Challenges in Genetic Interpretation of Hereditary Kidney Diseases

DRAGoN Study
Deciphering Diversities:
Renal Asian Genetics Network

RAPIDS
Renal Alliance for Precision Diagnosis in Singapore

NUS National University of Singapore

National University Hospital
National University Centre for Genomic Medicine

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Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore

DISCLOSURES

- No conflicts of interest

A Typical Kidney Biopsy Report

Most nephrologists are comfortable interpreting this

ADDENDUM/AMENDMENT:

ADDENDUM: HISTOPATHOLOGY REPORT 25:PR919

Toluidine blue stained semithin sections
The EM sample contains 5 glomeruli.
The glomeruli show increase in mesangial matrix. No overt tubular atrophy is seen; focal interstitial fibrosis is noted.

Ultrastructural study
There is approximately 10% effacement of podocyte foot processes. The glomerular basement membranes are generally of normal thickness, though there are segments which are slightly thinner (135nm) and thicker (599nm). Increased mesangial matrix is noted. Mesangial and focal para-mesangial / subendothelial electron dense deposits are identified. No tubuloreticular structures are noted.

Conclusion:
The electron microscopy findings are supportive of the original diagnoses.

NOTE: Please see below for original report.

Pathologist :

DR CHNG TZE WEI
13/11/25 1459 hrs

DIAGNOSIS:

<AP-AII>

Singapore General Hospital Pte Ltd
Outram Road, Singapore 169608
www.sgh.com.sg
Reg No 198703907Z

Renal biopsy:
Overall, features are in keeping with IgA nephropathy.

Comment:
Pending ultrastructural studies.

CLINICAL HISTORY:
12 year old male
- Subnephrotic proteinuria and haematuria for more than 1 year
- No family history or extra-renal conditions
- Normal eGFR
- Genetic test: VUS in COL4A3

- DDx: IgAN, Alport's syndrome

GROSS DESCRIPTION:
(A) The specimen is received in Bouin's fixative, labelled with patient's data and designated "renal biopsy". It consists of 1 core of tissue measuring 1.5cm in length.
(A1; no reserve)

(B) Fresh tissue received for immunofluorescence. It consists of a 1 core of tissue measuring 0.25cm in length.
(B1; no reserve)

(C) Tissue received in glutaraldehyde for electron microscopy. It consists of 2 cores tissue measuring 0.1cm in length.
(C1; no reserve)

MICROSCOPIC DESCRIPTION:
Specimen type: Native kidney.

Light microscopy:

Sections show 1 core of renal cortico-medullary tissue containing 5 glomeruli, of which none are globally or almost globally sclerosed (%).

GLOMERULI
There is mild mesangial matrix expansion with without overt mesangial hypercellularity. No endocapillary hypercellularity is seen. No areas of segmental sclerosis or crescents are seen. Special stains do not highlight membranous spikes/vacuoles or obvious deposits.
<AP-AII>

TUBULES
No overt tubular atrophy is noted.

INTERSTITIUM
No overt inflammation or fibrosis is seen.

VESSELS
No atherosclerosis or arteriolosclerosis are seen.

Oxford Classification for IgA nephropathy (2016 update): M0 E0 S0 T0 C0

IMMUNOFLUORESCENCE
No. of gloms present: 12

IgG	: Negative.
IgA	: 3+ mesangial.
IgM	: 1+ mesangial.
C3	: 2+ to 3+ mesangial.
C1q	: Negative.
Albumin	: Negative.
Lambda	: 3+ mesangium.
Kappa	: 1+ mesangium.
C4	: Negative.
Fibrinogen	: Negative.

Collagen (a5+a2) = Glomerular basement membranes and Bowman's capsule + scattered (distal) tubules + (slightly weak).

Pathologist :

DR CHNG TZE WEI
28/08/25 1701 hrs

<AP-AII>

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www.sgh.com.sg
Reg No 198703907Z

A Typical Genetic Report

Most nephrologists are NOT comfortable interpreting this

How did you earn your confidence in interpreting biopsy reports?

That's what you need for genetic reports

Genetic reports will become as common as biopsy reports

Ambry Genetics

Final Report: 3/1/2024

SUMMARY

POSITIVE: Pathogenic & Likely Pat

RESULTS

Gene	Inheritance	Alteration	Proband
COL4A4 (NM_000092)	Autosomal dominant, Autosomal recessive	Variant, Likely Pathogenic: c.2 G>A (p.G R)	Heterozygous
		Pathogenic Mut	

INTERPRETATION

- This individual is heterozygous for the c.2 G>A (p.G R) likely pathoge mutation in the *COL4A4* gene.
- This result is consistent with a diagnosis of *COL4A4*-related Alport syndrome
- Familial testing would be necessary to determine if these alterations are on th somes (in *cis* or *trans*).
- The expression and severity of disease for this individual cannot be predicted.
- Genetic testing for pathogenic and/or likely pathogenic variants in family members can be helpful in identifying at-risk individuals.
- Genetic counseling is a recommended option for all individuals undergoing genetic testing.

This individual was also found to have a variant of uncertain significance in the *ADAMTS13* gene, which may or may n clinical history. Refer to the supplementary pages for additional information on this variant. No additional pathogenic m significance, or gross deletions or duplications were detected.

Laboratory Director: Chia-Ling Gau, PhD, DABMGG. CLIA# 05D0981414
Toll Free 866.262.7943 | Ph 949.900.5500 | Fx 949.900.5501 | www.ambrygen.com | 7 Argonaut, Aliso Viejo, CA 92656

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COL4A4 Additional Information

GENE INFORMATION:

VARIANT DETAILS:

- The c.2 G>A (p.G R) alteration is located in exon 31 (coding exon 30) of the *COL4A4* gene. This alteration results from a G to A substitution at nucleotide position 2752, causing the glycine (G) at amino acid position 918 to be replaced by an arginine
- This variant was reported in multiple individ

VARIANT DETAILS:

- The c. C>T (p. 23*) alteration, located in exon 41 (coding exon 40) of the *COL4A4* gene, consists of a C to T substitution at nucleotide position 3967. This changes the amino acid from a glutamine (Q) to a stop codon at amino acid position 1323. This alteration is expected to result in loss of function by premature protein truncation or nonsense-mediated mRNA decay.
- This variant has been reported in the heterozygous state, and in conjunction with another alteration in *COL4A4*, in individuals with clinical features

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All content hereafter is supplemental information to the preceding report.

Variant(s) of Uncertain Significance

	Population Frequency[3]	*In Silico*[4]	Notes/ References	Proband
GC (p.Q7 del)	0.02%	N/A	N/A	Heterozygous

Note that only genes with characterized gene-disease relationships based on clinical validity assessment will

ad dominant.

ufficiency, or dominant-negative effect.

- Cerkauskaite A, et al. (2022) *From Med (Lausanne)* PMID:35419377
- Fallerini C, et al. (2021)
- PMID:36338941
- PMID:32965
- PMID:35675912
- Kidney Dis. Nephrol. 24(12):1945-54. PMID:24052634
- Xie J, *et al.* (2014) *J Mol Cell Biol* 6(6):498-505. PMID:25596306
- Zhang Y, *et al.* (2021) *Pediatr Nephrol* 36(9):2719-2730. PMID:33772369
- Zhou L, *et al.* (2023) *J Nephrol* 36(5):1415-1423. PMID:37097554

Genes Analyzed

(84 total): *ACTN4, ADAMTS13, AGXT, AMN, ANLN, APOL1, ARHGAP24, ARHGDIA, C3, CD2AP, CD46, CFB, CFH, CFHR5, CR, CLCN5, COL4A3, COL4A4, COL4A5, COQ2, COQ6, COQ8B, CRB2, CTNS, CUBN, DGKE, DHTKD1, DLC1, EMP2, FAN1, FAT1, FN1, GLA, GRHPR, INF2, ITGA3, ITGB4, KANK1, KANK2, KANK4, LAGE3, LAMA5, LAMB2, LMX1B, LYZ, MAFB, MAGI2, MYH9, MYO1E, NPHS1, NPHS2, NUP107, NUP133, NUP160, NUP205, NUP85, NUP93, NXF5, OCRL, OSGEP, PAX2, PDSS1, PDSS2, PLCE1, PODXL, PTPRO, REN, SCARB2, SEC61A1, SGPL1, SMARCAL1, TBC1D8B, THBD, TP53RK, TPRKB, TRIM8, TRPC6, TTC21B, TTR, UMOD, WDR4, WDR73, WT1 and XPO5.*

and is available for download through AmbryPort or can be e-mailed by request.

d not achieve 100% coverage at 10X for all nucleotides in the coding regions:

PODXL (94.28%), *TRPC6* (97.32%)

ered at ≥10X

Laboratory Director: Chia-Ling Gau, PhD, DABMGG. CLIA# 05D0981414
Toll Free 866.262.7943 | Ph 949.900.5500 | Fx 949.900.5501 | www.ambrygen.com | 7 Argonaut, Aliso Viejo, CA 92656

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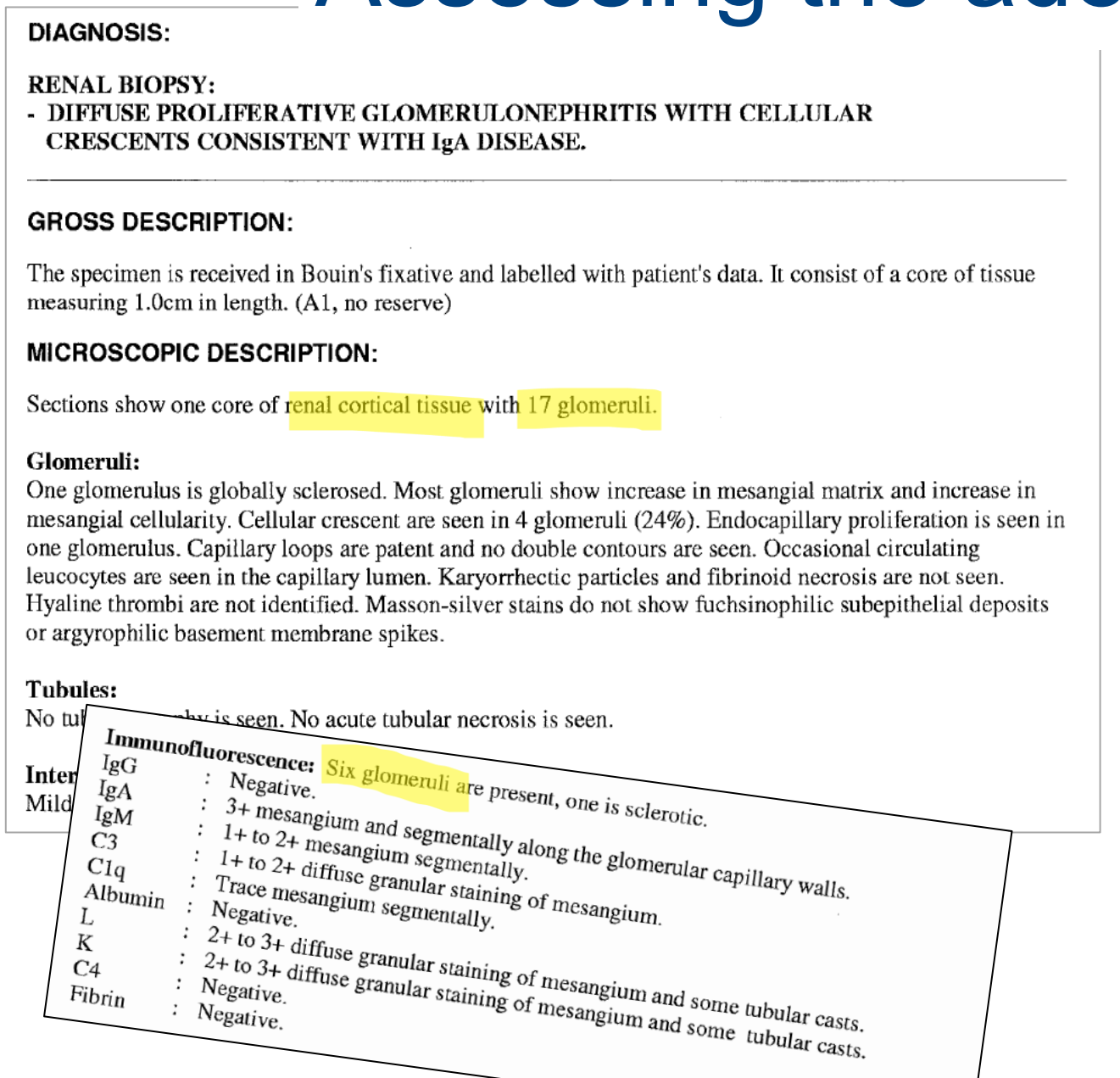
Outline: Interpreting genetic reports

- Basic 101: What nephrologists should know
- Understanding the limitations and caveats

Assessing the adequacy of the biopsy



DIAGNOSIS:

RENAL BIOPSY:
- **DIFFUSE PROLIFERATIVE GLOMERULONEPHRITIS WITH CELLULAR CRESCENTS CONSISTENT WITH IgA DISEASE.**

GROSS DESCRIPTION:

The specimen is received in Bouin's fixative and labelled with patient's data. It consist of a core of tissue measuring 1.0cm in length. (A1, no reserve)

MICROSCOPIC DESCRIPTION:

Sections show one core of renal cortical tissue with 17 glomeruli.

Glomeruli:
One glomerulus is globally sclerosed. Most glomeruli show increase in mesangial matrix and increase in mesangial cellularity. Cellular crescent are seen in 4 glomeruli (24%). Endocapillary proliferation is seen in one glomerulus. Capillary loops are patent and no double contours are seen. Occasional circulating leucocytes are seen in the capillary lumen. Karyorrhectic particles and fibrinoid necrosis are not seen. Hyaline thrombi are not identified. Masson-silver stains do not show fuchsinophilic subepithelial deposits or argyrophilic basement membrane spikes.

Tubules:
No tu... ...is seen. No acute tubular necrosis is seen.

Inter
Mild

Immunofluorescence: Six glomeruli are present, one is sclerotic.

IgG	:	Negative.
IgA	:	3+ mesangium and segmentally along the glomerular capillary walls.
IgM	:	1+ to 2+ mesangium segmentally.
C3	:	1+ to 2+ diffuse granular staining of mesangium.
C1q	:	Trace mesangium segmentally.
Albumin	:	Negative.
L	:	2+ to 3+ diffuse granular staining of mesangium and some tubular casts.
K	:	2+ to 3+ diffuse granular staining of mesangium and some tubular casts.
C4	:	Negative.
Fibrin	:	Negative.

1) Tests:
Light microscopy
Immunofluorescence
Electron microscopy

2) Clinical history

3) Sample amount:
Number of glomeruli
Cortex, corticomedullary, medulla

Assessing the adequacy of the genetic analysis

Ambry Genetics

Final Report: 3/1/2024

3) Exome/ Genome: Clinical history submitted to laboratory

ExomeNext®-Select: Analysis of Selected Genes

SUMMARY

POSITIVE: Pathogenic & Likely Pathogenic Alterations Detected

RESULTS

Gene	Inheritance		Proband
COL4A4 (NM_000092)	Au	2G>A (p.G918R)	Heterozygous
		T (p.Q1323*)	Heterozygous

INTERPRETATION

- This individual is het… he **c.3967C>T (p.Q1323*)** pathogenic mutation in the *COL4…*
- This result is consiste…
- Familial testing would … nt chromosomes (in *cis* or *trans*).
- The expression and se…
- Genetic testing for path… t-risk individuals.
- Genetic counseling is a…

This individual was also found … in the *ADAMTS13* gene, which may or may not contribute to this individual's clinical history. Refer to the sup… pages for additional information on this variant. No additional pathogenic mutations, variants of uncertain significance, or gross deletions or duplications were detected.

1) What kind of test?
Gene panel
Targeted exome
Exome
Genome

Patient Name: [redacted]
MRN #: NPM Accession #: 24-096784

All content hereafter is supplemental information to the preceding report.

Variant(s) of Uncertain Significance

Gene (RefSeq ID)	Associated Condition(s) (Inheritance)[1,2]	Alteration	Population Frequency[3]	*In Silico*[4]	Notes/ References	Proband
ADAMTS13 (NM_139025)	*ADAMTS13*-related thrombotic thrombocytopenic purpura (AR)	c.215_220delAGAGGC (p.Q72_R73del)	0.02%	N/A	N/A	Heterozygous

[1]Disease/p… nt will have asso…
[2]AD= autb… Recessive
[3]The numb…
[4]Predictor…

Is the suspected gene included? Which genes did not achieve adequate coverage 10-30x**?**

Repo…

- Gao Y, *et al.* (2022) *Front Genet* **13**:1064491. **PMID:**36699462
- Isaranuwatchai S, *et al.* (2023) *Sci Rep* **13**(1):805. **PMID:**36646731
- Lee JM, *et al.* (2019) *J Clin Med* **8**(2):178. **PMID:**30717457
- Longo I, *et al.* (2006) *Nephrol. Dial. Transplant.* **21**(3):665-71. **PMID:**16338941
- Lu L, *et al.* (2022) *Clin Genet* **101**(5):541-551. **PMID:**…
- Papazachariou L, *et al.* (2…
- Savige J, *et al.* (2022) *Cli…*
- Storey H, *et al.* (2013) *J. A…*
- Xie J, *et al.* (2014) *J Mol C…*
- Zhang Y, *et al.* (2021) *Ped…*
- Zhou L, *et al.* (2023) *J Nep…*

2) List of genes analyzed Metrix and Coverage

Genes Analyzed

(84 total): *ACTN4, ADAMTS13, AGXT, AMN, ANLN, APOL1, ARHGAP24, ARHGDIA, C3, CD2AP, CD46, CFB, CFH, CFHR5, CFI, CLCN5, COL4A3, COL4A4, COL4A5, COQ2, COQ6, COQ8B, CRB2, CTNS, CUBN, DGKE, DHTKD1, DLC1, EMP2, FAN1, FAT1, FN1, GLA, GRHPR, INF2, ITGA3, ITGB4, KANK1, KANK2, KANK4, LAGE3, LAMA5, LAMB2, LMX1B, LYZ, MAFB, MAGI2, MYH9, MYO1E, NPHS1, NPHS2, NUP107, NUP133, NUP160, NUP205, NUP85, NUP93, NXF5, OCRL, OSGEP, PAX2, PDSS1, PDSS2, PLCE1, PODXL, PTPRO, REN, SCARB2, SEC61A1, SGPL1, SMARCAL1, TBC1D8B, THBD, TP53RK, TPRKB, TRIM8, TRPC6, TTC21B, TTR, UMOD, WDR4, WDR73, WT1 and XPO5.*

Metrics and Coverage

Complete coverage data for this proband is available for download through AmbryPort or can be e-mailed by request.

The following genes (coverage)* did not achieve 100% coverage at 10X for all nucleotides in the coding regions:

NXF5 (94.35%), ***PDSS1*** (97.36%), ***PODXL*** (94.28%), ***TRPC6*** (97.32%)

*percentage of the coding region covered at ≥10X

Variant interpretation:
What nephrologists need to know

```
@ERR000589.41 EAS139_45:5:1:2:111/1
CTTTCCTCCCTGCTTTCCTGGCCCCACCATTTCCAGGGAACATCTTGTCAT
+
3IIIIIIIIIIIII>1IIIFF9BG08E00I%IG+&?(4)%00646.C1#&(
@ERR000589.42 EAS139_45:5:1:2:1293/1
AGTTGTTAAAATCCAAGCCAATTAAGATAGTCTTATCTTTTTAAAAGAAAT
+
IIIIIGII.AIIII=?I9G-/II=+I=4?761BA2C9I+5A711+&>1$/I
```

6 billion nucleotides

Patient's genetic sequence

compare

Reference sequence

GRCh37 = hg19

GRCh38 = hg38
(newer and more accurate)

Telomere-to-telomere
(T2T-CHM13)

>5 million variants per person

How?

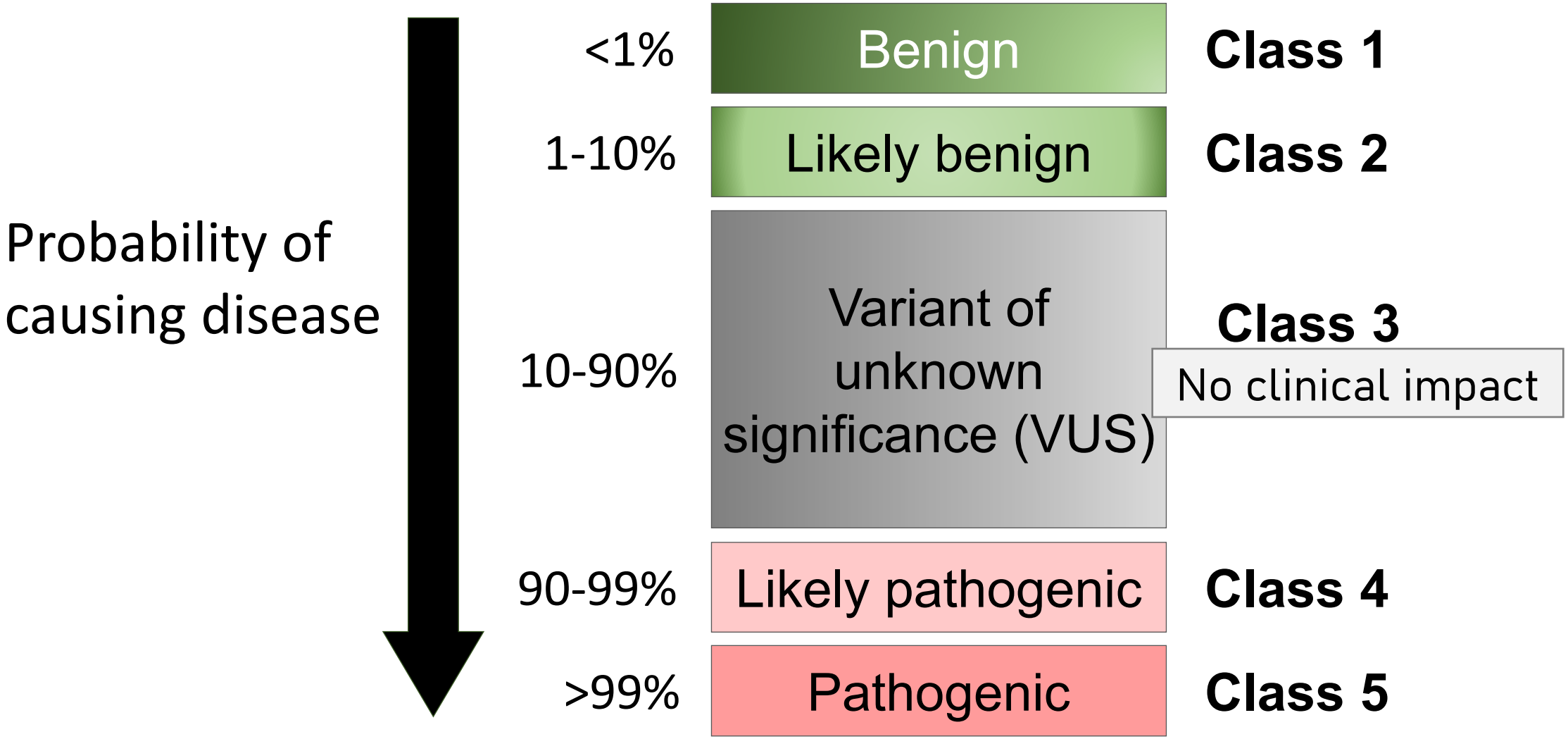
2 disease-causing variants (high impact)

Carrier for at least 2 variants in AR diseases

Xue. Am J Hum Gen 2012:1022.
Fridman H. Am J Hum Gen 2021:608

Genetic variants: 5 categories

American College of Medical Genetics and Genomics (ACMG)
Association for Molecular Pathology (AMP)



Genetic variant X

Is this variant pathogenic?

Criteria to assign pathogenicity

(Very) Strong	BA1							PVS1	PS1	PS2	PS3	PS4
Moderate	BS1	BS2	BS3	BS4				PM1	PM2	PM3	PM4	PM5	PM6
Supporting	BP1	BP2	BP3	BP4	BP5	BP6	BP7	PP1	PP2	PP3	PP4	PP5

ACMG 2015 guidelines

PATHOGENIC
1 very strong + 1 mod+ 1 supporting
1 strong + 1 mod+ 4 supp

LIKELY PATHOGENIC
1 very strong + 1 mod
1 mod + 4 supp

Benign
2 Strong

Likely Benign
1 Strong + 1 Supporting

Benign

Likely benign

Variant of unknown significance

Likely pathogenic

Pathogenic

Genet Med. 2015;17:405

Genetic variant X

Is this variant pathogenic?

Criteria to assign pathogenicity

(Very) Strong	BA1							PVS1	PS1	PS2	PS3	PS4
Moderate	BS1	BS2	BS3	BS4				PM1	PM2	PM3	PM4	PM5	PM6
Supporting	BP1	BP2	BP3	BP4	BP5	BP6	BP7	PP1	PP2	PP3	PP4	PP5

Bayesiam framework of scoring variants

Strength	Pathogenic	Benign
Indeterminate	0	0
Supporting	1	-1
Moderate	2	-2
Strong	4	-4
Very strong	8	-8

<= -7 **Benign**

Likely benign -1 to -6

Variant of unknown significance 0-5

Likely pathogenic >=10

Pathogenic 6-9

Genet Med. 2015;17:405

Liu, J Med Gen. 2025

Is the variant causing the disease?

BA1						
BS1	BS2	BS3	BS4			
BP1	BP2	BP3	BP4	BP5	BP6	BP7

PVS1	PS1	PS2	PS3	PS4	
PM1	PM2	PM3	PM4	PM5	PM6
PP1	PP2	PP3	PP4	PP5	

Laboratory

- Population frequency
- In silico tools
- Nature of variant
- Hot spot for mutations
- Functional studies
- Nearby variants
- Previous reported cases

Report: VUS

Clinician

- Gene-phenotype
- Mode of inheritance
- Phenotype specificity
- Family segregation
- De novo
- Functional studies

Genomic board meeting

Likely pathogenic

Is the variant causing the disease?

BA1						
BS1	BS2	BS3	BS4			
BP1	BP2	BP3	BP4	BP5	BP6	BP7

PVS1	PS1	PS2	PS3	PS4	
PM1	PM2	PM3	PM4	PM5	PM6
PP1	PP2	PP3	PP4	PP5	

Laboratory

- Population frequency
- In silico tools
- Nature of variant
- Hot spot for mutations
- Functional studies
- Nearby variants
- Previous reported cases

??

Clinician

- Gene-phenotype
- Mode of inheritance
- Phenotype specificity
- Family segregation
- De novo
- Functional studies

???

Do these variants explaining the disease of the patient?

- 15 years old, Chinese boy
- Persistent isolated haematuria with no albuminuria
- Mother has microscopic haematuria

Variant(s) of Uncertain Significance

Gene (RefSeq ID)	Associated Condition(s) (Inheritance)[1,2]	Alteration	Population Frequency[3]	*In Silico*[4]	Notes/References	Proband
COL4A4 (NM_000092)	*COL4A4*-related Alport syndrome (AD, AR)	c.1805G>A (p.G602E)^	N/A	Deleterious	Isaranuwatchai, 2023	Heterozygous
FAT1 (NM_005245)	*FAT1*-related nephrotic syndrome (AR)	c.13484C>T (p.P4495L)	0.11%	Tolerated	N/A	Heterozygous

Is FAT1 consistent with the phenotype? No

Is the mode of inheritance and zygosity consistent? No

Do these variants explaining the disease of the patient?

- 15 years old, Chinese boy
- Persistent isolated haematuria with no albuminuria
- Mother has microscopic haematuria

Variant(s) of Uncertain Significance

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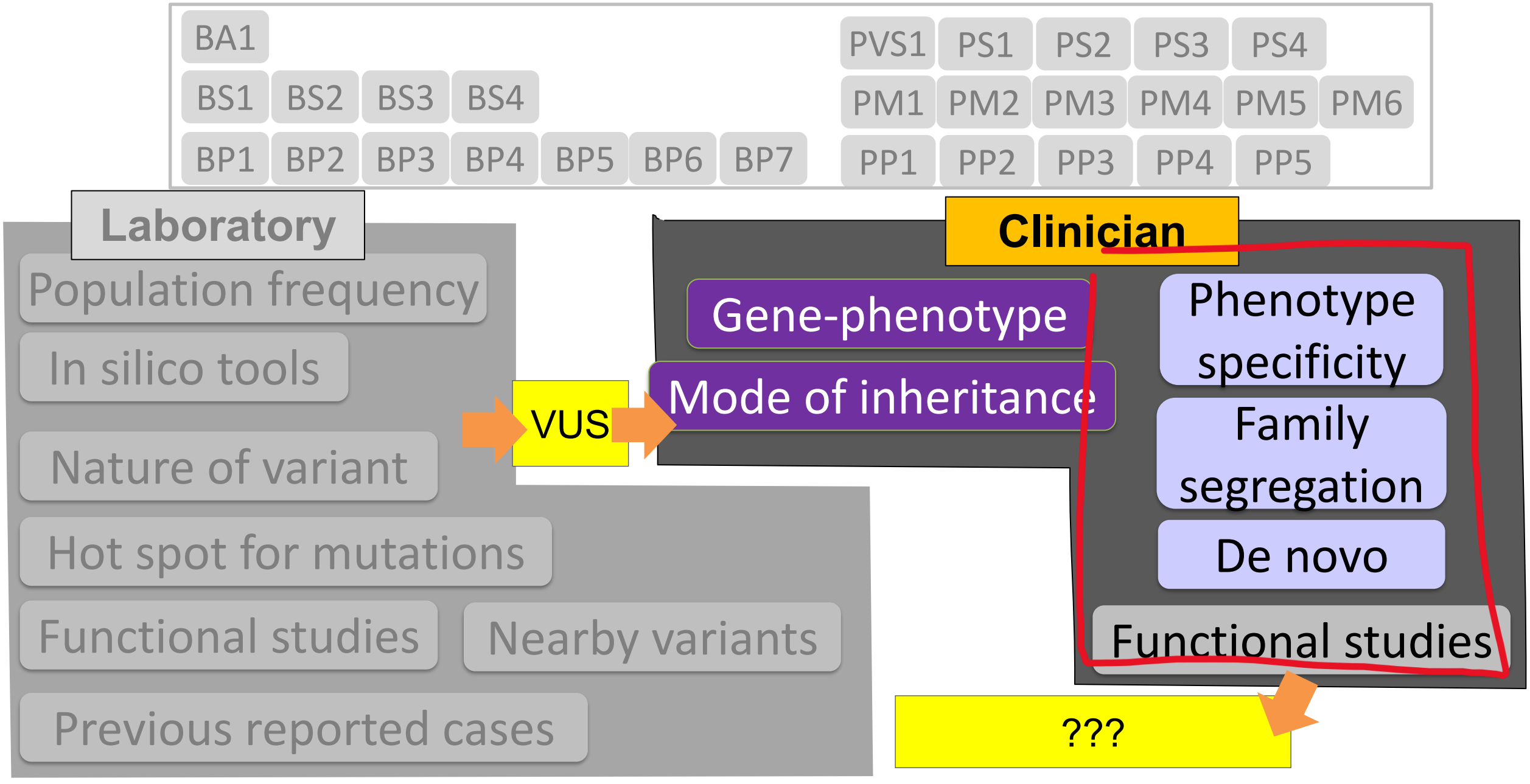
COL4A4 (NM_000092)	*COL4A4*-related Alport syndrome (AD, AR)	c.1805G>A (p.G602E)^	N/A	Deleterious	Isaranuwatchai, 2023	Heterozygous
FAT1 (NM_005245)	*FAT1*-related nephrotic syndrome (AR)	c.13484C>T (p.P4495L)	0.11%	Tolerated	N/A	Heterozygous

Is COL4A4 consistent with the phenotype? Yes

Is the mode of inheritance and zygosity consistent? Yes

Can this COL4A4 variant of uncertain significance be upgraded? Maybe

Is the variant causing the disease?



NUHS National University Health System

National University Hospital

High burden of Variants of Uncertain Significance in Asia

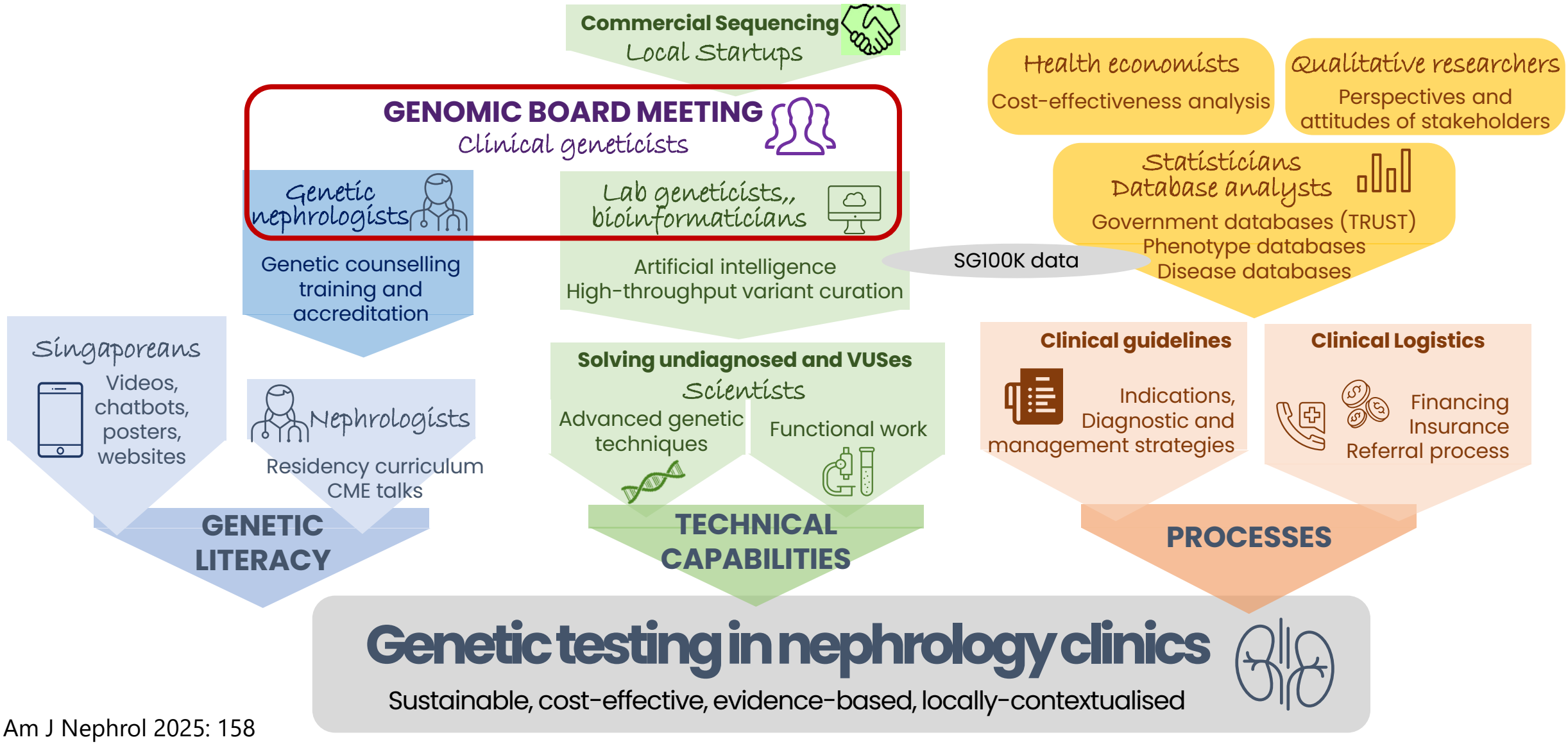
Asian genomes represent

6.6% of Genome Aggregation Database (gnomAD): Lack of population-specific allele frequency data

3% of genomic research studies: Lack of functional or clinical evidence for many variants

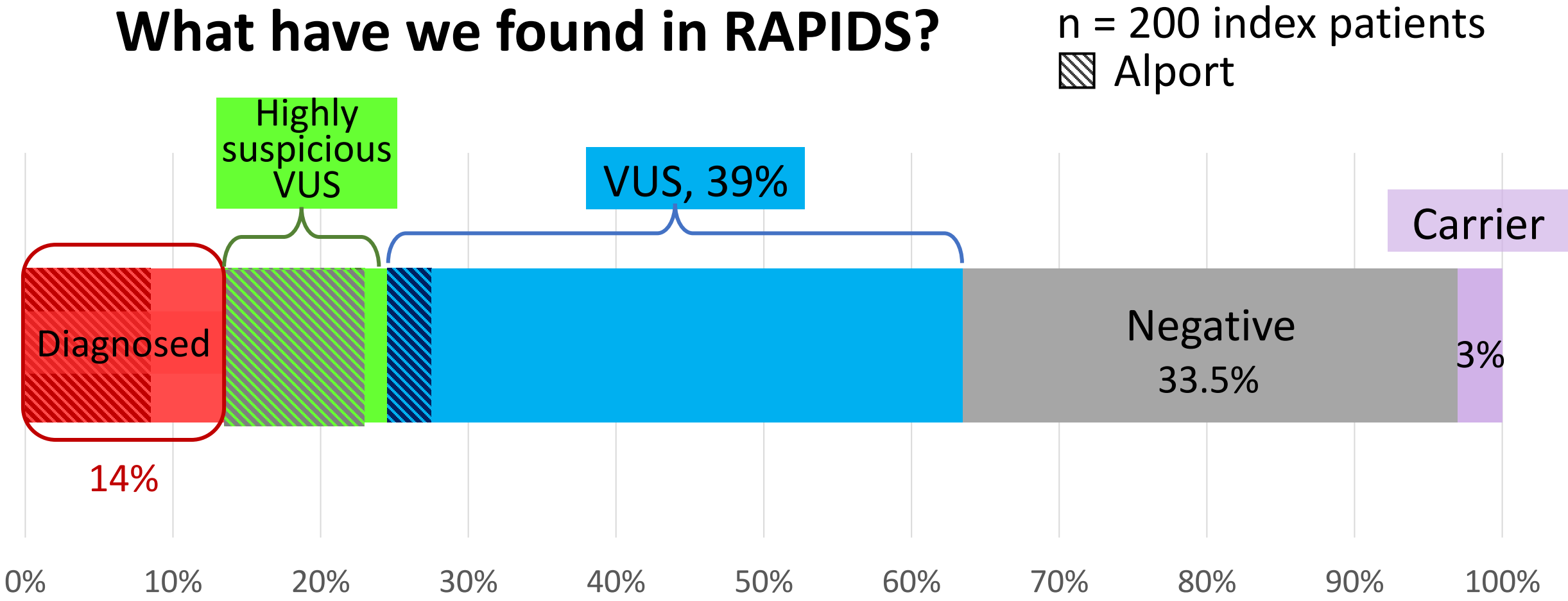
Chen JAMA Network Open. 2023:e2339571
Bianco Molecular Genetics and Genomics : MGG. 2025:86

RAPIDS Renal Alliance for Precision Diagnosis in Singapore



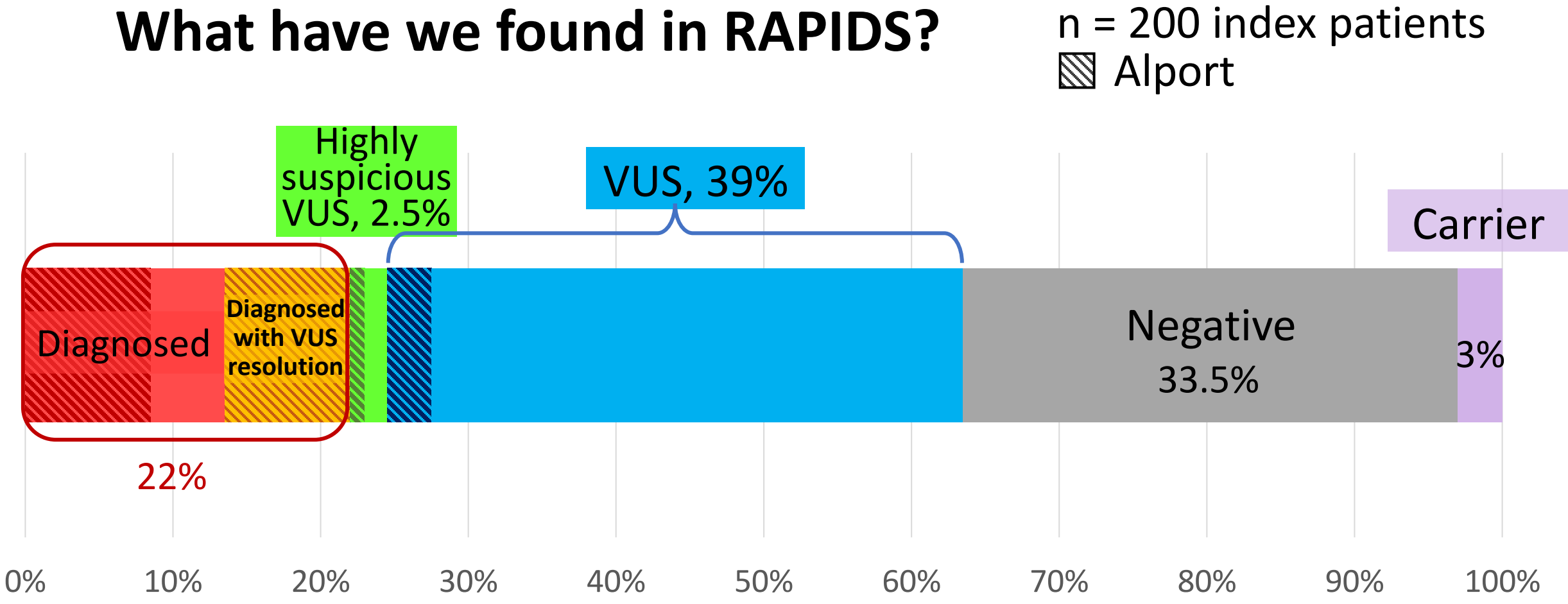
Lim. Am J Nephrol 2025: 158

What have we found in RAPIDS?



Lim. Am J Nephrol 2025: 158

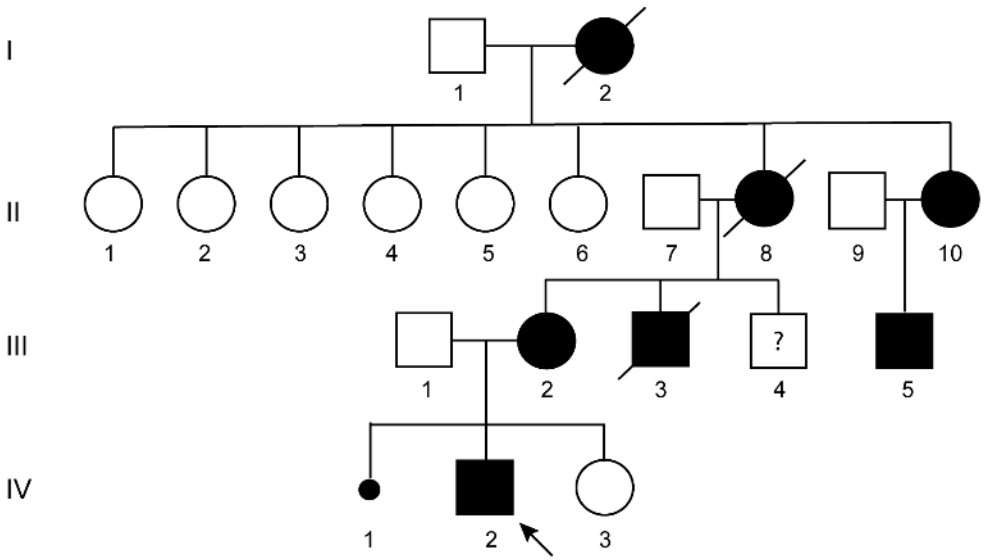
What have we found in RAPIDS?



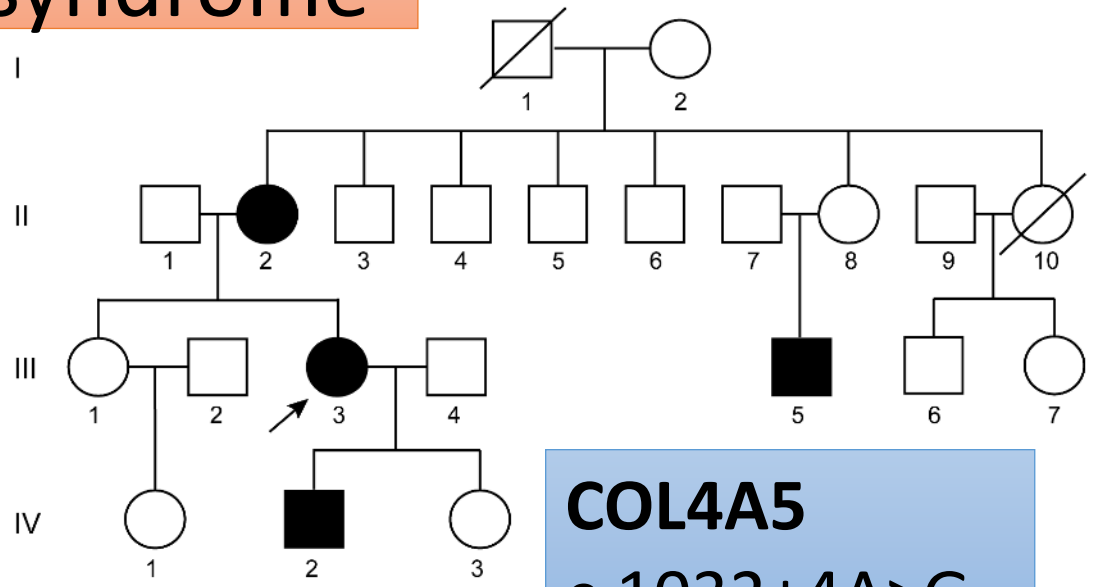
Lim. Am J Nephrol 2025: 158

Functional studies to resolve variants of uncertain significance

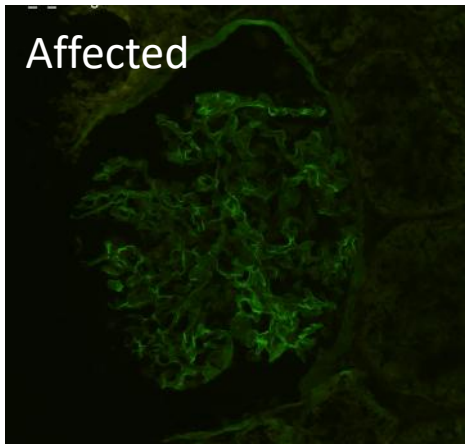
X-linked Alport syndrome



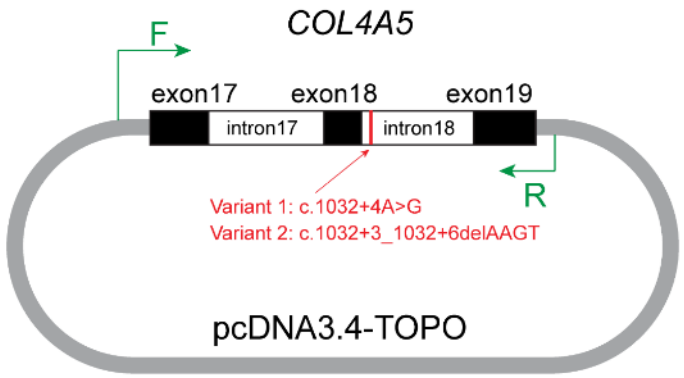
COL4A5
c.1032+3_1032+6delAAGT

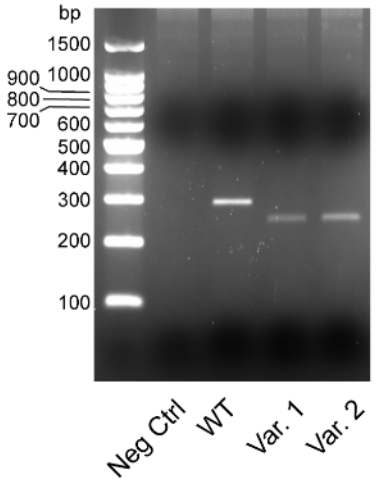


COL4A5
c.1032+4A>G



Immunostaining of collagen 4



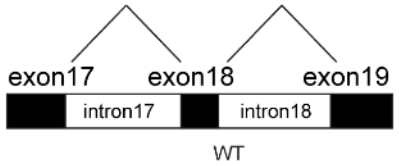


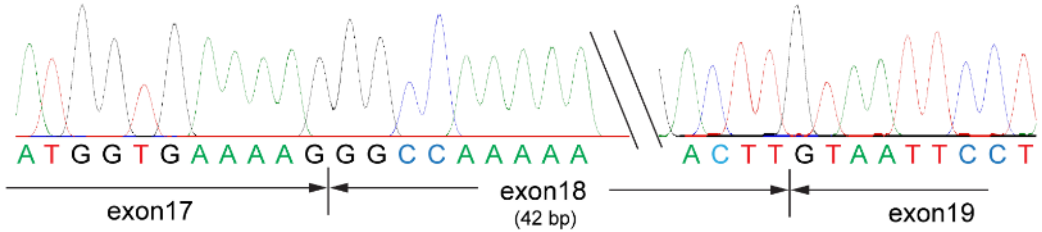
Zhang Yaochun

Tina Lim

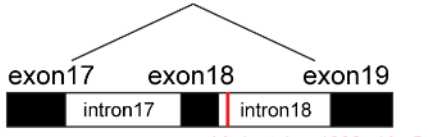
Mini-Gene assay

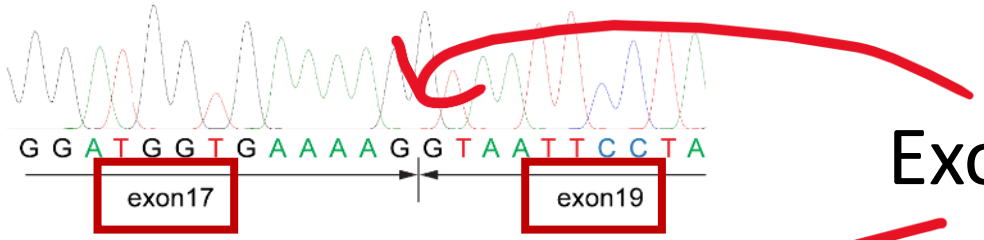
Wild type



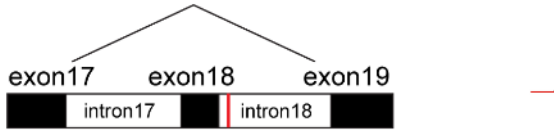


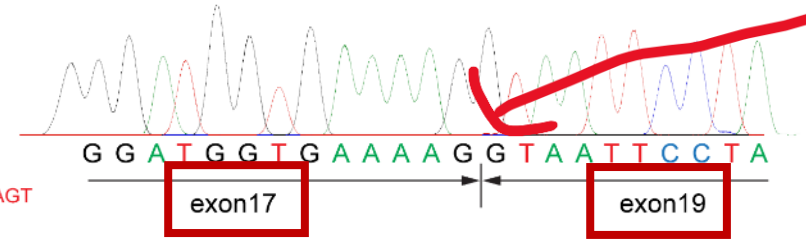
Variant 1





Variant 2





Exon 18 is missing

Koh. Front Med 2025:1611334

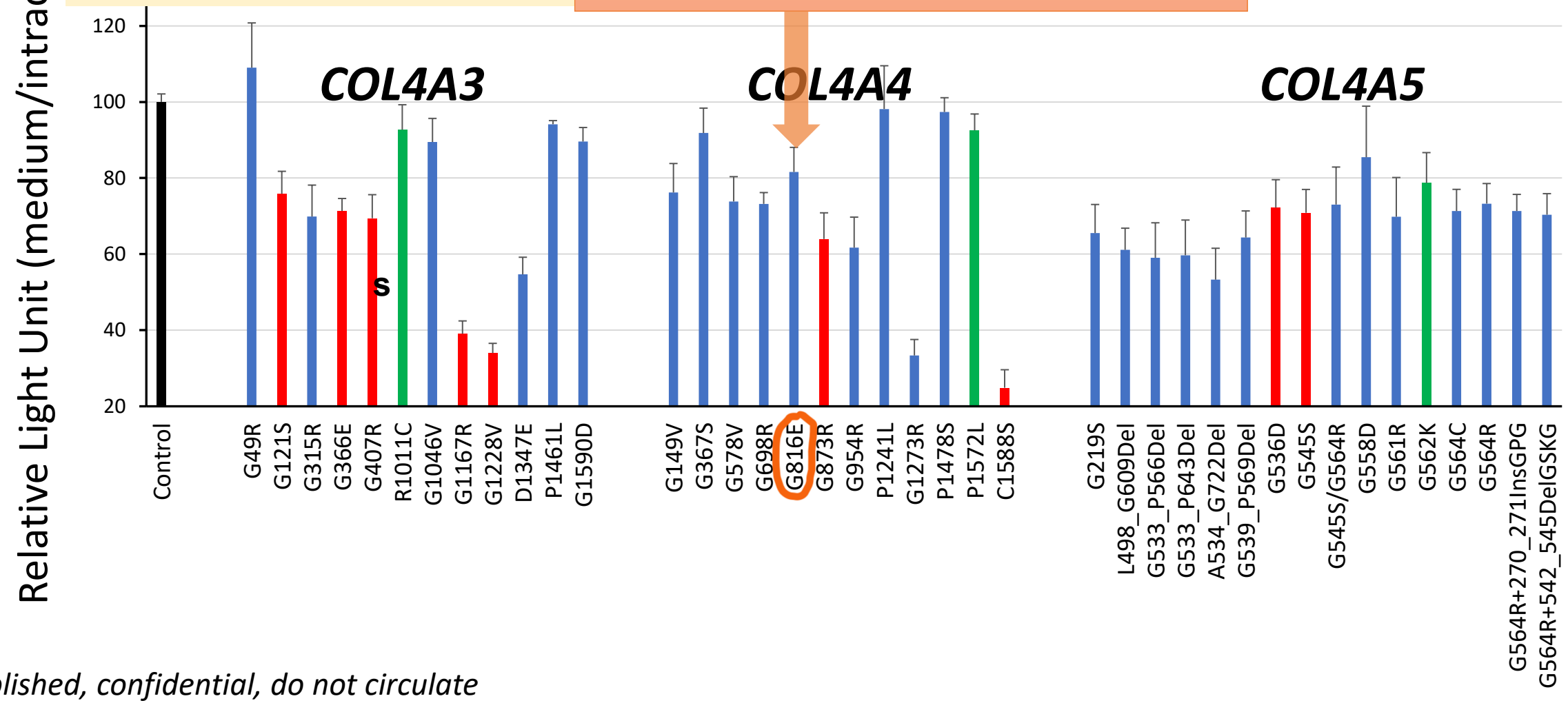
Split-luciferase assay

(Likely) benign
(Likely) pathogenic
Variant of uncertain s

COL4A4, c.2447G>A p.G816E
GnomAD: 0.0334% in East Asians
SG10K All: MAF 0.0736%
SG10K Chinese: MAF 0.1221%


Zhang Yaochun


Tina Lim



Outline: Interpreting genetic reports

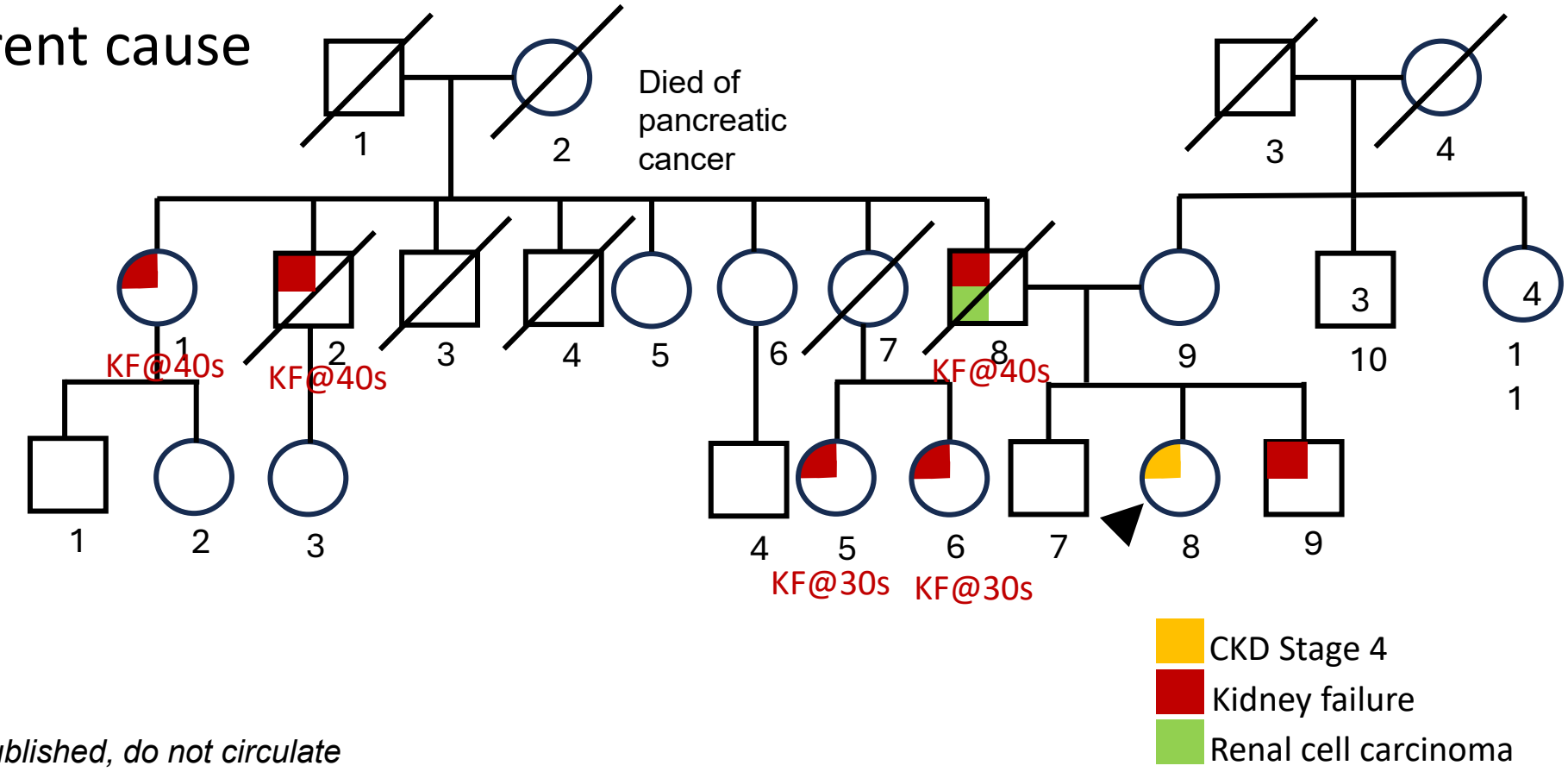
- Basic 101: What nephrologists should know
- Understanding the limitations and caveats

31 year old Chinese lady

Exome: no pathogenic variants

Biopsy: Tubulointerstitial nephritis

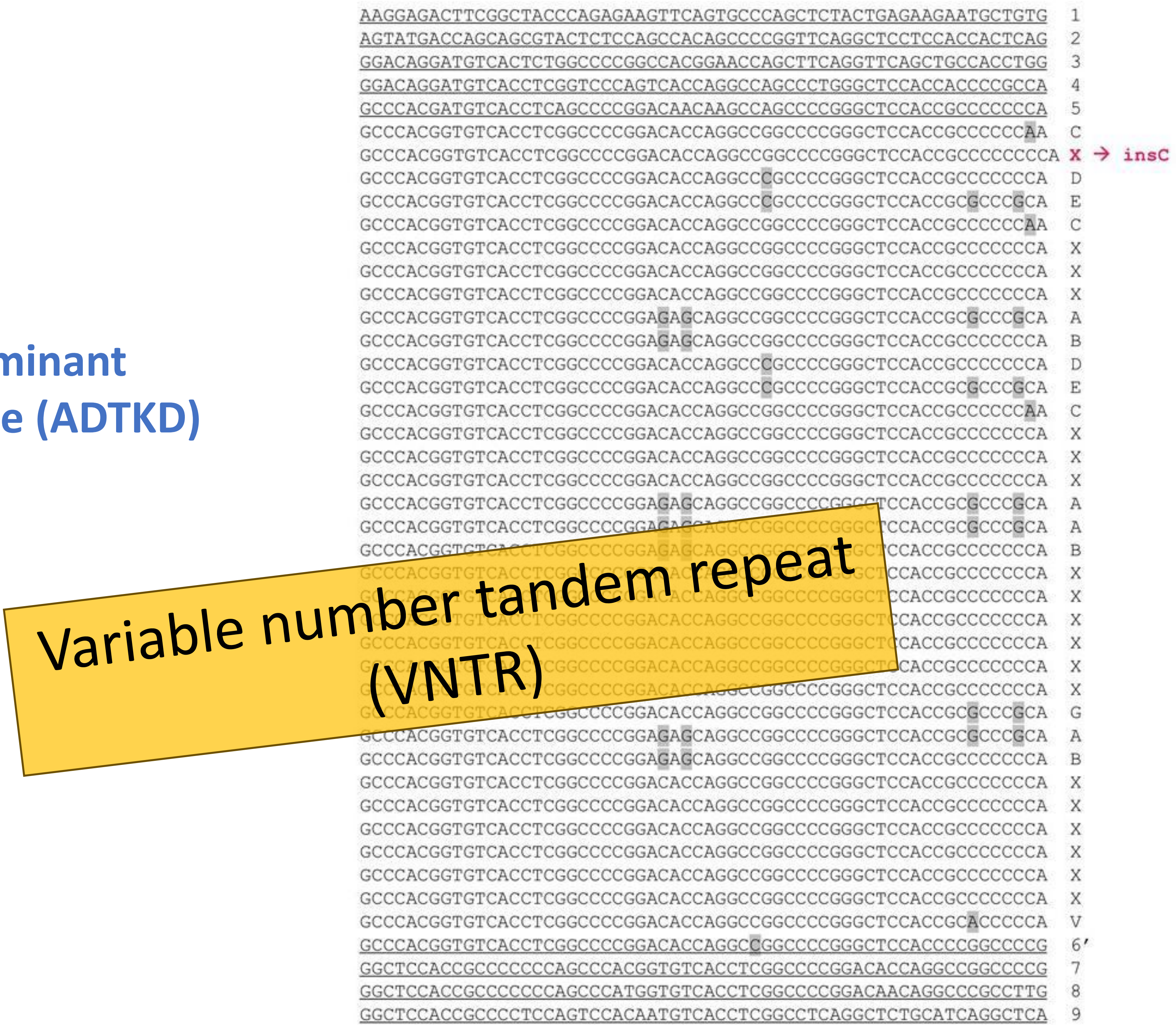
- Incidental CKD Stage G3A1 at age 29
- Ultrasound: Increased bilateral kidney echogenicity
- Bland urine sediments
- No apparent cause



MUC1 (Mucin-1) gene testing

Specific Cytosine duplication

Diagnosed:
Mucin-1 related autosomal dominant tubulointerstitial kidney disease (ADTKD)



Confidential, unpublished, do not circulate

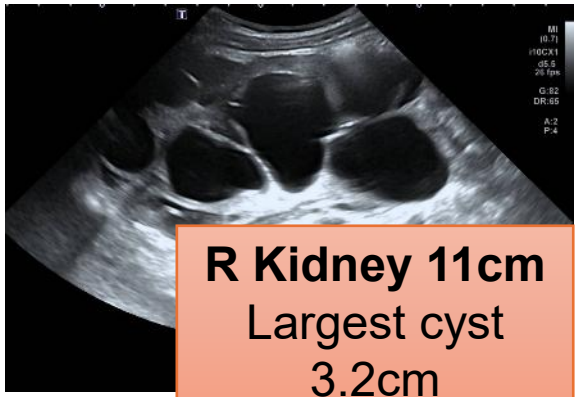
3 year old Chinese girl

- Known **tuberous sclerosis** (classic skin features)

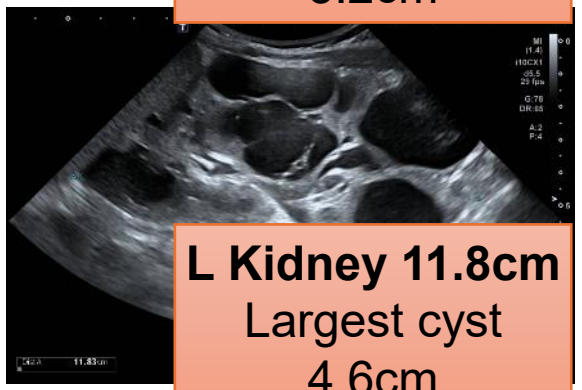
- **Renal cysts** since 1.5 years old
- CKD G1A1

- No family history

Ultrasound

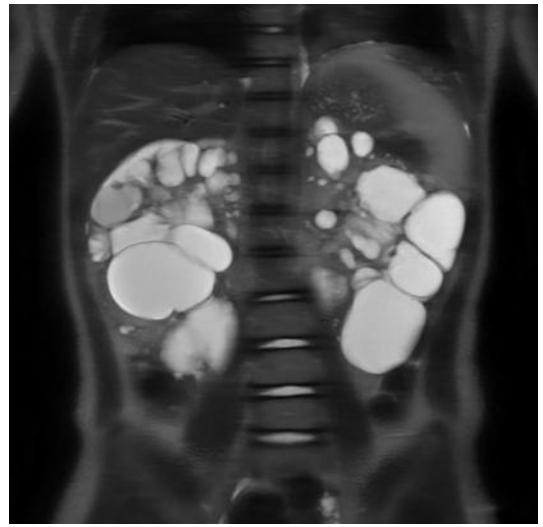


R Kidney 11cm
Largest cyst
3.2cm



L Kidney 11.8cm
Largest cyst
4.6cm

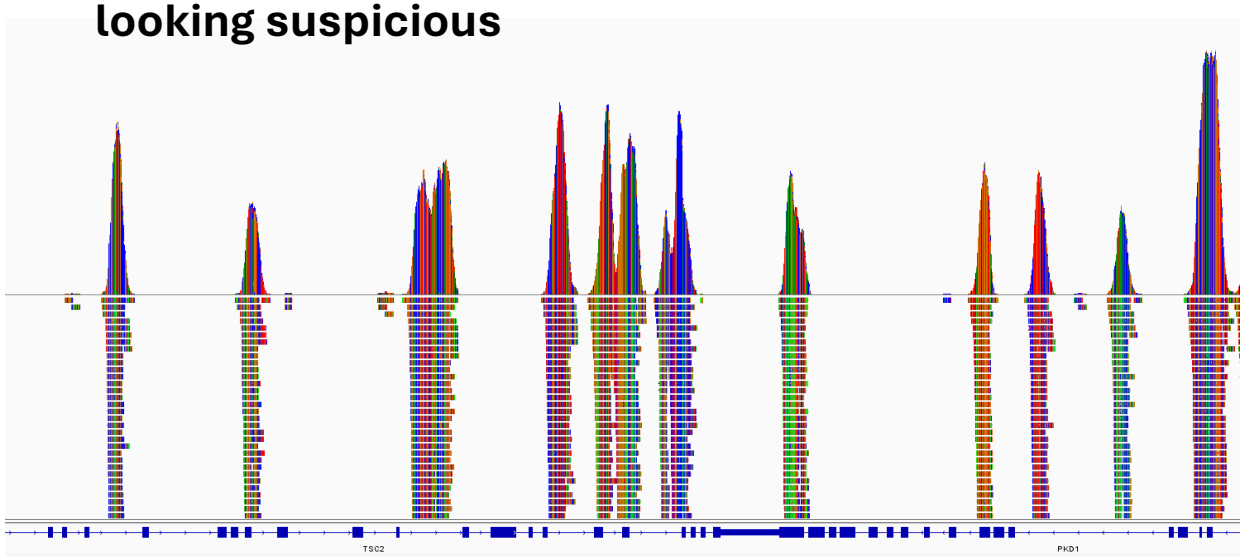
MRI



Cystic gene panel
TSC2 gene (autosomal dominant):
Pathogenic mutation **5'UTR_3'UTRdel**

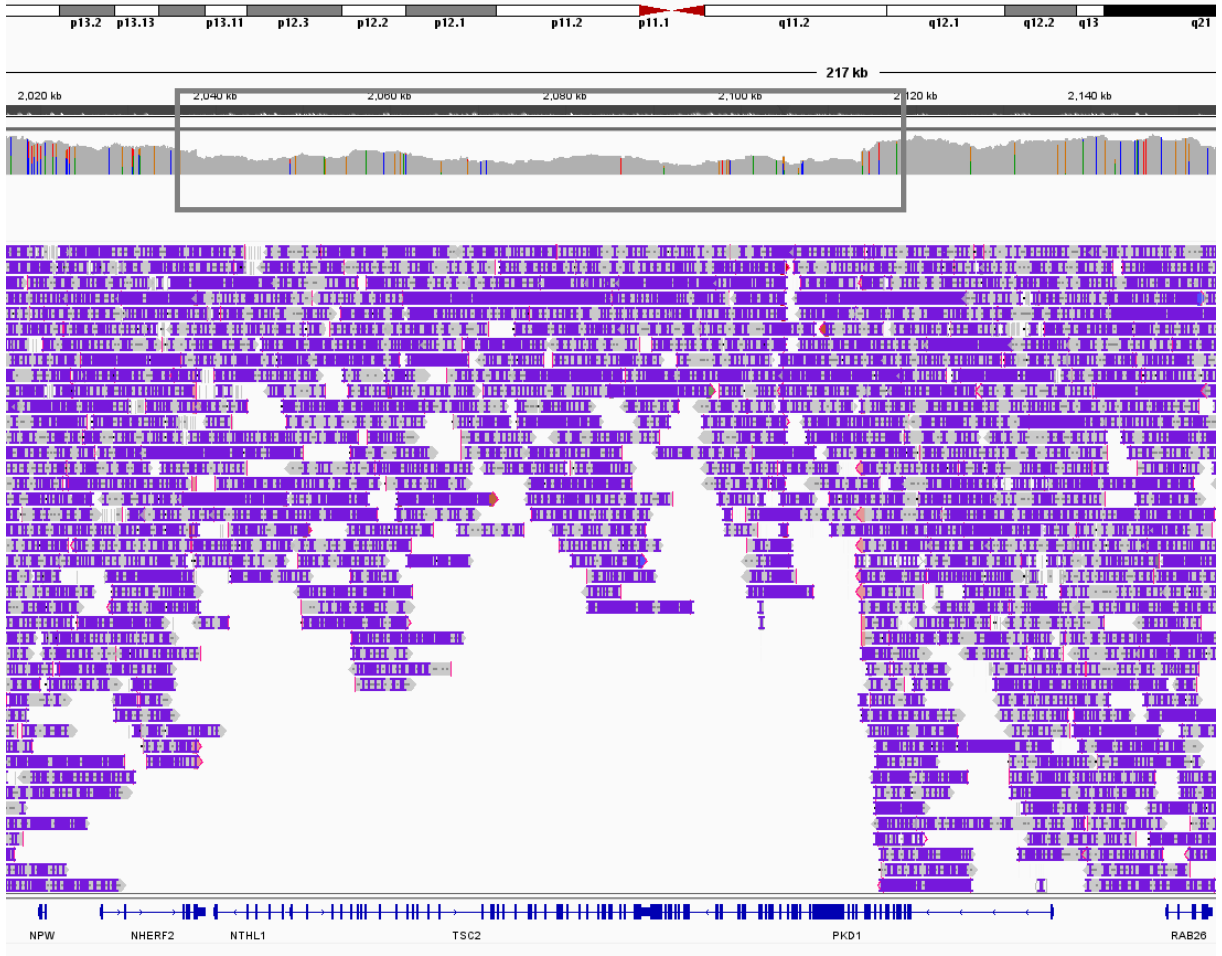
PKD1?

Exome short read sequencing: looking suspicious

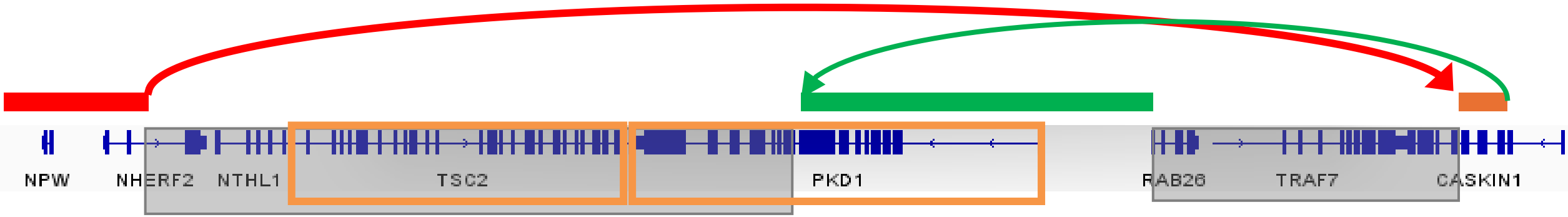


Oxford Nanopore Technologies

Long read sequencing



Long read sequencing



chr16:g.2037884_2113847delins2190369_2190550

Complete deletion: *TSC2*, *NTHL1, TRAF7*

Partial deletion: PKD1, *NHERF2*

Partial duplication: *CASKIN1*

Homologous recombination

Diagnosed:
TSC2-PKD1 contiguous tuberous sclerosis-polycystic kidney disease syndrome

Which type of genetic tests should be ordered in patients with kidney diseases?

PHENOTYPE

CLEAR

?

UNCLEAR OR CKDX

Panels
~50-150 genes

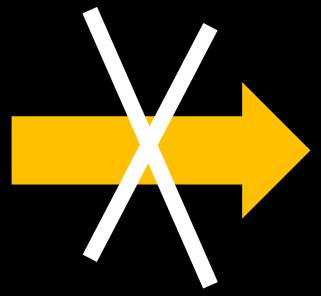
Kidney panel
~400-500 genes

Exome or Genome
~22,000 genes

Same diagnostic yield as exome

Giovanella. Clinical Genetics. 2025

Negative genetic test



No genetic disease

<u>Variant problem</u>

Variant of uncertain significance

Non-coding variants (e.g. splice)

Structural variant (e.g. large deletion / duplication)

Gene not in the panel or not yet associated with diseases

NUS National University of Singapore

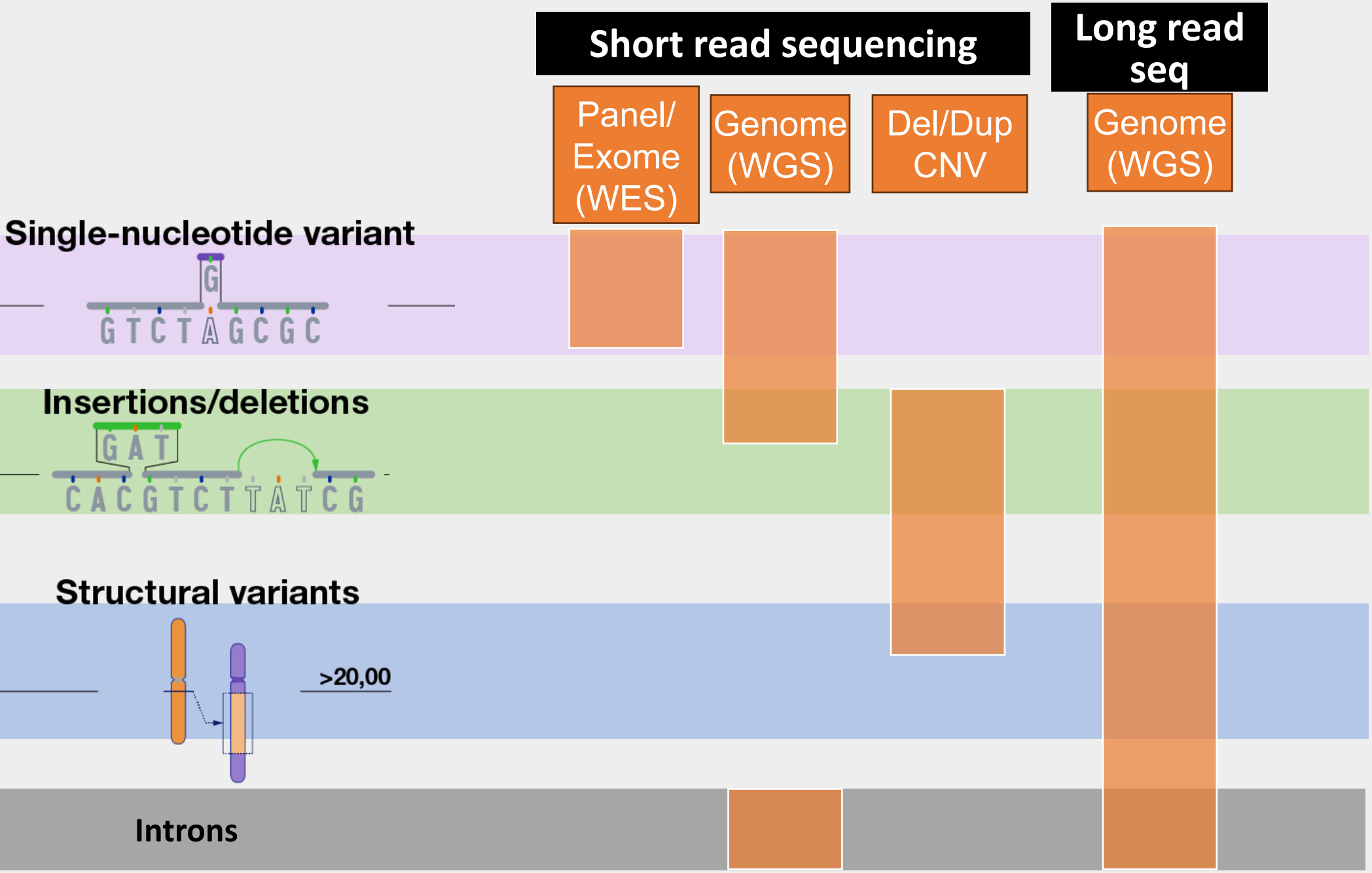
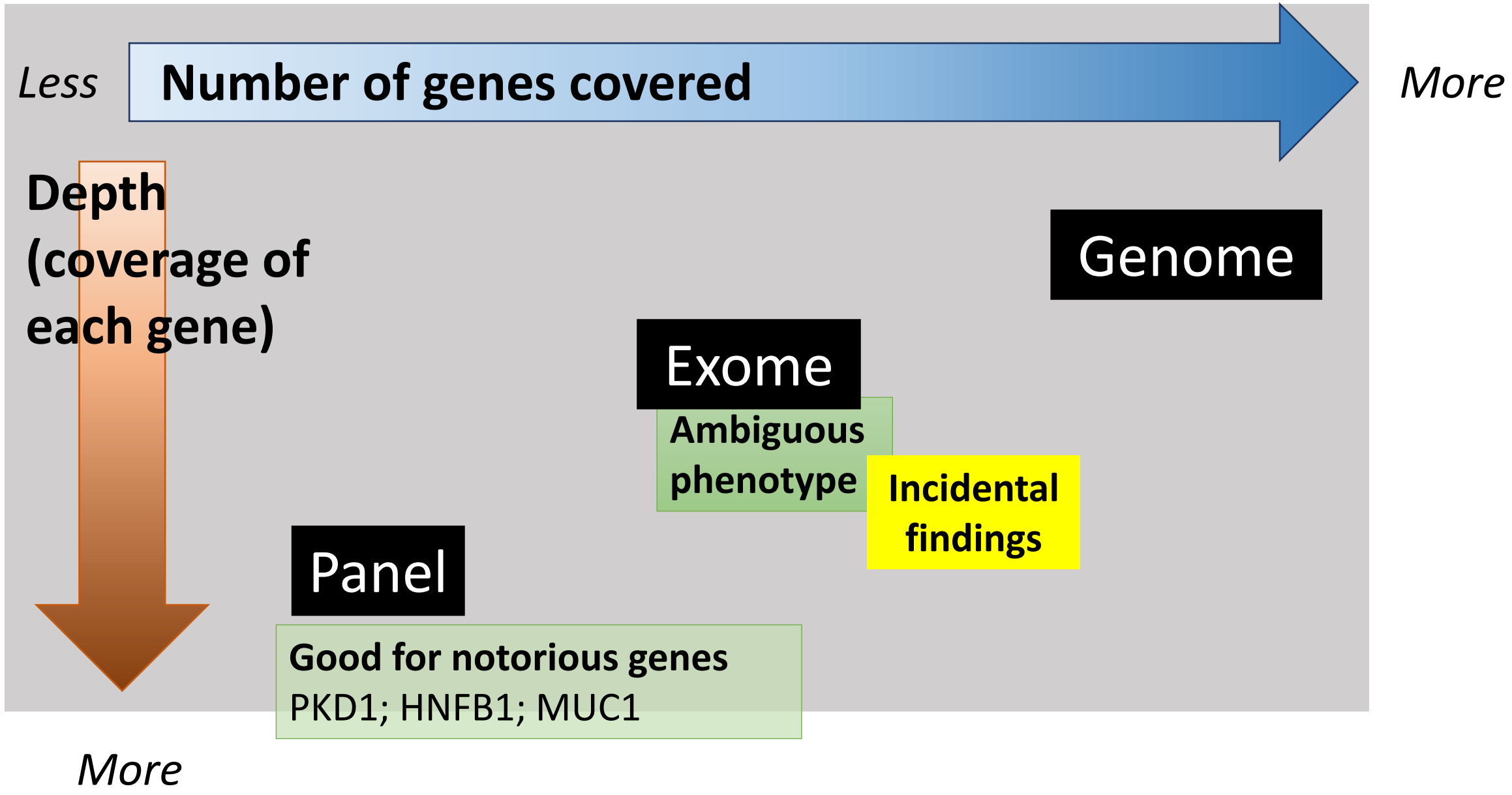
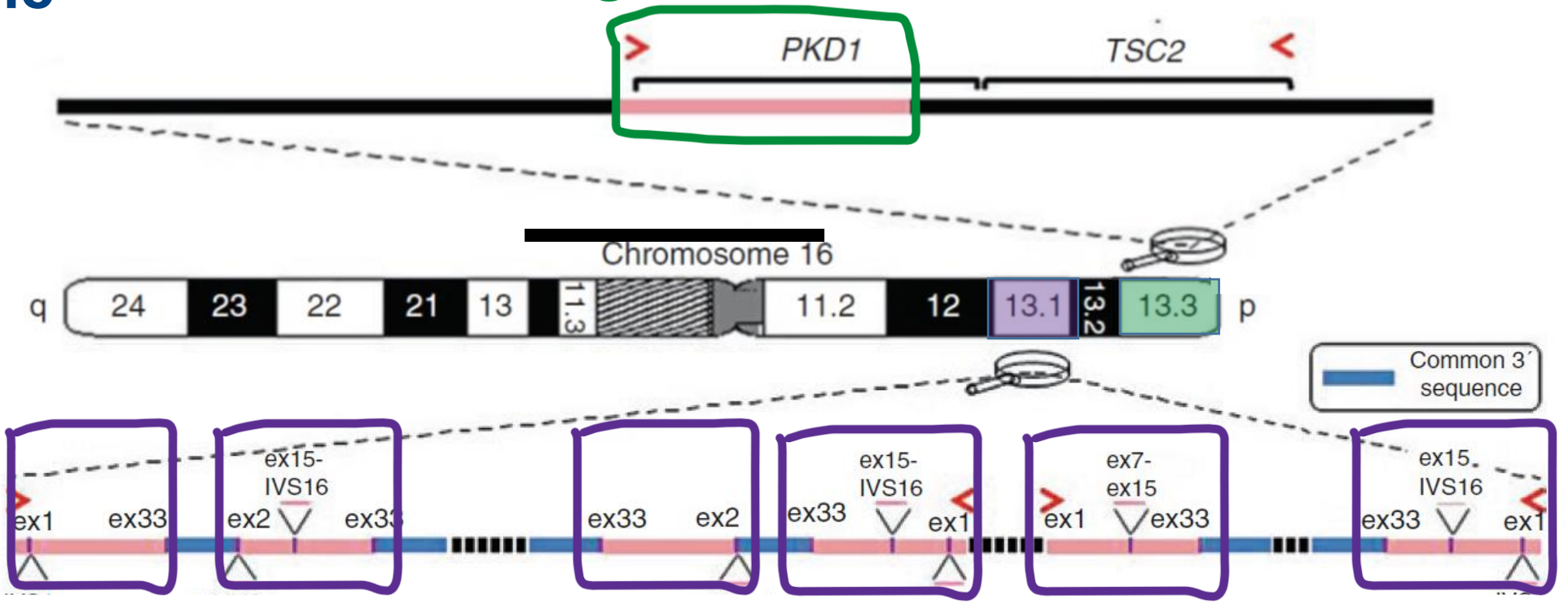


Image source: https://www.genome.gov/


Less
Number of genes covered
More
Depth
(coverage of
each gene)
Genome
Exome
Ambiguous
phenotype
Incidental
findings
Panel
Good for notorious genes
PKD1; HNFB1; MUC1
More

PKD1 gene

Real gene, exons 1-46



6 pseudogenes exons 1-33
98% homology as the real gene

Is it in the real gene or the pseudogenes?

Whole exome sequencing: usually bad PKD1 coverage

Gall. Polycystic Kidney Disease. Ed Cowley BJ, Bissler JJ, Chapter 1, p.4

TAKE HOME MESSAGES

1. Check the adequacy of a genetic report
   - Type of test, gene list, gene coverage

2. Check consistency in gene-phenotype and mode of inheritance

TAKE HOME MESSAGES

3. Resolution of variants of uncertain significance requires multi-disciplinary efforts and is iterative

4. Limitations of genetic tests:
   - **Genes**: Missing, challenging gene regions (pseudogenes, multiple repeats)
   - **Variants**: Non-coding, large deletions / duplications

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