

IgE reactivity to profilin in *Platanus acerifolia* pollen-sensitized subjects with plant-derived food allergy

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Abstract. *Background:* The presence of profilin-specific IgE antibodies is a cause of cross-reactivity between botanically-unrelated allergen sources. Recently, the association between *Platanus acerifolia* pollinosis and plant-derived food allergy has been described. The aim of this study was to ascertain whether the *P. acerifolia* profilin is involved in such cross-reactivity.

Methods: Twenty-three patients suffering from *Platanus acerifolia* pollinosis and plant-derived food allergy were evaluated in an allergy department. Specific IgE levels to *P. acerifolia* pollen, *P. acerifolia* profilin and food extracts were measured. Molecular masses of IgE-binding proteins were calculated by Western blotting and cross-reactivity studies among *P. acerifolia* profilin and different food extracts were evaluated by Enzyme AllergoSorbent Test (EAST)-inhibition assays. Also, EAST-inhibition assays with the two known *P. acerifolia* allergens, Pla a 1 and Pla a 2, were performed.

Results: Surprisingly, a high IgE-binding prevalence (90%) of *P. acerifolia* profilin was found. EAST-inhibition showed high inhibition values when *Platanus acerifolia* pollen extract was used as free phase and plant-derived food extracts as solid phase, whereas the other way round showed low inhibition values.

IgE reactivity to profilin was studied using a pool of patient sera, by EAST-inhibition assays with hazelnut, apple peel, peanut, chickpea and peanut extracts as solid phase and no inhibition was obtained when *P. acerifolia* profilin was used as inhibitor phase. The same results were obtained when purified Pla a 1 and Pla a 2 were also used as inhibitor phase.

Conclusions: The clinical association observed between *Platanus acerifolia* pollen and plant-derived food could be explained by the in vitro IgE cross-reactivity detected by EAST-inhibition. However, it appears that neither *P. acerifolia* profilin nor the two major allergens described (Pla a 1 and Pla a 2) can explain such a strong cross-reactivity.

Key words: oral allergy syndrome, plant-derived food allergy, *Platanus acerifolia* pollinosis, Profilin.

Introduction

The plane tree or *Platanus acerifolia*, an hybrid of *Platanus occidentalis* and *Platanus orientalis*, is a common tree in the majority of Western European cities. The occurrence of *P. acerifolia* pollinosis is not generally

considered, although high concentrations of its pollen are detected during the flowering season in several cities of the United States and Southern of Europe [1-4].

The association between *P. acerifolia* pollinosis and plant-derived food allergy has recently been reported. Foods most frequently implicated were nuts, fruits (peach, apple, melon and kiwi), legumes and vegetables

such as lettuce and green beans [5-7]. Moreover, in a recent study on *Platanus acerifolia* pollinosis and food allergy, an IgE-binding band with a molecular mass of 14-15 kDa appeared to be the cross-reactive structure between the *P. acerifolia* pollen allergens and those from some plant-derived food [6]. Profilins are well known allergens in pollen of trees, grasses and weeds and the presence of profilin-specific IgE antibodies has been described as a cause of cross-reactivity among botanically-unrelated allergen sources [8]. The majority of the studies on pollen allergy report that 20% of pollinic patients are sensitised to profilins [9], however, in the case of *P. acerifolia* pollinosis a 47% of patients showed IgE binding reactivity to profilin [10].

The aim of this study was to ascertain whether *Platanus acerifolia* pollen is involved in the cross-reactivity detected between *P. acerifolia* pollen and plant-derived foods.

Material and methods

Patients

The study population was selected from 720 consecutive outpatients referred to the Allergy Department of the Institut Universitari Dexeus in Barcelona because of pollinosis.

All patients underwent cutaneous tests by the skin prick test (SPT) performed according to standard procedure with a panel of inhalant allergens containing the most frequent allergens prevalent in our environment: dust-mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), moulds (*Alternaria alternata*, *Cladosporium herbarum*, *Aspergillus fumigatus*, and *Penicillium notatum*), cat and dog dander, latex and pollens such as grass, *Parietaria judaica*, *Artemisia vulgaris*, *Plantago lanceolata*, *Chenopodium album*, *Mercurialis annua*, *Olea europea*, *Cupressus arizonica*, *Corylus avellana* and *Platanus acerifolia* (Bial-Arístegui, Bilbao, Spain).

SPT with the vegetables suspected of causing allergy according to the clinical histories were performed with commercially-available extracts (Leti, Barcelona, Spain) and by the prick-prick method with the implicated fresh food. Histamine dihydrochloride 10 mg/ml and phosphate-buffered saline solution served as positive and negative controls, respectively. The SPT was considered positive if the wheal area was greater than 7 mm² (diameter > 3 mm) 15 minutes after testing.

Pollen crude extract preparation, purification of pollen profilins and *P. acerifolia* allergens Pla 1 and Pla 2

Crude extract of pollen from *P. acerifolia* was prepared as previously described [11]. Protein content

of the extract was determined by the Bradford method [12]. Profilin, Pla 1 and Pla 2 were purified as previously described [10, 13-15]. Briefly, profilin purification was accomplished from *P. acerifolia* pollen, hazelnut or peanut extract by poly-L-proline (PLP) affinity chromatography [13]. Pla 1 was purified from the *P. acerifolia* pollen extract by ion exchange chromatography, gel filtration chromatography and reverse-phase chromatography [10,14] and Pla 2 by ion exchange chromatography and gel filtration chromatography [15].

Specific IgE measurement

Specific IgE was measured using an Enzyme AllergoSorbent Test (EAST); the allergen extracts were coupled to CBrN activated paper discs at 10 mg/mL (Bial-Arístegui, Bilbao, Spain); values equal to or greater than 0.35 kU/L were considered positive.

IgE inhibition experiments

These experiments were performed with allergen extracts coupled to CBrN-activated paper discs (10 mg/mL) (Bial-Arístegui, Bilbao, Spain). Heterologous and homologous extracts were added as inhibitors in the liquid phase. Patients sera showing a specific IgE value higher than 0.70 kU/L to the studied food extract were selected.

SDS-PAGE and SDS-PAGE immunoblotting

Sodium dodecylsulfate-polyacrylamide gel electrophoresis (SDS-PAGE) was carried out according to the discontinuous method described by Laemmli in 12.5% polyacrylamide gel, with parallel application of a reference standard of proteins with known molecular masses. Twenty mg of protein, according to Bradford, were applied per lane.

After electrophoresis, gels were stained in 0.1% Coomassie Brilliant Blue R-250 dissolved in methanol/acetic/distilled water (4:1:5). To prepare the samples under reducing conditions, they were dissolved in 0.125 M HCl-Tris buffer, pH 6.8 and were dissociated with SDS and 5% b-mercaptoethanol at 100°C for 5 min.

Separated protein bands were electrophoretically transferred to polyvinylidene difluoride membranes (Immobilon-P, Millipore, Milford, MA). After the Immobilon membrane had been blocked with PBS-Tween-20 0.05% (v/v) (1 h at 25°C), immunodetection was performed using a chemiluminescent detection reagent (Lumigen PS-3) following the manufacturer's instructions (ECL + Plus Western blotting detection reagents. Amersham Pharmacia Biotech, Amersham, UK).

Molecular masses were evaluated using an Imagen densitometer System (Bio Rad).

Results

Evaluation of patient data

Twenty-three patients suffering from *P. acerifolia* pollinosis and plant-derived food allergy were selected to ascertain whether *P. acerifolia* profilin is involved in the previously described cross-reactivity between this pollen and some kind of foods [6].

Rhinitis and rhinoconjunctivitis were the most frequent symptoms and only 39% of the patients reported asthma. Up to 26% of these patients were monosensitized to *P. acerifolia* pollen (Table 1).

Plant-derived food allergy related symptoms were anaphylaxis in 21%, oral pruritus in 43% and urticaria-angioedema in 36% of the patients. Foods most frequently implicated were hazelnuts, fresh fruits (peach, apple, melon and kiwi), peanuts, maize, chickpea and vegetables such as lettuce and green beans (Table I). Since systemic and even life-threatening reactions were common in the study population (21% of the patients had anaphylaxis and 36% had angioedema), challenge test were not performed.

Almost all the patients sera had specific IgE values higher than 0.70 kU/L (class II) to the *P. acerifolia* pollen and to the studied food extracts. A surprisingly high

Table 1. Clinical characterization of food allergy patients.

Patients		Allergies			Clinical Symptoms	
No.	Age (years)	Pollen	Food	Other	Pollen	Food
1	36		MI,K		RC,As	OP
2	24	w,mu	N,P,M,Ce,V,K	mi,ct	R	AE
3	54	t,g,w,mu	MI		RC	OP
4	42	t,g,w,mu	N,K,Ce		RC	A
5	38	t,g,w,mu	M,MI		RC	OP
6	26		N	Mi	R,As	OP
7	33	t,g,w,mu	N,Ce,P,M,V,L,Ro		RC,As	A
8	29		N,P,V,Ro,MI		RC,As	A
9	32		Pe,MI,K		RC	OP
10	29	t,w	Pe		RC	U
11	25	t,g,w,mu	N,P,M,L	mi,ct,d	RC,As	U
12	50	t,g,w,mu	N,Ce,L		RC,As	U
13	43	t,g,w,mu	N	ct,d	R,As	OP
14	28	t,w,mu	N,P,Ce,M,V,L	Ct	RC	U
15	30		N,Pe,MI,Ro		RC	AE
16	32	mu	N,P,K,V	mi,ct	RC	A
17	36		N		RC	OP
18	32	mu	N,P,M,V	Ct	RC	A
19	24		MI,Ro	Mi	RC	OP
20	32	t,g,w,mu	N,Pe,MI		R,As	OP
21	37	g,m	Pe		R	AE
22	24	t,w,mu	N,P,K	mi,ct,d	RC	AE
23	43		MI		RC,As	OP

Pollen (allergies): t, trees; g, grass; w, weed; mu, mugwort. Food (allergies): N, nuts; K, kiwi; Ce, cereals; P, peach; M, maize, V, vegetables; L, legumes; MI, melon; Pe, peanut; Ro, Rosaceae fruits; B, banana. Others (allergies): ct, cat dander; mi, mites; d, dog dander; mo, mold. Pollen (symptoms): RC, rhinoconjunctivitis; R, rhinitis; As, asthma. Food (symptoms): A, anaphylaxis; U, urticaria; OP, oral pruritus; AE, angioedema.

number (90%) of the patients sera showed specific IgE level higher than 0.35 kU/L, class I (Table II), to *P. acerifolia* profilin.

Immunoblotting and IgE inhibition experiments

When *Platanus acerifolia* pollen extract was studied by SDS-PAGE immunoblotting, different IgE-binding

proteins with molecular masses ranging from 14 to 70 kDa could be detected.

Previously, in EAST-inhibition assays [6], we obtained an inhibition value of 90% when extracts of apple peel, chickpea, peanut or hazelnut were used in solid phase and *P. acerifolia* pollen extract was used as inhibitor phase, whereas in the inverse situation only a maximum 20% inhibition was obtained (Table III).

Table 2. Relationship between prevalence of pulmonary diseases and domestic pollution

Patient No.	Serum specific IgE						
	<i>Platanus</i> Pollen	Haz elnut	Apple	Chickpea	Peanut	<i>Platanus</i> Profilin	
1	2	0	0	2	0	2	
2	2	1	3	2	3	0	
3	2	0	2	1	1	1	
4	3	0	1	2	2	1	
5	3	ND	0	1	ND	ND	
6	3	1	2	2	2	1	
7	3	2	2	2	2	2	
8	3	1	2	0	1	1	
9	3	0	0	2	0	0	
10	3	2	2	2	3	ND	
11	3	2	2	2	2	2	
12	3	ND	2	2	ND	2	
13	3	ND	2	2	2	ND	
14	4	2	3	3	2	2	
15	4	2	2	2	2	2	
16	4	0	2	2	2	2	
17	5	3	1	1	1	2	
18	5	2	2	2	2	2	
19	5	3	3	3	4	3	
20	1	0	0	1	0	1	
21	2	ND	0	1	ND	1	
22	2	0	0	0	1	2	
23	3	1	0	1	1	1	

Specific IgE to *Platanus acerifolia* pollen and plant-derived foods studied. ND: not done. Class 0: <0.35 kU/L. Class 1: 0.35-0.70 kU/L. Class 2: 0.70-3.5 kU/L. Class 3: 3.5-17.5 kU/L. Class 4: 17.5-50 kU/L. Class 5: >50 kU/L.

In order to study the contribution of profilin specific IgE in this observed cross-reactivity, EAST-inhibition assays were performed using both pool and individual sera. When pools of patient sera were used, four different EAST-inhibition assays were carried out using plant-derived food extracts as solid phase (hazelnut, apple peel,

chickpea, and peanut), *P. acerifolia* profilin as inhibitor phase and a different and suitable pool of patients sera in each of the assays. To prepare the assay pool of sera, patients sera with specific IgE to each of the food extracts higher than 0.7 kU/L were pooled (hazelnut pool: patient sera No.: 7, 10, 14, 15, 17, 18 and 19; apple peel pool:

Table 3. EAST-inhibition assay results.

Solid phase*	Inhibitor	% inhibition**
Apple peel	<i>P. acerifolia</i> pollen	72.7%
Chickpea	<i>P. acerifolia</i> pollen	70%
Peanut	<i>P. acerifolia</i> pollen	86%
Hazelnut	<i>P. acerifolia</i> pollen	78%
<i>P. acerifolia</i> pollen	Apple peel	20%
<i>P. acerifolia</i> pollen	Chickpea	11%
<i>P. acerifolia</i> pollen	Peanut	16%
<i>P. acerifolia</i> pollen	Hazelnut	11%
Hazelnut	<i>P. acerifolia</i> profilin	No inhibition
Apple peel	<i>P. acerifolia</i> profilin	No inhibition
Chickpea	<i>P. acerifolia</i> profilin	No inhibition
Peanut	<i>P. acerifolia</i> profilin	No inhibition
Patient No. 14		
Hazelnut	<i>P. acerifolia</i> pollen	68%
	<i>P. acerifolia</i> profilin	No inhibition
	Pla a 1	No inhibition
	Pla a 2	No inhibition
Patient No. 7		
Hazelnut	<i>P. acerifolia</i> profilin	42%
	Pla a 1	No inhibition
	Pla a 2	No inhibition

*Assays performed with pool of sera unless individual serum number is indicated.

**Percentage of inhibition obtained when almost 100% of inhibition was obtained with the homologous extract.

patient sera No.: 2, 3, 6, 7, 8, 11, 12, 14, 15, 16, 18 and 19; chickpea pool: patient sera No.: 1, 2, 7, 9, 11, 12, 13, 14, 15, 16, 18 and 19; peanut pool: patient sera No.: 2, 4, 7, 11, 13, 14, 15, 16, 18 and 19). No inhibition was obtained in any of the assays (Table III).

Two EAST-inhibition assays were carried out using individual sera and hazelnut extracts as solid phase. When serum from patient No. 14 was assayed, 64% inhibition was obtained when *P. acerifolia* pollen extract

was used as inhibitor phase whereas no inhibition was detected when neither *P. acerifolia* profilin nor purified Pla a 1 or Pla a 2 were used as free phase. On the contrary, when patient No. 7 serum was used, 42% inhibition was obtained when *P. acerifolia* profilin was used as inhibitor phase (Table III).

SDS-PAGE immunoblotting of hazelnut (Figure 1a) and peanut (Figure 1b) extracts incubated with the individual sera from patients 3, 7 and 12, revealed no

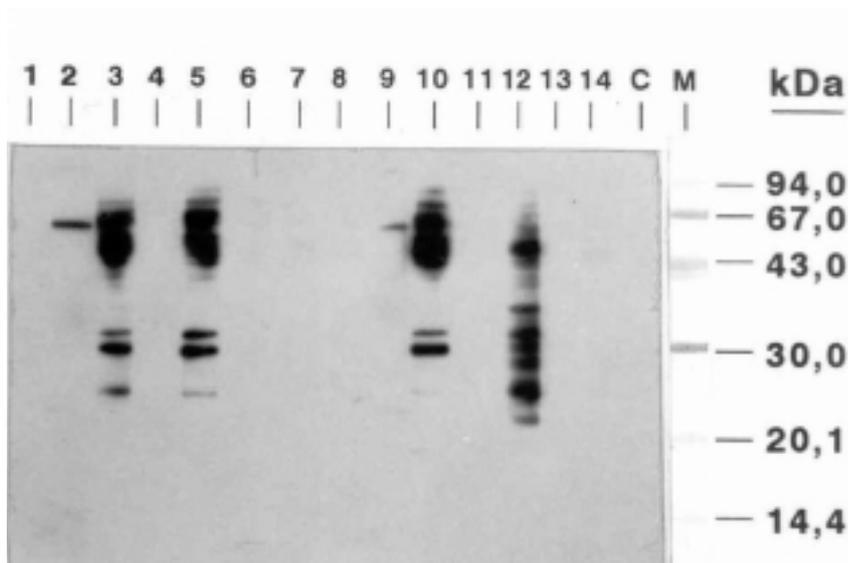


Figure 1a. Hazelnut SDS-PAGE immunoblotting. Lane 1, patient 4. Lane 2, patient 14. Lane 3, patient 7. Lane 4, patient 23. Lane 5, patient 17. Lane 6, patient 15. Lane 7, patient 9. Lane 8, patient 18. Lane 9, patient 19. Lane 10, patient 11. Lane 11, patient 2. Lane 12, patient 13. Lane 13, patient 16. Lane 14, patient 3. Lane C, non-atopic control. Lane M, Molecular mass marker.

Figure 1b. Peanut SDS-PAGE immunoblotting. Lane 1, patient 4. Lane 2, patient 14. Lane 3, patient 7. Lane 4, patient 15. Lane 5, patient 9. Lane 6, patient 18. Lane 7, patient 19. Lane 8, patient 11. Lane 9, patient 2. Lane 10, patient 13. Lane 11, patient 16. Lane C, nonatopic control. Lane M, Molecular mass marker.

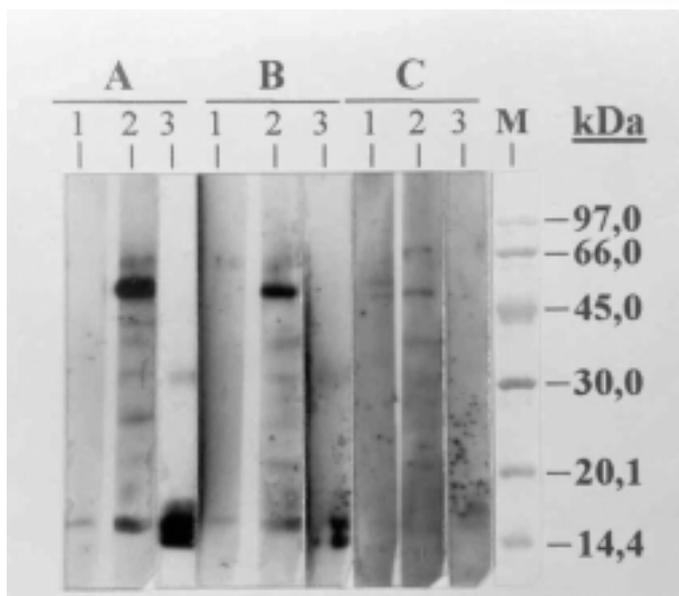
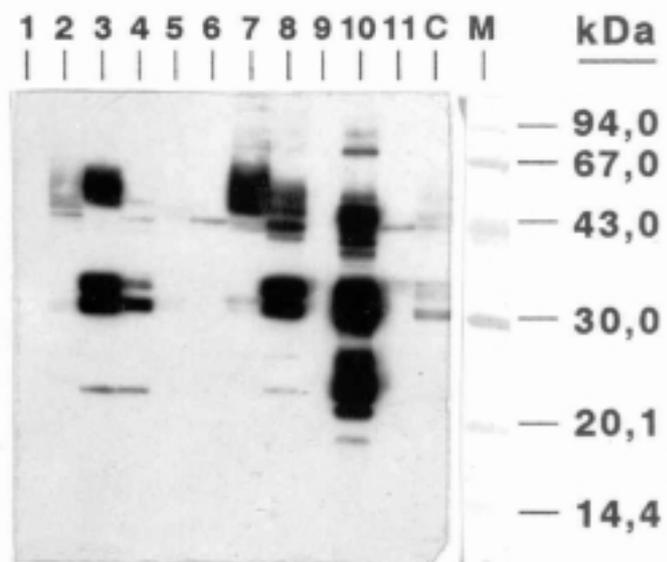


Figure 2. SDS-PAGE immunoblotting. A) patient 7. B) patient 3. C) patient 12. Lane 1) purified peanut profilin. Lane 2) purified hazelnut profilin. Lane 3) purified *Platanus acerifolia* profilin. M) Molecular mass marker.

IgE-binding bands at 14kDa. However, IgE reactivity to purified profilin from *P. acerifolia* and from both plant-derived foods (hazelnut and peanut) was detected by the same method in these patients sera. (Figure 2).

Discussion

Profilin is a protein present in almost all eukaryotic cells; it was first identified as a minor allergen in birch pollen [16], and it has been pointed out as a highly IgE cross-reactive structure [8,17]. Over the last years, an association between plant-derived food allergy and pollinosis has been described [18], although the responsible cross-reactive structures have not been completely elucidated in all cases. In the geographical areas where birch is the most common tree, Bet v 1 counterparts have been usually referred to as the causative agents of this syndrome; however in birch-free areas, profilins have been described as one of the most frequently implicated structures [19].

Platanus acerifolia pollen is a highly represented pollen in the atmosphere of many Mediterranean cities. Air concentration of this allergenic pollen has its main peak in early spring [2-3]. In the present study, a strong association was observed between *P. acerifolia* pollinosis and food allergy and, among the symptoms, a great number of systemic reactions were referred to (anaphylaxis in 21% and urticaria-angioedema in 36%). Although the clinical significance of sensitisation to profilin remains unclear, the most frequently reported symptoms associated to profilin cross-reactivity have been mild reactions related to the oral allergy syndrome, systemic symptoms have been sometimes attributed [20], although strong evidence to support this fact is still lacking [21].

Due to the high number of patients sera which show specific IgE reactivity to profilin in this study, this protein appears as an ideal candidate to be the cause of the cross-reactivity found. However, the results obtained by means of EAST-inhibition assays, when pool of sera were used, do not point to profilins as being responsible for the detected cross-reactivity. Only in some cases, according to the results obtained by EAST-inhibition assays using individual serum (patient 7) (Table III) and those obtained by western blotting with purified profilins (Figure 2), we could suspect of profilin as a possible cause of in vitro cross-reactivity, although we ignore its clinical significance. Thus, neither the kind of symptoms nor the in vitro results point to profilin as a relevant structure responsible for the high cross-reactivity observed between *P. acerifolia* pollen and plant-derived food extracts.

A further interesting question deals with the fact that some patient sera (Figure 2) showed an IgE-binding band protein in SDS-PAGE immunoblotting against *P. acerifolia* pollen and some purified food profilins, however a 14 kDa IgE-binding band protein was not shown when hazelnut or peanut extract SDS-PAGE

immunoblotting was performed (Figure 1a and 1b). This fact could be explained by the low amounts of profilins present in food extracts.

So far, two *P. acerifolia* pollen allergens have been identified: Pla a 1, a 18-kDa non-glycosylated protein which reacts with up to 92% of the sera from monosensitised *P. acerifolia* allergic patients and 83% from polysensitised patients; and Pla a 2, a 43-kDa protein, with an IgE binding prevalence of 83% in monosensitised patients (10). None of these allergens appear to be implicated in the food-pollen cross-reactivity, since the EAST-inhibition assays failed to show any positive result when these proteins were used as inhibitor phase.

Further studies are required to identify the cross-reacting structures and their importance in eliciting food allergy in patients allergic to *Platanus acerifolia* pollen. Recently, a clear partial cross-reactivity between Lac s 1 (Lipid transfer protein from lettuce) and *P. acerifolia* pollen extract has been reported [22], suggesting the presence of an homologous pollen LTP. Lipid transfer protein is a pan-allergen with a degree of cross-reactivity similar to profilin, and because of its high resistance to pepsin digestion, it is a potentially severe food allergen [23]. So, it is tempting to speculate that *P. acerifolia* LTP could be the responsible structure for the cross-reactivity between *Platanus acerifolia* pollen and plant-derived foods.

In summary, the association observed between *P. acerifolia* pollen and plant-derived food could be explained by the in vitro IgE cross-reactivity detected by EAST-inhibition. However neither *Platanus acerifolia* profilin nor the two major allergens described (Pla a 1 and Pla a 2) appear to account for such a strong cross-reactivity.

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