

What Causes Hypertrophic Cardiomyopathy?

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Hypertrophic cardiomyopathy (HCM) is a global and relatively common cause of patient morbidity and mortality and is among the first reported monogenic cardiac diseases. For 30 years, the basic etiology of HCM has been attributed largely to variants in individual genes encoding cardiac sarcomere proteins, with the implication that HCM is fundamentally a genetic disease. However, data from clinical and network medicine analyses, as well as contemporary genetic studies show that single gene variants do not fully explain the broad and diverse HCM clinical spectrum. These transformative advances place a new focus on possible novel interactions between acquired disease determinants and genetic context to produce complex HCM phenotypes, also offering a measure of caution against overemphasizing monogenics as the principal cause of this disease. These new perspectives in which HCM is not a uniformly genetic disease but likely explained by multifactorial etiology will also unavoidably impact how HCM is viewed by patients and families in the clinical practicing community going forward, including relevance to genetic counseling and access to healthcare insurance and psychosocial wellness. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>) (Am J Cardiol 2022;00:1–9)

“The workings of all our scientific approaches are assumed to be controlled by the same set of rules, [but reductionism] breaks down when confronted with the twin difficulties of scale and complexity.” —P.W. Anderson in *Science*, 1972

Introduction

Hypertrophic cardiomyopathy (HCM) is a primary myocardial disorder characterized by substantial biological and clinical variability. Despite 60 years of study in thousands of patients of all ages, an uncertainty as to the cause of HCM persists. Recent scientific progress, including studies of tissue from patients, have caused a shift in the conceptual framework explaining this complex disease. This new direction diverges sharply from the strict traditional dogma tethering HCM to single gene variants (the monogenic hypothesis), now replaced by a more flexible paradigm that allows individual genetic context and acquired determinants of disease to explain phenotypic heterogeneity.

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A postmonogenic era of HCM invites a multitude of new opportunities with the potential to advance disease etiology into clinically relevant areas. Achieving this goal, however, requires acknowledging an uncomfortable realization: that overemphasis on the monogenic determinants of HCM over the past 3 decades has diverted time away from efforts to discover alternative disease mechanisms. In this discussion, we present emerging evidence in support of a novel research pathway, distinct from single gene variants toward a contemporary model that integrates genetic context, post-transcriptional events, and acquired determinants of disease to create insights into the true basic cause of HCM.

Background

HCM has an estimated clinical prevalence of 1 : 200 to 1 : 500 in the general population, identified worldwide in at least 125 countries on all continents and is responsible for significant morbidity and mortality in patients of all ages.¹ HCM affects patients of both genders and a multitude of cultures, notably with remarkably similar but heterogeneous clinical expression. Despite its clinical and genetic diversity,¹ HCM has become a highly treatable condition along personalized care pathways, now resulting in the likelihood of low morbidity and mortality and the possibility of normal life expectancy.^{1,2} Nevertheless, even in the current era of effective diagnosis and management using sophisticated clinical tools,^{1,2} understanding the basic mechanisms responsible for HCM at its earliest stages of development remains an important aspiration.

HCM is a complex disease that may be inherited according to an autosomal dominant pattern, albeit with unpredictable expressivity, genotype-phenotype uncoupling, and either variable, low, or no penetrance of clinically overt disease.³ Dominant transmission of HCM is well documented in some families,^{4–6} sarcomere mutations can precede development of the disease phenotype,¹ and left ventricular

hypertrophy is an endophenotypic tracking marker of disease inheritance.^{1,3,4,6}

Therefore, it is undeniable that genetic factors play a role in disease evolution for some patients with HCM, presumably as 1 or several potential triggers for susceptibility pathways. Clinically, genetic context has a crucial role in the development of HCM, including commercial genetic testing and cascade screening of families to identify affected relatives without left ventricular hypertrophy who may ultimately develop and/or transmit the disease.^{4,5}

Such observations led to widespread belief for over 30 years that HCM is by definition (always) a genetic disease of autosomal transmission,⁶ which paradoxically has likely introduced a measure of confusion to patients and relatives, creating uncertainty regarding disease etiology and concerns and guilt implicit in harboring and transmitting a genetic “defect” to offspring. Furthermore, this issue poses wider societal implications inherent in the consequences of inaccurate genetic profiling, including discrimination in life and disability insurance as well as other healthcare disparities. Additionally, promoting HCM as a distinctive disease of genetic etiology has led to unnecessary exclusion of patients with HCM from natural history studies of heart failure, potentially stunting research progress.

Contemporary reports leveraging new approaches to analyzing big data have exposed a much more complex pathogenicity for HCM. From these advances, it is increasingly evident that a new global strategy incorporating information on complex genomic context, acquired disease determinants, and post-translational molecular mechanisms will ultimately be required to decipher basic disease causes, advance precision medicine, and develop more personalized early interventions that may prevent progression of HCM.

The Monogenic Hypothesis

The DNA-based hypothesis that is currently used to explain HCM is largely based on genetic studies of circulating lymphocytes from patients with clinically established HCM. This initiative has reported >2,000 variants in 8 core genes encoding contractile myofilament proteins of the cardiac sarcomere and Z-band. Most common are *MHY7* and *MBPC3*, together representing >90% of pathogenic variants.⁷ More recently, rare protein-altering minor variants (novel sarcomeric and also nonsarcomeric) have been reported with HCM and in some instances inferred as pathogenic, adding to the complex molecular heterogeneity of this disease.⁸ These genes/variants have been identified by whole genome sequencing studies in single large families (some with linkage analysis) or in individual probands with established HCM and *FHOD3* and *MLP* (*CSRP3*). These genetic nonsarcomeric observations are additional evidence that HCM may not be exclusively a sarcomeric disease.

Variant assignments for pathogenicity are considered probabilistic, that is, with some inherent uncertainty potentially created by the multiple nonuniform criteria and interpretations that can differ among experts and genetic testing laboratories. Ultimately, these approaches introduce the possibility of mutational misclassification and genetic misdiagnosis. At present, much of the mechanistic work

related to sarcomeric proteins associated with HCM continues as laboratory experimentation in cell cultures, in murine HCM models, or as part of gene editing initiatives.^{9,10}

Research over the last 3 decades that investigated the determinants of HCM have focused almost exclusively on single gene variants that encode cardiac sarcomere myofilament proteins as being responsible for all disease features. The impetus for this highly specific view of HCM can be traced to genotype-phenotype studies very early in the genomic era identifying familial autosomal dominant inheritance patterns in a few multigenerational kindreds. Such studies marked the beginning of a widely accepted paradigm anchored in the view that a single molecular event (i.e., a gene variant alone) was sufficient evidence to account for HCM, albeit with the basic underlying mechanisms unresolved. The advent of commercial genetic testing for HCM seemed to consolidate the exceedingly broad disease spectrum under a narrow umbrella, defined solely by sarcomere gene mutations.

Consequently, HCM has been described widely and uniformly as a monogenic (Mendelian) disorder. However, novel evidence has emerged in several recent publications (discussed in detail later in the text), providing evidence that deviates from the strict monogenic hypothesis and supports the alternative view that a diverse range of pathobiologic mechanisms beyond a single molecular event may be fundamental to HCM pathogenesis.

Monogenics in HCM: the Pendulum Swings

Clinical evidence against monogenics

A number of assumptions that are part of the monogenic hypothesis are inconsistent with the clinical expression of HCM. First, and the most compelling, only about 30% of consecutive patients with an established HCM diagnosis demonstrate gene variants that are judged pathogenic (or likely pathogenic) and potentially responsible for the disease process, albeit not increased significantly by factoring in variants of unknown significance (Figure 1).¹¹ Consequently, the vast majority of patients with HCM evaluated in clinical settings (about 70%) do not demonstrate evidence of a (mono)genetic cause.

Second, a substantial proportion of HCM family members who carry the same pathogenic sarcomere mutation identified in a relative having a clinical diagnosis of HCM never develop phenotypic evidence of HCM or the diseases.¹ Third, on the basis of clinical, autopsy, and/or contemporary imaging with echocardiography and CMR in thousands of patients with clinically diagnosed HCM, certain morphologic features of the disease phenotype are fundamentally inconsistent with the presumption that HCM is caused solely by genes encoding proteins of the cardiac sarcomere.¹²

Such findings inconsistent with strict inference of the monogenic sarcomere hypothesis include: abnormally elongated mitral valve leaflets, causing LV outflow obstruction, phenotypic expression often differing measurably among related patients with identical genetic substrate, vasculopathy involving small intramural coronary arterioles responsible for microvascular ischemia, and the expanded

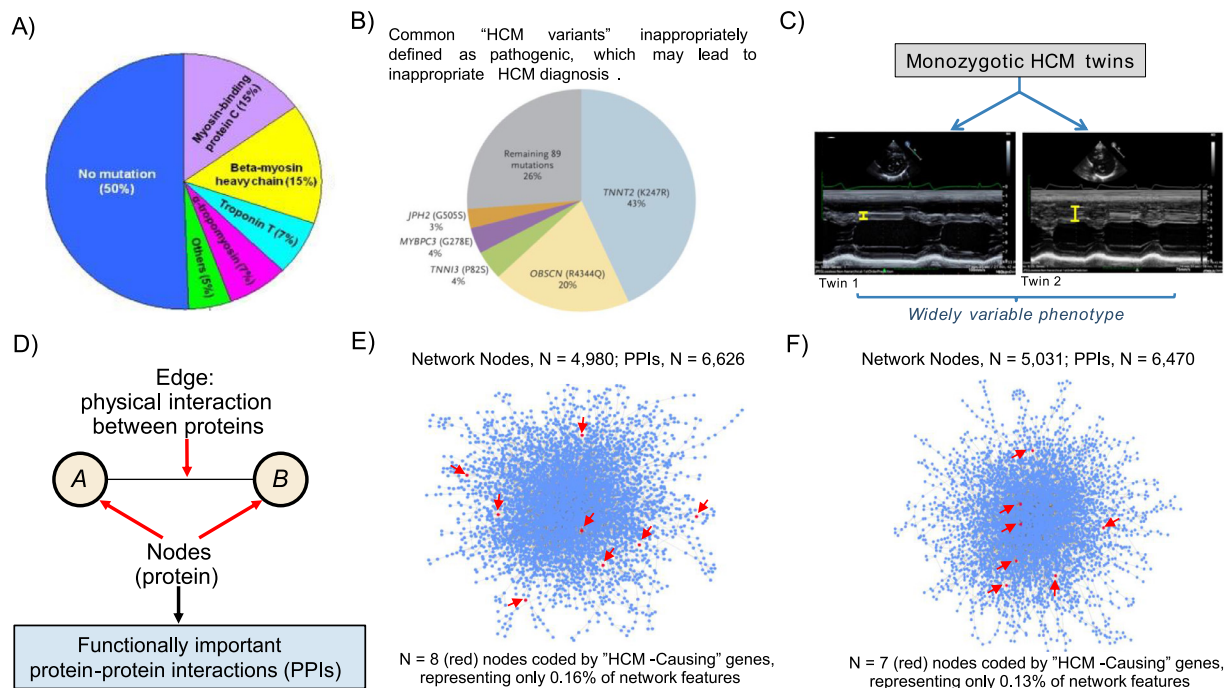


Figure 1. Determinants of HCM. (A) Distribution of variants in genes coding for sarcomere proteins in patients with HCM assessed in clinical practice. It is notable that 50% of HCM patients have no sarcomere gene mutation. However, only 30% of consecutive HCM patients have mutations that can be considered pathogenic (disease-causing). (B) Prevalence of putative HCM-causing gene variants is greater than expected in large genetic databases comprising non-affected populations: *TNNT2* (K247R), *OBSCN* (R4344Q), *TNNT3* (P82S), *MYBPC3* (G278E), and *JPH2* (G505S) are top 5 most common gene variants inappropriately defined as pathogenic, and account for most (74%) of HCM diagnoses judged misclassified. Reproduced with permission from Manrai et al.¹⁵ (C) Recent data from the Seidman laboratory shows widely divergent HCM phenotypes in monozygotic twins, supporting the hypothesis that factors other than genotype are critical to understanding the totality of HCM. Ventricular septal thickness on echocardiographic imaging differs substantially in the twins. Reproduced from Repetli GG, et al²⁸ with permission. (D) Network features, emphasizing that network connections represent functionally important protein-protein interactions (PPIs). (E, F) Using myectomy specimens from patients with obstructive HCM, PPI networks are dense, complex, and vary widely between patients,³¹ suggesting that sarcomere genes alone are unlikely to explain the pathogenesis of this disease. Network topology was not informed by putative HCM-causing sarcomere genes, which in fact represented only <0.1% of all network features. Two representative patient networks are shown, which underscore: (i) HCM pathobiology is complex and (ii) a vast majority of functionally important molecular signaling pathways do not involve any of 17 genes commonly designated as HCM disease-causing (red arrows). Images derived from methods and results reported originally in Maron et al.³¹ Heterogeneity in PPI networks is akin to differences observed in wiring maps of other complex systems.

interstitial (collagen) matrix and extracellular space, contributing significantly to increased LV wall thickness. Alternatively, in support of the monogenic hypothesis,^{13,14} some investigators argue that sarcomere mutations convey more significant disease burden than is evident in the absence of these variants.

Genetic evidence against monogenics

In 2016, Manrai et al¹⁵ analyzed sequencing data from 3 large publicly available repositories to estimate the frequency of HCM-causing variants in white and black Americans. Using such accessible exome data, the authors found that variants that were previously considered causal for HCM were over-represented in general (control) populations, whereas patients with HCM of African or unspecified ancestry more frequently had benign variants that were misclassified as pathogenic for HCM. Additionally, a paucity of black Americans in the control populations of previous genetic studies have contributed to the likelihood of misclassified genetic diagnoses (Figure 1).

These data showing the potential for genetic overdiagnosis of HCM in black Americans substantiate that misclassification of gene pathogenicity is not uncommon in clinical HCM practice, with benign variants often misrepresented as HCM-causing. Furthermore, multicenter collaborative data from Australia report that 2/3 of curated genes, many of which are included in commercially available diagnostic tests, offer little or no evidence of an association with HCM.¹⁶

The totality of these observations suggests that mutations in genes of the cardiac sarcomere may not be causative of HCM, but possibly facilitators of key susceptibility pathways that could increase the likelihood of developing the HCM phenotype. On the other hand, this does not exclude the possibility that HCM can develop by triggering nonsarcomere mutation mechanisms. This could include patients with a nonsarcomeric genetic context in the setting of other biological or environmental triggers or most likely a multifactorial etiology.¹⁷ Indeed, a variety of nongenetic, environmental, or lifestyle variables have been suggested as contributing to development of the HCM phenotype and pathophysiology, including gender, race, obesity, and blood pressure.^{13,18–24}

Furthermore, some investigators have recently pursued a polygenic causative hypothesis for HCM,^{25–27} however, generalizability of this to patients across the HCM spectrum is unlikely. Additionally, this approach again shifts focus away from modifiable causes of disease. Tadros et al²⁵ underscored the case for the causal polygenic component postulated for the HCM phenotype.²⁶

Additionally, Harper et al²⁷ leveraged 2 independent genome-wide association studies, including 2,780 unselected HCM cases versus 47,486 controls, which identified 13 independent genome-wide common variants in 12 susceptibility loci that are associated significantly with HCM. Results of a 2-sample Mendelian randomization strategy inferred a causal relation of sarcomere mutation-negative HCM with systemic hypertension, such that an increase in diastolic blood pressure by at least 11 mm Hg was associated with a >4-fold increase in the risk for HCM. This report importantly diversifies the framework underlying HCM to include nongenetic factors and doing so is consistent with the recent observation from the Seidman laboratory²⁸ that widely divergent LV hypertrophy patterns can occur in monozygotic twins with HCM (Figure 1).

Furthermore, there is emerging evidence for a common nonfamilial form of HCM, of genetic etiology.²⁹ In some cohorts, up to 40% of patients with HCM have neither a family history of the disease or a pathogenic sarcomere mutation. In this sporadic non-Mendelian form of HCM, systemic hypertension has also emerged as a contributor to the disease, again reporting a common HCM phenotype that is independent of sarcomere gene variants.^{1,12,13,16,29–31} Taken together, the evidence for the causative polygenic HCM hypothesis appears to undercut the classical monogenic proposal. Notably, these principles can be particularly relevant to patients and families. The historical mantra that HCM is a genetic (autosomal dominant) disease can misrepresent the true context of this disease to some families and unnecessarily encumber parents with perceived responsibility and guilt for potentially transmitting an inherited disease to offsprings, which may instead ultimately prove to be nongenetic and nonfamilial.

The Case for Network Medicine

It is tempting to simplify a complex biological processes by implicating a single molecular event (e.g., a genetic mutation). However, this view is reductionist and thus, susceptible to major flaws in a complex human disease, such as HCM.³² First, reductionism obligates that a myriad of HCM morphologic and structural features, observed to varying degrees within families and across patients and involving a diverse range of cell and tissue types, is due to a single sarcomere gene mutation. Second, most HCM-causing genetic variants are identified from association studies, which do not yield insight into the biofunctionality of gene variants or their downstream pathways. Third, the role of post-transcriptional events that contribute to genotype-phenotype relations is not evident in data from these analyses. Fourth, information on the effect of acquired environmental determinants of HCM clinical expression are sparse.

Network medicine obviates these restraints of reductionism by considering multiple (functional signaling) pathways simultaneously.^{33,34} In this approach, a wiring diagram is assembled to map important molecular interactions that underlie disease pathogenesis (Figure 1). The networks use the consolidated human interactome,^{30,33,34} which represents a compendium of known protein-protein interactions (connections) occurring in human biology, describing functionally important molecular signaling pathways.

Networks can be analyzed further by focusing on pathways that regulate endophenotypes (i.e., disease features) acknowledged as important to the morphology of HCM, such as myocardial fibrosis. Of the multiple signaling pathways that have emerged in HCM networks, those related to fibrosis potentially identify an underappreciated role for collagen formation as a fundamental disease element. Consequently, network medicine is well positioned to uncover unexpected relevant endophenotypes that are important in HCM and thereby generate powerful hypotheses for pursuing novel disease etiologies. Analyzing network topology itself is potentially informative because connectivity patterns can relate to pathobiology.

Finally, it should be underscored that network medicine is not exclusive of genetics. Instead, genetic context may be integrated with post-transcriptional events to localize determinants of the phenotype or understand the true relevance of genes that are absent from the network.^{30,31,33,34,35}

Network Evidence against Monogenics

Our group has innovated a strategy in which next-generation RNA sequencing technology was used to explore the basic mechanisms of HCM by analyzing heart tissue resected from symptomatic patients at surgical myectomy.³¹ Compared with control tissue from a cohort of rejected heart donors, we identified >2,200 mRNA transcripts in significantly different quantities in patients with HCM, underscoring the molecular complexity of this disease. However, to avoid overstating the importance of any particular mRNA transcript simply on the basis of - fold-change in HCM versus controls or a priori knowledge of gene function, we focused on functional protein-protein interactions (PPIs) and constructed PPI networks unique to individual patients with HCM.

The personalized PPI networks were dense, inclusive of 3,700 functional PPIs on average, and demonstrated basic biological differences among the 18 individual patients with HCM. This approach unmasked 28 different PPI functional categories (i.e., endophenotypes), many of which are related to environmental drivers of cell function, such as inflammation, oxidant stress, and hypoxia signaling (Table 1). Notably, among the myriad of connected proteins, sarcomeric proteins, (preported to be HCM-causing) proved to be exceedingly rare, involving <0.1% of all PPIs in the HCM networks, and representing clear evidence against the causal role of sarcomere protein mutations. Overall, the (1) molecular diversity across patient-specific networks; (2) broad functional diversity of PPIs within individual patients; and (3) insignificant contribution to network topology from classical “disease-causing (pathogenic)

Table 1
Diverse landscape of HCM endophenotypes

HCM Endophenotype ³⁰	Relevance to HCM	Selected Supporting References
Autoimmunity	Association studies linking HCM with Anti-HLA-17 and β 1-receptors and Muscarin-2-receptors; Prevalence studies linking HCM with autoimmune connective tissue disease including systemic sclerosis, systemic lupus erythematosus, others.	39–45
Cell transformation	Endothelial-to-mesenchymal transition and cardiac fibrosis; TGF- β -associated fibrosis in noncardiomyocyte cell types	46,47
DNA damage	Cardiomyocyte-specific telomere shortening and heart failure in hypertrophic hearts	48
DNA repair deficiency	G:C base excision repair editing ameliorates HCM phenotype	49
Fibrosis	Left ventricular thickening due to interstitial collagen deposition, and replacement fibrosis from microvascular ischemia	50–53
Hyperplasia	Junctophilin-2-mediated cardiomyocyte hyperplasia <i>ex vivo</i> , and hyperplastic remodeling in zebra fish model of HCM <i>in vivo</i>	54–57
Hypertension	Polygenic risk for HCM associates positively with diastolic blood pressure	27
Immunological derangement	Tacrolimus use associated with HCM in a pediatric cohort and in other case series in adults	37, 58, 59
Metabolic derangement	Dysregulated mitochondrial Ca ²⁺ handling linked to abnormal LV contractility; \uparrow plasma branched chain amino acids, triglycerides and ether phospholipids in HCM; \downarrow phosphocreatine:ATP in HCM vs. control	60–65
Inflammation	\uparrow circulating IL-6, IL-1 β , IL-1RA, IL-10	66, 67
Metaplasia	Juxtaglomerular metaplasia in feline HCM, linked to renin-angiotensin axis overactivation	68
Mitochondrial dysfunction	\downarrow cardiolipin \rightarrow lipotoxicity in HCM	69,70
Neoplastic signaling	Dysregulated RAS-RAF-MEK-ERK MAPK pathway	71–73
Neovascularization	Abnormal diastolic coronary vascular reserve related to vasculopathy of microcirculation	74
Thromboembolism	Impaired von Willebrand factor \uparrow thrombin generation \uparrow platelet reactivity	75–77
Senescence	Leukocyte telomere length correlates with HCM phenotypic parameters (e.g., inversely with LVOT gradient)	78
Vasculitis	HCM incidence in associations with mixed cryoglobulinemia vasculitis, hepatitis C virus, polyarteritis nodosa	79–82
Hypoxia	HIF1- α -PPAR γ axis regulates glycolytic and lipid metabolism pathways in hypertrophic cardiomyopathies	83
Oxidant stress	Disruption to redox potential of cardiomyocytes slinked to fibrosis and LV thickening in HCM	31, 84–86

ATP = adenosine triphosphate; ERK = extracellular signal-regulated kinase; HCM = hypertrophic cardiomyopathy; HIF = hypoxia inducible factor; HLA = human leukocyte antigen; IL = interleukin; LV = left ventricle; LVOT = left ventricular outflow tract; MAPK = mitogen-activated protein kinase; PPAR = peroxisome proliferator-activated receptor; TGF = transforming growth factor.

Endophenotypes that are implicated as a cause of HCM or a response to HCM.

genes” of the sarcomere proteins provides further tangible evidence against the monogenic hypothesis as solely and primarily responsible for the development of HCM (Figure 1).

Interaction between Genetics and Environment to Potentially Explain HCM

Identifying and integrating the determinants underlying HCM will require an innovative and expansive approach to data collection and analysis. To date, epidemiologic information on HCM has been limited to small case series that linked disease onset to puberty, specific toxic exposures, and systemic hypertension.^{36–38} By contrast, systematically collected data on environmental, dietary, behavioral, psychosocial, economic, racial, and geographic risk factors that already frame the etiology of other cardiovascular diseases (e.g., atherosclerotic coronary artery disease, myocardial infarction, heart failure, and pulmonary hypertension) have not yet been studied in HCM.³⁰

Therefore, a major knowledge gap exists for identifying and connecting potential environmental triggers with

patient-level genetic information to predict HCM onset and disease course (Figure 2). To address this unmet need, research is needed to focus on interactions between genetic context and perinatal events, drug exposure, dietary profile, co-morbidities, and socioeconomic status, all of which are known mediators of LV hypertrophy, myocardial fibrosis, and other HCM endophenotypes.

Conclusions

After 60 years of clinical recognition, definitive understanding of the basic mechanisms responsible for the development and expression of the expansive HCM disease spectrum remains largely elusive. Over the last 30 years, much of what we have learned about this complex and heterogeneous disease has been viewed through the restrictive prism of the monogenic sarcomere hypothesis. From our perspective, we do not de-emphasize the significant role of the genetic context in HCM, that is, the genetic profile of patients, which includes variants but also undoubtedly involves nongenetic factors. Recent application of network medicine to HCM demonstrated a previously unappreciated

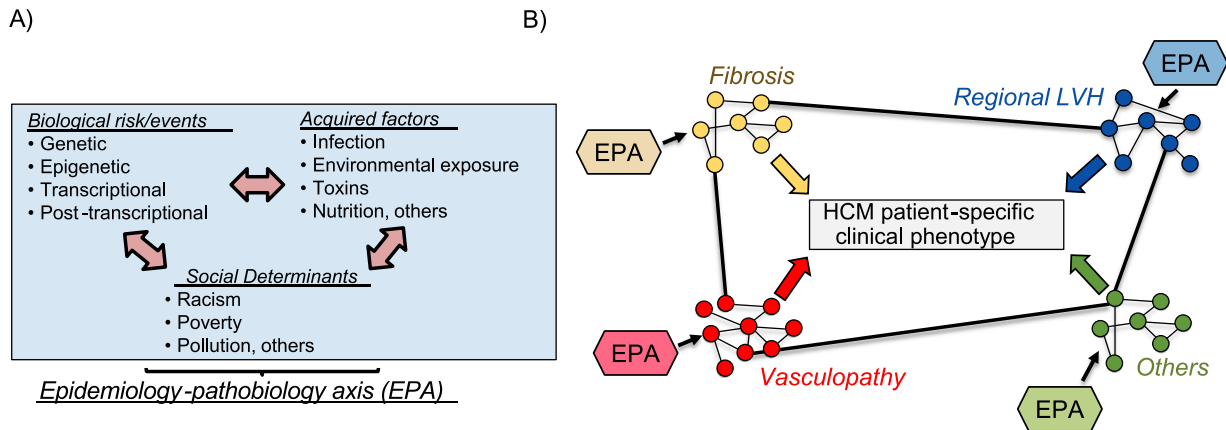


Figure 2. HCM is a disease of converging endophenotypes, regulated by complex interaction between genetic, post-transcriptional, and environmental determinants. (A) Genetic, biological, acquired, and social profiles likely influence individual functional protein-protein interaction patterns in individual patients with HCM. (B) This paradigm sets the framework for a model that integrates genetic context with environmental determinants of disease to explain HCM. Cross-talk among PPIs between endophenotypes, which may vary between patients, explains heterogeneity in clinical phenotypes evident in HCM populations. EPA = epidemiologic-pathological axis.

multitude of protein-PPIs underlying disease pathobiology, largely independent of the contractile myofilaments of the sarcomere. Therefore, it is notable and likely that determinants of the HCM phenotype will ultimately prove to be multifactorial, not confined to the sarcomere, and involve environmental and/or other nongenetic factors.

It is now evident that to regard HCM as a disease solely of genetic etiology can be misleading to patients and families. Consequently, a more complex understanding of HCM etiology requires a change in investigative direction beyond strict adherence to the traditional monogenic and (now) polygenic theories. Success in this approach will likely depend on the expansive use of network medicine, functional genetics, and other contemporary methods.

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