

## Letter to the Editor



# Milk-Specific IgE Reactivity Without Symptoms in Albumin-Sensitized Cat Allergic Patients

Antonina V. Karsonova ,<sup>1</sup> Ksenja A. Riabova ,<sup>1</sup> Musa R. Khaitov ,<sup>2</sup> Olga G. Elisyutina ,<sup>2</sup> Nataliya Ilina ,<sup>2</sup> Elena S. Fedenko ,<sup>2</sup> Daria S. Fomina ,<sup>1,3</sup> Evgeny Beltyukov ,<sup>4</sup> Natalya L. Bondarenko ,<sup>1</sup> Irina V. Evsegneeva ,<sup>1</sup> Polina A. Glazkova ,<sup>5</sup> Dmitry Yu. Semenov ,<sup>5</sup> Marianne van Hage ,<sup>6</sup> Hans Grönlund ,<sup>7</sup> Alexander V. Karaulov ,<sup>1</sup> Rudolf Valenta ,<sup>1,2,8,9</sup> Mirela Curin <sup>8\*</sup>

## OPEN ACCESS

**Received:** Sep 11, 2020

**Accepted:** Oct 30, 2020

### Correspondence to

**Mirela Curin, PhD**

Division of Immunopathology, Department of Pathophysiology and Allergy Research, Center for Pathophysiology, Infectiology and Immunology, Medical University of Vienna, Waehringer Guertel 18-20, 1090 Vienna, Austria.

Tel: +43-1-40400-51090

Fax: +43-1-40400-51300

E-mail: mirela.curin@meduniwien.ac.at

Copyright © 2021 The Korean Academy of Asthma, Allergy and Clinical Immunology · The Korean Academy of Pediatric Allergy and Respiratory Disease

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

### ORCID iDs

Antonina V. Karsonova

<https://orcid.org/0000-0002-8697-9816>

Ksenja A. Riabova

<https://orcid.org/0000-0003-0520-0936>

Musa R. Khaitov

<https://orcid.org/0000-0003-4961-9640>

Olga G. Elisyutina

<https://orcid.org/0000-0002-4609-2591>

Nataliya Ilina

<https://orcid.org/0000-0002-3556-969X>

Elena S. Fedenko

<https://orcid.org/0000-0003-3358-5087>

<sup>1</sup>Department of Clinical Immunology and Allergology, Laboratory of Immunopathology, Sechenov First Moscow State Medical University, Moscow, Russian Federation

<sup>2</sup>National Research Center - Institute of Immunology FMBA of Russia, Moscow, Russian Federation

<sup>3</sup>Clinical City Hospital #52 Moscow City Centre of Allergology and Immunology, Moscow, Russian Federation

<sup>4</sup>Ural State Medical University, Yekaterinburg, Russian Federation

<sup>5</sup>Moscow Regional Research and Clinical Institute ("MONIKI"), Moscow, Russian Federation

<sup>6</sup>Division of Immunology and Allergy, Department of Medicine Solna, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden

<sup>7</sup>Department of Clinical Neuroscience, Therapeutic Immune Design Unit, Karolinska Institutet, Stockholm, Sweden

<sup>8</sup>Division of Immunopathology, Department of Pathophysiology and Allergy Research, Center for Pathophysiology, Infectiology and Immunology, Medical University of Vienna, Vienna, Austria






<sup>9</sup>Karl Landsteiner University for Health Sciences, Krems, Austria

To the Editor,

Serum albumin (Fel d 2) is a cross-reactive animal dander allergen, which can be found in animal-derived foods such as meat and milk.<sup>1</sup> In a population study conducted in Moscow, Russia, we noted that milk albumin, Bos d 6, was more frequently recognized than the major milk allergens caseins, lactalbumin and lactoglobulin.<sup>2-4</sup>

We hypothesized that immunoglobulin E (IgE) sensitization to Bos d 6 could be attributed to original IgE-sensitization to cat dander via the respiratory tract and may be caused by IgE cross-reactivity between Fel d 2 and Bos d 6. Therefore, we studied a cohort of 85 patients with clinically documented allergy to cat. Using a panel of purified cat allergen molecules (**Supplementary Data S1**), we identified 15 patients who showed specific IgE reactivity (0.45–100 kU<sub>A</sub>/L) to cat albumin, Fel d 2 as tested by quantitative IgE ImmunoCAP (**Supplementary Table S1**, patients 1–15). These patients suffered from various symptoms of allergy upon contact with a cat; however, each of them regularly consumed cow's milk and albumin-containing food, such as pork and beef, without experiencing any allergic symptoms. Further testing of these 15 Fel d 2-positive patients' sera showed that 7 out of the 15 patients showed IgE reactivity > 0.1 kU<sub>A</sub>/L to Bos d 6, 9 displayed IgE reactivity to cow's milk allergen extract and 5 were even positive to fx5, the mix of food allergen extracts including cow's milk in ImmunoCAP (**Supplementary Table S1**).

Interestingly, IgE levels were always higher to Fel d 2 than to Bos d 6, suggesting that respiratory sensitization to Fel d 2 may have induced IgE antibodies in these patients which cross-reacted with Bos d 6.

Daria S. Fomina   
<https://orcid.org/0000-0002-5083-6637>  
 Evgeny Beltyukov   
<https://orcid.org/0000-0003-2485-2243>  
 Natalya L. Bondarenko   
<https://orcid.org/0000-0002-1418-2517>  
 Irina V. Evsegneeva   
<https://orcid.org/0000-0002-6624-1363>  
 Polina A. Glazkova   
<https://orcid.org/0000-0002-8830-7503>  
 Dmitry Yu. Semenov   
<https://orcid.org/0000-0003-2845-1703>  
 Marianne van Hage   
<https://orcid.org/0000-0003-3091-1596>  
 Hans Grönlund   
<https://orcid.org/0000-0003-4882-7624>  
 Alexander V. Karaulov   
<https://orcid.org/0000-0002-1930-5424>  
 Rudolf Valenta   
<https://orcid.org/0000-0001-5944-3365>  
 Mirela Curin   
<https://orcid.org/0000-0003-2575-4127>

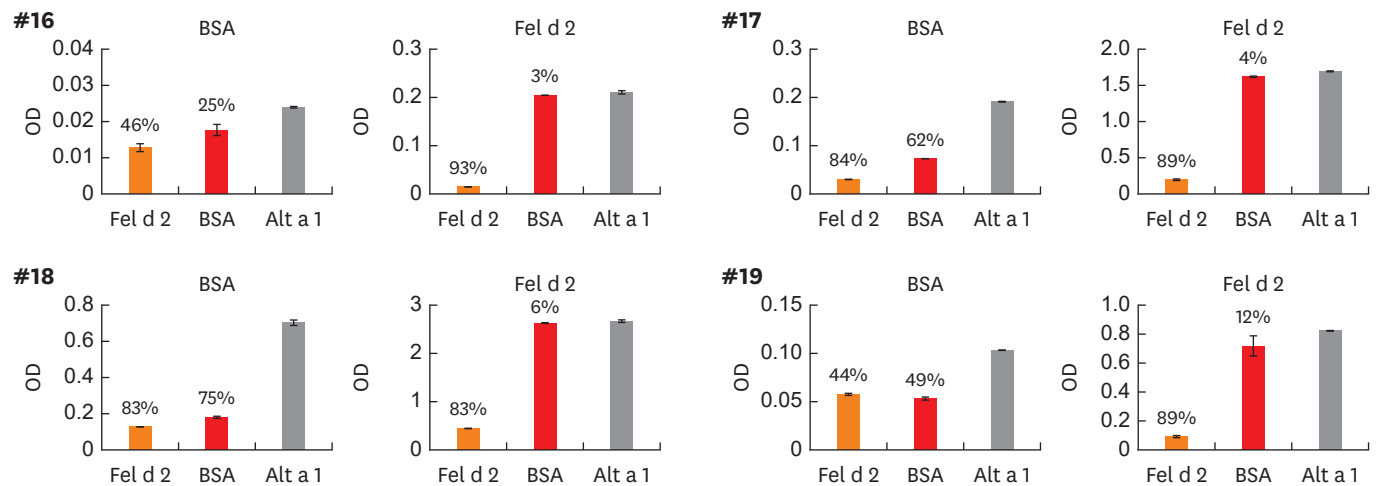
**Disclosure**

There are no financial or other issues that might lead to conflict of interest.

To investigate this, we performed a series of ELISA IgE inhibition experiments with sera from additional cat-allergic patients who were Fel d 2-sensitized according to ELISA testing and from whom we had sufficient volumes of serum available (**Supplementary Table S1**, patients 16–19).<sup>5</sup> Also, these patients regularly consumed cow's milk and meat without showing any allergic symptoms.

Pre-incubation of these sera with Fel d 2 inhibited IgE binding to BSA in the range of 44%–84% (**Figure**, left panels), whereas pre-incubation of sera with BSA had almost no effect on IgE binding to Fel d 2 with inhibitions rates of 3%–12% (**Figure**, right panels). BSA inhibited IgE binding to BSA (25%–75%) (**Figure**, left panels), while Fel d 2 inhibited IgE-binding to Fel d 2 almost completely (83%–93%) (**Figure**, right panels). Pre-incubation of sera with the unrelated control allergen, Alt a 1, had no effects on IgE binding to Fel d 2 and BSA giving similar OD values as buffer alone (**Figure**, Alt a 1 columns). As in the ImmunoCAP measurements, we noted that, in the ELISA experiments, the IgE levels specific for BSA (**Figure**, left panels, OD values Alt a 1) were much lower than those specific for Fel d 2 (right panels, OD values Alt a 1), corroborating that Fel d 2, but not Bos d 6, was the originally sensitizing allergen.

A previous study by Vicente-Serrano *et al.*<sup>6</sup> reported a group of patients who were sensitized first to milk and then showed cross-reactivity with dander-derived albumin without direct contact with animals. However, our findings are different from their results because we describe patients with first sensitization to cat albumin and subsequent cross-reactivity with milk, without milk-related clinical symptoms. In summary, cross-reactivity between Fel d 2 and Bos d 6 may give false positive IgE test results for albumin-sensitized cat allergic patients when cow's milk allergen extracts are used to determine allergen-specific IgE and insinuate IgE sensitization to cow's milk. Since a considerable proportion of the world population suffers from clinical symptoms caused by non-IgE-mediated cow's milk intolerance (10%–100%),<sup>7</sup> our finding is clinically relevant and should be considered in the serological detection of IgE sensitization to cow's milk.<sup>8</sup> According to birth cohort studies,<sup>9</sup> almost 7% of the population in Sweden is sensitized to Fel d 2 and at the same time approximately 30% will suffer from adverse reactions to milk due to lactose intolerance<sup>7</sup> making the differential diagnosis a relevant clinical problem.



**Figure.** IgE cross-reactivity between Fel d 2 and Bos d 6 (BSA). IgE binding (y-axes: OD values corresponding to bound IgE) of cat allergic patients (#16, 17, 18, and 19) to BSA (left panels) or Fel d 2 (right panels) are shown after pre-incubation of sera with an unrelated control allergen (Alt a 1), Fel d 2 or BSA (x-axes). ODs are displayed as means ± standard deviation of duplicates. Percentages of the inhibition of IgE binding are indicated on the tops of the bars. OD, optical density; IgE, immunoglobulin E.

## ACKNOWLEDGMENTS

This study was funded by a Megagrant of the Government of the Russian Federation, grant number 14.W03.31.0024 and by the “Russian Academic Excellence Project 5-100,” by the Austrian Science Fund (FWF) SFB project F4605 and by The Region Stockholm (ALF project), the Swedish Asthma and Allergy Research Foundation, the Swedish Heart-Lung Foundation, the Swedish Research Council.

## SUPPLEMENTARY MATERIALS

### Supplementary Data S1

Supplementary methods

[Click here to view](#)

### Supplementary Table S1

Demographic, clinical and immunological characterization of Fel d 2-positive cat allergic patients

[Click here to view](#)

## REFERENCES

1. Spitzauer S, Pandjaitan B, Söregi G, Mühl S, Ebner C, Kraft D, et al. IgE cross-reactivities against albumins in patients allergic to animals. *J Allergy Clin Immunol* 1995;96:951-9.  
[PUBMED](#) | [CROSSREF](#)
2. Fiocchi A, Brozek J, Schünemann H, Bahna SL, von Berg A, Beyer K, et al. World Allergy Organization (WAO) diagnosis and rationale for action against cow' milk allergy (DRACMA) guidelines. *World Allergy Organ J* 2010;3:57-161.  
[PUBMED](#) | [CROSSREF](#)
3. Hochwallner H, Schulmeister U, Swoboda I, Balic N, Geller B, Nystrand M, et al. Microarray and allergenic activity assessment of milk allergens. *Clin Exp Allergy* 2010;40:1809-18.  
[PUBMED](#) | [CROSSREF](#)
4. du Toit G, Meyer R, Shah N, Heine RG, Thomson MA, Lack G, et al. Identifying and managing cow' milk protein allergy. *Arch Dis Child Educ Pract Ed* 2010;95:134-44.  
[PUBMED](#) | [CROSSREF](#)
5. Reininger R, Swoboda I, Bohle B, Hauswirth AW, Valent P, Rumpold H, et al. Characterization of recombinant cat albumin. *Clin Exp Allergy* 2003;33:1695-702.  
[PUBMED](#) | [CROSSREF](#)
6. Vicente-Serrano J, Caballero ML, Rodríguez-Pérez R, Carretero P, Pérez R, Blanco JG, et al. Sensitization to serum albumins in children allergic to cow' milk and epithelia. *Pediatr Allergy Immunol* 2007;18:503-7.  
[PUBMED](#) | [CROSSREF](#)
7. Bayless TM, Brown E, Paige DM. Lactase non-persistence and lactose intolerance. *Curr Gastroenterol Rep* 2017;19:23.  
[PUBMED](#) | [CROSSREF](#)
8. Valenta R, Hochwallner H, Linhart B, Pahr S. Food allergies: the basics. *Gastroenterology* 2015;148:1120-31.e4.  
[PUBMED](#) | [CROSSREF](#)
9. Asarnoj A, Hamsten C, Wadén K, Lupinek C, Andersson N, Kull I, 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.e7.  
[PUBMED](#) | [CROSSREF](#)