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REVIEW

Molecular insights into cardiomyopathies associated with desmin (*DES*) mutations

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Abstract

Increasing usage of next-generation sequencing techniques pushed during the last decade cardiogenetic diagnostics leading to the identification of a huge number of genetic variants in about 170 genes associated with cardiomyopathies, channelopathies, or syndromes with cardiac involvement. Because of the biochemical and cellular complexity, it is challenging to understand the clinical meaning or even the relevant pathomechanisms of the majority of genetic sequence variants. However, detailed knowledge about the associated molecular pathomechanism is essential for the development of efficient therapeutic strategies in future and genetic counseling. Mutations in *DES*, encoding the muscle-specific intermediate filament protein desmin, have been identified in different kinds of cardiac and skeletal myopathies. Here, we review the functions of desmin in health and disease with a focus on cardiomyopathies. In addition, we will summarize the genetic and clinical literature about *DES* mutations and will explain relevant cell and animal models. Moreover, we discuss upcoming perspectives and consequences of novel experimental approaches like genome editing technology, which might open a novel research field contributing to the development of efficient and mutation-specific treatment options.

Keywords Desmin · Cardiomyopathy · Desminopathy · Cardiovascular genetics · Intermediate filaments

Abbreviations

ACM	Arrhythmogenic cardiomyopathy
ACMG	American College of Medical Genetics and Genomics
AF	Atrial fibrillation
AFM	Atomic force microscopy
ALVC	Arrhythmogenic left ventricular cardiomyopathy
ARVC	Arrhythmogenic right ventricular cardiomyopathy
aSNOM	Apertureless scanning near-field microscopy
ATP	Adenosine triphosphate
AVB	Atrioventricular block
CM	Cardiomyopathy
DCM	Dilated cardiomyopathy
DRM	Desmin-related myopathy
DSC2	Desmocollin-2
DSG2	Desmoglein-2
DSP	Desmoplakin
EPR	Electron paramagnetic resonance
GFAP	Glial fibrillary acidic protein
GGA	Geranylgeranylacetone
HCM	Hypertrophic cardiomyopathy
HOCM	Hypertrophic obstructive cardiomyopathy
HTx	Heart transplantation
IF	Intermediate filament
LAFB	Left anterior fascicular block
LBBB	Left bundle-branched block
LGMD	Limb-girdle muscular dystrophy
LVNC	Left ventricular noncompaction cardiomyopathy
LW	Limp weakness
MAF	Minor allele frequency
MFM	Myofibrillar myopathy
MRI	Magnetic resonance imaging
NCM	Noncompaction cardiomyopathy
NMD	Nonsense-mediated RNA decay

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PG	Plakoglobin
PKP2	Plakophilin-2
PTC	Premature termination codon
PTM	Posttranslational modification
RBBB	Right bundle-branched block
RCM	Restrictive cardiomyopathy
SCD	Sudden cardiac death
SM	Skeletal myopathy
SMD	Smooth muscle defect
SNP	Single nucleotide polymorphism
SQTS	Short QT syndrome
TAC	Transverse aortic constriction
TEM	Transmission electron microscopy
ULF	Unit length filament
VUS	Variant of unknown significance

Introduction

In clinical practice and historically, cardiomyopathies are classified according to their morphological and clinical symptoms into dilated (DCM), hypertrophic (HCM), restrictive (RCM), arrhythmogenic (ACM), and noncompaction (NCM) cardiomyopathy (McKenna et al. 2017). All these different forms of cardiomyopathies can be caused by genetic or nongenetic factors (Maron et al. 2006). The first cardiomyopathy causing genetic mutation was identified in 1990 in *MYH7*, encoding myosin heavy chain, by the group of Geisterfer-Lowrance et al. (1990). Pushed by the human genome project in the 1990s and by the development of efficient next-generation sequencing technology in the 2000s, a large number of different mutations in over 170 different genes were discovered, which are associated with cardiomyopathies, isolated channelopathies, or syndromes with cardiac involvement (Cahill et al. 2013).

In the last years, it became more and more evident that different cardiomyopathies can be caused by mutations in the same gene(s). *DES*, encoding the intermediate filament (IF) protein desmin (Figs. 1 and 2), is such a gene, where mutations are associated with DCM (Taylor et al. 2007; Brodehl et al. 2016a), HCM (Harada et al. 2018), RCM (Ojrzynska et al. 2017), ACM (Klauke et al. 2010), or left ventricular noncompaction cardiomyopathy (LVNC) (Miszalski-Jamka et al. 2017) (Figs. 3 and 4). In addition, *DES* mutations might cause different isolated or combined skeletal myopathies (Schirmer et al. 2018; Cetin et al. 2013; Goldfarb et al. 1998; Dalakas et al. 2000) (for details, see Table 1).

In this article, we review the genetic, cellular, molecular, and biophysical pathomechanisms of *DES* mutations with a focus on cardiomyopathies. In addition, we summarize relevant in vitro experiments using recombinant desmin as well as existing cell culture and animal models, which were used in combination with biochemical and biophysical methods to investigate the underlying pathomechanism of *DES* mutations.

Cellular functions of desmin

Three filamentous systems build the eukaryotic cytoskeleton. Actin filaments are important for the structural integrity and stability of nearly all mammalian cells and are essential components of the thin sarcomeric filaments in (cardio)myocytes. Microtubules are composed of α- and β-microtubulin and are necessary for the kinesin-mediated vesicle transport. In contrast to these filament types, IFs are formed by nonglobular, highly flexible protein units, which consist mostly of α-helices. Therefore, IF proteins are nanomolecular springs, which provide enormous structural flexibility. In humans, 70 different genes including the *DES* gene encode members of the IF protein family (Szeverenyi et al. 2008). Desmin is expressed in cardiac, skeletal, and smooth muscle cells (Hnia et al. 2015; The Human Protein Atlas, https://www.proteinatlas.org; Uhlen et al. 2015). Due to their specific cellular expression pattern, several diverse genetic diseases like cardiomyopathies (Brayson and Shanahan 2017) and cutaneous (Coulombe 2017) or neurological diseases (Brenner et al. 2001) might be caused by mutations in genes encoding IF proteins.

Due to their assembling mechanism, IF proteins can be categorized into different groups, which were previously reviewed in detail (Herrmann and Aebi 2004). Desmin belongs to assembly group type III, which contains also vimentin and glial fibrillary acidic protein (GFAP). In general, desmin filaments connect and anchor different cell structures like desmosomes, mitochondria, and costameres or Z-bands to the cytoskeleton.

Desmosomes are cell-cell junctions, which mediate the cell-cell adhesion in a Ca^{2+}-dependent way (Patel and Green 2014) (Fig. 1). They are localized at the intercalated disc in myocardial tissue. Members of the cadherin family (desmocollins and desmogleins) bind via *trans* interaction to their counterparts from the neighboring cells (Harrison et al. 2016; Lapouge et al. 2006; Dieding et al. 2017). The cytoplasmic domains of these desmosomal cadherins are bound from proteins of the Armadillo family (plakophilins and plakoglobin) (Kami et al. 2009; Chen et al. 2002; Chitaev et al. 1998). These Armadillo proteins are connected to the cytolinker protein desmoplakin (Hofmann et al. 2000). Desmin filaments are linked via desmoplakin to the desmosomes (Choi et al. 2002), which reached a special interest since it became evident that mutations within the genes encoding for desmosomal structural proteins are the main cause of ACM (Gerull et al. 2004; Heuser et al. 2006; Bauce et al. 2005; Bhuiyan et al. 2009; McKoy et al. 2000).

Costameres are multiprotein complexes, which mediate the interactions of (cardio)myocytes with the extracellular matrix

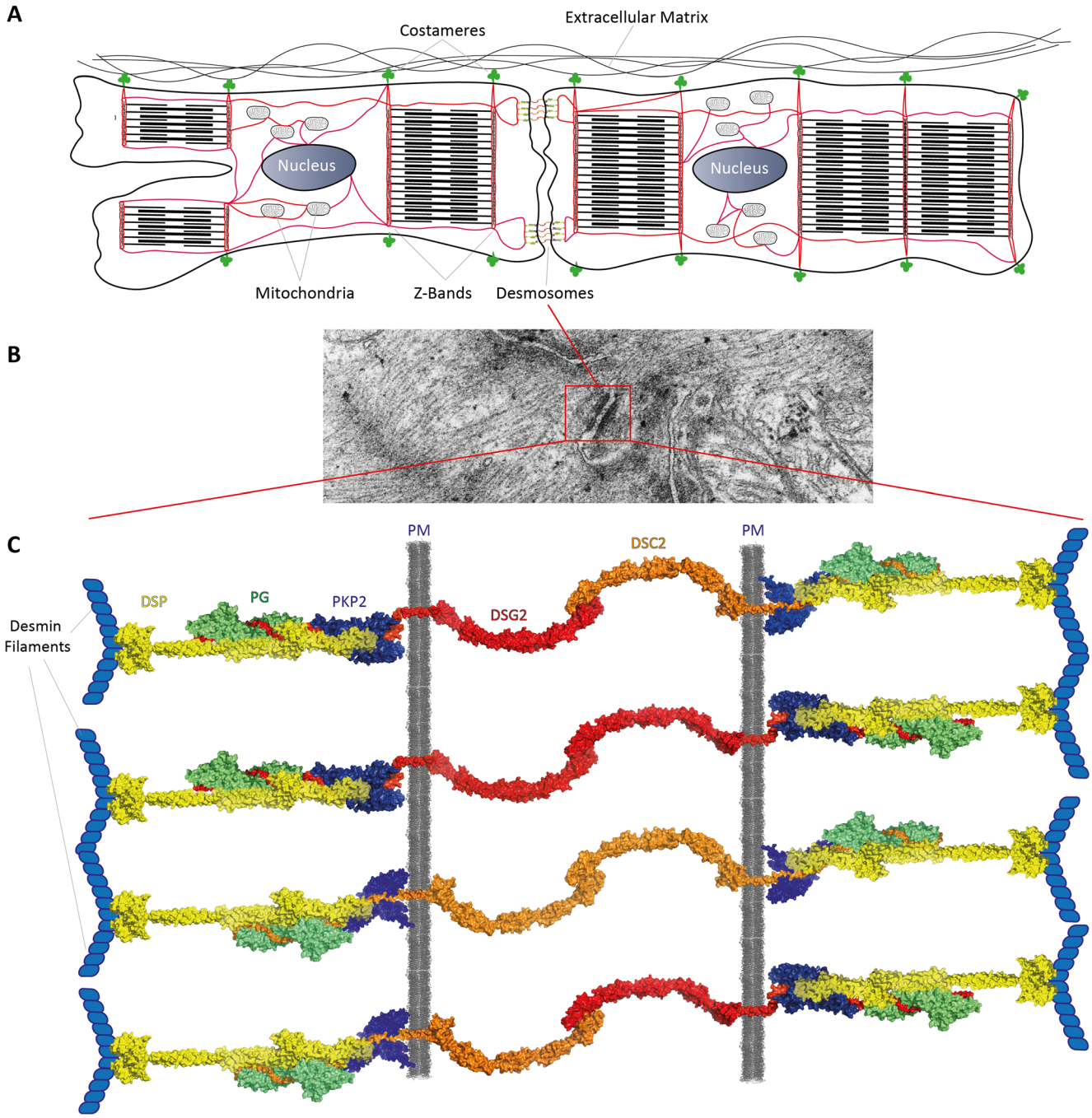

Fig. 1 **a** Schematic overview about the localization of desmin filaments (red) in cardiomyocytes. Of note, desmin filaments connect several protein-protein complexes (e.g., desmosomes) and cell organelles (mitochondria, nuclei) to the cytoskeletal network. **b** Transmission electron microscopy image of murine cardiac tissue. A typical desmosome connecting two cardiomyocytes is marked by the red box. **c** Schematic illustration of the cardiac desmosomes, which are connected to the desmin filaments. DSC2 = desmocollin-2, DSG2 = desmoglein-2, PKP2 = plakophilin-2, PG = plakoglobin, PM = plasma membrane, DSP = desmoplakin

and which are localized at the sarcolemma. The dystrophin-glycoprotein and the integrin-vinculin-talin systems are the main components of the costameres (Jaka et al. 2015). Desmin forms heteropolymers with the IF-protein synemin (encoded by *SYNM*) (Granger and Lazarides 1980; Price and Lazarides 1983; Bellin et al. 1999). Synemin is expressed in all muscle cell types (Olive et al. 2003; https://www.proteinatlas.org) and co-localizes with desmin at the Z-bands in striated muscle (Bellin et al. 1999; Bilak et al. 1998; Hirako et al. 2003). In addition to the characteristic rod domain, synemin has a short N-terminal head and a large C-terminal tail domain (Becker et al. 1995). Synemin links the IFs via binding to α-actinin within the Z-bands (Bellin et al. 1999, 2001; Lund et al. 2012). In addition, synemin binds to

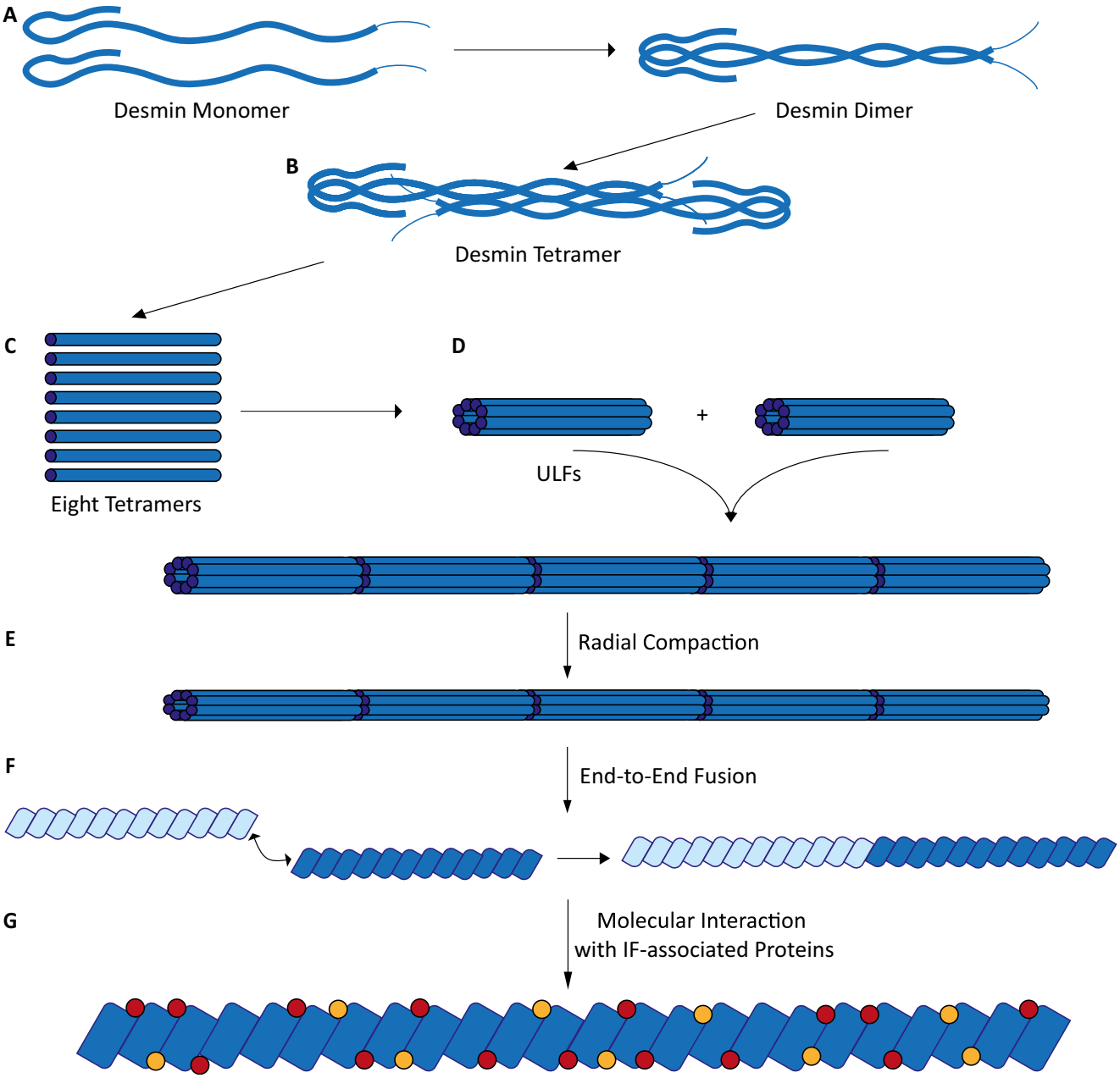

Fig. 2 Schematic overview about the desmin filament assembly. **a** Desmin dimers are formed as coiled-coils by the rod domains. **b** Two desmin dimers anneal into anti-parallel tetramers. Based on a 'divide and conquer' strategy, the molecular tetrameric structure of the homologous protein vimentin has been proposed (Chernyatina et al. 2015). **c** Eight tetramers associate laterally into unit length filaments (ULFs). ULFs are the essential building blocks of the desmin filaments, which are formed by longitudinal elongation (**d**) followed by a radial compaction step (**e**). Desmin filaments could also fuse end-to-end to elongate into longer filamentous structures (**f**). In addition, several IF-associated proteins (shown in red or yellow) bind to desmin filaments (**g**)

different costameric proteins like vinculin, dystrophin, and talin and mediates the interaction of IFs with costameres (Bellin et al. 2001; Bhosle et al. 2006; Sun et al. 2008). Interestingly, *DES* missense mutations leading to an abnormal cytoplasmic desmin aggregation cause also a co-aggregation of the binding partner synemin (Chourbagi et al. 2011). Although no human *SYNM* mutations are described so far, *Synm* knock-out mice develop cardiomyopathies (Garcia-Pelagio et al. 2018).

Structural organization of desmin filaments

Nearly all IF proteins including desmin are built by a central homologous rod domain flanked by head and tail domains of

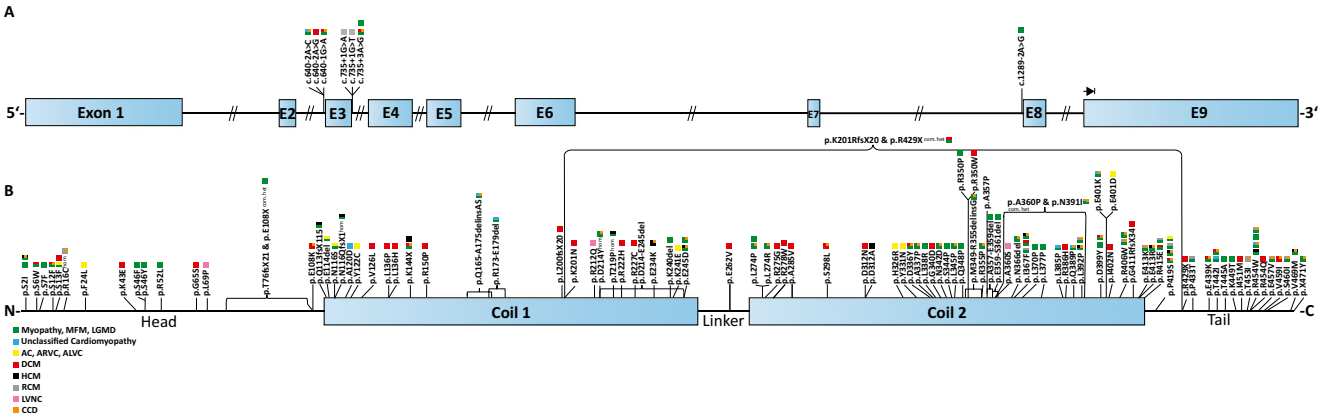

Fig. 3 **a** Schematic overview of the *DES* gene and known splice site mutations. **b** Schematic overview of the desmin protein including the positions of known missense and small deletion mutations. Colored squares indicate the clinical phenotypes of *DES* mutation carriers

different sizes and sequences (Carlsson and Thornell 2001). Linker sequences divide the rod domain into two coil subdomains. Because of the high oligomerization of IF proteins, it is difficult to crystallize and determine their molecular structure. Therefore, a 'divide and conquer' strategy was applied leading to a tetrameric detailed molecular model of the IF-protein vimentin (Chernyatina et al. 2012, 2015). However, the structure and architecture of the completely assembled IFs remains still widely unknown.

Desmin filaments are assembled in a stepwise process (Herrmann et al. 2009) (Fig. 2). A repeated heptade sequence with hydrophobic amino acids at positions A and D is characteristic for IF proteins (Chernyatina et al. 2015). These amino acids form a hydrophobic seam, which is essential for the dimerization into coiled-coils (Herrmann et al. 2000). Two highly conserved motifs at the beginning and the end of the rod domain are essential for the assembly process (Hatzfeld and Weber 1992; Albers and Fuchs 1992). In the second step, desmin dimers anneal into anti-parallel tetramers (Herrmann et al. 2009; Potschka et al. 1990; Kooijman et al. 1995; Geisler et al. 1985). Because the anti-parallel tetramers have no orientation, IFs have in contrast to actin filaments or microtubules no polarity. Eight of these tetramers anneal laterally into unit length filaments (ULFs), which are the essential building blocks of desmin filaments (Herrmann et al. 2009). ULFs are longitudinally elongated and compacted into regular IFs (Herrmann et al. 2009). Ando and colleagues demonstrated a helical right-handed twist of the homologous vimentin filaments (Ando et al. 2004), which was previously also shown for desmin filaments by atomic force microscopy (Brodehl et al. 2012a, 2016a). In addition, IFs can fuse end-to-end to elongate longitudinally (Colakoglu and Brown 2009;

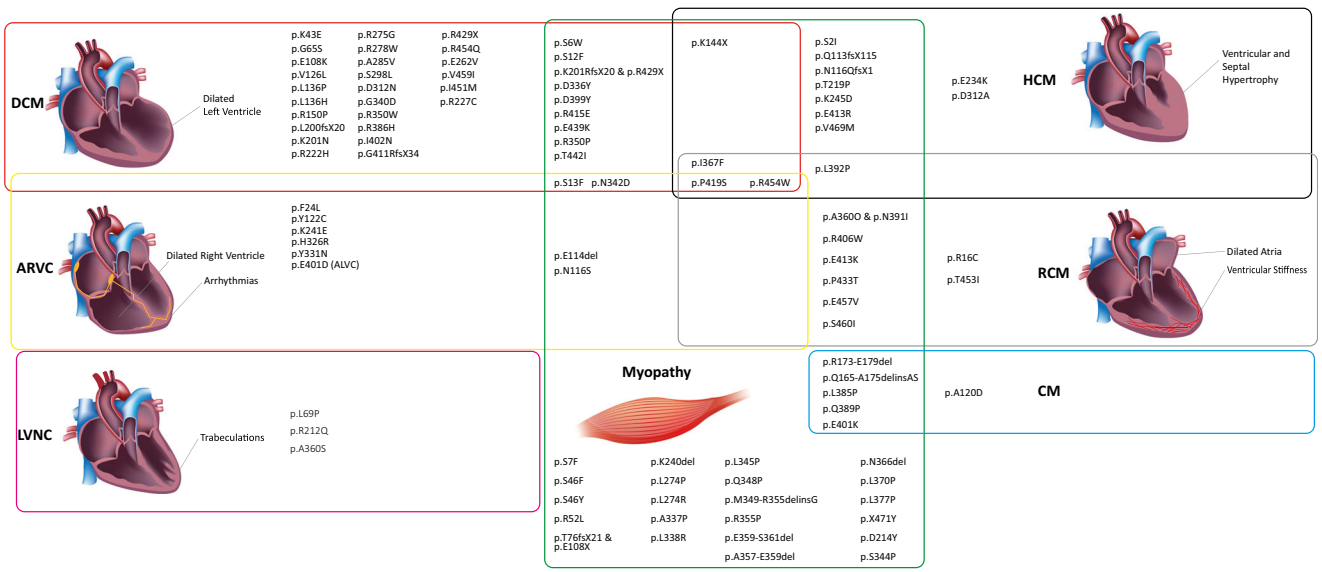

Fig. 4 Venn diagram indicating the different cardiac and skeletal phenotypes of *DES* mutation carriers. Of note, the associated clinical phenotypes of different mutations overlap significantly. DCM = dilated cardiomyopathy, HCM = hypertrophic cardiomyopathy, ARVC = arrhythmogenic right ventricular cardiomyopathy, RCM = restrictive cardiomyopathy, LVNC = left ventricular cardiomyopathy, CM = atypical or unknown cardiomyopathy. (Images for DCM and HCM are licensed from shutterstock.de)

Table 1 Overview about the known missense and deletion mutations

Mutation	Comments	Family anamnesis	MAF (gnomAD, 11th May 2018) (Lek et al. 2016)	Categorization	Clinical symptoms	References
p.S2I		NO (Selcen et al. 2004); 2 mutation carriers (Wahbi et al. 2012)	–	Pathogenic	MFM (Selcen et al. 2004); HCM, bifascicular block, SM (Wahbi et al. 2012)	Sharma et al. (2009), Selcen et al. (2004), Wahbi et al. (2012)
p.S6W		2 mutation carriers	–	Pathogenic	DCM, atrial arrhythmias, SM	Weihl et al. (2015)
p.S7F		2 mutation carriers	–	Pathogenic	MFM	Vattemi et al. (2011)
p.S12F		4 mutation carriers	–	Pathogenic	DCM, AVB, SCD, SM, LW, dysphagia	Hong et al. (2011), Hong et al. (2010)
p.S13F		Eight families with several mutation carriers (van Spaendonck-Zwarts et al. 2012; Bergman et al. 2007; van Tintelen et al. 2009)	–	Pathogenic	DCM (Walsh et al. 2017)	Brodehl et al. (2012a), van Spaendonck-Zwarts et al. (2012), McCormick et al. (2015), Bergman et al. (2007), Sharma et al. (2009), van Tintelen et al. (2009), Walsh et al. (2017), van Spaendonck-Zwarts et al. (2013)
p.R16C	Homozygous	1 (homo.) mutation carrier (Arbustini et al. 2006)	–	Pathogenic	RCM, biatrial dilation, AVB, HTx	Sharma et al. (2009), Arbustini et al. (2006)
p.F24L		NO	–	VUS	ARVC	Walsh et al. (2017)
p.K43E		NO	–	VUS	DCM	Walsh et al. (2017), Pugh et al. (2014)
p.S46Y		NO	–	Pathogenic	MFM	Sharma et al. (2009), Selcen et al. (2004)
p.S46F		NO	–	Pathogenic	MFM	Sharma et al. (2009), Selcen et al. (2004), Baker et al. (2013)
p.R52L		De novo	–	Pathogenic	LGMD	Yu et al. (2017)
p.G65S		NO	0.00002139	VUS	DCM	Walsh et al. (2017), Pugh et al. (2014)
p.L69P		NO	0.00001067	VUS	LVNC	Miszalski-Jamka et al. (2017)
p.T76fsX21 and p.E108X	Compound heterozygous	2 (c. h.) mutation carriers	–	Pathogenic	SM	Henderson et al. (2013)
p.E108K		NO	–	Pathogenic	DCM, LAFB	Taylor et al. (2007)
p.Q113RfsX115		Sporadic case	–	Pathogenic	HCM, arrhythmias, SM, LW	Hong et al. (2011)
p.E114del		3 mutation carriers	–	Pathogenic	ARCV, atrial dilation, arrhythmias, SCD, SM	Brodehl et al. (2012a), Vernengo et al. (2010), Hedde et al. (2012)
p.N116S		De novo	–	Pathogenic	ARVC, HTx, SM	Klauke et al. (2010), Brodehl et al. (2012a), Hedde et al. (2012), Maerkens et al. (2013), Brodehl et al. (2012b)
p.N116QfsX2	Homozygous	2 (homo.) mutation carriers	–	Pathogenic	HCM, respiratory failure, SM, LW	Durmus et al. (2016)
p.A120D		3 mutation carrier + 3 obligate mutation carriers	–	Pathogenic	CM, biatrial dilation, arrhythmias, HTx, Ebstein's anomaly, SCD	Brodehl et al. (2013a)
p.Y122C		NO	–	Likely pathogenic	ARVC	Walsh et al. (2017)
p.V126L		NO	–	VUS	DCM	Haas et al. (2015)
p.R127P		NO	–	Pathogenic	DCM, SCD	Golbus et al. (2014)
p.L136P		NO	–	Likely pathogenic	DCM	Brodehl et al. (2016a)
p.L136H		NO	0.00006302	VUS	DCM	Pugh et al. (2014), Wilson et al. (2015)
p.K144X		2 mutation carriers	–	Pathogenic	DCM, LBBB, SM; HCM	Wahbi et al. (2012)

Table 1 (continued)

Mutation	Comments	Family anamnesis	MAF (gnomAD, 11th May 2018) (Lek et al. 2016)	Categorization	Clinical symptoms	References
p.R150P		NO	–	VUS	DCM	Walsh et al. (2017)
p.Q165-A174delinsAS		NO	–	Likely pathogenic	CM, AVB, SM	Schirmer et al. (2018)
p.E173-E179del		Yes	–	Pathogenic	CM, SM, SMD, respiratory failure	Munoz-Marmol et al. (1998), Pinol-Ripoll et al. (2009)
p.L200fsX20		NO	–	Likely pathogenic	DCM	Walsh et al. (2017)
p.K201fsX20 and p.R429X	Compound heterozygous	2 (homo.) mutation carriers	–	Pathogenic	DCM, arrhythmias, SM	McLaughlin et al. (2013)
p.K201N		NO	0.000007214	Likely pathogenic	DCM	Dal Ferro et al. (2017)
p.R212Q		NO	0.0002092	VUS	LVNC	Miszalski-Jamka et al. (2017)
p.D214Y	Homozygous	NO	–	Pathogenic	Arrhythmias, conduction disease, SM	Monies et al. (2017)
p.D214-E245del		NO	–	Pathogenic		Walsh et al. (2017)
p.T219P	Homozygous		–	Pathogenic	HCM, SM	Harada et al. (2018)
p.R222H		NO	0.0004004	Likely pathogenic	DCM	Dal Ferro et al. (2017)
p.R227C		6 mutation carriers	0.000008122	Pathogenic	DCM	Liu et al. (2017)
p.E234K	*MYPN*-p.R989H *CACNA1C* -p.R1973P	2 mutation carriers	–	Likely pathogenic	HCM, AVB, SQTS	Chen et al. (2017)
p.K240del	Mutation corrected (Schroder et al. 2007)	NO	–	Pathogenic	SM, ventricular arrhythmias	Schroder et al. (2007), Schroder et al. (2003)
p.K241E	*PKP2*-p.T816RfsX10	NO	–	VUS	ARVC	Lorenzon et al. (2013)
p.E245D		2 mutation carriers (Wahbi et al. 2012); 5 mutation carriers (Strach et al. 2008)	–	Pathogenic	HCM, AVB, atrial flutter, SM (Wahbi et al. 2012); AVB, RBBB, SM (Strach et al. 2008)	Conover et al. (2009), Wahbi et al. (2012), Baker et al. (2013), Maerkens et al. (2013), Strach et al. (2008)
p.E262V		NO	0.0002472	VUS	DCM	Pugh et al. (2014)
p.L274R		6 mutation carriers	–	Pathogenic	AVB, SM, LW	Hong et al. (2011)
p.L274P		6 mutation carriers (Hong et al. 2011); de novo (Yu et al. 2017)	–	Pathogenic	AVB, SCD, SM, LW (Hong et al. 2011); LGMD (Yu et al. 2017)	Hong et al. (2011), Hong et al. (2010), Yu et al. (2017)
p.R275G		NO	–	VUS	DCM	Haas et al. (2015)
p.R278W		NO	0.000004077	VUS	DCM	Walsh et al. (2017)
p.A285V		NO	–	Pathogenic	DCM, arrhythmias, SCD	Tse et al. (2013)
p.S298L		NO (Taylor et al. 2007)	0.00007944	Likely pathogenic	DCM, LBBB (Taylor et al. 2007)	Taylor et al. (2007), Andreasen et al. (2013), Ng et al. (2013)
p.D312N		NO (Taylor et al. 2007; Pugh et al. 2014)	0.0001879	VUS	DCM, SCD	Taylor et al. (2007), Pugh et al. (2014), Andreasen et al. (2013)
p.D312A	*MYBPC3*-p.R1002W *MYH7*-p.D43N	NO	0.0003974	VUS	HCM, SCD	Mook et al. (2013)
p.H326R			–	VUS	ARVC	Brodehl et al. (2013a)

Table 1 (continued)

Mutation	Comments	Family anamnesis	MAF (gnomAD, 11th May 2018) (Lek et al. 2016)	Categorization	Clinical symptoms	References
		2 mutation carriers + 1 obligate carrier				
p.Y331N		NO	–	VUS	ARVC	Walsh et al. (2017)
p.D336Y		NO	–	Pathogenic	DCM, trifascicular block, SM	Wahbi et al. (2012)
p.A337P		3 mutation carriers	–	Pathogenic	RBBB, SM	Goldfarb et al. (1998), Goudeau et al. (2006)
p.L338R		(Goudeau et al. 2006)	–	Pathogenic	SM, LW, respiratory insufficiency	Goudeau et al. (2006)
p.G340D		NO	–	VUS	DCM	Walsh et al. (2017)
p.N342D		NO (Wahbi et al. 2012); 2 affected and 1 unaffected mutation carrier (Dalakas et al. 2003)	–	Pathogenic	AVB, SM (Wahbi et al. 2012)	Dalakas et al. (2000), Brodehl et al. (2012a), van Spaendonck-Zwarts et al. (2012), Wahbi et al. (2012), Brodehl et al. (2012b), Dalakas et al. (2003)
p.S344P		De novo	–	Pathogenic	LGMD	Yu et al. (2017)
p.L345P		NO	–	Pathogenic	RBBB, SM (Wahbi et al. 2012)	Sjoberg et al. (1999)
p.Q348P		2 mutation carriers	–	Pathogenic	SM, LW	Fichna et al. (2014)
p.M349-R355delinsG		6 affected and 3 unaffected mutation carriers (Cao et al. 2013)	–	Pathogenic	AVB, SCD, SM	Cao et al. (2013)
p.R350P		6 mutation carriers (Strach et al. 2008)	–	Pathogenic	SM (Strach et al. 2008)	Clemen et al. (2015), Winter et al. (2016), Durmus et al. (2016), Bar et al. (2005b), Strach et al. (2008), Bonakdar et al. (2012), Levin et al. (2010), Walter et al. (2007)
p.R350W		NO (Taylor et al. 2007)	0.00002437	Likely pathogenic	DCM	Taylor et al. (2007), Andreasen et al. (2013)
p.R355P		NO (Wahbi et al. 2012)	–	Pathogenic	AF, SCD, SM, atrial dilation, bifascicular block, SM (Wahbi et al. 2012)	Wahbi et al. (2012), Fidzianska et al. (2005)
p.A357P		2 mutation carriers (Dagvadorj et al. 2003)	–	Pathogenic		Chourbagi et al. (2011), Dagvadorj et al. (2003), Fischer et al. (2006)
p.A357-E359del		13 mutation carriers (3 families)	–	Pathogenic	SM, LW	Fichna et al. (2014)
p.E359-S361del		4 mutation carriers (2 families)	–	Pathogenic	SM, LW	Kaminska et al. (2004)
p.A360S	*LDB3*-p.I615N	NO	–	Pathogenic	LVNC	Miszalski-Jamka et al. (2017)
p.A360P and p.N393I	Compound heterozygous	3 (c. h.) mutation carriers	–	Pathogenic	RCM, AVB, respiratory insufficiency, SM	Goldfarb et al. (1998), Goudeau et al. (2006)
p.N366del		NO	–	Pathogenic	Left anterior hemi-block, SCD, SM	Kaminska et al. (2004)
p.I367F		NO (Olive et al. 2007); 11 mutation carriers (Ripoll-Vera et al. 2015)	–	Pathogenic	HCM, RCM, AVB, SCD, SM (Olive et al. 2007); RCM, SCD, SM (Kreplak and Bar 2009)	Olive et al. (2007), Ripoll-Vera et al. (2015)
p.L370P		NO (Dagvadorj et al. 2003); de novo (Yu et al. 2017)	–	Pathogenic	LGMD (Yu et al. 2017)	Chourbagi et al. (2011), Yu et al. (2017), Dagvadorj et al. (2003), Arias et al. (2006), Olive et al. (2011)
p.L377P		Sporadic	0.000004061	Pathogenic	SM	Strach et al. (2008)
p.L385P		De novo	–	Pathogenic	CM, SM, LW	Sugawara et al. (2000)
p.R386H		NO	0.000004061	Pathogenic	DCM	Zhao et al. (2015)
p.Q389P		Sporadic	–	Pathogenic	CM, RBBB, SM	Chourbagi et al. (2011), Goudeau et al. (2001)

Table 1 (continued)

Mutation	Comments	Family anamnesis	MAF (gnomAD, 11th May 2018) (Lek et al. 2016)	Categorization	Clinical symptoms	References
p.L392P		NO	–	Pathogenic	HCM, RCM, CCD, SCD, SM, LW, respiratory insufficiency (Olive et al. 2007)	Maerkens et al. (2013), Olive et al. (2007), Olive et al. (2011)
p.D399Y		NO (Strach et al. 2008; Goudeau et al. 2006)	–	Pathogenic	SM (Strach et al. 2008); DCM, AVB, SCD, SM, LW (Goudeau et al. 2006)	Chourbagi et al. (2011), Maerkens et al. (2013), Strach et al. (2008), Goudeau et al. (2006), Fokstuen et al. (2016)
p.E401D		23 mutation carriers + 2 obligate carriers	–	Pathogenic	ALVC	Bermudez-Jimenez et al. (2017)
p.E401K		NO	–	Pathogenic	CM, heart block, SM, LW (Goudeau et al. 2006)	Chourbagi et al. (2011), Goudeau et al. (2006)
p.I402N		2 mutation carriers	–	Pathogenic	DCM, arrhythmias, SCD, respiratory insufficiency, dysphagia	Weihl et al. (2015)
p.R406W		3 mutation carriers (Arbustini et al. 2006); NO (Wahbi et al. 2012)	–	Pathogenic	RCM, biatrial dilation, AVB (Arbustini et al. 2006); AVB, AF, SM (Wahbi et al. 2012)	Dalakas et al. (2000), Chourbagi et al. (2011), Wahbi et al. (2012), Arbustini et al. (2006), Punetha et al. (2016)
p.G411RfsX34		NO	–	Likely pathogenic	DCM	Dal Ferro et al. (2017)
p.E413K		3 mutation carriers + 1 obligate carrier	–	Pathogenic	RCM, AVB, AF, SCD (Pruszczyk et al. 2007)	Chourbagi et al. (2011), Levin et al. (2010), Pruszczyk et al. (2007), Bar et al. (2007)
p.E413R		2 mutation carriers (Wahbi et al. 2012)	–	Pathogenic	HCM, LBBB, SM	Wahbi et al. (2012)
p.R415E		5 mutation carriers	–	Pathogenic	LVRC, SCD, DCM, SM, RCM, SM	Ripoll-Vera et al. (2015)
p.P419S		3 mutation carriers (Wahbi et al. 2012); 2 mutation carriers (Olive et al. 2007); 2 mutation carriers (Ripoll-Vera et al. 2015); 7 mutation carriers (Hedberg et al. 2012)	–	Pathogenic	DCM, HCM, bifascicular block, SM (Wahbi et al. 2012); HCM, left atrial dilation, heart block, SM (Olive et al. 2007); RCM, SM (Ripoll-Vera et al. 2015)	Hedberg et al. (2012), Brodehl et al. (2013b), Wahbi et al. (2012), Maerkens et al. (2013), Olive et al. (2007), Ripoll-Vera et al. (2015), Olive et al. (2011), Hedberg et al. (2013)
p.R429X		NO (Walsh et al. 2017)	0.000008122	Likely pathogenic	DCM (Walsh et al. 2017)	McLaughlin et al. (2013), Walsh et al. (2017), Pugh et al. (2014), Zhu et al. (2015)
p.P433T		NO	–	Pathogenic	RCM, SM	Jurcu et al. (2017)
p.E439K		2 mutation carriers	–	Pathogenic	DCM, AF, RBBB, respiratory insufficiency, SM	Wahbi et al. (2012)
p.T442I		3 mutation carriers (Wahbi et al. 2012)	–	Pathogenic	CM, arrhythmia, SM; DCM, SCD, RBBB, LBBB, respiratory insufficiency, SM (Wahbi et al. 2012)	Chourbagi et al. (2011), Wahbi et al. (2012), Bar et al. (2007)
p.T445A		Sporadic case	0.00003243	Pathogenic	SM, LW, respiratory insufficiency	Hong et al. (2011)
p.K449T		NO	–	Pathogenic	MFM	Chourbagi et al. (2011), Selcen et al. (2004), Bar et al. (2007), Maddison et al. (2012)
p.I451M		3 affected and 3 unaffected mutation carriers (Dalakas et al. 2003)	0.00006598	VUS	DCM	Chourbagi et al. (2011), Dalakas et al. (2003), Bar et al. (2007), Li et al. (1999)
p.T453I		Sporadic case	–	Pathogenic	RCM, left atrial dilation, AVB	

Table 1 (continued)

Mutation	Comments	Family anamnesis	MAF (gnomAD, 11th May 2018) (Lek et al. 2016)	Categorization	Clinical symptoms	References
						Chourbagi et al. (2011), Arbustini et al. (2006), Baker et al. (2013)
p.R454W	*MYOT*-p.Q74K (Bar et al. 2007)	De novo (Bar et al. 2007); 2 mutation carriers (Weihl et al. 2015); NO (Wahbi et al. 2012; Vattemi et al. 2011)	–	Pathogenic	HOCM, SM (Bar et al. 2007); CM, biatrial dilation, SCD, arrhythmias, SM (Weihl et al. 2015); MFM (Vattemi et al. 2011); RCM, AF, AVB, HTx, SM (Wahbi et al. 2012)	Brodehl et al. (2012a), Wahbi et al. (2012), Weihl et al. (2015), van Spaendonck-Zwarts et al. (2013), Hedde et al. (2012), Levin et al. (2010), Punetha et al. (2016), Bar et al. (2007), Cerino et al. (2017), Haskell et al. (2017), Shanks et al. (2017), Ackerman et al. (2016)
p.R454Q		NO	–	VUS	DCM	Haas et al. (2015)
p.E457V		5 mutation carriers	–	Pathogenic	RCM, AVB, AF, SCD, SM, LW	Hong et al. (2011)
p.V459I		2 unrelated mutation carriers (Taylor et al. 2007)	0.003191	VUS	DCM, AVB (Taylor et al. 2007)	Taylor et al. (2007), Weihl et al. (2015), Andreasen et al. (2013), Nouhravesh et al. (2016)
p.S460I		NO (Bar et al. 2007)	–	Pathogenic	RCM, AVB, SCD, SM	Chourbagi et al. (2011), Bar et al. (2007)
p.V469M	*LMNA*-p.R644C	NO	–	VUS	HCM, heart block, SM (Muntoni et al. 2006)	Chourbagi et al. (2011), Bar et al. (2007), Muntoni et al. (2006)
p.X471Y		NO	–	Pathogenic	AVB, SM	Wahbi et al. (2012)

AF = atrial fibrillation, *ALVC* = arrhythmogenic left ventricular cardiomyopathy, *ARVC* = arrhythmogenic right ventricular cardiomyopathy, *AVB* = atrioventricular block, *CM* = cardiomyopathy, *DCM* = dilated cardiomyopathy, *VUS* = genetic variant of unknown significance, *HCM* = hypertrophic cardiomyopathy, *HOCM* = hypertrophic obstructive cardiomyopathy, *HTx* = heart transplantation, *LAFB* = left anterior fascicular block, *LBBB* = left bundle-branched block, *LGMD* = limb-girdle muscular dystrophy, *LW* = limp weakness, *MAF* = minor allele frequency, *MFM* = myofibrillar myopathy, *NMD* = nonsense-mediated RNA decay, *NO* = not observed, *RBBB* = right bundle-branched block, *RCM* = restrictive cardiomyopathy, *SCD* = sudden cardiac death, *SM* = skeletal myopathy, *SMD* = smooth muscle defect, *SQTS* = short QT syndrome

Winheim et al. 2011). Interestingly, different disease-causing *DES* mutations interfere at different stages within this assembly process (Brodehl et al. 2012a; Bar et al. 2005a). The sequences of the head and rod domains are highly variable. Site-directed spin labeling in combination with electron paramagnetic resonance (EPR) spectroscopy revealed that the head domain of type III IF proteins interacts at specific sites with the rod domain (Aziz et al. 2009, 2010). Therefore, the head domain is essential for IF assembly, whereas deletion studies revealed that the tail domain of desmin and vimentin is not essential for the formation of IFs (Herrmann et al. 1996; Kaufmann et al. 1985). Thus, the exact molecular function of the desmin tail domain is unknown. However, it was suggested that the tail domain is involved in width control of ULFs (Herrmann et al. 1996) and mediates Ca^{2+}- or Mg^{2+}-dependent cross-linking (Lin et al. 2010).

Biochemical and biophysical experimental approaches

Originally, desmin was purified from muscle tissue (Izant and Lazarides 1977). Human monomeric desmin has a molecular mass of about 55 kDa and consists of 470 amino acids. Because posttranslational modifications (PTMs) are not essential for the assembly process, recombinant desmin can be efficiently expressed in bacterial cells (*Escherichia coli*). It can be isolated from inclusion bodies and purified under denaturing conditions (8 M urea) by ionic exchange and immobilized metal affinity chromatography followed by refolding through a stepwise dialysis, to reduce the urea concentration (Brodehl et al. 2012a; Kreplak and Bar 2009).

The assembly of recombinant desmin can be initiated in vitro by adding sodium chloride (Kreplak and Bar 2009). Transmission electron microscopy (TEM) or atomic force microscopy (AFM) can be applied for visualization of the assembly process (Brodehl et al. 2012a; Harder et al. 2013; Bar et al. 2006). Of note, desmin contains one cysteine residue (p.C333), which can be used for site-specific labeling with chemical fluorescent dyes (Harder et al. 2013). Apertureless scanning near-field microscopy (aSNOM) was previously used in combination with Atto740-conjugated recombinant desmin to investigate the co-assembly of mutant and wild-type desmin (Brodehl et al. 2016a; Harder et al. 2013) (Fig. 5e).

Because IF proteins including desmin are important for the cellular stability and integrity, several studies developed techniques to investigate the nanomechanical properties of IFs. Kreplak and Bär used the cantilever tip of an AFM to stretch single desmin filaments in lateral orientation (Kreplak and Bar 2009) (Fig. 5a). Guzman et al. (2006) used a tip of an AFM to push single IFs into holes of a porous membrane to determine elasticity and Young's module (Fig. 5b). Kiss et al. (2006) used also the AFM tip to lift coiled-coil desmin dimers from assembled filaments (Fig. 5c). This approach is useful to investigate the stretching and sliding of the dimers from single IFs. A further approach published by Kiss et al. used the centrifugal force of a centrifuge to displace a droplet containing preassembled desmin filaments on mica surface (Kiss and Kellermayer 2014). In this approach, the desmin filaments are stretched longitudinally by the withdrawing meniscus of the buffer droplet (Kiss and Kellermayer 2014) (Fig. 5f). The cellular stiffness of transfected cells can also be investigated using AFM (Fig. 5d). Plodinec et al. (2011) revealed that the molecular changes caused by *DES* missense mutations are associated with altered nanomechanical properties of the cells, which might contribute to disease progression. A similar approach consisting of two microplates, which are used as a stretching device for single cells, revealed that traction forces of myoblasts expressing mutant desmin are altered (Charrier et al. 2016).

Animal models

Besides some rare exceptions (Mencarelli et al. 2011), insects express only nuclear IF proteins but do not express cytoplasmic IF proteins (Herrmann and Strelkov 2011). Therefore, the model organism *Drosophila melanogaster* (fruit fly) has limited value for the investigation of *DES* mutations.

Li et al. (1996) and Capetanaki et al. (1997) generated independently *Des* knock-out mouse models by homologous recombination. Surprisingly, *Des* knock-out mice were viable and fertile but developed defects of all three muscle types. Magnetic resonance imaging (MRI) revealed a biventricular reduced ejection fraction and a decreased cardiac output (Sprinkart et al. 2012). Homozygous *Des* knock-out mice develop a severe cardiomyopathy including hemorrhaging, extensive fibrosis, and calcification in the septum and the ventricular walls, whereas heterozygous mice were not affected (Li et al. 1996; Capetanaki et al. 1997). Degeneration of cardiomyocytes, accumulation of macrophages, and severe fibrosis were also found in these *Des* knock-out mice (Thornell et al. 1997). Of note, calcified lesions were mainly present in the right ventricular wall and the septum (Thornell et al. 1997), which is in good agreement with the identification of human *DES* mutations associated with predominantly right ventricular cardiomyopathy (Klauke et al. 2010). ARVC is mainly caused by mutations in genes, encoding desmosomal structural proteins (Gerull et al. 2004; Rampazzo et al. 2002; Gehmlich et al. 2011, 2012). Interestingly, gene expression analysis revealed a remarkable overlap of differentially expressed gene networks between mouse models for desmosomal genes and the *Des* knock-out mice suggesting comparable molecular pathomechanisms (Brodehl et al. 2017a; Psarras et al. 2012). For example, genes encoding matricellular proteins like osteopontin (*Spp1*) are highly upregulated in both mouse models, which might explain the

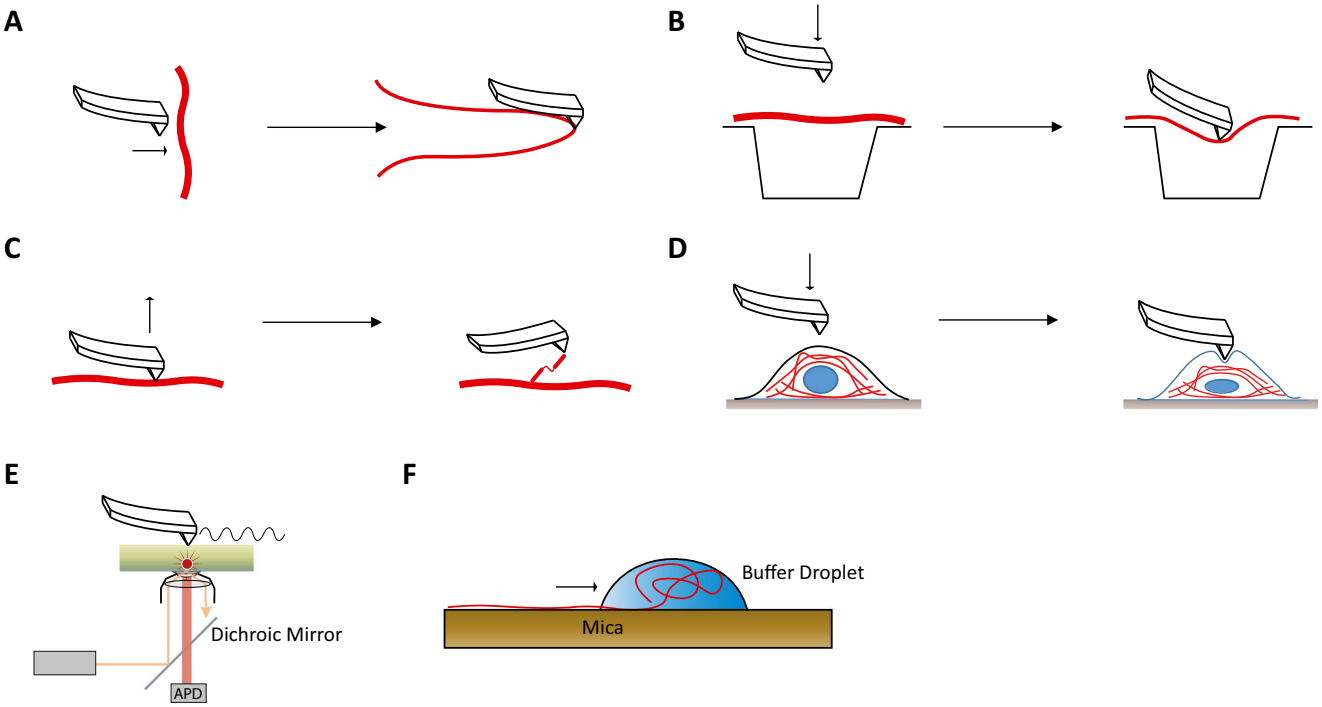

Fig. 5 Overview of biophysical approaches to investigate the nanomechanical and structural properties of different desmin filaments. **a** Longitudinal stretching of isolated desmin filaments using the tip of an atomic force microscopy (Kreplak and Bar 2009). **b** Lateral stretching of IFs by pushing desmin filaments into small holes using the tip of an atomic force microscope (Guzman et al. 2006). **c** Molecule force spectroscopy using an atomic force microscope (Kiss et al. 2006). **d** Cellular stretching of transfected cells expressing mutant desmin (Plodinec et al. 2011). **e** Schematic overview of apertureless scanning near-field optical microscopy (aSNOM) (Harder et al. 2013). **f** Longitudinal stretching of desmin filaments using the withdrawing meniscus of a buffer droplet. Centrifugation is used to apply centrifugal forces (Kiss and Kellermayer 2014)

extensive fibrotic remodeling of the extracellular matrix (Brodehl et al. 2017a; Psarras et al. 2012). Ventricular arrhythmias are frequently observed in human patients with *DES* mutations. However, the *Des* knock-out mice present atrial fibrillation but do not develop severe ventricular tachycardia (Schrickel et al. 2010). Interestingly, the phenotype of *Des* knock-out mice can be decreased by adeno-associated viruses, encoding the cDNA of wild-type desmin (Heckmann et al. 2016) suggesting a compensatory therapeutic approach for *DES* null mutations. However, the *Des* knock-out mice have some limitations, because only a few *DES* null mutations have been described in humans at all (McLaughlin et al. 2013) and the majority of *DES* mutations induce a dominant aggregation by functional alterations.

Therefore, different transgenic and knock-in mouse models expressing mutant desmin have been developed and characterized (Raats et al. 1996; Kostareva et al. 2008; Joanne et al. 2013; Diermeier et al. 2017a; Clemen et al. 2015) (Fig. 6). However, some of these mice develop only a mild or even no obvious phenotype (Kostareva et al. 2008). In contrast, the *Des*-p.R345P knock-in mice develop DCM in combination with cardiac arrhythmias and conduction disease, which is quite comparable to the clinical phenotype of human patients with the corresponding *DES* mutation (Clemen et al. 2015). Only homozygous animals develop, in addition, skeletal myopathy. These mice present mitochondrial abnormalities (Winter et al. 2016), increased stiffness of myoblasts (Diermeier et al. 2017a), and age-dependent myofibrillar changes (Diermeier et al. 2017b). Using optical voltage mapping in a transgenic mouse model with the cardiac-specific expression of mutant desmin (seven amino acid deletion), Gard et al. (2005) demonstrated the impairment of ventricular conduction by this mutation.

Recently, Rainer et al. (2018) applied transverse aortic constriction (TAC) in mice and demonstrated that toxic preamyloid oligomers containing cleaved desmin species accumulate in this heart failure model. This report indicates that in addition to *DES* mutations, also environmental factors can contribute to altered desmin structural and functional properties leading as a consequence to heart failure (Rainer et al. 2018).

Besides mutations in *DES*, DRM could be also caused by mutations in *CRYAB*, encoding the small heat shock protein αB-crystallin (Vicart et al. 1998). αB-crystallin is a binding partner of desmin filaments (Elliott et al. 2013). Mutations in both genes cause an abnormal co-aggregation of both proteins. Because mutations in *CRYAB* (αB-crystallin) cause also DRM, a transgenic mouse model with a cardiac-specific overexpression of mutant αB-crystallin (p.R120G) has been developed to investigate DRM. These mice are characterized by high mortality in early adulthood (Wang et al. 2001), toxic cardiac

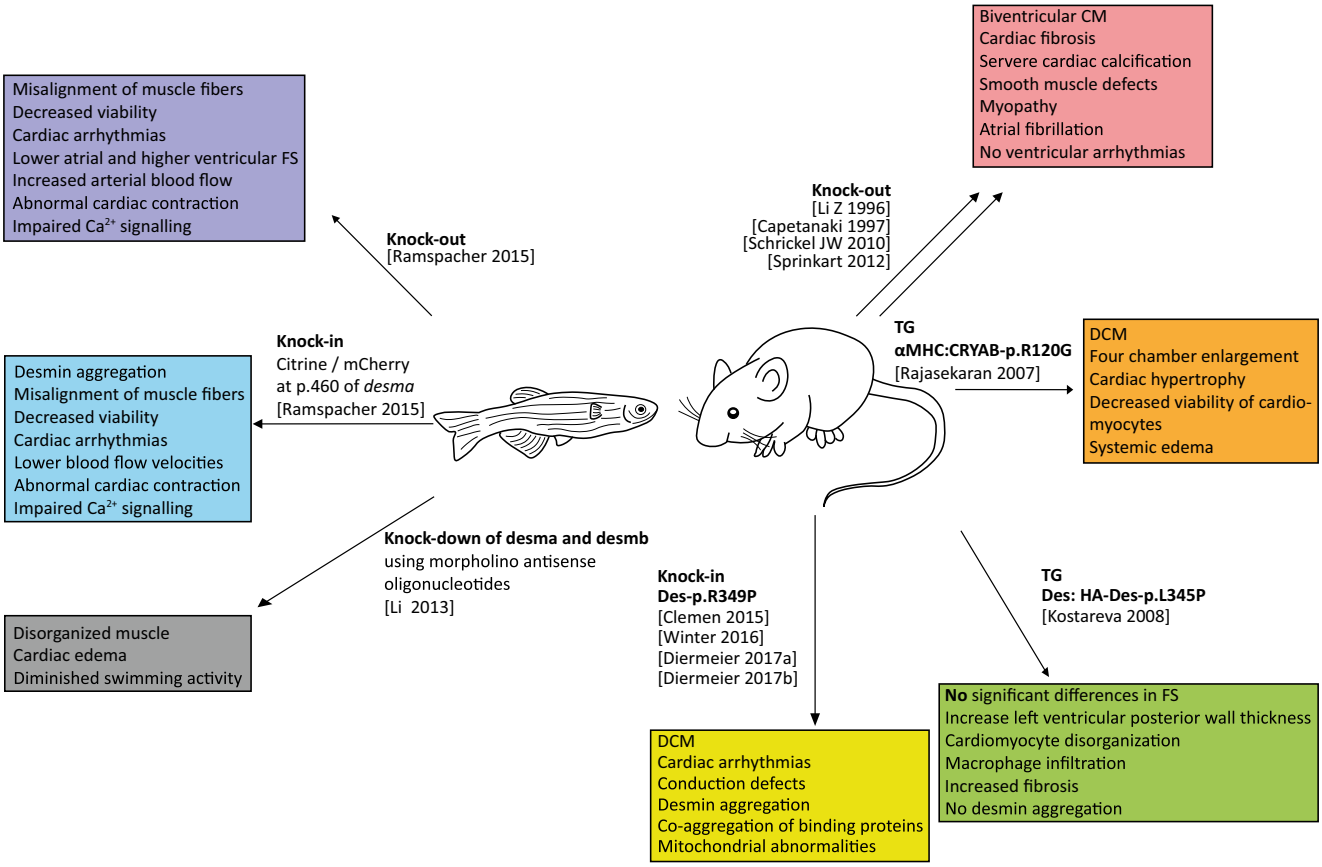

Fig. 6 Overview of animal models used for modeling desminopathies. CM = cardiomyopathy, DCM = dilated cardiomyopathy

aggresomes containing desmin and αB-crystallin (Sanbe et al. 2004), increased apoptosis of cardiomyocytes (Maloyan et al. 2005), and oxido-reductive stress (Rajasekaran et al. 2007). However, it is currently unclear if all findings might be also relevant for *DES* mutations.

The zebrafish (*Danio rerio*) has two different desmin genes *desma* and *desmb*, which are 81 or 83% homologous to human *DES* (Ramspacher et al. 2015), respectively. Using morpholino antisense oligonucleotides, Li et al. (2013) knocked down by 50% the expression *desma* and *desmb* (Fig. 6). These embryos developed cardiac edema and presented a diminished swimming activity through disorganized muscles (Li et al. 2013). Ramspacher et al. generated different zebrafish lines to compare *desma* null lines with aggregate-forming lines. Both models developed embryonic cardiac defects like altered cardiac fractional shortening, perturbed heart biomechanics, and impaired Ca^{2+} signaling but showed also specific functional alterations (Ramspacher et al. 2015).

Genetic overview about human *DES* mutations

The American College of Medical Genetics and Genomics (ACMG) suggested a classification system for the interpretation of genetic sequence variants according to several criteria like co-segregation within the family, absence in controls, in silico prediction, or functional analysis (Richards et al. 2015). According to these guidelines, genetic sequence variants can be categorized into five classes: benign, likely benign, genetic variants with unknown significance (VUS), likely pathogenic, or pathogenic, respectively. The interpretation of novel *DES* sequence variants should follow these guidelines to increase the quality of genetic counseling of affected families and to prevent overinterpretation of rare sequence variants. Based on the minor allele frequency (MAF) in controls, Kostareva et al. (2011) demonstrated for example that *DES*-p.A213V is rather a benign single nucleotide polymorphism (SNP) than a pathogenic mutation.

During the 1980s and 1990s, several reports described an abnormal cytoplasmic desmin accumulation in muscle tissue of patients with cardiac and/or skeletal myopathies without identifying the relevant molecular trigger (Stoeckel et al. 1981; Goebel 1997; Osborn and Goebel 1983; Schroder et al. 1990). Several different terms like desmin-related myopathy (DRM), desminopathy, or inclusion body myopathy were used to describe this disease (Goebel 1997). The term DRM is mainly used to describe an abnormal accumulation of desmin and associated proteins leading to skeletal and cardiac myopathies. Although DRM and desminopathy are sometimes used as

synonyms, most authors want to underline by using the term desminopathy that a pathogenic mutation in *DES* is the most likely genetic factor. However, specific cases with an abnormal desmin aggregation caused by mutations in further genes like *CRYAB* are also known (Vicart et al. 1998). The genetic trigger for DRM remained unknown until the end of the 1990s. Vicart et al. (1998) identified in a French family with DRM a pathogenic mutation in *CRYAB* (p.R120D). *CRYAB* encodes the small heat shock protein αB-crystallin, which is a binding partner of desmin filaments (Elliott et al. 2013). Although it was discovered as a structural component of the eye lenses, it is also highly expressed in (cardio)myocytes (Dubin et al. 1989). Small heat shock proteins are chaperones preventing the aggregation of misfolded proteins (Garrido et al. 2012). Interestingly, *CRYAB* mutations cause a co-aggregation of desmin and αB-crystallin (Vicart et al. 1998). Biochemical studies revealed later on that the protein-protein interaction between αB-crystallin and desmin is affected by mutations in both genes leading to an abnormal cytoplasmic co-aggregation of both proteins and in consequence to comparable clinical symptoms (Elliott et al. 2013; Rajasekaran et al. 2007; Brodehl et al. 2017b).

Shortly after the identification of the *CRYAB* mutation, two independent research groups described in parallel the first *DES* mutations causing DRM (Goldfarb et al. 1998; Munoz-Marmol et al. 1998). The human *DES* gene contains nine exons and has been mapped to chromosome 2 (2q35) (Li et al. 1989). In the last decades, it became more and more evident that *DES* mutations can cause different forms of skeletal and cardiac myopathies or variable combinations of both. Most of the known *DES* mutations are missense mutations or small in-frame deletions (Fig. 1). Many missense mutations introduce prolines (Brodehl et al. 2016a; Harada et al. 2018; Clemen et al. 2015; Fichna et al. 2014). Because of the cyclic imidic residue, prolines are incompatible with the formation of hydrogen bonds within the peptide bonds of α-helices and destabilize therefore the desmin structure.

The majority of *DES* mutations are heterozygously inherited indicating a dominant negative genetic mechanism or putative haploinsufficiency (Hedberg et al. 2012). This is in good agreement with the findings that mutant and wild-type desmin partially or completely co-aggregate (Brodehl et al. 2012a). However, some rare cases with compound heterozygous or homozygous *DES* truncating mutations were also described indicating that in specific cases the inheritance can be also recessive (Cetin et al. 2013; McLaughlin et al. 2013; Henderson et al. 2013; Tian et al. 2016; Pinol-Ripoll et al. 2009; Durmus et al. 2016). Frequently, mRNA molecules of genes with premature termination codons (PTCs) are degraded by nonsense-mediated mRNA decay or the truncated proteins are instable and consequently degraded (Alonso 2005). Consequently, patients carrying compound heterozygous *DES* truncating mutations do not express any desmin (McLaughlin et al. 2013). Heterozygous family members with one wild-type allele and a *DES* truncating mutation did not develop a phenotype excluding haploinsufficiency as the main molecular mechanism (McLaughlin et al. 2013; Henderson et al. 2013; Durmus et al. 2016). This is in agreement with heterozygous *Des* knock-out mice, which develop also no obvious phenotype (Li et al. 1996).

Of note, *DES* mutations might also occur de novo, and in these specific cases, it is difficult to recognize the genetic etiology based on the family anamnesis alone (Klauke et al. 2010; Park et al. 2000a; Dagvadorj et al. 2004; Sugawara et al. 2000). Furthermore, some *DES* splice site mutations were described (Ojrzynska et al. 2017; Khudiakov et al. 2017; Park et al. 2000b; Dunand et al. 2009; Kostareva et al. 2006; Gudkova et al. 2013) (Fig. 1a). However, it is challenging to predict the molecular consequences of splice site mutations at the mRNA and protein level because multiple unknown cryptic splice sites might be used or because exons can be completely skipped.

Clinical phenotypes associated with *DES* mutations

The clinical phenotypes associated with *DES* mutations are heterogeneous and range from isolated myopathies to different kinds of isolated cardiomyopathies and/or cardiac conduction disease. Most of the patients with *DES* mutations present a combined skeletal and cardiac myopathy. A meta-analysis published by van Spaendonck-Zwarts et al. (2011) revealed that about 75% of the patients with *DES* mutations present cardiac symptoms and only 22% of them have an isolated cardiac phenotype. However, it cannot be excluded that these patients might develop later also a phenotype of skeletal muscles since the onset of the disease appears to be independent in the different muscle systems and not predictable from the mutation. In addition, there is no evidence that the smooth muscle is concerned in desminopathies.

Some *DES* mutations are associated with an incomplete penetrance and diverse expressivity (Brodehl et al. 2016a). Even within the same family expressivity and severity of the associated clinical phenotypes of different mutation carriers might be remarkably heterogeneous (Palmio et al. 2013; van Spaendonck-Zwarts et al. 2012; McCormick et al. 2015; Bergman et al. 2007; Pica et al. 2008). Of note, the specific clinical phenotype can develop progressively and might change age dependently. In this context, data from clinical follow-up studies over longer periods are missing for most *DES* mutation carriers. Typically, DRM is clinically diagnosed during the third decade of life (van Spaendonck-Zwarts et al. 2011). However, the onset of disease is also highly variable and juvenile and even infantile onsets were reported (Klauke et al. 2010; Pinol-Ripoll et al. 2009).

Remarkably, there is no clear correlation between the position of the *DES* mutation and the associated clinical entities affecting the cardiac and skeletal muscle to a different degree (Figs. 3 and 4).

Furthermore, there is currently no molecular explanation for the broad spectrum of clinical phenotypes associated with *DES* mutations. Therefore, it has to be assumed that further genetic, epigenetic, and environmental factors modulate the clinical phenotype.

Cellular and molecular pathomechanisms caused by *DES* mutations

The histopathological hallmark of many but not of all *DES* mutations is an abnormal cytoplasmic desmin aggregation in (cardio)myocytes (Brodehl et al. 2012a; Goldfarb and Dalakas 2009; Herrmann et al. 2007). This desmin aggregation can be observed in cell transfection studies (Bar et al. 2005b; Brodehl et al. 2013a), in animal models (Clemen et al. 2015), and also in explanted myocardial tissue from *DES* mutation carriers (Brodehl et al. 2013a; Goebel and Muller 2006). However, there is a controversial on-going debate in what respect these desmin aggregates are toxic or whether the disturbed IF network is the molecular trigger for the degeneration of the cardiomyocytes (Goldfarb and Dalakas 2009; McLendon and Robbins 2011; Capetanaki et al. 2015). It has been suggested that mutant desmin inhibits the ubiquitin-proteasome system (Liu et al. 2006a, b). Several further secondary and tertiary molecular and cellular pathomechanisms have been reported, which contribute consequently to the disease progression. Conover et al. (2009) demonstrated that in addition to the IF system, also the actin filaments are affected by *DES*-p.E245D mutation. This can be explained by the finding that the IF system is cross-linked with several cytoskeletal components. In consequence, the force generation of myoblast and the complete cell elasticity can be altered by *DES* mutations (Charrier et al. 2016; Even et al. 2017). Different protein-protein interactions of desmin and IF-associated proteins can also be affected by *DES* mutations leading to a co-aggregation of these binding proteins (Chourbagi et al. 2011; Elliott et al. 2013). Interestingly, several studies reported a structural or functional impairment of the mitochondria by *DES* mutations (Winter et al. 2016; Henderson et al. 2013; McCormick et al. 2015; Smolina et al. 2014). The interplay between IFs and mitochondria was previously reviewed in detail (Schwarz and Leube 2016).

It has to be mentioned that not every pathogenic *DES* mutation causes desmin aggregation. Especially, mutations localized in the tail domain do not cause abnormal aggregation (Sharma et al. 2009; Brodehl et al. 2013b; Bar et al. 2010), which is in agreement with the finding that the deletion of the tail domain has no obvious effect on filament assembly (Kaufmann et al. 1985). However, different studies indicate that the nanomechanical properties and the network formation can nevertheless be changed by these mutations (Kreplak and Bar 2009; Bar et al. 2010).

Because desmin filaments are cellular scaffolds connecting different cellular components with the cytoskeleton, it is not surprising that *DES* mutations cause multiple pathomechanisms leading to death of cardiomyocytes and contributing accordingly to disease progression. Although the detailed molecular pathways triggered by the abnormal desmin aggregates are currently unknown, it was shown that desmin filaments are also substrates of caspases promoting apoptosis (Chen et al. 2003). Comparable abnormal protein aggregates caused by the *CRYAB* mutation p.R120G lead to an increased apoptosis including activation of caspase-3 in transgenic mice (Maloyan et al. 2005; Maloyan et al. 2010). However, it was also suggested that necrosis contributes to the pathogenicity in desmin knock-out mice (Sprinkart et al. 2012).

Therapeutic approaches

Currently, there is no specific molecular treatment available for desminopathies or DRM, respectively. However, some experimental reports using different mouse or cell culture models describe first putative therapeutic approaches, which will we summarized in the following paragraph. Sanbe et al. used oral administration of geranylgeranylacetone (GGA) to induce the expression of small heat shock proteins in a transgenic mouse model expressing mutant αB-crystallin (*CRYAB*-p.R120G), which is a model for DRM (Rajasekaran et al. 2007). Small heat shock proteins are adenosine triphosphate (ATP)-independent chaperones, which bind unfolded proteins and prevent protein accumulation and aggregation (Garrido et al. 2012). Remarkably, GGA protected *CRYAB*-p.R120G transgenic mice significantly against cardiac death by inducing the expression of small heat shock proteins and inhibiting protein aggregation (Sanbe et al. 2009). Nicorandil is a small compound, which is cardioprotective (Zhao et al. 2014). Recently, it was demonstrated that the administration of nicorandil improves the fractional shortening and reverses cardiac electrical remodeling in the *CRYAB*-p.R120G transgenic mouse model (Matsushita et al. 2014; Sanbe et al. 2011). Pharmacological analysis using C2C12 cells transiently expressing mutant desmin revealed that inhibition of the Rac1 pathway, activation of autophagy pathways using PP242, and further inducers of autophagy and antioxidant treatment significantly reduce the desmin aggregation (Cabet et al. 2015). However, it is unclear how or if these preclinical data can be translated to the treatment of patients with *DES* mutations.

Despite these pilot experiments, there is currently no molecular gene therapy available. In general, gene therapy

suffered in the last decades several setbacks (Yla-Herttuala and Baker 2017), and before applicable under standard clinical conditions, several ethical and technical issues have to be solved.

Future perspectives

The majority of *DES* mutations are missense or small deletion mutations, which might be classified into two groups: aggregate-forming and filament-forming mutations. For most of the filament-forming mutations, the exact pathomechanisms are widely unknown and future molecular studies are necessary to elucidate them. Several mutations in further genes like *CRYAB* (Brodehl et al. 2017b), *FLNC* (Brodehl et al. 2016b), *BAG3* (Schanzer et al. 2018), and *MYOT* (Maerkens et al. 2016) cause also an abnormal protein aggregation leading in consequence to cardiac and skeletal myopathies.

However, for the majority of *DES* mutations, the aggregate formation seems to be a first direct trigger of the disease. However, the downstream effects are diverse and heterogeneous. Hopefully, new developments in molecular and cell biology will help to develop molecular therapies for desminopathies. Because the aggregate formation is a direct consequence of *DES* mutations, it can be suggested to focus primarily on the prevention of aggregate formation. Targeting *DES* gene regulation leading to a decreased expression of the mutant *DES* allele might be a promising strategy. Several putative approaches based on DNA genome editing using CRISPR-Cas9 or TALENs (Jinek et al. 2012), RNA-targeted therapeutics (Crooke et al. 2018), or the modulation of protein degradation (Clift et al. 2017) or folding are relevant for preclinical proof-of-concept studies to specifically treat *DES* mutation carriers. However, at present, these novel technologies are far away from a transfer to clinical application.

Summary

Different forms of cardiomyopathies and skeletal myopathies can be caused by *DES* mutations. Novel *DES* mutations should be carefully interpreted according to ACMG guidelines to improve genetic counseling. The majority of pathogenic *DES* mutations cause an abnormal cytoplasmic desmin aggregation, which can be verified by cell transfection experiments (Brodehl et al. 2013a). Because desmin is a scaffolding protein connecting different cell organelles, the secondary and tertiary molecular and cellular pathomechanism in vitro and in vivo are diverse and affect different cellular compartments. Currently, there is no specific therapy for desminopathies available. Therefore, there is a strong need for the development of efficient molecular therapies in the future.

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Compliance with ethical standards

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Conflicts of interest Andreas Brodehl declares that he has no conflicts of interest. Anna Gaertner-Rommel declares that she has no conflicts of interest. Hendrik Milting declares that he has no conflicts of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Additional databases 1. Human Intermediate Filament Database, www.interfil.org (Szeverenyi et al. 2008).

2. The Human Protein Atlas, https://www.proteinatlas.org (Uhlen et al. 2015).

3. ClinVar, https://www.ncbi.nlm.nih.gov/clinvar (Landrum et al. 2016).

4. Leiden Open Variation Database, http://www.dmd.nl.

5. Exome Aggregation Consortium (ExAC), http://exac.broadinstitute.org/ (Lek et al. 2016).

6. Genome Aggregation Database (gnomAD), http://gnomad.broadinstitute.org/ (Lek et al. 2016).

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