A hereditary disease has an identifiable gene or set of genes that underlie its occurrence. The public database Online Mendelian Inheritance in Man (OMIM) has cataloged >1700 diseases with an unknown molecular basis. Although some of these diseases, with a known molecular basis, plus >1700 others with an unknown molecular basis, are called "secondary" or "complex" diseases because we suffer from an abnormally high prevalence of deleterious mutations. As a species, we have accumulated damaging mutations much faster than we have cleared them. Here's why: The rate of nonsynonymous DNA mutations in protein-coding genes is constant, ≈1x10^-5/gene/generation. Fitness loss for a mutated protein (ie, the odds that a nonsynonymous mutation will be damaging) is also constant, ≈1%. Damaging mutations tend to be cleared from the population through evolutionary suppression for many generations. Thus, in a stable long-term population, negative selection restrains the prevalence of damaging DNA mutations. However, the human population has been anything but stable for a relatively short period of evolutionary time. In 5000 BC, there were ≈5 million Homo sapiens on the planet. The advent of agriculture and transition from nomadic life to urban civilizations prompted an exponential increase in population, resulting in ≈500 million humans by the middle ages, a 100-fold increase. The industrial revolution and modern technologies stimulated a second exponential increase in population, from 1 billion in 1800 to >7 billion now. Thus, in just a few hundred generations, human population has increased by 3 orders of magnitude (doubling just within the authors' lifetimes!). This represents a tremendous number of new genomes to accumulate damaging mutations with insufficient time to clear them. Accordingly, 73% of all protein-coding variants and 86% of all deleterious single-nucleotide polymorphisms are only 5000 to 10000 years old. Mathematically, every person currently alive is carrying ≥1 severely damaging DNA mutations, and every protein-coding gene is represented by someone carrying a dysfunctional variant, most of which are rare or private.

Mutations in MYH7 and MYBPC3, which encode β myosin heavy chain and myosin binding protein C, respectively, account for approximately half of inherited HCM. Clinical genetic testing for HCM has become more commonplace and revealed marked interindividual variability in disease, that is, the same gene mutation is present in individuals with a spectrum of HCM, even within the same family. Differences in disease phenotype (ie, symmetrical versus asymmetrical hypertrophy and the occurrence of arrhythmias), variable disease severity, and different patterns of onset all suggest a role for modifiers that may be genetic or environmental.

Blankenburg et al examined 3 MYH7 mutations, V606M, R453C, and R719W, mapping to unique regions of the
β-myosin heavy chain (MHC) head domain. V606M has been characterized as a mild HCM-associated mutation in humans associated with late-onset disease and less severe hypertrophy. V606 lies in the 50-kDa portion of the myosin S1 head, where it contributes to the actin-binding site. R453C has been associated with more severe human HCM and is located within the γ-phosphate sensing domain of the myosin ATPase. When engineered in vitro into human β myosin, the R453C mutation has reduced actin-activated ATPase and directs slower in vitro sliding of actin filaments. The final mutation, R719W, is also associated with more severe human HCM, is located within the myosin converter domain, and has been linked to increased elastic distortion of individual myosin heads.

To better evaluate their individual and combined phenotypes on identical genetic backgrounds, Blankenburg et al introduced these 3 human MYH7 HCM mutations into the respective positions of the mouse Myh6 gene (encoding αMHC, the major myosin heavy chain protein found in the murine heart). Somewhat recapitulating the human genotype–phenotype spectrum, R453C caused hypertrophy by 26 weeks of age in mice, whereas V606M had no significant effect on left ventricular hypertrophy at that same time. Even when homozygous, the V606M mutation was insufficient to produce cardiac hypertrophy. However, when the V606M mutant mice were crossed with the R453C mutant mice, the dual heterozygous mutant progeny mice developed more hypertrophy than either of the parent mutant strains, demonstrating additive phenotypic effects of these 2 mutations.

Functionally, these allelic combinations offer the potential for fresh molecular insight. The V606M mutation with its ability to modify actin binding is insufficient to produce HCM, even when homozygous (ie, in the absence of any normal MHC). However, altered actin binding plus reduced ATPase evoked significantly more hypertrophy, suggesting a disease model wherein the cardiac sarcomeres contain a mixture of myosin heads, some with different actin binding and others with reduced ATPase. These mixed mutations may or may not reflect a situation where each allele produces half the total MHC protein, because V606M and R719W is also associated with more severe human HCM, is located within the myosin converter domain, and has been linked to increased elastic distortion of individual myosin heads.

These population-based estimates and the current findings in mice show how individual DNA variants that contribute little or nothing to cardiac phenotypes in otherwise normal individuals may lead to more severe disease in the context of a more pathogenic HCM mutation. Although these analyses focused on the MYH7 gene, the second genetic hit principle is certainly not restricted to this gene; functional significance of other sarcomere gene DNA variants is likely to be revealed in the context of a pathogenic MYH7 HCM mutation. For this reason, Blankenburg et al advocate more broad-based genetic screening to help identify those at highest risk for faster progression.

A markedly increased potential for gene–gene interactions is one of the consequences of a human genetic landscape replete with mutations that are both rare and predicted to be damaging. If a given mutation is causal, other functionally significant DNA variants can almost certainly act as phenotypic modifiers. Depending on genetic context, DNA variants may therefore be categorized as primary or driver, associated, or comorbid mutations and may exhibit variable expression or reduced penetrance. This genetic reality not only provokes interindividual variability in phenotype but also blurs the distinction between monogenic, bigenic, and polygenic or complex inheritance. It is likely that the genetic component of phenotype can only be explained by the cumulative functional consequences of all coding and noncoding DNA sequence variants in the same gene, in other genes of the same pathway, and finally in all genes that impact the affected organ system (Figure). And, this approach still fails to incorporate epigenetic and environmental influences. Serious attempts at this type of systems-level genetic integration will need to be both comprehensive and unbiased. Accordingly, the initial discovery of a genetic disease might be accomplished using conventional genetic linkage of the suspected primary mutation in a relatively few affected subjects, but to understand fully how the spectrum of personal genotypes help determine individual phenotype will require identifying all genomic DNA variants in large cohorts of subjects presenting with the disease phenotype, regardless of primary mutation.

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References


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