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Gene mutations analysis in Iranian children with Nephronophthisis: A two-Centre Study

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Abstract

Introduction—Nephronophthisis (NPHP) is the most commonly inherited ciliopathies that leads to end-stage renal disease in children. The *NPHP1* gene is the first identified gene responsible for nephronophthisis and related diseases. This study assessed mutations of the *NPHP1* gene in 16 Iranian families with at least one member presenting features of nephronophthisis.

Method—Fifty-seven patients diagnosed with chronic kidney disease or end-stage renal disease were referred to Imam Hossein Children Hospital, in Isfahan, Iran. The gene analysis study was carried on 16 patients and their first-degree relatives (40 DNA samples) suspicious of having nephronophthisis. The *NPHP1* deletion analysis was performed for exons 5, 7, and 20 of the *NPHP1* gene.

Results—The patients' median age was 15 years. The mean and median age of the first presentation was 10.06± 2.59 years and 10.5 years, respectively. A homozygous deletion was identified in the *NPHP1* gene spanning at least from exon 5 to exon 20 in two families. High-throughput mutation analysis identified a homozygous truncating mutation (c.1504C>T, p.R502*) in the *NPHP5* in 5 families.

Conclusion—By combining *NPHP1* deletion analysis with multiplex-polymerase-chain-reaction based high-throughput mutation analysis we could identify the molecular disease-cause in 7 of 15 families from Iran. In 8 families, the molecular disease cause remained unknown.

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Introduction

Nephronophthisis (NPHP) is the most inherited ciliopathies, manifested as a cystic kidney disease that leads to end-stage renal disease (ESRD) in the early two decades of life [1-4]. Three distinctive clinical presentations of NPHP have been reported by age of onset of ESRD: infantile, juvenile, and adolescent [5-8]. Extra-renal manifestations have been reported in more than 10% of the patients; including cerebellar vermis aplasia (Joubert syndrome; JS), retinal degeneration (Senior-Loken syndrome; SLS), cone-shaped epiphyses, and liver fibrosis [9-13]. Homozygous single-gene mutations/deletions or compound heterozygous mutations may lead to different clinical presentations of NPHP and related ciliopathies [14]. NPHP1 gene is the first identified gene among at least 12 genes responsible for NPHP and related diseases. The gene has been detected by positional cloning [15]. NPHP1 homozygous deletion has been identified in NPHP and related syndromes such as SLS. Limited studies have been reported cases of SLS and JS in Iranian families. However, there is no study on children and adolescents with chronic kidney diseases in Iran to evaluate NPHP1 mutations. In this study, we assessed the mutations of NPHP1 gene as the most frequent gene responsible for NPHP in 16 families with at least one member presenting features of NPHP.

Methods and participants

From December 2011 to January 2013, 57 patients diagnosed as either chronic kidney diseases (CKD) or ESRD were referred to Imam Hossein Children Hospital, Isfahan, Iran. Among them, we identified 16 patients suspicious of having NPHP. The gene analysis study was carried on 16 patients and their first-degree relatives (40 DNA samples). Nine families were native people of the Qeshm Island in the Persian Gulf and seven families were native to the Isfahan province in the central part of Iran. All participants were examined for any possible ophthalmic abnormalities by an expert ophthalmologist. Possible diagnosis of NPHP was based upon meeting the following criteria [14, 16 and 17]:

1. Median age of onset of chronic kidney disease or ESRD in the first or second decade of life.
2. Polyuria and polydipsia (and salt wasting) in early childhood.
3. Urinary concentration defect (less than 400 mosm/kg for fasting urine.
4. Growth retardation (secondary to salt wasting, dehydration, and renal insufficiency)
5. Absence of (or minimal) haematuria and proteinuria
6. Renal ultrasound findings including renal cortical hyperechogenicity, loss of corticomedullary differentiation, and corticomedullary cysts.
7. Renal biopsy; if it was done before reaching ESRD shows interstitial nephritis, tubular atrophy, and tubular dilatations.
8. Presence of extra-renal disorder mentioned in the introduction.

DNA samples were extracted from whole blood. Genomic DNA was extracted from peripheral EDTA-treated samples using Qiagen DNA Mini kit (cat No: 51304) and then was subjected to the PCR amplification.

NPHP1 deletion analysis

NPHP1 deletion analysis was performed using specific primers for exon 5, 7, and 20 of the NPHP1 gene. Exon 4 and 6 of the LHX9 gene served as controls. These 5 primer pairs were used in a multiplex PCR setting with a final concentration of 10 pMol. Exonic DNA was amplified from purified genomic DNA using a two-step PCR protocol with an initial annealing temperature of 72°C for 24 cycles and a decreased annealing temperature of 55°C for the second part of 24 cycles. The PCR products were analyzed on a 1.5% agarose gel. Two control samples with either known presence or absence of an NPHP1 deletion were included as reference.

High-throughput mutation analysis

Using the Fluidigm 48.48-Access Arrays™ system patient samples were screened for mutations in 15 known NPHP genes, as previously described by Halbritter J et al namely NPHP1, INVS, NPHP3, NPHP4, IQCB1, CEP290, GLIS2, RPGRIP1L, NEK8, SDCCAG8, TMEM67, TTC21B, WDR19, ANKS6, and IFT172 [18]. With the use of barcoded multiplex PCR this system allows the simultaneous screening of ~ 600 amplicons in 48 patients in each run. After amplification, samples were pooled and sequenced on an Ilumina next-generation sequencing instrument (MiSeq®). Subsequently, sequence reads were aligned to normal reference sequence using CLC Genomics Workbench™ (CLC-bio, Aarhus, Denmark)[18]. Synonymous variants and single nucleotide polymorphisms with a minor allele frequency above 1% in a heathy control population (NHLBI Exome Sequencing Project (ESP) - Exome Variant Server) were excluded. The remaining variants were validated for their likelihood to explain the disease phenotype considering the severity of the allele (protein-truncating, or splice vs. missense), web-based prediction score systems (PolyPhen-2, SIFT, Mutation Taster), and previous descriptions in the human gene mutational database (biobase HGMD®). All variants were confirmed by Sanger sequencing. With regards to the autosomal-recessive mode of inheritance of NPHP, variants were only considered as disease-causing when they occurred in biallelic state.

Results

Among the patients, seven were from Isfahan and eight were from the Qeshm Island. There was a female preponderance, with female/male ratio of 1.6/1 (6 male and 10 female). The patients' median age was 15 years. The mean age of patients was 15.81± 2.85 years. The mean and median age of the first presentation was 10.06± 2.59 years and 10.5 years, respectively. For the patients from Isfahan and Qeshm Island, the median age of the first presentation was not significantly different (age of 11 and 10, respectively). The mean values of height and weight were 139.18± 24.99 cm and 40.37± 17.61 kg, respectively. The mean values of systolic and diastolic blood pressure were 124.06± 19.08 and 87.81± 11.87

mmHg, respectively. Approximately, 62.5% and 75% of the patients had systolic and diastolic hypertension, respectively.

In four families, at least one other member was affected. Seven patients (43.8%) were diagnosed with symptoms of acute on chronic renal failure. Among the remaining patients, six have been evaluated because of poor weight gain and/or polyuria and polydipsia. Three patients have been diagnosed during routine school examination. However, most patients had polyuria and polydipsia in their past history. Only one patient had edema while demonstrating symptoms of acute on chronic renal failure. None of the patients had mental retardation or liver fibrosis. Ultrasound imaging showed kidney hyper-echogenicity in almost all the patients. However, small-sized kidneys were found in 15 patients (88%). Corticomedullary cysts were reported in seven patients (41%). Five out of 17 patients (30%) had no ophthalmic involvement. Ocular findings are given in Table 1. Significant proteinuria and/or microscopic hematuria were not reported. Laboratory parameters of the participants are tabulated in Table 2.

NPHP1 deletion analysis identified a homozygous deletion in the NPHP1 gene spanning at least from exon 5 to exon 20 in families 008 and 012.

High-throughput mutation analysis identified a homozygous truncating mutation (c. 1504C>T, p.R502*) in NPHP5 (IQCB1) in 5 families (B, C, D, F, G). Interestingly, the exact same allele occurred in two additional families (A, E) in heterozygous state. Since a second allele could not be identified in these two families the molecular disease cause remained unsolved.

Discussion

In this study, we evaluated the incidence of NPHP1 gene mutations in children with CKD who met the criteria of NPHP from two different regions of Iran. To the best of our knowledge, it is the first study in Iran that evaluated NPHP1 mutations in this group of patients.

NPHP is an uncommon but worldwide disease. The incidence of diseases has been reported differently from 1.12 per million populations in the USA to 20 per million populations in Canada [4, 19, and 20]. Unfortunately, the incidence of the disease has not been determined in Iran.

Nephronophthisis-related ciliopathies include heterogeneous diseases that have similar phenotypes irrespective of various gene mutations. The phenotypes include renal cyst, retinal degeneration, and cerebellar agenesis [21]. Up to now, mutations in eight genes (NPHP1-8) have been identified [22]. Nephrocystin that is encoded by NPHP1 has interrelation with components of cell-cell and cell-matrix signaling comprising p130Cas, tensin, and filamin [23-25]. Recently, the ciliary theory has been proposed. This theory explains defects in signaling mechanism involving two pathways; the non-canonical Wnt and sonic hedgehog signaling pathways, which lead to failure in cell polarity and cell preservation. In addition, this theory describes multiple organ involvement in NPHP [26]. Mutation in NPHP1 gene is the most prevalent mutation causes for juvenile type of

nephronophthisis, in which renal failure symptoms are the dominant feature [27]. About 10% of patients show extra-renal manifestations including eye and cerebellar involvement [28]. However, mutation in NPHP5 gene has been defined as the gene responsible for Senior-Loken syndrome, in which retinal degeneration and blindness occur even before the symptoms of renal failure [29].

Although nephronophthisis has been reported at the median age of 1 year (infantile form), most patients present the features of ESRD at a median age of 13-19 years (juvenile and adolescent forms) [5-8, 30]. The median age of our patients at the time of the diagnosis was 10.5 year. Most patients from Qeshm met the criteria of Senior-Loken syndrome. All of them had either blindness or retinitis pigmentosa and retinal dystrophy. Although juvenile NPHP equally affects both sexes, we observed a female predominance [4].

Hypertension is not a common feature of NPHP [31]. We found either systolic or diastolic hypertension in more than half of our patients. Hypertension was commonly detected in the patients who went under dialysis. However, most of these patients did not have the symptoms of fluid overload.

Considering gene deletion, Otto et al. carried out a worldwide cohort study on patients who met the criteria of NPHP. According to their study, the most frequent mutations in NPHP patients were homozygous NPHP1 deletion followed by NPHP5 deletion [22].

Since 20-40% of NPHP patients have NPHP1 mutation, it has been recommended to evaluate suspicious patients firstly for homozygous or heterozygous NPHP1 deletion [31]. The patients with ophthalmic involvement but not having NPHP1 deletion are candidate for analysis for NPHP5 gene mutation [31].

We assessed all patients suspicious for NPHP1 mutations. Nevertheless, we did not find NPHP1 deletion in any patients from Qeshm. By using high-throughput mutation analysis a homozygous truncating mutation (c.1504C>T, p.R502*) in NPHP5 (IQCB1) in 5 families (B, C, D, F, G) were identified. Furthermore, in two additional families (A, E) the exact same allele occurred in heterozygous state. Since a second allele could not be identified in these two families the molecular disease cause remained unsolved.

Interestingly, almost all patients from Qeshm had blindness or retinal pigmentation. However, two patients from Isfahan had homozygous NPHP1 mutation (approximately 28% of Isfahanian patients). In a similar study, Soleiman et al. evaluated 20 children from 17 unrelated families and showed NPHP1 deletion in 29.4% of the patients [32]. Using combined approach of DNA pooling followed by massively parallel re-sequencing (MPR) ascertained gene mutations in approximately 25% of NPHP patients [33]. Irrespective of sensitivity of this method, mutation was not found in 75% of patients; declaring wide heterogeneity in NPHP [33].

Although three published studies in Iran have assessed gene mutations in familial cases with ciliopathy-related diseases (Senior-Loken and Jubert syndromes), no one has evaluated NPHP1 gene deletion in unrelated patients with NPHP phenotype and chronic kidney disease [34-36].

Our study demonstrated a frequency of 28% for NPHP1 gene deletion in patients with NPHP phenotype without ophthalmic involvement.

Conclusion

By combining NPHP1 deletion analysis with multiplex-PCR based high-throughput mutation analysis we could identify the molecular disease-cause in 7 out of 15 families from Iran. In 8 families the molecular disease cause remained unknown.

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Table 1

Ophthalmic findings of the participants.

Ocular finding	***Frequency/percentage in Qeshm***	***Frequency/Percentage in Isfahan***	***total***
Optic atrophy	6 (37.5%)	5 (31.2%)	68.75%
Narrowed retinal vessels	9 (56.2%)	7	100%
Pigmented spot	9 (56.2%)	5 (31.2%)	87.5%
Choroidal atrophy	7 (43.7%)	5 (31.2%)	75%
Generalized depigmentation	6 (37.5%)	4 (25%)	62.5%
Decreased visual acuity	2 (12.5%)	3 (18.75%)	31.2%
Blindness	7 (43.7%)	0	43.7%
Refractory error	0	3 (18.75%)	18.7%

Table 2

Laboratory findings of the participants.

Laboratory Parameter	**Minimum**	**Maximum**	**Mean**	**SD**
Creatinine *mg/dl*	1.3	6.7	3.2	2.37
Albumin *gm/dl*	3.6	4.5	4.01	0.29
Glomerular filtration rate *ml/min/1.73m*^{2}	15	80	40.06	25.52
Hemoglobin *gm/dl*	6.5	11	8.58	1.46
Calcium *mg/dl*	7.80	9.50	8.56	0.46
Phosphorus *mg/dl*	2.5	8	4.96	1.42
Serum bicarbonate *meq/l*	13	19	15.06	1.56
24-h urine protein *mg/l*	45	350	138.31	75.33
Fasting urine specific gravity	120	360	230	74.38
AST *mg/dl*	10	33	21.5	6.58
ALT *mg/dl*	11	40	23.75	8.2

Table 3

Clinical and genetic characteristics of the participants.

label for genetic study	Family	gender	Age (year)	Age at onset (year)	Initial presentation	Ophthalmic signs	Modality	Cysts on ultrasound	histopat hology	*NPHP 1* homozygous deletion
A	A5225	female	12	4	AOC/ P&P	RP	HD	+	ND	No
B	A5226	female	15	12	AOC	RP/RD	HD	−	ND	No
C	A5227	Male	20	10	P&P/D P/GD	RD	KTx	+	ND	No
D1	A5228-111	female	15	8	P&P	RP	mRRT	+	ND	No
D2	A5228-112	female	22	7	AOC	RP	KTx	+	ND	No
E	A5229	female	14	11	P&P/ GR	RD	HD	−	ND	No
F	A5230	male	16	12	AOC	RP/RD	HD	+	ND	No
G	A5231	female	20	10	AOC	RD	KTx	−	ND	No
006	A5232	female	16	11	P&P/G D	RP	KTx	+	Yes	No
007	A5233	female	17	12	P&P/D P/GD	RFD	mRRT	+	Yes	No
008	A5234	male	12	7	P&P	RFD	mRRT	+	Yes	Yes
009	A5235	male	15	14	AOC	RFD	mRRT	+	yes	No
011	A5236	male	14	10	P&P/ DP	RP/RD	mRRT	+	yes	No
012	A5237	female	17	14	AOC	RFD	KTx	+	ND	Yes
013	A5238	male	12	11	AOC	RP	HD	−	ND	No
014	A5239	female	15	6	P&P/G D	RFD	PD	+	Yes	No

A to G are families from Qeshm and 006 to 014 are families from Isfahan province. mRRT: medical renal replacement therapy, RTx: renal transplantation, HD: hemodialysis, PD: peritoneal dialysis, ND: not done. Histopathological triad: tubular basement membrane thickening and disruption, interstitial infiltration and fibrosis, and tubular atrophy and dilatation with or without cyst formation. P&P: polyuria and polydipsia, DP: delayed puberty, GR: growth retardation, RP: retinitis pigmentosa, RD: retinal dystrophy, RFD: Refractory disturbances, AOC: acute on chronic renal failure.