

# Succinate Dehydrogenase Deficiency Is Rare in Pituitary Adenomas

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**Abstract:** Germline mutations in the succinate dehydrogenase genes (*SDHA*, *SDHB*, *SDHC*, and *SDHD*) are established as causes of pheochromocytoma/paraganglioma, renal carcinoma, and gastrointestinal stromal tumor. It has recently been suggested that pituitary adenomas may also be a component of this syndrome. We sought to determine the incidence of *SDH* mutation in pituitary adenomas. We performed screening immunohistochemistry for *SDHB* and *SDHA* on all available pituitary adenomas resected at our institution from 1998 to 2012. In those patients with an abnormal pattern of staining, we then performed *SDH* mutation analysis on DNA extracted from paraffin-embedded tissue, fresh frozen tissue, and peripheral blood. One of 309 adenomas (0.3%) demonstrated an abnormal pattern of staining, a 30 mm prolactin-producing tumor from a 62-year-old man showing loss of staining for both *SDHA* and *SDHB*. Examination of paraffin-embedded and frozen tissues confirmed double-hit inactivating somatic *SDHA* mutations (c.725\_736del and c.989\_990insTA). Neither of these mutations was present in the germline. We conclude that, although pathogenic *SDH* mutation may occur in pituitary adenomas and can be identified by immunohistochemistry, it appears to be a very rare event and can occur in the absence of germline mutation. *SDH*-deficient pituitary adenomas may be larger and more likely to produce prolactin than other pituitary adenomas. Unless suggested by family history and physical examination, it is difficult to justify screening for *SDH* mutations in pituitary adenomas. Surveillance programs for

patients with *SDH* mutation may be tailored to include the possibility of pituitary neoplasia; however, this is likely to be a low-yield strategy.

**Key Words:** succinate dehydrogenase, *SDHB*, *SDHA*, pituitary adenoma

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The reported prevalence of pituitary adenomas is up to 1 in 1000.<sup>1</sup> At least 5% are hereditary, and there are clear associations with multiple endocrine neoplasia type 1 (MEN1, associated with *MEN1* mutation), familial isolated pituitary adenoma (often associated with *AIP* mutation), Carney complex (often associated with *PRKARIA* mutation), and MEN4 (associated with *CDKN1B* mutation).<sup>2,3</sup> However, there remain cases of hereditary pituitary adenoma for which no clear syndromic or genetic cause has been identified.

The succinate dehydrogenase (*SDH*) genes *SDHA*, *SDHB*, *SDHC*, and *SDHD* encode the protein subunits of the mitochondrial complex II, a key respiratory enzyme that links the Krebs cycle and the electron transport chain.<sup>4</sup> These genes also function as tumor-suppressor genes, and germline *SDH* mutations are associated with a tumor syndrome characterized by pheochromocytoma/paraganglioma,<sup>5</sup> a unique subtype of gastrointestinal stromal tumor (GIST) known as *SDH*-deficient GIST<sup>6</sup> and a distinctive type of renal carcinoma.<sup>7</sup> It is noteworthy that loss of immunohistochemical (IHC) staining for *SDHB* has been consistently identified in pheochromocytomas/paragangliomas,<sup>8,9</sup> GISTs,<sup>6,10–14</sup> and renal carcinomas<sup>7,15</sup> associated with *SDH* mutation regardless of which *SDH* subunit is mutated. In addition to loss of *SDHB* staining, negative staining for *SDHA* also occurs in pheochromocytomas/paragangliomas<sup>16</sup> and GISTs<sup>17,18</sup> associated with *SDHA* mutation. To date, *SDHA* mutation has not been reported in association with renal carcinoma. Tumors that show negative staining for *SDHB* are known as succinate dehydrogenase deficient, and IHC for *SDHB* and *SDHA* is used routinely to screen patients presenting with compatible tumors for germline *SDH* mutation.<sup>4</sup>

There is now emerging evidence that pituitary adenomas may also be associated with *SDH* mutation. Briefly, 35 cases of coexistent pheochromocytoma/paraganglioma

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and pituitary adenoma in individuals or kindreds have been reported,<sup>3,19–26</sup> and second-hit inactivation has been demonstrated by either loss of heterozygosity<sup>19</sup> or acquired mutation<sup>23</sup> in 2 pituitary adenomas arising in the setting of germline *SDH* mutation. However, to date, the evidence linking *SDH* mutation and pituitary neoplasia has been based on case reports, and the incidence and clinical significance of *SDH* mutation in pituitary adenomas is unknown.

In this study, we sought to estimate the incidence and clinicopathologic associations of *SDH* mutation in pituitary adenomas.

## METHODS

### Patient and Tumor Samples

The computerized database of the Department of Anatomical Pathology Royal North Shore Hospital was searched for all pituitary adenomas resected during the calendar years 1998 to 2012 with material available in archived formalin-fixed paraffin-embedded (FFPE) blocks.

The original slides were reviewed to confirm the diagnosis and select areas of definite tumor for tissue microarray (TMA) construction. The TMA was constructed with duplicate 1 mm cores of neoplastic tissue from all available cases.

### Immunohistochemistry

IHC for SDHB and SDHA was performed on the TMA sections using commercially available mouse monoclonal antibodies against both SDHB (ABCAM ab14714, clone 21A11, dilution of 1 in 100) and SDHA (Mitosciences Abcam MS204, Clone 2E, dilution of 1 in 1000) as previously described.<sup>6,7,9,17,23</sup> IHC was interpreted independently by 2 observers with extensive experience in interpreting these stains (A.J.G. and C.W.T.) who were blinded to all clinical and pathologic features. Cases with definite granular cytoplasmic staining were classified as positive. Cases with absent cytoplasmic

staining in the presence of an internal positive control of non-neoplastic cells were classified as negative. If there was any uncertainty in interpreting the staining on TMA sections (for example due to weak or absent internal positive controls) or if the staining pattern was anything other than definite, strong, diffuse, granular, and cytoplasmic then IHC was repeated on whole sections.

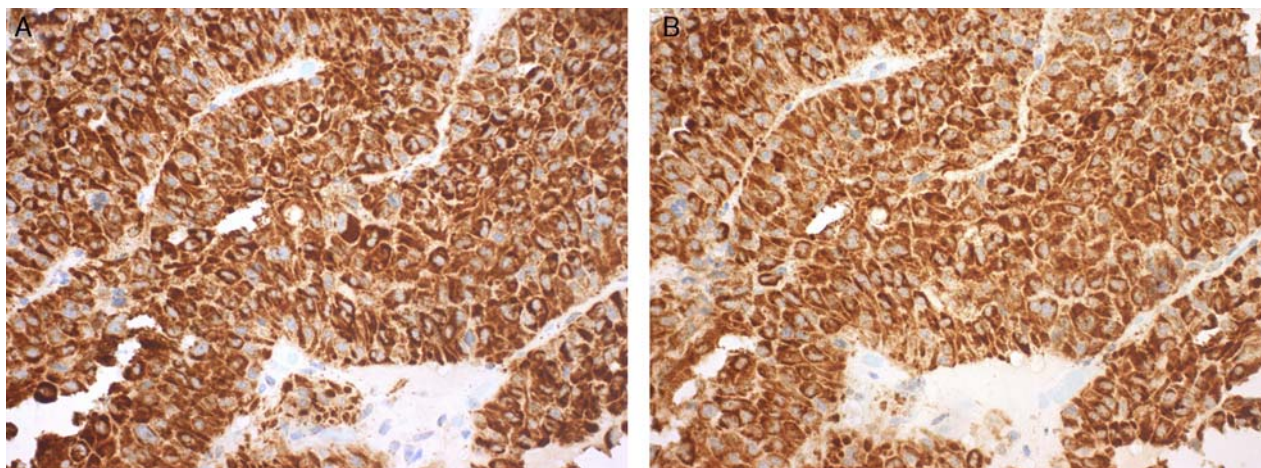
### Mutation Analysis

Mutation analysis was performed in all tumors exhibiting loss of SDHB or SDHA staining by IHC. DNA was extracted from FFPE tissue blocks of macrodissected neoplastic tissue and, where available, from fresh frozen neoplastic tissue and whole blood both prospectively banked at the time of surgery (QIAamp DNA FFPE tissue kit and QIAamp DNA blood minikit; Qiagen, Melbourne, Vic., Australia). Mutation analysis of the entire coding sequence, including exon-intron boundaries, was performed for the 15 exons of *SDHA* (NCBI Ref Seq: NM\_004168.2). Primer sequences were specifically designed to avoid amplification of the 3 pseudogenes (*SDHAP1*, *SDHAP2*, *SDHAP3*) as described previously,<sup>17</sup> and human control genomic DNA (Promega) was used to confirm that none of the pseudogenes were amplified. In some instances, 2 rounds of polymerase chain reaction were required to amplify the DNA from paraffin-embedded tissues. Mutations were confirmed by sequencing of 2 independent polymerase chain reactions. Mutation analysis of *SDHB*, *SDHC*, and *SDHD* was not performed as there were no tumors found to exhibit loss of SDHB alone by IHC.

This study was approved by the Northern Sydney Local Health District Human Research Ethics Committee.

## RESULTS

A total of 336 adenomas from 314 patients were identified from the time period 1998 to 2012. Twenty-seven (8%) of the adenomas were excluded due to



**FIGURE 1.** Most of the pituitary adenomas demonstrated readily recognizable diffuse and strong granular cytoplasmic staining for both SDHA (A) and SDHB (B) (A and B, IHC).

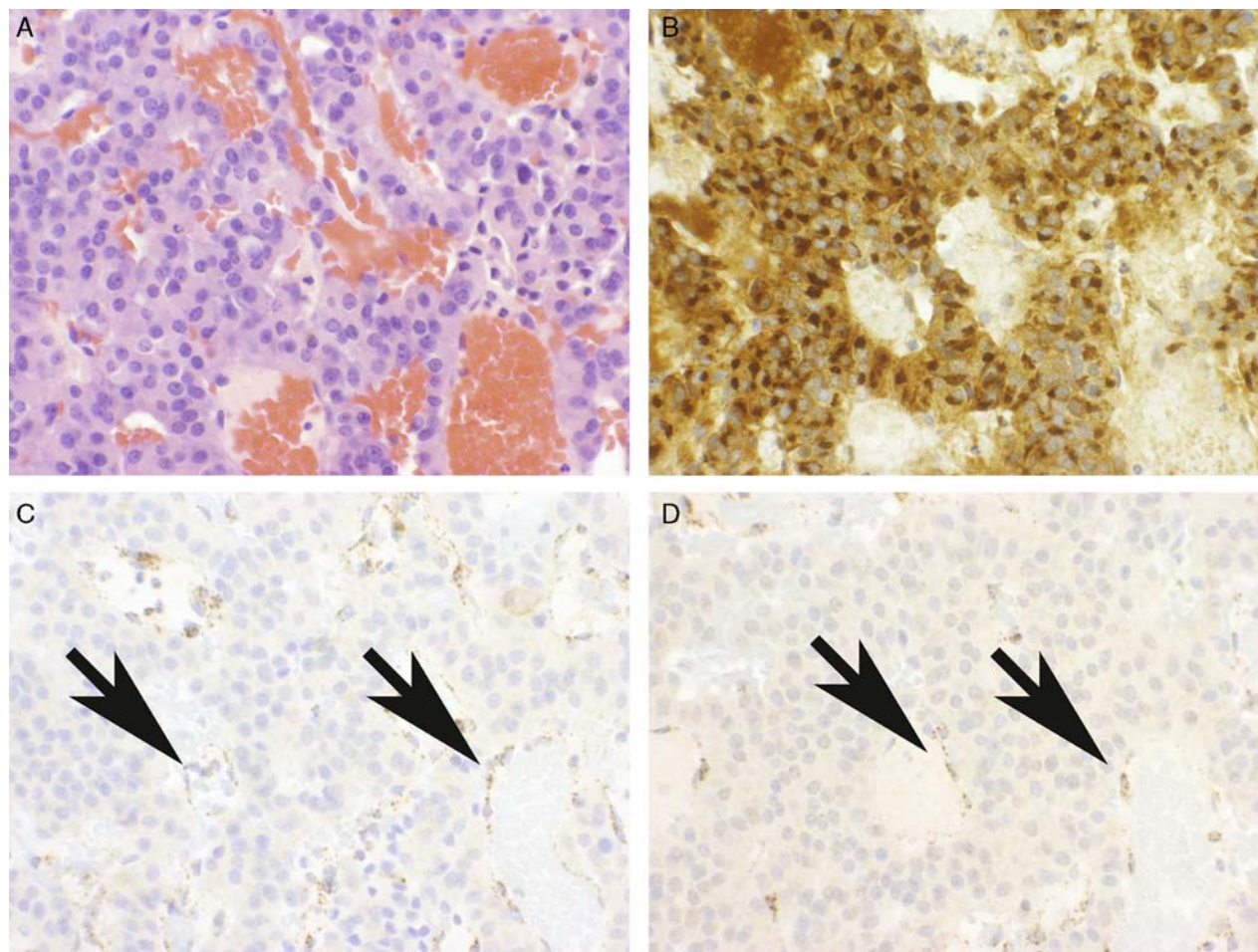
insufficient tissue, leaving a study cohort of 309 adenomas from 287 patients. The mean age at surgery was 57 (range, 17 to 88) years; 164 (54%) patients were male.

A total of 299 adenomas demonstrated diffuse strong granular cytoplasmic staining for both SDHA and SDHB on the TMA sections (Fig. 1). One of 309 adenomas (0.3%) showed negative staining for both SDHB and SDHA. This negative staining was identified by both observers and was present when staining was repeated on whole sections. This was a clinically nonfunctioning pituitary adenoma in a 62-year-old man with no relevant personal or family history to suggest syndromic disease. On preoperative MRI, the tumor demonstrated extensive cystic change. It was 30 mm in diameter and extended from the pituitary fossa to the suprasellar cistern to compress the optic pathways. Despite being clinically nonfunctioning, by IHC the adenoma demonstrated diffuse strong prolactin expression with intense paranuclear (Golgi) accentuation (Fig. 2B)—a staining pattern in-

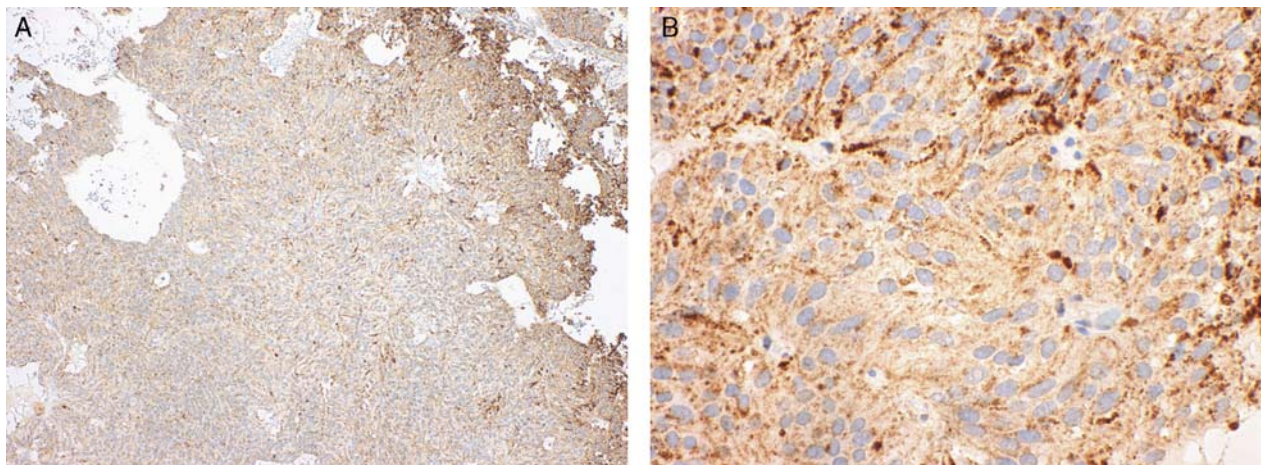
dicative of the sparsely granulated variant of prolactinoma. It is noteworthy that all the neoplastic tissue highlighted by prolactin expression demonstrated loss of SDHB and SDHA expression implying that SDH deficiency was an early clonal event. There was strong positive staining for SDHB in the non-neoplastic pituitary and tumor-associated endothelial cells, which served as an internal positive control (Figs. 2C, D).

Nine adenomas demonstrated less intense but still recognizably positive staining on the TMA sections. Staining of these adenomas was confirmed to be unequivocally diffusely positive when repeated on whole mount sections (Fig. 3).

Both macrodissected FFPE and fresh frozen tumor tissue from the SDHA/B-negative pituitary adenoma underwent targeted sequencing for *SDHA*. In both the FFPE and frozen tissue the same 2 inactivating mutations were identified—a deletion in exon 6 (c.725\_736del) and an insertion in exon 8 (c.989\_990insTA). The entire



**FIGURE 2.** Pituitary adenoma demonstrating loss of staining for SDHB and SDHA. The neoplastic area (A), which demonstrates uniform strong prolactin expression (B), demonstrates completely absent staining for both SDHA (C) and SDHB (D). Note: The non-neoplastic endothelial cells (arrows) demonstrate strong positive staining for both SDHA and SDHB and serve as a positive internal control (A, H&E; B, Prolactin; C and D, IHC).



**FIGURE 3.** Nine pituitary adenomas demonstrated less intense staining but were still recognizably positive. For example, in this case, although positive staining was not readily apparent at low power (A), at high power (B) distinct granular staining was apparent (A and B SDHB IHC)

coding region of germline *SDHA* obtained from the blood sample was sequenced and did not reveal any mutations (Fig. 4).

The patient is currently well with no evidence of recurrence 45 months after surgery.

## DISCUSSION

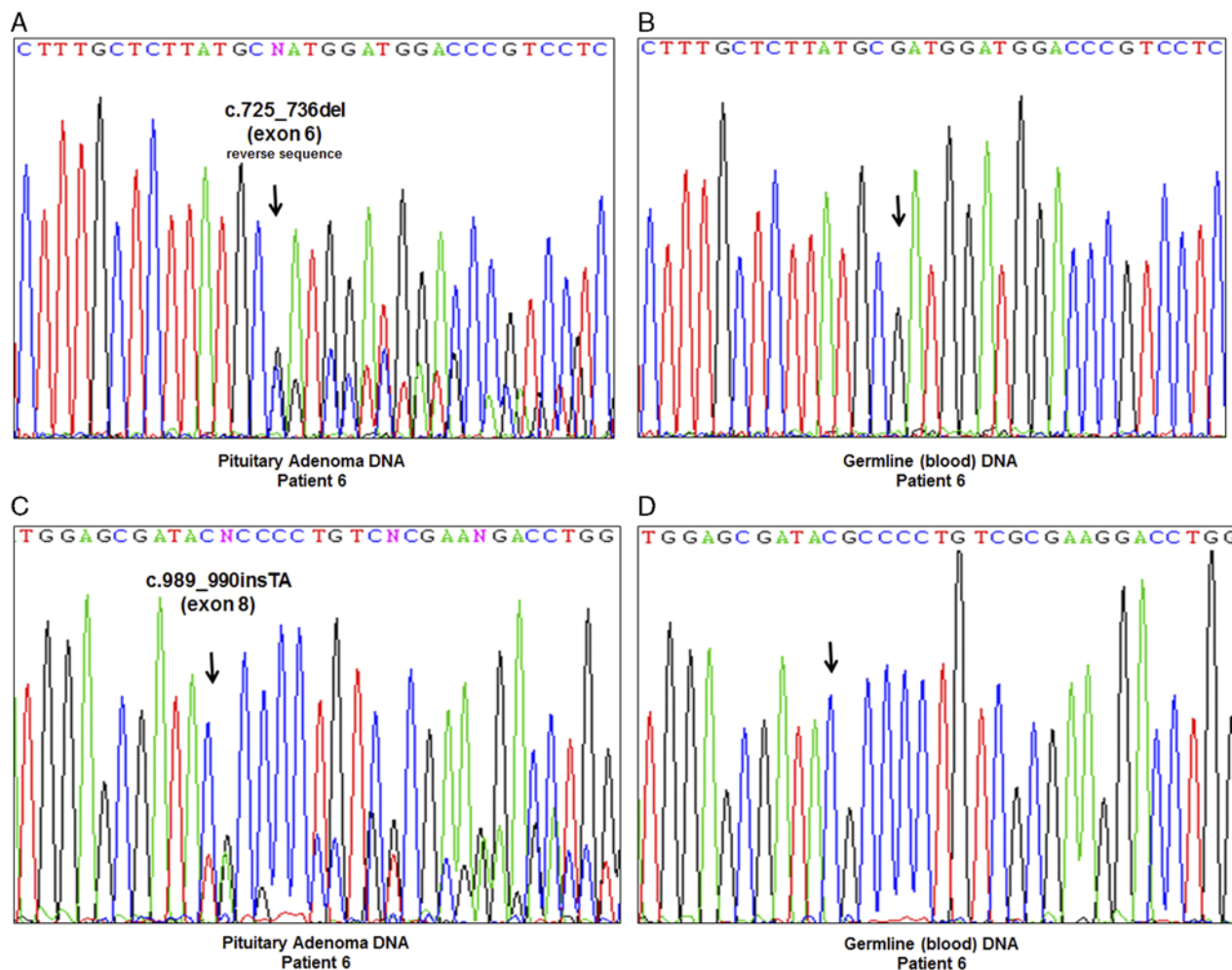
There have been 8 previously reported cases of pituitary adenoma occurring in association with confirmed germline *SDH* mutation,<sup>20,21,23–26</sup> comprising 1 adenoma associated with mutation of *SDHA*,<sup>23</sup> 3 with *SDHB* mutation,<sup>20,21</sup> 2 with *SDHC* mutation,<sup>21,26</sup> and 2 with *SDHD* mutation<sup>24,25</sup> (summarized in Table 1). The causal link between *SDH* mutation and pituitary neoplasia is strengthened by: the presence of confirmed double-hit inactivation in *SDH* in this and 2 other pituitary adenomas<sup>23,25</sup> and the fact that all the neoplastic cells in this case demonstrated loss of expression of *SDHA* and *SDHB* by IHC (implying that *SDH* inactivation is an early clonal event); the fact that *SDH* is an established tumor-suppressor gene in pheochromocytoma/paranglioma, GIST, and renal carcinoma; and the coexistence of pituitary adenoma and pheochromocytoma/paranglioma in 27 other reported cases, albeit without confirmation of *SDH* mutation.<sup>19</sup>

A clinical phenotype of *SDH*-deficient pituitary neoplasia is now emerging. Including this case, of the 9 pituitary adenomas reported in association with confirmed *SDH* mutation, the mean age has been 45 years (range, 30 to 62 y), and 6 have occurred in men. Seven have had hormone production documented clinically or by IHC, of which 6 have been prolactin-producing macroadenomas<sup>21,24,26</sup> and 1 a growth hormone-secreting macroadenoma.<sup>25</sup> In addition, the clinically non-functioning pituitary macroadenoma arising in the setting of germline *SDHA* mutation, which we recently de-

scribed,<sup>23</sup> also demonstrated positive IHC staining for prolactin (previously unreported data).

Taken together the findings suggest that *SDH*-deficient pituitary adenomas may occur at a young age, may commonly be macroadenomas, may more commonly produce prolactin (on the basis of clinical or IHC findings), and may show a slight male predisposition. However, prolactin-producing adenomas in male patients tend to be larger at presentation than in female patients, and prolactinomas in general do not usually come to surgery unless they are large or not responsive to medical therapy. Furthermore, relatively few *SDH*-deficient pituitary tumors have been reported to date. Therefore, more cases will need to be identified before a strong phenotype-genotype correlation for *SDH*-deficient pituitary tumors can emerge to further investigate this suggestion that prolactin-producing macroadenomas in young male patients are more likely to be *SDH* deficient.

Presuming that IHC for *SDHB* is as sensitive for *SDH* deficiency in pituitary adenomas as it is in other tumors, our study indicates that *SDH*-deficient pituitary adenomas are rare, accounting for only 0.3% of unselected pituitary adenomas. Furthermore, germline *SDH* mutation presenting with pituitary neoplasia is extremely rare (none in 309 consecutive adenomas). This is in contrast to pheochromocytoma/paranglioma, in which *SDH* deficiency occurs in up to 15% of cases arising in an unselected population (3% in adrenal pheochromocytomas and up to 40% in extra-adrenal parangliomas),<sup>9</sup> and gastric GIST, in which *SDH* deficiency occurs in 5% to 7.5% of all cases,<sup>6,13</sup> and more in keeping with the low incidence of succinate dehydrogenase deficiency in renal cancer, which is estimated to be 0.6%.<sup>27</sup> On this basis it is hard to justify IHC screening for *SDHB* in all pituitary tumors as has been suggested for all pheochromocytomas/parangliomas as well as GISTs and renal carcinomas with compatible morphology.<sup>4,6–8,15</sup> Instead, we would recommend that IHC screening be considered only



**FIGURE 4.** Sequencing chromatograms of the *SDHA*-mutated pituitary adenoma and the patient's corresponding blood. A, Region of exon 6 harboring the c.725\_736del mutation (A and C, pituitary adenoma; B and D, blood). B, Region of exon 8 harboring the c.989\_990insTA mutation (A and C, pituitary adenoma; C and D, blood). Germline (blood) analysis of the entire coding region of *SDHA* did not reveal any mutations.

in pituitary adenomas with suggestive clinical features such as a young age at onset (particularly if a large prolactin-producing adenoma) or a personal or family history suggestive of syndromic disease.

The very low incidence of *SDH* deficiency in pituitary adenomas has important implications for the development of surveillance guidelines for individuals known to carry *SDH* mutations. Currently, we recommend annual physical examination with blood pressure documentation and fasting fractionated plasma metanephrine and normetanephrine as well as a third yearly MRI from the base of the skull to the coccyx, including kidneys and adrenal glands.<sup>23</sup> Because this field of imaging does not encompass the pituitary, we have considered extending the field to include the sellar region in patients already scheduled for an MRI scan. However, given the high incidence of clinically insignificant pituitary incidentalomas,<sup>28</sup> the benefits of this approach will

have to be carefully weighed against the risk of overdiagnosing and overtreating clinically insignificant incidental pituitary adenomas. In the interim, we recommend that the possibility of pituitary disease, particularly associated with hyperprolactinemia, be specifically considered in the annual history and physical examination for patients with known *SDH* mutation.

The occurrence of 2 somatic *SDHA* mutations in the absence of a germline mutation is very unusual. In other tumors associated with *SDH* deficiency, somatic inactivation of *SDH* in the absence of a germline mutation is a very rare event. In fact, we are only aware of 2 reports of somatic mutation in *SDH* occurring in pheochromocytoma/paraganglioma (1 *SDHB* and 1 *SDHD*) in the absence of germline mutation and none in GIST or renal cancer.<sup>29,30</sup> Although the identification of *SDH* mutation in a tumor is usually considered prima facie evidence of germline *SDH* mutation,<sup>4,6,8,9,12,13</sup> we caution

**TABLE 1.** Reported Cases of Pituitary Adenoma Arising in the Setting of Confirmed SDH Mutation

Case	Germline Mutation	Double-hit Inactivation Confirmed in Tumor	Age (y)	Sex	Size	Hormone Production	Reference
1	SDHB (c.137G → A)	No	49	Female	Unknown	Unknown	Benn et al <sup>20</sup>
2	SDHC (c.256–257insTTT)	No	60	Male	Macroadenoma	Prolactin	López-Jiménez et al <sup>26</sup>
3	SDHD (c.298_301delACTC)	Yes (LOH studies)	37	Male	Macroadenoma	Growth hormone	Xekouki et al <sup>25</sup>
4*	SDHB (c.298T > C)	Yes (LOH studies)	33	Male	Macroadenoma	Prolactin	Denes et al <sup>21</sup>
5*	SDHB (c.298T > C)	No	?	Female	Macroadenoma	Prolactin	Denes et al <sup>21</sup>
6	SDHC (c.380A > G)	No	53	Male	Macroadenoma	Prolactin	Denes et al <sup>21</sup>
7	SDHA (c.1873C > T)	Yes (C.1865G > A)	30	Male	Macroadenoma	Prolactin†	Dwight et al <sup>23</sup>
8	SDHD (c.242C > T)	No	36	Female	Macroadenoma	Prolactin	Varsavsky et al <sup>24</sup>
9	No	Yes, SDHA (c.725_736del) (c.989_990insTA)	62	Male	Macroadenoma (30 mm)	Prolactin†	This case

\*Case 5 is the mother of case 4.

†Clinically nonfunctioning, but prolactin expression demonstrated by IHC. LOH indicates loss of heterozygosity.

that this is not always the case and that inactivation of the *SDH* genes can occur as a truly somatic event. This reinforces that IHC for SDHB, which is also negative in the syndromic but nonhereditary association of gastric GIST, paraganglioma, and pulmonary chondroma known as Carney Triad,<sup>6,10,12,13</sup> should only be considered a screening test to triage formal genetic testing for the *SDH* genes rather than proof of germline mutation.

In conclusion, it appears that pituitary adenomas are a legitimate albeit very rare component of the hereditary syndromes associated with *SDH* mutation, and therefore the possibility of pituitary neoplasia should be considered clinically in patients with *SDH* mutation who are under surveillance. *SDH*-deficient pituitary adenomas may be more frequently large and prolactin producing, may show a slight male sex preponderance, and may more commonly occur at a younger age. However, the issue of whether these associations represent a strong phenotype-genotype correlation awaits confirmation in further cases. Although somatic inactivation of the *SDH* genes in the absence of a germline mutation does occur in pituitary adenomas, it appears to be a rare event, and IHC for SDHA and SDHB can be used to triage formal genetic testing in pituitary adenomas when clinical suspicion of hereditary disease arises.

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