Mutation-in-Brief

A Novel Deletion Mutation of the Arginine Vasopressin Receptor 2 Gene in a Japanese Infant with Nephrogenic Diabetes Insipidus

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Introduction

Arginine vasopressin (AVP) is released from the posterior pituitary. It controls water balance homeostasis. It binds to arginine vasopressin receptor 2 (AVPR2) on the basolateral membrane of the kidney collecting duct and triggers activation of Gs proteins, which leads to increases in intracellular cAMP and the activity of protein kinase A. These increases cause trafficking of aquaporin-2 (AQP2) water channels to the apical membrane of collecting duct cells, resulting in increased water permeability and antidiuresis. The AVPR2 gene encodes a 7-transmembrane-spanning G protein-coupled receptor, which is located on chromosome Xq28. AVPR2 mutations, which are typically loss-of-function mutations, explain approximately 90% of cases of hereditary nephrogenic diabetes insipidus (NDI) (OMIM 304800). NDI is characterized by an inability to concentrate urine, resulting in excessive urine production, dehydration and thirst. Administration of exogenous AVP cannot restore

the normal balance of water in most patients with AVPR2 mutations.

We describe a Japanese infant with NDI who has a novel deletion mutation of the AVPR2 gene.

Case Report

A 4-mo-old boy was admitted to our hospital presenting with vomiting, failure to thrive, and hypernatremia. He was born at 40 wks' gestation, weighing 2,887 g, and there were no problems in the perinatal period. He had no family history of NDI. At 3 mo of age, vomiting and failure to thrive began.

On admission, his body length was 59.5 cm (−0.5 SD) and body weight was 5,464 g (−1.2 SD). His skin turgor was normal and anterior fontanelle was flat. The results of laboratory findings on admission are summarized in Table 1. His serum sodium level was 150 mEq/L, and his chloride level was 110 mEq/L. His venous gas values were within normal limits. His urine volume was 1,085 mL/d (3,616 mL/m²/d), and his urine osmolality was low, in spite of high serum osmolality and an elevated AVP level.

He was diagnosed as having congenital NDI. Management was started by intravenous and oral fluid administration, followed by sodium restriction (1.0 mEq/kg/d) and administration of oral hydrochlorothiazide (2 mg/kg/d). Water intake and urinary volume before the therapies were about 1,400 mL/d and about 1,000 mL/d,

Received: March 17, 2014

Accepted: May 19, 2014

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Table 1 Laboratory data on admission

Blood chemistry and serology	
BUN	7.5 mg/dL
Crea	0.26 mg/dL
BS	97 mg/dL
Na	150 mEq/L
K	4.1 mEq/L
Cl	118 mEq/L
Ca	10.6 mg/dL
P	4.7 mg/dL
Blood gas analysis	
pH	7.401
PaCO ₂	40.2 mmHg
HCO ₃ ⁻	24.4 mmol/L
BE	0.2 mmol/L
Urinalysis	
Protein	–
Sugar	–
RBC	<1/HPF
WBC	<1/HPF
Endocrine test	
S-Osm	303 mOsm/kg
U-Osm	70 mOsm/kg
AVP	25 pg/mL (0.3–3.5)
PRA	32 ng/mL/h (1.5–5.5)
Ald	198 pg/mL (10.9–48.9)

S-Osm, serum osmolality; U-Osm, urine osmolality; PRA, plasma renin activity; Ald, Aldosterone.

respectively. After therapy, they were about 1,100 mL/d and about 800 mL/d, respectively. Two weeks after admission, his levels of serum electrolytes were normal.

Mutational Analysis

Informed consent, based on the Helsinki Final Act of 1975, for a mutational analysis was obtained from the patient's parents. Genomic DNA was extracted from white blood cells. PCR and direct sequencing were conventionally performed. Analysis of the AVPR2 gene revealed a novel one-nucleotide deletion at position 368 (c.368delT) (Fig. 1). This mutation resulted in a

Fig. 1. Sequence of the AVPR2 gene in the patient. The patient had a one-nucleotide deletion at position 368 (c.368delT). An arrow indicates the deletion site.

frameshift and premature stop codon (M129*) in the third transmembrane domain. The analysis of the AQP2 gene was negative. Specimens from the parents were not available for analysis.

Discussion

At present, according to the Human Gene Mutation Database (HGMD; www.hgmd.cf.ac.uk), more than two hundred mutations in the AVPR2 gene have been detected, including nonsense mutations and frameshift mutations leading to stop codons. Although a correlation between genotype and phenotype has not been previously reported, partial correlation is thought to be present. For example, a large number of these mutant receptors fail to fold properly and therefore are not routed to the cell surface (1), resulting in a complete inability to concentrate urine.

The present patient had a novel one-nucleotide deletion at position 368 (c.368delT). This mutation resulted in a frameshift and premature stop codon (M129*) in the third transmembrane domain.

We consider that the M129* mutation is a causative mutation of NDI. There are at least 18 nonsense mutations beyond this codon (M129*), namely, W156*, W164*, S167*, Q180*, W193*, W200*, Q225*, E231*, E242*, W284*, W293*, W296*, L312*, W323* and R337*, and at least 28 types of deletion mutation introducing a stop codon beyond this codon (M129*). A nonsense mutation of the C-terminal intracellular tail (R337*) is a cause of NDI (2) and is predicted

to produce a truncated mutant protein, which was reported not to be transported to the plasma membrane (3). The mutation in our case is also predicted to produce a truncated protein that is shorter than the R337* mutant protein.

References

1. Morello JP, Salahpour A, Laperrière A, Bernier V, Arthus MF, Lonergan M, *et al.* Pharmacological chaperones rescue cell-surface expression and function of misfolded V2 vasopressin receptor mutants. *J Clin Invest* 2000;105: 887–95. [\[Medline\]](#) [\[CrossRef\]](#)
2. Moses AM, Sangani G, Miller JL. Proposed cause of marked vasopressin resistance in a female with an X-linked recessive V2 receptor abnormality. *J Clin Endocrinol Metab* 1995;80: 1184–6. [\[Medline\]](#)
3. Sadeghi HM, Innamorati G, Birnbaumer M. An X-linked NDI mutation reveals a requirement for cell surface V2R expression. *Mol Endocrinol* 1997;11: 706–13. [\[Medline\]](#) [\[CrossRef\]](#)