

# Cystinuria

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## Abstract

*Cystinuria is an autosomal recessive disorder characterized by an impaired transport of cystine, lysine, ornithine and arginine in the proximal renal tubule and in the epithelial cells of the gastrointestinal tract. An elevated cystine concentration in the urinary tract is responsible for the formation of renal stones. Symptoms are those related to renal stone disease: renal colic is often the first symptom, but renal stones may also be detected following a urinary tract infection or unexpectedly found in patients undergoing an abdominal X-ray or ultrasound scan for other reasons. The estimated prevalence of cystinuria ranges from 1:2,500 in the Libyan Jewish population to 1:100,000 in some reports. Treatment requires several different approaches: increased urine pH with alkali to improve cystine solubility, administration to a large amounts of fluids to reduce urine osmolality, using molecules (like  $\alpha$ -mercaptopyropionylglycine and D-Penicillamine) forming chemical bonds with the sulfhydryl domains of the cystine, as they lower the amount of free cystine in the urine. Recent developments in the genetics and physiology of cystinuria do not support the traditional classification, which is based on the excretion of cystine and dibasic amino acids in obligate heterozygotes. A reliable classification should therefore only rely on genetic characterization. We propose that mutations on both alleles of SLC3A1 on chromosome 2 should be called cystinuria type A; mutations on both alleles of SLC7A9 on chromosome 19 should be called cystinuria type B; it is unlikely, although still unclear, that the occurrence of a mutation on a single allele on chromosome 2 and another on a single allele on chromosome 19 is responsible for cystinuria. If this was confirmed, it would be called AB.*

## Keywords

autosomal recessive disorder, Impaired amino acids transport, cystine, lysine, ornithine and arginine, renal stones, SLC3A1, SLC7A9

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## Disease name

Cystinuria

the gastrointestinal tract. An elevated cystine concentration in the urinary tract is responsible for the formation of renal stones.

## Definition

Cystinuria is an autosomal recessive disorder characterized by an impaired transport of cystine, lysine, ornithine and arginine in the proximal renal tubule and in the epithelial cells of

## Differential diagnosis

Any renal stones should be considered in the differential diagnosis of cystinuria.

### Etiology and classification

Cystinuria is an autosomal recessive disease caused by the defective transport of cystine and dibasic amino acids (lysine, ornithine and arginine) in the brush border of proximal renal tubules and intestinal tract. The low solubility of cystine induces its precipitation into the urinary tract.

The traditional classification of cystinuria consists of three subtypes: type I, II and III. In all three subtypes patients show a severe increase in cystine and dibasic amino acids. The three types are differentiated mainly on the basis of urinary amino acids patterns in heterozygotes. According to this classification, type I heterozygotes show a normal amino acid urinary pattern, whereas types II and III have a moderate increase of cystine, lysine, ornithine and arginine urinary excretion. Type II differs from type III by a more severe impairment of intestinal transport, as demonstrated by the lack of increase in plasma level after an oral load of cystine or lysine.

*SLC3A1*, (solute carrier family 3 [cystine, dibasic, and neutral aminobacid transporter], member 1) a gene whose mutations are responsible for type I cystinuria, was first identified in 1994. *SLC3A1* maps to chromosome 2 and encodes rBAT. Thereafter, the defect associated with the most common cystinuria-specific *SLC3A1* mutation was described and over 40 mutations were identified. In 1999, a second gene locus, responsible for the non- type I type cystinuria, was mapped to chromosome 19, *SLC7A9* encoding bo,+AT, was identified. This second gene is thought to encode a subunit that associates with rBAT to form the active transporter. Mutations in this gene appear to cause both type II and III cystinuria. Over 30 mutations in *SLC7A9* have been described so far.

We have recently demonstrated that urinary excretion patterns in heterozygotes are not always sufficiently reliable to provide a good basis for classification.

In a large population from Italy, Spain and Israel, we studied cystine and dibasic amino acid urine levels of 47 type A carriers (due to two mutations of *SLC3A1* (rBAT) on chromosome 2); and 142 type B carriers (due to two mutations of *SLC7A9* on chromosome 19). Amino acid urinary excretions were also measured in 83 healthy subjects, relatives of the affected patients, who accepted to undergo genetic analysis and did not carry the mutations of the probands.

The attribution of healthy carrier to each group was genetically confirmed. The sums of cystine and dibasic amino acids in type A heterozygotes were within the range of the controls, but these values were also within the 95<sup>th</sup> percentile of the

controls in 14 % of type B. Thus, if the classification was based solely on urinary excretion patterns, these findings would lead to an erroneous classification of the offspring (fig 2). The overlapping was also confirmed when we logged plotted cystine and lysine, according to Rosenberg. It is important to note that 5.5 % (*i.e.*, 8 individuals) and 80.5% of type B heterozygotes had amino acid urine levels within the range of type II and type III heterozygotes, respectively, in accordance with the classification of Kelly. Therefore, according to the old classification system, mutations in *SLC7A9* were associated with the three phenotypic types of cystinuria

A reliable classification should therefore only rely on genetic characterization. We propose that:

- mutations on both alleles of *SLC3A1* on chromosome 2 should be called cystinuria type A;
- mutations on both alleles of *SLC7A9* on chromosome 19 should be called cystinuria type B.

It is unlikely, although still unclear, that the occurrence of a mutation on a single allele on chromosome 2 and another on a single allele on chromosome 19 is responsible for cystinuria. If this was confirmed, it would be called AB.

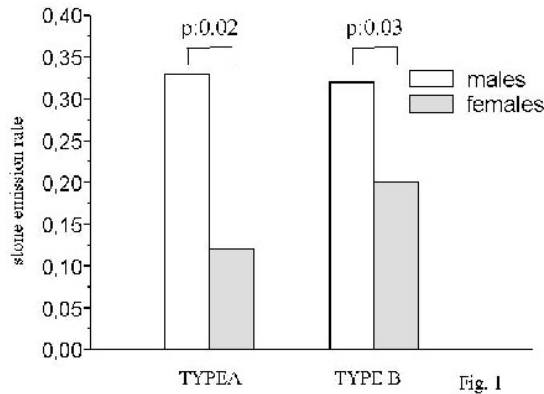
### Clinical description

Symptoms are those related to renal stone disease: renal colic is often the first symptom, but renal stones may also be detected following a urinary tract infection or unexpectedly found in patients undergoing an abdominal X-ray or ultrasound scan for other reasons.

We collected data of 225 patients from Italy, Spain and Israel. In these patients, clinical manifestations almost always occurred early.

Average age at detection of first renal stone was 13.1 y (Standard Deviation SD:± 9.3) for type A and 11.7 y (SD:±8) for type B (p: not significant n.s.). Males and females had similar average age at onset. In all patients, except one, the first renal stone was detected before age 40.

On average, renal stone emissions occurred once every four years, with no difference between type A and B and males had one emitted stone every 3 years, while females had 1 every 5 years (p:0.02) (Fig. 1).



**Fig. 1: spontaneous stone emission per year of life**

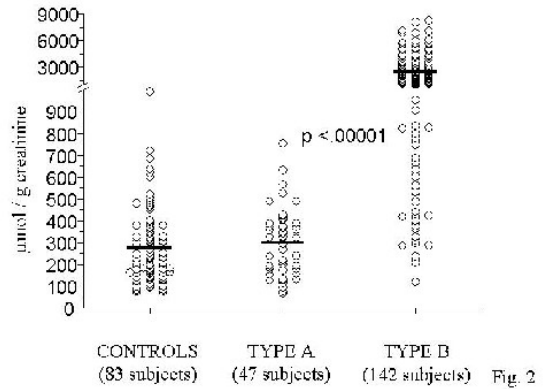
Total stone events (spontaneously emitted stones plus those surgically removed) represented 0.42 episodes per year in males and 0.21 per year in females. Clinical symptoms are almost similar between groups A and B. Renal failure is not a common finding in cystinuria: 17% of our patients had mild renal insufficiency, but only one of them reached end-stage renal failure; 146 patients (out of 176 with reported data) had a plasma creatinine below 120  $\mu\text{mol/l}$  and this value was higher than 200  $\mu\text{mol/l}$  in 6 patients.

**Diagnosis methods**

Diagnosis of cystinuria is based on the detection of a cystine stone in a patient with increased urinary excretion of cystine, lysine, ornithine and arginine, or on the identification of mutations on both alleles of one of the two involved genes. Although the identification of a mild, isolated, increased output of cystine, lysine, ornithine and arginine is an important clue, it is not sufficient for making the diagnosis as some type B healthy carriers could be misdiagnosed as cystinuric patients on the basis of these findings. However, they may be highly suspected of having cystinuria, even in the absence of renal stone, if cystine urine excretion is above 1300  $\mu\text{mol/g}$  creatinine or 150  $\mu\text{mol/mmol}$  creatinine (95° percentile of type B carriers), or if the sum of cystine, lysine, arginine and ornithine urine excretion is above 5900  $\mu\text{mol/g}$  creatinine or 670  $\mu\text{mol/mmol}$  creatinine (95° percentile of type B carriers).

**Prevalence**

The prevalence of cystinuria is unknown. Many cases are probably undetected, as screening programs are not performed in most parts of the world. Moreover, cystinuria is not always looked



**Fig 2: Sum of cystine, lysine, ornithine, arginine in parents of probands (obligated heterozygotes), with a precise genetic characterization and in controls (relatives of the affected, without the mutation of the probands).**

for, even in case of renal stone emission. Its estimated prevalence ranges from 1:2,500 in the Libyan Jewish population to 1:100,000 in some reports. In Europe and the US, prevalence is estimated between 1:10,000 and 1:20,000. It represents 1 to 2 % of all urinary lithiasis.

**Treatment**

Treatment requires several different approaches, regardless of the type of cystinuria:

Urine pH should be increased with alkali (sodium bicarbonate or potassium citrate) to a value above 7.5 to improve cystine solubility

Large amounts of fluids should be administered to reduce urine osmolality, as is advisable for any renal stone disease

Molecules forming chemical bonds with the sulfhydryl domains of the cystine molecule may be used, as they lower the amount of free cystine in the urine (like, for instance,  $\alpha$ -mercaptopyronylglycine and D-Penicillamine).

These drugs may be responsible for several side effects. Among these, the occurrence of proteinuria is not rare; urines must therefore be tested routinely with dipsticks to detect proteinuria.

D-Penicillamine should be withdrawn at least 6 weeks before starting a pregnancy because of possible teratogenicity (although pregnancies have been successfully completed in women receiving the drug).

In Europe,  $\alpha$ -mercaptopyronylglycine is more frequently used. We usually start in children with a dose of 50 mg/kg /day in three doses with a maximum of 750 mg/day. Subsequently, at least every four months, we monitor the free urine cystine level in order to maintain it under 200  $\mu\text{mol/mmol}$  of creatinine.

Data supporting the efficacy of a cystine- or methionine-free diet are currently not available,

while mild restriction of sodium intake is advisable.

### Unresolved questions

Siblings sharing the same mutations and, at least partly the same environment, may have a very different clinical outcome: one may have very frequent stone emissions and/or production, while the other may have a much less severe disease. The reasons for this are unclear: cofactors of lithogenesis or modifier genes need to be identified.

Males present with a more severe form of the disease. This difference is already evident in the very first years of life, much prior puberty, as shown by the different incidence in the first three years of life. Once again, the cofactors of lithogenesis that are involved are still unknown. Medical treatment is difficult: available drugs may have important side effects. New drugs are necessary to improve the clinical outcome.

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