Family History of Dilated Cardiomyopathy among Patients with Heart Failure from the HF-ACTION Genetic Ancillary Study

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Abstract

Background: The value of family history (FH) is well established, but its sensitivity to detect familial dilated cardiomyopathy (FDC) has been infrequently examined.

Methods: A genetic ancillary study was created as a component of the HF-ACTION trial, a multicenter, prospective, randomized clinical trial of exercise in patients with heart failure and an ejection fraction <35%. A FH-based study using a structured questionnaire mailed to all consenting individuals was incorporated into the genetic ancillary. FH responses were analyzed for dilated cardiomyopathy (DCM) in family members.

Results: Of the 741 individuals with data available, 358 (48.3%) had nonischemic and 383 (51.6%) had ischemic etiology, and of these 164 (45.8%) and 201 (52.4%), respectively, returned evaluable questionnaires. Of those with nonischemic etiology, 14/164 (8.5%) reported at least one first-degree family member with DCM or an enlarged heart; another 21/164 (12.8%) reported a FH of "cardiomyopathy," a less specific term to indicate DCM.

Conclusion: At least 8.5% of patients with nonischemic etiology in the HF-ACTION genetic ancillary study provided FH indicating familial DCM, information important to inform further genetic analyses of this cohort and to plan other studies. Clin Trans Sci 2013; Volume 6: 179–183

Keywords: family history, dilated cardiomyopathy

Introduction

The value of family history (FH) has been established for assessing cardiovascular risk for coronary heart disease,[1] as has its role to establish the diagnosis of familial dilated cardiomyopathy (FDC).[2,3] However, the sensitivity of FH to detect FDC has been infrequently assessed with one earlier estimate of 5%.[4]

The HF-ACTION study provided a recent opportunity to further assess the ability of FH to detect FDC. HF-ACTION (**H**eart **F**ailure and **A** **C**ontrolled **T**rial **I**nvestigating **O**utcomes of Exercise Trai**N**ing) was a multicenter, prospective, randomized clinical trial that aimed to determine whether exercise could reduce morbidity and mortality in adult patients with symptomatic heart failure and an ejection fraction of 35% or less.[5]

During the design of the HF-ACTION clinical trial we proposed a genetic ancillary study to augment study findings and to explore other questions related to dilated cardiomyopathy (DCM) and heart failure. Because of our interest in the genetic basis of DCM,[6-9] a FH-based study focused on DCM was designed and incorporated into the HF-ACTION genetic ancillary.

Methods

Subject ascertainment

Subjects were ascertained from the HF-ACTION study; its entry criteria included patients with a left ventricular ejection fraction <35% and New York Heart Class II–IV heart failure on optimal medical therapy.[5] A total of 2,331 patients were enrolled at 82 centers in the United States, Canada, and France.[10] All patients participating in the HF-ACTION trial at sites with IRB approval for a genetic ancillary study were eligible for enrollment, which included providing a peripheral blood sample that would be used to prepare DNA for storage and later use. A component of the genetic ancillary was a FH study, which was based at the Oregon Health & Science University (OHSU) with the principal investigator (REH). Patients who were recruited to the genetic ancillary study were also asked if they wished to participate in the FH study, which included providing contact information to study personnel at OHSU and completing mailed questionnaires regarding personal medical and FH.

Subject consent

The genetic ancillary and FH study was approved by the Institutional Review Board at OHSU and at each of the other participating sites. Signed informed consent was obtained from all individuals participating in the genetic ancillary and the FH study at each of the individual's respective enrolling center.

Data and sample collection

For those individuals who enrolled in the FH study, the enrolling HF-ACTION site's study team, who had available clinical data to characterize the heart failure phenotype, adjudicated whether the subject had ischemic or nonischemic disease. A member of the research team at each HF-ACTION participating site communicated via a standardized fax form (Supporting Information *Data S1*) that was transmitted to OHSU for participating patients. The faxed information included the study participant's contact information and their cause of heart failure (ischemic or nonischemic), and if nonischemic, whether the cause was known, and if so, whether it was attributed to idiopathic, valvular, hypertension, alcohol, radiation, or some other cause (*Data S1*). Consenting patients were then sent one of two questionnaires based on the data received from the site at which they were enrolled. Patients reported to be ischemic were sent the first six pages of a questionnaire that asked for basic demographic information and questions specific to ischemic disease (heart attack, bypass surgery,

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Rank	History	Descriptors
1	Dilated cardiomyopathy	Dilated cardiomyopathy, enlarged heart
2	Cardiomyopathy	Weak heart, damage to heart muscle
3	Heart failure	Heart failure, congestive heart failure
4	Heart disease	Heart problems, heart related, heart blockage, angina, blocked arteries, broken heart, heart attack, valvular disease, sudden cardiac death, coronary artery disease, cardiac arrest/cessation, arrhythmia, slow beat, fast beat, beat problems, atrial fibrillation, hole in heart, mural thrombus, angina
5	Cardiovascular disease, other	Hypertension, hypotension, stroke, blood clots, thrombosis, hemorrhage, aortic aneurysm
6	Suspected cardiac disease	"Died in sleep," "died suddenly," "stopped breathing," dropped dead, seizure, other miscellaneous cardiovascular-related items that raise suspicion of cardiac etiology
7	Other	Cancer, noncardiovascular related accident, renal disease, infection
8	Unable to assess	Illegible entries, old age, natural causes, left blank
9	None	Explicitly stated "none"

Table 1. Family history categories.

	Total	Ischemic	Nonischemic
Consented to family history study	766	383	358
Gender			
Males	516	297	204
Females	247	86	151
Unknown or no data	3	0	3
Age			
Male and female, (mean, median, range, *n*)	61, 61, 23–90, 375	66, 67, 28–90, 204	55, 56, 23–84, 163
Males (mean, median, *n*)	62, 62, 23–90, 252	66, 67, 28–90, 160	56, 56, 23–84, 89
Females (mean, median, *n*)	58, 59, 29–82, 122	65, 66, 34–82, 44	54, 55, 29–79, 22
Race			
White	274	162	106
Black	84	26	55
Native American	20	14	6
Asian	4	3	1
Pacific Islander	1	1	0
Unknown[1]	383	177	190

[1]In most cases race was unknown because questionnaires were not returned.

Table 2. Participant demographics.

angioplasty/stent, coronary artery disease, angina, blocked arteries per cardiac catheterization) to confirm their ischemic diagnosis (Supporting Information *Data S2*). Patients with reported nonischemic disease were sent the full questionnaire that included the first six pages and an additional six pages containing a more extensive set of questions designed to gather information regarding the cause of their cardiomyopathy and heart failure (Supporting Information *Data S3*). Both questionnaires (ischemic and nonischemic) contained a detailed family medical history questionnaire. Participants were asked to return the questionnaire to OHSU by mail. Nonresponders were sent up to 3 reminder postcards at 1–2-month intervals soliciting questionnaire completion and return. Completed questionnaires received from study participants were filed in locked cabinets that were subsequently transported to the University of Miami and then to the Ohio State University upon relocation of study operations. The research team at the University of Miami entered all available questionnaire data, including pedigrees and all FH data, into Progeny (Delray Beach, FL, USA), a database designed for family based genetic research in use by the FDC Research Project.[6] Data entry was verified by study personnel and stored in the Progeny database.

Data analysis

A database query was conducted to collect the following FH information from each family member reported in the FH: cause of death, history of heart problems, type of heart problems, and other health history. All of the information reported was qualitatively analyzed and assigned eight possible categories (*Table 1*). The categories were ranked by relevance with the highest rank category taking precedence for analysis. After analyzing the medical history of all reported family members, the same rubric was applied to the entire family. For example, if an individual categorized as having heart disease had a relative with a "weak heart" (cardiomyopathy, rank 2, *Table 1*), the FH was categorized as positive for cardiomyopathy. All FH assignments were adjudicated by a genetic counselor (AM) with prior DCM research training and experience[3,8] and those ranked in categories 1 and 2 were reviewed by the study principal investigator (REH).

Results

Demographics

A total of 766 individuals from 38 study centers consented to the overall genetic ancillary and provided consent for participation in the OHSU family history study, of which 741 of the 766 (96.7%) had data available that allowed for adjudication of ischemic or nonischemic etiology; 383 (51.7%) were ischemic and 358 (48.3%) were nonischemic (*Table 2*). Of the patients who consented to the OHSU family history study, 383 of the 741 (50.0%) returned medical and FH questionnaires, and of these 383, 164 (45.8%) and 201 (52.4%) were from nonischemic and ischemic etiology, respectively. The average age of those with ischemic disease was approximately 10 years older than the nonischemic group (*Table 2*).

Clinical characteristics

Selected clinical characteristics from those with nonischemic etiology provide insight into this study cohort (*Table 3*). Symptoms leading to heart failure were conventional. Most patients had undergone coronary angiography, indicating that their assignment to a nonischemic category had been validated.

	N	% of total
Symptoms leading to diagnosis		
Fatigue	115	70.1%
Shortness of breath	108	65.9%
Dyspnea on exertion	108	65.9%
Orthopnea	79	48.2%
Paroxysmal nocturnal dyspnea	77	47.0%
Edema	71	43.3%
Irregular heart beat, palpitations	69	42.1%
Weight loss or gain	52	31.7%
Dizziness, fainting, loss of consciousness	51	31.1%
Flu-like symptoms	49	29.9%
Chest pain	47	28.7%
Tests and procedures		
Echocardiogram	158	96.3%
ECG	158	96.3%
Coronary angiogram	138	84.1%
Pacemaker	57	34.8%
Implantable cardiac defibrillator	54	32.9%
Ventricular assist device	8	4.9%
Heart transplant	1	0.6%
Pertinent social history		
Alcohol (past)	68	41.5%
Alcohol (current)	51	31.1%
Cigarettes (past)	66	40.2%
Cigarettes (current)	17	10.4%
Recreational drugs history	11	6.7%

Table 3. Clinical characteristics from questionnaires of 164 patients with nonischemic cardiomyopathy.

	Total
Ischemic cardiomyopathy	383
Coronary artery bypass surgery	194
Received one or more coronary stents	156
Myocardial infarction	297
Nonischemic cardiomyopathy	358
IDC	159
Negative coronary angiogram	107
FDC	2
PPCM	8
Valvular	13
Mitral valve replacement	6
Aortic valve replacement	6
Not specified	2
Hypertension	51
Alcoholic	2
Adriamycin	6
Radiation	1
Other[1]	21
Not specified	105

[1]Myocarditis/viral ($n = 12$), rheumatic fever ($n = 2$), arrhythmia/cardiac arrest ($n = 1$), lupus ($n = 1$), muscular dystrophy ($n = 1$), nonobstructive coronary artery disease ($n = 1$), sarcoid ($n = 1$), thrombocytopenic purpura ($n = 1$), obesity ($n = 1$).

Table 4. Study site coordinator assignments.

Substance abuse was minimal consistent with recruitment of a selected population for a clinical trial.

Study site coordinator diagnostic assignments

Study site coordinator etiologic assignments were congruent with diagnoses from the medical history questionnaires in all cases except one patient with nonischemic disease (*Table 4*). By study site coordinator data, most patients with ischemic etiology had a myocardial infarction, coronary artery bypass grafting, or a percutaneous coronary intervention, confirming their ischemic etiology, and all had information supporting of ischemic etiology noted on the medical history questionnaires.

The nonischemic group contained a variety of study coordinator assigned causes (*Table 4*). In only one case did the study site coordinator assignment (IDC) vary from that of the patient's medical history (coronary artery disease), although it is also possible that the patient may have developed coronary artery disease after the IDC diagnosis.

Family history

Participants with nonischemic disease reported 1,019 first-degree, 1,245 second-degree, and 5 third-degree relatives. Participants with ischemic disease reported 1,317 first-degree, 349 second-degree, and 14 third-degree relatives.

Of the 358 probands with nonischemic etiology, 14 of the 164 with evaluable questionnaires (8.5%) reported at least one family member with DCM (*Table 5*). To describe their family history of DCM, respondents used the terms "dilated cardiomyopathy" ($n = 1$) or "enlarged heart" ($n = 21$), the latter term considered as a surrogate lay term for DCM. Of these 22 relatives, 15 were first-degree, 6 were second-degree and one was a third-degree relative.

Twenty-one other respondents of the 164 with evaluable questionnaires in the nonischemic group (12.8%) indicated they had a FH of "cardiomyopathy" (*Table 5*), which was considered less specific for DCM than "dilated cardiomyopathy" or "enlarged heart," although this terminology may well have represented DCM in some cases.

We also tabulated progressively more general terms reflecting cardiovascular disease in the family histories of those respondents of the nonischemic group. These terms included "heart failure," reported in the family histories of 34, or an even more generic term "heart disease" in 75 (*Table 5*). Again, because of the limited study design we were unable to obtain medical records of family members to validate these family histories.

Among the 383 participants with ischemic heart disease for whom FH information was available, 8 reported at least one other relative with DCM, only 2 reported a FH of cardiomyopathy (type not specified), fewer than those in the nonischemic group (*Table 5*). However, 47 and 115 reported a FH of heart failure or heart disease, more than the nonischemic respondents.

	Nonischemic	Ischemic
Total number	358	383
Number of questionnaires assessed	164	201
Number of questionnaires not returned or no data	194	182
Data components[1]	*N* (% of total; % of questionnaires assessed)	*N* (% of total; % of questionnaires assessed)
Dilated cardiomyopathy	14 (3.9%; 8.5%)	8 (2.1%; 4.0%)
Cardiomyopathy	21 (5.9%; 12.8%)	2 (0.5%; 1.0%)
Heart failure	34 (9.5%; 20.7%)	47 (12.3%; 23.4%)
Heart disease	75 (20.9%; 45.7%)	115 (30%; 57.2%)
Cardiovascular disease, other	5 (1.4%; 3.0%)	14 (3.7%; 7%)
Suspected cardiovascular disease	1 (0.3%; 0.6%)	1 (0.3%; 0.5%)
Other	9 (2.5%; 5.5%)	12 (3.1%; 6%)
None	5 (1.4%; 3.0%)	2 (0.1%; 1%)

[1]Data components from family history questionnaires as described in *Table 1*.

Table 5. Family history questionnaires.

Discussion

This OHSU Family History study was undertaken as a component of the HF-ACTION genetic ancillary in an effort to detect FDC diagnoses in those HF-ACTION participants who had nonischemic DCM as an etiology. The study utilized a comprehensive medical and FH questionnaire that was sent to consenting individuals. The questionnaire was designed to accomplish two objectives: to validate nonischemic or ischemic diagnoses provided by the HF-ACTION site personnel where an individual was recruited, and to determine if familial DCM was present from FH. We note that, to our knowledge, this is the first study to attempt to define the frequency of familial DCM in an NHLBI-sponsored cardiovascular clinical trial.

The first objective was attained, as the questionnaire data from patients agreed with site personnel diagnoses in all cases except one, in which nonischemic cause by site personnel was reported while the patient questionnaire indicated ischemic disease. However, it is possible that the ischemic disease occurred after the diagnosis of nonischemic disease. The second objective was also attained, as a family history of cardiomyopathy was identified in some patients with nonischemic diagnoses, and of the 164 who returned questionnaires, the frequency of familial DCM was reported by 14, or 8.5% of the cohort who returned questionnaires.

Of the 358 assigned as nonischemic by study coordinators (Table 4), 159 (44%) were assigned as IDC, of which 2 had FDC and 8 were indicated to have peripartum cardiomyopathy. This estimate of IDC as a fraction of those with nonischemic cardiomyopathy appears low when compared to the Beta-Blocker Evaluation of Survival Trial (BEST), another NIH-supported heart failure trial, that assigned IDC to 379 of 563 (67.3%) with nonischemic etiology.[11] However, in our study 105 had no etiologic assignment provided beyond classifying into the "nonischemic" category, which may explain this difference. Further, 94 had a variety of other diagnoses assigned (valvular, hypertension, alcohol, adriamycin, radiation and others) beyond that of nonischemic cardiomyopathy. While a consensus has emerged that FDC has a genetic basis, whether IDC shares a similar genetic basis remains uncertain. Further, whether any of these subcategories of nonischemic cardiomyopathy may have a rare variant genetic background, similar to FDC or IDC, remains unknown but now becomes a testable hypothesis.

This information is valuable because it will help to inform genetic analyses of the DNA specimens collected from these individuals who participated in the HF-ACTION genetic ancillary study, especially for studies that may be undertaken to evaluate a genetic basis of the nonischemic cardiomyopathies of the 358 individuals so categorized. The HF-ACTION genetic ancillary study was a multisite NHLBI-sponsored heart failure study that recruited from a very broad geographic area of North America with participants from 38 sites in North America, which may be particularly helpful to generalize any results from genetic studies to the larger heart failure population.

It has been well established that FH is less sensitive than the clinical screening of first-degree family members by history, exam, echocardiography and ECG,[2,9] with one study showing that only 5% of FDC was detected by family history while 20% was detected by clinical screening of family members.[4] This information suggests that the estimate of FDC ranging up to 12.5% suggested in this study may be plausible, and that to identify the true fraction of patients whose family members have DCM, family members must undergo clinical screening (echocardiogram, ECG), procedures that exceeded the scope of this study.

Limitations

None of the diagnoses provided by the index patients (i.e., the HF-ACTION participants) for their family members and attributed as DCM were validated by review of the family members' medical records. Nevertheless, all of these patients were recruited at medical centers that provided information about the family study, its background and its goals, including information that DCM may run in families, and most patients with nonischemic cardiomyopathy, as inferred from their questionnaire responses that showed almost universal concordance with their coordinator-specified diagnosis, understood that their DCM was not a consequence of coronary artery disease, which increases the likelihood that the DCM they reported in their relatives correctly assigned ischemic or nonischemic etiology. We presume that the 164 who returned questionnaires were a representative sample of the 358 in the nonischemic group, although it is possible that those with a positive family history of DCM may have preferentially participated in this study. Even so, the most conservative estimate of familial DCM would be 14 of 358, or 3.9%.

Conclusion

This family history study, a component of the HF-ACTION genetic ancillary, suggested that at least 8.5% of patients with nonischemic DCM had family history consistent with familial DCM.

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Supporting Information.

Additional Supporting Information may be found in the online version of this paper:

Data S1. Standardized fax form.
Data S2. The Genetic Basis of Dilated Cardiomyopathy Study (GDC Study), Screening Questionnaire.
Data S3. The Genetic Basis of Dilated Cardiomyopathy Study (GDC Study), Comprehensive Questionnaire.

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