Clinical evolution of women with XLAS

Κ. ΔΕΡΜΙΤΖΆΚΗ[1], Δ. ΛΥΓΕΡΟΎ[1], Π. ΙΩΆΝΝΟΥ[2], Π. ΣΥΓΓΕΛΆΚΗ[1], Σ. ΣΤΡΑΤΆΚΗΣ[1], Σ. ΣΤΡΑΤΉΓΗΣ[1], Κ. ΠΕΡΆΚΗΣ[1], Ε. ΝΤΑΟΥΝΤΆΚΗ[3], Γ. ΠΕΡΥΣΙΝΑΚΗ[3], Γ. ΤΖΑΝΆΚΗΣ[4], Ε. ΔΑΦΝΉΣ[1], Κ. ΔΈΛΤΑΣ[5], Κ. ΣΤΥΛΙΑΝΟΎ[1].

[1]ΝΕΦΡΟΛΟΓΙΚΉ ΚΛΙΝΙΚΉ ΠΑΓΝΗ, [2]ΠΑΘΟΛΟΓΙΚΉ ΚΛΙΝΙΚΉ ΠΑΓΝΗ, [3]ΝΕΦΡΟΛΟΓΙΚΉ ΚΛΙΝΙΚΉ Γ.Ν. ΡΕΘΎΜΝΟΥ, [4]ΝΕΦΡΟΛΟΓΙΚΉ ΚΛΙΝΙΚΉ Γ.Ν. ΧΑΝΊΩΝ, [5]ΤΜΉΜΑ ΒΙΟΛΟΓΙΚΏΝ ΕΠΙΣΤΗΜΏΝ, ΠΑΝΕΠΙΣΤΗΜΙΟ ΚΎΠΡΟΥ.

Natural history of disease…

- 1927, Alport A. :

"male members of a family tend to develop nephritis and deafness and do not as a rule survive…the females have deafness and hematuria and live to old age."

- 1964, Percoff GT. :

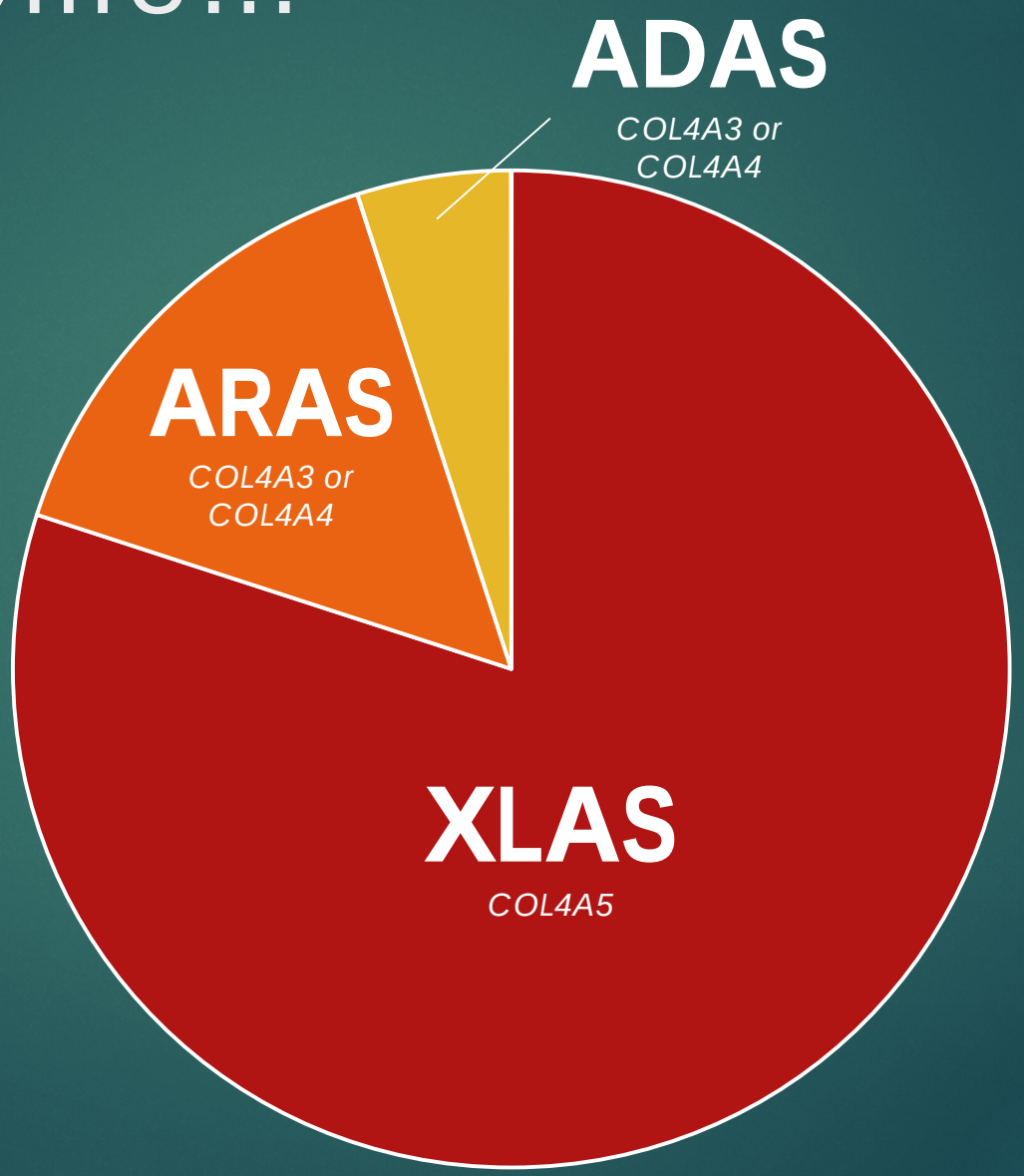
"females usually remain well throughout life…and only rarely have women died of the disease"

- 2003, Gubler et al. :

substantial burden of kidney disease in female population

Alport AC, Br Med J , 1927, vol. 1 (pg. 504-506)
Perkoff GT (1964), Annu Rev Med 15:115–124
Jais et al.(2003), J Am Soc Nephrol 14:2603–2610

Alport syndrome…



Kashtan CE. Collagen IV-related nephropathies (Alport Syndrome and Thin Basement Membrane Nephropathy, *GeneReviews at GeneTests: Medical Genetics* (pg. 1997-2005)

Potential pathogenesis mechanism of AS

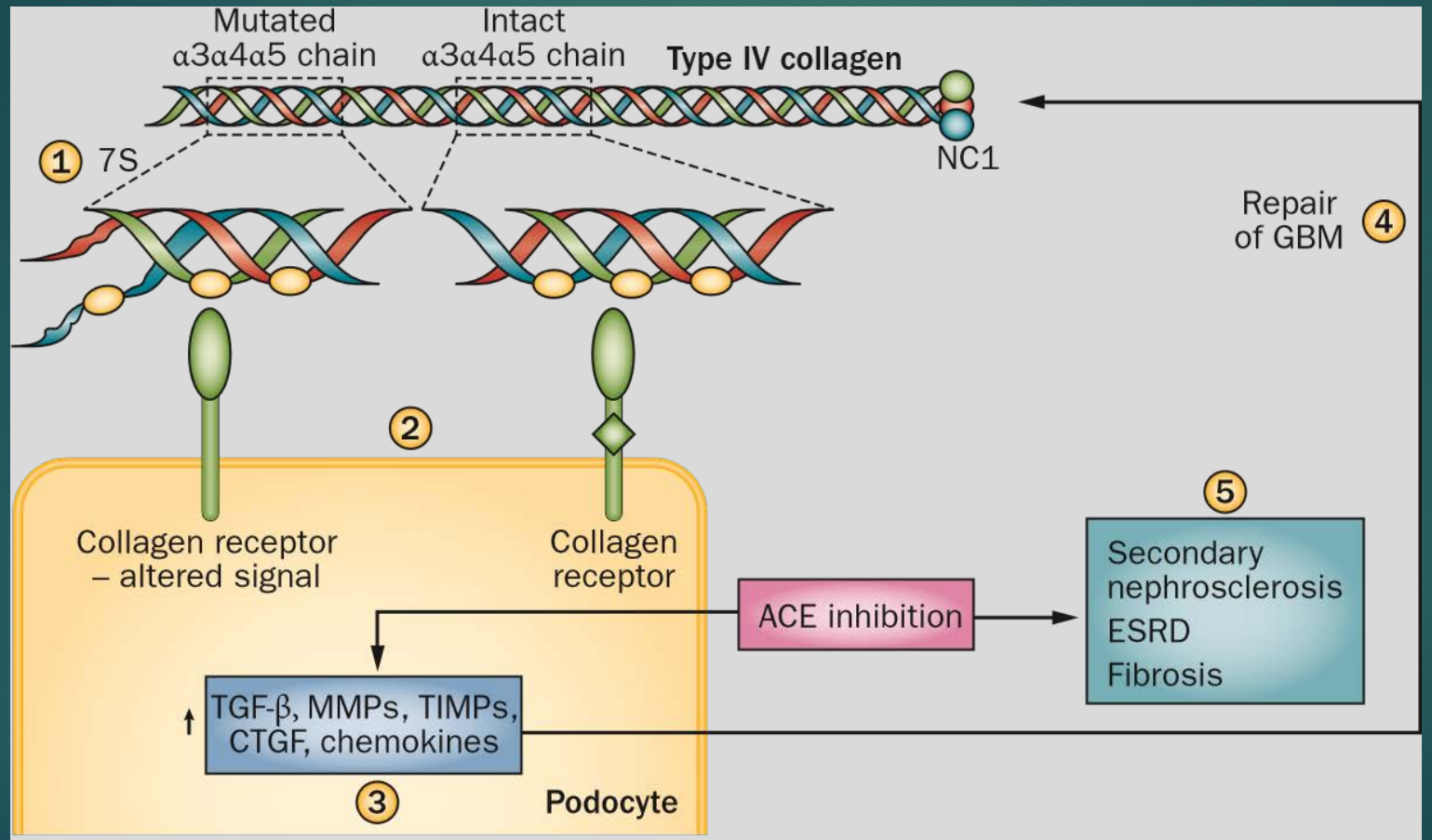


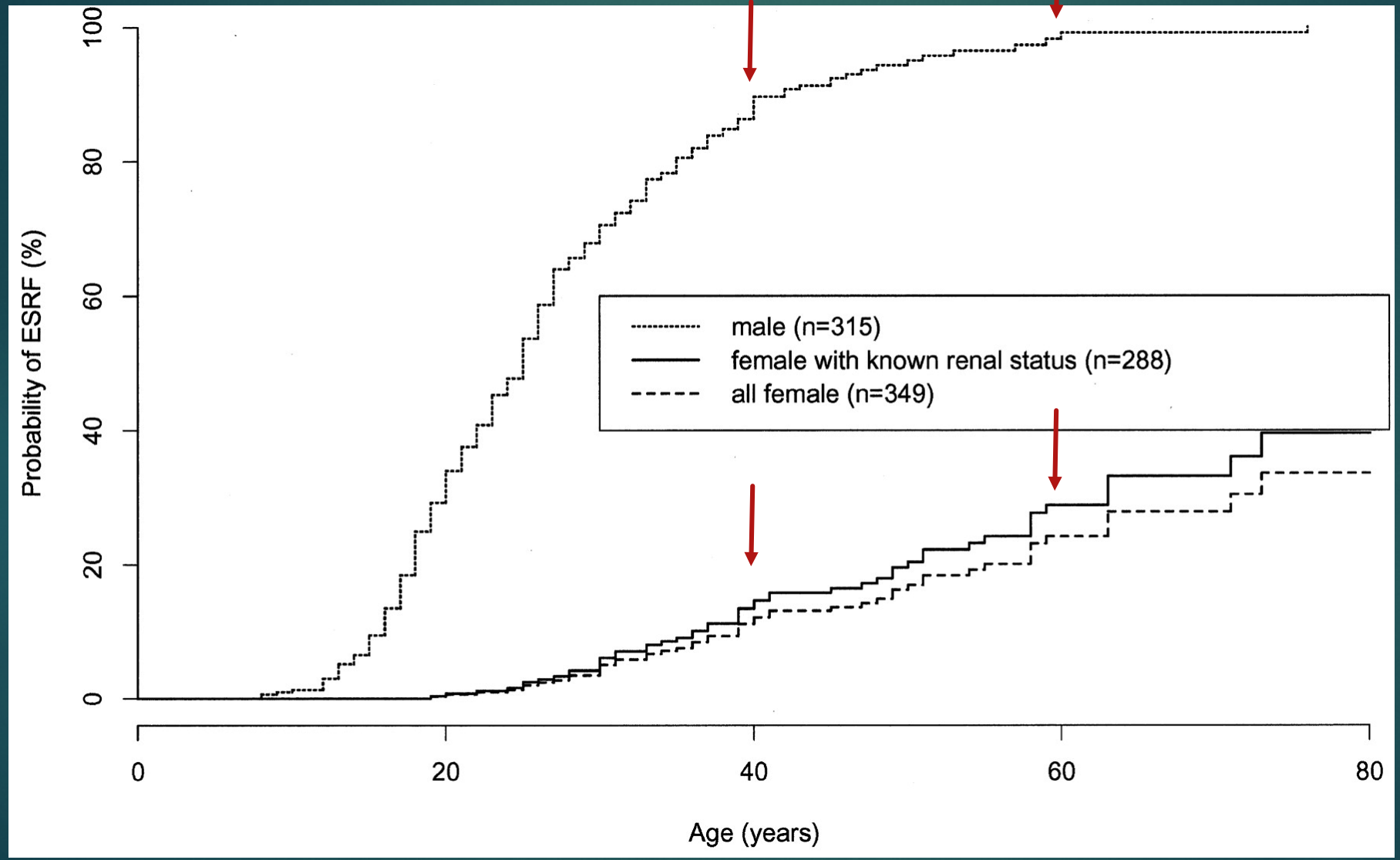
Figure 1 | Potential mechanisms underlying chronic renal disease occurring in Alport syndrome

Summary of clinical and pathologic findings in the 195 Alport syndrome families with proven COL4A5 mutation

Variable	Families with Proven COL4A5 Mutation
[a]ESRD, end-stage renal disease; GBM, glomerular basement membrane; GN, glomerulonephritis.	
Consanguinity	5 of 192 (2.5%)
Familial history	171 of 193 (88.5%)
Hematuria	191 of 193 (99%)
ESRD	146 of 193 (76%)
Hearing loss	156 of 189 (82.5%)
Ocular changes	66 of 149 (44%)
Leiomyomatosis	9 of 176 (5%)
Ultrastructural GBM changes	115 of 117 (98%)
Immunohistochemical GBM changes	23 of 27 (85%)
Transplantation	106 of 195 (54%)
Posttransplantation anti-GBM GN	3 of 80 (4%)

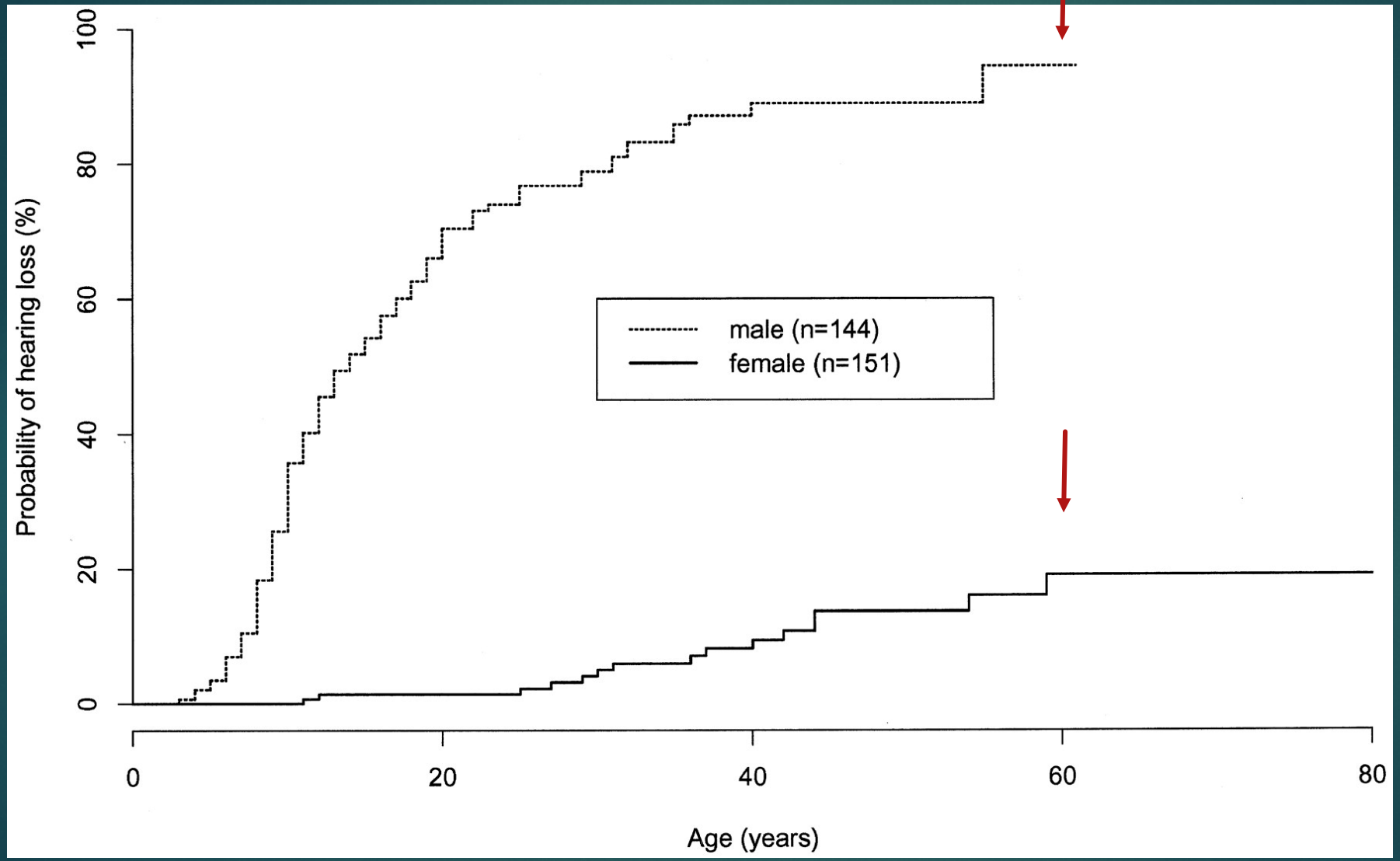
Jais JP et al., *J Am Soc Nephrol* **11**: 649–657, 2000

Probability of end-stage renal disease (ESRD) in 315 boys and men and 288 girls and women with COL4A5 mutation.



Jean Philippe Jais et al. JASN 2003;14:2603-2610

Probability of hearing loss in 144 boys and men and 151 girls and women with COL4A5 mutation.



Jean Philippe Jais et al. JASN 2003;14:2603-2610

Clinical evolution of women with XLAS

- 7 families with different mutations
- 48 family members (18 males/30 females), 30 of them with a X-linked transmission (8 men/22 women)
- 7/22 performed kidney biopsy before genome analysis
- follow-up for 5 years

Results...

- Age between 7 and 78 yo (mean age 32 yo)

- 7 biopsies performed
  - 2 Alport syndrome
  - 2 FSGS
  - 1 TBMD
  - 1 post-infectious GN
  - 1 IgM nephropathy

Results…

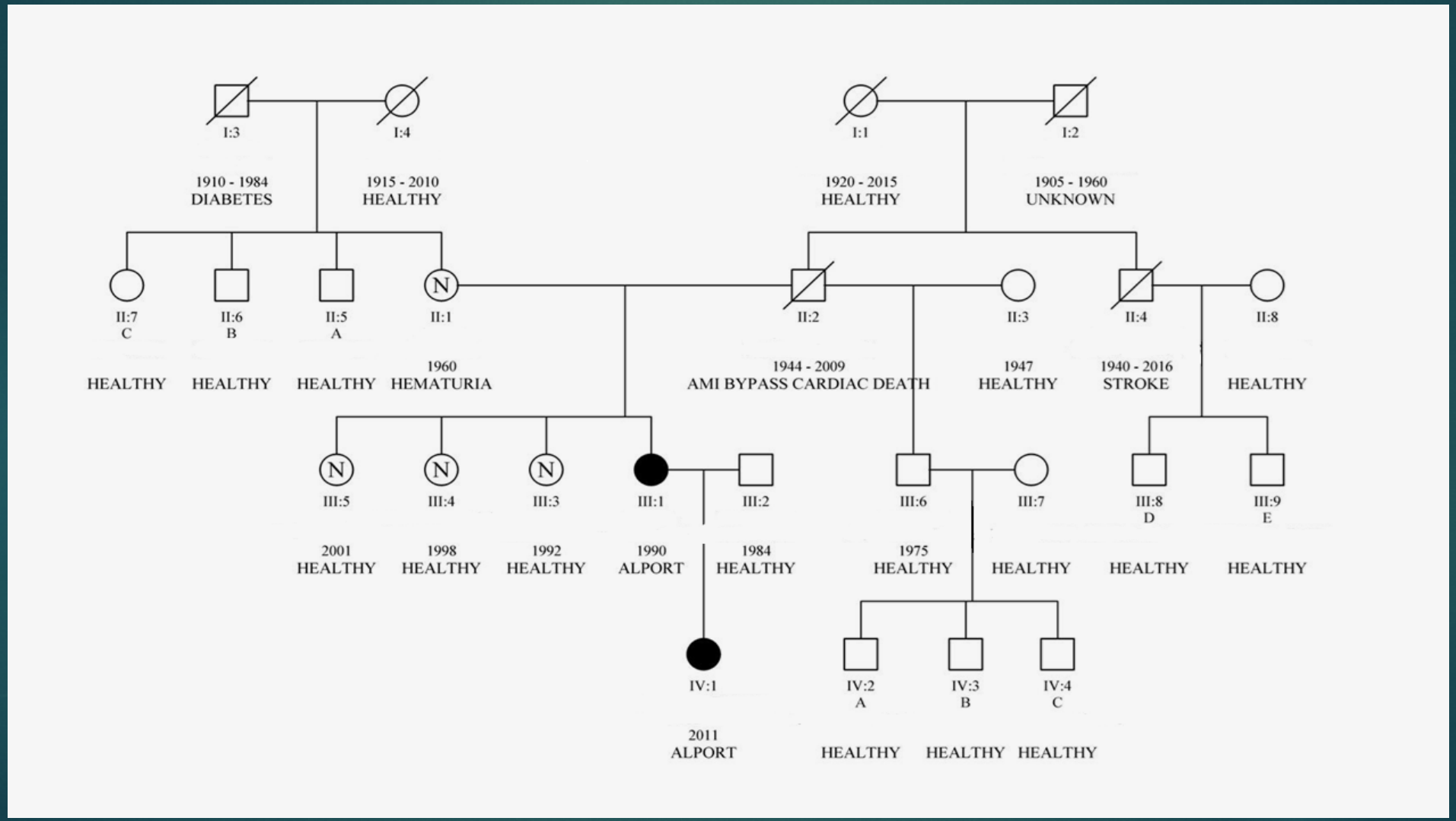
- 54%, (7-46 yo) presents hematuria, but no CKD
- 18% CKD (renal impairment or proteinuria >1gr, 7-60 yo)
- 27% ESRD (20-70 yo)

Family	Carriers ♀	Mutation		Hematuria (Age)	CKD (Age)	ESRD (Age*)
5459	4	c.2228G>T	p.G743V	2 (18, 18)	1 (52)	1 (70)
5315	3	c.3106G>A	p.G1036R	1 (38)	1 (60)	1 (21)
1000	2	c.4688+5G>A		0	1 (7)	1 (21)
5359	4	c.1094G>T	p.G365V	4 (28, 30, 32, 33)	0	0
4208	1	2946delT*fs	Stop995	1 (46)	0	0
4210	3	c.682G>T	p.E228X	1 (7)	1 (55)	1 (70)
5360	5		p.P907S	3 (27, 28, 28)	0	2 (34, 50)
Total	22			12 (54%)	4 (18%)	6 (27%)

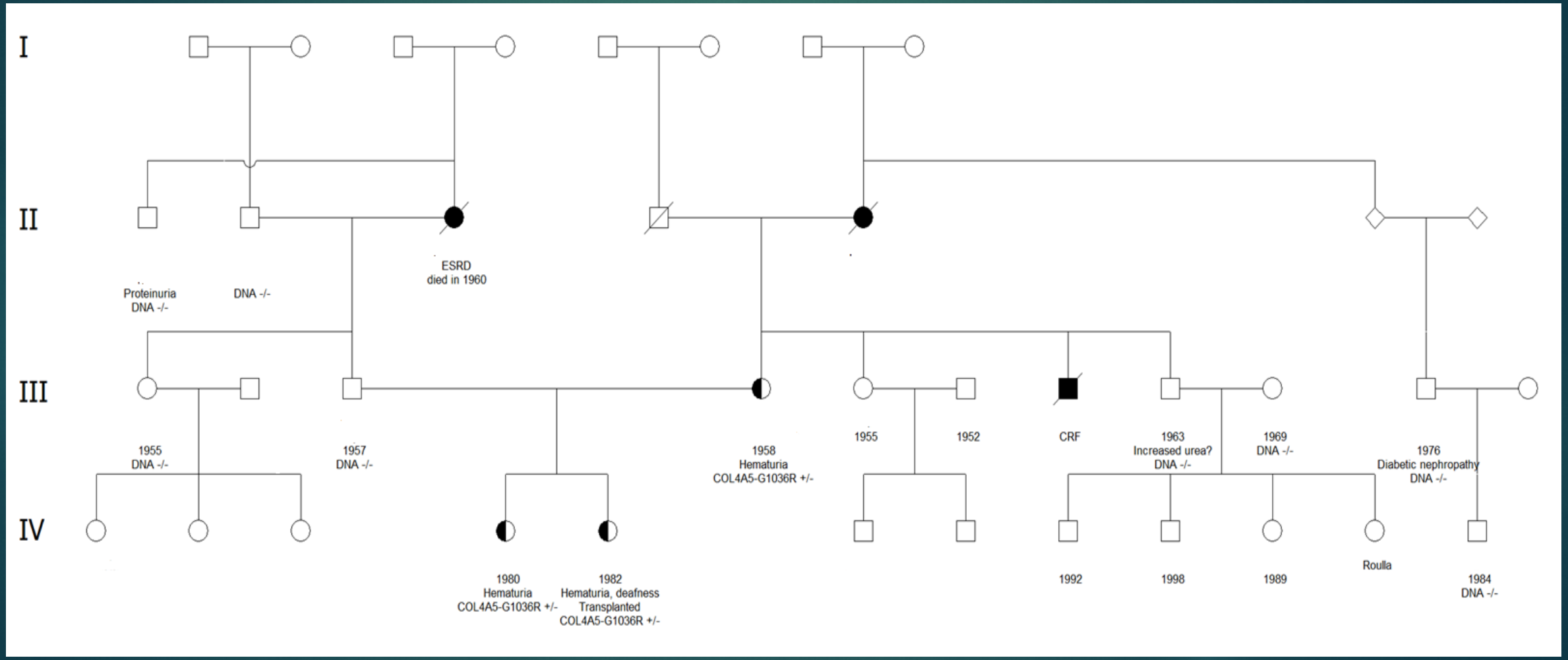
Mutation in c.4688+5G>A in COL4A5 gene

- not described yet
- located in a region of the gene where the changes are pathogenic
- not found in normal individuals / found only in the affected members of the family
- refers to a highly conserved nucleotide at the intron-exon limit, which may affect the splicing process
- C.4688+4G described before

Family 1000


I:3
1910 - 1984
DIABETES
I:4
1915 - 2010
HEALTHY
I:1
1920 - 2015
HEALTHY
I:2
1905 - 1960
UNKNOWN
II:7
C
HEALTHY
II:6
B
HEALTHY
II:5
A
HEALTHY
II:1
1960
HEMATURIA
II:2
1944 - 2009
AMI BYPASS CARDIAC DEATH
II:3
1947
HEALTHY
II:4
1940 - 2016
STROKE
II:8
HEALTHY
III:5
2001
HEALTHY
III:4
1998
HEALTHY
III:3
1992
HEALTHY
III:1
1990
ALPORT
III:2
1984
HEALTHY
III:6
1975
HEALTHY
III:7
HEALTHY
III:8
D
HEALTHY
III:9
E
HEALTHY
IV:1
2011
ALPORT
IV:2
A
HEALTHY
IV:3
B
HEALTHY
IV:4
C
HEALTHY

Family 5315


I
II
III
IV
ESRD
died in 1960
Proteinuria
DNA -/-
DNA -/-
1955
DNA -/-
1957
DNA -/-
1958
Hematuria
COL4A5-G1036R +/-
1955
1952
CRF
1963
Increased urea?
DNA -/-
1969
DNA -/-
1976
Diabetic nephropathy
DNA -/-
1980
Hematuria
COL4A5-G1036R +/-
1982
Hematuria, deafness
Transplanted
COL4A5-G1036R +/-
1992
1998
1989
Roulla
1984
DNA -/-

Conclusions…

- Renal biopsy in pt with XLAS is often non-diagnostic
- XLAS IS NOT a benign disease for heterozygous women:
  - 27% of them ESRD
  - Almost half of the affected women reach ESRD in young age (same with men)

Possible explanation: asymmetric inactivation of the X chromosome or the existence of modifying genes can affect phenotype