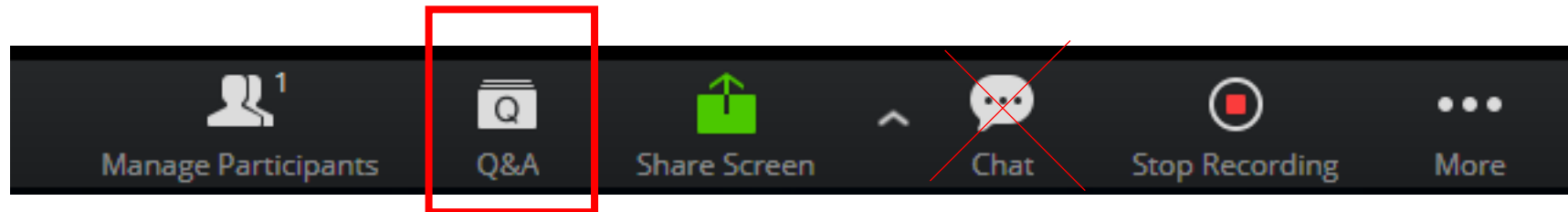


The Link Between Fabry Disease and Your Kidneys

Michael Mauer, MD

Technical overview

- Please stay on '**mute**' throughout the duration of the webinar.
- The chat box has been disabled.
- If you have questions for the speaker or for the AKF team:
 - Please type it into the **Q&A box** in your control panel.
 - We will answer questions out loud during the Q&A portion of the presentation.





Thanks to our speaker!

Michael Mauer, MD

- Pediatric nephrologist at the University of Minnesota
- Early developer of hemodialysis and kidney transplantation for infants and small children
- 15 years of research in Fabry disease

Objectives

- Signs and symptoms of Fabry disease
- How Fabry disease causes kidney disease
- Treatment for people with Fabry disease
- How Fabry disease affects families

Disclosures

- Member of NA and International Fabry Registry Boards
- Recipient of investigator-initiated research grants from Sanofi/Genzyme and Amicus*
- Research kidney biopsy lab studies for Sanofi/Genzyme and Amicus
- Consultant to Genzyme, Amicus, Freeline Therapeutics, Avrobio and Sangamo for clinical trial design in Fabry disease*
- Speaker at Sanofi/Genzyme and Amicus non-promotional educational meetings*

* This interest has been reviewed and managed by the University of Minnesota in according to its conflict of interest policies.

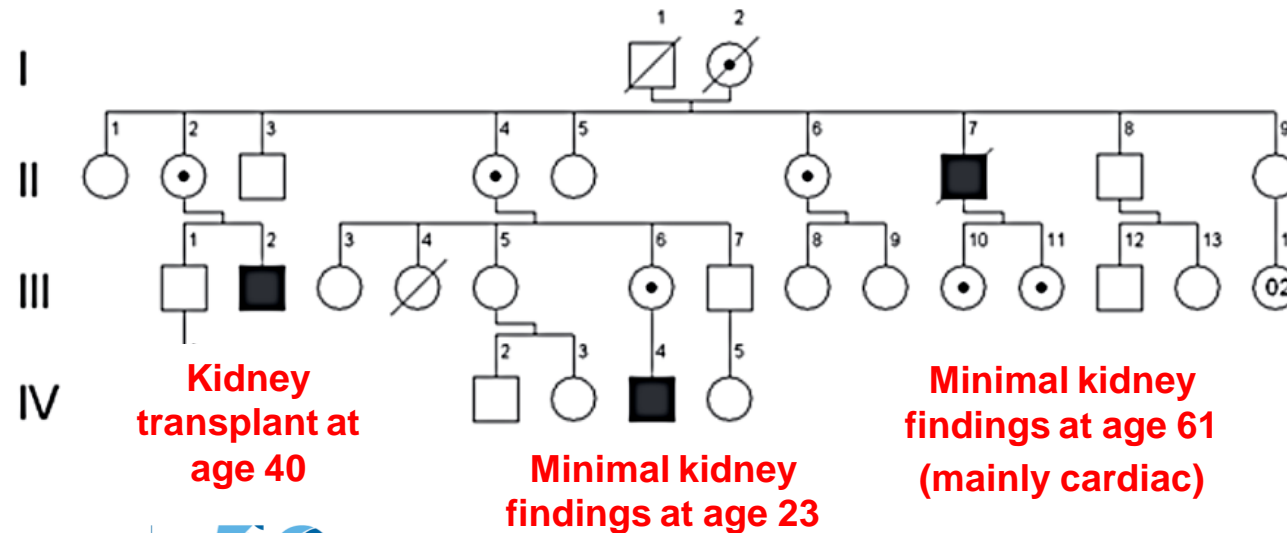
What is Fabry disease?

Fabry is a heterogeneous inherited disease

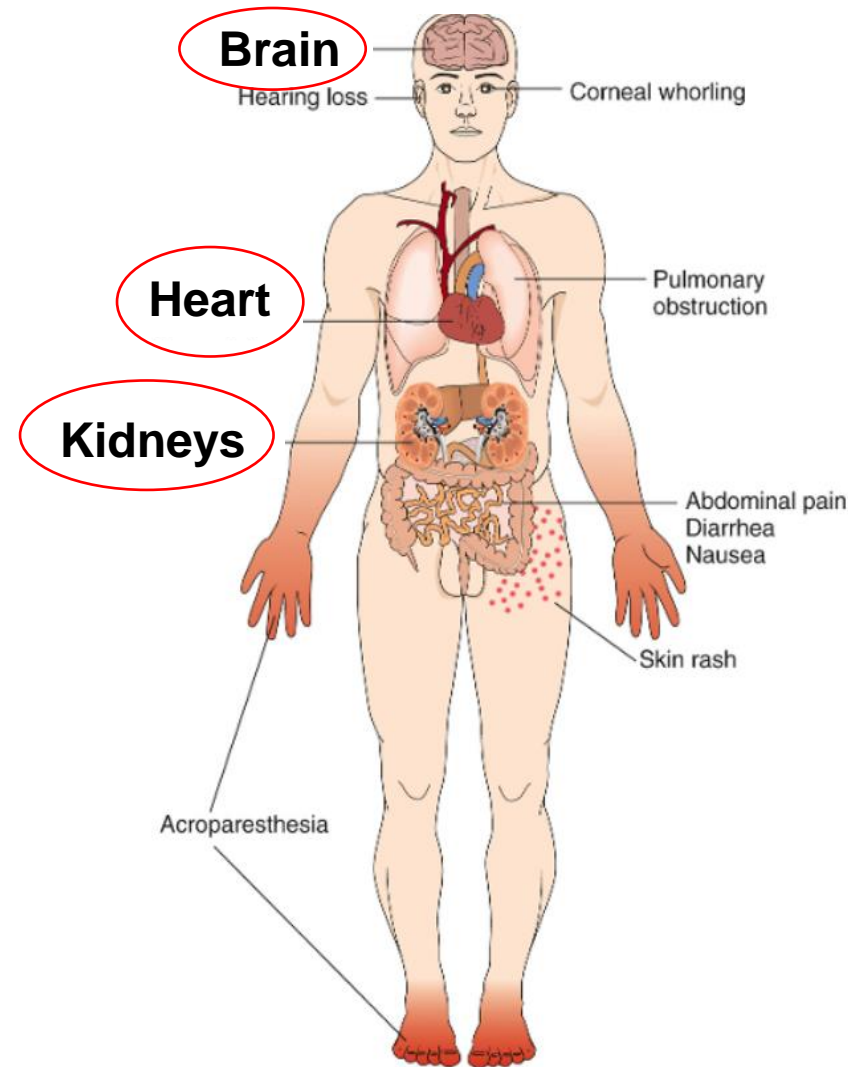
- Fabry is an inherited disease, which means it is a disease that runs in families.
- Fabry is caused by an altered gene on the X chromosome, the **GLA gene**. The GLA gene provides instructions for making the **alpha galactosidase enzyme**.
- Over 1,000 different alterations of the GLA gene can cause Fabry disease.
 - More severe gene alterations lead to the classic, more severe form of disease.
 - Less severe alterations lead to milder (later onset) disease.

Fabry is a heterogeneous inherited disease

- Fabry is a heterogeneous disease, which means it affects people differently.
- Males have only 1 X-chromosome. Females have 2 X-chromosomes, only 1 of which is working in each cell. So, only about ½ of the cells in females are abnormal, while all are abnormal in males.
- Males with classic Fabry disease have very high risks of injury to vital organs.
- There is no perfect relationship between the gene abnormality and disease severity within a given family.



Fabry can affect multiple organs



What are the signs and symptoms of Fabry disease?

Skin

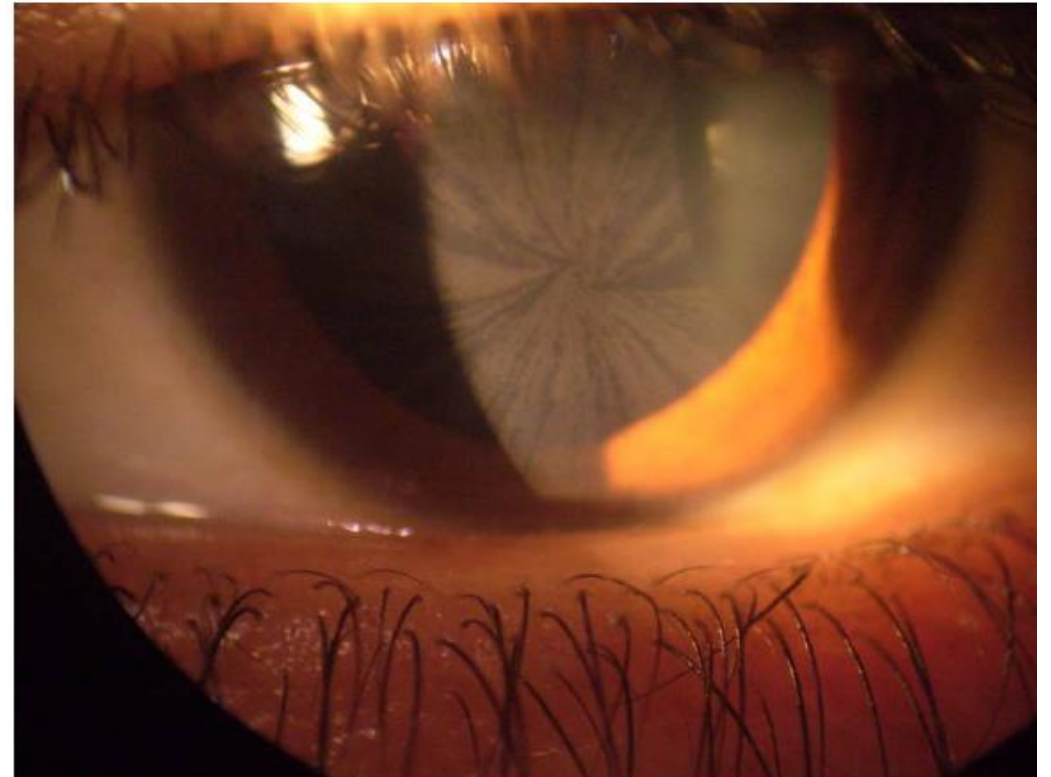
- **Dark red/purple raised dots that do not blanch (fade or disappear) with pressure**
- Rash begins in adolescence or young adulthood.
- Happens in all classical males and 30% classical females
- May not appear in milder cases
- **Rash is diagnostic.**



Rashes appear on buttocks, groin, umbilicus and upper thighs

Eyes

- Whorled or spoke-like pattern called “**cornea verticillate**”
- Present in almost all classic males and 70% of classic females; **present early**
- Does not impair vision
- **Cornea verticillate is diagnostic.**



Neurological complications

- **Acroparesthesia – pain mainly in hands and feet**
 - Due to nerve damage
 - Begins in childhood
- **Pain crisis induced by exercise, fever and hot weather**
 - Patients avoid exercise
- **Deafness**
 - One or both ears
 - Sudden or gradual
- **Decreased sweating, heat intolerance**
 - Due to injury to small vessels and nerves
 - Production of tears and saliva are also reduced in 40%
- **Stroke or transient ischemic attack (TIA)**
 - Clotting of small arteries in the brain

Gastrointestinal complications

- Abdominal pain
- Diarrhea
- Nausea

GASTROINTESTINAL COMPLICATIONS OFTEN HAVE
A MAJOR NEGATIVE IMPACT ON QUALITY OF LIFE.

Cardiac complications

- **Enlargement of the left side of the heart (hypertrophy) /scarring of the heart (myocardial fibrosis)**
 - Usually in patients older than 30 years
 - Can lead to heart failure and death
 - Females often have scarring on MRI without heart enlargement
- **Electrocardiographic (EKG) abnormalities**
 - Problems with heart rhythm
 - Sudden death
- **Heart valve abnormalities**

**CARDIAC COMPLICATIONS ARE THE LEADING
CAUSE OF DEATH IN FABRY DISEASE.**

Cardiac variant of Fabry disease

- Residual but reduced GLA enzyme activity
- Presents later in life, no other manifestation
- Under-recognized
- In one study, 3% (7 of 230 men) with enlarged left side of the heart had low GLA enzyme activity.

Psychological complications

- People with Fabry are at higher risk for:
 - **Anxiety**
 - **Depression**
 - **Suicide**

How is Fabry disease diagnosed?

Diagnosis of Fabry disease

- Family history; new mutations 5%
- “Classic” males: GLA enzyme activity <5% (usually <1%) of normal; DNA
- “Classic” females: low/normal Fabry enzyme activity; DNA, kidney or heart biopsy
- Typical skin and/or eye findings – confirmed with above or family history

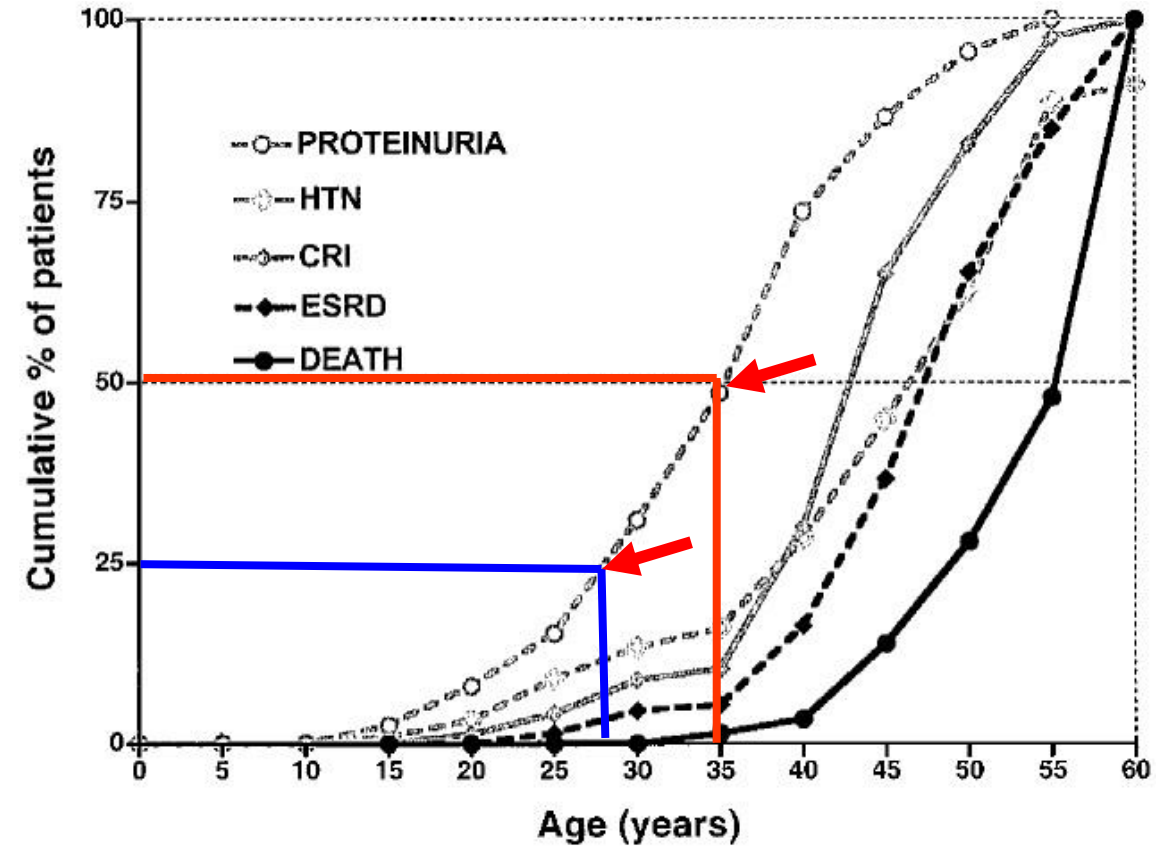
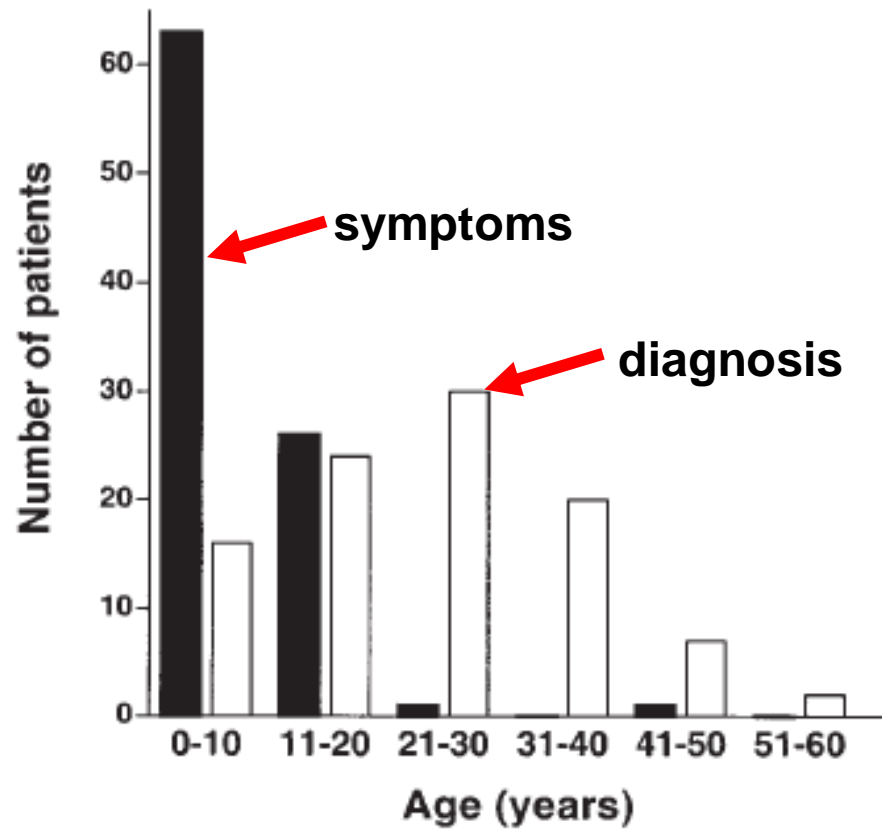
Timing of diagnosis

- Age of diagnosis including those with family history (~50%)
 - 16 ± 13 (0-40) years
- Age of diagnosis with no family history (~50%)
 - 28 ± 12 years
- Diagnosed by:
 - Dermatologist (28%)
 - Ophthalmologist (26%)
 - Neurologist (23%)
 - Nephrologist (19%) – usually as an unexpected biopsy finding; screening male dialysis – Tx (transplant) patients?

Timing of diagnosis

DIAGNOSIS IS RARELY MADE BY PEDIATRICIANS OR INTERNISTS.

Diagnosis is often late



Early diagnosis is important

- The earlier you find out you have Fabry disease, the sooner you can track your symptoms and learn how to manage the condition.

How does Fabry disease affect the kidneys?

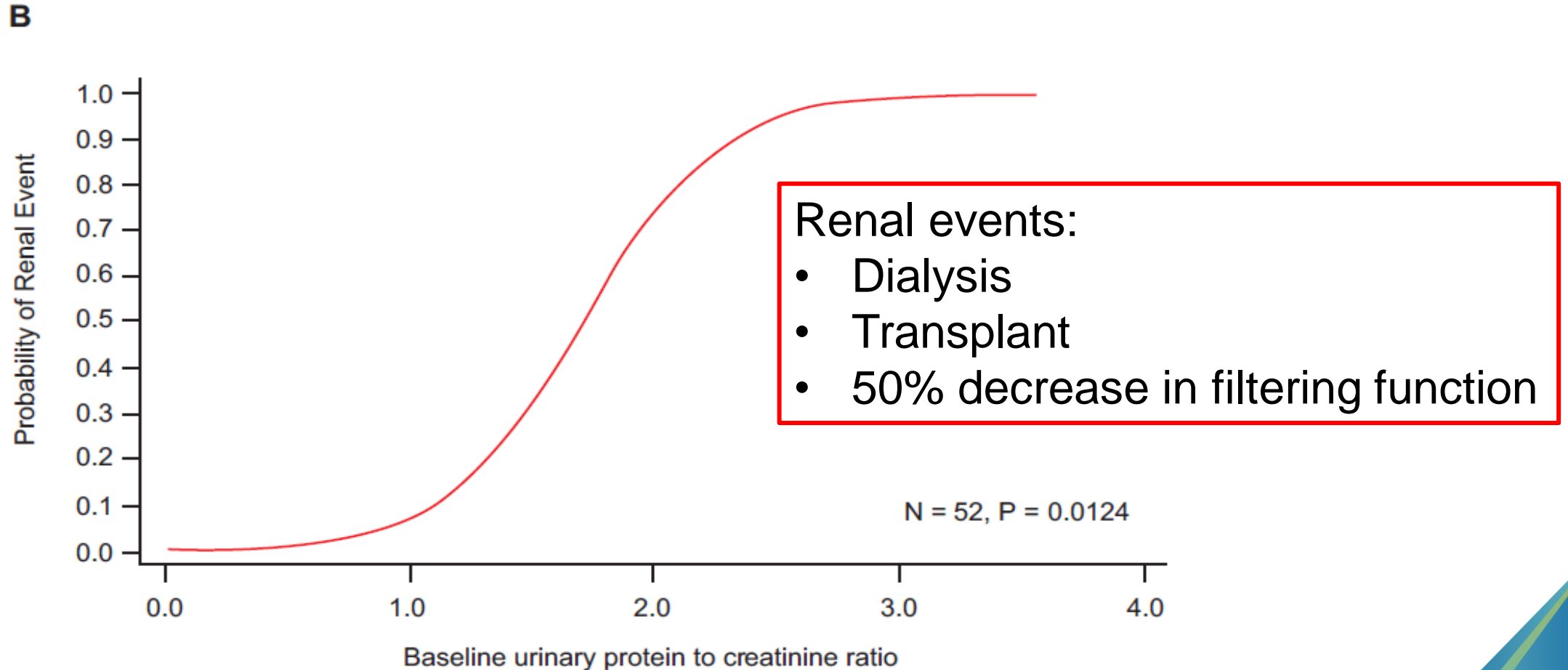
How Fabry leads to kidney damage

- Alpha-GAL is an enzyme your body makes to break down GL-3, a fatty substance in your cells.
- People with Fabry disease do not make enough alpha-GAL enzyme to break down GL-3.
- Over time, GL-3 buildup in the kidneys can damage kidneys.

Natural history of Fabry renal disease

- The first sign is an increase in urinary total protein (all proteins in the urine) or albumin.
 - This can occur as early as 14 years old with peak onset in the 40s.
- Age of chronic kidney disease (CKD): 42 (19-54)
- Total kidney failure or end-stage renal disease (ESRD) develops in most classic males
 - ~10 years after the onset of proteinuria (protein in the urine)
 - 4 ± 3 years from onset of stage 3 CKD (eGFR = 30-59; loss of >40% of kidney filtering function)
- ESRD can occur as early as 21 years old with peak incidence in the 50s.
- More recent registry data found males and females with preserved renal function into their late 60s.

Males are more likely to have a renal event as proteinuria increases



Effect of proteinuria on filtering function loss in untreated adults

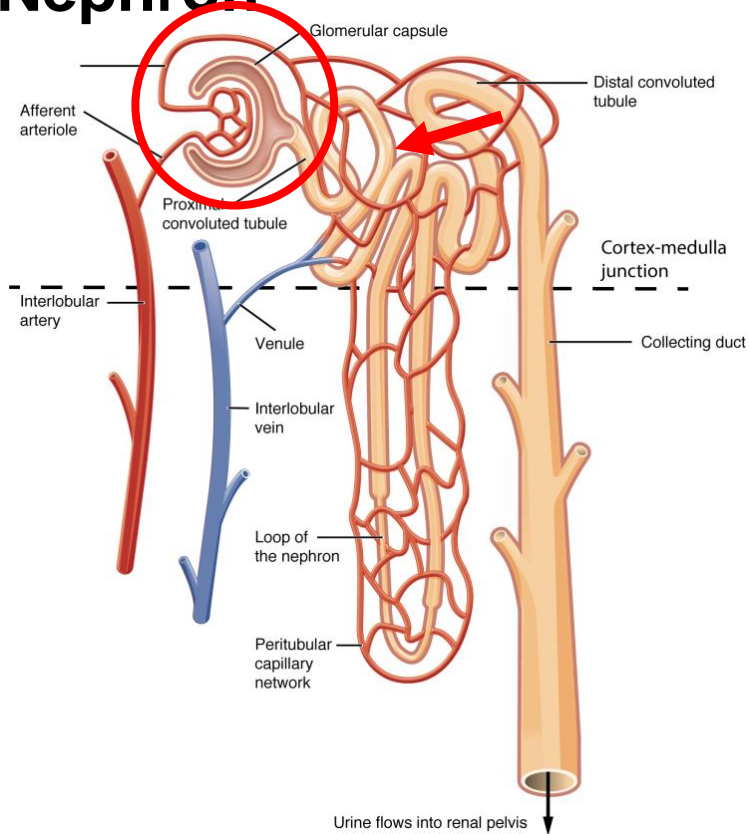
Rate of filtering function loss ranked by quartiles; lowest 25% to highest 25%

	Males		Females	
	PCr	GFR loss	PCr	GFR loss
3 rd	0.8-1.5	-3.3%/yr	0.3-1.2	-0.7%/yr
4 th	1.5-7.3	-5.6%/yr	1.2-6.4	-1.3%/yr

URINE PROTEIN LEVELS IN MALES AND FEMALES HAVE VASTLY DIFFERENT MEANING.

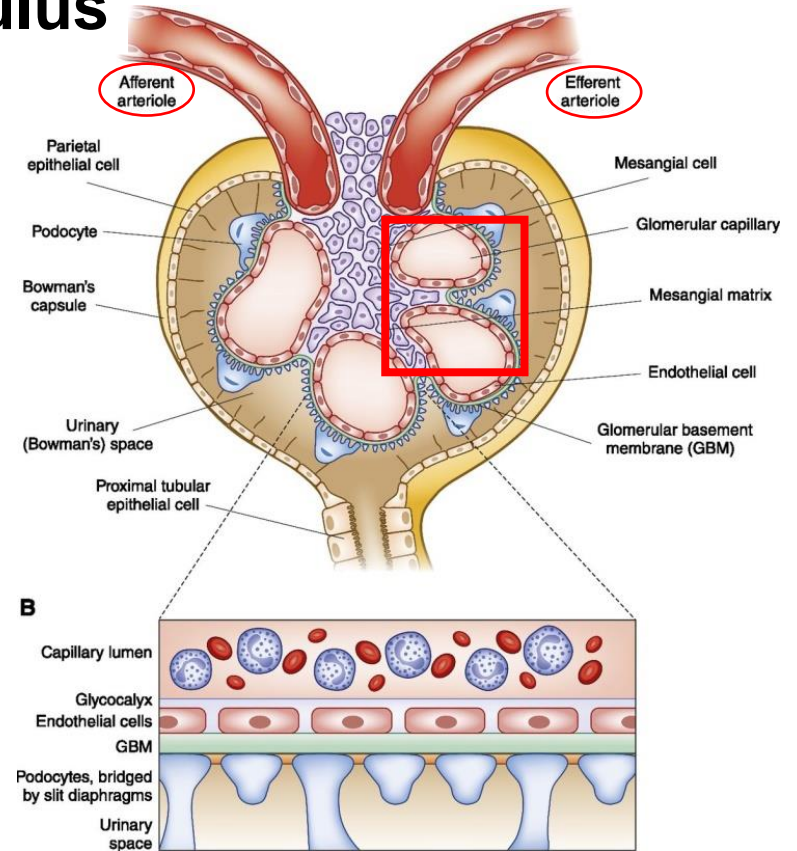
Basic kidney structure

Nephron



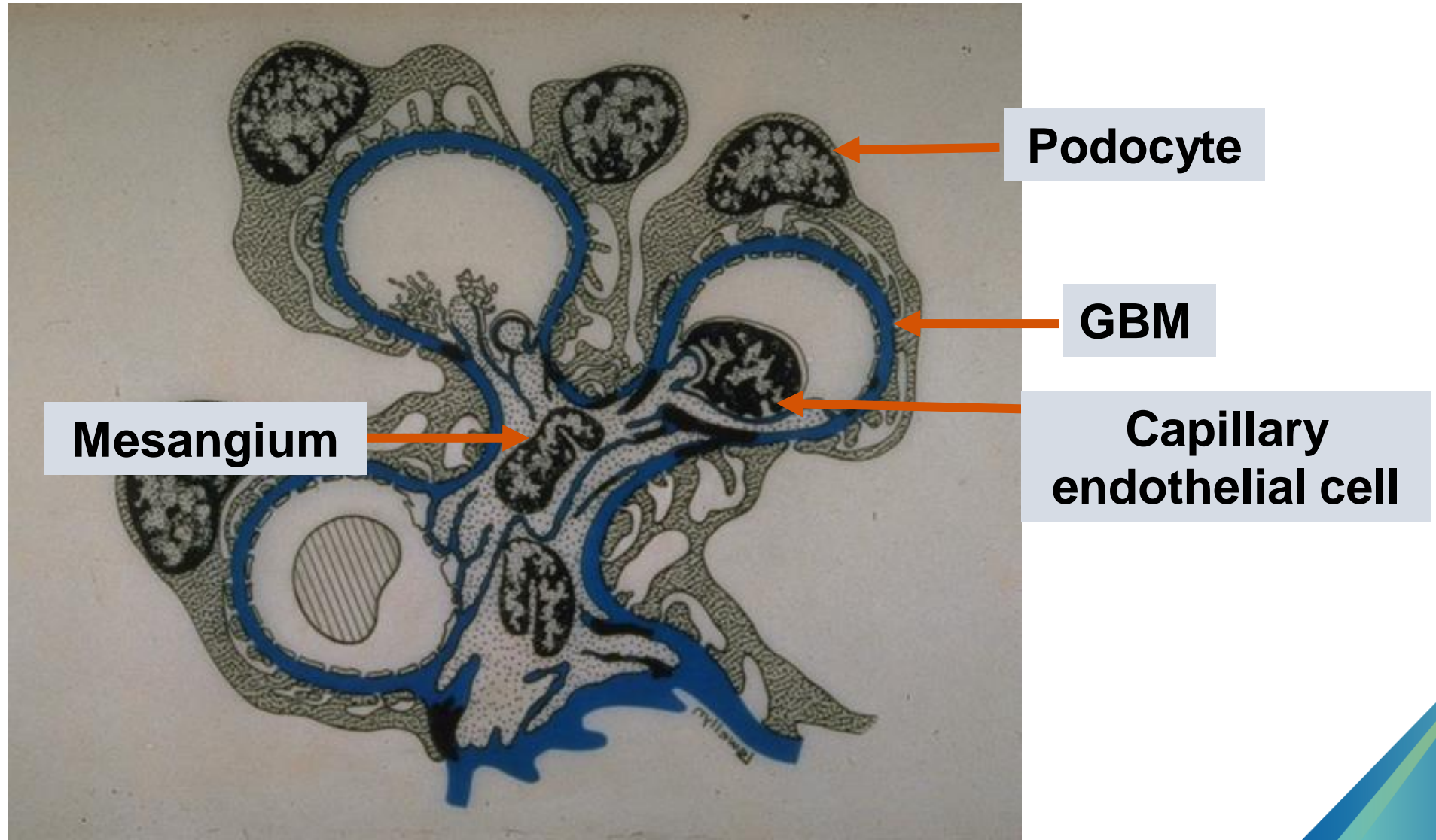
Source: Open Oregon State Education: chapter/25; anatomy of the nephron

Glomerulus



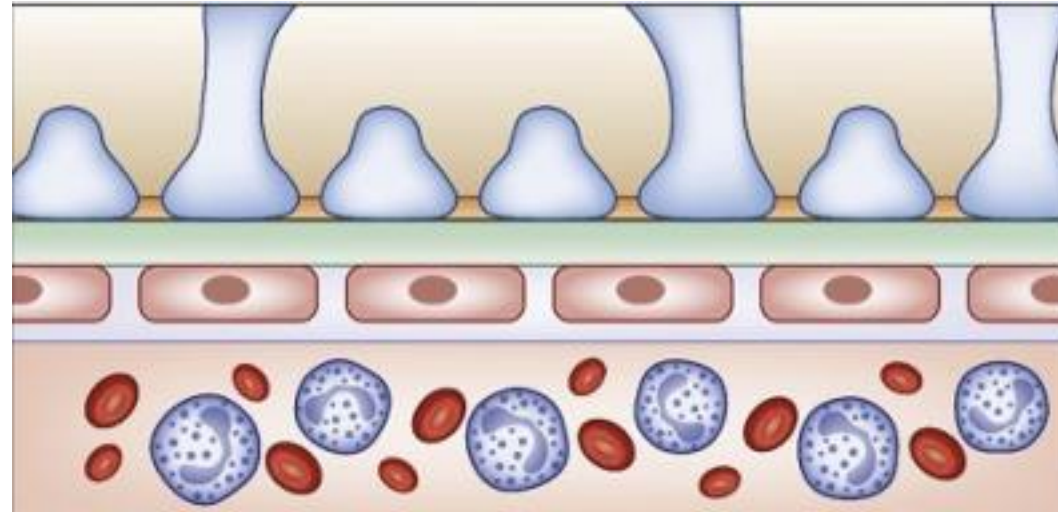
Source: CJASN 2016, 11 (9) 1664-1674

Basic kidney structure



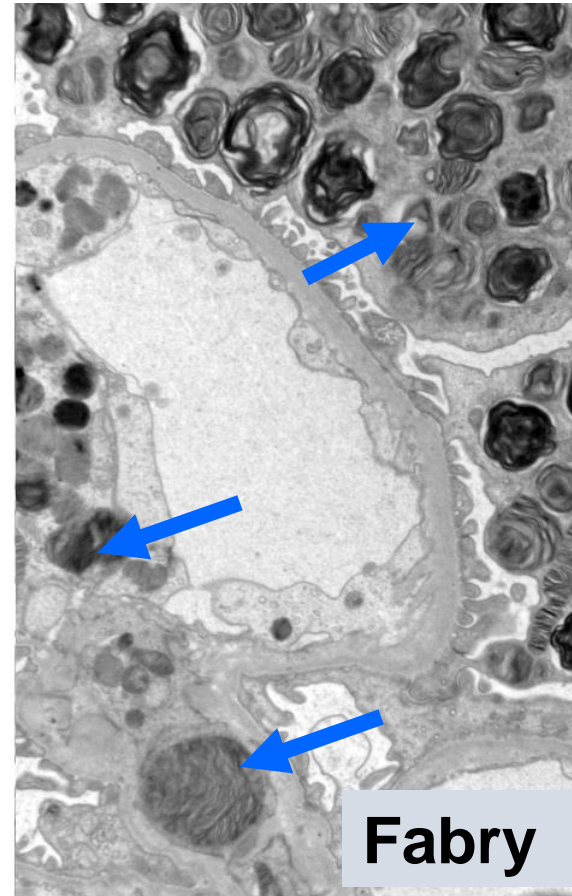
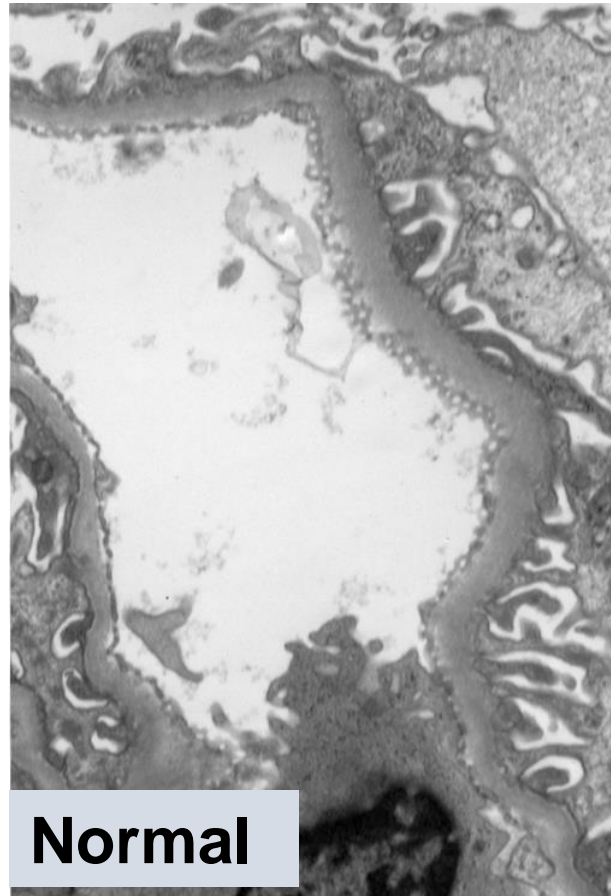
Basic kidney structure

Podocyte
GBM
Endothelial cell
Blood

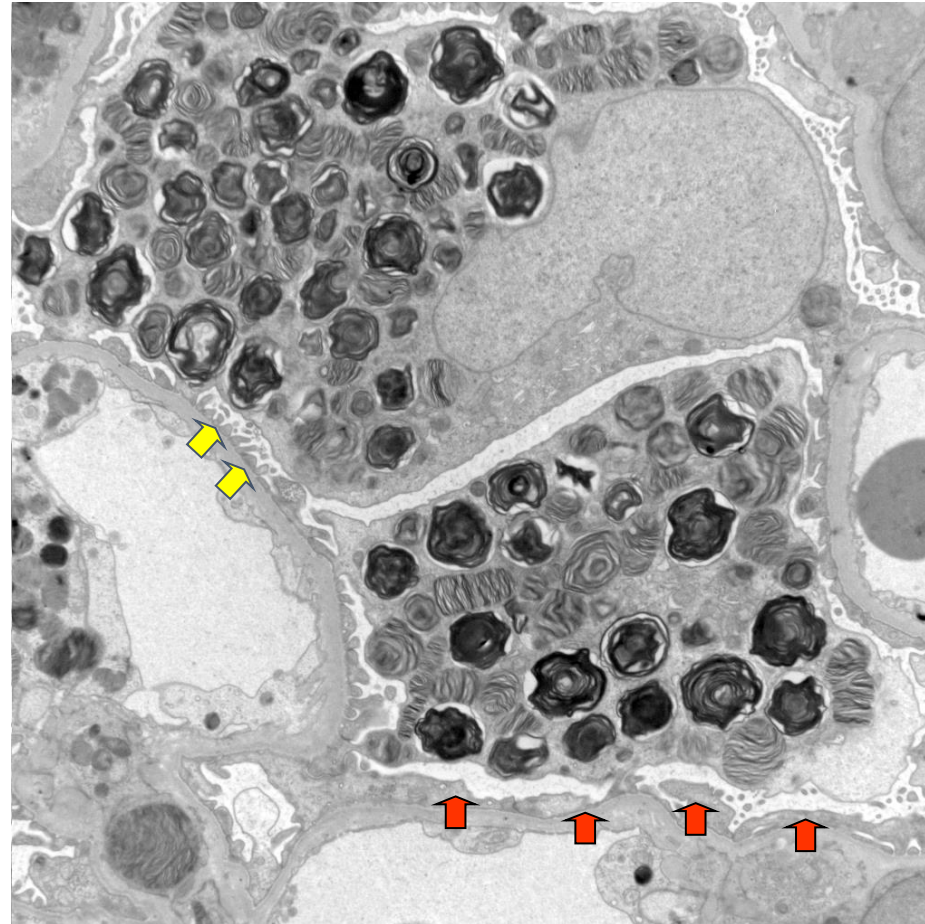




Electron microscopy



Electron microscopy



Glomerular GL-3 inclusions in children

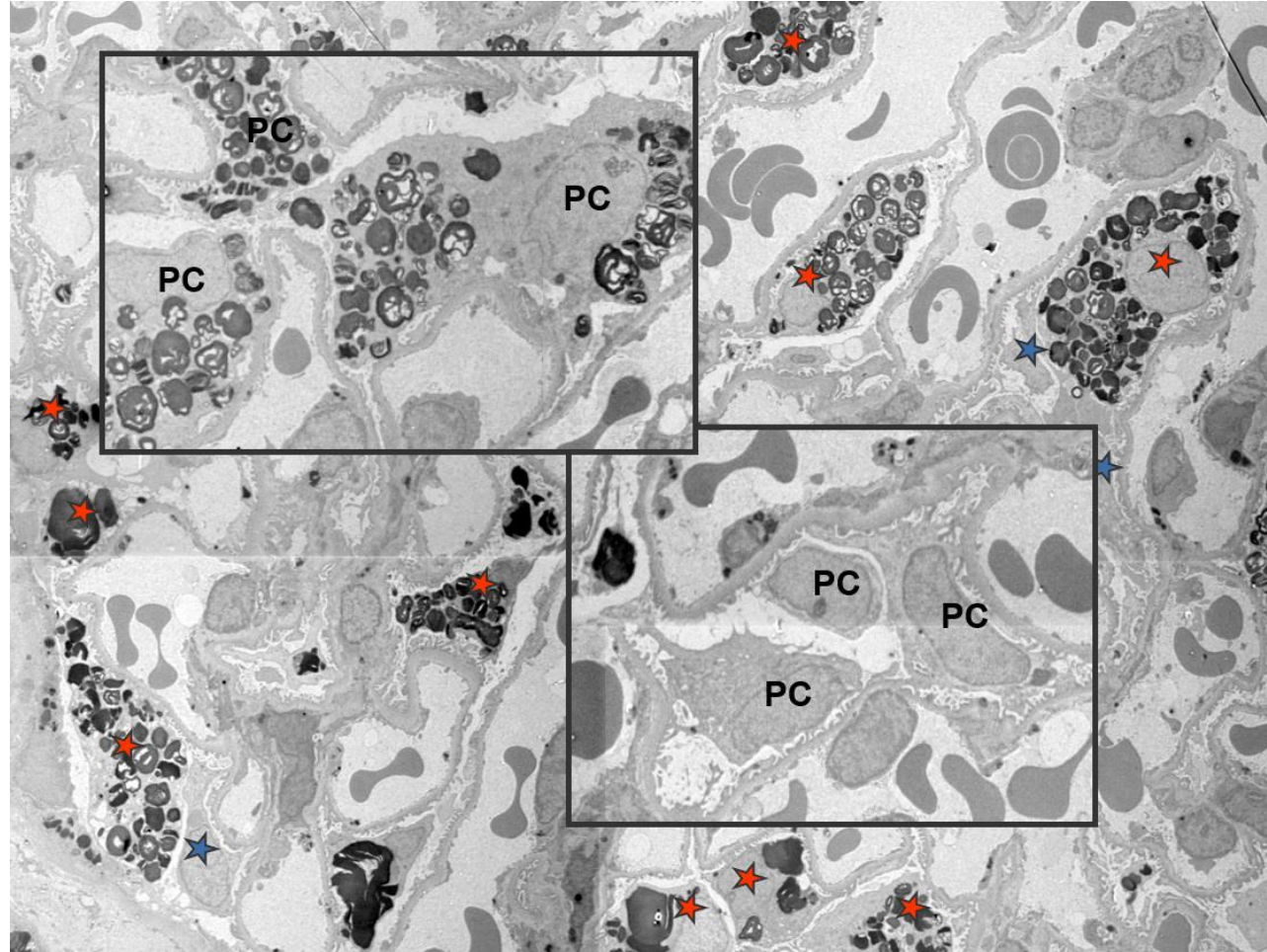
- Children 4 –19 years of age
- 8 boys and 6 girls
- GL-3 inclusions increased with age in podocytes BUT not in endothelial cells or mesangial cells.
- GL-3 inclusions in podocytes correlated with proteinuria but not with inclusions in the other cells.
- Podocyte foot process width correlated with proteinuria

Progressive podocyte loss with age in males with classic Fabry disease

Research findings:

- Podocytes replicate very poorly, if at all
- In 35 untreated males with classic Fabry disease ranging in age from 4 to 60 years, we found a progressive decrease in numbers of podocytes in glomeruli with increasing age.
- Podocyte loss is associated with scarring of glomeruli, proteinuria and loss of filtering function.

Podocyte mosaicism in females with Fabry disease



Podocyte mosaicism in females with Fabry disease

Research findings:

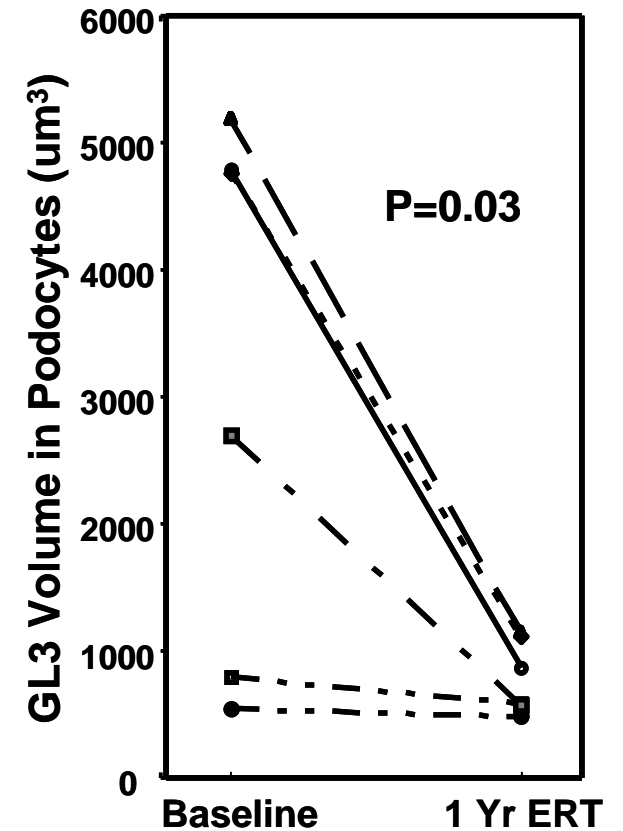
- An average of 57% of podocytes in females had no inclusions.
- Virtually all podocytes in males had inclusions.
- In podocytes with inclusions, the amount of inclusions was virtually identical in F and M, consistent with an all or nothing phenomenon.
- The % of podocytes with inclusions decreased with increasing age in females, consistent with a survival advantage in the non-Fabry podocytes.

How are people with Fabry disease treated?

Podocyte GL-3 inclusions decrease in adult males following 1 year of enzyme replacement therapy (ERT)

Research findings:

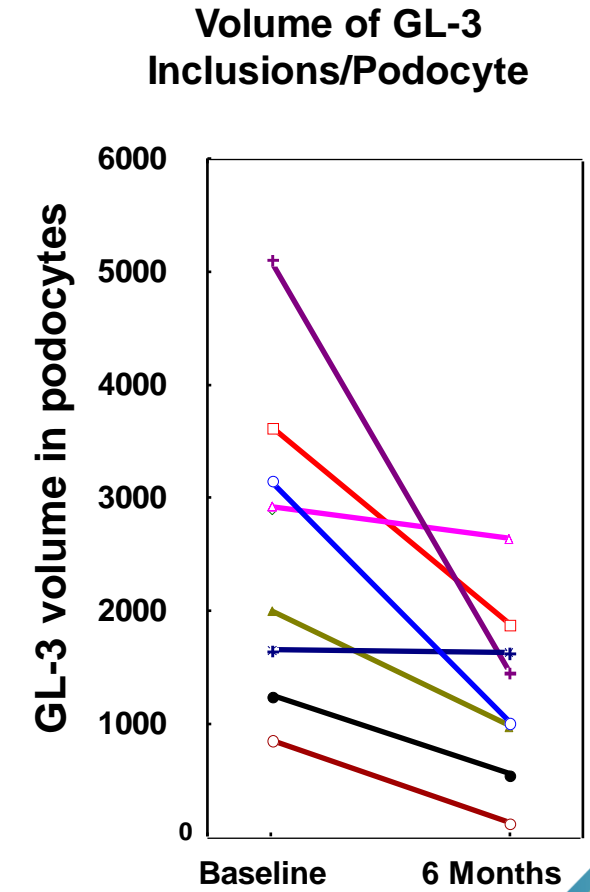
- We studied kidney biopsies before and after ~1 year of ERT from 6 adult male Fabry patients.
- Inclusion volume per podocyte decreased from baseline in all.
- Reduction in inclusion volume/podocyte was greatest in biopsies with greater inclusion volume at baseline.
- Reduction in inclusion volume/podocyte correlated with the reduction in podocyte size from baseline to 1 year.
- Reduction in inclusion volume/podocyte correlated with the reduction in podocyte foot process width.



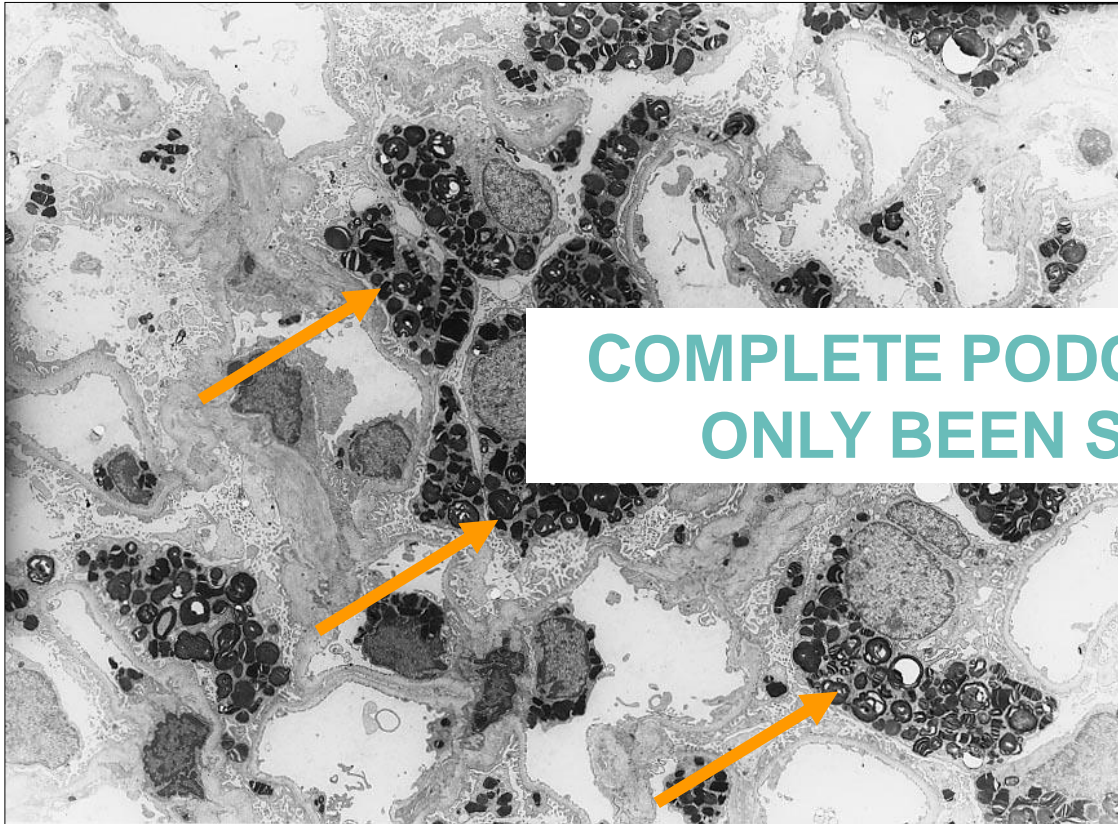
PC GL-3 reduces in adults males after 6 months of Migalastat

Research findings:

- We studied kidney biopsies before and after 6 months of Migalastat from 8 adult males Fabry patients.
- Inclusion volume per podocyte decreased from baseline in 7 and was stable in 1.
- Reduction in inclusion volume/podocyte correlated with the reduction in podocyte volume.
- Reduction in inclusion volume/podocyte correlated with the reduction in podocyte foot process width.



Age of treatment institution matters



Baseline (age 7 years)



5 years ERT (1 mg/kg/2w)

COMPLETE PODOCYTE GL-3 CLEARANCE HAS ONLY BEEN SEEN IN YOUNG CHILDREN

Novel Fabry disease treatments

- Substrate reduction therapy
- Gene therapy

Fabry disease treatment team

- It can take a team of specialists to help manage your symptoms.
- Your care team may include a:
 - Cardiologist (heart doctor)
 - Neurologist (nervous system doctor)
 - Nephrologist (kidney doctor)
 - Gastroenterologist (digestive system doctor)
 - Audiologist (ear doctor) or otolaryngologist/ENT (ear, nose and throat doctor)
 - Psychologist, psychiatrist or mental health counselor

How does Fabry disease affect families?

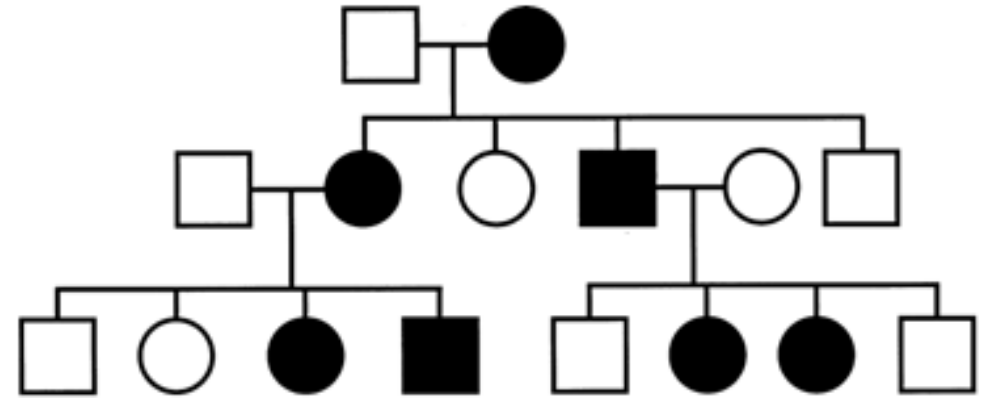
Fabry disease runs in families

- When one person has Fabry, an average of five other family members (including siblings, children, parents, aunts, uncles, and cousins) may also be affected.
- If you or someone in your family is diagnosed with Fabry, it is important for other family members to talk to their doctor about being tested.



Who is at risk?

- Talk to your family about how Fabry disease is passed on.
- Draw up a medical family tree to find out who is at risk.
- Remember, genetics is not a choice, it just is. There is no fault and there is no blame.



Everyone responds differently

Some are very proactive in seeking help for themselves and family members. These are the ones doctors have contact with.



Some don't want to know or are in denial. These are the ones doctors need family help to reach!

Discussing Fabry: Dealing with denial

- **Guilt may be a paralyzing block to acceptance**
- Be patient, it may take time.
- Point out the positive aspects of care and treatment.
- Discuss your concerns about lack of action for oneself and other family members.
- Point to examples from your own experiences or those of others you know about.



**“I look healthy
and my
children are
perfect”**

Tips for Fabry patients and caregivers

- Build a strong support network.
- Find people you can talk to, share experiences with and learn from. This breaks down the feelings of isolation and loneliness.
- Make sure to take care of yourself.
- Consider talking to a mental health professional.

Q & A

**If you have a question for the speaker:
Please type it into the Q&A box in your control panel.**

Thank You

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