Food antigen-specific IgE in dogs with suspected food hypersensitivity

Futtermittelantigen-spezifisches IgE bei Hunden mit vermuteter Futtermittelunverträglichkeit

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ZUSAMMENFASSUNG

Gegenstand und Ziel Für die richtige Wahl einer Eliminationsdiät und somit der Langzeittherapie von Hunden mit Futtermittelallergie ist es notwendig, mehr über den Einfluss von Kreuzreaktionen bei Hunden mit Futtermittelallergie zu wissen. Ziel der Studie war, Futtermittelallergen-spezifisches IgE von vermutlich allergischen Hunden auf gleichzeitig auftretende positive Reaktionen als möglichen Hinweis für Kreuzreaktionen zwischen diesen Allergenen zu untersuchen.

Material und Methoden Ergebnisse von Serum-IgE-Tests von 760 vermutlich allergischen Hunden, die 2 Labore zur Verfügung stellten, wurden statistisch evaluiert. Nach Gruppierung der Allergene hinsichtlich ihrer phylogenetischen Verwandtschaft wurden die Odds Ratios ermittelt sowie eine Sensitivitätsanalyse der Odds Ratios durchgeführt, um zu ermitteln, ob gleichzeitige positive Reaktionen auf 2 Allergene häufiger als erwartet vorkommen.

Ergebnisse Ein gleichzeitiges Auftreten positiver Reaktionen konnte zwischen 27% (Labor 1) und 72% (Labor 2) der verwandten Allergenpaare festgestellt werden. Bei den nicht verwandten Allergenpaaren ergaben nur 6,8% und 10,6% gleichzeitig eine positive Reaktion. Starke Zusammenhänge ließen sich vor allem zwischen Rind und Lamm und innerhalb der Getreidegruppe nachweisen. Häufige gleichzeitig positive Rektionen zeigten sich zudem innerhalb der Geflügelgruppe (v. a. zwischen Huhn und Ente), zwischen Allergenen von Schwein und Wiederkäuern sowie zwischen Soja und Getreideallergenen.

Schlussfolgerung Da nicht nur zwischen verwandten, sondern auch zwischen nicht verwandten Allergenpaaren Zusammenhänge nachweisbar waren, stellt die mögliche Relevanz von Panallergenen und Kohlenhydratresten bei der Nahrungsmittelallergie des Hundes eine weitere interessante Fragestellung dar. Mit unserer Studie ließen sich zwar Zusammenhänge zwischen Allergenpaaren feststellen, doch ist keine Unterscheidung zwischen einer Kreuzreaktion und einer Kosensibilisierung möglich. Hierfür und für die Bestimmung der klinischen Relevanz von futtermittelspezifischen IgE-Reaktionen sind weitere Untersuchungen notwendig.

Klinische Relevanz Aufgrund möglicher Kreuzreaktionen sollten verwandte Allergene, vor allem Rind- und Lammfleisch sowie Getreideallergene, bei einer Eliminationsdiät nicht verwendet werden, um falsche Ergebnisse zu vermeiden.

ABSTRACT

Objective Knowledge of cross-reactions in food-sensitive dogs will influence the choice of elimination diets and the long-term management of those patients. The objective of this study was to evaluate food allergen-specific IgE tests of suspected allergic dogs for concurrent positive reactions as possible evidence for cross reactions between allergens.

Material and methods Results of serum IgE tests from 760 suspected allergic dogs submitted to 2 laboratories were evaluated statistically. After the tested allergens were grouped by their phylogenetic relationship, odds ratios as well as a sensitivity analysis of the odds ratios were performed to evaluate if concurrent positive IgE results to 2 allergens occurred more often than expected.

Results Within related allergen pairs 27% (laboratory 1) and 72% (laboratory 2) of the pairs could be considered as associated. For the unrelated allergen pairs only 6.8% and 10.6% of the analyzed pairs were considered associated respectively. Strong correlations were shown in the group of ruminant allergens, especially beef and lamb, and grain allergens. High rates of concurrent reactions were also detected in the poultry group, especially between chicken and duck, as well as between pork and ruminant allergens, and soy and grain allergens.

Conclusion As our results showed not only correlations within related but also between non-related allergens, the possible relevance of carbohydrate moieties as well as panallergens for canine hypersensitivities warrants further study. Further investigations are necessary to distinguish co-sensitization from cross-reactions and determine the clinical relevance of food-specific IgE reactivity.

Clinical relevance Due to possible cross reactivity related allergens, especially beef and lamb as well as grain allergens, should not be used for an elimination diet to avoid false results.

Introduction

Adverse food reactions are a common cause of cutaneous and gastrointestinal problems in dogs [1]. Clinical signs may be immune-mediated and thus represent a true allergy or anaphylaxis, but can also be due to toxic, metabolic, pharmacologic or idiosyncratic reactions without involvement of IgE antibodies or T cells [2]. In practice, the exact underlying pathomechanism is rarely identified. Food-specific serum IgE is commonly identified in allergic and normal dogs [3]. The exact incidence of adverse food reactions is not known, cutaneous signs are reported to be due to food antigens in 1–25% of allergic dogs [4][5][6][7]. There is no age, sex or breed predisposition [1][5]. First clinical signs may occur before the age of 1 year [8][9]. In other dogs, they occur after the offending food was fed for longer than 2 years [4][10]. Food-sensitive dogs can show nonspecific gastrointestinal signs such as vomiting, diarrhoea, intermittent abdominal pain, an increased faecal frequency or flatulence [1]. Frequent cutaneous signs are pruritus and secondary infections with bacteria and yeast [4][8][9][10][11]. The pruritus may be generalised or can be restricted to the face, ears, paws, axillary, inguinal or perineal region [4][8][9][10][11][12]. Cutaneous signs are not pathognomonic for adverse food reaction [1][13], atopic dermatitis (AD) due to environmental allergens is clinically indistinguishable from food-induced AD. Intradermal tests, in vitro tests for food-specific serum IgE and salivary IgA and IgM [14] and gastroscopic food sensitivity testing are not reliable diagnostic tools for adverse food reactions [15][16][17][18], thus an elimination diet (with improvement of clinical signs) and subsequent provocation with the old food (and concurrent rapid clinical deterioration), followed by a repeated improvement with the trial diet is needed to confirm the diagnosis [1][19]. Long-term management of adverse food reaction consists of avoiding the offending food allergen [1]. In humans, cross-reactions between related allergens are recognized and complicate the life of affected patients [20]. Most common are cross-reactions between different kinds of milk and between meat of phylogenetically related mammalian species [21][22][23], between eggs of related poultry species [24] and between fish species [25].

In veterinary medicine bovine IgG seems to be a major allergen in cow's milk as well as a source of cross-reactivity with beef and probably with lamb because of the high homology with ovine immunoglobulins [26]. In a recent study Bexley et al. [27] measured food-specific serum IgE in a large number of dogs. There were more significant associations between related (32 of 43 tested pairs) than between unrelated allergen pairs (39 of 128). Additionally, an inhibition assay with the antigens cow's milk, beef and lamb confirmed the presence of cross-reactive IgE-binding epitopes in beef, lamb and cow's milk [27].

Cross-reactions could be responsible for the failure of elimination diets as well as for problems in the long-term management of food-sensitive dogs. Additionally, cross-reactions would lead to a higher incidence of concurrent positive reactions on food-specific serum IgE tests, similar to what is reported in dogs reacting to dust and storage mites [28]. The aim of this study was to evaluate food allergen-specific IgE to a variety of antigens in suspected allergic dogs with different in vitro tests for food allergen-specific IgE and to look for evidence of IgE-mediated cross-reactivity or co-sensitization of related and not-related allergen pairs.

Materials and methods

Results of IgE tests submitted by 2 different laboratories were evaluated. Specimens were submitted from suspected allergic dogs. The age, gender, breed or clinical history of most of those dogs was not known. Serum IgE antibodies against potato, egg, wheat, soy, corn, beef, lamb, pork, rice, duck, barley, cow's milk, oat, whiting, chicken, turkey, venison, rabbit and salmon were measured in 389 dogs using a modified protocol of a previously described assay [29] by laboratory 1 (LABOKLIN GmbH & Co. KG, Bad Kissingen, Germany). In a second group (n = 371), IgE antibodies against duck, turkey, salmon, potato, beef, horse, pork, lamb, chicken, fish-mix, cow's milk, egg, corn, wheat, soy and rice were measured by laboratory 2 (SYNLAB.vet, Augsburg, Germany) with an Allercept™ system, using the recombinant Human FcRI chain to detect allergen-specific IgE as described previously [3]. Results were interpreted as positive or negative based on the recommendations of the individual laboratories. All reaction classes with detectable antibodies were considered positive whereas tests with no detectable antibodies were interpreted as negative.

Because cross-reactions were expected primarily between related allergens, allergens were grouped as far as possible due to their phylogenetic relations. We considered allergens derived from ruminants, fish, poultry and grain as closer related and thus grouped them in group 1–4 respectively. The other allergens were grouped in group 5 (▶ **Table 1**).

Statistical analyses

To find out if concurrent positive IgE reactions to 2 allergens occurred more often than expected, 2 different methods were used. Odds ratios (ORs) were the first method of evaluation. Therefore, we descriptively analyzed ratios between the chances to produce antibodies against one allergen (allergen B) if there were already antibodies against another allergen (allergen A) or not to produce these antibodies. The respective ratios are denoted by A | B. Sensitivity analysis was performed to adjust the ORs from the influence of being sensitized, and thus developing IgE antibodies against at least one allergen. In this study, more than 50% of the dogs did not develop antibodies against any food antigen and some dogs developed antibodies against all allergens tested. Thus, ORs were separately calculated and adjusted for the parameter of liability to allergies. To account for a flexible effect of the liability to allergies an additive model was used based on the formula:

$$\log\left(P\left(A=1 \mid B\right)\right)=\beta_0+f(x_A)$$

In this formula $f(x_A)$ indicates the number of tested allergens to which the dog reacted with a positive IgE result. In order to flexibly account for the number of tested allergen pairs, we included the variable in semiparametric manner [30].

To estimate the β-coefficient in logistic models the Fisher algorithm was used. This consists of loops and after each cycle an estimator is calculated. If there is only a small change in the estimators of each loop the algorithm stops and due to the convergance of the estimators the value shown in the heatmap arises. If there is no convergance it is not possible to calculate the estimator and empty fields are shown in the heatmap. This happens for example if a combination of allergens is seen rarely and thus there is not enough data to be evaluated. All calculations were performed by using the statistical software R [31].

Based on the results of the sensitivity analysis, subsets of the reactions between related and unrelated allergen pairs were calculated. The positive reactions within the allergen group were determined and set in proportion to the total number of reactions (positive and negative) within the group. The same method was used to calculate the number of reactions between unrelated allergen pairs. Group 5 was only taken into account for the unrelated allergen pairs.

▶ **Table 1** Grouping of allergens. All allergens were grouped due to their phylogenetic relationship. Allergens without relationships to other allergens were allocated to group 5.

▶ **Tab. 1** Gruppierung der Allergene. Alle Allergene wurden nach ihrer phylogenetischen Verwandtschaft gruppiert. Allergene ohne Verwandtschaft zu anderen Allergenen bildeten die Gruppe 5.

Group	Allergens derived from
Group 1: ruminants	beef, lamb, venison, milk
Group 2: fish	fish mix, salmon, whiting
Group 3: poultry	chicken, turkey, duck, hen's egg
Group 4: grain	wheat, barley, rice, oatmeal, corn
Group 5: others	horse, pork, rabbit, brewer's yeast, carrot, pea, potato, seaweed, soy, tomato

Results

The allergen with the most frequent positive IgE test results was venison, followed by beef, lamb and cow's milk. Because of the small sample sizes, the allergens seaweed, tomato, carrot, millet and brewer's yeast were excluded from further analysis. Similarly, horse meat and salmon were excluded due to the small number of positive reactions.

Test results of the 2 laboratories were evaluated separately. From laboratory 1, we received 389 test results. Odds ratios were all > 1 (▶ **Fig. 1**). Thus, for all allergen pairs the chance to generate antibodies against allergen 2 increased if there were already antibodies against allergen 1. Only within the grain group values were constantly high. In the other groups only single allergen combinations showed high values (beef-lamb, duck-chicken, duck-turkey, pork-rabbit). Between groups there were high values for the combination of grains with turkey as well as with soy and the allergen pairs turkey-soy and pork-rabbit.

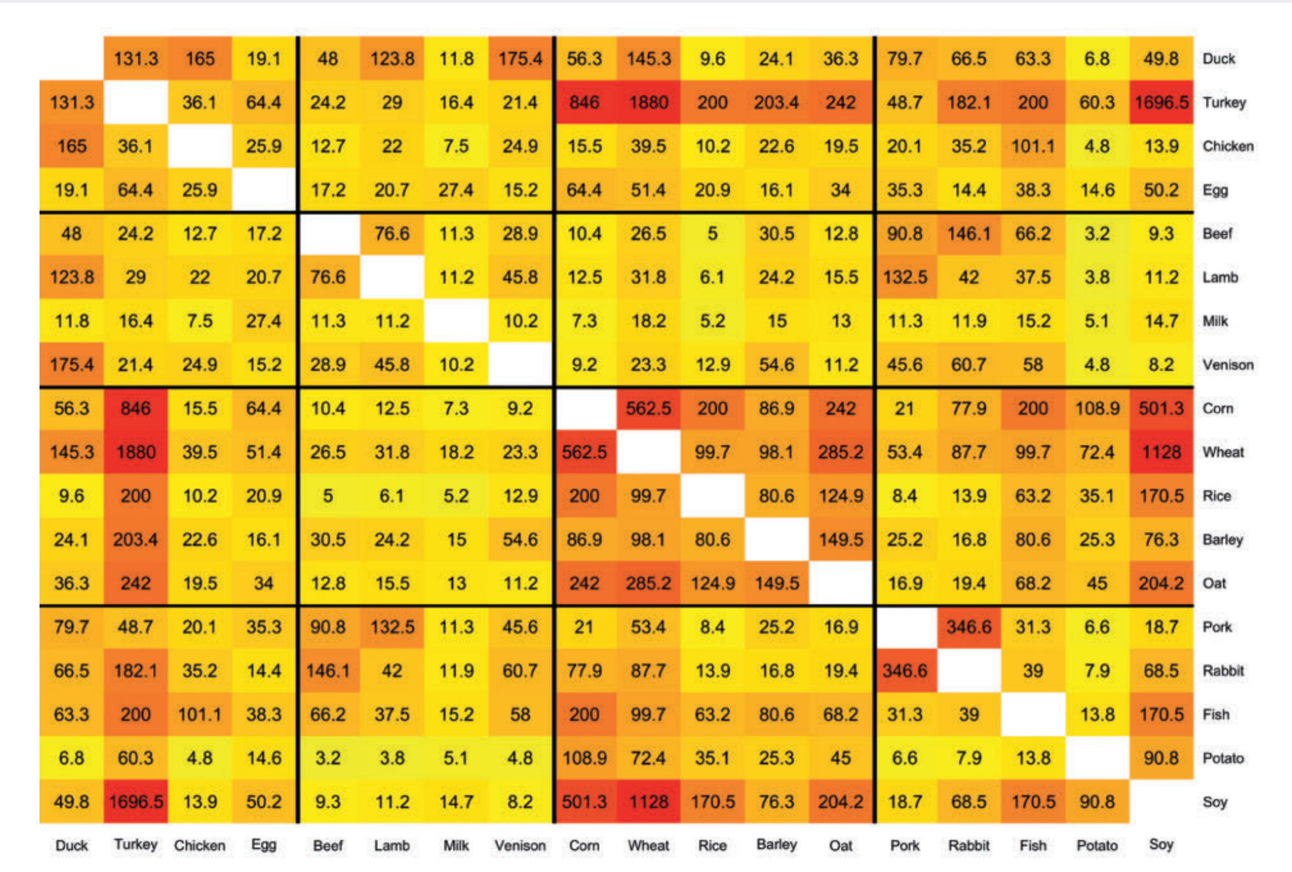
After adjusting the ORs, the values within the grain group remained high as well as for the combination beef and lamb and duck and chicken. Between groups only the allergen pair grains and potato showed high values (▶ **Fig. 2**).

From laboratory 2, 371 results were evaluated. Odds ratios within as well as between groups were all > 1 (▶ **Fig. 3**). Consistently high values were shown in the poultry as well as the grain and ruminant group. Between groups high values were measured for the combination of grains and poultry. Strong correlations also appeared between the fish and the poultry group. After adjusting the ORs, values within the grain group remained high. In the ruminant group only reactions between beef and lamb showed high values. High values were also shown for the allergen combination turkey and rice as well as soy and corn (▶ **Fig. 4**).

Within related allergen pairs 27% (laboratory 2) and 72% (laboratory 1) of the pairs could be considered as associated. For the unrelated allergen pairs only 6.8% and 10.6% of the analyzed pairs were considered associated respectively.

Discussion

The aim of this study was to evaluate food antigen-specific IgE in a large number of dogs with suspected food hypersensitivity and to identify IgE-mediated cross-reactivity or co-sensitization of various allergen pairs. In our study, there was a higher number of significant associations with related allergen pairs, which confirms the results of a previous study by Bexley et al [27]. In this study 32 of 43 related pairs were significantly associated compared with 49 of 128 unrelated pairs. However, in both Bexley's study and our study the OR of any pair was > 1, meaning that once an allergic response to one food antigen was mounted, there was an increased likelihood for further allergic responses to other allergens. To eliminate the influence of this fact, ORs were adjusted for the parameter of liability to allergies, which decreased the number of allergen pairs



▸ **Fig. 1** Heatmap of the odds ratios from laboratory 1. Source: © S. A. Baumann.

▸ **Abb. 1** Heatmap der Odds Ratios von Labor 1. Quelle: © S. A. Baumann.

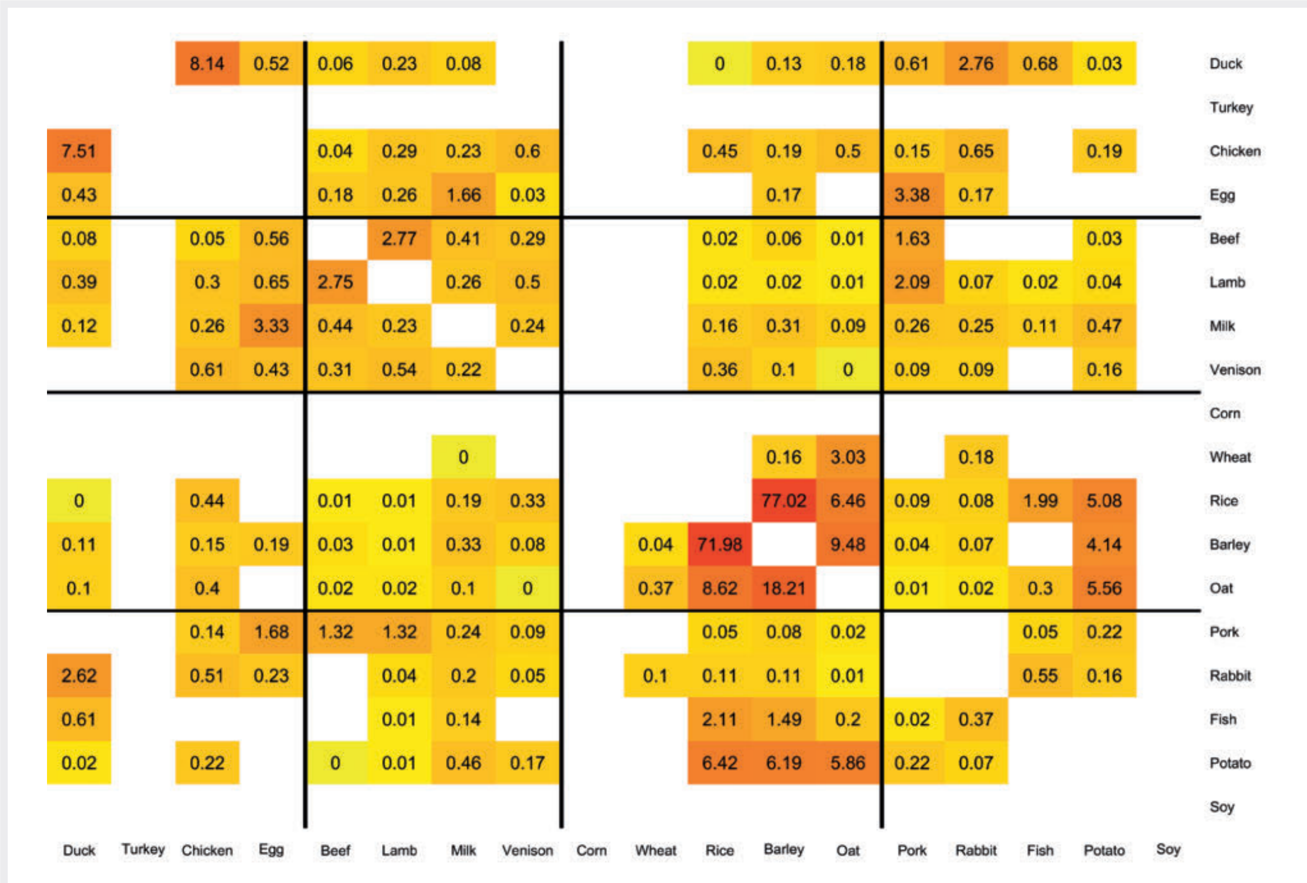
with significant correlations. If those statistically significant correlations are also clinically more relevant, should be the topic of further prospective studies.

After analyzing the data with different statistical methods, we received accumulations of allergen combinations in the group of ruminants, especially between beef and lamb. Cross-reactivity within this group has been shown in a number of studies in human medicine. Bovine IgG was identified as one of the major meat allergens responsible for cross reactivities in human medicine [32]. In a study by Martìn et al. [26], IgG heavy chain and phosphoglucomutase were detected as major allergens in dogs with specific IgE to lamb, cow's milk and beef. IgG was the major allergen in cow's milk and considered a source of cross reactivity with beef and probably also with lamb due to the high homology with ovine immunoglobulins [26]. For cross reactivity between IgE antibodies against different antigens, a homology of at least 70% is necessary and it is more likely to see cross reactivity between phylogenetically related species than between unrelated ones. Thus the likelihood for a cross reactivity increases with increased taxonomic proximity [20]. Since cattle and sheep belong to the same family of Bovidae, there is a high likelihood that they share similar antigens which may lead to cross reactivities in allergic patients. Beef was reported to be the most common food antigen in dogs with food allergy [33]. Consequently, lamb meat should not be used for an elimination diet to avoid false results due to possible cross reactivity to beef.

Venison as the allergen with the most frequent positive IgE reactions is suprising as venison meat is often used for elimination diets. In a study of Leistra et al. [34] a venison and rice comercial diet was only tolerated by a small number of food allergic dogs as a novel protein source. Cross-reactivity with other allergens of the ruminant group could be one possible explanation for these results.

Within the poultry group, ORs showed significant correlations between all allergen pairs with the lowest values for egg-chicken and the highest for duck-chicken and duck-turkey. These findings were confirmed by the sensitivity analysis. As chicken is the third most commonly reported food antigen in dogs with food allergy [33], poultry meat should only be used in an elimination diet, if the dog never recived any kind of poultry before. In humans, allergic reactions to poultry meat are considered rare. Cross-reactions between chicken and turkey allergens have been confirmed in 2 patients by immunoblotting. In both patients no reactions against egg or parts of eggs could be established [35]. Low correlations between poultry meat and egg were also shown in our study.

The high incidence of concurrent positive reactions within the grain group may be due to their sequence similarity, but could also be explained by a reaction to a panallergen. Panallergens are minor allergens which have been shown to occur in many related



▶ **Fig. 2** Heatmap of the adjusted odds ratios from laboratory 1. Empty fields arose due to non-convergence of the estimators of the regression model on which the allergen pairs are based. Source: © S. A. Baumann.

▶ **Abb. 2** Bereinigte Heatmap nach Sensitivitätsanalyse der Odds Ratios von Labor 1. Leere Felder in der Heatmap ergeben sich durch eine Nichtkonvergenz der Schätzer der logistischen Regressionsmodelle, die den Allergenkombinationen zugrunde liegen. Quelle: © S. A. Baumann.

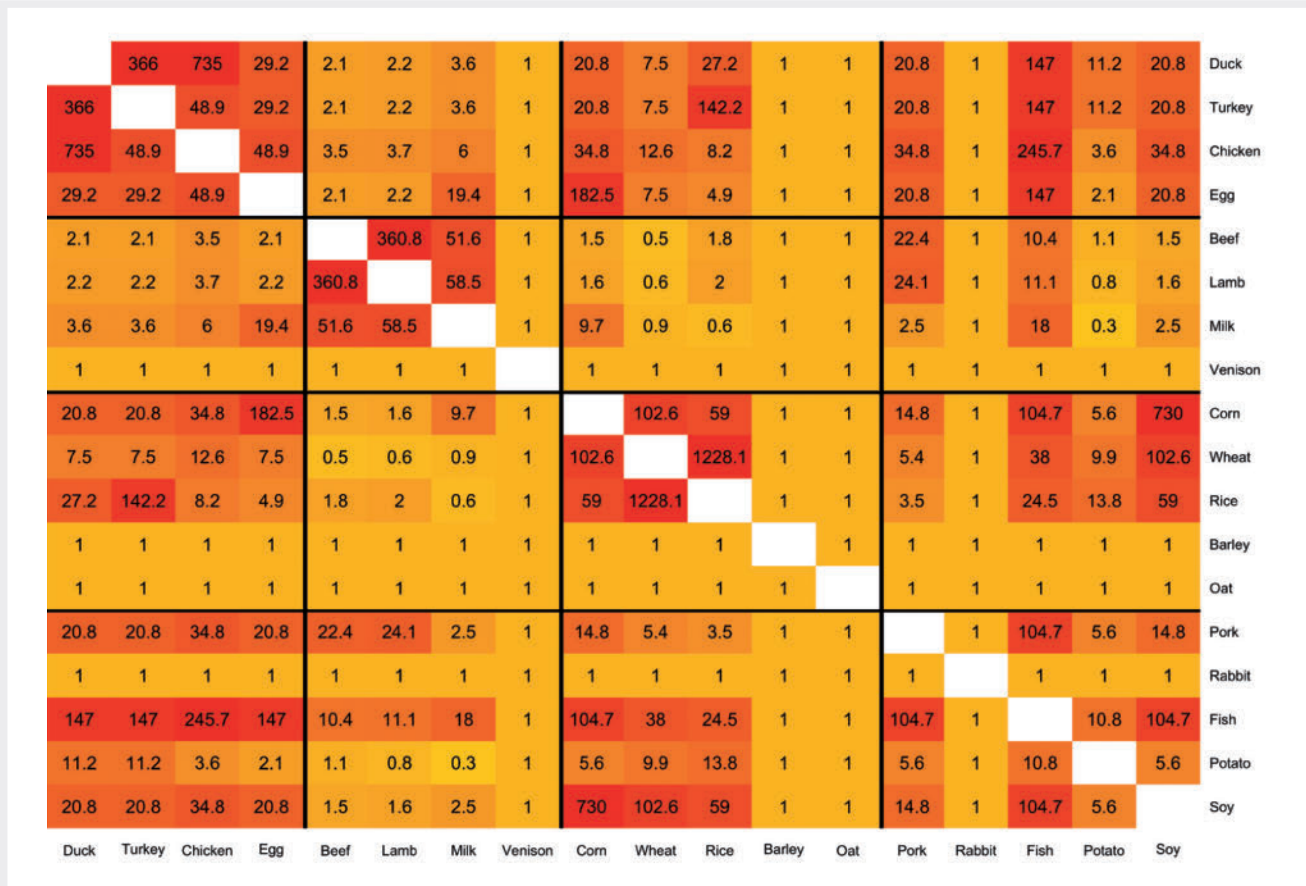
and unrelated plant species. Many of them are involved in general vital functions. These molecules have highly conserved sequence regions and three-dimensional structures and hence can fulfill the requirements for IgE cross-recognition [36]. The clinical relevance of panallergens and particularly of IgE against grain allergens in dogs is unclear at this time.

Our results also show interesting relations between non-related allergen pairs. High ORs were seen for the combinations of pork and lamb and pork and beef. In human medicine, a retrospective study evaluating serum IgE of allergic patients showed a strong correlation between positive reactions to beef and pork [37] due to IgE antibodies to the carbohydrate moiety galactose-α-1,3-galactose (alpha-gal). It has been proposed that tick bites are a cause of the IgE antibody response to alpha-gal in humans [38]. Galactose-α-1,3-galactose is produced by dogs and thus classical hypersensitivity will not develop against this self-antigen. However, other carbohydrate moieties could be relevant in canine allergic reactions and could be a potential explanation for our results.

Strong correlations could also be found between the unrelated combination of soy with the allergens of the grain group, possibly due to panallergens. One study in human medicine showed cross-reactions between wheat and lupin and reactions against the panallergens LTP and profilins were considered responsible for that cross-reactivity. Carbohydrate moieties could also play a role [39]. Lupins (like soy) belong to the Fabaceae family, it is likely that panallergens are also responsible for reactions between soy and wheat allergens.

The higher inter-group correlation between poultry and grains in the sensitivity analysis could be a result of relatively small positive amplitudes for poultry allergens which could lead to falsely elevated values for the ORs as well as those in the sensitivity analysis. Another explanation could be a sensitization against corn and rice because of the feeding of ducks and turkey with corn and rice, leading to the availability of these proteins in dog food made of poultry derivatives either because the poultry derivatives contain gut content or alternatively because the grain allergens cross the gut barrier in the birds. This phenomenon is seen in breastfed infants which become sensitized to cow's milk when the mother is consuming milk – as the cow's milk allergen crosses the gut-blood and blood-milk barrier [40][41]. Alternatively, cross-reactions between panallergens existing in rice, corn, turkey and duck could occur.

Cross-reactivty between chicken meat and fish is wideley discussed as a new syndrome in human medicine [42]. In a recent study from Bexley et al. [43] cross-reactive IgE binding proteins were found in chicken, white fish and salmon and suggest cross-reactivity between the unrelated species chicken and fish in dogs.



	Duck	Turkey	Chicken	Egg	Beef	Lamb	Milk	Venison	Corn	Wheat	Rice	Barley	Oat	Pork	Rabbit	Fish	Potato	Soy
Duck		366	735	29.2	2.1	2.2	3.6	1	20.8	7.5	27.2	1	1	20.8	1	147	11.2	20.8
Turkey	366		48.9	29.2	2.1	2.2	3.6	1	20.8	7.5	142.2	1	1	20.8	1	147	11.2	20.8
Chicken	735	48.9		48.9	3.5	3.7	6	1	34.8	12.6	8.2	1	1	34.8	1	245.7	3.6	34.8
Egg	29.2	29.2	48.9		2.1	2.2	19.4	1	182.5	7.5	4.9	1	1	20.8	1	147	2.1	20.8
Beef	2.1	2.1	3.5	2.1		360.8	51.6	1	1.5	0.5	1.8	1	1	22.4	1	10.4	1.1	1.5
Lamb	2.2	2.2	3.7	2.2	360.8		58.5	1	1.6	0.6	2	1	1	24.1	1	11.1	0.8	1.6
Milk	3.6	3.6	6	19.4	51.6	58.5		1	9.7	0.9	0.6	1	1	2.5	1	18	0.3	2.5
Venison	1	1	1	1	1	1	1		1	1	1	1	1	1	1	1	1	1
Corn	20.8	20.8	34.8	182.5	1.5	1.6	9.7	1		102.6	59	1	1	14.8	1	104.7	5.6	730
Wheat	7.5	7.5	12.6	7.5	0.5	0.6	0.9	1	102.6		1228.1	1	1	5.4	1	38	9.9	102.6
Rice	27.2	142.2	8.2	4.9	1.8	2	0.6	1	59	1228.1		1	1	3.5	1	24.5	13.8	59
Barley	1	1	1	1	1	1	1	1	1	1	1		1	1	1	1	1	1
Oat	1	1	1	1	1	1	1	1	1	1	1	1		1	1	1	1	1
Pork	20.8	20.8	34.8	20.8	22.4	24.1	2.5	1	14.8	5.4	3.5	1	1		1	104.7	5.6	14.8
Rabbit	1	1	1	1	1	1	1	1	1	1	1	1	1	1		1	1	1
Fish	147	147	245.7	147	10.4	11.1	18	1	104.7	38	24.5	1	1	104.7	1		10.8	104.7
Potato	11.2	11.2	3.6	2.1	1.1	0.8	0.3	1	5.6	9.9	13.8	1	1	5.6	1	10.8		5.6
Soy	20.8	20.8	34.8	20.8	1.5	1.6	2.5	1	730	102.6	59	1	1	14.8	1	104.7	5.6	

▶ **Fig. 3** Heatmap of the odds ratios from laboratory 2. Source: © S. A. Baumann.

▶ **Abb. 3** Heatmap der Odds Ratios von Labor 2. Quelle: © S. A. Baumann.

Clinical proof of these concurrent reactions still needs to be provided. Our results show strong correlations between the poultry group and fish before adjusting the ORs, afterwards there is only a mild correlation between duck and fish as well as chicken and fish.

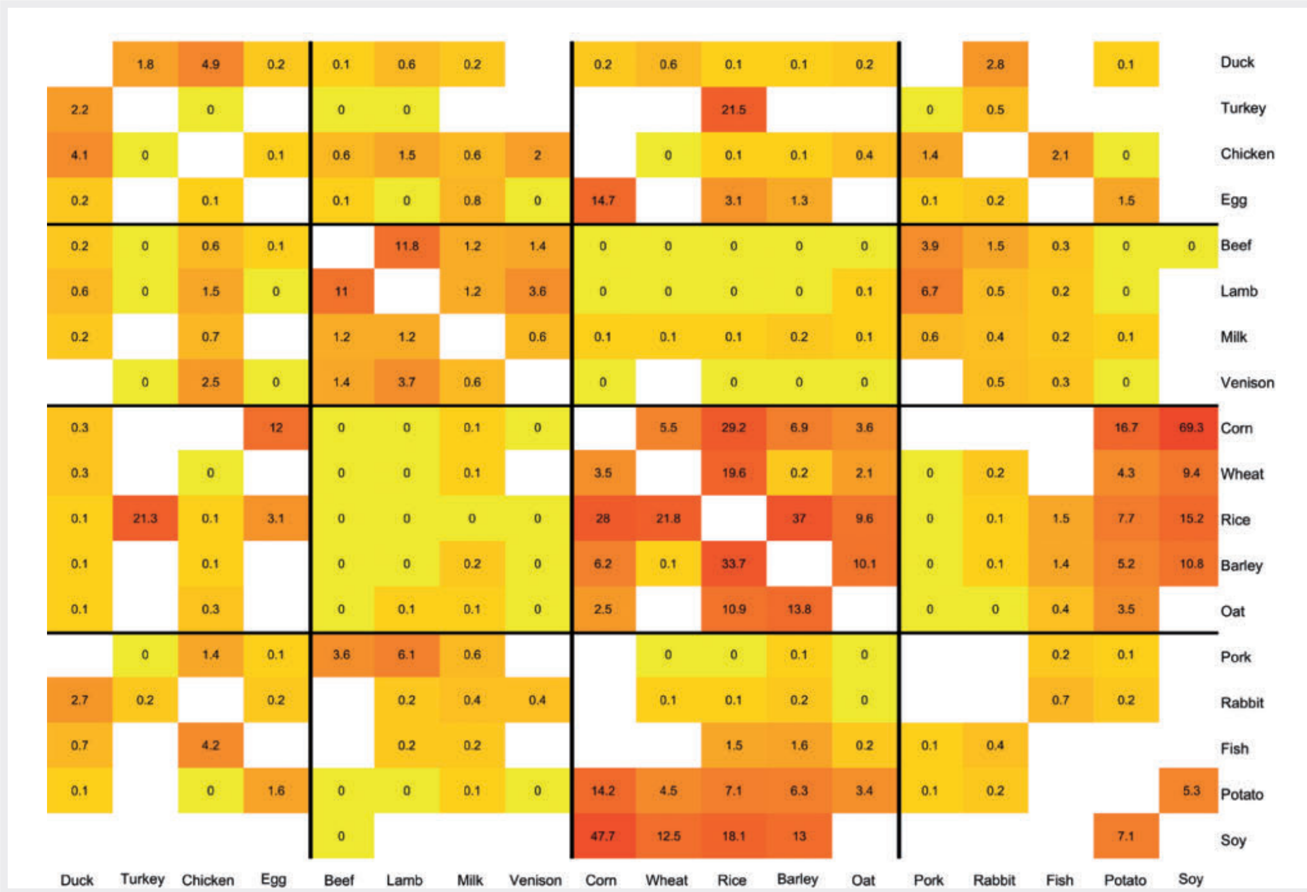
Comparing the number of correlations between related and not related allergen pairs between laboratory 1 and 2 significant different numbers can be noticed. Having a closer look at the positive reaction for each laboratory, there are in general fewer positive reactions to the tested allergens in laboratory 2 compared to laboratory 1. For the allergen beef for example 195 of 389 (50%) tested dogs showed positive reactions in laboratory 1 whereas only 32 of 369 (8%) showed positive IgE reactions in laboratory 2. Because of these differences lower rates of cross reactivity are seen for laboratory 1. One possible explanations are the 2 different methods used by each laboratory.

The major limitation of our study is the inability to differentiate between cross-reactivity and co-sensitization by testing for allergen-specific IgE. For that purpose ELISA cross inhibition would be necessary. Based on the results of this study, allergens of the ruminant group especially beef and lamb, the grain group, duck and chicken as well as soy and the grain allergens and pork and the ruminant group would be suitable pairs for further investigations.

Furthermore, no historical or clinical details were known of the dogs providing the serum specimens. Several studies have illustrated that food-specific IgE does not indicate a clinical relevant allergy in dogs [3][15][44]. It would be helpful to evaluate serum of dogs whose offending allergens were identified clinically by sequential provocation trials. However, evaluating IgE reactions in a large number of dogs has shed some light on sensitization patterns and identified areas of more specific interest for further study.

CONCLUSION FOR PRACTICE

Further investigations are necessary to distinguish co-sensitization from cross-reactions and the clinical relevance of food-specific IgE reactivity. Our study pointed to allergens of ruminants, especially beef and lamb, and grain allergens as areas of interest. We were also able to detect a high rate of concurrent positive reactions in the poultry group, especially between chicken and duck. The high rate of concurrent reactions to pork and ruminant allergens as well as to soy and grain allergens should be evaluated more closely. Carbohydrate moieties of meat proteins and panallergens may be involved. In this context, the possible clinical relevance of carbohydrate moieties as well as panallergens for canine hypersensitivities warrants further study.



▶ **Fig. 4** Heatmap of the adjusted odds ratios from laboratory 2. Empty fields arose due to non-convergence of the estimators of the regression model on which the allergen pairs are based. Source: © S. A. Baumann.

▶ **Abb. 4** Bereinigte Heatmap nach Sensitivitätsanalyse der Odds Ratios von Labor 2. Leere Felder ergeben sich durch die Nichtkonvergenz der Schätzer der logistischen Regressionsmodelle, die den Allergenkombinationen zugrunde liegen. Quelle: © S. A. Baumann.

Conflict of interest

Ralf Mueller has been a consultant, lecturer, or has received financial support for studies from Artuvet, Bayer Animal Health, Ceva Animal Health, Elanco Animal Health, Greer Laboratories, Heska Laboratories, Hill's, Royal Canin, MSD Animal Health, Nextmune, Synlab, Virbac Animal Health and Zoetis.

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