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Somatic Mutations in Inherited Pheochromocytomas and Paragangliomas

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Pheochromocytomas and paragangliomas (PCC/PGL) are tumors derived from chromaffin cells in the adrenal medulla or extra adrenal sites, respectively. There are eleven known susceptibility genes including *NF1, VHL, RET, SDHA, SDHB, SDHC, SDHD, SDHAF2, TMEM127*, *MAX* and *EPAS1*. Mutations in these genes account for up to a third of PCC/PGL cases. Despite the identification of these susceptibility genes, very little is known about the activated cellular pathways or the somatic genetic and genomic changes leading to tumor development and progression to malignancy. Approximately 25% of PCC/PGLs are malignant, defined as having distant metastases which can be present at initial diagnosis or develop even 20 years later. This potential latency period emphasizes the need for clinical biomarkers of aggressive disease, especially since patients with malignant PCC/PGL only have a 50% five year survival rate. Our objective is to comprehensively characterize the somatic genetic mutations and genomic aberrations in PCC/PGL using massively parallel sequencing. We have selected PCC/PGLs with both low and high malignant potential to identify somatic genetic and genomic alterations leading to tumorigenesis and malignant potential. We performed whole exome sequencing on matched germline and tumor DNA from a discovery set of four *VHL* and five *SDHB* associated PCC/PGL, representing low and high malignant potential tumors, respectively. In *SDHB* associated tumors, we have identified somatic mutations in a gene, known to contribute to tumor progression in other cancer types, but not previously reported in PCC/PGL. Results are being confirmed in an independent validation set of tumors and we have performed immunohistochemistry on a PCC/PGL tissue microarray. We also have identified genomic aberrations that may provide insight towards novel pathways contributing to tumorigenesis in PCC/PGL. These studies will contribute to our understanding of the development of PCC/PGL, and may pave the way for novel therapies for this disease.