

Case Report

Two Japanese patients with the renal form of pseudohypoaldosteronism type 1 caused by mutations of *NR3C2*

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Abstract. Pseudohypoaldosteronism type 1 (PHA1) is a disease characterized by neonatal salt loss due to aldosterone resistance. Two types of PHA1 are known: an autosomal recessive systemic form and an autosomal dominant renal form. The cause of the renal form of PHA1 is heterozygous mutations in *NR3C2*, which encodes the mineralocorticoid receptor (MR). We encountered two female Japanese infants with the renal form of PHA1 and analyzed *NR3C2*. The two patients had poor weight gain, and one was developmentally delayed. Genetic analysis identified one novel mutation (c.492_493insTT, p.Met166LeufsX8) and one previously reported mutation (p.R861X). The two produced a premature stop codon, resulting in haploinsufficiency of the MR. In conclusion, genetic analysis of *NR3C2* is useful for diagnosis and planning therapeutic strategies.

Key words: pseudohypoaldosteronism type 1 (PHA1), *NR3C2*, mutation

Introduction

Pseudohypoaldosteronism type 1 (PHA1) is a rare disease manifested by mineralocorticoid resistance of the kidney and/or other mineralocorticoid target tissues. Despite very high plasma aldosterone and renin

levels, patients with PHA1 have excessive salt wasting (1–3). There are two types of PHA1. The systemic form of PHA is inherited in an autosomal recessive manner and manifests severe life-long salt wasting resulting from mineralocorticoid resistance in multiple target tissues, such as sweat glands, salivary glands, the colonic epithelium; and the lung. On the other hand, with the renal form of PHA1, aldosterone resistance is shown only in the kidney, and its inheritance is autosomal dominant. In this latter form, clinical symptoms of salt loss gradually improve with age (1–3).

The renal form of PHA is caused by mutations of *NR3C2*, which encodes the mineralocorticoid receptor (MR), and many mutations have been

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reported thus far (1–6). Moreover, it is noted that phenotypic variability is present even in patients sharing identical mutations (3–5).

Here we report one novel mutation and one previously reported mutation of *NR3C2* in two Japanese infants with the renal form of PHA1.

Methods

The Institutional Review Board Committee of Hokkaido University School of Medicine approved this study. Each patient's parents provided written informed consent. Genomic DNA was extracted from peripheral blood leukocytes. The *NR3C2* exon was amplified by polymerase chain reaction (PCR) as reported previously (7). PCR products were purified and sequenced directly using an Applied Biosystems 3130 Genetic Analyzer (Applied Biosystems, Foster City, CA, USA).

Case Report

Patient 1

Patient 1 was a girl. She was the first child in her family and was delivered by caesarian section at 38 wk gestation because of fetal distress. Body weight at birth was 2010 g. There was no consanguinity, and the parents were healthy. Her external genitalia were normal for a female. At one mo of age, her body weight was 2420 g. As her weight gain was insufficient, she was followed by regular health examinations. Because her weight gain continued to lag (2556 g) at 2 mo of age, a more extensive medical examination was performed. Laboratory examinations showed hyponatremia (124 mmol/l) and hyperkalemia (5.9 mmol/l). In addition, an extremely elevated plasma aldosterone concentration (5318 pmol/l; normal range at 2 mo, 746.2–2102 pmol/l) and extremely elevated plasma rennin activity (PRA, > 20 µg/l/h; normal range 3.66–12.05 µg/l/h) were found. Her urinary Na and K levels were 28 mmol/l and 56.2 mmol/l, respectively, and urinary Na excretion was thought to be inappropriately high

in spite of hyponatremia. Her adrenal and renal functions were normal. Based on these findings, she was diagnosed as having the renal form of PHA1, and oral salt supplementation (2 g/d) was initiated. Thereafter, her weight gain improved, and at this time, her growth is satisfactory.

Patient 2

Patient 2 was a girl. She was the third child born to nonconsanguineous parents. No obvious family history was pointed out. The patient was born at 40 wk gestation with a body weight of 2768 g. She had normal female genitalia. At one mo of age, poor weight gain was noticed, and regular monthly health examinations were implemented. However, her growth failure continued and developmental milestones were delayed. Because she could not sit on her own or roll over at 10 mo of age, she was referred to us. At this time, her body weight was 5230 g (–3.5 SD for a normal Japanese girl of this age) and height was 63.3 cm (–3.3 SD for a normal Japanese girl). Laboratory examinations showed hyponatremia (125 mmol/l) and hyperkalemia (5.1 mmol/l). Endocrinological evaluation revealed extremely elevated plasma aldosterone (30999 pmol/l) and PRA (> 20 µg/l/h) levels. Her adrenal and renal functions were normal. She was therefore thought to have the renal form of PHA1, and salt supplementation (5 g/d) was started, after which her serum sodium level returned to the normal range and body weight gain improved. She is now 22 mo of age and her height is 75.4 cm (–2.0 SD for a normal Japanese girl), and her weight is 10.0 kg (0 SD for a normal Japanese girl). Her development has gradually improved but is still delayed. She was not able to walk alone until the age of 21 mo, and her speech was limited to only babbling. Her developmental quotient is 72.9.

Results

Sequence analysis demonstrated a heterozygous two-base insertion (c.492_493insTT) in exon 2, resulting in a premature stop codon

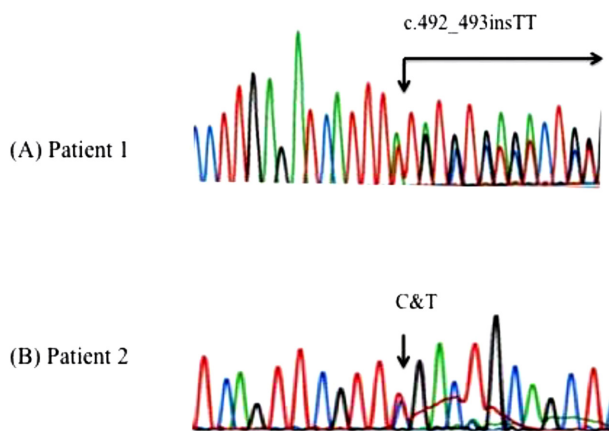


Fig. 1. Mutations of *NR3C2*. (A) In patient 1, a heterozygous two-base insertion (c.492_493insTT) in exon 2 resulting in a premature stop codon (p.Met166LeufsX8) was found. (B) Patient 2 had a nucleotide change at position 2683 and a nonsense mutation of p.R861X in exon 8.

(p.Met166LeufsX8) in patient 1 (Fig. 1A). Patient 2 had a nucleotide change at position 2683 and a nonsense mutation of p.R861X in exon 7 (Fig. 1B). This mutation was previously reported in a Japanese patient (8).

Discussion

In the current study, we identified a novel mutation and one previously reported mutation of *NR3C2*. The two mutations had premature stop codons resulting in haploinsufficiency of the MR, and they were the causes of aldosterone resistance in the kidney.

Patient 2 was diagnosed at 10 mo of age. Oral NaCl supplementation improved her physical development; however, psychomotor development is still delayed at 22 mo. This strongly indicates that early awareness of the renal form of PHA1 is critical, although this disease gradually improves with advancing age.

It was reported that in adult cases carrying *NR3C2* mutations systolic and diastolic blood pressure and serum sodium and serum potassium values were normal in spite of high plasma

aldosterone and renin levels (9). Recently, two detailed studies of adults carrying mutations of *NR3C2* were reported (10, 11). One study demonstrated that these adults had elevated plasma cortisol levels and urinary cortisol excretion (11). In addition, low HDL cholesterol and central adiposity were found. Because it is considered that the MR plays a role in the negative feedback loop of the hypothalamic-pituitary-adrenal (HPA) axis (12, 13), haploinsufficiency of the MR may cause activation of the HPA system and lead to hypersecretion of cortisol (11). This may lead to metabolic consequences in those individuals. Further study of this concept is required. However, this notion suggests that regular health examinations should be considered for children and adults with mutations of *NR3C2* even though they do not require medical treatment. From this point of view, confirmation of mutations of *NR3C2* is also important for clinical management the renal form of PHA1 in addition to its diagnosis.

In conclusion, we report three Japanese patients with the renal form of PHA1 and confirm the importance of a genetic diagnosis.

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