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Dent Disease

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Summary

Clinical characteristics

Dent disease, an X-linked disorder of proximal renal tubular dysfunction, is characterized by low molecular weight (LMW) proteinuria, hypercalciuria, and at least one additional finding including nephrocalcinosis, nephrolithiasis, hematuria, hypophosphatemia, chronic kidney disease (CKD), and evidence of X-linked inheritance. Males younger than age ten years may manifest only LMW proteinuria and/or hypercalciuria, which are usually asymptomatic. Thirty to 80% of affected males develop end-stage renal disease (ESRD) between ages 30 and 50 years; in some instances ESRD does not develop until the sixth decade of life or later. The disease may also be accompanied by rickets or osteomalacia, growth restriction, and short stature. Disease severity can vary within the same family. Males with Dent disease 2 (caused by pathogenic variants in *OCRL*) may also have mild intellectual disability, cataracts, and/or elevated muscle enzymes. Due to random X-chromosome inactivation, some female carriers may manifest hypercalciuria and, rarely, renal calculi and moderate LMW proteinuria. Females rarely develop CKD.

Diagnosis/testing

The diagnosis is established in a male proband with the typical clinical findings and a family history consistent with X-linked inheritance who has a pathogenic variant in either *CLCN5* (known as Dent disease 1) or in *OCRL* (known as Dent disease 2). Heterozygous females are usually asymptomatic, but some exhibit LMW proteinuria and hypercalciuria, and others with kidney stones have also been described. Heterozygous females are most likely to be identified by familial molecular genetic testing related to a male proband.

Management

Treatment of manifestations: The primary goals of treatment are to decrease hypercalciuria, prevent kidney stones and nephrocalcinosis, and delay the progression of CKD. Interventions aimed at decreasing hypercalciuria and preventing kidney stones and nephrocalcinosis have not been tested in randomized controlled trials. Although

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thiazide diuretics can decrease urinary calcium excretion in boys with Dent disease, side effects limit their use. The effectiveness of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in preventing or delaying further loss of kidney function in children with proteinuria is unclear. Renal replacement therapy is necessary in those with ESRD.

Prevention of secondary complications: Bone disease, when present, responds to vitamin D supplementation and phosphorus repletion. Growth failure may be treated with human growth hormone without adversely affecting kidney function.

Surveillance: Monitor at least annually urinary calcium excretion, renal function (glomerular filtration rate), and the parameters used to stage CKD (i.e., blood pressure, hematocrit/hemoglobin, and serum calcium and phosphorous concentrations). Monitor more frequently when CKD is evident.

Agents/circumstances to avoid: Exposure to potential renal toxins (nonsteroidal anti-inflammatory drugs, aminoglycoside antibiotics, and intravenous contrast agents).

Evaluation of relatives at risk: Clarify the genetic status of at-risk male relatives either by molecular genetic testing (if the pathogenic variant in the family is known) or by measurement of urinary excretion of low molecular weight proteins (LMWPs).

Genetic counseling

Dent disease is inherited in an X-linked manner. The father of an affected male will not have the disease nor will he be hemizygous for the pathogenic variant. If the mother of the proband has a 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 carriers and will usually not be significantly affected. Affected males pass the pathogenic variant to all of their daughters (who become carriers) and none of their sons. Carrier testing for at-risk female relatives and prenatal and preimplantation genetic testing are possible if the pathogenic variant in the family has been identified.

Diagnosis

Suggestive Findings

Dent disease **should be suspected** in an individual with the three criteria below in the absence of other known causes of proximal tubule dysfunction [Hoopes et al 2004, Edvardsson et al 2013]. Note: A possible diagnosis of Dent disease is considered if LMW proteinuria and at least one other criterion are present.

1. LMW proteinuria (the pathognomonic finding of Dent disease) at least five times (and often 10x) above the upper limit of normal. Commonly screened LMW proteins are retinol binding protein and α1 microglobulin.

   Note: β2 microglobulin is also often measured to screen for LMW proteinuria. To the authors' knowledge, no known cases of Dent disease have been missed using this screening method; however, its use is cautioned since it is not stable in even minimally acidic urine [Davey & Gosling 1982] and thus could theoretically yield a false negative result.

2. Hypercalciuria
   - **Adults (age >18 years).** >4.0 mg calcium (0.1 mmol) /kg in 24 hours or >0.25 calcium/creatinine mg/mg (0.57 mmol/mmol) in spot urine
   - **Children.** See Table 1 for 95th percentile calcium/creatinine mg/mg reference values in random urine collections.

3. At least one of the following:
    - Nephrocalcinosis (diffuse renal calcification)
    - Nephrolithiasis (kidney stones; composed of calcium oxalate and/or calcium phosphate)
    - Hematuria (microscopic or macroscopic blood in the urine)
    - Hypophosphatemia (low blood phosphorous concentration)
    - Chronic kidney disease (CKD); measured or estimated glomerular filtration rate (GFR) that is below the normal limits for age
    - Family history consistent with X-linked inheritance

Table 1. Calcium/Creatinine (mg/mg) Reference Values in Children (age <18 yrs)

Age (yrs)	95th percentile
0-1	<0.81
1-2	<0.56
2-3	<0.50
3-5	<0.41
5-7	<0.30
7-10	<0.25
10-14	<0.24
14-17	<0.24

In random urine collections
Matos et al [1997]

Establishing the Diagnosis

Male proband. The diagnosis of Dent disease **is established** in a male proband with the identification of a hemizygous pathogenic variant in either *CLCN5* (Dent disease 1) or *OCRL* (Dent disease 2) by molecular genetic testing (see Table 2).

Female proband. Female carriers, who are heterozygous for a pathogenic variant in either *CLCN5* (Dent disease 1) or *OCRL* (Dent disease 2), are usually asymptomatic. However, some exhibit LMW proteinuria and hypercalciuria, and others with kidney stones have also been described [Hoopes et al 1998]. Rare females with CKD have been reported. Although biallelic pathogenic variants could occur, it has been assumed that any manifestations are due to skewed X-chromosome inactivation, and many of these symptomatic carriers have other unaffected male children [Dinour et al 2009].

Molecular testing approaches can include **single-gene testing**, use of a **multigene panel**, and **more comprehensive genomic testing**.

Single-gene testing can be considered:

- **For males or females.** Sequence analysis of *CLCN5* is usually performed first; if a pathogenic variant is not identified, sequence analysis of *OCRL* is performed next.
- **In a female.** If a pathogenic variant is not detected in either gene by sequence analysis, consider gene-targeted deletion/duplication analysis of *CLCN5*, followed by *OCRL*.

A multigene panel that includes *CLCN5*, *OCRL*, and other genes of interest (see Differential Diagnosis) can also be considered as a first step. 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 multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which

multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

More comprehensive genomic testing (when available) including exome sequencing and genome sequencing may be considered. Such testing may provide or suggest a diagnosis not previously considered (e.g., mutation of a different gene or genes that results in a similar clinical presentation).

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 2. Molecular Genetic Testing Used in Dent Disease

Gene [1]	Proportion of Dent Disease Attributed to Pathogenic Variants in Gene [2]	Proportion of Pathogenic Variants [3] Detectable by Method	
		Sequence analysis [4]	Gene-targeted deletion/duplication analysis [5]
CLCN5	60%	~92%	~8% [6]
OCRL	15%	~95%	~5% [7]
Unknown [8]		NA	

1. See Table A. Genes and Databases for chromosome locus and protein.
2. Claverie-Martín et al [2011]
3. See Molecular Genetics for information on allelic 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. Of the 245 different *CLCN5* pathogenic variants known to cause Dent disease 1 identified to date, 7.8% are complex rearrangements (large deletions, insertions, or indels) (HGMD 2016).
7. Of the 42 different *OCRL* pathogenic variants known to cause Dent disease 2 identified to date, 4.7% are multiexon deletions (HGMD 2016).
8. In a cohort of affected individuals, approximately 18% (20/110) of males with a Dent disease phenotype did not have a pathogenic variant identified in *CLCN5* and *OCRL1* [Authors, unpublished observation].

Clinical Characteristics

Clinical Description

Presentation. In the early stages of Dent disease, children (typically <~10 years) may manifest only low molecular weight (LMW) proteinuria and/or hypercalciuria, both of which are usually asymptomatic [Claverie-Martín et al 2011]. In the asymptomatic individual, detection of proteinuria may occur on a urinalysis done for screening or other purposes.

LMW proteinuria and/or hypercalciuria can be accompanied by stone disease or nephrocalcinosis, and less frequently by other manifestations of proximal tubular dysfunction including aminoaciduria, phosphaturia, and glycosuria [Hodgin et al 2008].

- Hypercalciuria is typically accompanied by elevated or high-normal levels of 1,25-dihydroxyvitamin D, and depressed or low-normal levels of intact parathyroid hormone (PTH) [Scheinman 1998].

- Hypercalciuria largely or completely resolves with dietary calcium restriction, suggesting that the major component of hypercalciuria is intestinal hyperabsorption.

Renal biopsy. Since patients often present with CKD and proteinuria, a renal biopsy is often obtained. Findings consistent with Dent disease include nephrocalcinosis, interstitial fibrosis, and focal segmental glomerulosclerosis and/or focal global glomerulosclerosis [Copelovitch et al 2007, Frishberg et al 2009]. However, a kidney biopsy alone cannot definitively diagnose Dent disease, and is not required to make the diagnosis.

Other features. The disease may also be accompanied by rickets or osteomalacia, growth restriction, and short stature [Bökenkamp et al 2009].

Short stature is common, although not usually profound in Dent disease 1. In one series height was -0.58 SD of the age-appropriate mean value for Dent disease 1, but more significantly reduced at -2.10 SD for Dent disease 2 [Bökenkamp et al 2009].

Disease progression. An estimated 30%-80% of affected males develop end-stage renal disease (ESRD) between ages 30 and 50 years; in some instances ESRD does not develop until the sixth decade or later [Wrong et al 1994, Lloyd et al 1997]. Of note, deterioration of renal function can occur even in the absence of nephrocalcinosis. Disease severity can vary even within the same family.

Dent Disease 1 (caused by pathogenic variants in *CLCN5*)

The renal phenotypic findings in Dent 1 vary considerably.

Scheinman et al [2000] reported a family in which all affected individuals had the same *CLCN5* missense variant (c.1517G>A; p.Gly506Glu) and the Dent disease phenotype ranged from severe in several members to isolated hypercalciuria without proteinuria, nephrocalcinosis, or chronic kidney disease (CKD) in one individual. It is not currently known how often an individual with a *CLCN5* pathogenic variant manifests only asymptomatic hypercalciuria and/or proteinuria without developing CKD.

Some individuals with a pathogenic variant in *CLCN5* and a family history of Dent disease developed ESRD with proteinuria, but without other typical features of Dent disease (i.e., kidney stones, nephrocalcinosis, and bone disease) [Copelovitch et al 2007, Frishberg et al 2009]. Renal biopsy revealed focal segmental glomerulosclerosis (FSGS) and focal global glomerulosclerosis. The findings in these individuals illustrate that the spectrum of Dent disease includes persons with proteinuria and a biopsy consistent with FSGS and that the diagnosis is only considered when evaluations for LMW proteinuria and/or hypercalciuria are performed.

It is currently unclear whether Dent disease will be diagnosed among a larger number of individuals with clinical FSGS, although it is now known that focal global sclerosis is very common in Dent disease [Wang et al 2016] and instances of Dent disease being misdiagnosed as FSGS continue to be reported [Fervenza 2013].

Dent Disease 2 (caused by pathogenic variants in *OCRL*)

To date, 42 pathogenic variants have been identified in males with a Dent disease 2 phenotype and have been reported in the literature.

In addition to the Dent disease-related renal findings, individuals with Dent disease 2 may also have:

- Mild intellectual disability
- Cataracts (rare)
- Elevated muscle enzymes (LDH, CK)

Symptomatic Females

There have been occasional reports of renal calculi and moderate LMW proteinuria when carrier females have been studied in large kindreds. Rarely, heterozygous females manifest clinically significant kidney disease resulting from skewed X-chromosome inactivation. One female from a family with Dent disease developed renal insufficiency and nephrocalcinosis; however, she did not have molecular genetic testing [Wrong et al 1994]. Another carrier female with a known pathogenic variant, developed symptomatic nephrolithiasis and stage 3B CKD by age 65 [Hoopes et al 1998].

Although not reported in the literature, a symptomatic female could have an X-chromosome abnormality (e.g., absence of one X chromosome [45,X] and a *CLCN5* or *OCRL* pathogenic variant on the remaining X chromosome).

Although not reported in the literature, a female with biallelic pathogenic variants in *CLCN5* or *OCRL* (inherited from a carrier mother and an affected father) would be predicted to manifest clinically significant kidney disease.

Genotype-Phenotype Correlations

CLCN5. Genotype-phenotype correlations have yet to be established.

OCRL. It has been suggested that pathogenic variants in *OCRL* are associated with a phenotypic spectrum ranging from Lowe syndrome at the severe end (see Genetically Related Disorders) to Dent disease 2 at the mild end.

Note: Although the renal tubulopathy in Lowe syndrome (which is mainly characterized by altered protein reabsorption) and Dent disease is similar, it is generally milder in Dent disease. Of note, this milder Dent disease phenotype could not be attributed to lesser protein expression or enzyme activity.

Frameshift and nonsense *OCRL* variants associated with Dent disease 2 have been mapped to exons different from those causing Lowe syndrome [Hichri et al 2011]; however, *OCRL* missense and splicing variants and in-frame deletions that cause these two disorders do not map exclusively to specific gene regions.

- Frameshift and nonsense variants associated with Dent disease 2 are in the first seven exons. Missense variants associated with Dent disease 2 are most often, but not exclusively, located in exons 9-15, which encode the catalytic phosphatase domain.
- Frameshift and nonsense variants associated with Lowe syndrome are located in the middle and later regions of the gene, exons 8-23, which encode the catalytic phosphatase and the Rho-GAP-like domain [Tosetto et al 2009, Hichri et al 2011].

Prevalence

To date about 250 affected families have been reported [Devuyst & Thakker 2010]. However, the wide variability of clinical presentation in Dent disease and (in some cases) absence of family history make diagnosis difficult; thus, the disorder is likely underdiagnosed.

Genetically Related (Allelic) Disorders

CLCN5. No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *CLCN5.*

OCRL. Pathogenic variants in *OCRL* are known to cause Lowe syndrome (oculocerebrorenal syndrome), characterized by involvement of the eyes, central nervous system, and kidneys. Dense congenital cataracts are found in all affected boys and infantile glaucoma in approximately 50%. Generalized central hypotonia noted at

birth may slowly improve with age, but normal motor tone and strength are never achieved and motor milestones are delayed. Almost all affected males have some degree of intellectual disability (ID): 10%-25% function in the low-normal or borderline range, approximately 25% in the mild-to-moderate range of ID, and 50%-65% in the severe-to-profound range of ID. Affected males have profound short stature and varying degrees of proximal renal tubular dysfunction of the Fanconi type, including bicarbonate wasting and renal tubular acidosis, phosphaturia with hypophosphatemia, renal rickets, aminoaciduria, LMW proteinuria, sodium and potassium wasting, and polyuria. Fanconi syndrome is usually not clinically apparent in the first few months of life, but symptoms may appear by age six to 12 months. Glomerulosclerosis associated with chronic tubular injury usually results in slowly progressive chronic renal failure and end-stage renal disease (ESRD) after age ten to 20 years. Molecular genetic testing of *OCRL* detects pathogenic variants in approximately 95% of affected males and carrier females.

Given the finding of *OCRL* pathogenic variants in about 15% of individuals with Dent disease, it has been suggested that pathogenic variants in *OCRL* are associated with a phenotypic spectrum ranging from Lowe syndrome at the severe end to Dent disease 2 at the mild end.

Differential Diagnosis

The differential diagnosis of Dent disease includes other causes of proximal tubular dysfunction.

Renal Fanconi syndrome. The presence of more generalized proximal tubular dysfunction (glucosuria, amino aciduria, renal tubular acidosis) would suggest the possibility of a renal Fanconi syndrome. Causes of renal Fanconi syndromes can be hereditary (e.g., Wilson disease, glycogen storage disease) or acquired (e.g., exposure to heavy metal, toluene, or cisplatin).

Glomerular disease. Some individuals with Dent disease 1 with more severe proteinuria were found to have focal segmental glomerulosclerosis (FSGS) or global sclerosis on kidney biopsy [Copelovitch et al 2007, Frishberg et al 2009]. Most cases of FSGS are idiopathic, but FSGS can be seen in association with obesity or progressive chronic kidney disease of any cause. FSGS associated with Dent disease can be identified by the prominent low molecular weight (LMW) proteinuria and confirmed by genetic testing.

Donnai-Barrow syndrome, caused by biallelic pathogenic variants in *LRP2*, which encodes a 600-kd megalin protein, bears some similarities to Dent disease [Kantarci et al 2007]. Clinical manifestations of this rare disorder include hypertelorism, large anterior fontanelle, agenesis of the corpus callosum, and congenital diaphragmatic hernia [Pober et al 2009]. LMW proteinuria and high myopia have been consistently observed in these patients [Pober et al 2009]. However, other typical findings of Dent disease, including nephrolithiasis, nephrocalcinosis, hypercalciuria, chronic kidney disease, or bone disease, have not been reported to date.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with Dent disease, the following evaluations are recommended if they have not already been completed:

- Assessment of renal function (measured or estimated GFR; urine protein excretion)
- Assessment for nephrocalcinosis and kidney stones by imaging studies, typically low-dose noncontrast CT scan or ultrasound

  For those with evidence of renal stones or nephrocalcinosis, urine studies for kidney stone risk factors (including calcium and citrate excretion)

- Assessment of risk for bone disease (serum calcium, phosphorus, and alkaline phosphatase)

  Note: Elevated alkaline phosphatase has been reported in all individuals with clinical rickets [Wrong et al 1994].

  For those with evidence of bone disease and/or growth delay, more complete assessment of bone health (i.e., serum vitamin D concentration and PTH level; x-ray of long bones for evidence of osteomalacia)

- In children, evaluation of stature using standard growth charts. If short stature is present, evaluation by an endocrinologist for the possibility of growth hormone therapy can be considered.
- Evaluation for intellectual disability
- Careful eye exam for cataracts, especially if there is any concern for visual impairment
- Consultation with a clinical geneticist and/or genetic counselor
- Although it is not necessary to specifically screen for the possibility, elevated serum muscle enzyme levels are often seen in patients with Dent disease.

Treatment of Manifestations

No guidelines have been established for treatment of Dent disease. The primary goals of treatment are to decrease hypercalciuria, prevent kidney stones and nephrocalcinosis, and delay the progression of chronic kidney disease (CKD).

Interventions aimed at decreasing hypercalciuria and preventing kidney stones and nephrocalcinosis have not been tested in randomized controlled trials. Thiazide diuretics in doses greater than 0.4 mg/kg/day have decreased urinary calcium excretion by more than 40% in boys with Dent disease [Raja et al 2002, Blanchard et al 2008]. However, frequent side effects included hypokalemia, volume depletion, and cramping. Careful dosing and close monitoring for these side effects are necessary.

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) have been used in children with proteinuria to prevent or delay further loss of kidney function; however, their effectiveness has not been clear. Although treatment with ACE inhibitors or ARB may be somewhat beneficial for individuals with focal segmental glomerulosclerosis (FSGS), they are not known to be helpful for the focal global glomerulosclerosis that is associated with Dent disease, and angiotensin blockade is not thought to significantly affect LMW proteinuria or any potential ill effects of it. A kidney biopsy to exclude other causes of proteinuria and CKD is reasonable.

While a high-citrate diet has been shown to slow progression of CKD in *Clcn5* knockout mice [Cebotaru et al 2005] and has been used in the treatment of Dent disease, no human trials have proven its effectiveness. Note: Citrate is commonly used in Lowe syndrome to treat the metabolic acidosis resulting from renal tubular acidosis.

If males with Dent disease progress to ESRD, renal replacement therapy becomes necessary. Hemodialysis, peritoneal dialysis, and renal transplantation are appropriate options. Because Dent disease manifestations are largely localized in the kidney, the disease will not recur.

School-aged individuals with mild intellectual disability will benefit from individual educational plans and special educational services.

Cataracts, if present, are treated in a standard manner.

Prevention of Secondary Complications

Bone disease has not been a prominent component of Dent disease in a recent case series based in France [Blanchard et al 2016] but was more prominent in a Chinese population [Li et al 2016]; whether this reflects environmental or genetic effects is not known. When present it has been reported to respond to vitamin D supplementation and phosphorus repletion in those with elevated serum alkaline phosphatase levels [Wrong et al 1994].

Limited reports suggest that growth failure can be successfully treated with human growth hormone without adversely affecting kidney function [Sheffer-Babila et al 2008].

Surveillance

Renal function measured as glomerular filtration rate (GFR) should be monitored at least annually together with the parameters used to stage chronic kidney disease (i.e., blood pressure, hematocrit/hemoglobin, urinary calcium excretion, and serum calcium and phosphorus concentrations).

More frequent visits and monitoring for complications of chronic kidney disease (i.e., hypertension, anemia, and secondary hyperparathyroidism) as well as consideration of intensified treatment of cardiovascular risk factors may be indicated if GFR falls below 45 mL/min/1.73 m^2 (CKD Stage 3B).

Agents/Circumstances to Avoid

Exposure to potential renal toxins (nonsteroidal anti-inflammatory drugs, aminoglycoside antibiotics, and intravenous contrast agents) should be avoided, especially if renal function is below 45 mL/min/1.73 m^2 (CKD stage 3B).

Evaluation of Relatives at Risk

It is appropriate to evaluate male relatives at risk for Dent disease 1 (caused by mutation of *CLCN5*) or Dent disease 2 (caused by mutation of *OCRL*) in order to identify as early as possible those who would benefit from initiation of treatment and preventive measures.

- If the pathogenic variant in the family is known, molecular genetic testing can be used to clarify the genetic status of at-risk relatives.
- If the pathogenic variant in the family is not known, measurement of urinary excretion of low molecular weight proteins (e.g., alpha 1 microglobulin, retinol binding protein) is a sensitive and specific test.

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

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

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

Dent disease is inherited in an X-linked manner.

Risk to Family Members

Parents of a male proband

- The father of an affected male will not have the disease nor will he be hemizygous for a *CLCN5* or *OCRL* pathogenic variant; therefore, he does not require further evaluation/testing.
- In a family with more than one affected individual, the mother of an affected male is an obligate carrier. Note: If a woman has more than one affected child and no other affected relatives and if the 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 carrier or the affected male may have a *de novo* pathogenic variant and, thus, the mother is not a carrier. The frequency of *de novo* pathogenic variants is not known.

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

- If the mother of the proband has a *CLCN5* or *OCRL* 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 carriers and will usually not be significantly affected. However, due to the possibility of skewed X-chromosome inactivation, some female heterozygotes may manifest clinically significant kidney disease (see Clinical Description, Symptomatic Females).
- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is slightly greater than that of the general population (though still <1%) because of the possibility of maternal germline mosaicism.

Offspring of a male proband. Affected males transmit the pathogenic variant to:

- All of their daughters, who will be heterozygotes and, in rare cases, manifest clinically significant kidney disease (see Clinical Description, Symptomatic Females);
- None of their sons.

Other family members. The proband's maternal aunts may be at risk of being carriers and the aunts' offspring, depending on their sex, may be at risk of being carriers or of being affected.

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 (Carrier) Detection

Molecular genetic testing. Carrier testing for at-risk female relatives is possible if the *CLCN5* or *OCRL* pathogenic variant in the family has been identified.

LMW proteins are often found to be elevated in female carriers; however, the sensitivity and specificity of such testing for carrier detection have not been established.

Related Genetic Counseling Issues

See 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 carrier 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 carriers, or are at risk of being carriers.

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).

Prenatal Testing and Preimplantation Genetic Testing

Once the *CLCN5* or *OCRL* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While use of prenatal testing is 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.

- **Metabolic Support UK**
  United Kingdom
  Phone: 0845 241 2173
  metabolicsupportuk.org

- **Kidney Foundation of Canada**
  Canada
  Phone: 514-369-4806; 800-361-7494
  Email: info@kidney.ca
  www.kidney.ca

- **National Kidney Foundation**
  Phone: 855-NKF-CARES; 855-653-2273
  Email: nkfcares@kidney.org
  kidney.org

- **Rare Kidney Stone Consortium Registry**
  Phone: 800-270-4637 (toll-free)
  Email: hyperoxaluriacenter@mayo.edu
  Rare Kidney Stone Consortium Registry

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. Dent Disease: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
CLCN5	Xp11.23	H(+)/Cl(-) exchange transporter 5	CLCN5 @ LOVD	CLCN5	CLCN5
OCRL	Xq26.1	Inositol polyphosphate 5-phosphatase OCRL	OCRL @ LOVD at NCBI	OCRL	OCRL

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 Dent Disease (View All in OMIM)

300008	CHLORIDE CHANNEL 5; CLCN5
300009	DENT DISEASE 1; DENT1
300535	OCRL INOSITOL POLYPHOSPHATE-5-PHOSPHATASE; OCRL
300555	DENT DISEASE 2; DENT2

CLCN5

Gene structure. The *CLCN5* reference sequence NM_000084.2 has 12 exons. Alternatively spliced transcript variants encoding different isoforms have been found for this gene (see Table A, **Gene**). The genomic reference sequence is NG_007159.2.

Pathogenic variants. To date, 228 different *CLCN5* pathogenic variants are known to cause Dent disease type 1 (HGMD 2016); the majority of these are private: approximately74% of all pathogenic variants have been found in only one family; ~53% are truncating, 39% non-truncating, and 7% complex rearrangements (large deletions, insertions, or indels).

More than 100 different nonsense or missense variants, insertions or deletions, and splicing variants in *CLCN5* have been reported [Devuyst & Thakker 2010, Claverie-Martín et al 2011], meaning that the spectrum of *CLCN5* pathogenic variants is highly varied and *de novo* pathogenic variants are frequent.

CLCN5 pathogenic variants are scattered throughout the coding sequence of the gene and generate truncated or absent clC-5 channels in approximately 60% of cases.

Most *CLCN5* pathogenic variants have not yet been fully investigated functionally. Nine that were functionally investigated [Grand et al 2011] were classed according to their functional consequences (see Table 3):

- Group 1. Pathogenic variants that lead to the retention of the mutated protein in the endoplasmic reticulum
- Group 2. Pathogenic variants that generate a functionally defective protein devoid of electric currents and resulting in failure of endosomal acidification
- Group 3. Pathogenic variants that lead to abnormal subcellular localization of the mature protein
- Group 4. Pathogenic variants that generate a protein normally localized at the plasma membrane but with reduced membrane currents

Table 3. *CLCN5* Pathogenic Variants Discussed in This *GeneReview*

Variant Group Classification	DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
Group 1 [1]	c.731C>T	p.Ser244Leu	NM_000084.2 NP_000075.1
	c.815A>G	p.Tyr272Cys	
Group 2 [1]	c.674T>C	p.Leu225Pro	
	c.1020C>A	p.Asn340Lys	
	c.1537G>A	p.Gly513Arg	
Group 3 [1]	c.779G>T	p.Gly260Val	
	c.834G>C	p.Leu278Phe	
	c.1637A>G	p.Lys546Glu	
	c.1639T>G	p.Trp547Gly	
Unknown	c.1517G>A	p.Gly506Glu	

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.
1. Grand et al [2011]

Normal gene product. The clC-5 isoform NP_000075.1, encoded by transcript NM_000084.2, comprises 746 amino acids. The protein is a voltage-dependent two chloride/proton exchanger. In human kidney, it is expressed in proximal tubular cells, in alpha and beta intercalated cells of the cortical collecting tubule, and in the thick ascending limb of Henle's loop. The protein localizes in the intracellular subapical endosomes that are involved in the reabsorption of low molecular weight proteins filtered through the glomerulus, which are normally completely reabsorbed [Smith et al 2009]. The function of the protein is to modulate the chloride concentration during proton transport [Carraro-Lacroix et al 2010, Novarino et al 2010].

Abnormal gene product. The abnormal gene products can be either shorter due to the presence of pathogenic truncating variants (nonsense or frameshifts or large DNA rearrangements) or functionally abnormal when an amino acid substitution is present. Defective activity of the protein leads to abnormal protein trafficking and reabsorption. How this causes renal failure and stones is not understood.

OCRL

Gene structure. The gene comprises 5,152 nucleotide base pairs and 24 exons, of which 23 are coding. For a detailed summary of gene and protein information, see Table A, **Gene**.

Benign variants. One small (24-bp) alternatively spliced exon, 18a, encodes an additional eight amino acids and is expressed in neurologic tissues [Nussbaum et al 1997, Nussbaum & Suchy 2001]. It has been hypothesized that brain (but not kidney) can express an exon 8-15 splice variant [Shrimpton et al 2009] (see Lowe Syndrome).

Pathogenic variants. Forty-two different pathogenic variants are known to cause Dent disease type 2; however, this number may be over- or underestimated due to the phenotypic overlap of Dent disease type 2 with Lowe syndrome. The majority (~85%) of pathogenic variants are private.

As detailed in Genotype-Phenotype Correlations, *OCRL* frameshift and nonsense variants associated with Dent disease 2 have been mapped to different exons from those causing Lowe syndrome [Hichri et al 2011]. Note that missense, splicing, and in-frame deletion variants causative of either disease do not map exclusively to specific gene regions. Missense variants associated with Dent disease 2 are most often (but not exclusively) located in exons 9-15, which encode the catalytic phosphatase domain. One deletion of exons 3 and 4 was reported in an

affected male [Hichri et al 2011]. Of the known *OCRL* Dent disease 2-causing variants, 47.5% are truncating, 47.5% non-truncating, and 5% multiexon deletions.

Normal gene product. *OCRL* encodes a phosphatidylinositol 4,5-biphosphate 5-phosphatase (OCRL-1), comprising 884 amino acids, which localizes in the *trans* Golgi network and the lysosomes. The protein acts as a phosphatase and removes a 5' phosphate group from the phosphatidilinositol-4,5-biphosphate, a second messenger that plays a role in the regulation of the vesicular trafficking.

Abnormal gene product. The abnormal gene products can be either shorter due to the presence of truncating variants (nonsense or frameshifts or large DNA rearrangements) or functionally abnormal when an amino acid substitution is present.

The mechanism by which loss of OCRL-1 protein function leads to disease has not yet been elucidated. However, OCRL-1 protein was localized to early endosomes and the *trans* Golgi apparatus, and clathrin coated transport intermediates [Choudhury et al 2005, Ghanekar & Lowe 2005]. Depletion of OCRL-1 perturbs trafficking at the TGN/endosome interface, suggesting a role in regulating transport between these compartments.

The abnormal vesicular trafficking shared with the CLC-5 protein may explain the overlapping clinical features associated with pathogenic variants in *CLCN5* and *OCRL*.

Chapter Notes

Author Notes

Rare Kidney Stone Consortium

The Rare Kidney Stone Consortium is a resource for patients, their families, and physicians. The center facilitates collaborative research to provide better understanding of Dent Disease and other rare types of kidney stones. For more information about Dent disease, please email the Rare Kidney Stone Consortium at rarekidneystones@mayo.edu or call 800-270-4637.

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