Ganesh Santhi K (Orcid ID: 0000-0002-3663-5249)

Spontaneous Coronary Artery Dissection is Infrequent in Individuals with Heritable Thoracic Aortic Disease Despite Partially Shared Genetic Susceptibility

Andrea M. Murad[1]; Hannah L. Hill[2,3]; Yu Wang[2,3]; Michael Ghannam[2]; Min-Lee Yang[2,3]; Norma L. Pugh[4]; Federico M. Asch[5]; Whitney Hornsby[2,6]; Anisa Driscoll[6]; Jennifer McNamara[6]; Cristen J. Willer[2,3,7]; Ellen S. Regalado[8]; GenTAC Investigators[9]; Montalcino Aortic Consortium Investigators[10]; Dianna M. Milewicz[8]; Kim A. Eagle[2]; Santhi K. Ganesh[2,3]

Author Affiliations:

1. Division of Genetic Medicine, Department of Internal Medicine, University of Michigan, Ann Abor, Michigan
2. Division of Cardiovascular Medicine, Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan
3. Department of Human Genetics, University of Michigan, Ann Arbor, Michigan
4. Center for Clinical Research Network Coordination, Biostatistics and Epidemiology Division, RTI International, Research Triangle Park, NC
5. MedStar Health Research Institute, Hyattsville, MD
6. Cardiovascular Health Improvement Project (CHIP) biorepository
7. Department of Computational Medicine and Bioinformatics, University of Michigan, Ann Arbor, Michigan
8. Division of Medical Genetics, Department of Internal Medicine, McGovern Medical School, The University of Texas Health Science Center at Houston, Houston, Texas
9. Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC) Consortium
10. Montalcino Aortic Consortium (MAC)

Running Title: Spontaneous coronary artery dissection in thoracic aortopathy

Corresponding Author:
Santhi K Ganesh, MD
University of Michigan
MSRBIII / 7220A
1150 West Medical Center Drive
Ann Arbor, MI 48109
sganesh@umich.edu
(734) 764-4500

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/ajmg.a.62661

Conflict of Interest

AMM is a paid consultant for Concert Genetics. CJW husband works for Regeneron. No other authors have financial conflicts of interest.

ABSTRACT

Purpose

Spontaneous coronary artery dissection (SCAD) is a potential precipitant of myocardial infarction and sudden death for which the etiology is poorly understood. Mendelian vascular and connective tissue disorders underlying thoracic aortic disease (TAD), have been reported in ~5% of individuals with SCAD. We therefore hypothesized that patients with TAD are at elevated risk for SCAD.

Methods and Results

We queried registries enrolling patients with TAD to define the incidence of SCAD. Of 7,529 individuals enrolled, 11 (0.15%) were found to have SCAD. Of the sequenced cases (9/11), pathogenic variants were identified (N=9), including *COL3A1* (N=3), *FBN1* (N=2), *TGFBR2* (N=2), *TGFBR1* (N=1), and *PRKG1* (N=1). Individuals with SCAD had an increased frequency of iliac artery dissection (25.0% vs. 5.1%, p=0.047).

Conclusion

The prevalence of SCAD among individuals with TAD is low. The identification of pathogenic variants in genes previously described in individuals with SCAD, particularly those underlying vascular Ehlers Danlos, Marfan Syndrome, and Loeys-Dietz syndrome, is consistent with prior reports from clinical SCAD series. Further research is needed to identify specific genetic influences on SCAD risk.

Key words: Spontaneous Coronary Artery Dissection, Familial Thoracic Aortic Aneurysm and Dissection, Arterial disease, Genetic Susceptibility

INTRODUCTION

Thoracic aortic disease (TAD) predisposes individuals to life threatening aortic complications, including aortic dissection, aneurysm, and rupture potentially precipitating sudden death. Most genes conferring a highly penetrant risk for TAD cause syndromic genetic disorders, including Marfan syndrome (MFS), Loeys-Dietz syndrome (LDS), and vascular Ehlers-Danlos syndrome (vEDS), although risk for TAD may be inherited in the absence of syndromic diagnosis. Heritable thoracic aortic disease (HTAD) conditions may be complicated by extra-aortic arterial tortuosity, aneurysms, and/or dissection, including spontaneous coronary artery dissection (SCAD). SCAD describes an atraumatic separation of the coronary artery wall caused by rupture of the arterial intima with false lumen formation or coronary vasa vasorum with intramural hematoma compressing the arterial lumen (Alfonso et al., 2012; Hayes et al., 2018; Saw et al., 2016). This clinical scenario has the potential to precipitate sudden cardiac death and is increasingly recognized as a cause of myocardial infarction (MI), particularly in young women (Sato et al., 2014).

The genetic basis of SCAD is currently understood as partly complex and monogenic in <5% of cases, implicating genes for HTAD (Henkin et al., 2016; Kaadan et al., 2018). Familial clustering of SCAD has been observed though pedigree studies are lacking (Goel et al., 2015; Turley et al., 2019). Common genetic variation is associated with SCAD and partly overlaps associations with fibromuscular dysplasia (FMD), in particular a single nucleotide variant on chromosome 6 in the *PHACTR1* gene (rs9349379) with minor allele frequency ~0.4 and associated with both FMD and SCAD Saw et al., 2020). FMD is a systemic arteriopathy in which dissections occur in

approximately 26% of individuals, including SCAD in 2.7% (OR_{SCAD}=1.7 OR_{FMD}=1.4) (Adlam et al., 2019; Kadian-Dodov et al., 2016; Kiando et al., 2016). FMD is not associated with TAD, and as such likely may represent a distinct association with SCAD, with FMD reported in 25-86% of SCAD patients (Hayes et al., 2018).

The true population prevalence of SCAD is unknown due to under-diagnosis. Current estimates of SCAD prevalence based upon series of patients with acute coronary syndrome is 1.7-4.0% (Nishiguchi et al., 2016; Rashid et al., 2016). In the clinic, consideration is often given to whether testing for genes underlying aortopathies should be pursued. Knowing the incidence of SCAD among those with TAD may be informative for this consideration. We hypothesized that SCAD occurs more frequently in the TAD patient population than in the general population and that affected individuals share clinical and/or genetic features. However, after querying 7,529 individuals in three TAD registries, the incidence of SCAD was 0.15%. Genetic syndrome diagnoses aligned closely with prior reports (Henkin et al., 2016; Kaadan et al., 2018).

MATERIALS & METHODS

Data Sources

Data was compiled from three registries including 24 clinical centers worldwide enrolling individuals with a genetic risk for thoracic aortic aneurysm. The Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC) study is an NIH-supported longitudinal observational cohort study enrolling individuals between

2006-2016 with either known or suspected genetic mutations predisposing to thoracic aortic aneurysm and/or dissection (Eagle & GenTAC Consortium, 2009). The Montalcino Aortic Consortium (MAC, http://www.montalcinoaorticconsortium.org/), is an international scientific collaboration of clinical centers with expertise in TAD contributing to a multicenter retrospective registry of patients with HTAD since 2013 (Jondeau et al., 2016). The Cardiovascular Health Improvement Project (CHIP) is a biorepository at the University of Michigan, Michigan Medicine, with a historical collection of genotype and phenotype data, family history, DNA, and aortic tissue from participants with thoracic aortic disease (Wolford et al., 2019).

Data Collection

Registries were queried in March 2017 for SCAD case identification via free text word search and ICD codes (Supplemental Table 1**)**. All cases of documented or referenced coronary artery dissection were reviewed for clinical context by study authors (SKG or MG). Events resulting from retrograde aortic dissection into a coronary bed, those identified during or immediately following blunt trauma, surgery, or arterial instrumentation, and unconfirmed reports were excluded from our case sample.

Patient-level demographic, phenotype, genotype, and family history data were collected as available. Variants in specific genes of interest to a given registry was shared during data collection. Both GenTAC and MAC maintained record of variants in *ACTA2*, *TGFBR1*, *MYH11* and *TGFBR2*. GenTAC uniquely recorded variants in *COL3A1*, *COL5A1*, *COL5A2*, *FBN1*, *FBN2*, and Tenascin X genotypes. MAC additionally tracked variants in all HTAD genes except *FBN1*, including *PRKG1* and

SMAD3. Individuals in these registries were not necessarily sequenced for all genes of interest as some chose to forego DNA analysis while others underwent only clinical genotyping. Pathogenic variants in the genes of interest were collected.

Clarification was requested from the enrolling site investigator and/or the referring physician when uncertainties or discrepancies in data were noted. Enrollment objectives, data collection, and access protocols varied across registries, therefore, detailed clinincal information was not available for all registries. Because most SCAD cases were identified in GenTAC, the largest cohort queried, tests of independence were conducted exclusively on GenTAC participants.

All registries were approved by the institutional review board and written informed consent was obtained from study participants at time of enrollment. For each variant identified, seven databases were searched to identify previously reported variant carriers: ClinVar, dbSNP, Leiden Open Variation Database (LVOD) v3.0, Human Gene Mutation Database (HGMD), Ehlers Danlos Syndrome Variant Database, UMD-FBN1, and Uniprot.

Statistical Analysis

Tests of independence conducted using two-tailed, two-sample t-tests, and Fisher's exact tests for continuous and binary independent variables, respectively, or Kruskal-Wallis test for age. Analyses were executed in Stata/IC software (Version 15.0, StataCorp, College Station, Texas) and a statistical significance threshold was set at p-value ≤0.05.

RESULTS

Among 7,568 individuals enrolled in the GenTAC (N=3,540), CHIP (N=3,000), and MAC (N=1,028) registries, 11 unrelated SCAD cases were identified (GenTAC, N=8; MAC, N=3). Using the combined queried sample as a denominator, the incidence of SCAD in individuals with TAD was 0.15%. The registry-specific incidence of SCAD was 0.25% in GenTAC and 0.30% in MAC. No cases of SCAD were identified in CHIP. Detailed information about the MAC cohort is included in Supplemental Table 2.

Clinical features

Of the 11 identified SCAD cases, the majority of affected individuals were female (81.8%) and self-reported European ancestry (81.8%). The average age at the time of SCAD was 39 years. Detailed clinical data on the 11 SCAD cases is included in Supplemental Table 3. Among female cases, no events occurred in the peripartum period although only one woman was known to have children. Four individuals (36.4%) had a known smoking history and two (18.2%) had been diagnosed with hypertension (Table 1). Aortic root dilatation was documented in a woman with a pathogenic *PRKG1* variant (Case 10) who had undergone valve-sparing aortic root replacement with coronary artery reimplantation. A woman harboring a pathogenic *TGFBR1* variant causing LDS (Case 9) was found to have mild aortic root dilation. No history of stroke, bicuspid aortic valve, or FMD were identified.

At first occurrence, dissections involved the left main coronary artery (N=4) most often followed in frequency by the right coronary artery (N=3), left anterior descending (N=2), and ramus intermedius (N=1). All dissections precipitated myocardial injury and infarction, and the majority of cases (N=9) were managed with coronary artery bypass

grafting relative to conservative medical therapy (N=2). A woman with vEDS (Case 2) experienced two sequential SCAD events occurring simultaneously two months after the initial SCAD event. Each event in this case involved a different epicardial coronary artery. In Case 10, a proximal left main coronary artery trifurcation aneurysm developed following spontaneous dissection of the left main. Five individuals had a family history of sudden unexpected death (Supplemental Table 2).

Systemic Arterial Abnormalities

Four individuals (36.4%) were found to have additional spontaneous arterial dissections involving vascular beds other than the aorta or coronary arteries. These included the iliac (N=2), internal carotid (N=2), subclavian (N=1), celiac (N=1), and vertebral (N=1) arteries. Extra-coronary arterial dissections all occurred in the setting of pathogenic *COL3A1* or *TGFBR1* variants and one of these individuals had an extra-aortic aneurysm. The only individual with a *COL3A1* variant without an extra-coronary dissection was known to have an extra-aortic aneurysm.

Genetic diagnoses

All individuals with SCAD had either a known clinical diagnosis of a genetic syndrome and/or a molecularly confirmed pathogenic variant in a gene conferring highly penetrant risk for TAD (Table 2). Of the 9 genotyped patients, affected genes included *COL3A1* (N=3), *FBN1* (N=2), *TGFBR2* (N=2), *TGFBR1* (N=1), and *PRKG1* (N=1). Associated genetic syndromes were thus vEDS (*COL3A1*), MFS *(FBN1*), and LDS (*TGFBR1 and TGFBR2*), respectively. The two individuals who did not undergo genetic testing carried clinical diagnoses of MFS and HTAD.

Detailed variant information was available in 6 cases (Supplemental Table 2). Of mutations in *COL3A1*, one is a pathogenic nonsense variant in exon 46 situated near the end of the protein's triple helical domain (Case 1). This variant has been reported twice in ClinVar in association with vEDS (Variation ID: 101427) and has been referenced (Pepin et al., 2014). A second variant in Case 3 is a classic *COL3A1* pathogenic missense variant disrupting a glycine residue of exon 8 early in the triple helical domain. This variant has been submitted to ClinVar once in association with vEDS (Variation ID: 101123) and referenced (Pepin et al., 2000; Smith et al., 1997). Details of the third individual's reported genetic variant in *COL3A1* (Case 2) were not available for review.

Identified variants in *FBN1* included missense and donor splice site variants. A missense variant involving a cysteine residue in the protein's first hybrid domain was found in Case 5 (Jensen et al., 2009). This domain is part of the FBN1E2cbEGF1 fragment known to bind latent TGF-β binding proteins, the major reservoir of TGF-β in the extracellular matrix (Robertson et al., 2017). This variant has been previously identified in an individual with MFS, as indexed in ClinVar (submission SCV000787216) as likely pathogenic, and reported twice as a heterozygous variant in males of French descent with MFS per the UMD-FBN1 database (Stheneur et al., 2009). In Case 4, a donor splice site alteration two nucleotides into IVS61 was detected. This variant was also identified in the proband's mother and son who also have MFS. It has not been previously reported in ClinVar or the UMD-FBN1 database. The locus is adjacent to a functional donor site and a variant one nucleotide upstream (c.IVS61+1G>A) is expected to result in a splice recognition alteration with 30% variation in consensus

value between the mutant and wild type donor sequence according to the UMD algorithm. This variant affects the fibrillin-1 EGF-like domain where disulfide pairing is critical for proper protein folding (Dietz et al., 1992).

A woman without a syndromic diagnosis (Case 9) who has a history of multi-vessel dissection including SCAD at age 37 years was found to have an inherited pathogenic missense variant in exon 5 of *TGFBR1 (*Table 2). The variant occurs in the receptor's serine/threonine kinase domain at a position with notable evolutionary conservation (Singh et al., 2006). This case was previously reported in a family study with TAD (Tran-Fadulu et al., 2009). Neither the proband's mother nor son, who also carry the variant, were found to have had clinically evident SCAD. An unrelated male fulfilling the Ghent diagnostic criteria for MFS but who was not evaluated for features of LDS reportedly has the same *TGFBR1* variant without mention of coronary dissection (Singh et al., 2006).

The second individual with nonsyndromic TAD carried a known pathogenic *PRKG1* variant. The identified gain-of-function variant causes an arginine substitution at a highly conserved residue in the CNB-A domain resulting in increased type I cGMP-dependent protein kinase (PKG-1a) activity and decreased vascular smooth muscle cell contraction (Guo et al., 2013). This case was recently described in a natural history study of individuals with *PRKG1* variant and nonsyndromic TAD (Shalhub et al., 2019).

In the majority of cases (N=6, 54.5%), the first known medical documentation of a syndromic or genetic diagnosis occurred during the same month as clinical care sought for management of acute coronary syndrome precipitated by SCAD. In three cases,

SCAD preceded genetic testing by at least 6 months and in one situation genetic diagnosis was delayed by 10 years.

This investigation did not identify a distinct genotype or phenotype associated with SCAD (Table 1). Individuals experiencing SCAD appeared more likely to have had an iliac artery dissection (25.0% vs. 5.1%, p=0.047), whereas this was not necessarily observed for carotid artery or subclavian artery dissection which each occurred in only 1 individual with SCAD (12.5% vs. 2.4%, p=0.120 and 12.5% vs. 3.7%, p=0.180 respectively). This finding was based on the identification of two iliac artery dissections in our small case sample. In both cases, iliac artery dissection occurred in the context of abdominal aortic dissection extending into the iliac arteries.

DISCUSSION

In the current sample of 7,529 individuals across three TAD registries the incidence of SCAD was 0.15%. Dissection of extra-coronary arterial beds, particularly the iliac artery, was observed at higher frequency in individuals with SCAD. The demographic profile of our SCAD sample is similar to that of much larger SCAD cohorts, the majority being young women of European-ancestry with limited cardiovascular disease risk factors (Hayes et al., 2018). Compared to the general population (Kim et al., 2021), our SCAD sample was similar in demographic profile and cardiovascular disease risk factors, with the exception of tobacco use (Table 3). Relative to previously described SCAD cohorts, those with SCAD identified in our study had a younger age of onset (39 years versus 45 to 53 years), more proximal coronary artery involvement, and more frequent requirement for invasive and surgical revascularization, consistent with a

relatively severe SCAD phenotype (Hayes et al., 2018; Henkin et al., 2016; Kaadan et al., 2018).

The finding of pathogenic variants in *COL3A1*, *FBN1*, *TGFBR1*, *TGFBR2*, and *PRKG1*, is consistent with previously reported clinical series and cohort studies (Carss et al., 2020; Henkin et al., 2016; Kaadan et al., 2018; Verstraeten et al., 2020). Large cohort studies have found that among individuals with connective tissue disease, SCAD events are rare and sporadic in individuals with MFS, LDS, and vEDS (Eleid et al., 2014; Fattori et al., 2012; Hampole et al., 2011; Henkin et al., 2016; Kaadan et al., 2018; Nakamura et al., 2008; Saw et al., 2014; Sato et al., 2014). No individuals with SCAD in our study had FMD, consistent with a clinical genetic series of patients with SCAD, showing that monogenic conditions were identified in individuals without FMD, supporting a heterogeneous genetic architecture of SCAD (Kaadan et al., 2018). Whether novel genes underlying "monogenic" forms of SCAD are present will require systematic unbiased studies; the role of the known aortopathy genes appears to be in a small minority of patients with SCAD. The finding of a low rate of SCAD in genetically triggered aortic disease is notable and highlights that these disease processes may differ in pathophysiology. These vascular regions have differing developmental origins of neural crest and/or somatic mesoderm, and they experience different hemodynamic flow patterns and wall stress. Further, the aorta is characterized by greater elastin content as compared to the coronary artery.

The presence of SCAD in some TAD patients raises implications for clinical risk counseling. Close clinical characterization of individuals in TAD family studies have proven that the underlying gene predicts not only who in the family is at genetic risk, but

also (1) associated syndromic features, including those typical of MFS and LDS; (2) aortic disease presentation (age, dissection versus aneurysm), (3) risk for dissection at a given aortic diameter, and (4) risk for additional systemic vascular arteriopathy (Pinard et al., 2019). Identifying the causative genetic variation in TAD provides important information for disease counseling and management to prevent high morbidity and mortality of vascular complications. Using this as a model, selective genetic testing prompted by personal or family history of SCAD should be recommended.

This data is important to clinicians for developing surveillance recommendations and informing differentials when evaluating clinical symptoms suspicious for arterial events. Secondary prophylaxis with aspirin therapy is indicated following a SCAD event; although its effectiveness as a primary prevention measure has not yet been proven. Individuals with a known predisposition for SCAD, such as those with a known arteriopathy, should receive anticipatory guidance (Hayes et al., 2018).

The limitations of this study include the retrospective nature of our data collection and the fact that study participants may have been enrolled many years following their SCAD event(s), limiting cross-sectional phenotype and clinical data assessment at the time of SCAD. Enrollment protocols for queried registries were not designed for our research question and thus, resulted in some areas of missing data. Ascertainment of SCAD cases may have been incomplete in our queries due to reliance on clinical diagnostic codes and/or free text descriptions. Complete clinical data was not always available. Data on individuals with SCAD who also had acute coronary syndrome and/or annuloaortic ectasia was not reported, thefore we are unable to make any conclusions about how often SCAD is associated with these two findings in this patient population.

Our study focused on defined pathogenic variants in the genes that were analyzed. Whether additional variants in the same genes or pathways that are predicted to be deleterious and would therefore likely be classified as variants of uncertain significance is unknown. Polygenic risk was not assessed. The small number of individuals identified with SCAD in this study limited statistical power to identify phenotypic and genetic factors that might predict elevated risk for SCAD.

Conclusion

This work is among ongoing efforts to expand our understanding of molecular mechanisms underlying SCAD. The prevalence of SCAD among individuals with TAD is low yet showed a strong female predominance, similar to more general SCAD populations. The anatomic involvement of proximal coronary arteries and higher utilization of surgical revascularization suggest a more severe SCAD phenotype in individuals with TAD. Notably, the genes identified are concordant with those described in other clinical SCAD series, primarily highlighting genes associated with MFS, vEDS, and LDS. These findings support the need for further research to determine whether additional variants in the same genes and biologic pathways could act as disease modifiers or to identify additional genes implicated in the pathogenesis of SCAD.

DATA AVAILABILITY

The GenTAC Registry is a NHLBI supported project, with the data accessible on BioLINCC: https://biolincc.nhlbi.nih.gov/studies/gentac/. MAC data was provide by Dianna M. Milewicz, MD, PhD.

ACKNOWLEDGEMENTS

The GenTAC Registry has been supported by US Federal Government contracts HHSN268200648199C and HHSN268201000048C from the National Heart Lung and Blood Institute and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (Bethesda, MD). Subject enrollment and sample collection for the University of Michigan Health System CHIP biorepository was supported by the Frankel Cardiovascular Center. Study efforts were further supported by the Frankel Cardiovascular Center M-BRISC program, University of Michigan Taubman Institute, and NHLBI (R01 HL139672, PI: SKG and R01 HL109942, PI: DMM). The Montalcino Aortic Consortium is supported by Genetic Aortic Disorder Association Canada, Temerty Family Foundation, and John Ritter Foundation.

AUTHOR INFORMATION

Conceptualization: SKG; Data curation: AMM, YW, MG, NLP, AD, ESR, DMM, SKG; Formal analysis: AMM, MLY, NLP, SKG; Project administration: NLP, FMA, WH, AD, JM, CJW, ESR, DMM, SKG; Resources: NLP, FMA, WH, AD, JM, CJW, ESR, DMM; Supervision: SKG; Visualization: AMM, SKG; Writing – original draft: AMM, HLH, SKG; Writing – review & editing: YW, MG, MLY, NLP, FMA, WH, AD, JM, CJW, ESR, DMM, KAE

ETHICS DECLARATION

Studies were carried out with the approval of the genTAC Scientific Advisior Committee (Rockville, MD) https://biolincc.nhlbi.nih.gov/studies/gentac/?q=GenTAC, the Insittutional Review Board at Michigan Medicine (Ann Arbor, MI) https://www.umcvc.org/cardiovascular-health-improvement-project-chip-study, and the Committee for the Protection of Human Subjects at the UTHSC-H https://www.montalcinoaorticconsortium.org/.[15-17] Informed consent was obtained for all participants as required by IRB or REC and in accordance with the Declaration of Helsinki. All data was de-identified.

References

Adlam, D., Olson, T. M., Combaret, N., Kovacic, J. C., Iismaa, S. E., Al-Hussaini, A., O'Byrne, M. M., Bouajila, S., Georges, A., Mishra, K., Braund, P. S., d'Escamard, V., Huang, S., Margaritis, M., Nelson, C. P., de Andrade, M., Kadian-Dodov, D., Welch, C. A., Mazurkiewicz, S., Jeunemaitre, X., … Bouatia-Naji, N. (2019). Association of the PHACTR1/EDN1 Genetic Locus With Spontaneous Coronary Artery Dissection. *Journal of the American College of Cardiology*, *73*(1), 58–66. https://doi.org/10.1016/j.jacc.2018.09.085

Alfonso, F., Paulo, M., Gonzalo, N., Dutary, J., Jimenez-Quevedo, P., Lennie, V., Escaned, J., Bañuelos, C., Hernandez, R., & Macaya, C. (2012). Diagnosis of spontaneous coronary artery dissection by optical coherence tomography. *Journal of the American College of Cardiology*, *59*(12), 1073–1079. https://doi.org/10.1016/j.jacc.2011.08.082

Carss, K. J., Baranowska, A. A., Armisen, J., Webb, T. R., Hamby, S. E., Premawardhana, D., Al-Hussaini, A., Wood, A., Wang, Q., Deevi, S., Vitsios, D., Lewis, S. H., Kotecha, D., Bouatia-Naji, N., Hesselson, S., Iismaa, S. E., Tarr, I., McGrath-Cadell, L., Muller, D. W., Dunwoodie, S. L., … Adlam, D. (2020). Spontaneous Coronary Artery Dissection: Insights on Rare Genetic Variation From Genome Sequencing. *Circulation. Genomic and precision medicine*, *13*(6), e003030. https://doi.org/10.1161/CIRCGEN.120.003030

Dietz, H. C., Saraiva, J. M., Pyeritz, R. E., Cutting, G. R., & Francomano, C. A. (1992). Clustering of fibrillin (FBN1) missense mutations in Marfan syndrome patients at

cysteine residues in EGF-like domains. *Human mutation*, *1*(5), 366–374. https://doi.org/10.1002/humu.1380010504

Eagle, K. A., & GenTAC Consortium (2009). Rationale and design of the National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC). *American heart journal*, *157*(2), 319–326. https://doi.org/10.1016/j.ahj.2008.10.005

Eleid, M. F., Guddeti, R. R., Tweet, M. S., Lerman, A., Singh, M., Best, P. J., Vrtiska, T. J., Prasad, M., Rihal, C. S., Hayes, S. N., & Gulati, R. (2014). Coronary artery tortuosity in spontaneous coronary artery dissection: angiographic characteristics and clinical implications. *Circulation. Cardiovascular interventions*, *7*(5), 656–662. https://doi.org/10.1161/CIRCINTERVENTIONS.114.001676

Fattori, R., Sangiorgio, P., Mariucci, E., Ritelli, M., Wischmeijer, A., Greco, C., & Colombi, M. (2012). Spontaneous coronary artery dissection in a young woman with Loeys-Dietz syndrome. *American journal of medical genetics. Part A*, *158A*(5), 1216–1218. https://doi.org/10.1002/ajmg.a.35277

Goel, K., Tweet, M., Olson, T. M., Maleszewski, J. J., Gulati, R., & Hayes, S. N. (2015). Familial spontaneous coronary artery dissection: evidence for genetic susceptibility. *JAMA internal medicine*, *175*(5), 821–826. https://doi.org/10.1001/jamainternmed.2014.8307

Guo, D. C., Regalado, E., Casteel, D. E., Santos-Cortez, R. L., Gong, L., Kim, J. J., Dyack, S., Horne, S. G., Chang, G., Jondeau, G., Boileau, C., Coselli, J. S., Li, Z., Leal, S. M., Shendure, J., Rieder, M. J., Bamshad, M. J., Nickerson, D. A.,

GenTAC Registry Consortium, National Heart, Lung, and Blood Institute Grand Opportunity Exome Sequencing Project, … Milewicz, D. M. (2013). Recurrent gain-of-function mutation in PRKG1 causes thoracic aortic aneurysms and acute aortic dissections. *American journal of human genetics*, *93*(2), 398–404. https://doi.org/10.1016/j.ajhg.2013.06.019

Hampole, C. V., Philip, F., Shafii, A., Pettersson, G., Anesi, G. L., Patel, J. B., & Menon, V. (2011). Spontaneous coronary artery dissection in Ehlers-Danlos syndrome. *The Annals of thoracic surgery*, *92*(5), 1883–1884. https://doi.org/10.1016/j.athoracsur.2011.03.136

Hayes, S. N., Kim, E., Saw, J., Adlam, D., Arslanian-Engoren, C., Economy, K. E., Ganesh, S. K., Gulati, R., Lindsay, M. E., Mieres, J. H., Naderi, S., Shah, S., Thaler, D. E., Tweet, M. S., Wood, M. J., & American Heart Association Council on Peripheral Vascular Disease; Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; Council on Genomic and Precision Medicine; and Stroke Council (2018). Spontaneous Coronary Artery Dissection: Current State of the Science: A Scientific Statement From the American Heart Association. *Circulation*, *137*(19), e523–e557. https://doi.org/10.1161/CIR.0000000000000564

Henkin, S., Negrotto, S. M., Tweet, M. S., Kirmani, S., Deyle, D. R., Gulati, R., Olson, T. M., & Hayes, S. N. (2016). Spontaneous coronary artery dissection and its association with heritable connective tissue disorders. *Heart (British Cardiac Society)*, *102*(11), 876–881. https://doi.org/10.1136/heartjnl-2015-308645

Jensen, S. A., Iqbal, S., Lowe, E. D., Redfield, C., & Handford, P. A. (2009). Structure and interdomain interactions of a hybrid domain: a disulphide-rich module of the fibrillin/LTBP superfamily of matrix proteins. *Structure (London, England : 1993)*, *17*(5), 759–768. https://doi.org/10.1016/j.str.2009.03.014

Jondeau, G., Ropers, J., Regalado, E., Braverman, A., Evangelista, A., Teixedo, G., De Backer, J., Muiño-Mosquera, L., Naudion, S., Zordan, C., Morisaki, T., Morisaki, H., Von Kodolitsch, Y., Dupuis-Girod, S., Morris, S. A., Jeremy, R., Odent, S., Adès, L. C., Bakshi, M., Holman, K., … Montalcino Aortic Consortium (2016). International Registry of Patients Carrying TGFBR1 or TGFBR2 Mutations: Results of the MAC (Montalcino Aortic Consortium). *Circulation. Cardiovascular genetics*, *9*(6), 548–558. https://doi.org/10.1161/CIRCGENETICS.116.001485

Kaadan, M. I., MacDonald, C., Ponzini, F., Duran, J., Newell, K., Pitler, L., Lin, A., Weinberg, I., Wood, M. J., & Lindsay, M. E. (2018). Prospective Cardiovascular Genetics Evaluation in Spontaneous Coronary Artery Dissection. *Circulation. Genomic and precision medicine*, *11*(4), e001933. https://doi.org/10.1161/CIRCGENETICS.117.001933

Kadian-Dodov, D., Gornik, H. L., Gu, X., Froehlich, J., Bacharach, J. M., Chi, Y. W., Gray, B. H., Jaff, M. R., Kim, E. S., Mace, P., Sharma, A., Kline-Rogers, E., White, C., & Olin, J. W. (2016). Dissection and Aneurysm in Patients With Fibromuscular Dysplasia: Findings From the U.S. Registry for FMD. *Journal of the American College of Cardiology*, *68*(2), 176–185. https://doi.org/10.1016/j.jacc.2016.04.044

Kiando, S. R., Tucker, N. R., Castro-Vega, L. J., Katz, A., D'Escamard, V., Tréard, C., Fraher, D., Albuisson, J., Kadian-Dodov, D., Ye, Z., Austin, E., Yang, M. L., Hunker, K., Barlassina, C., Cusi, D., Galan, P., Empana, J. P., Jouven, X., Gimenez-Roqueplo, A. P., Bruneval, P., … Bouatia-Naji, N. (2016). PHACTR1 Is a Genetic Susceptibility Locus for Fibromuscular Dysplasia Supporting Its Complex Genetic Pattern of Inheritance. *PLoS genetics*, *12*(10), e1006367. https://doi.org/10.1371/journal.pgen.1006367

Kim ESH, Saw J, Kadian-Dodov D, Wood M, Ganesh SK. (2021). FMD and SCAD: Sex-Biased Arterial Diseases With Clinical and Genetic Pleiotropy. *Circulation Research.* 128(12), 1958-1972. doi:10.1161/CIRCRESAHA.121.318300

Nakamura, M., Yajima, J., Oikawa, Y., Ogasawara, K., Uejima, T., Abe, K., & Aizawa, T. (2009). Vascular Ehlers-Danlos syndrome--all three coronary artery spontaneous dissections. *Journal of cardiology*, *53*(3), 458–462. https://doi.org/10.1016/j.jjcc.2008.09.007

Nishiguchi, T., Tanaka, A., Ozaki, Y., Taruya, A., Fukuda, S., Taguchi, H., Iwaguro, T., Ueno, S., Okumoto, Y., & Akasaka, T. (2016). Prevalence of spontaneous coronary artery dissection in patients with acute coronary syndrome. *European heart journal. Acute cardiovascular care*, *5*(3), 263–270. https://doi.org/10.1177/2048872613504310

Pepin, M., Schwarze, U., Superti-Furga, A., & Byers, P. H. (2000). Clinical and genetic features of Ehlers-Danlos syndrome type IV, the vascular type. *The New England*

journal of medicine, *342*(10), 673–680. https://doi.org/10.1056/NEJM200003093421001

Pepin, M. G., Schwarze, U., Rice, K. M., Liu, M., Leistritz, D., & Byers, P. H. (2014). Survival is affected by mutation type and molecular mechanism in vascular Ehlers-Danlos syndrome (EDS type IV). *Genetics in medicine : official journal of the American College of Medical Genetics*, *16*(12), 881–888. https://doi.org/10.1038/gim.2014.72

Pinard, A., Jones, G. T., & Milewicz, D. M. (2019). Genetics of Thoracic and Abdominal Aortic Diseases. *Circulation research*, *124*(4), 588–606. https://doi.org/10.1161/CIRCRESAHA.118.312436

Rashid, H. N., Wong, D. T., Wijesekera, H., Gutman, S. J., Shanmugam, V. B., Gulati, R., Malaipan, Y., Meredith, I. T., & Psaltis, P. J. (2016). Incidence and characterisation of spontaneous coronary artery dissection as a cause of acute coronary syndrome--A single-centre Australian experience. *International journal of cardiology*, *202*, 336–338. https://doi.org/10.1016/j.ijcard.2015.09.072

Robertson, I. B., Dias, H. F., Osuch, I. H., Lowe, E. D., Jensen, S. A., Redfield, C., & Handford, P. A. (2017). The N-Terminal Region of Fibrillin-1 Mediates a Bipartite Interaction with LTBP1. *Structure (London, England : 1993)*, *25*(8), 1208–1221.e5. https://doi.org/10.1016/j.str.2017.06.003

Sato, C., Wakabayashi, K., & Suzuki, H. (2014). Natural course of isolated spontaneous coronary artery dissection in Marfan syndrome. *International journal of cardiology*, *177*(1), 20–22. https://doi.org/10.1016/j.ijcard.2014.09.061

Saw, J., Aymong, E., Sedlak, T., Buller, C. E., Starovoytov, A., Ricci, D., Robinson, S., Vuurmans, T., Gao, M., Humphries, K., & Mancini, G. B. (2014). Spontaneous coronary artery dissection: association with predisposing arteriopathies and precipitating stressors and cardiovascular outcomes. *Circulation. Cardiovascular interventions*, *7*(5), 645–655. https://doi.org/10.1161/CIRCINTERVENTIONS.114.001760

Saw, J., Mancini, G. B., Humphries, K., Fung, A., Boone, R., Starovoytov, A., & Aymong, E. (2016). Angiographic appearance of spontaneous coronary artery dissection with intramural hematoma proven on intracoronary imaging. *Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions*, *87*(2), E54–E61. https://doi.org/10.1002/ccd.26022

Saw, J., Yang, M. L., Trinder, M., Tcheandjieu, C., Xu, C., Starovoytov, A., Birt, I., Mathis, M. R., Hunker, K. L., Schmidt, E. M., Jackson, L., Fendrikova-Mahlay, N., Zawistowski, M., Brummett, C. M., Zoellner, S., Katz, A., Coleman, D. M., Swan, K., O'Donnell, C. J., Million Veteran Program, … Ganesh, S. K. (2020). Chromosome 1q21.2 and additional loci influence risk of spontaneous coronary artery dissection and myocardial infarction. *Nature communications*, *11*(1), 4432. https://doi.org/10.1038/s41467-020-17558-x

Shalhub, S., Regalado, E. S., Guo, D. C., Milewicz, D. M., & Montalcino Aortic Consortium (2019). The natural history of type B aortic dissection in patients with

PRKG1 mutation c.530G>A (p.Arg177Gln). *Journal of vascular surgery*, *70*(3), 718–723. https://doi.org/10.1016/j.jvs.2018.12.032

Singh, K. K., Rommel, K., Mishra, A., Karck, M., Haverich, A., Schmidtke, J., & Arslan-Kirchner, M. (2006). TGFBR1 and TGFBR2 mutations in patients with features of Marfan syndrome and Loeys-Dietz syndrome. *Human mutation*, *27*(8), 770–777. https://doi.org/10.1002/humu.20354

Smith, L. T., Schwarze, U., Goldstein, J., & Byers, P. H. (1997). Mutations in the COL3A1 gene result in the Ehlers-Danlos syndrome type IV and alterations in the size and distribution of the major collagen fibrils of the dermis. *The Journal of investigative dermatology*, *108*(3), 241–247. https://doi.org/10.1111/1523-1747.ep12286441

Stheneur, C., Collod-Béroud, G., Faivre, L., Buyck, J. F., Gouya, L., Le Parc, J. M., Moura, B., Muti, C., Grandchamp, B., Sultan, G., Claustres, M., Aegerter, P., Chevallier, B., Jondeau, G., & Boileau, C. (2009). Identification of the minimal combination of clinical features in probands for efficient mutation detection in the FBN1 gene. *European journal of human genetics : EJHG*, *17*(9), 1121–1128. https://doi.org/10.1038/ejhg.2009.36

Tran-Fadulu, V., Pannu, H., Kim, D. H., Vick, G. W., 3rd, Lonsford, C. M., Lafont, A. L., Boccalandro, C., Smart, S., Peterson, K. L., Hain, J. Z., Willing, M. C., Coselli, J. S., LeMaire, S. A., Ahn, C., Byers, P. H., & Milewicz, D. M. (2009). Analysis of multigenerational families with thoracic aortic aneurysms and dissections due to

TGFBR1 or TGFBR2 mutations. *Journal of medical genetics*, *46*(9), 607–613. https://doi.org/10.1136/jmg.2008.062844

Turley, T. N., Theis, J. L., Sundsbak, R. S., Evans, J. M., O'Byrne, M. M., Gulati, R., Tweet, M. S., Hayes, S. N., & Olson, T. M. (2019). Rare Missense Variants in TLN1 Are Associated With Familial and Sporadic Spontaneous Coronary Artery Dissection. *Circulation. Genomic and precision medicine*, *12*(4), e002437. https://doi.org/10.1161/CIRCGEN.118.002437

Verstraeten, A., Perik, M., Baranowska, A. A., Meester, J., Van Den Heuvel, L., Bastianen, J., Kempers, M., Krapels, I., Maas, A., Rideout, A., Vandersteen, A., Sobey, G., Johnson, D., Fransen, E., Ghali, N., Webb, T., Al-Hussaini, A., de Leeuw, P., Delmotte, P., Lopez-Sublet, M., … Collaborators of the European/International Fibromuscular Dysplasia Registry and Initiative (FEIRI) (2020). Enrichment of Rare Variants in Loeys-Dietz Syndrome Genes in Spontaneous Coronary Artery Dissection but Not in Severe Fibromuscular Dysplasia. *Circulation*, *142*(10), 1021–1024. https://doi.org/10.1161/CIRCULATIONAHA.120.045946

Wolford, B. N., Hornsby, W. E., Guo, D., Zhou, W., Lin, M., Farhat, L., McNamara, J., Driscoll, A., Wu, X., Schmidt, E. M., Norton, E. L., Mathis, M. R., Ganesh, S. K., Douville, N. J., Brummett, C. M., Kitzman, J., Chen, Y. E., Kim, K., Deeb, G. M., Patel, H., … Yang, B. (2019). Clinical Implications of Identifying Pathogenic Variants in Individuals With Thoracic Aortic Dissection. *Circulation. Genomic and*

precision medicine, *12*(6), e002476.

https://doi.org/10.1161/CIRCGEN.118.002476