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Spontaneous coronary artery dissection is infrequent in individuals with heritable thoracic aortic disease despite partially shared genetic susceptibility

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Abstract

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. We queried registries enrolling patients with TAD to define the incidence of SCAD. Of 7568 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%, $p = 0.047$). 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.

KEYWORDS
arterial disease, familial thoracic aortic aneurysm and dissection, genetic susceptibility, spontaneous coronary artery dissection

1 | 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 underdiagnosis. Current estimates of SCAD prevalence based upon series of patients with acute coronary syndrome are 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 7529 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).

2 | MATERIALS AND METHODS

2.1 | 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).

2.2 | Data collection

Registries were queried in March 2017 for SCAD case identification via free text word search and ICD codes (Table S1). All cases of documented or referenced coronary artery dissection were reviewed for clinical context by study authors (S.K.G. or M.G.). 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 were 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 clinical 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.

2.3 | 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.) and a statistical significance threshold was set at p value ≤ 0.05.

3 | RESULTS

Among 7568 individuals enrolled in the GenTAC ($N = 3540$), CHIP ($N = 3000$), and MAC ($N = 1028$) 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 Table S2.

3.1 | 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 Table S3. 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 was 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 2 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 (Table S2).

TABLE 1 Demographic and clinical features of subjects enrolled in the GenTAC databank ($N = 3540$)

Variable	*N*	SCAD	No SCAD	*p* value
N	3540	8	3532	
Demographics				
Sex (female)	1456	6	1450	0.071
Caucasian	3119	7	3112	1.000
Age (years)[a]	3540	47.1 ± 7.07 [36.0–55.2]	37.1 ± 18.97 [0.2–97.2]	0.100
Vascular risk factors and comorbidities				
Tobacco use	613	4	609	0.475
Hypertension	560	2	558	1.000
Non-aortic arterial dissections				
Carotid	87	1	86	0.120
Iliac	181	2	179	0.047
Subclavian	132	1	131	0.180
Genes affected				
FBN1	216	2	214	1.000
TGFBR1	26	0	26	1.000
TGFBR2	88	1	87	0.302
COL5A1	6	0	6	1.000
COL5A2	1	0	1	1.000
COL3A1	134	3	131	1.000

Note: Unaffected individuals were those with no record of a SCAD event. Values are presented as count or mean ± standard deviation [range] as appropriate.

[a]Age at time of registry enrollment.

3.2 | 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.

3.3 | 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 nine 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 six cases (Table S2). 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

TABLE 2 Clinical phenotypes and genetic variants in individuals with spontaneous coronary artery dissection (SCAD)

Case number	Sex, ethnicity	Gene, variant	Clinical syndrome	Age (years) at SCAD	Coronary artery features
1	F, Hawaiian/ Pacific Islander	*COL3A1*, c.3325C>T (p.Arg109Ter)	vEDS/ FTAAD	33	Distal LMCA dissection
2	F, Caucasian	*COL3A1*, NR	vEDS	37	Mid LAD, proximal-mid LCx, proximal-mid RCA dissections
3	F, Caucasian	*COL3A1*, c.601G>C (p.Gly201Arg)	vEDS	49	LMCA dissection
4	F, Caucasian	*FBN1*, IVS61+2T>C	MFS	34	LMCA dissection
5	M, Caucasian	*FBN1*, c.626G>A (p.Cys209Tyr)	MFS	36	Proximal RCA dissection
6	F, Caucasian	NA[a]	MFS	52	Proximal-mid RCA dissection
7	F, Caucasian	*TGFBR2*, NR	LDS	45	Distal LAD dissection
8	M, Caucasian	NA[a]	FTAAD	23	RCA dissection
9	F, Caucasian	*TGFBR1*, c.934G>A (p.Gly312Ser)	–	37	Ramus intermedius, dissection
10	F, Caucasian	*PRKG1*, c.530G>A (p.Arg177Gln)	–	44	LMCA dissection
11	F, NR	*TGFBR2*, NR	LDS	NR	NR

Note: –, lack of notable findings on clinical data review.

Abbreviations: FTAAD, Familial Thoracic Aortic Aneurysm/Dissection; LAD, left anterior descending; LMCA, left main coronary artery; LCx, left circumflex; LDS, Loeys–Dietz syndrome; MFS, Marfan syndrome; NA, not applicable; NR, not reported; RCA, right coronary artery; vEDS, vascular Ehlers–Danlos syndrome.

[a]Individuals who did not undergo genetic testing.

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 one 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.

TABLE 3 SCAD in subjects with TAD in the GenTAC databank compared to general population

Variable	SCAD in individuals with TAD ($N = 8$)	SCAD in general population[a]
Demographics		
Female sex	75%	88%–96%
Caucasian	87.5%	34%–94%
Age (years)[b]	47.1 ± 7.07 [36.0–55.2]	47–53
Vascular risk factors and comorbidities		
Tobacco use	50%	12%–28%
Hypertension	25%	31%–37%
Genetic testing		
Pathogenic variant	62.5%	3.6%–10.6%

Note: Values are presented as proportion (%) or mean ± standard deviation [range] as appropriate.
Abbreviations: NR, not reported; SCAD, spontaneous coronary artery dissection.
[a]Data from Kim et al. (2021).
[b]Age at time of registry enrollment.

4 | DISCUSSION

In the current sample of 7529 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 vs. 45–53 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., 2009; 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, therefore, 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.

5 | 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 indicate 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.

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CONFLICT OF INTERESTS

Andrea M. Murad is a paid consultant for Concert Genetics. Cristen J. Willer's husband works for Regeneron. The other authors declare no conflict of interests.

AUTHOR CONTRIBUTIONS

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DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Studies were carried out with the approval of the genTAC Scientific Advisory Committee (Rockville, MD) https://biolincc.nhlbi.nih.gov/studies/gentac/?q=GenTAC, the Institutional 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/. Informed consent was obtained for all participants as required by IRB or REC and in accordance with the Declaration of Helsinki. All data were de-identified.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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