THE KOREAN SOCIETY OF NEPHROLOGY
APCN & KSN 2024
June 13(Thu) - 16(Sun), 2024 Coex, Seoul, Korea
APSN
Promoting Sustainable Kidney Health: The Asia-Pacific and Beyond

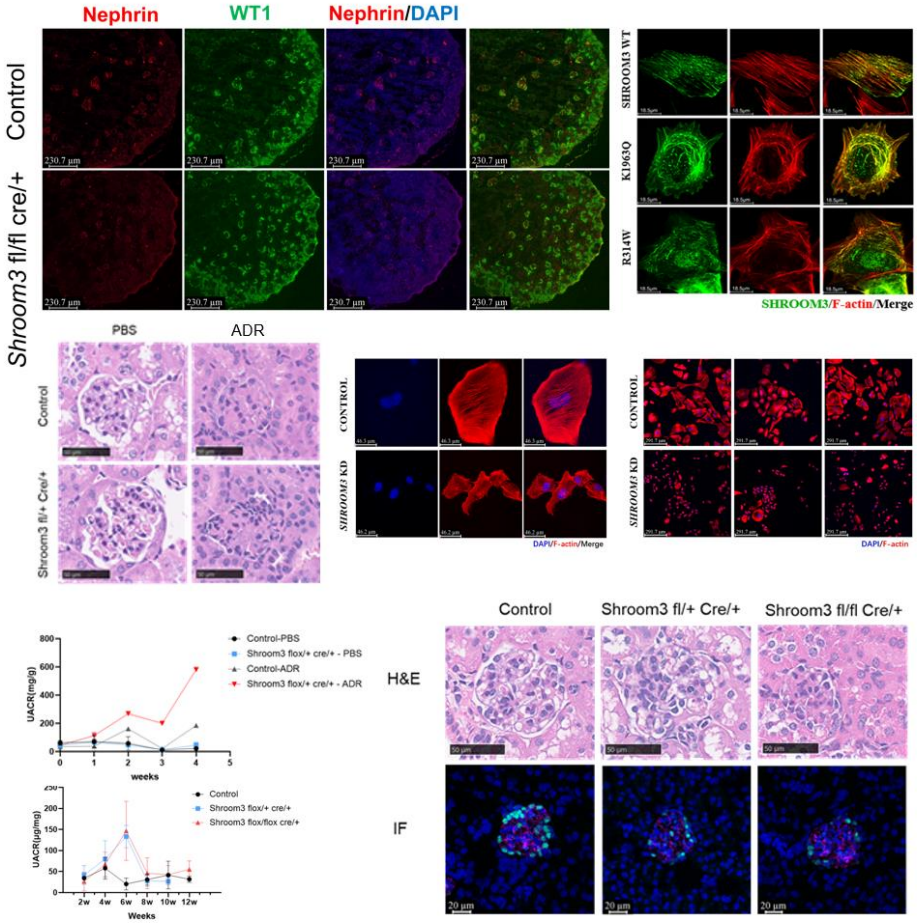
Abstract Submission No.: A-0122

Deficiency of Shroom3 Delays Kidney Development Process and Increases Susceptibility to Injury

Li-nan Xu, Ye Fang, Tian-chao Xiang, Qian Shen, Hong Xu, Jia Rao
Department of Pediatrics-Nephrology, Department of Nephrology, Children's Hospital affiliated with Fudan University, Shanghai 200200, China, China

Objectives : The Shroom3 gene has been associated with chronic kidney disease through GWAS study. In this study we investigated the pathogenetic mechanism of SHROOM3 in proteinuric nephropathy and the kidney developmental disorder.
Methods : We screened the variants of SHROOM3 in children with proteinuric nephropathy to identify a monogenetic cause of the disease through exome sequencing. To elucidate the Shroom3's function in podocytes, we generated a podocyte-specific Shroom3 knockout mouse model (Shroom3$^{\blacktriangle ex5\ flox/+}$; Nphs2-Cre mice and Shroom3$^{\blacktriangle ex5\ flox/flox}$; Nphs2-Cre mice) and a human podocyte cell line featuring knockdown of SHROOM3 to analyze the phenotypes of kidney development and function.
Results : Variants in SHROOM3 (c.940C>T, p.R314W and c.5887A>C, p.K1963Q), were identified in two families featured by proteinuria and renal insufficiency. In vitro, podocytes with SHROOM3 depletion led to reduced cell volume, adhesion, and disorganized F-actin. Downregulation of adhesion proteins and elevated calpain activity were shown in podocytes with SHROOM3 deficiency. RNA-seq analysis revealed that SHROOM3 knockdown in podocytes suppressed various pathways related with kidney development, including Wnt signaling pathways. Reintroduction of wild-type SHROOM3 rectified F-actin fiber structure, an effect not replicated by the R314W and K1963Q variants. In conditional Shroom3 knockout mice, transient proteinuria was found between 4 to 8 weeks of age. Shroom3$^{\blacktriangle ex5\ flox/+}$; Nphs2-Cre mice were more susceptible to Adriamycin nephropathy and lipopolysaccharide exposure. Shroom3 ablation correlated with increased immature nephrons in neonatal mice and substantial cortical thickening.
Conclusions : The study elucidates the pathological influence of SHROOM3 deficiency on podocyte architecture and signaling pathways, advancing our understanding of proteinuria's molecular underpinnings.

Figure1.jpg


Nephrin
WT1
Nephrin/DAPI
Control
Shroom3 fl/fl cre/+
SHROOM3 WT
K1963Q
R314W
SHROOM3/F-actin/Merge
PBS
ADR
Control
Shroom3 fl/+ Cre/+
CONTROL
SHROOM3 KD
DAPI/F-actin/Merge
Control-PBS
Shroom3 flox/+ cre/+ - PBS
Control-ADR
Shroom3 flox/+ cre/+ - ADR
UACR(mg/g)
weeks
Control
Shroom3 flox/+ cre/+
Shroom3 flox/flox cre/+
UACR(μg/mg)
Weeks
H&E
IF
Control
Shroom3 fl/+ Cre/+
Shroom3 fl/fl Cre/+