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Commentary

Markers Commonly Used in Clinical Practice to Classify PPGL-Related VUS

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DESCRIPTION

Pheochromocytomas and Paragangliomas (PPGLs) are rare tumors originating from neural crest cells, typically arising in the adrenal glands or extra-adrenal locations, respectively. These tumors are notable for their association with catecholamine secretion, leading to significant clinical symptoms. However, not all PPGLs exhibit this trait, adding complexity to diagnosis and classification, especially when dealing with Variants of Uncertain Significance (VUS) in genes related to PPGLs. VUS classifications pose unique challenges, as their pathogenicity is uncertain, and the specific markers used in clinical practice can help stratify these variants for better diagnosis and management.

Genetic markers

Genetic testing has significantly transformed the approach to PPGL diagnosis, identifying mutations in over a dozen genes associated with these tumors. Many of these genes relate to two primary pathways: The hypoxia pathway and the kinase signaling pathway. Understanding mutations in these pathways helps clinicians classify VUS with greater confidence.

SDHx gene mutations

The succinate dehydrogenase complex, including *SDHA*, *SDHB*, *SDHC*, and *SDHD* (collectively known as SDHx genes), is particularly relevant in PPGLs. SDHx mutations can lead to abnormal succinate accumulation, inhibiting prolyl hydroxylases and leading to pseudohypoxia. *SDHB* mutations, in particular, are often associated with more aggressive tumors and are generally linked with malignant PPGLs. In cases with a VUS in one of the SDHx genes, measuring succinate levels may help determine the variant's impact.

VHL and *EPAS1* mutations

Von Hippel-Lindau (*VHL*) and *EPAS1* (also known as *HIF2A*) mutations are associated with a hypoxia-driven pathway, commonly seen in PPGLs. Variants in these genes can lead to increased angiogenesis and cellular growth due to dysregulated responses to oxygen levels. In VUS cases, functional assays examining the activity of HIF-targeted genes can be helpful. Additionally, correlating clinical findings with known *VHL* or *EPAS1*-related disease manifestations may assist in further classifying VUS.

Biochemical markers

Biochemical markers are critical in PPGL diagnosis and can help classify VUS by indicating whether a suspected mutation affects catecholamine production or other metabolic pathways relevant to PPGL biology.

Plasma and urinary catecholamines

Measurement of plasma and urinary catecholamines and their metabolites, metanephrines, remains essential in diagnosing PPGLs. Elevated levels of norepinephrine, epinephrine, and their metabolites can indicate active catecholamine secretion. For a VUS associated with a suspected catecholamine-producing pathway gene, such as *RET* or *NF1*, measuring catecholamine levels can provide insights into the functional effects of the variant.

Chromogranin A (CGA)

CgA is a glycoprotein co-stored and co-secreted with catecholamines in chromaffin cells, making it a valuable marker in PPGL assessment. Elevated levels of CgA suggest secretory activity, which can support the pathogenicity of VUS in genes like *RET* or *VHL*. However, CgA is a non-specific marker, and elevated levels may be seen in other neuroendocrine tumors and some non-tumor conditions, such as renal insufficiency. Despite its limitations, CgA measurement can be useful in the context of other clinical and biochemical findings.

Immunohistochemistry (IHC) Markers

Immunohistochemistry provides a window into the protein expression patterns within tumor tissue and is particularly

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valuable for distinguishing VUS effects on specific pathways or molecular characteristics.

SDHB IHC

SDHB immunostaining is a well-established marker for identifying loss-of-function mutations in SDHx genes. Loss of SDHB expression, as seen on IHC staining, indicates dysfunction in the SDH complex and is highly specific for pathogenic SDHx mutations. For a PPGL-related VUS in an SDHx gene, lack of SDHB expression in tumor samples may strongly indicate pathogenicity. Conversely, retained SDHB expression may suggest a benign variant.

Tyrosine Hydroxylase (TH)

TH is the rate-limiting enzyme in catecholamine synthesis and is often evaluated to assess catecholamine production. Positive TH staining supports active catecholamine synthesis and can suggest a pathogenic VUS in catecholamine-related genes, such as RET or NF1. The presence or absence of TH staining in the tumor tissue can therefore provide valuable functional information.

Metabolic markers

Several metabolic markers reflect the biochemical alterations in PPGLs and may help in classifying VUS by revealing metabolic disruptions typical of certain mutations.

Succinate-to-fumarate Ratio

In tumors with SDHx mutations, the ratio of succinate to fumarate increases due to a defect in the Tricarboxylic Acid (TCA) cycle. Elevated succinate relative to fumarate can thus be an indicator of pathogenic SDHx variants. For PPGL cases involving VUS in SDHx genes, measuring the succinate-to-fumarate ratio may provide additional insights into variant classification.

2-Hydroxyglutarate (2-HG)

Mutations in *IDH1* and *IDH2*, though rare in PPGL, lead to the accumulation of the oncometabolite 2-HG, which promotes tumorigenesis by inhibiting α-ketoglutarate-dependent enzymes. If a VUS is identified in an IDH gene, 2-HG levels in the tumor can help assess variant pathogenicity. Elevated 2-HG levels suggest metabolic dysfunction associated with IDH mutations, supporting the classification of the variant as pathogenic.

Radiological markers

Imaging studies play an essential role in PPGL diagnosis and can provide clues regarding tumor location, size, and biochemical activity. Certain radiological findings may correlate with specific genetic backgrounds, thereby supporting the classification of VUS.

Metaiodobenzylguanidine (MIBG) scintigraphy

MIBG scintigraphy is widely used in detecting catecholamine-secreting tumors, as MIBG is taken up by adrenergic tissue. Uptake on MIBG imaging can suggest a functional tumor and may support the pathogenic classification of VUS in catecholamine-synthesis genes. In cases with negative MIBG uptake, Fluorodeoxyglucose (FDG)-PET may be used as an alternative imaging modality, particularly for tumors with SDHB mutations.

18F-FDOPA PET imaging

This imaging modality is valuable for identifying PPGLs associated with the hypoxia pathway. For instance, PPGLs with SDHx or VHL mutations frequently exhibit high uptake on FDOPA PET. If a VUS is identified in a gene from the hypoxia pathway.

CONCLUSION

The classification of PPGL-related VUS is a complex and multifaceted challenge, relying on a combination of genetic, biochemical, immunohistochemical, metabolic, and radiological markers. Together, these markers help clinicians navigate the uncertainty surrounding VUS by providing insights into the functional and clinical impacts of these variants.