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Is Routine Genetic Testing Warranted in Head and Neck Paragangliomas?

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BACKGROUND
Paragangliomas are rare neural crest-derived tumors associated with ganglia of the autonomic nervous system. Within the head and neck, these neoplasms commonly arise from parasympathetic ganglia and present as carotid body, tympanic, jugular foramen, and vagal tumors. Nearly all germline mutations that lead to hereditary head and neck paragangliomas are attributable to the mutations in the genes associated with the succinate dehydrogenase (SDH) enzyme.1,2 Mutations in each subunit of SDH have unique phenotypic features and are characterized by a distinct paraganglioma syndrome (PGL).1 Despite the known association with heritable germline mutations and PGL, the role of genetic testing is not well integrated into the practice of many head and neck surgeons. The aim of this article is to define the best practice for incorporating genetic testing into the management of head and neck paragangliomas based on presenting symptoms, pathologic features, familial risk, and cost considerations.

LITERATURE REVIEW
Paragangliomas are rare, highly vascularized tumors that often present in the head and neck. These neoplasms are frequently benign, but can give rise to significant morbidity due to their anatomic location adjacent to major blood vessels and cranial nerves. Over half of head and neck paragangliomas are associated with genetic mutations that contribute to their pathogenesis.3 Specifically, germline mutations in the mitochondrial complex II, SDH, are implicated in the pathogenesis of familial paragangliomas that present in the head and neck.

Succinate dehydrogenase subunits are mitochondrial membrane proteins that play a central role in cellular metabolism. Succinate dehydrogenase mutations affect oxidative phosphorylation along the electron transport chain of the mitochondria, leading to complete enzymatic loss of mitochondrial complex II. This cellular dysfunction is postulated to result in cellular hypoxia, upregulation of vascular endothelial growth factor, and ultimately tumorigenesis. Mutations in specific subunits are associated with defined clinical characteristics such as age of tumor onset, rate of malignancy, and multifocal nature of the disease.

The two most common germline mutations in head and neck paragangliomas involve subunits D and B, which predispose to syndromes PGL-1 and PGL-4, respectively.4 Both of these mutations are associated with paraganglioma syndromes in which tumors appear at an early age, on average 14 years earlier than correlate patients with sporadic paragangliomas.3 The SDHD mutation accounts for as many as 54% of all mutations associated with head and neck paragangliomas.3 The inheritance pattern of PGL-1 follows maternal imprinting secondary to DNA methylation, which is unique compared to the autosomal dominant pattern of SDHB and SDHC mutations. From a clinical perspective, PGL-1 patients frequently present with multifocal disease, with as many as 74% of patients with SDHD mutations developing more than one tumor, compared to only 28% of patients with SDHB (P < 0.001).4 Patients with SDHB mutations, seen in PGL-4, commonly present with a solitary paraganglioma. Due to the autosomal dominant pattern of disease inheritance, multiple family members may carry the mutation; however, only 31% of known mutational carriers are found to have a head and neck paraganglioma.4 Unique to SDHB mutations is the increased incidence of malignant tumors, 37.5% of patients develop malignant paragangliomas.
versus only a 3.1% incidence of malignant tumors in patients with SDHD mutations ($P < 0.001$).

The remaining paraganglioma syndrome, PGL-3, is associated with the least common SDHC mutation, found in 4% of all paragangliomas. The clinical features of PGL-3 are nearly identical to those patients with sporadic tumors, which lack detectable mutations. Neither group of patients has been found to be associated with malignant tumors in registry studies. SDHC and sporadic paragangliomas both have multifocal tumors in only 10% of patients and present at a median age of 46 years, which is slightly older than patients with SDHB and SDHD mutations.

When developing a genetic screening algorithm for SDHx mutations, cost-reduction strategies are an important consideration due to limitations of healthcare funding. Although multiple genes are associated with these neoplasms, only a single mutation has been identified in any individual. Therefore, a sequential screening regimen is recommended rather than testing for multiple mutations concurrently. Routine access to testing can be limited and is often offered at larger laboratories on a weekly basis. Neumann et al. and Burnichon et al. offered screening algorithms for patients presenting with a head and neck paragangliomas. Genetically testing a patient for all SDHx mutations is estimated at $2,691, whereas a sequential testing algorithm offers up to a 60% cost reduction. The screening regimen in Figure 1 recommends that all head and neck paraganglioma patients be considered for screening, with the exception of isolated tympanic paragangliomas due to the extremely rare genetic mutation profile. Initial screening includes individuals with an isolated neoplasm and advanced age; Burnichon et al. found over 16% of such suspected sporadic cases were found to have mutations that would have been missed. Both authors’ algorithms recommend initial SDHD testing for patients with specific risk factors: multiple tumors, early age of onset < 40 years of age, or a positive family history. If an initial SDHD test returns negative, subsequent screening is indicated for SDHB followed by SDHC. Exceptions to this algorithm are individuals found to have a malignant neoplasm or a solitary PGL with no family history; they should be initially screened for SDHB (Fig. 1). Once an initial mutation is identified, no subsequent testing is required, and genetic counseling should be provided for patients and associated family members as needed.

Of note, clinical testing should include screening for tumors along the entire paraganglial system to search for secondary neoplasms with anatomic imaging, computed tomography, and/or magnetic resonance imaging from the skull base to the abdomen. Furthermore, because SDH mutations are associated with pheochromocytomas that can contribute to severe and life-threatening paroxysmal hypertension, blood pressure and catecholamine levels screening are warranted in all patients with an SDH mutation. Although pheochromocytomas are also associated with other germline mutations such as RET and VHL, these mutations contribute to less than 1% percent of head and neck paragangliomas. Therefore, testing for RET and VHL should be reserved for individuals with a suspicious clinical feature or a family history of multiple endocrine neoplasia type 2 or von Hippel-Lindau.

**BEST PRACTICE**

All individuals presenting with an extratympanic paraganglioma of the head and neck should undergo genetic testing. Even sporadic appearing tumors, presenting as a single tumor at an advanced age, can be associated with an underlying SDH mutation that contributes to the tumorigenesis. Initial genetic screening.
should be determined by risk factors associated with each mutation, which obviates unnecessary testing expenses. An equally important consideration for all clinicians is to offer genetic counseling to provide guidance, support, and insight on clinical features of the disease that has hereditary implications.

**LEVEL OF EVIDENCE**

The studies cited include five retrospective studies (level 3) investigating paraganglioma registries.

**BIBLIOGRAPHY**