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The Value of Genetic Testing in Polycystic Kidney Diseases Illustrated by a Family With *PKD2* and *COL4A1* Mutations

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Abstract

The diagnosis of autosomal dominant polycystic kidney disease (ADPKD) relies on imaging criteria in the setting of a positive familial history. Molecular analysis, seldom used in clinical practice, identifies a causative mutation in >90% of cases, in the genes *PKD1*, *PKD2,* or rarely *GANAB*. We report the clinical and genetic dissection of a seven-generation pedigree, resulting in the diagnosis of two different cystic disorders. Using targeted next generation sequencing of 65 candidate genes in a patient with a ADPKD-like phenotype who lacked the familial *PKD2* mutation, we identified a *COL4A1* mutation (p.Gln247*), and made the diagnosis of HANAC syndrome (hereditary angiopathy with nephropathy, aneurysms, and muscle cramps). While four individuals had ADPKD-*PKD2*, various *COL4A1*-related phenotypes were identified in five patients, and three individuals with likely digenic *PKD2/COL4A1* disease reached ESRD around 50 years of age, significantly earlier than observed for either monogenic disorder. Thus, using targeted next-generation sequencing as part of the diagnostic approach in patients with cystic diseases provides differential diagnoses and identifies factors underlying disease variability. As

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specific therapies are rapidly developing for ADPKD, a precise etiologic diagnosis should be paramount for inclusion in therapeutic trials and optimal patient management.

Index words

autosomal dominant polycystic kidney disease (ADPKD); PKD2; COL4A1; HANAC; genetic testing; targeted next-generation sequencing (TNGS); pedigree; case report; phenotypic variability

Introduction

Autosomal dominant polycystic kidney disease is characterized by progressive, bilateral cyst development with highly variable renal disease.[1] *PKD1* and *PKD2* mutations are, respectively, identified in ~78% and ~15% of the pedigrees,[2, 3] with mutation of a third gene, *GANAB,* occurring rarely (~0.3%); the genetic lesion in approximately 7% remains unresolved.[4, 5] Genetic variability strongly influences the severity of ADPKD, with median age at ESRD of 58y in individuals with *PKD1* truncating mutations, about 67y for those with *PKD1* nontruncating mutations, and approximately 79y in those with mutations in *PKD2*.[6] An ADPKD diagnosis is presently based on the conjunction of age-dependent imaging criteria with a positive familial history; molecular testing is rarely employed.[6–9] However, the phenotypes associated with mutations in several genes can occasionally mimic ADPKD: *PKHD1,* causing autosomal recessive polycystic kidney disease (ARPKD); *HNF1B*, autosomal dominant tubulointerstitial disease (ADTKD-*HNF1B*); the tuberous sclerosis genes *TSC1* and *TSC2*; and the autosomal dominant polycystic liver disease (ADPLD) genes (*SEC63*, *PRKCSH*, *LRP5, ALG8, SEC61B*).[6] Mutations to *COL4A1* can also cause bilateral renal cysts and decline in kidney function after 50y, as part of HANAC syndrome.[10, 11] Here we report how genetic testing of a multigenerational “ADPKD” pedigree explains the marked intra-familial variability due to finding two distinct genetic disorders.

Case Report

The index case, V.5, in pedigree M625 (Fig 1A), had experienced microscopic hematuria since 14y and was diagnosed with PKD at 21y (Table 1). His family history was significant for ADPKD in 4 generations. At 56y, he had more than 20 cysts per kidney, no liver cysts (Fig 1D) and an estimated glomerular filtration rate (eGFR) of 47ml/min/1.73m^2 by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. The patient and three affected relatives participated in the HALT-PKD clinical trial; VI.2 was a participant in Study A (eGFR >60ml/min/1.73m^2 at enrollment) and V.4, V.5, and VI.1 were participants in Study B (eGFR of 25–60ml/min/1.73m^2).[12, 13] Molecular analysis[3] of *PKD1* and *PKD2* led to the identification of a frameshifting variant of *PKD2* (c.715_718dupTACG [a duplication of the indicated 4-nucleotide sequence], predicted to lead to a frameshift at the glycine at amino acid 240 [p.Gly240fs]) in subjects V.4, VI.1 and VI.2 but was not detected in V.5 (Fig 1A, C). As opposed to that seen in the three mutation-positive individuals, height-adjusted total kidney volume (HtTKV) was normal in V.5 (Table 1, Fig 1D–F). At age 57y, V.5 was diagnosed with proximal stenosis of the left carotid artery and underwent

endarterectomy. At reevaluation one year later for recurrent spells of dizziness and an episode of memory loss and confusion, gadolinium-enhanced MRI showed periventricular and subcortical leukoencephalopathy, consistent with chronic cerebral small-vessel disease (CSVD; Fig 1H). MR angiography of the carotid arteries was this time unremarkable.

We expanded the genetic analyses by rescreening subject V.5 by targeted next-generation sequencing to analyze all of the exons and flanking intronic sequences of *PKD1, PKD2, PKHD1, GANAB, HNF1B, UMOD, PRKCSH, SEC63, LRP5, TSC1, TSC2, COL4A1, SEC61B* and 52 candidate genes. Libraries were enriched using custom capture baits (SureSelect; Agilent) and paired-end sequencing of 150 base pairs was performed on an Illumina HiSeq4000. After alignment of the resulting FASTQ files to the human genome 19 (hg19) reference sequence and realignment and recalibration (using Genome Analysis Toolkit (GATK)), multi-sample variant calling was performed (with GATK Haplotype Caller) and variants filtered with Variant Quality Score Recalibration. Variant mining was performed with Golden Helix SNP & Variation Suite v.8. From this analysis we identified a cytosine to thymine substitution at nucleotide 739 of the coding sequence (c.739C>T) in exon 13 of *COL4A1*, predicted to lead to a nonsense mutation (introduction of a premature stop codon) at the glutamine at amino acid 247 (p.Gln247*); the nucleotide variant was confirmed by Sanger sequencing (Fig 1B, C). The diagnosis of HANAC-like syndrome was consistent with the clinical presentation, associating longstanding microscopic hematuria, renal cysts and CSVD; the patient also reported intermittent myalgia.

We broadened the familial investigation and identified several other family members with *COL4A1*-related phenotypes. Individual V.1 and her mother IV.1 had microscopic hematuria, mild proteinuria, atrophic cystic kidneys, and decreased kidney function/kidney failure (Table 1). The latter had a transient ischemic stroke at 36y, and recurrent strokes after 70y. Individual VII.1, a child, suffered from developmental delay associated with ataxia, global hypotonia, and absence epilepsy. She had moderate cerebellar hypoplasia (Fig 1I), and proved positive for the *COL4A1* mutation, likely underlying her neurologic phenotype. Her father, VI.4, was subsequently diagnosed with HANAC-like syndrome; he had muscles cramps and elevated CPK since 32y, urinalysis revealed microhematuria, and an abdominal MRI showed bilateral kidney cysts (Fig 1G). Considering the dominant inheritance of *PKD2* and *COL4A1* related disease, the family history, and lack of phenotype in IV.4, IV.3, deceased at 51y from ESRD, was an obligate carrier for the *COL4A1* mutation and likely had the *PKD2* mutation. Although retrograde pyelography showed enlarged cystic kidneys, ADPKD was considered “unlikely to be the only cause to his renal insufficiency”, as he had systemic symptoms including severe Raynaud’s phenomenon, migraines, and myalgia and because his kidneys were “not massively enlarged”. Fundus examination showed, “a curly-cue extension of many of the arterioles bilaterally, probably congenital”. His mother, III.2, who died from uremia at 46y, was also likely carrying both the *PKD2* and the *COL4A1* mutations. Subject V.2 had ADPKD and started hemodialysis at 51y. Medical history was also significant for myalgia with elevated CPK, hearing loss, and gout. The ADPKD course was significantly more severe in V.2 than in his 3 sons and his sister, all with ADPKD-*PKD2* and negative for the *COL4A1* variant, suggesting that V.2 inherited both variants (Table 1).

Discussion

In the setting of a single family with multiple individuals fullfiling the ADPKD diagnosis criteria,[8] we describe here how targeted next-generation sequencing revealed two separate genetic etiologies, ADPKD-*PKD2* and *COL4A1,* clarifying the disease heterogeneity over six generations.

COL4A1 and *COL4A2* encode procollagen type IV α1 and α2, which assemble to form the heterotrimeric helix α1/α1/α2, and are present in almost all basement membranes (BM). In the kidney, α1/α1/α2 is expressed in the Bowman capsule and the tubular BM, but replaced by the heterotrimer α3/α4/α5 in the glomerular BM after embryogenesis. Consistent with this expression pattern, *COL4A1*-related phenotypes encompass cerebrovascular, ophthalmologic, renal, cardiac, and muscular abnormalities.[14] Less than eighty *COL4A1* pedigrees have been reported to date, including eight with the full HANAC phenotype.[10, 11, 14, 15] The disease presentation in the four HANAC-like patients reported is consistent with these previous descriptions. Interestingly, tortuosity of the retinal arteries, a hallmark of the COL4A1 vascular phenotype, was described in this family more than 50y ago. Unexpectedly, identifying the cause of subject V.5's renal phenotype led to an etiological diagnosis in his 4 year-old granddaughter, affected by developmental delay and hypotonia. Simultaneous intrafamilial occurrence of these divergent phenotypes was not previously reported.[11] HANAC syndrome is classically attributed to missense mutations affecting glycine residues within the COL4A1 triple-helix domain (a dominant-negative mechanism), while rare truncating mutations (haploinsufficiency), as in our pedigree, have mostly been reported with cerebrovascular disease.[14, 16, 17] Noteworthy, we identified three deceased individuals with suggested (although unconfirmed) digenic *PKD2/COL4A1* disease. All reached ESRD around 50y, significantly earlier than usually observed for either monogenic disorder, suggesting an aggravating effect of the *COL4A1* variant on the PKD2 phenotype.[6, 10, 14, 15, 17] Only a handful of digenic cystic diseases have been reported, involving *PKD1*, *PKD2*, or *HNF1B*,[18, 19] but these cases are likely under-diagnosed, illustrating the value of targeted next-generation sequencing of multiple cystic genes.

As specific therapies become available for ADPKD, obtaining a precise diagnosis is a prerequisite to provide appropriate treatment. However, ADPKD imaging-based diagnostic criteria require a positive familial history, lacking in 10 to 25% of the patients, and genetic diagnostics are presently rarely performed in ADPKD patients, although they are part of the diagnostic algorithm of other kidney diseases.[6] In our study, although the proband met the imaging criteria, he was affected by a totally different condition, phenocopying ADPKD. Inclusion of cases as presented herein in clinical trials, along with others with slowly progressing renal phenotypes, can reduce the likelihood of a positive outcome,[20] supporting systematic genetic screening of ADPKD patients considered for treatment or inclusion in trials. While the high cost of ADPKD genetic testing has long been a disincentive, improvement of the screening protocols, together with the rapid development of specific next-generation sequencing approaches will undoubtedly increase its accessibility.[6] The routine analysis of multiple cystic genes in ADPKD patients may eventually reveal the full genetic and phenotypic spectrum of cystic kidney diseases.

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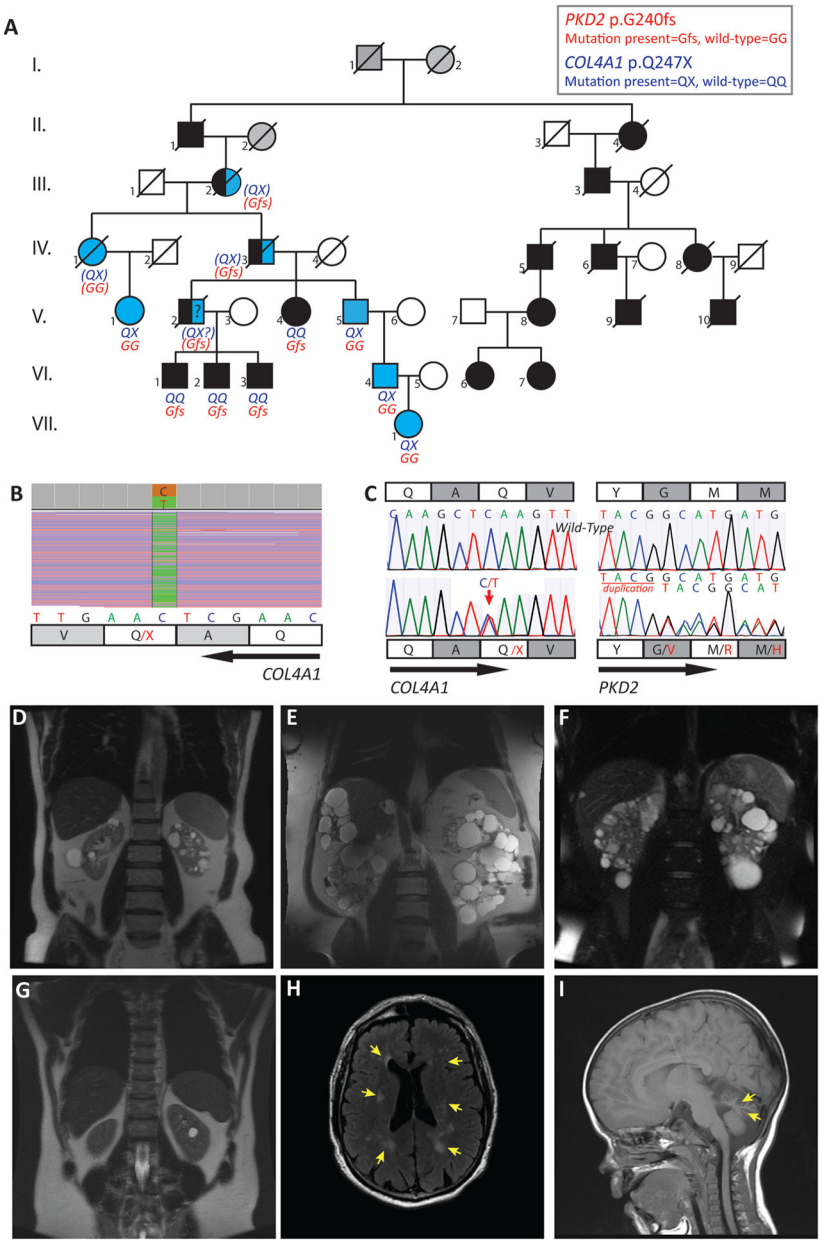

Figure 1. Molecular and imaging data for Pedigree M625 with ADPKD-*PKD2* and *COL4A1*-associated diseases

A. Disease segregation in pedigree M625. Black symbols denote ADPKD-*PKD2* affected individuals, blue symbols denote patients with *COL4A1*-associated diseases, and gray shading is used when the status of the individuals is unknown. Blue and black symbols are used in individuals with suspected digenic *COL4A1-PKD2* disease. Slash over symbols denotes death. Genetic results were not available in III.2, IV.1, IV.3 but their status could be inferred from their medical records (IV.1 and IV.3) and/or from the dominant inheritance pattern of both diseases (III.2, IV.1, IV.3) (inferred genotype within parentheses). Subject II. 1, who died at 63y, had a positive familial history of ADPKD (The ADPKD-affected descendants of II.4 are represented on the pedigree, and live in Europe, but no further

information is available). Whether he also carried the *COL4A1* variant is uncertain. Subject III.2 died at 46y from uremia; she was likely carrying both variants that she passed on to IV. 1 and IV.3; for her husband (III.1), who died at age 72, no relevant past medical history was mentioned. **B.** IGV (integrative genomics viewer, Broad Institute) view of the next-generation sequencing of IV.6 shows *COL4A1* variant c.739C>T (p.Gln247*) (reverse strand). Read depth: 2822, C=49%, T=51%. **C.** Sanger sequencing confirmation of heterozygous *COL4A1* variant c.739C>T (p.Gln247*) in V.5, and *PKD2* variant c. 715_718dupTACG in VI.3. The wild-type sequences are shown for comparison. **D.** MRI, T2 weighted, of the COL4A1 subject V.5, 61y, showing bilateral renal cysts without kidney enlargement (HtTKV=200ml/m). **E.** MRI, T2 weighted, of PKD2 patient VI.1 at 53y, showing enlarged polycystic kidneys (HtTKV=1953 ml/m). **F.** MRI, T2, of PKD2 patient VI.2, who has moderately enlarged polycystic kidneys at 46y (HtTKV=470ml/m). **G**. MRI, T2, of COL4A1 individual VI.4 who has non-enlarged kidneys at 35y, with six cysts in the left kidney (the largest shown here measures 1.6 cm) and two millimeter sized cysts in the right kidney. **H.** Cerebral MRI of COL4A1 subject V.5, Axial FLAIR (fluid-attenuated inversion recovery) sequence demonstrating bilateral areas of signal hyperintensity in the centra semiovale (arrows). **I.** Cerebral MRI in COL4A1 subject VII.1 (4y), sagittal T1 weighted sequence showing marked volume loss in the superior cerebellar vermis (arrows).

Table 1

Clinical presentations and genetic analyses of 12 affected family members

Pt	Sex	eGFR[a]	HTN[b]	Microscopic hematuria [b]	Proteinuria[b,c]	Kidney Morphology	Myalgia[b]	Elevated CPK[b,d]	CNS involvement	Cause of death	Other conditions[b]	Genetic results[g]	Diagnosis
IV.1	F	ESRD (71 y)	Y (50 y)	Y (70 y)	Y (70 y)	US at 71 y: atrophic RK (6.6 cm), 2 cysts in LK, 5 in RK	NA	NA	CSVD (CT scan, 71 y), TIA (36 y), recurrent ischemic strokes (70 y)	Stroke in 1995 (79 y	NA	NA	HANAC-like syndrome [e]
V.1	F	33 (67 y)	N (67 y)	Y (25 y)	Y (62 y): 0.7	US at 59 y: atrophic RK (7.7cm), LK (9.3 cm), 2 cysts	Y (NA)	NA	Vertigo (64 y), normal non-enhanced CT (67 y)	-	Hypothyroidism (21 y), Gout (67 y)	*COL4A1:* Q247* *PKD2:* WT	HANAC-like syndrome
V.5	M	47 (67 y)	Y (57 y)	Y (14 y)	N (66 y)	MRI at 61 y: >15 cysts/kidney, no liver cyst, HtTKV[f] = 200	Y (65 y)	NA	Migraines, dizzy spells since age 63; CSVD (MRI 58 y)	-	Gout (52 y), DM (65 y), Carotid endarteriectomy (57)	*COL4A1:* Q247* *PKD2:* WT	HANAC-like syndrome
VI.4	M	112 (32 y)	N (35 y)	Y (35 y)	N (35 y)	MRI at 35 y: 6 cysts in LK, 2 in RK	Y (32 y)	Y (32 y): 527	Migraines since age 30, normal enhanced CT (32 y)	-	None	*COL4A1:* Q247*	HANAC-like syndrome
VII.1	F	129 (3 y)	N (4 y)	Y (3 y)	N (3 y)	NA	NA	NA	Global developmental delay, Hypotonia, absence epilepsy, MRI: thin cerebellar folia (4 y)	-	None	*COL4A1:* Q247*	*COL4A1*-related CNS disorder
III.2	F	ESRD (48 y)	NA			NA	NA	NA	NA	ESRD (46 y)	NA	NA	Likely *PKD2/COL4A1*[e]
IV.3	M	ESRD (51 y)	N (53 y)	Y (50 y)	Y (50 y)	Pyelography: enlarged kidneys, numerous renal cysts	Y (50 y)	NA	Migraines (50 y)	ESRD (51 y)	Tortuosity of the retinal arteries (50 y), Raynaud phenomena (50 y)	NA	Likely *PKD2/COL4A1*[e]
V.2	M	ESRD (51 y)	Y (NA)	NA	NA	Non-enhanced CT at 56 y: Enlarged polycystic kidneys, polycystic liver	Y (56 y)	Y (55 y): 206	Normal non-enhanced CT (56 y)	ID (57 y)	Gout (<50 y), hearing loss (56 y), aseptic necrosis of the femoral head (56 y), spontaneous cecum perforation (56 y)	NA	ADPKD-PKD2[e]; Possible *PKD2/COL4A1*
V.4	F	30 (66 y)	N (59 y)	NA	N (59 y)	US: Enlarged polycystic kidneys, polycystic liver	N	NA	none	-	None	*PKD2:* c.715_718dupTACG *COL4A1*: WT	ADPKD-PKD2
VI.1	M	21 (54 y)	Y (25 y)	N (55 y)	Y (53 y): 0.8	MRI at 53 y: enlarged polycystic	N	NA	none	-	T2DM (52 y); obesity, with BMI 40 kg/m2	*PKD2:* c.715_718dupTACG *COL4A1*: WT	ADPKD-PKD2

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Pt	Sex	eGFR[a]	HTN[b]	Microscopic hematuria [b]	Proteinuria[b,c]	Kidney Morphology	Myalgia[b]	Elevated CPK[b,d]	CNS involvement	Cause of death	Other conditions[b]	Genetic results[g]	Diagnosis
						kidneys, HtTKV[f]=1953							
VI.2	M	56 (50 y)	Y (41 y)	NA	N (50 y)	MRI at 46 y: enlarged polycystic kidneys, HtTKV[f]=470	N	NA	none	-	None	*PKD2:* c.715_718dupTACG *COL4A1*: WT	ADPKD-PKD2
VI.3	M	36 (47 y)	Y (24 y)	N (47 y)	Y (34 y)	US at 31 y: LK 14.5 cm, LK 13.3 cm, >15 cysts/ kidney	Y (47 y)	Y, under statins (33 y)	none	-	T1DM (11 y), MN (31 y)	*PKD2*:c.715_718dupTACG *COL4A1*: WT	ADPKD-PKD2

[a]Expressed in mL/min/1.73 m^2 on the basis of the last data available; obtained with the CKD-EPI equation for adults and with the Bedside Schwartz formula in the child.

[b]Values in parentheses is age when first reported if present, or when last available data available if not present.

[c]When available, proteinuria is expressed in grams per gram of urinary creatinine.

[d]When available, expressed in UI/L

[e]The patient is likely digenic carrier considering the familial history and the dominant inheritance of each condition.

[f]Height adjusted total kidney volume, calculated by stereology and expressed in ml/m

[g]WT: wild-type; Q247*: frame shift leading to stop codon instead of glutamine at amino acid 247; c.715_718dupTACG: a duplication of the indicated 4-nucleotide sequence, predicted to lead to a frameshift at the glycine at amino acid 240

List of abbreviations and definitions: CNS=central nervous system, CPK=Creatine Phosphokinase, CSVD=cerebral small-vessel disease, CT=computed tomography, LK=left kidney, RK=Right Kidney, NA= not available, US=ultrasound; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; pt, patient; TIA, transient ischemic attack; ID, infectious disease; MN, Membranous nephropathy;