

DIAGNOSIS of ENDOCRINE DISEASE: SDHx mutations: beyond pheochromocytomas and paragangliomas

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Abstract

Mutations in one of the five genes encoding the succinate dehydrogenase (*SDHx*) or mitochondrial complex II cause the corresponding family syndromes characterized by the occurrence of pheochromocytomas (PHEO) and paragangliomas (PGL). Recently, other solid growths, such as gastrointestinal stromal tumors (GISTs), renal cell carcinomas (RCCs) and pituitary adenomas (PAs) have been associated with these syndromes. In the absence of prospective studies assessing their frequency, at present, their occurrence seems too infrequent to suggest systematic screening for *SDHx* mutation carriers. However, SDHB immunohistochemistry (IHC) on tumor tissues or *SDHx* genetic testing on blood or tumor samples should be performed in patients affected by GISTs, RCCs or PAs with clinicopathologic phenotypes suggesting an etiologic role of *SDHx* genes.

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Introduction

Pheochromocytomas (PHEO) and paragangliomas (PGL) are rare neural crest-derived tumors (1, 2). They comprise adrenal and extra-adrenal chromaffin, sympathetic, catecholamine releasing tumors, namely secreting PGL (sPGL) and tumors of the parasympathetic ganglia in the head and neck region, namely head and neck PGL (HNPGGL). These tumors are the most common heritable tumors recorded to date (3, 4). Approximately 35% of them are caused by germline mutations and an additional 10–15% show somatic mutations in the same or other susceptibility genes, which include those encoding the succinate dehydrogenase (SDH) or mitochondrial complex II (5).

SDH is functionally involved in both the Krebs cycle, where it transforms succinate into fumarate, and the electron transport chain. The complex consists of four structural subunits: two hydrophilic catalytic subunits,

A and B, encoded by the corresponding *SDHA* and *SDHB* genes and two hydrophobic subunits, C and D, encoded by *SDHC* and *SDHD* genes anchoring the catalytic subunits to the inner mitochondrial membrane (6). Enzymatic activity requires a functional unit, succinate dehydrogenase complex assembly factor 2 (*SDHAF2*), responsible for flavination of the catalytic subunit A and encoded by the corresponding *SDHAF2* gene (7).

Mutations in any of these five genes cause disassembly of the mitochondrial complex, with loss of SDH enzymatic activity (8, 9) as well as of SDHB expression at immunohistochemistry (IHC) while SDHA is lost, together with SDHB, in *SDHA*-mutated tumors, but its expression is retained in tumors with other SDH mutations.

Consequently, SDHB IHC (10) has been assumed as a rapid and inexpensive preliminary test on tumor tissue to investigate on tumor's SDH insufficiency.

Mutations in any of these five genes cause impairment of SDH enzymatic activity and loss of SDHB expression, whereas loss of SDHA expression is only detected in *SDHA* mutations (8, 9). SDH immunohistochemistry (IHC) has therefore become a rapid and inexpensive tool for testing SDH insufficiency in tumor tissue (10).

Mutations in any of the five SDH genes are responsible for the occurrence of PHEO/PGL.

In 2000, Baysal *et al.* (5) demonstrated that *SDHD* mutations result in an inherited familial syndrome, known as familial paragangliomatosis type 1 (PGL1) characterized by the presence of both sPGL and HNPGL (11). Subsequently, other *SDHx* genes also proved to be PHEO/PGL susceptibility genes (12, 13, 14, 15), and their germline mutations are associated with the corresponding familial syndromes, namely PGL2 to PGL5 (Table 1). The clinical picture of these five PGL syndromes differs in some aspects, but they are all characterized by the presence of PHEO/PGL (16, 17, 18, 19, 20).

In recent years, germline mutations in *SDHx* genes have been rarely associated with other solid tumors beyond PHEO/PGL, such as gastrointestinal stromal tumors (GISTs) (21), renal cell carcinomas (RCC) (22) and pituitary adenomas (PAs) (23). To our knowledge, no systematic prospective study has been conducted in *SDHx* mutation carriers to define the true prevalence of solid tumors other than PHEO/PGL. These additional solid tumors have been sometimes found incidentally in *SDHx* mutation carriers and most of the papers evaluating the role of SDH in the pathogenesis of these tumors report retrospective studies performed by SDHB IHC on paraffin-embedded tumor tissue. Tumors have been labeled as 'SDH

deficient' in case of negative SDHB immunostaining but not all the tumors or the patients have then undergone genetic analysis looking for the correspondent *SDHx* somatic or germline mutations.

This paper reviews these tumors and their characteristics.

Gastrointestinal stromal tumors (GISTs)

GISTs are the most common mesenchymal tumors of the gastrointestinal tract (24), occurring as sporadic or familial with an incidence of 6.8–20 per million (25, 26, 27).

In 85–90% of cases, GISTs result from activating mutations of *KIT* or *PDGFRA* genes (28, 29). The other 10–15% non-*KIT*/*PDGFRA*-mutated GISTs, incorrectly labeled as 'wild type', mainly affect children. Mutations in *NF1* (30, 31) or *BRAF* (32) genes account for 50% of these cases, while the remaining 50% prove negative for SDHB on IHC, and are referred to as SDH-deficient GISTs. They can be sporadic or part of two syndromes, i.e. Carney-Stratakis (33) syndrome and Carney triad (34). In Carney-Stratakis syndrome, dominantly inherited and due to germline *SDHx* mutations, GISTs are associated with PGL (35, 36), whereas they are associated with PGL and pulmonary chondromas in Carney triad.

Etiology of Carney triad is uncertain (37). Comparative genomic hybridization has shown alterations in the 1q, 1p and less frequently in the 14 q and 22 q chromosomal loci (38). Although *SDHB* is located on chromosome 1p36.1-p35 and *SDHC* on 1q21-q23.3, germline mutations of *SDHx* genes have rarely been found. Nonetheless, the

Table 1 Clinical characteristics of the *SDHx*-related syndromes.

Gene	Lesions	Multiple lesions	Penetrance	Malignancy	Paternal transmission	Associated neoplasms
<i>SDHD</i> PGL1	HNPGL Thoracic PGL Abdominal PGL PHEO	Yes	High	Very rare	Yes	GIST PA RCC PTC (?)
<i>SDHB</i> PGL4	Abdominal PGL HNPGL PHEOs	Yes (rare)	Low	Frequent	No	GIST RCC PA PTC (?)
<i>SDHC</i> PGL3	HNPGL Abdominal PGL	Rare	Unknown	Unknown	No	GIST RCC PA PA
<i>SDHAF2</i> PGL2	HNPGL	Rare	Unknown	Unknown	Yes	PA
<i>SDHA</i> PGL5	Abdominal PGL	Rare	Unknown	Unknown	No	GIST PA

HNPGL, head and neck paragangliomas; PA, Pituitary adenoma; PHEO, pheochromocytomas; PGL, paragangliomas; PTC, Papillary Thyroid Carcinoma; RCC, Renal cell carcinoma.

GISTs from Carney triad display loss of immunoreactivity for SDHB (39). This finding can be explained by SDHx somatic losses or by epigenetic silencing of SDHC promoter (40).

SDH-deficient GISTs account for 5–7.5% of all GISTs. Nearly all are located in the stomach, usually multiple, and frequently multinodular, they may metastasize to lymph nodes, but generally present a protracted and indolent course (35, 37, 41).

In summary, GISTs occur rarely in SDHx mutation carriers and therefore systematic screening for these tumors does not seem to be cost-effective. However, in the case of a GIST showing characteristics such as childhood onset, gastric location, multiple lesions, nodular/plexiform histology or a positive personal or family history for PHEO/PGL, SDHB immunostaining of the tumor or SDHx genetic testing on patient or tumor DNA should be performed. Indeed, the diagnosis of a familial form has important consequences on the clinical management of the patient and of his/her family members.

Renal cell carcinomas (RCCs)

SDHx mutated RCCs are rare tumors, estimated to account for 0.05–0.2% of all RCCs (42). The first report on SDHB-mutated patients affected by both PHEO/PGL and RCCs was by Vanharanta *et al.* in 2004 (22). The renal cancers diagnosed in these SDHB mutation carriers appeared to originate from the epithelial cells of the proximal tubule and were composed of a mixture of clear cells and cells with granular-eosinophilic cytoplasm arranged in a variably solid or nested architecture.

In a more recent paper, Gill *et al.* evaluated the morphology of 36 SDH-deficient RCCs from 27 patients and concluded that the most distinctive histologic feature was the presence of cytoplasmic vacuoles and inclusion-like spaces containing either pale eosinophilic fluid or flocculent material (42). Nonetheless, in some cases, these inclusions were focal and not easy to identify. Ricketts *et al.* also reported that in 21 cases of SDH-deficient RCC, most tumors exhibited ‘oncocyctic’ features although renal tumor histology was variable (43).

SDH-deficient RCC has been recognized as novel entity in the 2016 WHO classification of renal tumors (44, 45). It may show a morphologic spectrum wider than has been previously described (46) and some cases may be essentially indistinguishable from other non-SDH-related RCCs at histology. Of the SDH-deficient RCCs, the most common are those due to SDHB mutations.

According to Gill (42), SDH-deficient RCCs commonly present at a mean age of 37 years (range 14–76) while in the series of Williamson (47), the mean age is 40 years (range 22–72). Multifocal or bilateral tumors are detected in 30% of patients at long-term follow-up.

In summary, the very low prevalence of SDH-deficient RCCs seems to make their systematic research non-cost-effective in SDHx mutation carriers. SDH IHC or SDHx genetic testing should however be considered in RCCs occurring in patients younger than 40 years, as multiple or recurrent tumors, or in the case of a positive personal or family history of PHEO/PGL, GISTs or RCCs.

Pituitary adenomas (PAs)

The first report of an SDH (in this case C) mutation carrier affected by a single HNPGL and a PA was by Lopez-Jimenez *et al.* in 2008 (48). The authors found loss of heterozygosity (LOH) in the HNPGL but could not verify SDH deficiency of the PA since the tumor tissue was not available. The first description of PAs related to an SDH (in this case D) mutation was by Xekouki *et al.* in 2012 (23). They published the case of a 37-year-old male SDHD mutation carrier who presented multiple PGL in the neck, thorax and abdomen and a GH-secreting PA exhibiting LOH and downregulation of SDHD protein at immunoblotting and IHC. In 2013, Dwight *et al.* reported a case of PA arising in the setting of germline SDHA mutation (49).

In 2014 Gill *et al.* (50) immunohistochemically assessed 309 PAs detecting only one SDHA-negative PA as the result of a double SDHA somatic mutation. Subsequently, Xekouki *et al.* (51) performed genetic testing on 168 patients affected by PA, of which 146 were sporadic and 22 were familial.

Among the patients with sporadic PAs, 3 also displayed PHEO/PGL, but none of them was an SDHx mutation carrier. Conversely, in the group of patients with familial PAs, 4 also presented PHEO/PGL, 2 were SDHB and 1 SDHD germline mutation carriers.

To the best of our knowledge, 74 patients affected by both PHEO/PGL and PA have been reported so far (52, 53). Of the 72 patients collectively analyzed by O’Toole *et al.* (52), 23 (32%) harbored no mutations but had a personal or family history suggestive of a hereditary endocrine syndrome, 28 (39%) had no mutations and no suggestive personal or family history and 21 (29%) were found to be mutated for a susceptibility gene, such as menin (4 patients), RET (1 patient), SDHB (6 patients), SDHD (5 patients), SDHC (1 patient) and SDHAF2 (1 patient).

The patient age at diagnosis ranged from 15 to 84 years with a mean of 44 years. Of the 72 patients, 34 (47.2%) presented a macroadenoma, 11 (15.3%) a microadenoma and in 27 (37.5%), the size of the PA was unavailable.

PA secretion varied but consisted mainly of GH (27 patients, 37.5%) and PRL (23 patients 31.9%). Overall, 13 (18.1%) patients had a non-functioning PA, 2 (2.8%) an ACTH-secreting tumor and 1 (1.4%) a mixed GH/PRL-secreting adenoma. In 1 (1.4%) patient, PA was diagnosed as chromophobic, and in 5 (6.9%), the secretion was not determined.

In summary, the occurrence of PAs in SDH germline mutation carriers is rare, and systematic screening does not seem to be recommended. Conversely, *SDHx* genetic testing or SDHB IHC is advisable in the case of familial PAs, phenotypically aggressive and/or therapy-resistant PAs, early-onset PAs or patients with a positive personal or family history for PHEO/PGL.

Other tumors

In addition to GISTs, RCCs and PAs, other tumors have been reported to be associated with PHEO/PGL in *SDHx* germline mutation carriers; however, very few cases have been found to be related to SDH deficiency.

In 2004, Neumann *et al.* (16) reported the occurrence of papillary thyroid carcinoma (PTC) in one out of 53 SDHB mutation carriers and in one out of 47 SDHD mutation carriers, although the tumor SDH dependency was not investigated.

The causal role of SDH in differentiated thyroid cancers (DTC) was evaluated by Ni *et al.* (54) in 754 cases. Germline *SDHx* missense variants were found in 48 (6%) patients, but were generally classified as non-pathogenic. However, papillary and follicular thyroid tumors showing consistent loss of *SDHC/D* gene expression were associated with earlier disease onset and higher pathologic stage. Although these findings identify *SDHx* as modifier genes in the clinical presentation of DTC, Papathomas *et al.* argued against a positive link between PTC and SDH-deficient state (55). Indeed, all the 60 cases of PTC under study proved immunoreactive for SDHB. Similarly, the authors did not find any SDHB-negative tumor among 47 neuroblastic tumors, 50 testicular seminomas and 10 adenomatoid adrenal tumors.

An association between *SDHx* mutations and lymphoid malignancies has been recently reported by Renella *et al.* (56) in two families. In one family, a young female *SDHB* mutation carrier was affected with abdominal

PGL and nodular lymphocyte-predominant Hodgkin lymphoma staining for SDHB. The pedigree of the other family included a 15-year-old *SDHC* mutation carrier with metastatic GIST/PHEO and a 24-year-old maternal aunt diagnosed with stage IV-B Hodgkin lymphoma whose specimen was not available for IHC.

Finally, a pancreatic neuroendocrine tumor showing SDHB negativity, SDHA positivity and LOH has been reported in an *SDHD* mutation carrier who was also affected with oligodendroglioma and multiple HNPGL (53).

Discussion

In addition to PHEO/PGL, *SDHx* gene mutations are responsible for the occurrence of other solid tumors, mainly GISTs, RCCs and PAs.

The frequency of these non-neural-crest-derived tumors seems to be very rare, although the cases reported in the literature may result underestimated as no systematic studies aimed at diagnosing these tumors have been performed in *SDHx* mutation carriers. Nevertheless, *SDHx* mutation carriers are generally (and hopefully) enrolled in a lifelong screening looking for the occurrence of HNPGL as well as of PHEO/PGL and therefore tumors like RCC and PA should be diagnosed during radiological screening procedures, by CT or MRI, carried out on the abdomen or head and neck respectively.

Therefore, at present, a systematic search for neoplasms other than PHEO/PGL in *SDHx* mutation carriers does not seem advisable although prospective studies aimed at establish their frequency are necessary. Nevertheless, these tumors may at times present clinical or histologic features suggestive of *SDHx* dependency, thereby recommending SDHB IHC on tumor tissue or *SDHx* genetic testing on patient's blood or tumor DNA. However, when testing tumor tissue by IHC, it must be recalled that SDHB IHC should be interpreted with caution, due to possible false positive (i.e. positive or weakly diffuse SDHB staining) sometimes observed in SDHD-mutated tumors (57). As a whole, a negative SDHB immunostaining proves that the tumor depends on a loss of SDH expression. This result should then be confirmed by genetic analysis on blood and/or tumor DNA to detect the type of mutation and whether the mutation is germline or somatic. When available, tumor DNA analysis for *SDHx* mutations should be performed for first. Other tools aimed at proving tumor SDH impairment are SDHB expression by western blot analysis or the measurement of SDH activity in tumor tissue.

Finally, in spite of the low frequency of tumors other than PHEO/PGL, when screening *SDHx* mutation carriers clinicians should accurately inquire on signs or symptoms associated to GISTs, RCCs or PAs. Conversely, in patients affected by GISTs, RCCs or Pas, clinicians should collect an accurate personal and family history searching for the occurrence of PHEO/PGL. Indeed, the diagnosis of a genetic syndrome is clinically relevant both for the index case as well as for the family members.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review reported.

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