Adult-Diagnosed Nonsyndromic Nephronophthisis in Australian Families Caused by Biallelic *NPHP4* Variants

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There is increasing appreciation of nephronophthisis (NPHP) as an autosomal recessive cause of kidney failure and earlier stages of chronic kidney disease among adults. We identified 2 families with presumed adult-diagnosed nonsyndromic NPHP and negative diagnostic genetic testing results from our Renal Genetics Clinic. Both had 2 affected siblings without extrarenal phenotypes. After informed consent, research whole-genome sequencing was undertaken. Biallelic *NPHP4* variants were identified *in trans* and clinically confirmed in all 4 affected individuals, confirming a genetic diagnosis. Participant 1 of the first family (F1P1) had kidney failure diagnosed at 19 years of age. An affected younger sibling (F1P2) reached kidney failure at age 15 years after kidney biopsy suggested NPHP. Pathogenic variants detected in *NPHP4* in this family were NM_015102.4:c.3766C>T (p.Gln1256*) and a 31-kb deletion affecting exons 12 to 16. In the second family, F2P3 reached kidney failure at age 27 years having undergone kidney biopsy suggesting NPHP. An affected younger sibling (F2P4) has chronic kidney disease stage 4 at age 39 years. The *NPHP4* variants detected were NM_015102.4:c.1998_1999del (p.Tyr667Phefs*23) and c.3646G>T (p.Asp1216Tyr). The latter variant was initially missed in diagnostic sequencing due to inadequate *NPHP4* coverage (94.3% exonic coverage). With these reports, we identify *NPHP4* as an appreciable genetic cause for adult-diagnosed nonsyndromic NPHP that should be considered by adult nephrologists.

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Introduction

Nephronophthisis (NPHP) is a ciliopathy and the most common genetic cause of chronic kidney disease (CKD) in children, exhibiting an autosomal recessive pattern of inheritance.[1-4] Three clinical spectra have been described stratified by age: infantile, juvenile, and adolescent, with mean ages of onset of 1, 13, and 19 years, respectively.[4,5] Kidney failure generally occurs within the first 2 to 3 decades of life.[2] The occurrence of NPHP in adult patients has been reported,[6] though prevalence among adult patients with kidney failure has been underappreciated.[7]

Nephrocystin proteins encoded by NPHP genes localize to the primary cilia, basal bodies, and centrosomes.[1,4,8-10] *NPHP* variants result in impaired ciliary function.[11] NPHP is characterized clinically by impaired sodium reabsorption and urinary concentrating ability, bland urinalysis, and chronic tubulointerstitial nephritis.[2] The disease may be isolated to the kidneys or may involve other organs (eg, liver, pancreas, central nervous system, eyes, and bones), with syndromic forms of NPHP having multiple eponymous descriptions.[11]

A major challenge of NPHP and related ciliopathies is phenotypic variability and genetic heterogeneity.[11] Pathogenic variants in at least 20 different genes (*NPHP1*-*NPHP20*) have been identified,[4] with these variants causing complex multiorgan disorders or isolated renal phenotypes.[11] Although *NPHP3*- *NPHP20* variants are established as disease associated, data are still insufficient to generate solid allelic or genotype-phenotype correlations. *NPHP4* is located on chromosome 1p36 and encodes nephrocystin 4.[1] We postulate that the clinical presentation associated with *NPHP4* variants may not uncommonly be restricted to a renal phenotype with later onset and slower progression to kidney failure. Further, greater consideration of the diagnosis of NPHP in adults with nonsyndromic kidney failure or advanced CKD with a similar phenotype to autosomal dominant tubulointerstitial kidney disease, albeit with a sporadic or autosomal recessive pedigree, is indicated.

Case Reports

We describe 2 families diagnosed with adolescent nonsyndromic NPHP. All affected participants were assessed for extrarenal manifestations, particularly retinal and hepatic, with none being apparent. Detailed methods are provided in Item S1 and an overview of the workflow is given in Figure S1.

Family 1

The first family included 2 male siblings with NPHP diagnosed at 19 and 14 years of age, respectively (Fig 1A). Participant 1 (F1P1) reached kidney failure at 19 years of age and received a living related donor kidney transplant a year later. Initial clinical genetic testing returned a single heterozygous variant in *NPHP4*, NM_015102.4:c.3766C>T (p.Gln1256*). This variant, a cytosine to thymidine substitution at nucleotide 3,766 that is predicted to lead to the glutamine at amino acid 1,256 being replaced by a stop codon (and thus prematurely terminating the protein), is pathogenic (class 5) in the classification system of the American College of Medical Genetics (ACMG). Chromosomal microarray or other copy number variant analysis was not undertaken.

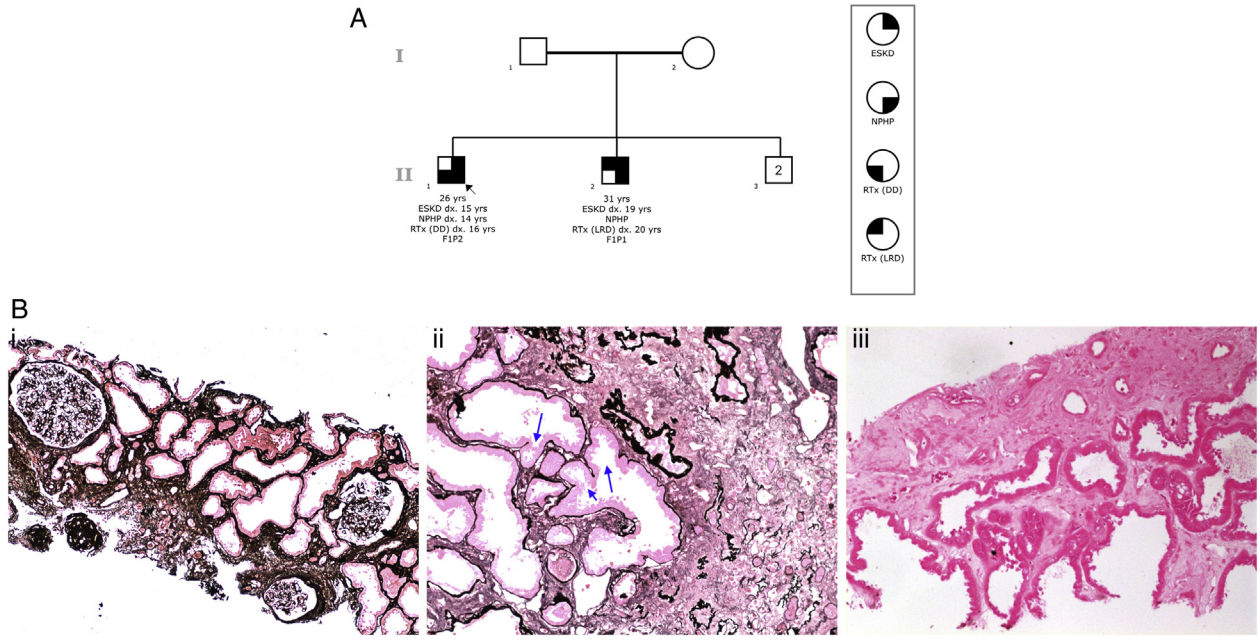

Figure 1. Family 1. (A) Pedigree. (B) Kidney biopsy histopathology (family 1 participant 2 [F1P2]): (i) generalized and established interstitial fibrosis (periodic acid–silver methenamine stain; original magnification, ×100); (ii) complex tubular profiles with diverticular outpouchings (arrows) in nonatrophic tubules and adjacent tubular atrophy (periodic acid–silver methenamine stain; original magnification, ×200); and (iii) cystic dilatation of some tubules (hematoxylin and eosin stain; original magnification, ×200). Abbreviations: dx, diagnosed at; ESKD, end-stage kidney disease; NPHP, nephronophthisis; RTx (DD), renal transplant, deceased donor; RTx (LRD), renal transplant, living related donor.

The participant's affected younger brother (F1P2) had CKD diagnosed at 14 years of age, with kidney biopsy being suggestive of NPHP, revealing generalized established interstitial fibrosis with 40% of glomeruli showing obliteration (Fig 1B-i). Several tubules showed irregular tubular profiles with diverticular outpouchings (Fig 1B-ii.). There was also prominent tubular dilatation and epithelial atrophy in the distal nephron segments, including cystic dilatation of some tubules (Fig 1B-iii.). He subsequently progressed to kidney failure at age 15 years and underwent deceased donor kidney transplantation at age 16 years.

For both affected brothers, research genomic sequencing identified compound heterozygous *NPHP4* variants *in trans*. These included the previously identified heterozygous variant (NM_015102.4:c.3766C>T (p.Gln1256*)), as well as a 31-kb deletion of *NPHP4* exons 12 to 16 (1p36.31:5951836_5982747del), which was also classified as pathogenic (ACMG class 5; Fig S2). This second variant was confirmed on chromosomal microarray by the original diagnostic genetic laboratory as being disease causing in concert with the previously identified *NPHP4* pathogenic variant. Together, this was then disclosed as a positive diagnostic result with further genetic counseling.

Family 2

The second family consisted of a brother and sister with NPHP diagnosed at 26 and 39 years of age, respectively (Fig 2A). The brother (F2P3) reached kidney failure at age 27 years and underwent a deceased donor kidney transplantation at age 28 years. His kidney biopsy specimen was suggestive of NPHP, with 4 of 12 examined glomeruli being globally sclerosed in the setting of periglomerular fibrosis, moderate tubular atrophy, some tubular dilatation, patchy interstitial fibrosis, and chronic interstitial inflammation (Fig 2B-i and ii.). Areas of tubular basement membrane thickening and crowding of epithelial nuclei were also present (Fig 2B-iii.). Clinical genetic testing identified a heterozygous pathogenic (ACMG class 5) variant in *NPHP4*, NM_015102.4:c.1998_1999del (p.Tyr667Phefs*23), which corresponds to a deletion of nucleotides 1,998 and 1,999 in the coding sequence, leading to a frameshift starting with the substitution of tyrosine to phenylalanine at amino acid 667 and ending in a termination codon 23 residues downstream. Overall, 94.3% of the exonic sequence had a minimum read depth of 20×, but 4 regions of *NPHP4* had inadequate sequence coverage.

The brother's affected younger sister (F2P4) had CKD stage 4 diagnosed at age 39 years. Research genomic sequencing identified compound heterozygous *NPHP4* variants, NM_015102.4:c.[1998_1999del];[3646G>T] (p.[Tyr667Phefs*23];[Asp1216Tyr]), in both affected siblings. The variant that had not been detected with clinical genetic testing is a guanosine to thymidine substitution at nucleotide 3,646 of the coding sequence, predicted to lead to an aspartate to tyrosine substitution at

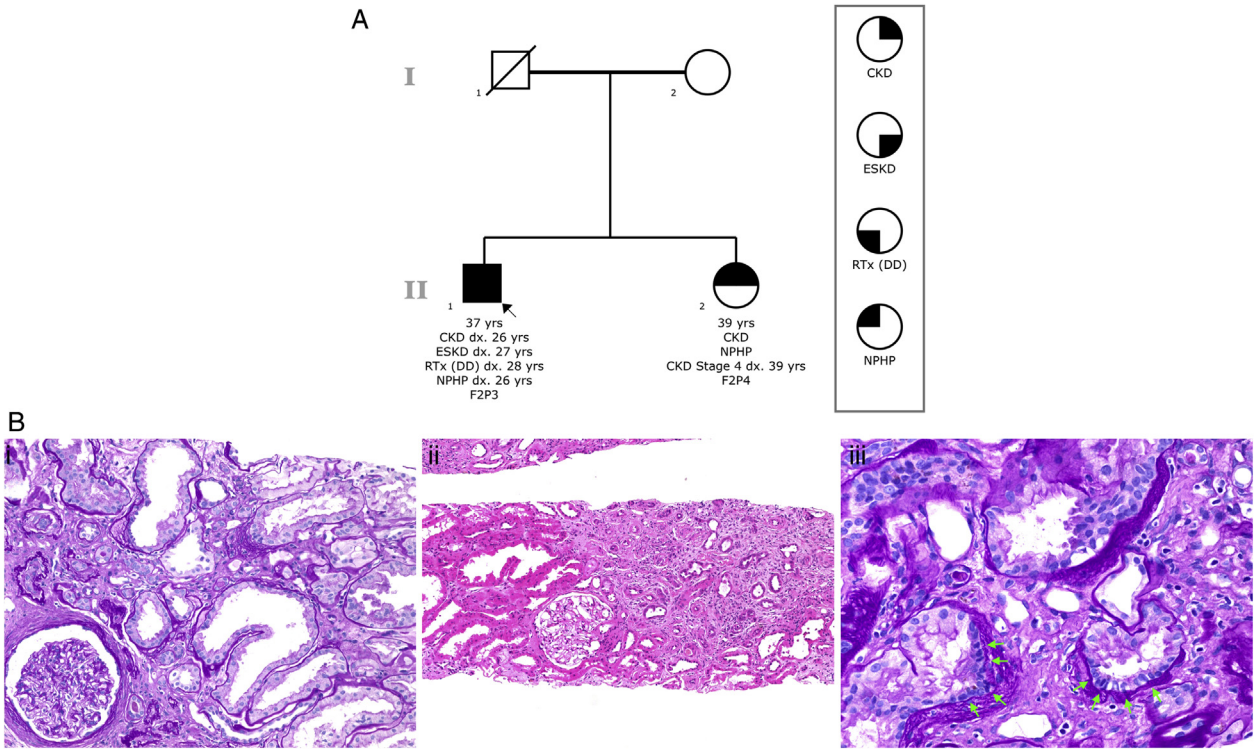

Figure 2. Family 2. (A) Pedigree. (B) Kidney biopsy histopathology (family 2 participant 3 [F2P3]): (i) periglomerular fibrosis, moderate tubular atrophy, and some tubular dilatation (periodic acid–silver methenamine stain; original magnification, ×200); (ii) patchy interstitial fibrosis and chronic interstitial inflammation (hematoxylin and eosin stain; original magnification, ×100); and (iii) irregular tubular basement membrane thickening with nuclear crowding in overlying tubular epithelium (arrows) (periodic acid–Schiff stain; original magnification, ×400). Abbreviations: CKD, chronic kidney disease; dx, diagnosed at; ESKD, end-stage kidney disease; NPHP, nephronophthisis; RTx (DD), renal transplant, deceased donor.

amino acid 1,216. This single-nucleotide substitution is of uncertain pathogenic significance (ACMG class 3) and is located in 1 of the 4 *NPHP4* sequence gaps that had previously been identified. It is not present in unaffected population variant databases, is evolutionarily conserved in vertebrates, and is predicted *in silico* (by the SIFT, PolyPhen, MutationTaster, and PROVEAN tools) to have a deleterious effect on protein function. This second *NPHP4* variant was confirmed and reported using Sanger sequencing by the original diagnostic genetic laboratory in concert with the previously identified *NPHP4* pathogenic variant. This information was then disclosed as a likely positive diagnostic result with further genetic counseling.

In summary, biallelic *NPHP4* variants were identified *in trans* and clinically confirmed in all 4 affected individuals from both families, thus confirming a genetic diagnosis. In both families, the preceding clinical diagnosis in early adulthood of nonsyndromic NPHP had been identified initially based on: (1) 2 affected individuals per family, raising suspicion of kidney disease heritability; (2) family history compatible with autosomal recessive inheritance; and (3) histopathology of the native kidney demonstrating significant tubulointerstitial disease.

Discussion

Kidney disease is a significant cause of morbidity and mortality worldwide, affecting health service use and costs. NPHP is the most common genetic cause of kidney failure in children and young adults,[1] with an estimated incidence of 1:50,000,[11,12] accounting for 6% to 10% of incident kidney failure and 15% of transplantations among children.[2,3] Early diagnosis, close follow-up, and supportive clinical care strategies around progression to kidney failure and associated complications are the mainstay of its management.[5,8] Until recently, the prevalence of NPHP in adult patients with kidney failure had been underappreciated.[7] A greater consideration of the diagnosis of NPHP in adult kidney failure and progressive CKD populations is required, allowing for timely diagnosis, informed prognostication and referral for transplantation, targeted screening of at-risk family members, and expedited preventative and management strategies of kidney function decline. We have reported 2 families affected by adolescent nonsyndromic NPHP diagnosed in young adulthood due to biallelic variants in *NPHP4*. This has implications for formulating clinical diagnosis in similarly presenting patients, although NPHP has previously been a less-considered differential diagnosis. Further, the context of

these cases and their diagnostic odysseys demonstrate that persistent multidisciplinary intersection and collaboration is key to clinically realizing the promise of genomics in nephrology.

NPHP has significant genetic heterogeneity, with biallelic pathogenic variants in 20 different genes identified as causative[4] and *NPHP1* (20%) being the most common.[4,9,13] NPHP may have renal involvement exclusively or may involve diverse extrarenal manifestations. In particular, it can be associated with renal phenotypes and: (1) retinal degeneration (Senior-Løken syndrome)[14]; (2) cerebellar vermis aplasia/hypoplasia, retinal degeneration, and mental retardation (Joubert syndrome)[15]; (3) retinal degeneration and osseous phenotypes (Mainzer-Saldino syndrome)[16]; (4) skeletal phenotypes (Jeune syndrome); and (5) oculomotor apraxia (Cogan syndrome).[17] NPHP's genetic and clinical phenotype heterogeneity has been a challenge for clinicians,[8,11] with this diversity potentially due to 3 genetic mechanisms: gene locus heterogeneity, allelism, and modifier genes.[10] Phenotypic differences in NPHP, particularly age of presentation, may be a combination of environmental and epigenetic factors, oligogenic inheritance, and modifier genes.[5] Sound genotype-phenotype associations have not been formed due to the lack of data for *NPHP3*-*NPHP20* variants, owing to a combination of autosomal recessive inheritance, small numbers of patients identified, and until recently, limited access to comprehensive sequencing techniques.[11] The variable phenotypic presentations associated with NPHP remain only partially justified by gene locus heterogeneity and the nature of individual variants, with the complete explanation of clinical variety observed in affected individuals, even those within the same family, remaining elusive.[11]

In a registry cohort of 152 children with NPHP observed for a mean of 7.5 ± 6.1 (standard deviation) years, the *NPHP4* subgroup (n = 5) had an older age of diagnosis (average, 12.0 ± 4.4 years), with only 1 developing kidney failure (at age 14 years).[11] These children presented predominately with a restricted renal phenotype of a urinary concentration defect and CKD[11] and suggested later onset and/or slower progression of CKD in comparison to NPHP due to defects in other NPHP-associated genes, albeit this was a small cohort.[11] This aligns with earlier reports of *NPHP4*-related disease associating with kidney failure occurring at age ranges of 6 to 20[1] and 6 to 35[18] years, corresponding to median ages of 12.7 and 22 years, respectively. Another cohort of 250 patients with NPHP included 26 *NPHP4* cases,[3] of whom 13 presented with an isolated renal phenotype. Bakkaloglu et al[5] identified 4 consanguineous siblings affected by a homozygous *NPHP4* pathogenic variant, 2 of whom presented with isolated renal phenotypes, and 2, with the additional extrarenal manifestation of growth retardation. A further case report identified 3 consanguineous siblings[19] with NPHP presenting with a renal-isolated phenotype due to a homozygous *NPHP4* pathogenic variant. Taken together, this supports consideration of *NPHP4* variants in patients presenting in late childhood, adolescence, or young adulthood with nonsyndromic NPHP in which homozygous *NPHP1* deletion has been excluded.[11]

Although almost 50% of cases of NPHP due to biallelic pathogenic *NPHP4* variants develop an extrarenal phenotype,[10] there is clinical variability, and the most commonly reported presentation is an isolated renal phenotype manifesting with insidious progression to kidney failure.[11] All 4 cases reported here have variants in *NPHP4* and presented with such an isolated renal phenotype and later disease onset. NPHP has been thought to progress to kidney failure by adolescence or early adulthood, with the rate of kidney disease progression and extrarenal phenotype being influenced by the underlying genotype.[2] We identified *NPHP4* as an appreciable genetic cause for adult-diagnosed nonsyndromic NPHP, in keeping with previous reports that age of kidney failure extends to adulthood.[1,18] These cases highlight that this diagnosis should be considered among adults presenting with nonsyndromic kidney failure or progressive CKD. Further, this would be of particular interest among patients having a clinical phenotype consistent with tubulointerstitial kidney disease and a family history consistent with autosomal recessive inheritance, heightened if there is an affected sibling or cousin. Proactive inclusion of NPHP within the differential diagnosis of such patients may enable timely disease identification.

Clinical genomics is translating rapidly into health care and nephrology in clinical and research settings.[20] The application of clinical genomics along with in-depth clinical information, such as in these 2 families, builds evidence supporting emerging clinical indications for diagnostic genetic testing among patients with kidney disease. Future comprehensive and longitudinal cohort analysis and outcome evaluation from implementation, economic, and clinical perspectives are indicated to direct evidence-based evolution of genomic nephrology.

There are several limitations inherent with this report. There were a small number of cases identified, albeit this is in the setting of a rare autosomal recessive condition. Additionally, there were technical issues with securing a primary genetic diagnosis within the diagnostic clinical laboratory. However, formal diagnoses were confirmed upon research analysis and then clinical reconfirmation, demonstrating the benefits associated with multidisciplinary care and integrated clinical research teams. This reinforces the need for persistence in pursuing a genetic diagnosis with rapidly advancing technologies, especially when a single pathogenic allele is identified in relationship to a compatible phenotype, and where other variant types might be unappreciated. Many adults presenting with nonsyndromic NPHP are unlikely to undergo kidney biopsy, which given the lack of pathognomonic features means at-risk individuals may not have an underlying genetic condition considered. This makes these cases so unique because despite having autosomal recessive inheritance, these 2 families each had 2 siblings identified with

nonsyndromic NPHP secondary to variants in *NPHP4*. The identification of an affected second sibling prompted consideration of a genetic diagnosis; in the absence of a family history of an affected sibling, it is unlikely that this would have happened. It is possible that earlier genetic diagnosis for the probands may have resulted in different clinical care and management.

CKD is a significant cause of morbidity and mortality worldwide. Although NPHP is the most common genetic cause of CKD in children, its prevalence in the adult population has been underappreciated. With no specific management available, treatment focuses on supportive and preventative strategies to preserve kidney function and early referral for transplantation. Transplantation is the preferred kidney replacement therapy, with no recurrence of NPHP.[8,9] The cases we outline highlight that *NPHP4*-related NPHP predominately manifests with isolated renal phenotypes and older age of disease onset. This report emphasizes the importance of genetic testing when possible to allow for timely and correct diagnosis, enabling appropriate genetic counseling and treatment. Further studies are necessary to determine the extent to which NPHP contributes to kidney disease among adults.

Supplementary Material

Supplementary File (PDF)

Figure S1: Clinical and research genomic study workflow.

Figure S2: *NPHP4* variants identified across both families.

Item S1: Supplementary methods.

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