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Role of Genetic Factors in Dilated Cardiomyopathy

Cieslewicz Artur and Jablecka Anna
Karol Marcinkowski Medical University in Poznan, Department of Clinical Pharmacology
Poland

1. Introduction

Dilated cardiomyopathy (DCM) is a heart muscle disease characterized by cardiac chamber enlargement and impaired systolic (and almost always diastolic) function. It is usually associated with heart failure, arrhythmias and/or conduction system disease and thromboembolic disease but may also be asymptomatic. DCM is diagnosed in the presence of left ventricular enlargement and systolic dysfunction (left ventricular ejection fraction less than 50% or fractional shortening of less than 25-30%). It is considered one of the most common causes of heart failure, resulting in considerable morbidity and mortality. Patients with DCM suffer from heart failure, arrhythmia and are at risk of premature death. The prevalence of dilated cardiomyopathy is one case out of 2500 patients with an incidence of 7/100 000/year and it is 3 times more frequent in blacks and males than whites and females (Bender et al., 2011, Hershberger et al., 2007, Taylor et al., 2006).

DCM may appear sporadic in a single member of family and is called then idiopathic DCM (IDC). Dilated cardiomyopathy may be also inherited and is termed familial DCM (FDC), contributing for 20-48 % of DCM. According to Mestroni et al. (1999), the diagnosis of FDC is made in the presence of two or more affected individuals in a single family or in the presence of a first-degree relative of a dilated cardiomyopathy patient with well documented unexplained sudden death at < 35 years of age. The principle causes of FDC are genetic mutations affecting cardiac myocytes (Taylor et al., 2006). Knowledge about genes involved in development of dilated cardiomyopathy can be used to create genetic tests for assessing the risk of DCM.

As DCM is a multigenic disorder, there are many genes contributing to development of this disease. More than 30 genes, coding a variety of proteins such as nuclear envelope proteins, cardiac sarcomere units, ion channels, transcription factors, or dystrophin-associated cytoskeletal complex, were identified as causes of dilated cardiomyopathy (Hershberger et al., 2009a). Some of these genes (discussed in this chapter) are presented in Table 1. For additional information see Hershberger et al. (2010) and UpToDate® website.

2.Major genetic causes of DCM

2.1 Lamins A/C (LMNA)

Nuclear lamins (see Figure 1) are intermediate filament-type proteins that are major building blocks of the nuclear lamina – a meshwork underlying the inner nuclear

membrane. They can also be localized in the nuclear interior. Nuclei assembled *in vitro* in the absence of lamins are fragile, indicating the role of lamins in stabilizing the cell nucleus. Lamins also take part in DNA replication, chromatin organization, spatial arrangement of nuclear pore complexes, nuclear growth and anchorage of nuclear envelope proteins (Stuurman et al., 1998). Patients carrying mutations in LMNA gene are known to be at risk of conduction disorders and arrhythmic events in addition to ventricular dilatation and heart failure (Haugaa et al., 2009).

Gene	Encoded protein	Function
Major genetic factors		
LMNA	lamins A/C	building blocks of nuclear lamina
TNNT2	cardiac troponin T (cTnT)	regulation of muscle contraction
β-MYH7	β-myosin heavy chain	conversion of chemical energy into mechanical force
Other genetic factors		
SCN5A	alpha subunit of type V voltage-gated sodium channel	control of the flow of sodium ions into cardiac muscle cells
TCAP	titin-cap (telethonin)	regulation of sarcomere assembly
HBEGF	heparin-binding epidermal growth factor	regulation of cell growth and differentiation
SRA1	steroid receptor RNA activator 1	stimulation of proliferation and apoptosis
IK	cytokine	down-regulation of expression of HLA class II antigens
TPM1	α-tropomyosin	regulation of actin-myosin interaction
PSEN 1/2	presenilin 1 / 2	multi-pass transmembrane proteins
Dnm1l	dynamin-1-like	establishing mitochondrial morphology
LDB3	LIM domain binding 3	interaction with α-actinin-2 and protein kinase C

Table 1. Genes associated with dilated cardiomyopathy

Many studies suggest that defects in LMNA gene, encoding lamins A/C, are one of the most significant genetic causes of dilated cardiomyopathy. According to Colombo et al. (2008), the LMNA gene is involved in up to 30-50% of patients with cardiac conduction disorders and DCM. Arbustini et al. (2002) were one of the first to reveal the role of LMNA mutations in developing dilated cardiomyopathy. The researchers investigated the prevalence of LMNA gene defects in familial and idiopathic DCM associated with atrioventricular block or increased serum creatine-phosphokinase (sCPK). 73 cases of DCM (15 with atrioventricular block) were analysed, revealing five LMNA mutations (K97E, E111X, R190W, E317K and 4 base pair insertion at 1713 cDNA) in five cases of familial autosomal dominant DCM with atrioventricular block (33%). The role of LMNA mutations was further confirmed by Hermida-Prieto et al. (2004) in the study on 67 consecutive patients with DCM (18 with FDC, 17 with possible FDC and 32 with idiopathic DCM). The researchers observed two disease-causing mutations in LMNA gene, a novel R349L substitution and R190W (the same as in Arbustini et al. study). Both mutations were associated with severe forms of familial DCM. Another

discovery concerning lamins was brought by Kärkkäinen et al. (2006). The study was carried out on 66 DCM patients, who received heart transplant. DNA sequencing revealed 6 mutations in LMNA gene (A132P, S143P, R190W, T1085 deletion, G1493 deletion, and R541S) which explained DCM in 9% patients. Moreover, one of these mutations (S143P) explained 7 % of all cases in an unselected DCM population.

Fig. 1. Structure of human lamin.

In order to investigate mechanism responsible for electrophysiologic and myocardial phenotypes caused by dominant human LMNA mutations, an experiment was carried out on heterozygous *Lmna* +/- mice (Wolf et al., 2008). Cardiac function and electrophysiology were examined in heterozygous mice which underwent a targeted deletion of LMNA gene resulting in reduced level of lamin A/C protein in hearts. The researchers found out that despite normal structure and function in young *Lmna* +/- mice, older mice had altered atrioventricular nodal architecture, functional electrophysiological deficits and arrhythmias. Moreover, aged *Lmna* +/- mice, similar to humans with LMNA mutations, developed DCM, sometimes without overt conductions system disease. 50-week old *Lmna* +/- mice had enlarged ventricular chambers in systole ($p=0.01$) and diastole ($p=0.002$) corresponding to significantly decreased fractional shortening ($p=0.02$). Cardiac sections of these mice also showed more fibrosis than wildtype mice. Cell and sarcomere shortening were decreased in *Lmna* +/- myocytes compared to wildtype ($p<0.001$) with ventricular dilatation and depressed cardiac contractility consistent with DCM in aged *Lmna* +/- mice. These findings confirmed lamin A/C haploinsufficency as a possible mechanism leading to DCM.

Parks et al. (2008) were one of the first to carry out a research concerning lamins A/C mutation on a large group of patients. DNA from 324 patients with DCM (187 with FDC) was sequenced for nucleotide alterations in LMNA gene. 18 protein-altering variants (14 novel) were identified in 5.9% cases (7.5% of FDC and 3.6% of IDC). 11 alterations were missense mutations (which changed conserved amino acid), three were nonsense, another three were insertion/deletion and one was a splice site alteration. Conduction system disease and DCM were common among the carriers of these LMNA variants. These findings were further investigated by Cowan et al. (2010), who expressed in COS7 cells GFP-prelamin A constructs including 13 LMNA variants identified by Parks et al. (see Table 2). Confocal immunofluorescence microscopy was then used to characterize GFP-lamin A localization and nuclear morphology. Abnormal phenotypes were observed for 10 out of 13 analyzed variants, providing evidence which supported pathogenicity of these variants.

Recently, Botto et al. (2010) described additional novel LMNA mutation in FDC. Sequencing of the patient's LMNA coding exons revealed heterozygous missense mutation cytosine to thymine at nucleotide 565 in exon 3 which caused a substitution of arginine to hydrophobic tryptophan (R189W mutation) in a conserved residue located in the coil 1b of the alpha-helical rod domain. This mutation was located near the most prevalent lamin A/C mutation R190W, suggesting a "hot-spot" region at exon 3 and was not identified in a group of 50 healthy volunteers. Moreover, the mutation was identified in 3 relatives of patient, who will then benefit from regular clinical cardiac follow-up and early treatment.

LMNA variant	Mutation type	Pathogenicity of mutation (+/-)
R89L	substitution: Arg to Leu	+
R101P	substitution: Arg to Pro	+
R166P	substitution: Arg to Pro	+
R190Q	substitution: Arg to Gln	+
E203K	substitution: Glu to Lys	+
I210S	substitution: Ile to Ser	+
L215P	substitution: Leu to Pro	+
A318T	substitution: Ala to Thr	-
R388H	substitution: Arg to His	+
R399C	substitution: Arg to Cys	-
S437Hfsx1	substitution: Ser to His, frameshift, STOP codon (nonsense)	+
R471H	substitution: Arg to His	-
R654X	STOP codon (nonsense)	+

Table 2. LMNA variants inspected in patients with DCM (Cowan et al., 2010).

2.2 Cardiac troponin T (TNNT2)

Troponin T is the tropomyosin-binding protein in the troponin regulatory complex located on the thin filament of the contractile apparatus (see Figure 2). There are three isotype forms of troponin T: fast skeletal muscle, slow skeletal muscle and cardiac troponin T. These muscle-specific isoforms are expressed by different genes. Further diversity of troponin T comes from alternative splicing of RNA molecule (Katus et al., 1992).

Fig. 2. Location of troponin T in the troponin regulatory complex.

Cardiac troponin T is encoded by TNNT2 gene, which alterations significantly contribute to dilated cardiomyopathy. Kamisago et al. (2000) were one of the first to show the role of TNNT2, identifying a deletion of AGA triplet resulting in deletion of lysine in residue 210 (K210 deletion) of troponin T protein chain in samples from two unrelated families suffering DCM. K210 mutation is one of the most frequent variants observed in patients suffering DCM. Otten et al. (2010) carried out a study, identifying 6 DCM patients carrying K210 deletion from 4 Dutch families. These patients showed severe form of DCM with early disease manifestation (mean age of DCM manifestation was 33 years). Moreover, heart transplantation was required in three patients at ages 12, 18 and 19 years.

The evidence from large cohort of patients was further provided by Mogensen et al. (2004). The researchers performed the study on 235 patients suffering DCM (102 with FDC). Mutation analysis of TNNT2 resulted in identification of three novel mutations (R131W, R205L and D270N) and one reported previously(K210 deletion) in 13 patients from 4 families. Three out of 13 patients received cardiac transplants, three died of heart failure, another three died suddenly and four remained stable on conventional heart failure therapy. All mutations segregated with the disease in each family and were absent in the control group and in the group of patients with hypertrophic cardiomyopathy (HCM). Identified mutations were considered disease-causing, because they co-segregated with disease in each family, were absent in control and HCM groups and were localized in conserved and functionally important regions of gene. Moreover, functional studies of mutated protein revealed altered troponin protein-protein interactions.

Additional data concerning the role of TNNT2 mutations in DCM was delivered by Hershberger et al. (2009b). The researchers carried out bidirectional sequencing of TNNT2 using DNA samples from 313 unrelated probands with DCM (183 with FDC and 130 with IDC). Six protein-altering mutations were identified in 9 probands (2.9% of all patients). None of these variants were present in control group (253 patients). Five variants were missense mutations altering highly conserved amino acids (four novel mutations: R134G, R151C, R159Q, R205W and one previously reported in HCM:E244D)and one was K210 deletion. All of these mutations were considered possibly or likely disease-causing based on the clinical, pedigree and molecular genetic data (see Table 3). Additional functional studies of these mutations, carried out in cardiac myocytes reconstituted with mutant troponin T proteins revealed decreased Ca^{2+} sensitivity of force development (a hallmark of DCM), supporting disease-causing potential of these genetic variants.

TNNT2 variant	Mutation type	Disease-causing
R134G	substitution: Arg to Gly	yes (segregated with disease in other affected family members)
R151C	substitution: Arg to Cys	yes (homozygous mutation associated with aggresive disease)
R159Q	substitution: Arg to Gln	yes (replacement of conserved amino acid)
R205W	substitution: Arg to Trp	yes (similar to disease-causing R205L mutation reported by Mogensen et al., 2004)
E244D	substitution: Glu to Asp	yes (reported as disease-causing in patient with HCM)
K210del	deletion of lysine	yes (reported as disease-causing in several cases)

Table 3. Disease-causing TNNT2 variants observed in patients with DCM (Hershberger et al., 2009b)

Mutations in TNNT2 may be also associated with more than one type of cardiomyopathy. For example, Menon et al. (2008) study conducted on a family with autosomal dominant heart disease variably expressed as restrictive cardiomyopathy (RCM), HCM and DCM revealed cosegregation of TNNT2 mutation with disease phenotype. Sequencing of TNNT2 identified a heterozygous missense mutation resulting in I79N substitution inherited by all 9

affected family members but none of the six unaffected relatives. Mutation carriers were diagnosed with RCM (2 patients), HCM (3 patients), DCM (2 patients), mixed cardiomyopathy (1 patient) and mild concentric left ventricular hypertrophy (1 patient).
An experiment on mice, carried out by Ahmad et al. (2008) revealed the role of cardiac troponin T quantity and function in development of heart and in dilated cardiomyopathy. The researchers created heterozygous $TNNT2^{+/-}$ mice (i.e. lacking one TNNT2 allele) and then crossbred them to obtain homozygous null $TNNT2^{-/-}$ embryos. Moreover, transgenic mice overexpressing wildtype (TG^{WT}) or mutant ($TG^{K210\Delta}$: K210 deletion) TNNT2 were also generated and used to create individuals lacking one allele of TNNT2 and carrying wildtype ($TNNT2^{+/-}$/ TG^{WT}) or mutant ($TNNT2^{+/-}$/ $TG^{K210\Delta}$) transgenes. The scientists found out that $TNNT2^{+/-}$ mice compared to wildtype had significantly reduced transcript but not protein. Moreover, $TNNT2^{+/-}$ mice had normal hearts. On the other hand $TNNT2^{+/-}$/ $TG^{K210\Delta}$ mice had severe DCM while$TG^{K210\Delta}$ only mild DCM, suggesting the role of greater ratio of mutant to wildtype TNNT2 transcript in $TNNT2^{+/-}$/ $TG^{K210\Delta}$ mice compared to $TG^{K210\Delta}$ individuals. $TNNT2^{+/-}$/ $TG^{K210\Delta}$ also showed muscle Ca2+ desenization but no difference in maximum force generation. The $TNNT2^{-/-}$ embryos had normally looped hearts but thin ventricular walls, large pericardial effusions, noncontractile hearts and severely disorganized sarcomers.

2.3 β-myosin heavy chain (MYH7)

Myosin is a protein that converts chemical energy into mechanical force through hydrolysis of ATP. Within the cell, it is organized as a pair of heavy chains and two pairs of light chains. The myosin heavy chain is a highly asymmetric molecule with a predominantly globular head and a rod-like tail, which is formed of two α-helices and accounts for the formation of the thick filament backbone (see Figure 3). The globular head contains a light-chain-binding domain and a catalytic domain with actin and ATP-binding sites (Kabaeva 2002).

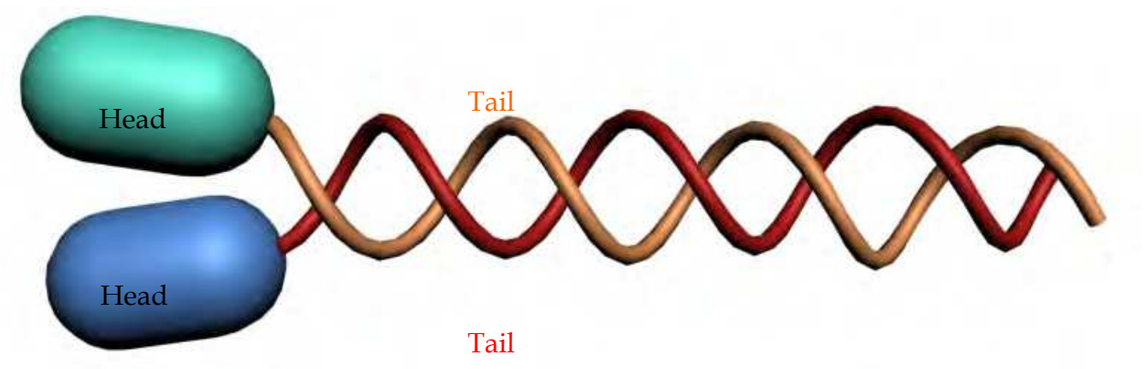

Fig. 3. A pair of myosin heavy chains.

Currently, more than 70 different mutations have been identified in MYH7 gene in association with DCM (Tanjore et al., 2010). Moreover, mutations in MYH7 have been reported in 4.2% cases of dilated cardiomyopathy (Hershberger et al., 2008). Clinical evaluations carried out in 21 kindreds with FDC delivered first data suggesting the role of MYH7 mutations in dilated cardiomyopathy (Kamisago et al., 2000). A genome-wide linkage study revealed genetic locus for mutations associated with DCM located at chromosome 14q11.2-13, encoding the gene for

cardiac β-myosin heavy chain. Disease-causing dominant mutations of MYH7 (S532P and F764L) were identified in 4 kindreds, resulting in early-onset ventricular dilatation (average age: 24 years) and diminished contractile function.

Two novel mutations were identified in the study conducted by Kärkkäinen et al. (2004), carried out on 52 DCM Finnish patients. Screening of MYH7 coding regions resulted in identification of R1053Q and R1500W mutations in two patients. The R1500W mutation was associated with typical DCM phenotype. On the other hand, patient with R1053Q variant had dilated left ventricle and impaired systolic function, but other family members carrying this mutation had septal hypertrophy, suggesting that this variant was primarily an HCM mutation which could also lead to DCM.

Additional MYH7 mutations were identified by Villard et al. (2005). The researchers screened all coding regions of MYH7 and TNNT2 gene in 96 independent patients (54 with FDC and 42 with IDC), identifying seven new mutations in MYH7 gene (see Table 4). Moreover, contrasting clinical features were observed between MYH7 and TNNT2 mutation carriers: mean age at diagnosis was late, penetrance was incomplete in adults and mean age at major cardiac event was higher in MYH7 mutation carriers compared to TNNT2.

MYH7 variant	Mutation type	Affected part of myosine heavy chain
I201T	substitution: Ile to Thr	head
T412N	substitution: Thr to Asn	head
A550V	substitution: Ala to Val	head
T1019N	substitution: Thr to Asn	tail
R1193S	substitution: Arg to Ser	tail
E1426K	substitution: Glu to Lys	tail
R1634S	substitution: Arg to Ser	tail

Table 4. Disease-causing MYH7 variants observed in patients with DCM (Villard et al., 2005)

Hershberger et al. (2008) in a study carried out on a cohort of 313 patients identified 12 mutations in MYH7 gene (9 novel): R237W, V964L, A970V, R1045C, D1096Y, R1359C, R1500W, E1619K, V1692M, G1808A, H1901Q and R1863Q. These variants were observed in 13 out of 313 probands (4.2%), revealing that MYH7 was the most commonly mutated gene in studied group. All observed variants were considered possibly or likely disease-causing.

Additional two mutations were described by Boda et al. (2009) in the group of 100 DCM patients. Screening of MYH7 gene revealed a substitution G377R in one DCM patient, diagnosed at the age of 11 years and R787H substitution in another patient, diagnosed at the age of 7 years. Møller et al. (2009) identified three MYH7 mutations (K637E, resulting in charge change in actin cleft, L1038P introducing helix-breaking proline in the rod and R1832C resulting in loss of plus charge in light meromyosin and introduction of reactive cysteine) in one-quarter of studied DCM patients.

Tanjore et al. (2010) in the study carried out on 292 individuals (100 healthy controls, 95 HCM and 92 DCM) revealed common genetic variation (5 SNPs) in exons 7, 12, 19 and 20 of MYH7 gene for DCM and HCM patients. However, three out of 5 variants were heterozygous in HCM, whereas the same SNPs were found to be homozygous in DCM patients, revealing the dose effect of the protein with the gross anatomical variations in the ventricles leading to heart failure in DCM cases.

Rare mutations explain only a small percentage of DCM cases. Rampersaud et al. (2009) assumed that more common variants may also play a role in increasing susceptibility to DCM, similarly to observations in other common complex diseases. To verify that hypothesis, case-control analyses were performed on all DNA polymorphic variation identified in a resequencing study of six genes associated with DCM carried out on 477 individuals (289 probands with DCM and 188 controls). Multivariate analyses revealed that a block of 9 MYH7 variants was strongly associated with DCM.

3. Other genes involved in development of DCM

Variation in three genes discussed above is considered to explain abut 10% of DCM cases. There are however other genetic factors that can also play role in development of dilated cardiomyopathy.

SCN5A gene encodes alpha subunit of type V voltage-gated sodium channel (see Figure 4), which is abundant in cardiac muscle and controls the flow of sodium ions into cardiac muscle cells, playing major role in signalling start of each heartbeat, coordinating the contractions of the upper and lower chambers of heart and maintaining normal heart rhythm.

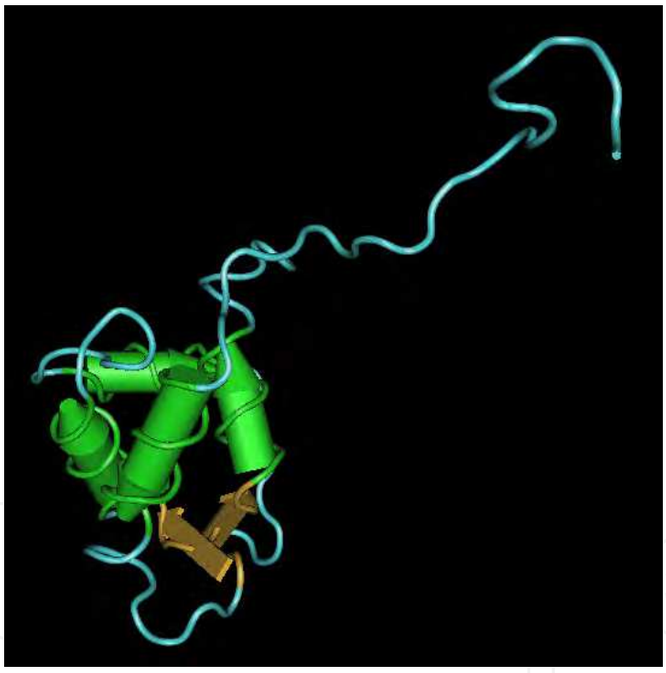

Fig. 4. Structure of the C-terminal Ef-hand domain of human cardiac sodium channel. Available from http://www.ncbi.nlm.nih.gov/Structure/mmdb/mmdbsrv.cgi?uid=68594 (Chagot et al., 2009).

Mutations in SCN5A has been described as causative in long QT syndrome and dilated cardiomyopathy. McNair et al. (2004) carried out a research on a large family affected by an autosomal cardiac conduction disorder associated with sinus node dysfunction, arrhythmia and ventricular dilatation and dysfunction. Linkage analyses mapped the disease phenotype to a region on chromosome 3p22-p25, containing cardiac sodium channel gene SCN5A. SCN5A gene was screened in 21 subjects, revealing a heterozygous G to A substitution at

position 3823, changing aspartic acid to asparagine (D1275N) in highly conserved residue. The mutation was present in all affected family members (19 patients), while being absent in 300 control chromosomes, and predicted a change of charge within the S3 segment of protein domain III. All of mutations changed conserved amino acids. Two novel variants segregated with FDC in families and were considered likely disease-causing. On the other hand, two variants associated also with Brugada syndrome (R526H) and long QT-syndrome (A572D) did not segregate with DCM.

SCN5A variant	Mutation type	Pathogenicity of mutation (+/-)	Also associated with
S216L	substitution: Ser to Leu	+	LQT syndrome
R222Q	substitution: Arg to Gln	+	-
R526H	substitution: Arg to His	-	Brugada syndrome
A572D	substitution: Ala to Asp	-	LQT syndrome
P648L	substitution: Pro to Leu	+	LQT syndrome
I1835T	substitution: Ile to Thr	+	-
P2005A	substitution: Pro to Ala	+	LQT syndrome

Table 5. SCN5A variants observed in patients with DCM (Hershberger et al., 2008)

A study performed on 338 DCM patients from Familial Cardiomyopathy Registry revealed 5 missense SCN5A mutations, including novel E446K, F1520L, V1279I and already described D1275 and R222Q. Mutations were detected in 1.7% of DCM families. Most of them were localized to the highly conserved homologous S3 and S4 transmembrane segments , suggesting a shared mechanism of disruption of the voltage-sensing mechanism of this channel leading to DCM. Patients carrying SCN5A mutations showed strong arrhythmic pattern that had clinical and diagnostic implications (McNair et al., 2011).

Titin-cap (or telethonin), encoded by **TCAP** gene, is a protein regulating sarcomere assembly. It has kinase activity and serves as attachment for myofibrils and other muscle-related proteins (Valle et al., 1997). Mutations in TCAP gene were described in association with cardiomyopathies. Hayashi et al. (2004) analyzed TCAP genotype in 346 patients with HCM and 136 with DCM (34 FDC, 102 IDC), revealing two mutations in patients with HCM and one (E132Q substitution) in patient with DCM. Moreover, the researchers demonstrated that HCM-associated mutations augmented the ability of titin-cap to interact with titin and calsarcin-1, whereas DCM-associated mutations impaired the interaction of titin-cap with muscle LIM protein, titin and calsarcin-1. The role of TCAP in development of DCM was also confirmed by Hershberger et al. (2008), who found three protein-altering variants of TCAP in 3 out of 313 DCM patients (with two variants segregating with disease).

LDB3 (LIM domain binding 3), also known as ZASP or CYPHER is another gene associated with DCM. It encodes a protein containing PDZ domain which interacts with α-actinin-2 through its N-terminal PDZ domain and with protein kinase C through C-terminal LIM domains (a cysteine-rich motif containing two zinc-binding modules). It also interacts with myozenin family members.

First data revealing the role of LDB3 in DCM was delivered by Vatta et al. (2003). The research was carried out on 100 DCM probands and resulted in identification of 5 mutations

(substitutions: S196L, I352M, D117N, K136M and T213I) in 6 patients (two families and four sporadic cases). None of these mutations were identified in the control group (200 individuals). 5 out of 6 mutations resulted in substitutions in conserved regions and all lied within the linker between PDZ and LIM domains. *In vitro* studies showed cytoskeleton disarray in cells transfected with mutated LDB3. One additional mutation in LDB3 was discovered by Arimura et al. (2004) in the study carried out on 96 unrelated Japanese patients with DCM. D626N substitution located within the LIM domain was identified in a familial case but not in the unrelated controls. A family study showed that all affected siblings had the same mutation, associated with late onset cardiomyopathy. A yeast two-hybrid assay demonstrated that described mutation increased the affinity of LIM domain for protein kinase C, suggesting a novel biochemical mechanism of the pathogenesis of DCM. Hershberger et al. (2008) identified two mutations in the LIM domain of LDB3 (A371T and A698T). Second mutation was identified in two unrelated probands and was predicted to change highly conserved amino acid; therefore it was considered disease-associated.

TPM1 is a gene encoding tropomyosin α-1 protein and another candidate gene for DCM. Tropomyosines are highly conserved actin-binding proteins involved in the contractile system of striated and smooth muscles and cytoskeleton of non-muscle cells. TPM1 forms predominant tropomyosine of striated muscle and functions in association with troponin complex to regulate calcium-dependent interaction of actin and myosin during muscle contraction. Mutations in this gene are associated with HCM and also DCM. Lakdawala et al. (2010) performed direct sequencing of 6 sarcomere genes on 334 probands with DCM, revealing D230N missense mutation in TPM1 gene, which segregated with DCM in two large unrelated families. Additional *in vitro* studies demonstrated major inhibitory effects on sarcomere function with reduced Ca^{2+} sensitivity, maximum activation and Ca^{2+} affinity compared to wildtype TPM1.

A role of **presenilin** genes in dilated cardiomyopathy was described by Li et al. (2006). Presenilins are multi-pass transmembrane proteins which function as a part of γ-secretase intramembrane protease complex. There are two presenilin genes in human genome: **PSEN1** and **PSEN2**, both showing conservation between species. Mutations in these genes are the most common cause of Alzheimer's disease. They are also expressed in the heart and play critical role in cardiac development. The researchers analyzed sequence variation of PSEN1 and PSEN2 in 315 patients with DCM, revealing novel PSEN1 mutation D333G in one family and a single PSEN2 mutation S130L in two other families. Both mutations segregated with DCM and heart failure. PSEN1 mutation was associated with complete penetrance and progressive disease that resulted in the necessity of cardiac transplantation or in death, whereas carriers of PSEN2 mutation showed partial penetrance, milder disease and more favourable prognosis. Moreover, calcium signalling was altered in cultured fibroblasts from mutation carriers.

Genes that are associated with complex diseases can also be organized as linkage disequilibrium clusters that are often inherited together. Friedriechs et al. (2009) described such 600-kb region of linkage disequilibrium on 5q31.2-3 chromosome, harboring multiple genes to be associated with DCM in three independent Caucasian populations. Functional assessments in zebrafish demonstrated that at least three genes from this region (**HBEGF** – heparin-binding epidermal growth factor, **IK** cytokine and **SRA1** – steroid receptor RNA activator 1) resulted independently in a phenotype of myocardial contractile dysfunction under the condition of reduced expression.

Most of the genes associated with DCM phenotype are present in nuclear genome. There are however examples of mitochondrial genes that can also contribute to development of dilated cardiomyopathy. Ashrafian et al. (2010) described C452F mutation in highly conserved region of the M domain of **Dnm1l** (dynamin1-like gene) in mice, resulting in reduced levels of mitochondria enzyme complexes in hearts, which then suffered from ATP depletion (energy deficiency that might contribute to DCM).

4. Conclusions

It is always difficult to find genetic cause of multigenic disorders, such as dilated cardiomyopathy, especially if it is considered that mutations in genome are only one of factors contributing to disease. Nevertheless, knowledge about genetic basis underlying such diseases proves to be very useful both in diagnostics and treatment, providing the possibility of early diagnosis and thus increasing the chance of successful therapy.

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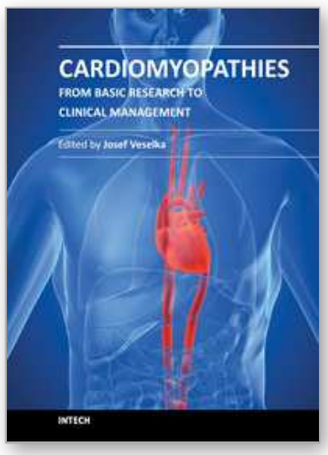

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Cardiomyopathy means "heart (cardio) muscle (myo) disease (pathy)". Currently, cardiomyopathies are defined as myocardial disorders in which the heart muscle is structurally and/or functionally abnormal in the absence of a coronary artery disease, hypertension, valvular heart disease or congenital heart disease sufficient to cause the observed myocardial abnormalities. This book provides a comprehensive, state-of-the-art review of the current knowledge of cardiomyopathies. Instead of following the classic interdisciplinary division, the entire cardiovascular system is presented as a functional unity, and the contributors explore pathophysiological mechanisms from different perspectives, including genetics, molecular biology, electrophysiology, invasive and non-invasive cardiology, imaging methods and surgery. In order to provide a balanced medical view, this book was edited by a clinical cardiologist.

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51000 Rijeka, Croatia
Phone: +385 (51) 770 447
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Phone: +86-21-62489820
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