

A Novel Mutation in the *AVPR2* Gene in a Palestinian Family with Nephrogenic Diabetes Insipidus

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Abstract

Nephrogenic diabetes insipidus (NDI) is a urinary concentrating defect resulting from resistance of the collecting duct to the antidiuretic action of vasopressin (AVP). The X-linked recessive form is the most frequent genetic cause of inherited NDI and can be caused by mutations in the gene encoding the V2 vasopressin receptor (*AVPR2*). A Palestinian male infant presented in the neonatal period with failure to thrive, vomiting, irritability, fever, and polyuria, and had biochemical findings consistent with NDI. The diagnosis of NDI was established based on the clinical picture, absent response to desmopressin, and a similarly affected elder brother. Sequencing of the *AVPR2* gene for the patient and his affected brother revealed a novel missense mutation with replacement of G by A in codon 82 located in exon 2 (TGC → TAC), causing a cysteine to tyrosine substitution (C82Y). Testing of the mother showed that she was the carrier of that mutation. This is the identified *AVPR2* mutation in a Palestinian family. Knowledge of these mutations will allow genetic counseling and early diagnosis of affected males.

Keywords

- ▶ nephrogenic diabetes insipidus
- ▶ *AVPR2*
- ▶ hypernatremia
- ▶ vasopressin
- ▶ vasopressin receptor

Introduction

Nephrogenic diabetes insipidus (NDI) is a clinical disorder characterized by a urinary concentrating defect resulting from resistance of the collecting duct to the antidiuretic action of vasopressin (AVP). X-linked NDI is the most common inherited form of NDI and is caused by mutations in the gene encoding the V2 vasopressin receptor (*V2R*).^{1,2} Mutations of *AVPR2* are implicated in nearly 90% of all cases of congenital NDI.³

Affected males with X-linked NDI develop a renal concentrating defect which is unresponsive to desmopressin administration. These affected individuals usually present with symptoms of dehydration, hypernatremia, renal insufficiency, mental retardation, and failure to thrive (FTT).

Heterozygous females exhibit variable degrees of polyuria and polydipsia due to skewed X-chromosome inactivation.⁴

Early recognition and treatment allow having a normal lifespan with appropriate physical and mental development.⁵ To date, 280 different mutations in the *AVPR2* gene have been identified for V2R NDI, and the mutations spread throughout all portions of the protein.⁶

Case Report

A 2-month-old, 3.6 kg male infant, was born to nonconsanguineous Palestinian parents in good health. The family history was notable for an elder brother having evidence of NDI based on clinical description by the parents but unfortunately he was not diagnosed previously or adequately

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treated because referral to our tertiary center was not made by the treating physician in that area. Over a period of a month, the infant displayed increasing irritability associated with vomiting and FTT. The child was hospitalized, and was found to be cachectic and irritable. Weight, height, and head circumference were all below the third percentile. Laboratory evaluation revealed hypernatremia (sodium 150 mmol/L), a serum osmolality of 304 mOsm/L, and urine osmolality of 145 mOsm/L, urine output 9 mL/kg/h, and urine specific gravity 1.005. A renal ultrasound was normal. To determine whether the child had central or nephrogenic DI, DDAVP 20 µg was administered as a single dose followed by serial measurements of serum sodium, serum osmolality, and urine osmolality. No changes in these values were noted, and a presumptive diagnosis of NDI was made and the child was managed appropriately. His management included adequate fluid and nutritional therapy, advice for low-salt, low-protein diet, and pharmacological treatment with diuretics (hydrochlorothiazide 3–4 mg/kg/d) and nonsteroidal anti-inflammatory drugs (indomethacin 2 mg/kg/d). The child was discharged home and continues to grow and develop as expected.

Sequencing of the AVPR2 Gene

Before genetic studies, an informed consent was obtained from the study participants or their guardians. The study was approved by the Institutional Review Boards of Makassed Islamic Hospital.

Automated DNA sequencing was performed using the Big-Dye terminator cycle sequencing chemistry from Applied Biosystems (ABI, Foster city, California, United States), the ABI PRISM 3700 DNA analyzer and ABI's data collection software. Results were analyzed with the sequence analysis software and compared with the sequence available from the National Center for Biotechnology Information (NCBI) database (340298).

Results

Sequencing the coding region of the AVPR2 gene of the affected patient showed hemizygous missense G to A mutation at nucleotide 606 in codon 82 (TGC → TAC) (numbering based on AVPR2 sequence in GenBank—accession number L22266). This mutation results in a substitution of tyrosine for cysteine (C82Y) in exon 2 located in transmembrane domain II (►Fig. 1). The same mutation was found in the affected brother. No other mutations were found in the coding sequence of AVPR2. The mother and sister were heterozygous for this mutation while the father and unaffected brother did not have the mutation (►Fig. 1).

Discussion

NDI is a rare disease which is caused by mutations of the V2R. AVPR2 belongs to the subfamily of G-protein coupled receptors with seven transmembrane domains.⁷ AVPR2 is a polypeptide of 371 amino acids and mediates the AVP.

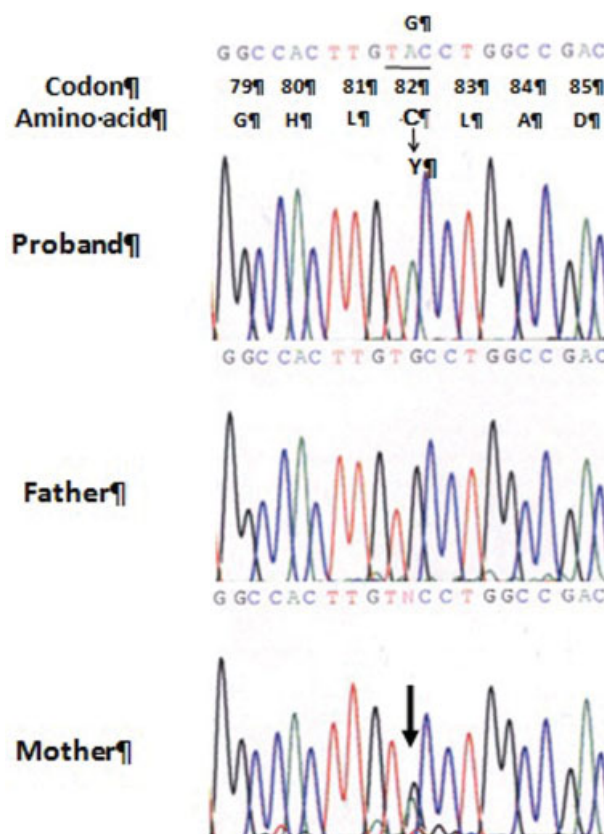


Fig. 1 Mutational analysis of the proband, father, and mother. A missense G to A mutation at nucleotide 606 (thin arrow) in codon 82 results in a substitution of tyrosine for cysteine (C82Y). Note the double band at this site (thick arrow) in the mother's sequence indicating that she is heterozygous for the mutation.

NDI usually presents with polyuria, polydipsia, volume depletion, hypernatremia, hyperthermia, irritability, constipation, FTT, developmental delay, and mental retardation, decreased appetite and poor food intake due to consumption of large amount of water, growth abnormalities, and behavioral problems including hyperactivity.

The high urine flow associated with NDI may complicate to hydronephrosis and may progress to loss of renal function and possible end-stage renal disease.

The missense mutation identified in our patient induced a (C82Y) amino acid substitution. This mutation is located in the transcellular domain II of the gene. Based on the database of human AVPR2 mutations (available at: <http://www.medicine.mcgill.ca/nephros>), this would appear to be a new mutation.⁸ This is a region with a predilection to mutations as there have been numerous reports of mutations in this domain including missense and deletion mutations involving amino acids 80, 81, 83, 84, 85, and 88 (see ►Fig. 1). No functional studies were performed and we considered the amino acid change in the gene as pathogenic (i.e., mutation) based on the following: positive segregation in the family (heterozygous mother and healthy sister, hemizygous mutated in the affected boys, hemizygous normal father,

and unaffected brother, the amino acid change is in a region with a predilection to mutation (as stated above), the changed amino acid is in a conserved residue. All of the reported mutations have been associated with clinical disease. D85 is a highly conserved residue which has a role in receptor activation in many G-protein-coupled receptors.⁹ Albertazzi et al showed in functional studies that A84 is important for both protein sorting to the plasma membrane and reduced receptor affinity.¹⁰ It is likely that our mutation, similar to the other nonconservative mutations in this segment affect protein folding thereby affecting protein trafficking and the protein's affinity for its ligand.

Although congenital NDI is rare, it is important to identify it very early in life to prevent hypernatremia, dehydration, and their associated consequences. Early intervention with fluid therapy, a decreased solute diet and administration of pharmacologic therapies such as diuretics (hydrochlorothiazide) and nonsteroidal anti-inflammatory drugs (indomethacin) are effective therapies and can prevent the development of hydronephrosis. All measures are in parallel with providing adequate nutrition by providing appropriate amount of calories and special nutrients to try correct the associated FTT. Knowledge of the mutation allows for genetic counseling.

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