

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

## RenalTube Group

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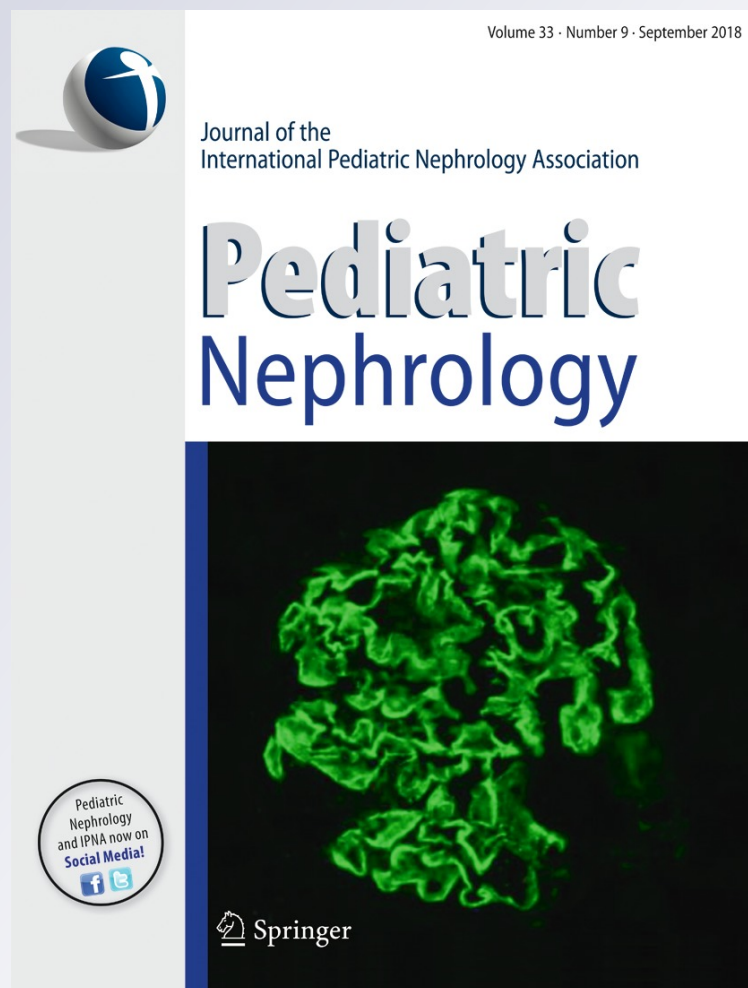
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# Distal renal tubular acidosis. Clinical manifestations in patients with different underlying gene mutations

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## 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 ( $X \pm SD$ ) was higher in *SLC4A1* group ( $3.66 \pm 0.44$  mEq/L) than in *ATP6V0A4* group ( $2.96 \pm 0.63$  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 <sup>+</sup> transporting V0 subunit A4
ATP6V1B1	ATPase H <sup>+</sup> transporting V1 subunit B1
SLC4A1	Solute carrier family 4 member 1

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## 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  $\alpha$ -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<sup>+</sup>-ATPase of the  $\alpha$ -intercalated cells [6]. The B1 isoform of the H<sup>+</sup>-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<sup>-</sup>/HCO<sub>3</sub><sup>-</sup> (AE1) placed on the basolateral surface of  $\alpha$ -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*, *ATP6V0A4*, 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  $\times$  serum creatinine/serum potassium  $\times$  urine creatinine)  $\times$  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.  $\chi^2$  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 ( $p = 0.046$ ).

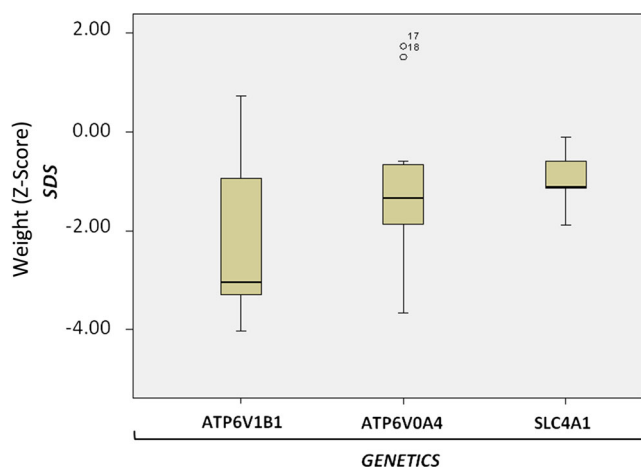
## Discussion

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

Group	Age (Months)	Sex	Ethnic Background	Weight (SDS)	Height (SDS)	NC	NL	Hearing loss	Inheritance	Mutations
<b>Group <i>ATP6V1B1</i></b>										
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
<b>Group <i>ATP6V0A4</i></b>										
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.I789P / 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	Heterozygous	c.1111 del TGT; 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	Heterozygous	c.1468 del 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
<b>Group <i>SLC4A1</i></b>										
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	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		
<b>Group <i>ATP6V1B1</i></b>										
Total	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		
<b>Group <i>ATP6V0A4</i></b>										
Total	120 (60) <sup>a</sup>	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		

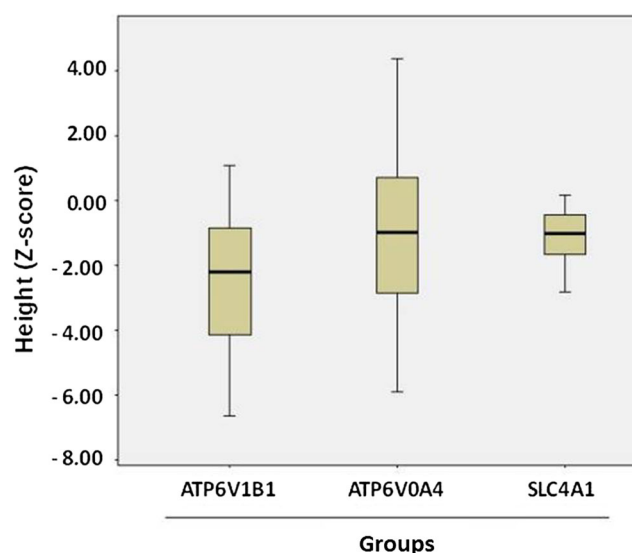
Roman numerals denote different families. Mean ± SD of quantitative variables are given for each group and for all patients except groups' age which is expressed as median (interquartile range). NC nephrocalcinosis, NL nephrolithiasis, M male, F female, A African, C Caucasian, H Hispanic-American, U unknown, Y yes, N no.  
<sup>a</sup> 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

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 somewhat 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



**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

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  $Cl^-/HCO_3^-$  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)	Citratuna
<b>Group ATP6V1B1</b>												
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
<b>Group ATP6V0A4</b>												
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
<b>Group SLC4A1</b>												
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 <sup>a</sup>	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<sup>a</sup> 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

<sup>a</sup> 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<sup>+</sup>-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.

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### 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.

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