Clinical Pediatric Endocrinology

Vol.30 / No.2
April 2021
pp 115–118

Mutation-in-Brief

Nephrogenic diabetes insipidus caused by a novel missense variant (p.S127Y) in the *AVPR2* gene

Takatoshi Maeyama[1], Yuri Etani[1], Satsuki Nishigaki[1], and Masanobu Kawai[1, 2]

[1]*Department of Gastroenterology, Nutrition and Endocrinology, Osaka Women's and Children's Hospital, Osaka, Japan*

[2]*Department of Bone and Mineral Research, Research Institute, Osaka Women's and Children's Hospital, Osaka, Japan*

Key words: nephrogenic diabetes insipidus, *AVPR2*, novel variant

Introduction

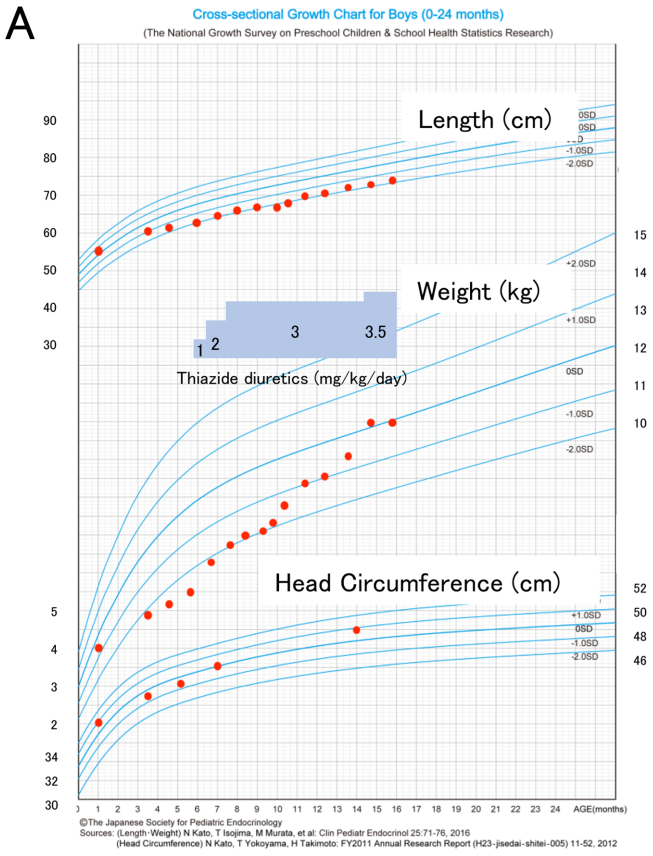
Nephrogenic diabetes insipidus (NDI) is a rare disease, wherein the principal cells of the collecting duct of the kidney are refractory or less responsive to the antidiuretic hormone AVP, resulting in impaired urinary concentration (1). The main clinical manifestations include polyuria and polydipsia, but these symptoms are not often evident during the infantile period; therefore, affected infants often present with poor feeding, and growth and developmental delays. NDI pathogenesis is categorized into two forms: congenital and acquired forms, with approximately 90% of congenital cases being caused by loss of function variants in the *arginine vasopressin receptor type 2* (*AVPR2*) gene and pathogenic variants in the *aquaporin 2* (*AQP2*) gene being responsible for the remaining 10%. *AVPR2* is located on the X chromosome (Xq28); therefore, NDI patients with a pathogenic variant in *AVPR2* exhibit an X-linked recessive inheritance pattern (OMIM # 304800). In contrast, *AQP2* is located on chromosome 12 (12q13), and both autosomal dominant and recessive inheritance patterns have been reported.

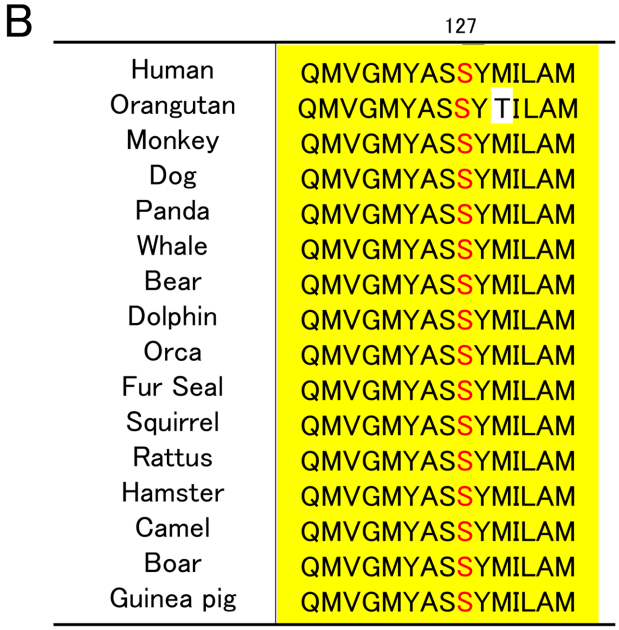
Approximately 180 missense/nonsense variants have been reported in *AVPR2* according to the Human Gene Mutation Database (HGMD) (http://archive.uwcm.ac.uk/uwcm/mg/hgmd0.html). Genotype-phenotype association analyses revealed that some of the pathogenic variants in *AVPR2* are associated with partial NDI; thus, accumulation of information on underlying variants will help clarify the clinical characteristics of NDI patients. We report a case of NDI with a novel missense variant in *AVPR2*, which was categorized as likely pathogenic based on the ACMG/AMP standards and guidelines for interpretation of sequence variants (2).

Case Report

A 4-mo-old male presented with growth and developmental retardation, and he was referred to our hospital. He was born to non-consanguineous Japanese parents at 38 wk of gestational age, with a birth weight of 3,285 g (0.5 SDS) and a height of 49.5 cm (0.7 SDS). Pregnancy and delivery had no complications. No growth or developmental delay was noted at 1 mo; however, he demonstrated impaired weight gain thereafter, associated with neurodevelopmental and motor developmental delays (**Fig. 1a**). At 4 mo, his height was 62.5 cm (–1.6 SDS), weight was 5.44 kg (–2.4 SDS), and head control was incomplete. The patient had a daily water intake of approximately 1,000 ml and a urine volume of approximately 700 ml (2,300 ml/m^2/day). Biochemical evaluation (**Table 1**) revealed a high serum Na level and increased serum osmolality, which were associated with an inappropriately low urine osmolality. Plasma AVP levels were not low. In the pitressin test, urinary osmolality and urine volume were unresponsive, leading to a clinical diagnosis of NDI. Magnetic resonance imaging of the brain revealed that the anterior pituitary and pituitary stalk were normal; no hyperintensity of the posterior pituitary was observed in T1-weighted images. Concerning family history, his maternal great-grandfather had diabetes insipidus, and his mother has chronic polydipsia and polyuria

Received: December 18, 2020 Accepted: January 8, 2021
Corresponding author: Masanobu Kawai, M.D., Ph.D., Department of Gastroenterology, Nutrition and Endocrinology, Osaka Women's and Children's Hospital, 840 Murodo, Izumi, Osaka 594-1101, Japan
E-mail: kawaim@wch.opho.jp





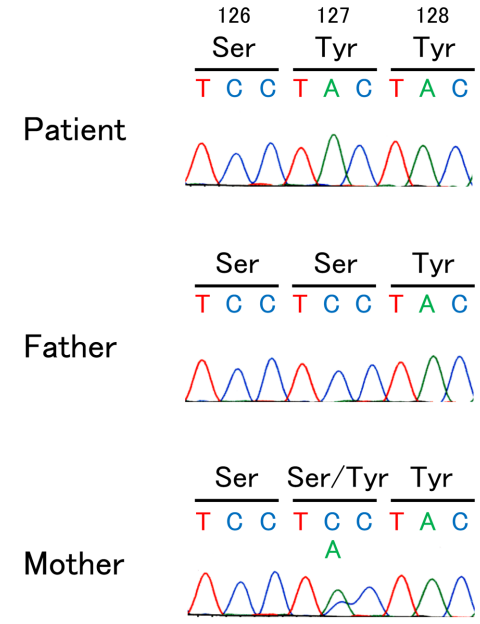


Fig. 1. Growth characteristics and genetic testing of the patient. A: Growth characteristics of the patient from 0 to 16 mo of age. B: Sanger sequencing of the *AVPR2* gene in the patient and parents. A hemizygous variant (c.380C>A, p.S127Y) was identified in the patient. The same variant, in a heterozygous form, was noted in the mother. C: Homologs of the *AVPR2* gene showing the S127 residue (red), which is conserved across mammals. The conserved amino acids are highlighted in yellow.

not requiring medication. Familial history reflected an X-linked inheritance pattern. He was treated with thiazide diuretics, which led to weight gain (**Fig. 1a**). Although his developmental milestones were still delayed, he showed developmental catch-up wherein he was able to walk with support at 16 mo.

Mutation Analysis

Written informed consent for publication and genetic testing was obtained from the patient's parents. All studies were conducted in accordance with the 1964 Declaration of Helsinki, the 2003 Japanese Ethical Guidelines for Clinical Research, and their later amendments.

doi: 10.1297/cpe.30.115

Table 1. Clinical characteristics evaluated upon admission to the hospital

Variables	Results
WBC (× 10^4/μL)	1.1
Hb (g/dL)	10.5
Plt (× 10^4/μL)	21.5
Na (mEq/L)	159
K (mEq/L)	4.2
Cl (mEq/L)	124
BUN (mg/dL)	16.5
Cre (mg/dL)	0.43
Ca (mg/dL)	10.8
P (mg/dL)	5.9
CPK (IU/L)	61
S-Osm (mOsm/L)	322
Free T_3 (pg/mL)	3.16
Free T_4 (ng/dL)	1.13
TSH (μU/mL)	2.256
ARC (pg/mL)	190.4
Aldosterone (ng/dL)	32.1
AVP (ng/mL)	24.8
Venous blood gas	
pH	7.42
pCO_2 (mmHg)	37.8
pO_2 (mmHg)	55.9
HCO_3 (mEq/L)	24
BE (mEq/L)	0.2
Urinalysis	
Urine specific gravity	1.003
pH	6.5
glucose	–
protein	–
blood	–
ketone	–
Urine Na (mEq/L)	< 20
Urine K (mEq/L)	21
Urine Cl (mEq/L)	< 20
Urine Cre (mEq/L)	7
U-Osm (mOsm/L)	108

T_3, 3,5,3'-triiodothyronine; T_4, thyroxine; TSH, thyroid-stimulating hormone; S-Osm, serum osmolality; U-Osm, urine osmolality; ARC, active renin concentration; AVP, arginine vasopressin; BE, base excess; WBC, white blood cell; Hb, hemoglobin; Plt, platelet; BUN, blood urea nitrogen; Cre, creatinine; CPK, creatine phosphokinase.

Based on the X-linked dominant inheritance pattern, genetic analysis of *AVPR2* was performed. DNA was collected from the peripheral blood lymphocytes. Sanger sequencing of the coding region and exon-intron boundaries of *AVPR2* revealed a hemizygous variant c.380C>A (p.S127Y) (**Fig. 1b**). The primer sequences used are available upon request. The identified variant was not observed in the variant database (gnomAD, https://gnomad.broadinstitute.org/), ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/), or the HGMD (http://www.hgmd.cf.ac.uk/). Based on *in silico* analyses, the variant was predicted as "deleterious" with a score of 0.03 by SIFT and "possibly damaging" with a score of 0.977 by PolyPhen-2. The mutated amino acid was conserved across mammals (**Fig. 1c**). Sanger sequencing of the region containing the identified variant in parents revealed the heterozygous presence of the same variant in the mother, whereas the variant was not observed in the father (**Fig. 1b**).

Discussion

We report a case of NDI harboring a novel missense variant in *AVPR2*. Although functional analysis of the identified variant was not performed, we considered it as a causative for NDI based on the following: (a) the identified variant was rare; (b) a different missense variant of the same amino acid is reported to be involved in NDI (3); (c) the variant was damaging based on multiple *in silico* analyses; (d) the patient's mother, who exhibits mild polyuria and polydipsia, is heterozygous for the same variant; and (e) the mutated amino acid is conserved across mammals (**Fig. 1c**). According to the ACMG/AMP standards and guidelines for interpreting sequence variants (2), the identified variant was categorized as "likely pathogenic" (PM2, PM5, PP3, and PP4).

AVP exerts its effects by interaction with AVPR2, which is a 7-transmembrane G protein-coupled receptor (GPCR), located on the basement membrane of the renal collecting duct, and activates downstream signaling molecules. The AVPR2 protein consists of 371 amino acids, with four extracellular and four intracellular domains, and the identified variant is located in the third transmembrane domain (TMD3). The importance of TMD3 may be owing to the Asp-Arg-Tyr (DRY) motif in its C-terminal region, which is evolutionarily conserved in most rhodopsin-like GPCRs and involved in receptor function (4). In the case of AVPR2, this motif comprises 136D-137R-138H, and pathogenic variants in this region have been previously reported in the HGMD to cause NDI. However, the influence of the substitution of S127 on the functionality of this motif is unclear. Another plausible explanation for the pathogenicity of the identified variant is the inability of AVP to interact with AVPR2. *In silico* molecular docking analysis has revealed the involvement of S127 of AVPR2 in interacting with AVP (5); therefore, the identified variant may interfere with the binding of AVP to AVPR2, thereby causing NDI.

An accurate NDI diagnosis is clinically important because a diagnostic delay may cause developmental delays due to repeated dehydration and cerebral edema. Therefore, appropriate diagnostic interventions and management are essential to improve the prognosis of patients with NDI. Particularly, genetic testing is an important tool for diagnosing NDI, and this approach has become more prevalent and accessible in clinical settings. Therefore, further accumulation of information on genetic variants associated with NDI is necessary to enable precise interpretation of identified variants and accurate diagnosis of NDI.

Ethical considerations: Written informed consent for publication and genetic testing was obtained

doi: 10.1297/cpe.30.115

from the patients' parents. All studies were carried out in accordance with the 1964 Declaration of Helsinki, the 2003 Japanese Ethical Guidelines for Clinical Research, and their later amendments.

Conflict of interests: The authors declare no conflict of interest.

References

1. Refardt J, Winzeler B, Christ-Crain M. Diabetes insipidus: an update. Endocrinol Metab Clin North Am 2020;49: 517–31. [Medline] [CrossRef]
2. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, *et al*. ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17: 405–24. [Medline] [CrossRef]
3. Arthus MF, Lonergan M, Crumley MJ, Naumova AK, Morin D, De Marco LA, *et al*. Report of 33 novel AVPR2 mutations and analysis of 117 families with X-linked nephrogenic diabetes insipidus. J Am Soc Nephrol 2000;11: 1044–54. [Medline]
4. Rovati GE, Capra V, Neubig RR. The highly conserved DRY motif of class A G protein-coupled receptors: beyond the ground state. Mol Pharmacol 2007;71: 959–64. [Medline] [CrossRef]
5. Jankowski M, Danalache BA, Plante E, Menaouar A, Florian M, Tan JJ, *et al*. Dissociation of natriuresis and diuresis by oxytocin molecular forms in rats. PLoS One 2019;14: e0219205. [Medline] [CrossRef]