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rBlo t 5 is a potential contributor to the severity of atopic dermatitis in a Brazilian population

To the Editor,

Atopic dermatitis (AD) is the most common inflammatory skin disease worldwide. Brazilian ISAAC data show a prevalence of AD in 8.2% schoolchildren (6 and 7 years old) and 5% of teenagers (13 and 14 years old). It is classified as severe in 5% and 4.4% of the cases of the before-mentioned ages, respectively.¹

The underlying pathogenesis of AD is very complex since it may evolve genetic issues, immunologic and cutaneous barrier disruptions, and external factors as allergic sensitization, irritants, and altered microbiome. Different endotypes have been described.² Higher total IgE serum levels were correlated with a more severe spectrum of manifestations.³ Sensitization patterns among allergic patients are important to be determined in order to correlate with clinical symptoms and provide a better control of the disease.

We hypothesized that mild and severe AD have different patterns of sensitization. In order to investigate that, AD outpatients from the Division of Allergy of the Federal University of São Paulo, a tertiary-level clinic of the biggest city in Brazil, São Paulo, were randomly invited to take part in this study in the period of June 2013 to June 2014. Patients in treatment with systemic immunosuppressants were excluded. Sera samples were obtained from these patients and were analyzed using ImmunoCAP-ISAC[®]. This assay allows a broad investigation of IgE sensitization to 112 allergen components simultaneously. Precision medicine is at the door, and there is little known of IgE sensitization profile from AD Brazilian patients using component-resolved diagnosis. Total IgE serum levels were also determined. The study was approved by the local ethical committee (12551413.2.0000.5505), and a signed informed consent and/or assent was mandatory.

The AD diagnosis was established using Hanifin and Rajka criteria.⁴ Its severity was assessed using SCORAD.⁵ SCORAD subjective questions were fulfilled by the parents in children less than 8 years old. As a pilot study with a small n, in order to observe sensitization trends, patients were considered as having a severe AD when scoring 40 or more and mild, when less than that. Sensitization profiles of non-atopics and atopics (including AD patients) were compared on a previous study.⁶

Venous blood samples of all patients were collected at the same day SCORAD was determined, and obtained serum probes were aliquoted and stored at -20°C until further analysis. Total IgE serum levels were quantified by fluorescence enzyme immunoassay using ImmunoCAP System[®] (Thermo Fisher Scientifics, Uppsala, Sweden). Results were obtained in kilounits per liter (kU/L).

ImmunoCAP-ISAC[®] (Thermo Fisher Scientifics), version 112, was used for the molecular IgE profile study according to the

manufacturer's recommendations. This assay comprises a microarray in triplicate of 112 purified or recombinant allergen components of 51 different sources. Results are expressed in ISAC units (ISU) in four given categories: undetectable (<0.3 ISU), low (0.3 to 1 ISU), moderate to high (1 to 15 ISU), and very high (≥15 ISU). No interference from very high total IgE has been observed yet for this assay.⁷

Statistical analysis was performed using SPSS Statistic 17.0 and R version 3.5.0 (2018-04-03) (<https://www.R-project.org/>), especially for microarray data. All statistical tests were two-sided, and comparisons were considered significant at a P value less than 0.05. Kendall's correlation and partial least squares (PLS) model (R package "PLS", version 2.6-0) were determined in order to analyze the association between presence of specific IgE to allergen and AD severity.

Fifty-nine patients were enrolled in this study. Twenty-eight (47%) were female. Age varied from 9 months to 23.4 years (median 8.4 years). Twenty-nine (49%) were considered to have mild AD (SCORAD < 40), and the rest was classified as severe AD (SCORAD ≥ 40). Mean SCORAD for the mild group was 24.5 (range: 5-34.9) and 61 (range: 50.5-75) to the severe one. Total serum IgE levels were significantly higher ($P < 0.001$) in the severe AD group (median > 5000 kU/L, ranging from 797 kU/L to > 5000 kU/L vs 791 kU/L, ranging from 47.8 kU/L to > 5000 kU/L in mild AD group). Clinical and total IgE sensitization data are provided in Table S1 (online support).

A visualization of the ImmunoCAP-ISAC[®] data is presented in Figure 1. Rate of positivity in ImmunoCAP-ISAC[®] (≥0.30 ISU) was only significantly higher among severe AD patients for rBlo t 5 (83.3% vs 41.4%, $P < 0.001$), a major allergen from *Blomia tropicalis*.

The Kendall's rank correlation with the severity of AD was calculated for each of the 96 ISAC components that had concentration results. *Blomia tropicalis* mite component rBlo t 5 had the highest correlation (Figure 2).

A PLS model was selected by demonstrating the best performance from the inner-loop results of double cross-validation. However, the PLS model was not much better at classifying the severity of AD compared to single component rBlo t 5. The classifier performance statistics are summarized in Table 1 where condition positive has been defined as severe AD. Sensitization to rBlo t 5 (>0.7 ISU) was associated with 69% specificity and 80% sensitivity of having severe AD (Table 1).

Sensitization to Der p 11, a house dust mite body component, has been proposed as a serological marker of AD patients from

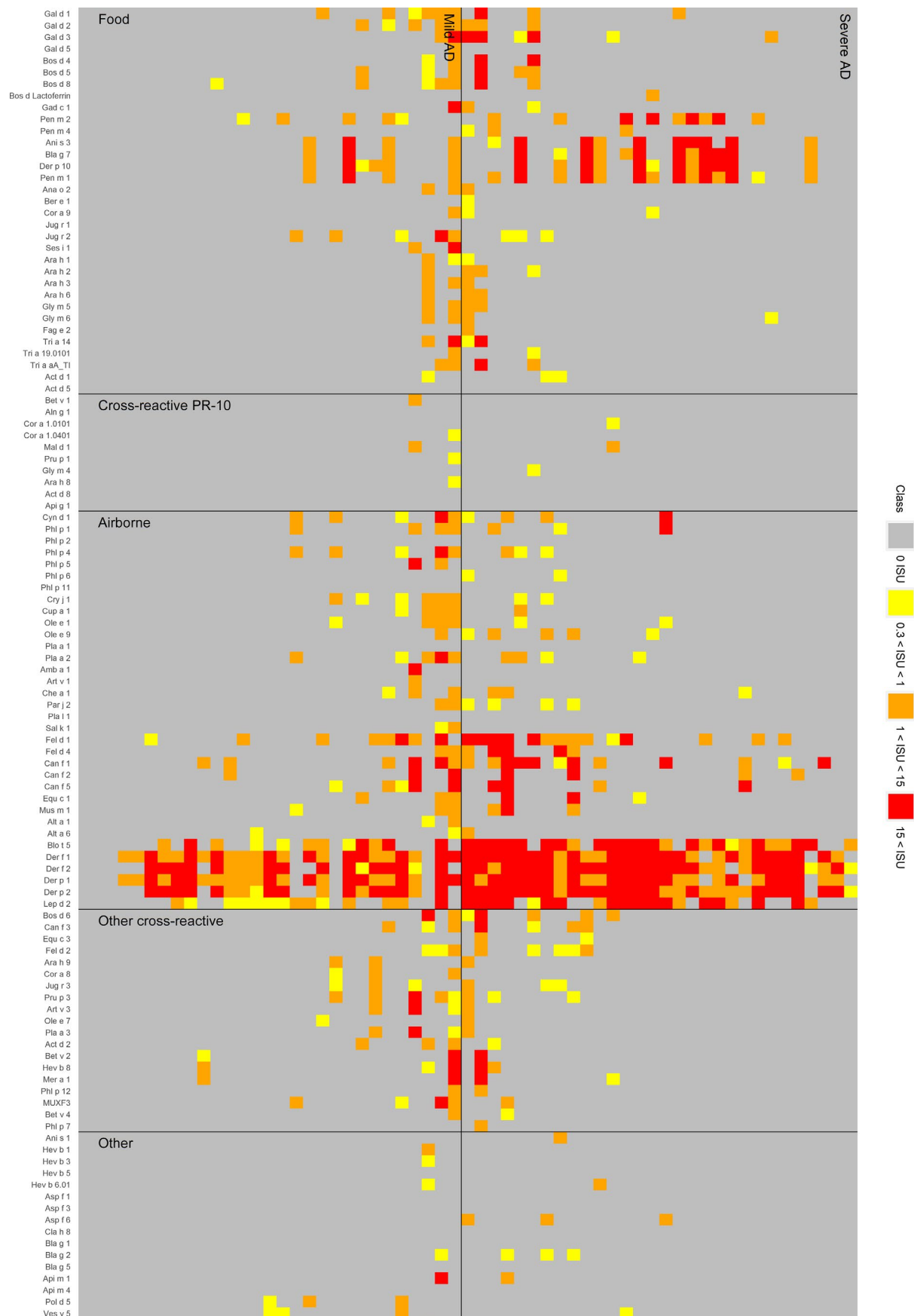


FIGURE 1 Class distribution of ImmunoCAP-ISAC® results for each component for both mild and severe AD groups [Colour figure can be viewed at wileyonlinelibrary.com]

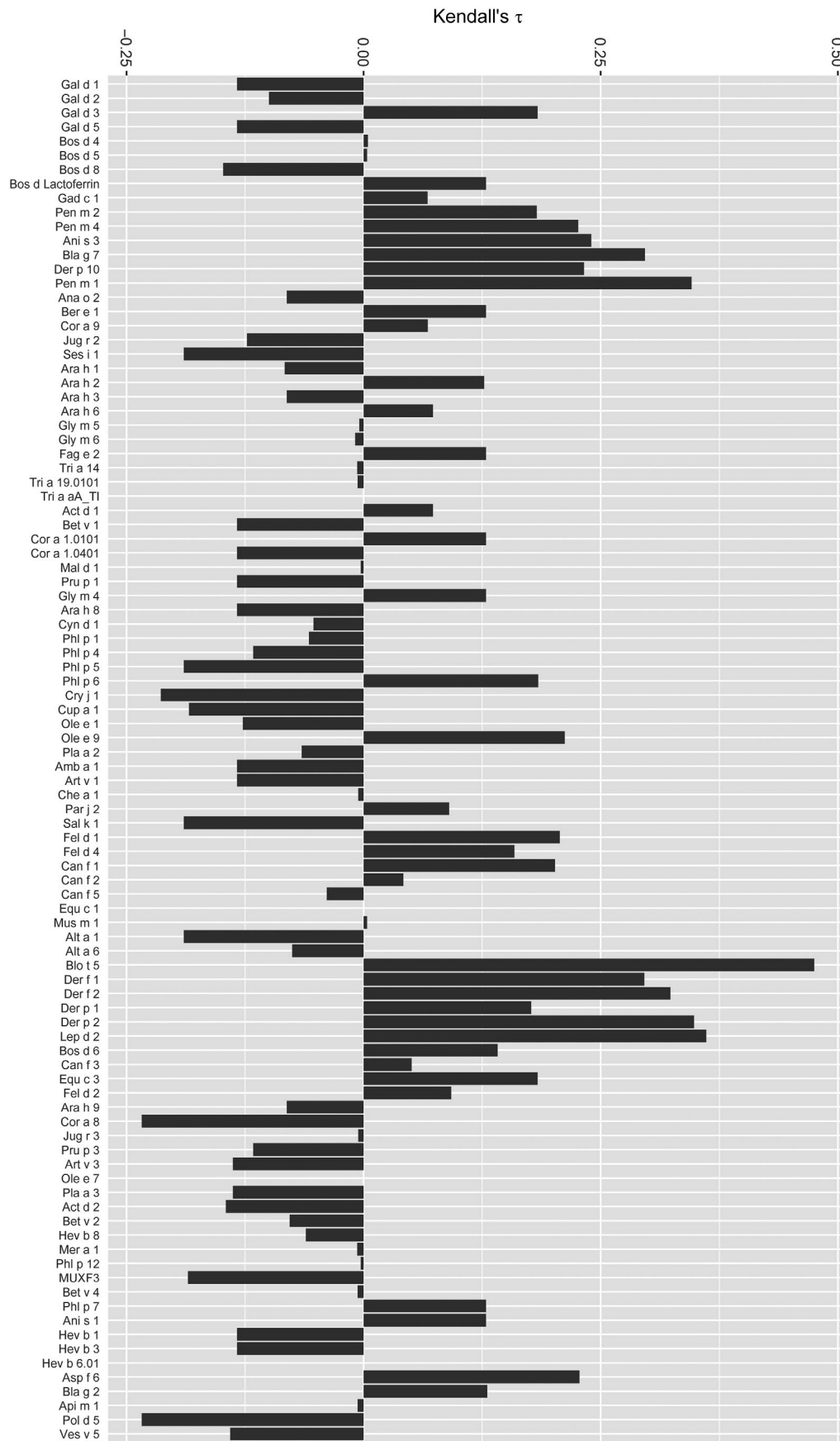


FIGURE 2 Kendall's rank correlation for each non-constant ImmunoCAP-ISAC® component

Classifier	Sensitivity	Conf. Int ^a	Specificity	Conf. Int ^a	LR ^b +	LR ^b -
Blo t 5	80.0	61.4-92.3	69.0	49.2-84.7	2.58	3.45
PLS	86.7	69.3-96.2	65.5	45.7-82.1	2.51	4.91
PLS	83.3	65.3-94.4	65.5	45.7-82.1	2.42	3.93
PLS	83.3	65.3-94.4	65.5	45.7-82.1	2.42	3.93
PLS	83.3	65.3-94.4	65.5	45.7-82.1	2.42	3.93

^aConfidence interval.

^bLikelihood-Ratio.

TABLE 1 Sensitivity and specificity considering either positivity to rBlo t 5 (>0.7 ISU) or the partial least squares (PLS) model

Europe and Africa.⁸ Component-resolved diagnosis was poorly studied in Brazilian AD patients. Bouffleur *et al* observed that nDer p 1/nDer f 1 and rDer p 2/nDer f 2 were the most common inhalant allergens (82% and 85% sensitization rates) among adults with moderate and severe AD.⁹ Our study showed also high sensitization to those components (nDer p 1/nDer f 1 79.3% in the mild AD group and 90% for nDer f 1 and 86.7% for nDer p1 in severe AD group), which shows 82% amino acid sequence identity and high cross-reactivity.¹⁰ In our study, sensitization patterns to Der p 1 and Der f 1 could not distinguish mild and severe AD patients as rBlo t 5, which shows a trend in this sense. No data were presented by Bouffleur *et al*¹¹ in relation to *Blomia tropicalis* although it is considered a common sensitizer in Brazilian atopic children (57.4%). rBlo t 5 may be a potential contributor to the severity of AD Brazilian patients yet not fully studied. A similar study conducted in Sweden with adult AD patients showed higher frequency of specific IgE to rFel d 1, rDer p 4 and 10, probably due to different allergen exposure.¹²

It is estimated that one third of moderate-to-severe AD have food allergy.¹³ Among our patients, food components with highest sensitization were egg nGal d 1 (20.7%) in the mild ones and shrimp tropomyosin nPen m 1 (46.7%) followed by nPen m 2 (30%) in the severe AD group without statistically significant difference between groups. Sensitization to nPen m 1 may be in this case partially explained due to cross-sensitization to house dust mite since nPen m 2 specie-specific component also showed high sensitization.

One possible weakness of our study may be that, as a cross-sectional study, it included patients followed up for distinct periods of time and not when the diagnosis of AD was established. In this way, initially severe cases may be actually classified as mild because of regular treatment. One cannot affirm that the classification in mild or severe expresses the phenotype of the disease by itself besides treatment interference. To minimize treatment interference, the use of systemic immunosuppressants, considered as disease severe modifying factor, was an exclusion criterion.

The hypothesized IgE profile difference between mild and severe AD patients was only seen for rBlo t 5, which has already been implicated in Brazilian asthma patients as an important allergen.¹⁴ In São Paulo, sensitization to rBlo t 5 may be associated with severe AD manifestation. Further investigation with broader recently diagnosed AD population is needed. Detection

of allergen exposure would also be interesting to correlate sensitization profile to symptomatology in such population. Determining the offending allergen is essential for a better disease control or choosing a precise immunotherapy.

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CONFLICTS OF INTERESTS

None.

AUTHOR CONTRIBUTIONS

Lucila Camargo Lopes de Oliveira contributed to conception and design of the work, data collection, data analysis and interpretation, and drafting of the manuscript. Felipe Faria Pierotti involved in ImmunoCAP and ImmunoCAP-ISAC execution. Marcia Carvalho Mallozi, Renata Rodrigues Cocco, Nelson Rosário and Isabel Rugue Genov involved in data collection and approved the final version to be published. K. Magnus Åberg, Magnus P. Borres contributed to ImmunoCAP-ISAC data analysis and approved the final version to be published. Dirceu Solé contributed to conception and design of the work, data collection, and critical revision of the article, and approved the final version to be published.

ORCID

Lucila Camargo Lopes de Oliveira  <https://orcid.org/0000-0003-2065-571X>

Magnus P. Borres  <https://orcid.org/0000-0002-9045-2304>

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Lucila Camargo Lopes de Oliveira¹ 

Felipe F. Pierotti¹

Marcia Mallozi¹

Renata Rodrigues Cocco¹

Nelson Rosário²
 Isabel Rugue Genov¹
 K. Magnus Åberg³
 Magnus P. Borres^{3,4} 
 Dirceu Solé¹

¹Federal University of São Paulo, São Paulo, Brazil

²Federal University of Paraná, Curitiba, Brazil

³Thermo Fisher Scientific, Uppsala, Sweden

⁴Department of Maternal and Child Health, Uppsala University, Uppsala, Sweden

Correspondence

Lucila Camargo Lopes de Oliveira, Federal University of São Paulo, São Paulo, Brazil

Email: lucila_camargo@yahoo.com

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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A case series of pediatric oncology patients undergoing successful rapid etoposide desensitization

To the Editor,

Etoposide is a podophyllotoxin used in the treatment of various pediatric neoplasms. Hypersensitivity reactions (HSRs) to etoposide have a reported incidence of about 1%-3%, with symptoms ranging from mild cutaneous reactions to fatal anaphylaxis.^{1,2} Hypersensitivity reactions to etoposide are thought to be related to the vehicle used to dissolve etoposide, polysorbate 80, rather than the drug.³ In an animal model, polysorbate 80 has been shown to cause HSR, given its histamine-releasing properties.⁴ Patients experiencing HSR to etoposide may have their treatment substituted with etoposide phosphate, a water-soluble prodrug of etoposide that does

not contain polysorbate 80. In August 2016, etoposide phosphate went on national backorder, limiting therapeutic options for patients who experienced a clinically significant hypersensitivity reaction to etoposide. Rapid drug desensitization allows temporary tolerance to a drug in order for a medication-allergic patient to receive the optimal agent based on their clinical condition and offers an option for patients in need of etoposide who have had an HSR.⁵ Drug desensitization protocols have been successfully reported with a variety of chemotherapeutic agents, including etoposide. However, the majority of reported protocols were designed for adult patients.⁵⁻⁸ We describe the development and successful implementation of both a

Table 1. Clinical and sensitization data of studied population.

AD severity	Sex	Comorbidities	SCORAD	Age (in months)	total IgE (kU/L)
Mild					
1	M	ARC	5	127	338
2	F	ARC, FA (cow's milk, beef, soy, fish, seafood)	21.3	113	47.8
3	M	FA (cow's milk)	34.9	77	2598
4	M	ARC, FA (hen's egg)	32.3	49	357
5	F	FA (cow's milk, avocado, banana)	33	20	2222
6	M		21	9	780
7	F	ARC	20.4	46	4025
8	M	ARC	26	49	>5000
9	M	ARC, FA (wheat)	21	77	601
10	M	EoE	30	72	>5000
11	F	ARC, Asthma	14	263	654
12	F	ARC, FA (kiwi, papaya, pineapple)	23.7	281	67.5
13	F	ARC, Asthma	32	120	729
14	M		28.3	15	111
15	F	ARC	24.7	122	2196
16	M	Asthma, FA (hen's egg, soy)	33.6	163	2345
17	F		13	34	183
18	F	Asthma, ARC, FA (avocado, banana)	17	87	3061
19	F	ARC, Asthma	17.7	144	791
20	F	ARC, Asthma	21	48	NA
21	M	ARC, Asthma	32	96	NA
22	F	ARC, Asthma	34	144	2345
23	F	ARC, Asthma	22.6	144	545
24	M	ARC, asthma	23	144	1860
25	F	ARC, asthma	32	108	1079
26	F	ARC, Asthma	24	60	137
27	M	ARC, Asthma	17.2	156	1848
28	M	ARC, Asthma	22	108	NA
29	M	ARC, Asthma			
Severe					
1	F	ARC, FA (peanut)	53.5	148	>5000
2	F		51	159	>5000
3	M	ARC, Asthma	60.2	101	>5000
4	F	Asthma	70.4	158	>5000
5	M	ARC, FA (cow's milk)	73	102	>5000
6	F	Asthma	75	96	>5000
7	M	ARC, Asthma	62	200	1393
8	M	ARC	56	66	>5000
9	M	ARC	72.5	234	>5000
10	M		56	87	>5000
11	M	ARC	55.8	121	2982
12	M		67.9	125	>5000
13	M		62.3	32	1528
14	M	Asthma	70.5	96	>5000
15	M		55.3	51	>5000
16	M	ARC, Asthma	50.5	100	>5000
17	F		61	41	4931
18	F	ARC	65	80	>5000
19	F	ARC	72.5	67	>5000
20	F	ARC, Asthma	53.5	45	>5000
21	F		56.9	143	>5000
22	F		75	132	1579
23	F	FA (cow's milk, egg, soy, wheat)	73.2	79	>5000
24	M	ARC, Asthma	52	160	797
25	F	ARC, Asthma, FA (cow's milk, egg, wheat)	54.3	50	2413
26	F	ARC	56	120	NA
27	M	ARC, Asthma	53	84	NA
28	M	ARC, Asthma	60.3	132	NA
29	M	ARC, Asthma	51	120	NA
30	M	ARC	55.3	120	NA

ARC= allergic rhinoconjunctivitis, FA= food allergy (patient's complain) NA= not available EoE= Epsinophilic esophagitis