

## FIGURE S1

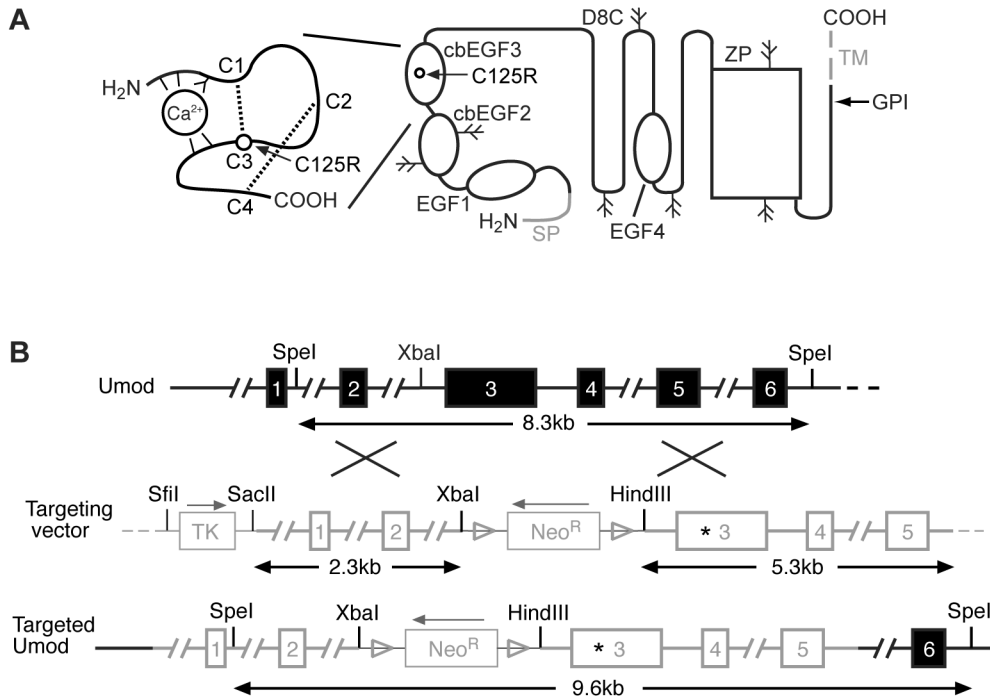


Fig. S1. Generation of mutant Umod125R mice by targeted knock-in. (A) Schematic diagram of uromodulin protein: the C125R mutation (open circle) alters the third cysteine (C3) residue of cbEGF3 (calcium-binding epidermal growth factor-like domain 3), which forms a disulphide bond with C1 of cbEGF3, as does C2 with C4 of cbEGF3 (black dashed lines). SP: signal peptide; D8C: domain of 8 cysteines; ZP: zona pellucida domain; TM: transmembrane domain; GPI: glycosylphosphatidylinositol anchor attachment site; branches indicate likely glycosylation sites. (B) Targeting strategy: endogenous mouse Umod (top). Black filled boxes: exons; black lines: introns. The targeting vector (middle) contained ~7.6kb of Umod, with the C125R mutation in exon 3 (asterisk), a neomycin resistance (Neo<sup>R</sup>) cassette in intron 2 and a thymidine kinase (TK) cassette 5' of Umod. Grey boxes: coding regions; thick grey lines: Umod introns; thin grey lines: sequences deriving from plasmids; triangles: LoxP sites. Homologous recombination introduced the C125R mutation and Neo<sup>R</sup> cassette into the targeted Umod allele (bottom).

**Supplementary Table 1.** Comparison of uromodulin mutant mouse models

Study/Reference	(Bernascone et al., 2010)	(Takiue et al., 2008a; Takiue et al., 2008b)	(Kemter et al., 2009; Kemter et al., 2013)	(Kemter et al., 2013)	Piret et al (Current study)
Derivation	Transgenic	Transgenic	ENU	ENU	HR
Background strain	FVB	C57/Bl6	C3HeB/FeJ	C3HeB/FeJ	C57/Bl6
Mutation	Human C148W	Human C148W	A227T	C93F	C125R
Genotype	[overexpression]	[overexpression]	Het & hom	Het & hom	Het & hom
Clinical features					
Renal failure	✓	X	✓	✓ <sup>e</sup>	✓
Plasma uric acid	–	NR	↑ <sup>a</sup>	NR	–
Plasma calcium	NR	NR	↑ <sup>b</sup>	↑ <sup>e</sup>	↑
Plasma ALP	NR	NR	↑ <sup>b</sup>	↑ <sup>e</sup>	↑ <sup>c</sup>
Plasma osmolality	↑	NR	NR	NR	↑
Urine concentrating defect	✓	NR	✓	✓ <sup>e</sup>	✓
Urinary UA excretion	NR	NR	↓	↓ <sup>e</sup>	↓
Urinary pH	↓	NR	NR	NR	↓
Urinary calcium	↑	NR	↑	↑ <sup>e</sup>	↑
Urinary uromodulin excretion	↓	↓ (human protein only)	↓	↓	↓
Histological features					
Fibrosis	✓	X	✓ <sup>c</sup>	✓	✓
Glomerulosclerosis	X	NR	X <sup>d</sup>	NR	✓ <sup>c</sup>
Immune infiltration	✓	NR	✓ <sup>c</sup>	✓	✓
Tubular dilation/cysts	✓	NR	X <sup>d</sup>	✓ <sup>e</sup>	X
Uromodulin ER retention	✓	NR	✓ <sup>d</sup>	✓ <sup>e</sup>	✓
ER stress	NR	NR	NR	NR	✓
Apoptosis	X	NR	NR	NR	✓

ENU: *N*-ethyl-*N*-nitrosourea; HR: homologous recombination; het: heterozygotes; hom: homozygotes; ALP: alkaline phosphatase; UA: uric acid; ER: endoplasmic reticulum; ✓: present; X: absent; ↑: increased; ↓: decreased; –: not altered; NR: not reported; <sup>a</sup> this mouse mutation corresponds to the human mutation C126R found in ADTKD-*UMOD* patients; <sup>a</sup>homozygous females only; <sup>b</sup>homozygous males only; <sup>c</sup>homozygotes only; <sup>d</sup>only homozygotes studied; <sup>e</sup>only heterozygotes studied.