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Clinical research

α_{2C}-Adrenoceptor polymorphism is associated with improved event-free survival in patients with dilated cardiomyopathy

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Aims The sympathetic nervous system plays a central role in cardiac growth but its overstimulation is associated with increased mortality in patients with chronic heart failure. Pre-synaptic α_2-adrenoceptors are essential feedback regulators to control the release of norepinephrine from sympathetic nerves. In this study we tested whether a deletion polymorphism in the human α_{2C}-adrenoceptor gene (α_{2C}Del322–325) affects progression of heart failure in patients with dilated cardiomyopathy (DCM).

Methods and results We genotyped and phenotyped 345 patients presenting with DCM in the heart transplant unit of the German Heart Institute, starting in 1994. Patients were treated according to guidelines (99% ACEI, 76% β-blockers) and were followed until December 2002 or until a first event [death, heart transplantation, or implantation of a left ventricular assist device (LVAD) for a life-threatening condition] occurred. Mean follow-up time was 249 weeks (4.9 years) in event-free patients and 104 weeks (2 years) in patients with events. During follow-up, 51% of the patients exhibited an event: death (18%), implantation of LVAD as bridging for transplantation (7%), or heart transplantation (25%). By Kaplan–Meier analysis, DCM patients with the deletion variant Del322–325 in the α_{2C}-adrenoceptor showed significantly decreased event rates ($P = 0.0043$). Cox regression analysis revealed that the presence of the deletion was associated with reduced death rate (relative risk: 0.129, 95% CI: 0.18–0.9441, $P = 0.044$) and event rates (relative risk: 0.167, 95% CI: 0.041–0.685, $P = 0.012$).

Conclusion α_{2C}-Adrenoceptor deletion may be a novel, strong, and independent predictor of reduced event rates in DCM patients treated according to guidelines.

Introduction

Activation of the sympathetic nervous system is an essential mechanism to adapt cardiac function to increased demand. However, in patients with chronic heart failure, sympathetic overactivity is associated with accelerated disease progression and increased morbidity and mortality.[1,2] β-Adrenoceptor antagonists exert a beneficial long-term effect on the survival of patients with congestive heart failure.[3–5]

The activity of the sympathetic system is controlled by inhibitory pre-synaptic α_2-adrenoceptors.[6] They are involved in the inhibition of neurotransmitter release, regulation of blood pressure, regulation of insulin release and lipolysis, and a broad spectrum of other physiological functions.[7,8] Molecular cloning has led to the identification of the three α_2-adrenoceptor subtypes, α_{2A}, α_{2B}, and α_{2C}.[9] Two of these receptors, α_{2A} and α_{2C}, predominantly control norepinephrine release from sympathetic nerves as shown by studies in gene-targeted mice.[7] Several functional differences were identified between pre-synaptic α_{2A}- and α_{2C}-receptor subtypes.[7,10] In mouse atria, the α_{2A}-subtype inhibited norepinephrine release at high stimulation frequencies, whereas the α_{2C}-receptor operated at lower levels of sympathetic nerve activity.[7] In addition, α_{2C}-adrenoceptors are required as feedback regulators of catecholamines in adrenal chromaffine cells.[11]

The α-adrenergic receptors in the myocardium are required for physiological cardiac growth processes and have been shown to transmit growth signals in double-knockout mice.[12] In addition, they contribute to feedback control of sympathetic transmitter release and their deletion causes increased circulating catecholamine levels, which will lead to increased β-adrenergic stimulation,

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development of cardiac hypertrophy and fibrosis, and increased mortality from heart failure after left ventricular pressure overload.[13] The clinical relevance of these findings was highlighted by the identification of a four-amino acid deletion polymorphism of the human α_{2C}-adrenoceptor (α_{2C}Del322–325), which was associated with decreased G-protein-coupling of this receptor variant.[14] Human beings carrying this mutation may be more prone to sympathetic overstimulation than people with the fully functional α_{2C}-adrenoceptors if β-adrenergic receptors are unblocked. However, in the presence of β-blockade, the effects of α-adrenoceptors on myocardial growth may dominate. The present study was undertaken to determine the effect of the α_{2C}Del322–325 variant on mortality and event-free survival in a cohort of patients with dilated cardiomyopathy (DCM) treated according to present guidelines, including a high percentage of β-blockade and use of antibradycardiac and antitachycardiac pacemakers in almost half of the patients.

Methods

Patients

Patients were recruited from the transplant unit of the German Heart Institute from April 1994 until August 1999 through the enrolment of all eligible patients who gave informed consent. Criteria for enrolment were an age of 20–79 years and a diagnosis of DCM. All patients had been referred to the transplant unit for evaluation for heart transplantation. All patients had undergone cardiac catheterization, and diagnosis of DCM was based on exclusion of significant coronary artery disease, primary hypertensive heart disease, primary valvular disease, hypertrophic obstructive and non-obstructive cardiomyopathy, and myocarditis. All patients were accepted for transplantation and they were treated according to guidelines, including the use of ACE-inhibitors, β-blockers whenever possible, and AICD-implantation in the case of malignant arrhythmia. Exercise testing with measurement of cardiopulmonary function by oxygen uptake (spiroergometry) was introduced as a routine procedure in 1998; therefore, data are only available in a subgroup ($n = 18$). Patients were followed up in 3 or 6 month intervals in the transplant unit up until December 2002 or until one of the following endpoints occurred: heart transplantation, death, or implantation of LVAD. Listing with normal or high priority for transplantation was made according to the clinical condition. Implantation of an LVAD was used as bridging to transplantation if the patient's condition was judged to be deteriorating in an acutely life-threatening manner and a donor organ was not available. All patients gave informed written consent for genotyping. The rules of WHO were followed throughout the study.

Statistics

The SPSS program (version 11.5) was used for statistical analysis. Categorical data were compared by χ^2 testing. Survival was analysed using Kaplan–Meier curves and tested by the log-rank test. To test for confounding factors, we also performed Cox regression analysis. We included in the Cox regression models the α_{2C} polymorphism a priori and factors known to have an influence on the endpoint death or the combined endpoint death/LVAD implantation/heart transplantation (age, age at diagnosis of cardiac disease, gender, body mass index, blood pressure, NYHA classification, ejection fraction measured by echocardiography, and presence of malignant ventricular arrhythmia).

Besides all cause mortality, we used the combined endpoint (death/LVAD implantation/heart transplantation), because the occurrence of death was assumed to be frequently prevented by LVAD or urgent transplantation. The combined endpoint thus better describes the occurrence of end-stage cardiac disease.

Results

Characterization of patients

A total of 345 patients were included in this study. Characterization of the patients is shown in *Tables 1–3*:

Table 1 Baseline characteristics of the study population at study entry

Characteristic	All patients	Surviving patients without events	Patients with event (death, HTx, LVAD)	*P*
n (male/female)	345 (288/57)	170 (144/26)	175 (144/31)	
Mean follow-up (weeks)	178.0 ± 144.0	249.0 ± 145.7	104.3 ± 99.0	<0.05
Age at onset of disease (years)	45.3 ± 10.0	44.1 ± 10.9	46.4 ± 8.9	0.023
Age at study entry (years)	48.7 ± 10.2	47.1 ± 11.1	50.3 ± 9.0	0.02
Age at event (years)	51.4 ± 10.4	–	51.4 ± 10.4	
NYHA class	2.4 ± 0.7	2.2 ± 0.70	2.7 ± 0.70	<0.001
Heart transplantation (*n*)		0	63	
LVAD (*n*)		0	25	
Death (*n*)		0	87	
BMI (kg/sqm)	26.4 ± 3.8	26.7 ± 4.0	26.0 ± 3.7	n.s.
LVEDD (mm)	71.9 ± 9.1	69.7 ± 9.2	74.2 ± 8.3	<0.001
LVEF (%)	23.1 ± 7.1	25.3 ± 7.9	21.04 ± 5.6	<0.001
BP sys (mmHg)	122.3 ± 19.9	126.6 ± 20.6	117.2 ± 17.8	<0.001
BP dia (mmHg)	75.7 ± 12.6	77.0 ± 13.4	74.1 ± 11.5	n.s.
HR (b/min)	86.0 ± 17	83.8 ± 16.6	87.8 ± 17.7	0.023
PAPm (mmHg)	29.5 ± 11.9	27.0 ± 12.0	31.9 ± 11.4	<0.001
β-AR autoantibodies (U/L)	3.8 ± 2.3	3.6 ± 2.4	4.0 ± 2.2	n.s.
Sinus rhythm (*n*, %)	244 (70.7)	126 (74.1)	118 (67.4)	n.s.
Malignant ventricular arrhythmia (*n*, %)	130 (37.7)	56 (32.9)	74 (42.3)	0.017

Data are mean ± SD. β-AR, β-adrenoreceptor; BP, blood pressure; HR, heart rate; PAPm, pulmonary artery pressure mean.

Table 2 Basic demographics and selected clinical data at study entry

Characteristic	All patients	Patients without α_{2C}-adrenoceptor deletion	Patients with α_{2C}-adrenoceptor deletion	*P*
n (male/female)	345 (288/57)	320 (267/53)	25 (21/4)	0.91
Age at onset of cardiac disease (years)	45.3 ± 10.0	45.6 ± 9.8	41.5 ± 11.44	0.97
Age at study entry (years)	48.7 ± 10.2	49.047 ± 9.9324	44.615 ± 12.8073	0.103
NYHA class	2.4 ± 0.7	2.23 ± 0.718	2.23 ± 0.69	0.642
VO_2 max[a] (maximal oxygen uptake/ min × kg BW) (number of patients)	15.49 ± 4.974	15.1 ± 4.8 ($n = 111$)	21.6 ± 3.8 ($n = 7$)	0.003
Slope[b] (ventilation (L/min)/exhaled CO_2 (L/min)) (number of patients)	35.37 ± 9.569	35.8 ± 9.8 (96)	29.6 ± 2.8 (7)	0.001
BMI (kg/sqm)	26.4 ± 3.8	26.4 ± 3.9	25.4 ± 3.4	0.141
LVEDD (mm)	71.9 ± 9.1	72.08 ± 9.013	70.44 ± 10.296	0.446
LVEF (%)	23.1 ± 7.1	22.9 ± 7.0	25.5 ± 8.4	0.169
BP sys (mmHg)	122.3 ± 19.9	121.72 ± 19.855	128.80 ± 19.109	0.097
BP dia (mmHg)	75.7 ± 12.6	75.45 ± 12.331	79.20 ± 15.389	0.245
Malignant ventricular arrhythmia (n, %)	113 (32.7)	109 (34.1)	4 (16)	0.064

Continuous data are given as mean ± SD.

98.26% patients were Caucasians of central European origin and the remaining six were of Turkish origin; 16.5% were women. Patients exhibited severely impaired systolic cardiac function, as indicated by reduced left ventricular ejection fraction (LVEF) and ventricular dilatation (LVEDD), and increased pulmonary artery pressure (*Table 1*). Malignant ventricular arrhythmia defined as non-sustained or sustained VT or ventricular fibrillation was identified by 24-h ECG in about one-third of the patients.

Mean follow-up was 249 weeks (4.9 years) in event-free patients and 104 weeks (2 years) in patients with events. During follow-up, 51% of patients exhibited an event: death (18%), heart transplantation (25%), or implantation of LVAD as bridging to transplantation (7%) (*Table 1*).

Comparison of patients by genotype indicated that differences between deletion carriers (α_{2C}Del322–325) and patients without deletion existed in cardiopulmonary function measured by spiroergometry (*Table 2*). In a subgroup that was studied by spiroergometry, deletion carriers had a significantly higher oxygen uptake and greater ventilatory efficiency (lower slope of the ratio ventilation/VCO_2), indicating better cardiopulmonary function. In this subgroup, all other clinical parameters, including EF and LVEDD, did not differ significantly between α_{2C}Del322–325 carriers and wild types (data not shown).

Medical treatment and use of pacemakers

Starting at the first visit in the transplant unit, the therapy was optimized according to guidelines leading to treatment with ACEI in 99% of patients, β-blockers in 76%, and aldosterone antagonists in 60% of patients. As a β-blocker, the β1-selective agent metoprolol was generally used. At presentation, 25% of patients were treated with a β-blocker which was subsequently, if no contraindications were found, uptitrated to the highest individually possible dose, resulting in the use of >100 mg metoprolol in 55%. Arrhythmia was systematically monitored by 24-h ECG. Forty-seven per cent of the patients received a pacemaker, 15% an antibradycardia system, and 32% an antitachycardia system or defibrillator (AICD). Documented malignant arrhythmia or cardiac syncope was a prerequisite for AICD implantation. If necessary, oral treatment with amiodarone was added to the regimen.

Table 3 Genotype distributions and allelic frequency of the α_{2C}Del322 variant

Genotype		Allelic frequency	
α_{2C}Del322–325/ α_{2C}Del322–325	0%	α_{2C}Del322–325	3.6%
α_{2C}Del322–325/WT	7.2%		
WT/WT	92.8%	WT	96.4%

Hardy–Weinberg equilibrium was present. WT, wild type.

Genotypes and allele frequencies

Patients heterozygous for α_{2C}Del322–325 were 7.2%. No α_{2C}Del homozygote patients were detected. The frequency of the wild-type allele was 96.38% and for α_{2C}Del, it was 3.62%. All genotype distributions were in Hardy–Weinberg equilibrium (*Table 3*).

Outcome analysis

Kaplan–Meier analysis showed survival differences with respect to the α_{2C}Del adrenoceptor polymorphism (*Figure 1A*). Cox regression analysis demonstrated that the presence of the α_{2C}Del adrenoceptor variant reduced the risk for death on the waiting list for cardiac transplantation to 0.129 (95% CI 0.18–0.94). The effect of the α_{2C}Del polymorphism on mortality was independent of age, duration of cardiac disease, gender, body mass index, blood pressure, NYHA classification, ejection fraction measured by echocardiography, and presence of malignant ventricular arrhythmia. Survival was also independently affected by left ventricular systolic function (LVEF) (*Table 4*, column 5).

Kaplan–Meier analysis for the combined endpoint death/LVAD implantation/heart transplantation likewise revealed a significant impact ($P = 0.044$) of the α_{2C}Del polymorphism

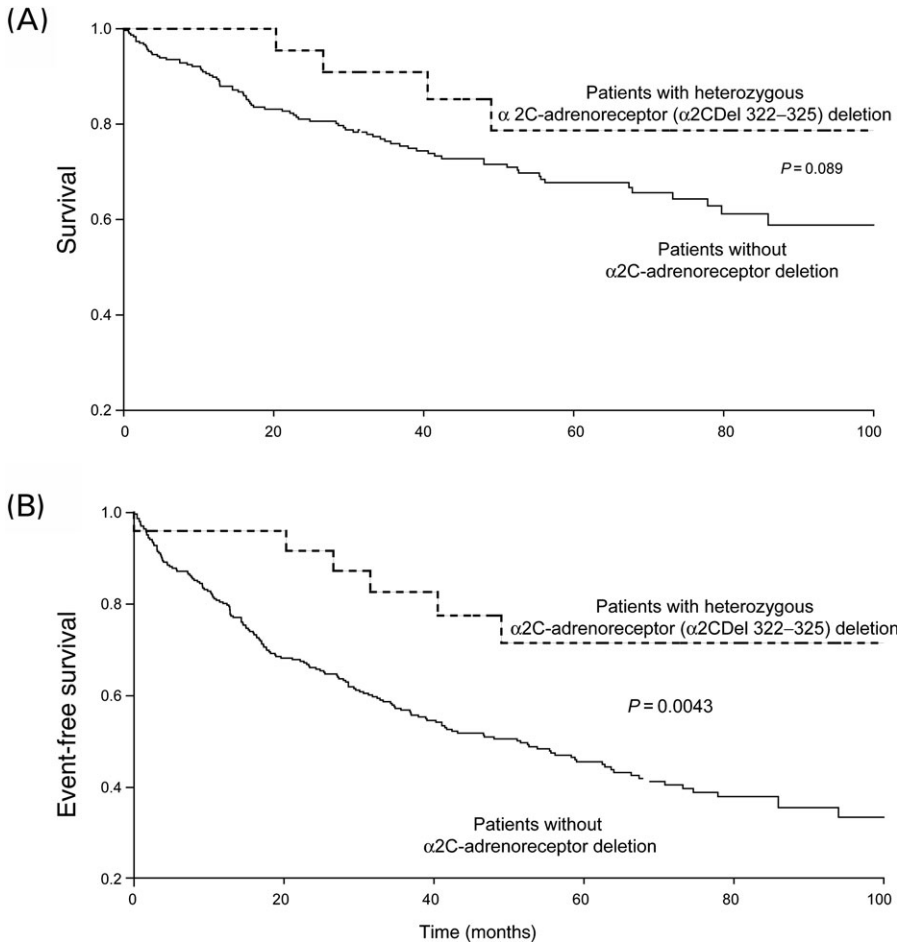

Figure 1 Kaplan–Meier analysis for mortality (*A*) or the combined endpoint (*B*): death, implantation of an LVAD, or heart transplantation. Four out of 25 patients heterozygous for the deletion (α_{2C}Del322–325) in the α_{2C}-adrenoreceptor died, whereas 83 out of 320 patients without deletion in the α_{2C}-adrenoreceptor died. Only 6 of 25 patients heterozygous for α_{2C}Del322–325 reached the combined endpoint death, LVAD implantation, or heart transplantation, whereas 169 out of 320 patients without deletion in the α_{2C}-adrenoreceptor reached the combined endpoint. Curves were compared using the log-rank test.

on event-free survival (*Figure 1B*). Cox regression revealed that relative risk for carriers of the α_{2C}Del adrenoceptor variant was reduced to 0.167 (95% CI: 0.041–0.685, $P = 0.012$) (*Table 4*). Event-free survival was also independently affected by NYHA classification, left ventricular systolic function (LVEF), and left ventricular size (LVEDD) (*Table 4*, column 8).

Discussion

In the present study we demonstrate for the first time that genetic variation in the α_{2C}-adrenoceptor gene (α_{2C}Del322–325) is independently associated with survival and absence of events in patients with severe heart failure due to dilated DCM. Statistical analysis was done for two endpoints: death and the combined endpoint of death and transplantation and implantation of an LVAD. As the occurrence of death was probably assumed to be frequently prevented by LVAD or urgent transplantation, the combined endpoint gives a more realistic estimate of the occurrence of end-stage cardiac disease.

It is generally known that the number of patients may be a potential study limitation in genetic association studies. Our cohort of advanced DCM patients represents the largest possible cohort of our centre of well-characterized DCM patients with a long follow-up. The principle findings seen in the initial Kaplan–Meier analysis remained statistically significant after consideration (by Cox regressions) of well-known confounding factors. The relevance of known independent confounders such as LVEF, NYHA class, and left ventricular size was confirmed in our study. This clearly suggests that the α_{2C}-adrenoceptor gene (α_{2C}Del322–325) polymorphism represents an important and independent genetic factor that determines survival in patients with advanced DCM. However, it is now well recognized that genetic association studies need confirmation in independent populations for a variety of reasons that will not be discussed here. Interested reader may refer to the work of Colhoun *et al*.[15] We would be happy if our study could form the rationale for a larger multi-centre study. This is especially important, as the current study strongly suggests the use of the α_{2C}-adrenoceptor gene (α_{2C}Del322–325) polymorphism as an additional factor for the determination of the priority of patients on the waiting list for heart transplantation. Our data are thus potentially of major clinical impact.

Norepinephrine and epinephrine induce multiple actions in the cardiovascular system via six different α-adrenoceptor subtypes (α_{1A}, α_{1B}, α_{1D}, α_{2A}, α_{2B}, α_{2C}) and three different β-receptor subtypes ($\beta_{1,2,3,}$).[9] α_1- and β-Adrenoceptors may induce myocardial hypertrophy in both postnatal and

Table 4 Cox proportional hazards analysis of factors predicting death or the combined endpoint: death, implantation of an LVAD, or heart transplantation in our entire study population

	Risk factor	Death			Death, LVAD, or heart transplantation		
		Relative risk	95% CI	*P*-value	Relative risk	95% CI	*P*-value
Heterozygous for α_{2C} − Del322–325 deletion	Yes	$1/7.75 = 0.129$	0.18–0.9441	0.044	$1/5.99 = 0.167$	0.18–0.944	0.013
Gender	Male	0.889	0.417–1.894	0.761	1.222	0.736–2.029	0.439
Age (years)	Per additional year	1.045	0.978–1.116	0.194	1.037	0.989–1.086	0.130
Age at diagnosis of heart disease	Per additional year	0.987	0.923–1.056	0.708	0.979	0.933–1.027	0.388
NYHA classification	Per additional NYHA class	1.311	0.908–1.895	0.149	1.514	1.178–1.945	0.001
Ejection fraction	Per addition % of EF	0.947	0.904–0.992	0.021	0.960	0.929–0.992	0.016
Body mass index	Per additional BMI point	0.978	0.913–1.048	0.526	0.963	0.916–1.012	0.135
Left ventricular end-diastolic diameter	Per additional mm of LVEDD	1.027	0.997–1.058	0.076	1.023	1.001–1.045	0.037
Systolic blood pressure	Per additional mmHg	0.992	0.978–1.006	0.251	0.992	0.982–1.002	0.137
Presence of malignant ventricular arrhythmia	Yes	0.849	0.500–1.442	0.545	1.100	0.760–1.592	0.613

adult life, depending on pathophysiological conditions. Studies in gene-targeted mice have shown that α-adrenoceptors are required for physiological growth during normal postnatal cardiac development and for an adaptive response to cardiac stress.[12] In combination, α_1- and β-adrenoceptors contribute to the adaptation of heart rate and the initiation of physiological and pathophysiological cardiac hypertrophy.

Several lines of evidence support a link between the functional α_{2C}-Del322–325 adrenoceptor variant and activation of the sympathetic nervous system. Deletion of four amino acids in the third intracellular loop of the human α_{2C}-receptor (α_{2C}Del322–325) leads to the impairment of G-protein-coupling when this receptor variant is expressed in cell lines *in vitro*.[14] In mice, deletion of α-adrenoceptors impairs feedback inhibition of catecholamine release. α_{2C}-Receptor-deficient mice had elevated circulating catecholamines after transverse aortic constriction compared with wild-type mice.[13] Deficiency of α_{2C}-receptors may thus lead to increased activation of myocardial α_1- and β-adrenoceptors. This may be responsible for initiating cardiac hypertrophy and failure if β1-adrenoceptors are unblocked.[16,17] However, if β1-adrenoceptors are blocked, catecholamines may predominantly stimulate growth processes via α_1- and β2-adrenoceptors.

As the effect of the α_{2C}Del polymorphism modifies the activity of the adrenergic system, it may be speculated that α_{2C}Del patients may particularly benefit from β-blocker treatment. In our own previous study, we observed a decreased cardiac function in Caucasian heart failure patients carrying the α_{2C}Del polymorphism who were not treated with β-blockers or antitachycardiac pacemakers.[13,18] However, in the present study, 99% of patients were treated with ACEI and 76% received β-blockers. More than 50% of patients reached a dose of >100 mg metoprolol. This may effectively inhibit β1-adrenergic overstimulation. At the same time, α_1- and β2 adrenoceptors are not inhibited by metoprolol treatment. $\alpha_{1A/C}$ and α_{1B} are required for physiological cardiac hypertrophy and their deletion is associated with a worse prognosis in pressure overload.[12] Thus, maintained stimulation of α_1- and β2- adrenoceptors in the presence of β1-adrenergic blockade may be the basis for beneficial effects of α_{2C}Del322–325 in our cohort.

In our current study, we included patients with nearly end-stage heart failure suffering from DCM and referred for heart transplantation. As only patients with advanced stages of heart failure and very low ejection fractions are considered as candidates for heart transplantation, the ejection fraction was below 30% and similar in all genotypes. However, in our previously published study the inclusion criteria were different. There, HF patients with an ejection fraction of below 55% of different aetiologies and in different stages of HF were included. Given that the α_{2C}Del322–325 deletion acts as a survival factor in DCM patients, the deletion carriers with low EF would be expected to accumulate in such a sample, as there is a higher likelihood that patients without this deletion will die. Such a selection bias may have contributed to the results of the first study. Indeed, some clinical findings in the present study point towards a potential survival advantage for the deletion carriers. Deletion carriers had a highly significant greater maximal oxygen uptake and better ventilatory efficiency. This difference is highly significant even though only data from a subgroup are available. Thus it seems that deletion carriers have better cardiopulmonary exercise tolerance in the presence of comparable impairment of left ventricular function. However, exercise tolerance is one of the best predictors of survival. Therefore, this survival advantage in the deletion carriers may be the focus of further investigations.

Patients with DCM are susceptible to arrhythmias caused by α-adrenergic overactivation, and high-dose β-blocker therapy may induce bradycardia. Both risks were limited in our cohort by close follow-up for arrhythmias and by medical antiarrhythmic treatment, preferentially with amiodarone and with regular use of antibradycardiac and antitachycardiac pacemakers and defibrillators. The latter were strictly used only if malignant arrhythmia was

documented in the ECG, or a syncope was strongly believed to be due to arrhythmia. Therefore, the use of AICDs reflects the presence of life-threatening arrhythmia quite well. The number of malignant arrhythmia showed a trend towards lower values in the deletion carriers, but the difference did not achieve statistical significance and can therefore not contribute to a better understanding of the effect of the deletion.

For still unknown reasons, the prevalence of the α_{2C}Del322–325 polymorphism is higher in black than in white Americans.[19] Higher allele frequencies were observed in black heart failure patients (61%) in comparison with controls (41%),[19] but comparable differences were not observed in Caucasians and no data are available for Turkish patients.

Interestingly, it is generally accepted that black heart failure patients respond particularly well to β-blockers. Thus, further studies may test the hypothesis that the presence of the α_{2C}Del322–325 is associated with a greater response to β-blockers. We cannot confirm this hypothesis, as the number of patients treated with β-blockers increased continuously from 25% at presentation to 76% during the study period. Indeed, β-blockers were started in all patients without contraindications and were titrated up and continued in the highest individually acceptable dose. Thus, we cannot define meaningful and comparable β-blocker-treated and non-β-blocker-treated subgroups.

In conclusion, our data suggest that Caucasian patients with the α_{2C}322–325 deletion do have a functional advantage in the presence of an equally impaired left ventricular function in comparison with the 'wild-types'. The functional benefit was observed under intensive medical and device therapies in the present study. More data are needed to analyse the effect of this polymorphism on the clinical course of patients with DCM and its implications for therapy.

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