Pituitary adenomas causing clinical symptoms occur in about 1/1000 of the general population, making them one of the main tumors encountered by endocrinologists [1]. In practice, pituitary tumor etiology is rarely known, with 5% of cases having a genetic or hereditary background [2]. These include syndromes like multiple endocrine neoplasia (MEN) 1, familial isolated pituitary adenomas (FIPA), MEN4, Carney complex, McCune-Albright syndrome and X-linked acrogigantism (X-LAG), among others [3, 4].

Among the genetic causes, mutation of the ary hydrocarbon receptor interacting protein (AIP) gene has received the most research interest in recent times. The publication by Ramírez-Rentería and colleagues in the current issue of Endocrine adds the Mexican experience to this body of work from around the world [5]. It is now the 10th anniversary of the discovery of AIP as a pituitary adenoma predisposition gene by Vierimaa et al. [6]. In that study germline AIP mutations led generally to the familial occurrence of acromegaly and prolactinomas. Primarily, that study was focused on large kindreds from Finland that had a p.Q14X AIP mutation, while other AIP mutations were also reported, including p.R304X in Italy. This latter mutation, present in the current Mexican cohort, has been shown to be the most frequently reported AIP mutation worldwide and founder mutations have been established in Italy and Northern Ireland [7, 8].

Over the last decade more than 150 publications have dealt with aspects of AIP function and its role in pituitary tumorigenesis [9]. From this body of work some characteristics of the role of AIP mutations in the clinical setting have emerged. While acromegaly and prolactinomas account for the vast majority of AIP mutation related pituitary adenomas, rare cases of non-functioning adenomas, Cushing’s disease and TSH-secreting adenomas have been reported. In general pituitary adenomas associated with AIP mutations are more aggressive than non-mutated cases. They occur at a younger age and are larger at first symptoms and diagnosis. In the setting of acromegaly, this is also accompanied by a reduced responsiveness to somatostatin analogs, which complicates management [10]. While the mechanism behind this is still unclear, AIP staining intensity is now acknowledged as a marker of somatostatin analog responsiveness in acromegaly irrespective of AIP mutation status [11, 12]. Despite this profile, it remains uncertain if somatostatin analog resistance per se is a criterion for defining a suitable population for screening for AIP mutations.

Among FIPA kindreds about 15–20% are carriers of AIP mutations. Patients with sporadic pituitary macroadenomas that occur during childhood/adolescence and early adulthood also should be considered to be at risk for an AIP mutation (12–20%). The young age at onset and the propensity for causing somatotropinomas means that AIP mutations are strongly associated with pituitary gigantism and represent the single most frequent genetic cause of pituitary gigantism [13]. The study by Ramírez-Rentería et al. confirms that AIP mutations explain a small minority (7%) of sporadic acromegaly patients and that these patients exhibit aggressive features and an earlier age at onset than non-mutated cases. They also studied DNA extracted from a
AIP variant that previously was reported as being non-pathological. It may be that this gigantism case is part of the >50% of cases in which no known genetic cause has been found to date. It also raises the question of how we call an AIP variant as being non-pathological vs. a pathological mutation. This is a challenge in many genetic conditions, particularly with the routine use of next-generation sequencing and whole exome sequencing that provide rich datasets that are heavily laden with variants. While in silico models can help, they are often contradictory in their conclusions and no single model should be relied upon. There are now multiple in vitro models of AIP function, each of which appears to target a different pathway. While the results of these experiments can be persuasive, they raise an important issue. Although there is agreement that AIP mutations are associated with aggressive pituitary adenomas, there is still no consensus on how this occurs and whether AIP is always the primary driver of tumorigenesis. Should AIP have a multifaceted functionality in the pituitary (as suggested by the multiple in vitro models), it may be that AIP mutations could drive or facilitate tumor formation via a variety of routes. As more information accrues, variants that are considered as clinically pathological today could be reclassified as innocuous based on integrated analyses of in silico and in vitro models. The reverse would also be true. After the first decade of research on AIP in the pituitary we have a good understanding of what AIP mutations do in the clinical setting but we have a way to go before determining how they do it.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

References


