Scientific letter

Genetic testing in suspected inherited aortopathies: usefulness in diagnosis and follow-up

Estudio genético de pacientes con sospecha de aortopatías hereditarias: utilidad para el diagnóstico y el seguimiento

To the Editor,

Thoracic aortic aneurysms are often asymptomatic, remaining undiagnosed until the appearance of catastrophic complications, such as aortic dissection, with very high mortality.[1]

At present, certain genetic variants are known to predispose individuals to aortic root and ascending aorta disorders, known as hereditary thoracic aortic aneurysm/aortic dissection (HTAAD). Genetic testing (GT) to detect these variants can be very useful for identifying at-risk individuals.[2]

Traditionally, HTAADs have been considered syndromic (eg, Marfan, Loeys-Dietz, or vascular Ehlers-Danlos syndromes) or nonsyndromic (thoracic aortic aneurysm as an isolated finding). However, the distinction between the two has become less clear, in view of the wide phenotypic variability seen in many of the variants discovered.

We believe that an outpatient office specifically for inherited aortopathies (IA) would help identify these patients more effectively by implementing GT in a more complete and efficient manner.

This single-center retrospective analysis included patients studied in the IA outpatient office of a tertiary hospital between 2010 and 2020. The first visit included a thorough physical examination to look for the clinical signs classically associated with syndromic HTAAD plus a transthoracic echocardiogram to obtain aortic root and ascending aorta measurements, as per current recommendations.[3] Afterwards, blood or saliva samples were collected for GT from patients who met the following criteria: body size- and age-adjusted aortic diameters above normality (Z-score > 2) in the absence of other risk factors; increased diameters along with other phenotypic traits classically associated with syndromic HTAAD or a family history of aortic events or sudden cardiac death; or first-degree relatives of patients with any of the above characteristics and/or who have a known genetic variant possibly associated with an aortopathy. GT was performed by combining massive sequencing (NGS) and Sanger methods. The first patient from a family to visit the outpatient office was considered the index case. When a genetic variant with a certain probability of being pathogenic was found, cascade screening was initiated, offering GT to all first-degree relatives. Screening was not performed in patients who declined or whose first-degree relationship was uncertain. The study was approved by the local ethics committee, and patients signed written informed consent before samples were collected for GT.

After evaluating 389 index patients, targeted GT was ordered for 259 (66.6%). A genetic variant of interest was obtained in 132 (50.9%) (figure 1), 46 of which were pathogenic or likely pathogenic (17.7%). Based on these findings, 291 relatives were evaluated and GT was subsequently ordered for 207 (71.1%). In this latter group, 90 (43.5%) were positive for the variant studied and 117 were negative. Patients who had variants, whether pathogenic or not, and patients with negative GT but persistent suspicion of a predisposition to aortopathy received regular follow-up.

In all, 140 patients were carriers of *FBN1* variants, 11 had variants in genes coding for TGF-B or its receptors, 19 in *COL3A1*, 22 in other collagen-forming proteins, and 22 in genes coding for vascular smooth muscle cell proteins. The characteristics of these

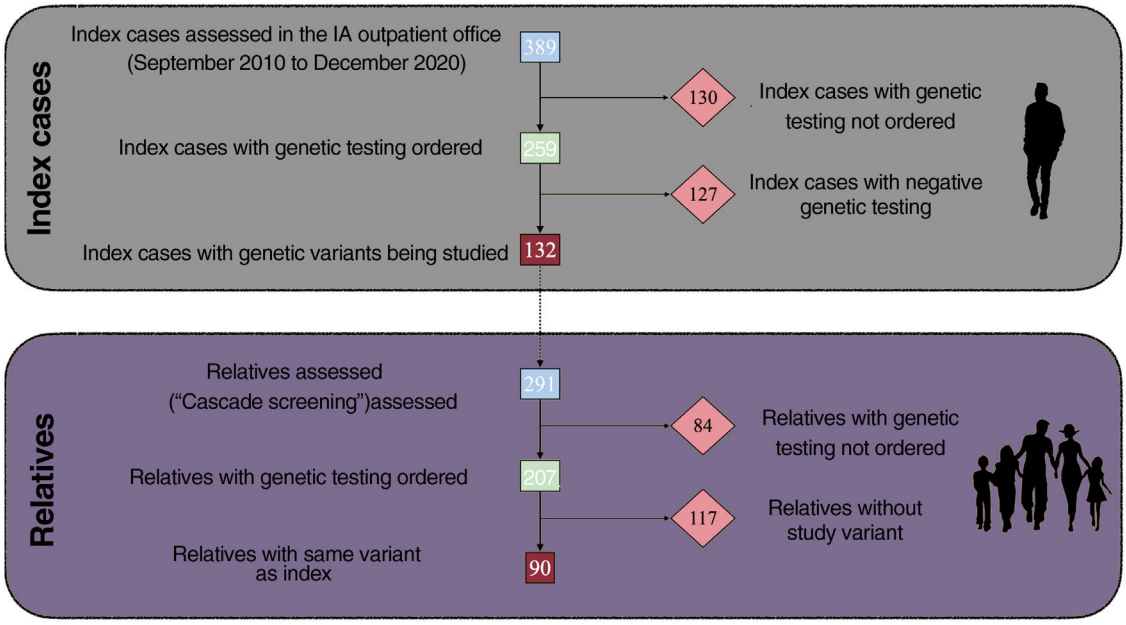

Figure 1. Flow chart of patients included in the study. IA, inherited aortopathies.

Table 1
Characteristics of patients with suspicion of hereditary thoracic aortic aneurysms and dissections and finding of a variant of interest in genetic testing

	Total (N = 222)	Variants in *FBN1* (n = 140)	Variants in *TGFBR1*, *TGFBR2*, or *TGB3* (n = 11)	Variants in *Col3A1* (n = 19)	Variants in other collagen-coding genes *(1A1, 1A2, 5A1)* (n = 22)	Variants in other VSMC protein genes *(ACTA, JAG, etc.)* (n = 22)
Syndrome diagnostic criteria						
Marfan syndrome	125 (56.3)	125 (89.3)	–	–	–	–
Loeys-Dietz syndrome	10 (4.5)	–	10 (90.9)	–	–	–
Vascular Ehlers-Danlos syndrome	14 (0.6)	–	–	14 (73.7)	–	–
Index cases	132 (59.5)	86 (61.4)	6 (54.5)	8 (42.1)	12 (54.5)	12 (54.5)
Carrier relatives	90 (40.5)	54 (38.6)	5 (45.5)	11 (57.9)	10 (45.5)	10 (45.5)
Age, y	34.8 ± 18.1	32.7 ± 17.4	31.0 ± 19.1	39.1 ± 18.9	34.1 ± 18.1	45.2 ± 14.9
Men	118 (53.2)	72 (51.4)	7 (63.6)	8 (42.1)	13 (59.1)	15 (68.2)
Ascending aorta						
Mild aortic dilatation	105 (47.3)	79 (56.4)	1 (9.1)	7 (36.8)	7 (31.8)	6 (27.3)
Ascending thoracic aortic aneurysm	39 (17.6)	26 (18.6)	5 (45.5)	0	2 (9.1)	5 (22.7)
Type A dissection	13 (5.9)	11 (7.9)	0	0	0	2 (9.1)
Aortic rupture	1 (0.5)	0	1 (5.3)	0	0	0
Surgical procedure	48 (21.6)	34 (24.3)	4 (36.4)	0	2 (9.1)	7 (31.8)
Bono-Bental	20 (41.7)	14 (41.5)	1 (25)	0	0	5 (71.4)
Yacoub	15 (31.3)	11 (32.4)	2 (50)	0	0	2 (9.1)
David	11 (22.9)	9 (26.5)	1 (25)	0	0	1 (14.3)
Aneurysms in other locations	7 (3.2)	0	2 (10.6)	2 (10.5)	2 (9.1)	0
Bicuspid aortic valve	4 (1.8)	2 (1.4)	0	0	0	1 (4.5)
Mitral valve prolapse	59 (26.6)	48 (34.3)	1 (9.1)	7 (36.8)	2 (9.1)	0
Ectopia lentis	46 (320.7)	46 (32.9)	0	0	0	0
Characteristics of genetic variants						
Pathogenic/likely pathogenic*	146 (65.7)	121 (86.4)	9 (81.8)	12 (63.2)	0	1 (4.5)
Possibly pathogenic	6 (2.7)	1 (0.7)	1 (9.1)	0	0	4 (18.2)
VUS	70 (31.5)	18 (12.9)	1 (9.1)	7 (36.8)	22 (100)	17 (77.3)
Previously described in the literature	76 (34.2)	66 (47.1)	4 (36.4)	1 (5.3)	0	4 (18.2)

*The genetic variants identified were chosen following the recommendations of the Human Genome Variation Society (HGVS) and the American College of Medical Genetics (ACMG). In the specific case of *FBN1*, variants were classified as pathogenic if they met the criteria for causal *FBN1* mutations according to the modified Gante criteria.
Qualitative variables are expressed as No. (%) and quantitative variables as mean ± standard deviation.

patients plus the clinical characteristics of carrier patients are listed in table 1.

In short, more than 50% of the tests yielded a variant of interest. Renner et al.[4] found variants in 40.7% of 199 individuals with clinical characteristics of syndromic or nonsyndromic HTAAD. Conversely, a series of unselected patients with only a history of thoracic aortic aneurysm or dissection reported 3.9% to 5% positive reactions for pathogenic or likely pathogenic variants and around 25% when including variants of uncertain significance (VUS).[5] Hence, GT requests should be based on clinically guided criteria. In our study, 90 relatives were found to have the study variants, which could have direct implications for follow-up, medical treatment, prophylactic surgical repair, and family planning.

The highest percentage of pathogenic or likely pathogenic variants was obtained in *FBN1*, a gene associated with Marfan syndrome, the most thoroughly studied IA. Follow-up of patients with a VUS will be of particular interest, as it could shed light on the possible prognostic significance of these variants. Initiatives such as the Spanish Network for Genetic Aortic Pathologies (REPAG) would undoubtedly help reach this goal.

In summary, an outpatient office specifically for IA could help guide individualized treatment for these patients, as well as make sense of the immense amount of information obtained from GT.

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AUTHORS' CONTRIBUTIONS

V.M. Becerra-Muñoz performed the analyses and wrote the manuscript; V.M. Becerra-Muñoz, A. Díaz-Expósito, and V. Doncel-Abad collected the clinical and genetic data; P. Fernández-García, J.L. López-Benítez, and F. Cabrera-Bueno attended patients in the inherited aortopathy outpatient office; F. Cabrera-Bueno is the coordinator of the inherited aortopathy unit; and V.M. Becerra-Muñoz, A. Díaz-Expósito, V. Doncel-Abad, P. Fernández-García, J.L. López-Benítez, and F. Cabrera-Bueno reviewed and corrected the final content of the text.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interests related to this study.

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Use of POCUS in cardiovascular screening of young athletes: diagnostic value in the era of international electrocardiographic criteria

POCUS en el reconocimiento cardiológico de deportistas jóvenes: valor diagnóstico en la era de los criterios electrocardiográficos internacionales

To the Editor,

The use of electrocardiographic (ECG) assessment in preparticipation cardiological screening is currently supported by the clinical guidelines due to its ability to detect heart disease, a common cause of sudden cardiac death in athletes younger than 35 years.[1] The 2017 publication of the international criteria for ECG interpretation in athletes[2] defines normal, borderline, and pathological findings, which substantially improved the sensitivity and specificity compared with previous criteria.[3] Despite this, the assessment continues to generate false positives that cause worry in athletes and their relatives and temporarily limit their sporting activity.

Point-of-care ultrasound (POCUS) could improve the diagnostic yield of these electrocardiographic criteria through the use of focused protocols. Their usefulness in detecting structural findings with prognostic value has been demonstrated in several studies.[4]

Our study was designed with the main objective of evaluating the applicability of POCUS in cardiovascular screening programs and its role in determining eligibility for competitive sports if there are pathological ECG findings according to international criteria. To do so, we included a total of 978 athletes from different types of sport, with a mean age of 16.7 ± 3.7 years, mostly soccer players (65%), and mostly male (81%) (table 1). All the athletes were registered with an association, training 3 to 5 days per week and competing at the weekend. Cardiologists specialized in the care of athletes performed the assessment, which included a history, physical examination, resting ECG, and POCUS focusing on the diagnosis of structural heart disease. The POCUS protocol involved measurement in M mode of septal thickness and posterior wall thickness; measurement of the aortic diameter, left atrial diameter, and left ventricular end-diastolic diameter on the parasternal long axis view; measurement of the right ventricular outflow tract diameter and checking the aortic valve and the coronary ostia on the parasternal short axis view, and study of the mitral and aortic valves with Doppler (including mitral filling pattern, septal tissue Doppler, aortic flow continuous Doppler, and color Doppler of both valves), as well as a general cardiac or 4-chamber view. The athletes were classified based on the interpretation of their ECG in line with international criteria. The study was approved by the Hospital IMED Valencia ethics committee, and all the athletes gave signed informed consent.

Pathological ECG criteria were found in 35 athletes (3.6% of the total): 27 due to negative T waves or ST-segment depression, 6 due to the presence of 2 or more ectopics on ECG, 1 due to prolonged QT interval, and 1 due to pre-excitation syndrome (table 2). POCUS during the screening visit, estimated to take < 5 minutes, showed an excellent diagnostic yield in the assessment of repolarization abnormalities classified as pathological according to the international criteria. This allowed significant structural heart disease to be ruled out in 25 of the 27 athletes with negative T waves (in this context, a reduction in the rate of ECG false positives of up to 92.5%). In the 2 remaining athletes, a suspected diagnosis of hypertrophic cardiomyopathy was reached. In the first case, this was on the basis of septal hypertrophy with a maximum midapical thickness of 15 mm in the presence of negative T waves on ECG in the inferior leads and V_5-V_6. In the second case, it was on the basis of negative T waves with ST-segment depression in III and V_4-V_6, a lateral hypertrabeculation pattern with spongiform appearance on POCUS, and cardiac magnetic resonance showing a nonobstructive hypertrophic cardiomyopathy pattern.

In the patients with the other pathological findings described (long QT, ventricular ectopics and pre-excitation syndrome), POCUS did not lead to changes in the impression from the electrocardiographic assessment, and therefore eligibility was delayed due to the need for other diagnostic tests.

Therefore, POCUS was especially useful in patients with repolarization abnormalities on ECG, present in 3% of the sample and in line with previous studies.[5] In addition, and although it was not the aim of this study, it was able to detect other structural abnormalities not detected on ECG, such as coronary anomalies (we were able to confirm the normal position of the ostia in more than 90% of the athletes) or common valvulopathies such as bicuspid aortic valve or mitral valve prolapse. Although these conditions rarely affect prognosis in athletes, their early detection enables regular cardiological follow-up and treatment if required.

The limitations of this study include the sample size, the high percentage of male soccer players, and the analysis of results from a single medical center.

Despite these limitations, we can conclude that POCUS as part of the cardiovascular screening of young athletes is a fast and simple technique that allows exclusion of the presence of significant structural heart disease in individuals with repolarization abnormalities that are classified as pathological according to international ECG interpretation criteria.