WEBINAR

14/06/22

# Welcome to

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

## When to perform genetic testing in CAKUT (and what to test)?

Speaker: Nine Knoers (Groningen, Netherlands)

Moderator: Max Liebau (Cologne, Germany)

ERKNet
The European Rare Kidney Disease Reference Network

european society for paediatric nephrology

# Disclosures

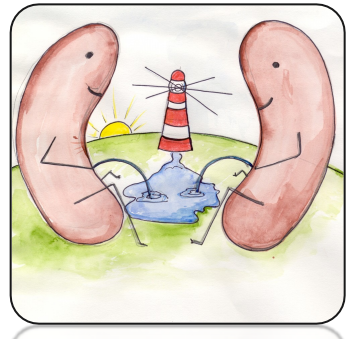
Presenter has no financial or other conflicts of interest to report

University Medical Center Groningen

university of groningen

# Outline

- Epidemiology CAKUT
- Disturbed nephrogenesis
- Etiology CAKUT: genetic, epigenetic and environmental factors
- Current molecular diagnostic tools for CAKUT
- When to perform genetic testing and what to test?
- Take home messages



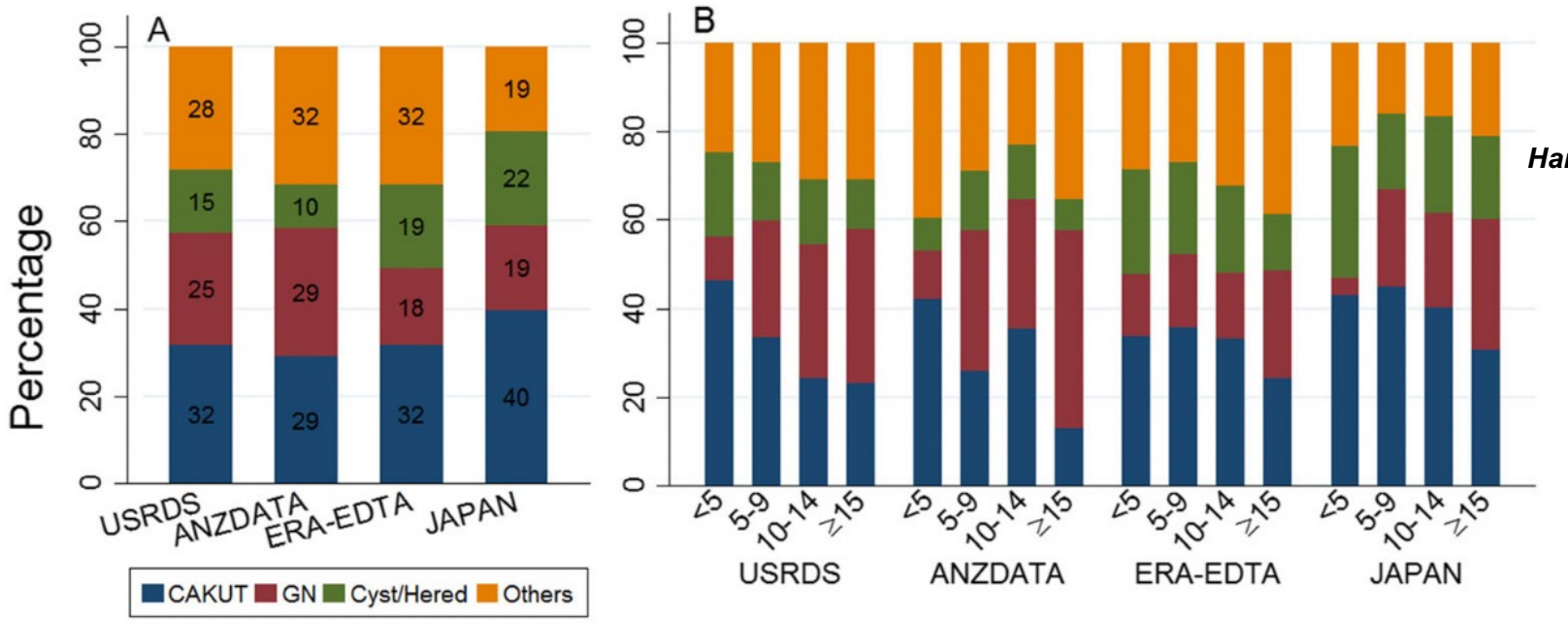
# Poll question

My background knowledge on the genetics of kidney diseases in general, and CAKUT in particular is:

1. Low
2. Moderate
3. High
4. I am an expert

# Congenital anomalies of the kidney and urinary tract (CAKUT): Epidemiology

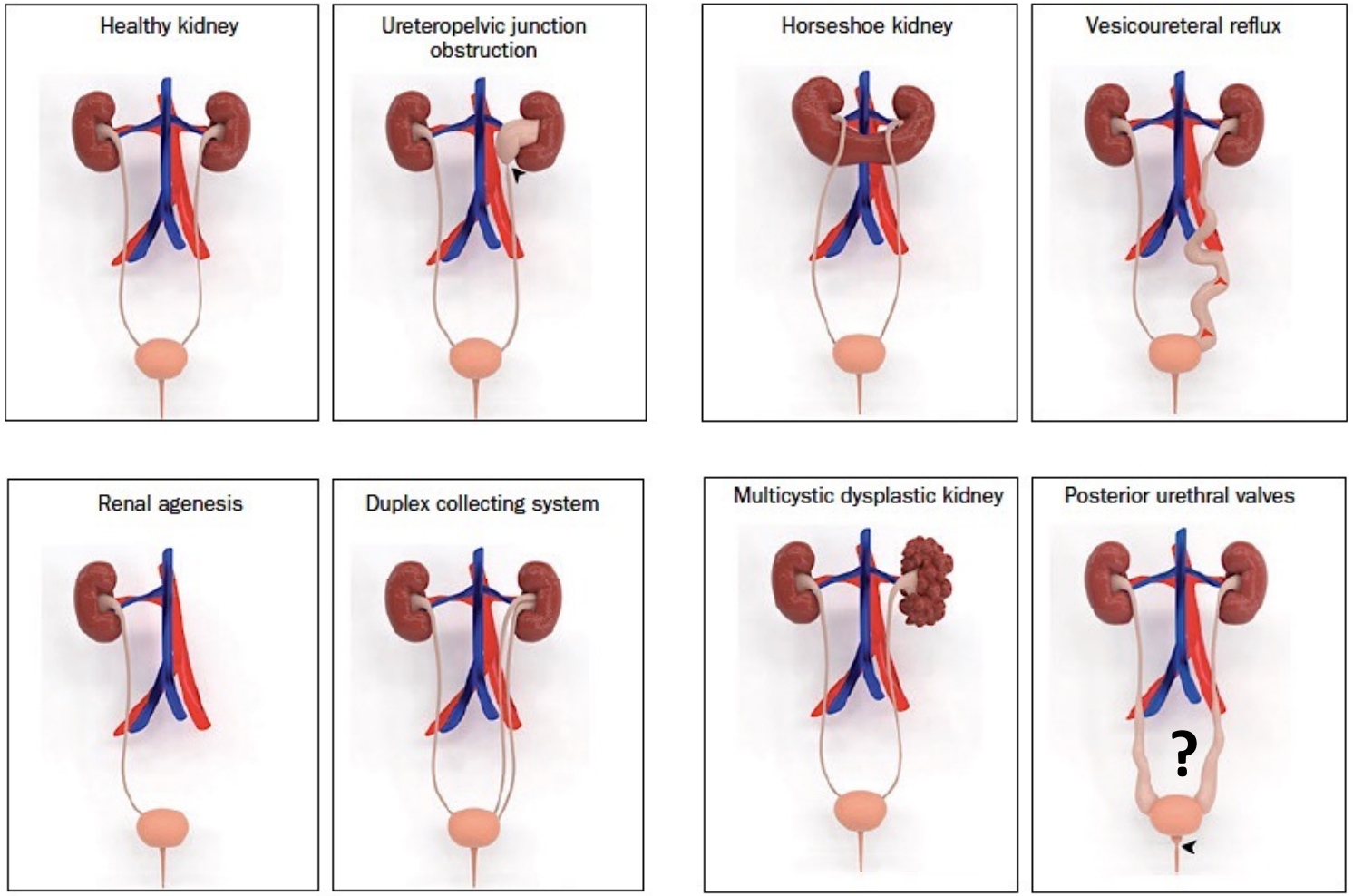
- ~ 20% of prenatally detected anomalies
- 1:100-500 live births
- Most frequent developmental disorder in humans
- Leading cause (30-40%) kidney failure in children; accounts for underestimated proportion of CKD of unknown origin in adults




*Harada et al., Ped. Nephrol 2022*

*Levi, Ultrasound Obstet Gynecol 2003; Sanna- Cherchi et al., KI 2009, Wühl et al., CJASN 2013, Harambat et al., Ped Nephrol 2016*

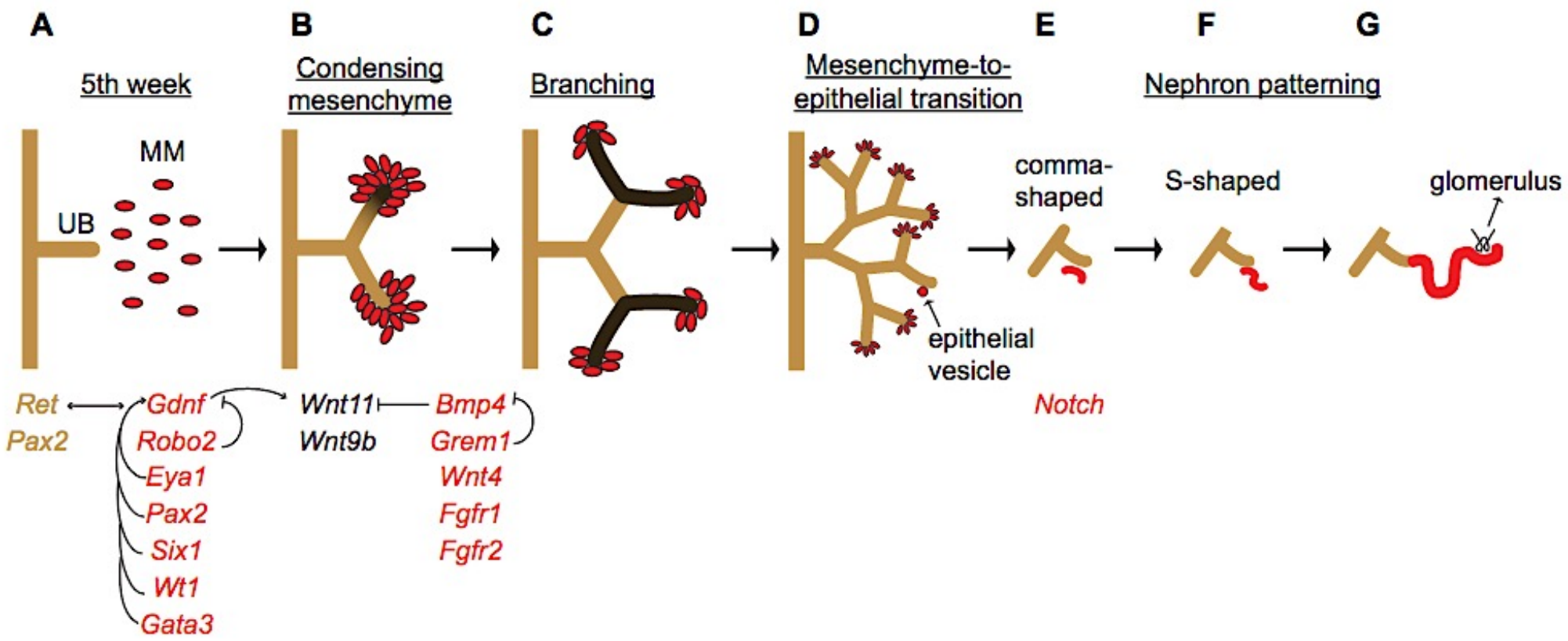
# Congenital anomalies of the kidney and urinary tract (CAKUT): spectrum of structural malformations




Co-occurrence different anomalies within same individual

*Nicolaou et al., Nature Rev Nephrol 2015; Schreuder et al., 2009; Westland et al., NDT 2013*

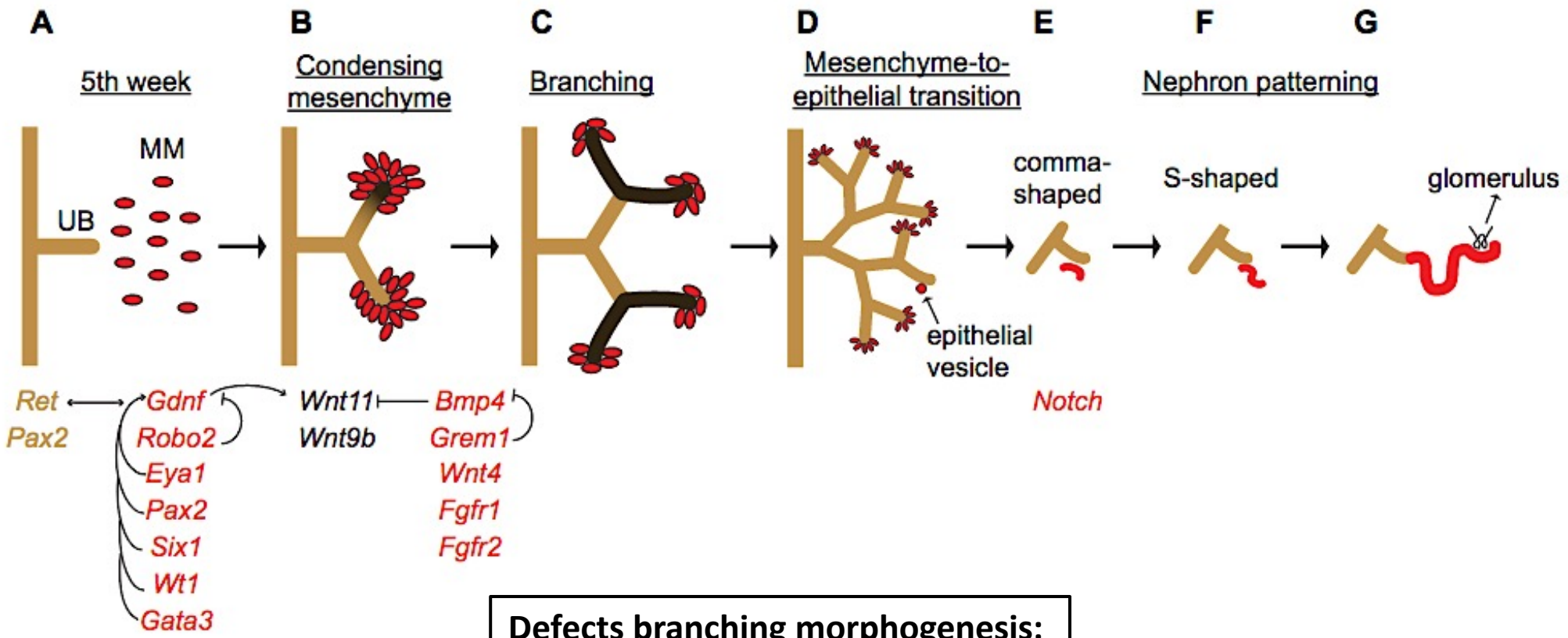
# CAKUT have in common: disturbed embryonic kidney and UT development




*Nicolaou, thesis 2016*

# CAKUT have in common: disturbed embryonic kidney and UT development

**Defects UB outgrowth: kidney agenesis**
**Ectopic UB outgrowth: duplex collecting system**

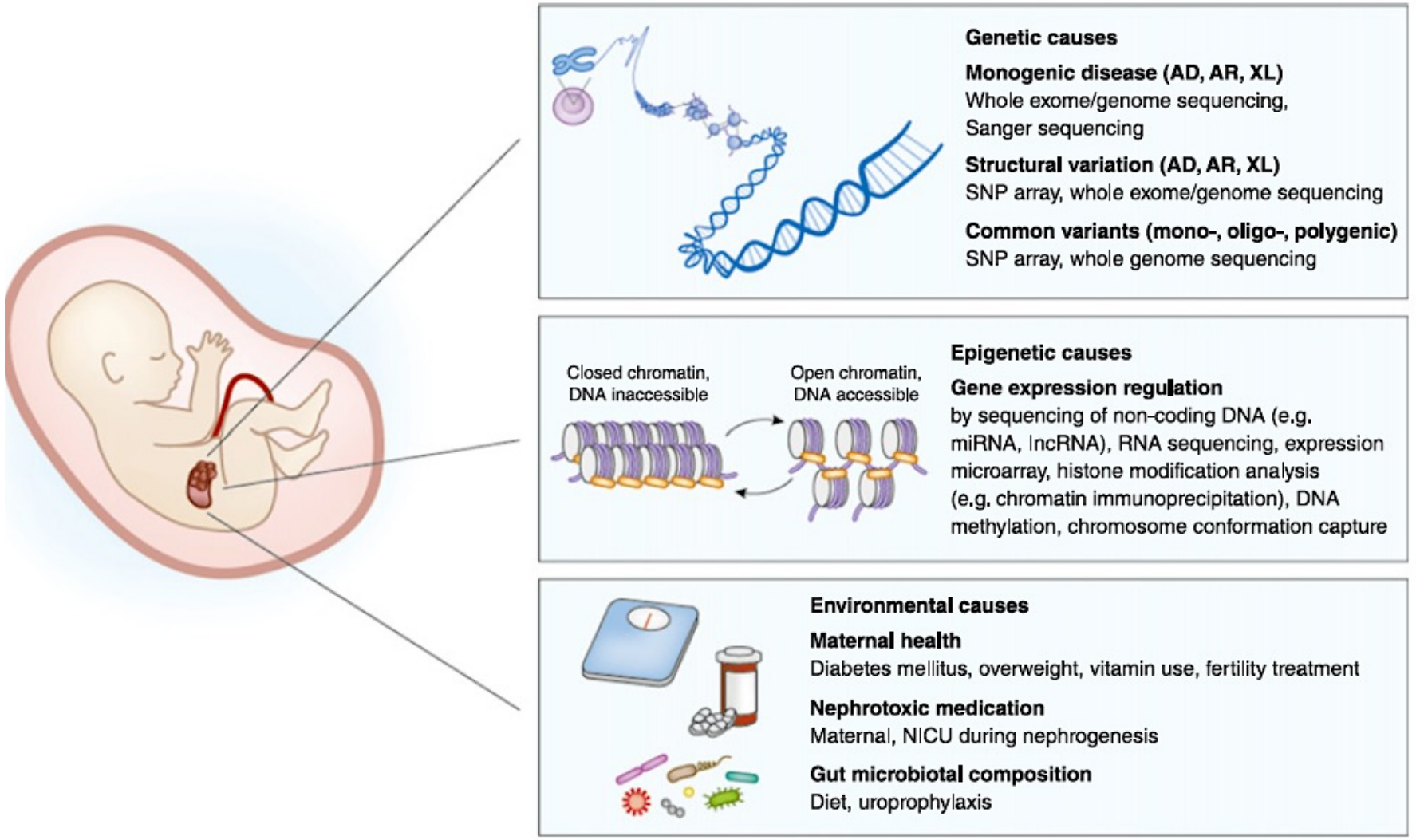



**Defects branching morphogenesis: Kidney hypoplasia**

*Nicolaou, thesis 2016*

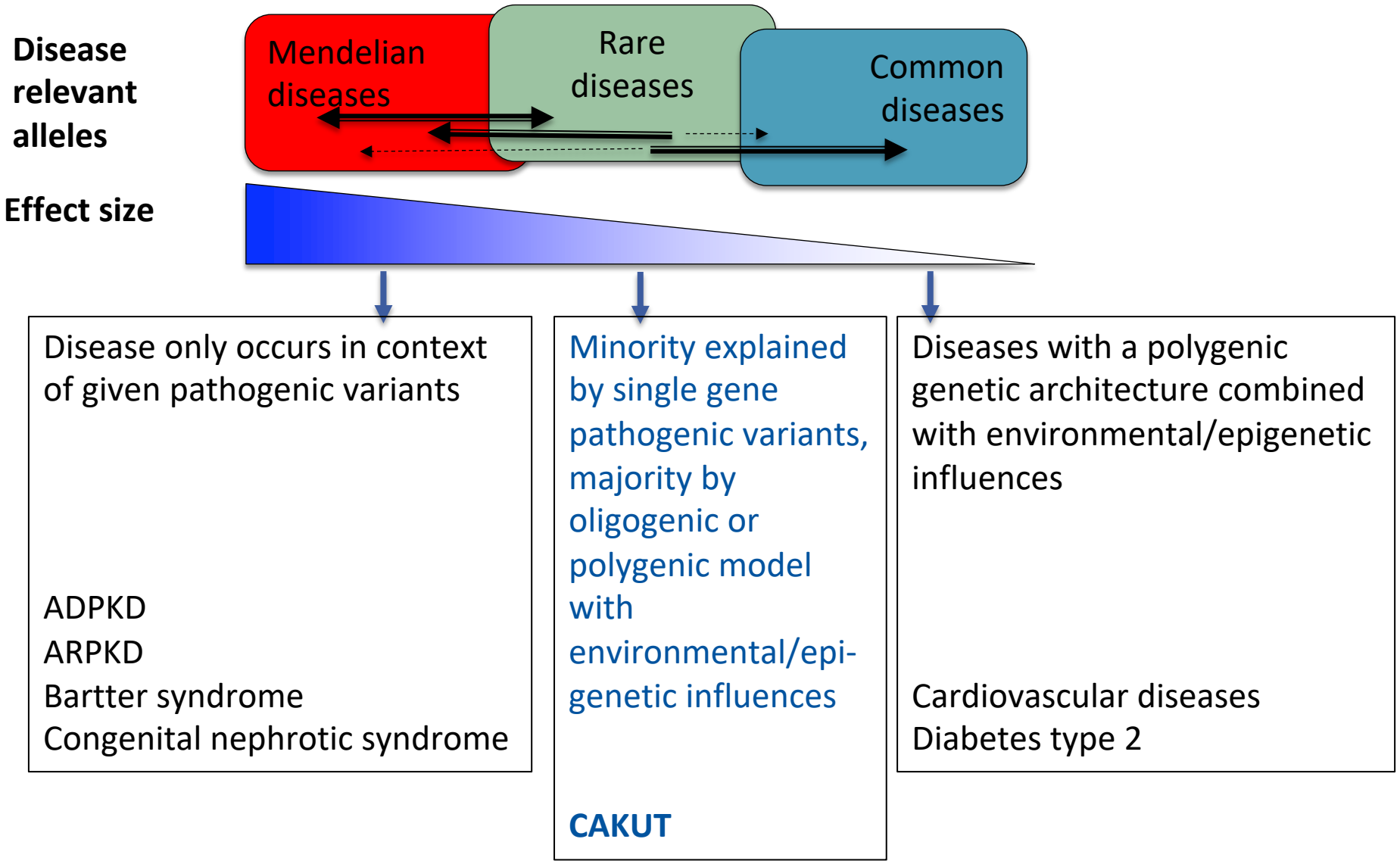
# CAKUT etiology

**Hypothesis:** Genes essential for kidney development are subject to environmental, epigenetic, and genetic modifications, which disrupt their regulation and result in increased susceptibility to CAKUT




*Westland et al., CJASN 2021*

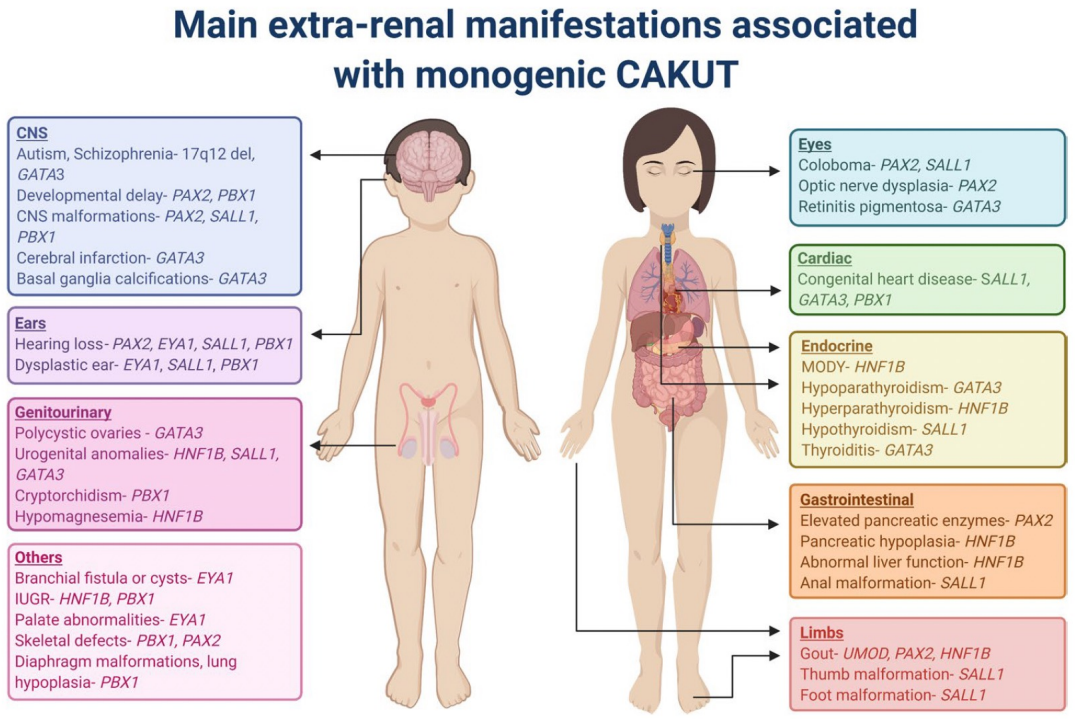
# CAKUT: monogenic towards complex etiology



# Genetic causes: Monogenic CAKUT

- Only minority (10-15%) CAKUT cases explained by **single gene pathogenic variants**
  - Autosomal dominant
  - Autosomal recessive
  - X-linked
  - de-novo (high frequency)

- Sometimes part of **multi-organ syndrome**:
  - Renal coloboma syndrome (*PAX2*)
  - Branchio-oto-renal syndrome (*EYA1, SIX1*)
  - Fraser syndrome (*FRAS1, FREM1, FREM2, GRIP1*)




*Kagan et al., Ped Nephrol 2022*

- ~ 5% of CAKUT cases explained by pathogenic **copy number variants (CNVs):** both in syndromic and non-syndromic cases

# Genetic causes: Monogenic CAKUT

- Genetically very **heterogenous**: >50 genes involved
  - ***PAX2, HNF1B, EYA1*** most frequently involved
  - Full list involved genes and associated phenotypes in *Knoers et al., NDT 2021*
  - Regularly involvement of novel genes detected: bi-allelic pathogenic variants ***ROBO1*** in syndromic CAKUT (eye, heart, central nervous system, gonad, kidney) *Munch et al., KI 2022*
- **Variable expressivity**

**Table 2** Single genes that have been linked to CAKUT*

| Gene symbol | Gene name | Inheritance |
|---|---|---|
| *ACE* | Angiotensin I converting enzyme | AR |
| *AGT* | Angiotensinogen | AR |
| *AGTR1* | Angiotensin II receptor type 1 | AR |
| *ANOS1*** | Anosmin 1 | XLR |
| *BMP4* | Bone morphogenetic protein 4 | AD |
| *BNC2* | Basonuclin 2 | AD |
| *CHD1L* | Chromodomain helicase DNA binding protein 1 like | AD |
| *CHRM3* | Cholinergic receptor muscarinic 3 | AR |
| *CHRNA3* | Cholinergic receptor nicotinic alpha 3 subunit | AR |
| *COL4A1* | Collagen type IV alpha 1 chain | AD |
| *CRKL* | CRK like proto-oncogene, adaptor protein | AD |
| *DSTYK* | Dual serine/threonine and tyrosine protein kinase | AD |
| *EYA1* | EYA transcriptional coactivator and phosphatase 1 | AD |
| *FGF20* | Fibroblast growth factor 20 | AR |
| *FOXC1* | Forkhead box C1 | AD |
| *FRAS1*** | Fraser extracellular matrix complex subunit 1 | AR |
| *FREM1*** | FRAS1 related extracellular matrix 1 | AR |
| *FREM2*** | FRAS1 related extracellular matrix 2 | AR |
| *GATA3* | GATA binding protein 3 | AD |
| *GFRA1* | GDNF family receptor alpha 1 | AR |
| *GREB1L* | GREB1 like retinoic acid receptor coactivator | AD |
| *GREM1*** | Gremlin 1, DAN family BMP antagonist | AR |
| *GRIP1*** | Glutamate receptor interacting protein 1 | AR |
| *HNF1B* | HNF1 homeobox B | AD |
| *HPSE2* | Heparanase 2 (inactive) | AR |
| *ITGA8*** | Integrin subunit alpha 8 | AR |
| *LIFR* | Leukemia inhibitory factor receptor | AD |
| *LRIG2* | Leucine-rich repeats and immunoglobulin-like domains 2 | AR |
| *MYH11* | Myosin heavy chain 11 | AR |
| *NRIP1* | Nuclear receptor interacting protein 1 | AD |
| *PAX2* | Paired box 2 | AD |
| *PBX1* | PBX homeobox 1 | AD |
| *RET* | Ret proto-oncogene | AD |
| *ROBO2* | Roundabout guidance receptor 2 | AD |
| *SALL1* | Spalt-like transcription factor 1 | AD |
| *SIX1* | SIX homeobox 1 | AD |
| *SIX2* | SIX homeobox 2 | AD |
| *SIX5* | SIX homeobox 5 | AD |
| *SLIT2* | Slit guidance ligand 2 | AD |
| *SLIT3* | Slit guidance ligand 3 | AR |
| *SOX11* | SRY-box transcription factor 11 | AD |
| *SOX17* | SRY-box transcription factor 17 | AD |
| *SRGAP1* | SLIT-ROBO Rho GTPase activating protein 1 | AD |
| *TBC1D1* | TBC1 domain family member 1 | AD |
| *TBX18* | T-box transcription factor 18 | AD |
| *TNXB* | Tenascin XB | AD |
| *TRAP1*** | TNF receptor associated protein 1 | AR |
| *UPK3A* | Uroplakin 3A | AD |
| *WNT4* | Wnt family member 4 | AD |
| *WNT9B* | Wnt family member 9B | AR |
| *ZMYM2* ** | Zinc finger MYM-type containing 2 | AD |

***Kagan et al., Ped. Nephrol 2022***

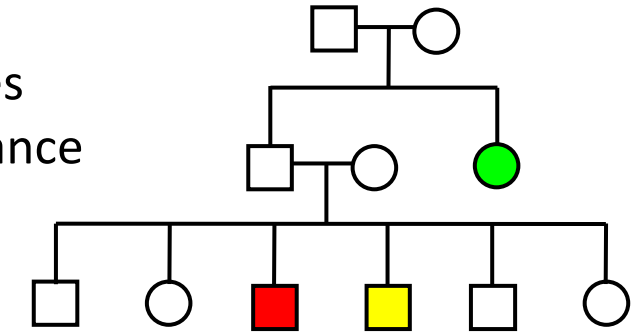
# Variable expressivity

In individuals carrying pathogenic variants in same gene or even same pathogenic variant

- **Intra-individual variability**: co-occurrence of different anomalies within same individual
  - Meta-analyses: ~ 1 in 3 cases with unilateral kidney agenesis or multicystic dysplastic kidneys have VUR or ureteropelvic junction obstruction on contralateral side (*Schreuder et al., 2009; Westland et al., NDT 2013*)
  - Discordant phenotypes in monozygotic twins (*Iatropoulos et al., Ped. Nephrol. 2012; Jin et al., AJKD 2014)*

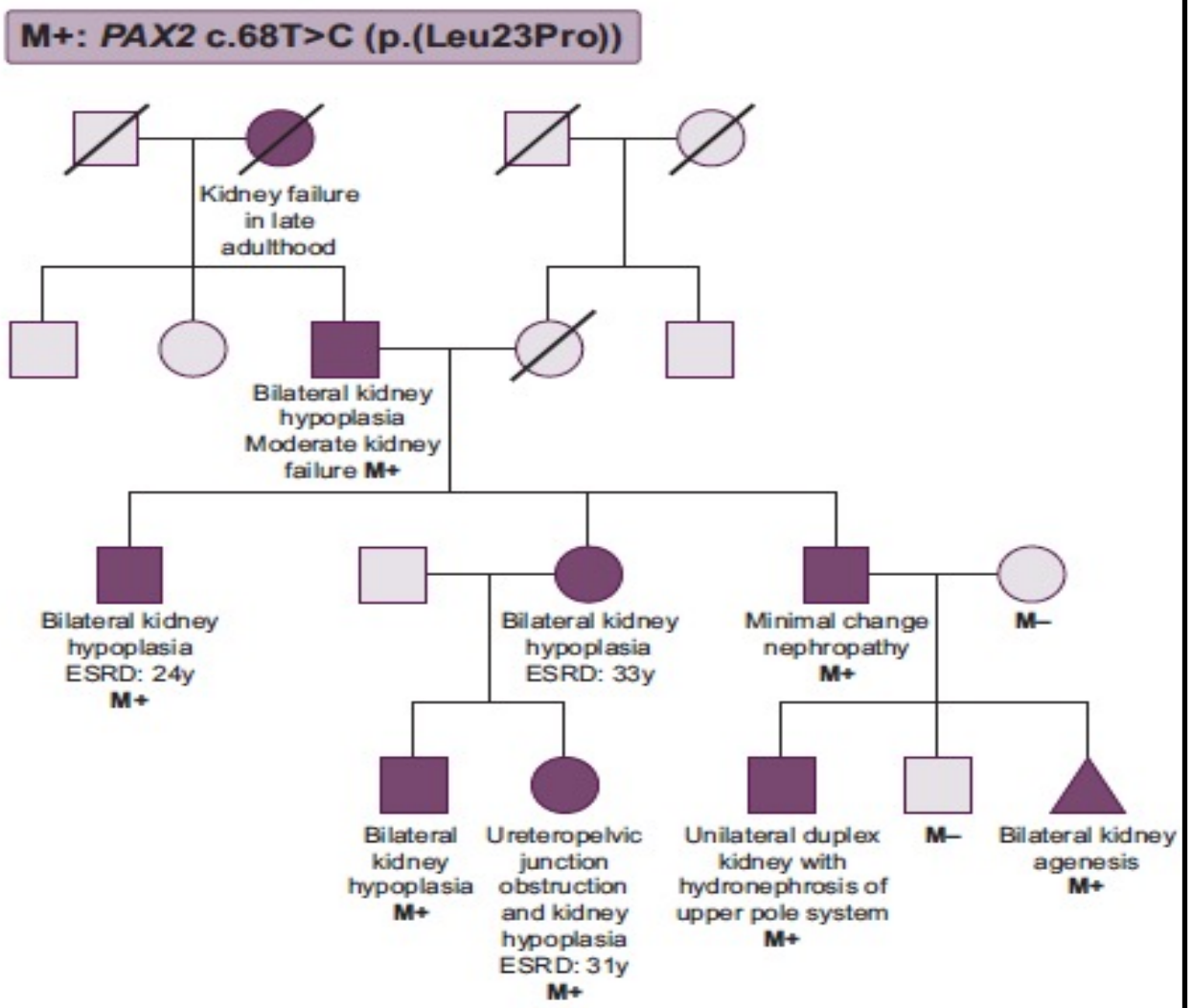
- **Inter-individual variability:** identical pathogenic variation can result in different CAKUT phenotypes and in variable severity, with/without extrarenal features, even within same family

  - Variable phenotypes
  - Incomplete penetrance



** Stoll et al., EJMG 2014; Isert et al., Front Pediatr 2020*

# Example variable expressivity




*Rasmussen et al., Clin Kidney J. 2021*

# Copy number variants (CNVs) in syndromic and isolated CAKUT

**CNVs**: Structural variations in genome of individual in form of gains (duplications) or losses (deletions) of DNA fragments

Genome-wide analysis of CNVs in
**~3000 CAKUT patients** and >21,000 population-based controls

**Full phenotypic CAKUT spectrum**

Increased burden of **large, rare, exonic CNVs** in CAKUT:

- Remained after excluding syndromal cases
- Patients with kidney anomalies mostly exonic deletions
- Patients with VUR or PUV mostly exonic duplications

*Sanna-Cherchi et al., Nat Genet 2019*

# Copy number variants (CNVs) in syndromic and isolated CAKUT

6 loci account for most CAKUT cases caused by CNVs

| Locus | CNV type | Renal phenotype driver gene | Associated syndromes/main extra-renal manifestations |
|---|---|---|---|
| 1q21 | Deletion/duplication | N/A | Neurodevelopmental disorders, cardiac malformations, skeletal malformations, endocrine abnormalities, cataracts, and GI abnormalities |
| 4p16.1-p16.3 | Deletion | N/A | Wolf–Hirschhorn syndrome |
| 16p11.2 | Deletion/duplication | *TBX6* | ASD, obesity, CHD, vertebral anomalies, macrocephaly, and hearing impairment |
| 16p13.11 | Deletion/duplication | N/A | Neurodevelopmental disorders, cardiac malformations, CNS malformations, skeletal malformations, and dysmorphic features |
| 17q12 | Deletion/duplication | *HNF1B* | *HNF1B*-associated syndrome, neurodevelopmental and neuropsychiatric disorders |
| 22q11.2 | Deletion/duplication | *CRKL* | DiGeorge/velocardiofacial syndrome |

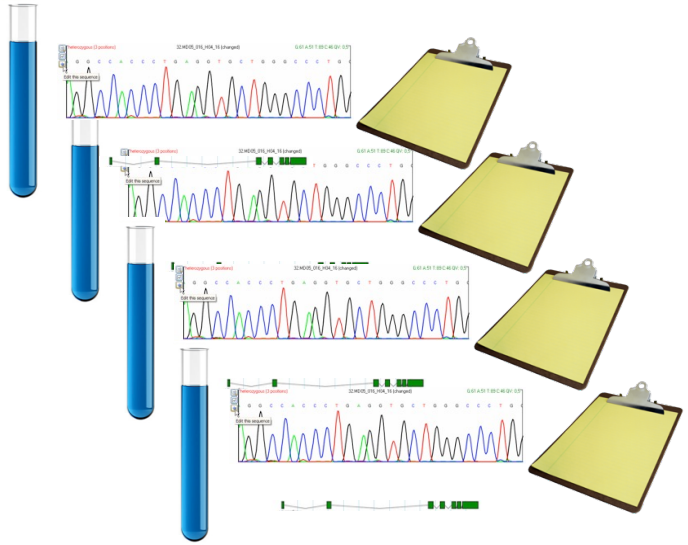
***Adapted from Kagan et al., Ped Nephrol 2022***

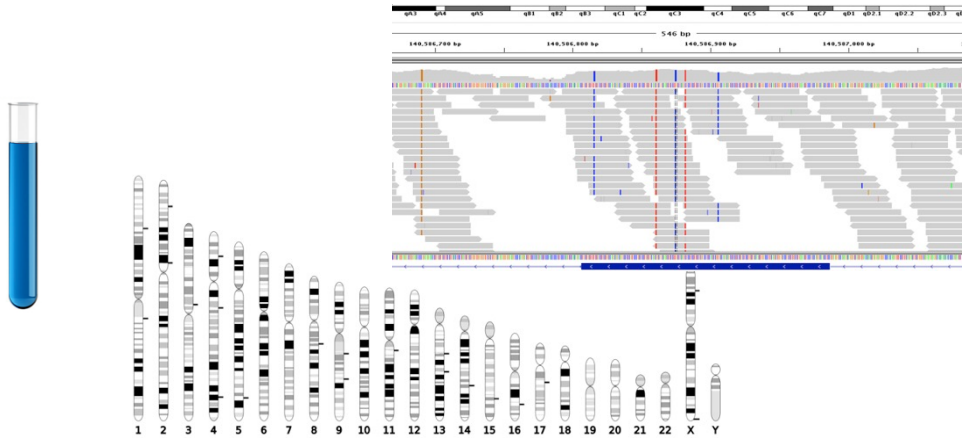
***Sanna-Cherchi et al., Nat Genet 2019***

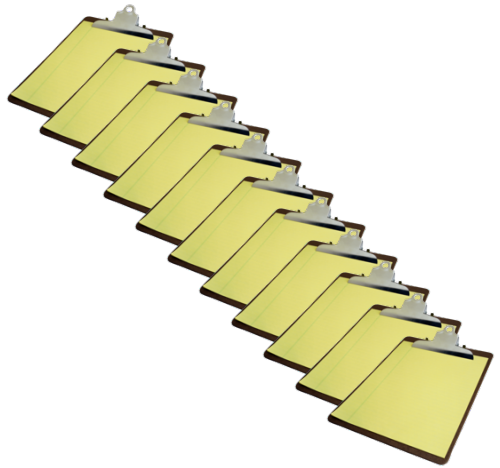
# Massively Parallel Sequencing (MPS) changed paradigm clinical genetic testing

**From one test per gene to one test for all (involved) genes**

- Disease-specific multigene panels
- Whole Exome sequencing (WES: all genes)
- Whole Genome sequencing (WGS: complete DNA)





**Rapid and cost-effective sequencing of large amounts of DNA**

# Current molecular diagnostic tools for CAKUT

Massively Parallel Sequencing (MPS)-based tests for identification single gene mutations

## Targeted phenotype-associated gene panel

Simultaneous sequencing of specific preselected set of genes relevant to CAKUT

**Advantage**: will not yield incidental findings in genes unrelated to primary indication for testing

**Disadvantage**: updating with newly discovered relevant genes requires redesign and validation of assay

## Targeted Exome Sequencing (virtual gene panel)

Exome (21.000 genes) sequenced, only CAKUT-relevant genes analysed and interpreted by using in silico bioinformatics tools

**Advantages:**

1. dynamic gene content update with minimal design and validation
2. possibility to 'open up' exome backbone data and look beyond known genes (with increased chance of incidental findings)

## Genome sequencing

Currently used infrequently in diagnostic testing but expected to replace all other genome diagnostic methods within few years

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☐ **Congenital anomalies of the kidney and urinary tract (CAKUT)** (NEF03v21.1; 100 genes)

*ACE, ACTA2, ACTG2, AGT, AGTR1, ANOS1, BICC1, BMP4, BNC2, CBWD1, CENPF, CEP55, CHD1L, CHD7, CHRM3, CHRNA3, COQ7, DACT1, DHCR7, DOCK4, DSTYK, EVX1, EYA1, FAM58A, FGF20, FGF8, FOXF1, FRAS1, FREM1, FREM2, GATA3, GDNF, GDF6 , GFRA1, GLI3, GREB1L, GREM1, GRIP1, HAAO, HNF1B, HOXA10, HOXA13, HOXD13, HPSE2, HSPA6, ISL1, ITGA8, ITGB4, JAG1, KCTD1, KIF14, KYNU, LHX1, LMOD1, LPP, LRIG2, LRP10, LRP4, MKKS, MYH11, MYLK, NAALADL2, NCAPG2, NOTCH2, NPHP1, NPHP3, NPHP4, NPNT, PAX2, PAX8, PBX1, RBM8A, REN, RET, ROBO1, ROBO2, SALL1, SALL4, SIX1, SIX2, SIX5, SKAP2, SLIT2, SLIT3, SOX17, STRA6, TBC1D1, TBX18, TBX6, TNXB, TP63, TRAP1, TSHZ3, UMOD, UPK3A, WNT4, WNT9B, WT1, ZEB2, ZIC3*

UMC Utrecht, The Netherlands

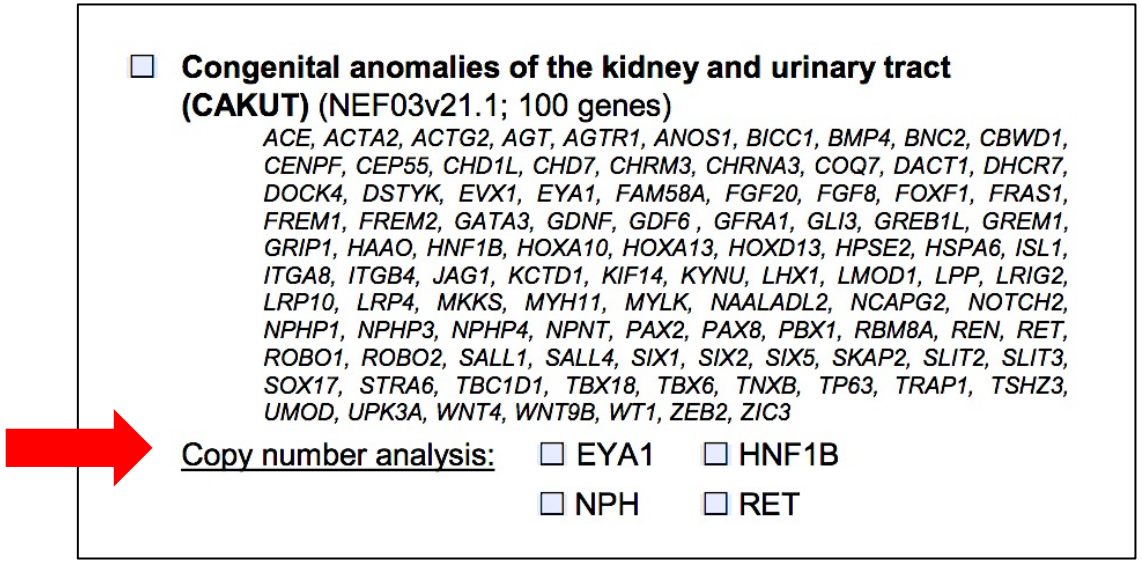
# CNV detection in diagnostics

CNVs Involved in CAKUT not easily picked up by MPS-based gene panels or exome sequencing

- Sophisticated bioinformatic tools necessary to detect those large CNVs from gene panel or ES data
- Not yet routinely used in all diagnostic laboratories

Preferred methodologies for routine diagnostics of large CNVs in many labs:

- Microarray-based technique (CGH- or SNP-arrays)
- Multiplex ligation-dependent probe amplification (MLPA)



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Copy number analysis: ☐ EYA1 ☐ HNF1B ☐ NPH ☐ RET

# Poll question

I order genetic tests for my CAKUT patients:

1. Every week
2. Once or twice every month
3. Few times per year
4. Never
5. I would like to order genetic tests but have no access to an accredited lab

# Implementation of genomic diagnostics in daily practice for CAKUT patients

**Possible reasons for slow implementation**

- Doubts about diagnostic value
- Risk identifying variants of unknown significance (VUS)
- Risk identifying medically actionable incidental findings
- Financial issues and logistic impracticalities
- Nephrologists unaccustomed to using genetic tests as diagnostic and prognostic clinical modalities

# Poll question

Genetic testing for CAKUT in my view is:

1. Useful to confirm the diagnosis
2. Useful in management of the patient
3. Useful for orientation on extra-renal manifestations
4. 1,2, and 3
5. Not useful

# Implementation of genomic diagnostics in daily practice for CAKUT patients

**Opportunities/predicted clinical benefit**

- Genetics-first approach could prevent invasive diagnostic procedures
- Genetic testing can give exact diagnosis important for management (i.e. strict BP control in children with kidney hypo-dysplasia)
- Molecular diagnosis helpful for orientation on extra-renal manifestation and specific follow-up
  - ***HNF1B*** mutation: monitoring diabetes
  - ***PAX2*** mutation: ocular defect (risk retinal detachment)
- Molecular diagnosis useful in light of living related kidney transplantation
- Molecular diagnosis useful for genetic counseling, family planning

# Diagnostic yield targeted sequencing screens

Range from 0 to 20%, heavily depended on (1) cohort characteristics: CAKUT phenotype, inclusion criteria, population of cases and controls, (2) genes included in screens, (3) analysis large CNVs?

**453 unrelated Caucasian patients, P and A**

- Mainly sporadic cases
- Full phenotypic spectrum of CAKUT

208 genes (known and candidate genes)
Large CNV analysis: only for *HNF1B* by MLPA
**Yield 3%**
mainly ***PAX2, HNF1B, SIX5,***

*Nicolaou et al., KI 2015*

**94 unrelated Korean pediatric patients**

- Only severe CAKUT, 62 patients extrarenal features

Targeted exome analysis (60 genes), including analysis large CNVs
**Yield 13.8%,** much higher in syndromic than in isolated CAKUT (34.4% vs. 3.2%)
Mainly ***HNF1B, PAX2, EYA1***

*Ahn et al., J Clin Med 2020*

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**Yield 1,3%**
Mainly ***PAX2, HNF1B, SIX5,***

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Mainly ***HNF1B, PAX2, EYA1***

*Ahn et al., J Clin Med 2020*

**69 Indian pediatric patients**

- History of consanguinity in 22%
- Full phenotypic spectrum CAKUT, majority VUR and PUV

31 known CAKUT genes
No analysis large CNVs
**Yield 0%**
Only Variants of unknown significance (VUS)

*Narikot et al., BMC Nephrology 2022*

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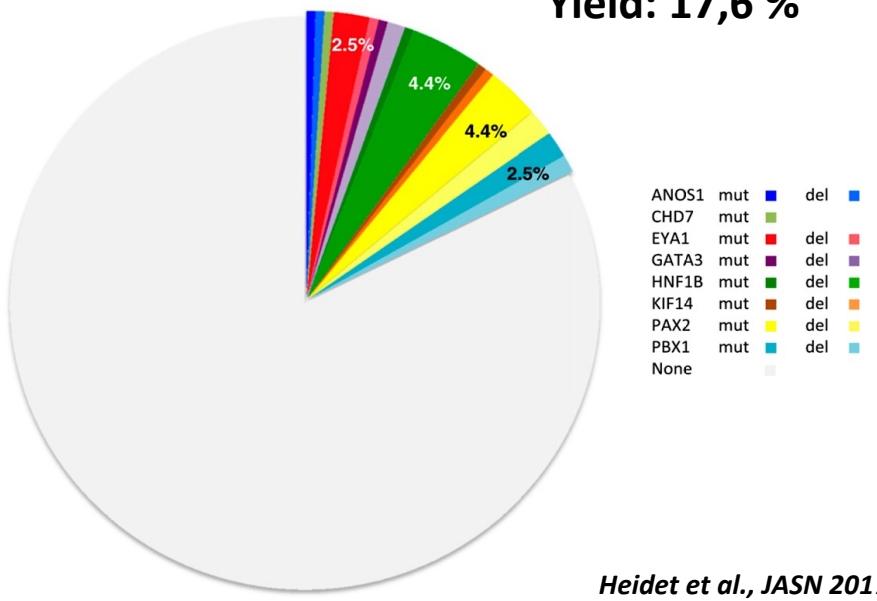
*Ahn et al., J Clin Med 2020*

**204 unrelated patients**

- Only cases with both kidneys affected and/or familial cases and/or syndromic forms, no PUV
- 45% severe fetal cases
- Targeted exome analysis (330 genes), including analysis large CNVs

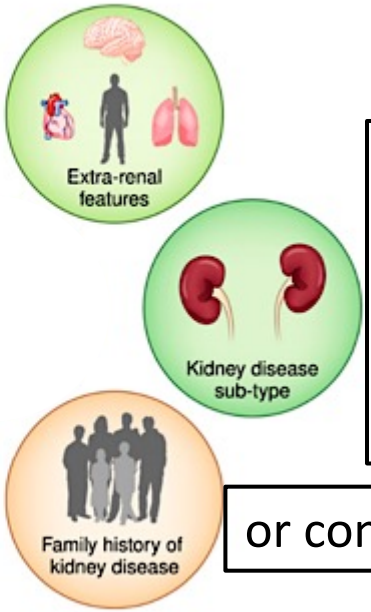
**Yield: 17,6 %**




*Heidet et al., JASN 2017*

# When to perform genetic testing and what to test?

Predictors high diagnostic yield




Higher in severe CAKUT affecting both renal parenchymas, with or without urinary tract defects

PUV/isolated ureteral phenotypes rarely associated with known monogenic cause

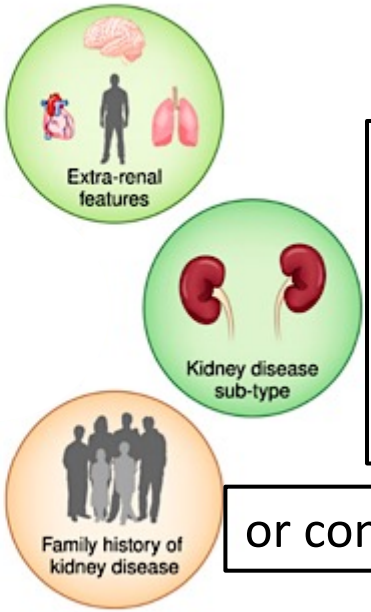
or consanguinity

***Adapted from Cocchi et al., CJASN 2020***

***Westland et al., CJASN 2021, Knoers et al., NDT 2021***

# When to perform genetic testing and what to test?

Predictors high diagnostic yield

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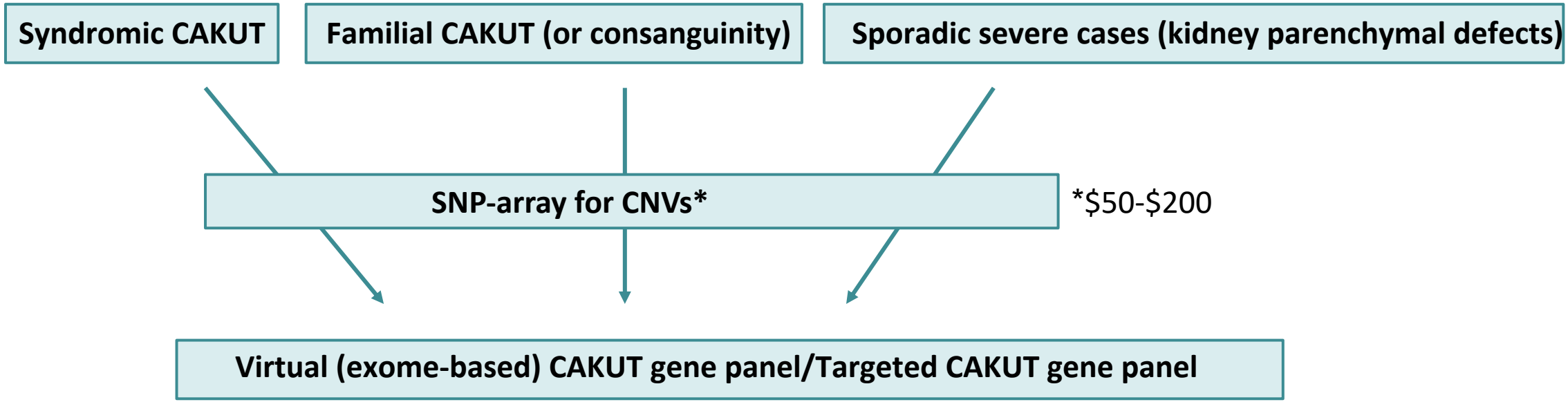
*Adapted from Cocchi et al., CJASN 2020*

**No one-size-fits all approach:**
Consider:

- Potential diagnostic yield/ clinical clues for monogenic CAKUT
- Test's costs
- Payer's situation
- Ethical issues (Incidental findings)

*Westland et al., CJASN 2021, Knoers et al., NDT 2021*

# When to perform genetic testing and what to test?




In case of PUV/isolated ureteral phenotypes: no standard genetic screening

# Pathogenicity identified variants?

All testing and molecular classification should be undertaken in accredited molecular genetics laboratories

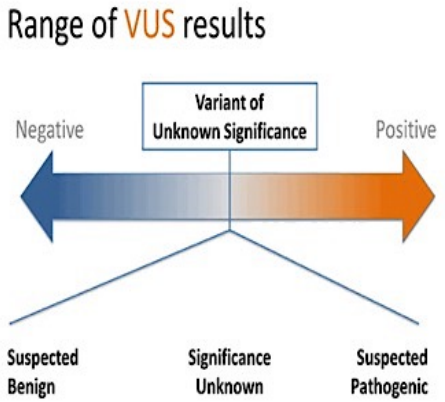
Interpretation of test results preferably in multidisciplinary setting

**American College of Medical Genetics and Genomics (ACMG) variant classification**

| Class | Description |
|---|---|
| 1 | Clearly not pathogenic |
| 2 | Unlikely to be pathogenic |
| 3 | Unknown significance (VUS) |
| 4 | Likely to be pathogenic |
| 5 | Clearly pathogenic |

Most difficult outcome: class 3, **variants of unknown significant (VUS)**

Local hospital policies differ whether or not to disclose VUS to patients




**ACMG recommendations:**

- VUS should not be used in clinical decision-making
- Efforts to resolve classification (i.e. segregation analysis, functional studies, data sharing)

# Pathogenicity identified variants?

Pathogenicity of some variants previously reported as pathogenic mutations questionable with available knowledge of large databases (i.e. gnomAD)

Difficult to definitely rule out causality of some variants, as expressivity and penetrance can vary greatly in monogenic CAKUT with autosomal dominant inheritance

Consult updated clinical variant databases:

- **ClinVar** https://www.ncbi.nlm.nih.gov/clinvar/
- **LOVD** https://www.lovd.nl

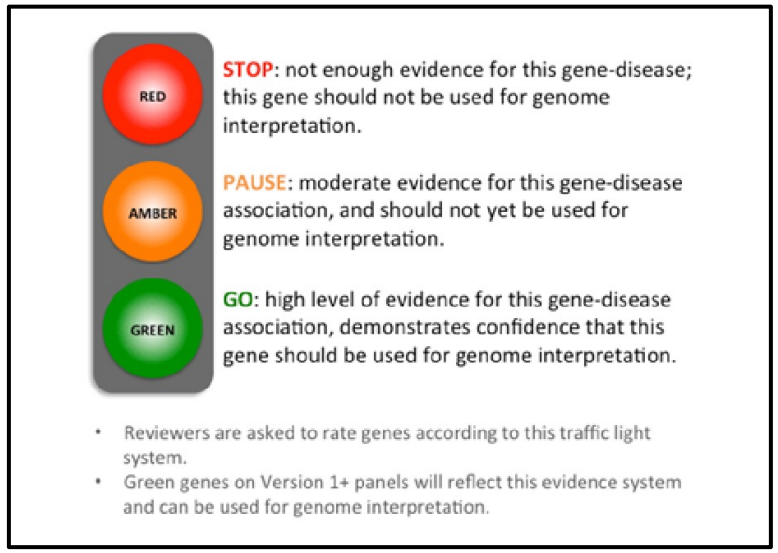
Curation of data:

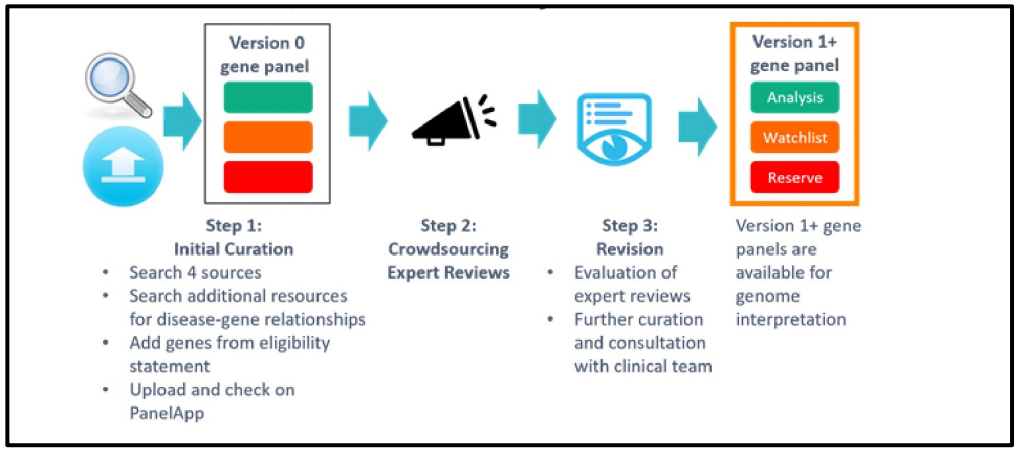
- **ClinGen** (https://clinicalgenome.org): specific clinical domain groups/expert panels helpful in defining clinical relevance identified genes/variants for various forms of genetic kidney diseases
  No specific WG for CAKUT yet
- **Genomics England PanelApp/PanelApp Australia:** Crowdsourcing tools to allow gene panels to be shared, downloaded, viewed, and evaluated by Scientific Community. Both have panels for CAKUT

*Nicolaou et al., KI 2015, Heidet et al., JASN 2017; Knoers et al., NDT 2021*

# Genomics England PanelApp

## For CAKUT: https://panelapp.genomicsengland.co.uk/panels/234/




| Date | Panel | Item | Activity |
|---|---|---|---|
| Filter activities | | | 375 actions |
| 11 Jun 2022 | CAKUT v1.168 | TMEM260 | Eleanor Williams Classified gene: TMEM260 as Green List (high evidence) |
| 11 Jun 2022 | CAKUT v1.168 | TMEM260 | Eleanor Williams Gene: tmem260 has been classified as Green List (High Evidence). |
| 11 Jun 2022 | CAKUT v1.167 | TMEM260 | Eleanor Williams Tag Q4_21_rating was removed from gene: TMEM260. |
| 11 Jun 2022 | CAKUT v1.167 | TMEM260 | Eleanor Williams commented on gene: TMEM260 |
| 10 Jun 2022 | CAKUT v1.167 | ROBO1 | Laura Claus gene: ROBO1 was added<br>gene: ROBO1 was added to CAKUT. Sources: Literature<br>Mode of inheritance for gene: ROBO1 was set to BIALLELIC, autosomal or pseudoautosomal<br>Publications for gene: ROBO1 were set to 35227688<br>Phenotypes for gene: ROBO1 were set to unilateral kidney agenesis; bilateral kidney agenesis; vesicoureteral junction obstruction; vesicoureteral reflux; posterior urethral valve; genital malformation; increased kidney echogenicity<br>Review for gene: ROBO1 was set to GREEN<br>Added comment: Sources: Literature |
| 08 May 2022 | CAKUT v1.167 | TRAP1 | Eleanor Williams Tag gene-checked tag was added to gene: TRAP1. |
| 07 May 2022 | CAKUT v1.167 | GREB1L | Eleanor Williams Tag gene-checked tag was added to gene: GREB1L. |
| 16 Mar 2022 | CAKUT v1.167 | ISCA-37432-Loss | Arina Puzriakova commented on Region: ISCA-37432-Loss |
| 16 Mar 2022 | CAKUT v1.167 | ISCA-37432-Loss | Arina Puzriakova GRCh38 position for ISCA-37432-Loss was changed from 36458167-37854617 to 36458167-37854616.<br>Required Overlap Percentage for ISCA-37432-Loss was changed from 80 to 60. |
| 01 Mar 2022 | CAKUT v1.166 | LIFR | Eleanor Williams Added comment: Comment on mode of inheritance: Mode of inheritance of MONOALLELIC is correct for the CAKUT phenotype. |
| 01 Mar 2022 | CAKUT v1.166 | LIFR | Eleanor Williams Mode of inheritance for gene: LIFR was changed from MONOALLELIC, autosomal or pseudoautosomal, NOT imprinted to MONOALLELIC, autosomal or pseudoautosomal, NOT imprinted |
| 28 Oct 2021 | CAKUT v1.165 | TMEM260 | Sarah Leigh edited their review of gene: TMEM260: Changed rating: AMBER |
| 28 Oct 2021 | CAKUT v1.165 | TMEM260 | Sarah Leigh changed review comment from: Associated with relevant phenotype in OMIM and as probable Gen2Phen gene. At least eight variants have been reported in at least six unrelated cases. The variants included: one multi-exon deletion resulting in a frameshift, two smaller frameshifting deletions, two nonsense, one splicing change and two missense changes, one of which was shown by cDNA sequencing to result in skipping of exon 3 (PMID 34612517).; to: Associated with relevant phenotype |

# Take Home Messages

- CAKUT assumed to have monogenic towards complex etiology, involving genetic factors, environmental and epigenetic factors
- Monogenic cause, including CNVs, in ~ 15% of patients
- Monogenic CAKUT is characterized by phenotypic variability and reduced penetrance
- CAKUT patients can benefit from genetic diagnostic testing, allowing personalized management and follow-up, appropriate genetic counseling
- Predictors of high diagnostic yield of genetic testing: syndromic CAKUT, familial CAKUT (consanguinity), and sporadic severe cases (kidney parenchymal defects)
- In those cases: genetic testing using MPS-based (virtual) gene panels is advised
  It may be cost effective to first start with SNP-microarray testing to detect pathogenic CNVs
- Standard genetic screening is currently not advised in cases of PUV/isolated ureteral phenotypes
- Be critical in judging pathogenicity of identified variants. This is best done in a multidisciplinary setting

# Acknowledgements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DUTCH KIDNEY FOUNDATION
Life comes first.

ZonMw

AGORA