THE XPLORER

EDITION #6

BIG DATA-BASED DESIGN OF ALEX^3

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INTERVIEW: HOW MOLECULAR ALLERGOLOGY IS RESHAPING ALLERGY DIAGNOSIS

With Robert G. Hamilton, PhD, D.ABMLI

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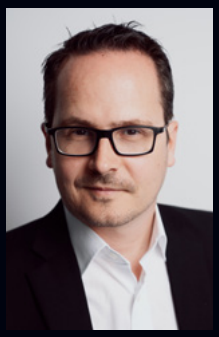


DEAR READERS,

After last year's special edition of THE XPLORER, which served as an introduction to the world of molecular allergy diagnostics, our team has created another great issue all about the newest version of our allergy test, ALEX^3.

In this edition, we highlight many new allergens included in ALEX^3 and explain why we chose them, how they are characterised, and what diagnostic value they offer. Furthermore, you can look forward to our "World Allergen Map", an amazing visual showcase of where the coverage of tested allergens has improved thanks to ALEX^3.

Finally, we will also update you on the new marketing materials the MADx team has created and share insights into an exciting new platform for patients we have been working on.

We hope you enjoy this edition of THE XPLORER!

Christian Harwanegg
CEO Macro Array Diagnostics

Big Data-Based Design of ALEX³

Improving global coverage of exposomes and diagnostic resolution of the ALEX macroarray

Only nine years after the launch of the first version of the ALEX macroarray in 2016 and an update in 2019 (ALEX²), the third version of ALEX, i.e., ALEX³, will become available in 2025. Despite excellent performance of ALEX², there were two main reasons why the second major update is being implemented relatively soon after version two: The first aim was to scrutinise the complete array of allergens and extracts included in ALEX² in terms of positivity rates, average sIgE levels, and co-reactivity patterns, in order to assess coverage of allergen sources that are represented on the test, and to identify potential redundancies.

Second, the ALEX test was designed for global use. To this end, coverage of diverse exposomes from distinct regions of the world is key. While most major allergen sources with global occurrence, such as cat or house dust mites, shed the same repertoire of molecular allergens worldwide, other allergens are only relevant in particular regions as triggers of allergic sensitisations and symptoms. This may be due to predominantly regional prevalence, for example, of particular plants or foods, but also to distinct habits leading to exposure to specific allergens. Since ALEX² is used in a growing number of countries (currently more than 90), we are continuously investigating coverage of global exposomes by the existing panel of allergens and extracts on the test.

In general, selection of allergens and extracts to be included in or removed from a multiplex IgE test is largely dependent on information available in the scientific literature and on the test's performance data. Such data sets are usually limited to a few hundred or thousand results, for uncommon sources of allergic sensitisation even less. For optimisation of the ALEX test, we at MADx are in the privileged position of having a large and growing data set of ALEX² test results at our disposal. This is because results from most tests done worldwide are stored on a GDPR-compliant cloud server called "RAPTOR server", for secure data storage and to facilitate remote customer support. These data are used for research projects and for continuous post-market surveillance, in line with applicable terms and conditions. When ALEX³ was designed (mid-2023), approximately 400,000 ALEX² test results were available. Currently, the total number of ALEX² results amounts to almost 1,000,000, representing a rapidly growing and globally unique dataset.

For the selection of allergens to be included in ALEX³, the RAPTOR data were used to address the following questions: (1.) For allergen sources that were represented on ALEX² by both an extract and at least one allergen, we assessed whether the respective allergen source was sufficiently covered by that allergen. Samples that tested positive for the extract but negative for the component were further analysed for reactivity to panallergens, e.g., profilins or polcalcins, or to the CCD marker on the ALEX² test (Hom s LF). Those specificities can cause an extract to yield a positive result even if the sample does not contain IgE directed against a specific marker allergen from that allergen source. In cases where a substantial share of remaining test results was positive for the extract only, the latter was kept on the allergen list for ALEX³, such as for spreading pellitory (Parietaria

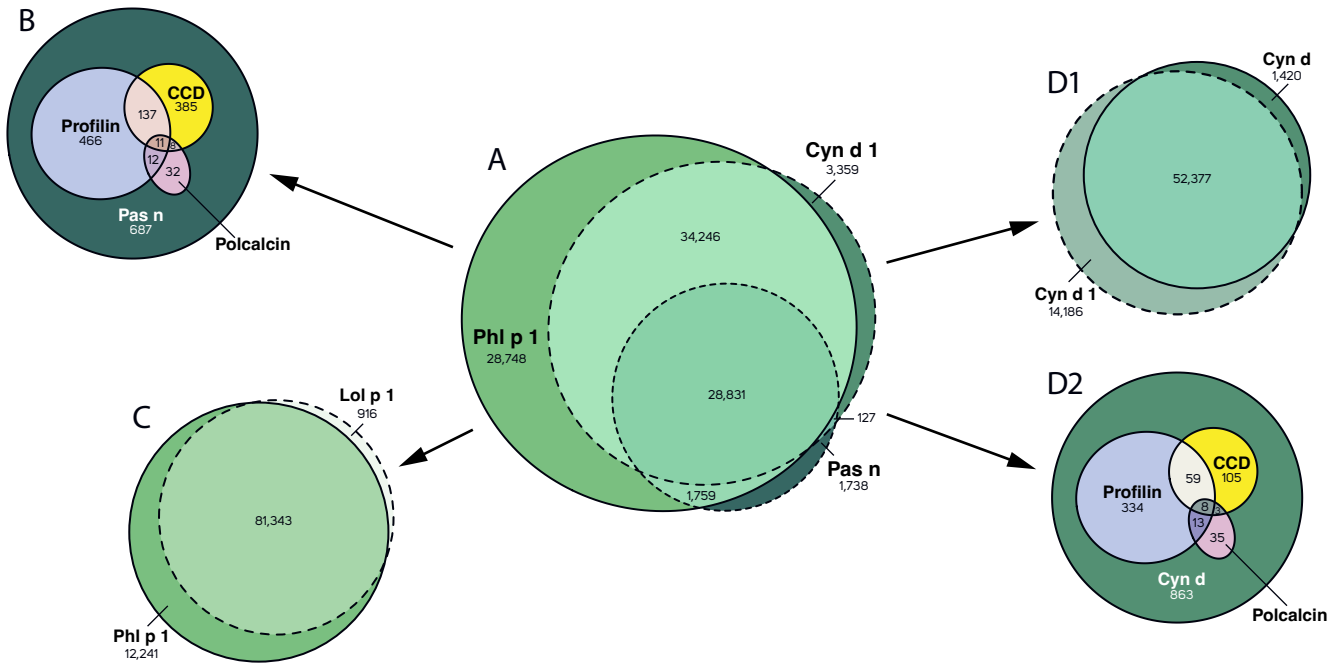


Figure 1

judaica). Otherwise, the extract was cleared, e.g., for ribwort plantain (Plantago lanceolata). (2.) We identified allergens or extracts with very low prevalence rates (<<1%) and removed them from the array, e.g., extracts from oregano, caraway or bell pepper. (3.) We investigated for which allergen families (or subgroups thereof) individual members could be identified as suitable surrogate markers for sensitisation to that family. This was possible for families with a high degree of co-reactivity (i.e., reactivity to all or most representatives on ALEX[2]), e.g., for profilins or PR-10. In contrast, families such as 2S albumins or nsLTP showed heterogeneous reactivity patterns, with generally low levels of co-reactivity. Those findings indicated that a broad panel of allergens from those families needed to be kept on the test to ensure high sensitivity for the detection of sensitisation. For those non-redundant families, no allergen was discontinued but additional ones were added to the array.

As a representative example, Figure 1 shows the results for group 1 grass pollen allergens (Phl p 1, Lol p 1, Cyn d 1) and extracts from Bermuda grass (Cyn d) and Bahia grass (Pas n). As surrogate markers for temperate or tropical grasses, Phl p 1, Cyn d 1 and Pas n-extract will be included on ALEX[3] (Figure 1 A, B). In contrast, Lol p 1 was identified as redundant, since it is highly co-reactive with Phl p 1 (Figure 1 C). Likewise, Bermuda grass extract turned out to be covered to the biggest extent by Cyn d 1 (Figure 1 D1). Of the remaining cases, 40 % were reactive to panallergens and/or CCDs (Figure 1 D2). The remainder exhibited sIgE levels close to the test's cut-off, i.e., 0.3 kU_A/L. Therefore, both Lol p 1 and Cyn d were cleared from the array. More details on these analyses within the scope of the design of ALEX[3] will be published in an original article (Lupinek et al., submitted to the International Journal of Molecular Sciences).

New allergens on ALEX[3] provide coverage of additional respiratory, food and insect venom allergens which will be described in greater detail in the following articles in the current issue of THE XPLORER. In summary, ALEX[3] will comprise 52 new molecular allergens, amounting to a total of 218, and 82 extracts, compared to 178 and 117, respectively, on ALEX[2]. Thus, the new version of ALEX will cover 80 allergen families and 145 allergen sources.

In the following section, a selection of new allergens included in ALEX^3 will be presented in a "fact sheet" format.

Please refer to our ALEX^3 World Allergen Map (p. 26) to see how the coverage of allergens has improved globally due to their inclusion.

Pollen

ALLERGEN SOURCE

BIRCH

Betula verrucosa

ALLERGEN NAME

Bet v 7

ALLERGEN BIOCHEMICAL NAME

Cyclophilin

ROUTE OF ALLERGEN EXPOSURE

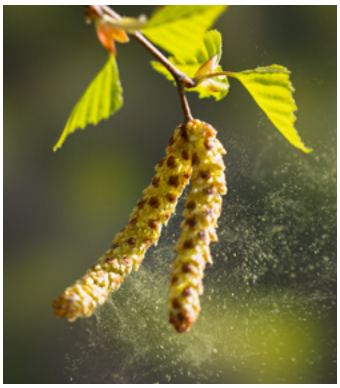
Respiratory allergen

GEOGRAPHICAL RELEVANCE

Temperate regions

DIAGNOSTIC BENEFIT

Higher sensitivity & resolution of cross-reactivities



Bet v 7, an allergen derived from birch pollen (Betula verrucosa), belongs to the cyclophilin protein family, a family of highly conserved ubiquitous proteins involved in protein folding [1].
Bet v 7 is encountered primarily through airborne exposure. Testing for this 18 kDa molecular allergen is particularly valuable for identifying hidden sensitisations in patients who test negative for other birch allergens like Bet v 1, 2, and 4 but continue to exhibit positive reactions to pollen extracts.

CROSS-REACTIVITY

Cyclophilins, like profilins, polcalcins, and PR-10s, are panallergens with significant cross-reactivity among family members. In individuals with unexplained sensitisations to pollens such as ragweed, mugwort, pellitory, plantago, and plane tree, IgE levels to these extracts showed strong correlations with IgE levels to rBet v 7 [2].

CONCLUSION

Bet v 7 is a valuable addition to molecular allergy diagnostics as it can identify previously unrecognised sensitisations.

Insects

ALLERGEN SOURCE

AMERICAN COCKROACH

Periplaneta americana

ALLERGEN NAME
Per a 6

ALLERGEN BIOCHEMICAL NAME
Troponin C

ROUTE OF ALLERGEN EXPOSURE
Respiratory allergen

GEOGRAPHICAL RELEVANCE
Americas, Southern Europe, Southeast & East Asia, Oceania

DIAGNOSTIC BENEFIT
Higher sensitivity & resolution of cross-reactivities

Per a 6 is a minor allergen with a recognition rate of 14 % in cockroach-sensitised patients [3].

CROSS-REACTIVITY

The degree of cross-reactivity with its related allergen from the German cockroach is very high. It is also high with allergens from mites and medium for troponin C proteins from seafood.

CONCLUSION

Per a 6 is a minor allergen with a high potential of cross-reactivity with related proteins from various animal allergen sources.

Microorganisms

ALLERGEN SOURCE

SMOKY MOULD

Aspergillus fumigatus

ALLERGEN NAME
Asp f 8

ALLERGEN BIOCHEMICAL NAME
Ribosomal protein P2

ROUTE OF ALLERGEN EXPOSURE
Respiratory allergen

GEOGRAPHICAL RELEVANCE
Global, except for arid regions

DIAGNOSTIC BENEFIT
Higher sensitivity & resolution of cross-reactivities

Aspergillus fumigatus has been identified as a relevant allergen source in severe asthma and allergic broncho-pulmonary aspergillosis (ABPA) [4]. Asp f 8 plays an important role in protein synthesis.

CROSS-REACTIVITY

Allergens from the same allergen family can be found in Cladosporium herbarum (Cla h 5), Alternaria alternata (Alt a 5) and Fusarium culmorum (Fus c 1) [5].

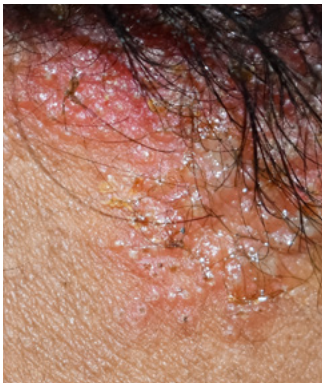
CONCLUSION

Mould extracts are difficult to standardise. Therefore, additional allergens improve the diagnostic routine.

ALLERGEN SOURCE

SKIN-COLONISING YEAST

Malassezia sympodialis



ALLERGEN NAME
Mala s 13

ALLERGEN BIOCHEMICAL NAME
Thioredoxin

ROUTE OF ALLERGEN EXPOSURE
Skin

GEOGRAPHICAL RELEVANCE
Global

DIAGNOSTIC BENEFIT
Marker allergen for severe atopic dermatitis [6] [7]

IgE sensitisation to Malassezia allergens plays a role in triggering and sustaining eczema in patients suffering from atopic dermatitis [7]. Mala s 13 is part of the thioredoxin allergen family, a ubiquitous protein.

CROSS-REACTIVITY

Thioredoxins from different allergen sources, like cereals, moths and moulds, share IgE epitopes [8] [9]. Cross-reactivity with human thioredoxin can contribute to the exacerbation of severe atopic diseases [10] [11].

CONCLUSION

Thioredoxins are panallergens involved in the pathogenesis of atopic dermatitis.

Venoms

ALLERGEN SOURCE

BALD-FACED HORNET VENOM

Dolichovespula maculata

ALLERGEN NAME

Dol m 2, Dol m 5

ALLERGEN BIOCHEMICAL NAME

Hyaluronidase (Dol m 2), Antigen 5 (Dol m 5)

ROUTE OF ALLERGEN EXPOSURE

Injection, sting

GEOGRAPHICAL RELEVANCE

USA, Canada

DIAGNOSTIC BENEFIT

Higher sensitivity & resolution of cross-reactivities

Dol m 2 is a member of the hyaluronidase allergen family and present in all vespid venoms. It is designated as a minor allergen. Dol m 5 is a member of the antigen 5 family, which are the most potent allergens in vespid venoms [12] [13] [14].

BIOLOGICAL FUNCTION

Hyaluronidase is an enzyme that cleaves hyaluronic acid, a crucial component of connective tissue. With this, it decreases the viscosity of the extracellular matrix and supports the spreading of the venom at the site of injection. The biological function of Dol m 5 and its sequence-related proteins is not known.

CROSS-REACTIVITY

Dol m 2 shows 92 % amino acid (a.a.) sequence identity to Ves v 2, the hyaluronidase from wasp venom, and 56 % a.a. sequence identity with Api m 2 from bee venom [12]. The extent of cross-reactivity between Api m 2 and Dol m 2 seems to be limited. Dol m 5 shows 65 % and 63 % a.a. sequence identities with the homologous proteins from common wasp (Ves v 5) and paper wasp (Pol d 5), respectively [14] [15].

CONCLUSION

Dol m 2 and Dol m 5 permit a more detailed assessment of the sensitisation profile and enhance the diagnostic sensitivity of wasp venom allergy.

ALLERGEN SOURCE

HONEYBEE VENOM

Apis mellifera

ALLERGEN NAME

Api m 2

ALLERGEN BIOCHEMICAL NAME

Hyaluronidase

ROUTE OF ALLERGEN EXPOSURE

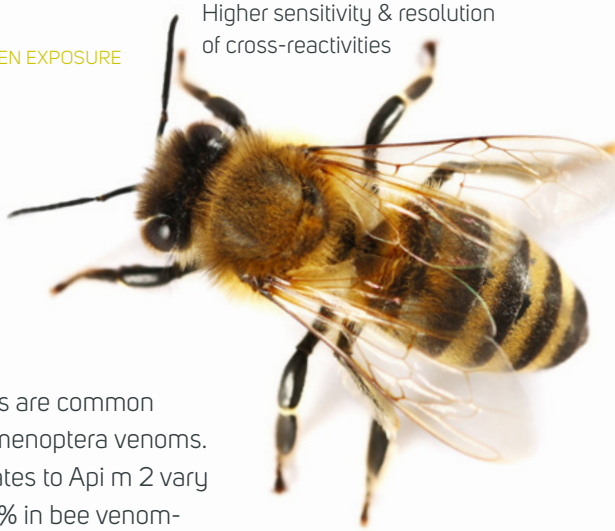
Injection, sting

GEOGRAPHICAL RELEVANCE

Global

DIAGNOSTIC BENEFIT

Higher sensitivity & resolution of cross-reactivities



Hyaluronidases are common proteins in Hymenoptera venoms. Sensitisation rates to Api m 2 vary from 28 to 60 % in bee venom-allergic patients. Natural Api m 2 contains cross-reactive carbohydrate determinants (CCDs) [16].

CROSS-REACTIVITY

Cross-reactivity of hyaluronidases from different venoms depends on the primary sensitising insect venom. Bee venom-allergic patients sensitised to Api m 2 show almost no cross-reactivity with wasp venom hyaluronidases, whereas wasp venom-allergic patients sensitised to Ves v 2 (hyaluronidase from common wasp) and/or Pol d 2 (hyaluronidase from paper wasp) exhibit cross-reactivity with Api m 2 [17].

CONCLUSION

Api m 2 is a cross-reactive allergen and also serves as a VIT indicator for honeybee venom.

Nuts & Seeds

ALLERGEN SOURCE

ALMOND

Prunus dulcis

ALLERGEN NAME
Pru du 6

ALLERGEN BIOCHEMICAL NAME
11S globulin, amandin

ROUTE OF ALLERGEN EXPOSURE
Food allergen

GEOGRAPHICAL RELEVANCE
Europe, USA, China, Western Asia, Indian subcontinent

DIAGNOSTIC BENEFIT
Risk assessment

Pru du 6 is a seed storage protein from the 11S globulin allergen family. Almonds are a leading cause of allergy to tree nuts and can cause severe allergic reactions.

CROSS-REACTIVITY

Pru du 6 shows a low to medium level of cross-reactivity with its relatives in other tree nuts (based on a.a. sequence alignment). The highest degree of cross-reactivity is to be expected with its homologues in hazelnut and walnut as well as pecan [18].

STABILITY

Pru du 6, like most storage proteins, is stable to heat and digestion.

CONCLUSION

Pru du 6 is the dominant allergen in almond allergy and can cause severe allergic reactions. Almond paste is made from peeled and blanched almonds – therefore, it can also contain substantial amounts of Pru du 6 [18]. Avoidance is the only treatment option currently available.

ALLERGEN SOURCE

CASHEW

Anacardium occidentale

ALLERGEN NAME
Ana o 1

ALLERGEN BIOCHEMICAL NAME
7/8S globulin

ROUTE OF ALLERGEN EXPOSURE
Food allergen

GEOGRAPHICAL RELEVANCE
Global

DIAGNOSTIC BENEFIT
Higher sensitivity & enhanced risk assessment

Ana o 1, a 50 kDa 7/8S globulin (seed-storage protein), is a major food allergen found in cashews [19]. Cashews are a common cause of severe allergic reactions, including food-induced anaphylaxis [20] [21]. Studies indicate that cashew allergy may result in more frequent and severe reactions than peanut allergy, with children being at higher risk compared to other tree nuts or peanuts [22] [23] [24].

CROSS-REACTIVITY

Cashew and pistachio, both belonging to the Anacardiaceae family, exhibit extensive cross-reactivity [19] [25]. Furthermore, Ana o 1 showed high epitope similarity with Cor a 11 (hazelnut), Jug r 2 (walnut), and, to a lesser extent, Ara h 1 (peanut) [26] [27] [28].

STABILITY

Ana o 1 has been shown to be very stable to heat and digestion [19] [21].

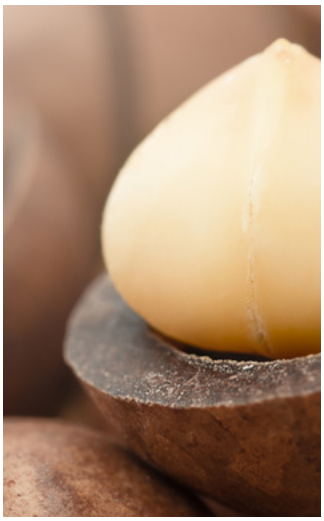
CONCLUSION

Ana o 1 enhances the accuracy of identifying high-risk patients and improves the understanding of cross-reactivity, particularly for patients with tree nut and peanut allergies.

ALLERGEN SOURCE

MACADAMIA

Macadamia integrifolia



ALLERGEN NAME
Mac i 1.0101

ALLERGEN BIOCHEMICAL NAME
7/8S globulin (with N-terminal α-hairpinin peptides)

ROUTE OF ALLERGEN EXPOSURE
Food allergen

GEOGRAPHICAL RELEVANCE
North America, Western & Central Europe, Australia, New Zealand, Japan, Korea, South Africa

DIAGNOSTIC BENEFIT
Higher sensitivity & enhanced risk assessment

Mac i 1.0101 belongs to the 7/8S globulin family. It contains α-hairpinin peptides at its N-terminal end [29]. Mac i 1.0101 is specifically recognised by macadamia-allergic patients while showing minimal IgE reactivity in tolerant individuals [29] [30].

CROSS-REACTIVITY

Mac i 1.0101 shares up to 50 % a.a. sequence identity with Jug r 2 (walnut) and matches several of its epitopes [31] [32].

STABILITY

α-hairpinins are antimicrobial peptides with a unique helix-loop-helix structure stabilised by two disulfide bonds, providing exceptional heat and digestion stability [33] [34].

CONCLUSION

Recent findings further indicate that IgE sensitisation to α-hairpinins could serve as key indicators of systemic reactions, highlighting the importance of incorporating Mac i 1.0101 in the diagnostic workup.

ALLERGEN SOURCE

PECAN

Carya illinoinensis

ALLERGEN NAME
Car i 1

ALLERGEN BIOCHEMICAL NAME
2S albumin

ROUTE OF ALLERGEN EXPOSURE
Food allergen

GEOGRAPHICAL RELEVANCE
Asia, Australia, North America, Egypt, Europe

DIAGNOSTIC BENEFIT
Higher sensitivity & enhanced risk assessment

Car i 1 belongs to the 2S albumin seed storage protein family. In a study of 28 pecan-allergic patients, 79 % showed IgE binding to recombinant Car i 1, confirming it as a major allergen [35] [36].

CROSS-REACTIVITY

Cross-reactivity is usually low for 2S albumins. Interestingly, a high sequence identity is observed between pecan allergens and their walnut counterparts [28] [33] [37] [38]. When comparing Car i 1 with other 2S albumins, it shows the highest a.a. sequence identity to Jug r 1 (88 %) followed by Cor a 14 (56 %) and Ana o 3 (41 %) [36].

STABILITY

Car i 1, like other 2S albumins, is a highly stable allergen due to its compact structure.

CONCLUSION

Given the prevalence and severity of pecan allergies, including Car i 1 in molecular allergy diagnostics is essential.

ALLERGEN NAME
Car i 2

ALLERGEN BIOCHEMICAL NAME
7/8S globulin

ROUTE OF ALLERGEN EXPOSURE
Food allergen

GEOGRAPHICAL RELEVANCE
Asia, Australia, North America, Egypt, Europe

DIAGNOSTIC BENEFIT
Higher sensitivity & enhanced risk assessment

Car i 2 is a member of the seed storage protein family. 7/8S globulins are typically referred to as vicilins. Co-allergy between pecans and walnuts is highly prevalent. The strong correlation between walnut and pecan allergies may stem from the high a.a. sequence similarity of pecan allergens to their walnut counterparts [33] [35].

CROSS-REACTIVITY

Car i 2 shows a.a. sequence identity to 7/8S globulins from other tree nuts, such as the walnut allergens Jug r 2 (92 %) and Jug r 6 (44 %) [33]. Furthermore, Car i 2 shares 59 % a.a. sequence identity with Ana o 2 (cashew) [35].

STABILITY

Car i 2 has demonstrated reasonable stability to heat and digestion [39].

CONCLUSION

The inclusion of Car i 2, in contrast to the pecan extract, enhances in-vitro diagnosis of pecan allergies. It increases test specificity and offers an enhanced patient risk assessment.

ALLERGEN NAME
Car i 4

ALLERGEN BIOCHEMICAL NAME
11S globulin

ROUTE OF ALLERGEN EXPOSURE
Food allergen

GEOGRAPHICAL RELEVANCE
Asia, Australia, North America, Egypt, Europe

DIAGNOSTIC BENEFIT
Higher sensitivity & enhanced risk assessment

Car i 4 is a major allergen in pecans and a member of the 11S globulin allergen family.

CROSS-REACTIVITY

Car i 4 shares 95 % a.a. sequence identity to Jug r 4 (walnut), 72 % with Cor a 9 (hazelnut), 58 % with Pis v 2 (pistachio), and 54 % with Pru du 6 (almond). Additionally, epitope mapping confirmed cross-reactivity with walnut and hazelnut legumins [36].

STABILITY

11S globulins like Car i 4 are highly resistant to heat due to their stable structure.

CONCLUSION

Utilising Car i 4, rather than whole pecan extract, enhances test sensitivity and allows for more precise identification of pecan allergy sufferers.

ALLERGEN SOURCE

PINE NUT

Pinus pinea

ALLERGEN NAME
Pin p 1

ALLERGEN BIOCHEMICAL NAME
2S albumin

ALLERGEN FAMILY
Prolamin superfamily

ROUTE OF ALLERGEN EXPOSURE
Food allergen

GEOGRAPHICAL RELEVANCE
Asia, Mexico, Southern USA, Southern Europe

DIAGNOSTIC BENEFIT
Higher sensitivity & enhanced risk assessment

Since the initial documentation of pine nut allergy in 1958 [40], there have been numerous reports of allergic reactions, many of which involve severe anaphylactic responses. Pin p 1 is the major allergen from pine nut. Severe anaphylactic reactions following pine nut consumption account for most reported reactions [41].

CROSS-REACTIVITY

The epitopes of Pin p 1 share significant similarities with those of allergenic 2S albumins from peanut (Ara h 2 and 6) and Brazil nut (Ber e 1). However, Pin p 1 demonstrates a low frequency of cross-reactivity with other tree nuts and peanut [42].

STABILITY

Pin p 1, like other 2S albumins, is highly resistant to heat and digestion.

CONCLUSION

The inclusion of Pin p 1 enhances in-vitro diagnosis of pine nut allergy by increasing test sensitivity and offering an enhanced risk assessment.

ALLERGEN SOURCE

POPPY SEED

Papaver somniferum

ALLERGEN NAME
Pap s 1.0101

ALLERGEN BIOCHEMICAL NAME
7/8S globulin with N-terminal α-hairpinin peptides

ROUTE OF ALLERGEN EXPOSURE
Food allergen

GEOGRAPHICAL RELEVANCE
North America, Central & Southern Europe, Russia, Western Asia, India

DIAGNOSTIC BENEFIT
Higher sensitivity & enhanced risk assessment

Pap s 1.0101 belongs to the 7/8S globulin allergen family. It contains α-hairpinin peptides at its N-terminal end. Pap s 1.0101 has proven effective in distinguishing allergic individuals from tolerant ones, as allergic patients exhibit IgE reactivity to it, while only 58 % of tolerant individuals exhibit sensitisation. This makes it a reliable marker for predicting clinical reactions to poppy seeds [30] [43].

CROSS-REACTIVITY

Pap s 1.0101 shares similarities with the α-hairpinins Pru du 8 (almond) and Mac i 1.0101 (macadamia). Pre-incubation with these allergens reduced IgE binding to Pap s 1.0101 by about 30 %, while Pap s 1.0101 inhibited binding to Pru d 8 by 65 % and Mac i 1.0101 by 58 %, suggesting cross-reactivity [43].

STABILITY

Like other α-hairpinins, Pap s 1.0101 is very stable to heat and proteolysis [34].

CONCLUSION

While rare, poppy seed allergy is an important concern due to the potential for severe reactions, including anaphylaxis. With Pap s 1.0101, a high-performance marker can be integrated in the diagnostic workup [44] [45].

Grains

ALLERGEN SOURCE

WHEAT

Triticum aestivum

ALLERGEN NAME
Tri a 36

ALLERGEN BIOCHEMICAL NAME
Low molecular weight glutenin

ROUTE OF ALLERGEN EXPOSURE
Food allergen

GEOGRAPHICAL RELEVANCE
Global

DIAGNOSTIC BENEFIT
Enhanced risk assessment

Tri a 36 is found in cereals [46], and it is part of the gluten fraction. Tri a 36 is an allergen especially important for paediatric patients, leading to immediate food allergy rather than exercise-induced anaphylaxis which has been reported to affect mostly adults [47].

CROSS-REACTIVITY

Tri a 36 is important for distinguishing genuine wheat sensitisation from cross-reactivity with grass pollen as often found with wheat extracts [46]. Tri a 36 is cross-reactive with proteins found in rye, barley, oats, spelt and rice [48].

STABILITY

Tri a 36 is stable to heat and digestion.

CONCLUSION

Wheat is one of the most complex allergen sources and displays different clinical phenotypes. Tri a 36 is a valuable building block in the diagnostic workup of true wheat allergy, especially in paediatric populations.

ALLERGEN NAME
Tri a 37

ALLERGEN BIOCHEMICAL NAME
α-purothionin

ROUTE OF ALLERGEN EXPOSURE
Food allergen [49]

GEOGRAPHICAL RELEVANCE
Global

DIAGNOSTIC BENEFIT
Enhanced risk assessment

Tri a 37 is an α-purothionin found in wheat. It helps to distinguish genuine wheat sensitisation from cross-reactivity with grass pollen as is often found with wheat extracts. Tri a 37 might be a marker for severe anaphylactic reactions [49].

CROSS-REACTIVITY

It is highly cross-reactive with α-purothionins found in rye and barley, but less cross-reactive with α-purothionins found in oat and rice [49].

STABILITY

Tri a 37 is stable to heat and digestion [50].

CONCLUSION

Allergy diagnosis for wheat is still challenging, however ALEX³ covers five molecular allergens indicating true wheat sensitisation. Testing of molecular wheat allergens enables a comprehensive diagnosis of true wheat allergy.

Legumes

ALLERGEN SOURCE

LENTIL

Lens culinaris

ALLERGEN NAME

Len c 1, Len c 3

ALLERGEN BIOCHEMICAL NAME

7/8S globulin (Len c 1), Non-specific lipid transfer protein (Len c 3, nsLTP)

ROUTE OF ALLERGEN EXPOSURE

Food allergen

GEOGRAPHICAL RELEVANCE

Mediterranean, Middle East, Asia, North America

DIAGNOSTIC BENEFIT

Higher sensitivity & enhanced risk assessment

Len c 1 is the major lentil allergen, classified as a gamma-vicilin seed storage protein (7/8S globulin). Len c 3, a non-specific lipid transfer protein (nsLTP), is also considered a significant allergen although it is present in lower quantities compared to Len c 1.

CROSS-REACTIVITY

Len c 1 exhibits a high degree of cross-reactivity with chickpeas, peas and peanuts [51] [52]. Vicilin and convicilin, major allergens in peas, cross-react with Len c 1 [53]. Similarly, the epitopes of vicilin allergens Ara h 1 (from peanuts), Len c 1 (from lentils), and Pis s 1 (from peas) are similar, which explains the frequent IgE binding cross-reactivity observed among these edible legumes [54]. Also, Len c 3 can cross-react with Pru p 3 [55].

STABILITY

Lentil allergens include both heat-labile and heat-stable components. While some studies suggest that heating lentils reduces IgE binding, boiled lentil extracts still retain significant allergenicity because certain immunoreactive proteins remain resistant to heat (i.e., Len c 1 and Len c 3) even after intensive treatments [56] [57].

CONCLUSION

Len c 1 and Len c 3, in contrast to an extract, enhance the diagnosis of lentil allergies by boosting test sensitivity and will assist in assessing the clinical relevance of legume nsLTPs in allergic reactions.

ALLERGEN SOURCE

PEA

Pisum sativum

ALLERGEN NAME

Pis s 1, Pis s 2, Pis s 3

ALLERGEN BIOCHEMICAL NAME

7/8S globulin (Pis s 1 & Pis s 2), Non-specific lipid transfer protein (Pis s 3, nsLTP)

ROUTE OF ALLERGEN EXPOSURE

Food allergen

GEOGRAPHICAL RELEVANCE

Global

DIAGNOSTIC BENEFIT

Higher sensitivity & enhanced risk assessment

As consumer exposure to pea protein rises – particularly with the use of high-protein, pea-based ingredients in processed foods – a rise in pea allergy is expected. Pis s 1, Pis s 2 and Pis s 3 are the only three pea proteins registered as allergens [58]. Pis s 1 (7/8S globulin) and Pis s 2 (7/8S globulin) are both seed storage proteins that are considered major allergens in peas. They exhibit a high a.a. sequence identity (~70 %) and share serological cross-reactivity. In addition, Pis s 1 has been demonstrated to be a major allergen in pea-allergic children. Pis s 3 is a non-specific lipid-transfer protein (nsLTP).

CROSS-REACTIVITY

Cross-reactivity has been observed between Pis s 1 and both Len c 1 (lentil) and Ara h 1 (peanut) [53] [59] [60]. Research also suggests that many children with peanut allergies may have allergic reactions to other legumes, such as peas [61]. Moreover, children may show reactivity to peas, lentils and chickpeas. Additionally, Pis s 3 has been identified as exhibiting IgE cross-reactivity with Pru p 3, a key allergen in peaches [60].

STABILITY

Limited studies report on the effect of food processing on the allergenicity of peas. However, some research suggests that pea allergens have limited heat stability and become more digestible with heat processing, and steaming may reduce their allergenic potential [60] [62].

CONCLUSION

Pis s 1, 2 and 3 will improve the accuracy of food allergy diagnoses by better understanding cross-reactivities and risk stratification, especially as vegan protein sources become more popular.

ALLERGEN SOURCE

PEANUT

Arachis hypogaea

ALLERGEN NAME

Ara h 18

ALLERGEN BIOCHEMICAL NAME

Cyclophilin

ROUTE OF ALLERGEN EXPOSURE

Food allergen

GEOGRAPHICAL RELEVANCE

Global

DIAGNOSTIC BENEFIT

Increased sensitivity, enhanced risk assessment & resolution of cross-reactivities

Ara h 18 is a recently identified peanut allergen from the cyclophilin allergen family. Accordingly, Ara h 18 may help explain positive peanut sensitisation test results in the absence of IgE to currently available peanut components [63].

CROSS-REACTIVITY

Ara h 18 is typically encountered through peanut consumption but may also present as a cross-reactive allergen [63]. Ara h 18 shares 88–91 % a.a. sequence identity with cyclophilins in birch (Bet v 7), olive (Ole e 15), and periwinkle (Cat r 1) pollen, indicating that cross-reactive pollen sensitisation could lead to a positive peanut test result even in the absence of primary peanut sensitisation [63].

STABILITY

The heat stability of Ara h 18 has not yet been elucidated.

CONCLUSION

The use of this marker allergen will help explain positive peanut sensitisation test results in the absence of IgE to currently available peanut components.

Fruits

ALLERGEN SOURCE

AVOCADO

Persea americana

ALLERGEN NAME
Pers a 1

ALLERGEN BIOCHEMICAL NAME
Class I chitinase

ROUTE OF ALLERGEN EXPOSURE
Food allergen

GEOGRAPHICAL RELEVANCE
USA, Mexico, South America, Australia

DIAGNOSTIC BENEFIT
Higher sensitivity, enhanced risk assessment & resolution of cross-reactivities

Pers a 1 is a major allergen found in avocado. It has been identified as the panallergen involved in latex-fruit syndrome [64]. In one study, Pers a 1 triggered positive skin reactions in 7 out of 8 patients with latex-fruit syndrome [64] [65]. In another study, IgE reactivity was observed in 15 of 20 patients with avocado and/or latex allergies, indicating its role as a significant allergen in individuals sensitised to both [66].

CROSS-REACTIVITY

Pers a 1 results in extensive cross-reactivity with foods from different food families (e.g., banana, chestnut, kiwi, green bean, etc.) and has been shown to cross-react with a major latex allergen, hevein (Hev b 6) [64] [67] [68] [69] [70] [71] [72] [73]. Amino acid sequence analysis has revealed that Pers a 1 shares 70 % similarity with prohevein in their chitin-binding domains [66]. This structural similarity underlines the cross-reactivity between avocado, latex, and other fruits, contributing to allergic reactions in individuals with latex-fruit syndrome.

STABILITY

Pers a 1 is a 32 kDa heat-labile protein that undergoes significant degradation when exposed to simulated gastric fluid [66] [73] [74].

CONCLUSION

Pers a 1 helps distinguish between primary avocado allergy and latex-related reactions, making it an important component in the molecular diagnosis of food and latex allergies.

ALLERGEN SOURCE

BANANA

Musa acuminata

ALLERGEN NAME
Mus a 2, Mus a 5

ALLERGEN BIOCHEMICAL NAME
Class 1 chitinase (Mus a 2), β-1,3-glucanase (Mus a 5)

ROUTE OF ALLERGEN EXPOSURE
Food allergen

GEOGRAPHICAL RELEVANCE
Global

DIAGNOSTIC BENEFIT
Higher sensitivity, enhanced risk assessment & resolution of cross-reactivities

Mus a 2 is a major allergen found in bananas. Studies have shown that purified Mus a 2 allergens triggered positive skin prick test (SPT) reactions in over 50 % of patients with banana allergy [72]. Additionally, Mus a 2 fully inhibited the IgE binding by the crude banana extract when tested by immunoblot inhibition [72]. Mus a 5 is a major allergen found in bananas. It is particularly important among paediatric patients, with studies showing IgE binding in 74–84 % of cases [75] [76]. Mus a 5 can be classified as a marker for banana allergy diagnosis, especially in banana-allergic patients with negative test results for banana extract [75].

CROSS-REACTIVITY

Mus a 2 is cross-reactive, particularly for individuals with latex allergy, as both banana and latex share common protein structures (i.e., hevein-like domain) [77] [78]. The allergen is significant because it shares similarities with chitinases found in other fruits and nuts such as avocado and chestnut, which may explain the cross-sensitisation among these foods [78]. Mus a 5 shares similarities with glucanases found in latex (Hev b 2) and olive pollen (Ole e 9).

STABILITY

Mus a 2, like other class 1 chitinases, is resistant to heat and digestion. Mus a 5, like other β-1,3-glucanases, is labile to heat and digestion.

CONCLUSION

Mus a 2 and Mus a 5 will enhance the accuracy of identifying banana-allergic patients and improve diagnostic accuracy by distinguishing true banana allergy from potential cross-reactivity with other allergens, particularly for patients with multiple food and latex allergies.

ALLERGEN SOURCE

MANGO

Mangifera indica

ALLERGEN NAME
Man i 1

ALLERGEN BIOCHEMICAL NAME
Class IV chitinase

ROUTE OF ALLERGEN EXPOSURE
Food allergen

GEOGRAPHICAL RELEVANCE
Asia, Mexico, USA

DIAGNOSTIC BENEFIT
Higher sensitivity, enhanced risk assessment & resolution of cross-reactivities

Man i 1 is a major allergen found in mango. It can trigger immune responses in sensitive individuals, leading to symptoms ranging from mild to severe, including anaphylaxis in some cases [79] [80].

CROSS-REACTIVITY

Man i 1 shares similarities with chitinases found in other plant species, such as those in latex and certain pollens (e.g., mugwort and birch), which can contribute to cross-reactivity between different allergen sources [81].

STABILITY

Man i 1, found in all parts of the mango, including peel and pulp, is heat-stable [79] [82].

CONCLUSION

Man i 1 will enhance the accuracy of identifying mango-specific sensitisation, distinguishing it from cross-reactivity with other allergen sources like latex, pollen, or other fruits.

ALLERGEN SOURCE

PEACH

Prunus persica

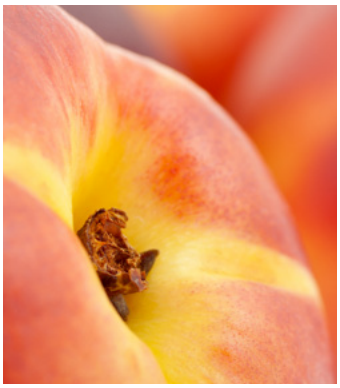
ALLERGEN NAME
Pru p 7

ALLERGEN BIOCHEMICAL NAME
Gibberellin-regulated protein

ROUTE OF ALLERGEN EXPOSURE
Food allergen

GEOGRAPHICAL RELEVANCE
Europe, Japan, unknown for other regions

DIAGNOSTIC BENEFIT
Enhanced risk assessment



Pru p 7 is a cysteine-rich allergen found in peaches. It is present in both peel and pulp. Furthermore, Pru p 7 is associated with severe peach allergy, especially in countries with high numbers of Cupressaceae trees like cypress and Japanese cedar. Presumably, the primary sensitisers are gibberellin-regulated proteins from Cupressaceae pollen [83].

CROSS-REACTIVITY

Homologous allergens with a potentially high degree of cross-reactivity have been described in mountain cedar, cypress and sugi pollen (Jun a 7, Cup s 7, Cry j 7). Related allergens have also been identified in bell pepper, chili, Japanese apricot, pomegranate, sweet cherry, and sweet orange (Cap a 7, Pru um 7, Pun g 7, Pru av 7, Cit s 7).

STABILITY

The high number of cysteines and therefore disulfide bridges leads to a very high stability to heat and digestion [83].

CONCLUSION

Pru p 7 can induce severe reactions after peach consumption. Regions with a high load of Cupressaceae pollen and high peach consumption harbour populations that can react strongly. The degree of cross-reactivity with other fruit is high. Avoidance is the only therapeutic option available.

Vegetables

ALLERGEN SOURCE

CELERY

Apium graveolens

ALLERGEN NAME
Api g 7

ALLERGEN BIOCHEMICAL NAME
Defensin-like protein 1

ROUTE OF ALLERGEN EXPOSURE
Food allergen

GEOGRAPHICAL RELEVANCE
Australia, Japan, Europe, USA, Canada

DIAGNOSTIC BENEFIT
Higher sensitivity, enhanced risk assessment & resolution of cross-reactivities

Api g 7 belongs to the defensin allergen family. Defensins are small proteins that have been linked to allergens in a range of sources, including mugwort pollen, ragweed pollen, peanut, soy and horseradish [84]. Api g 7, a major allergen in celery stalk, is primarily encountered through food exposure and contributes to allergic reactions, particularly in people with pollen-food syndrome [85] [86]. Its presence in celery extracts is often underrepresented, and patients with negative celery extract tests may still test positive for Api g 7 [87].

CROSS-REACTIVITY

Api g 7 is particularly notable for its cross-reactivity with Art v 1, a major allergen in mugwort pollen, and plays a key role in what is known as the celery-mugwort-spice syndrome (CMSS) [85] [86]. This syndrome is characterised by cross-reactions between mugwort pollen and certain vegetables and spices, including celery [85] [86].

STABILITY

Api g 7 is resistant to heat and gastric digestion [85] [86].

CONCLUSION

Api g 7 enhances the diagnostic workup of celery allergy by boosting test sensitivity and improving diagnostic accuracy in cases of suspected CMSS.

Animal-Based Foods

ALLERGEN SOURCE

COW'S MILK

Bos domesticus

ALLERGEN NAME
Bos d 9, Bos d 10, Bos d 11, Bos d 12

ALLERGEN BIOCHEMICAL NAME
α-S1-casein, α-S2-casein, β-casein, κ-casein

ROUTE OF ALLERGEN EXPOSURE
Food allergen

GEOGRAPHICAL RELEVANCE
Global

DIAGNOSTIC BENEFIT
Higher sensitivity & enhanced risk assessment

Four distinct casein proteins are recognised as individual allergens: α-S1-casein (Bos d 9), α-S2-casein (Bos d 10), β-casein (Bos d 11), and κ-casein (Bos d 12) [58] [88] [89] [90].

CROSS-REACTIVITY

Bos d 9–12 contain IgE epitopes that are both cross-reactive and non-cross-reactive within the group. Research measuring IgE reactivity to purified recombinant caseins has demonstrated that patients' IgE antibodies can distinguish between the different casein allergens [90].

STABILITY

Caseins are highly heat-resistant but vulnerable to digestion (susceptible to enzymatic degradation) [89].

CONCLUSION

Bos d 9–12 provide valuable information when cow's milk allergy is suspected. The use of these marker allergens not only confirms sensitisation but also offers a clearer understanding of specific sensitisation regarding cross-reactivity and the risk of severe reactions.

ALLERGEN SOURCE

RED MEAT

Beef, goat, lamb, pork, veal, venison
(Source: allergen.org)

ALLERGEN NAME
Galactose-α-1,3-galactose (short: α-gal)

ROUTE OF ALLERGEN EXPOSURE
Food allergen

GEOGRAPHICAL RELEVANCE
Global

DIAGNOSTIC BENEFIT
Diagnosis of α-gal syndrome

α-gal is an oligosaccharide from non-primate mammals and is present in all forms of tissue including red meat, innards like kidney, gelatine and gelatine-based vaccines, cat IgA and some drugs (e.g., cetuximab), and is the major cause of red meat allergy [91] [92]. α-gal syndrome (AGS) is the term used to describe allergic reactions to mammalian meat. The only confirmed route of sensitisation is through tick bites [93] [94] [95] [96]. The clinical features of AGS are different from classical type I allergies. The onset of symptoms occurs 2–6 hours after consumption of α-gal-containing foods. The clinical picture includes urticaria, gastrointestinal symptoms as well as anaphylactic reactions.

CROSS-REACTIVITY

As α-gal is present in all non-primate mammalian red meat, the degree of cross-reactivity is very high. Innards, like kidneys, contain higher concentrations of α-gal than muscle meat.

STABILITY

α-gal is stable to heat.

CONCLUSION

α-gal, unlike other IgE binding sugars (CCDs), can cause severe allergic reactions. In contrast to other type I allergies, the onset of symptoms is delayed by several hours. The diagnostic workup includes anamnesis, PTP, and sIgE analyses to red meat extracts and α-gal itself. Avoidance is the only therapeutic option available.

Seafood

ALLERGEN SOURCE

COMMON CARP

Cyprinus carpio

ALLERGEN NAME
Cyp c 2

ALLERGEN BIOCHEMICAL NAME
β-enolase

ROUTE OF ALLERGEN EXPOSURE
Food allergen

GEOGRAPHICAL RELEVANCE
Asia, Egypt, Europe

DIAGNOSTIC BENEFIT
Higher sensitivity & resolution of cross-reactivities

Cyp c 2, a β-enolase, is a glycolytic enzyme that is highly expressed in the muscle of fish.

CROSS-REACTIVITY

β-enolases from different species share a high degree of sequence identity and might therefore be highly cross-reactive. There is a high degree of a.a. sequence alignment between Cyp c 2 and Gad m 2 (cod), Sal s 2 (salmon), Thu a 2 (tuna) and Gal d 9 (chicken) [97] [98].

STABILITY

Enolases are potentially heat-labile. The way fish is prepared can vary greatly, from raw to highly processed. Given its potential heat lability, β-enolase monosensitised patients can benefit from this diagnosis by limiting their consumption to heat-treated fish.

CONCLUSION

Considering the presence of β-enolases in various species and their conserved amino acid sequence, sensitisation to Cyp c 2 will help to understand clinical implications for various allergen sources.

ALLERGEN SOURCE

GIANT FRESHWATER PRAWN

Macrobrachium rosenbergii

ALLERGEN NAME
Mac r 1

ALLERGEN BIOCHEMICAL NAME
Tropomyosin

ROUTE OF ALLERGEN EXPOSURE
Food allergen

GEOGRAPHICAL RELEVANCE
Tropical & subtropical countries (e.g., Thailand) [99]

DIAGNOSTIC BENEFIT
Higher sensitivity & resolution of cross-reactivities

Mac r 1 is a member of the tropomyosin allergen family and can elicit severe reactions.

CROSS-REACTIVITY

Mac r 1 and other members of the tropomyosin family exhibit strong cross-reactivity with crustaceans, while cross-reactivity is lower for molluscs, insects (incl. edible insects), and mites. Sensitisation to one tropomyosin may trigger allergy to others. Although cross-reactivity between tropomyosins is often observed, some cases of children with specific allergy to either Penaeus monodon (marine shrimp) or Macrobrachium rosenbergii (freshwater shrimp) have been reported.

STABILITY

Mac r 1 is highly heat-stable [100].

CONCLUSION

Mac r 1 is the first commercially available tropomyosin for freshwater shrimp.

ALLERGEN NAME
Mac r 2

ALLERGEN BIOCHEMICAL NAME
Arginine kinase

ROUTE OF ALLERGEN EXPOSURE
Food allergen

GEOGRAPHICAL RELEVANCE
Tropical & subtropical regions

DIAGNOSTIC BENEFIT
Higher sensitivity & resolution of cross-reactivities

Mac r 2 is a member of the arginine kinase allergen family and is considered the second most important shrimp allergen. Studies show that between 10–51 % of individuals with shrimp allergy exhibit IgE binding to arginine kinase [101].

CROSS-REACTIVITY

Amino acid sequence analysis of Mac r 2 revealed significant differences compared to arginine kinases from other crustaceans[102]. Additionally, a study with 68 shrimp-allergic children observed differences in binding patterns between Macrobrachium rosenbergii (freshwater shrimp) and Penaeus monodon (marine shrimp).

STABILITY

Mac r 2 is heat-stable [100].

CONCLUSION

Mac r 2 is an important allergen in crustacean allergy. Species-specific epitopes on arginine kinase molecules create the necessity to test for species-specific allergens to ensure the correct allergy diagnosis.

ALLERGEN SOURCE

SALMON

Salmo salar

ALLERGEN NAME
Sal s 6

ALLERGEN BIOCHEMICAL NAME
Collagen

ROUTE OF ALLERGEN EXPOSURE
Food allergen

GEOGRAPHICAL RELEVANCE
Europe, Japan, Korea, USA

DIAGNOSTIC BENEFIT
Higher sensitivity

Sal s 6 is a collagen-derived protein from salmon. Fish collagen is widely used in medicine, cosmetics, and the food industry. Collagen's insolubility in aqueous solutions leads to a low abundance in commercially available in-vitro and skin prick test solutions for fish allergy [103].

CROSS-REACTIVITY

The degree of cross-reactivity between Sal s 6 and other members of this family is moderate to high [103].

STABILITY

Sal s 6 is stable to heat and digestion.

CONCLUSION

Although most fish-allergic patients react to allergens from the parvalbumin allergen family, Sal s 6 is a valuable addition to the diagnostic workup of fish-allergic patients – especially due to its use in cosmetics, medicines, and in the food industry in general. As Sal s 6 is hardly soluble in water, it could be underrepresented in test extracts (both in vivo and in vitro).

ALLERGEN SOURCE

WHITELEG SHRIMP

Litopenaeus vannamei

ALLERGEN NAME
Lit v 7

ALLERGEN BIOCHEMICAL NAME
Hemocyanin

ROUTE OF ALLERGEN EXPOSURE
Food allergen

GEOGRAPHICAL RELEVANCE
Asia, Southern Europe, South America, West Africa, Southern USA

DIAGNOSTIC BENEFIT
Higher sensitivity & resolution of cross-reactivities

Lit v 7 belongs to the hemocyanin family and is found in the haemolymph of invertebrate animals (e.g., cephalothorax). Shrimp extracts for skin prick testing and specific IgE determination are often made from deveined abdominal muscles and therefore lack this allergen [104].

CROSS-REACTIVITY

Sequence alignment showed high sequence identity between Lit v 7 and Pen m 7 (>90 % a.a. sequence identity). Some studies suggest cross-reactivity for hemocyanin between arthropods and shrimps [105].

STABILITY

Lit v 7 has low heat stability.

CONCLUSION

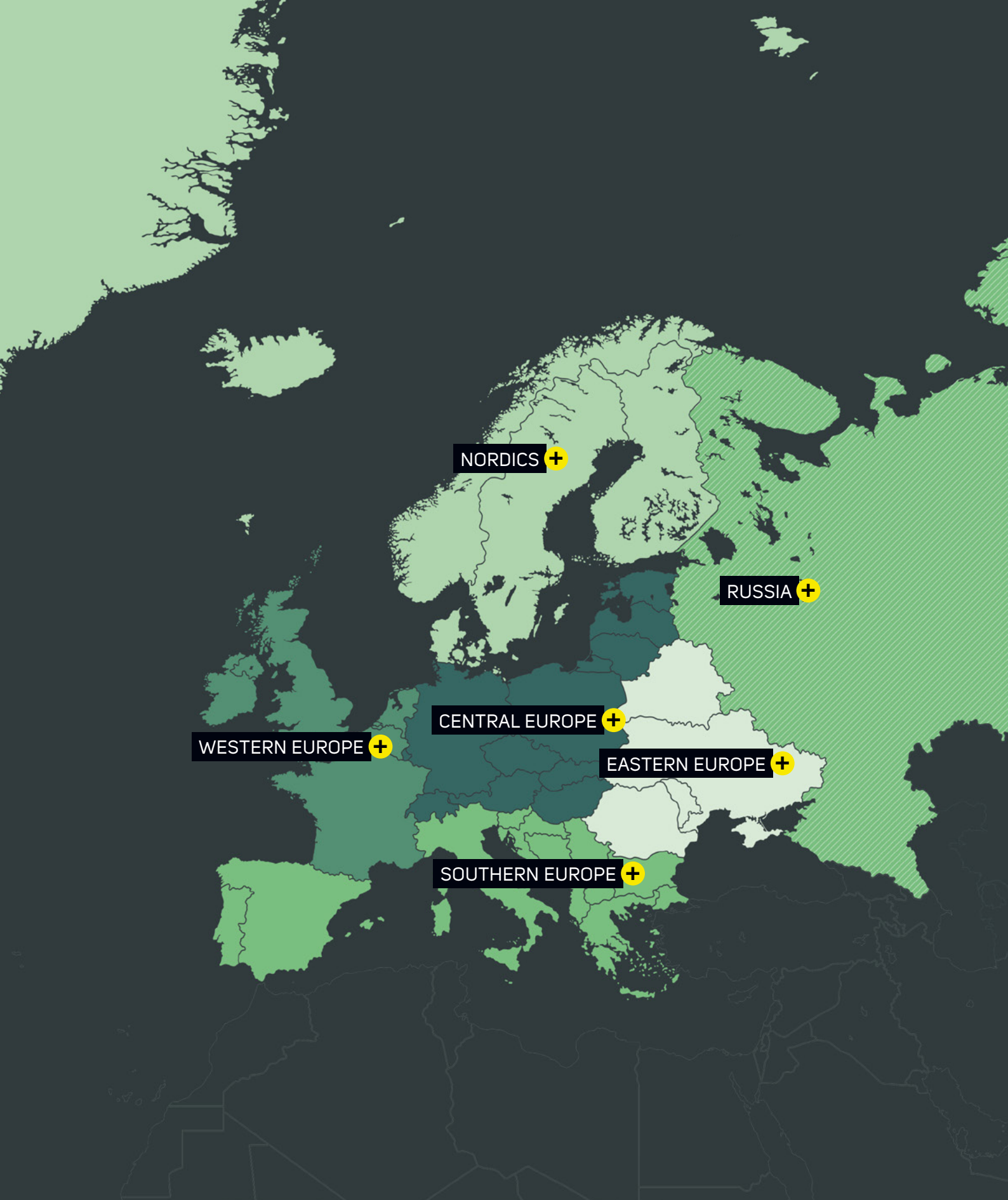
In shrimp-allergic patients, for whom commonly tested allergens remain negative, hemocyanin might be responsible [104]. For correct diagnosis, the dietary habits of patients reporting allergic reactions are often important, as their sensitisation pattern to food allergens may be affected [104].

Europe

A visual representation of the test's improved coverage of allergens worldwide.

CATEGORY	ALLERGEN SOURCE	GLOBAL	Nordics	Western Europe	Central Europe	Southern Europe	Eastern Europe	Russia
POLLEN	Birch pollen		●	●	●		●	●
	Maize pollen		●	●	●	●	●	●
	Oak pollen		●	●	●	●	●	●
	Russian thistle pollen					●	●	●
MITES	B. tropicalis*							
	D. farinae			●	●	●	●	●
	T. putrescentiae	●						
INSECTS	American cockroach					●	●	●
PETS	Golden hamster		●	●	●	●	●	●
	Rat	●						
MICROORGANISMS	Aspergillus fumigatus			●	●		●	●
	Malassezia sympodialis		●	●	●			
VENOMS	Bald-faced hornet venom*							
	Honeybee venom	●						
NUTS & SEEDS	Almond			●	●	●		
	Cashew		●	●	●	●		●
	Coconut		●	●	●	●	●	●
	Macadamia			●	●			
	Pecan		●	●	●	●	●	
	Pine nut			●		●		●
	Poppy seed				●	●		●
	Sunflower seed				●		●	●
GRAINS	Wheat	●						
LEGUMES	Lentil			●	●	●		
	Pea	●						
	Peanut		●	●	●	●	●	●
FRUITS	Avocado			●	●	●		
	Banana			●	●	●	●	●
	Mango		●	●	●	●	●	●
	Peach			●	●	●	●	●
	Strawberry			●	●	●	●	
VEGETABLES	Celery		●	●	●	●	●	
ANIMAL-BASED FOODS	Chicken	●						
	Cow's milk	●						
	Red meat	●						
SEAFOOD	Carp				●		●	●
	Giant freshwater prawn			●		●		
	Salmon		●	●	●	●	●	●
	Whiteleg shrimp		●	●	●	●	●	●

*) low or no occurence in this region


NORDICS
RUSSIA
CENTRAL EUROPE
WESTERN EUROPE
EASTERN EUROPE
SOUTHERN EUROPE

Americas

CATEGORY	ALLERGEN SOURCE	GLOBAL	Canada & Alaska	Northern USA	Southern USA	Mexico	Central America	Northern South America	Southern South America
POLLEN	Birch pollen		●	●					●
	Maize pollen			●	●	●	●	●	
	Oak pollen		●	●	●	●		●	●
	Russian thistle pollen				●	●			●
MITES	B. tropicalis				●	●	●	●	
	D. farinae		●	●	●	●	●	●	●
	T. putrescentiae	●							
INSECTS	American cockroach				●	●	●	●	●
PETS	Golden hamster		●	●	●				
	Rat	●							
MICROORGANISMS	Aspergillus fumigatus			●	●			●	
	Malassezia sympodialis				●[1]			●	
VENOMS	Bald-faced hornet venom		●	●	●	●			
	Honeybee venom	●							
NUTS & SEEDS	Almond		●	●	●	●			
	Cashew		●	●	●	●	●	●	●
	Coconut		●	●	●	●	●	●	
	Macadamia		●	●	●			●	
	Pecan		●		●[1]	●		●	●
	Pine nut		●	●	●	●			
	Poppy seed		●	●	●	●			
	Sunflower seed		●	●	●	●		●	●
GRAINS	Wheat	●							
LEGUMES	Lentil		●	●	●	●		●	●
	Pea	●							
	Peanut		●	●	●	●	●	●	●
FRUITS	Avocado			●	●	●	●	●	●
	Banana		●	●	●	●	●	●	●
	Mango				●	●	●	●	
	Peach		●	●	●	●	●	●	●
	Strawberry		●	●	●	●	●	●	●
VEGETABLES	Celery		●	●	●	●	●	●	●
ANIMAL-BASED FOODS	Chicken	●							
	Cow's milk	●							
	Red meat	●							
SEAFOOD	Carp		●	●	●				
	Giant freshwater prawn*								
	Salmon		●	●	●				
	Whiteleg shrimp		●	●	●	●	●	●	

*) low or no consumption in this region 1) + California


CANADA & ALASKA
NORTHERN USA
SOUTHERN USA
MEXICO
CENTRAL AMERICA
NORTHERN SOUTH AMERICA
SOUTHERN SOUTH AMERICA

Africa

CATEGORY	ALLERGEN SOURCE	GLOBAL	North Africa	Sub-Saharan Africa	South Africa
POLLEN	Birch pollen*				
	Maize pollen			●	●
	Oak pollen				●
	Russian thistle pollen		●		●
MITES	B. tropicalis			●	
	D. farinae			●	●
	T. putrescentiae	●			
INSECTS	American cockroach			●	
PETS	Golden hamster*				
	Rat	●			
MICROORGANISMS	Aspergillus fumigatus			●	●
	Malassezia sympodialis			●	●
VENOMS	Bald-faced hornet venom*				
	Honeybee venom	●			
NUTS & SEEDS	Almond		●		●
	Cashew		●	●	●
	Coconut			●	●
	Macadamia			●	●
	Pecan				●
	Pine nut		●		
	Poppy seed		●		●
	Sunflower seed		●	●	●
GRAINS	Wheat	●			
LEGUMES	Lentil		●	●	●
	Pea	●			
	Peanut		●	●	●
FRUITS	Avocado			●	●
	Banana		●	●	●
	Mango			●	●
	Peach		●		●
	Strawberry		●	●	●
VEGETABLES	Celery		●		●
ANIMAL-BASED FOODS	Chicken	●			
	Cow's milk	●			
	Red meat	●			
SEAFOOD	Carp		●[1]	●	●
	Giant freshwater prawn		●[1]	●	●
	Salmon				●
	Whiteleg shrimp*				

*) low or no consumption/occurence in this region; [1)] Egypt only


NORTH AFRICA
SUB-SAHARAN AFRICA
SOUTH AFRICA

Asia

CATEGORY	ALLERGEN SOURCE	GLOBAL	Western Asia	Central Asia	Northern Asia	Eastern Asia	Southern Asia	Southeast Asia
POLLEN	Birch pollen			●	●			
	Maize pollen				●	●	●	●
	Oak pollen			●	●	●	●	●
	Russian thistle pollen		●	●	●			
MITES	B. tropicalis					●	●	●
	D. farinae				●	●	●	●
	T. putrescentiae	●						
INSECTS	American cockroach				●	●	●	●
PETS	Golden hamster				●			
	Rat	●						
MICROORGANISMS	Aspergillus fumigatus		●			●	●	●
	Malassezia sympodialis		●		●	●	●	●
VENOMS	Bald-faced hornet venom*							
	Honeybee venom	●						
NUTS & SEEDS	Almond		●	●	●	●	●	●
	Cashew		●		●	●	●	●
	Coconut					●	●	●
	Macadamia				●	●	●	●
	Pecan		●		●	●	●	
	Pine nut		●	●	●	●	●	●
	Poppy seed		●	●		●	●	
	Sunflower seed		●	●	●	●	●	●
GRAINS	Wheat	●						
LEGUMES	Lentil		●	●			●	●
	Pea	●						
	Peanut		●	●	●	●	●	●
FRUITS	Avocado				●	●	●	●
	Banana		●		●	●	●	●
	Mango				●	●	●	●
	Peach		●		●	●		
	Strawberry				●	●	●	
VEGETABLES	Celery		●		●	●		
ANIMAL-BASED FOODS	Chicken	●						
	Cow's milk	●						
	Red meat	●						
SEAFOOD	Carp		●[1]		●	●	●	●
	Giant freshwater prawn					●	●	●
	Salmon		●		●	●		
	Whiteleg shrimp				●	●	●	●

*) no occurence in this region; 1) Iraq only


CENTRAL ASIA
NORTHERN ASIA
WESTERN ASIA
EASTERN ASIA
SOUTHERN ASIA
SOUTHEAST ASIA

Oceania

CATEGORY	ALLERGEN SOURCE	GLOBAL	Australia & Papua New Guinea	New Zealand
POLLEN	Birch pollen			●
	Maize pollen		●	●
	Oak pollen		●	●
	Russian thistle pollen		●	
MITES	B. tropicalis		●	●
	D. farinae		●	●
	T. putrescentiae	●		
INSECTS	American cockroach		●	●
PETS	Golden hamster*			
	Rat	●		
MICROORGANISMS	Aspergillus fumigatus		●	●
	Malassezia sympodialis		●	●
VENOMS	Bald-faced hornet venom*			
	Honeybee venom	●		
NUTS & SEEDS	Almond		●	●
	Cashew		●	●
	Coconut		●	●
	Macadamia		●	●
	Pecan		●	●
	Pine nut		●	
	Poppy seed		●	●
	Sunflower seed		●	●
GRAINS	Wheat	●		
LEGUMES	Lentil*			
	Pea	●		
	Peanut		●	●
FRUITS	Avocado		●	●
	Banana		●	●
	Mango		●	●
	Peach		●	●
	Strawberry		●	●
VEGETABLES	Celery		●	●
ANIMAL-BASED FOODS	Chicken	●		
	Cow's milk	●		
	Red meat	●		
SEAFOOD	Carp*			
	Giant freshwater prawn		●	
	Salmon		●	●
	Whiteleg shrimp		●	●

*) low or no consumption in this region


AUSTRALIA & PAPUA NEW GUINEA
NEW ZEALAND

Children's Book

We created our own children's book about allergy testing!

Our children's book is entitled "Achoo! Emma and the mysterious sniffles" and tells the story of little Emma, who develops suspicious symptoms such as sneezing and itchy eyes after playing with her best friend's dog. But does this mean that Emma's family can't adopt a dog from the animal shelter, as was originally planned?

This little book aims to familiarise the youngest readers and especially their parents with the topic of allergies and the importance of early allergy testing. From the beginning, it was clear to us that we wanted to work with the renowned German publishing house Carlsen for the project. In 1954, Carlsen launched their popular children's book format called "Pixi books", with more than 2,000 different stories told already and over 450 million copies sold worldwide.

"Especially in German-speaking countries, Pixi books are simply iconic with a long-standing tradition. Either you read the books yourself as a child, or you read them to your own children or grandchildren today," says MADx CEO Dr Christian Harwanegg, who is himself the father of four daughters.

"Achoo! Emma and the mysterious sniffles" is available in three languages (German, English and Spanish) and was of course produced in the familiar 10 × 10 cm Pixi book format. It is available in doctors' practices in Austria, Germany and Spain.

If you are interested in obtaining copies of the MADx Pixi book, please contact us at **marketing@madx.com.**

New Patient Folders

Check out our new patient material!

Over the past year, the marketing and product management teams have been working on new patient material to be displayed in doctor's practices. The aim of these folders is to teach patients more about allergies, help them understand their symptoms, and encourage early testing.

The new ALEX patient folder comes in four versions tailored to different medical specialties such as allergology, dermatology, ENT medicine, and paediatrics. They all explain in simple terms how the test procedure works, why it is important to test for allergies early, and highlight all the benefits of the test.

Depending on the doctor's specialisation, the different folders explain, for example, the correlation between allergies and skin symptoms, how cross-allergies cause itchiness while eating certain foods, and whether a food source is completely taboo after a positive test result.

The ALEX patient material is available in multiple languages, including English, German, Spanish, French, Italian, Greek, and Czech. Furthermore, there is a blank space reserved for the address stamp of the doctor's practice. If you are interested in obtaining one of the existing language versions or creating your own, please contact us at **marketing@madx.com.**

Patient Portal

No extra effort – no costs

Recommend our patient portal!

At MADx, our goal is to help improve and optimise patient care! For this purpose, we created the MADx patient portal: it makes patients' ALEX test results digitally available and offers personalised nutrition tips and lifestyle ideas for dealing with allergies based on those results.

For doctors, the benefits of the patient portal are obvious: it improves patient satisfaction and loyalty through personalised care and supports patients on their path to a healthier life. Familiarising themselves with the patient portal can help patients save time at follow-up appointments since they come in well-prepared with knowledge of their results, enabling them to focus on medically relevant questions. Furthermore, the MADx patient portal facilitates greater acceptance of immunotherapies and nutritional recommendations, which is also beneficial for doctors offering these additional services.

All patients can access the patient portal through a QR code on their ALEX test result. By scanning the code, they are taken directly to their personalised portal, where they can sign up, confirm their profile, and benefit from the contents! The patient portal is available in English and German, with more languages to come.

Please contact our team at **marketing@madx.com** to obtain flyers explaining the patient portal for your practice!

ALEX³ Allergen List

300 ALLERGENS

- 218 molecular allergens & 82 extracts
- 52 new molecular allergens
- 109 unique molecular allergens
- 80 allergen families
- 145 allergen sources

Check out the full ALEX³ allergen list

How Molecular Allergology Is Reshaping Allergy Diagnosis

Interview with Robert G. Hamilton, PhD, D.ABMLI

How has molecular allergology changed the understanding of allergic disease?

Dr Hamilton: Complex allergen extracts have been used in the diagnosis and management of allergic patients since 1921. Prausnitz and Küstner first observed an erythema-wheal reaction that followed an intracutaneous injection of serum from a fish allergic patient into a healthy subject, followed by next-day challenge of the skin site with the fish-allergen extract. An age of enlightenment then occurred with the emergence of molecular allergens and the concept of 'patient-tailored treatment' as put forth by Rudolf Valenta and his Austrian team in the 1990s. This has led to a more granular dissection of the IgE antibody response as a part of diagnosis and more precise targeted immunotherapy management of human allergic disease across the globe.

How does molecular allergology contribute to the development of treatment approaches?

Dr Hamilton: Since my 45-year experience with allergic disease in the US has centred on diagnosis and not patient treatment, I will confine my thoughts to diagnostic issues. More precise identification of a patient's IgE antibody sensitisation profile during a diagnostic evaluation has led to (1) more accurately targeted allergen immunotherapy or planned avoidance strategies, (2) more accurate decisions about relative risk associated with a particular allergen's re-exposure (e.g., IgE anti-Ara h 2 positivity associated with increased risk of a reaction upon peanut re-exposure), and (3) better discrimination of genuine from cross-reactive allergen-specific IgE immune responses, including insight into how cross-reactivity among the 11 well-defined protein allergen families contributes to primary and collateral IgE response-driven reactions. In immunology, 'cross-reactivity' refers to a reaction between an antibody and an antigen that differs from its immunogen. A 'collateral reaction' due to cross-reactivity occurs when IgE binds to a cross-reactive secondary allergenic epitope or molecule (e.g., PR-10 family Cor a 1 from hazelnut) that is subordinate to the allergen specificity inducing the primary sensitisation (birch pollen Bet v 1).

ABOUT

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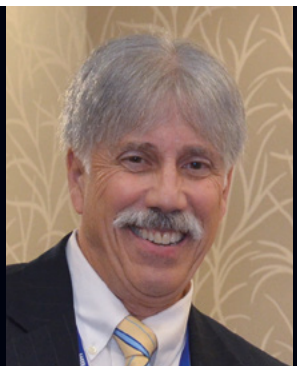
> "An age of enlightenment occurred with the emergence of molecular allergens."



How can multiplex IgE testing improve allergy research and patient care?

Dr Hamilton: In 1967, the paper disc-based singleplex radioallergosorbent emerged from Sweden as the first serological assay for detection of the newly defined reagin (IgE antibody) as the gatekeeper of the immediate-type allergic response. Since then, technology has continued to enhance our ability to accurately quantify IgE antibody levels in the clinical immunology laboratory through developments such as increased automation; improved higher density allergosorbents using different solid phase matrices (beads, carbohydrate sponges, nitrocellulose strips, chips); safer non-isotypic labels (enzymes, fluorophores); the first multi-allergen single allergosorbent (e.g., Phadiatop); and, in our modern era, true chip-based multiplex microarrays (ISAC and ALEX) with up to 300 spotted allergenic molecules and extracts. The multiplex microarray has greatly enhanced modern-day patient care and research efforts by permitting the simultaneous quantification of total and allergen-specific IgE antibodies to the major clinically relevant allergenic specificities (genuine and cross-reactive allergen families) using small amounts of serum/plasma. For allergists who are accustomed to ordering IgE antibody serology only for those allergen specificities indicated by the patient's clinical history, they are initially overwhelmed by the large amount of comprehensive serological IgE antibody data, some of which identify asymptomatic sensitisation that can be difficult to explain to their patient who reports no objective symptoms associated with that allergen specificity. With experience, they become more comfortable with using comprehensive molecular allergen-based IgE antibody profiles.

Where do you see the strengths and weaknesses of single- and multiplex IgE testing?

Dr Hamilton: The strengths and weaknesses of single- and multiplex assays are constantly changing with improved technology on both sides of the technology spectrum. More experience with molecular allergen macroarrays is changing the impression of practising allergists toward more acceptance. Quantitative singleplex assays have been analytically well-documented over years of use and they are the predicate devices used to judge performance of the newer molecular allergen-heavy multiplex macroarrays. The third-generation ALEX, for instance, can go effectively head-to-head with their best singleplex assay counterparts as both interpolate IgE antibody data quantitatively from total serum IgE reference curves traceable to the WHO IgE IRP. TThe comprehensive nature of the test – with 300 allergen specificities, requiring a small 200 µl sample size, offering equivalent analytical and diagnostic performance and greater simplicity – makes it the future of molecular allergen-based microarray diagnostics.

> "The third-generation ALEX can go effectively head-to-head with the best singleplex assay."

How is the USA different from Europe when it comes to IgE testing?

Dr Hamilton: There are several differences between Europe and the USA when it comes to trends in IgE antibody testing. In the USA, the allergist is not reimbursed for ordering an IgE antibody serology, so skin testing has historically been a diagnostic modality of choice, as it helps financially support their practice. The American allergy community is roughly 10 years behind in its knowledge and experience with molecular allergology both as it relates to diagnosis and using molecular allergen-specific IgE data to help plan avoidance or immunotherapy management. This is because much of the research identifying, cloning and characterising molecular allergens has occurred in Europe since the 1990s, while the US research community has focused more heavily on mechanisms of allergic disease. Finally, multiplex assays like the ISAC and ALEX were cleared for patient testing in the EU many years before the stringent requirements of the US-FDA could be met. This means that publications using molecular microarray assay data from European researchers are the first to appear in peer-reviewed journals. This is changing: US allergists are now convinced of the diagnostic value of peanut and hazelnut components, which are clinically tested using singleplex autoanalysers. More and more are added to their 'accepted list' each year as published science supports their use. Gradually, the molecular macroarray is being introduced to the US research community, and eventually it will be FDA-cleared and available for patient testing.

Insights on Molecular Allergy Testing in Southeast Asia

Interview with Narissara Suratannon, MD, PhD

What are the main allergen sources (respiratory, food, and venom) that impact allergic patients in Thailand?

Dr Suratannon: In Thailand and Southeast Asia, the most common inhalant allergens are house dust mites, particularly Dermatophagoides pteronyssinus (Der p) and Dermatophagoides farinae (Der f). Interestingly, Blomia tropicalis is also a significant contributor to respiratory allergies in our region but remains underrecognised and frequently underdiagnosed.

For food allergens, hen's egg, cow's milk, and wheat are most common among children. In adolescents and adults, shrimp is the most prevalent allergen. Cashew nuts and certain fish species, such as cod, are also increasingly reported in our population. With respect to venom allergy, fire ants and wasps are major triggers of severe, life-threatening allergic reactions, while honeybee venom allergy is rarely seen in Thailand.

Are these sources covered by molecular IgE tests at your disposal, or are there only extracts available?

Dr Suratannon: For Der p and Der f, both extract-based IgE tests and component-resolved diagnostics (CRD) are available. However, Blomia tropicalis is often overlooked in centres that do not utilise multiplex platforms like ALEX², leading to misdiagnosis in a notable proportion of patients. In the case of wheat, seafood, and fire ant allergy, current IgE tests – whether crude extract-based or CRD – are still limited in diagnostic accuracy. We are optimistic that the upcoming ALEX^3 platform, which includes new recombinant allergens relevant to shrimp and wheat, will significantly improve diagnostic precision in our setting.

Since when do you use molecular allergology in a multiplex format for the diagnostic work-up of your patients, and how did that impact your therapeutic decisions?

Dr Suratannon: I began incorporating multiplex molecular allergology into clinical practice in 2023, particularly for patients with multiple sensitisations. This tool has been immensely valuable in identifying true sensitisers, minimising false positives (thanks to the inclusion of CCD inhibitors), resulting in appropriate selection of allergens for immunotherapy (AIT).
Furthermore, ALEX is the only platform that allows for longitudinal monitoring of specific IgE changes during and after AIT, which provides clinical insights not achievable through conventional testing.

What are the pros and cons of using molecular IgE multiplex tests?

Dr Suratannon: The pros: they distinguish genuine sensitisations from cross-reactive allergens; they are crucial for tailored AIT selection; they enable broad allergen screening in a single test ("top-to-bottom" approach), they allow for monitoring of sIgE levels over time; they reduce the need for ordering multiple tests; they require only a small amount of blood; and the total IgE levels obtained from the ALEX test are generally comparable to those measured by standard testing methods.
The cons: the interpretation can be complex and requires expertise in molecular allergology; also, some relevant allergens are still missing from current panels.

What is your favourite allergen family and why?

Dr Suratannon: One of my preferred allergen components is Der p 23, a major molecule found in house dust mite bodies. Its detection is highly influential when selecting HDM AIT products, as not all formulations include adequate representation of mite body components, often resulting in suboptimal AIT responses.
I also find arginine kinase (e.g., Bla g 9) particularly intriguing. It has broadened our understanding of cross-reactivity between shellfish and insect allergens in our population, even more so than tropomyosin. Such findings allow clinicians to contribute to regional allergen profiling and global insights into unique sensitisation patterns.

> "Hen's egg, cow's milk, and wheat are the most common food allergens among children."

What are your expectations for the in-vitro diagnostic industry regarding new developments?

Dr Suratannon: I hope to see ongoing advancements in accuracy and the inclusion of newly identified, clinically relevant allergens, which MADx has, indeed, done an excellent job of supporting over the years. Customisable or smaller microarray panels for follow-up testing would also enhance cost-effectiveness, allowing patients to avoid repeating full panels unnecessarily. Additionally, innovations such as IgE testing from dried blood spots could greatly improve access to testing in remote areas, enabling centralised testing at referral centres.

Finally, I deeply appreciate MADx's continued openness to collaboration with physicians and their commitment to improving allergy diagnostics worldwide.

ABOUT

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> "I use multiplex testing particularly for patients with multiple sensitisations."

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