

Genetics and Kidney Disease

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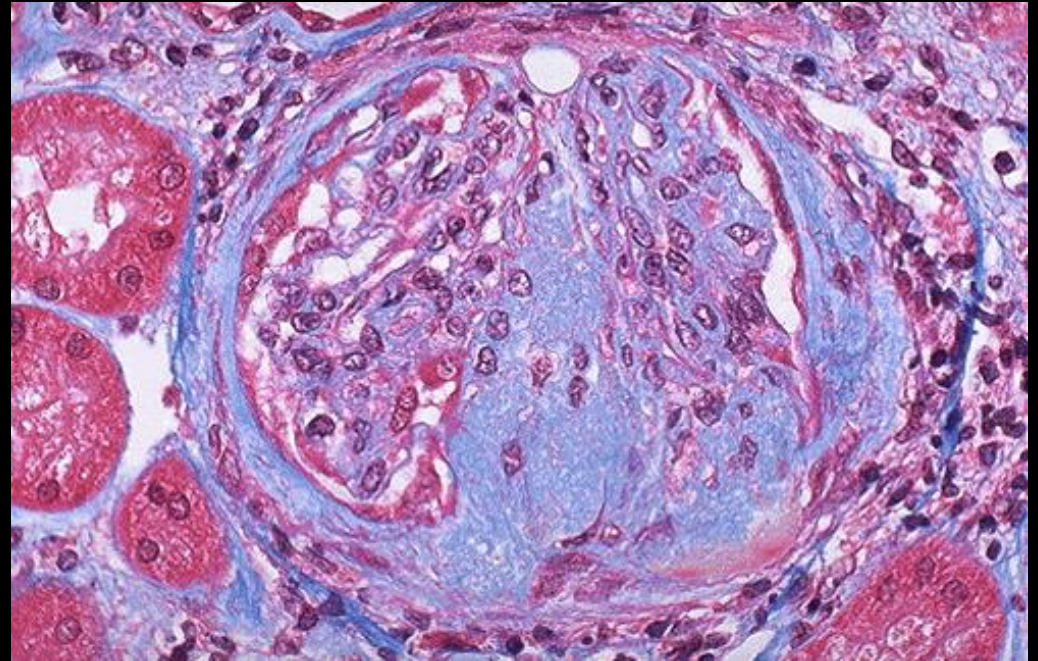


- Chief, Div. of Nephrology, Boston Children's Hospital - Harvard Medical School
- William E. Harmon Professor of Pediatrics, Harvard Medical School
- Clinical: **Monogenic CKD**
- Research: **Gene discovery and dz mechanisms of CKD**

Disclosure

Cofounder of Goldfinch-Bio

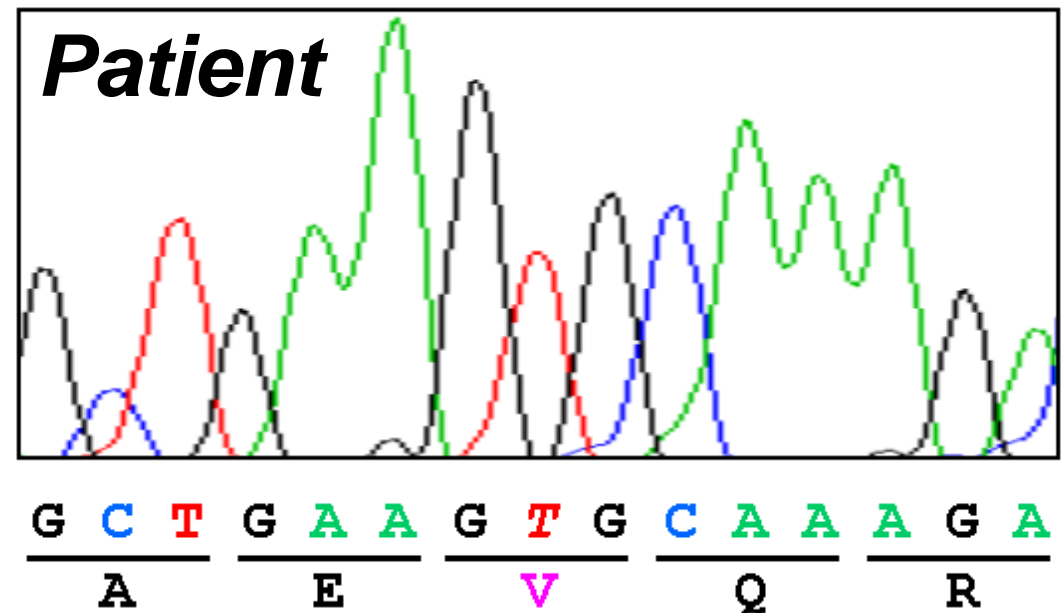
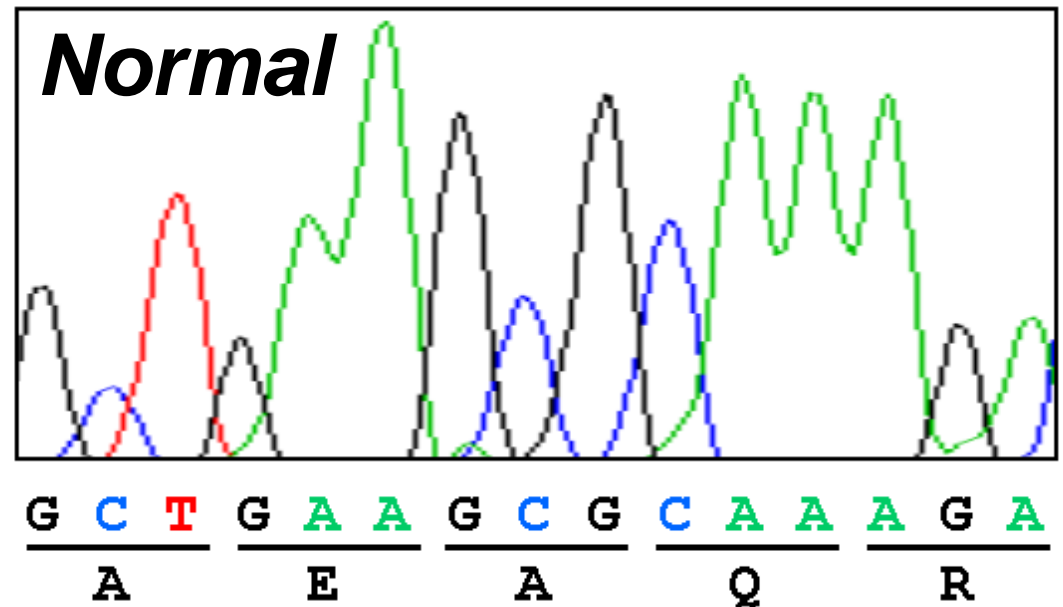
Steroid-Resistant Nephrotic Syndrome



Focal segmental glomerulosclerosis (FSGS)

Homozygous Point Mutation in the *Podocin* Gene

A mutation in 1 bp of the 3,300,000,000 bp of the total genome is sufficient to cause FSGS

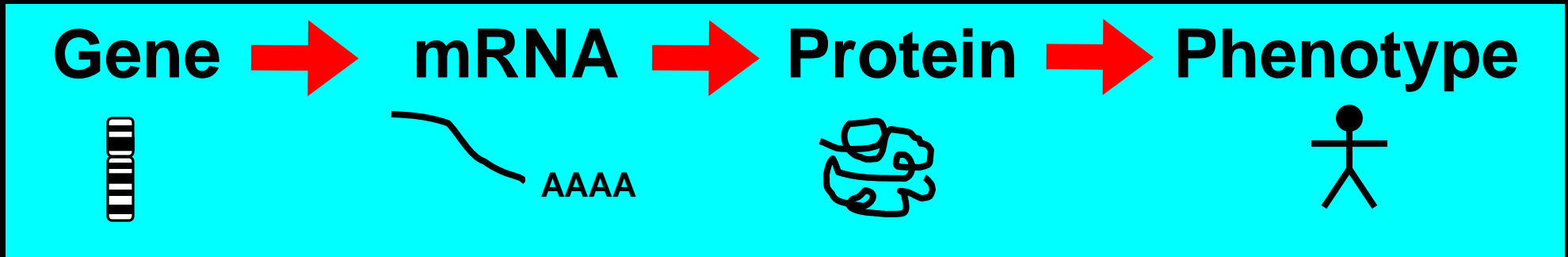


Definition: Monogenic disease (Single-gene disorder)

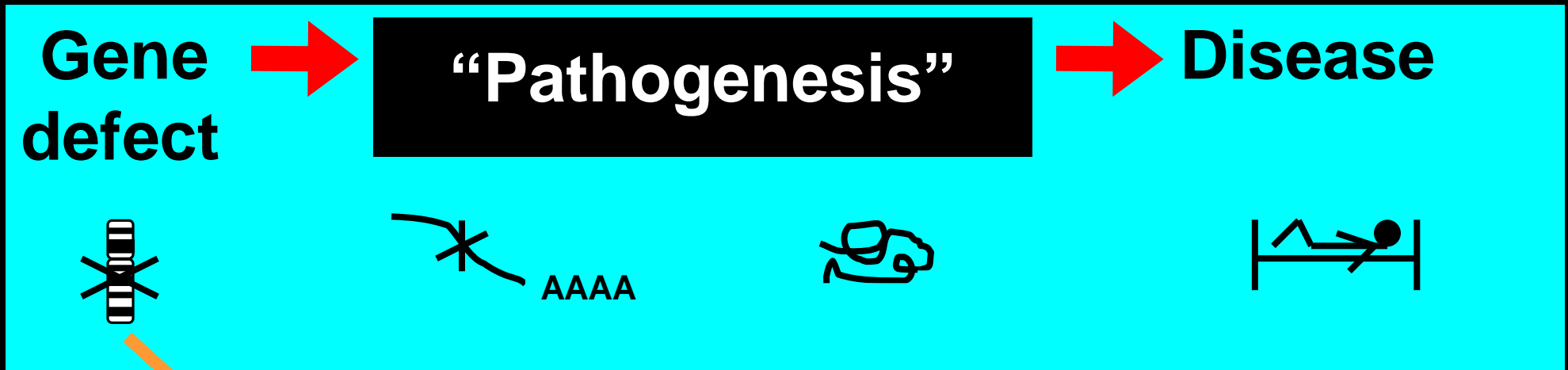
Definition

- In 1 patient the disease is caused by mutation of **1 gene only** of ~20,000 genes (recessive, e.g. ARPKD; dominant, e.g. ADPKD)
- In **different** patients **different** genes may cause a similar disease:
("genetic locus heterogeneity", e.g. podocin, nephrin)
- **51** recessive, **8** dominant genes for SRNS

Flow of Genetic Information (Central dogma)

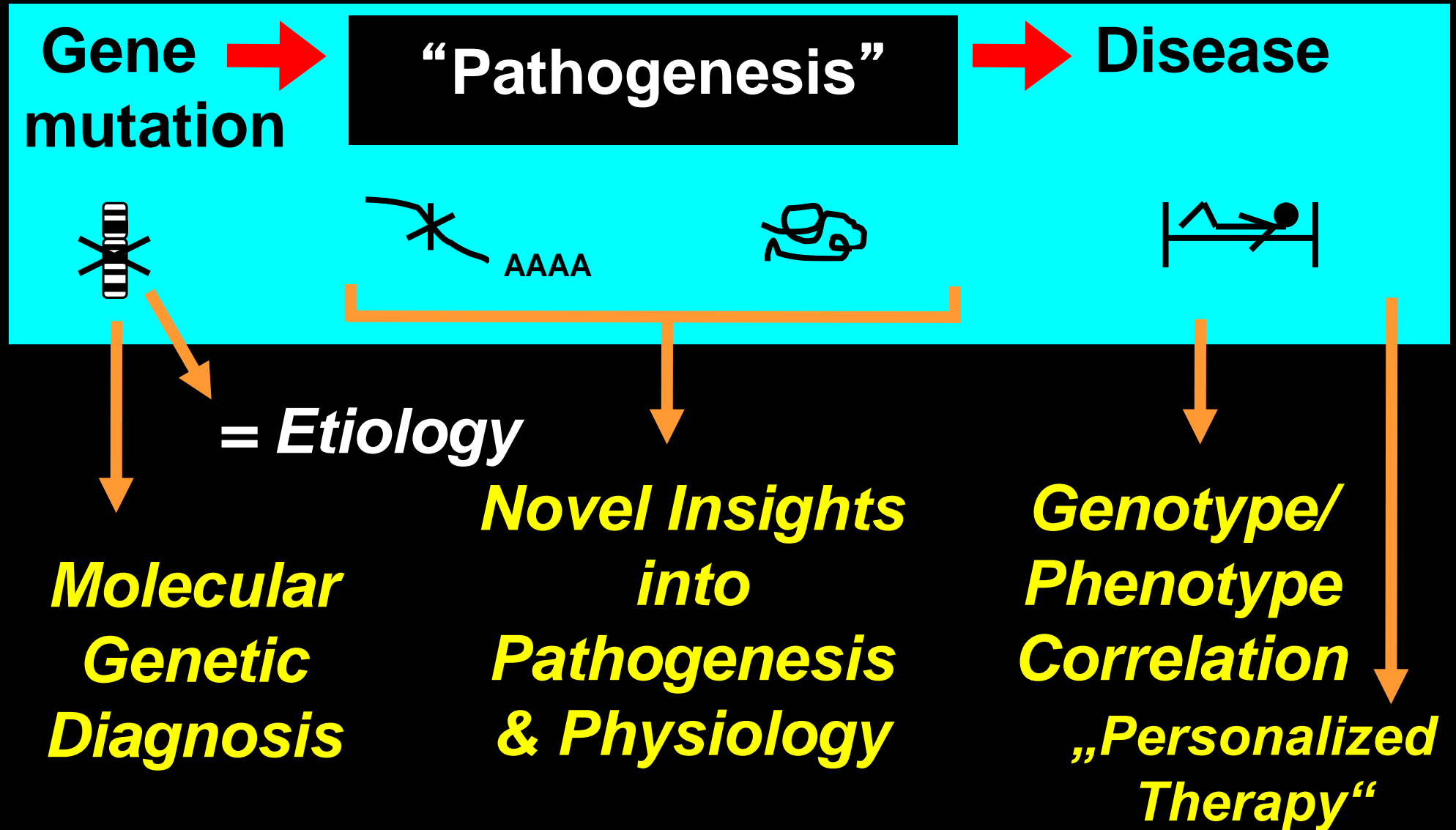


Monogenic Disease



= *Etiology*

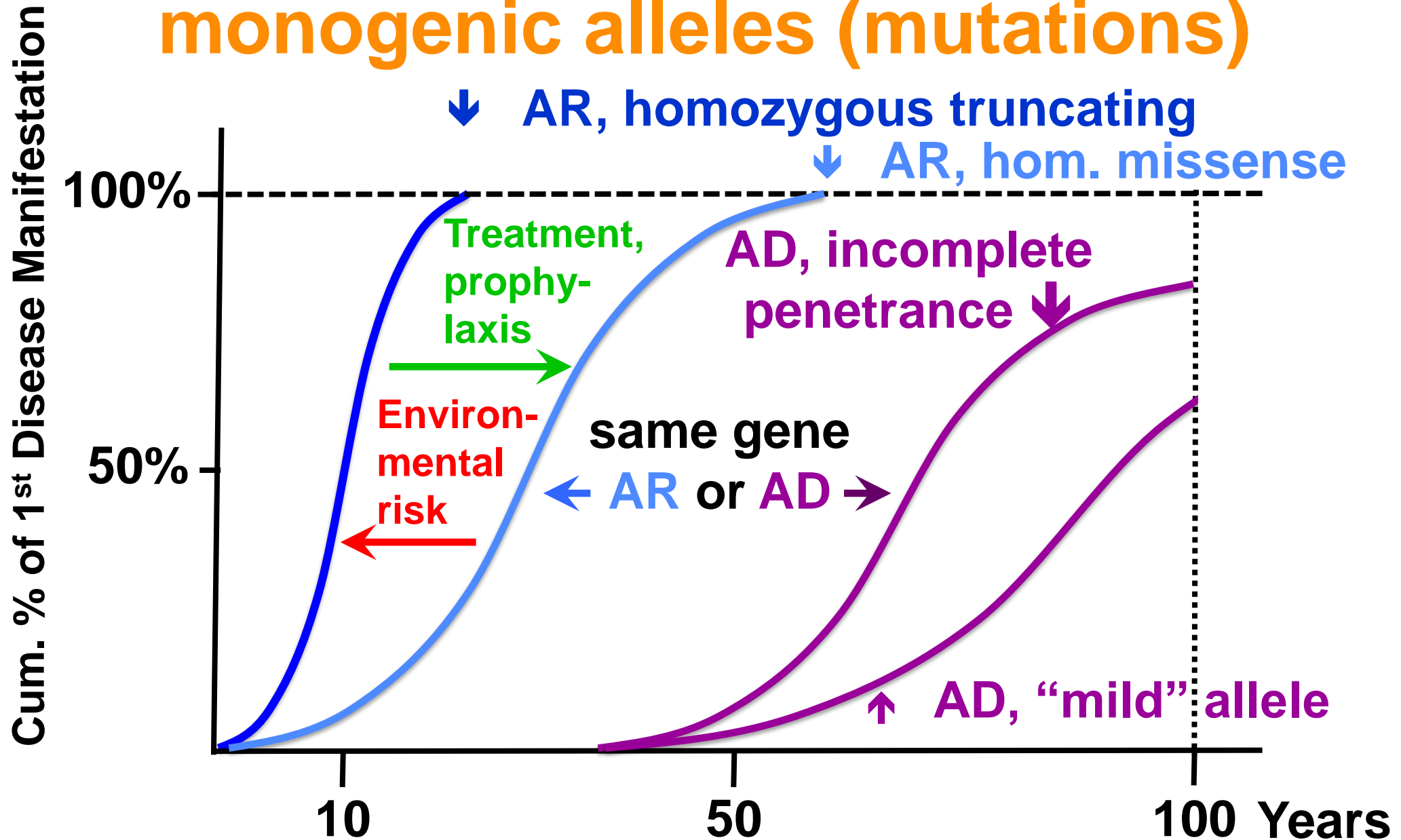
Consequences from Disease Gene Identification



Genetic causality and predictive power in monogenic and polygenic diseases

	Recessive monogenic	Dominant monogenic	Polygenic
Genetic causality	Strong	Intermediate	Weak
Penetrance	~100%	Incomplete	Weak
Predictive power of mut. analysis	Almost 100%	Strong	Weak
Onset	Fetus, child	Adolescent	Adult
Molecular genetic approach	Mapping, Exon sequencing, CNV	Mapping, Exon sequencing, CNV	GWAS “association”
Animal model	Very feasible	feasible	difficult
Frequency	~ 1 in 40,000	~ 1 in 1,000	~ 1 in 5

Age related penetrance of monogenic alleles (mutations)



Boards question

The term “monogenic disease” ...

- A. Is synonymous with “single-gene” disease and “Mendelian disorder”.**
- B. Describes autosomal recessive, autosomal dominant, and X-linked disorders.**
- C. Describes a genetic “association”.**
- D. Means that a mutation in a single gene is sufficient to cause disease in an individual.**
- E. A, B, and D.**

What percentage of
chronic kidney disease
(onset <25 yrs)

**is caused by single-gene
mutations?**

Causes of CKD <25 yrs

Chronic Kidney Disease	Cause
CAKUT (<u>C</u> ongenital <u>A</u> nomalies of the <u>K</u> idneys & <u>U</u> rinary <u>T</u> ract)	50%
STERIOD RES. NEPHROTIC SYNDROME	15%
CHRONIC GLOMERULONEPHRITIS MPGN, SLE, IgA, Alport's, aHUS	14%
CYSTIC KIDNEY DISEASE ARPKD, ADPKD, Nephronophthisis, ADTKD	6%
NEPHROLITHIASIS / NEPHROCALINOSIS	3%
OTHER	12%
TOTAL (n=8,990) (NAPRTCS 2008)	100%

Many monogenic genes cause CKD <25 yrs

Chronic Kidney Disease	Cause	# Genes (FH lab)
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NEPHROLITHIASIS / NEPHROCALINOSIS	3%	30 (2)
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TOTAL (n=8,990) (NAPRTCS 2008)	100%	>244 (83)

Many monogenic genes cause CKD <25 yrs

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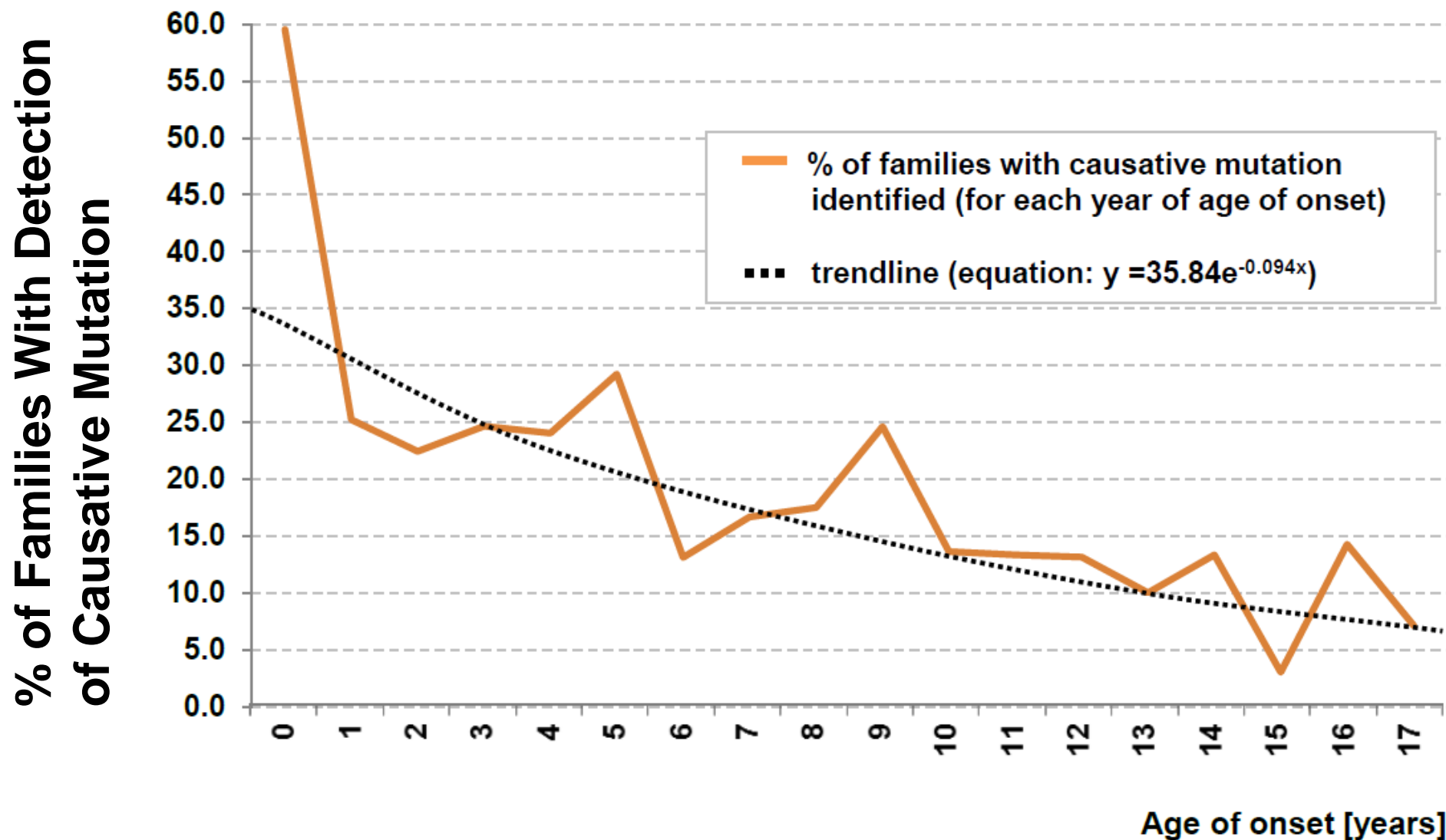
**What percentage of
Steroid-Resistant Nephrotic
Syndrome (SRNS) is
caused by single-gene
mutations?
(onset <25 yrs)**

In 30% of 1,780 worldwide SRNS families (<25 yr) the causative mutation was detected (26 genes)

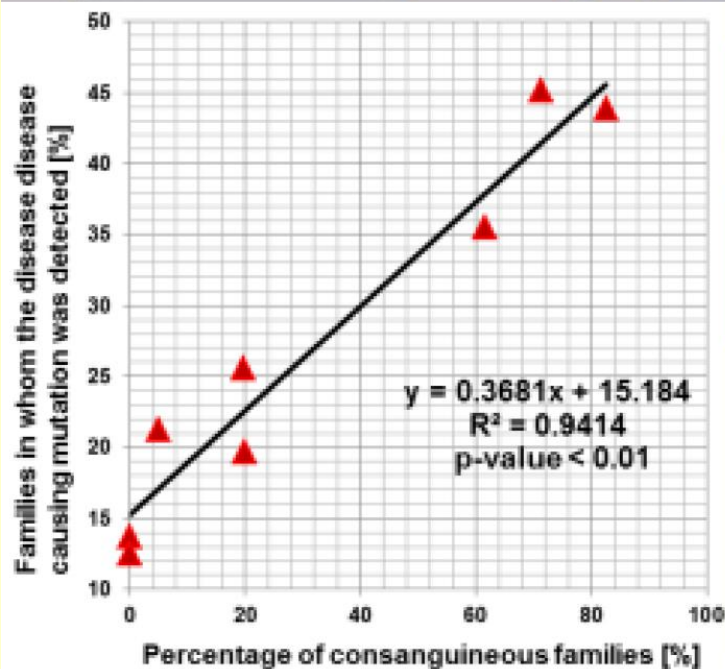
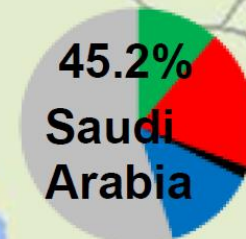
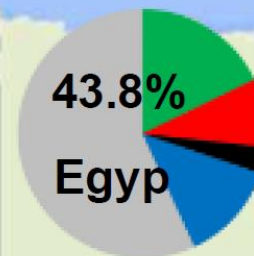
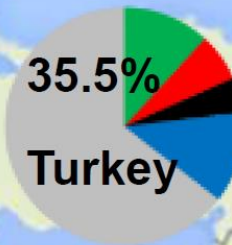
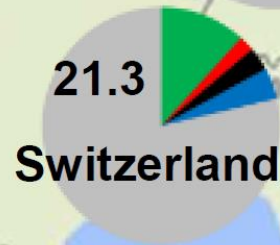
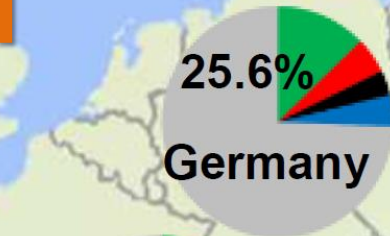
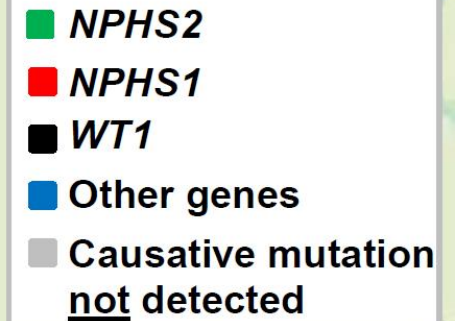
Causative Gene	N Families	% of Total Families
<i>NPHS2 (podocin)</i>	170	10%
<i>NPHS1 (nephrin)</i>	125	7%
<i>WT1</i>	85	5%
<i>PLCE1</i>	35	2%
22 Other Genes	105	6%
<u>Total</u>	<u>520</u>	<u>30%</u>

(Sadowski & Lovric *JASN* 26:1279, 2015) (www.renalgenes.org)

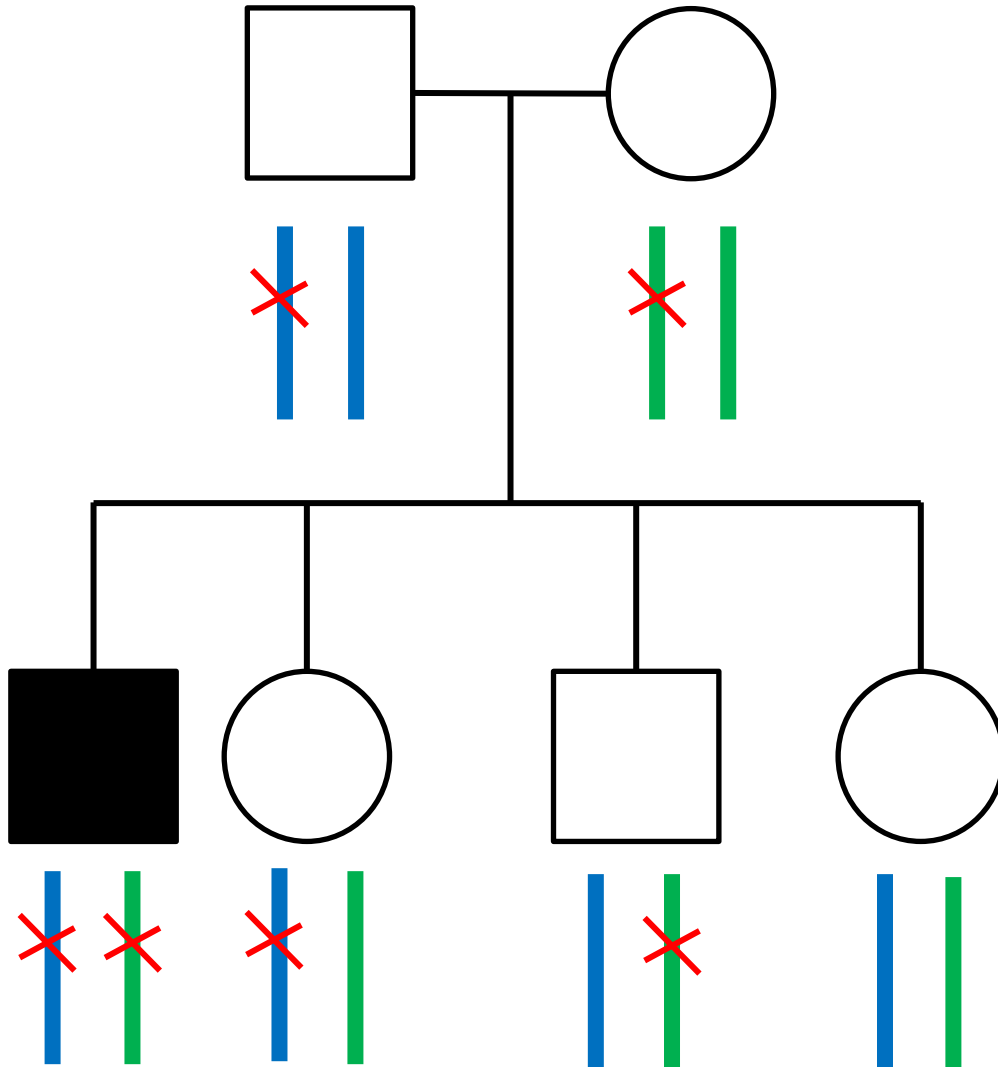
Single-gene causation of SRNS is higher in early manifestation



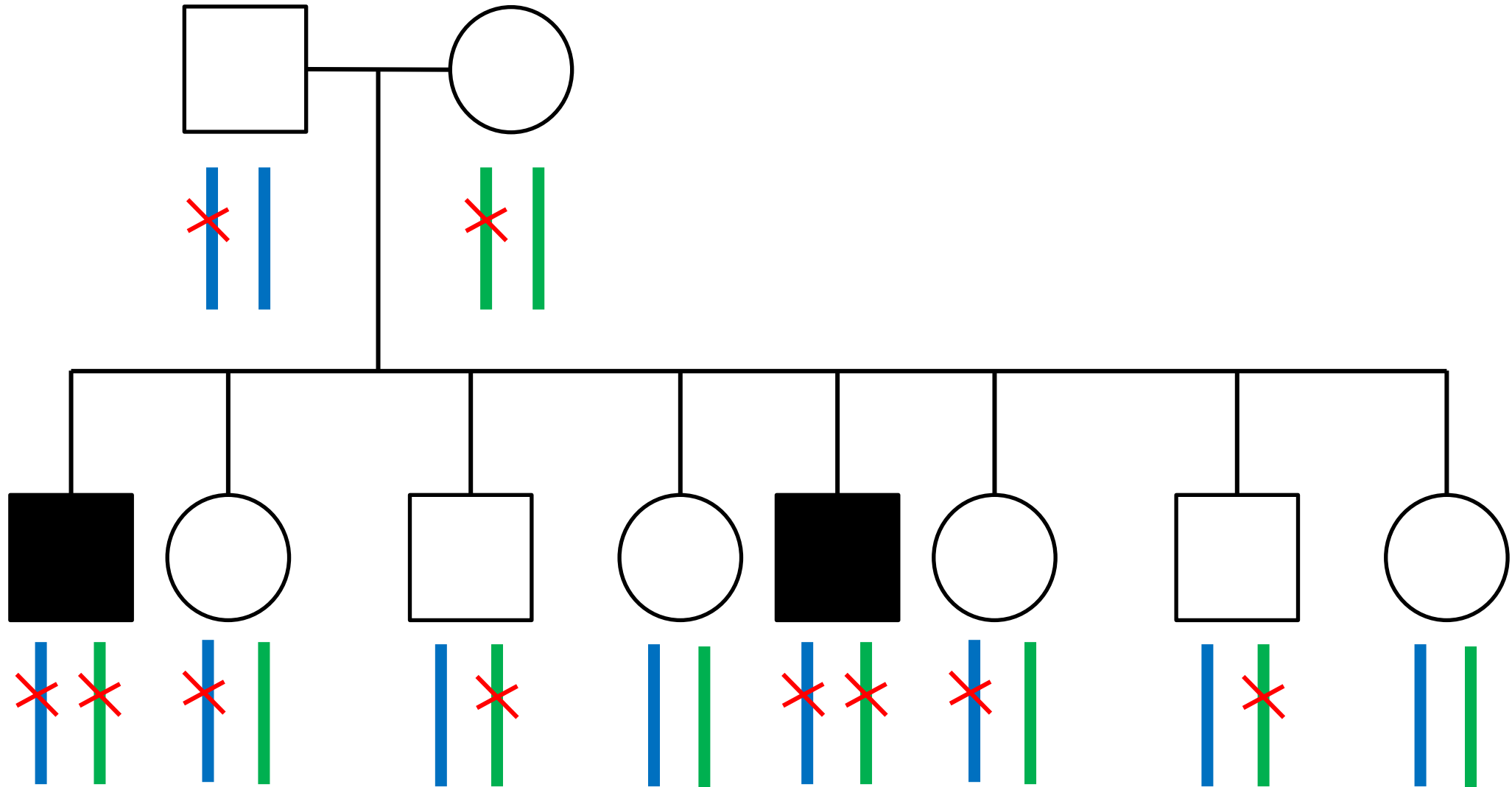
Causative mutation found (% cases)



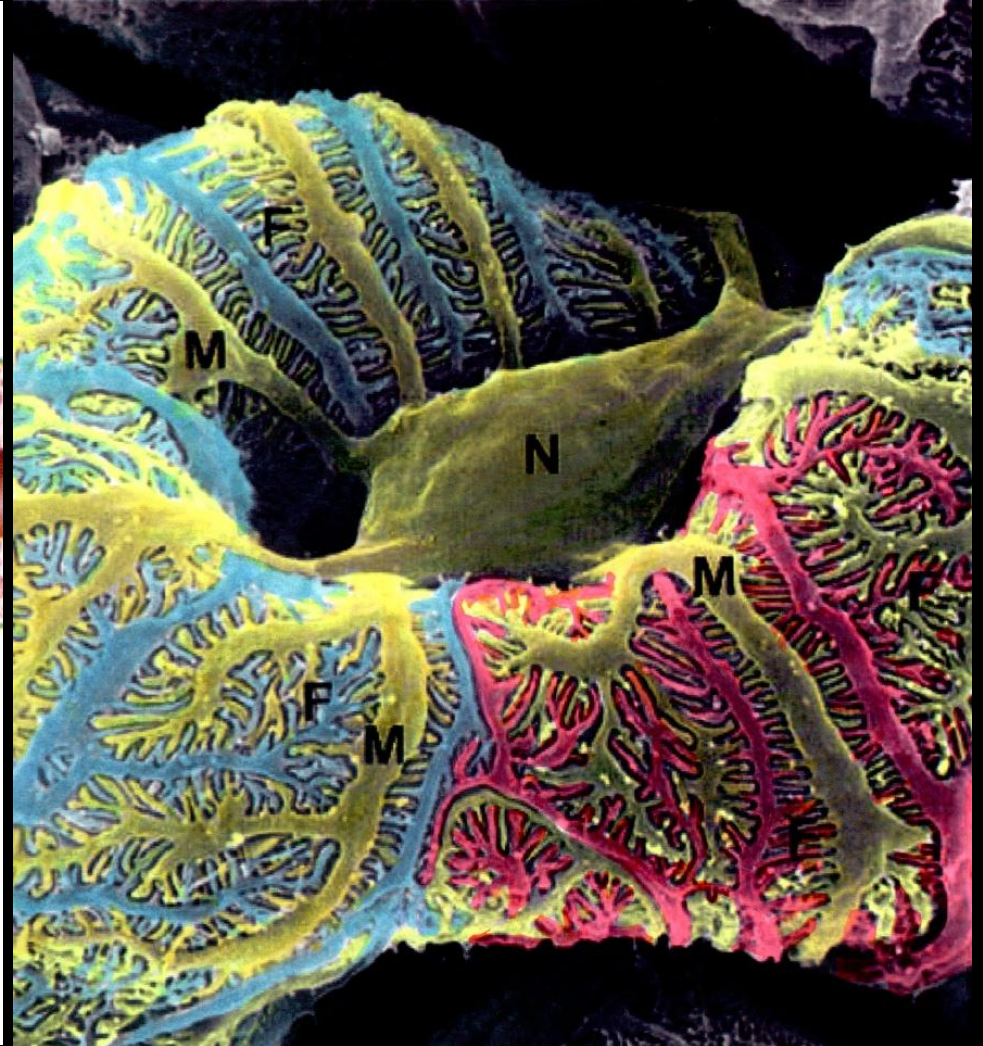
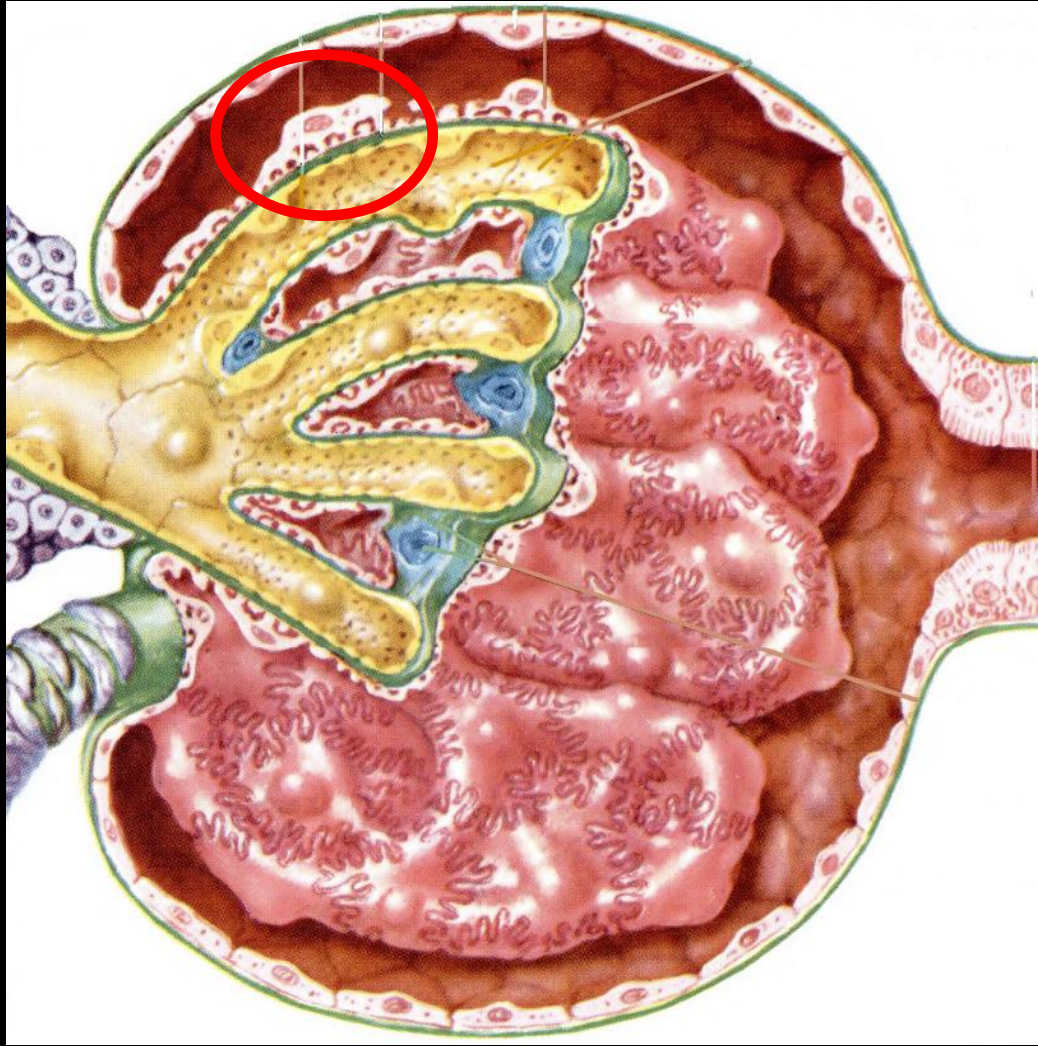
A recessive disease will most likely appear sporadic (non-familial) in your clinic



**Statistically, there need to be ≥ 8 sibs
for >1 to be affected (= “familial cases”)**

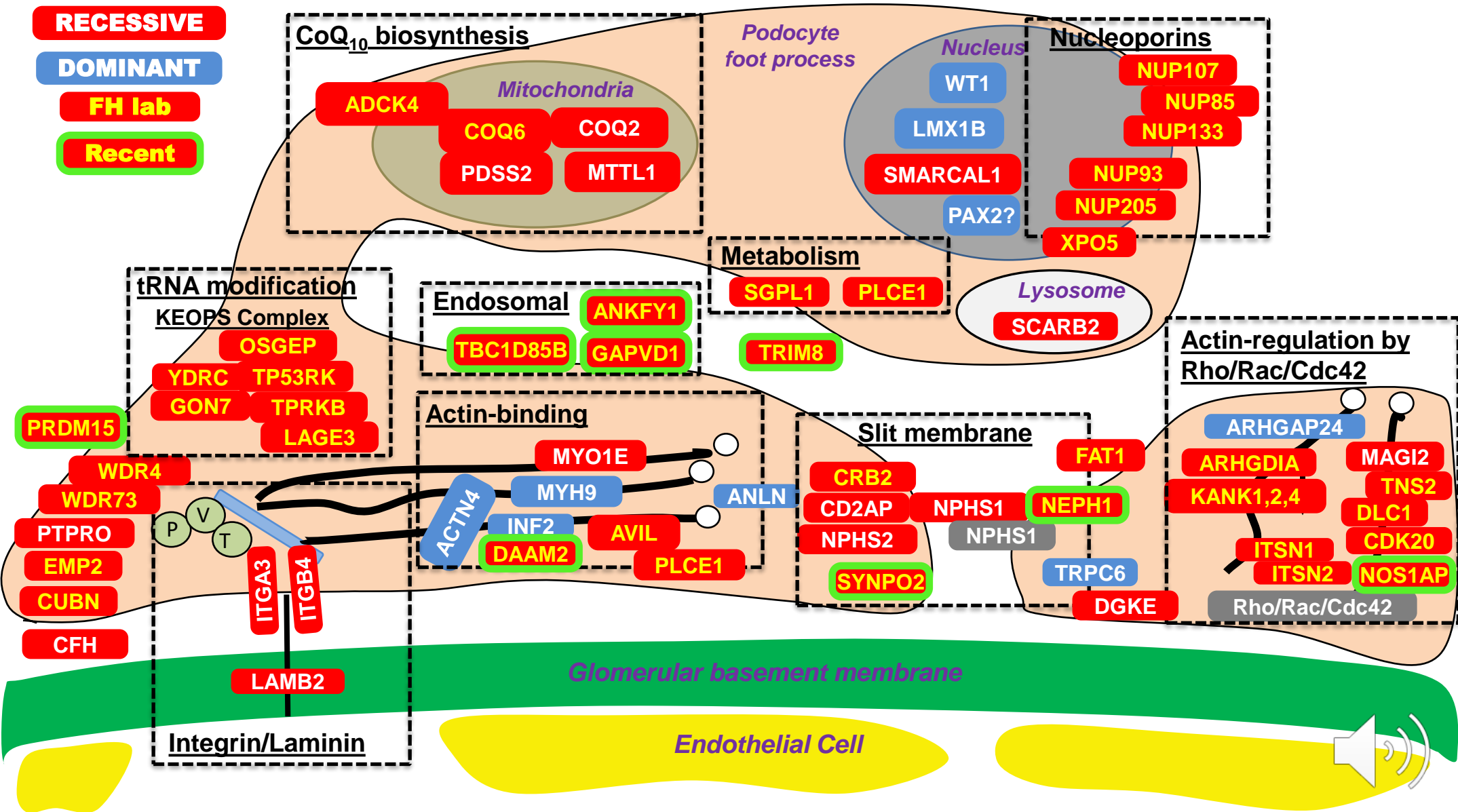


Gene Identification Moved the Glomerular Podocyte to Center Stage of SRNS Pathogenesis

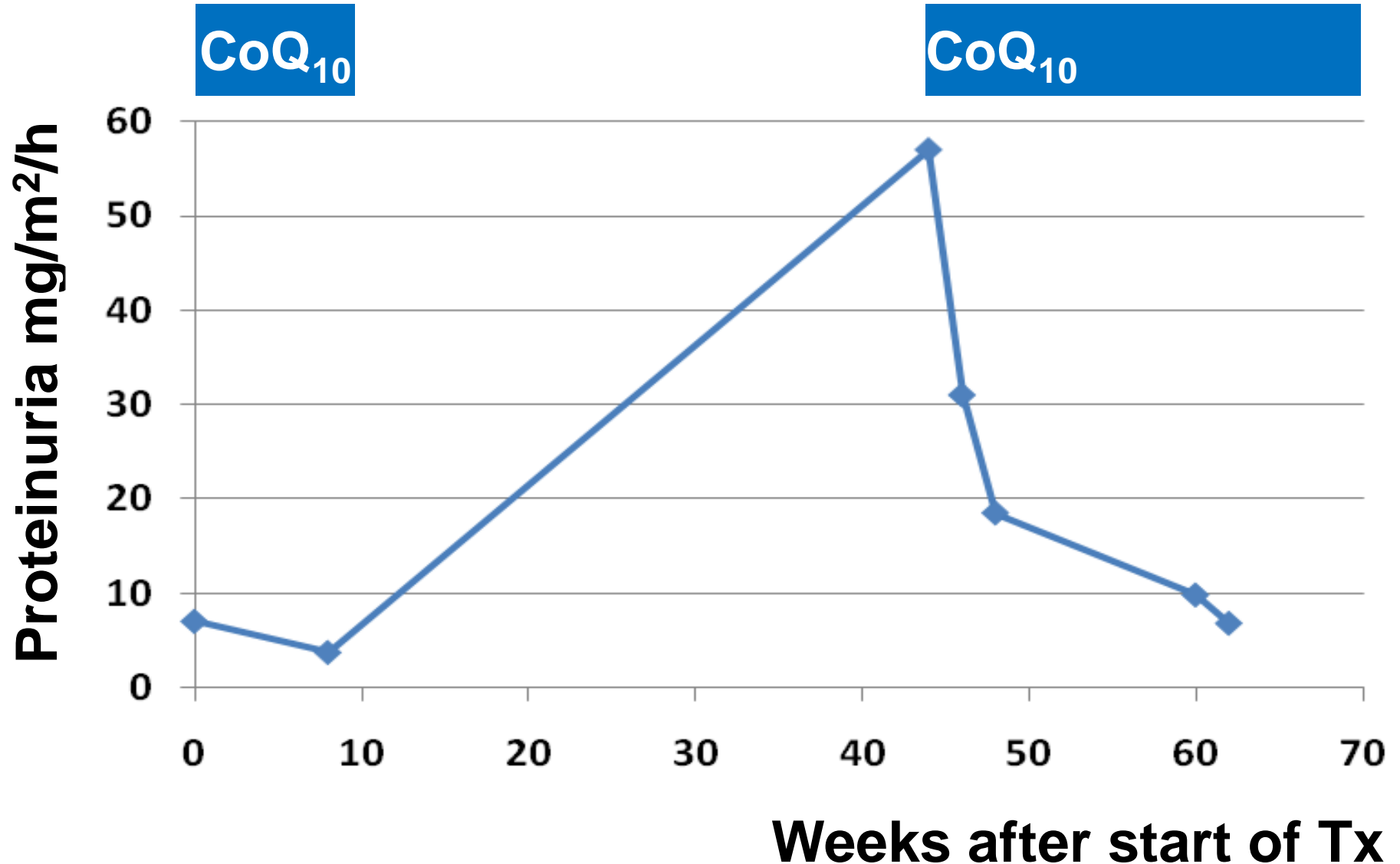


68 Monogenic Causes of SRNS/FSGS

(mapping to >10 pathways)



Q₁₀ treatment in SRNS & COQ6 mutation



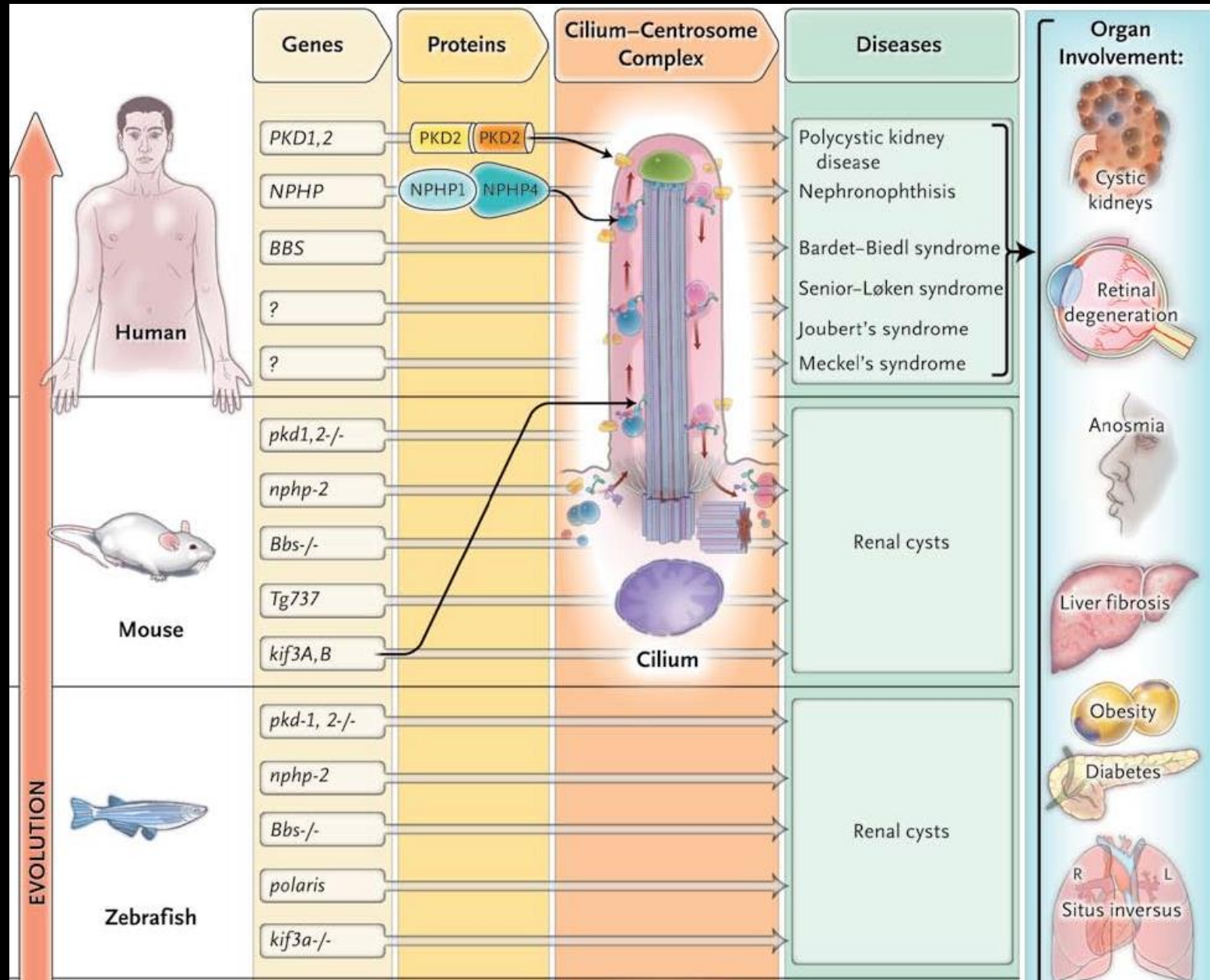
**Detection of monogenic
causes of SRNS may
reveal existing
therapeutic options.**

(e.g. Coenzyme Q₁₀)

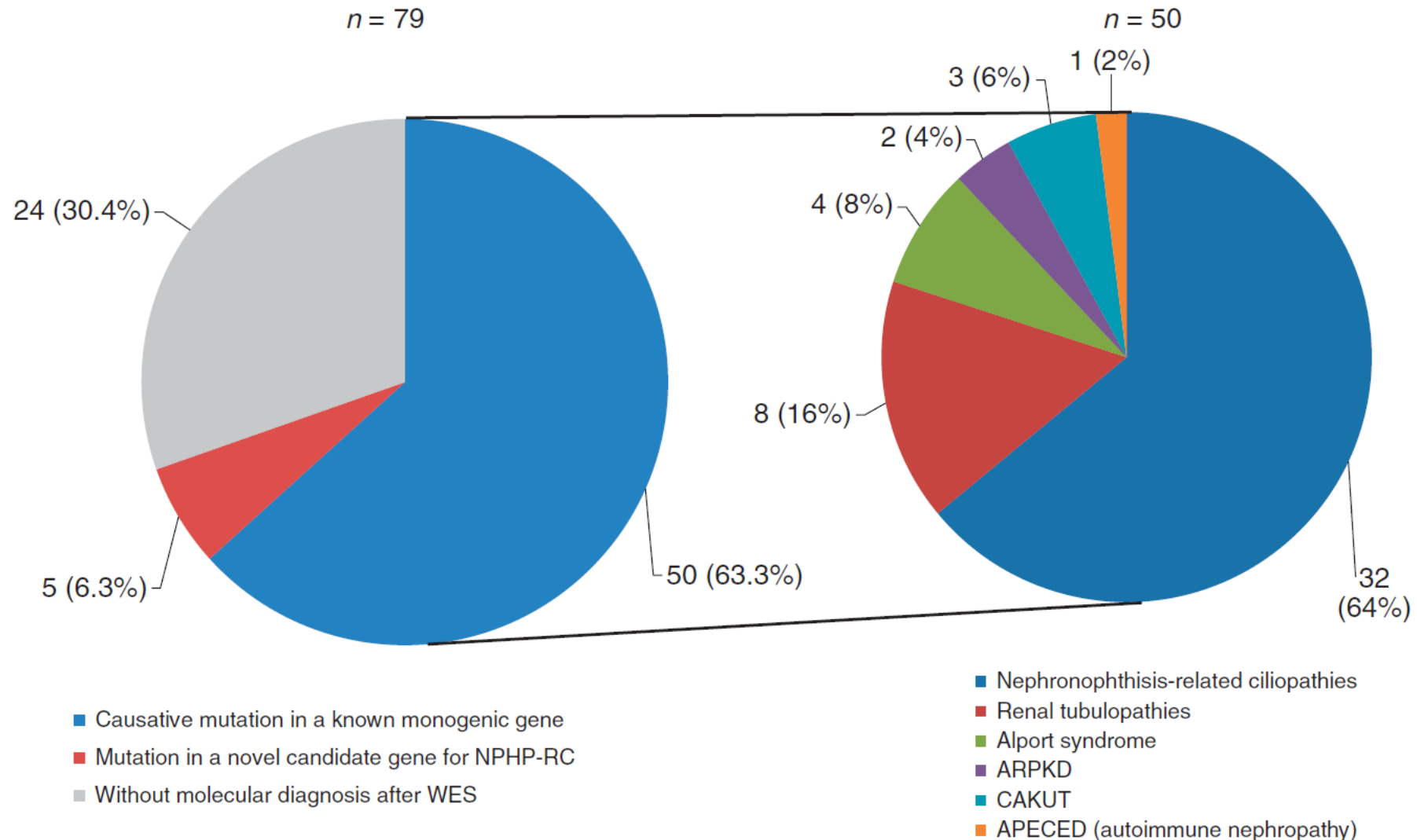
Many monogenic genes cause CKD <25 yrs

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Cystic kidney diseases are “ciliopathies”



Increased renal echogenicity: Causative mutation detected in ~63% of cases

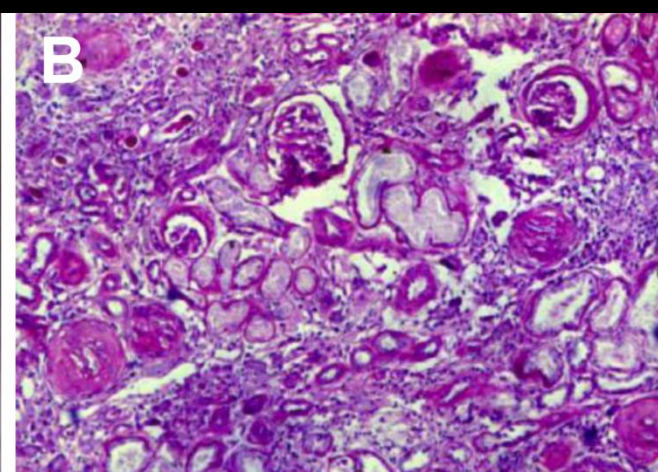


(Braun *Kidney Internat* 89:468, 2016)

**Whole exome sequencing
may reveal the disease
cause in a difficult
differential diagnosis.**

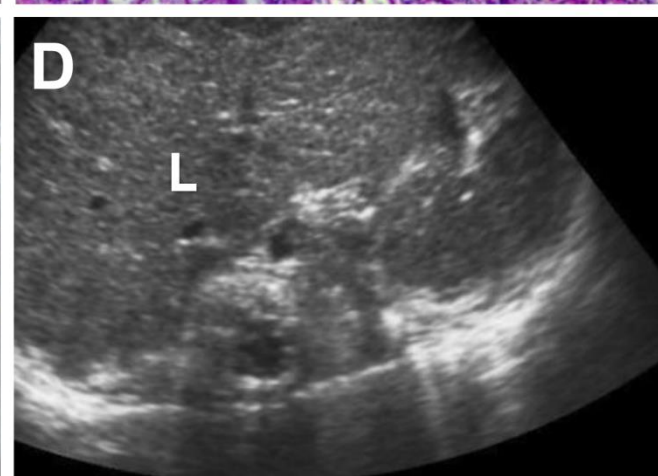
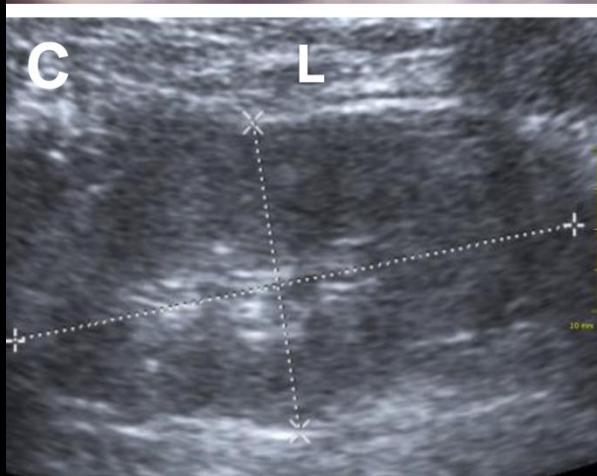
**(Clinical entry criteria: Cysts and/or
↑ echogenicity on renal US <25 yrs)**

NPHP4



SLC41A1

PKHD1



AGXT



SLC4A1

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15% (11-21%) of **nephrolithiasis** is caused by **single-gene** mutations

Fourteen Monogenic Genes Account for 15% of Nephrolithiasis/Nephrocalcinosis

Jan Halbritter,* Michelle Baum,* Ann Marie Hynes,[†] Sarah J. Rice,^{†‡} David T. Thwaites,[‡] Zoran S. Gucev,[§] Brittany Fisher,* Leslie Spaneas,* Jonathan D. Porath,* Daniela A. Braun,* Ari J. Wassner,^{||} Caleb P. Nelson,[¶] Velibor Tasic,[§] John A. Sayer,[†] and Friedhelm Hildebrandt***
(Halbritter *JASN* 26:543, 2015)

Prevalence of Monogenic Causes in Pediatric Patients with Nephrolithiasis or Nephrocalcinosis

Daniela Anne Braun, Jennifer Ashley Lawson,* Heon Yung Gee,*[†] Jan Halbritter,*[‡] Shirlee Shril,* Weizhen Tan,* Deborah Stein,* Ari J. Wassner,[§] Michael A. Ferguson,* Zoran Gucev,^{||} Brittany Fisher,* Leslie Spaneas,* Jennifer Varner,* John A. Sayer,[¶] Danko Milosevic,** Michelle Baum,* Velibor Tasic,^{||} and Friedhelm Hildebrandt*^{†‡}*

(Braun *cJASN* 11:664, 2016)

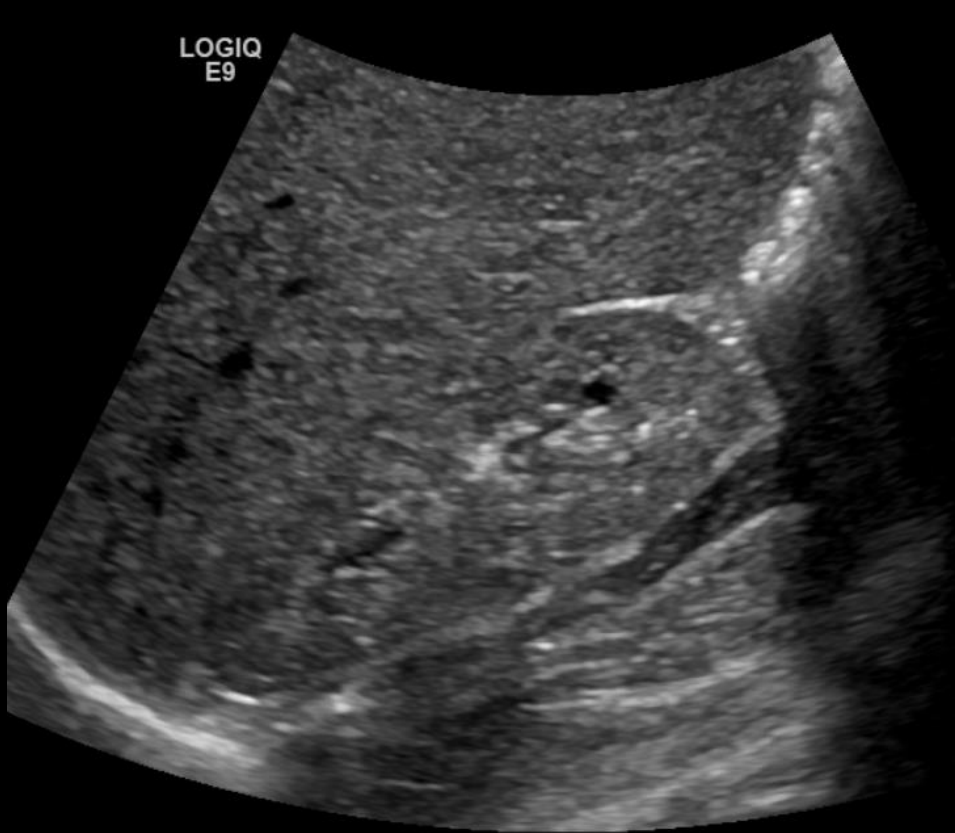
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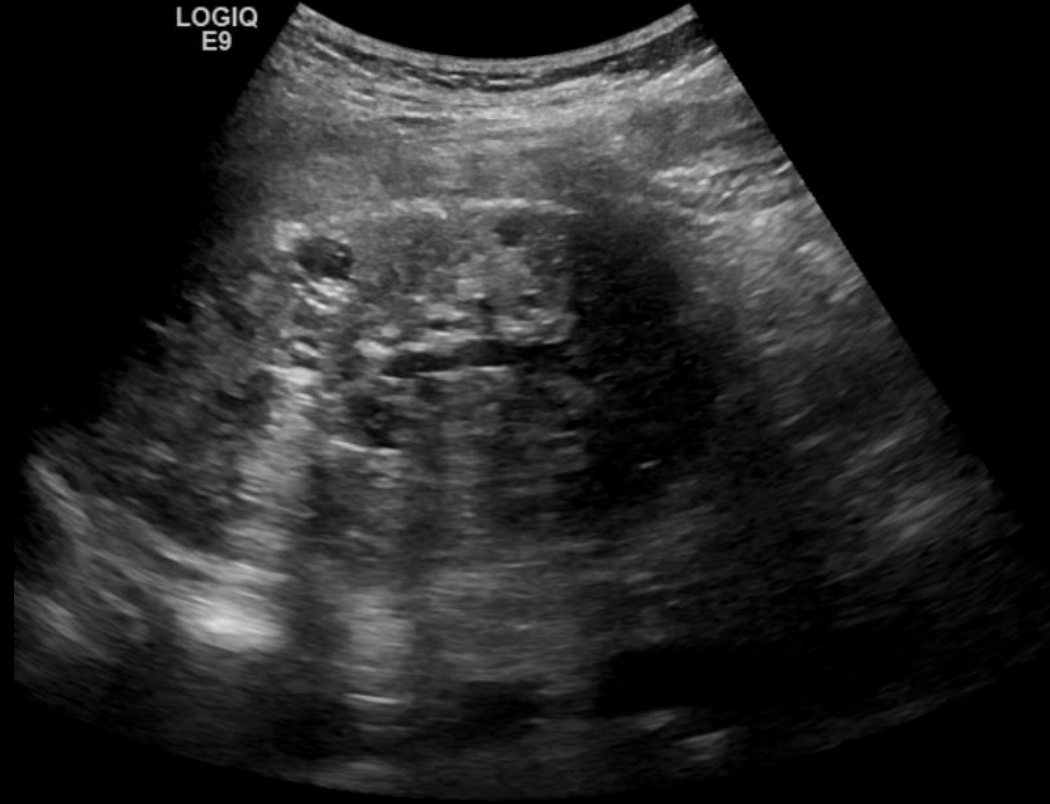
Case: A 7-year-old boy with cystic kidney disease, hyperuricemia and ASD

- Normal renal function, BP and urinalysis
- No systemic abnormalities related to his CKD
- Additional findings:
 - Hyperuricemia (5.6-7.4 mg/dL)
 - Slightly low Mg (1.5 mg/dL)
 - Autism spectrum disorder
 - Significant positive family history as his father, paternal uncles and paternal grandmother have similar condition.

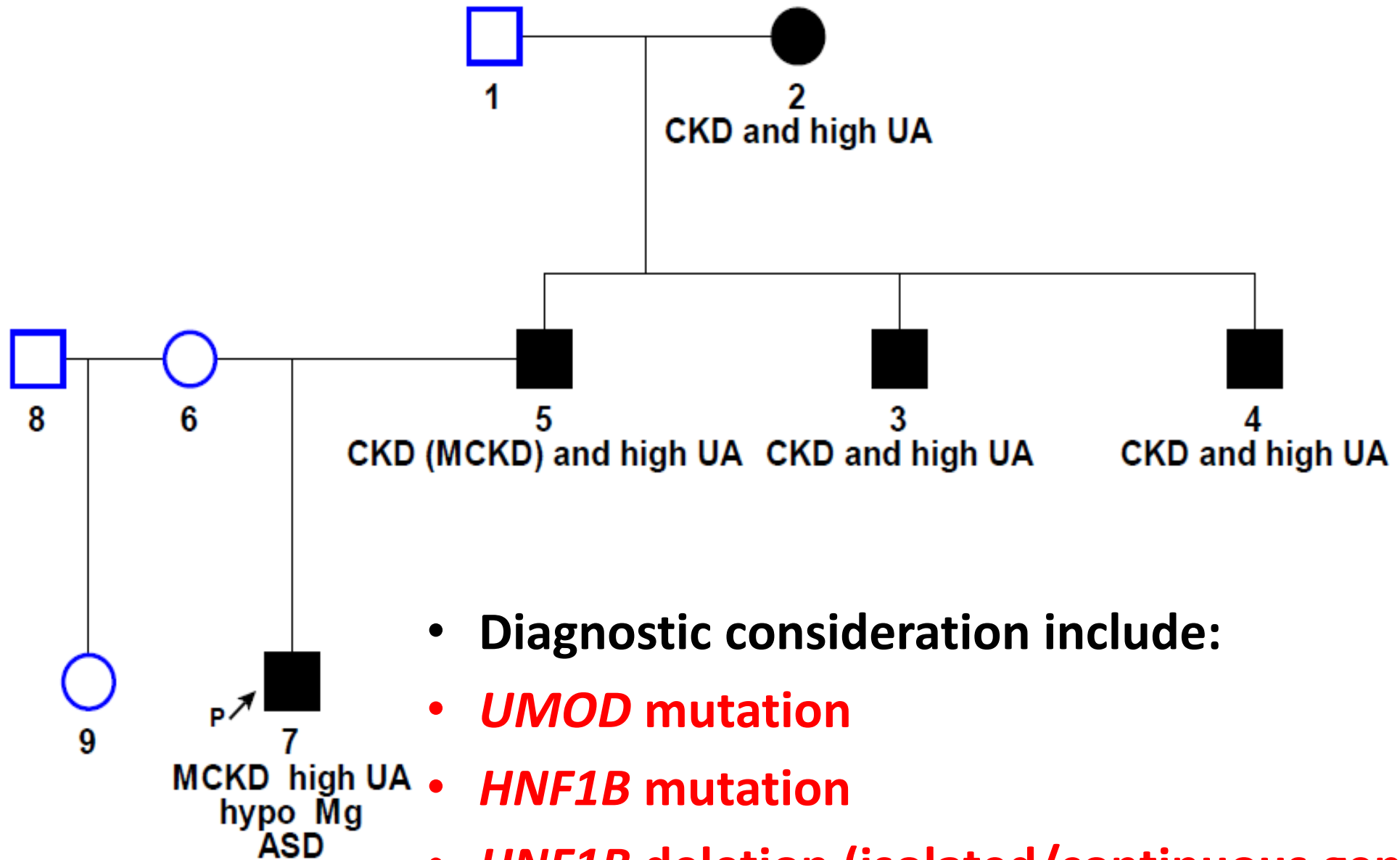
Renal US - age 7y



SAG RT KIDNEY



SAG LT KIDNEY



- Diagnostic consideration include:
- ***UMOD* mutation**
- ***HNF1B* mutation**
- ***HNF1B* deletion (isolated/continuous gene del)**

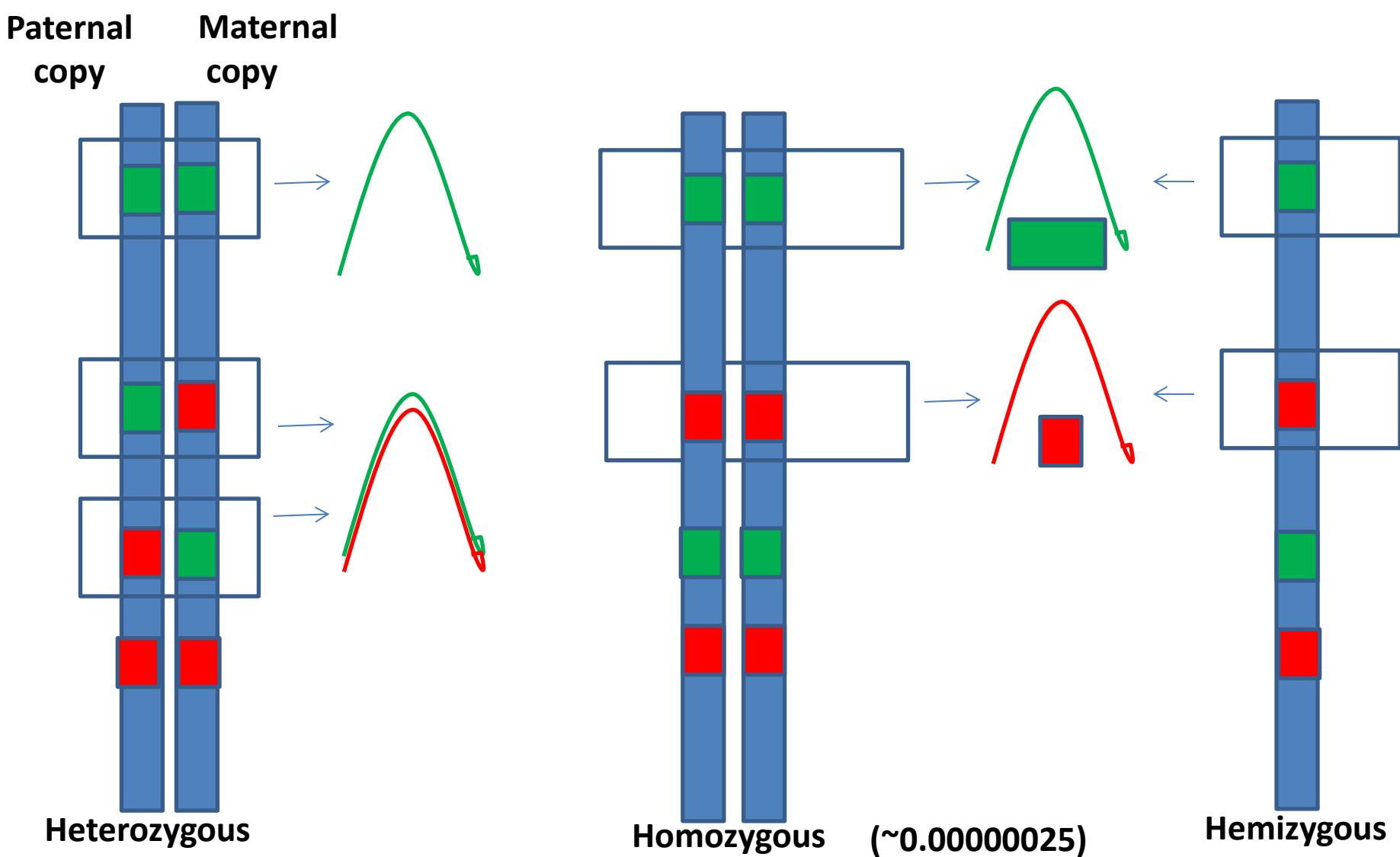
Uromodulin (UMOD) mutations may cause Autosomal Dominant Tubulointerstitial Disease (ADTKD)

- The *Uromodulin (UMOD)* gene encodes the Tamm-Horsfall protein.
- Mutations in *UMOD* can also lead to two additional clinical entities named:
 - (1) familial juvenile hyperuricemic nephropathy (FJHN)
 - (2) glomerulocystic kidney disease (GCKD).
- Although ADTKD represents a subtype of CAKUT, among cases of isolated CAKUT it is estimated that *UMOD* mutations are very rare.

Molecular diagnostic analysis

- ***UMOD* sequencing – Negative**
- ***HNF1B* mutation - Negative**
- ***HNF1B* deletion (isolated/continuous gene del)
– traditionally deletions can not be detected with Sanger sequencing and we referred the patient for genetic counseling in order to perform CNV analysis.**
- **Nonetheless, sequencing of all *HNF1B* exons, showed absence of heterozygosity, suggesting that the patient has heterozygous deletion.**

Absence of Heterozygosity may indicate deletion of 1 allele, consanguinity, or uniparental disomy



HNF1B mutations cause a multi-system disorder

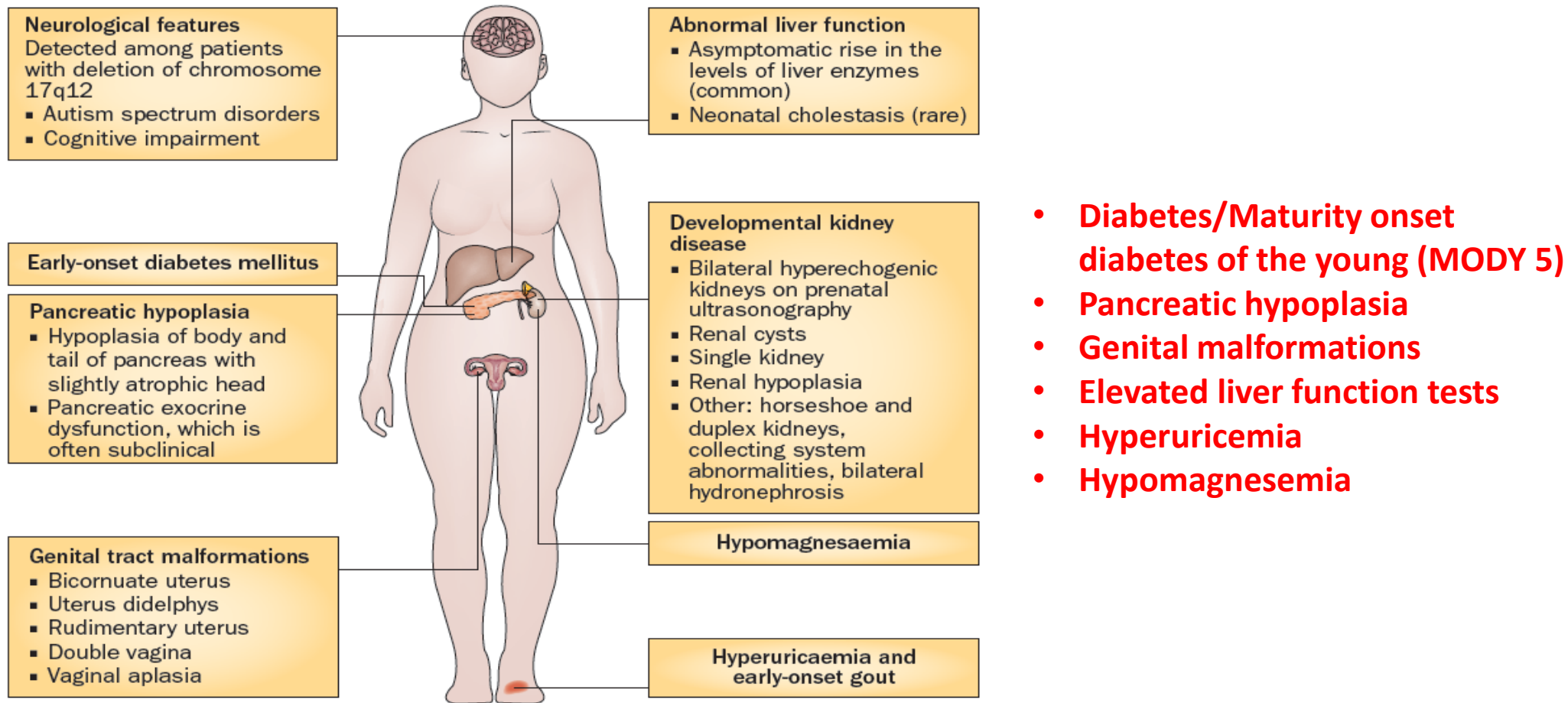


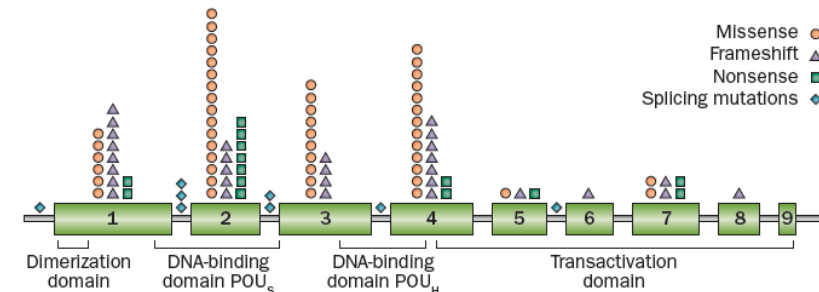
Figure 1 | Renal and extra-renal phenotypes frequently observed among patients with hepatocyte nuclear factor 1 β -associated disease.

(Clissold RL, Nature Rev Neph, 2015; Bockenhauer D, Pediatr Nephrol, 2015)

HNF1B spectrum disorders – genetic findings

- More than 150 different *HNF1B* genetic mutations have been reported, and so far there is no evidence for genotype-phenotype correlation, other than the continuous gene deletion.
- About 50% of the genetic abnormalities in *HNF1B* are heterozygous deletions of the entire gene. Those large deletions, cannot be identified using Sanger sequencing or WES and require copy number variation analysis
- De novo occurrence of *HNF1B* deletions/mutations can be as high as 50%. This explains why often there is no family history of affected individuals.

(Clissold RL, Nature Rev Neph, 2015)



Clinical implications of genetic diagnosis for patients with *HNF1B* spectrum of disorders

- **Provides a definitive diagnosis and allows genetic counseling.**
- **Allows avoidance of unnecessary diagnostic procedures.**
- **Early detection and treatment of extra-renal manifestations:**
 - **Monitoring Mg and uric acid levels**
 - **Monitoring for the development of diabetes and reducing future risk for diabetic (e.g. minimization of prodiabetic drugs, such as glucocorticoids and tacrolimus)**
 - **Take into consideration for parent donor selection prior to transplantation.**

Indication-driven mutation analysis panels for single-gene causes of CKD <25 yrs

Indication	# of genes	Detect cause in
<u>Steroid-resistant nephrotic syndrome</u> Proteinuria	59	11-30%
<u>Cystic kidney disease</u> US: cysts or echogenicity	100	>70%
<u>CAKUT</u> Imaging	45	>20%
<u>Renal stones</u> Stone or nephrocalcinosis	30	>20%
<u>The “Nephrome”</u> All CKD <25 yrs	~234	>20%

State of the Art

Every patient with a kidney disease manifesting <25 yrs should be offered molecular genetic diagnostics, if consenting, because:

- ... it is now available**
- ... provides an unequivocal diagnosis**
- ... may (rarely) reveal a potential treatment**
- ... allows etiologic classification for therapeutic trials, and potentially personalized treatment**
- ... provides the missing pieces for the puzzle of pathogenic pathways**
- ... enables generation of gene-specific animal models**
- ... enables screening for therapeutic molecules**

Thank You!