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Identification of Novel Pathogenic Genes and Variants in IFT-A Complex Related Genes in Children with Nephronophthisis

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Objectives : Nephronophthisis (NPHP) is an autosomal recessive cystic kidney disease leading to end-stage renal disease (ESRD) in children and adolescents. The cause of NPHP is attributed to abnormalities in primary cilium, pivotal cellular organelles responsible for sensing extracellular cues and signal transduction. The IFT-A complex, comprising 8 proteins, is integral to the ciliary transport. This study aims to identify novel pathogenic variants in children with NPHP by focusing on 8 genes associated with the IFT-A complex.
Methods : Trio exome sequencing (WES) was conducted on a cohort of Chinese children with NPHP from the Chinese Children Genetic Kidney Disease Database (CCGKDD) to screen for pathogenic variants in IFT-A complex related genes. Additionally, functional studies were performed to elucidate the molecular mechanisms of pathogenic variants in IFT-A subunits.
Results : The study revealed biallelic pathogenic variants of IFT122, IFT140, IFT144, and IFTAP in 10 children with NPHP, with a total of 15 identified pathogenic variants. Notably, IFTAP was identified as a novel gene implicated in NPHP. Renal and extrarenal phenotypes in these patients were characterized, including proteinuria, renal damage, retinitis pigmentosa, hearing loss, scoliosis, psychomotor retardation, and submandibular rhabdomyosarcoma. Functional experiments on HK2 cells demonstrated significant reductions in primary cilia length and ciliated cell percentage in IFT122-KD, IFT140-KD, IFT144-KD, or IFTAP-KD cell lines compared to the control group. Moreover, 3D-culture of IMCD3 cells revealed additional abnormalities in IFT-A defective cells, including decreased ciliation, shortened cilia, enlarged 3D spheroids, increased cystic rates, and loss of polarity. In vitro experiments confirmed the involvement of pathways including Wnt/β-catenin, Shh, and autophagy.
Conclusions : Screening for pathogenic variants in IFT-A complex can aid in establishing the monogenetic basis of NPHP. Furthermore, the identification of these IFT-A mutations through WES can expedite precise diagnosis and typing of NPHP. Future genetic and functional investigations are warranted to further elucidate the underlying mechanisms of NPHP.

figure 1.png

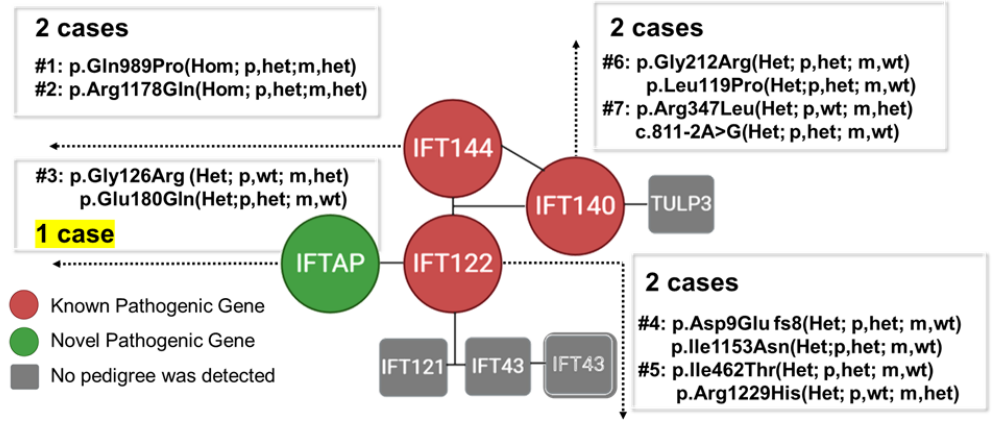

Fig. 1: Structure of IFT-A complex and variants screened from patients

figure 1.png

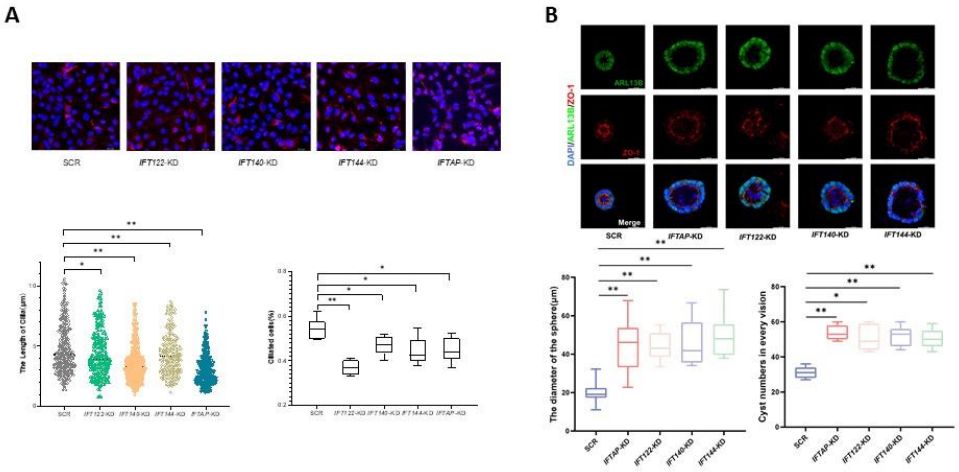

Fig. 2: Cilia length and the percentage of ciliated cells in HK-2 cells and 3D-culture of IMCD3 cells.
A, scale bar=58.2μm, DAPI(Blue), ac-α-tubulin(Red). B, scale bar=23.1 μm, DAPI(Blue), ARL13B(Green), ZO-1(Red).