

Association of Urinary Bladder Paragangliomas with Germline Mutations in the SDHB and VHL Genes

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Background: Paragangliomas (PGLs) are extra-adrenal chromaffin cell-derived tumors of the sympathetic and parasympathetic paraganglia. Currently, about 35-40% of PGLs and their adrenal counterparts, pheochromocytomas, have been linked to underlying germline mutations in one of thirteen susceptibility genes. Of these, some of the most common are members of the succinate dehydrogenase (SDH) family, particularly the B subunit (SDHB), and the von Hippel-Lindau (VHL) gene.

PGLs can occur in anatomical locations throughout the body, but tumors in the urinary bladder (UBPGLs) are rare. Therefore, we sought to characterize these tumors with regards to their genetic backgrounds, biochemical phenotypes, and clinical outcomes.

Methods: A chart analysis of patients who presented to the National Institutes of Health was conducted.

Results: Twenty-seven patients with UBPGLs were identified, 17 (63%) of whom had germline mutations. Fourteen patients (51.9%) had SDHB mutations, and 3 (11.1%) had VHL mutations. With regards to biochemistry, 19 of the 22 patients with available pre-operative biochemical data (86.4%) presented with a noradrenergic biochemical phenotype, and 7 (31.8%) had tumors that also secreted dopamine. One patient (4.5%) had elevated metanephrine levels. Three patients (13.6%) did not have biochemically active tumors. Seven patients (25.9%) had multiple primary tumors concurrent with the UBPGL; an additional 3 patients (11.1%) had primary PGLs diagnosed before or after the diagnosis of the UBPGL. In addition, 13 (48.1%) were diagnosed with metastatic disease, either at first presentation or upon follow-up; 6 (46.1%) had SDHB mutations.

Conclusions: UBPGLs are frequently associated with underlying germline mutations in SDHB or VHL, suggesting that patients who present with these tumors should undergo genetic screening. Patients with these tumors typically present with a noradrenergic phenotype, although some may also have dopamine-secreting tumors. Finally, patients with UBPGLs should undergo careful follow-up, as almost half the patients in this series presented with metastatic disease.