

Means, Motive, and Opportunity: SDH Mutations Are Suspects in Pituitary Tumors

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These are heady times in endocrinology, with the application of new techniques revolutionizing our understanding of the genetic pathophysiology of many syndromes of endocrine deficiency and excess. It seems that not a month goes by without a new genetic discovery, and last year's teaching slides are already looking out of date. This ferocious pace of progress is uncovering pathways and potential targets for treatment in many rare conditions. Some discoveries are entirely new genetic causes, whereas others are known genes in new disease settings. This situation is analogous to the work of criminologists using the selfsame genetic techniques to link unsolved "cold" cases to known culprits via studies of archived evidence. In the medical setting, similar good clinical detective work is leading to known genetic culprits in other neuroendocrine tumors being hauled in for interrogation in connection with their links to pituitary tumors.

In this issue of the *JCEM*, Dwight et al (1) describe the occurrence of a pituitary adenoma in the setting of a familial succinate dehydrogenase subunit A (*SDHA*) gene mutation associated with paraganglioma in a first-degree relative. This finding expands the field of the tumor features associated with succinate dehydrogenase subunit (SDHx) mutations into the pituitary, joining the first report from the Stratakis group (2) that definitively linked a succinate dehydrogenase subunit D (*SDHD*) germline mutation to acromegaly. Also, a case from Spain associated with a succinate dehydrogenase subunit C (*SDHC*) germline mutation was reported, although without pituitary tumoral DNA confirmation (3). Data from the literature back to 1952 that were reviewed by Xekouki and Stratakis (4) have included 29 instances of coexisting pituitary adenomas and pheochromocytomas/paragangliomas. Some

modern cases that were negative for existing causative gene mutations appear to be persuasive for further investigation of SDHx status (4). Indeed, the clinical impact of these mitochondrial protein abnormalities already encompasses a remarkably wide range of tumors from renal cell cancers to sporadic and syndromic gastrointestinal stromal tumors (Carney triad and Carney-Stratakis syndrome) and beyond (5–9). The addition of pituitary adenomas to the expanding phenotype related to inheritable pheochromocytoma/paraganglioma syndromes is intriguing and represents both an opportunity and a challenge.

An important area for future study will be to define whether SDHx mutation-associated pituitary adenomas have particular features that differentiate them from the general sporadic population. Clinically relevant pituitary adenomas occur in about 1 in 1000 people in the general population, and prolactinomas account for up to two-thirds of these (10). Pituitary adenomas that occur in recognized genetic or familial settings account for about 5% of cases in our experience (11). Most occur in the setting of familial isolated pituitary adenoma—either with or without a germline aryl hydrocarbon receptor interacting protein (*AIP*) gene mutation—and multiple endocrine neoplasia (MEN) 1 (11–13). Rarer syndromes like that of Carney complex due to protein kinase A regulatory subunit 1A (*PRKAR1A*) mutations or MEN4 due to cyclin-dependent kinase inhibitor 1B (*CDKN1B*) gene mutations also feature pituitary adenomas as part of the described clinical spectrum (14, 15). Large collaborative studies of pituitary adenomas that occur against these known genetic backgrounds have revealed features related to more aggressive behavior, which are useful pointers when determining which patients to offer genetic testing to. *AIP*

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Abbreviations: AIP, aryl hydrocarbon receptor interacting protein; MEN, multiple endocrine neoplasia; SDH, succinate dehydrogenase subunit.

mutations are associated with a very characteristic profile of pituitary tumors that mainly occur in childhood or adolescence/young adulthood, usually (but not exclusively) as somatotropinomas that are large, and treatment resistant, and occur most often in males (11, 16). *MEN1*-related pituitary adenomas are most frequently (again, not exclusively) prolactinomas, but are more difficult to control with medical therapy (13) and may also occur in young patients (17). Pituitary adenomas that occur in association with *CDKN1B* germline mutations (*MEN4*), or with *PRKAR1A* mutations in Carney complex, don't appear to lead to particularly aggressive features.

Considering that more SDHx-mutated pituitary adenomas are likely to be discovered, it would be important to determine whether they, too, are relatively more aggressive or lead to a particular subtype of adenoma. Taking into account the Dwight et al study (1) and those of Xekouki et al (2) and López-Jiménez et al (3), it appears that SDHx mutations can lead to multiple pituitary tumor phenotypes: somatotropinoma, prolactinoma, and non-functioning adenoma. It is interesting to note that all 3 pituitary adenomas displayed aggressive features. All were macroadenomas that required surgery. The nonfunctioning adenoma occurred at a relatively young age (30 y), whereas the prolactinoma occurred in a male; male sex has been previously shown to associate with more aggressive behavior in prolactinomas (18). The acromegaly case described by Xekouki et al (2) in association with an *SDHD* mutation had a "giant" (43 mm maximum diameter) invasive adenoma that compressed the optic chiasma that had a poor response to somatostatin analogs (2). Fascinatingly, the hormonal hypersecretion from the somatotropinoma appears to have boosted the production of catecholamines from the patient's coexisting pheochromocytoma, which strongly expressed the GH receptor. That this synchronous pathological relationship possibly led to worsening of the pheochromocytoma adds impetus to further investigating the role of the pituitary in SDHx-related disease. Although admittedly this is a tiny sample of pituitary adenomas, it suggests that mutation-associated pituitary adenomas, like those related to *AIP* and *MEN1* mutations, might also occupy the more severe end of the clinical spectrum.

Histopathological studies also promise to provide greater clarity about the role of SDHx mutations in pituitary tumorigenesis. Like the impressive work done in the setting of pheochromocytoma/paraganglioma, gastrointestinal stromal tumors, and beyond (19–21), SDHx immunohistochemical studies of archival tumor blocs after pituitary neurosurgery will probably help to identify cases in which germline mutation testing may be warranted. Similarly, tumor-based genetic studies will help us under-

stand the pathophysiological role of somatic SDHx mutations in sporadic pituitary tumors. Together, these approaches could represent a relatively efficient way (in terms of cost and time) to determine whether SDHx mutations are, in fact, an unexpectedly frequent player in pituitary tumorigenesis.

From a practical perspective, it is too early to integrate SDHx mutation analyses into routine clinical genetic investigation of pituitary tumors. The advent of next generation sequencing panels has facilitated such expansion of diagnostic efforts significantly. First, however, we need to establish the epidemiology of this potential SDHx mutation link to pituitary tumor risk in order to tailor genetic, hormonal, and imaging screening activities to aid the clinician's work. Given the extensive collaborative research networks that exist to study pheochromocytomas and paragangliomas, this type of epidemiological work should be feasible (22). As noted in the study by Dwight et al (1), current magnetic resonance imaging screening for carriers of SDHx mutations does not routinely include the sellar region. Initial epidemiological work will, therefore, need to rely on existing clinical information and resurvey of patients and family members for pituitary disorders. Given that incidentalomas are a common occurrence in the pituitary, radiological screening studies will need to carefully weigh the risk of "overdiagnosis" of clinically nonrelevant incidental (micro)adenomas and thus avoid skewing the importance of the pituitary component of this emergent endocrine neoplasia syndrome (23). The Dwight et al study (1) and the work of Xekouki et al (2) also serve as a reminder to all to delve into the medical records and investigate those with atypical or crossover *MEN1*/*MEN2* phenotypes and, importantly, to make connections between related patients with this previously unrecognized association.

Although SDHx mutations like those described by Dwight et al (1) and others may currently be an unfamiliar cause of inherited pituitary tumor risk, it should not come entirely as a surprise, given the experience with multiorgan tumor syndromes like *MEN1*. In contrast to these highly penetrant conditions, the true clinical phenotypes of variably penetrant conditions can be slow to reveal themselves. This can cause particular challenges in tumors that cross the border between traditionally endocrine and non-endocrine sites, such as the clinical scenarios related to *PTEN* mutations (24). Furthermore, recent large-scale cancer genetic studies provide a new and compelling argument that cancers may be better understood not by where they arise but by the genetic mutations/abnormalities that they have in common. Newly minted research shows remarkable similarities in the genetic makeup of common cancers affecting different organs such as the en-

dometrium, ovary, and breast (25). Hence, cancer behavior may be better understood not as a physical geographic map (site of the primary), but based on shared “cultural” elements (what genetic language the tumor uses to express itself). For those working outside of inherited neoplasia syndromes, this paradigm shift may be a bit jarring. In contrast, it enjoins us to persevere in the investigation, like Georges Simenon’s famous detective Commissaire Maigret, and to keep our eyes open for new clues in unlikely places.

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