**SDHB—A Gene for All Tumors?**

Charis Eng

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 conversion 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 To date, no mutations have been found in SDHA in the PGL syndromes (C. Eng, unpublished data).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 (90% of which was tertiary referral-based), and renal cell carcinoma (RCC) with a very specific histology—type II papillary.

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

<table>
<thead>
<tr>
<th>Family</th>
<th>SDHB mutation</th>
<th>RCC histology</th>
<th>Age at RCC Dx</th>
<th>PGL/Pheo (age)</th>
<th>Age, last follow-up</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Proband</td>
<td>Arg46Ter</td>
<td>Clear cell</td>
<td>24</td>
<td>None</td>
<td>58</td>
<td>Ricketts (14)</td>
</tr>
<tr>
<td>1 Father</td>
<td>Arg46Ter</td>
<td>Clear cell</td>
<td>24</td>
<td>None</td>
<td>Deceased</td>
<td>Ricketts (14)</td>
</tr>
<tr>
<td>1 Uncle</td>
<td>Arg46Ter</td>
<td>Clear cell</td>
<td>73</td>
<td>None</td>
<td>73</td>
<td>Ricketts (14)</td>
</tr>
<tr>
<td>2</td>
<td>Arg46Gln</td>
<td>Clear cell</td>
<td>30</td>
<td>None</td>
<td>44</td>
<td>Ricketts (14)</td>
</tr>
<tr>
<td>3</td>
<td>Arg111His</td>
<td>Chromophobe</td>
<td>38</td>
<td>None</td>
<td>46</td>
<td>Ricketts (14)</td>
</tr>
<tr>
<td>4 Proband</td>
<td>Arg27Ter</td>
<td>Clear cell</td>
<td>28</td>
<td>None</td>
<td>34 Deceased</td>
<td>Vanharanta (13)</td>
</tr>
<tr>
<td>4 Mother</td>
<td>Arg27Ter</td>
<td>None</td>
<td>N/A</td>
<td>PGL (55)</td>
<td>Deceased</td>
<td>Vanharanta (13)</td>
</tr>
<tr>
<td>5 Proband</td>
<td>c.847delTCTC</td>
<td>Solid</td>
<td>24</td>
<td>PGL (16)</td>
<td>34</td>
<td>Neumann (8)</td>
</tr>
<tr>
<td>5 Sib</td>
<td>c.847delTCTC</td>
<td>Solid</td>
<td>26</td>
<td>PGL (34)</td>
<td>36 Deceased</td>
<td>Vanharanta (13)</td>
</tr>
<tr>
<td>6</td>
<td>Trp47X</td>
<td>Papillary, II</td>
<td>26</td>
<td>PGL (10)</td>
<td>27</td>
<td>Neumann (8)</td>
</tr>
</tbody>
</table>

* 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.

Extraparagangial 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.

References


Notes

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