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Key genetic mutations could be new hope for adrenocortical tumor patients

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Chinese researchers from Rui-Jin Hospital, Shanghai Jiao-Tong University School of Medicine, BGI, and other institutions have discovered that the activating hotspot L205R mutation in PRKACA gene was closely associated with adrenocortical tumors (ACTs), and the relationship of recurrently mutated DOT1L and CLASP2 with ACTs' other subtypes. The latest study published online in *Science* opens a new insight into diagnosis and treatment of Adrenal Cushing's syndrome.

Adrenal Cushing's syndrome results from autonomous production of cortisol (ACTH-independent) from adrenocortical tumors (ACTs), which may lead to a series of metabolic disorders such as obesity, glucose intolerance and hypertension. However, the genetic architecture of Adrenal Cushing's syndrome remains largely uncharacterized, hampering the development of diagnostic and therapeutic approaches for Cushing's syndrome.

In this study, researchers performed whole-exome sequencing of 49 blood-tumor pairs and RNA sequencing of 44 tumors from cortisol-producing adrenocortical adenomas (ACAs), ACTH-independent macronodular adrenocortical hyperplasia (AIMAH), and adrenocortical oncocytoma (ADO). They found there was a hotspot L205R mutation in PRKACA gene, and two novel mutated genes that have never been reported: One is DOT1L, which may contribute the tumorigenesis of AIMAH; the other is HDAC9, which would be responsible for ADOs.

In the large-scale validation stage, researchers found that L205R

mutation was only found in the ACTs, and located in the highly conserved functional domain-P+1 loop of PKA catalytic subunit-plays an important role in the combination of kinase and substrate. The further molecular and cell function validation proved that L205R mutation caused the increase of protein activity and enhanced the catalytic capability of the phosphorylation, and promoted the occurrence of tumor and the production of steroid by substrate phosphorylation.

Yanan Cao, Endocrinologist from Rui-Jin Hospital, said,"ACTs and Cushing's syndrome belong to one important kind of diseases in endocrine metabolic disorders. Our study revealed several key mutated genes closely associated with adrenocortical tumors. Furthermore, we systematically analyzed the function of L205R mutation by structure and molecular biology technologies, laying a solid foundation for developing new treatment strategies for Adrenal Cushing's syndrome."

Minghui He, Project Manager of BGI, said, "Using high-throughput sequencing and bioinformatics technologies, we characterized mutation landscape of adrenocortical tumor, and found L205R mutation in PRKACA gene was closely associated with adrenocortical tumors. These findings provide new insights into the clinical diagnosis and treatment of adrenocortical tumors."

Provided by BGI Shenzhen