Succinate Dehydrogenase (SDH) D Subunit (SDHD) Inactivation in a Growth-Hormone-Producing Pituitary Tumor: A New Association for SDH?

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Background: Mutations in the subunits B, C, and D of succinate dehydrogenase (SDH) mitochondrial complex II have been associated with the development of paragangliomas (PGL), gastrointestinal stromal tumors, papillary thyroid and renal carcinoma (SDHB), and testicular seminoma (SDHD).

Aim: Our aim was to examine the possible causative link between SDHD inactivation and somatotropinoma.

Patients and Methods: A 37-yr-old male presented with acromegaly and hypertension. Other family members were found with PGL. Elevated plasma and urinary levels of catecholamines led to the identification of multiple PGL in the proband in the neck, thorax, and abdomen. Adrenalectomy was performed for bilateral pheochromocytomas (PHEO). A GH-secreting macroadenoma was also found and partially removed via transsphenoidal surgery (TTS). Genetic analysis revealed a novel SDHD mutation (c.298_301delACTC), leading to a frame shift and a premature stop codon at position 133 of the protein. Loss of heterozygosity for the SDHD genetic locus was shown in the GH-secreting adenoma. Down-regulation of SDHD protein in the GH-secreting adenoma by immunoblotting and immunohistochemistry was found. A literature search identified other cases of multiple PGL and/or PHEO in association with pituitary tumors.

Conclusion: We describe the first kindred with a germline SDHD pathogenic mutation, inherited PGL, and acromegaly due to a GH-producing pituitary adenoma. SDHD loss of heterozygosity, down-regulation of protein in the GH-secreting adenoma, and decreased SDH enzymatic activity supports SDHD’s involvement in the pituitary tumor formation in this patient. Older cases of multiple PGL and PHEO and pituitary tumors in the literature support a possible association between SDH defects and pituitary tumorigenesis. (J Clin Endocrinol Metab 97: E357–E366, 2012)
Coeexistence of pituitary adenomas and paraganglioma (PGL) or pheochromocytoma (PHEO) has not been recognized as a syndrome. We have identified 25 cases of acromegaly since 1964 copresenting with PHEO and one report of extraadrenal PGL and acromegaly (1). Such cases may represent a new multiple endocrine neoplasia (MEN) rather than a fortuitous coexistence.

Mutations in the subunits B, C, and D and recently in subunit A (SDHB, SDHC, SDHD and SDHA, respectively) of the succinate dehydrogenase (SDH) mitochondrial complex II are known to be associated with the development of PGL, PGL and gastrointestinal stromal tumors (Carney-Stratakis syndrome), as well as with renal, and papillary thyroid cancer, neuroblastoma, and adrenal medullary hyperplasia (2–12). A case of testicular seminoma has also been reported in association with SDHD mutation (13).

In the present report, we had the opportunity to study a unique family with multiple members affected by PGL caused by a novel SDHD-inactivating mutation. The proband presented with acromegaly, PHEO and PGL. Genetic studies in his GH-secreting adenoma showed loss of SDHD expression consistent with a possible tumor suppression function in the pituitary tumor of this patient.

**Subjects and Methods**

**Clinical studies and tissue samples**

The institutional review boards of the participating institutions have approved all studies. Blood and tissue samples were collected from the patient and the family members after informed consent was obtained. Tissues were collected at surgery and processed for routine histopathology and immunohistochemistry after formalin fixation and paraffin embedding.

**Hormonal assays**

Plasma and urinary catecholamines and metanephrines were measured using standard assays, as described previously, at the National Institutes of Health Warren Magnuson Clinical Center and Mayo Clinical Medical Laboratories.

**DNA preparation and sequencing studies**

DNA was extracted from peripheral blood leukocytes, frozen tissue samples, or cell lines according to manufacturer protocols (QIAGEN, Valencia, CA). Mutation analysis for exons and the surrounding intron boundaries was performed for SDHB, SDHC, SDHD, MEN1, AIP, and CDKN1B genes; the four exons of SDHD, eight exons of SDHB, six exons of SDHC, six exons of AIP, and two exons of CDKN1B were amplified and sequenced by PCR-based bidirectional Sanger sequencing. The primers used for SDHB, SDHC, SDHD, and MEN1 have been described elsewhere (14, 15). The primers for AIP and CDKN1B mutation analysis are described in Supplemental Table 1. Mouse monoclonal IgG (Novus Biologicals, Littleton, CO); SDHB, HPA002868, rabbit polyclonal IgG (Sigma-Aldrich Inc., St. Louis, MO); and GH receptor (GHR) [N3C2], internal, GTX101192, rabbit polyclonal IgG (Gene Tex, Irvine, CA).

**Immunohistochemistry (IHC)**

All IHC was performed in collaboration with Histoserve, Inc. (Germantown, MD) using standard procedures. Slides from the patient’s pituitary tumor and PHEO were compared with those from a pituitary adenoma from a patient negative for any known mutations, from tissue from a normal pituitary gland and from sporadic PHEO. The following primary antibodies were used: SDHD, sc-67195, rabbit polyclonal IgG (Santa Cruz Biotechnology, Santa Cruz, CA); SDHB, HPA002868, rabbit polyclonal IgG (Sigma-Aldrich Inc., St. Louis, MO); and GH receptor (GHR) [N3C2], internal, GTX101192, rabbit polyclonal IgG (Gene Tex, Irvine, CA).

**Quantitative real-time PCR**

SDHD loss of heterozygosity (LOH) was analyzed by quantitative real-time PCR using SYBR Green in an ABI 7700 Sequence Detection System (Applied Biosystems). The PCR cycling conditions were as follows: 2 min at 95 C, 40 cycles of 95 C for 15 sec and 60 C for 30 sec, and a final step at 72 C for 30 sec. The primer sequences for wild-type (WT) and mutant SDHD alleles are available in Supplemental Table 1. A cycle threshold (C<T>) value in the linear range of amplification was selected for each sample in triplicate. SDHD dosage was determined using the 2^-ΔΔCT method. The normalized value (ΔC<T>) for the WT and mutant SDHD allele in the tumor sample was then compared with the ΔC<T> of both alleles in the peripheral DNA to produce a fold change ratio (normal dosage = 1).

**Immunoblotting**

Western blot analysis was performed following standard procedures. Briefly, cells were lysed by homogenization in 20 mM Tris-HCl (pH 7.5), 100 mM NaCl, 5 mM MgCl2, 1% Nonidet P-40, 0.5% sodium deoxycholate, and protease inhibitor cocktail I (EMD Biosciences, La Jolla, CA) with subsequent centrifugation at 10,000 rpm for 10 min at 4 C. Equal amounts of protein lysate were subjected to SDS-PAGE, transferred to nitrocellulose membranes, and probed with antibodies. The following antibodies were used for immunoblotting: SDHD, H00006392-M04, mouse monoclonal IgG (Novus Biologicals, Littleton, CO); SDHB, HPA002868, rabbit polyclonal IgG (Sigma-Aldrich Inc., St. Louis, MO); GHR [N3C2], internal, GTX101192, rabbit polyclonal IgG (Gene Tex); and hypoxia-inducible factor-1α (HIF-1α), NB100-479, rabbit polyclonal IgG (Novus Biologicals).

**Enzyme assay**

For enzymatic assays, tissue homogenates were prepared using a mechanically driven (500 rpm/six strokes) Potter-Elvejhem homogenizer (Vineland, NJ) in 500 µl of an ice-cold solution consisting of 0.25 M sucrose, 20 mM Tris-HCl (pH 7.2), 2 mM EGTA, 40 mM KCl, and 1 mg/ml BSA. Activities of respiratory chain complexes were measured by spectrophotometry using a Cary 50 UV-visible spectrophotometer (Varian Inc., Les Ulis, Ghris).
France) as previously described (16, 17). All chemicals were from Sigma-Aldrich (St. Quentin, Falavier, France).

**Statistical analysis**

All statistical analyses were performed with the SPSS version 16.0 (SPSS Inc., Chicago, IL). Continuous data are expressed as mean ± se. A two-sample t test was used for statistical analysis of gene dosage between WT and mutant alleles. A P value < 0.05 was considered significant.

**Results**

**Clinical course and investigation**

The proband was a 41-yr-old man who was first evaluated at 37 yr for a pituitary mass detected on brain magnetic resonance imaging (MRI). He had a 3-yr history of hypertension controlled with calcium channel blockers, diuretics, and angiotensin II receptor inhibitors. The family history was remarkable for hypertension and type 2 diabetes in the patient’s mother, whereas the patient’s father passed away from lung cancer at the age of 65 (Fig. 1A). The patient was clearly acromegalic upon presentation. Hormonal evaluation revealed GH of 10.70 ng/ml (normal is 5 ng/ml) and IGF-I of 492 ng/ml (normal is 109–284 ng/ml). Calcitonin and PTH were normal; serum prolactin (PRL) was mildly increased at 25.5 ng/ml (normal is <18); testosterone was decreased at 78 ng/dl (normal is 200–980 ng/dl). The patient had impaired fasting glucose according to standard criteria (18) and mild dyslipidemia with cholesterol at 225 mg/dl (normal is 130–200 mg/dl), high-density lipoprotein at 77 mg/dl (normal is >55 mg/dl), and low-density lipoprotein at 135 mg/dl (normal is <165 mg/dl). A pituitary MRI showed a 3.5-× 3.4- × 3.3-cm pituitary mass. The mass had invaded the right cavernous sinus and extended into the suprasellar region compressing the optic chiasm (Fig. 1B1).

The patient was placed on long-acting somatostatin analog (LASMSA) and showed a partial clinical and laboratory response (Table 1). The patient was scheduled for
transsphenoidal surgery (TSS) after a year of treatment led to no improvements. Five tumors with characteristics typical for PGL were detected by computed tomography and MRI of the neck: two originating from the carotid bodies, two located in the jugular fossae, and one in the soft tissue at the carotid bifurcation (Fig. 1B2) and the base of the skull. There were also three masses in the thorax; one at the paraspinal region (fifth thoracic vertebra), one at the left pulmonary hilum, and the third at the epicardium. Two additional tumors were found in the retroperitoneum below the diaphragm and one in each adrenal gland (Fig. 1B3). [18F]Fluorodopa positron emission tomography imaging was also performed that showed avid concentration of the radionuclide in each of these tumors.

Plasma norepinephrine was 847 pg/ml (normal is 120–350 pg/ml), and urine normetanephrine was 3506 µg/24 h (normal is <500 µg/24 h). Plasma dopamine was also elevated at 153 ng/liter (normal is 30–120 ng/liter) as well as chromogranin A at 1087 ng/ml (normal is <98 ng/ml). Initially, the patient underwent bilateral adrenalectomy, and the diagnosis of PHEO was confirmed by histology. The pheochromocytoma of the adrenal gland scaled score (PASS) was 8, and Ki67 was 1%. Ten months later at the National Institutes of Health, just before TSS, plasma normetanephrine was 2396 pg/ml (normal is <112 pg/ml), 24-h urine normetanephrine was 2220 µg/24 h (normal is <419 µg/24 h), norepinephrine was 361 µg/24 h (normal is <80 µg/24 h), metanephrine was less than 29 µg/24 h, and IGF-I was 774 ng/ml (normal is <284 µg/24 h) (Table 1). The GHRH serum level was within the normal range at 9 pg/ml (normal is 5–18 pg/ml). The pituitary tumor in relation to the patient’s peripheral blood showed also diffuse SDHB staining (Fig. 4.5) unlike what was present in normal pituitary as well as in extracts from the patient’s pituitary tumor showed almost no expression of SDHD (Fig. 3B).

We then looked for SDHD LOH in tumor cells. Indeed, the SDHD WT allele was significantly reduced in the pituitary tumor in relation to the patient’s peripheral blood (SDHD WT allele copy number at 0.3 ± 0.04 vs. 1.0 ± 0.01; P < 0.0001) (Fig. 3A). In addition, Western blot of extracts from the patient’s pituitary tumor showed almost no expression of SDHD (Fig. 3B).

The 15-kDa band corresponding to the SDHD protein was present in normal pituitary as well as in extracts from pituitary tumor cells from another patient with acromegaly who did not have SDHx mutations (Fig. 3B). Consistent with the LOH and Western blot studies, IHC for SDHD was negative in the patient’s pituitary tumor (Fig. 4.1) compared with that in normal pituitary cells (Fig. 4.2). Staining for SDHB showed diffuse but patchy staining in some areas of the tumor (Fig. 4.3); in other areas, SDHB staining was negative (Fig. 4.4). Normal pituitary showed also diffuse SDHB staining (Fig. 4.5) unlike what has been reported (19). We then looked for the expression of SDHB, a significant decrease in plasma and urine normetanephrine was detected (Table 1 and Fig. 2A). The size of the PGL was stabilized.

### Table 1. Clinical and biochemical response to treatment over time

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<th>Baseline</th>
<th>3 months after LASMSA Rx</th>
<th>6 months after LASMSA Rx</th>
<th>12 months after LASMSA Rx</th>
<th>24 months after LASMSA Rx (before TSS)</th>
<th>3 months after TSS</th>
<th>14 months after TSS</th>
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<td>8.24</td>
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<td>456</td>
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Rx, Treatment.
of SDHB in the patient’s pituitary tumor cells by Western blot. The 34-kDa band corresponding to the SDHB protein was weaker compared with the ones detected in extracts from normal pituitary as well as the GH-secreting adenoma without SDHx mutation (Fig. 3C). Staining for SDHB and SDHD in patient’s PHEO was negative (Fig. 4.6 and 4.7). HIF-1α expression was found to be increased in our patient’s tumor extracts compared with normal pituitary (Fig. 3C).

We also looked for any expression of GHR in extracts from PHEO from patients with SDHB and SDHD mutations and in paraffin-embedded tissue derived from our patient’s resected PHEO and from two other patients with sporadic PHEO. Western blot of extracts from PHEO harboring SDHx mutations showed a strong expression of GHR: the 72-kDa band corresponding to the GHR protein was present in both samples (Fig. 2B). IHC for GHR showed positive diffuse staining in our patient’s sample (Fig. 2C1). Staining was weaker in the two samples from sporadic PHEO without any known mutations (Fig. 2C2 and -3).

**Enzymatic activity**

To assess the effect of the identified mutation on respiratory chain function, we performed enzymatic assays on homogenates prepared from the pituitary tumor tissue or control samples. The assay involved the measurement of the oxidation of added reduced cytochrome c (cytochrome oxidase activity) and subsequent reduction of added oxidized cytochrome triggered by succinate (complex II + III activity) or decylubiquinone (complex III activity). Upon addition of oxidized cytochrome c, before addition of any reducing substrate, a significant reduction of cytochrome c took place in the tumor homogenate, suggesting the presence of a significant amount of an endogenous reducing substance. Upon the subsequent addition of succinate, complex II substrate, increased rates of cytochrome c reduction in both set-ups were noted that were essentially sensitive to malonate, a specific inhibitor of complex II (Fig. 5). We next performed an isolated complex II activity assay using decylubiquinone (in the presence of dichlorophen indophenol) as an electron acceptor. A 15–20% decrease in activity was measured in tumor tissue compared with control ($P < 0.08$).
Discussion

We describe for the first time the association of a novel germline SDHD pathogenic mutation with inherited PGL and a GH-producing pituitary adenoma. SDH participates in the electron transfer of the respiratory chain and in the conversion of succinate to fumarate as the complex II in oxidative phosphorylation as well as in the citric acid cycle (4, 20); its function and expression in the pituitary gland is as important as in all other tissues. It has been shown that SDH subunits act as tumor suppressor genes following the Knudson two-hit hypothesis (20, 21). The precise pathway leading from SDH mutation to tumorigenesis is not yet fully elucidated, but one of the mechanisms proposed is through accumulation of HIF-1α and -2α (22–25). SDH-inactivating mutations create a pseudohypoxia state that is characterized by succinate and reactive oxygen species accumulation, resulting in increased HIFα levels that in turn activate oncogenes (20, 22–27). Indeed, HIF1α immunoblotting in our patient’s tumor showed increased expression compared with a GH-secreting adenoma without SDHx mutations (C). Panel B, Western blot of SDHB expression in patient’s pituitary tumor (P) as well as in extracts from pituitary tumor cells from a patient with acromegaly without SDHx mutations (C). Panel C, Western blot of SDHB expression in patient’s pituitary tumor (P) was decreased, whereas HIF1α was significantly increased, compared with normal pituitary (NP) and with a patient with acromegaly without SDHx (C).
form the hydrophobic membrane anchor (28). Subunit D has four helices: helix 1S (D36–D62), helix 2S (D66–D92), helix 3S (D95–D123), and helix 4S (D126–D136) (27). There are at least two ubiquinone-binding sites in eukaryotic mitochondrial succinate-ubiquinone oxidoreductase. One site (Qp) is on the matrix side, and the second (Qd) is near the intermembrane-space side. The latter is formed by the loop between the helix 1S and helix 2S and helix 4S and the C terminus of CybL (29). The mutation reported in the present case is a 4-bp deletion (ACTC) at position c.298_301, which, based on the described structure, would result in missing both helices 3S and 4S of subunit D. This most probably would prevent ubiquinone from binding to the Qd site, disrupting the transportation of the high-energy electrons through the respiratory chain.

Since the discovery of the SDHx genes (30) and its relation to familial PGL/PHEO, other forms of tumors associated with inactivating SDH subunit mutations have been described in recent years in gastrointestinal stromal tumors and in Carney-Stratakis syndrome (2, 3), in renal cancer (10, 11), in patients with PTEN-negative Cowden and Cowden-like syndrome (7), in thyroid cancer (10), and in patients with adrenal medullary hyperplasia (12). We were able to identify 25 cases of pituitary adenoma and PHEO in the literature (1). The pituitary tumors have included GH- and ACTH-secreting and nonfunctioning adenomas.

Given these data, we examined whether the pituitary tumor in our kindred was due to the SDHD mutation. The patient did not have any mutations in MEN1, AIP, and CDKN1B genes. Because SDHD acts as tumor suppressor gene, we examined whether LOH was present in the patient’s pituitary tumor. Indeed, the mutated allele was primarily expressed in the pituitary tumor, whereas both alleles were equally expressed in the peripheral blood. In fact, the detection of any expression of the normal allele in the pituitary tumor was most likely due to contamination by normal cells as often is the case in tissue lysates (31). SDHD expression by Western blot and IHC was decreased in the patient’s pituitary tumor, compared with a GH-secreting adenoma negative for SDHD mutation and with normal pituitary. SDHB expression was also significantly reduced by immunoblotting (Fig. 3C). SDHB staining was positive for parts of the pituitary tumor (Fig. 4.3), whereas other parts of the tumor were completely negative (Fig. 4.4).
We also measured the SDH enzymatic activity in a tissue sample from normal pituitary as well in a tissue sample from our patient’s pituitary adenoma. It is interesting that initially, when we added oxidized cytochrome c, a significant reduction of cytochrome c took place in the tumor homogenate, suggesting the presence of a significant amount of one or more endogenous reducing substances (Fig. 5). This could represent either reducing acids resulting from SDH impairment or oxidatively modified compounds resulting from unstable reactive oxygen species, possibly produced as a result of SDHx mutations (23). When we measured the activity of SHD alone, a 15–20% reduction was found in tumor tissue compared with control ($P < 0.08$). One possible explanation for the fact that the SDH activity was not completely abolished in the tumor may be that the homogenate contained normal cells, which compensated for the reduced activity of the tumor cells. Unfortunately, we did not have enough tumor cell lines with homogeneous cell populations to answer these questions properly.

Studies in family members (Fig. 1) did not reveal any pituitary tumors. Whether carriers develop the tumor depends on many factors (33); in addition, the age-related penetrance of SDHD-linked PGL is 54% by the age of 40 yr and 68% by the age of 60 yr, reaching a maximum of 87% by the age of 70 yr (34). Review of the other cases reported in the literature did not reveal the presence of PGL and pituitary adenomas in other family members. Genetic analysis was not performed in most cases, except for RET (35, 36). It is also possible that some of these cases are due to GHRH-secreting neuroendocrine tumors (37, 38).

Another interesting finding in our index case was a noticeable decrease (almost three times) of plasma and urinary norepinephrine and normetanephrine levels 14 and 26 months after TSS, which was greater than the one noted 10 months after adrenalectomy (Fig. 2A). No progression in the size of the multiple PGL was noticed. One possibility is that LASMSA had an effect on catecholamine release; however, the decline was not seen before TSS despite the patient being on LASMSA for 10 months, and it was sustained after TSS even when the patient stayed off LASMSA.
for brief periods of time. Thus, we assumed that normalization of GH levels after TSS contributed significantly to such biochemical changes. We showed that GHR was expressed in two PHEO samples from other patients harboring each an SDHB and an SDHD mutation, respectively, as well as in the PHEO from our patient. As far as we know, this is the first time that the expression of GHR is shown in PHEO. There are only reports for the differential expression of ghrelin and GHRH receptors in various adrenal tumors (PHEO included) (39, 40). Clearly, larger and more detailed studies are needed to address and confirm this very interesting observation and the role of GHR in SDHx-mutant tumors.

In conclusion, we have identified a novel SDHD mutation in a patient with multiple functioning PGL and a pituitary adenoma. Whether the SDH genes are indeed predisposing genes for pituitary tumors requires additional studies; this report only suggests that a careful family history regarding pituitary tumors should be considered in patients with multiple PGL or with any germline genetic defects of the SDH genes.

Acknowledgments
We thank the patients of this large family for participating in the described studies.

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This work was supported by the intramural program of the NICHD, NIH (Project Z01 HD000642-04; principal investigator C.A.S.), by the Agence Nationale de la Recherche (Project MitOxy; principal investigator P.R.), and in part, by a 1-yr grant to P.X. on the molecular investigation of pituitary tumors by the Hellenic Endocrine Society, Athens, Greece.

Disclosure Summary: The authors have nothing to disclose.

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