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EDITORIAL

Cystinosis as a lysosomal storage disease with multiple mutant alleles: Phenotypic-genotypic correlations

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Abstract

Cystinosis is an autosomal recessive lysosomal storage disease with an unclear enzymatic defect causing lysosomal cystine accumulation with no corresponding elevation of plasma cystine levels leading to multisystemic dysfunction. The systemic manifestations include a proximal renal tubular defect (Fanconi-like), endocrinal disturbances, eye involvements, with corneal, conjunctival and retinal depositions, and neurological manifestations in the form of brain and muscle dysfunction. Most of the long-term ill effects of cystinosis are observed particularly in patients with long survival as a result of a renal transplant. Its responsible *CTNS* gene that encodes the lysosomal cystine carrier protein (cystinosin) has been mapped on the short arm of chromosome 17 (Ch17 p13). There are three clinical forms based on the onset of main symptoms: nephropathic infantile form, nephropathic juvenile form and non-nephropathic adult form with predominant ocular manifestations. Avoidance of eye damage from sun exposure, use of cystine chelators (cysteamine) and finally renal transplantation are the main treatment lines. Pre-implantation genetic diagnosis for carrier parents is pivotal in the prevention of recurrence.

Key words: Cystinosis; *CTNS* gene; Phenotypic-genotypic correlation

Core tip: Cystinosis is an autosomal recessive lysosomal storage disease of cystine manifested primarily in the eye and kidneys; corneal cystine deposition detected by slit lamp and a proximal renal tubular defect (Fanconi-like) are the main clinical features. Its responsible gene, called *CTNS*, encodes the lysosomal cystine carrier protein (cystinosin) and has been mapped on the short arm of chromosome 17. Clinical forms of cystinosis depend upon age of onset of main symptoms. Besides cystine chelation, treatment includes eye protection from sun exposure and renal support up to transplantation. Carrier detection among parents and prenatal genetic diagnosis is the mainstay of prevention.

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CLASSIFICATIONS OF INHERITED FORMS OF RENAL TUBULAR ACIDOSIS

Inherited forms of proximal renal tubular acidosis

Proximal renal tubular acidosis (RTA) resulting from Fanconi syndrome is a frequent part of systemic syndromes. Among systemic disorders that result in RTA, the inheritance pattern is usually autosomal recessive. Some of these disorders are cystinosis, tyrosinemia, galactosemia, Fanconi Bickel Syndrome and others. These syndromes are heterogeneous groups of disorders. Their genes are mapped in many chromosome regions[1]. These inherited forms are demonstrated in Table 1[2].

Proximal RTA unrelated to Fanconi syndrome is a rare disorder and might be sporadic, autosomal dominant

Table 1 Chromosomal mapping of some inherited proximal renal tubular acidosis

Inherited proximal RTA	Gene	Chromosomal mapping
Autosomal recessive	*SLC4A4*	4q21
Dent´s syndrome	*CLCN5*	Xp11.22
Cystinosis	*CTNS*	17p13.2
Tyrosinemia type 1	*FAH*	15q23-q25
Galactosemia	*GALT*	9p13
Wilson´s disease	*ATP7B*	13q14.3-q21.1
Fanconi Bickel Syndrome	*SLC2A2*	3q26.1-26.3

RTA: Renal tubular acidosis.

or autosomal recessive. The autosomal recessive disorder is associated with ocular abnormalities and frequent coursing with mental retardation. Other clinical features are short stature, dental enamel defects, pancreatitis and basal ganglia calcification[3]. Loss-of-function mutations in the gene that encodes the NBC-1 protein (*SLC4A4* gene) were first identified in two Japanese patients with proximal RTA associated with cataracts, glaucoma and band keratopathy[4].

NBC-1 is formed by 1035 amino acids and contains ten transmembrane domains and two cytoplasmic termini. It is present in the kidney, brain, eye, pancreas, heart, prostate, epididymis, stomach and intestine. In the kidney, NBC-1 is expressed mainly at the basolateral membrane of the proximal tubule. At least two genes encode the NBC-1 proteins. Mutations were identified in the human NBC-1 gene (*SLC4A4*) mapped at chromosome 4q21[5,6]. Another interesting candidate gene for proximal RTA is the *TASK* gene. Its expression is located in the pancreas, placenta, lung, small intestine, colon and kidney. *TASK* seems to be important to HCO_3^- reabsorption in renal proximal tubules[7]. Another inherited form of proximal RTA is the one resulting from mutations in the gene *CA2* that encodes CA Ⅱ. The carbonic anhydrases are members of a family of zinc metalloenzymes that catalyze the hydration of CO_2. The human CA Ⅱ maps to the chromosome region 8q22. In the kidney, the majority of CA activity is attributable to CA Ⅱ, which is localized in the proximal tubular cells and in α-intercalated cells of the cortical and outer medullary collecting tubules[8]. Due to their localization, this RTA courses with some proximal and distal components. In terms of clinical aspects, this form of RTA presents with osteopetrosis, cerebral calcification and different levels of mental retardation.

The autosomal dominant proximal RTA was originally described in a large Costa Rican family[9], consisting of nine individuals presenting with growth retardation and osteomalacia. No gene was found to be associated with this clinical presentation. Later on, another family with isolated proximal RTA inherited as an autosomal dominant disease was described[10].

Inherited forms of type III RTA

Type Ⅲ RTA is a mixed type that exhibits both impaired proximal HCO_3^- reabsorption and distal acidification. The condition is due to an inherited deficiency of CA Ⅱ caused by a recessive mutation in the CA2 gene (*SLC26A6*) on chromosome 8q22, which encodes this widely expressed enzyme. The expression of CA Ⅱ is affected in bone, kidney (in both proximal and distal nephron segments, explaining the mixed acidosis) and brain[11,12]. The mechanisms that underlie the clinical course in type Ⅲ RTA, apart from much slower conversion of carbonic acid to and from HCO_3^-, apparently also involve a direct interaction between CA Ⅱ and the kidney NBC1 or Cl^-/HCO_3^- exchanger[13]. Mutations of the identified CA Ⅱ binding site reduce SLC26A6 activity, demonstrating the importance of this interaction[11,14]. Patients with this deficiency exhibit osteopetrosis and cerebral calcification, as well as mixed RTA with proximal and distal components[15]. There is a considerable degree of heterogeneity, both in the predominance of proximal or distal acidosis and in the osteopetrotic phenotype. In different kindred, mild or severe mental retardation has also been described[12]. Different mutations in CA2 gene have been described; for example, the common "Arabic" mutation, consisting of loss of the splice donor site at the 5' end of intron 2[12,15].

Inherited forms of Type IV RTA

Type IV RTA is a heterogeneous group of disorders associated with hyperkalemia due to aldosterone deficiency or impairment in aldosterone molecular signaling. The inheritance might be autosomal dominant or autosomal recessive. The autosomal dominant form is a frequent and milder form without other organ involvement. It seems to be associated with loss-of-function mutations in the mineralocorticoid receptor gene, the *MRL* gene. MRL-knockout mice develop symptoms of pseudohypoaldosteronism. In humans, clinical presentation varies from non-symptomatic to important neonatal Na^+ loss. The autosomal recessive form is associated with Na^+ transport defects in all aldosterone target tissues, not only kidney, but also colon, lungs, salivary and sweat glands. The recessive form is more severe with more pronounced salt wasting. However, both types of inheritance might result in the same degree of natriuresis, hyperkalemia and metabolic acidosis[16].

Other inherited causes of type IV RTA include hyperkalemia associated with hypertension and low or normal levels of plasma aldosterone[17,18]. This syndrome is called pseudohypoaldosteronism type 2 (PHA2) or Gordon's syndrome, which results in renal aldosterone resistance. It is inherited as an autosomal dominant pattern. Mutations in the gene of two isoforms of WNK serine-threonine kinases (*WNK4* and *WNK1* genes) were identified in patients with PHA2[19]. WNKs are serine kinase proteins lacking a lysine residue at the active site, being the WNK type 1, a regulatory protein from WNK 4. WNK4 is found in the distal nephron and controls Na^+ and Cl^- re-uptake and inhibits K^+ efflux[12].

CLINICAL BACKGROUNDS OF CYSTINOSIS

Cystinosis has been classified as a lysosomal storage disorder based on the intralysosomal localization of stored cystine; however, it differs from the other lysosomal diseases in that the principal lysosomal enzyme of acid hydrolysis is not known to play a role in the metabolic disposition of cystine. Moreover, plasma cystine levels are well below saturation, indicating that the defect is a cellular one. With electron microscopy of cystine-laden cells, cystine is compartmentalized with acid phosphatase and is membrane-bound, as demonstrated by electron microscopy.

In heterozygotes, concentration of free cystine was found to be several times the normal in the leukocytes of parents of patients[20], proximal renal tubular deposition of cystine results in Fanconi-like syndrome[2,21]. Teree *et al*[22] studied 2 male sibs physiologically and anatomically with cystinosis. Microdissection of the kidney tubules suggested that the morphological abnormality of the proximal tubule is "acquired" and progressive; however, these changes did not develop in renal transplants among four cystinosis children[23]. Endocrinal disturbances in the form of hypothyroidism due to extensive cystine deposition have been reported and represents one of the factors that could explain growth retardation of cystinosis patients[24-26]. Jonas *et al*[27] described a cystinosis patient who started at the age of one year, in end-stage renal failure at the age 7 years and at the age of 24 years, she was very dwarf (her height was 123 cm). She had marked photophobia, corneas and conjunctiva laden with refractile material, and a patchy retinopathy. There were signs of ovarian failure, intermittent confusion, short-term memory loss and cerebral atrophy on computerized axial tomography. Autopsy examination at the age of 25 showed cystine storage in multiple tissues, including pancreatic islet cells, the aorta, the atrophic ovaries and brain[27]. Myopathy with generalized muscle weakness and wasting due to accumulation of cystine in and around muscle fibers has been reported in a 22-year-old man who had a renal allograft at the age of 10 years[28]. In a patient who underwent renal transplantation aged 30 mo, cystinosis was the only detected cause for progressive renal failure[29]. The long-term ill effects of cystinosis, observed particularly in patients with long survival as a result of renal transplant, include pancreatic endocrine and exocrine insufficiency[30,31] and, as mentioned earlier, recurrent corneal erosions, CNS involvement and severe myopathy. Oral motor function was assessed in 43 cystinosis patients aged 3-30 years, 24 of whom had received a renal transplant. Approximately half of them were slow eaters and the marked oral motor dysfunction increased with age[32]. In studies of intelligence in 14 families of children with infantile nephropathic cystinosis, Williams *et al*[33] found that the IQs of 15 children with cystinosis were significantly lower on average than those of their sibs and parents. Even although the mean IQ of the children with cystinosis (94.4 ± 10) was within the average range, there was evidence that they had a mild global intellectual deficit compared to their expected IQ based upon the IQs of their relatives. Several have commented that patients with cystinosis have skin and hair pigmentation noticeably lighter than that of their unaffected sibs. It has been speculated that pigment formation may be impaired in the melanosomes, which are the melanocyte counterparts of lysosomes[34]. Most children with nephropathic cystinosis display an inability to produce the normal volume of sweat, resulting in heat intolerance and avoidance, flushing, hyperthermia and vomiting in small children, although sweat electrolyte concentrations are normal[35].

CLINICAL VARIANTS OF CYSTINOSIS

Accumulation of the amino acid cystine in lysosomes occurs throughout the body. Depending on the age at presentation and the degree of disease severity, three clinical forms of cystinosis are distinguished: (1) Nephropathic infantile form (OMIM #219800), the most frequent and severe form of the disease; (2) Nephropathic juvenile form (OMIM #219900); synonyms: intermediate cystinosis, late-onset form, adolescent form; and (3) Non-nephropathic adult form (OMIM #219750); synonyms: benign non-nephropathic cystinosis, ocular non-nephropathic cystinosis.

All three forms of the disease are autosomal recessive and caused by mutations of the *CTNS* gene and have phenotypic overlap[36].

Nephropathic infantile cystinosis

Patients with infantile cystinosis are generally born from uneventful pregnancies and have normal birth weight and length. Despite cystine accumulation starting in utero, clinical symptoms are absent at birth and gradually develop during the first months of life. The kidneys are the first affected organs and progressively lose function of their proximal tubular transporters. This results in urinary loss of water, Na^+, K^+, HCO_3^-, Ca^{2+}, Mg^{2+}, phosphate, amino acids, glucose, proteins and many other solutes reabsorbed in this nephron segment. Asymptomatic aminoaciduria can appear during the first weeks of life and is followed by glucosuria, phosphaturia and urinary HCO_3^- losses during the first months of infancy. In one sibling of a known patient with cystinosis longitudinally followed from birth, the excretion of low molecular weight protein (α-1 microglobulin) was only increased at the age of 6 mo. This observation indicates that diverse proximal tubular transporters have a differential sensitivity to the cystinosin dysfunction and that the diagnosis of cystinosis can be missed during the first months of life, especially when only a limited number of urinary markers are used to identify renal Fanconi syndrome[36,37]. At the age of 6 mo, a full-blown Fanconi syndrome is usually present and causes clinical symptoms of polyuria, thirst, failure to thrive, growth retardation, vomiting, periods of dehydration, constipation, developmental delay and rick-

ets in some patients. Biochemically, patients present with hypokalemia, hypophosphatemia, metabolic acidosis, low serum uric acid, low serum carnitine and sometimes hyponatremia[38]. Occasionally, hypokalemia in combination with hypochloremic metabolic alkalosis and an elevated plasma rennin activity can mimic Bartter syndrome[39,40]. Proteinuria can reach grams per day and consists of LMW proteins, albumin and high molecular weight proteins[41]. Excessive losses of calcium and phosphate can cause the development of nephrocalcinosis and the formation of renal stones[42]. In most untreated patients, glomerular filtration rate remains normal for up to two years and then progressively deteriorates towards end stage renal disease (ESRD) at the end of the first decade[43]. Renal transplantation is the treatment of choice in patients with ESRD as the disease does not recur in the grafted organ. Cystine crystals can be observed in graft biopsies but originate from the host mononuclear cells and are of no pathological value[44].

Nephropathic juvenile form

It is diagnosed in a minority of the patients (about 5%) and manifests with a spectrum of symptoms, varying from milder (compared with the infantile form) proximal tubulopathy to an apparent nephrotic syndrome. Most of the patients described were older than ten years. The deterioration of renal function also occurs in the late-onset form but the rate of renal disease progression is mostly slower compared with the infantile form of cystinosis[38].

Non-nephropathic adult form

Ocular non-nephropathic cystinosis manifests only with complaints of photophobia due to cystine accumulation in the cornea of the eye, which is also present in nephropathic cystinosis. The kidney, retina and other organs are spared in these patients[45]. The coexistence of juvenile and ocular forms of cystinosis was described in one family, suggesting that there might be a continuum between mild forms of cystinosis and thus warranting the follow-up of renal functions in patients with adult cystinosis[46].

EXTRA-RENAL SYMPTOMS OF CYSTINOSIS

Cystinosis is accompanied by other organ involvement. Untreated teenagers may develop painful corneal erosions, peripheral corneal neovascularization, punctate, filamentous or band keratopathy, iris crystals and retinal degeneration[47,48]. In addition, impairment of endocrinal glands is reported, including hypothyroidism, IDDM and hypogonadism. Cystinosis could be accompanied by encephalopathy, stroke-like episodes, benign intracranial hypertension and myopathy[36]. A novel truncating mutation has been described with recognizable heart malformations in Egyptian families[49].

DIAGNOSIS OF CYSTINOSIS

Cystinosis is an autosomal recessive disease that should be suspected in all patients with failure to thrive and signs of renal Fanconi syndrome. After one year of age, the observation of cystine crystals in the cornea is pathognomonic for cystinosis; however, the absence of the crystals beyond the age of 2 years excludes the diagnosis. Detection of elevated intracellular cystine content is the cornerstone for the diagnosis. The methods for cystine determination differ depending on the cell type: mixed leukocyte preparation or polymorphonuclear leukocytes. Furthermore, several biochemical methods are currently used for cystine measurement, such as a cystine-binding assay, amino acid chromatography or high performance liquid chromatography, making it difficult to compare the results of different laboratories[50].

The cystine-binding assay has been used as a standard method for cystine measurements for years. However, at present, most laboratories have switched to other methods of detection because of the lower price and avoidance of radioactivity. In this respect, tandem mass spectrometry is the most sensitive method and is currently widely used for cystine determination in cystinosis. Each laboratory performing cystine measurements should provide their own reference values for patients at the time of diagnosis and also for heterozygotes and healthy subjects[51]. Prenatal diagnosis of cystinosis can also be made by measuring 35S-labeled cystine accumulation in cultured amniocytes or chorionic villi samples (CVS) and by a direct measurement of cystine in uncultured CVS[52].

TREATMENT

All patients with cystinosis should avoid sun exposure because of photophobia and the risk of dehydration. The specific therapy for cystinosis is cysteamine. It depletes lysosomal cystine content by a disulfide exchange reaction with cystine. The administration of cysteamine at 1.3-1.9 g/m^2 in four daily doses dramatically lowers the cystine content of the lysosomes, postpones or even prevents the deterioration of renal functions and the development of extra-renal complications. Furthermore, cysteamine treatment improves growth[53,54]. It could be used also topically for the eye[55]. Cysteamine should be administered as soon as the diagnosis of cystinosis is made and continued for life, even after renal transplantation, to protect the extra-renal organs. Recently, a prodrug long acting cysteamine has been introduced to overcome some side effects of the old preparations[56].

In addition, symptomatic therapy, including good nutrition, fluid and electrolyte balance and treatment of rickets, is indicated. A follow up schedule is mandatory, including growth monitoring, slit lamp and fundus examination. White blood cell cystine measurements are also needed for adapting the cysteamine dose. In addition, yearly check-ups by an endocrinologist and neurologist are required to monitor the extra-renal complications of the disease[36].

An experimental study using *CTNS*-knockout mice demonstrated a beneficial effect of syngeneic bone marrow and hematopoietic stem cell transplantation on cys-

Table 2 Summary of mutation variants of *CTNS* gene and with its phenotypic correlation

Phenotype	Mutation
Five nephropathic: 3 by Town *et al*[58]	*CTNS*, GLY95TER and *CTNS*, 2-BP DEL, 397TG[58], *CTNS*, TRP138TER[58,73].
2 forms by Shotelersuk *et al*[66]	*CTNS*, GLY169ASP and *CTNS*, 5-BP DEL, NT545[66].
Two nephropathic forms in adolescents	*CTNS*, 4-BP DEL, 18GACT[58,65], *CTNS*, 57-KB DEL[61], originally reported by Town *et al*[58] as a 65-kb deletion
Two atypical nephropathic	*CTNS*, VAL42ILE, *CTNS*, IV-S7AS, C-G, -10[67]
Two ocular non-nephropathic	*CTNS*, IVS10AS, C-G, -3, *CTNS*, GLY197ARG[45]
Three forms by Phornphutkul *et al*[68]	*CTNS*, -295G-C[68]
Nephropathic	*CTNS*, -303G-T, *CTNS*, 1-BP INS, 303T[68]
Ocular non-nephropathic	
Nephropathic	*CTNS*, GLY339ARG[69]
Adolescent nephropathic	*CTNS*, ASN323LYS[70]
Atypical nephropathic	*CTNS*, GLY110VAL[62]
Adolescent nephropathic Atypical nephropathic	*CTNS*, SER139PHE[65]

tine accumulation in various organs and on renal function survival, emphasizing the novel potential therapeutic possibilities for cystinosis patients[57].

MOLECULAR VARIANTS

The responsible gene (*CTNS* gene) that encodes the lysosomal cystine carrier cystinosin was cloned in 1998 and is located on the short arm of chromosome 17 (p13)[58]. Molecular analysis of the *CTNS* gene allows early diagnosis and can be used for prenatal diagnosis of the disease. Since the cloning of *CTNS* in 1998, over 90 mutations have been reported, with a detection ratio close to 100%[59,60]. The most common mutation accounting for approximately 75% of the affected alleles in Northern Europe is a 57-kb deletion, affecting the first 10 exons of *CTNS*[61]. A genotype-phenotype correlation related to the clinical forms of cystinosis was observed, with severe truncating mutations mostly found in patients with the infantile form of the disease and at least one mutation in patients with intermediate or adult cystinosis. However, several unexplained exceptions were reported[62].

Selected examples of allelic variants of the *CTNS* gene are listed in Table 2, with some phenotypic correlations. Recently, we described a novel G > A substitution in exon 10 of the *CTNS* gene (c.734 G > A) causing a nonsense truncating mutation (TGG > TAG) due to premature stop codon at position 245 of cystinosin protein (p.W245X). Two patients were diagnosed as homozygous for this mutation, whereas their parents were heterozygous. The patients ran a severe infantile nephropathic course and have recognizable heart malformations in the form of ventricular and atrial septal defects in one case and mild mitral and aortic incompetence in the other[21].

Five different forms of *CTNS* gene mutation were associated with nephropathic cystinosis[58]: (1) a gly95-to-ter mutation; (2) a 2-bp deletion of the *CTNS* gene: a deletion of TG at 397/399 resulted in a stop codon at the site of the mutation; (3) a (TGG-to-TGA) transition was detected at nucleotide 753 resulting in a trp138-to-ter non-sense mutation; (4) a deletion of four nucleotides (GACT) was found at nucleotide 357 of the *CTNS* gene. This resulted in a frameshift and premature termination; and (5) a 65-kb deletion that removes the first 10 exons of *CTNS* gene[58]. The fifth mutation (65-kb del) was originally reported by Town *et al*[58] to be the most common form of *CTNS* gene responsible for nephropathic cystinosis. This deletion was modified to be 57-kb rather than 65-kb after sequencing 200kb surrounding the *CTNS* gene[61]. This mutation was found in a homozygous state later[38,63]. A FISH method was developed, permitting cytogenetic laboratories to test for the 57-kb deletion[64]. A compound heterozygosity for the 57-kb deletion was found with a (928G-A) transition, resulting in a glycine to arginine substitution at codon 197 and with a (416C-T) transition in the *CTNS* gene, resulting in a ser139-to-phe respectively[45,65].

Among seven missense mutations, two mutations were linked to the nephropathic form: (1) a gly169-to-asp substitution; and (2) a 5-bp deletion starting at nucleotide 545 resulting in an (I69R) amino acid substitution and a stop codon at position 73 of the *CTNS* gene[66].

Attard *et al*[67] found different forms of mutations with different presentations. They found a (G > A) transition in the *CTNS* gene, resulting in a val42-to-ile substitution in the non conserved region toward the N terminus. This mutation was consistent with a milder phenotype. In addition, they identified an intronic mutation of the *CTNS* gene, a (C > G) transversion at nucleotide (801-10) in a patient with adolescent cystinosis.

For ocular non-nephropathic type, a (G > A) transition at nucleotide 928 was found, resulting in a glycine to arginine substitution at codon 197 (G197R). In addition, a (C > G) transversion was reported at the -3 position of the acceptor splice site of IVS10 of the *CTNS* gene[45]. Phornphutkul *et al*[68] identified heterozygosity for a (G197R) mutation and a promoter mutation, a (G > T) transversion at nucleotide 303 in the *CTNS* gene. In addition, they identified heterozygosity for a (G197R) mutation and a promoter mutation, an insertion of a single base (T) after position -303 in the *CTNS* gene. Phornphutkul *et al*[68] and Rupar *et al*[69] found mutations linked to the classic form of nephropathic cystinosis. The former identified heterozygosity for a 57-kb deletion and a promoter mutation, a (G > C) change at nucleotide 295 involving the Sp-1 regulatory element in the *CTNS* gene. The latter identified a (G > A) transition at nucleotide 1354. This transition resulted in a glycine-to-arginine substitution at residue 339 (G339R)[68,69].

For adolescent nephropathic variant, Thoene *et al*[70] identified homozygosity for a (1308C-G) mutation in the *CTNS* gene, resulting in the substitution of lysine for the conserved asparagine at position 323 (N323K). In two unrelated Spanish patients with juvenile-onset

nephropathic cystinosis, Macías-Vidal *et al*[65] identified a compound heterozygosity for a (416C-T) transition in the *CTNS* gene and a 4-bp deletion, resulting in a ser139-to-phe (S139F) substitution and a 57-kb deletion respectively.

In a patient who had atypical nephropathic cystinosis (presenting with Fanconi syndrome and end-stage renal disease but surprisingly without extra renal symptoms even late in life), a gly110-to-val (G110V) mutation was detected in the N-terminal region of the *CTNS* gene[62].

GENETIC COUNSELING FOR A PREVENTIVE STRATEGY

As cystinosis is an autosomal recessive disease, parents of a proband are obligate heterozygotes and thus carry one mutant allele, the heterozygotes (carriers) are asymptomatic. Genetic counseling is a method of prevention of recurrence. Recurrence risk is estimated for each sib of an affected individual to be 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 him/her being a carrier is 2/3. However, offspring of a proband are obligate heterozygotes for a mutant allele for *CTNS* gene. Carrier detection has been done in two Egyptian families with reported cases of cystinosis, both biochemically, using freshly prepared leukocytes, and molecularly, defining disease-causing mutations. Marriage of obligate carriers was prevented in one family to prevent the overall disease incidence among these suffering families. With the definition of mutation-causing cystinosis in a target family, we succeeded in preventing recurrence of the disease through the use of pre-implantation genetic diagnosis[49].

The optimal time for determination of the 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, carriers or at risk of being carriers. Women with cystinosis have had successful pregnancies resulting in healthy newborns; however, the potential teratogenic effects of cysteamine on fetuses have not been studied in humans. No data on fertility in males with cystinosis exists; however, spermatogenesis in testicular biopsies was sufficient. Cryopreservation of sperm could be considered in affected males[71].

Prenatal diagnosis allows for early detection of diseases and early cysteamine treatment. This is very important in delaying the onset of renal failure and other complications in cystinosis. In addition, it allows for an early link to cystinosis supporting groups that play important roles in supplying them with unavailable medications and tests[54,72]. Prenatal testing includes both biochemical and molecular tools: (1) Biochemical testing based upon the measurement of cystine concentrations in either chorionic villi obtained at approximately 10-12 wk gestation by CVS or amniocytes obtained by amniocentesis usually performed at approximately 15-18 wk gestation[34]; and (2) Molecular genetic testing is possible by analysis of DNA extracted from fetal cells obtained either by amniocentesis usually performed at approximately 15-18 wk gestation or CVS at approximately 10-12 wk gestation. Both disease-causing alleles of an affected family member must be identified before prenatal molecular testing[54,72]. To sum up, using these advanced optimal methods, obligate carrier parents of *CTNS* gene mutant alleles could be helped to have normal asymptomatic offspring.

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