

Mutated ATRX gene linked to brain tumors potential biomarker for rare adrenal tumors too

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A somatic mutation in the ATRX gene has recently been shown as a potential molecular marker for aggressive brain tumors, such as gliomas, neuroblastomas and pancreatic neuroendocrine tumors. Now, for the first time, researchers at Penn's Abramson Cancer Center have found that the same mutated gene may serve as a much-needed biomarker for the pheochromocytomas and paragangliomas (PCC/PGL) that become malignant. These rare neuroendocrine tumors are typically benign, but when they go rogue, they become very aggressive.

The study was published online ahead of print today in *Nature Communications*.

Several inherited mutated genes, such as VHL and RET, have been found to be associated with PCC/PGL; however, little is known about the somatic genetic changes leading to tumorigenesis in these patients.

"This is the first step towards a better understanding of this type of disease, and to try to identify better biomarkers of poor outcomes," said senior author Katherine Nathanson, MD, an associate professor in the division of Translational Medicine and Chief Oncogenomics Physician for the ACC. "The mutation could not only serve as that biomarker for [metastatic disease](#), but also a potential therapeutic drug target in the future."

PGLs are rare tumors of nerve ganglia in the body, whereas PCCs form in the center of the adrenal gland, which is responsible for producing adrenaline. The tumor causes the glands to overproduce adrenaline, leading to elevated blood pressure, severe headaches, and heart palpitations. Both are found in about two out of every million people each year. An even smaller percentage of those tumors become malignant. For that group, the five-year survival rate is about 50 percent.

No reliable predictors of aggressive disease exist other than an inherited mutation in the SDH gene, but only half of patients who develop metastatic disease carry that mutation, meaning the other half have no known predictors.

About 60 percent of PCC/PGLs are sporadic, while the remaining 40 percent are hereditary. Most recurrent somatic mutations are observed almost exclusively in sporadic PCC/PGLs.

Researchers, including Lauren Fishbein, MD, PhD, MTR, an instructor in the division of Endocrinology, Diabetes and Metabolism at the Perelman School of Medicine, investigated the mutations using whole exome sequencing on a set of 21 tumor/matched germline DNA samples of either sporadic or inherited PCC/PGL. The idea was to compare benign tumors to clinically aggressive ones in order to spot markers of malignant potential.

Somatic ATRX mutations were identified in two of seven SDHB-associated tumors, the team reported. To determine the frequency of somatic ATRX mutations in PCC/PGL, the team sequenced the ATRX coding region in a separate set of 103 tumors samples. They found that 13 percent of tumors had ATRX mutations.

"Although our sample set of PCC/PGL with ATRX variants is too small to identify statistically significant associations, many had clinically

aggressive features, inherited SDHx mutations and ALT, suggesting an interaction between the somatic and inherited genomes in solid cancers, which needs to be investigated further," the authors wrote.

The findings come in the wake of new clinical guidelines for PCC/PGL put forth by professional societies, calling for a more personalized and multidisciplinary approach to testing and treating patients.

In the summer of 2014, the Endocrine Society issued the first ever clinical practice guidelines for the management of patients with PCC/PGL. They recommended consideration of genetic testing in all patients, among other evidence-based guidance. Patients with paraganglioma should be tested for SDHx mutations, and those with metastatic disease for SDHB [mutations](#), the report said.

"The Endocrine Society Guidelines on PCC/PGL go a long way to recommend consideration of clinical genetic testing for all patients with these tumors," said Dr. Fishbein. "It is especially important to identify SDHx mutation carriers who have higher incidence of multifocal disease and SDHB mutation carriers at higher risk of malignant disease. Our study suggests that [tumor-specific somatic mutations](#), such as those in ATRX, also may help identify patients within that group at the highest risk for more clinically aggressive disease."

Provided by University of Pennsylvania School of Medicine

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