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Screening for Fabry disease in patients undergoing dialysis for chronic renal failure in Turkey: Identification of new case with novel mutation

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ABSTRACT

Background: Chronic renal failure (CRF) is a serious complication of Fabry disease (FD). The aims of the present study were to determine the prevalence of unrecognized FD in Turkish hemodialysis population and to investigate the molecular background.
Method: Primarily, α-galactosidase A (α-Gal A) activity was investigated on DBS in 1136 patients of both sexes who underwent dialysis for CRF in Turkey. The disease was confirmed by analyzing enzyme activity in leukocyte and *GLA* gene sequencing in all patients in whom α-Gal A level was 40% of normal or less.
Results: Mean age of the patients (44.5% female, 52.5% male) was 56.46 ± 15.85 years. Enzyme activity was found low with DBS method in 12 patients (four males, eight females). Two men, but no women, were diagnosed with FD by enzymatic and molecular analysis. In consequence of genetic analysis of a case, a new mutation [hemizygote c.638C>T (p.P214S) missense mutation in exon 5] was identified, which was not described in literature. Family screening of cases identified six additional cases.
Conclusion: As a result of this initial screening study performed on hemodialysis patients for the first time with DBS method in Turkey, the prevalence of FD was detected as 0.17%. Although the prevalence seems to be low, screening studies are of great importance for detecting hidden cases as well as for identifying other effected family members.

1. Introduction

Fabry disease (FD) (OMIM, ID 301500) is a rare X-linked lysosomal storage disorder caused by deficient activity of the enzyme α-Gal A resulting from mutations affecting the *GLA* gene (OMIM, ID 300644). It is characterized by severe multisystemic involvement that leads to major organ failure and premature death in affected men and in some women. The α-Gal A deficiency results in progressive accumulation of undegraded glycosphingolipids, predominantly globotriaosylceramide (Gb3), within cell lysosomes throughout the body (Desnick et al., 2001; Mehta et al., 2009). The condition has conventionally been considered to be rare, affecting only 1 in 40,000 to 1 in 238,000 male individuals (Meikle et al., 1999; Poorthuis et al., 1999; Poupetová et al., 2010). However, a newborn screening study suggested that the incidence of FD might be 1 in 3100 to 1 in 4100 births for late-onset disease and 1 in 37,000 births for classic phenotype (Mechtler et al., 2012; Spada et al., 2006). The frequency of FD is obviously higher in high-risk populations, such as patients with CRF requiring dialysis, left ventricular hypertrophy (LVH), and stroke (Linthorst et al., 2010).

In patients with classic phenotype, characteristic findings of the disease occur as a result of accumulation of substrate in endothelium. Significant findings of the disease, such as angiokeratoma, hypohydrosis, corneal and lenticular opacities, and acroparesthesia begin in childhood. In patients at the second or third decade, progressive proteinuria, decline in glomerular filtration rate (GFR), and tubular damage occur usually, and renal failure develops in the fourth decade. Life-threatening renal, cardiac, and cerebrovascular diseases are added in later decades. Primary cause of death commonly seen in the fourth and fifth decades is renal failure, particularly in affected male patients (Eng et al., 2006; Sessa et al., 2001). When compared to normal population, death occurs approximately 20 years earlier in male patients, and 15 years earlier in

Abbreviations: α-Gal A, alpha-galactosidase A; CKD, chronic kidney disease; CRF, chronic renal failure; DBS, dried blood samples; DNA, deoxyribonucleic acid; DP, dialysis patients; EDTA, ethylenediaminetetraacetic acid; FD, Fabry disease; Gb_3, globotriaosylceramide; GFR, glomerular filtration rate; HD, hemodialysis; HGVS, Human Genome Variation Society; LVH, left ventricular hypertrophy; MI, myocardial infarction; PCR, polymerase chain reaction; PD, peritoneal dialysis; RF, renal failure.

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Table 1
Distribution of gender and age, mean enzyme activities, and results of screening test of patient and control groups.

	Age (Mean ± SD)	Enzyme activity in DBS (μmol/L/st)	Positive screening test[a] (n)	Patients with FD[b] (n)
Dialysis patients				
Female (n = 521)	56.13 ± 17.01	2.98 ± 2.31	8	0
Male (n = 615)	56.73 ± 14.83	3.01 ± 2.58	4	2
Total (n = 1136)	56.46 ± 15.85	2.98 ± 2.43	12	2
Control (n = 30)	32.40 ± 8.86	3.13 ± 1.28	–	–

[a] Number of cases with enzyme activity in DBS 40% lower than control group.
[b] Number of cases (n) confirmed with intra-leukocyte enzyme analysis and genetic analysis.

female patients (Mehta et al., 2009). Therefore, early diagnosis is of vital importance in cases with FD.

Although the disease has an X-linked recessive inheritance pattern, female carriers may present with some symptoms, and rarely, with complete clinical manifestations of the disease related to random X-chromosomal inactivation (Wilcox et al., 2008). As in other lysosomal storage diseases, clinical findings in FD also differ from case to case. In milder cardiac and renal variants, residual α-Gal A is found, symptoms begin in adulthood, and clinical findings are limited to heart or kidneys (Meroni et al., 1997; Nakao et al., 2003). Diagnosis of FD is made by measuring α-Gal A activity in plasma or leukocytes. Enzyme replacement therapy, that became available especially in recent years, has changed and improved natural course of the disease by preventing deposition in the organs (Schaefer et al., 2009). Recognition of FD before clinical findings emerged has become crucial, for the success in its therapy and development of new therapy methods. Therefore, patients with stroke of unknown cause and cardiovascular diseases and those who undergo dialysis for CRF at an early age should be considered high-risk group and screened for Fabry disease, thus, early diagnosis of the patients in the family of the patients detected should be ensured by family screening.

The present study aimed to screen Fabry disease enzymatically and molecularly in a patient group that underwent dialysis for CRF in Ankara city, Turkey. Although there are reports about the screening of this target population in various countries, there is lack of data from Turkey in the literature.

2. Method

Totally, 1136 patients (521 females, 615 males) who underwent dialysis for CRF in 16 dialysis centers in the province of Ankara were recruited in the study. The study was initially approved by the Local Ethical Committee of Gazi University Medical School, and written consent was obtained from the patients before the samples were collected. Distribution of gender and age, mean enzyme activities, and results of screening test of dialysis patients and control groups are given in Table 1.

2.1. Blood collection

Primarily, venous blood samples of patients on dialysis treatment were collected for evaluation with a syringe before dialysis. Four drops of the blood were transferred to a filter paper, allowed to dry at room temperature, and stored at 2–4 °C before being centrally processed. Enzyme activity in leukocytes was analyzed by collecting 10 cc blood samples into test tubes containing ethylenediaminetetraacetic acid (EDTA) from the patients whose α-Gal A activity in DBS samples was 40% lower than control sample. DNA sequencing of the *GLA* gene was carried out after collecting 3 cc blood samples into test tubes containing EDTA from patients with low the α-Gal A activity. All laboratory tests were performed in Pediatric Metabolic Disorders and Genetics Laboratory, Gazi University, School of Medicine, Ankara, Turkey.

2.2. Measurement of α-Gal A activity

Measurement of enzyme activity in dried blood spot samples was performed using the method by Chamoles et al. (2001). The enzyme activities were calculated in μmol/L/h.

The determination of α-Gal A activity in leukocyte was done using the technique previously described by Desnick et al. (1973). Values between 9–31 nmol/h/mg proteins were considered normal.

2.3. DNA sequencing of the GLA gene

Sequence analysis was carried out for the *GLA* gene, using genomic DNA samples. Genomic DNA was extracted from buffy coat cells using the QIAamp DNA Blood Midi Kit (Qiagen, Valencia, CA) according to the manufacturer's instructions. The genomic primers covered the intron–exon boundaries as well as the exons. Primers are available upon request. The PCR amplification of the *GLA* exons 1 to 7 was performed in a 50 μL reaction mixture which contained 100 ng of genomic DNA, 25 mM $MgCl_2$, 10 mM of each deoxynucleotide triphosphate, 2.5 U of DNA polymerase (Gold Taq, Applied Biosystems), and 20 pmol of each primer. PCR products were resolved by electrophoresis on a 1% agarose gel. After cleaning-up, the products were sequenced in both directions

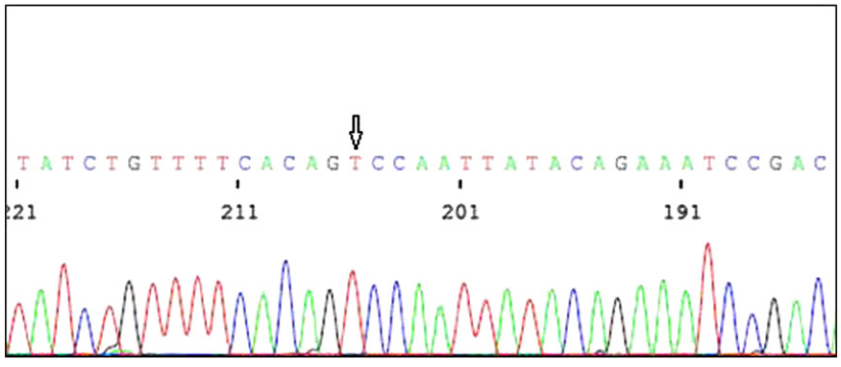

Fig. 1. The hemizygote c.638 C>T change in *GLA* gene of the case 2, which it has not been reported previously in FD.

Table 2
The age, sex, clinical symptoms and laboratory findings of two cases with FD.

	Case 1	Case 2
Age (years)/Sex	48/Male	52/Male
Known etiology of RF	Unknown	Pyelonefrit
Age at onset of dialysis (years)	40	29
Clinical findings	Cornea verticillata Osteoporosis Renal failure Left ventricular hypertrophy Peripheral neuropathy Acroparesthesia, hypohydrosis Sensorineural hearing loss CNS involvement	Cornea verticillata Renal failure Left ventricular hypertrophy Myocardial infarction Peripheral neuropathy Acroparesthesia, hypohydrosis Sensorineural hearing loss
Enzyme activity in DBS[a] (μmol/L/h)	0.18	0.26
Enzyme activity in leukocyte[b] (nmol/h/mg protein)	1.06	1.23
Genetic analysis	Hemizygote c.823C>T in exon 6	Hemizygote c.638C>T in exon 5

[a] Control range: 3.13 ± 1.28 μmol/L/st.
[b] Normal range: 21.8 ± 10.29 nmol/h/mg protein; RF, renal failure.

using the forward and reverse primers using the BIG DYE Dye Terminator Cycle Sequencing Kit (Applied Biosystems). For the description of alterations, nucleotide numbering using the A of the ATG translation initiation start site of the coding DNA reference sequence, was denoted as nucleotide + 1. The alteration nomenclature was arranged according to the current guidelines at the Human Genome Variation Society (HGVS) website [http://www.hgvs.org/mutnomen/].

3. Results

A total of 1136 dialysis patients with end-stage renal disease from 16 dialysis centers in the province of Ankara in Turkey were screened in the present study. Of the study patients, 615 (54.1%) were male, and 521 (45.9%) were female. Mean age of all patients was 56.46 ± 15.85 years (range, 18–90 years).

Mean α-Gal A activities in DBS of all patients and 30 healthy controls were 2.98 ± 2.43 μmol/L/st and 3.13 ± 1.28 μmol/L/st, respectively. The results of the control group were consistent with the data in literature (Chamoles et al., 2001).

In 12 (1.05%; 4 males, 8 females) of 1136 patients, the screening test with DBS was positive. The enzyme analysis in leukocyte and genetic testing were performed in all of the 12 patients. In two of 12 patients, the enzyme activities in leukocytes were too low. Both of the two patients were male. The enzyme activities in leukocytes were determined as normal in eight female and two male patients with positive screening test and the results of their genetic testing were negative. Genetic testing revealed presence of missense mutations in both patients with markedly decreased α-Gal A activity. Case 1 was found to carry hemizygote c.823C>T (p.L275F) missense mutation in exon 6, which was reported previously in literature. Case 2 was found to carry hemizygote c.638C>T (p.214S) missense change in exon 5, and this change has not been reported previously in FD patients (Fig. 1). The age, sex, clinical symptoms and laboratory findings of two cases with FD are given in Table 2.

As a result, the prevalence of FD in all dialysis patients of the study was 0.17% (0.32% in men, 0.0% in women).

Family screenings of the patients detected to have FD as a result of the study were performed as enzyme analysis in leukocytes and genetic testing. Single daughter of case 1 was determined as carrier and her leukocyte enzyme activity was in normal range. In family screening of case 2 who has a new unknown change in *GLA* gene, the disease was detected as carrier in three daughters and a granddaughter and they have the enzyme activities in leukocyte ranging from normal to very low activities (14.5, 12.04, 6.87 and 3.9 nmol/st/mg protein; NR, 21.8 ± 10.29). His grandson, is 14 years-old, has acroparesthesia of unknown etiology since the age of 8 and LVH. His leukocyte enzyme activity was too low (0.12 nmol/st/mg protein; NR, 21.8 ± 10.29). The results of family screening of the patients—along with the family trees, clinical findings, enzyme activities, and results of genetic screening of the cases—are shown in Figs. 2 and 3.

4. Discussion

This is the first comprehensive FD screening study including both genders carried out in Turkey. Diagnosis of FD is difficult. The symptoms are usually nonspecific, and the findings can easily be overlooked. Chronic kidney disease (CKD) is a prominent feature of classical and variant FD and the main cause of premature death in the classical phenotype. Especially after enzyme therapy came up, long-term complications of the disease, notably renal failure, have become preventable. Therefore,

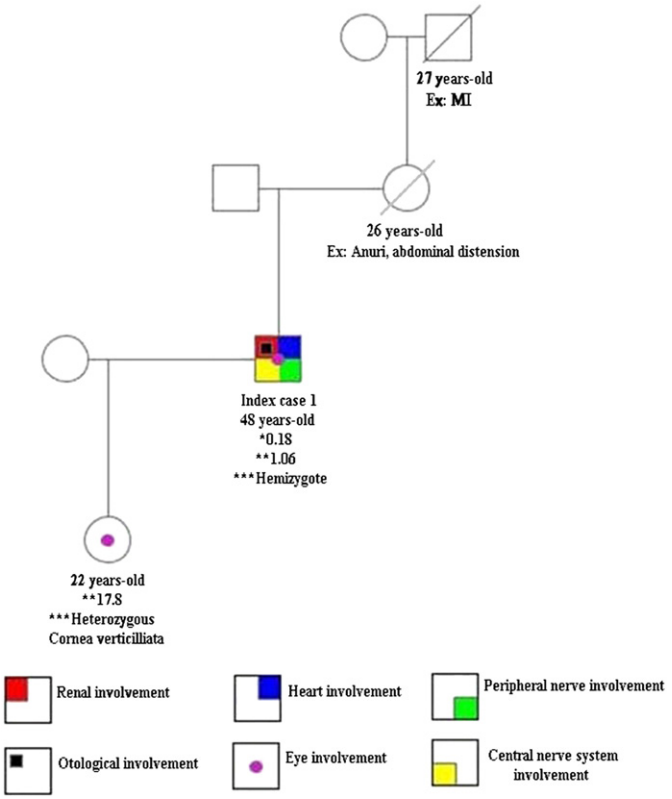

Fig. 2. The result of family screening and pedigree of case 1. Enzyme activity in *dried blood samples (μmol/L/h) and **leukocyte (nmol/h/mg protein). ***Analysis of whole genome sequencing in *GLA* gene (c.823C>T in exon 6). MI, myocardial infarction.

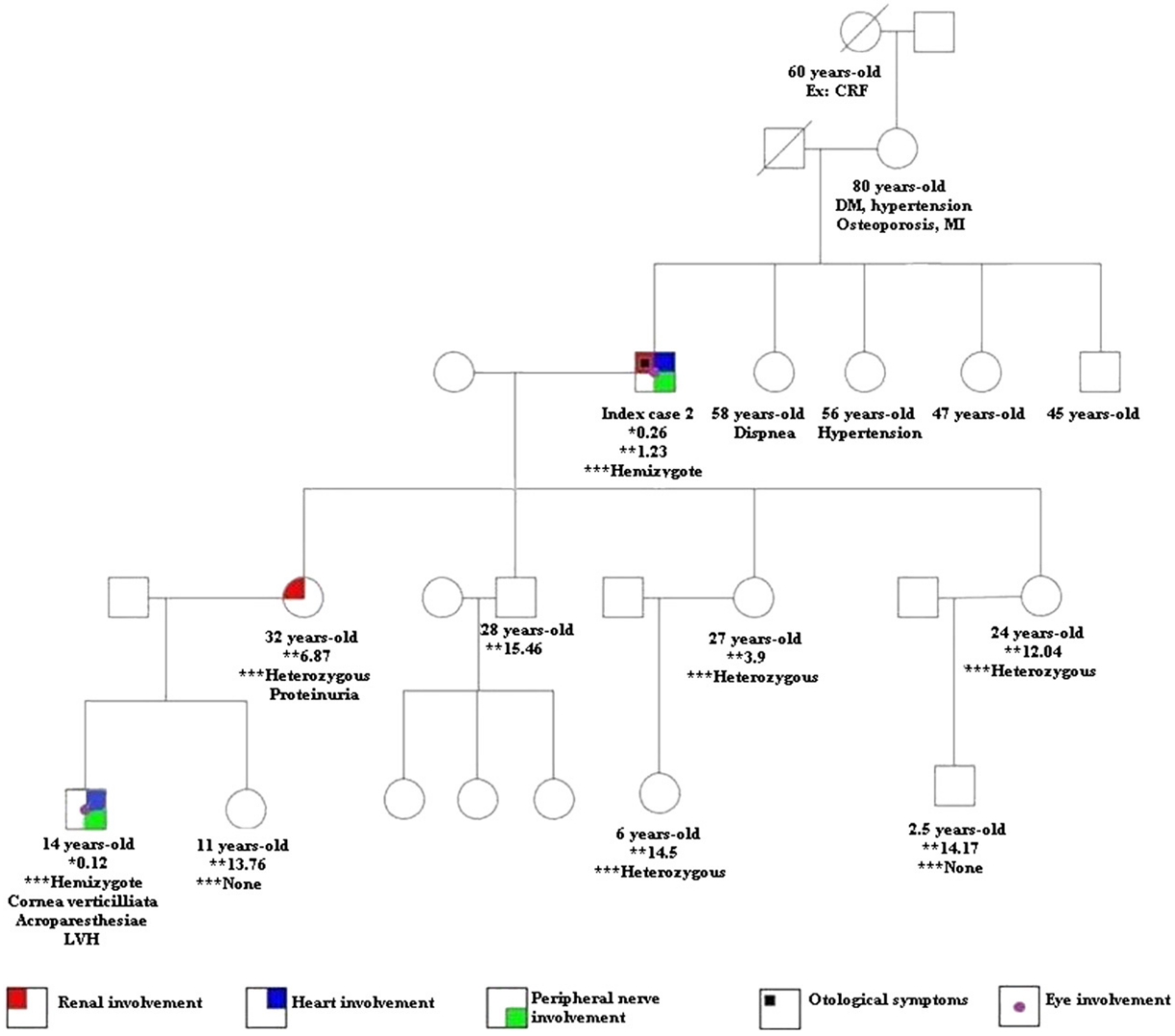

Fig. 3. The result of family screening and pedigree of case 2. Enzyme activity in *dried blood samples (μmol/L/h) and **leukocyte (nmol/h/mg protein). ***Analysis of whole genome sequencing in *GLA* gene (c.638C>T in exon 5). CRF, chronic renal failure; DM, diabetes mellitus; MI, myocardial infarction; and LVH, left ventricular hypertrophy.

enzymatic screenings have been started in the world particularly in populations at risk, such as patients with CRF, especially to determine potential patients and then their relatives with the disease. Although the prevalence is low in all studies, screening studies are of great importance for detecting new patients with family screening of the patients detected in the studies and diagnosing FD before life-threatening findings such as renal involvement.

The first study on dialysis patients in literature was carried out in Japan by Utsumi et al. in, 2000. Plasma enzyme activities of 722 patients were analyzed and one male patient was detected (prevalence, 0.14%). Walters et al. (2002) determined the prevalence as 0.47% in 1903 male patients. In the screening carried out in Japan by Nakao et al. (2003), plasma α-Gal A activity was measured in 514 male patients undergoing hemodialysis for CRF, and plasma α-Gal A activities of six (1.2%) patients were found low. In the study by Linthorst et al. (2003) in the Netherlands, plasma α-Gal A activity was measured in complete blood samples of 508 male dialysis patients, and the activity was detected low in one patient (prevalence, 0.22%) whose diagnosis was previously known. The screening on 2480 Australian hemodialysis patients by Kotanko et al. (2004) revealed leukocyte α-Gal A activity extremely low in four patients, and the prevalence was 0.161%. In the screening on 106 hemodialysis patients carried out in France by Bekri et al. (2005), α-Gal A activity in leukocyte was found low in one patient (0.94%). Porsch et al. (2008) screened 558 male patients undergoing hemodialysis in South Brasilia by analyzing α-Gal A activity in dried blood spots, and found the enzyme activity very low in two patients (prevalence, 0.36%). In the study by Lv et al. (2009) in China, 1662 dialysis patients (1544 hemodialysis, 118 peritoneal dialysis) between 18–87 years were first screened by analyzing enzyme activity in dried blood spots, then those found positive for test results were confirmed by determining low intra-leukocyte enzyme activity and mutation, and total prevalence was determined to be 0.12% (two patients).

When all screening studies carried out between 2003–2008 were analyzed, mean prevalence in dialysis patients was reported to be 0.33% (0.20–0.47%) in male patients in 12 studies, and 0.10% (0.0-0.19%) in female patients in six studies, and mean prevalence in renal transplantation patients was 0.38 (0.07–0.69%) in two studies. When the studies carried out on other risk groups were analyzed in the same report, the prevalence was 0.9–3.4% in male patients with hypertrophic cardiomyopathy in three studies, and 0.0–4.9% in patients with stroke in two studies (Linthorst et al., 2010).

The studies carried out after 2009 determined the prevalence as 0.0–0.76% (Fujii et al., 2009; Gaspar et al., 2010; Kalkan Uçar et al., 2012; Lv et al., 2009; Nishino et al., 2012; Wallin et al., 2011). When all screening studies up to date were analyzed, totally 55 patients (44 males, 11 females) were detected in a total of 18,837 dialysis patients, and

mean prevalence was 0.29% (0.0–0.96%). In 10 of those 18 screening studies, DBS method was primarily used, and in all studies, except for one, positive cases were confirmed by plasma enzyme activity, leukocyte enzyme activity, and/or DNA (Table 3).

First screening study in Turkey was carried out in a group of 808 male hemodialysis patients using a plasma α-Gal A test by Kalkan Uçar et al. (2012). Two new cases of FD were identified, both in patients previously diagnosed with type II diabetes mellitus. According to these results, the prevalence of FD in Turkish male individuals undergoing HD was detected as 0.24%.

Although the α-Gal A activity in male hemizygotes patients is always lower, approximately 33% of female carrier patients have a normal α-Gal A activity because of skewed inactivation of the X chromosome. It is recommended that screening of female patients is only reliably performed by mutation analysis of the α-Gal A gene. Since no single predominant mutation is found in Fabry disease, screening for mutations would involve sequencing the entire a-Gal A gene in each individual (Linthorst et al., 2005; Terryn et al., 2013). Sequence analysis of the α-Gal A gene is both very expensive and very laborious as a screening method of large patient groups. Therefore, female dialysis patients were included in this screening study by using DBS method so as to catch the affected ones with decreased enzyme levels. Another study is planned to screen all the females in this study for *GLA* mutations.

In the present study, the patients were first screened using DBS method, then, positive cases were confirmed with enzyme analysis in leukocyte and genetic analysis. This is the first screening study that used DBS method for Fabry disease for both males and females, carried out on risk groups in Turkey. The prevalence of FD was found to be 0.17% in all dialysis patients and 0.32% in male dialysis patients. Our prevalence results are similar to the results of studies performed in larger patient groups (Table 3). The result is thought to reflect the overall prevalence of Fabry disease in Turkish dialysis patients, because Ankara is the capital where dialysis patients have been referred from all over Turkey. As a result of genetic testing, a new unknown change was detected as hemizygous on a man patient (case 2) and his grandson whose enzyme activities are too low in leukocyte and DBS (Fig. 1). New cases were determined as a result of family screening of the patients detected, and follow-up and treatments for FD were recommended to those patients. The present study demonstrated that screening studies were important to detect new cases, and so were early diagnosis and therapy to affect the prognosis of the patients.

Conflict of interest

The authors have no conflict of interest. The authors alone are responsible for the content and writing of the paper.

Table 3
Analysis and results of all screening studies carried out on dialysis patients up to date (until 2013).

Study	Population	Material	Confirmation method	FD/DP		Prevalence (%)	
				M	F	M	Total
Utsumi et al. (2000) Japan	HD + PD	Plasma	DNA	1/440	0/282	0.22	0.14
Walters et al. (2002) USA	HD	Plasma	DNA	9/1903	–	0.47	–
Nakao et al. (2003) Japan	HD	Plasma	L, DNA	6/514	–	1.20	–
Linthorst et al. (2003) Netherlands	HD + PD	Whole blood	DNA	1/508	–	0.20	–
Kotanko et al. (2004) Austria	HD	DBS	L, DNA	4/1516	0/964	0.26	0.16
Bekri et al. (2005) France	HD	L	DNA	1/59	0/47	1,70	0.94
Ichinose et al. (2005) Japan	HD	Plasma	L, DNA	1/450	–	0.22	–
Tanaka et al. (2005) Japan	HD	Plasma	L, DNA	4/401	1/295	0.99	0.71
Maslauskiene et al. (2007) Lithuania	HD	DBS	–	0/536	–	0	–
Andrade et al. (2008) Canada	HD + PD	Plasma	L, DNA	0/499	–	0	–
Merta et al. (2007) Czech Repub.	HD	DBS	P, L, DNA	4/1521	1/1849	0.26	0.14
Terryn et al. (2008) Belgium	HD	DBS	L, DNA	1/180	2/742	0.55	0.32
Porsch et al. (2008) Brazil	HD	DBS	DNA	2/558	–	0.36	–
Lv et al. (2009) China	HD + PD	DBS	L, DNA	2/876	0/786	0.23	0.12
Gaspar et al. (2010) Spain	HD	DBS	L, DNA	4/543	3/368	0.74	0.76
Fujii et al. (2009) Japan	HD	DBS	DNA	1/625	2/399	0.16	0.29
Wallin et al. (2011) United King.	HD	DBS	L	0/155	–	0	0.0
Kalkan Uçar et al. (2012) Turkey	HD	Plasma	DNA	2/888	–	0.24	–
Nishino et al. (2012) Japan	HD	DBS	DNA	1/557	2/376	0.18	0.32
Total				44/ 12729	11/ 6108	M: 0.35 F: 0.18	0.29
Present study (2011) Turkey	HD	DBS	L, DNA	2/615	0/521	0.32	0.17

FD, Fabry disease; DP, dialysis patients; HD, hemodialysis; PD, peritoneal dialysis; DBS, dried blood samples; L, leukocyte; and DNA, deoxyribonucleic acid.

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