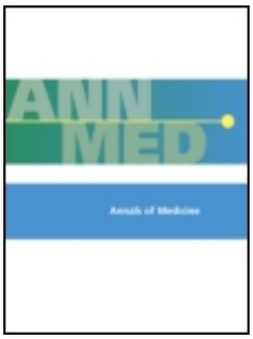

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REVIEW ARTICLE

Genetics of dilated cardiomyopathy

SATU KÄRKKÄINEN & KEIJO PEUHKURINEN

Kuopio University and Kuopio University Hospital, Kuopio, Finland

Abstract
Dilated cardiomyopathy (DCM) is a myocardial disease characterized by dilatation and impaired systolic function of the left or both ventricles. The etiology of DCM is multifactorial, and many different clinical conditions can lead to the phenotype of DCM. During recent years it has become evident that genetic factors play an important role in the etiology and pathogenesis of idiopathic DCM. The genetics of DCM have been under intensive investigation lately, and thereby the knowledge on the genetic basis of DCM has increased rapidly. The genetic background of the disease seems to be relatively heterogeneous, and the disease-associated mutations concern mostly single families and only few affected patients. Disease-associated mutations have been detected e.g. in genes encoding sarcomere, cytoskeletal, and nuclear proteins, as well as proteins involved with regulation of Ca^{2+} metabolism. The mechanisms, by which mutations eventually result in clinical heart failure, are complex and not yet totally resolved. DCM causes considerable morbidity and mortality. Better knowledge of the genetic background and disease-causing mechanisms would probably help us in focusing early treatment on right subjects and potentially also developing new treatment modalities and improving cardiac outcome in the affected patients. This review deals with DCM of genetic origin.

Key words: *Cardiomyopathy, dilated, gene*

Introduction

Dilated cardiomyopathy (DCM) is a primary myocardial disease characterized by dilatation of the left or both ventricles and impaired systolic function (1). DCM causes considerable morbidity and mortality, and it is one of the major causes of sudden cardiac death. DCM can manifest itself at any age, but most commonly after middle age. DCM is clinically a very heterogeneous disease, and patients having this disease may be symptomless but may also have severe heart failure. DCM is the most common cardiomyopathy explaining about 60% of all cardiomyopathies (2,3). The incidence of dilated cardiomyopathy has been increasing, which is explained by more accurate diagnosis and a higher index of suspicion among clinicians (4). The incidence of DCM has been suggested to be 5–8 in 100,000 per year in the United States and also in European populations (4–7), and the prevalence approximately 40 in 100,000 in the United States (4,8). The annual incidence of dilated cardiomyopathy in the pediatric population has been reported to be 0.57 cases per 100,000 in USA (9). In the Finnish pediatric population the incidence was found to be 0.34 per 100,000 per year and the prevalence 2.6 per 100,000 per year (10).

The frequencies of familiarity of DCM vary between different studies, but common estimation is that approximately 30%–50% of cases of idiopathic DCM has a genetic origin (11–14). Autosomal dominant inheritance is the most common inheritance form (12,15,16). Although genetic factors seem to play an important role in the pathogenesis of DCM, hitherto reported mutations explain only a minority of familial DCM. The first familial cardiomegaly was characterized in 1949, but the first DCM-associated mutation (in the dystrophin gene) was described as late as in 1993 (17–19). Since the beginning of 1990s, the genetics of DCM have been investigated more intensively, especially during the last 8 years. To date, DCM-associated mutations in many different genes with subsequent alterations in protein structure have been reported, but still these mutations explain only a minority of the etiology of DCM (Figure 1) (18–49).

Correspondence: Satu Kärkkäinen, MD, PhD, Department of Internal Medicine, Kuopio University Hospital, PO Box 1777, 70211 Kuopio, Finland. Fax: +358 17 173959. E-mail: satu.karkkainen@kuh.fi

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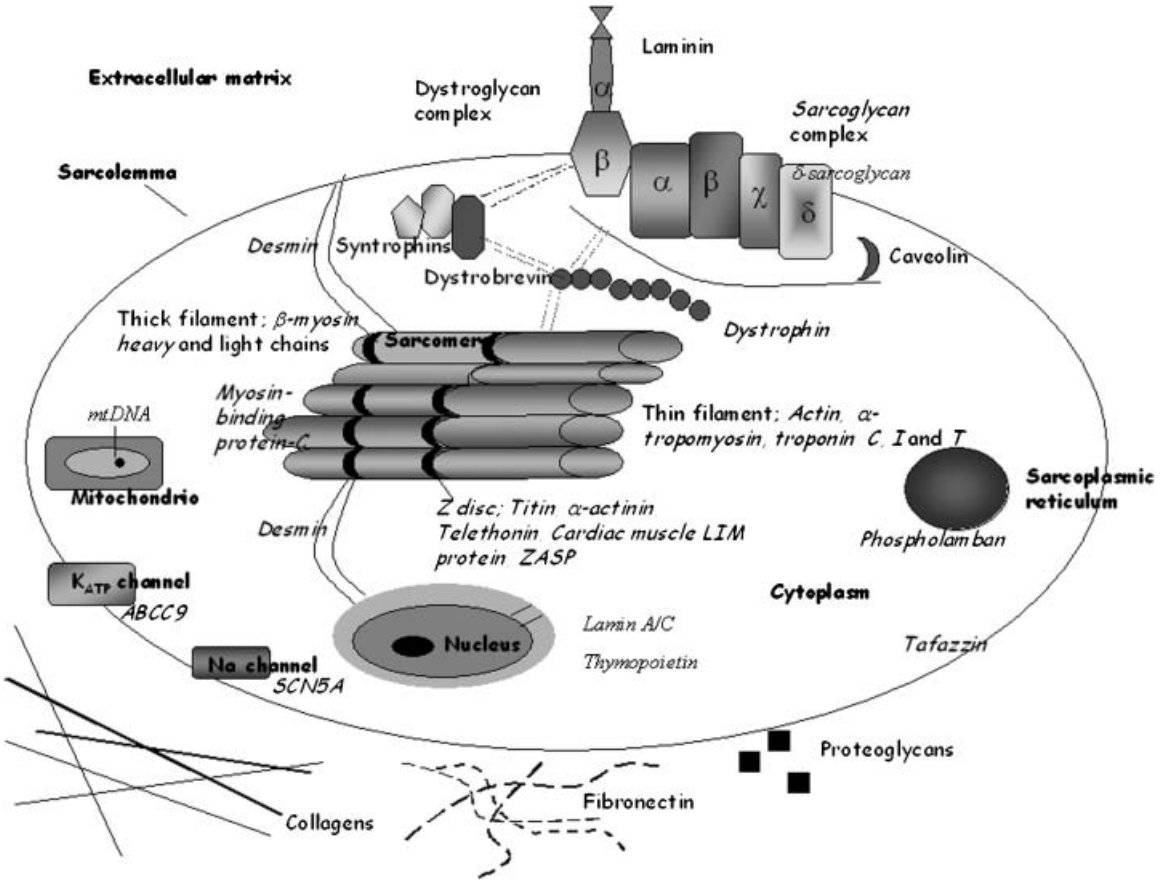

Figure 1. A schematic structure of the myocyte. Dilated cardiomyopathy (DCM)-associated proteins are marked by italic font.

During the last years, research results have highlighted the importance of the lamin A/C gene in familial DCM. The mutations in the lamin A/C gene are one of the most frequently detected mutations in DCM populations (20,25,29,32,50–52). The phenotype of DCM patients is very similar in different mutations of the lamin A/C gene. On the other hand, the phenotype seems to differ somewhat from that of a 'typical' DCM patient, and therefore we can say that patients with mutations in the lamin A/C gene may form a special subgroup in the DCM population (20,25,29,32,50–52).

Although the prognosis of DCM has improved during the last decades, it still causes considerable morbidity and mortality. Identification of mutations in genes associated with this disease adds not only information on the pathogenesis of DCM, but also provides important prognostic information and helps screening other asymptomatic family members.

Monogenetic dilated cardiomyopathy

The prevalence of familial DCM varies between 10% and 50%. The lowest prevalence is reported in studies without systematic screening of family members. If family members are systematically screened, the prevalence of familiarity varies between 20% and 50% (12,13,16,44). The mode of inheritance of DCM can be autosomal dominant (~60%), autosomal recessive (~16%), X-linked (~10%) or mitochondrial (~8%) (53). Also mutations without genetic inheritance can exist (*de novo* mutations), but these kinds of mutations are quite rare (54). The penetrance of DCM is variable, and it is dependent at least on gene, mutation, and age. Also modifying factors can affect the phenotype of a single patient. For example, in the lamin A/C gene the penetrance of the disease is nearly 100% in patients over 40 years.

Although genetic factors play a role in the pathogenesis of DCM, the genetic background of DCM is still largely unknown. Linkage analysis has not been very useful due to the limited size of families and difficulties in the diagnosis of DCM. However, linkage analysis has been applied, and several chromosomal loci for DCM have been found. Specific genes have not yet been identified in all loci, but some clinical characteristics are associated with known loci, e.g. skeletal muscle

disease and mitral prolapse. Chromosomal loci reported to be associated with DCM are listed in Table I.

The most commonly used research method in familial DCM is the candidate gene approach. To date, gene defects have been reported in over 20 genes: cardiac actin, desmin, dystrophin, δ-sarcoglycan, troponin T and β-myosin heavy chain, α-tropomyosin, tafazzin, titin, lamin A/C, metavinculin, myosin-binding protein-C, cardiac muscle LIM protein (named according to closely related Lin-11, Isl-1 and Mec-3 genes), phospholamban, α-actinin, troponin I, troponin C, thymopoietin, SCN5A (sodium channel, voltage gated, type V, alpha polypeptide), ZASP/cypher, and ABCC9 (ATP-binding cassette, sub-family C (CFTR/MRP), member 9) genes (20,21,23,27,28,30,33–38,40–42,45–49,55,56). These genes can be classified according to their locations or disease-causing mechanisms. Classification according to disease-causing mechanisms is presented in Figure 2.

Genes associated with dilated cardiomyopathy

Sarcomere protein and sarcomere-associated protein genes (Figure 1 and Table I)

Cardiac actin. The cardiac actin gene (ACTC) on chromosome 15q14 has six exons. Actin is the major component of the thin filament, and it forms a complex with α-tropomyosin and troponins (troponin C, I and T), essential components of the contraction unit of heart muscle. The cardiac actin gene was the first sarcomere protein gene reported to be associated with DCM. Olson et al. (36) found two missense mutations, Arg312His and Glu361Gly, in the ACTC gene in two DCM families. These mutations are located in the region that encodes the immobilized end of the actin filament. This region is near the dystrophin-binding site, which binds the protein domain to Z bands and intercalated discs (44,56,57). These mutations are suggested to affect force transmission to adjacent sarcomeres and myocytes. Gene defects in the cardiac actin gene, which affect force generation, have not been reported since. The mechanisms by which the mutations lead to clinical disease have remained unclear. Overall, the mutations in the cardiac actin gene are thought to be a rare cause of DCM, and therefore it is difficult to describe the typical phenotype of DCM caused by a mutation in the ACTC gene (58–60).

α-*Tropomyosin.* The α-tropomyosin gene (TPM1) on chromosome 15q22 has ten exons in the cardiac isoform of the gene. α-Tropomyosin is a component of the thin filament, and it interacts with troponin T. This interaction is needed in heart muscle contraction. The interaction can be Ca^{2+}-sensitive or not. Only two DCM-associated mutations have been reported in the TPM1 gene. Olson et al. (37) described two mutations, Glu40Lys and Glu54Lys, in two small DCM families. These two mutations in the TPM1 gene are thought to alter electrostatic interactions between actin and tropomyosin or compromise the structural integrity of tropomyosin (37). The family with the Glu40Lys mutation had a variable phenotype. One family member had severe disease and underwent heart transplantation at the age of 10, whereas one family member developed a mild DCM phenotype at the age of 40. The Glu54Lys mutation has been associated with sudden cardiac death at young ages. Other DCM-associated mutations in the TPM1 gene have not been published yet, and therefore TPM1 gene defects seem to be relatively uncommon in DCM.

β-*Myosin heavy chain.* The β-myosin heavy chain gene (MYH7) on chromosome 14q11 has 38 coding exons. The β-myosin heavy chain forms part of the thick filament of the sarcomere. The β-myosin heavy chain protein has two different domains, a heavy meromyosin domain, which consists of two subfragments (S1 and S2) and a light meromyosin (LMM) domain (61). The S1 locates in the head domain and has actin and ATP-binding regions, and it is therefore essential for generation of movement needed in contraction (61). The S2 joins the heads at the neck region. The LMM portion forms binding sites for myosin-binding protein-C and titin and is essential for maintaining assembly of the filament and stability of the protein (61).

Several DCM-causing mutations have been detected in the MYH7 gene. Kamisago et al. (25) found two mutations, Ser542Pro and Phe764Leu, in the MYH7 gene in two different DCM families. The Ser542Pro mutation was associated with sudden death and heart transplantation at young ages, while the Phe764Leu mutation manifested at birth or at the age of 2 months. These mutations are thought to disrupt interactions between myosin and actin or diminish the efficiency of contraction, respectively (30). Daehmlow et al. (23) reported two mutations, Ala223Thr and Ser642Leu, in two sporadic DCM patients. The Ala223Thr mutation is thought to affect thermostability and protein folding, and the Ser642Leu mutation in turn conformational structure of protein near the actin-binding site (23). In our own studies we detected two novel mutations in

Table I. Chromosomal loci, clinical characteristics and suggested disease-causing mechanisms associated with DCM.

Locus	Gene	Clinical characteristics	Disease-causing mechanism	Reference
1p1-q21	Lamin A/C	CSD, SCD, LBBB, SVT, SMD, AF, PM, HT, SCD	Nuclear membrane damage leads to disruption of the cell causing myocyte death and tissue damage, loss of protein expression, altered localization of protein at the inner nuclear membrane, dysregulation of cellular functions	(20,25,26,29,32,43, 50–52,54,116,154)
1q32	Troponin T	DCM, CSD, AF, SCD	Affects troponin C binding and diminished activation of calcium-stimulated actomyosin ATPase	(28,30,35,65,155)
1q42-q43	α-Actinin	DCM, early onset	Disrupts the interaction with CLP and inhibits α-actinin function	(41)
2q14-q22	?	CSD		(156)
2q31	Titin	DCM, ICD, CSD, arrhythmias	Disrupts core sequence of immunoglobulin fold near Z-disc–I-band transition zone, decreases the binding affinity of titin to telethonin and α-actinin, mutations in the cardiac-specific region of titin cause truncated nonfunctional molecule	(27,68,71,157)
2q35	Desmin	DCM, muscular dystrophy, early onset		(34,75)
3p21	Troponin C	DCM, severe disease	Impairs troponin interaction leading to altered contractility	(46)
3p22-p25	SCN5A	CSD, DCM		(45,158)
5q33	δ-Sarcoglycan	DCM, SCD, early onset, mild disease	Alters the secondary structure of the protein	(56)
6q12-q16	?			(159)
6q22.1	Phospholamban	DCM		(40)
6q23	?	Sensorineural hearing loss, skeletal myopathy, CSD		(160)
9q13-q22	?	DCM		(161)
10q21-23	?	Mitral valve prolapse		(162)
10q22-q23	Metavinculin	DCM, HT	Disrupts force transmission at the thin filament-intercalated disc interface	(38)
10q22.2-23.3	Cypher/ZASP	DCM, LVH, CSD	Disarray of actin cytoskeleton	(48,103)
11p11	Myosin-binding protein-C	DCM, variable phenotype, SCD	Affects tropomyosin-binding domain, truncates A band	(23)
11p15	Cardiac muscle LIM protein	DCM, early onset	Defect in the CLP/telethonin interaction → interferes stretch sensor machinery; abolishes interaction between MLP and α-actinin, changes localization of MLP	(33,41)
12p12	Regulatory SUR2A subunit of cardiac K_{ATP} channel	DCM, VT	Disrupts catalysis-dependent gating and impairs metabolic decoding, establishing a therefore unrecognized mechanism of channel malfunction	(49)
12q22	Thymopoietin	DCM, severe disease	Affects LAP2α and A-type lamin binding	(47)
14q12	β-Myosin heavy chain	DCM, HT, SCD, early onset HCM/DCM	Disrupts interactions between actin and myosin; alters the magnitude or polarity of transmitted movement → efficiency of contraction ↓; affects the ATP-binding site	(23,30,62,63)
15q14	Cardiac actin	DCM	Defect in force transmission	(36)
15q22	α-Tropomyosin	DCM, variable phenotype, early onset, HT, SCD	Alters the interaction between actin and tropomyosin or compromised structural integrity	(37)
17q12	Telethonin	DCM, SCD, early onset	Loss of interaction between cardiac muscle LIM protein and telethonin	(33)
19q13	Troponin I	Recessive DCM, severe disease	Impairs interaction between troponin I and troponin T→contraction ↓	(42)

Table I. (*Continued.*)

Locus	Gene	Clinical characteristics	Disease-causing mechanism	Reference
Xp21	Dystrophin	Skeletal muscle disease or isolated DCM, HT, SCD, early-onset DCM	Affects the structural and functional integrity of myocyte sarcolemma; changes polarity (alters the secondary and tertiary structure of dystrophin), affects dystrophin expression in the heart	(18,19)
Xq28	Tafazzin	Endocardial fibroelastosis, Barth syndrome, left ventricular noncompaction		(21,24)

AF=atrial fibrillation; CSD=conduction system disease; DCM=dilated cardiomyopathy; HCM=hypertrophic cardiomyopathy; HT=heart transplantation; ICD=implantable cardioverter-defibrillator; LBBB=left bundle branch block; LVH=left ventricular hypertrophy; PM=pacemaker; SCD=sudden cardiac death; SMD=skeletal muscle disease; SVT=supraventricular tachycardia; VT=ventricular tachycardia.

this same gene (62). One of the mutations, Arg1053Gln, caused mainly hypertrophic cardiomyopathy (HCM), and only one patient had a phenotype resembling DCM. The Arg1500Trp mutation was found only in one patient with classical DCM. Villard et al. (63) screened a large number of familial and sporadic DCM patients and detected eight DCM-associated mutations. In their study population mutations in the MYH7 gene explained approximately 10% of the cases. In other populations, however, mutation frequencies of MYH7 gene have not been so high.

Troponin T, I and C. The troponin T gene (TNNT2) on chromosome 1q32 has 17 exons. The troponin T forms the troponin complex with troponin C and I, and they are all part of the thin filament. Troponin T has interaction sites with tropomyosin and other troponins. Several DCM-causing mutations have been reported in this gene. Kamisago et al. (30) found one deletion, ΔLys210, in two DCM families. Later Hanson et al. (28) detected this same deletion in another DCM family. This deletion reduces ionic interactions between troponin C and troponin T and decreases the activation of calcium-stimulated actomyosin-ATPase. These changes are thought to lead to a decrease in power stroke (30). Morimoto et al. (62) explored the effect of the ΔLys210 mutation under physiological conditions in cardiac muscle fibers of the rabbit. The ΔLys210 mutation was found to decrease Ca^{2+}-sensitivity of force generation in the sarcomere, which could be one of the primary mechanisms for the pathogenesis of DCM.

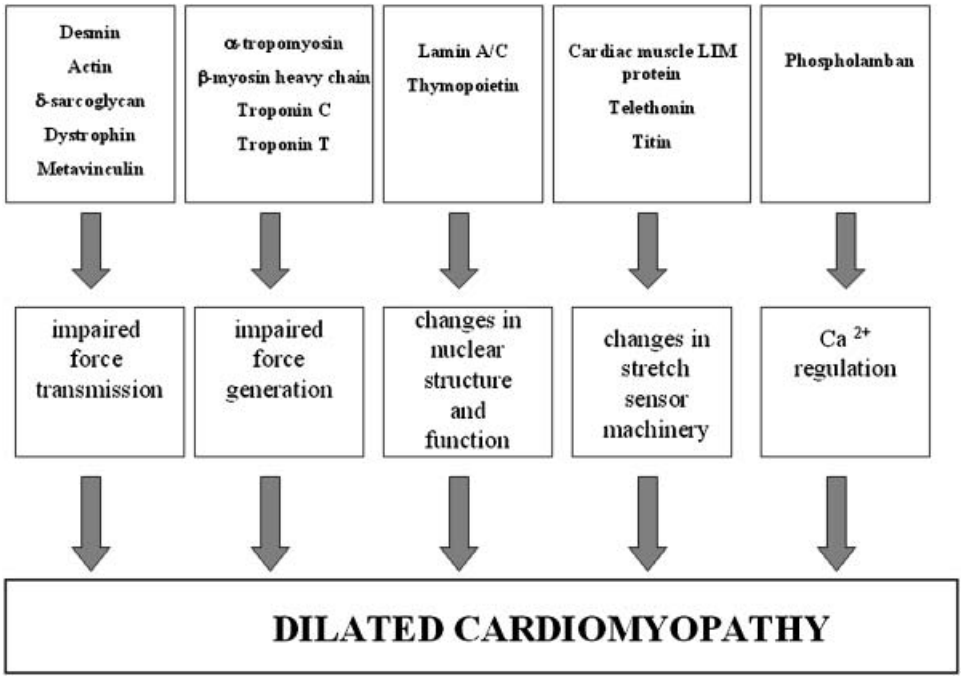

Figure 2. A schematic figure of the Dilated cardiomyopathy (DCM)-causing mechanisms.

Robinson et al. (64) compared the changes in thin filament function caused by the mutations in DCM and HCM. The DCM-associated mutation, ΔLys210, decreases ATPase activity, which in turn speeds filament sliding, and Ca^{2+}-activation becomes non-cooperative (64). One single mutation, Arg141Trp in the troponin T gene, has been found in one DCM family (35). The mutation Arg141Trp is located within the tropomyosin-binding domain of cardiac troponin T and alters the charge of the residue. Mogensen and co-workers reported about three new DCM-associated mutations (Arg113Trp, Arg205Leu, and Asp270Asn) in troponin T (46). Stefanelli et al. (65) found one novel mutation, Ala172Ser, which caused a severe phenotype with sudden cardiac death and low ejection fraction. The previously described ΔLys210 deletion is associated with sudden cardiac death, heart failure, and conduction system disease.

The troponin I gene (TNNI3) on chromosome 19q13 has eight exons. Troponin I is one part of the troponin complex. The role of troponin I is to control heart muscle contraction by inhibiting actomyosin ATPase and revealing active sites of tropomyosin. Murphy et al. (42) found the first recessive DCM-associated mutation, Ala2Val, in this gene. This mutation was shown to impair the interaction between troponin I and troponin T, leading to diminished myocardial contraction. The phenotype of the Ala2Val mutation seemed to be severe.

The troponin C gene (TNNC1) on chromosome 3p21 has six exons. Troponin C forms the last component of the troponin complex. Its function is to take up and bind calcium-ion to the troponin complex leading to structural changes, which allow the interaction of actin with myosin. The actin connection with myosin is necessary for heart muscle contraction. Mogensen et al. (46) reported one DCM-associated mutation in the troponin C gene with a severe clinical disease.

Myosin-binding protein-C. The myosin-binding protein-C gene (MYBPC-3) on chromosome 11p11 has 34 exons. The protein of the MYBPC-3 gene has different regions and one cardiac-specific region. There are at least two interacting domains with other proteins e.g. myosin and titin (66). Only one DCM-associated mutation, Asp948Thr, in one sporadic DCM patient has been reported for this gene (23). The specific effect of this mutation is not known, and because only one patient with the mutation has been reported, the clinical phenotype remains unclear.

Titin and telethonin. The titin gene (TTN) on chromosome 2q24 has 362 exons. The main components of the sarcomeric cytoskeleton, which provides a scaffold for the sarcomere, are titin, α-actinin, and myomesin (67). Titin, also called connectin, is a giant protein, which spans from the Z line to the M line in the sarcomere. Titin has several functions including the control of thin filament assembly, force transmission, maintenance of resting tension, and elasticity of the muscle (68–70). Titin also binds myosin filaments into the Z discs and interacts with myosin-binding protein-C, α-actinin, and telethonin (68,70). Gerull et al. (27) found two DCM-associated mutations, a 2-bp insertion and Trp930Arg, in the TTN gene. The 2-bp insertion is predicted to truncate the protein, and the Trp930Arg mutation affects the Z disc/I band transition zone (27). Itoh-Satoh et al. (68) reported four DCM-associated mutations in the titin gene. Two of these mutations, Val54Met and Ala743Val, are located in the Z line region of titin. These mutations are thought to decrease binding affinities of titin to Z line proteins. Two other mutations, Glu4053ter and Ser4465Asp, are located in the cardiac-specific N2-B domain of titin. The Glu4053ter mutation is thought to encode truncated nonfunctional protein. The main clinical findings in patients with titin mutations are DCM with arrhythmias or conduction system abnormalities and need for implantable cardioverter-defibrillator (ICD). Recently, Gerull et al. (71) reported a novel heterozygous 1-bp deletion mutation (c.62890delG) in TTN that cosegregated with DCM in a large Australian pedigree. The TTN deletion caused a frameshift, thereby generating a truncated A band titin due to a premature stop codon and the addition of ten novel amino acid residues. In this case the penetrance was incomplete and expressivity was variable (71).

The telethonin gene (TCAP) on chromosome 17q12 probably has two exons. Telethonin is actually a substrate of titin. Interaction of titin with telethonin at the Z disc is necessary for proper function of the sarcomere. Telethonin has a role in the assembly of the sarcomere by providing spatially defined binding sites for other sarcomeric proteins. After activation by phosphorylation and calcium/calmodulin binding, titin phosphorylates the C-terminal domain of telethonin (72). Knöll et al. (33) recently reported one mutation, Arg87Gln, in the TCAP gene in one DCM patient. The mutated telethonin gene leads to a defect in the interaction between cardiac muscle LIM protein and telethonin. Hayashi et al. (73) described one TCAP mutation, E132Q, in a DCM patient. This mutation is suggested to impair the interaction of TCAP with titin, muscle LIM protein, and calsarcin-1.

The clinical disease in patients with telethonin mutations seems to be quite severe. Sudden cardiac death and early onset of the disease were clinical findings in one family with E132Q mutation (73).

Cytoskeletal protein genes (Figure 1 and Table I)

Desmin. The desmin gene (DES) on chromosome 2q35 has nine exons. Desmin belongs to the intermediate filaments and has typical structural components of intermediate filaments; a central rod, head, and tail domains. Desmin encircles the Z discs and radiates out to connect adjacent myofibrils. It also forms a link between actin and the dystrophin-sarcoglycan complex (74). Desmin attaches and stabilizes the sarcomere, connects adjacent myofibrils together and Z bands to plasma membrane and nuclear envelope. In the desmin gene, one DCM-associated mutation, Ile451Met, has been reported (34,75). The Ile451Met mutation is located in a region of the gene encoding the tail domain of the protein, the specific function of which is unknown. It has been speculated that DCM-causing mechanism in the desmin gene is related to ineffective force transmission (34,76).

Clinically, the Ile451Met mutation has been shown to be associated with a classical type of DCM and sudden death. Gene defects in the desmin gene have also been shown to cause skeletal muscle disease combined with cardiomyopathy and desmin-related myopathy, which is caused by abnormal accumulation of desmin in skeletal muscle (77–79). Generally, mutations in the desmin gene are thought to be rare causes for DCM, at most accounting for about 2% of the cases (60,75).

Dystrophin. The dystrophin gene (DMD) on chromosome Xp21 has 79 exons. Dystrophin is a large cytoskeletal protein, which is part of the dystrophin-associated glycoprotein complex (DAG). The DAG complex includes dystroglycan, sarcoglycan, syntrophin complex and caveolin. The DAG complex forms a transmembrane link between the extracellular matrix and the intracellular cytoskeleton (80). Dystrophin interacts with actin and thereby links the sarcomere to the extracellular space. Dystrophin is thought to play a role in force transduction, membrane stability, and intracellular organization. Badorff et al. (81) showed that an enterovirus infection can lead to cleavage of dystrophin. This leads to disruption of the cytoskeleton resulting in myocyte dysfunction, decreased force transmission, and increased cell permeability.

Dystrophin mutations are better known to cause skeletal muscle disease with elevated levels of creatine kinase, such as Duchenne and Becker muscular dystrophies, than dilated cardiomyopathy (82,83). In a few cases, however, gene defects in the dystrophin gene have been shown to be associated with isolated cardiomyopathy without skeletal muscle disease. This disease is called X-linked dilated cardiomyopathy (XLCM) (84). XLCM often presents in young male patients with heart failure and no signs of skeletal muscle disease. XLCM mutations in the dystrophin gene can be divided into two groups according to localization, 5′end region mutations and midrod domain region mutations (85). The majority of the DCM-associated mutations are located in the 5′end region and are malignant in nature (18,19,39,86–89). Patients with malignant disease have suffered from sudden cardiac death and heart transplantation. Several mutations, mainly deletions, have been reported in the midrod domain of the protein, and usually these mutations cause a more benign disease (85,87,88,90,91).

Metavinculin. The metavinculin gene (VCL) on chromosome 10q22 has 22 exons. Metavinculin is an isoform of vinculin, encoded by an additional insert of genome (68 amino acids) in the C-terminal end. Metavinculin belongs to the group of membrane-associated proteins, which are located in the intercalated discs, costameres and the T tubule system (92,93). They are thought to have a role in the anchoring of thin filaments, force transmission, and stability of the cellular membrane, but their specific function in the heart is unknown (38,66,94). Maeda et al. (95) demonstrated an association between metavinculin deficiency and dilated cardiomyopathy due to a defect in alternative mRNA splicing. Olson et al. (38) have found one missense mutation, Arg975Trp and one 3-bp deletion (Leu954del), in the metavinculin gene in two DCM patients. These authors suggested that the mechanism probably causing DCM was the disruption of force transmission at the thin filament-intercalated disc interface. Later, Vasile et al. (96) detected the same mutation in a patient with hypertrophic cardiomyopathy. This finding highlights the effect of remodeling in the pathophysiology of cardiomyopathies.

The clinical findings in patients with metavinculin mutations are variable. Part of the mutation carriers had well preserved left ventricular diameter and ejection fraction, but one patient presented with rapid progression of heart failure and needed heart transplantation after some years of diagnosis (38).

δ-*Sarcoglycan.* The δ-sarcoglycan gene (SGCD) on chromosome 5q33 has eight exons. δ-Sarcoglycan has three domains: intracellular, transmembrane, and extracellular domains (97). Tsubata et al. (56) detected two DCM-causing mutations, Ser151Ala and ΔLys238, in the SGCD gene in single DCM cases. Both mutations are thought to alter the secondary structure of the protein, and the DCM-causing mechanism may be a defect in force transmission. The DCM-associated mutations are located in the extracellular domain. Gene defects in the SGCD gene can also lead to limb girdle muscular dystrophy, which is sometimes associated with DCM (98). In animal studies, Nigro et al. (99) showed that a deletion of the first exon caused a complete absence of the δ-sarcoglycan protein in the Syrian hamster. This deletion was associated with skeletal muscle disease, ventricular hypertrophy and dilatation, and premature death. In our own study we found one mutation, Arg71Thr, in a small family with DCM, which was, however, associated with a relatively mild phenotype (31).

Cardiac muscle LIM protein. The cardiac muscle LIM protein gene (CLP) on chromosome 11p15 has four exons. The CLP protein has two LIM domains, and these domains are highly conserved (66). The CLP protein is located in the Z disc, and interacts with α-actinin and telethonin, and telethonin in turn interacts with titin (33). CLP together with telethonin is the key component of the cardiomyocyte stretch sensor machinery (33). CLP is also localized in the nucleus, and its function there is to promote myogenesis (100). Knöll et al. (33) found one DCM-associated mutation, Trp4Arg, in the CLP gene in ten European patients. The Trp4Arg mutation results in a defect in interaction with telethonin interfering with the cardiac mechanical stretch sensor machinery (33). Clinically the Tpr4Arg mutation causes typical DCM with low ejection fraction, but only slightly dilated left ventricle. Mohapatra et al. (41) found this same mutation in an European family, but the mutation did not cosegregate with DCM. Therefore, it is possible that the substitution of tryptophan to arginine (W4R) mutation is a modifier mutation rather than a disease-causing mutation. Mohapatra et al. (41) detected another DCM-associated mutation, Lys69Arg, in the CLP gene. The Lys69Arg mutation abolishes the interaction of telethonin with CLP and α-actinin and changes the localization of CLP. It is associated with early onset of DCM.

α-*Actinin.* The α-actinin gene (ACTN2) on chromosome 1q42 has 21 exons. α-Actinin is localized in the Z disc, where it helps to anchor myofibrillar actin filaments. It consists of an N-terminal actin binding domain, a central rod domain, and a C-terminal domain, and it functions as a homodimer to cross-link actin filaments. The rod domain determines the distance between cross-linked actin filaments and also serves as an interaction site for several cytoskeletal and signaling proteins (101). Recently, Mohapatra et al. (41) detected one mutation, Gln9Arg, in the α-actinin gene in one DCM patient with severe disease. The Gln9Arg mutation was predicted to alter the secondary structure of the protein. DCM-associated mutations in this gene are rare, and therefore clinical characteristics of these gene mutations are difficult to summarize.

Cypher/ZASP. The cypher gene on chromosome 10q22 has 16 exons. It is a cardiac and skeletal muscle-specific Z line protein, which is expressed in cytoplasm. The proteins in the N-terminal end interact with each other in cytoskeletal assembly or with other proteins involved in targeting and clustering of membrane proteins. The cypher/ZASP plays a role in bridging the sarcomere to the cytoskeletal network. The interaction site with α-actinin-2 has been found (48). Vatta et al. reported five mutations (Ser196Leu, Ile352Met, Asp117Asn, Lys136Met, and Thr213Ile) in this gene (48). Two of the mutations were found in familial cases, and three were sporadic ones. The authors suggest that the mutated gene could affect the stability of actin cytoskeletal network (48). The cypher/ZASP knockout mouse developed congenital myopathy and dilated cardiomyopathy (102). Later, Arimura et al. (103) found an Asp626Asn mutation in the Japanese population. This mutation was shown to increase affinity of the LIM domain for protein kinase C.

Clinical characteristics for these mutations were dilated cardiomyopathy with severe left ventricular hypertrophy. Some patients had also conduction system disease, but no signs of skeletal muscle disease were found.

Nuclear protein genes (Figure 1 and Table I)

Lamin A/C gene. The lamin A/C gene (LMNA) on chromosome 1p1 contains 12 exons. Lamin A and C have an identical sequence for the first 566 amino acids in exons 1–10, but differ in the 3′ end of the gene. The nuclear envelope is a double-layered structure (outer and inner layer) located between the nucleus and cytoplasm. The outer layer of the

envelope is directly connected to the endoplasmic reticulum, and ribosomes are attached to it. The nuclear lamina, which is composed of lamins A, B and C, is attached to the inner layer of the nuclear envelope. Lamins connect the nuclear envelope, nuclear matrix and chromatins together. Lamin A/C is also thought to have a role in cell dividing, nuclear growth, and anchorage of nuclear envelope proteins (104–107). Lamins are major structural components of the lamina network underlying and supporting mechanically the nuclear envelope (107). The lamin A/C protein has three different domains, an N-terminal head, a coiled-coil rod, a C-terminal tail, and several different binding domains, for example lamin B, chromatin, emerin, and lamin-associated protein binding domains (106,108).

Defects in the lamin A/C gene have been shown to be responsible for different diseases e.g. Emery-Dreifuss muscular dystrophy, limb girdle muscular dystrophy type 1B, Dunnigan-type familial partial lipodystrophy, Charcot-Marie-Tooth disease, mandibuloacral dysplasia, Hutchinson-Gilford progeria, and dilated cardiomyopathy with conduction abnormalities or mild skeletal muscle disease (20,22,25,109–114). Mutations in the lamin A/C gene seem to be the most frequent causes of familial DCM reported so far. During the past 2 years several independent research groups have reported different or similar DCM-associated mutations in this gene.

It has been speculated that gene defects in the lamin A/C gene could disrupt nuclear function or decompose nuclear structure (66). Arbustini et al. (20) showed that nuclear membrane damage is associated with gene defects in the lamin A/C gene. It is believed that nuclear membrane damage can lead to disruption of the cell causing myocyte death and tissue damage (20,108). Verga et al. (52) showed that lamin A/C mutations can cause loss of integrity of myocyte nuclei with blebs of the nuclear membrane, herniations and delamination of the nuclear lamina, and nuclear pore clustering. The authors suggest that gene defects in the lamin A/C gene are associated with loss of protein expression in the selective compartment of noncycling myocyte nuclei. Recently, Nikolova et al. (115) reported lamin A/C-deficient mice, which developed rapidly progressive DCM. Lamin A/C deficiency caused detachment of desmin at the nuclear-cytoskeletal interface, and lamin A/C deficiency is expected to impair binding between lamin B and desmin (115). All known DCM-associated mutations seem to cause abnormalities in either nuclear structure or function.

It has been estimated that approximately 5% of the DCM population carry the lamin A/C mutation (116,117). In our own studies we found that 9% of patients with heart transplantation carried some mutation in the lamin A/C gene (54). The phenotype caused by mutations in the lamin A/C gene forms its own subgroup of DCM. Typical clinical findings are progressive conduction system abnormalities, atrial fibrillation, need for permanent pacemakers or automatic implantable cardioverter-defibrillator (AICDs), ventricular tachycardias, need for heart transplantation and elevated risk for sudden cardiac death (32,43,116). These findings can exist with or without skeletal muscle disease. Malignant arrhythmias and need for heart transplantation and ICDs are more common in lamin A/C mutation patients than in other DCM patients (32,43,116). Survival is also worse in lamin A/C mutation carriers.

The penetrance of the disease is age-dependent in the cases of lamin A/C mutation. Almost all patients over 40 years have some kind of sign of the disease, but younger patients might only have first-degree atrioventricular block. Dilatation of the left ventricle is a later manifestation of the disease, and the left ventricle overall can be only slightly dilated. To our understanding the current diagnostic criteria are not necessarily suitable for these patients.

Thymopoietin. Thymopoietin, which is also called lamina-associated polypeptide 2 (LAP2), on chromosome 12, has eight exons. Different isoforms due to alternative splicing are localized in the nuclear membrane and nucleoplasm (118,119). Lamina-associated proteins are one group of lamin-binding proteins, and thereby their function is to participate in maintaining nuclear integrity and nuclear functions. The only nucleoplasmic isoform is LAP2α, and it interacts with A-type lamins (120). Other domains of the LAP2α are the N-terminal domain containing LEM-domain (LAP2-emerin-MAN1), chromosome binding domain, and unique C terminus, which has a critical role during nuclear reassembly (114). Taylor et al. (47) screened the LAP2 gene and detected one putative mutation, Arg690Cys, in one familial DCM pedigree. This mutation altered interaction with LAP2α and lamin A, but the final consequences remain unknown. However, this finding supports the importance of disturbed nuclear functions in the pathogenesis of DCM. Some of the patients with mutation in the thymopoietin gene have severe disease without signs of skeletal muscle disease (47).

Ion channel protein genes or genes regulating Ca^{2+} metabolism

SCN5A. The SCN5A gene on chromosome 3 has 28 exons. This cardiac sodium channel gene

contains four homologous domains, each of which has six putative membrane-spanning regions. The defects in this gene are better known to cause Brugada syndrome and long QT syndrome (121). McNair et al. (45) detected one mutation (Asp1275Asn) in a family with DCM. The clinical characteristics for this mutation were atrial fibrillation, conduction abnormalities, and early onset of the disease. The disease-causing mechanism is different compared with other disease-causing mechanisms in DCM, i.e. altered ion homeostasis (45).

ABCC9. The ABCC9 gene on chromosome 12 has 39 exons. This gene is a member of the superfamily of ATP-binding cassette (ABC) transporters. ABC proteins transport various molecules across extra- and intra-cellular membranes. Bienengraeber et al. (49) identified two heterozygous mutations in the ABCC9 gene, which encodes the C-terminal domain of SUR2A specific to the cardiac splice variant of the regulatory K(ATP) channel subunit. The authors suggest that these defects in the regulatory K(ATP) channel subunit disrupt catalysis-dependent gating and impair metabolic decoding, establishing a hitherto unrecognized mechanism of channel malfunction in human disease.

Patients with mutations in the ABCC9 gene have severe DCM with ventricular tachycardia as a common feature. The mutations identified resulted in dysfunction of the SUR2A subunit by disruption of the C terminus (49).

Phospholamban. The phospholamban gene on chromosome 6q22 has two exons. Phospholamban has an essential role in Ca^{2+} metabolism by modulating calcium-ATPase activity. Thereby phospholamban is a regulator of cardiac relaxation. Schmitt et al. (40) detected one DCM-causing mutation, Arg9Cys, in the phospholamban gene in one DCM family. This Arg9Cys mutation is thought to cause DCM by directly disturbing the myocellular Ca^{2+} metabolism due to constitutive SERCA2a (sarcoplasmic reticulum calcium-ATPase) inhibition. The authors also developed a transgenic mouse model with this mutation, which appeared to have a similar type of disease as mutation carriers (heart failure with premature death). Family members with the Arg9Cys mutation had severe disease with frequent heart transplantations and premature deaths.

Unclassified group

G4.5/Tafazzins. The G4.5 gene on chromosome Xq28 encodes tafazzins. G4.5 is expressed in cardiac and skeletal muscle. Tafazzins do not have known similarities to other proteins, and therefore tafazzins compose their own group of proteins. There are two important regions: the N terminus part of the gene may serve as a membrane anchor, and the central portion may serve as an exposed loop interacting with other proteins. Mutations in this gene are known to cause a phenotype of DCM, Barth syndrome, noncompaction of left ventricular myocardium, and endocardial fibroelastosis (21,24).

Mitochondrial mutations. The mitochondrial genome is a double-stranded circular molecule. The mitochondrial genome has some specific features compared with genomic DNA. Mitochondria do not have introns and histones, and they lack an effective DNA repair system. The mutation rate is higher in mtDNA than in nuclear DNA, partially due to ineffective DNA repair and abundant free radical formation (122). Maternal inheritance is typical for mitochondria, but inheritance according to Mendelian laws can also occur. Mitochondria play an important role in energy generation and thus in contractile function, and disturbances in these functions may lead to DCM in some cases. Gene defects in the mitochondrial genome can cause syndromes like MELAS (mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes), Kearns-Sayre syndrome and MERFF (myoclonus epilepsy with ragged red fibers), which are caused by point mutations and deletions in the mtDNA. Different cardiac abnormalities are accompanied with these syndromes, especially HCM. Few cases of DCM have been detected in patients with MELAS and Kearns-Sayre syndrome (123–129).

Genetic defects in Finnish population of dilated cardiomyopathy

We have examined clinically and screened genetically 52 DCM patients from Kuopio University Hospital region and 38 DCM patients from Helsinki University Hospital region. An additional study group consisted of heart transplantation patients (n=66) from all over Finland. The genetic analyses were performed during the last 7 years. We screened all coding regions of nine candidate genes (cardiac actin, lamin A/C, troponin C, I, T, α-tropomyosin, β-myosin heavy chain, desmin, δ-sarcoglycan) and a part of the tenth gene (metavinculin) in the above Finnish patient groups with DCM. The screened number of patients for different candidate genes varied between 32 and 156. Nine disease-associated mutations in three different genes were detected in the analyses. Altogether these mutations accounted

for 9.6% of the etiology of the 156 DCM patients. The Ser143Pro mutation in the lamin A/C gene was found to be quite common in Finnish patients with familial DCM. Haplotype analysis strongly suggested that the Ser143Pro mutation is a founder mutation, probably the first founder mutation described for DCM (32). Five other LMNA mutations (Ala132Pro, Arg190Trp, T1085 deletion, G1493 deletion, and Arg541Ser) were detected in patients with heart transplantation (54). T1085 deletion was found in two unrelated families.

All LMNA mutation carriers have a very similar phenotype. The main characteristic features are progressive conduction defect (66%), early need for a pacemaker, slow atrial fibrillation, sudden cardiac death, and overt heart failure leading to heart transplantation in some cases. All mutation carriers over 40 years had some manifestation of DCM, and only the young mutation carriers under 30 years were free from clinical disease. The penetrance of the disease in our patient population is almost 100% in subjects over 40 years. The LMNA mutations overall, and especially the Ser143Pro mutation, can be classified as a relatively malignant mutation, because several sudden cardiac deaths occurred in the families carrying the mutation. The index patients with the Ser143Pro mutation had a more severe prognosis than noncarriers (32). Also, heart transplantations are frequent among LMNA mutation carriers.

Other mutations (Arg1053Gln and Arg1500Trp in the β-myosin heavy chain gene, and Arg71Thr in the δ-sarcoglycan gene) seem to be less common in Finnish DCM patients (31,62), the prevalence being quite low, approximately 1% in our studies.

Genetic screening in dilated cardiomyopathy and its clinical significance

Dilated cardiomyopathy is known to be heterogeneous in etiology, clinical features, and prognosis, and it seems that genetics of this disease do not make an exception to the rule. So far, over 20 disease-causing genes have been reported, and most of these mutations explain the disease only in single families or single patients. The disease-causing mechanisms vary as well, and they are far from resolved yet. There are some mechanisms that have been proposed to cause the clinical disease of DCM. Sarcomere and cytoskeletal protein genes are generally thought to affect force generation or force transmission, and mitochondrial mutations in turn are assumed to affect energy production (76). DCM-associated mutation in the phospholamban gene probably disturbs the myocellular Ca^{2+} metabolism (40). Defects in the cardiac muscle LIM protein and telethonin complex in Z disc have been proposed to affect the cardiomyocyte stretch sensory machinery (33). Defects in the nuclear protein gene, such as lamin A/C and thymopoietin, cause disturbances in nuclear structure and function (20,43,52).

Although 50% of patients with idiopathic DCM may have a genetic disease, a specific mutation can be diagnosed only in a small proportion of patients and families at the moment. Our view is, however, that in the near future more DCM-associated gene defects will be reported in the literature, and at the same time the heterogeneity of the disease genetics will increase. For almost all of the gene defects identified so far, the population carrying the mutation is quite small, and therefore an exact description of gene-specific clinical phenotypes is difficult to give. Furthermore, at the moment we do not have good prognostic factors for specific gene defects. Several different clinical characteristics have been shown to correlate with poor prognosis in idiopathic DCM, but these characteristics are quite common in congestive heart failure in general (130–147).

The lamin A/C gene, however, seems to be an exemption in the rule. Mutations in the lamin A/C gene are probably the most frequent gene defects reported to cause DCM. Moreover, lamin A/C mutations are usually associated with a severe phenotype, which also differs somewhat from the classical or typical phenotype of DCM fulfilling the current international diagnostic criteria (148). The clinical manifestations of DCM caused by the mutations in the lamin A/C gene are relatively well described. The main characteristic features are slow atrial fibrillation, some degree of atrioventricular conduction system disorder, need for a permanent pacemaker, only slight dilatation of left ventricle, and an elevated risk for sudden cardiac death (32,43,148), as already described earlier in this review. Overall, in our experience the generally accepted diagnostic criteria for DCM might not be applicable for all patients with mutations of the lamin A/C gene, and at least with a positive family history a strong suspicion for a lamin A/C mutation should arise also in the presence of mild to moderate alterations in electrocardiogram (ECG) (conduction defects) or echocardiography (mild dilatation or moderate systolic dysfunction).

In families with two or more patients with DCM, clinical examination, ECG, and echocardiography of the first-degree relatives seem warranted. In cases of even mild alterations in the above investigations, proper follow-up should be organized. With clinical features resembling phenotypes typical of lamin A/C

mutations, genetic screening for these mutations, whenever possible, should be performed. Genetic screening for lamin A/C mutations is important, because these gene defects are relatively malignant in nature. Mutation carriers should be directed to proper genetic counseling, follow-up, and treatment including medication, automatic defibrillators, and eventually cardiac transplantation. On the other hand, with genetic screening noncarriers in the family can be liberated from follow-up. So far, other gene defects associated with DCM seem to be too rare to arrange genetic screening procedures. However, more research is needed to identify novel gene defects in DCM, and on the other hand, to identify patients and families carrying the hitherto reported gene defects. Larger populations with known mutations should be better characterized clinically to allow genotype-specific phenotyping and prognostic evaluation.

Vatta et al. reported that disruption of integrity of dystrophin may be reversed in patients with cardiomyopathy, provided that patients are treated with left ventricular assist device (LVAD), suggesting that gene defect-specific treatments may be identified in the future (149). On the other hand, it may be that specific polymorphisms, such as angiotensin converting enzyme (ACE) polymorphism and β-adrenoreceptor polymorphisms as modifier genes may affect the natural course and prognosis in DCM patients with various specific disease-causing gene defects (150,151). McNamara et al. (152) reported that higher doses of ACE inhibitors diminished the impact of the ACE D allele, and the benefits of beta-blockers and high-dose ACE-inhibitors appeared maximal for DD patients. Thus in the future, the genotype may also affect the medication chosen for patients with heart failure (152,153).

In Finland there is a plan to organize uniform diagnostics, follow-up, and treatment of all idiopathic DCM patients. According to the plan, we are going to identify one or two cardiologists responsible for cardiomyopathy patients (both DCM and HCM) in bigger hospitals covering the whole country. In clear family cases, first-degree relatives should be investigated, and blood samples for genetic screening (at least for detection the common founder mutation Ser143Pro) should be taken. The genetic screening in Finland is centralized in the gene laboratory of the Department of Internal Medicine, Kuopio University, the most experienced center for genetic screening of cardiomyopathies.

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