VIA MEDICA
REVIEW ARTICLE
2014, Vol. 21, No. 4, pp. 331–342
DOI: 10.5603/CJ.a2014.0037

ISSN 1897–5593

Lamin A/C mutations in dilated cardiomyopathy

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Abstract

Dilated cardiomyopathy (DCM) is one of the leading causes of heart failure and heart transplant. Mutations in 60 genes have been associated with DCM. Approximately 6% of all DCM cases are caused by mutations in the lamin A/C gene (LMNA). LMNA codes for type-V intermediate filaments that support the structure of the nuclear membrane and are involved in chromatin structure and gene expression. Most LMNA mutations result in striated muscle diseases while the rest affects the adipose tissue, peripheral nervous system, multiple tissues or lead to progeroid syndromes/overlapping syndromes. Patients with LMNA mutations exhibit a variety of cellular and physiological phenotypes. This paper explores the current phenotypes observed in LMNA-caused DCM, the results and implications of the cellular and animal models of DCM and the prevailing theories on the pathogenesis of laminopathies. (Cardiol J 2014; 21, 4: 331–342)

Key words: genetics, dilated cardiomyopathy, LMNA

Introduction

Dilated cardiomyopathy (DCM) is a disease of the heart muscle characterized by the dilatation of the left or both ventricles and reduced systolic function in the absence of abnormal loading conditions (hypertension, valve disease) or coronary artery disease (CAD) sufficient to cause global systolic impairment [1]. DCM is a significant health concern. It is the third most frequent cause of heart failure in the United States after CAD and hypertension [2]. Furthermore, DCM is also a primary indication for heart transplantation [2] and is marked by considerable morbidity as well as mortality. It is believed that 20% to 50% of idiopathic dilated cardiomyopathy (IDC) cases have familial causation [3, 4]. So far, more than 60 genes including the lamin A/C gene (LMNA) have been associated with DCM. The pattern of the disease inheritance is mostly autosomal dominant [4]. Despite recent technological progress that makes gene screening both less time-consuming and cost-efficient, genetic screening currently reveals that only 30–35% of familial DCM follow the Mendelian model of disease inheritance [5], while the remaining have a more complex multi-variant origin, which also encompasses the non-rare variants. In majority of the cases, incomplete age-related penetrance is observed [6–8]. It was reported that 7% of LMNA mutation carriers exhibit cardiac-related phenotypes if under 20 years of age, 66% when carriers are between 20 and 39 years, 86% when carriers are between 40 and 59 years, and 100% when carriers are over 60 years of age [6]. Another complicating factor that clouds the genetic diagnosis is the variability of expression within one phenotype. While some mutation carriers may develop all the symptoms of the disease, other family

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Received: 28.07.2013 Accepted: 10.04.2014

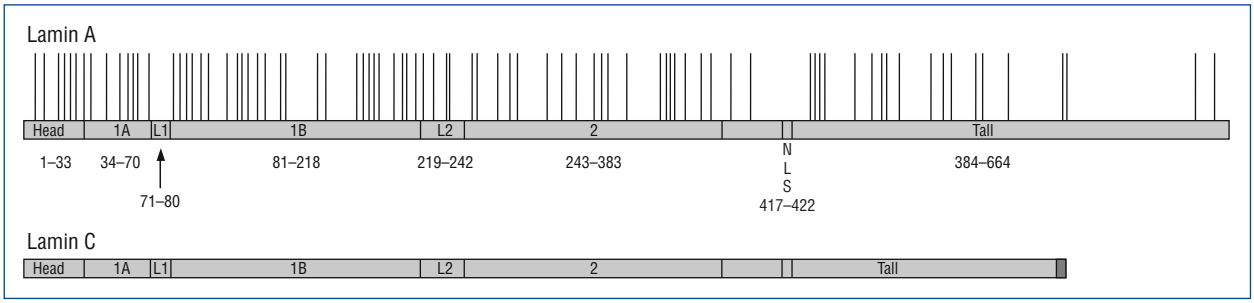

Figure 1. Protein map of lamin A and lamin C with currently known mutations of both transcripts plotted onto lamin A protein; NLS — nuclear localization signal. Dark shaded area at the C-terminal of lamin C represents lamin C-unique sequence.

members carrying the mutation exhibit only some aspects of it and may remain with a subclinical form of the disease. The onset of DCM can vary greatly as can the severity and the rate of progression of the disease. The variability may also pertain to the range of phenotypes such as in the case of 960delT LMNA mutation, which presented with 3 differing phenotypes within 1 family: pure DCM, DCM with Emery-Dreifuss muscular dystrophy (EDMD)-like symptoms and DCM with limb girdle muscular dystrophy (LGMD)-like symptoms [9].

Mutations in LMNA were first identified in a family with EDMD in 1999 [10]. In the same year, the association between LMNA mutations and DCM was reported [11]. Since then, an ever--growing number of mutations in LMNA have been identified defining a group of diseases called laminopathies. Laminopathies can be divided according to the observed phenotype. Most LMNA mutations have been associated with striated muscle diseases (79.1%), followed by adipose tissue (8.6%) and peripheral nervous tissue disorders (0.3%). 9.3% of LMNA mutations lead to progeroid syndromes while 10.9% cause overlapping syndromes with multiple tissue involvement [12].

Table 1 encompasses the most current list of LMNA mutations that lead to DCM, either isolated, with sole cardiac features or as a part of diagnosis of other, more complex conditions commonly affecting skeletal muscle such as EDMD or LGMD, but also encompassing other tissues which for instance leads to Charcot-Marie-Tooth disease, familial partial lipodystrophy, general lipodystrophy, hypogonadism, Hutchinson-Gilford progeria syndrome or diabetes mellitus. Table 1 also summarizes the span of phenotypic traits reported to be associated with a given mutation. It was created by combining information from four main LMNA mutation databases: the Human Intermediate Filament Database [13], the Leiden Muscular Dystrophy website (www.dmd.nl), the HGMD® Professional 2012.4, the Universal Mutation Database (www.umd.be/LMNA/) and from the literature. We were able to find 165 LMNA mutations leading to DCM (Fig. 1).

LMNA gene encodes the A-type lamins which are involved in maintaining the structural integrity of the nucleus, chromatin organization and gene expression [14]. LMNA is composed of 12 exons and encodes lamin A and lamin C by alternative splicing in exon 10 [15]. Both lamin isoforms are identical for the first 566 amino acids after which lamin C contains a unique sequence of 5 basic amino acids while amino acids from 567 to 664 are unique to lamin A [15]. In addition, prelamin A contains a CaaX motif at the COOH-terminal, which undergoes posttranslational modifications [15]. Lamins are divided into 3 domains: a short globular head, an α-helical rod and a globular tail. The rod domain comprises several coiled-coil domains separated by linker regions which are evolutionarily highly conserved (Fig. 1) [16].

Most lamin mutations leading to DCM are found in the head and rod domains covering more than half of lamin A and two-thirds of lamin C. DCM mutations are rarely found in the tail domain which contains many phosphorylation sites as opposed to mutations linked to EDMD, familial partial lipodystrophy and Hutchinson-Gilford progeria syndrome ([13]; Human Genome Mutation Database). However, hot spot(s) for DCM or other diseases affecting the striated muscle cannot be identified. Conversely, in adipose tissue defects, approximately 80% of cases carry a substitution of the p.Arg482 residue while 85% of mandibuloacral dysplasia cases are caused by a homozygous mutation at the p.527 residue and 77% of HGPS patients carry the c.1827C>T substitution within exon 11 [16].

Studies of cellular phenotypes associated with LMNA mutations

DCM patients with LMNA mutations display highly variable cardiomyocyte phenotype. A DCM patient encompassing exons 3–12 deletion showed diminished lamin A and C staining in the endomyocardial biopsy with discontinuous nuclear envelopes and invasion of mitochondria into the nuclear space [17]. Another DCM patient carrying a LMNA mutation displayed dramatic morphological alterations in approximately 30% of the cardiomyocyte's nuclei including a complete loss of the nuclear envelope [18]. However, other mutation carriers did not present with such dramatic abnormalities [17, 18]. Nevertheless, cardiomyocytes from DCM patients with LMNA mutations usually display reduced lamin A and C in the nuclei with nuclear membrane damage such as focal disruptions, blebs and nuclear pore clustering [19, 20].

Skin fibroblasts isolated from patients with cardiac-or-skeletal-specific laminopathies most often had abnormal nuclear shape including blebs and herniation [21]. Lamin A and C distribution were affected in these cells and were either present in a honeycomb pattern [21] or distributed unevenly along the inner nuclear lamina [22]. Some fibroblasts had lamin A and C aggregates close to the lamina which did not interact with emerin, DNA or RNA [23]. Patient tissue heart samples and skin fibroblasts provide a method to visualize the pathophysiology of disease-associated mutations; however, they are not easy to acquire. Currently, no specific therapy exists for patients with LMNA-related DCM. This has encouraged researchers to establish both mice and cellular models in an effort to elucidate the mechanisms leading to the disease phenotypes. Unraveling the molecular mechanisms might provide insights into the pathophysiology of this disease which could be translated into novel therapy in the future.

A *Lmna* null mouse based on genetrap technology has been developed [24]. The mouse is characterized by postnatal maturation defects of cardiac, muscle, and adipose tissues. Premature death occurred by 2–3 weeks of age. However, in this study, age matched heterozygous mice were indistinguishable from wild-type mice [24]. Only 1 study reported $Lmna^{+/-}$ mice with 50% of normal cardiac lamin A/C levels and displaying cardiac abnormalities [25]. The $Lmna^{H222P/H222P}$ mice harbouring the EDMD mutation developed muscular dystrophy and DCM with atrio-ventricular conduction defect at adulthood and died by 13 months of age [26]. Male $Lmna^{H222P/H222P}$ mice developed significant left ventricular dilatation and by 16 weeks of age had decreased ejection fraction [26]. In another study, $Lmna^{N195K/N195K}$ mice harboring a DCM with conduction system disease mutation, died at an early age due to arrhythmia. Surprisingly, both $Lmna^{H222P/+}$ and $Lmna^{N195K/+}$ mice were found to have a phenotype and life expectancy similar to the wild-type [26, 27]. Cells derived from both $Lmna^{-/-}$ and $Lmna^{N195K/N195K}$ mice were observed to have damaged and misshapen nuclei, showed increased fragility under mechanical strain and impaired gene transcription [27–30].

Lamin A/C is found in almost all cells except in certain differentiated cells of hematopoietic origins [31]. Cellular models have shown that lamin A and C proteins are found distributed together in a homogeneous meshwork. However, wild type lamin A transfected alone has consistently shown to localize to the inner nuclear lamina with some nucleoplasmic localization. Conversely, lamin C has been shown to localize as intranuclear aggregate [18, 32–36]. Intranuclear lamin C has shown to be more mobile than intranuclear lamin A [36, 37]. Likewise, the lamin C only mouse model expressed lamin C at the inner nuclear lamina as established in wild type cells [35]; thus indicating the existence of compensatory mechanisms. Pugh et al. [32] studied the incorporation of the lamin A and C in Swiss 3T3 cells and found that the incorporation of lamin C into the lamina was made possible by lamin A.

In an attempt to identify deregulation in striated muscle specific laminopathies including DCM and EDMD, researches have been focused on skeletal muscle differentiations. Lamin A and C play a pivotal role in myoblast differentiation. In vitro, cells expressing disease-associated LMNA mutations displayed an inhibition of myoblast differentiation [38] (F. Tesson personal communication) and myoblasts lacking lamin A and C expression showed decreased differentiation potential with downregulation of MyoD and pRb and upregulation of Myf5 [39]. These studies suggest that disruption of lamin A and C may weaken contractile tissues such as skeletal and cardiac muscle.

Lamin A and C also play a role in the regulation of signaling cascades such as the Sumo pathway. Sumo pathway regulates a wide range of cellular processes through the attachment of small ubiquitin-related modifier (sumo) to various substrates. Sumo1 was found to be mislocalized in the presence of lamin A and C mutants both in vitro (C2C12 and Cos7 cells) and in vivo (primary myoblasts and myopathic muscle tissue from

the Lmna$^{H222P/H222P}$ mice) [18, 40]. In cell models, trapping of sumo1 correlated with an increased steady-state level of sumoylation. Ubc9, the E2 conjugating enzyme of the Sumo pathway was also mislocalized to the mutant aggregates [40]. Lamin A has been shown to be covalently modified by Sumo 2 and 3 [41]. The disruption of a critical post-translational modifying process has the potential to affect the post-translational regulation of tissue-specific sumoylated proteins which may lead to the tissue-specific symptoms observed in patients with various laminopathies [40].

Recent studies using induced pluripotent stem cells derived cardiomyocytes (iPSCS-CMs) from DCM patients with LMNA mutations showed accelerated nuclear senescence and apoptosis under electrical stimulation. This study also showed that activation of stress response MEK1/ERK1/2 pathway contributes to increased apoptosis in LMNA$^{R225X/WT}$ dermal fibroblasts after electrical stimulation [42]. Moreover, this apoptotic effect could be attenuated by pharmacological blockade of the MEK1/ERK1/2 pathway. Study of gene expression profile showed that mouse models of laminopathies also displayed ERK pathway activation in heart muscle [43, 44]. Importantly, the pharmacological blockade of the ERK1/2 pathway prevented the development of DCM in this model [45]. These studies have shed new light on MEK1 pathway as a potential therapeutic target in LMNA-associated DCM.

Conclusion: The mechanistic hypotheses

Until now, 3 main hypotheses have been proposed to explain the mechanism of pathogenesis of laminopathies: the structural, the gene expression and the toxicity hypotheses. The structural hypothesis states that mutations within lamin A/C lead to disorganization of the proteinaceous meshwork, instability of the nuclear envelope and disorganization of chromatin, which in turn leads to the overall inability of the cell to properly function in contracting tissue environment such as striated muscles [46, 47]. Building on this hypothesis, recent studies identified repetitive disruptions of the nuclear envelope in the presence of lamin A/C mutations [17, 48]. These disruptions impaired protein distribution into cell compartments. Translocations of large amounts of protein into the cytoplasm could trigger aggresome formation or even induce cell apoptosis [48]. On the other hand, translocation of transcription factors into the cytoplasm might impair gene expression. The gene expression hypothesis is based on the regulatory role of lamin A/C in chromatin organization and DNA transcription. Mutated lamins might disrupt the protein meshwork through their interaction with other proteins of the nuclear envelope which may lead to epigenetic changes in the chromatin, which may then in turn disrupt various complex signaling pathways [49]. Lastly, the cell toxicity hypothesis proposes that mutated prelamin A may accumulate within patients' nuclei to the point that they might become toxic to the cell and lead to development of the disease [50]. These hypotheses are likely to be not mutually exclusive and combining them might allow describing the mechanisms underlying the initiation and/or the development of laminopathies. Ultimately, a better understanding of the pathogenesis of the disease may suggest novel strategies targeting the underlying molecular defects.

Conflict of interest: none declared

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Table 1. LMNA mutations associated with dilated cardiomyopathy from four databases — Human Intermediate Filament Database [13] (database updated 2014/01/15), Leiden Muscular Dystrophy website (www.dmd.nl; database updated 2014/01/05), HGMD® Professional 2014.4 (database updated 2014/02/02) and the Universal Mutation Database (www.umd.be/LMNA/).

Nucleotide change	Protein change	DCM phenotype range	Domain	Reference*
674bp deletion incl. start codon	Deletion of 5′ part	1° AVB, LBBB, AF, PVB, VT, HF, SCD	Head	[1]
c.16C>T	p.Gln6X	1°-2° AVB, AF, AFL, PAB, PVB, VT, HF, SCD	Head	[2]
c.28_29insA	p.Thr10AsnfsX31	1°-2° AVB, AF, PVB, MD	Head	[3]
c.31delC	p.Arg11AlafsX85	(2°) AVB	Head	[4, 5]
c.46_49dup	p.Ser18GlnfsX24	AVB	Head	[6]
c.48_51dupCAGC	p.Ser18GlnfsX23	n/a	Head	[6]
c.65C>T	p.Ser22Leu	PVB, HF	Head	[7]
c.73C>T	p.Arg25Cys	CA, AF, PVB, MD, HF	Head	[8]
c.73C>G	p.Arg25Gly	1°/3° AVB, TC, AF, PVB, PAB, LGMD, HF	Head	[9]
c.78C>T	p.Ile26Ile	HF, LBBB, AF	Head	[10]
c.82C>T	p.Arg28Trp	AVB, AF, PM, FPLD, HF	Head	[4, 11]
c.94_96delAAG	p.Lys32del	LAFB, CA, AF, EDMD	Head	[12, 13]
c.99G>T	p.Glu33Asp	1° AVB, Br, AF, CA, CMT2, MD, leuconychia	Head	[14]
c.106C>T	p.Gln36X	1°-2° AVB, VT	Coil 1A	[15]
c.134A>G	p.Tyr45Cys	AF, AFL, MD	Coil 1A	[16]
c.154C>G	p.Leu52Val	n/a	Coil 1A	[17]
c.155T>C	p.Leu52Pro	AVB, LBBB, RBBB, AF, PVB, HF	Coil 1A	[18]
c.158A>T	p.Glu53Val	AVB, AF, HF	Coil 1A	[19]
c.165delC	p.Asn56ThrfsX40	2° AVB, HF	Coil 1A	[5]
c.169G>C	p.Ala57Pro	Atypical WS, hypogonadism, sloping shoulders	Coil 1A	[20]
c.176T>G	p.Leu59Arg	CCD, hypogonadism, ovarian failure, MAD	Coil 1A	[21, 22]
c.178C>G	p.Arg60Gly	1°/3° AVB, LBBB, Br, AF, VA, DM, FPLD, PN, HF, SCD	Coil 1A	[23–26]
c.184C>G	p.Arg62Gly	CCD, 1° AVB, AF, PM, FPLD, HF	Coil 1A	[11, 26]
c.203_208delAGGTGG	p.Glu68_Val69del	3° AVB, EDMD(2)	Coil 1A	[4, 27]
c.215G>T	p.Arg72Leu	n/a	Linker 1	[17]
c.232A>G	p.Lys78Glu	1° AVB, VT, ICD	Linker 1	[96]
c.244G>A	p.Glu82Lys	1°-3° AVB, LBBB, AF, VF, SVT, HF	Coil 1B	[28, 29]
c.254T>G	p.Leu85Arg	CCD, PM, AF, HF, SCD	Coil 1B	[23]
c.266G>T	p.Arg89Leu	1°-3° AVB, AF, VT, MA, HF/AVB, AF, VT, EDMD, HF	Coil 1B	[4, 5, 30–32]
c.274C>T	p.Leu92Phe	LBBB, AF, PVB, HF	Coil 1B	[33, 34]
c.289A>G	p.Lys97Glu	1°/3° AVB, LBBB, PVB, HF	Coil 1B	[4, 5, 35]
c.302G>C	p.Arg101Pro	AF, HF / AVB, AF, PVB, VT, LGMD	Coil 1B	[31] / [94]
c.331G>T	p.Glu111X	3° AVB, PVB, HF	Coil 1B	[4, 5, 35]
c.348_349insG	p.Lys117GlufsX10	AVB, AF, SCD	Coil 1B	[36]
c.356+1G>T	n/a	n/a	Coil 1B	[37]
c.357-1G>T	n/a	LBBB, AF, PVB, VT, VF, HF	Coil 1B	[4, 31, 34]
c.357C>T	p.Arg119Arg	CCD, PM, LGMD, HF	Coil 1B	[16]
c.367_369del	p.Lys123del	1°-3° AVB, LBBB, PVB, VT, VF, MP, SCD	Coil 1B	[38]
c.380_381ins24bp	p.Ile128_Ala129ins-ArgValThrLeuIle-SerSerArg	CCD	Coil 1B	[34]
c.384ins24	p.Ile128delinsIleSer	n/a	Coil 1B	[33]

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Nucleotide change	Protein change	DCM phenotype range	Domain	Reference*
c.394G>C	p.Ala132Pro	1° AVB, Br, AF, HF	Coil 1B	[39]
c.398G>T	p.Arg133Leu	CCD, LD	Head	[40]
c.405_425dup	p.Asn142delinsLysLys	1° AVB, AF, VT, PVB	Coil 1B	[41]
c.425_426insGGCACTG GAGGCTCTGCTGAA	p.Leu141_Asn142insLys-AspLeuAspAlaLeuLeu	1° AVB, AF, PVB, VT, HF	Coil 1B	[41]
c.427T>C	p.Ser143Pro	1°-3° AVB, LBBB, LAFB, SSS, Br, AF, PVB, VF, VT, HF	Coil 1B	[39, 42]
c.481G>A	p.Glu161Lys	AVB, LBBB, Br, AF, PVB, LAFB, VT, HF	Coil 1B	[4, 3, 19, 34, 43]
c.497G>C	p.Arg166Pro	AVB, LBBB, AF, VT, HF	Coil 1B	[31, 44]
c.514-1G>A	n/a	VT, VF	Coil 1B	[4]
c.548T>C	p.Leu183Pro	AVB	Coil 1B	[4]
c.556G>A	p.Glu186Lys	CCD, HF	Coil 1B	[19]
c.565C>T	p.Arg189Trp	PVB	Coil 1B	[45]
c.568C>T	p.Arg190Trp	1° AVB, RBBB, Br, LAFB, AF, AFL, PVB, HF	Coil 1B	[4, 5, 7, 19, 35, 39, 46, 47]
c.569G>A	p.Arg190Gln	1°-3° AVB, Br, AF, AFL, VT, HF	Coil 1B	[31, 43]
c.575A>G	p.Asp192Gly	1° AVB, LAFB, HF	Coil 1B	[46, 48, 49]
c.575A>T	p.Asp192Val	LBBB, FLPD, HF	Coil 1B	[26]
c.585C>G	p.Asn195Lys	1°-3° AVB, Br, AF, HF, SCD	Coil 1B	[8, 23]
c.585C>A	p.Asn195Lys	1°, 3° AVB, AF, HF, SCD	Coil 1B	[8]
c.607G>A	p.Glu203Lys	1° AVB, LBBB, RBBB, HF	Coil 1B	[50]
c.608A>G	p.Glu203Gly	1°-2° AVB, AF, HF, SCD	Coil 1B	[23]
c.608A>T	p.Glu203Val	2° AVB, Br, SWMA, HF	Coil 1B	[23, 43]
c.622_624delAAG	p.Lys208del	1° AVB, PVB, VT, LGMD	Coil 1B	[8]
c.629T>G	p.Ile210Ser	AF, HF	Coil 1B	[31, 51]
c.640-10A>G	n/a	1°-3° AVB, LBBB, RBBB, AF, VT, HF	Coil 1B	[52]
c.644T>C	p.Leu215Pro	1°-2° AVB, SSS, Br, LBBB, AF, AFL, SVT, VT, PVB, SCD, HF	Coil 1B	[53]
c.656A>C	p.Lys219Thr	(3°) AVB	Linker 2	[4, 43]
c.657G>C	p.Lys219Asn	1° AVB, VT, PM	Linker 2	[54]
c.673C>T	p.Arg225X	(1°) AVB, Br, AF, LVE, PVB, SCD	Linker 2	[8, 44, 50]
c.676C>G	p.Leu226Val	n/a	Linker 2	[37]
c.694G>C	p.Gly232Arg	AVB, RBBB, PVB, EDMD	Linker 2	[18]
c.700C>T	p.Gln234X	2° AVB, Br, HF	Linker 2	[31]
c.736C>T	p.Gln246X	AVB	Coil 2	[4]
c.746G>A	p.Arg249Gln	AVB, PVB, EDMD or LGMD(1B)	Coil 2	[18]
c.767T>G	p.Val256lGly	AVB	Coil 2	[55]
c.775T>C	p.Tyr259His	AVB, AF, VT	Coil 2	[44]
c.780G>C	p.Lys260Asn	AVB, SSS, ASS, HF	Coil 2	[4, 56]
c.781_783del3ins18	p.Lys261delins6	AVB, LBBB, AF, PVC, EDMD(2)	Coil 2	[18]
c.799T>C	p.Tyr267His	CCD, SCD	Coil 2	[57]
c.800A>G	p.Tyr267Cys	AVB, TC, EDMD(2)	Coil 2	[4, 58]
c.810G>A	p.Lys270Lys	CCD, AF, PM, EDMD, LGMD	Coil 2	[16]
c.811-3C>T	n/a	n/a	Coil 2	[37]
c.812T>C	p.Leu271Pro	AF, Br, SVT, VT, EDMD, HF	Coil 2	[16, 59]
c.815_818delACA AinsCCAGAC	p.Asp272AlafsX208	AVB, AF, VT	Coil 2	[44]
c.832G>A	p.Ala278Thr	AVB, AF, VF, SVT, PM, PVB	Coil 2	[60]
c.855delG	p.Ala287LeufsX191	AF, ASS, LGMD	Coil 2	[58]
c.859insC	p.Ala287fs	AF	Coil 2	[34]
c.883T>C	p.Ser295Pro	CCD, MD	Coil 2	[16]
c.906_907delCT	p.Ser303CysfsX27	AVB, PM, HF, Br, PAB, PVB, CCD, SVA, AF, SCD	Coil 2	[95]

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Nucleotide change	Protein change	DCM phenotype range	Domain	Reference*
c.908_909delCT	p.Ser303CysfsX26	1° AVB, Br, SSS, AF / 1°-3° AVB, AF, PVB, VT, LGMD, HF	Coil 2	[61, 62]
c.936G>C	p.Gln312His	AVB, AF, CCD, HF	Coil 2	[63]
c.976T>A	p.Ser326Thr	VT, AVB, CCD, XL-EDMD, MP, PM	Coil 2	[97]
c.IVS5+1G>T (c.936+1G>T)	n/a	1°-2° AVB, VT, PM	Coil 2	[4, 56, 64]
c.937-11C>G	p.Leu313GlyfsX31	1°-3° AVB, LGMD(1B), VT, AF	Coil 2	[65]
c.949G>A	p.Glu317Lys	1°/3° AVB, AFL, LBBB, HF	Coil 2	[4, 5, 35, 34]
c.952G>A	p.Ala318Thr	TC, PVB, HF	Coil 2	[31]
c.958delC	p.Leu320fs	n/a	Coil 2	[17]
c.959delT	p.Leu320fsX160	2°-3° AVB, LBBB, AF, VT, SVT, PVB, LGMD, EDMD, HF, SCD	Coil 2	[66, 67]
c.961C>T	p.Arg321X	1° AVB, RBBB, AF, VT, HF	Coil 2	[68, 69]
c.[992G>A; =]+[=; 1039G>A]	p.[Arg331Glu; =]+[=; Glu347Lys]	AF, PM	Coil 2	[58]
c.992G>C	p.Arg331Pro	AVB, PM, LGMD	Coil 2	[58]
c.992G>A	p.Arg331Gln	1° AVB, AFL, VT, HF	Coil 2	[69]
c.1003C>T	p.Arg335Trp	3° AVB, RBBB, SSS, AF, VT	Coil 2	[17, 70]
c.1004G>A	p.Arg335Gln	n/a	Coil 2	[37]
c.1039G>A	p.Glu347Lys	AF, PM, SCD	Coil 2	[13, 71]
c.1044G>T	p.Met348Ile	EDMD, PM, CCD	Coil 2	[72]
c.1045C>T	p.Arg349Trp	CCD, SVA, MD, HF, SCD	Coil 2	[8]
c.1046G>T	p.Arg349Leu	AF, HF	Coil 2	[73]
c.1048G>C	p.Ala350Pro	AVB, LBBB, AF, PVB	Coil 2	[18]
c.1057C>A	p.Gln353Lys	CA, MP, HF	Coil 2	[48]
c.1063C>T	p.Gln355X	2° AVB, AF, VT, HF	Coil 2	[7, 69]
c.1069G>C	p.Asp357His	AVB, VT	Coil 2	[74]
c.1070A>C	p.Asp357Ala	2° AVB, Br, AF, VES, VT, VF, HF, SCD	Coil 2	[70]
c.1072G>T	p.Glu358X	1°-2° AVB, VT	Coil 2	[75]
c.1085_1085delT	p.Leu363TrpfsX117	1°-2° AVB, AF, VT, HF	Coil 2	[39]
c.1102_1130dupGCCCTGGACATGGAGATCCACGCCTACCG	p.Lys378ProfsX112	LBBB, VT, LGMD, HF	Coil 2	[76]
c.1111_1125del15	p.Met371_Ala375del	n/a	Coil 2	[17]
c.1114delG	p.Glu372ArgfsX107	1° AVB, Br, AF, HF	Coil 2	[31]
c.1129C>T	p.Arg377Cys	LGMD, HF	Coil 2	[77]
c.1130G>A	p.Arg377His	1o-3o AVB, LBBB, RBBB, AF, PVB, VT, VF, LGMD, EDMD, HF, SCD	Coil 2	[3, 8, 18, 30, 41, 78]
c.1130G>T	p.Arg377Leu	(2°) AVB, Br, SSS, AF, AFL, ASS, ATC, VT, LGMD(1B), EDMD, HF, SCD	Coil 2	[4, 8, 79, 80]
c.1157G>C	p.Arg386Thr	FPLD, CCD	Tail	[81]
c.1157+1G>A	n/a	VT, VF	Tail	[4]
c.1157+1G>T	p.Arg386SerfsX21	VES, VF, HF	Tail	[70]
c.1163G>A	p.Arg388His	Br, PVB, HF, SCD	Tail	[31]
c.1189C>T	p.Arg397Cys	n/a	Tail	[37]
c.1195C>T	p.Arg399Cys	HF	Tail	[31]
c.1197_1240del44	p.Gly400Argfs*11	AVB, SSS	Tail	[55]
c.1292C>G	p.Ser431*_	AVB	Tail	[55]
c.1294C>T	p.Gln432X	3° AVB, LBBB, RBBB, AF, VT, HF	Tail	[69]
c.1303C>T	p.Arg435Cys	HF	Tail	[13]
c.1307_1308insGCAC	p.Ser437HisfsX1	2° AVB, Br, TC, AF, PVB, HF, SCD	Tail	[31]

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Nucleotide change	Protein change	DCM phenotype range	Domain	Reference*
c.1318G>A	p.Val440Met	LAFB, VES	Tail	[69]
c.1370delA	p.Lys457SerfsX21	AF, LGMD	Tail	[58]
c.1380+1G>A	n/a	(1°) AVB, AF, VF, HF	Tail	[8, 34]
c.1397_1397delA	p.Asn466IlefsX14	1° AVB, LBBB, Br, AF, VF, VT, HF, SCD	Tail	[41, 82]
c.1412G>A	p.Arg471His	AF, VT, HF	Tail	[31]
c.1424_1425insAGA	p.Gly474_Asp475insGlu	HF, ICD	Tail	[31]
c.1443C>G	p.Tyr481X	2° AVB, RBBB, SVT, VT, HF	Tail	[46, 48, 49]
c.1489-1G>T	p. Ile497-Glu536del	2° AVB, Br, AF, AFL, VT, EDMD	Tail	[70]
c.1492T>A	p.Trp498Arg	AVB, EDMD(2)	Tail	[4]
c.1493_1493delG	p.Ala499LeufsX47	AF, VT, HF	Tail	[39]
c.1496delC	p.Ala499Val	1°-2° AVB, RBBB, Br, ATC, ASS, AN	Tail	[83]
c.1512_1513insAG	p.Thr505ArgfsX44	1° AVB, AF, PVB, HF, SCD	Tail	[8]
c.1526_1527insC	p.Thr510TyrfsX42	1° AVB / AVB, EDMD(2)	Tail	[4] / [84]
c.1549C>T	p.Gln517X	3° AVB, AF, EDMD, VF, SCD	Tail	[70]
c.1560G>A	p.Trp520X	2° AVB, LBBB, Br	Tail	[70]
c.1567G>A	p.Gly523Arg	LBBB	Tail	[33, 34]
c.1579_1580insCTGC	p.Arg527ProfsX26	1°-2° AVB, LBBB, LAFB, HF	Tail	[4, 5, 35]
c.1583C>T	p.Thr528Met	1°-3° AVB, Br, AF, SVA	Tail	[10]
c.1608+1G>T	n/a	n/a	Tail	[37]
c.IVS9-3C>G (c.1609-3C>G)	Loss of exon 10	3° AVB, Br, PM, LGMD(1B)	Tail	[85]
c.1621C>T	p.Arg541Cys	LBBB, VT, VF, PVB, fibrosis, SWMA, SCD	Tail	[86–88]
c.1621C>A	p.Arg541Ser	VT, HF / LGMD(1B), HF	Tail	[16] / [46, 39, 48]
c.1621C>G	p.Arg541Gly	IVB, LBBB, Br, SVA, PVB, VA, TC	Tail	[89]
c.1622G>A	p.Arg541His	AVB, AF, PVB	Tail	[18]
c.1622G>C	p.Arg541Pro	PVB, VT, HF	Tail	[8]
c.1711C>A	p.Arg571Ser	1°-3° AVB, Br, AF	Tail	[23]
c.1713C>A	p.Ser571Arg	2°, 3° AVB, PM, HF, AF	Tail	[23]
c.1714insCTGC	p.Ser572LeufsX8	1°, 2° AVB, PM, LBBB	Tail	[35]
c.1718C>T	p.Ser573Leu	AVB, VT	Tail	[4, 30]
c.1904G>A	p.Gly645Asp	HF	Tail	[90]
c.1930C>T	p.Arg644Cys	AVB, AF, VT, HF / LGMD(1B), HF, SCD	Tail	[4, 43, 69] / [91]
c.1960C>T	p.Arg654X	AVB, LBBB, SSS, AF, VT, HF, SCD	Tail	[31]
c.1964_1965insG	p.Thr655fsX49	PM, VT, MH, POS, HF, SCD	Tail	[92]
c.[1699 to 183_1699–160inv24; 568_1699–184del; 1699 to 159_1995+6997del]	Double deletion with break points in exon 3, intron 10, downstream of gene	1°-3° AVB, AF, AFL, Br, VA, SCD	Coil/Tail	[93]
Deletion exons 3-12	Deletion > 4,704 bp	VT, HF	Coil/Tail	[48]

1°, 2°, 3° — atrio-ventricular block degree, in parenthesis when degree specified only in some studies; AF — atrial fibrillation; AFL — atrial flutter; AN — axonal neuropathy; ASS — atrial standstill; ATC — atrial tachycardia; AVB — atrio-ventricular block; Br — bradycardia; CA — cardiac abnormalities; CCD — cardiac conduction disease; CMT2 — Charcot-Marie-Tooth disease; DCM — dilated cardiomyopathy; DM — diabetes mellitus; EDMD(2) — Emery-Dreifuss muscular dystrophy (type 2); FPLD — familial partial lipodystrophy; HF — heart failure; IVB — intra-ventricular block; ICD — implantable cardiac defibrillator; LAFB — left anterior fascicular block; LBBB — left bundle branch block; LGMD(1B) — limb girdle muscular dystrophy (type 1B); LVE — left ventricular exosystoly; MA — muscular atrophy; MAD — mandibuloacral dysplasia; MD — muscular dystrophy; MH — muscular hypertrophy; MP — myopathy; n/a — not available; PAB — premature atrial beats; PM — pacemaker implantation; PN — peripheral neuropathy; POS — polycystic ovary syndrome; PVB — premature ventricular beats; RBBB — right bundle branch block; SCD — sudden cardiac death; SSS — sick sinus syndrome; SVA — supraventricular arrhythmia; SVT — supraventricular tachycardia; SWMA — segmental wall motion abnormalities; TC — tachycardia; VA — ventricular arrhythmia; VES — ventricular extra systoles; VF — ventricular fibrillation; VT — ventricular tachycardia; LD — lipodystrophy; WS — Werner syndrome; "/" used to separate differing phenotypes; *References are listed in "Supplement 1"

SUPPLEMENT 1: Table 1 References

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