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STATE-OF-THE-ART PAPER

Clinical and Genetic Issues in Familial Dilated Cardiomyopathy

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Idiopathic dilated cardiomyopathy (IDC) is characterized by left ventricular dilatation and systolic dysfunction after known causes have been excluded. Idiopathic dilated cardiomyopathy occurring in families, or familial dilated cardiomyopathy (FDC), may occur in 20% to 50% of IDC cases. Sixteen genes have been shown to cause autosomal dominant FDC, but collectively may account for only a fraction of genetic causation; it is anticipated that additional genes causative of FDC will be discovered. Familial dilated cardiomyopathy demonstrates incomplete penetrance, variable expression, and significant locus and allelic heterogeneity, making clinical and genetic diagnosis complex. Echocardiographic and electrocardiographic screening of first-degree relatives of individuals with IDC and FDC is indicated, as detection and treatment are possible before the onset of advanced symptomatic disease. Genetic counseling for IDC and FDC is also indicated to assist with family evaluations for genetic disease and with the uncertainty and anxiety surrounding the significance of clinical and genetic evaluation. Genetic testing is not yet commonly available, but its emergence will provide new opportunities for presymptomatic diagnosis. (J Am Coll Cardiol 2005;45:969–81) © 2005 by the American College of Cardiology Foundation

Idiopathic dilated cardiomyopathy (IDC) is a diagnosis that continues to puzzle many cardiovascular specialists. The diagnosis of IDC is one of exclusion; that is, all obvious or detectable causes should be excluded before its assignment. Yet thoughtful clinicians recognize that some cause, albeit unseen or undetected, underlies the myocardial dysfunction. Multiple causes have been suggested and include previous viral infections, excessive alcohol exposure, severe hypertension, and autoimmune or other phenomena.

An alternative cause, also unseen and difficult to detect, is underlying genetic disease. The clinical and genetic data to support genetic causation, and preliminary recommendations for cardiovascular specialists to deal with this disease, are the focus of this review. That cardiovascular disease can be caused by mutations in genes that encode for key proteins important in cardiovascular biology has been elegantly described for other myocardial diseases, most notably for hypertrophic cardiomyopathy (HCM), now recognized largely as a genetic disease of contractile proteins (1). Other genetic cardiovascular diseases include the long QT syndrome (2), arrhythmogenic right ventricular dysplasia (3), and Marfan syndrome (4). Recent clinical studies have also suggested that bicuspid aortic valve is heritable (5), and atrial fibrillation may be familial in 5% to 15% (6) to 30% (7) of cases.

Genetic disease also underlies a considerable proportion of what has been previously understood to be IDC. The clinical and molecular genetic data gleaned from studies of familial dilated cardiomyopathy (FDC, defined as the presence of IDC in two or more family members) indicate that gene mutations, largely single base changes in key autosomal genes, cause FDC and IDC. The identity of the genes involved, their mutation frequency, mechanisms of disease, and phenotype/genotype correlations are beginning to emerge.

FDC CLINICAL AND FAMILY STUDIES

A genetic basis for IDC was thought to be distinctly uncommon until the mid-1980s. Familial transmission in 1% to 2% of subjects with IDC had been postulated from earlier scattered case reports (for earlier reviews, see references 8–15). Before the widespread availability of echocardiography to screen family members, the research devoted to hereditary cardiomyopathy had difficulty sorting hypertrophic from dilated cardiomyopathy (DCM). Other recent overviews of FDC are available (16–23).

The recognition that DCM may aggregate in families has evolved significantly since the early case reports (8,24–41) (Table 1). Based on family history, two initial studies in 1982 and 1985 reported FDC rates of 2% and 6.5% respectively (8,25) (Table 1). In 1988, a small prospective echocardiographic-based study suggested a much higher rate of 33% (27). That same year in children >2 years of age, the FDC rate was observed to be 25% (28). In 1992, prospective echo screening of first-degree relatives in patients diagnosed with IDC estimated the rate of FDC at 20.3% (32). In this study, 315 relatives of the 59 index patients with IDC underwent screening with echocardiography, including coronary angiography in those ≥40 years of age to exclude coronary artery disease. Idiopathic dilated

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Abbreviations and Acronyms

AD = autosomal dominant
CK = creatine kinase
CLIA = Clinical Laboratories Improvement Act
DCM = dilated cardiomyopathy
ECG = electrocardiography
FDC = familial dilated cardiomyopathy
HCM = hypertrophic cardiomyopathy
HF = heart failure
IDC = idiopathic dilated cardiomyopathy
LVE = left ventricular enlargement

cardiomyopathy was found in 18 relatives (20.3% of the index patients) by echocardiography, whereas only 5% had been suspected of having familial disease based on family history alone. Of the 18 relatives, 12 were asymptomatic and 15 were given new diagnoses.

In 1997, a prospective study of 56 probands estimated the "definite" FDC rate at 25%, where "definite" was defined as a first-degree relative with a diagnosis of IDC, or both an echocardiographic left ventricular end-diastolic dimension >2 standard deviations above the mean and an ejection fraction <50% (37). An additional 27% of probands had a first-degree relative with one of these two echocardiographic criteria, or premature sudden death (unexplained <50 years of age); these were categorized as "possible" FDC. The sum of both "definite" and "possible" FDC rates was 52% (37).

Two reports (38,39), published simultaneously in 1998, indicated that FDC rates among patients with IDC ranged from 35% (38) to 48% if left ventricular enlargement (LVE) was included as a clinical indicator of FDC (39) (Table 1). In the former study (38), family history was obtained in 445 of 481 consecutive subjects (92.5%) with IDC. Dilated cardiomyopathy was discovered in 65 subjects from 48 of the 445 families (10.8%) as determined by full cardiac evaluation or at autopsy. Of the 65 subjects observed to have DCM during the study, 38 were newly identified by prospective screening. In an additional 108 of the 445 families (24.2%), FDC was eventually diagnosed on the basis of sudden cardiac death (75 families), heart failure (HF) (23 families), or abnormal echocardiography (10 families). In the remaining 289 families (65%), no evidence of familial disease was observed. The latter study (39) identified 110 consecutive patients with documented IDC; of these, 408 subjects from 89 different families (an average of 4.6 members per family) agreed to undergo full clinical screening. Forty-five of the relatives screened had LVE; 7 of the 45 had DCM (LVE and decreased systolic function). With LVE included as early evidence of disease, the prevalence of FDC among index patients with IDC was 48% (39).

Clinical screening, regardless of family history, was offered to 350 patients with IDC in Trieste, Italy, identified between 1991 and 1997 (40), and 281 family members from 60 families were investigated based on their geographic proximity. Thirty-nine of the 60 families (65%) had familial disease. When familial disease was compared to nonfamilial disease, only a younger age of onset was predictive. The investigators concluded that although FDC was frequent, no particular clinical or morphologic features of individual patients distinguished FDC from IDC, and thus family screening was required to detect it.

FDC DISEASE GENES AND CHROMOSOMAL LOCI

Autosomal dominant (AD). Familial dilated cardiomyopathy has been reported most commonly (approximately 90%) with AD inheritance (40). The genetic and clinical heterogeneity suggests causation by a single gene, with multiple other genetic and environmental factors altering its expressivity (40). To date mutations in 16 autosomal genes (42–66) have been suggested to be causative of FDC and have been categorized as FDC and FDC with conduction system disease (Table 2). The former category has no specific or unique phenotypic features. The latter category includes families with mutations in lamin A/C who frequently present with sinoatrial and atrioventricular node dysfunction, heart block commonly requiring pacemakers, atrial fibrillation, and other supraventricular arrhythmias; later DCM, ventricular arrhythmias, and death from sudden cardiac death or pump failure are observed. Based on these preliminary reports (Table 2), mutations in the lamin A/C and beta-myosin heavy chain genes may each be responsible for 5% to 10% of FDC. However, these estimates have been derived from patients and their families seen in specialist or referral clinics that may not be representative of overall population frequencies. Actin (67–69) and desmin (69) genes appear to be quite uncommon causes (<1%) of IDC and FDC. Preliminary estimates of the frequencies of the other FDC genes are largely based upon the primary reports (Table 2), but appear to be less common causes of FDC than the lamin A/C and beta-myosin heavy chain genes. Studies designed to survey disease gene frequencies in larger populations will be required to clarify these issues.

X-linked. X-linked FDC is reported to account for approximately 5% to 10% of FDC (Table 2) (38–40), usually resulting from mutations in the dystrophin gene that have been identified in several families displaying X-linked inheritance (70–78). In some cases, DCM has also been noted to be the only or presenting feature in individuals who have Becker muscular dystrophy or in female carriers (79,80). Furthermore, Becker muscular dystrophy and IDC have been seen in the same family (81), suggesting that it may be difficult to draw conclusions about phenotype from genotype. Individuals with X-linked FDC may have skeletal muscle weakness, and whereas most have elevated creatine kinase (CK) levels, normal levels have been reported (40). Dystrophin mutations have also been identified in male patients diagnosed with IDC, suggesting that this may be a rare cause of sporadic cases (20,82).

Mutations in the gene G4.5, which encodes the tafazzin

family of proteins, cause Barth syndrome (83) and neonatal non-compaction of the left ventricular myocardium (84). G4.5 mutations have also been implicated as the cause of a nonsyndromic, lethal infantile form of X-linked FDC (85).

Autosomal recessive. A mutation in cardiac troponin I has been shown to cause recessive FDC in one family (86) (Table 2). Autosomal recessive inheritance is more common among certain ethnic groups and may be responsible for some cases of especially young (<10 years) onset (87).

FDC with skeletal muscle disease. Minor skeletal muscle weakness has also been described in a few families with AD FDC (40,88), including two families with lamin mutations (60,61). Affected subjects may have elevated CK levels, but values have been noted to fluctuate from normal to overtly abnormal over time.

Mitochondrial mutations. Mitochondrial point mutations and/or deletions have been reported in individuals with IDC (89–92) and FDC (93,94). However, many of these mutations are found in control subjects as well and may not be the primary cause of the disease, but rather a cofactor in its development (40).

Additional chromosomal loci identified through linkage analysis. Autosomal dominant FDC has been linked to seven additional loci at which no disease genes have been identified. In four of these, cardiac dilatation has been the primary and presenting feature (95–98); in one of these mitral valve prolapse preceded the onset of cardiomyopathy (96) and in another sensorineural hearing loss was associated (97). The remaining three linkage reports describe DCM associated with conduction system disease (88,99,100).

CLINICAL GENETICS OF FDC

Establishing causality of DCM from gene mutations. One of the most challenging issues in the investigation of genetic causes of DCM is the establishment of causation from a mutation, which in the case of AD inheritance is usually a single base missense or nonsense mutation. How is one convinced that the identified mutation actually causes DCM? The disease phenotype should segregate with the mutation in a large family containing members that have both normal and affected phenotypes. Ideally, these associations can be identified in multiple families. Other evidence that builds the case includes the absence of the mutation in a large control group, the occurrence of the disease gene in a conserved region, finding a de novo mutation, and a plausible pathophysiologic role of the putative disease gene in the development of DCM. Further evidence of DCM in an animal model harboring the same mutation also strengthens the case.

Penetrance and disease expression. Penetrance is a measure of the percentage of individuals who carry a particular gene mutation who are affected by the disorder. For example, for a disorder with 80% penetrance, of those who carry the gene mutation 80% will manifest its effects. This is referred to as incomplete penetrance. Familial dilated cardiomyopathy demonstrates incomplete age-dependent penetrance (for example, see accounts of lamin cardiomyopathy [40,59,62,63]) as well as variable expression. Among individuals carrying a particular gene mutation, there may be wide variability in phenotypic effects and severity, both within and between families. Families therefore often demonstrate a wide range of mild to severe disease across all generations. Within the same family, the disease may range from subtle clinical symptoms and/or mild arrhythmias to sudden death or DCM leading to HF and/or cardiac transplantation. Therefore, it can be difficult to recognize FDC as a single genetic entity when investigating family pedigrees. This variability is crucial to convey in genetic counseling, as an adult with mild or nonpenetrant disease remains at risk for having offspring with a more severe phenotype.

CLINICAL SCREENING RECOMMENDATIONS FOR FDC

Idiopathic dilated cardiomyopathy can be divided into presymptomatic and symptomatic stages. The symptomatic presentation of IDC most commonly includes HF, arrhythmia including sudden cardiac death, or thromboembolism. Cardiovascular evaluation for other reasons, such as routine or prenatal exams, sports physical examinations, preoperative screening, and so on, may also detect asymptomatic disease.

Family history and pedigree analysis. A thorough family history should be taken on every individual with IDC (101–103). Usually targeted family history questions can be used to elicit any obvious family history of DCM or HF. However, recording a three-generation pedigree (including siblings, children, parents, grandparents, aunts and uncles, and nieces and nephews of the index patient) is a more complete, but time-consuming, approach. Pedigree analysis and medical history can provide crucial information but are insensitive when used alone. Nevertheless, until genetic testing is ready for widespread use, clinical screening will remain the most efficient method for early detection of FDC. Furthermore, a distinction should be made between a family history that is negative for cardiovascular disease and one that is inconclusive. In the former case, the patient provides a clear family history, the family is of relatively good size, and no suspicious cardiovascular signs or symptoms or history of known cardiovascular disease are present. In the latter case, the patient may provide a poor or incomplete family history, may have information on few or no family members, and/or the patient or their parents may be adopted. Even though the latter situations reduce the value of family history in a particular case, they do not decrease or exclude the possibility of a heritable cardiovascular disease.

The primary goals of pedigree analysis are to diagnose IDC versus FDC and to identify at-risk family members in order to recommend that they be screened. In the absence of another family member with known IDC, a high level of

Table 1. Clinical and Family Studies to Assess Frequency of Familial Dilated Cardiomyopathy

Author and Year	Location of Study	Patient Population	Method to Identify Familial Disease	Number of FDC/ Number of IDC (%)	Reference
Fuster, 1981	Rochester, MN	Consecutive IDC patients diagnosed 1960–1973, Mayo Clinic	Retrospective chart review of available history	2 of 104 (2%)	(8)
Lengyel, 1981	Budapest, Hungary	All patients studied with echocardiography and IDC, 1973–1979, Hungarian Institute of Cardiology	Not stated	5 of 98 (5%)	(24)
Michels, 1985	Rochester, MN	Patients <50 yrs with IDC, 1976–1982, Mayo Clinic	Retrospective chart review, prospective family history screening questionnaire	11 of 165 (7%)	(25)
Pongpanich, 1986	Bangkok, Thailand	Consecutive pediatric patients with congestive cardiomyopathy, 1969–1984, Mahidol University	Family history of sibling with same condition	5 of 50 (10%)	(26)
Fragola, 1988	Rome, Italy	12 of 43 patients with IDC in 1985–1986 consented to participate, none with positive FH, University of Rome	Prospective echocardiographic screening	4 of 12 (33%)	(27)
Griffin, 1988	St. Louis, MO	Children diagnosed with IDC 1975–1985, Washington University	Telephone follow-up; group I <2 yrs of age at presentation, group II >2 yrs of age at presentation	Group I: 0 of 20 (0%); group II: 3 of 12 (25%)	(28)
Valantine, 1989	Stanford, CA	All cardiac transplant recipients 1976–1986, Stanford University	Retrospective history review	11 of 179 (6%)	(29)
Keren, 1990	Jerusalem, Israel; Stanford, CA	Patients with mildly dilated cardiomyopathy, Hadassah and Stanford universities	Not stated	9 of 16 (56%)	(30)
Mestroni, 1990	Trieste, Italy	Consecutive patients with IDC, 1979–1988, University of Trieste	Prospective historical screening	12 of 65 (7%)	(31)
Michels, 1992	Rochester, MN	Patients with ejection fraction <50% and IDC identified by medical record review, 1987–1989, Mayo Clinic	Prospective echocardiographic screening of relatives of patients with IDC	12 of 59 (20%)	(32)
Zachara, 1993	Rome, Italy	Consecutive patients with diagnosis of IDC	Retrospective historical screening for FDC	12 of 105 (11%)	(33)
Keeling, 1995	London, England	Prospectively identified cases of IDC at St. Georges Hospital	Prospective echocardiographic screening of first degree relatives	10 of 40 (25%)	(34)
Honda, 1995	Kobe, Japan	Patients with IDC 1973–1990 at Kobe University Hospital	Prospective evaluation of relatives	10 of 117 confirmed (9%), 29 of 117 suspected (25%)	(35)
Goerss, 1995	Rochester, MN	59 IDC patients from 1992 Michels report and 36 new IDC patients, Mayo Clinic	Prospective echocardiographic screening of relatives of patients with IDC	23 of 95 (24%), (27 of 95 indeterminate)	(36)
McKenna, 1997	Dublin, Ireland	Patients with IDC with family members and who participated in FDC screening, University College	Prospective echocardiographic screening of first degree relatives	14 of 56 (25%) definite, 15 of 56 (27%) possible	(37)
Grünig, 1998	Heidelberg, Germany	Consecutive patients with IDC 1988–1994, University of Heidelberg	Prospective family history and clinical screening in some (see text)	156 of 445 (35%)	(38)

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Table 1 Continued

Author and Year	Location of Study	Patient Population	Method to Identify Familial Disease	Number of FDC/ Number of IDC (%)	Reference
Baig, 1998	London, England	Consecutive patients with IDC at St. Georges Hospital	Prospective clinical and echocardiographic screening of relatives	52 of 110 (48%) when LVE included	(39)
Mestroni, 1999	Trieste, Italy	Consecutive patients referred to the International Centre for Genetic Engineering and Biotechnology, 1991–1997; 60 of 350 patients screened based on feasibility	Prospective clinical and echocardiographic screening of relatives	39 of 60 (65%)	(40)
Michels, 2003	Rochester, MN	Patients with IDC who participated in earlier family studies (Michels 1992, Goerss 1995) at Mayo Clinic	Family follow-up study	30 of 101 (30%)	(41)

FDC = familial dilated cardiomyopathy; IDC = idiopathic dilated cardiomyopathy; LVE = left ventricular enlargement.

suspicion should be raised by the occurrence of heart transplantation, HF at an early age (<60 years), or nonspecific unexplained sudden death without associated symptoms or history consistent with ischemic heart disease in one or more first or second degree relatives. When the accuracy of medical and family history is in question, medical records and death certificates may be obtained and carefully reviewed to establish accurate histories. The logistics of this is very time consuming, and a referral to a cardiovascular genetics specialist or geneticist may be appropriate in cases where obtaining this documentation is time-prohibitive. Should the clinician undertake this effort, consent for contact is sought via the proband for his or her family members, followed by interaction by the clinician and his/her staff to gain the requisite clinical information.

Despite the importance of family history and pedigree analysis in the care of individuals with IDC and FDC, these elements do not seem to be a routine component of the cardiovascular evaluation for these individuals. Even when a family history is taken in the cardiology clinic setting, complexities of incomplete penetrance and variable expression can easily preclude the diagnosis from those with limited knowledge of clinical genetics. From a survey of 643 Dutch cardiologists (104) regarding their experience with genetic aspects of HCM (a known genetic disease), their self-reported genetic knowledge and skills indicated that 41% did not give genetics information to their HCM patients. Self-reported knowledge about genetics was low, but higher for those who had established a working relationship with a clinical geneticist. It has been proposed that the collaboration of cardiologists and genetics professionals will be most effective to optimize the care of patients with genetic cardiac disease (104,105).

Echocardiographic and electrocardiographic (ECG) screening. Echocardiography and electrocardiography permit safe, sensitive, noninvasive risk assessment. Clinical screening (exam, echocardiogram, ECG) of relatives of patients with IDC and FDC is warranted because a significant proportion of IDC patients have familial disease that may not be detected without formal screening, and once detected may assist in identifying more distant family members who are at risk. Also, FDC gene carriers often do not manifest symptoms of HF or arrhythmias until late in the disease process, usually with moderate or severe LVE and systolic dysfunction. Perhaps most important, early detection by clinical screening may lead to earlier treatment interventions that may slow disease progression.

We have previously recommended that all first-degree relatives (including parents) of patients with IDC undergo echocardiographic and ECG screening regardless of their family history (101,103). The recent American College of Cardiology/American Heart Association HF guidelines have also suggested that screening family members should be considered, and that for a highly positive family history of DCM referral to a cardiovascular genetics center is indicated (102). Despite careful pedigree analysis, it will

Table 2. FDC Disease Genes

Gene	Protein	Function	Disease Presentation/Characteristics	References
Autosomal Dominant FDC Dilated Cardiomyopathy Phenotype				
ACTC	cardiac actin	sarcomeric protein; muscle contraction	MMs in 2 unrelated families. Family 1 affected ages 2, 5, and 36 yrs; one unaffected at 15 yrs. Family 2 had 4 mutation carriers: 2 with IDC (14 and 14 yrs), and 2 borderline affected.	(42)
DES	desmin	dystrophin-associated glycoprotein complex; transduces contractile forces	MM, 1 family, 2 affected, 2 unaffected. Other deceased family members died between 15–37 yrs of HF.	(43)
SGCD	δ-sarcoglycan	dystrophin-associated glycoprotein complex; transduces contractile forces	MM in 1 family, onset of HF/SCD from 14–38 yrs; 2 IDCs with HF at 9 months and 14 yrs.	(44)
MYH7	β-myosin heavy chain	sarcomeric protein; muscle contraction	Ref. (45): MMs in 2 of 20 families. Family 1: age at diagnosis 2–57 yrs, 6 of 19 < 20 yrs at diagnosis; aggressive disease, HF, SCD. Family 2: 4 with very early onset (at birth, 2 and 11 yrs; 1 SCD at 2 months). Ref. (46): 2 MMs in 46 pts with IDC (mean age of IDC onset 29 years).	(45,46)
TNNT2	cardiac troponin T	sarcomeric protein; muscle contraction	Ref. (45): 2 unrelated families, same 3 bp deletion; early-onset DCM (of 14 affected, 2 infants, 3 teens, and 4 in 20s), prominent SCD. Ref. (48): 1 family, MM in 20; 14 affected, highly variable severity (HF, death in 2-yr-old, to minor symptoms later). Ref. (47): 1 family, same 3 bp deletion as Ref. (45), highly variable age of onset of HF.	(45,47,48)
TPM1	α-tropomyosin	sarcomeric protein; muscle contraction	MMs, 2 pts with FDC (of 350 unrelated pts with IDC/FDC). Family 1: onset at 26 yrs with NSVT; subsequent death while awaiting transplant. Family 2: onset at 3 months, transplanted at 10 years; mother with IDC.	(49)
TTN	titin	sarcomere structure/extensible scaffold for other proteins	1 MM, 1 NM, 2 large families. 1 family with LVE in teens. DCM, HF: transplant in 3rd–6th decades.	(50)
VCL	metavinculin	sarcomere structure; intercalated discs	3 bp deletion in a 39-year-old man with IDC; MM, 52-yr-old woman, 2 affected relatives.	(51)
MYBPC	myosin-binding protein C	sarcomeric protein; muscle contraction	MM in 1 of 46 young pts with IDC.	(46)
MLP/CSRP3	muscle LIM protein	sarcomere stretch sensor/Z discs	W4R mutation in 9 German pts (three families) from a cohort of 536 German patients with IDC: 0 of 136 Japanese IDC patients had the W4R mutation.	(52)
ACTN2	α-actinin-2	sarcomere structure; anchor for myofibrillar actin	MM in proband with DCM, died at 7 yrs; father died of IDC at 42 yrs (no DNA).	(53)
PLN	phospholamban	sarcoplasmic reticulum Ca^{++} regulator; inhibits SERCA2 pump	Ref. (54): NM, 1 family (of 20 screened) with aggressive, early-onset DCM, HF in 3rd decade; 4 of 12 transplanted. Ref. (55): 2 Greek families with same NM (from 76 unrelated pts screened), with DCM in 3rd decade in homozygous NM carriers; variable onset.	(54,55)
ZASP/LBD3	Cypher/LIM binding domain 3	cytoskeletal assembly; involved in targeting and clustering of membrane proteins	From a cohort of 100 unrelated individuals with DCM (15 with isolated noncompaction of LV myocardium, or INLVM), mutations identified in 6 pts, 2 (1 INLVM) FDC and 4 IDC (3 INLVM). Wide range of age of onset, from infancy to 2nd to 5th decades.	(56)
MYH6	α-myosin heavy chain	sarcomeric protein; muscle contraction	Preliminary report of 3 MMs from 66 FDC families	(57)

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Table 2 Continued

Gene	Protein	Function	Disease Presentation/Characteristics	References
Autosomal Dominant FDC Dilated Cardiomyopathy Phenotype				
ABCC	SUR2A	regulatory subunit of Kir6.2, an inwardly rectifying cardiac K_{ATP} channel	1 insertion/deletion mutation, 1 MM in 2 of 323 subjects with IDC. Age at diagnosis 40 and 55 yrs. Both with DCM, HF, ventricular tachycardia.	(58)
LMNA	lamin A/C	xinner leaflet, nuclear membrane protein; confers stability to nuclear membrane; gene expression	Ref. (59): MMs in 5 of 11 families (39 total affected) with DCM and CSD. Disease onset mean 38 yrs (range 19–53 yrs) with asymptomatic ECG changes in rate/rhythm, then progressive sinus/AV node dysfunction, 1st, 2nd, 3rd degree heart block; >50% had atrial fibrillation or flutter, >50% required pacemakers; >65% with DCM (mild LV dysfunction in 12, HF in 13); 6 transplants, 11 SCD; no MD. Ref. (60): 1 family, 5 affected (4–30 yrs), 3 with MD, mildly increased CK. Ref. (62): 2 large families with CSD progressive to DCM, HF, transplant, or SCD. Family 1: 11 affected of 18 MM+, mean disease onset at 43 yrs. Family 2: 12 affected of 14 NM+, mean disease onset at 31 yrs. No MD. Other reports with prominent CSD, age of onset usually 30–50 yrs, some HF, occasional MD. See Ref. (63) for CSD summary. Ref. (65) reported 4 MMs after screening 40 FDC and 9 IDC DNAs.	(59–66)
X-linked FDC				
DMD	dystrophin	primary component of dystrophin-associated glycoprotein complex; transduces contractile force	Males present at 20–40 yrs and have rapid disease progression; carrier females may be affected with a milder phenotype. May have skeletal myopathy. Creatine kinase levels may be increased.	(70,71)
TAZ/G4.5	tafazzin	unknown	Infantile, lethal dilated cardiomyopathy.	(83,85)
Recessive FDC				
TNN13	cardiac troponin I	sarcomeric protein, muscle contraction	One nuclear family, 2 homozygous siblings with DCM, and 1 sibling and parents who were heterozygous and had normal cardiovascular evaluations.	(86)

bp = base pair; CSD = conduction system disease; DCM = dilated cardiomyopathy; DNA = deoxyribonucleic acid; FDC = familial dilated cardiomyopathy; HF = heart failure; IDC = idiopathic dilated cardiomyopathy; LV = left ventricle; LVE = left ventricular enlargement; MD = muscular dystrophy; MM = missense mutation; NM = nonsense mutation; NSVT = non-sustained ventricular tachycardia; pts = patients; SCD = sudden cardiac death.

often not be possible to diagnose FDC without such formal cardiac testing, as relatives with cardiovascular abnormalities (who, if found to be affected, would establish the diagnosis of familial disease) may be asymptomatic. In one study 83% of relatives thought to have preclinical disease on echocardiograms or ECGs were asymptomatic (101). Clinical screening (echocardiogram and ECG) lead to the diagnosis of familial disease in 12% to 15% of apparently isolated (negative family history) IDC cases (32,40), demonstrating its greater sensitivity versus family history alone. When X-linked FDC is suspected, at-risk second-degree relatives should be screened as well.

Diagnosis of FDC. The diagnosis of FDC is made with two or more IDC diagnoses in closely related family members. Echocardiographic diagnosis is most straightforward for individuals with clear LVE accompanied by systolic dysfunction, who thus meet the diagnostic criteria for DCM; these individuals should undergo a full cardiovascular evaluation to rule out detectable causes of DCM such as ischemic etiology before being diagnosed with IDC (or FDC). Additional family members of an FDC kindred who meet diagnostic criteria for IDC can also be given the diagnosis of FDC.

Other diagnostic considerations for affected status in an FDC family. Perhaps the greatest difficulty that arises in screening relatives is determining whether subtle echo and ECG findings are significant and represent early signs of FDC. It has been suggested that LVE may be the single most useful criterion in identifying those with preclinical disease (32,39,106), but other criteria (e.g., the presence of multiple "minor" echocardiographic and/or ECG abnormalities) have also been proposed (19,106). Unlike in some genetic cardiac diseases (e.g., long QT syndrome), no ECG abnormalities are specific to FDC. Common findings include first- or second-degree heart block; atrial, supraventricular, or ventricular arrhythmias; typical or atypical intraventricular conduction delays; or loss of anterior or inferior forces suggestive of infarct patterns. As previously noted, FDC resulting from mutations in lamin A/C (Table 2) should be suspected in families with prominent CSD. Subtle echo findings, especially of ventricular size, are also common, and standardized criteria should be used to assess LV dimensions such as those based on body surface area (107) or the more recent height- and gender-based standards from the Framingham study (108). In some families, reviewing medical records on known affected individuals can provide a partial profile of the initial presentation and natural history of the disease in a particular family. However, because of intrafamilial variability, such retrospective review should only increase suspicion of preclinical disease and not decrease the suspicion of disease in an individual whose phenotype differs from that of known affected subjects.

STEPWISE SCREENING. If a family member has abnormal screening results and is suspected to have preclinical or clinical FDC, stepwise screening has been proposed, where first-degree relatives of any newly diagnosed individual would undergo screening (101). Stepwise screening would continue until first-degree relatives of all individuals with clinical or preclinical FDC have been screened.

Serial screening. Because the age of onset varies considerably, normal screening results do not exclude the possibility of future disease (109). Hence, we have suggested that adults with normal screening who have a first-degree relative with FDC should have a repeat echocardiogram and ECG every three to five years (101,109). Those with mild abnormalities or unexplained symptoms may wish to undergo more frequent screening. It may be reasonable to increase the time interval between screening studies for older individuals whose previous studies have been normal.

Considerations in affected but asymptomatic family members. A subset of family members identified to have asymptomatic echocardiographic or ECG abnormalities will progress to have symptomatic disease, including DCM, HF, arrhythmia, and/or sudden death (109). In one study, 27% of relatives found to have asymptomatic LVE by echocardiography progressed to symptomatic DCM over an average three-year follow-up period (39). However, early detection may enable the treatment and prevention of such problems. The use of angiotensin-converting enzyme inhibitors to slow disease progression in patients with asymptomatic IDC and left ventricular systolic dysfunction (as observed in the Studies Of Left Ventricular Dysfunction [SOLVD] prevention trial [110]) may, in a family with FDC, extend to relatives with asymptomatic LVE and normal systolic function. Such therapy has been recommended for some individuals with findings consistent with early disease (101), but outcomes studies to validate this approach in FDC have not yet been undertaken. Similar salutary effects with beta-blockers have been observed when treating subjects with symptomatic HF from either ischemic or idiopathic DCM (102). Both angiotensin-converting enzyme inhibitors and beta-blockers are generally well tolerated; therefore, physicians may wish to maintain a low threshold for their use in family members with evidence of presymptomatic disease, especially significant LVE.

Other recommendations. The potential role of lifestyle modifications for those at risk or with preclinical disease is unknown. Whether the avoidance of activities such as intensive aerobic or strength training may be beneficial is unknown. These issues have been addressed in the HF consensus guidelines (102). Certainly the avoidance of alcohol and illicit drugs should be encouraged; however, the contribution of these environmental factors to the pathogenesis of disease remains to be established. Because of the sudden cardiac death risk it is appropriate for family members to learn cardiopulmonary resuscitation techniques.

Screening children. In screening asymptomatic members of FDC families, clinical disease has been identified in small children and infants. Several of the benefits and limitations of screening adults extend to children, including the possi-

bility for treatment and the unknown significance of some screening results. Guidelines for the age at which children of a parent with IDC or FDC should be screened have not been established. Parents should be alert for symptoms of cardiac disease in at-risk children and should have a low threshold for having them evaluated. More aggressive presymptomatic screening is appropriate with disease onset in childhood in other family members. Echocardiograms and ECGs on children should be evaluated by centers that can interpret pediatric studies.

Limitations of recommendations. No expert panel or consensus guidelines regarding clinical care for patients or families with FDC have been developed. Further, formal prospectively designed studies are needed to substantiate the clinical benefit and cost-effectiveness of these screening and treatment recommendations.

GENETIC COUNSELING AND TESTING FOR FDC

Definition and goals of genetic counseling. Genetic counseling is a communication process that includes both educational and therapeutic elements targeted to patients and their families who face the risk of a genetic disorder (111). The majority of genetic counseling has traditionally been provided by masters' trained genetic counselors or geneticists; however, with greater recognition of genetic disease in all medical specialties, it will be increasingly important for other health providers to provide some level of genetic counseling as well.

A genetic counseling session for patients with or at risk for FDC typically includes 1) a review of the characteristics, genetics, and inheritance pattern(s) of FDC; 2) a thorough family history and pedigree analysis to ascertain the likely pattern of inheritance in the family and identify at-risk relatives; 3) an explanation of the benefits, risks, and limitations of clinical and/or genetic testing for affected individuals and their at-risk relatives; and 4) assisting the family in making psychosocial adjustments to the recognition of a potentially heritable disorder in the family (103,112,113).

Provision of genetic counseling for FDC. There are no established guidelines as to when it is appropriate to refer a patient with IDC/FDC for genetic counseling and, as a result, patients with IDC/FDC seldom receive genetic counseling from any source. As the potential genetic basis for IDC and FDC becomes more widely recognized by the cardiovascular community, cardiologists may provide more information regarding the genetics of IDC/FDC to their patients. Referrals to specialists (e.g., genetic counselors, geneticists, or cardiovascular specialists recognized as experts in genetic cardiomyopathies) may also become more common, especially in cases with severe phenotypes or extended family histories, or upon patient request. In any case, it is imperative for those providing genetic counseling to have the expertise to deal with the genetic and related psychosocial issues within the context of appropriate and up-to-date cardiovascular and genetic diagnosis, management, and insight into prognosis.

Psychosocial issues in counseling. Family members of patients with FDC should be counseled about the potential positive and negative consequences of screening, including clinical and genetic testing, and the associated uncertainties (Table 3). Many report significant anxiety regarding their own risk to develop disease. Undergoing clinical screening and following appropriate interventions may alleviate some anxiety, whether or not screening results are normal. However, that DCM can present with sudden death creates an obstacle to alleviation of anxiety for some.

The current state of genetic testing. Genetic testing for FDC is currently not widely available for two reasons. First, the number of different genes involved in IDC/FDC and the number of different possible mutations in each of these genes (i.e., locus and allelic heterogeneity) makes the development of a comprehensive genetic test difficult. Second, a significant proportion of FDC cases are not attributable to any of the known putative genes, making genetic testing relatively insensitive. It is expected that genetic testing will emerge with the identification of several additional genes that cause or contribute to the FDC phenotype and with advances in deoxyribonucleic acid (DNA) testing technologies. Nevertheless, although sensitive, comprehensive genetic testing may not be widely available for several years, it is prudent to consider the role genetic testing likely will play in the management of individuals with FDC and their families, as well as key issues related to genetic testing. For example, some phenotypes, such as prominent conduction system disease (especially in families requiring pacemakers,

Table 3. Possible Outcomes of Clinical Screening for Familial Dilated Cardiomyopathy*

	If Clinical Screening Normal:	If Clinical Screening Abnormal:
Positive consequences	Relief; removal of some uncertainty No immediate medical costs; insurance is not affected	Relief; removal of some uncertainty
Negative consequences	Survivor guilt possible	Anxiety, guilt, jealousy, anger Anticipation of worsening disease Medical costs; insurability concerns Offspring are at risk
Uncertainties remaining	Possibility of future disease Question of how often to rescreen Offspring remain at risk	Significance of screening results How aggressively to follow up Whether or not to begin treatment

*Clinical screening includes a medical and family history, electrocardiography, and echocardiogram; but not DNA testing.

see reference 63 for summary), raise the suspicion for specific etiologies such as lamin cardiomyopathy, for which testing may soon emerge. The discovery of additional FDC disease genes will augment genetic counseling by enabling prospective studies of gene penetrance, genotype-phenotype correlations, and the true incidence and prevalence of FDC.

Usual indications for genetic testing. Usual indications for genetic testing include confirmation of a known or suspected diagnosis, prediction of the possibility of future illness (presymptomatic testing), detection of the presence of a carrier state in unaffected individuals (whose children may be at risk), and prediction of response to therapy. Because not all IDC is due to inherited susceptibility, other individuals who might consider genetic testing include those with IDC who have a positive family history, family members of individuals with FDC who have an identified mutation, or individuals who have early-onset IDC.

Presymptomatic genetic testing. Presymptomatic genetic testing is testing performed on asymptomatic individuals who are at-risk for a particular genetic condition. The discovery of a gene mutation in such individuals indicates a heightened risk of development of findings related to the condition at some future point. Such testing must begin with an affected family member in order for the testing to be informative. If a putative causative mutation is identified in an affected individual, only then is it possible to offer informative testing to at-risk relatives; otherwise, the purported cause of FDC in the family has not been identified, and a negative test result may not reduce that individual's risk of FDC.

Benefits of genetic testing. CONFIRMATION OF DIAGNOSIS. Genetic testing is often used to facilitate the confirmation of a clinical diagnosis. Although the criteria to establish a diagnosis of IDC are straightforward, establishing a diagnosis of FDC is more difficult and in cases of negative or inconclusive family history, genetic testing may be the only way to confirm FDC.

EARLY DETECTION AND PREVENTION. The possibility of prophylactic intervention for those confirmed to be mutation carriers exists; however, the efficacy of such treatments remains uncertain. Clinical screening (albeit more vigilant) will remain the cornerstone of monitoring for disease presentation in mutation-positive individuals. It is for these reasons that genetic testing remains a case-by-case, individual decision.

EXCLUSION OF A CAUSATIVE MUTATION. In a family with a known mutation causative of FDC, excluding the mutation in an at-risk family member can be extremely beneficial. Periodic clinical screening would not be required and concerns regarding reproductive choices can be addressed.

Limitations of genetic testing. Genetic testing can provide only limited information about an inherited condition. Such testing cannot determine whether a person will show symptoms of a disorder, the severity of the symptoms, or its natural history. Although some prophylactic treatment measures may improve outcomes for individuals at risk for FDC, they have not been proven, and for some individuals there will be a lack of treatment strategies. Also, testing is limited by the sensitivity to detect genetic causation.

Informed consent process. Many commercial DNA laboratories require written documentation by a specialist before accepting DNA samples for presymptomatic genetic testing.

Clinical versus research genetic testing. Clinical genetic testing is performed by a laboratory subject to regulation by the federal Clinical Laboratories Improvement Act (CLIA), a law passed by Congress in 1988. Most research laboratories are not CLIA-certified and are therefore unable to provide clinical genetic results. Clinical and research genetic testing options are listed in a continuously updated database at the GeneTests/GeneClinics website (114).

Genetic counseling in the absence of genetic testing. For some genetic conditions, the demand for genetic counseling services has been driven by availability of genetic testing. For example, even though genetic counseling for individuals at-risk for breast and ovarian cancer was performed before the widespread availability of BRCA1 and BRCA2 testing, the demand for genetic counseling services increased significantly with the advent of the genetic tests (115). It seems logical that the same pattern would emerge once genetic testing for FDC becomes available.

Facilitating decisions about genetic testing is, however, only one aspect of genetic counseling. Counseling can be beneficial for patients with FDC and their family members for several other reasons. First, early detection and treatment of DCM is beneficial. Dilated cardiomyopathy causes substantial morbidity and mortality and treatment of advanced disease is costly, justifying measures to prevent or ameliorate it in its initial stages through the identification and clinical screening of at-risk individuals. Second, cardiologists often do not recognize FDC in their practices; among those who do, it is likely that few provide accurate risk assessment, genetic education, and screening recommendations. Third, with a diagnosis of FDC a host of difficult psychological, social, and ethical issues unique to genetic disease emerge, which often cannot be addressed in a routine cardiology clinic visit.

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