Clinical and Molecular Genetic Correlations in Families with *UMOD* Variants

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OBJECTIVES

Mutations in the Uromodulin (UMOD) gene on chromosome 16 underlie uromodulin associated kidney disease (UAKD), including medullary cystic kidney disease (MCKD2) (OMIM 603860), familial juvenile hyperuricaemic nephropathy (FJHN) (OMIM 162000) and glomerulocystic kidney disease (GCKD) (OMIM 609886).

UMOD mutations result in a urinary concentration defect, urinary salt wasting, hyperuricaemia, gout, hypertension and end-stage renal disease (ESRD). Over 100 mutations and sequence variants have been associated with UAKD.

UAKD is inherited in an autosomal-dominant pattern & leads to ESRD in adulthood. FJHN may present with hyperuricaemia in childhood and early adult life.

UAKD causes chronic kidney disease with variable rates of progression even within affected families. Most individuals do not reach CKD stage 3 until their 3rd decade, and have highly variable trajectories towards ESRD.

METHODS

Families with suspected autosomal dominant tubulointerstitial kidney disease were investigated including renal USS, biochemical data and genotyping of *UMOD*. Exon PCR and Sanger sequencing of all coding exons was performed. Segregation analysis was performed where possible.

Clinical characteristics including gout and progression of chronic kidney disease were retrospectively obtained from case-notes and electronic records. Serum creatinine values were obtained from a regional laboratory database allowing calculation of MDRD eGFR.

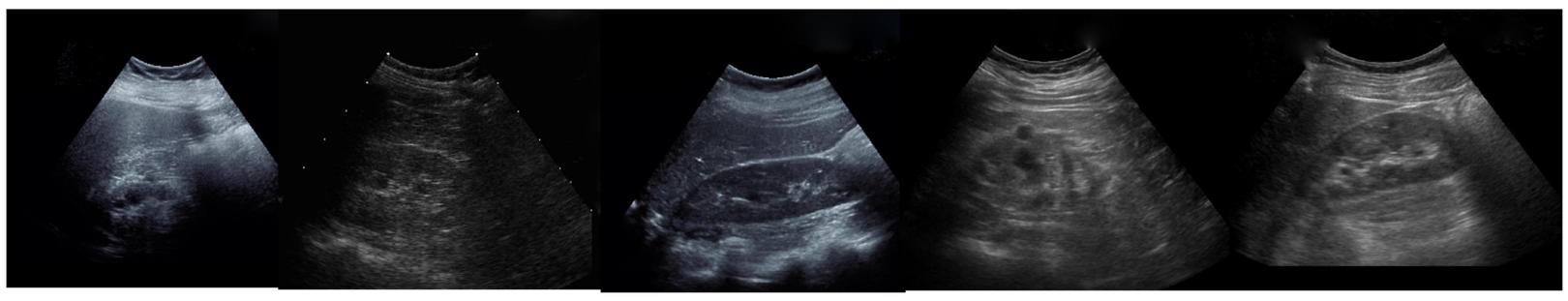


Fig 1. Renal US images: Patients 1, 9, 14, 17, 21 (left to right).

RESULTS

13 index cases with *UMOD* mutations allowed the identification of 12 families with MCKD type 2. Testing of other family members identified 26 cases of confirmed *UMOD* mutations and *UMOD* sequence variants.

Individuals with *UMOD* mutations/variants suffered from CKD with a variable age of onset of ESRD ranging from 36 to 68 years.

Cases with eGFR <60ml/min/1.73m² and >5 recorded sCr values are shown in **Chart1**. Mean decline in eGFR for 13 patients with progressive CKD was 4.64ml/min/1.73m²/year (95% CI: 3.80 – 5.49ml/min/1.73m²/year).

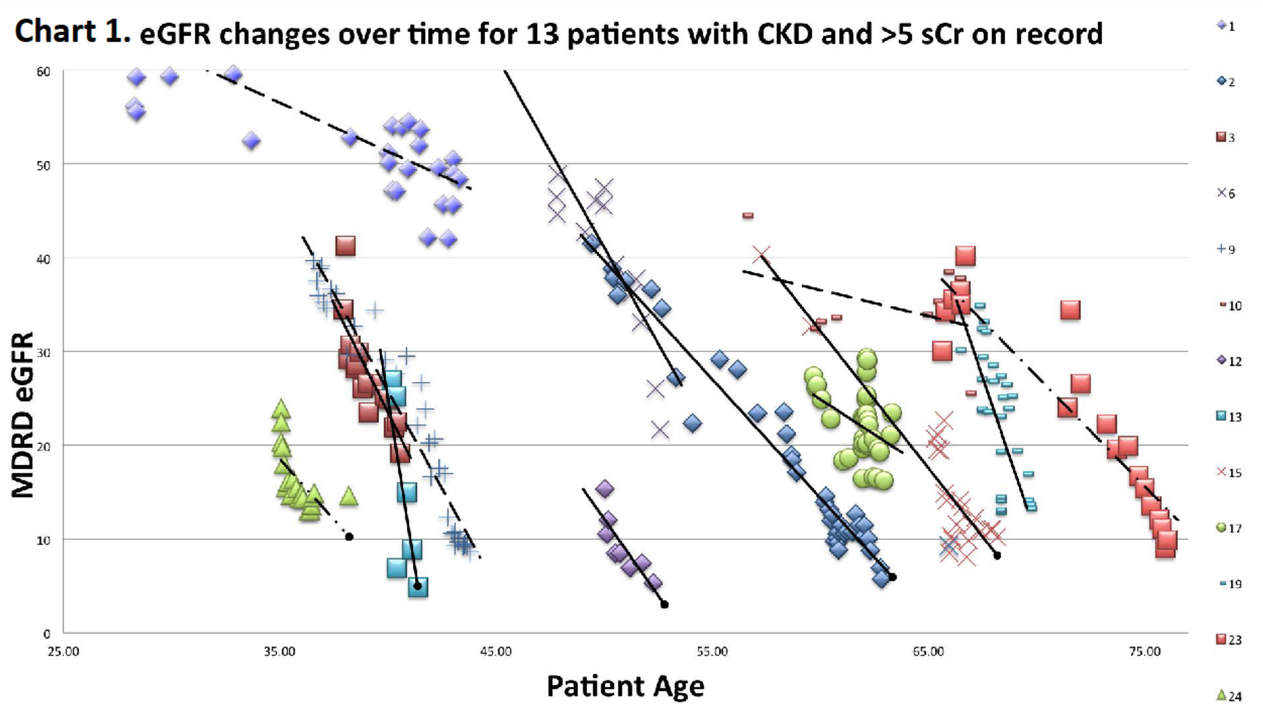
Renal USS of 22 individuals showed atrophic kidneys / cortical thinning in 6 cases and renal cysts in 4 cases. 9 families had a strong history of gout preceding renal impairment. Cysts were seen in some individuals with CKD 4/5, but not found in patients with early stages of CKD.

One individual from a consanguineous family had a homozygous *UMOD* variant. The remaining sequence changes were all heterozygous.

The c.278del12ins9 deletion/insertion mutation affecting exon 4 was seen in 4 families (B, C, E &F). The T62P variant of uncertain significance was seen in 3 families (G, H & I), all of which had early onset gout and bland urinary sediment. Affected patients within families G & H reached ESRD in adulthood whilst Case 23 (Family I) aged 76 was the eldest patient in this series without ESRD.

The synonymous variant p.G88G seen in families J & K is of uncertain significance. Both families have a history of CKD progressing to ESRD in adulthood along with bland urine and early onset gout. *HNF1b* variants have been excluded. Variants in *MUC1* and *REN* need to be excluded.

Chart 1. eGFR changes over time for 13 patients with CKD and >5 sCr on record



Family	Mutation	Number of cases (n. with CKD)
A	**c.359G>A p.Cys174Tyr**	1(1)
B	**c.278del12ins9 p.Val93_Gly97delinsAlaAlaSerCys**	3(2)
C	**c.278_289delins p.Val93_Gly97delinsAlaAlaSerCys**	4(2)
D	**c.688T > C p.W230R**	2(2)
E	**c.278del12ins9 p.Val93_Gly97delinsAlaAlaSerCys**	4(2)
F	**c.278del12ins9 p.Val93_Gly97delinsAlaAlaSerCys**	5(4)
G	**c.184A>C p.T62P**	2(1)
H	**c.184A>C p.T62P**	1(0)
I	**c.184A>C p.T62P**	1(1)
J	**c.264C>T p.G88G**	1(1)
K	**c.264C>T p.G88G**	1(1)
L	**c.425G>A p.R142Q**	1(1)

CONCLUSIONS

This data agrees with previously published case series. *UMOD* mutations lead to a highly variable rate of CKD onset, progression of CKD and age of ESRD, even when they carry the same mutation or sequence variant.

Identification of *UMOD* mutations in patients with CKD allows a definitive diagnosis to be made . *UMOD* mutations account for one form of autosomal dominant tubulointerstitial kidney disease Mutations in genes *MUC1*, *REN* and *HNF1b* should be also be screened .

Further research into disease pathogenesis and treatment interventions to slow the progression of CKD are urgently needed.

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