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Review

Are we ready for pharmacogenomics in heart failure?

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Abstract

Heart failure is a major health problem and is associated with a high mortality and morbidity. Recently, the role of the genetic background in the onset and development of the disease has been evidenced in both heart failure with and without systolic dysfunction, and in familial and non-familial forms of this condition. Familial forms of dilated cardiomyopathy are more frequent than previously thought. Various modes of inheritance and phenotypes have been reported and this condition appears genetically highly heterogenous. Five genes (dystrophin, cardiac actin, desmin, lamin A/C and delta-sarcoglycan), and additional loci, have been identified in families in which dilated cardiomyopathy is isolated or associated with other cardiac or non-cardiac symptoms. It has been postulated that the molecular defect involved could lead to abnormal interactions between cytoskeletal proteins, responsible either for defect in force transmission or for membrane disruption. More recently, the identification of mutations in genes encoding sarcomeric proteins has led to a second hypothesis in which the disease might also result from a force generation defect. In non-monogenic dilated cardiomyopathy, susceptibility genes (role in the development of the disease) and modifier genes (role in the evolution/prognosis of the disease) have so far been identified. Some data suggest that the efficacy of angiotensin converting enzyme inhibitors, and side-effects, might be related to some genetic polymorphisms, such as the I/D polymorphism of the angiotensin converting enzyme gene. Although preliminary, these data are promising and might be the first step towards application of phamacogenetics in heart failure. This is of paramount importance as the medical treatment of heart failure is characterized by the need for polypharmacy. One of the major challenges of the next millenium, therefore, will be to identify genetic factors which might help define responders to major treatment classes, including angiotensin converting enzyme inhibitors, β-adrenoreceptor antagonists, angiotensin AT_1 receptor antagonists, spironolactone, vasopeptidase inhibitors and endothelin receptor antagonists.

Keywords: Heart failure; Gene; Cardiomyopathy, dilated; Pharmacogenomics

Heart failure is a condition associated with a high morbidity and mortality and is the final pathway of many cardiovascular problems. Thus, the socioeconomic impact of this syndrome is important. Another characteristic is the need for polypharmacy, three or even more, different pharmacologic classes often being prescribed to a single patient. The understanding of factors associated with the development and progression of heart failure has evolved considerably during the past decade, and the potential role of genetic factors has been identified. Current knowledge of the genetics of familial and non-familial heart failure, and the impact of the unprecedented advance in the understanding of molecular defects on the rational approach to pharmacotherapy are reviewed here.

Patients considered here are usually affected by idiopathic dilated cardiomyopathy, a myocardial disease characterized by dilatation and impaired systolic function of one or both ventricles (International Society and Federation of Cardiology Task Force on the Definition and Classification of Cardiomyopathies, 1996). The prevalence of dilated cardiomyopathy has been estimated to be 36.5/100,000 in a population-based study in the USA (Olmsted County, MN) and the incidence rate is estimated to be 6/100,000 persons/year (Codd et al., 1989). Relatively similar results were found in other countries. The true prevalence is probably higher, however, since all available studies were retrospective and asymptomatic cases were therefore not identified and not taken into account. Some cases are familial cases but most cases are believed to be sporadic, and except for familial history, no

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phenotypic characteristics distinguish familial from non-familial cases (Michels et al., 1992).

1. Familial and monogenic forms of dilated cardiomyopathy

Familial forms of dilated cardiomyopathy had long been underestimated until prospective studies were performed. With such an approach, Michels et al. (1992) found that dilated cardiomyopathy was familial in at least 20% of cases (12 of 59 index patients). This was confirmed subsequently for other populations (familial forms, 20–56% of cases, depending on the studies) (Keeling et al.,1995; Grünig et al., 1998; Mestroni et al., 1999a,b). In addition, while the diagnosis of dilated cardiomyopathy is obvious in most cases, minor abnormalities are sometimes found in other cases. The most common mild abnormality in relatives is isolated left ventricle dilatation (9% in Michels et al., 1992, and 20% in Kamran Baig et al., 1998 and in Mangin et al., 1999). Interestingly, this abnormality might be an early marker of the disease, since in the study of Kamran Baig et al., 27% of subjects with this abnormality developed symptomatic dilated cardiomyopathy over an average 39-month follow-up period (Kamran Baig et al., 1998). Because of the broad-spectrum of the disease (clinical situations with mild abnormalities or with other cardiac or non-cardiac abnormalities), and because there was no consensus as to diagnostic criteria, guidelines with new criteria were recently proposed for the study of familial dilated cardiomyopathy (Mestroni et al., 1999a,b). The penetrance of the disease (percentage of subjects who express the disease among carriers of the mutations) is incomplete in most familial studies, and also appears to be influenced by age and sex (Mangin et al., 1999).

Familial dilated cardiomyopathy is a very heterogenous disorder, as suggested by the different patterns of inheritance, the different phenotypes (clinical expression of the disease) and the different genes or loci identified.

Based on the analysis of pedigrees, *different patterns of inheritance* are described: autosomal dominant inheritance prevails (Michels et al., 1992; Mangin et al. 1999; Mestroni et al., 1999a,b) but autosomal recessive forms are described (Zachara et al., 1993), as well as X-linked forms (Beggs, 1997; Towbin, 1998), mitochondrial forms characterized by a matrilineal transmission (Remes et al., 1994; DiMauro and Hirano, 1998) and unclassified forms. In studies by Mestroni et al. (1999a,b), percentages were 64%, 16%, 10%, 0% and 10%, respectively. In another study, X-linked dilated cardiomyopathy represented about 6.5% of the cases (Arbustini et al., 2000).

Based on clinical evaluation, *different phenotypes* can be observed. Isolated dilated cardiomyopathy is the most frequent, but other cardiac or non-cardiac abnormalities are sometimes described. In some families, an atrioventricular conduction defect and/or sinus bradycardia and/or supraventricular arrhythmia were observed, usually before the onset of left ventricular dysfunction. In other families, mitral valve prolapse, or sensorineural hearing loss, or skeletal myopathy with various types of muscular dystrophy were present. Elevation of plasma creatine kinase is most often found in X-linked dilated cardiomyopathy or when skeletal myopathy is present.

Based on molecular genetics, five *genes* have been identified as responsible for familial dilated cardiomyopathy, and nine other loci are described as responsible for autosomal dominant transmitted dilated cardiomyopathy (Table 1).

- In isolated and autosomal dominant inherited dilated cardiomyopathy, three genes, cardiac actin (Olson et al., 1998), desmin (Li et al., 1999), and delta-sarcoglycan (Tsubata et al., 2000); and five chromosomal loci have been identified (1q32; 2q31; 2q14–q22; 6q12–q16 and 9q13–22) (Krajinovic et al., 1995; Durand et al., 1995; Siu et al., 1999; Jung et al., 1999; Sylvius et al., 2001).

Table 1
Genetics of familial DCM

Transmission	Locus	Gene	Reference
Autosomal dominant	1q32	?	Durand et al., 1995
	2q31	?	Siu et al., 1999
	2q14–q22	?	Jung et al., 1999
	2q35	desmin	Li et al., 1999
	5q33–34	δ-sarcoglycan	Tsubata et al., 2000
	6q12–q16	?	Sylvius et al., 2001
	9q13–22	?	Krajinovic et al., 1995
	15q14	cardiac actin	Olson et al., 1998
+ mitral valve prolapse	10q21–23	?	Bowles et al., 1996
+ conduction defect/arrhythmias	1p1–q1	lamin A/C	Fatkin et al., 1999
	3p22–25	?	Olson and Keating, 1996
+ muscular dystrophy	6q23	?	Messina et al., 1997
+ hearing loss	6q23–24	?	Schönberger et al., 2000
Autosomal recessive	?	?	
X-linked	Xp21	dystrophin	Muntoni et al., 1993

· Dilated cardiomyopathy with conduction defects and arrhythmias with an autosomal dominant pattern have been associated with one gene, lamin A/C, and one locus (3p22) (Fatkin et al., 1999; Olson and Keating, 1996).

· An autosomal dominant form of dilated cardiomyopathy with mitral valve prolapse has been associated with a locus on chromosome 10q21–23 (Bowles et al., 1996).

· An autosomal dominant variety of dilated cardiomyopathy associated with conduction disorders and myopathy has been linked to chromosome 6q23 (Messina et al., 1997).

· An autosomal dominant form of dilated cardiomyopathy associated with sensorineural hearing loss was described on chromosome 6q23–24 (Schonberger et al., 2000).

· Autosomal recessive forms of the disease have occasionally been reported and no location has been published (for isolated dilated cardiomyopathy).

· Dilated cardiomyopathy linked to chromosome X is related to mutations in the dystrophin gene (Beggs, 1997; Towbin, 1998; Muntoni et al., 1993; Ortiz-Lopez et al., 1997; Melis et al., 1998).

· Large deletions of mitochondrial DNA have been associated with dilated cardiomyopathy, however, the alterations of mitochondrial DNA have been reported for many other diseases, thus the causal role of these genetic alterations is not definitely established (Remes et al., 1994; DiMauro and Hirano, 1998).

The first gene responsible for dilated cardiomyopathy was identified in 1993, *the dystrophin gene*, as responsible for X-linked dilated cardiomyopathy (Muntoni et al., 1993). Numerous reports with other different mutations in this gene were subsequently published (review in Beggs, 1997; Towbin, 1998). The genetically affected individuals usually develop a severe form of dilated cardiomyopathy at adolescence or in young adulthood. Although no skeletal muscle involvement is evident (in contrast with Duchenne or Becker muscular dystrophy, where the dystrophin gene is also involved), plasma creatine kinase levels are usually high. DNA alterations involved in the dystrophin gene are located (i) in the muscular promotor-first, muscular exon-first intron regions. These alterations consist of deletions or of a point mutation in the splice consensus site of the first intron. They result in absence of the protein in the cardiac muscle, whereas dystrophin expression is preserved or slightly reduced in skeletal muscle; (ii) in exons 2–7, 9, 45–49, 48–49, 49–51 where other genetic alterations have been identified (deletions, duplication, missense mutations). Dystrophin is a large (427 kDa) cytoskeletal protein that localizes to the inner fangiotensin converting enzyme of the plasma membrane or sarcolemma (Beggs, 1997). Through the amino-terminal actin-binding domain, dystrophin is related with F-actin and the sarcomere. The carboxy-terminal domain is associated with a large transmembrane complex of glycoproteins, termed the dystrophin associated glycoprotein complex (DAG) complex. In this manner, dystrophin is believed to play a critical role in establishing connections between the internal cytoskeleton and/or the sarcomeric structure and the external basement membrane. The absence of dystrophin leads to a disruption of the DAG complex, a loss of integrity of the plasmalemma, and fiber necrosis.

The cardiac actin gene was the first gene identified as responsible for the autosomal dominant form of dilated cardiomyopathy (Olson et al., 1998). Two missense mutations (Arg312His and Glu361Gly) were identified in exons 5 and 6 of the gene in two unrelated small families with isolated dilated cardiomyopathy. Both mutations affect universally conserved amino acids in the domain of actin that attach to Z bands and intercalated discs. Moreover, the Glu361Gly substitution is within a common binding domain for actinin, a protein comprising Z bands and intercalated disc and dystrophin (Olson et al., 1998). This gene, however, seldom appears to be involved in dilated cardiomyopathy since several populations were subsequently screened for mutations in this gene and no other mutations were found: 44 probands recorded in the USA (Li et al., 1999), 30 Japanese familial dilated cardiomyopathy patients and 106 Japanese sporadic cases (Takai et al., 1999), 11 patients belonging to eight families and 46 sporadic cases of mostly black African origin (Mayosi et al., 1999), and in our own experience of 43 probands of familial forms and 43 sporadic cases of European origin (Tesson et al., 2000).

The desmin gene was also identified as responsible for the autosomal dominant inherited form of dilated cardiomyopathy (Li et al., 1999). A missense mutation in exon 8, Ile451Met, was characterized in a family with isolated dilated cardiomyopathy without evidence of skeletal muscle abnormalities (and plasma creatine kinase was normal). The mutation was found in this family in the two patients and in two clinically healthy subjects. The mutation is located in the desmin tail domain, the function of which remains unknown. Desmin is the chief intermediate filament of skeletal and cardiac muscle (Goebel, 1997). It functions as a cytoskeletal protein linking Z bands to the plasma membrane and nuclear membrane, and it maintains the structural and functional integrity of the myofibrils. This gene is probably uncommon in dilated cardiomyopathy since only one proband among 40 had a mutation in the study of Li et al. (1999) and we found no mutations in 41 probands of familial dilated cardiomyopathy and 22 sporadic cases (Tesson et al., 2000). In addition, clinicians should be aware that the desmin gene was also identified as responsible for restrictive cardiomyopathy in several families (Dalakas et al., 2000).

The lamin A/C gene was identified as responsible for the autosomal dominant form of dilated cardiomyopathy associated with a particular phenotype. Fatkin et al. (1999) screened 11 families with dilated cardiomyopathy associated with atrioventricular conduction defect and/or sinus bradycardia, and/or supraventricular arrhythmia. No

skeletal myopathy was observed and plasma creatine kinase was normal in most patients and mildly elevated in some. Interestingly, 54% of clinically affected subjects had pangiotensin converting enzyme makers. A mutation in the lamin A/C gene was found in five families. There were five missense mutations, four in the alpha-helical rod domain of the lamin A/C gene and one in the lamin C tail domain. It is noteworthy that this gene is also responsible for two skeletal myopathies: Emery–Dreifuss (Bonne et al., 1999) and limb-girdle muscular dystrophy (Muchir et al., 2000). Lamin A and C are components of the nuclear envelope and are located in the lamina, a multimeric structure associated with the nucleoplasmic surfangiotensin converting enzyme of the inner nuclear membrane (Fatkin et al., 1999). Lamin contributes to the structural integrity of the nuclear envelope and provides mechanical support for the nucleus. Missense mutations may alter interactions with cytoplasmic proteins (in particular, intermediate filaments of cytoskeleton) but this has not yet been demonstrated. A mutation in this gene (T959 deletion) was also found in a family (five subjects) with both dilated cardiomyopathy and skeletal myopathy (mild Emery–Dreiffus or limb-girdle muscular dystrophy, plasma creatine kinase were elevated in three among five subjects) (Brodsky et al., 2000).

More recently, the *delta-sarcoglycan gene* was also demonstrated to be responsible for dilated cardiomyopathy. In one family with autosomal dominant mode of inheritance, a Ser151Ala mutation was found in three patients with isolated dilated cardiomyopathy at a young age (Tsubata et al., 2000). Neuromuscular examination was normal and creatine kinase was normal in all patients except one. A mutation (Δ 238 lysine) was also found in two sporadic cases (they were de novo mutation). Delta-sarcoglycan is a component of the DAG and serves as a link between cytoplasmic actin, the membrane and the extrangiotensin converting enzyme cellular matrix of myocytes via laminin-alpha2.

Other chromosomal loci have been characterized (see Table 1), including the locus on chromosome 6q12–q16 reported by our group (Sylvius et al., 2001), and responsible genes remain to be identified. Of course, dilated cardiomyopathy can be observed in other familial syndromes or diseases such as Duchenne or Becker myopathies, limb-girdle muscular dystrophy, Emery–Dreifuss myopathy, Barth syndrome, non-compacted myocardium, etc.

How do these genetic defects result in dilated cardiomyopathy? No functional studies are yet available to allow an understanding of the precise functional abnormalities that lead a mutation to cause the disease. Only speculations can be offered (Graham and Owens, 1999). Dystrophin, and delta-sarcoglycan, are cytoskeletal proteins that interact with both the plasma membrane or sarcolemma and with the sarcomere (through actinin) near the Z band. The actin mutations result in amino acid modifications located in domains of the protein which are immobilized and attached to the Z band or intercalated disc, and thus, are involved with the transmission of contractile force (from one sarcomere to the other, or from one myocyte to the neighbouring ones) rather than affecting the myosin cross-bridges and the generation force (Olson et al., 1998). Similarly, desmin attaches to the sarcomere Z band, the nuclear membrane, and is known to serve as a means of transmission of force and other signals (Li et al., 1999). The interactions between lamin A/C and other proteins of the cytoskeleton are largely unknown and the role of this nuclear membrane component is more intriguing. The current working hypothesis is that the common molecular basis of genetic defects in dilated cardiomyopathy is related to abnormal interactions between cytoskeletal proteins (especially between plasma membrane, sarcomere near the Z band and nuclear membrane), responsible either for a defect in force transmission or for membrane disruption, resulting in cellular death. Interestingly, mutations in sarcomeric protein genes (beta-myosin heavy chain and cardiac troponin T) were recently found in four kindred (Kamisago et al., 2000). This suggests that another mechanism, namely defect of force generation, might also be involved in the pathogenesis of dilated cardiomyopathy.

2. Genetic factors for left ventricular dimensions and function in the general population

In the general population, studies performed in monozygotic and dizygotic twins do not suggest a significant genetic component for left ventricular dimensions (except for left ventricular mass), or for systolic function at rest (Bielen et al., 1991). However, some data indicate that during exercise tests, there is a significant genetic component for the increase of end-diastolic left ventricular dimensions, or of fractional shortening and for the maximal oxygen uptake (Bielen et al., 1991; Fagard et al., 1987). The specific effect of some genetic polymorphisms was analyzed and an association was found by Kupari et al. (in a population of 84 Finnish subjects) between a polymorphism (−344 C/T) in the aldosterone synthase gene (CYP11B2) and left ventricular diameters, mass and diastolic function (Kupari et al., 1998). However, the association was not confirmed by the study of Schunkert et al. (1999) in two different white populations of the MONICA project (1445 and 562 subjects).

3. Genetic factors for non-monogenic forms of systolic dysfunction

In idiopathic heart failure, most cases are sporadic and the disease is considered to be multifactorial with a possible genetic component. Some studies were therefore conducted to identify genetic factors involved in such cases. These factors are either susceptibility genes, factors in-

Table 2
Susceptibility genes for DCM

Gene	Polymorphism	Odds ratio (CI 95%)	Reference
PAF acetyl hydrolase	G994T	1.9 (1.3–2.9)	Ichihara et al., 1998
SOD 2	Val16Ala	2.3 (1.27–3.33)	Hiroi et al., 1999
HLA-DR	DRB1* 1401	3.46 (1.99–4.93)	Hiroi et al., 1999
ETA receptor	exon 8 + 1363 C/T	1.9 (1.2–3.0)	Charron et al., 1999

volved in the pathophysiology of the disease and which influence the emergence of the disease, either modifier genes, factors modifying the expressivity of the disease, and which influence the degree or the evolution of the disease once it has appeared.

3.1. Susceptibility genes

In this situation, the usual strategy is to look for an association between the disease and genetic markers of potential candidate genes, in case–control studies. The frequencies of alleles and genotypes in cases and in controls are compared to search for a significant difference (Table 2). The first studies analyzed the possible involvement of the I/D angiotensin converting enzyme gene polymorphism. Rigat et al. (1990) described a genetic polymorphism in intron 16 of the angiotensin converting enzyme gene, characterized by insertion (I) or deletion (D) of a 287 bp sequence. This angiotensin converting enzyme I/D polymorphism is strongly related to angiotensin converting enzyme plasma level (it accounts for nearly half of the plasma level variability) and myocardial concentration. Whether or not the angiotensin converting enzyme I/D polymorphism itself has a functional role, or is only a marker in linkage disequilibrium with a functional variant, remains debatable. In non-familial dilated cardiomyopathy, Raynolds et al. (1993) found an association between the D/D genotype of this polymorphism and the disease (frequency of the D/D allele: 35.7% in patients vs. 24% in controls, $p = 0.008$) in a small population (112 cases and 79 controls). However, five subsequent studies found a lack of association between I/D angiotensin converting enzyme polymorphism and the disease (Montgomery et al., 1995). These conflicting results may be the consequence of insufficient sample size and/or of bias in recruitment of patients or controls. To avoid these limitations, a national collaboration was established in France which allowed the collection of 433 patients (of European origin) with idiopathic dilated cardiomyopathy matched with 400 control subjects from the MONICA registry (the Cardigene network). No association was found in this study between the disease and the I/D angiotensin converting enzyme polymorphism (Tiret et al., 2000), or other polymorphisms of the renin–angiotensin–aldosterone system, the β_1-adrenorecepetor, tumor necrosis factor alpha, transforming growth factor beta1, nitric oxide synthase 3 and brain natriuretic peptide genes (Tiret et al., 2000; Tesson et al., 1999). In contrast, a polymorphism in the endothelin type A receptor (ETA) gene (+1363 C/T in exon 8) was associated with the disease in the Cardigene study. Since homozygotes for the T allele were at significantly increased risk for the disease (OR 1.9; 95% CI: 1.2–3.01) (Charron et al., 1999). It was the first genetic risk factor for heart failure identified in a Caucasian population. In Japanese populations, polymorphisms in genes involved in the defense against oxidative stress were identified as risk factors for the disease: the platelet-activating factor (PAF) angiotensin converting enzyme tylhydrolase gene (G/T 994 polymorphism; OR 1.9; 95% CI: 1.3–2.9; population: 112 cases and 226 controls) and the manganese superoxide dismutase (SOD 2) gene (Ala16Val polymorphism; OR 2.3; 95% CI: 1.23–3.33; population: 86 cases and 380 controls) (Ichihara et al., 1998; Hiroi et al., 1999). In this latter study, an association was also found between the disease and a human leucocyte antigene (HLA) polymorphism (HLA DRB1* 1401; OR 3.46; 95% CI: 1.99–4.93).

3.2. Modifier genes

The strategy here is to compare the severity of the disease in patients according to genotypes of a polymorphism in a candidate-gene. Kaplan–Meier cumulative survival curves are therefore usually constructed to evaluate the prognosis of patients according to genotypes (Table 3).

Table 3
Modifier genes in DCM

Gene	Variant	Survival rate	Reference
ACE	Ins/Del	49% vs. 72% at 5 years	Andersson and Sylven, 1996
Beta 2 adrenoreceptor	Ile164Thr	42% vs. 76% at 1 years	Liggett et al., 1998
AMPD1	non-sense mutation	7.6 vs. 3.2 years before HT	Loh et al., 1999
Beta 1 adrenoreceptor	Ser49Gly	46% vs. 23% vs. 20% at 5 years	Börjesson et al., 2000

The I/D polymorphism of the angiotensin converting enzyme gene was studied by Andersson and Sylven (1996) who found that long-term survival at 5 years was significantly worse in patients with the D/D genotype than in others (49% vs. 72%; OR 1.69; 95% CI: 1.01–2.82) in a population of 199 patients with idiopathic congestive heart failure. This result was different from that published by Montgomery et al. (1995) but the population was small (99 patients) and the follow-up was only 28 months in the latter study. More recently, two other genes were studied. The Thr164Ile polymorphism in the β_2-adrenoreceptor (AR) gene was associated with the prognosis of patients ($n = 259$) with congestive heart failure due to ischemic or idiopathic dilated cardiomyopathy (Liggett et al., 1998). The survival rate at 1 year was only 42% for patients with Ile164 genotype vs. 76% for others ($P = 0.019$). A nonsense mutation in the adenosine monophosphate deaminase 1 (AMPD1) gene was studied in a population of 132 patients with advanced heart failure (ischemic or idiopathic origin) referred for cardiac transplantation (Loh et al., 1999). The mutant AMPD1 allele was associated with a longer duration of heart failure symptoms before referral for transplantation evaluation (7.6 ± 6.5 years vs. 3.2 ± 3.6 years; $p < 0.001$). Finally, a polymorphism (Ser49Gly) in the beta1-adrenoreceptor gene was recently associated with survival in patients with apparently idiopathic heart failure (increased risk of death with the wild allele; OR 2.34, 95% CI: 1.30–4.20) (Börjesson et al., 2000).

All these findings, therefore suggest that the genetic background may influence the development and/or the progression of heart failure. However, in most studies, sample size was limited and the results should be considered as preliminary. There is obviously a need for such an approach in large and well-defined populations. The identification of genetic factors predisposing to heart failure is, therefore a major challenge for the next decade.

4. Towards pharmacogenomics

4.1. Genetic polymorphisms of the metabolism of drugs used in heart failure

The genetic determinants of the metabolism of certain drugs used in cardiology is one predictable cause of variability in their pharmacokinetics and effects. The main genetic polymorphisms of these drugs are polymorphisms of N angiotensin converting enzyme tylation and the cytochrome *P*-450 isozymes. Genetic polymorphisms are usually characterized by several metabolic phenotypes, two in most cases, which allow a distinction between fast and slow metabolisers (Funck-Brentano, 1991). For a given drug and a given metabolic pathway, slow metabolisers are unable to eliminate the parent product through hepatic metabolism, leading to plasma concentrations of the parent product which are several times higher than those observed in fast metabolisers. The pharmacodynamic consequences depend on the therapeutic index of the drug and on the activity of the metabolites. One example is the management of azathioprine given after heart transplantation. The drug is catabolized by thiopurine methyltransferase, which exhibits a genetic polymorphism (Schutz et al., 1996). According to the enzyme phenotype, the 6-thioguanine nucleotide could be very different, and thus, monitoring of this enzyme may contribute to the safer management of immunosuppressive therapy with azathioprine.

4.2. Genetic polymorphisms of the renin–angiotensin–aldosterone system

In ischemic heart disease, the influence of the I/D polymorphism of the angiotensin converting enzyme gene on the remodelling process, a key issue for the development and progression of heart failure, was demonstrated in the CATS study ($n = 96$ patients) (Pinto et al., 1995): left ventricular dilatation following an anterior myocardial infarction was significantly greater after 1 year of follow-up in subjects with the D/D genotype than in the other patients. Interestingly, the cardiac dilatation was blunted by angiotensin converting enzyme inhibitors in the D/D genotype group, suggesting that the effect of angiotensin converting enzyme inhibitors was particularly important for D/D genotype patients.

Two other studies suggest that the "renin profiling" may be useful for therapy with angiotensin converting enzyme inhibitors. Lim et al. (2000) analyzed the effect of angiotensin converting enzyme inhibitors on the neurohormone concentrations according to the plasma renin activity in 38 patients with chronic heart failure. At baseline, one third of the patients had low plasma renin activity, another third had normal activity, and the last third had high activity. The groups with low and normal plasma renin activity had lower concentrations of angiotensin II and aldosterone than the third group with high plasma renin activity. However, in patients treated with angiotensin converting enzyme inhibitors, the concentrations of neurohormones were equal in the three groups. This finding suggests that the efficacy of angiotensin converting enzyme inhibitors might be low in patients with normal or low plasma renin activity (Willenheimer and Swedberg, 2000). Conversely, patients with high plasma renin activity at baseline might benefit from high doses of angiotensin converting enzyme inhibitors. Data reported by O'Toole et al. also suggest that the I/D polymorphism is associated with responsiveness to angiotensin converting enzyme inhibitors. The influence of this polymorphism on the response to angiotensin converting enzyme inhibitors (blood pressure and renal function) was studied in 34 subjects with heart failure (O'Toole et al., 1998). There was a significant relation between angiotensin converting enzyme genotype and change in mean arterial pressure ($p = 0.02$) with captopril, but not with lisinopril.

Recently, the influence of the I/D polymorphism on the outcome of heart failure patients was studied in a group of 328 patients with systolic dysfunction. In the whole cohort, the D/D genotype was associated with an increased risk of death or cardiac transplant during follow-up (relative risk 1.80; $p = 0.04$) (McNamara et al., 2000). Interestingly, this effect was particularly increased in patients not treated with beta-blockers on study entry, and was not seen in those on therapy, therefore suggesting a potential pharmacogenetic interaction between the angiotensin converting enzyme I/D polymorphism and beta-blockers on the outcome.

Not only the efficacy, but also side-effects of angiotensin converting enzyme inhibitors, might be related to genetic polymorphisms. Mukae et al. (2000) recently demonstrated that a bradykinin B2 receptor gene polymorphism (−58 T/C) was associated with angiotensin converting enzyme inhibitor-related cough. The TT genotype was significantly higher in subjects with cough than in those without ($n = 30$ and 30 subjects, $p = 0.001$). This genetic variation might, therefore be an effective predictor of angiotensin converting enzyme inhibitor-related cough.

4.3. Genetic polymorphisms of the β-adrenoreceptors

β_1- and β_2-adrenergic receptors are G protein-coupled receptors for the catecholamines, epinephrine and norepinephrine. Coding and promoter polymorphisms of these receptors have been identified in the general population by the authors and others (Tesson et al., 1999; Ligett, 2000). These have been mimicked in transfected cell systems and transgenic mice, and show altered expression, ligand binding, coupling or regulation phenotypes (review in Ligett, 2000). Clinical studies of asthma have revealed that some of these polymorphisms have a significant disease modifying effect or alter the response to treatment. These remain to be studied in heart failure.

Recently, the influence of the Arg389Gly β_1-adrenoreceptor gene polymorphism was studied in a group of 297 patients with heart failure (Wagoner et al., 2000). The variant was associated with significant differences in exercise capacity (peak V02 and exercise time).

Finally, the results of the BEST study, which tested the influence of the non-selective β-blocker, bucindolol, in chronic heart failure, pointed to the role of genetic background on the response to β-blockers under these conditions. The trial was prematurely terminated on recommendation of the Data Safety Monitoring Board due to an overall lack of efficacy. However, predefined subgroup analyses revealed that there was an increased risk of mortality in the black population. Although ethnic origin is a crude method for identifying genetic factors that might influence the outcome under a given therapy, this is one of the first examples of potential genetic interactions with treatment in this syndrome. Interestingly, the Gly389 β_1-adrenoreceptor variant has been reported, with an increased incidence in the Afro–American population as compared to non-African. It is therefore possible that variants in the genes encoding the β-adrenergic system play a role in this unexpected unfavourable outcome.

5. Conclusion

Obviously, the genetic approach to heart failure is only starting and published results are preliminary. However, the analysis of the genetic aspects of heart failure appears promising and various DNA banks are currently being set up on national or international bases. Identification of the genetic alterations involved in either familial or non-familial heart failure should unravel the molecular mechanisms that lead from left ventricular dysfunction to overt heart failure, and allow the identification of patients at risk of developing heart failure. Other potentially promising perspectives are the early management of subjects at risk in order to prevent the progression of the disease and the targeting of therapy based on individual molecular defects. The identification of potential subgroups of patients' responders to the various pharmacological interventions available to date is a major issue for the third millenium and should lead to the development of cardiovascular pharmacogenetics. The need for large populations is crucial in order to avoid the identification of polymorphisms in biased or selected subgroups of patients.

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