UK Kidney Association

Registry of Rare Kidney Diseases

Alport Syndrome Natural History from the RaDaR registry: Associations with gene, variant type and sex

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RaDaR
Registry of Rare Kidney Diseases

UKKA

- Sanofi Genzyme
- Travere therapeutics
- Eloxx Pharmaceuticals Inc

Background

- Second commonest genetic kidney disease
- *COL4A3-COL4A5* genes
- **X linked Alport syndrome**
  1 : 2000
- **COL4A3 or COL4A4 variants**
  1 : 100[1]

- Clinical course can be highly variable
- Males with protein length altering *COL4A5* variants have a more severe phenotype
- Contradicting results in genotype - phenotype correlation studies in females [2,3]

- Small patient numbers
- Challenges in collecting sufficient, high quality, longitudinal data to accurately describe the natural history of Alport Syndrome

(1) Gibson, Joel[1]; Fieldhouse, Rachel[2]; Chan, Melanie M.Y.[3,4]; Sadeghi-Alavijeh, Omid[3,4]; Burnett, Leslie[2]; Izzi, Valerio[5]; Persikov, Anton V.[6]; Gale, Daniel P.[3,4]; Storey, Helen[7]; Savige, Judy[1]; on behalf of the Genomics England Research Consortium. Prevalence Estimates of Predicted Pathogenic COL4A3–COL4A5 Variants in a Population Sequencing Database and Their Implications for Alport Syndrome. JASN 32(9):p 2273-2290, September 2021.
(2) Bekheirnia MR, Reed B, Gregory MC, McFann K, Shamshirsaz AA, Masoumi A, Schrier RW. Genotype-phenotype correlation in X-linked Alport syndrome. J Am Soc Nephrol. 2010 May;21(5):876-83.
(3) Yamamura T, Nozu K, Fu XJ, et al. Natural History and Genotype-Phenotype Correlation in Female X-Linked Alport Syndrome. *Kidney Int Rep*. 2017;2(5):850855. Published 2017 May 4. doi:10.1016/j.ekir.2017.04.011

The UK National Registry of Rare Kidney Diseases (RaDaR)

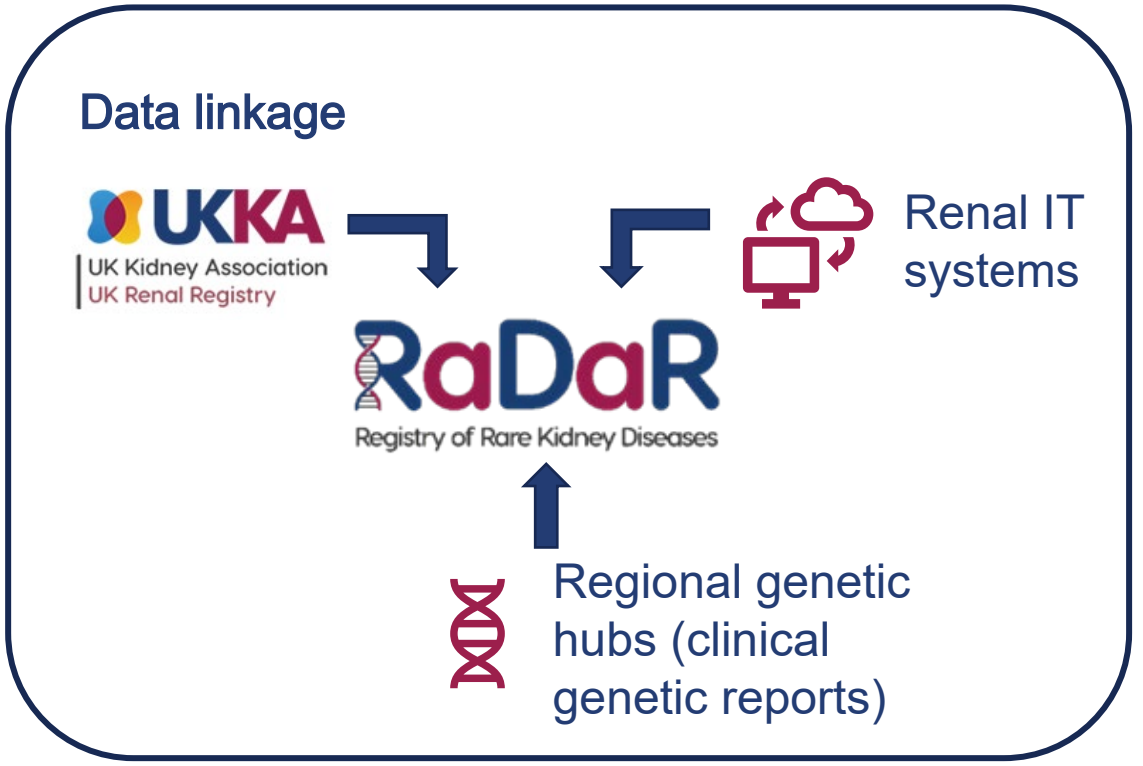
- Recruiting patients with Alport syndrome since 2013
- Longitudinal and retrospective data for patients with rare kidney diseases in the UK
- >100 UK renal units

Aims

To describe
- Demographics
- Renal outcomes

associated with
- **pathogenic variant type**
- in **Males** and **Females**

with Alport Syndrome

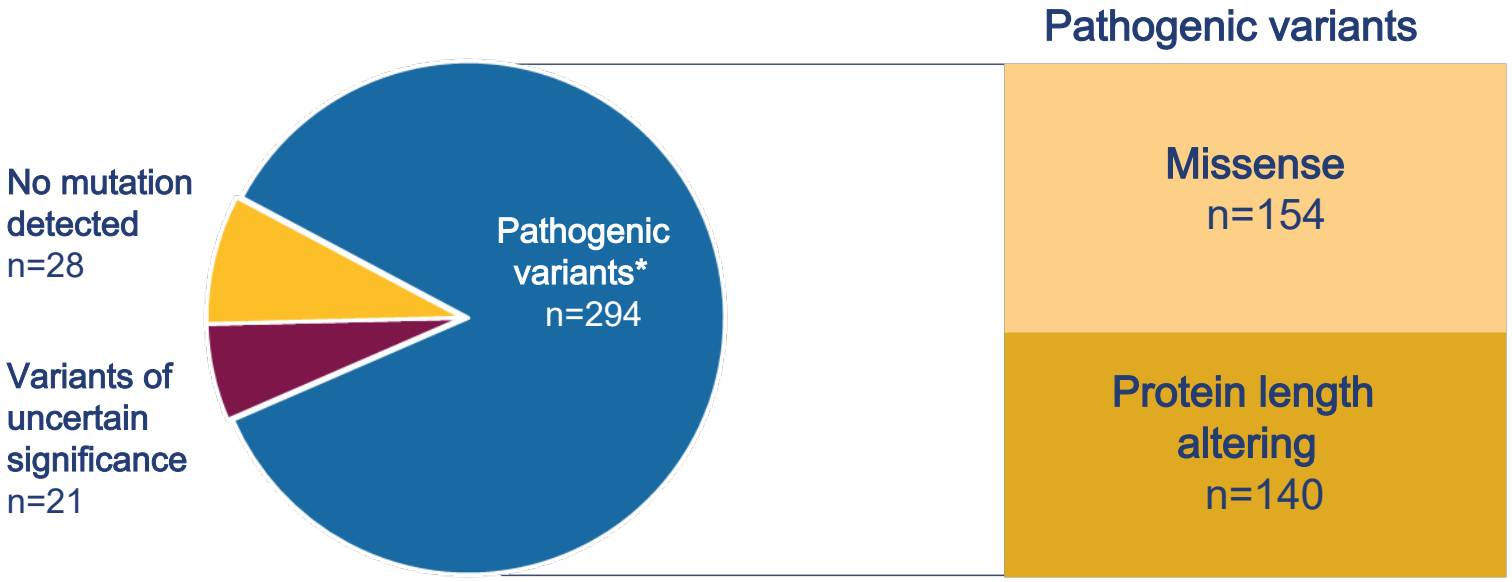


Results

920 Alport Syndrome Patients

- **Male** n=488 (53%)
- **Female** n=432 (47%)

- Clinical genetic reports available for **343/920 (37%)** patients



* American College of Medical Genetics (ACMG) criteria

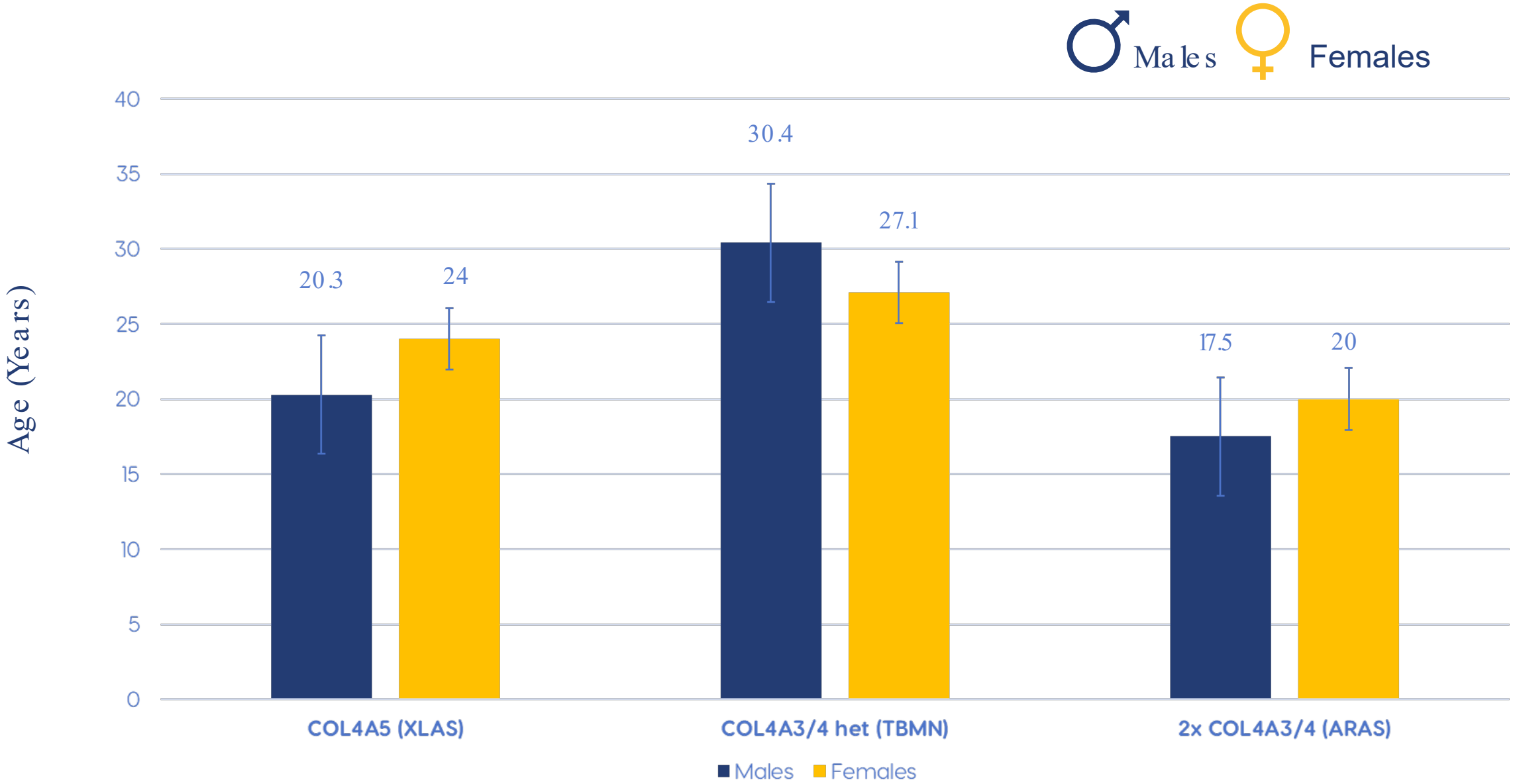
Demographics

Genotype, stratified by sex

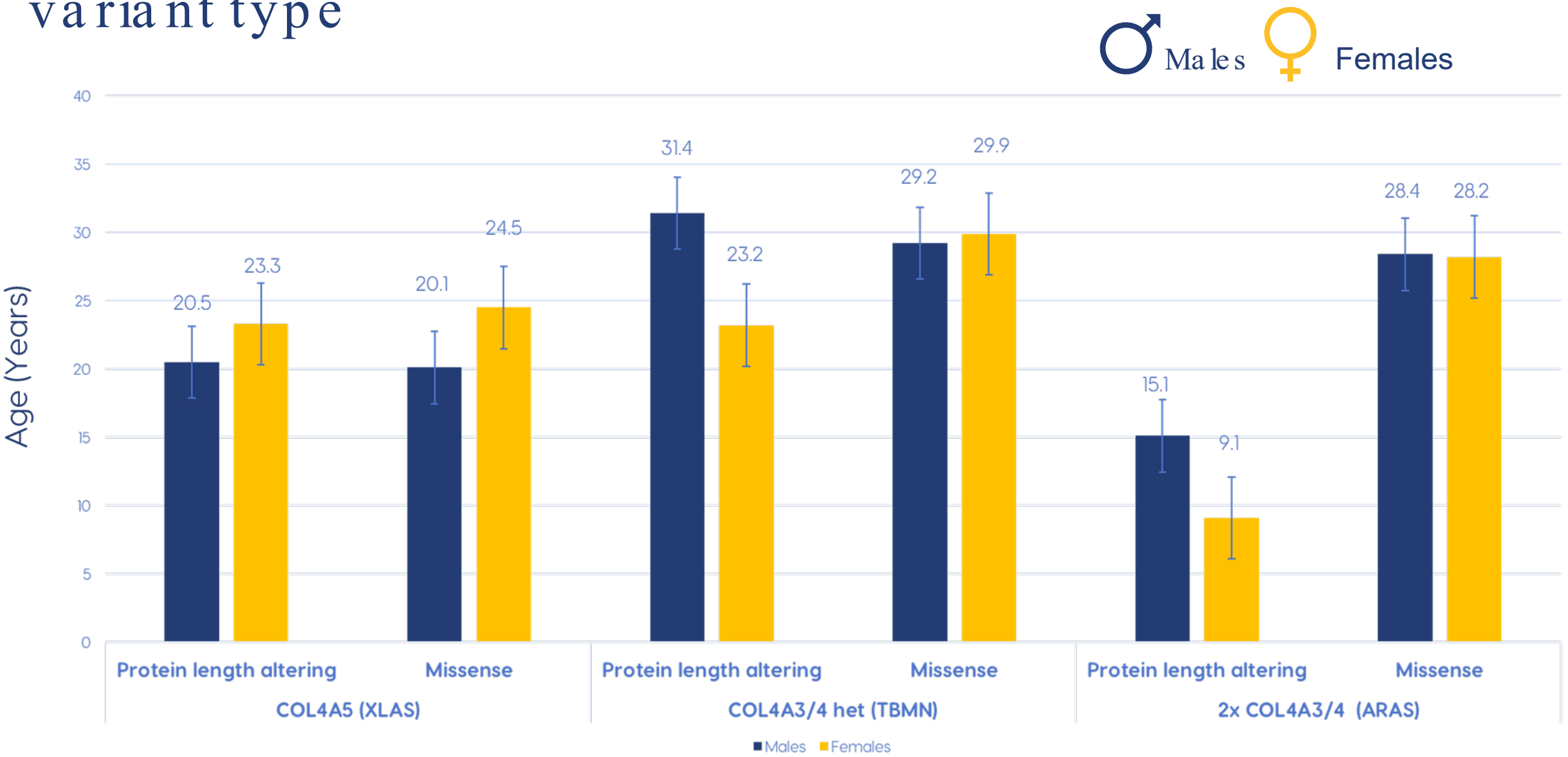
	Males n=148	Females n=146
	n	n
COL4A5	104	73
Protein length altering	48	36
Missense	56	37
COL4A3/4 **heterozygous**	26	57
Protein length altering	14	22
Missense	12	35
COL4A3/4 **homozygous or 2x variants***	18	16
Protein length altering	14	6
At least one missense	4	10

*11 confirmed biallelic

Median age at diagnosis, by genotype and Sex



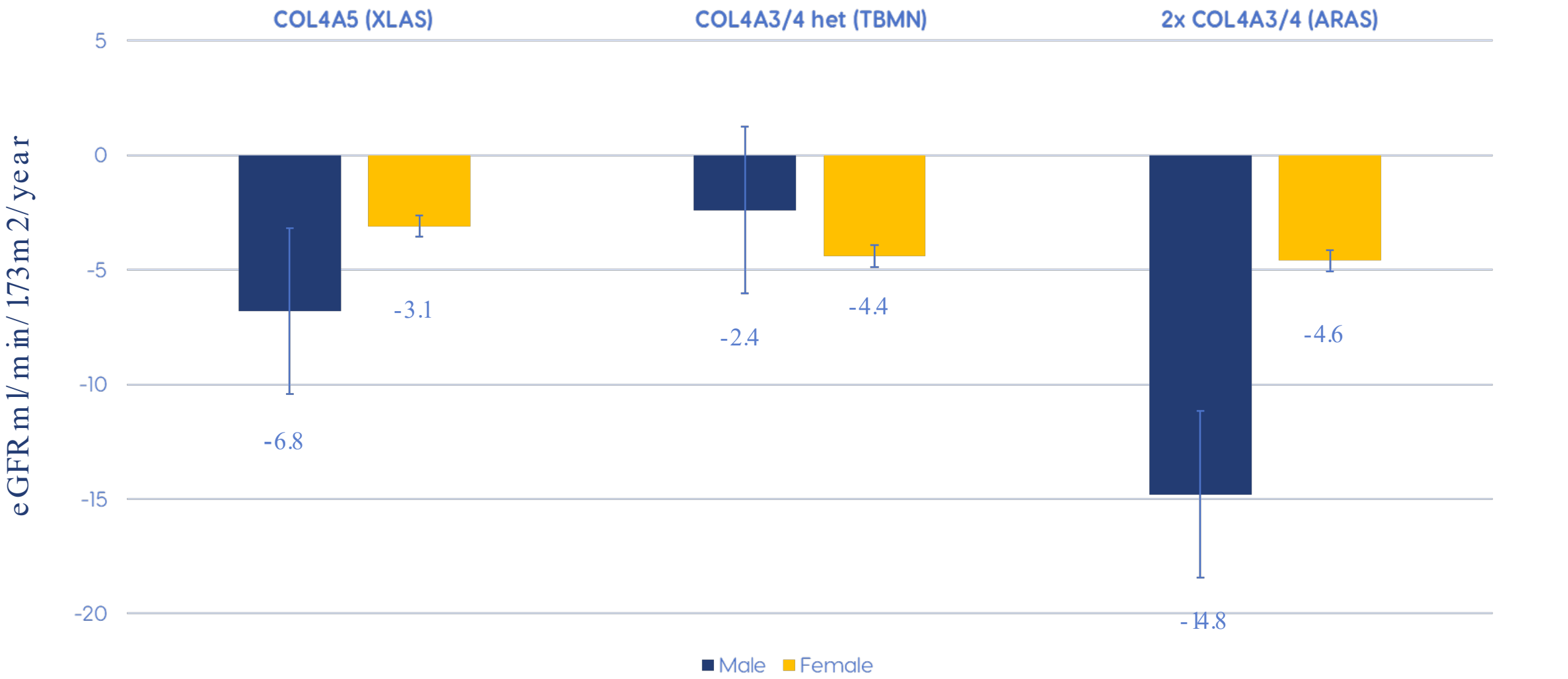
Median age at diagnosis, by genotype, Sex and variant type



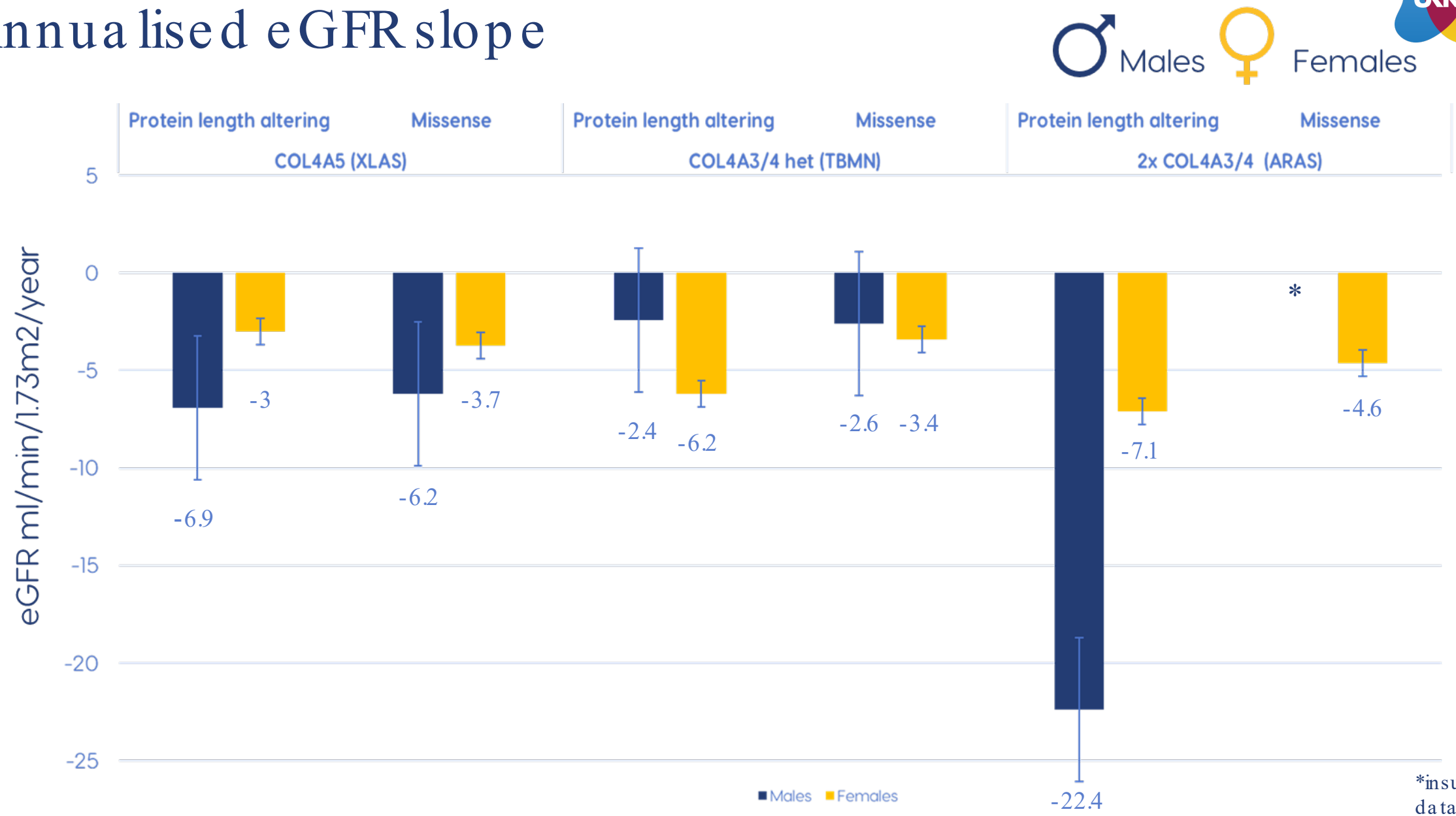
Renal outcomes

Annualised eGFR slope, by genotype and Sex

♂ Males ♀ Females

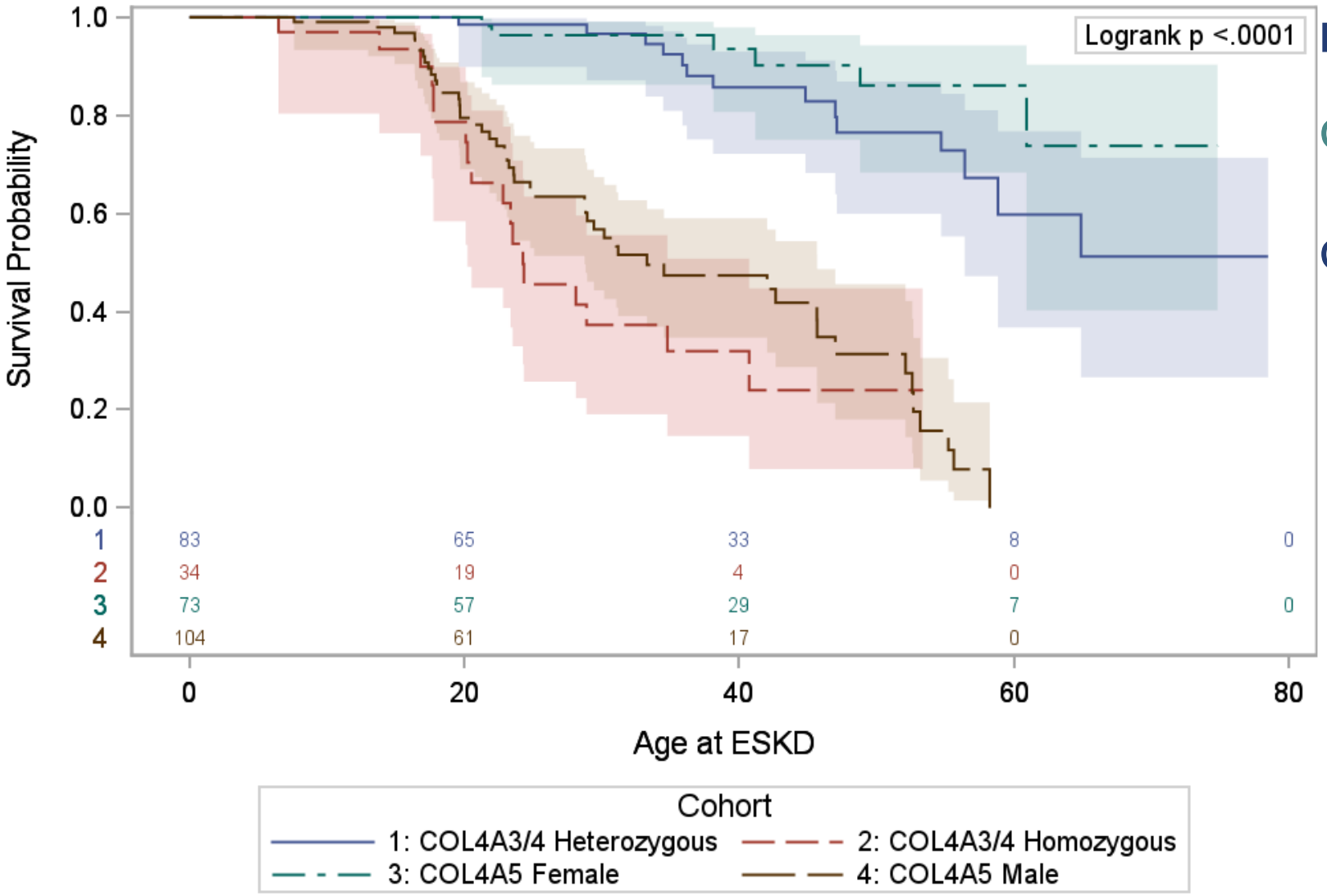


Annualised eGFR slope



*insufficient data

Age at End Stage Kidney Disease (ESKD)



Median age at ESKD

COL4A5 female 60.9 years (LQ)

COL4A3/4 heterozygous 54.7 years (LQ

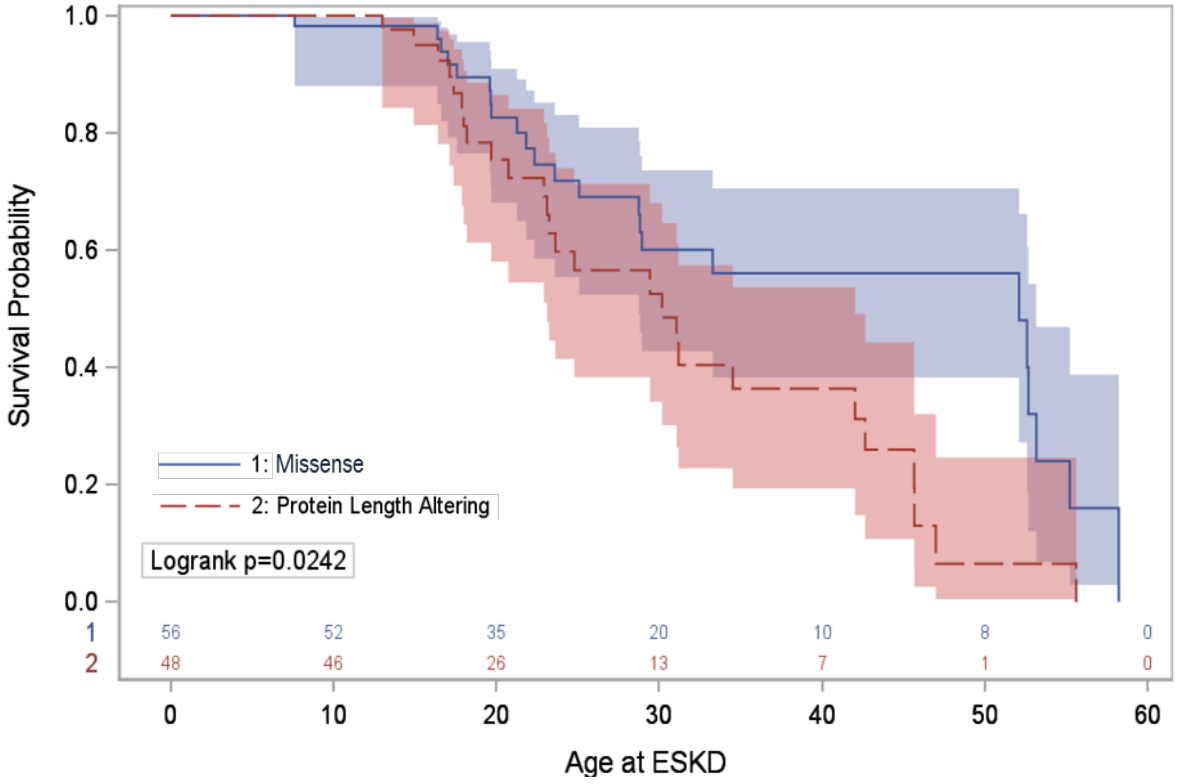
COL4A5 male 33.2 years

COL4A3/4 2x variants 24.2 years

COL4A5 variants

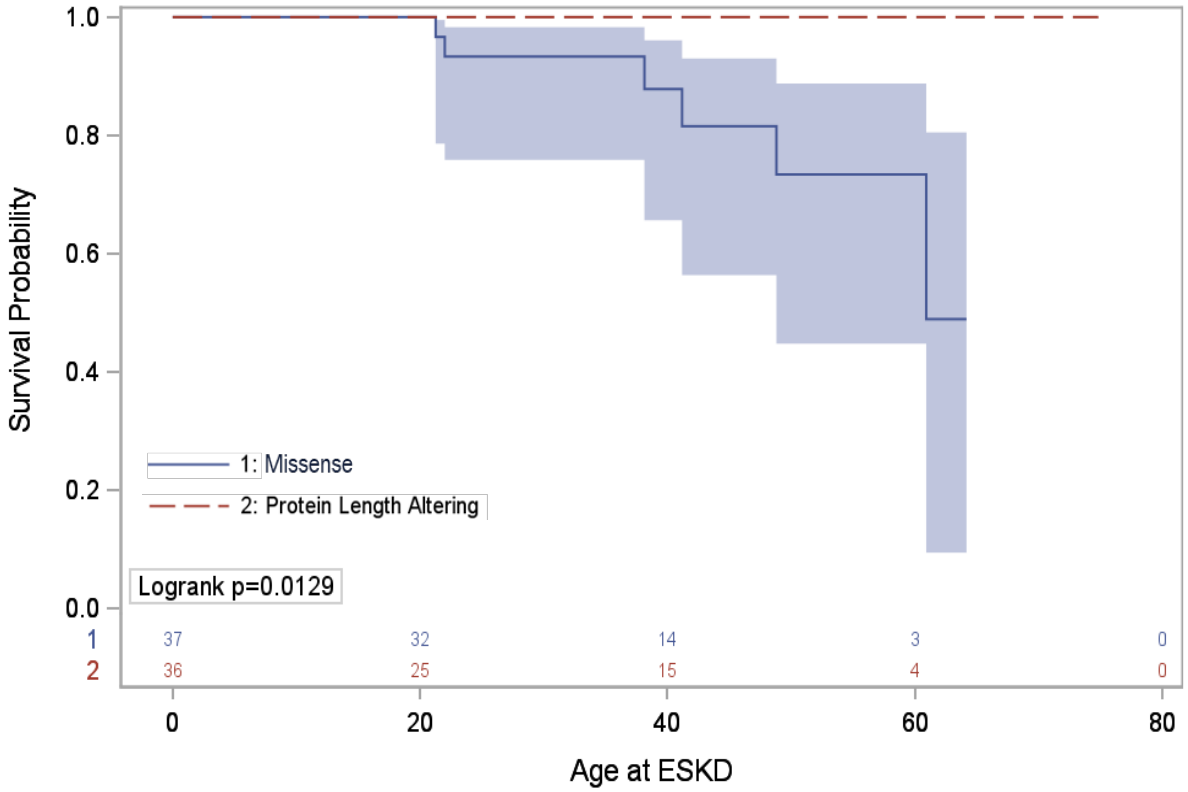
Males

	Median age at ESKD
Missense	52.1 years
Protein length altering	30.2 years



Females

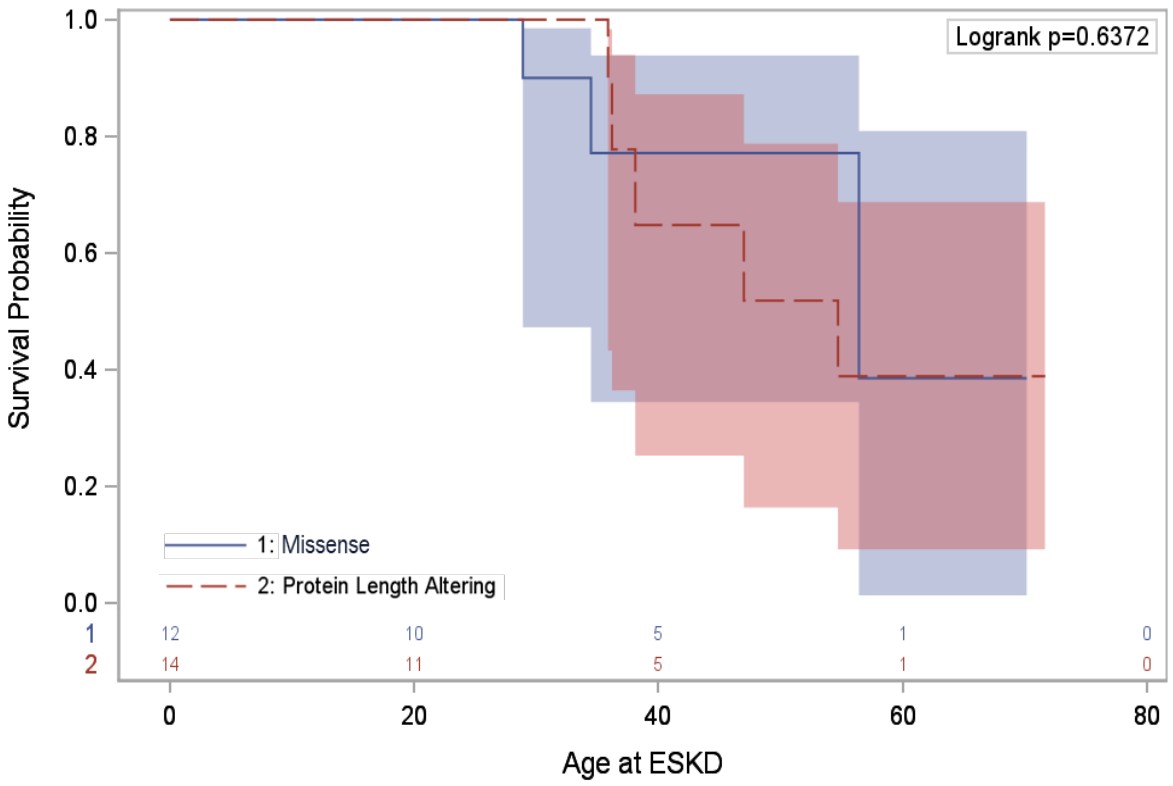
	Median age at ESKD
Missense	60.9 years
Protein length altering	0/36 started RRT



COL4A3/4 heterozygous variants

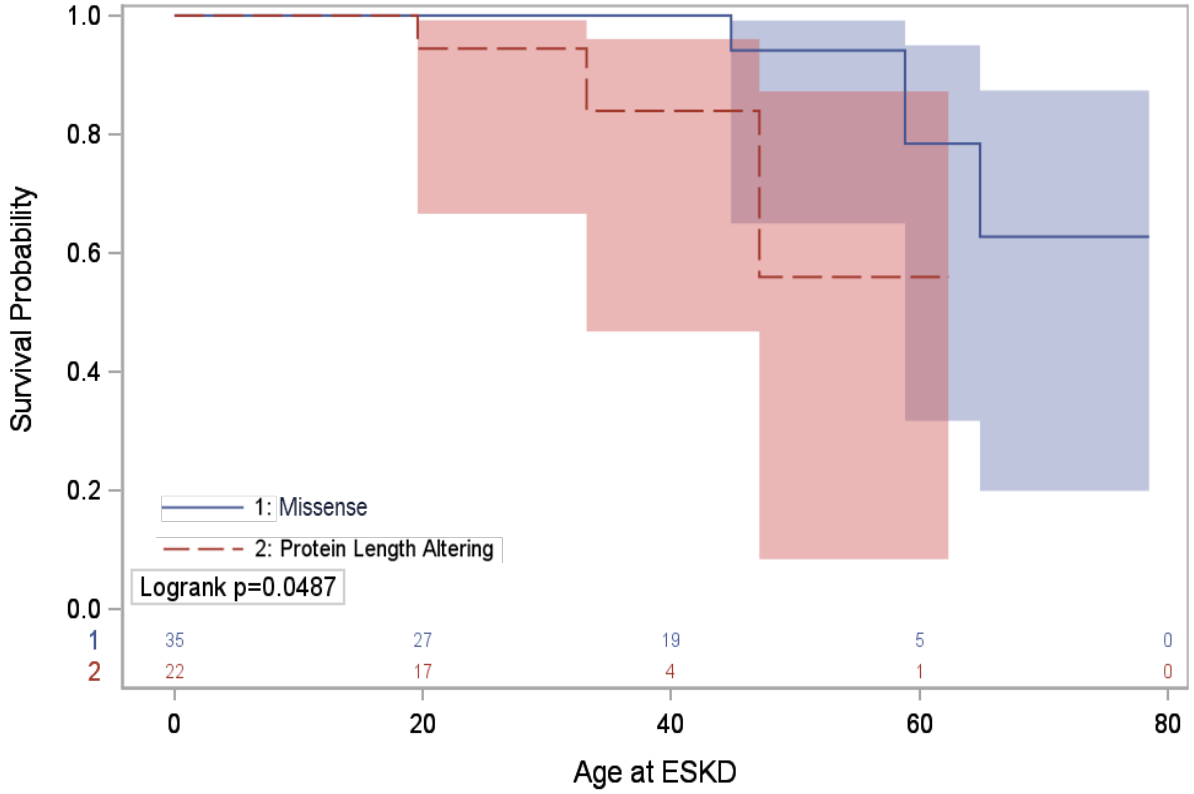
Males

	Median age at ESKD
Missense	56.4 years
Protein length altering	54.7 years



Females

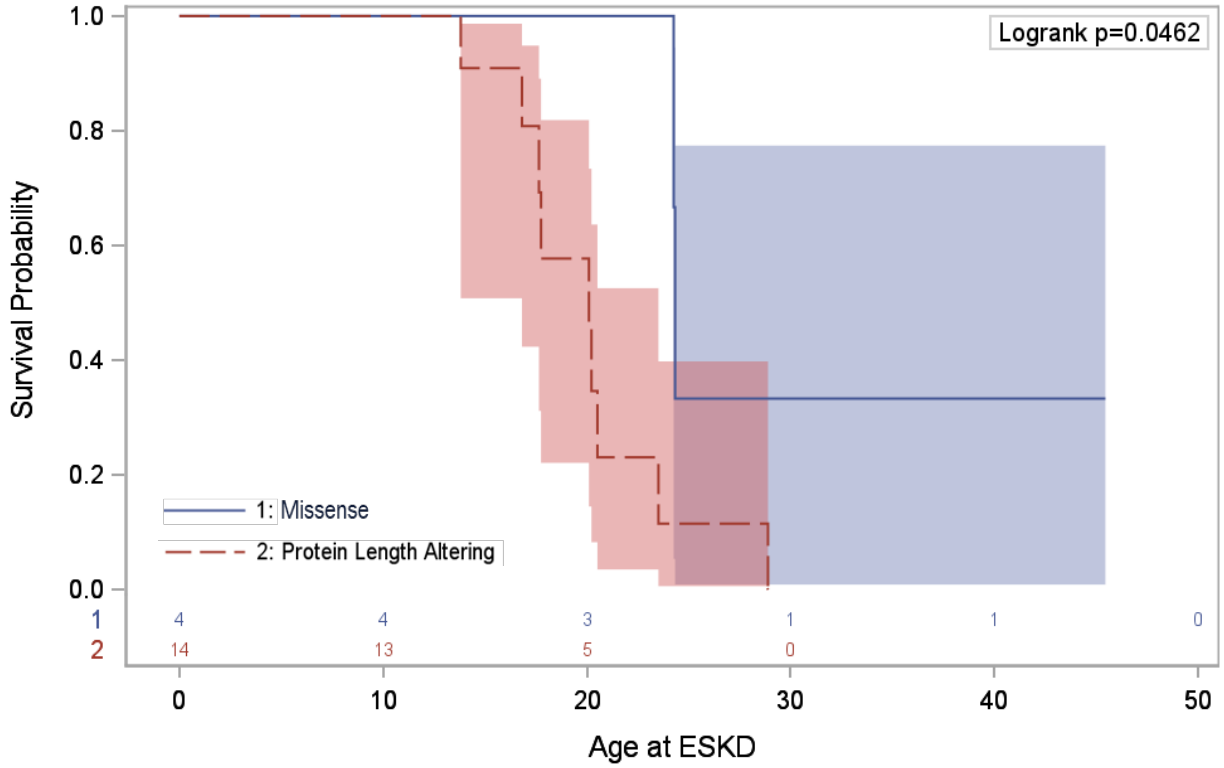
	Lower Quartile age at ESKD
Missense	64.9 years
Protein length altering	47.1 years



COL4A3/4 homozygous or 2x variants

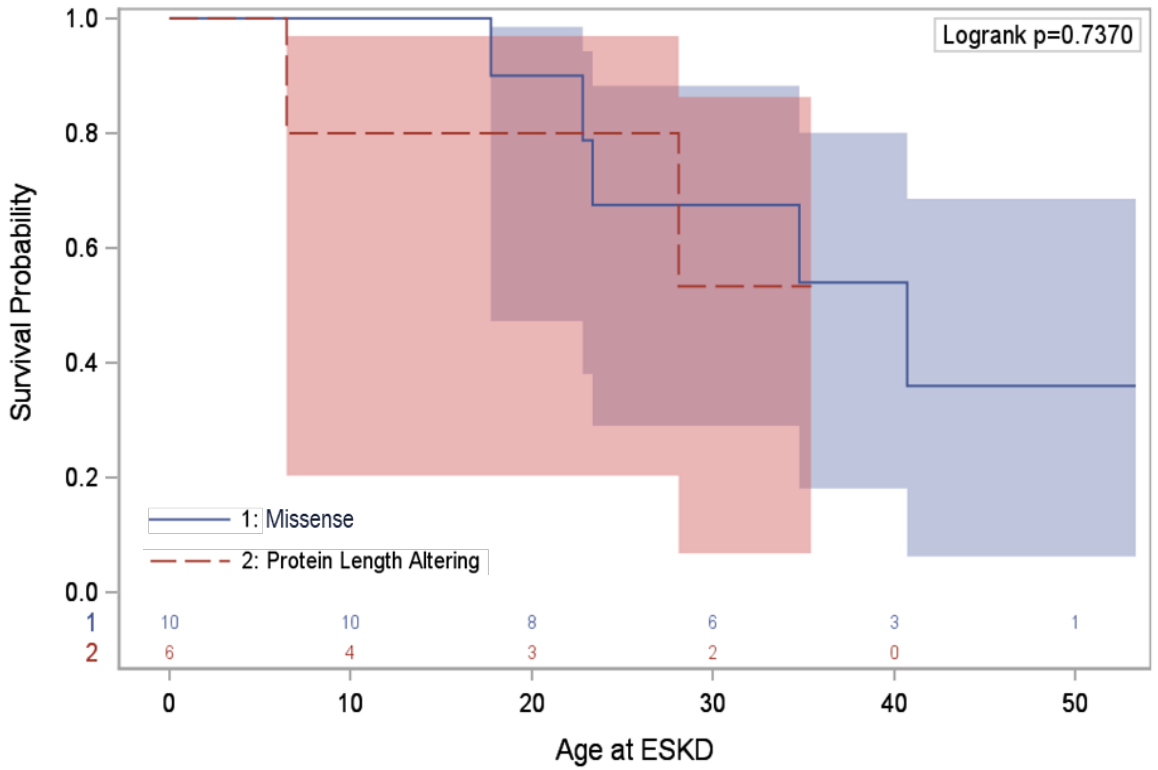
Males

	Median age at ESKD
Missense	24.3 years
Protein length altering	20.1 years



Females

	Lower Quartile age at ESKD
Missense	23.4 years
Protein length altering	28.1 years



Conclusions

- The observed effect of pathogenic variant type on renal outcomes varied by gene affected, number of mutations and sex.

- The relatively reduced severity among females harbouring a protein length altering *COL4A5* variant may represent an effect of skewed X -inactivation or a missense gain-of-function mechanism – needs confirmation with a larger cohort

Future

- We have used **large-scale registry data** from the UK to describe the renal outcomes for Males and Females with different pathogenic variant types

- These analyses are **scalable** : upload of clinical genetic reports is ongoing

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