KARDIOLOGIA POLSKA
Polish Heart Journal
The Official Peer-reviewed Journal of the Polish Cardiac Society since 1957
Online first
This is a provisional PDF only. Copyedited and fully formatted version will be made available soon
ISSN 0022–9032 e-ISSN 1897–4279

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Article type: Short communication

Received: June 6, 2023

Accepted: October 1, 2023

Early publication date: October 16, 2023

Genetic background assessment with whole exome sequencing in a giant coronary artery ectasia: A pilot study

Short title: Whole exome sequencing in coronary artery ectasia

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INTRODUCTION

Coronary artery aneurysm and ectasia (CAAE) is defined as a dilation of the coronary artery by at least 1.5 times compared to the adjacent reference segment. The incidence of CAAE is reported in 0.3%–5.3% of patients undergoing coronary angiography and in 1.4% of post-mortem examinations [1,2]. Giant CAAE is a rare phenomenon characterized by a dilation of a coronary artery exceeding 2 to 4 centimeters and it was found only in 0.02% of patients undergoing coronary angiography [1, 3]. The most common etiology of CAAE is atherosclerosis, followed by Kawasaki disease, infectious septic emboli, connective tissue disease and arteritis. Iatrogenic causes are less common [4].

There are few genetic reports on potential loci associated with CAAE [1]. Meta-analysis of genome wide association studies performed in European and Japanese population of children with Kawasaki disease has identified *ITPKC*, *FCGR2A*, *CASP3* and *FAM167A* genomic regions to be associated with susceptibility to develop CAAE [5]. Furthermore, 9p21 variant has been linked with coexistence of coronary artery disease, cerebral artery aneurysms and aortic aneurysms, mainly due to suspected potential adverse vascular remodeling [6]. Nevertheless, the direct association of specific genetic variants with CAAE formation, especially with those giants, has not been proven [1].

Therefore, we present our pilot data regarding the whole exome sequencing (WES) application in a patient with extremely giant coronary artery ectasia (CAE) and positive family history.

METHODS

Proband characteristic

A 70-year-old male, with previously diagnosed giant right CAE and multiple cardiovascular risk factors, was admitted for the assessment before planned thoracic surgery due to the tumor in the right lung apex. On admission the patient reported physical activity limitation with exertional fatigue and paroxysmal palpitations. His history was also remarkable for common iliac artery aneurysm, abdominal aortic stent graft implantation due to aortic aneurysm and bilateral adrenal adenomas with subclinical Cushing syndrome treated with right adrenalectomy. His family history included an aortic aneurysm in his father, hemorrhagic stroke in his paternal grandfather and fatal congenital heart disease in his child.

The CAE diagnosis has been established seven years before the present admission. At that time coronary angiography revealed partly thrombosed diffuse ectasia along the right coronary artery with maximum diameter of 15 mm in the proximal segment and in proximal left anterior descending and proximal to mid left circumflex artery (Figure 1A, B). Because coronary

lesions were not suitable for any interventions, Heart Team recommended optimal medical treatment. During follow-up the significant progression to 60 × 61 mm, 70 × 64 mm and finally to 86 × 60 mm was observed in the subsequent coronary computed tomography angiographies (CCTA) (Figure 1C, D). In the serial transthoracic and transesophageal examinations, the compression of right atrium, right ventricle and tricuspid annulus has been visualized (Figure 1E, F).

Since the suspicion of genetic background of the giant CAE, the patient was referred for WES. The targeted genetic tests and CCTA have been also proposed for three proband's daughters. The study protocol complied with the Declaration of Helsinki and was approved by the Jagiellonian University Medical College Ethics Committee (Consent No. 1072.6120.49.2022). It was registered at ClinicalTrials.gov (NCT06001957). Written informed consent to participate in this study was provided by the proband and his relatives.

Whole exome sequencing analysis

DNA from proband was obtained from peripheral blood and extracted using standard protocols. Library preparation for the WES was performed on proband's DNA sample with Twist Human Core Exome spiked-in with: Twist mtDNA Panel, Twist RefSeq Panel and Custom Panel covering variants located in noncoding regions that have been linked to clinical phenotypes according to the ClinVar database (Twist Bioscience, San Francisco, CA, USA). Enriched library was paired-end sequenced (2x100 bp) on NovaSeq 6000 (Illumina, San Diego, CA, US) to obtain 116 001 610 reads resulting in mean depth of 129.8x (99.5% of target bases were covered at a minimum of 20x, whereas 99.7% had coverage of min. 10×). Bioinformatic analysis of raw WES data and variants prioritization were performed as previously described [7–9]. Reads were aligned to the hg38 reference genome sequence and visualized by Integrative Genomic Viewer.

RESULTS AND DISCUSSION

The comprehensive analysis WES data showed neither SNV nor CNV that could explain the occurrence of giant CAE in the proband. Genes associated with the development of CAAE in Kawasaki disease [5] as well as potentially associated with the pathogenesis of CAAE (*ATG7*, *MMP-2*, *MMP-9*, *GRIN3A*, *TIMP2*, *TIMP3*, *ACE*) were analyzed in detail. CCTA screening of the patient's daughters showed the absence of CAAE. Considering all obtained results, genetic testing of the proband's daughters was abandoned.

To the best of our knowledge, the presented case is the second largest CAAE reported in Poland and one of the biggest described worldwide [10, 11]. Moreover, it is also one of the first reports on the WES application in CAAE [12]. The patient selected for genetic analyses was also initially characterized as a high-risk of genetic background. He had advanced CAE with dynamic progression but without significant stenoses in coronary arteries. Moreover, his aneurysms were identified in different vascular territories. He had neither history of any diseases that are of a proven etiological factor for CAAE nor previous cardiac interventions. In addition, his family history was strongly positive towards aneurysmal lesions. Nevertheless, as has been pointed the WES analysis did not reveal any62,69 pathogenic or potentially pathogenic variants.

Our pilot study has important limitation. The applied WES-based SNV/CNV analysis has limited sensitivity and specificity. Potentially, other methods, such as whole genome sequencing (WGS), optical genome mapping (OGM), high-resolution array comparative genomic hybridization (aCGH) or multiplex ligation-dependent probe amplification (MLPA) could lead to the identification of pathogenic variants. Finally, considering all mentioned above, further research on WES/WGS and its broader use in CAAE on larger groups of patients is warranted to identify novel pathogenic variants in different CAAE phenotypes [13, 14].

So far, there are no specific CAAE clinical guidelines. Furthermore, modern calculators and scales assessing coronary artery disease complexity omit the CAAE presence, despite their indisputable negative impact on the outcomes that arise from specific complications, such as thrombosis, distal embolism, rupture, or vasospasm [2, 15]. The results of further WES/WGS studies could provide more insights into the pathogenesis of CAAE and bring substantial benefits for the patients, such as better risk stratification, personalized management, additional monitoring, or familial screening.

Article information

Conflict of interest: None declared.

Funding: This work was supported by Jagiellonian University Medical College Students' Scientific Society Grant (NZ4-2021/2022 to AM).

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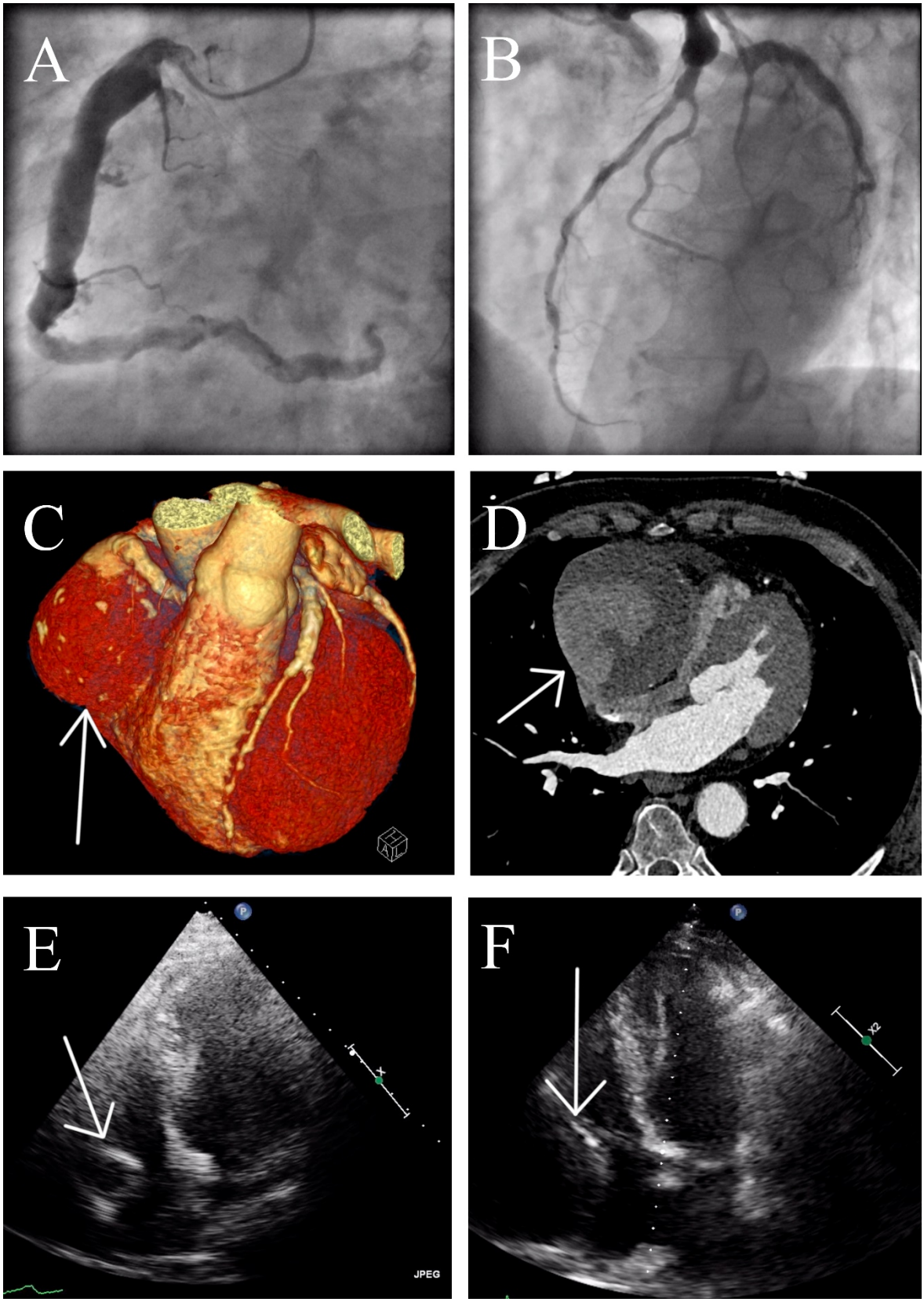

Figure 1. The diagnostic images of the coronary artery ectasia (CAE). **A, B.** The right CAE and disseminated ectasias in other vessels in an initial coronary angiography. **C.** The digital reconstruction of giant right CAE based on computed tomography angiography performed

immediately after diagnosis. **D.** The significant progression of giant right CAE diameter to 86 × 60 mm in the last computed tomography. **E, F.** The modeling of the right heart chambers by giant ectasia in echocardiography performed two years ago as well as recently