Sporadic arrhythmogenic right ventricular cardiomyopathy/dysplasia due to a de novo mutation

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We report the case of a 41-year-old man with a diagnosis of sporadic arrhythmogenic right ventricular cardiomyopathy (ARVC). Genetic screening identified the heterozygous missense mutation R49H in the desmoglein-2 gene. The mutation was absent in both parents, and we demonstrated that it was a de novo mutation. To the best of our knowledge, this is the first description of a de novo mutation in ARVC. This has important implications, including for clinical practice, since individuals with sporadic ARVC caused by a de novo mutation can transmit the disease gene to 50% of their offspring. This suggests that the benefit of molecular genetics can be extended to sporadic ARVC and may improve genetic counselling.

Case report

The proband, a 41-year-old male of European origin, was referred to his cardiologist for the exploration of atypical chest pains. The 12-lead electrocardiogram (ECG) displayed right-axial QRS deviation, T-waves inversion from V1 to V5, and polymorphic ventricular ectopies with left bundle branch block (LBBB) morphology (Figure 1). This patient had no medical history and showed no other symptoms. He did not mention any history of recent viral or inflammatory disease that could suggest myocarditis. He was used to exercising daily with a weekly average of 40 km cycling. The 24-h ECG monitoring documented more than 500 polymorphic ventricular ectopies, including triplets. The exercise test showed no ischaemia and led to the disappearance of ventricular ectopies during effort. Signal-averaged ECG with 40 Hz filter showed late potentials with two positive criteria out of three: LAS 40 and RMS 40 were measured at 42 ms and 13 μV, respectively, whereas filtered QRS duration was normal at 107 ms. The echocardiogram showed right ventricular (RV) abnormalities with global mild RV dilatation, wall motion abnormalities localized in the inferior wall and the apex, and excessive trabeculations. Left ventricle morphology and function were normal. Cardiac non-contrast cine-MRI in long- and short-axis confirmed typical segmental RV wall motion abnormalities, with local thinning of the RV wall and global mild RV dilatation. The electrophysiological study with stimulation of the RV in the apex and the outflow tract easily induced reproducible fast ventricular tachycardia with two different LBBB morphologies (Figure 2). Based on these results, the positive diagnosis of arrhythmogenic right ventricular cardiomyopathy (ARVC) was finally made according to the International Task Force diagnostic criteria.1 Family history was unremarkable and cardiac examination of relatives was normal.

After written informed consent, we performed in the patient a mutation screening by direct sequencing of the four desmosomal genes plakophilin-2, desmoplakin, desmoglein-2, and desmocollin-2, which have been shown to be the major genes involved in ARVC.2 We identified the heterozygous missense mutation R49H (G > A nt146 from BC099655) in desmoglein-2, which was not found in 600 chromosomes from ethnically matched controls. No additional mutation was found in the other three desmosomal genes. This mutation, previously described by others, is located in the highly conserved cleavage consensus motif RXK/RR that is recognized by Kex-2-like pro-proteins convertases and is predicted to prevent efficient pro-desmoglein-2 maturation.3 Thus, we considered this missense mutation as causal in this patient. Mutation screening of the parents was secondarily performed but did not identify the R49H mutation in either of them. A paternity test was carried out using the AmpFISTR SGM Plus® PCR Amplification Kit (Applied Biosystems®, Foster city, California, USA) that includes the study of 10 different short tandem repeats, confirming that the alleged father was the biological one (the probability of paternity was calculated at 0.99999). We therefore concluded that the proband carried a de novo mutation. Genetic analyses demonstrated subsequently that his 15-year-old son had not inherited the mutation (Figure 3).

Discussion

Arrhythmogenic right ventricular cardiomyopathy is familial in 30–50% of cases4 and mutations have been recently identified in genes encoding for desmosomal proteins, usually with autosomal dominant inheritance.2 Some mutations have been already described in

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apparently sporadic ARVC patients but either details about the parents were not provided, or analyses demonstrated the presence of the mutation in one parent, who did not exhibit cardiac expression of ARVC due to incomplete penetrance. Here, we report a desmoglein-2 gene mutation in a patient with sporadic ARVC and demonstrate that it was a de novo mutation, since the mutation was absent in both parents, and paternity was confirmed. To the best of our knowledge this is the first

Figure 1 Twelve-lead resting electrocardiogram of the proband (paper speed 25 mm/s). It shows sinus rhythm at 74 bpm, with right QRS axis. Note the T-wave inversion in precordial leads from V1 to V5 and the ventricular ectopy with left bundle branch block morphology, suggesting ectopy coming from the right ventricle.

Figure 2 Electrophysiological study of the proband. Stimulation of the right ventricle has been done in two different sites (apex and outflow tract) at 600 and 400 ms cycle base length with up to three extra stimuli. Two different sustained ventricular tachycardia with left bundle branch block morphology were induced at 600/280/240/240 ms. A second electrophysiological study was performed 2 months later under sotalol 240 mg per day and did not induce any tachycardia.
description of a de novo causal mutation identified in ARVC. In contrast, this mechanism has already been observed in other cardiac diseases such as hypertrophic cardiomyopathy or long-QT syndrome.

This observation has important implications. First, the appearance of a de novo mutation in the desmoglein-2 gene provides compelling genetic evidence for the involvement of this gene in ARVC. Desmoglein-2, one of the two desmosomal cadherin expressed in heart tissue, is an essential component of desmosome that mediates cell-to-cell adhesion. Mutations in desmoglein-2 have been previously identified in autosomal dominant non-syndromic ARVC, with or without left ventricular involvement, and no clear phenotype–genotype correlation has been described until now. Second, it provides evidence that sporadic ARVC is not a separate non-genetic entity but a particular case of a monogenic disease. Third, our findings have direct clinical applications since individuals with sporadic ARVC caused by a de novo mutation can transmit the disease gene to 50% of their offspring. This suggests that the benefit of molecular genetics can be extended to sporadic ARVC in order to improve genetic counselling. The exact proportion of sporadic ARVC due to de novo mutations remains, however, to be assessed.

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Conflict of interest: none declared.

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