Kidney outcomes and eGFR slope in patients with Alport Syndrome, using data from the National Registry of Rare Kidney Diseases (RaDaR)

David Pitcher[1, 2], Katie Wong[1, 2], Dane Rogers[1], 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]

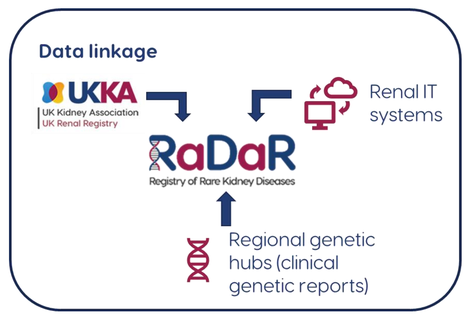
[1]National Registry of Rare Kidney Diseases, Bristol, UK, [2]Department of Renal Medicine, University College London, UK , [3] Bayer AG, Berlin, Germany , [4] Rare Disease and Rare Blood Disorders Development, Sanofi, Cambridge, MA, USA, [5] Alport UK, [6]JAMCO Pharma Consulting AB, Enskede, Sweden,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

Background and Methods

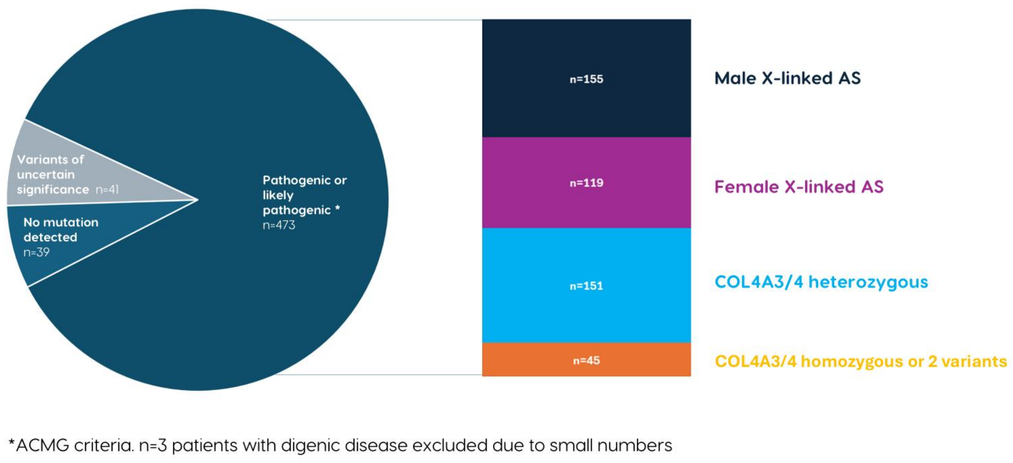
- Alport syndrome (AS) is the second commonest monogenic kidney disease and can lead to kidney failure (KF). Clinical course is highly variable,
- Previous genotype-phenotype studies have shown that males with X-linked AS and individuals with 2x or homozygous *COL4A3/4* mutations ("Severe" variants) reach KF at a younger age than females with X-linked AS or patients with heterozygous *COL4A3/4* mutations ("Heterozygous variants"). Two small observational studies have determined that eGFR slope for males with X-linked AS is faster than those with heterozygous COL4A3/4 variants, but were limited by small sample size and limited (<3 year) follow-up.
- Therefore, little is known about trajectory of eGFR decline for AS patients, and whether this differs throughout diseases course or by genotype. We aimed to address this evidence gap using long-term follow up data from the National Registry of Rare Kidney Diseases (RaDaR).

National Registry of Rare Kidney Diseases

- Recruiting patients with Alport syndrome since 2013
- > 100 UK renal units
- Data extracted on 09/05/2025
- Patients with clinical genetic reports available, and with variants reported clinically as "Pathogenic" or "Likely Pathogenic" by American College of Medical Genetics criteria were included.
- Kidney failure (KF) was defined as sustained eGFR≤15mL/min/1.73m^2 or chronic KRT.
- Kaplan-Meier analysis and the log-rank statistic were used to compare survival curves for age at KF and time from diagnosis to KF, stratified by genotype.
- eGFR slope was estimated for each CKD stage using multi-level linear models to account for individual patient trajectories.



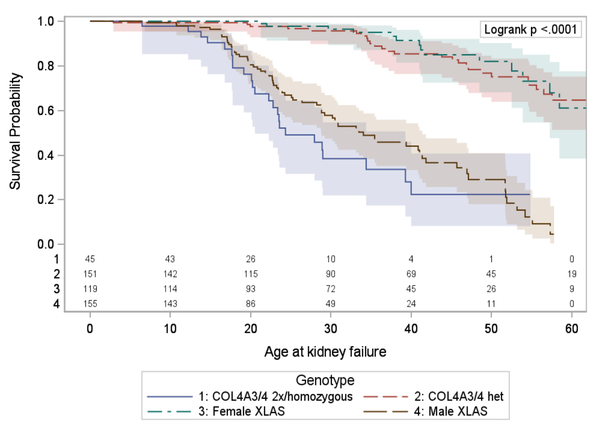
Demographics



*ACMG criteria. n=3 patients with digenic disease excluded due to small numbers

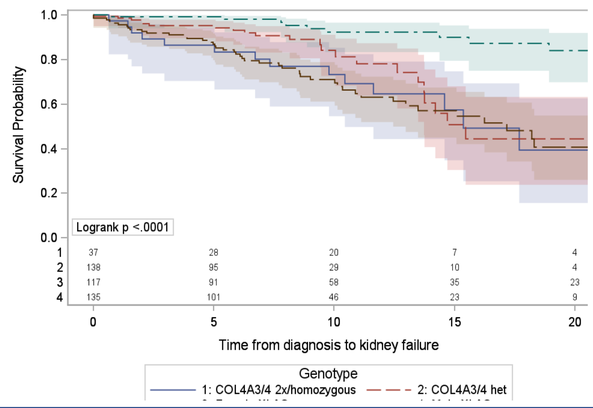
- 553/1192 (46%) patients in the Alport Syndrome cohort had clinical genetic reports available for review.
- Of those with pathogenic or likely pathogenic variants identified (n=470):
  - 241 (51%) were female
  - 302 (64%) were of White ethnicity
  - 234 (50%) had protein length altering variants and 236 (50%) missense variants

Age and time from diagnosis to kidney failure



Median age at kidney failure

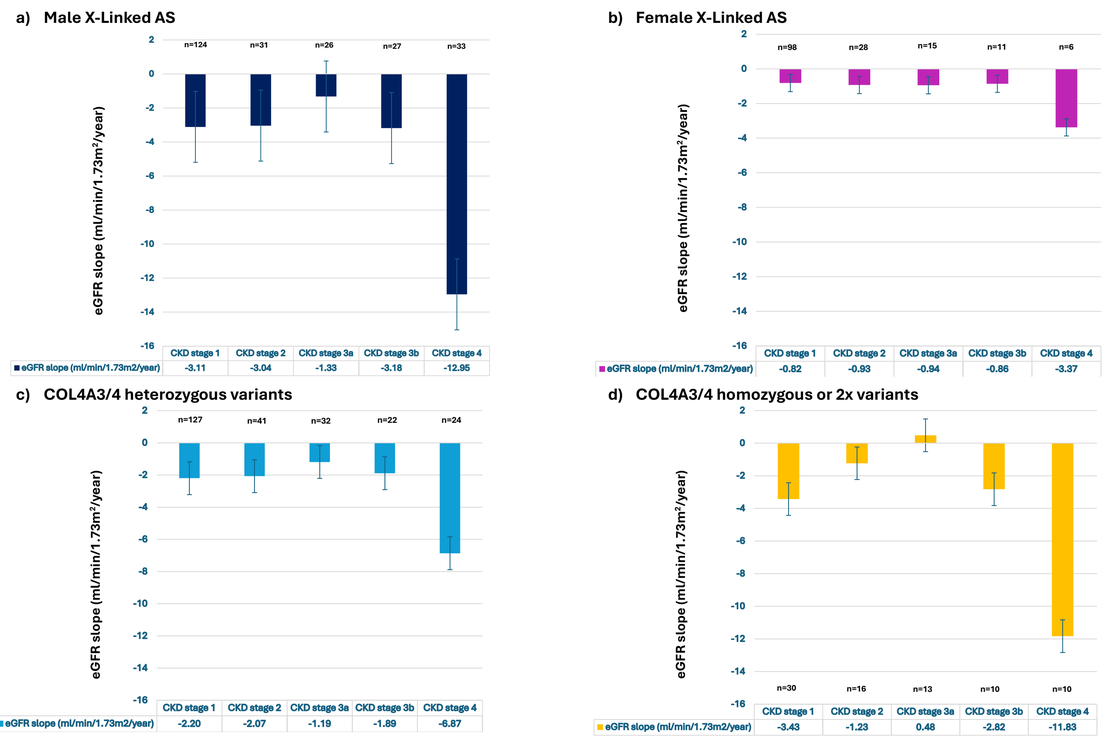
Male X-Linked AS:
34 years (95% CI 29 - 41)
Female X-Linked AS:
25th centile: 54 years (95% CI 41-63)
COL4A3/4 heterozygous:
71 years (95% CI 64 - 77)
COL4A3/4 homozygous/2x variants
24 years (95% CI 21 – 39)



Median time from diagnosis to kidney failure

Male X-Linked AS:
17 (95% CI 12 - 23)
Female X-Linked AS:
25th centile: 38 (95% CI 16-41)
COL4A3/4 heterozygous:
15 (95% CI 14 - NE)
COL4A3/4 homozygous/2x variants
15 (95% CI 10 – 27)

eGFR slope by CKD stage, stratified by genotype



Discussion and conclusion

- Those with COL4A3/4 heterozygous variants likely to represent a more severe form of disease due to ascertainment bias
- Our results are consistent with previous studies which found earlier age at kidney failure for those with severe genotypes compared to heterozygous genotypes
- We have demonstrated for the first time that
  - eGFR slope varies by genotype and CKD stage
  - eGFR slope accelerates for all genotypes on reaching CKD stage 4.
- These results will aid the design and interpretation of clinical trials in Alport Syndrome, inform preparation for Kidney Replacement Therapy, and enable more informed discussions with patients and family.

Contact: David.Pitcher@ukkidney.org

ukkidney.org

ukkw.org