Mutation of NROB1 and Double mutants in cis of CYP21A2 gene in a Chinese boy with primary adrenal insufficiency

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INTRODUCTION

X-linked Adrenal Hypoplasia Congenita(AHC) is a very rare hereditary cause of pediatric primary adrenal insufficiency(PAI) due to NROB1 mutation. Congenital adrenal hyperplasia(CAH) due to 21-hydrolase deficiency(21OHD) is most common hereditary cause of pediatric PAI due to mutated CYP21A2 gene with autodominal recessive inheritance.

AIM

To present a Chinese boy with PAI with the pathogenic mutation of NROB1 and Double mutants in cis of CYP21A2 gene

METHOD

Mutational analysis of CYP21A2 by Sanger sequencing and MLPA , and Tartget sequencing for PAI gene by Next-generation sequencing technology (NGS)

RESULTS

The one-month-old boy was the third child (birth weight, 2.9 kg, full term) of non-consanguineous healthy parents of Chinese Han ethnicity, who presented with salt losing adrenal insufficiency early in two days of life in local hospital. On physical examination, marked skin pigmentation was noted, he was found to have normal looking male genitalia. Hormonal evaluation revealed ACTH>440.4 pmol/L, cortisol 100.0nmol/L, P 0.3 ng/ml, 17(OH)P 2.89 ng/ml, Androstenedione >35 nmol/L, Na 113.1 mmol/L， Cl 79.8 mmol/L， K 5.98 mmol/L. CAH 21OHD was suspected and CYP21A2 gene mutation analysis was performed by Sanger sequencing and MLPA. Treatment was started with oral hydrocortisone (10-15 mg/m2/day), 9α-fluorocortisol (0.1mg/day), and salt supplementation (NaCl 1-2g/day) under adrenal insufficiency. 1 month later, The result of the CYP21A2 gene analysis showed two pathogenic mutations c.844G>T & c.920-921linsT , and the patient was diagnosed with CAH 21OHD in local hospital. The boy started growing properly.

At 6-month-old, serum androstenedione was less than 1.5 nmol/L. At age one year, he came to us and was admitted to our hospital for precise diagnosis, with the administration of oral hydrocortisone (9.2 mg/m2/day) and 9α-fluorocortisol (0.1 mg/day). Plasma ACTH>440.4 pmol/L, cortisol <0.08ug/dL, P <0.1 ng/ml, 17(OH)P 0.08 ng/ml, Androstenedione <1.5 nmol/L,DHEAs 0.08umol/L, T<0.13ng/ml, Na 138.0 mmol/L， Glu 4.9 mmol/L， K 4.8 mmol/L, normal plasma renin(55pg/ml). The adrenal glands was normal on abdominal ultrasound. Parental mutational analysis of CYP21A2 showed the same two mutation in the father, nor in the mother, indicaticating the patient carried double pathogenic mutants of CYP21A2 in cis, which cannot explain the patients clinical symptoms. Tartget sequencing for PAI gene was requseted. One month later, a heterozygous maternal pathogenic mutation of c.610G>T [p.(Glu204*) was found to NROB1 exon 1. X-linked Adrenal Hypoplasia Congenita（AHC）was determined.

CONCLUSIONS

We identified a mutation of NROB1 in a Chinese boy with primary adrenal insufficiency carrying double mutants in cis of CYP21A2 gene. Slightly elevated 17OHP and high level of Androstenedione in the early stage may contributed to the double mutants in cis of CYP21A2 gene.

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