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EDITORIAL

Genetic Testing in Pituitary Adenomas: What, How, and In Whom?

Genética en adenomas hipofisarias: ¿qué, cómo y a quién?

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Clinically diagnosed pituitary adenomas have a prevalence of approximately 1 per 1000 in the general population in Europe and are therefore encountered regularly by clinical endocrinologists in everyday practice[1]. Currently, it is believed that most pituitary adenomas arise from a clonal expansion derived from a somatic mutation in a single cell. For instance, a somatic mutation in *GNAS* is found in up to 40% of somatotropinomas in patients with acromegaly, while somatic *USP8* mutations are now known to account for many cases of Cushing's disease[2,3]. Such pituitary level mutations are only discovered *post hoc* following tumor resection, cannot readily be predicted in advance and are not inheritable. Germline mutations in genes associated with pituitary adenomas are quite rare, and overall, pituitary adenomas occurring in an inheritable or familial setting account for about 5% of cases[4]. As they are rare, generalized screening of pituitary adenoma patient populations to identify genetic mutation carriers is not currently a scientifically or economically valid approach. Most of these genetic causes are associated with a clinical presentation that differs from other pituitary adenomas, and these characteristics can be used to refine screening significantly.

In general, when considering genetic analyses in pituitary adenoma patients a good first step is to determine if the tumor is isolated to the pituitary or forms part of a multiorgan tumor syndrome. Pituitary adenomas can form part of classical endocrine tumor syndromes, such as, multiple endocrine neoplasia types 1 (MEN1) and 4 (MEN4), Carney complex and McCune-Albright syndrome (MAS)[5]. The initial clinical investigation of the patient with a pituitary adenoma should include a detailed personal and family history about tumors and pathologies at other sites, particularly in endocrine tissues[6,7]. Similarly, the family history should specifically search for related individuals with pituitary adenomas.

The focus for genetic testing in pituitary adenomas should primarily be on three main groups: pediatric-adolescent patients, those with a family history of pituitary adenomas and patients with a personal/family history suggestive of an endocrine tumor syndrome.

Pediatric and adolescent patients are a particularly important population, as certain genetic abnormalities leading to pituitary adenomas present more often in the young. For example, in MEN1, pituitary adenomas can have an early age at presentation, and testing guidelines recommend surveillance beginning as early as 5 years of age[8]. In MEN1, pituitary adenomas are generally larger and more difficult to control hormonally than non-MEN1 cases. Pituitary gigantism, by definition a disease that begins at an early age, is a high priority for genetic testing as nearly 50% of cases have a known genetic cause, such as *AIP* mutations/deletions (29%), X-LAG syndrome (10%), McCune-Albright syndrome (5%), and MEN1 or Carney complex (1% each) [9].

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Isolated pituitary adenomas can also occur in a hereditary setting as part of familial isolated pituitary adenomas (FIPA); FIPA is diagnosed in kindreds that have at least two pituitary adenomas in related individuals but in the absence of syndromic features in other organs, such as, MEN1[7]. Mutations in the *AIP* gene explain about 15-25% of FIPA families. *AIP* mutations have quite a low penetrance and about 20% of mutation carriers will develop a clinically significant pituitary adenoma[7]. While *AIP* mutations can lead to all subtypes of pituitary adenomas, they usually cause growth hormone-secreting (GH) or mixed GH-prolactin secreting pituitary macroadenomas during childhood or adolescence. While they most often occur in the setting of FIPA, *AIP* mutation related pituitary adenomas also can occur in isolated patients with young onset, large macroadenomas. In acromegaly, *AIP* mutated patients can be difficult to control, due to high levels of hormonal secretion and poor hormonal and tumoral responses to first-generation somatostatin analogs[7].

X-linked acrogigantism (X-LAG) syndrome is rare but has a very typical presentation as isolated GH-secreting pituitary adenoma and/or hyperplasia causing overgrowth that begins usually in the first 12 months of life[10]. It is due to a microduplication on chromosome Xq26.3 that encompasses the gene *GPR101* and if untreated leads to very severe pituitary gigantism. Diagnosis is made using array comparative genome hybridisation (aCGH). X-LAG syndrome can occur in rare gigantism-only FIPA families[11]. Also, low-level somatic mosaicism is seen in male sporadic patients, which can be detected using specific ddPCR assays[12].

Apart from MEN1 some other syndromic conditions include pituitary adenomas [4]. MEN4 is due to *CDKN1B* mutations, and is a rare syndrome seen in MEN1 negative individuals and kindreds. As relatively few pituitary adenomas have been described in MEN4, there is no specific phenotype to direct genetic testing and *CDKN1B* mutations have not been reported in patients with isolated pituitary adenomas. Carney complex is due to germline *PRKAR1A* mutations and is a multiorgan syndrome involving the adrenals, skin, testes and many other sites. Pituitary adenomas (generally GH secreting) occur in 10% of patients with Carney complex, although many patients will have disorders of GH, insulin-like growth factor 1 (IGF1) or prolactin on hormonal testing in the absence of a pituitary adenoma. *MEN1*, *CDKN1B* and *PRKAR1A* mutations are not considered to be an important cause of isolated sporadic pituitary adenomas.

Mosaicism may also occur in patients with isolated and syndromic pituitary adenomas. In McCune-Albright syndrome, for instance, a post-zygotic, activating mutation in the *GNAS* gene can lead to variable proportions of mutated and wild-type cells across different tissues. Traditional sequencing of *GNAS* for mutations in McCune-Albright syndrome is often negative for technical reasons due to low levels of mutated allele in blood or tumor specimens. Recently, droplet digital PCR (ddPCR) and related techniques have been validated to diagnose very low levels of the mutant *GNAS* allele in blood and tissue DNA, thereby facilitating routine diagnosis[13]. Early genetic confirmation of MAS is important for disease surveillance in the affected individual (it is not currently believed to be hereditary). This is particularly true for somatotropinomas in MAS which can have an early onset, exacerbate co-existing craniofacial fibrous dysplasia and are challenging to treat.

One further syndromic situation of growing interest is the potential for a pituitary adenoma, pheochromocytoma/paraganglioma association (3PA)[14]. In individuals or kindreds presenting with 3PA, a number of mutated genes have been identified, including the succinate dehydrogenase subunit genes (SDHx); recently, mutations and intragenic deletions in *MAX* have also been implicated in 3PA[15].

The increasing number of genes associated with pituitary adenomas has also been accompanied by an expansion in the methodologies needed to correctly identify pathological variations. Rather than Sanger sequencing of individual genes, most reference laboratories have migrated to Next Generation Sequencing (NGS) panels, which allow for parallel analyses of multiple potential genetic targets. Other methodologies need to be considered for specific conditions, such as aCGH for XLAG syndrome, or digital PCR, as mentioned above. Also, multiplex ligation dependent probe amplification (MLPA) kits are available to identify whole or partial gene deletions. MLPA has proven useful in identifying whole or intragenic deletions in genes such as *MEN1*, *AIP*, *SDHx*, and *MAX*, in patients and families with normal sequencing results.

Although rare, genetic causes of pituitary adenomas are important to be aware of, as their overall clinical course is often complicated by aggressive tumor characteristics and treatment is more difficult. Early diagnosis of genetic causes is important to allow for proper screening for syndromic disease and to counsel and identify at-risk mutation carriers. The increasing number of causative genes and emerging clinical syndromes means that clinical endocrinologists will increasingly act in partnership with clinical geneticists to optimise the management of patients with pituitary adenomas.

Bibliografía

1. Daly AF, Rixhon M, Adam C, Dempegioti A, Tichomirowa MA, Beckers A. High prevalence of pituitary adenomas: A cross-sectional study in the province of Liège Belgium. J Clin Endocrinol Metab. 2006;91:4769–75.
2. Peverelli E, Mantovani G, Lania AG, Spada A. cAMP in the pituitary: an old messenger for multiple signals. J Mol Endocrinol. 2014;52:R67–77.
3. Hernández-Ramírez LC, Stratakis CA. Genetics of Cushing's Syndrome. Endocrinol Metab Clin North Am. 2018;47:275–97.
4. Daly AF, Beckers A. Chapter 21 – Genetics of Pituitary Tumor Syndromes. Pituitary. 2017:619–30.
5. Goudie C, Hannah-Shmouni F, Kavak M, Stratakis CA, Foulkes WD. 65 YEARS OF THE DOUBLE HELIX: Endocrine tumour syndromes in children and adolescents. Endocr Relat Cancer. 2018;25:T221–44.
6. Caimari F, Korbonits M. Novel Genetic Causes of Pituitary Adenomas. Clin Cancer Res. 2016;22:5030–42.
7. Daly AF, Beckers A. Familial isolated pituitary adenomas (FIPA) and mutations in the aryl hydrocarbon receptor interacting protein (AIP) gene. Endocrinol Metab Clin North Am. 2015;44:19–25.
8. Thakker RV, Newey PJ, Walls GV, Bilezikian J, Dralle H, Ebeling PR, et al. Clinical Practice Guidelines for Multiple Endocrine Neoplasia Type 1 (MEN1). J Clin Endocrinol Metab. 2012;97:2990–3011.

9. Beckers A, Petrossians P, Hanson J, Daly AF. The causes and consequences of pituitary gigantism. Nat Rev Endocrinol. 2018;14:705–20.
10. Trivellin G, Daly AF, Faucz FR, Yuan B, Rostomyan L, Larco DO, et al. Gigantism and acromegaly due to Xq26 microduplications and GPR101 mutation. N Engl J Med. 2014;371:2363–74.
11. Beckers A, Lodish MB, Trivellin G, Rostomyan L, Lee M, Faucz FR, et al. X-linked acrogigantism syndrome: Clinical profile and therapeutic responses. Endocr Relat Cancer. 2015;22:353–67.
12. Daly AF, Yuan B, Fina F, Caberg J-H, Trivellin G, Rostomyan L, et al. Somatic mosaicism underlies X-linked acrogigantism syndrome in sporadic male subjects. Endocr Relat Cancer. 2016;23:221–33.
13. Romanet P, Philibert P, Fina F, Cuny T, Roche C, Ouafik L, et al. Using Digital Droplet Polymerase Chain Reaction to Detect the Mosaic GNAS Mutations in Whole Blood DNA or Circulating Cell-Free DNA in Fibrous Dysplasia and McCune-Albright Syndrome. J Pediatr. 2018.
14. Xekouki P, Brennand A, Whitelaw B, Pacak K, Stratakis CA. The 3PAs: An Update on the Association of Pheochromocytomas Paragangliomas, and Pituitary Tumors. Horm Metab Res. 2018.
15. Daly AF, Castermans E, Oudijk L, Guitelman MA, Beckers P, Potorac I, et al. Pheochromocytomas and pituitary adenomas in three patients with MAX exon deletions. Endocr Relat Cancer. 2018;25:L37–42.