TABLE I. Genotype frequencies for *IL4R* gene SNPs and SJS/TEN susceptibility

	Control (%) (N = 160)	SJS/TEN (%) (N = 70)	Allele 1 vs allele 2 *P* value (χ^2) OR (95% CI)	Genotype 11 vs 12+22 *P* value (χ^2) OR (95% CI)	Genotype 11+12 vs 22 *P* value (χ^2) OR (95% CI)
Val(G)50 Ile(A)					
11 GG	74 (46.2)	36 (51.4)	.60	.47	.99
12 GA	61 (38.1)	23 (32.9)	—	—	—
22 AA	25 (15.6)	11 (15.7)	—	—	—
Ser(T)478Pro(C)					
TT	135 (84.4)	60 (85.7)	.80	.79	—
TC	25 (15.6)	10 (14.3)	—	—	—
CC	0 (0)	0 (0)	—	—	—
Gln(A)551Arg(G)					
AA	115 (71.9)	63 (90.0)	.0019	.0025	—
AG	41 (25.6)	7 (10.0)	3.4	3.5	—
GG	4 (2.5)	0 (0)	(1.5-7.8)	(1.5-8.3)	—

TABLE II. Total serum IgE

Total IgE	SJS (N = 30)	Control (N = 160)
Normal (<173 IU/mL)	67% (20/30)	69% (111/160)
High (≥173 IU/mL)	33% (10/30)	31% (49/160)

TABLE III. Antigen specific serum IgE (MAST-26*)

No. of positive allergens	SJS (N = 30)	Control (N = 40)
0	36.7% (11/30)	30.0% (12/40)
1	10.0% (3/30)	22.5% (9/40)
2	13.3% (4/30)	17.5% (7/40)
3	13.3% (4/30)	10.0% (4/40)
4	16.7% (5/30)	10.0% (4/40)
≥5	10.0% (3/30)	10.0% (4/40)

*The 26 allergens in MAST-26 were house dust mite *Dermatophagoides farinae*, house dust, cat and dog epidermis, pollen from timothy, anthoxanthum odoratum, a ragweed mixture, mugwort, Japanese cedar, *Penicillium*, *Cladosporium*, *Candida*, *Alternaria*, *Aspergillus*, wheat, soy bean, rice, tuna, salmon, lobster, crab, cheddar cheese, milk, beef, chicken, and egg white.

may play a role in the inflammation seen in allergic diseases such as atopy and asthma.[2-5]

Ophthalmologically, the ocular surface inflammation seen in SJS/TEN is quite different from the allergic inflammation. In SJS/TEN, goblet cells in the conjunctiva are remarkably decreased or disappear,[7] whereas in allergic diseases, their number is increased.[8] IL4 induces the differentiation of IL4R-expressing epithelium into mucous goblet cells.[9] We confirmed IL4R-specific mRNA expression in conjunctival epithelial cells. IL4R on the ocular surface might play an important role in the ocular surface inflammation seen in not only allergic diseases but also SJS/TEN. The discharge from the ocular surface of patients with SJS/TEN in acute or subacute stage consists primarily of neutrophils (Fig 1, *C*); in patients with allergic and atopic conjunctivitis, it is mainly composed of eosinophils. Thus, on the basis of both dermatologic and ophthalmologic findings, SJS/TEN is quite different from allergic diseases.

Given the association between the onset of SJS/TEN and infections,[1] we considered the possibility that there is an association between SJS/TEN and a disordered innate immune response. Therefore, we performed gene expression analysis and found that *IL4R* gene expression was different in patients with SJS/TEN and the controls; on LPS stimulation, it was downregulated in patients with SJS/TEN and slightly upregulated in the controls (data not shown). We also found that in human corneal epithelial cells, IL4R-specific mRNA was downregulated on stimulation with polyinosine-polycytidylic acid, which mimics viral components (data not shown). Our findings suggest that IL4R might be linked with innate immunity.

We thank Ms C. Mochida for technical assistance.

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Supported in part by grants-in-aid for scientific research from the Japanese Ministry of Health, Labor and Welfare; the Japanese Ministry of Education, Culture, Sports, Science and Technology; Core Research for Evolutional Science and Technology from Japan Science and Technology Agency; a research grant from the Kyoto Foundation for the Promotion of Medical Science; and the Intramural Research Fund of Kyoto Prefectural University of Medicine.

Disclosure of potential conflict of interest: The authors have declared that they have no conflict of interest.

REFERENCES

1. Yetiv JZ, Bianchine JR, Owen JA Jr. Etiologic factors of the Stevens-Johnson syndrome. South Med J 1980;73:599-602.
2. Mitsuyasu H, Yanagihara Y, Mao XQ, Gao PS, Arinobu Y, Ihara K, et al. Cutting edge: dominant effect of Ile50Val variant of the human IL-4 receptor alpha-chain in IgE synthesis. J Immunol 1999;162:1227-31.
3. Howard TD, Koppelman GH, Xu J, Zheng SL, Postma DS, Meyers DA, et al. Gene-gene interaction in asthma: IL4RA and IL13 in a Dutch population with asthma. Am J Hum Genet 2002;70:230-6.

4. Oiso N, Fukai K, Ishii M. Interleukin 4 receptor alpha chain polymorphism Gln551Arg is associated with adult atopic dermatitis in Japan. Br J Dermatol 2000;142:1003-6.
5. Rosa-Rosa L, Zimmermann N, Bernstein JA, Rothenberg ME, Khurana Hershey GK. The R576 IL-4 receptor alpha allele correlates with asthma severity. J Allergy Clin Immunol 1999;104:1008-14.
6. Correia O, Delgado L, Ramos JP, Resende C, Torrinha JA. Cutaneous T-cell recruitment in toxic epidermal necrolysis. Further evidence of CD8+ lymphocyte involvement. Arch Dermatol 1993;129:466-8.
7. Ohji M, Ohmi G, Kiritoshi A, Kinoshita S. Goblet cell density in thermal and chemical injuries. Arch Ophthalmol 1987;105:1686-8.
8. Foster CS, Rice BA, Dutt JE. Immunopathology of atopic keratoconjunctivitis. Ophthalmology 1991;98:1190-6.
9. Dabbagh K, Takeyama K, Lee HM, Ueki IF, Lausier JA, Nadel JA. IL-4 induces mucin gene expression and goblet cell metaplasia in vitro and in vivo. J Immunol 1999;162:6233-7.

Available online September 27, 2007.
doi:10.1016/j.jaci.2007.07.048

Sensitization to *Cannabis sativa* caused by a novel allergenic lipid transfer protein, Can s 3

To the Editor:

The plant nonspecific lipid transfer protein (LTP) family includes a high number of 9-kd allergens, mainly from foods. These have been well-characterized as mediators of sensitization by ingestion.[1] However, there are also LTPs associated with pollinosis, with some of them responsible for cross-sensitization between pollen (ie, mugwort, plane tree) and plant foods (ie, peach, cabbage, chestnut).[2] Furthermore, sensitization by the respiratory route has been recently reported for food LTPs, such as those from rice[3] and wheat Tri a 14 linked to baker's asthma.[4]

Allergy to marijuana (*Cannabis sativa*) is rare, but several cases of allergic disorders caused by inhalation during smoking, injection, or even ingestion of *Cannabis* have been reported,[5-8] and cross-reactivity with plant foods, such as tomato, was suggested.[6] Interestingly, *Cannabis* is used not only for recreational activity but also as a medical drug to improve the quality of life in some illnesses. No marijuana allergen has ever been isolated and characterized to date. We describe the identification of the most probable allergen causing allergy to marijuana and several plant foods.

A 28-year-old man without any previous allergic symptoms initially reported contact urticaria with the marijuana plant. Subsequently, after smoking the plant, the patient presented sneezes, watery rhinorrhea, palpebral edema, itching, and eye redness, thus stopping the consumption. He presented the same symptoms in places where marijuana was being smoked. Some months later (no allergic reaction to food was previously shown), the patient had anaphylaxis (urticaria-angioedema, hypotension, dyspnea, and hypoxemia) after the ingestion of tomato and pepper, contact urticaria with peach peel, anaphylaxis by fig, and oral allergy syndrome by apple, almond, eggplant, and chestnut. Rubbing skin test with peach peel and marijuana leaves were positive, as well as skin prick tests with commercial extracts (ALK-Abelló, Madrid, Spain) of apple, peach, and tomato and with a crude extract from marijuana buds (0.5 mol/L NaCl, pH 3.0, 1:10 wt:vol, 1 hour at room temperature, 100 μg protein/mL) and purified Pru p 3 (the major LTP and allergen from peach fruit; 20 μg/mL). The serum of the patient was obtained for further evaluation (with written informed consent and approval from the Hospital Ethics Committee). Total IgE was 235 kU/L, and specific IgE to peach, 3.05 kU/L; apple, 1.96 kU/L; tomato, 1.51 kU/L; fig, 1.18 kU/L; almond, 0.77 kU/L; and hazelnut, 3.93 kU/L (CAP system FEIA; Phadia, Uppsala, Sweden).

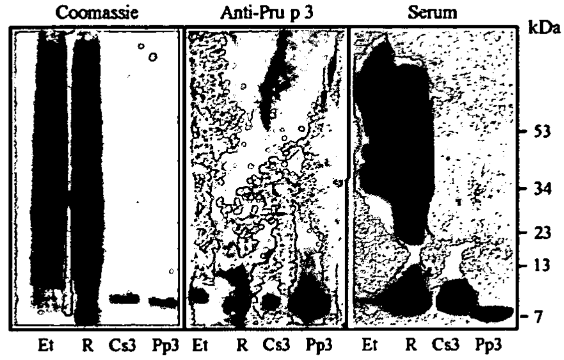

FIG 1. Protein staining (*Coomassie*) and immunodetection with polyclonal antibodies against Pru p 3 (*Anti-Pru p 3*) or with the patient's serum (*Serum*) of the following samples separated by SDS-PAGE: marijuana extract (*Et*; 20 μg), its retained (*R*; 15 μg) fraction after cation exchange chromatography, and purified allergens Can s 3 (*Cs3*) and Pru p 3 (*Pp3*; 5 μg each).

To search for potential allergens, the crude extract from marijuana was separated by SDS-PAGE and IgE immunodetected with the patient's serum (Fig 1). IgE-binding components of approximately 9 kd, 14 kd, and 35 to 100 kd were detected, being the same blot also recognized by rabbit polyclonal antibodies to peach Pru p 3 (Fig 1). This peach allergen weakly reacted with IgE from the patient's serum (Fig 1). All these results suggested that a LTP was involved in *Cannabis* sensitization.

To support this hypothesis, the 9-kd IgE-binding protein was purified from the marijuana extract by means of a 2-step chromatographic procedure: cation-exchange chromatography on an Acell Plus CM Waters SepPak Cartridge (Waters, Milford, Mass; retain fraction shown in Fig 1) followed by reverse-phase HPLC separation of the retained material on a Nucleosil 300-C4 column (8 × 250 mm; particle size, 5 μm; Scharlau Science, Barcelona, Spain). The purified protein, hereafter named Can s 3, showed a single band on SDS-PAGE, bound IgE from the patient's serum (Fig 1), and was identified as LTP according to its N-terminal amino acid sequence (XITCGQVASS), molecular size (9226 d as determined by matrix-assisted laser desorption/ionization analysis), and recognition by anti–Pru p 3 antibodies (Fig 1). *In vitro* tests (specific IgE determination, ELISA inhibition and basophil activation test) performed as previously described[9] supported the relevance of the purified protein as *Cannabis* allergen (Fig 2). IgE to Can s 3, as well as to Pru p 3, was found in the patient's serum, and inhibition