Eyes and the nephrologist

Ms A [born 1988]

- April 2005 Ankle oedema
  Urinalysis : Prot 3+ Blood 3+
  Albumin 19g/L
  Creatinine 59umol/L

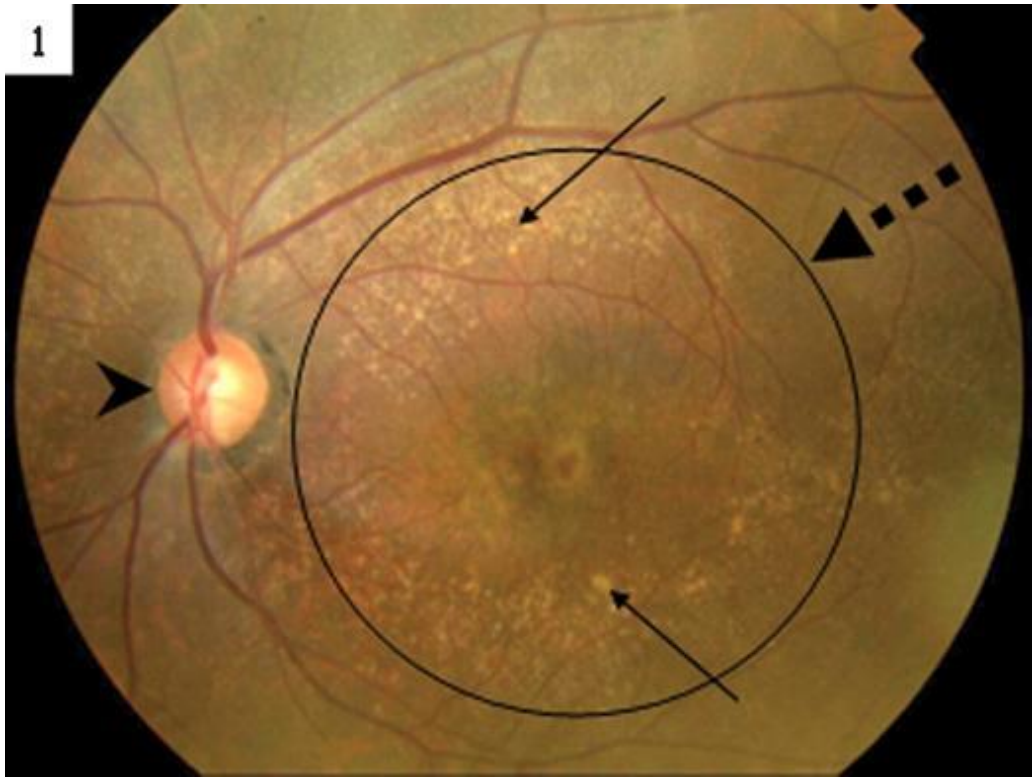
Eye in a patient with a Nephrotic Syndrome

What abnormality is shown?

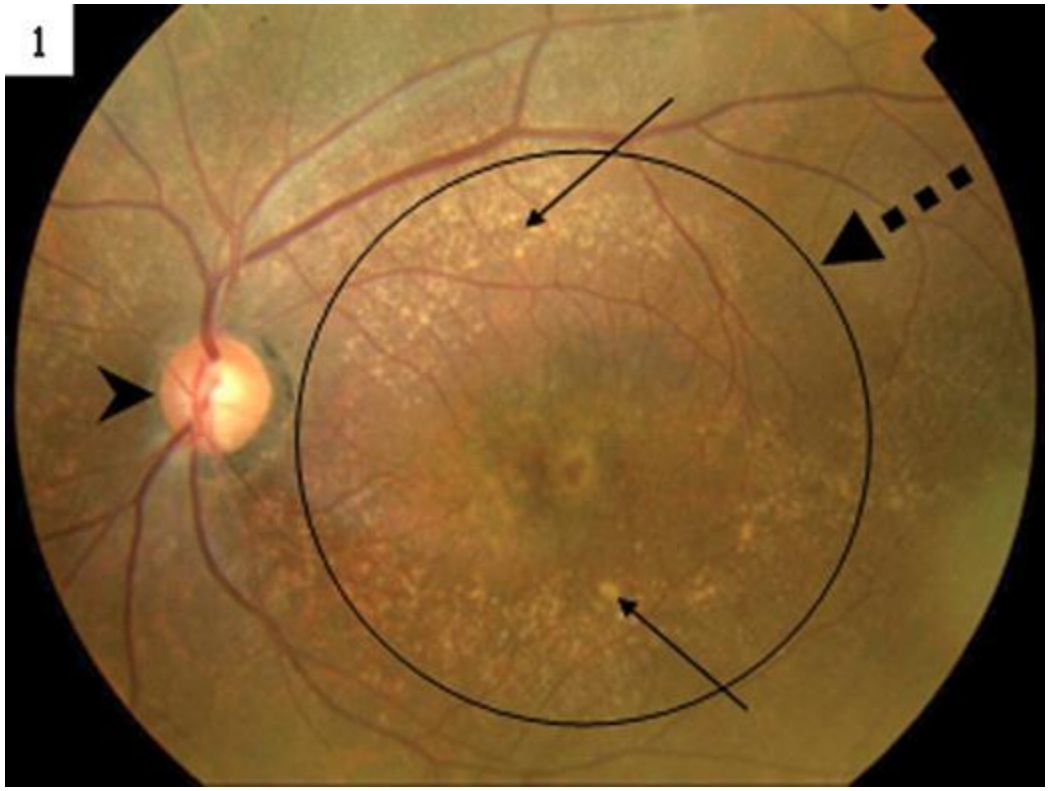
What other clinical features might you look for in this patient?

What investigation would you request?

What is the likely diagnosis?



Eye in a patient with Dense Deposit Disease (mesangiocapillary GN Type 11)

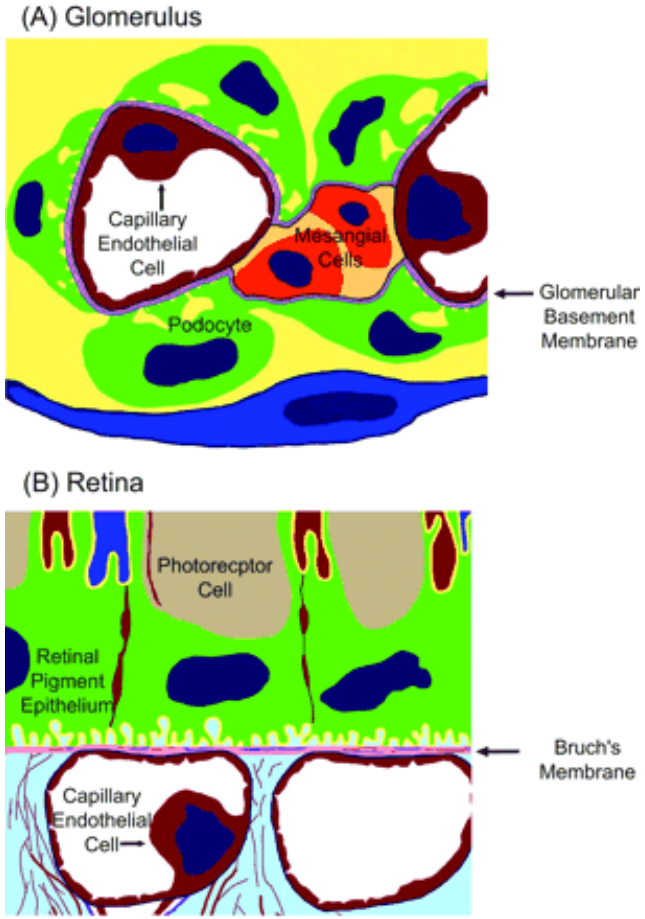


drusen

Dense deposit disease

- Haematuria and proteinuria, renal impairment by early adulthood.
- Facial and shoulder girdle lipodystrophy, C3 nephritic factor and low C3 levels may occur.
- Some forms are inherited with mutations and disease haplotypes identified in the complement Factor H (*CFH*) gene.
- The intramembranous GBM deposits and retinal drusen have an identical composition. Vision may be affected by retinal complications such as neovascular membranes.

Drusen in Mesangiocapillary GN

- 

Schematic drawings that compare the fenestrated capillary networks in the glomerulus (A) and retina (B). The glomerular podocytes are similar to the retinal pigment epithelial cells, both of which are separated by a basement membrane (either the glomerular basement membrane [GBM]or Bruch's membrane, respectively) from the fenestrated capillary endothelial cells of the glomerular capillary tufts and the choriocapillaris. Both basement membranes are sites of electron-dense deposits in membranoproliferative glomerulonephritis type II (MPGN II).

'Eye disorders associated with chronic kidney disease'

- RESULTS Among the 1936 participants who were photographed, 1904 (98%) had assessable photographs in at least one eye. Eye pathologies that required follow-up examination by an ophthalmologist were identified in 864 (45%) of these 1904 participants. These eye pathologies included, among others, retinopathy (diabetic and/or hypertensive), a finding that was observed in 482 (25%) of these 1904 participants. Three percent (65 participants) of the 1904 participants had serious eye conditions that required urgent follow-up and treatment. Lower estimated GFR and cardiovascular disease were associated with greater eye pathology.

  Chronic Renal Insufficiency Cohort Study [2012]

Eye and kidney disease

- Vasculopathy
  - *Hypertension
  - Diabetes
  - Thrombotic microangiopathy
  - Vasculitides (eg. Wegener's and necrotizing scleritis)
  - Non-arteritic anterior ischaemic optic neuropathy [NAAION]
- Cataract
  - Hypocalcaemia
  - Steroids
- Infection
  - Viral / bacterial
- Others

Mrs B (born 1937)

PH Hysterectomy for fibroids

Nov 2007 Painful hands

BP 117/76; Urinalysis Neg

Creat 78µmol/L

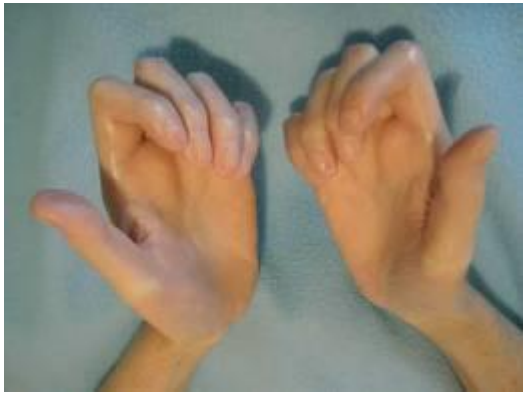
Positive ANA; Negative ENA

Diagnosis:

1. Osteoarthrosis
2. ? Connective tissue disorder

Mrs B (Contd)

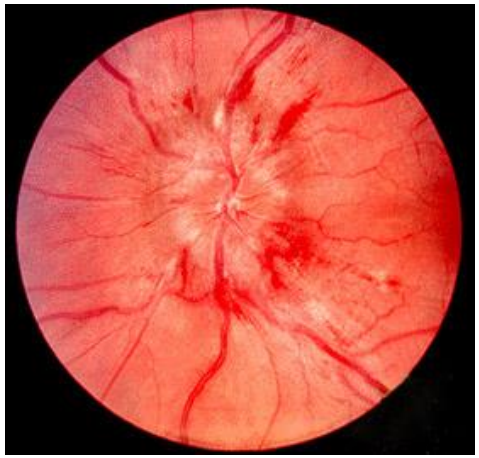
- 03/2008
  Raynauds
  CXR Normal; ECHO Normal
  Positive ANA; Other Ab's Negative
  Rx Methotrexate
- 08/2008
  Scleroderma
  BP 133/89
- 01/2009
  BP 156/85
  Creatinine 104µmol/L
  Rx Lisinopril
- 04/2009
  Creatinine 92µmol/L
  BP 126/70
  Lisinopril stopped
- 02/2010
  Creatinine 92µmol/L
  BP ?



Mrs B (contd)

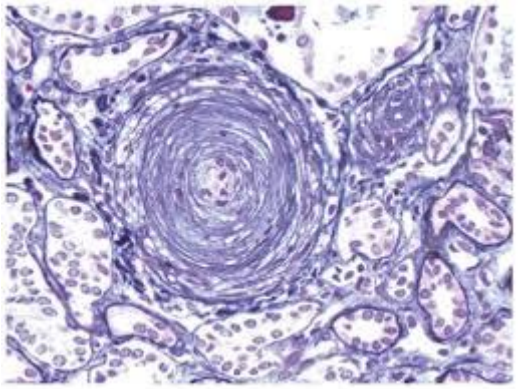
- 04/2010 Breathlessness; Headache; Thirst
  BP 222/124; Papilloedema

  Creat 490
  Pulmonary oedema



Mrs B (contd)

- 04/2010 Breathlessness; Headache; Thirst
  BP 222/124; Papilloedema
  Creat 490
  Pulmonary oedema
- Rx Labetalol infusion
  Captopril
  Haemodialysis (x4)
- Renal biopsy



Mrs B (contd)

- 07/2010 Exfoliative dermatitis ? captopril
- Now (June 2019) Furosemide 40mg
  Irbesartan 150mg bd
  Nifedipine 10mg bd
- Creatinine 134µmol/L
- <u>Conclusion</u>
  Hypertensive emergency in woman known to have scleroderma which responded to ACEi. Papilloedema important component of the diagnosis.

Eye and kidney disease

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  - Hypertension
  - Diabetes
  - *Thrombotic microangiopathy
  - Vasculitides (eg. Wegener's and necrotizing scleritis)
  - Non-arteritic anterior ischaemic optic neuropathy [NAAION]
- Cataract
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  - Steroids
- Infection
  - Viral / bacterial
- Others

Thrombotic microangiopathy (HUS) Morriston (1985 – 1997)

- 11 patients presented with AKI due to HUS
- All underwent retinal examination:

  5 – No abnormality

  6 – Retinal ischaemic changes (cotton wool spots flame haemorrhages; no papilloedema)

- 5 without retinal changes recovered
  6 with retinal changes reqd longterm RRT
- Those with retinal changes were subsequently found to have complement defects

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  - Steroids
- Infection
  - Viral / bacterial
- Others

Mrs C [Born 1962]

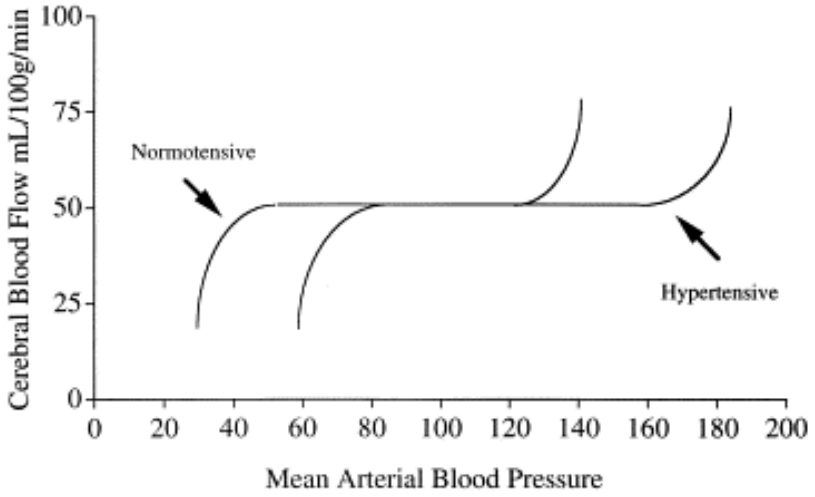
- 1996 Nephrotic
  Mesangiocapillary GN Type 1
- 1999 ERF Rx Satellite unit HD
- 2006 Home HD
- 2006 – 12 BP 110/70
- 2013 onwards BP 75/50
- 2018 Sudden onset loss of vision on right.

Right ocular ischaemic syndrome with secondary rubeosis and glaucoma.

Risk of hypotensive blindness

- Haemodialysis
  Non-arteritic anterior ischaemic optic neuropathy [NAAION]
- Occipital infarction during treatment of hypertensive emergencies.

Impact of autoregulation



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Retinal abnormalities in inherited renal disease

- Organogenesis for eyes and kidneys span the 4^{th} to 6^{th} week of gestation [PAX & WTE1 genes].
- Kidneys and retina share structural features including basement membrane collagen IV protomer composition and vascularity.
- Kidneys and retina are functionally dependent on ciliated cells.

Mutations in PAX & WT1 genes

- PAX genes encode nuclear transcription factors for development of kidney, eye, ear & brain.

  PAX2 mutations: Renal coloboma syndrome with vesico-ureteric reflux.

- WT1 gene necessary for ureteric bud formation and retinal ganglion cell differentiation

  WT1 mutations: Wilms tumour, WAGR, Frasier & Denys-Drash Syndromes

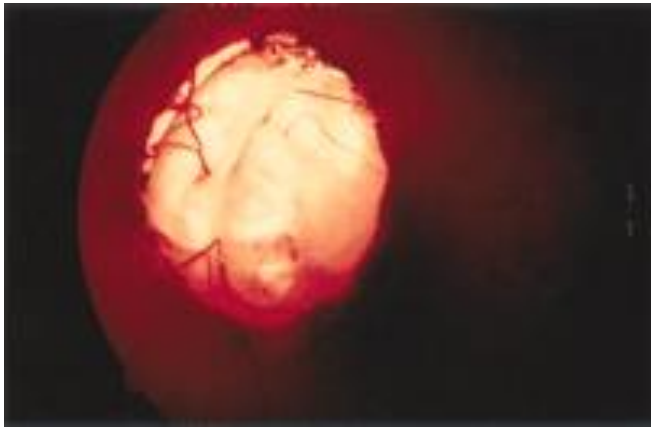
Coloboma

PAX2 mutations
COACH syndrome
CHARGE syndrome

A **coloboma** (from the Greek koloboma, meaning defect) is a hole in one of the structures of the **eye**, such as the iris, retina, choroid, or optic disc.

Renal Coloboma Syndrome

Coloboma involving optic disc and adjacent retina



- Defective closure of the embryonic fissure of optic cup
- Renal dysplasia; Reflux; auditory anomalies
- *Pax2 mutation (transcription factor)*

Renal coloboma Like Syndrome

- No *Pax2 mutations*
- Senior-Loken Syndrome

CHARGE syndrome:
Coloboma; heart abnormalities; choanal atresia; retarded growth; genitourinary abnormalities; ear anomalies

WAGR Syndrome

- Wilms tumour (nephroblastoma)
- Aniridia
- Genitourinary abnormalities (gonadoblastoma).
- Mental retardation

Caused by mutation of the WT1 gene – which encodes a transcription factor that is important in renal development

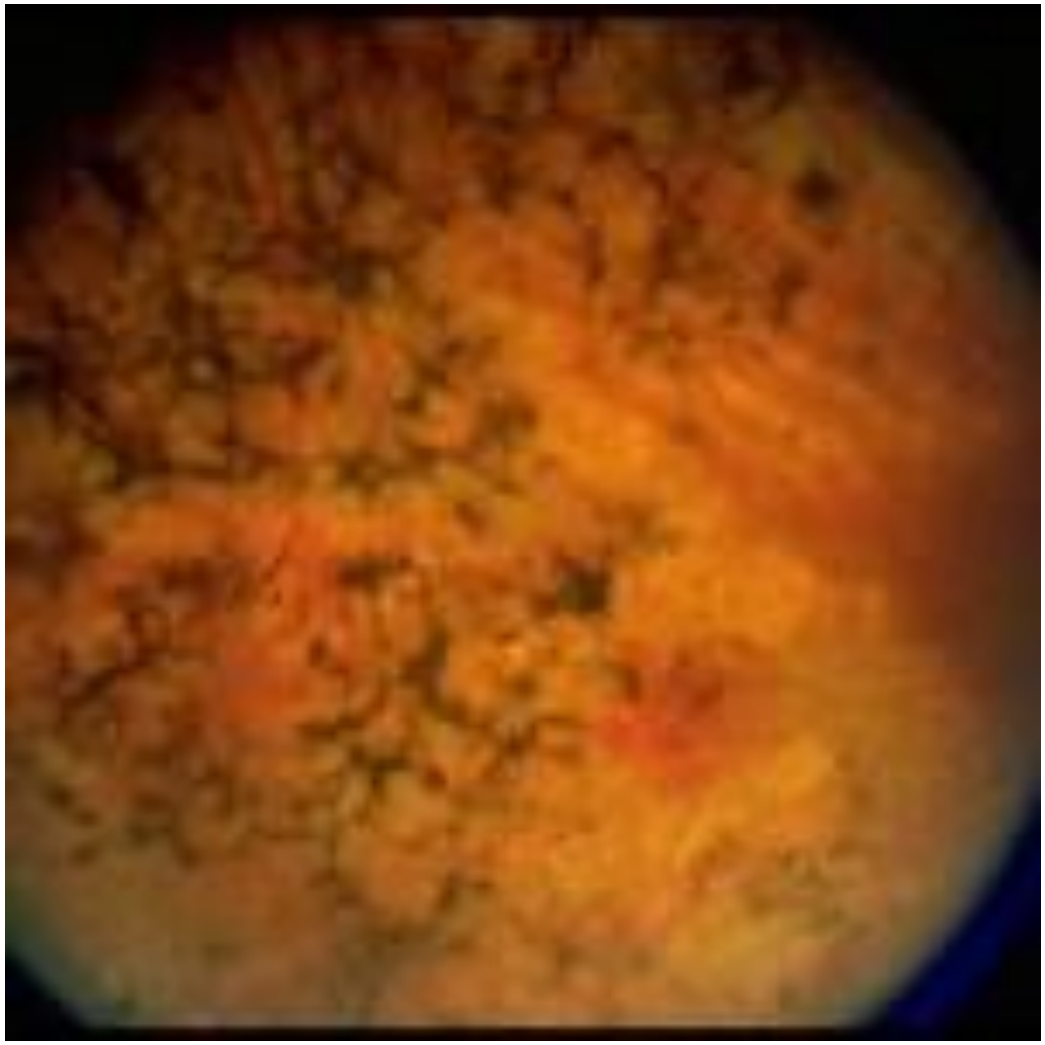
Cilial abnormalities

- Renal epithelial [Podocytes] and retinal pigment epithelial [RPE] cells depend on primary cilia for specialised cell functions.
- Mutations affecting proteins in podocyte cilia result in cystic kidney disease [nephronophisis] and Bardet Biedl Syndrome. The retina is commonly affected, and other clinical features include hearing loss, abnormal limb and digit development, developmental delay, *situs inversus*, liver and respiratory disease, and infertility

Ms D (born 1970)

- Age 17 Pregnant (Creat 134 - 260)
  ? Reflux
- Age 26 Pregnant (Creat 220 -520)
  CAPD
- Age 28 Renal transplant
- Age 30 Night blindness
  BMI 45 Creatinine 120
- Age 49 Blind
  BMI 37 Creatinine 269

Retinitis Pigmentosa



Clinical manifestations of Bardet-Biedl syndrome

- Syndactyly and/or polydactyly
- Truncal obesity
- Retinal dystrophy
- Male hypogenitalism
- Renal calyceal anomalies
- Retinitis pigmentosa
- Mental retardation
- Vaginal atresia
- Diabetes mellitus

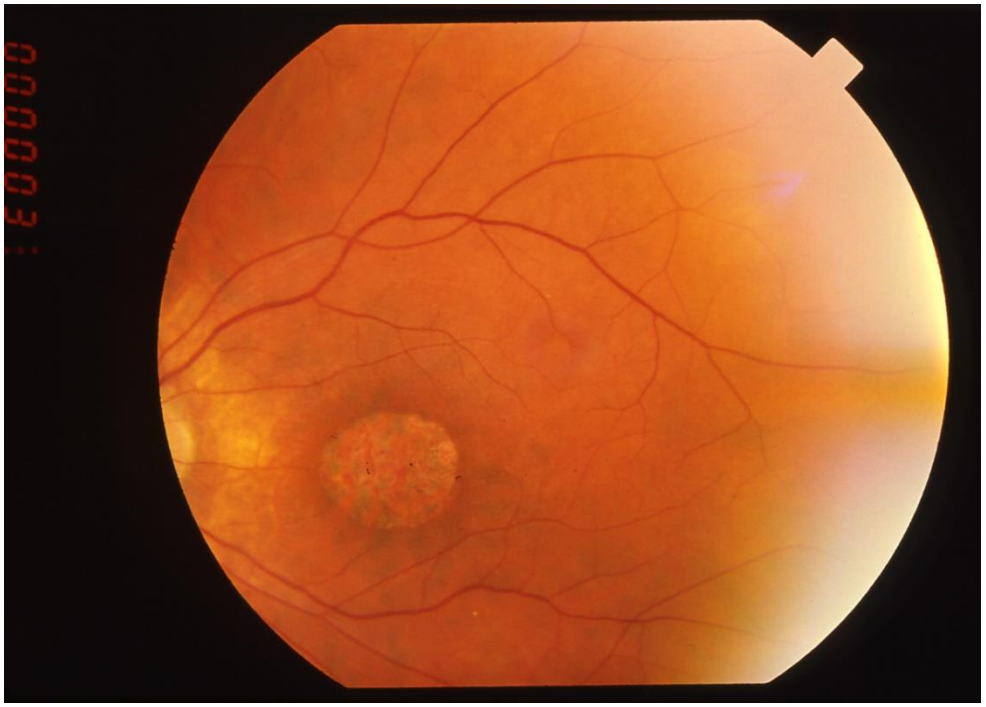
Structural renal abnormalities

- Calyceal clubbing / blunting
- Calyceal cysts / diverticula
- Fetal type lobulation
- Diffuse cortical scarring

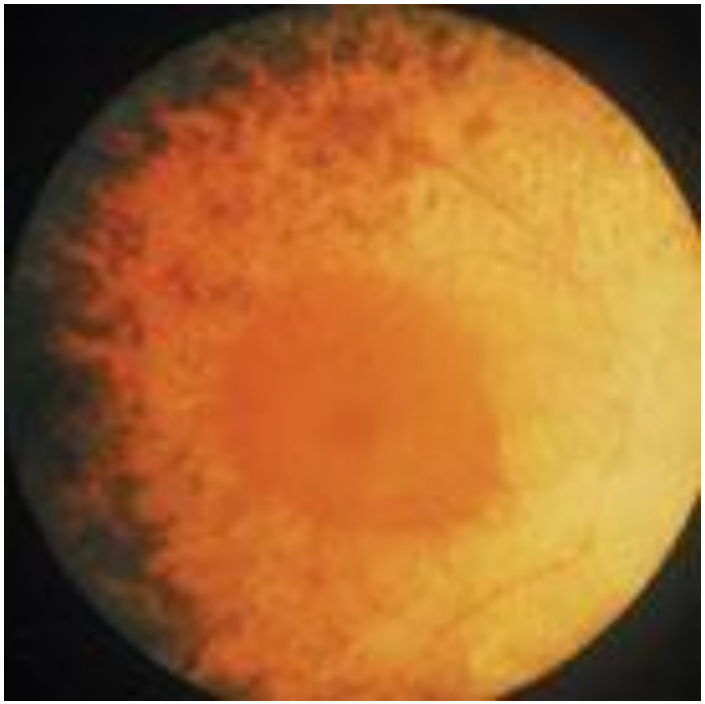
Functional renal abnormalities

- Hypertension
- CKD
- ERF
- Urine concentration defect
- Renal tubular acidosis

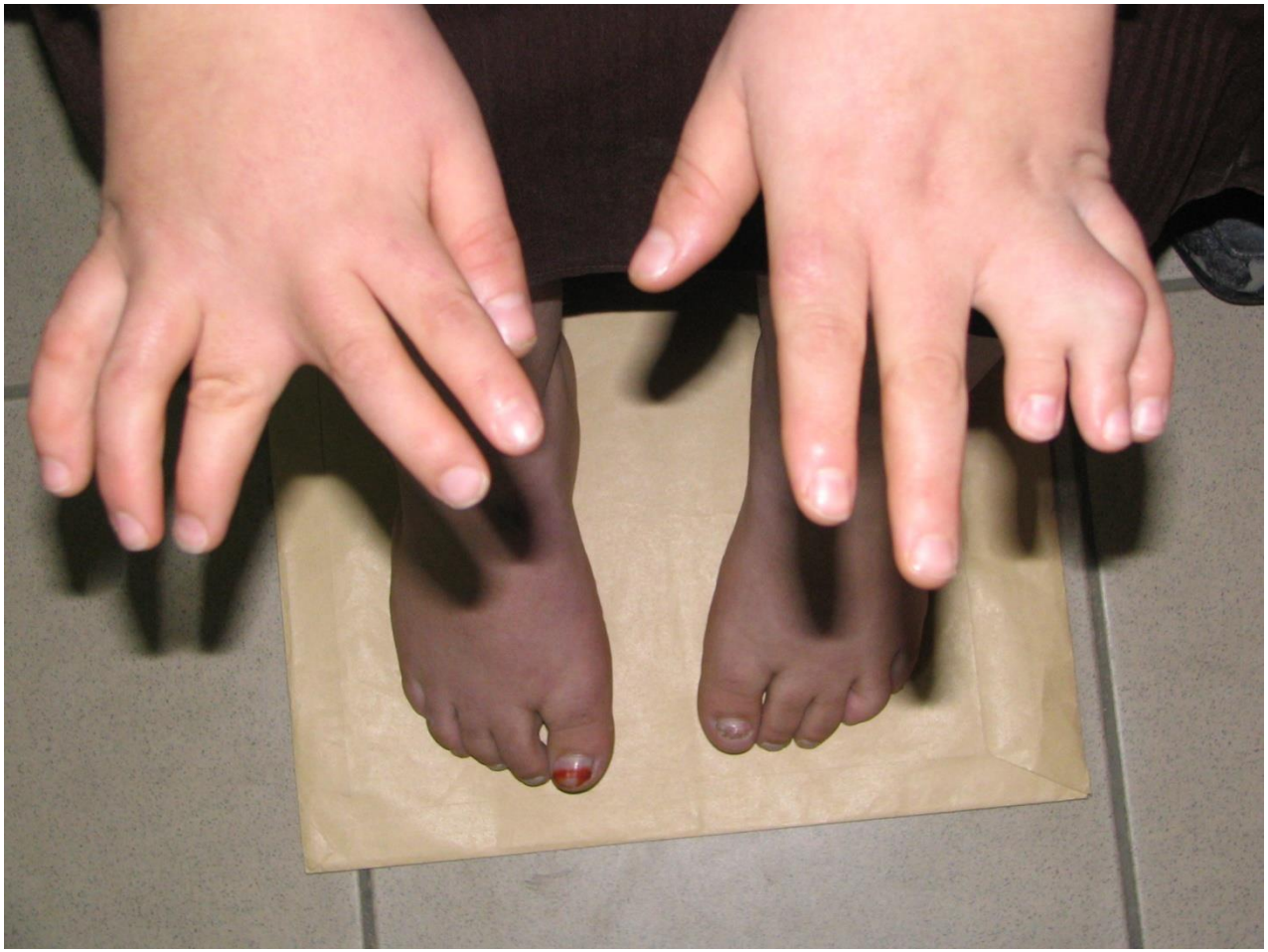
Early changes of retinitis pigmentosa in Bardet Biedl Syndrome



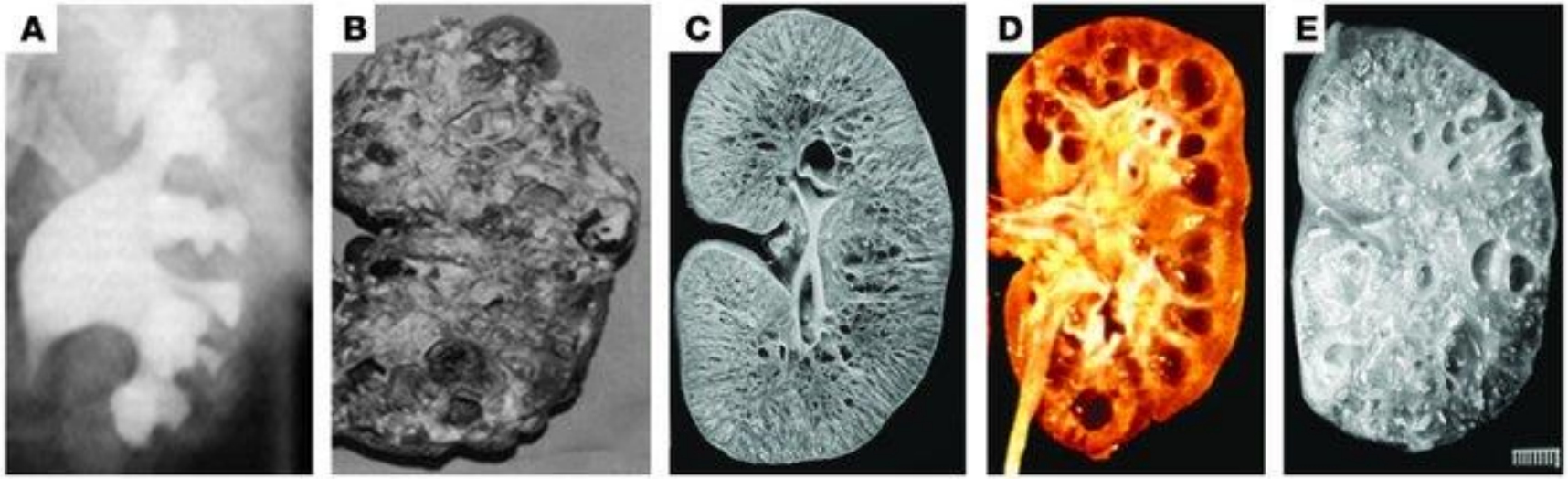
More extensive evidence of Retinitis Pigmentosa



Syndactyly and polydactyly in BBS



Bardet-Biedl



Bardet-Biedl syndrome

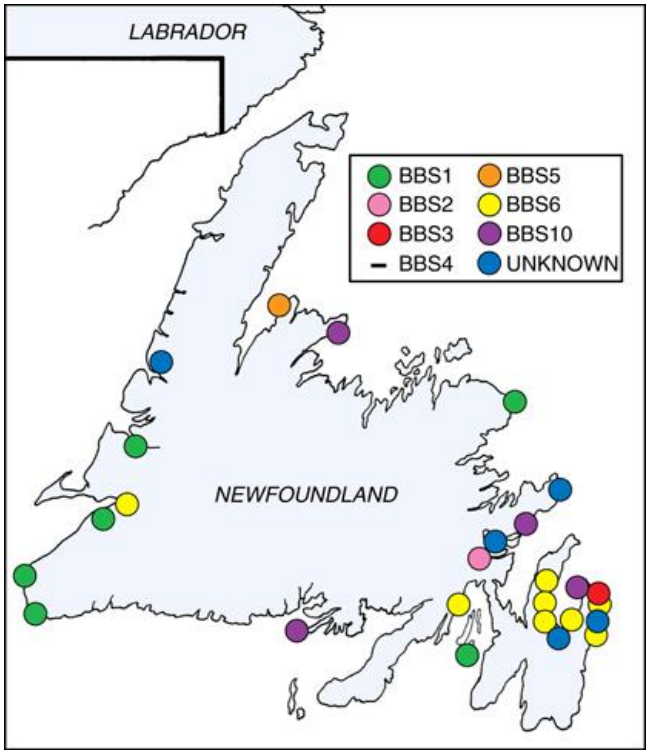
- A ciliopathy caused by autosomal recessive inheritance of mutations in over 12 genes.

Newfoundland

- Size of UK and surrounded by cod.
- Population 550,000; 90% arisen from 20,000 settlers….Waterford in Eire (catholic) and Devon/Dorset.
- Isolated small (<1000) coastal communities
- Geographical isolation, large families, high coefficient of kinship and founder effects.

Perfect incubator for recessive disease.

Geographic distribution of Bardet-Biedl families by genotype



Bardet-Biedl Syndrome in Newfoundland

- 46 cases in 26 families.
- Of 153 siblings 30% had BBS.
- Ten mutations in 6 BBS genes identified.
- Heterozygosity does not predispose to obesity, hypertension or renal impairment.

Ciliopathies

- Nephronophthisis
  Tubulointerstitial nephritis, retinitis pigmentosa and liver fibrosis
  (cf. medullary cystic kidney disease)

- Bardet-Biedl syndrome
  Metabolic abnormalities plus above

- Alstrom syndrome
  Retinitis pigmentosa
  Sensorineural hearing loss
  Normal intelligence
  Hepatic fibrosis
  Dilated cardiomyopathy
  Tubulointerstitial nephritis

Eye and renal disease

- Chromosomal abnormalities
  - WAGR syndrome (Aniridia)
  - Papillorenal Syndrome (Coloboma)
- Autosomal dominant
  - Alagilles syndrome (Posterior embryotoxon of eye)
  - TS (Retinal hamartomas; Chorioretinal depigmentation; Eyelid angiofibromas)
  - VHL (choroidal angiomas)
- Autosomal recessive
  - Bardet Biedl/ Alstroms (Retinitis pigmentosa)
  - Cystinosis (Cystine deposits in cornea)
- X-linked
  - Alports (lenticonus & macular abnormality)
  - Fabrys (Cornea verticillata)
  - Lowe oculocerebral syndrome (Multiple)
- Immune mediated
  - Tubulo-interstitial nephritis with uveitis (TINU)

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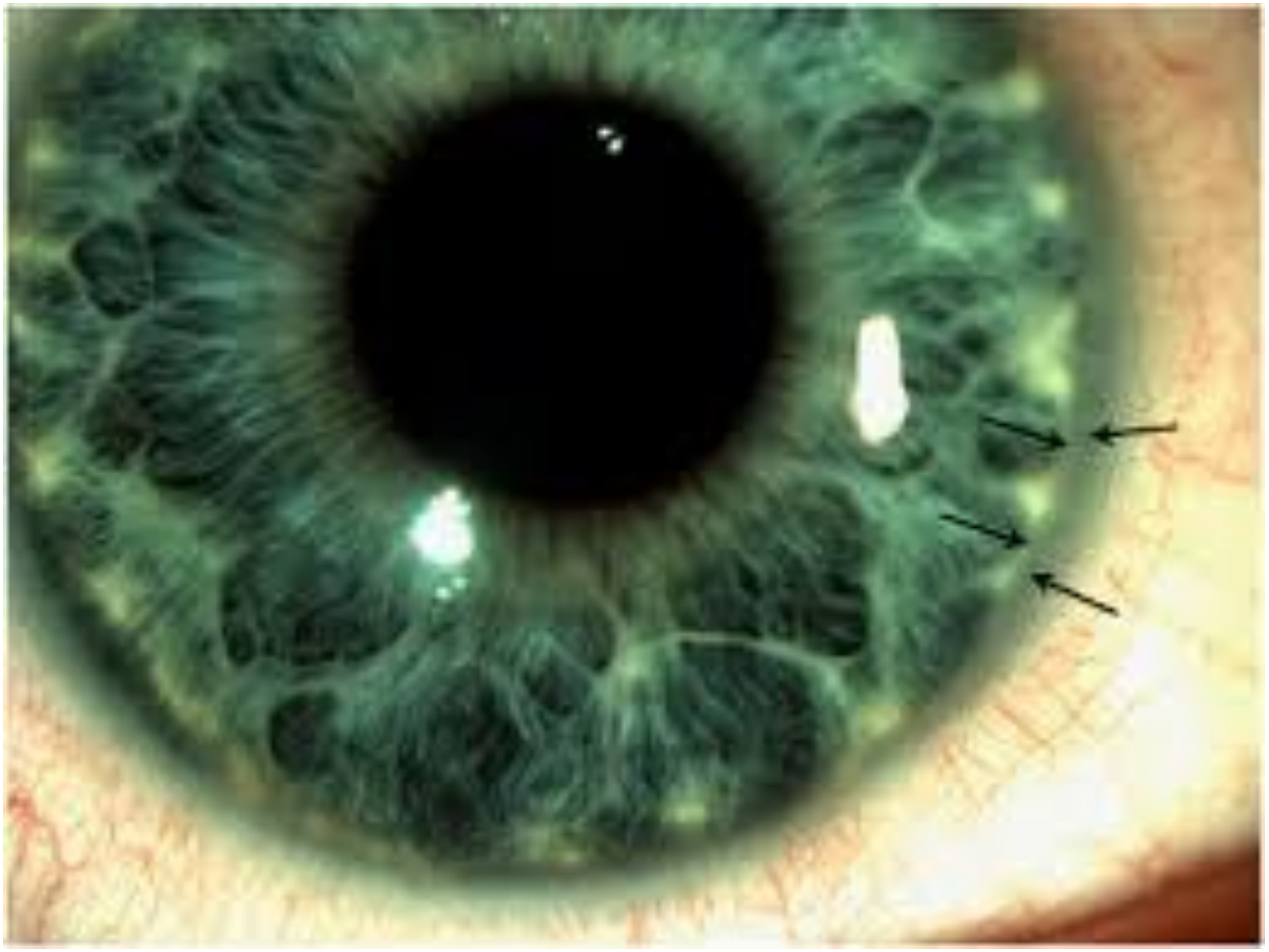
Miss E [Born 1970]

- October 1985 — Uraemic
  Dysmorphic with corneal abnormality
  [posterior embryotoxon]
  Pulmonary stenosis
  Raised Alk Phos
- January 1986 — Unit HD
- 1988 & 1990 — 3 Transplants
- 1997 — HD
- 2002 — Died – ca cervix

FH. — Uncle; Father [GD]; Cousin

Posterior embryotoxon in Alagille Syndrome



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- Autosomal dominant
  - Alagille syndrome-JAG1 mutation (Posterior embryotoxon of eye)
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Tuberous Sclerosis

- A multisystem disorder characterised by widespread hamartomas in brain, heart, skin, eyes, kidney, lung and liver.
- A disorder of one of two tumour suppressor genes.
- Affected genes are TSC1 and TSC2 encoding hamartin and tuberin respectively.
- The hamartin-tuberin complex inhibits the mammalian target of the rapamycin pathway which controls cell growth and proliferation.

Retinal hamartoma in TS

Eye and renal disease

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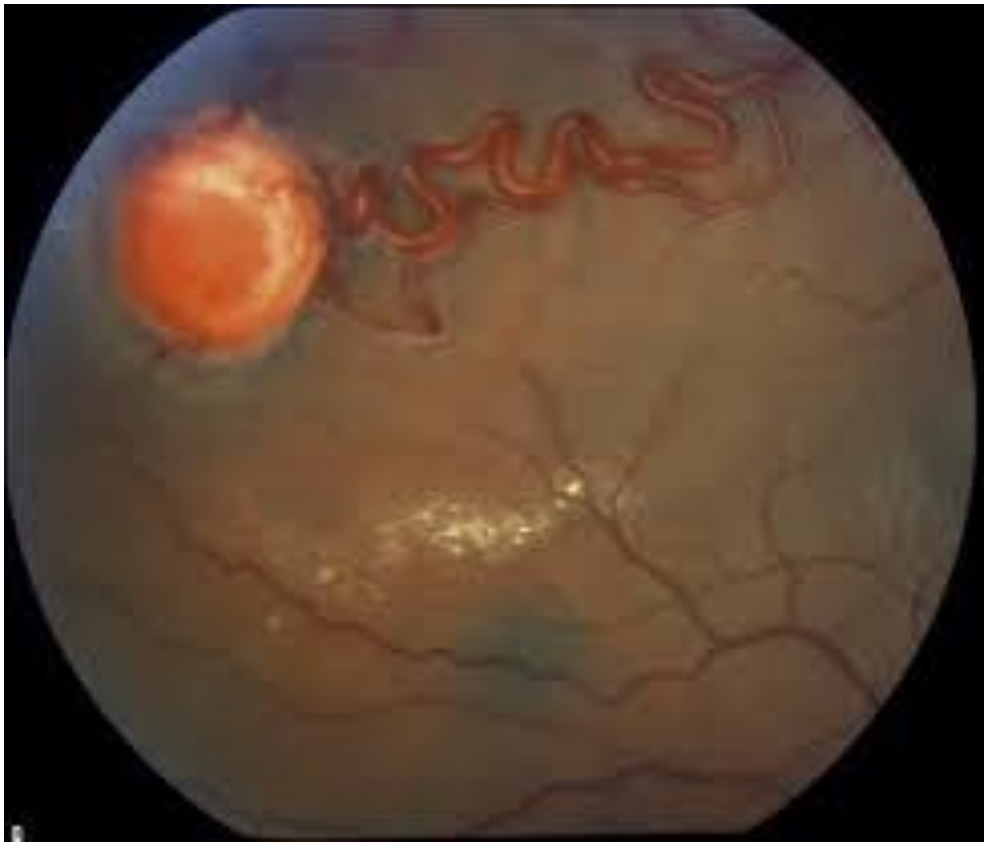
Angioma in von Hippel-Lindau Syndrome



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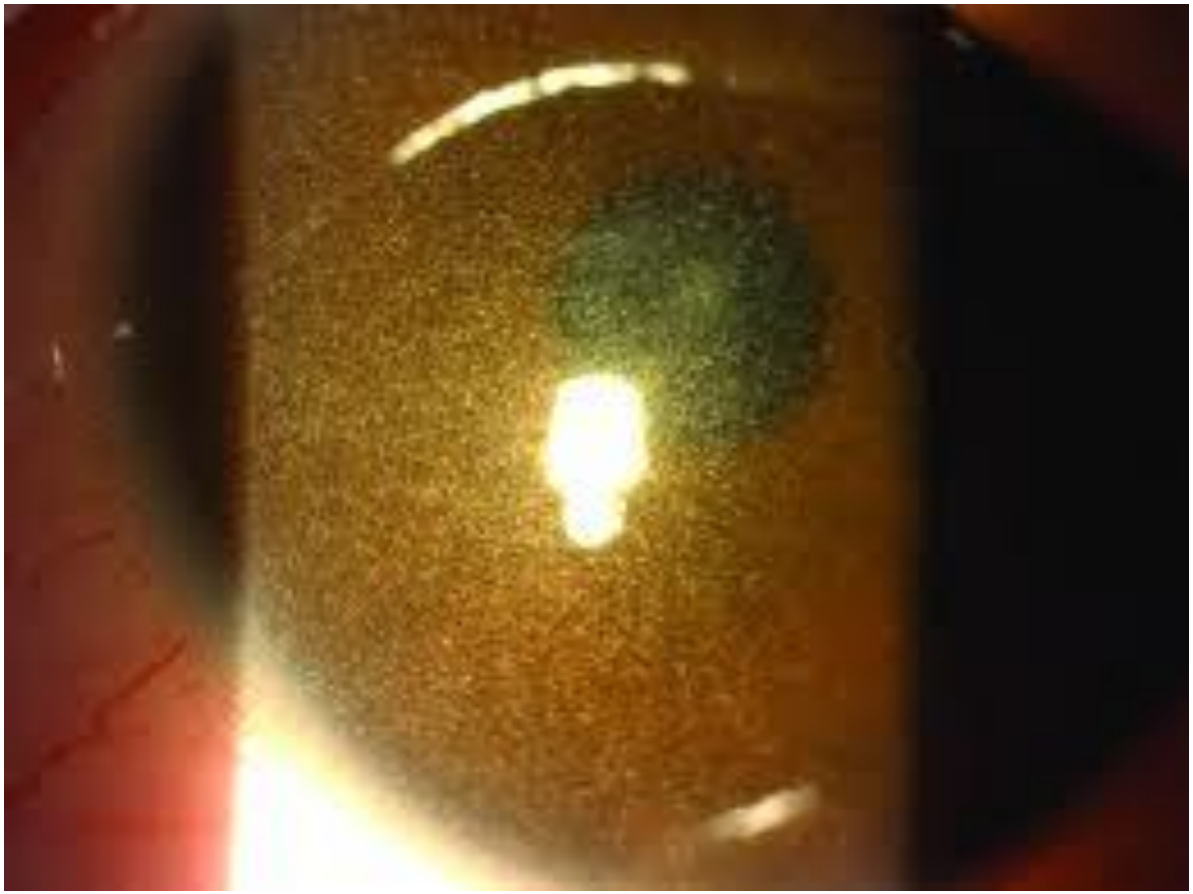
Corneal cystine deposits in Cystinosis



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Alports syndrome

- 80% X-linked; COL4A5 mutations
- Autosomal recessive; COL4A3
- Autosomal dominant; COL4A4

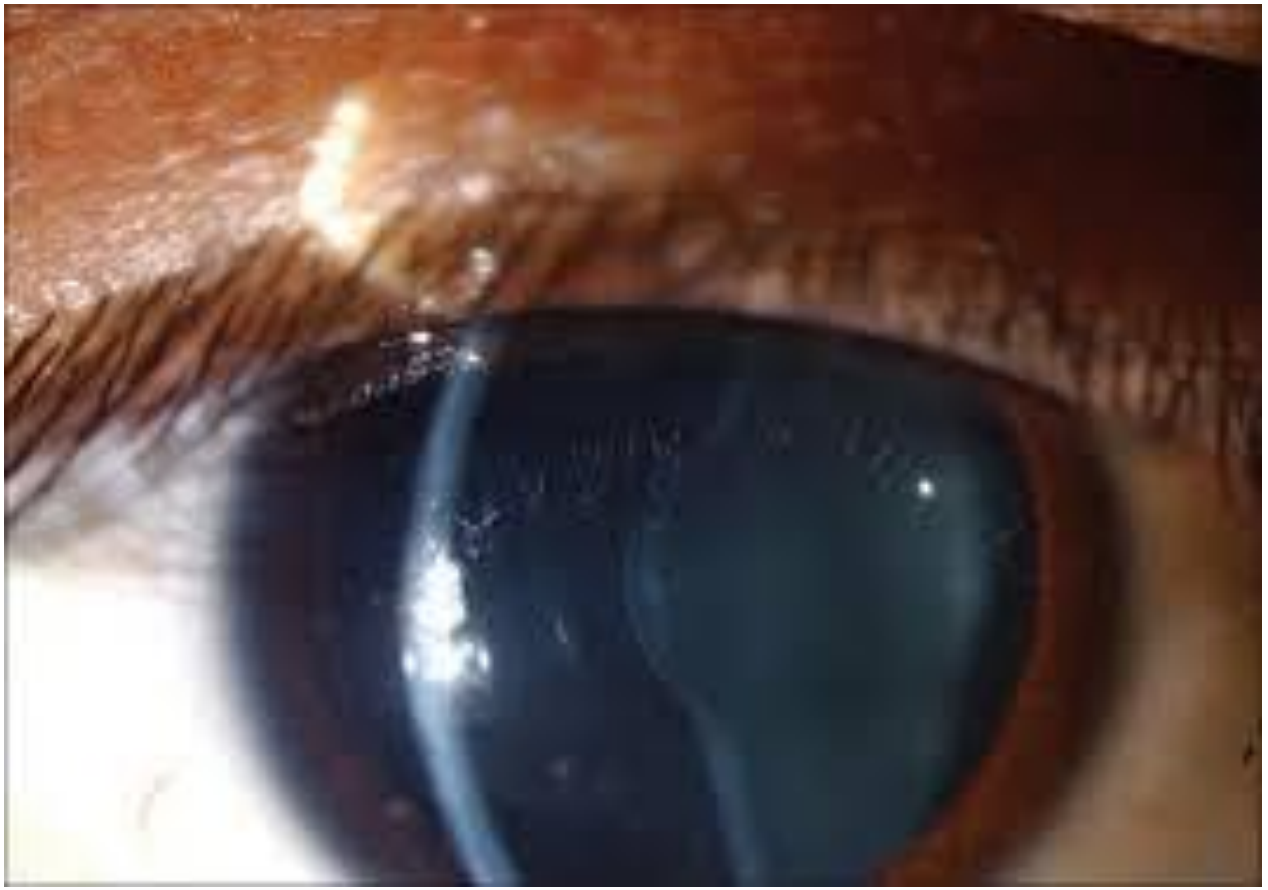
Genes code for chains that comprise collagen IV alpha 3, 4 & 5 protomers in GBM, stria vascularis of cochlea, cornea, lens & retinal Bruch's membrane.

Lenticonus – localised cone shaped deformation of lens

Central peri-macular dots and flecks

Rarely macular hole as result of retinal thinning

Lenticonus in Alport’s



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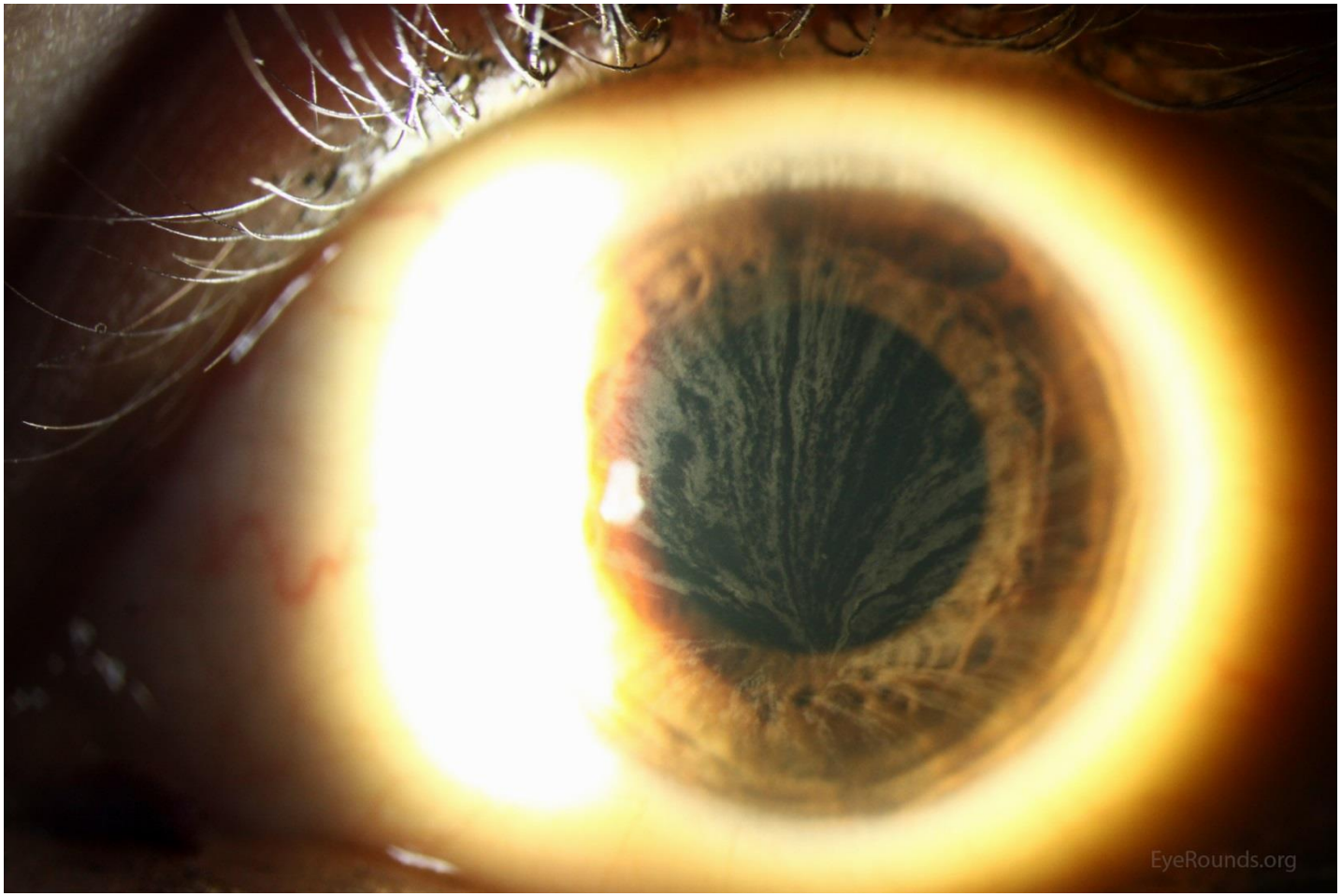
Fabry's disease

- X linked recessive [1in 40,000 males]
- Deficiency of lysosomal hydrolase alpha galactosidase A.
- Angiokeratoma, Acroparesthesiae, CNS, CVS & renal involvement
- Pale grey, brownish or yellow streaks in cornea – corneal verticillata

Corneal verticillata in Fabry's



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Mr F (Born 1994)

- Neonate : Hypophosphataemia
  Congenital cataracts
  Epilepsy
- Now: Blind (glaucoma; cataracts; aphakia)
  Renal rickets
  Severe subvalvular aortic stenosis
  Educationally severely impaired
- Treatment: Phosphate, bicarbonate, potassium and vitamin D supplements

Lowe oculocerebrorenal syndrome

- X-linked recessive
- Incidence 1:200,000 to 1:500,000
- Congenital cataracts, glaucoma, megalocornea and microphthalmos. Blind.
- Proximal tubular defects, aminaciduria, phosphaturia. Renal rickets.
- Severe intellectual impairment with behavioural problems.

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Ms G [born 1962]

- Crohn's Disease [2016]
  Rx Adalimubab Dec 2017
- May 2018 Creatinine 67umol/L
- Aug 2018 Creatinine 90umol/L
- Oct 2018 Bilateral uveitis
- 25-29 March 2019 Rx. Amoxycillin – oral surgery
- 9th April Creatinine 456umol/L
  Alb 42g/l; Urinary PCR 15

Ms G

- Clinical diagnosis confirmed with histology:
  Interstitial nephritis
  But what is the underlying aetiology?

Ms G

- Clinical diagnosis confirmed with histology:
  Interstitial nephritis
  But what is the underlying aetiology?
  TINU
  Amoxycillin
  Adalimubab
- Modest response to steroids –
  creatinine 277umol/L

Conclusion

- Eye manifestations are a common complication of renal disease (eg hypertensive retinopathy)
- Oculorenal syndromes are a rare but important cause of kidney disease.

- https://jasn.asnjournals.org/content/22/8/1403

“The overt message of this editorial, then, is to remind the nephrological community of the association between DDD and retinal drusen and report on the advances in understanding the composition of the abnormally deposited material.
So, what is the subliminal message? It is that even in the age of the human genome, metabolomics, genomics and proteomics, clinical nephrologists should continue to take a good look at the retina, and perhaps other anatomical structures, of their patients—who knows what might be seen and where it may lead?”