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SHORT REPORT

Non-dilated left ventricular cardiomyopathy with arrhythmias is commonly caused by the nonsense variant *DSP*:c.3793G>T in Slovenian patients

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Abstract

DSP-cardiomyopathy has recently been recognised as a specific type of cardiomyopathy. Using an in-house Mendelian disease registry, we aimed to identify probands with likely pathogenic or pathogenic *DSP* variants. We detected these variants in 4.8% and 77.8% of genotype-positive probands referred for dilated and non-dilated left ventricular cardiomyopathy (NDLVC), respectively. We identified six Slovenian probands with the *DSP*:c.3793G>T and characterised them along with further eight of their relatives at the molecular and phenotypic level. Medical records revealed NDLVC with arrhythmia in six individuals (five probands, one relative; 33 ± 14 years; three males, three females). All had subepicardial late gadolinium enhancement on cardiac MRI (CMRI), and five received an ICD. Four individuals (one proband, three relatives; 48 ± 14 years; all female) had no ECG and/or cardiac abnormalities on CMRI detected. Our analysis presents a Slovenian-specific molecular pathology of *DSP* cardiomyopathy, delineates the clinical manifestation of *DSP*:c.3793C>T, and thereby improves the understanding of the clinical outcomes associated with truncating *DSP* variants.

KEYWORDS
arrhythmogenic non-dilated left ventricular cardiomyopathy, cardiogenetic, cardiology, *DSP*, *DSP*:c.3793G>T, founder

1 | INTRODUCTION

Desmoplakin cardiomyopathy (*DSP*-cardiomyopathy), caused by pathogenic variants in *DSP*, affects one or both ventricles and manifests as the presence of excessive subepicardial fibrosis, arrhythmias, low QRS voltage, increased risk of heart failure, major arrhythmic events, and episodes of myocarditis.[1] Desmoplakin links plaque proteins to intermediate filaments and is alternatively spliced. Two major isoforms, DSPI and DSPII, are expressed in the heart and skin, with DSPI predominating in the heart. DSPIa, a third isoform, is expressed at lower levels in both tissues.[2] Protein truncating variants (*DSP*tv) are most commonly reported to be pathogenic, causing the disease in either a dominant or recessive fashion (OMIM:125647).

Previously, cardiomyopathy was not considered to be present in patients who had certain pathological heart conditions but did not meet the criteria for either arrhythmogenic or dilated cardiomyopathy.[3] Therefore, the new classification of cardiomyopathies proposed a new category of cardiomyopathy called non-dilated left ventricular

cardiomyopathy (NDLVC), which now includes these patients with intermediate phenotypes such as dilated cardiomyopathy (DCM) without left ventricular dilation, arrhythmogenic DCM without meeting diagnostic criteria for ARVC, arrhythmogenic left ventricular cardiomyopathy (ALVD) or left-dominant ARVD.[1]

The aim of this study was to describe the nation-specific molecular pathology of *DSP*-cardiomyopathy and to phenotypically characterise individuals with recurrently identified *DSP*:c.3793G>T.

2 | MATERIALS AND METHODS

Detailed information is available in Data S1.

2.1 | Study cohort

An in-house Mendelian disease registry was used to identify likely pathogenic and pathogenic (LP/P) *DSP* (NM_004415.4) variants in probands referred for cardiomyopathy. *DSP*:c.3793G>T, (p.Glu1265Ter), was observed recurrently in five cardiomyopathy referrals and additionally in one non-cardiac referral (P2.1). Subsequent segregation analysis identified *DSP*:c.3793G>T in eight out of 20 relatives.

2.2 | Sequencing and bioinformatics analysis

Sequencing and data analysis were performed routinely at CIGM.[4,5] Whole-genome sequencing (WGS) was performed as described[6] for haplotype analysis in five probands and both parents of one proband. Sanger sequencing was used for segregation analysis.

2.3 | Haplotype analysis

Annotated WGS data were uploaded to IGV.[7] Markers in and around the *DSP* were manually screened. The most probable haplotype was reconstructed.

2.4 | Phenotypic characterisation of the individual with *DSP*:c.3793G>T

Medical records, including patient history and examination results, were collected retrospectively.

3 | RESULTS

3.1 | Nation-specific molecular pathology of *DSP*-cardiomyopathy

Detected LP/P *DSP* variants are listed in Table S2 and were identified in 2 (4.8%) and 7 (77.8%) genotype-positive probands with DCM and non-dilated left NDLVC, respectively. *DSP*:c.3793G>T was detected in five (55.5%) genotype-positive probands with NDLVC.

DSP:c.3793G>T is classified as pathogenic,[8–10] because it is expected to cause loss-of-function in *DSP*[11] (PVS1_STR), is absent in gnomAD,[12] TOPMed,[13,14] and rare in the internal registry (1/∼10 000 exomes/genomes) (PM2), and has previously been reported in at least five patients with cardiomyopathy,[15–17] and twice in ClinVar in association with cardiac phenotype (ID:523474) (PS4). Haplotype analysis revealed that *DSP*:c.3793G>T is surrounded by the common haplotype rs2326883(C)-21xGA(20)-rs9505128(T)-23xAC(18)-rs9502608(G)-D6S1640(252)-28xTG(23)-rs2806211(T)-rs2842683(T)-variant(T)-rs9505259(T)-rs6928692(T)-rs12214906(C) (Data S1, Table S3). The probands with *DSP*:c.3793G>T did not have any other LP/P variant identified in genes associated with cardiomyopathy.[18]

3.2 | Phenotypic characteristics of individuals with *DSP*:c.3793G>T

Medical data were available for all probands and four relatives, among whom one was affected (Table 1). In the proband with non-cardiology referral, *DSP*:c.6577G>A was reported as an incidental finding. Subsequent clinical evaluation of her revealed no cardiac abnormalities.

The mean age at disease onset was 33 ± 16 years. Three were male. The initial presentation was myocarditis in three and ventricular arrhythmias in three. Five received an implantable cardioverter defibrillator (ICD), three for secondary prevention and two for primary prevention. Left ventricular (LV) ejection fraction was reduced in two and LV end-diastolic volume was increased in four. Three had a low QRS voltage and T wave inversions in the inferior and precordial leads V1–V5. All had areas of late gadolinium enhancement (LGE) confined exclusively to the LV wall. The presence of LGE was observed in all segments, ranging from segmental subepicardial to a ring-like enhancement pattern, with basal segments generally more affected.

Four were found to be unaffected by ECG screening (mean age 48 ± 15 years), two of whom also underwent cardiac magnetic resonance images (CMRI), which showed no cardiac abnormalities.

CMRI images were available for three affected and two unaffected individuals (Figure 1).

4 | DISCUSSION

In this study, we analyzed the nation-specific molecular pathology of *DSP*-cardiomyopathy and the clinical pathology associated with *DSP*:c.3793G>T.

Genetic analysis revealed five LP/P *DSP* variants in Slovenian probands with cardiomyopathy. These variants were the primary genetic cause in probands with NDLVC but rarely in those with DCM. *DSP*:c.3793G>T was found causative in over half of genotype-positive individuals with NDLVC. Haplotype analysis showed that *DSP*:c.3793G>T is located on a common haplotype in the probands, and together with pedigree analysis, suggested a likely founder origin of the variant.

TABLE 1 Clinical characteristics of individuals with *DSP*:c.3793G>T for whom clinical data were available.

	P1.1	P2.1	P3.1	P3.2	P4.1	P5.1	P5.2	P5.4	P5.5	P6.1
Sex	M	F	F	M	F	F	F	F	F	M
Affection status	Y	N	Y	Y	Y	Y	N	N	N	Y
Age at Dx (years)	24	NA	35	30	35	14	NA	NA	NA	62
First presentation	Myocarditis	NA	Myocarditis, syncope	Myocarditis	PVT	VF	NA	NA	NA	SVT
Age at evaluation	NA	59	NA	NA	NA	NA	57	54	22	NA
Phenotype	NDLVC	NA	NDLVC	NA	NDLVC	NDLVC	NA	NA	NA	NDLVC
End-stage HF	N	N	N	NA	N	N	NA	NA	NA	N
Elevated troponin	Y	NA	Y	Y	NA	Y	NA	N	N	Y
NT-proBNP (ng/L)	53	NA	248	NA	NA	954	NA	403	128	784
Electrocardiogram										
Conduction disorder	N	N	N	NA	N	N	N	N	N	AVB1
Low QRS voltages	N	N	Y	NA	Y	Y	N	Y	N	N
T wave inversion beyond V3	N	N	Y	NA	Y	Y	N	N	N	N
PVCs	N	N	N	Y	Y	Y	N	NA	N	N
Ventricular arrhytmia										
SCD	N	N	N	N	N	N	N	N	N	N
aSDC	N	N	N	N	N	Y	N	N	N	N
SVT	N	N	Y	N	Y	Y	N	N	N	Y
NSVT	Y	N	N	N	Y	Y	N	N	N	N
Presence of ICD	Y	N	Y	N	Y	Y	N	N	N	Y
Appropriate ICD therapy	N	N	N	NA	N	N	NA	NA	NA	N
Transthoracic echocardiogram										
LV EF (%)	62	NA	62	65	59	21	77	NA	NA	31
LV EDVi	76	NA	61	NA	72	107	54	NA	NA	101
Cardiac magnetic resonance imaging										
LV EF (%)	60	67	53	NA	NA	20	61	NA	NA	26
LV EDV (mL)	191	116	163	NA	Enlarged	NA	135	NA	NA	346
RV EF (%)	57	59	168	NA	NA	25	59	NA	NA	40
RV EDV (mL)	209	133	49	NA	Enlarged	NA	133	NA	NA	198
Presence of LGE	Y	N	Y	Y	Y	Y	N	NA	NA	Y

Abbreviations: aSCD, aborted SCD; AVB1, first-degree atrioventricular block; Dx, diagnosis; EDV, end-diastolic volume; EDVi, end-diastolic volume index; EF, ejection fraction; F, female; HF, heart failure; ICD, implantable cardioverter defibrillator; LGE, late gadolinium enhancement; LV, left ventricle; M, male; N, no; NA, not available/applicable; NDLVC, non-dilated left ventricular cardiomyopathy; NSVT, non-sustained ventricular tachycardia; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PVCs, premature ventricular contractions; PVT, polymorphic ventricular tachycardia; RV, right ventricle; SCD, sudden cardiac death; SVT, sustained ventricular tachycardia; VF, ventricular fibrillation; Y, yes.

Affected individuals with *DSP*:c.3793G>T exhibited clinical features consistent with *DSP*-cardiomyopathy: all had no significant LV dilatation, a subepicardial ring-like pattern of LGE surrounding the LV on MRI and ECG abnormalities, half had malignant arrhythmias and half had a myocarditis-like onset.[1,15] Interestingly, two women with *DSP*:c.3793G>T in their sixth decade had no ECG or CMRI abnormalities. A meta-analysis found that ~33% of relatives with *DSP*tv-s show no phenotypic changes.[15] Reporting detailed phenotypic data on ECG and CMRI findings in clinically unaffected individuals with pathogenic *DSP* variants will improve the management of these individuals, as current guidelines are mainly based on studies reporting on clinically affected individuals.[1] Furthermore, a recent meta-analysis highlights the need for gene-specific guidelines, as the existing ARVC risk calculator performs poorly in patients with LP/P *DSP* variants meeting the ARVC Task Force criteria.[19]

The exact pathomechanism why *DSP*tv-s cause either DCM, NDLVC or unobservable phenotype remains unclear. It is not uncommon for pathogenic variants in cardiomyopathy-associated genes to manifest across a spectrum of phenotypes, even within the same

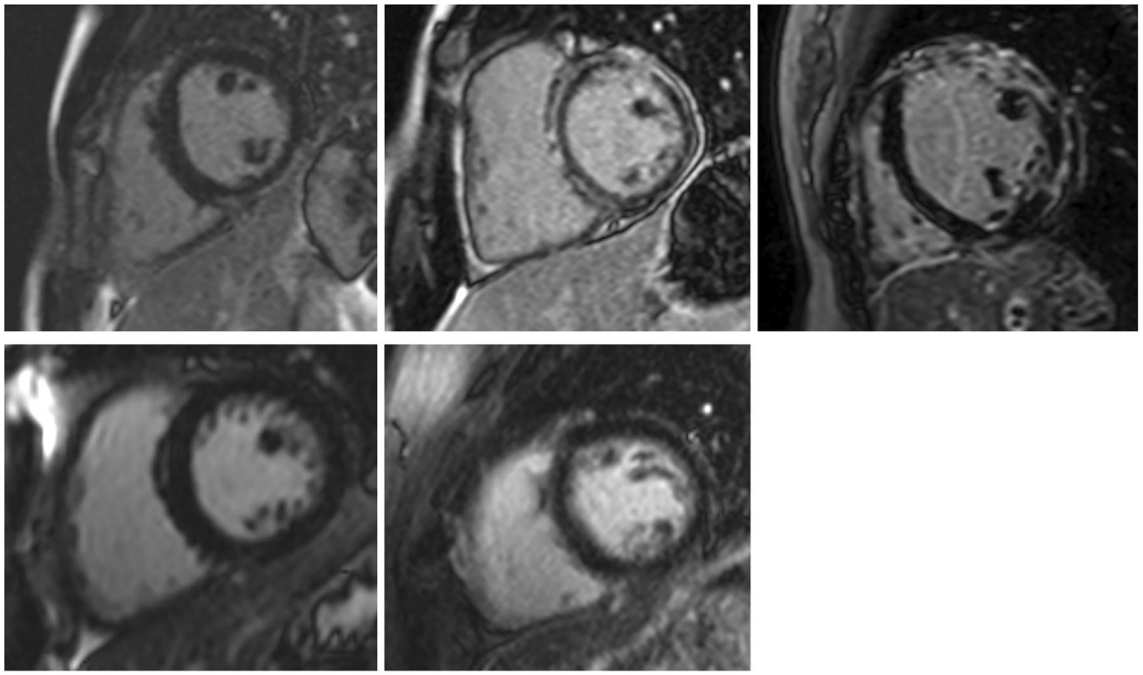

FIGURE 1 Cardiac magnetic resonance images of three affected (top) and two unaffected (bottom) individuals with *DSP*:c.3793G>T. Top left, P1.1; top middle, P3.1; top right, P5.1; bottom left, P2.1; bottom right P5.2. LGE distribution: top left, subepicardial mid inferolateral, inferior and inferoseptal segment of LV; top middle, subepicardial ring-like pattern; top right, subepicardial mid anterior, anterolateral, inferolateral and inferior segment of left ventricle; bottom left and right: no LGE.

family.[1,16] *DSP*:c.3793G>T affects DSPI, the major cardiac isoform, DSPIa, but not DSPII[2]. The variant is predicted to induce nonsense-mediated decay (NMD) and is expected to cause NDLVC through haploinsufficiency, a known pathomechanism of *DSP*tv-s.[15] As the functional characterisation of *DSP*:c.3793G>T was beyond study scope, we cannot exclude the dominant-negative effect as a pathomechanism, which has been observed for some more C-terminal variants.[20]

Studies have shown that *DSP*tv-s, particularly in the non-constitutive NMD complement region, like *DSP*:c.3793G>T, are associated with an increased risk of ventricular arrhythmias (HR, 3.2 [95% CI 1.3–7.9]; $p = 0.009$) in individuals with arrhythmogenic cardiomyopathy.[15] Our results support this association, with 83% of affected individuals experiencing major arrhythmic events or were identified at high risk.

The study elucidated the molecular pathology of *DSP*-cardiomyopathy in Slovenians and a spectrum of clinical manifestations of *DSP*:c.3793C>T, improving understanding of the genetic background of cardiomyopathies in the region and clinical implications of truncating *DSP* variants.

AUTHOR CONTRIBUTIONS

Nina Vodnjov: Conceptualisation; data curation; formal analysis; investigation; funding acquisition; writing—original draft; **Anja Zupan Mežnar:** Data curation; formal analysis; **Aleš Maver:** Software; **Ajda Dolinšek:** Data curation; visualisation; **Borut Peterlin:** Resources; supervision; **Karin Writzl:** conceptualisation; supervision. **All authors:** Writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Sponsors had no role in study design, execution, interpretation, or writing.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The study adhered to the Declaration of Helsinki and was approved by the National Medical Ethics Committee of Slovenia (Approval No. 0120-71/2022/3, dated 28 March 2022).

INFORMED CONSENT STATEMENT

Informed consent was obtained from all subjects involved in the study.

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