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RESEARCH

Reporting Two Novel Mutations in Iranian Nephrogenic Diabetes Insipidus Patients and a Review of the Literature

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Abstract

Introduction Nephrogenic diabetes insipidus (NDI) is a rare inherited disorder that causes excessive urine output and water consumption, because of unresponsiveness of the kidney to arginine-vasopressin (AVP). This condition, which is usually caused by *AVPR2* or *AQP2* gene variants, causes impaired water reabsorption in the kidney. This study investigated five patients from four unrelated families that were suspected of having NDI.

Materials and Methods Genomic DNA was extracted from blood samples, followed by PCR amplification of AVPR2 and AQP2, and Sanger sequencing was performed afterwards.

Results Four distinct variants were detected: three in the *AVPR2* gene and one in the *AQP2* gene. Notably, two *AVPR2* variants, c.676del and c.254_262del, were novel. The third *AVPR2* variant, c.887G>A, along with the *AQP2* variant, c.538G>A, had been previously reported.

Discussion According to the ACMG guidelines, all variants were considered to be likely pathogenic. Although our sample size was small, we found higher number of *AVPR2* gene variants as compared with the results reported in Iran. Our findings also indicated that most variations were concentrated in exon 3 of *AVPR2* gene, suggesting its importance as a critical region for this gene. Literature reviews conducted in the last 5 years in the Asian population showed a wide range of variants, with the most cases reported from China and Japan. It appears that some populations may experience recurrent variants (founder mutation), while others, reveal rare and unique genetic variants across subgroups in larger populations.

Keywords Nephrogenic diabetes insipidus · *AVPR2* · *AQP2* · Novel variant · Iran

Introduction

Nephrogenic diabetes insipidus (NDI) is a disease with impaired water reabsorption in the distal nephron caused by mutations in the vasopressin V2 receptor (AVPR2) and the aquaporin-2 protein (AQP2) [1]. In the tubular part of the nephron where urine composition is determined, AVP binds to the AVPR2 on the basal membrane of tubular cells. Subsequently, a signaling pathway involving cAMP and protein kinase A (PKA) is activated, resulting in the translocation of the AQP2 to the apical membrane for water reabsorption [2, 3]. The lack of response to AVP results in increased urine output (polyuria) and water intake (polydipsia), often accompanied by symptoms like vomiting, irritability and feeding difficulties. In most cases, patients develop the symptoms shortly after birth, and most diagnoses are made within the first year of life [4].

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(Likely) pathogenic variants in *AVPR2* or *AQP2* genes result in NDI. The *AVPR2* gene consists of three exons and is located in the Xq28. This gene encodes a G protein-coupled receptor (GPCR) [5]. It contains 371 amino acids and includes 7 transmembrane alpha helices and is the main reason for the NDI [6, 7]Since the inheritance is X-linked recessive, the majority of affected individuals are males and the prevalence is about one in 250,000 boys, but girls may show some degrees of polyuria and polydipsia as a result of skewed X-inactivation [8]. The remaining cases with autosomal inheritance patterns are caused by variants in the gene encoding the AQP2 [9]. The *AQP2* gene, which is located on the chromosome 12q13, encodes a transmembrane protein with 6 alpha helices. This protein consists of 271 amino acids [10].

In this study, we analyzed patients who were suspected to have NDI in order to identify the causative genetic variants and we also presented a literature review of NDI in Asian population in the past 5 years.

Material & Methods

Patients' Description

Genetic analysis was performed on 5 patients from 4 unrelated families suspicious of being affected by NDI who were referred to Ali Asghar Children's Hospital. Family history, clinical, laboratory information and informed consent were obtained from the patient's parents. The approval of this study was issued by the research ethics committee of the Iran University of Medical Sciences, IR.IUMS.FMD.REC.1399.579.

Molecular Genetic Study

Genomic DNA extraction was done according to the salting out technique [11]. Subsequently, the genes were sequenced by Sanger sequencing method using previously described procedure [12].

The sequences were aligned to the *AVPR2* gene (NM_000054.6) and the *AQP2* gene (NM_000486.6).

In Silico Analysis

The identified variants underwent analysis through a range of bioinformatics tools like Mutation Taster [13], CADD (Combined Annotation Dependent Depletion) [14], GERP (Genomic Evolutionary Rate Profiling) [15] and SIFT (scale-invariant feature transform) [16]. Subsequently, the variants were classified according to the guidelines established by the American College of Medical Genetics and Genomics (ACMG) [17].

Result

Patients

Patients displayed similar symptoms, including failure to thrive (FTT) in 4 infants, polyuria and polydipsia in all of them when admitted to the hospital. Further clinical and biochemical information is shown in Table 1. Additionally, the patients' pedigrees were revealed in Fig. 1.

In Silico Analysis

Four distinct variants were identified in five patients, including three in the *AVPR2* gene and one in the *AQP2* gene. Among them, two variants in the *AVPR2* are novel, while the others have been previously reported. Reported variants in this study are listed below in Table 2.

The novel variant found in patient P1 was c.676del, a hemizygous single nucleotide deletion. He was a one-month-old boy, and the variant was located in exon 3 of the *AVPR2* gene. According to the ACMG guideline, this variant is classified as likely pathogenic based on the following criteria: (1) PVS1: The variant is a null variant, which typically results in a loss of function, (2) PM2: It has an extremely low frequency in population databases such as gnomAD. Mutation Taster predicted this variant as a disease-causing one. The CADD score for this variant was 26.8. A CADD score above 20 is considered as highly deleterious, placing the variant in the top 1%, and scores above 10 place them among the 10% most deleterious substitutions in the human genome. Also, the GERP score for this variant is 3.71, indicating evolutionary conservation of genetic sequences. The GERP scores range from −12.3 to 6.17, the higher the score, the stronger the evolutionary constraints, meaning that this position is functionally important and less susceptible to change. The mother of the proband was heterozygous for this variant and did not present any clinical symptoms.

The second novel variant in the *AVPR2* gene is a 9 bp deletion of c.254_262del located at exon 3. This hemizygous variant was identified in a 1.5-month-old boy (P2). Mutation Taster analysis predicted this variant as disease-causing. This variant received a CADD score of 17.14, which exceeds the threshold for deleteriousness, indicating a potential harmful effect. Furthermore, GERP analysis provided a score of 4.03, indicating a high level of evolutionary conservation and functional significance of the affected region. While reviewing the family history, we noticed that his 33-year-old uncle (P3) showed signs of polyuria and

Table 1 Clinical and biochemical characteristics of Iranian patients with NDI disease

Families	F1	F2	F2	F3*	F4*
Patients	P1	P2	P3	P4	P5
Age of onset	1 months	1.5 months	N/A	2.5 months	3.5 months
Symptoms	Fever, FTT	Fever, FTT	Mental retardation	Fever, weakness, FTT	Vomiting (reflex), FTT
Polyuria/polydipsia	Yes	Yes	Yes	Yes	Yes
Appropriate growth (Before treatment)	No	No	No	No	No
Appropriate cognition	Yes	N/A	Yes	Yes	Yes
Na	**154**	**155**	N/A	142	138
K	4.6	4.7	N/A	4.3	3.8
Specific gravity	**1.010**	1.005	N/A	1.004	1.002
BUN	13	10	N/A	6.2	6.4
Kidney sonography	No kidney stones Normal eco	No kidney stones Normal eco	N/A	No kidney stones Normal eco	No kidney stones Normal eco
Drug	Indomethacin	Indomethacin Hydrochlorothiazide	Not received	Indomethacin	Indomethacin Hydrochlorothiazide

Blood urea nitrogen (BUN): newborn: 2–19 mg/dL, infant/child: 5–18 mg/dL, Sodium (Na): <1 year: 130–145 mEq/L, >1 year: 135–147 mEq/L, Potassium (K): newborn: 3.7–5.9 mEq/L, infant: 4.1–5.3 mEq/L, child: 3.4–4.7 mEq/L, Urine specific gravity: newborn: 1.002–1.004, infant: 1.002–1.006, ≥1 year: 1.001–1.030

Note * Indicates that the biochemical data presented for these patients were collected post-treatment

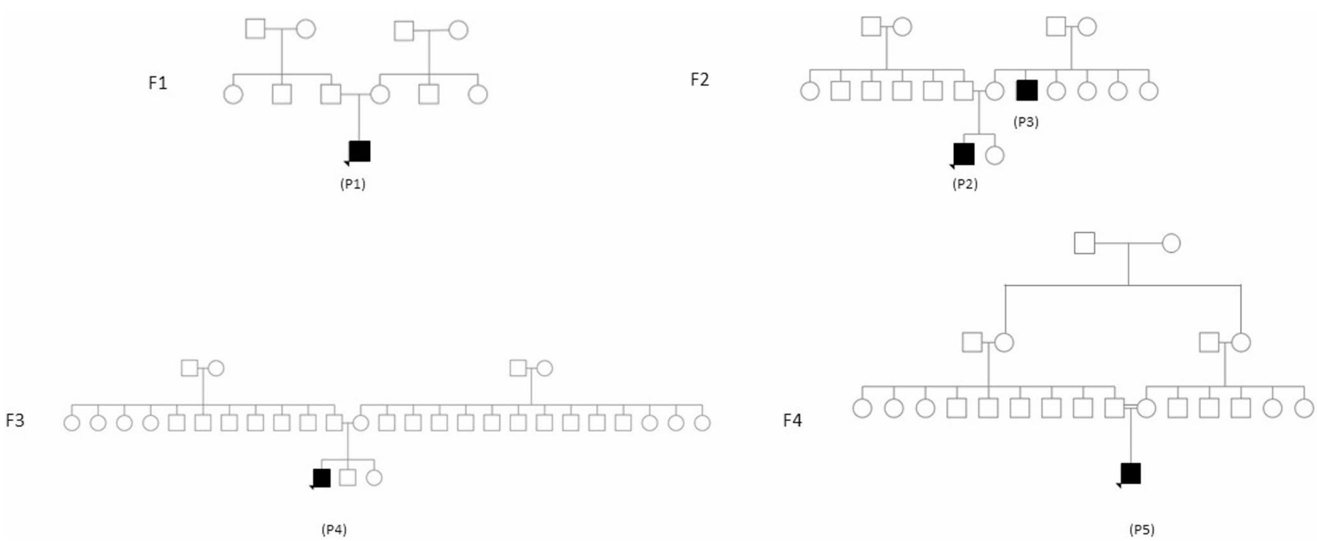

Fig. 1 Pedigree of the patients in this study

polydipsia. He did not take any kidney-related medications, he had short stature and mild intellectual disability. The same genetic alteration was also investigated in the case P3 and he was hemizygous for this variant and had not been diagnosed with this disease until this age. According to the ACMG guidelines, this variant is classified as likely pathogenic based on the following criteria: (1) PM2: low frequency in population databases, (2) PM4: alteration in protein length due to a frameshift caused by deletion/insertions, (3) PM1: located in a critical mutational hotspot or functional domain with no known benign variants.

The third *AVPR2* gene variant was a hemizygous nonsense variant at the position of c.887G>A in exon 3, observed in a 2.5-month-old boy (P4). This variant was documented in another study by Kotnik P et al. [18]. According to the ACMG guideline, it is classified as likely pathogenic, supported by criteria PVS1 and PM2. Bioinformatic tools, including Mutation Taster, predict this variant to be disease-causing. Additionally, a CADD score of 38 suggests a high level of deleteriousness, and the GERP score of 3.79 indicates strong conservation.

The final variant, identified in the *AQP2* gene, is a missense variant at the position c.538G>A, found in a male proband (P5) who was homozygous for this variant. According to the ACMG guideline, this variant is classified as likely pathogenic based on the following criteria: (1) PM1, (2)

Table 2 AQP2 & AVPR2 variants of Iranian patients with NDI disease

Families	Patient	Gene	Exon	c.DNA /protein	Position	Type	Mutation Taster	CADD	GERP	SIFT	Zygosity	ACMG classification
F1	P1	AVPR2	3	c.676del p.val226cysTer45	ChrX-153,171,634 AG>A	Frameshift	Disease causing	26.8	3.71	N/A	Hemizygote	likely pathogenic PVS1, PM2
F2	P2, P3	AVPR2	3	c.254_262del p.Asp85_Ala8797del	chrX-153,905,751 G CCTGGCCGA>G	In-frame	Disease causing	17.14	4.03	N/A	Hemizygote	Likely pathogenic PM2, PM4, PM1, PP4
F3	P4	AVPR2	3	c.887G>A p.w296Ter	ChrX-153,171,847 G>A	Nonsense	Disease causing	38	3.59	N/A	Hemizygote	likely pathogenic PVS1, PM2
F4	P5	AQP2	3	c.538G>A p.gly180ser	Chr12-50348425 G>A	Missense	Disease causing	27.7	5.3	0.03 deleterious	Homozygote	likely pathogenic PM1, PP2, PM2, PP3, PP5

PP2: Found in a gene with a low rate of benign missense variant, where pathogenic missense variants are common mechanism of the disorder, (3) PM2, (4) PP3: Multiple computational prediction tools support a deleterious effect on the gene or gene product, (5) PP5: Reported as pathogenic by a reputable source, though the evidence is not available for independent evaluation. Mutation Taster predicted this variant as disease-causing. The CADD score for this variant is 27.7, which is above the deleteriousness threshold. GERP score analysis, like the other variants, indicates a high level of conservation. Additionally, SIFT analysis gave a score of 0.03, which is considered intolerant as it is below the 0.05 threshold. This variant has been previously reported in several papers [12, 19–21]. The proband's parents were both found to be heterozygous for this variant. The proband's parents were both found to be heterozygous for this variant and were clinically asymptomatic, likely because the mutation disrupts tetramer formation in the homozygous state, similar to a missense mutation at an adjacent residue previously reported as recessive [22].

AVPR2 gene variants are shown schematically in the second structure of the protein, which is shown in Fig. 2. Also, these variants are confirmed by Sanger's method in Fig. 3.

Figure 1All patients except family 4 (F4) had a hemizygote variant in the AVPR2 gene. The patient of the family 4 (F4) had a homozygote variant in the AVPR2 gene. (a) Reference seq. (b) Proband. (c) Mother, uncle and father respectively in F1, F2 and F4 family.

Discussion

To date, 106 pathogenic and likely pathogenic variants associated with NDI have been identified in the ClinVar database in two critical genes: *AVPR2* and *AQP2*. Of these, 67 are in the *AVPR2* gene, while 39 are linked to the *AQP2* gene. Specifically, the *AVPR2* variants include 36 missense, 17 frameshift, 10 nonsense, 3 in-frame and 1 splicing. While, the *AQP2* presents 23 missense, 9 frameshift, 4 splice site and 3 nonsense variants [23, 24]. In this study, the distribution of variant types was as follows: two deletions and one nonsense in the *AVPR2* gene and one missense in the *AQP2* gene.

X-linked NDI is responsible for 90% of all congenital cases. The remaining 10% are linked to variants in the *AQP2* gene, which can follow either an autosomal dominant or recessive inheritance pattern [25]. To investigate this, we explored recent developments and performed a PubMed search using the keywords "nephrogenic diabetes insipidus, *AVPR2*, and *AQP2*" for studies published over the last five years in the Asian populations. These studies showed that

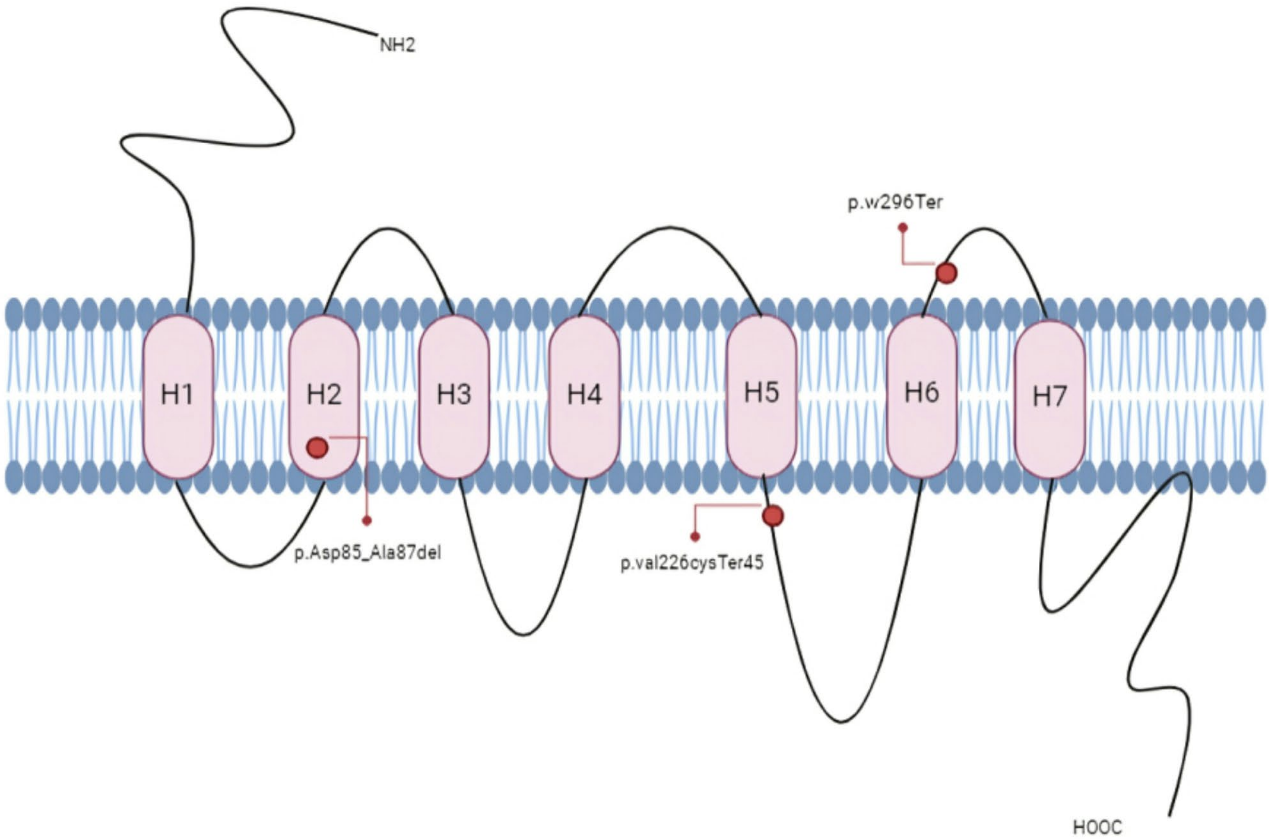

Fig. 2 Location of variants in the secondary structure of the membrane protein AVPR2

AVPR2 variants are more commonly observed than *AQP2*, which is consistent with previous studies [26].

Based on our observations of *AVPR2* variants in Asian populations, we identified a diverse list of variants with China and Japan reporting the highest number of cases, Table 3. The prevalence of variants in these countries was notably varied, demonstrating different types, including missense, nonsense, in-frame and frameshift variants. Countries like Japan, where variants such as *AVPR2*: c.383 A>C [27–29] have been reported multiple times, may

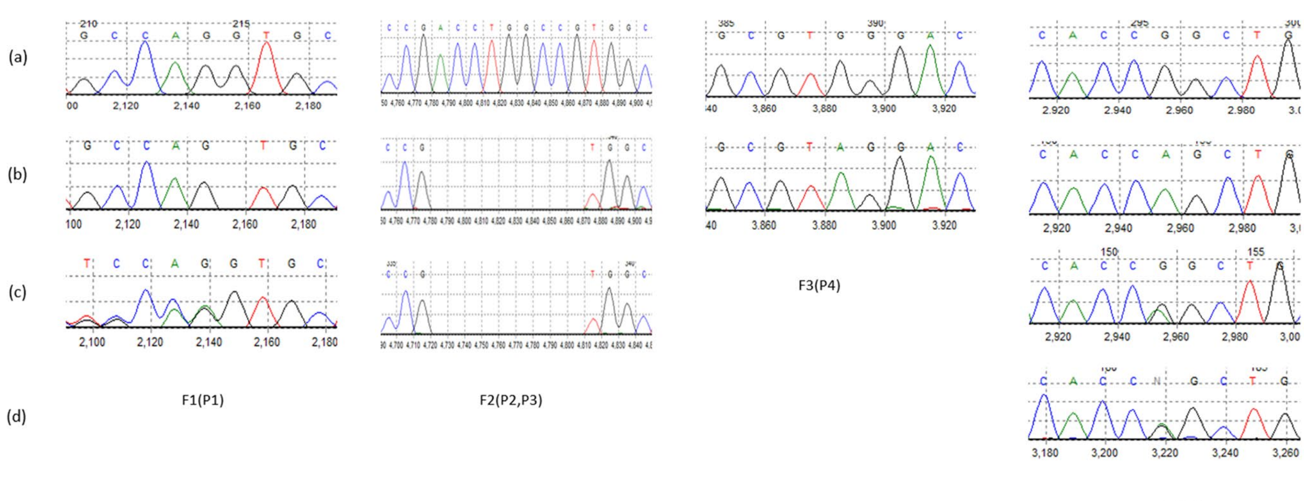

Fig. 3 Sequencing analysis of the AQP2 & AVPR2 gene

Table 3 List of variants that have been reported in the last 5 years in Asian countries

Mutation (c.DNA)	Amino acid change	Exon	Protein level	Type	Classification	Population	Reference
AVPR2							
AVPR2:c.520 C>T	p.Gln174*	Ex3	Transmembrane	Nonsense	Likely pathogenic	Japan	[36]
AVPR2:c.371 A>G	Tyr124Cys	Ex3	Transmembrane	Missense	VUS	Japan	[37]
AVPR2:c.380 C>A	p.S127Y	Ex3	Transmembrane	Missense	VUS	Japan	[38]
AVPR2:c.866T>C	p. L289P	Ex3	Transmembrane	Missense	Likely pathogenic	Japan	[39]
AVPR2: c.990_993 dup CAGC	p.Val332Gln Fs26X	Ex4	Cytoplasmic	Frameshift	Likely pathogenic	Japan	[40]
AVPR2:c.852G>A	p.Trp284*	Ex3	Transmembrane	Nonsense	Likely pathogenic	Japan	[36]
AVPR2: c.383 A>C	p.Y128S	Ex3	Transmembrane	Missense	Likely pathogenic	Japan	[27–29]
AVPR2: c.283 C>T	p.P95S	Ex3	Transmembrane	Missense	VUS	China	[41]
AVPR2: c.530T>A	p.I177N	Ex3	Transmembrane	Missense	Likely pathogenic	China	[42]
AVPR2: c.914dupC	p.Pro306fs	Ex4	Transmembrane	In-frame	Likely pathogenic	China	[43]
AVPR2: c.818 C>T	p.T273M	Ex3	Transmembrane	Missense	Likely pathogenic	China	[44]
AVPR2:c.255_263del	p.Asp85_Val88delinsGlu	Ex3	Transmembrane	In-frame	VUS	China	[45]
AVPR2: c.547G>A	p.V183M	Ex3	Extracellular	Missense	VUS	China	[33]
AVPR2: c.414_418del	p.Arg139Hisfs*51	Ex3	Cytoplasmic	Frameshift	Likely pathogenic	China	[46]
AVPR2: c.616G>C	p.Val206Leu	Ex3	Transmembrane	Missense	VUS	China	[47]
AVPR2: c.845T>C	p.Leu282Pro	Ex3	Transmembrane	Missense	VUS	China	[48]
AVPR2: c.419 C>A	p.Ala140Asp	Ex3	Cytoplasmic	Missense	VUS	China	[19]
AVPR2: c.645_646ins	p.Pro217_Ala223dup	Ex3	Transmembrane-cytoplasmic	In-frame	VUS	China	[19]
AVPR2:c.349T>G	p.Tyr117Asp	Ex3	Transmembrane	Missense	VUS	China	[32]
AVPR2:c.622T>C	p.W208R	Ex3	Transmembrane	Missense	VUS	China	[32]
AVPR2:c.938T>G	p.L313R	Ex4	Transmembrane	Missense	VUS	China	[32]
AVPR2:c.380_382del	p.S127del	Ex3	Transmembrane	In-frame	Likely pathogenic	China	[32]
AVPR2:c.229_231del	p.F77del	Ex3	Cytoplasmic	In-frame	VUS	China	[49]
AVPR2: c.500 C>T	p.Ser167Leu	Ex3	Transmembrane	Missense	Likely pathogenic	China	[49]
AVPR2: c.494 C>A	p.A165D	Ex3	Transmembrane	Missense	VUS	China	[49]
AVPR2: c.541 C>T	P.R181C	Ex3	Extracellular	Missense	Likely pathogenic	China, Thailand	[19, 31, 50]
AVPR2: c.492G>C	p. Trp164Cys	Ex3	Transmembrane	Missense	VUS	China	[51]
AVPR2:c.185T>C	p.Leu62Pro	Ex3	Transmembrane	Missense	Likely pathogenic	China	[49]
AVPR2:c.493G>C	p.Ala165Profs*47	Ex3	Transmembrane	Missense	Likely pathogenic	Qatar	[52]
AVPR2:c.632T>C	p.L211P	Ex3	Transmembrane	Missense	VUS	Turkey	[53]
AVPR2:c.835_837delGTC	p.Val279del	Ex3	Transmembrane	In-frame del	Pathogenic	Taiwan, Japan	[54, 55]
AVPR2: c.676del	p.Val226Cysfs*45	Ex3	Cytoplasmic	Frameshift	Likely pathogenic	Iran	Recent study
AVPR2: c.254_262del	p.Asp85_Ala87del	Ex3	Transmembrane	In-frame	VUS	Iran	Recent study
AVPR2:c.887G>A	p.Trp296*	Ex3	Extracellular	Nonsense	Likely pathogenic	Iran	Recent study
AVPR2:c.337 C>T	p.Arg113Trp	Ex3	Extracellular	Missense	Likely pathogenic	Iran, Korea, China	[12, 32, 56]

Table 3 (continued)

Mutation (c.DNA)	Amino acid change	Exon	Protein level	Type	Classification	Population	Reference
AQP2							
AQP2:c.803delG	p.Gly268Valfs*67	Ex4	Cytoplasmic	Frameshift	Likely pathogenic	China	[49]
AQP2:c.494G>A	p.G165D	Ex2	Transmembrane	Missense	VUS	China	[57]
AQP2:c.323 C>T	p.Thr108Met	Ex1	Extracellular	Missense	Likely pathogenic	China	[58]
AQP2:c.607-1G>A	N/A	N/A	N/A	Splicing	Pathogenic	China, Japan	[57, 59]
AQP2:c.538G>A	p.Gly180Ser	Ex3	Transmembrane	Missense	Likely pathogenic	China, Iran, Saudi Arabia	[12, 19, 60]
AQP2:c.501_502insC	p.Val168Argfs*32	Ex2	Transmembrane	Frameshift	Likely pathogenic	China	[57, 61]
AQP2:c.643G>A	p.G215S	Ex4	Transmembrane	Missense	VUS	China	[57, 61, 62]
AQP2:c.127_128delCA	p.Gln43Aspfs*63	Ex1	Transmembrane	In-frame	Pathogenic	China, Japan	[57, 59, 61, 63]
AQP2:c.764 A>G	p.Q255RfsTer72	Ex4	Cytoplasmic	Missense	VUS	China	[57]
AQP2:c.502G>A	p.Val168Met	Ex2	Transmembrane	Missense	Pathogenic	China, Iran	[57, 64]
AQP2:c.298G>A	p.Gly100Arg	Ex1	Transmembrane	Missense	Likely pathogenic	China, Japan, Saudi Arabia	[57, 60, 65]
AQP2:c.559 C>T	p.Arg187Cys	Ex3	Transmembrane	Missense	Pathogenic	China, Korea	[49, 66, 67]
AQP2:c.668T>C	p.Leu223Pro	Ex4	Cytoplasmic	Missense	VUS	Iran	[12]
AQP2:c.439G>A	p.Ala147Thr	Ex2	Transmembrane	Missense	Pathogenic	Iran Turkey/ Saudi Arabia	[12]
AQP2:c.140 C>T	p.Ala47Val	Ex1	Transmembrane	Missense	Likely pathogenic	Iran	[12]
AQP2:c.450T>A	p.Asp150Glu	Ex2	Cytoplasmic	Missense	Pathogenic	Iran	[12]
AQP2:c.374 C>T	p.Thr125Met	Ex2	Extracellular	Missense	Likely pathogenic	Jordan, Japan	[65, 68–70]

exhibit higher prevalence rates for certain variants due to an increased carrier frequency. This pattern may result from a founder mutation in which the initial mutation increases over generations, causing the population to be characterized by high frequencies of certain types of mutations [30]. In contrast, China's large and diverse population may harbor distinct genetic profiles across different subgroups, leading to the discovery of rare and unique variants [31–33].

There are considerable contrasts in the variant's frequencies across different populations. The pattern observed in Iran seems to be different. A previous study in this country showed that more than 90% of the identified variants were in the *AQP2* gene [12]. When we combine these findings with those of our study, both conducted in Iran, a higher prevalence of *AQP2* variants is consistently observed. This can be influenced by the high rate of consanguineous marriages in this society and on the other hand, the relatively small size of the sample used in these studies. More studies are needed to more accurately evaluate the distribution and diversity of varieties in the Iranian population.

Apart from the differences in mutation type in the *AVPR2* gene, studies from the last 5 years along with our identified variants in the present study, also showed that most of the identified variants were concentrated in the exon 3. Although no hotspot for mutations has been reported for this gene [34], this region may be prone to mutations, as variants appear to occur more frequently than other exons. Additionally, we noticed that *AVPR2* variants are mainly located within the transmembrane regions [35]. Typically, missense variants and INDELs fall into this category. Research and data from ClinVar indicate that these missenses and INDELs are among the most common variations. These changes prevent the protein from reaching the cell membrane, which is necessary for binding to AVP and initiating the signaling pathway.

Consistent with these general findings, the *AVPR2* variants identified in our study significantly impact the protein structure. The first variant, c.676del, leads to a premature stop codon at position 270, truncating 102 amino acids from the C-terminus of the protein and affecting two transmembrane helices, an extracellular topological domain, and a cytoplasmic domain. The second variant, c.254_262del, located within the second transmembrane helix, causes an in-frame deletion that removes three amino acids (positions 85 to 87). The third variant, c.887G>A, is a nonsense one positioned at the extracellular topological domain, introduced a premature stop codon. This variant leads to eliminating all amino acids from tryptophan at position 296 to the end of the protein, discarding portions of both the transmembrane and cytoplasmic domains. These variants lead to significant structural disruptions in the *AVPR2* protein, potentially impairing its normal function.

In conclusion, this study identified four distinct variants in four unrelated families, all classified as likely pathogenic based on the ACMG guidelines. Two newly identified variants in the *AVPR2* gene are a single nucleotide deletion (c.676del) and a 9 bp deletion (c.254_262del) -. Furthermore, the identification of two previously reported variants - nonsense variant in the *AVPR2* (c.887G>A) and a nonsense variant in the *AQP2* (c.538G>A) genes- whose pathogenicity is further supported by multiple bioinformatic tools, emphasizes its importance. Although our sample size was small, the prevalence of variants in the *AVPR2* gene was relatively higher than the previous study in Iran. Interestingly, all variants identified in this gene were located in exon 3. A review of the literature over the past five years shows that variants occur mostly in this exon, suggesting that it may serve as an important region for this gene.

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Author Contributions B.J. and M.M. conceptualized and designed the study. N.H. and H.E.M. were responsible for patient recruitment and clinical data collection. S.A. conducted the molecular genetic analyses and bioinformatics interpretation. B.J. and M.M. wrote the main manuscript text. All authors contributed to data interpretation, manuscript revision, and approved the final version for submission.

Data Availability The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics Approval and Consent to Participate This study was approved by the Ethics Committee of Iran University of Medical Sciences IR.IUMS.FMD.REC. No. 17572 and conforms to the ethical standards contained in the 1964 Declaration of Helsinki and its subsequent amendments. Informed consent was obtained from all patients and then they entered the study.

Competing Interests The authors declare no competing interests.

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