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ATMIN MODULATES *PKHD1* EXPRESSION AND THROUGH ALTERED NON-CANONICAL WNT/PLANAR CELL POLARITY (PCP) SIGNALLING MEDIATES ARPKD SEVERITY

Paraskevi Goggolidou[3,2], Taylor Richards[3], Kavindiya Modarage[3], Charlotte Dean[1], Jill Norman[2], Patricia Wilson[2]

[1]*National Heart and Lung Institute, Imperial College London, London, United Kingdom,* [2]*Centre for Nephrology, University College London, London, United Kingdom and* [3]*Faculty of Science and Engineering, University of Wolverhampton, Wolverhampton, United Kingdom*

INTRODUCTION AND AIMS: ARPKD is a genetic disorder with an incidence of ~1:20,000 that can lead to perinatal mortality. In the ~60% of ARPKD patients who survive the neonatal period, there is a range of disease severity, however, little is known about the genetic mechanisms that regulate ARPKD. ARPKD is caused by mutations in *PKHD1* which encodes the large membrane protein, fibrocystin, required for normal branching morphogenesis of the ureteric bud during embryonic renal development. The range of disease severity observed in ARPKD suggests that besides *PKHD1* that when mutated causes ARPKD, other genes might also play a role in ARPKD, acting as modifiers of disease severity.

METHODS: Quantitative Real-time PCR and immunohistochemistry in age-matched normal and ARPKD human kidneys were employed in addition to the $Atmin^{Gpg6}$ mouse and siRNA-mediated knockdowns in mIMCD3 cells, to investigate the relationship between fibrocystin and non-canonical Wnt signalling.

RESULTS: In normal human kidneys ATMIN, VANGL2, Inversin and β-catenin were expressed in ureteric bud-derived collecting tubules, whereas in age-matched ARPKD tissue, strong ATMIN and VANGL2 and moderate Inversin and β-catenin expression were observed in cyst-lining epithelia. Significant increases in *ATMIN*, *WNT5A*, *VANGL2* and *SCRIBBLE* mRNA expression were seen in human ARPKD versus normal kidneys; no considerable differences were seen in *DAAM2* or *NPHP2*. A striking increase in E-cadherin was also detected in ARPKD kidneys. Investigations of the $Atmin^{Gpg6}$ mouse showed that it is a novel mouse model of ARPKD. Further, loss of *Atmin* affected the transcriptional regulation of *Pkhd1* and restored cellular proliferation to normal levels.

CONCLUSIONS: This work suggests the novel role of non-canonical Wnt signalling in ARPKD and proposes *ATMIN* as a modifier of ARPKD that could in the long term be used as a biomarker of ARPKD severity and progression.