No Child Left Behind in SDHB Testing for Paragangliomas and Pheochromocytomas

Joshua D. Schiffman, High Risk Pediatric Cancer Clinic, Center for Children’s Cancer Research, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT

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Nearly 100 years ago, Warburg \(^1\) hypothesized that cancer resulted from faulty cellular respiration and the ability of tumors to generate energy through glycolysis, even in the presence of oxygen. Warburg’s theory initially caused confusion and controversy, but it is now generally accepted as true and has become known as the Warburg Effect. In fact, the past decade has seen the discovery of numerous mutations in cancer that lead to impaired respiration and increased glycolysis, supporting the Warburg Effect. This is especially true in familial paraganglioma and pheochromocytoma syndrome (FPSS) in which an inherited germline mutation in one of the four succinate dehydrogenase (SDH) genes (\(SDHA, -B, -C, -D\)) predisposes to the development of cancer.\(^2,3\) These genes comprise the four subunits for complex II of the mitochondrial respiratory chain and, when mutated, lead to stabilization of hypoxia inducible factor 1 with a subsequent state of pseudohypoxia in patients. This then causes an upregulation of the genes involved in angiogenesis, glucose transport, and glycolysis, all of which may contribute to tumorigenesis just as Warburg predicted.\(^3\) Inherited germline mutations in SDHAF2 (SDH assembly factor 2 or \(SDH5\); a gene responsible for SDHA flavination leading to SDH assembly and complex II function) have also been recently reported to cause respiratory chain dysfunction and head and neck paragangliomas (PGLs),\(^6\) presumably through the same end points of increased angiogenesis and glycolysis.

PGLs are neuroendocrine tumors that can occur anywhere in neural crest cells, which extend from skull base to pelvic floor. These tumors are most commonly located adjacent to oxygen-sensing tissues, such as the carotid body, although they can also be found in the adrenal glands, where they are called pheochromocytomas (PCCs). Head and neck PGLs arise along the parasympathetic trunk, whereas abdominal and adrenal tumors originate from the sympathetic trunk. The overlap between PGLs and PCCs is great; some clinicians refer to PGLs/PCCs as “extra-adrenal PCCs,” and others call PCCs “intra-adrenal PGLs.” Both PGLs and PCCs can secrete vasoactive hormones, including catecholamines and chromogranin-A (although catecholamine secretion is more common in the abdominal and adrenal tumors). PGLs are rare, with an estimated occurrence of up to 1,300,000 in the general public, and slow-growing tumors that can be surgically removed when detected. PCCs, on the other hand, occur slightly more often in up to 1,250 people, can be more aggressive over time, and are difficult to treat once they metastasize. Although the incidence of PGLs in the healthy public is relatively low, up to 30% of individuals with an inherited germline \(SDHB, SDHC,\) or \(SDHD\) mutation will develop PGLs by age 30 years and 70% to 100% will develop PGLs by age 80 years.\(^3,7\) Hereditary PGLs in FPSS are more aggressive than their nonhereditary counterparts and are associated with increased metastatic potential, morbidity, and mortality.\(^8-10\) Other tumors associated with FPSS and inherited \(SDH\)-gene mutations include thyroid cancer, GI stromal tumors (GISTs), renal cell carcinoma, pulmonary chondromas, and even neuroblastoma.\(^11\)

FPSS can be classified genetically into four clinical entities: PGL1, PGL2, PGL3, and PGL4. These four entities have been associated with specific inherited germline mutations in the SDH-related genes: \(SDHD\) (PGL1), \(SDHAF2\) (PGL2), \(SDHC\) (PGL3), and \(SDHB\) (PGL4). As with all types of cancers, a bilateral presentation of PGL or PCC suggests an underlying genetic predisposition. An aggressively metastatic presentation of the generally benign PGL also indicates an underlying genetic mutation as a cause of disease; especially an inherited \(SDHB\) mutation, which is associated with the most aggressive PGLs/PCCs. In fact, 30% to 35% of newly diagnosed PGLs/PCCs are thought to result from inherited gene mutations indicative of an underlying cancer predisposition syndrome.\(^12,13\) As a result of its rarity in childhood, the accurate percentage of PGLs/PCCs caused by inherited gene mutations is not known, but the rate is commonly thought to be higher than in the adult population.

In the article that accompanies this editorial, King et al\(^\text{14}\) attempt to answer the question of how many children or adolescents with metastatic PGLs/PCCs have an underlying \(SDHB\) mutation. The authors took advantage of a decade of patient enrollments into the National Institutes of Health (NIH) registry, which is a referral center for patients with PGLs and PCCs. Through this NIH registry, King et al captured data on 263 patients who enrolled with PGLs/PCCs. For this study, they focused on 32 younger patients (25 male and seven female) who had documented cases of PGL/PCC diagnosed before age 20 years and had developed metastasis to a non-neuroendocrine organ. They also reported data on an additional 17 patients with PGL/PCC who never developed metastatic disease. Genetic testing was performed on all 49 combined pediatric and adolescent patients for the PGL/PCC-associated genes: \(RET, VHL, SDHB, SDHC,\) and \(SDHD\). Of note, genetic testing did not include the relatively more recent genes described to be associated with PGLs/PCCs: \(SDHA,\)
SDHAF2, and TMEM127. The investigators found a staggering 39 patients (79.6%) younger than age 20 years in their PGL/PCC cohort with an underlying genetic mutation, including two patients without metastasis who had neurofibromatosis type 1. The rate of inherited gene mutations was even higher in the 32 patients with metastatic disease (total: 87.5%; SDHB: n = 23 [71.9%]; SDHD: n = 3 [9.4%]; VHL: n = 2 [6.3%]) compared with the 17 patients with nonmetastatic disease (total: 64.7%; SDHB: n = 4 [23.5%]; SDHD: n = 1 [5.9%]; VHL: n = 4 [23.5%]; NF1: n = 2 [11.8%]).

With a relatively large cohort of rare patients with PGL/PCC, King et al14 provide meaningful analysis of tumor characteristics in this group of young patients with metastatic disease. For instance, they report that patients with metastatic disease with underlying SDHB mutations tended to present with tumor-related symptoms at an earlier age (10.8 ± 4.43 years) compared with those with SDHD mutations, who first described symptoms at the age of 16.3 ± 4.62 years. Additionally, the PGLs/PCCs in patients with SDHB mutations were diagnosed earlier than patients with SDHD mutations (12.3 ± 3.81 vs 16.7 ± 4.04 years) and their metastases presented at earlier ages (19.9 ± 7.89 vs 31.0 ± 17.5 years). Similar to reports in the literature,2 the patients with SDHB mutations in the cohort presented with retropertioneal and adrenal disease, and all three of the patients with SDHD mutations presented only with head and neck PGs (and no abdominal tumors). The equally high percentage of metastatic patients with SDHB mutations and patients with SDHD mutations with increased levels of norepinephrine, normetanephrine, and chromogranin-A was also highlighted in this study. Each of these findings has important clinical management implications relevant to the use of laboratory testing and early cancer surveillance imaging.

The authors of the current study previously reported a rate of metastatic disease in 24% to 48% of a cohort of older patients with SDHB-related PGLs/PCCs,15,16 but in this expanded study, they report a much higher rate of SDHB-related tumor metastasis on the basis of the 23 (85.7%) of 27 pediatric patients who developed metastases. With the reported interval of nearly 7 years until metastasis, clinicians caring for children or adolescents with PGLs/PCCs have a clear window for early metastasis detection and intervention. However, consensus guidelines for early cancer detection is lacking for patients with FPPSs and underlying SDHB mutations. A recent study demonstrated the efficacy of laboratory screening and annual total-body magnetic resonance imaging (MRI) in Li-Fraumeni syndrome (LFS), another hereditary cancer syndrome with high cancer penetrance resulting from TP53 mutations.17 In this LFS study, Villani et al demonstrated that 3-year overall survival was 100% in the early cancer surveillance group and 21% (95% CI, 4% to 48%) in the nonsurveillance group (P = .0155), supporting the use of screening in high-risk cancer populations. Inherited SDH gene mutations have also been associated with the development of GISTs, and in one study, 100% of pediatric GISTs with no known KIT or PDGFRA mutations lacked SDHB protein expression in their tumors, indicating functional loss of the entire SDH unit and reflecting possible SDH-related mutations and respiratory chain defects.18 In fact, 12% of the patients in this pediatric GIST study contained inherited gene mutations in SDHB or SDHC. This has led to the adoption of total-body MRI screening (similar to the LFS screening protocol) by the NIH Pediatric and Wild-Type GIST Clinic for all patients with GIST who lack SDHB protein (and therefore a functional SDH complex) in their tumors as a result of a possible inherited SDH-gene mutation and the risk of other SDH-related cancers.

Other cancer screening recommendations for patients with inherited SDH-gene mutations include catecholamine/chromogranin testing, neck and abdominal ultrasounds, 123I-metaiodobenzylguanidine scintigraphy imaging, and 18F-fluorodopamine, 18F-fluorodihydroxphenylalanine, or [18F]fluorodeoxyglucose positron emission tomography imaging.3 However, caution must be used with excessive radiation exposure in a young population of patients who may receive annual screening; total-body MRI may ultimately be the safest imaging option for early cancer surveillance. As the current PGL/PCC study cohort by King et al14 matures, it will be helpful to learn which screening modalities prove most effective and what King et al recommend for early detection of metastases in this high-risk population of patients.

Regardless of the early cancer surveillance protocol ultimately recommended, it is still essential to identify those patients most at risk for inherited SDH-gene mutations. An overwhelming number of pediatric patients with GISTs lack SDHB protein staining in their tumors, suggesting these patients could have inherited mutations in one of the growing number of SDH-related genes. In fact, this approach of immunohistochemistry (IHC) staining for the SDHB protein has proven quite effective in several other SDH-related tumor studies in which individuals were identified based on negative IHC staining and subsequently shown to harbor inherited SDH-gene mutations.19-22 This is analogous to IHC analysis for MLH1, PMS2, MSH2, and MSH6, which is now advocated for all colorectal cancers to detect patients with hereditary nonpolyposis colorectal cancer (HNPCC; Lynch syndrome).23 New evidence even suggests that an antibody screen for two of the four mismatch repair genes may be just as effective for detecting patients with inherited mismatch repair deficiencies.24,25 By using IHC staining in colorectal cancer, we have learned that one in every 35 patients has HNPCC and that an additional three relatives with HNPCC can be identified for every one proband discovered.26,27 A similar approach of universal IHC staining (for SDHB) would be applicable to patients with PGLs/PCCs among whom we would expect, according to the current study by King et al,14 that more than half of the pediatric patients would lack SDHB tumor staining and ultimately test positive for inherited SDHB mutations. When considering the same young patients with metastases, the percentage of tumors lacking SDHB staining as a result of inherited SDHB mutations alone would jump to nearly 75%.

Identifying these young patients with inherited SDH-gene mutations has implications not just for the patient but for the entire family. The study by King et al14 describes the high rate of SDHB mutations in children and adolescents with PGLs/PCCs. The parents of these pediatric patients may be young themselves and may not yet have presented with their first tumors. SDHB-related tumors are the most aggressive of those occurring with FPPSs; therefore early detection will lead to early intervention with decreased morbidity and mortality. In addition to the parents, the siblings and extended relatives can be tested for inherited SDHB mutations and an early cancer screening program can be implemented for SDHB mutation carriers if found. It took nearly a century to fully understand the implications of Warburg’s theories about the role of mitochondrial respiration and glycolysis in tumorigenesis. King et al demonstrate that the Warburg Effect is relevant for pediatric PGLs/PCCs given the high rate of inherited
SDHB mutations. Furthermore, tumorigenesis resulting from mitochondrial dysfunction and increased glycolysis affect children as much as, if not more than, adult patients. These metabolic aberrations may ultimately prove to be targets for novel therapies. The clinical challenge now is how we will use the findings of such a high rate of inherited SDHB mutations in pediatric PGLs/PCCs to diagnose future pediatric patients as mutation carriers, clarify genetic risk in other family members, and implement the most effective cancer surveillance programs.

AUTHOR’S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
The author(s) indicated no potential conflicts of interest.

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