Genetic alterations show promise in diagnosis and treatment of bladder cancer

16 October 2013

A Chinese research team composed of Shenzhen Second People's Hospital, BGI and other institutes reports their latest study on bladder cancer genomics that was published online in *Nature Genetics*. The discoveries were made using whole-genome and exome sequencing technologies and provide evidence that genetic alterations affecting the sister chromatid cohesion and segregation (SCCS) process may be involved in bladder tumorigenesis and open a new way for the treatment of bladder cancer.

Transitional cell carcinoma (TCC) is the most common type of bladder cancer diagnosed, accounting for 90% of all bladder malignancies in North America, South America, Europe, and Asia. It's reported that there were an estimated 386,300 new bladder cancer cases and 150,200 deaths in 2008 alone. And the number was up to 170,000 deaths in 2010. Until now, there has been no complete genomic data available for developing new therapeutic approaches to combat bladder cancer.

To have a deeper understanding of the genetic basis underlying TCC, Chinese scientists conducted exome sequencing on the tumor and matched peripheral blood samples from 99 TCC patients, and identified 1,023 somatic substitutions and 67 indels respectively. They performed whole genome sequencing (WGS) to detect copy number alterations (CNAs) and obtained 4-fold mean haploid coverage for each sample.

After evaluating the genetic alterations or variants, researchers found frequent alterations in two genes, STAG2 and ESPL1, which are associated with the sister chromatid cohesion and segregation (SCCS) process. Among them, STAG2 was particularly notable as to harbor a greater number of nonsynonymous mutations and a higher ratio of nonsynonymous to synonymous mutations. Their study indicated that chromosomal instability and aneuploidy had an influence on bladder cancer, and provided evidence that bladder cancer became the first type of cancer with major genetic lesions in SCCS genes.

Furthermore, researchers detected a recurrent fusion involving two other SCCS-associated genes, FGFR3 and TACC3, by transcriptome sequencing of 42 DNA-sequenced tumors. They suggested that FGFR3/TACC3 is related with bladder tumorigenesis, and the high expression of TACC3 was mediated by transcriptional regulatory elements in the promoter of the fusion partner, FGFR3, not the amplification of TACC3.

Chao Chen, Senior researcher from BGI, said, "This is a great progress for genetic research of bladder cancer. We discovered frequent alterations in STAG2/ESPL1 and recurrent fusion FGFR3-TACC3, which provide evidence that genetic alterations affecting the SCCS process may be involved in bladder tumorigenesis and implicate a novel therapeutic approach for bladder cancer. In addition, the genomic data yielded in this study also lay a solid foundation for our further research on bladder cancer."

Provided by BGI Shenzhen