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NLM Citation: Knoers N, Lemmink H. Hereditary Nephrogenic Diabetes Insipidus. 2000 Feb 12 [Updated 2020 Feb 27]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Hereditary Nephrogenic Diabetes Insipidus

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Created: February 12, 2000; Updated: February 27, 2020.

Summary

Clinical characteristics

Hereditary nephrogenic diabetes insipidus (NDI) is characterized by inability to concentrate the urine, which results in polyuria (excessive urine production) and polydipsia (excessive thirst). Affected untreated infants usually have poor feeding and failure to thrive, and rapid onset of severe dehydration with illness, hot environment, or the withholding of water. Short stature and secondary dilatation of the ureters and bladder from the high urine volume is common in untreated individuals.

Diagnosis/testing

The diagnosis of hereditary NDI is established in a male proband with NDI by identification of a hemizygous pathogenic variant in *AVPR2* or identification of a compound heterozygous or homozygous pathogenic variant in *AQP2* by molecular genetic testing. The diagnosis of hereditary NDI is usually established in a female proband with NDI by identification of a heterozygous pathogenic variant in *AVPR2* or identification of a compound heterozygous or homozygous pathogenic variant in *AQP2* by molecular genetic testing.

Management

Treatment of manifestations: Management by a multidisciplinary team (nutritionist, pediatric nephrologist/endocrinologist, clinical geneticist); free access to drinking water and to toilet facilities; reduction of polyuria (and thus polydipsia) up to 50% without inducing hypernatremia by use of a thiazide diuretic (e.g., hydrochlorothiazide, chlorothiazide) often used in combination with either amiloride (a potassium-sparing diuretic) or indomethacin; dietary restriction of sodium; in individuals with dehydration or shock, establish whether the deficit is primarily in free water (through water deprivation or excessive urine, stool, or sweat) or in extracellular fluid (bleeding, fluid extravasation) to avoid inappropriate treatment of dehydration with normal saline (0.9% NaCl); when "NPO" (nothing *per ora*), individuals with NDI *must* have intravenous replacement of their usual oral intake of water as 5% dextrose in water; treat hydronephrosis, hydroureter, and megacystis with

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medical management to reduce urine output and continuous or intermittent bladder catheterization when post-void urinary bladder residuals are significant.

Prevention of secondary complications: Reduction of urine production by drug therapy and voiding at two-hour intervals may prevent or reduce serious renal, ureteral, or bladder dilatation.

Surveillance: Monitor growth and development at least every three months in infants and at least every six months in older children; measurement of serum sodium concentration to identify unrecognized hyperosmolality and early dehydration at least every three months in infants, at least every six months in older children, and annually in adults or only as needed; annual kidney ultrasound examination to monitor for hydronephrosis and megacystis.

Agents/circumstances to avoid: Water intake must not be restricted.

Evaluation of relatives at risk: Evaluation of at-risk infants as early as possible to allow for prompt diagnosis and treatment to reduce morbidity from hypernatremia, dehydration, and dilatation of the urinary tract.

Genetic counseling

Hereditary NDI is most commonly inherited in an X-linked manner (~90% of individuals). Hereditary NDI can also be inherited in an autosomal recessive manner (~9% of individuals) or in an autosomal dominant manner (~1% of individuals). The risks to sibs and offspring depend on the mode of inheritance and the genetic status of the parents, which can be established in most families using molecular genetic testing. Prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible if the disease-causing pathogenic variant(s) in the family have been identified.

Diagnosis

Suggestive Findings

Hereditary nephrogenic diabetes insipidus (NDI) **should be suspected** in an individual with the following clinical and laboratory findings.

Clinical

- Polyuria (excessive urine production)
- Polydipsia (excessive drinking)
- Family history of NDI
- Note: In the first few months after birth, polyuria and polydipsia may not be immediately noticed; infants with NDI usually present with poor feeding, failure to thrive, and irritability.

Laboratory

- **Increased serum sodium concentration** (>145 mEq/L) in the presence of a low urine specific gravity and in the absence of excessive sodium intake
- **Failure to concentrate the urine** normally in the presence of high plasma arginine vasopressin (AVP) concentration and after parenteral administration of desmopressin (DDAVP®) is diagnostic of NDI. DDAVP (10 mg for infants age <1 year, 20 mg for children age >1 year) is administered intranasally. Urine is collected during the subsequent 5.5 hours. The first collected portion of the urine should be discarded. The maximal urine osmolality in any collected aliquot is chosen as a measure of the concentrating capacity. After DDAVP administration, individuals with NDI:

- Are unable to increase urinary osmolality, which remains below 200 mOsm/kg H_2O *;

  * Normal urinary osmolality values by age:

  - <1 year: >600 mOsm/kg H_2O
  - 1-2 years: 600 - 800 mOsm/kg H_2O
  - >2 years: >800 mOsm/kg H_2O

- Cannot reduce urine volume or free water clearance [Knoers & Levtchenko 2016].

Note: (1) The results of these laboratory tests may be difficult to interpret in individuals with "partial diabetes insipidus," which results from either subnormal amounts of AVP secretion (partial neurogenic DI) or partial response of the kidney to normal AVP concentrations (partial nephrogenic DI). These two disorders can be distinguished by comparing the ratio of urine osmolarity to plasma AVP concentration against normal standards. However, direct measurement of AVP is hampered by technical difficulties. Copeptin, the C-terminal component of the AVP-precursor and co-secreted with AVP, is much easier to measure than plasma AVP and is therefore a valuable surrogate of plasma AVP concentration. It has been shown to be a useful candidate biomarker for the differential diagnosis in polyuria-polydipsia syndromes [Timper et al 2015, Nigro et al 2018]. (2) An overnight urinary concentration test proposed as a method to identify heterozygous females with *AVPR2*-NDI is unreliable.

Establishing the Diagnosis

Male proband. The diagnosis of hereditary NDI **is established** in a male proband with NDI by identification of one of the following on molecular genetic testing (see Table 1):

- A hemizygous pathogenic (or likely pathogenic; see Note) variant in *AVPR2* (X-linked NDI)
- Biallelic pathogenic variants in *AQP2* (autosomal recessive NDI)
- A heterozygous pathogenic variant in *AQP2* located in the carboxy-terminal region of aquaporin-2, a region important for targeting of the protein (see Molecular Genetics) (autosomal dominant NDI)

Female proband. The diagnosis of hereditary NDI **is usually established** in a female proband with NDI by identification of one of the following by molecular genetic testing (see Table 1):

- A heterozygous pathogenic variant in *AVPR2* (X-linked NDI)
- Biallelic pathogenic variants in *AQP2* (autosomal recessive NDI)
- A heterozygous pathogenic variant in *AQP2* located in the carboxy-terminal region of aquaporin-2, a region important for targeting of the protein (see Molecular Genetics) (autosomal dominant NDI)

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of variant(s) of uncertain significance cannot be used to confirm or rule out the diagnosis.

Molecular genetic testing approaches can include **serial single-gene testing** or a **multigene panel**.

Serial single-gene testing

- Sequence analysis of *AVPR2* can be performed first in **most males and females** to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: (1) Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications in *AVPR2*. (2) If no pathogenic variant in *AVPR2* is found perform sequence analysis of *AQP2*. If only one

pathogenic variant is found outside of the carboxy-terminal region of aquaporin-2 (see Molecular Genetics) or no pathogenic variant is found, perform gene-targeted deletion/duplication analysis of *AQP2*.

- In **affected children (male or female) from consanguineous parents**, *AQP2* sequence analysis can be performed first. Note: (1) Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one pathogenic variant is found outside of the carboxy-terminal region of aquaporin-2 (see Molecular Genetics) perform gene-targeted deletion/duplication analysis of *AQP2*. If no *AQP2* pathogenic variant is identified, perform *AVPR2* sequence analysis. If no *AVPR2* pathogenic variant is found on sequence analysis perform *AVPR2* gene-targeted deletion/duplication analysis.

A hereditary NDI multigene panel that includes at least *AQP2*, *AVPR2*, and *AVP* (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting incidental findings. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some larger multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis and deletion/duplication analysis. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Table 1. Molecular Genetic Testing Used in Hereditary Nephrogenic Diabetes Insipidus (NDI)

Gene [1, 2]	Proportion of Hereditary NDI Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [3] Detectable by Method	
		Sequence analysis [4]	Gene-targeted deletion/duplication analysis [5]
AQP2	10%	>99%	<1% [6]
AVPR2	90%	~90%	~10% [7]

1. Genes are listed in alphabetic order.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. See Molecular Genetics for information on variants detected in this gene.
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Peces et al [2019]
7. Bichet & Bockenhauer [2016]

Clinical Characteristics

Clinical Description

Hereditary nephrogenic diabetes insipidus (NDI). Individuals with NDI typically have polyuria and polydipsia. However, in infants, polydipsia and polyuria are often unappreciated or unremarkable. Infants usually present with poor feeding, poor weight gain, and irritability. Infants are eager to suck but may vomit during or shortly after feeding. Dehydration is evident with dryness of the skin, loss of normal skin turgor, recessed eyeballs, increased periorbital folding, depression of the anterior fontanel, and a scaphoid abdomen. Intermittent high fever is a common complication of dehydration, predominantly in very young children. Seizures can occur but are rare and most often seen during therapy, particularly if rehydration proceeds too

rapidly. Constipation is a common symptom in children with NDI. Nocturia and nocturnal enuresis are common later in childhood.

The majority of affected individuals are diagnosed in the first year of life [van Lieburg et al 1999]. The initial symptoms in autosomal dominant NDI usually appear later, in some individuals not before early adulthood.

Sometimes infants as well as older individuals may present with rapid onset of severe dehydration associated with water deprivation, a hot environment, or intercurrent illnesses associated with decreased water intake and/or increased free water losses through vomiting, diarrhea, or fever. Seizures and/or coma may occur with rapid increases or decreases in plasma osmolality. Occasionally, the presenting sign is hydronephrosis, hydroureter, or megacystis.

Dehydrated individuals in whom the diagnosis of NDI has not been made or who are unable to communicate their complaints run the risk of being improperly treated with IV administration of normal saline, especially in emergency situations. This may exacerbate hypernatremia. Prolonged, unrecognized, or repeated episodes of hypernatremic dehydration may result in seizures, permanent brain damage, developmental delay, and cognitive impairment. With early diagnosis and proper management, intelligence and life span are usually normal [Sharma et al 2018].

Chronic excretion of large volumes of urine can result in hydronephrosis, hydroureter, and megacystis (huge bladder). Some degree of urinary tract distention may be seen on ultrasound examination even in infants [Yoo et al 2006]. Potential complications of urinary tract dilatation are rupture of the urinary tract, infection, intractable pain, improper bladder function, and/or kidney failure. These complications may occur as early as the second decade of life [Shalev et al 2004]. Activities of daily living are substantially affected by the need to have constant access to potable water and by the increased frequency of urination. The unavailability of restroom facilities, even for a short time, is a problem in societies in which public urination is taboo. School and other social or group activities may be disrupted.

Failure to thrive or short stature may result from unsuccessful management or inadequate nutrition related to polydipsia [van Lieburg et al 1999]. In a recent report on the long-term follow up of individuals with NDI, growth was normal in the vast majority, although median height was slightly below the average (-0.9 SD) [Sharma et al 2018].

Partial nephrogenic diabetes insipidus. Individuals with partial NDI tend to be diagnosed in later childhood. They usually do not have growth or developmental delay and are able to concentrate the urine in response to dehydration or DDAVP® administration, but to a lesser extent than unaffected individuals.

Heterozygotes for X-linked NDI. Females who are heterozygous for an *AVPR2* pathogenic variant may have no symptoms or a variable degree of polyuria and polydipsia, or they may be as severely affected as males. Skewed X inactivation is believed to cause symptoms in some females heterozygous for *AVPR2* pathogenic variants, although these symptoms do not necessarily correlate with the X inactivation pattern in leukocytes [Namatame-Ohta et al 2018].

Phenotype Correlations by Gene

With few exceptions, there is no difference in onset or clinical symptoms between *AVPR2*-NDI (X-linked) and autosomal recessive *AQP2*-NDI. However, a minority of individuals with *AVPR2*-NDI (X-linked) have *AVPR2* pathogenic variants associated with partial insensitivity to AVP; in these individuals onset is later in childhood. In general the initial symptoms in most individuals with autosomal dominant NDI also appear later in childhood.

Genotype-Phenotype Correlations

AVPR2. A minority of *AVPR2* pathogenic variants result in partial insensitivity to AVP or DDAVP®, and disease onset may be later in childhood. At present, 18 *AVPR2* pathogenic variants resulting in partial NDI have been reported. These include:

- p.Asn317Lys, p.Asn317Ser, p.Asn321Tyr, p.Met311Val; reach the cell surface with impaired ligand capacity and partial AVP/DDAVP binding. See review in Neocleous et al [2012],
- p.Asp85Asn; decreased ligand-binding affinity and decreased coupling to G_s [Sadeghi et al 1997]
- p.Gly201Asn; decreased number of cell surface AVPR2 receptors [Sadeghi et al 1997]
- p.Pro322Ser and p.Val88Met; reduced cell surface expression and decreased binding affinity for AVP [Bockenhauer et al 2010]
- p.Ser334del, p.Tyr128Ser, p.Thr273Met and p.Ser329Arg; impaired intracellular trafficking [Faerch et al 2009, Takahashi et al 2012, Makita et al 2016]
- p.Arg104Cys; decreased AVP binding most likely due to conformational changes [Faerch et al 2009]
- p.Leu161Pro and c.276A>G (splice site); identified in individuals with partial NDI [Yamashita et al 2016, Schernthaner-Reiter et al 2016]

AQP2. Pathogenic variants causing autosomal dominant NDI are associated with a milder phenotype and later onset when compared to pathogenic variants causing autosomal recessive NDI.

- **Autosomal recessive NDI.** At least 52 pathogenic variants that give rise to autosomal recessive NDI have been detected in *AQP2*. These include 42 missense variants, two nonsense variants, two small deletions, one gross deletion, one small insertion, and four splice site variants [Knoers & Monnens 1999, Knoers & Deen 2001, Morello & Bichet 2001, Lin et al 2002, Marr et al 2002a, Tajima et al 2003, Iolascon et al 2007, Sahakitrungruang et al 2008, Moon et al 2009, Wesche et al 2012, Milano et al 2017, Long et al 2019, Peces et al 2019, Stenson et al 2020].
- **Autosomal dominant NDI.** At least 13 pathogenic variants (6 missense variants, a 1-bp insertion, and 6 small deletions) that give rise to autosomal dominant NDI are located in the carboxy-terminal region of aquaporin-2, a region considered to be important for targeting of the protein [Kamsteeg et al 1999, Kuwahara et al 2001, Marr et al 2002b, Sohara et al 2006, Wesche et al 2012, Milano et al 2017, Stenson et al 2020].

Nomenclature

The name "nephrogenic diabetes insipidus" was coined by Williams and Henry in 1947. In the literature it has been used synonymously with the terms "vasopressin- or ADH-resistant diabetes insipidus" or "diabetes insipidus renalis."

Prevalence

The exact prevalence of hereditary NDI is not known but it is assumed to be rare. The prevalence of hereditary NDI in Quebec, Canada is estimated at 8.8:1,000,000 males [Arthus et al 2000]. This estimate may be representative of the prevalence worldwide. However, due to chance genetic events in specific populations (e.g., a founder effect), the incidence of NDI is elevated in certain regions – for example, in Utah and Nova Scotia [Bockenhauer & Bichet 2015].

Genetically Related (Allelic) Disorders

AVPR2. Pathogenic gain-of-function variants in *AVPR2* were reported to produce a very rare disorder called "nephrogenic syndrome of inappropriate antidiuresis" (OMIM 300539).

AQP2. No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *AQP2*.

Differential Diagnosis

Diabetes insipidus is the excretion of abnormally large volumes (i.e., >50 mL/kg body weight in 24 hours) of dilute urine (i.e., specific gravity <1.010 or osmolality <300 mOsm/kg). In addition to hereditary nephrogenic diabetes insipidus (NDI), causes of diabetes insipidus include the following:

- **Deficiency in synthesis of the antidiuretic hormone** arginine vasopressin (AVP) in the supraoptic nuclei or secretion by the posterior pituitary (also called neurogenic, hypothalamic, cranial, central, or vasopressin-responsive diabetes insipidus).
  - Acquired causes include trauma, malignancy, granulomatous disease, infection, vascular disease, and autoimmune disease.
  - Autosomal dominant neurohypophyseal diabetes insipidus (OMIM 125700) is caused by pathogenic variants in *AVP* (encoding vasopressin-neurophysin II-copeptin).
- **Acquired NDI** is much more common than hereditary NDI, is usually less severe, and is associated with downregulation of *AQP2*. Known causes include prolonged lithium treatment; hypokalemia; hypercalcemia; vascular, granulomatous, and cystic kidney disease; infection; and urinary tract obstruction [Wesche et al 2012, Knoers & Levtchenko 2016, Kavanagh & Uy 2019]. Rarer reported causes include antibiotics and antifungal, antineoplastic, and antiviral agents [Garofeanu et al 2005].
- **Primary polydipsia** may result from mental illness (called psychogenic polydipsia or compulsive water drinking) or disturbance of the thirst mechanism (called dipsogenic diabetes insipidus). The presence of plasma osmolarity >295 mOsm/kg or serum sodium concentration >143 mEq/L in the context of *ad libitum* fluid intake effectively excludes primary polydipsia.

Diabetes mellitus. Polyuria associated with diabetes mellitus is characterized by glucose in the urine and increased urine specific gravity.

Other. Because of the nonspecific nature of the presenting signs of NDI, infants with NDI may go undiagnosed or be misdiagnosed while under care for failure to thrive, unexplained fever, urinary reflux, or other symptoms.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with hereditary nephrogenic diabetes insipidus (NDI), the evaluations summarized in Table 2 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 2. Recommended Evaluations Following Initial Diagnosis in Individuals with Hereditary Nephrogenic Diabetes Insipidus

System/Concern	Evaluation	Comment
Nephrology	Kidney ultrasound exam	To evaluate for hydronephrosis, dilatation of urinary tract, & megacystis
Other	• Consultation w/clinical geneticist &/or genetic counselor • Developmental eval in children w/history of episode of severe dehydration or delay in diagnosis	

Treatment of Manifestations

Management is usually best accomplished by a team consisting of a nutritionist, a pediatric (or adult) nephrologist or endocrinologist, and a clinical geneticist.

General management. The essence of management is the provision of free access to drinking water and to toilet facilities. Infants, who are naturally unable to seek out water when thirsty, must be offered water between regular feedings. Children and adults who are heavy sleepers may need to be awakened at night by a family member or an alarm clock in order to drink water and to urinate. As long as an individual's thirst mechanism remains intact and the person is otherwise well, these measures prevent hypernatremic dehydration. Education of friends, teachers, caretakers, and neighbors and a willingness to find creative solutions are helpful.

Polyuria (and thus polydipsia) can be reduced by up to 50% without inducing hypernatremia by the use of one of the following drugs/combinations. Therapy is considered effective when urine output declines below a documented baseline in individuals with *ad libitum* water intake. Objective measurements of 24-hour urine volume are more valuable than subjective reports of the volume or frequency of voiding, although reduction in the latter provides a benefit to lifestyle.

- **Thiazide diuretics** (e.g., hydrochlorothiazide, chlorothiazide) in standard to high doses. Since these diuretics cause potassium wasting, serum potassium concentration should be monitored and supplemental potassium provided in the diet or pharmacologically as needed. Thiazides are often used in combination with either amiloride (a potassium-sparing diuretic) or indomethacin.

  Note: When thiazide diuretic therapy is initiated, a transient increase in urine output may occur as a result of salt diuresis.

- **Dietary restriction of sodium** to 1 mmol/kg/day to maximize the effectiveness of thiazide diuretics in reducing urine output. Although previously a diet low in protein (2 g/kg/day) to reduce the renal osmolar load and obligatory water excretion was recommended, severe limitation of dietary protein may introduce nutritional deficiencies. Thus, it is preferable to prescribe dietary restriction of sodium only.

- **Nonsteroidal anti-inflammatory drugs (NSAIDs),** such as indomethacin, to potentially improve urine concentrating ability and reduce urine output. NSAIDs have been used individually and in combination with thiazide diuretics (with or without amiloride). Prolonged use of prostaglandin-synthesis inhibitors, however, is often complicated by gastrointestinal and hematopoietic side effects. Gastrointestinal complaints and complications include anorexia, nausea, vomiting, abdominal pain, ulceration, perforation, and hemorrhage. Hematopoietic reactions include neutropenia, thrombocytopenia, and, rarely, aplastic anemia. In addition, kidney dysfunction has been described during indomethacin therapy, most often consisting of a slight reduction in glomerular filtration rate. Therefore, caution is warranted in the chronic use of NSAIDs for treatment of hereditary NDI.

Emergency treatment for dehydration. When individuals with hereditary NDI present with dehydration or shock, it is essential to establish whether the deficit is primarily in free water (through water deprivation or excessive urine, stool, or sweat) or in extracellular fluid (bleeding, fluid extravasation). The natural tendency of health care providers to treat dehydration with normal saline (0.9% NaCl) is dangerous in individuals with hereditary NDI if the deficit is primarily in free water.

- Acute hypovolemic shock may be treated with isotonic fluid until the blood pressure and heart rate are stabilized, after which 5% dextrose in water is the preferred solution [Bockenhauer & Bichet 2017].
- Dehydration associated with free water deficit is treated by gradually replacing the deficit water as well as ongoing urinary losses. Whenever possible, rehydration should occur with the oral intake of drinking water. If administration of IV fluids is required, 5% dextrose in water and/or quarter-normal saline should be used.

If significant hypernatremia is present, serum sodium concentration should be monitored and the hydration solution modified to avoid reducing serum sodium concentration faster than 1 mEq/L per hour. Rapid increases or decreases in plasma osmolality can cause seizures, coma, brain damage, and death.

Special situations. Individuals being prepared for surgery are often denied oral intake for many hours and are described as having "NPO" (nothing *per ora*) status. In individuals with hereditary NDI, an IV **must** be provided from the beginning of NPO status and the person's oral intake of water for that period, which is typically much larger than that of an individual who does not have NDI, should be given intravenously as 5% dextrose in water [Moug et al 2005].

Hydronephrosis, hydroureter, and megacystis. Treatment involves medical management to reduce urine output and continuous or intermittent bladder catheterization when significant post-void urinary bladder residuals are present.

Psychomotor development. Children with a history of an episode of severe dehydration, delayed developmental milestones, or a delay in establishing the correct diagnosis and management warrant a formal developmental evaluation and intervention before school age.

Prevention of Primary Manifestations

Prevention of primary manifestations (see Treatment of Manifestations) is possible when the diagnosis is made promptly after birth via molecular genetic testing. Genetic testing for NDI may be performed a few days after birth; treatment and monitoring may then start immediately.

Prevention of Secondary Complications

Prevention or reduction of serious renal, ureteral, or bladder dilatation may be achieved by reduction of urine production by drug therapy and voiding at two-hour intervals.

Surveillance

There are no published guidelines available on recommended surveillance for children or adults with hereditary NDI. The frequency of follow up should take into consideration the medications being used and compliance with medications and diet recommendations.

Table 3. Recommended Surveillance for Individuals with Hereditary Nephrogenic Diabetes Insipidus

System/Concern	Evaluation	Frequency
Constitutional	Monitoring of growth & development	At least every: • 3 mos in infants • 6 mos in older children
Renal	Measurement of serum sodium concentration to identify unrecognized hyperosmolality & early dehydration [1]	At least every: • 3 mos in infants • 6 mos in older children Annually in adults or only as needed, as determined on an individual basis
	Kidney ultrasound exam to monitor for hydronephrosis & megacystis	Annually

1. Urine output and urine specific gravity are useless as indicators of hydration status.

Agents/Circumstances to Avoid

Water intake must not be restricted.

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of at-risk infants as early as possible to allow for prompt diagnosis and treatment to reduce morbidity from hypernatremia, dehydration, and dilatation of the urinary tract. Evaluations can include:

- Molecular genetic testing if the *AVPR2* or *AQP2* pathogenic variant(s) in the family are known;
- In a newborn at risk for NDI who is not receiving breast milk: serum sodium, serum osmolality, and urinary osmolality can be performed while waiting for molecular results. Note: Infants at risk for NDI who are fed breast milk usually do not develop dehydration. Human milk has a low salt and protein content and therefore a low renal osmolar load.

Note: Autosomal dominant NDI is usually less severe than X-linked or autosomal recessive NDI. Therefore, genetic testing of sibs of children with autosomal dominant NDI may be performed at a later age (e.g., at 10 years younger than earliest diagnosis in the family).

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Heterozygous females with *AVPR2*-NDI (X-linked-NDI) may experience a mild increase in urinary output and associated thirst during pregnancy.

No pregnancies in women with *AQP2*-NDI have been reported to date.

Polyhydramnios is found in a minority of pregnancies in which the fetus is affected by NDI. In pregnant women with severe polyhydramnios and maternal discomfort, frequent amniotic fluid drainage may be necessary [Kollamparambil et al 2011].

Therapies Under Investigation

In a few individuals with a milder *AVPR2* pathogenic variant resulting in a partial response to AVP and DDAVP®, high doses of DDAVP® in combination with a thiazide diuretic significantly decreased urinary volume [Mizuno et al 2003, Bockenhauer et al 2010, Schernthaner-Reiter et al 2016]. Effectiveness and safety of this treatment in partial NDI need to be explored further.

Because of the known gastrointestinal safety of selective cyclooxygenase (COX)-2 inhibitors compared to nonselective COX inhibitors (e.g., indomethacin), use of these drugs has been proposed for the treatment of hereditary NDI. The effectiveness of a specific COX-2 inhibitor in decreasing free water losses was demonstrated in male infants with hereditary NDI [Pattaragarn & Alon 2003, Soylu et al 2005]. However, in view of the recent discovery that prolonged use of this COX-2 inhibitor can cause severe cardiac side effects, it is not appropriate to use these inhibitors in the treatment of hereditary NDI until it has been determined which of the specific COX-2 inhibitors are completely safe.

Because in vitro expression studies reveal that the majority of *AVPR2* pathogenic variants in X-linked NDI and all *AQP2* pathogenic variants in autosomal recessive NDI result in normal protein that is retained within the endoplasmic reticulum (ER), agents that restore plasma routing are under investigation as potential treatments. Promising agents for X-linked NDI are cell-permeable *AVPR2* antagonists or agonists that in vitro rescue the intracellular retention of several *AVPR2* mutants [Morello et al 2000, Tan et al 2003, Bernier et al 2004, Robben et al 2006, Robben et al 2007, Robben et al 2009, Erdem Tuncdemir et al 2019]. The feasibility of treatment with

these so-called pharmacologic "chaperones" has been tested in vivo; in individuals with *AVPR2*-NDI who have pathogenic missense variants, Bernier et al [2006] showed that treatment with a non-peptide V_{1a} receptor antagonist had beneficial effects on urine volume and osmolality starting a few hours after administration. However, the long-term effect of this drug could not be tested because the clinical development of this V_{1a} receptor antagonist was interrupted during the course of the study as a result of possible interference with the cytochrome P450 metabolic pathway. Confirmation of the putative beneficial effect of pharmacologic chaperones in hereditary NDI awaits further in vivo testing.

Other therapeutic approaches relying on AVP-independent trafficking of AQP2 to the apical membrane have been suggested and tested in vitro and/or in animal models. A comprehensive summary of these strategies is given in Jung & Kwon [2019]. One example of these AVP-independent approaches is activation of the cAMP pathway by stimulating other G-protein coupled receptors (GPCRs) such as the E-prostanoid receptors. By stimulation of the E-prostanoid receptor EP4, NDI symptoms were greatly reduced in a conditional *AVPR2*-deletion mouse model [Li et al 2009] as a consequence of raised AQP2 levels, most probably the result of cAMP production caused by EP4 stimulation. A similar effect was seen after stimulation of the EP2 receptor by the agonist butaprost [Olesen et al 2011]. The EP2 receptor is a more interesting candidate for treatment of NDI than the EP4 receptor since EP2 agonists have already been tested in clinical studies for other diseases and have shown promising results concerning safety issues. However, clinical trials in hereditary NDI have not yet been performed and are necessary to evaluate the effects and safety of EP2 agonists for this disorder.

Since metformin, an oral antidiabetic drug, had been shown to increase AQP2 phosphorylation and accumulation in the apical membrane in animal models, a trial in a small number of individuals with hereditary NDI was started in 2015. However, it was also quickly terminated because of lack of efficacy (ClinicalTrials.gov).

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Hereditary nephrogenic diabetes insipidus (NDI) may be transmitted in an X-linked manner (90% of families), an autosomal recessive manner (~9% of families), or an autosomal dominant manner (~1% of families).

X-Linked Inheritance – Risk to Family Members

Parents of a male proband

- The father of an affected male will not have NDI nor will he be hemizygous for the *AVPR2* pathogenic variant.
- In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote. Note: If a woman has more than one affected child and no other affected relatives and if the *AVPR2* pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism.
- If a male is the only affected family member (i.e., a simplex case), the mother may be a heterozygote or the affected male may have a *de novo AVPR2* pathogenic variant, in which case the mother is not a

heterozygote. About half of affected males represent simplex cases [Arthus et al 2000, Kobayashi et al 2010].

Sibs of a male proband. The risk to sibs depends on the genetic status of the mother:

- If the mother of the proband has an *AVPR2* pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will be heterozygotes and may have no symptoms or a variable degree of polyuria and polydipsia, or they may be as severely affected as males.
- If the proband represents a simplex case and if the *AVPR2* pathogenic variant cannot be detected in the leukocyte DNA of the mother, the recurrence risk to sibs is low but greater than that of the general population because of the possibility of maternal germline mosaicism.

Offspring of a male proband. Affected males transmit the *AVPR2* pathogenic variant to all of their daughters who will be heterozygotes and to none of their sons.

Other family members of a male proband. The proband's maternal aunts may be at risk of being heterozygotes for the pathogenic variant and the aunts' offspring, depending on their sex, may be at risk of being hemizygous for the pathogenic variant and affected or heterozygotes for the pathogenic variant and possibly developing clinical findings related to the disorder.

Note: Molecular genetic testing may be able to identify the family member in whom a *de novo* pathogenic variant arose, information that could help determine genetic risk status of the extended family.

Heterozygote detection in asymptomatic female relatives. Molecular genetic testing of at-risk asymptomatic female relatives to determine their genetic status is most informative if the *AVPR2* pathogenic variant has been identified in an affected family member.

- Identification of asymptomatic female heterozygotes requires either (a) prior identification of the *AVPR2* pathogenic variant in the family or, (b) if an affected male or female family member is not available for testing, molecular genetic testing first by sequence analysis, and if no pathogenic variant is identified, by gene-targeted deletion/duplication analysis.
- Females who are heterozygous for this X-linked disorder may have no symptoms or a variable degree of polyuria and polydipsia, or they may be as severely affected as males (see Clinical Description, **Heterozygotes for X-linked NDI**).

Autosomal Recessive Inheritance – Risk to Family Members

Parents of a proband

- The parents of an affected individual are obligate heterozygotes (i.e., presumed to be carriers of one autosomal recessive *AQP2* pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *AQP2* pathogenic variant and allow reliable recurrence risk assessment. (*De novo* variants are known to occur at a low but appreciable rate in autosomal recessive disorders [Jónsson et al 2017].)
- Heterozygotes are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for an autosomal recessive *AQP2* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with autosomal recessive NDI are obligate heterozygotes (carriers) for a pathogenic variant in *AQP2*.

Other family members. If both parents are known to be heterozygous for an autosomal recessive *AQP2* pathogenic variant, each sib of the proband's parents is at a 50% risk of being a carrier of an *AQP2* pathogenic variant.

Carrier detection. Molecular genetic carrier testing for at-risk relatives requires prior identification of the *AQP2* pathogenic variants in the family.

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- The proportion of individuals with autosomal dominant NDI who have an affected parent is unknown because the number of reported cases is small.
- A proband with autosomal dominant NDI may have the disorder as the result of a *de novo* pathogenic variant. The proportion of cases caused by *de novo* pathogenic variants is unknown.
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo AQP2* pathogenic variant.

Sibs of a proband. The risk to sibs of the proband depends on the clinical/genetic status of the proband's parents:

- If a parent of a proband is affected and/or is known to have the *AQP2* pathogenic variant identified in the proband, the risk to the sibs is 50%.
- If the proband has a known autosomal dominant *AQP2* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].

Offspring of a proband. Each child of an individual with autosomal dominant NDI is at a 50% risk of inheriting the *AQP2* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *AQP2* pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk, clarification of genetic status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are heterozygotes, or are at risk of being heterozygotes.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the NDI-causing pathogenic variant(s) have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and in families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)**
  Phone: 800-860-8747
  Email: healthinfo@niddk.nih.gov
  Diabetes Insipidus
- **NDI Foundation**
  Main Street
  P.O. Box 1390
  Eastsound WA 98245
  Phone: 888-376-6343
  Fax: 888-376-6356
  Email: info@ndif.org
  www.ndif.org
- **European Rare Kidney Disease Reference Network (ERKNet)**
  Phone: 49 0 6221 56-34191
  Email: contact@erknet.org
  www.erknet.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Hereditary Nephrogenic Diabetes Insipidus: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
AQP2	12q13.12	Aquaporin-2	AQP2 @ LOVD	AQP2	AQP2
AVPR2	Xq28	Vasopressin V2 receptor	AVPR2 @ LOVD	AVPR2	AVPR2

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Hereditary Nephrogenic Diabetes Insipidus (View All in OMIM)

107777	AQUAPORIN 2; AQP2
125800	DIABETES INSIPIDUS, NEPHROGENIC, 2, AUTOSOMAL; NDI2

Table B. continued from previous page.

300538	ARGININE VASOPRESSIN RECEPTOR 2; AVPR2
304800	DIABETES INSIPIDUS, NEPHROGENIC, 1, X-LINKED; NDI1

Molecular Pathogenesis

AVPR2 encodes vasopressin V_2 receptor, a member of the G protein-coupled receptor superfamily that preferentially activates the G protein G_s, resulting in the activation of adenylyl cyclase. The first step in the antidiuretic action of AVP is binding the vasopressin V_2 receptor on the basolateral membrane of collecting duct cells. This step initiates a cascade of events – receptor-linked activation of G protein (G_s), activation of adenylyl cyclase, production of cyclic adenosine-monophosphate (cAMP), and stimulation of protein kinase A (PKA) – that lead to the final step in the antidiuretic action of AVP: the exocytic insertion of specific water channels AQP2 into the luminal membrane, thereby increasing the water permeability of that membrane.

AQP2 encodes aquaporin-2 (AQP2), the vasopressin-sensitive water channel of the renal collecting duct cells. AQP2 is one of a family of water-transporting proteins that facilitates osmotically driven water movement across plasma cell membranes. Vasopression, acting through cAMP and PKA after binding to its V_2 receptor at the basolateral membrane of collecting duct cells, triggers the insertion of intracellular vesicles containing AQP2 proteins in the apical membrane, resulting in increased water permeability of this membrane. Phosphorylation of a PKA consensus site in AQP2 (p.Ser256) in the carboxy terminus is essential for AQP2 delivery to the apical membrane [van Balkom et al 2002]. AQP2 is constantly retrieved from the membrane by endocytosis, so that ongoing water permeability depends on delivery of AQP2 to the membrane, either by recycling or generation of new channels. In addition to PKA-mediated phosphorylation of AQP2, cAMP – via cAMP-responsive element binding protein-1 (CREB1) –increases transcription of AQP2.

Mechanism of disease causation. X-linked and autosomal recessive NDI occur through a loss-of-function mechanism. Autosomal dominant NDI occurs through a dominant-negative mechanism.

- **X-linked NDI.** Some *AVPR2* pathogenic variants interfere with proper transcription, mRNA processing, and translation, resulting in truncated proteins, which are rapidly degraded**.** Most *AVPR2* pathogenic variants result in a receptor that is trapped intracellularly and unable to reach the plasma membrane [Robben et al 2005]. A minority of abnormal receptors reach the cell surface but are unable to bind to AVP or to trigger an intracellular cAMP signal [Albertazzi et al 2000, Pasel et al 2000, Postina et al 2000, Inaba et al 2001].
- **Autosomal recessive NDI.** Abnormal AQP2 proteins show impaired transport from the endoplasmic reticulum to the plasma membrane, indicating that the major cause of autosomal recessive NDI is misrouting of abnormal AQP2.
- **Autosomal dominant NDI.** All abnormal AQP2 proteins found in autosomal dominant NDI appeared to be folded functional water channels that were sorted to other subcellular locations than normal AQP2 (e.g., late endosomes/lysosomes and the basolateral membrane). Because none of these abnormal proteins were misfolded, they were able to interact and form heterotetramers with wild type AQP2. As a result of this normal-abnormal interaction and the dominance of the missorting signals in the abnormal protein, the normal-abnormal complexes are also missorted (dominant-negative effect of pathogenic *AQP2* variants).

  One sixteenth of all tetramers formed are normal-AQP2-only tetramers, explaining the relatively milder phenotype in autosomal dominant NDI compared to autosomal recessive NDI [Kamsteeg et al 1999, Marr et al 2002b, Asai et al 2003, Kamsteeg et al 2003, de Mattia et al 2005].

Table 4. Hereditary Nephrogenic Diabetes Insipidus: Notable *AVPR2* Pathogenic Variants by Gene

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_000054.4 NP_000045.1	c.253G>A	p.Asp85Asn	Recurrent pathogenic variants [Bichet & Bockenhauer 2016, Stenson et al 2020]
	c.262G>A	p.Val88Met	
	c.337C>T	p.Arg113Trp	
	c.383A>C	p.Tyr128Ser	
	c.410G>A	p.Arg137His	
	c.500C>T	p.Ser167Leu	
	c.541C>T	p.Arg181Cys	
	c.604C>T	p.Arg202Cys	
	c.880G>C	p.Ala294Pro	
	c.945C>G	p.Ser315Arg	
	c.213G>A	p.Trp71Ter	Founder variants [Fujiwara & Bichet 2005, Stenson et al 2020]
	c.935T>A	p.Leu312Ter	
NM_000054.4 NP_000045.1	c.253G>A	p.Asp85Asn	Variants that result in partial NDI (See Genotype-Phenotype Correlations.)
	c.262G>A	p.Val88Met	
NM_000054.4	c.276A>G	--	
NM_000054.4 NP_000045.1	c.310C>T	p.Arg104Cys	
	c.383A>C	p.Tyr128Ser	
	c.482T>C	p.Leu161Pro	
	c.602G>A	p.Gly201Asn	
	c.818C>T	p.Thr273Met	
	c.931A>G	p.Met311Val	
	c.951C>A	p.Asn317Lys	
	c.950A>G	p.Asn317Ser	
	c.961A>T	p.Asn321Tyr	
	c.964C>T	p.Pro322Ser	
	c.987C>A	p.Ser329Arg	
	c.999_1001delCTC	p.Ser334del	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Chapter Notes

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Revision History

- 27 February 2020 (sw) Comprehensive update posted live
- 14 June 2012 (me) Comprehensive update posted live
- 4 March 2010 (me) Comprehensive update posted live
- 8 June 2007 (cd) Revision: deletion/duplication analysis no longer available on a clinical basis
- 8 March 2007 (me) Comprehensive update posted live
- 5 January 2005 (me) Comprehensive update posted live
- 28 February 2003 (me) Comprehensive update posted live
- 12 February 2000 (pb) Review posted live
- 13 January 1999 (rw) Original submission

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