Scientists report new findings on mutations identification of esophageal cancer

March 18 2014

In a collaborative study, researchers from Chinese Academy of Medical Sciences and Peking Union Medical College, BGI, Shantou University Medical College and other institutions identified important alterations of tumor-associated genes and tumorigenic pathways in esophageal squamous cell cancer (ESCC), one of the leading cause of cancer death worldwide. The all-round work was published online today in the international journal *Nature*, providing a new eye-opening insight into developing novel biomarkers for therapeutic strategies of this most common form of esophageal cancer.

ESCC is the most common type of esophageal cancer, accounting for 90% histopathological forms. Currently, there is poor clinical approaches for early diagnosis and treatment for ESCC patients and the five-year overall survival rate is about 10 per cent. Meanwhile, the full repertoire of genomic events leading to the pathogenesis of ESCC remains unclear. As such, there is an urgent need for discovering biomarkers from whole genomic level that can greatly improve therapeutic strategies of ESCC.

In this study, researchers conducted a comprehensive genomic analysis in 158 Chinese ESCC patients, including whole-genome sequencing in 17 ESCC cases and whole-exome sequencing in 71 cases, of which 53 cases and additional 70 ESCC cases were subjected to array comparative genomic hybridization (a-CGH) analysis. This work is as part of the International Cancer Genome Consortium (ICGC) Research Projects.

Based upon the sequencing data, they identified 8 significantly mutated genes related to ESCC, including six well-known ESCC-implicated genes (TP53, RB1, CDKN2A, PIK3CA, NOTCH1 and NFE2L2), one tumor-associated gene (ADAM29) which has never been described in ESCC, and one novel gene (FAM135B) that has not been reported in cancers before but was observed that it could significantly enhance cell growth, colony formation, migration and invasion and other cellular malignant phenotypes, which suggested that FAM135B can contribute to the development of ESCC.

The 11q13.3-13.4 region has been previously reported to be amplified in many human cancers. In this study, researchers identified one microRNA (MIR548K) encoded in this region, and found it was characterized as a novel oncogene and functional assays which demonstrated that MIR548K enhances malignant phenotypes of ESCC cells. Authors referred in the paper that this is the first time that MIR548K has been demonstrated in human cancers. In addition, they also found that several important histone regulator genes such as MLL2, ASH1L, MLL3, SETD1B and CREBBP/EP300 are frequently altered in ESCC.

Subsequently, the pathway assessment revealed that somatic aberrations were mainly involved in the Wnt, cell cycle and Notch pathways. Interestingly, genomic analyses suggested that ESCC and head and neck squamous cell carcinoma (HNSCC) shared some common pathogenic mechanisms, and ESCC development is associated with alcohol drinking.These findings would provide a brand-new insight into the understandings of ESCC tumorigenesis, and would help clinicians to develop more effective diagnostic and therapeutic approaches for ESCC.

Dr. Qimin Zhan, Principal Investigator of this project and the Director of State Key Laboratory of Molecular Oncology, Chinese Academy of Medical Sciences Cancer Hospital, said, "For sure, the findings of this

project provide novel insights into understanding of underlying mechanism for this malignant ESCC, and enable us to explore potential diagnostic biomarkers and drug targets, and to develop useful clinical therapeutic approaches. More significantly, the completion of the project is of great significance since esophageal cancer is one type of cancers with high prevalence and mortality in China, and thus Chinese scientists have our own historical duty to develop new ways for ESCC prevention and treatment. Additionally, we are happy to see that such success is achieved through the joint effort of multiple research institutions and hospitals."

Lin Li, Primary Investigator of this project at BGI, said, "This is a great progress for genetic research of oesophageal squamous cell cancer. These findings would provide a brand-new insight into the understandings of ESCC tumorigenesis, and would help clinicians to develop more effective diagnostic and therapeutic approaches for ESCC. Moreover, the genomic data yielded in this study also lay a solid foundation for our further research on ESCC."

Provided by BGI Shenzhen