Impact of human-like knock-in mutation on glomerular structure in a mouse model of Sanfilippo Syndrome (MPS IIIC)

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Mucopolysaccharidosis type IIIC, also known as Sanfilippo syndrome type C, is a lysosomal storage disease caused by a deficiency of heparan sulfate acetyl-CoA: alpha glucosaminide N-acetyltransferase (HGSNAT). HGSNAT is one of the key enzymes involved in the degradation of heparan sulfate, a glycosaminoglycan present in proteoglycans and basement membranes. The absence of HGSNAT activity leads to an accumulation of heparan sulfate in lysosomes, causing cellular dysfunction and progressive neurological degeneration. This study examined the glomerular renal pathology in a CRISPR-Cas9-generated knock-in mouse model expressing the Pro304Leu HGSNAT variant, which replicates the human Pro311Leu mutation. The model showed early-onset MPS IIIC with dominant-negative effects and stress on the endoplasmic reticulum and lysosomes. Wild type (WT, n=3, 7 months old) and HGSNAT knock-in (KI, n=3, 7 months old) mice were used for each experiment. Kidneys were collected and processed for histological and ultrastructural analysis by light and electron microscopy. ImageJ was used to quantify the stained area of the mesangial matrix. Compared with WT, KI mice exhibited a more intense Periodic acid Schiff staining of the glomerular mesangial matrix, an accumulation of empty vesicles in the podocytes, distorted mesangial cells, and severely affected podocytes filled with lysosomes and enlarged pedicels. In conclusion, the increased deposition of heparan sulfate in the mesangial matrix is associated with glomerular distortion and mesangial proliferation, findings that could be consistent with the development of mesangial proliferative glomerulonephritis.