A large family with a novel mutation in the SCNN1A gene causing a mild and transient form of autosomal recessive Pseudohypoaldosteronism type 1 (PHA1)

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BACKGROUND AND OBJECTIVE

Pseudohypoaldosteronism type 1 (PHA1) is a rare inherited disease characterized by resistance to aldosterone action and distinguished in two forms: the autosomal dominant renal form caused by mutations of the *NR3C2* gene (MR) and the autosomal recessive systemic form caused by mutations of the subunit genes *SCNN1A, SCNN1B, SCNN1G* of the epithelial sodium channel (ENaC). The classic phenotype of the autosomal recessive form of PHA1 is usually severe, lifelong, and expressed with multiorgan symptoms, whereas the autosomal dominant form is milder, transient and restricted to the kidneys.

In this study we describe the clinical and biochemical manifestations and genetic analysis of nine children diagnosed with PHA1, all members of a large consanguineous family.

PATIENTS AND METHODS

Nine patients, most of their parents and some siblings were studied. Clinical and biochemical data were analyzed. The coding regions and the intron/exon boundaries of the *NR3C2* and *SCNN1A* genes were bidirectionally sequenced. A structural model of the SCNN1A was constructed based on the protein threading method. *In silico* analysis was carried out employing the software: Mutation Taster, Polyphen 2 and SHIFT.

RESULTS

Patients were diagnosed between 8 and 60 days of age presenting with failure to thrive, vomiting or during the course of a respiratory illness, with hyperkalemia, hyponatremia, elevated renin and aldosterone levels and a positive sweat test. All patients responded well to sodium supplementation with decreasing requirements with age until discontinuation of treatment. No mutation was detected in the *NR3C2* gene. Subsequent analysis of the *SCNN1A* gene revealed that all patients were homozygous for the nucleotide 776 T>G transversion that results to a novel aminoacid change from Phe to Cys at position 226 of the protein (F226C). Their parents were heterozygous for the mutation except of two mothers who were homozygous without any medical history and with normal biochemical findings. Additionally two siblings were found to be homozygous, one with a short history of sodium supplementation in infancy and the other with no symptoms, while both of them have normal clinical and laboratory findings.

Phenylalanine is highly conserved among different species and the *in silico* analysis revealed that the mutation F226C is pathogenic. The structural model constructed showed that F226 is located at the extracellular domain of the *α* subunit and possibly affects the formation of the epithelial Na^+ channel by disrupting its interactions with the *β* and *γ* subunits that form the channel.

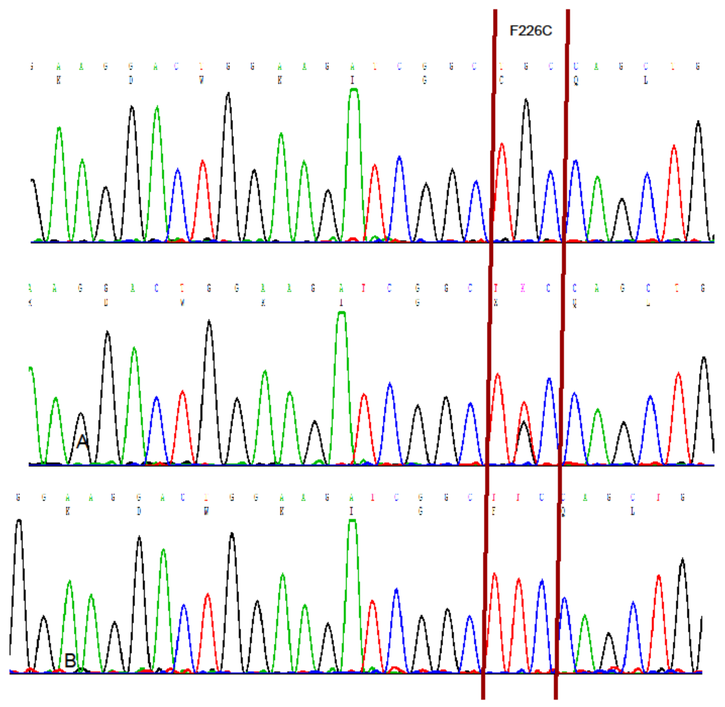

Figure 1. Part of the sequencing chromatogram of exon 3 of the *SCNNA1* gene (NCBI Reference Sequence: NM_001038.5) showing the change at nucleotide cDNA 776T>G resulting to the F226C novel mutation A: patient homozygote for the mutation F226C, B: patient heterozygote for the mutation F226C, C: wild type.

Clinical and biochemical data of patients with PHA1 – F226C homozygous

Case	Case 1	Case2	Case 3	Case 4	Case 5	Case 6	Case 7 Sister of case 6	Case 8	Case 9
Age of diagnosis (days)	35	23	10	10	32	30	9	8	60
Clinical symptoms	Failure to thrive	Vomiting	Vomiting Bronchiolitis	Vomiting	Prematurity Failure to thrive	Viral illness	Viral illness	Prematurity RDS	Viral illness
Serum Na (mEq/L)	130	129.5	129.4	130.6	132	132	121	133.3	133
Serum K (mEq/L)	5.9	5.9	6.9	6.6	7.7	6.2	9.0	5.8	6.7
Serum aldosterone (pg/ml)	7660	11500	16200	4840	15200	13760	15100	12920	6000
Plasma renin (pg/ml)	161	-	-	-	719.6	126	>310	>310	197
Sweat test (mmol/L)	80	-	111	-	110	71	107	37	45
Initial Na supplementation (mEq/Kg)	8.1	6.7	7.6	6.1	5.3	6.3	17.7	8.0	3.0
Age at discontinuation of treatment / Ongoing Na supplementation	3.8 yrs	3.6 yrs	5 yrs	4.1 yrs	3 yrs	2.3 yrs 1.85mEq/Kg	1 yr 10.9 mEq/Kg	0.5yrs 7.35mEq/Kg	1.1 yrs 3mEq/Kg
Aldosterone (pg/ml) after discontinuation of treatment / on treatment	1350	1202	192	1289	636	1038	1186	3500	1533
Renin (pg/ml) after discontinuation of treatment / on treatment	50.6	62.3	13.4	39	30.6	29.9	71.8	39.2	46

CONCLUSIONS

We present a large family with a mild and transient form of autosomal recessive PHA1 due to a novel homozygous mutation in the *SCNN1A* gene, demonstrating that there is a great variability in the phenotype of a usually severe disease.

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