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Morphomechanic phenotypic variability of sarcomeric Cardiomyopathies: a multifactorial polygenic perspective

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Abstract

Morphology underlies subdivision of the primary/heritable sarcomeric cardiomyopathies (CMs) into hypertrophic (HCM) and dilated (DCM). Next-generation DNA-sequencing (NGS) has identified important disease-variants, improving CM diagnosis, management, genetic screening, and prognosis. Although monogenic (Mendelian) analyses directly point at downstream studies, they disregard coexisting genomic variations and gene-by-gene interactions molding detailed CM-phenotypes. In-place of polygenic models, in accounting for observed defective genotype–phenotype correlations, *fuzzy* concepts having gradations of significance and unsharp domain-boundaries are invoked, including pleiotropy, genetic-heterogeneity, incomplete penetrance, and variable expressivity. HCM and DCM undoubtedly entail cooperativity of unidentified/elusive causative genomic-variants. Modern genomics can exploit comprehensive electronic/digital health records, facilitating consideration of multifactorial variant-models. Genome-wide association studies entailing high-fidelity solid-state catheterization, multimodal-imaging, molecular cardiology, systems biology and bioinformatics, will decipher accurate genotype-phenotype correlations and identify novel therapeutic-targets, fostering personalized medicine/cardiology. This review surveys successes and challenges of genetic/genomic approaches to CMs, and their impact on current and future clinical care.

Graphical abstract

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1. Introduction

“A cause so small as to escape our attention, determines a considerable effect that we cannot help but see. We then say that this was the result of chance. If we knew the laws of Nature exactly...”

— H. Poincaré: Science and Method

In the past 3 decades, the Human Genome Project (HGP), gene therapy/editing, cloning, stem cell research, nanotechnology and other developments have revolutionized medicine and generated entirely new methodologies for treating heart diseases, including the primary/heritable sarcomeric cardiomyopathies (CMs). Most of genetics addresses how genes associate to phenotypic traits. Nowadays, a wide range of DNA mutations are recognized, many affecting regulatory gene-elements. High-tech genomics advancements have fostered personalized/precise diagnostics and therapies, integrating elements from molecular biology, bioinformatics and other basic sciences. Application of genetic mutation discoveries in treatments impacting pathogenic molecular mechanisms and pathways creates a versatile feedback-loop providing crucial information about their role in morphomechanical disturbances and in restoring normality.

Genomic-information becomes manifest as the *genotype* in our DNA; the encoded proteins operate to produce a *phenotype*, encompassing outwardly observable/measurable traits (Figure 1). Genomic variations can cause phenotypic alterations in health and disease.^{1,2} Genomic DNA exemplifies versatile software, a cellular universal programming-language. Coding and noncoding/regulatory DNA represents a powerful language,^{3,4} which can express any algorithm for building and running cells, tissues, organs and the organism (Figure 1). Even though every cell contains a complete copy of this DNA-software, it uses only parts of it, contingent on the tissue and conditions.

As François Jacob and Jacques Monod state in “*Genetic Regulatory Mechanisms in the Synthesis of Proteins*” (*J Mol Biol*, 1961;3:318–56): “...the genome contains not only a series of blueprints, but a coordinated program of protein synthesis and the means of controlling its execution.” This coordination is closely connected to how DNA is packaged in *chromatin* (the complex of DNA, RNA and nucleosome-proteins that provides

functionality to the genome; cf. Figure 1) within cell nuclei. Chromatin is highly dynamic; broad plasticity is developed by placing chemical tags/barcoding on cytosine at the DNA level and on histones at the nucleosome-proteins level, providing on top of the genomic info an index referencing different cellular environments and dynamic contexts.²

2. Translational perspective on genomic cardiomyopathy (CM) variants

To understand inherited CMs, we consider the software, whose *variants* underlie normal and abnormal phenotypic traits. Changes in DNA, RNA and protein sequences – named variants, mutations, or polymorphisms – are usually detected by DNA nucleotide-sequencing (Figure 1). NGS² enables sequencing of large arrays of genes or genomes in a single run, provoking translational downstream work to convert basic-research findings into new molecular diagnosis-and-treatment approaches. NGS discovery of novel pathogenic mutations can confirm clinical CM diagnoses.

People with suspected CM-disorders should be afforded NGS access. Our genome holds a treasure-trove of information about pathology,⁵ and NGS yields whole-genome snapshots instead of studying disorders one-gene-at-a-time. By applying “reversed genetics,”⁶ to examine how genetic-variants influence sarcomeric molecular and morphomechanical traits, numerous CM-studies currently target correlating genotype variations to disease-phenotypes.⁷ However, genetics is not decreative; CM-syndromes embody changes encompassing not only genetic, but also epigenetic and environmental factors partaking in cardiogenesis and variant (re)modeling.¹

2.1. Epigenetics in CMs

Epigenetics studies phenotypic traits/phenotypes not involving DNA sequence changes. It concerns gene activity – *how* genes are expressed and used. Its focus are information-processing *metadata* marking which genes are switched-on-or-off, by a system of chemical tags/barcoding. Epigenome refers to the entire pattern of epigenetic modifications across all genes, including methyl DNA-tags, methyl histone-tags, acetyl histone-tags, etc. Epigenetics examines how these labels are recognized and how this translates into specific-gene regulation and interpretation of the functionality of DNA elements. Genes provide instructions for assembly, not comprehensive plans for versatile products synchronized over time with changing conditions/needs. Future CM diagnosis will incorporate myocardial biopsies to examine epigenetic modifications/metadata.

2.2. Alternative splicing yields multiple mRNA and protein isoforms, and a susceptibility to splicing mutations resulting in clinically abnormal phenotypes

The *exome*, or coding genome, represents $\approx 1\%$ of total genomic DNA and consists of $\approx 20,000$ genes, 30 million base-pairs (bp), 180,000 *exons* coding for protein or peptide sequences, and sometimes-long *intron* sequences, intervening between exons.² Not only protein-coding, but also noncoding DNA-sequences encoding RNA-regulatory-molecules are important in controlling gene expression at the post-transcriptional level (Figure 1) and should be deemed “genes.” Accordingly, variants outside the exome can disrupt normal gene-regulation, contributing to CM-syndromes; systematic screening of the genome for

variants affecting gene regulation should lead to the identification of alleles that modify CM-risk. The regulatory landscape must be considered too, in studying genomic CM-variants.^{8,9}

Our species is comparatively gene-poor;² presumably many occurrences of pleiotropy (genes affecting multiple traits, see below) and gene-multifunctionality await discovery. Furthermore, by letting a single multi-exonic gene to code for multiple proteins, alternative splicing increases encoded-protein biodiversity. Splicing activators and repressors modulate usage of particular exons, so that alternative splicing-products are expressed depending on conditions.^{2,7-9} Thus, human organismal complexity arises.

Before exiting the nucleus, RNA undergoes alternative splicing² into multiple isoforms of mature messenger RNA (mRNA) and derived proteins. Typically, an allele originates $\approx$ 8–12 mRNA versions containing linked exon-combinations differing in function-to-be-expressed,^{2,10} or *translated* proteins/peptides. Through assorted epigenetic molecular tags, epigenetic-related noncoding RNAs can regulate other RNA, switching genes on-or-off and fine-tuning their expression at the transcriptional and post-transcriptional levels. Thus, diverse processes (Figure 1) regulate which genes are expressed, when, and how intensely.⁹

As alternative splicing affects numerous genes, it is not surprising that about half of genetic disease-causing mutations affect splicing, and considerable research focuses on the significance of genomic variants – such as may result from faulty alternative splicing – for CM molecular diagnosis, prevention and therapy.^{2,8,9,11} Alternative splicing is responsible for generating proteins with very different, sometimes even antagonistic roles. In healthy individuals, this flexibility contributes to the clockwork functioning of human biology. It is, however, like the sword of Damocles, as aberrant alternative splicing can also contribute to diseases, perhaps encompassing HCM/DCM, which can have a shared recognized genetic variant and strongly contrasting phenotypes. It can be confidently projected that, on the basis of future detailed molecular understanding, splicing-changing preparations will become part of CM treatments. Targeting and manipulating RNA avoids many of the risks of DNA-based gene therapy, such as random gene insertion and limited levels of control.

2.3. Mutations/variants are inevitable – NGS and downstream research in CMs

During DNA replication, in gametogenesis and post-zygotically, mutations arise; it is unfeasible to replicate >3 billion DNA bp in 23 chromosome-pairs error-free. Consequently, diversity increases in successive generations. Phenotype-affecting errors can also occur during mRNA translation in cardiomyocyte ribosomes.^{2,11} NGS can process multigene testing-panels and perform whole-exome/-genome sequencing (WES/WGS), obviating the need for sequential-testing in cases where the phenotype is not conclusively defined, and prompting evaluations of polygenic CM risk-scores.^{2,8,9,12,13} Such sophisticated analyses of complex CM syndromes suggest that, rather than a restricted variant-assortment around a Mendelian “causal”-mutation, flaws involving numerous (1000s) networked genetic loci in cardiomyocytes may add-up to expressed CM-morphomechanics. Sequencing coverage quantifies how much of the targeted genomic region is covered by a given NGS dataset; because some genomic regions are difficult to sequence, high-throughput NGS coverage risks missing harmful variants, especially when the phenotype entails high genetic heterogeneity; needed NGS coverage levels depend on various factors.¹⁴ Typically, disease-

variant knowledge demands downstream molecular and bioinformatics analyses, to complement DNA-sequencing advancements.^{5,8}

As a general rule, making sense of the output of WES/WGS and determining which variants are clinically important in CMs are major challenges. Studying the genotype-phenotype correlation or the diagnostic significance of variants is challenging and requires specific as well as reproducible results. The analyses entail literature review and sophisticated curation, i.e., extracting biological data from the literature and organizing/integrating it into a biological databank, in order to make available the effect(s) of variants with regard to several biological data encompassing: protein-coding changes, affected amino acids, known single-nucleotide polymorphisms (SNPs), allele frequency, conserved regions, and projected pathogenicity scores. All of this information can be integrated parsimoniously to filter and prioritize detected variants, to discern those that are in all probability most relevant clinically in CMs.

2.4. Downstream research complements upstream NGS

Pictured like a river, *downstream* research complements NGS *upstream* research with genome/exome-wide association studies (GWAS/EWAS) probing genotype-phenotype connections.^{2,7-9} This research should remove correlations involving non-causal variants-of-unknown-significance (VUS) from causal/contributing variants underlying expressed hemodynamic traits/phenotypes. Subsequent downstream studies on disease pathogenesis can then round-out upstream genome-sequencing. To wit, computer methods are gleaning information by DNA *homology*,^{2,8,9} to infer function from sequence-data. Downstream findings can guide CM disease-risk prediction and hypothesis-driven translational research.

3. Classification of CMs and their variable penetrance and expressivity

CMs are commonly genetic myocardial diseases exhibiting distinctive structural-functional phenotypes not attributable to congenital defects, hypertension, valvular, or coronary disease. The MOGE(S) system describes their morphofunctional phenotype (M), organ involvement (O), genetic inheritance pattern (G), etiology (E), and functional status (S) using ACC/AHA stage and NY Heart Association class.¹⁵ They comprise 4 principal groups: hypertrophic (HCM), dilated (DCM), restrictive (RCM), and arrhythmogenic RV cardiomyopathy (ARVC); LV hypertrabeculation often accompanies noncardiac maladies.¹⁶

HCM and DCM are the major CM phenotypes; both are produced by sarcomere-gene mutations that can also induce miscellaneous CM-phenotypes, with intermixed morphofunctional features. This indicates that different variants within the same sarcomere-gene can underlie overlapping *and* separate phenotypic traits; nonsarcomeric-gene, epigenetic, and environmental modifiers (Figure 1) may modulate phenotypes.^{1,2,7-9} I wish to point out here that, as suggested by its Title and as I stress in Section 4. and expound in the subsequent sections of this Survey, a multifactorial polygenic perspective is fundamental in attempting to explain the striking morphomechanic phenotypic differences of CMs – specifically, familial DCM and HCM – that can have matching *recognized/identified* genetic variants. Parenthetically, topics pertaining to non-genetic secondary/compensatory

adaptations (e.g., pressure overload-induced myocardial hypertrophy, heart failure-driven ventricular dilatation) are outside the purview of the present Article.

Heart and sarcomeres are high-complexity systems integrating diverse genetic, epigenetic and environmental factors. Even Mendelian approaches in professedly “monogenic” CMs compelled geneticists to assert that genotype–phenotype correlations lack consistency. In genotype–phenotype correlations, penetrance and expressivity are central concepts,^{2,7–9} explaining why CMs can occasionally be transmitted through unaffected parents. The frequency with which a dominant or homozygous recessive gene manifests itself in a population is its *penetrance*, affected by genotype (unknown contributing/suppressor loci), epigenome, and environment. *Expressivity* specifies qualitatively/quantitatively phenotypic expression levels of a genotype, and cannot be assessed if genotype does not “penetrate” to phenotype. It too may be variable,^{7,8} subject to genotype (unidentified susceptibility/suppressor loci), epigenetics, and environment.

The absence of cardiomyopathic genotype–phenotype consistency likely suggests that the “core” gene-variant’s product is incorporated within an array/network of nonallelic mutations affecting it in unidentified ways and is modified by epigenetic and environmental influences. Collectively, these factors can underlie phenotypic variability.^{2,7–9} Mutations showing reliable correlations with CM disease-phenotype imply that the function of the essential gene-variant exceeds a *threshold*, above which co-acting influences cannot compromise the combined morphomechanical outcome/trait or, alternatively, that it remains below *another* threshold, beneath which the dysfunction of the mutant-protein cannot be upgraded by other counteracting homeostatic elements. Between these 2 thresholds lies a range within which the mutant-function/product has a level that can be variably affected by accompanying interacting factors, yielding inconsistent phenotypes even in a single family.^{2,7}

Contemporary DNA-sequencing renders molecular diagnosis and management increasingly achievable. Nonetheless, genotype–phenotype inconsistencies are a stumbling block to CM phenotyping; they confound functional/clinical effects of novel mutations and underlie variable penetrance and expressivity of established variants.

4. Radically conflicting morphomechanical phenotypes and Hi-Fi hemodynamics in sarcomeric disorders having matching *recognized/identified* genetic variants

As Figure 2 illustrates, LV hypertrophy (LVH, especially of the interventricular septum) with encroached-on chamber and hyperdynamic systolic function typifies HCM pathology; conversely, DCM exhibits an enlarged, thin-walled chamber with impaired systolic function.¹ Coronary microvascular function is anomalous in both, reflecting disparate mechanisms.¹⁷ Both disorders can cause arrhythmias/sudden-death. With multisensor, micromanometric/velocimetric, high-fidelity catheterization and multimodal cardiac digital-imaging, extensive quantitations of HCM and DCM hemodynamic phenotypes are feasible.^{1,7,18,19} Functional Imaging¹ (discussed below) and high-fidelity catheterization yield superior quantitation of

multifaceted HCM/DCM phenotypic changes (Figures 3–4) in systolic and diastolic dynamics; e.g., note the hyperdynamic systolic and impaired diastolic HCM-dynamics at both exercise-and-rest.

In examining Figures 2–4 and the associated discussions in the following subsections it needs be recognized that, as shown in Table 1, gene variants such as *MYH7* and *MYBPC3* encoding sarcomeric proteins are associated with *both* HCM and DCM. Accordingly, these morphomechanically, hemodynamically, and clinically contrasting CMs may share genetic etiology;^{1,2,7–9} and, presumably, the contrasting phenotypes of HCM and DCM reflect dissimilar genetic backgrounds in which the mutations operate. As is discussed in section 2.2., alternative splicing can contribute to diseases, conceivably encompassing HCM/DCM, which can have a shared recognized genetic variant and strongly contrasting phenotypes. Furthermore, the effects of single gene variants ought to be considered in the context of their genetic and Bernardian environmental backgrounds (Figure 1) in different patients, which modulate the overall effect of the particular *presently recognized* disease determinant,^{2,7–9} hindering a reliable prediction of the phenotype.

As I will argue later, explaining quantitative- or categorical-trait variation requires comprehensive accounting for genetic and nongenetic factors and their intricate interactions. Rare variants are apt to impart larger effect sizes than common variants, which typically impart small effect sizes responsible for complex CM-phenotypes. Generally, however, genetic variant backgrounds and other modifier-factors having a bearing on the phenotypic variability of HCM and DCM, as well as other hereditary cardiomyopathies, remain largely unknown at present.

Such backgrounds/modifier-factors are both *complicated* (they have numerous interacting components) and also *complex* (they exhibit behaviors that are unexpected or difficult to fathom). Their behaviors can be so complex as to be counterintuitive. This kind of unanticipated behavior is referred to as *emergent* behavior;^{2,7,8} it could be contributing to the spectacular phenotypic trait differences observed between HCM and DCM in the face of shared recognized variants. As NGS technology advances and genetic testing becomes more comprehensive, poly-/multigenic pathogenetic mechanisms underlying HCM, DCM, and other heritable cardiomyopathies will be identified, and with rising frequency, ushering possibly spectacular advances in our understanding of their pathogenesis.

4.1. HCM multisensor-catheter hemodynamics

HCM exhibits what I have previously called “polymorphic pressure-gradients”.^{1,18,20} These polymorphic gradients reflect dynamically dissimilar intraventricular flow-regimes in early, mid- and late-systole, as I demonstrated in a classic *Basic Concepts In Cardiology* article in *JACC*, in 1990¹⁸: In early systole, the gradients are accounted for by inertial forces opposing local and convective blood accelerations; increasingly in mid- and late-systole, viscous forces play a major role, as well. The huge late-systolic gradients reflect extraordinary flow-passage area shrinkage/obliteration. The intensified convective Bernoulli gradients in the subaortic region may induce a Venturi mechanism, sucking the mitral leaflets toward the septum.^{1,18} Coexisting prominent biventricular diastolic abnormalities are also demonstrated in Figure 3, especially during acute submaximal exercise.^{1,21}

The interacting factors underlying inflow-dynamics in HCM^{1,22}, and the inconsistency in relative contributions to the overall diastolic dysfunction by relaxation defects,^{23–25} asynchrony,²⁶ altered passive myocardial properties and geometry,^{27,28} offer manifold opportunities for translational research. In particular, intracellular Ca²⁺ mishandling has been implicated in HCM as one plausible link between the underlying genetic causes and the downstream signaling-cascade, leading to abnormal traits. Apparently, this involves 2 dysregulated Ca²⁺ modulators^{29,30}: the sarcoplasmic endoplasmic reticular Ca²⁺ ATPase-2 (SERCA2), whose weakened function impairs cardiomyocyte relaxation; and the Ca/calmodulin-dependent protein kinase type-II (CaMKII), whose function is activated, promoting cardiomyocyte hypertrophy.

In the CaMKII signaling-cascade,³¹ inositol triphosphate receptors lead to activation of CaMKII in the nucleus, whereas important targets downstream of CaMKII include histone deacetylases (HDAC) mediating gene-expression changes leading to cardiac hypertrophy. Distinct SERCA2- and CaMKII-implicating mechanisms highlight distinct disease-pathways that could present independent therapeutic targets. Hypertrophy and impaired relaxation often coexist in patients with HCM and in LV pressure overload, as in aortic stenosis (AS) and polygenic hypertension,^{22,23,27,32} culminating in holodiastolic dysfunction (cf. Figure 3).

4.2. DCM multisensor-catheter hemodynamics

DCM (phenotype with diverse causes, aka *congestive* CM) demonstrates the other extreme in ventricular chamber-size, which prompted my formulation of the concept of *ventriculoannular disproportion*.^{1,18,33} the relative size-disproportion between the DCM *chamber-endocardial* and *aortic-ring* areas is functionally equivalent to an outflow-port stenosis. The *ratio* of aortic-ring to LV inner-surface areas is a major determinant of intraventricular ejection gradients.^{18,19} Both *local* and *convective acceleration* components of intraventricular and transvalvular pressure-gradients are accentuated, the convective more intensely, when this area-index is depressed, as in AS. The crux of AS is a reduced outflow-orifice area relative to the endocardial area, from which the converging intraventricular ejection flow-streamlines originate. Post-valvuloplasty, intraventricular and transvalvular ejection-gradients fall sharply, reflecting the augmented outflow orifice-to-endocardial surface area ratio.³³

In DCM, as also in chronic volume-overload conditions including wide aortic regurgitation, chamber-enlargement engenders systolic ventriculoannular disproportion. The unsteady Bernoulli equation accurately allocates the time-varying intraventricular ejection-gradient into local- and convective-components throughout ejection.¹ The larger augmentation of the convective effects provokes characteristic gradient-configuration changes, qualitatively reminiscent of AS.^{1,18,33,34} Consider in Figure 4 the multisensor catheter-derived DCM signals: although small compared with that typifying AS, the instantaneous transvalvular pressure-difference is distributed quite symmetrically over the ejection interval at rest-and-exercise; this dovetails with reduced upstroke-slopes and prolonged times-to-peak-flow in the aortic root.

The resulting ejection flow waveforms are more symmetric than normal. This reflects diminished upstroke with augmented downstroke-steepness; i.e., the DCM-phenotype exhibits *both* depressed ejection acceleration and enhanced deceleration. The rapid downstroke of the ejection waveform, especially during exercise, reflects high LV wall-stress levels maintained *throughout* ejection and the operation of the inverse force-velocity relation.^{1,2,18} In the dilated DCM ventricle, the normally swift decrease in wall stress ensuing from wall-thickening and radial contraction, a ventricular “*self-unloading*,”^{1,2} is restrained.

4.3. The Functional Imaging (FI) method

Analogous fluid dynamic considerations pertain to generally unrecognized but important aspects of diastolic ventricular function. These parallel diastolic concepts were derived using the FI method developed at the Duke/NSF Center for Emerging Cardiovascular Technologies. FI encompasses real-time 3-D echocardiography, sonomicrometry, and computational fluid dynamics (CFD), and is developed at length in *Heart's Vortex*¹ and elsewhere.^{35,36} It reveals detailed blood flow patterns in the hearts of individual experimental animals and human subjects, enabling us to show that chamber dilatation underlies formerly unappreciated alterations in the intracardiac diastolic flow field, with major physiological and clinical implications.^{33,35–40} A fluid dynamic *convective deceleration load*,^{38,39} was revealed to be an important determinant of diastolic inflow during the upstroke of the *E*-wave, its magnitude affecting strongly peak *E*-wave velocities. The larger the chamber, the larger becomes the convective deceleration load. This underlies my concept of a *diastolic* ventriculoannular disproportion²³ in heritable DCM and in acquired chronic volume-overload conditions characterized by chamber dilatation.

5. From gene-variants to CM-phenotypes

Early reports on CM genetics^{41,42} advanced fundamental understanding of disease pathogenesis and phenotypic abnormalities; e.g., gene-variants coding Z-disc components (Figure 5) underlie increased/decreased sarcomere and myocardial stiffness in HCM/DCM, respectively. Mutations in genes encoding sarcomere components – e.g., myosin proteins – are well-established causes of HCM and genetically-acquired DCM. Since the disorders apparently comply with autosomal-dominant attributes, sarcomeres have combinations of normal and mutated myosin proteins; the resultant contractile performance will depend on the summed-force produced by normal/variant myosins.⁴³ Poor HCM prognoses characterize *compound* or *double* heterozygosity – 2 different mutated-alleles, at 1 or 2 gene-loci, respectively. Pathogenic mutations (PMs) represent reliable DNA-encoded prognostic information useful in risk-stratification, with multiple PMs predisposing toward earlier disease onset and higher severity.⁴⁴ However, recent findings suggest that double PMs enhance risk but not HCM severity.⁴⁵

Sarcomeric genetics advances⁴⁶ have already identified PMs in patients with CMs previously classified as idiopathic. Although rarer mutations in additional protein-coding genes have been associated with HCM, numerous studies have confirmed PMs mainly in ≈ 10 sarcomeric genes (Figure 5), as follows: b-myosin heavy chain (*MYH7*), cardiac

myosin binding protein-C (*MYBPC3*), α -tropomyosin (*TPM1*), cardiac troponin T (*TNNT2*), myosin regulatory light chain (*MYL2*), myosin essential light chain (*MYL3*), cardiac troponin I (*TNNI3*), cardiac troponin C1 (*TNNC1*), LIM-binding domain 3 protein (*LDB3*), and cardiac α -actin (*ACTC1*). Jointly *MYBPC3* and *MYH7*, the most commonly affected genes, account for ≈ 50 –80% of identified sarcomeric HCM-PMs.^{2,7–9,47–49}

5.1. Sarcomeric function of gene-variants connected with HCM and DCM

Intriguingly, PMs of most of the above genes are also responsible for heritable DCM.^{47,50–52} Recent research encompassing other genes having sporadic PMs identified several rare variants underlying both HCM and DCM.⁵³ Seeing how pleiotropic PMs of sarcomeric genes can elicit such strikingly *contrasting* (Figures 2–4) phenotypes as HCM and DCM has spurred sarcomere-biology research,⁵⁴ and the sarcomere's chemomechanical cross-bridge kinetics/dynamics cycle clarified how cardiomyopathic PMs perturb force-production.⁵⁵ Briefly, myosins consist of a head motor-domain (MD), which generates movement, and a neck (lever-arm) transitioning into the tail domain and associated with several regulatory light-chain subunits (cf. Figure 5). Contraction occurs through time-shifted, conformational swings in the MD, which elicit ATP-hydrolysis, increase affinity for actin and create a powerstroke transferring force by rotations of the myosin-lever domains.⁵⁶ After contraction, myosin-heads rebind ATP and detach from actin, resuming a relaxed prepowerstroke state; during relaxation, 2 myosin-heads pack-together into an interacting-heads motif (IHM).

HCM myosin-variants boost MD power, raising contractility and ATP-consumption and provoking hypertrophy. They disrupt IHM interactions and decrease percentages of docked myosin-heads, diminishing normally relaxed myosin populations.⁴³ The recognition of sarcomeric PMs impairing relaxation affords new opportunities to target the IHM to improve diastolic function. Conversely, DCM myosin-variants *diminish* MD functions, particularly nucleotide binding, resulting in reduced ATP-consumption and sarcomere power, but with minimal impact on relaxation. Contractility decline ensues, proportionate to the depressed summed-force generated by myosin molecules encoded by DCM-PM loci.⁴³ The underperformance of sarcomeres expressing DCM-PMs actuates Frank–Starling response/dilatation.¹ Further studies may well elucidate how various PMs disturb cyclic protein-interactions and force-generation in CM.^{43,57} Studies of HCM/DCM PMs should correlate large-scale DNA sequencing, sarcomeric protein structure/function, and the resulting Hi-Fi catheterization *hemodynamic phenotypic data* (cf. Figures 3 & 4).^{7,58,59}

5.2. Sarcomeric gene PMs in other CMs and unidentified variants' effects

Sarcomeric gene-variants are also found in less common CM-phenotypes, e.g., RCM, in which myocardial compliance is impaired and, gradually, cardiac pumping reserve is lost causing diastolic failure.^{60–62} PMs in RCM reveal that sarcomeric mutations can underlie diversiform CM-syndromes. The diverse phenotypes also suggest that multiple *coexistent* – albeit unidentified – mutations entailing interactions between predisposing, causal, and contributing loci, including noncoding regulatory gene-elements, can have multilayered effects (Figure 1) on type, severity and management of the resultant CMs.^{2,7,9} These effects confound predictions of potential risk, disease phenotypes and outcomes. They complicate

such diverse matters as : bioinformatics/computational models for analyzing genomic CM-data in a clinical context; genomic markers of clinical risk and prognosis; associations between known genomic CM signatures and therapeutic response; molecular CM-subgroups having clinically-relevant phenotypic disparities; and the like.

6. Ways PMs are expressed in CMs and polygenic/multifactorial interplay effects

Deficiencies in current CM-knowledge involve the ways PMs are expressed, when, why, and how. Clinical unpredictability suggests that unidentified determinants/modifiers⁴⁹ influence presently identified variant pathogenicity. CM severity depends on expression of known/identified PMs, but also on elusive genetic etiologies/variants that may raise disease-diathesis and severity or cause disease-suppression, and on other factors. These encompass: epigenetics; regulatory-DNA polymorphisms that modify the expression-level of a transcript or its isoforms through noncoding-RNAs with multimodal gene-regulating abilities;⁶³ post-translational modifications of sarcomeric proteins affecting structure-function relationships in HCM/DCM;⁶⁴ age-related lapses in protein quality-control; and multifaceted environmental triggers, possibly including (subclinical) infections.^{2,7-9}

CMs embody sizeable genetic heterogeneity and pleiotropy.^{65,66} When investigating phenotype-genetics, we are really asking what gene-variants cause or impact the phenotype/clinical-disorder. Some variants affecting a trait/function will entail genes encoding proteins directly involved in the underlying disorder. But others could exert only very indirect effects – *multiple-pathway* effects, often involved so subtly that no demonstrable relationship appears between the phenotype and cellular roles of the encoded protein(s).

Each variant's recognized effects evidently depend on the CM-traits being studied and on how much detail we can provide in characterizing them quantitatively, e.g., through multisensor Hi-Fi catheterization.¹ And, considering regulatory-DNA polymorphisms, most known regulatory polymorphisms are located in gene promoter regions and function by altering gene transcription. Indeed, the concentration of any given mRNA allele is regulated both by *cis*-regulatory factors (e.g., DNA polymorphisms and methylation) in the DNA sequence *adjoining* a gene and by *trans*-regulatory elements (transcription factors, see below) that are themselves regulated by other [non-*adjoining*] genetic and environmental elements, and bind to the *cis*-acting sequences to control gene expression.

6.1. Genetic heterogeneity confounds determination of causal-variant(s)

Genetic investigations can best contribute to effective therapeutic target discovery if the genes/variants underlying genotype–phenotype relationships can be comprehensively determined. However, as noted earlier, phenotypic-variation generally shows a more complex relationship to genotype and not a one-to-one (bijective) correspondence. Heterogeneity denotes matching-phenotypes derived through >1 genotype (Figure 6). Pathogenetic heterogeneity signifies distinct PMs causing the same CM-phenotype.^{2,7-9,67} Understanding its mechanisms should educe effective prevention and treatment methods.

Pathogenetic heterogeneity can confound diagnosis and therapy of a CM-syndrome observed among different patients. Heterogeneity is notable in several contexts (Figure 6): (i) singly rare mutations *cooperatively* play a substantial role in causing complex disorders; (ii) the same gene may contain numerous distinct, uncommon, severe mutations in *unrelated* affected persons; and (iii) different gene-variants in the same or related pathways may lead to the *same/related* disorders. Thus, interpretation of NGS-based genomic studies can be inconclusive: numerous potentially responsible identified mutations make it difficult to pinpoint *actual* causal-variants.⁶⁸

6.2. Pleiotropy and mechanisms underlying it complicate CM diagnosis and therapy

Pleiotropy refers to 1 gene-variant affecting >1 phenotypic traits⁶⁵ or clinical syndromes in the same or different individuals (Figure 6); thus, a pleiotropic variant may simultaneously influence some or all traits. The mechanism underlying pleiotropy mostly entails effect(s) of a gene coding for a product that is either used by diverse cells or exerts cascade-like signaling affecting metabolic pathways/networks impacting different traits. The concept of a *cascade*, one gene influencing others in-sequence, is instructive. Genes most often work in-concert with others and with signals from the inner-and-outer environments. They function as parts of elaborate gene-networks in which the expression of one is a precondition for that of the next. The product/effect of one gene may be needed to switch-on another; an early-firing gene may activate several intermediate and late-firing genes.

Transcription factors (TFs) are gene-products regulating other genes and coordinating the whole gene-network/system by conveying biochemical/physiological information to it, switching genes on-or-off. Their function entails teamwork; they can bind to DNA and control the expression of dependent gene(s), or they cooperate by physical protein-protein interactions among members of a TF-family. A single regulatory gene at the top of a complex network can indirectly launch a cascade of multiple others. Considering the interdependent, interactive nature of sarcomeric constituents, many CM-genes are plausibly pleiotropic. Pleiotropy is important in understanding CM-variant pathways and assessing their impacts, sometimes encompassing dangerous *side-effects* of therapeutic genetic manipulations. Mechanisms of pleiotropy can involve miscellaneous functions of an individual gene-product, or multipronged consequences of a specific molecular function.⁶⁹

6.3. An open view of genetic architecture will promote greater etiologic precision in CMs

Genetic architecture denotes the genetic foundation underlying phenotypic normal/abnormal traits and their variations, as revealed by NGS: how a multilocus-genotype collection maps onto phenotypes, and how environment and epigenetics influence this mapping. Pleiotropy in the genetic architecture of sarcomeric CMs is well-known,^{2,7-9,70} although molecular mechanisms remain unresolved. The diverse clinical CM-phenotypes suggest that individual genetic architecture expressions are customized by *multifactorial* polygenic interactions. These draw together variant polymorphisms and modifier-genes, *plus* epigenetics, *plus* environmental factors influencing phenotypes (Figure 1).

Conceivable are alternate approaches to cardiomyopathic genetic architecture. Genetic mechanisms are complex and their effects can be averaged and treated like statistical noise

affecting image clarity/sharpness. However, I submit that all variant interactions may matter: it becomes obligatory to ascertain comprehensively coding and regulatory individual genetic architectural-component inputs to CM genetics. As described in Section 4., multimodal imaging and Hi-Fi catheterization phenotypic data can be utilized to accurately infer genetic/genomic architectures, amending views concerning pathogenesis and improving CM diagnosis and therapy.

7. Complex phenotype–genotype pairing expresses multifactorial etiologies

Myocardial cells and their constituents are subjected to epigenetic controls and interactions with their Bernardian internal *microenvironment*,¹ which includes not only outside-influences but also factors originating within the body.⁹ Myocardial phenotype – encompassing heart morphology and dynamic functions blending biochemical processes, myocardial, and fluid mechanics – accrues from selective expression of the genome and embodies cell “experiences” and responses to multifactorial influences.^{1,2,7–9,23,71–76}

That mutations can radically affect cardiac structure/function is certain.^{20,21,71} However, even having the entire Genome Map we cannot predict phenotypes. Mouse-models are effective tools for recapitulating human phenotypes under a specific/fixed genetic background. This is fruitful when studying a CM with phenotypic variability, because variability attributable to environmental can be distinguished from that caused by genetic factors. By keeping the latter constant, through “backcrosses” of the mutant to an inbred-strain [successive matings between a heterozygous animal and a homozygous one for either allele], the genetic heterogeneity between individual mutant-mice is minimized, enabling isolation of the effects of superimposed environmental factors.

I have previously proposed^{1,2,7–9,23,71–76} that diastolic laminar vortical shear and centrifugal “squeeze” forces are ordinarily exerted on the endocardium and myocardial walls by the poloidally rotating blood: shear viscous forces act tangentially to the endocardium; centrifugal forces push it out radially. By Newton’s 3rd Law, a centrifugal force is exerted by the revolving blood on the LV/RV walls that impart on it its centripetal acceleration.^{1,37–40} The diastolic vortical shear and centrifugal “squeeze” forces exert important, albeit mostly unappreciated, epigenetic actions on endocardium and cardiomyocytes. The time is now to decipher how heart cells react to wide-ranging, graded-levels, or an abnormal absence of combined vortical shear and centrifugal “squeeze,” as seen in HCM and DCM.

8. Sarcomeric-variant makeup: monogenic or polygenic?

Multivalued-levels of the genetic architectural complexity underlying CM-phenotypes are disregarded, and fuzzy (see below) concepts or statistical noise approaches (see above) are employed to account for defective/inconsistent genotype–phenotype correlations. Nonetheless, phenotypic inconsistencies of CMs dispute the precept of “monogenic Mendelian disorders,” even conceding that monogenic inheritance does not necessarily imply a bijective phenotype-to-genotype correspondence. Specifically, the variable expressivity found in ostensibly monogenic CMs, even among subjects with the same

identified genetic defect, is a major obstacle to defining genotype-based risk-stratification algorithms. It looks as if 1 gene may be *primarily* responsible for CM pathogenesis, but with 1 independently inherited *modifier-genes*, which variably modulate phenotypes. However, the genetic architecture underlying variable CM-traits is a topic of debate; it is mainly the number, effect-size and frequency of mutations that are at issue.

“*Causative*” mutations for Mendelian traits/disorders must have large effects so that individuals can be classified into genotype-classes using their phenotype, despite the background variation caused by other genes and environmental/epigenetic effects. Besides the monogenic Mendelian, there is a *frequent-variant* hypothesis, where genetic susceptibility to CM is the result of many high-frequency mutations each with small effect, and an alternate *rare-variant* scheme, where low-frequency mutations have large effects (Figures 6 & 7). Genetic interactions provoke interindividual variability in normal/abnormal phenotypes, and blur monogenic/polygenic-inheritance distinctions; such confounding interactions among multiple gene-loci/variants can beget inconsistent phenotypes.^{2,7-9,72}

8.1. Arrays of pathogenetic variants underlie CM-phenotypes

Genetic pathogenesis generally comprises a sequence with diminishing-influence (Figure 7), from 1 causal-variant modulated by modifier-genes, to a collective-makeup progressively involving multiple contributing-variants.⁷⁷ Modifier-genes’ effects can be subtle (e.g., slightly altered disease-diathesis) or profound (e.g., complete disease-suppression, even in causal-variant carriers). Disease-suppressing genes can change widely the threshold for disease-trait expression, which can differ even among family members with the same causal-variant. Thus, personalized genetic treatments could mimic gene expression patterns and the effects of such *protective* genes.

Intriguingly, identical causal-variants often produce distinct phenotypes across different inbred laboratory-mouse strains. By keeping the genetic background constant through “backcrosses,” its variation in individual mutant-animals is effectively removed, enabling isolation of the phenotypic effects of a PM. The presence of important modifier-loci can then be established, if large phenotypic-variation is present when comparing the mutant-phenotype on *different* genetic-backgrounds (backcrossing to 2 different inbred-strains).

In an apparently monogenic Mendelian-disorder, there can be 1 causal-variant invoked as largely responsible for its pathogenesis, perhaps with additional, independently inherited, modifier-genes impacting in ancillary ways the expressed phenotype. Although highly-penetrant variants have been associated with Mendelian disorders, genetics of complex disease-phenotypes, as HCM and DCM, remain unsettled.^{63,78,79} Comorbidity among Mendelian phenotypes and complex diseases strongly suggests that gene-variants for Mendelian phenotypes also partake in complex disorders,⁸⁰ likely including CMs.

9. From “a gene for” to “multiple variants with [±]-impacts on CM risk and traits”

The inadequacy of the monogenic sarcomeric CM model is attested by extensive/sizable phenotypic variability among individuals having *identical* alleles at the implicated

Mendelian-locus. Such intragenotypic variability is presumed attributable to non-genetic (epigenetic/environmental) perturbations; but, mechanisms by which varying CM-phenotypes arise from a uniform genetic background remain elusive. If interaction of 2 PM-loci is required to express particular disease-phenotypes, then this could become overlooked if a polygenic model is not considered, because the variant allele will be present in both normal and affected individuals; the affected carry a mutation at a 2nd or more contributing loci. If any such supplementary-locus is *unknown*, the first locus is implicated in the purportedly “monogenic” disease, and invocations of *incomplete penetrance*, *variable expressivity*, etc., then account for/rationalize defective genotype–phenotype correlations.

Such terms, and the fuzzy, imprecise, concepts that they connote, represent, in my view, proxy-variables used to indirectly allow for unknown effects of as yet *unidentified* genomic-loci, involving coding or noncoding (regulatory-DNA) variants. They disregard coexisting genetic/genomic architecture variations and gene-by-gene interactions influencing cardiomyopathic phenotypic traits.² In-place of polygenic models, to account for observed defective genotype–phenotype correlations, the fuzzy-concepts⁸¹ are invoked, which have gradations of significance and unsharp boundaries of application, varying according to context or conditions. Although a proxy-variable is not a direct measure of the desired quantity, a good proxy-variable is related to the unidentified genomic variable(s).

Proxy-variables are worthwhile when used judiciously, because of obscurity of some/many underlying phenotypic determinants. However, reliance on fuzzy proxy-variables entails many deficiencies and does *not* lessen the urgent clinical need to discover/characterize as yet unknown polygenic-/multifactorial-disease components. Computational and quantitative genetics, using cutting-edge genomics, bioinformatics and statistics, must be applied efficiently to sort systematically through increasingly rich, massive genome-wide datasets. In science the facts keep changing inexorably and prevailing models (e.g., the Mendelian in CM) need to be altogether supplanted by more comprehensive and accurate ones (polygenic/multifactorial).

Disparate viewpoints are a natural occurrence in knowledge-building, and scientific progress requires thinking flexibly and examining the data from evolving new perspectives, enhancing accuracy and precision. Such a perspective should enable us to identify components of complex genetic patterns, and to dissect multifactorial CM-phenotypes integrating interacting polygenic, epigenetic and environmental elements. It should help resolve fuzzy Mendelian correlations into explicit and precise polygenic linkages lying at the heart of pathogenetic understanding of CMs, and, making rational treatments visible, explicit, and accessible.

For complex poly-/multigenic syndromes,⁸ there is no preeminence of any causal-PM; rather, it is the interaction of multiple independently-inherited variants (Figure 7), most probably influenced by ancillary modifier-genes and other factors, that culminates in the expressed CM-phenotype. Given Section 8.’s framework, it becomes evident that actual “single-gene” CMs are much less prevalent than commonly averred. Modifier-genes, remarkably common in humans, effectively convert Mendelian disorders into intricate polygenic traits. We are thus moving onto a paradigm shift: from a mindset of “*a gene for*”

to one of “*multiple variants contributing to inconsistent disease severity and outcomes*”^{2,7–9} Indeed, the complex polygenetic/multifactorial nature of cardiovascular disease is already well-recognized in the case of multiple common coronary artery disease-variants.⁸²

9.1. Quantitative trait loci (QTL) conjointly control HCM/DCM phenotypic traits

A QTL is a DNA locus (segment) that correlates with variation in a phenotypic quantitative trait. Polygenic traits entail QTLs,⁸ i.e., sets of genes that collectively control a *quantitative* (vs. *categorical*, e.g., blood groups) phenotypic trait or trait-ensemble, not fully determined by 1 gene/variant (**panels A & C**, Figure 6). Such quantitative trait-variation (e.g., LV chamber-size or wall-thickness) is ubiquitous in biomedicine and virtually invariably has polygenic origins. By integrating the coalescing pieces of the massive genomic jigsaw puzzle, we will eventually discern the polygenic architecture of complex CM syndromes, encompassing multiple contributing-variants and their regulation (Figure 6). As I stated already, such syndromes are currently characterized operationally in terms of variable penetrance and expressivity, heterogeneity and pleiotropy (**panel B**, Figure 6) of already identified “causal”-variants.^{2,7–9,82}

This approach can conveniently be applied to CM-traits embodying cooperativity of as yet unknown genetic and epigenetic/environmental factors; however, fuzzy edges render precise pathogenesis elusive. Polygenic architecture models are not yet established. But *notably* it is generally accepted that, contingent upon particular mutation(s) present, CM penetrance and expressivity depend on age, sex, and conditioning: all key factors *also* in the common *polygenic* compensatory/adaptive type of myocardial hypertrophy.^{1,75,76}

Deciding genetic causality of a CM is challenging, because of confounding pleiotropy and genetic heterogeneity,⁸³ and also because of *phenocopies* – i.e., phenotypes spuriously mimicking a genetically distinct CM.⁷ And the genetic architectural background modulates the main variants’ effects in sarcomeric CMs, because most traits regarding cardiac morphology, myocardial mechanics and hemodynamics are quantitative, displaying continuous variation rather than discrete/categorical phenotypes.^{1,2,7–9,23,71–76} Notably, having multiple variants controlling a trait/syndrome also raises trait-variabilities, and thus the individual phenotypes are not discrete, but continuous – exhibiting fuzzy gradations.

9.2. Polygenic CM (PCM) models should supersede the fuzzy monogenic precepts

Thus, *PCM* models, in which different combinations of PMs can augment disease-variability, represent an overdue amendment that should supersede the fuzzy monogenic viewpoint. At the same time, *clinical* or, at least, *conscious* chronically-instrumented animal downstream pathophysiologic studies and findings are indispensable.^{18,19,27,37,84–87} Otherwise, confounding effects of anesthesia, recent surgery, and acute manipulation of tissues ensue in any in-vitro, ex-vivo, or even anesthetized-animal experiments. Furthermore, high-level factors present in intact humans/animals (e.g., pulsatile shear and “squeeze” in different settings) cannot be comprehensively reproduced.

As illustrated in Figure 7, complex trait variation is usually a consequence of many interacting loci of small-to-moderate phenotypic effects, modulated by epigenetic and

environmental influences (Figure 1). Next to the conventional Mendelian/monogenic model in Figure 7 are displayed 4 (columns 2–5) representative PCM models, to exemplify predictable genetic-architecture potentials. In the PCM models the expressed syndrome accrues from a combination of rare and common variants, which can assemble in many different combinations in the population to exceed a clinical liability-threshold.⁷² Thus, variations in an identified causal-variant's effects across diverse individual genetic-backgrounds may be due to coexisting *unidentified* variants across many loci (QTLs) that may have small contributory effects – even though these effects can become manifest (liability-threshold) only in the presence of the causal-variant. Penetrance and expressivity, heterogeneity and pleiotropy provide a colorful metaphor for this interpretation.

10. Challenges, hiatuses, and outlook

As clinical CM genetic testing advances, an understanding of variant pathogenicity is becoming increasingly important. There has been progress in identifying genetic origins of sarcomeric CM-phenotypes. Nonetheless, many key questions must yet be answered to translate bioinformatics/genomics findings from multigene testing-panels, WES/WGS, and GWAS into morphomechanic and hemodynamic phenotypic CM-traits. Some say that DNA determines “the Information” needed for the observed phenotypes and, in a sense, this is not far off: just delete “the.” But even if DNA-coding did specify disease-traits uniquely, we would still need to elucidate how. We have seen that it takes a lot more than a list of DNA codes : epigenetic and environmental factors must also be appraised.

Cardiac disorders including the CMs are an area in which epigenetic processes are operative and could provide actionable knowledge, but many pertinent questions remain.^{88,89} For instance, can epigenetic and regulatory processes be exploited and mobilized in diseased cardiomyocytes to reduce the morphomechanical disturbance(s), attempting to restore and preserve normal adult phenotypes, thus augmenting normality/survival? There is evidence that epigenomic processes play a substantive role in the development of cardiovascular disease through widespread reprogramming of histone modifications, DNA methylation, and protein binding. Targeting individual histone-modifying enzymes, chromatin remodelers, chromatin structural components, and regulatory RNAs may induce or prevent CM pathology. Technologies have been developed for studying chromatin, genome function and gene regulation and expression in living cells.^{88–94} Forthcoming advancements will augment our understanding of how chromatin controls gene expression and could have considerable implications for CM management. Epigenetic therapies involving, e.g., histone deacetylase inhibition, chromatin structural protein modulation, and chromatin loop or DNA methylation gene-targeting using CRISPR/Cas9 tools, could be possibly designed to reverse disease changes by targeting chromatin features, such as accessibility and structure.⁸⁹

High-quality databases linking genotypes and phenotypes will only grow in importance as NGS is adopted in the clinic. Extracting meaning from DNA information is very arduous indeed; pluridisciplinary analysis and supplemental genotype–phenotype correlation studies are essential. New technologies may help elucidate mechanisms of the complex and incapacitating CM syndromes. As more defects in numerous genes are found, their polygenic etiology is coming into sharper focus at the expense of the Mendelian/monogenic

model, as is summed up in the **Graphical Abstract**. Future work will inevitably be geared toward elucidation of the interacting elements engendering the genotype–phenotype relations, aiming to enhance CM classification, diagnosis, risk-stratification, prevention and treatments. What’s more, the presence of modifying genetic loci that *attenuate* sarcomeric causal-variant expression may prove pivotal in defining corresponding therapeutic parallels *ameliorating* disease manifestations and prognosis.

When connecting complex disease-phenotypes to underlying genetics, we should abjure the reductive fallacy: just because A is associated with B, A alone causes B. In actual fact, the logical jump between a DNA molecular-variation and a disease is huge. Identified precise genetic causes, accounting for experiential fuzzy-attributes of statistical correlations in CM genotype–phenotype databases, are currently deficient. As the epigram epitomizes, probability/statistics may be a handy substitute for missing precise information and understanding. The difficulty revolves around disregarded influences and *cooperativity* of presently unidentified polygenic inheritance variants that influence various CM phenotypic traits, and by the *emergence* of novel genotype–phenotype properties when such variant-components of lower complexity become integrated and interact at a higher complexity-level. As Aristotle’s holism suggests,⁷ the whole is greater than the sum of its parts and contains *emergent* properties,^{2,7,8,73,74,76} which cannot be construed from single/few known component elements, just as flat surfaces cannot by themselves reveal volume properties.

In probing etiologies of CMs, we need to consider developmental trajectories : numerous genetic loci may well contribute to phenotype/traits, working-in-concert and with epigenetic/ environmental factors – flipping-the-switch between one trait-and-another. When multiple interacting individual constituents are abnormal/variant, new states may emerge as emergent properties of the faulty system; this might be one possible route to apparent *pleiotropy* in CM syndromes (HCM/DCM). In exploring properties of such syndromes, we should analyze the *cooperativity* among their causative elements and in forthcoming downstream studies we should prudently bear in mind that distinguishing correlation from causality is the essence of experimental science, and of clinical trials alike.

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Figure 1.

Besides the developmental algorithms encoded in it, the genome integrates intrinsic and environmental signals. The Bernardian environment^{1,4,7–9,73,74,83} and epigenetic regulatory factors influence variable gene transcription and expression through (bidirectional) information-flow and signaling pathways, while sarcomeric protein-levels and function are affected by various post-translational adjustments. Since epigenetic states are reversible, they can be modified by environmental factors promoting normal/abnormal phenotypes. Factors modifying chromatin-state can possibly interfere with the expression of undesirable gene-variants. The human is effectively a “*supraorganism*,” a blend of human and microbiome genes-and-traits, including the metabolome. The relationship between different “ome/omics” components, protein levels, post-translational modification, protein localization and activity affecting cardiomyopathic phenotypic traits, is shown schematically in this general overview. mRNA: messenger RNA; miRNA: microRNA. Slightly modified from Pasipoularides,⁷ with permission of the *Revista Española de Cardiología* and the Spanish Society of Cardiology.

Figure 2.

Morphologically, HCM commonly exhibits asymmetric LV growth with severe thickening of the interventricular septum and posterior wall, which encroach upon the chamber, greatly reducing its size; histomorphologically, there is also cardiomyocyte (CMC) disarray; these changes bring about diastolic dysfunction. DCM entails CMC elongation and eccentric LV hypertrophy with rightward-bulging interventricular septum, and thin ventricular walls; there ensues deteriorated systolic pumping function.

Figure 3.

A Deep left-ventricular (LVP) and aortic-root (AOP) pressures in HCM at rest and during exercise, which elicits an abnormal LVP diastolic decay, suggesting impaired ventricular relaxation; LVP decays throughout diastole, in sharp contrast to the normal pattern in the lower right. **B** Pressure-flow relationship with large early and enormous mid- and late-systolic dynamic pressure-gradients in HCM. From-top-downward: aortic velocity, and deep LVP, left ventricular outflow-tract (LVOT), and AOP micromanometric signals, by retrograde triple-tip pressure-plus-velocity multisensor left-heart catheter. Left atrial (LA) micromanometric signal was measured simultaneously by trans-septal catheter. The vertical straight line identifies onset of SAM-septal contact, determined from simultaneous M-mode mitral-valve echocardiogram (not shown); most of aortic ejection flow is already completed by then. The huge mid- and late-systolic gradient (hatched area) is maintained despite minuscule forward or even negative aortic velocities. **C** Normal left-heart hemodynamics at rest and exercise. Adapted from Pasipoularides,^{1,9,83} with permission of PMPH-USA, the *Journal of Molecular and Cellular Cardiology* and Elsevier, and the *Journal of Thoracic*

Disease and the Society for Thoracic Disease (China), respectively. SAM, systolic anterior motion of the mitral valve.

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Figure 4. Left-ventricular (LVP) and aortic (AOP) multisensor catheterization in dilated cardiomyopathy showing elevated LV filling pressures and more rounded and symmetric than normal ejection waveforms and transaortic pressure-gradients, at rest-and-exercise. Note the reduced upstroke-slopes in the aortic flow-signals, with prolonged times to peak-flow. By enhancing convective effects, *ventriculoannular disproportion* induces these configuration-changes that are qualitatively reminiscent of the pattern in AS. Slightly modified from Pasipoularides,¹ with permission of PMPH-USA.

Figure 5.

Sarcomeric protein genes subject to mutation in HCM[†] and DCM[‡]. Variants in sarcomeric *genes* (*italicized*, as shown) encoding cardiac myosin-binding protein C (*MYBPC3*), β-myosin heavy chain (*MYH7*), α-actinin (*ACTC1*), α-tropomyosin (*TPM1*), and troponin T type 2 (*TNNT2*) can provoke either DCM or HCM. Variants in genes for cardiac troponin I type 3 (*TNNI3*) and the ventricular regulatory light chain (*MYL3*) cause HCM, whereas titin (*TTN*) variants trigger DCM. A sarcomere encompasses the region between 2 Z-bands, where titin and thin filaments are anchored and interact with other Z-disc proteins. Myosin molecules are composed of a head, which is capable of binding to actin, and a tail that contains a neck region; myosin tails pack together, comprising the thick filament backbone with the heads protruding to form helical tracks. The thick myosin-filament fulfills motor- and regulatory functions through proteins such as MYH7 and MYBPC3. The thin-filament system contains actin and the TPM1-TNNT2/TNNI3-calcium-regulatory apparatus that controls actomyosin interactions.

Figure 6.

Relationships between genotype and phenotype can be ambiguous and open to investigation. Cardiomyopathy phenotypic traits may be due to a Mendelian causal variant/locus with large effects, or to multiple loci (DNA-sections), each with smaller, nonlinearly additive, poly-/multigenic effects. Shown are interactions between genotype (blue circle outline) and phenotype (orange circle outline), comprising genes (solid blue circles) and phenotypic traits (solid orange-brown circles), respectively; arrows indicate directional relationships between genes and traits. **A** Quantitative Trait Loci (QTL) analysis identifies multiple genomic-*loci* involved in the expression of a single quantitative phenotypic trait. **B** In Pleiotropy a single gene is responsible for the expression of multiple phenotypic traits. **C** QTL can be determined for multivariate (M) phenotypic trait ensembles by MANOVA statistics.

Figure 7.

Genetic architecture: rare variants (RVs) of large- or common variants (CVs) of small-effect? Complex cardiomyopathic phenotypes likely involve many interacting loci of small-to-moderate effects, modulated by epigenetic and environmental influences. In the diagram, the rows represent the type of individual: those afflicted by a cardiomyopathy and those with risk-factors insufficient for clinical-syndrome manifestation (sub-threshold). The columns represent the basic genetic-model categories considered. Variant symbol-size quantifies effect-magnitude/severity. For convenience, the cardiomyopathy models are presented as distinct categories, whereas disease-risk is apt to follow a continuous distribution. In the **1st-column polygenic cardiomyopathy (PCM) model**, the disorder results from a combination of CVs that exceed a tolerance threshold. The **2nd- and 3rd-column PCM models** entail a rare variant (RV) in a genetic background of CVs that results in a PCM syndrome provided that: a) the burden of attendant-CVs is enough to exceed the disease-threshold, or b) a combination of applying RVs and CVs of various magnitudes exceeds the threshold. The **4th-column PCM model** involves 2 genetic flaws, wherein 1 RV is tolerated but 2 bring about a disease-syndrome.

Table 1.

Genes commonly implicated in assorted Cardiomyopathies in descending order of frequency.

	Gene	Protein name
% of HCM associated with mutation of this gene		
40%	<i>MYH7</i>	Myosin-7
40%	<i>MYBPC3</i>	Myosin-binding protein C, cardiac type
5%	<i>TNNT2</i>	Troponin T, cardiac muscle
5%	<i>TNNI3</i>	Troponin I, cardiac muscle
2%	<i>TPM1</i>	Tropomyosin alpha-1 chain
% of DCM associated with mutation of this gene		
20%	<i>TTN</i>	Titin
6%	<i>LMNA</i>	Lamin-A/C
4.2%	<i>MYH7</i>	Myosin-7
3%–4%	<i>MYH6</i>	Myosin-6
2%–4%	<i>MYBPC3</i>	Myosin-binding protein C, cardiac-type

Table prepared using data from pertinent chapters of *GeneReviews* [Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2015].

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