IFT57 May Cause Bardet-Biedl Syndrome with Retinal Dystrophy

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Introduction: Primary cilia are critical organelles found on the surface of most cells, and play an important role in cell signalling. When this process goes wrong, patients develop ciliopathies, which are a genetically and clinically heterogenous group of diseases that cause a wide range of co-morbidities. The connecting cilium of the photoreceptor is a homologous structure of the primary cilia, allowing transfer of proteins from the inner segment to the outer segment of the photoreceptor.

Methods: A 29-year old male has rod-cone degeneration which led to legal blindness. He also has features including polydactyly, mild cognitive impairment, and a fatty liver, which are suggestive of a Bardet-Biedl Syndrome (BBS) ciliopathy. Following negative clinical genetic testing, genome sequencing identified biallelic variants in IFT57 in trans, which were predicted to be highly conserved by in silico tools. The variants included a deletion in exon 6 that caused a frameshift and loss of function, and a c.1190T>A; p.(Val397Glu) missense variant in exon 11 that is predicted to be damaging by in silico algorithms. Due to their rarity, these variants were labelled of unknown significance according to the ACMG criteria. IFT57 is part of complex B of the intraflagellar transport IFT proteins. The IFT machinery is a bidirectional transport system of proteins from the cilia base to the tip and back. This plays an important role in the maintenance of cilia. IFT57 variants have not yet been associated with BBS or a human retinal dystrophy.

Results: Using patient-derived fibroblasts (PDF), immunofluorescence revealed lower cilia count/percentage and cilia that are abnormal in length and shape. We also show that Val397Glu variant IFT57 and other IFT-B complex proteins like IFT88 exhibit impaired anterograde transport in PDF cilia. Transfection of IFT57 knockout IMCD3 cells with WT IFT57 rescues the abnormal cilia phenotype, while transfection with Val397Glu only partially rescues the cilia phenotype. In RPE1 IFT57 knockout cell lines, transfection with Val397Glu does not rescue cilia, indicating that the role of IFT57 may be cell autonomous.

Conclusion: Taken together, these results suggest that the Val397Glu missense variant in IFT57 destabilises the IFT-B complex, affecting cilia formation and anterograde transport. Elucidating the link between IFT57 and BBS is important to clarify the genetic nature of BBS and inherited retinal dystrophies, opening new research avenues.