Next generation sequencing study to unravel the genetic basis of congenital bile-duct dilatation

View session detail

Author Block: **C. Tang**[1], Q. Lin[1], P. Sham[2], P. Tam[1,3]; [1]Department of Surgery, The University of Hong Kong, Hong Kong, China, [2]Department of Psychiatry, The University of Hong Kong, Hong Kong, China, [3]Faculty of Medicine, Macau University of Science and Technology, Macau, China

Congenital bile-duct dilatation (CDD), also known as choledochal cyst, is a complex congenital anomaly characterized by abnormal dilatation of the extrahepatic and/or the intrahepatic bile ducts. Type I with dilatation limited to the common bile duct represents the most common disease subtype, which accounts for 50%-80% of the CDD cases. Our previous genetic study suggested a genetic predisposition in the pathogenesis of the disease. To further elucidate the genetic causes of CDD, we performed trio-based whole exome and genome sequencing on type I CDD patients of Chinese ancestry. De novo analysis identified thirty-six damaging protein-altering variants, including five protein truncating variants and twenty-eight nonsynonymous variants. Truncating de novo mutations in evolutionarily constrained genes and missense changes with regional constraint were found to be enriched in cancer-related genes such as *PIK3CA*, *TLN1*, *CYLD*, *NK1*, and *MAP2K1*. Recessive and compound heterozygous damaging mutations were also identified in related pathways. Additionally, we detected significant enrichment of damaging mutations in cytoskeleton and microtubule-associated pathways. Spatiotemporal expression of these candidate gene was further evaluated using fetal single cell transcriptomic data. While CDD was reported to be associated with increased risk of developing biliary tract cancer, our findings of cancer gene predisposition may help stratification of patients with higher cancer risk to improve clinical outcomes.