Heart failure is a common condition responsible for at least 290,000 deaths each year in the United States alone. A small minority of heart failure cases are attributed to Mendelian or familial cardiomyopathies. The majority of systolic heart failure cases are not familial but represent the end result of 1 or many conditions that primarily injure the myocardium sufficiently to diminish cardiac output in the absence of compensatory mechanisms. Paradoxically, because they also injure the myocardium, it is the chronic actions of the compensatory mechanisms that in many instances contribute to the progression from simple cardiac injury to dilated cardiomyopathy and overt heart failure. Thus, the epidemiology of common heart failure appears to be just as sporadic as its major antecedent conditions (atherosclerosis, diabetes, hypertension, and viral myocarditis).

Familial trends in preclinical cardiac remodeling and risk of developing heart failure reveal an important role for genetic modifiers in addition to clinical and environmental factors. Candidate gene studies performed over the past 10 years have identified a few polymorphic gene variants that modify risk or progression of common heart failure. Whole-genome sequencing will lead to the discovery of other genetic modifiers that were not candidates. The imminent availability of individual whole-genome sequences at a cost competitive with available genetic tests for familial cardiomyopathy will no doubt further expand the list of putative genetic heart failure modifiers. Heart failure risk alleles along with traditional clinical factors will need to be considered by clinical cardiologists in their design of optimal disease surveillance and prevention programs and in individually tailoring heart failure management.

The use of individual genetic make-up is likely to have the earliest and greatest impact on managing patients with heart failure by tailoring available pharmacotherapeutics to optimize patient response and minimize adverse effects (ie, the area of pharmacogenetics). Modern heart failure management has been derived and directed by the results of large, randomized, multicenter clinical trials. When standard therapies are applied according to the selection criteria used in these trials, they prolong average survival across affected populations or decrease the incidence of heart failure in populations at risk. For this reason, standardized treatment guidelines prescribe heart failure therapies according to trial designs, aiming for the same target doses and general treatment approaches, and largely ignore individual characteristics. In this article, we review established and emerging knowledge of genetic influence on common heart failure and try to anticipate how these genetic factors may be best used to eschew the cookie-cutter approach to heart failure management and move toward implementing a personalized medicine approach for the treatment and prevention of this important and prevalent disease.

The Concept of Genotype-Directed Personal Medical Management in Heart Failure

Variation in clinical heart failure progression and therapeutic response (either benefits or side effects) supports the need for a more individualized approach to disease management. On the basis of clinical stratification (eg, by etiology of heart failure as ischemic versus nonischemic, functional status, comorbid disease), physicians try to match each patient’s specific heart failure syndrome with a therapeutic regime devised to provide the most benefit. Standard heart failure pharmacotherapy currently comprises a minimum of 3 medications (angiotensin-converting enzyme [ACE] inhibitors, β-blockers, and aldosterone antagonists), with consideration of additional medications (hydralazine/isosorbide, angiotensin receptor blockers) and diuretics. The recommended target dosages for these agents, derived from their respective clinical trials, is rarely achieved, partly because of untoward clinical side effects such as low blood pressure or renal dysfunction. Accordingly, the published guidelines most often are applied in each individual patient using ad hoc approaches derived from personal experience and the “art of medicine.”

Technological advances in human genomics promise a different approach and are bringing cardiology into an era of clinically applied pharmacogenetics (whether we want to or not). As sequencing costs decline, it is not hard to envision that patients will present having had their entire genome already sequenced. The imperative to apply genome information in clinical settings will increase, as demonstrated by recent proof-of-concept studies. Our field seems poorly prepared for this type of evolution in care; Roden et al...
identified 3 major barriers: First is the absence of rapidly available genotype information in the clinical workflow. This barrier is being overcome with whole-genome sequencing, which (with proper analysis) promises a permanent and largely immutable genetic roadmap for individual disease risk and drug response at a cost comparable to many other clinical tests. Second, we must have the knowledge to properly apply information on genetic variants for the diseases we are managing and the drugs we are using. As we describe, this knowledge is accumulating for heart failure and for other cardiac conditions, and the rate at which we are gaining additional information and developing further expertise appears to be accelerating.

The third and perhaps most formidable barrier is the lack of clinical evidence showing how real-time application of genetic information can best benefit patients. As has been broadly communicated to the medical community and lay public, common functional gene variants in CLCNKA and Dorn14 can impair the transformation of clopidogrel into its active metabolite, leading to increased risk of stent thrombosis after percutaneous coronary intervention. The relevant question thus becomes the following: If physicians have this information at the time of clinical care and reacted by adjusting clopidogrel dose or substituting prasugrel, which is unaffected by CYP2C19 genotype, would there be any improvement in clinical outcome? It is also important to consider whether any observed benefits justify the additional costs of genetic testing and for the alternate drug. Studies are currently examining these questions, and similar clinical trials will prospectively examine whether a genotype-guided strategy of warfarin dosing will be superior to the standard genotype-blinded approach in reaching target anticoagulation goals. At this time, there are no similar prospective, randomized, blinded trials of genotype-guided care for common heart failure.

What We Know of the Genetics of Common Heart Failure and How We Might Use This Information

Most cases of common heart failure represent a clinical condition where decreased cardiac function from primary myocardial injury is no longer fully compensated by endogenous mechanisms. The most common causes of myocardial injury include hypertension, flow-limiting (or obstructive) coronary artery disease, cardiac valvular disease, and diabetes. Relevant compensatory systems include the adrenergic/catecholaminergic system, which primarily increases cardiac inotropy and chronotropy, and the renin-angiotensin-aldosterone axis, which primarily modulates vascular resistance and renal salt-waterhandling. Individual variation in these compensatory mechanisms may contribute to individual variation in disease risk and progression. Because there is no cure for heart failure, the main management goal is to maintain cardiac output and delay or prevent further myocardial damage. In the next section, we describe genetic variants that are believed to modify heart failure either by influencing heart failure progression or by independently contributing to heart failure risk (Figure 1). We then propose ways in which individual genetic information related to these variants might be used to personalize disease management.

Variants That Influence Catecholaminergic Signaling in the Heart

The β1-Adrenergic Receptor Arg389Gly Variant

The β-adrenergic receptors are highly polymorphic; that is, they exhibit a large number of relatively common DNA sequence variants among populations in which this has been studied. Many candidate gene studies have evaluated the association of genetically variant adrenergic receptors or associated signaling factors with heart failure risk, outcome, or response to β-blocker therapy (reviewed in detail in Dorn35). Because the β1-adrenergic receptor constitutes ~80% of all β-receptors in normal myocardium and β1-receptors are responsible for most of the positive chronotropic, inotropic, and lusitropic effects of catecholamines, polymorphisms of β1-adrenergic receptors have been considered most likely to affect myocardial contraction and therefore are studied most extensively in heart failure.

The strongest clinical association between heart failure and a β1-adrenergic receptor gene variant encodes a Gly substitution for the highly conserved Arg389 within a region of the receptor

![Figure 1. Genetic variants modify heart failure. Myocardial injury is initially buffered by compensatory mechanisms. Heart failure occurs when this compensation is no longer sufficient. Over time, compensatory mechanisms worsen myocardial injury, and drugs and devices are used to oppose or delay disease progression. Genetic variants are believed to affect heart failure at every stage. Pictured here are the most strongly supported genetic modifiers of heart failure, including variants associated with heart failure risk (CLCNKA Arg83Gly) and with progression of established disease (ADRB1 Arg389Gly, GRK5 Gln41Leu, ACE in-del). Emerging variants that require additional study are also indicated. Over the next few years, it is expected that a substantial number of additional heart failure modifiers will be discovered. In-del indicates insertion-deletion.](http://circgenetics.ahajournals.org/)

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**Heart Failure Risk**

- Myocardial Injury
- Compensatory mechanisms

**Heart Failure Progression**

- Compensatory mechanisms
- Drugs and Devices

**Normal**

**Heart Failure**

**Death**

**CLCNKA Arg83Gly**

**ADRB1 Arg389Gly**

**GRK5 Gln41Leu**

**ACE in-del**

**EMERGING VARIANTS**

- 10q25 (BAG3)
- 15q22 (USP3)
- 12p14 (LRIG3)
- 3p22 (CMTM7)
that couples to intracellular signaling molecules. Laboratory studies revealed increased signaling of the Arg389 β1-adrenergic receptor and enhanced sensitivity to pharmacological β-blockade. In contrast, the Gly389 β1-adrenergic receptor signals as if it were partially β-blocked. In early studies, homozygous Arg389 subjects with New York Heart Association functional class III/IV heart failure show significantly better peak oxygen consumption during graded exercise testing (a positive prognostic indicator) than homozygous Gly389 subjects, reflecting the comparatively better cardiac catecholamine signaling by Arg389 β1-adrenergic receptors. For the same reason, Arg389 subjects are more sensitive to the β-blockade with metoprolol or carvedilol, exhibiting beneficial left ventricular remodeling.

In a large (n=2460) longitudinal study of patients with heart failure from Cincinnati, Ohio and Philadelphia, Pennsylvania, we found that white patients homozygous for Arg389 and not treated with β-blockers had significantly longer survival times than Gly389 carriers also not treated with β-blockers, consistent with the beneficial effects of the Arg/Arg389 genotype described by studies evaluating contractile function and oxygen consumption in heart failure. In this study, β-blocker treatment extended survival equally in both Arg389 homozygotes and Gly389 carriers. From these and other published data, we concluded that the gain-of-function Arg389 β1-adrenergic receptor polymorphism has a modest effect on cardiac function and may affect heart failure risk, progression, or both. The results further demonstrate that β-blockers currently used to treat heart failure are equally effective, at usual clinical doses, in blocking both the Arg389 and Gly389 receptors and in extending heart failure survival.

The GRK5 Gln41Leu Variant

G protein-coupled receptor kinases (GRKs) phosphorylate and uncouple agonist-bound adrenergic receptors from their downstream signaling effectors, a process referred to as desensitization. Because termination of agonist-stimulated β-adrenergic receptor signaling by this endogenous mechanism closely recapitulates the effects of pharmacological β-blockers used to treat heart failure, GRKs were also compelling candidates for gene polymorphism studies in heart failure. Unlike adrenergic receptors, nonsynonymous polymorphisms of major cardiac-expressed GRKs, GRK2 and GRK5, are infrequent. One GRK5 polymorphism encoding a Leu substitution for the highly conserved Gln at amino acid 41 is rare in whites but common among individuals of African ancestry (allele prevalence ≈40%). Experimental studies showed that the Leu41 substitution accelerated β-adrenergic receptor desensitization, mimicking pharmacological β-blockade. In the first study of the effects of the GRK5 Leu41 polymorphism of heart failure (n=375 African Americans), β-blocker naïve subjects carrying 1 or 2 GRK5 Leu41 alleles had better transplant-free survival than subjects homozygous for GRK5 Gln41 (hazard ratio, 0.28; 95% CI, 0.12–0.66; P=0.004). The protective effect was similar in magnitude to that afforded by pharmacological β-blockade in GRK5 Gln41 homozygous subjects (hazard ratio, 0.19; 95% CI, 0.10–0.34; P<0.001). We confirmed the major findings of the first study in a subsequent, larger, 2-center study. More recently, protection conferred by the GRK5 Leu41 variant was also observed on the combined end point of death, myocardial infarction, and stroke among participants with hypertension in the International Verapamil SR/Trandolapril Study GENEtic substudy.

Clinical Application of Genetic Data About Cardiac Adrenergic Signaling Pathways

The Arg381Gly β1-adrenergic receptor variant and Gln41Leu GRK5 variant each affect agonist-promoted β-adrenergic receptor signaling. Neither interferes with pharmacological β-adrenergic receptor blockade, at least by β-blockers currently used to treat heart failure. Thus, standard treatment regimens are appropriate for patients with heart failure with either (or both) adrenergic signaling pathway variant. The insight gained from understanding how these genetic variants affect adrenergic signaling, however, has helped to resolve a longstanding controversy regarding the efficacy of β-blocker therapy in patients with heart failure of African descent. Data from some of the original clinical β-blocker trials suggest that the benefit accruing from β-blocker therapy in heart failure was less in African American subjects than in subjects of European descent. We observed a similar pattern when comparing genotype-blinded survival curves in our 2-center study of heart failure survival off or on β-blockers: There was no difference in survival between whites and African Americans not treated with β-blockers; but whites treated with β-blockers lived significantly longer (P=0.0005). We realized that because the Arg381Gly β1-adrenergic receptor is more common in whites and the Gln41Leu GRK5 polymorphism is almost exclusively observed in individuals of African descent, stratification by race unintentionally also stratified by genotype. Strikingly, when the same data were analyzed by race and matched for genotype, the β-blocker survival benefit was equal in white and African American subjects with heart failure. This is an example of how genetic information can and should be incorporated into clinical trial design to prevent misestimation of drug efficacy based on confounding effects of common polymorphisms. Our studies found improved survival conferred by these polymorphisms only in the β-blocker-untreated groups. The impact of these polymorphisms on other favorable consequences of β-blocker therapy in heart failure (improved ventricular function, favorable ventricular remodeling, suppression of arrhythmias) has not been examined. Thus, in the absence of a clinical contraindication, β-blockers continue to be recommended for all patients with heart failure.

Variants That Influence the Renin-Angiotensin-Aldosterone System

ACE Insertion/Deletion Polymorphism

ACE is a zinc metallopeptidase that converts angiotensin I to angiotensin II. Circulating ACE levels vary widely among individuals but show familial clustering, suggesting a genetic component. A related polymorphism was identified as a common 287 bp inserted (I) or deleted (D) Alu repeat fragment within intron 16 of the ACE gene (located at 17q23). It is estimated that ≈50% of interindividual variation
in plasma ACE levels is determined by ACE in/del genotype. Subjects carrying 2 del alleles (ACE DD genotype) have higher plasma ACE activities, those carrying the ID genotype have intermediate activities, and those carrying 2 insertion alleles (II genotype) have lower activities. It is likely that rather than causing the variation in ACE expression, the ACE in/del polymorphism is in tight functional linkage disequilibrium with, and is therefore a marker for, 1 or more causal ACE polymorphisms.

The ACE DD genotype has been implicated in myocardial infarction and ischemic and nonischemic cardiomyopathies and variably in hypertension, promoting the idea that renin-angiotensin-aldosterone system (RAAS) activation controlled by ACE DD genotype affects many different cardiovascular diseases. Accumulating evidence favors a modifier effect of ACE in/del genotype on progression of cardiac hypertrophy and heart failure but not on myocardial ischemic syndromes. A large Swedish heart failure study found that ACE DD genotype was associated with increased left ventricular mass and that survival time was decreased, linking the ACE polymorphism, left ventricular hypertrophy (LVH), and heart failure prognosis. Multiple other studies have also identified adverse associations between ACE DD genotype and cardiac function or heart failure prognosis.

Angiotensin II stimulates LVH, and ACE DD genotype has been associated with LVH or hypertrophic cardiomyopathy. Case-control and cross-sectional studies have found increased DD genotype prevalence among subjects with LVH, suggesting a modifier, of other hypertrophy stimuli. The concept that the ACE in/del genotype acts as a disease modifier rather than as a primary cause of disease is supported by the results of several small studies that concluded that ACE DD genotype in healthy individuals is not sufficient to cause LVH, but measurably increases LVH in the context of hypertension and chronic renal insufficiency.

The CLCNKA Arg83Gly Variant

Each of the gene variants described previously was first identified as a heart failure risk allele based on established (or biased) pathophysiological associations between adrenergic receptor or renin-angiotensin-aldosterone pathway factors and heart disease. Although the data appear solid for the 3 variants described thus far, dozens of other candidate gene associations with heart failure have failed the tests of time and independent replication. Recently, multiple studies using unbiased genome-wide or subgenome single-nucleotide polymorphism (SNP) arrays revealed a previously unsuspected heart failure locus at 1p36, which includes HSPB7 and CLCNKA.

The initial description of the 1p36 heart failure risk locus used the IBC (ITMAT Broad Care) cardiovascular SNP array (≈50,000 SNPs covering ≈2000 genes selected for their likelihood of involvement in cardiovascular disorders) in a 2-stage case-control analysis of advanced systolic heart failure in whites. We identified a strong association with rs1739843 located at 1p36 in the second intron of HSPB7 that encodes a small cardiovascular heat shock protein. This SNP association was similar in strength for ischemic and nonischemic cardiomyopathies. Importantly (because replication of genetic findings in separate and unrelated cohorts by independent investigators is essential for validation), the same genomic locus has since been linked to idiopathic cardiomyopathy in a European study that also used the IBC array and in a recently published genome-wide association study. Three independent reports using multiple heart failure cohorts from 2 continents and 2 different SNP array platforms make 1p36 the most thoroughly validated common genetic risk association with heart failure to date.

Resequencing of HSPB7, within which rs1739843 resides, revealed that the gene is highly polymorphic. Of 19 common SNPs, 12 were associated with heart failure (including the seminal rs1739843 SNP reported by the IBC array), but all of the heart failure-associated HSPB7 SNPs were intronic or synonymous, suggesting the presence of an expression quantitative trait locus or that the HSPB7 SNPs were marking the location of the causal polymorphism elsewhere at 1p36. To examine the possibility that the HSPB7 SNP marked an expression quantitative trait locus, we measured HSPB7 mRNA expression in left ventricular myocardium of 111 white subjects with heart failure. Neither microarray nor real-time quantitative polymerase chain reaction showed an effect of rs1739843 genotype on HSPB7 mRNA levels.

For this reason, we determined whether rs1739843 was telegraphing the position of a functional heart failure risk allele within adjacent CLCNKA, which encodes the renal CIC-Ka chloride channel and is also at 1p36. Resequencing CLCNKA coding exons identified 40 nonsynonymous polymorphisms, most of which were rare. Case-control analyses demonstrated a significant heart failure association for 1 common CLCNKA SNP, rs10927887, encoding a Gly substitution for Arg at amino acid 83. Genotyping in 3 heart failure populations (combined n = 5489) demonstrated an association between the CLCNKA Gly allele and heart failure (odds ratio, 1.27 per allele copy; P = 8.3 × 10⁻⁷). The association was significant for both ischemic and nonischemic cardiomyopathy, suggesting that it was a true heart failure risk allele and not a marker of atherosclerosis or myocardial infarction. Analysis of chloride channel currents in cells recombinantly expressing wild-type Arg83 or variant Gly83 human CIC-Ka channels revealed a ≈50% diminished current amplitude in the Gly variant channels.

The finding that recombinant variant CIC-Ka channels showed a ≈50% loss of chloride channel function suggested a pathological mechanism similar to that described for a similar, but rare, loss-of-function CLCNKA mutation that, in combination with deletion of functionally homologous CLCNKB, was described in a single case of congenital Bartter syndrome. A common feature of Bartter syndrome caused by all of its many genetic lesions is hyperreninemic hyperaldosteronism, reflecting autonomous activation of the RAAS. Clinical, experimental, and genetic data have implicated the RAAS in heart failure development and progression. Thus, we postulate that the RAAS is genetically primed in individuals carrying 1 or more alleles encoding the variant Gly83 CIC-Ka channel, providing a silent genetic first “hit” that
predisposes to developing heart failure in the context of a second pathophysiological hit that directly injures the heart.

**Clinical Application of Genetic Data on Renin-Angiotensin-Aldosterone Signaling**

The pathophysiological association among the **CLCNKA** heart failure locus, the ACE in/del polymorphism, and renin-angiotensin-aldosterone signaling suggests a pharmacogenetic approach to patients. The rationale is as follows: Patients with hypertension are at increased risk to develop cardiac hypertrophy and heart failure because of the primary damage done to myocardium by chronic pressure overload.62,63 Those who harbor the **CLCNKA** Gly83 variant, ACE DD genotype, or both might be at even greater risk because of their genetic tendency toward exaggerated RAAS activation and hyperaldosteronism. These genotypes may contribute to the “aldosterone escape” phenomenon described in some subjects after ACE inhibition.64 It is also possible that the ACE DD and CLCNKA Gly83 genotypes can interact to affect hypertrophy and heart failure risk. This gene-gene interaction needs to be examined. Either way, if these assumptions are correct, then early use of aldosterone antagonists in addition to ACE inhibitors could neutralize the increase in risk conferred by ClC-Ka Gly83 and ACE DD. There is a need for prospective, blinded clinical trials that can evaluate this possibility and directly test whether genotype-directed therapy will modify hypertrophy progression or heart failure development in at-risk populations (Figure 2).

**Emerging Variants**

The variants described here are established, but new ones are emerging. Although findings in heart failure genome-wide association studies have been limited, we can expect additional common heart failure variants to emerge as sample sizes increase.65 The CHARGE (Cohorts for Heart and Aging Research in Genomic Epidemiology) consortium published a genome-wide association study of incident heart failure that tested for associations between >2.4 million HapMap-imputed polymorphisms in >20,000 subjects.7 They identified 2 loci associated with heart failure, rs10519210 (15q22, containing **USP3** encoding a ubiquitin-specific protease) in subjects of European ancestry and rs11172782 (12q14, containing **LRIG3** encoding a leucine-rich, immunoglobulin-like domain-containing protein of uncertain function) in subjects of African ancestry.66 In a companion study using the same population and genotyping results, mortality analysis of the subgroup of individuals who developed heart failure implicated an intronic SNP in **CMTM7** (CKLF-like MARVEL transmembrane domain-containing 7).67 These genetic associations require independent replication and further study to identify the underlying biological mechanisms.

A recently published genome-wide association study by a European consortium on dilated cardiomyopathy identified common variants in **BAG3** (BCL2-associated athanogene 3) associated with heart failure67 and identified rare **BAG3** missense and truncation mutations that segregate with familial cardiomyopathy. These findings were consistent with an earlier exome-sequencing study that identified **BAG3** as a familial dilated cardiomyopathy gene and showed recapitulation of cardiomyopathy with **BAG3** morpholino knockdown in zebra fish.68 Together, these studies convincingly support variation in **BAG3** as a genetic risk factor of cardiomyopathy and heart failure. It is noteworthy that both common and rare functional variations were identified at this locus. A unifying hypothesis for these findings, which needs to be formally tested, is that common variants in **BAG3** serve as proxies for rare functional **BAG3** mutations with large impact.
effects. In this situation, the underlying genetic lesion is a rare variant with a large functional effect. This has recently been described for common variants in MYH6 that correlated with rare functional MYH6 variants to cause sick sinus syndrome.69 It is premature to speculate on the clinical applications of these newer findings.

Moving Knowledge to Practice
A small number of genomic variants have been identified that modify heart failure by affecting well-understood physiological systems. The principal barrier preventing their adoption in practice may be lack of evidence showing how application of this information can best be used for clinical benefit. Trials testing genotype targeting of antiplatelet therapy and anticoagulation will be completed in the coming years. The findings from these studies will likely determine the level of enthusiasm for conducting genotype-guided trials of β-blockers and RAAS antagonists in heart failure. Given that the lifetime risk of heart failure in the United States is estimated at 1 in 5, even a small favorable effect on heart failure prevention or outcome through use of genome-guided therapy has the potential for a large public health impact. We therefore believe that a near-term goal should be to conduct pharmacogenomic trials in heart failure based on our current understanding of heart failure variants.

Looking ahead, unbiased approaches will continue to reveal a large number heart failure-modifying variants (both common and rare). Based on experience in other complex phenotypes, such has height70 and plasma lipid levels,71 the underlying genetic mechanisms for many new heart failure variants will be completely unknown, and their sheer number will preclude detailed experimentation using murine models to figure them out. Leveraging these variants for clinical application is a challenge that we will be forced to confront.

As our ability to identify rare, disease-causing variants improves through personal genome sequencing, we will be faced with the additional problem of how best to estimate the disease risk conferred by a sequence variant for which there has been no biological validation. In probabilistic terms, because there are 3 billion nucleotides in the human genome and over twice that many humans on the planet, it is likely that a nucleotide substitution for every position is represented in someone. Obviously, it will be impossible to recombinantly express and functionally characterize every DNA variant that is going to be implicated in heart failure. Bioinformatics filters have been used to try and separate functionally significant from insignificant variants based on the likelihood of changing transcript expression or protein function. These tools are limited but will improve if we tailor their results to the known characteristics of each gene product. For example, current approaches to categorize amino acid substitutions as conservative or nonconservative based only on charge or side chains can be improved by molecular modeling that incorporates protein-specific structure-function information. This approach has been used to estimate the pathogenicity of myosin heavy chain (MHC) mutations in an effort to determine which mutations are likely to cause familial cardiomyopathy when linkage analysis is not feasible.72 In concept, this approach can be applied to any protein for which structure-function activities have been finely mapped to distinct domains.

A promising extension of this approach may be to use evolutionary genetics to infer disease causality. Again, using the MHC genes as examples, human genome data show a greater prevalence of nonsynonymous gene variants in MYH6, which encodes the minor cardiac α-MHC isoform, compared with the adjacent MYH7, which encodes the major β-MHC isoform. This disparity suggests a greater tolerance for protein changes in the α-MHC isoform and negative selection against these in β-MHC. We can infer, therefore, that amino acid changes are more likely to have adverse impacts in MYH7-encoded β-MHC. If this paradigm survives prospective testing, then the forthcoming explosion of individual genetic data not only will present a massive problem in interpretation, but also will provide the genetic information by which analyses of rare sequence variants across large unaffected populations can help to differentiate the tolerable variants from those that are more likely to alter disease risk.

A complementary approach may be to use scalable experimental systems, such as zebra fish and fruit flies. These 2 model organisms have genomes that are readily manipulated on a large scale and cardiac phenotypes that can be assayed en masse. In specific instances where putative heart failure loci are identified within genes of uncertain function, these biological platforms may be useful in helping to define mechanisms of action and in providing insights into potentially altered drug responses.73,74 Regardless of whether function is established or simply inferred, this knowledge can be deployed in clinical practice only if proven to positively affect clinical outcome. This requires prospective, blinded clinical trials testing treatment regimens rationally designed on the basis of integrated information from population genomic surveys, mechanistic studies, the best bioinformatics predictions for the gene variant of interest, and the presence of gene-drug interactions identified and validated in experimental biological systems.

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