Belgian Thyroid Club

3rd December 2011

BELGIAN THYROID CluB

Thyroid and the Thymus

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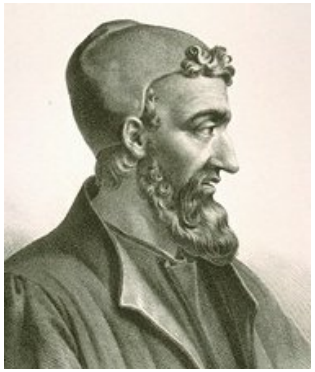
Université de Liège

GIGA

Thymaide
www.eurothymaide.org

The moving place of the thymus in the history of medicine

Claude Galen – 2nd 'father' of Western medicine (129 – 210 or 216 AD)

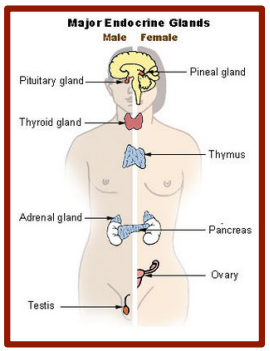


« The thymus is the seat of soul, eagerness and fortitude. »

"Troubles thymiques" in French medical language
= mood disorders, i.e. bipolar and unipolar depression.

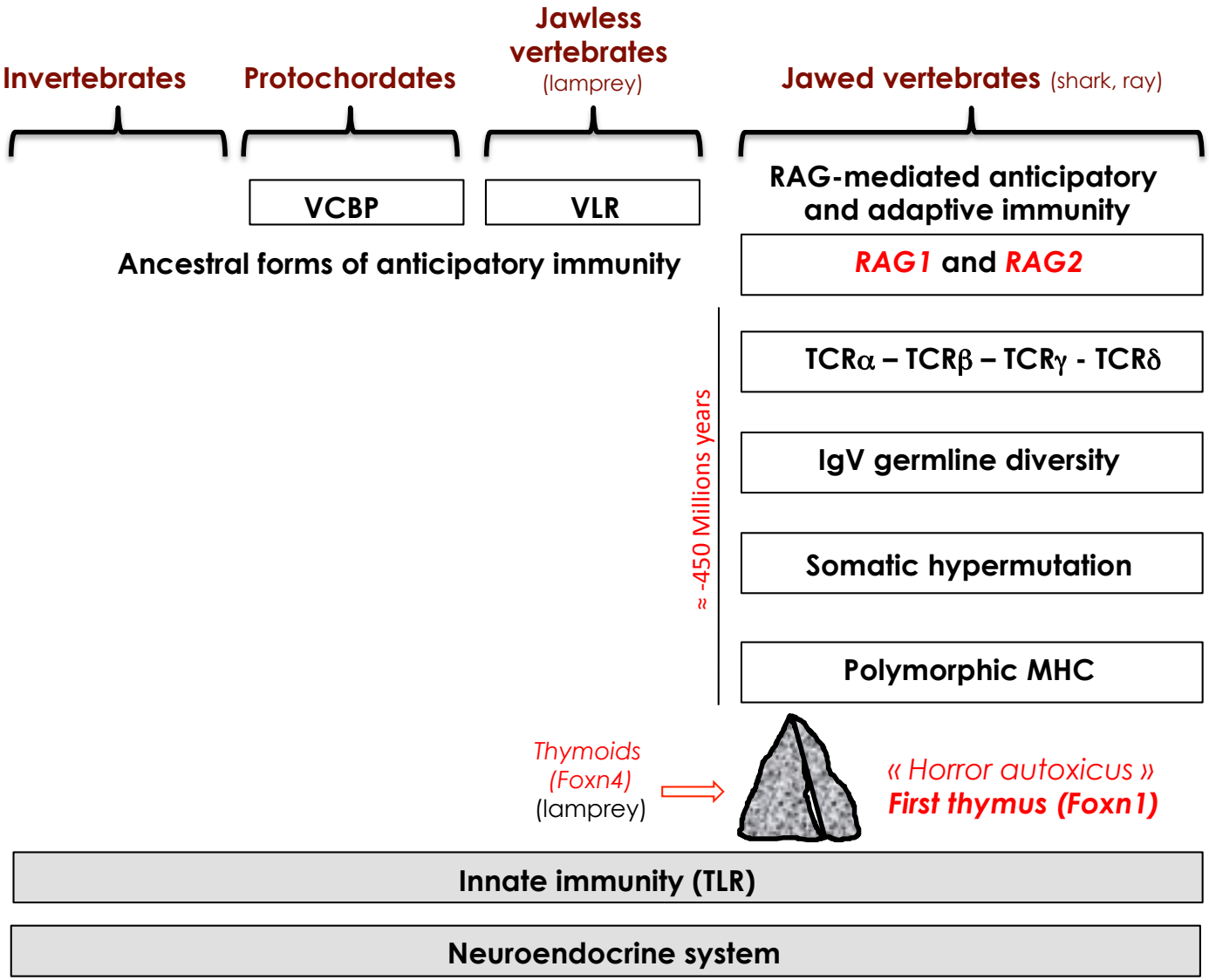
The new views as to the morphology of the thymus gland and their bearing on the problem of the function of the thymus. **JA Hammar** (1921) *Endocrinology* **5**: 43-73.

« The cases in which hyperplasia of the thymus is found are relatively rare. Such findings have been made chiefly after castration, in Graves' disease, myasthenia and acromegaly. »



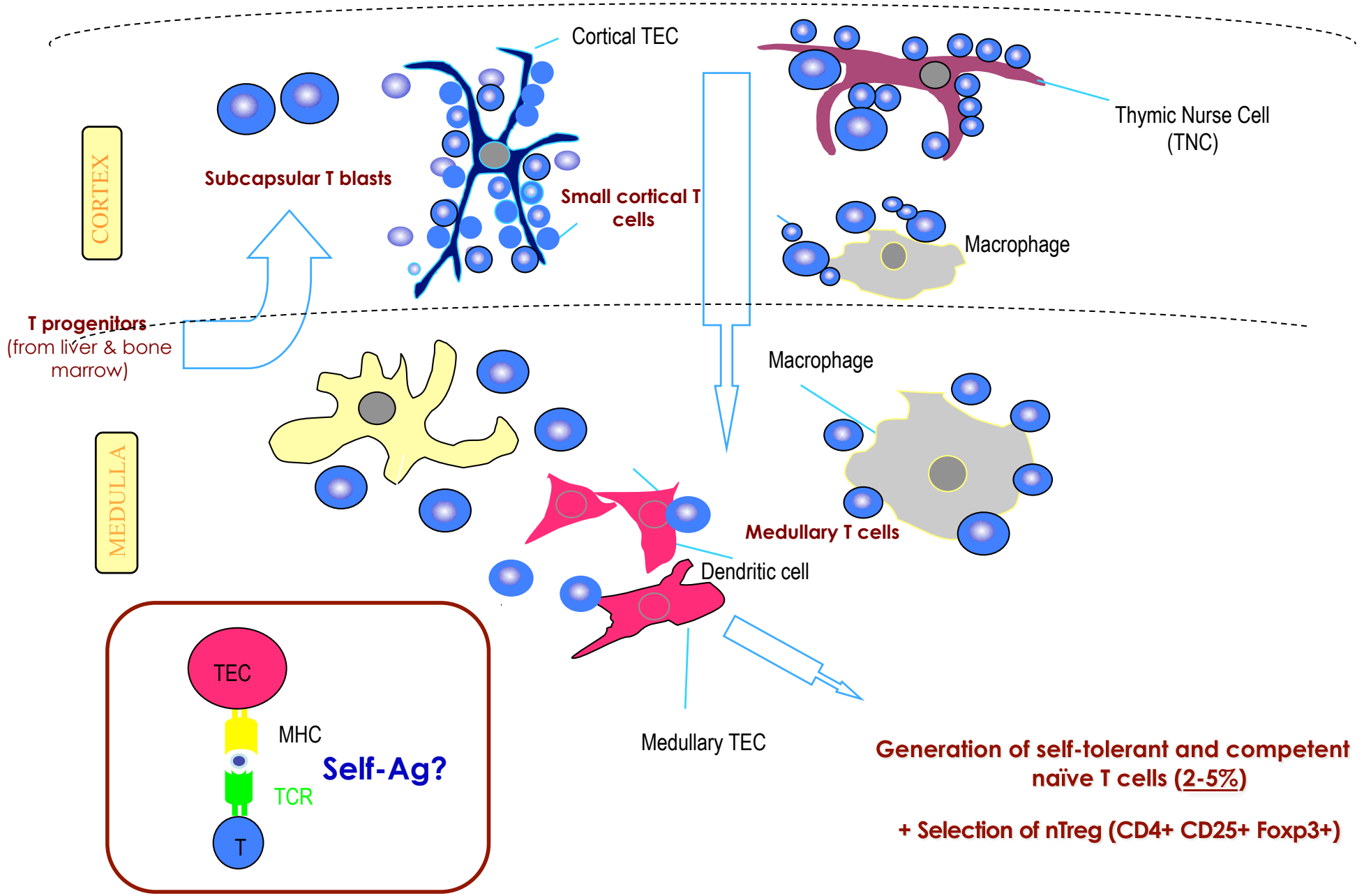
Role of the thymus in murine leukaemia. **JFAP Miller** (1959) *Nature* **183**: 1069.
Immunological function of the thymus. **JFAP Miller** (1961) *Lancet* **2**: 748-9.

Integrated evolution of the immune and neuroendocrine systems



Geenen V (2012) *Ann NY Acad Sci*, in press

T-cell differentiation in the thymus

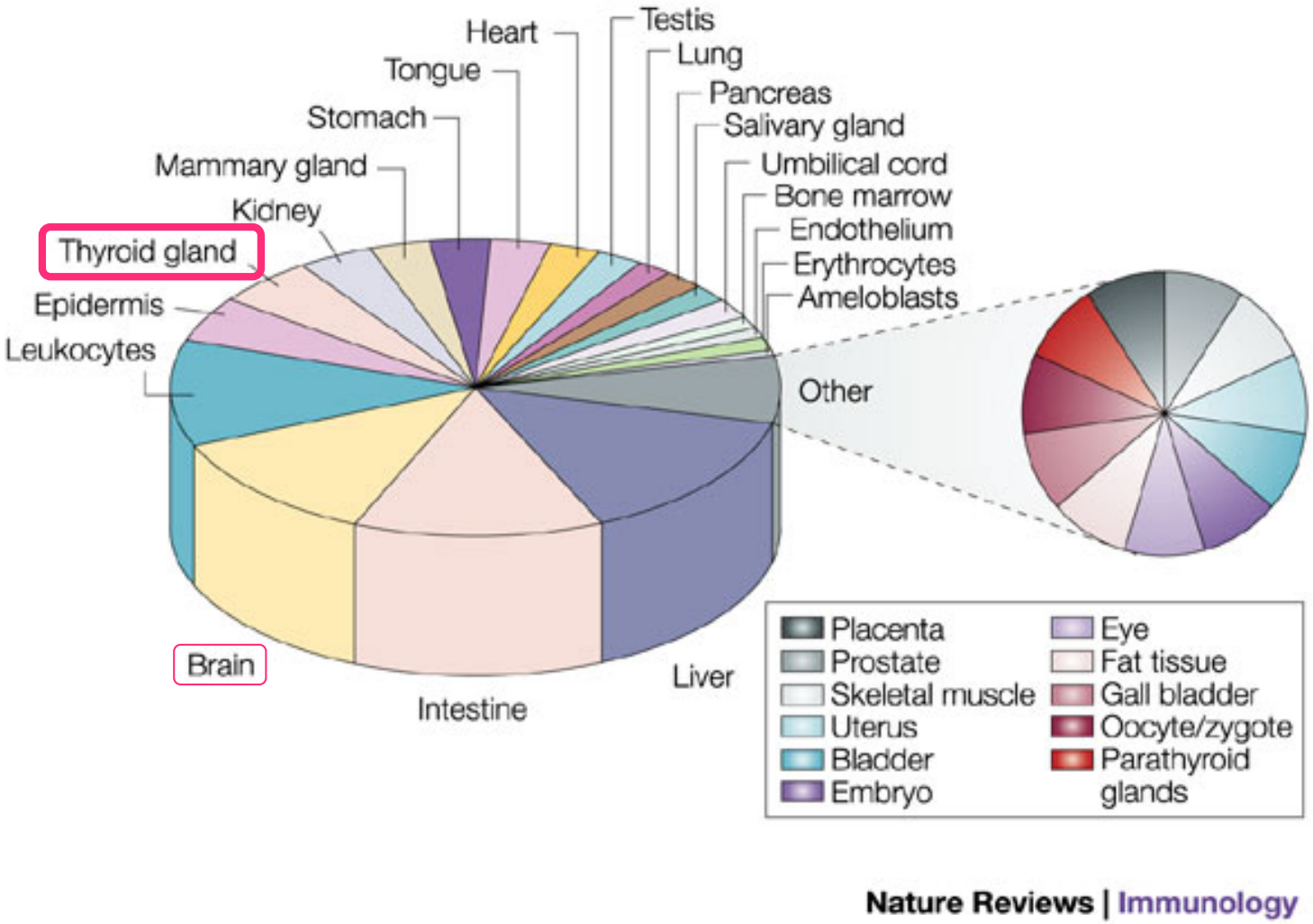


Thymic repertoire of neuroendocrine *self* precursors

FAMILY	THYMIC *SELF* ANTIGENS
Neurohypophysial peptides	Oxytocin / OT (>> Vasopressin / VP)
Neurotensin/ Neuromedins	Neurotensin / NT
Tachykinins	Neurokinin A
Natriuretic peptides	ANP
Somatostatins	Cortistatin
Insulin family	IGF-2 (> IGF-1 > Insulin)

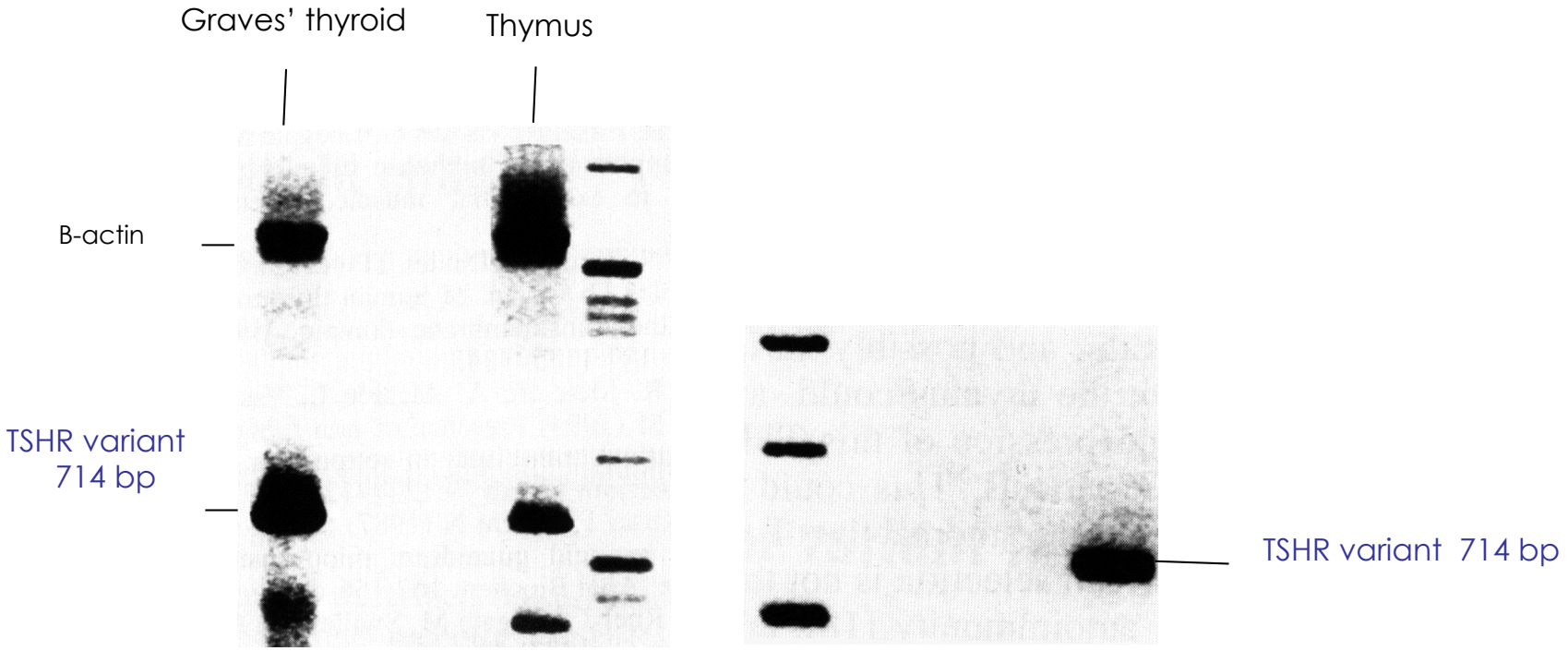
Geenen et al. (2004) *Encyclopedia of Neuroscience 3rd Edition*

Thymic expression of tissue-restricted antigens (TRA)



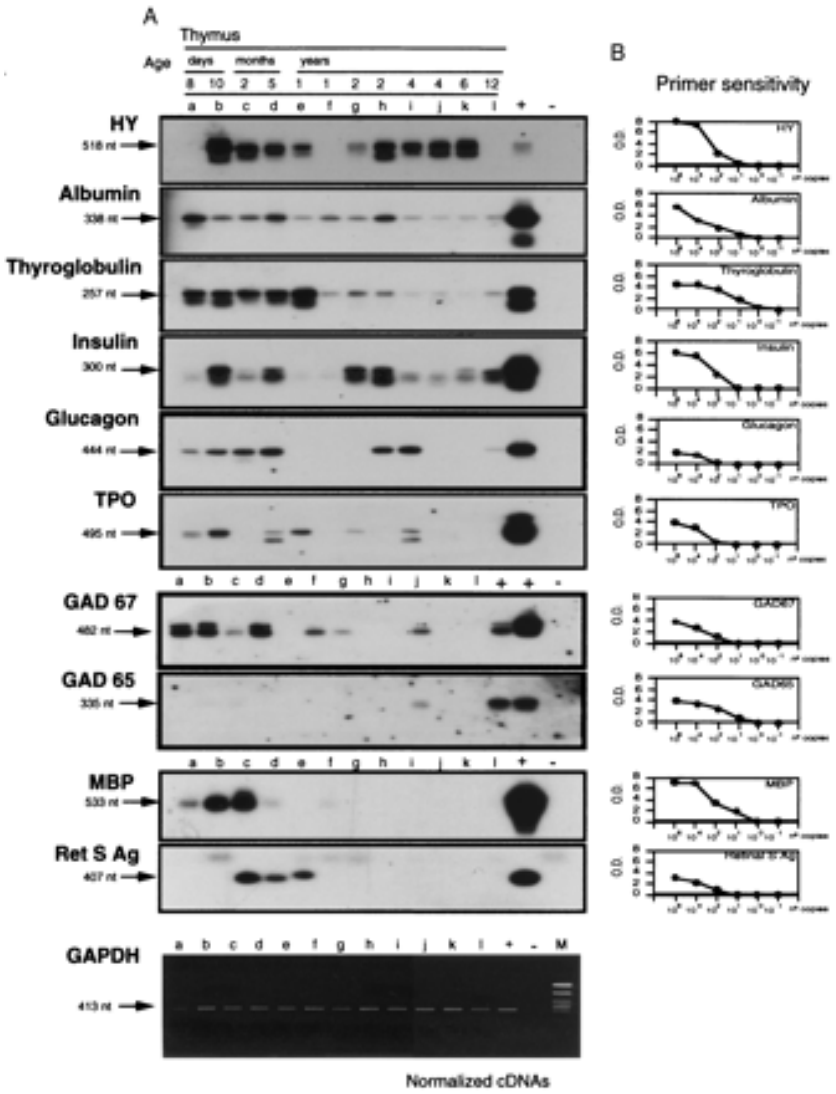
Kyewski *et al.* (2004) *Nat. Rev. Immunol.*

TSHR expression in the thymus



Paschke R & Geenen V (1995) *J. Mol. Med.* **73**: 577-580.

Thymic expression of thyroid antigens



Sospedra J. *et al.* (1998) *J Immunol* **161**: 5918-5929
Dutton *et al.* (1997) *Thyroid* **6**: 879-884
Spitzweg *et al.* (1999) *Thyroid* **9**: 133-141

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Graves' Disease and Massive Thymic Hyperplasia

Maria Raquel Carvalho, Teresa Dias, Fernando Baptista, and Isabel do Carmo

Dear Editor:

Graves' disease is an autoimmune thyroid condition in which autoantibodies against the thyrotropin (TSH) receptor stimulate the autonomous production of thyroxine and triiodothyronine. It is characterized by diffuse goiter and thyrotoxicosis and may be accompanied by an infiltrative orbitopathy and dermatopathy. A seldom-recognized feature of this disease is thymic hyperplasia. We would like to highlight this association and consider the pitfalls that can occur when this is encountered by describing a patient with Graves' disease and massive thymus hyperplasia.

A 22-year-old woman presented with Graves' disease. Serum biochemistry revealed TSH receptor autoantibodies (TRAbs) 178 U/L (normal range: <10 U/L; RIA TRAK-assay [Brahms, patterns MRC LATS-B 65/22 and TSAb Who 90/672), TSH <0.01 μU/mL (0.35–5.5 μU/mL), free thyroxine 4.37 ng/dL (0.89–1.8 ng/dL), and free triiodothyronine 19.41 pg/mL (2.3–4.2 pg/mL). TSH, free triiodothyronine, and free thyroxine levels were determined by a chemiluminescent assay (ADVIA Centaur; Bayer). The patient had marked Graves' ophthalmopathy and an incidentally discovered anterior mediastinal mass (8×5 cm) with no invasive characteristics on magnetic resonance imaging (Fig. 1a, b). She was started on treatment with methimazole. There was marked improvement of her thyrotoxic state and concomitant reduction in the size of her thymus (Fig. 2a, b). The patient was treated with total thyroidectomy. Ten months after surgery, the thymic mass regressed to its normal involutionated size at this age—total reduction of 80% (Fig. 3a, b).

Thymic hyperplasia is a common and reversible feature in Graves' disease (1). There are no consistent data between thymic hyperplasia and other hyperthyroid states. It has been suggested that one-third of patients with Graves' disease have microscopic abnormalities in the thymus (2). In most cases, however, thymic enlargement is minimal. Indeed, massive enlargement of the thymus has been reported only infrequently in Graves' disease (1,3). The pathophysiology of thymic hyperplasia in this setting has not been fully determined. However, the fact that treatment of the hyperthyroid state in Graves' disease with concomitant decrease in TRAbs leads to regression of the dimensions of the thymus suggests that thymic hyperplasia is more likely to be the result of Graves' disease (4). Actually, Murakami *et al.* postulated that both an indirect action of the lowering of thyroid hormone levels and the lowering of TRAbs could induce reduction in the thymus size. It seems that antithyroid drugs, besides causing a blockade of thyroid hormone synthesis, can also have an immunosuppressive effect, namely, reducing TRAbs levels. The same authors have demonstrated the presence of TSH receptor in nonneoplastic thymic tissue, suggesting that this receptor may serve as an autoantigen (5). Their findings support the concept that TRAbs in Graves' disease stimulate that thymic receptor causing thymus enlargement as they induce goiter in Graves' disease.

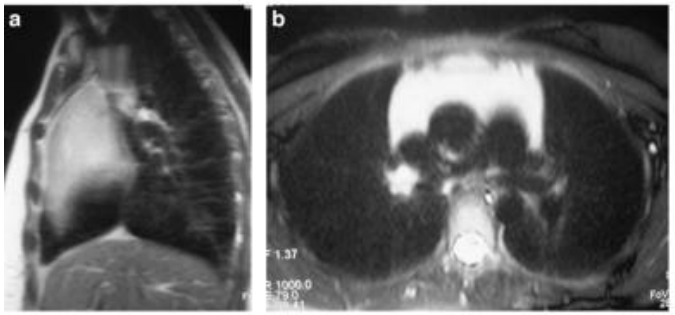
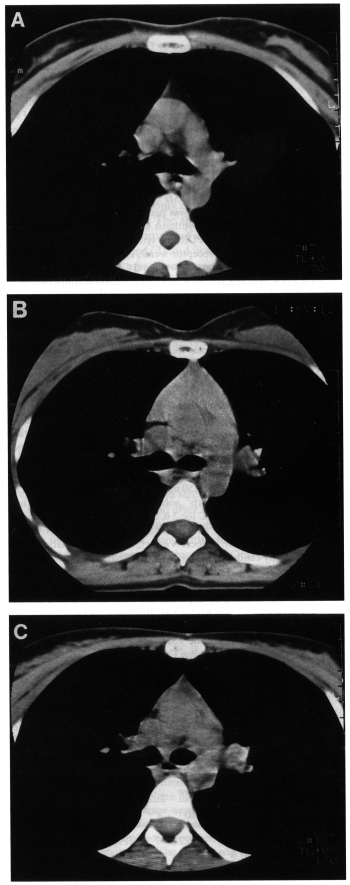


FIG. 1. (**a**, **b**) Thoracic MRI (pretreatment). MRI, magnetic resonance image.

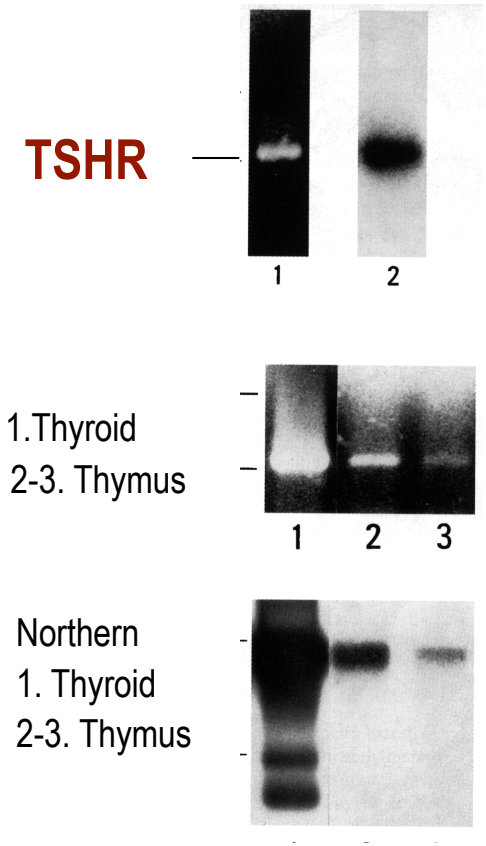
Endocrinology Department, Santa Maria Hospital, Lisbon, Portugal.

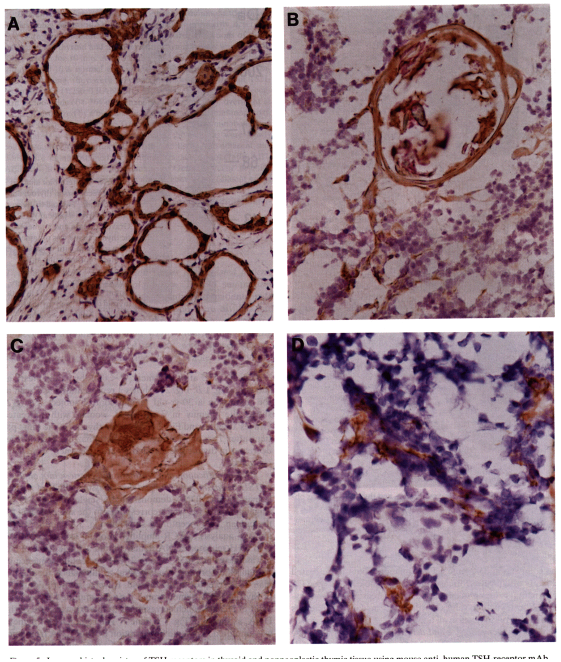
Thymus and Graves disease



CT-scan

A. Control
B. Before treatment
C. After treatment



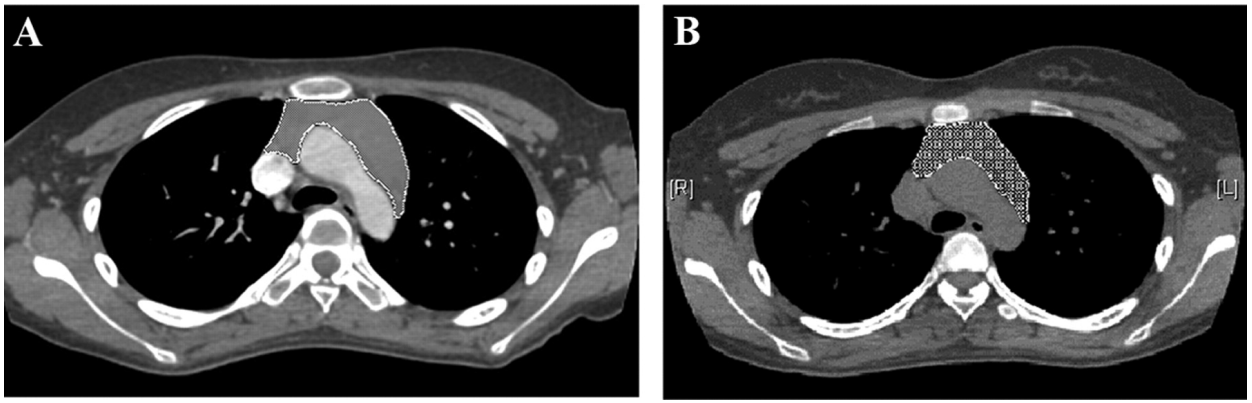


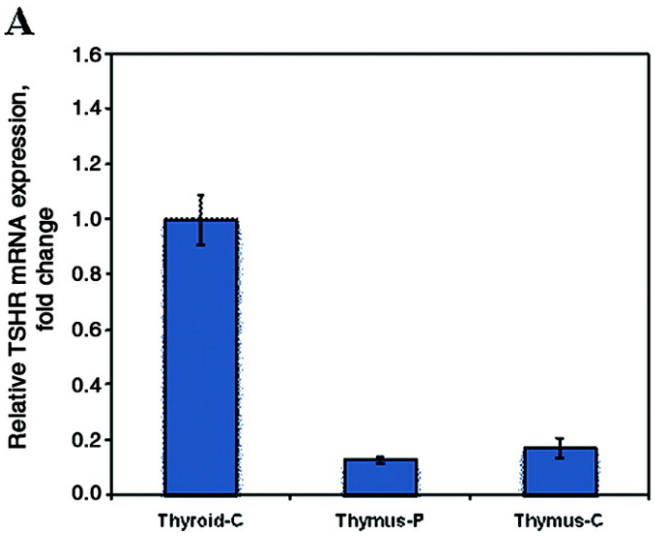
ICC forTSHR

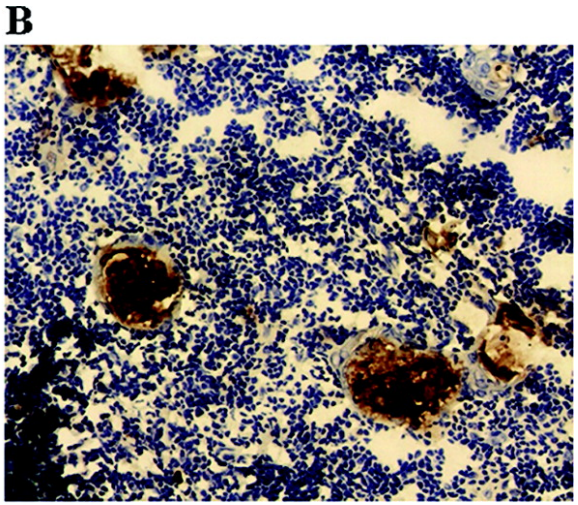
A. Thyroid
B-D. Thymus

Murakami *et al.* (1996) *J. Clin. Invest.* **98**: 2228-2234

Graves disease and thymus hyperplasia



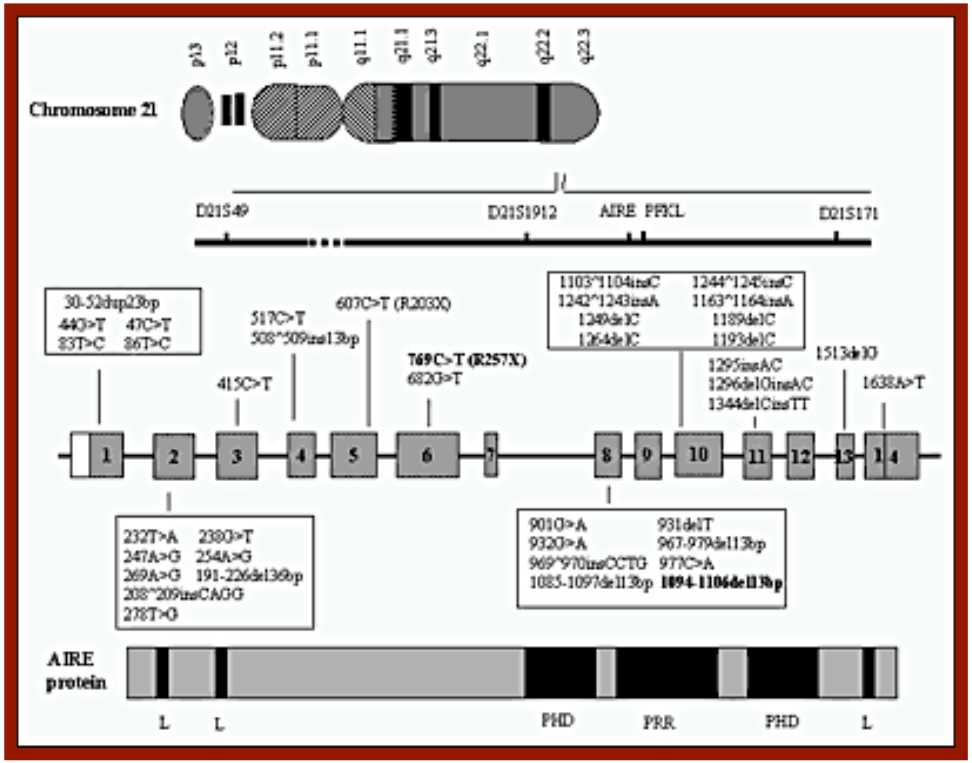




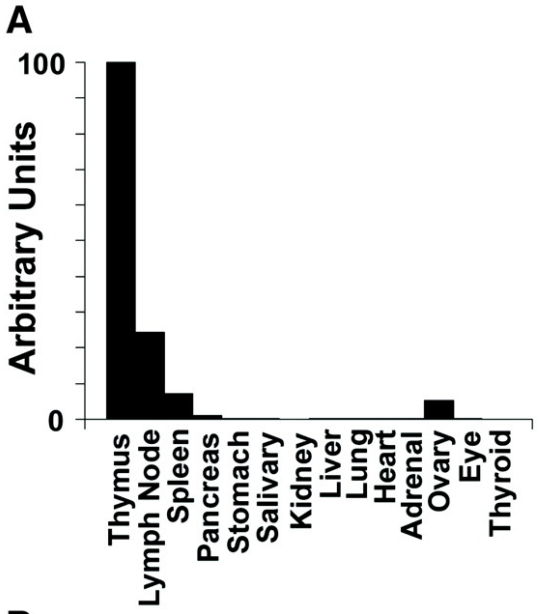
Rubicky RA *et al*. (2010) *Pediatrics* **125**: e433

APS-I or APECED syndrome

- Very rare autosomal recessive disease
- *AIRE* identified on 21q22.3 (positional cloning)
- 14 exons, transcription factor of 545 aa, > 45 mutations
- Maximal transcription in ***thymic epithelium***

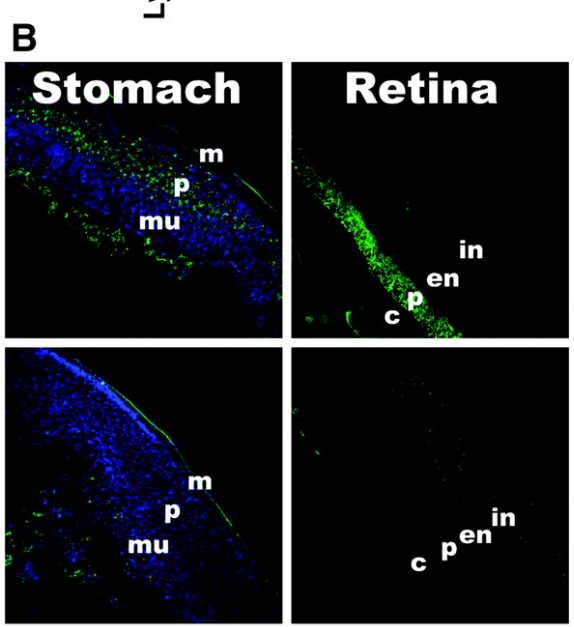


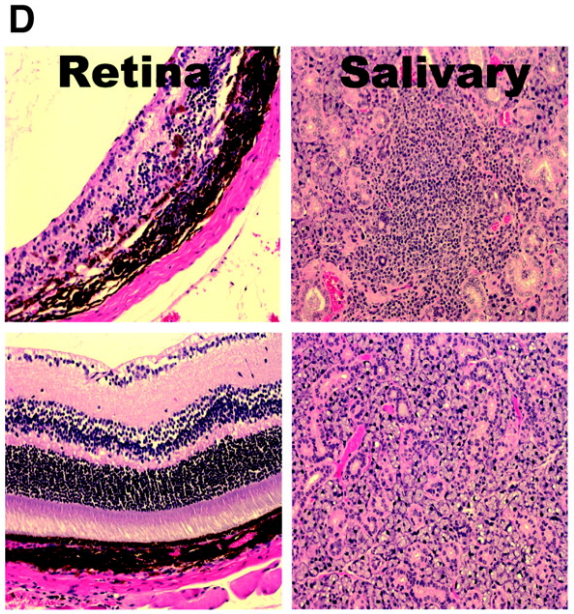
The thymus is essential for development of AIRE-associated autoimmunity



C

	Salivary	Retina	Stomach
WT Donor	0/4	0/4	0/4
KO Donor	3/5	2/5	3/5





A. Level of *Aire* expression in tissues

B-D. Tranplantation of *Aire*$^{-/-}$ thymus

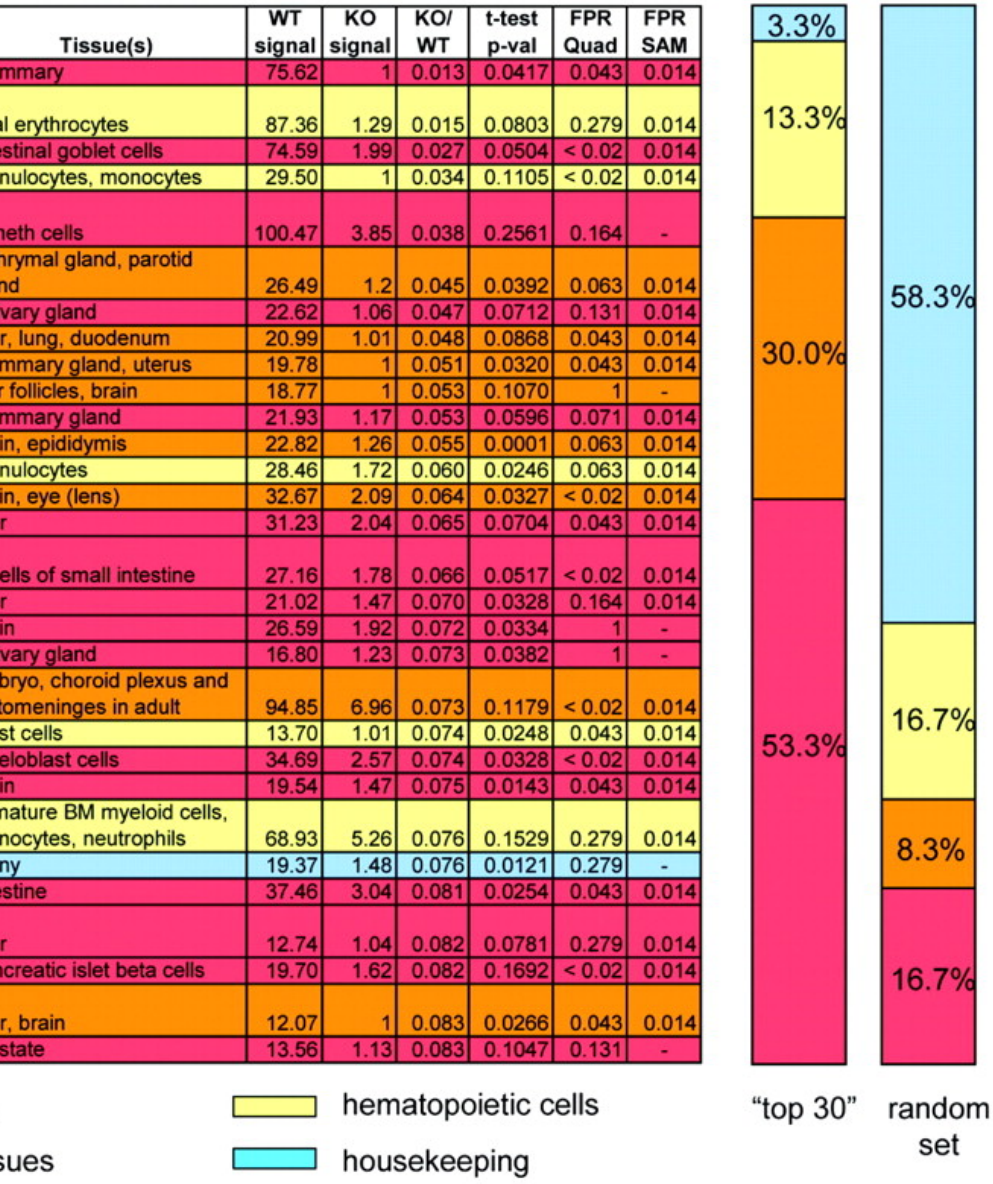
Anderson M *et al.* (2002) *Science* **298**: 1395-1401

Aire controls thymic transcription of tissue-specific Ags

A

Probe name	Gene name	Tissue(s)	WT signal	KO signal	KO/ WT	t-test p-val	FPR Quad	FPR SAM
96030_at	casein alpha	mammary	75.62	1	0.013	0.0417	0.043	0.014
97180_f_at	hemoglobin y, beta-like embryonic chain	fetal erythrocytes	87.36	1.29	0.015	0.0803	0.279	0.014
100106_at	intestinal trefoil factor	intestinal goblet cells	74.59	1.99	0.027	0.0504	< 0.02	0.014
101820_at	neurotoxin homologue	granulocytes, monocytes	29.50	1	0.034	0.1105	< 0.02	0.014
94738_s_at	cryptdin,related sequence 2	Paneth cells	100.47	3.85	0.038	0.2561	0.164	-
101682_f_at	major urinary protein IV	lachrymal gland, parotid gland	26.49	1.2	0.045	0.0392	0.063	0.014
94153_g_at	salivary protein 1	salivary gland	22.62	1.06	0.047	0.0712	0.131	0.014
102998_at	cytochrome P450 1a2	liver, lung, duodenum	20.99	1.01	0.048	0.0868	0.043	0.014
101115_at	lactotransferrin	mammary gland, uterus	19.78	1	0.051	0.0320	0.043	0.014
92353_at	serine protease (BSSP)	hair follicles, brain	18.77	1	0.053	0.1070	1	-
100463_at	gamma-casein precursor	mammary gland	21.93	1.17	0.053	0.0596	0.071	0.014
92546_r_at	prostaglandin D	brain, epididymis	22.82	1.26	0.055	0.0001	0.063	0.014
96153_at	neutrophilic granule	granulocytes	28.46	1.72	0.060	0.0246	0.063	0.014
160899_at	Purkinje cell protein 4	brain, eye (lens)	32.67	2.09	0.064	0.0327	< 0.02	0.014
161815_f_at	major urinary protein I	liver	31.23	2.04	0.065	0.0704	0.043	0.014
98858_at	glucose dependent insulinotropic polypeptide	K cells of small intestine	27.16	1.78	0.066	0.0517	< 0.02	0.014
101910_f_at	major urinary protein 3	liver	21.02	1.47	0.070	0.0328	0.164	0.014
94775_at	oxytocin	brain	26.59	1.92	0.072	0.0334	1	-
101636_at	salivary protein 2	salivary gland	16.80	1.23	0.073	0.0382	1	-
98623_g_at	insulin-like growth factor II	embryo, choroid plexus and leptomeninges in adult	94.85	6.96	0.073	0.1179	< 0.02	0.014
99958_at	mast cell protease-2	mast cells	13.70	1.01	0.074	0.0248	0.043	0.014
94707_s_at	amelogenin	ameloblast cells	34.69	2.57	0.074	0.0328	< 0.02	0.014
103235_at	preproneuropeptide y	brain	19.54	1.47	0.075	0.0143	0.043	0.014
103887_at	S100 calcium binding protein A9	immature BM myeloid cells, monocytes, neutrophils	68.93	5.26	0.076	0.1529	0.279	0.014
162341_r_at	aldose reductase	many	19.37	1.48	0.076	0.0121	0.279	-
97889_at	fatty acid binding protein	intestine	37.46	3.04	0.081	0.0254	0.043	0.014
94045_at	α-1-microglobulin/bikunin precursor	liver	12.74	1.04	0.082	0.0781	0.279	0.014
100150_f_at	preproinsulin II	pancreatic islet beta cells	19.70	1.62	0.082	0.1692	< 0.02	0.014
100002_at	inter-alpha-inhibitor H3 chain	liver, brain	12.07	1	0.083	0.0266	0.043	0.014
98830_at	spermine binding protein	prostate	13.56	1.13	0.083	0.1047	0.131	-

B



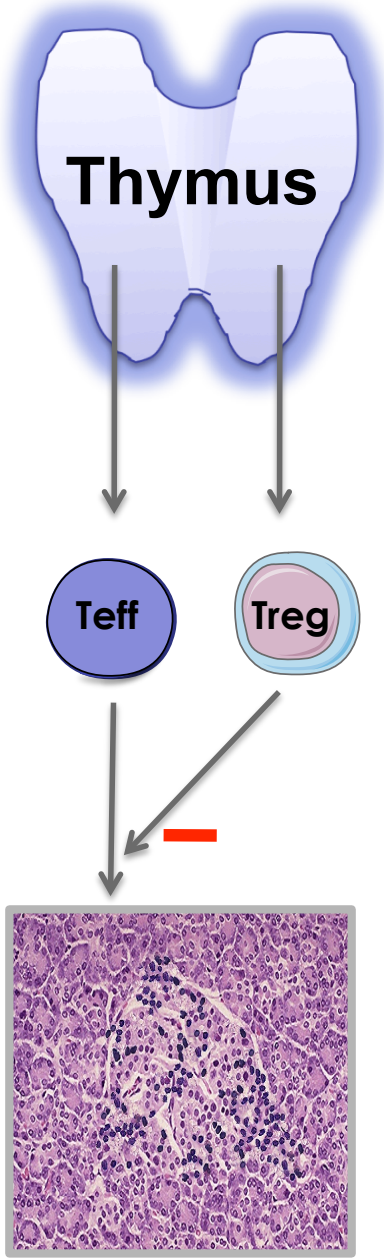
Anderson M *et al.* (2002) *Science* **298**: 1395-1401

The role of the thymus in the development of autoimmunity

Thymus physiology

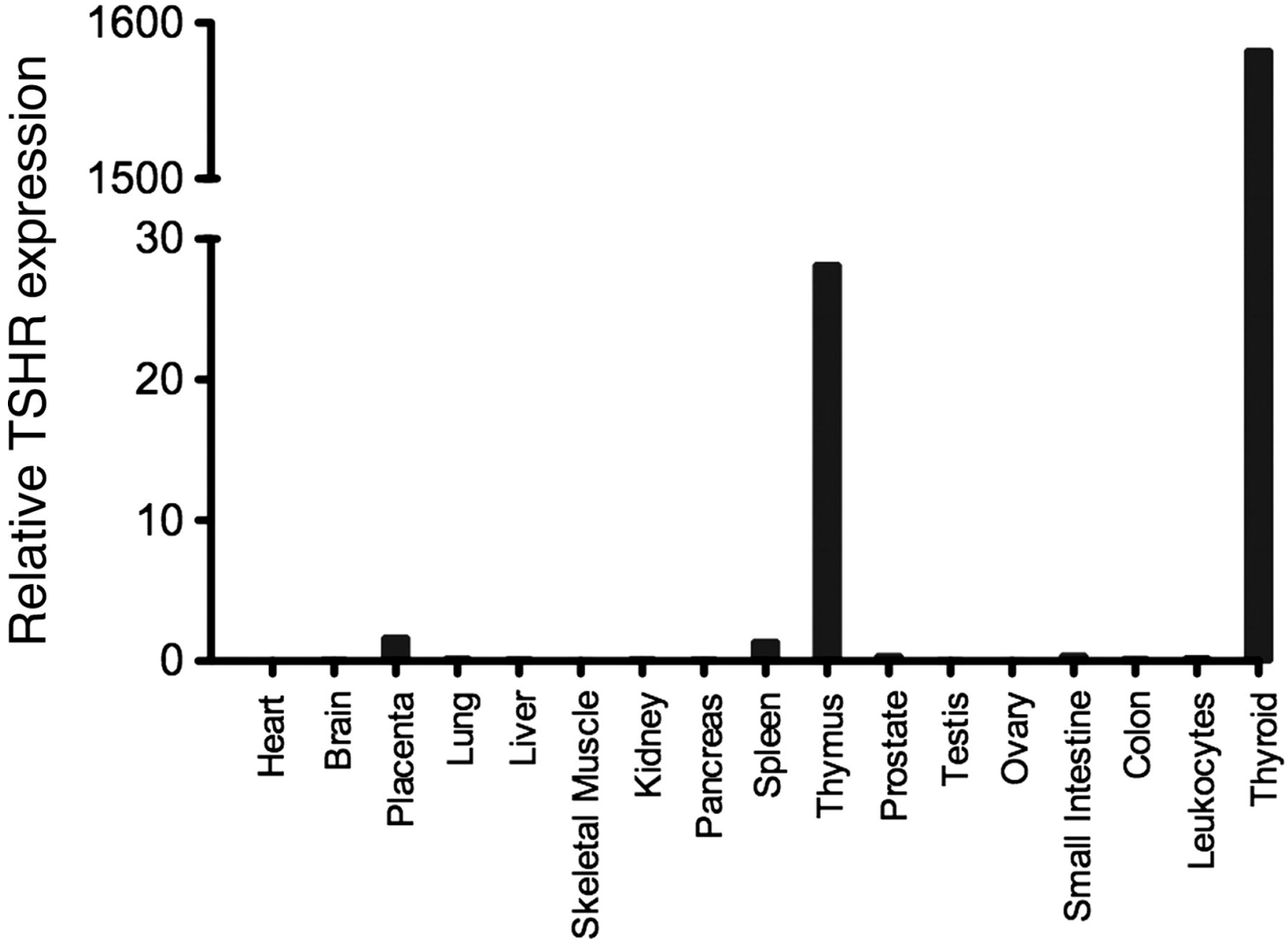
- Intrathymic AIRE-mediated transcription of neuroendocrine and 'peripheral' genes (TSA).
- Deletion of T cells with high affinity for TSA.
- Selection of CD4+ CD25+ Foxp3+ nTreg, specific of TSA.

A defect in thymus T-cell education to self ?



Geenen V & Chentoufi AA (2011) *Clin Dev Immunol*

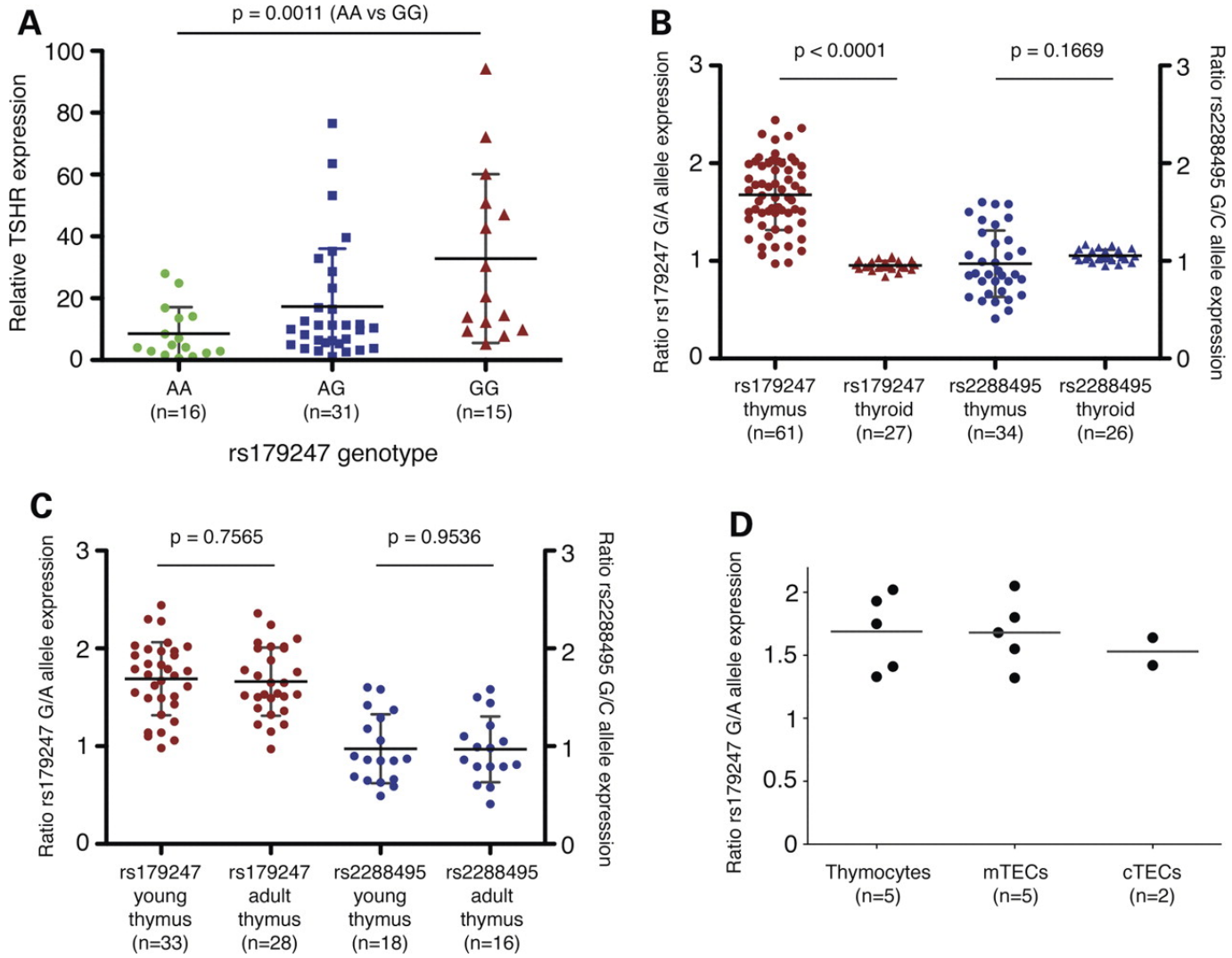
TSHR mRNA expression in 17 human tissues



Colobran R *et al. Hum. Mol. Genet.* 2011;hmg.ddr247

Human Molecular Genetics

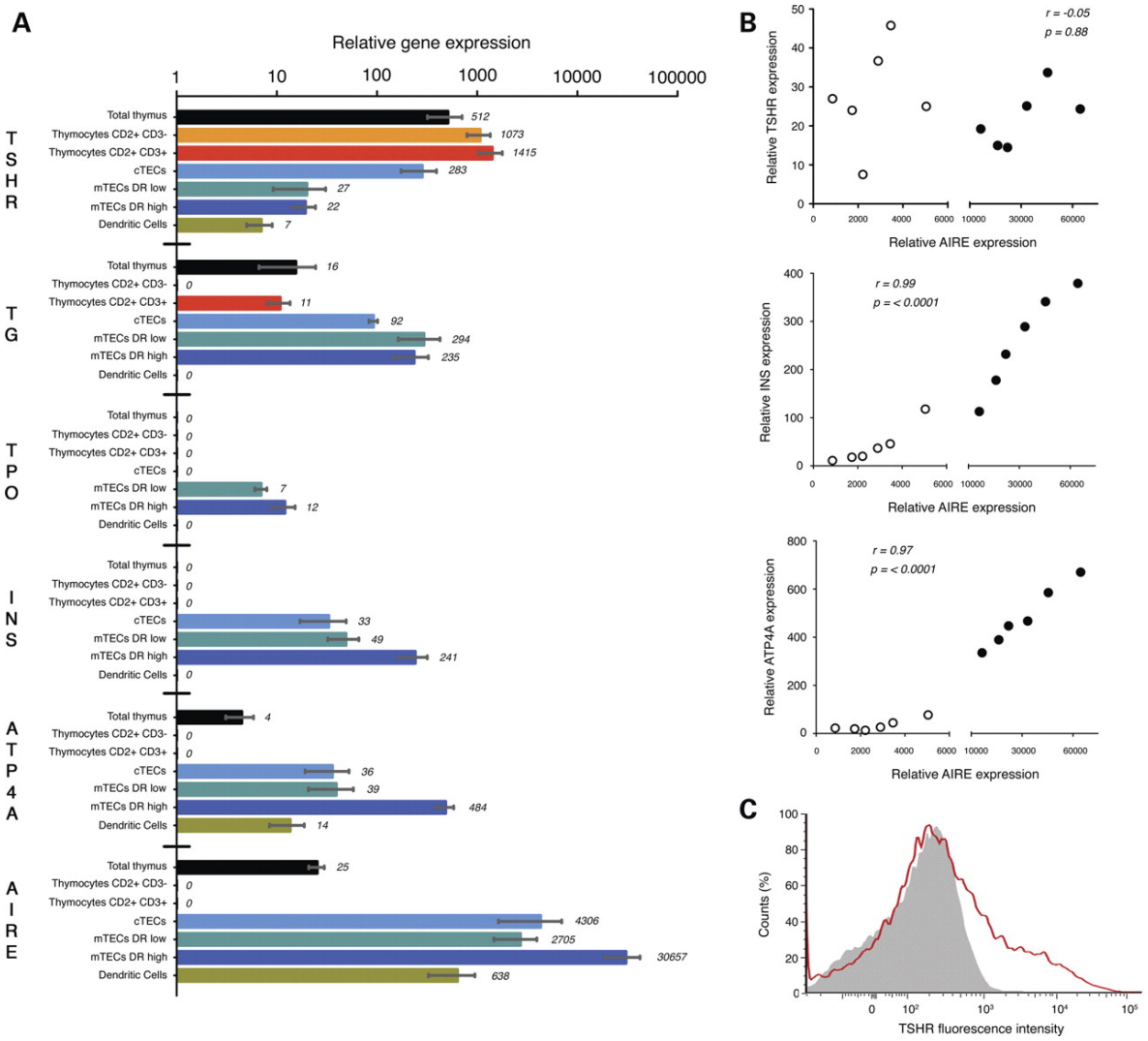
TSHR expression in the human thymus related to rs179247



Colobran R et *al. Hum. Mol. Genet*. 2011;hmg.ddr247

Human Molecular Genetics

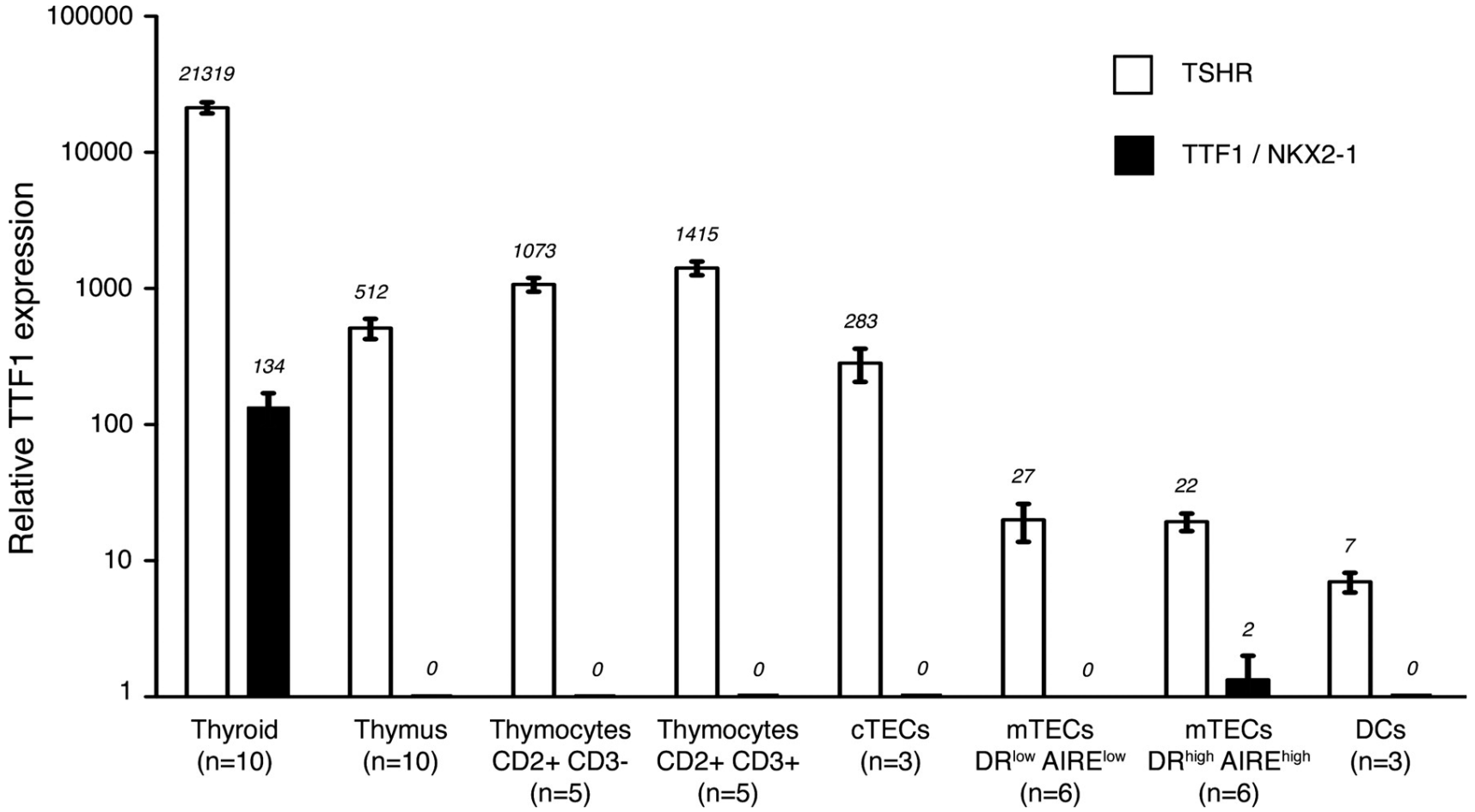
TSHR expression in thymic cell populations



Colobran R *et al. Hum. Mol. Genet*. 2011;hmg.ddr247

Human Molecular Genetics

TTF1 expression in *TSHR*-expressing thymic cell populations

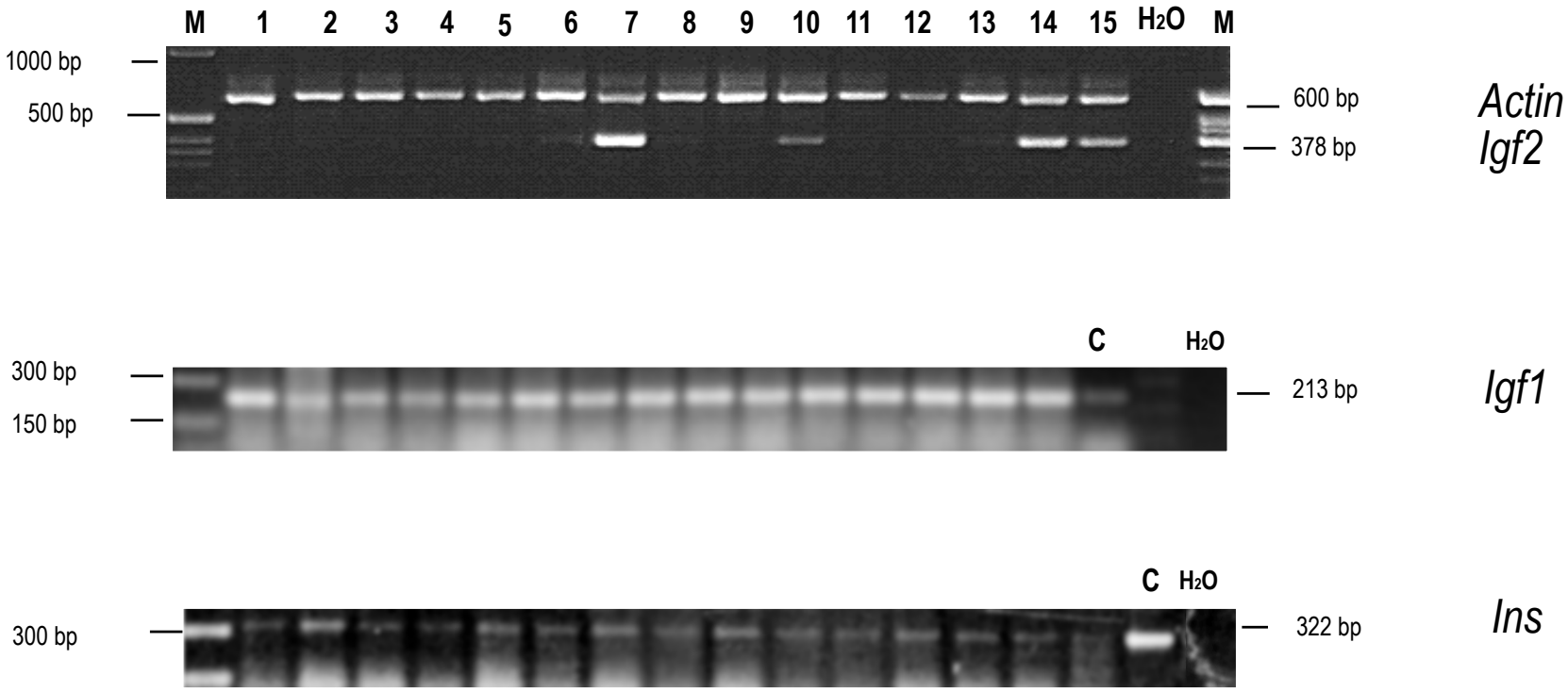


Colobran R *et al. Hum. Mol. Genet.* 2011;hmg.ddr247

Human Molecular Genetics

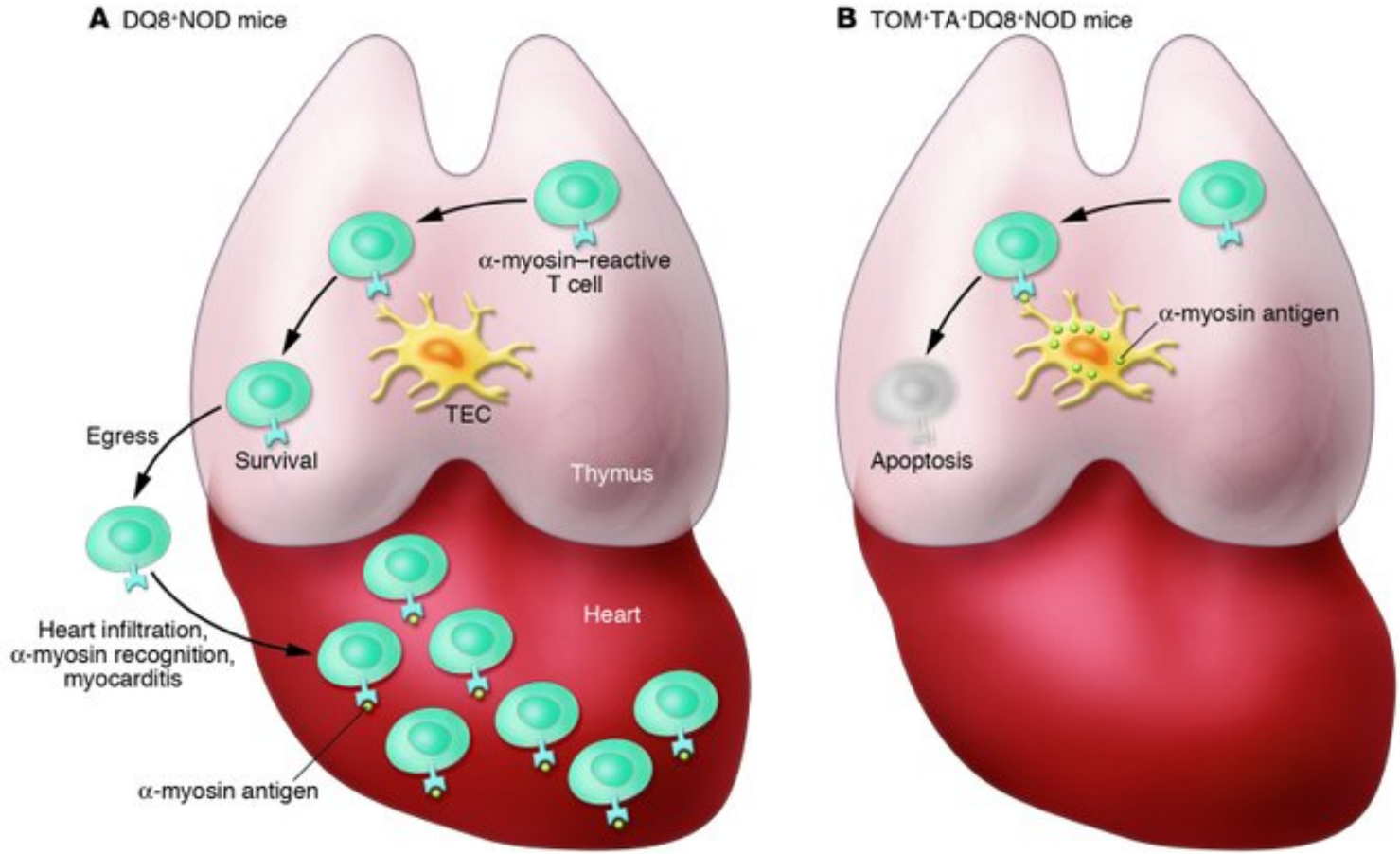
Transcription of *Insulin*-related genes in the thymus of BB rats

Diabetes-prone BB rats



Kecha O *et al.*, *Diabetes Metabolism Research*, 2001

Impaired thymic tolerance to α-myosin directs autoimmune myocarditis



Lv H *et al.* (2011) *J Clin Invest* **121**:1561-73

The role of the thymus in the development of autoimmunity

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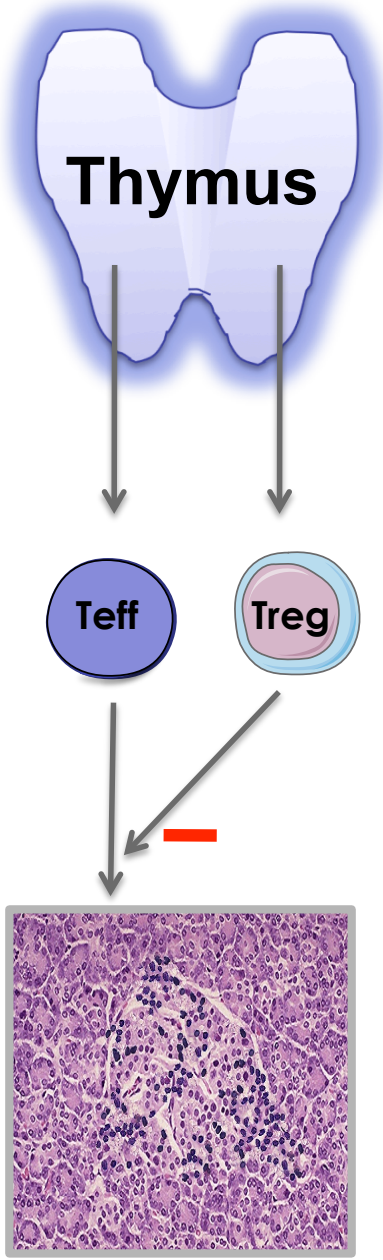
- Deletion of T cells with high affinity for TSA.
- Selection of CD4+ CD25+ Foxp3+ nTreg, specific of TSA.

Thymus physiopathology

- Absence or decrease in thymic expression/presentation of TSA
  (APECED, Down syndrome, BB rat, NOD…)
- Enrichment of T-cell repertoire with 'forbidden' self-reactive T cells (Teff).
- Decrease in selection of nTreg with specificity TSA.

Bridge between self-reactive Teff and peripheral autoantigens

- Role of intra- and extra-MHC loci.
- Role of environmental factors (viruses, diet, vitamin D deficiency, stress…).



Geenen V & Chentoufi AA (2011) *Clin Dev Immunol*

General conclusions

« Take-home message »

- ✓ A thymus dysfunction in T-cell education to self-antigens is the primary event in the development of organ-specific autoimmunity (such as autoimmune thyroiditis).
- ✓ Since T-cell self-education occurs during fetal development, most of autoimmune diseases are programmed during fetal life.
- ✓ Resulting form this thymic defect in T-cell self-education, the enrichment of T-cell repertoire with self-reactive T cells and its deficiency in self-specific nTreg is a condition **necessary but not sufficient** for priming the autoimmune response.

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Jean Rubay, MD, PhD

RÉGION WALLONNE

Waleo 3 - Tolediab

First Spin-off - ThymUP

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