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UKKA
UK Kidney Association
Rare Renal

RaDaR
Registry of Rare Kidney Diseases

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Kidney outcomes and the effect of proteinuria in Alport Syndrome: a longitudinal analysis usin g data from the National Registry of Rare Kidney Diseases (RaDaR)

Dr Katie Wong

UK National Rare Kidney Disease Registry (RaDaR) Clinical Research Fellow

University College London Department of Renal Medicine PhD student

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- Alport UK
- Sanofi
- Travere therapeutics
- Bayer

Background

Alport Syndrome is the 2nd commonest genetic kidney disease and can lead to kidney failure (KF)

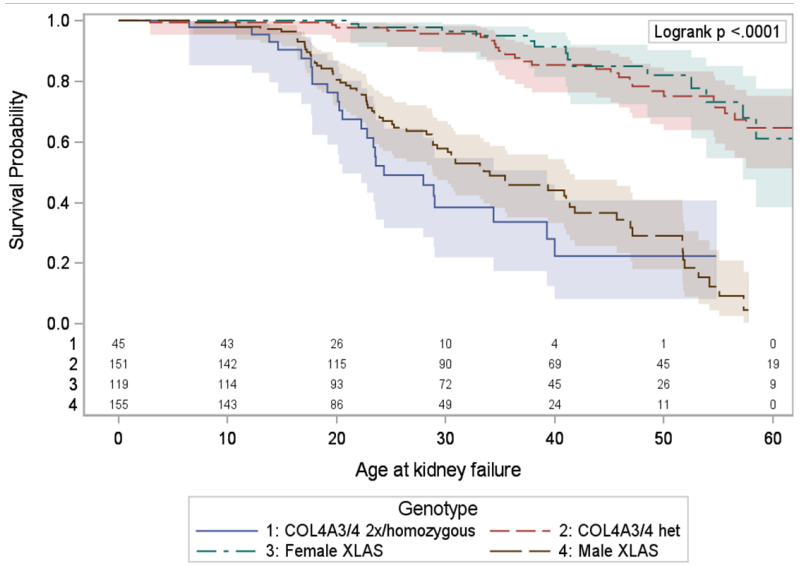
Previous genotype-phenotype correlation studies have found a younger age at kidney for certain genotypes.

However, little is known about the trajectory of eGFR decline in Alport Syndrome across disease course

- Genotype
- Proteinuria

We aimed to address this evidence gap using long-term follow up data from the National Registry of Rare Kidney Diseases (RaDaR)

Age at kidney failure, stratified by genotype



RaDaRdata May 2025

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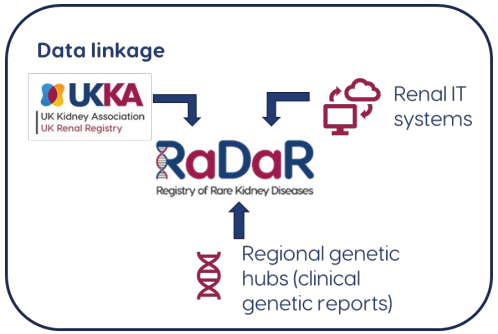
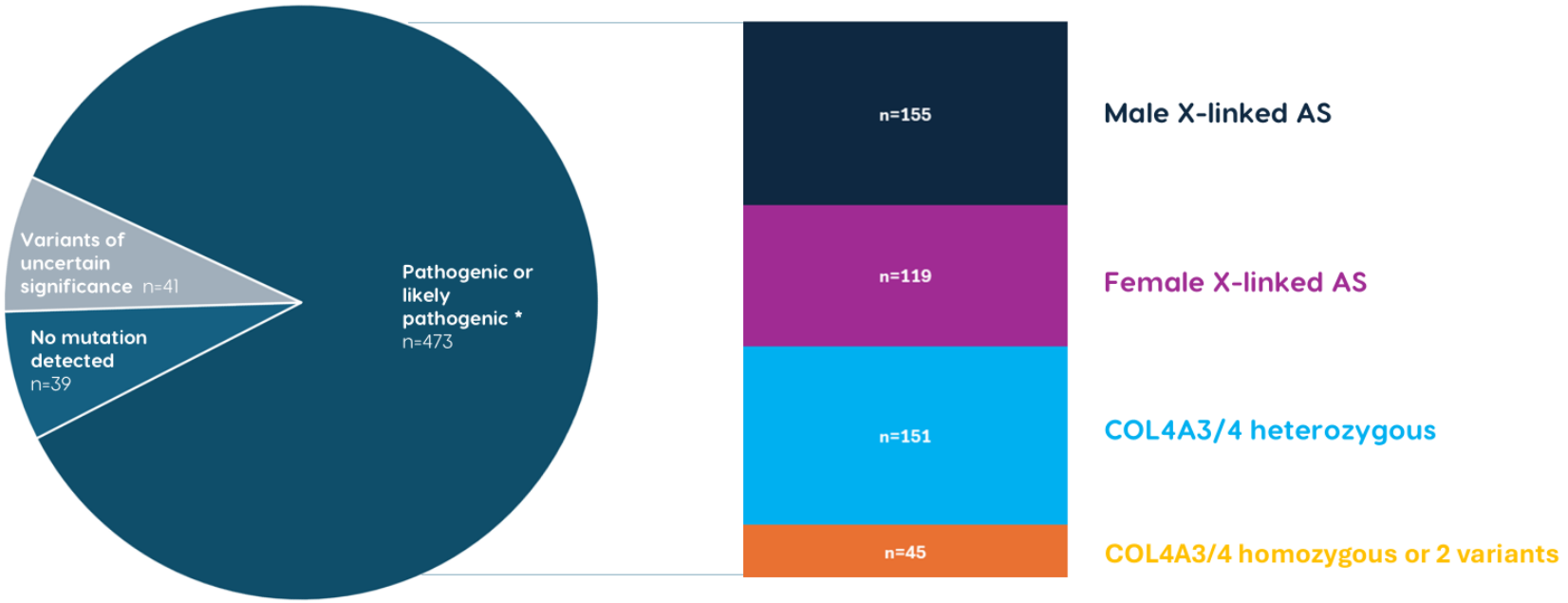
National Registry of Rare Kidney Diseases (RaDaR)

- Recruits from >100 UK renal units
- Began recruiting patients with Alport Syndrome in 2013



- Data extracted 09/04/2025
- 553/1192 (46%) patients in the Alport Syndrome cohort had clinical genetic reports available for review

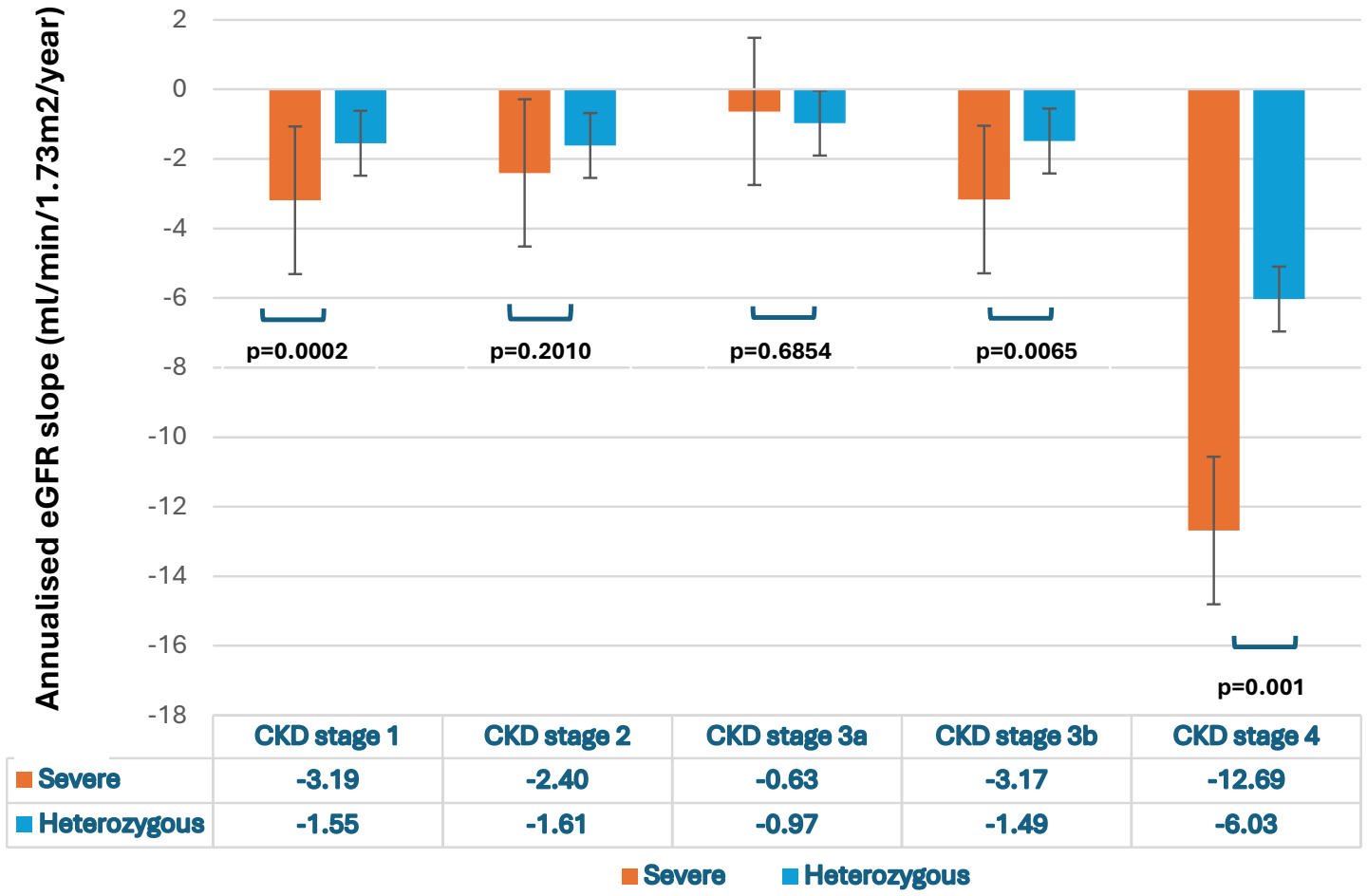


*ACMG criteria

*16 homozygous, 5 compound heterozygous confirmed *in trans.*
3 patients with digenic disease excluded due to small numbers

eGFR trajectory

Annualised eGFR slope by CKD stage, stratified by severe and heterozygous genotypes



	CKD stage 1	CKD stage 2	CKD stage 3a	CKD stage 3b	CKD stage 4
Severe	-3.19	-2.40	-0.63	-3.17	-12.69
Heterozygous	-1.55	-1.61	-0.97	-1.49	-6.03

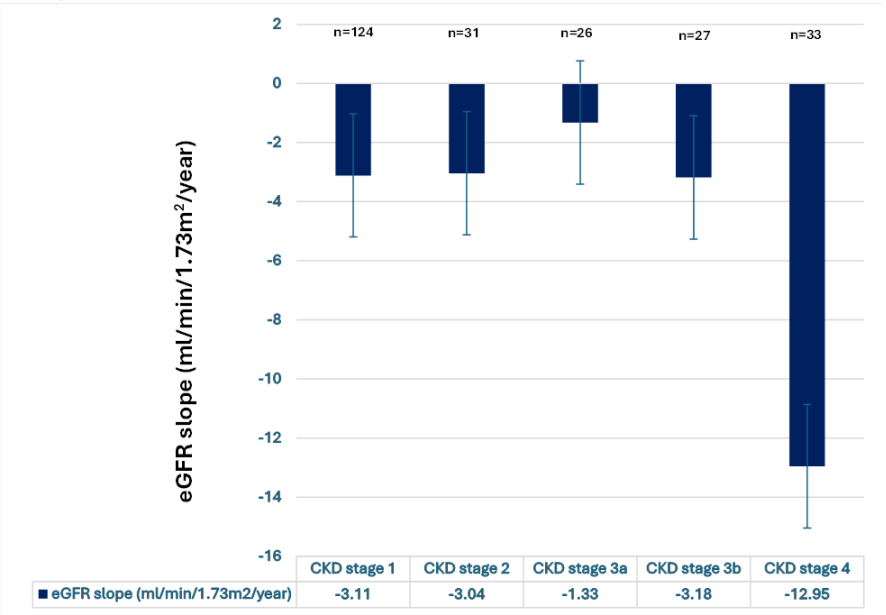
Severe : Male X-Linked AS, 2x *COL4A3/4* variants

Heterozygous : Female X-Linked AS, *COL4A3/4* heterozygotes

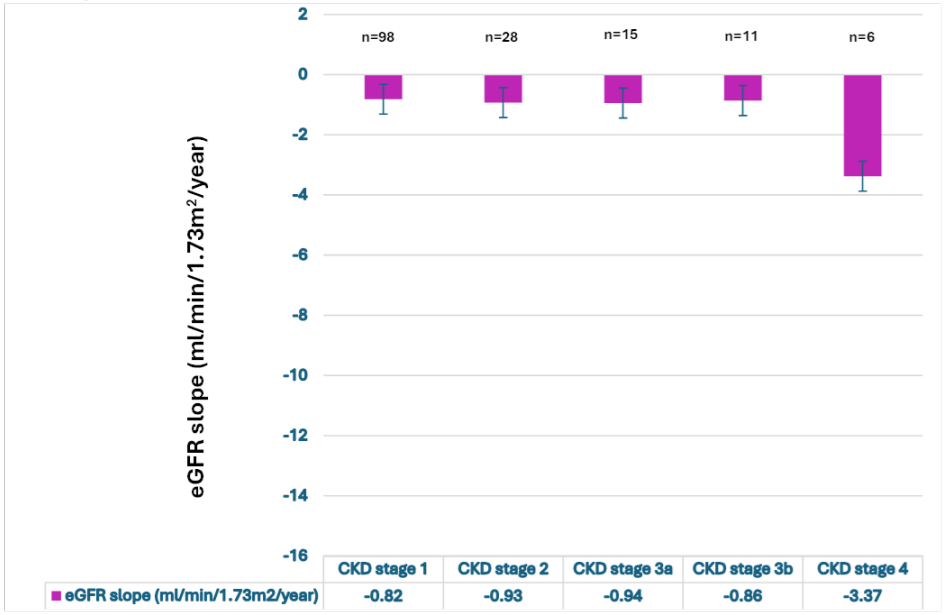
- Faster eGFR decline for patients with severe genotypes in all CKD stages except CKD stage 3a
- Particularly marked in CKD stage 4

Annualised eGFR slope, stratified by CKD stage and genotype

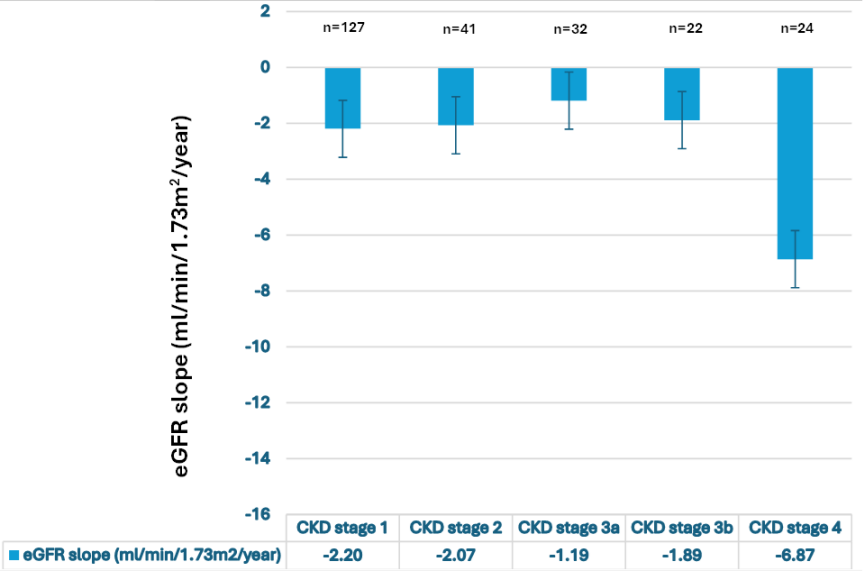
a) Male X-Linked AS



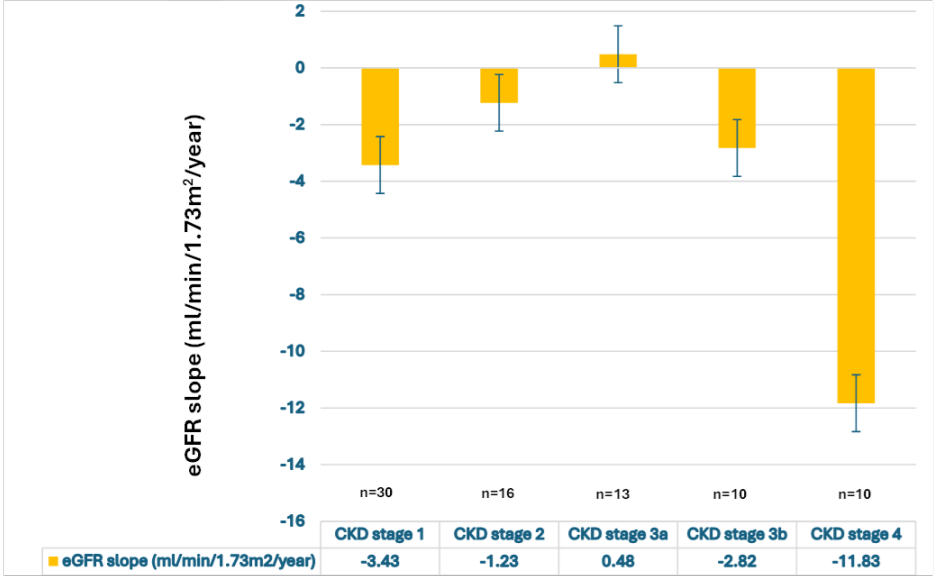
b) Female X-Linked AS



c) COL4A3/4 heterozygous variants



d) COL4A3/4 homozygous or 2x variants



- Acceleration in eGFR decline in CKD stage 4 for all genotypes
- Time to progress from CKD stage 4 to 5 for *COL4A3/4* heterozygotes only **2.2 years**

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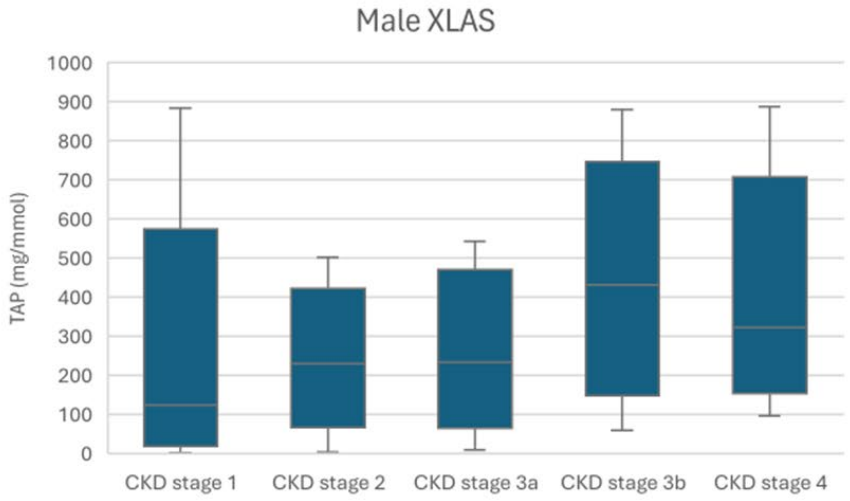
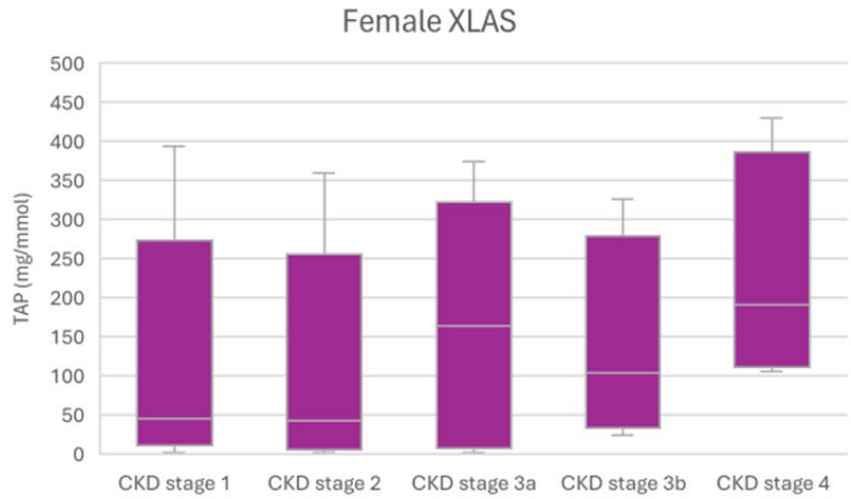
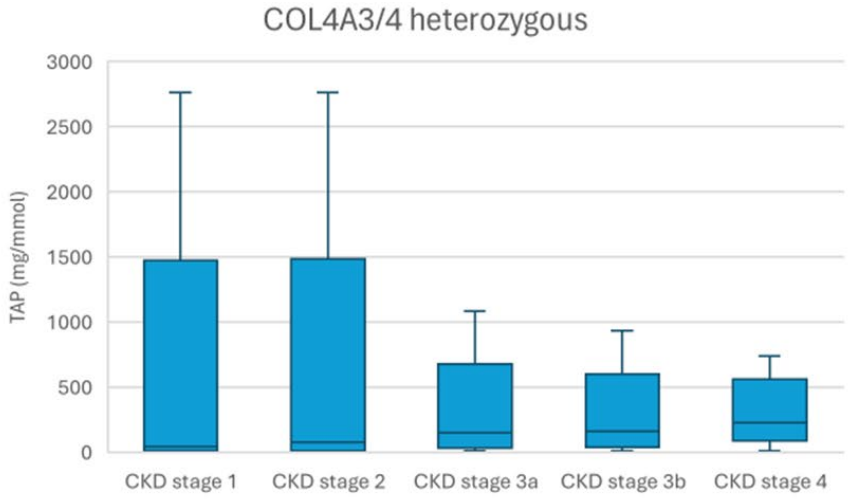
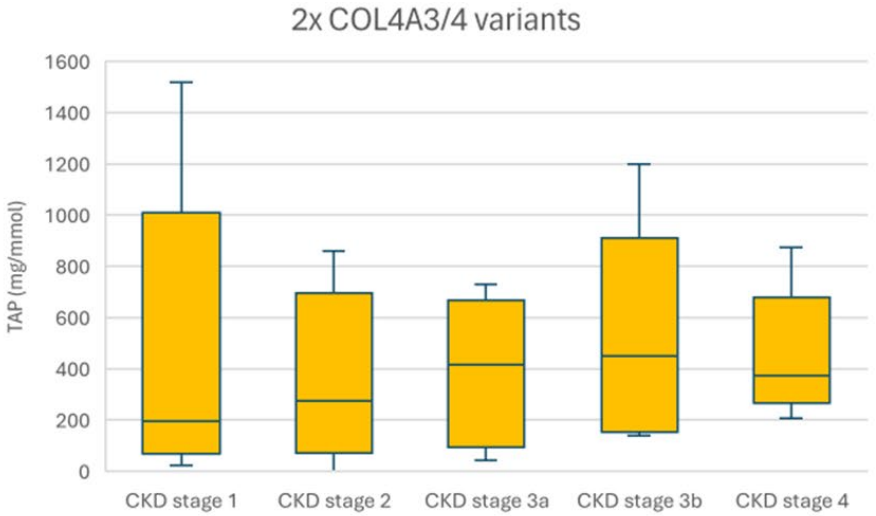
Progression of proteinuria

Median time averaged proteinuria, by CKD stage and stratified by genotype

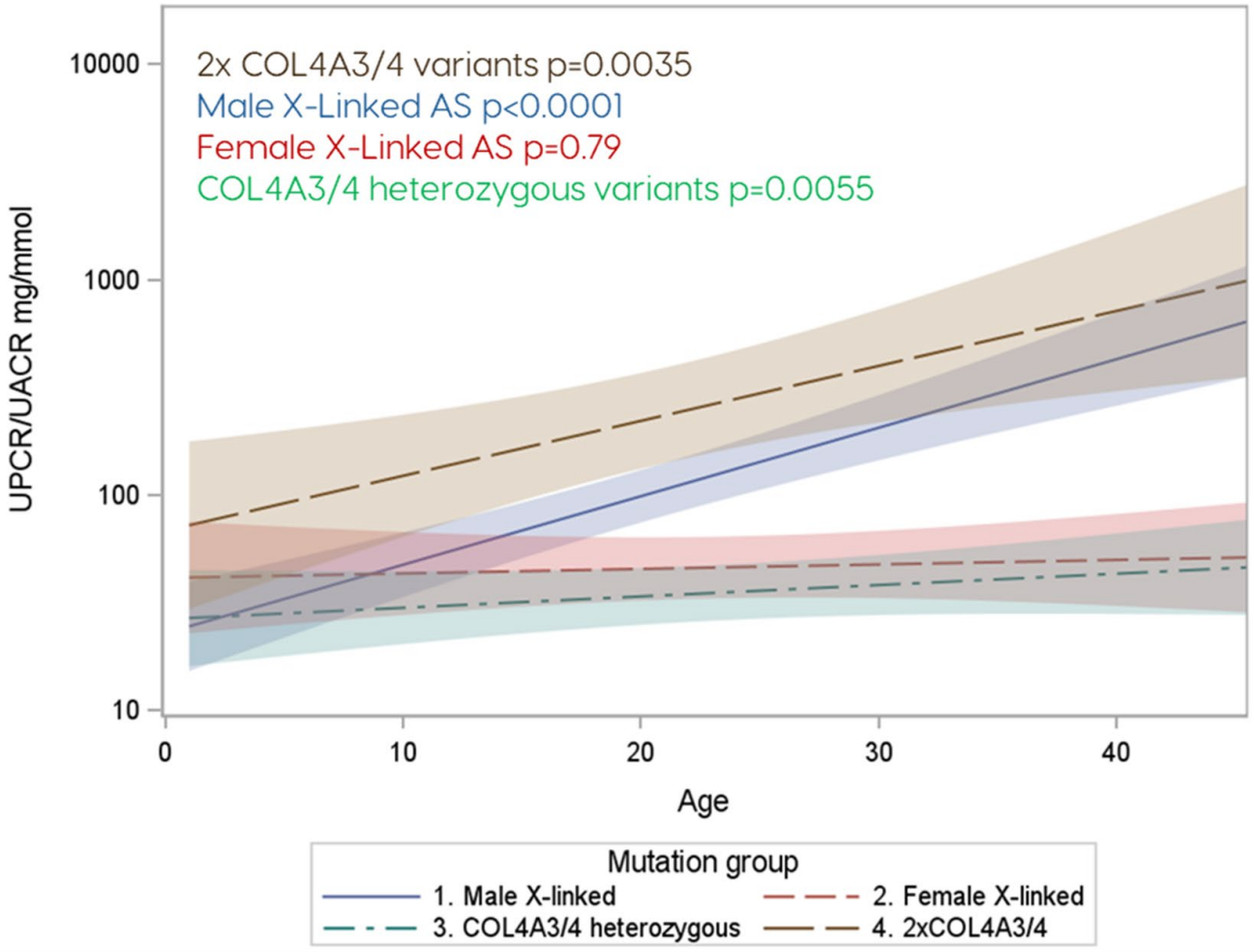








Linear mixed model of proteinuria (UPCR) trajectory, by genotype



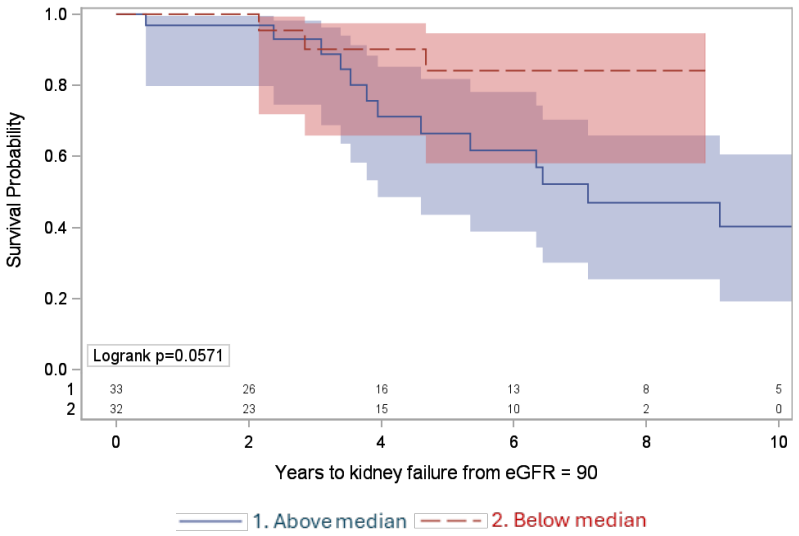
- Males with X-Linked AS and those with 2x *COLA3/4* variants had a statistically significant rise in proteinuria over time .
- For those with *COL4A3/4* heterozygous variants this reached borderline statistical significance (p=0.055).
- We did **not** observe a significant rise in proteinuria over time for Females with X-Linked AS (p=0.79)

* Results from linear mixed model testing for difference from zero slope

Proteinuria and time to kidney failure from a) eGFR 90 b) eGFR 60 c) eGFR 45 ml/min/1.73 [2]

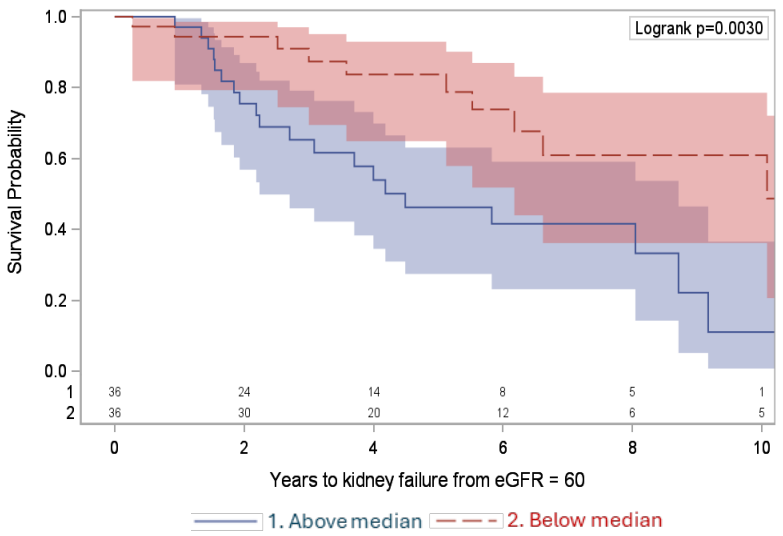
All 1192 patients recruited to Alport Syndrome cohort

eGFR 90 ml/min/1.73m [2]



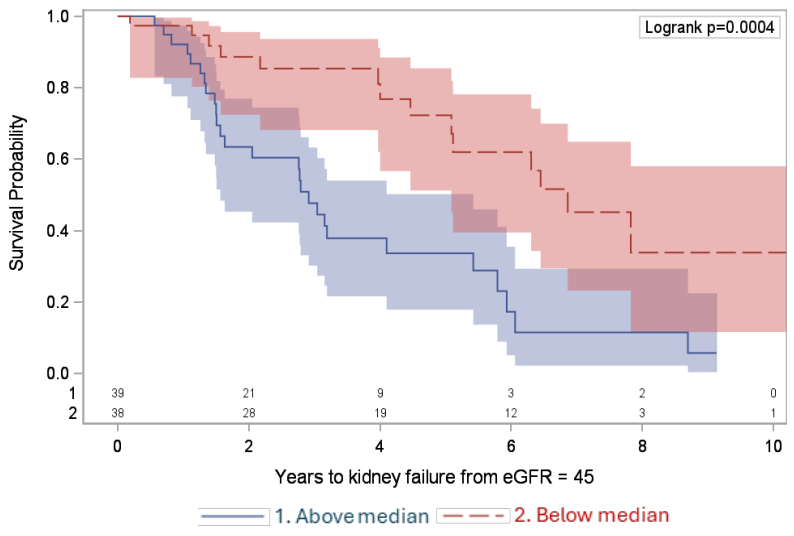
Median: 180 mg/mmol

eGFR 60 ml/min/1.73m [2]



Median: 222.5 mg/mmol

eGFR 45 ml/min/1.73m [2]

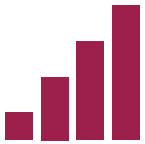


Median: 299 mg/mmol

Conclusions & Discussion

We have demonstrated that

- eGFR slope varies by **genotype** and **CKD stage**
- eGFR decline accelerates for all genotypes on reaching **CKD stage 4** in Alport syndrome



- Proteinuria progression varies by genotype
- **Higher proteinuria levels were significantly associated with earlier age at kidney failure** at eGFR 60 and 45 ml/min/1.73m^2 thresholds, and reached borderline statistical significance at eGFR 90ml/min/1.73m^2

These results aid the design and interpretation of clinical trials in Alport Syndrome , enable more accurate prognostication and inform discussions with patients and family

Limitations

- Patients recruited to RaDaRwith heterozygous *COL4A3/4* variants are likely to represent a severe form of disease due to preferential ascertainment of patients reaching the threshold for diagnosis and hospital follow-up
- The effect of medication use, and other patient characteristics such as ethnicity and BMI have not been assessed in these analyses.

Acknowledgements

All patients and families who have kindly agreed to participate in RaDaR

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