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Somatic and germline mutations in the pathogenesis of pituitary adenomas

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Abstract

Pituitary adenomas are frequently occurring neoplasms that produce clinically significant disease in 1:1000 of the general population. The pathogenesis of pituitary tumors has been a matter of interest as it could help to improve diagnosis and treatment. Until recently, however, disruptions in relatively few genes had been shown to predispose to pituitary tumor formation. In the last decade several more genes and pathways have been described. Germline pathogenic variants in *the aryl hydrocarbon receptor-interacting protein (AIP)* gene were found in familial or sporadic pituitary adenomas, usually with an aggressive clinical course. *Cyclin-dependent kinase inhibitor 1B (CDKN1B)* pathogenic variants lead to multiple endocrine neoplasia type 4 (MEN4) syndrome, in which pituitary adenomas can occur. Xq26.3 duplications involving the gene *GPR101* cause X-linked acrogigantism. The pheochomocytoma and/or paraganglioma with pituitary adenoma association (3PAs) syndrome suggest that pathogenic variants in the genes of the succinate dehydrogenase complex or *MYC-associated factor X (MAX)* might be involved in pituitary tumorigenesis. New recurrent somatic alterations were also discovered in pituitary adenomas, such as, *ubiquitin specific protease 8 (USP8)* and *USP48* pathogenic variants in corticotropinomas. The aim of the present review is to provide an overview on the genetic pathophysiology of pituitary adenomas and their clinical relevance.

Introduction

Pituitary adenomas are benign neoplasms that are found in up to 20% of pituitaries on MRI or autopsy [1], while clinically relevant pituitary adenomas have a prevalence of approximately 1:1000 people [2]. Usually they are monoclonal in origin, expanding from molecular genetic abnormalities in a single somatic cell [3]. However, there is evidence demonstrating that pituitary adenomas could be polyclonal, especially recurrent tumors[4]. Tumorigenesis involves differential expression of tumor suppressors or oncogenes, hormones and growth factors and their receptors, adhesion molecules and microRNAs that lead to disruption of the cell cycle and abnormalities in various signal transduction pathways [5-9]. Often, however, the initial trigger of the tumorigenic cascade remains largely unknown. In the last decade significant progress has been made with the discovery of several genetic defects implicated in pituitary tumor pathogenesis in previously recognized or new clinical conditions. Among these newer genetic discoveries are germline pathogenic variants in the *aryl hydrocarbon receptor- interacting protein (AIP)* gene that were found in familial and sporadic pituitary adenomas [10, 11]. *Cyclin-dependent kinase inhibitor 1B (CDKN1B)* pathogenic variants were ascribed to a MEN1-like condition, known as MEN4 syndrome [12]. Xq26.3 duplications involving the gene *GPR101* have been demonstrated in X-linked acrogigantism (X-LAG)[13]. The 3P (pheochromocytoma and/or paraganglioma, and pituitary adenoma) association (3PAs) is related to pathogenic variants of the succinate dehydrogenase complex genes, among others, and suggests that pheochromocytoma/paraganglioma related genes might rarely cause pituitary adenomas [14, 15]. Many adenomas arising in the context of germline pathogenic variants or syndromic conditions have an aggressive clinical behavior and poor responses to standard treatments. However, the prevalence of known germline pathogenic variants in the pool of unselected sporadic adenomas is still low [9, 11]. Regarding somatic pathogenic variants, until recently, only stimulatory *guanine nucleotide (GTP)-binding protein alpha (GNAS)* pathogenic variants were known to be causally related to somatotropinoma pathogenesis in a sizeable proportion of cases [16, 17]. Current genomic techniques allowed the identification of other frequently recurrent somatic genetic alterations - *phosphatidylinositol 3 kinase alpha subunit (PIK3AC)* gene in various types of pituitary adenomas [18, 19] and *ubiquitin specific protease 8 (USP8)* [20, 21]and *USP48* gene pathogenic variants in corticotropinomas [22].

Somatic mutations in pituitary adenomas

GNAS mutations

The deregulation of the cyclic AMP (cAMP)-Protein kinase A (PKA) signaling pathway is strongly implicated in pituitary tumor pathogenesis through different PKA-dependent and -independent mechanisms, which together lead to hormonal hypersecretion and cell cycle disruption [6, 23, 24]. One of the most common somatic disruptions seen are activating *GNAS* gene (OMIM *139320) pathogenic variants, found in about 40% (up to 63% some series) of growth hormone (GH)-producing adenomas

and rarely in other pituitary adenoma types [16, 17, 25] . *GNAS* encodes the *gsp* oncogene – the stimulatory G-protein subunit alfa (Gsα). The most frequent alterations result in amino acid substitution of the highly conserved Arg201, and to a lesser extent Gln227, with subsequent constitutive activation of the mutated Gsα subunit, increased adenylate cyclase activity, cAMP production and downstream signaling with abnormal GH transcriptional activation and somatotrope proliferation [26].

GNAS mutation positive adenomas have been considered to have a favorable clinical profile, including an older age at diagnosis, smaller tumor size, less invasive features and densely granulated microscopic tumor appearance in comparison to their non-mutated counterparts, however, this is not confirmed in all studies [27-35]. With respect to treatment, and particularly *GNAS* status in relation to somatostatin responsiveness, the literature is inconsistent. Some studies show a favorable effect of *GNAS* mutational status [29, 34], while others show no effect [25, 28, 33, 35, 36]. A recent meta-analysis evaluating GH suppressive responses after an acute octreotide test showed significantly higher GH reduction in the *GNAS* mutated pituitary adenomas [17]. The influence of *GNAS* pathogenic variants on the long-term SSA response is also debatable – a better response by measuring GH is reported by some [30, 37] but no higher percentage of IGF-1 normalization has been shown by others [28, 31, 37]. Thus, the presence of a *GNAS* pathogenic variant is one of many factors that influence the response to SSA treatment [38].

USP8 mutations

Resistance to the negative glucocorticoid feedback is typical for corticotropinomas. However, somatic pathogenic variants in the *nuclear receptor subfamily 3 group C member 1 NR3C1* (OMIM *138040) encoding the glucocorticoid receptor are quite rare [21, 22, 39-41]

In 2014 next generation sequencing techniques allowed the identification of recurrent somatic pathogenic variants of the *USP8* gene (OMIM *603158) in significant number of corticotropinomas. USP8 is a deubiquitinase that inhibits lysosomal degradation of the epidermal growth factor receptor (EGFR). Hotspot pathogenic variants in exon 14 affect the binding motif of the protein that regulates its activity, leading to gain-of-function. USP8 is cleaved, which enhances its catalytic activity, resulting in subsequently impaired down-regulation of EGFR and sustained EGF signaling [20, 21]. In *USP8*-mutated corticotropinomas, enhanced transcription of proopiomelanocortin (POMC) was observed [21, 42]. Higher ACTH levels have been demonstrated in *USP8* mutated adenomas [20, 43, 44]. In another study no absolute difference in ACTH secretion between *UPS8* mutated *vs.* non-mutated tumors was noted, but the smaller size of the mutated adenomas suggested that they had relatively high ACTH production [21]. *USP8* pathogenic variants have not been found in other pituitary tumor types to date [21, 40, 45-51].

The overall prevalence of *USP8* somatic pathogenic variants is 21-62% in corticotropinomas [20, 21, 42, 43, 52-54]. Females predominate over males in some [21, 42, 43, 53] but not other studies [54, 55]. In a large cohort of 120 corticotropinomas, smaller tumor size and a lower rate of parasellar expansion was reported in *USP8* mutated tumors [21]. No such correlation was found in other studies [53, 55]. There is inconsistency regarding differences in basal hormonal values between *USP8* mutated and wild-type adenomas [20, 21, 42-44, 52, 53, 55].

In pediatric series, female predominance and an older age at diagnosis of *USP8* mutated vs. wild-type adenomas was noted [52]. In regard to treatment, there is high discrepancy in the cure rates after transsphenoidal adenomectomy – higher remission rates in *USP8* mutated adenomas in some studies [42, 53], but not in others [21, 43, 55]. Higher postoperative free urinary cortisol and ACTH levels were demonstrated in *UPS8* mutated patients [43, 44, 52]. Up to 5-year recurrence rates were similar with regard to *USP8* mutational status [21, 53], although a higher 10-year recurrence rate in *USP8* mutated adenomas (58% vs. 18%) was reported recently [55]. In pediatric series, higher recurrence rates were also observed in *USP8* mutated adenomas [52].

In respect to medical treatment, an enhanced effect of pasireotide might occur due to increased transcript levels of SST5R in *USP8* mutated adenomas [42]. Another potentially useful therapy could be the EGFR inhibitor gefitinib which reduces ACTH secretion in *USP8* mutated adenomas *in vitro* [21].

USP48 and *BRAF* mutations

A recent study described two other recurrently mutated genes in *USP8* wild-type adenomas – *BRAF* (OMIM *164757) and *USP48* (OMIM *716445) in 23 and 16.4% of *USP8* wild-type corticotropinomas, respectively [22]. There was no clinical difference with wild type *BRAF/USP8* patients, except for the higher midnight ACTH and midnight serum cortisol levels in *BRAF* V600E-variant-harbouring patients. However, as previous studies failed to identify a role of *BRAF* pathogenic variants in pituitary tumorigenesis[39] [56, 57], these results need further independent confirmation.

PIK3CA

Phosphatidylinositol 3-kinase is part of the PI3K/Akt signaling pathway which is implicated in the cell survival, proliferation, adhesion, motility and spread [58]. It phosphorylates phosphatidylinositol 4, 5-bisphosphate to phosphatidylinositol 3,4,5-triphosphate, which is essential for the phosphorylation of AKT [59]. Pathogenic variants in hotspots, located on exons 9 and 20 and amplifications of the *PIK3CA* gene (OMIM *171834) are found in various tumor types and lead to increased PI3K activity, and subsequent phosphorylation and activation of AKT [18, 58].

Frequent genetic alterations in the *PIK3CA* gene have been found in various types of pituitary adenomas [18, 19]. In a Chinese series of 353 pituitary adenomas, 2.3 % harboured somatic *PIK3CA* pathogenic variants. All of the mutated adenomas were invasive and they constituted 8.8% (8/91) of the invasive tumors in that series (1 corticotropinoma, 2 prolactinomas, 4 non-functioning adenomas and 1 plurihormonal adenoma). Furthermore, gene amplifications (defined by copy number of *PIK3CA* ≥ 4) were found in 32.9% (30/91) of invasive and in 26.3% (69/262) of non-invasive pituitary adenomas, with similar distribution among different tumor types [18]. In a Brazilian cohort, *PIK3CA* gene mutations were present in 12% of adenomas (4/33; non–invasive corticotropinoma and 3 invasive non-functioning adenomas), while genomic amplifications were found in 21.2% (7/33) [19]. No pathogenic variants in the *PIK3CA* gene were found in a cohort of GH-secreting adenomas [45].

As PI3K could be a downstream effector of RAS, screening for *RAS* pathogenic variants has been performed by Lin et al. [18, 59, 60]. *HRAS* (OMIM *190020) pathogenic variants were found in 6.6% (6/91) of the invasive pituitary adenomas, one of which had a co-existent *PIK3CA* mutation [18]. Individual cases of *HRAS* pathogenic variants were reported by other groups [61-63]. Regarding the clinical presentation of *PIK3CA* mutated adenomas, a higher degree of recurrence after surgery has been observed in mutated vs. wild-type adenomas 63% vs. 25% respectively [18].

Whole-exome/genome sequencing

After the breakthrough discovery of *USP8* pathogenic variants in corticotropinomas, several study groups reported results from whole-exome/genome sequencing in other pituitary tumor types, confirming the relatively silent somatic landscape [40, 45-47, 49-51]. However, in two series of GH-secreting adenomas, despite the absence of recurrent somatic pathogenic variants (except *GNAS*), abnormalities of several different genes involved in Ca^{2+} [45, 46] and cAMP signaling [45] were noted. These studies suggest that disruption of calcium signaling could contribute to somatotropinoma formation. On the basis of data from other human tumor types it was speculated that the trigger event could be different in the various tumor types but by targeting the same molecular pathway these could contribute to tumorigenesis [46, 64]. A recent study identified variants (in two pituitary adenomas each) in several genes (*KIF5A, GRB10, LARS, SP100, TRIP12)* whose role remains to be further elucidated [40].

Copy number variations

Frequent copy number variations (CNV) have also been reported [40, 46, 47, 50]. Chromosomal losses are particularly interesting in the context of the two-hit model inactivation of tumor suppressor genes [46]. In the absence of subsequent somatic mutation, tumorigenesis might be driven by the coexistence of somatic deletion and epigenetic silencing leading in biallelic inactivation of tumor suppressor genes [46]. In respect to clinical relevance of CNVs, it has been demonstrated that highly genomically disrupted adenomas are more frequently hormonally functional and pathologically atypical, while tumors with rare CNVs are principally non-functional [50]. Frequent gains in regions encoding cohesin complex genes have been found, however without an apparent influence of clinical characteristics of the disrupted adenomas [40]. A recent study, focusing on CNVs in pediatric patients with Cushing's disease, showed that 18.5% (5/27 samples) had a high degree of chromosomal instability (>22% of the genome). There were no differences with respect to clinical characteristics but the adenomas with large genomic aberrations were significantly larger and had higher rates of invasion of the cavernous sinus [65].

A new approach is that of targeting circulating tumor DNA in the plasma. Using a next-generation sequencing approach, Megnis et al. for the first time detected gene variants in circulating free DNA that were also present in the pituitary adenoma tissue of the same patients [66].

Germline mutations in familial and sporadic pituitary adenomas

Small proportion of pituitary adenomas, approximately 5%, could arise as part of a heritable syndrome. Such adenomas carry significant clinical burden as they are usually more aggressive, occurring at an early age, having larger tumor size, increased invasiveness, and resistance to standard treatment [67, 68]. These features determine the need for efficient screening and early recognition.

Familial isolated pituitary adenomas (FIPA)

Familial pituitary adenomas can be either part of multiple endocrine syndromes or may arise as isolated pituitary adenomas in a familial setting. Over the period 1999-2006 we identified and described familial isolated pituitary adenomas (FIPA) (OMIM #605555) as a novel condition associated with pituitary adenomas (without the presence of other endocrine neoplasia syndromes) in two or more related members of the same kindred. [69] [70]. FIPA represents around 2% of all pituitary tumors [70]. All types of secreting and non-secreting adenomas are described in FIPA, with a predominance of prolactinomas, somatotropinomas, and non-functioning pituitary adenomas. Kindreds can all share the same pituitary adenoma subtype in affected members (homogeneous FIPA) or different pituitary adenoma subtypes can occur within the same family (heterogeneous FIPA) [70]. Notably, pituitary adenomas in the setting of FIPA have some clinical characteristics that distinguish them from sporadic adenomas. In FIPA kindreds, prolactinomas, although most prevalent, have lower frequency in comparison with non-FIPA cases – around 38%. It could be partly explained by the higher frequency of somatotropinomas (35%) as compared with the general population. FIPA patients usually have earlier disease onset (approximately 4 years) *vs.* non-FIPA cases. In homogenous acromegaly kindreds, the disease onset is early and somatotropinomas are usually large and invasive. Similarly, non-functioning adenomas and prolactinomas in the FIPA setting are larger and more invasive than their non-FIPA counterparts [11, 67, 71]

***AIP* mutations in FIPA and sporadic pituitary adenomas**

In 2006 Vierimaa et al. reported that pathogenic variants of the *AIP* gene (OMIM *605555) were associated with pituitary tumorigenesis in large kindreds in Finland and elsewhere [10]. *AIP* is a tumor suppressor gene located on chromosome 11q13 [10]. The gene encodes a 330-amino acid cytoplasmic protein - the aryl hydrocarbon receptor (AHR) interacting protein. Different types of pathogenic variants have been described leading to truncated protein in many cases [11, 71]. Besides AHR, AIP has multiple other partners, including chaperones, phosphodiesterases, Gαi proteins, survivin, RET, nuclear receptors, such as thyroid hormone receptor β1, estrogen receptor-α, peroxisome proliferator-activated receptor-α, viral proteins and others [11, 72, 73].

The cAMP-PKA signaling pathway is strongly implicated in pituitary tumorigenesis and the loss of AIP in mutated adenomas has been related to increased cAMP signaling through defective inhibitory Gα protein signaling. Furthermore, the loss of AIP has been associated with reduction in Gαi -2 protein expression in mutated somatotropinomas [74, 75]. Loss of this inhibitory G protein signal may be permissive for cellular proliferation and tumor growth. A strongly positive correlation between AIP and Gαi -2

protein expression has also been confirmed in sporadic somatotropinomas [73]. The complex interplay between AIP and PKA signaling is further supported by the evidence that AIP interacts physically with both the regulatory (R1α) and the catalytic (Cα) subunits of PKA separately, as well as in complex [76]. AIP overexpression led to a decrease in nuclear Cα expression and total PKA activity. Silencing of AIP resulted in PKA pathway activation, and furthermore, the activation was disproportionately elevated under PDE4-specific inhibition, suggesting additional functional interaction. Of note, the mutant AIP p.R304* interacted to a lesser degree with both PKA subunits [76]. Disrupted mutant AIP-PDE4A5 interaction has also been previously reported [77].

Although the role of AHR (the dioxin receptor) in the xenobiotic response has been widely studied, its potential role in the pathogenesis of pituitary adenomas has been recently described [78]. Acromegaly was observed with increased incidence in a highly polluted industrial region in Italy (Messina, Sicily) [79]. The current prevalence of acromegaly there is thought to be 330 cases per million inhabitants and the relative risk of developing the disease was estimated to be 8-fold higher in comparison with non-polluted area in the same province [79, 80]. In a subsequent study it was found that 9/23 (39%) patients from different highly polluted areas in Italy bore a genetic variant of *AHR* or *AIP*, as compared with 25.3% (44/187) of patients from non-polluted regions. Notably, genetically variant adenomas in polluted areas had a more severe course of acromegaly, characterized by higher IGF-1 values and larger tumor size and worse response to first-line SSAs in comparison with the other groups. [80]It is known that AIP forms a complex with AHR, stabilizing it in the cytoplasm together with a dimer of heat-shock proteins 90 and the co-chaperone p23 and AIP protein expression could influence AHR expression [78, 81, 82]. On the other hand, AHR nuclear translocation can be cAMP-dependent[83], which is the main signaling pathway disruption in AIP silencing. However, the exact mechanisms of the link between AHR and AIP in terms of tumorigenesis in the pituitary remains to be further elucidated.

Large populations of FIPA kindreds, as well as sporadic adenoma patients have been screened for germline pathogenic variants of *AIP*. *AIP* mutation positive carriers, irrespective of the familial status, had some distinct clinical characteristics in comparison with their mutation negative counterparts: predominance of somatotropinomas, younger age at diagnosis (about 24.6 yrs), larger and more invasive adenomas [11, 84]. In the FIPA setting, *AIP* pathogenic variants are demonstrated in about 20% of families, while in cohorts of unselected apparently sporadic pituitary adenomas *AIP* pathogenic variants are rarely found – in less than 4% [11, 84]. However, in young adults (diagnosed<30 yr of age) with apparently sporadic adenomas (mostly macroadenomas), the prevalence of *AIP* pathogenic variants was higher, ranging between 1.6-13%[85-93]. Further decreasing the age of diagnosis (pediatric/adolescent patients <18 yr/old) increases the frequency of *AIP* pathogenic variants – 11-25% [85, 87, 94-98]. In our large international cohort of giantism patients, the overall frequency of *AIP* pathogenic variants was 29% [99]. Another feature related more commonly to *AIP* mutated adenomas is pituitary apoplexy [89, 100-102], especially in pediatric population [89].

Tumoral AIP protein expression may be low in some somatotropinomas even without *AIP* pathogenic variants and these tumors can have higher invasive rates [103]. Decreased AIP protein staining could potentially serve as a marker of invasive potential, along with more traditional markers such as, Ki-67 index and p53 positivity [104].

Apart from the unfavorable clinical characteristics, such as young age and macroadenoma at presentation, *AIP*-mutated adenomas are difficult to treat. In a multicenter collaborative study we demonstrated that although the overall rates of disease control were comparable (70.4% vs. 80.5% for *AIP* mutated somatotropinomas and controls respectively), *AIP* mutated somatotropinomas (n=75) required significantly more neurosurgical interventions than their non-mutated acromegaly counterparts (n=232) - 22 *vs.*6%, respectively [105].

AIP-mutated somatotropinomas appear to be more resistant to first generation somatostatin analogues, having significantly lower decreases of GH and IGF-1 and less tumor shrinkage [77, 85, 105-107]. Pretreatment with octreotide increases AIP protein expression [108, 109], while the role of AIP expression level for SSA responsiveness is debatable [68, 103, 104, 108-110]. Overexpression of wild-type AIP increases ZAC1 expression, while AIP knockdown leads to ZAC1 silencing[108]; ZAC1 is known to correlate with IGF-1 reduction and tumor shrinkage under octreotide/lanreotide treatment in acromegaly[111, 112]. Another causal link was suggested recently through reduced expression of $G\alpha_{i-2}$ which mediates somatostatin signaling via the SSTRs [73, 113, 114]. Unlike first-generation SSA, similar SSTR5 expression and similar responsiveness to pasireotide irrespective of the AIP expression levels was observed in patients with sporadic acromegaly [107].

Given the well documented hormonal and tumoral resistance of *AIP*-mutated somatotropinomas to first generation SSAs, treatment with growth hormone receptor antagonist is an alternative option [115]. Such adenomas can also be good candidates for pasireotide treatment. Recently, clinical evidence for long-term pasireotide efficiency in first generation SSA-resistant *AIP* mutated adenomas has been reported [116]. Ten-year treatment with pasireotide LAR in one patient led to hormonal control and significant tumor remnant reduction, which allowed discontinuation of the medication with continuous hormonal control (off therapy) for more than a year. Similarly, in a second patient hormonal and tumoral control was observed but this hormonal control was lost after switching to octreotide. AIP protein and SST2 expression was lost, while SST5 staining was positive on immunohistochemistry in that case [116].

Similarly to somatotropinomas, treatment in *AIP* mutated prolactinomas is also challenging. Only 40% (5/12) were controlled by dopamine agonists in our multicenter study and 4/7 uncontrolled patients required multiple neurosurgeries [105]. The explanation behind the lower responsiveness to DA remains to be further elucidated.

Given the aggressive features of *AIP* mutated adenomas, questions about genetic screening for index cases and relatives are raised. Based on the more prominent characteristics of *AIP* mutation positive adenomas, experts' opinion on the screening referral includes pediatric/adolescence disease onset, pituitary gigantism, FIPA kindreds, macroadenomas (particularly somatotropinomas), occurring ≤30

years of age [117-119]. Some of the FIPA families (8.3-9.5%), negative for *AIP* pathogenic variants by direct sequencing, could have large genomic deletions, which warrants for the use of multiplex ligation-dependent probe amplification (MLPA) when genetic testing is considered appropriate [98, 100]. Recently a clinical risk category system for *AIP* gene variant screening in pituitary adenomas was proposed, confirming the role of young age at onset (including gigantism), FIPA, macroadenomas and GH excess as independent risk factors. The highest risk (76%) was produced combining homogeneous FIPA somatotropinomas families presenting with a macroadenoma at early age (<18 years) and the risk fell significantly when either of the factors (FIPA, macroadenoma or age>18 years) was absent[120]. However, there is little data on the real-life validity of these recommendations. A recent single tertiary centre retrospective study reports results on *AIP* and *MEN1* pathogenic variants/deletions applying many of the known characteristics of *AIP* mutated tumors, in addition to novel factors such as SSA resistance in somatotropinomas, or DA resistance in prolactinomas [68]. None of the patients had pathogenic variants/deletion in *AIP* or *MEN1* genes. In the series most of the pediatric onset patients had Cushing's disease, which reinforces the concept that *AIP* and *MEN1* rarely cause pediatric Cushing's disease. Furthermore, only one patient with gigantism was identified, who did not carry an *AIP*/*MEN1* pathogenic variant. Having in mind that the genetic causes are unknown in 50% of gigantism cases, this result is perhaps not very surprising. The results of that recent study suggest that criteria should be carefully interpreted and applied. The age at onset used to trigger screening for *AIP*-related pituitary adenomas in sporadic patients could be revised downward to below 30 years, and should focus primarily on extensive and/or invasive sporadic macroadenomas [68].

Identifying a germline *AIP* pathogenic variant raises the need to consider familial genetic screening. Pituitary adenomas in *AIP* pathogenic variant carriers in this setting has low penetrance - 20-23% [71, 105, 121, 122]. The decision is guided by the possibility of diagnosing the disease before manifestation as an invasive macroadenoma, which could bring potential treatment benefits [71, 105]. Genetic screening should be particularly targeted at young (pediatric-adolescent) family members who are at higher risk of developing aggressive adenomas. In pathogenic variant carriers, regular clinical observation is warranted [11, 120, 123]. The screening could start early in life as a patient as young as six years of age with preceding clinical symptoms has been diagnosed with an *AIP* pathogenic variant and pituitary macroadenoma [124].

X-linked acrogigantism syndrome.

The X-LAG syndrome (OMIM #300942) was described for the first time in 2014 when a syndrome of early infant-onset pituitary gigantism was linked to microduplications of Xq26.3 region, encompassing the *GPR101* gene (OMIM *300393) [13]. It is a rare condition and less than forty cases have been described so far [13, 125-131]. Historically, some of the tallest humans bear clinical features suggestive of X-LAG [132]. For example, a recent paleogenetic study found increased copy number of the *GPR101* gene in an historic giant (2m 59 cm) from the early 20th century [133].

In X-LAG the common duplicated region on chromosome Xq26.3 usually encompasses several genes, among which only *GPR101* is differentially overexpressed in the affected pituitary adenoma [13]. Indeed, in one X-LAG patient a duplication was identified in which only the *GPR101* gene was duplicated [127]. Duplications were germline in females and somatic in sporadic males with variable level of mosaicism in the latter [126, 127, 130]. In three families the duplication was transmitted from mother to son and all carriers of the duplication had gigantism [131]. The *GPR101* gene encodes an orphan G protein-coupled receptor [13, 131]. The exact mechanisms of tumorigenesis remain to be fully clarified, but there is some evidence that cAMP-PKA dependent signaling pathway and increased GHRH secretion could be involved [129, 131, 134].

X-LAG syndrome is characterized by some clinical features that discriminate it from other forms of pituitary gigantism. It is a pediatric condition and most of the patients are born with normal height and weight. However, during the first months of their life, as early as 6-12 months, they start to grow excessively and the diagnosis is almost invariably made before the age of 5 years, when their median height standard deviation score (SDS) is about +4-5 SDS, as well as weight +4.4 SDS. Females prevail over males (2/3 of the cases). Patients have acromegalic features (facial coarsening, including broad nasal bridge, prominent mandible, increased interdental space, and enlarged extremities) and about a third have an increased appetite [125, 126]. Most of the patients harbor macroadenomas at diagnosis, generally mixed GH – and PRL-secreting tumors, while a minority have hyperplasia alone. A pattern of multiple microadenomatous foci against hyperplasia background has also been described. The proliferation index of such adenomas is generally low (Ki-67 LI below 3%) [125, 126, 128] but if the condition is left untreated it eventually ends with aggressive adenoma progression [128]. GH and IGF-1 are markedly elevated at diagnosis, with concomitant hyperprolactinemia in more than 80% of the patients. Increased levels of GHRH have been detected in some patients, however not in the extent typical for the ectopic GHRH secretion [13, 125, 129]. With respect to treatment, it is complex and a multimodal approach is necessary. Surgery alone can lead to cure but even if GH control is achieved, hypopituitarism remains a life-long burden in many cases. None of the patients responded to first-line somatostatin analogs even at doses typical for adults. The reason for this phenomenon needs to be further clarified as studied tissues from pituitary adenomas of X-LAG patients show preserved SST2 and AIP expression [125]. Pegvisomant, alone or in combination, is able to induce IGF-1 normalization [123, 125, 126]. Radiotherapy has been applied in a few of patients with unconvincing effects on hormonal hypersecretion [125, 126].

When compared with gigantism in the setting of *AIP* pathogenic variants or genetically negative cases, X-LAG syndrome could be distinguished by the early childhood or infant onset of disease symptoms, female predominance, presence of acromegalic features in such early age, increased appetite, marked hormonal hypersecretion, histologically presence of mixed GH-PRL-secreting adenomas and/or hyperplasia; a poor response to SSAs occurs in both *AIP* mutated and X-LAG related gigantism [99, 126].

In patients with sporadic acromegaly a missense variant has been observed (p.E308D), affecting the intracellular loop 3 of *GPR101*. It is relatively rare and its role in pituitary pathogenesis is unknown [13,

[126, 135-137]. Other missense variants have been detected in prolactinomas and corticotropinomas with unknown impact on tumorigenesis [137, 138].

Recently the first prenatally diagnosed case of X-LAG was described, offering a unique prospective observation of the natural course of the disease. The mother had a distant history of acrogigantism starting at 4 months of age with complete cure after the resection of the pituitary adenoma at 24 months. She had typical characteristics of X-LAG and the Xq26.3 microduplication was found at preconception testing. The same genetic abnormality was found in her son on a chorionic villus sample, who grew rapidly and had tumor extirpation at the age of 15 months. The immunohistochemical analysis of both adenomas (mother's and son's) revealed elevated Ki-67 proliferation index, multiple lineage specific transcription factors and stem cell markers [139].

Multiple endocrine neoplasia 1 (MEN1)

MEN1(OMIM #131100) is a multiorgan disorder including endocrine and non-endocrine tumors. Clinically it is characterized by the occurrence in a patient of at least two of the three following disorders: hyperparathyroidism, pituitary adenoma, and pancreatic neuroendocrine tumors (NET). Among the other tumor presentations are facial angiofibroma, collagenomas, lipomas, adrenocortical tumors and carcinoid tumors [140]. The *MEN1* gene (OMIM *613733) is located on chromosome 11q13 and encodes menin, which is a 610 amino-acid nuclear protein [141, 142]. Menin interacts with various proteins involved in transcriptional regulation, genome stability, cell division and proliferation [143]. The disorder has autosomal dominant inheritance with high penetrance and in about 10% may arise from *de novo* pathogenic variants [144]. Pituitary adenomas occur in about 15-50% of MEN1 patients [144-151].

The most prevalent pituitary subtypes are prolactinomas (60-80% of the cases), followed by non-functioning pituitary adenomas (in more recent series – up to 42%), or somatotropinomas (in older series – up to 25%) and corticotropinomas (<5%)[144, 146-149]. In rare cases GH hypersecretion could be caused by ectopic GHRH secretion from NETs [152]. A distinctive but uncommon feature of MEN1 pituitary adenomas is the plurihormonal profile (especially prolactin-ACTH and/or GH positive tumors on immunohistochemistry), as well as the presence of multiple pituitary adenomas [152-155]. In about 15-30% of patients a pituitary adenoma is the first presentation of MEN1 syndrome [140, 147-149]. Among sporadic pituitary adenomas the occurrence of MEN1 is quite rare- less than 3% [152, 156, 157]. However, in the pediatric population, similarly to the *AIP* mutations, the frequency of MEN1 may be higher - up to 6.5% [96, 97] and pituitary adenomas can occur as early as 5 years of age [158]. Gigantism due to MEN1 occurs in less than 1% of all pituitary gigantism cases [99]. In the setting of MEN1 with pituitary adenomas, females prevail over males (approximately two thirds of the cohorts), partly due to the higher prevalence of females with prolactinomas [148-151]. Interestingly, when pituitary adenoma was the first presentation of the syndrome, MEN1 was more frequently diagnosed in males than females (67.3% *vs.* 44.2% respectively), explained by the smaller of initial pituitary lesions in women, or the higher prevalence of sporadic pituitary adenomas in females, leading to delayed diagnosis by clinicians [149] In series including

patients before the introduction of routine screening programs MEN1 pituitary adenomas were predominantly macroadenomas (approximately 80%) and more invasive than their sporadic counterparts [146, 152]. A recent nationwide Dutch study on MEN1 pituitary adenomas shows higher frequency of microadenomas – in approximately two thirds of the cases. Notably, approximately half of the adenomas diagnosed in asymptomatic patients by MRI screening were microadenomas. In the absence of tissue confirmation these could represent incidentalomas, which are commonly seen in the general population and could be a source of bias. In that study pituitary adenomas diagnosed clinically prior to the genetic diagnosis of MEN1 were more frequently macroadenomas versus screening-detected pituitary tumors (81.2% vs. 46.3%, $p<0.001$) and more often functional (70.2% vs. 47.0%, $p=0.009$)[148]. In the French-Belgium cohort, a poor response to treatment was reported, with normalization of prolactin in only 44% of the patients [146], while in the Dutch series more that 90% of the prolactinomas responded to dopamine agonists [148]. According to the last guidelines the treatment approach towards MEN1 pituitary adenomas should be identical to non-MEN1 adenomas [144]

However, moving beyond the MEN1 guidelines, due to the high penetrance of the syndrome, the first presentation with pituitary adenoma in up to a third of the patients, and a higher frequency in young patients with aggressive macroadenomas[96, 144, 146, 159], genetic screening for *MEN1* (and *AIP*), could be considered in patients with young onset, invasive macroadenomas.

MEN4

On genetic testing about 10% of patients with familial and possibly more sporadic MEN1 cases do not harbor *MEN1* pathogenic variants [143]. MEN4 (OMIM #610755) emerged as a new condition in 2006, when pathogenic variants in *CDKN1B* gene (OMIM *600778) was described in a family with a MEN1-like phenotype, including acromegaly, primary hyperparathyroidism and other tumors [12]. *CDKN1B* is located on chromosome 12p13 [160] and encodes p27, a cyclin dependent kinase inhibitor implicated in the regulation of cell cycle progression and arrest [161, 162]. Up to the present, approximately 20 cases harboring *CDKN1B* germline pathogenic variants have been published, explaining 1.5-3.7% of *MEN1* pathogenic variant negative patients with the corresponding phenotype [163-166]. In the setting of MEN4, pituitary adenomas arose in about 37% of reported cases including somatotropinoma, corticotropinoma, non-functioning pituitary adenoma and prolactinomas, with an age range at onset of 30-79 years [163]. In as study of 21 pitutiary adenomas (20 corticotropinomas) no somatic *CDKN1B* alterations were present [167]. No germline *CDKN1B* pathogenic variants have been found in a series of 88 sporadic or familial pediatric pituitary adenomas [97] and in the FIPA setting it was a very rare and questionable finding [168]. Genetic screening for this condition should be probably performed only in *MEN1* negative kindreds or individuals and routine screening of patients with isolated pituitary adenomas is unlikely to identify *CDKN1B* mutation carriers.

Carney complex (CNC)

Carney complex (OMIM #160980) is a rare autosomal dominant disease that is characterized by the presence of myxomas, spotty skin pigmentation (lentigines) and endocrine hyperactivity [169, 170]. Some of the most common endocrine abnormalities are primary pigmented nodular adrenocortical disease (PPNAD), pituitary adenomas, thyroid nodules, testicular tumors and ovarian cysts. More than 750 cases have been described to date [171] and most cases have *PRKAR1A* (OMIM *1888830) pathogenic variants [172, 173]. Another locus associated with the disease is located on chromosome 2p16 [174] and lately copy number gain at the *PRKACB* gene locus (OMIM *176892) was described in a patient with abnormal skin pigmentation, myxomas and acromegaly [175]. *PRKAR1A* pathogenic variants lead to loss of function of the protein kinase A 1α regulatory subunit resulting in increased cAMP-dependent PKA activity [171]. In the setting of Carney complex the presentation of pituitary adenomas is generally in the third or fourth decade and it is usually preceded by other syndromic feature [171]. Approximately 75% of the patients have high but asymptomatic levels of GH, IGF-1 and prolactin with abnormal responses to dynamic testing, however only up to 12% develop overt acromegaly, while prolactinomas are rare[176]. CNC contributes less than 1% of gigantism cases. In sporadic pituitary adenoma cohorts pathogenic variants of *PRKAR1A* or in other subunits of PKA do not play frequent role in tumorigenesis [97, 177-179]. In cases with single adenomas surgery could be potentially curative. However, similar to X-LAG, in the setting of CNC, multiple adenomas with surrounding hyperplasia is a known finding [180, 181] and clinical management could require partial or total hypophysectomy [181]. Medical treatment with somatostatin analogues or a GH receptor antagonist could also be considered [171].

McCune-Albright syndrome

MAS (OMIM #174800) is a well established syndromic condition predisposing to acrogigantism and includes the classic triad of precocious puberty (endocrine hyperactivity), fibrous dysplasia and café-au-lait macules [182, 183]. It is caused by a post-zygotic, mosaic, gain-of function mutation in *GNAS* and the clinical manifestation is determined by the number of affected tissues, and possibly the timing of the mutation's occurence [184, 185]. In the context of MAS, 10-25% of the patients could have GH hypersecretion leading to gigantism or acromegaly, often accompanied by hyperprolactinemia. MAS account for about 5% of gigantism cases [99]. Similarly to CNC and X-LAG, pituitary hyperplasia or a distinct pituitary adenoma could be found in the gland [186-189]. Treatment in these patients is challenging due to various factors: difficult surgical access due to bone thickening, presence of diffuse pituitary hyperplasia, partial response to somatostatin analogues, risk of sarcoma transformation of affected bone, following radiotherapy. Treatment with pegvisomant could be useful in such cases [123, 187-191]

Pheochromocytoma/Paraganglioma and Pituitary adenomas Association (3PAs)

The coexistence of these tumors, termed 3PAs [15], is quite rare, although it had been described historically [192]. The interrelation between the tumors has been strengthened recently by the finding of a germline *SDHD* (OMIM *602690) pathogenic variant in a patient with pheochromocytoma, paragangliomas and

acromegaly, strengthening a pathogenetic role of the mutation by loss of heterozygosity for *SDHD* and down-regulation of the corresponding protein in the pituitary adenoma tissue [14]. Approximately 80 cases with this association have been described in literature and genetics studies in recent cases revealed genetic defects in approximately one third of cases [193-198]. Most of the patients had mutations in one of the four genes encoding SDH subunits that are previously known to predispose to pheochromocytoma/paraganglioma [193].

The succinate dehydrogenase complex forms the mitochondrial complex II on the inner mitochondrial membrane and consists of four subunits (A, B, C and D) and an associated assembly factor (SDHAF2). It is responsible for electron transfer in the respiratory chain and converts succinate to fumarate [199]. An impaired SDH complex mimics hypoxia, and oncogenesis is likely to be mediated by hypoxia-inducible factor-1 α (HIF-1α) related pathways [200].

Clinically, the potentially *SDHx*-mutated pituitary adenomas can be prolactinomas, somatotropinomas or non-functional adenomas. Most are macroadenomas with an aggressive clinical course – requiring surgery and with poor response to somatostatin analogues [193]. One carcinoma has been described [196]. A distinctive pathologic feature of *SDHx*-mutated pituitary adenomas is an extensive vacuolization of the cytoplasm [201].

Recently, the 3PA syndrome was associated with germline *MYC-associated factor X (MAX)* (OMIM *154950) pathogenic variants or intragenic deletions in five patients (three prolactinomas and two somatotropinomas) [194, 195, 202]. Single cases of 3PAs have also been described in the setting of MEN1, MEN2 or von Hippel-Lindau disease [193] Screening for *SDHx* mutations in the pool of sporadic pituitary adenomas without personal or familial syndromic history is not warranted as they are quite rare [15, 201, 203, 204]. Of note intragenic deletions such as those seen in *MAX* require MLPA analysis as they are not detectable on Sanger sequencing [195].

Other germline conditions

Growth hormone excess causing acromegaly or gigantism can rarely be part of neurofibromatosis type 1 (NF1) (OMIM #162200), characterized by neurofibromas, *café-au-lait* macules, intertriginous freckling, osseous lesions, Lisch nodules and optic pathway gliomas [205, 206]. GH hypersecretion with an increase in growth velocity has been observed in about 10% of children with optic pathway gliomas, which is more frequent than previously thought [207]. In accordance with other data in the literature affected children have an optic chiasm tumor but not a pituitary adenoma [207]. In such cases the pathogenesis of GH excess has been considered to be either due to loss of somatostatingergic inhibition, or presence of overactive GHRH secretion in the optic pathway tumor [207, 208]. In a series of 10 patients with overgrowth and NF1 in the National Institute of Health, including children and adults, a link between pituitary tumorigenesis, NF1 and GH excess has been confirmed. Of note, similarly to MAS and CNC, pituitary hyperplasia has been described in some cases. Given the probability of increased

oncological risk, or worsening neurofibromas, pain, or endocrinopathies, it is strongly advisable to investigate NF1 patients for GH excess, including appropriate sellar region and optic tract imaging [208].

Pituitary blastomas (pituitary tumor with embryonic origin) are very rare and could arise in the setting of DICER1 syndrome (OMIM #601200), known also as pleuropulmonary blastoma- familial tumor. *DICER1* (OMIM *606241) encodes a protein responsible for microRNA maturation. Clinically it presents in early infancy with Cushing's syndrome with high mortality [9, 209-211].

Recently, another potential pituitary adenoma predisposition gene has been described - *CABLES1* (CDK5 and ABL1 enzyme substrate 1) (OMIM *609194) [212]. CABLES1 protein is implicated in the negative cell cycle regulation in corticotropes in response to glucocorticoids. Usually the physiologic adrenal-pituitary negative feedback is disrupted in corticotropinomas and CABLES1 protein expression is often lost [213]. Given this background, germline and/or tumor DNA samples from an international cohort of 146 pediatric and 35 adult patients was studied for *CABLES1* gene variants or copy number variations [212]. Four heterozygous missense variants were found in two pediatric and two young adult Cushing's disease patients. Functionally these variants appeared to interfere with the normal inhibition of cell growth by CABLES1 in vitro. The possible tumorigenic mechanism could be linked to increased CDKN1B degradation as all mutated samples showed markedly reduced nuclear CDKN1B staining and preserved, although weaker, CABLES1 immunohistochemical expression. Clinically, all four corticotropinomas were macroadenomas with high Ki-67 index, three of them had extrasellar extension and three required second transsphenoidal surgery [212]. Isolated cases of corticotropinomas in the setting of congenital adrenal hyperplasia (OMIM #201910) with pathogenic variants in the 21-hydroxylase enzyme gene (*CYP21A2*) (OMIM *613815) and in the setting of X-linked congenital adrenal hypoplasia (OMIM #300200) with pathogenic variant in the NR0B1 (nuclear receptor subfamily 0 group B member 1) (OMIM *300473) gene have been reported [214-216].

Discussion and Conclusions

Scientific progress has led to the discovery of numerous new genetic and genomic disruptions in patients with pituitary tumors. The most frequent genetic causes are summarized in Table 1. While for somatic pathogenic variants discriminative clinical features can be quite subtle, most germline pathogenic variants, though rare, present with particular clinical features. To help prompt diagnosis and treatment, integrated screening could be offered for germline variants (Figure 1). Pediatric patients (up to 18 years) with isolated pituitary adenomas and young adults (<30 years) with isolated aggressive or large pituitary macroadenomas should be screened for *AIP* and *MEN1* gene variants or deletions. Very early onset cases of somatotropinomas in children should be screened for *GPR101* duplications via array comparative genome hybridization, and droplet digital PCR can be used for confirmatory purposes. Patients with FIPA should undergo genetic screening for *AIP* variants/deletions (*AIP*-negative FIPA families with gigantism cases should be considered for X-LAG screening). Patients or kindreds with MEN1 phenotype without *MEN1* pathogenic variants could be screened for *CDKN1B* gene variants;

CDKN1B pathogenic variants rarely lead to isolated pituitary adenomas. Genetic screening for Carney complex tends to be guided more by the presence of typical syndromic features rather than any specific characteristics of the pituitary adenomas that occur in Carney complex. The combination of pheochromocytoma and/or paraganglioma and pituitary adenoma could be indicative of *SDHx* or *MAX* genetic alterations, including pathogenic variants and deletions. As the availability of multi-gene panels is increasing, a more straightforward approach is to use multigene panels in next generation sequencing platforms: *GNAS, PRKAR1A, MEN1, CDKN1B, SDHx, MAX* in patients with extra-pituitary pathology, and *AIP, MEN1* and *GPR101* in patients with familial history of pituitary adenomas or young patients with aggressive adenomas. The relatives of index cases could be offered genetic counseling or screening, or close clinical and radiological surveillance according to the genetic disruption. Prospectively diagnosed mutation carriers are managed according to the current guidelines or clinical recommendations for each condition, where they exist.

Apart from clarifying their pathogenesis, new genetic findings provide insight into the clinical characteristics and behaviors of mutated adenomas that could discriminate them from the whole pool and possibly serve as a basis for targeted molecular and individualized treatment approach. Overall the genetic causes of sporadic and hereditary pituitary adenomas are unknown in most cases, which argues for collaborative research studies to identify novel molecular genetic mechanisms.

579 **Legends**

580

581 **Figure 1**. Screening for genetic causes of pituitary adenomas.

582 MAS – McCune Albright syndrome; *GNAS* - guanine nucleotide (GTP)-binding protein alpha
583 stimulating*;* CNC – Carney complex; *PRKAR1A* – protein kinase type I-alpha regulatory subunit gene;
584 *PRKACB* - Protein Kinase cAMP-Activated Catalytic Subunit Beta; PA/PGL/PHEO – pituitary
585 adenoma/paraganlioma/pheochromocytoma; *SHDx* – succinate dehydrogenase complex genes;
586 *SDHAF2* – succinate dehydrogenase assembly factor 2 gene; *MAX* – MYC-associated factor X; *MEN1*
587 – multiple endocrine neoplasia type 1 gene; PHPT – primary hyperparathyroidism; *CDKN1B* – Cyclin-
588 dependent kinase inhibitor 1B; MEN4 – multiple endocrine neoplasia type 4; FIPA – familial isolated
589 pituitary adenoma; *AIP* – aryl hydrocarbon receptor-interacting protein gene; *GPR101* – G protein-
590 coupled receptor 101 gene; X-LAG – X-linked acrogigantism. The figure is adapted by the authors
591 from Rostomyan L and Beckers A. Screening for genetic causes of growth hormone hypersecretion.
592 *Growth Hormone & IGF Research* 30-31 (2016) 52-57 with permission.

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