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Hereditary Predisposition and Clinical Presentation of Patients with Pheochromocytomas and Paragangliomas: Insights from a Large Clinical Cohort

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BACKGROUND

Approximately 30-40% of paragangliomas (PGL) and pheochromocytomas (PCC) harbor an underlying hereditary cause. Early identification of at-risk individuals is imperative given the early-onset, aggressiveness of tumors, and other tumor/cancer risks associated with hereditary PGLs/PCCs. This study analyzes the clinical presentations and genetic histories of patients with PGL/PCC and/or hereditary risk to contribute to the expanding knowledge in this rare population.

METHODS

Retrospective chart review identified two cohorts of patients seen in cancer genetics clinics at an academic medical center and a safety-net hospital between August 2016 and December 2022. Cohort 1 consisted of patients with likely pathogenic/pathogenic variants (LPV/PV) in hereditary PGL/PCC predisposition genes (*FH, MAX, MEN1, NF1, RET, SDHA, SDHAF2, SDHB, SDHC, SDHD, TMEM127, VHL*). Cohort 2 consisted of patients with a personal history of a PGL/PCC. Demographics, personal/family history, and genetic testing outcomes were analyzed.

RESULTS

A total of 560 patients met study criteria (Cohort 1, n=364; Cohort 2, n=269). In Cohort 1, 77 (21.1%) patients had an incidental LPV/PV in a PGL/PCC gene. Nearly half (n=36, 46.8%) were in SDHx genes, with a majority in *SDHA* (n=21). In Cohort 2, 86 patients tested positive for 87 LPV/PV in a hereditary cancer predisposition gene). The SDHx genes were most likely to have a LPV/PV identified (*SDHB* n=24, *SDHD* n=23, *SDHA*=7). Patients at the safety-net hospital most frequently had an LPV/PV in syndromic genes (*VHL, NF1* and *FH*) compared to patients at the academic medical center.

CONCLUSIONS

Multigene panels identify patients at risk for hereditary PGL/PCC, many of whom are incidentally found. While SDHA LPV/PVs were the most frequent incidental finding, they were less common in patients with PGL/PCC, indicating the need for longitudinal studies to better understand the prevalence and penetrance of these tumors.

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