

ORIGINAL ARTICLE

A female with X-linked Nephrogenic diabetes insipidus in a family with inherited central diabetes Insipidus: Case report and review of the literature

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Abstract

There are two forms of diabetes insipidus, central (neurohypophyseal), and nephrogenic, caused by pathogenic variants in the *AVP* gene and the *AVPR2* or *AQP2* genes, respectively. We report on a four-generation family, seven individuals had central diabetes insipidus (CDI) and the female index patient seen from age 16 to 26 years had (mild) nephrogenic diabetes insipidus. In her father with CDI, a known pathogenic heterozygous *AVP* variant c.232_234del p.(Glu78del) was identified, confirming the diagnosis of CDI in him and the other affected family members. In the proband, molecular analysis disclosed a novel heterozygous *AVPR2* gene variant, c.962A > T p.(Asn321Ile) and an extremely skewed X-inactivation, confirming X-linked nephrogenic diabetes insipidus (XL-NDI). Whole exome sequencing showed no further causative mutation. This is the first report on the co-existence of CDI and NDI in one family. Our review of symptomatic female *AVPR2* heterozygotes includes 23 families with at least one affected female (including this study). There were 21 different causative mutations. Mutation types in females did not differ from those in males. Both severe XL-NDI and mild forms were reported in females. All six females with severe XL-NDI had complete loss-of-function (null) mutations. The remaining 17 female probands had milder XL-NDI caused by 14 missense variants and three null variants of the *AVPR2* gene. X-inactivation was studied in nine of these females; all showed extreme or slight skewing. The review underlines that XL-NDI in female *AVPR2* heterozygotes is always accompanied by skewed X-inactivation, emphasizing a need for X-inactivation studies in these females.

KEYWORDS

affected female, *AVP*, *AVPR2*, central (neurohypophyseal) diabetes insipidus, gender medicine, nephrogenic (renal) diabetes insipidus

1 | INTRODUCTION

Depending on the cause, diabetes insipidus is categorized into central and nephrogenic forms. The central (neurohypophyseal) diabetes

insipidus (CDI, OMIM #125700) is caused by pathogenic variants in the arginine vasopressin gene (*AVP*, OMIM *192340) with autosomal dominant inheritance. Nephrogenic diabetes insipidus (NDI) is associated with two genes: ~90% of patients have X-linked

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recessive NDI, caused by pathogenic variants in the arginine vasopressin receptor 2 in renal collecting duct cells (*AVPR2* gene, OMIM *300538). In the remaining 10%, NDI is inherited in autosomal recessive or dominant form caused by pathogenic variants in the aquaporin-2 water channel gene (*AQP2* gene, OMIM *107777). Hence, central and nephrogenic diabetes insipidus are distinct disorders caused by different mechanisms. In the OMIM catalog of Mendelian disorders, XL-NDI is annotated as a recessive disorder. The vast majority of reported XL-NDI patients have been severely affected males with a hemizygous pathogenic variant in the *AVPR2* gene. While there have been numerous reports on XL-NDI in males, far less attention has been given to symptomatic female carriers with XL-NDI (Arthus et al., 2000; Bichet & Bockenhauer, 2016; Sasaki, Chiga, Kikuchi, Rai, & Uchida, 2013). Recently an underestimation of symptoms in female carriers was described for another X-linked disorder, myotubular myopathy (*MTM1* gene) (Savarese et al., 2016).

Here we report on a family presenting both CDI and NDI. Seven individuals demonstrated CDI caused by a previously described *AVP* pathogenic variant, whereas one female family member had NDI likely due to a novel *AVPR2* missense variant. There has been no previous report on the coexistence of CDI and NDI in one family. XL-NDI in females is very rare and therefore we have also reviewed the literature on symptomatic females with XL-NDI and a documented *AVPR2* mutation.

2 | MATERIALS AND METHODS

2.1 | Sequence and copy number analyses

Genomic DNA from probands III:4 and IV:1 were extracted from peripheral blood using standard procedures. Sequence analysis of the *AVPR2* gene (transcript NM_000054.2) was first conducted at the Stichting Klinisch-Genetisch Centrum Nijmegen, The Netherlands, using their standard method (de Ligt et al., 2012). Further molecular analysis of *AVP* (transcript ENST00000380293), *AVPR2* (ENST00000358927, exonic area identical to NM_000054.2), *AQP2* (ENST00000199280), *GJB2* (ENST00000382848.5) and a total of 4,187 further genes was performed in our laboratory using whole exome sequencing (WES) as previously described (Kahrizi et al., 2019). Variants were confirmed using Sanger sequencing; the targeted exons were amplified by polymerase chain reaction analysis and sequenced in the CEQ Genetic Analysis System (Beckmann Coulter, Brea, CA). Deletion/Duplication analysis of the *AVPR2* gene was conducted with the CytoScan™ XON array (~6,850,000 markers genome wide, Affymetrix, Santa Clara, CA) according to the manufacturer's protocol.

2.2 | X-inactivation study

The X-inactivation status was determined by methylation analysis of the human androgen receptor (*HUMARA*) gene as described previously (Allen, Zoghbi, Moseley, Rosenblatt, & Belmont, 1992). According to their X-inactivation status, females can be classified into three groups:

(a) random inactivation (50:50–65:35%), (b) slightly skewed (65:35%–80:20%), and (c) extremely skewed inactivation (>80:20%) (Harris, Collins, Vetrie, Cole, & Bobrow, 1992).

2.3 | Literature review

A detailed PubMed search was performed using the following keywords: “*AVPR2*”; “nephrogenic diabetes insipidus”, “V2R” plus “female” in text to fish out the reported female symptomatic individuals with heterozygous *AVPR2* variants. We did not include female individuals published before 1995, because mutation information was not provided. For each variant, we used the recommended nomenclature for the description of sequence variations (<http://www.hgmd.cf.ac.uk>).

3 | CLINICAL REPORT AND RESULTS

3.1 | Editorial policies and ethical considerations

Written informed consent was obtained from the patients (IV:1 and III:4 in Figure 1).

3.2 | Clinical report

Proband IV:1 was first assessed by one of us (R.B.) at the age of 16 years. Her parents had noted an increased water intake as well as profound deafness from early childhood. At age 12 to 13 years her water intake had become remarkable and had reached 6–8 L per day. As central diabetes insipidus was a known disorder in the family, her parents treated her with antidiuretic hormone (desmopressin) nasal spray twice per day without a medical evaluation, however, this treatment failed to improve her symptoms. At age 16 years, she showed extreme urination 6–10 times per day, with ~5 L urine per day. In the water deprivation test (Table 1A) she showed an elevated level of serum Na⁺ and permanently reduced urine osmolality. The test had to be terminated prematurely due to a reduced general condition. Six hours after the start of the test, her body weight had declined by 2 kg and urine osmolality had stabilized at a maximum level of 171 mosmol/L. No significant increase in urine osmolality was detected in the desmopressin challenge test on the next day (Table 1B), indicating NDI. Treatment with hydrochlorothiazide (25 mg twice daily) was initiated in combination with amiloride (2.5 mg twice daily). This treatment resulted in a decrease in urine production and the drinking volume was reported as 1,000 ml 3 months later. When the proband returned to our internal medical consultation at the age of 26 years, she had discontinued her medication long before. Her daily water intake had again increased to 6–8 L per day and she had to get up for drinking and micturition twice per night, which she tolerated well. Serum creatinine was normal (74 mg/dl) and the estimated glomerular filtration rate (eGFR) was 112 ml/min × 1.73 sqm. Sodium, potassium, and chloride were in the normal range.

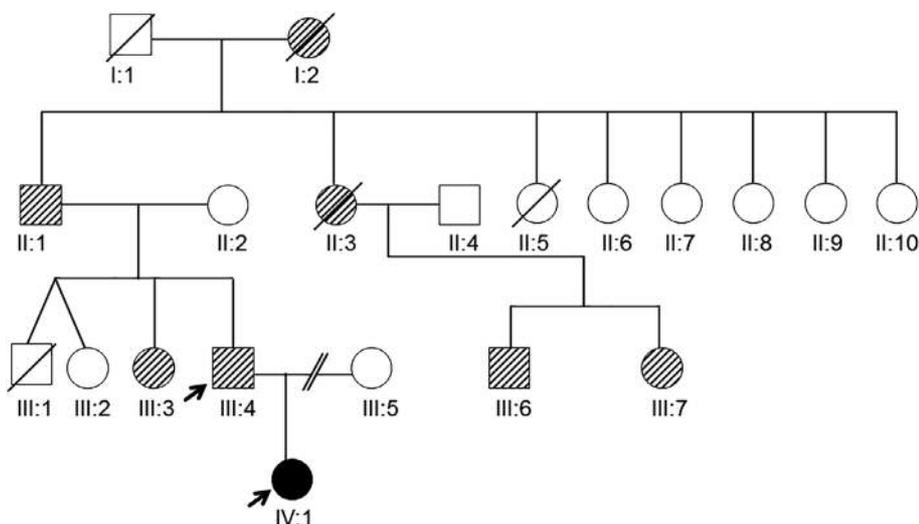


FIGURE 1 Pedigree of the family. Arrows indicate the probands studied by molecular analyses. Family members with central diabetes insipidus are represented by striped symbols. The index patient with nephrogenic diabetes insipidus (and surdity) is indicated by a black symbol

The proband's father (III:4) and six other family members (Figure 1) were affected with diabetes insipidus and responded to treatment with desmopressin, but not all affected family members took desmopressin regularly. Diabetes insipidus was not known in the proband's mother (III:5) and her family.

Additionally, proband IV:1 had bilateral profound sensorineural (prelingual) deafness. Results with hearing aids had been unsatisfactory and she had received a right ear cochlear implant at age 6 years. The deafness was attributed to a homozygous variant c.35del in the *GJB2* gene, which is the most common genetic cause of prelingual sensorineural hearing loss (Tekin, Arnos, & Pandya, 2001). The *GJB2* variant was found in heterozygous form in her father (III:4) with normal hearing. The mother (III:5) was not available for study.

3.3 | Molecular results (diabetes insipidus genes)

3.3.1 | Proband (IV:1)

Molecular analysis revealed a heterozygous *AVPR2* variant c.962A > T, p.(Asn321Ile). A deletion or duplication (possibly altering the other allele) of the *AVPR2* gene was excluded using an exon-specific array. The X-inactivation status in blood lymphocyte DNA was found to be extremely skewed (83:17%). Whole exome sequencing disclosed no other variants of clinical significance in *AVP* and further CDI or NDI related genes. Therefore, together with the clinical findings and the extremely skewed X-inactivation pattern, the *AVPR2* variant c.962A > T, p.(Asn321Ile) was considered as likely cause of NDI in the proband.

3.3.2 | Proband's father (III:4)

Following whole exome sequencing, we identified in the *AVP* gene a likely pathogenic heterozygous variant c.232_234del, p.(Glu78del), and then confirmed the variant using Sanger sequencing. The *AVPR2* c.962A > T variant was absent in the father by whole exome

sequencing and Sanger sequencing. Whole exome sequencing disclosed no additional causative variants in other diabetes insipidus related genes. This *AVP* variant was previously reported as disease-causing for autosomal dominant CDI (Lee et al., 2008; Yuasa et al., 1993), corroborating the diagnosis of CDI in the father.

3.3.3 | Proband's mother (III:5) and other family members

Unfortunately, the proband's mother was not available for study, as were the other affected family members (Figure 1) who lived elsewhere or were deceased.

4 | DISCUSSION

We report on a four-generation family with eight affected members, including seven individuals with CDI and the female proband (IV:1 in Figure 1) with XL-NDI. Except for her, all other affected family members responded very well to ADH treatment. A known pathogenic *AVP* variant was detected in her father (III:4 in Figure 1), confirming the diagnosis of CDI in him. CDI is caused by heterozygous pathogenic variants in the *AVP* gene. Over 80 disease-causing *AVP* variants have been reported, including the c.232_234del variant detected in proband's father (Lee et al., 2008; Yuasa et al., 1993). Hence, we attributed the CDI to the recurrent *AVP* c.232_234del variant.

Proband IV:1 presented with diabetes insipidus, which did not respond to ADH treatment. She did not carry the familial *AVP* variant but was found to carry a heterozygous variant, c.962A > T, p.(Asn321Ile) in the *AVPR2* gene, which causes NDI with an X-linked recessive inheritance. She also showed an extremely skewed X-inactivation pattern. No second mutation of the *AVPR2* gene could be identified and no other causative mutation was found in the other diabetes insipidus related genes. Taken together, the *AVPR2* variant was classified as likely pathogenic.

TABLE 1A Proband IV:1, results of the water deprivation test

Minute	Na+ (mmol/L)	K+ (mmol/L)	Cl- (mmol/L)	ADH (pg/ml)	Serum osmolality (mosmol/kg)	Urine osmolality (mosmol/kg)	Urine specific gravity
0 (8 a.m.)	140	3.9	112	n.a.	293	122	1.005
120 (10 a.m.)	143	4.0	113	2.6	292	138	1.005
240 (12 a.m.)	144	3.8	115	3.4	300	152	1.005
360 (2 p.m.)	148	3.9	116	6	296	171	1.005

Abbreviations: ADH, normal range: 1–5 pg/ml; n.a. not available; serum osmolality, normal range: 275–299 mosmol/kg; urine osmolality, normal range: >800 mosmol/kg; urine specific gravity, normal range: 1.010–1.030.

TABLE 1B Proband IV:1, results of the desmopressin challenge test

Minute	Urine osmolality (mosmol/kg)	Urine specific gravity
–120 (8 a.m.)	75	1.005
0 (desmopressin at 10 a.m.)	117	1.005
120 (12 a.m.)	134	1.005

Additionally, proband IV:1 had profound prelingual neurosensory hearing loss caused by a well-known pathogenic homozygous *GJB2* gene variant, c.35del p.(Gly12Valfs*2). *GJB2* encodes the cochlear gap junction protein Connexin 26 and biallelic *GJB2* mutations are the most frequent cause of autosomal recessive nonsyndromic deafness (Denoyelle et al., 1999) (DFNB1A, OMIM #220290). There has been no report on interactions between the AVPR2 and GJB2 proteins or genes in humans and other species, and therefore most likely the *GJB2* mutation had no impact on the XL-NDI in this family.

The AVPR2 gene is located on chromosome Xq28 and inheritance of the AVPR2-associated nephrogenic diabetes insipidus is X-linked recessive (OMIM #304800). More than 280 putative disease-causing AVPR2 mutations have been reported in over 300 NDI families (Bichet & Bockenhauer, 2016). Approximately half (55.8%) of the reported AVPR2 mutations were missense mutations. The other half comprised of nonsense mutations (12.8%), small frameshift deletions (10.4%), and splice-site mutations, in-frame deletions, an insertion, a duplication and a complex gene rearrangement (Spanakis, Milord, & Gragnoli, 2008). Loss-of-function mutations likely lead to severe phenotypes, whereas the milder forms of NDI are caused by missense mutations (Bichet & Bockenhauer, 2016; Spanakis et al., 2008). The Asn321Ile variant detected in our proband is a novel missense mutation listed neither in ClinVar nor in the gnomAD database. Additionally, the amino acid 321 is a highly conserved residue, including Zebrafish and *C. elegans*. Furthermore, three other missense variants (Asn321Asp, Asn321Lys, Asn321Tyr) have been reported at codon 321 in male patients with NDI (Arthus et al., 2000; Wildin, Cogdell, & Valadez, 1998) and Asn321Lys is annotated in ClinVar as likely pathogenic and listed in gnomAD with a frequency of 1 in 172,431 alleles. The other variants (Asn321Asp, Asn321Tyr) are absent in ClinVar and gnomAD. The combined data corroborate the pathogenicity of the Asn321Ile mutation.

Most female AVPR2 heterozygotes are asymptomatic, but a subset of heterozygous females exhibits variable degrees of polyuria, polydipsia, and in rare instances additional signs and symptoms. Until recently, symptomatic females were considered to be extremely rare. In a cohort of 117 families, only 3 females were reported as symptomatic (Arthus et al., 2000). Other authors anticipated a frequency of ~1% (Dong, Sheng, Chen, Yin, & Su, 2006). Since then there has been a growing number of reports on symptomatic female individuals (Table 2). In a study from Japan of 64 female heterozygotes, 16 (25%) demonstrated some degree of polyuria and polydipsia and of these, four (6%) were diagnosed with NDI (Sasaki et al., 2013). In another cohort from Spain, an even higher frequency (50%) of symptomatic AVPR2 mutation carriers was reported: 5 of 12 female heterozygous carriers (42%) complained of polyuria and polydipsia and one (8%) was diagnosed with NDI (García Castaño et al., 2015). These high frequencies could possibly represent an ascertainment bias in the collection of the cohorts. The growing number of reports on symptomatic female individuals could also reflect an increased medical awareness for symptoms in females. Although by definition our proband has “mild” NDI, the disorder has remarkable disease significance, as the polydipsia and polyuria do not respond to ADH treatment and strongly impacts her everyday life, including the necessity to disrupt sleep often twice per night. The prevalence of symptoms in female AVPR2 heterozygotes needs further investigation.

There has been no previous review on XL-NDI in females. Our review comprised 23 female AVPR2 heterozygotes with XL-NDI and 21 mutations (see Figure 2). The types and frequencies of the AVPR2 mutations in the female heterozygotes were similar to those in the male hemizygotes (Spanakis et al., 2008). 14 of 23 heterozygous females (60%) showed missense mutations altering a single amino acid residue, 3 (13%) displayed nonsense mutations, 3 (13%) had small frameshift deletions, and the remaining 3 subjects had a 1-bp frameshift duplication, a 1-bp (frameshift) insertion, and a whole gene deletion, respectively.

Further, this review provides the first evidence for an association between the clinical severity in females and the combined molecular findings (mutation type, X-inactivation status). Six of the 23 reviewed females had severe NDI. For two cases, the clinical severity was judged based on the descriptions in the publications, the probands were reported as “severely affected” (Ala et al., 1998; Nomura et al., 1997). For other cases, polyuria and polydipsia were classified as mildly affected; and probands with additional symptoms such as severe hypernatremia, severe vomiting, low birth weight, growth

TABLE 2 Clinical and molecular data of 23 symptomatic female individuals with XL-NDI (From 23 families, including this study)

Mutation	Female probands				Intrafamilial variability			Literature
	Protein change	Ethnic origin	Age at presentation	Polyuria, polydipsia, Other symptoms mentioned	XCI	Asymptomatic heterozygous female	Other symptomatic females	
1 c.162C > A	p.(Ser54Arg)	Spanish		+	n.i.			García Castaño et al., 2015
2 c.253G > A	p.(Asp85Asn)	Turkish	Neonatal	+	Extremely Skewed (93.7%)	Mother with random XCI (65.45%)		Faerch et al., 2010
3 c.262G > A	p.(Val88Met)	Spanish		+	n.i.			García Castaño et al., 2015
4 c.269C > T	p.(Leu90Pro)	Spanish		+	n.i.		Mother	García Castaño et al., 2015
5 c.316C > T ^a	p.(Arg106Cys)	Japanese	Childhood	+	n.i.		No	Namatame-Ohta et al., 2018
6		Spanish		+	n.i.			García Castaño et al., 2015
7 c.492G > C	p.(Trp164Cys)	Chinese	Adulthood	n.a.	n.i.	One	Yes, milder symptoms	Zhang et al., 2019
8 c.620C > A	p.(Thr207Asn)	Greek		+	n.i.		Paternal aunt and her daughter	Joshi et al., 2018
9 c.649C > A	p.(Pro217Thr)	France		n.a.	Extremely Skewed (84.16%)			Arthus et al., 2000
10 c.656 T > G	p.(Leu219Arg)	Austrian	7 months	n.a.	n.i.	Mother		van Lieburg et al., 1995
11 c.818C > T	p.(Thr273Met)	Spanish		+	n.i.			García Castaño et al., 2015
12 c.872A > C	p.(Gln291Pro)	Danish		+	n.i.	Daughter		Joshi et al., 2018
13 c.945C > G	p.(Ser315Arg)	Brazilian		+	Extremely skewed (89.11%)			Arthus et al., 2000
14 c.962A > T	p.(Asn321Ile)	Polish	Childhood	+	Extremely skewed (83.17%)			This study
15 c.296G > A	p.(Trp99*)	Japanese	4 years	+	Slightly skewed (67.43%)	No	Mother	Namatame-Ohta et al., 2018

(Continues)

TABLE 2 (Continued)

Mutation	Female probands			Intrafamilial variability					
	Protein change	Ethnic origin	Age at presentation	Polyuria, polydipsia mentioned	Other symptoms mentioned	XCI	Asymptomatic heterozygous female	Other symptomatic females	Literature
16 ^b c.1009C > T ^a	p.(Arg337*)	n.a.		+	"Severe" NDI	n.i.	Daughter		Moses, Sangani, & Miller, 1995
17 ^b		Korean	Birth		Low birth weight, frequent vomiting since birth, developmental delay at 2 years	n.i.			Hong et al., 2014
18	c.91_92del	p.(Thr31Profs*160)	Japanese	Adulthood	+	Symptoms markedly worsened after surgery at age 51 years, with severe hypernatremia	Slightly skewed (70:30%)		Kinoshita et al., 2004
19 ^b	c.268_269del	p.(Leu90Valfs*101)	Dutch	14 weeks		Growth retardation, persistent feeding problems, hypernatremia 157 mmol/L	n.i.	Mother	van Lieburg et al., 1995
20 ^b	c.691del	p.(Glu231Argfs*40)	Dutch	5 months	+	Severe vomiting, 3 kg weight decrease, excessive thirst	n.i.	Proband's mother, and others	van Lieburg et al., 1995
21 ^b	c.738dup	p.(Arg247Alafs*12)	Japanese		+	"Proband severely affected"	Extremely skewed (94:6%)	Niece with random XCI	Nomura et al., 1997
22 ^b	c.927_928insT	p.(Leu310Serfs*47)	n.a.		+	"Severely affected", severe polydipsia	Extremely skewed (93%:7%)		Ala et al., 1998; Arthus et al., 2000
23	Whole gene deletion	No protein production	British	12–36 months	+		n.i.	Mother	Giri, Hart, Jones, Ellis, & Ramakrishnan, 2016

Note: Reported families were numbered according to the position and the type of their mutations.

Abbreviations: +, symptoms present; n.a., not available; NDI, nephrogenic diabetes insipidus; n.i., not investigated; XCI, X-chromosome inactivation analysis.

^aRecurrent mutations.

^bSevere X-linked nephrogenic diabetes insipidus.

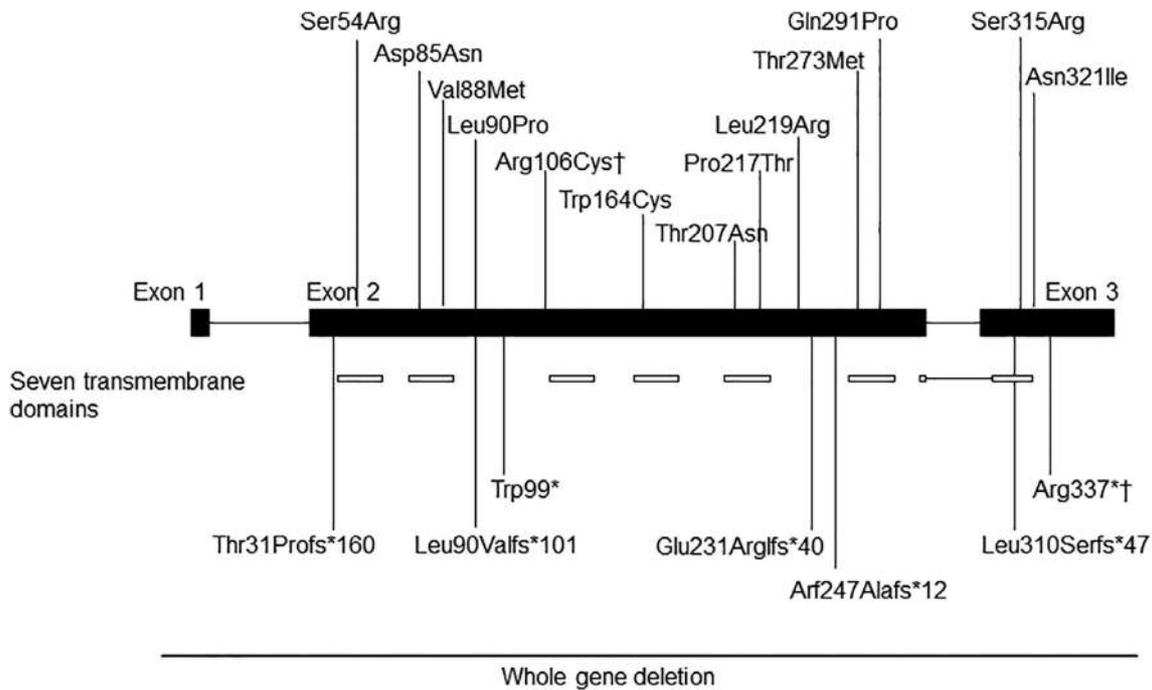


FIGURE 2 Locations of the 21 pathogenic AVPR2 gene variants in females with XL-NDI from 23 families. The two recurrent mutations, each identified in two families, are denoted by a dagger (†). Exons are numbered and drawn to scale (introns and UTRs not drawn to scale). The positions of the seven transmembrane domains of the AVPR2 protein are indicated by boxes under the exons. Mutations are distributed without particular hot spots

retardation, and/or significant bodyweight decrease were classified as severely affected. An extremely skewed X-inactivation was documented in two severely affected females; for the other subjects, no X-inactivation data were available. Seventeen probands had mild NDI manifesting with polydipsia and polyuria and of these, 14 (including our proband) demonstrated missense variants. For four of the 14 subjects, X-inactivation data were reported and showed extremely skewed X-inactivation. The remaining three mildly affected females displayed null variants and of these, two showed a slightly skewed X-inactivation. No data on X-inactivation was provided for the third individual. Thus, all female probands with XL-NDI for whom data were available demonstrated a skewed X-inactivation pattern. The combination of complete loss-of-function mutation and extremely skewed X-inactivation was associated with severe XL-NDI (to date, 2/2 unequivocally documented cases). The combination of loss-of-function mutation with slightly skewed X-inactivation was associated with mild XL-NDI (two unequivocally documented case), and missense mutations with extremely skewed X-inactivation were associated with mild NDI (4/4 cases, including this study). These numbers are small but indicate a trend and require further confirmation studies. We had no technical possibility to study which allele is inactivated, but it is widely accepted that the normal allele is inactivated in individuals manifesting X-linked recessive disorders. In the other case, they should be nonmanifesting.”

Finally, our review supports the hypothesis that the variable NDI phenotype in female carriers depends on the degree of

methylation of the normal AVPR2 allele. This hypothesis is especially supported by the findings in families 2 and 21 (Table 2). In family 21 (Arg247Alafs*12 mutation), the asymptomatic niece showed random X-inactivation, her mildly affected daughter was reported with moderately skewed X-inactivation, and the severely affected proband demonstrated extremely skewed X-inactivation (Nomura et al., 1997). In family 2 (Asp85Asn mutation), the asymptomatic heterozygous mother displayed a random pattern (65:35%), whereas the mildly symptomatic heterozygous daughter showed extremely skewed X-inactivation (93:7%) (Faerch et al., 2010).

In summary, our report confirms the importance of molecular testing of rare diseases, as the assumption of CDI in the proband due to the family condition had led to ineffective treatment. There has been no previous report of a co-existence of CDI and NDI in a family, but currently, there is no means to tell whether this represents a chance coincidence. Our review provides the first evidence for an association between the clinical severity in females and the combined molecular findings (mutation type, X-inactivation status). The review underlines that XL-NDI in female AVPR2-heterozygotes is always accompanied by skewed X-inactivation, emphasizing a need for X-inactivation studies in these females.

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CONFLICT OF INTEREST

The authors indicate they have no financial relationships relevant to this article to disclose. The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

C.D. conducted genetic analysis, made tables, and figures and wrote the manuscript. R.B. provided data for individual patients and edited the manuscript. G.R. conducted a genetic analysis and edited the manuscript. O.B. gathered patient data, critically read, and edited the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author, CD. The data are not publicly available due to their containing information that could compromise the privacy of research participants.

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