Clinical phenotype of nephrogenic diabetes insipidus in females heterozygous for a vasopressin type 2 receptor mutation

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Abstract Nephrogenic diabetes insipidus (NDI) usually shows an X-linked recessive mode of inheritance caused by mutations in the vasopressin type 2 receptor gene (AVPR2). In the present study, three NDI families are described in which females show clinical features resembling the phenotype in males. Maximal urine osmolality in three female patients did not exceed 200 mosmol/kg and the absence of extra-renal responses to l-desamino-8-D-arginine vasopressin was demonstrated in two of them. All affected females and two asymptomatic female family members were shown to be heterozygous for an AVPR2 mutation. Skewed X-inactivation is the most likely explanation for the clinical manifestation of NDI in female carriers of an AVPR2 mutation. It is concluded that, in female NDI patients, the possibility of heterozygosity for an AVPR2 gene mutation has to be considered in addition to homozygosity for mutations in the aquaporin 2 gene.

Introduction

Congenital nephrogenic diabetes insipidus (NDI) is a hereditary renal disorder occurring predominantly in males. The disease is characterized by failure of the kidney to concentrate urine in response to the neurohypophyseal hormone arginine vasopressin. As a consequence, large volumes of urine are produced (polyuria), resulting in a water loss that has to be compensated by ingestion of a similar quantity of fluid (polydipsia). Most patients present in their first year of life with aspecific symptoms, such as vomiting, anorexia, growth retardation and fever. After infanthood, the clinical picture is dominated by the less alarming symptoms of polyuria and polydipsia.

In most families, NDI shows an X-linked recessive mode of inheritance; female carriers have no or only mild symptoms of the disease. In 1992, this form of NDI was found to be caused by mutations in the vasopressin type 2 receptor gene (AVPR2) (van den Ouweland et al. 1992; Pan et al. 1992; Rosenthal et al. 1992). Several families have been reported, however, in which females are affected by the disease from childhood (Table 1). One explanation for the complete manifestation of the disease in females was recently found when mutations in the aquaporin 2 (AQP2) water channel gene were shown to cause autosomal recessive NDI (Deen et al. 1994; van Lieburg et al. 1994). Furthermore, affected females have been described in families in which inheritance of NDI seemed dominant (Cannon 1955; Robinson and Kaplan 1960; Olszewski et al. 1984; Matsumoto et al. 1988; Niiaudet et al. 1985). This heredity pattern could, theoretically, reflect the presence of another defect that interferes with signal transduction somewhere between the receptor and water channel. Finally, it has been suggested that the expression of X-linked NDI can be nearly complete in female carriers but, to our knowledge, this hypothesis has never been substantiated by DNA analysis (Wiggelinkhuizen et al. 1973; Culpepper et al. 1983; Braden et al. 1985; McKusick 1986; Aggarwal et al. 1986; Moses et al. 1988). Here, we report three NDI families in which female carriers of an AVPR2 mutation show a clinical phenotype similar to male NDI patients.

Patients, materials and methods

The human studies performed by the NDI research group have been reviewed by the Ethics Committee of the University of Nijmegen.

Patients

Family 1

The female patient (IV.1) in this Austrian family (Fig. 1A) was born at term after an uncomplicated pregnancy. Family history was neg-
Table 1  Female NDI-patients\(^a\) reported in literature (to months, years, DHT dehydration test, AVP after AVP; DDAVP after DDAVP, ONFD overnight fluid deprivation)

<table>
<thead>
<tr>
<th>Author</th>
<th>Age at presentation</th>
<th>Maximal urine osmolality or s.g.(^b)</th>
<th>Affected family members</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dancis et al. (1948)</td>
<td>6.5 m</td>
<td>1016(^b) (DHT) 1006(^b) (AVP)</td>
<td>No</td>
</tr>
<tr>
<td>Carter and Simpkins (1956)</td>
<td>In childhood</td>
<td>1016(^b) (ONFD)</td>
<td>Son</td>
</tr>
<tr>
<td>Broedel and Braun (1964)</td>
<td>2 m</td>
<td>80 (during dehydration)</td>
<td>Father (mildly affected)</td>
</tr>
<tr>
<td>Feigen et al. (1970)</td>
<td>3 y</td>
<td>82 (DHT)</td>
<td>2 brothers, 1 half-brother</td>
</tr>
<tr>
<td>Wiggelinkhuizen et al. (1973)</td>
<td>3 m</td>
<td>80 (AVP)</td>
<td>Brother</td>
</tr>
<tr>
<td>Zimmermann and Green (1975)</td>
<td>2.8 y</td>
<td>55 (AVP)</td>
<td>No</td>
</tr>
<tr>
<td>Schreiner et al. (1978)</td>
<td>1.3 y</td>
<td>75 (AVP)</td>
<td>No</td>
</tr>
<tr>
<td>Niaudet et al. (1985)</td>
<td>?</td>
<td>Completely unresponsive (DDAVP)</td>
<td>Several females</td>
</tr>
<tr>
<td>Aggarwal et al. (1986)</td>
<td>3 m</td>
<td>148 (AVP)</td>
<td>No</td>
</tr>
<tr>
<td>Brenner et al. (1988)</td>
<td>7–11 y</td>
<td>82 (AVP)</td>
<td>2 brothers</td>
</tr>
<tr>
<td>Schauer et al. (1990)</td>
<td>6 m</td>
<td>160 (AVP)</td>
<td>1 brothers</td>
</tr>
<tr>
<td>Moses et al. (1988)</td>
<td>In childhood</td>
<td>101 (DDAVP)</td>
<td>No</td>
</tr>
<tr>
<td>Langley et al. (1991)</td>
<td>1 m</td>
<td>1000(^b) (AVP)</td>
<td>Sister</td>
</tr>
<tr>
<td>Pallicks et al. (1991)</td>
<td>3 m</td>
<td>?</td>
<td>Father</td>
</tr>
</tbody>
</table>

\(^a\) Only patients reported to be affected from childhood are mentioned

\(^b\) s.g. Specific gravity

ative for NDI and her parents were not known to be consanguineous. On the seventh day of life, the girl was hospitalized because of diarrhoea with hypertonic dehydration. At admission, serum sodium was 156 mmol/l; urine osmolality was not measured. *Escherichia coli* was isolated from her blood. She was treated successfully with intravenous fluid and antibiotics and discharged two weeks after admission.

The following year her brother (IV.2) was born. He was admitted on the tenth day of life in a dehydrated condition (serum sodium 116 mmol/l, urine osmolality 357 mosmol/kg). Diarrhoea and fever had been present for one week. Despite dehydration, urine osmolality was low (118 mosmol/kg). After intravenous fluid therapy, the child was noticed to be excessively thirsty and polyuric (intake 360 ml/kg per day). A dehydration test with subsequent administration of 1-desamino-8-d-arginine vasoressin (DDAVP) was performed, resulting in a maximum urine osmolality of 152 mosmol/kg with a concurrent serum osmolality of 313 mosmol/l (Table 2). He was treated with hydrochlorothiazide and an ample supply of fluid, a regimen on which daily urine production amounted to 250 ml/kg and serum osmolality remained in the normal range. Now, at the age of 19 months, his fluid intake is 250–290 ml/kg per day (medication hydrochlorothiazide and amiloride). Growth and mental development are normal.

Because of the diagnosis of NDI in this boy, attention was again focussed on his sister. A renewed medical history revealed that she had been excessively thirsty and polyuric since birth. At the age of two years, the girl was hospitalized for further evaluation. She was in good general condition (weight and stature P\(_{75}\)). Serum osmolality, sodium and potassium were normal; random urine osmolality was low (82 mosmol/kg). Oral fluid intake ranged from 260 to 350 ml/kg/day. A dehydration test did not result in a normal increase of urine osmolality, neither did intravenous administration of DDAVP (Table 2). Now, at the age of 3 years, she has a fluid intake of 300 ml/kg per day (medication hydrochlorothiazide and amiloride). Growth and mental development are normal. The mother of these children has no symptoms of NDI (daily urine production 1 l).

Family 2

The female proband (IV.15) in this Dutch family (Fig.1B) was born at term. The pregnancy was complicated by fluxus and hypertension after 3 months, mild hypertension and maternal varicosis for which aspirin was used. The girl had feeding problems from birth; she vomited frequently and showed aversion to solid foods. Growth retardation became manifest at the age of 14 weeks. When she was 8 months old, she was referred to a pediatrician because of persistent feeding problems and growth retardation (length P\(_{25}\), weight < P\(_{25}\)). At laboratory examination, a high serum sodium concentration (157 mmol/l) and serum osmolality (319 mosmol/kg) were found. A DDAVP test showed a minimal increase of urine specific gravity (Table 2). An intravenous pyelogram (IVP) revealed no abnormalities. Fluid intake ad libitum and administration of hydrochlorothiazide in combination with a salt-restricted diet resulted in normalization of serum sodium and osmolality and she was discharged 9 weeks after admission. At present (age 13), daily urine production amounts to 150 ml/kg (medication hydrochlorothiazide). She shows normal mental development but is small for her age (< P\(_{25}\)).

Family history revealed that the mother (III.7) had a large fluid intake since childhood. When she was in primary school, she was hospitalized because of severe vomiting. In the same period, diabetes mellitus was excluded as a possible cause of her polydipsia. At the age of 33, as a consequence of the diagnosis made in her daughter, a DDAVP test was performed, which showed impairment of her anti-diuretic response (Table 2). An IVP showed slight dilatation of the right pyelum and ureter. Treatment with chlorothalidone and a salt-restricted diet resulted in a decrease of polydipsia and polyuria. Except for bile stones, for which cholecystectomy was performed, she has had no major medical problems. Symptoms of NDI were absent from the other family members. Urine osmolality after overnight fluid deprivation of the father of patient IV.15 was normal (905 mosmol/kg). Her sister showed a borderline value (735 mosmol/kg).
Fig. 1A–C. Pedigrees of the NDI families. Black symbols denote affected individuals; hatched symbols indicate that NDI is suspected; symbols with diagonal slashes denote deceased individuals; SB depicts stillborn infants. Presence of the mutant alleles is depicted by the relevant amino acid substitution (L219R) or V2R deletion (del); normal alleles are denoted by a plus sign.
Table 2: Data on dehydration and (DD)AVP tests performed in patients in the three studied families. The age when the test was performed is expressed in years (y) or months (m) (i.v. intravenously, i.n. intranasally)

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age</th>
<th>Max. urine osmolality</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Before test</td>
<td>After test</td>
</tr>
<tr>
<td>IV.1 family 1</td>
<td>2 y</td>
<td>82</td>
<td>105</td>
</tr>
<tr>
<td>IV.2 family 1</td>
<td>1 m</td>
<td>64</td>
<td>152</td>
</tr>
<tr>
<td>IV.15 family 2</td>
<td>8 m</td>
<td>1000</td>
<td>1006*</td>
</tr>
<tr>
<td>III.7 family 2</td>
<td>33 y</td>
<td>240</td>
<td>270</td>
</tr>
<tr>
<td>III.10 family 3</td>
<td>11 y</td>
<td>200</td>
<td>309</td>
</tr>
<tr>
<td>III.10 family 3</td>
<td>16 y</td>
<td>1005</td>
<td>1014</td>
</tr>
<tr>
<td>III.11 family 3</td>
<td>1 m</td>
<td>1000*</td>
<td>No increase</td>
</tr>
<tr>
<td>IV.3 family 3</td>
<td>8 m</td>
<td>150</td>
<td>No increase</td>
</tr>
</tbody>
</table>

* Specific gravity

Family 3

The female patient (patient III.10) in this Dutch family (Fig.1C) presented at the age of 5 months with severe vomiting. Symptoms had started after discontinuation of breastfeeding and resulted in a 3-kg decrease of weight in the following two weeks. Soon thereafter, she was admitted to a hospital, where the diagnosis of hypertrophic pyloric stenosis was made (no additional medical data available). Despite surgical intervention, vomiting and anorexia continued for some time but eventually decreased. During childhood, her craving for water was remarkable; when she was playing outside for a long time, she used to eat snow or drink from puddles on the road. For this reason, she was hospitalized at the age of 5 years and a diagnosis of psychogenic diabetes insipidus was made. Six years later, she was again examined for excessive thirst and polyuria. A dehydration test with subsequent administration of pitressin showed an abnormal response (Table 2). No diagnosis was made, however, until she was 16 years old. At that time, her half-brother (patient III.11) was found to suffer from NDI; after a neonatal meningitis, he showed persistent hypernatremia and polyuria and no response to pitressin (Table 1). The diagnosis in this boy made it reasonable to evaluate his half-sister for a third time: a dehydration test revealed a maximal urine osmolality of 200 mosmol/kg, despite serum hyperosmolality, and pitressin induced no additional rise (Table 2). Antidiuretic hormone concentrations during dehydration were 6 times the normal value, with concurrent hypotonic urine. Now, at adult age, daily urine volume amounts to 8–10 l/day (no medication).

When patient III.10 was 29 years old, her son (patient IV.3) was born. At the age of 8 months, he was referred to hospital because of growth retardation, anorexia, polyuria and a positive family history for NDI. Serum sodium concentration was 174 mmol/l. Urine osmolality varied between 100 and 150 mosmol/kg and did not rise in response to DDAVP (Table 2); the same diagnosis was therefore made as for his mother and uncle.

Family history revealed that two maternal uncles of patient III.10 had died in their first year of life with symptoms of dehydration. Her aunt died from a cause not related to NDI. Interpretation of symptoms of her mother (II.7) was hampered by her history of a borderline diabetes mellitus type II and unilateral nephrectomy during adulthood, performed for an unknown reason. However, she mentioned stress incontinence during childhood, excessive thirst during pregnancy and inability to maintain fluid depriviation prior to surgery. The sister of patient III.10 had no symptoms at all.

DDAVP test with measurement of extra-renal parameters

Parents of the patients gave informed consent prior to the tests. Tests were performed independently in two different centres, resulting in a few procedural differences.

Procedure 1 (family 1)

A dose of 0.3 µg/kg DDAVP (Minrin, Ferring, Malmö, Sweden) was administered intravenously over 30 min. Blood pressure and pulse rate were recorded every 10 min. A 2.7-ml blood sample was collected at time points: −60, 0, 30, 60, 90 and 120 min. Blood samples were transferred to tubes containing 0.3 m citrate solution and briefly kept in iced water until centrifugation at 2000 rpm. The time between blood sampling and performance of the factor VIII coagulant (FVIIIc) activity assay did not exceed 4 h. FVIIIc activity was quantified by a one-stage clotting assay using factor-VIII-deficient human plasma according to Lechner (1982). Remaining plasma was stored at −70°C. In these samples, tissue type plasminogen activator antigen (tPA:Ag) was measured by an enzyme-linked immunosorbent assay (Coiliza t-PA, Chromogenix).

Procedure 2 (family 2)

Protocol 2 is identical to the protocol described by Knoers and Monnens (1991). Briefly, DDAVP (0.3 µg/kg was administered intravenously over 10 min. Blood pressure and heart rate were recorded at 3-min intervals during the first 25 min and at 10-min intervals thereafter. Blood samples were collected and handled as described previously (Knoers and Monnens 1991). t-PA:Ag levels were measured by an enzyme-linked immunosorbent assay (Innotest, Inno-geenetics).

DNA analysis

Genomic DNA was isolated from blood cells by the salt-extraction technique (Miller et al. 1988). Linkage analysis was performed by...
standard procedures using markers defining the loci DXS134, DXS52 and F8 (family 2) or DXS52, DXS707 and DXS605 (family 3) (Knoers et al. 1994). Amplification and direct sequencing of AVPR2 exons and introns and AQP2 exons were performed as described elsewhere (van den Ouweland et al. 1992; Deen et al. 1994).

In family 1, Smal restriction fragment analysis was used to assess inheritance of the mutation. A 526-bp fragment was generated by the polymerase chain reaction (PCR) using primers 297 and 300 (Fig. 2, Table 3). After digestion with Smal, fragments were resolved on a 3% agarose gel and visualized by UV irradiation.

In family 2, a PCR fragment with the expected length of 319-bp in wild-type DNA was generated with primers 295 and 296. In the last cycle, αβPdCTP was added to the reaction mixture. PCR products were digested with BglII and resulting fragments were separated by electrophoresis on a 15% non-denaturing polyacrylamide gel and subjected to autoradiography.

In family 3, PCR was performed using combinations of primers 366 and 291, primers 289 and 291, and primers 301 and 291. Carrier detection in this family was performed as follows: total DNA was digested with BamHI, fragments were separated by electrophoresis on a 0.6% agarose gel and the standard procedure for Southern blotting was applied. A PCR fragment generated with primers 301 and 304 and normal genomic DNA as a template, radio-actively labelled as described above, was used as the probe.

Results

DDAVP tests

A DDAVP test with measurement of extra-renal parameters was performed in the patients of family 1 and their parents, and in patient IV.15 of family 2. In none of these individuals a significant change of blood pressure was found during the test (data not shown). Both parents showed a slight increase of pulse rate during the DDAVP infusion which was absent in the three patients (data not shown). Facial flushing was observed only in the father. The increase of t-PA:Ag and FVIIIc activity found in the parents did not occur in the patients (Fig. 3, 4). In patient IV.15 of family 2, no significant rise of t-PA:Ag was detected (FVIIIc not measured) (Fig. 3).

DNA analysis

Family 1

Direct sequencing of all exons and introns of the AVPR2 gene demonstrated the presence of a T727 to G transversion in exon 2, resulting in substitution of an arginine for a leucine (L219R) in the fifth transmembrane region of the predicted AVPR2 model, in both affected children. The Smal restriction site introduced by this mutation was present in both affected children and their asymptomatic mother, but was absent in their father, maternal grandparents and aunt. The 526-bp fragment was also present in the affected girl and her mother. In the affected girl, sequencing of the complete coding region of the AQP2 gene revealed no mutations.

Fig. 2 Schematic representation of the AVPR2 gene with the location of the primers indicated by arrows. Open boxes denote the sequences encoding the predicted domains of the V2 receptor (E: extracellular; TM: transmembrane; C: cellular). Hatched boxes represent intron sequences.
Table 3 Primers

<table>
<thead>
<tr>
<th>Nr.</th>
<th>Position</th>
<th>Sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>366</td>
<td>14–34</td>
<td>5'-CAGAGGCTGAGTCCCGACATC-3'</td>
</tr>
<tr>
<td>295</td>
<td>intron 1, 97–101</td>
<td>5'-TGGCTCTGTCAAGGAAAATGC-3'</td>
</tr>
<tr>
<td>297</td>
<td>334–353</td>
<td>5'-ACTTCACGGCCCGACACAGG-3'</td>
</tr>
<tr>
<td>296</td>
<td>420–401</td>
<td>5'-TTGGGCCCTCTCGCTCTCTC-3'</td>
</tr>
<tr>
<td>300</td>
<td>560–579</td>
<td>5'-GACAGGTCGCTCCCTCAGC-3'</td>
</tr>
<tr>
<td>301</td>
<td>859–840</td>
<td>5'-GAGATTCATGCCAGTCTGC-3'</td>
</tr>
<tr>
<td>291</td>
<td>1067–1047</td>
<td>5'-ACGCTGCTGCTGAAAGATGC-3'</td>
</tr>
<tr>
<td>304</td>
<td>1252–1233</td>
<td>5'-ACGGAAGGACCCGACAGG-3'</td>
</tr>
</tbody>
</table>

Fig. 3 Tissue type plasminogen activator antigen response to DDAVP in patients IV.1 (■■) and IV.2 (●●) from family 1 and their mother (▼▼) and father (▲▲), and in patient IV.15 (●●) from family 2. DDAVP was administered over 10 min (0–10 min) in patient IV.15 from family 2 and over 30 minutes (0–30 min) in members of family 1.

Fig. 4 Factor VIIIc activity response to DDAVP in patients IV.1 (■■) and IV.2 (●●) from family 1 and their mother (▼▼) and father (▲▲). DDAVP was administered over 30 min (0–30 min).

Family 2

Linkage analysis with polymorphic markers for the Xq28 region showed that the Xq28 allele shared by the clinically affected women originated from the maternal grandfather of the proband (data not shown). The AVPR2 gene sequence of the proband revealed a deletion of one of two adjacent CT nucleotide doublets (337–340) in exon 2, resulting in a frameshift 3' to codon 90 in the second transmembrane region with a premature stop codon 101 codons downstream. Segregation of the deletion in the family was analysed by detection of a 2-nucleotide size reduction of the wild-type 42-bp fragment generated by BglII digestion of the PCR fragment (primers 295 and 296). This proce-
dure confirmed the presence of the deletion in the proband and revealed that this deletion was also present in her mother, but absent in her sister and maternal aunts and uncles. The 42-bp fragment was also detected in both affected females. Sequencing of the complete AQP2 coding region in the affected girl revealed no mutations.

**Family 3**

Linkage analysis with markers DXS52 and DXS605 (DXS707 was not informative) showed that all patients inherited the same Xq28 allele from their mother. The unaffected brother (III.9) of patients III.10 and III.11 received the other allele. The asymptomatic female and the clinically affected female in generation III shared the same Xq28 haplotype (data not shown).

In the two affected males, no PCR product could be generated using primers 366 and 291 and primers 289 and 291. The combination of primers 301 and 291, however, resulted in the generation of a fragment of approximately 400bp (including intron 2), indicating a deletion in the 5'-region of the gene prior to nucleotide 761. In the affected female (III.10), no absence or abnormalities of any PCR products were found and sequencing of the AVP2R gene revealed no mutations. In order to assess the carrier status of the females in this family, the Southern blot procedure was employed. In the two male patients, a BamH1 fragment with a length approximately 1kb larger than that of the fragment found in control individuals was detected (data not shown). In individuals II.7, III.8 and III.10, both the normal BamH1 fragment and the larger fragment were detected, indicating that these females are all heterozygous for the deletion in the AVP2R gene.

**Discussion**

In most families, NDI shows an X-linked recessive inheritance. Variable expression of the disease occurs in some of the mothers of these patients, but polyuria and polydipsia are generally of such a minimal degree, that these symptoms are either not noticed or accepted as a personal characteristic. In addition to these subclinical carriers, severely affected females, both isolated and familial cases, have been described in the literature (Table 1). Except for the autosomal recessive form caused by mutations in the recently discovered AQP2 gene (Deen et al. 1994; van Lieburg et al. 1994), the genetic cause of the disease in female patients has not been elucidated. The present study shows that female carriers of an AVP2R mutation can present in early childhood with symptoms resembling the clinical phenotype of male NDI patients, with three of the four females demonstrating a maximal urine osmolality not exceeding 200 mosmol/kg (normally > 805 mosmol/kg).

In family 1, the apparent autosomal recessive inheritance of NDI suggests the presence of an AQP2 defect. Because of the severity of the disease in the girl and the recent origin of the AVPR2 mutation, the classical X-linked recessive pattern of heredity is lacking. Although conclusive evidence that the L219R substitution causes NDI can only be obtained by in vitro expression studies, the change of a hydrophilic for a hydrophobic residue in a region in which hydrophobicity has been conserved during evolution (Fahrenholz et al. 1993) indicates that the L219R substitution abolishes the normal function of the receptor. Moreover, the absence of extra-renal responses in both patients is in accordance with a V2 receptor defect (Bichet et al. 1988; Knoers and Monnens 1991). The deletions found in the other two families undoubtedly impair the function of the receptor.

Several explanations for the complete manifestation of NDI in females deserve consideration. One explanation could be homozygosity or compound heterozygosity for an AVPR2 mutation or carriahership of an AVP2R mutation in combination with an abnormal karyotype (45,XO; 45,XO/46,XX; 46,XY); a second AVPR2 mutation was excluded in our patients, and both haplotype analysis and Smal, BglI and BamH1 digestion patterns confirmed the presence of two AVPR2 alleles. The latter findings make the possibility of sex chromosome aneuploidy less likely, although mosaicism cannot be excluded. Another possibility is the presence of other causes of NDI; the involvement of the AQP2 gene was ruled out in two of the female patients, and indications of secondary NDI were present in none of the patients. Clustered occurrence of female symptomatic carriers in certain families could reflect the presence of an AVPR2 mutation with more severe functional consequences. Mutations, however, that can be regarded as deleterious to the AVP2R protein as the deletions described here have been reported in asymptomatic female carriers (Bichet et al. 1993). Moreover, the intrafamilial variability of expression observed in families 1 and 3 is not in accordance with this explanation.

Skewed X-inactivation, resulting in predominant expression of the mutant AVPR2 allele, is by far the most plausible mechanism underlying the occurrence of different phenotypes, varying from no symptoms to full manifestation of the disease, in female carriers of an AVPR2 gene mutation. This phenomenon has been described in female carriers of mutations causing other X-linked recessive diseases, including haemophilia A and B, Hunter disease and Duchenne muscular dystrophy (Ingerslev et al. 1989; Nisen et al. 1989; Winchester et al. 1990; Richards et al. 1990; Tilly et al. 1994). In our female patients, the absence of extra-renal responses to DDAVP suggests that predominant inactivation of the X-chromosome carrying the wild-type allele occurs in both renal collecting duct cells and the extra-renal cells that mediate vasodilatation and release of coagulation and fibrinolysis factors. Similarity of X-inactivation patterns in different tissues has also been described for Duchenne muscular dystrophy (Richards et al. 1990). On the other hand, variation in the pattern of X-inactivation between different tissues has been reported (Brown et al. 1990) and could result in a discrepancy between renal and extra-renal response to DDAVP in female carriers of an AVPR2 mutation.
The observation that female carriers of a mutation in the AVPR2 gene can show the clinical phenotype of NDI has important implications for genetic counselling and DNA research into NDI. We observed this phenomenon in a relatively high percentage, viz. 8.8% (3 out of 34) of the NDI families in which we found an AVPR2 mutation. Therefore, if consanguinity of parents is lacking, heterozygosity for an AVPR2 mutation is a likely cause of NDI in sporadic female patients. Furthermore, the present study suggests that, in some of the families in which NDI shows a dominant mode of inheritance, an AVPR2 gene defect could be the cause of the disease. Consequently, in clinical practice, it is important to realize that, in female carriers of an AVPR2 mutation, clinical and laboratory data can be found that resemble those obtained in male NDi patients.

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