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Whole Exome Sequencing Identifies Somatic *ATRX* Mutations in Pheochromocytomas and Paragangliomas

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Background: Pheochromocytomas and paragangliomas are tumors of the autonomic nervous system. Approximately one-fourth of tumors are malignant, defined by the presence of distant metastases. There are eleven known susceptibility genes for which the presence of a germline mutation will increase the risk of developing a pheochromocytoma or paraganglioma (PCC/PGL). However, very little is known about the somatic genetic mutations leading to tumorigenesis or malignant transformation.

Methods: In order to identify somatic genetic changes which may be drivers in PCC/PGL tumorigenesis and malignant transformation, we performed whole exome sequencing in 21 matched tumor and germline DNA samples from patients with either sporadic or inherited PCC/PGL, enriching for those with germline mutations in *VHL* or *SDHB* to represent tumors of low and high malignant potential, respectively.

Results: We identified somatic variants in *ATRX* in two of seven *SDHB* associated tumors in the discovery set. In a separate validation set of 103 samples, we found somatic *ATRX* variants of undetermined significance or deleterious or likely deleterious variants in 13.6% of tumors. PCC/PGLs with somatic *ATRX* variants were associated with alternative lengthening of telomeres and clinically aggressive behavior.

Conclusions: ATRX functions in chromatin remodeling and is somatically mutated in several cancer types including pancreatic neuroendocrine tumors. Our findings indicate that ATRX is the most frequently somatically altered genes in PCC/PGL, other than genes involved in the inherited syndromes. Although our sample set of PCC/PGL with *ATRX* variants is small, many had clinically aggressive features, inherited *SDHx* mutations and alternative lengthening of telomeres. Our findings suggest that mutations in genes involved in epigenetic regulation may be important for tumorigenesis in pheochromocytomas and paragangliomas with clinically aggressive behavior.