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Molecular classification of pituitary adenomas

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Purpose

The 2004 edition of the WHO text “Histological typing of endocrine tumors” classified pituitary adenomas (PA) on the basis of their histological and immunohistochemical characteristics. Recent advances on the knowledge of the molecular patterns of these tumours may allow establishing a molecular classification with higher accuracy and specificity than previous one.

Methods

Within the pale of the multicenter Spanish Molecular Registry of Pituitary Adenomas (REMAH), a multicentre clinical-basic project, we had obtained the molecular phenotype of 172 PA. Expression levels of 26 genes were measured by qRT-PCR, including all pituitary hormones, receptors for somatostatin, dopamine, and others: growth hormone-releasing hormone receptor, gonadotropin-releasing hormone receptor, type 1 corticotropin-releasing hormone receptor, arginine vasopressin receptor 1b and type 1 ghrelin receptor, and three housekeeping genes for normalization. 9 healthy pituitary from autopsies were used as calibrator reference.

Results

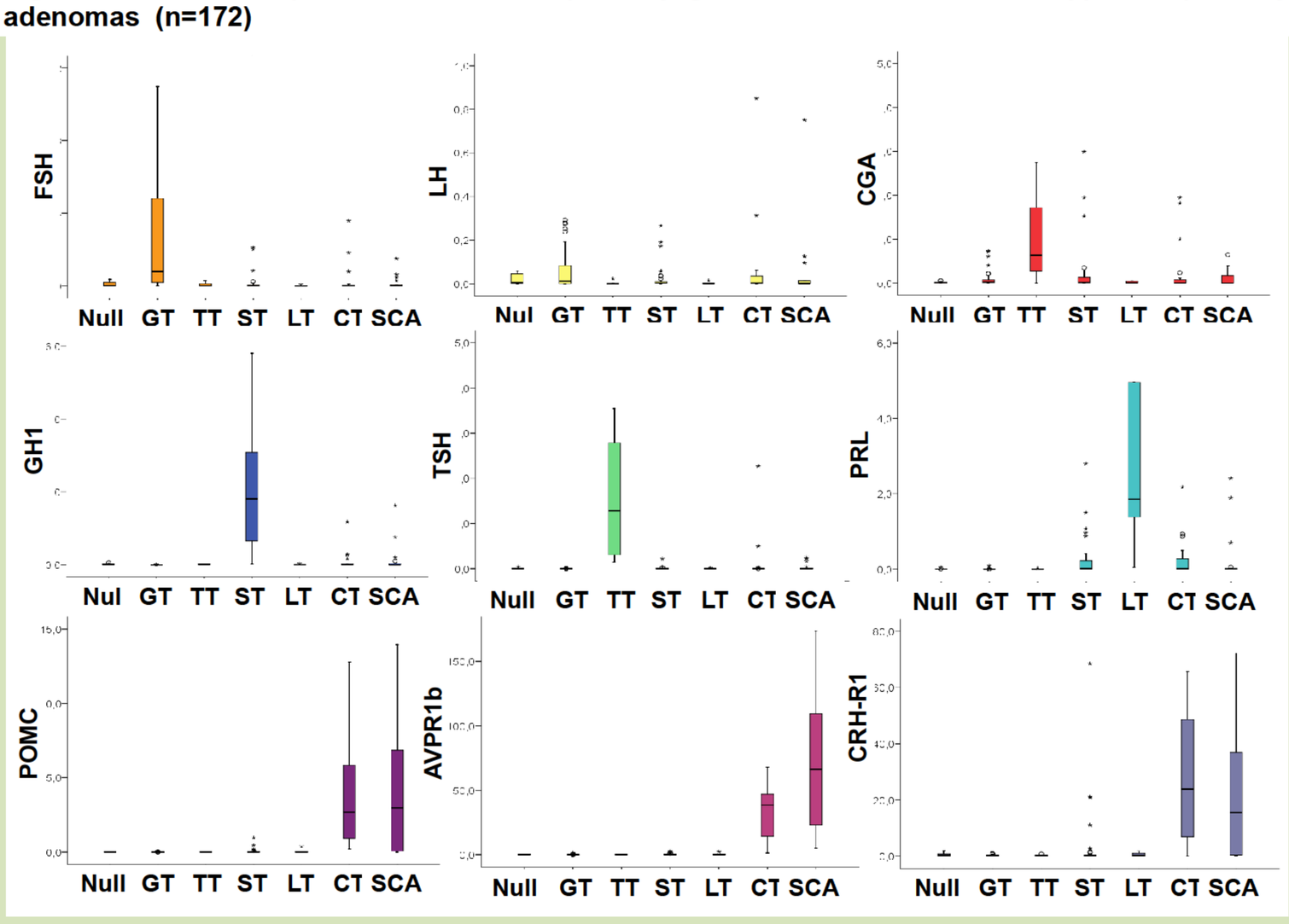
Based on the established clinical diagnosis: **Functioning PA** (**FPA**: somatotroph, corticotroph, tirotroph and lactotroph adenomas) and **Non-Functioning PA** (**NFPA**: gonadotroph, silents and null cell adenomas), and on the immunohistochemical data, we have determined the gene expression ranges in each adenoma subtype.

FPA and NFPA presenting expression of several genes, were subclassified depending on the dominant expression (fig. 1). We established as "gold standard” the p25 expression of each gene in the complete sample of each adenoma subtype. On the basis of our results, we have been able to define the molecular classification of pituitary adenomas showed in table 1.

Table 1. Molecular classification of pituitary adenomas

Subtype PA		Dominant Expression	Clinical symptoms
Corticotrophs (CT)		POMC, AVPR1 and CRH-R1	Cushing’s syndrome
Somatotrophs (ST)	Pure	GH	
	Mixed	GH, PRL	Acromegaly
	Plurihormonal		
Lactotrophs (LT)		PRL	Galactorrhea and/or hypogonadism
Thyrotrophs (TT)		TSH and α-Subunit	Hyperthyroidism
Gonadotrophs (GT)		FSH, LH or/and α-subunit	
	FSHomas	FSH	
	LHomas	LH	
	Mixed	combinations of FSH, LH and α-Subunit	
Silent Corticotrophs (SCA)		POMC, AVPR1 and CRH-R1	Nonfunctioning PA
Silent Tirotrophs		TSH	
Null Cell Adenomas (Null)		Without any hormone’s gene expression	
Multihormonal		Combination of different hormones	

Figure 1. Level of expression of several pituitary genes in the different subtypes of pituitary adenomas (n=172)



Pituitary hormones (FSH: Follicle Stimulating Hormone; LH: Luteal Hormone; CGA: Gene encoding alpha subunit; POMC: Proopiomelanocortin (ACTH precursor); GH: Growth hormone), and receptors involved in the synthesis and secretion of ACTH (AVPR1b: Vasopressin Receptor 1b; CRH-R1: Corticotropin Releasing Hormone Receptor 1).

Conclusions

Advances in the molecular knowledge of the pathogenesis of PA may allow a more specific classification of PA, with higher accuracy than the immunohistochemical one, especially in the case of NFPA, helping physicians to better identify and manage these tumors.

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