

Letter to the Editor

Sensitization phenotypes based on protein groups and associations to allergic diseases in children

To the Editor:

Traditionally, allergic sensitization is assessed using mixed allergen extracts from the same allergen source to measure specific immunoglobulin E (sIgE) levels in serum and/or for skin prick testing. Although these tests are sensitive in the direct or indirect demonstration of allergen-specific IgE, they lack specificity.^{1,2} Allergen component-resolved diagnostics (CRD) have attracted considerable attention in recent years, offering the potential for a more accurate assessment of allergic sensitization. Today, the identification of allergic sensitization to specific proteins and molecular components of allergens is most frequently used to help detect cross-reactivity,³ to indicate who can undergo an oral food challenge and who will most likely benefit from immunotherapy.⁴ We propose to use CRD to identify different patterns of sensitization, created on the basis of biologically meaningful protein groups reflecting evolutionary relationships between allergens from different sources, which may increase analytical specificity (selectivity), separating sensitizations to major allergens from cross-reactive minor components, and could possibly lead to an improved selection of targets for immunotherapy.

This study reports the results from a cross-sectional cohort of 269 children included from November 2011 to April 2013 from the Jaffe Food Allergy Institute, our pediatric, university-based, outpatient practice that draws referrals from the New York City area. All children seen at the clinic between the ages of 1 and 18 years were eligible for enrollment in the study.

The primary objective was to explore how sensitization to any of the protein groups that included inhalant allergens was associated with asthma and allergic rhinitis. As a secondary outcome, we investigated how the most recent sIgE level of 7 inhalant allergens was linearly associated with each of the components that constituted the allergen in question.

IgE antibodies to 112 components were evaluated in our laboratory with the ImmunoCAP Immuno Solid-phase Allergen

Chip (ISAC). A child was considered sensitized to the component in question if the level of antibody was more than or equal to 0.3 ISAC standard units.

Fifteen protein groups were created on the basis of World Health Organization/International Union of Immunological Societies Allergen Nomenclature Database.⁵ For further details, please see this article's [Online Repository including Table E1 at www.jacionline.org](http://www.jacionline.org). A child was considered positive to a protein group if he or she had a detectable IgE antibody level to any of the components within the group.

The most recent sIgE levels (if any) to the following inhalant allergens were noted from the electronic medical record: birch, ragweed, timothy grass, dog, cat, *Dermatophagoides pteronyssinus*, and *Dermatophagoides farinae*.

Asthma and allergic rhinitis were determined on the basis of questionnaires filled out by the parents. The children were all seen by a physician just before the parents filling out the questionnaire, and their symptoms and diagnosis of asthma and/or allergic rhinitis were reviewed.

Associations between protein groups, asthma, and allergic rhinitis were estimated using logistic regression analysis calculating odds ratios (ORs). Results were reported as both crude ORs and adjusted ORs (aORs), where we adjusted for sex and age. The results that remained significant after correction for multiple analyses using Bonferroni correction were marked in red. We did additional analyses of the main results using a cutoff of 1.0 ISAC standard units (see [Tables E2 and E3 in this article's Online Repository at www.jacionline.org](http://www.jacionline.org)). We also analyzed associations between all the individual components of the significant protein groups and the outcomes using logistic regression. These results are reported as crude ORs and aORs in this article's [Online Repository at www.jacionline.org](http://www.jacionline.org).

Additional analyses were run to analyze the association between most recent sIgE level and individual components of the allergen by linear regression. The results were expressed as coefficient of determination (*R*) and as estimates with 95% CIs. These results were also visualized using scatterplots, where all

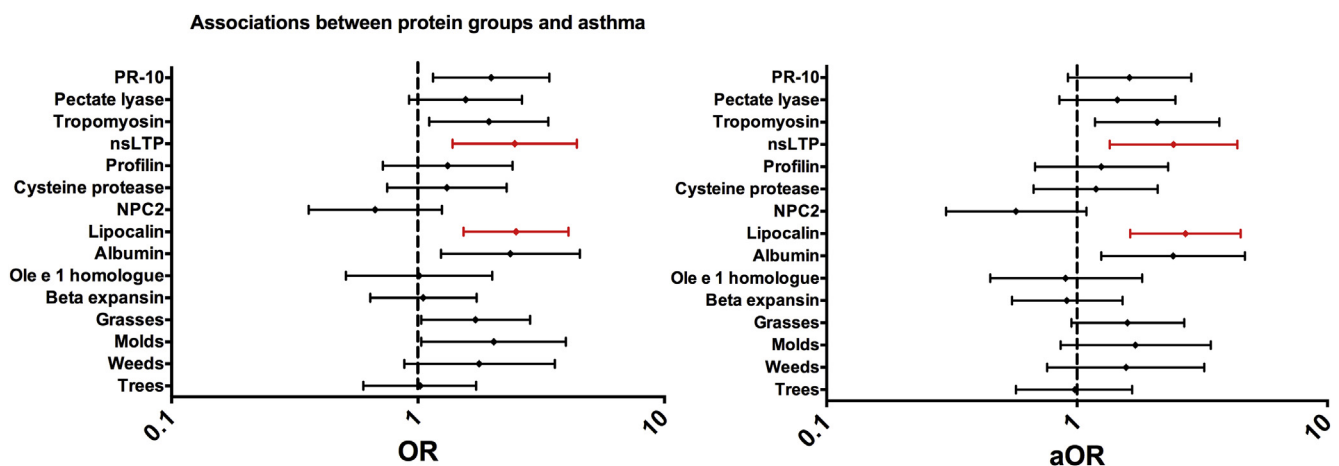


FIG 1. Associations between protein groups and asthma. Results are shown as crude and adjusted figures for sex and age. The bar marked in red indicate that the association remains significant after correcting for multiple testing. NPC2, Niemann-Pick disease type C2 protein.

Associations between protein groups and allergic rhinitis

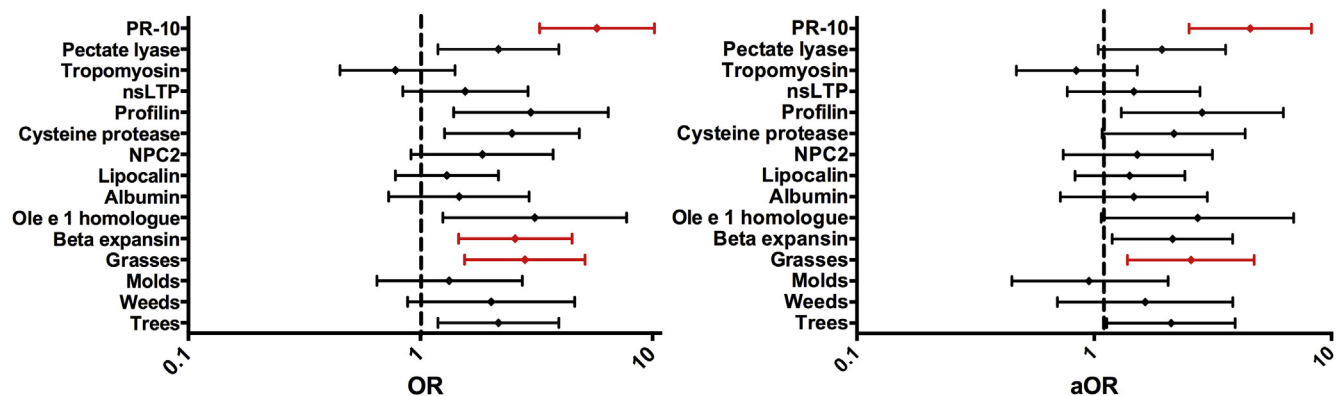


FIG 2. Associations between protein groups and allergic rhinitis. Results are shown as crude and adjusted figures for sex and age. The bars marked in red indicate that the associations remain significant after correcting for multiple testing. NPC2, Niemann-Pick disease type C2 protein.

components of each protein were plotted in the same graph and compared with the sIgE level.

The sIgE values to whole proteins and components were square root transformed to improve the normal distribution of the data.

Statistical analyses were performed with SAS 9.2 for Windows (SAS Institute, Cary, NC) using a significance level of P less than .05.

This study included 269 children ranging in age from 1.25 to 17.33 years (mean, 8.4 years; median, 8.2 years). Baseline characteristics and median sIgE levels with interquartile ranges are outlined in Table E4 in this article's Online Repository at www.jacionline.org.

We found significant associations between being sensitized to the lipocalin protein group and the nonspecific lipid transfer protein (nsLTP) group and asthma after adjusting for sex, age, and multiple testing (aOR, 2.71; 95% CI, 1.63-4.50; $P < .001$, and aOR, 2.43; 95% CI, 1.35-4.37; $P = .003$, respectively) (Fig 1; see Table E5 in this article's Online Repository at www.jacionline.org). The associations between individual components of the significant protein groups and asthma are presented in Table E6 in this article's Online Repository at www.jacionline.org.

We also found significant associations between sensitization to components in the pathogenesis-related proteins of class-10 (PR-10) and grasses protein groups and allergic rhinitis after adjusting for sex, age, and multiple testing (aOR, 4.55; 95% CI, 2.51-8.24; $P < .001$, and aOR, 2.56; 95% CI, 1.38-4.72; $P = .003$, respectively) (Fig 2; see Table E7 in this article's Online Repository at www.jacionline.org).

The associations between individual components of the significant protein groups and allergic rhinitis are presented in Table E8 in this article's Online Repository at www.jacionline.org.

The associations between the most recent sIgE level and the components of each allergen are outlined in Table E9 and visualized in scatterplots in Figs E1-E7 in this article's Online Repository at www.jacionline.org. We found that sIgE to birch was most closely associated to Bet v 1, timothy grass to Phl p 5, dog to Can f 1, cat to Fel d 1, *D pteronyssinus* to Der p 2, and *D farinae* to Der f 2.

The major strength of this study is that it is the first to investigate sensitization to multiple protein groups and their association to asthma and allergic rhinitis.

The major weakness is the selected high-risk study population. It is possible that this population differs from others with regard to

allergen exposures (house cleaning, pet exposure, etc), which may impact sensitization in childhood.⁶ Another limitation includes the definition of asthma and allergic rhinitis. Being based on a questionnaire, there is always a risk of misclassification.

Other studies have shown an association between sensitization to dog, cat, and/or horse and asthma.⁷⁻⁹ One Swedish study of 65 children with asthma (6-18 years old) with sensitization to a furry animal found that being sensitized to 3 or more components of the lipocalin protein group was associated with having more severe asthma,⁹ matching our findings.

We could not find any previous studies that have looked at sensitization to protein groups and association with allergic rhinitis. It was no surprise that sensitization to the PR-10 and grass pollen protein groups was associated with allergic rhinitis because tree and grass pollens are the main constituents of these groups. However, it was interesting that we did not see an association between sensitization to any of the other protein groups and allergic rhinitis because they all included inhalant allergens.

Studies of sensitization typically look at monosensitization or polysensitization to allergen extracts made from animal dander or other whole allergens and compare them to a clinical outcome.^{7,8} The problem is that this method cannot distinguish whether the sensitization is primary (species-specific) or a result of cross-reactivity to proteins with similar protein structures.

We found that asthma was associated with sensitization to the lipocalin protein group and the nsLTP group and allergic rhinitis was associated with sensitization to the PR-10 and grass pollen protein groups. This study suggests a novel way of analyzing and interpreting allergen sensitization. For example, if a patient with asthma tests positive to a number of airborne allergens, we suggest that sensitization to the lipocalin protein group or the nsLTP group should be of most concern clinically. This approach also suggests different immunotherapeutic strategies. It may be more effective and induce fewer adverse effects to target immunotherapy to a specific relevant protein group in patients with severe asthma and allergic rhinitis, and not to use a mixture of allergen extracts as is currently practiced today.

The materials used in this study have been provided by Thermo Fisher Scientific. We gratefully express our gratitude to the children, families, clinicians, and clinical staff who participated in this project.

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Supported by the David H. and Julia Koch Research Program in Food Allergy Therapeutics.

The materials used in this study were provided by Thermo Fisher Scientific. J.D.K. is supported by the National Heart, Lung, and Blood Institute, Mount Sinai Emergency Medicine Research Career Development Program (grant no. 5K12HL109005-03). H.A.S. is supported in part by grants from the National Institute of Allergy and Infectious Diseases (grant nos. AI44236 and AI066738) and the National Center for Advancing Translation Sciences (grant no. RR026134), National Institutes of Health. Disclosure of potential conflicts of interest: H. A. Sampson and J. D. Kattan received research support from the National Institutes of Health. The rest of the authors declare that they have no relevant conflicts of interest.

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<http://dx.doi.org/10.1016/j.jaci.2015.09.035>

Sensitization Phenotypes Based on Protein-groups and Associations to Allergic Diseases in Children

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Online Repository

Protein-groups:

Fifteen protein-groups were created based on the WHO/IUIS Allergen Nomenclature Database (PR-10, pectate lyase, tropomyosin, nsLTP, profilin, cysteine protease, NPC2 family, lipocalin, albumin, Ole e 1 homologue, beta expansin, grasses, molds, weeds and trees). We only created a protein-group if there was more than one component from the ImmunoCAP ISAC that belonged to the particular group, if at least one component was derived from an inhalant allergen, and where at least 10% of the children (i.e. 27) were positive. The latter criteria only excluded the polcalcin group (Bet v 4 and Phl p 7), to which only 6 children demonstrated sensitization.

Of the 15 protein-groups, 4 consisted of the remaining components from the grass, mold, weed, and tree allergens that could not be grouped based on protein-class, and were therefore not created using the strict biochemical criteria used to establish the other 11 groups. It is important to keep in mind that, for example, the “trees” protein-group does not include all components that are part of any tree allergen. The groups established based on these criteria are listed in **Table E1**.

Figure E1: Scatter-plot of association between sIgE level to birch and the level of birch components. Values are square root transformed. The highest coefficient of determination (R) is noted.

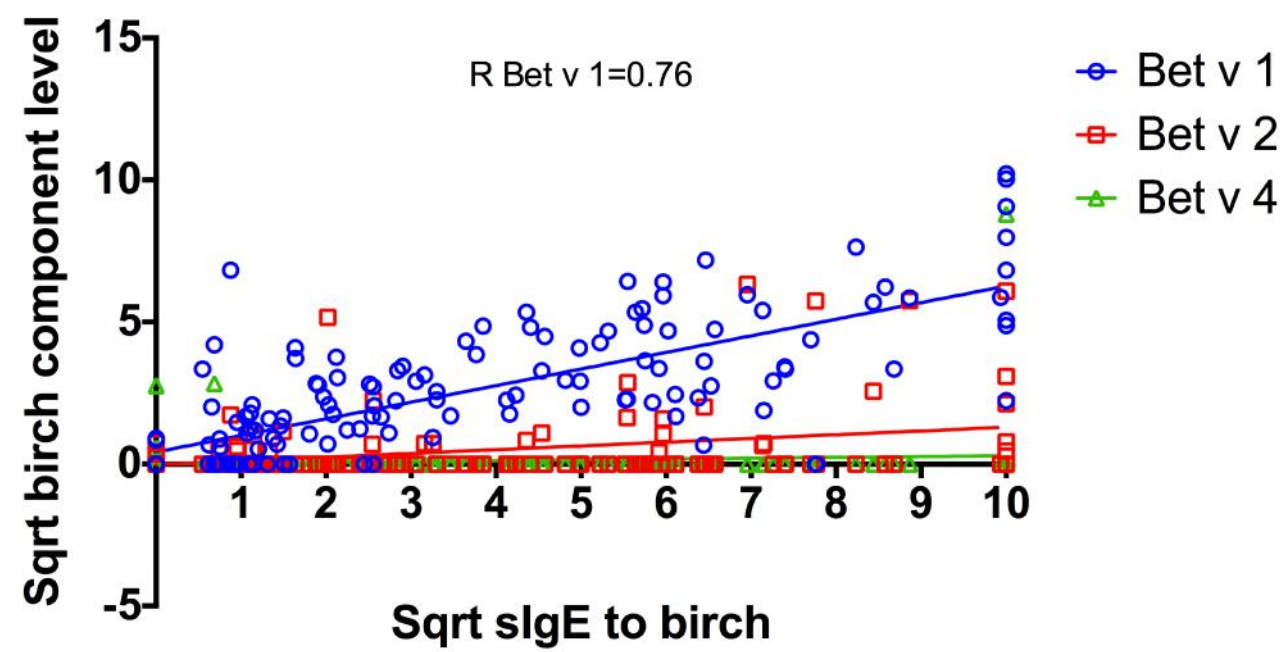


Figure E2: Scatter-plot of association between sIgE level to ragweed and the level of ragweed component Amb a 1. Values are square root transformed. The coefficient of determination (R) is noted.

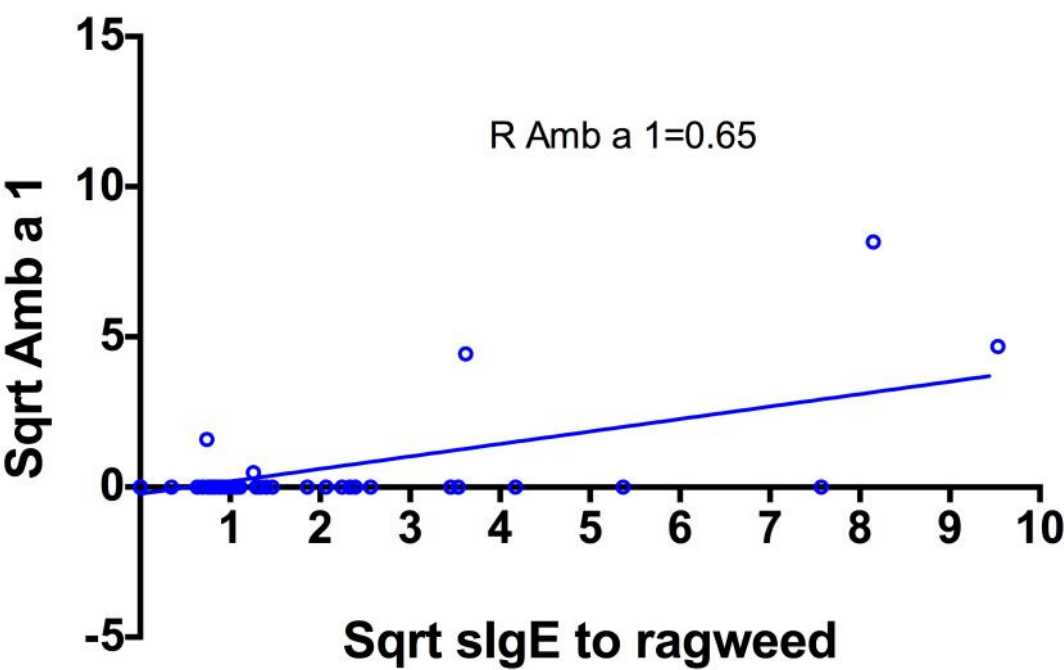


Figure E3: Scatter-plot of association between sIgE level to timothy grass and the level of timothy grass components. Values are square root transformed. The highest coefficient of determination (R) is noted.

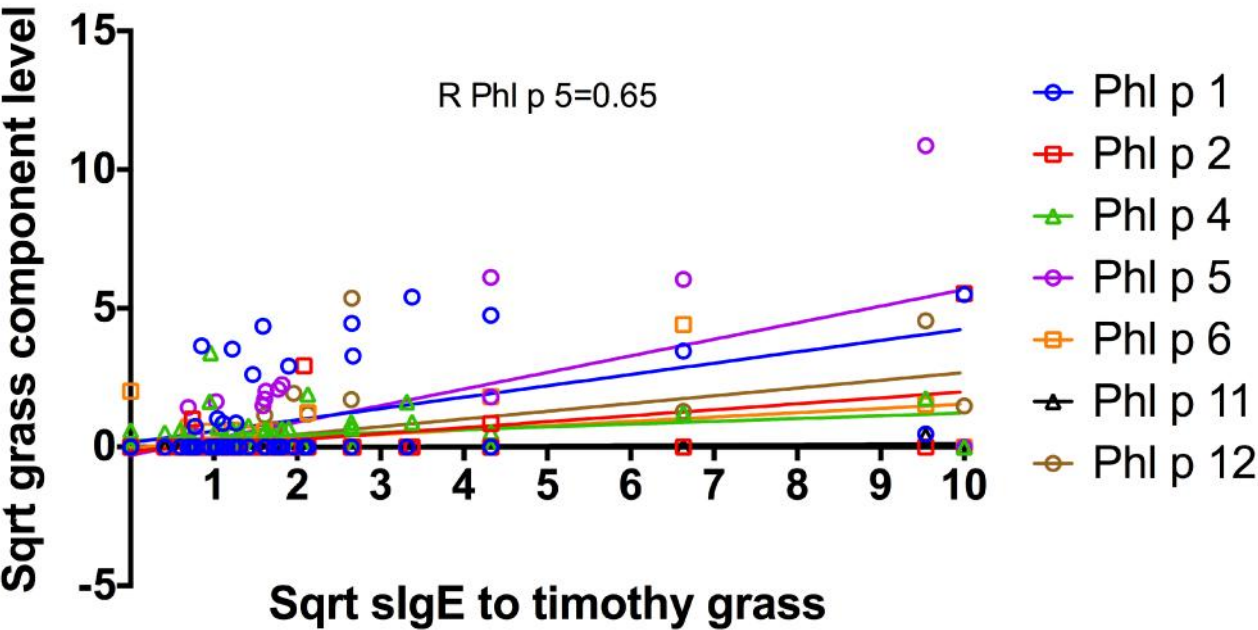


Figure E4: Scatter-plot of association between sIgE level to dog and the level of dog components. Values are square root transformed. The highest coefficient of determination (R) is noted.

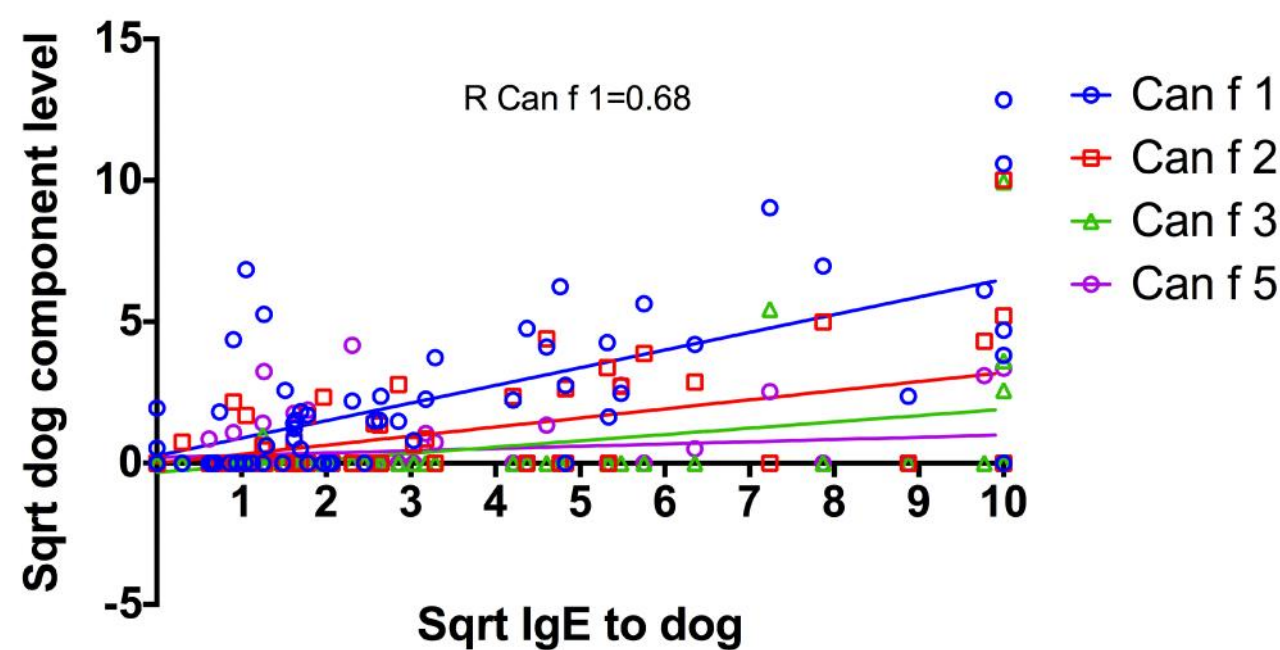


Figure E5: Scatter-plot of association between sIgE level to cat and the level of cat components. Values are square root transformed. The highest coefficient of determination (R) is noted.

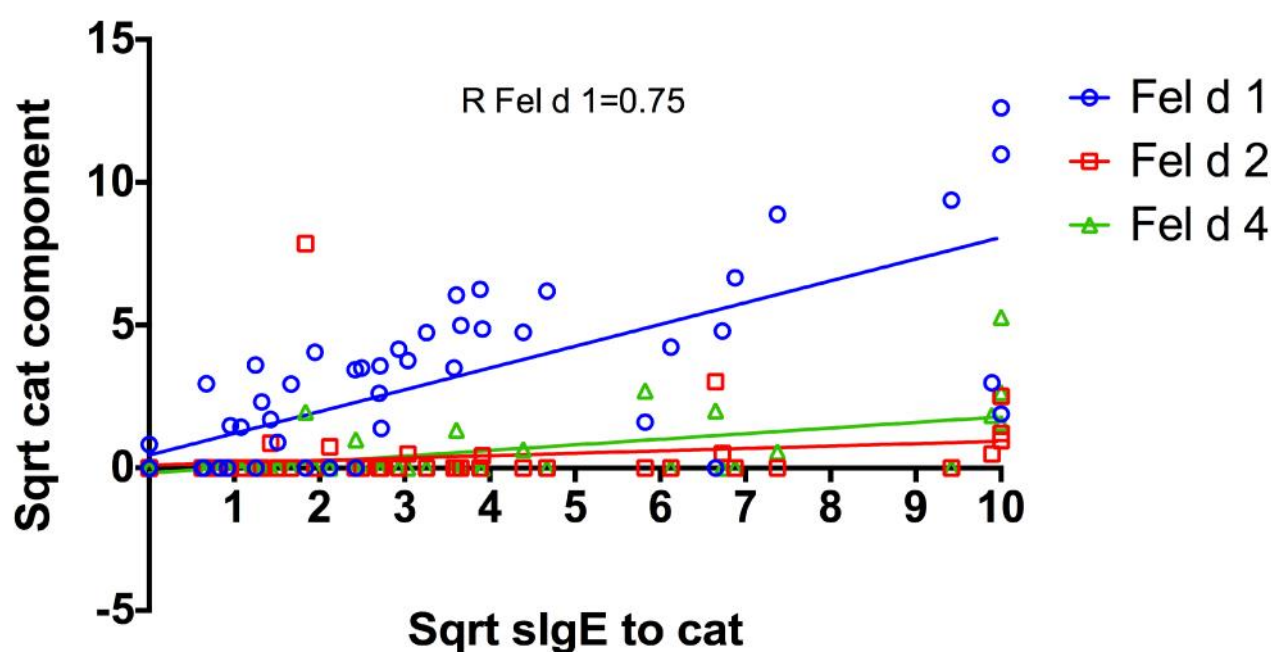


Figure E6: Scatter-plot of association between sIgE level to *D. pteronyssinus* and the level of *D. pteronyssinus* components. Values are square root transformed. The highest coefficient of determination (R) is noted.

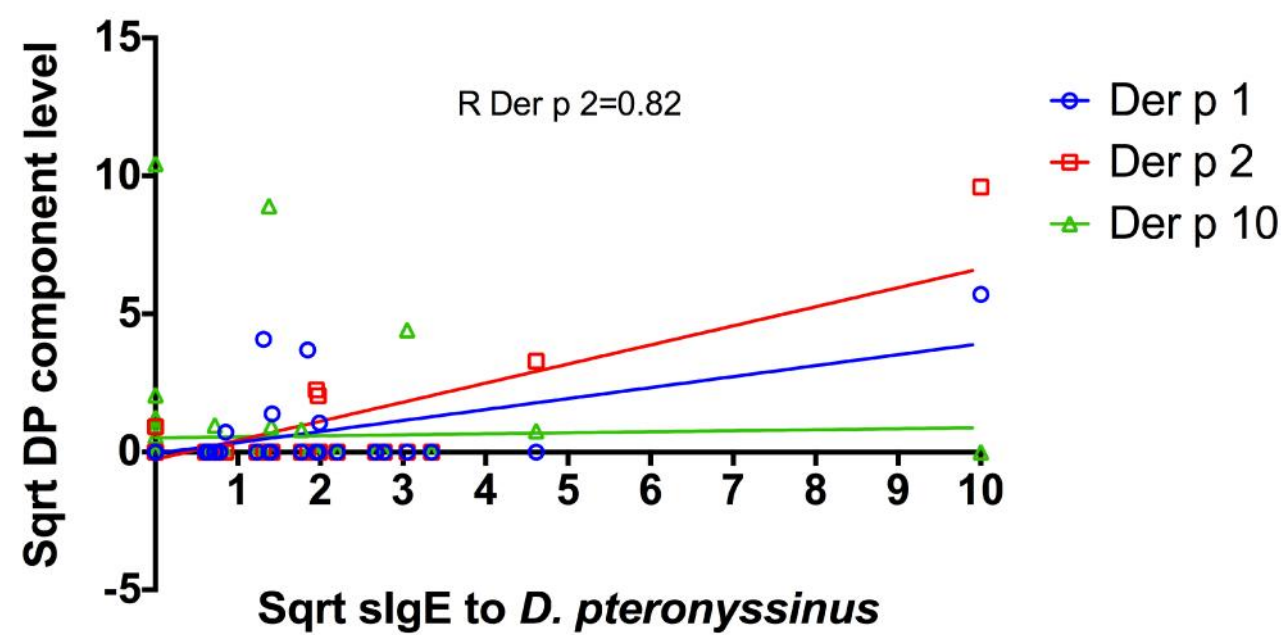


Figure E7: Scatter-plot of association between sIgE level to *D. farinae* and the level of *D. farinae* components. Values are square root transformed. The highest coefficient of determination (R) is noted.

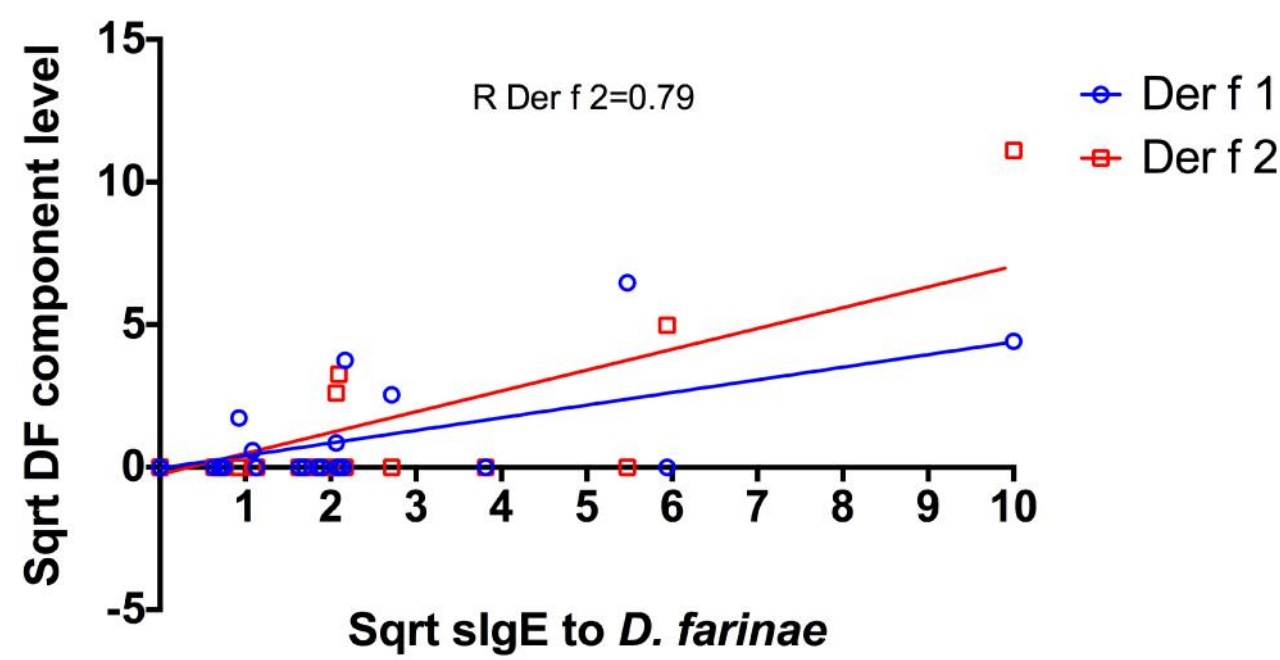


Table E1: Description of the different protein-groups and number of children with a detectable IgE level to at least one of the components included in each protein-group.

Protein-groups	Components included	N positive /total
PR-10	Aln g 1, Bet v 1, Cor a 1-0101, Cor a 1-0401, Mal d 1, Pru p 1, Gly m 4, Act d 8, Api g 1 and Ara h 8	190/269
Pectate lyase	Amb a 1, Cry j 1, Cup a 1	80/269
Tropomyosin	Ani s 3, Bla g 7, Der p 10, Pen m 1	69/269
nsLTP	Ara h 9, Cor a 8, Jug r 3, Pru p 3, Tri a 14, Art v 3, Ole e 7	64/269
Profilin	Bet v 2, Hev b 8, Mer a 1, Phl p 12	53/269
Cysteine protease	Act d 1, Der f 1, Der p 1	65/269
NPC2 family	Der f 2, Der p 2, Lep d 2	51/269
Lipocalin	Can f 1, Can f 2, Equ c 1, Fel d 4, Mus m 1	127/269
Albumin	Bos d 6, Gal d 5, Can f 3, Equ c 3, Fel d 2	48/269
Ole e 1 homologue	Ole e 1, Che a 1, Phl p 11, Pla l 1	38/269
Beta expansin	Phl p 1, Cyn d 1	102/269
Grasses	Phl p 2, Phl p 4, Phl p 5, Phl p 6	91/269
Molds	Alt a 1, Alt a 6, Asp f 1, Asp f 3, Asp f 6, Cla h 8	42/269
Weeds	Art v 1, Par j 2, Sal k 1	37/269
Trees	Ole e 9, Pla a 1, Pla a 2	80/269

Table E2: Associations between protein-groups and asthma using a cut-off of 1.0 ISU.

Protein-groups	N/total	aOR [^]	p
PR-10	97/269	1.17 [0.69;2.00]	0.55
Pectate lyase	48/269	1.24 [0.65;2.34]	0.52
Tropomyosin	46/269	1.54 [0.80;2.95]	0.20
nsLTP	41/269	3.09 [1.49;6.42]	0.0025
Profilin	38/269	1.28 [0.63;2.56]	0.49
Cysteine protease	50/269	1.28 [0.68;2.40]	0.44
NPC2	39/269	0.58 [0.29;1.19]	0.14
Lipocalin	111/269	2.49 [1.49;4.14]	0.0005
Albumin	30/269	5.36 [2.09;13.7]	0.0005
Ole e 1 homologue	20/269	1.60 [0.62;4.13]	0.33
Beta expansin	65/269	0.79 [0.44;1.42]	0.43
Grasses	49/269	1.15 [0.61;2.15]	0.67
Molds	32/269	1.53 [0.71;3.29]	0.28
Weeds	19/269	1.08 [0.42;2.80]	0.99
Trees	36/269	0.87 [0.43;1.79]	0.71

[^] Adjusted for gender and age

ORs marked with **red** remain significant after Bonferroni correction (multiply p-value by 15)

Table E3: Associations between protein-groups and allergic rhinitis using a cut-off of 1.0 ISU.

Protein-groups	N/total	aOR [^]	p
PR-10	97/269	5.07 [2.85;9.03]	<0.0001
Pectate lyase	48/269	1.56 [0.73;3.31]	0.25
Tropomyosin	46/269	0.65 [0.33;1.28]	0.21
nsLTP	41/269	2.65 [1.10;6.40]	0.0298
Profilin	38/269	3.16 [1.24;8.02]	0.0157
Cysteine protease	50/269	1.78 [0.84;3.77]	0.13
NPC2	39/269	1.35 [0.61;2.99]	0.45
Lipocalin	111/269	1.37 [0.80;2.35]	0.26
Albumin	30/269	2.19 [0.84;5.71]	0.11
Ole e 1 homologue	20/269	1.87 [0.59;5.99]	0.29
Beta expansin	65/269	2.58 [1.25;5.34]	0.0106
Grasses	49/269	2.50 [1.13;5.53]	0.0233
Molds	32/269	0.88 [0.38;2.04]	0.77
Weeds	19/269	2.34 [0.64;8.55]	0.20
Trees	36/269	2.94 [1.15;7.52]	0.0240

[^] Adjusted for gender and age

ORs marked with **red** remain significant after Bonferroni correction (multiply p-value by 15)

Table E4: Baseline characteristics, total N=269

	N (%)
Gender, male	183 (68%)
Current or history of asthma	127 (47%)
Current or history of allergic rhinitis	178 (66%)
- spring	168 (62%)
- summer	38 (14%)
- fall	87 (32%)
- winter	18 (6.7%)
sIgE measurements (kU_A/L)	Median (25%-75%)
Birch, N=153	5.75 (0.56-32.7)
Ragweed, N=74	0.61 (0-1.67)
Timothy grass, N=60	1.16 (0.17-3.14)
Dog, N=69	2.89 (0.55-21.2)
Cat, N=59	3.37 (0-13.4)
<i>D. pteronyssinus</i> , N=61	0 (0-1.72)
<i>D. farinae</i> , N=61	0 (0-1.2)

Table E5: Association between protein-groups and asthma.

Protein-groups	N/total	OR [CI]	p	aOR [^]	p
PR-10	190/269	1.98 [1.15;3.41]	0.0127	1.62 [0.92;2.86]	0.10
Pectate lyase	80/269	1.56 [0.92;2.64]	0.10	1.45 [0.85;2.47]	0.17
Tropomyosin	69/269	1.94 [1.11;3.38]	0.0185	2.09 [1.18;3.70]	0.0113
nsLTP	64/269	2.47 [1.38;4.41]	0.0020	2.43 [1.35;4.37]	0.0032
Profilin	53/269	1.32 [0.72;2.42]	0.36	1.25 [0.68;2.31]	0.47
Cysteine protease	65/269	1.31 [0.75;2.29]	0.34	1.19 [0.67;2.10]	0.56
NPC2	51/269	0.67 [0.36;1.25]	0.20	0.57 [0.30;1.09]	0.09
Lipocalin	127/269	2.50 [1.53;4.08]	0.0002	2.71 [1.63;4.50]	0.0001
Albumin	48/269	2.37 [1.24;4.54]	0.0078	2.42 [1.25;4.68]	0.0086
Ole e 1 homologue	38/269	1.01 [0.51;2.00]	0.98	0.90 [0.45;1.82]	0.78
Beta expansin	102/269	1.05 [0.64;1.73]	0.83	0.91 [0.55;1.52]	0.72
Grasses	91/269	1.71 [1.03;2.85]	0.0380	1.59 [0.95;2.68]	0.08
Molds	42/269	2.03 [1.03;3.98]	0.0379	1.71 [0.86;3.42]	0.13
Weeds	37/269	1.77 [0.88;3.59]	0.11	1.57 [0.76;3.22]	0.22
Trees	80/269	1.02 [0.60;1.72]	0.95	0.98 [0.57;1.66]	0.93

[^] Adjusted for gender and age

ORs marked with **red** remain significant after Bonferroni correction (multiply p-value by 15)

Table E6: Association between components of significant protein-groups and asthma

Components	N/total	OR [CI]	p	aOR [^]	p
Fel d 4 (lipocalin)	34/269	1.71 [0.82;3.54]	0.15	1.86 [0.88;3.95]	0.11
Can f 1 (lipocalin)	109/269	2.26 [1.38;3.72]	0.0012	2.48 [1.48;4.15]	0.0005
Can f 2 (lipocalin)	58/269	4.33 [2.26;8.30]	<0.0001	4.46 [2.30;8.67]	<0.0001
Equ c 1 (lipocalin)	35/269	2.40 [1.14;5.04]	0.00187	2.35 [1.10;5.00]	0.0271
Mus m 1 (lipocalin)	27/269	1.72 [0.77;3.85]	0.19	1.76 [0.78;3.99]	0.18
Ara h 9 (nsLTP)	24/269	1.98 [0.83;4.69]	0.12	2.11 [0.88;5.05]	0.09
Cor a 8 (nsLTP)	12/269	3.53 [0.94;13.4]	0.0485	3.40 [0.89;13.0]	0.07
Jug r 3 (nsLTP)	34/269	2.63 [1.23;5.65]	0.0107	2.52 [1.16;5.47]	0.0191
Pru p 3 (nsLTP)	22/269	2.08 [0.84;5.12]	0.11	2.18 [0.87;5.46]	0.09
Art v 3 (nsLTP)	23/269	3.50 [1.34;9.19]	0.0073	3.49 [1.32;9.23]	0.0120
Ole e 7 (nsLTP)	13/269	3.96 [1.06;14.7]	0.0278	3.90 [1.04;14.7]	0.0444
Pla a 3 (nsLTP)	19/269	10.8 [2.45;47.8]	0.0001	10.7 [2.41;47.6]	0.0018
Tri a 14 (nsLTP)	27/269	5.74 [2.10;15.7]	0.0002	6.05 [2.19;16.7]	0.0005
Bos d 6 (albumin)	29/269	4.04 [1.66;9.82]	0.0011	4.11 [1.67;10.1]	0.0021
Gal d 5 (albumin)	11/269	0.63 [1.18;2.19]	0.46	0.64 [0.18;2.29]	0.49
Can f 3 (albumin)	21/269	5.33 [1.74;16.3]	0.0013	5.82 [1.88;18.0]	0.0023
Equ c 3 (albumin)	13/269	17.5 [2.26;135]	0.0002	20.1 [2.57;156]	0.0042
Fel d 2 (albumin)	31/269	5.56 [2.20;14.0]	<0.0001	5.64 [2.21;14.4]	0.0003
Ani s 3 (tropomyosin)	42/269	1.43 [0.74;2.77]	0.29	1.45 [0.74;2.85]	0.28
Bla g 7 (tropomyosin)	52/269	1.53 [0.83;2.82]	0.17	1.72 [0.92;3.22]	0.09
Der p 10 (tropomyosin)	58/269	1.80 [1.00;3.24]	0.0494	1.73 [0.98;3.07]	0.0271
Pen m 1 (tropomyosin)	61/269	1.85 [1.04;3.30]	0.0357	2.06 [1.14;3.75]	0.0173

[^] Adjusted for gender and ageORs marked with **red** remain significant after Bonferroni correction (multiply p-value by 22)

Table E7: Associations between protein-groups and allergic rhinitis.

Protein groups	N/total	OR [CI]	p	aOR [CI]	p
PR-10	190/269	5.76 [3.26;10.2]	<0.0001	4.55 [2.51;8.24]	<0.0001
Pectate lyase	80/269	2.17 [1.19;3.95]	0.0106	1.93 [1.04;3.58]	0.0379
Tropomyosin	69/269	0.78 [0.45;1.41]	0.43	0.84 [0.47;1.52]	0.57
nsLTP	64/269	1.56 [0.84;2.91]	0.16	1.47 [0.77;2.79]	0.24
Profilin	53/269	2.99 [1.39;6.45]	0.0038	2.85 [1.30;6.27]	0.0092
Cysteine protease	65/269	2.48 [1.27;4.84]	0.0068	2.17 [1.08;4.33]	0.0286
NPC2	51/269	1.85 [0.91;3.73]	0.08	1.52 [0.74;3.15]	0.26
Lipocalin	127/269	1.30 [0.78;2.17]	0.31	1.41 [0.83;2.41]	0.20
Albumin	48/269	1.47 [0.73;2.94]	0.28	1.47 [0.72;3.00]	0.30
Ole e 1 homol	38/269	3.11 [1.25;7.73]	0.0112	2.73 [1.07;6.93]	0.0351
Beta expansin	102/269	2.56 [1.46;4.50]	0.0009	2.14 [1.19;3.83]	0.0108
Grasses	91/269	2.82 [1.55;5.12]	0.0005	2.56 [1.38;4.72]	0.0027
Molds	42/269	1.33 [0.65;2.75]	0.43	0.95 [0.45;2.05]	0.90
Weeds	37/269	2.02 [0.88;4.62]	0.09	1.64 [0.70;3.84]	0.26
Trees	80/269	2.17 [1.19;3.95]	0.0106	2.11 [1.13;3.93]	0.0184

^ Adjusted for gender and age

ORs marked with red remain significant after Bonferroni correction (multiply p-value by 15)

Table E8: Association between components of significant protein-groups and allergic rhinitis.

Components	N/total	OR [CI]	p	aOR^	p
Bet v 1 (PR-10)	168/269	4.73 [2.75;8.12]	<0.0001	3.83 [2.19;6.72]	<0.0001
Cor a 1_0101 (PR-10)	78/269	6.72 [3.07;14.7]	<0.0001	5.29 [2.37;11.8]	<0.0001
Cor a 1_0401 (PR-10)	173/269	5.11 [2.96;8.81]	<0.0001	4.07 [2.30;7.20]	<0.0001
Mal d 1 (PR-10)	165/269	7.52 [4.27;13.2]	<0.0001	6.33 [3.55;11.3]	<0.0001
Pru p 1 (PR-10)	117/269	5.58 [3.05;10.2]	<0.0001	4.58 [2.46;8.54]	<0.0001
Gly m 4 (PR-10)	96/269	5.24 [2.72;10.1]	<0.0001	4.57 [2.34;8.95]	<0.0001
Ara h 8 (PR-10)	114/269	4.34 [2.42;7.79]	<0.0001	3.56 [1.95;6.51]	<0.0001
Act d 8 (PR-10)	50/269	4.65 [1.90;11.4]	0.0003	3.98 [1.60;9.90]	0.0029
Api g 1 (PR-10)	50/269	34.2 [4.64;252]	<0.0001	28.1 [2.80;209]	0.0011
Aln g 1 (PR-10)	109/269	7.02 [3.64;13.5]	<0.0001	5.84 [2.98;11.5]	<0.0001
Amb a 1 (pectate lyase)	16/269	1.13 [0.38;3.37]	0.82	0.85 [0.27;2.67]	0.78
Cup a 1 (pectate lyase)	66/269	2.54 [1.30;4.97]	0.0052	2.23 [1.12;4.43]	0.0225
Cry j 1 (pectate lyase)	61/269	2.80 [1.46;5.35]	0.0188	1.97 [0.99;3.95]	0.05
Bet v 2 (profilin)	48/269	3.01 [1.34;6.74]	0.0056	2.60 [1.14;5.94]	0.0232
Hev b 8 (profilin)	40/269	4.21 [1.59;11.2]	0.0020	5.13 [1.89;14.0]	0.0013
Mer a 1 (profilin)	35/269	4.59 [1.57;13.4]	0.0027	4.99 [1.67;14.9]	0.0040
Phl p 12 (profilin)	25/269	6.60 [1.52;28.7]	0.0042	6.64 [1.51;29.3]	0.0124
Ole e 1 (Ole e 1 homol.)	28/269	7.61 [1.76;32.8]	0.0016	7.06 [1.62;30.8]	0.0093
Che a 1 (Ole e 1 homol.)	9/269	1.82 [0.37;8.95]	0.45	1.47 [0.28;7.76]	0.65
Phl p 11 (Ole e 1 homol.)	4/269	-	-	-	-
Pla l 1 (Ole e 1 homol.)	1/269	-	-	-	-
Cyn d 1 (beta expansin)	85/269	2.28 [1.75;6.17]	0.0001	2.81 [1.47;5.36]	0.0018
Phl p 1 (beta expansin)	61/269	2.50 [1.25;4.99]	0.0079	1.76 [0.85;3.63]	0.13
Phl p 2 (grasses)	11/269	2.37 [0.50;11.2]	0.26	1.39 [0.28;6.81]	0.69
Phl p 4 (grasses)	70/269	2.52 [1.32;4.84]	0.0045	2.47 [1.26;4.84]	0.0083
Phl p 5 (grasses)	32/269	3.08 [1.14;8.28]	0.0204	2.64 [0.96;7.28]	0.06
Phl p 6 (grasses)	22/269	2.45 [0.80;7.46]	0.11	2.09 [0.66;6.62]	0.21
Ole e 9 (trees)	12/269	0.70 [0.22;2.28]	0.56	0.53 [0.16;1.78]	0.30
Pla a 1 (trees)	14/269	3.22 [0.70;14.7]	0.11	3.32 [0.70;15.6]	0.13
Pla a 2 (trees)	71/269	2.26 [1.65;6.46]	0.0004	3.18 [1.58;6.42]	0.0012
Act d 1 (cysteine protease)	21/269	2.30 [0.75;7.04]	0.14	2.62 [0.81;8.29]	0.10
Der f 1 (cysteine protease)	44/269	2.23 [1.02;4.87]	0.0403	1.69 [0.75;3.82]	0.21

Der p 1 (cysteine protease)	34/269	2.15 [0.90;5.14]	0.08	1.55 [0.63;3.84]	0.34
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^Adjusted for gender and age

ORs marked with **red** remain significant after Bonferroni correction (multiply p-value by 31)

Table E9: Relationship between most recent sIgE level and component levels using linear regression, where sIgE level is the explanatory variable and component level is the dependent variable.

Component	N	R	Estimate	95% CI	p-value
Birch sIgE vs. Bet v 1	153	0.76	0.58	[0.50;0.66]	<0.0001
Birch sIgE vs. Bet v 2	153	0.35	0.13	[0.07;0.19]	<0.0001
Birch sIgE vs. Bet v 4	153	0.10	0.03	[-0.01;0.07]	0.16
Ragweed sIgE vs. Amb a 1	74	0.65	0.42	[0.30;0.53]	<0.0001
Timothy grass sIgE vs. Phl p 1	60	0.51	0.41	[0.23;0.59]	<0.0001
Timothy grass sIgE vs. Phl p 2	60	0.52	0.22	[0.12;0.31]	<0.0001
Timothy grass sIgE vs. Phl p 4	60	0.32	0.10	[0.02;0.18]	0.0160
Timothy grass sIgE vs. Phl p 5	60	0.65	0.60	[0.41;0.78]	<0.0001
Timothy grass sIgE vs. Phl p 6	60	0.44	0.16	[0.07;0.24]	0.0005
Timothy grass sIgE vs. Phl p 11	60	0.53	0.01	[0.01;0.02]	<0.0001
Timothy grass sIgE vs. Phl p 12	60	0.57	0.28	[0.17;0.39]	0.0009
Dog sIgE vs. Can f 1	69	0.68	0.62	[0.46;0.94]	<0.0001
Dog sIgE vs. Can f 2	69	0.53	0.32	[0.20;0.44]	<0.0001
Dog sIgE vs. Can f 3	69	0.46	0.22	[0.12;0.33]	<0.0001
Dog sIgE vs. Can f 5	69	0.24	0.08	[0.003;0.16]	0.00422
Cat sIgE vs. Fel d 1	59	0.75	0.76	[0.59;0.94]	<0.0001
Cat sIgE vs. Fel d 2	59	0.22	0.08	[-0.02;0.18]	0.10
Cat sIgE vs. Fel d 4	59	0.62	0.20	[0.13;0.26]	<0.0001
<i>D. pteronyssinus</i> sIgE vs. Der p 1	61	0.62	0.40	[0.27;0.53]	<0.0001
<i>D. pteronyssinus</i> sIgE vs. Der p 2	61	0.82	0.69	[0.57;0.82]	<0.0001
<i>D. pteronyssinus</i> sIgE vs. Der p 10	61	0.00	0.04	[-0.26;0.34]	0.24
<i>D. farinae</i> sIgE vs. Der f 1	61	0.68	0.44	[0.32;0.57]	<0.0001
<i>D. farinae</i> sIgE vs. Der f 2	61	0.79	0.73	[0.58;0.88]	<0.0001

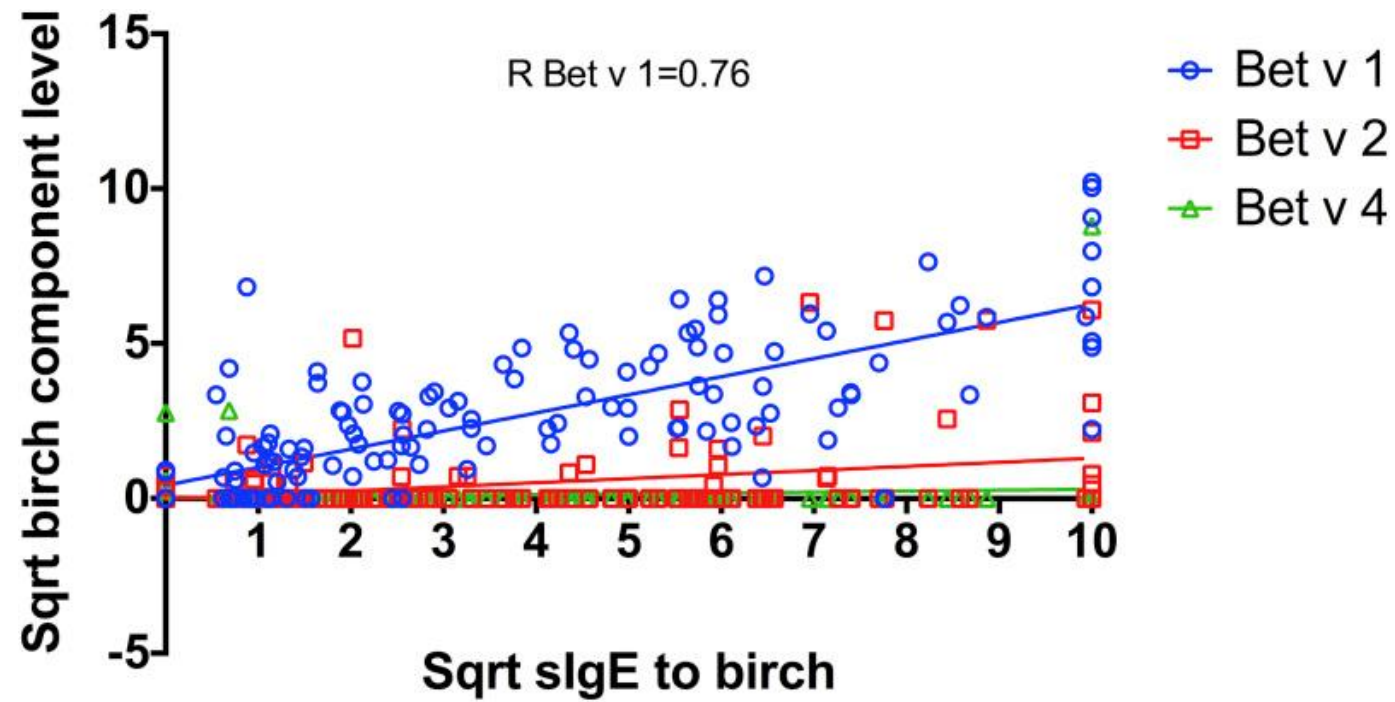


Fig E1.

Ann-Marie M. Schoos, Jacob D. Kattan, Gustavo Gimenez, Hugh A. Sampson

Sensitization phenotypes based on protein groups and associations to allergic diseases in children

Journal of Allergy and Clinical Immunology, 2015, Available online 12 November 2015

<http://dx.doi.org/10.1016/j.jaci.2015.09.035>

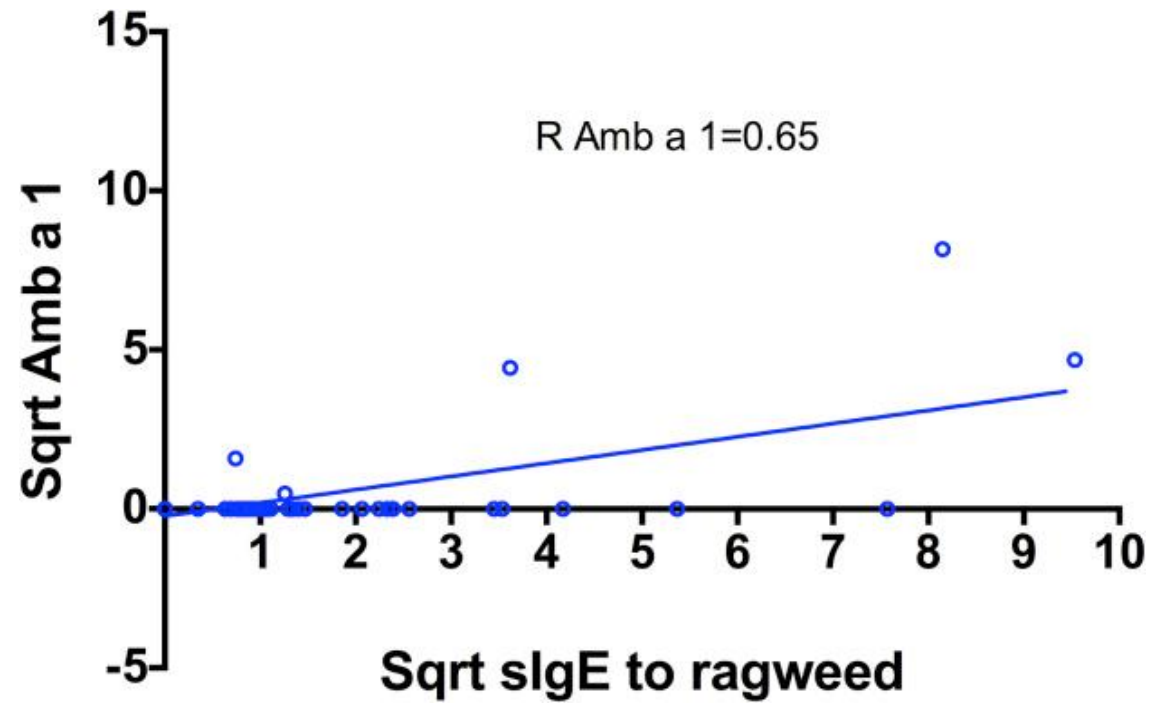


Fig E2.

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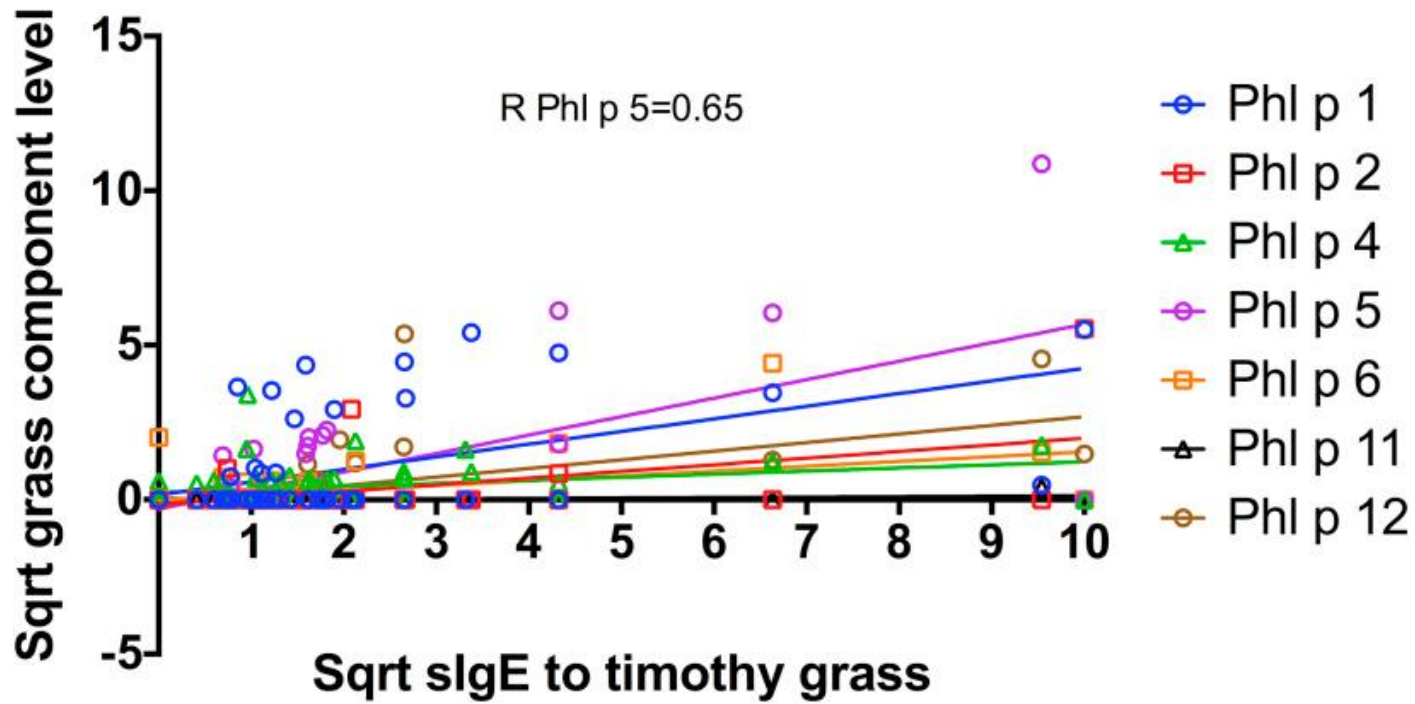


Fig E3.

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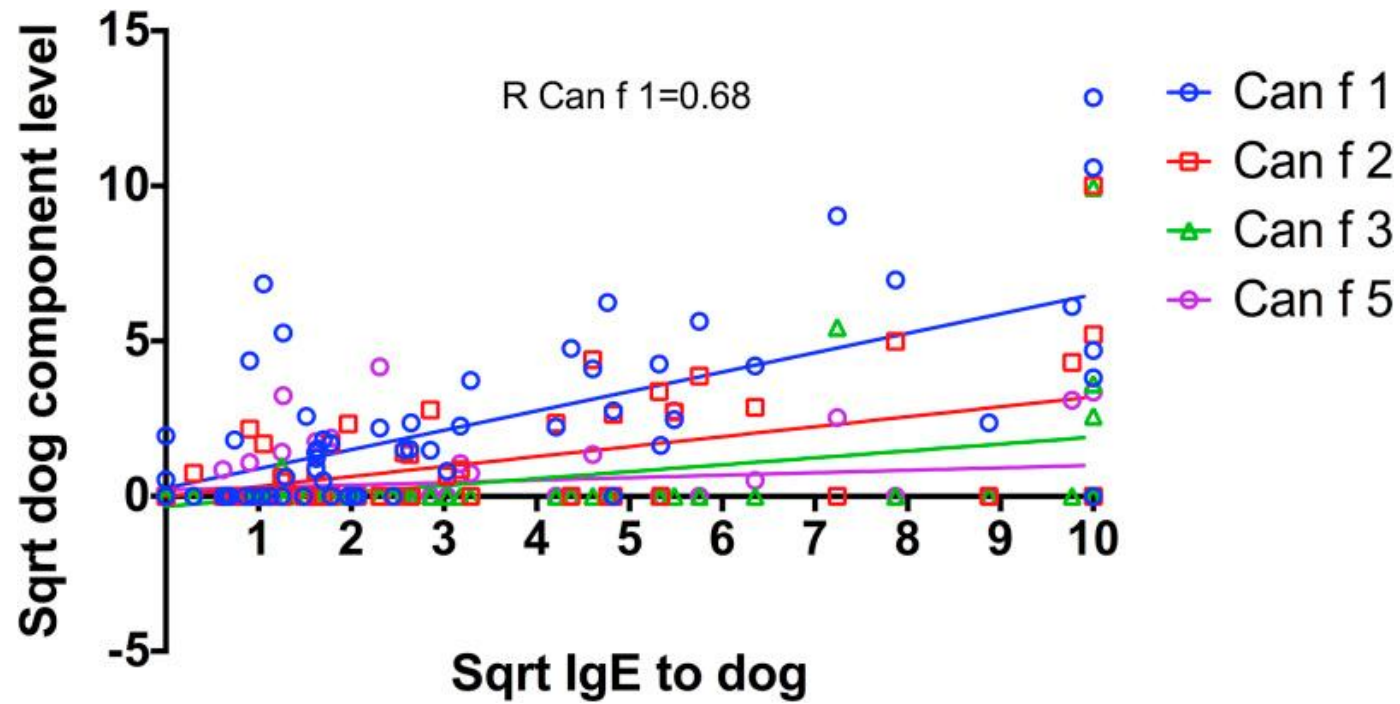


Fig E4.

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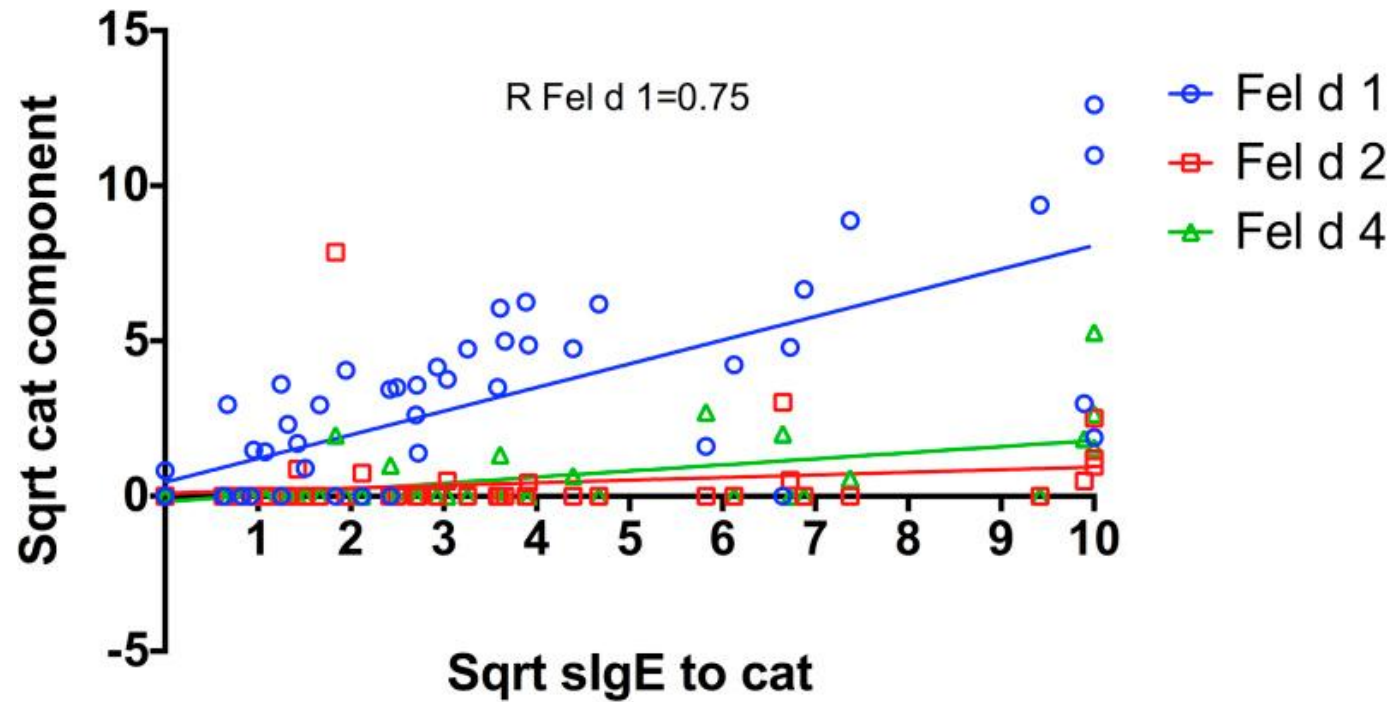


Fig E5.

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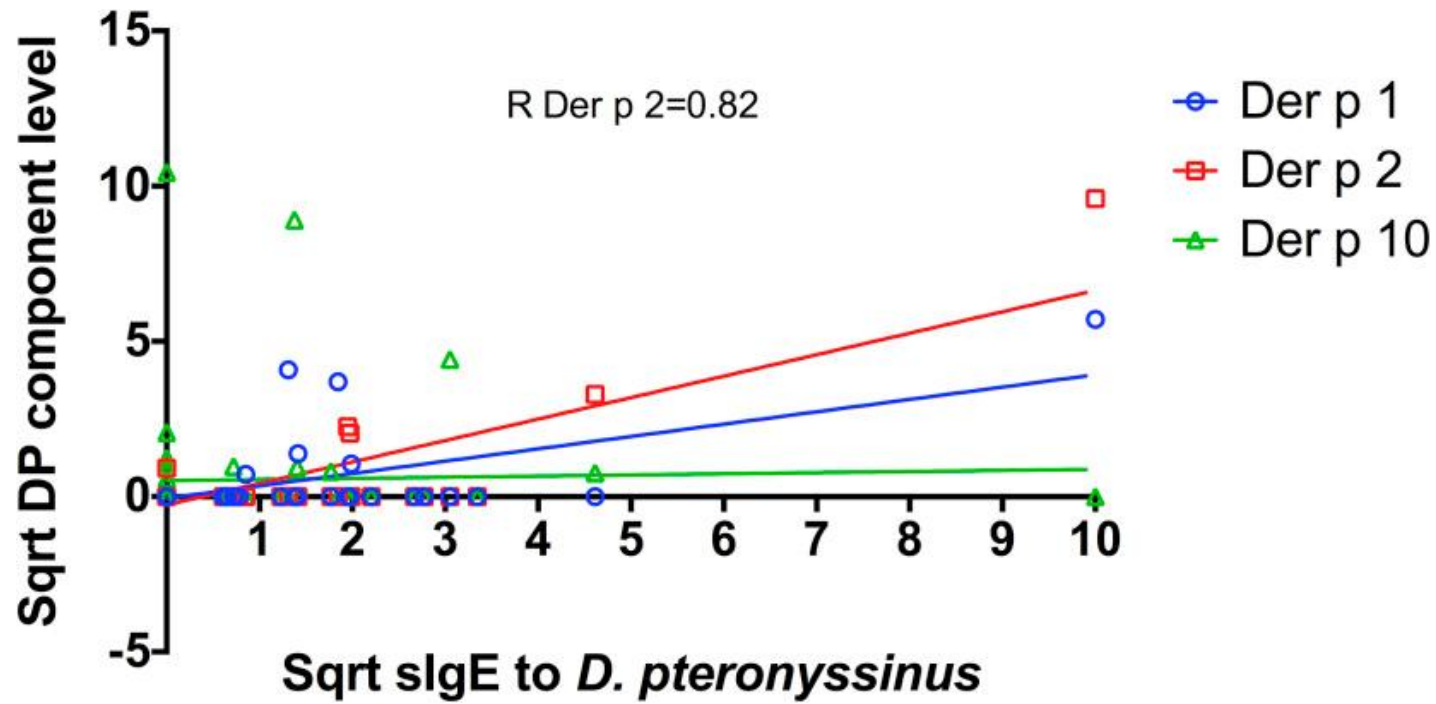


Fig E6.

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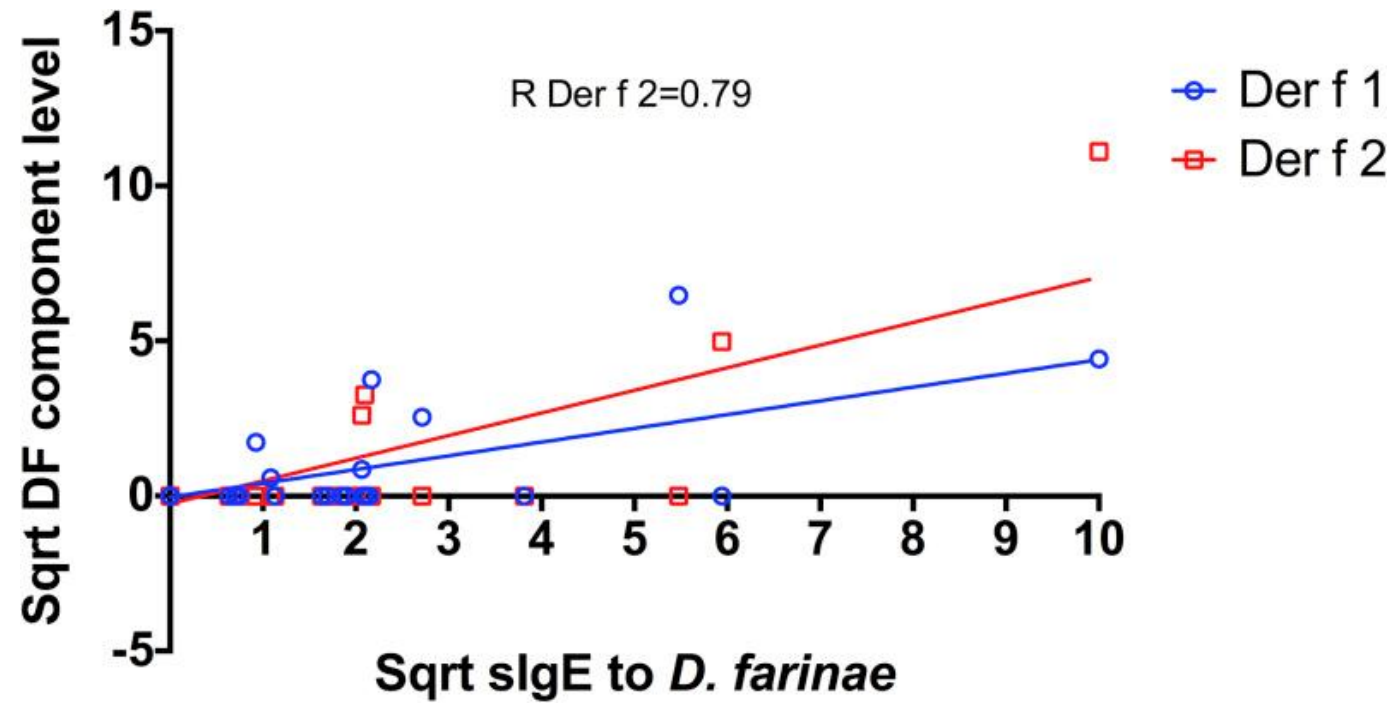


Fig E7.

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