Molecular genetics of paragangliomas of the skull base and head and neck region: implications for medical and surgical management

A review

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Paragangliomas are rare, slow-growing tumors that frequently arise in the head and neck, with the carotid bodies and temporal bone of the skull base being the most common sites. These neoplasms are histologically similar to pheochromocytomas that form in the adrenal medulla and are divided into sympathetic and parasympathetic subtypes based on functionality. Skull base and head and neck region paragangliomas (SHN-PGs) are almost always derived from parasympathetic tissue and rarely secrete catecholamines. However, they can cause significant morbidity by mass effect on various cranial nerves and major blood vessels. While surgery for SHN-PG can be curative, postoperative deficits and recurrences make these lesions challenging to manage. Multiple familial syndromes predisposing individuals to development of paragangliomas have been identified, all involving mutations in the succinate dehydrogenase complex of mitochondria. Mutations in this enzyme lead to a state of “pseudohypoxia” that upregulates various angiogenic, survival, and proliferation factors. Moreover, familial paraganglioma syndromes are among the rare inherited diseases in which genomic imprinting occurs. Recent advances in gene arrays and transcriptome/exome sequencing have identified an alternate mutation in sporadic SHN-PG, which regulates proto-oncogenic pathways independent of pseudohypoxia-induced factors. Collectively these findings demonstrate that paragangliomas of the skull base and head and neck region have a distinct genetic signature from sympathetic-based paragangliomas occurring below the neck, such as pheochromocytomas. Paragangliomas serve as a unique model of primarily surgically treated neoplasms whose future will be altered by the elucidation of their genomic complexities. In this review, the authors present an analysis of the molecular genetics of SHN-PG and provide future directions in patient care and the development of novel therapies.

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Key Words • carotid body tumor • glomus jugulare • glomus tympanicum • glomus vagale • paraganglioma • oncology

Abbreviations used in this paper: CDK = cyclin-dependent kinase; CN = cranial nerve; ENG = endoglin; HIF = hypoxia-inducible factor; HRE = HIF-responsive elements; MAX = MYC-associated factor X; miRNA = microRNA; SHN-PG = skull base and head and neck region paraganglioma; SRS = stereotactic radiosurgery; TGF-β = transforming growth factor–β; VEGF = vascular endothelial growth factor.

This article contains some figures that are displayed in color online but in black-and-white in the print edition.
are predominantly benign and asymptomatic, often being discovered as incidental findings. However, they can cause significant morbidity by virtue of their proximity to critical neural and vascular structures in the brain and neck, including the carotid artery, jugular vein, and cranial nerves (CNs) VII–XII. In this regard, the most common presenting symptoms include pain, dysphagia, hoarseness, pulsatile tinnitus, and conductive hearing loss. Malignancy occurs in 3%-16% of cases of SHN-PG, with vagal paragangliomas possessing the highest risk.

The majority of SHN-PGs are diagnosed in middle-aged adults, with younger patients and children more likely to have a recognized predisposing genetic mutation. Diagnosis is usually achieved by CT or MRI, but for extremely rare secretory SHN-PG, measurement of urine or plasma fractionated metanephrines, radionuclide scintigraphy, and PET can be used for confirmation. When these tumors occur in the jugular foramen and temporal bone region of the skull base, it is important to distinguish them from schwannomas and meningiomas, which can have similar presentations and imaging findings. While SHN-PGs are often encapsulated, adherence to nerves and blood vessels can make gross-total resection difficult, and postoperative CN deficits, strokes (often secondary to carotid artery sacrifice), and Horner’s syndrome are common complications. Although resection remains the primary treatment for symptomatic SHN-PG (Fig. 1A and C), radiosurgery has become increasingly popular for residual tumors and cases not amenable to surgery. Due to their highly vascular nature (Fig. 1B) and tendency to bleed intraoperatively, preoperative coil embolization has been used for SHN-PGs. Currently, this approach remains a surgeon- and center-dependent decision.

While pheochromocytomas and sympathetic paragangliomas are seen more frequently in individuals with inherited cancer predisposition syndromes, including multiple endocrine neoplasia Type 2, neurofibromatosis Type 1, and von Hippel–Lindau disease, parasympathetic SHN-PGs are observed in less than 0.8% of individuals with these syndromes. However, up to 30% of SHN-PGs have a distinct familial component, which has had critical to identifying key susceptibility genes through linkage analysis studies. Most notably, mutations in genes coding for the succinate dehydrogenase enzyme complex, which participate in the citric acid cycle and mitochondrial electron transport chain, have been found to be the most significant drivers of paraganglioma tumorigenesis. Mutations in the family of SDHx genes results in a state of pseudohypoxia and subsequent upregulation of the hypoxia-inducible factor 1-α (HIF-1-α) transcription factor and its downstream targets. Mutations in different subunits of succinate dehydrogenase not only confer an increased risk of developing SHN-PG but have also been linked to the development of multiple tumors, earlier age of initial presentation, and malignant potential. With the recent advent of comparative gene arrays and exonic sequencing approaches, other susceptibility genes have been identified, such as TMEM127. Inheritance patterns involving genomic imprinting have also demonstrated just how complex the molecular genetics of these tumors are, which has had profound implications on counseling, screening, and surveillance. In this review, we examine the current literature on the molecular genetics of familial and sporadic SHN-PG and provide insight as to how these findings will dictate future medical and surgical management.

**Nomenclature**

The nomenclature for paragangliomas has been a source of confusion among physicians and surgeons due to historic terms and various anatomical locations. Many of these terms are still commonly used today, but the medical community has encouraged cessation of their use in order to provide unifying, accurate, and understandable terminology across multiple disciplines. For example, paragangliomas have classically been referred to as “glomus” tumors, using the word glomus followed by the Latin adjective for the anatomical structure involved (for example, glomus jugulare, glomus tympanicum, glomus vagale). This is based on their vascular and histological similarity to glomus bodies and glomus body tumors, which are normally found in the skin and soft tissue. Other antiquated names for the most common SHN-PG, carotid body paraganglioma, are “carotid body tumors” and “chemodectomas” (which roughly translates...
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to “chemoreceptor tumor”). In addition, all parasympathetic paragangliomas were previously classified in the broad category of nonchromaffin paragangliomas, owing to their lack of catecholamine staining when exposed to chromium salts.

The current nomenclature for extra-adrenal paragangliomas is based on the associated structure or ganglion plus the term “paraganglioma.” For example, paragangliomas of the vagus nerve (most often the nodose ganglion) and carotid body are vagal paragangliomas and carotid body paragangliomas, respectively. Middle ear and jugular fossa (arising from adventitia of the jugular bulb) tumors of the temporal bone are accurately referred to as tympanic and jugular paragangliomas, respectively, or when expansive, jugulotympanic paragangliomas (Table 1).

While the carotid bodies and temporal bone region are the most common sites of SHN-PG, other sites of development include Jacobson’s nerve (CN IX), Arnold’s nerve (CN X), and the superior and inferior laryngeal ganglia. There have been rare reports of sellar and paraseptal paragangliomas as well.1,85 Outside of the head and neck region, paragangliomas can arise from various thoracic and abdominal ganglia, including the pre-aortic, aorticopulmonary, and sympathetic trunk ganglia.

Inheritance Patterns

Initial linkage analyses of pedigrees from 15 Dutch families with inherited paragangliomas demonstrated an autosomal dominant pattern with incomplete penetrance.92 By mapping a mutation to chromosome 11 and referring to this region as paraganglioma locus 1 (PGL1), researchers discovered a genotype-phenotype discordance that was the result of genomic imprinting.7,13 When PGL1 is transmitted through fathers, disease occurs in their offspring, whereas there is no disease phenotype when PGL1 is transmitted maternally. Genomic imprinting occurs when the maternally derived gene is inactive during oogenesis, but because the gene is only reactivated during spermatogenesis, only males can pass the disease to their children.63 This process, as seen in other known syndromes including Prader-Willi syndrome62 and Beckwith-Wiedemann syndrome,71 is the result of epigenetic-mediated DNA methylation and histone modification. Although other paraganglioma-associated disease loci have been discovered that are transmitted in the classic autosomal dominant pattern, the recent discovery of SDHAF2 (PGL2) demonstrates that genomic imprinting may be involved in its inheritance as well.37

Further linkage analyses of families with multiple generations of paragangliomas mapped a genetic mutation more precisely to 11q22.3–q23.1, which encompasses the SDHD gene.13 SDHD codes for a small subunit of the succinate dehydrogenase enzyme of complex II in the inner mitochondrial membrane.13 Inherited paragangliomas caused by mutations in the SDHD gene are now designated as familial paraganglioma Type 1. Subsequent studies have determined additional genetic mutations affecting this complex, including SDHB, SDHC, SDHA, and SDHAF2 (collectively referred to as SDHx genes). Of these genes, SDHD and SDHC have the highest risk of producing SHN-PG (Table 2).32

Familial Paraganglioma Mutations

SDHD

Mutations in SDHD were the first mutations to be described among families with inherited paragangliomas. Benign SHN-PG develops in 79%–97% of individuals with SDHD mutations, and in the majority of cases multiple tumors are seen at diagnosis.22,73 Furthermore, 86% of SDHD mutation–derived SHN-PGs are carotid body paragangliomas, presenting a unique and specific marker for predictive risk assessment.7,22 Over half of the population with SDHD mutations is also at increased risk for the development of pheochromocytomas; therefore, individuals harboring SDHD mutations should undergo abdominal imaging to rule out adrenal masses. Since this was the first mutation to be linked to familial paragangliomas, extensive studies have now demonstrated that more genetically devastating mutations, such as splice site and nonsense mutations, result in earlier age of onset as well as an increased risk of developing multiple SHN-PGs and pheochromocytomas.73 These findings suggest that less severe mutations (for example, missense mutations) result in a semifunctional protein that can compensate for cellular function.55 Interestingly, although multiple head and neck paragangliomas are consistent with SDHD mutations, only 3% of these tumors become malignant.22,73

Attempts to model SDHD–derived SHN-PG by Bayley et al.11 and Diaz-Castro et al.32 have independently demonstrated the enormous genomic complexity of these tumors. First, complete absence of Sdhd in mice (as in Sdhd−/− knockout mice) results in embryonic lethality, signifying that mammals are not viable without a functioning succinate dehydrogenase enzyme. Second, Sdhd+/− mice, which recapitulate the loss of heterozygosity observed in human tumors, do not demonstrate carotid body hyper-

<table>
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<tr>
<th>Location/Associated Structure</th>
<th>Historical Term(s)</th>
<th>Preferred Terminology</th>
<th>% of SHN-PGs</th>
<th>% Malignant</th>
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<tr>
<td>carotid body</td>
<td>carotid body tumor, chemodectoma</td>
<td>carotid body paraganglioma</td>
<td>44–58</td>
<td>6</td>
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<tr>
<td>jugular fossa/bulb (temporal bone)</td>
<td>glomus jugulare</td>
<td>jugular paraganglioma†</td>
<td>33–34</td>
<td>3–4</td>
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<tr>
<td>middle ear (temporal bone)</td>
<td>glomus tympanicum</td>
<td>tympanic paraganglioma†</td>
<td>7–13</td>
<td>3–4</td>
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<tr>
<td>vagus nerve</td>
<td>glomus vagale</td>
<td>vagal paraganglioma</td>
<td>1–7</td>
<td>10–16</td>
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* SHN-PG = skull base and head and neck paraganglioma.
† Often referred to collectively as jugulotympanic paragangliomas.
plasia or paraganglioma formation despite a 50% reduction in SDHD protein levels. Third, attempts to generate a mouse model with heterozygous knockdown of the candidate imprinted modifier gene H19 on a heterozygous Sdhd background (Sdhd+/−; H19+/− mice) also fail to develop paragangliomas in mice at any age. While attempts in paraganglioma animal modeling are ongoing, these findings underscore the complexity of SDHD-related tumorigenesis, and studies of alternate imprinted modifier genes within chromosome 11 may provide clarity.

Other SDHx Mutations

SDHB codes for subunit B of the succinate dehydrogenase complex and is also known as the iron-sulfur subunit of mitochondrial complex II. Found on chromosome 1 at 1p35-p36.1, mutations in SDHB are more strongly associated with thoracic, abdominal, and pelvic paragangliomas than SHN-PG, which occur in 29%–43% of individuals.5,11,46 This gene has the strongest association with gliomas than SHN-PG, which occur in 29%–43% of individuals who are negative for other SDHx gene mutations.11,47 Moreover, mutations in SDHB confer susceptibility to other cancers, including gastrointestinal stromal tumors, papillary thyroid cancer, neuroblastoma, and renal cell carcinoma.39,84,90

SDHC (also referred to as PGL3), coding for succinate dehydrogenase complex, subunit C, integral membrane protein, is found on chromosome 1 at position 1q23.3. While mutations in SDHC are far more rare than SDHD and SDHB mutations,22,78,87 they result in SHN-PG in 88% of cases and the affected patients rarely present with more than one lesion.13,44 Moreover, there has not been a single case of malignancy reported with SDHC mutations in SHN-PG.31,47

SDHA mutations on chromosome 5 (at 5p15) were only recently described in small subsets of paragangliomas and pheochromocytomas (< 3%).19,56 Although data from these studies suggest that SDHA acts as a tumor suppressor gene, the risk of developing SHN-PG with this mutation remains unclear, and clinical genetic testing for this mutation is not currently available.99,36 Conversely, mutations in SDHAF2 (also referred to as SDH5), which produces a protein involved in flavination of SDHA in complex II of mitochondria, leads to succinate dehydrogenase complex instability and a reduction in enzymatic activity.42 In a pedigree analysis of a large single-family cohort of individuals with SHN-PG, 42% were found to possess SDHAF2 mutations and 91% of affected individuals had more than one SHN-PG.57 None of the tumors were malignant. The exact prevalence of SDHAF2 mutations in sporadic SHN-PG remains controversial, however, with a larger study identifying only one SDHAF2 mutation in 315 patients negative for mutations in other SDHx genes.10 Current guidelines recommend that individuals with multiple SHN-PGs who are negative for other SDHx gene mutations be tested for SDHAF2 mutations.36

Emerging Data

TMEM127 and MAX

The TMEM127 gene is found on chromosome 2 at position 2q11.2 and codes for transmembrane protein 127 (TMEM127). Mutation of this gene does not result in dysfunction of the succinate dehydrogenase enzyme complex but has been associated with SHN-PG. An association between TMEM127 mutation and pheochromocytoma was initially discovered through global expression profiling and high-density copy number mapping, with TMEM127 mutations being identified in almost one-third of familial cases.21,81 Subsequent direct sequencing analyses have now demonstrated that 2%–4% of individuals with SHN-PG possess TMEM127 mutations.80,94 Although the exact mechanism by which TMEM127 mutations result in paraganglioma tumorigenesis is the focus of current research, preliminary studies indicate it is a negative regulator of mTOR (mammalian target of rapamycin), a cellular growth and proliferation protein of the PI3-kinase family.49,74

The most recent gene to be implicated in paraganglioma tumorigenesis is MYC-associated factor X (MAX), described initially in 2011 in hereditary pheochromocytomas and subsequently, in 2012, in paragangliomas.20,29 This gene encodes a member of the helix-loop-helix leucine zipper family of transcription factors that dimerize with the myc oncoprotein to regulate cellular proliferation, differentiation, and apoptosis.13 Only 1% of individuals who are negative for SDHx and TMEM127 mutations possess MAX mutations, and 16% of the individuals in this subset present with SHN-PG. These initial studies emphasize that these are extremely rare mutations, but

<table>
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<th>Table 2: Familial paraganglioma syndromes*</th>
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<td><strong>Disease</strong></td>
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<tr>
<td>familial paraganglioma Type 1 (PGL1)</td>
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<td>familial paraganglioma Type 2 (PGL2)†</td>
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<td>familial paraganglioma Type 3 (PGL3)</td>
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<td>familial paraganglioma Type 4 (PGL4)</td>
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* AD = autosomal dominant; NA = not applicable.
† Data derived from the only two studies in the literature analyzing this gene.
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future larger studies may help determine their exact epidemiological prevelance.20

Expression of miRNA and mRNA

MicroRNAs (miRNAs) are key regulators of gene expression independent of DNA genetic profiles. In 2013, initial reports of miRNA profiling studies in paragangliomas helped elucidate their role in the genetic pathogenesis of these tumors. Recently, de Cubas et al. leveraged miRNA expression profiles to demonstrate that miR-137 and miR-382 were globally upregulated in all paragangliomas with the exception of MAX-related tumors, whereas miR-96, miR-183, and miR-210 were specifically upregulated in SDHB-related tumors.30 While the exact mechanism by which miRNA aberrations contribute to paraganglioma formation in genetically predisposed individuals remains unclear, initial mRNA profiling data suggest that miRNA-mediated mRNA degradation results in a reduction in neuronal and neuroendocrine-associated development pathways.30 Future studies in this area may leverage advances in RNA sequencing technologies to decipher the exact role of miRNA and mRNA in familial and sporadic paraganglioma tumorigenesis.

Molecular Pathogenesis

Clues to the molecular pathogenesis of SHN-PG formation initially stemmed from carotid body physiological studies. Paraganglial tissue, like that found in the carotid bodies at the bifurcation of the carotid arteries, has a chemoreceptor function and is sensitive to circulating levels of oxygen, carbon dioxide, pH, and temperature. States of chronic hypoxia, such as those caused by chronic obstructive pulmonary diseases, cyanotic heart disease, and high altitude, lead to hyperplasia of this tissue.59 In fact, studies from the 1970s demonstrated that Peruvians living in the Andes mountains had significantly larger carotid bodies as the result of chief cell hyperplasia.2 Hypobaric pressure models of altitude hypoxia in rats also demonstrate carotid body hyperplasia, with a 3- to 4-fold increase in size within 12–16 days of exposure to chronic hypoxia.25,26 Consequently, there is an increased incidence of extra-adrenal paraganglioma (including SHN-PG) in individuals living at higher altitudes.5,32 Oxygen deprivation sensed by the carotid body leads to neurotransmitter release, altering cardiopulmonary function, as well as an upregulation of hypoxia-inducible factors that regulate oxygen-dependent gene expression and mitochondrial oxidative phosphorylation.36

The succinate dehydrogenase complex is part of the inner mitochondrial membrane and participates in the citric acid cycle and the electron transport chain. Through an oxidation reaction, succinate dehydrogenase converts succinate to fumarate using FADH2 as a cofactor. Complex II of mitochondria consists of 4 subunits (SDHA, SDHB, SDHC, SDHD) and mutations in all of these subunits have been described in the pathogenesis of paragangliomas. Disruption in any of these subunits compromises the succinate dehydrogenase complex, which results in the failure to transfer electrons and generate ATP (adenosine 5'-triphosphate), despite the availability of oxygen.

Molecular studies originating in pheochromocytoma research have now translated to our understanding of paragangliomas. In this regard, hypoxia-inducible factor-1α (HIF-1α) has emerged as one of the key regulators of tumorigenesis in the group of familial paraganglioma syndromes. Under normoxic conditions, proline residues on HIF-1α are hydroxylated by prolyl hydroxylase, with oxygen serving as a cofactor. This allows recognition by the VHL-E3 ubiquitin complex and subsequent degradation by the 26s proteasome (Fig. 2A).68 However, with SDHx mutations, there is accumulation of succinate, which directly inhibits prolyl hydroxylase-mediated hydroxylation of HIF-1α.54,88 This process simulates hypoxic conditions whereby prolyl hydroxylase cannot function, and therefore is termed a state of “pseudohypoxia.” Nondegraded HIF-1α then binds to HIF-1β, stabilizing its structure and allowing it to pass to the nucleus, where it binds to HIF-responsive elements (HRE) (Fig. 2B). Activation of HRE results in the transcription of different pathways relevant to tumorigenesis, as well as other hypoxia-driven physiological compensatory pathways, such as pH regulation, glucose metabolism, and erythropoiesis33,100.

Among the proteins that have increased expression resulting from activation of HRE by the HIF-1α/β complex are endoglin (ENG), vascular endothelial growth factor (VEGF),9,28,51,80,89 and platelet-derived endothelial cell growth factor (PD-ECGF).51 Endoglin is a transforming growth factor-β (TGF-β) co-receptor expressed mainly in proliferating endothelial cells and in conjunction with VEGF and PD-ECGF; these factors regulate angiogenesis and vascular remodeling, processes essential for tumor formation and maintenance.38,62,86 Furthermore, VEGF expression is dramatically increased in malignant SHN-PG, which is indicative of its role in potential malignant transformation.89 Increased levels of these proteins also provide an explanation for the robust vasculature associated with paragangliomas and why bleeding is among the biggest challenges in surgical control.

In addition to angiogenic factors, HRE activation in paragangliomas results in increased transcription of cell survival and proliferation genes, including BNIP310,80,94 and CCND154,80 respectively. The BNIP3 product is an apoptosis-regulating protein that is postulated to play a role in tumor cell survival.35 In normal cells, there is a balance between apoptosis and autophagy, which is a cytoprotective adaptive response through the degradation of unnecessary cellular components during oxygen-dependent energy droughts. However, in tumor cells, hypoxia and pseudohypoxia induce upregulation of BNIP3 to influence tumor cells towards autophagic pathways as opposed to apoptotic pathways, resulting in tumor cell survival. The mechanism by which BNIP3 shifts tumor cells towards autophagy occurs in an mTOR-dependent fashion, such that mTOR inhibitors enhance tumor cell death.47 Furthermore, autophagy inhibitors, such as chloroquine, result in a reduction in BNIP3 expression and subsequently tumor growth.47 In vivo demonstrations of these agents have already shown effectiveness in hypoxia-induced glioblastoma models, and therefore may provide a promising new therapy for paragangliomas.47
Immunoreactivity of the CCND1 protein product, cyclin D1, has also been reported in SHN-PG. Cyclins are a family of proteins that function as regulators of cyclin-dependent kinases (CDKs), which govern cell cycle control. Cyclin D1 specifically interacts with CDK4 and CDK6 to promote G1 to S transition during the mitotic phase of the cell cycle. Overexpression of cyclin D1 has been documented in other cancers as well, including breast, colon, and parathyroid cancers. Although first-generation CDK-inhibitors for various solid and hematological malignancies did not meet expectations in the early 21st century, recent trials have shown encouraging results from more specific, second-generation drugs. For example, the CDK 4/6 inhibitor PD0332991 coupled with letrozole has shown promising results in preliminary Phase II studies of ER+/HER2- breast cancer. To this end, other targeted CDK4/6 inhibitors may one day show benefit as potential chemotherapeutic options for paragangliomas with upregulated CCND1 signatures.

Gain-of-function mutations in HIF-2-α can also lead to paraganglioma development; such mutations are independent of and do not require SDHx mutations. HIF-2-α functions in the same manner as HIF-1-α in that it dimerizes with HIF-2-β and translocates to the nucleus, where it is involved in the activation of HRE. While some genes relevant to tumorigenesis are influenced by HIF-1-α, no tumor-relevant genes are uniquely under the control of HIF-2-α. Furthermore, HIF-2-α mutations have only been described in abdominal and pelvic paragangliomas.

**Stereotactic Radiosurgery**

Stereotactic radiosurgery (SRS) is an effective modality for the management of individuals with SHN-PG, with control rates of 90%–94% ten years following treatment. Whether SRS is used as a primary or salvage treatment modality is dictated by tumor location, the patient’s preoperative status, and protocols at respective medical centers. Nonetheless, as a primary treatment modality, radiosurgery achieves local control rates comparable to those achieved with surgical approaches, while...
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salvage SRS and can be used as an adjunctive treatment for tumors that are subtotally resected, with excellent progression-free survival and minimal side effects. Conventional fractionated radiation therapy doses of 45–55 Gy are commonly implemented, with relatively low incidences of postprocedural sequelae related to parenchymal radionecrosis, osteonecrosis of the temporal bone, mastoiditis, and mucositis. In general, individuals with SDHD mutations may be more amenable to SRS, given that these individuals are more likely to have multiple tumors and are at higher risk for recurrence. While the determination of genotype of individuals with SHN-PG has contributed greatly to diagnostic management, there is a paucity of data linking outcomes from primary and salvage SRS to genetic signature. Future SRS focused studies will benefit from collecting genetic data, as this may contribute to the understanding of tumor radiobiology and the development of personalized management strategies for those not amenable to surgery.

Impact on Screening and Therapeutic Management

Multiple groups have now proposed algorithms that call for genetic testing in individuals at high risk of developing paragangliomas. Specifically, those with a family history of SHN-PG or malignant paragangliomas anywhere in the body should have genetic sequencing of known familial predisposition genes. Based on the clinical and genetic sequencing data available, it is apparent that paragangliomas occurring in the neck and head have a genetic signature that is distinct from that of paragangliomas occurring below the neck. In this respect, nonsecretory parasympathetic paragangliomas are predominantly skull base and head and neck region tumors, are more likely to possess SDHD or SDHC mutations, and are less likely to be malignant. The largest series of genetic evaluation of SHN-PG, reported by Burnichon et al., demonstrated that less than 3% of SHN-PGs are secretory, that up to 97% and 87% of SDHD and SDHC mutation carriers develop SHN-PG, respectively, and that only 3% of SDHD mutation carriers develop malignant tumors. Furthermore, this series further strengthened the observation that SDHC mutation carriers do not develop malignant tumors. Based on comprehensive cost-effectiveness data, initial tests should include direct exonic sequencing of SDHB, SDHC, and SDHD, with those negative for mutations in these genes subsequently tested for SDHAF2 and TMEM127 mutations. Future individualized management will also rely on the exact mutation within these known susceptibility genes. Since patients with SDHD mutations resulting from nonsense and splice-site mutations are known to present at younger ages and with multiple lesions, appropriate counseling can be offered to expecting parents as well as more aggressive surveillance in those identified earlier in life. Our group predicts that whole-genome sequencing will replace direct sequencing approaches over the next 10 years—a change brought on by increased cost and time efficiency of next-generation sequencing platforms. This approach will also allow more comprehensive cataloging of potential imprinting modifiers associated with SDHD and SDHAF2 mutations in familial paraganglioma syndromes, as well as a better understanding of the genomic landscape in individuals who develop SHN-PG sporadically. Coupled with individualized genetic signatures, advances in CT, MRI, and nuclear imaging may also have an impact on the way individuals with paragangliomas are managed. Earlier detection of high-risk asymptomatic tumors may allow closer follow-up and surveillance, with resection when appropriate, leading to higher rates of remission. In addition, more accurate visualization of the vascularity of these tumors would allow surgeons to make informed decisions on which patients would benefit most from preoperative coil embolization. Although animal modeling of paragangliomas has presented many challenges, the generation of an accurate model would provide a platform for further target discovery as well as preclinical studies of candidate drugs prior to clinical trials in humans.

While understanding of the exact genetic determinants of SHN-PG is still in its infancy, future studies will evaluate response rates to various therapies based on genetic and genomic signatures. In this regard, mutations in specific SDHx genes may be more amenable to radiation therapy/radiosurgery as opposed to resection. This is especially true for individuals with SDHD-associated SHN-PG, who develop multiple tumors throughout adulthood. This approach could help reduce the psychological and physical burden of pre- and postoperative complications associated with multiple surgeries. Moreover, personal genomics and precision medicine will allow physicians to provide tailored drug regimens that have a high likelihood of response, either as single therapy or as part of multimodality regimes. For example, angiogenesis inhibitors, which are widely used in clinical oncological practice today as neoadjuvant therapies for colorectal, breast, and brain cancers, may expand treatment options for paraganglioma management as well. Recent reports utilizing the multiple tyrosine kinase inhibitor sunitinib have demonstrated a reduction in primary and metastatic tumor sizes and increased progression-free survival for individuals with malignant paragangliomas. Moreover, patients carrying the SDHB mutation experienced the greatest clinical benefit from this therapy, offering a unique perspective for the development of personalized management protocols. A multicenter, single-arm Phase II clinical trial is currently underway to further evaluate the effectiveness of sunitinib in patients with recurrent paragangliomas (Study of Sunitinib in Patients with Recurrent Paraganglioma/Pheochromocytoma [SNIPP], clinicaltrials.gov identifier NCT00843037), which may also shed light on the utility of this therapy for subtypes of SHN-PG.

Conclusions

In summary, SHN-PGs are rare tumors that can present significant challenges to the individuals, families, and physicians that have to manage them. These formidable neoplasms have demonstrated how the elucidation

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of genomic complexities can assist in the development of personalized management strategies and therapies.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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