

A novel AVPR2 missense mutation in an Asian family with inherited nephrogenic diabetes insipidus

A case report

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Abstract

Rationale: X-linked nephrogenic diabetes insipidus (NDI) is a rare inherited disease, and is characterized by renal resistance to arginine vasopressin (AVP). Its diagnosis can be clinically challenging. The application of molecular genetic analysis can provide a rapid and definitive diagnosis.

Patient concerns: A 75-year-old woman presented with recurrent nausea and vomiting was admitted to the Department of Gastroenterology. The patient had a strong family history of polydipsia and polyuria. Sequencing analysis of the antidiuretic hormone arginine vasopressin receptor 2 (AVPR2) revealed the novel missense mutation p. Trp164Cys (c.492G>G/C) in exon 2. There was a heterozygous mutation in the patient's sister and niece, while there was a mutation in her sons, brother and nephews. The locus is located on the X chromosome Xq28, and its mutation can lead to X linked recessive NDI. The p. Trp164Cys mutation of AVPR2 gene has not been reported in literature before. The mutation was predicted to be probably damaging by several prediction methods, including SIFT and PolyPhen-2. There was no significant abnormal variation in other detection regions of the gene. And there was also no abnormal variation in AVP and AQP2 genes in this family.

Diagnosis: X-linked NDI was diagnosed according to the patient's family history and DNA sequencing analysis.

Interventions and outcomes: After treated with desmopressin, antiemetic drugs and massive infusion glucose transfusion, the patient's urine volume decreased and electrolyte disturbance was corrected, and the symptoms of nausea and vomiting gradually disappeared.

Lessons: The patients with suspected congenital NDI should undergo genetic sequencing analysis of AVPR2, AVP and AQP2 genes. A definitive diagnosis can benefit patient and avoid unnecessary investigations.

Abbreviations: β -HCG = β -human chorionic gonadotropin, AFP = alpha-fetoprotein, AQP2 = aquaporin2, AVP = arginine vasopressin, AVPR2 = arginine vasopressin receptor2, CA125, 153, 199, 724 = cancer antigen 125, 153, 199, 724, cAMP = cyclic adenosine monophosphate, CEA = carcinoembryonic antigen, CT = computed tomography, Cys = cysteine, DDAVP = desmopressin, ECG = electrocardiogram, mOSM = milliosmole, MRI = magnetic resonance imaging, NDI = nephrogenic diabetes insipidus, PET-CT = positron emission tomography computed tomography, SCC-Ag = squamous cell carcinoma antigen, Trp = tryptophane.

Keywords: AVPR2, DNA sequencing, X-linked nephrogenic diabetes insipidus

Editor: N/A.

The present study was supported by a grant from the National Natural Science Foundation of China (no. 81770528) (to QY).

The authors have no conflicts of interest to disclose.

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Medicine (2019) 98:17(e15348)

Received: 30 November 2018 / Received in final form: 21 March 2019 /

Accepted: 29 March 2019

<http://dx.doi.org/10.1097/MD.00000000000015348>

1. Introduction

Nephrogenic diabetes insipidus (NDI) is a relatively rare inherited disease, which is commonly diagnosed by main symptoms such as polyuria and polydipsia. It is usually caused by a mutation of the arginine vasopressin receptor 2 (AVPR2) gene or the aquaporin 2 (AQP2) gene.^[1,2] AVPR2 is a G protein-coupled receptor,^[3] which acts as the primary mediator of the water-conserving action of AVP in the kidney. AVP binds to AVPR2 on the basolateral membrane of principal cells in the renal collecting ducts, which stimulates adenylyl cyclase to produce cAMP and activate protein kinase A.^[4] Ultimately it leads to the translocation of AQP2 to the apical surface of the principal cells in the kidney collecting duct, therefore increasing water reabsorption and urine osmolality.^[5]

About 90% of NDI cases are X-linked hereditary and characterized by renal resistance to antidiuretic effect of AVP.^[6–8] This is a kind of condition which affected male patients are symptomatic during infancy, while heterozygous females present with a broad phenotypic spectrum.^[2,7,9] The

AVPR2 gene that is responsible for NDI has been mapped to chromosome Xq28 and consists of 3 exons.^[3] To date, more than 220 AVPR2 variants have been recognized to cause X-linked NDI.^[10] Missense mutations can lead to partially preserved receptor expression and function and hence a milder diabetes insipidus.^[11]

In this work, we present a case of a Chinese pedigree with NDI that has a novel missense mutation detected through sequence analysis of the AVPR2 gene.

2. Ethics statement

As a case report, our institution does not require formal ethical approval. Written informed consent was obtained from the patient for publication of this case report.

3. Case report

A 75-year-old woman, presenting with recurrent nausea and vomiting for several months, was admitted to the Department of Gastroenterology in our hospital on 15 March 2018 with the preliminary diagnosis of chronic gastritis. A few months ago, the patient developed nausea and vomiting after catching a cold. The vomit was gastric contents, no black stool, no fever, dizziness and headache occurred. Gastrosocopy in the local hospital showed chronic gastritis, then treated by acid suppression and gastric care medicine, but vomiting relief was not obvious, so she came to our hospital clinic and was admitted to the ward. Since the onset of the disease, the weight loss of the patient has more than 5 kg. Cholecystectomy was performed 20 years ago, and right breast mastectomy for breast cancer 9 years ago. The patient had complained of polydipsia and polyuria since birth. She drank 5 to 6 L of water per day, and her urine output was large as well. She denies recent history of using renal injury agents. Her family history showed her brothers and sisters have the same symptoms of polydipsia and polyuria, but her brothers' symptoms are more serious than her sisters. Her younger brother died of unknown

reason and one of her nephews died of infection. Because of her seniority and siblings sharing the same symptoms, she had not paid attention to the disease, and received no diagnosis or treatment.

On examination, she had a blood pressure of 130/100 mm Hg, regular pulse rate of 110 beats/min, and body temperature of 36.7°C. There were no other abnormal findings on physical examination. Laboratory data were as follows: white blood cells $8.85 \times 10^9/L$, red blood cells $3.93 \times 10^{12}/L$, platelet count $284 \times 10^9/L$, hemoglobin 122 g/L, serum liver and renal functions were normal. Serum tumor markers including AFP, CEA, CA125, 153, 199, 724, SCC-Ag and total β -hCG were normal. Thyroid and adrenal function were normal. Serum sodium and chloride levels were increased above normal values (159.6 mmol/L and 117.4 mmol/L, respectively), with an effective osmolality of 307 mOSM/kg (normal range: 275–295 mOSM/kg). Urine pH was 5.0, urine-specific gravity was 1.003 with a decreased urine osmolality level of 83 mOSM/kg (normal range: 150–1150 mOSM/kg), whereas urine creatinine and electrolyte levels were normal. Fluid intake volume was 3840 ml/day and urinary volume was 6200 mL/day. Electrocardiogram (ECG) suggested sinus tachycardia and no abnormality in cardiac function was found by echocardiography. Computed tomography (CT)-scan of the head suggested mild lacunar cerebral infarction. And CT angiography in the head and neck showed mild arteriosclerosis. Magnetic resonance imaging (MRI) of the pituitary was normal. Positron emission tomography computed tomography (PET-CT) image did not show any sign of tumor recurrence and metastasis. Based on the clinical symptoms and laboratory tests, diabetes insipidus was suspected. Combined with the family analysis (Fig. 1), the primary diagnosis of X-linked hereditary NDI was made. In order to make a molecular diagnosis, DNA sequencing analysis was carried out on samples from the patient, her 3 first-degree relatives (her brother, sister and son), 2 second-degree relatives (her niece and nephew) and one third-degree relative (her grandnephew, who is her niece's son). Her other relatives refused to have genetic testing, therefore they were not included.

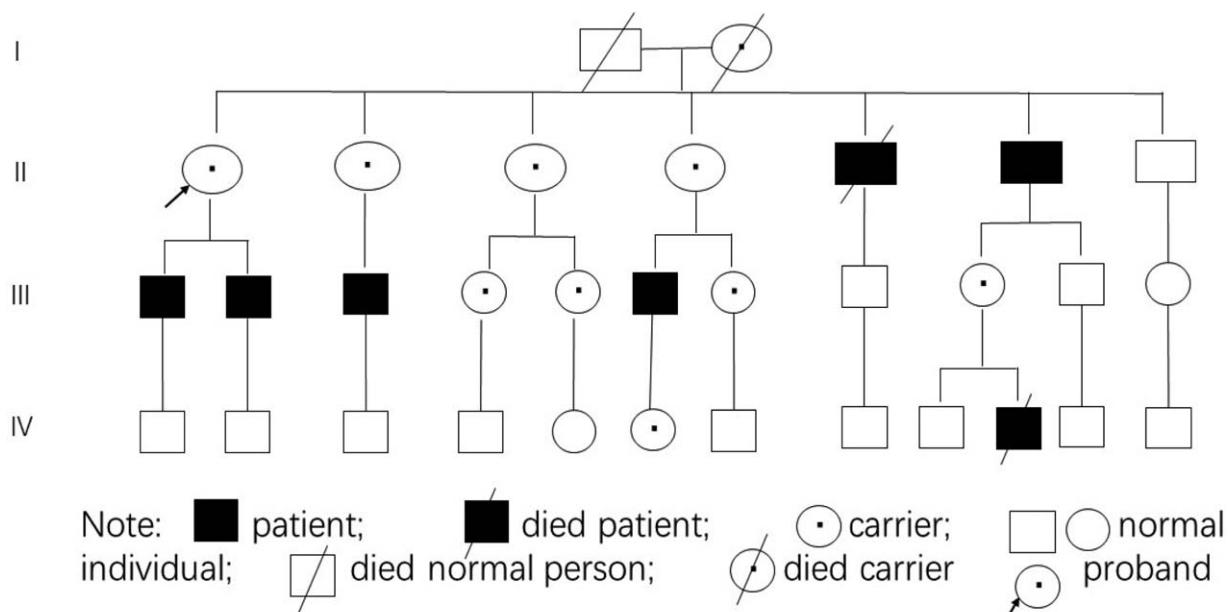


Figure 1. Pedigree of X-linked nephrogenic diabetes insipidus in the patient's family.

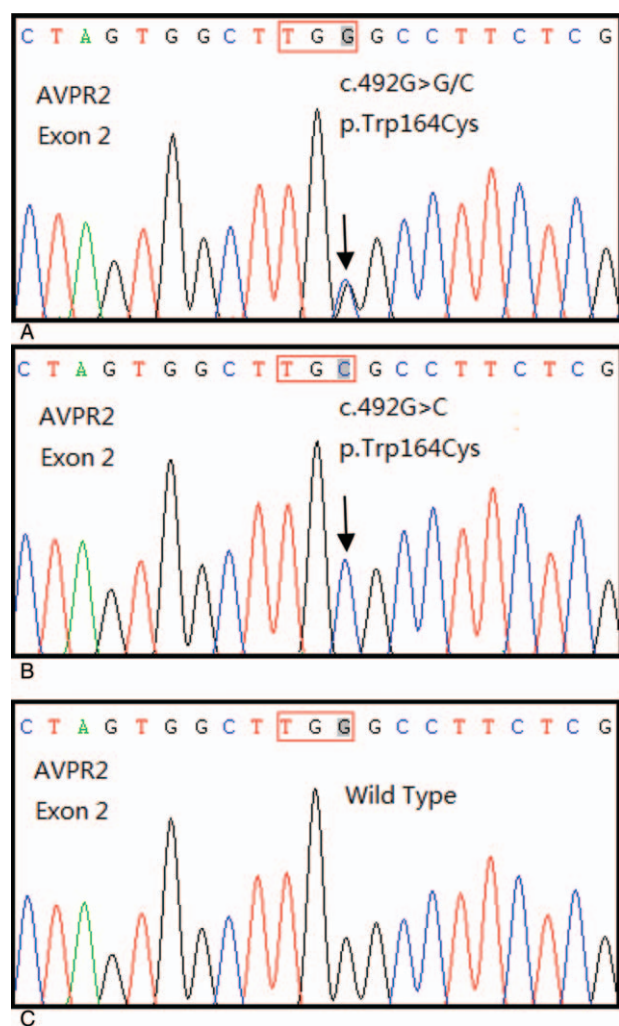


Figure 2. DNA sequencing results for the 75-year-old female with suspected diabetes insipidus and her 3 first-degree relatives (her brother, sister and son), two second-degree relatives (her niece and nephew) and one third-degree relative (her grandnephew, that is her niece's son). Arrows represent the mutation site. (A) DNA sequencing revealed a novel missense mutation [c.492G>C (arrow), resulting in a substitution of Trp with Cys at codon 164] in the AVPR gene, which was heterozygous in proband, the proband's sister and niece. (B) DNA sequencing revealed a missense mutation which was hemizygous in the proband's son, brother and nephew. (C) DNA sequencing showed normal in the proband's grandnephew.

Direct sequencing analysis of the antidiuretic hormone arginine vasopressin receptor 2 (AVPR2) identified the novel missense mutation (c.492G>G/C) in exon 2, leading to a p. Trp164Cys (T164C) amino acid substitution in the patient. There was a heterozygous mutation in the patient's sister and niece (Fig. 2A), while there was a mutation in her sons, brother and nephews (Fig. 2B), and her grandnephew is normal (Fig. 2C). The locus is located on the X chromosome Xq28, and its mutation can lead to X linked recessive NDI. The p. Trp164Cys mutation of AVPR2 gene has not been reported in literature before. The possible effect of the T164C mutation was predicted to be probably damaging by several prediction methods, including SIFT^[12] and PolyPhen-2.^[13] There was no significant abnormal variation in other detection regions of the gene. Also there was also no abnormal variation in AVP and AQP2 genes in this family.

Then we treated the patient with desmopressin (DDAVP), antiemetic drugs, and massive infusion glucose transfusion. The patient's urine volume decreased, about 3 to 4 L per day, then electrolyte disturbance was corrected, and the symptoms of nausea and vomiting gradually disappeared. The electrolyte results of the re-examination showed that the serum sodium and chloride levels were 141.9 mmol/L and 103.3 mmol/L respectively, which were in the range of normal values.

Six months after discharging from hospital, we followed up the patient by telephone. The patient was generally in good condition, the electrolytes were normal, no nausea and vomiting occurred, and her weight increased by 4 kg.

4. Discussion

We here described a female from a Chinese family, with congenital NDI putatively caused by a novel missense mutation (c.492G>G/C; p. Trp164Cys) in the AVPR2 gene. The clinical diagnosis of congenital NDI was made according to the clinical manifestations, laboratory data, and family history. Molecular analysis by DNA sequencing further confirmed the diagnosis. Interestingly, the patient was admitted to gastroenterology with nausea and vomiting and other gastrointestinal symptoms. Combined with previous breast cancer history, the patient underwent a series of examinations including digestive endoscopy and imaging to exclude tumor recurrence and metastasis. Later, it was found that the electrolytes of the patient were obviously abnormal, and the family history of polyuria and polydipsia was existed. Only when the electrolyte disturbance caused by diabetes insipidus was considered, could the digestive symptoms of the patient be explained. After a diagnosis of NDI was confirmed, subsequent treatment affirmed our inference. The patient's symptoms disappeared after the disturbance of electrolytes was corrected. Why did this patient have this electrolyte disturbance but not before? We inferred that the virus infection may be related, then a vicious circle was formed afterward, and vomiting aggravates electrolyte disorders.

AVPR2 mutations causing NDI can vary in their functional severity, therefore clinical symptoms and the response to DDAVP can be diverse. As in previous literature reported,^[5] the most common AVPR2 mutations causing NDI are missense mutations. Independently from AVPR2, missense mutations responsible for various genetic disorders are often situated in regions of a protein that are not necessarily part of the active site or the binding site. Among the different missense mutations already published, arginine and tyrosine appear to be among the most frequently mutated amino acids in AVPR2. A recent study examined the spectrum of 44 different proteins causing disease by missense mutations, and identified arginine as the amino acid with the highest mutability rate.^[14] It may more likely cause clinically significant disease compared to mutations in other amino acids due to its importance in Drosophila RNA binding proteins^[15] and taking part in the post-translation process of several proteins.^[16] On the other hand, alanine and glutamate are the significantly less frequently mutated AVPR2 amino acids among the missense mutations.^[5] In our case, we identified the novel missense mutation (c.492G>G/C) in exon 2, leading to a p. Trp164Cys (T164C) amino acid substitution in the patient's family, which has not been reported before in literature. By several different prediction methods, the mutation p. T164C was consistently predicted to be pathogenic,^[12,13] which would be reliable than by just using a single prediction method. Except one

female carrier, the other female carriers and male patients in this family all have symptoms, but the symptoms of female carriers are much milder. The asymptomatic female carrier may be explained by skewed inactivation of the X-chromosome. In addition, the patient is partly effective in the treatment of DDAVP. It is also worth mentioning that there were phenotypic differences in disease severity of those carriers and patients, which means that the degree of functional impairment of AVPR2 caused by this missense mutation has individual difference.

In this family, 2 male patients died, 1 was at the age of 2 owing to infection and the other died at the age of more than 40, but the cause of death was unknown. As indicated, severe complications of NDI were not highly prevalent in patients who received a correct diagnosis at an early age.^[17,18] However, for those patients with severe complications of NDI, the primary signs of the congenital NDI were easily overlooked, especially when influenced by other complicated or life-threatening factors acquired with the disease, which may cause difficulties in the diagnosis and treatment.^[19] As described in this case, the patient presented with other signs of NDI, while the symptoms of polyuria and polydipsia were ignored. Considering the age of the patient, we did not combine the digestive symptoms with NDI at the beginning. Therefore, we emphasize the importance of awareness about the primary signs of congenital NDI, and of molecular diagnosis and treatment.

Standard management of X-linked NDI includes hydrochlorothiazide and indomethacin.^[20] However, these treatments only partially improve symptoms, and partial NDI can be treated with high dose of DDAVP. In the last years, several promising agents such as chaperones for X-linked NDI have been under investigation and have shown therapeutic potential. The likelihood of treatment with these chaperones has been tested in vivo in NDI patients who have missense AVPR2 mutations, showing that treatment with a chaperone antagonist had beneficial effects a few hours after administration.^[21,22] Although this approach seems to be promising, confirmation of the effect of pharmacologic chaperones in NDI needs further in vivo testing.

5. Conclusion

In conclusion, patients with NDI of unknown etiology can harbor site mutations whose pathogenicity may initially be underestimated. By investigating an elderly female patient with recurrent nausea and vomiting, we identified a novel AVPR2 missense mutation in p. Trp164Cys (c.492G>G/C) in an Asian family with NDI. We suggest patients with polyuria and polydipsia should undergo genetic analysis of AVPR2 and AQP2 genes. A definitive diagnosis can benefit patient and avoid unnecessary investigations.

Acknowledgments

We are grateful for the cooperation of the patient's family.

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Investigation: Jian Han, Bin Cheng.

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