Rare desmin variant causing penetrant life-threatening arrhythmic cardiomyopathy

Ad W.G.J. Oomen, MD,* Katherine Jones, BSc, BTeach,† Laura Yeates, BSc GDipGC,†‡ Christopher Semsarian, MBBS, PhD, MPH, FHRS,*†‡ Jodie Ingles, MPH, PhD,†‡ Raymond W. Sy, MBBS, PhD, FHRS*‡

*From the *Department of Cardiology, Royal Prince Alfred Hospital, Camperdown, Australia, †Agnes Ginges Centre for Molecular Cardiology, Centenary Institute, Camperdown, Australia, and ‡Sydney Medical School, University of Sydney, Camperdown, Australia.*

Introduction

Desmin-related myopathy (DRM) is a rare condition characterized by skeletal muscle weakness with frequent cardiac involvement because of abnormalities of desmin, which is the main component of intermediate filament protein expressed in skeletal, cardiac, and smooth muscle. The clinical manifestations of DRM have been reported to be highly variable. The present article highlights a specific desmin variant (*DES*, c.1360C>T; p.Arg454Trp) in 2 unrelated cases, which is highly penetrant, portends poor prognosis, and warrants careful electrophysiological evaluation.

Case reports

Case 1

The first patient was a Southeast Asian woman who presented at the age of 18 years for the investigation of palpitations. Holter monitoring showed frequent premature ventricular complexes (800 over 24 hours). Her echocardiogram was normal, and she was managed conservatively. At the age of 24 years, she presented with fatigue and had complete atrioventricular block (Figure 1A). A dual-chamber pacemaker was implanted.

The patient then presented at the age of 30 years with sudden collapse; she was successfully defibrillated, and interrogation of her pacemaker confirmed ventricular fibrillation (Figures 1B and 1C). The arrhythmia was not pause-dependent, and her pacemaker was functioning normally. Her echocardiogram, computed tomography scan, and positron emission tomography scan were normal. There was no family history of premature sudden death or syncope. Her pacemaker was upgraded to an implantable cardioverter-defibrillator (ICD).

Whole exome sequencing filtering for rare variants (allele frequency <0.001) in 174 cardiac genes revealed a heterozygous missense variant in *DES* (NM_001927.3: c.1360C>T; p.Arg454Trp), which was classified as likely pathogenic. There was also a missense variant in *KCNH2* of uncertain significance, *KCNH2* (NM_000238.3: c.1982C>T; p.Ala661Val). To date, all other family members have declined genetic testing. Although the proband denied overt neurological symptoms, subsequent neurological examination revealed mild peripheral weakness. No further arrhythmias have been detected, and her left ventricular function has remained preserved over a 30-month follow-up.

Case 2

The second patient was a Caucasian man who presented at the age of 17 years with fatigue and exertional dyspnea. A year later, he had 2 seizures that were initially thought to be due to epilepsy. At the age of 20 years, he presented with further seizures and was found to have complete heart block (Figure 2). His echocardiogram showed mild concentric left ventricular hypertrophy with preserved systolic function. A diagnosis of hypertrophic cardiomyopathy was considered, and a dual-chamber pacemaker was implanted. During follow-up of the pacemaker, several episodes of VT were recorded and the pacemaker was upgraded to an ICD. His left ventricular function progressively deteriorated, and he underwent cardiac transplantation at the age of 24 years. The pathology of the excised heart demonstrated biventricular cardiomyopathy with areas of fibrosis, myocyte disarray with anisonucleosis, and dysplastic changes in intramyocardial arteries. The left ventricular wall thickness was 15–20 mm.

Genetic testing (using a commercial 65-gene "cardiomyopathy panel") revealed a missense variant in the *DES* gene (NM_001927.3: c.1360C>T; p.Arg454Trp). No other pathogenic variants were identified. There was no family history

KEYWORDS Cardiomyopathy; Desmin; Heart block; Heart failure; Ventricular arrhythmia
(Heart Rhythm Case Reports 2018;4:318–323)

Dr Semsarian and Dr Ingles are recipients of the National Health and Medical Research Council Fellowship (fellowship no. #1059156) and the National Heart Foundation of Australia Fellowship (fellowship no. #100833), respectively. **Address reprint requests and correspondence:** Dr Raymond W. Sy, Department of Cardiology, Royal Prince Alfred Hospital, Camperdown 2050, Australia. E-mail address: raymond.sy01@gmail.com.

https://doi.org/10.1016/j.hrcr.2018.04.007

KEY TEACHING POINTS

- Desmin-related myopathy (DRM) is characterized by skeletal muscle weakness with frequent cardiac involvement. The clinical manifestations of DRM are variable.
- The desmin variant (*DES*, c.1360C>T; p.Arg454Trp) is highly penetrant and is associated with an accelerated and severe cardiac phenotype with a high incidence of ventricular arrhythmias, progressive cardiomyopathy, and death.
- Genetic testing should be considered in patients with early-onset atrioventricular conduction disease with or without cardiomyopathy.
- Urgent electrophysiological intervention and early referral for transplantation evaluation may improve outcomes in patients with this specific desmin variant.

of heart disease or premature sudden death. Cascade genetic testing of his parents was negative, suggesting a de novo event. At the age of 31 years, he reported increasing skeletal muscle weakness. Neurological investigations confirmed peripheral myopathy. He has remained well since the transplant, although his muscle weakness has slowly progressed.

Discussion

DRM is rare inherited skeletal and cardiac myopathy that was first described in 1998 by Goldfarb et al[1] and Muñoz-Mármol et al.[2] It is usually due to mutations in the *DES* gene, although it may be infrequently caused by mutations in the alpha-B crystallin gene (*CRYAB*).[3] DRM is usually inherited in an autosomal-dominant pattern, but de novo mutations have been described.

Desmin is located at the Z lines where it connects the intermediate filament to the sarcolemmal membrane and nuclei (Figure 3A). Desmin plays an important role in maintaining muscle cell integrity and stability. It is also involved in mitochondrial function and positioning. Desmin is more abundant in cardiac muscle than in skeletal muscle, and it is highly expressed in the Purkinje system.[4]

The *DES* gene is localized to chromosome 2q35 and consists of 9 exons spanning 8.4 kb. The mature protein consists of 470 amino acids that assemble into a head, alpha-helical rod, and tail domain.

Currently more than 50 *DES* mutations have been identified.

Although the exact pathophysiological mechanism is not fully understood, it is hypothesized that abnormal desmin function increases the susceptibility of muscle fibers to degeneration, especially after repetitive strain.[5] Mutations in *DES* alter the intrinsic biophysical properties of the filament itself and/or its ability to bind with other cytoskeletal proteins.[6,7] *DES* mutations have also been associated with mitochondrial dysfunction and abnormalities in the intercalated disc.

DRM is characterized by progressive skeletal muscle weakness, cardiomyopathy, and cardiac conduction disease. Clinical presentation, onset, and rate of progression are highly variable. The first symptom of the disease is usually muscle weaknesses with onset in the second or fourth decade of life. Distal weakness and atrophy of the lower extremities is typical. As disease progresses, the upper extremities, proximal leg, and the trunk muscles may also become affected.

Cardiac involvement is reported in up to 70% of patients. Cardiomyopathy, arrhythmias, and conduction disturbances can be observed in varying degrees and can occur independently of each other with inter- and intrafamilial variability. Different phenotypes of cardiomyopathy related to DRM have been described, including dilated, restrictive, and hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy.[3,8–10] In general, conduction system disease coincides with cardiomyopathy but it has also been reported in patients without overt cardiomyopathy.[3]

In a recent review of DRM, van Spaendonck-Zwarts et al[3] reported that the onset of cardiac disease occurred at a mean age of 35 years. Patients with isolated cardiac disease were more likely to harbor mutations in the head or tail domains of the *DES* gene. Atrioventricular block and ventricular arrhythmia were observed in 30% and 5% of *DES* mutation carriers, respectively. Cardiomyopathy was observed in 49% of carriers. Cardiac transplantation was performed in 4%, and ICD implantation in 4% of carriers. Death was reported in 26% of carriers at a mean age of 49 years. Specifically, sudden cardiac death was observed in 4% and death from heart failure was observed in 8% of carriers.

The specific variant *DES* c.1360C>T; p.Arg454Trp is located in the carboxy-terminal "tail" domain (Figure 3B). In vitro studies have suggested that it has deleterious effects on the myoblast cytoskeleton with diminished biomechanical properties and altered myocyte metabolism.[11] Immunohistochemistry of myocardial tissue showed that the variant was associated with abnormalities in the intercalated disc, with absence of desmin, and with reduced expression of desmoplakin, plakophilin 2, and connexin 43.[10]

The variant is absent from the Exome Aggregation Consortium and Genome Aggregation databases, and a literature review yielded 8 other characterized cases of the same variant described in 4 publications.[10–13] It was also included in a compendium of mutations in patients with myopathy in 2 other articles but individual phenotypic information was not available.[14,15] The presentation of the patients is summarized in Table 1. Patients presented at a mean age of 17 ± 4 years, and 70% were male patients. Complete atrioventricular block was observed in 80% of patients during follow-up. Ventricular arrhythmias requiring ICD implantation was observed in 30%. Progressive left ventricular impairment occurred in 80% of patients. A combined end point of ICD implantation, transplantation, or cardiac death

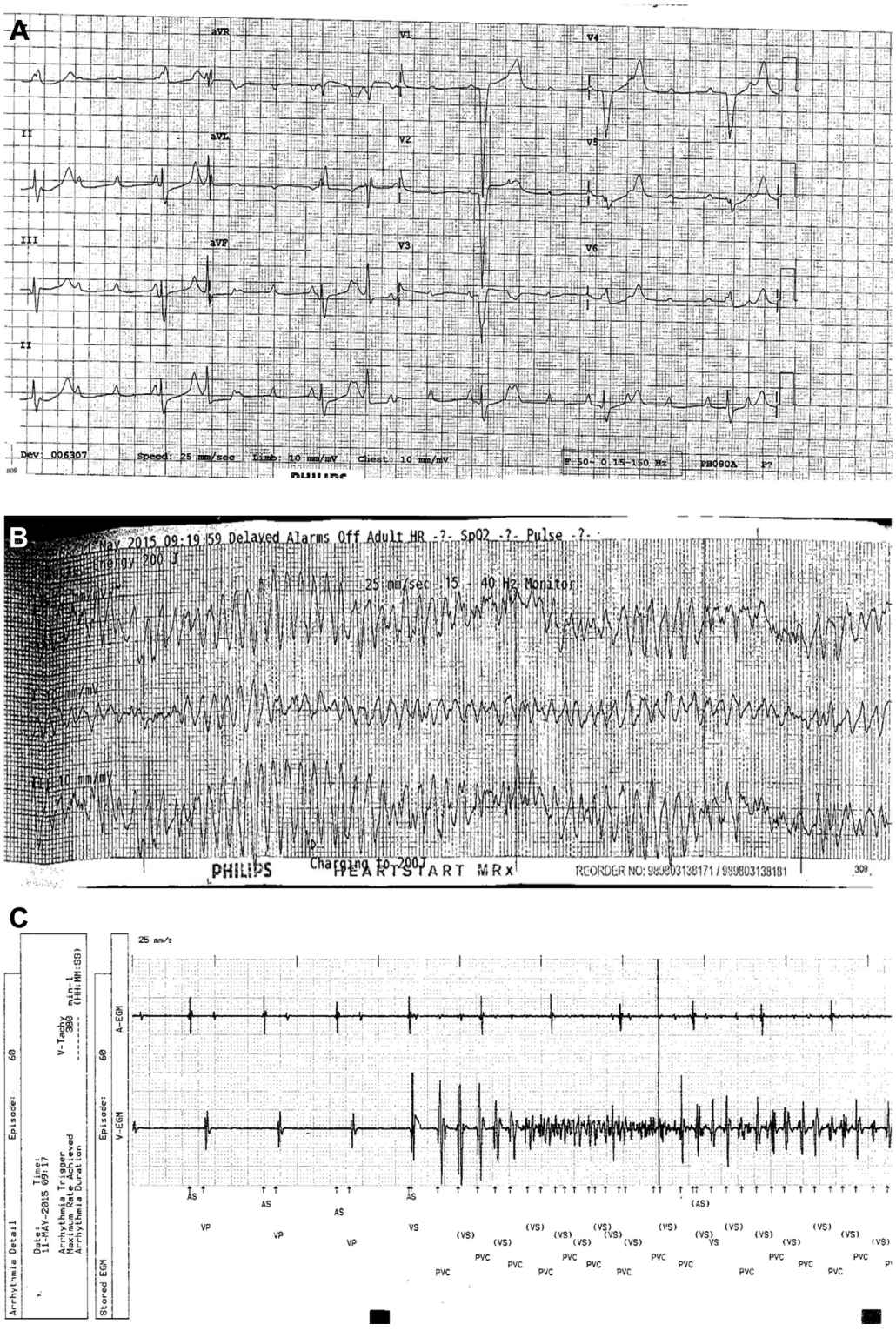

Figure 1 **A:** Twelve-lead electrocardiogram showing complete atrioventricular block. **B:** Monitor strip from an external defibrillator showing ventricular fibrillation. **C:** Pacemaker interrogation showing onset of ventricular fibrillation. AS = atrial sensed event; PVC = premature ventricular contraction; VP = ventricular paced event; VS = ventricular sensed event.

was observed in 80% of patients at a mean age of 27 ± 3 years.

Compared to other cases of DRM, this specific *DES* variant identifies a subgroup of patients that have an earlier onset of disease (typically before the age of 20 years) with a very severe cardiac phenotype. The variant appears highly penetrant, with the majority of patients developing heart block at an early age, followed by progressive heart failure necessitating ICD implantation and cardiac transplantation. In fact, 80% of patients with this specific *DES* variant

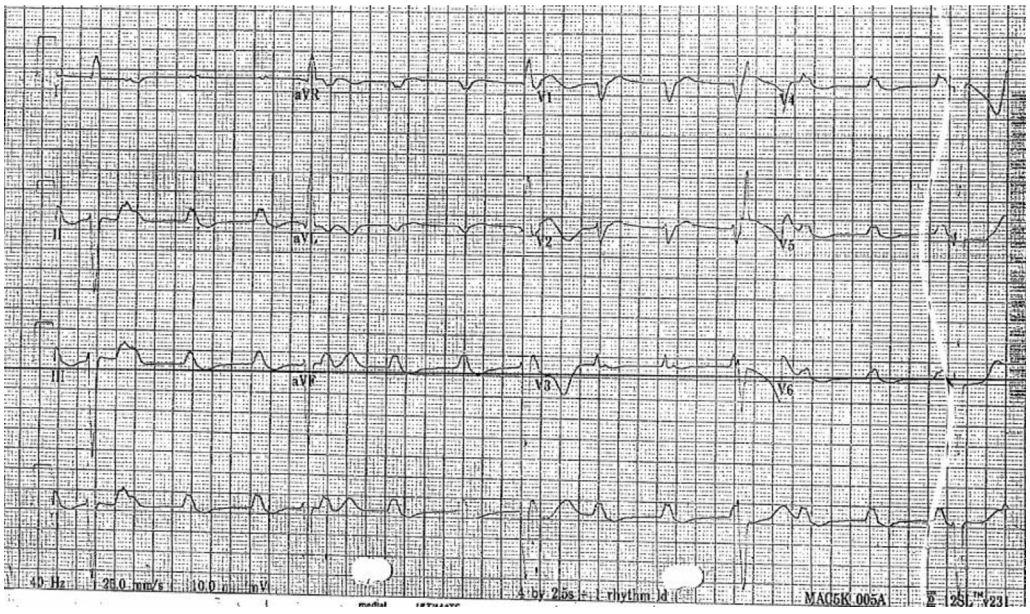

Figure 2 Twelve-lead electrocardiogram showing complete atrioventricular block.

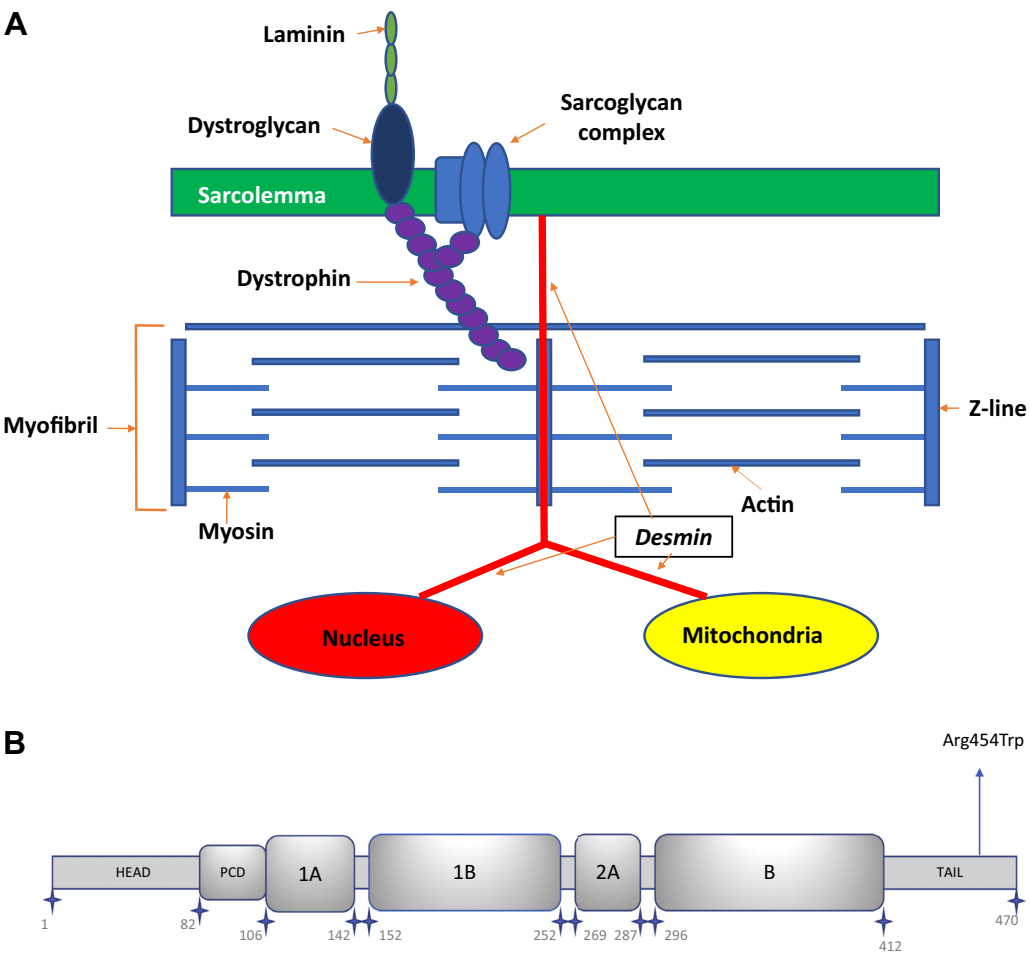

Figure 3 **A:** Schematic representation of desmin in relation to other proteins involved in the cytoarchitecture of the myocyte. **B:** Protein structure of desmin showing precoil domain (PCD) and rod domains. The Arg454Trp causative variant is highlighted in the tail region.

Table 1 Summary of patients with *DES* c.1360C>T; p.Arg454Trp

Case no.	Sex	Age of onset (y)	Arrhythmic manifestations					Cardiomyopathic manifestations		Cardiac death/transplant	Neurological manifestations
			CHB	PM	VA	ICD	Other	Phenotype	LV impairment		
1	Female	18	+ (24)	+ (24)	VF (30)	+ (30)	PVC (18)	Nil	–	No	Subtle peripheral weakness
2	Male	17	+ (20)	+ (20)	VT (22)	+ (22)	–	Hypertrophic	+ (20s)	Transplant (24)	Distal myopathy
3[11]	Male	15	–	–	–	–	–	Hypertrophic	+ (20s)	Transplant (25)	Distal myopathy Dysphonia Bilateral ptosis Weak facial muscles
4[10]	Female	9	+ (9)	+ (19)	–	–	–	Nil	+ (20s)	Death from CCF (28)	Nil
5[10]	Male	17	+ (17)	+ (19)	–	–	AF (24)	Nil	+ (20s)	Death from CCF (27)	Nil
6[10]	Male	19	+ (20)	+ (21)	–	–	–	Nil	+ (19)	Death from CCF and PE (31)	Nil
7[12]	Male	19	–	–	–	–	–	Hypertrophic	+ (19)	Transplant	Nil
8[12]	Male	24	+	+	VT	+	–	Restrictive	+	No	Nil
9[13]	Male	NK	+ (39)	+ (39)	–	–	–	Nil	+	No	Distal weakness
10[13]	Female	NK	+ (36)	+ (36)	–	–	–	Nil	–	No	Distal weakness

The age of onset is given in parentheses.
+ = present; – = absent; AF = atrial fibrillation; CCF = congestive cardiac failure; CHB = complete heart block; ICD = implantable cardioverter-defibrillator; LV = left ventricular; NK = nil known; PE = pulmonary embolism; PM = pacemaker; PVC = premature ventricular complex; VA = ventricular arrhythmia; VF = ventricular fibrillation; VT = ventricular tachycardia.

required ICD implantation or cardiac transplantation or died within the first 10–20 years of diagnosis. Neurological symptoms were typically absent or mild at the onset of disease. Although other clinical and genetic factors may further modulate phenotype expression, this variant is a highly penetrant cause of DRM on the basis of clinical and experimental data.

Conclusion

Genetic testing should be considered in patients with early-onset atrioventricular conduction disease with or without cardiomyopathy. The testing should include *DES* as well as other recognized genes such as *LMNA* and *SCN5A*. Identification of a pathogenic variant facilitates family screening and clinical management. Specifically, the *DES* variant c.1360C>T; p.Arg454Trp should be a "red flag" for clinicians, as it is associated with an accelerated and severe cardiac phenotype with a high incidence of ventricular arrhythmias, progressive cardiomyopathy, and death. As illustrated by the present cases, implantation of an ICD rather than a pacemaker in the setting of heart block as well as early referral to a transplantation center may potentially improve outcomes in patients with this specific desmin variant.

Acknowledgments

We acknowledge the assistance of Professor Peter Macdonald and Dr Yemima Berman for providing clinical information for the study.

References

1. Goldfarb LG, Park KY, Cervenáková L, Gorokhova S, Lee HS, Vasconcelos O, Nagle JW, Semino-Mora C, Sivakumar K, Dalakas MC. Missense mutations in desmin associated with familial cardiac and skeletal myopathy. Nat Genet 1998;194:402–403.
2. Muñoz-Mármol AM, Strasser G, Isamat M, et al. A dysfunctional desmin mutation in a patient with severe generalized myopathy. Proc Natl Acad Sci U S A 1998;95:11312–11317.
3. van Spaendonck-Zwarts KY, van Hessem L, Jongbloed JDH, de Walle HE, Capetanaki Y, van der Kooi AJ, van Langen IM, van den Berg MP, van Tintelen JP. Desmin-related myopathy. Clin Genet 2011;80:354–366.
4. Lazarides E. Intermediate filaments as mechanical integrators of cellular space. Nature 1980;283:249–256.
5. Paulin D, Li Z. Desmin: a major intermediate filament protein essential for the structural integrity and function of muscle. Exp Cell Res 2004;301:1–7.
6. Sharma S, Mucke N, Katus HA, Herrmann H, Bär H. Disease mutations in the "head" domain of the extra-sarcomeric protein desmin distinctly alter its assembly and network-forming properties. J Mol Med 2009; 87:1207–1219.
7. Liu J, Tang M, Mestril R, Wang X. Aberrant protein aggregation is essential for a mutant desmin to impair the proteolytic function of the ubiquitin-proteasome system in cardiomyocytes. J Mol Cell Cardiol 2006;40:451–454.
8. Bergman JEH, Veenstra-Knol HE, Van Essen AJ, van Ravenswaaij CM, den Dunnen WF, van den Wijngaard A, van Tintelen JP. Two related Dutch families with a clinically variable presentation of cardioskeletal myopathy caused by a novel S13F mutation in the desmin gene. Eur J Med Genet 2007;50:355–366.
9. Van Tintelen JP, Van Gelder IC, Asimaki A, et al. Severe cardiac phenotype with right ventricular predominance in a large cohort of patients with a single missense mutation in the *DES* gene. Heart Rhythm 2009;6:1574–1583.
10. Otten E, Asimaki A, Maass A, van Langen IM, van der Wal A, de Jonge N, van den Berg MP, Saffitz JE, Wilde AA, Jongbloed JD, van Tintelen JP. Desmin mutations as a cause of right ventricular heart failure affect the intercalated disks. Heart Rhythm 2010;7:1058–1064.
11. Bär H, Goudeau B, Wälde S, et al. Conspicuous involvement of Desmin tail mutations in diverse cardiac and skeletal myopathies. Hum Mutat 2007;28:374–386.

12. Wahbi K, Béhin A, Charron P, Dunand M, Richard P, Meune C, Vicart P, Laforêt P, Stojkovic T, Bécane HM, Kuntzer T, Duboc D. High cardiovascular morbidity and mortality in myofibrillar myopathies due to *DES* gene mutations: a 10-year longitudinal study. Neuromuscul Disord 2012;22:211–218.
13. Weihl C, Iyadurai S, Baloh R, Pittman SK, Schmidt RE, Lopate G, Pestronk A, Harms MB. Autophagic vacuolar pathology in desminopathies. Neuromuscul Disord 2015;25:199–206.
14. Vattemi G, Neri M, Piffer S, Vicart P, Gualandi F, Marini M, Guglielmi V, Filosto M, Tonin P, Ferlini A, Tomelleri G. Clinical, morphological and genetic studies in a cohort of 21 patients with myofibrillar myopathy. Acta Myol 2011; 30:121–126.
15. Punetha J, Kesari A, Uapinyoying P, et al. Targeted re-sequencing emulsion PCR panel for myopathies: results in 94 cases. J Neuromuscul Dis 2016; 3:209–225.