A 23-year-old female professional dancer died suddenly following physical activity. Routine postmortem examination failed to establish the cause of death. No cardiac structural abnormalities were revealed. She had a history of presyncopal episodes during the last two months preceding her sudden cardiac death (SCD). Following the proband's death, her family was referred to our department for clinical evaluation, which was carried out with use of a standard protocol. All individuals underwent detailed non-invasive evaluation followed by genetic testing. It was discovered that the proband's uncle had been diagnosed with arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) almost 5 years before his niece's SCD. The proband was positive for a plakophilin-2 mutation and both her father and uncle had a typical form of the ARVC/D disease. To strengthen our diagnostic assessment an immunohistochemical analysis was undertaken of a myocardial sample obtained at autopsy, which finally pointed towards the diagnosis of ARVC/D. Probably, the mutation had been inherited from her paternal grandfather. Although he had never been clinically evaluated, and no tissue was available for genetic analysis, he had a history of SCD at the age of 72, thus, raising suspicion of cardiac disease.

Sudden cardiac death (SCD) is generally defined as natural, unexpected death within 1 hour of the onset of symptoms. Non-specific prodromal symptoms, for example chest pain, palpitations, or dyspnea, can be present during the days or weeks before cardiac arrest. SCD remaining unexplained after thorough postmortem investigation is termed unknown-cause SCD. In at least 4% of sudden death cases, a full coroner’s post-mortem examination, a toxicological screening and an expert cardiac autopsy fail to reveal any underlying cause of death. Tan et al published data from the comprehensive evaluation of 43 families with a high frequency of unexplained SCD. Seventeen families (40%) were identified with inherited cardiac disease including catecholaminergic polymorphic ventricular tachycardia, long QT syndrome, Brugada syndrome, hypertrophic cardiomyopathy, and arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D), stressing the importance of defining the cause of
death for appropriate prophylaxis of family members. We herein describe the case of a young woman who died suddenly. Postmortem examination was unremarkable; however, further investigation and clinical evaluation of the family finally identified the cause of death.

**CASE REPORT**

A 23-year-old female professional dancer died suddenly following physical activity. Routine macroscopic and microscopic postmortem investigation failed to establish the cause of death. No cardiac structural abnormalities were revealed. Both left and right ventricle were deemed normal. The proband had a history of presyncopal episodes during the last two months preceding her SCD. Following her death, her family was referred to our department for clinical evaluation. During the course of clinical investigation and search for retrospective clinical data, an electrocardiogram (ECG) of the young woman taken 6 months prior to her death was reviewed; it showed inverted T-waves in leads V1 and V2 as well as in leads II, III and aVF (Fig. 1).

Following informed consent, family members were evaluated with a standard protocol. All individuals underwent detailed non-invasive evaluation including clinical examination, 12-lead resting ECG, two-dimensional (2-D) and Doppler echocardiography, signal-averaged electrocardiography (SAECG), 24-hour Holter monitoring and exercise testing.

**FAMILY CLINICAL FINDINGS**

The proband’s uncle was the first family member to undergo clinical investigation. He admitted that he had been diagnosed with ARVC/D at the age of 43, almost 5 years before his niece’s SCD. Resting 12-lead ECG exhibited negative T-waves in leads V1 to V3 (Fig. 2A), his SAECG was positive for late potentials and 24-hour Holter monitoring recorded.

![Figure 1](image1.png)

**Figure 1.** 12-lead ECG of the proband, 6 months prior to her sudden death, showed inverted or flat T-waves in leads V1 and V2 as well as in leads II, III and aVF.
>1000 ventricular ectopic beats (VEBs) and episodes of nonsustained ventricular tachycardia (VT). 2-D echocardiography showed an aneurysmal formation in the right ventricular (RV) apex (Fig. 2B). The patient fulfilled 1 major plus 3 minor criteria for ARVC/D diagnosis. During an electrophysiology study, sustained VT of two morphologies had been induced, one with left bundle branch block (LBBB) morphology with a superior axis and another with LBBB and an inferior axis. He had finally received an implantable cardioverter-defibrillator and had been discharged home with a diagnosis of typical ARVC/D. Unfortunately, the rest of the family had not been informed about the hereditary nature of the disease and family screening of first-degree relatives had not been performed.

The proband’s father had been previously undergone evaluation for palpitations which failed to appreciate abnormalities consistent with structural heart disease. At that time, only hypertension was diagnosed and the patient was put on medication. When he was reevaluated after his daughter’s SCD, at the age of 59, he demonstrated T-wave inversion in all precordial leads (Fig. 3A), abnormal late potentials, and >1000/day VEBs on Holter monitoring. ECG displayed VEBs with LBBB morphology and inferior or superior axis. Echocardiography revealed a left ventricle of normal size and function and no atrial or ventricular septal defect. The RV was dilated with an RV outflow tract (RVOT) of 32 mm at a parasternal short-axis view, alongside a dyskinetic region in the RVOT and poster-diaphragmatic wall (Fig. 3B). These findings constituted 2 major plus 2 minor diagnostic criteria of ARVC/D.

Cardiac evaluation of proband’s sister, cousins and paternal aunt with clinical examination, 12-lead and 24-hour ambulatory ECG, SAECG, and 2-D echocardiography were negative. With both her father and uncle affected by the disease, it seemed most likely that ARVC/D might have been the cause of the young woman’s SCD. However, based on the limited data that were available, diagnosis was borderline with 1 major
family history of ARVC/D) and 1 minor (T-wave inversion in
leads V₁-V₂) criteria fulfilled. It was obvious that we needed
more information in order to make a more definitive diagnosis.

Why did we start with the clinical evaluation of the fam-
ily? One reason is that there are data that familial evaluation
in case of sudden arrhythmic death syndromes can identify
inherited heart diseases in the majority of families. Indeed,
this case of a young woman who died suddenly of unknown
reasons led us to the clinical evaluation of her family revealing
2 relatives, her father and uncle, who suffered from a typical
form of ARVC/D.

Was there an indication for genetic testing? Since two
of the proband’s surviving relatives presented with typical
ARVC/D (Fig. 4), we proceeded to genetic testing for muta-
tions in the five most frequent disease-causing desmosomal
genes. Mutation analysis was undertaken in the two surviving
relatives who had phenotypic abnormalities suggestive of
ARVC/D (targeted, clinically-guided genetic analysis) and
in the dead woman who was suspected of having the disease.
Following the identification of an ARVC-causative mutation in
both her father and uncle, mutation-specific genetic testing of
the SCD victim was strongly indicated (class I recommendation).

GENETIC TESTING RESULTS

Screening for plakoglobin, desmoplakin, desmoglein-2 and
desmocollin-2 did not reveal any nucleotide changes. Screen-

FIGURE 3. A) 12-lead rhythm strip of the proband’s father exhibiting
negative T-waves in leads V₁-V₆, ventricular couplets and VEBs. B)
Aneurysm of right ventricular postero-diaphragmatic wall in subcostal
four-chamber view in the same patient. LA = left atrium; LV left ven-
tricle; RV = right ventricle; VEB = ventricular ectopic beats.
ing for plakophilin-2 (PKP2), however, revealed a single-base deletion (2509delA). The mutation is predicted to introduce a number of novel amino-acid residues at the C-terminal domain of the protein followed by a termination codon (S837fsX930). Both proband’s father and uncle were carriers of this deletion, while the mutation was not identified in none of the other unaffected family members who were screened. The mutation, which showed 100% penetrance amongst the living family members, was not found in 400 control chromosomes and was thus considered pathogenic.

Following the results of the genetic diagnosis, a formalin-fixed, paraffin-embedded myocardial sample obtained from the proband at autopsy, was retrieved from the forensic medicine department and subjected to DNA extraction. The proband was positive for the specific mutation (Fig. 5).

**IMMUNOHISTOCHEMISTRY**

In an effort to confirm the diagnosis, a myocardial sample obtained from the proband at autopsy was immunostained using methods that have been validated in a previous study.8 Myocardium obtained at autopsy from two age-matched individu-
diagnostic assessment, an immunohistochemical analysis was undertaken of a myocardial sample obtained at autopsy, which pointed towards ARVC/D. Moreover, tissue paraffin blocks from various sites of the right ventricle were sent for histological analysis to an expert cardiac pathologist. This time fibrotic areas with a patchy distribution were detected. Some of the tissue samples revealed extensive fibrofatty tissue replacement with myocardial atrophy, whereas others had a completely normal myocardium. Thus, her death was attributed to ARVC/D. Probably, the mutation had been inherited from her paternal grandfather. Although he had never been clinically evaluated, and no tissue was available for genetic analysis, he had a history of SCD at the age of 72, thus, raising suspicion of cardiac disease.

**DISCUSSION**

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) has a prevalence of 1:1000 to 1:5000 in the general population, while in certain parts of the world it is the major cause of SCD in individuals ≤35 years of age. These numbers may be underestimated because wide phenotypic variation, age-related progression and low genetic penetrance may obscure the diagnosis. ARVC/D has an unusually prominent arrhythmogenic phenotype that is manifest early in the natural history of the disease, often preceding the development of ventricular remodeling or contractile dysfunction. Sometimes, SCD is the first manifestation. Accurate and timely diagnosis of the disease in its early, asymptomatic phase is, therefore, pivotal in preventing unexpected SCD. Individuals with an early phase disease are often asymptomatic, but may nonetheless be at risk of SCD. This phase is characterized by propensity towards ventricular arrhythmia in the setting of preserved morphology, histology, and ventricular function. As the disease progresses, myocyte loss, inflammation, and fibroadiposis become evident. Structural abnormalities range from regional wall motion abnormalities, ventricular aneurysms, and increased trabeculations to global ventricular dilation and dysfunction.

A molecular genetics approach that would identify individuals at risk, even before the disease manifests, might be of help. In the absence of the victim’s detailed medical history and clues from the postmortem examination, it would be impossible to correctly “target” genetic testing. Screening for all genes implicated in both electrical syndromes and cardiomyopathies...
ECG in combination with ARVC/D family history (her uncle). ARVC/D can still be missed at early stages because physicians are often unable to recognize or appreciate early or subtle signs and may have little comprehension of its hereditary nature. When a patient is diagnosed with a familial cardiomyopathy, physicians and health care systems should respond immediately by referring all first and second-degree relatives for clinical investigation. Referral of family members to a specialized center is crucial, since family history and routine cardiac evaluation often fail to establish a diagnosis. Clinical diagnosis of inherited SCD syndromes is often impeded by phenotypic diversity and age-related disease progression. Most SCD victims have never sought medical attention prior to their death, therefore clinical data might be absent. ARVC/D, particularly when the disease initially is localized, might be misdiagnosed at autopsy.

Targeted genetic analysis has a major role when dealing with unknown cause sudden death families. Definitive genetic diagnosis in an index case offers an attractive solution by enabling cascade screening of families. In a typical family with an autosomal dominant inheritance pattern, approximately half of the relatives will test gene-negative, affording them with permanent reassurance and obviating the need to screen their children. In our case, the identification of a pathogenic mutation in already diagnosed typical forms of the disease (father and uncle of the proband) gave us the opportunity to seek the specific mutation in the dead proband who fulfilled only 1 major (family history of ARVC/D) and 1 minor (inverted T waves in leads V1-V2) criteria, exhibiting a subclinical form of the disease. Genetic analysis revealed that the proband, as well as her father and uncle, had a mutation in PKP2.

**CONCLUSION**

This report highlights the importance of family screening, not only in SCD cases, but also when an individual is diagnosed with an inherited disease of the heart. It also emphasizes the role of genetic testing in facilitating postmortem diagnosis and cascade screening of surviving relatives, stressing, however, that it should complement, not replace, clinical investigations.

**REFERENCES**


