scientific reports

Check for updates

OPEN

Age at onset and clinical course of *RBM20*-mediated cardiomyopathy

Ramin Garmany[1,2], Matteo Castrichini[2,3], Raquel Neves[2], Naveen L. Pereira[3], Ciorsti MacIntyre[2,3], Jay W. Schneider[4], Michael J. Ackerman[2,3,5] & John R. Giudicessi[2,3]✉

Disease-causative variants in *RBM20*-encoded RNA-binding motif protein 20 cause a severe arrhythmogenic dilated cardiomyopathy (DCM). We aimed to characterize the clinical course of *RBM20*-mediated DCM in comparison to other familial and non-familial forms of DCM. The Mayo Clinic Genetic Arrhythmogenic Cardiomyopathy (ACM) Registry was used to identify *RBM20*- and *TTNtv*-positive individuals. Additionally, patients with idiopathic non-ischemic DCM were included in this study. Ventricular arrhythmic (VA) events were defined as sustained ventricular arrhythmia, sudden cardiac arrest (SCA), or ventricular tachycardia (VT)/ventricular fibrillation (VF)-terminating implantable cardioverter defibrillator (ICD) therapy and advanced heart failure (AHF) events defined as ventricular assist device implantation or heart transplantation. Overall, we identified 43 *RBM20*- (49% female) and 108 *TTNtv*- positive individuals (44% female). *RBM20 variant-positive* individuals were younger at time of diagnosis at 31 years vs. 45 years old for *TTNtv*-positive individuals ($p < 0.0001$). Additionally, *RBM20 variant-positive* individuals were more likely to have a family history of SCA (67% vs. 30%; $p < 0.0001$) and cardiomyopathy (88% vs. 61%; $p = 0.0008$). Interestingly, the prevalence of AHF (14% vs. 5%) events was higher in *RBM20* variant-positive patients. *RBM20 variant-positive* individuals had earlier times to both VA ($p = 0.007$) and AHF ($p = 0.0008$) events. Findings were similar in comparison to idiopathic DCM. In this single center study, *RBM20* patients had an earlier progressing disease with a higher prevalence of advanced heart failure compared with *TTNtv* patients. *RBM20* patients progressed to VA and AHF endpoints earlier.

Keywords Arrhythmogenic cardiomyopathy, Dilated cardiomyopathy, Genotype, Heart failure, *RBM20*, *TTN*

Dilated cardiomyopathy (DCM) arises secondary to the disruption of contractile function due to a range of environmental and genetic risk factors[1,2]. Understanding the etiology of DCM has prognostic implications[3] and clinically meaningful genotype–phenotype associations for genetic DCM have recently emerged[4–8]. For example, DCM mediated by pathogenic variants in *FLNC* and *LMNA* generate an arrhythmogenic DCM (A-DCM) phenotype resulting in disease-specific recommendations regarding SCD risk-stratification and the timing of primary prevention ICD implantation[4–8]. More recently *RBM20,* a gene encoding the ribonucleic acid (RNA)-binding motif protein 20 which functions as a splicing factor for tissue-specific isoform expression of *TTN, RYR2*, and other genes implicated in calcium handling/arrhythmogenesis and cardiomyopathy[9–12] has been shown to generate an A-DCM or arrhythmogenic left ventricular cardiomyopathy (ALVC)[12].

Although recent studies suggest that *RBM20*-cardiomyopathy results in an A-DCM/ALVC akin to that seen in *FLNC* and *LMNA*[6,7] with increased arrhythmogenicity compared to DCM caused by TTN truncating (*TTNtv*) variants, prior *RBM20*-cardiomyopathy studies were focused largely on ventricular arrhythmia (VA) risk rather than advanced heart failure (AHF) or combined outcomes and did not address the time course of VA/AHF events (i.e. time-to-event analyses) in comparison to other DCM genotypes/subtypes[6,7]. Therefore, we conducted a single-center, retrospective analysis of *RBM20*-cardiomyopathy, *TTN*-cardiomyopathy and idiopathic DCM patients evaluated at a single tertiary academic medical center to better characterize the clinical course of *RBM20*-cardiomyopathy via time-to-event analyses, effect of variant class (i.e., missense versus truncating), and sex.

[1]Mayo Clinic Graduate School of Biomedical Sciences, Mayo Clinic Alix School of Medicine and the Mayo Clinic Medical Scientist Training Program, Rochester, MN, USA. [2]Department of Molecular Pharmacology & Experimental Therapeutics, Windland Smith Rice Sudden Death Genomics Laboratory, Mayo Clinic, Rochester, MN, USA. [3]Department of Cardiovascular Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA. [4]Department of Cardiovascular Medicine, Mayo Clinic, Jacksonville, FL, USA. [5]Department of Pediatric and Adolescent Medicine/Division of Pediatric Cardiology, Windland Smith Rice Genetic Heart Rhythm Clinic, Mayo Clinic, Rochester, MN, USA. ✉email: Giudicessi.john@mayo.edu

Results

RBM20 variant-positive individuals have more severe, earlier onset disease

The cohort consisted of 43 *RBM20* variant-positive individuals (49% Female) and 108 TTNtv-positive individuals (44% female; Fig. 1A). The prevalence of a cardiac phenotype was similar between *RBM20* variant-positive (N = 39; 91%) and TTNtv-positive patients (N = 88; 81%; p = 0.2; Fig. 1A). The difference in the prevalence of AHF (14% vs. 5%; p = 0.08) or VA event (23% vs 16%; p = 0.3) did not reach statistical significance (Fig. 1A). Notably, *RBM20* variant-positive patients were more likely to have a family history of SCA (67% vs. 30%; p < 0.0001) and family history of cardiomyopathy (88% vs. 61%; p = 0.0008) (Fig. 1A). Although no difference in prevalence of AHF or VA events was observed, *RBM20* variant-positive patients were diagnosed at a younger age (31 ± 13 vs. 45 ± 16 years; p < 0.0001) and were younger at their last follow-up appointment (39 ± 17 vs. 49 ± 18 years; p = 0.002; Fig. 1B,C). There was no difference in proportion of patients that underwent primary or secondary prevention ICD implantation (37% vs 29%; p = 0.3) or the proportion of patients with ICDs that received ≥ 1 appropriate ICD therapy (44% vs. 29%; p = 0.3; Fig. 1D). Next, multivariate logistic regression was used to control for sex and follow-up time while comparing prevalence of VA and AHF events. When controlling for sex and follow-up time, *RBM20* variant-positive individuals trended towards being more likely to have VA events (p = 0.09; Supplemental Table 1). When controlling for sex and follow-up time *RBM20* variant-positive individuals were more likely to have AHF events (odds ratio = 4.1; p = 0.02; Supplemental Table 2).

RBM20-mediated cardiomyopathy results in a more rapidly progressive disease

Time-to-event analysis was performed to determine if there is a difference in disease progression between *RBM20* variant-positive and *TTNtv*-positive individuals. *RBM20 variant-positive* had earlier progression to VA events with a restricted mean survival time of 58 years compared to 64 years for *TTNtv*-positive (p = 0.007, hazard ratio = 2.9, Fig. 1E). Interestingly, *RBM20 variant-positive* also had more rapid progression to AHF events with a restricted mean survival time of 64 years compared to 72 years for *TTNtv*-positive (p = 0.0008, hazard ratio = 6.3, Fig. 1F). Consequently, *RBM20* variant-positive results in earlier progression to VA events and requirement for AHF therapies. Pharmacologic management was similar between the groups (Supplemental Table 3).

Structural features of RBM20 variant-positive individuals

Figure 2A–C summarize the most recent echocardiographic findings between *RBM20* variant-positive (N = 38) and *TTNtv*-positive (N = 101) patients. Although reduced left ventricular ejection fraction was observed in both groups, no appreciable difference in the severity of LV dysfunction was observed (44 ± 16% vs. 46 ± 13%; p = 0.3). On average left ventricular (LV) dilation as measured by left ventricular end diastolic diameter (LVEDD) was larger in *RBM20* variant-positive patients (59 ± 12 vs. 55 ± 9 mm; p = 0.03) and *RBM20* variant-positive patients

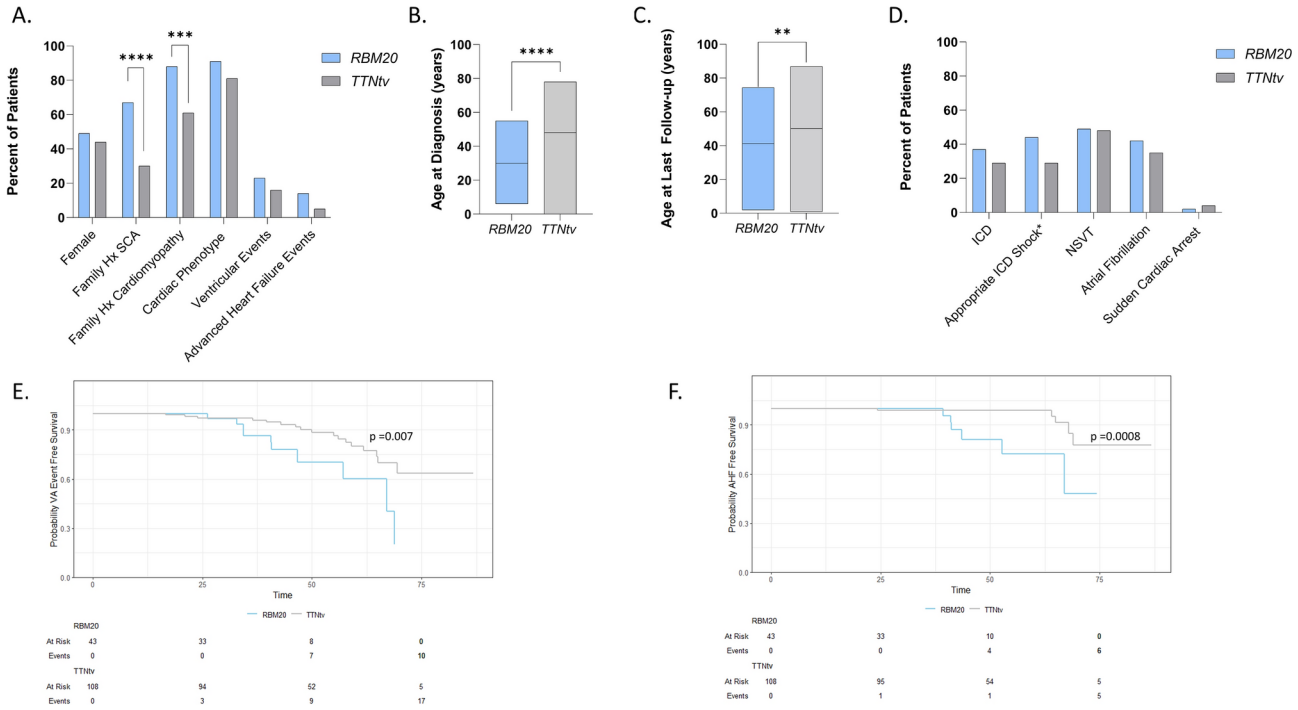

Fig. 1. Demographic and clinical comparison of *RBM20* variant-positive and *TTNtv* variant-positive patients. (**A**) Demographic information and clinical outcomes. (**B**) Age at diagnosis for patients with a cardiac phenotype. (**C**) Age at last follow-up appointment. (**D**) ICD and arrhythmia information. (**E**) Time to VA event. (**F**) Time to AHF event. *AHF* advanced heart failure, *Hx* history, *ICD* implantable cardioverter defibrillator, *NSVT* nonsustained ventricular tachycardia, *VA* ventricular arrhythmia. *Refers to proportion of patients with an ICD that received a shock.

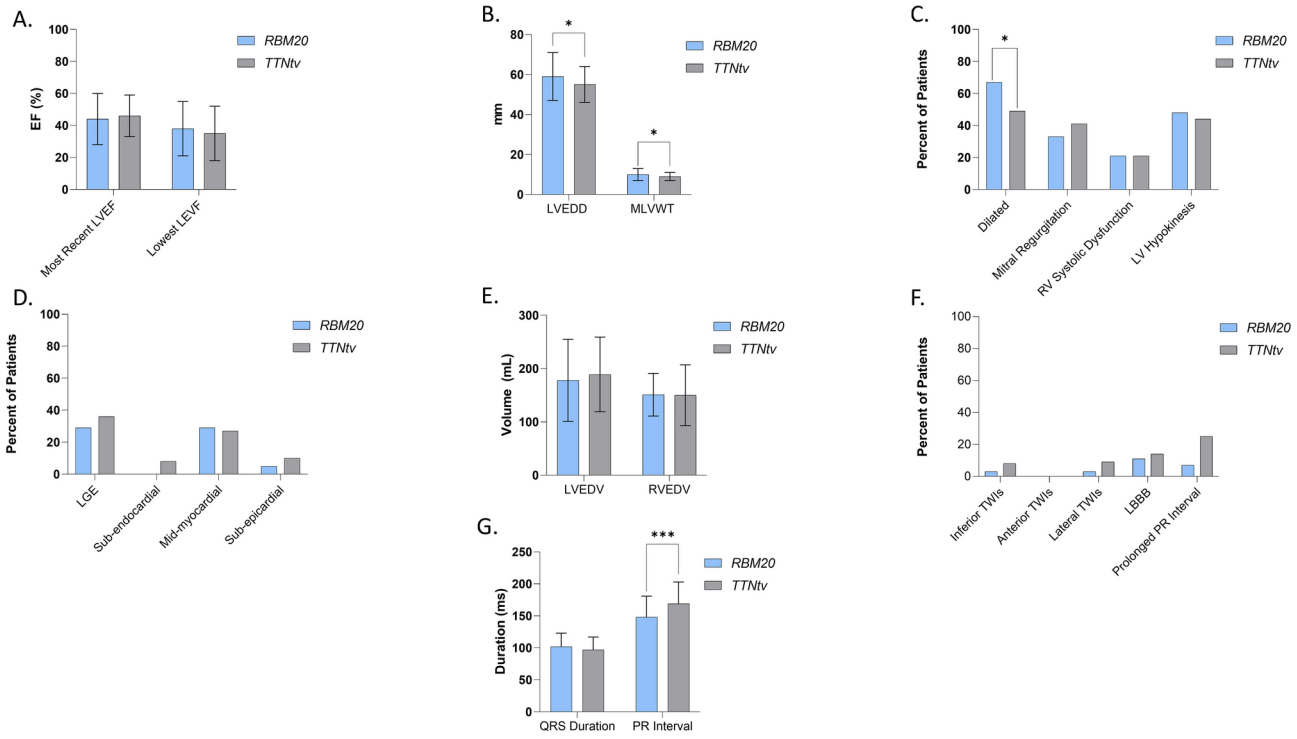

Fig. 2. Structural imaging and electrocardiograms comparing *RBM20* variant-positive and *TTNtv* variant-positive patients. (**A**) Comparison of most recent and lowest ejection fraction from echocardiography report. (**B**) Left ventricular chamber dimensions measured by echocardiography. (**C**) Prevalence of structural and functional deficiencies on echocardiography report. (**D**) Late gadolinium enhancement on cardiac MRI. (**E**) LV and RV chamber dimensions measured using cardiac MRI. (**F**) Prevalence of ECG findings. (**G**) PR and QRS duration. *ECG* electrocardiogram, *EF* ejection fraction, *LBBB* left bundle branch block, *LGE* late gadolinium enhancement, *LV* left ventricle, *LVEDD* left ventricular end diastolic diameter, *LVEDV* left ventricular diastolic volume, *LVEF* left ventricular ejection fraction, *MLVWT* maximum left ventricular wall thickness, *MRI* magnetic resonance imaging, *RV* right ventricle, *RVEDV* right ventricular diastolic volume, *RWMAs* regional wall motion abnormalities, *TWI* t-wave inversion.

were more likely to have LV dilation defined as LVEDD greater than or equal to 56 mm for men and 51 mm for women (67% vs. 49%; p = 0.05). Other parameters were similar between the groups.

The most recent cardiac MRI (CMRI) findings are presented in Fig. 2D,E for *RBM20* (N = 21) and *TTNtv* (N = 59) patients. Late gadolinium enhancement (LGE) was observed in 29% of *RBM20* variant-positive patients with no significant difference compared with *TTNtv*-cardiomyopathy. The most common distribution was mid-myocardial enhancement (29%) with a small proportion having sub-epicardial (5%). Left ventricular and right ventricular dimensions were not different between *RBM20* variant-positive and *TTNtv*-positive individuals.

Electrical features of RBM20 variant-positive individuals

The baseline electrocardiogram (ECG) features for *RBM20*-positIve (N = 38) and *TTNtv*-positive (N = 101) patients are presented in Fig. 2F,G. Interestingly, the average PR interval on baseline ECG was longer for *TTNtv*-positive compared with *RBM20* variant-positive (169 ± 34 ms vs. 148 ± 33 ms; p = 0.002); however, there was no difference in prevalence of prolonged PR interval (≥ 200 ms) between the two groups (16% vs. 7%; p = 0.2) possibly due to being underpowered.

Comparison of sex differences in RBM20 variant-positive individuals

Next the clinical outcomes of *RBM20* variant-positive females and males were compared. Females presented earlier with a phenotype (27 ± 12 vs. 35 ± 12 years; p = 0.04; Fig. 3A) and clinically differences between sexes did not reach statistical significance (Fig. 3B–D). Males trended towards being more likely to have VA events (32 vs. 14%; p = 0.3) and a higher proportion of patients with an ICD having appropriate shocks (56% vs. 29%; p = 0.4) but neither reached statistical significance.

Comparison of RBM20 variants

Mouse studies have shown that missense variants produce a more severe phenotype than truncating/null variants[13]; thus, we compared genotype subgroups. We identified 5 *RBM20* variant-positive patients with truncating variants and 34 *RBM20* variant-positive patients with missense variants. The sample size of truncating variants was small so there were no appreciable differences in age of phenotype or clinical severity between the genotypes (Fig. 3E,F). Time-to event analysis showed no statistically significant difference for VA events (p = 0.2;

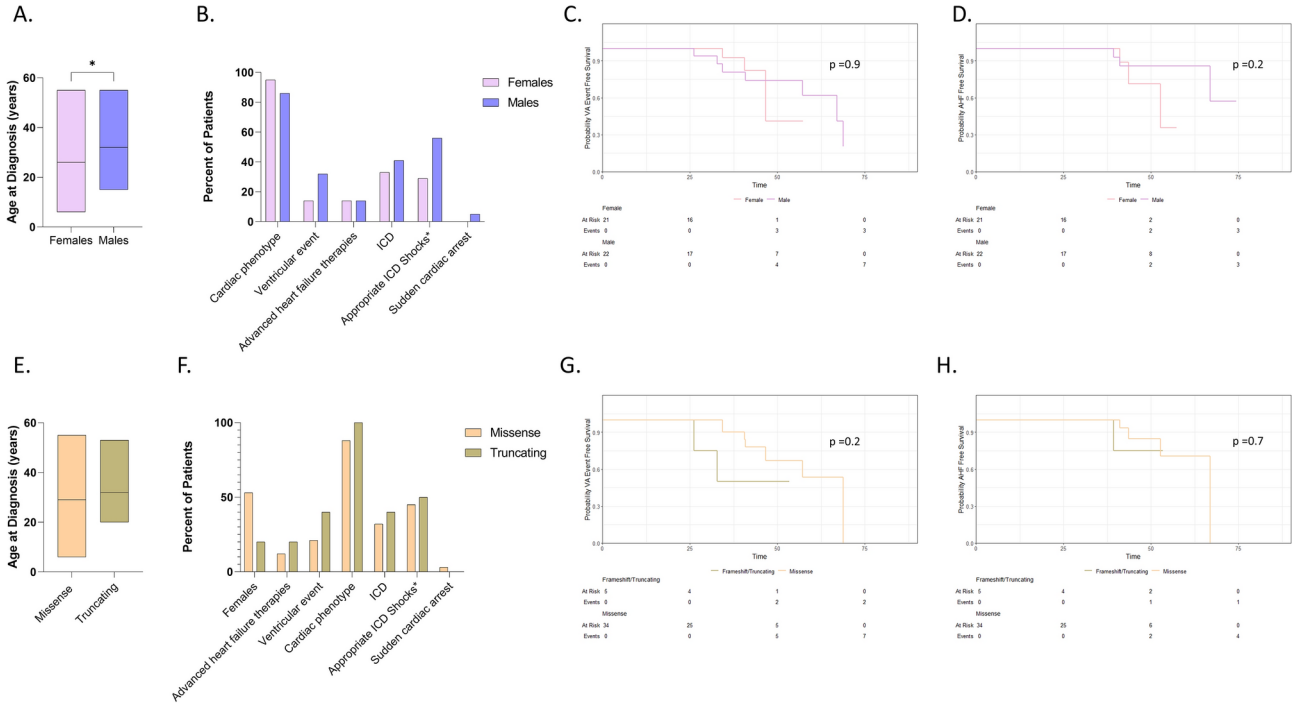

Fig. 3. Subgroup comparisons of *RBM20* variant-positive individuals. (**A**) Age at diagnosis for males and females with a cardiac phenotype (**B**) Comparison of clinical outcomes between males and females. (**C**) Time to VA event males and females. (**D**) Time to AHF event males and females. (**E**) Age at diagnosis for patients with *RBM20* missense variants and truncating variants with a cardiac phenotype. (**F**) Comparison of clinical outcomes missense and truncating variants. (**G**) Time to VA event missense and truncating variants. (**H**) Time to AHF event missense and truncating variants. *AHF* advanced heart failure, *Hx* history, *ICD* implantable cardioverter defibrillator, *NSVT* nonsustained ventricular tachycardia, *VA* ventricular arrhythmia. *Refers to proportion of patients with an ICD that received a shock.

Fig. 3G) or AHF events (p = 0.7; Fig. 3H). Thus, the relationship between variant type and clinical outcomes in *RBM20*-cardiomyopathy remains unclear.

RBM20-cardiomyopathy compared with idiopathic non-ischemic DCM

Finally, we compared *RBM20*-cardiomyopathy to a cohort of idiopathic, non-ischemic DCM (N = 193) to determine if *RBM20*-cardiomyopathy portends a more severe clinical phenotype at a tertiary referral center. To make comparisons equivalent, only patients with phenotypic expression of *RBM20*-cardiomyopathy were included. *RBM20*-cardiomyopathy presented at a much younger age (31 ± 13 vs. 52 ± 16; p < 0.0001; Fig. 4A) and patients were younger at last follow-up (42 ± 16 vs. 64 ± 16; p < 0.0001; Fig. 4B). There were more females in the *RBM20* cohort than the idiopathic, non-ischemic DCM cohort (51% vs. 33%; p = 0.03). There was no difference in the rates of ICD placement (41% vs. 49%; p = 0.4) or proportion of patients that experienced an appropriate ICD shock(s) (44% vs. 37%; p = 0.6; Fig. 4C). Interestingly, the prevalences of AHF events (15% vs. 19%; p = 0.6) and VA events (26% vs. 24%; p = 0.8) were similar between *RBM20*-cardiomyopathy and idiopathic DCM (Fig. 4C).

However, time to event analysis showed *RBM20*-cardiomyopathy presented with a younger time to VA event with a restricted mean survival time of 58 years compared to 65 years idiopathic DCM (Hazard ratio of 2.3.; p = 0.0001; Fig. 4D). Time to HF event did not reach statistical significance (64 years versus 69; Hazard ratio of 3.8; p = 0.6; Fig. 4E).

Given the difference in sex composition between the groups, we compared males and females with idiopathic DCM to see if sex could be a confounding variable and found there were sex-specific differences in prevalence of ICD shocks, and VA events (Supplemental Table 4). Thus, we performed multiple logistic regression analyses for each variable controlling for sex and follow-up time and found no differences in VA events or AHF events (Supplemental Tables 5, 6).

Discussion

Higher prevalence of advanced heart failure and increased arrhythmia risk

Herein, we provide the largest single-center experience with *RBM20*-cardiomyopathy and compare it to *TTNtv*-mediated and idiopathic DCM. Consistent with a previous multi-center study[7], we found that RBM20-cardiomyopathy is more penetrant than *TTNtv*-cardiomyopathy based on the prevalence of a family history of cardiomyopathy (87% vs. 59%) and SCA (67% vs. 30%). We found when accounting for age that *RBM20*-

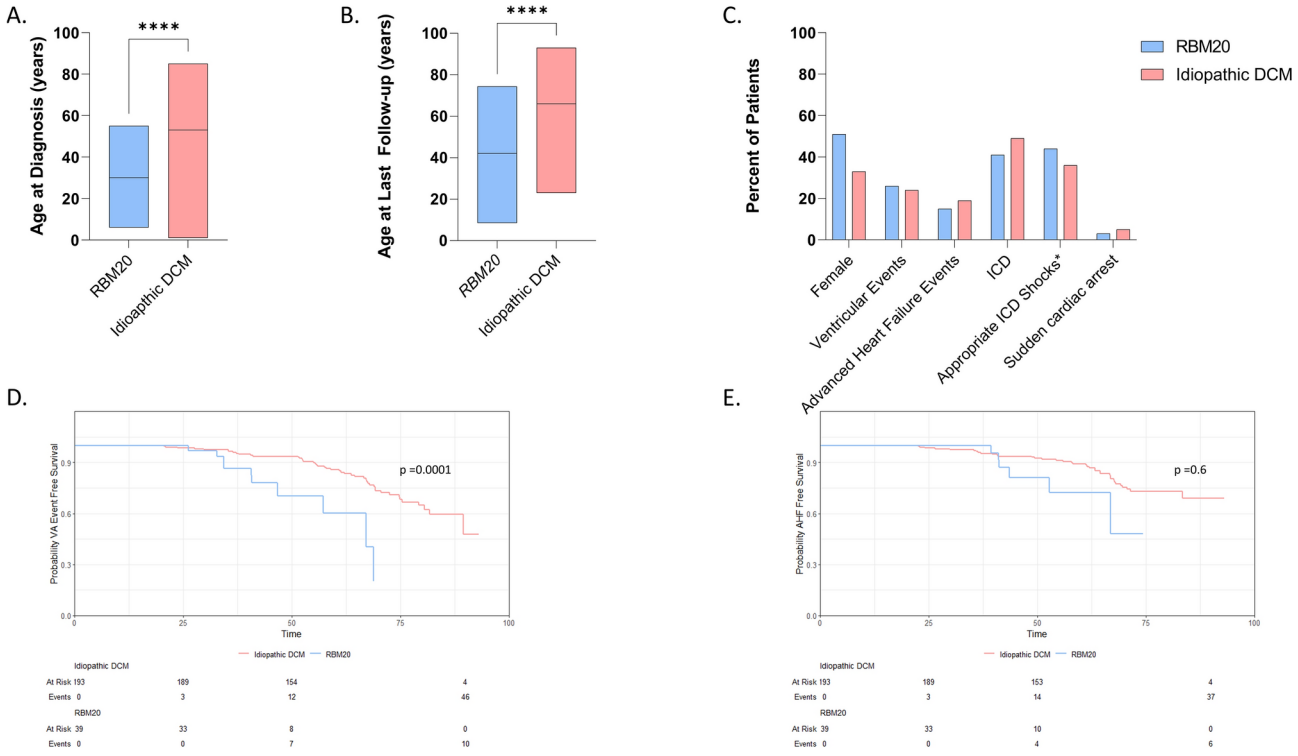

Fig. 4. Comparison of *RBM20*-cardiomyopathy with Idiopathic Non-ischemic DCM. (**A**) Age at diagnosis for patients with a cardiac phenotype. (**B**) Age at last follow-up appointment. (**C**) Summary of demographic information and clinical outcomes. (**D**) Time to VA event *RBM20*-cardiomyopathy and idiopathic non-ischemic DCM. (**E**) Time to AHF event *RBM20*-cardiomyopathy and idiopathic non-ischemic DCM. *AHF* advanced heart failure, *DCM* dilated cardiomyopathy, *Hx* history, *ICD* implantable cardioverter defibrillator, *NSVT* nonsustained ventricular tachycardia, *VA* ventricular arrhythmia. *Refers to proportion of patients with an ICD that received a shock.

patients did have an increased need for advanced heart failure therapies consistent with a meta-analysis looking at genotype–phenotype associations in DCM which found an increased risk of heart failure for *RBM20 variant-positive* individuals[14].

Similar to the study by Parikh et al.[7], we found that patients with *RBM20*-cardiomyopathy trended towards having increased prevalence of VA events in comparison to those TTNtv-positive individuals at our tertiary medical center. The difference in VA event rate was not as large between our cohorts, at least in part, due to either 1) more severe disease amongst TTNtv-positive patients (16% experienced sustained VA) presenting to a tertiary medical center in the United States, 2) less severe disease amongst the TTNtv-positive individuals identified through the Royal Brompton Hospital (United Kingdom) Cardiovascular biobank[15] (2.2% experienced sustained VA) utilized in the study by Parikh et al.[7] or 3) an additive combination of both phenomenon.

That said, the fact that other studies have also reported substantially higher VA rates in TTNtv-positive individuals[16] raises the possibility that the comparison of *RBM20* variant-positive individuals presenting predominantly to tertiary referral centers to TTNtv-positive individuals identified via single-center cardiac MRI-derived biobank has the potential to over-exaggerate differences in disease severity.

Although not reflective of the severity of a given genetic substrate at the population level, the current study does have the advantage of eliminating the potential effect of differences in referral bias by comparing the disease severity of *RBM20* variant-positive and TTNtv-positive patients evaluated in the context of the same sub-specialty genetic cardiomyopathy/heart failure clinics. Thus, at least in our single center experience, the overall risk of VA events for *RBM20*-cardiomypathy appear to be similar or only slightly higher than *TTNtv*-cardiomyopathy, but longitudinal studies are necessary to verify this as the cohort ages.

In addition, only 37% of *RBM20 variant-positive* had an ICD compared with almost 60% in other published cohorts; however, almost half of patients in our cohort with ICDs had appropriate shocks while only 28% in other studies did[7]. There was no difference in ICD placement rate between *RBM20* and *TTNtv*. Other arrhythmogenic/dilated cardiomyopathy genes such as *LMNA, PLN,* and, *FLNC* have been put forth as higher-risk genotypes with a lower threshold to consider primary prevention ICD placement[17]. To this end, the consensus statement on genetic testing for cardiac diseases recommends implementation of genetic testing in the management of DCM patients with special consideration of ICD placement in those with pro-arrhythmogenic substrates such as *LMNA*[18,19]. Although *RBM20*-cardiomyopathy is not listed as a higher-risk genotype in the HRS ACM guidelines, the early onset of VA events observed in this study and increased VA event rates in prior studies

supports the need to better define the risk factors for VA events and threshold for ICD implantation in *RBM20*-mediated disease.

RBM20 results in an early-onset arrhythmogenic dilated cardiomyopathy

Unlike prior studies which focused on prevalence of events or time to event since beginning of the study[6,7,20], the time-to-event analyses in the current study demonstrate that *RBM20*-cardiomyopathy patients experience VA events and require AHF therapies decades earlier than either *TTNtv*-mediated or idiopathic DCM. Thus, *RBM20*-cardiomyopathy is best described as an early onset form of A-DCM/ALVC and therefore more aggressive screening of younger *RBM20* variant-positive, but currently phenotype-negative patients may be necessary.

Interestingly, previous studies looking at A-DCM genotypes (e.g., *LMNA*, *FLNC*) compared with a non-arrhythmogenic genotypes showed no difference in time to AHF events thus suggesting RBM20-cardiomyopathy is unique from other A-DCMs[21]. Mechanistic studies demonstrate that *RBM20* mutations result in altered *TTN* splicing contributing to the phenotype[11,22]; however, this alone would not explain earlier progression. *RBM20* mutations result in altered splicing of cardiac ion channel genes which could explain the increased arrhythmogenicity[6,10,11]. Altered splicing results in increased intracellular calcium[6] and may result in progression towards heart failure[23]. Although, there was no difference in pharmacologic therapy between *RBM20*-mediated cardiomyopathy and *TTNtv*-mediated cardiomyopathy, there was more rapid progression to heart failure and arrhythmic events suggesting a need for different therapeutic strategies. For instance, targeting calcium channels has shown promise in alleviating the arrhythmia burden in *RBM20* knockout mouse cardiomyocytes[6]. Recently, adenine base editing shows promise *in vito* and in vivo in treating *RBM20*-mediated DCM[24].

The role of sex in RBM20-cardiomyopathy remains undefined

One previous study suggested that males with *RBM20*-cardiomyopathy had a more severe phenotype with earlier time to a cardiovascular event than females[25]. Another study comparing sexes did not observe this in their *RBM20*-cardiomyopathy cohorts[26]. More recently a multi-center study found that males were more likely to progress to end-stage heart failure[20]. Our study found no differences between sexes. Clearly cohort composition impacts differences observed across groups and large sample sizes are necessary to ensure enough power to observe even small differences. Thus, there is a need for a meta-analysis of existing studies to determine whether sex influences the natural history of *RBM20*-mediated cardiomyopathy.

RBM20-cardiomyopathy is structurally similar to TTNtv-mediated cardiomyopathy

Since there are structural differences in DCM based on genotype, our study explored basic structural differences between *RBM20*- and *TTNtv*- positive individuals[27]. We found that *RBM20*-cardiomyopathy showed right ventricular involvement in only about 20% of cases like *TTNtv*-cardiomyopathy. Surprisingly, cardiac MRI findings were similar between both groups with no difference in proportion of patients with LGE or in LGE distribution despite LGE being associated with earlier ventricular arrhythmias and heart failure events in DCM[28]. This may add further credence to the theory that the arrhythmogenic mechanism in *RBM20* cardiomyopathy differ from other genetic causes of A-DCM (e.g. related to perturbed calcium handling rather than burden of myocardial fibrosis). Thus, further studies are necessary to identify if certain imaging or electrocardiographic findings can be predictive of the increased risk observed in *RBM20*-mediated cardiomyopathy.

Limitations

This retrospective single-center study has an inherent referral bias as the cohort is from a specialty genetic cardiomyopathy clinic. However, both *TTNtv* and RBM20 cohorts were derived from the same center allowing a valid comparison between genotypes. Only10 months elapsed between the release of the 2022 AHA/ACC/HFSA guidelines and the cessation of data collection for this study, so the uptake of new medication recommendations do not yet reflect the guidelines. As a single-center study the sample size for some of the subgroup analyses especially comparing between missense and truncating variants is underpowered and larger studies are necessary. Of note, the idiopathic DCM patients included in this study were largely evaluated during an era when genetic testing was recommended only for cases with a personal history of conduction disease and/or a family history of sudden cardiac death/cardiomyopathy. Although all idiopathic DCM patients included did not have a personal history of high-grade/complete atrioventricular block or a family history of sudden cardiac death/cardiomyopathy, genetic testing was not performed in all cases due to the guidelines in place at the time their evaluation.

Conclusion

RBM20-mediated cardiomyopathy represents a penetrant form of arrhythmogenic dilated cardiomyopathy characterized by an early onset ventricular arrhythmias and more rapid progression towards advanced heart failure therapies in comparison to *TTNtv*-mediated and idiopathic dilated cardiomyopathies. Further large cohort studies are necessary to identify risk factors for increased arrhythmogenicity such as imaging findings or type of mutation and mechanistic studies are necessary to develop novel therapeutics.

Methods

Cohort selection and data abstraction

The Mayo Clinic Institutional Review Board approved this minimal risk retrospective study and waived the requirement for consent. The study was conducted in accordance with the tenets in the Declaration of Helsinki. Retrospective analysis was performed on 445 patients in the Genetic Arrhythmogenic Cardiomyopathy (ACM) Registry to identify those with ultra-rare *RBM20* missense or truncating variant or *TTN* truncating variant

(TTNtv) who were seen from January 1, 2002 to May 11, 2023. Genetic variants were identified using clinical genetic testing and variants with a minor allele frequency less than 0.004% were considered ultra-rare. In addition, patients seen from January 1, 2002 to February 8, 2023 diagnosed with idiopathic, non-ischemic DCM were included as a comparator group. To avoid patients with familial DCM who might not have received genetic testing, any patient with a family history of SCD or cardiomyopathy was excluded from the idiopathic, non-ischemic DCM cohort. Supplemental Table 7 summarizes the values for each cohort also present in the main figures. Supplemental Table 8 summarizes all the identified genetic variants.

For the purposes of this study, a ventricular arrhythmia (VA) event was defined as sustained VA, sudden cardiac arrest (SCA), or an appropriate ventricular tachycardia (VT)/ventricular fibrillation (VF)-terminating implantable cardioverter defibrillator (ICD) shock and an advanced heart failure (AHF) event was defined as ventricular assist device implantation, heart transplantation, or cardiac death. Medication information was pulled from last appointment. Any individual with evidence of left ventricular dilation, reduced ejection fraction (≤ 50%), VA events, or AHF events were considered to have a cardiac phenotype.

Statistics and data analysis

Figures were generated and statistical analysis performed using GraphPad Prism. For categorical variables Chi-squared tests and Fisher's exact tests were used when applicable. Continuous variables were compared using two-tailed two-sample t-Tests. Time-to-event analysis were performed in R (4.1.3) using the Survival package to generate Kaplan–Meier curves with log-rank testing. Restricted mean survival times were calculated using the survRM2 package. A multiple logistic regression model was developed in GraphPad Prism to account for sex differences and differences in follow-up time when necessary.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Received: 7 March 2024; Accepted: 19 March 2025
Published online: 28 March 2025

References

1. Lund, L. H. et al. The Registry of the international society for heart and lung transplantation: Thirtieth official adult heart transplant report–2013; focus theme: age. *J. Heart Lung Transpl.* **32**, 951–964 (2013).
2. Reichart, D., Magnussen, C., Zeller, T. & Blankenberg, S. Dilated cardiomyopathy: from epidemiologic to genetic phenotypes: A translational review of current literature. *J. Intern. Med.* **286**, 362–372 (2019).
3. Felker, G. M. et al. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. *N. Engl. J. Med.* **342**, 1077–1084 (2000).
4. Njoroge, J. N., Mangena, J. C., Aribeana, C. & Parikh, V. N. Emerging genotype-phenotype associations in dilated cardiomyopathy. *Curr. Cardiol. Rep.* **24**, 1077–1084 (2022).
5. Begay, R. L. et al. Filamin C truncation mutations are associated with arrhythmogenic dilated cardiomyopathy and changes in the cell-cell adhesion structures. *JACC Clin. Electrophysiol.* **4**, 504–514 (2018).
6. van den Hoogenhof, M. M. G. et al. RBM20 mutations induce an arrhythmogenic dilated cardiomyopathy related to disturbed calcium handling. *Circulation* **138**, 1330–1342 (2018).
7. Parikh, V. N. et al. Regional variation in RBM20 causes a highly penetrant arrhythmogenic cardiomyopathy. *Circ. Heart Fail.* **12**, e005371 (2019).
8. Kumar, S. et al. Long-term arrhythmic and nonarrhythmic outcomes of lamin A/C mutation carriers. *J. Am. Coll. Cardiol.* **68**, 2299–2307 (2016).
9. Li, S., Guo, W., Dewey, C. N. & Greaser, M. L. Rbm20 regulates titin alternative splicing as a splicing repressor. *Nucleic Acids Res.* **41**, 2659–2672 (2013).
10. Maatz, H. et al. RNA-binding protein RBM20 represses splicing to orchestrate cardiac pre-mRNA processing. *J. Clin. Invest.* **124**, 3419–3430 (2014).
11. Guo, W. et al. RBM20, a gene for hereditary cardiomyopathy, regulates titin splicing. *Nat. Med.* **18**, 766–773 (2012).
12. Brauch, K. M. et al. Mutations in ribonucleic acid binding protein gene cause familial dilated cardiomyopathy. *J. Am. Coll. Cardiol.* **54**, 930–941 (2009).
13. Ihara, K. et al. A missense mutation in the RSRSP stretch of Rbm20 causes dilated cardiomyopathy and atrial fibrillation in mice. *Sci. Rep.* **10**, 17894 (2020).
14. Kayvanpour, E. et al. Genotype-phenotype associations in dilated cardiomyopathy: meta-analysis on more than 8000 individuals. *Clin. Res. Cardiol. Off. J. German Cardiac Soc.* **106**, 127–139 (2017).
15. Tayal, U. et al. Phenotype and clinical outcomes of titin cardiomyopathy. *J. Am. Coll. Cardiol.* **70**, 2264–2274 (2017).
16. Akhtar, M. M. et al. Clinical phenotypes and prognosis of dilated cardiomyopathy caused by truncating variants in the TTN gene. *Circ. Heart Fail.* **13**, e006832 (2020).
17. Sammani, A. et al. Predicting sustained ventricular arrhythmias in dilated cardiomyopathy: a meta-analysis and systematic review. *ESC Heart Fail.* **7**, 1430–1441 (2020).
18. Wilde, A. A. M. et al. European heart rhythm association (EHRA)/heart rhythm society (HRS)/Asia pacific heart rhythm society (APHRS)/Latin American heart rhythm society (LAHRS) expert consensus statement on the state of genetic testing for cardiac diseases. *Eur. Eur. Pac. Arrhythm. Cardiac Electrophysiol. J. Work. Groups Cardiac Pac. Arrhythm. Cardiac Cell. Electrophysiol. Eur. Soc. Cardiol.* **24**, 1307–1367 (2022).
19. Towbin, J. A. et al. 2019 HRS expert consensus statement on evaluation, risk stratification, and management of arrhythmogenic cardiomyopathy. *Heart Rhythm* **16**, e301–e372 (2019).
20. Cannie, D. E. et al. Risks of ventricular arrhythmia and heart failure in carriers of RBM20 variants. *Circ. Genom. Precis. Med.* **16**, e004059 (2023).
21. Spezzacatene, A. et al. Arrhythmogenic phenotype in dilated cardiomyopathy: Natural history and predictors of life-threatening arrhythmias. *J. Am. Heart Assoc.* **4**, e002149 (2015).
22. Beqqali, A. et al. A mutation in the glutamate-rich region of RNA-binding motif protein 20 causes dilated cardiomyopathy through missplicing of titin and impaired Frank-Starling mechanism. *Cardiovasc. Res.* **112**, 452–463 (2016).
23. MacLeod, K. T. Changes in cellular Ca(2+) and Na(+) regulation during the progression towards heart failure. *J. Physiol.* https://doi.org/10.1113/JP283082 (2022).

24. Nishiyama, T. et al. Precise genomic editing of pathogenic mutations in RBM20 rescues dilated cardiomyopathy. *Sci. Transl. Med.* https://doi.org/10.1126/scitranslmed.ade1633 (2022).
25. Hey, T. M. et al. Pathogenic RBM20-variants are associated with a severe disease expression in male patients with dilated cardiomyopathy. *Circ. Heart Fail.* **12**, e005700 (2019).
26. Lennermann, D. C. et al. Deep phenotyping of two preclinical mouse models and a cohort of RBM20 mutation carriers reveals no sex-dependent disease severity in RBM20 cardiomyopathy. *Am. J. Physiol. Heart Circ. Physiol.* **323**, H1296-h1310 (2022).
27. Smith, E. D. et al. Desmoplakin cardiomyopathy, a fibrotic and inflammatory form of cardiomyopathy distinct from typical dilated or arrhythmogenic right ventricular cardiomyopathy. *Circulation* **141**, 1872–1884 (2020).
28. Mirelis, J. G. et al. Combination of late gadolinium enhancement and genotype improves prediction of prognosis in non-ischaemic dilated cardiomyopathy. *Eur. J. Heart Fail.* **24**, 1183–1196 (2022).

Acknowledgements
RG was supported by the National Institute of General Medical Sciences (T32 GM 65841).

Author contributions
RG, MJA, and JG conception and design; RG, MC, and RN data collection and assembly; RG data analysis and interpretation; RG manuscript writing; RG, MC, RN, NLP, CM, JWS, JRG, and MJA final manuscript approval.

Declarations

Competing interests
MJA is a consultant for Abbott, Boston Scientific, Bristol Myers Squibb, Daiichi Sankyo, Invitae, Medtronic, Tenaya Therapeutics, and UpToDate. MJA and Mayo Clinic have a royalty/equity relationship with AliveCor, Anumana, ARMGO Pharma, Pfizer, and Thryv Therapeutics. JRG is a consultant for Avidity Biosciences and serves as the principal investigator for clinical trials sponsored by Tenaya Therapeutics. However, none of these entities have contributed to this study in any manner. RG, MC, RN, NLP, CM, and JWS have no conflicts to declare.

Additional information
Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-025-95409-9.

Correspondence and requests for materials should be addressed to J.R.G.