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My Journey

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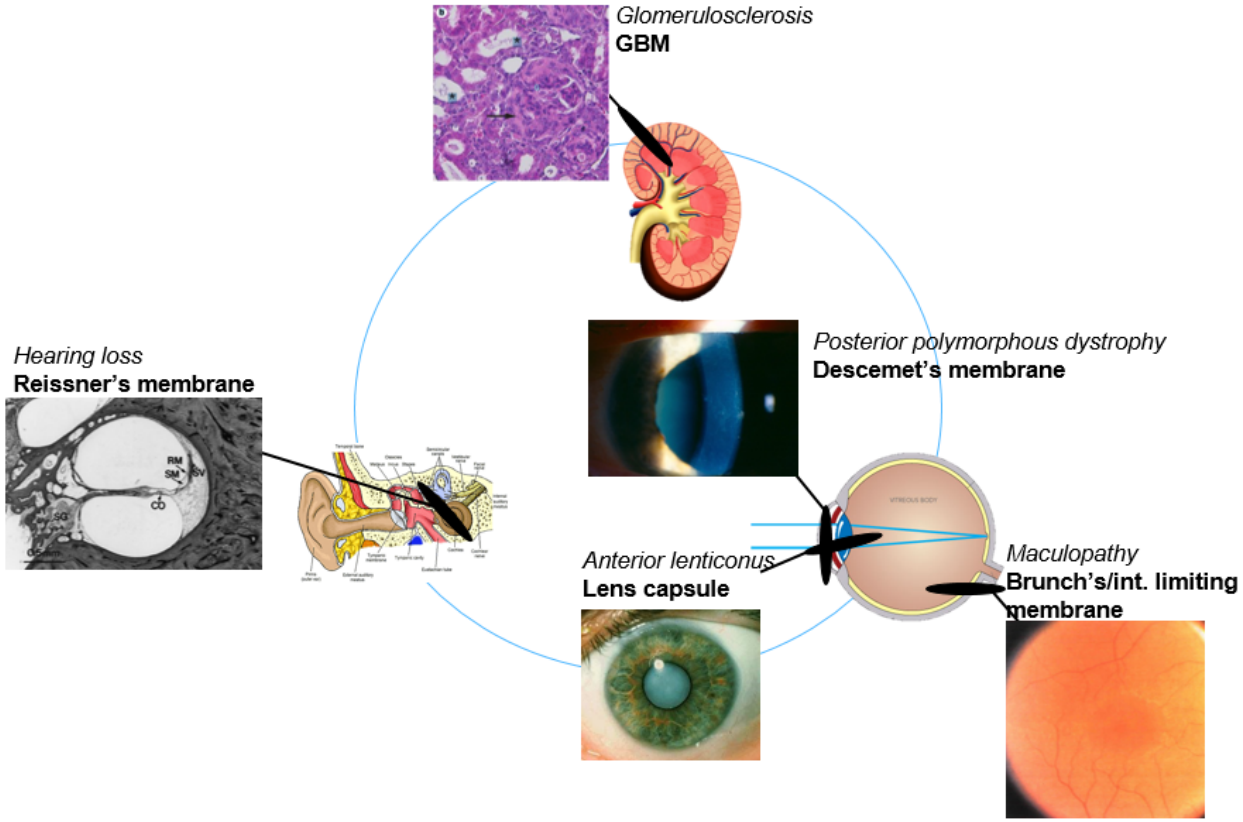
What is Alport Syndrome?

Rare Type IV Collagen Disease

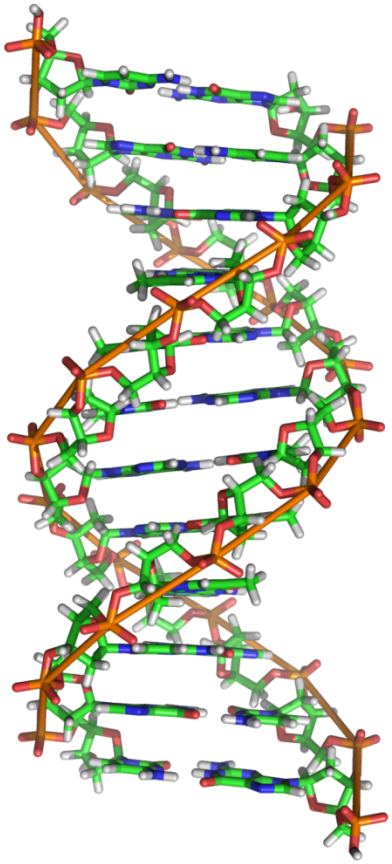


Int J Ophthalmol. 2010;3(2):149-51 Nat Rev Nephrol. 2013 Mar;9(3):170-8 Adv Otorhinolaryngol. Basel, Karger, 2000, vol 56, pp 218–232

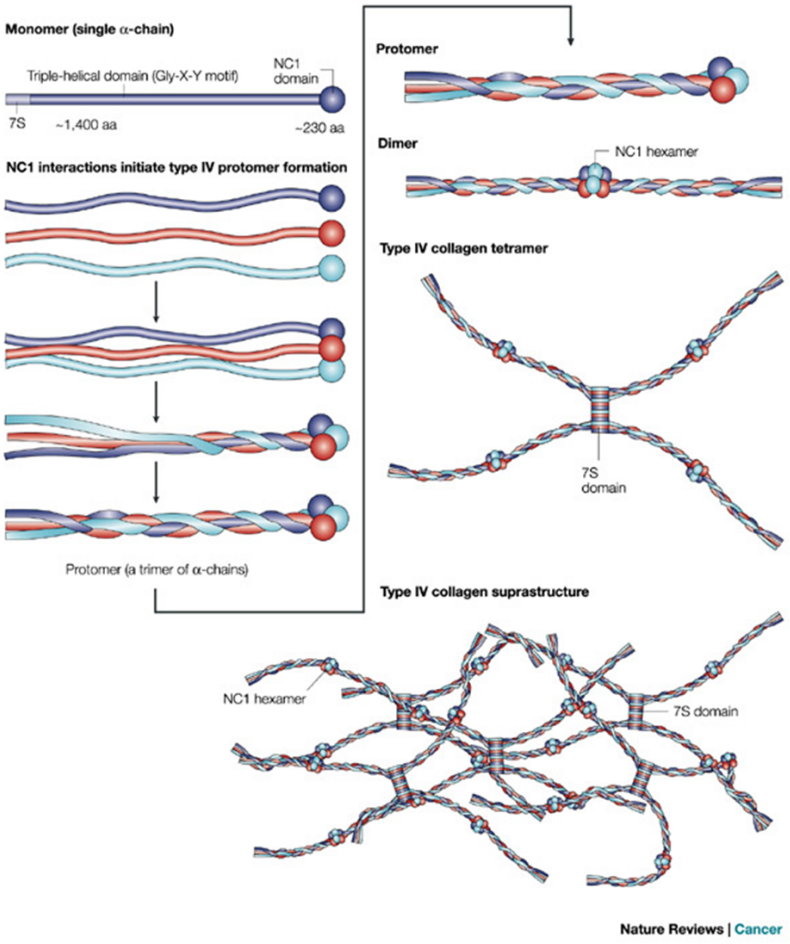
Mutations in 3 genes cause Alport Syndrome

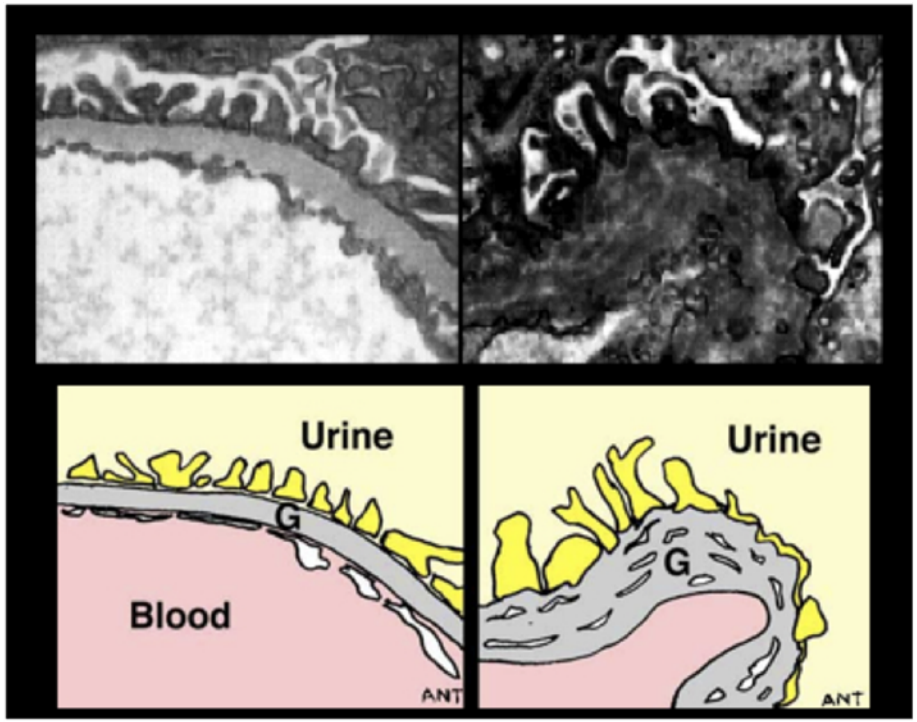
- **COL4A5** (type IV collagen alpha 5)
  - X Chromosome
  - Mutations cause X-linked Alport Syndrome

- **COL4A3** (type IV collagen alpha 3)
- **COL4A4** (type IV collagen alpha 4)
  - Chromosome 2
  - 2 Mutations cause Autosomal Recessive
  - 1 Mutation cause Autosomal Dominant



Type IV collagen

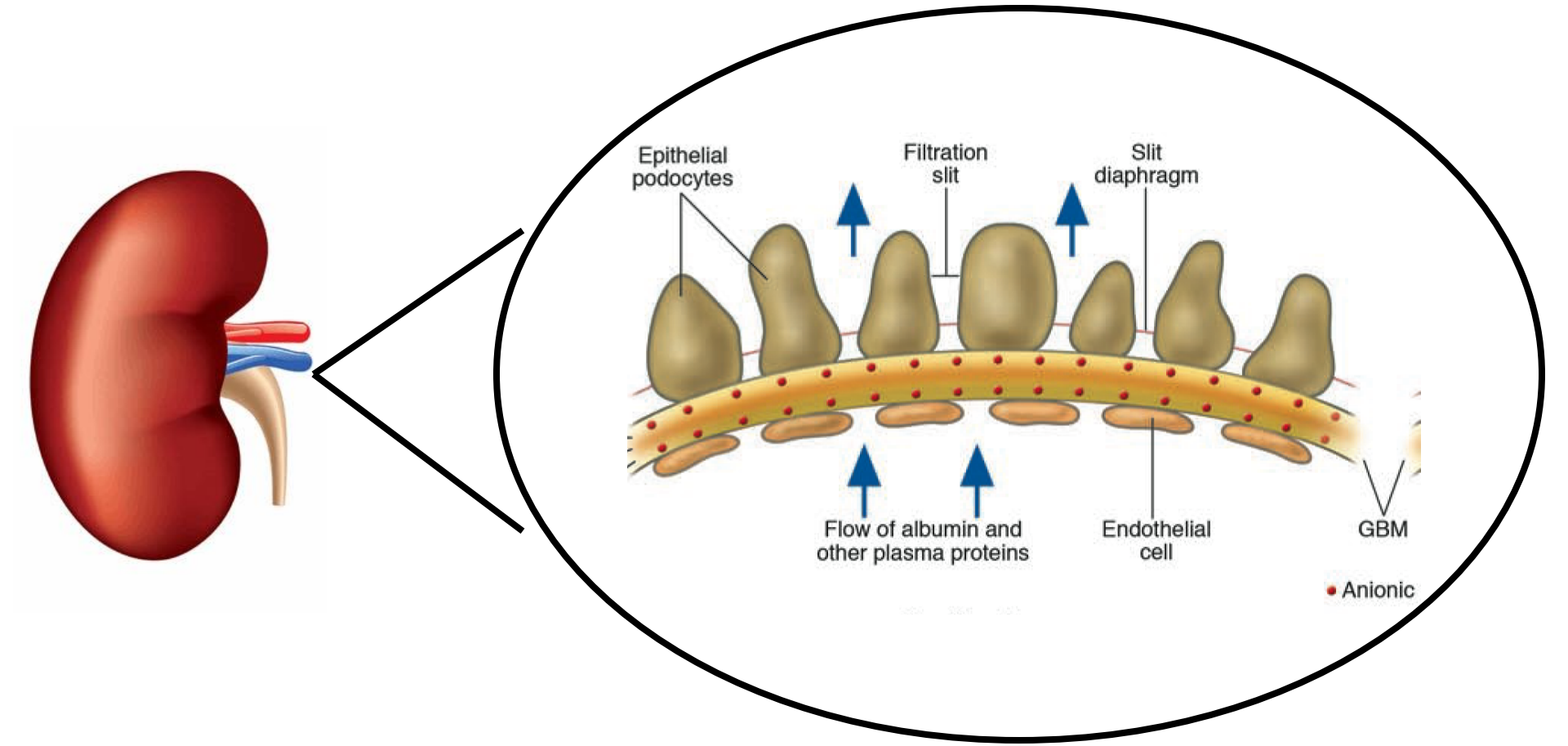




Normal **Alport**

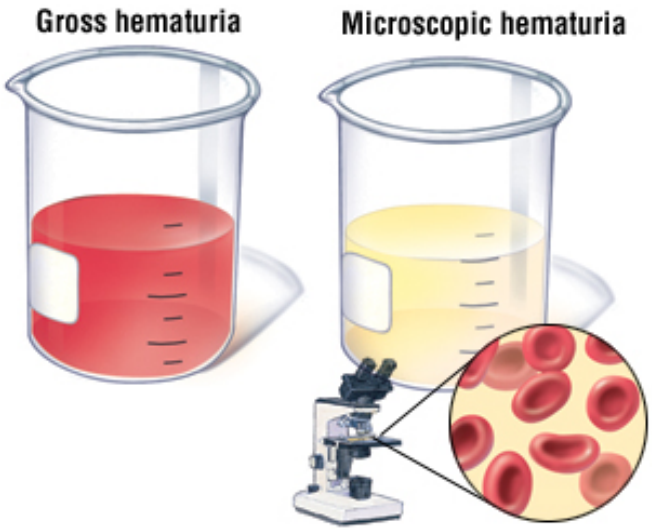
A very highly enlarged view of the filter in the glomerulus. These electron microscope images are magnified x100,000, and show glomerular basement membrane (**G**) in a normal glomerulus (LEFT) and in Alport syndrome (RIGHT). The diagrams below illustrate the thickening and 'falling apart' of Alport GBM.

Type IV collagen is required to make up the normal kidney filtration barrier



Farquhar, *JCI* (2006) 116:2273

Kidney disease in Alport Syndrome



Hematuria

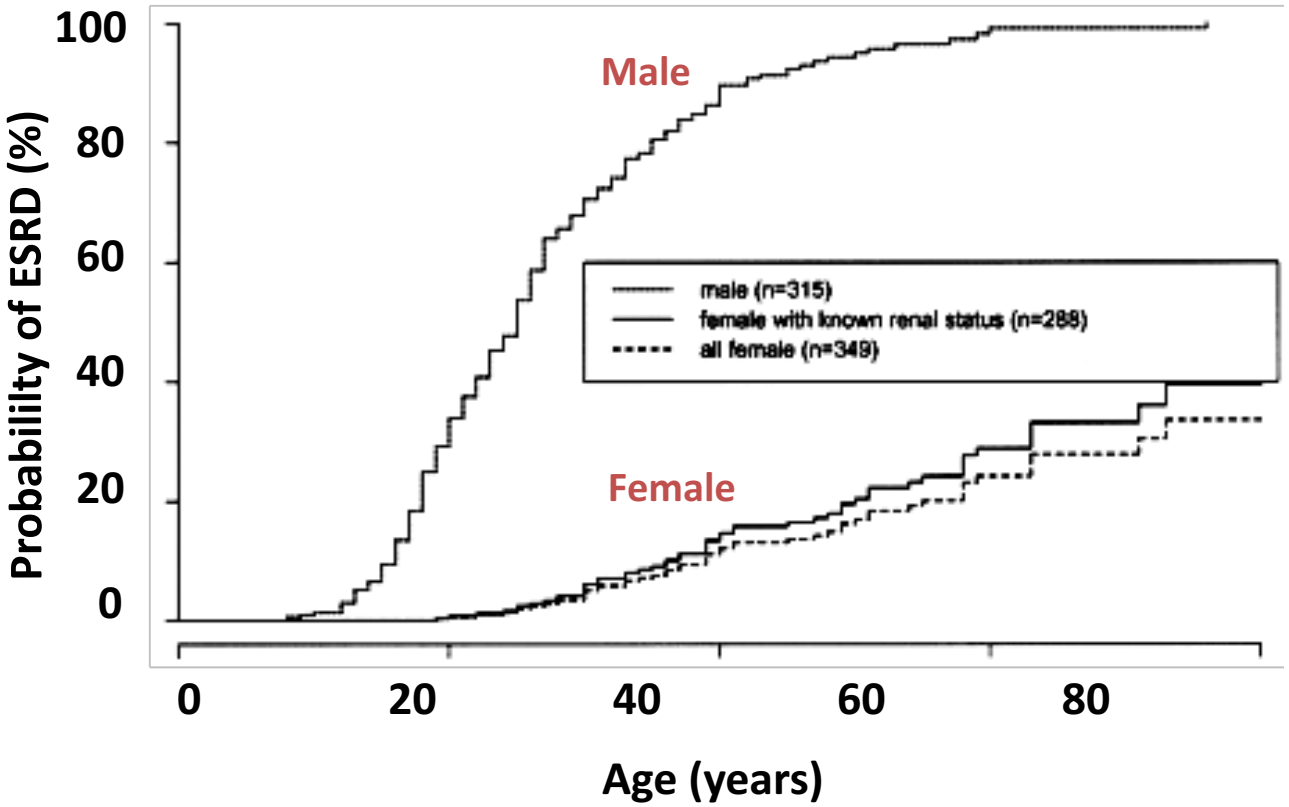
Hematuria + Microalbumin -uria

Proteinuria+ Chronic Kidney Disease

https://www.drugs.com/health-guide/hematuria.html

http://www.beaumont.ie

X-linked Alport Syndrome: Risk of End Stage Renal Disease (ESRD)



Jais et al, JASN 2003

Autosomal dominant Alport syndrome progresses less rapidly than X-linked Alport Syndrome

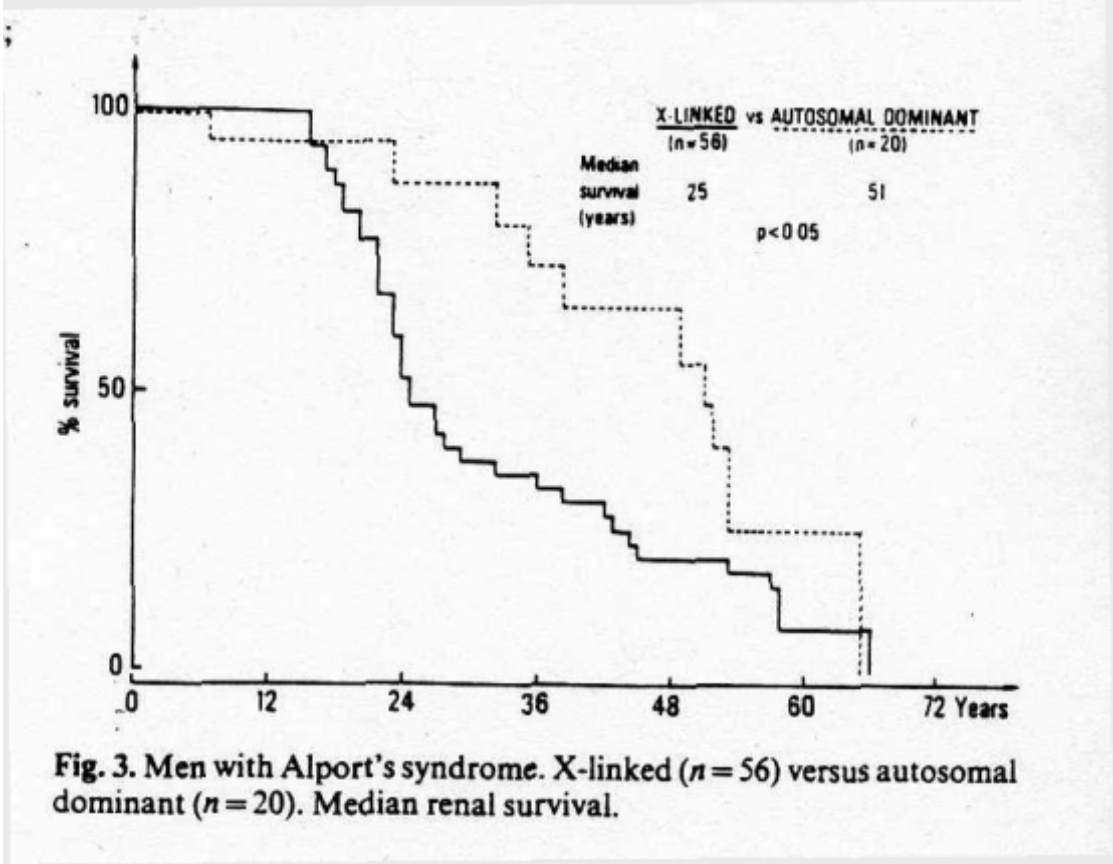
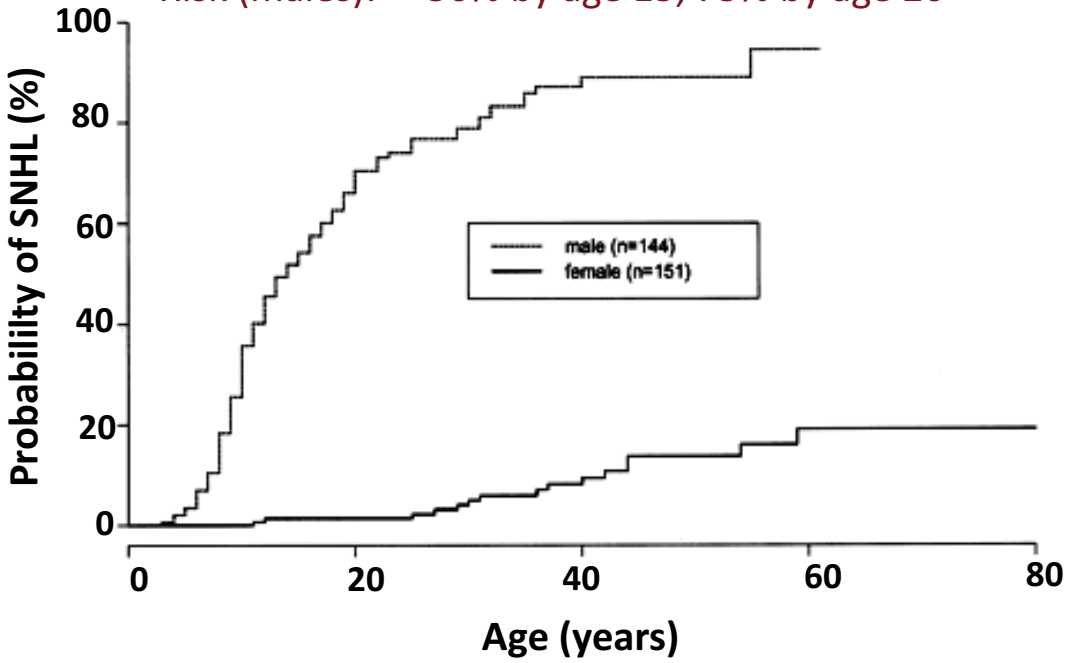


Fig. 3. Men with Alport's syndrome. X-linked ($n = 56$) versus autosomal dominant ($n = 20$). Median renal survival.

Pochet et al, Kidney Int 1989

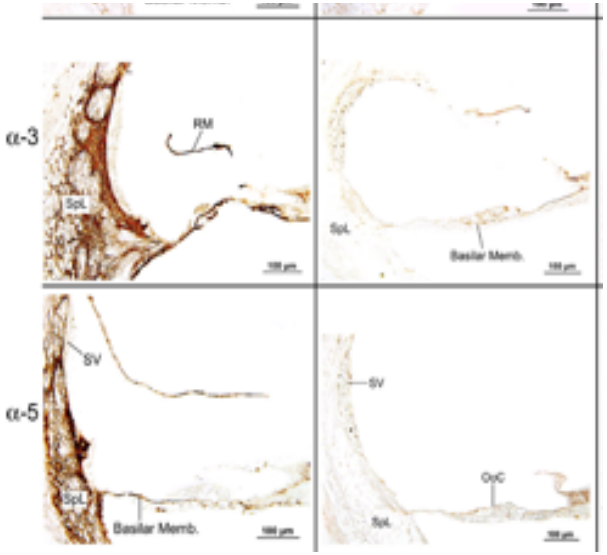
Hearing Loss in Alport Syndrome

Risk (males): ~ 50% by age 15, 75% by age 20



Due to abnormal cochlear basement membranes?

Control Alport



Hearing loss is:

- not congenital
- always bilateral
- first detectable after about 5 yrs by audiometry
- sensorineural, initially affecting high frequency sounds

Jais et al, 2000, 2003; Merchant et al, 2004; 2005

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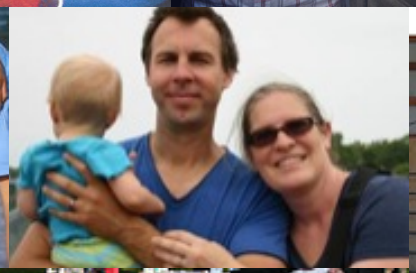
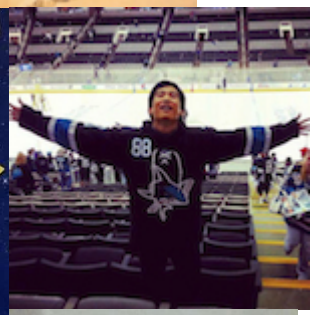
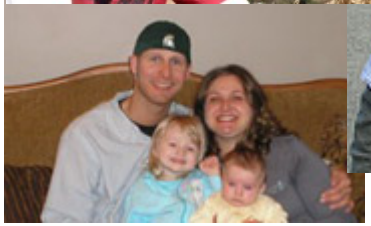




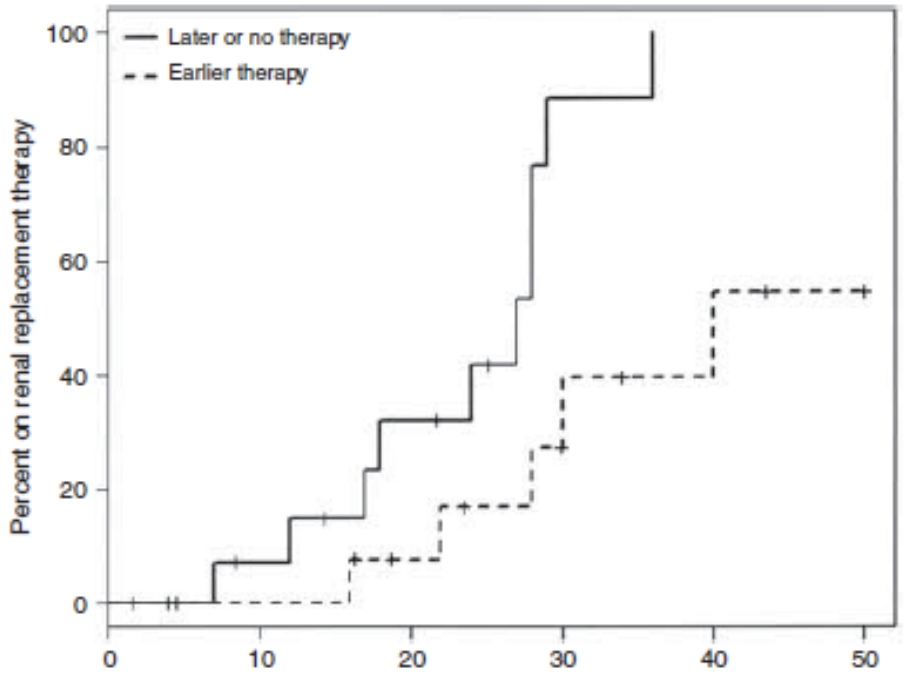




There are NO FDA approved treatments for Alport Syndrome!

Current Standard of Care
Delays but does not Prevent Kidney Failure

- Renin-angiotensin-aldosterone system (RAAS)
  - Maintains fluid balance and blood pressure, ensures optimal renal blood flow
  - RAAS is overactive in various chronic kidney diseases and promotes renal fibrosis (scarring)
- RAAS blockers
  - Angiotensin converting enzyme (ACE) inhibitors: block the production of angiotensin II, the active form of angiotensin
  - Angiotensin receptor blockers (ARBs): block the action of angiotensin II
  - Aldosterone inhibitors: block the action of aldosterone

Early ACE inhibition delays ESRD: Comparison of Siblings



No. at risk											
Later or no therapy	15	14	12	10	8	6	1	1	0	0	0
Earlier therapy	15	13	13	13	10	8	6	4	4	2	2

In sibling pairs where elder sibling started therapy later

⬇

Median age of ESRD was 27 years in elder sib, 40 younger sib

Gross et al, Kidney Int 2012

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MISSION is to improve the lives of those affected by Alport Syndrome through education, empowerment, advocacy, and research.

VISION is to conquer Alport Syndrome by finding new treatments and a cure to prevent kidney failure and hearing loss.



STRATEGY is to put all the pieces in place to bridge the gap and set the landscape

ASF Research Program

Since 2011
$1 Million USD in Basic Science and Drug Repurposing Research
Provide seed or proof of concept funding

Global projects include:

- Stem Cells – Amniotic Fluid and Induced Pluripotent
- CRISPR
- Formation of COL4A3/4/5
- Podocyte response to injury in Alport
- MicroRNA-21
- 4 Drug Repurposing Studies

www.alportsyndrome.org

ASF Supports
Alport Patient Registry

University of Minnesota

11/06/2016

Participant Enrollment Summary

Total Number of Participants: 895

Enrollment Categories	Male	Female
Total Participants (US)	410	484
Total Affected (US)*	277	327
Total Affected on Medications (US)	146	121
Total Unaffected (US)*	90	93
Total Unknown (US)*	43	64
Age Range for Affected (US)	2 - 77	3 - 1952
Age Range for Unaffected (US)	6 - 59	4 - 72
Age Range for Unknown (US)	2 - 60	3 - 67
A Prospective Study of Microalbuminuria in Untreated Boys with Alport Syndrome	45 boys, age < 18	
Urinary Biomarker Studies	42	38
R21 Data Collection	342	245

* Total Affected: Individuals with confirmed diagnosis of Alport Syndrome
* Total Unaffected: Individuals evaluated and reported no evidence of Alport Syndrome
* Total Unknown: Individuals who have not been evaluated but have a documented family history of Alport Syndrome

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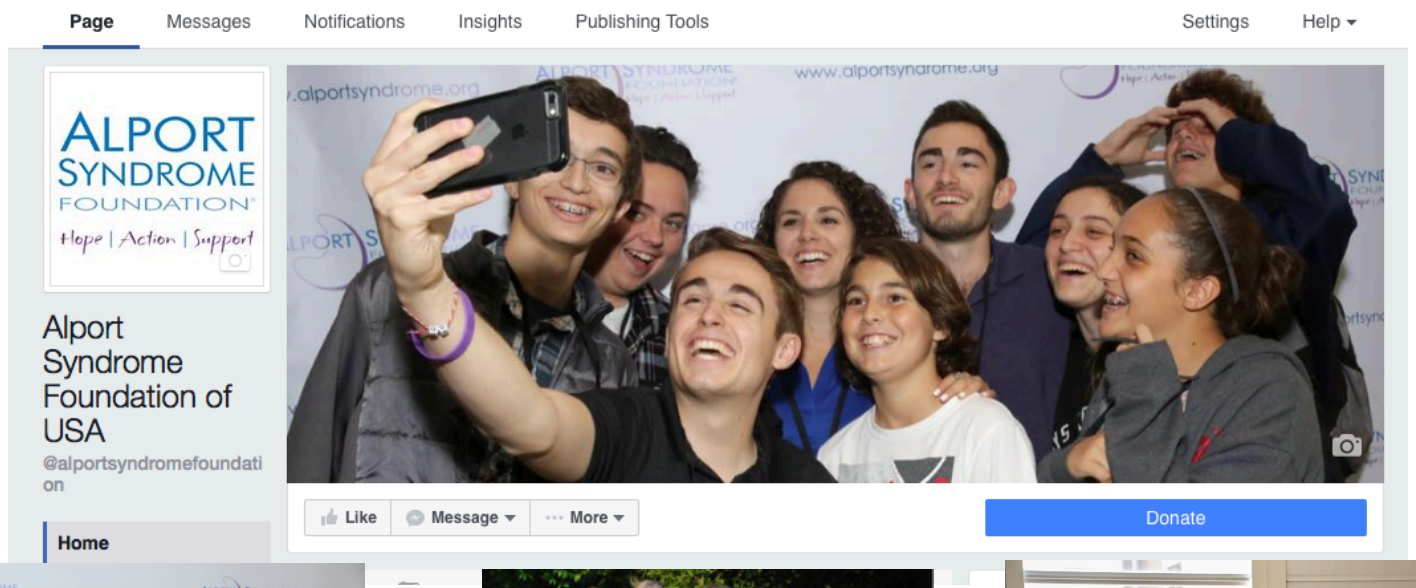
ASF Patient Network



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ASF Advocacy and Awareness

- Medical Conferences/Symposiums
- Kidney Patient Summit/Rare Disease Day
- Provides Clinical Guidelines to Providers

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ASF Supports Clinical Trials

- Attend FDA meetings
- Participate in discussions on trial design
- Connect with Medical Advisory Committee
- Promote awareness in patient community

Current studies:

- ATHENA Natural History Study (International)
- HERA Phase 2 anti-miRNA-21 (International)
- EARLY PRO-TECT Phase 3 Trial (Germany)

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Alport Syndrome International Collaborations

Australia, Belgium, Canada, China, FEDERG Europe, France,
Germany, Israel, Italy, The Netherlands, Spain, UK, USA

Shared vision to improve the lives of those affected by Alport Syndrome to find novel treatments and a cure.

ALPORT SYNDROME FOUNDATION®
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- Alport Syndrome has a **huge unmet medical need**, as do all rare diseases
- **Expedite the advancement of therapies** to treat/cure Alport Syndrome and other rare diseases
- **Continue to build international collaboration** between clinical and basic scientists, patient organizations, pharma/biotech companies, and government funding/regulatory organizations
- **Support innovative and collaborative efforts to accelerate the translational process** to get novel and effective treatments for all rare diseases
- To **hope that Alport Syndrome could be considered an initial candidate** in the new ***Swiss Center for Therapeutic Discovery***

Thank you!