

SDHB—A Gene for All Tumors?

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Succinate dehydrogenase (SDH) or mitochondrial complex II, comprising four subunits (A–D) in the inner mitochondrial membrane, lies at the crossroads of electron transport and the Krebs tricarboxylic acid cycle (1). SDH, whose subunits are encoded by autosomal genes, catalyzes the conversion of succinate to fumarate. In turn, the fumarate to malate conversation is catalyzed by fumarate hydratase (FH). It is well documented that germline homozygous or compound heterozygous mutations of SDH genes (typically *SDHA*) and of genes encoding other mitochondrial complexes cause a group of recessive syndromes (eg, Leigh syndrome) that are characterized by relatively severe encephalomyelopathy, myopathy, cardiomyopathies, and/or hepatopathies, typically resulting in death in childhood (1). Similarly, germline homozygous or compound heterozygous mutations in *FH* also result in severe neurodegeneration and early death. Thus, it came as a surprise to both those with interest in mitochondrial metabolism and the oncology community when germline heterozygous mutations in *SDHD* were found to cause familial and apparently sporadic pheochromocytoma/paraganglioma (PGL) (2,3). Subsequently, germline heterozygous mutations in *SDHB* and *SDHC* were also found in heritable pheochromocytoma and PGL (4,5). To date, no mutations have been found in *SDHA* in the PGL syndromes (C. Eng, unpublished data). Interestingly, germline heterozygous mutations in *FH* have been found to cause hereditary leiomyomatosis and renal cell carcinoma syndrome (HLRCC) (6). HLRCC is an autosomal dominant disorder that is characterized by cutaneous and uterine leiomyomatosis and renal cell carcinoma (RCC) with a very specific histology—type II papillary.

In the 4 years following the discovery that germline *SDHD* mutations cause heritable pheochromocytoma/PGL syndrome, all evidence suggested that heterozygous mutations in *SDHB*, *SDHC*, or *SDHD* were associated only with pheochromocytomas and PGLs and not with other types of neoplasia (2,4,5,7–12). Then, in 2004, RCC was first described as a bona fide component neoplasia of the pheochromocytoma/PGL syndromes that was associated in particular with *SDHB* germline mutations (8,13). In a population-based registry of symptomatic pheochromocytoma and/or PGL presentations, two of 28 (7%) *SDHB* mutation carriers were found to have RCC (Table 1, family 5) (8). They were siblings diagnosed at ages 34 and 36 with RCCs with a solid-type histology, likely not clear cell (8,13). In the same study, a population-based registry of early-onset RCC based in Finland was searched for germline *SDHB* mutations and one index case, who was diagnosed with clear cell RCC at age 28, was found to carry a nonsense mutation at Arg-27 (Table 1, family 4) (13). At the time of his death at age 34, he had yet to develop PGL. Registry-enabled family tracing and documentation revealed that this person's mother was found at age 55 to have a cardiac tumor that turned out to be a malignant cardiac PGL. She was found to carry the same nonsense mutation

(Arg27Ter) (13). The estimated prevalence of germline *SDHB* mutation in this population-based registry of early-onset RCC was 1% or less (13).

In this issue of the Journal, Ricketts et al. (14) have confirmed the 2004 findings that germline *SDHB* mutations confer susceptibility to RCC after examining 68 probands with nonsyndromic RCC (Table 1, families 1–3) (14). From their series, they estimate the prevalence of *SDHB* mutations in RCC to be 4.4%. Unlike the 2004 population-based series, this series comprised highly selected, “tertiary referral-based” RCC cases with multicentric disease, early ages of onset, and/or familial occurrence. Despite the more prevalent *SDHB* mutation frequency in this series, the same group found no *SDHB* mutations in 55 primary RCCs and nine RCC lines in a previous study (15), and the authors of the 2004 series found no *SDHB-D* germline mutations in an independent series of 60 tertiary referral-based nonsyndromic RCC cases with various ages of onset (13). Therefore, we must conclude that *SDHB* is a susceptibility gene for RCC, mainly of clear cell histology, and of early onset, and accounting for a small but finite subset of RCC, estimated at no more than 1%–4%.

Is *SDHB* a susceptibility gene for nonsyndromic RCC, as Ricketts et al. (14) posit? These authors argue that none of their young RCC patients, and, to their knowledge, families have pheochromocytoma or PGL. To suggest that their RCC is nonsyndromic is likely premature, however, given the well-documented age-related penetrance of *SDHB* mutations. In both population-based registry- and consortium-based selected series of pheochromocytoma/PGL associated with germline *SDHB* mutations, mean age-related penetrance is 50% by age 45 years and 75% by age 55 years (8). Ages at death or at last known follow-up of the three RCC patients studied by Ricketts et al. were only 58, 46, and 44 years, and, thus, pheochromocytoma and PGL penetrance would be likely be 50% or less. If these patients had survived or had longer follow-up, then they would have a likelihood of developing these neuroendocrine tumors. Furthermore, the incomplete penetrance of *SDHB* mutations may account for the apparent lack of family history of pheochromocytoma or PGL. Indeed, in some series, 90% of *SDHB* mutation carriers did not have a family

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See “Notes” following “References.”

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Table 1. Individuals carrying germline *SDHB* mutations diagnosed with renal cell carcinoma*

Family	<i>SDHB</i> mutation	RCC histology	Age at RCC Dx	PGL/Pheo (age)	Age, last follow-up	Reference
1 Proband	Arg46Ter	Clear cell	24	None	58	Ricketts (14)
1 Father	Arg46Ter	Clear cell	24	None	Deceased	Ricketts (14)
1 Uncle	Arg46Ter	Clear cell	73	None	73	Ricketts (14)
2	Arg46Gln	Clear cell	30	None	44	Ricketts (14)
3	Arg11His	Chromophobe Eosinophilic	38	None	46	Ricketts (14)
4 Proband	Arg27Ter	Clear cell	28	None	34 Deceased	Vanharanta (13)
4 Mother	Arg27Ter	None	N/A	PGL (55)	Deceased	Vanharanta (13)
5 Proband	c.847delTCTC	Solid	24	PGL (16)	34	Vanharanta (13) Neumann (8)
5 Sib	c.847delTCTC	Solid	26	PGL (34)	36 Deceased	Vanharanta (13) Neumann (8)
6	Trp47X	Papillary, II	26	PGL (10)	27	Srirangalingam (20)

* RCC = renal cell carcinoma; Dx = diagnosis; PGL = paraganglioma; Pheo = pheochromocytoma; Sib = sibling.

history of any neoplasias (16). Another equally likely explanation for the apparent lack of familial occurrence is the difficulty in documentation of such tumors or in sorting out their symptoms and signs from more common mimics (eg, hypertension, stroke, myocardial infarction).

Although the total number of individuals found to have germline *SDHB* mutations and RCC is small, two associations are striking. First, of the six different germline *SDHB* mutations represented in those with RCC, five lie within codons 11 and 46 (inclusive) (Table 1). This contrasts with seven different germline *SDHB* mutations found within codons 11–46 among 29 different mutations in PGL cases from an international consortium series ($P = .011$, Fisher two-tailed exact test), four of 23 from a highly selected tertiary referral single-institutional series ($P = .006$) and six of 18 from a population-based register ($P = .06$) (8,16,17). Second, and even more striking, is the observation that seven of the 10 individuals with *SDHB* mutations and RCC harbor mutations that alter arginine codons (Table 1). In contrast, the three largest series of individuals with germline *SDHB* mutations and pheochromocytoma and/or PGL show that 23 of 99 *SDHB* mutations involve arginines (8,16,17) ($P = .004$, Fisher’s two-tailed exact test). Of the RCC-related mutated arginine codons, all occur at the N-terminal of the protein, involving Arg-11, Arg-27, and Arg-46. In fact, of the six different mutations found involved in *SDHB* mutation–positive individuals with RCC, five occur between codons 11 and 47. The catalytic core of SDH is formed by SDHA and SDHB, while SDHC and SDHD are the structural anchoring domains (1). SDHA is the flavoprotein, and SDHB, the iron–sulfur protein of complex II. SDHB codons 1–28 represent the transit peptide that allows translocation of SDHB into the inner mitochondrial membrane. Substitution of Arg-11 with histidine may physically disrupt the transit peptide and prevent translocation of SDHB into the mitochondrial membrane. Arg27Ter is predicted to truncate SDHB near the end of its transit peptide, allowing a protein comprising the transit peptide without the ferredoxin domain entry into the mitochondrial membrane. This most likely will result in haploinsufficiency as well as a dominant-negative effect. Finally, Arg-46 is a highly conserved cationic residue that lies within the 2Fe–2S cluster and likely plays an important role in the structural organization of the iron–sulfur clusters (18). In a *Saccharomyces*

cerevisiae model, mutation of the equivalent residue, Arg-47, to Cys, Glu, or Lys results in reduced ubiquinone reductase activity resulting in accumulation of succinate, which, in turn, may inhibit prolyl hydroxylase enzymes, with consequent increased hypoxia-inducible factor-1 (HIF-1) signaling. This explains, at least in part, the genesis of pheochromocytoma and paraganglioma as well as renal carcinogenesis, which is well documented to be dependent on HIF-1 upregulation.

Extraparaganglial cancers have yet to be found or well documented in individuals with germline *SDHD* or *SDHC* mutations, suggesting that these mutations may result in different downstream mechanisms of dysfunction (1,7,8,19). This is plausible because both SDHC and SDHD are the structural components of complex II, in contrast to SDHB. What is surprising, however, is the lack of germline *FH* mutations found by Ricketts et al. (14) in their RCC series. Most human geneticists would expect that at least a small subset of familial and apparently sporadic RCC to be a forme fruste of HLRCC and so *FH* mutations should be found in that subset. However, it is possible that insufficient numbers of type II papillary RCC have been explored.

Finally, and most importantly, how have the observations by Ricketts and colleagues altered medical practice? Data validation is vital before translation of research findings to the routine clinical armamentarium. In this regard, the authors have succeeded: they have confirmed the original observations that *SDHB* is a RCC susceptibility gene (8,13,14). Therefore, it is entirely appropriate, at this time, to counsel patients carrying *SDHB* mutations, especially those with Arg mutations, that they have a small but finite likelihood of developing RCC. Those of us who are conservative practitioners of clinical cancer genetics have been counseling our patients with germline *SDHB* mutations, irrespective of presenting or current clinical features, of the small but finite RCC risk since the first evidence appeared in 2004 (8,13). However, this point is moot in regards to changing the actual clinical surveillance. The clinical surveillance uses imaging that clearly visualizes the kidneys already. The converse, which the authors are advocating—that all patients presenting with RCC be screened for *SDHB* mutations—must be reconsidered given a lack of validation at this time and the implications of the added screening for cost-effective health care. What should be suggested, instead, is for

others to independently replicate the Ricketts et al. findings in very large series of RCC comprising a broad range of histologies and to determine if clinical or biochemical information can guide to whom to offer *SDHB* testing. For example, early hints based on the small number of RCC-*SDHB* patients show the mean age at RCC diagnosis to be 33 years, with all but one such patients presenting before the age of 39 (Table 1). Thus, RCC patients diagnosed over 40, without a family history, may not need to be offered *SDHB* analysis.

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Notes

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