Genotypic and phenotypic features of the cystinosis patients from the South Eastern part of Turkey

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We have conducted this study for the purposes of demonstrating the spectrum of mutations and of identifying their effects on the phenotype, with a particular focus on the clinical course, prognosis and response to treatment. A total of 25 patients from 20 families, who have been treated and followed up after being diagnosed with cystinosis.

Nine patients were identified with mutations of homozygous c.451A>G, 7 patients with homozygous c.681G>A, 6 patients with homozygous c.834_842del, 2 patients with homozygous c.18_21delGACT and 1 patient with compound heterozygous for c.451A>G/ c.1015G>A. The c.834_842del mutation identified in six patients from four families has not been previously identified.

Progression to renal failure occurred earlier in the patients identified with the new mutation, despite treatment. Larger patient series are required to demonstrate the genotypic properties of the patients with cystinosis and their relationship with the clinical course.

Key words: CTNS, cystinosin, cystinosis, Fanconi syndrome, mutations.

Cystinosis is an autosomal recessive disease that can affect many tissues and organs, though it primarily invades the kidneys. It is characterized by the accumulation of an amino acid called cystine in all the lysosomes of the body due to the deficiency of cystinosin, the lysosomal membrane cystine transporter protein[1]. The disease has three clinical types, depending on the age of onset and the grade of the disease: the nephropathic or classical infantile cystinosis, the late-onset juvenile or adolescent nephropathic cystinosis and the ocular nonnephropathic cystinosis. The incidence rate of nephropathic or classical infantile cystinosis is estimated to range from 1:100000 to 1:200000 in North America[2]. In West Brittany, France, the incidence rate is much higher (1:26000) compared to the rest of the country (1:320000)[3]. The indicating signs of renal involvement are dominant in that group, which is also the most frequent type with severe phenotype. Patients develop renal Fanconi syndrome and renal failure in the first decade of life[4]. Retinal changes, such as painful photophobia, may develop due to the corneal deposits in the eye, one of the other organs that is frequently affected by the disease. In those cases when the eye is affected by cystinosis, they can also be diagnosed through a renal functional evaluation, such as hypophosphatemic rickets, renal Fanconi syndrome[5]. The problems associated with extrarenal involvement other than the eye may include hypothyroidism and hypogonadism

in male patients, endocrine and exocrine pancreatic insufficiency, distal myopathy, dysphagia, reduced respiratory functions and neurological complications[2]. The late-onset juvenile or adolescent nephropathic type may show a clinical spectrum varying from mild proximal tubulopathy to severe nephropathic syndrome[1,6]. Most of these patients are older than 10 years. Compared to the adult type, infantile type renal involvement is much faster[7]. The difference of non-nephropathic cystinosis from the other types is, that it is characterized by corneal cystine crystals and photophobia; renal involvement is not seen in this type[7]. Approximately 95% of cystinosis cases concern the nephropathic type[2]. Recently, a family has been reported to have the juvenile and ocular forms simultaneously[8]. This indicates that there may be transitions between the mild forms of cystinosis, and therefore, the renal function of the adult patients with cystinosis should necessarily be monitored.

It is essential to provide supportive treatments to maintain the fluid-electrolyte balance in the management and treatment of cystinosis. Early diagnosis and treatment with appropriate doses of cysteamine provide considerable reduction in the cystine level in the lysosomes, and in addition, may prevent development of renal dysfunction and extrarenal complications[9,10]. They also increase the growth rate. Life-long cysteamine treatment should be maintained in order to protect the extrarenal organs following kidney transplantation. Topical eye drops with cysteamine should be used, as systemic cysteamine therapy does not have any effect on the cystine crystals accumulated in the cornea. These drops are highly effective and can completely dissolve the cystine crystals in 8 to 41 months[5].

There are only a limited number of studies regarding the mutation spectrum of patients diagnosed with cystinosis in Turkey. In this study, we aimed to report the results of *CTNS* mutation analysis in 25 patients with cystinosis in a region where consanguineous marriage is more prevalent than the national average, and to present the implications of the results on the phenotype.

Material and Methods

Patients: A total of 25 patients from 20 families, who have been treated and followed after being diagnosed with cystinosis at Çukurova University Faculty of Medicine, Departments of Pediatric Metabolism and Nutrition and Pediatric Nephrology, were enrolled in the study. Informed consents were obtained from all cases (if older than 18 years obtained from patients, and if younger than 18 years from their parents).

Molecular analysis: Primers designed with PRIMER© – Primer Designer v.2.0 (Scientific & Educational Software programme) software for all the encoding regions, exon-intron junctions and the promoter region of the *CTNS* gene. DNA isolation was conducted from the EDTA treated blood samples collected from the patients by using the spin column method. Sequencing reaction was performed using the automated ABI Prism 3130 GeneticAnalyser (Applied Biosystems, Inc., Foster City, Ca, ABD) capillary electrophoresis instrument for DNA sequence analysis. The sequence reaction was performed with the Big Dye Terminator cycle sequencing kit (Applied Biosystems, Inc., Foster City, Ca, US) using the forward and reverse primers, employed in the standard PCR, as primer. For this reason, the reaction mixture was prepared by diluting 2 μl of purified PCR product, 3 μl of big dye and 2 μl (3.2 pmol/ul) of primer, resulting in a total volume of 10 μl with the inclusion of distilled water. The cycle sequencing process was done with the obtained mixture using the same study protocol in the PCR device, and the resulting product was purified. After, formamide was added into the product, and following denaturation at 95°C for 5 minutes, the product was immediately placed onto ice and allowed to stand for 2 minutes before operating the sequence device following the loading process. Loading process was done with the standard protocol given in user manual of the capillary electrophoresis device. The reference sequence obtained from the Ensembl database and the sequences from the samples examined were compared using the software developed by ABI for the comparison of DNA sequences.

Blood was collected from the patients into 10 ml heparin tubes to determine the leukocyte cystine level. The leukocytes were then isolated. The cystine level in the isolated leukocytes was studied using the LC-MS/MS method (Watres Acquity UPLC, Zevo TQ-S mass spectrometry,

Table I. Clinical Features of Patients

Number of patient	Sex	Age (year)	Age of diagnosis (months)	Consanguinity	Affected sibling	Leukocyte cystine level nmol (½cyst/mgptn) Normal range <0,2	Eye involvement (At the time of diagnosis)	Other organ involvement	Renal status	RRT
1	M	12,5	24	Yes	No	12.7	Yes	GR	ESRD at the age of 10y	CAPD
2	F	13	108	No	No	2.1	Yes	No	RTA	
3	F	18	120	Yes	Sib of 4	2.2	Yes	GR	RTA	
4	M	9	24	Yes	Sib of 3	2.9	Yes	GR	RTA	
5	F	6	48	Yes	Sib of 6	11.9	Yes	GR,	RI	
6	M	3	10	Yes	Sib of 5	8.2	Yes	GR, Hypothyroidism	RTA	
7	F	2.5	6	No	No	2.4	No	No	RTA	
8	M	10.5	60	Yes	No	12	Yes	GR	ESRD	CAPD
9	F	2.5	9	Yes	No	4.5	No	GR	RTA	
10	F	6	24	Yes	No	8.7	Yes	GR	RTA	
11	M	15	108	No	Sib of 12	7	Yes	GR	RTA	
12	M	19.5	168	No	Sib of 11	5.2	Yes	GR, Hypothyroidism	RTA	
13	M	10	20	Yes	No	2.1	No	GR	RI	
14	M	6.5	30	Yes	No	6.8	Yes	GR	RTA	
15	M	2	9	Yes	No	7.3	No	No	RTA	
16	M	19	132	No	Yes	4.6	Yes	GR, Hypothyroidism	ESRD	HD
17	M	9.5	34	Yes	Sib of 18	4.9	Yes	GR	RI	
18	M	8	24	Yes	Sib of 17	4.5	Yes	GR	RI	
19	M	3	21	Yes	Sib of 25	3.8	No	GR	RTA	
20	F	8	84	Yes	No	5.8	No	GR, Hypothyroidism	RTA	
21	F	4.5	48	Yes	No	28.6	Yes	GR, Hypothyroidism	RI	
22	F	2	17	Yes	No	2.9	Yes	Hypothyroidism	RTA	
23	M	6.5	63	Yes	No	8.5	Yes	GR, Hypothyroidism	ESRD	CAPD
24	M	1.5	8	Yes	No	3.1	No	No	RTA	
25	F	1	6	Yes	Sib of 19	4.2	No	No	RTA	

M: Male; F: Female; CAPD: Continuous ambulatory peritoneal dialysis; ESRD: End-stage renal disease; HD: Hemodialysis; GR: Growth retardation; RI: Renal insufficiency; RRT: Renal replacement therapy; RTA: Renal tubular acidosis

Ireland). The results were given in nmol ½cyst/mgptn. In general, leukocyte cystine levels are > 2 nmol ½cyst/mgptn in affected patients, whereas normal subjects have levels < 0.2 nmol ½cyst/mgptn.

Results

A total of 25 patients, 15 males and 10 females, ranging in age from 1 to 19 years, from 20 independent families were evaluated in terms of genotype and phenotype. Second degree cousin marriage was the case in 16 families, and 18 patients were from the same province. Four of these families had two affected children. The age of the patients at the time of diagnosis varied from 6 months to 14 years. All of the patients had been receiving treatment with cysteamine bitartrate (1.3-1.95 g/m²/day) at the time of the diagnosis. Three patients were receiving continuous ambulatory peritoneal dialysis (CAPD) due to the end-stage renal disease, and one patient was receiving hemodialysis twice a week. Five patients developed chronic renal disease without the need for dialysis.

All of the patients were screened for mutations in *CTNS* gene by sequence analysis. Mutations were given by using ENST00000046640 transcript. A total of five mutations, one of which had not previously been identified, were determined. Nine patients were identified with homozygous NM_004937.2(*CTNS*):c.451A>G (p. R151G) missense mutation, 7 patients with homozygous NM_004937.2(*CTNS*):c.681G>A splice site mutation, 6 patients with homozygous NM_004937.2(*CTNS*):c.834_842del mutation, 2 patient with homozygous NM_004937.2(*CTNS*): c.18_21delGACT (p.T7Ffs*7) frameshift mutation, and 1 patient with compound heterozygous for NM_004937.2(*CTNS*):c.451A>G (p. R151G) / NM_004937.2(*CTNS*): c.1015G>A (p.G339R) missense mutations. Allele frequency was performed on the basis of family to avoid a sampling error, as the patients 3-4, 5-6, 11-12, 17-18 and 19-25 were siblings. Although among 50 alleles of 25 patients, c.451A>G mutation was identified in 19 alleles, c.681G>A in 14 alleles, c.834_842del in 12 alleles, c.18_21delGACT in 4 alleles and c.1015G>A in 1 allele, when the study evaluated one individual for each of the 20 families, c.451A>G

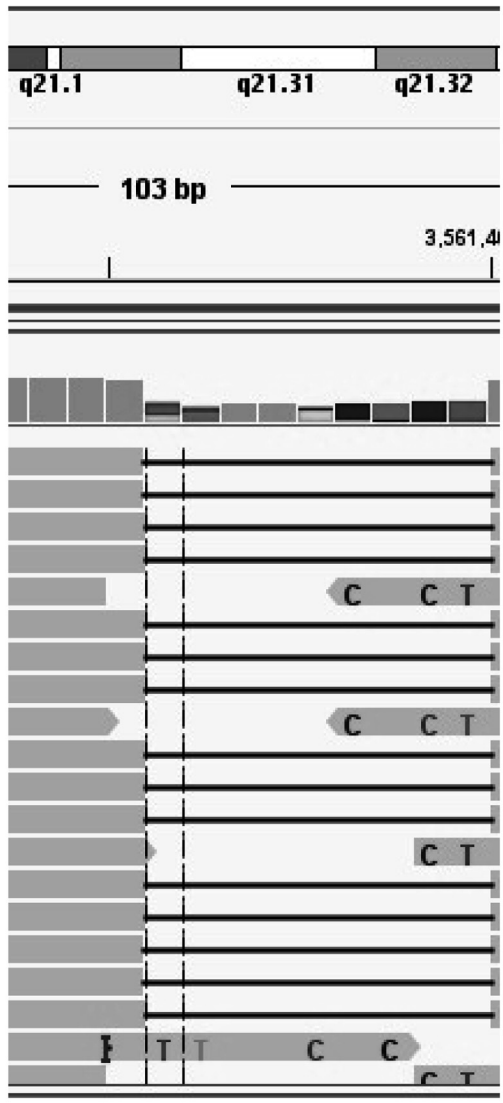

Fig. 1. Novel mutation detected in this study

mutation was identified in 15 alleles (37,5%), c.834_842del in 8 alleles (20%), c.681G>A in 12 alleles (30 %), c.18_21delGACT in 4 alleles (10%) and c.1015G>A (2.5%) in 1 allele out of 40 alleles in the allele frequency study performed. The c.834_842del mutation identified in six patients was a mutation that had not been described before. This mutation, resulting from the homozygous 9-nucleotide deletion leading to loss of 3 amino acids in Exon 10, was determined in 4 families (Fig. 1). The families' pedigree are shown in figure 2. Further, 10 patients were identified with c.451A>G mutation, which was described for the first time in Turkey. Table I, II, III and Table IV show the clinical characteristics of

Table II. Mutations of the Patients (novel mutations written in bold)

Number of patient	Position	Base change	AA change	Reference	
1	Exon 10 Exon 10	c.834_842del c.834_842del	p.V279_Y281del		In-frame deletion the loss of three amino acids
2	Exon 7 Exon 7	c.451A>G c.451A>G	p.R151G	Topaloğlu et al. 2012	
3	Exon 7 Exon 7	c.451A>G c.451A>G	p.R151G	Topaloğlu et al. 2012	
4	Exon 7 Exon 7	c.451A>G c.451A>G	p.R151G	Topaloğlu et al. 2012	
5	Exon 10 Exon 10	c.834_842del c.834_842del	p.V279_Y281del		In-frame deletion the loss of three amino acids
6	Exon 10 Exon 10	c.834_842del c.834_842del	p.V279_Y281del		In-frame deletion the loss of three amino acids
7	Exon 7 Exon 12	c.451A>G c.1015G>A	p.R151G p.G339R	Topaloğlu et al. 2012 Shotelersuk et al. 1998	
8	Exon 9 Exon 9	c.681G>A c.681G>A	p.E227E	Aldahmesh et al. 2009	
9	Exon 9 Exon 9	c.681G>A c.681G>A	p.E227E	Aldahmesh et al. 2009	
10	Exon 7 Exon 7	c.451A>G c.451A>G	p.R151G	Topaloğlu et al. 2012	
11	Exon 7 Exon 7	c.451A>G c.451A>G	p.R151G	Topaloğlu et al. 2012	
12	Exon 7 Exon 7	c.451A>G c.451A>G	p.R151G	Topaloğlu et al. 2012	
13	Exon 10 Exon 10	c.834_842del c.834_842del	p.V279_Y281del		In-frame deletion the loss of three amino acids
14	Exon 7 Exon 7	c.451A>G c.451A>G	p.R151G	Topaloğlu et al. 2012	
15	Exon 3 Exon 3	c.18_21delGACT c.18_21delGACT	p.T7fs	Town 1998	
16	Exon 7 Exon 7	c.451A>G c.451A>G	p.R151G	Topaloğlu et al. 2012	
17	Exon 10 Exon 10	c.834_842del c.834_842del	p.V279_Y281del		In-frame deletion the loss of three amino acids
18	Exon 10 Exon 10	c.834_842del c.834_842del	p.V279_Y281del		In-frame deletion the loss of three amino acids
19	Exon 9 Exon 9	c.681G>A c.681G>A	p.E227E	Aldahmesh et al. 2009	
20	Exon 7 Exon 7	c.451A>G c.451A>G	p.R151G	Topaloğlu et al. 2012	
21	Exon 9 Exon 9	c.681G>A c.681G>A	p.E227E	Aldahmesh et al. 2009	
22	Exon 9 Exon 9	c.681G>A c.681G>A	p.E227E	Aldahmesh et al. 2009	
23	Exon 9 Exon 9	c.681G>A c.681G>A	p.E227E	Aldahmesh et al. 2009	
24	Exon 3 Exon 3	c.18_21delGACT c.18_21delGACT	p.T7fs	Town 1998	
25	Exon 9 Exon 9	c.681G>A c.681G>A	p.E227E	Aldahmesh et al. 2009	

H: homozygote, h: heterozygote

Table III. Mutation Details Detected in Our Study Group

Position	Mutation	Allele frequency (%)	References	HGMD-Public	Notes
Exon 3	c.18_21delGACT (p.T7Ffs*7)	10	Town 1998	CD982561	Frame shift mutation causing premature stop codon. Pathogenic due to Mutation taster software.
Exon 8	c.681G>A (p.E227E)	30	Aldahmesh et al. 2009		Last nucleotide of exon 8. Splice site mutation.
Exon 7	c.451A>G (p.R151G)	37.5	Topaloğlu et al. 2012	CM1110321	Pathogenic due to Mutation taster, SIFT, SIFT Provean and Polyphen prediction softwares.
Exon 10	c.834_842del (p.V279_ Y281del)	20	Novel Mutation		In-frame deletion the loss of three amino acids (VKY aminoacids). K and Y aminoacids is conserved in different species. This deletion is on transmembrain Helical domain and PQ-loop 2. Mutation taster prediction: Disease-causing (0.967821779118879).
Exon 12	c.1015G>A (p.G339R)	2.5	Shotelersuk et al. 1998	CM980461	rs121908127. Pathogenic due to Mutation taster, SIFT, SIFT Provean and Polyphen prediction softwares.

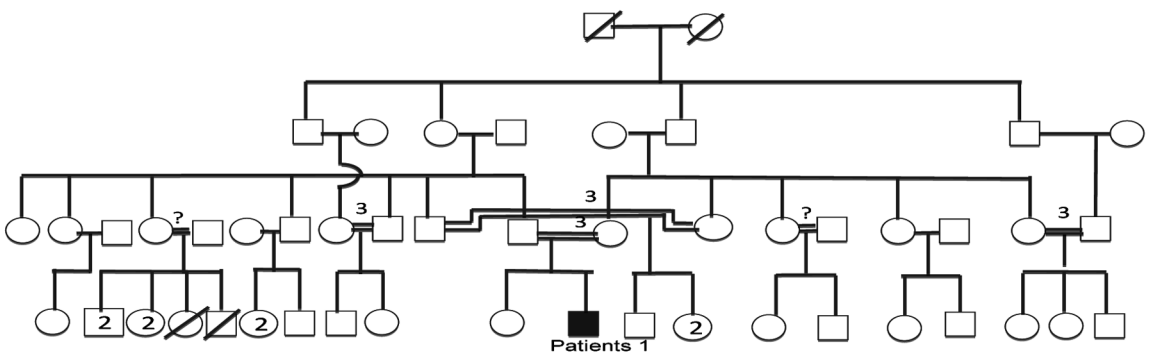

Fig. 2a. Pedigree of patient 1

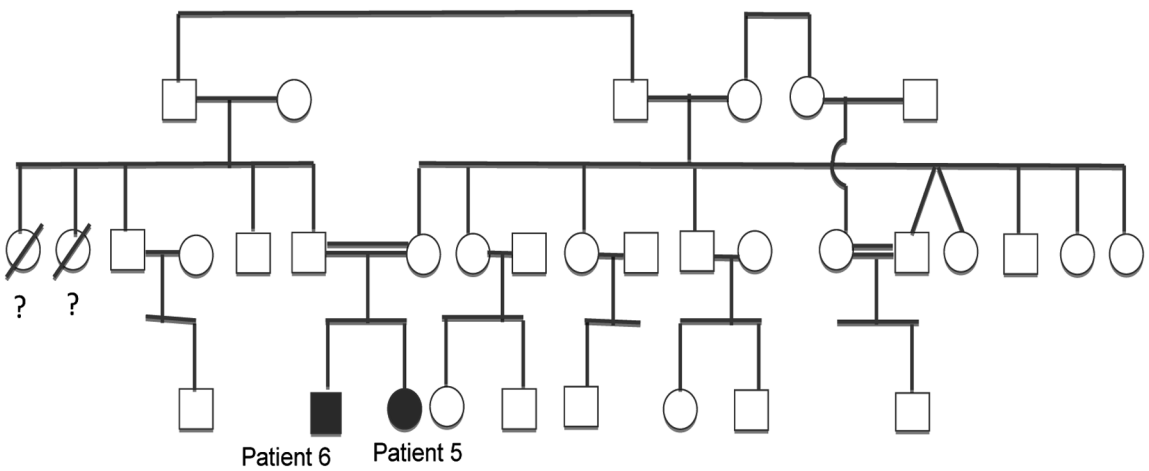

Fig. 2b. Pedigree of patients 5-6

Table IV. Conservation Table of Mutation c.834_842del (p.V279_Y281del)

Species	Match	Gene	AA	Alignment
Human		ENST00000046640	279	C F S Y I K L A V T L V K Y F P Q A Y M N F Y Y K S
mutated		ENST00000046640	279	C F S Y I K L A V T L - - - F P Q A Y M N F Y Y K
P. troglodytes	all identical	ENSPTRG00000008572	254	C F S Y I K L A V T L V K Y F P Q A Y M N F Y Y K
M. mulatta	all identical	ENSMMUG00000023389	279	C F S Y I K L A V T L V K Y F P Q A Y M N F H Y K
F. catus	all identical	ENSFCAG00000007923	279	C F S Y I K L A V T L V K Y F P Q A Y M N F Y Y K
M. musculus	all conserved	ENSMUSG00000005949	279	C F S Y I K L I I T L I K Y F P Q A Y M N F Y Y K
G. gallus	all conserved	ENSGALG00000004628	290	C F S Y I K L A V T L I K Y F P Q A Y M N F R R K
T. rubripes				
D. rerio	all identical	ENSDARG00000008890	284	Y F S Y I K L G V T L V K Y I P Q A H M N Y R R K
D. melanogaster	all conserved	FBgn0039045	284	Y C S Y V K L T I T I I K Y V P Q A L M N Y R R K
C. elegans	partly conserved	C41C4.7	281	S L S Y I K M A V T C C K Y F P Q A Y F N Y T R K
X. tropicalis	all conserved	ENSXETG00000005795	289	C F S Y I K L A I T L I K Y F P Q A Y M N F R R K

Multiple amino acid alignment of human CTNS with other species CTNS proteins. The valine 279_tyrosine 281 residues of CTNS are marked with grey.

the patients and the results of the genetic analysis, respectively.

Discussion

In this study, we reported the molecular genetic analysis results of 25 patients with cystinosis. We have identified five different *CTNS* mutations, one of which had not been described before and one of which was described for the first time in Turkey. The 57-kb deletion is the most common type, affecting the first 10 exons and the intron region of the *CTNS* gene, at a rate of 37% in patients with cystinosis in Europe and North America[11-13]. In parallel with the results obtained by Topaloğlu et al.[14] in Turkey, none of the patients were identified with 57-kb deletion. Therefore, it would be safe to conclude that the patients with cystinosis in Turkey have a different mutation spectrum from those of Europe and the USA. In a study performed by Shahkarami et al.[15], 57-kb deletion could not be demonstrated in Iran, but rather, the c.681G>A mutation was reported as the most common type of mutation, a discovery described by Aldahmesh et al.[16] for the first time in Arabian society.

In this study the c.451A>G mutation was determined in 10 patients, one of which was a compound heterozygote. c.451A>G mutation was described by Topaloğlu et al.[14] for the first time in 2012 in Turkey[14]. Having been identified in 19 out of 50 alleles (38%) obtained from 25 patients, this mutation was the most common type in the study group. The frequency of this mutation was determined to be 37.5% in the evaluations performed on the basis of families. The c.834_842del mutation, which also had never been described in the literature, was observed in 12 out of 50 alleles (frequency of allele 24%). This frequency was determined as 20% in the evaluation performed on the basis of families. This indicates that these two mutations, which have only been described in Turkey, are observed in 57.5% of the alleles studied in the region. The allele frequency was determined as 30% for c.681G>A mutation. The allele frequency of c.18_21delGACT mutation described for the first time by Town et al.[11] was found as 10% in two patients, whereas the allele frequency of c.1015G>A mutation, being a compound heterozygous for c.451A>G, described by Shotelersuk et

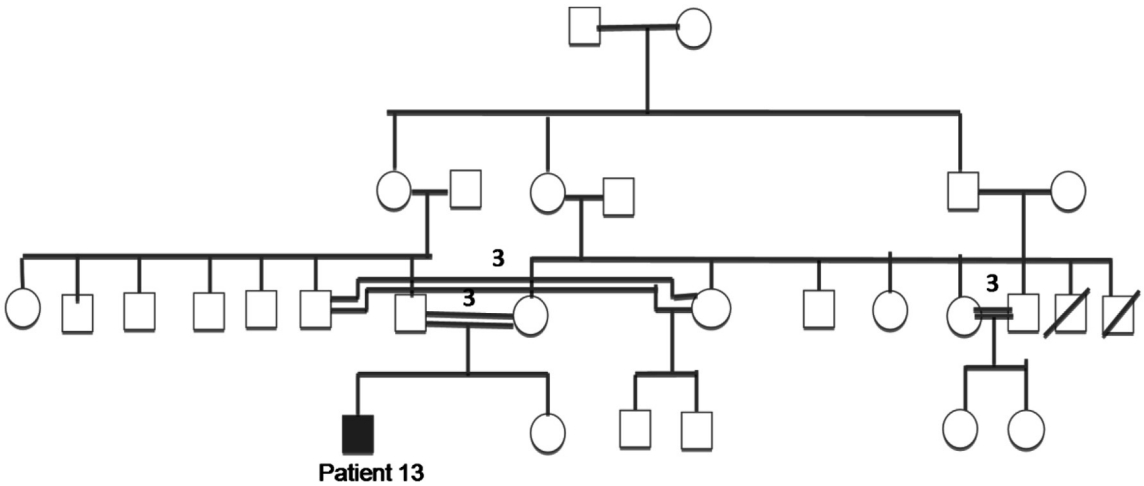

Fig. 2c. Pedigree of patient 13

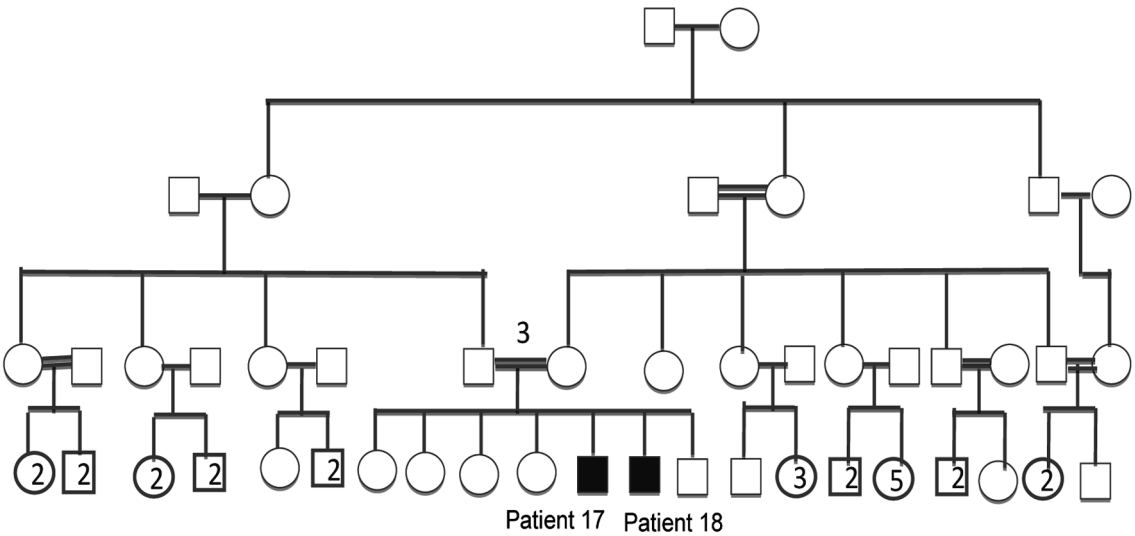

Fig. 2d. Pedigree of patients 17-18

al.[12] was found as 2.5%. Homozygous variants were identified in patients 2, 11, 12, and 16 despite the absence of known consanguineous relationship between the partners. This may be explained by the fact that these families present with the most common type in our country, the c.451A>G mutation, or that the information obtained from the families regarding the consanguineous relationship could have been inaccurate. A compound heterozygous variant was identified in patient 7, whose parents do not have a consanguineous relationship. With regards to evaluation in terms of phenotypic properties, among 6 patients identified with a new mutation, patient 1 was on CAPD program due to end-stage renal disease (ESRF), with an aggressive clinical and severe course at the age of 10 years, and four patients with numbers 5, 13, 17, and 18 were monitored as a result of their renal insufficiency (RI). Therefore, it can be concluded that the new mutation leads to a rapid progression to renal failure (5/6) and is associated with severe clinical course, despite early diagnosis and treatment. The most common type in our study, the c.451A>G mutation, was previously described in Turkey and associated with a moderate clinical course[16]. Similarly, all of our patients with the c.451A>G mutation (2, 3, 4, 10, 11, 12, 14, 16, 20) were diagnosed between the ages of 2 to 14 years with renal tubular acidosis (RTA), excluding only one patient. Patient 16, who was on

hemodialysis program due to ESRF.

Patient 7, who has compound heterozygous for c.451A>G and c.1015G>A, was diagnosed at age 6 months and is still being monitored for RTA. The presentation of the clinical indications in a patient identified by Topaloğlu et al.[14] with a similar mutation association at early stage may indicate that these two mutations together result in a mild clinical course.

Three out of seven patients with the c.681G>A mutation are on the CAPD program due to renal failure. Similarly, Topaloğlu et al.[14] reported the same mutation in homozygosity in three patients with early age diagnosis and an aggressive course. This mutation was first described in Saudi Arabia and then reported as being the most common mutation, which results in an early-onset clinical course, as also shown by a study in Iran.[15,16] All of these findings suggest that this mutation may be of Middle East origin and emerged in Turkey as a result of migrations from the Middle East.

Patients 15 and 24 were diagnosed early with c.18_21delGACT mutation, and are being followed for RTA at our clinic. Similarly, the studies performed in Italy and Turkey have reported that this mutation presented early indications and a slow course.[14,17]

Consequently, upon comparison of the patients with cystinosis in this particular region with the European and North American patients, it is clear that different *CTNS* variants result in this disease. Sharing of some of the mutations between the Middle East countries and Turkey is likely due to the historical and geographical proximity. However, c.451A>G and c.834_842del mutations appear to be specific to the Turkish society. While c.451A>G mutation is associated with a moderate clinical course, c.834_842del mutation is associated with a severe clinical course. Larger patient series are required to demonstrate the genotypic properties of the patients with cystinosis and their relationship with the clinical course.

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