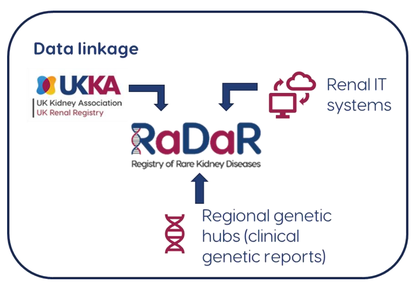
The effect of proteinuria on kidney outcomes in Alport Syndrome: a longitudinal analysis of 1192 patients from the National Registry of Rare Kidney Diseases (RaDaR)

Dane Rogers[1], David Pitcher[1,2], Katie Wong[1,2], Sherry Masoud[1,2], Sascha Van Boemmel-Wegmann[3], Klaus Francke[3], Julie Lin[4], Shiguang Liu[4], Hannah Russell[5], Susie Gear[5], Alex Mercer[6], Bruce Hendry[7], A. Neil Turner[8], Daniel P. Gale[1,2]

[1]National Registry of Rare Kidney Diseases, Bristol, UK, [2]Department of Renal Medicine, University College London, UK , [3] Bayer AG, Berlin, Germany , [4] Rare Disease and Rare Blood Disorders Development, Sanofi, Cambridge, MA, USA, [5] Alport UK, [6]JAMCO Pharma Consulting AB, Enskede, Sweden, [7]Travere Therapeutics Ltd, San Diego CA, USA, [8]Edinburgh Medical School, University of Edinburgh, Edinburgh, UK

Background and methods

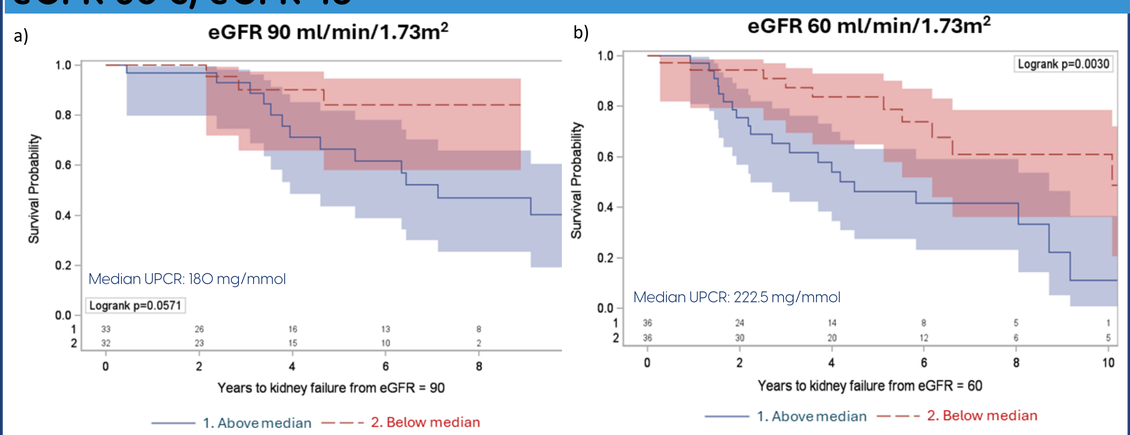
- Alport Syndrome (AS) is characterised alterations of the glomerular basement membrane, most frequently due to pathogenic variants in type IV collagen genes *COL4A3/4/5*.
- Resulting haematuria and proteinuria can lead to downstream consequences, including chronic inflammation and fibrosis.
- Whilst the implications of proteinuria in glomerular disorders such as IgA nephropathy have been well delineated, little is known about progression of proteinuria and whether it predicts kidney outcomes in AS.
- Here, we describe associations between proteinuria and kidney outcomes in a large UK cohort of AS patients, using data from the National Registry of Rare Kidney Diseases (RaDaR).

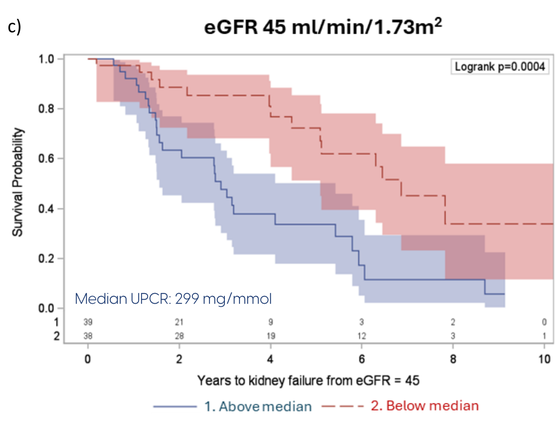


National Registry of Rare Kidney Diseases

- Recruiting patients with Alport syndrome since 2013
- > 108 renal units across all 4 nations of the UK
- All patients recruited to the RaDaR Alport Syndrome cohort at time of analyses (09/05/2025) were analysed.
- RaDaR has data linkage with regional genomics hubs for clinical genetics reports. This allowed patients with pathogenic variants according to ACMG criteria to be stratified by genotype: Male X-Linked AS, Female X-Linked AS, COL4A3/4 heterozygous, COL4A3/4 homozygous/2x pathogenic variants. Patients with variants of uncertain significance or no reports available were classified as "VUS" or "Unknown".
- Kidney failure (KF) was defined as sustained eGFR≤15mL/min/1.73m^2 or chronic KRT. Kaplan-Meier analysis was used to estimate a) age at KF b) time from eGFR 90/60/45mL/min/1.73m^2 to KF or death and compared using the log-rank statistic. Results were stratified by proteinuria level at time of eGFR 90/60/45 mL/min/1.73m^2 (estimated as mean uPCR over year prior to each eGFR threshold).
- For patients with genotype data available, proteinuria progression was investigated by a) calculating median time- averaged proteinuria at each CKD stage b) modelling each patient's uPCR by age using linear mixed models, stratified by genotype.

Proteinuria and time to kidney failure from a) eGFR 90 b) eGFR 60 c) eGFR 45





- Patients with above median proteinuria had poorer kidney survival compared to those with below median proteinuria at each eGFR threshold:

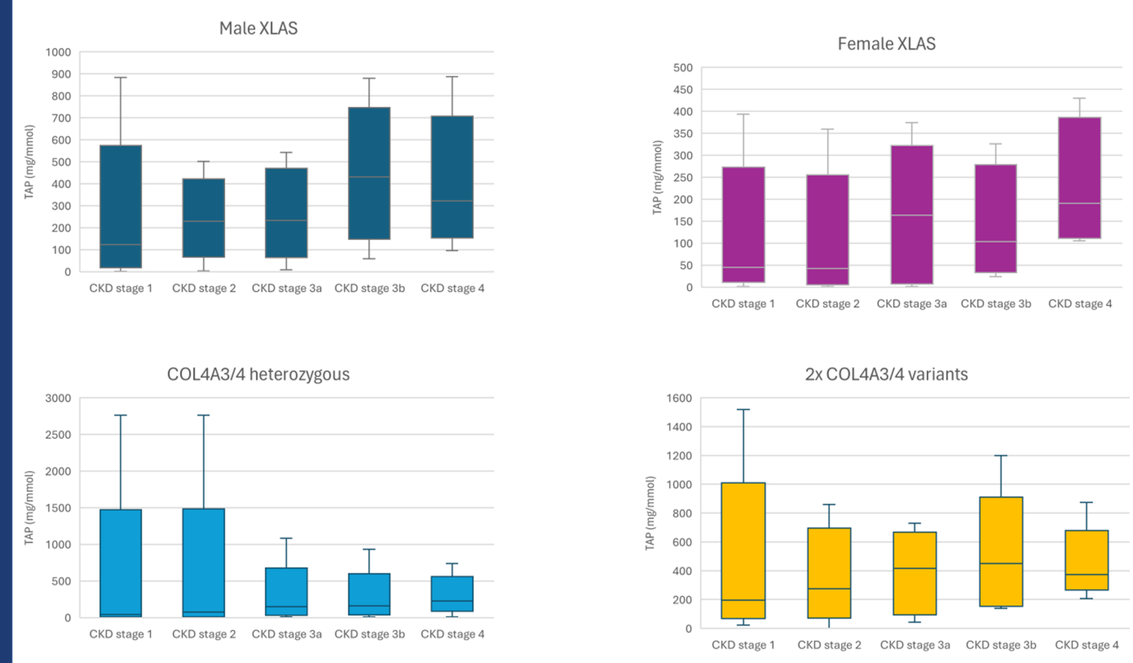
	Time to Kidney Failure (Years), 95% CI		P value
	Above median UPCR	Below median UPCR	
eGFR 90	7.1 years (3.9- NE)	NE	p=0.0057
eGFR 60	4.5 years (2.2-8.7)	10.1 (6.2-NE)	p=0.003
eGFR 45	2.9 (1.6- 5.4)	6.9 (5.1- NE)	p=0.0004

*NE- not estimated

- Median time to KF from eGFR 45 ml/min/1.73m^2 for patients with above median proteinuria (>299mg/mmol) was **<3 years** (2.9 years, 95% CI 1.6-5.4).

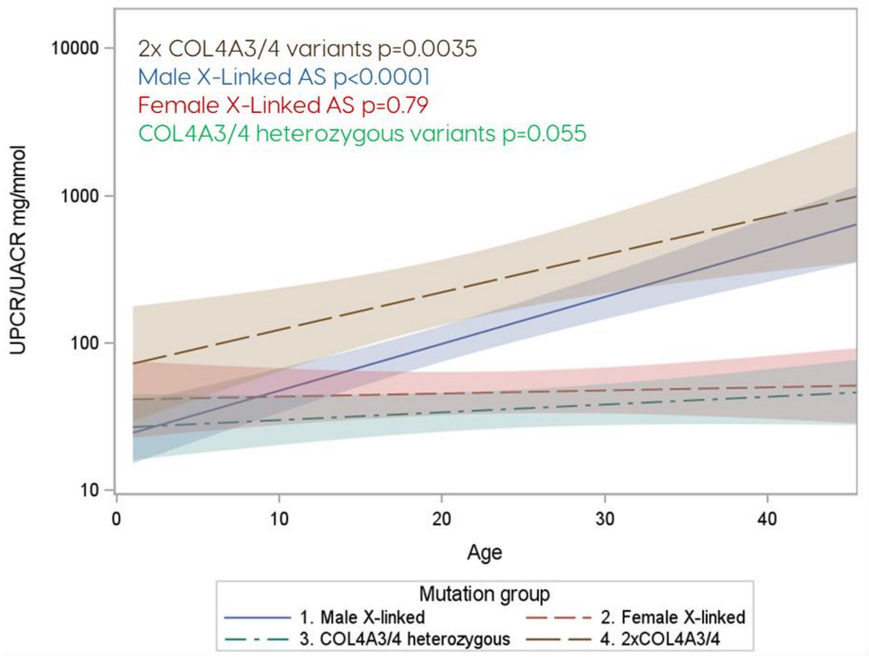
Time averaged proteinuria, by CKD stage and genotype

- 470/1192 (40%) patients had genotype data available: n=155 Male X-Linked AS, n=119 Female X-Linked AS, n=151 COL4A3/4 heterozygous, n=45 COL4A3 homozygous or 2x variants



- Median time averaged proteinuria varied by CKD stage and genotype

Linear mixed model of UPCR trajectory, stratified 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 significance (p=0.055).

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

- We did **not** observe a significant rise in proteinuria over time for Females with X-Linked AS (p=0.79)

Discussion and conclusions

- This study examines the effect of proteinuria in Alport Syndrome.

Limitations

- Patients recruited to RaDaR with 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.

Conclusions

- We have described proteinuria progression and the effect of proteinuria on kidney outcomes in Alport Syndrome
- Proteinuria progression varies by genotype; for females with X-linked AS we did not find a statistically significant rise in proteinuria over time.
- 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

Contact: Katie.Wong@ukkidney.org

ukkidney.org ukkw.org