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

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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 7-generation pedigree, resulting in the diagnosis of 2 different cystic disorders. Using targeted next-generation sequencing of 65 candidate genes in a patient with an ADPKD-like phenotype who lacked the familial *PKD2* mutation, we identified a *COL4A1* mutation (p.Gln247*) and made the diagnosis of HANAC (hereditary angiopathy with nephropathy, aneurysms, and muscle cramps) syndrome. While 4 individuals had ADPKD-*PKD2*, various *COL4A1*-related phenotypes were identified in 5 patients, and 3 individuals with likely digenic *PKD2*/*COL4A1* disease reached end-stage renal disease at 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 specific therapies are rapidly developing for ADPKD, a precise etiologic diagnosis should be paramount for inclusion in therapeutic trials and optimal patient management.

Complete author and article information (including a list of HALT Progression of Polycystic Kidney Disease Group Investigators) provided before references.

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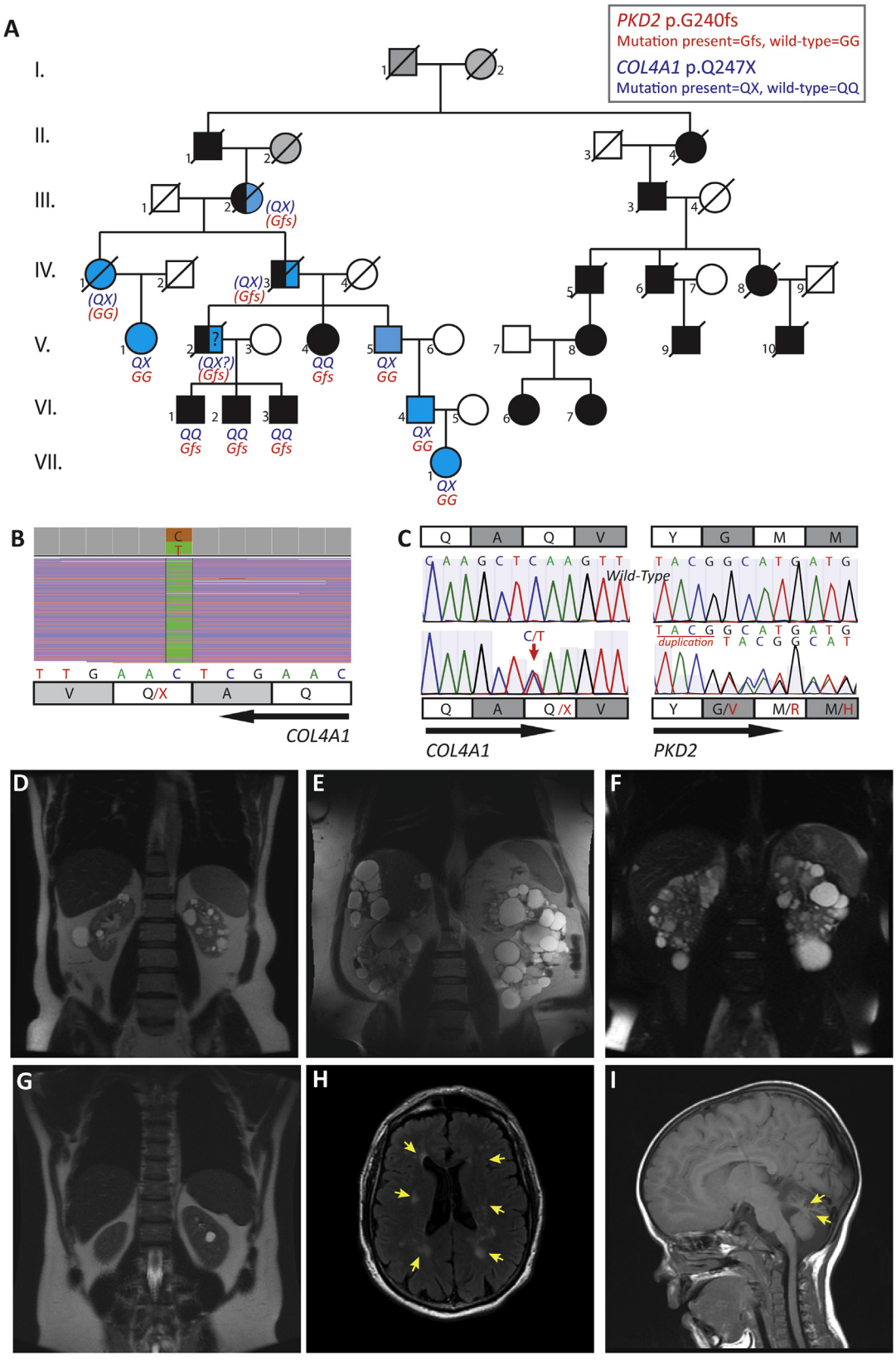
Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is characterized by progressive bilateral cyst development with highly variable kidney 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 ~7% remains unresolved.[4,5] Genetic variability strongly influences the severity of ADPKD, with median age at end-stage kidney disease of 58 years in individuals with *PKD1* truncating mutations, about 67 years for those with *PKD1* nontruncating mutations, and approximately 79 years 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 used.[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*, and *SEC61B*).[6] Mutations to *COL4A1* can also cause bilateral renal cysts and decline in kidney function after 50 years, as part of HANAC (hereditary angiopathy with nephropathy, aneurysms, and muscle cramps) syndrome.[10,11] We report how genetic testing of a multigenerational "ADPKD" pedigree explains the marked intrafamilial variability due to finding 2 distinct genetic disorders.

Case Report

The index case, V.5, in pedigree M625 (Fig 1A) had experienced microscopic hematuria since age 14 years and PKD was diagnosed at 21 years (Table 1). His family history was significant for ADPKD in 4 generations. At 56 years of age, he had more than 20 cysts per kidney, no liver cysts (Fig 1D), and an estimated glomerular filtration rate of 47 mL/min/1.73 m^2 by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. The patient and 3 affected relatives participated in the HALT-PKD clinical trial; VI.2 was a participant in Study A (estimated glomerular filtration rate > 60 mL/min/1.73 m^2 at enrollment) and V.4, V.5, and VI.1 were participants in Study B (estimated glomerular filtration rates of 25-60 mL/min/1.73 m^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 amino acid 240 [p.Gly240fs]) in individuals V.4, VI.1 and VI.2, but was not detected in V.5 (Fig 1A and C). As opposed to that seen in the 3 mutation-positive individuals, height-adjusted total kidney volume was normal in V.5 (Table 1; Fig 1D-F). At age 57 years, V.5 had proximal stenosis of the left carotid artery diagnosed and underwent endarterectomy. At re-evaluation 1 year later for recurrent spells of dizziness and an episode of memory loss and confusion, gadolinium-enhanced magnetic resonance imaging showed periventricular and subcortical leukoencephalopathy, consistent with chronic cerebral small-vessel disease (Fig 1H). Magnetic resonance


A
PKD2 p.G240fs
Mutation present=Gfs, wild-type=GG
COL4A1 p.Q247X
Mutation present=QX, wild-type=QQ
I.
II.
III.
IV.
V.
VI.
VII.
(QX)
(Gfs)
(QX)
(GG)
QX
GG
(QX?)
(Gfs)
QQ
Gfs
B
T T G A A C T C G A A C
V
Q/X
A
Q
COL4A1
C
Q A Q V
Wild-Type
C/T
Q A Q /X V
COL4A1
Y G M M
duplication
Y G/V M/R M/H
PKD2
D
E
F
G
H
I