Unraveling the genetic predisposition to non-syndromic Biliary atresia through genomic investigations

View session detail

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Biliary atresia (BA) is a rare congenital cholangiopathy and is the most common reason for liver transplantation in the pediatric population. Elucidating the genetic predisposition of BA may help decode the underlying molecular mechanisms to improve disease outcomes. To uncover novel disease-susceptibility genetic factors, rare damaging mutations were identified in a dataset of whole exome/genome sequencing of 188 BA patients and 324 unaffected parents. Through bioinformatic analyses, four gene sets were found to be associated with the development of BA: (i) cilia, (ii) extracellular matrix (ECM), (iii) NOTCH, and (iv) transforming growth factor-beta (TGFβ) signaling pathways. *THBS1* emerged as the central hub of candidate genes in the protein-protein interaction (PPI) network analysis. Additionally, the integration of transcriptome data identified several candidate genes related to liver diseases, including two known BA-associated genes, *EFEMP1* and *KRT19*, and a novel candidate, *MAT1A*. Gene-based burden tests on the rare damaging variants highlighted the involvement of the catabolic process in the development of BA, which was relevant to the pathomechanism of MAT1A. Cell type enrichment and gene expression deconvolution analyses using single-cell RNA sequencing data further highlighted the significance of hepatic stellate cells (HSCs) and their interplay with ECM in BA. Overall, this study utilized various genomic methodologies to uncover novel disease-susceptibility genes, biological processes, and pathways involved in the development or progression of BA.