Genetic Counseling & Alport Syndrome

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Modes of Inheritance

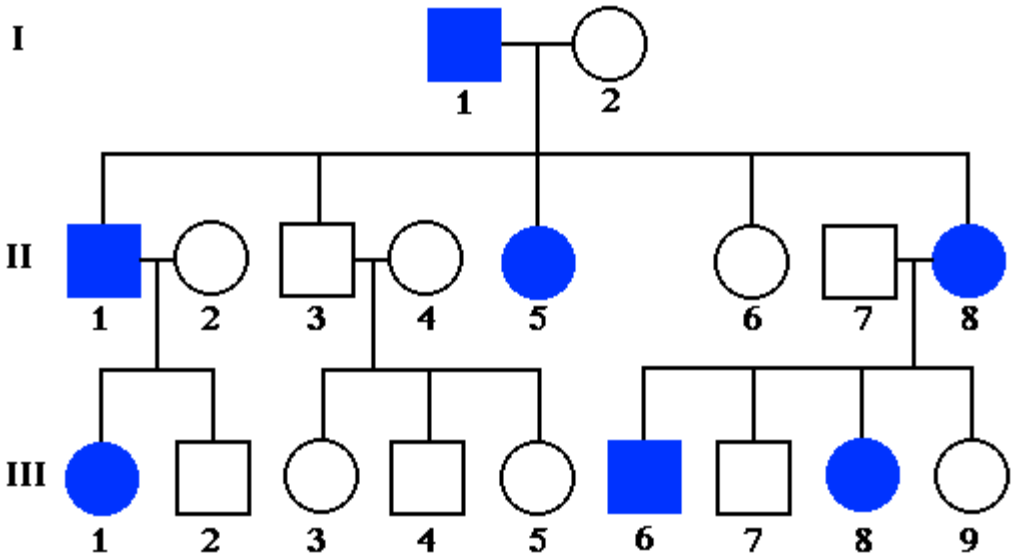
- X-linked (XLAS)
  - COL4A5 on chromosome Xq22 85% of cases
- Autosomal
  - COL4A3 or COL4A4 on chromosome 2q36-37
  - Recessive (ARAS) 10-15% of cases
  - Autosomal Dominant (ADAS) 1-5% of cases
- Diseases mimicking AS
  - MYH9 disorders: Epstein and Fechtner syndromes

Clinical Findings

- In patients with XLAS, the disease is consistently severe in males and female carriers are generally less symptomatic.
- The female carrier variable phenotype is due to lyonization by which only one X chromosome is active per cell.
- In patients with ARAS, the disease is equally severe in male and female homozygotes and the course is similar to that of XLAS.
- In ADAS, the renal manifestations are typically milder and present later than XLAS and ARAS.

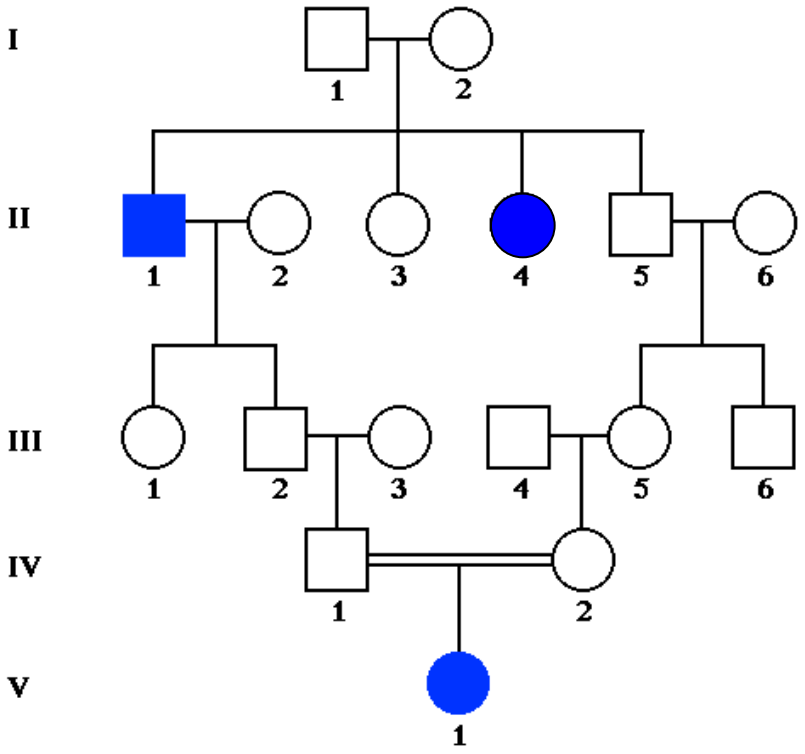
Autosomal Dominant AS

- Rare, mild
- Vertical pattern of inheritance
- Male to male transmission
- Mutation in COL4A3 or COL4A4



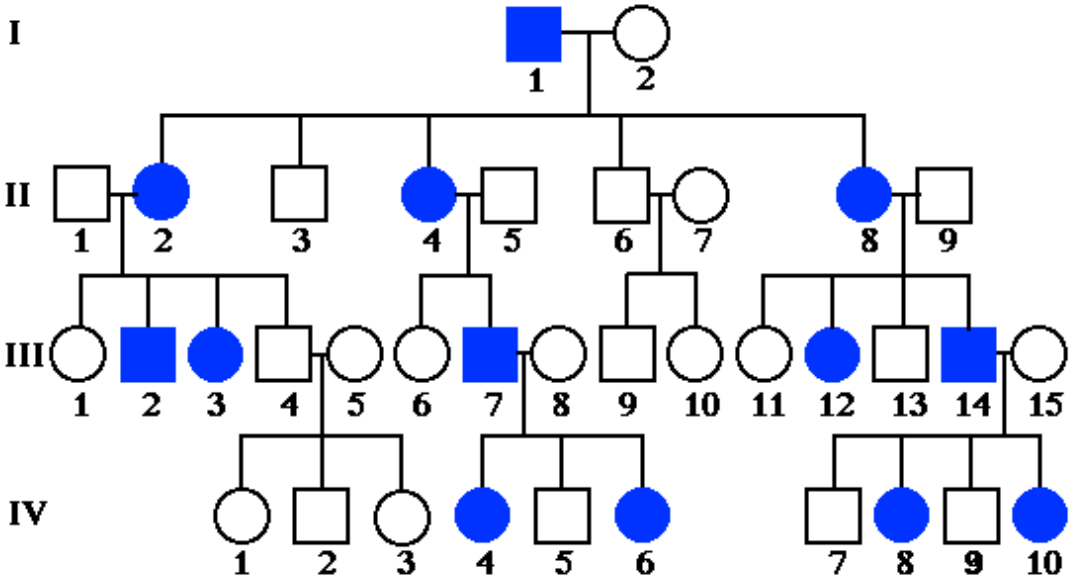
Autosomal Recessive AS

- Uncommon
- Horizontal pattern of inheritance
- Consanguinity
- Mutations in COL4A3 or COL4A4
- Parents are “carriers”: they have TBMN



X-linked AS

- Most common
- Vertical pattern of inheritance
- NO male to male transmission
- Mutations in COL4A5



Relevance of Specific Mutations in XLAS

- Large deletions and truncations cause the most severe phenotype.
- Splice-site mutations: intermediate severity
- Missense mutations: relatively mild disease.
- In US, but not Europe, mutations in the NC1 domain are more benign than those in the triple helical domain

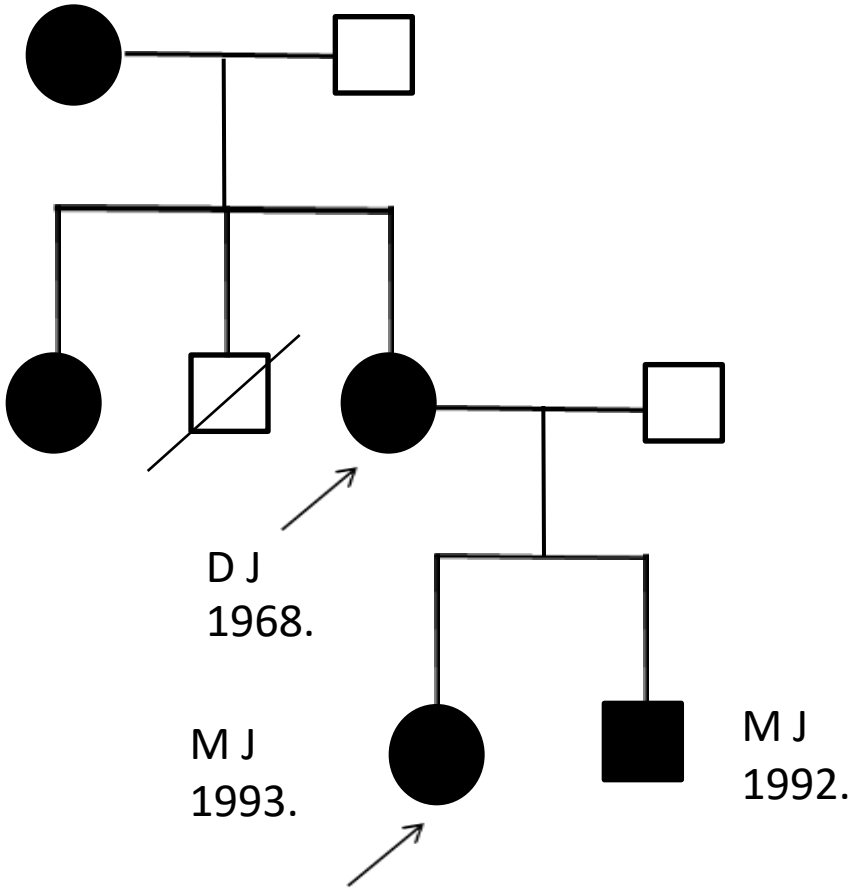
Goals of our Genetic Counseling

For Families and Individuals to:

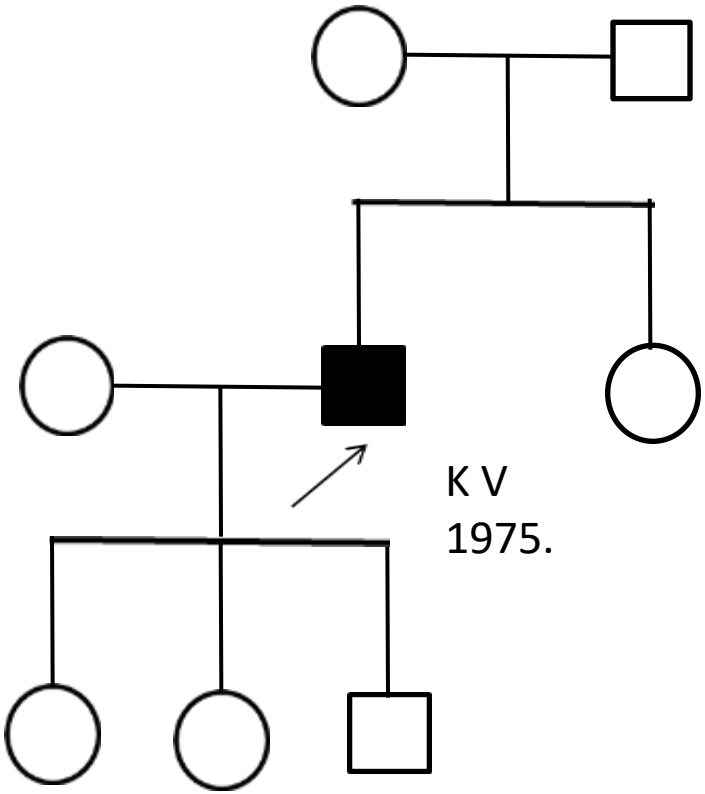
- Understand their family history and how it is related to a condition
- Discuss and understand the impact of genetic conditions on relatives and the immediate family
- Provide supportive counseling, especially around time of new diagnosis, pregnancy, etc.
- Provide education that is meaningful for families
- Discuss, coordinate, and interpret genetic tests

Family 1

COL4A5
Stop Gained
NM_033380.2
c.2950C>T
p.Gln984Ter
Heterozygous



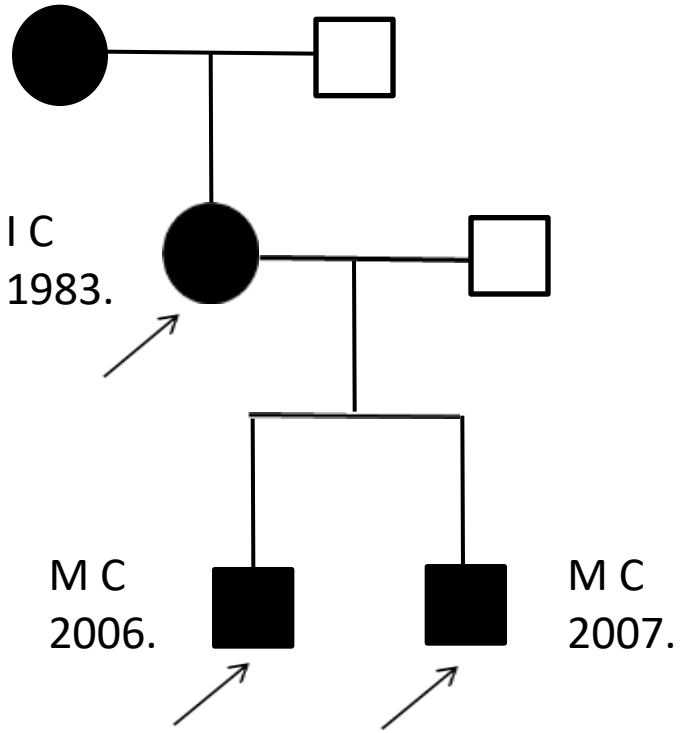
Family 2



COL4A5
Missense Variant
NM_033380.2
c.1871G>A
p.Gly624Asp
Homozygous

Family 3

VUS
C4804 G>T
Gly 1602Cys




Thank you for your attention…