Genetic Aspects of Pituitary Adenomas

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KEYWORDS

• Pituitary tumor • Genetics • FIPA • AIP • XLAG • MEN1 • MEN4 • Carney complex

KEY POINTS

- Most pituitary adenomas are sporadic and histologically benign; nevertheless, they can cause significant burden due to hormonal hypersecretion and tumor mass effects.
- Both gene expression changes and genetic alterations, including germline (for example *MEN1* and *AIP* genes) or somatic (for example in *GNAS* or *USP8* genes) mutational events, can be identified in pituitary adenomas.
- Five percent of the pituitary adenomas arise in a familial setting occurring either isolated or as part of a syndrome.
- Isolated pituitary adenomas can be observed in *AIP* gene mutation-positive cases and in X-linked acrogigantism due to *GPR101* duplications, but in most familial isolated pituitary adenomas, the disease-causing mutations have not been identified.
- Syndromic presentations occur in MEN1, MEN4, Carney complex, McCune-Albright syndrome, and rarely, mutations in *DICER1* and *SDH* genes can also predispose to pituitary adenomas.

INTRODUCTION

Pituitary adenomas (PAs) are common monoclonal tumors arising from adenohypophysis cells.[1] PAs account for 15% of all intracranial tumors, being the third most common type of intracranial neoplasms, after meningiomas and gliomas.[2] The prevalence of PAs is remarkably high in autopsy and radiological studies, ranging from 14.4% to 22.5%,[2–4] although many correspond to lesions with no clinical relevance.[5,6] Clinically relevant PAs are significantly less common, with a prevalence varying from 1:1064 to 1:1470 in the general population.[7–11] PAs are usually benign, but they can cause significant burden to patients, due to excessive or low hormonal secretion and to tumor

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mass effects, including compression and invasion of relevant surrounding structures. The most common PAs are prolactinomas (46.2%–66.2%), followed by nonfunctioning PAs (NFPAs) (14.7%–37%), somatotropinomas (9%–16.5%), corticotropinomas (1.58%–5.9%), and rarely, thyrotropinomas (0%–1.2%).[2,7–11]

Most PAs occur sporadically (95%). They have a lower level of somatic mutation rate compared with other tumors, but have altered expression profile of numerous pathways, including cell cycle proteins and growth factors, often due to epigenetic mechanisms.[12] Genetic alterations in sporadic PAs may include somatic mutations typically in oncogenes, due to point mutations, such as in the guanine nucleotide-activating α-subunit (*GNAS*) gene, leading to somatotropinomas, or in ubiquitin-specific protease 8 (*USP8*) gene in corticotropinomas,[1,13–15] or changes in gene copy number, such as in the phosphatidylinositol 3-kinase (PI3K) subunit p110α (*PIK3CA*).[16,17]

Five percent of PAs occur in a family setting, because of a genetic defect that predisposes to PA development, either isolated or as part of a syndrome (**Fig. 1**). Despite their relative rarity, hereditary PAs are important entities because they often present in younger patients, have a more aggressive course, and are more refractory to therapy.[18] Syndromic presentation occurs in multiple endocrine neoplasia type 1 (MEN1), MEN4, Carney complex (CNC), McCune-Albright syndrome (MAS), and, more rarely, in *DICER1* and succinate dehydrogenase (*SDH*)-related syndromes. Isolated PAs can be observed in aryl hydrocarbon receptor interacting protein (*AIP*) mutation-positive cases, in X-linked acrogigantism (XLAG) syndrome due to *GPR101* duplications and in *AIP* and *GPR101*-negative familial isolated PAs (FIPA). Although *PRKAR1A*,[19] *DICER1*,[20] and *AIP*[21] occur as germline mutations, *GNAS* mutations can occur in a mosaic or pituitary-specific somatic setting.[22,23] *GPR101* mutations can be germline and mosaic,[24,25] and *MEN1* and *SDH* mutations are primarily germline but a few somatic mutations have also been described.[26,27]

The aim of this article is to review the current knowledge regarding the genetics of PA, in both sporadic and familial PAs and in associated syndromes, from a genetic, molecular, and clinical point of view.

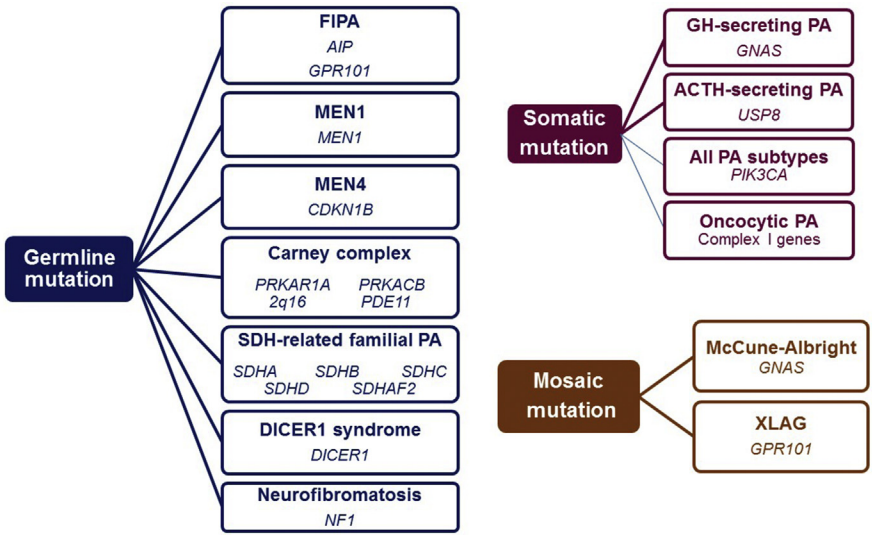

Fig. 1. Pituitary tumors due to genetic origin.