Three Chinese Patients from Two Kindreds with Aldosterone Synthase Deficiency : Clinical Characteristic with Mutation Analysis Report

The First Affiliated Hospital of Sun Yat Sen University, Guangzhou, China

Wijaya Melati, Huamei Ma, Jun Zhang, Minlian Du, Yanhong Li, Qiuli Chen, Hongshan Chen, Song Guo

Abstract: Aldosterone Synthase deficiency (ASD) is a rare autosomal recessive disease caused by inactivating mutation in the CYP11B2 gene, usually presenting with severe salt-wasting in infancy or stress-induced hyperkalaemia and postural hypotension in adulthood. ASD is unable to be detected by Neonatal screening of 17-hydroxyprogesterone, hence patients would not be diagnosed until they suffer from salt-wasting crisis. Due to this potentially life-threatening risk, early detection and adequate replacement therapy will significantly improve the prognosis.

Objective: We summarized the clinical features of three cases from two unrelated families with ASD; to improve physicians in the understanding and diagnosing of ASD.

Method: By describing clinical symptoms, biochemical characteristics and outcomes; conducting CYP11B2 molecular genetic analysis using direct DNA sequence.

Result: 3 patients from two unrelated, non-consanguineous families. Two brothers (M1 and M2) visited our unit for the first time at 2 m and 2.5y respectively; the other patient is a girl (F) at 5 m. All of three patients had repeated vomiting with poor feeding at newborn period (1~2w) and failure to thrive. They all visited local hospitals and were found to have hyperkalaemia, hyponatremia and metabolic acidosis. Treatment of underlying condition was started at that time, followed by giving additional sodium supplementary 2.0-4.5g/day. Patient F also received “Sodium bicarbonate, Sodium polystyrene sulfonate, etc” to reduce blood potassium concentration. Patient F has a healthy elder sister; and a baby brother who died 10 days after birth, he presented similar symptom during his first week after birth, was also suspected to be affected. No hyperpigmentation were observed on all 3 patients, all of them have normal external genitalia. Patients M1 and F's laboratory test revealed: hyperkalaemia [K^+ 7.64~7.69 mmol/l], hyponatremia [Na^+ 123-132mmol/l], patient F had metabolic acidosis [TCO2 13.4mmol/l]. Plasma ACTH, Cortisol, Testosterone, Progesterone, 17-hydroxyprogesterone, Androstenedione were in normal range. Plasma renin was highly elevated [864.3~1287pg/ml; the normal range in adult is 4-24 pg/ml], while plasma aldosterone was in normal range for patients age [117-672.11 pg/ml; NR 10-160 pg/ml].

Sequencing of CYP11B2 gene showed that patients M1 and M2 both carried same heterogenous pathogenic mutation: c.1121G>A (p.Arg374Gln) was inherited from their father and c.1486delC p.(Leu496fs) was inherited from their mother. Patient F homozygous for c.1303G>A p.(Gly435Ser) which is a known pathogenic mutation. We later learnt that her mother has the same mutation site and she also has generalized weakness with unknown newborn condition; her father doesn’t have any mutation on CYP11B2 gene. Patient M2 had been given only sodium supplementation treatment till 6 month old then gradually discontinued. He presented normal growth development and normal blood electrolyte till his last follow up at 4.33 years old. Patients M1 and F received fludrocortisone therapy at dosages of 0.1 mg Qd, and 0.1 mg Bid respectively, with sodium supplementation 2-3g/d and 3-6g/d respectively. Patient M1's mother only gave him fludrocortisone at 0.1g Qd and discontinued sodium supplement therapy by herself when M1 started to receive his food supplements at 6 months old. He regularly followed up till his last visit at 1 years old. He didn’t present any undesirable clinical effect; his blood electrolyte and growth was in normal range. Patient F last visit was at 1 years old, still needed NaCl 3-6g/d supplementation and fludrocortisone therapy 0.1 g Bid. Her blood electrolyte was normal but her growth is slower than others her age.

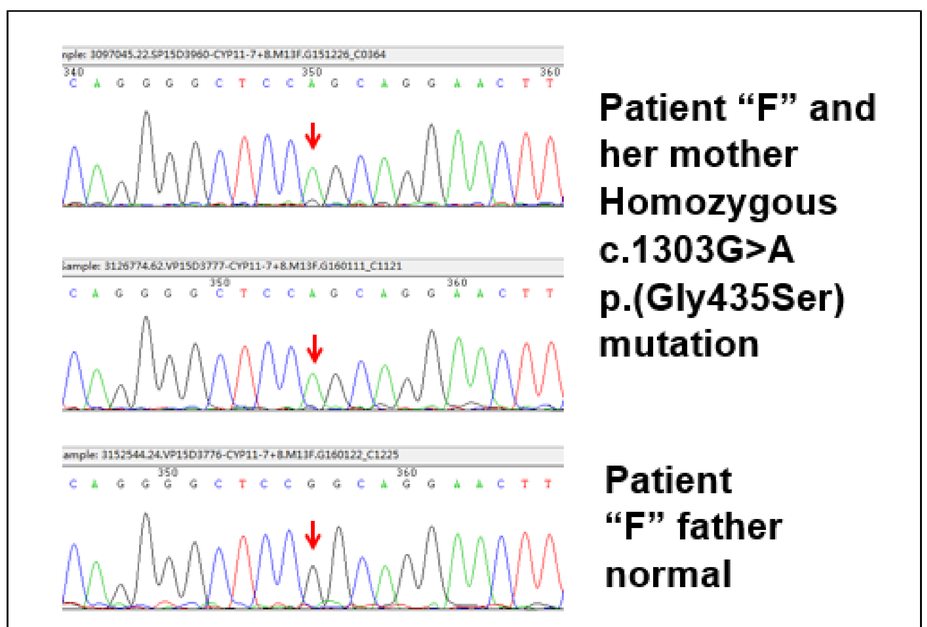

Fig1. Patient “F” family direct sequencing CYP11B2 result

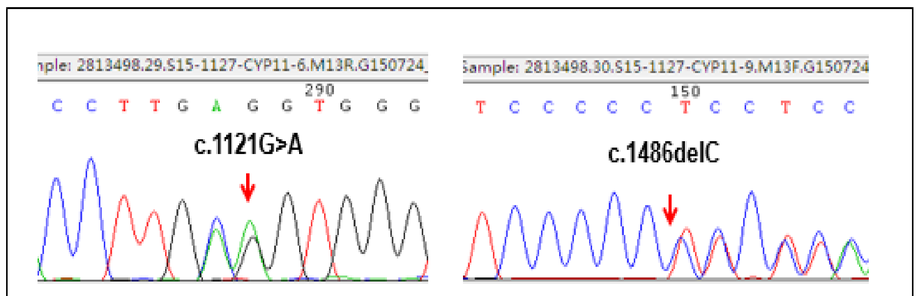

Fig 2. “M1” and “M2” CYP11B2 direct sequence heterozygous for c.1121G>A p.(Arg374Gln) and c.1486delC p.(Leu496fs) mutation

Conclusion: We reported 3 Chinese patients from two kindreds that have newborn salt-wasting clinical features; molecular genetic testing will very helpful for accurate diagnostic. Adequate fludrocortisone replacement therapy and sodium treatment brings good prognosis for patients.

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