Case report

A novel missense mutation for Fabry disease detected by echocardiographic screening in left ventricular hypertrophy patients

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Fabry disease is an X-linked lysosomal storage disease caused by mutations in the α-galactosidase A gene (*GLA*), leading to the absence or a reduction of the enzymatic activity of the encoded enzyme and subsequent progressive tissue accumulation of glycosphingolipids throughout all the body, with consequent multiorgan failure.[1]

Clinical manifestations of the disease are usually slowly progressive, with a wide range of variability in time of onset, severity and course, making the correct differential diagnosis challenging. As regards the cardiac manifestations, glycosphingolipids accumulation leads to left ventricular (LV) concentric remodeling and subsequent hypertrophy, conduction abnormalities and valve diseases.[2]

Since a prompt instauration of the enzyme replacement therapy (ERT) has the great potential to modify the natural course of the disease and reduce morbidity and mortality, a correct and early diagnosis are mandatory. Nowadays, new and quickly available screening technique can be used to determine the enzymatic activity of α-Gal A in plasma or urine; genetic screening for mutations on the *GLA* gene can be also easily performed.[3] So, more than 900 mutations (Human Gene Mutation Database, www.hgmd.org, last accessed Sept 2019) in the coding *GLA* regions, on the long arm of chromosome X (Xq22), are known.[4]

Here, we report the case of a 57-year-old woman with Fabry disease due to a novel *GLA* gene mutation.

A 57-year-old woman with a past medical history of acroparesthesias, recurrent headache and abdominal pain was admitted to our echo-lab through a cardiovascular primary screening program, in absence of known cardiac problems. Her family history was unremarkable, as well as her physical examination.

ECG showed a sinus rhythm of 71 bpm with unspecific abnormalities of repolarization (Fig. 1).

Echocardiography revealed concentric LV hypertrophy (LVH) (Fig. 2; interventricular septum and posterior wall thickness in tele-diastole 14 mm), normal LV ejection fraction (56%) and grade I diastolic dysfunction. Of note, the global longitudinal strain was slightly reduced (−18.7%, n.v. <−19%) (Fig. 3).

Exams showed microalbuminuria not previously detected (47 mg/24 h, n.v. <20 mg/24 h).

Given the clinical suspicion of Fabry disease, particularly for her past medical history, in addition to findings of unexplained LVH and microalbuminuria, a blood sample was collected to perform a screening for this disease, after obtaining written informed consent. Both enzyme activity determination and genetic screening were performed in an outside laboratory by staff blinded to clinical data using dried blood spot sampled on filter paper.

Genetic examination revealed a previously unreported heterozygous missense mutation in exon 3 of the *GLA* gene [c.388A>G (p.Lys130Glu)]. Moreover, a high level of plasma concentration of the degradation product of the accumulating Gb3, the lyso-Gb3 (4.0 ng/ml, n.v. ≤1.8 ng/ml) was detected.[5]

No apparent neurological deficit at physical examination, no signs of tortuous vessels or cornea verticillata and no angiokeratomas were detected.

Considering all clinical and instrumental data, the novel *GLA* gene mutation was considered as pathogenic, according to the last diagnostic criteria for Fabry disease.[6]

Of note, familiar screening revealed the same gene mutation in her asymptomatic 27-year-old son, with decreased α-Gal A enzymatic activity (<0.8 μmol/l/h,

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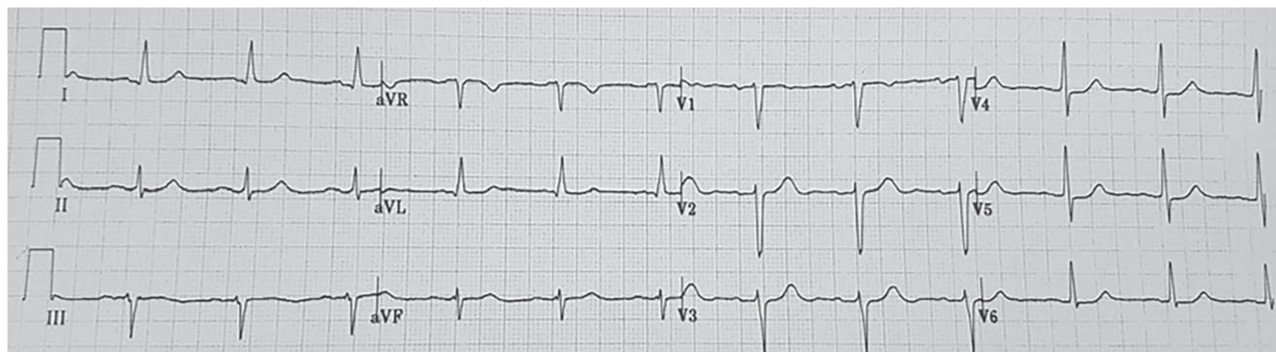
Fig. 1



Patient's ECG, showing sinus rhythm and unspecific abnormalities of repolarization.

n.v. ≥15.3 μmol/l/h) and elevated lyso-Gb3 levels (26.1 ng/ml, n.v. ≤1.8 ng/ml). His past medical history was unremarkable except for unspecific gastrointestinal disorders; no angiokeratomas or corneal opacities were detected. Instrumental examinations revealed a mild subclinical cardiac and renal involvement. ECG showed a sinus rhythm with incomplete right bundle branch block and electrocardiographic signs of LV hypertrophy, while echocardiography showed interventricular septum thickness of 11 mm and mildly dilated left atrium. Cardiac magnetic resonance confirmed LV parietal thicknesses and myocardial mass within normal limits, revealing no myocardial fibrosis but a reduced T1-mapping. High-sensitive cardiac troponin T and N-terminal pro–B-type natriuretic peptide resulted within the normal range, while microalbuminuria (28.4 mg/24 h, n.v. <20 mg/24 h) and glomerular hyperfiltration (creatinine clearance of 175 ml/min) were detected.

Both patients refused enzymatic replacement therapy; they were not suitable for chaperone therapy.

Carrier's mother and daughter have been screened, showing no *GLA* gene mutation in both; her father died from cancer at age 68; genetic screening in her sister was not performed due to the patient's refusal.

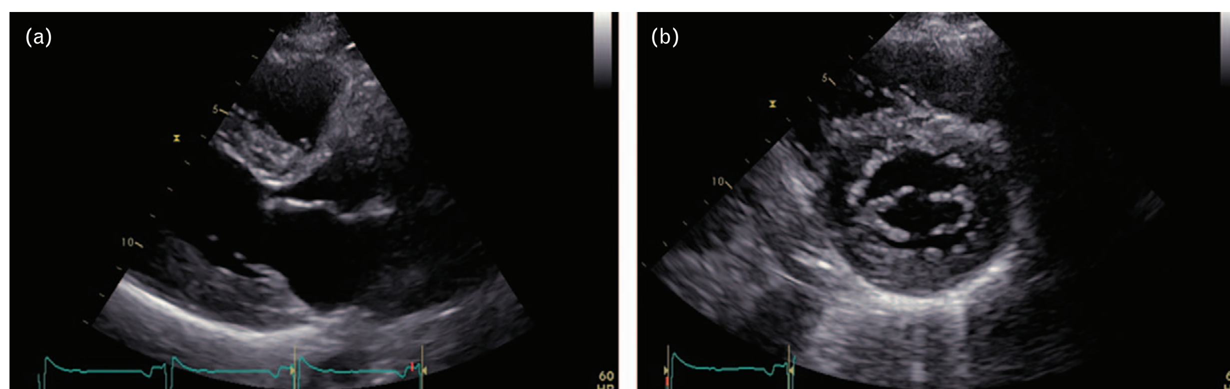
All patients enrolled gave written informed consent and the study was approved by the local ethics committee.

To the best of our knowledge, this is the first report in the literature of a classical phenotype of Fabry disease caused by the missense mutation c.388A>G (p.Lys130Glu) in exon 3 of the *GLA* gene.

Indeed, a variant interpretation was studied through public databases and tools. Variant was neither found in ExAC nor 1000G or Clinvar; Polyphen 2 reported the variant as probably damaging, Sift as damaging and mutation tester as disease causing.

This *GLA* variant c.388A>G p.(Lys130Glu) in exon 3 causes an amino acid change from Lys to Glu at position 130 (Fig. 4); consequently, the enzymatic activity of α-Gal A is impaired, as confirmed by reduced enzymatic

Fig. 2



Patient's echocardiography parasternal long-axis (a) and short-axis (b) views, showing a mild left ventricular hypertrophy.

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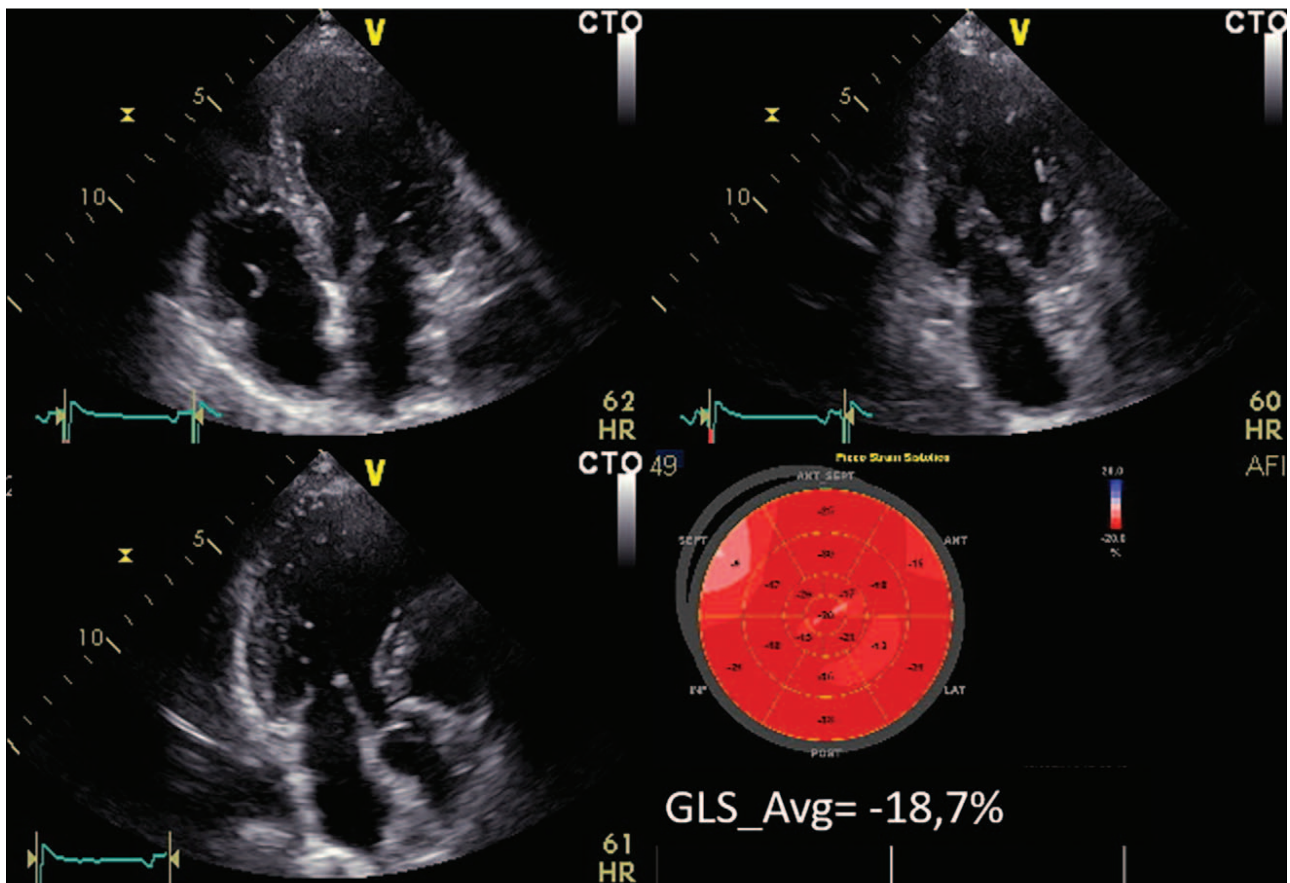
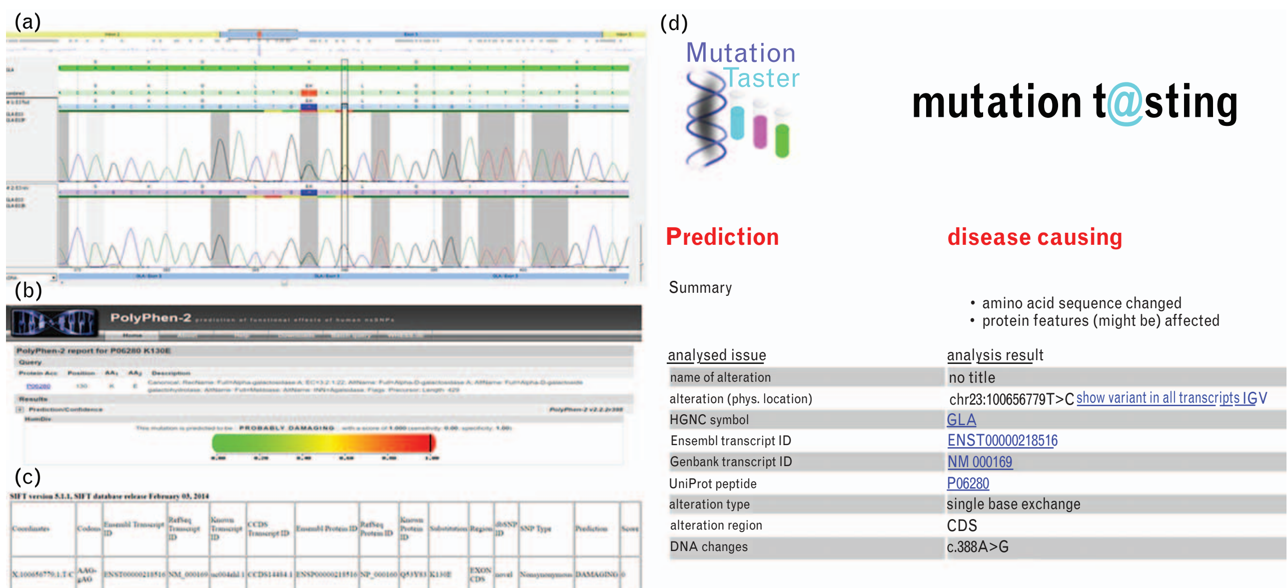
Fig. 3



Patient's global longitudinal strain bull's eye plot derived from two-dimensional speckle tracking imaging, showing a slightly reduced mean global longitudinal strain value.

Fig. 4



Portion of the electropherogram of exon 3 of the galactosidase A gene gene showing c.388A>G p.(Lys130Glu) mutatio, as highlighted by rectangle form (a); Polyphen 2 reported the variant as probably damaging (b), Sift as damaging (c) and mutation tester as disease causing (d).

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activity in the son of the proband. Moreover, both the proband and the son showed an increase in the biomarker (Lyso-Gb3). This is perfectly coherent with the milder and more variable symptomatology in women in comparison to male individuals.[7]

Significantly, this novel mutation has been detected during a screening program for infiltrative disease, in patients presenting to our echo-lab with LVH and signs and symptoms suggestive of Fabry disease. Due to its wide range of variability in time onset and clinical manifestations, the real incidence Fabry disease is still understimated; a screening program, in a metropolitan area not already explored for this disorder, is mandatory to avoid missing Fabry disease diagnosis in daily cardiologic clinical practice.

Mutation analysis of the *GLA* gene is a fundamental step for the diagnosis of Fabry disease in suspected subjects.[3] It is extremely important to diagnose affected patients for early therapeutic intervention with α-galactosidase A replacement therapy (ERT), whose efficacy is due to its ability to reduce or to stop the lysosomal glycosphingolipid accumulation in the target sites.[8] Moreover, cascade family screening is a very powerful and definitive tool to recognize new mutated patients early on, in the absence or mild presence of organ involvement.

A previously unreported missense mutation in the *GLA* gene was identified; in addition, familiar screening allowed another Fabry disease patient to be identified at a very early stage, before irreversible organ damage had occurred.

The identification of novel mutations in patients with symptomatology referable to Fabry disease increases the molecular knowledge of the *GLA* gene giving important support to the clinicians for proper diagnosis and treatment.

Conflicts of interest

There are no conflicts of interest.

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