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Molecular Genetics of Congestive Heart Failure

Heribert Schunkert

From the Klinik und Poliklinik für Innere Medizin II, Universität Regensburg, Germany

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The manifestation of congestive heart failure occurs secondary to a great variety of cardiac or systemic disorders that share a temporal or permanent loss of cardiac function. In order to enhance our knowledge about the genetics of heart failure it is mandatory to analyse the aetiologic factors of these underlying disorders separately. Monogenic forms of congestive heart failure have initially been described by observant physicians in consecutive generations of affected families. Molecular genetic analyses of these families subsequently allowed us to localise and identify some of the genes that cause hypertrophic, dilative, or restrictive cardiomyopathies, congenital heart disease, as well as a number of inborn errors of metabolism. However, the great majority of patients develops heart failure as a final consequence of multifactorial conditions such as hypertension, cardiac hypertrophy, or coronary artery disease. Each of these conditions may be the product of a complex equation that includes environmental and genetic factors. Indeed, some of these factors may be harmful, others protective and for most it takes decades before a phenotype will be clinically detectable. Given this complex scenario it was not unexpected that early studies on candidate genes came up with partially controversial information. This review aims to summarize and to comment on the principal findings of this work.

Key words: human, hypertension, left ventricular hypertrophy, coronary artery disease, remodeling, angiotensin converting enzyme, angiotensinogen.

Priv.- Doz. Dr. Heribert Schunkert, Klinik und Poliklinik für Innere Medizin II, Universitätsklinikum Regensburg, Franz-Josef-Strauß Allee 11, D-93053 Regensburg, Germany, Tel: +49 941 944 7233. Fax: +49 941 944 7213.

MONOGENIC CAUSES OF HEART FAILURE

Albeit rather uncommon, monogenic forms of cardiac disorders have received wide attention for pioneering molecular genetics from a methodological point of view. In particular, the systematic approach included the chromosomal localisation of affected genes by linkage analysis, consequent searches of respective regions for genes that might explain the phenotype, followed by sequencing of these genes and identification of underlying mutations. The most pertinent monogenic forms of cardiac failure are listed in Table 1.

Hypertrophic cardiomyopathy

The clinical presentation of patients with hypertrophic obstructive cardiomyopathy includes asymmetric left ventricular hypertrophy, dynamic obstruction of the left ventricular outflow tract, arrhythmias including sudden death, and congestive heart failure (26). Analyses in affected families most often revealed autosomal dominant traits. Initially, the responsible gene was localized by linkage analysis on chromosom 14, q11 (15). Previously, the cardiac myosin heavy chain gene had been mapped to the same region. Thus, there was a candidate gene that, if mutated, could plausibly explain the phenotype. Subsequently, sequencing of the cardiac myosin heavy chain gene resulted in the identification of several genomic alterations in affected families (15). It was estimated that this gene accounts for about 50% of familial forms and 30% of sporadic cases of hypertrophic obstructive cardiomyopathy (57). More recently further loci on chromosoms 1q3 (cardiac troponin T; (51)), 11p13-q13 (cardiac myosin binding protein C; (56)), and 15q2 (α-tropomyosin; (51)) have been found to harbor genes that cause hypertrophic obstructive cardiomyopathies. All these mutations have in common that they affect genes coding for contractile proteins such that this disease can be attributed to the cardiac sarcomer.

Dilative cardiomyopathy

Albeit the mode of inheritance is poorly defined, familial factors seem to contribute to the development of dilative cardiomyopathies as well (3). In a recent study, 20% of patients with dilative cardiomyopathy were found to have family members with depressed cardiac contractility (32). However, the underlying molecular mechanisms causing dilative cardiomyopathies remain elusive in most patients at the present time. Some cases have been found to be related to disorders affecting fatty acids or carnitine metabolism,

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Table 1. *Inherited cardiomyopathies*

Examples () and chromosomal locations [] are given in parenthesis

I. Inborn errors of metabolism
storage disease / diminished energy production
Glycogen (Pompe etc.),
Mucopolysaccharide (Hurler etc.),
Glycosphingolipid (Fabry),
Glucosylceramide (Gaucher)
Mitochondrial DNA deletions (Kearns-Sayre),
Impaired fatty acid metabolism (carnitine deficiency)
II. Neuromuscular disorders
Duchenne muscular dystrophy [Xp21]
Becker-type muscular dystrophy
Friedreich ataxia
Refsum disease
III. Malformation syndromes / congenitial heart disease
Chromosomal aberrations (Down syndrome)
Single gene / dominant or recessive
Holt Oram syndrome [TBX 5 gene mutation, 12q24.1]
Septum defects
Valve malformations
Conduction malformations
IV. Hypertrophic / dilated / restrictive cardiomyopathy
Cardiac myosin β heavy chain [14q11-q12]
Cardiac troponin T [1q3]
α-tropomyosin [15q2]
Cardiac myosin binding protein C [11q11]
With WPW syndrome [7q3]
Linked to [1p]
With mitochondrial DNA deletions
With mutations of cytoskeletal proteins (metavinculin)
Familial restrictive cardiomyopathy
Arrhythmogenic right ventricle

which were either propagated by autosomal-recessive or mitochondrial transmission (49). X-chromosomal transmission of cardiomyopathy is a potential indication for Duchenne's or Becker's dystrophy. These patients lack the membraneous protein dystrophin or reveal mutations at the cardiac muscle specific promoter of the gene at locus Xp21 (52). Just recently, another patient with cardiomyopathy has been found to carry a mutation of metavinculin, a cytoskeletal protein that interacts with talin and α-actinin to link the sarcomere with adherin or the integrin receptor in the cardiomyocyte membrane (30). Thus, molecular alterations of the cytoskeleton may result in cardiomyopathy as well, offering a group of candidate genes for future investigation. Finally, the gene causing cardiomyopathy in the Syrian hamster has been localized on chromosome 9qa2.1-b1 and awaits identification (36).

MULTIFACTORIAL CAUSES OF HEART FAILURE

Recent progress in epidemiologic research has enabled us to clearly delineate the predominant aetiologic factors of congestive heart failure in Western societies. In particular, the long-term follow-up in the Framingham Heart Study has demonstrated that the majority of cases was predicted by one or more of four conditions: arterial hypertension, coronary artery disease, diabetes mellitus, and left ventricular hypertrophy (27). In fact, the population attributable risk of these four factors combined accounted for about 90% of all cases with congestive heart failure (Fig. 1) (27). Interestingly these predictors share the feature that they are caused by both environmental and genetic factors. In order to estimate the impact of genetic predisposition to congestive heart failure it is thus important to understand the role of genetics in these underlying disorders.

Table 2. *Genes linked to / associated with human hypertension*

Gene	Reference
Angiotensinogen	22
Aldosterone-synthase	28
Epithelial sodium channel	50
Kallikrein	4
11β-hydoxylase	12
Glucocorticoid-receptor	58
Atrial natriuretic peptid	44
Glycogen synthase	19
Metabolic syndrome	60

Hypertension

In recent years a number of monogenic causes of arterial hypertension have been identified (28, 50). However, like with monogenic cardiomyopathies, these mostly autosomal dominant traits play quantitatively only a minimal role in the etiology of hypertension.

Hypertension is rather seen as a multifactorial condition that integrates numerous environmental and genetic factors. Given that all components of the cardiovascular system and an array of central-nervous and neurohormonal regulatory mechanisms are involved in blood pressure regulation it is obvious that many genes are potentially contributing to this process (18). Not surprisingly, studies on allelic polymorphisms of these candidate genes identified numerous associations with elevated blood pressure (Table 2). A number of association studies on promising candidate genes have been negative. However, association studies are intrinsically at risk to come up with false negative or false positive results. Thus, these data need to be confirmed in additional populations before firm conclusions can be drawn. In particular, a failure to demonstrate an association with a polymorphism does not exclude that the same allele may be involved in blood pressure regulation when environmental conditions or the genetic context are different. In addition, it cannot be excluded that other alleles of the same gene or other genes in the particular chromosomal location may affect the phenotype.

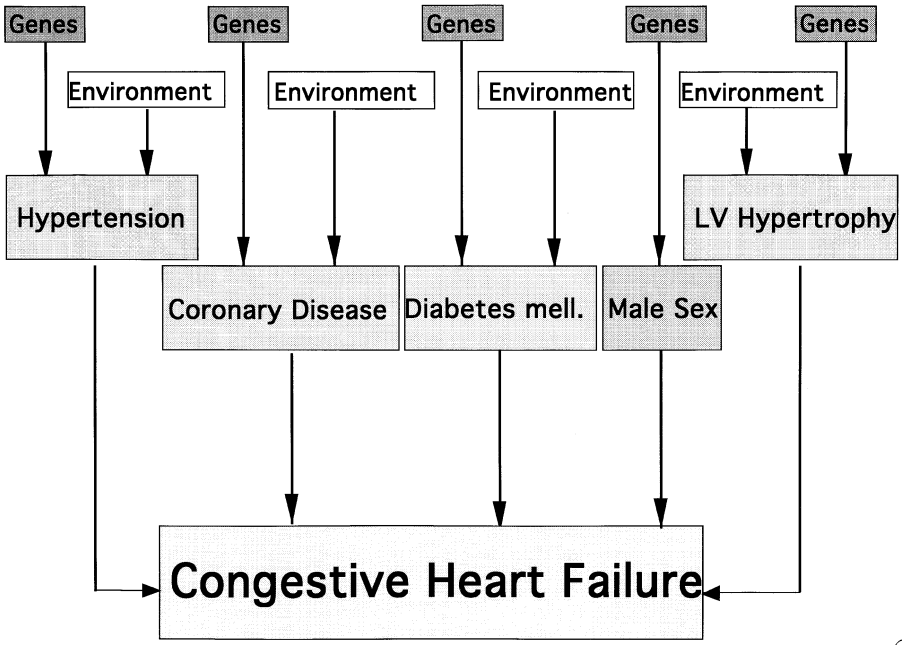

Fig. 1. The flow chart displays etiologic factors of congestive heart failure. Most important predictors of heart failure result from complex genetic-environmental interactions reflecting the multifactorial basis of the common disease.

Another methodological approach is the investigation of affected families (22, 58). When, for example, two siblings share a phenotype such as hypertension they may also share the genes that contribute to this phenotype. When many of such sib-pairs are genotyped by the use of multiallelic markers, statistical analyses may allow us to trace the chromosomal location of the affected genes. The drawback of this method is that hundreds or thousands of affected families need to be studied to detect a modest contribution of a gene that is suspected to contribute to arterial hypertension or for that matter congestive heart failure. In addition, it needs to be pointed out that this type of analysis establishes linkage only with the chromosomal location but not with a candidate gene itself.

The angiotensinogen gene is currently best characterized for its role in the multifactorial genetics of human hypertension. Affected sib-pair analyses have repeatedly documented that this chromosomal locus carries a gene that is linked to hypertension (22, 9). In addition, association studies demonstrated that a diallelic polymorphism (M235T) is related to both

Table 3. *Genes linked to / associated with coronary artery disease*

Gene	Chromosomal location	Phenotype	Study design (reference)
Lipid metabolism			
LDL-receptor	19p13.2-p13.12	familial hyper-cholesterolemia, myocardial infarction	Association / (6) Linkage/ (17)
ApoA-I	11q23-q24	HDL-deficiency, ApoA level, stroke	Association / (62)
ApoB	2p23-p24	dysfunctional ApoB, myocardial infarction	Association / (37, 5, 53)
ApoAI-CIII-AIV complex	11q11-q13	combined hyperlipoproteinemia	Association / (53) Linkage / (61)
ApoE	19q13.2	type III hyperlipoproteinemia	Association / (54)
Apo(a)	6q26-q27	elevated Lp(a) myocardial infarction	Association / (1)
Lipoprotein lipase	8p22	type I hyperlipoproteinemia	Association / (38, 31)
Cholesterol ester-hydrolase	10q23.2-q23.3	cholesterol ester storage disease	Association /
Platlet function/coagulation			
Fibrinogen	4q26-q28	fibrinogen level Arteriosclerosis	Association / (14, 45)
Platelet glycoprotein IIIa		myocardial infarction	Association / (59)
Others			
Cystathionine b-synthase	21q22.3	homocysteinuria	Association / (13)
Angiotensin converting enzyme (ACE)	17q23	elevated ACE levels, myocardial infarction	Association / (8)
Angiotensinogen		myocardial infarction	Association / (24)

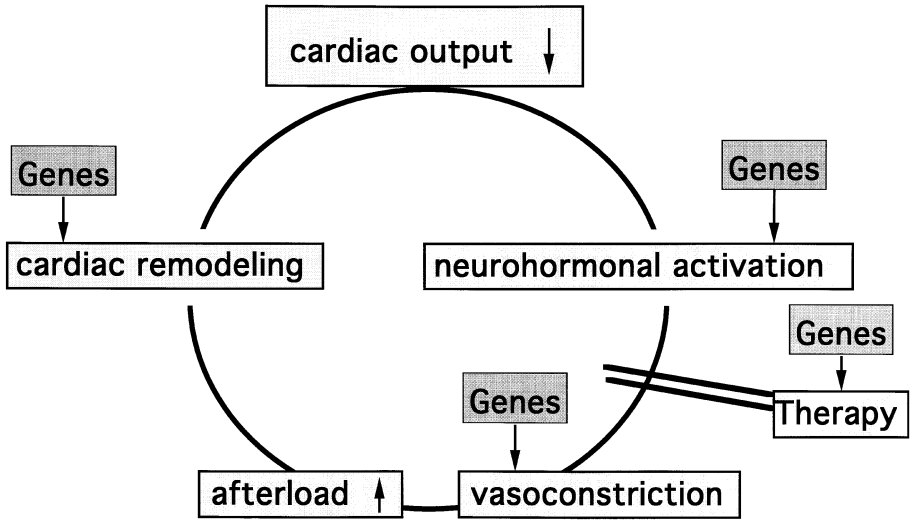

Fig. 2. Congestive heart failure is known to be propagated by a vicious circle. The figure displays a hypothetical model for genetic interaction with adverse cardiac remodeling. In particular, neurohormonal activation, elevation of afterload, structural adaptations, and the response to therapy may be modulated by genetic predisposition.

angiotensinogen protein and blood pressure levels (22, 47). However, at present there is no indication that this gene also affects cardiac function.

Coronary artery disease / myocardial infarction

Like hypertension, coronary artery disease is considered to represent a multifactorial condition. From a genetic point of view, the traditional risk factors for myocardial infarction (hypertension, hypercholesterolaemia, diabetes mellitus, smoking) allow an aetiologic subclassification that may more directly elute to the pathogenesis of coronary artery disease. Table 3 offers a list of genes that have been suggested by association studies or linkage analyses to confer an increased risk of myocardial infarction. The contribution of most of these genes is still subject to scientific debate. Larger studies and scrutinous analysis of affected sib-pairs are awaited to shed more light on this important subject.

Left ventricular hypertrophy

Twin studies as well as studies on affected sib-pairs suggest that left ventricular mass and left ventricular hypertrophy (LVH) are partially determined by genetic factors (55, 34). Given that LVH confers an enormous and rather specific risk for the development of congestive heart failure (23), the identification of genes that contribute to this phenotype may be of great interest.

Experimental evidence points to the angiotensin converting enzyme (*ACE*) gene as an attractive candidate gene for LVH. Both *ACE* gene expression and protein levels are induced in experimental and clinical left ventricular hypertrophy (46). In addition, pharmacological ACE inhibition has been shown to ameliorate cardiac hypertrophy in clinical and experimental studies (10, 7). Finally, linkage analysis in rats suggest that the *ACE* gene locus harbours a gene that affects left ventricular mass (20). In parallel, a deletion/insertion (D/I) polymorphism of the human *ACE* gene has been discovered and related to 20–50% of the interindividual variance of serum and cardiac ACE activity (43, 11). Studying a population based sample of subjects with left ventricular hypertrophy as suggested by typical ECG findings ($n = 290$) and the same number of controls, we found that men with the *ACE* DD genotype were at increased risk to develop this condition (48). However, Lindpaintner et al reported data on the Framingham Heart Study that did not confirm this association between *ACE* genotype and left ventricular hypertrophy (29). Nevertheless, positive associations continue to be reported from numerous investigators (21, 42, 2, 16, 33, 39). Most interestingly, recent data from Montgomery et al suggest that physical activity may affect the impact of the *ACE* DD genotype on cardiac mass (33). The authors studied young healthy subjects before and after a rigorous excercise protocol. Only those participants that carried the *ACE* deletion allele displayed an increase of left ventricular mass as estimated by echocardiography, electrocardiography, and BNP measurements. Taken together, despite extensive investigation, the role of the *ACE* DD genotype in the development of cardiac hypertrophy is not settled, but *ACE* remains a promising candidate gene for modulating left ventricular mass.

CARDIAC REMODELING

A decrease of cardiac output, irrespective of the underlying condition, can result in the activation of neurohormonal systems. This adaptive mechanism may initially help to preserve the perfusion of vital

organ systems. However, the consecutive elevation of afterload in combination with direct growth promoting effects of neurohormones induces progressive structural alterations that result in further loss of cardiac function. This vicious circle has been termed cardiac remodeling and represents the final common pathway that eventually leads to terminal failure of the heart (25, 40). On the other hand, pharmacological blockade of neurohormonal systems, e.g. the use of ACE inhibitors or beta-adrenergic receptor blockers, offers the most valuable treatment option in congestive heart failure (Fig. 2).

The extent of myocardial damage may be the most significant predictor of cardiac remodeling (40). However, clinical experience teaches us that the occurrence of cardiac remodeling is difficult to anticipate. In fact, a relatively small myocardial infarction may be followed by adverse remodeling whereas severe hypertension sometimes is without perceivable effects on cardiac function. Thus, it may be hypothesized that genetics may modulate the manifestation or progression of cardiac remodeling. In fact, it seems plausible that genetic factors interact at several crucial stages of the vicious circle (Fig. 2).

Presently, there is no definitive evidence to prove this hypothesis. However, the *ACE* insertion/deletion polymorphism has been found to be related to cardiac remodeling in several populations (35, 41). For example, both the *ACE* DD genotype as well as higher ACE activity were associated with more pronounced ventricular dilatation after anterior myocardial infarction (41). Similarly, the *ACE* DD genotype has been related to increased ventricular dimensions and elevated mortality in patients with idiopathic dilated cardiomyopathy (2). The notion that genetics may affect the response to medication was questioned by a recent observation in subjects carrying the angiotensinogen 235T allele. These individuals were found to more often require a more intensive antihypertensive medication than carriers of the 235M allele (47).

Taken together, there is accumulating information proving a significant contribution of genetics to the intrinsic mechanisms that are responsible for the initiation and progress of congestive heart failure. However, it is also evident that genetic factors involved in heart failure are highly diverse. Future studies involving large numbers of affected individuals and advanced analytical methods will be required to precisely trace the molecular basis of this common disorder.

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