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Is there a common genetic basis for all familial cardiomyopathies?

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The most exciting phrase to hear in science, the one that heralds new discoveries, is not “Eureka! (I found it!)” but rather “Hmm... that's funny...”Isaac Asimov, author and biochemist (1920–1992).

According to the 1995 World Health Organization definition, cardiomyopathies are “diseases of the myocardium associated with cardiac dysfunction” [1]. Traditionally, cardiomyopathies are differentiated according to the pathologic changes in cardiac morphology and function using cardiac imaging and invasive methods to exclude coronary artery disease. The two distinct patterns of cardiac remodelling, hypertrophy and dilation, are the main criteria for classifying a patient's disease as a hypertrophic or a dilated cardiomyopathy; cardiac filling is used to define restrictive cardiomyopathy. For the practicing physician, hypertrophic (HCM), dilated (DCM), and restrictive cardiomyopathy (RCM) are clearly distinct disorders.

The birth of modern cardiomyopathy research is pegged to the 1989 publication defining the first genetic locus for familial HCM on chromosome 14q1 [2]. In the following years, a knowledge explosion took place regarding new disease genes and mutations as well as the production of gene-targeted animal models (for review see [3] and [4]). The field received an additional boost from the completion of the human genome project and refined genetic maps, as well as the rapid progress in transgenic technologies. Whereas HCM is regarded now as a inherited monogenic disease [3], familial DCM may occur in about 20% to 50% of idiopathic cases (dependent on study population as well as criteria and clinical methods used) [5]. Due to this fact and the earlier identification of HCM disease genes, the number of known mutations is much higher in familial HCM compared to familial DCM (as also shown for three selected genes in Fig.2). The genetic results of most studies underscored the differences in familial cardiomyopathies. It was shown that mutations in genes encoding for sarcomeric proteins of the thin and thick filaments exclusively cause familial HCM while mutations in genes encoding for cytoskeletal proteins cause familial DCM. As a result, the overall picture seemed well structured and conclusive.

However, the “funny” thing is that reality is more complex than our perceptions. Recent studies changed our earlier view and showed a substantial overlap in disease-causing genes between the three main cardiomyopathy forms (see Fig.1). To date, there are eleven genes described causing at least two different forms of “pure” heart muscle disease. We will select detailed data concerning three of these genes as fitting examples for that overlap (see Fig.2).

The most impressive discovery is that mutant cardiac troponin I (Fig.2C), a regulatory protein of the thin filament, can cause all three cardiomyopathy forms. While the first mutations causing HCM were described in 1997 [6], several years elapsed until mutations in patients with RCM and DCM were identified by the McKenna group [7]

and [8]. The DCM mutation (A2V) appears to be an exception, because A2V is transmitted as a recessive trait (in contrast to the majority of mutations) and is located at the far N-terminal end of the protein. However, no such distinction is possible for the HCM and RCM causing mutations. Indeed, they cluster very closely in the same exons and protein domains at the C-terminus of troponin I.

A second example involves mutations in the cardiac muscle LIM protein (Fig.2B) that can cause both HCM and DCM. In families with HCM, we were the first to describe mutations in muscle LIM protein (a Z-disk protein) suggesting that HCM is not exclusively a disease of the thick and thin filaments [9] as confirmed later on by Bos et al. [10]. Functional and genetic data from Knoll et al. showed that muscle LIM protein also plays an important role in DCM [11]. Although all detected mutations cluster in the first half of the protein, the DCM mutation K69R is located in close proximity to a number of HCM causing mutations.

Last but not least, mutations in titin-cap/telethonin (Fig.2A), an additional protein located in the Z-disc, resulted in either HCM or DCM. As shown by two groups and us [10], [12] and [13], mutations causing cardiomyopathies could be distributed over the whole gene. Again, no obvious segregation is possible according to the form of cardiomyopathy. An HCM mutation could follow a DCM mutation located only five codons upstream.

These discoveries and others not mentioned here suggest a common genetic basis for familial cardiomyopathies. Although there are a number of DCM genes that do not cause either HCM or RCM as far as we know (see Fig.1), the cardiomyopathies seem to be true allelic disorders. So the next logical step would be to supplement the traditional classification of cardiomyopathies by taking into account the underlying gene mutations and affected molecular structures. Corrado et al. recently suggested that cytoskeletalopathies, desmosomalopathies, and sarcomyopathies should be distinguished; they also integrated the channelopathies, arrhythmogenic disorders caused by mutant ion channels [14].

Unfortunately, there is still a wide knowledge gap between the specific genetic cause and the mechanism producing a specific clinical phenotype in all its broad heterogeneity. There is no doubt that the kind and localization of a mutation, namely the genotype, influences the development and expression of the disease. However, also certain is the fact that the ultimate phenotype represents the sum of all the parts: the influence of RNA and protein expression, the complex regulation and interaction of these expressed RNA and protein molecules, and the predisposition of genetic variation for monogenic disease. Further, we do not yet understand what happens when an individual mix of genes and expression patterns collides with something in the environment, such as infectious agents or alcohol.

A high number of critical signals driving cardiac remodelling have been identified in myocyte force

generation and transmission and metabolic pathways, as well as in calcium homeostasis, apoptosis, and survival pathways [15] and [16]. According to Kenneth R. Chien's 2003 commentary, "the major protagonists and antagonists of this (cardiomyopathy) story have yet to enter the stage" [17]. To identify all the key players, we believe that improved data synthesis from clinical sources, namely the patients and their families, with experimental data from in vitro and animal experiments is urgently need. There is no alternative to an extensive dialog between clinicians caring for the patients and basic scientists conducting the experiments. Only such translational communication can lead us to the "funny" insights we need that will provide the new perspectives to better understand the familial cardiomyopathies.

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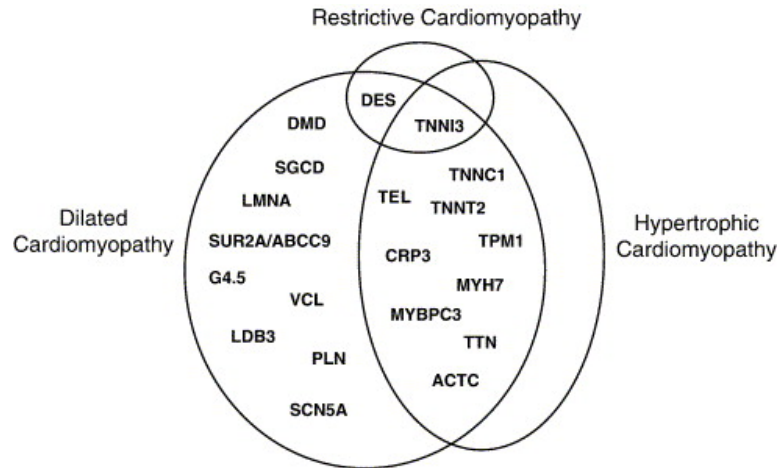


Fig.1. Overlap of disease genes causing the three main cardiomyopathy forms are shown. Twenty genes have been reported of which eleven cause at least two different forms of “pure” cardiomyopathy. The cardiomyopathy disease genes are: β -myosin heavy chain (MYH7), cardiac troponin T (TNNT2), cardiac troponin I (TNNI3), cardiac troponin C (TNNC1), cardiac α -actin (ACTC), α -tropomyosin (TPM1), myosin-binding protein C (MYBPC3), titin (TTN), titin-cap/telethonin (TEL), muscle LIM protein (CRP3), metavinculin (VCL), cypher/ZASP (LDB3), dystrophin (DMD), δ -sarcoglycan (SGCD), desmin (DES), lamin A/C (LMNA), cardiac sodium channel (SCN5A), ATP-sensitive potassium channel (SUR2A/ABCC9), phospholamban (PLN), tafazzin (G4.5).

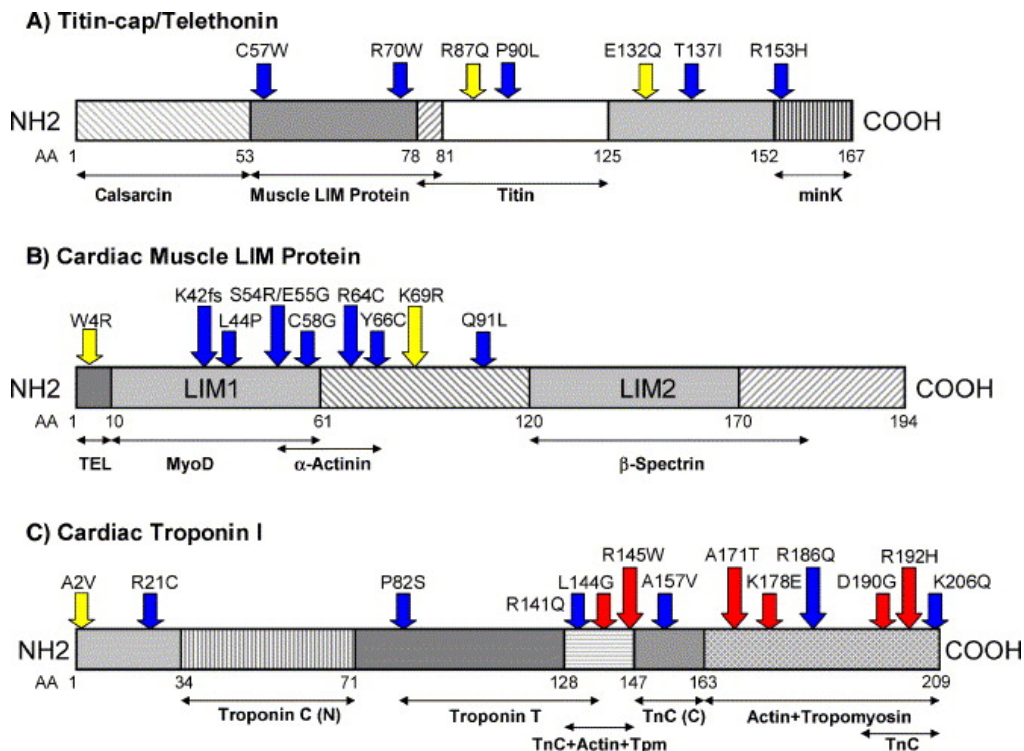


Fig.2. The distribution of cardiomyopathy-causing mutations in the genes encoding A) titin-cap/telethonin, B) cardiac muscle LIM protein, and C) cardiac troponin I. All known mutations in these genes are shown. For a better overview, an exception was made for the troponin I mutations causing HCM (in which about 20 mutations have been described). Mutations causing DCM are shown with yellow arrows, RCM with red arrows, and HCM with blue arrows. One-letter symbols are used for the amino acids (AA). The protein domains are shown as blocks with the known interaction partners of the respective protein shown below.