Welcome to

ERKNet/ESPN/ERA Educational Webinars on Pediatric Nephrology & Rare Kidney Diseases

WEBINAR

22/03/22

Mendelian and non-mendelian inheritance

Speaker: Kalman Tory (Budapest, Hungary)

Moderator: Elena Levtchenko (Leuven, Belgium)

ERKNet The European Rare Kidney Disease Reference Network

european society for paediatric nephrology

ERA LEADING EUROPEAN NEPHROLOGY

May I ask your specialty?

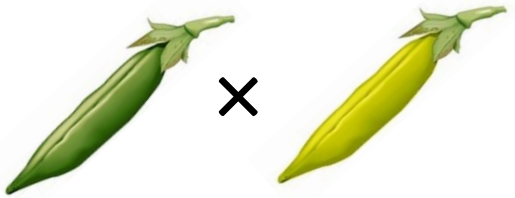
- clinical genetics
- pediatric nephrology
- adult nephrology
- research, molecular biology
- other

Mendel's Principles of Heredity

Seven *binary* characters of pea plant

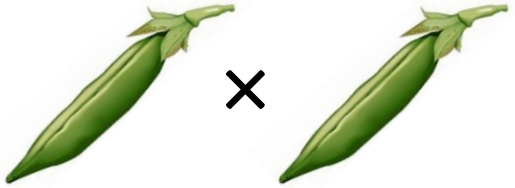
20/07/1822 – 1884
‚chronic nephritis'

P



characters are unitary : *not a blend*, and corresponds to one of the parental character: ‚**the dominant**'

F1



the ‚**recessive'** characters ***reappear unlinked*** in the second generation **in 25%** of the offspring

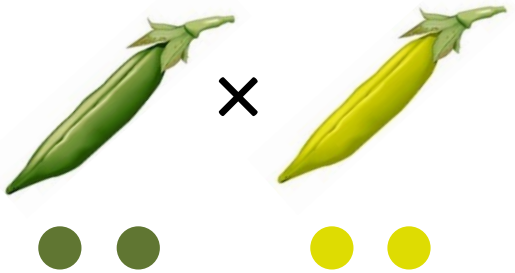
F2

Mendel's Principles of Heredity

20/07/1822 – 1884
‚chronic nephritis'

Seven *binary* characters of pea plant

P



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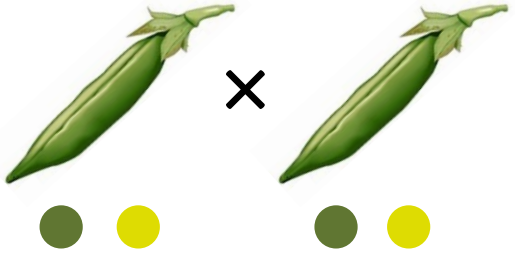
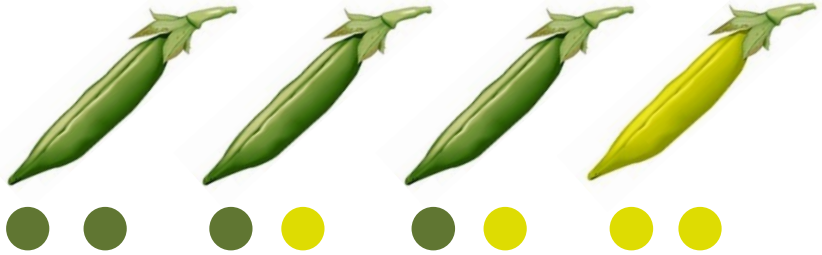


the ‚**recessive'** characters ***reappear unlinked*** in the second generation **in 25%** of the offspring

F2



alternate forms (alleles) of hereditary factors (genes) are created random and unlinked in the gametes

Differences between Mendel's experiments and the human monogenic disorders

pea plant in Mendel's experiments

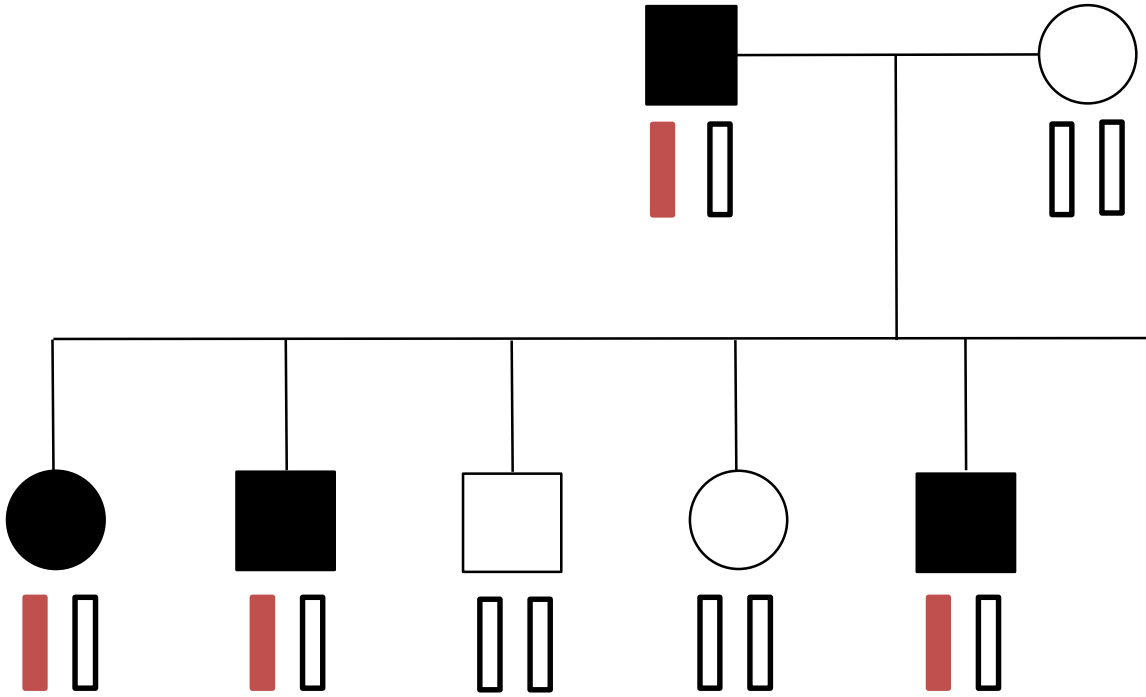
- inbred, homogeneous population
- single allele for each phenotype
- each allele gave 50% of all, in each generation

human monogenic disorders

- heterogeneous population
- both the disease-causing and the benign alleles are heterogeneous
- pathogenic alleles are rare

Mendelian genetics in clinical practice

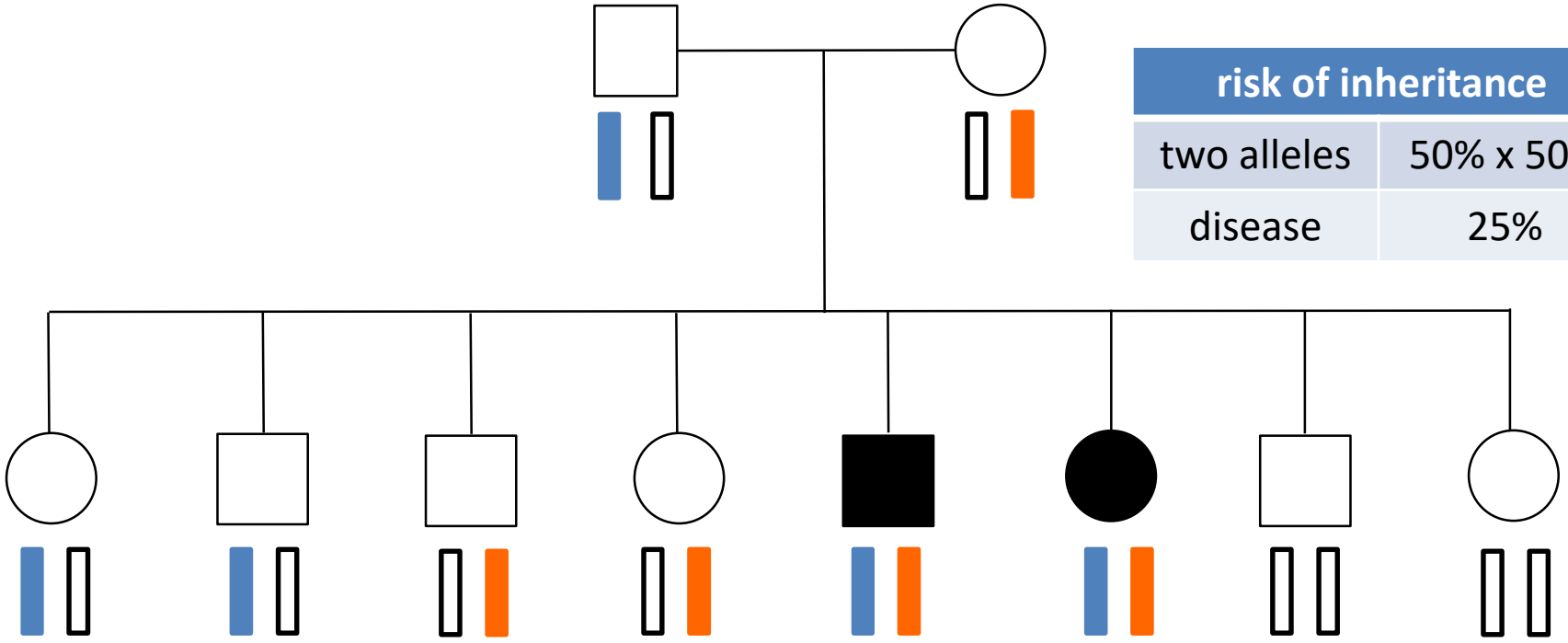
1. the disease-causing allele is dominant and located on an autosome



risk of inheritance	
single allele	50%
disease	50%

Mendelian genetics in clinical practice

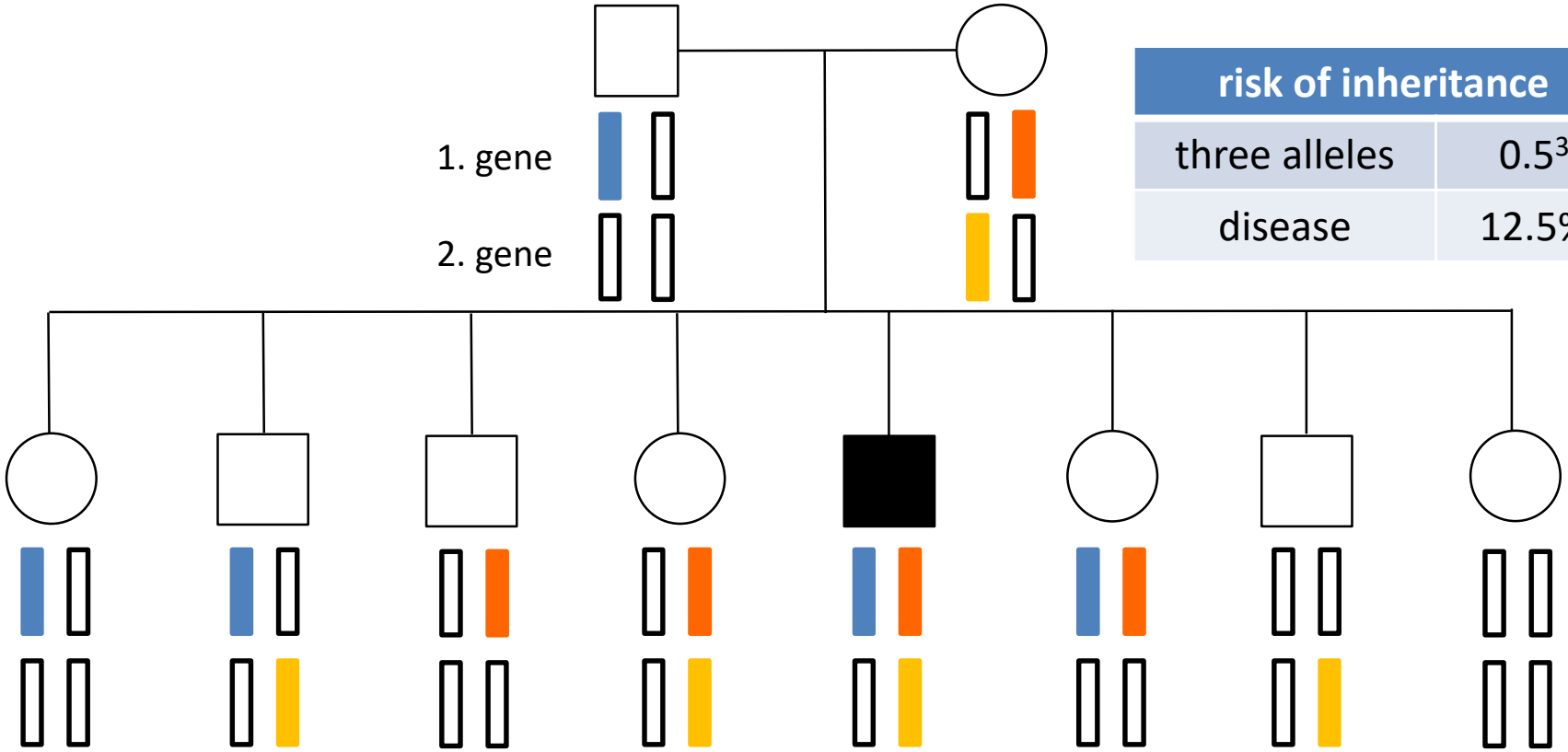
2. the disease-causing allele is recessive and located on an autosome



risk of inheritance	
two alleles	50% x 50%
disease	25%

Two affected siblings, at least one of whom is girl: AR

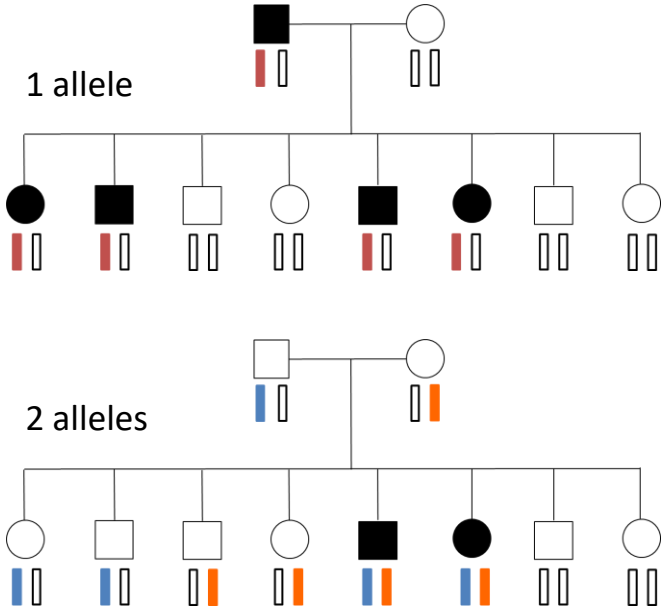
Oligogenic inheritance - two genes, three alleles

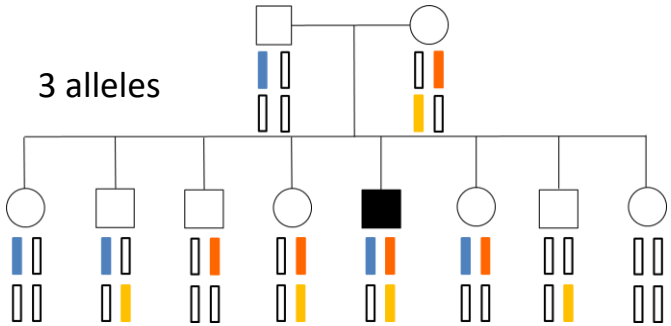


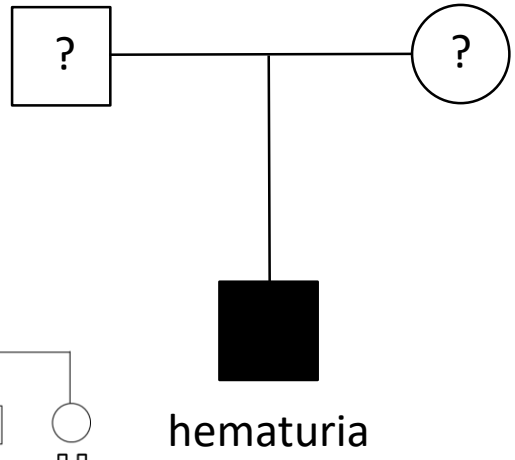
risk of inheritance	
three alleles	0.5^3
disease	12.5%

Monogenic disorders are clustered in families, rare multifactorial disorders are sporadic

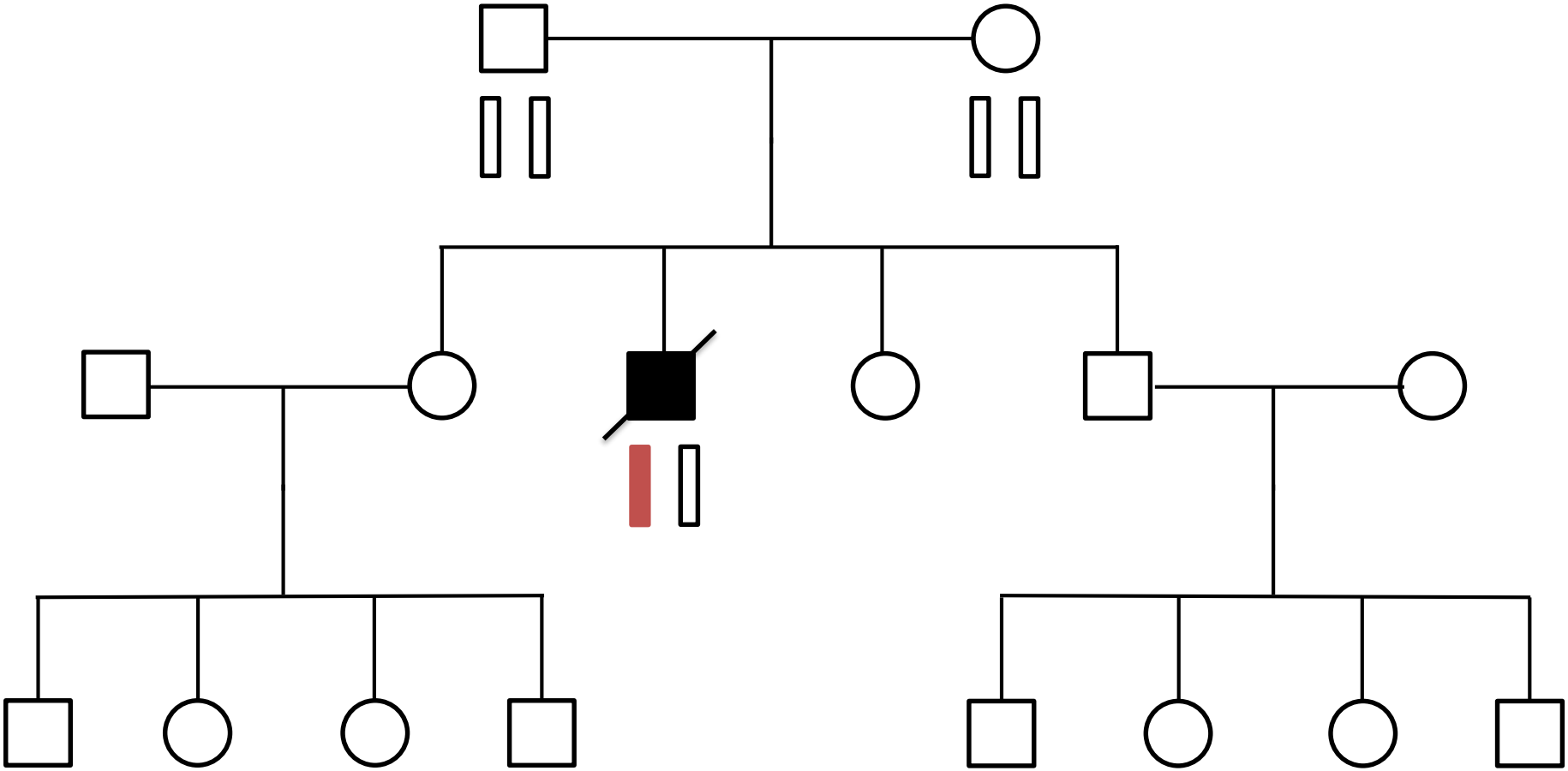
- The higher the number (n) of the alleles required for a disease, the less likely is its inheritance (0.5^n): **the less likely is familial clustering**
- The more family members are affected by the same disorder, the more likely it is monogenic







Severe AD disorders cannot be transmitted, thus always result from *de novo* mutations: mendelian but no familial clustering



Monogenic vs. non-mendelian diseases

monogenic / mendelian

1. determined by a *single* gene
   - completely penetrant
   - possibility of presymptomatic / prenatal diagnosis

2. familial clustering is possible
   - in some families they show typical transmission pattern / clustering
   - most are still sporadic

non-mendelian

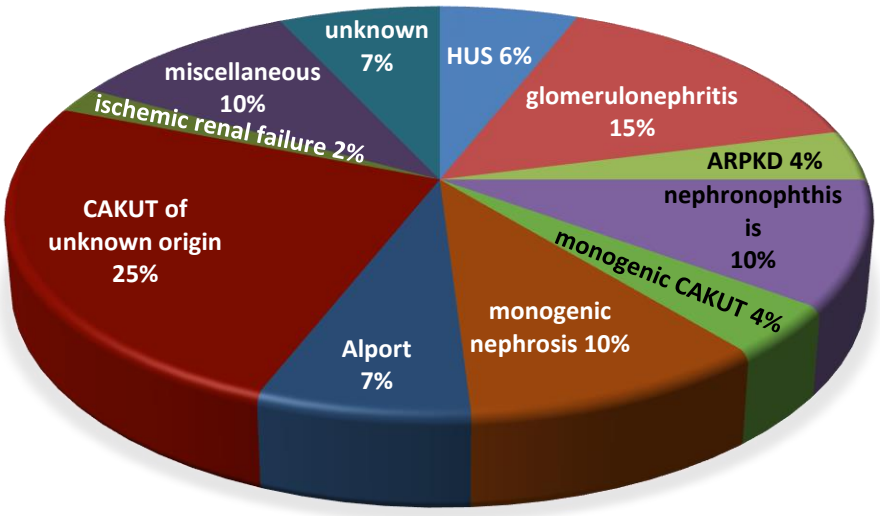
1. determined by several genes / environmental factors
   - ‚incompletely penetrant'
   - only a risk might be estimated

2. sporadic in general
   - ***no familial clustering***
   - unless a relatively frequent disorder (diabetic nephropathy)

Mendelian disorders are frequent in childhood ESRD

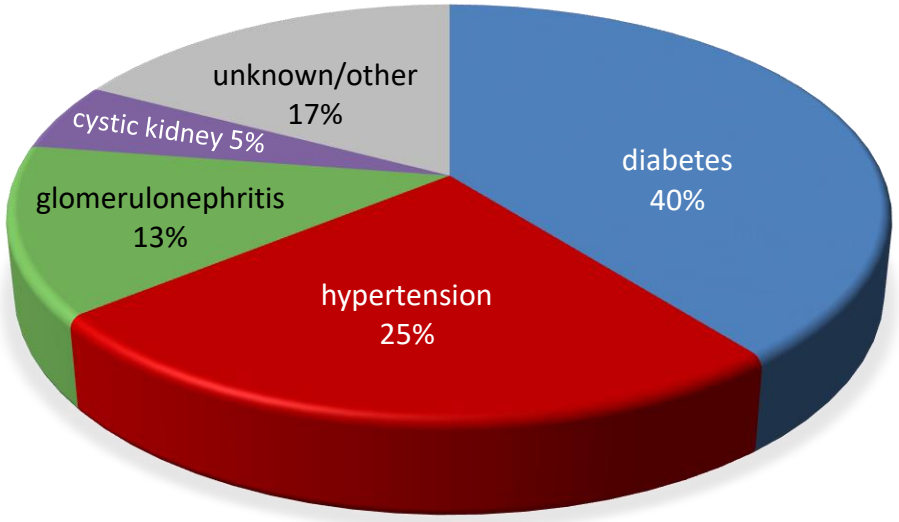
Etiology of end-stage renal disease

Childhood



ERA/EDTA registry

Adulthood

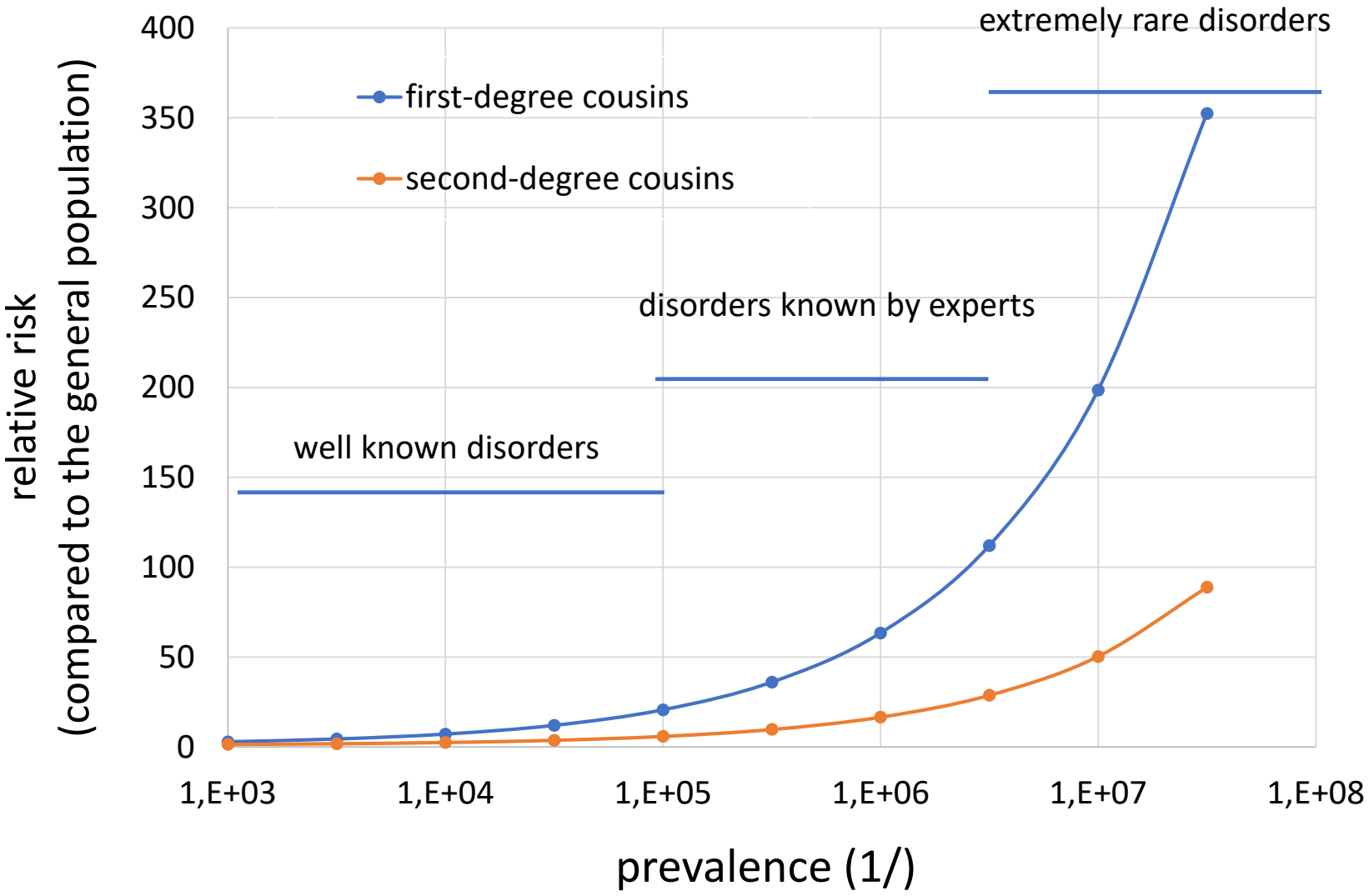


https://www.usrds.org/reference.aspx

Do you ask the parents about their potential consanguinity when you consult a child with a nephropathy of unknown etiology?

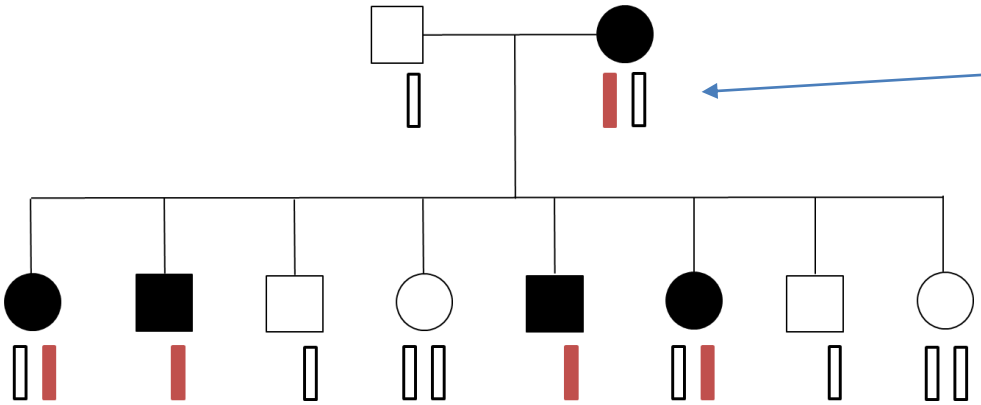
1. most of the time
2. only if they come from populations with a high degree of CS
3. I prefer not, it can be insulting
4. I am an adult nephrologist...

Risk of having an affected child in consanguineous families in function of the prevalence of autosomal recessive diseases



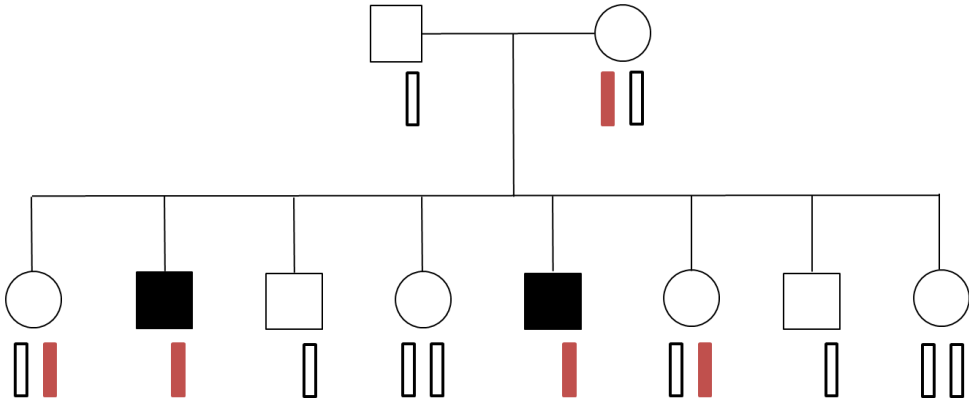
Monogenic nephropathies with an unexpected transmission pattern

This is the phenotype that is transmitted in a dominant or a recessive fashion



X-linked dominant

The variant may be dominant or recessive, but always transmitted with a 50% risk

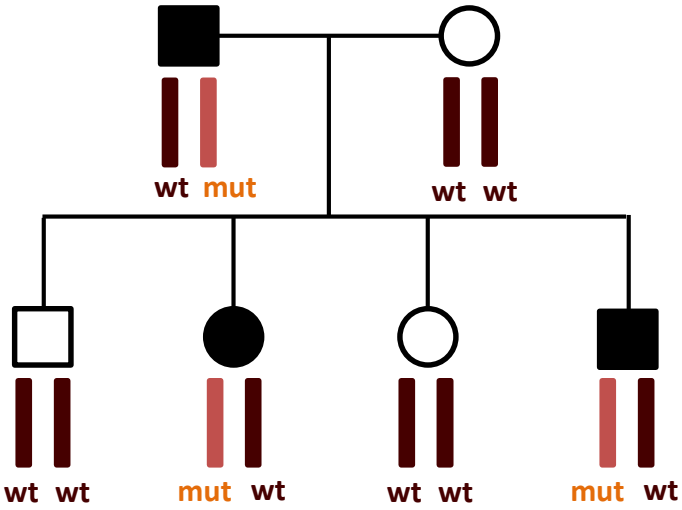


X-linked recessive

The transmission pattern reflects the underlying pathophysiology

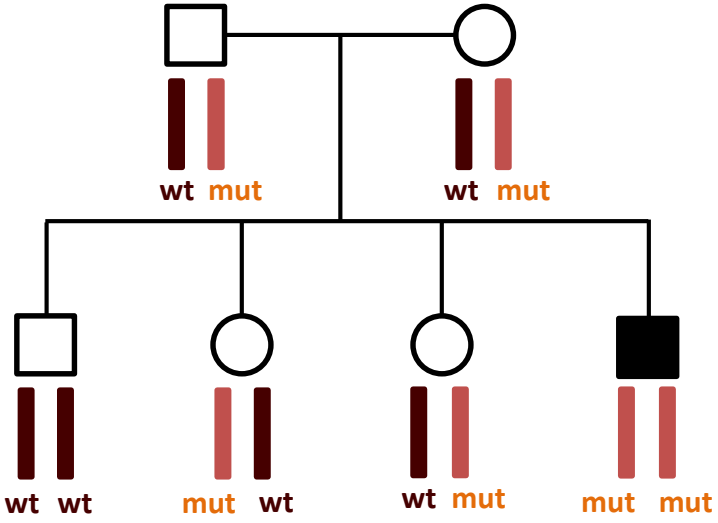
1. 50% function loss (haploinsufficiency)
2. dominant negative effect
3. gain of function
4. second hit

autosomal dominant
n ~ 2900 disorders



(almost) complete loss of function

autosomal recessive
n ~ 3400 disorders

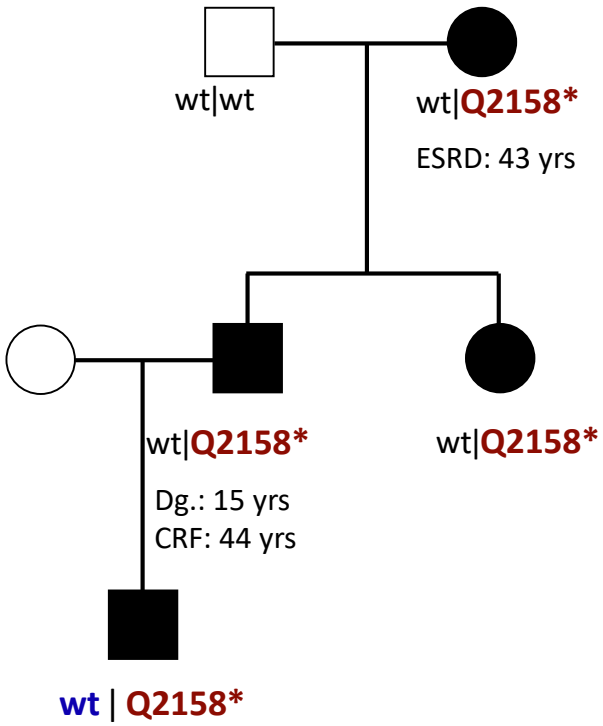


A protein may be dysfunctional through different mechanisms

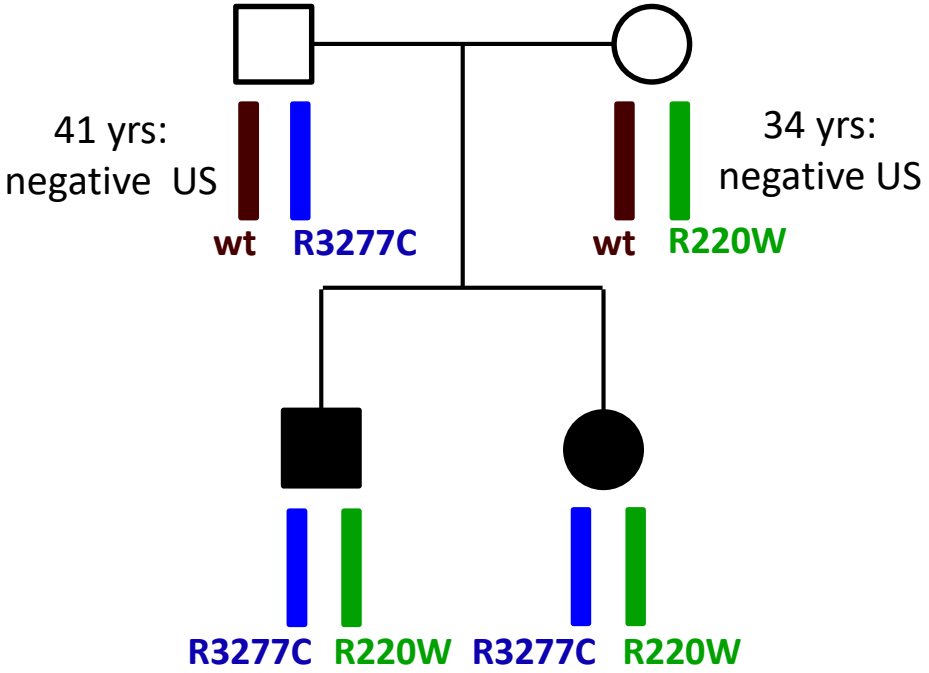
The transmission pattern related to the same gene may vary

PKD1-related polycystic kidney disease may occasionally be transmitted in an AR fashion

null mutation of *PKD1:* ADPKD



hypomorphic mutations of *PKD1*: autosomal recessive transmission

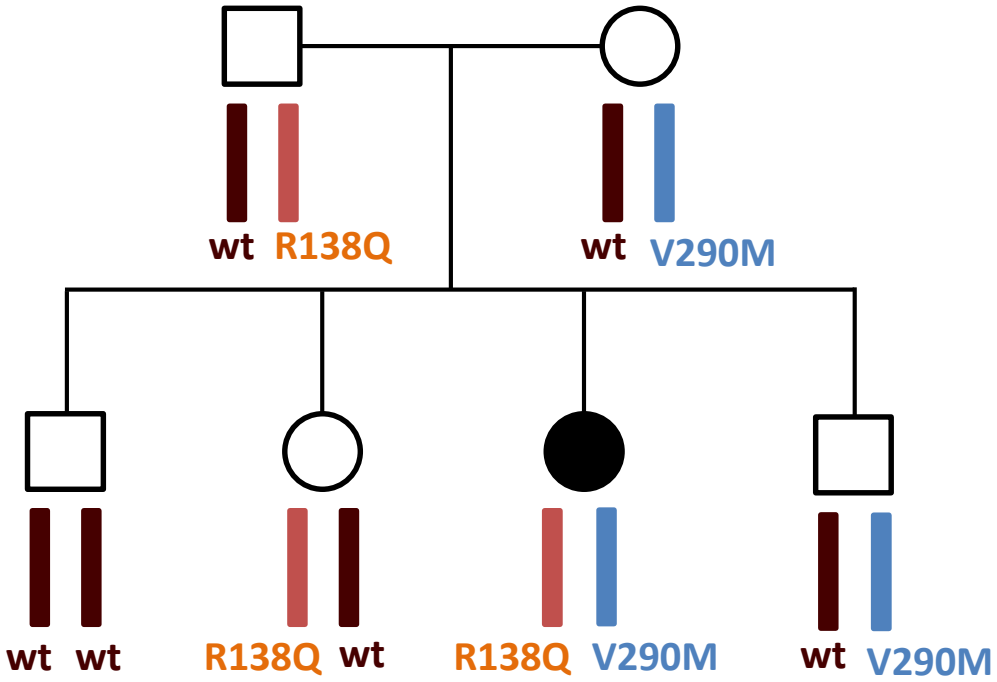


hyperechogenic, enlarged kidneys in utero, neonatal respiratory insufficiency

Vujic M et al., JASN, 2010

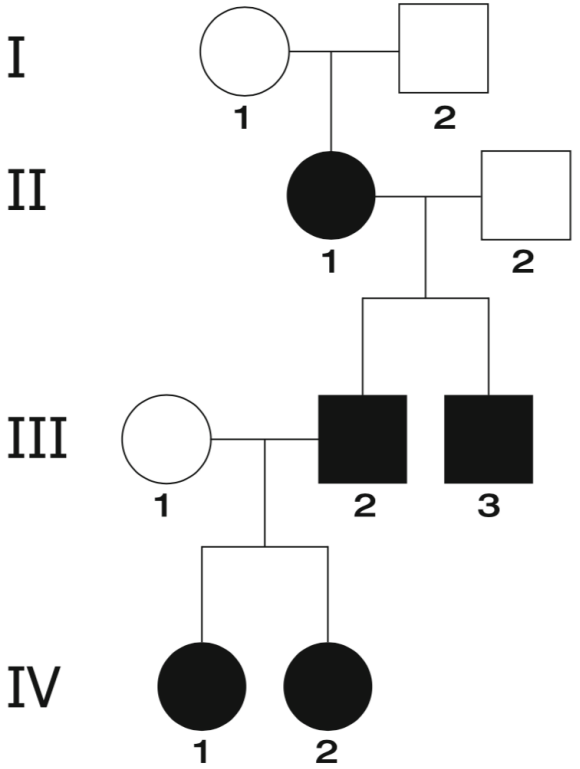
NPHS2-associated podocytopathy exceptionally transmitted in an AD fashion

NPHS2, encoding podocin - AR SRNS



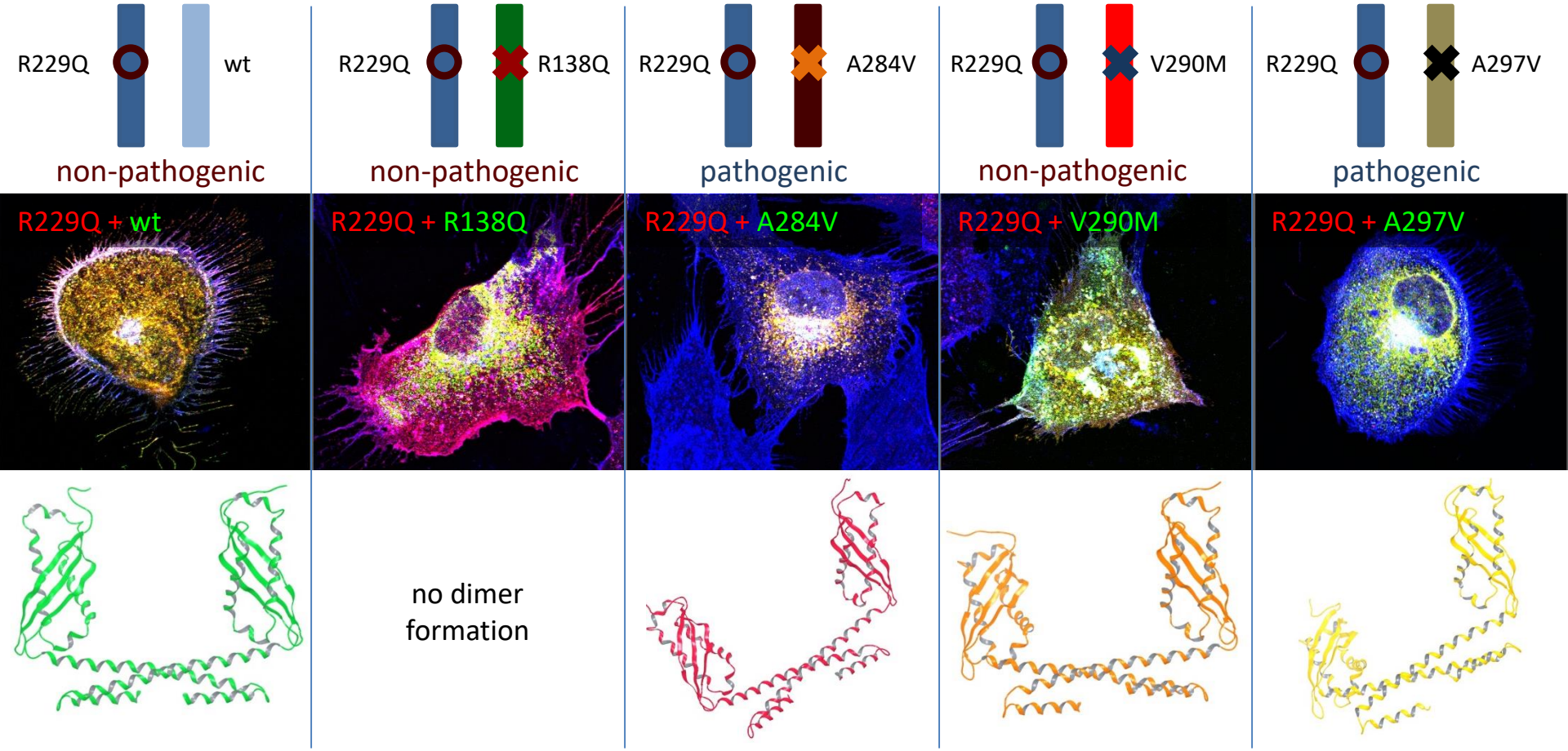
Boute et al, Nat Genet, 2000

de novo NPHS2 mutation (L330Vfs*15), AD FSGS



Suvanto et al, Clin Exp Nephrol, 2016

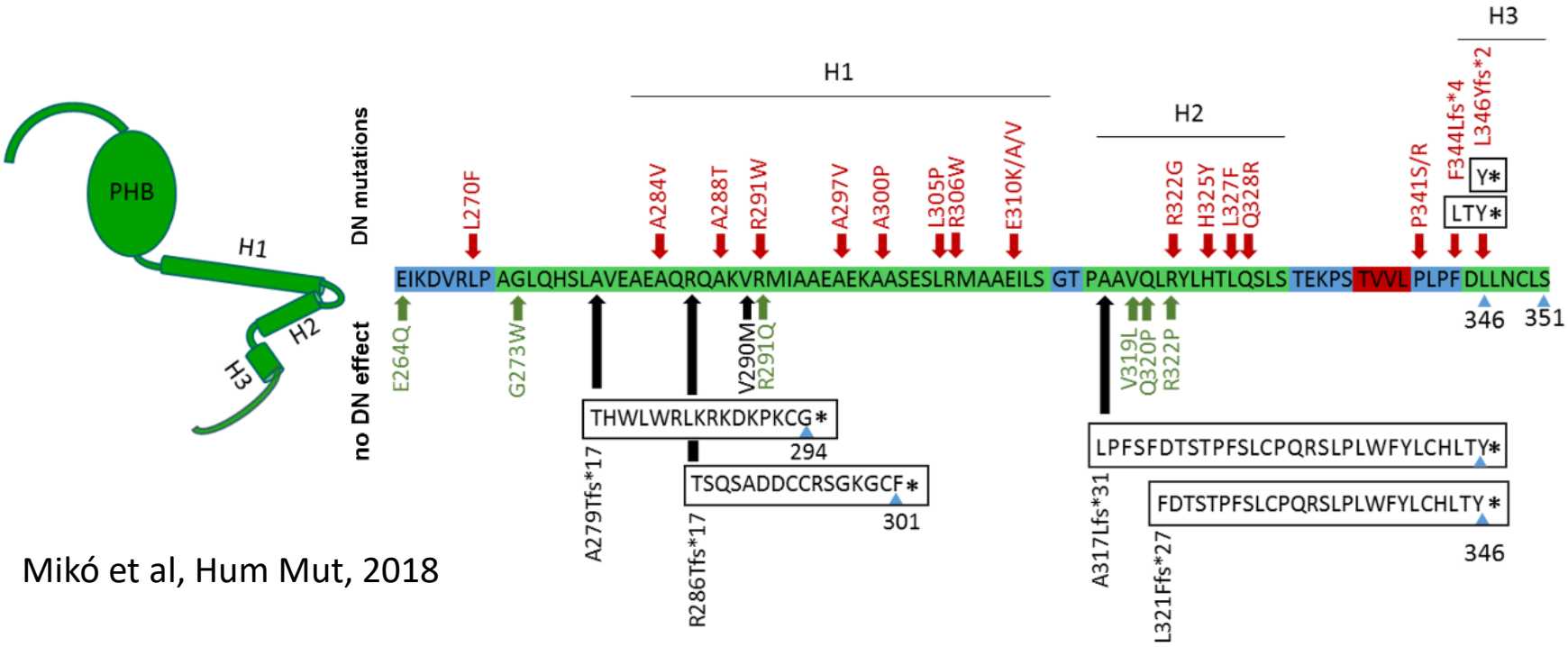
NPHS2 R229Q: a benign variant that is dominant over most pathogenic variants but recessive with others



Tory et al., Nat Gen, 2014

For genetic counseling we need to know which variants are pathogenic in trans with R229Q

1. The variant affects an evolutionary conserved amino acid,
2. located in the region of oligomerization (residues 270–351)
3. The substitution results in change of size, polarity, or hydrogen bonding capacity, but
4. does not disrupt the oligomerization!



Mikó et al, Hum Mut, 2018

Incomplete penetrance and oligogenism in nephropathies

How many families have you ever seen with an incompletely penetrant genetic nephropathy?

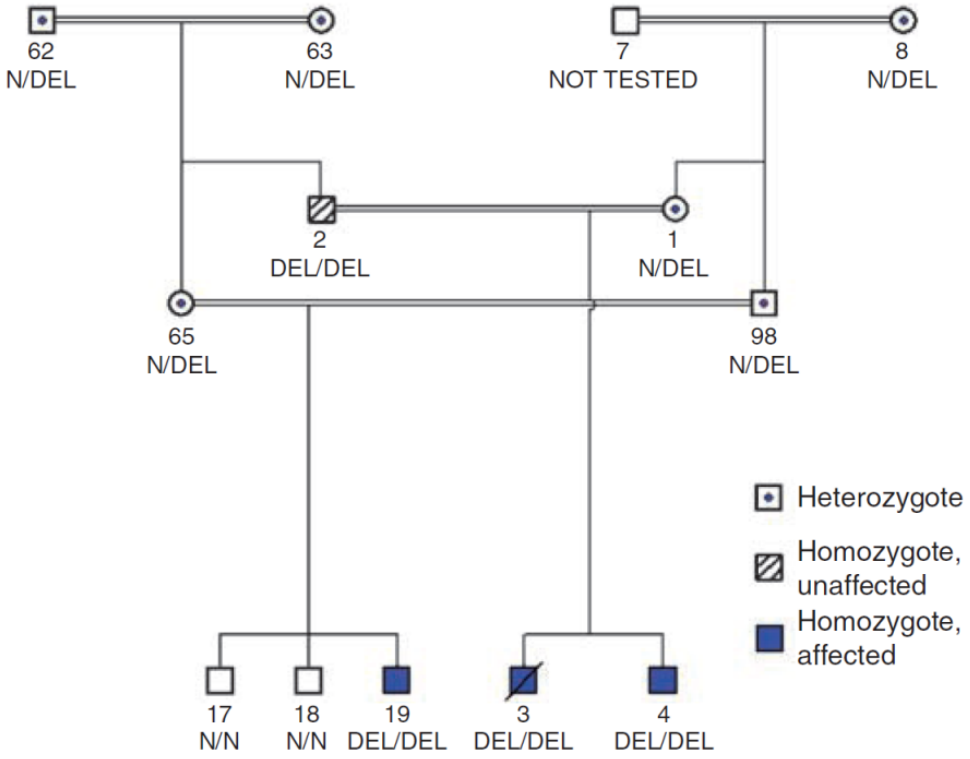
- 0
- 1-5
- 6-10
- >10

PLCE1-associated nephrotic syndrome is incompletely penetrant

‚Autosomal recessive' diseases with *homozygous loss-of-function mutations* may be incompletely penetrant

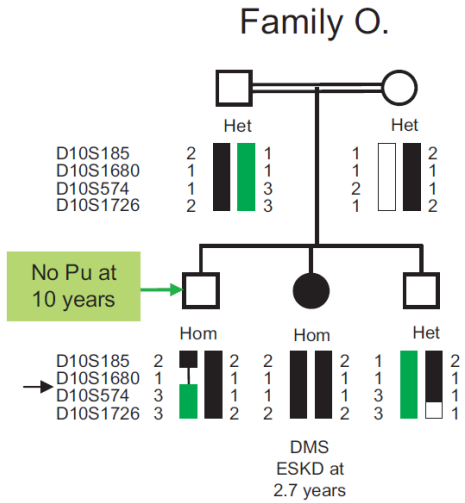
Gilbert et al, Kidney Int, 2009

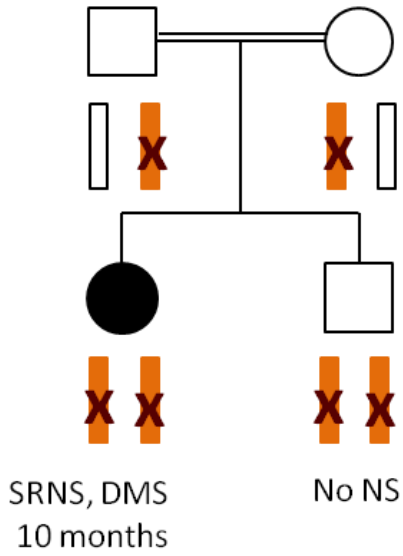
c.1303_1306delAGGA, hom, p.R434*



Boyer et al, J Med Genet, 2010

c.6448C>T, hom, p.R2150*

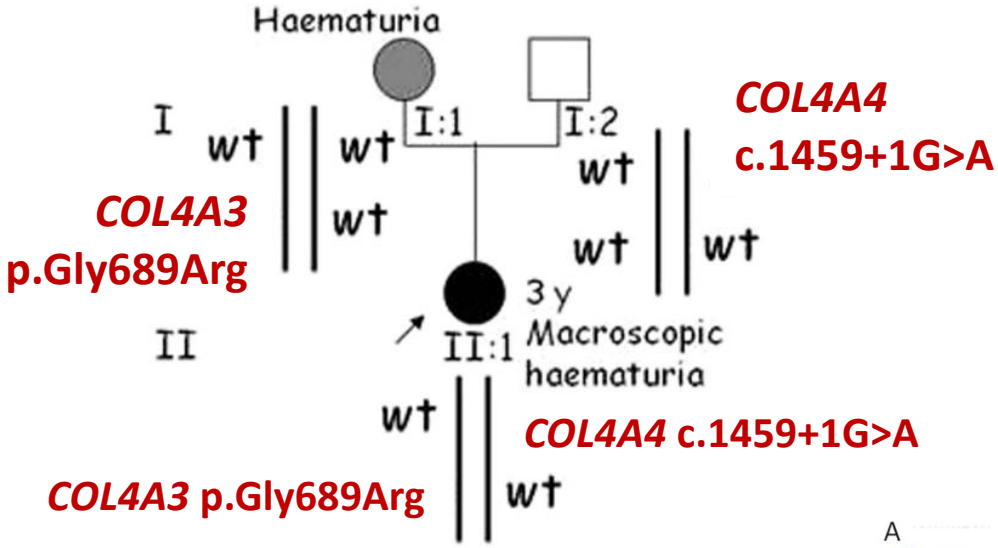


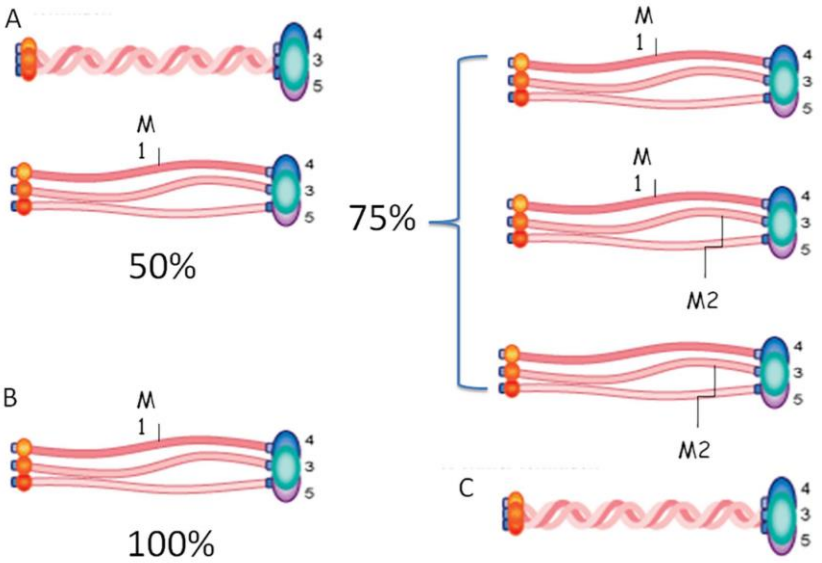


c.1477C>T, hom, p.R493*

Hinkes et al, Nat Genet, 2006

Digenic inheritance in Alport syndrome

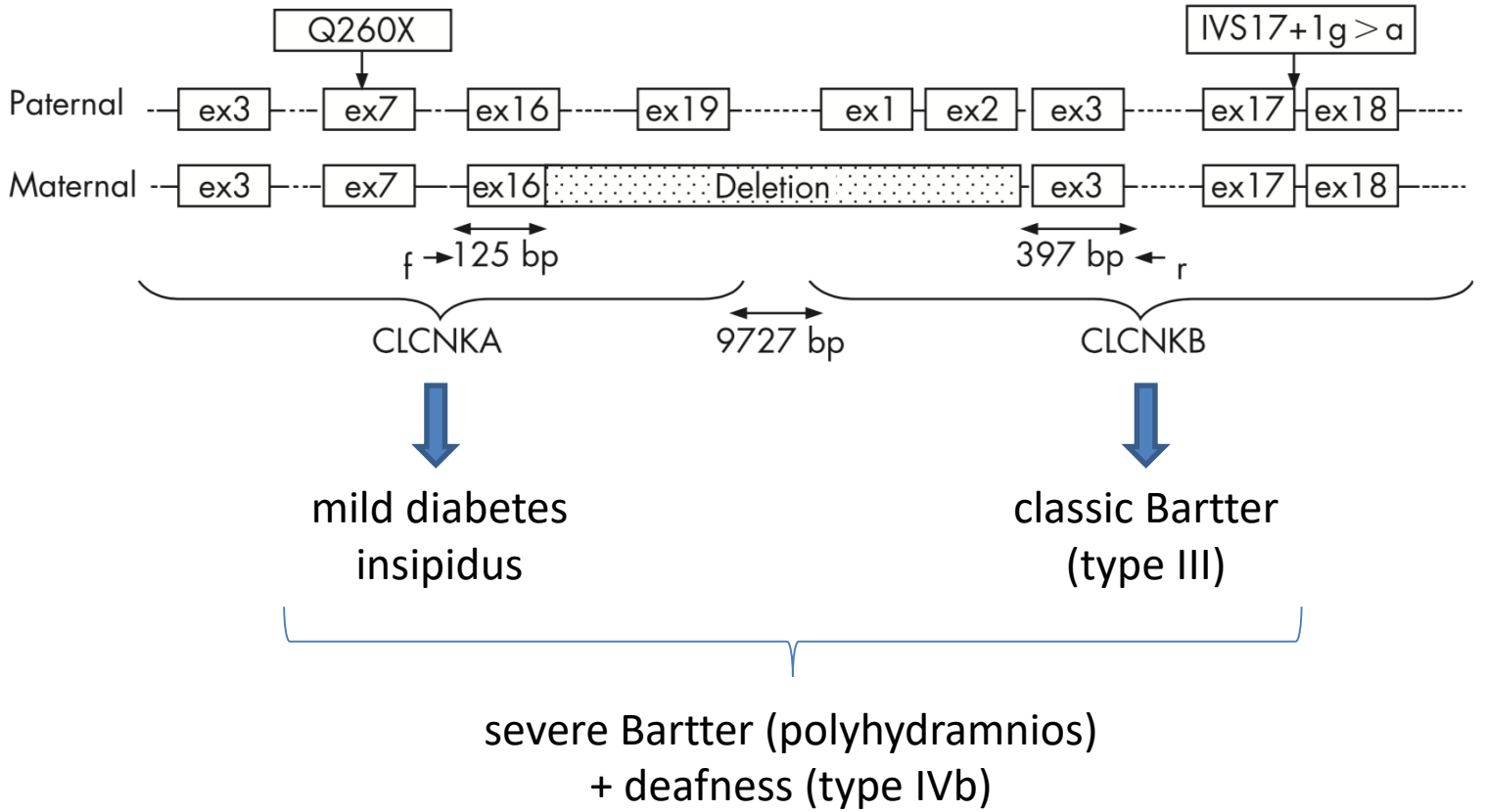




Mencarelli et al, J Med Genet, 2014

Digenic inheritance in Bartter IVb

Biallelic loss-of-function mutations in both the *CLCNKA* and *CLCNKB* genes

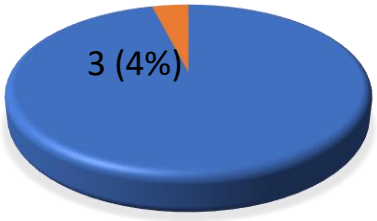


Schlingmann et al, N Engl J Med, 2004

Extra-renal involvement associated to *NPHP1* may be the consequence of second-locus variants

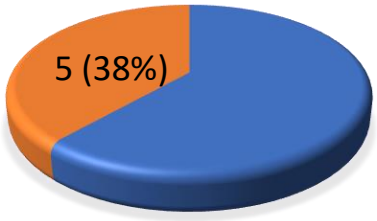
Frequency of *AHI1* het. R830W in patients with *NPHP1* mutations

isolated nephronophthisis
n=76

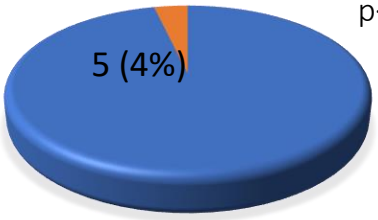


p=0.0014

nephronophthisis and Joubert syndrome
n=13

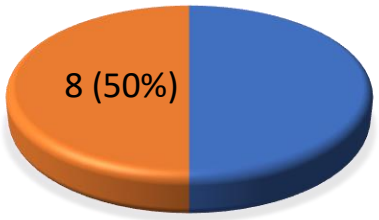


isolated nephronophthisis
n=137



p<0.0001

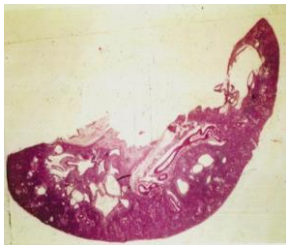
nephronophthisis and retinitis pigmentosa
n=16

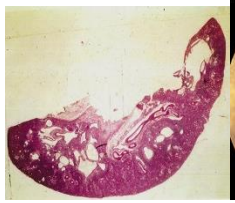


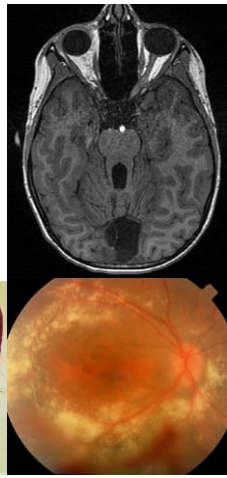
NPHP1 biallelic damaging variants

Tory et al. J Am Soc Nephrol, 2007.

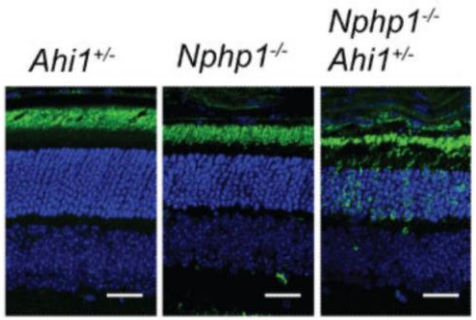
NPHP6, *AHI1* variants (in 7/13 families)

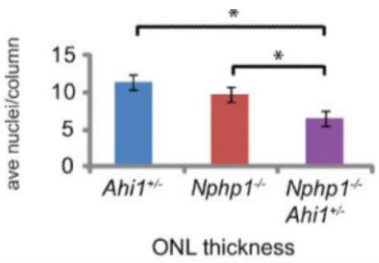




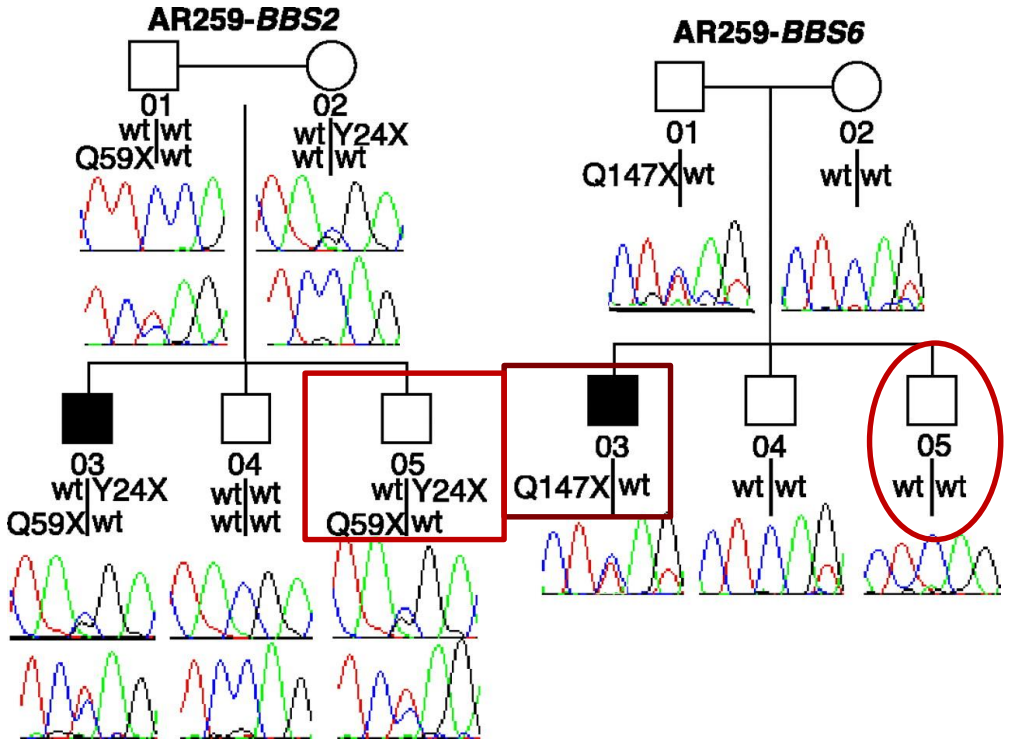


Louie et al., Nat Gen, 2010





’Triallelic inheritance’ in Bardet-Biedl syndrome



Katsanis et al., Science, 2001

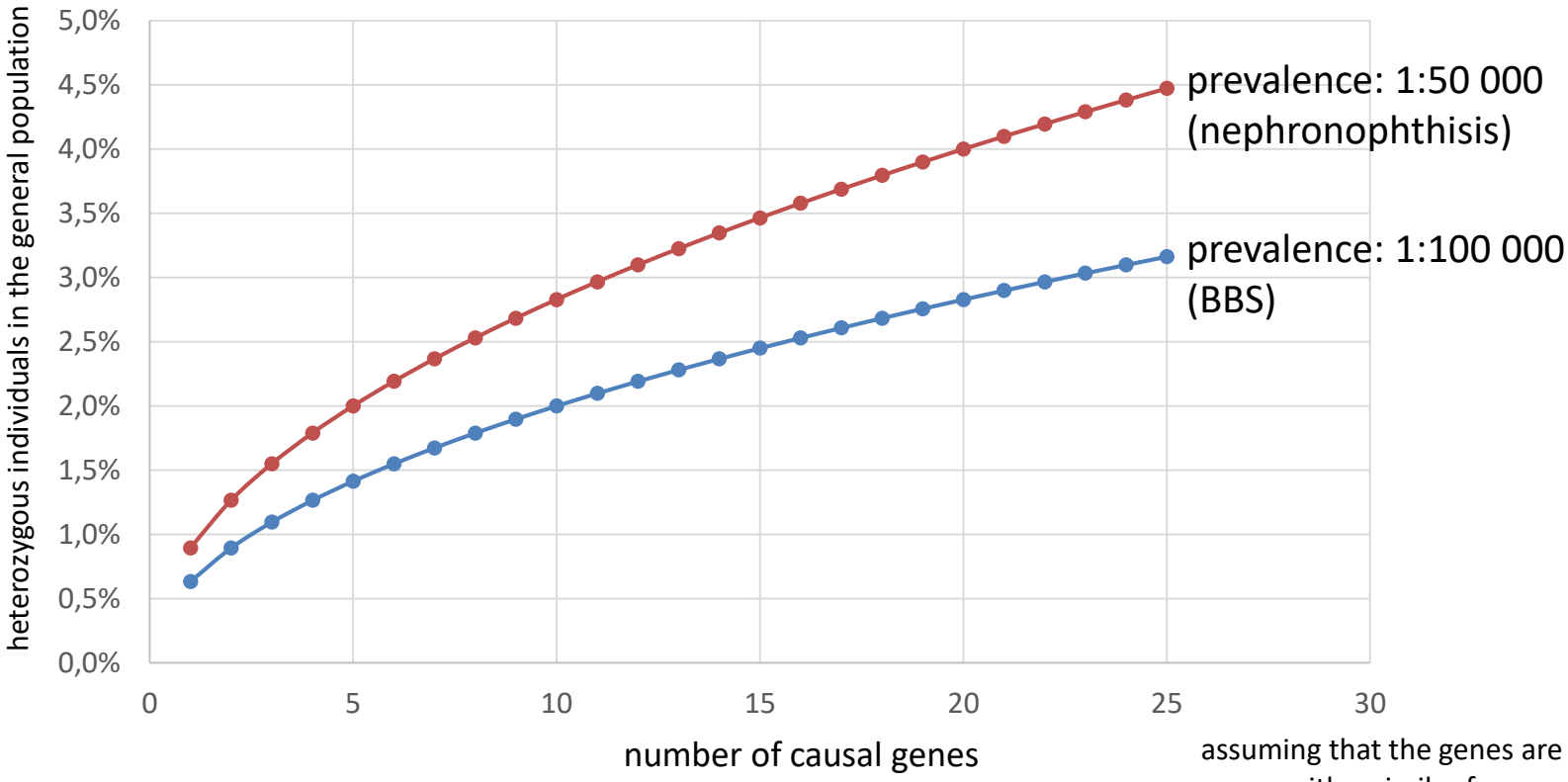
Ciliopathies are nevertheless mendelian disorders

	Ciliopathy group	Control	p
Shaheen et al, Genome Biol, 2016	n = 31	n = 64	
additional variants in second ciliopathy genes (n=98) with a MAF<1%	7.0 / sample	6.98 / sample	0.91
MAF<1% + CADD > 20	1.13 / sample	1.19 / sample	0.68
	JBTS group	control	
Phelps et al, Genet Med, 2018	n = 386	n = 1082	
single heterozygous rare deleterious variants (MAF < 0.2% + CADD > 15) in at least two JBTS genes	19 (4.9%)	53 (4.9%)	0.99

No difference in the mutational load between patients with ciliopathy and healthy individuals.

Reasons potentially explaining the oligogenism theories in ciliopathies

- There is a wide variation in expressivity
- During the 1st decade of this century, it was challenging to assess the pathogenicity of rare variants: many were falsely considered pathogenic
- Ciliopathies are genetically highly heterogeneous: the higher the number of the causal genes, the more frequent are heterozygous carriers in the general population

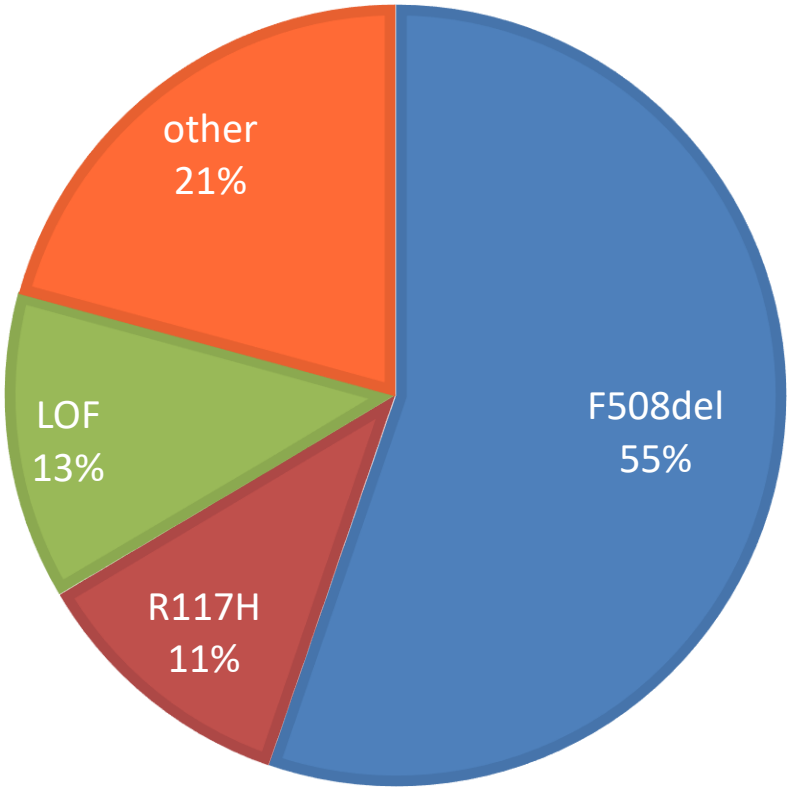


assuming that the genes are mutated
with a similar frequency
and the variants are all completely penetrant

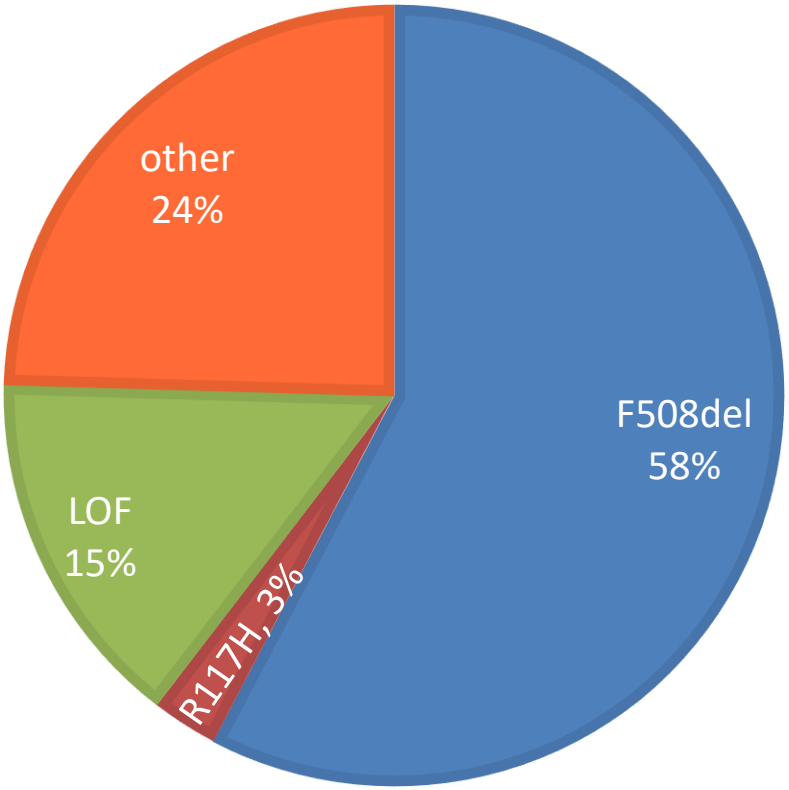
Identification of incompletely penetrant (non-mendelian) variants in AR disorders

Calculation of the penetrance in AR disorders

Pathogenic *CFTR* alleles in the European general



and in the patient population



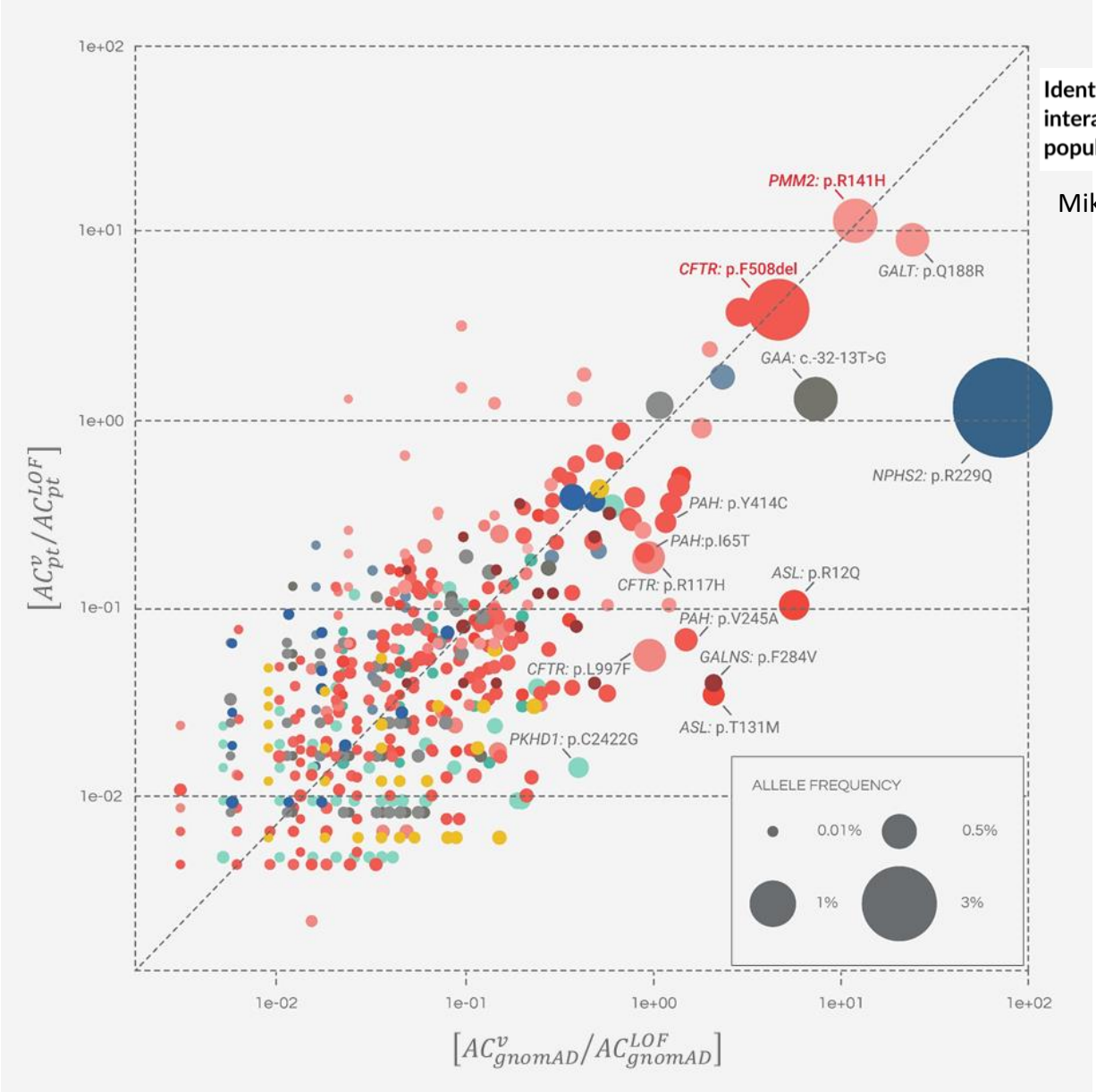
allele count in populations

	general	patient	penetrance
R117H	311	89	20.7%
LOF	353	481	p=9.07E-34

$$P \simeq \frac{AC^{v}_{pt}/AC^{LOF}_{pt}}{AC^{v}_{gnomAD}/AC^{LOF}_{gnomAD}}$$

Mikó et al, Hum Mutat, 2021

Incompletely penetrant variants can be identified by a population-genetic approach



Identification of incompletely penetrant variants and interallelic interactions in autosomal recessive disorders by a population-genetic approach

Mikó et al, Hum Mutat, 2021

IP variants in *NPHS2* and *PKHD1*

gene	variant	AF in Europe		LOF_{pt}/ LOF_{gnomAD} (AC in Europe)	enrichment pt vs. gen pop (p)	penetrance (p)	Origin
		patient population	gnomAD				
NPHS2	c.686G>A R229Q	81/434 (18.66%)	4537/126346 (3.59%)	72/67	5.2x ($1.16x10^{-33}$)	1.66% ($1.37x10^{-76}$)	USA, AUS, CZE, FRA, ENG, DEU, TUR, GRC, HUN, ITA, POL, PRT, SVN, ESP
PKHD1	c.4870C>T R1624W	5/580 (0.86%)	28/126656 (0.02%)	220/209	39x ($4.13x10^{-7}$)	16.96% ($4.39x10^{-05}$)	FRA, NLD, USA
	c.5498C>T S1833L	2/580 (0.34%)	37/126386 (0.003%)		11.78x (0.0138)	5.14% ($3.15x10^{-9}$)	ESP, USA
	c.6992T>A I2331K	8/580 (1.38%)	47/126480 (0.04%)		37.12x ($1.81x10^{-10}$)	16.17% ($1.05x10^{-7}$)	DNK, DEU, USA
	c.7264T>G C2422G	3/580 (0.52%)	78/126580 (0.06%)		8.39x (0.00619)	3.65% ($2.43x10^{-18}$)	AUT, DEU

Mikó et al, Hum Mutat, 2021

For the proper description of the transmission: the phenotype, the gene and the variant are all needed

- The *NPHS2* p.R138Q-related nephrotic syncrome is AR.
- The *NPHS2* p.L330Vfs*15-related FSGS is AD.

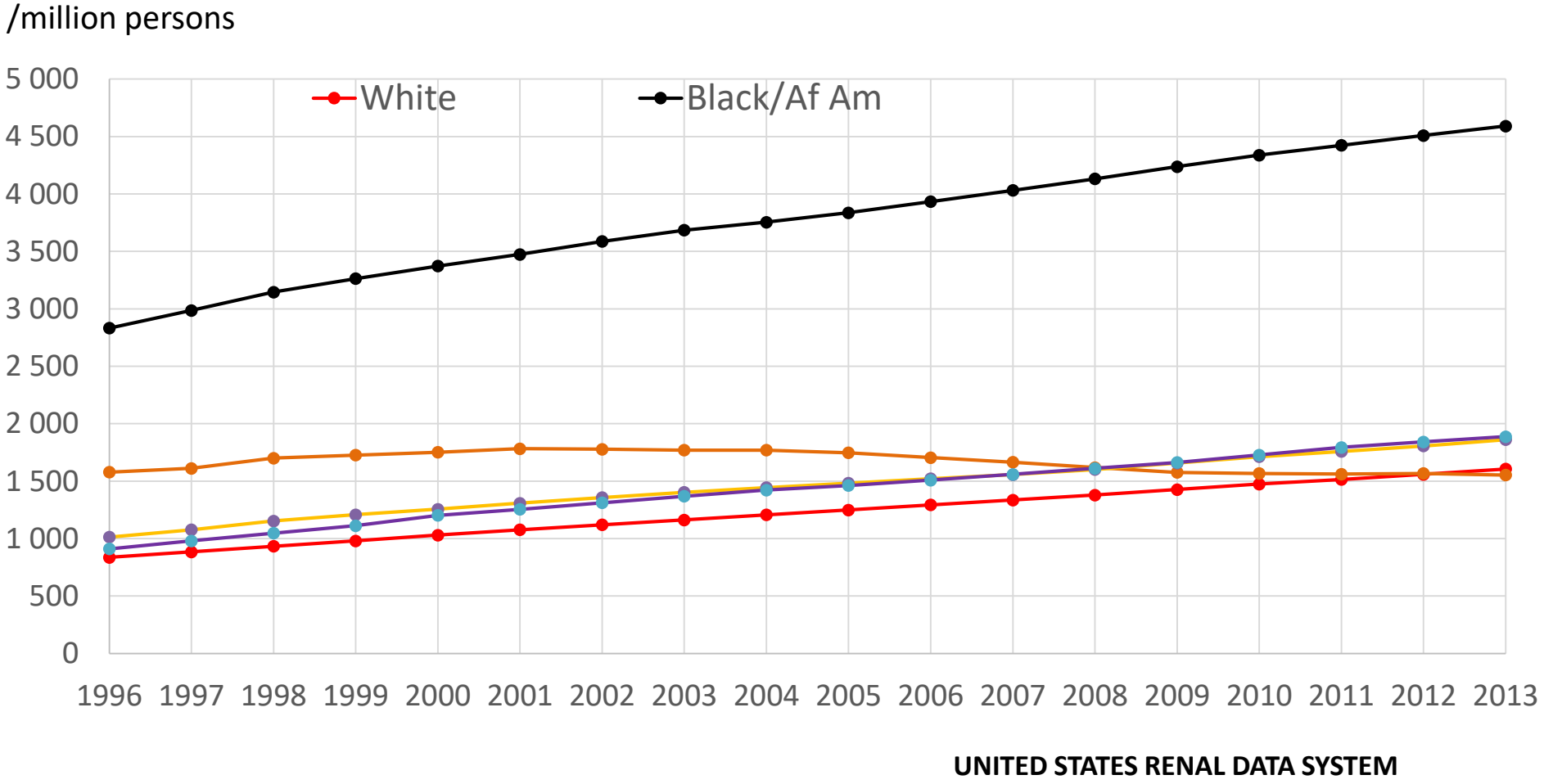
- The *PKD1* p.Q2158*-related polycystic kidney disease is AD.
- The *PKD1* p.R220W-related polycystic kidney disease is AR.

- The *PKHD1* p.T36M-related polycystic kidney disease is AR.
- The *PKHD1* p.I2331K-related polycystic kidney disease is incompletely penetrant.

- The *NPHP1* homozygous deletion-related NPH is AR.
- The *NPHP1* homozygous deletion-related retinitis pigmentosa is multifactorial.

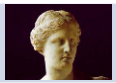
A multifactorial nephropathy

End-stage renal disease is 2-3x more frequent in the African American population than in the others



APOL1 G1 and G2 alleles: protection and risk

	African American FSGS, n=205	African American control n=180	p	African general pop n=5181	European general pop n=33307
G1 (S342G and I384M)	52%	23%	1.07×10^{-23}	23%	0,01%
G2 (N388_Y389del)	23%	15%	4.38×10^{-7}	14%	0,006%

	wt/wt	G1/G2 + wt	G1/G2 + G1/G2
Trypanosoma b. brucei			
Trypanosoma b. rhodesiense			
Trypanosoma b. gambiense			
hypertensive nephropathy	1	1.26x (95% CI: 1.01-1.56)	7.3x (95% CI: 5.6 to 9.5)
FSGS	1	NS	10x (95% CI:6-18.4) 17x (95% CI: 11 to 26) **4% lifetime risk**
HIV-associated nephropathy	1	NS	29x (95% CI: 13 to 68) **50% risk if untreated**

Genovese et al. Science 2010;329:841-845, Kipp et al. J Am Soc Nephrol 2011;22:2129-37

Conclusions

- Nephropathies are typically either mendelian or multifactorial.
- Oligogenic inheritance is rare, but variants at second loci may modify the phenotype.
- It seems worth describing the transmission pattern in function of the causal variant and the organ involvement.
- Incompletely penetrant variants can be detected by a population-genetic approach in AR disorders and are more frequent than expected.

NEXT WEBINARS

05/04/22

Fabry disease
Olivier Lidove & Wladimir Mauhin (Paris, France)

19/04/22

Methylmalonic acidemia
Anais Brassier & Manuel Schiff (Paris, France)

03/05/22

Collagenopathies
Roser Torra (Barcelona, Spain)

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