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Cystinosis

[Includes: *Nephropathic Cystinosis, Intermediate Cystinosis, Non-Nephropathic Cystinosis*]

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Summary

Disease characteristics. **Nephropathic cystinosis** in untreated children is characterized by renal tubular Fanconi syndrome, poor growth, hypophosphatemic rickets, impaired glomerular function, and accumulation of cystine crystals in almost all cells, leading to tissue destruction. The typical untreated child has short stature, light complexion, rickets, and photophobia. Growth failure is generally noticed between ages six and nine months; signs of renal tubular Fanconi syndrome (polyuria, polydipsia, dehydration, and acidosis) appear as early as age six months; corneal crystals can be present before age one year and are always present after age 16 months. Prior to the use of renal transplantation and cystine-depleting therapy, the life span in nephropathic cystinosis was no longer than ten years. With

these therapies, affected individuals can survive at least into the mid forties or fifties with satisfactory quality of life. **Intermediate cystinosis** is characterized by all the typical manifestations of nephropathic cystinosis, but onset is at a later age. Renal glomerular failure occurs in all untreated affected individuals, usually between ages 15 and 25 years. **Non-nephropathic cystinosis** is characterized only by photophobia resulting from corneal cystine crystal accumulation.

Diagnosis/testing. The diagnosis of cystinosis is established by documenting: (1) renal tubular Fanconi syndrome, i.e., increased urinary losses of essential nutrients including electrolytes (sodium, potassium, bicarbonate), minerals (calcium, phosphate, magnesium), glucose, amino acids, carnitine, and water; (2) typical cystine crystals in the cornea on slit lamp examination; and (3) increased cystine content of leukocytes. Identification of two mutations in *CTNS*, the only gene known to be associated with cystinosis, is confirmatory.

Management. *Treatment of manifestations:* Renal tubular Fanconi syndrome is treated by replacement of renal losses; phosphate and vitamin D supplements prevent and treat severe hypophosphatemic rickets. Nutrition must be adequate to minimize failure to thrive in infants. Cysteamine hydrochloride eyedrops dissolve corneal crystals within months and relieve photophobia within weeks. Required hormone replacement therapies may include: L-thyroxine, insulin, growth hormone, and/or testosterone. Physical and speech therapy is helpful for the muscle deterioration and swallowing difficulties of older individuals. *Prevention of primary manifestations:* Therapy with cystine-depleting agents begun just after birth or as soon as the diagnosis is made can attenuate the renal tubular Fanconi syndrome and significantly slow the progression of glomerular damage; however, renal damage present at the time of diagnosis is irreversible. With optimal symptomatic and cystine-depleting therapy affected individuals grow at a normal rate but do not recover lost height unless human growth hormone is administered. *Surveillance:* evaluation by a nephrologist every 3-6 months depending upon the severity of renal impairment; ophthalmologic evaluation every 1-2 years; assessment of bone mineralization throughout the disease course; every 2-3 years fasting blood glucose concentration and testosterone concentration (in males starting before puberty); routine monitoring for late-onset complications in poorly treated adults. *Agents/circumstances to avoid:* dehydration; sun exposure if photophobia is

present. *Testing of relatives at risk:* Biochemical and/or molecular genetic testing (if the mutation status of the proband is known) allows early diagnosis and treatment.

Genetic counseling. Cystinosis is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has 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. Carrier testing for at-risk relatives and prenatal diagnosis for pregnancies at increased risk are possible when both disease-causing mutations have been identified in the family. For pregnancies at increased risk for nephropathic cystinosis, prenatal testing is also available biochemically, based upon elevated cystine concentration in both chorionic villi and amniocytes.

Diagnosis

Clinical Diagnosis

Nephropathic cystinosis (classic/infantile/early onset). The diagnosis of classic nephropathic cystinosis depends upon the findings of renal tubular Fanconi syndrome in the untreated child in the first year of life, growth retardation after age six months, and progressive deterioration of renal glomerular function to end-stage renal disease (ESRD) over the first ten years of life [[Gahl et al 2001](#), [Gahl et al 2002](#)].

Renal tubular Fanconi syndrome is established in the untreated child by documenting increased urinary losses of essential nutrients [[Gahl et al 2001](#), [Gahl et al 2002](#)]. These include electrolytes (sodium, potassium, bicarbonate), minerals (calcium, phosphate, magnesium), glucose, amino acids, tubular protein including β 2-microglobulin, and water. These renal losses result in symptoms such as hypophosphatemic rickets, evident both clinically and radiographically. Hypercalciuria and hyperphosphaturia can lead to medullary nephrocalcinosis detected by renal ultrasound examination.

Growth retardation is usually apparent in the untreated child from age six months and is characterized by a growth rate that is 50%-60% of normal.

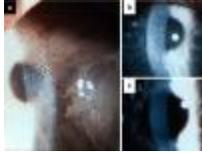


Figure 1. Findings on slit lamp examination of the (more...)

Corneal cystine crystals cause photophobia and often blepharospasm and corneal erosions. A slit lamp examination of the cornea showing typical cystine crystals is diagnostic for cystinosis ([Figure 1b](#)). Corneal crystals may be present before age one year and are always present after age 16 months [[Gahl et al 2000](#)].

Intermediate nephropathic cystinosis (juvenile/late onset). This rare variant of cystinosis is characterized by the same renal and corneal events as those observed in untreated infantile nephropathic cystinosis, but with delayed onset and decreased severity. The tubular Fanconi syndrome can be so mild that it is not recognized, and rickets, growth retardation, electrolyte imbalance, and photophobia may be absent or clinically insignificant in childhood. In all cases, however, end-stage renal disease secondary to glomerular involvement occurs, usually between ages 15 and 25 years.

Ocular (non-nephropathic) cystinosis. Untreated individuals with this variant never have impairment of renal function or growth. Photophobia is the sole symptom, although cystine crystals are present in the bone marrow and conjunctiva as well as in the cornea. Diagnosis is usually made on routine eye examination with a slit lamp.

Testing

Leukocyte cystine measurement. The clinical diagnosis of cystinosis should be confirmed by measurement of cystine concentrations in polymorphonuclear leukocytes.

- Measurement is best performed using mass spectrometry or the cystine binding protein assay, a competitive radioassay that detects nanomole quantities of cystine [[Gahl et al 2001](#), [Gahl et al 2002](#)].

- Individuals with nephropathic cystinosis generally have values of 3.0-23.0 nmol half-cystine/mg protein.
- Individuals with non-nephropathic cystinosis have values of 1.0-3.0 nmol half-cystine/mg protein.
- Heterozygotes have ≤ 1.0 nmol half-cystine/mg protein.
- Normal values are ≤ 0.2 nmol half-cystine/mg protein.
- Measurement by amino acid analysis, i.e., anion exchange chromatography, is less sensitive, and can give spurious results if small amounts of leukocyte protein are available.

Note: In preparing leukocytes for assay, care must be taken to avoid a significant number of lymphocytes, which store only fivefold normal amounts of cystine compared with 50-fold normal amounts in polymorphonuclear leukocytes, and contamination with red blood cells, which contribute protein but not cystine to the calculated cystine value. Both interfering substances produce artifactually low leukocyte cystine levels.

Other cystine measurements. Cystinosis can also be diagnosed by the demonstration of increased cystine content in cultured fibroblasts or in the placenta at the time of birth [[Gahl et al 2001](#)].

Crystals. On tissue biopsy of bone marrow, conjunctiva, kidney, liver, intestine, and other tissues, cystine crystals appear as hexagonal or rectangular in shape and are birefringent under polarizing light [[Gahl et al 2001](#), [Gahl et al 2002](#)].

Note: (1) The tissue should be fixed in 100% alcohol, as aqueous solutions can dissolve the crystals. (2) A skin biopsy does not contain crystals; neither do cultured cells of any type.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the [GeneTests Laboratory Directory](#) by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a

laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.—ED.

Gene. *CTNS* is the only gene known to be associated with cystinosis.

Clinical testing

- **Targeted mutation analysis**

- In the United States and northern European populations, approximately 50% of individuals with nephropathic cystinosis are homozygous for a 57-kb deletion that encompasses the first nine exons and introns of *CTNS* and interrupts exon 10 [Shotelersuk et al 1998, Town et al 1998, Touchman et al 2000].

In individuals with intermediate and non-nephropathic cystinosis, the 57-kb deletion can be present in the heterozygous state, along with a more "benign" mutation, but not in the homozygous state [Anikster et al 1999a, Forestier et al 1999]

- Testing for a panel of mutations optimized for the French-Canadian population is available on a clinical basis.
- **Sequence analysis** of the entire coding region detects mutations other than the 57-kb deletion in northern Europeans and other population groups.

Research testing. A FISH methodology testing for the common 57-kb deletion is available on a research basis only [Bendavid et al 2004].

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Cystinosis

| Gene Symbol | Test Method | Mutations Detected | % of Northern Europeans with Nephrotic Cystinosis | % of Non-Northern Europeans with Cystinosis | Mutation Detection Frequency by Test Method | Test Availability |
|-------------|----------------------------|--|---|---|---|----------------------------|
| CTNS | | 57-kb deletion ¹ | 40% | 0% | ~100% | Clinical Testing |
| | Targeted mutation analysis | Mutation panel optimized for the French-Canadian population ² | 65% | Unknown | ~100% | |
| | Sequence analysis | Sequence variants | Unknown | Unknown | Unknown | |

1. The 57-kb deletion encompasses the first nine exons and introns of CTNS and interrupts exon 10 [Shotelersuk et al 1998, Town et al 1998, Touchman et al 2000].

2. 57-kb deletion, p.Trp138X, p.Thr7Phe, p.Gln128X, p.Trp182Arg, p.Leu158Pro, p.Gly308Arg, p.Asp205del, p.Ile133Pro; total 55 mutations known [Kalatzis & Antignac 2003]

Testing Strategy

Establishing the diagnosis in a proband. The diagnosis of renal tubular Fanconi syndrome is established by documenting:

- Renal tubular Fanconi syndrome. Increased urinary losses of essential nutrients including electrolytes (sodium, potassium, and bicarbonate), minerals (calcium, phosphate, and magnesium), glucose, amino acids, carnitine, and water

- Typical cystine crystals in the cornea on slit lamp examination
- Increased cystine content of leukocytes
- Two mutations in *CTNS*

Note: Although the finding of typical hexagonal or rectangular cystine crystals in any of a variety of tissues can establish the diagnosis of cystinosis, tissue biopsy is no longer indicated for diagnosis.

Carrier testing for at-risk relatives requires prior identification of the disease-causing mutations in the family.

Note: Carriers are heterozygotes for this autosomal recessive disorder and are not at risk of developing the disorder.

Predictive testing for at-risk asymptomatic family members requires prior identification of the disease-causing mutations in the family.

Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies require prior identification of the disease-causing mutations in the family.

Genetically Related (Allelic) Disorders

No other phenotypes are associated with mutations in *CTNS*.

Clinical Description

Natural History

The three types of cystinosis, i.e., nephropathic (classic renal and systemic disease), intermediate (a late-onset variant of nephropathic cystinosis), and non-nephropathic (clinically affecting only the cornea) are allelic disorders caused by *CTNS* mutations [Thoene et al 1999, Anikster et al 2000].

Nephropathic cystinosis. The clinical characteristics of untreated nephropathic cystinosis include those associated with poor growth, renal tubular Fanconi syndrome, renal glomerular failure, and nonrenal

involvement of a variety of tissues and organ systems. With effective cystine-depleting therapy, cystinosis was transformed from a progressive, fatal renal disease to a treatable chronic multisystemic disease, with life span increasing from about age ten years to at least age 50 years [[Nesterova & Gahl 2008](#)].

- **Growth.** Infants with untreated nephropathic cystinosis are normal at birth. In untreated individuals, failure to grow is generally noticed between ages six and nine months. A high frequency of vomiting, poor appetite, and feeding difficulties, combined with renal losses of nutrients, causes poor nutrition and failure to thrive. Typically, infants are at the third percentile for height and weight by age one year [[Gahl et al 2001](#), [Gahl et al 2002](#)]. Later, growth occurs at 60% of the normal rate. Bone age is usually delayed one to three years compared with chronologic age. Head circumference is normal for age. With early and optimal symptomatic and cystine-depleting therapy, individuals grow at a normal rate but their height often remains below the third centile and weight remains slightly above the third centile. Growth hormone administration improves height velocity in prepubertal children.
- **Renal tubular Fanconi syndrome.** Infants with untreated nephropathic cystinosis show signs of renal tubular Fanconi syndrome as early as age six months. The Fanconi syndrome involves failure of the renal tubules to reabsorb water, electrolytes, bicarbonate, phosphate, calcium, glucose, carnitine, amino acids, and tubular proteins. Individuals with untreated cystinosis have polyuria (two to six liters per day), polydipsia, dehydration, and hypochloremic metabolic acidosis, sometimes requiring hospitalization as a result of life-threatening hypovolemia, particularly during a gastrointestinal illness.

Hypophosphatemic rickets, characterized by high excretion of phosphate, elevated serum alkaline phosphatase, and bone deformities, makes walking painful enough to delay ambulation. Hypocalcemia can cause seizures and tetany.

Severe hypokalemia can threaten cardiac conduction. Occasionally, hyponatremia and hypomagnesemia also occur.

Treatment with replacement of renal losses resolves the rickets, tetany, acidosis, and laboratory abnormalities, and cystine-depleting therapy begun just after birth can attenuate the renal tubular Fanconi syndrome [Kleta et al 2004a]. However, renal tubular damage present at the time of diagnosis (i.e., approximately age one year) is irreversible.

- **Renal glomerular failure.** In the natural history of untreated nephropathic cystinosis, glomerular function gradually deteriorates, resulting in renal failure at approximately age ten years [Gahl et al 2001, Gahl et al 2002]. The serum creatinine concentration may not exceed 1.0 mg/dL until age five years, but once it rises, it increases exponentially. Many affected individuals have significant proteinuria, sometimes in nephrotic ranges, along with granular casts and microhematuria.

Early treatment with cystine-depleting therapy (i.e., oral cysteamine) slows or stops the progression of glomerular damage and can delay or prevent the need for renal transplantation [Kleta et al 2004a], which is successful because cystine does not accumulate in the cells of the donated kidney.

- **Non-renal involvement.** Without therapy, cystine accumulation occurs in virtually all organs and tissues, including bone marrow, liver, intestine, muscle, brain, spleen, eye, thyroid, pancreas, and testes. Without therapy, several complications of cystinosis occur prior to renal transplantation:
 - Infants and children can have poor appetite and vomit regularly, usually in the morning.
 - Photophobia develops when the cornea becomes packed with crystals, generally at the end of the first decade of life.

- Affected individuals typically develop hypothyroidism at the end of the first decade of life.
 - Sweating is impaired and affected individuals can suffer heat prostration [[Gahl et al 2001](#), [Gahl et al 2002](#)].
 - Intelligence is normal in cystinosis, although neurobehavioral abnormalities, including visual memory defects, have been reported [[Gahl et al 2001](#), [Gahl et al 2002](#)].
 - Benign intracranial hypertension presents with headaches and papilledema [[Dogulu et al 2004](#)].
 - Puberty is generally delayed one to two years. Untreated males exhibit primary hypogonadism [[Chik et al 1993](#)].
 - No male with untreated cystinosis has fathered a child; a few females with untreated cystinosis have delivered healthy children [[Haase et al 2006](#)].
 - It is currently not known whether diligent cysteamine treatment can prevent primary hypogonadism in males.
- **Late-onset abnormalities.** Well after renal transplantation, i.e., at approximately age 20 to 40 years, another set of complications can occur from the longstanding accumulation of cystine crystals in nonrenal organs in individuals not treated with cysteamine [[Servais et al 2008](#)].

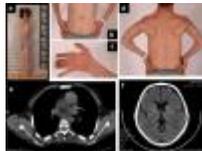


Figure 2.

a. A 37-year-old man with nephropathic (more...)

Increased cystine content in the muscles causes vacuolar myopathy in 60% of patients [[Gahl et al 2007](#)] Generalized myopathy leads to progressive muscle wasting and weakness

(Figure 2a,c,d) [Ishak et al 1994]. Oral motor dysfunction causes swallowing and feeding difficulties [Trauner et al 2001, Sonies et al 2005]. Electromyography demonstrates a myopathic pattern.

- Extrinsic chest muscle impairment causes extraparenchymal restriction of ventilation leading to pulmonary insufficiency with decreased values of FVC and FEV1 on routine pulmonary function tests [Anikster et al 2001].
- Gastrointestinal findings can include reflux, dysmotility, esophagitis, gastric/duodenal ulcers, hepatomegaly with nodular regenerating hyperplasia of the liver with portal hypertension, exocrine pancreatic insufficiency [O'Brien et al 2006, DiDomenico et al 2004], inflammatory bowel disease, bowel perforation, and peritonitis [Gahl et al 2007].
- Cardiovascular manifestations can include arteriopathy caused by the combination of vascular calcifications and obstructive atherosclerosis with hypercholesterolemia (Figure 2e) [Ueda et al 2006]; ESRD and renin-dependent hypertension; dilated cardiomyopathy; and aortic aneurysms. All of these factors contribute to cardiovascular morbidity and increase the risk for myocardial infarction and neurovascular incidents.
- Metabolic bone disease develops as a result of direct deposition of cystine crystals in bone, mineral imbalance, and renal osteodystrophy prior to renal transplantation [Zimakas et al 2003].
- Hypercoagulopathy and hypocoagulopathy occur as a result of renal failure and platelet aggregation dysfunction [Nesterova & Gahl 2008].

- CNS calcifications ([Figure 2f](#)), benign intracranial hypertension with non-absorptive hydrocephalus, and parenchymal deterioration of the central nervous system with cerebral atrophy lead to various degrees of encephalopathy [[Gahl et al 2001](#), [Gahl et al 2002](#)]. Occasionally, cerebrovascular incidents with paresis or pseudobulbar palsy occur [[Gahl et al 2007](#)].
- **Intellectual abilities** are low-normal; affected children have mainly average school performance. They have impaired visual and spatial cognition with preserved language and intellectual function [[Spilkin et al 2007](#)]. Their distinctive behavioral and psychosocial difficulties are related to their chronic disease including ESRD, renal dialysis, prolonged hospitalizations, and treatment with multiple therapeutic agents, including steroids [[Ballantyne & Trauner 2000](#), [Delgado et al 2005](#)].
- **Late ocular complications.** Crystal deposition in the anterior chamber, iris and ciliary body, choroid, fundus and optic nerve manifests as [[Tsilou et al 2007](#)]:
 - Anterior segment problems. Crystals in the anterior lens surface, band keratopathy ([Figure 1a](#)), peripheral corneal neovascularization, and posterior synechiae
 - Posterior segment problems. Pigmentary retinopathy with degeneration of the photoreceptors that contributes to the impaired visual function in the late-stage of the disease [[Tsilou et al 2002](#)]. Electroretinogram (ERG) is used to confirm the retinopathy.

Intermediate cystinosis. All the early manifestations of untreated nephropathic cystinosis, including the renal tubular Fanconi syndrome, growth delay, photophobia, and glomerular failure, occur in individuals with untreated intermediate cystinosis, but at a later age, mostly during adolescence.

Non-nephropathic cystinosis. Individuals with untreated non-nephropathic cystinosis experience only photophobia.

Histopathology. Electron microscopy of the glomeruli reveals fusion of foot processes, thickening of Bowman's membrane, and localization of cystine crystals in interstitial cells. Cystinotic glomeruli show focal glomerulosclerosis [Mahoney & Striker 2000].

Pathophysiology. The pathophysiology of renal tubular Fanconi syndrome is under investigation. Two mechanisms have been suggested: (1) inhibition of the Na-phosphate co-transporter resulting from cystine accumulation in the proximal tubular cells with depletion of intracellular ATP [Baum 1998, Kleta & Gahl 2002, Park et al 2002]; and (2) degeneration of the proximal tubules, which is well-documented in nephropathic cystinosis [Mahoney & Striker 2000].

Genotype-Phenotype Correlations

Some genotype-phenotype correlations can be made:

- Within the group of individuals with nephropathic cystinosis, truncating *CTNS* mutations, as well as the 57-kb deletion, result in severe, classic (early-onset or infantile type) disease [Shotelersuk et al 1998, Attard et al 1999].
- Individuals with apparent residual activity (i.e., lower levels of cystine accumulation in leukocytes) often have missense mutations in *CTNS* [Attard et al 1999]. Individuals with intermediate cystinosis (i.e., nephropathic but late-onset) or non-nephropathic cystinosis (i.e., corneal and bone marrow crystals but no renal involvement) have one severe *CTNS* mutation, typical for nephropathic cystinosis, and one mild mutation. The mild mutations include p.Gly197Arg and c.853-3C>G [Anikster et al 1999b]. The organ specificity in benign cystinosis may result from tissue-specific splicing factors.
- The clinical manifestations associated with two "mild" mutations are unknown.

- Deletions of *CTNS* and its flanking genes may lead to contiguous gene deletion syndromes with more complex phenotypes than those of classic cystinosis [[Kalatzis & Antignac 2003](#)].
- Other factors, such as modifying genes and environmental factors likely influence the severity of the phenotypic effects of lysosomal accumulation [[Anikster et al 1999b](#)].
- Heterozygotes have 50% of transport capacity in their lysosomes [[Thoene 1995](#), [Gahl et al 2002](#)].

Nomenclature

The terms "adult cystinosis" and "benign cystinosis" should be replaced by "ocular cystinosis" and "non-nephropathic cystinosis."

Prevalence

Cystinosis occurs with a frequency of approximately one in 100,000 to 200,000 and has been found worldwide in all ethnic groups. The frequency of cystinosis in Brittany has been given as one in 26,000 [[Gahl et al 2001](#), [Gahl et al 2002](#)].

Cystinosis accounts for 5% of childhood renal failure [[Middleton et al 2003](#)].

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see [GeneTests Laboratory Directory](#). —ED.

Untreated nephropathic cystinosis is the most common identifiable cause of the renal tubular Fanconi syndrome in childhood. Other causes:

- [Wilson disease](#) is a disorder of copper metabolism that can present with hepatic, neurologic, or psychiatric disturbances, or a combination of these, from age three to over 50. Diagnosis depends in part upon the detection of low serum copper

and ceruloplasmin concentrations and increased urinary copper excretion. Molecular genetic testing of the *ATP7B* is available. Inheritance is autosomal recessive.

- Oculocerebrorenal syndrome of Lowe is found in males and involves the eyes (cataracts, glaucoma, decreased visual acuity), central nervous system (hypotonia, mental retardation), and kidneys (Fanconi syndrome). Slowly progressive glomerulosclerosis and renal failure are often noted after age ten years. It is diagnosed by demonstrating reduced (<10% of normal) activity of phosphatidylinositol 4,5-bisphosphate 5-phosphatase in cultured skin fibroblasts. Mutations in the responsible gene, *OCRL1*, are detectable in most males and carrier females. (Mutations in *OCRL1* can also cause Dent's disease, which can present with findings typical for renal Fanconi syndrome.) Inheritance is X-linked.
- Galactosemia is a disorder of galactose metabolism that can result in feeding problems, failure to thrive, hepatocellular damage, bleeding, and sepsis in untreated infants. It is most often caused by deficient activity of the enzyme galactose-phosphate uridylyltransferase (GALT), and can be diagnosed by measurement of erythrocyte GALT enzyme activity and by isoelectric focusing of GALT. Molecular genetic testing of GALT is available for individuals with biochemically confirmed galactosemia.
- Glycogen storage disease type I presents mainly with hepatomegaly and hypoglycemia.
- Tyrosinemia type I presents with severe liver disease in infancy and shows abnormal tyrosine metabolites on organic acid analyses.
- Glucosuria associated with renal tubular Fanconi syndrome can result in misdiagnosis as diabetes mellitus.
- Polyuria often leads to a misdiagnosis of diabetes insipidus (see Nephrogenic Diabetes Insipidus).
- Electrolyte abnormalities can suggest Bartter syndrome.

- The rickets of cystinosis can falsely suggest vitamin D deficiency.
- Multiple myeloma can cause photophobia and corneal crystals similar to those in ocular cystinosis [Kleta et al 2004b].

Management

Evaluations Following Initial Diagnosis

At the time of diagnosis, the following evaluations are recommended in all individuals with cystinosis regardless of age:

- Height and weight, plotted on age-appropriate growth charts
- Renal tubular and glomerular function, especially serum concentrations of creatinine, phosphate, bicarbonate, and potassium; and urine concentrations of creatinine, phosphate, bicarbonate, potassium, glucose, and protein
- Glomerular filtration rate (GFR) or creatinine clearance test
- Thyroid function studies
- Lipid panel
- Renal ultrasound examination for evaluation of nephrocalcinosis
- Ophthalmologic evaluation, including slit lamp examination of the cornea to assess corneal involvement, ERG to assess retinal involvement, and fundoscopic examination for possible intracranial hypertension

The following are recommended in individuals who are initially diagnosed at an older age:

- In pre- and postpubertal males, measurement of serum concentration of testosterone, FSH, and LH
- Glucose tolerance test to assess for diabetes mellitus if symptoms are present.

Treatment of Manifestations

It is recommended that a multidisciplinary team that includes nephrologists, metabolic disease specialists, ophthalmologists, neurologists, gastroenterologists, nutritionists and psychologists manage individuals with cystinosis.

Renal tubular Fanconi syndrome is treated by replacement of renal losses:

- For children, free access to water and bathroom privileges and supplementation with citrate to alkalinize the blood
- Phosphate replacement to prevent and heal hypophosphatemic rickets; vitamin D supplementation to assist the gastrointestinal absorption of phosphate
- Potassium, calcium, magnesium, or carnitine supplementation as needed
- Careful attention to fluid and electrolyte replacement during gastrointestinal illnesses. (Obligatory urinary losses amount to 2-6 liters of electrolyte-rich water per day.)
- Reduction of cellular cystine concentration through treatment with the cystine-depleting agent cysteamine (see [Prevention of Primary Manifestations](#))
- ACE inhibitors might be used to slow the progression of renal insufficiency attributed to proteinuria [[Levtchenko et al 2004](#)].
- Renal transplantation. Renal replacement is usually indicated when the creatinine clearance falls below 20 mL/min/1.73 m² and azotemia and hypertension rapidly progress. The time frame for appropriate renal replacement is the point at which the reciprocal serum creatinine value plotted against age reaches approximately 0.1. Symptoms often determine the exact time of transplantation.

Ophthalmologic problems are treated symptomatically and with cystine-depleting agents:

- The photophobia, resulting from corneal crystal accumulation, can be ameliorated by sun avoidance, dark glasses, and lubrication with over-the-counter eyedrops (see [Prevention of Primary Manifestations](#)).

- Corneal transplantation is very rarely required for intractable pain resulting from recurrent corneal ulcerations.
- Retinal involvement is irreversible.

Growth for children with cystinosis requires good nutrition, adequate phosphate supplementation, and robust intracellular cystine depletion (see Prevention of Primary Manifestations):

- Nutrition must be adequate for growth.
- Growth hormone therapy has proven beneficial for children with cystinosis in providing catch-up growth and bringing them into the normal percentiles for height [Gahl et al 2001, Wühl et al 2001, Gahl et al 2002].
- Early and diligent treatment with supplements and oral cysteamine can obviate the need for growth hormone [Kleta et al 2004a].

Other

- Oral L-thyroxine replacement for hypothyroidism
- Insulin for diabetes mellitus
- Testosterone to induce secondary sexual characteristics in males with primary hypogonadism
- Specific exercises for the muscle deterioration and swallowing difficulties of older individuals with cystinosis; hand tendon transfer has been partially successful in improving strength.
- Speech therapy and physical therapy
- Standard treatment for benign intracranial hypertension; other central nervous system complications are irreversible.
- Feeding via gastrostomy for those with dysphagia, poor nutrition, and risk of aspiration (Figure 2b)

Prevention of Primary Manifestations

Cystine depletion therapy with cysteamine bitartrate (Cystagon[®]) has revolutionized the management and prognosis of nephropathic cystinosis. Cysteamine is now the treatment of choice for cystinosis throughout the world. This free thiol can deplete cystinotic cells of more than 90% of their cystine content [Kleta & Gahl 2004]. Cysteamine therapy should be considered for all affected individuals, regardless of age and transplantation status [Gahl et al 2007]. With early, diligent treatment many individuals with cystinosis have survived into their twenties without the need for renal transplantation [Gahl et al 2002].

- Chronic and diligent cysteamine therapy prevents or delays end stage renal disease (ESRD) [Markello et al 1993] and hypothyroidism, enhances growth, and depletes muscle parenchyma of cystine [Gahl et al 2002].
- It is critical to initiate cysteamine therapy immediately after diagnosis to allow for kidney growth and acquisition, rather than loss, of renal function [Kleta et al 2004a].
- Cystagon[®] is taken orally every six hours at 60 to 90 mg of free base per kg per day (1.3 to 1.95 g/m² per day). The recommended adult dose is 500 mg free base every six hours; however, for both children and adults, the dose is titrated to reduce, if possible, leukocyte cystine concentration (measured 5-6 hours after a dose) to below 1.0 nmol half-cystine/mg protein [Belldina et al 2003, Kleta & Gahl 2004, Kleta 2006].
- Side effects of cysteamine treatment include nausea and vomiting, in part because of its repulsive odor and taste [Schneider 2004]. Cysteamine increases gastrin synthesis and gastric acid production. Omeprazole may be of benefit for oral cysteamine treatment [Dohil et al 2003].
- With long-term cystine-depleting therapy most late complications of cystinosis can be avoided.
- Despite diligent oral cysteamine therapy, cysteamine hydrochloride eyedrops are required to achieve sufficient tissue concentration to dissolve corneal crystals [Gahl et al 2000]. Cysteamine eyedrops are given 10-12 times per day as a 0.55% solution with benzalkonium chloride 0.01% as a preservative [Tsilou et al 2007]. With good compliance photophobia is relieved within weeks (Figure 1b,

1c) [[Kaiser-Kupfer et al 1987](#), [Gahl et al 2000](#)]. Systemic cysteamine treatment ameliorates or postpones retinal deterioration [[Tsilou et al 2006](#)]. Cysteamine eyedrops remain investigational.

Prevention of Secondary Complications

Post-transplant patients should be monitored for the signs of immunodeficiency and infection.

Carnitine supplementation is used in some patients to improve muscle strength.

Proton pump inhibitors can be used for relief of discomfort associated with cystinosis or with cysteamine therapy.

Surveillance

Clinical and laboratory examinations should be performed in individuals with nephropathic cystinosis according to disease severity and may include renal, endocrinologic, ophthalmologic, neurologic, and cardiac examinations [[Kleta et al 2005](#)]:

- Evaluation by a nephrologist every 3-6 months depending upon the severity of renal impairment
- Renal function tests, electrolytes, and thyroid function tests at least every 3-6 months in those who are stable

Serum concentration of calcium, phosphate, alkaline phosphatase and intact parathyroid hormone. Plain bone radiographs as well as DEXA scans to detect osteopenia and bone fragility predisposing to fractures, starting as soon as diagnosis is made and continued throughout the course of the disease:

- Ophthalmologic evaluation every 1-2 years for those being treated appropriately
- Fasting blood glucose concentration throughout the course of the disease and testosterone concentration (in males) every 2-3 years, starting at pre-pubertal age

- In advanced disease (i.e., poorly treated adults) and in late stages of disease, perform every 2-3 years:
 - Chest CT for detection of coronary and other vascular calcification
 - ECG
 - Brain CT or MRI for evaluation of cerebral atrophy or calcifications
 - Evaluation for the presence of progressive muscle weakness and swallowing difficulties using electromyography (EMG), oral sensorimotor examination, and modified barium swallowing studies with videofluoroscopy
 - Pulmonary function tests
 - Neurologic and behavioral psychological evaluations

Agents/Circumstances to Avoid

Avoid the following:

- Dehydration, which compromises remaining renal function
- Sun exposure, which can exacerbate photophobia

Testing of Relatives at Risk

Relatives at risk (e.g., newborn sibs of a proband) can undergo biochemical testing and/or molecular genetic testing if the disease-causing mutations in the family are known. Early diagnosis is critical to prevent life-threatening complications of cystinosis.

See [Genetic Counseling](#) for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search [ClinicalTrials.gov](https://clinicaltrials.gov) 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.

Other

Development of a newborn screening test for cystinosis potentially will allow broader therapeutic success [[Nesterova & Gahl 2008](#)].

Therapies proven to be ineffective include dietary restriction of sulfur-containing amino acids, supplementation with ascorbic acid, and the use of dithiothreitol.

Genetics clinics, staffed by genetics professionals, provide information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the [GeneTests Clinic Directory](#).

See [Consumer Resources](#) for disease-specific and/or umbrella support organizations for this disorder. These organizations have been established for individuals and families to provide information, support, and contact with other affected individuals.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the [GeneTests Clinic Directory](#).

Mode of Inheritance

All forms of cystinosis are inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes and thus carry one mutant allele.
- Heterozygotes (carriers) are asymptomatic.

Sibs of a proband

- At conception, each sib of an affected individual has 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.
- Once an at-risk sib is known to be unaffected, the chance of his/her being a carrier is 2/3.
- Heterozygotes are asymptomatic.

Offspring of a proband. The offspring of an individual with cystinosis are obligate heterozygotes (carriers) for a mutant allele causing cystinosis. Rarely, families with two-generation involvement (sometimes called “pseudodominance”) have been identified; two-generation involvement results from an affected individual having children with a partner who is heterozygous (i.e., a carrier) for a *CTNS* mutation.

Other family members of a proband. Each sib of the proband's parents is at a 50% risk of being a carrier.

Carrier Detection

Biochemical testing. Carrier testing can be performed biochemically; it requires freshly prepared leukocytes and appropriate controls.

Molecular genetic testing. Carrier testing for at-risk family members is possible if the disease-causing mutations in the family are known.

Related Genetic Counseling Issues

See Management, [Testing of Relatives at Risk](#) for information on testing 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 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. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant when the sensitivity of currently available testing is less than 100%. See [Testing](#) for a list of laboratories offering DNA banking.

Prenatal Testing

Biochemical testing. For pregnancies at risk for nephropathic cystinosis, prenatal testing is available biochemically, based upon elevated cystine concentrations in both chorionic villi, obtained at approximately ten to 12 weeks' gestation by chorionic villus sampling (CVS), and amniocytes, obtained by amniocentesis usually performed at approximately 15-18 weeks' gestation [[Gahl et al 2001](#)].

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Molecular genetic testing. Molecular-based prenatal diagnosis is possible by analysis of DNA extracted from fetal cells obtained either by CVS or by amniocentesis. Both disease-causing alleles of an affected family member must be identified before prenatal testing using molecular genetic testing methods can be performed.

Requests for prenatal testing for conditions such as cystinosis that do not affect intellect and have some treatment available are not common. Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD). Preimplantation genetic diagnosis may be available for families in which the disease-causing mutations have been identified. For laboratories offering PGD, see [Testing](#).

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. Cystinosis: Genes and Databases

| Gene Symbol | Chromosomal Locus | Protein Name | HGMD |
|----------------------|-------------------|--------------|----------------------|
| CTNS | 17p13 | Cystinosin | CTNS |

Data are compiled from the following standard references: gene symbol from [HGNC](#); chromosomal locus, locus name, critical region, complementation group from [OMIM](#); protein name from [UniProt](#). For a description of databases (Locus Specific, HGMD) linked to, click [here](#).

Table B. OMIM Entries for Cystinosis ([View All in OMIM](#))

| | |
|------------------------|-----------------------------------|
| 219750 | CYSTINOSIS, ADULT NONNEPHROPATHIC |
| 219800 | CYSTINOSIS, NEPHROPATHIC; CTNS |

| | |
|--------|---|
| 219900 | CYSTINOSIS, LATE-ONSET JUVENILE OR ADOLESCENT NEPHROPATHIC TYPE |
| 606272 | CYSTINOSIN; CTNS |

Normal allelic variants. The normal *CTNS* gene is 26 kb in length and has 12 exons with coding region of 1104 bp [Town et al 1998]. Several normal allelic variants have been reported.

Pathologic allelic variants. At least 80 different mutations including promotor mutations in *CTNS* have been reported; they are found in different combinations in individuals with cystinosis [Shotelersuk et al 1998, Town et al 1998, Attard et al 1999, McGowan-Jordan et al 1999, Thoene et al 1999, Anikster et al 2000, Kleta et al 2001, Phornphutkul et al 2001, Kalatzis et al 2002, Kiehntopf et al 2002, Mason et al 2003]. By far the most common mutation (50% of affected individuals) is the 57-kb del involving exons 1-9 and part of exon 10; this mutation apparently represents a founder effect [Shotelersuk et al 1998]. The mutations include missense, nonsense, and splice site mutations, deletions, and insertions leading to downstream stop codons or abolition of splice sites [Kiehntopf et al 2002]. The missense mutations are usually present within transmembrane regions [Anikster et al 1999b]. There are no mutational hot spots. Another relatively common mutation is p.Trp138X. A higher incidence of infantile cystinosis was reported in the French province of Brittany, with an incidence of 1:26000. The splice site mutation c.898-900+24del27 segregates in certain unrelated families [Kalatzis et al 2002]. (For more information, see Table A: locus-specific databases and HGMD.)

Table 2. Selected *CTNS* Pathologic Allelic Variants

| DNA Nucleotide Change (Alias ¹) | Protein Amino Acid Change | Reference Sequences |
|--|---------------------------|------------------------|
| g.36,254_93,510del(57-kb del) ² | -- | AF168787 |
| c.198_218del(c.198del21bp or 537del21) | p.Ile67_Pro73del | NM_004937.2NP_004928.2 |

| | |
|--------------------------------------|-----------------|
| c.414G>A | p.W138X |
| c.473T>C | p.L158P |
| c.589G>A | p.G197R |
| c.613G>A | p.D205N |
| c.696dupC(c.696_697insC or 1035insC) | p.V233RfsX63 |
| c.853-3C>G | -- ³ |
| c.898-900+24del27 | -- |

See [Quick Reference](#) for an explanation of nomenclature. *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org).

1. Variant designation that does not conform to current naming conventions
2. [Touchman et al \[2000\]](#)
3. [Anikster et al \[2000\]](#)

Normal gene product. Cystinosin, the protein product of *CTNS*, is a 367-amino acid peptide with seven transmembrane and two lysosomal targeting motifs, a 128-amino acid N-terminal region bearing seven potential N-glycosylation sites, and a ten-amino acid cytosolic C-terminal tail [[Town et al 1998](#); [Kalatzis & Antignac 2002](#), [Kalatzis & Antignac 2003](#)]. Cystinosin is expressed in the cells of virtually all tissues. Cystinosin transports the disulfide amino acid cystine out of the lysosome and into the cytoplasm [[Gahl et al 2002](#), [Kleta & Gahl 2002](#)]. Cystinosin is highly conserved between man and mouse [[Cherqui et al 2002](#)].

Abnormal gene product. The 57-kb deletion allele produces no *CTNS* mRNA, while most other alleles produce some residual mRNA [Shotelersuk et al 1998]. The mutant alleles of *CTNS* are predicted to produce truncated cystinosin in the case of severely affected individuals and to produce cystinosin that retains some residual function in the case of mildly affected individuals.

Resources

See Consumer Resources for disease-specific and/or umbrella support organizations for this disorder. These organizations have been established for individuals and families to provide information, support, and contact with other affected individuals. *GeneTests* provides information about selected organizations and resources for the benefit of the reader; *GeneTests* is not responsible for information provided by other organizations.—ED.

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page [PubMed](#)

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Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Chapter Notes

Author Notes

Dr. Gahl is a pediatrician, medical geneticist, and biochemical geneticist who performs clinical and basic research into rare diseases. He has seen approximately 300 patients with cystinosis and published more than 85 articles and reviews on the subject.

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- 9 April 2009 (me) Comprehensive update posted live
- 18 October 2005 (me) Comprehensive update posted live
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