COMPLEX ROADS FROM GENOTYPE TO PHENOTYPE IN DILATED CARDIOMYOPATHY: Scientific update from the Working Group of Myocardial Function of the European Society of Cardiology

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ABSTRACT:

Dilated cardiomyopathy (DCM) frequently affects relatively young, economically and socially active adults, and is an important cause of heart failure and transplantation. DCM is a complex disease and its pathological architecture encounters many genetic determinants interacting with environmental factors. The old perspective that every pathogenic gene mutation would lead to a diseased heart, is now being replaced by the novel observation that the phenotype depends not only on the penetrance -malignancy of the mutated gene- but also on epigenetics, age, toxic factors, pregnancy and a diversity of acquired diseases. This review discusses how gene mutations will result in mutation-specific molecular alterations in the heart including increased mitochondrial oxidation (sarcomeric gene e.g. *TTN*), decreased calcium sensitivity (sarcomeric genes), fibrosis (e.g. *LMNA* and *TTN*) or inflammation. Therefore, getting a complete picture of the DCM patient will include genomic data, molecular assessment by preference from cardiac samples, stratification according to co-morbidities, and phenotypic description. Those data will help to better guide the heart failure and anti-arrhythmic treatment, predict response to therapy, develop novel siRNA-based gene silencing for malignant gene mutations, or intervene with mutation-specific altered gene pathways in the heart.

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DCM: AN OVERLAPPING PHENOTYPE FOR MULTIPLE CONDITIONS

Dilated cardiomyopathy (DCM) encompasses etiologically heterogeneous myocardial disorders that are defined by the presence of left ventricular or biventricular dilation and depressed myocardial performance, in the absence of overloading (hypertension, valvular or congenital heart disease) or chronic ischemic conditions.[1] Interactions between the genetic and non-genetic factors may influence the severity and the outcome of DCM cases, including heart failure, rhythmic disorders, stroke, and the need for cardiac transplantation.[1] The early identification of the causative gene mutation or the acquired cause is an important step to implement pre-symptomatic interventions, as some gene mutations, e.g. *LAMIN A/C* or *RBM20,* are highly penetrant and can be pro-arrhythmogenic.[1,2] In this review, we describe the most advanced scientific achievements on genetic and cellular defects, diagnostic assessment and future therapeutic perspectives for this heterogeneous disease.

Modern epidemiological studies considering disease heterogeneity and variable clinical presentation are lacking regarding DCM, and it is now recognized that DCM prevalence was underestimated in the initial population studies.[3-5] Based on heart failure prevalence, considering left ventricular (LV) dysfunction as a surrogate for DCM, and extrapolating data from hypertrophic cardiomyopathy (HCM), it is now admitted that DCM could be as prevalent as HCM and reach 1/250-500 in clinical practice.[2] Also, in the European registry on cardiomyopathies, the DCM proportion was unexpectedly high (almost 40 % of all cardiomyopathies) supporting that DCM prevalence in Europe could be close to the one of HCM.[6] Recent and reliable population data are required to strengthen this statement. Overall, the recognition of a complex architecture for DCM not only in terms of gene-environment interactions, but also regarding its clinical presentation (with early stages of the disease being now recognized and defined by the presence of hypokinetic and non-dilated cardiomyopathy, preceding overt dilatation and heart failure) has made of DCM the most common cardiomyopathy.[2,7]

A positive familial history can be detected in up to 30 to 50 % of DCM cases,[7] and a genetic determinant can be identified following a screen of more than 40 genes in up to 40 % of DCM cases.[1,2,8] Sarcomeric, mitochondrial and neuromuscular disorders are frequent etiologies in the presence of a “familial” history, where additional acquired conditions like exposure to toxics, diabetes, arrhythmia, myocarditis and pregnancy also contribute to the phenotype and outcome. Often, genetic determinants increase the susceptibility or are modifying factors in the presence of an external cause for DCM. The overlap between a genetic disorder and acquired disease becomes more and more ambiguous (Figures 1 and 2), raising

complexity in the assessment of these patients, but also opening new avenues in understanding and treating this etiologically heterogeneous disease.

1-THE TUNNEL PERSPECTIVE: DCM SEEN AS AN INHERITED CARDIAC CONDITION

Familial DCM is genetically heterogeneous and generally inherited as a monogenic trait transmitted in a dominant negative fashion, with incomplete penetrance (Table 1).[1,2,9,10] Autosomal recessive, X-linked inheritance and mitochondrial inheritance are less frequent.[1,2,9,10]

Autosomal dominant forms of DCM are linked to variants in more than 40 genes encoding proteins with functions in cardiac muscle contraction and relaxation (Table 1). Although those variants have been associated with DCM, the pathogenic role in DCM remains uncertain for many of them.[11]

Mutations in the *TTN* gene coding for titin, the giant protein functioning as a nano-spring, is perceived as the most common cause for DCM, although with incomplete penetrance and variable, often milder phenotypes.[12,13] Importantly, *TTN*-truncating variants in the presence of acquired diseases may be related to more ventricular arrhythmias in 2 studies,[14,15] enhanced cardiac fibrosis,[14] reduced hypertrophy[14] and pronounced alterations in cardiac mitochondrial function.[14] Analysis in other cohorts is required to verify and better understand those novel phenotyping findings.

RBM20, the regulator of TTN splicing, has also been described as a cause of familial DCM with approx. frequency of 2-3%.[16,17] Outcome of *RBM20* mutation carriers may be worse, with higher frequency of atrial fibrillation and progressive heart failure. Also, mutations in the *LMNA* gene (lamin A/C),[18-21] in *FLNC* (filamin C),[22] *DES* (desmin),[23,24] *PLN* (phospholamban),[25-27] and *SCN5A*[1,28] have been identified as a malignant cause of DCM. These mutations are associated with a typical time-course of rhythm disturbances ranging from atrio-ventricular blocks (*LMNA*, *DES*, *SCN5A*) to supraventricular and ventricular malignant arrhythmias (*LMNA*, *FLNC, PLN* and *SCN5A*). Importantly, ventricular arrhythmias can precede systolic dysfunction conferring a risk of sudden cardiac death irrespective of LV dysfunction.[1,18,29,30] This implicates the use of genetic information in sudden cardiac death risk estimation, and careful stratification of arrhythmogenic risk in DCM patients. In the presence of easy to assess clinical factors, prophylactic defibrillator implantation should be considered for these patients.[31,32] In summary, DCM patients with mutations in *LMNA*, *PLN*, *RBM20, FLNC, DES* or *SCN5A* are at risk for worse prognosis and/or a higher rate of malignant arrhythmia, the latter being the case in *TTN*-truncated variants,[14,33,34] and creating an overlap with arrhythmogenic cardiomyopathy.

In DCM with recessive inheritance, the mutated genes encode the proteins cardiac troponin I3 (*TNNI3*), titin (*TTN*), desmoplakin (*DSP*), dolichol kinase (*DOLK*), GATA zinc finger domain-containing protein 1 (*GATAD1*) and flavoprotein (*SDHA*). X-linked diseases associated with DCM include neuromuscular disorders (such as Becker and Duchenne muscular dystrophies). DCM occurs in both patients with mitochondrial diseases and inherited storage disorders (such as hemochromatosis) as the end-phenotype of early hypertrophic cardiomyopathy.[7,35,36] Mitochondrial cardiomyopathies demonstrate clinical and genetic heterogeneity, with variable syndromic manifestations.

Primary DCM patients with a positive family history for cardiomyopathies or with distinct hints for a genetic cause of the disease (red flags, e.g. conduction disease) should be offered the possibility of genetic testing and counseling.[7,31,37,38]

1.1. Sarcomeric mutations and DCM: from the contractile apparatus to the dilated phenotype

The sarcomere plays a central role in cardiomyocyte function and metabolism and the molecular link between sarcomeric mutations and the dilated phenotype has increasingly been elucidated. Mutations in beta-myosin heavy chain (*bMHC*) as well as in alpha-myosin heavy chains (*aMHC*) may cause familial hypertrophic cardiomyopathy (HCM) and DCM, with sometimes features of restrictive cardiomyopathy (RCM).[39-42] Thin filament mutations have highlighted a key role for calcium-dependent tension in the disease phenotype: these mutations are only a small fraction (~5-10%) of all HCM mutations and often cause an increase in myofilament calcium sensitivity, while thin filament mutations associated with DCM frequently show reduced calcium sensitivity of myofilament force development (Figure 3).[43] Hence, identification of the thin filament sarcomeric mutation, which causes the early contractile alteration, would predict the development of hypertrophic versus dilated cardiomyopathy. Importantly, sarcomeric gene mutations may disrupt the highly tuned balance between mechanical force generation and Ca^{2+}-cycling dynamics. A recent study tried to differentiate thin filament mutations that alter calcium-dependent tension (increase or decrease) into the spectrum of hypertrophic versus dilated cardiomyopathy.[43] Altering myofilament Ca2+ sensitivity in mice with specific *TNNC1* gene variants resulted in the activation of both calcineurin and MEK1-ERK1/2 signaling in the presence of a variant which, increased calcium-sensitivity, resulting in concentric hypertrophy (Figure 3).[43] In contrast, inhibition of MEK1-ERK occurred in the presence of a DCM-related variant, which reduced calcium-sensitivity and resulted in cell elongation,

suggesting that the combination of calcineurin activation and MEK1-ERK inhibition underlies the eccentric (dilated) remodeling. High-resolution structural information about multiprotein may help to characterize the baseline function and structure of the Tropomyosin overlap region of the thin filament, as mutations with differential phenotypes exert opposite effects on the Tropomyosin–Troponin overlap.[44]

Increased myofilament Ca^{2+}-sensitivity and improved cardiac contractility is also seen in a mutant *tropomyosin* (TM-E54K) mouse treated with a β-arrestin 2-biased ligand of the angiotensin II receptor.[45] The increase in myofilament Ca^{2+}-sensitivity resulted from enhanced phosphorylation of myosin light chain-2.[45]

The open question is how different defects in different proteins may cause a similar end-phenotype. Recent studies in human DCM samples demonstrated that a sarcomeric *TNNI3* (troponin I) mutation impaired length-dependent activation (i.e. Frank-Starling mechanism), and a *TNNT2* (troponin T) mutation increased passive stiffness, while a non-sarcomeric *LMNA* mutation did not cause direct sarcomere changes, but was associated with reduced force generation due to the disease-related cellular hypertrophy and reduced myofibril density.[46] A basic integrated-tension index could be used to differentiate DCM from HCM and, as a consequence, to understand the phenotype and to choose the best pharmacologic treatment.[43]

1.2 DCM, arrhythmogenic cardiomyopathy and channelopathies

The electrical instability observed in some DCM cases creates a clinical overlap between DCM and arrhythmogenic cardiomyopathy and channelopathies. The above-mentioned *LMNA* mutations are associated with high-risk malignant ventricular arrhythmias, regardless of the severity of LV dysfunction and dilatation.[38,47] Other genes linked to arrhythmogenic phenotypes in DCM are the gene encoding for filamin C (*FLNC)*, [22] RBM20,[16,17] phospholamban (*PLN*),[25,26] and more recently TTN-truncating variants.[14,15] Also, mutations in genes for desmosomal proteins, which are usually associated to arrhythmogenic right ventricular cardiomyopathy (ARVC) have now emerged as a cause of DCM with a propensity to ventricular arrhythmia too.[48-51]

Importantly, DCM may be caused also by genes encoding for/or modulating ion channels (i. e. *PLN, RYR2* and *SCN5A*)[38] Indeed, mutations involving sodium, calcium and potassium related proteins support an alternative disease mechanism of dilation primarily triggered by dysfunction in electrical excitability rather than a structural defect.[1,27,52] In particular, in familial DCM, missense mutations in *SCN5A,* that are also

linked to long QT and Brugada syndromes, carry a higher risk for arrhythmias.[3] The different roles of *SCN5A* in the myocardium and the conduction system produce a combination of arrhythmia and cardiomyocyte dysfunction, as witnessed by transgenic-directed inducible expression of the F1759A mutation in the *Scn5A* gene that leads to atrial fibrillation and persistent sodium currents in atria and ventricles and reduced ejection fraction.[1,53]

PLN mutations lead to variable phenotype with early onset DCM.[25,54] In order to assess mechanisms and impact of these mutations, iPSCs with the R14del PLN mutation were generated.[55] Aberrant Ca2+ handling after caffeine and abnormal Ca2+ transients, which could be reversed upon correction of the primary mutation by gene editing could be described in these cells,[55] while reduced developed force that could be improved after genetic correction was observed in 3-dimensional human cardiac tissue.[56]

Although those variants have been associated with DCM, their pathogenic role in DCM has to be reconsidered, with many of them being represented as much in large population controls than in DCM cases.[11]

1.3 Possible genetic basis and mechanisms of tachy-induced cardiomyopathy

The development of cardiomyopathy due to arrhythmia may take months to years, but recurrent arrhythmia can lead to LV dysfunction and heart failure.[57] Tachy-induced cardiomyopathy can also be associated with genetic factors. Serum and glucocorticoid-regulated kinase 1 (SGK1) is a component of the cardiac phosphatidylinositol 3-kinase signaling pathway that has proarrhythmic effects linked to biochemical and functional changes in the Na+ channel. These effects can be reversed by the Late Na+ current inhibitor, ranolazine.[58] Accordingly, inhibition of SGK1 in the heart protects against fibrosis, LV dysfunction, and Na+ channel alterations after hemodynamic stress.[58]

Whether tachyarrhythmia unmasks a latent cardiomyopathy, or whether genetic factors can induce both arrhythmia and DCM is still under debate. Recent advances in our understanding of channelopathies and the co-existence of arrhythmic and dilated phenotypes in some patients seems to foster this theory.[28,59,60] Mutations in the cardiac Na+ channel and in the ryanodine receptor can lead to arrhythmia, but also to LV dysfunction.[57,60]

1.4. Mitochondrial dysfunction in the complex road to dilated cardiomyopathies

Mitochondrial cardiomyopathy is a part of a heterogeneous group of multisystemic diseases that develop

as a consequence to mutations in nuclear or mitochondrial genes.[61] Inheritance follows matrilineal rule for mtDNA mutations and Mendelian rules for nuclear gene defects.[62] The cardiac phenotype is characterized by LV hypertrophy that commonly evolves through LV dilation and dysfunction.[63] A typical example of DCM associated with nuclear gene defects is Barth Syndrome (BTHS), an X-linked recessive disorder characterized by left ventricular non-compaction (LVNC) cardiomyopathy, skeletal myopathy, neutropenia, growth retardation, and 3-methylglutaconic acidurea.[64] BTHS is caused by mutations in the *TAFAZZIN* (*TAZ)* gene that lead to a defective phospholipid transacylase, termed tafazzin. Defective tafazzin activity leads to alterations in the content and composition of cardiolipin and the appearance of monolysocardiolipin.[65,66] mtDNA defects may range from large rearrangements (deletions) of the mtDNA to point mutations[67-69], that prevalently affect OXPHOS complexes. Moreover, a defective mtDNA repair system is evident in DCM human hearts, which is accompanied by activation of PGC-1α, abnormal mitogenesis, and increase in mtDNA deletion mutations.[70] This maladaptive compensatory response further contributes to the progression of the disease.

mtDNA alterations are common in human populations[71] and often lead to the replacement of amino acid residues without pathological significance. When affecting evolutionarily conserved residues, mitochondrial protein synthesis and specific respiratory enzyme activities mtDNA mutations can have pathogenic significance.[69] Defects in the mechanism of mtDNA repair can promote accumulation of mtDNA defects with wide variability in the age of onset and severity of the phenotype.[72] It is also needed to consider that nuclear genes, which further increase the complexity of the phenotypic effects of the gene-to-gene interactions, control mechanisms of mtDNA repair. Genetic mutations disturbing mitochondria dynamics are responsible for neurodegenerative conditions and cardiac failure.[73,74] Thus, defects involving the complex machinery of mitochondria repair/replacement can promote mtDNA defects and facilitate the occurrence of cardiac dysfunction. These considerations might be relevant in specific environmental contexts, for example in presence chronic exposure to the very low dose of ionizing radiation for occupational or health purpose (Figure 4).[75,76] Epigenetic or inherited defects in mitochondria dynamic and/or function, in particular, those with low penetrance and expressivity can lead to a cardiac phenotype when interacting with a specific environment, which may explain the sizeable phenotypic variability of mitochondrial cardiomyopathy.

1.5 DCM and primary restrictive cardiomyopathy

A broad overlap exists between cardiomyopathies and for some genes clinical presentation ranges from DCM to HCM, arrhythmogenic or restrictive cardiomyopathy, with sometimes features of non-compaction. Restrictive cardiomyopathy (RCM) is a rare disorder characterized by increased cardiac filling pressure related to enhanced wall stiffness, leading to severe atrial dilatation, despite a limited increase in cardiac chamber dimensions and wall thickness.[77,78] RCM is seen in primary myocardial disease, in infiltrative disorders, or can be associated with autoimmune diseases or metabolic disorders.[77,78]

Sarcomeric proteins play a central role in controlling myocardial tension and relaxation, and calcium-sensitivity is a key player in controlling this equilibrium (section 1.1).[43] In a series of 1226 HCM patients, 2,3 % had a restrictive phenotype, with on half of the RCM probands having mutations in *MYH7* or *TNNI3* genes.[42] Underlying this phenotypical overlap, previous linkage analysis have revealed that *TNNI3* mutations, a gene involved in HCM and DCM, are also associated with RCM,[79] and further analysis confirmed the role of *TNNI3* in RCM.[80,81] Cardiomyocytes of *cTnI* R193H mice showed shortened cell length and impaired relaxation.[82] Multiple phenotypes ranging from RCM, HCM and DCM were also observed in the same family in the presence of a I79N *TNNT2* mutation.[83] Reconsidering the old view that DCM presentation could be the end-stage presentation of several cardiac diseases, those results support a genetic base for overlapping phenotypes.

Another example of phenotypical overlap is given by non-sarcomeric genes. Variants in *TTN*, *DES*, *FLNC* and *MYOPALLADIN* (*MPN*) are also related to DCM, HCM and RCM.[78] Desmin accumulation leads to clinical phenotypes affecting peripheral and/or cardiac muscles, with sometimes predominant cardiac or peripheral involvement.[24] Altering cellular trafficking, cardiac desminopathy can present as DCM, HCM, or RCM with frequent involvement of the conduction system leading to AV blocks.[23] Other genes linked to rhythmic disorders in DCM including *FLNC*, *RBM20*, *PLN*, and *TTN* are also associated with RCM,[77,84] supporting the existence of a genetic base for this phenotypic continuum between cardiomyopathies.

Iron overload cardiomyopathy (IOC) usually presents with a myocardial concentric or asymmetric nonextreme hypertrophy with progressive left ventricular remodeling and dysfunction.[85] After an asymptomatic period, patients with in IOC present with mild heart failure symptoms, because of

restrictive physiology and may mimic heart failure with preserved ejection fraction. Later, ejection fraction regresses with the presence of end-stage heart failure.[86]

1.6 From genes to clinical tools: the noisy background in DCM genetics

The development of population genetics databases like the Exome Aggregation Consortium (ExAC) and the Genome Aggregation Database (gnomAD) have offered an unprecedented view of rare variation in the human genome.[87] These resources have revealed that the frequency of rare variation in many genes is much higher than hitherto appreciated, which has implications for variants and genes that have been previously associated with disease. A substantial proportion of variants reported as causative for DCM and other cardiomyopathies are present in these (clinically uncontrolled) population databases.[88,89] Comparing the total burden of rare variation in genes associated with DCM between ExAC and large cohorts of DCM cases has revealed that a significant excess in cases is observed in only a small number of well characterized DCM genes such as *TTN*, *LMNA* and the sarcomeric genes.[11] These findings suggest that the pleiotropic effects of variants associated with cardiac disease and the genetic overlap between DCM and other inherited cardiac conditions may have been overestimated.

The lack of an overall case excess does not necessarily preclude a role in DCM. In fact, pathogenic variants can be restricted to specific residues or small domains and therefore masked by the background benign variation in the rest of the gene, e.g. the DCM mutation hotspot found in the titin splicing regulator *RBM20*.[90] However, aside from founder mutations (such as the *PLN* R14del in 10-15% of DCM patients in the Netherlands),[26] variants in genes without a case excess are likely at best to be rarely causative in DCM. In order to reduce the uncertainty associated with standard clinical genetic testing, and the danger of false positive results, panels should be restricted to genes with strong evidence of pathogenicity. Initiatives such as ClinGen have been established to curate these gene to disease associations and identify panels of validated and interpretable genes for clinical genetic testing.[91] However, as shown by a recent study assessing the evidence for genes implicated in hypertrophic cardiomyopathy,[92] it is likely that genes with an excess of rare variants in case series will account for the vast majority of pathogenic variants detected in patients. This could be explained by a higher frequency of HCM, and a smaller proportion of asymptomatic mutation carriers in HCM as compared to DCM.

The extent of rare benign variation in the population is particularly prevalent for interpreting missense variants, particularly in genes that were implicated in DCM based on limited evidence and are regularly

included in clinical panels (such as *MYBPC3* and *MYH6*).[11,93] Truncating variants in several different genes have now been shown to be key determinants in DCM genetics and have been validated through burden testing between cases and controls (for *TTN*,[12,94] *DSP*[11,93] and *FLNC*[22]) or segregation in large families (*BAG3*[95,96]). Although variant interpretation guidelines produced by the American College of Medical Genetics (ACMG)[97] deem a truncating variant as actionable if it is sufficiently rare and a loss of function mechanism has been proven for the affected gene in the disease being tested, such variants in novel or poorly characterized DCM genes should not be assumed to be pathogenic given that each individual is estimated to harbor at least 100 truncating variants, of which approximately 20 will be rare.[87]

1.7 Deciphering missing heritability and incomplete penetrance in DCM

Although restricting genetic testing to validated genes is a prudent strategy in the clinic, whole exome or genome sequencing of large patient cohorts and family pedigrees now offers the opportunity for the discovery of novel genetic factors underlying DCM. This may include protein-coding variation in novel genes, non-coding and regulatory variants affecting known DCM genes, and the assessment of oligogenic inheritance which has been hypothesized as possible mode of transmission in DCM, factors that may underlie the low penetrance of this disease[1,7] Also the complex interaction between common and rare variation with other environmental and medical factors may be responsible for the clinically observed heterogeneity of DCM even in families carrying the same pathogenic variant. However, even when taking all knowledge about the impact of multiple high penetrance variants in single patients and common variants identified in GWA studies into account,[98,99] there is still a large fraction of heritability and a considerable phenotypic variability that cannot be explained.[100] The deciphering of epigenetic alterations could provide new clues to this obstacle: epigenetic changes can occur due to intrinsic and environmental factors and can, in variable degree, be transmitted to the progeny. Already during cardiac development, DNA methylation of gene bodies and post-translational modifications of histones of developmental and sarcomeric genes can be detected that also occur during heart failure.[101-103] In DCM, a first study was able to map the genome-wide DCM methylome and identify putative new players in its pathophysiology, such as *LY75*.[104] In a recent study embarking on a multi-omics design including whole-genome sequencing, transcriptome sequencing and high-density DNA methylation profiling, Meder et al. could delineate a significant role of DNA methylation patterns on cardiac gene expression and DCM.[105] They further raised a new paradigm, the

cross-tissue conservation of methylation alterations, rendering epigenetics a novel class of cardiac biomarkers and potential therapeutic target.[106]

2-THE BROADER VIEW: DCM AS A PHENOTYPE AT THE INTERSECTION BETWEEN GENES AND AQUIRED CONDITIONS.

2.1. Inflammation in genetic cardiomyopathy, viral infections and myocarditis: complex interactions

In DCM, the pathogenicity of a gene mutation is modulated by interfering factors: besides age and hormonal context, inflammation (i.e. virus infection, cardiac inflammation, systemic disease), hypertension, mitochondrial alterations, as well as other environmental triggers (like toxic exposure) are strong candidates to modulate the expression of genetic determinants and the prognostic of the disease.[12,74,75]

In particular, low grade chronic cardiac inflammation mediated by the innate immune system is often seen in genetic cardiomyopathies.[107] Importantly, autoimmune diseases, viral infections or toxic stimuli that trigger innate immunity may increase heart inflammation in a subject with a "genetic" predisposition to cardiomyopathy, worsening the prognosis.[108]

Not unfrequently, LV dysfunction can be caused by viral, bacterial, fungal, parasitic, rickettsial, and spirotricheal infections. In viral myocarditis, parvovirus B19, adenovirus, coxsackievirus B and other enteroviruses, influenza A, human herpes virus 6, cytomegalovirus, Epstein-Barr virus, herpes simplex virus type 1, and hepatitis C virus are the most common viruses identified by means of endomyocardial biopsies,[109,110] with coxsackievirus being predominant in the 1980s, adenovirus in the 1990s, and parvovirus B19 since 2000.[111]

TLRs are involved in early activation of the innate immune response against viruses and other infections. So far, specific roles in inflammatory cardiomyopathy and myocarditis have been described for TLR2, TLR3, TLR4, TLR7, and TLR9 along with their downstream adaptors MyD88 and TRIF.[112-116] In particular, enteroviruses, activate TLR3 signaling: animals lacking TLR3 exhibit enhanced mortality after being infected with enteroviruses.[117] Importantly, subjects affected by enteroviral myocarditis/cardiomyopathy present with a common TLR3 polymorphism.[118] Upon viral infection, patients who develop myocarditis have elevated TLR4 transcripts, while TLR4 deficient mice had heart inflammation in CVB3 myocarditis.[107]

On the other way, animal studies have shown that gene mutations may trigger inflammation, independent of other acquired immune activators, but more studies are needed in order to confirm this hypothesis.[107] In

the presence of myocardial derangements, such as the ones that occur in DCM, inflammation enhances fibrosis in the left ventricle and promotes fibrofatty degeneration in the right ventricle.[107] Parallel to this, stimulation of the immune system will lead to the appearance of circulating cardiac auto-antibodies, which are potential therapeutic targets.[107,119] Also, it is very likely that myocyte hypertrophy in DCM may act on macrophages via enhanced oxidative stress, that in turn favors further myocyte hypertrophy and fibrosis, hence letting cardiac disease to progress.[107]

2.2 The genetic influence on development of toxic cardiomyopathies

Alcohol and anthracyclines are well-known cardio-toxic triggers sharing the ability to induce a broad spectrum of cardiac impairments, going from asymptomatic cardiac remodeling and subclinical dysfunction to severe heart failure.[120-122] Recent studies highlight the potential role of genetic factors interacting with toxic triggers and potentially contributing to the inter-individual variability of cardiac phenotype.[123-127]

In alcoholic cardiomyopathy, alcohol metabolism and accumulation of its main metabolite, acetaldehyde, could contribute to the myocardial damage through alterations of sarcoplasmic reticulum, mitochondria, calcium transient and Ca2+ sensitivity of myofibrils, increased apoptosis, alterations in lipid energetic metabolism and protein synthesis, increased oxidative stress, activation of renin-angiotensin and sympathetic systems.[120] SNPs in genes involved in ethanol metabolisms such as *ADH1B* (A/A), *ALDH2* (A/G or A/A) and *CYP2E1*(T/C or T/T) increase genetic susceptibility to ethanol-induced cardiac dysfunction. In particular, fast *ADH1B* (A/A) induces a more rapid conversion of ethanol into acetaldehyde, whose degradation can be delayed due to the reduced enzyme activity of ALDH2 (A/G or A/A), and resulting in a toxic accumulation. *CYP2E1*(T/C or T/T) further worsens the impairment of ethanol metabolism inducing greater accumulation of both acetaldehyde and ROS.[123]

Anthracyclines cardiotoxicity (ACT) represents the most critical dose-limiting side effect of these wide-used antineoplastic drugs. Novel mechanisms of cardio-toxicity have been recently identified and explored in patients with malignancy treated with anthracyclines. First, anthracyclines can induce dsDNA break and cell death through reticence of Topoisomerase 2-beta (Top2β).[121] The SNP Ser427Leu in RARG is highly associated with ACT since this variant alters the ability to downregulate Top2β transcription, leading to its accumulation in cardiomyocytes where it is targeted by anthracyclines.[124] A potential role in the ACT might be played by the reduction of anthracyclines to cardiotoxic alcohol metabolites through carbonyl reductases (CBR). Indeed, individuals with CBR3 V244M homozygous G genotypes (CBR3 G/G) show a higher

cardiomyopathy risk, since this genetic variant increases synthesis of these metabolites.[125] The ACT pathophysiology involves unbalancing between ROS generation and intrinsic antioxidant species. This leads to impairment of calcium homeostasis, mitochondrial bio-energetic disruption, activation of the ubiquitin-proteasome system leading to sarcomeric structure dysregulation, activation of NFκB signaling and immune system, senescence of cardiac and endothelial progenitor cells (CPCs and EPCs).[121] Anthracyclines accumulation within the cardiomyocytes is the essential step to determine their oxidative potential. Accordingly, many of the other SNPs associated with higher risk of the ACT are located in genes able to influence anthracycline pharmacokinetics (*SLC28A3, SLC28A1, SLC10A2, ABCB1, ABCB4, ABCC1, UGT1A*).[126,128] Genetic susceptibility to ACT can also affect cardiac protective mechanisms. Indeed, the rs2232228 AA genotype in *HAS3* gene reduces hyaluronan synthesis leading to inadequate tissue remodeling and insufficient protection of the heart from ROS-mediated injury.[129] ACT also shows coexistence of two or more TNNT2 (cTNT) splicing variants, which lead to a temporally split myofilament response to increasing Ca2+ concentrations and could decrease myocardial contractility.[130] Individuals homozygous for the *CELF4* rs1786814 G allele are more likely to coexpress the embryonic and adult TNNT2 variants and, thus, to possibly enhance cardiotoxicity risk in response to anthracyclines.[127]

Recently, a further mechanism of doxorubicin-mediated cardiotoxic effects has been identified based on the downregulation of the crucial circular RNA regulator Quaking.[131] Doxorubicin leads to a significant downregulation of Quaking in the heart, thus making it more susceptible for cardiac apoptosis. In a therapeutic approach, AAV-mediated cardiac overexpression of Quaking rescued the heart from Doxorubicin-mediated toxicity thus presenting a potential future entry point of novel cardiac anti-toxic treatments.

Antineoplastic drugs can also cause cardiomyopathy by an interference with the innate immune system.[132] In particular, toll-like-receptors (TLRs) can “sense” anthracycline-mediated damage, with TLR2 KO mice showing partially preserved cardiac function and improved survival compared to WT animals in a model of acute doxorubicin administration.[107,133] Other TLRs exhibit a controversial behavior: for instance TLR4 KO mice showed protection from anthracycline-induced cardiac toxicity,[134]; while anti-TLR4 antibodies had opposite effects.[107,135]

Of notice, the innate and adaptive immune system has a pivotal role in the recognition and elimination of tumor cells. One of the supposed mechanisms by which anthracyclines are effective in cancer is the stimulation of an antitumor immunity by inducing immunogenic cell death. This effect is achieved via innate

immune receptors, including TLR3 and 4.[136] Intuitively, the immune system is involved also in cardiotoxicity developed after oncologic treatments with immune checkpoint inhibitors, that can cause, among other immune related adverse events, cardiac immune-related adverse effects such myocarditis and pericarditis.[107,137,138]

2.3 Genetic predisposition to peripartum heart failure: what about hormones?

Most genetic DCMs only become penetrant after puberty, indicating an hormonal change as a requirement to develop the phenotype. Peripartum cardiomyopathy (PPCM) is an example of interaction between hormonal changes and genetic predisposition. PPCM has been defined as "an idiopathic cardiomyopathy presenting with heart failure secondary to LV systolic dysfunction towards the end of pregnancy or in the months following delivery, where no other cause of heart failure is found".[139] PPCM is a severe complication of pregnancy with a high morbidity and mortality.[140,141] Meanwhile it is considered more a syndrome with different underlying disorders. Among those, genetic forms of cardiomyopathy seem to account for some cases since for example the disease is more frequent in certain geographical regions, Africa (1 in 100 to 1 in 1000 pregnancies) or Haiti (1 in 299 pregnancies), and since there are reports from PPCM patients with a clear family history of heart failure.[142,143] Indeed, more recently, several studies discovered mutations associated with familial forms of DCM in PPCM patients, i.e. mutations in *TTN, MYBPC3*, *MYH6*, *MYH7*, *PSEN2*, *SCN5A*, *TNNC1*, and *TNNT2*.[144-146] Beside the presence of mutations associated with familial forms of DCM in PPCM patients, it is also likely that additional mutations or polymorphism may be present in these patients and contribute to their susceptibility to peripartum heart failure. Extrinsic factors like viral infections could also mediate peripartum heart failure and it has been shown that virus including Epstein-Barr virus, human cytomegalovirus, human herpes virus 6, and parvovirus B19 could be identified in up to 30 % of cardiac samples in PPCM,[147] but their exact pathogenic role still needs to be defined.[148]

Interestingly, it seems that genetic and non-genetic forms of PPCM may merge on a common pathway including unbalanced oxidative stress and subsequent cleavage of the nursing hormone prolactin into an angiostatic fragment that initiates and drives progression of PPCM.[140,141] This discovery led to a disease specific treatment concept combining heart failure treatment with the prolactin blocker bromocriptine (BR), which is named "the BOARD therapy regime" (BR, Oral heart failure drugs, Anticoagulation, Diuretics) for PPCM.[149]

Although current data suggest that patients with PPCM of different etiologies seem to profit from the BOARD therapy, epidemiological studies suggest that PPCM in women with a familial history of cardiomyopathies have a poorer prognosis—a feature that might affect risk stratification and clinical management of these patients.[141] Therefore, further analysis of underlying pathophysiology is important for more personalized therapy regimes. Moreover, genetic counseling in patients with a family history of (peripartum) heart failure should be considered, which may contribute to a better understanding of the disease pathophysiology and for better and earlier treatment and management of relatives at risk.

2.4 Metabolic triggers in DCM: Diabetes and DCM

In diabetic patients, cardiovascular diseases represent a major cause of morbidity and mortality. In addition to increased coronary artery disease and hypertension, there is compelling evidence that diabetes has a direct negative effect on the heart,[150] being an independent risk factor for heart failure even after adjusting for age, sex, race and hypertension.[151-153] Mechanisms of such deleterious cardiac effects include mitochondrial dysfunction, oxidative stress, shift in energetic substrate utilization (increase in fatty acid oxidation and decrease in glucose metabolism), disturbed calcium homeostasis, and neurohumoral activation.[150,154]

Among the described gene mutations associated with DCM, mutations in *LMNA* gene, encoding nuclear intermediate filament proteins lamins A/C, more specifically the variant p.G602S was recently associated with type 2 diabetes.[155] Further molecular and physiological studies regarding this variant are needed to understand its predictive value in DCM.[155] Taken into consideration the increasing prevalence of diabetes, as well as its associated complications, an analysis of the correlation between genotypic and phenotypic patient characteristics deserves further investigations, intending to establish a disease-gene mutation association and apply an early intervention in disease progression. Therefore, the presence of diabetes –as well as hypertension or other metabolic conditions should be included in the patient phenotyping, and in order to assess gene-environmental interactions in DCM.

3-HOW CAN IMAGING HELP IN DCM PHENOTYPING?

Echocardiography remains the cornerstone for routine and quick assessment left ventricular function in DCM patients. In addition to confirming the clinical diagnosis, routine echocardiography provides additional prognostic information such as the severity of ventricular dysfunction, the presence of any

concurrent valvular disease and the pulmonary artery.[156] More sophisticated echocardiography reliant on tissue deformation parameters may provide additional risks stratification and/or prognostic information, such as global longitudinal strain, circumferential and radial strain.[157] Those parameters will help clinicians in deciphering the disease heterogeneity associated with DCM.

Cardiac magnetic resonance imaging (CMR) is currently embedded in routine clinical practice with respect to follow-up assessment of left ventricular volumes and accurate ejection fraction, due to its high reproducibility and accuracy.[115,116] CMR provides information on tissue characterization, such as the presence or absence of fibrosis, storage diseases and inflammation, and informs on the prognosis, including the risk of developing subsequent malignant arrhythmias.[32,158-160]

4-NEW NOSOLOGICAL FRONTIERS FOR MYOCARDIAL DISEASES: THE MOGE(S) CLASSIFICATION SYSTEM

Myocardial diseases include all those conditions in which the myocardium is not the victim of flow restrictions or does not have to adapt to abnormal flow or pressure loads such in valvular or coronary disease and hypertension. Integrating morphology as a cornerstone,[161] but also deciphering heterogeneity regarding organ involvement, genetic predisposition and functional consequences, a new classification system for cardiomyopathies called the "MOGES" classification was raised in 2013.[162-164] MOGE(S) is composed of four main (M, O, G, E) and one optional (S) attributes[162-164] and is supported by a dedicated and renewed app that is now linked with the ICD-10 coding system and workable for transfer individual data in any sort of database. The five attributes describe the morpho-functional cardiac phenotype (M),[165] the possible involvement of other organs and tissues (O), the genetic or non-genetic origin of the disease (G), the specific etiology (E) describing gene and mutation in case of hereditary diseases, or inflammation and infectious agents in case of myocarditis, or autoimmune causes or toxic causes in case of non-genetic diseases. The S attribute is dynamic and optional: it describes the functional status of the affected heart including both NYHA class and AHA stage. The application of MOGE (S) imposes a clinical work-up that starts with the phenotypic characterization of the disease and progresses with the investigation of involvement of extra-cardiac organs/tissues, the evaluation of the genetic/familial or non-familial disease through the clinical screening of the relatives of the patients and the identification, where possible, of the causes (Figure 5).

Since its first description, MOGE(S) has attracted the attention of experts in cardiomyopathies for possible applications in clinical practice: numerous implementations have been proposed to accommodate a synthetic but precise description of phenotypes and causes.[166-168] In 2015, Hazebroek and colleagues integrated multiple etiologic attributes to assess the possible predictive role of their combination on the clinical outcome; they observed that familial DCM associated with additional etiologic-environmental factors such as significant viral load, immune-mediated factors, rhythm disturbances, or toxic triggers, had worse outcome.[108] The novelty from their proposal was the idea of applying the MOGE(S) classification to assess clinical prognosis and risk stratification in patients with DCM.[169] Westphal and coworkers further considered those cardiomyopathies whose phenotype may not be unequivocally recognizable by echocardiography and highlighted the dynamic level of impairment of the left and/or right ventricular systolic (and diastolic) function during the course of myocardial diseases, including baseline and post-treatment evolution.[170] For phenocopies of cardiomyopathies, MOGE(S) describes the possible multiorgan/system involvement and summarizes big raw clinical and genetic data, in a short string of essential data that can facilitate the collection of large database.[171] A similar implementation can be easily obtained for genetic cardiomyoapthies.[172] Finally, the *hypokinetic non-dilated cardiomyopathy (HNDC) recently* proposed by the Working Group on Myocardial and Pericardial Diseases of the ESC perfectly fits with the need of describing the increasingly recognized probands' relatives presenting with early phenotypes in familial DCM.[7] Based on the same need of describing early phases of the disease, the recent guidelines for HCM of the ESC first introduced the concept of early diagnosis that applies to relatives of probands with HCM, when the maximal LV thickness is < 15mm.[173] MOGE(S) may appear complex, but the "complexity" reflects the modern diagnostics of myocardial diseases, providing a uniform tool to describe disease heterogeneity beyond a given phenotype, integrating genetic and acquired determinants.[164]

5. THERAPEUTIC PROSPECTS

The treatment of a genetic dilated cardiomyopathy will depend on the *i.* malignancy (or penetrance) of the gene mutation, *ii.* the phenotypic presentation, *iii.* The underlying molecular mechanisms leading cardiac involvement, and *iv.* the gene-environmental interactions determining the DCM phenotype.

The penetrance of gene mutations varies upon the different genes. E.g. a lamin A/C mutation is highly penetrant, and therefore would rather require gene correction through silencing of the mutated allele. SiRNA mediated silencing of the toxic allele may allow treating more malignant gene mutations. In contrast,

more benign gene mutations -such as Titin truncating mutations- with a high probability of improvement or recovery of cardiac function upon heart failure treatment would not benefit from gene silencing strategies. Also the phenotypic presentation of a gene mutation will determine the therapy. Anti-arrhythmic therapies are more often to be considered in *LMNA* or *RBM20* gene mutated DCM patients, whereas classical heart failure therapy may be sufficient in other more benign genetic DCM cases.

The underlying molecular mechanisms identified in experimental models and in the cardiac samples of genetic DCM results in novel therapeutic approaches. One example is the recently started phase 3 trial using p38 MAPK inhibitors in *LMNA*-related DCM, since loss of functional lamin proteins results in activation of the p38 MAPK pathway, and secondary cardiomyocyte apoptosis and interstitial fibrosis.[174] In *TTNtv* patients anti-oxidative therapies such as SS-31 or elamipretide could be considered, in view of the extreme hyperactivation of mitochondrial oxidative pathways.[175] In sarcomeric gene mutated DCM patients, interventions on calcium sensitivity may help to improve myofilament force development, and thereby prevent cardiomyocyte dysfunction.[43]

Finally, the knowledge how gene mutated hearts would react to environmental -additionally acquired diseases or hormonal factors during life- factors, may help to guide our therapeutic approach. E.g. *TTNtv* mutated patients do have a benign functional phenotype, but are prone to develop arrhythmias upon additional cardiac stress, such as alcohol, chemotherapy or pregnancy. Therefore, an isolated more benign gene mutation without additional environmental factors would require more conservative therapeutic approach, whereas a more penetrant *LMNA* mutations in multi-morbid person would require a more aggressive medical attitude.

CONCLUSION

In the last 20 years, growing evidence supported that DCM is the final morpho-functional phenotype for various diseases, for which a spectrum of genetic determinants plays either as a causative role (as in case of overt familial disease), or acts as disease modulators regarding another condition (like in sporadic cases and “acquired” DCM). By combining clinical characteristics, identifying acquired/environmental triggers, using multimodal imaging and genetics, disease heterogeneity becomes progressively a clinical reality, allowing improved management of those patients and personalized risk stratification. Genetic data provides more and more cues to understand the molecular mechanisms underlying this complex disease and its heritability. Nevertheless, caution has to be raised as the use of broad genetic screen exposes clinicians to

noisy background in DCM, requiring permanent evaluation of variant pathogenicity. Actual data support that inheritance is often complex, with many disease modifiers- going from causal diseases (e.g. anthracyclines) to modifying co-morbidities (e.g. diabetes) having to be taken into account including other genes, epigenetics and lifestyle. Deep molecular comprehension of DCM improves its assessment, and opens new avenues for personalized medicine and the development of new therapeutic strategies.

LEGENDS TO FIGURES

Figure 1: Gene-environmental interactions in dilated cardiomyopathies. DCM is a complex multifactorial disease related to genetic determinants interfering with environmental factors.

Figure 2: Interplay between genes and environmental factors in cardiomyopathies. Heart cartoon is reproduced from Wilde et al.[176] with permission from Nature Publishing Group (permission to be requested).

Figure 3: Cardiomyopathies: from altered calcium sensitivity to disease phenotype. Altered calcium sensitivity related to sarcomeric mutations lead to either hypertrophic cardiomyopathy (increased calcium sensitivity/tension with lower free cytosolic calcium) or DCM (decreased calcium sensitivity/tension with increased free cytosolic calcium).[43] Heart cartoons are reproduced from Wilde et al.[176] with permission from Nature Publishing Group (permission to be requested).

Figure 4: The interaction between DNA defects and failing of mitochondrial repair systems promotes the genesis of mitochondrial DCM. The exposure of cardiomyocytes to ionizing radiation (IR), antiblastic drugs, alcohol metabolites and many other sources of DNA damage leads to mutations in both mitochondrial and nuclear genes coding for mitochondrial proteins. When the number of gene defects overcomes cellular tolerance, mitochondria can recruit a complex pathway of self-repair and regeneration. As the above mechanisms fail, defects tend to accumulate further, leading at the end to mitochondrial dysfunction.

Figure 5: Three examples of MOGE(S) application in arrhythmogenic cardiomyopathy (ACM) (A), familial DCM (B) and sporadic DCM phenotype caused by chronic myocarditis (C). The left column shows the pedigrees of three families. The right column shows how family members are described by the MOGE(S) system including the imaging view of the proband (B) and the pathology features in endomyocardial biopsy of the index patient of family C (C). For arrhythmogenic cardiomyopathy, descriptors of the phenotype can detail the combination of major and minor criteria or define family members as diagnosed with definite, possible and borderline cardiomyopathy according to the 2010 Task Force. For dilated cardiomyopathy, the age dependency of the phenotype explains the absence of clinical signs in the two children (IV:1 and IV:5) of the IVth generation. The p.(Arg190Trp) in LMNA is a recurrent, highly penetrant, malignant and validated mutation (https://www.ncbi.nlm.nih.gov/clinvar/variation/66908/).

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CONFLICT OF INTEREST

TT filed and licensed patents in the field of noncoding RNAs and is founder of Cardior Pharmaceuticals GmbH.

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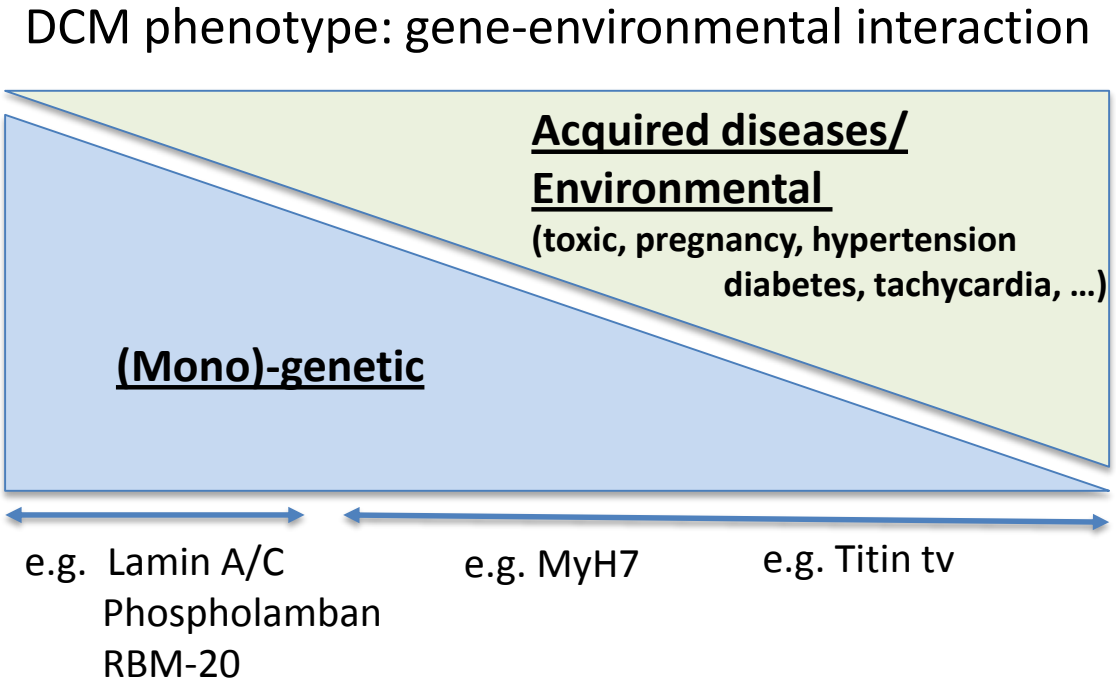
Table 1: Main Genes in DCM, isolated and syndromic

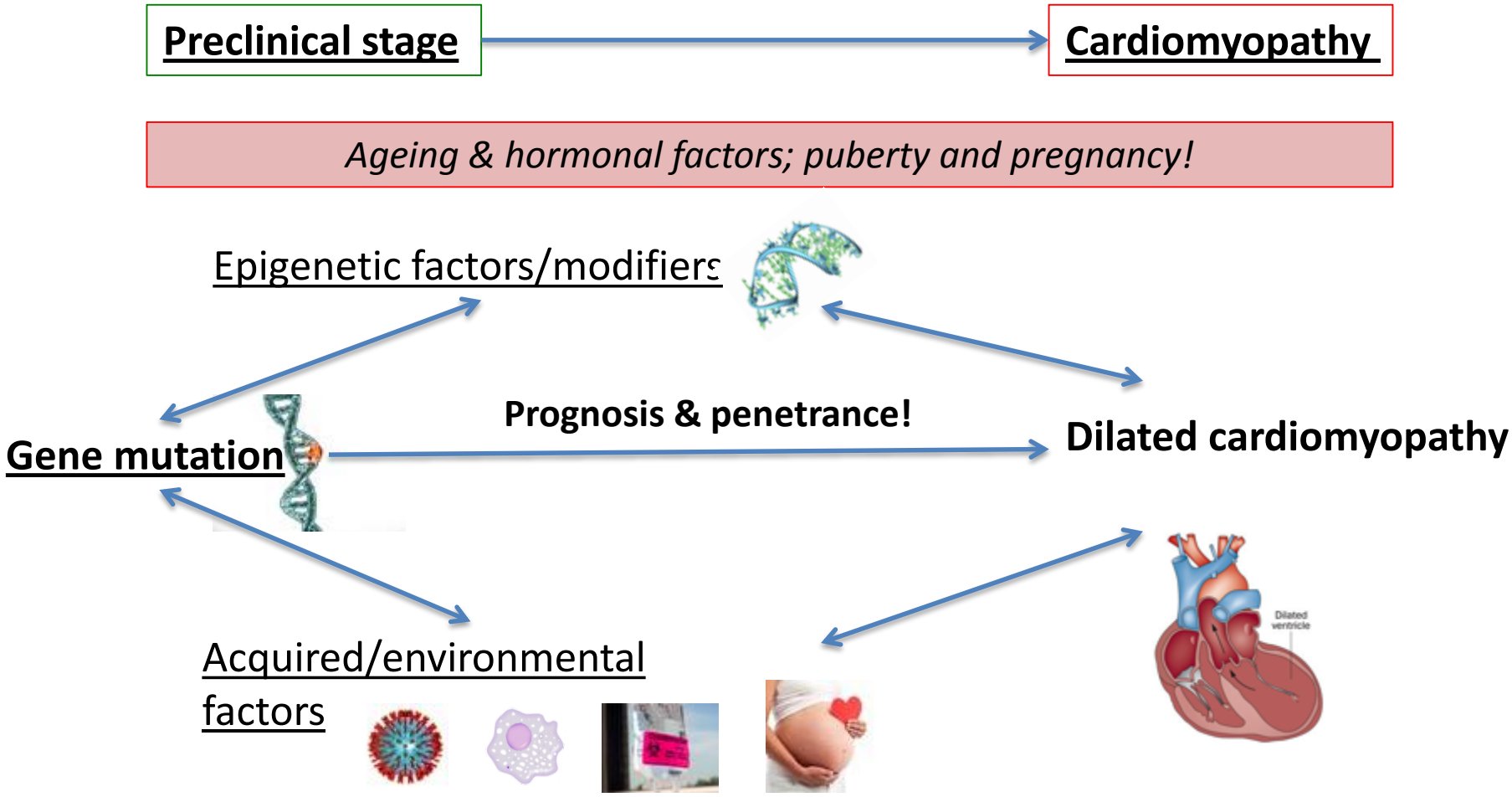
Gene Symbol	Inheritance	Cardiomyopathy overlap	Clinical characteristics
Cytoskeletal			
ACTN2	AD	HCM	
ANKRD1	AD	HCM	
CSRP3	AD	HCM	
LDB3	AD	HCM, LVNC	Myofibrillar myopathy Type 4
MYPN	AD, AR	HCM, RCM	Frequent overlapping phenotypes, Nemaline myopathy type 11 (AR)
TCAP	AD, AR	HCM	Limb-girdle muscular dystrophy 2G (AR)
TTN	AD, AR	HCM, RCM, ARVC	Most frequent, early onset myopathy, peripartum cardiomyopathy, truncated variants with rhythm disorders, limb-girdle muscular dystrophy 2J (AR)
VCL	AD	HCM	
Sarcomeric			
ACTC1	AD	HCM, RCM, LVNC	Atrial septal defect
MYBPC3	AD	HCM, RCM, LVNC	
MYH7	AD, AR	HCM, LVNC	Peripheral myopathy
TNNC1	AD	HCM	
TNNI3	AD, AR	RCM, HCM	
TNNT2	AD	RCM, HCM, LVNC	
TPM1	AD	HCM, LVNC	
Conduction disease			
DES	AD, AR	HCM, RCM	DES deposition, Limb-girdle muscular dystrophy 2R (AR), myofibrillar myopathy (AR/AD)
LMNA	AD, AR	HCM	Congenital muscular dystrophy, Emery-Dreifuss muscular dystrophy, limb-girdle muscular dystrophy 1B
SCN5A	AD, AR	ARVC	Brugada syndrome, sick sinus syndrome (AR), LQT3, atrial fibrillation, ventricular fibrillation, heart block
Arrhythmia			
DSC2	AD, AR	ARVC	Mild palmoplantar keratoderma and woolly hair
DSG2	AD	ARVC	
DSP	AD, AR	ARVC	Epidermolysis bullosa, keratodermia, wooly hairs
FLNC	AD	HCM, RCM, ARVC	Rhythmic disorders unrelated to LV dysfunction, myofibrillar myopathy 5
PLN	AD	HCM	
PKP2	AD	ARVC	
RBM20	AD		Atrial fibrillation
RYR2	AD	ARVC	Catecholaminergic polymorphic ventricular tachycardia
TTN truncated	AD	HCM, RCM, ARVC	
Mitochondrial			
CTF1	AD, AR		
DNAJC19	AR		3-methylglutaconic aciduria, type V, syndromic (DCMA) recurring in some

			populations (Canadian Hutterite population)
MT-TL1	Mito	HCM→ DCM-like evolution	MELAS
SDHA	AD,AR, Mito		Leigh syndrome (AR/Mito) and mitochondrial respiratory chain complex II deficiency (AR)
Metabolic / Neuromuscular			
BAG3	AD	RCM	Progressive myofibrillar myopathy
CPT2	AR, AD		Carnitine palmitoyltranferase III deficiency
CRYAB	AD,AR	RCM	Myofibrillar myopathy 2 (AR)
DMD	XLR		Duchenne/Becker muscular dystrophy
DOLK	AR		
EMD	XLR		Emery-Dreifuss muscular dystrophy
HADHA	AR	HCM	AR syndromic phenotypes with cardiomyopathy
HFE	AR	HCM, RCM	Iron Overload
LAMP2	XLD	HCM	Danon Disease
SGCD	AD, AR		Limb-girdle muscular dystrophy (delta-sarcoglycanopathy)
SLC22A5	AR	HCM	Carnitine deficiency
SYNE1	AD, AR		Emery-Dreifuss muscular dystrophy (AD), Spinocerebellar ataxia (AR)
TAZ	XLR		Endocardial fibroelastosis, BARTH Syndrome
TMPO	AD		Reclassified as non-pathogenic
Others			
EYA4	AD		Non-syndromic hearing loss and deafness
GATAD1	AR		
NEXN	AD	HCM	
PSEN1	AD		Familial Alzheimer disease
PSEN2	AD		Familial Alzheimer disease

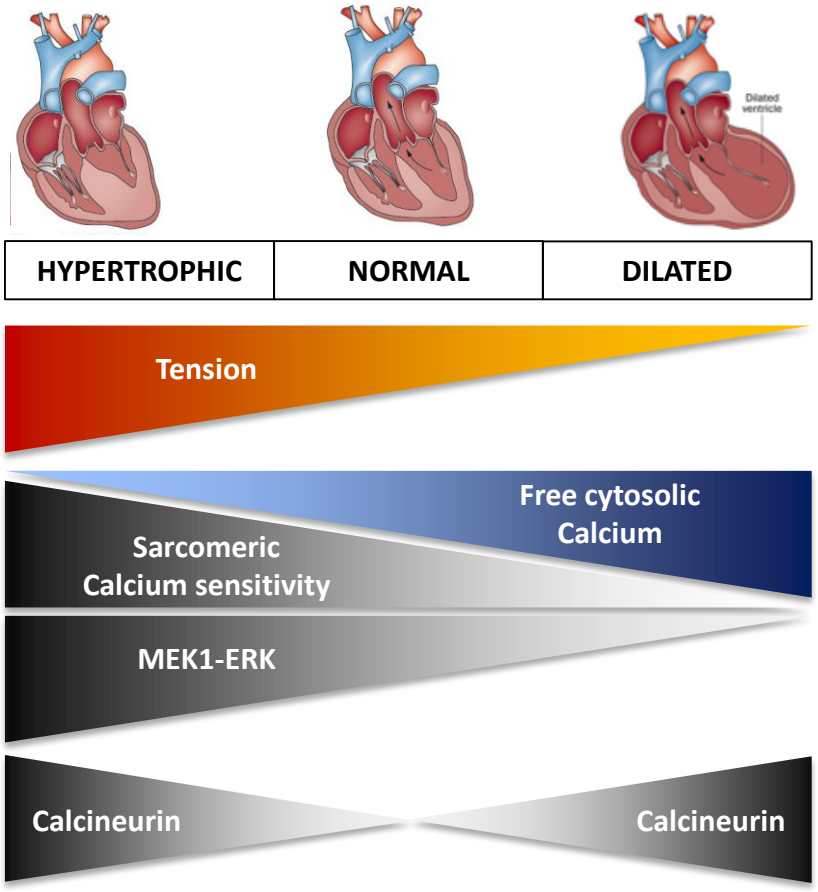
Genes presenting a statistically significant excess burden over controls in Exac are depicted in bold.[10] Figure content is adapted from Burke et al[9] and Lee et al[10].
AD: autosomal dominant; AR: autosomal recessive; ARVC: arrhythmogenic right ventricular cardiomyopathy; DCM: dilated cardiomyopathy; HCM: hypertrophic cardiomyopathy; LVNC: left ventricular non-compaction; Mito: mitochondrial; RCM: restrictive cardiomyopathy; XLD: X-linked dominant; XLR: X-linked recessive.



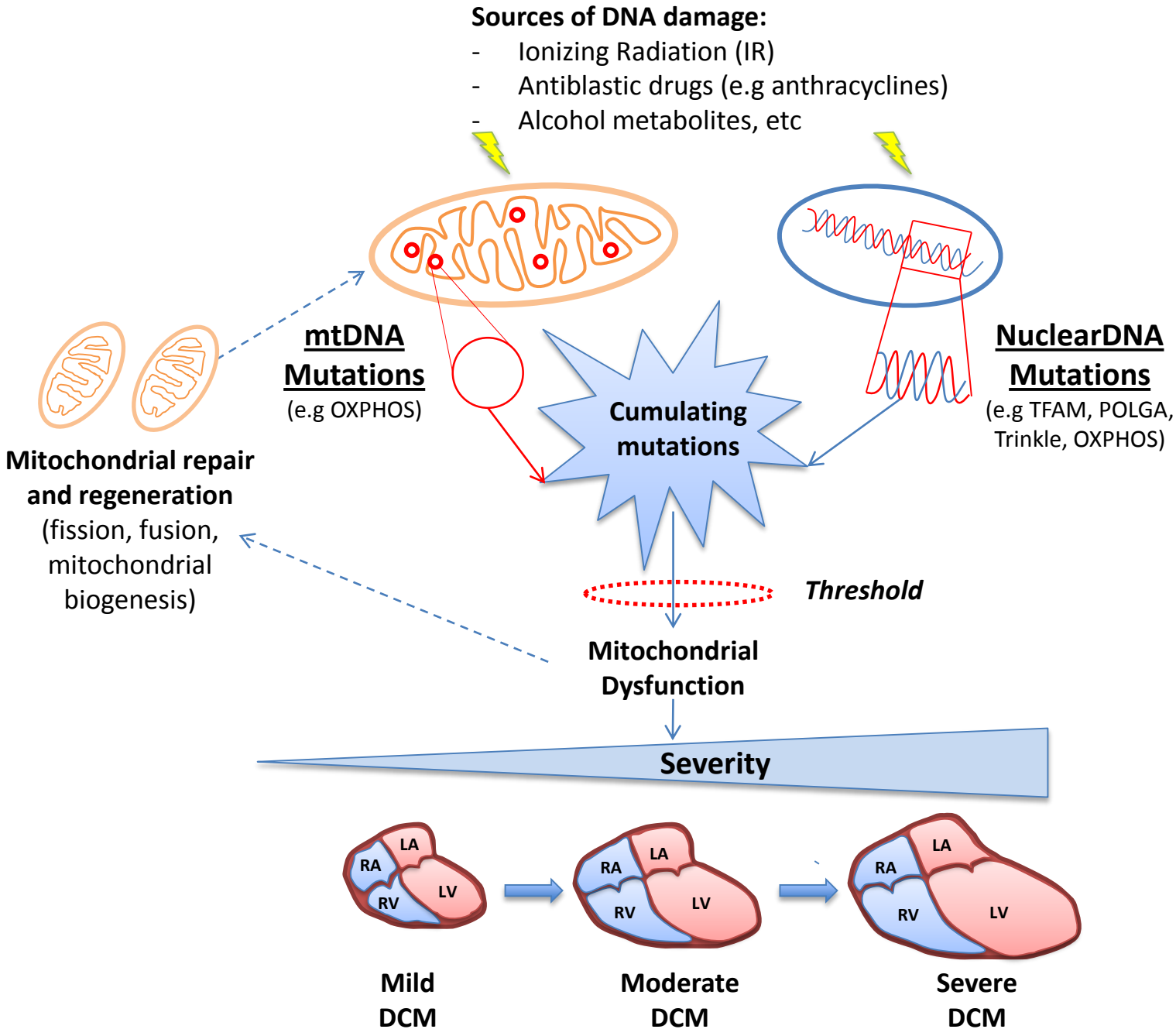
Bondue et al. Figure 1



Bondue et al. Figure 2

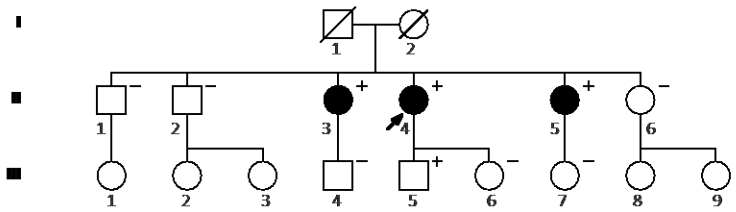
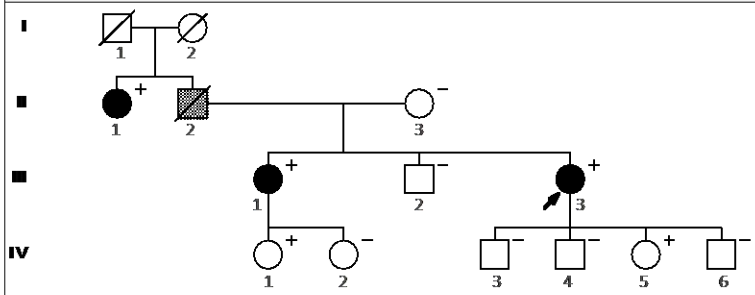
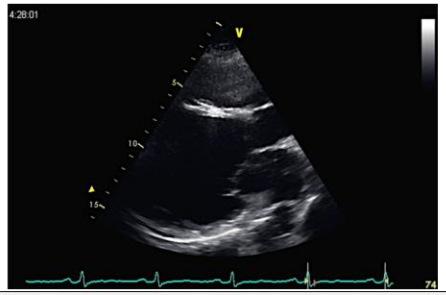
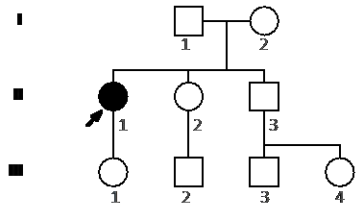
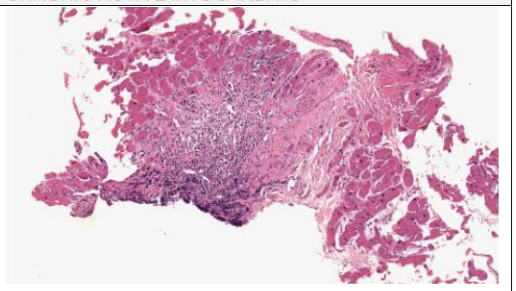


Bondue et al. Figure 3



Bondue et al. Figure 4

FIGURE MOGE(S)

FAMILY PEDIGREES	MOGE(S) AFTER CLINICAL AND GENETIC SCREENING IN THE FAMILY	
A) ARRHYTHMOGENIC CARDIOMYOPATHY (ACM): THE M DESCRIPTOR IN MOGE(S) INCLUDES THE SUM OF MAJOR AND MINOR CRITERIA		
	I:1, Prostatic Ca 78 yrs $M_0\ O_0\ G_U\ E_{G-0}$ I:2, SD, 85 yrs $M_0\ O_0\ G_U\ E_{G-0}$ II:1,II:2,II:6 (62,60,49 yrs) $M_0\ O_0\ G_{AD}\ E_{G-Neg}\ S_{A-I}$ II:3, 57 yrs, $M_{A[2M+2m]}\ O_H\ G_{AD}\ E_{G-PKP2\ [p.Thr50SerfsTer61]}\ S_{C-I}$ II:4 →53 yrs (proband) $M_{A[1M+1m]}\ O_H\ G_{AD}\ E_{G-PKP2\ [p.Thr50SerfsTer61]}\ S_{A-I}$ II:5, 51 yrs, $M_{A[2M+1m]}\ O_H\ G_{AD}\ E_{G-PKP2\ [p.Thr50SerfsTer61]}\ S_{C-II}$ III:1-III:3 (29,30,26 yrs) $M_0\ O_0\ G_{AD}\ E_{G-0}$ III:4, 26 yrs $M_0\ O_0\ G_{AD}\ E_{G-Neg}\ S_{A-I}$ III:5*, 25 yrs $M_0\ O_0\ G_{AD}\ E_{G-PKP2\ [p.Thr50SerfsTer61]}\ S_{A-I}$ III:6 (21 yrs), III:7 (28 yrs) $M_0\ O_0\ G_{AD}\ E_{G-Neg}$ III:8, III:9 $M_0\ O_0\ G_{Neg}\ E_{G-0}$	ALTERNATIVE DESCRIPTIONS ACCORDING TO TF CRITERIA 2010 II:3 $M_{A[2M+2m:\ Definite\ diagnosis]}\ O_H\ G_{AD}\ E_{G-PKP2\ [p.Thr50SerfsTer61]}\ S_{C-I}$ II:4 $M_{A[1M+1m:\ Borderline\ diagnosis]}\ O_H\ G_{AD}\ E_{G-PKP2\ [p.Thr50SerfsTer61]}\ S_{A-I}$ II:5 $M_{A[2M+2m:\ Definite\ diagnosis]}\ O_H\ G_{AD}\ E_{G-PKP2\ [p.Thr50SerfsTer61]}\ S_{C-II}$ III:5 $M_{A[1M:\ Possible\ diagnosis]}\ O_0\ G_{AD}\ E_{G-PKP2\ [p.Thr50SerfsTer61]}\ S_{A-I}$
B) FAMILIAL DILATED CARDIOMYOPATHY		
	III:2 → 2D-TTE – LEFT VENTRICULAR DILATION 	I:1, 68 yrs, $M_{NA}\ O_0\ G_U\ E_{G-0}$ I:2, 92 yrs, $M_{NA}\ O_0\ G_U\ E_{G-0}$ II:1, 73 yrs, $M_{D[AVB-PM]}\ O_H\ G_{AD}\ E_{G-LMNA\ [p.Arg190Trp]}\ S_{C-IIn}$ II:2, 61 yrs, $M_{D[Heart\ Failure]}\ O_H\ G_{AD}\ E_{G-DC-LMNA\ [p.Arg190Trp]}\ S$ II:3, 69 yrs, $M_0\ O_0\ G_U\ E_{G-Neg}\ S_{A-I}$ III:1, 39 yrs $M_{D[AVB]}\ O_H\ G_{AD}\ E_{G-LMNA\ [p.Arg190Trp]}\ S_{C-IIn}$ III:2, 37 yrs, $M_0\ O_0\ G_{AD}\ E_{G-Neg}\ S_{A-I}$ III:3, 31 yrs (proband) $M_{D[AVB]}\ O_H\ G_{AD}\ E_{G-LMNA\ [p.Arg190Trp]}\ S_{C-III}$ IV:1, 12 yrs, $M_0\ O_0\ G_{AD}\ E_{G-LMNA\ [p.Arg190Trp]}\ S_{A-I}$ IV:2,3,4, (10,16, 15 yrs) $M_0\ O_0\ G_{AD}\ E_{G-Neg}\ S_{A-I}$ IV:5, 13 yrs, $M_0\ O_0\ G_{AD}\ E_{G-LMNA\ [p.Arg190]}\ S_{A-I}$ IV:6, 11 yrs, $M_0\ O_0\ G_{AD}\ E_{G-Neg}\ S_{A-I}$	
C) SPORADIC DILATED CARDIOMYOPATHY		CHRONIC ACTIVE MYOCARDITIS
	Etiology: Myocarditis (E_M) I:1, 73 yrs, $M_0\ O_0\ G_N\ E_0\ S_{A-I}$ I:2, 66 yrs, $M_0\ O_0\ G_N\ E_0\ S_{A-I}$ II:1 → Proband, 42 yrs, $M_0\ O_H\ G_N\ E_M\ S_{C-II}$ II:2, 40 yrs, $M_0\ O_0\ G_N\ E_0\ S_{A-I}$ II:3, 36 yrs $M_0\ O_0\ G_N\ E_0\ S_{A-I}$ III:1, 13 yrs, $M_0\ O_0\ G_N\ E_0\ S_{A-I}$ III:2, 11 yrs, $M_0\ O_0\ G_N\ E_0\ S_{A-I}$ III:3, 9 yrs, $M_0\ O_0\ G_N\ E_0\ S_{A-I}$ III:4, 7 yrs, $M_0\ O_0\ G_N\ E_0\ S_{A-I}$	

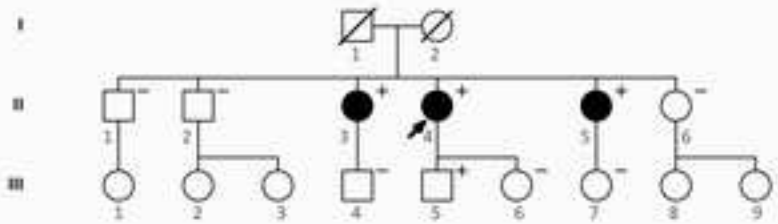
* regular monitoring with ECG, 2DTTE + 24H Holter ECG; first CMR: negative.

Bondue et al. Figure 5

FAMILY PEDIGREES

MOGE(S) AFTER CLINICAL AND GENETIC SCREENING IN THE FAMILY

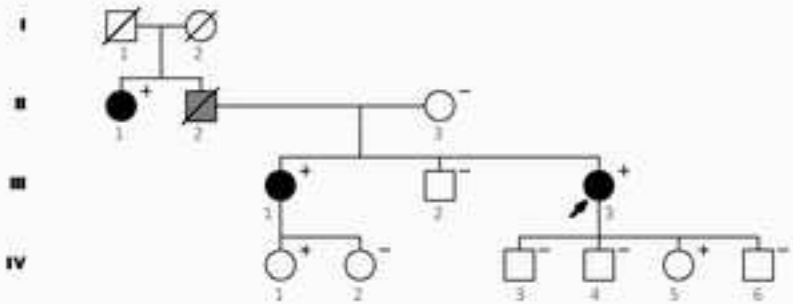
A) ARRHYTHMOGENIC CARDIOMYOPATHY (ACM): THE M DESCRIPTOR IN MOGE(S) INCLUDES THE SUM OF MAJOR AND MINOR CRITERIA



I:1, Prostatic Ca 78 yrs
I:2, SD, 85 yrs
II:1,II:2,II:6 (62,60,49 yrs)
II:3, 57 yrs,
II:4 → 53 yrs (proband)
II:5, 51 yrs,
III:1-III:3 (29,30,26 yrs)
III:4, 26 yrs
III:5*, 25 yrs
III:6 (21 yrs), III:7 (28 yrs)
III:8, III:9

ALTERNATIVE DESCRIPTIONS ACCORDING TO TF CRITERIA 2010

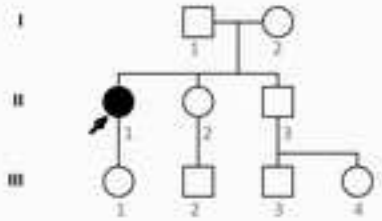
B) FAMILIAL DILATED CARDIOMYOPATHY



III:3 → 2D-TTE – LEFT VENTRICULAR DILATION

I:1, 68 yrs,
I:2, 92 yrs,
II:1, 73 yrs,
II:2, 61 yrs,
II:3, 69 yrs,
III:1, 39 yrs
III:2, 37 yrs,
III:3 → 31 yrs (proband)
IV:1, 12 yrs,
IV:2,3,4, (10,16, 15 yrs)
IV:5, 13 yrs,
IV:6, 11 yrs,

C) SPORADIC DILATED CARDIOMYOPATHY



Etiology: Myocarditis (Evi)

I:1, 73 yrs,
I:2, 65 yrs,
II:1 → Proband, 42 yrs,
II:2, 40 yrs,
II:3, 36 yrs
III:1, 13 yrs,
III:2, 11 yrs,
III:3, 9 yrs,
III:4, 7 yrs,

CHRONIC ACTIVE MYOCARDITIS

* regular monitoring with ECG, 2DTTE + 24H Holter ECG; first CMR, negative.