal syndrome (AGS)	alpha-gal	alpha-gal
Meat allergy related to milk	milk allergens	Bos d 4–6, Bos d 8
Primary meat allergy	meat allergens	Bos d 6, Sus s 1

Routes of sensitisation for allergens related to allergic reactions to meat.

Inhaled:	Cat albumins related to systematic reactions to pork
Oral:	Cow's milk allergens related to anaphylactic reactions to beef
Skin:	Tick bites leading to alpha-gal sensitisation

Allergy to mammalian meat B14

Diagnostic algorithm in patients with allergic reactions to meat:



B15 Fruit and vegetable allergy

Key points:

- These allergies can either be due to cross-sensitization with pollen allergens or are due to genuine sensitization.
- Frequently IgE cross-reactivity does not always coincide with clinical relevance.

Tips for molecular diagnosis

- Prick-to-prick testing using raw plant food is often superior to extract-based testing.
- Food challenges are the method of choice to rule out clinically silent IgE cross-reactivity.
- Allergens from peach are used for diagnosis in all types of Rosaceae fruit allergies.

Table of available components for IgE-diagnosis of allergy to fruits and vegetables.

Allergen source	Allergen	IgE prevalence/ Sensitisation	Cross-reactivity
FRUITS			
Apple (*Malus domestica*)	Mal d 1	15-70% of apple allergic patients	High cross-reactivity between PR-10 proteins, profilins, and nsLTPs. Bet v 1-(PR-10) related food proteins, profilin, and nsLTP sensitizations are not often accompanied by clinical symptoms.
	Mal d 3	1-50% of apple allergic patients	
Peach (*Prunus persica*)	Pru p 1	11% of peach allergic pediatric cohort, 7-13% in adults (ESP, ITA)	
	Pru p 3	96% of peach allergic children	
	Pru p 4	10% of peach allergic children (ESP), and 7-34% of adults (ESP, ITA)	
	Pru p 7	62-65% of peach allergic adults (FRA, JPN)	
Green Kiwifruit (*Actinidia deliciosa*)	Act d 1	5-32% (Central Europe – ISL)	It can be acquired via the gastrointestinal tract or via cross-sensitisation to birch or grass pollen and latex allergens. Cross-reactivity between Hev b 11, a chitinase from latex, and kiwifruit. Latex-associated food allergies have cross-reactivity to banana, avocado, chestnut, kiwifruit, and many more.
	Act d 2	2-18%	
	Act d 5	2-18%	
	Act d 8	7-58%	
VEGETABLES			
Celery (*Apium graveolens*)	Api g 1	75%	Sensitisation to Fagales tree pollen and IgE to Bet v 1 may develop cross-sensitisation to Apiaceae vegetables such as carrot and celeriac.

Abbreviations following the NATO country codes: ESP, Spain; ITA, Italy; FRA, France; JPN, Japan; ISL, Iceland.

Fruit and vegetable allergy B15

Diagnostic algorithm in Rosaceae fruit allergy:

Positive case history of a Rosaceae fruit allergy

Oropharyngeal symptoms (OAS)	history	Oropharyngeal symptoms associated with systematic reaction
SPT birch pollen SPT with fresh fruits and/ or fruit extracts*+	skin test	SPT birch pollen SPT with fresh fruits and/ or fruit extracts+
IgE Bet v 1$ IgE fruit extract*	in vitro test 1	IgE fruit extract+

IgE Bet v 1 if available Bet v 1 homologues in fruits (Mal d 1, Pru p 1)	IgE Pru p 3 if available nsLTP homologues in fruits (Mal d 3)	Optional IgE Bet v 2 or homologues in fruits (Pru p 4)
Food challenge	Food challenge depending on symptoms	Food challenge
Elimination diet of fresh fruits	Elimination diet of fresh and processed fruits	Elimination diet of fresh fruits

Food challenge* optional

Elimination diet of fresh fruits

*Patients with sensitisation to birch pollen or other Fagales tree pollen and history of Rosaceae fruit induced oropharyngeal symptoms usually do not need further investigation; + Sensitivity of skin test or *in vitro* IgE determination using fruit extracts might be low due to underrepresentation of Bet v 1 homologues; $ In patients from Mediterranean countries: OAS can also be linked to LTP or profilin sensitisation. In case of LTP-mediated OAS, strict elimination of fresh and processed food is recommended. SPT stands for Skin Prick Test

B16 Wheat and buckwheat allergies

Wheat allergy

Key points:

- Wheat allergy can manifest as childhood food allergy, wheat-dependent, exercise-induced anaphylaxis (WDEIA), baker's asthma, or contact urticaria.
- Wheat sensitisation is more prevalent than true clinical allergy.
- There are several well-characterized allergenic molecules such as gliadins, glutenins, and alpha-amylase inhibitors, but no single major allergen has been identified.
- IgE-mediated food allergy to wheat causes symptoms like those seen in milk or egg allergy.
- WDEIA severe symptoms develop after wheat ingestion followed by physical exercise, typically among young adults.
- Baker's allergy or asthma is an occupational allergy caused by the inhalation of wheat flour.
- Contact urticaria is a local skin symptom often associated with the use of cosmetics and sometimes together with food allergy.

Tips for molecular diagnosis

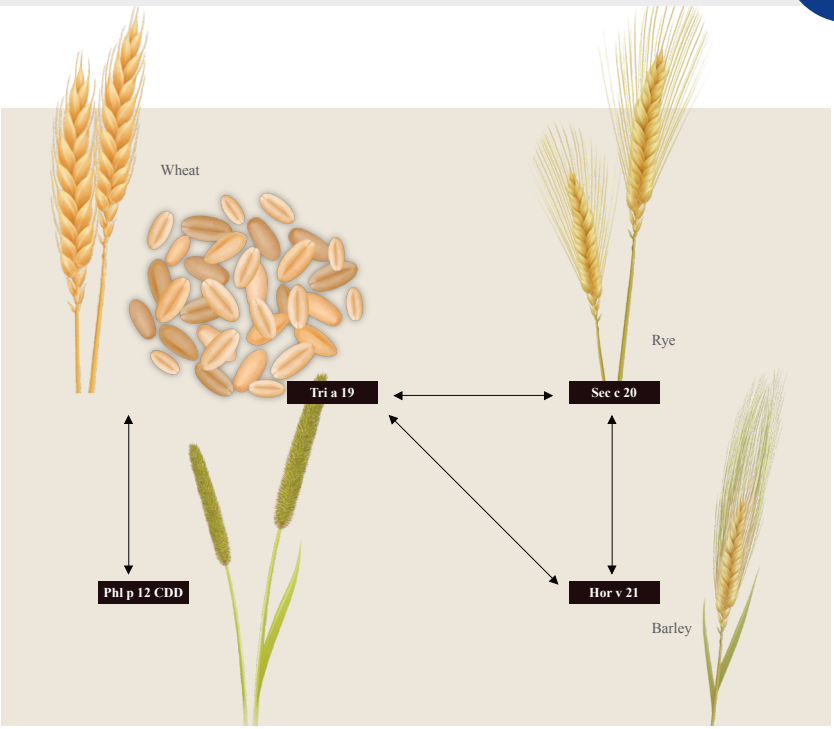
- Due to cross-reactivity with other allergens, including grasses, IgE measurement to whole wheat extract gives unreliable results with low specificity in diagnostics. However, extract-based diagnosis is still recommended in case of wheat-allergy due to baker's asthma (Chapter B22).

Table of commercially available allergens for IgE diagnosis of wheat allergy.
#Wheat (*Triticum aestivum*).

Allergen#	Component
Tri a 14	Wheat nsLTP-1 has no cross-reactivity with grass pollen.
Tri a 19	Omega-5-gliadin. Major allergen for WDEIA and food allergy. Cross-reactivity with rye gamma-70 and gamma-35 secalins and barley gamma-3 hordein.
Tri a aA/ TI	Alpha-amylase inhibitor, associated with both baker's asthma and food allergy.

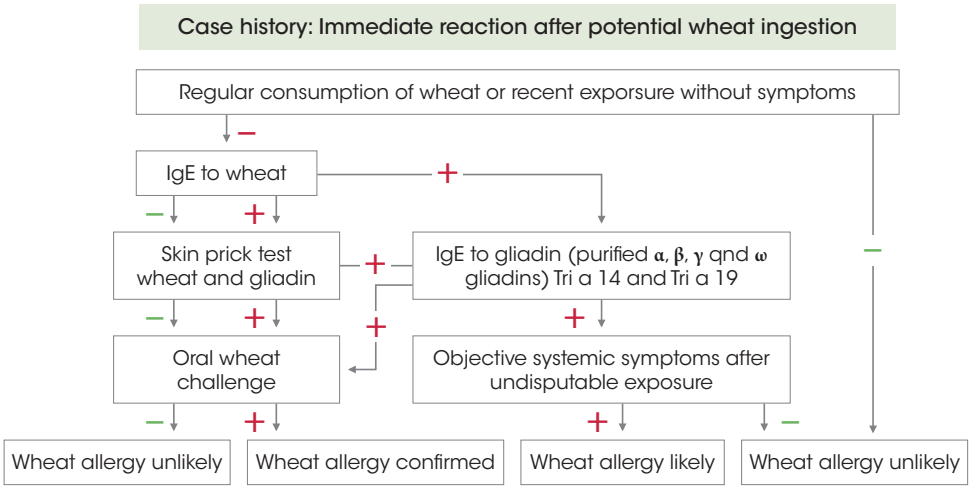
Wheat and buckwheat allergies

B16



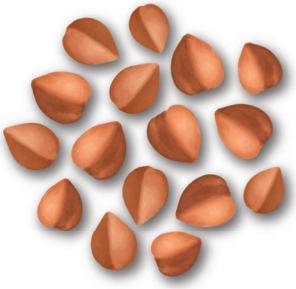
Cross-reactivity with wheat allergens.

Diagnostic algorithm for wheat allergy:



B16 Wheat and buckwheat allergies

Buckwheat allergy



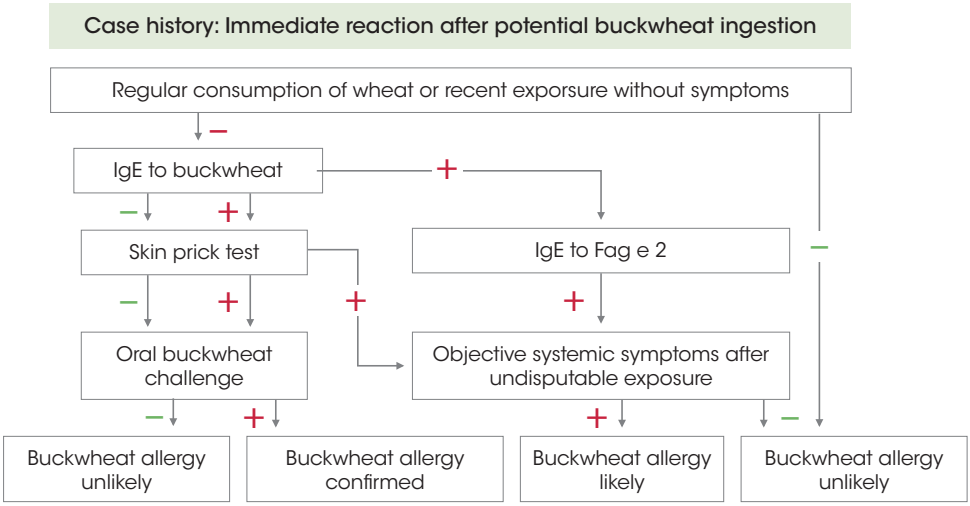
Key points:

- Clinically irrelevant sensitisation to buckwheat is common.
- Relatively infrequent, but can often cause anaphylactic reactions.
  Buckwheat is often consumed as a hidden food allergen. Remember the possibility of this allergy when investigating unclear anaphylaxis.

Tips for molecular diagnosis

- The diagnostic performance of IgE to buckwheat extract and skin prick tests is low.
- IgE to **Fag e 2** is associated with severe reactions, but well-defined commercially available buckwheat allergens for molecular allergy diagnostics are lacking.

Diagnostic algorithm for buckwheat allergy:



Soy Allergy B17

Key points:

- Soy allergens can induce food allergy and inhalant (occupational) allergies.
- Food allergic reactions to soy are caused by exposure to processed whole soybeans or soy protein products.
- Inhalant allergies are caused by inhaled dust from unprocessed soybeans.

Tips for molecular diagnosis

- Birch pollen-allergic individuals may experience allergic reactions after eating barely processed soybeans, soy protein powder-containing products, or soy drink products. These reactions, mediated by IgE-cross-reactivity between Bet v 1 or homologs and Gly m 4, are the most common type of soy allergy in regions with relevant birch pollen or alder pollen exposure.
- Oropharyngeal and sometimes severe reactions to Gly m 4 are limited to fresh, barely processed soy protein-containing products.
- Three clinical patterns can be identified in IgE-mediated sensitisation and the clinical symptoms of immediate hypersensitivity:

  A) Early, presumably epicutaneous or intestinal sensitisation to rather stable allergens (i.e., Gly m 5 and Gly m 6) in atopic individuals after ingestion of small amounts of soy or processed soy products.

  B) Exposure to *Fagales* pollen in atopic individuals developing Bet v 1-specific IgE with variable degrees of cross-reactivity to the soybean PR-10 protein Gly m 4 after consumption of mildly processed soy products (soy protein powder, soy milk, etc.).

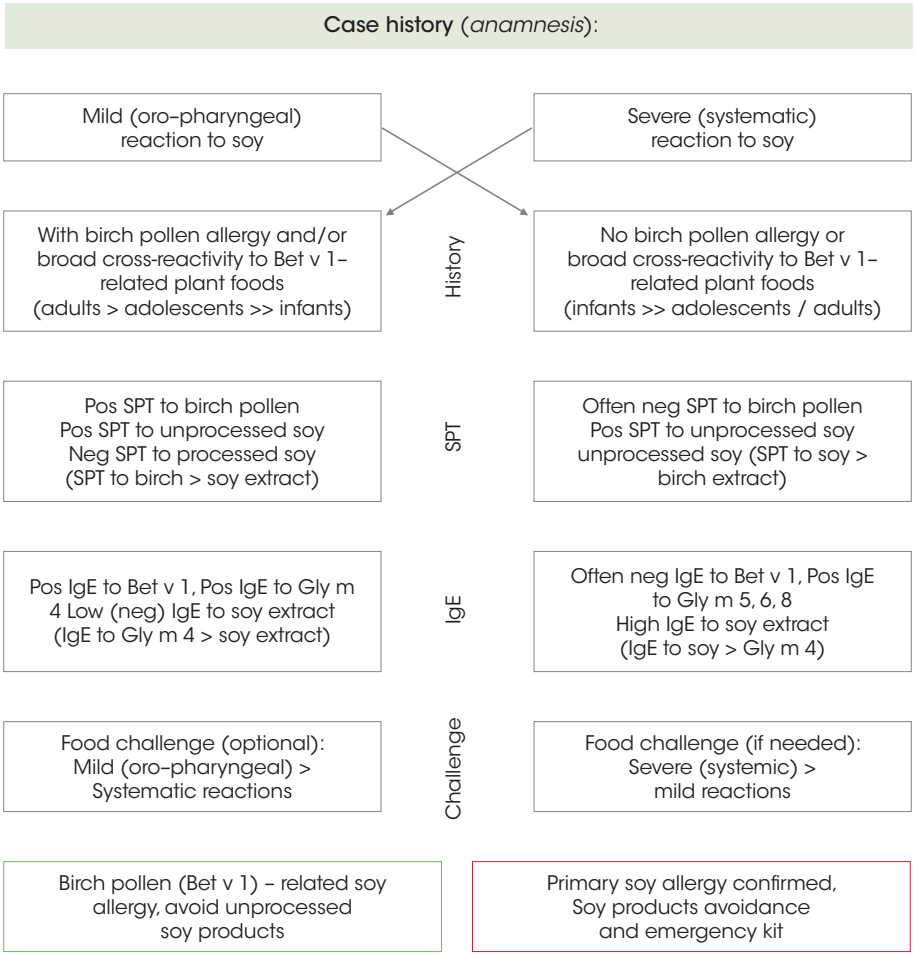
  C) Massive exposure to dust from unprocessed soybeans could induce IgE-mediated sensitisation to hull allergens (Gly m 1, Gly m 2).

Table of available allergens for IgE diagnosis of soy allergy. #Soy *(Glycine max)*.

Allergen#	Clinical relevance / Cross - reactivity
Gly m 4	Masks the differentiation between food reactions to stable allergens (i.e., Gly m 5 and Gly m 6) and cross-reactions to the Bet v 1-homologue in soy.
Gly m 5	These allergens are well-represented in soy extracts and are associated with severe allergic reactions to soy in children and adults.
Gly m 6	

B17 Soy Allergy

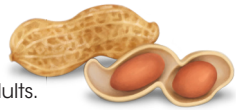
Diagnostic algorithm for soy allergy:



Diagnostic algorithm in soy-related allergic reactions (representing food allergy class II in left column and class I in right column). Arrows indicate that mild as well as severe reactions can be associated with different clinical features. Specific questions, proper interpretation of sensitisation tests (i.e., SPT and IgE), and optional food challenges help establish the diagnosis of soy allergy. Working hypothesis: Based on soy-related clinical patterns A–C. SPT; Skin Prick Test

Peanut Allergy B18

Key points:



- IgE reactivity to individual peanut allergens is a valuable tool for the clinician to diagnose and manage peanut allergy in children and adults.

Tips for molecular diagnosis

- Knowledge of the allergen to which the patient is sensitised can help to predict the severity of the allergic reaction and the prognosis for the patient.
- Sensitisation to seed storage proteins, which have high stability to thermal processing, (Ara h 1, 2, 3 and 6) is associated with severe allergic reactions.
- Labile proteins, Ara h 5 and 8, are less likely to cause severe reactions.

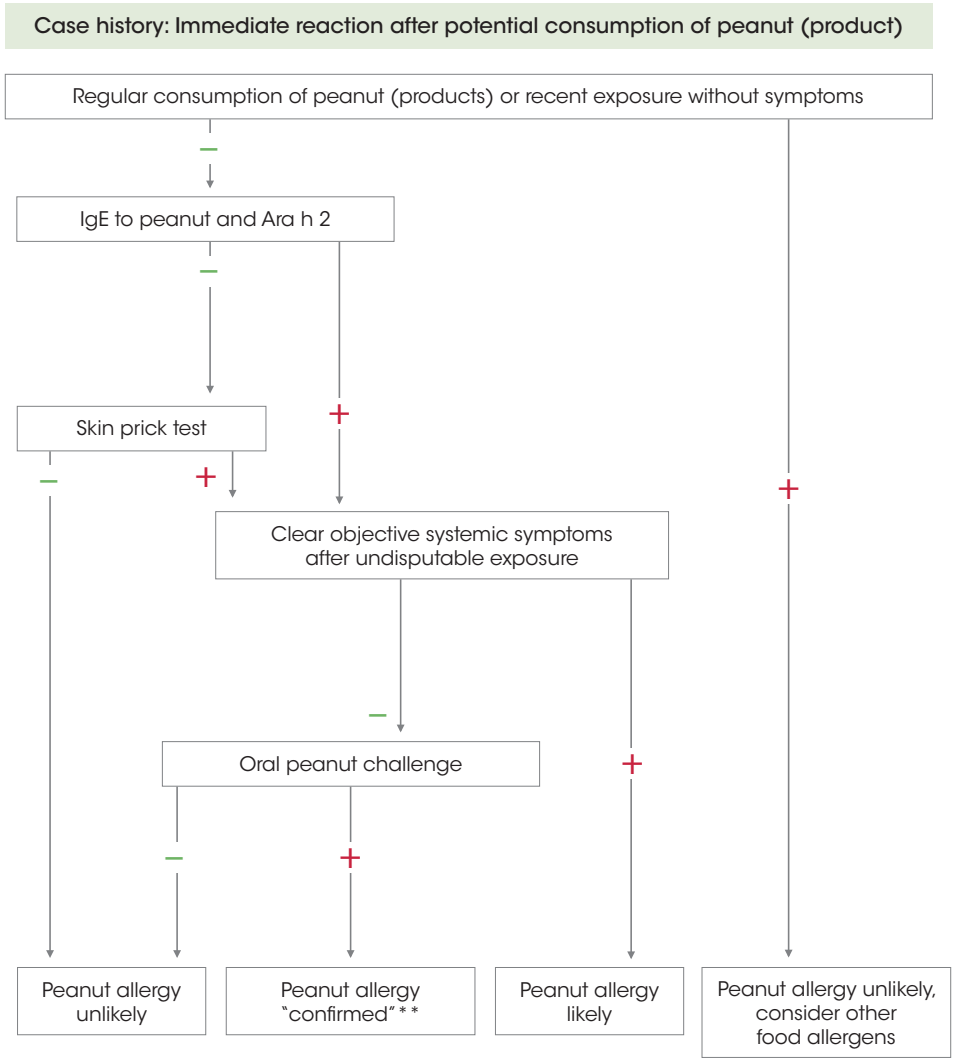
Table of peanut allergens

Allergen	Protein family	Other names	Molecular weight (kDa)	Heat stability
Ara h 1	Vicillin	7S globulin	64	Yes
Ara h 2	2S albumin	Conglutin	17	Yes
Ara h 3	Legumin	Glycinin, 11S globulin	60,37 (fragment)*	Yes
Ara h 4	Renamed to Ara h 3.02, number not available for future submissions			
Ara h 5	Profilin		15	No
Ara h 6	2S albumin	Conglutin	15	Yes
Ara h 7	2S albumin	Conglutin	15	Yes
Ara h 8	Bet v 1	Pathogenesis-related protein	17	No
Ara h 9	nsLTP-1		9.8	Yes
Ara h 10	Oleosin		16	Yes
Ara h 11	Oleosin		14	Yes
Ara h 12	Defensin		8 (reducing)*, 12 (non reducing)*, 5.184 (mass)*	To be expected
Ara h 13	Defensin		8 (reducing)*, 11 (non reducing)* 5.472 (mass)*	To be expected
Ara h 14	Oleosin		17.5	Yes
Ara h 15	Oleosin		17	Yes
Ara h 16	nsLTP-2		8.5	Yes
Ara h 17	nsLTP-1		11	Yes
Ara h 18	Cyclophilin-peptidyl-propyl cis-trans isomerase		21	???

*which molecular mass is indicated e.g. estimated by SDS-PAGE or theoritical molecular mass.
Allergens marked in bold are available for diagnosis.

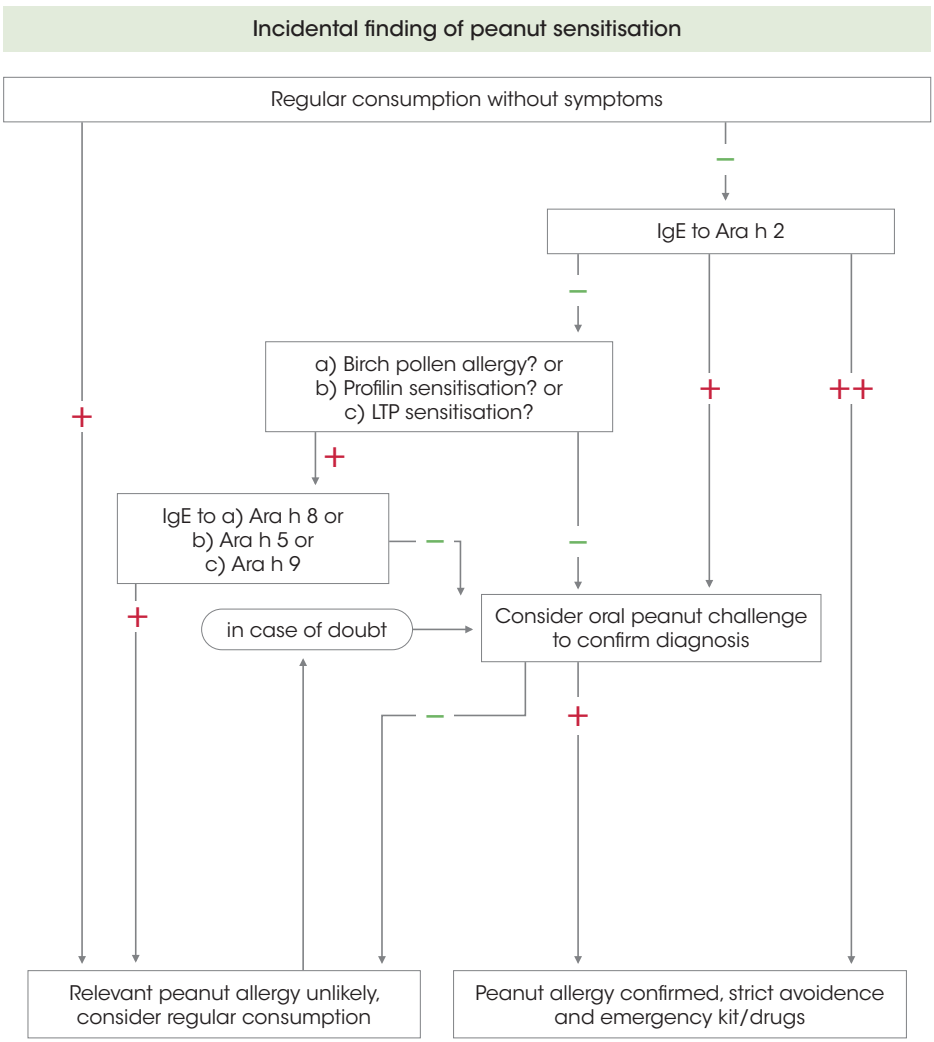
B18 Peanut allergy

Diagnostic algorithm for peanut allergy in a clinical setting:
Clear history of immediate reaction to peanut:



Peanut allergy B18

Diagnostic algorithm for peanut allergy in a clinical setting:
Uncertain peanut allergy history:



B19 Tree nut and seed allergies

Key points:

- Tree nuts, seeds and legumes are in fact all seeds, and the same allergen families are found in these foods.
- Co-sensitisation and *in vitro* cross-reactivity are often not clinically relevant, but cross-reactivity can occur *in vivo*.
- While clinically relevant sensitisation to pistachio and pecan nut usually implies clinically relevant sensitisation to cashew nut and walnut, respectively, the reverse is not always the case.

Tips for molecular diagnosis

- Sensitisation to Bet v 1 homologues such as Cor a 1 and Jug r 5 occurs mainly in the adult population of the Northern hemisphere (birch pollen endemic areas) and it often results in no or mild symptoms.
- Sensitisation to nsLTPs with peach Pru p 3 as a primary sensitiser occurs mainly in the Mediterranean region. However, the number of cases is increasing in Northern Europe
- Sensitisation to the hazelnut 2S albumin Cor a 14 is associated with severe allergic reactions, and such associations may also exist for 2S albumins of other tree nuts and seeds (e.g., Jug r 1, Ana o 3, Ses i 1).

Identified tree nut allergens. Overview of the different tree nut allergens divided into protein families.

Source	Seed storage proteins			Pathogenesis-related proteins		Profilins	Oleosins	Others
	2S albumins	7S albumins	11S globulins	PR-10 proteins Bet v 1-homologue	PR-14 proteins nsLTPs			
Hazelnut *Corylus avellana*	**Cor a 14**	**Cor a 11**	**Cor a 9**	**Cor a 1**	**Cor a 8**	**Cor a 2**	Cor a 12 Cor a 13 Cor a 15	
Almond *Prunus dulcis*	Pru du 2S albumin Pru du AP[4]	Pru du 8[3]	Pru du 6	**Pru du 1**	**Pru du 3**	Pru du 4		Pru du 2[1] Pru du 5[2]
Cashew nut *Anacardium occidentale*	**Ana o 3**	Ana o 1	**Ana o 2**					
Pistachio *Pistacia vera*	**Pis v 1**	**Pis v 3**	**Pis v 2** Pis v 5					Pis v 4[5]
Walnut *Juglans regia*	**Jug r 1**	**Jug r 2** Jug r 6	**Jug r 4**	Jug r 5	**Jug r 3** Jug r 8	Jug r 7		
Pecan nut *Carya illinoinensis*	Car i 1	Car i 2	Car i 4					
Brazil nut *Bertholletia excelsa*	**Ber e 1**		Ber e 2					
Macademia nut *Macademia integrifolia*		Mac i 1	Mac i 2		MiAMP2a			
Pine nut *Pinus pinea*	Pin p 1	Pin p vicilin						Pin p 17 kDa[6]
Coconut *Cocos nucifera*		Coc n 1 Coc n 2	Coc n 4			Coc n 5		

Bold font indicates the availability on commercial diagnostic platforms; ns LTP: non-specific lipid transfer protein, PR10: pathogenesis-related protein 10, 1: Thaumatin, 2: Ribosomal protein P2, 3: Antimicrobial seed storage protein, 4: conglutin, 5: Mn superoxide dismutase, 6: not known yet

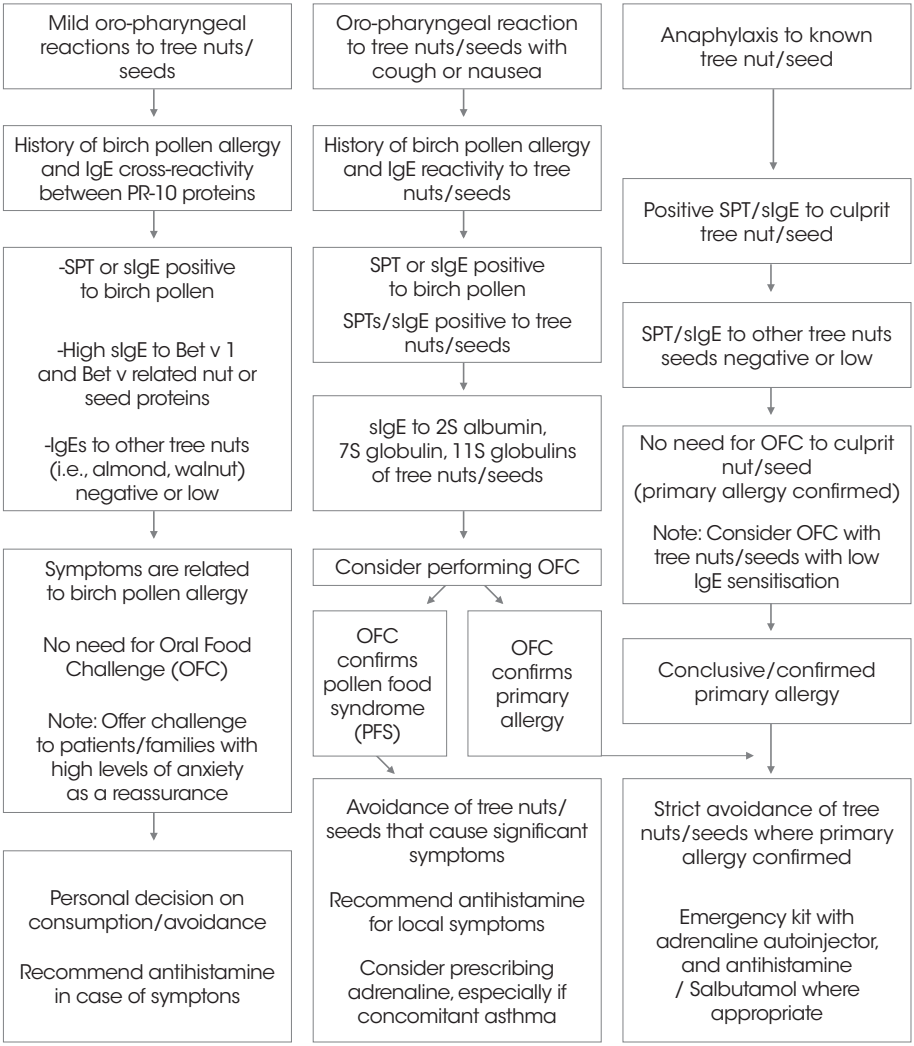
Tree nut and seed allergies B19

Identified seed allergens. Overview of the different seed allergens divided by protein families.

Source	Seed storage proteins			Pathogenesis-related proteins		Profilins	Oleosins	Others
	2S albumins	7S albumins	11S globulins	PR-10 proteins Bet v 1-homoloque	PR-14 proteins nsLTPs			
Sesame *Sesamum indicium*	Ses i 1 Ses i 2	Ses i 3	Ses i 6 Ses i 7			Ses i 8	Ses i 4 Ses i 5	
Mustard seed *Sinapis alba*	Sin a 1		Sin a 2		Sin a 3	Sin a 4		
Sunflower seed *Helianthus annuus*	Hel a 2S albumin				Hel a 3	Hel a 2		Hel a 4[4]
Pumpkin seed *Cucurbita maxima*	Cuc ma 5		Cuc ma 4			Cuc ma 2		
Poppy seed *Papaver somniferum*				Pap s 1		**Pap s 2**		Pap s 34kDa[5]
Buckwheat *Fagopyrum esculentum*	**Fag e 2**	Fag e 3 Fag e 4 Fag e 5	Fag e 1[4]					Fag e 10kDa[2] Fag e TI[3]
Flaxseed *Linum usitatissimum*	Lin u 1							

Bold font indicates the availability on commercial diagnostic platforms; ns LTP: non-specific lipid transfer protein, PR10: pathogenesis-related protein 10, 1: Defensin, 2: Alpha-amylase inhibitor, 3: Trypsin inhibitor, 4: 13S globulin, legumin-like protein, 5: not known yet. Chia seed not available.

B19 Tree nut and seed allergies



Diagnostic work-up in tree nut, peanut and/or seed-related allergic reactions. Arrows indicate potential diagnostic steps.

Hymenoptera venom allergy

B20
B21

Key points:

CRD in Hymenoptera venom allergy aims to streamline therapeutic decisions and is recommended:

- In case of multiple positive test results with different venoms to discriminate between true sensitization and cross-reactivity.
- For diagnosis in patients with an inconclusive history.
- In cases of discrepancies between clinical history and classical diagnostic results to identify the culprit insect(s).
- In case of negative test results with different venoms despite a convincing clinical history due to potentially enhanced sensitivity of CRD (e.g. in mastocytosis patients).

Tips for molecular diagnosis

- sIgE to Api m 1, Api m 3, Api m 4 and Api m 10 indicates primary bee venom allergy.
- sIgE to Api m 2 may be a helpful marker to detect primary bee venom allergy. Interpret results with care in the context of clinical history.
- sIgE to Api m 5 does not exclude primary vespid venom allergy.
- sIgE to Ves v 1 / Pol d 1 and Ves v 5 / Pol d 5 indicate primary vespid venom allergy.
- sIgE to Ves v 1 / Pol d 1 and Ves v 5 / Pol d 5 is no reliable marker to dissect between primary sensitization to yellow jacket and /or European paper wasp venom.

B20 B21 Hymenoptera venom allergy

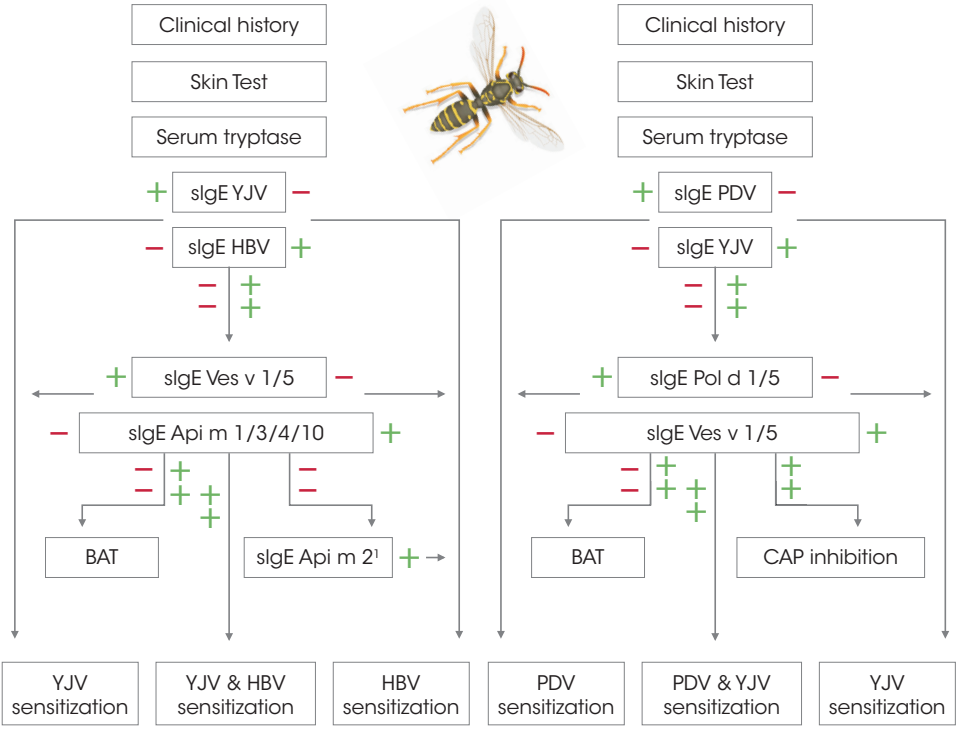
Characteristics of Hymenoptera venom allergens currently available for routine CRD.

Allergen	Significance
Honeybee venom (*Apis mellifera*)	
Api m 1 Phospholipase A2	Marker allergen for HBV sensitization; Allows discrimination between HBV and YJV/PDV sensitization
Api m 2 Hyaluronidase	Potential marker for HBV sensitization, due to limited cross-reactivity with Ves v 2 and Pol d 2 in the absence of CCDs (Cross-reactivity with Ves v 2 and Pol d 2 cannot be fully excluded)
Api m 3 Acid phosphatase	Marker allergen for HBV sensitization; Allows discrimination between HBV and YJV/PDV sensitization; Valuable marker allergen to diagnose HBV allergy in Api m 1-negative patients
Api m 4 Melittin	Marker allergen for HBV sensitization; Allows discrimination between HBV and YJV/PDV sensitization; Putative marker allergen for increased risk of VIT side-effects during up-dosing
Api m 5 Dipeptidyl peptidase IV	High cross-reactivity with Ves v 3 and Pol d 3 prevents its use as a marker allergen; In cases where HBV allergy is highly likely, but other tests have turned out negative, the use of Api m 5 still remains a diagnostic option to be considered
Api m 10 Icarapin	Marker allergen for HBV sensitization; Allows discrimination between HBV and YJV/PDV sensitization; Valuable marker allergen to diagnose HBV allergy in Api m 1-negative patients; Dominant Api m 10 sensitization suggested as putative marker for risk of VIT failure
Yellow jacket venom (*Vespula vulgaris*)	
Ves v 1 Phospholipase A1	Marker allergen for YJV sensitization; Allows discrimination between YJV and HBV sensitization; High cross-reactivity with Pol d 1 prevents its use as a marker allergen to discriminate between YJV and PDV sensitization
Ves v 5 Antigen 5	Marker allergen for YJV sensitization; Allows discrimination between YJV and HBV sensitization; High cross-reactivity with Pol d 5 prevents its use as a marker allergen to discriminate between YJV and PDV sensitization
European paper wasp venom (*Polistes dominula*)	
Pol d 1 Phospholipase A1	Marker allergen for PDV sensitization; Allows discrimination between PDV and HBV sensitization; High cross-reactivity with Ves v 1 prevents its use as a marker allergen to discriminate between PDV and YJV sensitization
Pol d 5 Antigen 5	Marker allergen for PDV sensitization; Allows discrimination between PDV and HBV sensitization; High cross-reactivity with Ves v 5 prevents its use as a marker allergen to discriminate between PDV and YJV sensitization

CCDs, cross-reactive carbohydrate determinants; HBV, honeybee venom; PDV, Polistes dominula venom; YJV, yellow jacket venom (Vespula spp. venom).

Hymenoptera venom allergy

B20
B21



Diagnostic algorithms for component-resolved diagnostics of (A) honeybee venom (HBV) and yellow jacket venom (YJV) allergy and (B) YJV and European paper wasp venom (PDV) allergy. Die algorithm in (A) can also be used to discriminate between HBV and PDV allergy using the PDV homologues of Ves v 1 and Ves v 5, Pol d 1 and Pol d 5. A plus indicates a positive, and a minus indicates a negative test result. [1]The HBV allergen Api m 2 might show limited cross-reactivity to homologous allergens of YJV and PDV that are not commercially available, so that a positive test result does not necessarily exclude YJV or PDV allergy. For the use of the HBV allergen Api m 5 for diagnosis please refer to the table in this chapter. Despite the potential of component-resolved diagnostics, clinical history, skin tests and the measurement of venom-sIgE and serum tryptase build an indispensable basis for accurate diagnosis in Hymenoptera venom allergy. Moreover, cellular tests such as basophil activation test (BAT) and CAP inhibition assays may be helpful diagnostic tools in dissecting primary sensitization.

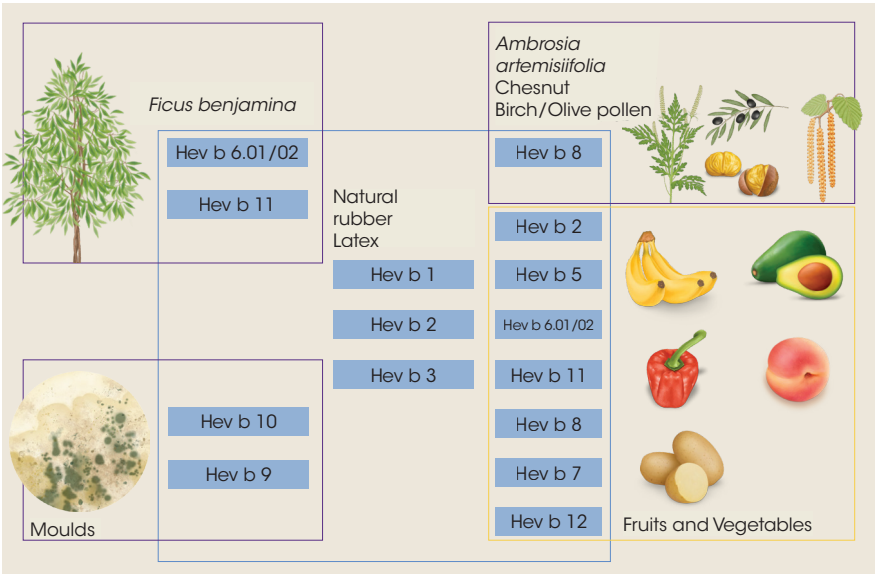
B22 Occupational allergy

Key points:

- More than 400 occupational sensitisers are identified, but only a limited number of them are characterized on the molecular level.
- Natural rubber latex (NRL) allergy is an excellent model for improving sIgE measurement with recombinant major allergens.
- Wheat flour proteins are allergens for 60-70% of symptomatic bakers, although other cereals like rye that is used frequently in Germany and northern Europe, barley, oats and corn, and non-cereal sources, enzymes and insects, may be involved.
- IgE-sensitisation profile in patients with baker's asthma showed great inter-individual variation

Tips for molecular diagnosis

- For diagnosis of wheat allergy due to baker's asthma, extract-based diagnostic is still recommended.
- Including baking enzymes into the test panel is highly recommended for diagnosis of baker's asthma.



[Figure 1] Molecular backround and association of latex-fruit/vegetable syndrome allergens with potential importance for cross-reactivity

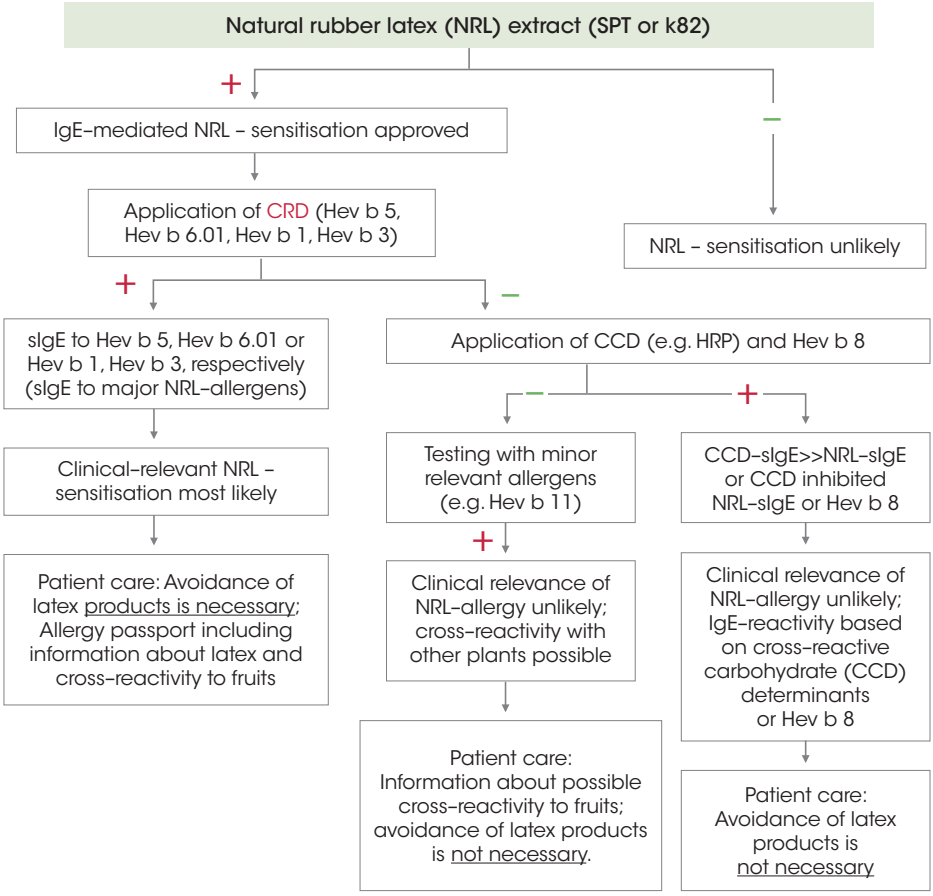
Occupational allergy B22

Table of available occupational plant and mold allergens (see also B07 and B22; for mammalian allergens, see B06, C04, and C07):

Allergen source	Protein	Relevance	Notes
Rice mold (*Aspergillus oryzae*)			
Asp o 21	α–amylase	Major allergen	Enzyme present in baking additives
Indian hemp (*Cannabis sativa*)			
Can s 3	nsLTP	Major allergen	Risk of likely-anaphylaxis to cannabis
Natural rubber latex (*Hevea brasiliensis*)			
Hev b 1	Rubber elongation factor	Major allergen in SB	
Hev b 3	Small rubber particle protein	Major allergen in SB	
Hev b 5	Acidic structural protein	Major allergen in HCW and important in SB	Potential cross-reactivity with fruits and vegetable allergens
Hev b 6.02	Hevein	Major allergen in HCW	Potential cross-reactivity with fruits and vegetable allergens
Hev b 7	Patatin-like	Minor allergen	Potential cross-reactivity with fruits and vegetable allergens
Hev b 8	Profilin	Minor allergen	Potential cross-reactivity with birch/olive pollen and fruits and vegetable allergens
Hev b 11	Class I chitinase	Minor allergen	Potential cross-reactivity with fruits and vegetable allergens
Wheat (*Triticum aestivum*)			
Tri a 14	nsLTP	Minor allergen in baker's asthma	
Tri a 19	Omega-5-gliadin	Not relevant for diagnosis of baker's asthma	omega-5-gliadin, involved in WDEIA and also important for the early childhood type I-wheat allergy

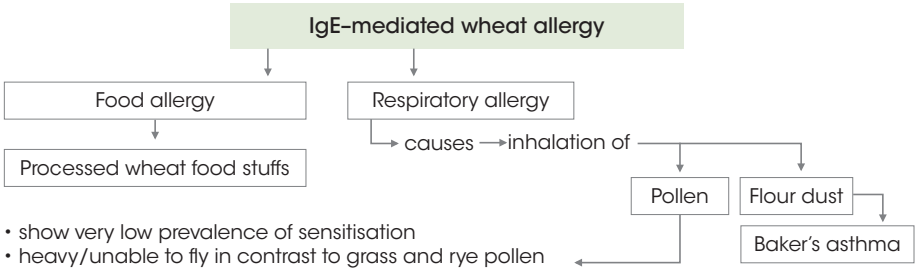
SB, spina bifida patients; HCW, health care workers; WDEIA, wheat dependent exercise-induced anaphylaxis

Diagnostic algorithm for natural rubber latex (type I allergy):

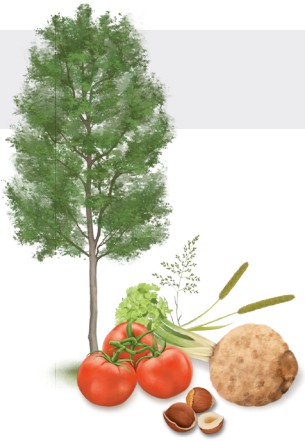


Occupational allergy B22

Different types of IgE-mediated wheat allergy (food allergy versus respiratory allergy):



C01 Profilins



Key points:

A) As an airborne allergen:

- Depending on pollen exposure, 5- 50% of pollen-allergic patients are sensitized to profilin.
- As a minor pollen allergen, sensitisation is almost always associated with the sensitisation to major pollen allergens (mainly grass pollen allergy).
- Clinical relevance is variable but potentially present.

B) As a plant food allergen:

- Up to 50% of sensitized patients may have food allergy, oral allergy syndrome in most cases.

Tips for molecular diagnosis

A) As an airborne allergen:

- On SPT most pollen sources score positive (Cypress and Pellitory mostly score negative).

B) As a plant food allergen:

- Oral provocation of food-allergic patients with low doses of purified profilin has proven to induce severe reactions in grass pollen (GP) allergic patients' resident in areas with high grass pollen exposure.
- Clinical reactivity to raw tomato, melon, watermelon, banana, and/or citrus fruits is typically associated with profilin hypersensitivity. Patients tolerate processed foods.

C) Natural rubber latex contains many allergenic proteins, including profilin (Hev b 8). Therefore, the crude extract of *Hevea brasiliensis* latex scores often positive in patients with multiple pollen sensitisation. Patients sensitised uniquely to profilin can undergo surgery without any risk as latex gloves and latex instruments lack this allergen.

Table of available allergens for IgE diagnosis of profilin allergy

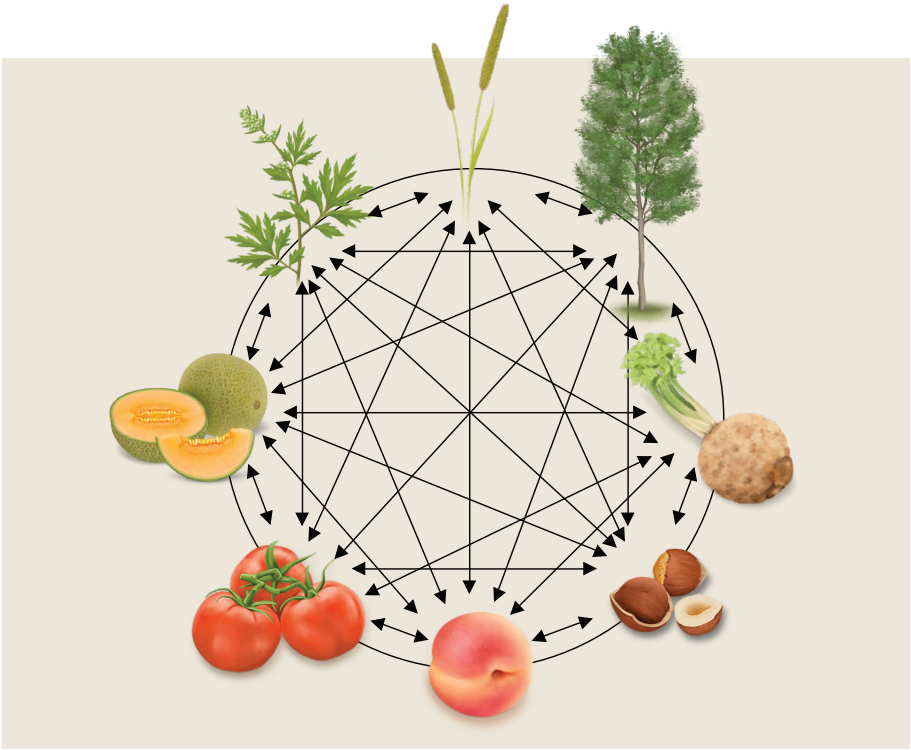
Profilins from pollen sources	
Allergen source	**Allergen**
Birch (*Betula pendula*)	Bet v 2
Timothy (*Phleum pratense*)	Phl p 12
Mugwort (*Artemisia vulgaris*)	Art v 4
Annual mercury (*Mercurialis annua*)	Mer a 1

Profilins from plant foods	
Allergen source	**Allergen**
Peach (*Prunus persica*)	Pru p 4

Table of additional tests

In vivo **diagnosis**	SPT using a commercial profilin-enriched date palm pollen extract (available only in Spain and Austria). The extract for skin testing is very close to that of the recombinant grass pollen profilin for *in-vitro* use (Phl p 12).
In vitro **tests**	There are different profilins available for *in vitro* diagnosis. In general, any vegetable profilin can identify profilin-positive patients. Whole *Parietaria judaica* and *Cupressus* pollen *in vitro* (and *in vivo*) diagnostics might not detect profilin positivity.

Cross-reactivity:



[Figure 1] – Cross-reactivity between profilins from different pollen sources and plant foods

C02 PR–10–like Allergens

Key points:

- The major birch pollen allergen Bet v 1 represents the archetype of all PR-10-like allergens and is the primary sensitiser in birch pollen endemic regions.
- The presence of homologous allergens in Fagales tree pollen explains the IgE cross-reactivity between pollen from hazel, alder, beech, oak, hornbeam and chestnut.
- Testing for Bet v 1-specific IgE is sufficient. The relevance of cross-reacting pollen or foods can be clinically clarified by seasonal and food-related symptoms without the need for further testing of Bet v 1 homologues.

Tips for molecular diagnosis

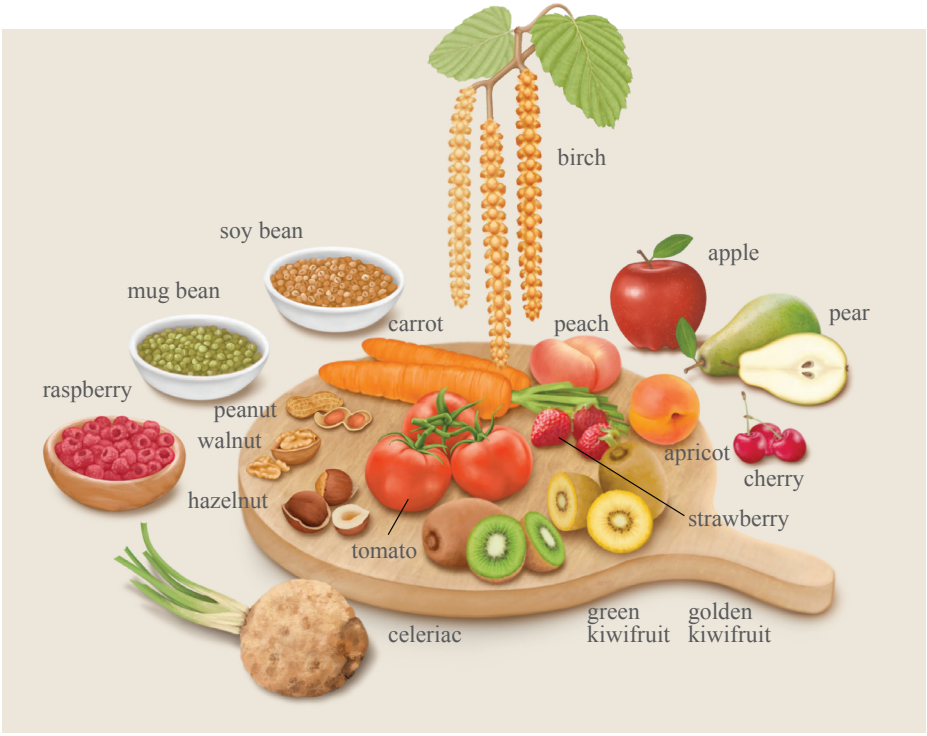
- Minute amounts of PR-10-like allergens in raw fruits, nuts, vegetables and legumes can induce patient-individual patterns of oropharyngeal symptoms and sometimes even severe allergic reactions in Bet v 1-sensitised individuals.

Table of commercially available allergens for IgE diagnosis of allergy to PR-10-like allergens

Allergen source	Allergen
Birch, *Betula pendula*	Bet v 1
Alder, *Alnus glutinosa*	Aln g 1
Hazel, *Corylus avellana*	Cor a 1.0101, Cor a 1.0103
Beech, *Fagus silvatica*	Fag s 1
Apple, *Malus domestica*	Mal d 1
Carrot, *Daucus carota*	Dau c 1
Celery, *Apium graveolens*	Api g 1
Peach, *Prunus persica*	Pru p 1
Soy bean, *Glycine max*	Gly m 4
Hazelnut, *Corylus avellana*	Cor a 1.0401
Peanut, *Arachis hypogea*	Ara h 8
Kiwi, *Actinidia deliciosa*	Act d 8

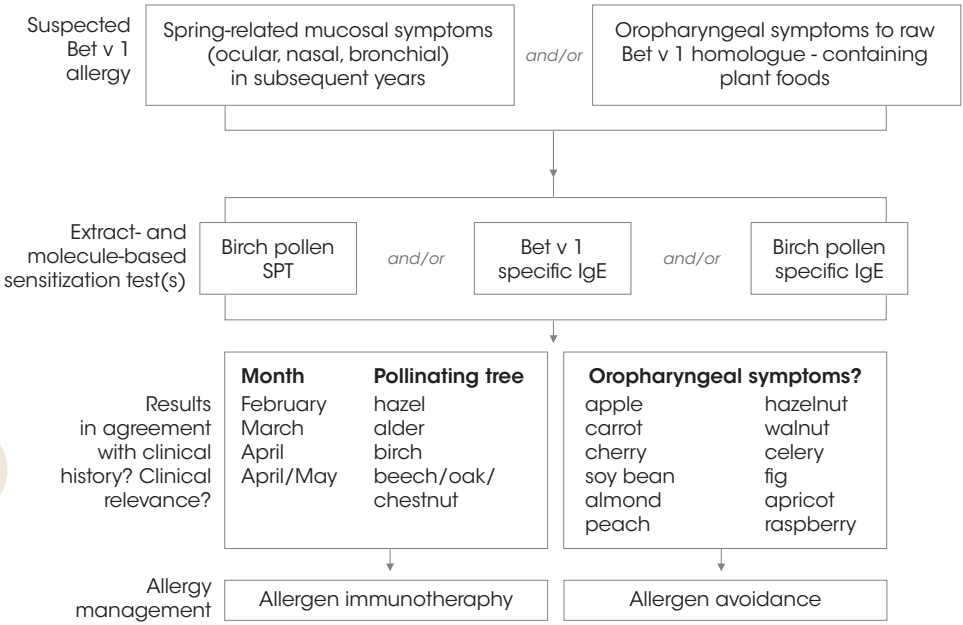
PR–10–like Allergens C02

Overview of Bet v 1-cross-reactive food sources containing PR-10-like allergens:



C02 PR–10–like Allergens

Diagnostic algorithm for suspected allergy to PR-10-like allergens



Clinical relevance

- Sensitization to the PR-10-like allergen Bet v 1 and its homologous proteins in pollen from Fagales tree species occurs worldwide except in South Africa and the tropics.
- Around half of all sensitized individuals will develop symptoms.
- Around 70% of birch pollen allergic individuals suffer from associated plant food allergy.
- Impact of IgE-cross-reactivity on clinical symptoms of food allergy is still unknown.

Non-specific lipid transfer proteins (nsLTP) C03

Key points:

- Most frequent type of food allergy in adults and adolescents in Southern European countries, while low prevalence in Central and Northern Europe.
- Severity of the reaction seems to be higher in monosensitised LTP patients and milder when patients are also sensitised to profilin, PR-10 or to pollen.
- Pru p 3, the major allergen of peach, plays a precursor role in the sensitisation to other nsLTP in most of the patients.

Tips for molecular diagnosis

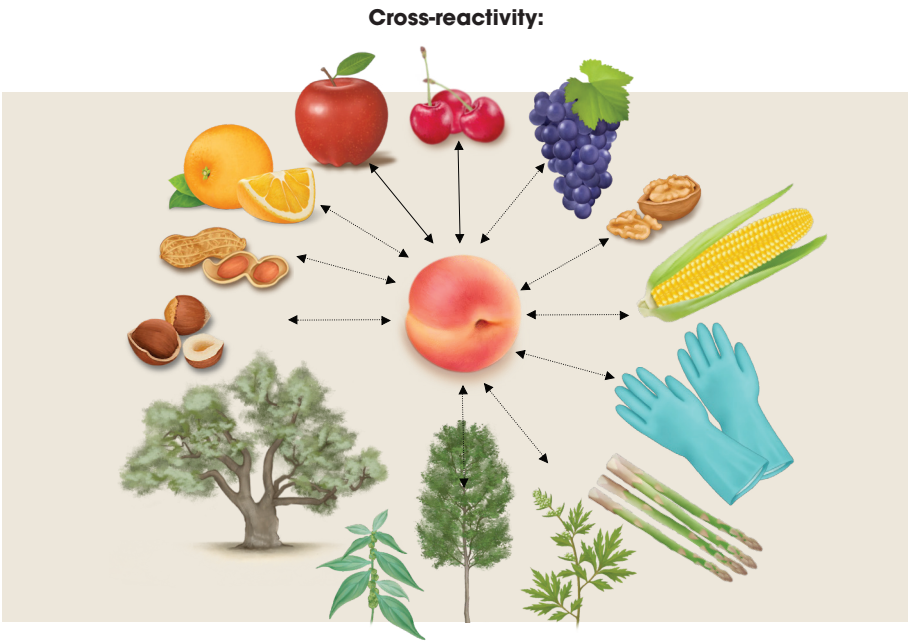
- The level of specific IgE to Pru p 3 does not correlate with the severity of reactions.
- Patients can present restricted IgE recognition to one LTP or a broad recognition spectrum (LTP syndrome).
- Most severe reactions are frequently associated with different cofactors such as NSAIDs intake or exercise.

Table of available components for IgE-diagnosis of nsLTP allergy.

Allergen source	Allergen	Cross-reactivity / Sensitisation
PLANT FOODS		
Peach (*Prunus persica*)	Pru p 3	Pru p 3 sensitisation correlates with the development of allergic reactions to a higher number of plant-foods than Pru p 1 and Pru p 4 sensitisation alone.
Apple (*Malus domestica*)	Mal d 3	IgE cross-reactivity has been observed within the Rosaceae family (high degree) and with citrus fruits, grapes, tomatoes, vegetables (asparagus, lettuce, etc.), nuts (hazelnut, walnut, peanut, etc.), maize, onion, carrot, rice, and spelt (partial cross-reactivity). Hemp nsLTP can start sensitization by a different route than Pru p 3.
Hazelnut (*Corylus avellana*)	Cor a 8	
Walnut (*Juglans regia*)	Jug r 3	
Peanut (*Arachis hypogaea*)	Ara h 9	
Wheat (*Triticum aestivum*)	Tri a 14	
Kiwi (*Actinidia deliciosa*)	Act d 10	
Corn (*Zea mays*)	Zea m 14	
Celery (*Apium graveolens*)	Api g 2, 6	
Grape (*Vitis vinifera*)	Vit v 1	
Tomato (*Solanum lycopersicum*)	Sola l 6	
Hemp (*Cannabis sativa*)	Can s 3	

C03 Non-specific lipid transfer proteins (nsLTP)

POLLEN		
Mugwort (*Artemisia vulgaris*)	Art v 3	Allergens from Parietaria and Olea show absent cross-reactivity with Pru p 3. Parietaria pollinosis is often linked to asthma. Ole e 7 has been reported to identify a severe allergic olive pollen phenotype, with an increased risk of asthma and side reactions during immunotherapy. Art v 3 and Pla a 3 display partial cross-reactivity with Pru p 3. Artemisia or Platanus should always be considered for potential cross-reactivity.
Olive (*Olea europoea*)	Ole e 7	
Plane (*Platanus acerifolia*)	Pla a 3	
Parietaria (*Parietaria judaica*)	Par j 2	
OTHERS		
Cannabis	Can s 3	In some European regions, Can s 3 is considered the major allergen (approximately 70%).



[Figure 1] – Cross-reactivity due to nsLTP molecules between different allergenic sources. Continuous lines indicate a high degree of cross reactivity among the Rosaceae family. Dashed lines indicate partial cross-reactivity.

Non-specific lipid transfer proteins (nsLTP)

C03

Diagnostic algorithms using molecular IgE diagnostics in the case of positive SPT/extract-based IgE test to A) peanut; B) peach; C) hazelnut or D) apple.

A

Peanut

- Ara h 9 +
Ara h 1/2/3 +/-
Ara h 8 - → Primary sensitisation
Risk of severe reactions
- Ara h 9 -
Ara h 1/2/3 +
Ara h 8 -
- Ara h 9 -
Ara h 1/2/3 -
Ara h 8 + → Secondary sensitisation
Cross-reactivity with birch pollen
Local reactions (OAS)

B

Peach

- Pru p 3 +
Pru p 1 -
Pru p 4 - → Primary sensitisation
Risk of severe reactions
- Pru p 3 +
Pru p 1 -
Pru p 4 +/- → Co-sensitisation
Protection against severe
systemic reactions
- Pru p 3 –
Pru p 1 +
Pru p 4 +/- → Secondary sensitisation
Cross-reactivity with birch pollen
Local reactions (OAS)

C

Hazelnut

- Cor a 8 +
Cor a 9/14 +/-
Cor a 1 - → Primary sensitisation
Risk of severe reactions
- Cor a 8 –
Cor a 9/ 14 +
Cor a 1 -
- Cor a 8 -
Cor a 9/14 -
Cor a 1 + → Secondary sensitisation
Cross-reactivity with birch pollen
Local reactions (OAS)

D

Apple

- Mal d 3 +
Mal d 1 –
Mal d 4 +/- → Primary sensitisation
Risk of severe reactions
- Mal d 3 –
Mal d 1 +
Mal d 4 +/- → Secondary sensitisation
Cross-reactivity with birch pollen
Local reactions (OAS)

C04 Serum albumins

Key points:

- Highly conserved sequences with high amino acid sequence identity.
- Minor respiratory allergens of animal dander.
- Food allergens of milk and meat.
- May elicit severe symptoms upon ingestion of uncooked or boiled food.
- Allergen implicated in pork-cat and bird-egg syndrome.

Tips for molecular diagnosis

- As mammalian serum albumins are highly cross-reactive, the choice of serum albumins included in the determination of allergen-specific IgE should be guided by clinical history.
- Specific IgE are mostly positive to Can f 3 and Fel d 2, whereas IgE-reactivity against Bos d 6 and Sus s 1 are less frequent.
- Gal d 5 should be considered as an independent allergen, as homology to mammalian albumins is relatively low.

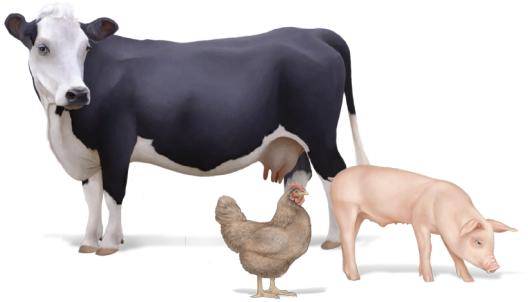
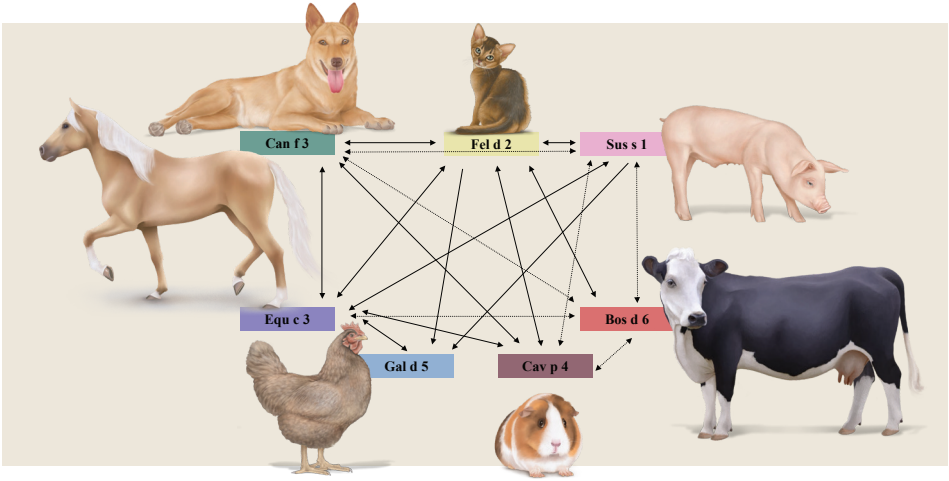


Table of available components for IgE-diagnosis of allergy related to animal products and albumin- containing sources

Cat	Fel d 2, albumin cross-reactive with meat/milk albumin, and other animal dander albumins.
Cattle	Bos d 6, albumin present in milk and meat and in cell culture media; Cross-reactive with other dander and milk albumins. Bos d 4, Bos d 5, Bos d 8, marker allergens for milk allergy.
Dog	Can f 3, albumin cross-reactive with meat/milk albumin, and other animal dander albumins.
Horse	Equ c 3, albumin cross-reactive with meat/milk albumin, and other animal dander albumins.
Pig	Sus s 1, albumin present in porcine meat, cross-reactive with other animal dander albumins.
Alpha-gal	Carbohydrate present in mammalian meat and dairy products, marker allergen of the alpha-gal syndrome.

Serum albumins C04



[Figure 1] – Cross-reactivities among allergenic serum albumins. All mammalian serum albumins are potentially IgE-cross-reactive. Clinical cross-reactivity between mammalian Fel d 2 and Sus s 1 and avian Gal d 5 are rare and have been documented only from mammal to bird. Solid lines represent documented IgE-cross-reactivity, and dashed lines show hypothetical cross-reactivity.

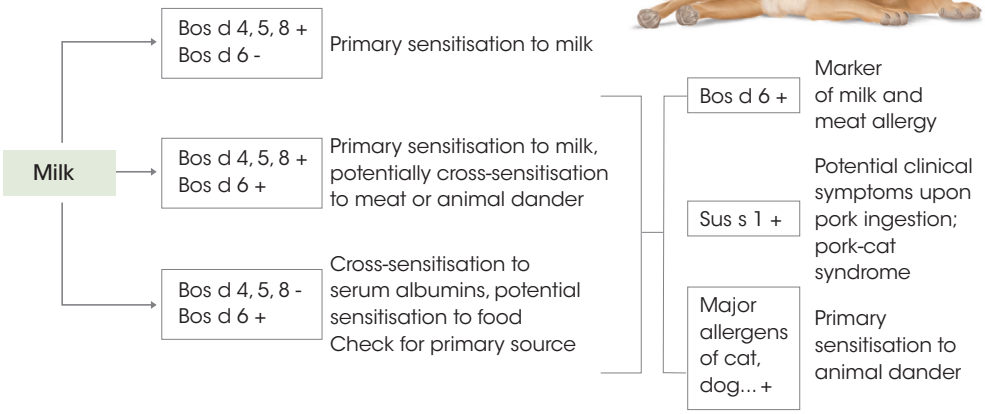
Diagnostic algorithms for component-resolved diagnosis of allergy to cat dander, milk or meat

Cat dander

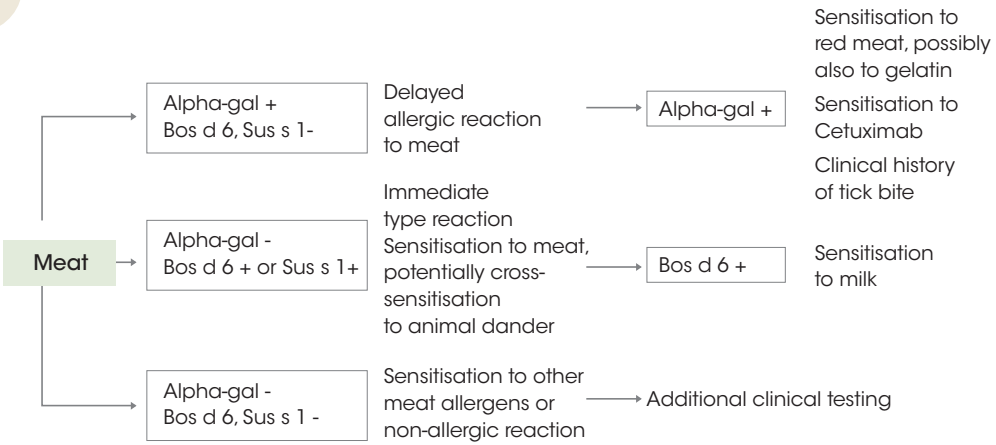
- Fel d 1 + / Fel d 2/4 - → Primary sensitisation to cat
- Fel d 1 + / Fel d 2/4 + → Primary sensitisation to cat, potentially cross-sensitisation or co-sensitisation to other animal or food
- Fel d 1 - / Fel d 2/4 + → Cross-sensitisation to serum albumins and lipocalins, potential sensitisation to food Check for primary source
  - Bos d 6 + → Marker of milk and meat allergy
  - Sus s 1 + → Potential clinical symptoms upon pork ingestion; pork-cat syndrome

[Figure 2] – Added value of the use of single allergens in the case of a positive IgE test to cat dander.

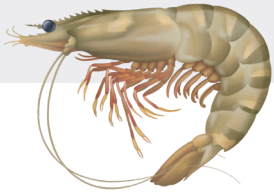
C04 Serum albumins



[Figure 3] – Added value of the use of single allergens in the case of a positive IgE test to milk.



[Figure 4] – Added value of the use of single allergens in the case of a positive IgE test to meat.



Tropomyosin C05

Key points:

- Tropomyosins are thermostable proteins with a high allergenicity potential and high degree of immunological and clinical cross-reactivity between different species.
- Due to their extensive cross-reactivity, they are considered pan-allergens.
- They are the main allergens inducing seafood allergy in most but not all patients. Sensitised patients might tolerate seafood, but this must be proven by food challenge.
- Immunotherapy is not currently available but there are studies to construct modified molecules for their use.

Tips for molecular diagnosis

- The shrimp tropomyosin is one of the most clinically relevant allergenic tropomyosins.
- Diagnostic steps could be starting with SPT with the whole extract, and detecting IgE antibodies to the extract, tropomyosin and other shellfish allergens, such as Pen m 2 (Arginine kinase), Pen m 4 (Sarcoplasmic calcium-binding protein), Pen m 3 (Myosin light chain), and Pen m 6 (Troponin C).

Table of available components for IgE-diagnosis of allergy to tropomyosins

Allergen source	Allergen
House dust mites *Dermatophagoides pteronyssinuss*	Der p 10
Storage mites *Blomia tropicalis*	Blo t 10
Shrimp *Penaeus aztecus*	Pen a 1
Shrimp *Peneaus monodon*	Pen m 1
Cockroach *Blattella germanica*	Bla g 7
American cockroach *Periplaneta americana*	Per a 7
Anisakis *Anisakis simplex*	Ani s 3
Storage mites *Blomia tropicalis*	Blo t 10
Shrimp *Peneaus monodon*	Pen m 1

C05 Tropomyosin

Table of some tropomyosins identified.

Species	Allergen
Aedes aegypti (Yellow fever mosquito)	Aed a 10
Anisakis simplex (Herring worm)	Ani s 3
Ascaris lumbricoides (Common roundworm)	Asc l 3
Blattella germanica (German cockroach)	Bla g 7
Blomia tropicalis (Storage mite)	Blo t 10
Bombyx mori (Silk moth)	Bomb m 3
Charybdis feriatus (Crab)	Cha f 1
Chironomus kiiensis (Midge)	Chi k 10
Chortoglyphus arcuatus (Storage mite)	Cho a 10
Coptotermes formosanus (Formosan subterranean termite)	Copt f 7
Crangon crangon (North Sea shrimp)	Cra c 1
Crassostrea angulata (Portuguese oyster)	Cra a 1
Crassostrea gigas (Pacific oyster)	Cra g 1
Dermatophagoides farinae (American house dust mite)	Der f 10
Dermatophagoides pteronyssinus (European house dust mite)	Der p 10
Exopalaemon modestus (White legged freshwater shrimp)	Exo m 1
Haliotis laevigata x Haliotis rubra (Jade tiger abaolone)	Hal l 1
Helix aspersa [Cornu aspersum] (Brown garden snail)	Hel as 1
Homarus americanus (American lobster)	Hom a 1
Lepidoglyphus destructor (Storage mite)	Lep d 10

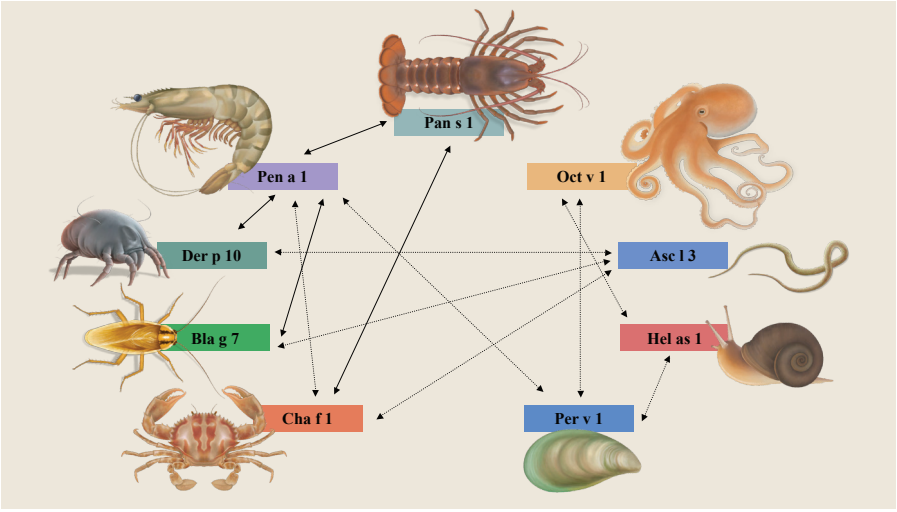
Species	Allergen
Lepisma saccharina (Silverfish)	Lep s 1
Litopenaeus vannamei (White shrimp)	Lit v 1
Macrobrachium rosenbergii (giant freshwater prawn)	Mac r 1
Melicertus latisulcatus (King prawn)	Mel l 1
Metapenaeus ensis (Shrimp)	Met e 1
Oreochromis mossambicus (Mozambique tilapia)	Ore m 4
Pandalus borealis (Northern shrimp)	Pan b 1
Pangasianodon hypophtalmus (Striped catfish)	Pan h 4
Panulirus stimpsoni (Spiny lobster)	Pan s 1
Penaeus aztecus (Brown shrimp)	Pen a 1
Penaeus indicus (Shrimp)	Pen i 1
Penaeus monodon (Black tiger shrimp)	Pen m 1
Periplaneta americana (American cockroach)	Per a 7
Portunus pelagicus (Blue swimmer crab)	Por p 1
Procambarus clarkii (Red swamp crayfish)	Pro c 1
Saccostrea glomerata (Sydney rock oyster)	Sac g 1
Salmo salar (Atlantic salmon)	Sal s 4
Scylla paramamosain (Mud crab)	Scy p 1
Todarodes pacificus (Japanese flying squid)	Tod p 1
Tyrophagus putrescentiae (Storage mite)	Typ p 10

Tropomyosin C05

List of clinically relevant tropomyosins

Allergen source	Allergen
Brown shrimp (*Penaeus aztecus*)	Pen a 1
Northern Red Shrimp (*Pandalus borealis*)	Pan b 1
Giant tiger prawn (*Penaeus monodon*)	Pen m 1
European Shrimp (*Litopenaeus vannamei*)	Lit v 1
Common Shrimp (*Crangon Crangon*)	Cra c 1
Spiny lobster (*Panulirus stimpsoni*)	Pan s 1
Common crab (*Charybdis feriatus*)	Cha f 1
Blue swimmer crab (*Portunus pelagicus*)	Por p 1
Brown garden snail (*Helix aspersa*)	Hel as 1
Green mussel (*Perna viridis*)	Per v 1
Common Octopus (*Octopus vulgaris*)	Oct v 1

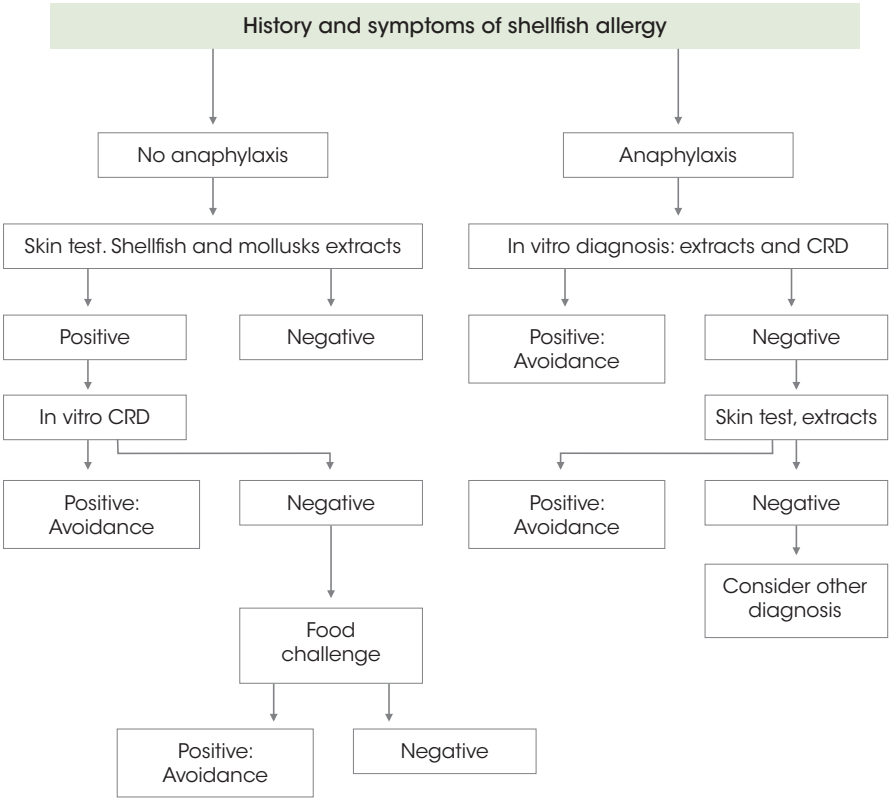
Allergen source	Allergen
Japanese flying squid (*Todarodes pacificus*)	Tod p 1
Pacific cupped oyster (*Crassostrea gigas*)	Cra g 1
Abalone (*Haliotis diversicolor*)	Hal d 1
House dust mite (*Dermatophagoides farinae*)	Der f 10
House dust mite (*Dermatophagoides pteronyssinus*)	Der p 10
Storage mite (*Blomia tropicalis*)	Blo t 10
American cockroach (*Periplaneta americana*)	Per a 7
German cockroach (*Blattella germanica*)	Bla g 7
Anisakis (*Anisakis simplex*)	Ani s 3
Roundworm (Ascaris lumbricoides)	Asc l 3



[Figure 1] – Cross-reactivity among allergenic tropomyosins from several sources. Lines represent documented IgE-cross-reactivity, dotted lines represent potential IgE cross-reactivity based on high sequence identities.

C05 Tropomyosin

Diagnostic algorithm for shellfish allergy. In vitro tests for IgE to molecular allergens (CRD) include Pen a 1, Pen m 2, and Pen m 4.



Polcacins C06

Key points:

- Polcalcins are EF-hand calcium-binding proteins.
- There is an extensive cross-reactivity of IgE between pollen polcalcins, but they are not present in plant foods.
- The most representative pollen polcalcin and the first cloned is Phl p 7 from *Phleum pratense* (timothy grass).

Tips for molecular diagnosis

- Specific IgE testing to pollen polcalcins can be performed with any member of the family.
- Polcalcins can be considered as markers of polysensitization with unknown clinical relevance for respiratory symptoms.
- Double positivity to polcalcin and profilin has been associated to real polysensitization and disease evolution and consequently bad clinical prognosis.

Table of available components to detect IgE sensitization to polcalcins

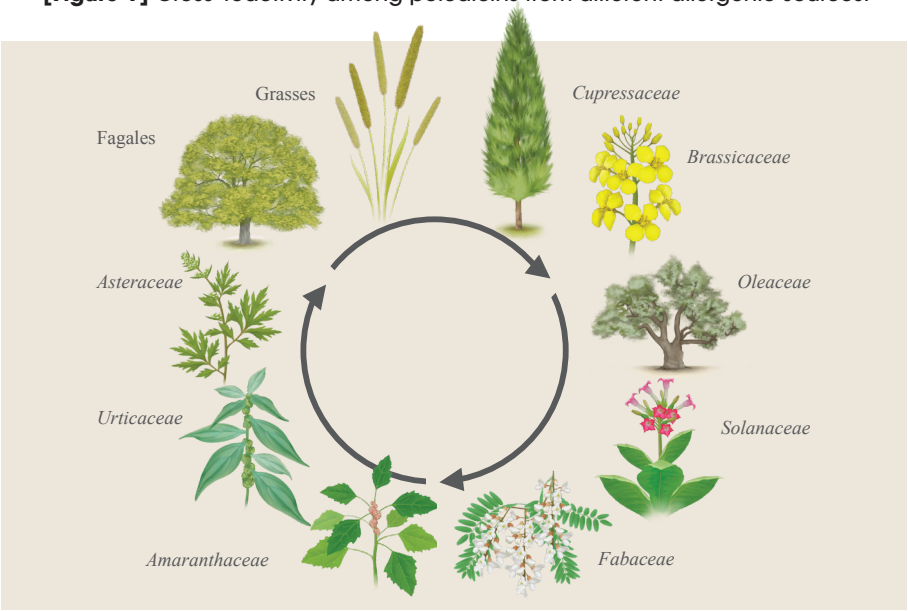
Allergen source	Allergen
Birch, *Betula verrucosa*	Bet v 4
Timothy, *Phleum pratense*	Phl p 7
Alder, *Alnus glutinosa*	Aln g 4

Prevalence of polcalcin sensitization in patients with pollen allergy.

Main sensitisation of the population studied	Prevalence of sensitisation to Polcalcin
Birch	Bet v 4: 5%
Chenopodium/Salsola	Che a 3: 46%; Che a 3: 41%
Olive	Ole e 3: 20-30%
Grass	Phl p 7: 2-10%
Alder	Aln g 4: 18%
Robinia pseudoacacia	Che a 3: 33%
Ash	Fra a 3: 16%
Cypress	Cup a 4: 10%
Polysensitized to pollen	Polcalcin: 31%
Birch, ash, mugwort, grass	Polcalcin: 10%

C06 Polcacins

[Figure 1] Cross-reactivity among polcalcins from different allergenic sources.



[Figure 2] Scheme to follow in case of polysensitization to pollen. Added value of the use of specific IgE to species-specific pollen allergens and to panallergens.

Polysensitisation to pollen (Skin prick tests, specific IgE to extracts)

Check for

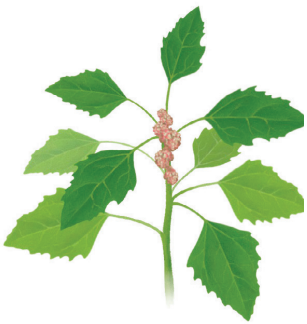
- sIgE to allergens specific to primary sensitisation (e.g.: Bet v 1, Ole e 1, Phl p 1, Phl p 5, Art v 1...)
- sIgE to panallergens (profilins, nsLTPs, polcalcin)

Positive to allergens specific to primary sensitisation

- Consider AIT to relevant pollen

Positive to polcalcin

- May explain polysensitization to pollen and explain more intense and longer duration of sensitization to pollen
- Do not modify potential indication for AIT



Lipocalins C07

Key points:

- Conserved tertiary structure with low sequence identity among family members.
- Airborne, easily spreading into the indoor environment.
- Sensitisation to multiple components is associated with disease severity.
- Risk factor for respiratory symptoms and asthma.
- Cross-reactive subgroup with high sequence identity.

Tips for molecular diagnosis

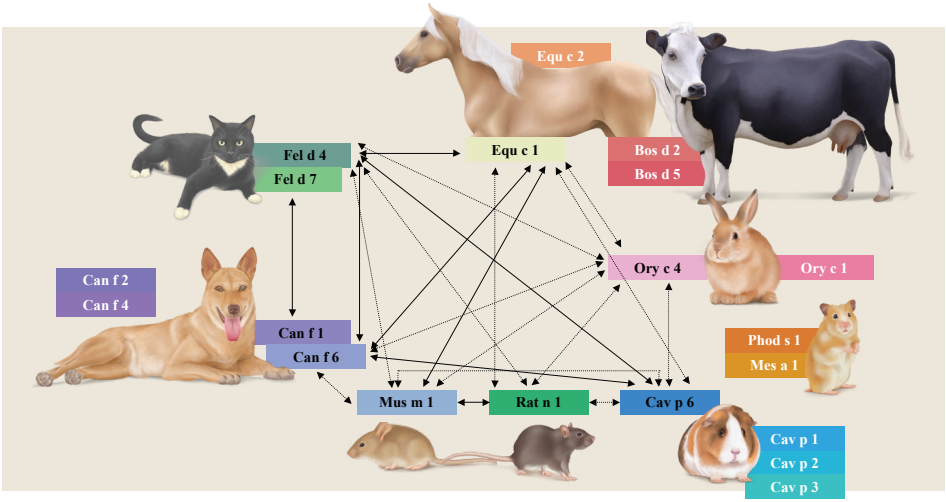
At the current state of the art, Fel d 1, Fel d 7, Can f 1, Can f 2, Can f 4, and Can f 5 are commercially available species-specific markers of sensitisation, although sensitisation to Can f 1 is not a specific dog marker in case of co-sensitisation to cat (see also chapter B06).

Table of available lipocalin components for IgE-diagnosis of allergy related to animal dander or milk

Allergen source	Specific lipocalin marker allergens	Lipocalin allergens with moderate cross-reactivity
Cat		Fel d 4, Fel d 7
Cattle	Bos d 2, Bos d 5	
Dog	Can f 2, Can f 4	Can f 1, Can f 6
Guinea-pig	Cav p 1	
Golden hamster	Mes a 1	
Dwarf hamster	Phod s 1	
Horse		Equ c 1
Mouse		Mus m 1
Rabbit	Ory c 1, Ory c 2	

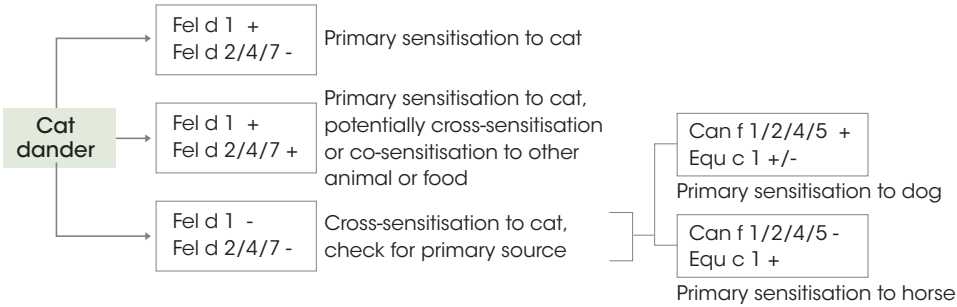
Lipocalins are major allergens in different furry pets and are present in dander, saliva, and urine. All mammalian lipocalin allergens are respiratory allergens, except the β-lactoglobulins (e.g., Bos d 5), which are present in milk and classified as food allergens.

C07 Lipocalins

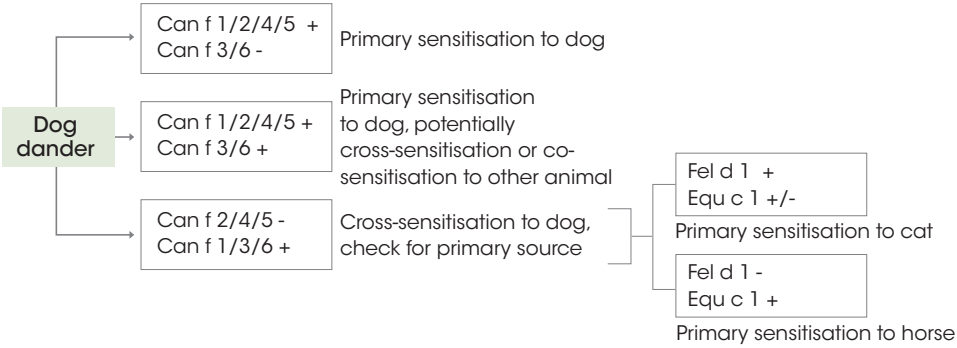


[Figure 1] Cross-reactivities among allergenic lipocalins. Solid lines represent documented IgE cross-reactivity. Dotted lines represent potential IgE cross-reactivity based on high sequence identities. Allergens depicted in the outer circle (white font) show overall low sequence identities with other family members and are candidates for species-specific marker allergens, but their cross-reactive potential still needs to be investigated.

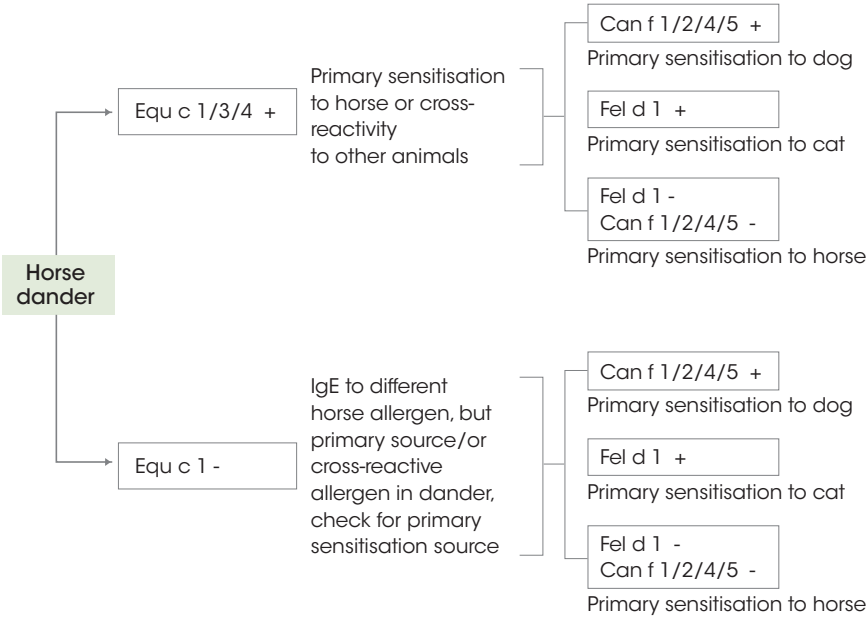
Diagnostic algorithms for the component-resolved diagnosis of allergy to cat, dog, or horse.



[Figure 2] – Single allergens are of added value to identify the primary sensitisation source in the case of a positive IgE–test to cat dander.



[Figure 3] – Single allergens are of added value to identify the primary sensitisation source in the case of a positive IgE–test to dog dander.



[Figure 4] – Single allergens are of added value to identify the primary sensitisation source in the case of a positive IgE–test to horse dander.

C08 Seed storage proteins

Key points:

- Seed storage proteins (2S albumins, 7S globulins and 11S globulins) are marker allergens for clinically relevant sensitizations to legumes, tree nuts and seeds.
- IgE-sensitization is associated with a high risk of developing an allergic reaction upon ingestion, from mild (e.g., oral itching) to anaphylaxis.
- IgE cross-reactivity usually occurs between members of the same protein family, mainly between allergens from related plants that have high protein sequence identities. However, it may also occur between allergens from different families of seed storage proteins.
- The clinical relevance of IgE co-sensitization and the impact of cross-reactivity are largely unknown, and more research is still needed.

Tips for molecular diagnosis

2S albumins

- Major allergens in peanut, seeds and tree nuts such as hazelnut, walnut and cashew nut.
- Marker allergens for clinically relevant sensitisations to peanut, seeds, and tree nuts.
- High risk of cross-reactivity between walnut and pecan nut or between cashew nut and pistachio.
- IgE specific for these allergens may elicit severe symptoms.

7S globulins (vicilins)

- Major allergens of legumes such as soy, pea, lentil, and lupine.
- Potential marker allergens for clinically relevant sensitisations to legumes.
- Risk of cross-reactivity between peanuts and peas or lupine.
- Risk of cross-reactivity between peas and lentils.

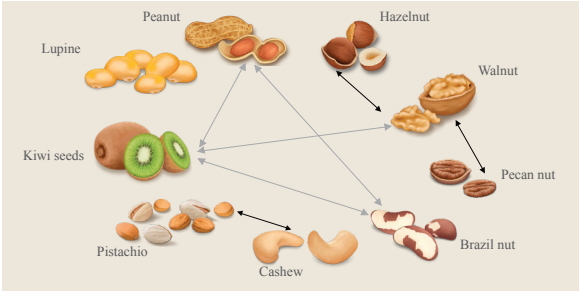
11S globulins (legumins)

- Major allergens in hazelnut and almond.
- Marker allergens for clinically relevant sensitisations to hazelnuts and almonds.
- IgE specific for these allergens may elicit severe symptoms.

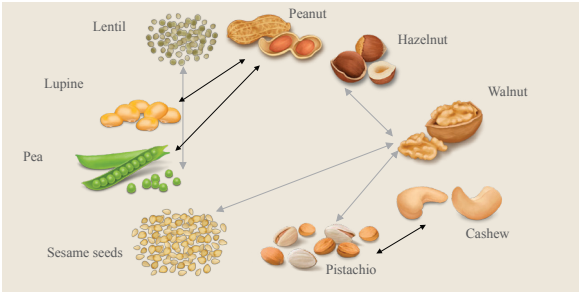
Table of available allergens for IgE-diagnosis of allergy to seed storage proteins

Allergen source	Allergen
Cashew nut, *Anacardium occidentale*	rAna o 2 (11S globulin), rAna o 3 (2S albumin)
Brazil nut, *Bertholletia excelsa*	rBer e 1 (2S albumin)
Hazelnut, *Corylus avellana*	nCor a 9 (11S globulin), rCor a 14 (2S albumin)
Walnut, *Juglans regia*	rJug r 1 (2S albumin)
Sesame seed, *Sesamum indicum*	rSes i 1 (2S albumin)
Peanut, *Arachis hypogaea*	rAra h 1 (7S globulin), rAra h 2 (2S albumin), rAra h 3 (11S globulin), rAra h 6 (2S albumin)
Soybean, *Glycine max*	nGly m 5 (B-conglycinin), nGly m 6 (Glycinin)
Buckwheat, *Fagopyrum esculentum*	nFag e 2 (2S albumin)

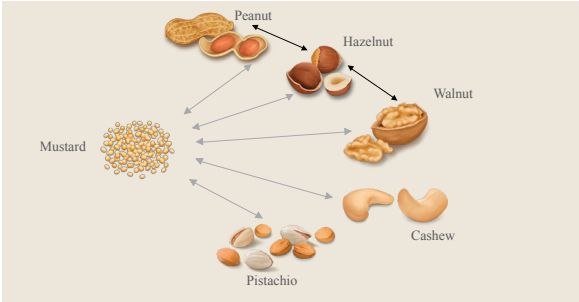
Seed storage proteins C08



In vitro cross-reactivity between 2S albumins from tree nuts and legumes. Strong cross-reactivity has been shown for walnut and pecan nut, cashew and pistachio, and for hazelnut and walnut. Cross-reactivity only confirmed in vitro and limited knowledge regarding clinical relevance is indicated with a grey arrow.



In vitro cross-reactivity between 7S globulins from tree nuts, seeds and legumes. Strong cross-reactivity has been shown for cashew and pistachio (black arrow). Cross-reactivity only confirmed in vitro and limited knowledge regarding clinical relevance is indicated with a grey arrow.



In vitro cross-reactivity between 11S globulins from tree nuts and seeds. Strong cross-reactivity has been shown for hazelnut and walnut (black arrow). Cross-reactivity only confirmed in vitro and limited knowledge regarding clinical relevance is indicated with a grey arrow.

C08 Seed storage proteins

Distinguishing between **primary and secondary sensitisation** to legumes, tree nuts, and seeds using molecular allergy diagnostics in routine care.

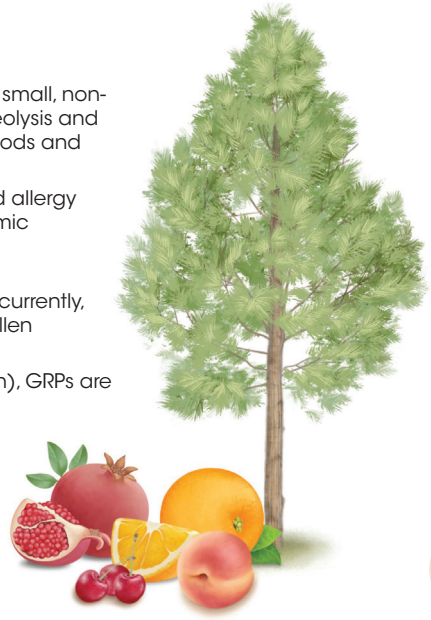
Sensitisation and symptoms to total extracts from legumes, tree nuts, or seeds

Sensitisation to seed storage proteins Ara h 1, Ara h 2, Ara h 3, Ara h 6, Gly m 5, Gly m 6, Cor a 9, Cor a 14, Ana o 2, Ana o 3, Jug r 1, Jug r 2, Ber e 1 or Ses i 1 AND NO sensitisation to birch pollen or PR-10 proteins Ara h 8, Gly m 4, Cor a 1, Bet v 1 or birch pollen	Sensitisation to seed storage proteins Ara h 1, Ara h 2, Ara h 3, Ara h 6, Gly m 5, Gly m 6, Cor a 9, Cor a 14, Ana o 2, Ana o 3, Jug r 1, Jug r 2 Ber e 1 or Ses i 1 AND sensitisation to birch pollen or PR-10 proteins Ara h 8, Gly m 4, Cor a 1, Bet v 1 or birch pollen	NO sensitisation to seed storage proteins Ara h 1, Ara h 2, Ara h 3, Ara h 6, Gly m 5, Gly m 6, Cor a 9, Cor a 14, Ana o 2, Ana o 3, Jug r 1, Jug r 2, Ber e 1, Ses i 1 AND sensitisation to birch pollen or PR-10 proteins Ara h 8, Gly m 4, Cor a 1, Bet v 1 or birch pollen	Seed storage proteins not available in routine care AND NO sensitisation to birch pollen or PR-10 proteins Ara h 8, Gly m 4, Cor a 1, Bet v 1 or birch pollen	Seed storage proteins not available in routine care AND sensitisation to birch pollen or PR-10 proteins Ara h 8, Glym 4, Cor a 1, Bet v 1 or birch pollen
Primary sensitisation: - Symptoms usually severe -Avoid offending food	Primary or (and) secondary sensitisation/ cross-reactiviy with birch pollen: -Symptoms severe or mild -Avoid offending food	Secondary sensitisation/ cross-reactivity with birch pollen: -Symptoms usually mild/less severe (exception of Gly m 4 and Ara h 8 which can cause severe reactions) -Avoid offending foods, sometimes processed foods may give less/no symptoms	Probably primary sensitisation: -Symptoms usually severe -Avoid offending food	Primary or (and) secondary sensitisation/ cross-reactivity with birch pollen: -Symptoms severe or mild -Avoid offending food

Gibberellin-regulated proteins C09

Key points:

- Gibberellin-regulated proteins (GRPs) are cationic, small, non-glycosylated monomeric proteins, resistant to proteolysis and heat, with anti-microbial activity, present in plant foods and pollen.
- GRPs are cross-reactive and involved in pollen food allergy syndromes, but they may also induce severe systemic reactions, without or with cofactors.
- Main fruits involved: peach and citrus but also pomegranate, cherry or apricot. *Cupressaceae* is, currently, the only tree family shown to express allergenic pollen GRPs.
- In areas of high cypress pollen exposure (as Japan), GRPs are involved in pollen/fruit allergy syndromes.



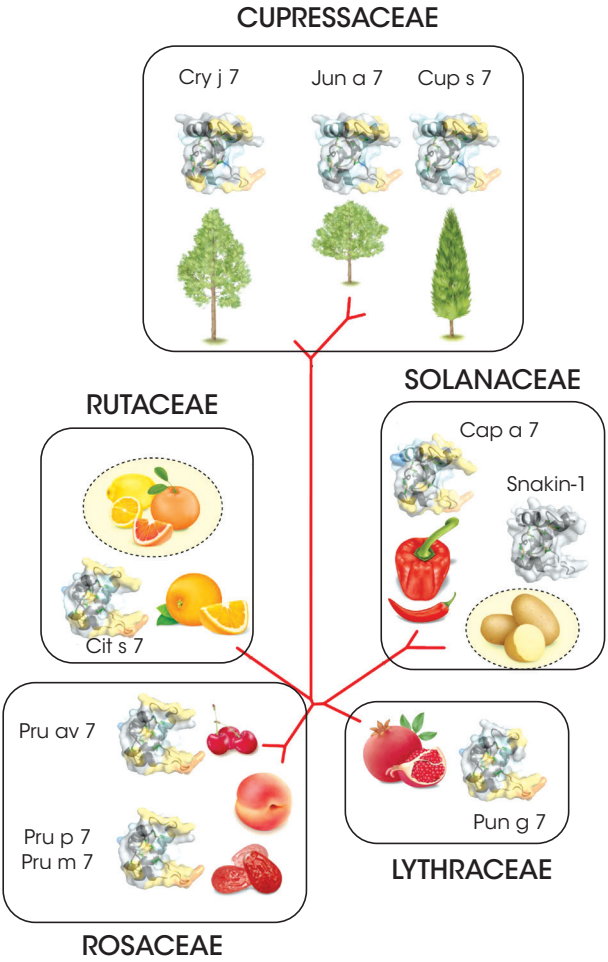
Tips for molecular diagnosis

- The recombinant Pru p 7-specific IgE test may support the diagnosis, although a positive GRP immunoassay may not be associated with a clinically pertinent IgE reactivity. It is commercially available in singleplex and multiplex assays.

Table reporting allergenic GRPs (*) and the prototype GRP Snakin-1 (Snakin-1 is not yet described as an allergen)

Protein	English name	Latin name	Family	Exposure
Cup s 7*	Commom cypress	*Cupressus sempervirens*	Cupressaceae	Pollen
Jun a 7*	Mountain cedar	*Juniperus ashei*	Cupressaceae	Pollen
Cry j 7*	Japanese cedar	*Cryptomeria japonica*	Cupressaceae	Pollen
Pru p 7*	Peach	*Prunus persica*	Rosaceae	Food
Pru m 7*	Japanese apricot	*Prunus mume*	Rosaceae	Food
Pru av 7*	Sweet cherry	*Prunus avium*	Rosaceae	Food
Cit s 7*	Sweet orange	*Citrus sinensis*	Rutaceae	Food
Pun g 7*	Pomegranate	*Punica granatum*	Lythraceae	Food
Cap a 7*	Bell Pepper	*Capsicum annuum*	Solanaceae	Food
Snakin-1	Potato	*Solanum tuberosum*	Solanaceae	

C09 Gibberellin-regulated proteins



[Figure 1] Evolutionary relationship of taxa (phylogenetic tree) and 3D modelling of GRPs

Gibberellin-regulated proteins C09

ANAMNESIS

- History of severe reaction after eating peach and/or other foods
- Association with cypress sensitisation
- Analysis of cofactors

SPT

- Cypress extract
- Peach extract
- Other food (prick-to-prick)

sIgE TESTING

EXTRACTS	COMPONENTS
– Cypress = Pos	– Cup a 1, Cry j 1 = Neg or Pos
– Peach = Pos	– Pru p 1, Pru p 3, Pru p 4 = Neg
– Other foods	– Pru p 7 = Pos

IMMUNOBLOTS

Unreduced native proteins from:

- Cypress pollen extract
- Food extract

BASOPHIL ACTIVATION TEST

- Pollen and food extracts
- Recombinant GRP allergen with and without cofactors

ORAL FOOD CHALLENGE

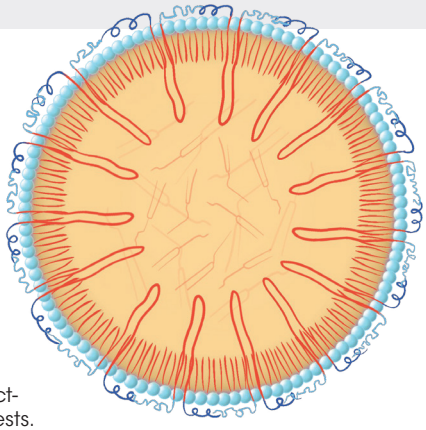
With or without cofactors

To go further

Requires a collaboration with laboratory facilities and/or hospital

[Figure 2] Diagnostic algorithm to assess GRP sensitisation

C10 Oleosins



Key points:

- Oleosins are lipophilic, resistant to enzymatic and thermal processing, and have a central hydrophobic domain flanked on each side by relatively hydrophilic domains.
- Oleosins are associated with severe allergic reactions.
- Oleosins are potential marker allergens for allergy severity following the consumption of peanuts or hazelnuts.
- Oleosins are underrepresented in aqueous extract-based in vivo- and in vitro- standard diagnostic tests.
- An increase of allergenicity has been recorded for hazelnut and peanut oleosins after roasting when compared to raw seeds.

Tips for molecular diagnosis

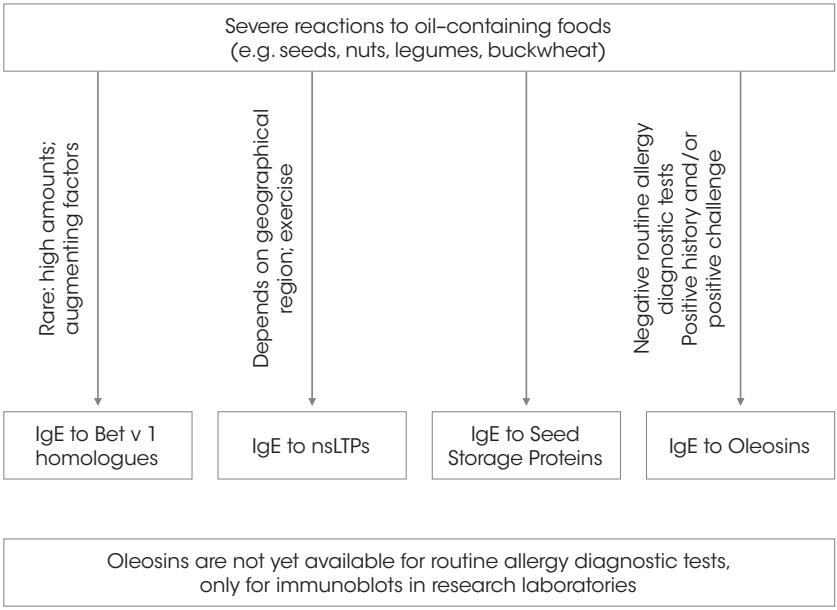
- Until recently, the lipophilic properties of this family of proteins have hindered the development of reliable diagnostic reagents for oleosins, both single and multiplex-array-based. There is now information on recombinant oleosins being used in arrays, that were engineered to be soluble in aqueous solutions.

Oleosins according to the WHO/IUIS Allergen Nomenclature Sub-Committee designation

Botanical family	Allergen source	Allergen	Molecular weight (kDa)
Fabales	Peanut *(Arachis hypogaea)*	*Ara h 10*	16
		Ara h 11	14
		Ara h 14	17.5
		Ara h 15	17
Fagales	Hazelnut *(Corylus avellana)*	*Cor a 12*	17
		Cor a 13	14-16
		Cor a 15	17
Lamiales	Sesame *(Sesamum indicum)*	*Ses i 4*	17
		Ses i 5	15
Caryophyllales	Tartarian buckwheat *(Fagopyrum tataricum)*	*Fag t 6*	18

Oleosins C10

Diagnostic algorithm to assess oleosin sensitisation



C11 Parvalbumins

Key points:

- Parvalbumins are fish panallergens; they are ingestion, respiratory and contact allergens.
- Clinical cross-reactivity is based on the presence of highly conserved IgE epitopes.
- Parvalbumins retain IgE-binding properties upon food processing.

Tips for molecular diagnosis

- Parvalbumin is a specific marker for fish allergy.
- Sensitization to multiple fish parvalbumins is associated with cross-reactive fish allergy.
- Monosensitization to a single parvalbumin (e.g., Sal s 1) points to a selective fish allergy.

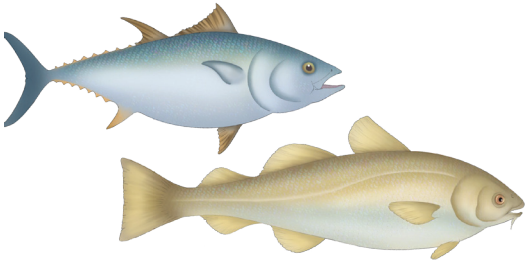


Table of available components for IgE-diagnosis of allergy to fishes

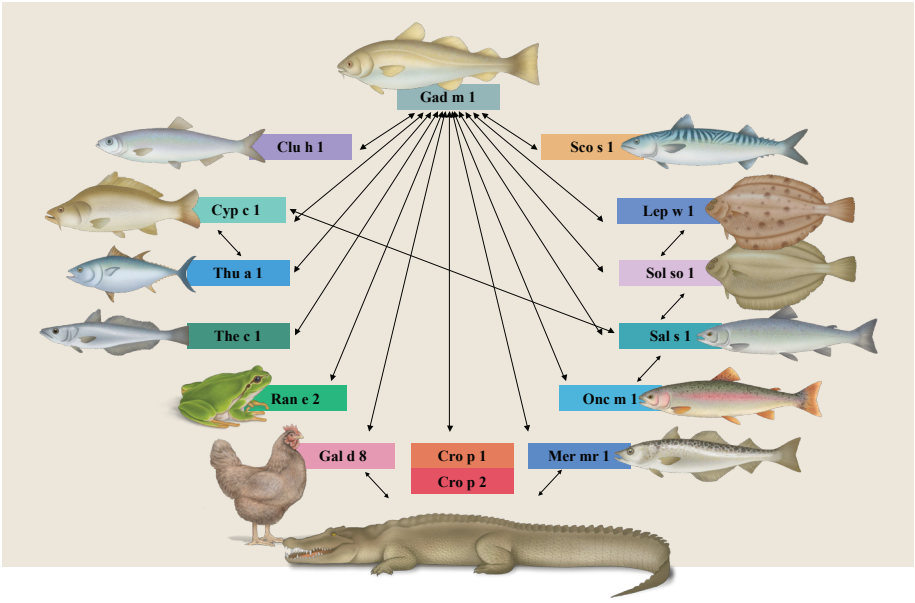
English name (Species)	Allergenic molecule	Biochemical name
Herring (*Clupea harengus*)	Clu h 1	β-parvalbumin
Carp (*Cyprinus carpio*)	Cyp c 1	β-parvalbumin
Atlantic cod (*Gadus callarias*)	Gad c 1	β-parvalbumin
Atlantic cod (*Gadus morhua*)	Gad m 1	β-parvalbumin
Tuna (*Thunnus albacares*)	Thu a 1	β-parvalbumin
Atlantic mackerel (*Scomber scombrus*)	Sco s 1	β-parvalbumin
Swordfish (*Xiphias gladius*)	Xip g 1	β-parvalbumin
Salmon (*Salmo salar*)	Sal s 1	β-parvalbumin
Thornback ray (*Raja clavata*)	Raj c PV	α-parvalbumin

Parvalbumins C11

Cross-reactivity scheme and clinical algorithm:

Allergenic parvalbumins belong to two different evolutionary lineages, alpha- and beta-parvalbumins. While beta-parvalbumins are potent allergens (e.g., bony fish), alpha-parvalbumins are better tolerated (e.g., cartilaginous fish). The cross-reactivity within beta-parvalbumins is high but is lower between alpha- and beta-parvalbumins.

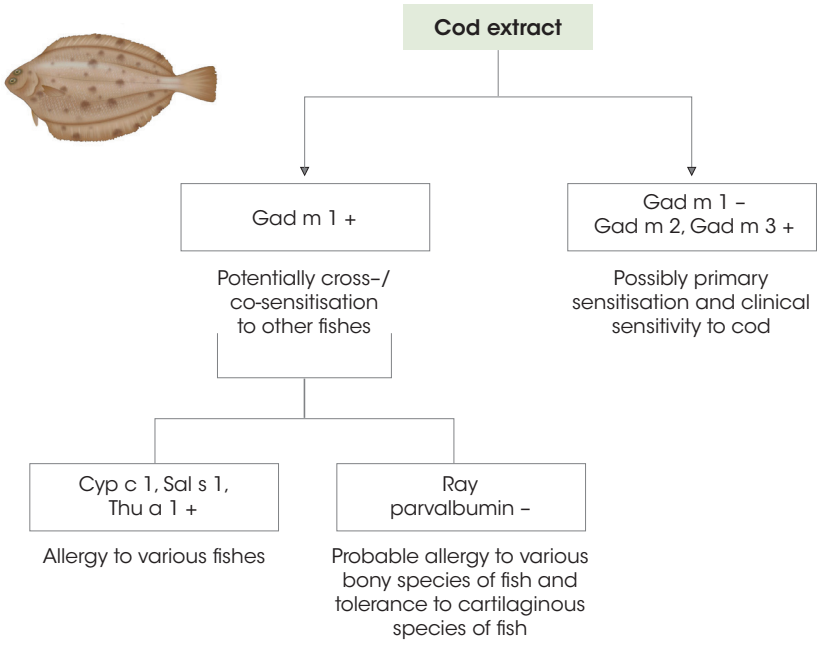
The Figure below represents documented and putative cross-reactivities among known fish and non-fish parvalbumins. During the past decade, new fish allergens have been characterized, beyond parvalbumins (see chapter B12 'Fish allergy'). Fish-allergic patients may cross-react with frog, chicken or crocodile meat due to parvalbumin-specific IgE. However, parvalbumins from such sources are not available yet for diagnostic testing.



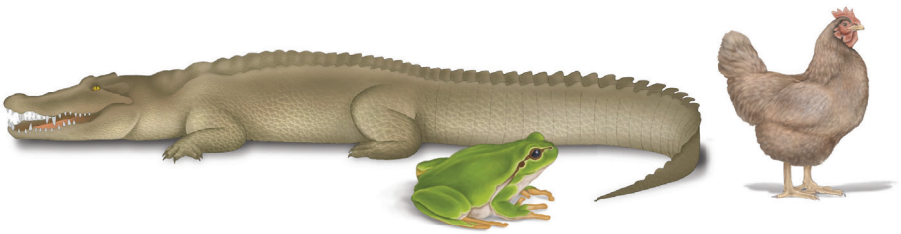
[Figure 1] Cross-reactivities among allergenic fish and non-fish parvalbumins.
All parvalbumins have a high potential for cross-reactivity based on high sequence homology. Lines represent documented IgE-cross-reactivity. Clockwise: Atlantic cod, Atlantic mackerel, megrim, common sole, Atlantic salmon, rainbow trout, Atlantic hake, crocodile, chicken, edible frog, Alaska Pollock, yellowfin tuna, common carp, Atlantic herring.

C11 Parvalbumins

With the advent of novel IgE-multiplexing platforms, the testing of sensitization to parvalbumins from distantly related bony fish as well as cartilaginous fish such as ray, is possible. Indeed, if this IgE-testing in parvalbumin-positive patients is negative as in Figure 2, there is a high probability that ray will be tolerated, which needs to be confirmed by oral provocation.



[Figure 2] – Added value of the use of single allergens in the case of a positive IgE test to cod extract.



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