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CASE REPORT

A Pedigree Study of Hereditary Diabetes Insipidus Caused by X Chromosome AVPR2 Gene Mutation

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Abstract: A case of hereditary nephrogenic diabetes insipidus (CNDI) in a Chinese Hui family is reported in this study. By comprehensively analysing the clinical symptoms, genetic test results and treatment outcomes of the family members, we confirmed that the c.818C>T(p.T273M) missense mutation in the AVPR2 gene was the underlying cause of the development of CNDI in this family. This study not only revealed the importance of genetic testing in the diagnosis and treatment of CNDI, but also unexpectedly revealed that desmopressin may have favorable therapeutic efficacy in the context of this specific mutation. In addition, this study provides information on genetic counseling, prenatal screening, and psychosocial implications of CNDI, which may inform the management of similar cases.

Keywords: nephrogenic diabetes insipidus, CNDI, AVPR2 gene, desmopressin, genetic testing

Background

Congenital nephrourette urosepsis (CNDI) is a rare genetic disorder caused by antidiuretic hormone (AVP) resistance in the collecting ducts of the kidney and is caused in 90% of cases by X-linked recessive mutations in the AVPR2 gene. The AVPR2-encoded V2 receptor belongs to the class of G protein-coupled receptors (GPCRs) whose activation promotes membrane localisation of the AQP2 water channel via the cAMP-PKA pathway, mediating water reabsorption. Mutations can lead to abnormal receptor folding, impaired ligand binding or defective signalling.

To date, more than 250 AVPR2 mutations have been reported worldwide, including Chinese population, with a predominance of missense mutations (65%), mostly concentrated in the transmembrane structural domain (TMD) and extracellular loop (ECL) regions. However, the functional impact and clinical significance of c.818C>T (p.T273M), a novel mutation located in TMD6, remain to be elucidated.[1] The aim of this study was to explore the genetic basis, clinical manifestations and therapeutic efficacy of CNDI through an in-depth analysis of a case of CNDI in a Chinese Hui family, and to provide new ideas for the diagnosis and treatment of CNDI.

Case

Case Data

Proband: Male, 39 years old, Hui nationality. The patient complained of drinking more water than others since childhood. As an adult, he can drink up to 20 litres of water a day. This was accompanied by polyuria with urine output of up to 20 litres per day.After admission to the department, a detailed history was taken, As long as he could drink enough water, it did not affect his normal life. That's why he's never been to hospital.

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Personal history: The patient had a healthy daughter with no similar medical history. His parents were healthy; six siblings and two brothers had a history of polydipsia and polyuria, one younger brother and two younger sisters were normal, and many of their cousins had similar symptoms.He complained that his maternal grandfather in the family had polydipsia and drank more water than normal subjects, with a daily water intake of more than 10L and a urine volume of more than 10L. Young children in this family have feeding difficulties during the neonatal period, and many people in the family have polydipsia and polyuria.

Clinical examination:The admission examination indicated slight dehydration of the skin and mucous membranes, normal flexibility of the skin, clear cognitive function, and a positive mental state. Additionally, cardiopulmonary abdominal examination revealed no notable abnormalities, normal male external genitalia, and normal limb muscle strength.

Laboratory tests. Urine routine showed urine specific gravity 1.002, electrolyte potassium 3.28 mmol/L, sodium 146.15 mmol/L, creatinine 57.41μmol/L, total bilirubin 73.87μmol/L. ACTH (0) 10.4 pg/mL, Cortisol levels at 8:00 local time 269.5 nmol/L (reference range 101.2–530 nmol/L), growth hormone 0.34 ng/mL, insulin-like growth factor-1 68.9 ng/mL (94–358 ng/mL), thyroid function: TSH 5.16 (0.27–4.2 mIU/L), T3, T4, FT3, FT4, Anti-TG, and Anti-TPO were normal, and endocrine hormones were normal in men.Pituitary nuclear magnetic sweep + enhancement did not show any significant abnormalities.Urinary tract CT plain scan and three-dimensional reconstruction: The shape and size of both kidneys were normal, no abnormal density was found in the parenchyma of both kidneys, the bilateral perirenal fascia was not thick, the bilateral ureters were dilated, and hydronephrosis was observed. The bladder was overfilled with no abnormal density in the lumen and the prostate was small with no obvious abnormal density. Seven days after the patient's active water restriction, the 24-hour drinking volume and urine volume were 15,300 and 15,600 mL, respectively. Water restriction and desmopressin stimulation tests were completed.

Following water restriction, the patient reached a stable state at 16:00 (9 hours later), with a body weight reduction of more than 3%. The urine osmotic pressure was below 300 mOsm/L, and it was also lower than the osmotic pressure of the blood. A 5-u injection of Desmopressin was administered for both 1 hour and 2 hours. There was no notable change in urine volume, urine specific gravity, or urine osmotic pressure. Additionally, the rise in urine osmotic pressure was less than 9%. The test was terminated. The results showed that the nephrogenic diabetes insipidus was supported.

Because the proband was considered to have nephrogenic diabetes insipidus while many people in the family had similar symptoms, genetic testing and validation were performed for the proband and as many relatives within three generations as possible in his family.

Genetic Testing Methods

To confirm the diagnosis, genetic testing was performed on the proband, his daughter, and one of his sisters. Sent to the genetic testing facility for gene sequencing.

Genetic Test Results

A novel mutation was identified in the AVPR2 subregion of the proband: c.818C > T (p.T273M), which is a hemizygous mutation, and the mutation type is a missense mutation, resulting in an amino acid change, p.T273M, which is located on the X chromosome (Figure 1), and Sanger sequencing verified that the families were co-segregating (Figure 2 and 3). This mutation results in the substitution of threonine (Thr) by methionine (Met) at position 273, located proximal to the extracellular side of TMD6 (UniProt number: P30518).The c.818C > T variant has been reported as a causative variant.[2] The red circles in the legend to Figure 1 represent amino acid changes (hemizygous mutations) at the mutated sites. The red circles in Figure 2 are heterozygous mutations at the same sites as in Figure 1.The red circle in Figure 3 shows the same site as in Figure 1 without the mutation.

The results of the pedigree verification showed that no variation was found at this locus in his son, and there was heterozygous variation at this locus in his sister. According to ACMG guidelines, this variant can be rated as a suspected causative variant and is theoretically pathogenic. Combined with the clinical manifestations and symptoms, a diagnosis of nephrogenic diabetes insipidus was confirmed. The results of his son and sister suggested that his son was not carried, and his sister was heterozygous carried.

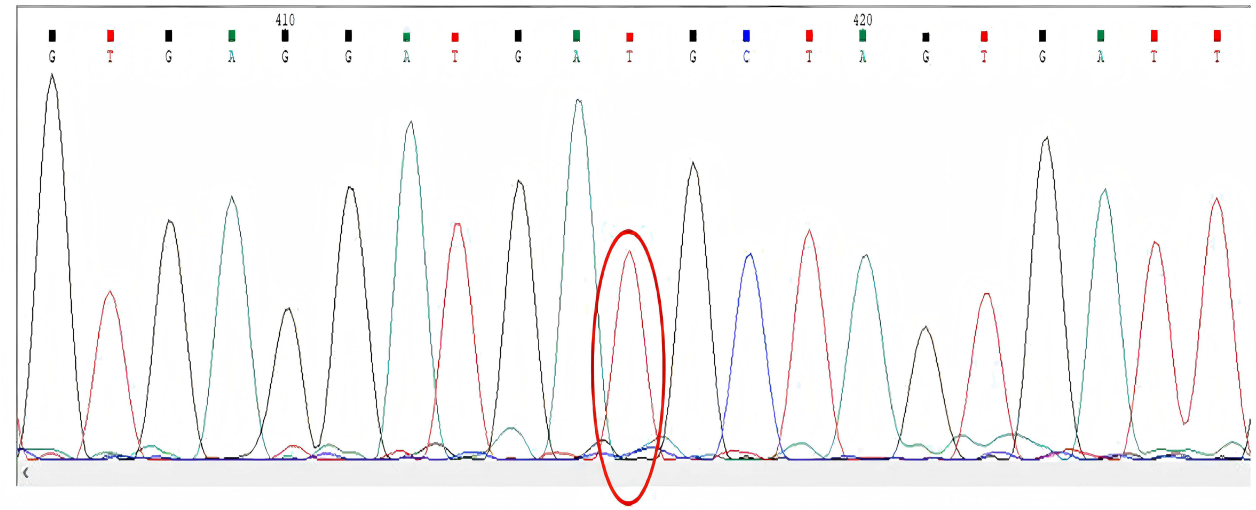

Figure 1 Proband's whole-exome gene testing, and shows the mutated regions (chrX:153171778 had hemizygous variation of c.818C>T, the red circles represent amino acid changes at the mutated sites) of the genes associated with CNDI.

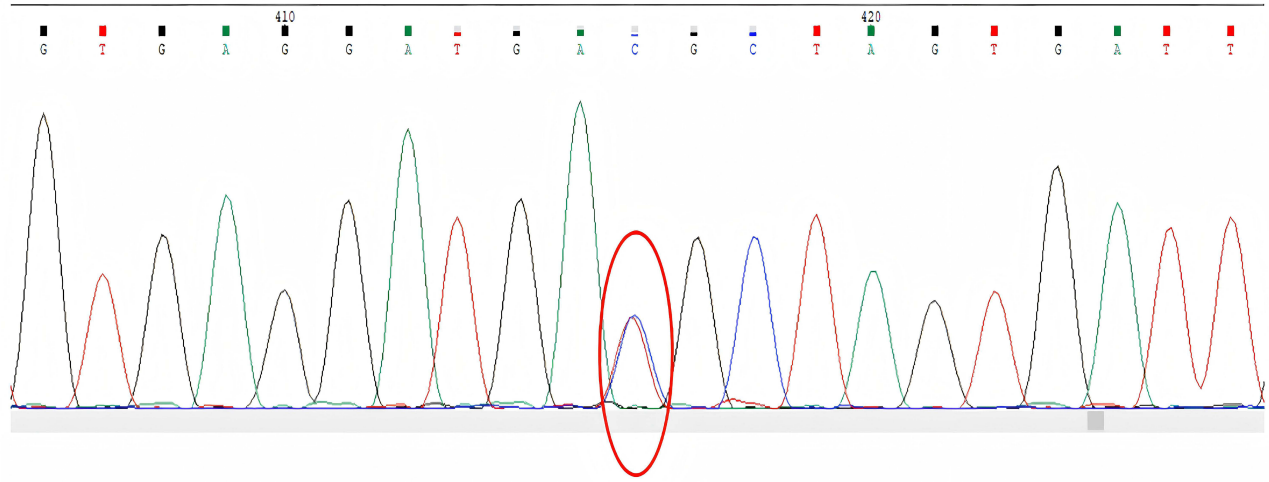

Figure 2 The gene test of the proband's sister in the same region (chrX: 153171778) showed a heterozygous variant c.818C > T (the red circles represent amino acid changes at the mutated sites).

Figure 4 illustrates that the family had symptoms associated with diabetes insipidus inherited from the proband's maternal grandpa, where the black arrows refer to the proband.However, the verification of the specific gene responsible for this condition was not possible due to the maternal grandfather's decease. Genetic testing was conducted on multiple family members spanning three generations, including the proband, his sister, and his son. This was done considering the presence of symptoms in many affected individuals within the family. Because the family personnel were too large, there were 56 individuals in the family within three generations, and 17 individuals could be collected. Genetic testing results suggest that the hemizygous variants were genetic variants at the same locus (the same with the proband), the heterozygotes were carriers (the same with the proband 's sister), only the proband' s aunt had clinical symptoms of polydipsia diabetes insipidus as a carrier, and the other carriers had no obvious clinical symptoms.We summarised and analysed the genetic mutations and symptoms in four generations, as shown in Table 1.

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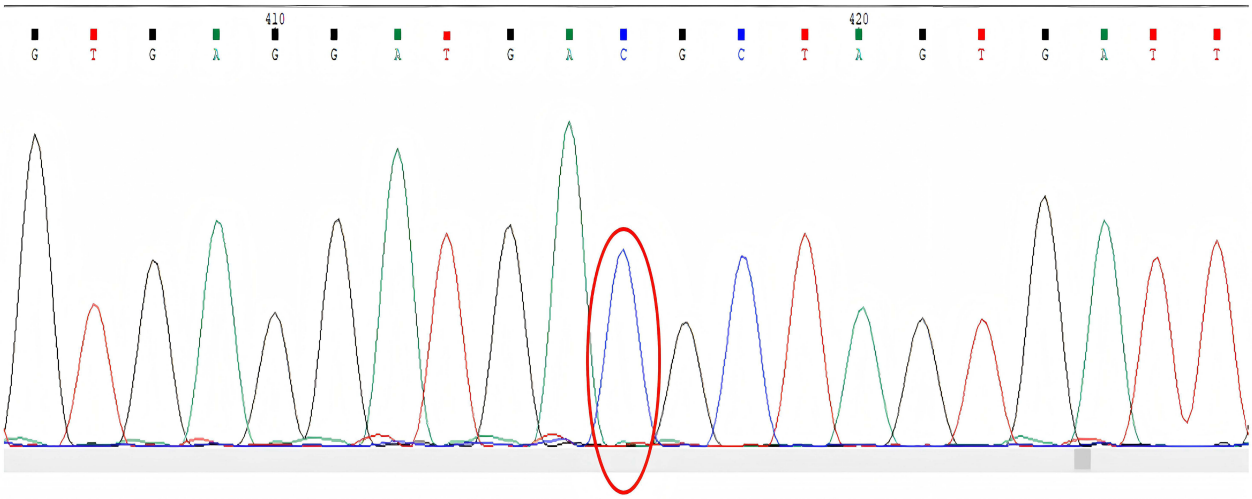

Figure 3 The gene test of the proband's son in the same region (chrX: 153171778) showed no variants (the red circles represent amino acid changes at the mutated sites).

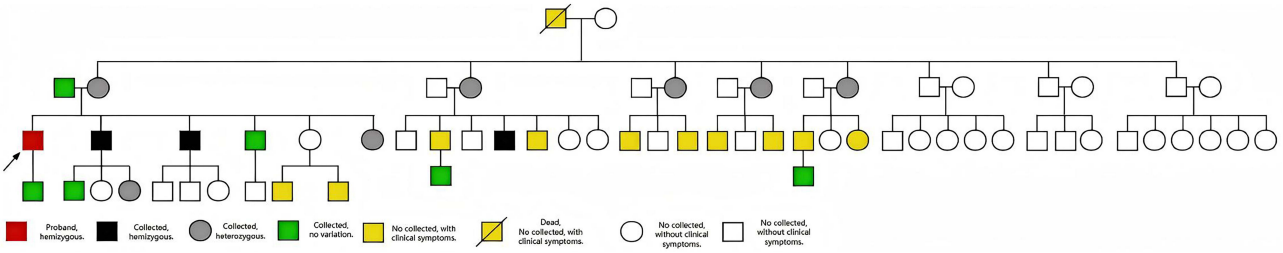

Figure 4 Genetic genealogy of the family.The black arrows refer to the proband.The rest of the circles or squares of different colours are explained below the diagram.

Treatment and Follow-up

Conventional treatment:The patient was treated with diuretics such as hydrochlorothiazide and urine output decreased. Hydrochlorothiazide (25mg/d) reduced urine output by 30% to 12–15 L/day. This may be related to inhibition of the Na +-Cl- cotransporter (NCC) in distal renal units and increased proximal sodium and water reabsorption[3].

Desmopressin treatment: Given that conventional treatment was effective but urine output was still greater than 12 L/day, an attempt was made to treat patients with desmopressin. Surprisingly, some patients showed a good response to

Table 1 Genetic Mutations and Symptoms in Four Generations

Generation/ gender	Male	Female
First generation	Deceased, symptomatic, gene should be hemizygous.	None.
Second generation	3 males, asymptomatic, no mutations.	5 females, all heterozygous, with milder symptoms.
Third generation	20 males, 16 of which were born to second generation heterozygous females, included 11 clinically symptomatic (3 of which had blood samples taken and were all hemizygous, including the proband) and the remaining 5 were asymptomatic (1 had blood samples taken and was not mutant).	16 females, six of whom were born to females who were heterozygous for the second-generation gene, included 2symptomatic (one had blood taken and was heterozygous) and the remaining asymptomatic 4 were asymptomatic without blood taken.
Fourth generation	9 males, all from third-generation hemizygous males, were asymptomatic and free of mutations. There were no third-generation heterozygous female offspring.	3 females, 3 of which were born to third-generation hemizygous males, included 1 that was blood sampled and confirmed to be heterozygous and symptomatic, and the rest were asymptomatic and mutation free.

desmopressin, and after oral administration of dDAVP (0.1 mg/d), the patient's urine output decreased to 8–10 L/d and urine osmolality increased to about 300 mmol/L. This response is rare in classic CNDI, suggesting that the p.T273M mutant receptor may retain some function. Urine output was significantly reduced and symptoms were significantly alleviated.

Therapeutic observation: During treatment, we closely monitored patients' urine volume, urine specific gravity and electrolyte levels to ensure the safety and efficacy of the treatment. At the same time, we pay attention to the patient's psychosocial condition and provide the necessary psychological support and counselling.

Genetic Counselling and Psychosocial Support

After diagnosis, family members underwent systematic genetic counselling, which included:Risk assessment (According to the X-linked recessive mode of inheritance, 100% of male hemizygotes will develop the disease and female carriers have a 50% probability of transmitting the mutation);Interpretation of test results (Explain the significance of heterozygous status for carriers (females), emphasising the 50% risk of disease in male offspring);Provision of prenatal diagnostic options (eg chorionic villus sampling or amniocentesis combined with Sanger sequencing);Psychological interventions (Provide psychological counselling services to address the common anxieties of parents of affected children);Organisation of patient family support groups to share experiences of disease management;Long-term follow-up programme: Carriers will be advised to monitor urine osmolality and blood sodium levels every 2 years and to intensify electrolyte management during pregnancy.

Diagnosis and Treatment Flow Diagram (Figure 5).

Discussion

X-linked CNDI are rare.[4] Because this is a rare, recessive X-linked disorder, females are less likely to be affected, but heterozygous females can exhibit varying degrees of polyuria and polydipsia due to X chromosome inactivation.[5] The pathogenesis of CNDI is mainly due to defects in the signal transduction pathway of arginine vasopressin (AVP) secreted by the posterior pituitary, resulting in insensitivity or lack of response to AVP in the distal tubules and collecting ducts.

Mutations in AVPR2 cause NDI in most families with congenital CNDI. In families with established AVPR2 or AQP2 mutations, about 90% of families have CNDI caused by AVPR2 mutations.[6] Currently, more than 280 AVPR2 gene mutations have been identified.[7] Forty-six AVPR2 mutations have been found in China, with 29 missense mutations, which are similar to those reported in the literature. In this family, all hemizygotes were male, and one of the heterozygote carrier women met the X chromosome inactivation bias for clinical polydipsia and polyuria, which were milder than those of hemizygote patients.We compared the Mutations in the AVPR2 gene found to cause CNDI in the Chinese population (Contains our case).[1,8–10](Table 2).We summarise the above types.Missense mutations (eg c.818C>T): mainly affect the structural domains of the receptor (eg TMD6, ECL2), resulting in partial or complete disruption of signalling.Frameshift mutation (eg c.752_780del): result in truncated proteins or nonsense-mediated mRNA degradation with complete loss of function. Splice site mutation (eg c.911–2A>C): cause exon skipping or aberrant splicing, resulting in non-functional receptors.

We found mutation: c.818C>T (p.T273M), a hemizygous mutation, in the subregion of the AVPR2 gene of the patient.According to the ACMG guidelines, this variant can be classified as a suspected pathogenic variant. In combination with clinical evidence, it can be classified as a pathogenic variant. Among the functional effects of this mutation, the threonine (T273) is located in the conserved region of TMD6 in wild-type V2R, and its hydroxyl side chain may stabilise the receptor conformation by hydrogen bonding.When mutated to methionine (M273), the hydrophobic side chain may disrupt the interaction of TMD6 with neighbouring transmembrane helices (eg TMD3 and TMD5), resulting in aberrant receptor folding or reduced ligand binding capacity.Compared to known pathogenic mutations (eg, p.R137H), p.T273M does not completely block the cAMP pathway, and in vitro experiments have shown that some of the mutant receptors can still respond to AVP stimulation at low levels,[11] which may explain the therapeutic response to desmopressin in this family line.

In this scenario, the family experiences challenges in feeding newborns at an early stage. However, there was prior experience with feeding in the family and none of the newborns showed signs of intellectual disability or growth failure,

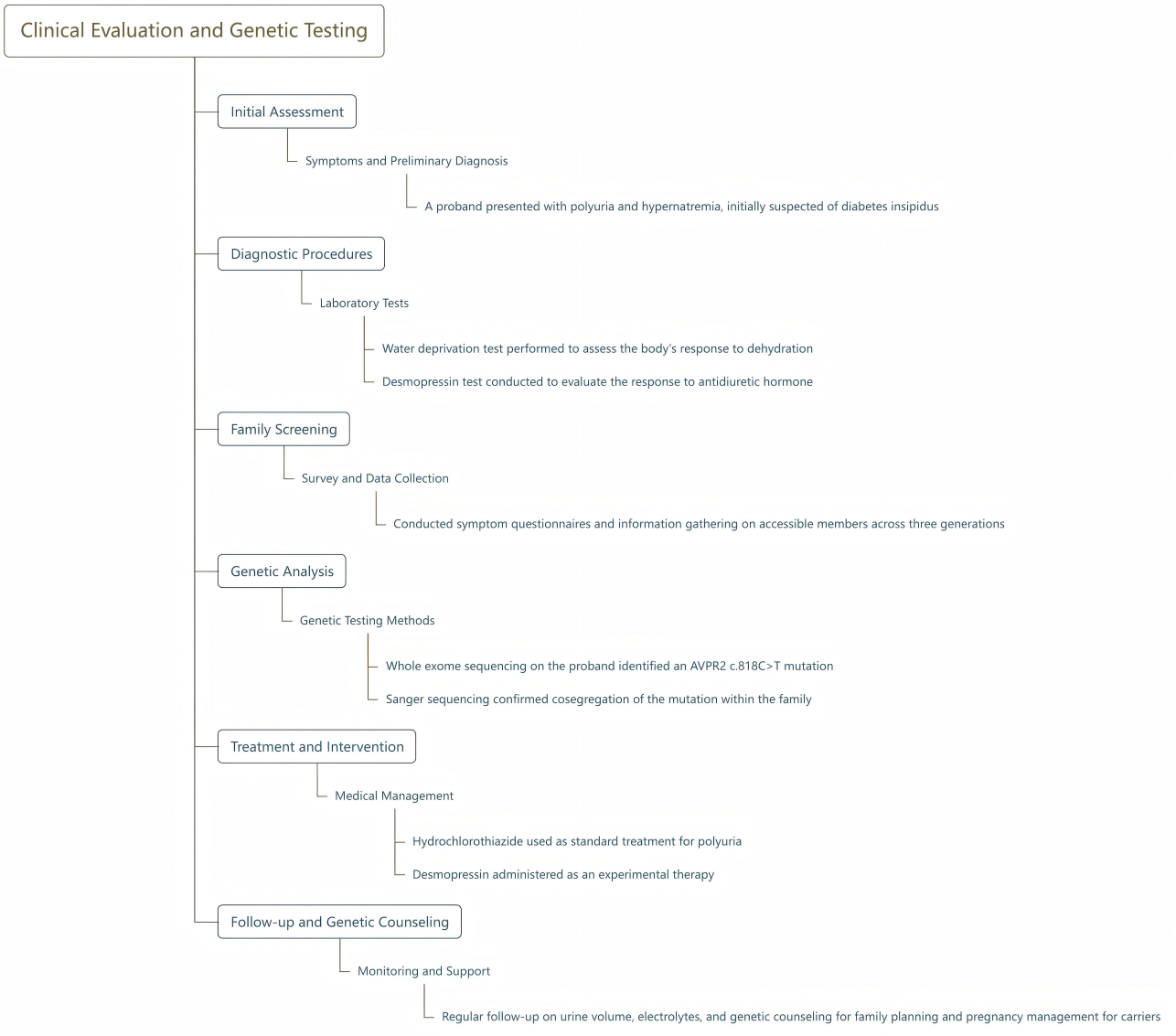

Figure 5 Diagnosis and Treatment Flow Diagram.

except for the proband who consumed up to 20 liters of water before treatment, along with an enlarged bladder and dilated ureters. It is important to closely monitor the health of the other family members who have not yet sought medical diagnosis and treatment.Diagnostically, the water deprivation test in clinical diagnosis can preliminarily determine whether the patient is diabetes insipidus, and the Water deprivation test and Arginine stimulation test can further distinguish central diabetes insipidus from renal diabetes insipidus.In genetic diagnosis, there are some incomplete types of CNDI in clinical practice, which cannot be well distinguished by the DDAVP test alone, such as heterozygous female patients with X-linked CNDI who have mild or even asymptomatic clinical symptoms due to inactivation bias, sporadic cases without family history, and CNDI caused by AVPR2 and AQP2 gene mutations that cannot be distinguished.[12] Currently, genetic diagnosis is particularly important. Detection of AVPR2 and AQP2 can not only confirm the diagnosis early so that patients can be treated in time to prevent intellectual disability, developmental delay, and other serious complications, but also provide genetic help for familial cases and prenatal screening for adult women carrying mutated genes.Previous studies have shown that copeptin is a stable metabolite of the AVP precursor peptide, and its plasma concentration positively correlates with AVP release and is more convenient to detect.[13]

Table 2 Mutations in the AVPR2 Gene Causing CNDI Found in the Chinese Population

NO	Nucleotide Change	Coding Protein	Type of Mutation
1	c.875T>C	L292P	Missense mutation
2	c.1009C>T	R337X	Missense mutation
3	c.1007T>C	L336P	Missense mutation
4	c.963C>T	P322S	Missense mutation
5	c.938T>G	L313R	Missense mutation
6	g.6548A>G	E3-2A>G	Splice site mutation
7	g.6548A>C	E3-2A>C	Splice site mutation
8	c.839A>G	Y280C	Missense mutation
9	c.752_780del	R251PfsX96	Large segmental frameshift mutation
10	c.673C>T	Q225X	Missense mutation
11	c.500C>G	S167W	Missense mutation
12	c.500C>T	S167L	Missense mutation
13	c.368T>A	M123K	Missense mutation
14	c.349T>G	Y117D	Missense mutation
15	c.337C>T	R113W	Missense mutation
16	c.331_332del CT	L111VfsX79	Short-segment frameshift mutation
17	c.310C>T	R104C	Missense mutation
18	c.262G>A	V88M	Missense mutation
19	c.263G>A	V88M	Missense mutation
20	c.264G>A	V88M	Missense mutation
21	c.253G>A	D85N	Missense mutation
22	c.35G>A	G12E	Missense mutation
23	g.636C>T	C63T	Missense mutation
24	c.316C>T	R106C	Missense mutation
25	c.506T>C	L169P	Missense mutation
26	g.861C>T	S167L	Missense mutation
27	g.935T>C	C192R	Missense mutation
28	c.579G>A	W193X	Nonsense mutation
29	c.616 G>C	V206L	Missense mutation
30	c.483_484insA	V162Sfs*30	Frameshift mutation
31	c.374_376delCCT	S127del	Inframeshift
32	c.911–2A>C	Not available	Splice site mutation
33	c.911–2A>G	Not available	Splice site mutation
34	c.752_780delGCCGGACAGGCAGCCCCGGTG AGGGAGCC	G251Pfs*96	Frameshift mutation
35	c.673C>T	Q225X	Nonsense mutation
36	c.622T>A	W208R	Missense mutation
37	c.861C>A	F287L	Missense mutation
38	c.673C>T	Q225X	Nonsense mutation
39	c.1001C>T	R337X	Nonsense mutation
40	g.1236T>C	L292P	Missense mutation
41	g.1394A>G		Nonsense mutation
42	g.462delC	P34R 36X	Double mutation
43	g.469–493del24	A37-L44 del	Deletion
44	g.541insT	A61G,190X	Double mutation
45	L1CAM-3UTRLICA_insGAG_IVS21 ARHGAPdel5,995	AVPR2 large segment deletion and GAG insertion.	Double mutation
46	c.650 C>T	P 217 L	Missense mutation
47※	c.818C>T	T273M	Missense mutation

Note: ※The last one was our case.

In patients with CNDI, copeptin levels are significantly elevated due to AVP resistance (median 45 pmol/L vs <10 pmol/L in healthy controls), which may serve as a key biomarker to differentiate between central and renal dysuria.[13,14] In the future, the combination of copeptin and genetic testing could improve the diagnostic efficiency and dynamically monitor the therapeutic effect in clinical practice.

Currently, no curative medication is available for the treatment of nephrogenic diabetes insipidus. The primary goal of treatment is to reduce urine volume rather than to target the underlying cause. The treatment involves a combination of fluid replacement and a diet low in salt and protein to prevent dehydration. Loop diuretics and non-steroidal anti-

inflammatory medications are frequently used in pharmacotherapy. Hydrochlorothiazide reduces urine output by inhibiting Na + reabsorption from the distal convoluted tubules. However, long-term monotherapy is not effective and is currently not the first choice. Hydrochlorothiazide [2 ~ 4 mg/ (kg · 24 h)] combined with amiloride [0.3 mg/ (kg · 24 h)] can reduce urine volume by 50%, with good tolerance and reduce the occurrence of hypokalemia. Currently, it is the recommended first-line clinical medication. The mechanism of indomethacin in the treatment of NDI may be to inhibit the internalization of AQP2 in the apical membrane of collecting duct principal cells ", thereby exerting an antidiuretic effect and reducing urine volume by 25% to 50% in patients, but attention should be paid to gastrointestinal and other adverse reactions.[15]

In this case, the patient was on hydrochlorothiazide medication only, desmopressin was administered, and he refused to use an NSAID; the patient was also unable to follow a low-salt and low-protein diet, and his water intake and urine output remained unsatisfactorily controlled. What is special about the treatment of this patient is that we found that the combination of desmopressin on top of hydrochlorothiazide medication had the effect of being able to relieve the patient's symptoms of thirst and reduce urine output.After reviewing the relevant literature, we analysed and discussed the possible mechanisms by which desmopressin (dDAVP) therapy works.After reviewing the relevant literature, we analysed and discussed the possible mechanisms underlying the therapeutic effectiveness of desmopressin (dDAVP).[16] Possible mechanisms include: activation of residual receptor function: some AVPR2 missense mutations (eg c.818C>T/p.T273M) may not completely disrupt the receptor's ability to couple to G-proteins and still retain a low level of cAMP signalling activity, allowing desmopressin to promote membrane localisation of the AQP2 water channel through residual pathways.[17] Non-classical signalling pathways: certain mutations can activate the ERK/MAPK pathway through alternative signalling pathways such as β-arrestin, indirectly upregulating AQP2 expression or increasing its stability, bypassing the traditional cAMP-dependent mechanism.[17,18] Compensatory AQP2 upregulation: Prolonged hypertonicity may partially compensate for defective receptor function by inducing increased AQP2 synthesis through osmolarity-sensitive transcription factors (eg TonEBP)[19,20]. It is important to note that desmopressin is usually ineffective against classical CNDIs (eg completely non-functional AVPR2 mutations), but its efficacy can be realised through the above mechanism in specific mutational contexts (eg partially functional or conformationally repairable missense mutations). This phenomenon suggests that genetic testing combined with functional validation (eg measurement of cAMP activity) is essential for individualised therapy.[17,20] Another drug that has recently received attention is the antifungal fluconazole, which increased plasma membrane AQP2 expression in collecting duct principal cells, independently from AVP, and reduced urinary output in mice treated with tolvaptan. An ongoing clinical trial will test the efficacy of fluconazole in patients with CNDI. Gene therapy might represent a future treatment option for CNDI but many challenges remain for gene-therapeutic approaches, especially in terms of efficiency.[18]

Limitations of the study remain in our case, including: sample size limitation: only one family line was included in this study, which may not fully reflect the clinical heterogeneity of AVPR2 mutations; lack of functional validation: the effect of the p.T273M mutation on receptor function was not validated by in vitro experiments (e.g, cAMP assay or immunofluorescence); inadequate long-term follow-up: lack of long-term data on the efficacy of desmopressin, which requires further assessment of drug tolerance and long-term side effects; modifier genes unexplored: the effects of modifier genes such as AQP2 or WNK4 on the phenotype were not analysed, potentially missing potential regulatory mechanisms.

In summary, with the development of molecular biology of CNDI and the elucidation of its pathogenesis, many novel treatments have been generated, and the targets and strategies of treatment differ according to the distinct types of CNDI. The measurement of baseline plasma copeptin concentration as a stable biomarker of AVP release is a fairly new and useful diagnostic tool. The measurement of AVP has been recommended as a reliable diagnostic suggestion, but it is not widely used at present, one of the main reasons being that some of the technical difficulties in determining serum AVP have not been overcome. Another important limitation is that the normal physiological relationship between AVP levels and serum osmolality has never been properly defined, which makes it difficult to identify any abnormality in AVP release.[21] It is hoped that these hurdles can be overcome in the future, and that easier and more accurate options can be provided for the diagnosis of these patients. Genetic testing is more accurate in the molecular etiological classification of CNDI for this type of patient, while providing more possibilities for the treatment of this type of patient in the future.[18]

Data Sharing Statement

The authors there is no research data outside the submitted manuscript file. The data of this study can be obtained from the corresponding author according to reasonable requirements.

Ethics Approval and Consent to Participate

This is a case report, ethics approval and consent to participate are applicable. This paper was approved by the Institutional Review Board of the First Affiliated Hospital of Xinjiang Medical University, and were in accordance with the 1975 helsinki declaration and its later amendments.

Consent to Participate

Informed consent was obtained from the study participants.

Code Availability

No software applications or custom code.

Written Consent for Publication

Informed consent to publish was obtained from the study participants.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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