Emerging role of genetic analysis for stratification of sudden cardiac death risk in dilated cardiomyopathy: An illustrative case

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Introduction

Dilated cardiomyopathy (DCM) is a common cause of heart failure, ventricular arrhythmias, and sudden cardiac death (SCD).[1] Current DCM guidelines recommend implantable cardioverter-defibrillator (ICD) insertion for prevention of SCD when left ventricular ejection fraction (LVEF) is less than 35%.[2,3] However, SCD can occur in those with relatively preserved LVEF[1] and also in those with recovered LVEF.[4] There is significant phenotypic heterogeneity and it has been proposed that certain subtypes of DCM predispose to ventricular arrhythmias independent of LVEF.[5] Genetic testing has recently emerged as a means of differentiating subtypes of DCM and predicting SCD risk. Several genes have been associated with a predilection for arrhythmias in this condition.[6] We describe a case of prevented SCD in an *RBM20* mutation carrier and highlight the importance of utilizing genomic medicine to personalize therapy in DCM beyond current practice.

The described patient and his immediate relatives are part of a larger study approved by the ethical review board at our hospital and provided informed consent for their medical data to be published in this report.

Case report

A 52-year-old man presented to the emergency department with new progressive dyspnea and orthopnea. Examination revealed elevated venous filling and pulmonary crepitations consistent with congestive cardiac failure. Chest radiograph showed cardiomegaly and early interstitial edema. Electrocardiogram demonstrated sinus rhythm with a left axis deviation (Figure 1).

KEYWORDS Arrhythmic cardiomyopathy; Dilated cardiomyopathy; Genetic testing; Personalized medicine; RBM20; Risk stratification; Sudden cardiac death

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The patient was a heavy smoker. There were no other notable medical problems. Family history was significant for DCM in several members. The patient's father was diagnosed with idiopathic DCM in his 50s and died of heart failure in his 70s. A paternal aunt had idiopathic DCM in her 60s and a paternal first cousin had DCM and underwent heart transplant at age 45 (Supplemental Figure).

The patient was diagnosed with new congestive cardiac failure with likely familial DCM. An echocardiogram supported this diagnosis with a dilated left ventricle at 6.5 cm and severe global systolic dysfunction, LVEF was 18%. Coronary angiography was normal. The patient was subsequently commenced on long-acting beta-blockade and angiotensin-converting enzyme inhibition for systolic heart failure.

In the first 3 months, LVEF remained poor, though symptomatically he improved to NYHA class I–II. He described no symptoms to suggest arrhythmias, including palpitations or presyncope. Owing to the persistent poor LV function he was referred for a primary-prevention ICD.

Over the ensuing months the patient's LV function did start to improve. At the time of ICD insertion LVEF was 37%. Four months following his ICD implantation, the patient woke suddenly from sleep after sensing a shock from his device. He attended the hospital, where ICD interrogation revealed an episode of ventricular fibrillation at a rate of 270 beats per minute, with successful cardioversion to sinus rhythm (Figure 2). Repeat echocardiogram showed stable LV function, which had further improved to LVEF 40% (Figure 3).

The patient was referred to our cardiac genetics service and genetic testing was performed using a next-generation sequencing panel consisting of 36 cardiomyopathy genes: *ABCC9, ACTC1, ACTN2, ANKRD1, ANO5, BAG3, CRYAB, CSRP3, DES, DMD, EMD, EYA4, FKTN, ILK, LAMP2, LDB3, LMNA, MYBPC3, MYH7, MYPN, NEBL, NEXN, PDLIM3, PLN, RBM20, SCN5A, SGCD, TAZ, TCAP, TMPO, TNNC1, TNNI3, TNNT2, TPM1, TTN,* and *TTR*. Variants were interpreted using the consensus guidelines of the

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KEY TEACHING POINTS

- Genetic testing is a useful tool for differentiating dilated cardiomyopathy (DCM) subtypes, predicting risk of sudden cardiac death, and guiding clinical management. Interpretation of genetic variants is complex and multidisciplinary cardiac-genetics clinics are important for assessing variants in specific clinical contexts.
- Sudden cardiac death can occur in patients with dilated cardiomyopathy and relatively preserved left ventricular function. Certain genes such as *LMNA* and *SCN5A* are associated with particularly arrhythmogenic forms of DCM.
- *RBM20* mutations are rare but cause a highly penetrant arrhythmic DCM. Sudden cardiac death is common in *RBM20* mutation carriers, including those with relatively preserved left ventricular ejection fraction.

American College of Medical Genetics.[7] A heterozygous missense variant was detected in *RBM20* (c.1900C>T p.Arg634Trp). This variant has previously been reported in patients with DCM including 1 family study.[8,9] It is absent in population databases, though frequency information is unreliable at this position owing to insufficient coverage in the ExAC database. Nonetheless, the arginine residue at this position is very highly conserved and occurs in a critical functional domain. A recent functional study showed that this variant disrupts nuclear localization of RBM20, resulting in altered *TTN* isoform expression, consistent with *RBM20*'s known role as a *TTN* splicing regulator.[9]

The patient's living affected relatives were not available for segregation testing. Predictive testing was extended to his 3 daughters (aged 32, 30, and 28), 2 of whom carry the *RBM20* variant. Both are well, with no cardiac symptoms and normal screening echocardiograms to date. They will have regular cardiac follow-up.

Discussion

DCM occurs in 1 in 2500 individuals.[1] While heart failure is the usual presentation, ventricular arrhythmias and SCD may be the presenting features. Distinguishing which DCM patients are at risk for SCD is an area of current interest. Recent cohort studies have suggested that DCM patients may not benefit from prophylactic ICDs when implanted according to current guidelines.[10] There are several explanations for this, including that (1) patients with LVEF below 30% are more likely to die from heart failure from SCD; (2) most DCM patients who die from SCD have LVEF >30%,[2] and (3) DCM is a highly heterogeneous condition and general recommendations fail to encompass the differing risk.

Genetic testing in DCM has been put forward as a means to distinguish those at higher risk of SCD.[1] Several genes are associated with particularly arrhythmogenic forms of DCM[5] (Table 1), and carriers of these genes warrant different SCD prevention management. In line with this, recent updates to ICD guidelines have acknowledged *LMNA* cardiomyopathy as a group requiring special treatment.[3] The recent 2019 Heart Rhythm Society expert consensus further reinforces individualized care for arrhythmic genes.[11]

RBM20 (RNA binding motif 20) is a splicing regulator, important in post-translational modification of several important cardiac genes including titin (*TTN*). Variants in *RBM20* have been described in several family and cohort studies and produce a remarkably consistent phenotype of highly penetrant arrhythmic DCM.[12,13] Pathogenic *RBM20* variants are

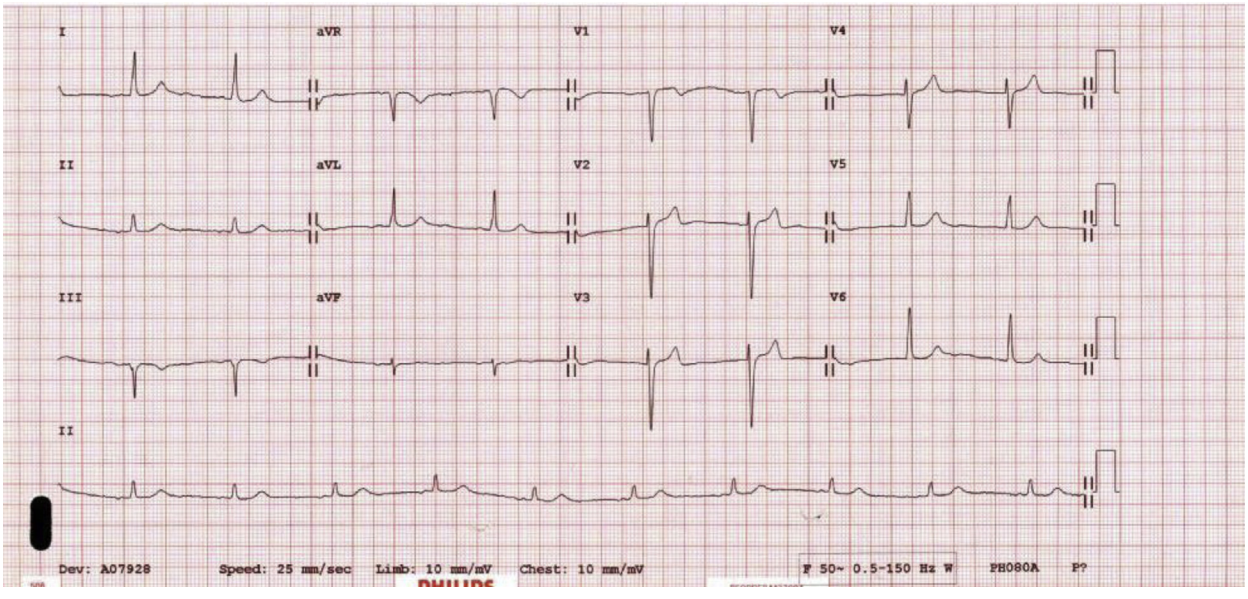

Figure 1 Baseline 12-lead resting electrocardiogram.

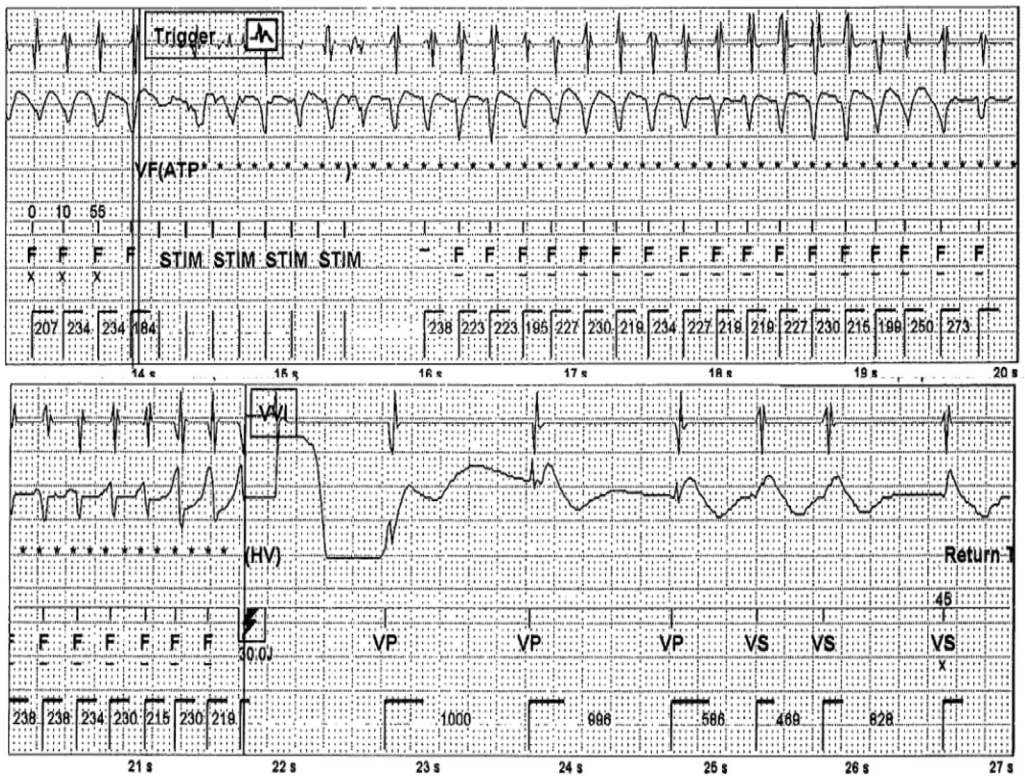

Figure 2 Ventricular fibrillation with rate of 270 beats per minute; successful cardioversion to sinus rhythm.

most commonly heterozygous missense variants occurring in functional domains that are critical for its splicing function.[13] Nonsense variants have been described but their contribution to a more severe phenotype remains unclear.[9,13] Across 2 large recently published cohorts the mean age of presentation was 37, with males presenting on average 10–20 years younger than females.[12] In almost all families there is a history of SCD or major arrhythmic events, and further, these events often occurred at relatively preserved LVEF.[12]

We present a case of primary DCM where an initial poor LVEF recovered, and the patient was considered low arrhythmic risk. Nonetheless, a prophylactic ICD effectively prevented sudden death from nocturnal VF. Insertion and replacement of ICDs in those with borderline or recovered LV function is a common dilemma for electrophysiologists; indeed, a recent meta-analysis demonstrated a significant reduction in appropriate ICD therapies in patients with recovered LV function.[14] On the other hand, SCD risk remains higher than average in recovered patients, and improved LV function does not necessarily correspond with the resolution of arrhythmic substrate.[4] Genetic testing has emerged as a valuable tool for refining diagnosis, risk, and management of cardiomyopathies and inherited arrhythmias, and this case is illustrative of how genetic testing may influence decision-making in sudden death prevention.[15]

Genetic testing in DCM is increasingly utilized, and there are circumstances where the specific result can inform clinical management. Nonetheless, variant interpretation in DCM is particularly complex owing to the large number of disease-associated genes and the heterogeneity of phenotypes. Testing within multidisciplinary cardiac-genetics clinics remains important so that the choice of test can be considered, and variants can be interpreted within the specific clinical setting. In many cases, combined genetic and cardiology expertise can refine the diagnosis and provide tailored management.[15] In the current case, the presence of an

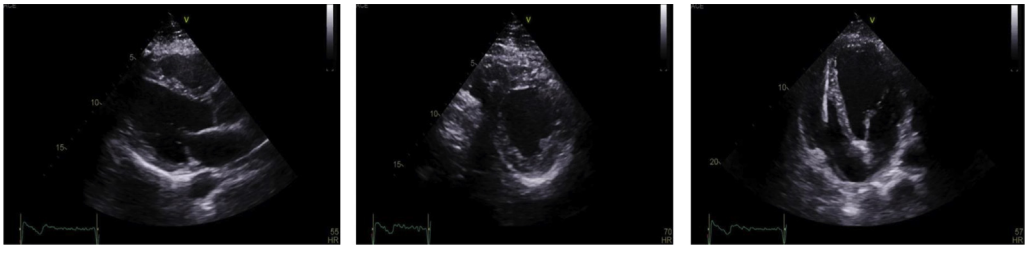

Figure 3 Transthoracic echocardiogram images 4 months post implantable cardioverter-defibrillator insertion. Parasternal long axis, parasternal short axis, and apical 4-chamber views (left to right). Left ventricle mildly dilated and left ventricular ejection fraction 40%.

Table 1 Dilated cardiomyopathy genes associated with predilection for ventricular arrhythmias and sudden cardiac death

Gene	DCM Phenotype
LMNA	Severe DCM, CD, VA, AA
SCN5A	DCM, CD, VA, AA
FLNC	Severe DCM, VA, AA
RBM20	Severe DCM, VA, AA
TTN	DCM, VA, AA
DES	DCM, CD, VA, ARVC
PLN	DCM, VA, ARVC
TMEM43	DCM, VA, ARVC
DSP	DCM, VA, ARVC
DSG2	DCM, VA, ARVC
DSC2	DCM, VA, ARVC

AA = atrial arrhythmias; ARVC = arrhythmogenic right ventricular cardiomyopathy; CD = conduction disease; DCM = dilated cardiomyopathy; VA = ventricular arrhythmias.

arrhythmic gene variant in *RBM20* provided explanation for heightened SCD potential, despite recovery of LV function, and illustrates the importance of personalized care.

Conclusions

Prevention of SCD in DCM has traditionally been centered on LVEF, which has limitations. Genetic testing is increasingly utilized and can provide a means of further refining patient risk. Our case exemplifies the arrhythmic potential of *RBM20* despite preserved or recovered LVEF, and the importance of individualizing management for certain subsets of patients. While guidelines now acknowledge increased risk with *LMNA* mutations, we highlight the importance of identifying and managing other arrhythmic genetic DCM subtypes.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrcr.2020.05.004.

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