Brief Report

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Clinical and genetic analysis of X-linked nephrogenic diabetes insipidus caused by a novel *AVPR2* mutation (NM_000054.6:exon3:c.245G>A (p.Cys82Tyr)) in a Chinese boy

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SUMMARY: X-linked nephrogenic diabetes insipidus (X-NDI) is a rare congenital disease caused by inactivating mutations of the vasopressin type-2 receptor (*AVPR2*), characterized by impaired renal concentrating ability, dramatic polyuria, polydipsia and risk of dehydration. This study aims to elucidate the pathogenic mechanisms associated with a novel variant in the *AVPR2* gene, which has been implicated in X-NDI. Whole exome sequencing (WES) was employed to identify genetic variants, complemented by bioinformatic analyses to predict the functional impact of these mutations. A male patient, aged 11.5 years, presented with polydipsia, polyuria, rapid weight gain, and associated physical anomalies, alongside hormonal imbalances and elevated serum sodium and chloride levels. Notably, WES revealed a hemi variant in the *AVPR2* gene (NM_000054.6:exon3:c.245G>A(p. Cys82Tyr)), classified as a variant of uncertain significance. The findings indicate that a combined pharmacological approach can effectively manage X-NDI symptoms without significant side effects, suggesting a favorable prognosis for the patient. After hydrochlorothiazide for one month, both serum sodium and chloride recovered a normal level. This study highlights the importance of early diagnosis and personalized treatment strategies in enhancing patient outcomes. Future research should focus on expanding genetic testing within the population to further elucidate the genetic underpinnings of X-NDI and explore the potential for targeted therapies, ultimately improving the management of this challenging condition. This newly identified mutation expands the spectrum of mutations in X-NDI.

Keywords: X-linked nephrogenic diabetes insipidus, *AVPR2*, hydrochlorothiazide, indomethacin

1. Introduction

Nephrogenic diabetes insipidus (NDI) is a rare but significant genetic disorder characterized by the inability of the kidneys to concentrate urine due to resistance to the antidiuretic hormone arginine vasopressin (AVP). This condition leads to excessive thirst and urination, resulting in risk of dehydration and electrolyte imbalances that can severely impact health and quality of life. Estimates of the incidence of congenital NDI indicate 8.8 per million male live births (*1*). 90% percent of all instances of nephrogenic diabetes insipidus (NDI) are attributed to X-linked inheritance (*AVPR2* gene mutations), while the remaining approximately 10% result from loss-of-function mutations in the aquaporin 2 (*AQP2*) gene (*2-6*). The significant expression of the receptor in the thick ascending limb (TAL), distal convoluted tubule (DCT), collecting duct (CNT), and collecting duct (CD), which play crucial roles in the reabsorption of water and solutes from glomerular filtrate, leads to a renal phenotype in X-linked (X-NDI) that is characterized by pronounced polyuria, hyposthenuria, compensatory polydipsia, hypernatremia, and elevated plasma osmolarity. This condition severely diminishes quality of life due to the constant need to urinate, even during sleep, the frequent requirement to consume water, and the necessity to adjust daily activities to accommodate these demands (*7-9*).

Current treatment options for X-NDI remain limited, primarily focusing on symptomatic management through fluid replacement and pharmacological interventions. Thiazide diuretics and nonsteroidal anti-inflammatory drugs have been utilized with varying degrees of success (*3*). Despite these approaches, many patients experience persistent symptoms, indicating an urgent need for further research into the underlying genetic mechanisms of X-NDI and the development of targeted therapies. Advances in genetic testing and whole exome sequencing (WES) have opened new avenues for identifying pathogenic variants associated with the

disorder, thereby enhancing our understanding of its molecular underpinnings (*10*).

Recent studies have identified numerous mutations within the *AVPR2* and *AQP2* genes, elucidating the complex relationship between genetic alterations and clinical manifestations of NDI (*11*). However, there remains a significant gap in our knowledge regarding the full spectrum of genetic variations contributing to X-NDI and their functional implications. This highlights the necessity for comprehensive genetic analyses in affected individuals, which can inform clinical management and facilitate personalized treatment approaches (*12*).

In this study, we employ whole exome sequencing to identify novel genetic variants in the *AVPR2* gene associated with nephrogenic diabetes insipidus. This approach allows for an in-depth investigation of the genetic landscape, aiming to elucidate pathogenic mechanisms underlying identified variants. By integrating genetic analysis with clinical evaluations, we seek to provide valuable insights that could enhance diagnostic accuracy and therapeutic strategies for individuals affected by X-NDI.

Our primary objective is to characterize the novel *AVPR2* variant identified in a patient with nephrogenic diabetes insipidus, exploring its potential clinical implications. We anticipate that our findings will contribute to a better understanding of the genetic basis of X-NDI and pave the way for future research aimed at developing targeted therapies that address underlying causes of this challenging condition. Ultimately, this research aims to improve patient outcomes through enhanced diagnostics and personalized treatment options based on genetic insights.

2. Materials and Methods

2.1. Patient

In 2025, an 11.5-year-old male patient visited the outpatient department of Paediatric Endocrinology, Shandong Provincial Hospital, for polydipsia, polyuria, and rapid weight gain. The parents of this patient are physically healthy, nonconsanguineous, and the maternal uncle of this patient has similar clinical manifestations. The clinical evaluation, baseline and dynamic hormonal levels, and genetic analyses were obtained from the patient with signed consent from the parents.

2.2. Clinical observations

The following hormones were measured in the serum samples: Insulin, luteinizing hormone (LH), C-peptide, progesterone, oestrogen, testosterone, adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4), and insulin-like growth factor-1 (IGF-1). Water deprivation vasopressin test and oral glucose tolerance test (those involving oral glucose, insulin, glucose, and C-peptide at baseline and +30', +60', +120', +180' after glucose oral) were conducted with standard procedures. All hormones were measured by chemiluminescent methods (Roche, Basel, Switzerland) following the manufacturer's instructions. Blood electrolyte levels, routine blood tests, urinalysis and urine osmolality were measured in the hospital laboratory. Additionally, pituitary magnetic resonance imaging (MRI), and bone age were also carried out in the hospital.

2.3. Genome sequencing

Peripheral venous blood (3-5 mL) was obtained from the proband and his parents. The DNA extracted from the peripheral blood was subjected to WES. The exonic regions of the genomic DNA from the patient were fragmented, ligated, amplified, and purified in accordance with the manufacturer's instructions, and subsequently analyzed utilizing the SeqCap EZ Med Exome Enrichment Kit (Roche NimbleGen) as per the provided guidelines. This process enabled capture of all known genes' exons and their adjacent regions. Following post-capture amplification and purification, the DNA library was constructed using the Illumina HiSeq system.

The sequence data were aligned to the human genome reference version 19 (hg19) using NextGene V2.3.4 to ensure adequate coverage and an appropriate mean depth of reading across the target regions. Information on conserved nucleotide bases and corresponding amino acids, frequencies within normal populations (sourced from the 1000 Genomes Project, ExAC, dbSNP DNA, and locus-specific databases), predictions regarding biological functions, and data acquired from The Human Gene Mutation Database (HGMD), ClinVar, and Online Mendelian Inheritance in Man (OMIM) were also gathered through NextGene V2.3.4. Variants were meticulously screened according to established criteria. The interpretation of pathogenic variants adhered to the guidelines set forth by the American College of Medical Genetics (ACMG) for assessment of sequence variants published in 2015, employing the Human Genome Variation Society (HGVS) nomenclature.

To confirm variants identified in the proband through WES, Sanger sequencing was performed, which also facilitated examination of co-segregation of identified variants within the family. The genome sequencing endeavor was executed in partnership with MyGenostics Co.

2.4. Bioinformatic analysis

To demonstrate spatial structure of the *AVPR2* protein and the affected protein regions after the mutation we used the SWISS-MODEL database (*https://swissmodel.expasy.org/*) to query the wild-type three-dimensional

model of the *AVPR2* gene. SWISS-MODEL is an automated protein structure homology modeling server that can be accessed through the Expasy web server or the program DeepView (Swiss Pdb Viewer). The purpose of this server is to allow all life science researchers around the world to access protein modeling. The wild-type model is named O88721.1.A, with a coverage range of 1-371, a sequence similarity of 57%, and a confidence level of 87.60%. The data obtained from the homology model is visualized using PyMOL (*https://pymol.org/2/*)

2.5. Ethical approval

The Institutional Human Ethics Review Board at Shandong Provincial Hospital affiliated to Shandong First Medical University approved this study (LCYJ:NO. 2019-147). The legal guardians of the participant were given written information to obtain the signed consent to participate in the study. This study conforms to the provisions of the Declaration of Helsinki.

3. Results and Discussion

3.1. Clinical characteristics and indicators of the patient

The patient had normal mental and nutritional status and a height of 152 cm (P50-75). He had obesity, acanthosis, male female breast, Turner stage B3, a micropenis (4 cm × 1 cm), micro-testis (2 mL). His parents had no similar symptoms. Evaluation of hormone levels revealed showed reduced testosterone (TO) (0.06 ng/ml), luteinizing hormone (LH) (2.14 mIU/mL) and follicle stimulating hormone (FSH) (5.39 mIU/mL) levels. The following parameters were used: normal adrenocorticotropic hormone (ACTH) (38 pg/mL, reference ranges: 7.2–63.3 pg/mL); cortisol (351 nmol/L, reference ranges: 166-507 nmol/L); insulin-like growth factor-1 (IGF-1) (295 ng/mL, reference ranges: 45–305 ng/mL); thyroid-stimulating hormone (TSH) (1.44 μIU/mL, reference ranges: 0.7–4.17 μIU/mL); free thyroxine (FT4) (20.3 pmol/L, reference ranges: 11.45–17.63 pmol/L); and prolactin (4.47 ng/ml, reference ranges: 4.04–15.2 ng/mL). Additionally, by regular blood tests, Glycosylated Hemoglobin, Type A1C (HbA1C), Neurospecific Enolase (NSE), Carcinoembryonic Antigen (CEA), Alpha-fetoprotein (AFP), and Human Chorionic Gonadotropin (HCG) were normal. An OGTT test indicates that the child currently has no abnormal glucose tolerance, but there is hyperinsulinemia and insulin resistance. Bone age of this 11.5-year old boy was 13. Abdominal ultrasound, adrenal ultrasound, and MRI of the pituitary were normal.

It is especially important to note serum electrolyte levels. Upon admission, the child's blood biochemistry indicated serum sodium (Na) 149.9 mmol/L (normal reference range 135-145 mmol/L), and chloride (Cl) 112.4 mmol/L (normal reference range 98-110 mmol/L). Considering the child's symptoms of polydipsia and polyuria, we conducted a water deprivation and vasopressin test on the patient. Water deprivation and vasopressin tests lasted for 9 hours, with urine osmolality of 125, 100, 125 mOsm/ L, all less than 300 mOsm/ L; urine specific gravity was 1.002, 1.001, 1.002, all less than 1.018, indicating impaired urine concentrating ability, supporting the diagnosis of diabetes insipidus. Administered pituitrin 6 U for the vasopressin test, urine osmolality was 260, 125 mOsm/L, both less than 300 mOsm/L; urine specific gravity was 1.003, 1.002, both less than 1.018; before water deprivation, plasma osmolality before the vasopressin test and 2 hours after the vasopressin test were 293.91, 310.82, 300.30 mOsm/ L, and blood sodium were 149.23, 156.3, 151.4 mmol/ L, respectively. After using pituitrin, the child's urine osmolality and specific gravity did not increase, which is thus not consistent with central diabetes insipidus, considering nephrogenic diabetes insipidus. We started oral hydrochlorothiazide, observing changes in the child's urine output.

NDI is a rare disorder characterized by the kidneys' inability to concentrate urine despite normal or elevated levels of the antidiuretic hormone, arginine vasopressin (AVP). This condition leads to significant clinical manifestations, including polyuria and polydipsia, which can result in severe dehydration and electrolyte imbalances, presenting considerable health challenges for affected individuals (*3,13*), and matched our patient's condition.

Cannon (*12*) documented three occurrences of male-to-male transmission of diabetes insipidus in a Mormon lineage traced back to 1813. He observed, however, a decrease in penetrance among females, as carriers did not exhibit the condition. This observation led to the hypothesis that the disorder within this family could indeed be X-linked. Subsequently, Cutler *et al*. (*14*) established the renal etiology of the condition within this family. Ten Bensel and Peters (*15*) reported hydronephrosis in affected male siblings within the lineage described by Cannon (*12*), and they concluded that the pedigree, which spanned five generations and included twelve affected males, was characteristic of X linkage. Nakano (*16*) documented familial nephrogenic diabetes insipidus across four generations of a Samoan family.

In a retrospective study, van Lieburg *et al.* (*17*) analyzed clinical data from thirty male patients diagnosed with nephrogenic diabetes insipidus, ranging in age from one month to forty years, across eighteen Dutch families. They identified seventeen distinct mutations in the *AVPR2* gene in twenty-eight patients, while two patients presented mutations in the *AQP2* gene. Notably, eighty-seven percent of the patients received their diagnosis within the first 2.5 years of life. The predominant symptoms at the time of clinical evaluation included vomiting, anorexia, failure to thrive, fever, and constipation. Most patients were treated with

hydrochlorothiazide-amiloride, which did not result in significant adverse effects. Two patients developed severe hydronephrosis alongside a minor urinary tract rupture following slight trauma, and two others experienced acute urinary retention episodes. Height standard deviation (SD) scores for age predominantly remained below the 50th percentile, whereas weight-for-height SD scores indicated catch-up growth after several years of being underweight. The majority of patients demonstrated normal intelligence, which contrasts with the prevailing notion that mental retardation is the most common long-term consequence of nephrogenic diabetes insipidus. No significant correlation between clinical manifestations and genetic information was identified, except for a potentially milder phenotype observed in patients harboring the *AVPR2* G185C mutation (300538.0003), and no clear relationship between clinical and genetic data could be found.

3.2. Genetic analysis and pathogenicity prediction

In this study, A novel variant in the *AVPR2* gene was observed by WES in the proband and confirmed by Sanger sequencing (*18*). Pedigree chart of the child and genetic testing results in Figure 1. *AVPR2* variant NM_000054.6:exon3:c.245G>A(p.Cys82Tyr) was identified. The score was PP3+PS4+PM2, which was regarded as an uncertain mutation according to the ACMG Guidelines (*19*). Sanger sequencing confirmed that this new variant was not transmitted from the mother of this patient. Although the genetic results are ambiguous, the clinical manifestations of the child and the mode of inheritance are consistent, and the child's uncle also exhibits the same manifestations. Therefore, it can be clinically diagnosed as X-NDI.

The PP3 protein function comprehensive prediction software REVEL predicts that it may be harmful; PS4_Supporting this variant has been detected in 1 case of diabetes insipidus (internal case database); PM2_Supporting the frequency in the normal population database is -; through family verification analysis, the father of the tested individual did not provide a sample, and the mother of the tested individual has a heterozygous variant at this locus.

Three-dimensional protein structure analysis of *AVPR2* indicates that the identified mutation c.245G>A (p.Cys82Tyr) changes the 82nd amino acid from cysteine to tyrosine. Before the mutation, the 82nd cysteine formed two hydrogen bonds with the 78th isoleucine and the 86th leucine. After mutation, the 82nd tyrosine forms two hydrogen bonds with the 78th isoleucine and the 86th leucine, predicting that stability of the protein structure remains unchanged (Figure 2).

Conservation analysis of *AVPR2* amino acids in humans, mice, pigs, bovines, and mantles suggests that c.245G>A (p.Cys82Tyr) causes a substitution of a highly conserved amino acid (Figure 3A), functional prediction of the missense mutation c.245G>A (p.Cys82Tyr) using PolyPhen-2 software indicates strong pathogenicity, classifying it as a deleterious mutation (Figure 3B). This mutation is not recorded in the ExAc, EVS, dbSNP, and 1000 Genomes databases.

A total of 348 mutation sites related to the *AVPR2* gene have been reported, including missense/nonsense mutations 211 (61%), small deletions 62 (18%), gross deletions 30 (9%), small insertions 25 (7%), splicing 6 (2%), complex rearrangements 5 (1%), small indels 5 (1%), and gross insertions/duplications 4 (1%) (Figure 4). However, *AVPR2* mutation locations have not been related to any clinical disorders yet.

The majority of congenital NDI cases are attributed to mutations in the *AVPR2* gene, which encodes the

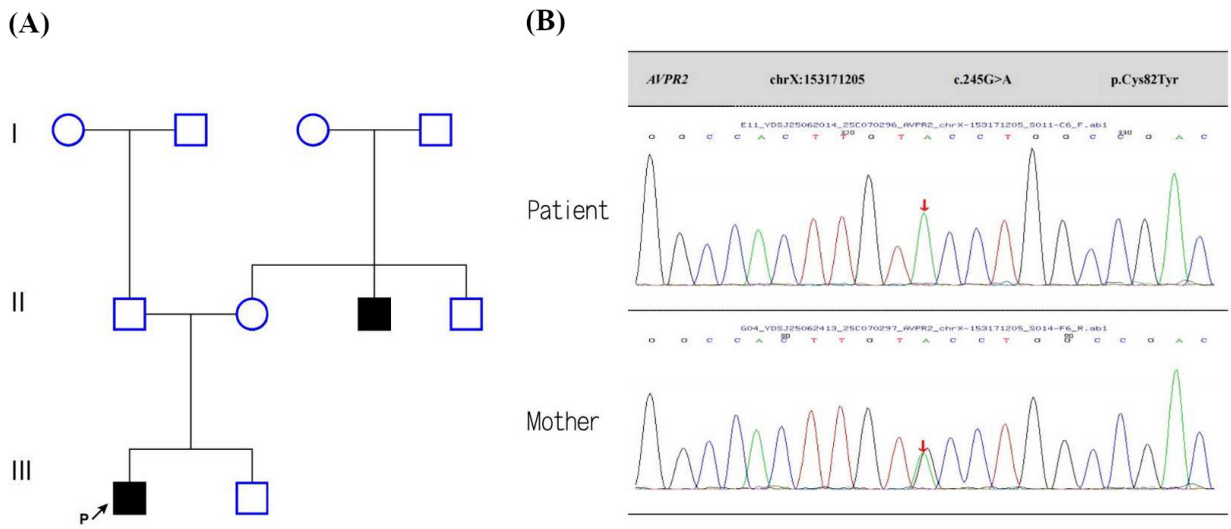

Figure 1. The Pedigree chart of the child and genetic analysis. (A) The pedigree of this family. **(B)** *AVPR2* gene mutation analysis of the patient (GenBank accession number: NM_000054.6).

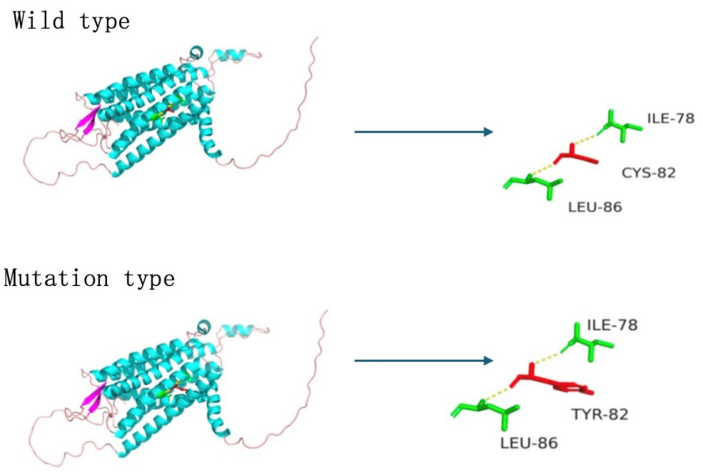

Figure 2. Three-dimensional protein structure analysis of *AVPR2*. Blue represents α-helix, purple represents β-sheet, and pink coils represents Loop structures. The observed hydrogen bonds are shown as stick structures, with blue dashed lines indicating hydrogen bonds.

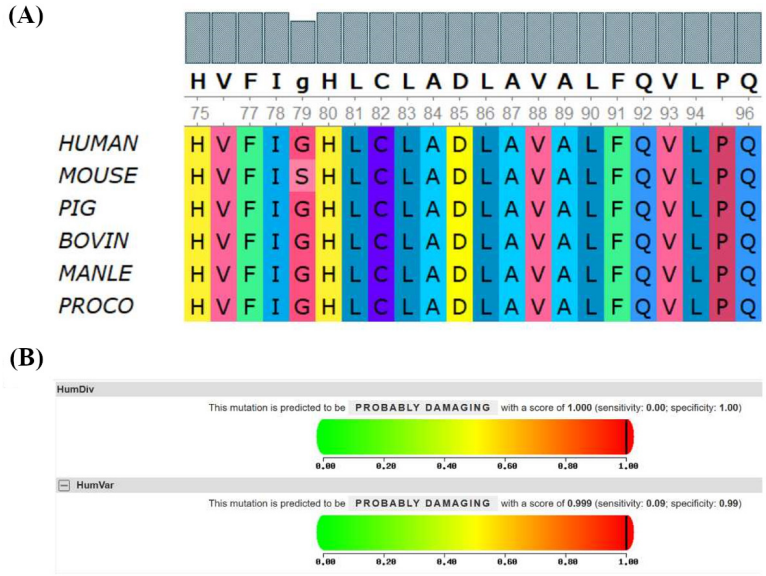

Figure 3. The conservation analysis of the protein sequence and protein structure prediction. (A) Multiple amino acid alignments of *AVPR2* homologs in the uniprot database. **(B)** The score of the newly disruptive c.245G>A (p.Cys82Tyr) mutation in Polyphen-2.

vasopressin V2 receptor located on the X chromosome, while a smaller percentage is linked to mutations in the *AQP2* gene, which encodes the aquaporin-2 water channel (*20,21*). Understanding the genetic underpinnings of NDI is critical for improving diagnostic and therapeutic strategies, especially as current treatments remain limited in efficacy and often come with significant side effects (*22,23*).

Our research employs WES to comprehensively analyze genetic variants and their potential impacts on protein function, thus elucidating the pathogenic mechanisms associated with this condition (*24,25*). This approach not only enhances our understanding of the genetic landscape of NDI but also aids in the development of targeted therapies. The findings presented herein will be discussed in relation to the patient's clinical profile, treatment plan, and significance of genetic biomarkers in guiding management strategies for nephrogenic diabetes insipidus (*26,27*).

This study represents a significant advancement in our understanding of NDI by identifying a novel variant in the *AVPR2* gene, which is crucial for the kidney's response to vasopressin. The implications of this discovery are profound, as it fills a critical knowledge gap regarding genetic underpinnings of NDI. Previous studies have extensively documented various mutations in the *AVPR2* gene, yet our research demonstrates for the first time in humans long-term efficacy of specific pharmacological interventions targeting this novel mutation, aligning with earlier animal studies that suggested unique therapeutic pathways (*23,26*). This integration of genetic analysis with clinical data not only enhances our diagnostic capabilities but also provides a foundation for developing targeted treatment strategies,

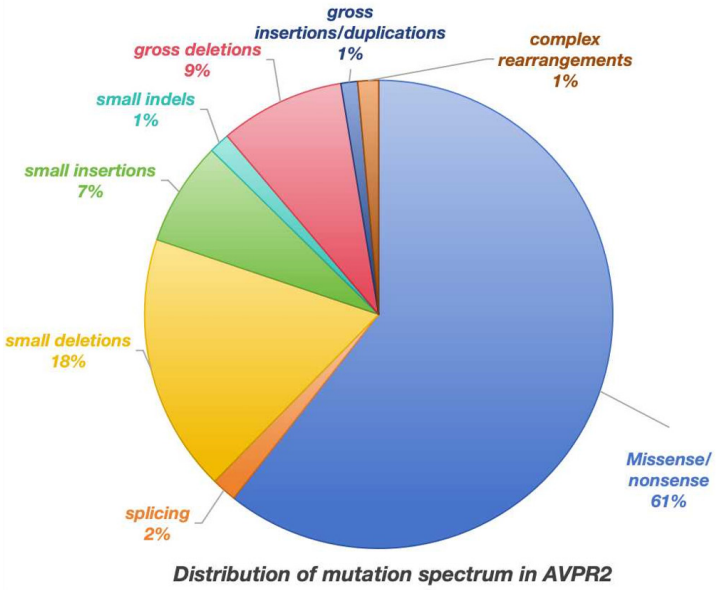

Figure 4. Distribution of mutation spectra in AVPR2. A total of 348 mutations in *AVPR2* include missense/nonsense mutations 211 (61%), small deletions 62 (18%), gross deletions 30 (9%), small insertions 25 (7%), splicing 6 (2%), complex rearrangements 5 (1%), small indels 5 (1%), and gross insertions/duplications 4 (1%).

emphasizing potential for personalized medicine in managing this rare disorder.

3.3. Treatment and follow-up

After hydrochlorothiazide 25 mg po bid for approximately one month, both Na 143.8 mmol/L and Cl 106.3 mmol/L recovered a normal level. Urine osmolality 175 mOsm/L (normal reference range 600–1000mmol/L), so we let the patient continue oral hydrochlorothiazide 25 mg po bid, while adding indomethacin 12.5mg po bid. The patient is under continued follow-up.

The identification of the *AVPR2* variant and its correlation with clinical symptoms underscores the necessity for early genetic testing and tailored therapeutic approaches. Successful treatment of our patient with a combination of hydrochlorothiazide and indomethacin demonstrates a promising avenue for enhancing patient outcomes. These findings suggest that similar patients may benefit from a multidisciplinary approach that includes genetic counseling and individualized treatment plans, leading to improved quality of life and reduced healthcare costs associated with complications from uncontrolled NDI (*3,13*).

Nonetheless, this study is not without limitations. The relatively small sample size and the nature of a single-case study may restrict the generalizability of our findings. Absence of extensive long-term follow-up data also limits our understanding of the chronic effects of the identified *AVPR2* mutation and pharmacological treatments employed. Future research should aim to include larger cohorts and longer follow-up periods to validate these findings and explore long-term efficacy and safety of the identified therapeutic strategies. Additionally, incorporation of experimental validation techniques could further strengthen our conclusions regarding pathogenicity of the *AVPR2* variant and its role in NDI (*26,28*).

In conclusion, this study presents a compelling case of a novel *AVPR2* variant associated with nephrogenic diabetes insipidus, underscoring the critical importance of early diagnosis and personalized treatment strategies. Successful management of the patient through pharmacological interventions illustrates potential for improved outcomes when genetic insights are integrated into clinical practice. Future investigations should aim to expand genetic screening efforts and explore functional consequences of identified variants, ultimately enhancing our understanding of this condition and informing development of targeted therapeutic approaches.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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