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

Anna Matrejek[1*], Konrad Stępień[2, 3*], Karol Nowak[2], Sylwia Iwańczyk[3, 4], Agnieszka Pollak[5], Rafał Płoski[5], Tomasz Miszalski-Jamka[6], Mateusz Podolec[2], Jadwiga Nessler[2], Jarosław Zalewski[2]

[1]Students' Scientific Group, Department of Coronary Artery Disease and Heart Failure, Jagiellonian University Medical College, Kraków, Poland
[2]Department of Coronary Artery Disease and Heart Failure, Institute of Cardiology, Jagiellonian University Medical College, Kraków, Poland
[3]"Club 30", Polish Cardiac Society, Poland
[4]1st Department of Cardiology, Poznan University of Medical Sciences, Poznań, Poland
[5]Department of Medical Genetics, Medical University of Warsaw, Warszawa, Poland
[6]Department of Radiology and Diagnostic Imaging, John Paul II Hospital, Kraków, Poland
*Both authors equally contributed to the study.

Correspondence to:
Konrad Stępień, MD, PhD, Department of Coronary Artery Disease and Heart Failure, Institute of Cardiology, Jagiellonian University Medical College, Prądnicka 80, 31–202 Kraków, Poland, phone: +48 12 6142218, e-mail: konste@interia.eu

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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 reported incidence of CAAE is 0.3%–5.3% of patients undergoing coronary angiography and 1.4% of post-mortem examinations [1, 2]. Giant CAAE is a rare phenomenon characterized by a dilation of a coronary artery exceeding 2 cm, 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]. A meta-analysis of genome-wide association studies performed in European and Japanese populations of children with Kawasaki disease has identified *ITPKC*, *FCGR2A*, *CASP3,* and *FAM167A* genomic regions to be associated with susceptibility to CAAE [5]. Furthermore, the 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 giant, has not been confirmed [1].

Therefore, we present our pilot data on applying whole exome sequencing (WES) in a patient with extreme 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 assessment before planned thoracic surgery due to a 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 a partly thrombosed diffuse ectasia along the right coronary artery with a maximum diameter of 15 mm in the proximal segment and in the proximal left anterior descending and proximal to the mid-left circumflex arteries (Figure 1A, B). Since coronary lesions were not suitable for any interventions, the Heart Team recommended optimal medical treatment. During follow-up, significant progression to

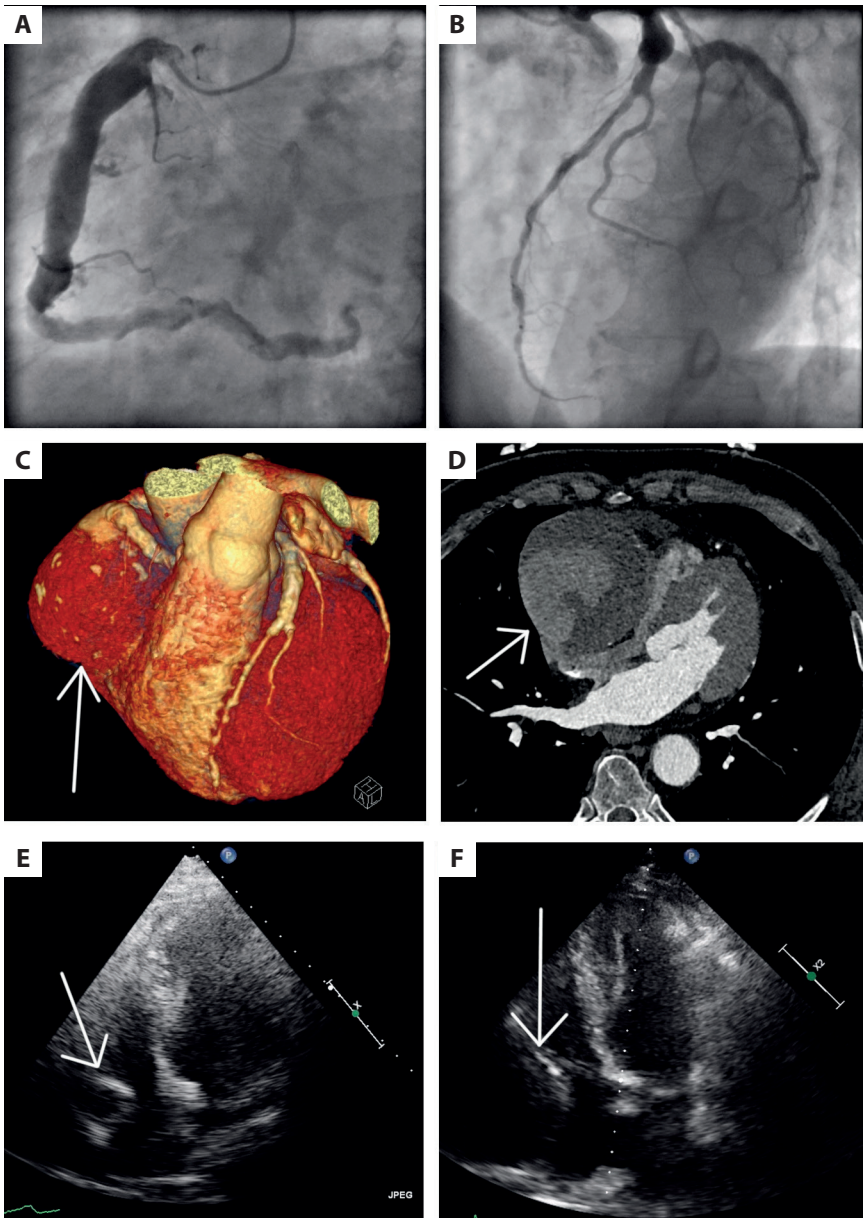

Figure 1. Diagnostic images of the coronary artery ectasia (CAE). **A, B.** The right CAE and disseminated ectasias in other vessels on initial coronary angiography. **C.** Digital reconstruction of the giant right CAE (arrow) based on computed tomography angiography performed immediately after diagnosis. **D.** Significant progression of the diameter of the giant right CAE to 86 × 60 mm (arrow) on the last computed tomography. **E, F.** The modeling of the right heart chambers by the giant ectasia (arrow) on echocardiography performed two years earlier and recently

60 × 61 mm, 70 × 64 mm, and finally to 86 × 60 mm was observed on subsequent coronary computed tomography angiographies (CCTA) (Figure 1C, D). In serial transthoracic and transesophageal examinations, the compression of the right atrium, right ventricle, and tricuspid annulus have been visualized (Figure 1E, F).

Due to the suspicion of a genetic background for the giant CAE, the patient was referred for WES. The targeted genetic tests and CCTA were also offered to 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, US). The enriched library was paired-end sequenced (2 x100 bp) on NovaSeq 6000 (Illumina, San Diego, CA, US) to obtain 116 001 610 reads resulting in a mean depth of 129.8x (99.5% of target bases were covered at a minimum of 20×, whereas 99.7% had coverage of min. 10×). Bioinformatic analysis of the 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 of the WES data showed neither single nucleotide variants (SNV) nor copy number variants (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 WES applications in CAAE [12]. The patient selected for genetic analyses was also initially characterized as having a high risk of genetic background. He had advanced CAE with dynamic progression but without significant stenoses in the coronary arteries. Moreover, his aneurysms were identified in different vascular territories. He had no history of any diseases that are a confirmed etiological factor for CAAE nor previous cardiac interventions. In addition, his family history was strongly positive towards aneurysmal lesions. Nevertheless, as has been pointed out, the WES analysis did not reveal any 62,69 pathogenic or potentially pathogenic variants.

Our pilot study has important limitations. 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. Considering the mentioned above limitations, 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 CAAE-specific clinical guidelines. Furthermore, modern calculators and scales for assessing the complexity of coronary artery disease omit the CAAE presence despite their indisputable negative impact on outcomes, which arises 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

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