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Mutation-in-Brief

An infantile case of pseudohypoaldosteronism type 1 (PHA1) caused by a novel mutation of *NR3C2*

Takeshi Goda[1, 2], Hiroshi Komatsu[2], Kandai Nozu[3], and Hisakazu Nakajima[2, 4]

[1]*Department of Pediatrics, Kyoto Chubu Medical Center, Kyoto, Japan*
[2]*Department of Pediatrics, National Hospital Organization Maizuru Medical Center, Kyoto, Japan*
[3]*Department of Pediatrics, Kobe University Graduate School of Medicine, Hyogo, Japan*
[4]*Department of Pediatrics, North Medical Center Kyoto Prefectural University of Medicine, Kyoto, Japan*

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Introduction

Pseudohypoaldosteronism type 1 (PHA1: OMIM # 177735) is an inherited salt wasting disorder, characterized by hyponatremia and hyperkalemia as a result of renal tubular insensitivity to aldosterone action during infancy (1). Cheek and Perry first reported an infant with PHA1 in 1958 (2). PHA1 has the two forms, namely renal PHA1 with autosomal dominant inheritance, and systemic PHA1 with an autosomal recessive inherited form. Renal PHA1 is caused by loss-of-function mutations in the human nuclear receptor subfamily 3 group C member 2 (*NR3C2*) gene (3).

Aldosterone plays an important role in regulating sodium reabsorption in the kidney and colon, exerting its action through the mineralocorticoid receptor (MR). Therefore, impairment of MR function leads to an inappropriate sodium loss. Riepe and colleagues have reported that mutations in *NR3C2*, the transcriptional gene for MR, are responsible for autosomal dominant PHA1 (4). MR functions impaired by *NR3C2* mutations provoke salt wasting during early infancy. To the best of our knowledge, several *NR3C2* gene mutations have been reported in individuals and families with PHA1, in Japan, as well as in other countries (3–11). Herein, we describe an infantile case of PHA1 due to a novel nonsense mutation.

Case Report

A 2-mo-old boy was referred to our hospital, presenting with unfavorable weight gain. He was born to non-consanguineous Japanese parents at 40 wk of gestational age, after an uneventful pregnancy and delivery. The birth weight was 3,850 g (+ 1.6 standard deviation (SD)). The newborn mass screening did not detect increased blood 17α-hydroxyprogesterone (data was not shown). Additionally, the child was breastfed. We observed no endocrinological or renal disorders in his family history (**Fig. 1A**). At referral, he weighed 5,400 g (–1.25 SD), with a height of 60.2 cm (–0.54 SD). He had normal genitalia, with no hyperpigmentation or abdominal mass. Blood examination revealed hyponatremia (serum sodium, 124 mEq/L), mild hyperkalemia (serum potassium, 5.4 mEq/L), and hypoosmosis (259.5 mOsm/kg H_2O). Blood urea nitrogen and serum creatinine were 8.5 mg/dL and 0.25 mg/dL, respectively. Serum cortisol was 29.58 μg/dL, and the plasma ACTH level was 15.7 pg/mL. Plasma renin activity was markedly elevated (> 20 ng/mL/h), and the plasma aldosterone level was 15,400 pg/mL. Urinalysis demonstrated no bacterial infection in the urinary tract. The fractional excretion of sodium (FENa) was 0.38%. Magnetic resonance imaging of the brain revealed no abnormalities. He was treated with oral sodium administration (sodium chloride (NaCl), 2.5 mEq/kg/day) to alleviate salt wasting. NaCl replacement was increased to 6.1 mEq/kg/, the maximum dose at 11 mo

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Corresponding author: Hisakazu Nakajima, M.D., Ph.D., Department of Pediatrics, North Medical Center Kyoto Prefectural University of Medicine, 481 Otokoyama, Yosano-cho Yoza-gun, Kyoto 629-2261, Japan
E-mail: hisakazu@koto.kpu-m.ac.jp

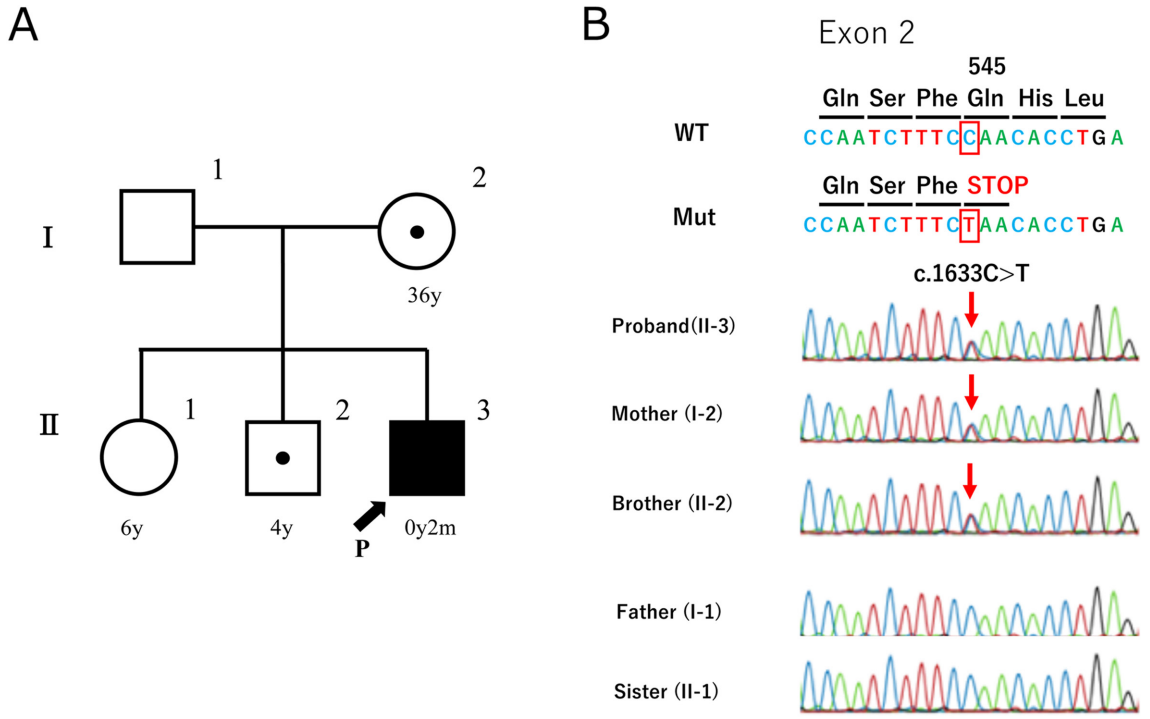

Fig. 1. A: Pedigree chart. The arrow (II-3, P) indicates the proband with a novel mutation (p.Gln545*) in *NR3C2*. The mother (I-2) and an older sibling (II-2) were asymptomatic individuals with the same mutation. B: Chromatograms demonstrating the mutation in exon 2 of *NR3C2*. The partial sequencing chromatograms demonstrate a novel mutation (c.1633C>T, p.Gln545*) in *NR3C2*. WT, wild type allele; Mut, mutated allele.

of age. Subsequently, NaCl administration was tapered with no deterioration in the clinical course. Replacement therapy was discontinued at 25 mo of age.

Regarding developmental milestones, he presented with physical and behavioral developmental delays, capable of lifting and controlling his head at 6 mo. He was able to sit without support at 15 mo, using meaningful words to communicate at 20 mo.

Mutation Analysis

We performed genetic analysis on the proband, his parents, and older siblings aged 6 (sister) and 4 (brother) after obtaining written informed consent. Except for the proband, the family members were asymptomatic in terms of PHA1; however, we had no opportunity to perform blood and urine biochemical investigations in the family members. All procedures were reviewed and approved by the Institutional Review Board of Kobe University School of Medicine and were performed in accordance with the ethical standards established in the 1964 Declaration of Helsinki. Genomic DNA was isolated from peripheral blood leukocytes of the patient, his parents, and siblings. The inherited PHA1-responsible genes, including *NR3C2*, *SCNN1A*, *SCNN1B,* and *SCNN1G,* were screened using next-generation sequencing (NGS) analysis with targeting sequencing. NGS samples were prepared using a HaloPlex Target Enrichment System Kit (Agilent Technologies, Santa Clara, USA) to capture the targeted genes according to the manufacturer's instructions. Amplified target libraries were sequenced utilizing MiSeq (Illumina, San Diego, USA) and analyzed with SureCall (v.3.0; Agilent Technologies). The detected variant was confirmed by Sanger sequencing. NGS capture and Sanger sequencing confirmed the heterozygous nonsense mutation (c.1633C>T [p.Gln545*]) in the proband, his mother, and the older brother (**Fig. 1B**). We used the Genebank transcript ID (NM_000901 or NM_001166104) as references to evaluate the pathological significance of the mutation.

Discussion

In the present case, we detected a novel pathogenic mutation (p.Gln545*) on the *NR3C2* gene. The current mutation has not been documented in open databases, including ClinVar, dbSNP (the latest version, Aug 8, 2019), the genome aggregation database (gnomADv2.1.1), and the Human Gene Mutation Database (HGMD professional 2019.4 released). The *NR3C2* gene is located on chromosome 4p31.1 and composed of 10 exons encoding 984 amino acids of the MR protein. The MR protein structure consists of three distinct domains: the N-terminal transcriptional activation domain, the central DNA-binding domain (DBD), and the C-terminal ligand-binding domain (LBD) (4). In the MR protein, the p.Gln545* position of the amino acid sequence is located in the N-terminal domain. The p.Gln545* mutation predicts a truncated MR protein, indicating a loss-of-

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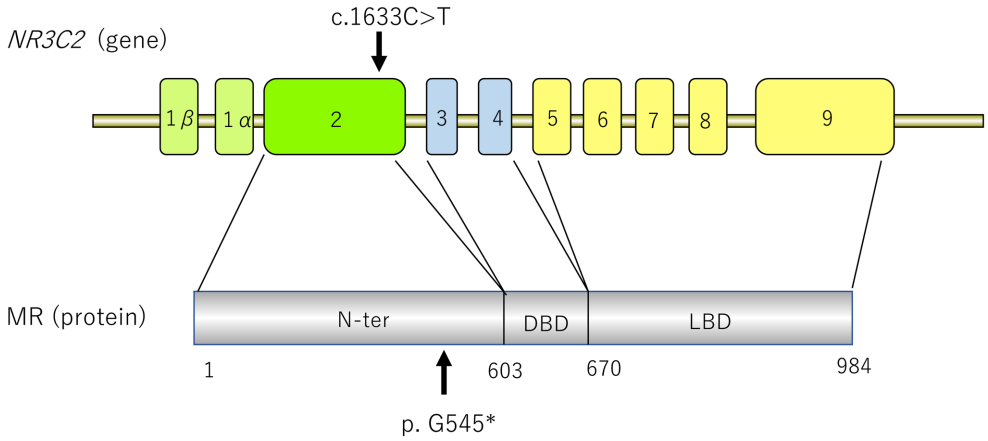

Fig. 2. Schematic representation of the *NR3C2* gene and the human mineralocorticoid receptor (MR) protein structures. The exon-intron structure of the *NR3C2* gene is shown. Arrow indicates the mutation location (c.1633C>T: p.G545*) in the current patient. The human MR protein has three major functional domains: an N-terminal domain (N-ter), followed by a central DNA-binding domain (DBD) and a C-terminal ligand-binding domain (LBD).

function protein (**Fig. 2**).

We postulate that the p.Gln545*mutation of *NR3C2* was related to a milder phenotype. In the present case, hyponatremia and hyperkalemia were substantially non-life-threatening to further worsen consciousness and lead to hypovolemic shock. Regarding the severity of the clinical course, the genotype-phenotype correlation in patients with renal PHA1 and the *NR3C2* mutation has been not established, although an accumulation of clinical cases is expected with genetic analysis. Interestingly, Hubert *et al.* (10) have previously reported that a renal PHA1 patient demonstrated life-threatening hyperkalemia instead of *NR3C2* mutations, with the disease inherited in a recessive inherited manner; the patient was as an extremely severe case, treated with high-dose NaCl treatment through a nasogastric tube or percutaneous endoscopic gastrostomy. Bowden *et al.* (11) have described a case with a large *NR3C2* deletion (a 130 kb loss, including the range from exon 3 to exon 5) manifesting a severe clinical course, as well as the case reported by Hubert and colleagues. Accordingly, the genotype-phenotype correlation remains controversial in renal PHA1 with *NR3C2* mutation.

Notably, the index patient's mother and sibling, presenting the p.Gln545* mutation, had never experienced any illness regarding PHA1. Additionally, we noted the expressivity of the genetic carriers of the p.Gln545* mutation in the current family. The cause of intrafamilial phenotypic diversity remains unknown. Infection, intercurrent events, and living circumstances could influence disease worsening. However, developmental milestones of the proband were delayed. In patients with PHA1, a long-term prognosis regarding neurological development should be established by including cases with the *NRC3C2* mutation. Moreover, the previous case reported by Huber *et al.* demonstrated growth retardation and psychomotor delay (10).

Compared with patients with systemic PHA1, patients with renal PHA1 present a milder phenotype (12). Patients with renal PHA1 require NaCl replacement during early infancy. Generally, salt replacement therapy ceases between 1 to 3 yr of age, demonstrating a good prognosis in renal PHA1 (2, 4). However, PHA1, which results from mutations in the three genes encoding the subunits of the epithelial sodium channel ENaC (*SCNN1A*, *SCNN1B,* and *SCNN1G*), is a clinically severe form with no remission (5, 12, 13). Patients with systemic PHA1 need a larger amount of salt replacement than that required in patients with renal PHA1 (12, 13). Our experience shows that genetic analysis is useful to reach a differential diagnosis between renal PHA1 and systemic PHA1. Moreover, genetic diagnosis is recommended to distinguish treatment and duration of treatment in infants with PHA1.

Conflict of interest: The authors declare that they have no conflict of interest.

References

1. Riepe FG. Clinical and molecular features of type 1 pseudohypoaldosteronism. Horm Res 2009;72: 1–9. [Medline] [CrossRef]
2. Cheek DB, Perry JW. A salt wasting syndrome in infancy. Arch Dis Child 1958;33: 252–6. [Medline] [CrossRef]
3. Geller DS, Rodriguez-Soriano J, Vallo Boado A, Schifter S, Bayer M, Chang SS, *et al*. Mutations in the mineralocorticoid receptor gene cause autosomal dominant pseudohypoaldosteronism type I. Nat Genet 1998;19: 279–81. [Medline] [CrossRef]

4. Riepe FG, Finkeldei J, de Sanctis L, Einaudi S, Testa A, Karges B, *et al*. Elucidating the underlying molecular pathogenesis of NR3C2 mutants causing autosomal dominant pseudohypoaldosteronism type 1. J Clin Endocrinol Metab 2006;91: 4552–61. [Medline] [CrossRef]
5. Zennaro MC, Fernandes-Rosa F. 30 YEARS OF THE MINERALOCORTICOID RECEPTOR: Mineralocorticoid receptor mutations. J Endocrinol 2017;234: T93–106. [Medline] [CrossRef]
6. Hatta Y, Nakamura A, Hara S, Kamijo T, Iwata J, Hamajima T, *et al*. Clinical and molecular analysis of six Japanese patients with a renal form of pseudohypoaldosteronism type 1. Endocr J 2013;60: 299–304. [Medline] [CrossRef]
7. Morikawa S, Komatsu N, Sakata S, Nakamura-Utsunomiya A, Okada S, Tajima T. Two Japanese patients with the renal form of pseudohypoaldosteronism type 1 caused by mutations of NR3C2. Clin Pediatr Endocrinol 2015;24: 135–8. [Medline] [CrossRef]
8. Kawashima Sonoyama Y, Tajima T, Fujimoto M, Hasegawa A, Miyahara N, Nishimura R, *et al*. A novel frameshift mutation in NR3C2 leads to decreased expression of mineralocorticoid receptor: a family with renal pseudohypoaldosteronism type 1. Endocr J 2017;64: 83–90. [Medline] [CrossRef]
9. Nishizaki Y, Hiura M, Sato H, Ogawa Y, Saitoh A, Nagasaki K. A novel mutation in the human mineralocorticoid receptor gene in a Japanese family with autosomal-dominant pseudohypoaldosteronism type 1. Clin Pediatr Endocrinol 2016;25: 135–8. [Medline] [CrossRef]
10. Hubert EL, Teissier R, Fernandes-Rosa FL, Fay M, Rafestin-Oblin ME, Jeunemaitre X, *et al*. Mineralocorticoid receptor mutations and a severe recessive pseudohypoaldosteronism type 1. J Am Soc Nephrol 2011;22: 1997–2003. [Medline] [CrossRef]
11. Bowden SA, Cozzi C, Hickey SE, Thrush DL, Astbury C, Nuthakki S. Autosomal dominant pseudohypoaldosteronism type 1 in an infant with salt wasting crisis associated with urinary tract infection and obstructive uropathy. Case Rep Endocrinol 2013;2013: 524647. [Medline]
12. Tajima T, Morikawa S, Nakamura A. Clinical features and molecular basis of pseudohypoaldosteronism type 1. Clin Pediatr Endocrinol 2017;26: 109–17. [Medline] [CrossRef]
13. Nur N, Lang C, Hodax JK, Quintos JB. Systemic pseudohypoaldosteronism type I: a case report and review of the literature. Case Rep Pediatr 2017;2017: 7939854. [Medline]