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Original Article

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Pseudohypoaldosteronisms, report on a 10-patient series

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Abstract

Background. Type 1 pseudohypoaldosteronism (PHA1) is a salt-wasting syndrome caused by mineralocorticoid resistance. Autosomal recessive and dominant hereditary forms are caused by Epithelial Na Channel and Mineralocorticoid Receptor mutation respectively, while secondary PHA1 is usually associated with urological problems.

Methods. Ten patients were studied in four French pediatric units in order to characterize PHA1 spectrum in infants. Patients were selected by chart review. Genetic, clinical and biochemistry data were collected and analyzed.

Results. *Autosomal recessive PHA1* ($n = 3$) was diagnosed at 6 and 7 days of life in three patients presenting with severe hyperkalaemia and weight loss. After 8 months, 3 and 5 years on follow-up, neurological development and longitudinal growth was normal with high sodium supplementation.

Autosomal dominant PHA1 ($n = 4$) was revealed at 15, 19, 22 and 30 days of life because of failure to thrive. At 8 months, 3 and 21 years of age, longitudinal growth was normal in three patients who were given salt supplementation; no significant catch-up growth was obtained in the last patient at 20 months of age.

Secondary PHA1 ($n = 3$) was diagnosed at 11, 26 days and 5 months of life concomitantly with acute pyelonephritis in three children with either renal hypoplasia, urinary duplication or bilateral megaureter. The outcome was favourable and salt supplementation was discontinued after 3, 11 and 13 months.

Conclusions. PHA1 should be suspected in case of severe hyperkalemia and weight loss in infants and need careful management. Pathogenesis of secondary PHA1 is still challenging and further studies are mandatory to highlight the link between infection, developing urinary tract and pseudohypoaldosteronism.

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Introduction

Type 1 pseudohypoaldosteronism (PHA1) was first described in 1958 by Cheek and Perry [1]. This rare syndrome mainly starts during the neonatal period with a wide spectrum: (i) two genetic forms: a renal form of autosomal dominant inheritance due to a mutation of the mineralocorticoid receptor (MR) and a severe systemic one of autosomal recessive inheritance due to a mutation of the epithelial sodium channel (ENaC) gene, and (ii) a secondary form usually in association with urinary tract malformation and acute pyelonephritis. We retrospectively analysed 10 cases in order to describe the clinical and biological course of the disease.

Patients and methods

We retrospectively investigated 10 patients with a picture of PHA1 from four paediatric centres, i.e. Lyon Edouard-Herriot ($n = 4$), Lyon Debrousse ($n = 4$), Saint-Etienne ($n = 1$) and Nouméa ($n = 1$) between February 1983 and June 2005. Patients with adrenal deficiency, salt-wasting syndrome without relevant hyperkalaemia ($K < 6$ mmol/l) and patients without aldosterone dosage were excluded. Plasma renin and aldosterone concentrations were determined from available radioimmunoassay kits (Beckman Immunotech; Marseille, France). For each patient, we collected data for age at diagnosis, clinical data and history, routine plasma and urine biochemistry at the time of diagnosis (sodium, potassium, chloride, bicarbonate, creatinine), ultrasonography, salt supplementation (nadir dose during the first week after diagnosis) and DNA analysis when available. Genetic analysis was performed by direct sequencing of all exons and intronic exon flanking regions of the genes encoding for the MR (*NR3C2*) and the three

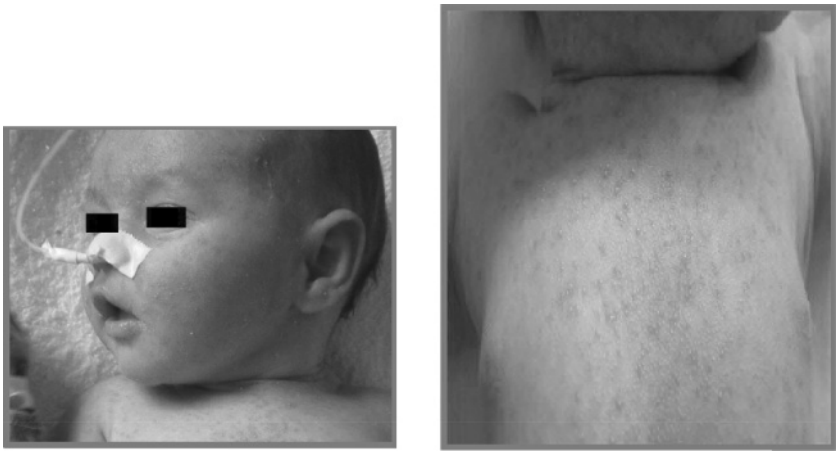

Fig. 1. Cutaneous lesions in a female newborn infant with autosomal recessive PHA1: neonatal miliaria crystallina (patient 1).

ENaC subunits (*SCNN1A, SCNN1B* and *SCNN1G*) using the ABI Prism Big Dye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems, Foster City, CA, USA) on an ABI Prism 3700 DNA analyser. Patients with the renal form of PHA1 were screened for NR3C2 mutations, while those who were affected by generalized PHA1 were screened for mutations in SCNN1A, SCNN1B and SCNN1G. Screening was done according to the clinical picture since NR3C2 mutations are not found in generalized PHA1 and mutations of the genes encoding for ENaC subunits are not found in renal PHA1. Screening included the entire NR3C2 gene (exons and intron–exon junctions) and all the three ENaC subunit genes. Secondary PHA1 was not analysed.

Results

Patient characteristics are listed in Table 1. All mutations identified were absent in 210–254 control chromosomes.

Three patients presented with the systemic form of PHA1

Patient 1 was born from consanguineous parents. She presented with neonatal onset bullous dermatitis (Figure 1a and b) that evolved towards chronic xerosis and required a high salt supplementation. Because of long-lasting digestive intolerance, a gastrostomy was performed. At 3 years of age, she was still fed by gastrostomy and she often suffered from severe dehydration attacks caused by intercurrent viral diarrhoea and respiratory distress episodes.

Patient 2 presented with severe dehydration and weight loss. There was no history of parental consanguinity but the first child had died at 6 days of life in the absence of a clear explanation. Further, she mainly suffered from respiratory symptoms. Her management was based on continuous sodium chloride administration by a nasogastric tube. After a 5-year follow-up period, she still experienced repeated severe dehydration episodes due to diarrhoea and repeated bronchitis attacks requiring inhaled steroid therapy and physiotherapy.

Patient 3 was born from consanguineous parents. Two earlier born siblings had died during the first days of life without diagnosis. She presented with severe weight loss during the neonatal period and was given salt supplementation from nasogatric tube. However, she experienced severe hyperkalaemia (8.9 mmol/l) during a gastroenteritis episode when she was 5 months old. She is now 8 months old and in good general condition. Three different loss-of-function mutations were identified in different subunits of the ENaC (Table 1, Figure 2).

Four additional patients presented with a renal PHA1 and were found to have different mutations

Patient 4 presented with renal PHA1 as soon as she was born. She promptly failed to thrive but catch-up growth was obtained with salt supplementation until 2 years of age. She is currently 3 years old and her neurological development and statural growth are normal. The same mutation of the MR gene was identified in her father in the absence of any symptoms (Figure 3).

Patient 5 presented with renal PHA1 and improved with sodium supplementation that was discontinued at 7 years of age. At 21 years of age, he has normal final height and intellectual development.

Patient 6 was diagnosed from routine biochemistry prior to surgery for inguinal hernia, which revealed hyponatraemia, hyperkalaemia and metabolic acidosis together with urine salt wasting. The diagnosis of renal PHA1 was done leading to continuous nasogastric tube feeding since high salt intake was required. However, his current growth profile is retarded (−2.5 SD) without significant catch-up growth. Her mother carries the same MR mutation (Figure 3); she presented growth delay during childhood and was still followed for epilepsy and moderate mental retardation.

Patient 7 presented with failure to thrive. At 8 months of age, he had a normal longitudinal growth under oral salt supplementation.

MR mutations were identified in all four patients (Table 1, Figure 3)

Another three patients exhibited a secondary form of PHA1

Patient 8 was admitted at 11 days of life because of failure to thrive and anorexia related to febrile urinary tract

Table 1. Patient characteristics. Systemic PHA1 (Pt 1 to Pt 3) was diagnosed during the first week of life in the presence of a positive sweat test and high salt requirements. Renal PHA1 (Pt 4 to Pt 7) occurred later during the first month of life. Secondary PHA1 (Pt 8 to Pt 10) experienced transient abnormalities

	Systemic PHA1			Renal autosomal dominant PHA1				Secondary PHA1		
	Pt 1	Pt 2	Pt 3	Pt 4	Pt 5	Pt 6	Pt 7	Pt 8	Pt 9	Pt 10
Age at presentation (days)	6	6	7	19	22	30	15	11	26	165
Symptoms	Bullous dermatitis	Weight loss	Weight loss	Failure to thrive	Failure to thrive	Routine investigation	Failure to thrive	Failure to thrive	Sepsis	Weight loss, dehydration
P Na (mmol/l)	126	130	129	125	127	133	132	124	120	121
P K (mmol/l)	6.8	9.8	8.5	8.0	7.2	6.4	6.3	7.4	6.6	7.4
P HCO_3 (mmol/l)	15	16	15	12	NA	NA	18	NA	20	12
P Cr (μmol/l)	NA	36	NA	33	NA*	NA	53	97	42	54
U Na (mmol/l)	82	NA	NA	27	75	18	NA	147	19	44
P aldosterone (pmol/l)	45 070	>15 000	20 136	26 768	>4460	18 374	43 048	42 472	10 248	46 605
P renine (pg/ml)	1335	>1400	960	NA	>340	350	>340	2400	218	5600
Sweat test	Positive	Positive	Positive	Negative	NA	Negative	Negative	NA	NA	NA
Ultrasonography ± cystography	Normal	Normal	Normal	Normal	NA	Normal	Normal	Left renal hypoplasia	Unilateral duplex system grade 3 VUR	Bilateral megaureter
Urine culture	NA	Sterile	Sterile	Sterile	NA	Sterile	Sterile	*E. coli*	*E. coli*	*E. coli*
DNA analysis	SCNN1B c.637 C > T/p Gln213stop	SCNN1A c.1621 C > T/p Arg508stop	SCNN1G c.1318 C > T/p Arg440stop	NR3C2 c.2310 C > A/p Asn770Lys	NR3C2 c.1757+ 1 G > A	NR3C2 c1029 C > A/p Tyr343stop	NR3C2 c.1954 C > T/p Arg652stop	NA	NA	NA
Duration of follow up (months)	35	66	8	42	260	20	8	13	17	16
Height/weight (percentile) at last visit	50th/50th	50th/50th	50th/20th	70th/70th	60th/70th	5th/2nd	70th/50th	60th/70th	60th/60th	80th/80th
Neurological status at last visit	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal

*Blood urea nitrogen = 10.4 mmol/l, NA: not available, VUR: vesicoureteral reflux; laboratory normal values: P aldosterone (pmol/l) in the first month of life; mean: 1800 with a large range; P renin (pg/ml) : 7–410 in the first 4 days, 7–125 in the following 4 days, 11–72 from the second week to the third month, 11–101 from the 4th month to the 12th, P Na (mmol/l) 137–145, P K (mmol/l) 3.5–4.7, HCO_3 (mmol/l) 22–30, P creatinine (μmol/l) 21–36.

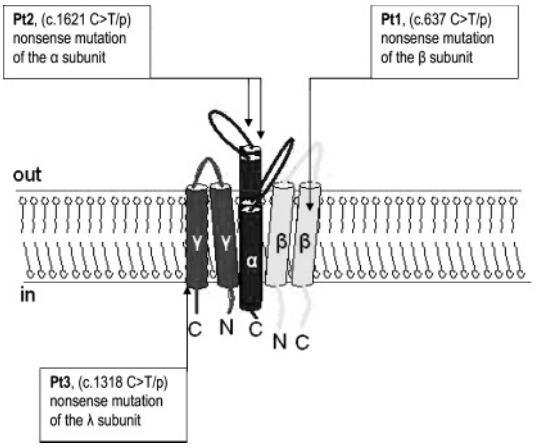

Fig. 2. ENaC mutations for three patients with the systemic form: view of the protein subunits, α, β and γ, which assemble as 2 α, 1 β and 1 γ to form the channel expressed on the cell surface. This channel is widespread in the organism and is found in kidney, colon, salivar gland, skin and lung. The three patients presented a nonsense mutation responsible for a stop codon and a loss of function of the protein.

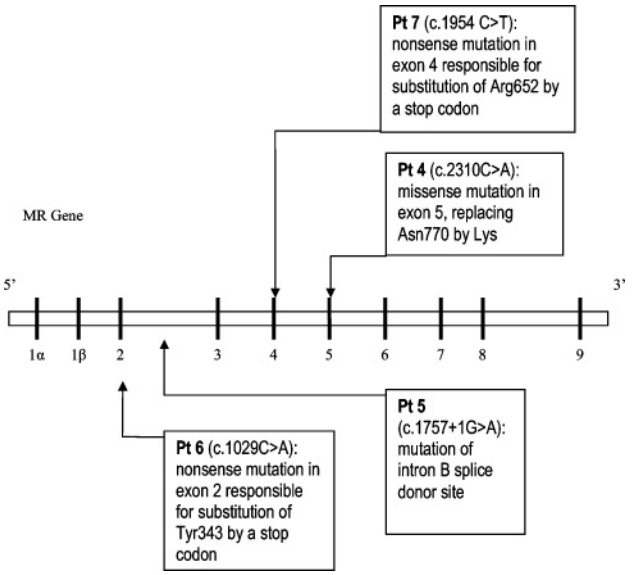

Fig. 3. Mutations of the MR gene in four patients with the renal form of PHA1. View of the gene: exons are represented by black lines and introns by space in between.

infection. A diagnosis of secondary PHA1 was made because of biological results (Table 1) and oral sodium supplementation was given for 11 months since growth velocity was normal and sodium supplementation was still tapered.

Patient 9 was admitted on the 26th day of life because of acute pyelonephritis and urinary tract malformation with poor haemodynamic tolerance. The initial biochemical analyses revealed hyponatraemia, hyperkalaemia and metabolic acidosis (Table 1). Four hours after admission, the electrolyte analysis revealed enhanced hyperkalaemia (from 6.6 to 7.7 mmol/l) as BUN decreased (from 7.1 to 6.3 mmol/l) strongly arguing for an 'MR paralysis' independent of haemodynamic status. A hormonal treatment with hydrocortisone and fludrocortisone was added to antibiotic therapy and sodium supplementation was increased from 4 to 6 mmol/kg per day. Under such a treatment, he recovered both haemodynamic and biochemical profiles. The 17-OH progesterone, ACTH and cortisol were normal leading to discontinuation of hormone supplementation. He is currently 17 months old, in good condition, with a normal growth velocity so that oral sodium supplementation could be discontinued at 13 months of age.

Patient 10 had a prenatal diagnosis of bilateral megaureter. At 5.5 months of age, he was admitted for weight loss, asthenia and vomiting without diarrhoea. The diagnosis of PHA1 was suspected from plasma electrolyte measurements and normal renal function (Table 1). After a short period of time with oral sodium supplementation, he looked healthy, and salt supplementation could be stopped at 9 months of age.

MR and ENaC genetic analysis was not performed in this group of secondary PHA1.

Discussion

PHA is a salt-wasting syndrome due to peripheric resistance to aldosterone. This may be either a primary (mutation of MR or ENaC) or a secondary (infection, uropathy, medication) phenomenon. In all cases, sodium reabsorption and potassium excretion are impaired in the principal cell of the collecting duct. The biological characteristics are hyponatraemia, hyperkalaemia and acidosis. After having excluded pseudohyperkalaemia due to haemolysis, the diagnosis may be challenging. If serum chloride is normal while serum sodium has decreased and GFR is not impaired, type 4 renal tubular acidosis and acute renal failure can be ruled out. Then, normal hormone dosage (ACTH, 17-OH progesterone, cortisol) allows exclusion of adrenal insufficiency. Finally, aldosterone and plasma renin dosage leads to the diagnosis of PHA (high aldosterone and renin concentrations), hypoaldosteronism (high renin, low aldosterone) or hyporeninaemic hypoaldosteronism (low aldosterone and renin) [2]. Around 100 patients have been published so far from both case reports and reviews on mineralocorticoid resistance [3,4].

This retrospective study is the first one to compare clinical and biological issues, as well as the outcome of the three forms of PHA. Nevertheless, this study was not able to provide any estimate of disease incidence. The clinical experience of paediatric tertiary care hardly suggests a higher frequency of secondary PHA. In this study, secondary forms represent 3/10 reports and may be underestimated because of milder symptoms ($K < 6$ mmol/l) or absence of routine aldosterone dosage during the acute phase so that patients did not fulfil the diagnostic criteria.

Systemic PHA1 is of autosomal recessive inheritance and is the most severe form of such a salt-wasting syndrome. It is due to ENaC gene mutation, involving defect in one of the three subunits and has been associated with 22 known homozygous or compound heterozygote loss-of-function mutations [5]. Mice with β or γ subunit mutation die from dehydration and hyperkalaemia during the first weeks of life whereas α subunit knockout leads to death from respiratory

distress [6–8]. The ENaC subunits are widespread in the organism (renal collecting duct, respiratory airway, colon and salivary and sweat glands). In our experience, patients with systemic PHA1 experienced a rather severe presentation with two different clinical pictures, i.e. life-threatening weight loss in patients 2 and 3, and early cutaneous involvement in patient 1 that is a rare feature [9,10]. This dermatitis is due to high salt concentration in sweat during the depletive crises causing inflammation and damage in eccrine structures. Cutaneous lesions are similar to those appearing in *miliaria rubra* [9]. The three patients experienced acute dehydration episodes during gastroenteritis, and patients 1 and 2 suffered from respiratory recurrent episodes. These episodes were often secondary to viral infection. This observation underlines the large distribution of the ENaC subunit and the phenotypic variety according to the subunit mutation.

In two families (patients 2 and 3), there was a history of neonatal death during the first week of life. None of our patients have been diagnosed after the first week of life, a delay that would favour the issue of fatality. A careful assessment of body weight and plasma electrolytes should therefore be recommended in children with a history of neonatal death in a sibling; in our three patients, the sweat test has suggested systemic PHA1 and should be proposed as a simple diagnostic procedure. Salt intake was rather high and required tube feeding. During the follow-up, patient 2 presented cystic fibrosis-like symptoms with frequent airway obstruction episodes, and patient 1 suffered from repeated dehydration attacks due to acute gastroenteritis. A better knowledge of both genotype and phenotype may improve outcome prediction [11]. The main short-term risk is death from hyperkalaemia whereas the long-term outcome depends on life-threatening dehydration episodes and pulmonary chronic obstruction. There is limited information on the outcome of systemic PHA with a wide range of symptoms from isolated growth failure to recurrent lower respiratory tract infections and dehydration episodes with life-threatening hyperkalaemia and cardiac arrest [11,12].

PHA cases are associated with mutations leading to the absence of normal-length α, β or γENaC, while a mild case has been found to be associated with a missense mutation in αENaC [5]. Our three observations were particularly severe and corroborate that the previous data underlining nonsense mutations are more frequent and more severe than missense mutation.

Our observation confirms previous recommendations: high salt intake (Figure 4) and cation exchange resins are mandatory from the very first days of life towards adulthood [11,12].

Renal PHA1 is the autosomal dominant form of PHA1 and is due to the allele invalidation in the human MR gene. The first mutation was described with familial aggregation [13] and sporadic cases have been further reported [14]. Homozygous mutation of the MR gene has been shown to be lethal in mice. Both autosomal dominant and sporadic forms are caused by more than 12 known heterozygous mutations, responsible for MR haploinsufficiency. In our four cases, the diagnosis was done during the first month of life. Failure to thrive was the most common initial symptom. The long-term outcome appeared to be favourable in most

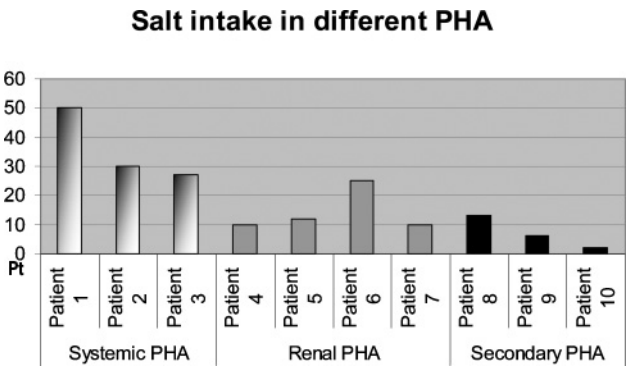

Fig. 4. Nadir salt supplementation in patients with pseudohypoaldosteronism (PHA).

cases. In the two older patients, salt intake could be discontinued at 2 (patient 4) and 7 years (patient 5) of age. The nadir salt intake ranged from 10 to 25 mmol/kg per day, a dose which did not require any tube feeding (Figure 3). Patient 6 needed high salt supplementation and did not catch up growth, maybe because of poor therapeutic compliance.

There was no family history of neonatal death, which is far different from the paper from Geller *et al*. [15] who report on bad outcome in sibling of PHA1. Nevertheless in this study, parents with renal PHA1 are clinically indistinguishable from their unaffected relatives. Affected mother of patient 6 presented with mental retardation, short size and epilepsy. These anomalies might be a consequence of salt depletion episodes during infancy.

No data on the neurodevelopmental outcome of PHA patients have been published.

Mutations of patients 4 and 6 have been recently published [14] whereas others mutations had been described previously in other patients.

Secondary PHA1 is due to transient aldosterone resistance and is often associated with urinary tract infection and/or malformation [16–18]. Any kind of congenital urinary tract obstruction (ureterohydronephrosis, ureterocele, ureteropelvic junction obstruction, posterior urethral valves) may lead to such PHA1. Other rare causes of secondary PHA have been observed: systemic lupus erythematosus, sickle cell nephropathy, acute renal allograft rejection and chronic allograft nephropathy [19]. The pathophysiology of secondary PHA associated with tubulointerstitial nephritis is still unclear. After 3 months of age, the prevalence rate of secondary PHA1 decreases dramatically [20]. Since it used to occur in neonates and infants, tubular immaturity has been advocated. The pathophysiology of tubular resistance may involve cytokine factors such as TGF-β that is known to decrease MR sensibility [21] and parenchymal scarring secondary to obstruction. Clinical and biological findings are comparable to those of renal PHA1. In our study population, the more precocious symptoms, the more severe salt wasting, arguing tubular immaturity. Urine culture and ultrasound examination are essential to differentiate secondary PHA1 from the genetic form. However, life-threatening symptoms may occur during the first hours of life, such as severe hyperkalaemia (7.7 mmol/l in patient 9). High salt intake is recommended

during the acute phase of infection with further progressive tapering. No data are available on the required time period for such a supplementation (ranging from 3 to 13 months in our hands); it seems that the youngest patients may require a long-lasting supplementation whereas older ones have lower salt requirements. Genetic analysis was not performed in the secondary forms because of their transient well-known outcome. Nevertheless, genotype investigation in the presence of secondary PHA may highlight MR or ENaC polymorphism and therefore help in understanding the pathophysiology of this disease.

No patient presented with hydramnios in our series which is different from previous description [22]. We have no explanation for this difference; all the pregnancies but one underwent serial systematic sonography. Prenatal polyuria might not be a constant feature. In all patients, the diagnosis came from routine blood electrolyte assessment [2] that may be sometimes completed by ACTH, cortisol, aldosterone and plasma renin concentration. Urinalysis and renal ultrasonography were always required in order to allow early recognition of secondary PHA1. An early onset of symptoms together with high aldosterone level and salt intake exceeding 30 mmol/kg per day strongly argues for systemic PHA1 (Figure 4, Table 1) but the severity of dehydration and hyperkalaemia is not pathognomonic of systemic PHA1. The long-term prognosis is rather good for renal and secondary PHA1 but it may be impaired in patients with the systemic form.

Conclusion

PHA1 has a wide clinical and pathophysiological spectrum. The most common clinical characteristics include failure to thrive and dehydration, and the diagnosis is based on plasma electrolyte assessment. Molecular biology of renal tubular principal cell has clarified the mechanism of genetic PHA1 whereas secondary PHA1 remains misunderstood. Other intracytoplasmic proteins that regulate ENaC activity (Nedd4, Small-G protein K, CAP1, CFTR) have been recently identified and could be involved [6,23]. The study of EnaC and MR polymorphisms in secondary PHA1 carriers is promising.

Conflict of interest statement. None declared.

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