Genetic Sequencing in ADPKD

National Health Research Instituties

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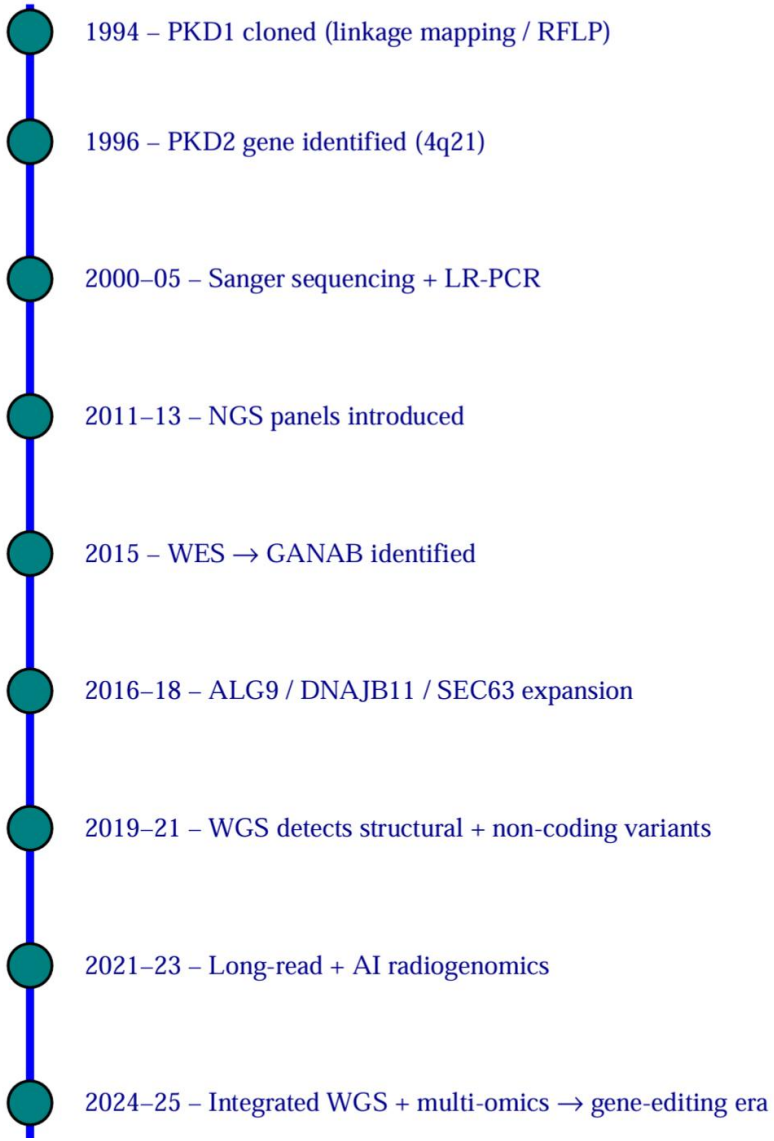
Time Gene Discovery in ADPKD



ADPKD Genetics

Gene	% screened families	# of families *	Disease designation	Kidney phenotype	Extrarenal phenotype	Comments
Unknown/not screened			ADPKD	Bilateral PKD, kidney enlargement, age-related CKD, may result in KF	Liver cysts, including severe PLD, increased risk of ICA	A wide phenotypic range in terms of TKV and KF risk and timing
PKD1	~48%	>3250	Truncating pathogenic variant: ADPKD-*PKD1*	Bilateral PKD, early kidney enlargement, CKD G3, ~ 40 y, KF in 50s	Liver cysts, including severe PLD, increased risk of ICA	Includes some disease variability including a more benign course, sometimes associated with mosaicism
	~19%	>1750	Nontruncating pathogenic variant: ADPKD-*PKD1*	Bilateral PKD, kidney enlargement, age-related CKD, may result in KF	Liver cysts, including severe PLD, increased risk of ICA	Phenotype ranges from severe as *PKD1* truncating to mild PKD in old age, partly depending on the degree of residual protein function
PKD2	~15%	>1000	ADPKD-*PKD2*	Bilateral PKD, milder and later kidney enlargement, CKD G3, ~55 y, KF in 70s	Liver cysts, including severe PLD, increased risk of ICA	Includes some disease variability including a more severe or more benign course
ALG5	<0.5%	<10	ADPKD-*ALG5*	Mild to moderate cyst development with limited kidney enlargement and fibrosis CKD and some KF in older subjects	A few liver cysts in a minority of people	
ALG6	<0.5%	<10	ADPKD-*ALG6*	Generally mild with or without preserved kidney function	Liver cysts including severe PLD	Can present as ADPLD.[‡]
ALG8	~1%	<40[†]	ADPKD-*ALG8*	Generally mild cystic kidney disease with preserved function into old age	Liver cysts, including severe PLD. ICA risk unclear	Can present as ADPLD. *ALG8* is likely a low penetrant genotype.[5, ‖]
ALG9	<0.5%	<20	ADPKD-*ALG9*	Mild to moderate cystic disease with significant CKD in older people	Liver cysts are common	
DNAJB11	<0.5%	<30	ADPKD-*DNAJB11*	Bilateral small cysts, limited or no kidney enlargement, progressive fibrosis, limited CKD G3a <55 y, but KF in 70s	Liver cysts, usually mild, ICA and vascular risk is possible	ADPKD-*DNAJB11* has similarities to ADTKD, because of the small, fibrotic kidneys, but visible cysts are usually present
GANAB	<0.5%	<20	ADPKD-*GANAB*	Mild cyst development, limited CKD, no KF	Liver cysts, including severe PLD. ICA risk unclear	Can present as ADPLD
IFT140	1%–2%	<50	ADPKD-*IFT140*	Few, large bilateral cysts resulting in kidney enlargement, with kidney function usually preserved into old age	Liver cysts only rarely seen, with risk of ICA unclear	
NEK8[¶]	<0.5%	<20	ADPKD-*NEK8*	Bilateral PKD, kidney enlargement, KF in childhood, occasionally later in cases of specific alleles and mosaicism	Liver cysts rare	De novo occurrence was reported in 75% of the published cases.[¶]
PKHD1	~1%	<50[†]	ADPKD-*PKHD1*	Generally, very mild cystic kidney development with preserved function into old age	Liver cysts are common, and can be see without kidney cysts	Biallelic pathogenic variants are associated with ARPKD. Can present as ADPLD. Monoallelic PKHD1 is likely a low penetrant genotype.[5]
Genetically unresolved by testing	~5%		ADPKD	Typically, mild cyst development with limited CKD and KF	Liver cysts	Most unresolved cases have relatively mild disease

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ADPKD Genetics

Table 5 | Other disorders that present with kidney cysts

Gene	Disease	Inheritance	Overlapping with ADPKD	Distinguishing from ADPKD	Comments
Developmental disorders					
HNF1B	*HNF1B*-related kidney disease	AD	Cystic kidney disease	Congenital kidney and urinary tract anomalies, early-onset diabetes, pancreatic disease, elevated liver enzyme levels, and hypomagnesemia	Sometimes presents as ADPKD spectrum alone
JAG1, NOTCH2	Alagille syndrome	AD	Kidney cysts	Hepatic bile duct paucity; cholestasis; cardiac, skeletal, facial, and eye abnormalities; and dysplastic kidneys	A major feature can be infantile, small cystic kidneys and abnormal kidney function.
Collagen disorders					
COL4A1	Hereditary angiopathy with nephropathy, aneurysms, and muscle cramps (HANAC)	AD	Kidney cysts	Hematuria, retinal arterial tortuosities, muscular contractures, and brain small-vessel disease	Presentation with mild cystic disease and few other phenotypes has been described.[93,99,100]
COL4A3, COL4A4, COL4A5	COL4A-related diseases	AD and X-linked	Kidney cysts	Thinning of the glomerular basement membrane, microhematuria	Occasionally, kidney cysts are the major presentation.[93,94]
Urinary stone diseases (USD)					
CYP24A1, SLC34A3, HOGA1	A variety of USDs	AR (AD)	Kidney cysts	Predominant phenotype of kidney stones, nephrocalcinosis, and/or other mineralization	Usually limited cyst involvement[101–103]; may apply to other USDs
Autosomal dominant tubulointerstitial kidney disease (ADTKD)					
MUC1, REN, SEC61A1, UMOD	ADTKD	AD	Kidney cysts	Reduced kidney function, normal- to small-sized kidneys due to fibrotic kidneys; a few kidney cysts may be detected; no liver cysts	Hyperuricemia (low FE_{urate}) and gout are prominent in ADTKD-*UMOD* and anemia and gout in ADTKD-*REN*.
Recessive PKD					
PKHD1, DZIP1L, CYS1, PKD1	Autosomal recessive polycystic kidney disease (ARPKD)	AR	Bilateral kidney cystic disease	Typical *in utero*/infantile presentation of extreme kidney enlargement, but later childhood/adult milder PKD possible; congenital hepatic fibrosis (CHF) rather than PLD	Later-onset kidney disease can mimic ADPKD, but kidneys usually do not increase in length over time and CHF is usually present. Biallelic *PKD1* changes can cause VEO to adult-onset disease.
PMM2	Hyperinsulinemic hypoglycemia and polycystic kidney disease (HIPKD)	AR	Kidney cysts	The kidney disease is ARPKD-like, but hyperinsulinemic hypoglycemia is also found; liver cysts are only rarely seen	Biallelic disease where at least one allele is the promoter variant (c.-167G>T); typical biallelic *PMM2* disease causes the congenital disorder of glycosylation type 1a (CDG1A)
Tumorous disorders					
FLCN	Birt-Hogg-Dubé syndrome	AD	Kidney cysts	Hair follicle hamartomas, kidney tumors, spontaneous pneumothorax, lung cysts	*FLCN* pathogenic variant described in person with "ADPKD" and lung cysts[88]
TSC1 TSC2	Tuberous sclerosis complex (TSC)	AD	Kidney cysts	Multisystem disorder with hamartomas in brain, skin, heart, kidneys (angiomyolipomas), and/or lung, plus CNS manifestations: epilepsy, learning difficulties, behavioral problems	Kidney cysts can be a major presentation with limited additional phenotypes.
PKD1/TSC2	*PKD1/TSC2*-Contiguous gene syndrome (CGS)	AD	Severe, infantile PKD	Hamartoma and CNS manifestations of TSC	Early-onset and severe PKD leading to early KF; mosaicism is common, which may be associated with less severe PKD[90,91]
VHL	Von-Hippel-Lindau syndrome	AD	Kidney and pancreatic cysts	Familial cancer syndrome with malignant and benign neoplasms in retina, cerebellum, spinal hemangioblastoma, RCC, pheochromocytoma, and pancreatic tumors	RCC develops from the kidney cysts.
FH	Hereditary leiomyomatosis and renal cell cancer (HLRCC)	AD	Small kidney cysts	Papillary RCC, leiomyomata of the uterus, and cutaneous piloleiomyoma	Kidney cysts that can metastasize at a small size
Syndromic ciliopathies					
OFD1	Oral-facial-digital syndrome 1	X-linked	Kidney cysts in female patients	Malformations of the face, oral cavity, including cleft lip/palate, and digits, and PKD with abnormal kidney function; usually, lethal in male patients	The PKD can mimic ADPKD, and the facial and digital phenotypes can be minimal.
NPHP1 and other NPHP genes	Nephronophthisis (NPHP)	AR	Cortico-medullary cysts	Childhood presentation with echogenicity, loss of corticomedullary differentiation, small atrophic kidneys, and CKD	NPHP1, and other forms of NPHP, can first present in adulthood.
Many genes	Syndromic ciliopathies such as Joubert, Bardet Biedl, Meckel syndrome, and short rib thoracic dystrophy	AR	Kidney cysts	Often infantile or childhood disorders; a wide range of extrarenal developmental phenotypes are seen depending on the disorder, including CNS, digital, ocular, skeletal, laterality, and hepatic disease	More than 100 genes associated with syndromic ciliopathies, including kidney cysts, have been described.
Acquired disorders					
None	Simple cysts	Sporadic	Kidney cysts	Small number, below the cyst number/age range to define ADPKD	The number of simple cysts increases with age.
None	Acquired cystic disease (ACD)	Acquired	Kidney cysts	Usually only seen with severe CKD or after KF; kidneys are not enlarged	ACD is a risk factor for kidney cancer.

ACD, acquired cystic disease; AD, autosomal dominant; AR, autosomal recessive; CHF, congenital hepatic fibrosis; CKD, chronic kidney disease; CNS, central nervous system; KF, kidney failure; PKD, polycystic kidney disease; PLD, polycystic liver disease; RCC, renal cell carcinoma; TSC, tuberous sclerosis complex; USD, urinary stone diseases; VEO, very early onset.

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Sequencing Methods

- Genotyping (family-based)
- Sanger sequencing (SC)
- Multiplex Ligation-dependent Probe Amplification (MLPA)
- Long-range PCR-SC (for PKD1)
- Gene panel (multiplex PCR or probe-hybridization)
- Exome sequencing (short-read sequencing, SRS)
- Genome sequencing (SRS)
- Long-range PCR-long-read sequencing (LRS)
- Genome sequencing (LRS)

Genetics of ADPKD in Asia

ADPKD Genetics-China

Country	Study / Year	Cohort Size	Methods	Main Genes Identified	Key Findings
China	Jin et al., 2016 (Sci Rep)	90 families	LR-PCR + NGS	**PKD1, PKD2**	80–90% detection rate; many novel variants; truncating PKD1 associated with earlier ESRD.
	Liu et al., 2015 (Sci Rep)	49 families	Sanger + MLPA	PKD1 (majority), PKD2	High heterogeneity; multiple novel frameshift and nonsense variants.
	Xu et al., 2018 (Kidney Blood Press Res)	38 families	NGS	PKD1, PKD2	Expands mutation spectrum; genotype–phenotype correlation consistent with classic PKD1 > PKD2 severity.
	Wang et al., 2019 (MGGM)	32 patients	WES	PKD1/PKD2 + rare genes (GANAB, PKHD1)	Shows variable phenotypes; highlights contribution of atypical cystic genes.
	Xu et al., 2021 (Clin Genet)	60 PKD2 carriers	NGS	**PKD2**	PKD2 variants mainly missense/truncating; milder renal decline vs PKD1 cohorts.

ADPKD Genetics-Japan

Study / Year	Cohort Size	Methods	Genes Identified	Key Findings
Inoue et al., 2002 (*Human Mutation*)	100 patients	Sanger sequencing	**PKD1**	First comprehensive Japanese PKD1 mutation map; demonstrated extensive allelic heterogeneity.
Kinoshita et al., 2016 (*PLoS One*)	129 patients	High-sensitivity NGS	**PKD1** (~80%), **PKD2** (~15%)	High diagnostic sensitivity in duplicated PKD1 regions; numerous private variants identified.
Mizuno et al., 2024 (*Kidney International Reports*)	ADPKD + severe PLD cohort	Targeted NGS	**PKD1, PKD2, GANAB, ALG8**	Severe polycystic liver disease enriched for **PKD2** and **GANAB** variants; expanded Japanese cystic disease gene spectrum.

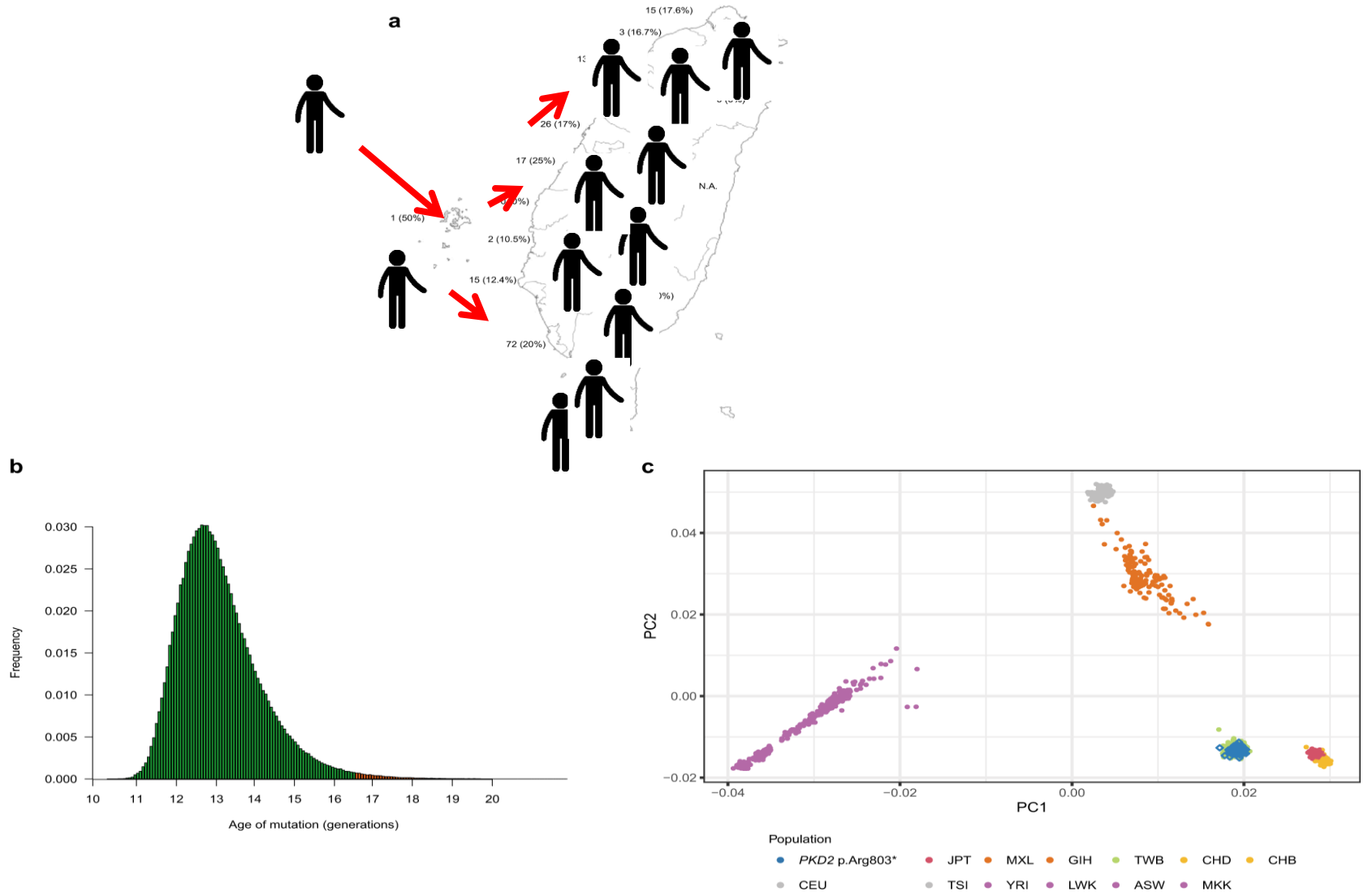
ADPKD Genetics-Korea

Country	Study / year (journal)	Cohort size & design	Genetic methods	Detection rate & PKD1 vs PKD2	Key genetic / clinical messages
South Korea	**Choi et al., 2014 (BMC Med Genet)**	20 unrelated adults with definite ADPKD (single-center)	LR-PCR to isolate PKD1, exon-specific PCR + Sanger; MLPA for large rearrangements	Pathogenic variants in **18/20 (90%)**; **PKD1 in 15**, **PKD2 in 3** (≈75% vs 15% of all probands; remaining 10% unsolved)	First full PKD1/PKD2 sequencing in Korean ADPKD; high proportion of PKD1 mutations in duplicated region; many novel variants, spectrum similar to Western cohorts.
	Kim et al., 2019 (Sci Rep; HOPE-PKD)	749 patients from **524 families** in a prospective ADPKD cohort	Targeted exome sequencing of PKD1/PKD2 + Sanger of PKD1 exon 1 + MLPA	Pathogenic variants in **423/524 families (80.7%)**; **PKD1 in 84% of families**, **PKD2 in 16%**; ~70.7% novel	One of the largest Asian ADPKD genetic datasets. Demonstrates strong genotype–phenotype gradient: PKD1-truncating → earlier diagnosis, larger TKV, earlier ESRD; PKD2 → milder course and ~5–8 years delay in ESRD vs PKD1. Establishes Korean mutation spectrum.
	Cho et al., 2023 (Kidney Res Clin Pract)	**725 adults** with ≥3 renal cysts from 8 centers; **560 typical ADPKD**, **165 atypical PKD**	Ciliopathy-focused targeted gene panel	Overall pathogenic variant yield **64.3%**; **62.3%** in typical ADPKD vs **41.8%** in atypical PKD	Nationwide multicenter genetic cohort. Confirms that most typical ADPKD cases in Korea have detectable mutations in known cystic genes (predominantly PKD1/PKD2), while atypical imaging patterns have lower yield and more heterogeneous genotypes. Provides integrated genetic + imaging risk stratification data.

ADPKD Genetics-Taiwan

Country	Study / Year	Cohort Size	Methods	Genes Identified	Key Findings
Taiwan	Chang et al., 2005, *Ren Fail*	14 families	Sanger sequencing	PKD2	Early Taiwanese PKD2 variant dataset; confirmed milder disease course associated with PKD2.
	Chang et al., 2013, *J Hum Genet*	64 patients	Sanger sequencing	PKD1, PKD2	Multiple novel variants; genotype–phenotype pattern consistent with severity gradient (PKD1 truncating > non-truncating > PKD2).
	Yu et al., 2022, *npj Genomic Medicine*	920 families	LR-PCR + targeted NGS	PKD1, **PKD2 p.Arg803***, PKHD1, GANAB	Identified major PKD2 founder mutation (17.8% of families); established full Taiwanese mutation landscape.

PKD2 p.Arg803* is unique in Taiwan
Founder migrated to Taiwan ~300 years ago



npj Genomic Medicine 2022

Non-Coding Variants

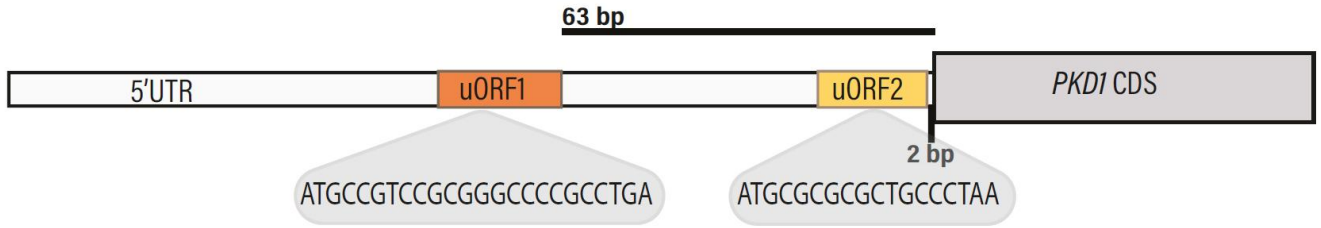


Fig. 1 ***PKD1* 5'UTR and putative uORFs.** Schematic showing the *PKD1* 5′UTR and putative uORFs, uORF1 (orange) and uORF2 (yellow). The uORF sequence is shown in the grey triangles. Black lines show distance at which each uORF terminates from the main ORF (63 bp for uORF1, and 2 bp for uORF2). CDS coding sequence.

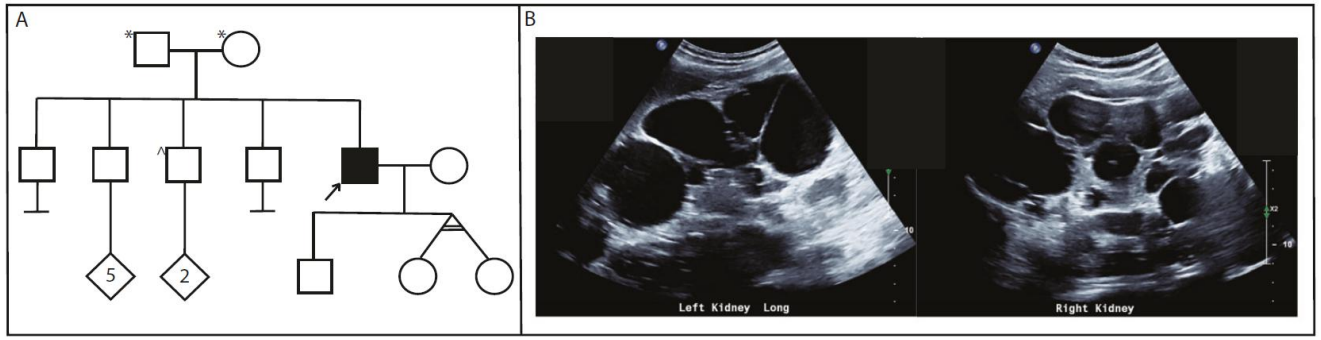


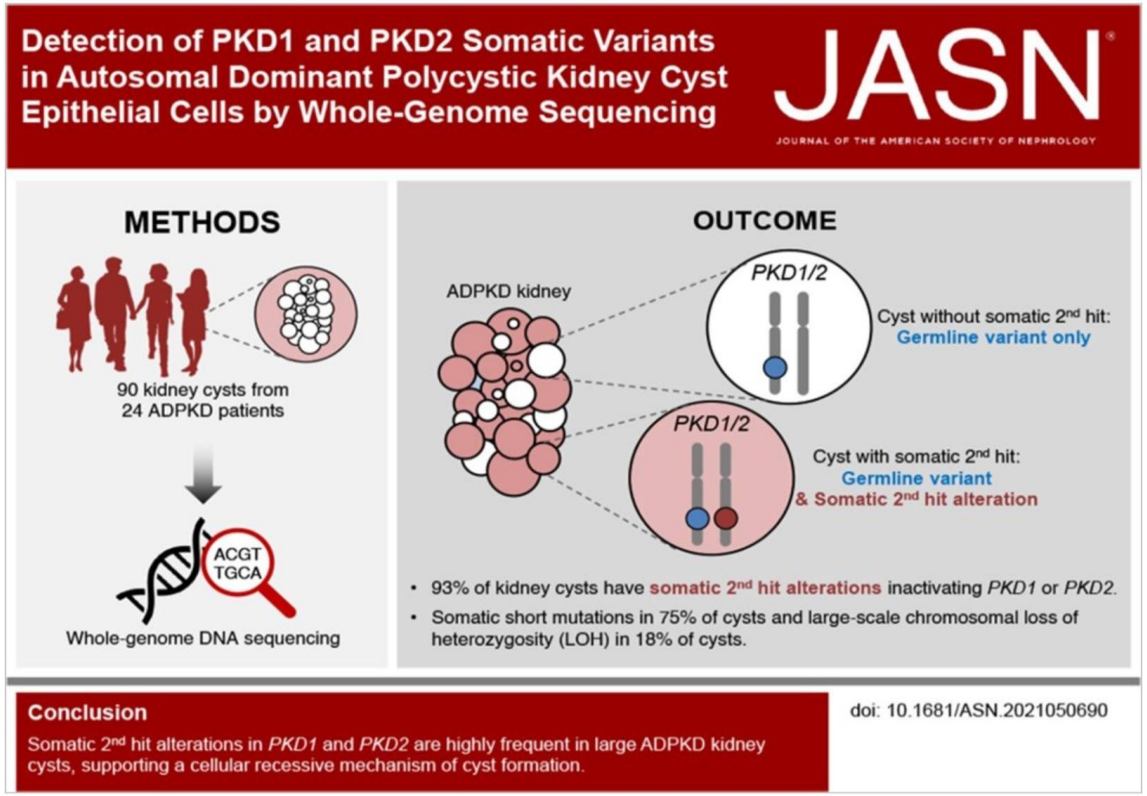
Fig. 2 **Pedigree of RBW402. A** Pedigree of RBW402, clinically diagnosed with ADPKD. No significant family history reported with parents having had normal ultrasound examinations in their 60 s. *normal ultrasound examination in 60's. ^ normal ultrasound examination in 30's. Arrow indicates proband (RBW402). **B** Kidney ultrasound images from RBW402 demonstrating bilateral kidney cysts.

European Journal of Human Genetics 2025

- In general, traditional LR-PCR-Sanger sequencing and gene panel can solve 70-90% of cases
- Diagnostic rate depends on enroll criteria, family history, etc
- Exome sequencing can identifed satypical PKD cases

Somatic Mutation in PKD
Two-Hit Theory

Stefan E. Reeders in 1992, suggesting that each cyst in ADPKD arises from the functional inactivation of both copies of a PKD gene (PKD1 or PKD2)



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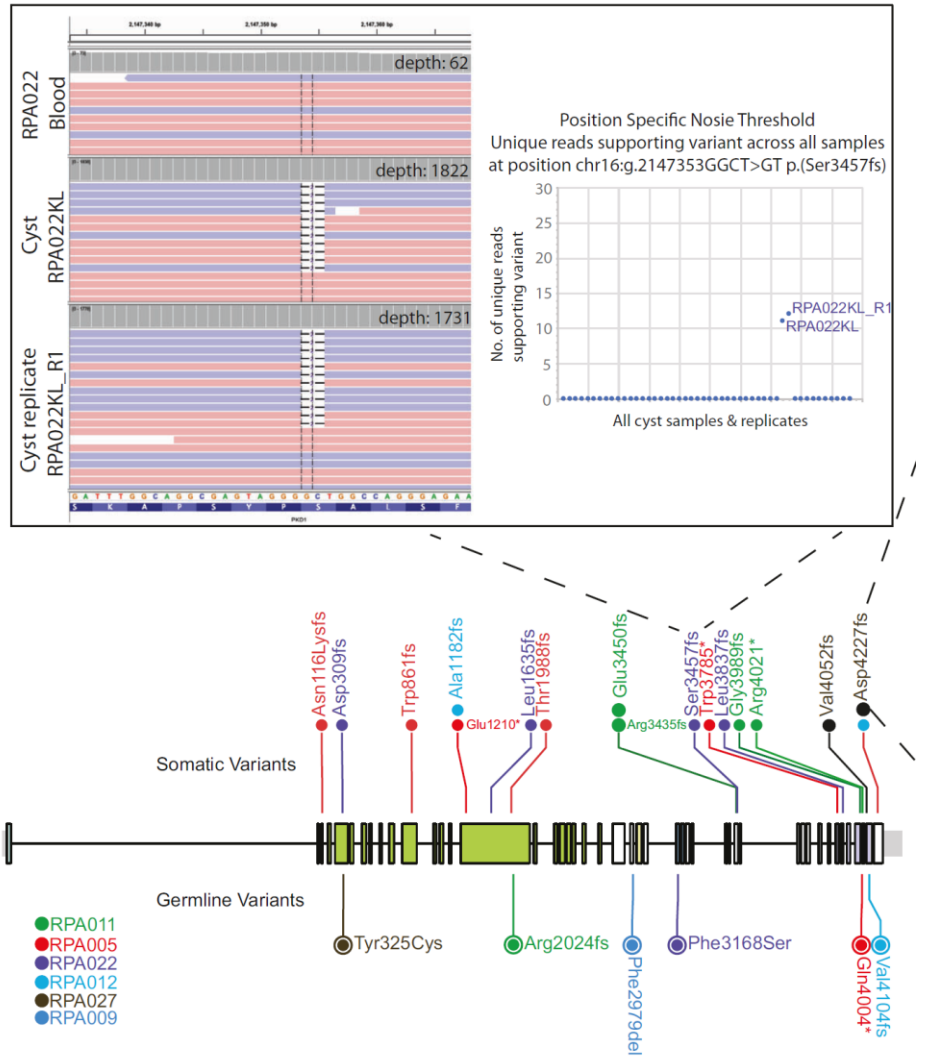
Somatic mutation in autosomal dominant polycystic kidney disease revealed by deep sequencing human kidney cysts

Check for updates

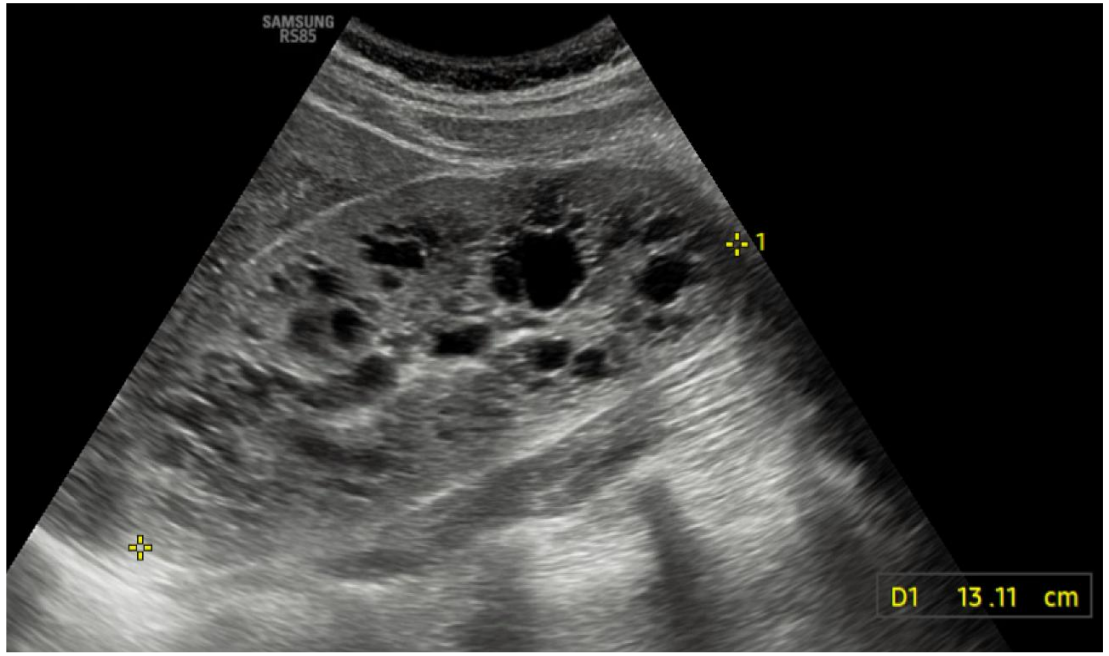
Amali C. Mallawaarachchi[1,2,3,4], Yvonne Hort[1], Laura Wedd[1,5,6], Kitty Lo[7], Sarah Senum[8], Mojgan Toumari[7], Wenhan Chen[7], Mike Utsiwegota[9], Jane Mawson[9], Scott Leslie[4,10,11], Jerome Laurence[10], Lyndal Anderson[4,12], Paul Snelling[9], Robert Salomon[7], Gopala K. Rangan[13,14], Timothy Furlong[1], John Shine[1,3] & Mark J. Cowley[3,7]

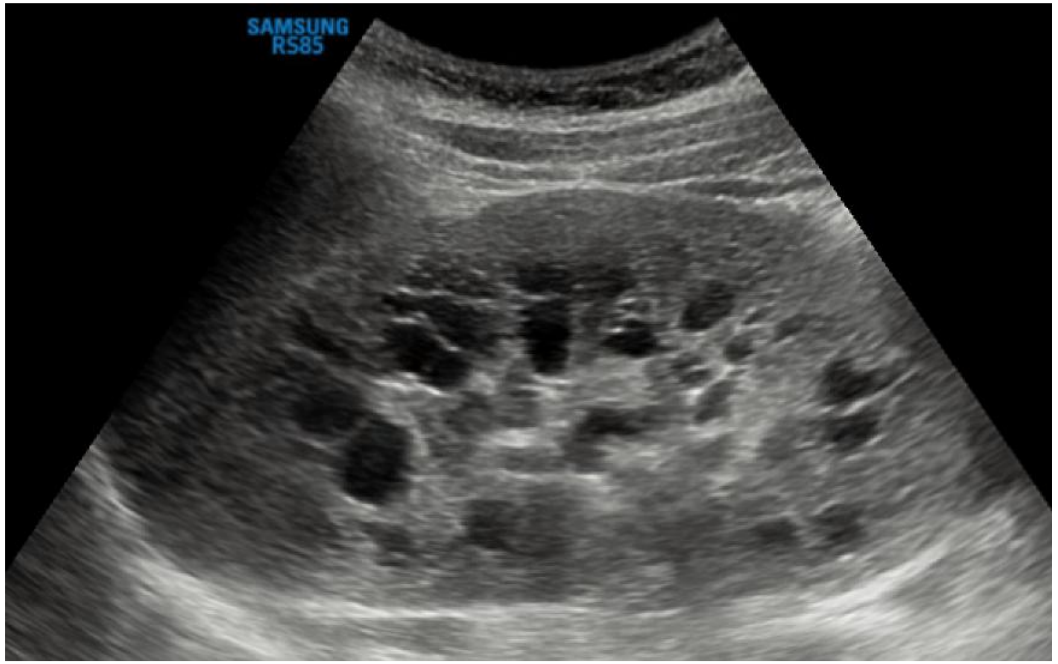
Somatic Mutation in PKD Two-Hit Theory



npj Genomic Medicine (2024)

OFD1 p.Ile229fs

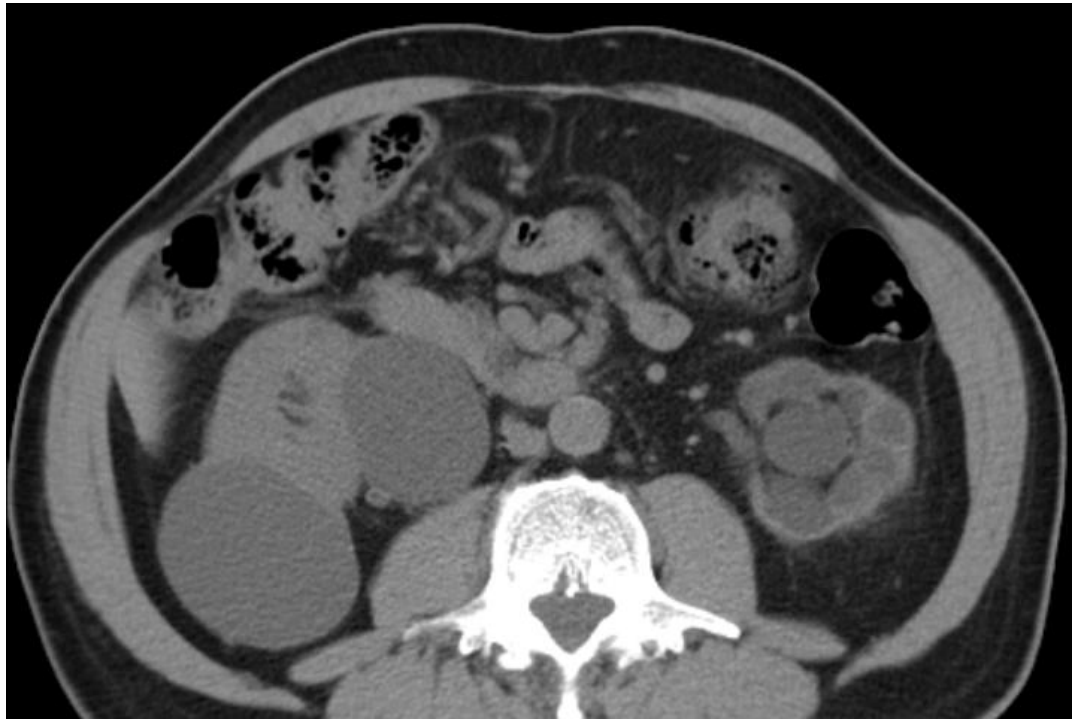


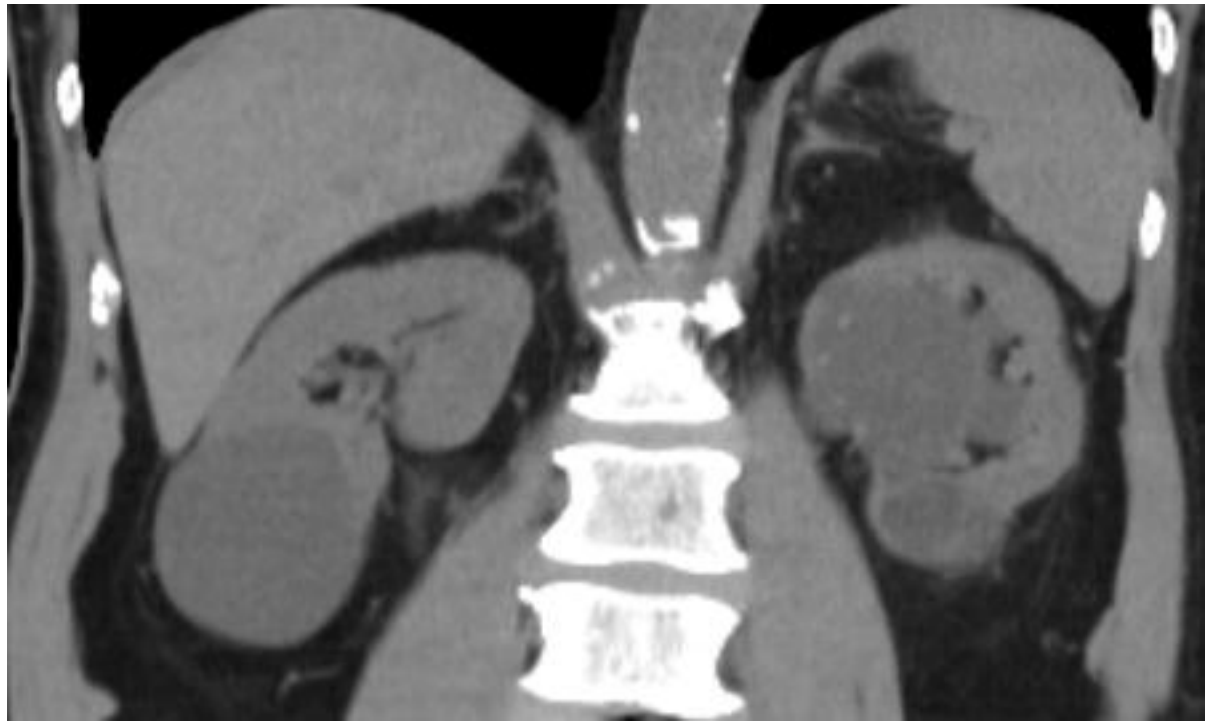


Courtesy of Dr. 王憲奕

Exome Sequencing Identified Atypical PKD

COL4A4 p.Gly134Asp





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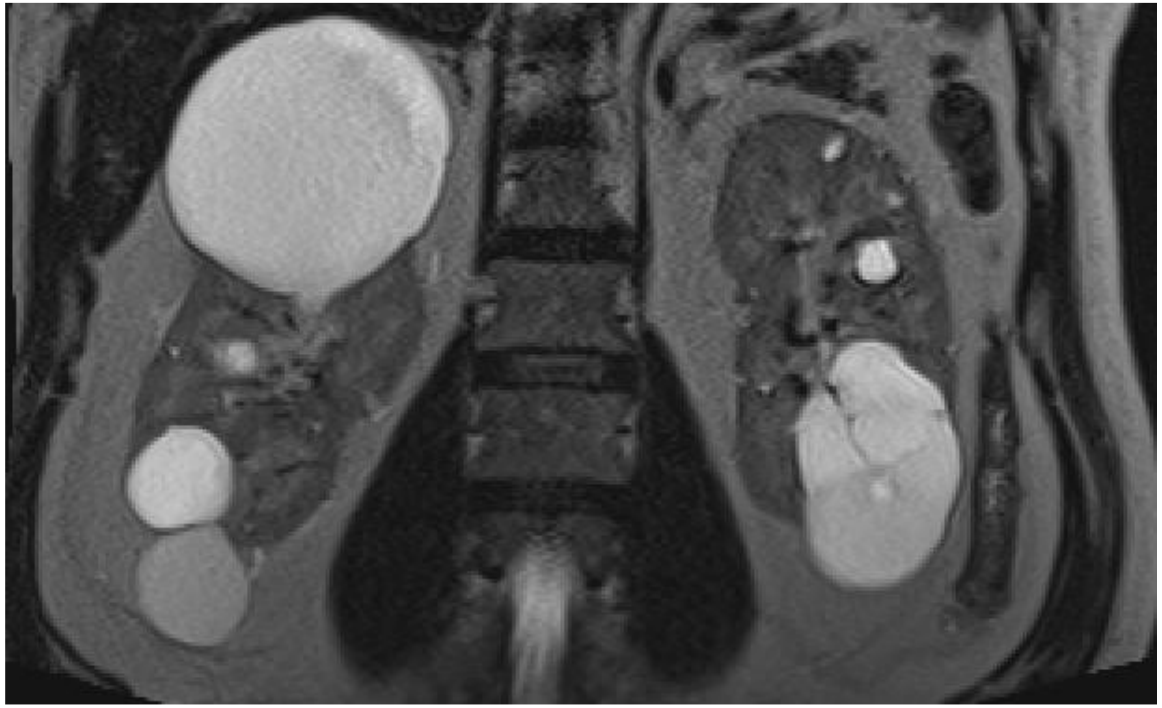
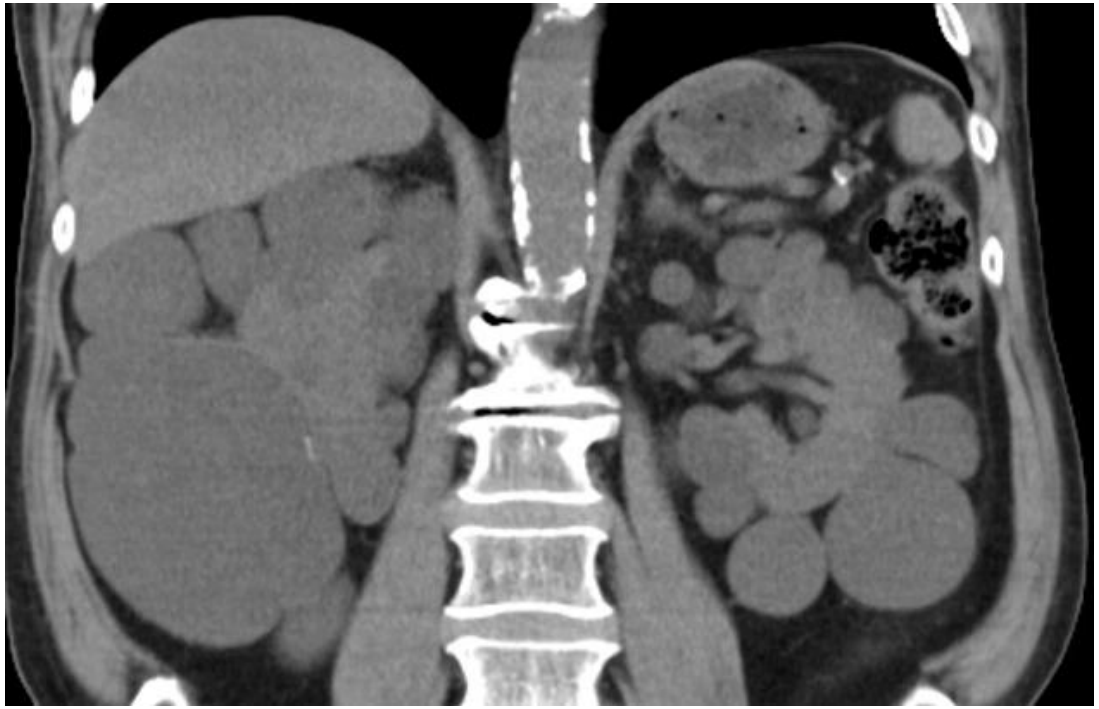
IFT140

p.Arg347*



p.Gln667*



Long-Read Sequencing (LRS) in ADPKD

- Unsolved ADPKD cases
- Mutation in deep intro region, large insertion-deletion, *PKD1* pseudogene conversion, and other structure changes

Long-Read Sequencing (LRS)

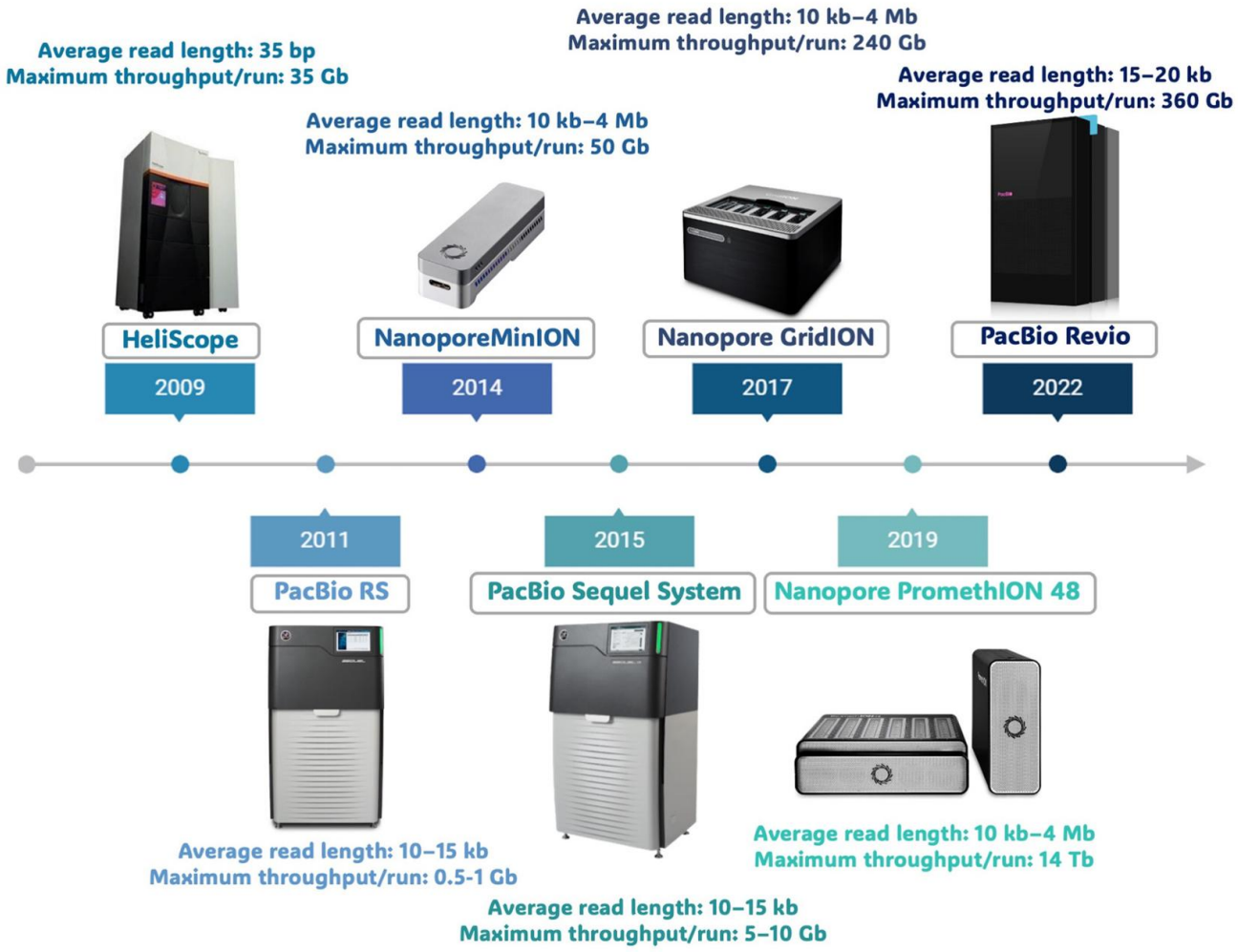
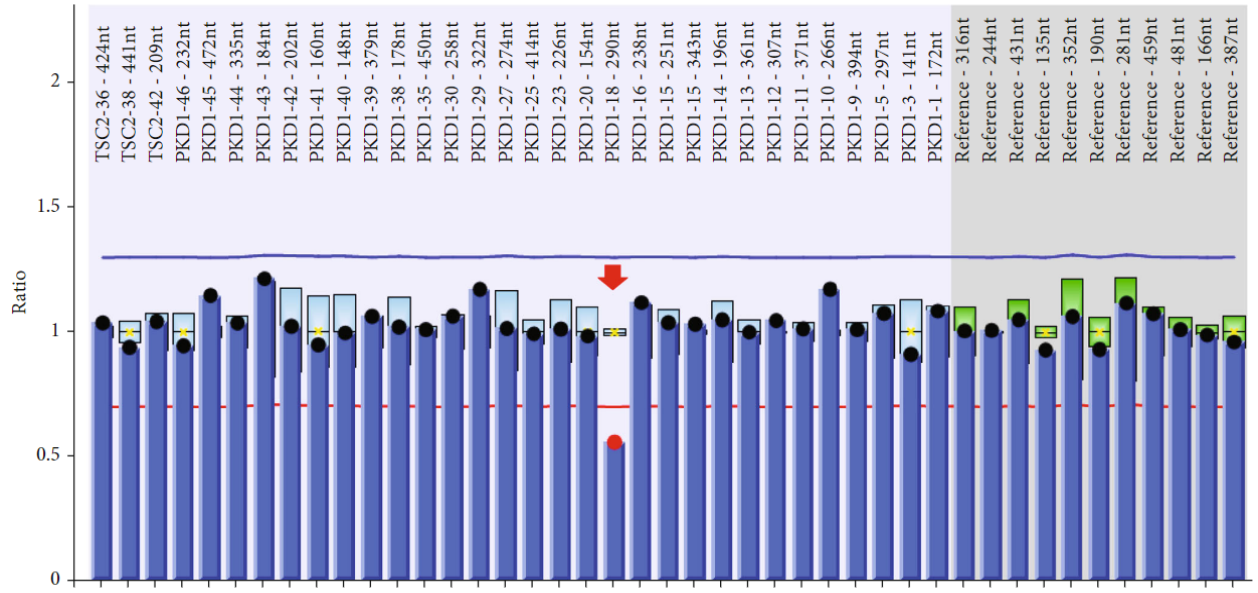


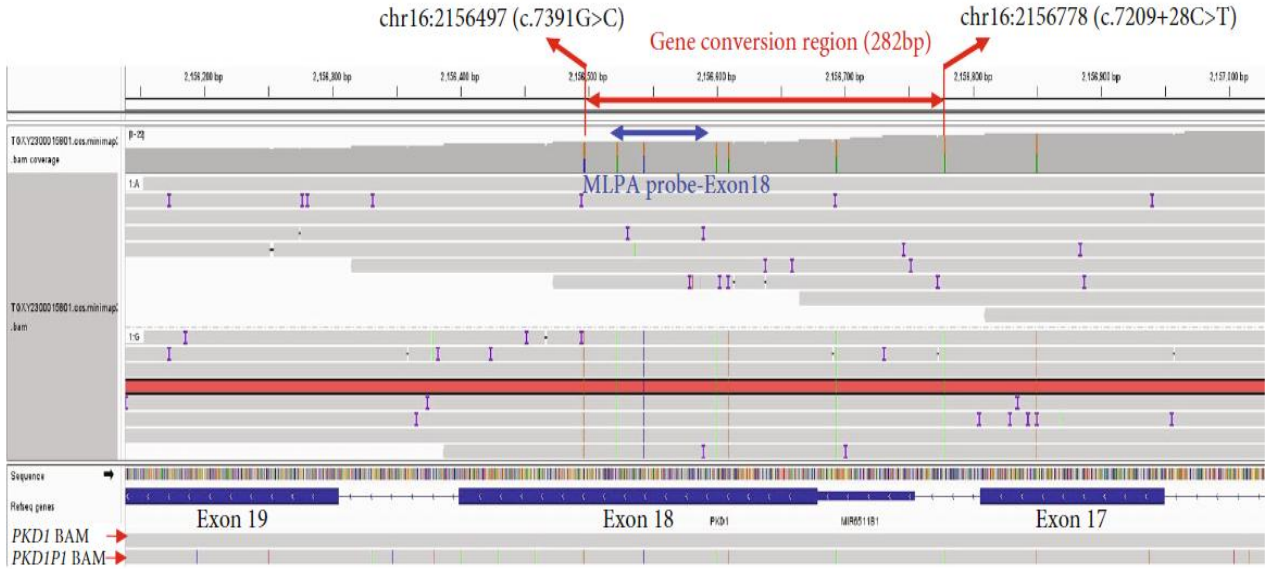
Figure 1. Third-generation sequencing timeline.

Biomolecules 2024

Exon18 Deletion VS *PKD1* Pseudogene Conversion

- MLPA showed *PKD1* exon18 deletion
- LRS found *PKD1* pseudogene conversion in Exon 18 region

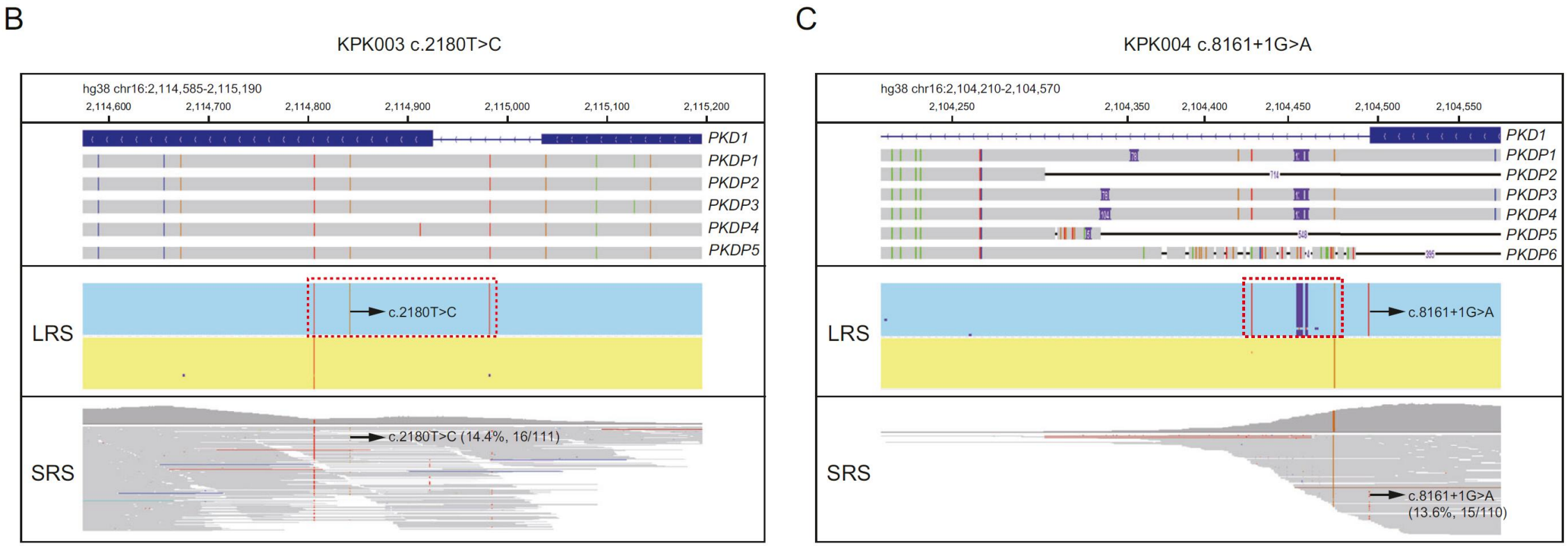




Hum Mutat 2024

LRS Identified *PKD1* Pseudogene Conversion

- Mutations of low mutation frequency in SRS indicats potential *PKD1* pseudogene conversion



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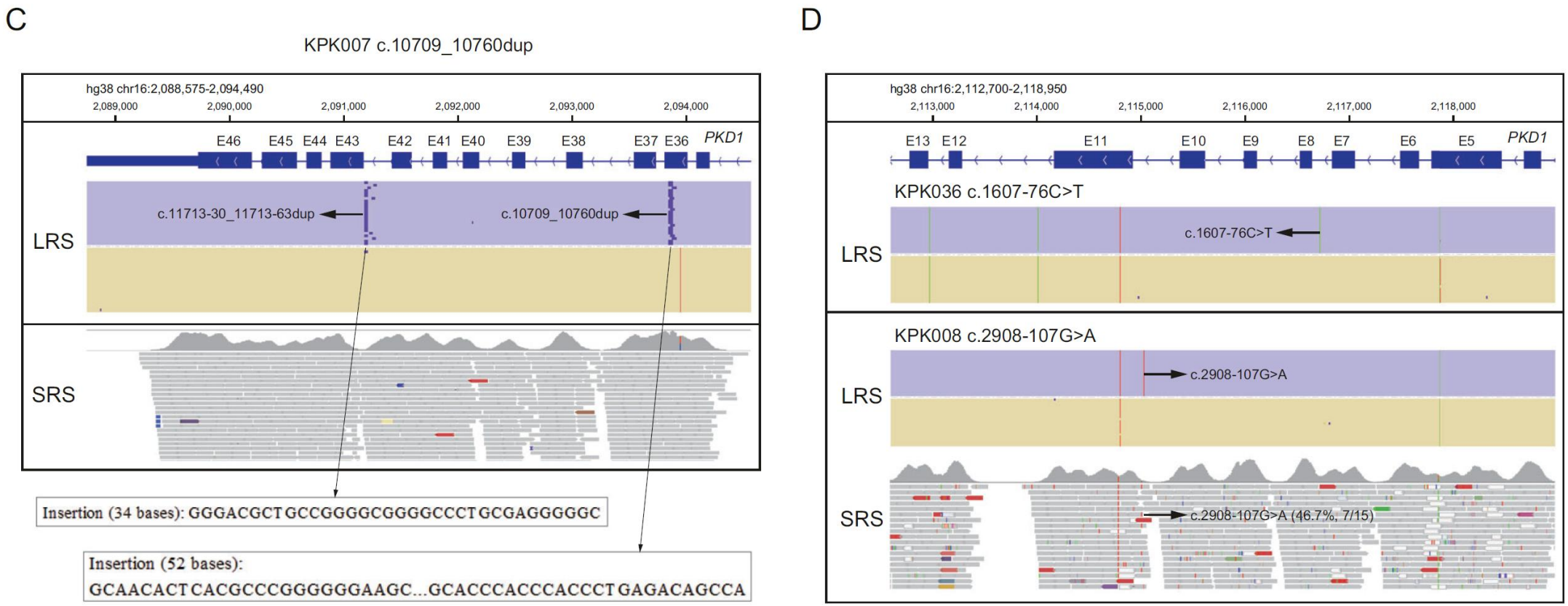
LRS Identified Large Insertion and Deep Intron Mutations



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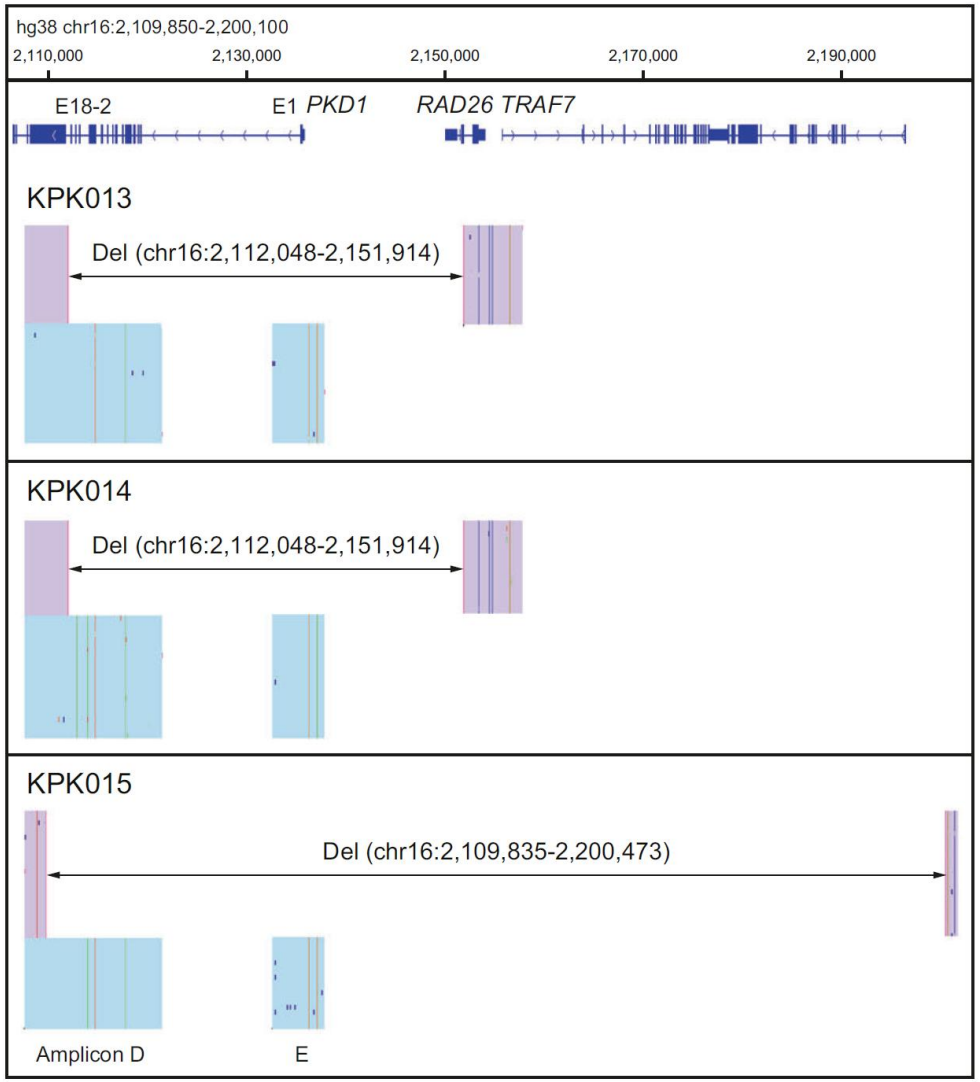
LRS Identified Large Deletion Mutations



- Need to perform WGS-LRS

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A world where children are free from PKD

- Sequencing in PKD should be a standard exam
- Molecular diagnosis can guide clinical treatment and family consultation