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Original article

Clinical and molecular findings in three Moroccan families with distal renal tubular acidosis and deafness: Report of a novel mutation of *ATP6V1B1* gene

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ABSTRACT

Background. – Primary distal renal tubular acidosis (dRTA) is a rare genetic condition characterized by an impaired acid excretion by the intercalated cells in the renal collecting duct. Recessive forms of this disease are caused by mutations in tow major genes: *ATP6V1B1* and *ATP6V0A4*. Causal mutations in *ATP6V1B1* gene are classically associated with early sensorineural hearing loss, however cases of tubular acidosis with early deafness have also been described in patients with mutations in the *ATP6V0A4* gene.
Methods. – The phenotype and genotype of three Moroccan consanguineous families with dRTA and deafness were assessed. Molecular analysis was performed by PCR amplification and direct sequencing of exon 12 of *ATP6V1B1* gene.
Results. – A novel c.1169dupC frameshift mutation of *ATP6V1B1* gene was identified in one family and the c.1155dupC North African mutation in the tow other families.
Discussion and conclusion. – In this report, we propose first line genetic testing based on screening of these two mutations both located in exon 12 of *ATP6V1B1* gene in Moroccan patients with recessive form of dRTA associated to precocious hearing loss. Molecular diagnosis of dRTA leads to appropriate treatment and prevention of renal failure in affected individuals and to provide genetic counseling for families at risk.

1. Introduction

Distal renal tubular acidosis (dRTA) is a heterogeneous group of genetic diseases characterized by failure of the urine acidification process leading to severe metabolic hyperchloremic acidosis with abnormally elevated urinary PH, hypokaliemia, hypercalciuria and hypocitraturia [1–3]. Clinical features are polyuro-polydipsic syndrome, failure to thrive, rickets or osteomalacia, nephrocalcinosis, urolithiasis and possible chronic renal failure in untreated patients [4–8]. Autosomal recessive forms of dRTA are rare entities of unknown prevalence [9]. The two major genes involved are *ATP6V1B1* on 2p13 and *ATP6V0A4* on 7q34 [10,11]. The presence or absence of hearing impairment is the major phenotypic criterion to direct molecular analysis to one of the two genes. Affected individuals with *ATP6V1B1* mutations show more frequently severe and early-onset sensorineural hearing loss (SNHL) than patients with *ATP6V0A4* mutations, although mutations in either of the two genes may cause early deafness [1,2,5,7,10]. *SLC4A1* is another gene implicated in distal RTA, indeed mutations in *this gene* were found to be associated with autosomal dominant form of the disease or more rarely with the autosomal recessive form [9,12].

ATP6V1B1 gene encodes the B1 subunit of vacuolar H+-ATPase located at the apical surface of the α-intercalated cells in the distal tubule and is also expressed in the human cochlea and in endolymphatic sac epithelium [5,6,9]. To date, at least 37 mutations were identified in*ATP6V1B1* gene [http://www.hgmd.cf.ac.uk/index.php]. Among them, c.1155dupC mutation in exon 12 is the most recurrent in North African populations [6,9,10]. We report clinical and molecular findings in three Moroccan families with distal renal tubular acidosis associated to hearing loss and a novel mutation of *ATP6V1B1* gene.

Abbreviations: PCR, polymerase chain reaction; dRTA, distal renal tubular acidosis; SNHL, sensorineural hearing loss.

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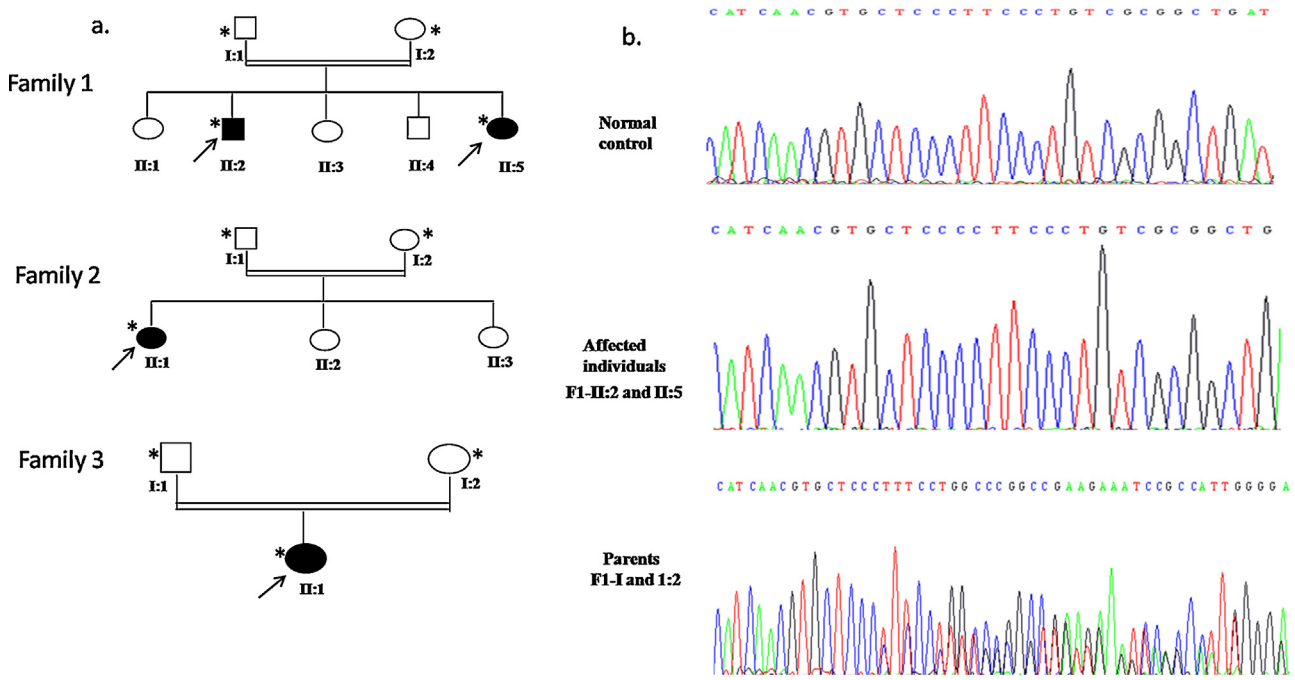

Fig. 1. a: pedigrees of families with dRTA and deafness. Affected individuals are shaded. Asterisks indicate individuals in whom molecular analysis was undertaken; b: electropherograms of identified novel *ATP6V1B1* mutation. Two patients (F1-II:2 and II:5) present homozygous c.1169dupC and both parents are heterozygous (F1-I:1 and I:2).

2. Patients and methods

2.1. Patients

Four patients belonging to three unrelated Moroccan families were investigated for autosomal recessive form of early distal renal tubular acidosis with sensorineural hearing loss (Fig. 1a). All families were consanguineous (first degree) from three different regions of Morocco, with no history of renal disease or deafness. dRTA individuals were all characterized by a homogeneous phenotype of metabolic acidosis with hypokaliemia, medullary nephrocalcinosis, moderate to severe bilateral SNHL and early-onset in the first year of life. Clinical and biochemical features of patients are summarized in Table 1.

Table 1
Clinical and biochemical details of individuals with dRTA.

	Family I		Family II	Family III
	II:2	II:5	II:1	II:1
Family–individual				
Origin	South Morocco	South Morocco	Central Morocco	West Morocco
Consanguinity	+	+	+	+
Sex	M	F	F	F
Age (years) last assessment	12	2.5	3	4.5
Age of onset (months)	14	8	1	21
Presenting manifestations	PP, V, A, C	PP, V, A, C	V, A	PP, V, A, C
Clinical features of rickets	+	–	–	+
Failure to thrive	−4 SD	−3 SD	−2 SD	−4 SD
Medullary nephrocalcinosis[a]	+	+	+	+
SNHL[b]				
Type	Perception	Perception	Perception	Perception
Bilateral or unilateral	B	B	B	B
Age (years) of diagnosis	3	2	3	2
Degree of hearing loss	Profound	Profound	Severe	Profound
Temporal bone imaging	NA	Normal	NA	NA
Treatment of deafness	HA	CI	HA	HA
Biochemical				
Serum Na mmol/l	133	127	137	141
Serum K mmol/l	2.33	2.61	3.8	2.4
Serum HCO_3^- mmol/l	11	9.3	12	11.4
Serum creatinine mg/l	4.8	4.2	4	5
Serum calcium mg/l	93	99	104	91.5
Serum phosphorous mg/l	41	45	66	26
Plasma anion gap mmol/l	3	3.7	12	13.6
Urine PH	7	8	7	7

M: male; F: female; SD: standard deviation; PP: polyuria polydipsia; V: vomiting; A: anorexia; C: constipation; B: bilateral; CI: cochlear implant; HA: hearing aid; NA: not available. Normal ranges: serum Na 130–151 mmol/l; serum K 3.5–5 mmol/l; serum HCO_3^- 20–28 mmol/l; serum creatinine 6–13 mg/l; serum calcium 80–100 mg/l; serum phosphorus: 25–45 mg/l, plasma anion gap: 10–20 mmol/; urine PH < 6 in the setting of metabolic acidosis.

[a] Diagnosed by renal ultrasound.

[b] Diagnosed by a auditory evoking responses and/or pure-tone audiometry.