OPEN ACCESS Freely available online

ISSN: 2161-1041
Hereditary Genetics: Current Research

Commentary

Tumor Characteristics in Hereditary and Apparently Hereditary Pheochromocytomas and Paragangliomas

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DESCRIPTION

Pheochromocytomas and Paragangliomas (PPGLs) are rare neuroendocrine tumors arising from adrenal medulla cells and extra-adrenal paraganglionic cells, respectively. Although traditionally considered sporadic, recent studies indicate a substantial genetic component, with around 30-40% of PPGLs attributable to hereditary mutations. The distinction between hereditary and apparently hereditary PPGLs is crucial, as it impacts diagnosis, management, and surveillance strategies. This article explores the tumor characteristics in hereditary and apparently hereditary PPGLs, highlighting the unique clinical features, genetic underpinnings, and implications for treatment.

Hereditary PPGLs: Genetic basis and clinical features

Hereditary PPGLs arise from germline mutations, with more than 15 genes implicated in their development. Mutations in genes such as *RET, VHL, SDHx* (*SDHA, SDHB, SDHC, SDHD*), and *NF1* are well-known contributors to hereditary PPGLs. The nature and penetrance of these mutations vary, giving rise to distinct syndromic presentations:

Multiple Endocrine Neoplasia type 2 (*MEN2*): Mutations in the *RET* gene are associated with *MEN2*, leading to pheochromocytomas alongside medullary thyroid carcinoma and parathyroid hyperplasia.

von Hippel-Lindau (*VHL*) disease: *VHL* mutations cause pheochromocytomas and paragangliomas, often alongside hemangioblastomas, renal cell carcinoma, and pancreatic cysts.

Succinate Dehydrogenase Mutations (*SDHx*): Mutations in the *SDH* gene complex (*SDHB, SDHD*, etc.) are among the most common genetic alterations in hereditary PPGLs. *SDHB* mutations, in particular, are associated with a higher risk of metastatic disease.

Neurofibromatosis type 1 (NF1): Individuals with *NF1* mutations may develop pheochromocytomas along with characteristic cutaneous and skeletal features, such as café-au-lait spots and neurofibromas.

Hereditary PPGLs typically present at an earlier age, are often bilateral or multifocal, and may recur. Due to the diverse spectrum of associated syndromic features, patients often undergo comprehensive genetic screening, allowing for early detection of other potential tumor types.

Apparently hereditary PPGLs: Phenotypic overlap and genetic variants of unknown significance

Apparently hereditary PPGLs refer to cases where there is a family history or phenotypic indication of hereditary predisposition but no identifiable mutation through current genetic testing. These cases may involve rare or novel mutations in known genes or yet-to-be-identified susceptibility genes. For instance, Variants of Unknown Significance (VUS) in *SDH* genes may be found in some patients, suggesting a hereditary link even though they do not meet the classic criteria for pathogenicity.

Clinically, apparently hereditary PPGLs may present with similar characteristics to confirmed hereditary cases, such as early age at onset, multifocality, or specific anatomical sites. In many cases, family members may also have related neoplasms, hinting at an underlying genetic predisposition that current testing does not detect. Some experts suggest that these cases may represent an underexplored spectrum of hereditary PPGLs, awaiting more refined genetic tools for proper classification.

Tumor characteristics in hereditary *vs.* apparently hereditary PPGLs

Several tumor characteristics help distinguish hereditary PPGLs from their sporadic counterparts and provide insights into the behavior of apparently hereditary cases.

Anatomical location: Hereditary PPGLs often appear in specific anatomical locations. For instance, *SDHD* mutations are more likely to produce head and neck paragangliomas, while *SDHB*

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Received: 06-Nov-2024, Manuscript No. HGCR-24-27455; **Editor assigned:** 08-Nov-2024, PreQC No. HGCR-24-27455 (PQ); **Reviewed:** 22-Nov-2024, QC No. HGCR-24-27455; **Revised:** 07-Jul-2025, Manuscript No. HGCR-24-27455 (R); **Published:** 14-Jul-2025, DOI: 10.35248/2161-1041.25.14.308

Citation: Yan J (2025) Tumor Characteristics in Hereditary and Apparently Hereditary Pheochromocytomas and Paragangliomas. Hereditary Genet. 14:308.

mutations are associated with abdominal and thoracic paragangliomas. Apparently hereditary PPGLs may also exhibit similar anatomical patterns, suggesting a genetic predisposition despite lacking confirmatory genetic mutations.

Tumor multifocality and bilaterality: Hereditary PPGLs frequently manifest as multifocal or bilateral tumors, particularly in cases of *VHL* or *SDHD* mutations. Apparently hereditary PPGLs may exhibit multifocality as well, suggesting a familial trend that is consistent with hereditary forms.

Age at diagnosis: Hereditary PPGLs generally present earlier than sporadic tumors, often in individuals under 40 years old. Apparently hereditary PPGLs tend to follow this trend, though age can vary significantly depending on other contributing factors.

Metastatic potential: Certain hereditary mutations, especially in *SDHB*, are linked with a higher risk of metastasis. Apparently hereditary PPGLs with similar phenotypic patterns but unidentified mutations may also exhibit elevated metastatic risk, making careful clinical surveillance essential.

Biochemical profile: Hereditary PPGLs often have distinct biochemical profiles. For example, *SDHx* mutations are frequently associated with elevated norepinephrine and dopamine levels due to impaired succinate dehydrogenase activity. Apparently hereditary PPGLs may display similar biochemical abnormalities, suggesting a shared metabolic disruption.

Implications for diagnosis, management, and genetic counseling

Understanding the differences and similarities between hereditary and apparently hereditary PPGLs has important implications for patient care. Genetic testing for known mutations is standard for patients with PPGLs, especially those with early-onset, multifocal tumors, or family history. Even if initial testing does not identify a mutation, the familial trend may warrant re-evaluation as genetic testing technologies advance.

Management strategies for hereditary and apparently hereditary PPGLs often involve active surveillance due to the risk of recurrence and metastasis. Patients with hereditary PPGLs may undergo regular imaging and biochemical testing, while those with apparently hereditary PPGLs may benefit from similar vigilance, particularly if they exhibit high-risk characteristics like multifocality or a family history of PPGLs.

Genetic counseling is crucial in both hereditary and apparently hereditary cases. For confirmed hereditary PPGLs, genetic counselors guide patients on the risk of transmission to offspring and recommend screening protocols. In apparently hereditary PPGLs, counseling focuses on the uncertainty surrounding VUS and the need for ongoing monitoring and potentially updated genetic testing as new discoveries emerge.

CONCLUSION

Hereditary and apparently hereditary pheochromocytomas and paragangliomas share several tumor characteristics, underscoring the influence of genetic factors in these conditions. Although apparent heredity presents unique challenges due to unidentified or inconclusive genetic mutations, careful clinical management and family history assessment remain critical. As genetic testing technology advances, our understanding of these tumors will likely deepen, leading to improved diagnostic precision, personalized management strategies, and enhanced outcomes for patients and their families.