Identification of a Novel DSP Variant in a Patient with Sudden Cardiac Death through Post-Mortem Genetic Investigation

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Arrhythmogenic cardiomyopathy (ACM) is an inherited cardiomyopathy characterized pathologically by fibrofatty myocardial replacement, and clinically by prominent ventricular arrhythmias and impairment in ventricular systolic function [1]. The prevalence of ACM among people experiencing sudden cardiac death is quite high. In the Veneto region of Italy, an autopsy investigation of 60 young people with sudden death identified that 12% had ACM on autopsy [2, 3]. Mutations in desmoplakin (DSP), the primary force transducer between cardiac desmosomes and intermediate filaments, have been found to cause ACM [4]. Here, we performed postmortem genetic analysis and autopsy in cases with sudden cardiac death diagnosed as ACM through forensic autopsy, and identified a pathogenic DSP variant (NM_004415.3: c.3930_3933del; p.K1310Nfs*38).

In the era of genetic-based personalized medicine, gene-centric strategies are crucial for postmortem analysis and accurate risk assessment. Postmortem genetic testing is an efficient and rapid method to investigate potential disease-causing mechanisms.

What is the main novel finding?
WES, a powerful tool for post-mortem genetic testing, provides an effective and rapid strategy for studying potential pathogenic mechanisms. In this study, we examined a proband with sporadic cardiomyopathy and SCD. The proband had myocarditis. Combining WES with cardiomyopathy-related gene filtering identified a novel deletion variant (NM_004415.3: c.3930_3933del; p.K1310Nfs*38) in DSP.

We collected 75 cases of patients with sudden death between 1 and 50 years of age. Postmortem genetic analysis autopsy was performed in sudden death cases caused by cardiomyopathy after exclusion of other causes of death. The sample was evaluated according to the postmortem measures of the International Society and Federation of Cardiology (ISFC) TFC. Anatomical assessment was performed by an expert forensic pathologist and confirmed by a second independent pathologist. Families of the participants provided informed consent. The study was approved by the Institutional Review Board of Changsha Forensic Appraisal Center.

Whole-exome sequencing (WES) and quality control were performed by Berry Genomics (Beijing,
China). The filtering method was as described in a prior article [5]. Suspicous variants were scored according to the American College of Medical Genetics (ACMG) criteria. Potential causative variants of SCD were screened.

The bioinformatics program Mutation Taster (http://www.mutationtaster.org) was used to predict the effects of mutations detected by WES. The mutation most likely to lead to the disease was verified by Sanger sequencing. The methods were as described in a previously published article [5].

We investigated 23 sudden death cases caused by cardiomyopathy by performing postmortem genetic analysis and autopsy. The case with positive genetic testing findings was in a 44-year-old man from central China, who presented with SD. According to postmortem measures of the ISFC TFC, the proband was postmortem. The proband had myocarditis, lymphocyte infiltration in the epicardium and focal interstitium, and more myocardial focal fibrosis and fibroblasts and scar tissue in the cardiac muscle (Figure 1A). Microscopic observation revealed wave-like changes and focal fragmentation in the myocardium.

We performed WES on the proband and screened a novel deletion variant (NM_004415.3: c.3930_3933del:p.K1310Nfs*38) in DSP, which was validated by Sanger sequencing in the proband (Figure 1B). In previous studies, DSP was confirmed to be closely associated with the occurrence of ARVC. The variant c.3930_3933del in exon 23 of the DSP gene results in a premature termination codon at amino acid 1348. This variant was absent in our cohort of 200 healthy control individuals as well as 1000 Genomes Project data. Further bioinformatics analysis revealed that this variant was

![Image](https://example.com/image1.png)

**Figure 1** A novel variant of DSP in the proband with SCD. A. HE staining of patient heart tissue, showing that cardiomyopathic fibrosis, fibrotic scar formation, and myocardial lymphocytes are risen. B. Sanger sequencing revealing the DSP gene mutation c.3930_3933del:p.K1310Nfs*38. C. The domain of DSP at the mutation position c.3930_3933del:p.K1310Nfs*38. D. Conservation analysis and comparison of the functional domains: sequence comparison of amino acid mutation sites (gray), showing high conservation among species. E. Protein structure prediction of DSP with variants.
located at a conserved rod domain site (Figure 1C). On the basis of the predicted protein structure variant, the variant caused changes in protein charge, as well as loss of the protein’s C-terminal region and part of the central fibrous rod domain, which mediates dimerization through coiled-coil interactions (Figure 1E). This site is highly conserved (Figure 1D).

We enrolled a sporadic proband with cardiomyopathy and SCD. Combining WES with cardiomyopathy-related gene filtering identified a novel deletion variant (NM_004415.3: c.3930_3933del:p.K1310Nfs*38) in DSP in the proband with myocarditis. Recent studies have demonstrated that cardiomyopathy caused by mutations in the DSP gene are accompanied by symptoms of myocarditis. Our patient also presented with symptoms of myocarditis.

DSP is located on chromosome 6 and encodes desmoplakin. Herein, we report a novel deletion variant (NM_004415.3: c.3930_3933del:p.K1310Nfs*38) in DSP. The 3930_3933 deletion variant is located in the rod domain of exon 23 in DSP and causes the insertion of a premature stop codon after 38 bases. The variant truncates the central fibrous rod domain and the carboxy terminus of the protein, thus inducing ARVC.

The novel heterozygous variant c.3930_3933del in the DSP gene is likely to be pathogenic and associated with SCD. The present work enriches the profile of mutations in DSP associated with sudden cardiac death. The findings may contribute to potential gene-targeted therapies for descendants of the proband and also underscore the importance of postmortem genetic analysis in such cases.

**Data Availability**

The datasets for this article are not publicly available because of concerns regarding participant/patient anonymity. Requests to access the datasets should be directed to the corresponding author.

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**Author Contributions**

Liangliang Fan performed genetic analysis. Jiao Xiao collected samples and clinical data. Yutong Su isolated the gDNA and performed PCR. Chenyu Wang wrote the manuscript. Xiang Rong and Lei Zhu supported the study. All authors reviewed the manuscript. Each author participated sufficiently and consents to publication.

**Ethical Statement**

Written informed consent for publishing this scientific report was obtained from a direct relative of the decedent in this case.

**Conflicts of Interest**

The authors report no conflicts of interest.

**REFERENCES**