Growth Hormone & IGF Research xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Growth Hormone & IGF Research

journal homepage: www.elsevier.com/locate/ghir

Review article

Screening for genetic causes of growth hormone hypersecretion

Liliya Rostomyan, Albert Beckers *

Department of Endocrinology, Centre Hospitalier Universitaire de Liège, University of Liège, Domaine Universitaire du Sart-Tilman, 4000 Liège, Belgium

ARTICLE INFO

Article history:
Received 26 September 2016
Received in revised form 10 October 2016
Accepted 11 October 2016
Available online xxxx

Keywords:
Acromegaly
Gigantism
Somatotropinoma
Aryl hydrocarbon receptor interacting protein gene
Familial isolated pituitary adenoma (FIPA)
X-linked acrogigantism (X-LAG) syndrome
GPR101
Multiple endocrine neoplasia
Carney complex
McCune-Albright syndrome

ABSTRACT

Growth hormone (GH) secreting pituitary tumors may be caused by genetic abnormalities in a variety of genes including *AIP*, *MEN1*, *CDKN1B*, and *PRKAR1A*. These can lead to GH secreting pituitary adenomas as an isolated occurrence (e.g. as aggressive sporadic adenomas or in familial isolated pituitary adenomas (FIPA)) or as part of syndromic conditions such as MEN1 or Carney complex. These tumors have more aggressive features than sporadic acromegaly, including a younger age at disease onset and larger tumor size, and they can be challenging to manage. In addition to mutations or deletions, copy number variation at the *GPR101* locus may also lead to mixed GH and prolactin secreting pituitary adenomas in the setting of X-linked acrogigantism (X-LAG syndrome). In X-LAG syndrome and in McCune Albright syndrome, mosaicism for *GPR101* duplications and activating *GNAS1* mutations, respectively, contribute to the genetic pathogenesis. As only 5% of pituitary adenomas have a known cause, efficient deployment of genetic testing requires detailed knowledge of clinical characteristics and potential associated syndromic features in the patient and their family.

1. Introduction

Modern genetic sequencing techniques have made genetic tests for patients with pituitary disease more accessible in routine clinical practice. Nevertheless, the indications for genetic screening in a distinct disease phenotype are continually evolving, which can make testing choices difficult for both the clinician and the patient.

Pituitary lesions are the most frequent cause of chronic growth hormone (GH) excess. When GH excess occurs before the closure of the epiphyseal plates it leads to increased linear growth and gigantism; GH excess leads to acromegaly when it occurs after epiphyseal closure. Pituitary gigantism and acromegaly can be due to isolated somatotropinomas or form part of complex syndromes, although sporadic non-familial presentation remains by far the most common form [1].

Despite recent advances over the last 20 years the genetic etiology of most pituitary adenomas is unknown [1,2]. Traditionally it is considered that about 5% of pituitary adenomas present in familial syndrome settings, most frequently multiple endocrine neoplasia (MEN) type 1 due to mutations in the *MEN1* gene or familial isolated pituitary adenomas (FIPA) in which 15–20% have mutations in the *AIP* gene. Rarer hereditary forms of pituitary adenomas include Carney complex, MEN4, and X-linked acrogigantism (X-LAG) as detailed in Table 1. Based on the characteristic phenotypes produced in these conditions, various recommendations can be made regarding the optimal choice of genetic tests.

2. Genes involved in pituitary tumorigenesis and associated syndromes

2.1. Multiple endocrine neoplasia type 1 syndrome

The *MEN1* gene that encodes the protein menin is mutated in patients with MEN1 syndrome [3]. Both familial and sporadic forms can be observed and 2.7% of all pituitary adenomas are estimated to be a part of this syndrome [4]. Pituitary adenomas are diagnosed in 30–40% of MEN1 patients, being more frequent in familial cases than sporadic. In about 17% of cases the pituitary tumor is the presenting manifestation of MEN1 [5]. Most MEN1- associated pituitary tumors are prolactinomas (50–60%), while acromegaly accounts for 10% [6]. Pituitary tumors can appear in association with other endocrine tumors, mainly primary hyperparathyroidism (95–98%) and gastroenteropancreatic neuroendocrine tumors (30–70%), less frequently with adrenal cortical lesions (25–40%), carcinoids (10%), neuroendocrine thymus tumors (2%) and pheochromocytomas (<1%), as well as non-endocrine lesions (angiofibromas (80%), collagenomas (70%) and lipomas (20–30%)) [7]. MEN1-associated pituitary adenomas are larger (macroadenomas in 85% of cases) and more aggressive with more frequent local compression symptoms and poorer response to treatment than sporadic non-MEN1 tumors [8,9].

* Corresponding author.
E-mail address: albert.beckers@chu.ulg.ac.be (A. Beckers).

http://dx.doi.org/10.1016/j.ghir.2016.10.004
1096-6374/

Table 1
Genes involved in the pathogenesis of the GH secreting pituitary lesions.

Gene	Pathological mechanism	Condition	GH secreting pituitary tumor characteristics
MEN1 (Ch11q13)	Decrease of menin expression and function	MEN1	Somatotropinomas diagnosed at a young age
CDKN1B (Ch12p13)	Decrease of $p27^{kip1}$ level and lack of tumor suppression	MEN4	Rare cases of GH-secreting pituitary adenomas
PRKAR1A (Ch17q22–24) *PRKACB* (Ch1p31.1)	Protein kinase A function alteration	Carney Complex	GH and GH/prolactin secreting adenomas
GNAS1 (Ch20q13.3)	Activation of the stimulatory alpha-subunit (Gsα) of protein G	McCune-Albright syndrome	Pituitary hyperplasia and adenomas, acrogigantism
AIP (Ch11q13.32)	Decrease of AIP (mRNA and protein) expression, alteration of regulation of AhR or phosphodiesterase function	FIPA	Somatotropinomas/ somatomammotropinomas, acrogigantism, age at onset mainly in adolescence. Homogeneous and heterogeneous families (all pituitary adenoma secretion subtypes involved)
GPR101 (ChXq26.3 microduplications)	Increased expression of GPR101 and GH hypersecretion	X-LAG FIPA	Early onset acrogigantism (younger than age of 5 years), sporadic, mosaic and in familial settings, mixed GH/prolactin adenomas with or without hyperplasia

MEN1—multiple endocrine neoplasia type 1; $p27^{kip1}$—cyclin-dependent kinase inhibitor 1B; MEN4—multiple endocrine neoplasia type 4; GH—growth hormone; AIP—aryl hydrocarbon receptor interacting protein; AhR—aryl hydrocarbon receptor; FIPA—familial isolated pituitary adenomas; X-LAG—X-linked acrogigantism.

MEN1 gene is a tumor suppressor gene with autosomal dominant transmission and high penetrance (95% of MEN1 patients have manifestations after age of 50 years) [8,10]. Menin participates in cell cycle and oxidative stress regulation [7]. >700 mutations in *MEN1* had been reported [11]. Gene inactivation can be caused by mutations or gross DNA changes (large genomic rearrangements). These large genomic rearrangements can be detected by Multiple Ligation Probe Amplification (MLPA) and represent about 1–5% of mutations in *MEN1*, most frequently being seen in familial cases [11].

2.2. Multiple endocrine neoplasia type 4 syndrome

Several cases of GH-secreting pituitary adenomas have been reported in the context of MEN4 syndrome due to germline mutations in *CDKN1B* gene, that encodes cyclin dependent kinase inhibitor 1B, $p27^{kip1}$ [12,13]. This MEN1-like syndrome has been described in rats as MENX, exhibiting multiple tumors, including pheochromocytoma, medullary thyroid cell neoplasia, parathyroid adenomas, paragangliomas, pancreatic hyperplasia and pituitary adenomas [13]. In humans, Pellegata et al. identified a nonsense mutation in the *CDKN1B* gene in a German kindred with acromegaly, primary hyperparathyroidism, renal angio-myolipoma, and testicular cancer [14]. Most MEN4 cases present pituitary and parathyroid lesions, and rarer clinical features include gastroenteropancreatic neuroendocrine, adrenal, thyroid tumors and other non-endocrine conditions. Although inactivating and missense mutations in this gene can produce acromegaly with or without MEN1-like phenotype [15], such alterations are considered as a very rare cause of somatotropinomas.

2.3. Carney complex

Acromegaly can occur as a manifestation of Carney complex [16,17]. In 70% of cases Carney complex is familial [17]. Two gene loci have been identified for this condition: the *PRKAR1A* gene on chromosome 17q22–24 and a second potential locus on 2p16 [18,19]. About 60–65% of Carney complex cases are due to *PRKAR1A* mutations [20–22]. Carney complex is a rare condition (<1000 cases described) [16,23] that presents as an association of skin pigmentation, cardiac and cutaneous myxomas, endocrine hypersecretion and schwannomas [24]. Among endocrine abnormalities the most common are primary pigmented nodular adrenocortical disease, thyroid nodules/tumors and testicular tumors (Leydig cell tumors, large cell calcifying Sertoli cell tumor) [25]. Although acromegaly due to a pituitary tumor is infrequent and is diagnosed in only 10% of cases, about 75% of patients exhibit asymptomatic elevations in GH, IGF-1 or prolactin levels. Therefore, in *PRKAR1A* mutation positive individuals GH, IGF-I and prolactin levels should be assessed on a yearly basis. It is interesting to note that there are some genotype-phenotype correlations for *PRKAR1A* mutations in relation to pituitary involvement. Acromegaly is more frequent with specific exon-located mutations, which are also associated with increased occurrence of schwannomas, lentigines and cardiac myxomas [21]. GH hypersecretion in Carney complex is usually caused by multifocal hyperplasia of somatomammotropic cells [26] that can then form GH/prolactin-secreting adenomas, and is frequently accompanied by elevated prolactin. Mixed pituitary tumors staining positively for thyroid-stimulating hormone, luteinizing hormone or alpha-subunit can be also found in some cases with Carney complex [27]. A pituitary MRI is recommended at baseline in newly diagnosed cases with the repeat imaging based on disease progression and hormonal disturbances during follow-up. In addition, clinical features similar to Carney complex have been reported in a case with triplication on chromosome 1p31.1, including the gene encoding the catalytic subunit of protein kinase A (*PRKACB* gene) that presented with acromegaly due to a pituitary tumor in association with pigmented spots and myxomas [28].

2.4. Pituitary adenoma and pheochromocytoma/paraganglioma

Another non-classical syndromic presentation of somatotropinoma in association with pheochromocytoma was first described in 1952 [29]. Recently, mutations in succinate dehydrogenase (SDH) subunit genes—*SDHA*, *SDHB*, *SDHC* and *SDHD*, were suggested as being implicated in pituitary adenoma formation in rare cases of coexisting pituitary tumors and pheochromocytoma/paraganglioma (3PAs syndrome) [30–32]. Familial and isolated cases have been described. *SDHx* mutation-associated pituitary lesions and pheochromocytoma/paraganglioma may occur simultaneously in one patient or be diagnosed in several members of the same family. Pathogenic mutations and variants of unknown significance in *SDHx* genes, in particular *SDHD* and *SDHA*, have been found in some 3PAs somatotropinoma cases, all with macroadenomas [33]. Interestingly LOH was detected in pituitary adenomas from patients with *SDHx* abnormalities. Thus, alterations in *SDHx* genes may play a pathogenic role in the development of somatotropinomas [30,32]. However, the association of pituitary adenomas and *SDHx* gene mutations is rare [34]. Therefore screening for *SDHx* mutations could be suggested only based on familial history and specific clinical presentation with pituitary adenoma and pheochromocytoma/paraganglioma.

It is important to consider such cases with atypical multiple endocrine neoplasia also for testing for alterations in *MEN1* [35,36]. However, adrenal medulla tumor formation in MEN1 patients appears to be a very rare event (<0.1%) [37].

Besides that, rare adrenal tumors can produce ectopic GH-releasing hormone (GHRH) with the consequent involvement of somatotrophs in the anterior pituitary. There are some cases described in the literature

Please cite this article as: L. Rostomyan, A. Beckers, Screening for genetic causes of growth hormone hypersecretion, Growth Horm. IGF Res. (2016), http://dx.doi.org/10.1016/j.ghir.2016.10.004