

Mutation-in-Brief

A novel mutation in the human mineralocorticoid receptor gene in a Japanese family with autosomal-dominant pseudohypoaldosteronism type 1

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Introduction

Pseudohypoaldosteronism type 1 (PHA1) is a rare disease that manifests in infancy with hyponatremia, hyperkalemia, and metabolic acidosis, regardless of renin-angiotensin system (RAS) hyperactivity. PHA1 has autosomal recessive systemic and autosomal dominant renal forms. The systemic form of PHA1 is characterized by severe resistance to aldosterone in multiple organs, including the kidney, colon, sweat and salivary glands, and lung. Patients with renal PHA1 are treated with supplemental oral salt, and they typically show gradual clinical improvement with regard to renal salt loss during childhood. Usually, sodium supplementation becomes unnecessary at one to three years of

age (1).

Systemic PHA1 is caused by mutations in the amiloride-sensitive luminal sodium channel (*ENaC*) gene, the protein product of which is responsible for sodium reabsorption. In contrast, in the renal PHA1 form, aldosterone resistance is present only in the kidney. Renal PHA1 results in renal salt loss and failure to thrive during infancy. It is caused by mutations in *NR3C2*, which encodes the MR. *NR3C2* consists of 10 exons; however, the first two (1 α and 1 β) are not translated. Translation starts from exon 2, which encodes the N-terminal domain (N-ter). Exons 3 and 4 encode the DNA-binding domain (DBD), whereas exons 5-9 encode the C-terminal ligand-binding domain (LBD). In 1998, Geller *et al.* identified four mutations in human *NR3C2*: two frameshift mutations and one nonsense mutation in exon 2, and one splicing mutation in intron 5 (2). To date, more than 100 mutations associated with PHA1 have been described (3–8), and several mutations have been identified in the LBD domain.

Herein we report a novel mutation in *NR3C2* in a Japanese family with renal PHA1. The results provide further information on the clinical consequences of *NR3C2* mutations.

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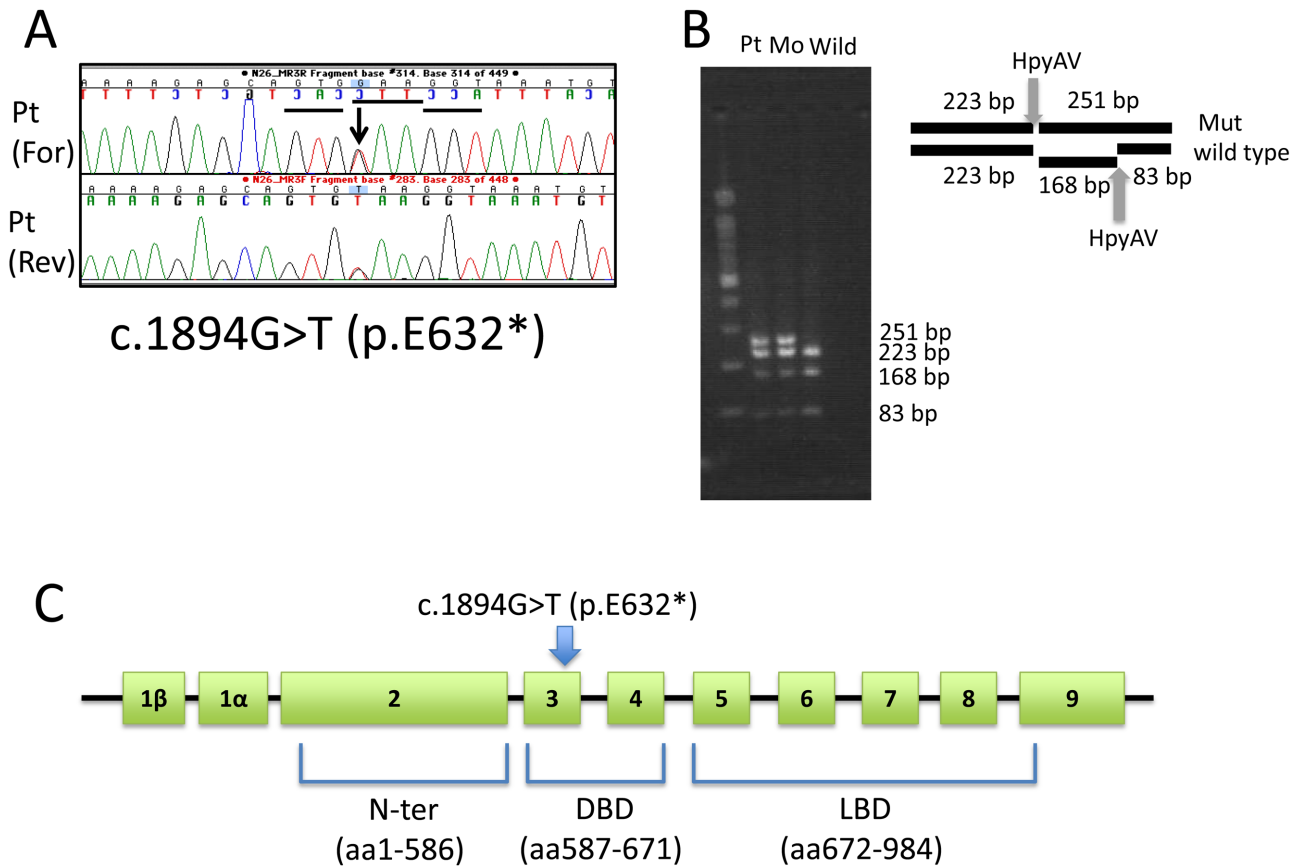


Fig. 1. Molecular analysis in *NR3C2*. A: Chromatogram showing the *NR3C2* mutation (c.1894G>T; p.E632X). The arrow indicates the mutated nucleotide. B: Enzymatic digestion of PCR products. The wild-type PCR product (474 bp) is digested into 223, 168, and 83 bp fragments, whereas the mutant PCR product is digested into 223 and 251 bp fragments by the restriction enzyme HpyAV. Pt, patient; Mo, mother; Mut, mutant allele. C: Scheme of the MR protein. The mature mutation is located in *NR3C2* within the DNA-binding domain coding region.

Case Report

The proband, a Japanese boy, was the first-born of nonconsanguineous healthy parents. His body weight was 3,395 g at birth, and 3,985 g at the age of 1 mo (+19 g/d gain). At the age of 4 mo, his weight was 5,246 g (+8 g/d), at which point a more extensive medical examination was performed. Laboratory testing showed hyponatremia (130 mEq/l) and hyperkalemia (5.4 mEq/l) without metabolic acidosis. Additionally, his plasma aldosterone level (2334.4 ng/dl) and plasma renin activity (PRA, 162.5 ng/ml/h) were extremely elevated. Despite the presence of

hyponatremia, his adrenal and renal functions were normal. Renal PHA1 was diagnosed based on these findings.

In addition to breast milk, he was fed approximately 500 ml/d (Na 3.5 mEq/kg/d) of a high-sodium formula (Na 90 mg/100 ml). He gained weight and plasma electrolytes normalized, although his plasmatic aldosterone level (220.6 ng/dl) remained elevated. After obtaining informed consent, sequencing analysis of *NR3C2* PCR products revealed a heterozygous nonsense mutation, c1894G>T (p.E632X), in exon 3 (Fig. 1A, B, C). Segregation analysis revealed an identical mutation in the patient's

mother, who had never exhibited symptoms of PHA1 in Fig. 1A, B. She reported poor weight gain until the age of 4 mo, after which her weight gain improved. She had never received inpatient treatment. At present, she is symptom-free and has normal plasma levels of electrolytes, aldosterone (19.7 ng/dl), and PRA (1.3 ng/ml/h).

This study was approved by the Institutional Review Board of Niigata University School of Medicine.

Discussion

We identified a novel mutation (p.E632X) in *NR3C2* in a Japanese family with renal PHA1. This mutation was absent in various databases, including dbSNP, the 1,000 Genomes Project, and the Human Genetic Variation Database (HGVD). Failure to thrive is the most common initial symptom of renal PHA1, which is usually diagnosed by the age of four months; this is consistent with our patient's poor weight gain until the age of four months.

Two aspects of the present case are noteworthy. First, metabolic acidosis was not detected in our patient. Renal PHA1 results in renal resistance to aldosterone, which causes renal salt loss, hyperkalemia, metabolic acidosis, elevated PRA, and elevated aldosterone levels in infancy. However, hyperkalemia is generally mild, and metabolic acidosis is not always detectable (1). Therefore, it is paramount for physicians to consider PHA1 in the differential diagnosis of failure to thrive and hyponatremia, even in the absence of metabolic acidosis.

Second, the patient's mother, with the E632X mutation in *NR3C2*, showed normal aldosterone and PRA levels in adulthood. She was symptom-free and had a steady plasma electrolyte balance. Previous studies noted phenotypic variability even in familial cases (6, 9) and found that an elevated aldosterone level was the only biochemical marker of renal PHA1 in adulthood (9). However, reports from several families suggest that adult carriers of causative

mutations can also have normal aldosterone levels (5).

The E632X mutation in *NR3C2* is located within the DNA-binding domain coding region. This novel mutation leads to a premature stop codon, theoretically resulting in a truncated protein. Geller *et al.* (2006) used RNA analysis to test nonsense-mediated mRNA decay (NMD) in a patient with a nonsense mutation in exon 3 (R590X), which is also located in the DNA-binding domain coding region (9). The authors concluded that the index patient was probably haploinsufficient because of NMD.

In conclusion, we identified a novel mutation in *NR3C2* in a Japanese family with renal PHA1. This finding increases our understanding of phenotypes resulting from *NR3C2* mutations.

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