

WHAT IS NEW IN ALLERGY AND COMPONENT TESTING?

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INTRODUCTION

Considerable progress has been made in the area of molecular allergology over the past few years. Molecular or component-resolved diagnostic (CRD) tests are promising and studies continue to emerge regarding their utility. A better understanding of allergen components and their role in the mechanisms of sensitisation and tolerance induction leads to a more targeted management of inhalant and food allergy.

The impact of molecular spreading of furry-animal components on clinical disease has been documented. The first case report is now published confirming that a dog-allergic patient mono-sensitised to Can f 5, prostatic kallikrein, was allergic to male dogs only. It has been shown that used together, Ara h 2 and Ara h 6 – both 2S albumins – can provide the highest diagnostic accuracy. New data shows that the measurement of serum tryptase is of value in the diagnosis of food-allergic reactions and especially in severe anaphylactic reactions. Measuring serum IgE (sIgE) to Der p 23 adds important information on disease progression, and may serve as a severity marker for asthma in patients allergic to house-dust mite (HDM).

This article focuses on recent publications but also provides general information that may be useful to those embarking on understanding the diagnosis and management of allergy and asthma.

INHALANT ALLERGENS

PREDICTING ASTHMA AND ALLERGY

Sensitisation in early childhood can precede respiratory allergy in adolescence.¹ Wickman et al used micro-array component data from a random sample of 786 children at ages four, eight and 16 years from their prospective birth cohort. The purpose was to identify markers that could predict the risk of future respiratory allergy. An English birth cohort was used as a comparison. They concluded that Bet v 1 (birch pollen), Fel d 1 (cat), Phl p 1 (grass pollen) and Ara h 1 (peanut) were predictive for the Swedish population. Relevant components in the group from the United Kingdom included Der p 1 & Der f 2 (HDM), Phl p 1 and Phl p 5 (grass pollen) and Fel d 1 (cat). The authors concluded that IgE-reactivity early in life to these allergen molecules identifies children with a high risk of asthma and/or rhinitis at 16 years.

Cipriani et al have studied the diagnostic relevance of IgE-sensitisation profiles to eight recombinant *Phleum pratense* molecules in 1 120 children (aged 4–18 years) with seasonal allergic rhinoconjunctivitis.² Sensitisation to Phl p 7 was a reliable biomarker of asthma, whereas Phl p 12 was useful as a marker of oral-allergy syndrome (OAS). Sensitisation to Phl p 7 was associated with a more severe form of seasonal allergic rhinitis (AR) and complex component profiles were associated with longer disease duration.

HOUSE-DUST MITE COMPONENTS

Twenty allergens in *D pteronyssius* have been identified thus far. The major allergens, Der p 1 and Der p 2, will identify between 63 and 97% of patients sensitised to *D pteronyssius* extracts, as shown in studies from Europe, North America and Japan.³ A significant proportion of HDM-sensitised patients may be missed if using only major allergens in the diagnostic work-up.

Up to 74% of *D pteronyssius*-allergic patients are sensitised to Der p 23. This is similar to the frequency of sensitisation to that of Der p 1 and Der p 2.⁴ Although levels of sIgE to Der p 23 are on average five times lower than to Der p 1 and Der p 2 in HDM-allergic patients, Der p 23 appears to be ten times more potent than Der p 1 in activating mast cells.³

Matricardi et al have shown that the number of HDM component-specific sensitisations increased with an increase in disease severity, as well as with age of onset. Importantly, sensitisation to Der p 1 and Der p 23 before the age of five was predictive of asthma at school-going age.⁵

Children with both HDM allergy and asthma were shown to be sensitised to a higher number of HDM allergen components than non-asthmatic children with HDM allergy. Furthermore, the IgE levels to Der p 1, Der p 2 and Der p 23 were higher in the asthmatic children than in non-asthmatic children.⁶

Specific IgE (s-IgE) to Der p 23 can add important information on the disease progression, and may serve as a severity marker for asthma in HDM allergy.

FURRY ANIMALS

Sensitisation to dog and/or cat in early life is a strong predictor of the development of childhood asthma.⁷ Sensitisation to furry

animals appears to be on the increase globally.^{8,9} Aranda et al have shown that sensitisation to dog increased from 8 to 40% in Brazilian children over a 12-year period (2004–2016). More than 40% of the households have at least one dog. Sensitisation to dog seems to start early in life and Nagao et al found that dog was the most common inhalant sensitiser in young Japanese children at risk of developing respiratory allergies.¹⁰ Schoos et al examined sensitisation trajectories in childhood by using a cluster analysis during the first six years of life.¹¹ They found that asthma was associated with a specific sensitisation pattern to dog, cat and horse in early childhood.

Davila et al have recently published a consensus document on dog and cat allergy in which they state that measurement of IgE antibodies to animal-dander extract is an established diagnostic tool, however, this has several limitations. In some cases, especially in polysensitised patients, molecular diagnosis is strongly recommended.¹² Molecular diagnosis is recommended in order to distinguish between co-sensitisation and cross-reactivity between various different animals. It is useful in polysensitised patients, in order to provide recommendations for avoidance as well as to identify allergens that are significant components in immunotherapy. Finally, molecular diagnosis may be useful for attempting to predict symptoms and disease severity, especially in patients with asthma and particularly in severe asthma.

DOG COMPONENTS

There are six known dog allergens. Four of these, Can f 1, 2, 4 and 6 belong to the lipocalin family and are present in dog dander, saliva and urine.¹³ Can f 1 is a major allergen and is detected in 50–90% of patients sensitised to dog. Sensitisation to Can f 2 and to the more recently characterised Can f 4 and Can f 6 is less common. These allergens can be detected in 15–35% of dog-sensitised patients and have been shown to cross-react with cat and horse lipocalins. Can f 3, the dog serum albumin, is a highly cross-reactive minor allergen detected in



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15–35 % of dog-sensitised patients. IgE reactivity to Can f 5, the prostatic kallikrein from a male dog, has been found in up to 70% of dog-sensitised individuals among whom 38% were not sensitised to Can f 1, 2 or 3. This suggests that there may be individuals who are allergic specifically to male dogs.

The first case report has recently been published confirming that a dog-allergic patient mono-sensitised to Can f 5 was allergic to only male dogs. This individual had a negative skin-prick test (SPT) and no reaction at ocular provocation test using female dog-dander extract.¹⁴

Sensitisation to the lipocalins in general has been shown to be associated with asthma.¹⁵ Konradsen et al found that sensitisation to Can f 2 was more common in patients with severe asthma.¹⁶ Ukleja-Sokolowska et al have been able to document the association between Can f 2 sensitisation and dyspnoea in pet-allergic patients.¹⁷

A number of studies have now shown the impact of molecular spreading of furry animal components on clinical disease. Käck et al show that polysensitisation to all six dog components conferred the overall highest risk for a positive reaction to dog nasal challenge.¹⁸ Sensitisation to more than three single lipocalins, prostatic kallikrein and secretoglobulin components from furry animals has been associated with asthma severity.¹⁹ Moreover, sensitisation to several components from the same species has shown to be a marker for clinical pet allergy.^{20,21} Käck et al also found that the presence of IgE to Can f 4 and 6, together with the serum albumin Can f 3, conferred the highest risk for a positive nasal challenge.²⁴

CAT COMPONENTS

The secretoglobulin Fel d 1 is the dominant allergen in cat-dander extract.¹³ Sensitisation to Fel d 1 often starts early in life and is most likely to precede the appearance of allergic symptoms. The first described cat lipocalin, Fel d 4 was reported to bind IgE antibodies in a high proportion (>60%) of cat-allergic subjects. Furthermore, the cat lipocalin Fel d 7 was recently identified and shown to bind IgE in 38% of a cat-allergic population. The minor cat allergen Fel d 2 (serum albumin) cross-reacts with other albumins, but its clinical significance is not yet fully

TABLE I: ANIMAL COMPONENTS

ANIMAL	COMPONENT		CLINICAL RELEVANCE
Cat	Fel d 1	Uteroglobin	True sensitisation Major cat allergen Risk factor for asthma
	Fel d 2	Serum albumin	Cross-reacts with other animal albumins Minor cat allergen
	Fel d 4	Lipocalin	Cross-reacts with other animals
Dog	Can f 1	Lipocalins	True sensitisation, major dog allergen
	Can f 2		
	Can f 4		
	Can f 6		
	Can f 5	Prostatic kallikrein	True sensitisation to male dogs
Can f 3	Serum albumin	Cross-reacts with other animals	



Cat: photo credit Elena Kouptsovasic

understood. Tsolakis et al found that sensitisation to Fel d 2 and 4 were independently associated with type-2 biomarkers, such as exhaled nitric oxide and blood eosinophils.²² Uriarte and Sastre found that sensitisation to albumins was associated with severe respiratory symptoms and with high odds ratios for asthma diagnosis.²³

FOOD ALLERGY

HEN'S EGG COMPONENTS

The most important allergens in egg white are Ovomuroid (Gal d 1), Ovalbumin (Gal d 2), Ovotransferrin (Gal d 3) and Lysozyme (Gal d 4). Ovomuroid is resistant to heat and digestion and it has been shown that children with persistent egg allergy have significantly higher levels of ovomucoid than children who outgrow their egg allergy. Modification of allergens is an important strategy in order to attempt to reduce allergenicity in food allergy. Gal d 2, 3 and 4 are heat-labile and thus hydrolysed egg is usually well tolerated by this group of egg-allergic patients.²⁵ Children with IgE-mediated egg allergy can often also tolerate baked egg within a wheat matrix.²⁶

COW'S MILK COMPONENTS

The main allergens in cow's milk are α -lactalbumin (Bos d 4), β -lactoglobulin (Bos d 5), Bovine serum albumin (Bos d 6) and

casein (Bos d 8). Bos d 4, 5 and 6 are whey proteins and are heat-labile. Casein remains stable when exposed to heat and digestive enzymes. Petersen et al studied whether CRD could predict duration and severity of allergy in cow's milk protein-allergic (CMPA) children. They found a correlation between sIgE level to cow's milk and casein and the severity of the allergic reaction elicited by food challenges.²⁷ They documented that high levels of sIgE to milk and its components, especially casein, were predictive of persisting CMPA. The levels of casein IgE tend to reflect the severity of the milk allergy, with children with higher levels being at risk of reacting to both fresh and baked milk as well as being less likely to outgrow their allergy. Children with higher levels of IgE to predominantly whey protein, are often able to tolerate baked-milk products.

WHEAT SENSITISATION AND GRASS POLLEN

Wheat sensitisation is common in grass pollen-allergic individuals and Nilsson et al recently found that 60% of the grass-pollen subjects were sensitised to wheat with a median of 0.5 kU/L. Wheat-sensitised subjects were more often sensitised to the two allergens – Phl p 12 and CCD – known to be cross-reactive between grass and wheat.²⁸ It is therefore a risk that grass-pollen allergy is misdiagnosed as wheat allergy. This could be avoided to a degree with the usage of the specific allergen components in order to diagnose a genuine sensitisation to wheat.

Beware of a patient with pollen allergy who tests positive to wheat, peanut and soy. This most likely represents cross-reactivity due to CCD, LTP, PR-10 protein or profilin, rather than true food allergy and may not be clinically significant.

TREE-NUT COMPONENTS

Cashew has been shown to cross-react with pistachio and pecan with walnut.²⁹ Brandstrom found that cashew-allergic children had IgE against novel citrus-seed allergens of lemon, orange and tangerine.³⁰ The individuals described in the report were all cashew-allergic and known to tolerate the fruit pulp. When ingesting foods that contained the seeds of these fruits, they developed anaphylaxis.

TABLE II: HEN'S EGG COMPONENTS

COMPONENT			CLINICAL RELEVANCE
Gal d 1	Egg white	Ovomucoid	Heat-stable React to all forms of egg High levels correlate with severe and persistent allergy
Gal d 2		Ovalbumin	Heat-labile Risk of reaction to raw and lightly cooked egg
Gal d 3		Ovotransferrin (Conalbumin)	Heat-labile Risk of reaction to raw and lightly cooked egg
Gal d 4		Lysozyme	Heat-labile Risk of reaction to raw and lightly cooked egg
Gal d 5	Egg yolk	Serum albumin	Found in yolk, chicken meat and feathers Associated with bird-egg syndrome

TABLE III: COW'S MILK COMPONENTS

COMPONENT		CLINICAL RELEVANCE
Bos d 4	α -lactalbumin	Heat-labile React to fresh milk May tolerate baked milk
Bos d 5	β -lactoglobulin	Heat-labile React to fresh milk May tolerate baked milk
Bos d 6	Bovine serum albumin	Heat-labile React to fresh milk May tolerate baked milk The main allergen in beef
Bos d 8	Casein	Heat-stable React to all forms of milk High levels correlate with severe and persistent allergy Cross react with other mammalian milks
Bos d lactoferrin	Lactoferrin	Heat-labile React to fresh milk



Birch tree forest: photo credit : Creative Commons Zero



Peanuts. Photo credit Stephen Firmender

The components Jug r 1 in walnut, Ana o 3 in cashew and Cor a 9 and 14 in hazelnut have been shown to be useful when diagnosing primary tree-nut allergy, rather than sensitisation due to cross-reactive components.

PEANUT COMPONENTS

Three peanut-specific storage proteins (Ara h 1, 2 and 3) and two cross-reactive proteins (Ara h 8 and Ara h 9) are used as diagnostic tools in clinical practice. The storage protein Ara h 2 appears to be the most useful in terms of both sensitisation frequency and in eliciting clinical symptoms in peanut-allergic patients.³¹ Ara h 6 is a major peanut allergen and is similar to Ara h 2 in many respects. Both are storage proteins of the 2S albumin type and are heat-stable and resistant to digestion. They are both associated with potentially severe systemic reactions.³² They are 58% homogenous at the amino-acid level,

and are highly immunogenic and potent in functional assays such as histamine-release and basophil-activation tests.³³ Adding Ara h 6 to a diagnostic panel of tests can thus improve the diagnostic accuracy for true peanut allergy.

In a pan-European study of both children and adults, 85% of subjects with early-onset peanut allergy had elevated sIgE to any peanut-storage protein.³⁴ Of these, 93% and 87% were positive to Ara h 2 and Ara h 6 respectively. In adult-only studies, the frequency of Ara h 6 sensitisation among peanut-allergic subjects is shown to be between 50% and 80%.³⁵⁻³⁷

Although sensitisation to Ara h 2 and 6 usually occurs together, sensitisation to Ara h 6 alone has been detected in up to 4% of study subjects.³⁸ Ara h 6 sensitisation in the absence of Ara h 2 s-IgE was reported in five Dutch children.³⁹ Three of these children reacted during a peanut oral-food challenge. Another report from Sweden described a child with no detectable sIgE to Ara h 1-3, who developed anaphylaxis during an oral peanut challenge.⁴⁰

The collective data so far demonstrate that Ara h 6 is an important marker of peanut allergy, with a diagnostic accuracy similar to that of Ara h 2. The sensitivity of Ara h 6 is reported to range from approximately 60 to 90%, while the specificity is reported to be above 95%. Several studies indicate that when used together, Ara h 2 and Ara h 6 can provide the highest diagnostic accuracy.^{38,41} Monosensitisation to Ara h 6 is seen in an important minority of patients.

TABLE IV: TREE-NUT COMPONENTS			
NUT		COMPONENT	CLINICAL RELEVANCE
Cashew	Storage protein	Ana o 3	Resistant to heat and digestion Associated with systemic reactions
		Cor a 9 Cor a 14	Resistant to heat and digestion Associated with severe systemic reactions
Hazelnut	PR-10 protein	Cor a 1	Heat-labile, may tolerate roasted hazelnut Associated with oral-allergy syndrome, birch and birch-related tree-pollen allergy
		LTP	Cor a 8
	Storage protein	Jug r 1	Primary walnut allergy Resistant to heat and digestion Associated with systemic reactions
Walnut	LTP	Jug r 3	Resistant to heat and digestion Associated with systemic and local reactions May cross-react with other LTP-containing foods

TABLE V: PEANUT COMPONENTS		
COMPONENT		CLINICAL RELEVANCE
Ara h 1	Storage proteins	Stable to heat and digestion Risk of systemic reactions
Ara h 2		
Ara h 3		
Ara h 6		
Ara h 5	Profilin	Associated with oral-allergy syndrome
Ara h 8	PR-10 protein	Heat-stable Associated with oral-allergy syndrome, birch and birch-related tree-pollen allergy
Ara h 9	LTP	Heat-stable Risk of severe systemic and local reactions, associated with peach and peach-related fruit allergy



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Apis mellifera (Honeybee) photo credit Zhiwei Zhou

LIPID-TRANSFER PROTEIN

Non-specific lipid-transfer protein (LTP) is by far the most frequent cause of primary food allergy in the Mediterranean area where it also induces the largest number of food-dependent anaphylactic reactions.⁴² LTP allergy is a fascinating food allergy and differs from other IgE-mediated food allergies such as egg, milk and peanut. China, Australia and central/northern Europe are starting to report LTP allergy and more reports are sure to come from other countries. LTP-sensitised patients may experience reactions upon the ingestion of a wide variety of plant foods. Pru p 3 – the peach LTP – is regarded as the ‘LTP sensitiser’. This is thought to be because it seems to pass through the gut epithelium via fast transcellular route which is not used by other less allergenic LTPs. There are recent reports that the presence of birch pollen may be protective against LTP-allergic symptoms. In some areas, high levels of birch pollen are correlated with a low prevalence of LTP hypersensitivity.⁴³

One of the most intriguing aspects of LTP hypersensitivity is the extreme variability of its clinical expression. LTP is probably the main cause of food-induced contact urticaria, at least in Spain. Peach-induced contact urticaria may be the only sign of LTP hypersensitivity in more than 60% of patients.

Co-factors are important in LTP hypersensitivity. In some cases, the co-factor is represented simply by the isolated ingestion of the offending food after fasting. It is possible that an empty gastrointestinal tract absorbs the allergen more rapidly. Other co-factors include exercise, alcohol and non-steroidal anti-inflammatory drugs (NSAIDs). It was recently shown that NSAIDs can enhance the IgE-mediated activation of basophils. In patients with otherwise mild or non-clinically significant allergy, taking an NSAID with that particular food may lead to a severe reaction, even anaphylaxis.⁴⁴

TRYPTASE

Preventive measures to decrease the frequency and intensity of anaphylactic events are essential to provide optimal care for the allergic patient. Worm et al have examined factors that increase the risk for a severe reaction in anaphylaxis using the European Anaphylaxis Registry.⁴⁵ The most important risk factors for severe anaphylaxis were mastocytosis and older age. This is in line with the known association of mastocytosis

with fatal Hymenoptera sting reactions. Gulen et al studied 122 consecutive patients with systemic mastocytosis in order to identify risk factors of anaphylaxis in these patients.⁴⁶ Factors that were predictive of anaphylaxis included male sex, absence of skin mastocytosis lesions, the presence of atopy, IgE >15 kU/L and baseline tryptase <40 ng/mL. It is therefore important to measure tryptase and in some cases perform mutation analysis of peripheral blood when evaluating patients with anaphylaxis.

Dua et al showed that serum tryptase rises in food-allergic reactions and is correlated with symptom severity. They also determined optimal sampling time points and a diagnostic cutoff for confirming reactions.⁴⁷ They performed a prospective study of 160 adult peanut-allergic patients who underwent oral-food challenges. They compared baseline tryptase levels with peak levels at two hours and showed that a rise in tryptase of 30% is associated with a clinical reaction. The rise in tryptase compared with the baseline occurred in 62% of all reactions and in 100% of anaphylactic reactions. The group is the first to demonstrate that moderate-to-severe respiratory symptoms during a challenge are associated with a higher tryptase. They failed to prove any correlation between baseline tryptase levels and reaction severity. The optimal time for sampling appears to be between 30 minutes and two hours after the onset of a reaction as tryptase may not be detectable during the first 15–30 minutes.

Thus tryptase is of value in food-allergic reactions and especially in severe anaphylaxis. It is important to measure tryptase between 30–120 minutes after the reaction and compare it with the baseline level. Mastocytosis patients are at higher risk of severe anaphylaxis. Tryptase measurement should be performed in all cases of anaphylaxis if possible.

CONCLUSION

CRD helps clinicians to discriminate between true IgE-mediated allergy and sensitisation without clinical relevance.

DECLARATION OF CONFLICT OF INTEREST

Magnus Borres is medical director at Thermo Fisher Scientific. Sarah Karabus declares no conflict of interest.

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REFERENCES

- Wickman M, Lupinek C, Andersson N, Belgrave D, et al. Detection of IgE reactivity to a handful of allergen molecules in early childhood predicts respiratory allergy in adolescence. *EBioMedicine* 2017;26:91–99.
- Cipriani F, Mastroianni C, Tripodi S, Ricci G, et al. Diagnostic relevance of IgE sensitization profiles to eight recombinant *Phleum pratense* molecules. *Allergy* 2018;73:673–682.
- Mueller GA, Randall TA, Glesner J, Pedersen LC, et al. Serological, genomic and structural analyses of the major mite allergen Der p 23. *Clin Exp Allergy* 2016;46:365–676.
- Nolte H, Plunkett G, Grosch K, Larsen JN, et al. Major allergen content consistency of SQ house dust mite sublingual immunotherapy tablets and relevance across geographic regions. *Ann Allergy Asthma Immunol* 2016;117:298–303.
- Posa D, Perna S, Resch Y, Lupinek C, et al. Evolution and predictive value of IgE responses toward a comprehensive panel of house dust mite allergens during the first 2 decades of life. *J Allergy Clin Immunol* 2017;139:541–549.
- Resch Y, Michel S, Kabesch M, Lupinek C, et al. Different IgE recognition of mite allergen components in asthmatic and nonasthmatic children. *J Allergy Clin Immunol* 2015;136:1083–1091.
- Stoltz DJ1, Jackson DJ, Evans MD, Gangnon RE, et al. Specific patterns of allergic sensitization in early childhood and asthma & rhinitis risk. *Clin Exp Allergy* 2013;43:233–241.
- Bunne J, Moberg H, Hedman L, Andersson M, et al. Increase in allergic sensitization in schoolchildren: Two cohorts compared 10 years apart. *J Allergy Clin Immunol Pract* 2017;5:457–463.
- Aranda CS, Cocco RR, Pierotti FF, Mallozi MC, et al. Increased sensitization to several allergens over a 12-year period in Brazilian children. *Pediatr Allergy Immunol* 2018;29:321–324.
- Nagao M, Borres MP, Sugimoto M, Petersson CJ, et al. Sensitization to secretoglobulin and lipocalins in a group of young children with risk of developing respiratory allergy. *Clin Mol Allergy* 2017;15:4.
- Schoos AM, Chawes BL, Melén E, Bergström A, et al. Sensitization trajectories in childhood revealed by using a cluster analysis. *J Allergy Clin Immunol* 2017;140:1693–1699.
- Dávila I, Domínguez-Ortega J, Navarro-Pulido A, Alonso A, et al. Consensus document on dog and cat allergy. *Allergy* 2018 doi: 10.1111/all.13391. (Epub ahead of print.)
- Konradsen JR, Fujisawa T, Van Hage M, Hedlin G, et al. Allergy to furry animals: New insights, diagnostic approaches, and challenges. *J Allergy Clin Immunol* 2015;135:616–625.
- Schoos AM, Bonnelykke K, Chawes BL, Stokholm J, et al. Precision allergy: Separate allergies to male and female dogs. *J Allergy Clin Immunol Pract* 2017;5:1754–1756.
- Schoos AM, Kattan JD, Gimenez G, Sampson HA. Sensitization phenotypes based on protein groups and associations to allergic diseases in children. *J Allergy Clin Immunol* 2016;137:1277–1180.
- Konradsen JR, Nordlund B, Onell A, Borres MP, et al. Severe childhood asthma and allergy to furry animals: Refined assessment using molecular-based allergy diagnostics. *Pediatr Allergy Immunol* 2014;25:187–192.
- Ukleja-Sokolowska N, Gawrońska-Ukleja E, Żbikowska-Gotz M, Socha E, et al. Association of IgE Can f 2 and dyspnea in pet allergic patients. *Ann Allergy Asthma Immunol* 2017;119:86–88.
- Käck U, Asarnej A, Grönlund H, Borres MP, et al. Dog allergy: Clinical relevance of molecular allergy diagnostics in children. *J Allergy Clin Immunol* 2018 (accepted).
- Nordlund B, Konradsen JR, Kull I, Borres MP, et al. IgE antibodies to animal-derived lipocalin, kallikrein and secretoglobulin are markers of bronchial inflammation in severe childhood asthma. *Allergy* 2012;67:661–669.
- Asarnej A, Hamsten C, Waden K, Lupinek C, et al. Sensitization to cat and dog allergen molecules in childhood and prediction of symptoms of cat and dog allergy in adolescence: A BAMSE/MeDALL study. *J Allergy Clin Immunol* 2016;137:813–821.
- Bjerg A, Winberg A, Berthold M, Mattsson L, et al. A population-based study of animal component sensitization, asthma, and rhinitis in schoolchildren. *Pediatr Allergy Immunol* 2015;26:557–563.
- Tsolakis N, Malinowski A, Nordvall L, Mattsson L, et al. Sensitization to minor cat allergen components is associated with type-2 biomarkers in young asthmatics. *Clin Exp Allergy* 2018 doi: 10.1111/cea.13135. (Epub ahead of print.)
- Käck U, Asarnej A, Grönlund H, Borres MP, et al. Molecular allergy diagnostics refine characterization of children sensitized to dog dander. *J Allergy Clin Immunol*. 2018 doi: 10.1016/j.jaci.2018.05.012. (Epub ahead of print.)
- Uriarte SA, Sastre J. Clinical relevance of molecular diagnosis in pet allergy. *Allergy* 2016;71:1066–1068.
- Ballmer-Weber BK, Brockow K, Fiocchi A, Theler B, et al. Hydrolysed egg displays strong decrease in allergenicity and is well tolerated by egg-allergic patients. *Allergy* 2016;71:728–732.
- Miceli Sopo S, Greco M, Cuomo B, Bianchi A, et al. Matrix effect on baked egg tolerance in children with IgE-mediated hen's egg allergy. *Pediatr Allergy Immunol* 2016;27:465–470.
- Petersen TH, Mortz CG, Bindslev-Jensen C, Eller E. Cow's milk allergic children. Can component-resolved diagnostics predict duration and severity? *Pediatr Allergy Immunol* 2018;29:194–199.
- Nilsson N, Nilsson C, Ekoff H, Wieser-Pahr S, et al. Grass-allergic children frequently show asymptomatic low-level IgE co-sensitization and cross-reactivity to wheat. *Int Arch Allergy Immunol*. 2018 Jun 12:1–10. doi: 10.1159/000489610. (Epub ahead of print.)
- Andorf S, Borres MP, Block W, Tupa D, et al. Association of clinical reactivity with sensitization to allergen components in multifoed-allergic children. *J Allergy Clin Immunol Pract* 2017;5:1325–1334.
- Brandström J, Lilja G, Nilsson C, Ingemarsson N. IgE to novel citrus seed allergens among cashew-allergic children. *Pediatr Allergy Immunol* 2016;27:550–553.
- Klemans RJ, Van Os-Medendorp H, Blankestijn M, Bruijnzeel-Koomen CA, et al. Diagnostic accuracy of specific IgE to components in diagnosing peanut allergy: A systematic review. *Clin Exp Allergy* 2015 ;45:720–730.
- Lehmann K, Schweimer K, Reese G, Randow S, et al. Structure and stability of 2S albumin type peanut allergens: Implications for the severity of peanut allergic reactions. *Biochem J* 2005;395:463–472.
- Van Erp FC, Knol EF, Pontoppidan B, Meijer Y, et al. The IgE and basophil responses to Ara h 2 and Ara h 6 are good predictors of peanut allergy in children. *J Allergy Clin Immunol* 2017;139:358–360.
- Ballmer-Weber BK, Lidholm J, Fernandez-Rivas M, Seneviratne S, et al. IgE recognition patterns in peanut allergy are age dependent: perspectives of the EuroPrevall study. *Allergy* 2015;70:391–340.
- Ackerbauer D, Bublin M, Radauer C, Varga EM, et al. Component-resolved IgE profiles in Austrian patients with a convincing history of peanut allergy. *Int Arch Allergy Immunol* 2015;166:13–24.
- Klemans RJ, Knol EF, Bruijnzeel-Koomen CA, Knulst AC. The diagnostic accuracy of specific IgE to Ara h 6 in adults is as good as Ara h 2. *Allergy* 2014 69:1112–1114.
- Peeters KA, Koppelman SJ, Van Hoffen E, Van der Tas CW, et al. Does skin prick test reactivity to purified allergens correlate with clinical severity of peanut allergy? *Clin Exp Allergy* 2007;37:108–115.
- Kukkonen AK, Pelkonen AS, Makinen-Kiljunen S, Voutilainen H, et al. Ara h 2 and Ara h 6 are the best predictors of severe peanut allergy: a double-blind placebo-controlled study. *Allergy* 2015;70:1239–1245.
- Van der Valk JP, Schreurs MW, El Bouch R, Arends NJ, et al. Mono-sensitisation to peanut component Ara h 6: A case series of five children and literature review. *Eur J Pediatr* 2016;175(9):1227–1234.
- Asarnej A, Glaumann S, Elfstrom L, Lilja G, et al. Anaphylaxis to peanut in a patient predominantly sensitized to Ara h 6. *Int Arch Allergy Immunol* 2012;159(2):209–212.
- Pedrosa M, Boyano-Martinez T, Garcia-Ara C, Caballero T, et al. Utility of specific IgE to Ara h 6 in peanut allergy diagnosis. *Ann Allergy Asthma Immunol* 2015;115:108–112.
- Asero R, Piantanida M, Pinter E, Pravettoni V. The clinical relevance of lipid transfer protein. *Clin Exp Allergy* 2018;48:6–12.
- Scala E, Abeni D, Cecchi L, Guerra EC, et al. Molecular recognition profiles and clinical patterns of PR-10 sensitization in a birch-free Mediterranean area. *Int Arch Allergy Immunol* 2017;173:138–146.
- Pascal M, Muñoz-Cano R, Milà J, Sanz ML, et al. Nonsteroidal anti-inflammatory drugs enhance IgE-mediated activation of human basophils in patients with food anaphylaxis dependent on and independent of nonsteroidal anti-inflammatory drugs. *Clin Exp Allergy* 2016;46:1111–1119.
- Worm M, Francuzik W, Renaudin JM, Bilo MB, et al. Factors increasing the risk for a severe reaction in anaphylaxis: An analysis of data from the European Anaphylaxis Registry. *Allergy* 2018.
- Gülen T, Ljung C, Nilsson G, Akin C. Risk factor analysis of anaphylactic reactions in patients with systemic mastocytosis. *J Allergy Clin Immunol Pract* 2017;5:1248–1255.
- Dua S, Doney J, Foley L, Islam S, et al. Diagnostic value of tryptase in food allergic reactions: A prospective study of 160 adult peanut challenges. *J Allergy Clin Immunol Pract* 2018;18:S2213–2198.