CLINICAL MANIFESTATIONS & MOLECULAR ANALYSIS OF FOUR PALESTINIAN PATIENTS WITH PSEUDOHYPOALDOSTERONISM TYPE 1 (PHA 1) REVEALING FOUR NOVEL MUTATIONS IN THE "ENAC" SUBUNIT GENES

Abdulsalam Abu-Libdeh ,MD, Amal Abedrabbo, MD, and Bassam Abu-Libdeh, MD

Division of Pediatric Endocrinology, Department of Pediatrics, Makassed Islamic Charitable Hospital, Mount of Olives, Jerusalem

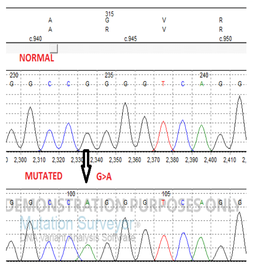
Objectives: Pseudohypoaldosteronism type 1 (PHA 1) is a rare hereditary disorder characterized by resistance to the actions of aldosterone. Two different modes of inheritance with different mechanisms & clinical manifestations have been described. Autosomal recessive that affects the epithelial sodium channel (ENaC), the defect is permanent and affects all aldosterone target organs. Autosomal dominant or sporadic PHA 1 affects the mineralocorticoid receptor in most patients.

Clinical presentation and Methods: Four unrelated Palestinian infants to a consanguineous Palestinian families presented in the first week of life with severe dehydration, hyponatremia, hyperkalemia and severe metabolic acidosis, assessed to have pseudohypoaldosteronism and were managed with hypertonic saline and kayexalate and did not improve on mineralocorticoids. Plasma renin activity & Aldosterone levels were extremely elevated.

Results: Whole exom sequencing and subunit genes of the ENaC were sequenced and revealed four novel mutations:

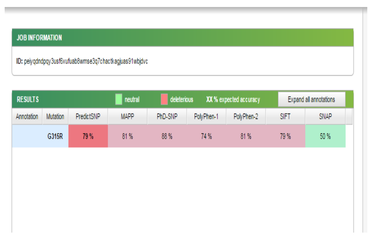
- G315R (Gly315Arg) in exon 6 of codon 315 of SCNN1B gene.
- C.69delG causing frameshift and stop codon (p.G23GfsX26) of SCNN1A gene.
- R73C (Arg73Cys) mutation in the SCNN1A gene.
- c.142-143insC mutation that leads to frameshift and premature stop codon (p.S47fsX69) of SCNN1G gene.

Case 1 :SCNN1B GENE

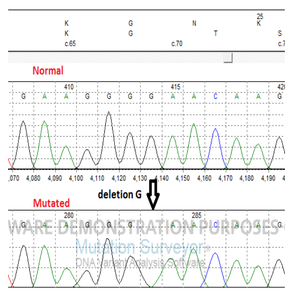


G315R (Gly315Arg) function: predicting the functional effect of amino acid substation in exon 6 of codon 315 done using the software PredictSNP for gene **SCNN1B** gene protein product, **gave (79%) deleterious effect on the protein function of this gene.**

G315R (Gly315Arg)

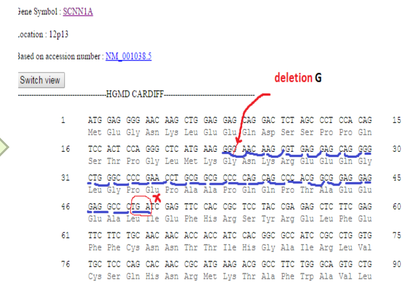


Case 2 :SCNN1A GENE

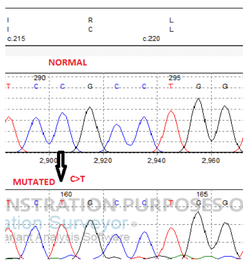


c.69delG mutation is a deletion mutation of G at codon 23 that leads to frame shift and premature termination of protein translation after 26 codons **(p.G23GfsX26)** of **SCNN1A** gene .

c.69delG

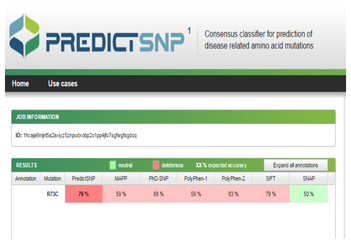


Case 3 :SCNN1A GENE

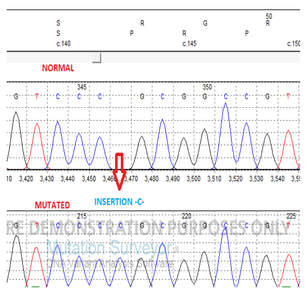


R73C (Arg73Cys) mutation: predicting the functional effect of amino acid substation in exon 2 of codon 73 done using the software PredictSNP for gene SCNN1A gene protein product, gave (76%) deleterious effect on the protein function of this gene.

R73C (Arg73Cys)



Case 4 :SCNN1G GENE



c.142-143insC mutation is a duplication mutation of C at codon 47 that leads to frame shift and premature termination of protein translation after 69 codons **(p.S47fsX69)** of **SCNN1G** gene .

c.142-143insC

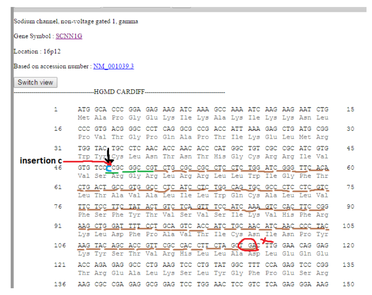


Table summarizing patients: clinical presentation, lab tests & molecular diagnosis

	Case 1- A.E	Case 2 - M.N	Case 3 - N.B	Case 4 - M.B
Address	Gaza	Gaza	Gaza	Jenin- Yabud
Consanguinity	1st cousins	2nd cousins	Far relatives	1st cousins
Perinatal history	FT, NVD, BW: 3.45Kg	FT, NVD, BW: 3.50 Kg	FT, NVD, BW: 3.00 Kg	FT, CS, BW:3.4Kg
Genitalia	Normal male genitalia	Normal male genitalia	Normal male genitalia	Normal male genitalia
Skin	No hyperpigmentation	No hyperpigmentation	No hyperpigmentation	No hyperpigmentation
Onset of symptoms	12th day of life	8th day of life	1st week of life	7th day of life
Symptoms	dehydration (vomiting, poor oral intake, hypoactivity)	dehydration (vomiting, poor oral intake, hypoactivity)	dehydration (vomiting, poor oral intake, hypoactivity)	dehydration (vomiting, poor oral intake, hypoactivity)
Labs	K 10, Na 130 Aldosterone: 150 Renin: 1040	K 8, Na 127 Aldosterone: 1570 Renin: 160	K 11, Na 131 Aldosterone: >2500 Renin: 12.4	K 11, Na 122 Aldosterone: >1000 Renin: 94.7
Blood Gas	PH:7.24, HCO3: 13	PH:7.20, HCO3: 15	PH: 7.25, HCO3: 17	PH:7.27, HCO3:18
Treatment	Kayexalate, HTS	Kayexalate, HTS	Kayexalate, HTS	Kayexalate, HTS
Genetic testing	**SCNN1B: G315R novel mutation**	**SCNN1A: c.69delG novel mutation**	**SCNN1A : R73C novel mutation**	**SCNN1G: c.142-143insC novel mutation**

Conclusions

❖ To our knowledge, this is the first description of this disease in a Palestinian family with molecular confirmation of four novel mutations in the *"ENaC"* subunit genes, allowing accurate genetic counseling, early diagnosis of affected kindreds, early therapeutic interventions and avoiding complications and checking if the clinical presentation does correlate well with the specific genotype.