Senior–Løken syndrome (SLS)

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Summary

- Overview of SLS
- Clinical Features
- Genetics
- Treatment
- Case Examples

Senior–Løken syndrome

- Ciliopathy
- Juvenile nephronophthisis and retinal dystrophy
- First reported in 1961
- Incidence: 1 in 1 million
- Other names:
  - Renal-Retinal syndrome
  - Renal dysplasia and retinal aplasia
  - Juvenile nephronophthisis w/ LCA

Features

Retinal dystrophy

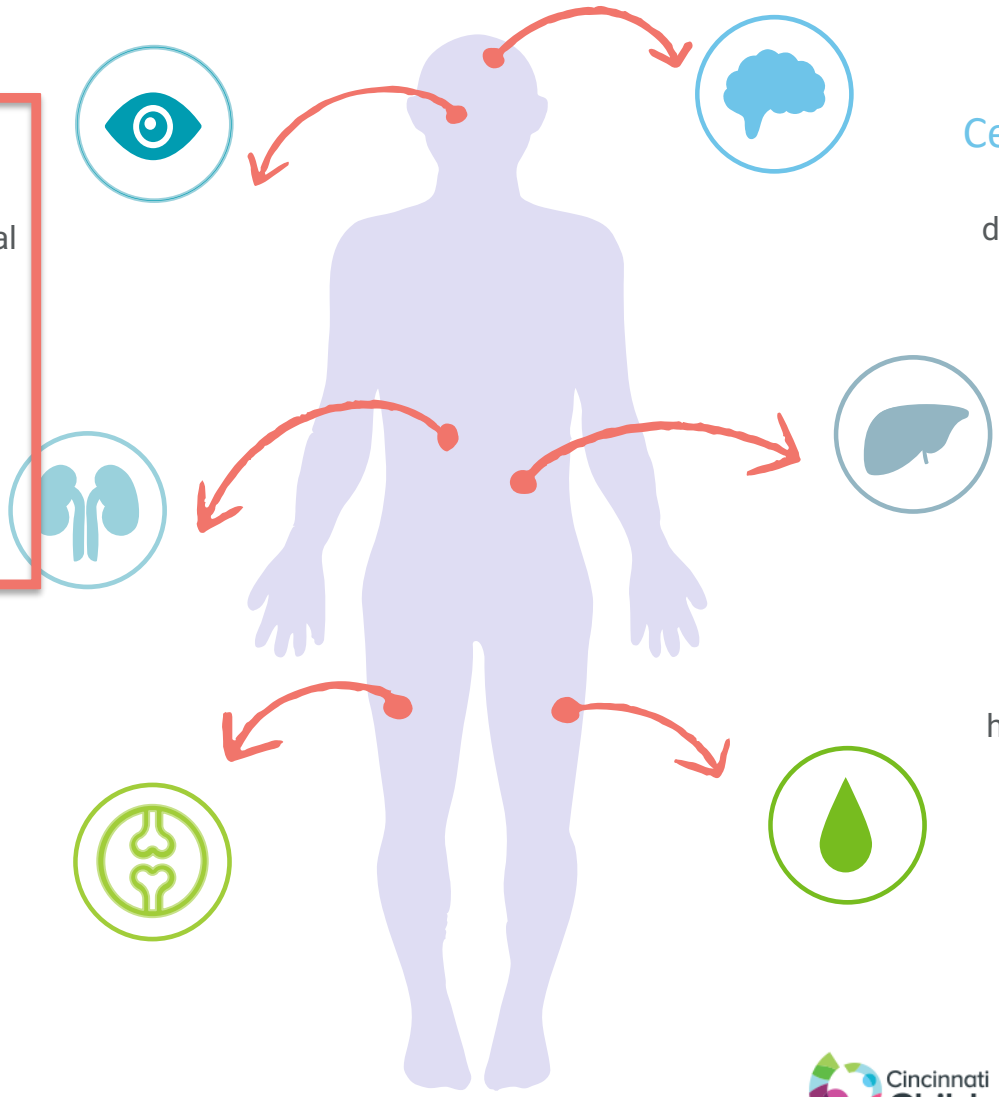
Commonly Leber congential amaurosis (LCA)

Nephronophthisis

Risk for end-stage renal disease (ESRD)

Skeletal anomalies

Polydactyly/brachydactly, short stature, scoliosis



Cerebellar hypoplasia

Seizures, developmental delay, intellectual disability

Liver defects

Hepatic fibrosis

Other

Anemia, sensorineural hearing loss, obesity, early growth failure

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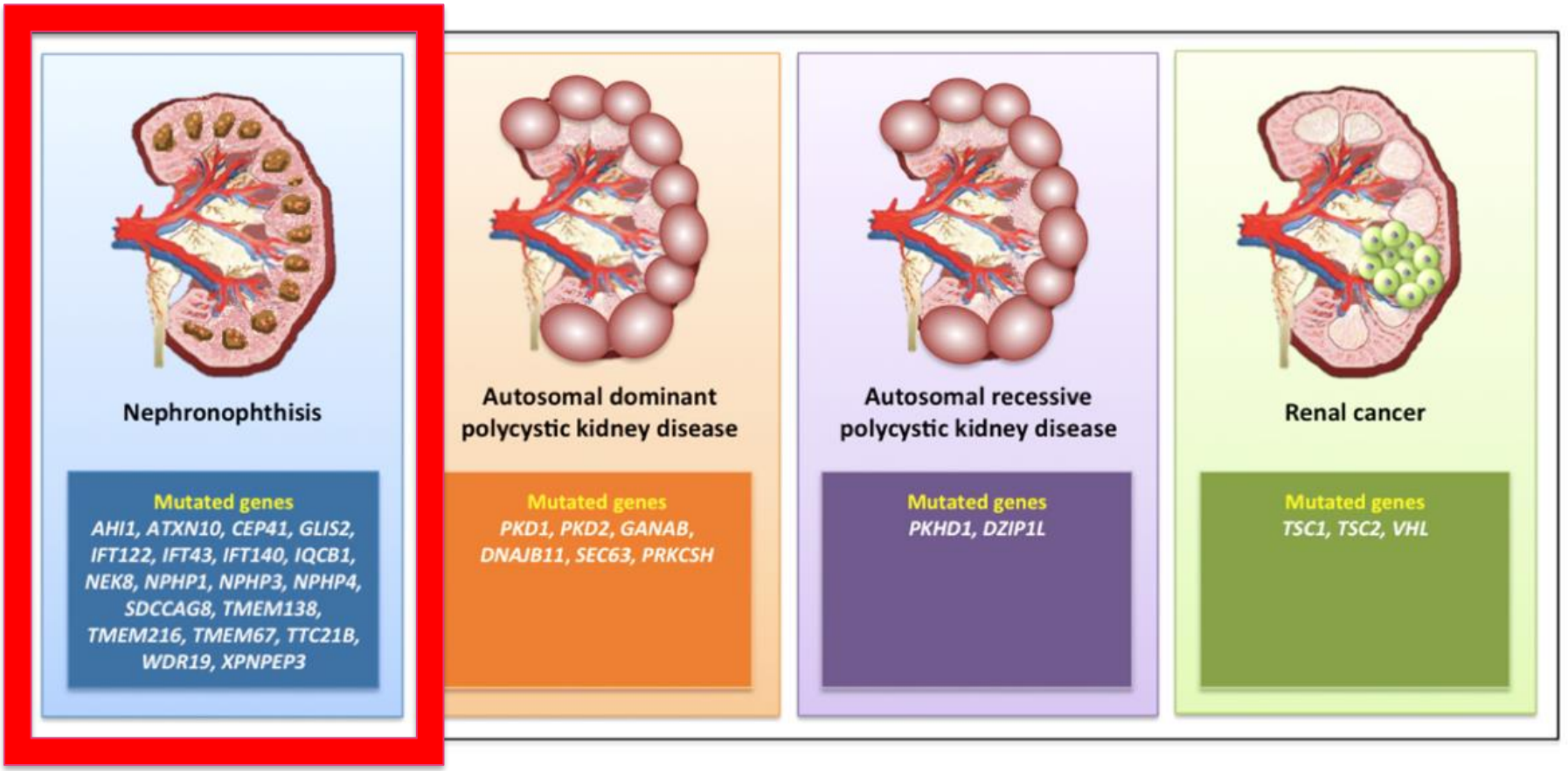
Nephronophthisis (NPHP)

- Medullary cystic kidney disease and loss of corticomedullary differentiation
- Isolated vs syndromic NPHP
- Variable range of onset: 1st decade – adulthood
- Progresses to end-stage renal disease
  - Polydipsia/polyuria
  - Treatment: dialysis, kidney transplant

Nephronophthisis (NPHP)



Santoni et al., 2020

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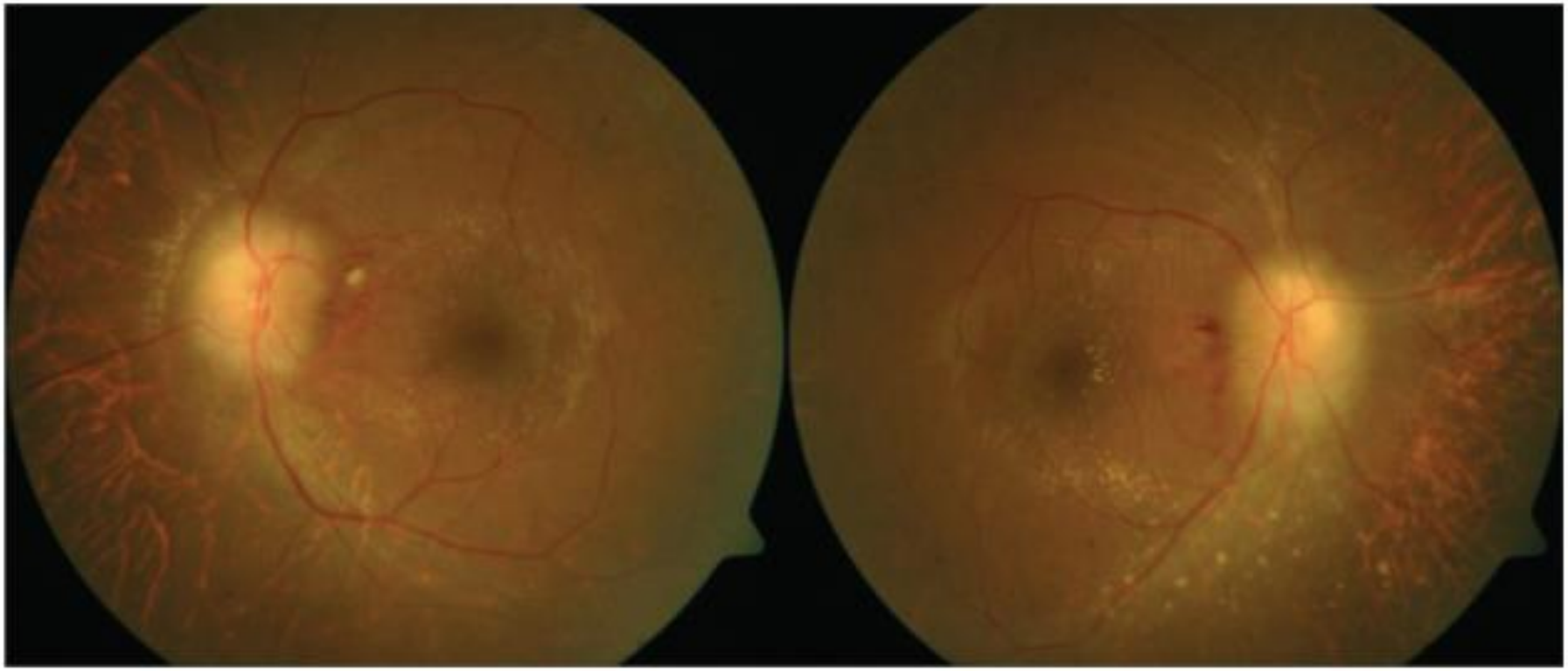
Retinal Dystrophy

- Ranges from Leber congenital amaurosis (most common) to typical retinitis pigmentosa
- Represents less than 1% of all infantile-onset retinal dystrophy cases
  - Nystagmus
  - Photophobia
  - Franschetti oculodigital sign
- Other: Juvenile cataracts, coloboma, keratoconus, and Coat's disease

Retinal Dystrophy



Harikrishan et al., 2013

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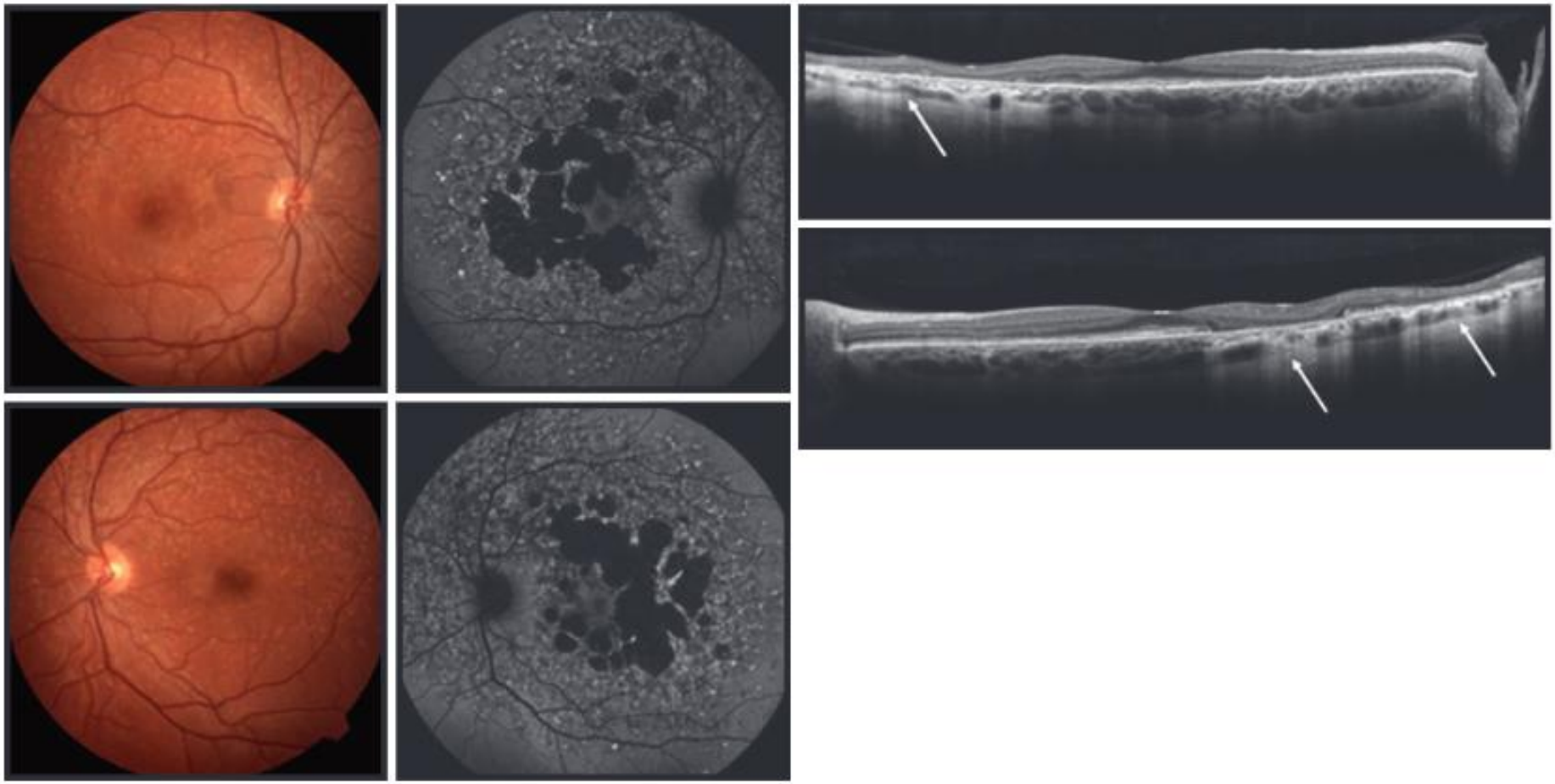

Fig. 34.1 This 37-year-old patient had a history of night blindness for the past 11 years and underwent renal transplantation about 10 years previously. Genetic testing showed a *WDR19(NPHP13)* mutation, characteristic of Senior-Løken syndrome. Areas of retinal pigment epithelium (RPE) changes are better seen on fundus autofluorescence (FAF), though color fundus images show a sort of flecked retina. Optical coherence tomography (OCT) shows disruption of the ellipsoid zone (EZ) line and RPE (*arrows*)

Tsang et al., 2018

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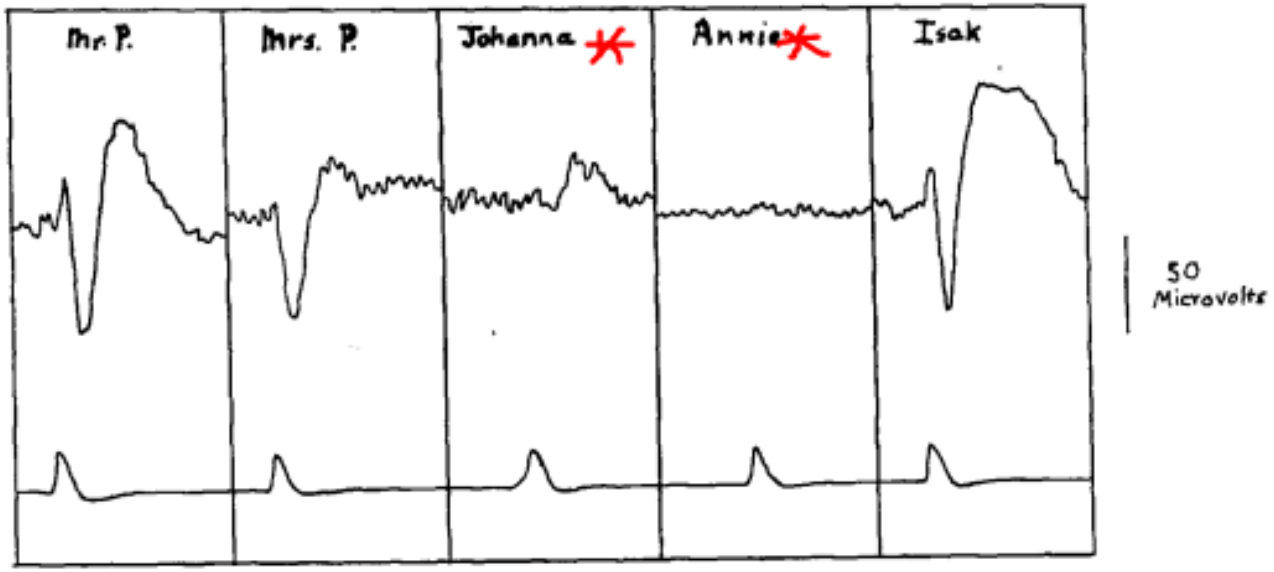
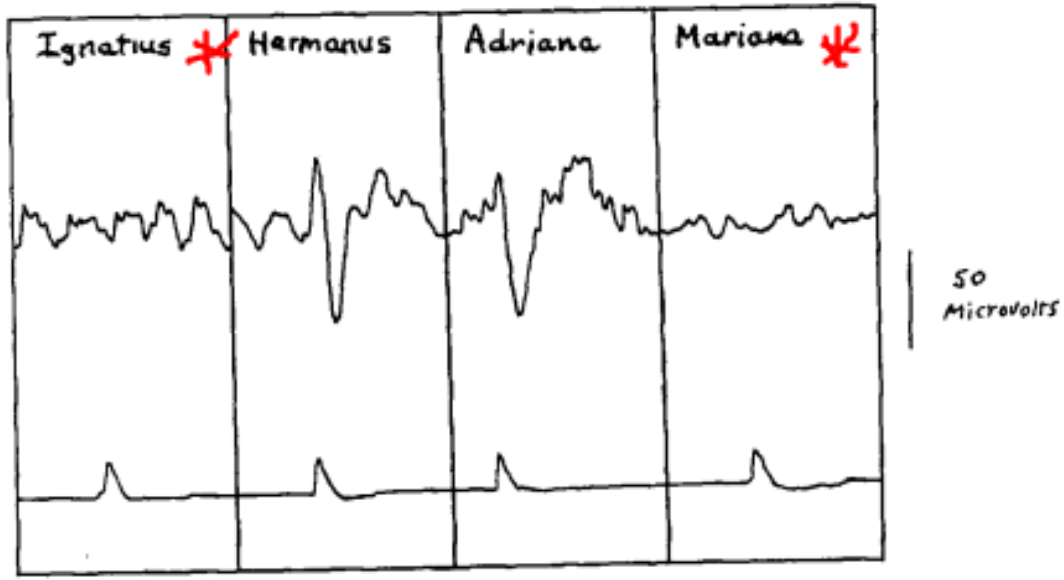




Senior et al., 1961

Additional Features

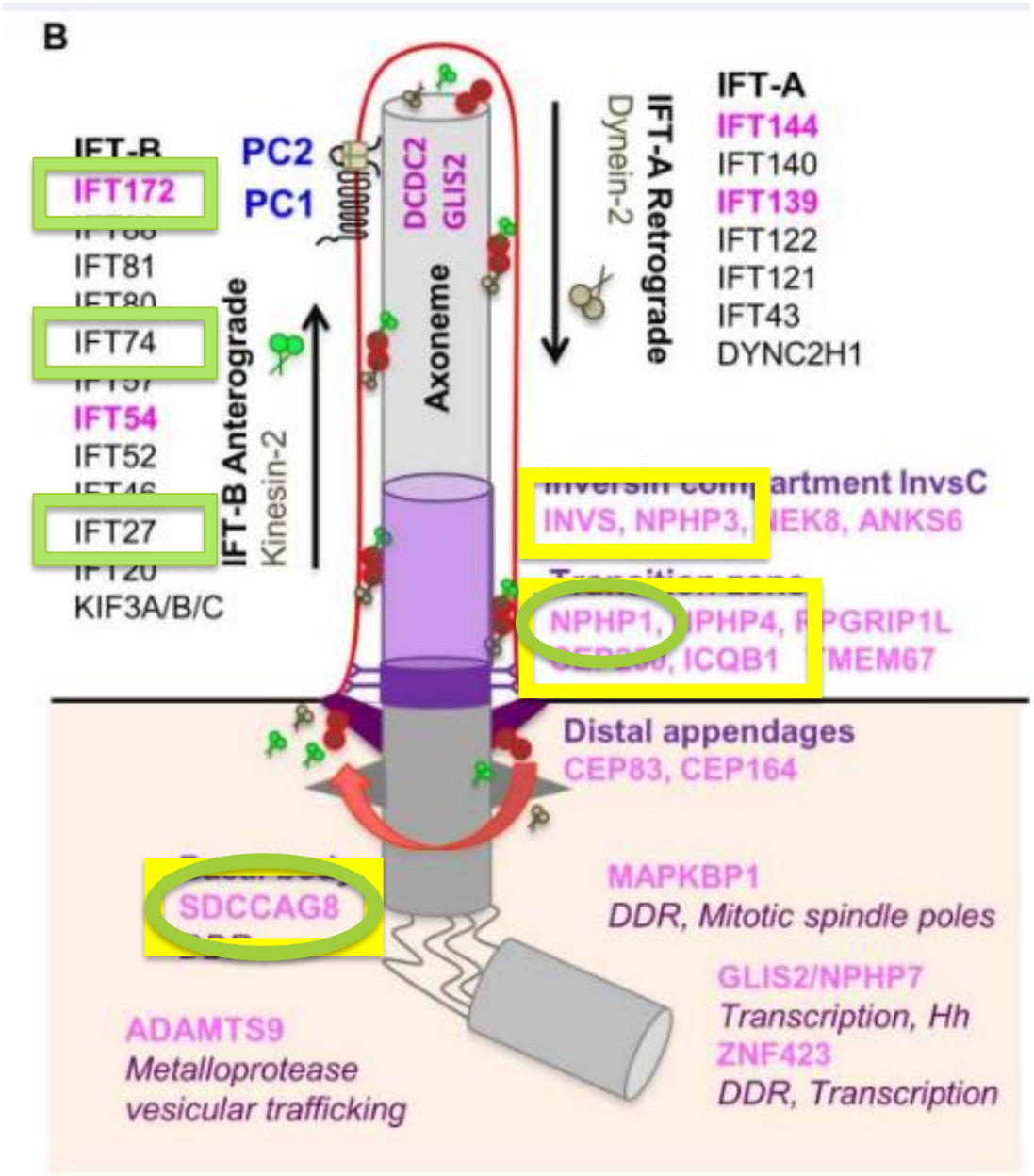
- Anemia
- Skeletal anomalies/early growth failure
- Hepatic fibrosis
- Cerebellar hypoplasia, seizures
- Developmental delay, intellectual disability
- Sensorineural hearing loss
- Obesity

Genetics

- Autosomal recessive
  - Homozygous and compound heterozygous
- Genetic heterogeneity
- Encode proteins involved with ciliogenesis/ciliary protein trafficking
- 9 subtypes

Genetics

Type	Gene	Phenotype	Genotype/Mechanism	Source
1	*NPHP1*	Juvenile NPHP + LCA	Homozygous deletion involving *NPHP1*, or comp. het deletions + LOF point mutations	Caridi et al., 1998, Hildebrandt et al., 1997, Saunier et al, 1997
2	*NPHP2*	NPHP + RP, anemia, short stature	Comp. het. LOF point mutations (nonsense/frameshift), possible heterozygous deletion	O'Toole et al., 2006; Otto et al., 2003
3	*NPHP3*	Adolescent NPHP + LCA, rare hepatic fibrosis	Presumed comp. het mutations on *NPHP3* (or possible digenic inheritance)	Omran et al., 2002; Olbrich et al., 2003
4	*NPHP4*	NPHP + RD	LOF missense mutations	Schuermann et al., 2002
5	***NPHP5 (IQCB1)***	**NPHP + RD (Most common type)**	**Nonsense mutations**	**Otto et al., 2005**
6	*CEP290*	NPHP+LCA/RD	Homozygous deletion at obligatory splice site	Sayer et al. 2006
7	*SDCCAG8*	NPHP+RD, intracranial hypertension	Homozygous/comp. heterozygotes at splice site mutation	Tay and Vincent, 2020; Otto et al., 2010
8	*WDR19*	NPHP+RD, hepatic/pancreatic manifestations	Biallelic variants; homozygous missense mutations	Coussa et al., 2013; Halbritter et al., 2013
9	*TRAF3IP1*	NPHP+RD, liver defects, skeletal anomalies	Homozygous/comp. heterozygotes	Bizet et al., 2015



Stokman et al. 2021

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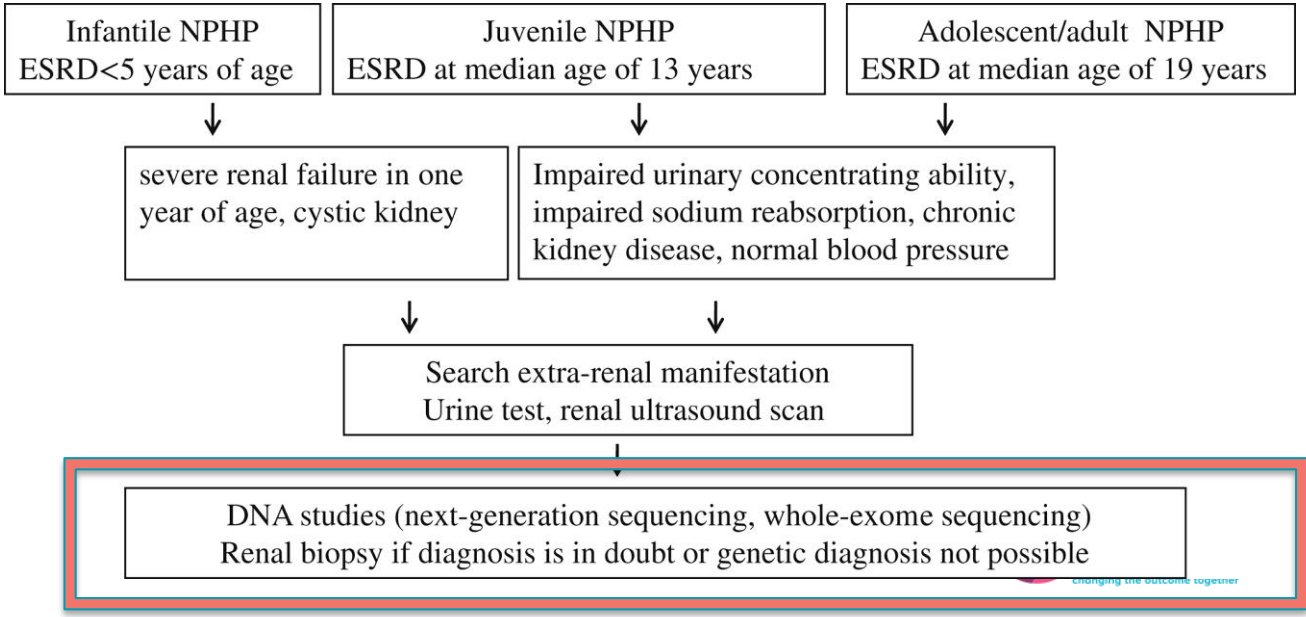
Clinical & Molecular Diagnosis

- No clinical diagnostic guidelines
- Molecular testing available
  - SLS, NPHP, and retinal dystrophy panels
  - Whole exome/genome sequencing



Treatment

- RP/LCA
- NPHP
  - Dialysis
  - Kidney transplant
- Benefits of early detection

Pharmacotherapy

- Difficult to target defective gene product
- Drug repurposing?
- Prediction and prevention of NPHP
  - C'IL-LICO RICM study, Hôpitaux de Paris
  - Objective: Produce a prognostic biomarker-based kit to predict the evolution of ciliopathy patients towards renal impairment

Gene Therapy

- RP/LCA
  - Gene therapy trials ongoing, none for the Senior Loken genes
- NPHP (proposed)
  - Antisense-oligonucleotide splicing modulator (CEP290)
  - CRISPR/Cas9
- Limitations: genetic heterogeneity of NPHP-related ciliopathies and RDs

Case Example 1

- 6 mo old male
- No birth complications, developmental concerns, or pertinent family history
- 6 mos: Infantile-onset nystagmus
- 7 mos: Genetics referral for suspected early-onset retinal dystrophy
- 9 mos: developed Franschetti oculodigital sign

Case Example 1

- Parents previously had prenatal carrier screening
- Panel: Blueprint Genetics Retinal Dystrophy Panel
- Result: Compound heterozygote in *IQCB1*, parents are confirmed carriers
  - VUS in *NDP*

Case Example 1

- Management: Negative findings on brain MRI and with nephrology
- Will undergo EUA to evaluate risk of retinal detachment
- Parents are motivated to involve him in research
- Can consider prenatal testing in future pregnancies

Case Example 2

- 36 yo male with atypical RP and family history of RP
- Signs of vision loss at ~6 mos, diagnosed with RP at 3 yo
- Stable vision for many years
- Reported signs of early kidney failure in 2018, no follow-up

Case Example 2

- Family history: sister with RP, similar disease course
  - Receiving genetic testing simultaneously?
- Panel: Blueprint Genetics RD Panel
- Result: compound heterozygote in *IQCB1*
- Referred back to nephrology
- Recommended prenatal genetic counseling prior to future pregnancies

Conclusions

- Highly variable condition that can overlap with other ciliopathies
- Early molecular diagnoses can change medical management and improve outcomes

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Questions?