Systemic pseudohypoaldosteronism type 1 due to 3 novel mutations in SCNN1A and SCNN1B genes

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Introduction:

Inactivating mutations of genes encoding epithelial sodium channel (ENaC) unable aldosterone to show its mineralocorticoid activity thereby cause pseudohypoaldosteronism type 1 (PHA1). PHA1 is a rare autosomal recessive inherited disorder with an estimated incidence rate of 1: 47 000 to 1: 80 000, and a prevalence of <1/1 000 000. The systemic form of PHA1 is characterized with defective sodium transport in many organ systems including kidney, lungs, colon, sweat glands and salivary glands. The systemic form is inherited in an autosomal recessive manner and caused by the loss of function mutations in the genes *SCNN1A*, *SCNN1B* and *SCNN1G* that encodes for the α, β and γ subunits of ENaC, respectively. Herein, we present the clinical and molecular genetic characteristics and management of 3 cases with systemic PHA1 due 3 novel mutation detected in *SCNN1A* and *SCNN1B*.

Case 1: Male patient presented at postnatal 9th day with vomiting, poor feeding, discomfort and skin rash. In laboratory investigations severe hyponatremia, hyperkalemia, metabolic acidosis, elevated plasma renin, elevated aldosterone and positive sweat test suggested the diagnosis of systemic PHA1. Molecular genetics analysis of SCNN1B gene revealed two novel pathogenic variants in compound heterozygous state [c.87C>A(p.Tyr29*)/IVS9+1G>A (c.1346+1G >A)].

Case 2: A female admitted at 10th day of life with vomiting, poor feeding, and weight loss. In laboratory investigations severe hyponatremia, hyperkalemia, metabolic acidosis, elevated plasma renin, elevated aldosterone and positive sweat test suggested the diagnosis of systemic PHA1. Molecular genetics analysis revealed a novel homozygous pathogenic variant [p.His69Arg(c.206A>G] in *SCNN1A* gene.

Case 3: A female neonate admitted to our clinic with the complaints of weakness and poor feeding at postnatal 5th day. In laboratory investigations severe hyponatremia, hyperkalemia, metabolic acidosis, elevated plasma renin, elevated aldosterone and positive sweat test suggested the diagnosis of systemic PHA1. In the molecular genetics analysis a homozygous p.A200Gfs*6 (c.598dupG) one base duplication was detected in *SCNN1A* gene.

Results:

In the molecular genetics analysis of Case 1 a novel compound heterozygous [c.87C >A (p.Tyr29*)/c.1346+1G >A] mutation was detected in *SCNN1B* gene. Molecular genetics analysis of Case 2 revealed a novel homozygous p.His69Arg (c.206A>G) mutation in *SCNN1A* gene. Molecular genetics analysis of Case 3 revealed a novel homozygous p.A200Gfs*6 (c.598dupG) mutation in *SCNN1A* gene.

Table 1. The clinical and laboratory characteristics of the cases

	Case 1	Case 2	Case3	Normal values
Age of presentation (day)	9	10	5	
Sex	M	F	F	
Symptoms	Vomiting, poor feeding, restless, skin rash	Vomiting, poor feeding, weight loss	Vomiting, poor feeding, fatigue	
Serum Na (mEq/L)	106	117	107	135-150
Serum K (mEq/L)	11.8	9.8	10.9	5.5-5.5
Serum HCO3 (mEq/L)	9	12.1	8.2	18-24
PH	7.16	7.24	7.11	7.35-7.45
Serum Creatinine (mg/dL)	0.7	0.6	0.9	
Urine Na (mEq/L)	102	92	132	
Urine K (mEq/L)	12	16	9	
Trans-tubular potassium gradient	4	5	2	
Aldosterone	3173	3032	5882	(86-1340 pg/mL)
Plasma renin	98.2	96.9	104.2	(2.4-37.0 ng/mL)
Sweat test Cl^- concentration(mEq/L)	147	112	134	
Urine culture	Negative	Negative	Negative	
Renal ultrasound	Normal	Normal	Normal	
Follow up period	5 months	6 months	1.5 months	
Number of salt wasting crises	6	1	3	
Site of mutation	*SCNN1B*	*SCNN1A*	*SCNN1A*	

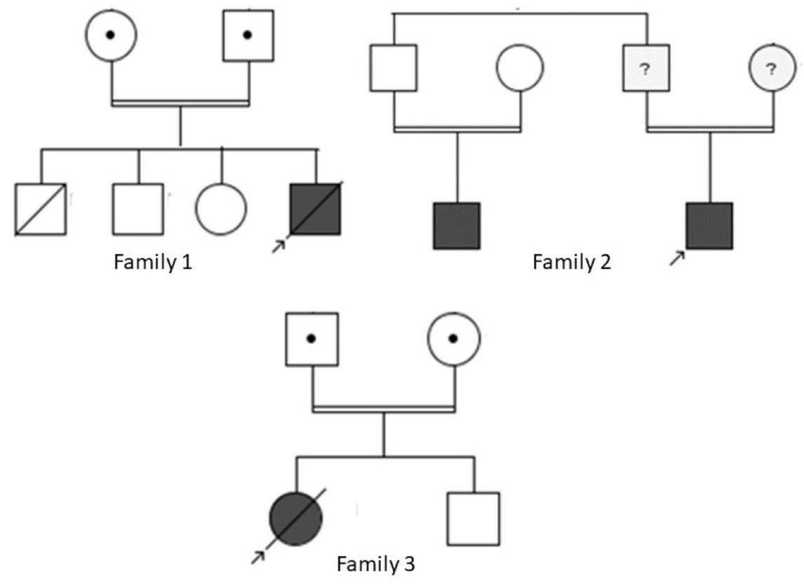

Figure 1. Pedigree of 3 families with ENaCs gene mutations

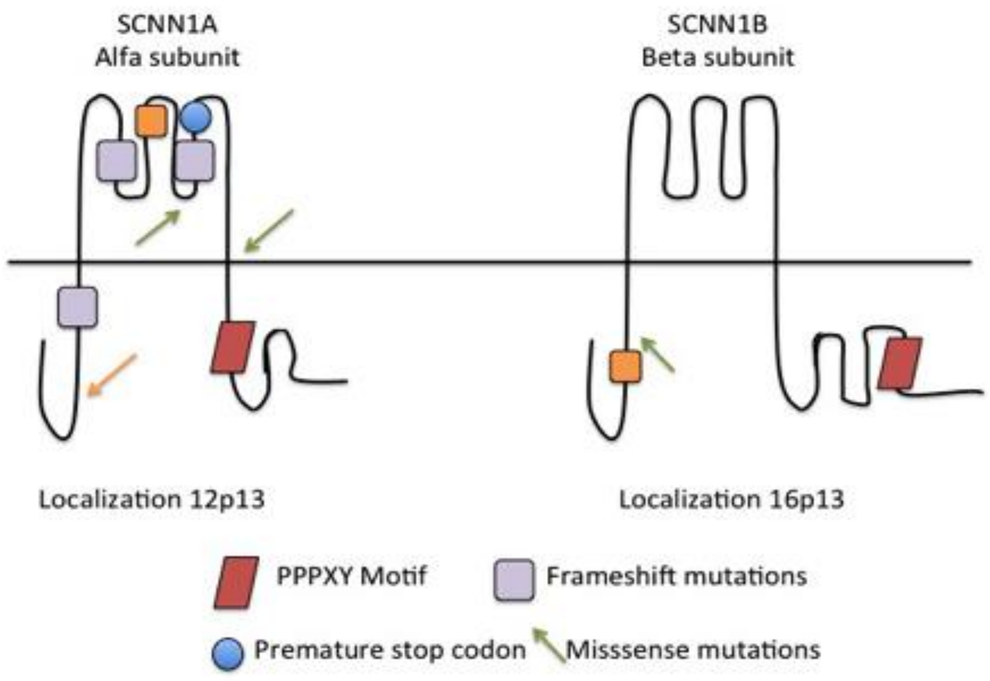

Figure 2. Schematic illustration of the two ENAC subunits encoded by genes *SCNN1A* and *SCNN1B*.

Conclusion

Patients with vomiting, diarrhea and growth retardation, and having hyponatremia, hyperkalemia and metabolic acidosis, PHA1 should be considered in the differential diagnosis. As the disease is rare and there is no strong phenotype-genotype correlation, it is still difficult to predict the prognosis of patients with PHA1. Therefore, to better understand the underlying molecular genetics and phenotype-genotype relationship, long-term follow up of patients whose phenotypes and genotypes have been defined is required. Present cases would expand the mutation database and help to better understand the phenotypical variability.

***Conflict of interest:** Nothing to disclose