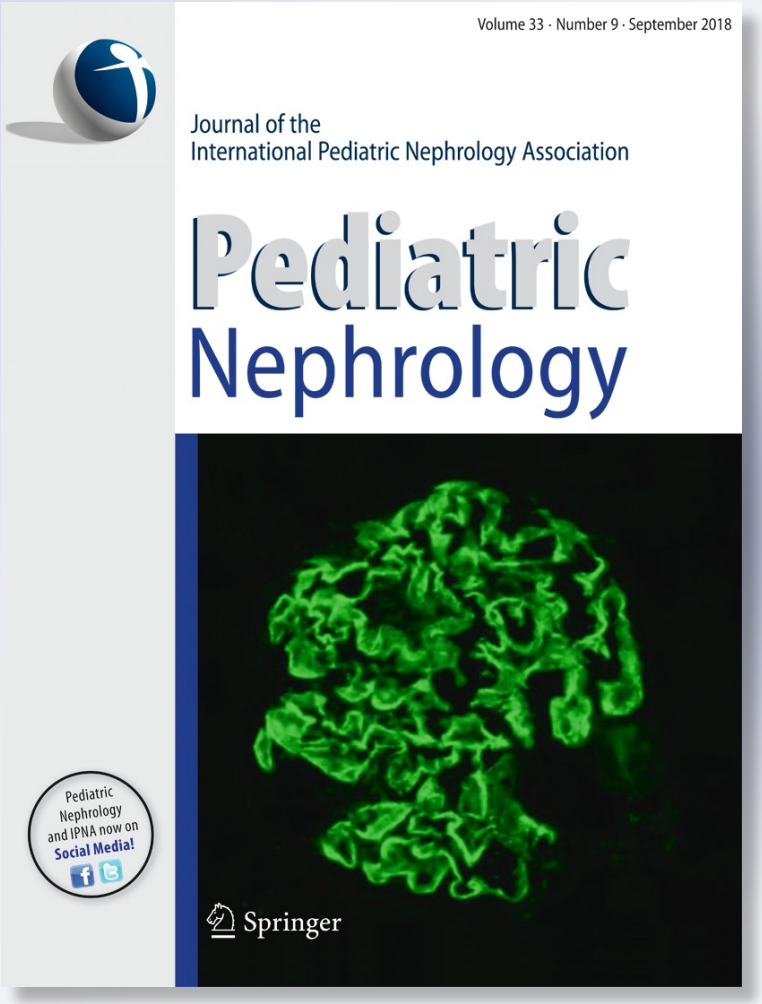
Distal renal tubular acidosis. Clinical manifestations in patients with different underlying gene mutations

RenalTube Group

Pediatric Nephrology
Journal of the International Pediatric Nephrology Association

ISSN 0931-041X
Volume 33
Number 9

Pediatr Nephrol (2018) 33:1523-1529
DOI 10.1007/s00467-018-3965-8



Springer

Pediatric Nephrology (2018) 33:1523–1529
https://doi.org/10.1007/s00467-018-3965-8

ORIGINAL ARTICLE

Distal renal tubular acidosis. Clinical manifestations in patients with different underlying gene mutations

Marta Alonso-Varela[1] · Helena Gil-Peña[1,2,3] · Eliecer Coto[1,3,4] · Juan Gómez[3,4] · Julián Rodríguez[1,2,3] · Enrique Rodríguez-Rubio[1] · Fernando Santos[1,2,3] · RenalTube Group

Received: 24 January 2018 / Revised: 28 March 2018 / Accepted: 6 April 2018 / Published online: 3 May 2018

Abstract

Background To evaluate whether there are differences in the phenotype of primary distal renal tubular acidosis (dRTA) patients according to the causal defective gene.

Methods Twenty-seven non-oriental patients with genetically confirmed dRTA were grouped according to the identified underlying mutations in either *ATP6V1B1* ($n = 10$), *ATP6V0A4* ($n = 12$), or *SLC4A1* ($n = 5$) gene. Demographic features, growth impairment, biochemical variables and presence of deafness, nephrocalcinosis, and urolithiasis at diagnosis were compared among the three groups.

Results Patients with *SLC4A1* mutations presented later than those with *ATP6V1B1* or *ATP6V0A4* defects (120 vs. 7 and 3 months, respectively). Hearing loss at diagnosis was present in the majority of patients with *ATP6V1B1* mutations, in two patients with *ATP6V0A4* mutations, and in none of cases harboring *SLC4A1* mutations. Serum potassium concentration (X ± SD) was higher in *SLC4A1* group (3.66 ± 0.44 mEq/L) than in *ATP6V0A4* group (2.96 ± 0.63 mEq/L) ($p = 0.046$). There were no differences in the other clinical or biochemical variables analyzed in the three groups.

Conclusions This study indicates that non-oriental patients with dRTA caused by mutations in the *SLC4A1* gene present later and have normokalemia or milder hypokalemia. Hypoacusia at diagnosis is characteristically associated with *ATP6V1B1* gene mutations although it may also be present in infants with *ATP6V0A4* defects. Other phenotypical manifestations do not allow predicting the involved gene.

Keywords Distal renal tubular acidosis · Genetic analysis · ATP6V1B1 · ATP6V0A4 · SLC4A1

Abbreviations and acronyms

dRTA	distal renal tubular acidosis
ATP6V0A4	ATPase H+ transporting V0 subunit A4
ATP6V1B1	ATPase H+ transporting V1 dubunit B1
SLC4A1	Solute carrier family 4 member 1

✉ Helena Gil-Peña
hgilpena@gmail.com

[1] University of Oviedo, Oviedo, Spain

[2] AGC de Pediatría, Hospital Universitario Central de Asturias, 33011 Oviedo, Spain

[3] Instituto de Investigación Sanitaria del Principado de Asturias (ISPA), Oviedo, Spain

[4] AGC Laboratorio – Genética, Hospital Universitario Central de Asturias, Oviedo, Spain

Introduction

Type 1, distal renal tubular acidosis (dRTA) is a rare disorder characterized by persistent hyperchloremic, normal plasma anion gap, and metabolic acidosis in the presence of inappropriately high urinary pH and low urinary excretion of ammonium [1]. dRTA is caused by inability of the α-intercalated cells of the collecting tube to acidify the urine. Proximal leak of bicarbonate does not occur, and glomerular filtration rate is characteristically normal [2].

In children, dRTA is usually primary, common presenting manifestations being growth retardation, vomiting and dehydration, loss of appetite, diarrhea or constipation, and polyuria [3]. Hypokalemia is often found and may lead to weakness and paralysis [4]. The association of hypocitraturia and elevated urine calcium excretion leads to nephrocalcinosis and increased risk of urolithiasis [5].

Primary dRTA results from genetic defects, the most frequently implicated genes being *ATP6V1B1*, located at chromosome 2 (2p13.3), and *ATP6V0A4*, at chromosome 7 (7q33-34), which, respectively, encode the B1 and A4 subunits of the H^+-ATPase of the α-intercalated cells [6]. The B1 isoform of the H^+-ATPase V1 domain is also expressed in the inner ear cells [7]. Loss of function mutations in *ATP6V1B1* and *ATP6V0A4* genes causes early onset and severe forms of autosomal recessive dRTA [8]. The *SLC4A1* gene, located at chromosome 17 (17q31.21), codifies the exchanger Cl^-/$HCO3^-$ (AE1) placed on the basolateral surface of α- intercalated cells and in erythrocyte membrane. Mutations in *SLC4A1* gene cause a milder form of dRTA that follows an autosomal dominant inheritance and often presents in adulthood [9–11], thereby few pediatric cases have been reported. Autosomal recessive dRTA caused by mutations in *SLC4A1* gene have particularly been described in Asian people in association with ovalocytosis and spherocytosis [12–14]. Recently, recessive missense mutations in *FOXI1* gene, encoding the transcription factor FOXI1 that regulates a group of membrane transport proteins in the collecting duct, have been found in two unrelated consanguineous families as responsible of sensorineural deafness and dRTA [15].

We used the RenalTube database [16] to better characterize the phenotypical spectrum of primary dRTA caused by *ATP6V1B1*, *ATP6VOA4*, or *SLC4A1* gene defects and find out whether clinical and/or biochemical manifestations might help differentiate these three types of dRTA.

Material and methods

Patients

Twenty-seven pediatric patients with primary dRTA aged from 1 month to 15 years (18 males) and corresponding to 25 families were selected from the RenalTube database and grouped according to the underlying genetic defect as follows: *ATP6V1B1*, *ATP6V0A4*, and *SLC4A1* groups. Sex, age, presenting manifestations, family history, biochemical data, and image studies at diagnosis were analyzed and compared.

Metabolic acidosis was diagnosed by a blood pH < 7.35 and/or serum bicarbonate concentration < 22 mEq/L. Hyperchloremia was defined by serum chloride values > 105 mEq/L, and hypokalemia was defined by serum potassium < 3.5 mEq/L. A urinary acidification defect was diagnosed by urinary pH > 5.5 in the presence of metabolic acidosis. Hypercalciuria was defined by calcium/creatinine ratio > 0.8 mg/mg in infants aged between 1 and 6 months, > 0.6 mg/mg in those aged 6–12 months, > 0.47 mg/mg in children of 1 year of age and > 0.22 mg/mg in those aged > 2 years [17]. The diagnosis of hypocitraturia was made when first morning urine citrate/creatinine ratio was < 400 mg/g. Fractional excretion of potassium (FEK) was calculated by the formula: (urine potassium × serum creatinine/serum potassium × urine creatinine) × 100.

Mutations of *ATP6V1B1*, *ATP6V0A4*, and *SLC4A1* genes were identified by next-generation sequencing (NGS) and validated by Sanger sequencing, as described [18].

Statistical analysis

Comparisons among the three groups were performed using SPSS software (SPSS V15.0 Windows). Age at diagnosis and Ca/Cr ratio were expressed as median and interquartile range for being not normal quantitative variables and were compared by non-parametric Kruskal-Wallis test. The normal quantitative variables, expressed as mean and standard deviation ($X \pm SD$), were compared using one-way Anova. χ^2 Pearson or the Fisher exact test was used to relate categorical variables. *P* values lower than 0.05 were considered statistically significant. Height and weight were represented graphically as boxplots (median and interquartile).

Results

Table 1 shows the demographic, clinical, and genetic data of the three groups of patients: 10, 12, and 5 cases harboring mutations in *ATP6V1B1*, *ATP6V0A4*, *SLC4A1* genes, respectively. Patients with *ATP6V1B1* or *ATP6V0A4* gene mutations (I.1-XX.1) were diagnosed earlier ($p < 0.002$) than patients with *SLC4A1* mutations (XXI.1-XXV.1), median ages being 7 (30) months for *ATP6V1B1*, 3 (9) months for *ATP6V0A4*, and 120 (60) months for *SLC4A1* patients. No differences were found in height and weight among groups (Figs. 1 and 2).

Hearing loss was recognized in eight children with *ATP6V1B1* mutations and two children with *ATP6V0A4* mutations. None of the *SLC4A1* patients had sensorineural hearing impairment.

Diagnostic laboratory tests are shown in Table 2. Differences were only found for serum potassium, higher in*SLC4A1* than *ATP6V0A4* patients ($p = 0.046$).

Discussion

This study provides interesting findings useful for the diagnosis and phenotypical characterization of primary dRTA. Few publications [18–21], such as those of Palazzo et al. [20] and Besouw et al. [22] recently reported, have compared the clinical manifestations of pediatric patients with dRTA classified according to the underlying genetic defect. Among the patients here presented, ten had mutations in the*ATP6V1B1* gene. Five of these children

Table 1 Demographic and clinical features of the three groups of patients at diagnosis

	Age (Months)	Sex	Ethnic Background	Weight (SDS)	Height (SDS)	NC	NL	Hearing loss	Inheritance	Mutations
Group *ATP6V1B1*										
I.1	2	M	A	–	–	–	–	–	Homozygous	c.1228 in. C; p.I386Hfs.
II. 1	10	F	A	–	–	Yes	No	Yes	Homozygous	c.1228 in. C; p.I386Hfs.
III.1	60	M	A	− 3.16	− 6.66	Yes	No	Yes	Homozygous	c.1228 in. C; p.I386Hfs.
III.2	1	F	A	+ 0.73	+ 0.04	No	No	Yes	Homozygous	c.1228 in. C; p.I386Hfs.
IV.1	13	F	A	− 3.43	− 1.73	Yes	No	No	Homozygous	c.1228 in. C; p.I386Hfs.
V.1	22	M	C	− 3.05	− 3.87	–	–	Yes	Homozygous	g.70960079; Intron 6 + 1 G > A, Splicing
VI.1	2	M	C	–	–	No	No	Yes	Homozygous	g.70960079; Intron 6 + 1 G > A, Splicing
VII.1	5	M	C	− 4.03	− 4.41	Yes	No	Yes	Compound heterozygous	g.70960079; Intron 6 + 1 G > A,Splicing / c.1061 G > A; p.E330K
VIII.1	60	F	C	− 1.39	− 2.21	Yes	Yes	Yes	Homozygous	g.70960079; Intron 6 + 1 G > A, Splicing
VIII.2	1	M	C	− 0.49	+ 1.09	Yes	No	Yes	Homozygous	g.70960079; Intron 6 + 1 G > A, Splicing
Group*ATP6V0A4*										
IX.1	36	M	C	− 0.80	− 0.83	No	No	No	Homozygous	c.1629 C > T; p.R449H
X.1	17	M	C	− 1.45	− 2.12	No	No	No	Homozygous	c.2224 del C; p. A647Vfs.
XI.1	3	F	H	− 2.43	− 2.87	Yes	No	No	Compound heterozygous	c. 2648 T > G; p.T789P / c. 837 A > G; p.F185S
XII.1	1	M	C	− 0.74	+ 4.38	Yes	No	No	Compound heterozygous	c. 592 in. T; p.L103Lfs. / g. 138,418,879; Intron 16 + 2 in. A, Splicing
XIII.1	1	F	A	–	–	Yes	No	No	Homozygous	c. 1111 del TGTT; p.Q276Qfs.
XIV.1	4	M	C	+ 1.73	− 5.92	Yes	Yes	No	Compound heterozygous	c. 1789 A > T; p.Y502X / g. 138,418,879; Intron 16 + 2 in. A, Splicing
XV.1	1	F	C	+ 1.51	+ 1.57	Yes	No	No	Compound heterozygous	c. 1789 A > T; p.Y502X / g. 138,418,879; Intron 16 + 2 in. A, Splicing
XVI.1	3	M	C	–	–	Yes	No	No	Compound heterozygous	c 1468 del G; p.P395Pfs. / c. 2540 G > A; p.Q753X
XVII.1	3	M	C	− 1.95	− 1.00	Yes	No	No	Homozygous	c 1468del G; p.P395Pfs.
XVIII.1	2	M	H	− 3.66	− 3.62	Yes	No	No	Homozygous	c. 2223 del G; p.A647Vfs.
XIX.1	12	M	H	–	–	Yes	Yes	Yes	Homozygous	c. 300 C > T; R6Qfs.
XX.1	1	M	C	–	–	Yes	Yes	Yes	Compound heterozygous	g. 138,444,625; Intron 7–2 T > C, Splicing / g.138418879;Intron 16 + 2 in. A, Splicing
Group*SLC4A1*										
XXI.1	96	F	C	− 1.13	+ 0.17	Yes	No	No	Heterozygous	c.1981C > T; p.G609R
XXII.1	120	M	C	− 0.59	− 0.44	Yes	No	No	Heterozygous	c.1922 C > T; p.R589H
XXIII.1	156	M	C	− 1.88	− 2.82	Yes	Yes	No	Heterozygous	c.1922 C > T; p.R589C
XXIV.1	180	F	C	− 0.11	− 1.04	Yes	No	No	Heterozygous	c.1922 C > T; p.R589C
XXV.1	120	M	C	− 1.11	− 1.66	Yes	No	No	Heterozygous	c.1981 C > T; p.G609R
Total *ATP6V1B1*	7 (30)	M/F: 6/4	A/C/H: 5/5/0	− 2.11 ± 1.76	− 2.53 ± 2.67	Y/N/U: 6/2/2	Y/N/U: 1/7/2	Y/N/U: 8/1/1		
Total *ATP6V0A4*	3 (9)	M/F: 9/3	A/C/H: 1/8/3	− 0.93 ± 1.73	− 1.08 ± 3.04	Y/N/U: 10/2/0	Y/N/U: 3/9/0	Y/N/U: 2/10/0		
Total *SLC4A1*	120 (60)[a]	M/F: 3/2	A/C/H: 0/5/0	−0.96 ± 0.66	−1.16 ± 1.15	Y/N/U: 5/0/0	Y/N/U: 1/4/0	Y/N/U: 0/5/0		
TOTAL	5 (58)	M/F: 18/9	A/C/H: 6/18/3	− 1.33 ± 1.60	− 1.58 ± 2.57	Y/N/U: 21/4/2	Y/N/U: 5/20/2	Y/N/U: 10/16/1		

Roman numerals denote different families. Mean ± SD of quantitative variables are given for each group and for all patients except groups' age which is expressed as median (interquartile range).

NC nephrocalcinosis, *NL* nephrolithiasis, *M* male, *F* female, *A* African, *C* Caucasian, *H* Hispanic-American, *U* unknown, *Y* yes, *N* no.

[a] Different from *ATP6V1B1* and *ATP6V0A4* groups

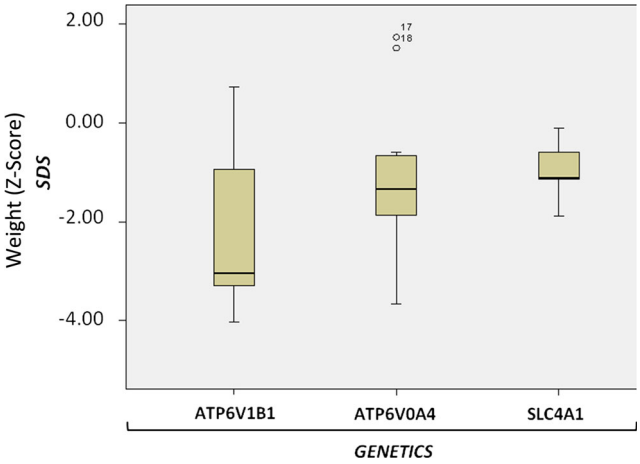


Fig. 1 Boxplot showing the weight SDS at diagnosis. ATP6V1B1 means patients with mutation in *ATP6V1B1* gene. ATP6V0A4 means patients with mutation in *ATP6V0A4* gene. SLC4A1 means patients with mutation in *SLC4A1* gene

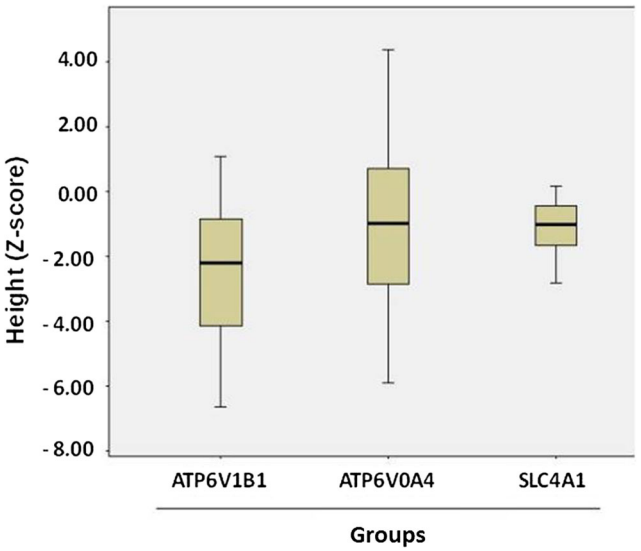


Fig. 2 Boxplot showing the height SDS at diagnosis. ATP6V1B1 means patients with mutation in *ATP6V1B1* gene. ATP6V0A4 means patients with mutation in *ATP6V0A4* gene. SLC4A1 means patients with mutation in *SLC4A1* gene

were Africans and harbored the same mutation (c.1228 in. C; p.I386Hfs.) in homozygosis, according to the founder effect of this variant proposed by Nagara et al. for dRTA patients from North-African geographical origin [22]. In this group, the five remaining patients were Caucasian and three (V.1, VI.1, and VII.1) carried the same mutation (g.70960079; Intron 6 + 1 G > A, Splicing), in spite of no known familiar relationship between them.

As for the *SLC4A1* group, it is of note that almost no data are available in the literature on children of Occidental origin with this variant form of autosomal dominant dRTA not associated with hemolytic anemia [23–27]. *SLC4A1* variants found in our patients have already been related with a late clinical onset of dRTA [18, 28, 29]. The median age at diagnosis of our patients with *SLC4A1* mutations was 10 years. Therefore, patients with this type of dRTA may present before adulthood, in the late childhood. There was no overlap in the age of diagnosis between dRTA caused by *SLC4A1* gene mutations and the other two types of dRTA. Patients with *ATP6V1B1* and *ATP6V0A4* gene defects in our series debut in infancy at a mean age of 7 and 3 months, respectively. However, it should be noted that two children having *ATP6V1B1*mutations and one child with *ATP6V0A4* mutations were diagnosed after the second year of life indicating that these forms of dRTA may not be detected during early infancy. Patients with *SLC4A1* gene mutations had less severe forms of dRTA and tended to have less marked growth retardation, less severe metabolic acidosis, and significantly milder hypokalemia which might someway justify the later diagnosis. Besouw et al. [21] found that children with H^{+}-ATPase pump defects needed higher alkali doses to correct acidosis than children with *SCL4A1* mutations. It has also been reported that the degree of acidosis or hypokalemia varies depending on whether the dRTA is autosomal recessive (*ATP6V0A4* and *ATP6V1B1* genes) or dominant (*SLC4A1* gene). Battle et al. [29] showed that individuals with autosomal-recessive pattern had serum potassium levels lower than those with an autosomal-dominant inheritance.

Neither the frequency of nephrocalcinosis or urolithiasis nor the urinary calcium excretion was different among the three groups.

The patient XXIII.1 of the *SLC4A1* group had a height *Z* score equal to − 2.82 DS, much greater growth retardation than the other group's cases. It is worth commenting that this patient, additionally to the de novo p.R589C mutation, had a polymorphism (rs148170067 SNP; c.889 C > T, p.V245 M) inherited from the father, who never manifested any symptom related to dRTA. Thus, this polymorphism could induce a synergistic negative effect, enhancing the harmful impact of the mutation and explaining why this patient had more severe metabolic acidosis and greater growth retardation.

Another noticeable finding of our study was that eight patients with mutations in the *ATP6V1B1* gene were deaf, out of ten in whom the symptom was sought, by contrast with only 2 out of 14 children with *ATPV0A4* gene mutations. As expected, none of patients harboring *SLC4A1* gene defects had deafness because the $Cl^{-}/HCO3^{-}$ anion exchanger does not express in the ears. It was classically assumed that dRTA caused by defective *ATP6V1B1* gene was associated with early nerve hearing loss [7, 28, 30–33], while *ATP6V0A4* mutations were related with either late-onset deafness or normal hearing, [34–40]. Vargas-Poussou et al. [41] challenged this assumption demonstrating genetic heterogeneity in dRTA associated with deafness and emphasizing the importance of mutational gene analysis for recessive forms of dRTA independent of

Table 2 Biochemical features of the three groups of patients at diagnosis

	Serum								Urine			
	Anion Gap	Creatinine (mg/dL)	pH	Bicarbonate (mEq/L)	K (mEq/L)	Cl (mEq/L)	Na (mEq/L)	pH	Anion Gap	FEK (%)	Ca/Cr (mg/mg)	Citraturia
Group *ATP6V1B1*												
I.1	–	–	–	–	–	–	–	–	NA	–	–	NA
II. 1	19	0.32	7.43	24.00	3.40	100	140	8.00	+	17.4	0.13	NA
III.1	13	0.31	7.27	19.30	3.38	109	138	7.00	+	33.6	0.40	L
III.2	16	0.32	7.13	15.00	3.70	108	136	–	NA	14.00	0.80	NA
IV.1	16	0.80	7.07	9.90	2.40	124	148	7.00	+	24.25	0.23	N
V.1	22	1.03	7.26	16.00	3.20	118	153	7.50	+	68.3	–	NA
VI.1	–	–	7.37	16.00	2.70	122	140	8.00	+	24.4	0.37	NA
VII.1	17	0.46	7.33	14.70	3.74	107	135	7.00	+	18.00	0.70	L
VIII.1	19	0.62	7.29	10.80	3.02	111	138	7.17	+	35.5	0.09	L
VIII.2	21	0.71	7.29	11.00	4.29	106	134	7.00	+	19.00	0.05	L
Group *ATP6V0A4*												
IX.1	25	0.40	–	15.00	1.60	102	141	–	NA	–	–	NA
X.1	23	0.41	7.30	19.50	3.70	99	138	8.00	+	16.6	5.30	NA
XI.1	14	0.94	7.33	21.10	3.10	104	136	7.00	+	12.84	0.12	NA
XII.1	–	–	–	–	–	–	–	–	NA	–	–	NA
XIII.1	15	0.40	7.24	14.30	3.20	112	138	7.50	+	21.70	0.61	L
XIV.1	29	0.60	7.32	16.00	2.70	105	148	7.50	NA	32.6	0.43	NA
XV.1	13	0.74	6.72	4.00	3.30	122	136	*5.00*	Ng	28.54	0.37	N
XVI.1	8	0.30	7.17	11.00	3.70	116	131	7.00	NA	–	–	NA
XVII.1	14	0.60	7.20	13.00	2.40	118	143	7.00	+	15.29	0.33	NA
XVIII.1	21	0.30	7.18	10.00	3.00	119	147	8.00	+	11.9	0.90	N
XIX.1	9	0.70	7.26	17.00	2.90	119	142	8.00	+	18.00	0.20	NA
XX.1	–	–	7.21	13.00	–	–	–	7.14	+	–	–	NA
Group *SLC4A1*												
XXI.1	16	0.56	7.24	19.70	3.18	108	140	7.00	+	16.73	0.20	NA
XXII.1	13	0.80	7.24	17.40	3.40	113	140	7.00	+	21.67	0.23	L
XXIII.1	11	0.90	7.18	16.40	3.50	119	143	6.50	+	18.00	0.35	NA
XXIV.1	21	0.69	7.33	20.70	4.30	106	143	–	NA	–	0.08	NA
XXV.1	17	0.71	7.20	17.50	3.90	111	142	7.50	+	12.63	0.23	L
Total *ATP6V1B1*	18 ± 3	0.57 ± 0.26	7.27 ± 0.11	15.19 ± 4.48	3.31 ± 0.57	112 ± 8	140 ± 6	7.33 ± 0.45	+/Ng/NA: 8/0/2	30.06 ± 16.89	0.23 (0.31)	L/N/NA: 4/1/5
Total *ATP6V0A4*	17 ± 7	0.54 ± 0.21	7.19 ± 0.18	13.99 ± 4.71	2.96 ± 0.63	112 ± 8	140 ± 5	7.18 ± 0.88	+/Ng/NA: 7/1/4	19.68 ± 7.45	0.40 (0.60)	Y/N/NA: 1/2/9
Total SLC4A1	15 ± 4	0.73 ± 0.13	7.24 ± 0.06	18.34 ± 1.79	3.66 ± 0.44[a]	111 ± 5	142 ± 2	7.00 ± 0.41	+/Ng/NA: 4/0/1	17.26 ± 3.73	0.23 (0.11)	Y/N/NA: 2/0/3
TOTAL	17 ± 6	0.59 ± 0.22	7.23 ± 0.14	15.29 ± 4.38	3.24 ± 0.61	112 ± 7	140 ± 5	7.20 ± 0.66	+/Ng/NA: 19/1/7	22.90 ± 12.50	0.57 (0.36)	Y/N/NA:7/3/17

Mean ± SD of quantitative variables are given for each group and for all patients except groups' Ca/Cr which is expressed as median (interquartile range)

K potassium, *Cl* chlorine, *Na*, sodium, *FEK*, fractional excretion of potassium, *Ca/Cr* calcium creatinine ratio, +, positive, *Ng* negative, *NA* not available, *L* low, *N* normal, *Y* yes, ***N*** no

[a] Different from *ATP6V0A4* group

hearing loss. However, although the early presence of neurosensorial deafness does not fully discriminate between the two types of dRTA caused by a loss of function of the H+ ATPase pump, our results indicate that, at early age, the detection of deafness in patients with dRTA is highly suggestive of an underlying mutation in the *ATP6V1B1* gene. It should be mentioned that the occurrence of deafness in dRTA has been related with the expansion of the vestibular aqueduct [42, 43], a finding unfortunately not explored in our series of patients.

In summary, we here presented clinical and biochemical data at diagnosis of non-oriental patients with different genetic forms of primary dRTA. At diagnosis, the patient's age, the severity of hypokalemia, and the presence of hypoacusia might be useful to differentiate the underlying molecular defect which needs to be confirmed by gene analysis.

Funding information This work was supported partially by GRUPIN 14-020 grant from "Principado de Asturias" Funds, ISCIII FIS PI14/00702, Plan Estatal I+D+I 2013-2016, FEDER Funds, and FundaciónNutrición y Crecimiento.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

There are no prior publications or submissions with any overlapping information.

References

1. Rodríguez Soriano J (2002) Renal tubular acidosis: the clinical entity. J Am Soc Nephrol 13:2160–2170
2. Gil-Peña H, Mejía N, Santos F (2014) Renal tubular acidosis. J Pediatr 164:691–698
3. Bockenhauer D, Bichet DG (2013) Inherited secondary nephrogenic diabetes insipidus: concentrating on humans. Am J Physiol Ren Physiol 304:F1037–F1042
4. Escobar L, Mejia N, Gil H, Santos F (2013) Distal renal tubular acidosis: a hereditary disease with an inadequate urinary H+ excretion. Nefrología 33:289–296
5. Nijenhuis T, Renkema KY, Hoenderop JG, Bindels RJ (2006) Acid-base status determines the renal expression of Ca^{2+} and Mg^{2+} transport proteins. J Am Soc Nephrol 17:617–626
6. Smith AN, Jouret F, Bord S, Borthwick KJ, Al-Lamki RS, Wagner CA, Ireland DC, Cormier-Daire V, Frattini A, Villa A, Kornak U, Devuyst O, Karet FE (2005) Vacuolar H+-ATPase d2 subunit: molecular characterization, developmental regulation, and localization to specialized proton pumps in kidney and bone. J Am Soc Nephrol 16:1245–1256
7. Karet FE, Finberg KE, Nelson RD, Nayir A, Mocan H, Sanjad SA, Rodriguez-Soriano J, Santos F, Cremers CW, Di Pietro A, Hoffbrand BI, Winiarski J, Bakkaloglu A, Ozen S, Dusunsel R, Goodyer P, Hulton SA, Wu DK, Skvorak AB, Morton CC, Cunningham MJ, Jha V, Lifton RP (1999) Mutations in the gene encoding B1 subunit of H+-ATPase cause renal tubular acidosis with sensorineural deafness. Nat Genet 21:84–90
8. Gil H, Santos F, García E, Alvarez MV, Ordoñez FA, Málaga S, Coto E (2007) Distal RTA with nerve deafness: clinical spectrum and mutational analysis in five children. Pediatr Nephrol 22:825–828
9. Bruce LJ, Cope DL, Jones GK, Schofield AE, Burley M, Povey S, Unwin RJ, Wrong O, Tanner MJ (1997) Familial distal renal tubular acidosis is associated with mutations in the red cell anion exchanger (band 3, AE1) gene. J Clin Invest 100:1693–1707
10. Jarolim P, Shayakul C, Prabakaran D, Jiang L, Stuart-Tilley A, Rubin HL, Simova S, Zavadil J, Herrin JT, Brouillette J, Somers MJ, Seemanova E, Brugnara C, Guay-Woodford LM, Alper SL (1998) Autosomal dominant distal renal tubular acidosis is associated in three families with heterozygosity for the R589H mutation in the AE1 (band 3) Cl-/HCO3 exchanger. J Biol Chem 273:6380–6388
11. Karet FE, Gainza FJ, Györy AZ, Unwin RJ, Wrong O, Tanner MJ, Nayir A, Alpay H, Santos F, Hulton SA, Bakkaloglu A, Ozen S, Cunningham MJ, di Pietro A, Walker WG, Lifton RP (1998) Mutations in the chloride-bicarbonate exchanger gene AE1 cause autosomal dominant but not autosomal recessive distal renal tubular acidosis. Proc Natl Acad Sci U S A 95:6337–6342
12. Tanphaichitr VS, Sumboonnanonda A, Ideguchi H, Shayakul C, Brugnara C, Takao M, Veerakul G, Alper SL (1998) Novel AE1 mutations in recessive distal renal tubular acidosis. Loss-of-function is rescued by glycophorin A. J Clin Invest 102:2173–2179
13. Vasuvattakul S, Yenchitsomanus PT, Vachuanichsanong P, Thuwajit P, Kaitwatcharachai C, Laosombat V, Malasit P, Wilairat P, Nimmannit S (1999) Autosomal recessive distal renal tubular acidosis associated with Southeast Asian ovalocytosis. Kidney Int 56:1674–1682
14. Bruce LJ, Wrong O, Toye AM, Young MT, Ogle G, Ismail Z, Sinha AK, McMaster P, Hwaihwanje I, Nash GB, Hart S, Lavu E, Palmer R, Othman A, Unwin RJ, Tanner MJ (2000) Band 3 mutations, renal tubular acidosis and South-East Asian ovalocytosis in Malaysia and Papua New Guinea: loss of up to 95% band 3 transport in red cells. Biochem J 350:41–51
15. Enerbäck S, Nilsson D, Edwards N, Heglind M, Alkanderi S, Ashton E, Deeb A, Kokash FEB, Bakhsh ARA, Van't Hoff W, Walsh SB, D'Arco F, Daryadel A, Bourgeois S, Wagner CA, Kleta R, Bockenhauer D, Sayer JA (2018) Acidosis and deafness in patients with recessive mutations in FOXI1. J Am SocNephrol 29:1041–1048
16. Mejía N, Santos F, Claverie-Martín F, Garcia-Nieto V, Ariceta G, Castaño L, Renal Tube Group (2013) RenalTube: a network tool for clinical and genetic diagnosis of primary tubulopathies. Eur J Pediatr 172:775–780
17. Garcia-Nieto V, Santos F (2006) Función renal basal. In: Garcia-Nieto V, Rodríguez-Iturbe B, Santos F (ed) Nefrologia Pediátrica, 2nd ed. Aula Médica, Madrid
18. Gomez J, Gil-Peña H, Santos F, Coto E, Arango A, Hernández O, Rodríguez J, Nadal I, Cantos V, Chocrón S, Vergara I, Madrid Á, Vazquez C, González LE, Blanco F (2016) Primary renal distal tubular acidosis: novel findings in patients studied by next-generation sequencing. Pediatr Res 79:496–501
19. Batlle D, Haque SK (2012) Genetic causes and mechanisms of distal renal tubular acidosis. Nephrol Dial Transplant 27:3691–3704
20. Palazzo V, Provenzano A, Becherucci F, Sansavini G, Mazzinghi B, Orlandini V, Giunti L, Roperto RM, Pantaleo M, Artuso R, Andreucci E, Bargiacchi S, Traficante G, Stagi S, Murer L, Benetti E, Emma F, Giordano M, Rivieri F, Colussi G, Penco S, Manfredini E, Caruso MR, Garavelli L, Andrulli S, Vergine G, Miglietti N, Mancini E, Malaventura C, Percesepe A, Grosso E, Materassi M, Romagnani P, Giglio S (2017) The genetic and clinical spectrum of a large cohort of patients with distal renal tubular acidosis. Kidney Int 91:1243–1255
21. Besouw MT, Bienias M, Walsh P, Kleta R, Van't Hoff WG, Ashton E, Jenkins L, Bockenhauer D (2017) Clinical and molecular aspects

of distal renal tubular acidosis in children. Pediatr Nephrol 32:987–996

22. Nagara M, Voskarides K, Nouira S, Ben Halim N, Kefi R, Aloulou H, Romdhane L, Ben Abdallah R, Ben Rhouma F, Aissa K, Boughamoura L, Kammoun T, Azzouz H, Abroug S, Ben Turkia H, Ayadi A, Mrad R, Chabchoub I, Hachicha M, Chemli J, Deltas C, Abdelhak S (2014) Molecular investigation of distal renal tubular acidosis in Tunisia, evidence for founder mutations. Genet Test Mol Biomarkers 18:741–748
23. Sritippayawan S, Kirdpon S, Vasuvattakul S, Wasanawatana S, Susaengrat W, Waiyawuth W, Nimmannit S, Malasit P, Yenchitsomanus PT (2003) A de novo R589C mutation of anion exchanger 1 causing distal renal tubular acidosis. Pediatr Nephrol 18:644–648
24. Yenchitsomanus PT (2003) Human anion exchanger1 mutations and distal renal tubular acidosis. Southeast Asian J Trop Med Public Health 34:651–658
25. Rungroj N, Devonald MA, Cuthbert AW, Reimann F, Akkarapatumwong V, Yenchitsomanus PT, Bennett WM, Karet FE (2004) A novel missense mutation in AE1 causing autosomal dominant distal renal tubular acidosis retains normal transport function but is mistargeted in polarized epithelial cells. J Biol Chem 279:13833–13838
26. Shao L, Xu Y, Dong Q, Lang Y, Yue S, Miao Z (2010) A novel *SLC4A1* variant in an autosomal dominant distal renal tubular acidosis family with a severe phenotype. Endocrine 37:473–478
27. Fry AC, Su Y, Yiu V, Cuthbert AW, Trachtman H, Karet Frankl FE (2012) Mutation conferring apical-targeting motif on AE1 exchanger causes autosomal dominant distal RTA. J Am Soc Nephrol 23: 1238–1249
28. Smith AN, Skaug J, Choate KA, Nayir A, Bakkaloglu A, Ozen S, Hulton SA, Sanjad SA, Al-Sabban EA, Lifton RP, Scherer SW, Karet FE (2000) Mutations in *ATP6N1B*, encoding a new kidney vacuolar proton pump 116-kD subunit, cause recessive distal renal tubular acidosis with preserved hearing. Nat Genet 26:71–75
29. Batlle D, Ghanekar H, Jain S, Mitra A (2001) Hereditary distal renal tubular acidosis: new understandings. Annu Rev Med 52:471–484
30. Batlle D, Moorthi KM, Schlueter W, Kurtzman N (2006) Distal renal tubular acidosis and the potassiumenigma. Semin Nephrol 26:471–478
31. Feldman M, Prikis M, Athanasiou Y, Elia A, Pierides A, Deltas CC (2006) Molecular investigation and long-term clinical progress in Greek Cypriot families with recessive distal renal tubular acidosis and sensorineural deafness due to mutations in the ATP6V1B1 gene. Clin Genet 69:135–144
32. Mohebbi N, Vargas-Poussou R, Hegemann SC, Schuknetch B, Kistler AD, Wüthrich RP, Wagner CA (2013) Homozygous and compound heterozygous mutations in the ATP6V1B1 gene in patients with renal tubular acidosis and sensorineural hearing loss. Clin Genet 83:274–278
33. Subasioglu Uzak A, Cakar N, Comak E, Yalcinkaya F, Tekin M (2013) *ATP6V1B1* mutations in distal renal tubular acidosis and sensorineural hearing loss: clinical and genetic spectrum of five families. Ren Fail 35:1281–1284
34. Stover EH, Borthwick KJ, Bavalia C, Eady N, Fritz DM, Rungroj N, Giersch AB, Morton CC, Axon PR, Akil I, Al-Sabban EA, Baguley DM, Bianca S, Bakkaloglu A, Bircan Z, Chauveau D, Clermont MJ, Guala A, Hulton SA, Kroes H, Li Volti G, Mir S, Mocan H, Nayir A, Ozen S, Rodriguez Soriano J, Sanjad SA, Tasic V, Taylor CM, Topaloglu R, Smith AN, Karet FE (2002) Novel *ATP6V1B1* and *ATP6V0A4* mutations in autosomal recessive distal renal tubular acidosis with new evidence for hearing loss. J Med Genet 39:796–803
35. Elhayek D, Perez de Nanclares G, Chouchane S, Hamami S, Mlika A, Troudi M, Leban N, Ben Romdane W, Gueddiche MN, El Amri F, Mrabet S, Ben Chibani J, Castaño L, Haj Khelil A, Ariceta G (2013) Molecular diagnosis of distal renal tubular acidosis in Tunisian patients: proposed algorithm for northern Africa populations for the *ATP6V1B1*, *ATP6V0A4* and *SCL4A1* genes. BMC Med Genet 14:119
36. Miura K, Sekine T, Takahashi K, Takita J, Harita Y, Ohki K, Park MJ, Hayashi Y, Tajima A, Ishihara M, Hisano M, Murai M, Igarashi T (2013) Mutational analyses of the ATP6V1B1 and ATP6V0A4 genes in patients with primary distal renal tubular acidosis. Nephrol Dial Transplant 28:2123–2130
37. Boualla L, Jdioui W, Soulami K, Ratbi I, Sefiani A (2016) Clinical and molecular findings in three Moroccan families with distal renal tubular acidosis and deafness: Report of a novel mutation of ATP6V1B1 gene. Curr Res Transl Med 64:5–8
38. Escobar LI, Simian C, Treard C, Hayek D, Salvador C, Guerra N, Matos M, Medeiros M, Enciso S, Camargo MD, Vargas-Poussou R (2016) Mutations in ATP6V1B1 and ATP6V0A4 genes cause recessive distal renal tubular acidosis in Mexican families. Mol Genet Genomic Med 4:303–311
39. Zeinali F, Mohseni M, Fadaee M, Fattahi Z, Najmabadi H, Otukesh H, Kahrizi K (2014) Investigation of ATP6V1B1 and ATP6V0A4 genes causing hereditary hearing loss associated with distal renal tubular acidosis in Iranian families. J Laryngol Otol 128:1056–1059
40. Gao Y, Xu Y, Li Q, Lang Y, Dong Q, Shao L (2014) Mutation analysis and audiologic assessment in six Chinese children with primary distal renal tubular acidosis. Ren Fail 36:1226–1232
41. Vargas-Poussou R, Houillier P, Le Pottier N, Strompf L, Loirat C, Baudouin V, Macher MA, Déchaux M, Ulinski T, Nobili F, Eckart P, Novo R, Cailliez M, Salomon R, Nivet H, Cochat P, Tack I, Fargeot A, Bouissou F, Kesler GR, Lorotte S, Godefroid N, Layet V, Morin G, Jeunemaître X (2006) Genetic investigation of autosomal recessive distal renal tubular acidosis: evidence for early sensorineural hearing loss associated with mutations in the *ATP6V0A4* gene. J Am SocNephrol 17:1437–1443
42. Lorente-Cánovas B, Ingham N, Norgett EE, Golder ZJ, Karet Frankl FE, Steel KP (2013) Mice deficient in H+-ATPase a4 subunit have severe hearing impairment associated with enlarged endolymphatic compartments within the inner ear. Dis Model Mech 6: 434–442
43. Andreucci E, Bianchi B, Carboni I, Lavoratti G, Mortilla M, Fonda C, Bigozzi M, Genuardi M, Giglio S, Pela I (2009) Inner ear abnormalities in four patients with dRTA and SNHL: clinical and genetic heterogeneity. Pediatr Nephrol 24:2147–2153