Genetics in heart failure

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REVIEW PAPER • CME

Genetics in Heart Failure: Where Are We Headed?

Heart failure is a complex disease with many precipitating factors. Novel insights into the genetic background of heart failure have boosted new areas of research that gave rise to the concept of genetic predisposition for heart failure. Various genetic defects and variances have been identified and subsequently linked to the onset of or progression to heart failure. Nevertheless, our understanding of the genetic basis for heart failure is incomplete because we lack knowledge of the functionality of genetic variances. We also do not understand the impact of genetic variances in noncoding DNA because of logistic problems in performing whole-genome scans and difficulties in statistical evaluation of large amounts of data generated by the genetic boom. It is expected that in the future we will be able to overcome these problems and apply the knowledge gained by genetic analyses to target and optimize treatment. (CHF. 2006;12:329–332) ©2006 Le Jacq

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Heart failure (HF) is an ever-increasing epidemic in our society. In the past decades, considerable progress has been made in the understanding and treatment of this complex and devastating disease, yet morbidity and mortality rates remain high. With the exponential increase in our knowledge of genetics, both researchers and clinicians are eager to extend novel molecular insights into new treatments that may ultimately improve outcome.

Although it is beyond doubt that our understanding of HF has gained by the genetic revolution, it is disappointing that this has not yet led to substantial changes in daily practice. Here we summarize some considerations that should be taken into account when conducting genetic studies in future research.

Genetics in HF: Where Are We Now?

Monogenic vs Multifactorial Forms of HF: Gene Defects vs SNPs. It has been recognized that some patients have a genetic predisposition for the development of or the progression toward HF. There is a clear distinction between defects in single genes *leading* to disease and genetic variances in genes *contributing* to disease.

For some specific forms of HF, the responsible gene defects were identified, ie, variants in single genes that are directly causing disease (monogenic disease). For instance, this is observed in some familial forms of dilated cardiomyopathy and hypertrophic cardiomyopathy, with defects in genes encoding cytoskeletal proteins and sarcomere proteins, respectively. There is ample evidence that it is feasible to predict the genetic defect by rigid phenotyping.[1] In specific forms of HF, the association between the genetic defect and disease is quite straightforward. This has prompted the creation of specialized clinics, mostly in university hospitals, that serve as reference centers for patients and families with cardiomyopathies. These clinics initiated planned family screening, which has resulted in the discovery of a considerable number of monogenetic defects responsible for various cardiomyopathies (dilated, hypertropic, and arrhythmogenic right ventricular cardiomyopathies).[2]

These findings have provided new insights into operative pathways, in specific, rare forms of HF: They have also been invaluable to the patients and family members of index patients and raised spirits and attention in the academic environment. These diseases, however, are rare and the genetic unraveling of rare diseases generally does not yield a population benefit.

The large majority of patients experience HF due to coronary artery disease, hypertension, diabetes mellitus, and other underlying multifactorial disease. In such forms of HF, the contribution of genetic defects is likely to be more modest. Accordingly, identifying genetic variants that affect disease severity is a much more challenging task. Thus far, most studies on genetic variety in such patients have been conducted using

Table. Common Terms in Genetic Science

Hardy-Weinberg equilibrium	A fundamental principle in population genetics stating that the genotype frequencies and gene frequencies of a large, randomly mating population remain constant provided immigration, mutation, and selection do not take place
Allele	One member of a pair or series of genes that occupies a specific position on a specific chromosome
Heterozygosity	Having 2 different alleles of the same gene
Homozygosity	Having 2 identical alleles of the same gene
Polymorphism	Having multiple alleles of a gene within a population, usually expressing different phenotypes, which include single nucleotide polymorphism (SNP)
Single nucleotide polymorphism	SNP (pronounced "snip") is a DNA sequence variation that occurs when a single nucleotide (A, T, C, or G) in the genome differs between members of the species. For example, 2 sequenced DNA fragments from different individuals, AAGCCTA to AAGCTTA, contain a difference in a single nucleotide. In this case we say that there are 2 alleles: C and T.
Haplotype	The set of alleles that determine different antigens but are closely linked on one chromosome and inherited as a unit, providing a distinctive genetic pattern used in histocompatibility testing

the candidate gene approach. Since it has become clear during the past 3 decades that maladaptive systems such as the renin–angiotensin system, the sympathetic nervous system, cytokines, and endothelin all contribute to the beginning and evolution of HF, genes encoding these pathways were probed and variants (mainly single nucleotide polymorphisms [SNPs]) (see Table for common terms in genetic science) in such genes were correlated with the presence, severity, and natural course of HF. This approach has led to an explosion in the number of research papers.

As a result of the Human Genome Project, we have become aware of the enormous genetic diversity in humans—the number of SNPs is particularly dazzling. The rise of genetics has witnessed a fascination with "markers," mostly polymorphisms in anonymous DNA segments. These proved ideal for tracing and were used to positionally clone rare disease genes to their position in the genome; however, we still have marginal knowledge about the extent and nature of sequence variation in genes and adjacent regulatory regions. We understand even less of what such variation means.

Although SNPs may be of importance in the pathophysiology of a disease, there are several matters that should be considered. First, despite the vast number of publications on the topic, the understanding of genetic background has not increased accordingly. A recent review by Bleumink and colleagues[3] discussed the effects of SNPs in candidate genes in HF. They conclude that most studies show a modest effect on outcome but, for many SNPs, contradictory outcomes have been reported. For instance, the importance of common variants in the β_1-adrenergic receptor has not been settled despite extensive research.[4–8] SNPs in the β_1-adrenergic receptor may not affect clinical outcome in HF,[4,5] whereas softer end points were shown to be associated with certain genotypes.[6] Possibly, other SNPs modulate their impact of a single SNP.[7] SNPs in the gene encoding the β_2-adrenergic receptor have convincingly been associated with adverse outcomes in HF.[8] Possible explanations for conflicting results are that many studies were underpowered, findings were flawed due to a large heterogeneity in the study population, and considerable publication bias resulted in overestimation of the true impact of certain SNPs. Often, we are not aware of whether the SNP confers a functional change or that the genetic variation is simply present without any functionality. For instance, a SNP may result in an increased or a decreased rate of transcription or cause a receptor to exhibit an altered affinity for ligands, and so forth. Furthermore, since we remain unaware of the precise pathophysiology of HF, many SNPs in (noncandidate) genes are not probed for their potential effects in HF.

Pharmacogenomics. Although most patients with HF are now treated according to international guidelines, it is nevertheless observed that standardized pharmacologic treatment leads to variable clinical outcome. A possible factor contributing to this variability is the modification of drug disposition and action by genetic traits. The influence of genetic polymorphisms, both in systems responsible for disposition of drugs used in HF patients and physiologic systems determining the effects of these drugs, has been extensively studied.[9] For instance, McNamara and colleagues[10,11] showed that the insertion/deletion polymorphism in the gene encoding angiotensin-converting enzyme predicts response to β-blockade and angiotensin-converting enzyme inhibitors in patients with congestive heart failure. Currently, no clinical guideline recommends genetic testing before the initiation of pharmacotherapy; it first has to be seen whether DNA can provide information about possible therapeutic choices.

Where Are We Headed?

What Genes Do We Evaluate: Candidate Genes vs Genome-Wide Screening. A fundamental choice is how to undertake genetic screening. Until recently, we were limited in our choices of testing because genome-wide screening (eg, with large-scale arrays) was not available. Accordingly, most studies were designed to evaluate the role of a specific genetic variant, usually a SNP commonly present in a study population, sometimes with certain functionality.

With ongoing improvements in technology and the availability of

high-throughput genetic tests, larger sets of genes and haplotype testing has become popular. We now have methodology that enables mapping of more than 100,000 SNPs in a single experiment.[12] This approach is very promising because (1) the scale and speed of new techniques may enable us to close the gap between our desire to unravel the genetic basis of disease and our current achievements; (2) it is expected to establish which SNPs are involved with which diseases; and (3) it will lead us to the discovery of genes that were previously not linked to specific diseases and, thus, enable us to generate novel hypotheses.

Obviously, there are major challenges to this approach, including how to pin down those SNPs that are important and make sense of the vast amount of data that will be generated. It has been suggested, however, that the SNP approach is not doomed. Determining how dense the SNP map should be, the associations between SNPs and functional differences, and the important haplotypes will provide definite answers.[13] It will require strict genotyping and phenotyping and firm cooperation between clinicians, geneticists, biostatisticians, and epidemiologists.

cSNPs vs rSNPs. For a SNP to cause alterations in an amino acid (protein) sequence, it has to be located in the coding sequence of a gene; in other words, in an exon. Such SNPs are referred to as coding SNPs, or cSNPs. cSNPs may or may not cause an altered amino acid sequence, and the coding refers to its location on the DNA. cSNPs that do not cause an amino acid sequence alteration are generally considered nonfunctional.

Most of our DNA, however, is outside the exon and, thus, intronic. Most SNPs are located in this region, yet we are less knowledgeable about the role and importance of SNPs in such regions. Of particular interest are those SNPs that are located in the vicinity of transcribed genes; we have identified the 5′ untranscribed region (UTR) (situated in front of the promoter) and the sequence after the primal transcript, the 3′-UTR (which often confers information on RNA stability, which also translates into increased abundance of transcript). It is conceivable that SNPs in these regions may have profound effects on gene expression, rather than on gene product. An increasing number of SNPs that regulate gene expression are being discovered and have been called regulatory SNPs, or rSNPs.[14]

We recently published a paper describing an association between a vascular endothelial growth factor promoter polymorphism and impaired prognosis in HF.[15] One other example of just how important rSNPs may be is described in the recent paper by Knight and colleagues.[16] They showed that a SNP in the tumor necrosis factor α (TNF-α) promoter (T308A) regulates the expression of lymphotoxin α, which is an upstream neighbor of TNF-α. The impact of this SNP has thus falsely been ascribed to a TNF-α effect.

Many large project groups are putting in considerable effort to map, identify, annotate, and interpret rSNPs. To date, we do not fully understand their significance.

Total Risk: How Do We Summate Genetic Factors and Other Disease Factors? Multifactorial diseases are caused by many risk factors, both genetic and environmental. To investigate the unresolved issues in the etiology of and individual susceptibility to multifactorial diseases, the research focus must move away from single determinant–outcome relations studying universal risk factors. Risk factors are categorized into genetic, environmental, and complex factors. In future studies, there should be a focus on how to incorporate all these factors into one model. Particular emphasis should be on gene–environment and gene–gene interactions.

Genetic Testing and Statistical Analyses. Common human diseases are complex traits. Genetic predisposition may make a person susceptible to a disease, but environmental and complex factors also play a role in the development of the disease. Yet despite this notion, many statistical geneticists continue applying methodologies that were developed to dissect much simpler diseases. Although our knowledge of genetics has dramatically increased over the past decades, due to complex interactions and staggering numbers, our statistical capacities are lagging behind. Certain features in genetic studies warrant special attention during statistical analyses.

Multiple independent variables (predictors) or multiple dependent variables (outcomes) complicate the analysis by creating heterogeneity. Allelic heterogeneity causes predictor variables to remain unmeasured or unobserved and, therefore, unavailable for inclusion in the disease model. In the case of trait heterogeneity, some outcome variables may be present, which have not been (or cannot be) distinguished based on the available phenotypic information. Heterogeneity may be overcome foremost by rigid genotyping and phenotyping, but also by using methods such as stratification and cluster analysis, among others.

Gene–gene interactions and gene–environment interactions are complex factors. There is a wide set of statistical methods to unravel these interactions, such as logistic and linear regression analyses and the multifactor-dimensionality reduction method, but there are also more sophisticated methods such as interaction entropy graphs, Bayesian belief networks, and artificial neural networks. Nevertheless, it may be difficult to dissect interactions from heterogeneity.

In general, it is advocated to use a 2-step approach in genetic statistical testing by first demasking heterogeneity and then using specific tests for interactions. Many standard criteria for genetic testing in multifactorial diseases have been proposed: power calculations should be performed for sufficient power; gene–environment interactions should be explored (with sufficient power to allow these analyses); investigators involved in genotyping should

be blinded with regard to phenotypes; the genotyping error should be stated (and low); it should be clear whether genotypes are in Hardy-Weinberg equilibrium in both subjects and controls; genotype frequencies and allele frequencies should be presented for all groups analyzed; the relative risks (odds ratios and 95% confidence intervals) or attributable risks should be noted; uncorrected and corrected *P* values should be reported; and investigators should seek a possible gene–dose effect.

Conclusions

Unraveling the genetics of HF will be a challenging task in the next decade. Undoubtedly, many new genes and pathways in HF will be discovered. Our challenge will be to understand the contribution of genetics to the initiation and progression of HF amidst the full range of factors determining the final phenotype. Only then will we be able to use this knowledge for the further improvement in treatment of HF to reduce its burden on health care.

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CME Questions

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INSTRUCTIONS FOR COMPLETING THIS FORM: Read the selected paper and answer *all* the questions that follow. After each question there is a series of possible correct answers. Please select the one best answer for each and place your selection on the answer grid. **YOU MUST ALSO COMPLETE THE CME EVALUATION SECTION** and return the form within 6 months of the paper's publication to receive credit. Letters of credit will be mailed to participants biannually.

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OBJECTIVE AND TARGET AUDIENCE: All health care practitioners are eligible to receive credit. At the conclusion of this activity, participants should be able to: (1) summarize the important points discussed in the paper reviewed, (2) identify patients to whom the paper is relevant, (3) modify management practices as new information is learned, and (4) identify deficiencies in their knowledge base.

Please Select the One Best Answer for Each and Place Your Selection on the Answer Grid.

1. Monogenic etiology defines all of the following types of heart failure except:

A. Cor pulmonale
B. Dilated cardiomyopathy
C. Hypertrophic cardiomyopathy
D. Arrhythmogenic right ventricular dysplasia

2. Which of the following physiologic entities is not involved with the evolution of heart failure?

A. Sympathetic nervous system
B. Renin–angiotensin system
C. Parasympathetic nervous system
D. Cytokines

3. It has been scientifically proven that single-nucleotide polymorphisms confer a functional molecular change in dilated cardiomyopathy

A. True
B. False

4. Standardized pharmacologic treatment of heart failure patients and the interpretation of their response supports which of the following statements?

A. All heart failure etiology is fundamentally the same.
B. Heart failure is refractory to pharmacologic intervention.
C. To be effective, heart failure pharmacokinetics must ignore patients' comorbidities.
D. Drug disposition is affected by genetic traits.

5. To scientifically advance heart failure treatment and outcomes, studies must be conducted on gene–gene and gene–environment interactions.

A. True
B. False

CME answers are available on the *Congestive Heart Failure* page at www.lejacq.com

CME Answer Grid

Answer the questions from the previous page by selecting the best choice of A, B, C, or D

Questions: 1.__ 2.__ 3.__ 4.__ 5.__

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	Agree				Disagree
1. My knowledge was enhanced by this activity.	1.__	2.__	3.__	4.__	5.__
2. The activity helped to clarify issues specific to heart failure patients.	1.__	2.__	3.__	4.__	5.__
3. The information obtained from this exercise will have an impact on my care of patients.	1.__	2.__	3.__	4.__	5.__
4. The format of the exercise was useful.	1.__	2.__	3.__	4.__	5.__

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