Endokrynologia Polska
DOI: 10.5603/EP.a2020.0090
Volume/Tom 72; Number/Numer 1/2021
ISSN 0423–104X, e-ISSN 2299–8306

Pituitary transcription factors in the immunohistochemical and molecular diagnosis of pituitary tumours — a systematic review

Iulia Florentina Burcea[1, 2], Valeria-Nicoleta Năstase[1], Cătălina Poiană[1, 2]

[1]*"C.I. Parhon" National Institute of Endocrinology, Bucuresti, Romania*
[2]*Department of Endocrinology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*

Abstract

Introduction: Although histopathology remains in the first line of the diagnosis of pituitary pathology, immunohistochemistry and molecular biology are currently in charge of providing a more accurate characterisation of tumours in this field.
Material and methods: A systematic review of the literature was performed, using the PubMed and SCOPUS databases, with terms that included transcription factors involved in the development of pituitary tumours: T-PIT, PIT-1, and SF-1.
Results: The results showed different perspectives, but the evidence is in favour of a multifold immunohistochemical analysis that must include pituitary transcription factors for a highly accurate diagnosis, prognosis, and guidance of (multimodal) therapy.
Conclusions: By using transcription factors, the understanding of the structure and function of the recently defined pituitary neuroendocrine tumours has made significant progress. This approach brings the (sub)classification of pituitary tumours, using cell types and cell lineages, with clinical and molecular implications and therapeutic results. **(Endokrynol Pol 2021; 72 (1): 53–63)**

Key words: *pituitary adenoma; pituitary transcription factors; immunohistochemistry; aggressive; systematic review*

Introduction

Although known as being of monoclonal origin, several studies showed that pituitary adenomas (PAs) have more than one cell type [1] and contain tumour clones that arise independently from individual cells [2]. There is a debated hypothesis about the existence of self-renewing sphere-forming cells, which resemble cancer stem cells and can also be considered as a sign of cell differentiation [3]. The supposed multipotent cells contained by the PAs are responsible for the growth, invasion, and resistance to specific therapy, being capable of differentiating into other cell types of the tumour [4, 5].

In 2017, the World Health Organisation (WHO) revised the classification of tumours of endocrine organs [6] and established more clear groups of primary adenohypophyseal tumours, concerning their cell lineages and resulting in a better way to classify these tumours. In consequence, the lineage transcription factors (TFs) have been proposed to be used in the diagnosis, associated with the clinical and imaging characteristics, immunohistochemistry of hormones, proliferation factors, and other specific markers.

The term pituitary neuroendocrine tumour (PitNET) was proposed to replace the term adenoma [7], based on the resemblance and unpredictable behaviour with extra-pituitary NETs, terminology considered rather confusing and debatable by other experts [8]. A multistep approach of these tumours is necessary. Besides the clinical and radiological characteristics, it is relevant to prepare a histological report that includes histology, immunohistochemistry (IHC) analysis (hormones, cytokeratin low-molecular-weight keratin (LMWK) pattern, proliferation markers, chromogranin A), TFs, and, if required, p53, somatostatin receptors (SSTRs), oestrogen receptor alpha (Erα), and methylation of O6-methylguanine-methyltransferase (MGMT) [9]. Validated on 1470 patients in four studies, the five-tiered classification proposed by the European Pituitary Pathology Group (EPPG) identifies seven main morphological and functional PAs types and has a defined prognostic value [10].

Although recent protocols for multimodal treatment of (functional) PAs have improved the control of the disease and the cure rate [11], the need for extensive and specific diagnosis is always required.

Dr Iulia Florentina Burcea, "C. I. Parhon" National Institute of Endocrinology, Blv. Aviatorilor nr 34–36, 011863 Bucuresti, Romania; e-mail: iuliafburcea@yahoo.com

Material and methods

We followed the PRISMA (preferred reporting items for systematic reviews and meta-analyses, 2015) guidelines in the literature review process.

In the present review, a comprehensive literature search was performed using PubMed and SCOPUS databases, from January 2000 to June 2020, with the following key words: (i) T-PIT and pituitary adenoma, (ii) PIT-1 and pituitary adenoma, and (iii) steroidogenic factor 1 (SF-1) and pituitary adenoma (Fig. 1). Cited references within articles were also searched for relevancy to the topic. The results were summarised, and the following article presents a critical discussion of the most significant results. Table 1 summarises the studies included in the review that evaluated a minimum of 30 patients and their main disclosures.

Exclusion criteria were as follows: (1) reviews, (2) case reports, (3) letters to editor, (4) editorials, (5) commentaries, (6) animal models, and (7) in vitro studies.

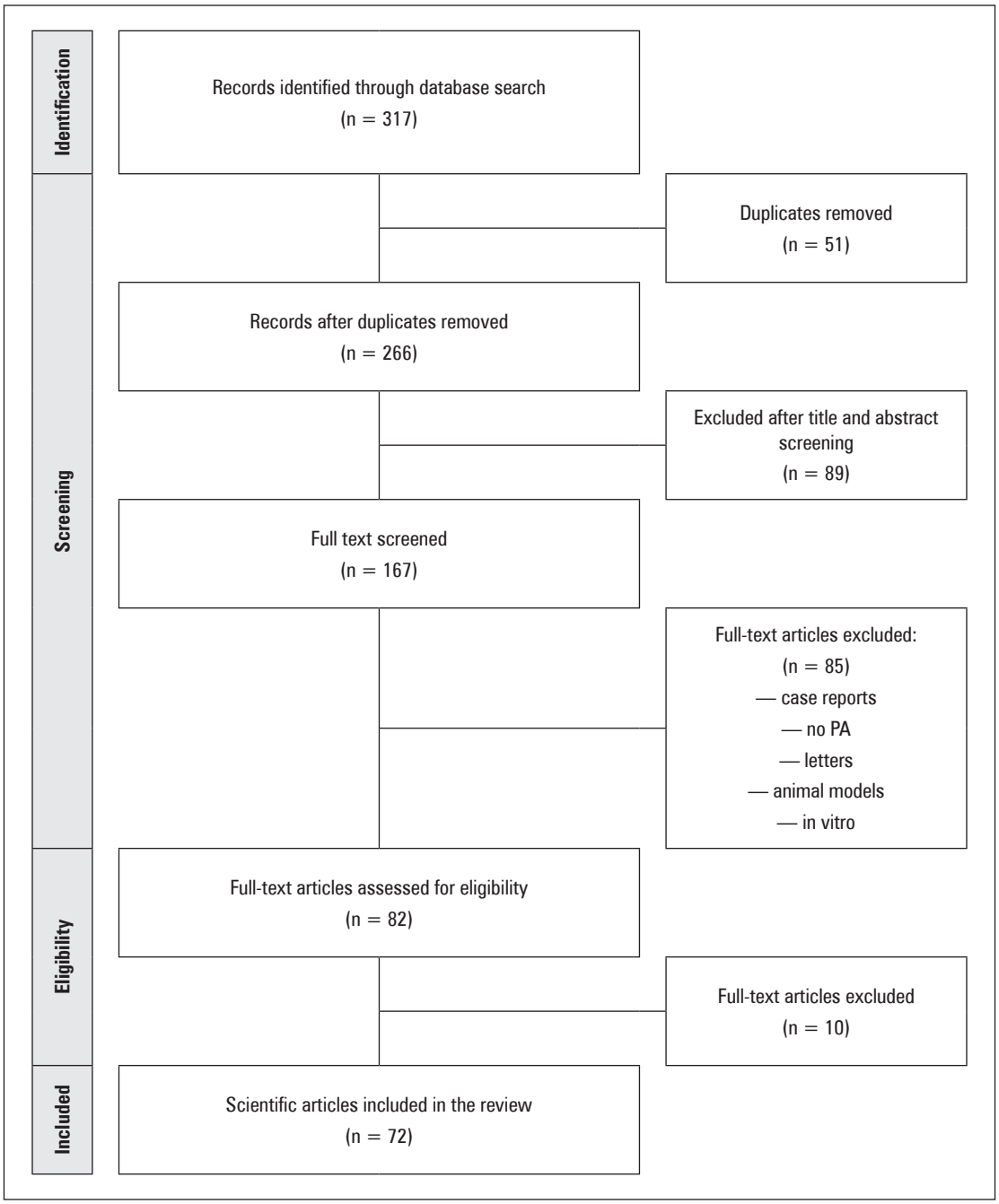

Figure 1. *Flow of literature review process*

Table 1. *Studies included in the review that evaluated at least thirty patients and their main disclosures*

Study details	Year	No. of patients	Studied TFs	Method	Relevant findings
Sano T. et al. [76]	2003	46	T-PIT SF-1	RT-PCR	"Honeycomb Golgi" vacuolar aspect can appear in corticotroph (T-PIT lineage) and gonadotroph (SF-1 lineage) PAs
Suzuki M. et al. [32]	2008	89	PIT-1 T-PIT SF-1	IHC RT-PCR	Aberrant TFs T-PIT and SF-1 function synergic during tumorigenesis PAs that express ACTH and a-subunit may derive from ACTH-committed progenitor cells, set up with T-PIT, NeuroD1, SF-1 and DAX-1 Null cell PAs also express various TFs
Cooper O. et al. [77]	2010	52	PIT-1 T-PIT SF-1	IHC	SCAs were positive for ACTH, SF-1, NeuroD1, DAX-1, but T-PIT negative, with 63% recurrence rate Functional corticotroph PAs were immunopositive for ACTH, SF-1, NeuroD1, T-PIT, but negative for DAX-1 GAs were immunopositive for SF-1, NeuroD1, DAX-1
Yunoue S. et al. [78]	2011	70		IHC RT-PCR	Absence of co-expression of PIT-1, SF-1, NeuroD1 or chromogranin A with CD133 in PAs CD133+ cells in PAs are involved in pituitary tumourigenesis as endothelial progenitors
Nishioka H. et al. [57]	2015	119	PIT-1 T-PIT SF-1	IHC RT-qPCR	2/3 of the hormone negative PAs were positive for SF-1 and/or ERα (gonadotrophs were ¾ of NFPAs) T-pit is a reliable marker of POMC-expressing pituitary cells justifies the role of RT-qPCR T-PIT over hormones in determining the corticotroph origin of PAs
Mete O. et al. [79]	2016	31 (954)	PIT-1 SF-1	IHC	All silent subtype 3 PAs were diffusely positive for PIT-1, most macroadenomas, high proportion associated with MEN1 Establishes the PIT-1 cell lineage origin of silent subtype 3 PAs and proposes the term "poorly differentiated PA of PIT-1 lineage"
Sjöstedt E. et al. [80]	2017	246	PIT-1 T-PIT SF-1	IHC	97.2% of PAs could be precisely classified into SF-1, PIT-1, and T-pit cell lineage PitNETs (7/246 null-cell PAs) A specific T-pit antibody has a potential importance for tumours of corticotroph differentiation of non-pituitary origin The anti-T-pit antibody is a reliable marker of corticotroph cell differentiation
Lee J. C. et al. [23]	2017	150	PIT-1 SF-1	IHC	PIT-1 positivity is rare in previously classified null-cell PAs Hormone-negative PAs of PIT-1 lineage are rare PIT-1 can be useful in identifying sparsely granulated somatotroph PAs negative for GH
Nishioka H. et al. [81]	2017	128	PIT-1 SF-1	IHC	SCAs and PIT-1 lineage silent adenoma are more aggressive than gonadotroph PAs
McDonald W. C. et al. [82]	2017	136	PIT-1 SF-1	IHC	Significant positive correlation between PIT-1 and PRL, GH, TSH and significant negative correlation with SF-1 SF-1 correlated with FSH and LH staining The routine use of FSH and LH can be replaced with SF-1 in IHC analysis of PAs
Mete O. et al. [16]	2018	1055	PIT-1 T-PIT SF-1	IHC	40% surgically resected PAs are clinically NFPA, the majority being GAs SF-1 is the most sensitive and specific factor for GAs The incidence of null-cell PAs was only 4.5%
Langlois F. et al. [34]	2018	39 (814)	PIT-1 SF-1	IHC	SCAs are aggressive, with recurrence rate of 36% T-PIT disfunction can be an initial disturbance in the development of SCA T-PIT is involved in phenotypic silence of SCAs Compared to SGAs, SCAs recurred 3 times more often and had 6 times more often the need for radiotherapy
Torregrosa-Quesada M.E. et al. [14]	2019	56 (251)	PIT-1 T-PIT SF-1	IHC RT-qPCR	RT-qPCR complements IHC and improves the typification of plurihormonal PIT-1 and unusual tumours CAs expressed T-PIT and GATA2, GAs expressed GATA2 and NeuroD1 High concordance found: T-PIT, PIT-1, no concordance of SF-1 GATA-2 gene expression was concordant to SF-1 IHC expression

Table 1. *Studies included in the review that evaluated at least thirty patients and their main disclosures*

Study details	Year	No. of patients	Studied TFs	Method	Relevant findings
Tamanini J. V. G. et al. [31]	2020	30	PIT-1 T-PIT SF-1	IHC	PIT-1 positivity was highest in acromegaly patients T-PIT positivity was higher in Cushing's disease than acromegaly and NFPA SF-1 did not differentiate NFPA from the other two groups
Turchini J. et al. [35]	2020	265	PIT-1 T-PIT SF-1	IHC	263 tumours were compared for GATA-3 and TFs expression 28% triple negative tumours, from which 64% had GATA-3 expression GATA-3 positivity is found in most of the gonadotroph PAs and all thyrotroph PAs
Peng A. J. et al. [15]	2020	235	PIT-1 T-PIT SF-1	IHC	A machine learning model using preoperative T2-weighted MRI images can IHC classify PA subtypes, with an MRI-based radiomic analysis SCAs and Crooke's cell PAs are more aggressive and recurrent after surgery

TF — transcription factor; T-PIT — T-box family member TBX19; PIT-1 — pituitary specific POU class homeodomain transcription factor; SF-1 — steroidogenic factor 1; IHC — immunohistochemistry; RT-PCR — real-time polymerase chain reaction RT-qPCR — real-time quantitative reverse transcription PCR; PA — pituary adenoma; ACTH — adrenocorticotropin; NeuroD1 — neurogenic differentiation 1; DAX-1 — transcription factor product of the gene NR0B1; SCA — silent corticotroph adenomas; ER — estrogen receptor; NFPA — non-functioning pituitary adenoma; POMC — pro-omiomelanocortin; PitNET — pituitary neuroendocrine tumors; GH — growth hormone; PRL — prolactin; TSH — thyroid-stimulating hormone; FSH — follicle-stimulating hormone; SGA — silent gonadotroph adenomas; MRI — magnetic resonance imaging

REVIEW

Epidemiology

Most pituitary tumours of adenohypophyseal cell differentiation are benign and indolent (99.9%), the largest percentage being clinically inapparent and detected at autopsy. From all PAs discovered during lifetime, the prevalence of clinical significance is 1:1000 and from the ones that go to surgery, 10% manifest an atypical, NET-like behaviour (excepting prolactinomas, which are rarely treated neurosurgically) [8].

The prevalence of PAs increases with age, the peak age for diagnosis being 30–60 years, and some are associated with sex: female patients account for the majority of somatotroph and corticotroph PAs, while males for the majority of gonadotroph PAs, as found in a cohort of 250 pituitary tumours [12]. Also, regarding the paediatric population, boys have a more aggressive forms of Cushing's disease than girls [13]. In the above-mentioned cohort, the proportion of invasive high-risk adenomas was 28.8%, having a recurrence rate of 17.8% and for apoplexy of 8.2% [12].

Plurihormonal adenomas appear at a mean age of 40.2 (± 12.5) years for PIT-1-positive ones, with female predominance, and 47.05 (± 16.4) years, with male predominance for the ones with unusual IHC combinations, as reported recently. Their frequency, found by molecular study to be 3.6%, was observed to rise substantially by IHC analysis alone (12.5%) in a study [14].

In a total of 235 histologically confirmed PAs, PIT-1 (59.09%) and T-PIT family tumours (58.18%) appeared more in females, in contraposition with SF-1 tumors, which were more frequent in males (58.57%) who presented with older age. Concerning age, the mean for T-PIT tumours was 58.73 years old, 42.87 years old for PIT-1 tumours, and 45.44 years old for SF-1 tumours [15]. The incidence of gonadotroph tumours was found to rise with age, as well as the predominance of PIT-1 lineage tumours in younger patients [16].

Histological evidence

Molecular considerations

Identifying the protein expression (by IHC) and the dominant gene (by qRT-PCR) of the pituitary transcription factors gives the opportunity to classify and define different PA subtypes. Differences between real-time polymerase chain reaction (RT-PCR) and real-time quantitative reverse transcription PCR (qRT-PCR)results reflect the higher sensitivity of the latter methodology in samples expressing low transcript levels.

The pituitary adenohypophyseal tumour cytogenesis involves three lineages that require the presence of transcription factors for hormonal gene expression. The PIT-1 family is the most complex of all and concerns somatotroph, lactotroph, mammosomatotroph, and thyrotroph cells. Despite the fact that PIT-1 mRNA transcripts are present in all pituitary cells, PIT-1 protein is present only in these types of tumours. It gives rise to densely or sparsely granulated tumours, the poorly differentiated tumours of PIT-1 lineage arising from a PIT-1 stem cell. For development of gonadotroph cells and tumours the following are required: SF-1, ERα, GATA-binding protein 2 (GATA-2), Lhn4, and T-PIT and neurogenic differentiation factor 1 (NeuroD1) for corticotrophs, giving rise also to densely granulated, sparsely granulated, and Crooke cell corticotroph tumours [17]. Using the 2017 WHO

classification, < 5% of pituitary tumours are diagnosed as null cell adenomas [12].

In a subset of 56 patients from a large series of PAs (n = 251), a good correlation was demonstrated between immunohistochemistry and molecular detection of pituitary transcription factors, the concordance being high in immunopositivity and expression of T-PIT and PIT-1. The gene expression and immunodetection of SF-1 did not correlate, as opposed to the good concordance found for GATA-2 [14]. This demonstrates the utility of RT-qPCR in complementing the IHC analysis, especially in null cell or plurihormonal tumours, and suggests that RT-qPCR should be added to routine clinical practice. In the same study, the incidence of null cell adenoma was reduced from 16.3% to 3.2% by using molecular studies of the specific TFs [14]. In several series, the percentage of null cell tumours decreased from 12.7% to 7% and from 17% to 12.5% by using molecular analysis [18, 19].

Silent pituitary tumours are hormone-immunoreactive tumours without clinical signs of hormone hypersecretion. In a cohort of silent somatotroph adenomas, they were more frequently sparsely granulated, with a lower percentage of immunoreactivity for growth hormone (GH), PIT-1, and $SSTR_{2A}$ than in acromegaly cases, suggesting the probability to be less differentiated and having clinically "aggressive" behaviour [20]. As demonstrated, silent corticotroph adenomas and the ones with PIT-1 positivity are more aggressive than silent gonadotroph adenomas [21].

Null cell adenomas are immunonegative for both hormones and TFs of anterior pituitary development. Although IHC is negative for all hormones, they have organelles for hormone synthesis and release, and some can produce glycoprotein subunits in vitro, thus sustaining the supposition of resemblance with silent gonadotroph adenomas [22]. Assessing 147 pituitary adenomas immunonegative for GH, prolactin (PRL), adrenocorticotropin (ACTH), and thyroid-stimulating hormone (TSH), 46% expressed SF-1. Of the other cases, 6% were positive for PIT-1, the other cases being potential null cell adenomas [23]. In a series of 1071 surgically treated pituitary adenomas, null cell tumours (0.6%) represented 5% of hormone-negative adenomas, 1.2% of non-functioning pituitary adenomas (NFPA), with a poor ultrastructural differentiation and aggressive clinical and neuroimaging aspects [24].

Although about 40% of surgically resected pituitary tumours are NFPAs, the majority are identified as of gonadotroph lineage [16]. However, as reported by the EPPG experts, about 15–20% of PAs have a limited/absent/unusual pituitary hormone expression. In such cases, chromogranin A and TFs are useful for defining the pituitary neuroendocrine origin and to classify some of them in corticotroph, gonadotroph, or plurihormonal PIT-1-positive PAs [9, 10].

Another part played by the TFs is enlightening the histopathological terminology of hyperplasia. Along with reticulin, TFs can help in distinguishing the pituitary hyperplasia from ectopic secretion of GHRH or CRH or that secondary to primary hyperthyroidism [25].

T-PIT

T-PIT is a T-box factor found in the two pituitary pro-opiomelanocortin (POMC) lineages, the melanotrophs, and corticotropes, and it can initiate differentiation into POMC-expressing lineages [26]. There is a strong correlation between mRNA expression of T-PIT and POMC in Cushing's disease (especially due to macroadenomas), but also in silent corticotroph adenomas [27]. T-PIT, along with NeuroD1, plays a very important role in the differentiation of corticotroph lineage and transcription of POMC gene, and both are required to achieve corticotroph differentiation (through interaction with Pitx1) in pituitary and non-pituitary tumours [28]. Cooperating with these two, Nur77 (nerve growth factor-inducible factor-B) also induces POMC expression, in some cases being the only factor to differentiate subclinical Cushing's disease from Cushing's disease, as demonstrated in a comparative study that included 13 ACTH-secreting adenomas [29].

Although NeuroD1 is considered corticotroph specific, it is overexpressed also in some non-corticotroph pituitary adenomas, possible due to the activation of molecular factors such as neurogenins. In a study on 51 pituitary adenomas, NeuroD1 expression was higher in corticotroph and NFPA, while neurogenin 2 expression was higher in PIT-1-dependent pituitary adenomas, especially in those with pre-operative pharmacological treatment [30]. Compared to T-PIT, which can be considered a marker of corticotroph tumours, NeuroD1 has poor discriminatory usefulness [14].

A study comparing 13 patients with Cushing's disease with 4 carcinoid tumours with ectopic ACTH secretion revealed that there is no difference on the expression of T-PIT and NeuroD1 between these two entities and they are also expressed in ACTH-negative carcinoid tumours, indicating that some other transcription factors can be involved in inducing POMC mRNA in ectopic ACTH-secreting tumours [28].

T-PIT family tumours occur with higher frequency in females, the mean age ranging from 23 to 75 years, and they are more frequently associated with grade 0–2 lesions, as observed by Peng et al. [15]. Cushing disease patients have the highest nuclear expression of T-PIT (versus acromegaly and NFPA) [31]. Most corticotroph cell adenomas belonging to the ACTH/POMC lineage are mono-hormonal [32].

Because of the lack of reliable T-PIT antibody, tumours that express this transcription factor are still difficult to diagnose; thus, combining IHC analysis with preoperative magnetic resonance imaging (MRI) coronal T2-weighted images adds precision to the diagnosis and classification [15].

Silent corticotroph adenomas (SCA) are tumours with clinical and morphological features of both corticotrope and gonadotroph adenomas. In a study conducted by Cooper et al., although they expressed ACTH to a similar degree as functional corticotroph adenomas, clinically they behaved more like an NFPA [33]. They lack T-PIT expression, but incorporate corticotroph markers ACTH and NeuroD1 and gonadotroph markers SF-1, alpha subunit of glycoprotein hormones (alpha-GSU) and DAX-1 [33]. In a large cohort of 814 surgically resected PAs, only 4.8% (39) were SCA and had similar tumour size and invasiveness compared to silent gonadotroph adenomas (SGA), but the first ones were three-times more aggressive. They have a special potential to change their phenotype in time, and their phenotypic silence is related to T-PIT, its dysfunctionality probably being a precocious abnormality in a SCA [34].

In 43 out of 283 cases, the application of the three transcription factors by IHC revealed the specific diagnosis. In the same cohort, there were a significant number of triple-negative tumours (28%, without hormonal or transcription factor expression) that showed GATA-3 expression, strongly indicating a gonadotroph or thyrotroph lineage [35]. Some corticotroph tumours also express GATA2, as well as some gonadotroph tumours, which express NeuroD1, this co-expression suggesting the existence of a cortico-gonadotroph entity that also expresses SF-1, but little or no T-pit, and clinically behaving like silent corticotroph adenomas [14].

In a cohort of 24 patients with pituitary tumours, T-PIT expression in corticotroph tumours was 27-fold higher than in controls. The expression of T-PIT had a constitutive pattern in somatotropinomas and a heterogeneous one in NFPA, respectively [36].

Regarding therapy, the effect of R-roscovitine on corticotroph tumours in a recent study showed that it inhibits POMC and T-PIT by targeting the cyclin E/E2F1 pathway, with decreased ACTH expression, thus being a therapeutic pathway in Cushing disease as an inhibitor of cyclin-dependent kinase 2 [37]. USP8-mutated corticotroph PAs showed higher SSTR5 expression, which helps in the prediction of response to somatostatin analogue pasireotide [38].

PIT-1

The role of PIT-1 in cytodifferentiation was acknowledged when PIT-1 gene expression was found to be closely related to the production of GH, PRL, and/or TSH in pituitary development [39].

PIT-1, a member of the POU-domain family, is a nuclear transcription factor involved in the normal differentiation and growth of somatotroph, mammosomatotroph, lactotroph, and thyrotroph cells, as well as in the abnormal cell proliferation of pituitary adenomas, PIT-1 protein being highly correlated with IHC tumour staining for GH, TSH, and PRL [40]. PIT-1 is expressed after Prophet of PIT-1 (PROP1) during embryogenesis and is maintained in the adult pituitary somatotropes, lactotropes, and thyrotropes [41]. PROP1 showed overexpression in tumour pituitary samples, 18-fold higher in corticotropinomas, 10-fold higher in somatotropinomas, and 3-fold higher in NFPA, although PROP1 is not associated with corticotroph differentiation but in maintaining the cells implicated in corticotroph differentiation [36].

A recent molecular classification of PAs using somatic, chromosomal alterations and miRNome, methylome, and transcriptome combined identified PIT-1 lineage as the main separator/classification driver in a total of 134 included patients. The PIT-1 lineage was associated with transcription of different markers and chromosomal instability [38].

Somatotroph cells are the only pituitary secretory cell expressing GDNF family receptor alpha-1 (GFRα1), glial cell line-derived neurotrophic factor (GDNF), and Ret, the last inducing PIT-1 and p53 over-expression, a pattern that is maintained in all somatotroph adenomas [42, 43]. For a precursor cell to become somatotroph, it requires PIT-1, and for sufficient PIT-1 expression, Ret is needed. Ret-induced PIT-1 over-expression determines apoptosis of aberrant somatotrophs, this explaining the fact that somatotropinomas have a normal Ret/GFRα1 and GDNF expression and do not metastasize [43].

By definition, somatotroph tumours have nuclear positivity for PIT-1 and cytoplasmatic GH positivity. Oestrogen receptor positivity in these tumours correlates with prolactin positivity. Poorly differentiated tumours of PIT-1 lineage (the former silent subtype 3 adenoma) express PIT-1 and a variable expression of GH, PRL, ER, or α-subunit [16].

In some of the first pituitary adenoma series studied by RT-PCR, a quantitative difference from normal pituitary tissue, with correspondence to sequencing of PIT-1 DNA in prolactinomas was not demonstrated, which revealed no mutation compared to normal pituitary tissue [44, 45]. In other studies, PRL/GH-secreting adenomas and GH- and PRL-secreting adenomas had a 2.5- to 5-times higher PIT-1 expression. PIT-1 was fond to be identical in size in normal pituitary and the above-mentioned adenomas, when it is overexpressed

to an extent correlated with the predominant cellular tumoral type [45]. PIT-1 gene expression was also found in NFPA, one explanation being the ability of stem cells to differentiate towards any of the three phenotypes [46].

In a subset of prolactinomas, a somatic mutation in splicing factor 3 subunit B1 was found to correlate with a stronger binding of PIT-1, which leads to excessive prolactin secretion, higher prolactin levels, and shorter progression-free survival [47]. In functioning prolactinomas, PIT-1 mRNA expression tends to be high, with a low GHRH-R mRNA expression, unlike the positive correlation found in functioning somatotroph adenomas. In the silent variants of both of these tumours, the levels of PIT-1 and GHRH-R are similar to the corresponding functional ones [48].

Known for their versatile clinical behaviour, TSH-producing pituitary adenomas range from typical to clinically silent, indicating the importance of adequate IHC analysis. In a subset of TSH-secreting pituitary tumours (silent macroadenomas and functional PA), all had the same histopathological features. PIT-1 was detected by immunostaining in 16 out of 18 functional tumours and in 9 of 10 of the silent ones, with GATA-2 co-expression in almost all (by IHC and/or RT-PCR). PIT-1 and GATA-2 expression did not correlate with age, tumour size, invasive character, or the level of TSH, but both were detected in all silent and two of the functional adenomas. No correlations were found between Ki-67 index, PIT-1, GATA-2, $SSTR_{2A}$, and $SSTR_5$ [49] Thyrotroph tumours are monohormonal and plurihormonal, the latter co-expressing GH or PRL, both expressing high levels of PIT-1 and $SSTR_{2A}$, with a predominance of clinical hyperthyroidism signs in the plurihormonal ones [50]. TSH-secreting adenomas may originate from early totipotent progenitor cells from which derive GH-, PRL-, and TSH-secreting cells, a mechanism that can be part of the plurihormonality of these tumours [51].

Plurihormonal pituitary tumours are divided into tumours with PIT-1 positivity and tumours with unusual immunohistochemical combinations (without a determinant transcription factor). They can be identified only by pathologic assessment and have an aggressive behaviour in about 55.5% of cases. The latter arise from different pituitary cell lineages. The PIT-1-positive plurihormonal adenomas (previously known as silent subtype 3 adenomas, although a criticised analogy) have a variety of focal-scattered immunoreactivity for GH, PRL, and TSH (the PIT-1 lineage hormones), usually clinically presenting as NFPAs, a few cases having clinical expression of GH or PRL secretion [52]. PAs that belong to the PIT-1 family often have an overexpression of alpha subunit, but this characteristic does not necessary classify them as being plurihormonal [53].

Multiple PAs comprise two or more distinct tumours with different pituitary cell types, with low incidence (0.4–1.3%) [53]. In a series of 1055 pituitary adenomas, 13 had synchronous multiple tumour components (1.2% of cases), 12 were double and one was triple. The triple association had an unusual plurihormonal tumour, which was positive for GH, gonadotropin (FSH), PIT-1, and SF-1, along with two other smaller tumours: a sparsely granulated lactotroph PIT-1 and ER-positive and a gonadotroph tumour positive for SF-1 and FSH, but negative for PIT-1 and GH. In all cases, the aggressive histological subtypes predicted the potential of recurrence and of persistent disease [54]. The highest incidence of plurihormonality has been found in PIT-1-positive tumours [16].

Regarding SSTR, $SSTR_3$ expression is higher in corticotroph adenomas compared to PIT-1 positive, gonadotroph, and NFPAs. $SSTR_5$ expression is highest in PIT-1-positive adenomas, followed by corticotroph, gonadotroph, and NFPAs. When comparing primary to recurrent adenomas, $SSTR_{2A}$, $SSTR_3$, and $SSTR_5$ are lower in recurrent PIT-1-positive pituitary adenomas when compared to the primary group [55].

Silent adenomas of PIT-1 lineage tend to be more common in the young and have a higher Ki-67 index, as found by a study on NFPAs. In the same study, 4 out of 5 patients with silent PIT-1 adenomas with incomplete tumour resection underwent adjuvant radiotherapy [56].

PIT-1-positive silent pituitary adenomas (indicating differentiation into somatomammothyrotroph family) and silent corticotroph adenomas have a more aggressive behaviour than gonadotroph adenomas [57], as well as giant adenomas, which tend to be resistant to surgical treatment and have a high incidence of recurrence, features more common in the mentioned histological subtypes [58].

SF-1

Steroidogenic factor 1 (SF-1) is expressed in gonadotroph cells, leading to their differentiation [59], as well as in gonadotroph PAs, acting also in the adrenals and reproductive system [60]. Using IHC for SF-1 in diagnosing tumours of gonadotroph lineage, the incidence of 'null cell' pituitary adenomas dropped to around 1% [61].

In a cohort of 30 pituitary adenomas, the frequency of SF-1 immunopositive cellularity was similar in all tumours. SF-1 can be detected along with PIT-1 or T-PIT in patients with acromegaly, Cushing's, or NFPA, leading to the idea of co-expression of TFs [31].

In a recent study, functional tumours proved to be the least common among SF-1 family tumours (8.47%), these being diagnosed with the highest frequency in PIT-1 family tumours (74.55%). The tumours with the

largest diameter and those with grade 3–4 had greater frequency in SF-1 family tumours compared to the ones with grade 0–2, which were more frequent in PIT-1 and T-PIT family tumours [15]. In another cohort (1055 adenohypophyseal tumours), gonadotroph tumours stained positive for SF-1 in 96% of cases, while ER was positive in 82% [16].

Among 89 cases of corticotroph PAs, all were immunopositive for SF-1 and DAX-1. ACTH immunostaining was localised in cytoplasm, whereas SF-1 and GATA-2 were positive in the nuclei. Expression of SF-1, DAX-1, and GATA2 was localised in the α-subunit immunopositive cells, but also diffusely in all tumour tissues. In a subset of 39 cases from the same cohort, immunopositive for only ACTH, all were immunonegative for SF-1 and GATA-2, which do not belong to ACTH cell lineage [32].

Unexpectedly, the gonadotroph subset of a pituitary tumour series expressed similar levels of SF-1 as other PitNET subtypes. Nonetheless, 36.62% of all gonadotroph tumours expressed SF-1 and SF-1 protein, with an expression of GATA2 of 87.32% [14].

In case of triple-negative tumours expressing FSH and LH or ambiguous SF-1 staining, GATA-3 can be an important indicator of thyrotroph or gonadotroph lineage [35].

In a recent molecular classification that analysed molecular classes of PAs by integrated pangenomics found gonadotroph signatures in some corticotroph and somatotroph PAs (GNAS-wild-type somatotrophs with SF1 expression), raising a challenge to the current SF1 lineage tumours and the specificity of this SF-1 for the gonadotroph lineage [38]. This raises a question about the presence of occasional tumours (collision tumours with different lineages) [54], for the presence of trapped non-tumorous tissue in the samples used [25], or for a questionable specificity of the SF-1 lineage [38].

Aggressivity

In PAs, as in all tumours of the central nervous system, a stem gene profile of tumour-initiating cells has been identified, which promote growth and tumour progression [62].

In defining aggressive behaviour, the algorithm should be based on clinical behaviour, neuroradiological features, growth rate, and response to treatment. Aggressive pituitary tumours are large (many are giant, over 4 cm diameter), invasive (Knosp grades 3 or 4, with invasion of the sphenoid sinus), have high growth rates (> 20% and at least 2 mm in 6 months), and resist standard medical treatment (> 20% growth despite surgical, medical, and radiotherapeutic care) [63, 64].

Invasion should be evaluated pre-operatively (MRI), intra-operatively (endoscopic examination), and post-operatively, with Ki-67 (≥ 3%) and mitotic count > 2/10 HPF. P53 is an independent marker of aggressivity and can aid in the diagnosis [65], but only 40% of reports describe a predictive role of this marker regrading invasiveness (comparing to 62% positive correlation for Ki-67) [66]. In several works, the histological proof of invasiveness (infiltration of the adjacent dura) is a more frequent finding than in the surgical evaluation [67, 68]. In a large series of patients, the plurihormonal PAs were the majority (92%) with a Ki-67 of < 3% [53].

As it is known, the entity "atypical adenoma" was removed in the 2017 WHO classification, and replaced to the 'high-risk adenoma', and some PA subtypes are seen as aggressive: lactotroph adenoma in men, sparsely granulated somatotroph adenoma, silent corticotroph adenoma, Crooke cell adenoma, and plurihormonal PIT-1 positive adenoma [69]. Excluding the first entity, which is demonstrated to be aggressive, the other ones are still under confirmation [70].

In AIP-positive PAs (isolated or syndromic) or those from MEN1 or MEN4 syndromes, tumour aggressiveness, larger dimensions, and resistance to conventional treatment has been reported, especially related to disruption of mesenchymal-to-epithelial transition [66, 71]. Other syndromic causes of PAs include Carney complex (PRKAR1A/PRKACB), McCune-Albright (GNAS), HPGL (SDHx, MAX), Dicer (DICER1), Lynch (MLH1, PMS2), or USP8-related (USP8) syndromes [72]. In several studies, only 2 genes (GNAS and USP8) were found mutated in >5% of PAs, no other driver alteration being found for the majority of PitNETs. USP8-mutated corticotroph PAs represent a group with limited aggressiveness (compared to USP8 wild-type PAs) [38, 73].

The exact differences between aggressive PAs and carcinomas are not very well defined and can be two sides of the same coin. After corticotroph PAs, lactotroph ones are the second most-frequent aggressive and malignant [74, 75]. Considering the results of different studies, a Ki-67 over 10% can be considered a marker of malignancy, but not taken per se [70]. Although useful in classifying PAs, pituitary transcription factors alone are not routinely used for the assessment of aggressiveness [64].

Conclusions and future perspectives

Along with hormone assessment, the routine use of pituitary transcription factors (PIT-1, SF1, TPit) in the immunohistochemical analysis of pituitary tumours should be a habit in current practice for a precise diagnosis and avoidance of a misleading one. Their role in pituitary cytodifferentiation and tumourigenesis is

clarified. Although most pituitary adenomas are mainly classified with immunohistochemistry staining for pituitary hormones, transcription factor immunostaining is important in special cases with doubtful differentiation, such as null-cell or plurihormonal adenomas.

The present review provides important information to support the utility of these transcription factors in establishing the origin of the pituitary adenomas and differentiating them from other pituitary entities, such as mesenchymal, stromal, or neuronal pituitary tumours.

The biological relevance and importance of pituitary transcription factors was stated by the WHO in 2017, but also by novel extensive molecular classifications, a bridge between the two being the goal in future management. Their immunohistochemical and molecular study has prognostic value confirmed by several studies on large cohorts of patients. Their analysis could also be useful in predicting the response to treatment and the tumour changes that can have important clinical consequences. Hence, specific analysis of pituitary adenomas should be integrated into the clinical context, with a multidisciplinary approach.

The grading of the aggressive behaviour of pituitary tumours is still under study and requires proliferative markers and complete immunodetection staining, the final diagnosis combining the first two with the clinical and radiological aspects, to correctly treat these unpredictable tumours.

References

1. Dworakowska D, Grossman AB. The pathophysiology of pituitary adenomas. Best Pract Res Clin Endocrinol Metab. 2009; 23(5): 525–541, doi: 10.1016/j.beem.2009.05.004, indexed in Pubmed: 19945021.
2. Melmed S. Pathogenesis of pituitary tumors. Nat Rev Endocrinol. 2011; 7(5): 257–266, doi: 10.1038/nrendo.2011.40, indexed in Pubmed: 21423242.
3. Mertens F, Gremeaux L, Chen J, et al. Pituitary tumors contain a side population with tumor stem cell-associated characteristics. Endocr Relat Cancer. 2015; 22(4): 481–504, doi: 10.1530/ERC-14-0546, indexed in Pubmed: 25921430.
4. Megnis K, Mandrika I, Petrovska R, et al. Functional Characteristics of Multipotent Mesenchymal Stromal Cells from Pituitary Adenomas. Stem Cells Int. 2016; 2016: 7103720, doi: 10.1155/2016/7103720, indexed in Pubmed: 27340409.
5. Vankelecom H, Chen J. Pituitary stem cells: where do we stand? Mol Cell Endocrinol. 2014; 385(1-2): 2–17, doi: 10.1016/j.mce.2013.08.018, indexed in Pubmed: 23994027.
6. Lopes MB. The 2017 World Health Organization classification of tumors of the pituitary gland: a summary. Acta Neuropathol. 2017; 134(4): 521–535, doi: 10.1007/s00401-017-1769-8, indexed in Pubmed: 28821944.
7. Asa SL, Casar-Borota O, Chanson P, et al. attendees of 14th Meeting of the International Pituitary Pathology Club, Annecy, France, November 2016. From pituitary adenoma to pituitary neuroendocrine tumor (PitNET): an International Pituitary Pathology Club proposal. Endocr Relat Cancer. 2017; 24(4): C5–C8, doi: 10.1530/ERC-17-0004, indexed in Pubmed: 28264912.
8. Ho KKY, Fleseriu M, Wass J, et al. A tale of pituitary adenomas: to NET or not to NET : Pituitary Society position statement. Pituitary. 2019; 22(6): 569–573, doi: 10.1007/s11102-019-00988-2, indexed in Pubmed: 31571098.
9. Villa C, Vasiljevic A, Jaffrain-Rea ML, et al. A standardised diagnostic approach to pituitary neuroendocrine tumours (PitNETs): a European Pituitary Pathology Group (EPPG) proposal. Virchows Arch. 2019; 475(6): 687–692, doi: 10.1007/s00428-019-02655-0, indexed in Pubmed: 31578606.
10. Trouillas J, Jaffrain-Rea ML, Vasiljevic A, et al. How to Classify the Pituitary Neuroendocrine Tumors (PitNET)s in 2020. Cancers (Basel). 2020; 12(2), doi: 10.3390/cancers12020514, indexed in Pubmed: 32098443.
11. Marinescu MC, Baciu I, Baculescu N, et al. Improvement of acromegaly control with multimodal therapy in Romania. Endokrynol Pol. 2020; 71(3): 235–239, doi: 10.5603/EP.a2020.0020, indexed in Pubmed: 32293700.
12. Liu J, He Y, Zhang X, et al. Clinicopathological analysis of 250 cases of pituitary adenoma under the new WHO classification. Oncol Lett. 2020; 19(3): 1890–1898, doi: 10.3892/ol.2020.11263, indexed in Pubmed: 32194684.
13. Pasternak-Pietrzak K, Moszczyńska E, Jurkiewicz E, et al. Paediatric Cushing's disease - a literature review of epidemiology, pathogenesis, clinical symptoms, and diagnostics. Endokrynol Pol. 2020; 71(1): 87–95, doi: 10.5603/EP.a2019.0040, indexed in Pubmed: 32129467.
14. Torregrosa-Quesada ME, García-Martínez A, Silva-Ortega S, et al. How Valuable Is the RT-qPCR of Pituitary-Specific Transcription Factors for Identifying Pituitary Neuroendocrine Tumor Subtypes According to the New WHO 2017 Criteria? Cancers (Basel). 2019; 11(12), doi: 10.3390/cancers11121990, indexed in Pubmed: 31835737.
15. Peng A, Dai H, Duan H, et al. A machine learning model to precisely immunohistochemically classify pituitary adenoma subtypes with radiomics based on preoperative magnetic resonance imaging. Eur J Radiol. 2020; 125: 108892, doi: 10.1016/j.ejrad.2020.108892, indexed in Pubmed: 32087466.
16. Mete O, Cintosun A, Pressman I, et al. Epidemiology and biomarker profile of pituitary adenohypophysial tumors. Mod Pathol. 2018; 31(6): 900–909, doi: 10.1038/s41379-018-0016-8, indexed in Pubmed: 29434339.
17. Mete O, Cintosun A, Pressman I, et al. Epidemiology and biomarker profile of pituitary adenohypophysial tumors. Mod Pathol. 2018; 31(6): 900–909, doi: 10.1038/s41379-018-0016-8, indexed in Pubmed: 29434339.
18. Sanchez-Tejada L, Sanchez-Ortiga R, Lamas C, et al. Contribution of molecular analysis to the typification of the non-functioning pituitary adenomas. PLoS One. 2017; 12(7): e0180039, doi: 10.1371/journal.pone.0180039, indexed in Pubmed: 28692683.
19. García-Martínez A, Sottile J, Fajardo C, et al. Is it time to consider the expression of specific-pituitary hormone genes when typifying pituitary tumours? PLoS One. 2018; 13(7): e0198877, doi: 10.1371/journal.pone.0198877, indexed in Pubmed: 29979686.
20. Chinezu L, Vasiljevic A, Trouillas J, et al. Silent somatotroph tumour revisited from a study of 80 patients with and without acromegaly and a review of the literature. Eur J Endocrinol. 2017; 176(2): 195–201, doi: 10.1530/EJE-16-0738, indexed in Pubmed: 27913611.
21. Nishioka H, Inoshita N, Mete O, et al. The Complementary Role of Transcription Factors in the Accurate Diagnosis of Clinically Nonfunctioning Pituitary Adenomas. Endocr Pathol. 2015; 26(4): 349–355, doi: 10.1007/s12022-015-9398-z, indexed in Pubmed: 26481628.
22. Balogun JA, Monsalves E, Juraschka K, et al. Null cell adenomas of the pituitary gland: an institutional review of their clinical imaging and behavioral characteristics. Endocr Pathol. 2015; 26(1): 63–70, doi: 10.1007/s12022-014-9347-2, indexed in Pubmed: 25403448.
23. Lee JC, Pekmezci M, Lavezo JL, et al. Utility of PIT-1 Immunostaining in Distinguishing Pituitary Adenomas of Primitive Differentiation from Null Cell Adenomas. Endocr Pathol. 2017; 28(4): 287–292, doi: 10.1007/s12022-017-9503-6, indexed in Pubmed: 28994039.
24. Nishioka H, Inoshita N, Mete O, et al. The Complementary Role of Transcription Factors in the Accurate Diagnosis of Clinically Nonfunctioning Pituitary Adenomas. Endocr Pathol. 2015; 26(4): 349–355, doi: 10.1007/s12022-015-9398-z, indexed in Pubmed: 26481628.
25. Mete O, Asa SL. Structure, Function, and Morphology in the Classification of Pituitary Neuroendocrine Tumors: the Importance of Routine Analysis of Pituitary Transcription Factors. Endocr Pathol. 2020; 31(4): 330–336, doi: 10.1007/s12022-020-09646-x, indexed in Pubmed: 32813227.
26. Lamolet B, Pulichino AM, Lamonerie T, et al. A Pituitary Cell-Restricted T Box Factor, T-PIT, Activates POMC Transcription in Cooperation with Pitx Homeoproteins. Cell. 2001; 104(6): 849–859, doi: 10.1016/s0092-8674(01)00282-3, indexed in Pubmed: 11290323.
27. Raverot G, Wierinckx A, Jouanneau E, et al. Clinical, hormonal and molecular characterization of pituitary ACTH adenomas without (silent corticotroph adenomas) and with Cushing's disease. Eur J Endocrinol. 2010; 163(1): 35–43, doi: 10.1530/EJE-10-0076, indexed in Pubmed: 20385723.
28. Tani Y, Sugiyama T, Izumiyama H, et al. Differential gene expression profiles of POMC-related enzymes, transcription factors and receptors between non-pituitary and pituitary ACTH-secreting tumors. Endocr J. 2011; 58(4): 297–303, doi: 10.1507/endocrj.k10e-389, indexed in Pubmed: 21383526.
29. Tabuchi Y, Kitamura T, Fukuhara A, et al. Nur77 gene expression levels were involved in different ACTH-secretion autonomy between Cushing's disease and subclinical Cushing's disease. Endocr J. 2016; 63(6): 545–554, doi: 10.1507/endocrj.EJ15-0695, indexed in Pubmed: 27025408.
30. Fratticci A, Grieco FA, Spilioti C, et al. Differential expression of neurogenins and NeuroD1 in human pituitary tumours. J Endocrinol. 2007; 194(3): 475–484, doi: 10.1677/JOE-07-0020, indexed in Pubmed: 17761887.

31. Tamanini JV, Dal Fabbro M, de Freitas LL, et al. Digital analysis of hormonal immunostaining in pituitary adenomas classified according to WHO 2017 criteria and correlation with preoperative laboratory findings. Neurosurg Focus. 2020; 48(6): E12, doi: 10.3171/2020.3.FOCUS2039, indexed in Pubmed: 32480373.
32. Suzuki M, Egashira N, Kajiya H, et al. ACTH and alpha-subunit are co-expressed in rare human pituitary corticotroph cell adenomas proposed to originate from ACTH-committed early pituitary progenitor cells. Endocr Pathol. 2008; 19(1): 17–26, doi: 10.1007/s12022-008-9014-6, indexed in Pubmed: 18228160.
33. Cooper O, Ben-Shlomo A, Bonert V, et al. Silent corticogonadotroph adenomas: clinical and cellular characteristics and long-term outcomes. Horm Cancer. 2010; 1(2): 80–92, doi: 10.1007/s12672-010-0014-x, indexed in Pubmed: 20717480.
34. Langlois F, Lim DS, Yedinak CG, et al. Predictors of silent corticotroph adenoma recurrence; a large retrospective single center study and systematic literature review. Pituitary. 2018; 21(1): 32–40, doi: 10.1007/s11102-017-0844-4, indexed in Pubmed: 29032459.
35. Turchini J, Sioson L, Clarkson A, et al. Utility of GATA-3 Expression in the Analysis of Pituitary Neuroendocrine Tumour (PitNET) Transcription Factors. Endocr Pathol. 2020; 31(2): 150–155, doi: 10.1007/s12022-020-09615-4, indexed in Pubmed: 32193825.
36. Araujo RV, Chang CV, Cescato VAS, et al. PROP1 overexpression in corticotrophinomas: evidence for the role of PROP1 in the maintenance of cells committed to corticotrophic differentiation. Clinics (Sao Paulo). 2013; 68(6): 887–891, doi: 10.6061/clinics/2013(06)26, indexed in Pubmed: 23778486.
37. Liu NA, Araki T, Cuevas-Ramos D, et al. Cyclin E-Mediated Human Proopiomelanocortin Regulation as a Therapeutic Target for Cushing Disease. J Clin Endocrinol Metab. 2015; 100(7): 2557–2564, doi: 10.1210/jc.2015-1606, indexed in Pubmed: 25942479.
38. Neou M, Villa C, Armignacco R, et al. Pangenomic Classification of Pituitary Neuroendocrine Tumors. Cancer Cell. 2020; 37(1): 123–134.e5, doi: 10.1016/j.ccell.2019.11.002, indexed in Pubmed: 31883967.
39. Asa SL, Puy LA, Lew AM, et al. Cell type-specific expression of the pituitary transcription activator pit-1 in the human pituitary and pituitary adenomas. J Clin Endocrinol Metab. 1993; 77(5): 1275–1280, doi: 10.1210/jcem.77.5.8077321, indexed in Pubmed: 8077321.
40. Wu J, Li X, Liu X. PIT-1 mRNA and protein expression in human pituitary adenomas. Int J Clin Exp Pathol. 2016; 9: 7060–8.
41. Orciani M, Davis S, Appolloni G, et al. Isolation and characterization of progenitor mesenchymal cells in human pituitary tumors. Cancer Gene Ther. 2015; 22(1): 9–16, doi: 10.1038/cgt.2014.63, indexed in Pubmed: 25525036.
42. Japón MA, Urbano AG, Sáez C, et al. Glial-derived neurotropic factor and RET gene expression in normal human anterior pituitary cell types and in pituitary tumors. J Clin Endocrinol Metab. 2002; 87(4): 1879–1884, doi: 10.1210/jcem.87.4.8383, indexed in Pubmed: 11932334.
43. Cañibano C, Rodriguez NL, Saez C, et al. The dependence receptor Ret induces apoptosis in somatotrophs through a PIT-1/p53 pathway, preventing tumor growth. EMBO J. 2007; 26(8): 2015–2028, doi: 10.1038/sj.emboj.7601636, indexed in Pubmed: 17380130.
44. Lew AM, Elsholtz HP. Cloning of the human cDNA for transcription factor PIT-1. Nucleic Acids Res. 1991; 19(22): 6329, doi: 10.1093/nar/19.22.6329, indexed in Pubmed: 1956794.
45. Pellegrini I, Barlier A, Gunz G, et al. PIT-1 gene expression in the human pituitary and pituitary adenomas. J Clin Endocrinol Metab. 1994; 79(1): 189–196, doi: 10.1210/jcem.79.1.8027225, indexed in Pubmed: 8027225.
46. Sanno N, Teramoto A, Matsuno A, et al. In situ hybridization analysis of PIT-1 mRNA and hormonal production in human pituitary adenomas. Acta Neuropathol. 1996; 91(3): 263–268, doi: 10.1007/s004010050424, indexed in Pubmed: 8834538.
47. Li C, Xie W, Rosenblum JS, et al. Somatic SF3B1 hotspot mutation in prolactinomas. Nat Commun. 2020; 11(1): 2506, doi: 10.1038/s41467-020-16052-8, indexed in Pubmed: 32427851.
48. Kobayashi I, Oka H, Naritaka H, et al. Expression of PIT-1 and growth hormone-releasing hormone receptor mRNA in human pituitary adenomas: difference among functioning, silent, and other nonfunctioning adenomas. Endocr Pathol. 2002; 13(2): 83–98, doi: 10.1385/ep:13:2:83, indexed in Pubmed: 12165656.
49. Wang ELu, Qian ZR, Yamada S, et al. Clinicopathological characterization of TSH-producing adenomas: special reference to TSH-immunoreactive but clinically non-functioning adenomas. Endocr Pathol. 2009; 20(4): 209–220, doi: 10.1007/s12022-009-9094-y, indexed in Pubmed: 19774499.
50. Căpraru OM, Gaillard C, Vasiljevic A, et al. Diagnosis, pathology, and management of TSH-secreting pituitary tumors. A single-center retrospective study of 20 patients from 1981 to 2014. Ann Endocrinol (Paris). 2019; 80(4): 216–224, doi: 10.1016/j.ando.2019.06.006, indexed in Pubmed: 31400861.
51. Teramoto A, Sanno N, Tahara S, et al. Pathological study of thyrotropin-secreting pituitary adenoma: plurihormonality and medical treatment. Acta Neuropathol. 2004; 108(2): 147–153, doi: 10.1007/s00401-004-0863-x, indexed in Pubmed: 15185102.
52. Aydin S, Comunoglu N, Ahmedov ML, et al. Clinicopathologic Characteristics and Surgical Treatment of Plurihormonal Pituitary Adenomas. World Neurosurg. 2019; 130: e765–e774, doi: 10.1016/j.wneu.2019.06.217, indexed in Pubmed: 31295602.
53. Rak B, Maksymowicz M, Grzywa TM, et al. Pituitary tumours — a large retrospective single-centre study of over 2300 cases. Experience of a tertiary reference centre. Endokrynol Pol. 2020; 71(2): 116–125, doi: 10.5603/EP.a2020.0011, indexed in Pubmed: 32154573.
54. Mete O, Alshaikh OM, Cintosun A, et al. Synchronous Multiple Pituitary Neuroendocrine Tumors of Different Cell Lineages. Endocr Pathol. 2018; 29(4): 332–338, doi: 10.1007/s12022-018-9545-4, indexed in Pubmed: 30215160.
55. Behling F, Honegger J, Skardelly M, et al. High Expression of Somatostatin Receptors 2A, 3, and 5 in Corticotroph Pituitary Adenoma. Int J Endocrinol. 2018; 2018: 1763735, doi: 10.1155/2018/1763735, indexed in Pubmed: 30627156.
56. Nishioka H, Hara T, Nagata Y, et al. Inherent Tumor Characteristics That Limit Effective and Safe Resection of Giant Nonfunctioning Pituitary Adenomas. World Neurosurg. 2017; 106: 645–652, doi: 10.1016/j.wneu.2017.07.043, indexed in Pubmed: 28735124.
57. Nishioka H, Inoshita N, Mete O, et al. The Complementary Role of Transcription Factors in the Accurate Diagnosis of Clinically Nonfunctioning Pituitary Adenomas. Endocr Pathol. 2015; 26(4): 349–355, doi: 10.1007/s12022-015-9398-z, indexed in Pubmed: 26481628.
58. Nishioka H, Inoshita N, Sano T, et al. Correlation between histological subtypes and MRI findings in clinically nonfunctioning pituitary adenomas. Endocr Pathol. 2012; 23(3): 151–156, doi: 10.1007/s12022-012-9208-9, indexed in Pubmed: 22569896.
59. Asa SL, Bamberger AM, Cao B, et al. The transcription activator steroidogenic factor-1 is preferentially expressed in the human pituitary gonadotroph. J Clin Endocrinol Metab. 1996; 81(6): 2165–2170, doi: 10.1210/jcem.81.6.8964846, indexed in Pubmed: 8964846.
60. Luo X, Ikeda Y, Parker KL, et al. A cell-specific nuclear receptor is essential for adrenal and gonadal development and sexual differentiation. Cell. 1994; 77(4): 481–490, doi: 10.1016/0092-8674(94)90211-9, indexed in Pubmed: 8187173.
61. Drummond J, Roncaroli F, Grossman AB, et al. Clinical and Pathological Aspects of Silent Pituitary Adenomas. J Clin Endocrinol Metab. 2019; 104(7): 2473–2489, doi: 10.1210/jc.2018-00688, indexed in Pubmed: 30020466.
62. Manoranjan B, Mahendram S, Almenawer SA, et al. The identification of human pituitary adenoma-initiating cells. Acta Neuropathol Commun. 2016; 4(1): 125, doi: 10.1186/s40478-016-0394-4, indexed in Pubmed: 27894339.
63. Kasuki L, Raverot G. Definition and diagnosis of aggressive pituitary tumors. Rev Endocr Metab Disord. 2020; 21(2): 203–208, doi: 10.1007/s11154-019-09531-x, indexed in Pubmed: 31808044.
64. Raverot G, Burman P, McCormack A, et al. European Society of Endocrinology. European Society of Endocrinology Clinical Practice Guidelines for the management of aggressive pituitary tumours and carcinomas. Eur J Endocrinol. 2018; 178(1): G1–G24, doi: 10.1530/EJE-17-0796, indexed in Pubmed: 29046323.
65. Trouillas J, Roy P, Sturm N, et al. members of HYPOPRONOS. A new prognostic clinicopathological classification of pituitary adenomas: a multicentric case-control study of 410 patients with 8 years post-operative follow-up. Acta Neuropathol. 2013; 126(1): 123–135, doi: 10.1007/s00401-013-1084-y, indexed in Pubmed: 23400299.
66. Serioli S, Doglietto F, Fiorindi A, et al. Pituitary Adenomas and Invasiveness from Anatomo-Surgical, Radiological, and Histological Perspectives: A Systematic Literature Review. Cancers (Basel). 2019; 11(12), doi: 10.3390/cancers11121936, indexed in Pubmed: 31817110.
67. Selman WR, Laws ER, Scheithauer BW, et al. The occurrence of dural invasion in pituitary adenomas. J Neurosurg. 1986; 64(3): 402–407, doi: 10.3171/jns.1986.64.3.0402, indexed in Pubmed: 3950720.
68. Meij BP, Lopes MBS, Ellegala DB, et al. The long-term significance of microscopic dural invasion in 354 patients with pituitary adenomas treated with transsphenoidal surgery. J Neurosurg. 2002; 96(2): 195–208, doi: 10.3171/jns.2002.96.2.0195, indexed in Pubmed: 11838791.
69. Lopes MB. The 2017 World Health Organization classification of tumors of the pituitary gland: a summary. Acta Neuropathol. 2017; 134(4): 521–535, doi: 10.1007/s00401-017-1769-8, indexed in Pubmed: 28821944.
70. Trouillas J, Jaffrain-Rea ML, Vasiljevic A, et al. Are aggressive pituitary tumors and carcinomas two sides of the same coin? Pathologists reply to clinician's questions. Rev Endocr Metab Disord. 2020; 21(2): 243–251, doi: 10.1007/s11154-020-09562-9, indexed in Pubmed: 32504268.
71. Rogoziński D, Gilis-Januszewska A, Skalniak A, et al. Pituitary tumours in MEN1 syndrome - the new insight into the diagnosis and treatment. Endokrynol Pol. 2019; 70(5): 445–452, doi: 10.5603/EP.a2019.0026, indexed in Pubmed: 31681967.

72. Srirangam Nadhamuni V, Korbonits M. Novel Insights into Pituitary Tumorigenesis: Genetic and Epigenetic Mechanisms. Endocr Rev. 2020; 41(6), doi: 10.1210/endrev/bnaa006, indexed in Pubmed: 32201880.
73. Bi WL, Horowitz P, Greenwald NF, et al. Landscape of Genomic Alterations in Pituitary Adenomas. Clin Cancer Res. 2017; 23(7): 1841–1851, doi: 10.1158/1078-0432.CCR-16-0790, indexed in Pubmed: 27707790.
74. Alahmadi H, Lee D, Wilson JR, et al. Clinical features of silent corticotroph adenomas. Acta Neurochir (Wien). 2012; 154(8): 1493–1498, doi: 10.1007/s00701-012-1378-1, indexed in Pubmed: 22619024.
75. Trouillas J, Delgrange E, Wierinckx A, et al. Clinical, Pathological, and Molecular Factors of Aggressiveness in Lactotroph Tumours. Neuroendocrinology. 2019; 109(1): 70–76, doi: 10.1159/000499382, indexed in Pubmed: 30943495.
76. Sano T, Mader R, Asa SL, et al. "Honeycomb Golgi" in pituitary adenomas: not a marker of gonadotroph adenomas. Endocr Pathol. 2003; 14(4): 363–368, doi: 10.1385/ep:14:4:363, indexed in Pubmed: 14739492.
77. Cooper O, Ben-Shlomo A, Bonert V, et al. Silent corticogonadotroph adenomas: clinical and cellular characteristics and long-term outcomes. Horm Cancer. 2010; 1(2): 80–92, doi: 10.1007/s12672-010-0014-x, indexed in Pubmed: 20717480.
78. Yunoue S, Arita K, Kawano H, et al. Identification of CD133+ cells in pituitary adenomas. Neuroendocrinology. 2011; 94(4): 302–312, doi: 10.1159/000330625, indexed in Pubmed: 21912092.
79. Mete O, Gomez-Hernandez K, Kucharczyk W, et al. Silent subtype 3 pituitary adenomas are not always silent and represent poorly differentiated monomorphous plurihormonal PIT-1 lineage adenomas. Mod Pathol. 2016; 29(2): 131–142, doi: 10.1038/modpathol.2015.151, indexed in Pubmed: 26743473.
80. Sjöstedt E, Bollerslev J, Mulder J, et al. A specific antibody to detect transcription factor T-Pit: a reliable marker of corticotroph cell differentiation and a tool to improve the classification of pituitary neuroendocrine tumours. Acta Neuropathol. 2017; 134(4): 675–677, doi: 10.1007/s00401-017-1768-9, indexed in Pubmed: 28823042.
81. Nishioka H, Hara T, Nagata Y, et al. Inherent Tumor Characteristics That Limit Effective and Safe Resection of Giant Nonfunctioning Pituitary Adenomas. World Neurosurg. 2017; 106: 645–652, doi: 10.1016/j.wneu.2017.07.043, indexed in Pubmed: 28735124.
82. McDonald WC, Banerji N, McDonald KN, et al. Steroidogenic Factor 1, PIT-1, and Adrenocorticotropic Hormone: A Rational Starting Place for the Immunohistochemical Characterization of Pituitary Adenoma. Arch Pathol Lab Med. 2017; 141(1): 104–112, doi: 10.5858/arpa.2016-0082-OA, indexed in Pubmed: 27227698.