BGI reports study results on frequent mutation of genes encoding UMPP components in kidney cancer

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BGI, the world's largest genomics organization, announced that a study on frequent mutation of genes encoding ubiquitin-mediated proteolysis pathway (UMPP) components in clear cell renal cell carcinoma (ccRCC) is published online today in *Nature Genetics*. In addition to BGI, co-leaders of the study included Peking University Shenzhen Hospital, Shenzhen Second People's Hospital, among others. The study reveals that alteration of UMPP may contribute to ccRCC by activation of the hypoxia regulatory network, providing new clues to trace the key molecular mechanisms and pathways that underlie the tumorigenesis and progression of ccRCC.

Clear cell renal cell carcinoma (ccRCC) is the most common and aggressive type of kidney cancer, with 102,000 deaths worldwide each year. It is characterized by high metastatic potential and poor prognosis. Up to 40% of patients have disease recurrence after nephrectomy. In this study, the research team specifically looked at alterations in ubiquitin-mediated proteolysis pathway and studied its potential impacts linked to ccRCC tumorigenesis. The UMPP has been reported to be associated with many diseases including cancer and plays a critical role in the protein metabolism as a major pathway for protein degradation in cells.

"Adding to the previous research effort of transitional cell carcinoma in bladder cancer published in Nature Genetics earlier this year, we and our partners continued our study of strongly aggressive ccRCC tumors to

identify the mutated genes associated with the process of tumorigenesis," said Guangwu Guo, one of the co-leading authors of the study and PI of this project at BGI. "The new discoveries in this study led us to a remarkable step in our understanding of the genetic landscape of ccRCCs and toward potential treatment against this aggressive tumor."

To gain a deep insight into the genetic basis of ccRCC, researchers analyzed ten primary tumors with matched morphologically normal renal tissues utilizing the whole exome sequencing approach on BGI's sequencing platform. The mutation prevalence was estimated by screen of ~1,100 genes with somatic mutations or that have been causally implicated in cancers in 88 additional ccRCCs for prevalence screen.

There were 23 significantly mutated genes identified in the 98 ccRCCs, including the five well-known renal cancer genes such as VHL and TP53, and genes involved in chromatin modification such as PBRM1, JARID1C and SETD2. "We have identified 12 genes which were previously unknown to be involved in ccRCC, including two tumor suppressor genes, BAP1 and TSC1. Integration of previous studies and our findings suggest that some of the genes may play important roles in ccRCC genesis," said Guo.

In addition to the attempt to identify all mutated genes associated with ccRCC, researchers also focused on specific genes, pathways and mechanisms that potentially play a key role in ccRCC tumorgenesis and warrant exploration as potential targets for treatments. One of the targets was mutations in VHL gene that were commonly suggested to be involved in ccRCC genesis in many previous genetic studies with reported prevalence ranging between 50% and 80%. Interestingly, researchers have found a much lower prevalence of 27% in this study. VHL promoter hypermethylation was only found in 6% of the tumors relative to their matched normal samples, also suggesting a lower prevalence of epigenetic VHL alternation, according to the researchers.

Although the alteration of VHL gene is widely known for its association with kidney cancer, researchers also revealed the frequent mutation of UMPP linked to ccRCC in this study and have sequenced all 135 genes in UMPP in the prevalence screen. A significantly high mutation frequency of UMPP was found in the 98 carcinoma samples. The pathway analysis suggested that alternation of UMPP could potentially play an important role in ccRCC tumorigenesis, and it may contribute by activating the hypoxia regulatory network.

"This study has enhanced our knowledge and laid an important foundation for future research of ccRCC. The new discovery on the potential contribution of UMPP to ccRCC justifies more comprehensive investigation of this pathway, including proteomics research of the protein network to fully elucidate its role in ccRCC genesis," said Professor Jun Wang, Executive Director of BGI.

Provided by BGI Shenzhen

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