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Available online 17 July 2018

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https://doi.org/10.1016/j.rec.2018.06.020
1885-5857/

First Reported Case of Fabry Disease Caused by a Somatic Mosaicism in the *GLA* Gene

Primer caso descrito de enfermedad de Fabry causada por un mosaicismo somático en el gen GLA

To the Editor,

Fabry disease is a rare progressive X-linked sphingolipid storage disorder caused by deficiency of lysosomal a-galactosidase A (a-galA) due to mutations in the *GLA* gene. The disease triggers an intracellular accumulation of globotriaosylceramide in various tissues and results in multiple organ damage. Male patients with the classic form develop early signs and symptoms in childhood or adolescence.[1] This classic form typically appears in male carriers of genetic variants that cause a severe decrease (or complete absence) of the a-galA enzymatic activity, as occurs with nonsense and frameshift variants.[2] Females are heterozygous for mutations in the *GLA* gene and show a heterogeneous clinical spectrum that ranges from asymptomatic to a clinical severity equal to that of males.[3]

We report the case of a male Fabry disease patient who developed a relatively mild phenotype despite carrying a classic nonsense *GLA* variant.

A 58-year-old male patient with hypertension and proteinuria was admitted to hospital due to abdominal pain. On electrocardiography, a short PR interval with left ventricular hypertrophy and subepicardial ischemia was observed (Figure 1A). A coronary angiogram was performed, showing a distal occlusion of the second diagonal branch; symptoms improved with medical treatment. His echocardiogram and cardiac magnetic resonance demonstrated a basal septal hypertrophy of 20 mm (Figure 1B, C). With a diagnosis of hypertrophic cardiomyopathy, the patient was referred to the inherited cardiovascular diseases unit. Fabry disease was suspected due to the presence of hypertrophic cardiomyopathy, proteinuria with mild renal failure (Cr 1.3 mg/dL), and a short PR on electrocardiography. A-galA activity in blood was reduced to 0.7 μmol/L/h (2.0-11.7), and renal biopsy showed typical "zebra bodies" on electron microscopy images (Figure 1D). Finally, 17 genes related to hypertrophic cardiomyopathy, including *GLA*, were sequenced by next-generation sequencing. A

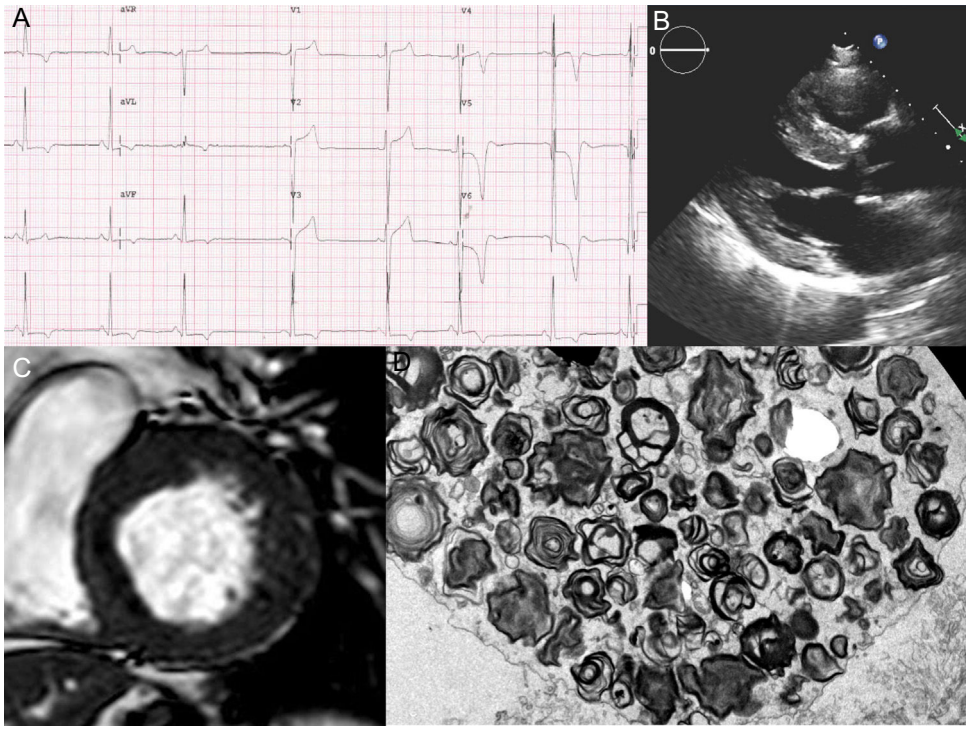

Figure 1. A: the patient's electrocardiogram showing short PR interval, left ventricular hypertrophy, and subepicardial ischemia. B and C: echocardiogram and cardiac magnetic resonance with left ventricular hypertrophy. D: electron microscopy images of the renal biopsy with the "zebra bodies" (cluster of glycolipid concentric membranous bodies sequestered within lysosome).

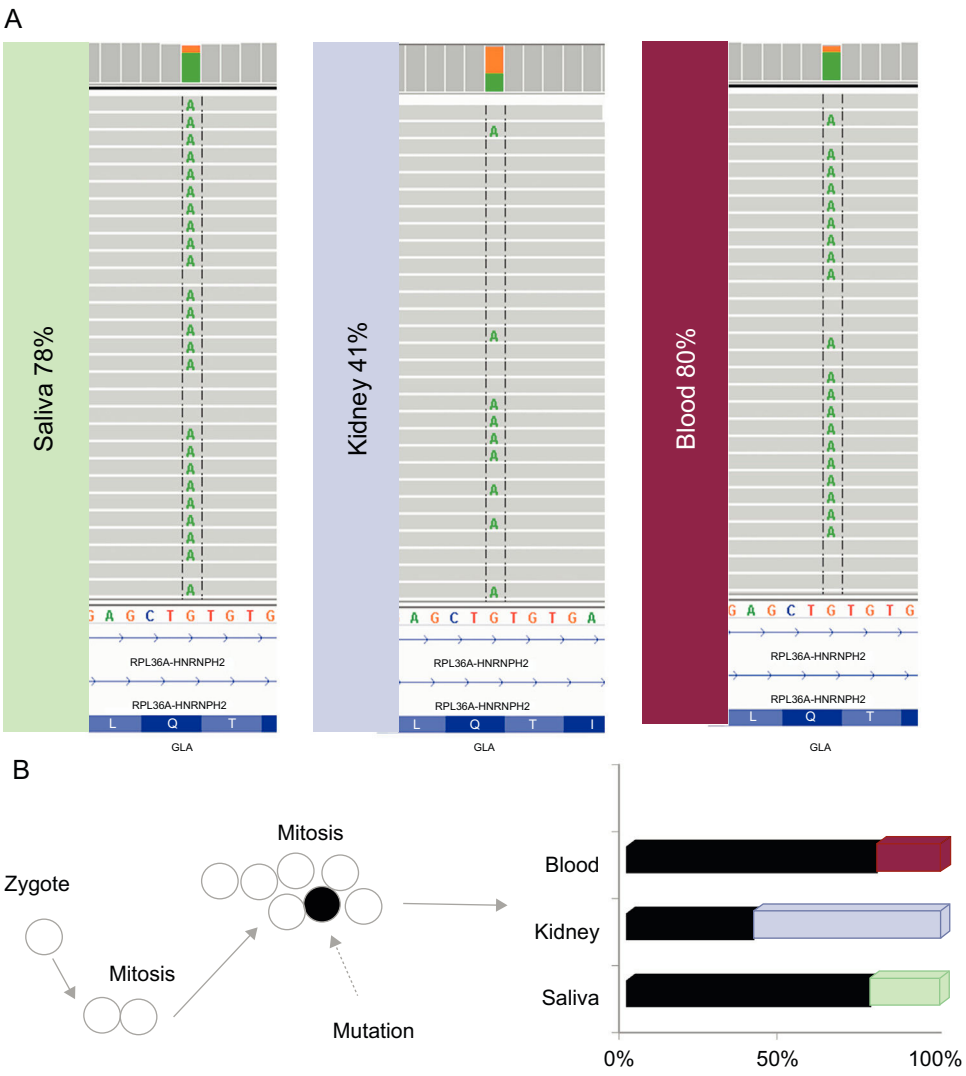

Figure 2. A: the readings obtained in the next-generation study of saliva, kidney and blood samples are shown between discontinued black lines. B: two cellular lines in the somatic cells of the patient: one (black) that shows the mutation (discontinued arrow) and another (white) wild-type. Bar diagram showing the proportion readings with the mutated allele.

previously described truncating mutation in *GLA* (p.Gln386*/g.10021C >T) associated with classic forms of Fabry disease was identified.[4] Therefore, the diagnosis was confirmed and enzyme replacement therapy was initiated.

The genetic study of the index case was initially performed on a saliva sample and showed that 78% of the readings had the mutated allele, when 100% is expected in hemizygous carriers; the mutation was confirmed by Sanger sequencing. An additional next-generation sequencing study was carried out in blood and paraffin samples (renal biopsy), showing that 80% and 41% of the readings, respectively, had the mutated allele, confirming the presence of a somatic mosaicism (Figure 2A). However, the Sanger method is imprecise when quantifying the percentage of mosaicism and evaluating the differences between tissues.

Both an unaffected daughter and sister of the proband (aged 30 and 55 years) were noncarriers of the variant.

This patient has a phenotype that is milder than that expected for a male carrier of a truncating mutation, in which the involvement of different organs begins at an early age and the phenotype is severe due to the total absence of the enzyme. In this particular case, this can be explained by the presence of 2 cell lines in the somatic cells of the patient: one that shows the mutation and another that is wild-type. Thus, in each tissue, there is a proportion of cells capable of maintaining certain levels of enzyme activity. This is also reflected in the a-galA activity of this patient, which is low but not in the levels expected for a hemizygous null *GLA* mutation carrier (Figure 2B).

Fabry disease is inherited in an X-linked manner, and therefore an affected male would transmit the pathogenic variant to all of his daughters. In this case, female offspring would inherit the mutation depending on whether the mosaicism is present in the germ cells of the patient or not. In the first case (a germinal mosaicism is present) the risk of inheriting the mutation in females is related to the proportion of mutated sperm.[5] Regrettably, this cannot be determined in this patient, because genetic testing was not performed on sperm tissue and the only genotyped daughter is a noncarrier of the variant. We have reported the first case of FD caused by a somatic mosaicism in the *GLA* gene. The patient exhibited a milder phenotype than that expected for a hemizygous carrier.

This case shows the importance of next-generation sequencing technologies in the genetic testing of patients with suspected Fabry disease, allowing detection of patients in early stages (even those with somatic mosaicism such as this case) who may benefit from enzyme replacement therapy.[6]

FUNDING

Supported by grant from the Centro de Investigación Biomédica en Red (CIBERCV), "Instituto de Salud Carlos III", CB16/11/00425 (R. Barriales-Villa and L. Monserrat), "Instituto de Salud Carlos III", FEDER "Unión Europea, Una forma de hacer Europa"

CONFLICTS OF INTEREST

J.P. Ochoa and J.L. Santomé-Collazo are employees of Health in Code S.L. R. Barriales-Villa have received personal fees from Health in Code S.L. L. Monserrat is a stakeholder and CEO of Health in Code S.L.

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Available online 18 July 2018

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https://doi.org/10.1016/j.rec.2018.06.013
1885-5857/

Measuring Patient Satisfaction in a Cardiology Service Using Associative Maps. A New Method

Medición de la satisfacción del paciente en un servicio de cardiología mediante mapas asociativos: un nuevo método

To the Editor,

The importance of measuring patient satisfaction in healthcare is clearly acknowledged in the literature. Measuring satisfaction is a way of monitoring management actions and might also provide information about the quality of the service and future patient behavior, such as treatment adherence.

How to measure satisfaction is still a widely debated issue, because of the complexity of the concept and the divergent options proposed for its measurement.[1] One of the key controversies about this topic is how to generate the attributes or factors linked to satisfaction.

We propose a way of eliciting satisfaction attributes in a cardiology service by employing associative maps, associative priming, and the first-person data approach.[2,3]

We collected a sample of 50 consecutive patients in a Spanish public hospital, who were admitted to the cardiology ward from March 1 to 18, 2018. A simple questionnaire was provided before the patients were discharged, in which participants had only to freely indicate attributes/concepts that they linked to satisfaction with the service received. Using the above-mentioned method, we obtained individual associative maps, which were finally aggregated in a consensus map representing the main shared satisfaction attributes and their weights. Thirteen questionnaires were excluded because of unintelligible and nonvalid responses and therefore the final sample analyzed was composed of 37 participants (78% men, mean age 64.7 years). The order of mention of each attribute represented its hierarchy in the mind of the patient, ie, its weight or importance in the definition of overall satisfaction. Then we used the frequency of

Table
Attributes of Satisfaction for the Aggregated Sample

Attributes	Frequency of mention, %	Frequency of first mention, %	Final weight
Professional and personal attention	97	86	0.37
Food	57	3	0.11
Cleanliness	35	5	0.08
Facilities	27	0	0.04
Waiting time for medical tests	14	5	0.03
Provided information	14	0	0.02