Familial Hyporeninemic Hyperkalemia and Hypertension (Pseudohypoaldosteronism Type II) Resulting from *KLHL3* Gene Mutations

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Background:

Pseudohypoaldosteronism type II (PHAII) is a renal tubular disease with an autosomal dominant inheritance characterized by hypertension, hyperkalemia, hyperchloremic acidosis and hyporeninemia. Recent studies have shown that *KLHL3* and *CUL3* mutations cause PHAII. *KLHL3* regulates Na+-Cl− cotransporter (NCC) in the distal nephron. It participates in the regulation of NCC trafficking and also possesses a BTB-BACK domain that is involved in substrate recruitment to Cullin3-containing ubiquitin ligase complexes thus promoting degradation of NCC. Hypertension (HT), an essential symptom of PHAII, manifests in adolescents and young adults. In the absence of family history it remains undiagnosed in infancy and childhood. Hyperkalemia may also be overlooked.

Objective:

We aimed to diagnose the underlying cause of hyporeninemic hyperkalemia and/or HT in two families in which the index cases presented with these manifestations.

Subjects and methods:

We evaluated two families with 25 subjects. Thirteen exons of the *KLHL3* gene were amplified by PCR and sequenced.

Results:

PHAII was diagnosed in 12 patients. Heterozygous mutations in *KLHL3* (Q309R or R528H) gene were identified in all. Borderline to very high K^+, very low plasma renin activity (PRA) and low to borderline bicarbonate levels were found in all affected individuals (Tables 1, 2).

Family 1

Identical twins, presented at age 8y, because of short stature. The mother and maternal grand mother are Jews of Iraqi origin. Investigations revealed persistent hyperkalemia in both twins (Fig 3 A). Follow-up in another medical center failed to diagnose PHAII. Family history of hyperkalemia and hypertension (mother, maternal grandmother respectively) were also overlooked. Seven affected members from three generations had a Q309R mutation (Fig. 1). The restriction enzyme Eco521 cleaved the single mutant allele but not the wild type allele of amplified exon 9 demonstrating the presence of a single mutant allele (Fig. 1C). Except the twin brothers, affected subjects had normal stature. Hypertension (HT) was found only in older subjects.

Family 2

A 2 y old male was born at 38 wks. of gestation weighing 3.400 kg. The parents were Arabic Muslims. After birth he developed respiratory distress requiring ventilation. At age of 7 days, he had hyperkalemia and hyperchloremia with undetectable PRA that persisted (Table 2, Fig. 3B). Hypertension appeared at 17 months of age. Thiazide diuretics normalized hyperkalemia and blood pressure. Mutation analysis revealed *KLHL3* mutation (R528H). Three of 4 sisters and the mother also have the mutation (Fig. 2). All had mild hyperkalemia (except propositus), hyperchloremia and acidosis. Except one, all had very low PRA. Systolic blood pressure was elevated in all (>95 P).

Discussion:

Two families with 12 affected subject described here highlight genetic heterogeneity of PHAII. Heterogeneous phenotypes ware previously noted in patients with *KLHL3* but the number of large pedigrees reported and the data especially in children are limited. A severe phenotype was found to be associated with *CUL3* mutations presenting at much younger ages than those with mutations in *KLHL3*, *WNK1*, *WNK4* and had more severe hyperkalemia, acidosis and were far more likely to have HT before age 18. Thus the presentation in infancy with hyperkalemia and HT is very unusual in children with *KLHL3* mutations.

Clinical and laboratory data in Family 1

Subject no.	I1	I2	II1	II2	II3	III1	III2	III3	III4
Age/sex	76/M	69/F	49/M	48/F	47/F	11/M	11/M	10/F	11.5/F
KLHL3 Q309R Mutation	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Ht SDS	-1.33	-0.77	+0.48	-0.44	-1.	-1.50	-1.70	-0.74	-
B.P	132/71	115/78*	149/80	147/95	132/85	104/61	108/71	104/61	108/71
K^+	4.8	5.4	4.6	4.9-5.2	5.1	5.7-6.6	5.9-7.2	5.1-5.3	5.3
Cl^-	107	102	105	108	108	113	110	109	108
Bicarb.	29	27	28	25.7	19.5	22.3	21.5	22.7	22
PRA	1.6	2.3	0.5	0.1	8*	0.1	0.1	0.7	11.6*

Family 2

Subject no.	II2	II3	III1	III2	III3	III4	III5
Age/sex	40/M	38/F	15/F	13/F	12/F	8/M	2/M
KLHL3 R528H Mutation	No	Yes	Yes	Yes	No	Yes	Yes
Ht SDS	+ 0.16	+0.41	+0.02	-0.03	+1.47	+ 0.40	+1.30
B.P	130/76	154/77	136/77	124/77	109/63	123/78	146/95
K^+	4.3	5.6	6	6.2	4.3	5.8	7
Cl^-	106	110	114	112	106	110	110
Bicarb.	23	18	19.7	19.8	22	19.1	22.6
PRA	2.6	3.6	0.3	0.3	3	0.7	0.3

Normal levels: K+, 3.5-5 mmol/l, Cl-, 98-105 mmol/l, HCO3=22-26 mmol/l, PRA, 0.5-2.7 ng/ml/h, *direct renin, µU/mL

Fig.1

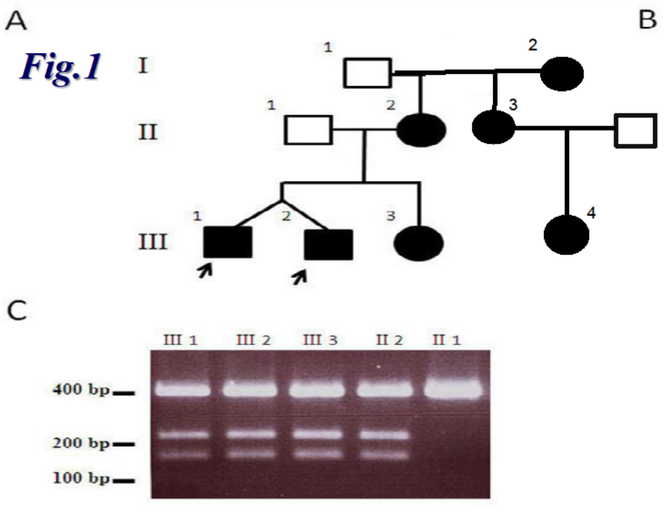
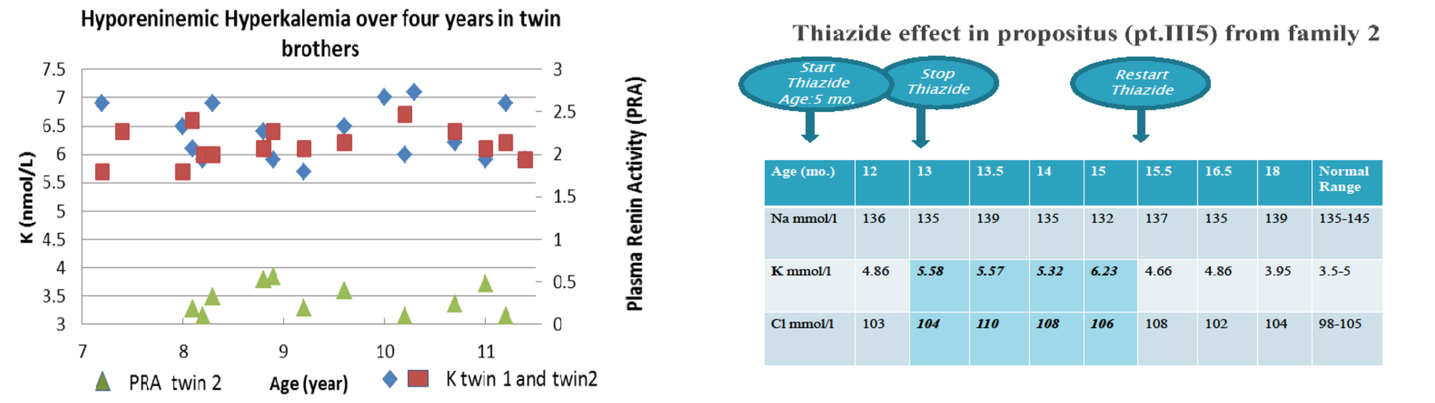
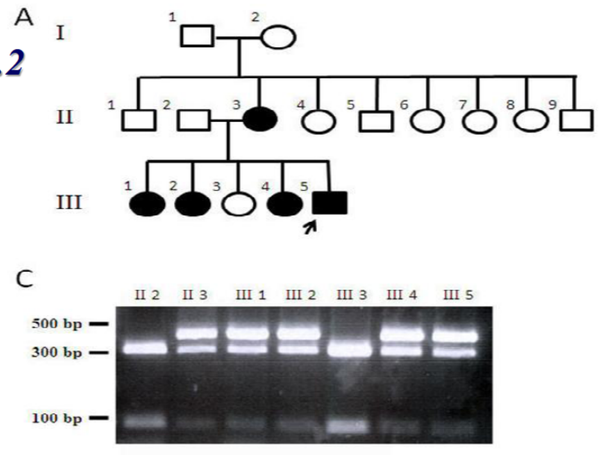


Fig. 3



Age (mo.)	12	13	13.5	14	15	15.5	16.5	18	Normal Range
Na mmol/l	136	135	139	135	132	137	135	139	135-145
K mmol/l	4.86	***5.58***	***5.57***	***5.32***	***6.23***	4.66	4.86	3.95	3.5-5
Cl mmol/l	103	***104***	***110***	***108***	***106***	108	102	104	98-105

Fig.2



Conclusions:

- Unexplained hyperkalemia and/or hypertension may be the first manifestations of PHAII
- In such cases family history and appropriate investigations may lead to correct diagnosis
- Early diagnosis is crucial for appropriate therapy (thiazides) and genetic counseling
- In patients with *KLHL* mutations, genetic heterogeneity may be found even among family members within the same pedigree

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Adrenals and HPA Axis

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