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Frequency and Phenotypes of Familial Dilated Cardiomyopathy

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Objectives. **This prospective study was performed to analyze the frequency and clinical characteristics of idiopathic dilated cardiomyopathy (DCM).**

Background. **Despite several previous reports on families with DCM, most cases are still believed to be sporadic, and specific clinical findings of the familial form are not well defined.**

Methods. **In 445 consecutive patients with angiographically proven DCM, we obtained detailed family histories to construct pedigrees and examined 970 first- and second-degree family members.**

Results. **Familial DCM was confirmed in 48 (10.8%) of the 445 index patients and was suspected in 108 (24.2%). The 156 patients with suspected or confirmed familial disease were younger at the time of diagnosis ($p < 0.03$) and more often revealed electrocardiographic changes ($p = 0.0003$) than patients with nonfamilial disease. Among the families of the 48 index patients with confirmed familial disease, five phenotypes of familial DCM could be identified: 1) DCM with muscular dystrophy; 2) juvenile DCM with a rapid progressive course in male relatives without muscular dystrophy; 3) DCM with segmental hypokinesia of the left ventricle; 4) DCM with conduction defects; and 5) DCM with sensorineural hearing loss.**

Conclusions. **Up to 35% of patients with DCM may have an inherited disorder. Distinct clinical phenotypes can be observed in some families, suggesting a common molecular cause of the disease.**

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The etiology of idiopathic dilated cardiomyopathy (DCM) is largely unknown (1). Accurate diagnosis of DCM in affected subjects and analysis of the molecular causes are limited because of the low sensitivity and specificity of diagnostic signs and symptoms and the low specificity of noninvasive diagnostic procedures. Therefore, most cases of DCM are still classified as sporadic, and segregation analysis is not part of routine clinical evaluation, despite several previous reports on familial aggregation of DCM (2–13). However, in recently published prospective studies on patients with DCM and their family members, (14,15) 20–25% of index patients were classified as having an inherited disease. Because the diagnosis of familial DCM depends on both the completeness of the pedigree analysis and the diagnostic criteria used, familial DCM may be even more prevalent. A careful analysis of the family members of patients with DCM may reveal a typical phenotype pattern within a single family. Based on these phenotypic characteristics of familial DCM, molecular causes of the disease were identified, such as mitochondrial DNA mutations in maternally transmitted cardiomyopathy (16–18) and mutations of the dystrophin gene in X-linked DCM (19–21). In families characterized by DCM and conduction defects, linkage analysis revealed linkage on chromosomes 1p1q1 (22,23), 3p22–p25 (24) and 9 (25). Recently, Bowles et al. (26) found a linkage of the disease with chromosome 10 in a family with the phenotype DCM and mitral valve prolapse.

Therefore, the aim of the present study was to perform segregation analysis in a large cohort of patients with invasively proven DCM to determine the frequency of familial disease. In case of evidence of familial disease, as many members of each family as possible were examined to describe the clinical characteristics of familial DCM. It was thought that by these analyses the role of genetic factors in DCM could be assessed, and more efficient approaches could be delineated to investigate the molecular causes of DCM and to risk stratify the affected family members.

Methods

Index patients. In this prospective study we analyzed 481 consecutive patients with DCM. DCM was confirmed by left ventricular and coronary angiography performed at the University Hospital of Heidelberg between January 1, 1988 and March 6, 1994. The diagnosis of DCM was based on the World Health Organization criteria (1). Only patients with an angiographic left ventricular ejection fraction <50% were included. Exclusion criteria were coronary artery disease (>50% diameter stenosis of at least one major coronary artery), valvular

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Abbreviations and Acronyms

ASD = atrial septal defect
AV = atrioventricular
CK = creatine kinase
DCM = idiopathic dilated cardiomyopathy
ECG = electrocardiogram, electrocardiographic
WPW = Wolff-Parkinson-White

heart more than trivial, congenital heart disease, long-standing hypertension with diastolic blood pressure >95 mm Hg, active myocarditis, type I insulin-dependent diabetes mellitus, hypothyroidism and hyperthyroidism, amyloid disease, thalassemia, sarcoidosis, hypertrophic cardiomyopathy with dilative course, alcohol ingestion >100 g/day and a history of exposure to cardiotoxic drugs. Forty-six patients with type II diabetes mellitus, two with ulcerative colitis and one with peripartum cardiomyopathy were included because these conditions may be a genetic predisposition for DCM. The study protocol was approved by the ethics committee on human research of the University of Heidelberg, and all participants gave written informed consent before entering the study.

Segregation analysis. A detailed family history was obtained by interviewing 445 of the 481 index patients. The remaining 36 patients either refused (n = 5), were unable to report (n = 7), were lost to follow-up (n = 22) or had a doubtful parentage (n = 2). The names, ages, causes of death, cardiac symptoms and known cardiac diseases of the family members of three to four generations were listed in the pedigrees. All living relatives of patients with suspected familial DCM were invited for a clinical examination, and their private and hospital physicians were asked for medical reports.

Clinical evaluation consisted of a careful patient and family history, physical examination, a 12-lead electrocardiogram (ECG), an echocardiogram and routine blood chemistry. Index patients and their relatives with suspected DCM also underwent chest radiography, exercise stress testing, 24-h Holter monitoring and left heart catheterization.

Blood samples were taken from all index patients and examined relatives and were analyzed as part of routine clinical workup. The analyses were used for the exclusion criteria for DCM listed above. A *12-lead ECG* was recorded for all patients and family members investigated.

Echocardiography. Two-dimensional echocardiography was performed using conventional equipment (Toshiba SSH 160A, Aloka SSD 870, 2.5-MHz transducers). Left and right ventricular and atrial diameters were measured using standard methods (27). Left ventricular function was classified as normal, mildly, moderately and severely impaired. Valvular function was evaluated using color and continuous wave Doppler techniques. The echocardiograms were read in blinded manner by a single experienced observer (H.K.).

Cardiac catheterization and endomyocardial biopsy. Left and right heart catheterizations, including coronary angiography, were performed using the standard transfemoral approach. Left ventricular ejection fraction was measured by the area–length method in the 30° right anterior oblique projection. Segmental wall motion abnormalities were classified as hypokinesia, akinesia or dyskinesia in one or two standard segments of the left ventricle (anterobasal, anterolateral, apical, diaphragmal, posterobasal, septal and posterolateral) obtained in the 30° right and left anterior oblique projections. Six endomyocardial biopsy specimens were taken from the free wall or interventricular septum of the left ventricle.

Histopathologic studies. Right and left heart endomyocardial biopsy specimens (n = 134), samples from explanted hearts (n = 29) and heart tissue obtained at necropsy (n = 8) were examined using light and electron microscopy. All histologic analysis were read in blinded manner by two investigators. Concordance between readers was >95%. Criteria for diagnosis of DCM were inhomogenous hypertrophy of cardiomyocytes, diffuse interstitial myocardial fibrosis, absence of fiber disarray and absence of inflammatory cells. The histologic findings were compatible with DCM in all patients in the study group.

Audiologic examination. In two families with suspected familial sensorineural hearing loss a detailed audiologic examination was performed, including otoscopy, pure tone audiometry, stapedial reflex measurement and tympanometry. In case of abnormal findings, acoustic brain stem reflexes and transitory evoked otoacoustic emissions were measured, and computer tomographic scans of the temporal bone were performed.

Follow-up examination. All index patients with familial disease and their relatives were requested to return for reevaluation within 6 to 12 months. At the follow-up visit, physical examination, blood chemistry testing, ECG recording and echocardiographic study were performed by the same physician (E.G.).

Definition of familial disease. Familial DCM was defined as *confirmed* when, in addition to the index patient, at least one first- or second-degree relative had DCM documented either by left heart catheterization or by autopsy. Familial DCM was defined as *suspected* when at least one additional first-degree family member had either died suddenly or died of chronic heart failure before the age of 65 years, or when impaired left ventricular function was documented by echocardiography.

Statistical methods. Results are presented as mean value ± SD. Differences in numeric clinical variables of index patients with familial and nonfamilial disease were assessed using the unpaired Mann-Whitney rank sum test; differences between proportions were analyzed using the Pearson chi-square or Fisher exact test, as appropriate; $p < 0.05$ was considered statistically significant.

Results

Frequency of familial DCM (Fig. 1). A detailed family history could be obtained in 445 (92.5%) of the 481 index patients with a definite DCM and complete pedigrees were constructed. This analysis revealed evidence of familial disease

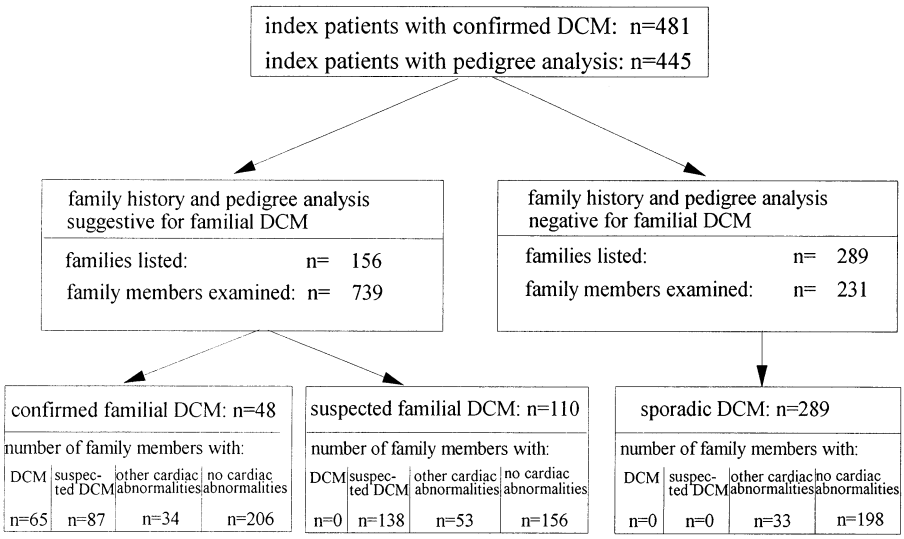


Figure 1. Patient groups.

in 156 patients. In this group, 739 first- and second-degree family members were examined clinically. Of the 289 patients without evidence for familial disease, 231 first- and second-degree family members were investigated. Based on hard data (invasive investigations or autopsy), DCM was found in the families of 48 index patients (10.8%) (confirmed familial DCM). In the families of these 48 patients, 65 additional members had definite DCM. Remarkably, 38 of the 65 DCM cases were newly identified during the family screening process. In 108 (24.2%) of the 445 index patients, familial DCM was eventually present because of a history of unexplained heart failure (n = 23) or sudden cardiac death (n = 75), or both, or unexplained depressed left ventricular function on echocardiography (n = 10) (suspected familial DCM). In the remaining 289 (65%) of the 445 index patients, family history did not reveal evidence for additional family members with DCM (nonfamilial DCM). On examination, concomitant cardiac abnormalities, such as unspecific ECG changes (n = 69), mitral valve prolapse (n = 22), Wolff-Parkinson-White (WPW) syndrome (n = 12), atrial septal aneurysm (n = 4), atrial septal defect (n = 2), ventricular septal defect (n = 1) and pulmonary stenosis (n = 1) were found in 120 of the 970 family members with normal left and right ventricular function. In five index patients with familial and four with sporadic disease, DCM was associated with WPW syndrome. Seven of the 481 index patients had identical twins; in 2 index patients, both twins were affected.

Clinical characteristics of index patients with familial or sporadic DCM. Index patients with suspected or confirmed familial DCM were examined clinically and investigated by left heart characterization at a significantly younger age than the index patients with a negative family history (Table 1). Patients with familial DCM more often revealed ST segment and T wave changes than did index patients with a negative family history. The distribution of the remaining variables tested, including functional status at a mean follow-up of 4.01 ± 3.58

Table 1. Clinical Characteristics of Index Patients With Familial or Nonfamilial Dilated Cardiomyopathy

	Familial DCM (n = 156)	Nonfamilial DCM (n = 289)	p Value
Baseline characteristics			
Age at 1st exam (yr)	49.79 ± 12.84	53.57 ± 11.91	0.007*
Age at cardiac cath (yr)	51.21 ± 12.72	54.34 ± 11.98	0.027*
Duration of disease (yr)	4.16 ± 4.36	3.93 ± 3.09	0.884*
Functional status			
NYHA I/II	75 (48.08%)	139 (48.10%)	0.997†
NYHA III/IV	81 (51.92%)	150 (51.90%)	0.997†
Course			
Stable	90/102 (88.24%)	149/176 (89.22%)	0.803†
Deteriorated	12/102 (11.76%)	18/176 (10.78%)	0.803†
Transplantation	20 (12.82%)	36 (12.46%)	0.921†
Death	37 (23.72%)	84 (29.07%)	0.272†
ECG findings			
AV block	23 (14.74%)	34 (11.76%)	0.370†
LBBB	52 (33.33%)	111 (38.41%)	0.289†
RBBB	7 (4.49%)	16 (5.54%)	0.633†
AF	52 (33.33%)	81 (28.03%)	0.243†
Lown class 4b	59/111 (53.15%)	89/178 (50.00%)	0.602†
HR >100 beats/min	58 (37.18%)	89 (30.80%)	0.172†
ST-T wave abnorm	83 (53.21%)	103 (35.64%)	0.0003†
Echo findings			
LA diameter (mm)	46.39 ± 7.51	46.43 ± 7.79	0.957*
LVED diameter (mm)	64.26 ± 8.99	65.36 ± 10.04	0.330*
LVES diameter (mm)	51.39 ± 12.48	52.10 ± 12.32	0.648*
FS (%)	20.72 ± 8.86	19.75 ± 7.47	0.425*
X-ray findings			
Cardiothoracic ratio	0.55 ± 0.06	0.55 ± 0.07	0.741*
Pulmonary congestion	58/134 (43.28%)	85/244 (35.25%)	0.105†

*Mann-Whitney rank-sum test. †Chi-square test. Data presented are mean value (±SD) or number (%) of patients. abnorm = abnormalities; AF = atrial fibrillation; AV = atrioventricular; cath = catheterization; DCM = dilated cardiomyopathy; ECG = electrocardiographic; Echo = echocardiographic; exam = examination; FS = fractional shortening; HR = heart rate; LA = left atrial; LBBB = left bundle branch block; LVED = left ventricular end-diastolic; LVES = left ventricular end-systolic; NYHA = New York Heart Association; RBBB = right bundle branch block.

Table 2. Phenotypes of Familial Dilated Cardiomyopathy and Their Clinical Definitions

Phenotype A (DCM with muscular dystrophy)	Phenotype B (juvenile DCM with rapid progressive course in males)	Phenotype C (DCM with heterogenous clinical course)	Phenotype D (DCM with early conduction system disease)	Phenotype E (DCM with segmental hypokinesia)	Phenotype F (families with DCM and sensorineural hearing loss)
Clinical Characteristics					
Cardiac symptoms predominant Elevated CK serum activity	Early onset of symptoms and rapid progression in males Normal CK serum activity	Relatives with no signs of DCM reveal other pathologic cardiac findings: (e.g., WPW, ASD) Clinical course highly variable	AV block AF	Regionally impaired LV function Stable course	Severely impaired LV and RV function Bilateral pantonal hearing loss
Mode of Inheritance					
X-chromosomal	X-chromosomal?	Autosomal dominant	Autosomal dominant	Autosomal dominant	Maternal or autosomal dominant
Molecular Genetic Definition					
Mutation of dystrophin gene	Unknown	Unknown	Chromosomes 1, 3, 9	Unknown	Mitochondrial DNA deletion?

ASD = atrial septal defect; CK = creatine kinase; LV = left ventricular; RV = right ventricular; WPW = Wolff-Parkinson-White syndrome; other abbreviations as in Table 1.

years, was not significantly different in patients with and without familial DCM.

Clinical phenotypes in index patients with confirmed familial DCM (Table 2). In 28 of 48 families with confirmed familial DCM, at least two members with definite DCM and two with suspected DCM in at least two generations were identified. Five distinct phenotypic presentations varying in mode of inheritance, clinical symptoms, disease progression and prognosis could be identified in 19 of these 28 families (Tables 3 and 4). Nine families were not classified as a distinct phenotype because of their heterogenous clinical findings.

Phenotype A: X-linked recessive DCM with muscular dystrophy. Two families were found in which six juvenile patients with a mean age of 28.4 years showed a rapidly progressive course of DCM, with elevated serum activity of total creatine kinase (CK). During a mean follow-up period of 4 years, two male patients have died, and one has undergone transplantation (Table 3). All patients revealed impaired right and left ventricular function. Depressed left ventricular function was also observed in two female patients 46 and 68 years old. The pedigree of family A is shown in Figure 2 as an example of this type of DCM. (*Note*: Only the core families are shown in

Table 3. Phenotypes of 28 of 48 Families With Confirmed Familial Dilated Cardiomyopathy and Their Clinical Characteristics

	Phenotype A (DCM with muscular dystrophy)	Phenotype B (juvenile DCM with rapid progressive course in males)	Phenotype C (DCM with segmental hypokinesia)	Phenotype D (DCM with early conduction system disease)	Phenotype E (DCM with sensorineural hearing loss)	Not Classified (DCM with heterogenous clinical course)
No. of families	2	5	5	6	1	9
No. of family members examined	26	89	65	76	27	151
Members with suspected DCM	0/26	10/89	13/65	18/76	4/27	24/151
Members with confirmed DCM	8/26	14/89	14/65	20/76	3/27	23/151
Age at diagnosis (yr)*						
Male	28.4 ± 13.6	23.6 ± 5.8	39.5 ± 22.4	46.6 ± 13.0	31	52.3 ± 13.3
Female	52.7 ± 15.0	60.3 ± 2.9	43.5 ± 6.9	46.0 ± 12.0	49	57.0 ± 10.1
Functional status at diagnosis						
NYHA I/II	5/8	5/14	9/14	6/20	1/3	6/23
NYHA III/IV	3/8	8/14	5/14	9/20	2/3	9/23
Functional status at 1-yr follow-up						
Unchanged	5/8	5/14	9/14	3/20	2/3	9/23
Deteriorated	0/8	2/14	2/14	5/20	0/3	2/23
Transplantation	1/8	6/14	0/14	2/20	0/3	2/23
Death	2/8	1/14	3/14	10/20	1/3	10/23

*Mean value ± SD. Abbreviations as in Table 1.

Table 4. Electrocardiographic and Echocardiographic Findings in 28 of 48 Families With Confirmed Familial Dilated Cardiomyopathy

	Phenotype A (DCM with muscular dystrophy)	Phenotype B (juvenile DCM with rapid progressive course in males)	Phenotype C (DCM with segmental hypokinesia)	Phenotype D (DCM with early conduction system disease)	Phenotype E (DCM with sensorineural hearing loss)	Not Classified (DCM with heterogenous clinical course)
ECG findings						
AF	0/8	1/14	3/14	14/20	2/3	8/23
PVBs, Lown class 4b	2/8	0/14	2/14	6/20	1/3	7/23
AV block I, II or III	0/8	0/14	1/14	7/20	2/3	8/23
LBBB	1/8	0/14	1/14	2/20	0/3	5/23
ST-T wave abnorm	1/8	8/14	5/14	3/20	0/3	7/23
Echo findings						
LVED diameter (mm)	57.6 ± 20.6	67.8 ± 10	62.1 ± 15.0	55.2 ± 9.4	59.0 ± 9.5	67.3 ± 9.2
Segmental dysfunction	0/8	0/14	14/14	0/20	0/3	0/23

Data presented are mean value ±SD or number of patients. PVBs = premature ventricular beats; other abbreviations as in Table 1.

Figures 2 to 7.) In this family, molecular genetic analysis revealed a new point mutation in the rod region exon 29 of the dystrophin gene (21).

Phenotype B: juvenile DCM with rapid progressive course in male patients. This phenotype was observed in five families in which 14 members were classified as confirmed DCM and 10 as having suspected DCM. Similar to group A, the clinical course of DCM was rapidly progressive in all nine male patients (mean age at diagnosis 23.6 years). During a mean follow-up period of 5.2 years, two patients deteriorated, 6 underwent heart transplantation, and one died. Mean age at diagnosis ($p < 0.0001$) and functional status after a 6- to 12-month follow-up period ($p < 0.0004$) in the male patients were significantly different from that of patients with DCM in groups C to F. In the five female patients with impaired left ventricular function, mean age at diagnosis was 60.3 years, and clinical status was unchanged at follow-up. In all affected male and female patients, total serum CK activity was normal. Dystrophinopathy was ruled out by histopathologic and molecular genetic analyses in one family of this group (data not shown; methods described elsewhere [21]). The pedigree of family B is shown in Figure 3.

Phenotype C: familial DCM with segmental hypokinesia. In five families comprising 14 patients, DCM was characterized by an autosomal dominant trait and by regional wall motion abnormalities. This finding, which was documented in all 14 patients by left ventricular angiography and echocardiography and was not seen in the other patients with DCM ($p < 0.0001$), was also documented in 9 of the 289 index patients with nonfamilial disease but in none of their examined relatives.

Figure 2. Family A: familial DCM with muscular dystrophy. The 21-year old index patient (IV-16) had DCM with right and left heart failure. He had no neurologic findings but had exercise-induced cramps in the lower limbs and revealed elevated total serum CK activity. His cardiac function deteriorated rapidly, requiring emergency heart transplantation. His 11-year old brother (IV-14) and 25-year old nephew (IV-12) showed elevation of serum CK activity and ECG changes. The female carriers of the disease (II-16, III-21, III-24) revealed ECG abnormalities. **Symbols** = symbol key for Figures 2 to 7.

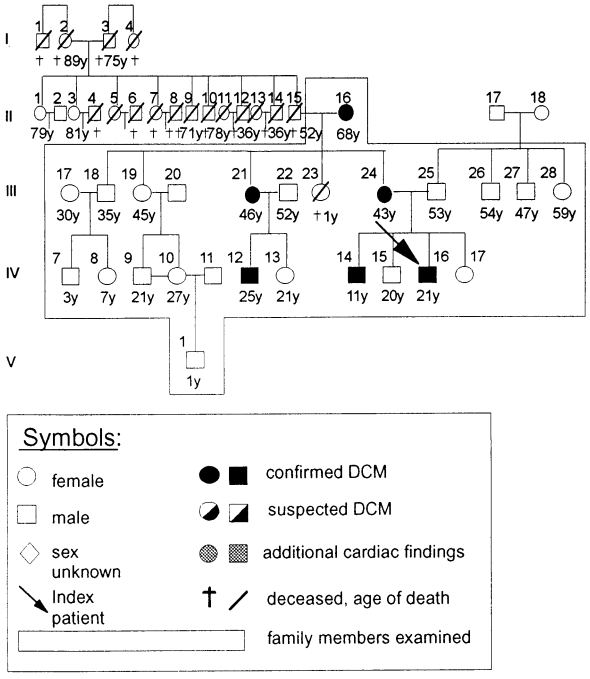
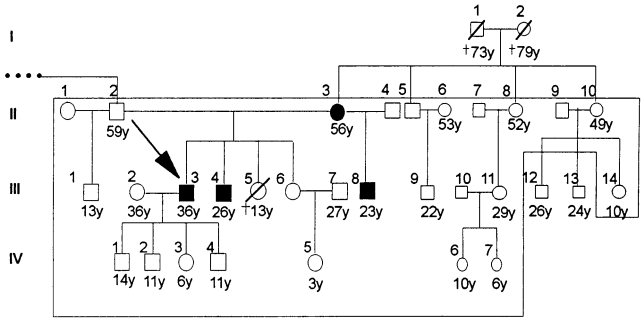


Figure 3. Family B: Juvenile DCM with rapid progressive course in male relatives. In this family, three brothers (two from their mother's first and one from her second marriage) underwent heart transplantation at 23, 26 and 36 years of age, respectively (III-8, III-4, III-3). The carrier of the disease is the 56-year old asymptomatic mother of the index patient (II-3), who showed impaired left ventricular function. The father of the index patient (II-2) and all 42 members of his family (not shown) had normal cardiac findings. Symbols as in Figure 2.



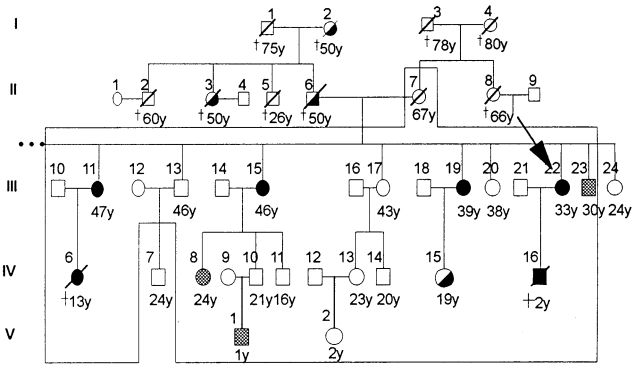


Figure 4. Family C: DCM with segmental hypokinesia. All affected living members revealed segmental hypokinesia, ECG changes and a stable course at 5-year follow-up. Child IV-6 died of proven DCM at 13 years of age. Child IV-16 died of heart failure awaiting transplantation. This child had a small atrial septal defect, mild pulmonary stenosis and a persistent open ductus ateriosus Botalli. Symbols as in Figure 2.

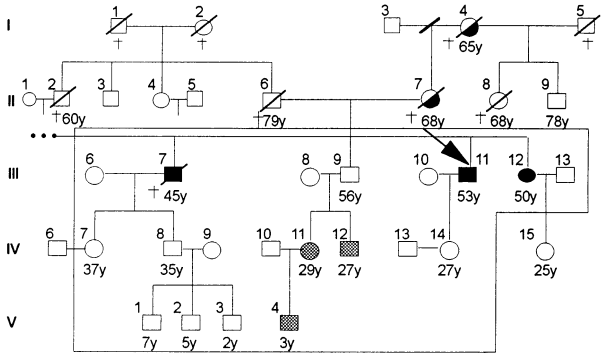
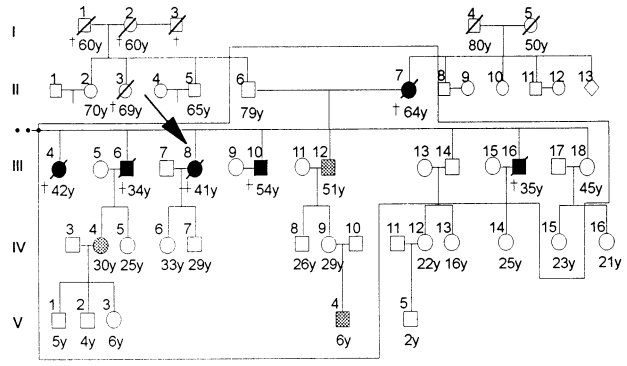


Figure 6. Family E: DCM with sensorineural hearing loss. DCM and bilateral pantonal sensorineural hearing loss were documented in three siblings (III-7, III-11, III-12). The mother (II-7) and grandmother (I-4) of the index patient died of sudden death at 65 and 68 years of age. All members of the family without cardiac disease showed normal results on audiograms. Symbols as in Figure 2.

Due to the presence of regionally impaired left ventricular function, 10 of the 14 patients with familial DCM were first diagnosed as having had a myocardial infarction, but subsequent coronary angiographic findings were normal in all 14. In 9 of the 14 affected patients, the mild clinical symptoms remained stable over a follow-up period of 4 to 10 years. The pedigree of family C is shown in Figure 4. Autosomal dominant inheritance was likely in this family and in the four other families of this group.

Phenotype D: familial DCM with early conduction defects. This group comprises six families. Of the 76 members examined, 20 developed DCM. In all 20 patients, either atrial fibrillation (n = 14) or atrioventricular (AV) block (n = 7) was documented before impaired left ventricular function could be documented. The incidence of atrial fibrillation and AV block was significantly higher ($p = 0.002$) in this group than in groups A to C and F. The pattern of inheritance was compatible with an autosomal dominant trait (Fig. 5).

Figure 5. Family D: DCM with early conduction system disease. Thirty of 64 family members were examined. Five of the eight siblings in generation III died of confirmed DCM at 34, 35, 41, 42 and 54 years of age, respectively (III-6, III-16, III-8, III-4, III-10). The carrier of the disease was probably the mother (II-7), who died of DCM at 64 years old. All affected members developed atrial fibrillation at a young age, and five of the six patients with DCM required permanent cardiac pacing because of AV blocks. Symbols as in Figure 2.



Phenotype E: familial DCM with sensorineural hearing loss. In one family DCM was associated with bilateral sensorineural hearing loss in 3 of 27 family members examined. The mode of inheritance in this family is most likely autosomal dominant or maternal. The pedigree of family E is shown in Figure 6.

Nonclassified families. In a further nine families, DCM was characterized by a highly variable clinical course in the affected 23 members within each family and by cardiac abnormalities, such as aneurysm of the interatrial septum, congenital heart disease and conduction abnormalities, in 18 other family members with normal left ventricular function. The mean age at diagnosis was 52.3 years in male and 57.0 years in female relatives. After a follow-up period of 6 to 12 months, nine patients remained unchanged, whereas two deteriorated, two underwent transplantation, and 10 died. The mode of inheritance in these families were autosomal dominant. Figure 7 shows the pedigree of family NC as an example.

Discussion

Frequency of familial DCM. In this prospective study of 451 consecutive index patients with invasively documented DCM, 10.8% had to be classified as having confirmed familial disease, that is, DCM definitely existed in at least 1 additional first-degree relative of the index patient. If more liberal diagnostic criteria of familial DCM are accepted (e.g., a history of unexplained heart failure or depressed left ventricular function in a first-degree relative), an additional 24.2% of all DCM cases can be classified as familial. Thus, ~35.0% of all patients with DCM may have a genetic disease. The frequency of familial aggregation of DCM documented in our study is slightly higher than that previously reported by others (14,15). The importance of familial screening can be stressed by the fact that 38 new DCM cases were detected by this method in our study.

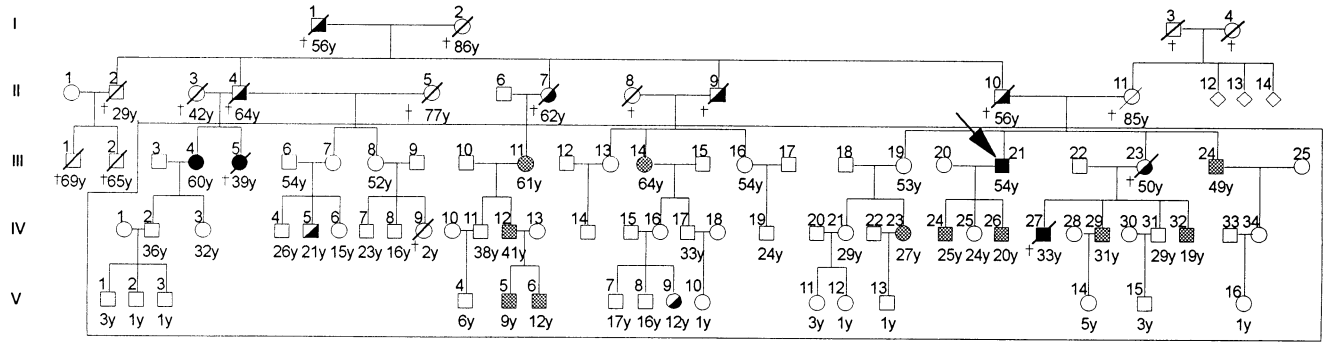


Figure 7. Family NC (not classified): familial DCM with heterogenous clinical course. Of 93 family members shown, 74 are still alive, and 70 were examined. In the first and second generations, five members died of heart failure at 55 to 64 years old. In the third and fourth generations, DCM was confirmed by left heart catheterization or autopsy in four members 33 to 54 years old. The clinical course of the affected members was highly variable. Eleven family members with no sign of DCM showed other pathologic ECG or echocardiographic abnormalities: atrial septal aneurysm (n = 2), mitral valve prolapse (n = 3), aortic regurgitation (n = 1), WPW syndrome (n = 1) and ST segment and T wave changes (n = 4). Two members (III-11, IV-12) of one branch of the family had asymmetric hypertrophy of the interventricular septum of 17 and 15 mm, respectively. Symbols as in Figure 2.

Clinical characteristics of patients with familial DCM. When index patients with familial DCM were compared with those with sporadic DCM, ECG ST segment and T wave changes were more frequently observed in those with familial disease. Similar differences were not reported in previous investigations (13–15). However, such ECG changes are not specific for familial DCM and are not useful for clinical classification. Furthermore, patients with familial disease were also identified at an earlier age (51.21 ± 12.72 years) than patients with sporadic disease (54.34 ± 11.98, $p < 0.03$). Because of the prospective nature of our study, the earlier identification of patients with familial DCM cannot be explained by a more extensive family screening but may instead be related to earlier manifestation of inherited than sporadic DCM.

Phenotypes of familial DCM. In families with hypertrophic cardiomyopathy, distinct mutations have been related to differences in symptoms and progression of the disease (28,29). Phenotyping of patients with familial DCM may therefore facilitate genetic screening and improve their diagnostic classification and risk stratification. The assumption underlying this proposal is that the phenotypic heterogeneity observed reflects underlying genetic heterogeneity of familial DCM.

In our study, although five different clinical phenotypes could be identified, this does not preclude the existence of additional phenotypes. The phenotype A (e.g., X-linked DCM with elevated total serum CK activity) has been described before (30), and mutations of the dystrophin gene have been reported as causing this type of DCM (19,20). In our study, this type of DCM was observed in 2 of 48 families with confirmed familial disease. In family A (represented in Fig. 3), a novel point mutation in exon 29 of the dystrophin gene was detected (21). Thus, it is likely that DCM with this phenotype is caused by mutations of dystrophin or dystrophin-associated proteins.

Many clinical characteristics of patients with X-linked dystrophin disease, such as rapid progressive deterioration of ventricular function in male patients and late onset of a slowly progressive disease in female patients, were observed in five families. However, the affected members of these families did not reveal elevated serum CK activity. Furthermore, linkage analysis and histologic examinations of muscle biopsy specimens of affected members were performed in one of these families. These investigations did not reveal evidence of dystrophinopathy. Therefore, the patients with this type of DCM were allocated to a separate group (group B).

Familial DCM may also manifest as a segmental disease of the left ventricular myocardium (phenotype C). Segmental hypokinesia was described earlier in patients with sporadic disease (31,32); however, familial aggregation of this type of DCM has not yet been reported. Because congenital heart disease coexisted in one of the affected family members, defects in the genes regulating cardiac development may be involved.

The five families of phenotype D are characterized by an autosomal dominant inheritance and the association of DCM with AV block or atrial fibrillation, or both, early in the disease process. This phenotype resembles that of families described previously in which linkage of DCM with polymorphic markers located on the centromeric region of chromosome 1 (22,23), chromosome 3p (24) and chromosome 9 (25) has been reported.

Finally, DCM associated with sensorineuronal hearing loss (phenotype E) has, to our knowledge, not been reported before. Because maternal inheritance is most likely in this family, this phenotype might be caused by mutations of mitochondrial DNA, which has been reported previously in patients with DCM and neurologic symptoms (18,33). Other candidate genes that might be responsible for DCM of phenotype E may include Shaker 1 and USH1b genes encoding nonsarcomeric myosins. Mutations in these genes have recently been identified as causing deafness (34) or severe bilateral hearing loss (35). The Jervell and Lange-Nielson

syndrome (36) was ruled out in this family by normal QT intervals in all family members examined. There was no evidence of Kearns-Sayre syndrome in this family.

The largest proportion of patients with familial DCM were characterized by heterogeneous clinical findings within the same families and were therefore not classified as having a distinct phenotype. In these families, autosomal dominant inheritance and cardiac abnormalities, such as WPW syndrome, aneurysms of the interatrial septum and ECG changes, were observed in family members with otherwise normal cardiac findings. These cardiac abnormalities may represent coincidental findings or may be causually related to the familial disease. In several reports of families with DCM, a high prevalence of WPW syndrome (4,37,38), mitral valve prolapse (26,39) and ST segment and T wave changes have been reported (13,14). Although a common molecular defect may not exist in this group, a single mutation with high variable penetrance and expression may explain the variability of this phenotype.

Study limitations. Although the present investigation examined a large number of family members (970) of 445 consecutive patients with definite DCM, they represent only part of all living family members listed in the pedigrees. However, clinical examination was focused on the families with a history of familial disease (739 members of 156 families), thus reducing the likelihood of missing familial disease. By contrast, examination of 231 family members of 289 index patients without incidence for familial disease did not reveal any evidence of further instances of DCM. Thus, although this study may underestimate the true prevalence of familial DCM, the thorough segregation analysis and the clinical examinations of 970 family members should reduce the significance of this possible error. Because most of the patients were referred to our institute, a random minor referral bias may have occurred and cannot be excluded.

Clinical implications. The results of our study indicate that DCM may be a genetic disorder in one-third of all cases. Consequently, pedigree analyses should be performed in all patients with DCM. If familial DCM is suspected, all first-degree relatives of the index patients should be examined. Using this strategy, 38 new patients with DCM and 120 with cardiac abnormalities were detected in the families of our 445 index patients. In sufficiently large families with aggregation of DCM, it may be possible to identify common clinical phenotypes. These common phenotypes of DCM may facilitate screening for genetic defects and may help in risk stratification. In particular, young male patients with suspected X-linked DCM (phenotype A and B) have rapidly progressive disease and should therefore be followed up closely.

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