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<http://dx.doi.org/10.1016/j.jaci.2013.10.024>

Reply

To the Editor:

In their correspondence, Liccardi et al¹ comment on the significance of the rabbit secretoglobulin Ory c 3 as a major sensitizing allergen from rabbits.² They point out that in real life allergic sensitization to common pets (cats/dogs) as well as

TABLE I. Rabbit-allergic patient data

Patient no.	Rabbit epithelium e82 (kU _A /L)	Cat dander e1 (kU _A /L)	Dog dander e5 (kU _A /L)	Pets at home	nOry c 3* secretoglobulin (kU _A /L)	rFel d 1 secretoglobulin (kU _A /L)	rOry c 4* lipocalin (kU _A /L)	rFel d 4* lipocalin (kU _A /L)	rCan f 6* lipocalin (kU _A /L)	nRabbit SA (kU _A /L)	nFel d 2* cat SA (kU _A /L)	nCan f 3* dog SA (kU _A /L)
1	24	<0.35	0.49	Rabbits	13.0	0.45	<0.35	<0.35	<0.35	<0.35	<0.35	<0.35
2	16	1.85	5.8	NI	19.6	3.19	<0.35	<0.35	<0.35	<0.35	<0.35	<0.35
3	47	<0.35	1.44	Dog	33.7	0.13	<0.35	<0.35	<0.35	<0.35	<0.35	<0.35
4	56	38	11	Rabbit	10.8	43.8	36.5	21.4	16.2	<0.35	<0.35	<0.35
5	30	NT	NT	Rabbit previously, dog	12.7	0.15	<0.35	5.9	5.2	<0.35	<0.35	<0.35
6	>100	7.8	3.1	Rabbit previously, cat	276.9	5.72	67.9	<0.35	<0.35	<0.35	<0.35	<0.35
7	82	NT	NT	NI	28.0	<0.1	<0.35	9.6	1.8	<0.35	<0.35	<0.35
8	20	3.73	14	Dog	17.2	6.9	<0.35	<0.35	1.5	<0.35	<0.35	<0.35
9	3.26	28.3	6.85	Cat	<0.35	60.5	<0.35	<0.35	<0.35	<0.35	<0.35	<0.35
10	22.4	<0.35	<0.35	Rabbit	9.3	0.38	13.0	<0.35	<0.35	<0.35	<0.35	<0.35
11	42.2	17.7	14.1	Rabbits, horse	35.6	24.9	4.5	<0.35	<0.35	<0.35	<0.35	<0.35
12	17	<0.35	27	NI	25.3	<0.1	8.3	0.9	17.8	<0.35	<0.35	<0.35
13	9.77	81	42	Dog, cat, ferret	9.6	37.5	14.6	<0.35	4.5	6.3	49.6	56.0
14	4.64	4.79	14	Rabbit, dog	<0.35	8.01	7.0	<0.35	0.4	<0.35	<0.35	<0.35
15	4.24	<0.35	<0.35	Rabbit	2.2	<0.1	<0.35	<0.35	<0.35	<0.35	<0.35	<0.35
16	78	1.76	0.34	Rabbit	74.8	0.19	33.4	<0.35	0.4	<0.35	<0.35	<0.35
17	7.43	>100	18	Rabbit, cat, dog, horse	8.9	169.2	6.7	7.7	4.0	<0.35	<0.35	<0.35
18	25	<0.35	<0.35	NI	11.3	<0.1	<0.35	<0.35	<0.35	<0.35	<0.35	<0.35
19	6.55	5.97	2.14	Rabbit previously, cat	<0.35	5.48	<0.35	<0.35	<0.35	0.95	<0.35	<0.35
20	9.61	<0.35	0.13	Rabbit	5.4	<0.1	4.2	<0.35	<0.35	<0.35	<0.35	<0.35
21	>100	>100	52	Rabbit, cat, guinea pig	96.0	>200	39.1	24.0	16.1	<0.35	<0.35	<0.35
22	27	NT	NT	Rabbit previously	15.5	0.29	<0.35	29.1	<0.35	<0.35	<0.35	<0.35
23	57	<0.35	<0.35	Rabbit	67.7	<0.1	<0.35	<0.35	<0.35	<0.35	<0.35	<0.35
24	18	NT	NT	NI	<0.35	<0.1	<0.35	<0.35	<0.35	<0.35	<0.35	<0.35
25	13	4.75	6.71	Rabbit previously, dog, horse	70.5	6.15	4.3	0.7	<0.35	<0.35	<0.35	<0.35
26	>100	47	32	Rabbit, horse	59.2	33.2	70.4	0.9	4.4	<0.35	<0.35	<0.35
27	4.18	<0.35	<0.35	Rabbit	<0.35	<0.1	<0.35	<0.35	0.6	<0.35	<0.35	<0.35
28	45	NT	NT	NI	7.2	<0.1	<0.35	<0.35	<0.35	<0.35	<0.35	<0.35
29	5.69	<0.35	0.68	Rabbit, guinea pig, hamster	<0.35	0.12	<0.35	<0.35	<0.35	<0.35	<0.35	<0.35
30	3.26	1.87	0.48	Rabbit	<0.35	2.11	6.8	<0.35	<0.35	<0.35	<0.35	<0.35
31	3.84	<0.35	3.27	Rabbit, dog	<0.35	<0.1	9.6	<0.35	<0.35	<0.35	<0.35	<0.35
32	4.95	7.7	3.5	Rabbit	5.6	0.1	<0.35	<0.35	0.7	<0.35	<0.35	<0.35
33	53	NT	NT	NI	47.3	<0.1	<0.35	<0.35	<0.35	<0.35	<0.35	<0.35
34	42	0.16	0.49	Rabbit previously	22.9	<0.1	<0.35	<0.35	<0.35	<0.35	<0.35	<0.35
35	3.81	<0.35	1.42	Rabbit	4.7	<0.1	1.0	<0.35	<0.35	<0.35	<0.35	<0.35

NI, No information; NT, not tested; rabbit, actual exposure to rabbit(s); rabbit previously, previously prolonged exposure to rabbit(s); SA, serum albumin.

IgE titers are shown in boldface when IgE cross-reactivity between rabbit and/or dog is likely.

*IgE antibodies were quantified by ELISA.

rabbits is not necessarily linked to pet ownership but could also be induced by other mechanisms such as indirect exposure or allergen cross-reactivity. They speculate that in a group of 129 patients of their database, who denied exposure to rabbits, but who had positive skin prick test results to rabbits and to cat/dog, the positive test results to rabbits were caused by a cross-reactive mechanism involving albumins and/or lipocalins. On the other hand, they assume that a group of 13 patients monosensitized to rabbit may have been sensitized to Ory c 3 without direct contact with rabbits. However, in addition to Ory c 3, further rabbit allergens such as the already partly identified Ory c 1 and Ory c 2 lipocalins might contribute to sensitization.^{2,3} In our study population, a small group of 4 persons (number 3, 8, 9, and 13) denied contact with rabbits but were exposed to other pets. Three of them (75%) were positive for Ory c 3, which pleads for indirect exposure and sensitization. In our study population, the sensitization rate to Ory c 3 is high (77%) and is comparable to that of Fel d 1 for cat-allergic patients.⁴ Fel d 1 and Ory c 3 are both secretoglobins without demonstrable IgE cross-reactivity (only 24% aa identity).² The level of Ory c 3 we measured in households with rabbits was in the same range as that measured for Fel d 1 in households with cats.² This makes carriage of Ory c 3 on clothing to other houses or public buildings likely and sensitization to Ory c 3 through indirect exposure possible.⁵

We also addressed the question whether the sensitization to rabbits could be induced by IgE cross-reactivity because of a primary sensitization to cat and dog albumins and/or lipocalins. We therefore analyzed the 35 patients for sensitization to cat, dog, or rabbit serum albumin⁶ and additionally for a sensitization to the highly cross-reactive dog and cat lipocalins Can f 6 and Fel d 4.⁷ We also looked for IgE to Ory c 4, a rabbit lipocalin we cloned previously (Ory c 4.0101, *IUIS Allergen Nomenclature Sub-Committee*) and which is the rabbit homologue to the above-referenced cross-reactive lipocalin family (shares 63% identity with Fel d 4 and 58% with Can f 6) (Table I). Eleven patients had IgE to more than 1 allergen of the albumin and/or lipocalin group. Only patient number 13 had higher IgE titers to dog albumin than to rabbit albumin, making a cross-sensitization from dog to rabbit possible. However, this patient is also sensitized to Ory c 3. Patients 12 and 17 have IgE to Can f 6 or Fel d 4 that are higher than those to Ory c 4, making a

dog or cat to rabbit IgE cross-reactivity possible. However, these patients also have IgE to Ory c 3. It is interesting and remarkable to notice that at the lipocalin level, cross-reactivity from rabbit to cat and/or to dog is possible for patients 4, 13, 14, 16, 21, 25, and 26. To conclude, Ory c 3 appears to be a major and specific rabbit allergen capable of inducing sensitization on indirect exposure. Specific IgE titers argue for a possible IgE cross-reactivity at the albumin and also at the lipocalin level from dog and cat to rabbit, but even more so in the opposite direction. To distinguish cross-reactivity from cosensitization, extensive cross-inhibition studies are needed.

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The project was supported by the Ministry of Higher Education and Research of Luxembourg.

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

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<http://dx.doi.org/10.1016/j.jaci.2013.10.027>