

KLHL3 Gene Mutation Presenting Clinical Features of Liddle's Syndrome

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Mutations in the Kelch-like 3 (KLHL3, NM_017415.2, 5q31.2) gene are known to be related to Pseudohypoaldosteronism type II (PHA II, OMIM 614495), a rare autosomal dominant disease manifesting as familial hyperkalemic hypertension. Here we report a case of a KLHL3 mutation with severe hypertension, hypertensive nephropathy, encephalopathy, retinopathy, and hypokalemia. A 42-year-old man was referred to our hospital for uncontrolled high blood pressure. He was diagnosed with hypertension 14 years ago but had voluntarily stopped taking antihypertensives for the past 6 months. He complained of visual disturbance and foamy urine which had begun a week prior. He had extremely high blood pressure (260/180mmHg) and severe obesity (BMI 39.85kg/m², height 166.9cm, weight 110.0kg). He also had a familial history of hypertension. Initial laboratory tests and results were as follows: serum BUN 25.5mg/dL, creatinine 1.84mg/dL, potassium 2.65mEq/L, bicarbonate 28.4mEq/L, urine dipstick 4+, urine protein creatinine ratio 13.1 g/g, urine potassium 37.60mEq/L, and transtubular potassium gradient (TTKG) 6.95. On admission, the patient was prescribed CCB, ARB, BB, and minoxidil with oral potassium supplementation. He gradually became drowsy and a brain MRI showed hypertensive encephalopathy; however, his neurologic status showed partial spontaneous recovery with remaining mild cognitive dysfunction. He also had retinal and disc hemorrhaging and severe concentric LVH, which are both consistent with hypertensive end-organ damage. A rapid ACTH stimulation test showed normal cortisol response and thyroid function tests were normal. In the urine, fractionated metanephrines and VMA (negative) were also normal. His serum aldosterone was normal (10.62ng/dL), but his plasma renin activity was elevated (29.42ng/dL/h) probably due to the use of ARB. An abdominal CT scan was negative for adrenal masses or renal artery stenosis. Interestingly, an NGS analysis reported a missense mutation c.159G>A (p.Met53Ile) in the KLHL3. In this case, the patient expressed hypokalemia rather than hyperkalemia in PHA II, and his hypokalemia was responsive to amiloride, just like Liddle's syndrome.

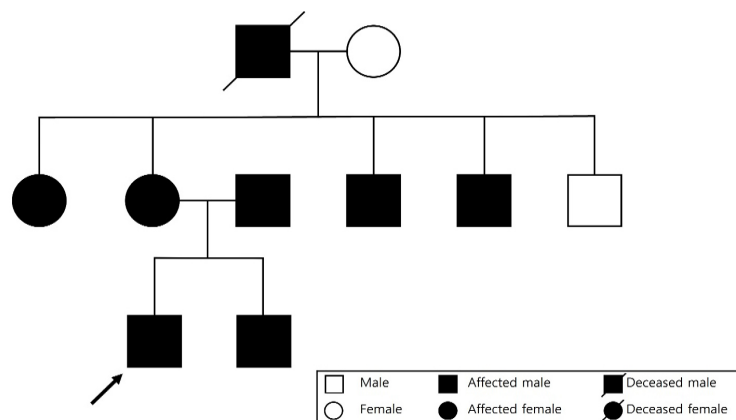


Figure 1. The patient's pedigree of hypertension.

	K (mEq/L)	Cr (mg/dL)	T.CO ₂ (mEq/L)	UPCR (g/g)	BP at 10am (mmHg)	Medication
2021-02-19	2.65	1.84	28.4	13.121	280/190	Amlodipine 10mg #1, Fimasartan 120mg #1
2021-02-21	3.32	1.93	-	-	162/108	Nicardipine 80mg #2, Fimasartan 120mg #1, Carvedilol 12.5mg #1
2021-02-23	4.12	1.72	22.5	-	141/119	Amiloride 10mg #2
2021-02-25	4.77	1.62	-	2.137	146/100	
2021-03-02	4.36	2.92	16.2	1.027	132/95	
2021-03-10	3.92	2.16	21.2	-	124/79	Fimasartan 120mg #1
2021-03-17	4.76	2.24	25.3	1.199	158/111	Fimasartan 120mg #1, Minoxidil 5mg #1
2021-04-28	4.7	1.55	-	1.043	151/93	
2021-06-02	4.88	1.85	21.1	0.234	119/70	
2021-07-07	4.87	1.64	23	0.985	131/84	

Table 1. Laboratory test results and clinical course