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Case Report

Could the BGN Gene Be Pathogenic with Spontaneous Coronary Artery Dissection (SCAD) and Fibromuscular Dysplasia (FMD)?

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Abstract: BACKGROUND. Spontaneous coronary artery dissection (SCAD) is a cause of myocardial infarction, especially in younger women without cardiovascular risk factors. Patient management and diagnostics are still largely based on retrospective and observational studies. Most patients with SCAD report chest pain and have elevated biomarkers with ECG findings. SCAD can lead to cardiogenic shock, ventricular arrhythmias and cardiac arrest, and is commonly associated with fibromuscular dysplasia (FMD). Genetic associations are still in their infancy with this disease process. **METHODS**. An Invitae 29 gene aortopathy panel was performed on a mother with a thoracic aortic aneurysm and her daughter who presented with SCAD and was noted to have FMD. **RESULTS**. The patient and her mother were both noted to have a heterozygous mutation of the Biglycan (BGN) gene (Variant c.1030T > G (p.Tyr344His)) of undetermined significance. An extensive literature review was performed, including a review of the UK Biobank. This is the first case to our knowledge showing a possible link between the BGN mutation and SCAD/FMD. **CONCLUSIONS**. The BGN mutation has been recognized to be correlated with aortic aneurysm and aortic dissection. It has not yet been explored to be associated with SCAD/FMD. This paper highlights the potential link between the BGN gene and SCAD/FMD. Further research looking at this association is warranted.

Keywords: SCAD; BGN variant; FMD; genetics; myocardial infarction

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1. Introduction

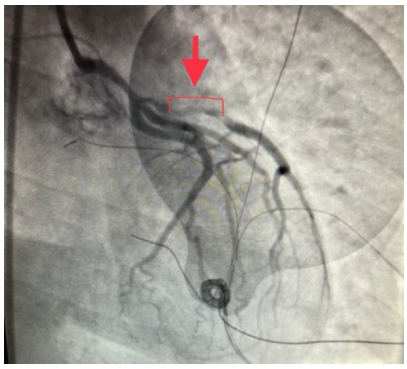
Spontaneous coronary artery dissection (SCAD) is a nonatherosclerotic and non-traumatic cause of acute coronary syndromes in young healthy patients (predominantly women) [1–3]. Acute coronary syndrome, myocardial infarction and sudden cardiac death have all been linked to SCAD [2]. The mechanism of SCAD causing myocardial injuries involves a high grade coronary artery obstruction [1]. SCAD is now well recognized but there is still a paucity of high-level, evidence-based recommendations for the best short- and long-term care as well as the appropriate workup [3]. In some cases, SCAD can be associated with connective tissue diseases such as Marfan's syndrome and Ehlers-Danlos type IV [3]. Specifically, SCAD has been linked *to FBN1, COL3A1, and SMAD3* mutations [4]. FMD is an idiopathic, non-atherosclerotic disease which is typically diagnosed in middle-aged women. Family relapse studies have shown genetic contributions to SCAD and fibromuscular dysplasia (FMD) [4]. At least half of all patients with SCAD will be diagnosed with FMD according to Georges et al., FMD is associated with four genetic variants that control gene expression in the arteries (*ATP2B1, LRP1, LIMA1, PHACTR1*) [5].

The Biglycan (BGN) gene is a member of the small leucine-rich proteoglycans (SLPRs) gene family and encodes a protein core that is modified to form a glycoprotein. BGN is a key component of the extracellular matrix; it participates in scaffolding the collagen fibrils and mediates cell signaling. It plays a role in bone growth, muscle development and regeneration and collagen fibril assembly in multiple tissues. There are no studies which show a link

between SCAD/FMD and the BGN gene. This case report aims to increase the understanding of the pathophysiology of SCAD and its possible genetic link with the BGN gene.

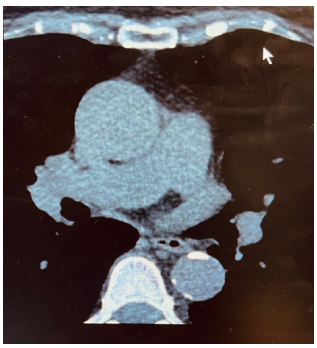
Our primary subject is a 40-year-old white female (KC). She was a healthy woman with no past medical history who was not taking any medications. She was a non- smoker and non-drinker who exercised several times per week. Aside from routine, patient visits and appropriate care during her two healthy pregnancies, she had not had any other contact with medical professionals.

KC was admitted to the hospital on 31 August 2021 with severe chest pain after exercise and was noted to have anST elevation myocardial infarction (STEMI) based on her ECG. Based on the ECG findings and the presence of probable cardiogenic shock (blood pressure 70/30), she was emergently prepped for a coronary angiogram. SCAD was found in the distal left main and proximal left anterior descending artery (see Figure 1a). Based on her clinical picture, a decision was made to intervene. She received percutaneous coronary intervention with two overlapping drug eluting stents in the proximal left-sided circulation and an intra-aortic balloon pump was placed. She was started on dual anti-platelet therapy (DAPT) as well as unfractionated heparin. Her chest discomfort resolved immediately after the procedure. An echocardiogram that day conveyed an ejection fraction of 35–40% with severe hypokinesia of the anterior wall and akinesia of the apex. She was subsequently started on a beta blocker and ace inhibitor. The following day, she described 10/10 pain in her left lower extremity. Her leg was noted to be swollen with severe pain to palpation around the entire calf region. Her pulses in her foot were not palpable. She was emergently taken to the operating room for fasciotomy in the setting of compartment syndrome, likely related to the DAPT and heparin causing a spontaneous bleed. KC ultimately recovered and was seen for follow up in the office.



(**a**)

(**b**)



(**c**)

Figure 1. (**a**) Cardiac catheterization showing the dissection of the proximal left anterior descending artery of patient KC. Cardiac catheterization conveying the dissection of the distal left main coronary artery and the proximal LAD (arrow). (**b**) CTA neck of patient KC. CTA of KC showing FMD involving the distal left internal carotid artery (arrow). There is a focal smooth short segment enlargement of the distal left cervical internal carotid artery. (**c**) CT chest of patient MC. CT of MC showing a mildly aneurysmal ascending aorta, measuring 4 cm.

Aside from some anxiety related to the event, she was overall feeling well. An echocardiogram performed in the office showed a slight improvement in cardiac function with an ejection fraction (58%), the resolution of anterior wall hypokinesia and persistent akinesia of the apex. She was instructed to remain on current pharmacotherapy. It was at this time that a CTA from neck to pelvis was ordered to assess for FMD and genetic testing was recommended due to the known association between SCAD and connective tissue diseases. The cardiologist managing KC (author J.R.) also happened to be the cardiologist of the patient's biological mother (MC). In reviewing her chart, it was recognized that MC a had small thoracic aortic aneurysm which was incidentally noted on a prior chest CT (Figure 1c). MC's only medical history was the remote history of the melanoma of the leg and mild dyslipidemia for which she was staking atorvastatin. Neither KC or MC had any obvious clinical pathologic features of aortopathy syndromes such as long wing span, valvular heart disease, hypertelorism, pectus deformity, joint hypermobility, contractures, or skeletal dysplasia. Both women are average in height at 66 inches.

2. Materials and Methods

An Invitae Aortopathy Comprehensive Panel was completed on KC and MC. The panel assessed 29 genes for variants associated with specific genetic orders. The examined genes included:

ACTA2
BGN
CBS
COL3A1
COL5A1
COL5A2
EFEMP2
FBN1
FBN2
FLNA
FOXE3
LOX
MED12
MFAP5
MYH11
MYLK
NOTCH1
PLOD1
PRKG1
SKI NM_
SLC2A10
SMAD2
SMAD3
SMAD4
TGFB2
TGFB3
TGFBR1
TGFBR2 NM_003242.5

Genomic DNA obtained from the submitted samples are enriched for targeted regions using a hybridization-based protocol, and sequenced using Illumina technology. Unless otherwise indicated, all targeted regions were sequenced with $\geq$50$\times$ depth or were supplemented with additional analysis. Reads are aligned to a reference sequence (GRCh37), and sequence changes are identified and interpreted in the context of a single clinically relevant transcript, as indicated below. Enrichment and analysis focused on the coding sequence of the indicated transcripts, 20 bp of flanking intronic sequence, and other specific genomic regions demonstrated to be causative of disease at the time of assay design. Pro-

moters, untranslated regions, and other non-coding regions are not otherwise interrogated. For some genes, only targeted loci are analyzed (as indicated in the table above). Exonic deletions and duplications are called using an in-house algorithm that determines the copy number at each target by comparing the read depth for each target in the proband sequence with both mean read-depth and read-depth distribution, obtained from a set of clinical samples. Markers across the X and Y chromosomes were analyzed for quality control purposes and may detect deviations from the expected sex chromosome complement. Such deviations may be included in the report in accordance with internal guidelines. The confirmation of the presence and location of reportable variants was performed as needed based on stringent criteria established by Invitae (1400 16th Street, San Francisco, CA 94103, USA, #05D2040778), using one of several validated orthogonal approaches (PubMed ID 30610921). The following analyses were performed if relevant to the requisition. For PMS2 exons 12–15, the reference genome was modified to force all sequence reads derived from PMS2 and the PMS2CL pseudogene to align to PMS2, and variant calling algorithms were modified to support an expectation of four alleles. If a rare SNP or indel variant was identified by this method, both PMS2 and the PMS2CL pseudogene were amplified by long-range PCR and the location of the variant was determined by Pacific Biosciences (PacBio) SMRT sequencing of the relevant exon in both long-range amplicons. If a CNV was identified, MLP or MLPA-seq is run to confirm the variant. If confirmed, both PMS2 and PMS2CL are amplified by long-range PCR, and the identity of the fixed differences between PMS2 and PMS2CL are sequenced by PacBio from the long-range amplicon to disambiguate the location of the CNV. The technical component of confirmatory sequencing was performed by Invitae Corporation (1400 16th Street, San Francisco, CA 94103, USA, #05D2040778). For C9orf72 repeat expansion testing, hexanucleotide repeat units are detected by repeat-primed PCR (RP-PCR) with fluorescently labeled primers followed by capillary electrophoresis. Interpretation reference ranges: benign (normal range): <25 repeat units, uncertain: 25–30 repeat units, pathogenic (full mutation): $\geq$31 repeat units. A second round of RP-PCR utilizing a non-overlapping set of primers was used to confirm the initial call in the case of suspected allele sizes of 22 or more repeats. For an RNA analysis of the genes indicated in the table showing the analyzed genes, complementary DNA was synthesized by reverse transcription from RNA derived from a blood specimen and enriched for specific gene sequences using capture hybridization. After high-throughput sequencing using Illumina technology, the output reads are aligned to a reference sequence (genome build GRCh37; custom derivative of the RefSeq transcriptome) to identify the locations of exon junctions through the detection of split reads. The relative usage of exon junctions in a test specimen is quantitatively assessed and compared to the usage seen in the control specimens. Abnormal exon junction usage was evaluated as evidence in the Sherloc variant interpretation framework. If an abnormal splicing pattern is predicted based on a DNA variant outside the typical reportable range, as described above, the presence of the variant is confirmed by targeted DNA sequencing. RNA sequencing is performed by Invitae Corporation (1400 16th Street, San Francisco, CA 94103, USA, #05D2094793). The technical component of fibroblast cell-culturing and gDNA extraction from skin punch biopsy was performed by Invitae Corporation (5 Technolog Drive, Irvine, CA 92618, USA, #05D1052995). A PMID is a unique identifier referring to a published, scientific paper. Search by PMID at http://www.ncbi.nlm.nih.gov/pubmed (accessed on 22 July 2022). An rsID is a unique identifier referring to a single genomic position, and is used to associate population frequency information with sequence changes at that position. Reported population frequencies are derived from a number of public sites that aggregate data from large-scale population sequencing projects, including ExAC (http://exac.broadinstitute.org (accessed on 22 July 2022)), gnomAD (http://gnomad.broadinstitute.org (accessed on 22 July 2022)), and dbSN (http://ncbi.nlm.nih.gov/SNP (accessed on 22 July 2022)). A MedGen ID is a unique identifier referring to an article in MedGen, NCBI's centralized database of information about genetic disorders and phenotypes. A searched was performed by MedGen ID at http://www.ncbi.nlm.nih.gov/medgen (accessed on 22 July 2022). An OMIM

number is a unique identifier referring to a comprehensive entry in Online Mendelian Inheritance of Man (OMIM). A searched was performed by OMIM number at http://omim.org/ (accessed on 22 July 2022). Invitae uses information from individuals undergoing testing to inform variant interpretation. If "Invitae" is cited as a reference in the variant details, this may refer to the individual in this requisition and/or historical internal observations. In addition, using the OVID search engine, an extensive literature search assessing for a link between genetic mutations and SCAD/FMD was performed. In addition, the UKB database was investigated by looking at the BGN gene and its relationship to SCAD/FMD.

3. Results

The analysis of the testing showed a heterozygous mutation of the BGN gene (variant c.1030T > G (p.Tyr344His)) in both the patient and her mother. At this time, this is considered a variant of uncertain significance. The clinical significance of the variant(s) identified in this gene is uncertain. These results suggest the exploration of the BGN mutation and its possible link with SCAD/FMD. Throughout the literature and the UKB database, an association between BGN and SCAD/FMD has not been described before.

4. Discussions

The BGN gene is associated with X-linked spondyloepimetaphyseal dysplasia (SEMD) and X-linked thoracic aortic aneurysm and dissection (TAAD), with or without additional features, also known as Meester–Loeys syndrome. According to Meester et al., the BGN gene mutation causes an X-linked TAAD. This study used Sanger sequencing and microarray. The findings show the clinical phenotype of BGN mutations showing up as early onset aortic aneurysm and dissection [6].

Although MC was noted to have a small aortic aneurysm, KC at age 40 exhibited none of the features described in these syndromes. Her sole vascular pathology at this time was SCAD/FMD. This report highlights the possibility that the BGN mutation may not only be pathogenic with aortic pathology, but also with SCAD/FMD. The BGN mutation has yet to be explored regarding its relationship with SCAD/FMD

In a study performed by Verstraeten et al., pathogenic variants in *SMAD2, COL3A1, FLNA, and LOX*, which are seen in Loeys–Dietz Syndrome, were seen in patients with SCAD. Their paper highlights the relationship between genes causing aortopathy and SCAD [4]. Current research regarding other genetic indicators for SCAD are emerging. According to Hayes, many genetic variants such as: *F11R, TLN1, TSR1, PHACTR1, and EDN1* are likely linked with SCAD [3].

The pathogenesis is still unknown for SCAD, but it is postulated that there are multiple contributors such as genetic factors, stressors, and other underlying health conditions. Further studies assessing the connection between SCAD/FMD and other genetic variants are necessary to close the knowledge gap. This report highlights the need for further study with the BGN mutation to increase our knowledge of the pathogenesis of these diseases. Understanding the genetic basis of the disease may lead to novel treatments and risk stratification models.

In conclusion, previous studies have suggested a relationship between TAAD and SCAD/FMD [4]. Genetic variants contributing to TAAD, SCAD and FMD have been described with some overlap. An aortopathy gene panel analysis here showed both patients to have a heterozygous mutation of undetermined significance of the BGN gene. Although this gene has been described to cause aortic aneurysm, as seen in the mother, this is the first report highlighting the possibility of a link between this variant and SCAD/FMD. As the pathophysiology of SCAD involves dissection, albeit of a coronary artery, a gene known to cause aortic dissection must not be ignored. Further investigation must be performed to confirm a link between the BGN gene and SCAD/FMD.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Written informed consent was obtained from the patient(s) to publish this paper.

Conflicts of Interest: The authors declare no conflict of interest.

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