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ADPKD Progression in Patients With No Apparent Family History and No Mutation Detected by Sanger Sequencing

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To the Editor:

Among patients with a clinical and imaging-based diagnosis of autosomal dominant polycystic kidney disease (ADPKD), a negative family history for ADPKD (FH^-) has been reported in 10%[1] and 14.2%[2] (this proportion is 27.8% in a broader PKD population[3]). Clinical reasons for an FH^- are unavailable information about the biological parents and

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Supplementary Material

Item S1: Detailed methods and additional results.

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undiagnosed mild or variable ADPKD associated with de novo mutations.[1–3] The genetic causes for clinically variable ADPKD include locus heterogeneity (*PKD1, PKD2*, and *GANAB*), allelic heterogeneity (truncating and non-truncating mutations), hypomorphic alleles, mosaicism, modifier genes, and rare combinations of these.[4–7] In 5% to 10% of patients with apparent ADPKD, no mutation is detected (NMD).[2,5,6] Seventeen patients in the Early HALT-PKD Trial had both FH^- and NMD[2]; we hypothesized that they would have a different disease course.

A total of 512 patients with ADPKD (418 families) in the Early HALT-PKD Trial[2] (part *a*, Item S1) were analyzed in 4 groups based on a positive family history (FH^+) versus FH^- and genetic classification (PKD1/PKD2 mutation or NMD): 414 patients with FH^+/PKD1/PKD2, 29 with FH^+/NMD, 52 with FH^-/PKD1/PKD2, and 17 with FH^-/NMD (table *a*, Item S1). Baseline characteristics (part *b*, table *b*, Item S1) and disease progression during 60 months were determined for the 4 groups using estimated change from baseline in total kidney volume (TKV), height-adjusted TKV (htTKV), estimated GFR (eGFR), and 24-hour urine albumin excretion (UAE).[2] In FH^- patients "a diagnosis of ADPKD was based on the presence of at least 20 kidney cysts bilaterally with features consistent with ADPKD."[8(pp. 103–104)] Detailed statistical and genetic methods are in parts *c* and *d* of Item SI.

Of FH^- and FH^+ patients, 24.6% and 6.5%, respectively, had NMD ($P < 0.001$; table *a*, Item S1). Estimated change from baseline in TKV (Fig 1; Table 1) and htTKV (table *c*, Item S1) differed significantly across the 4 groups over 60 months ($P = 0.03$ for both TKV and htTKV) and was lowest in the FH^-/NMD group. Annual percentage increases in TKV and htTKV were also significantly different across groups: 3.30% and 3.30%, respectively, in FH^-/NMD compared with 5.82% and 5.83% in FH^+/PKD1/PKD2, 4.65% and 4.62% in FH^+/NMD, and 6.00% and 6.08% in FH^-/PKD1/PKD2 ($P = 0.03$ for both TKV and htTKV; Table 1 and table *c* of Item S1, respectively). There was no significant difference across the 4 groups in annual change in eGFR (fig *a*, Item S1, $P = 0.09$), which was −1.6 mL/min/1.73 m^2 in FH^-/NMD patients, −2.9 mL/min/1.73 m^2 in FH^+/PKD1/PKD2, −2.4 mL/min/1.73 m^2 in FH^+/NMD, and −3.3 mL/min/1.73 m^2 in FH^-/PKD1/PKD2. Acute and chronic eGFR changes (part *e*, Item S1) and changes in UAE (fig *b*, Item S1; $P = 0.1$) were not significantly different. There were also no significant differences in baseline height-adjusted liver volumes (table *b*, Item S1). The older patient age at the time of ADPKD diagnosis in FH^-/NMD patients suggested milder disease (table *b*, Item S1).

Assessment of FH^- relies on each patient's personal and family history, renal imaging, and genetic analyses. Unlike Reed et al[1] and Iliuta et al,[3] we were unable to examine the parents of our trial participants. In a recent study, after extensive investigation of the parents of 209 patients with PKD, there were 58 FH^- patients: 32 (15.3%) had a de novo mutation, 22 (10.5%) still had indeterminate family history, and 4 (1.9%) had an FH^+ in retrospect.[3] Uniquely, our study provides longitudinal data on the course of FH^-/NMD patients, showing that they have evidence of slower disease progression. These results developed in a controlled clinical trial that eliminated a confounding effect from uncontrolled hypertension (part *a*, Item S1).[2] Because our criteria focused on ADPKD,[8] we believe that we minimized the inclusion of atypical cases of PKD with FH^{-2} that were less likely to be ADPKD.[3]

However, the onset of ADPKD in FH⁻/NMD patients could appear delayed when compared to its onset in FH⁻/PKD1/PKD2 patients if the latter group had predominantly de novo PKD1 mutations. Among our 52 FH⁻/PKD1/PKD2 patients, 48 (92.3%) had a presumed de novo PKD1 mutation, similar to results of others who reported that PKD1 mutations were more common in de novo disease.[1,3] The de novo PKD1 mutations in FH⁻/PKD1/PKD2 patients could have been responsible for more rapid disease progression and an earlier ADPKD diagnosis despite being FH⁻.

In summary, 17 FH⁻/NMD patients with clinically documented ADPKD had a lower annual increase in TKV and htTKV over 60 months, consistent with slower disease progression. This subset of ADPKD patients and their biological parents might be a rewarding group for study with advanced genetic techniques capable of determining with next-generation sequencing if there were undetected mutations at known loci, a new ADPKD locus, a de novo mutation, and/or mosaicism.[5,9]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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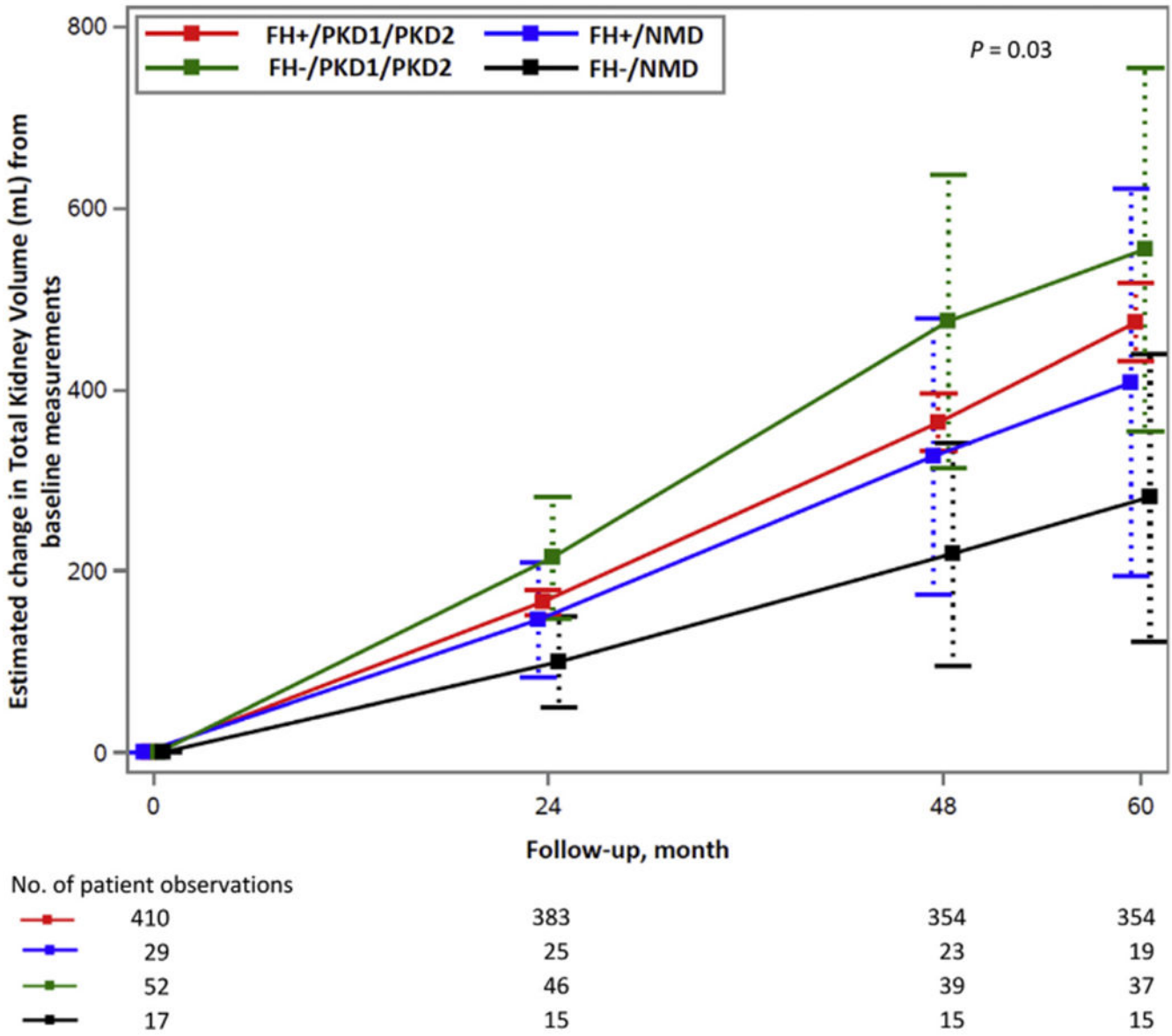

Figure 1.

Estimated change in TKV from baseline measurements in 4 patient groups during 60 months of follow-up with 95% confidence intervals. Across patient groups there was a significant difference in the increase in TKV ($P = 0.03$), with FH^{-}/NMD patients lowest.

Table 1.

Estimated Mean Change in TKV From Baseline Measurements in 4 Patient Groups During 60 Months of Follow-up With 95% Confidence Intervals

	Model Estimated Value at Baseline, mL	Change From Baseline, mL		
		24 mo	48 mo	60 mo
FH^+/PKD1/PKD2	1,210.68	165.32	364.01	474.11
Lower 95% CI	1,105.73	151.65	332.11	431.08
Upper 95% CI	1,331.21	179.00	395.91	517.14
FH^+/NMD	1,093.69	146.10	326.25	407.43
Lower 95% CI	1,000.32	79.45	166.09	180.44
Upper 95% CI	1,195.82	212.76	486.41	634.42
FH^-/PKD1/PKD2	1,353.09	214.70	474.83	554.60
Lower 95% CI	1,239.09	145.86	308.45	348.58
Upper 95% CI	1,477.62	283.54	641.21	760.61
FH^-/NMD	1,061.59	99.67	218.62	280.71
Lower 95% CI	972.22	44.53	84.67	107.79
Upper 95% CI	1,159.19	154.82	352.57	453.63

Note: P = 0.03. See part *c*, Item S1 for statistical methods and for the formula used to convert per-month slopes into annual percentage changes.