

Characteristics of allergy in autoimmune thyroid diseases

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Relationship between allergic responses and thyroid autoimmunity

IgE levels

- IgE deposits are present in Graves' thyroid and orbital tissues

(Werner SC et al., N Engl Med, 1972;287:421-425.; Raikow RB et al., Ophthalmol. 1990; 97:629-635.)

- Elevated IgE levels associated with hyperthyroid Graves' disease

(Akira S et al., J Clin Endocrinol Metab 1999; 84:3602-3605.; Takashi Y et al., J Clin Endocrinol Metab 2000; 85:2775-2778.)

- Evidence of immunoglobulin E autoantibodies to thyrotropin receptor (TSH rec) and thyroid peroxidase (TPO)

(Metcalf R et al., J Clin Endocrinol Metab 2002;87:1754-1761.; Gou J et al., Clin Immunol Immunopathol 1997; 82:157-162.)

Th2-derived cytokine profiles

- Elevated serum levels of IL-5 and IL-13 cytokines.

(Hidaka Y et al., Thyroid 1998; 8:235-239.; Ichiro K et al., J Clin Endocrinol Metab 2001; 86:3540-3544.)

Allergic rhinitis associated frequently with Graves' disease

(Amino N et al., Thyroid 2003; 13:811-814.; Hidaka Y et al., Thyroid 1996; 6: 349-351.)

Common key factors regulate the immune responses in both allergic and autoimmune conditions

(Rottem M et al., Dev Immunology 2002; 9: 161-167.)

Previous results

- Graves' ophthalmopathy associated with increased total IgE serum levels.

Molnár I et al., Eur J Med Rev 1996; 1:543-546.

- Hyperthyroid Graves' ophthalmopathy demonstrated elevated serum IL-5 levels compared to patients who had no eye signs.

Molnár I , Abstract: ACT International Suppl., 2000; 2: 220.

- Decreased serum levels of nerve growth factor (NGF) associated with hyperthyroid Graves' ophthalmopathy compared to those who had no eye signs.

Molnár I et al., Cytokine 2006; 35: 109-114.

- A difference in the balance shift of IL-12/IL-5 between Graves' patients with and without ophthalmopathy was demonstrated.

Molnár I , Autoimmunity 2007; 40:31-37.

Patients and methods

- **324 patients were investigated**, of whom 149 suffered from Graves' disease (57 with ophthalmopathy), 110 had Hashimoto's thyroiditis, and 65 euthyroid goitre formed controls.
- **Allergen-specific IgE detection was carried out with immunoblot** method using commercial **AllergyScreen™** test (MEDIWISS Analytic GmbH, Germany) and Kodak camera was used for evaluation. The levels of thyroid hormones and antibodies were measured using **commercial kits in a fully automated way**, except TSH receptor antibody, that was measured with radioimmunoassay (Brahms Diagnostics, Germany).
- Chi-squared with Yates correction and Mann-Whitney nonparametric comparative tests were used for **statistical** analysis.

Parameters	Graves'disease n=149	Hashimoto's thyroiditis n=110	Controls n=65
Age (years)	49 ± 13	50 ± 14	48 ± 13
Gender (male / women)	28 / 121	6 / 104	4 / 61
Duration of thyroid disease (months)	71 ± 81	44 ± 57	38 ± 45

Respiratory allergens

Prevalence of allergic symptoms in autoimmune thyroid diseases

Allergic symptoms	Graves' disease (n=149)	Hashimoto's thyroiditis (n=110)	Controls (n=65)	Total
No	94 (63,1%)	63 (57,3%)	54 (83,1%)	211 (65,1%)
Rhinitis *	11^a (7,4%)	20^a (18,2%)	10 (15,4%)	41 (12,7%)
Conjunctivitis	37^b (24,8 %)	21^c (19,1%)	0^{b, c}	58 (17,9%)
Urticaria	7 (4,7%)	5 (4,5%)	1 (1,5%)	13 (4%)
Asthma	0	1 (0,9%)	0	1 (0,3%)
Total	149	110	65	324

^a P < 0,014 , ^b P < 0,0001 and ^c P < 0,0004 after Yates correction

*P < 0,0007 after Yates correction between Graves' patients with (n=57) and without (n=92) eye signs: 32 (9,9%) vs 5 (1,5%).

The month of the onset of autoimmune thyroid diseases was similar to those characterized by the seasonal allergic attack

Month for thyroidal onset and seasonal allergic attack is common	Graves'disease (n=149)	Hashimoto's thyroiditis (n=110)	Controls (n=65)	Total
No	77 (81,9%)	90 (92,8%)	48 (78,7%)	215 (85,3%)
Common	17^a (18,1%)	7^{a,b} (7,2%)	13^b (21,3%)	37 (14,7%)
Total	94	97	61	252*

^a P < 0,04 and ^b P < 0,02

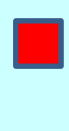
* No exact data were given in 72 cases

Prevalence of allergen-specific IgE in autoimmune thyroid diseases

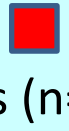
Allergen groups	Graves' disease (n=149)	Hashimoto's thyroiditis (n=110)	Controls (n=65)	Total
D (dust mite I-II)	33 (22,1%)	25 (22,7%)	7 (10,8%)	65 (20,1%)
T (alder, birch, hazel)	25^a (16,8%)	7^a (6,4%)	6 (9,2%)	38 (11,7%)
W (mugwort, plantain, ragweed)	35^b (23,5 %)	12^b (10,9%)	10 (16,4%)	57 (17,6%)
G (grass-mixture)	30 (20,1%)	14 (12,7%)	7 (10,8%)	51 (15,7%)
E (cat, dog and others epithelia, feather-mixture)	40 (26,8%)	23 (20,9%)	19 (29,2%)	82 (25,3%)
M (molds*)	10 (6,7%)	4 (3,6%)	4 (6,2%)	18 (5,6%)
Total	149	110	65	324

^a P < 0,02 and ^b P < 0,015 * Alternaria, Aspergillus, Cladosporium, Penicillium

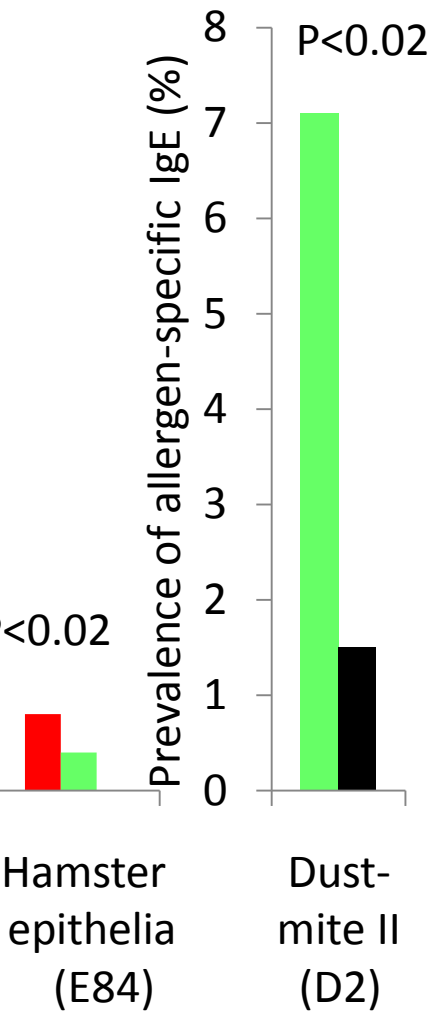
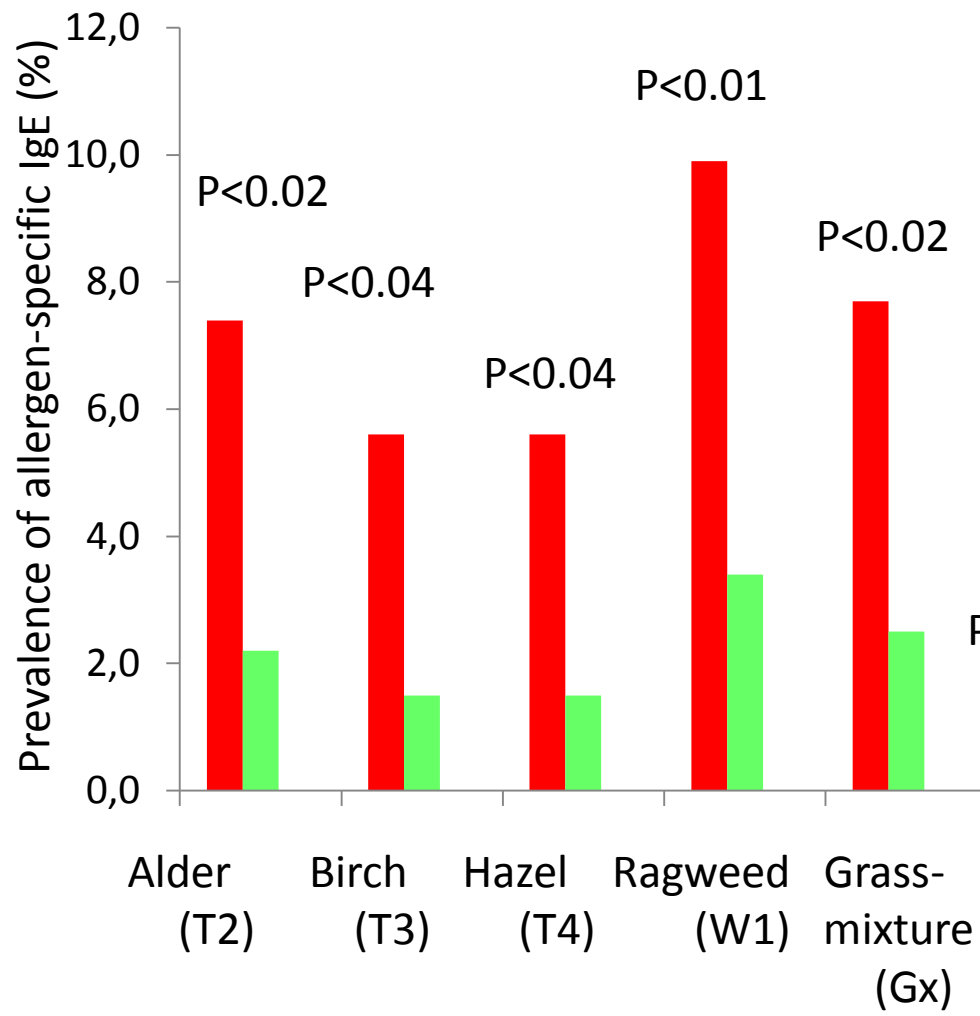
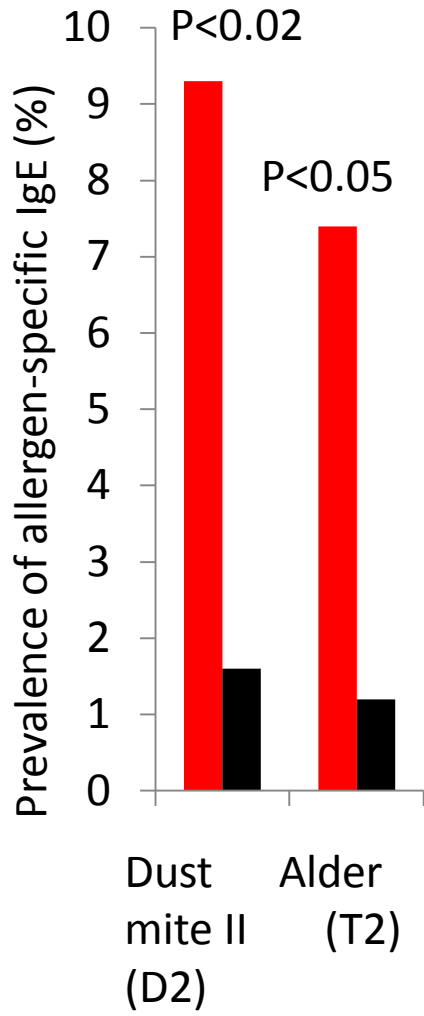
Graves' disease (n=149)
Controls (n=65)



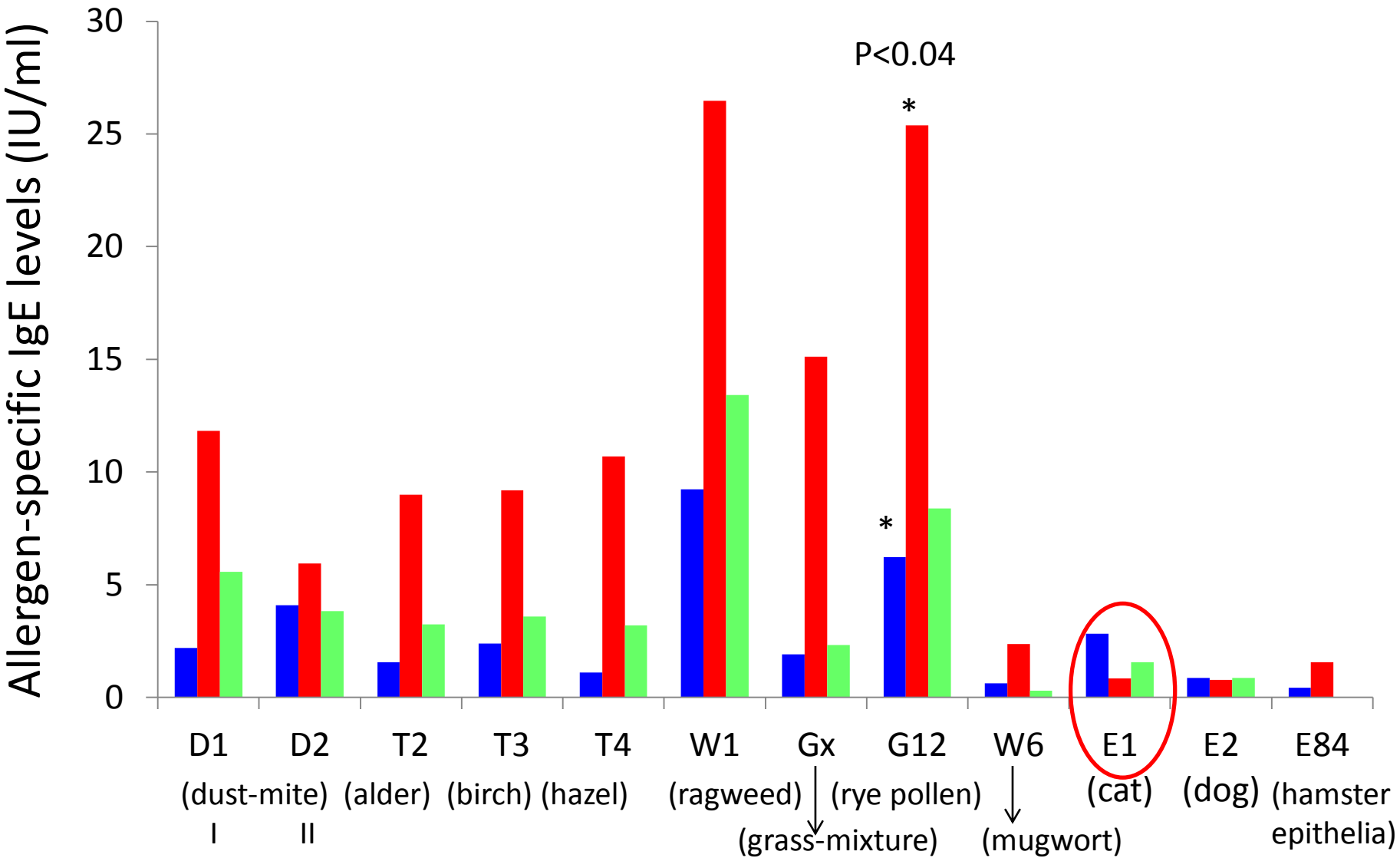
Graves' disease (n=149)
Hashimoto's thyroiditis (n=110)

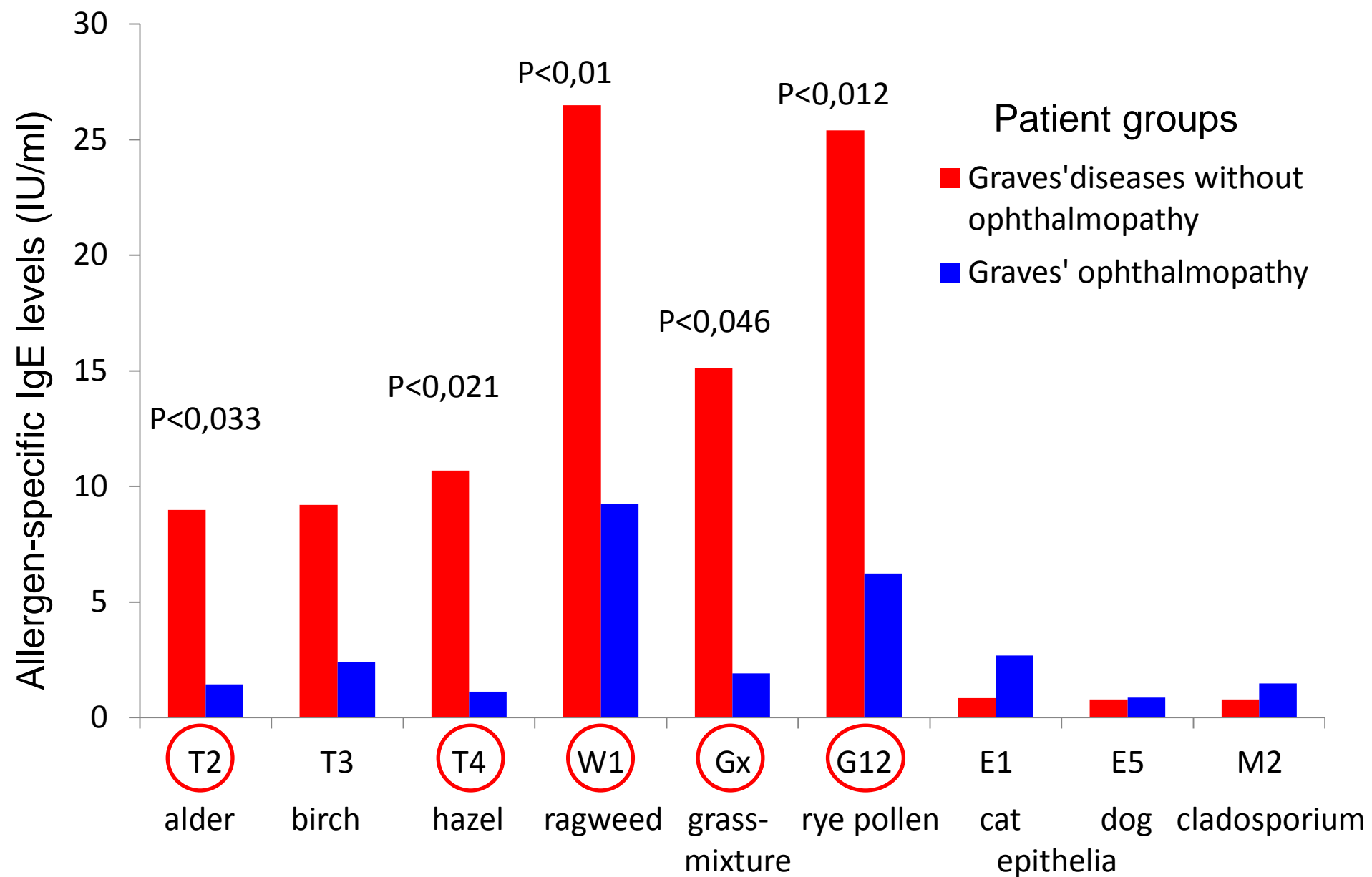


Hashimoto's
thyroiditis (n=110)
Controls (n=65)

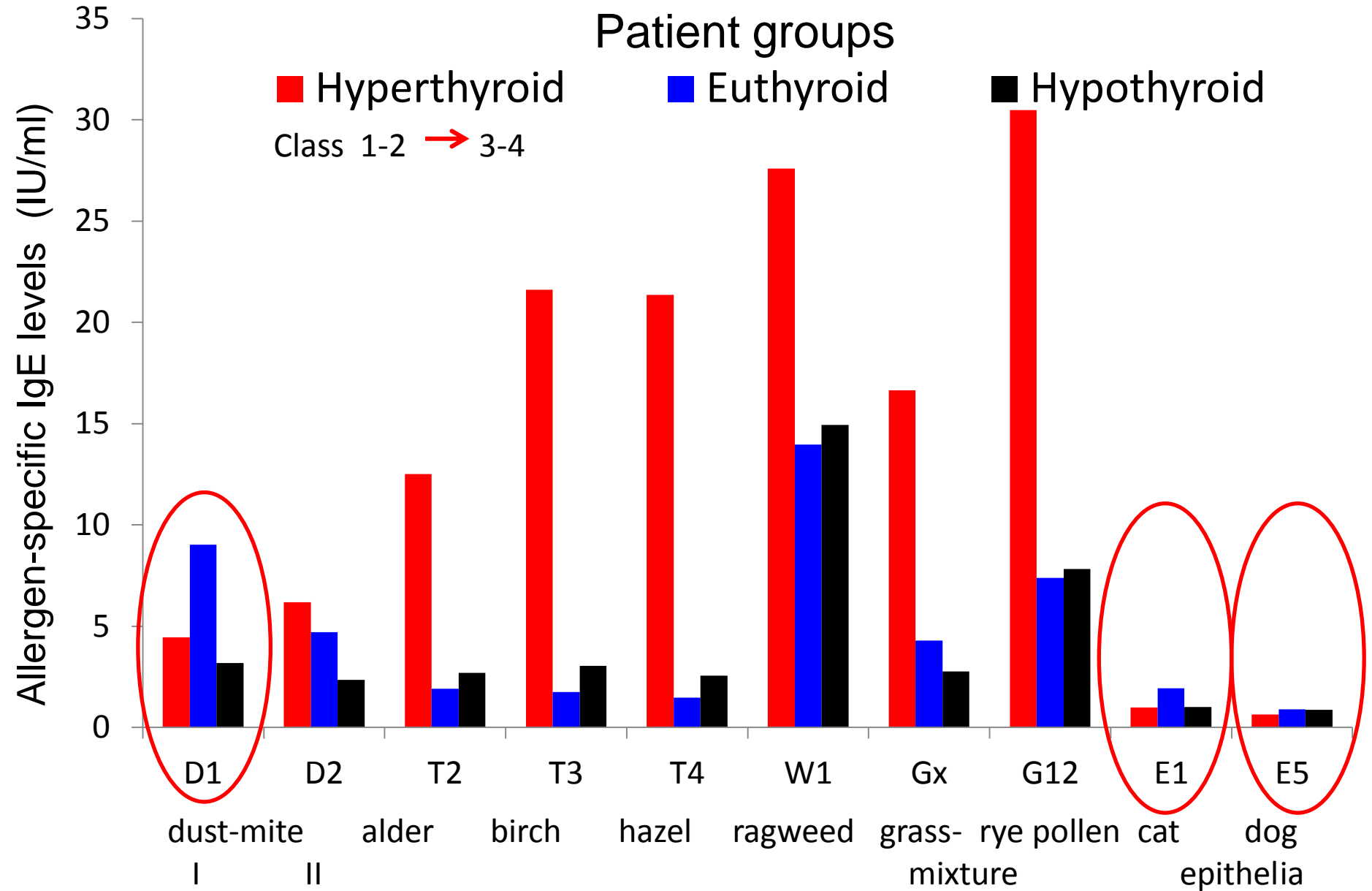


Graves' ophthalmopathy ■ Hashimoto's thyroiditis ■
 Graves' disease without eye signs ■

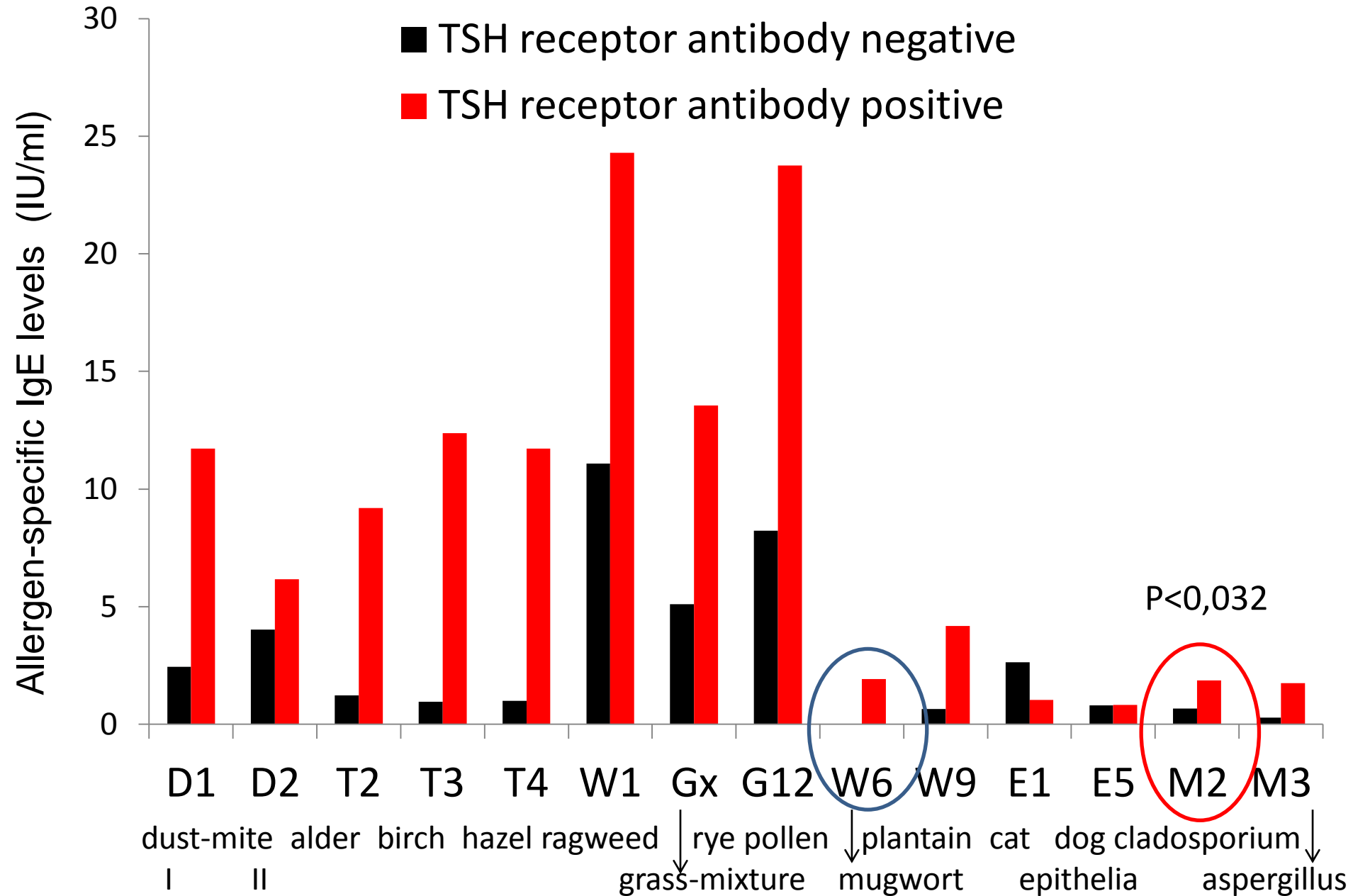




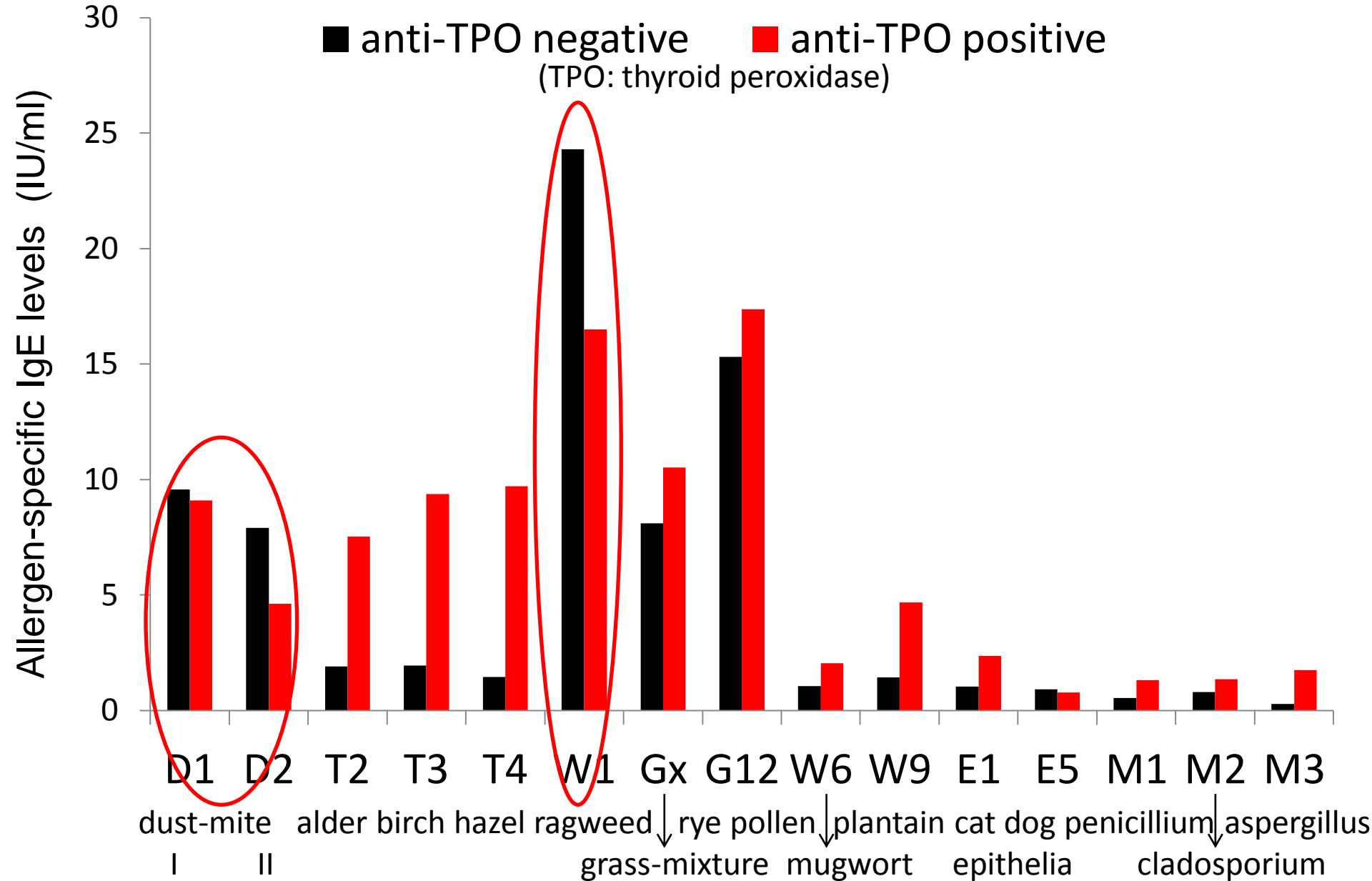
IU/ml	Class	Allergen-specific IgE content
<0,35	0	none
0,35 – 0,69	1	low
0,7 – 3,4	2	increased
3,5 – 17,4	3	significantly increased
17,5 – 49,9	4	high
50 - 100	5	very high
>100	6	extremely high



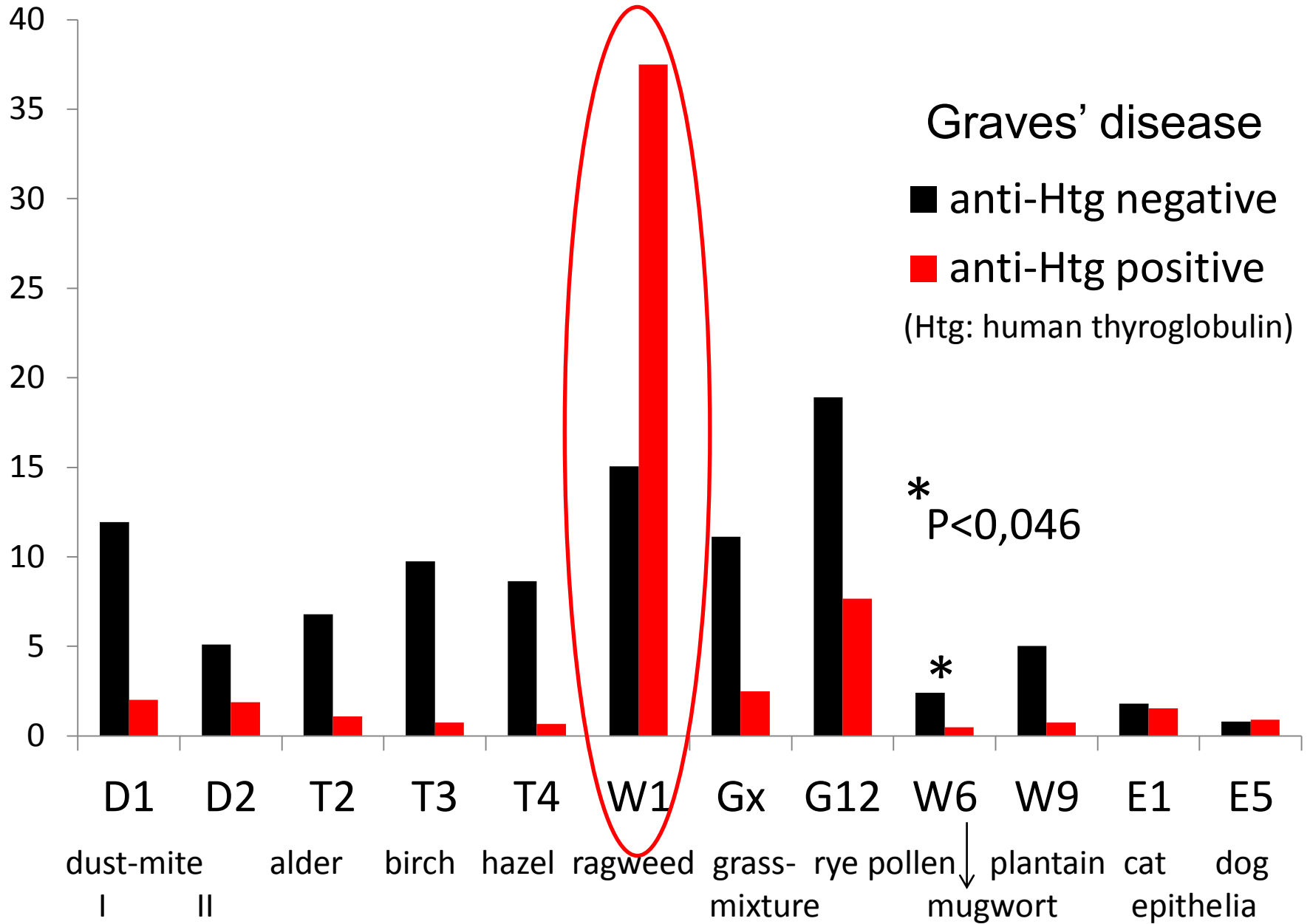
Graves' disease



Graves' disease

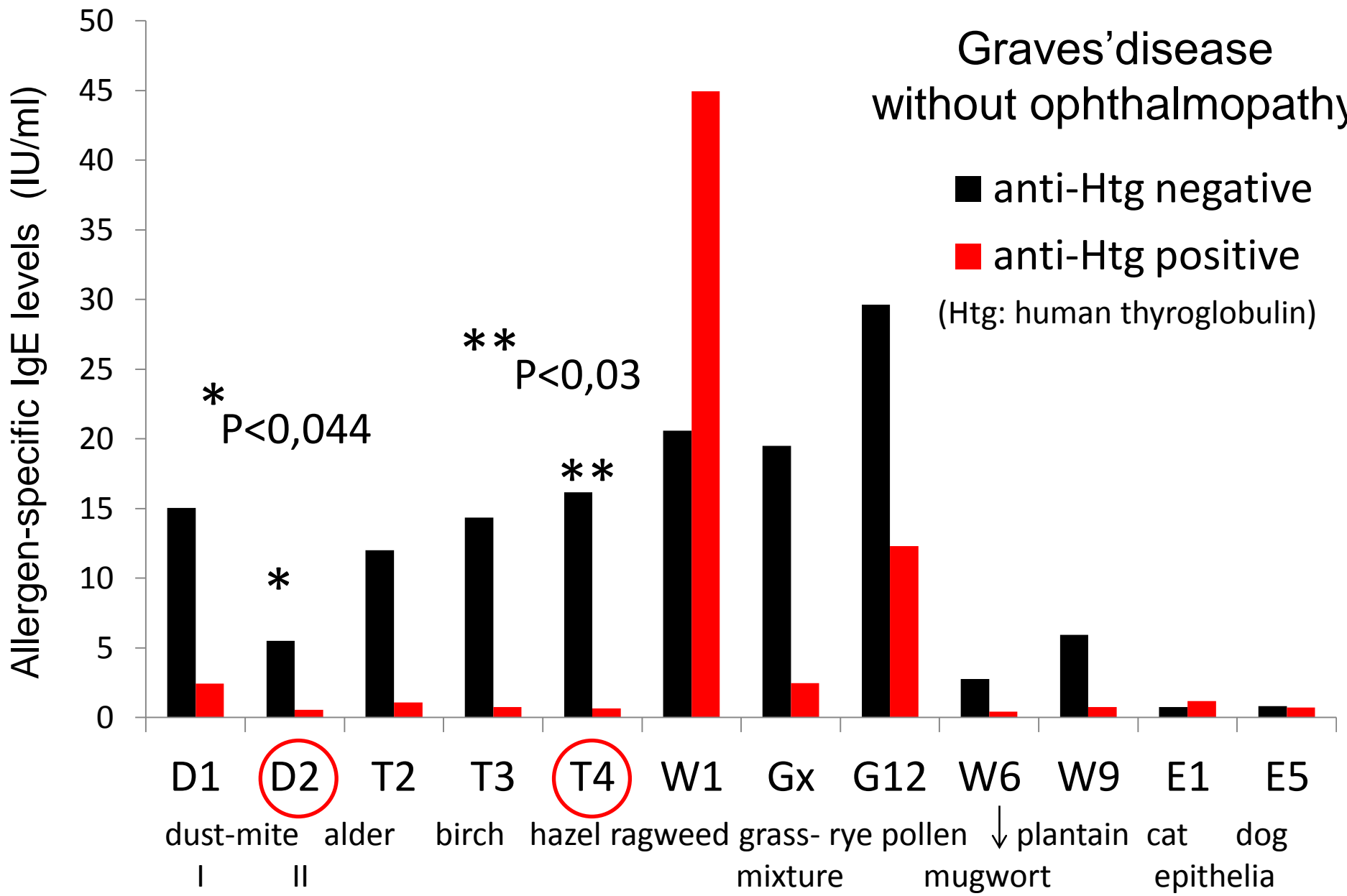


Allergen-specific IgE levels (IU/ml)

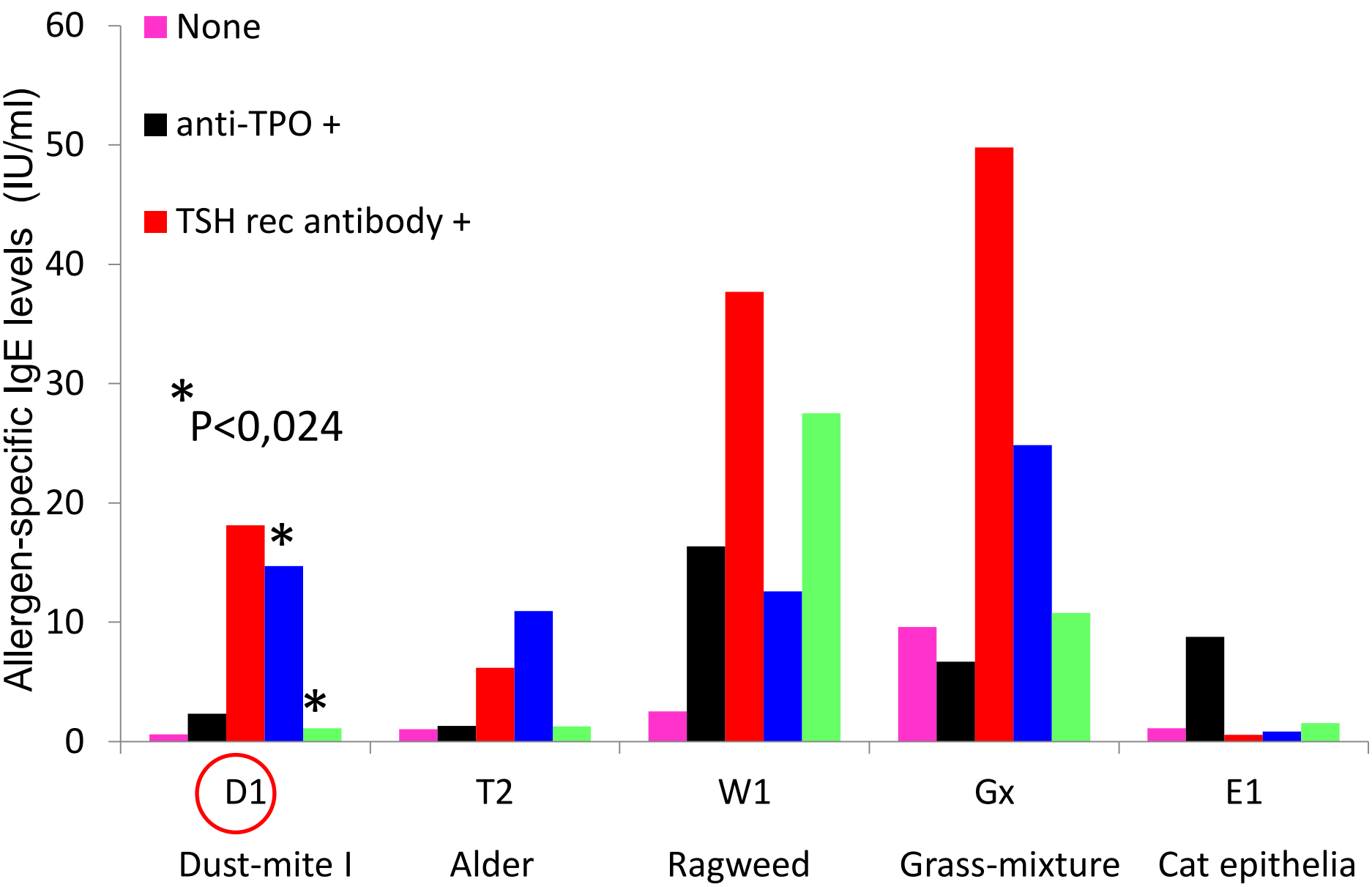


Graves' disease without ophthalmopathy

anti-Htg negative
 anti-Htg positive
 (Htg: human thyroglobulin)



Patient groups



Conclusions

- Allergic **rhinitis and conjunctivitis was more frequent** in autoimmune thyroid diseases
- However, the attack of allergic rhinitis was higher in Hashimoto's thyroiditis and allergic conjunctivitis in Graves' disease.
- **Seasonal allergic attack can play** as an inducer or aggravator role in the development of Graves' disease.
- The prevalence of allergen-specific IgE levels **against trees and weeds were more frequent in Graves' disease** than in Hashimoto's thyroiditis.
- Allergen-specific IgE levels **were lower in Graves' ophthalmopathy** compared to those without eye signs, as well as lower compared to Hashimoto's thyroiditis.
- **Hyperthyroidism was associated with elevated** allergen-specific IgE levels resulting in a higher class degree. (**Except cat epithelia.**)
- The presence of **antithyroid antibodies influenced** the allergen-specific IgE levels. TSH receptor antibody positive and sometimes anti-thyroid peroxidase positive patients showed higher IgE levels, but anti-thyroglobulin (Htg) positivity was associated lower IgE levels, particularly in Graves' ophthalmopathy.
- The frequent presence of allergic conjunctivitis in Graves' disease can lead to a **difficulty in the diagnosis of ophthalmopathy.**

Food allergens

Prevalence of food allergen-specific IgE in autoimmune thyroid diseases

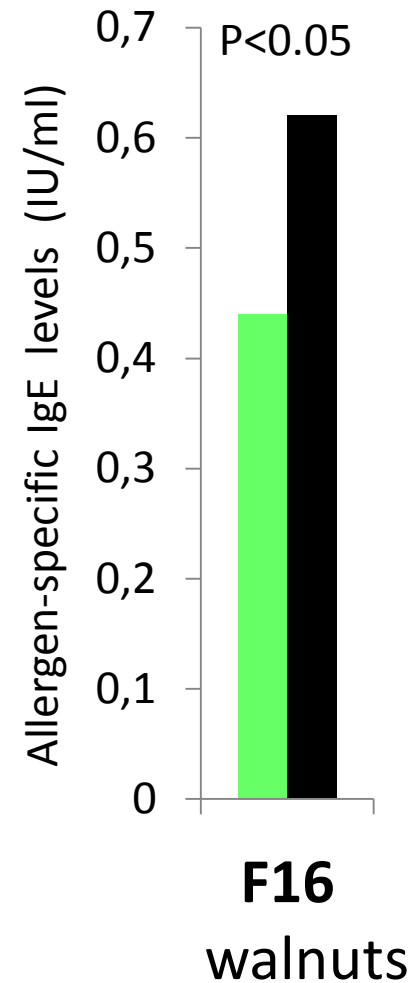
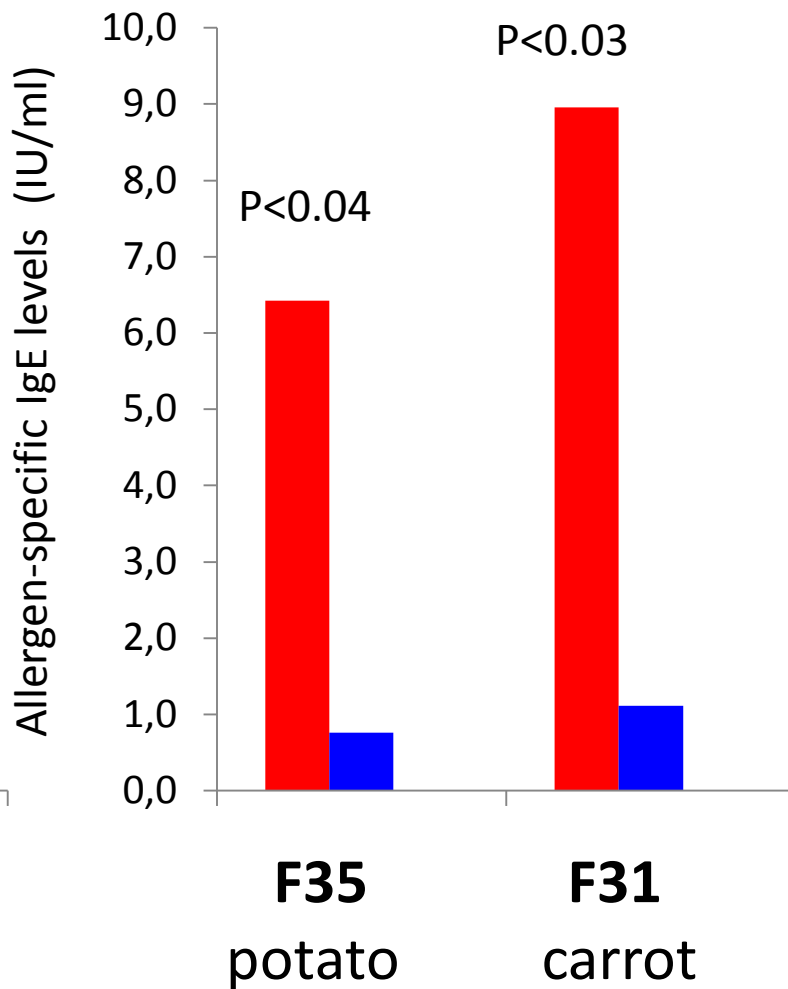
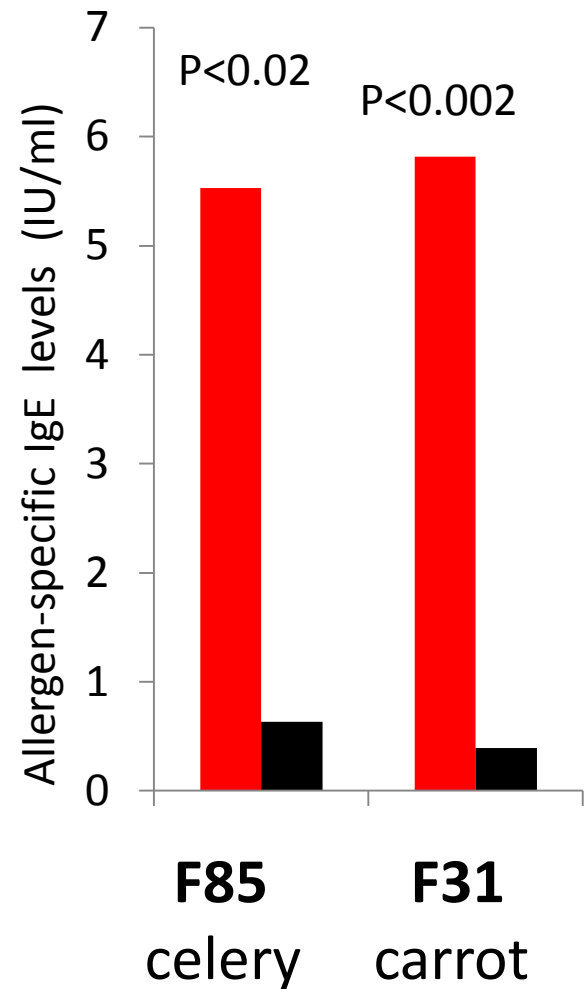
Allergen groups	Graves'disease (n=149)	Hashimoto's thyroiditis (n=110)	Controls (n=65)	Total
F17 (hazelnut)	13^a (8,7%)	1^a (0,9%)	2 (3,1%)	16 (4,9%)
F35 (potato)	16^{b,c} (10,7%)	3^b (2,7%)	1^c (1,5%)	20 (6,2%)
F85 (celery)	24^d (16,1%)	5^d (4,5%)	4 (6,2%)	33 (10,2%)
F31 (carrot)	25^e (16,8 %)	6^e (5,5%)	4 (6,2%)	35 (10,8%)
F25 (tomato)	10^f (6,7%)	1^f (0,9%)	0	11 (3,4%)
F33 (orange)	17^{g,h} (11,4%)	3^g (2,7%)	1^h (1,5%)	21 (6,5%)
F4 (wheat flour)	22ⁱ (14,8%)	4ⁱ (3,6%)	3 (4,6%)	29 (9%)
Total	149	110	65	324

^a P < 0.01, ^b P < 0.03, ^c P < 0.04, ^d P < 0.01, ^e P < 0.01, ^f P < 0.03, ^g P < 0.02, ^h P < 0.03 and ⁱ P < 0.01 with Yates corrections.

Graves' disease (n=149) ■
 Controls (n=65) ■

Graves' disease without (n=92) ■
 Graves' disease with ophthalmopathy (n=57) ■

Hashimoto's thyroiditis (n=110) ■
 Controls (n=65) ■



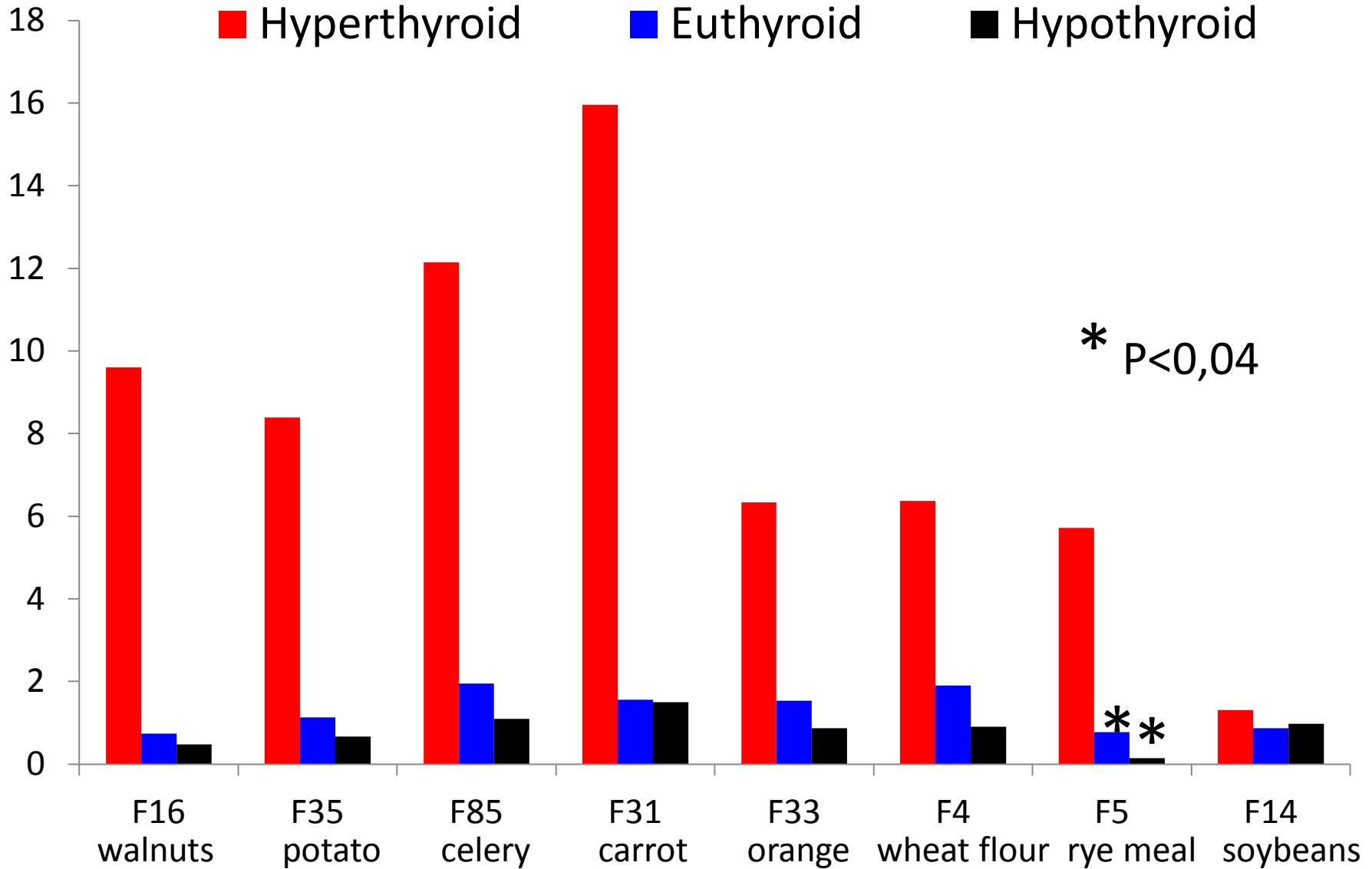
Patient groups

■ Hyperthyroid

■ Euthyroid

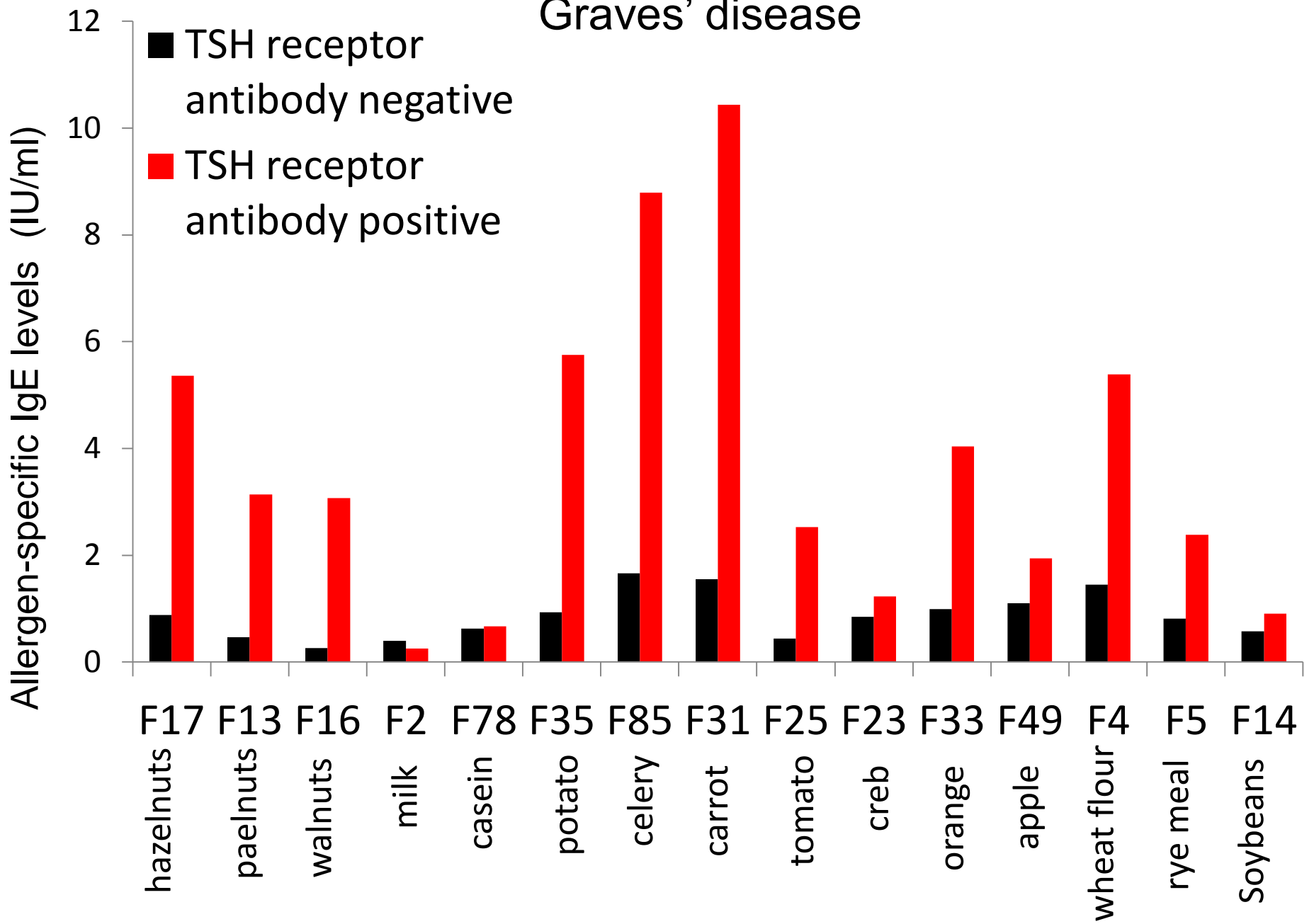
■ Hypothyroid

Allergen-specific IgE levels (IU/ml)

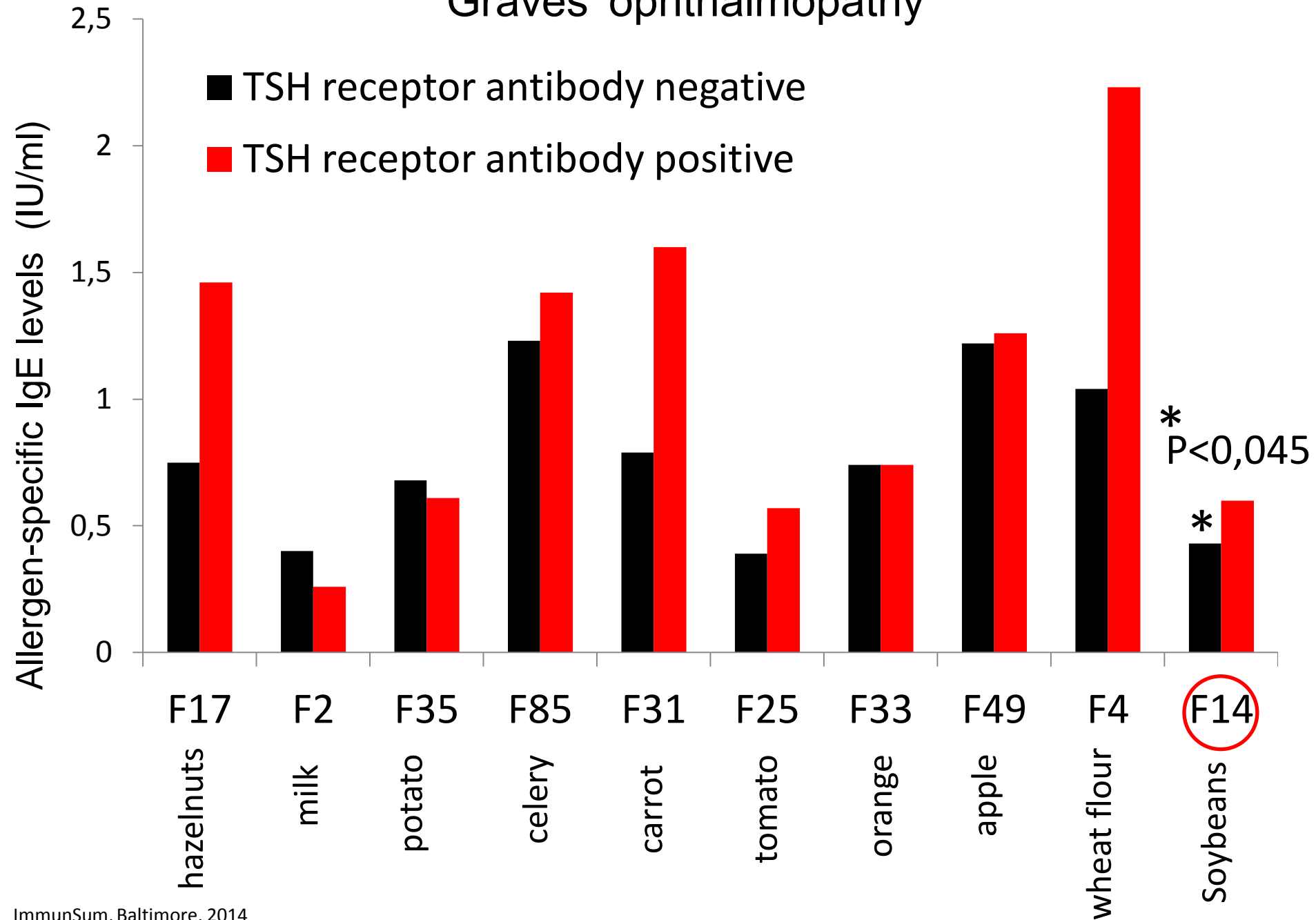


* P<0,04

Graves' disease



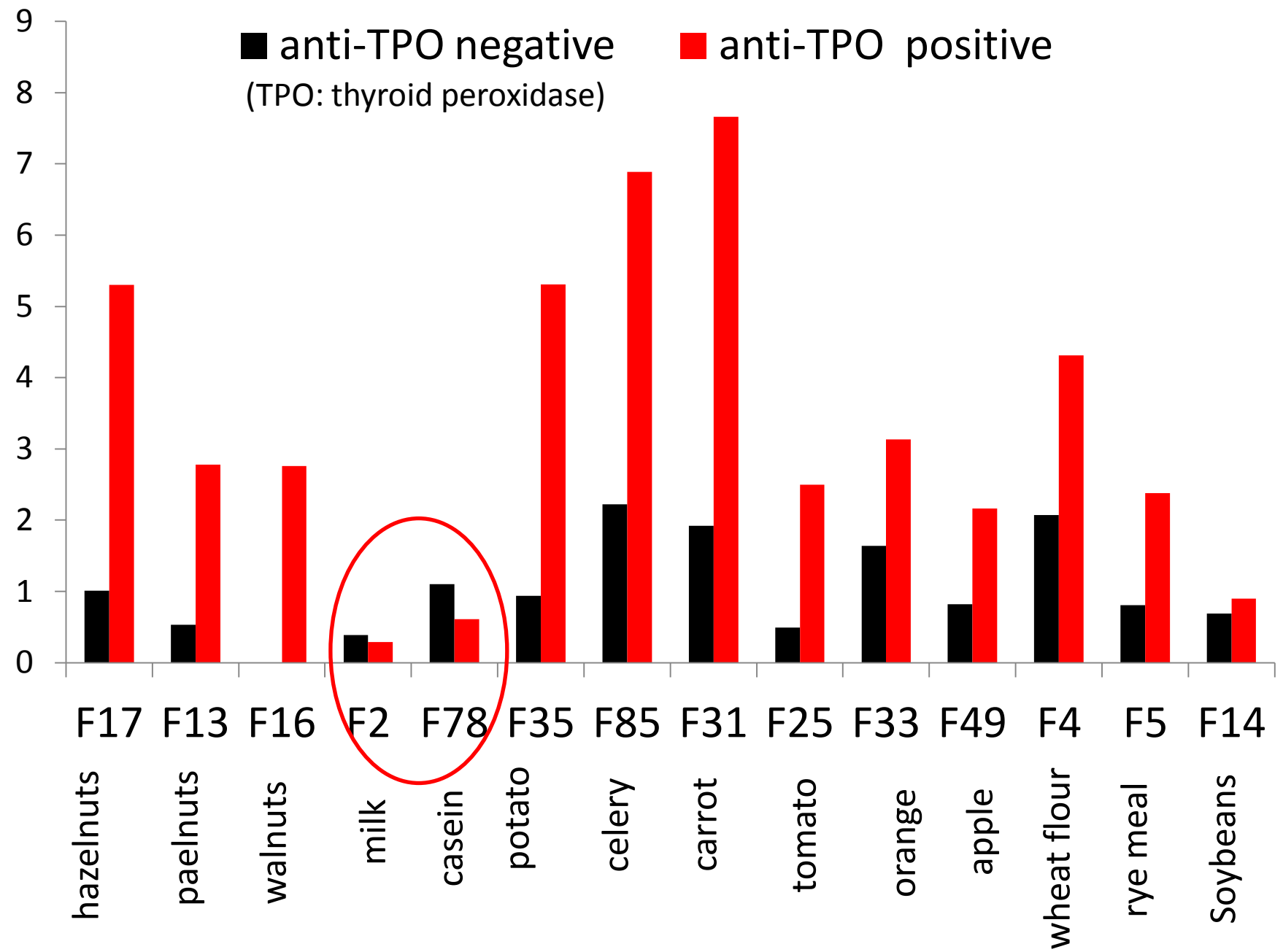
Graves' ophthalmopathy



Graves' disease

■ anti-TPO negative ■ anti-TPO positive
(TPO: thyroid peroxidase)

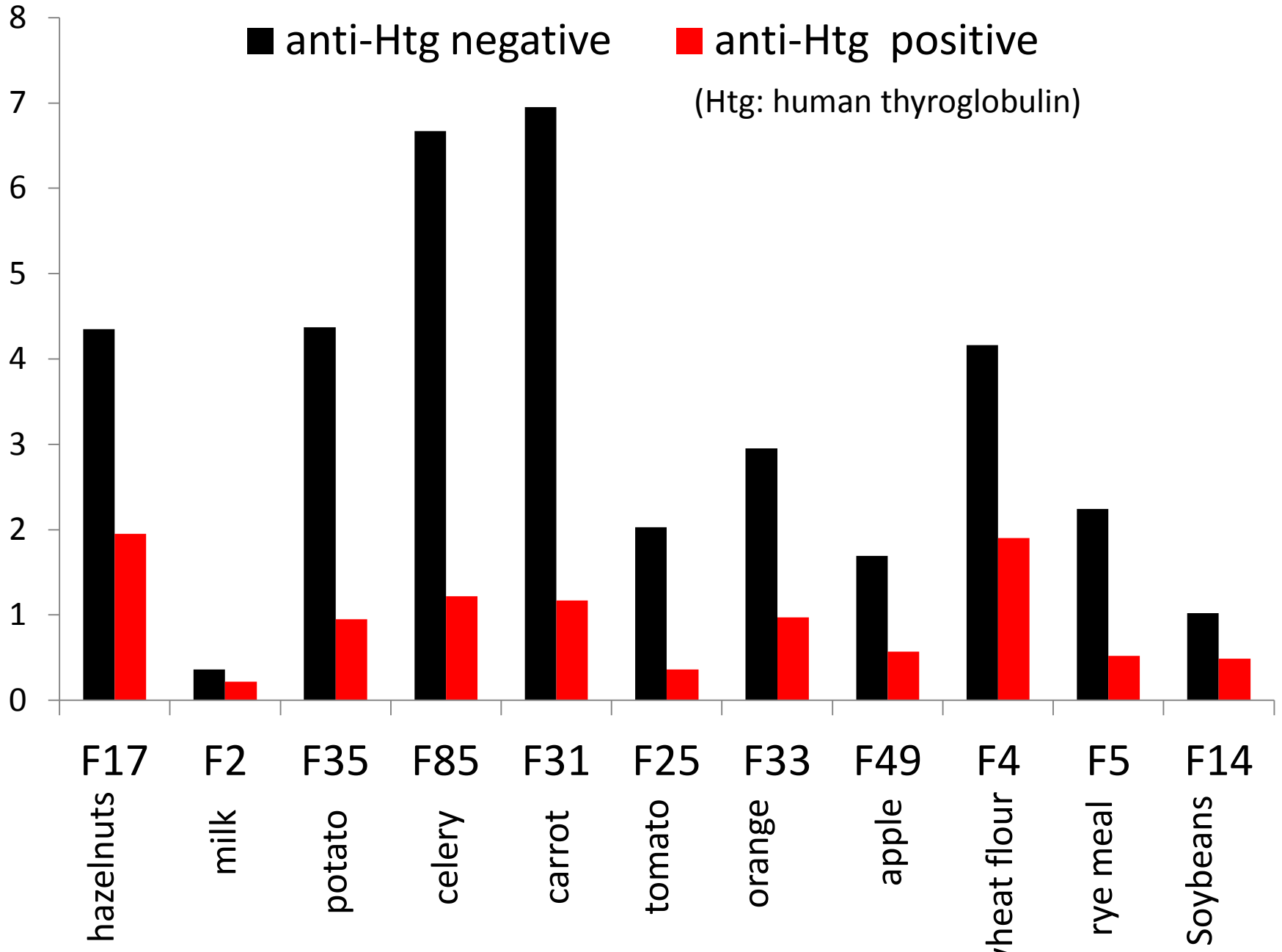
Allergen-specific IgE levels (IU/ml)

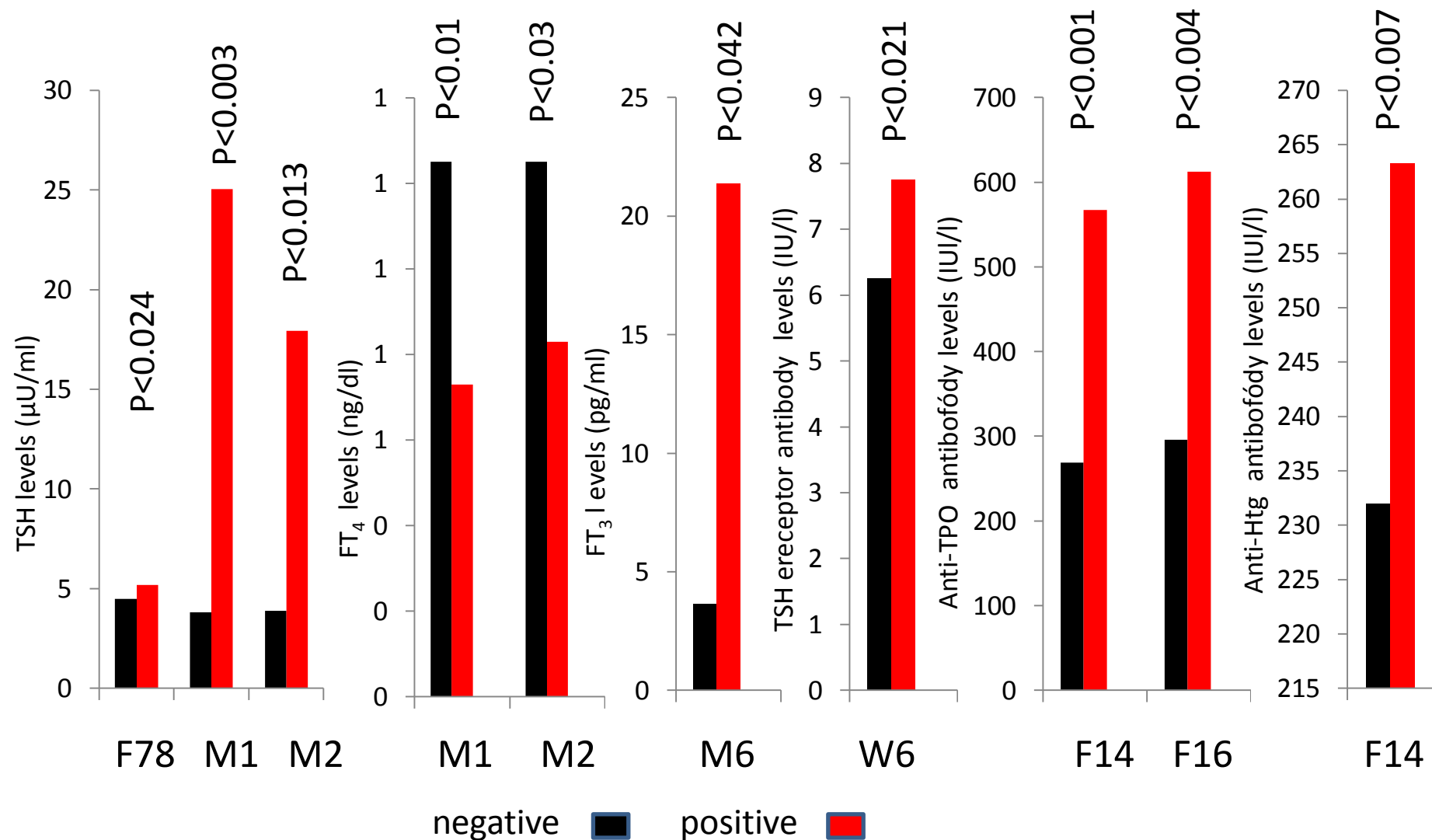


Graves' disease

■ anti-Htg negative ■ anti-Htg positive
(Htg: human thyroglobulin)

Allergen-specific IgE levels (IU/ml)



TSH**FT4****FT3****TSH rec
antibody****a-TPO****a-Htg**

F78: casein M1: Penicillium M2: Cladosporium M6: Alternaria
 W6: mugwort F14: soybeans F16: walnuts

Conclusions

- Food allergen-sensitization was more frequent in Graves' disease compared to that in Hashimoto's thyroiditis, and it can affect our daily meals.
- Allergen-specific IgE levels were higher in Graves' disease, but lower in Hashimoto's thyroiditis than controls.
- Hyperthyroidism was associated with elevated allergen-specific IgE levels.
- Anti-thyroid antibodies influenced the degree of IgE levels:
 1. TSH receptor and anti-TPO antibody levels were associated with higher IgE levels. (Except milk and casein allergens).
 2. Anti-Htg antibody levels were connected to lower IgE levels.

A close-up photograph of a Siamese cat with dark brown fur and lighter brown points on its face and ears. The cat is lying down, looking towards the left. It is wearing a blue and white patterned garment, possibly a shirt or a blanket, around its neck and chest. The background is dark and out of focus.

Thank you

for your attention !

This study contains works of
Erzsébet Kelemen MD, otolaryngologist
Láng Antalné, medical laboratory assistant