

NEPHROPATHY +: Am I missing something ?

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Ghent University Hospital
Nephrogenetics symposium
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Zebra, Ghent



The nephrogeneticist

- 'Helicopter' view
 - Personal history
 - Familial history - pedigree
 - Clinical examination
 - Search for additional clinical data
- Diagnostics
 - Additional exams in proband or family members
 - Genetic investigations in proband or family members
 - management
- Risks to family members
 - Depending on the diagnosis
 - Presymptomatic testing
- Child wish
 - PGT
 - PND
 - ultrasound
- What if the genetic test returns a normal result... ?

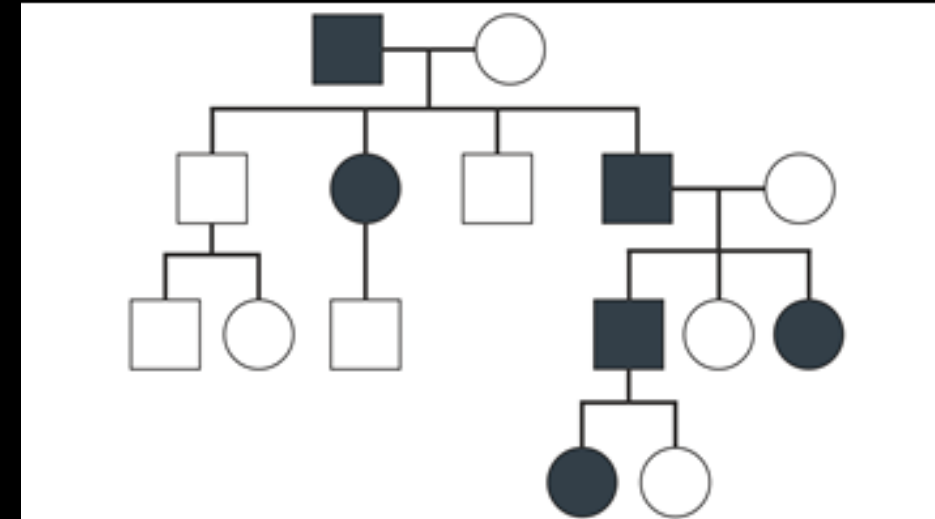


Pre- and post test counseling !
CONVENTION MEDICAL GENETICS



'Helicopter' view

- Other clinical problems/characteristics?
Development, eye, hearing, skeleton, endocrinology, gastroenterology, physical characteristics, ...
- What are the odds ?
- Syndromic diagnosis ?



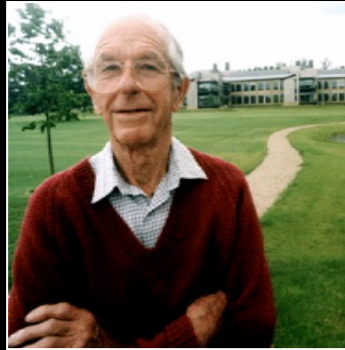
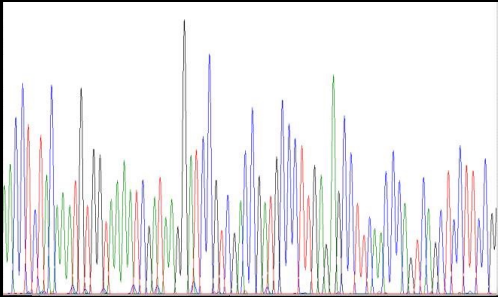
Isolated kidney disease

Syndromic disease

Molecular diagnostics

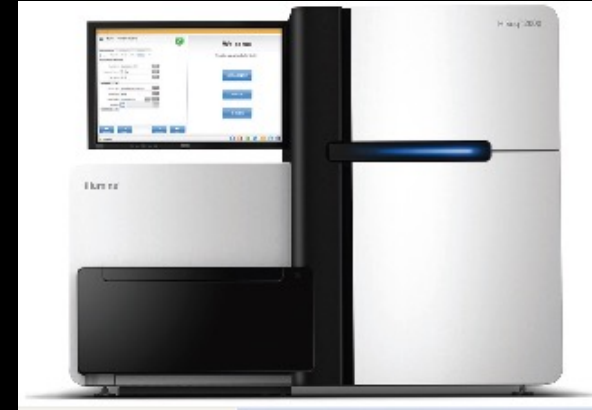
- Blood sample (EDTA), seldom urine
- Takes a while...
- Consent
- 'Trio'-analysis
- Most distant relatives with the SAME condition

Molecular diagnostic: evolution

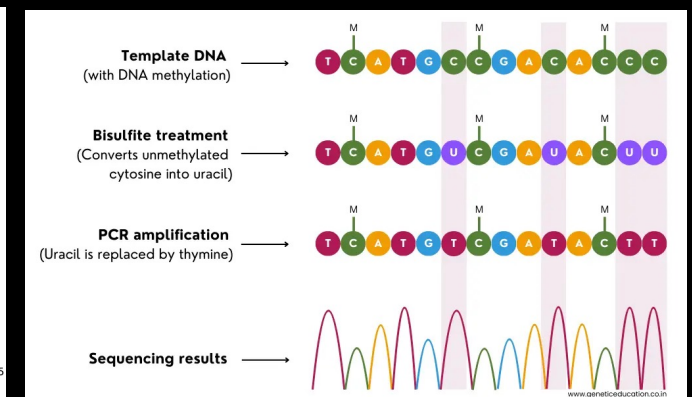
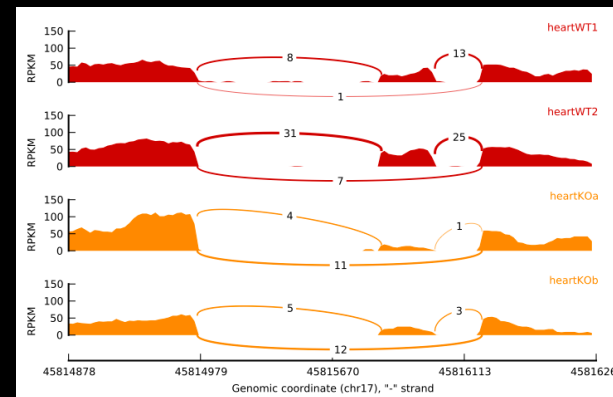


Fred Sanger
Nobelprijs 1980

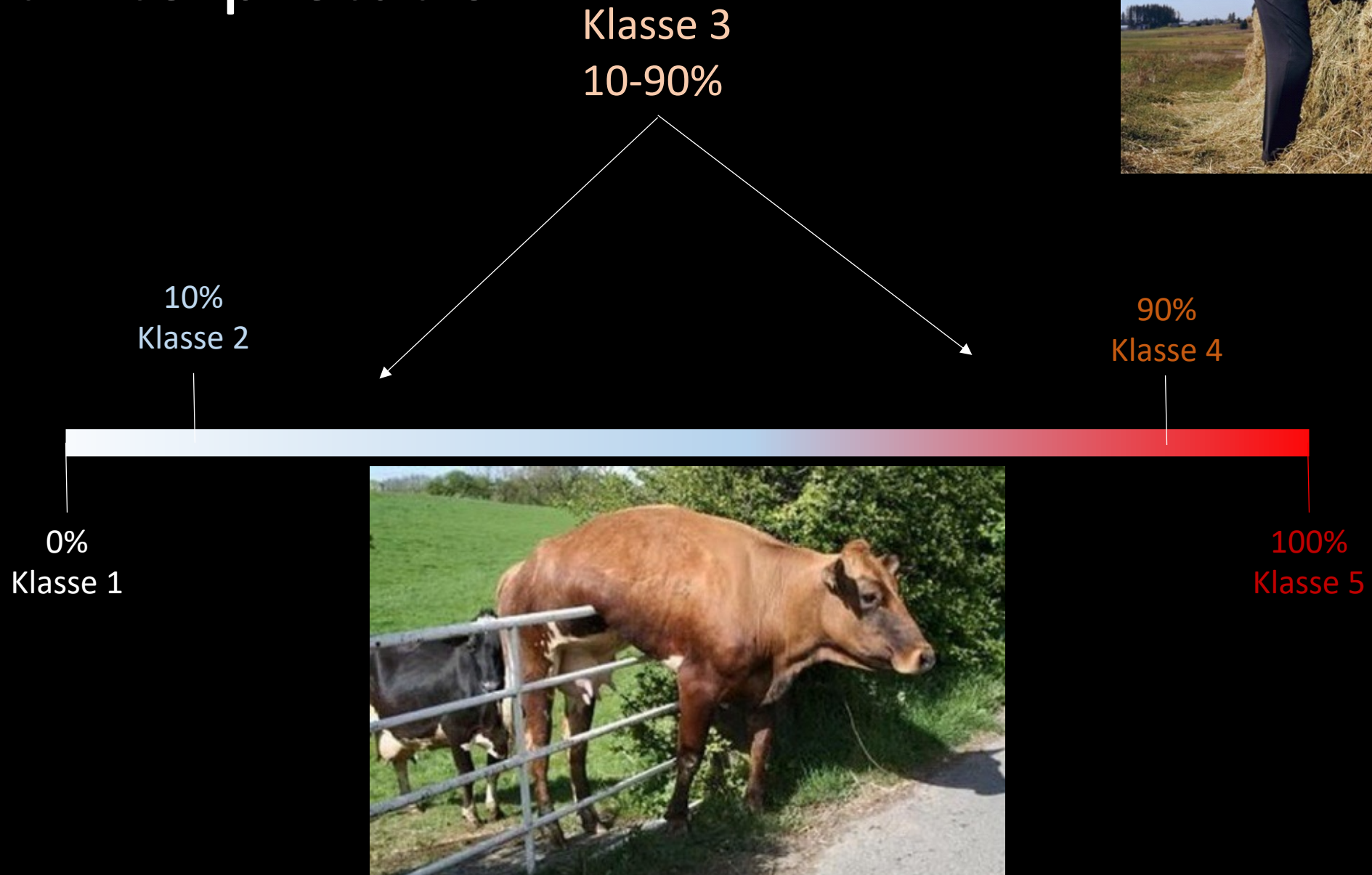
Sanger Sequencing



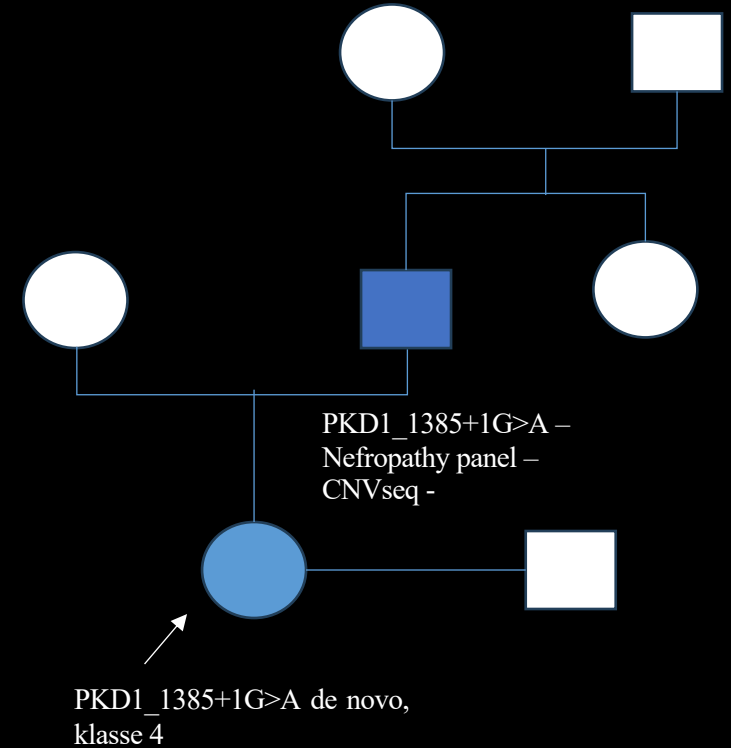
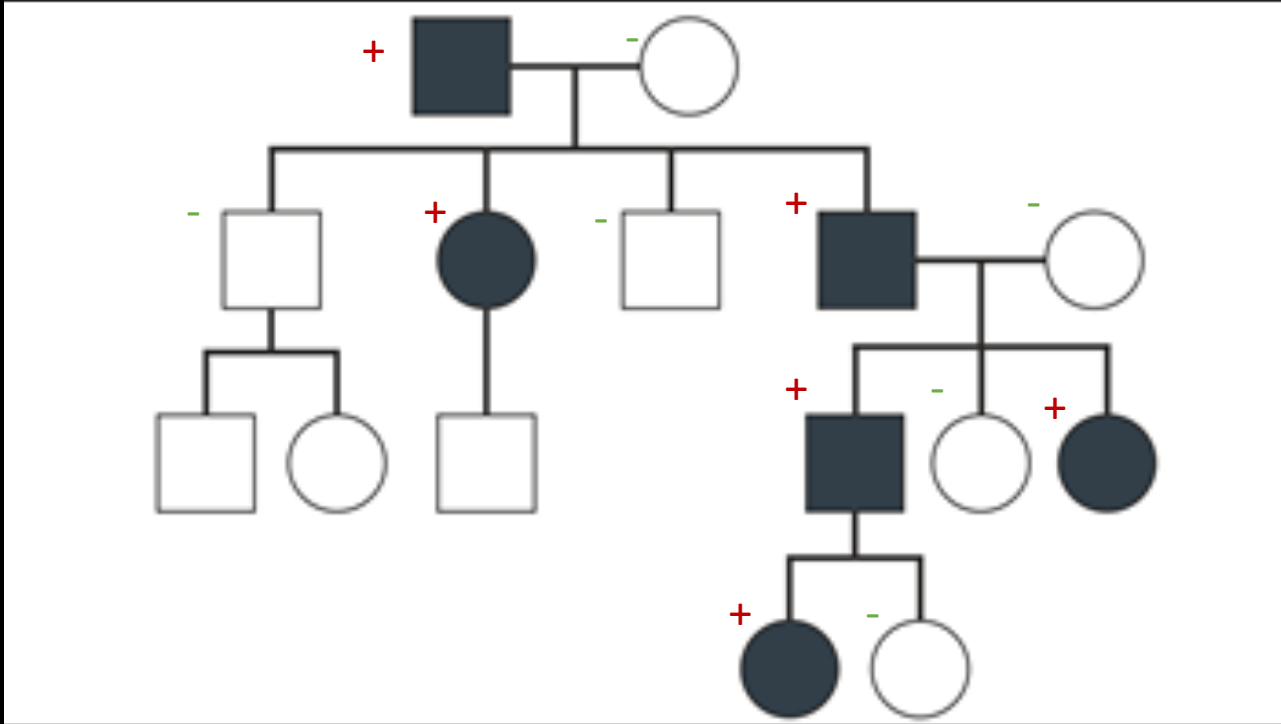
Next-/Third generation sequencing



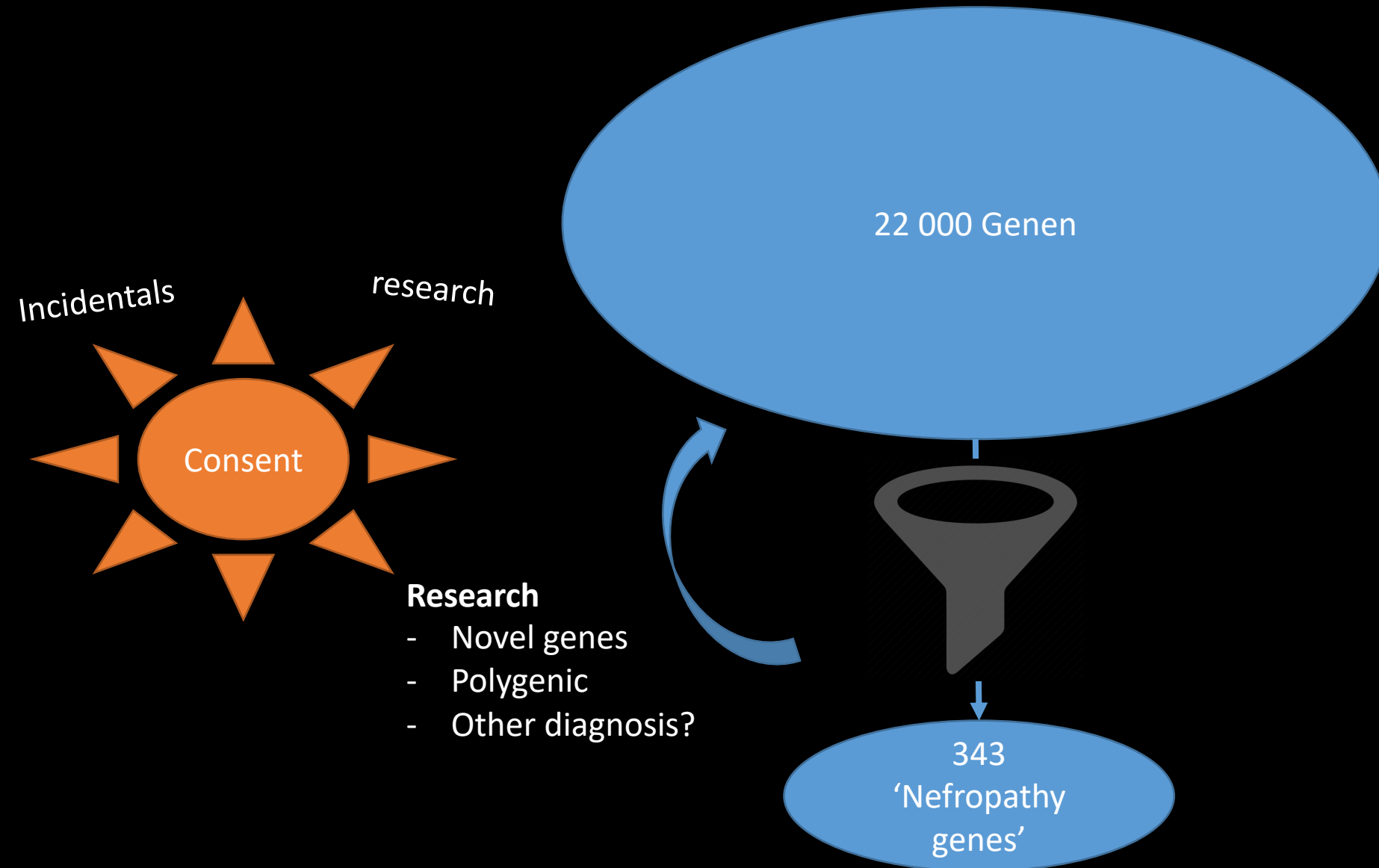
Variant interpretation



Interpretation of the result

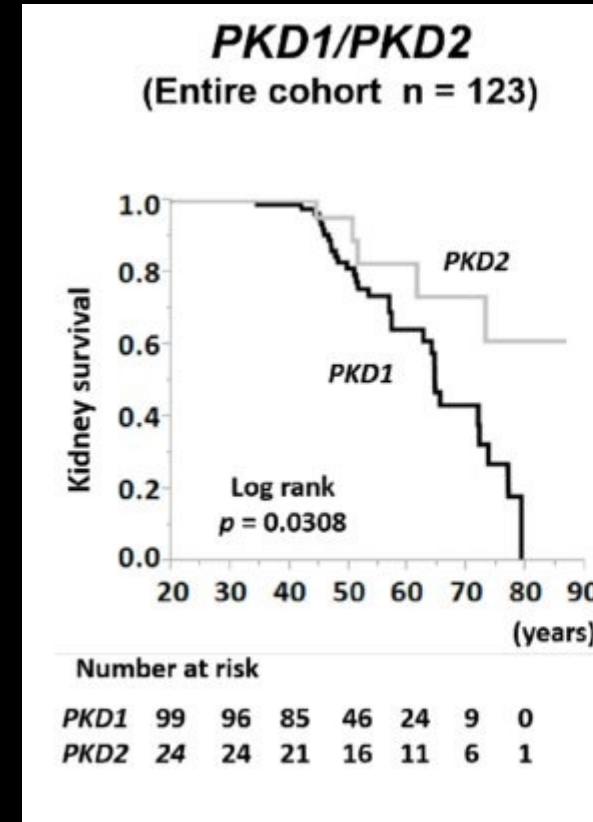


Molecular analysis



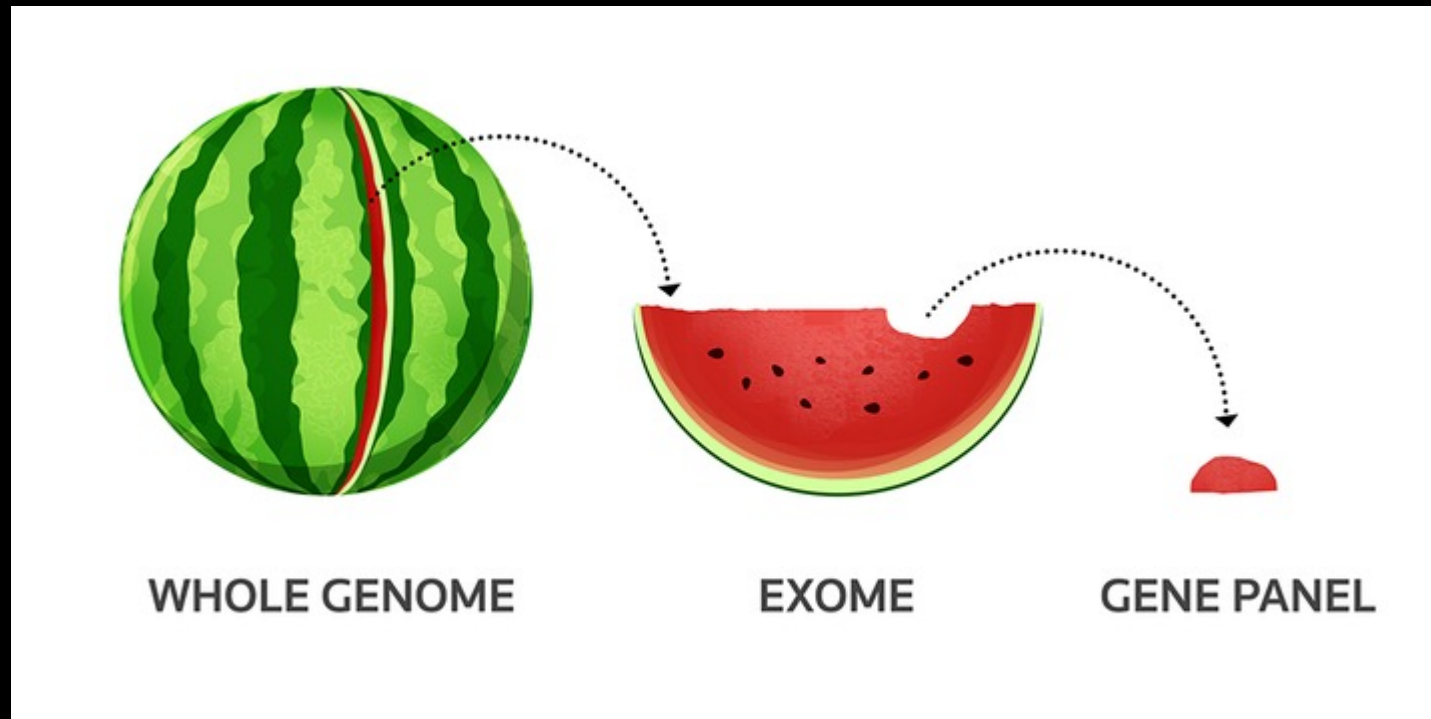
Importance of a diagnosis ?

- Management – prevention
- Prognosis?
 - Risk kidney insufficiency
 - Risk relapse in transplant
 - Prenatal
- Risk family members
- Preconception counseling



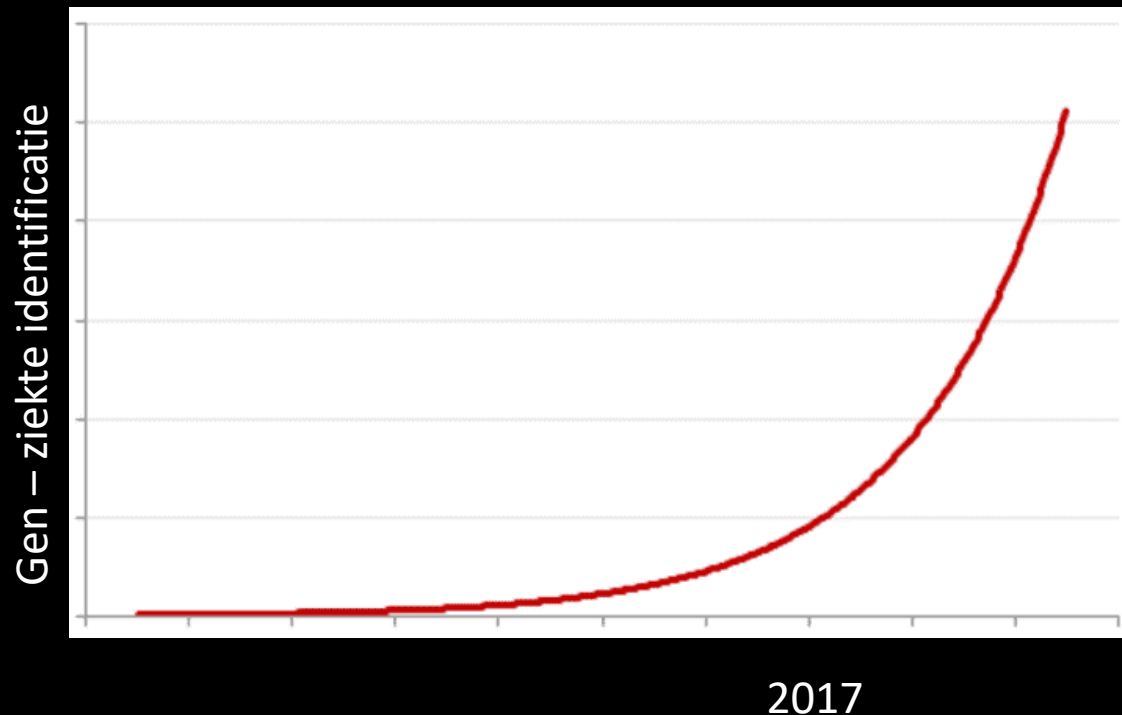
What if the molecular analysis shows a normal result?

1) Technically imperfect



What if the molecular analysis shows a normal result?

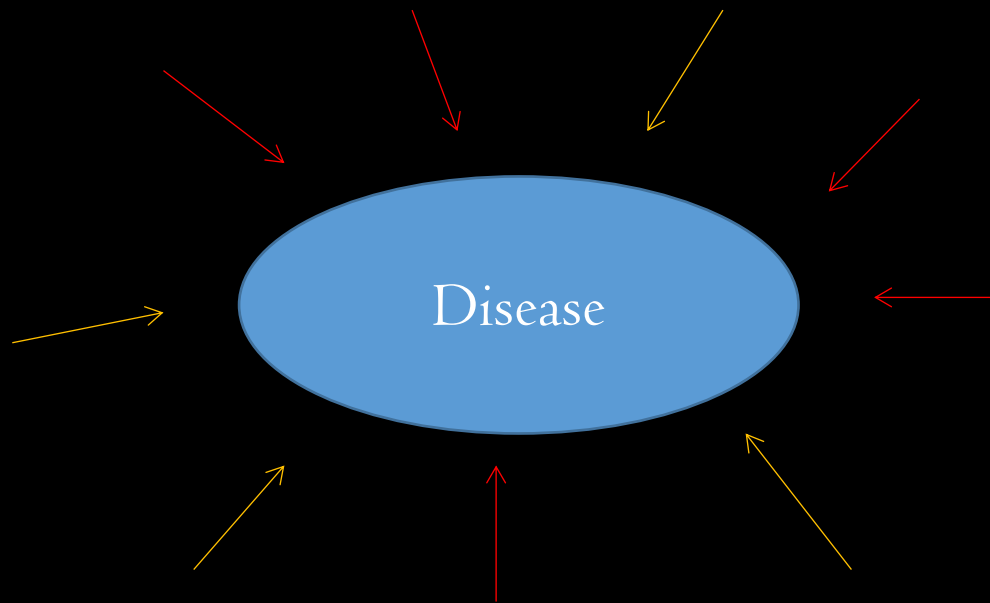
- 1) Technically imperfect
- 2) Unknown gene-disease association



What if the molecular analysis shows a normal result?

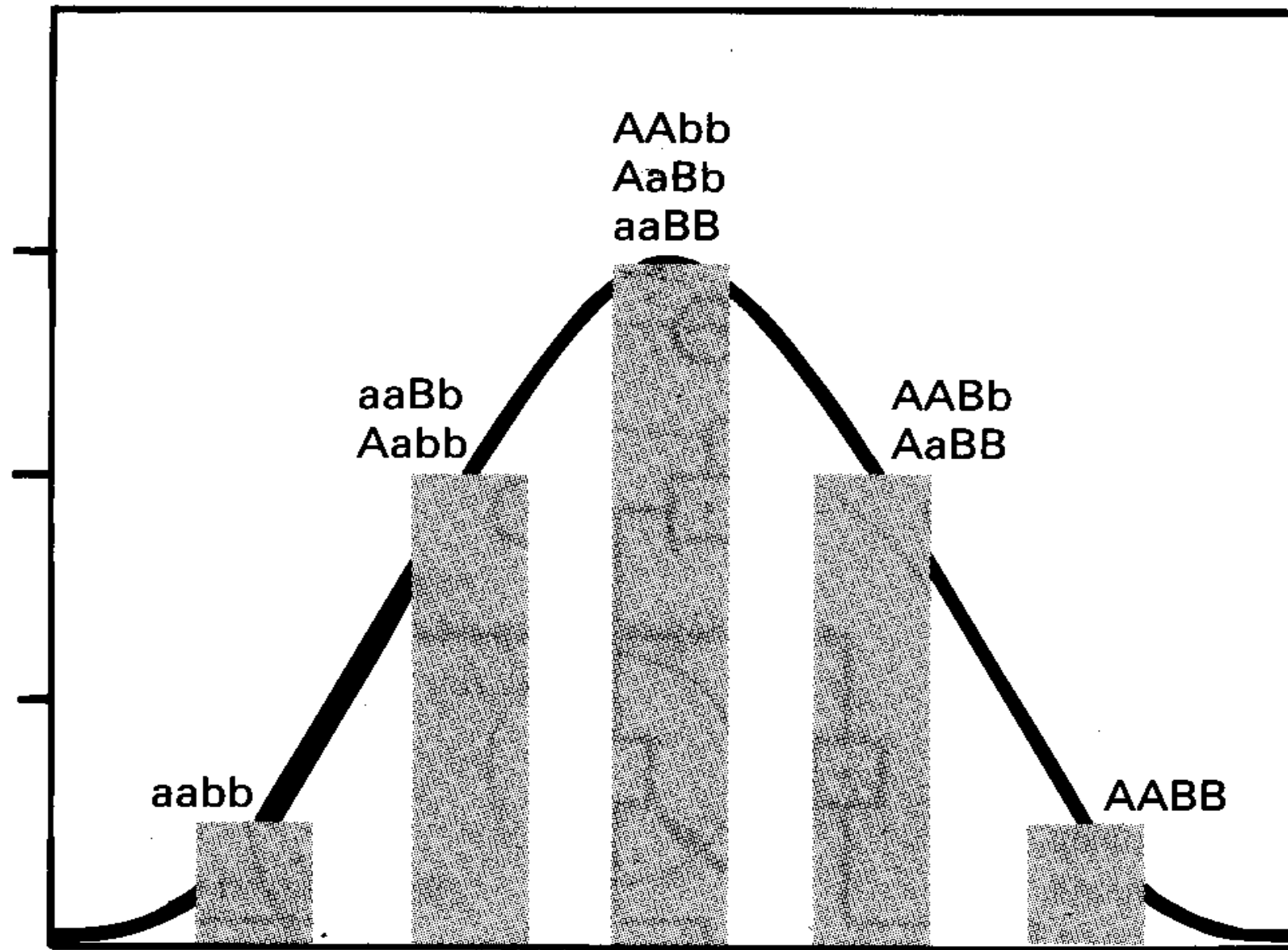
- 1) Technically imperfect
- 2) Unknown gene-disease association
- 3) Multifactorial disease (glomerulopathie, CAKUT)

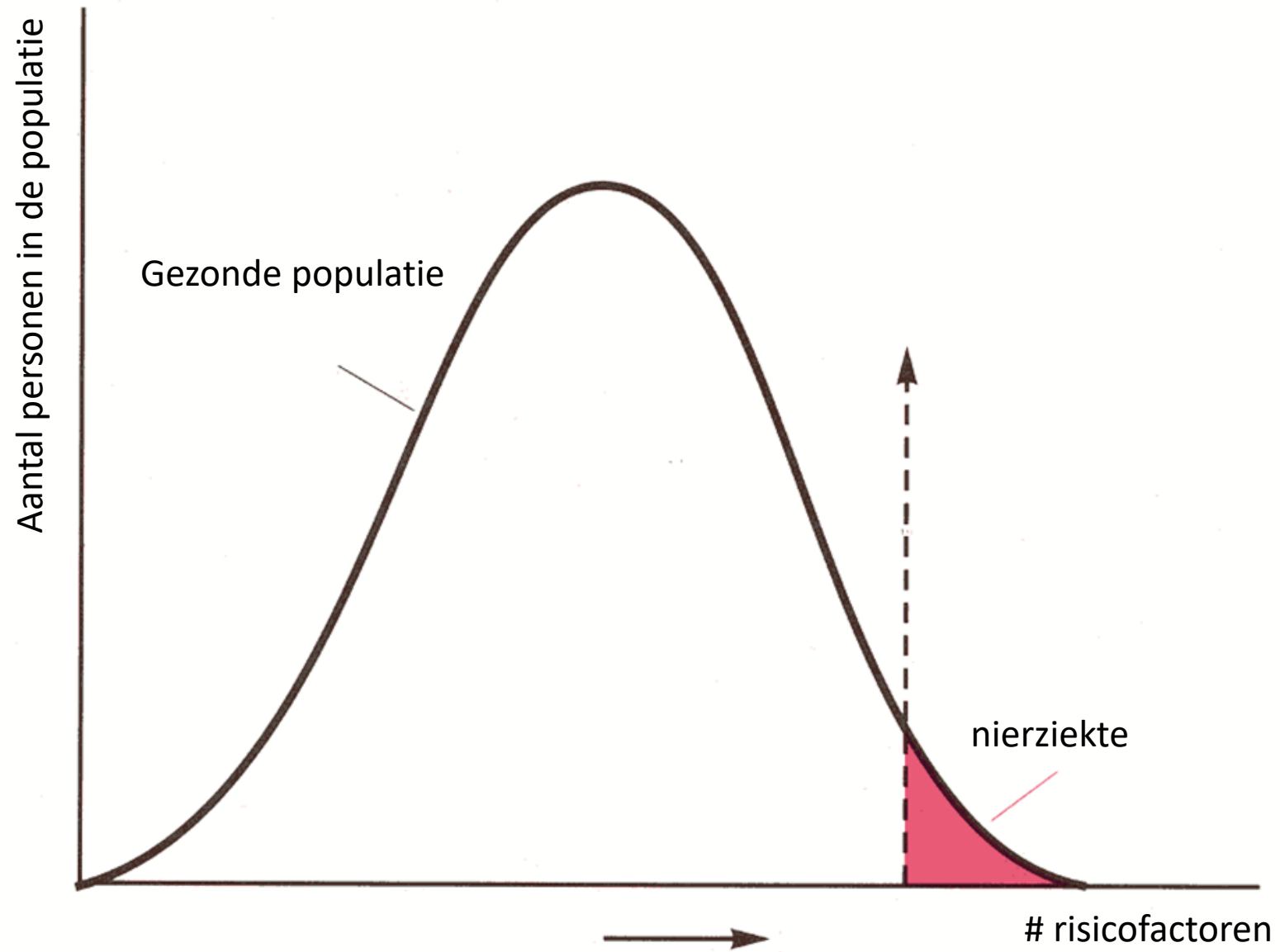
Normal molecular test result: multifactorial?



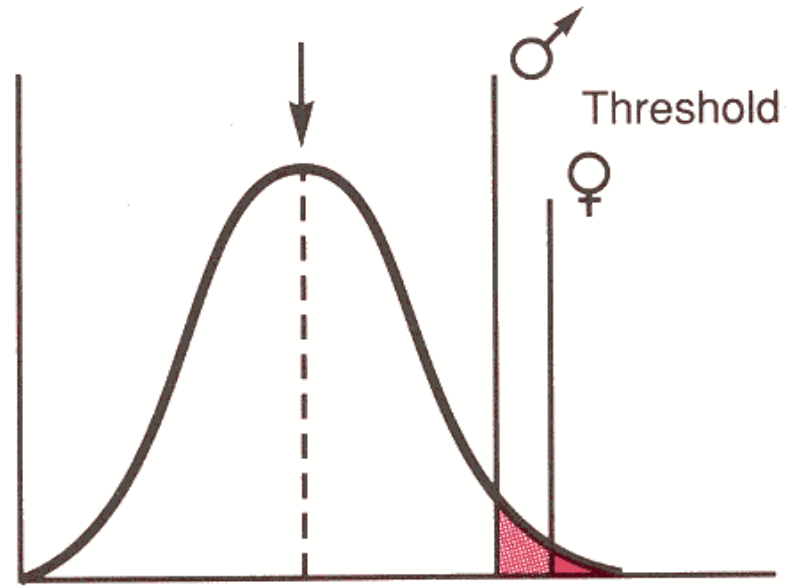
- Environmental factor
- Genetic factor

CAKUT
Glomerulopathy

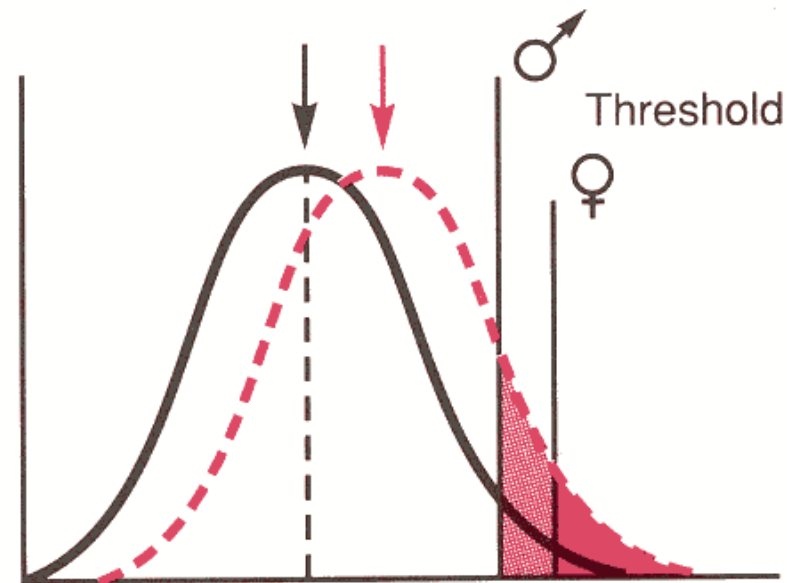


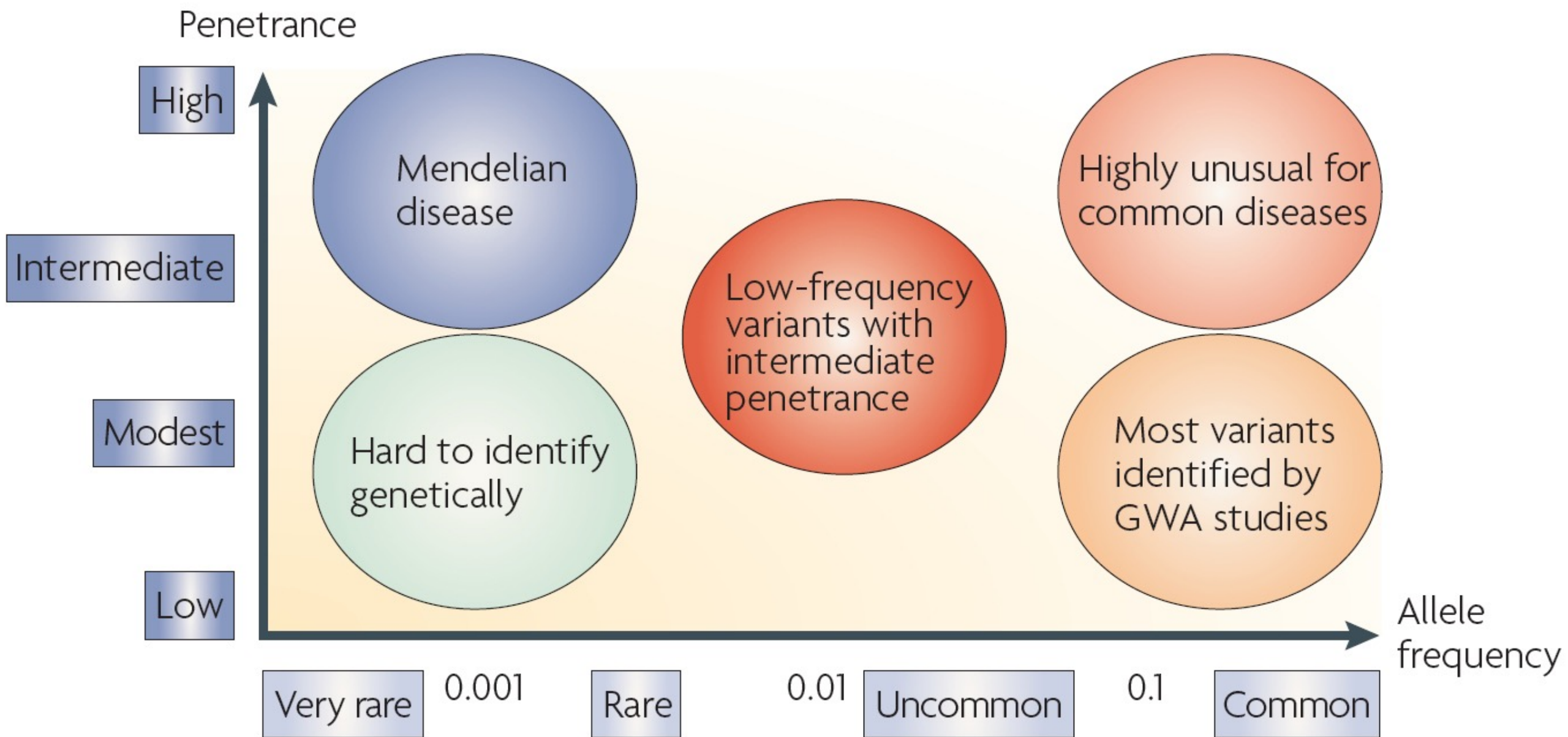


Reference population



1st degree relatives





What if the molecular analysis shows a normal result?

→ Re-evaluation

- After 3 - 5 - 10 years?
- Always when child wish (patient, family member)

Corticosteroid resistant NS

Pregnancy and partus: normal

After age 2: **Progressive stagnation of neuromotor development** (since age of 2 yrs)

→ short sentences at age 4

Progressive motor difficulties

→ Proprioceptive dysfunction

→ Spasticity

→ MRI: T2 hyperintensive periventricular signals

Age 4: CS resistant NS.

L: p90

W: p50

OFC: p3

Galloway-Mowat

? Genes ?

WDR73: -

Galloway-Mowat

Exome analysis:

homozygous TPRKB mutation

c.446A>G

p.(Tyr149Cys)

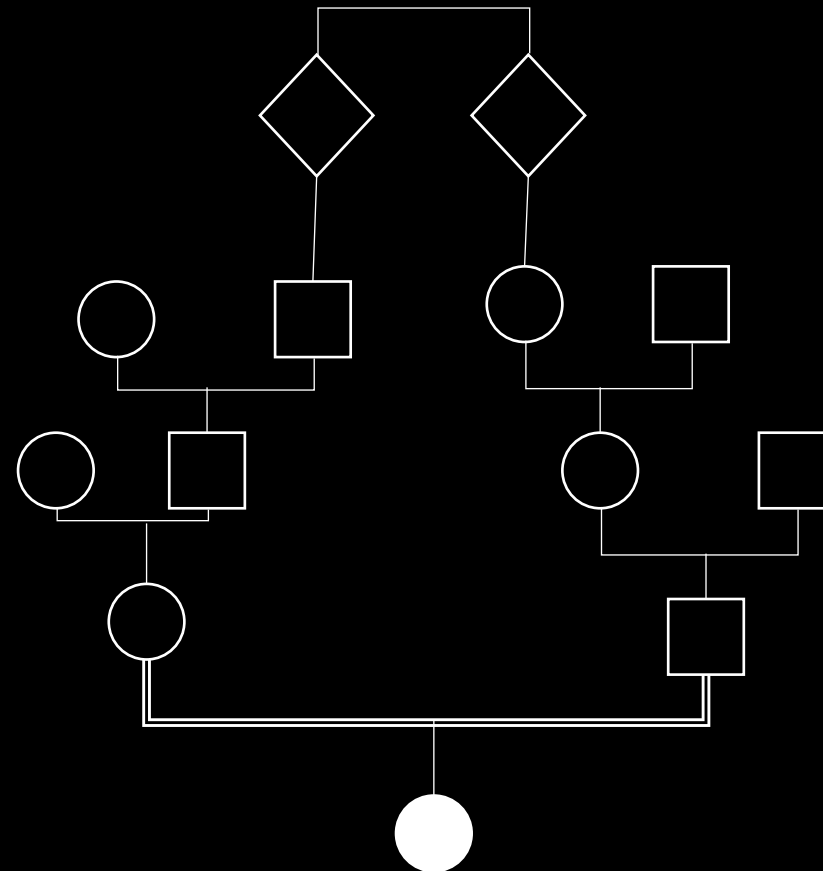
Highly conserved amino acid, Grantham
dist.: 194

SIFT: Tolerated

MutationTaster: disease causing (p-value:
1)

PolyPhen-2: Probably damaging

GWAS hit proteinuria/CKD



IBC: 1/256
Largest homozygous region on
chr 2q11.2 (14,1Mb)

Galloway-Mowat

- 85 patients (M. Zenker): -
- Friedhelm Hildebrandt
1000 exomes

Exome:

homozygous TPRKB mutation

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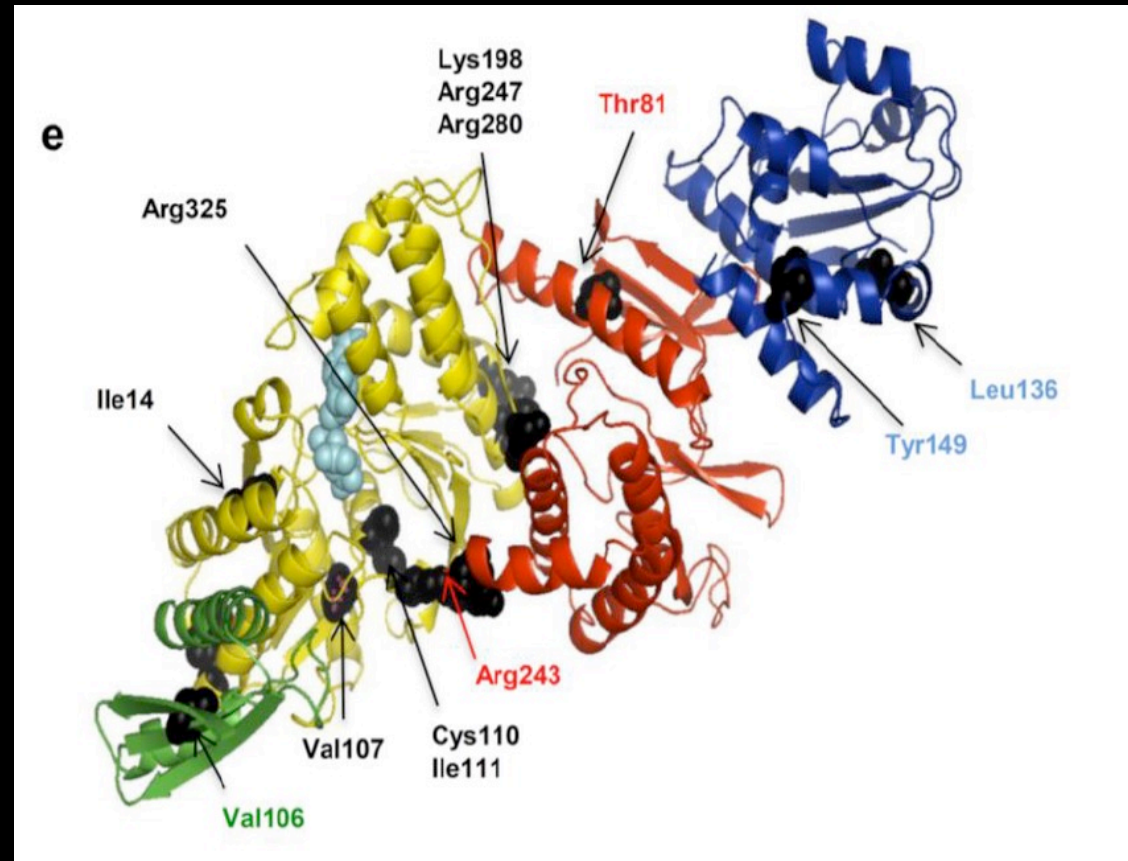
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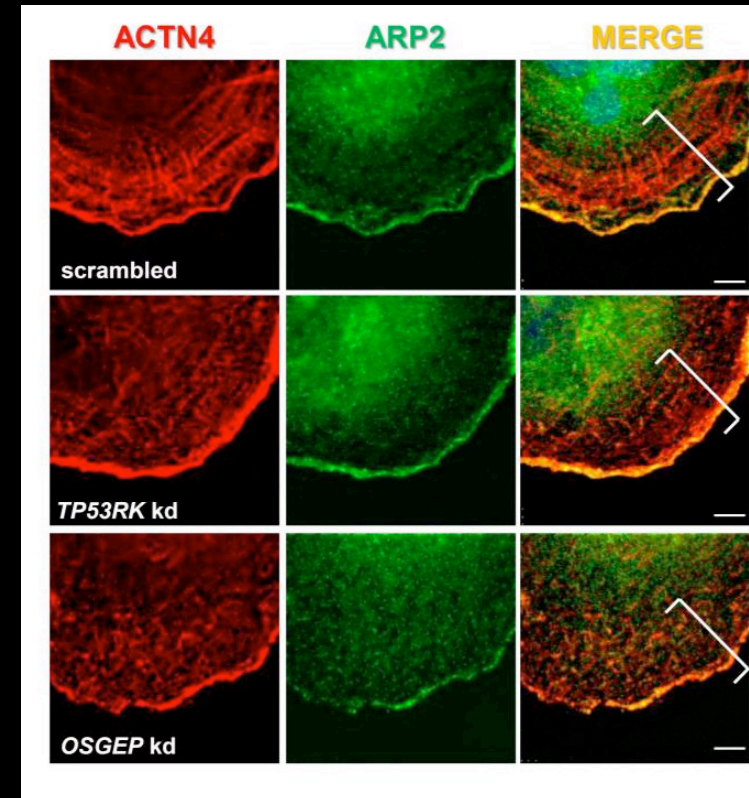
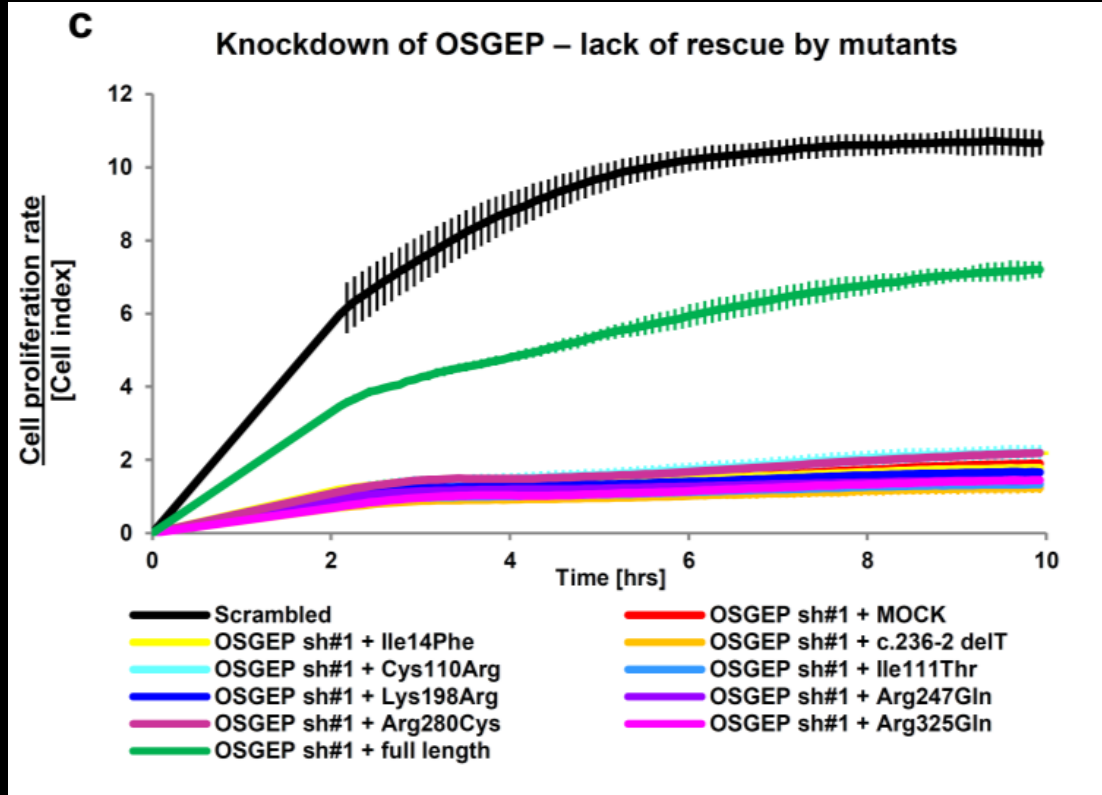
GWAS hit proteinuria/CKD



Telomer
uncapping

DNA (HDR)
repair

Galloway-Mowat



Townes - Brock

- Unilateral kidney agenesis
- Anal imperforation
- Septal defects



SATYR ear

BOR syndrome – EYAI, SIX1, SIX5

Hearing loss

- Sensorineural
- Conductive

Renal

- Renal agenesis
- Obstruction
- VUR

2nd arch defect

VACTERL ?

Shone complex

Hearing loss 40dB right side

anale atresia

Vertebral anomaly S1 - S2

Renal hypoplasia

Hypospadias

VACTERL ?

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Hearing loss 40dB right side

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Kabuki syndrome:

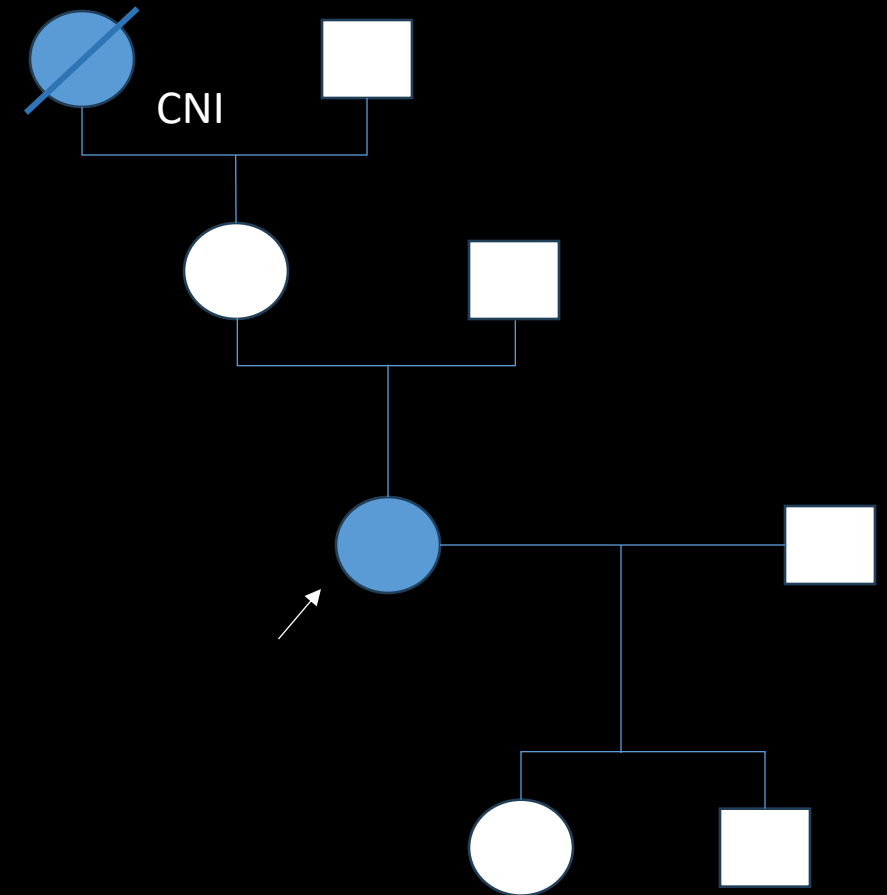
KMT2D: c.5785G>T; p. (Gly1929*)

VACTERL / Noonan ?

- L: -3.0 SD; W: >+2.0 SD; HO: p70(hemivertebrae L2-L3)
→ scoliosis
- hypoplastic 13th rib
- Normal motor development, special education
- Puberty: delay – hypogonadotropic hypogonadism –
testosterone deficit (R/ Sustanon)
– increased prolactin – GH normal
- Unique kidney, proteinuria (Ramipril)
- Mild hearing loss left
- Mild myopia
- MRI brain: normal (normal hypophyse)
- FA: single child, not informative
- Heterozygote frameshift variant in exon 6/12 of **PUF60**
c.478_479del, p.(Met160ValfsTer18)

CKD eci ?

- CKD, bilateral cysts (5) following G2 – preeclampsia
- Hearing loss
- Myalgia / fatigue, following traffic accident at age 28 y
- Traumatic social situation
- Borderline hyperglycemia
- 02-2015: niet -functioneel hypofysair micro-adenoom (9 mm) met secundaire centrale hypothyro
- Dolichocolon
- 2018: Fibromyalgia. Psychiatric disease



Nefropathiepanel: geen pathogene varianten

CNVseq: sseq(1-22,X)x2

mtDNA analyse: pathogenic variant m.13513G>A: (MT-ND5: Asp393Asn) (8.3%) ~MELAS / urinary cells 42%

Take home messages

- Genetic testing can be straightforward, but usually isn't
- Additional testing may be required
- Normal molecular results usually does not exclude a genetic condition
- Pre- and post test counseling – psychological support
- Explaining genetic test requests/results requires time

→ Convention genetics

Questions ?

