

Three Siblings with Corticosterone Methyloxidase Deficiency Type 2 due to c.1175T>C mutation + a Novel c.788T>A Mutation in CYP11B2 gene

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BACKGROUND

Corticosterone methyloxidase deficiency (CMOD) type 2 is an autosomal recessive disorder which presents with salt loss and failure to thrive in early childhood (Figure 1). We present three siblings with CMOD type 2 whose genetic analyses revealed a known c.1175T>C mutation (homozygous) and a novel c.788T>A mutation (homozygous) in CYP11B2 gene.

CASE 1:

The patient was admitted with salt loss and failure to thrive at the age of 6 months; he had hyponatremia and hyperkalemia despite elevated renin and normal aldosterone levels (Table 1). He was diagnosed clinically as isolated aldosterone deficiency; salt and fludrocortisone treatment was started. At the age of 3 years, he had normal growth. He had high corticosterone, 18-OH corticosterone and 18-OH corticosterone /aldosterone ratio (78) (Table 2). Treatment is summarised in Table 3. Genetic analysis revealed c.1175T>C mutation (homozygous) and a novel c.788T>A mutation (homozygous) in CYP11B2 gene confirming the diagnosis of CMOD type 2. Parents with consanguineous marriage were heterozygous for both mutations.

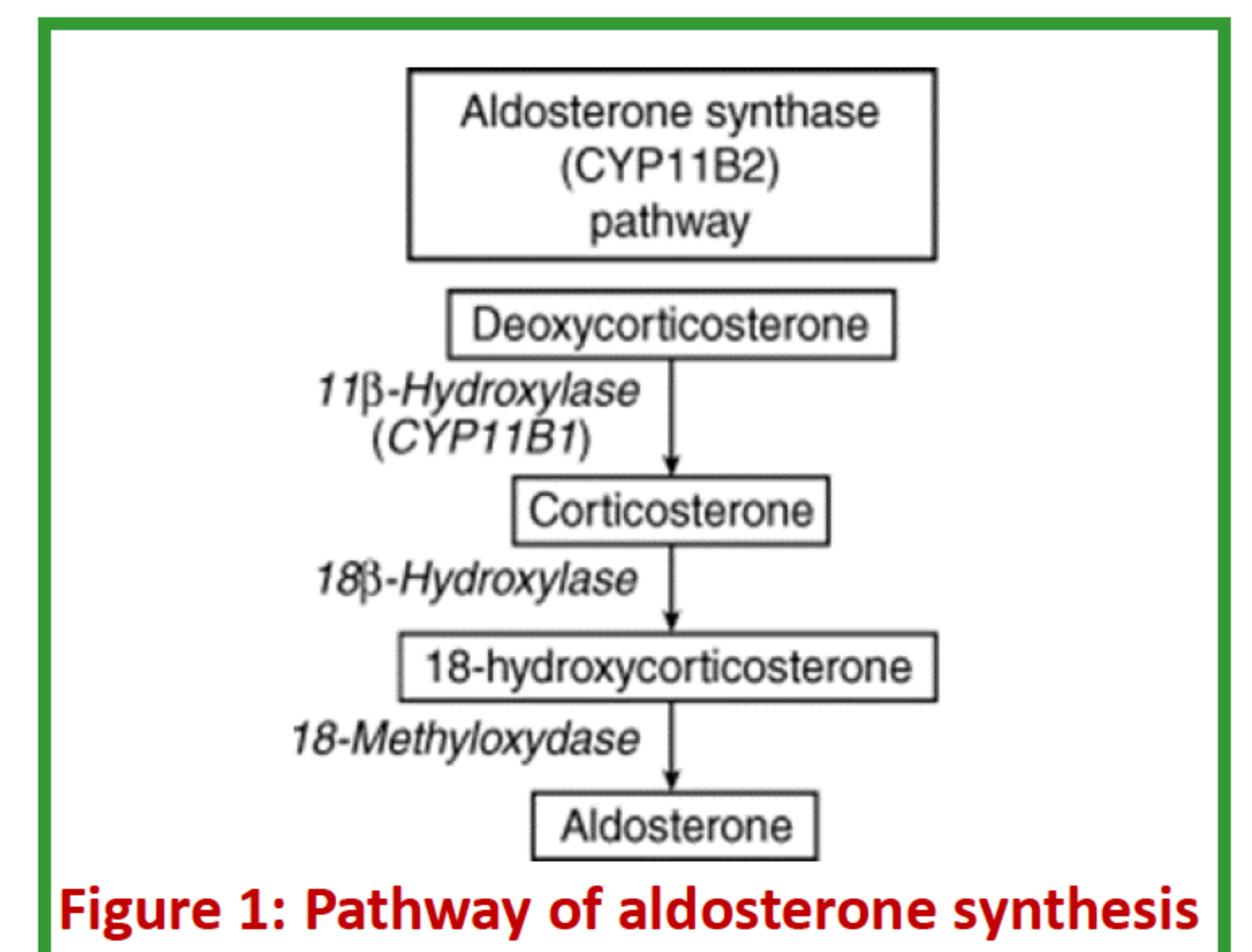


Figure 1: Pathway of aldosterone synthesis

CASE 2

At the age of 2 years, brother of case 1 admitted with failure to thrive. According to medical records, he had suffered from salt loss at the age of 3 months. Although his electrolyte levels were normal at admission, his height and weight SDS's were -1,99 and -2.14 respectively. With fludrocortisone treatment his growth normalized. Genetic analysis revealed the same mutation his brother had.

CASE 3

At the age of 3 months are admitted with poor weight gain, hyponatremia, mild hyperkalemia, increased renin and normal aldosterone levels. Fludrocortisone treatment resulted in adequate weight gain and normalized laboratory findings. Genetic analysis revealed the same mutation as her brothers had.

Table 1: Laboratory findings of cases

Case (Age)	Na (mmol/L)	K (mmol/L)	Renin	Aldosterone
1 (6 months)	124	5,2	500 (ng/ml/hour) (↑)	60 pg/ml (↑)
2 (2 years)	138	4,6	265,8 (uIU/ml) (↑)	<37 ng/dl (↑)
3 (3 months)	126	5,6	698 (uIU/ml) (↑)	56 ng/dl (↑)

Table 2: Steroid levels of case 1 in aldosterone synthesis pathway

Corticosterone (pmol/L)	18-OH corticosterone (pmol/L)	Aldosterone (pmol/L)	18-OH Corticosterone / Aldosterone	Corticosterone / 18-OH Corticosterone
8700 (↑)	5200 (↑)	65,86 (N)	78 (↑)	1,67
			N: 3 Type1: no sense Type2: >10 (usually ≥100)	Type1: ≥40 Type2: <10

Table 3: Dose regulation of fludrocortisone (FLDC) treatment in case 1

Age	Blood Pressure (TA)	Na (mmol/L)	K (mmol/L)	Blood N (mg/dl)	Cr (mg/dl)	Renin (ng/ml/hour)	Aldosterone (pg/ml)	Treatment
5 years 3 months	125/75 mmHg (↑) (crying)	140,9	5	51	0,6	841	<37	FLDC 100 mcgr ↓ FLDC 200 mcgr
5 years 5 months	Holter TA (↑)	141	3,7	27	0,4	18,3		FLDC 200 mcgr
	Holter TA (↑)	139	4,5	35	0,3			FLDC 125 mcgr
	Holter TA (↑)	179	4,7	64	0,5			FLDC 100 mcgr
	N	138	4,7	62	0,8	329		FLDC 75 mcgr

CONCLUSION

Genetical analyses are beneficial for diagnosis of the patients and other relatives at the risk of salt loss and failure to thrive. The mutation c.1175T>C is known as responsible for reduction of enzyme activity; although novel mutation of c.788T>A probably affects the enzyme structure or function. Functional analyses will confirm loss of gene production.

