Familial Hypertrophic Cardiomyopathy Is a Genetically Heterogeneous Disease

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Abstract

We demonstrate that familial hypertrophic cardiomyopathy (FHC), an autosomal dominant disorder of heart muscle, is a genetically heterogeneous disease. The locus responsible for FHC in members of one large kindred was recently mapped to chromosome 14q11-12 (FHC-1). We have characterized three additional unrelated families in which the gene for FHC segregates as an autosomal dominant trait to determine if these disease loci also map to FHC-1. All family members were clinically studied by physical examination, electrocardiogram, and two-dimensional echocardiography. Genetic studies were performed using DNA probes which are derived from loci that are closely linked to FHC-1. In one family the genetic defect maps to the previously identified FHC-1 locus. However, the loci responsible for FHC in two other families were not linked to FHC-1. We conclude that FHC can be caused by defects in at least two loci and is a genetically heterogeneous disorder. (*J. Clin. Invest.* 1990. 86:993–999.) Key words: familial hypertrophic cardiomyopathy • heterogeneity • linkage

Introduction

Familial hypertrophic cardiomyopathy (FHC)[1] is a primary disorder of cardiac muscle that is inherited in an autosomal dominant fashion (for reviews see 1, 2). It is characterized clinically by a spectrum of symptoms including dyspnea, chest pain, syncope, and sudden death. The pathologic findings of the disease include increased myocardial mass with right and/or left ventricular hypertrophy and myocyte disarray. There is significant heterogeneity in the clinical and pathologic expression of FHC (1) found in affected individuals from the same family, all of whom must bear the same genetic defect. The extent, distribution, and severity of myocardial hypertrophy may vary considerably and clinical symptoms can be debilitating, mild, or absent. Because of the variability in symptoms and diagnostic findings in affected individuals within families, clinical parameters which might distinguish different genetic etiologies between families have not been demonstrated. Thus, whether FHC is caused by defects in a single gene in all families, or whether it is genetically heterogeneous and caused by defects in different genes in unrelated families, is uncertain.

A number of diseases inherited as autosomal dominant traits, including polycystic kidney disease and neurofibromatosis, have been shown to be genetically heterogeneous (3, 4). The method for demonstrating genetic heterogeneity is now well defined (5) and requires three prerequisites: first, the map position of the locus responsible for the disease in one family must be identified; second, DNA markers that are linked to this locus and that recognize restriction fragment length polymorphisms (RFLPs) in human DNA must be available; third, a number of families in which the disorder segregates must be identified. Then, the co-inheritance or lack of co-inheritance of the disease with the linked loci can be defined, and the genetic heterogeneity or homogeneity of the disease ascertained.

We have recently mapped the FHC locus segregating in a large kindred to chromosome 14 band q11-12 (designated FHC-1) (6, 7). We have identified three DNA probes, CRI-L436, CRI-L329, and pSC14, that identify RFLPs in DNA and which correspond to loci that are closely linked to the FHC-1 locus. To determine whether defects in the FHC-1 locus are responsible for the disease in all families, we performed clinical and genetic evaluations of individuals from three unrelated families. We demonstrate that in one family the disease is due to defects in the FHC-1 locus. However, the genetic defect(s) responsible for FHC in two other families is not linked to FHC-1, establishing that FHC is a genetically heterogeneous disorder.

Methods

Clinical evaluations. Family members 16 yr of age or older and all individuals with known heart disease were evaluated by physical examination and 12-lead electrocardiography. Electrocardiograms were interpreted according to standard criteria (8). Complete two-dimensional echocardiography, with left and right ventricular views and Doppler ultrasonography, was performed in all family members in generation I of each pedigree, all children whose parents were affected, and any

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1. *Abbreviations used in this paper:* FHC, familial hypertrophic cardiomyopathy; LOD, logarithm of the odds; LVH, left ventricular hypertrophy; LVWT, left ventricular wall thickness; RFLP, restriction fragment length polymorphism.

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family member with an abnormal physical examination or electrocardiogram. Echocardiography was performed as previously described (6). Measurements of wall thickness and cavity dimensions and the presence or absence of systolic anterior motion of the mitral valve were determined according to established protocols (9, 10). The diagnosis of hypertrophic cardiomyopathy was based on the two-dimensional echocardiographic demonstration of unexplained left, right, or biventricular hypertrophy (11, 12), or characteristic EKG findings in a high-probability individual, and was made without knowledge of DNA patterns. None of the family members evaluated had a history of systemic hypertension or a resting blood pressure > 140/90 mm Hg. Disease status of deceased family members was determined by premortem diagnosis or postmortem examination. Clinical symptoms and diagnostic findings in these families were analyzed by contingency table analyses and one-factor analysis of variance.

Linkage analyses. Blood samples obtained from family members numbered in Fig. 1 were used to establish lymphoblastoid cell lines by Epstein-Barr virus transformation, as described previously (13, 14). DNA isolated from cell lines was used for genetic studies. RFLP analyses were performed to define alleles present in each family member using three DNA probes that are closely linked to the FHC-1 locus (6, 7). Both CRI-L436 (derived from an anonymous locus, D14S26) and CRI-L329 (derived from an anonymous locus, D14S25) were obtained from Collaborative Research Inc. (Cambridge, MA) and recognize Taq 1 polymorphisms (15). CRI-L436 identifies two alleles, a 4.2-kb fragment (allele 1, allele frequency, 0.52) or a 2.2-kb and a 1.8-kb fragment (allele 2, allele frequency 0.48). CRI-L329 identifies three alleles, a 12.0-kb fragment (allele 1, allele frequency 0.63), a 9.5-kb fragment (allele 2, allele frequency 0.01), and an 8.5-kb fragment (allele 3, allele frequency 0.36). Probe pSC14, kindly provided by Dr. H.-P. Vosberg, is derived from the β myosin heavy chain gene, and recognizes a Bam H1 polymorphism (16). This probe recognizes a 3.5-kb fragment (allele 1, allele frequency 0.68) and a 1.6-kb fragment (allele 2, allele frequency 0.32) (17).

Two of us analyzed the restriction fragment pattern identified by each DNA probe, independently and without knowledge of each family member's disease status, to determine the alleles present in an individual. A set of LOD (logarithm of the odds) scores was then ascertained for each DNA probe at given recombination fractions, θ, using the computer program MLINK (18). A LOD score represents a

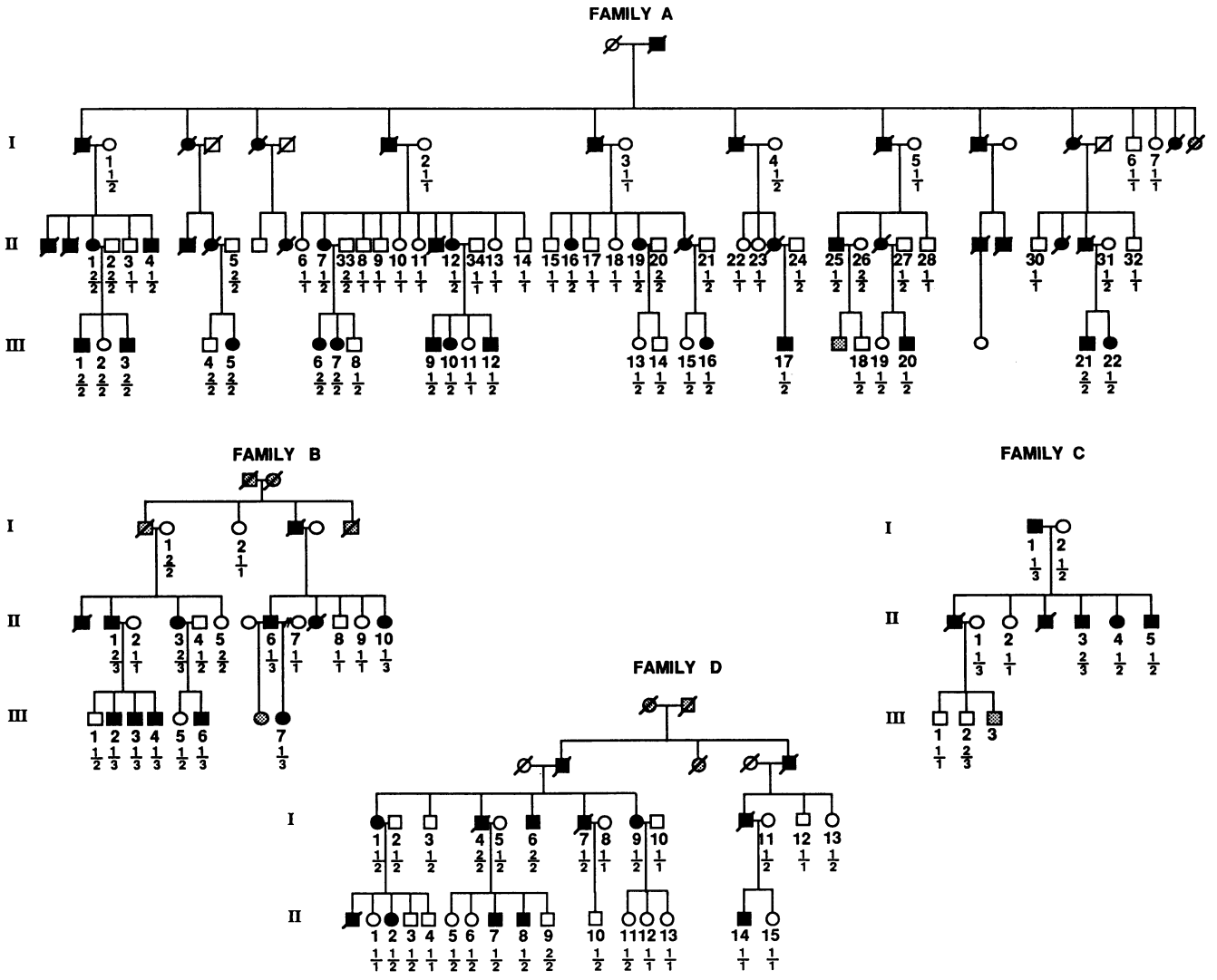


Figure 1. Pedigrees of four families with FHC. Alleles are shown for the most informative probe for each family: CRI-L436 for family A, pSC14 for family B, CRI-L329 for family C, and pSC14 for family D. Circles represent females, squares represent males. Darkened symbols indicate affected individuals, clear symbols indicate unaffected individuals, and hatched symbols indicate unknown disease status. Deceased individuals are slashed. The double slash in family B signifies divorce.

ratio of the probability of observing co-inheritance of two loci assuming they are linked, to the probability of detecting co-inheritance of loci assuming they are unlinked. LOD scores above +3 indicate that the observed data are 1,000-fold more likely to occur if the analyzed loci are linked than if they are unlinked, and is generally accepted as evidence of linkage. A LOD score of less than −2 is generally accepted to disprove linkage between a pair of loci at a given distance.

Multipoint analyses were performed using the LINKMAP program (19), assuming that the penetrance of the FHC gene is 0.95 (7). The physical order of probes used in multipoint analyses was based on linkage order data obtained by evaluating alleles identified by probes CRI-L436, CRI-L329, and pSC14 in unaffected individuals (7). Frequencies used in linkage calculations were determined independently in the population studied.

Data were also analyzed with the admixture test of genetic homogeneity (5). This test compares the likelihood that all families are linked to the marker loci with the likelihood that some of the families are linked and some of the families are not linked. This analysis was carried out with the computer program HOMOG (20).

Results

The four families analyzed in this study are shown in Fig. 1. Family A is a large French-Canadian kindred described previously (6). Family B is a family of Northern European descent, residing in the U.S. Family C is of Sikh-Indian descent, residing in the United Kingdom, and was previously known to Dr. McKenna. Family D is of Eastern European descent and resides in the United States. Families B and D were referred to us when one affected member was evaluated for cardiac transplantation. Individuals affected with FHC are present in multiple generations of these families and in each the disease segregates as an autosomal dominant trait. There is a high degree of disease penetrance in these families.

A summary of clinical and diagnostic findings in the affected members of these four families is shown in Table I. Six individuals without conventional echocardiographic criteria of FHC are classified as affected. In family A, subject II-4 had undergone septal myectomy 17 yr before this evaluation, with documented regression of left ventricular hypertrophy (LVH); subject III-6 has right ventricular hypertrophy (right ventricular wall thickness 12 mm) with hyperdynamic left ventricular systolic function and incomplete systolic motion of the anterior mitral valve. In family B, individual II-1 was referred for cardiac transplant evaluation and had been documented to have regression of LVH in association with left ventricular dysfunction; individual III-7 is an asymptomatic 16-yr old with an abnormal EKG showing T-wave inversion in leads V4-6. In family D individual I-1 underwent cardiac transplantation. The explanted heart weighed 350 g; the left ventricular free wall and septum measured 1.5 and 1.4 cm, respectively. Microscopic examination revealed dense interstitial fibrosis of the interventricular septum and right and left ventricular apices. Individual II-8 is a 34-yr-old asymptomatic male with an abnormal EKG showing a deep S wave (0.35 mV in V2), T-wave inversion in leads II, III, aVf, V6, and flat ST segments in leads I, aVl, and V5.

The echocardiographic findings in affected members of these families are typical of those seen in FHC. In each family there was an increase in the maximal thickness of left ventricular wall (mean values for families A, B, C, and D were 20, 25, 21, and 23 mm, respectively). Right ventricular hypertrophy was present in 40% of affected members from family A, 11% of affected members from family B, 25% of affected members from family C, and 22% of affected members from family D. Left atrial enlargement was present in affected family members (mean values for families A, B, C, and D were 44, 36, 34, and 40 mm, respectively).

Sudden cardiac and disease-related mortality was common in these families. 20 individuals from family A died prematurely (before age 45). 7 of 12 disease-related deaths were sudden; 2 deaths were of noncardiac causes; and 6 deaths were of undetermined causes. Deaths in affected individuals of family B were disease-related in three, of which one was sudden (age 16). Two individuals died prematurely in family C, one at age 30 (cerebral vascular accident), and one suddenly at age 22. Individual II-5 of family C was successfully resuscitated from ventricular fibrillation. Five individuals from family D had disease-related deaths; one occurred while awaiting cardiac transplantation (age 44) and four were sudden (ages 14, 43, 53, and 69).

Contingency table analyses were performed to determine if differences in symptoms or diagnostic findings (Table I) could be distinguished between these families. Only the symptom of chest pain was discriminating, being absent from all members of family D, but found in some affected members of all other families ($P < 0.05$). One-factor analysis of variance was performed to investigate differences between families in left ventricular wall thickness (LVWT) and left atrial size by echocardiogram. Mean LVWT was not significantly different between families, whereas left atrial size differed between members of family C and members of families A and D ($P < 0.05$).

Linkage analysis. We have previously shown that FHC-1 is closely linked to locus D14S26 identified by probe CRI-L436 (6). There was complete concordance between inherited alleles defined by probe CRI-L436 and disease status in family A (0 recombinants among 37 informative individuals, Fig. 1). The locus D14S26 is closely linked (4 cM) to locus D14S25, defined by probe CRI-L329 (15), and to the cardiac β myosin heavy chain gene, identified by probe pSC14 (2.2 cM) (7). We have recently shown that the FHC trait cosegregates with alleles defined by pSC14 in family A (7). If defects in the FHC-1 locus were responsible for disease found in members of families B, C, and D, we would have expected to find co-inheritance of the alleles defined by these three probes and disease.

Linkage between the locus responsible for FHC in families B, C, and D and each of the marker loci was assessed using two-point linkage analysis (Table II). LOD scores were calculated after assigning alleles defined by three probes, CRI-L436, CRI-L329, and pSC14, and determining the disease status of family members.

The small LOD scores achieved with probes CRI-L436 and CRI-L329 in family B indicate that only a limited number of informative individuals were detected with these probes (CRI-L436: two informative meioses; CRI-L329: three informative meioses). Analysis of family B with probe pSC14 demonstrated a new allele of 2.8 kb, designated allele 3, in addition to previously characterized alleles 1 (3.5 kb) and 2 (1.6 kb) (16). Allele 3 was inherited by all affected members of this family (Fig. 1). Probe pSC14 demonstrated significant linkage between the cardiac myosin β heavy chain gene and the gene responsible for FHC in family B (Table II). A maximum LOD score of 4.35 was achieved when individual III-7 is scored as affected (see Clinical analyses, above). A maximum LOD

Table I. Clinical Characteristics of Affected Family Members

		Clinical symptoms			Electrocardiogram			2-D Echocardiogram			
Subject	Age/Sex	Chest pain	Dyspnea	Syncope	BBB	Abn Q	LVH	Max LVWT	RVH	SAM	LA size
								mm			*mm*
AII-1	42/F	+	III	+	R	−	−	20	−	−	45
AII-4	35/M	−	III	−	L	−	−	10	+	+	49
AII-7	45/F	+	II	−	−	−	+	25	−	+	45
AII-12	41/F	+	II	−	−	−	+	20	−	−	45
AII-16	44/F	−	II	−	−	−	+	22	−	−	45
AII-19	47/F	+	II	−	−	+	+	15	+	−	37
AII-25	44/M	−	I	−	−	−	+	19	−	−	52
AIII-1	22/M	+	II	+	−	+	+	28	−	+	34
AIII-3	21/M	−	II	−	−	+	+	30	+	+	40
AIII-5	29/F	−	II	−	−	−	+	21	−	+	39
AIII-6	24/F	−	II	−	−	−	+	12	+	+	35
AIII-7	22/F	+	II	−	−	−	+	17	−	+	41
AIII-9	24/M	−	I	−	−	−	+	28	+	−	41
AIII-10	23/F	+	II	−	−	+	+	22	−	+	39
AIII-12	18/M	+	II	−	−	−	+	18	−	+	44
AIII-16	23/F	−	II	+	−	−	+	16	−	+	47
AIII-17	17/M	−	II	−	−	−	+	28	+	+	40
AIII-20	22/M	+	IV	−	−	+	+	22	+	+	65
AIII-21	23/M	+	I	−	−	−	+	30	−	++	49
AIII-22	22/F	−	I	−	R	−	−	34	+	++	55
BII-1	44/M	+	IV	−	R	−	−	12	−	−	55
BII-3	32/F	+	III	−	−	−	+	30	−	++	36
BII-6	43/M	−	II	−	−	−	+	25	−	+	33
BII-10	52/F	+	II	−	R	−	+	20	+	+	33
BIII-2	16/M	+	II	−	−	+	+	24	−	+	32
BIII-3	9/M	+	II	−	L	−	+	20	−	++	40
BIII-4	13/M	−	II	−	−	−	+	35	−	+	33
BIII-6	12/M	+	II	−	−	−	+	23	−	+	32
BIII-7	16/F	−	I	−	−	−	+	10	−	+	28
CI-1	63/M	−	I	+	−	−	−	20	−	−	33
CII-3	28/M	−	I	−	−	−	+	18	+	+	37
CII-4	25/F	+	I	−	−	−	+	28	−	+	34
CII-5	22/M	−	I	+	−	−	+	20	−	−	32
DI-1	56/F	−	IV	−	L	−	−	15	−	−	52
DI-4	69/M	−	II	−	−	−	+	26	−	−	46
DI-6	47/M	−	I	−	−	−	+	25	−	−	49
DI-7	41/M	−	IV	−	−	+	+	17	+	−	49
DI-9	52/F	−	I	−	−	+	+	35	−	−	35
DII-2	25/F	−	II	+	−	−	+	27	−	++	37
DII-7	35/M	−	I	−	−	−	+	25	−	+	39
DII-8	34/M	−	I	−	−	−	+	13	−	−	38
DII-14	35/M	−	I	−	−	+	−	17	+	+	29

Electrocardiograms were performed and the presence of bundle branch block (BBB; *R*, right, *L*, left), abnormal Q waves (ABN Q) and left ventricular hypertrophy with or without associated ST changes (LVH) were noted. Echocardiographic findings include maximum left ventricular wall thickness (MAX LVWT), right ventricular hypertrophy (RVH), systolic anterior motion of the mitral valve (SAM; + incomplete, ++ complete) and left atrial size (LA SIZE).

score of 3.04 is achieved if individual III-7 is scored as unaffected. These data demonstrate that the locus responsible for the disease gene in family B maps to the FHC-1 locus.

Linkage analysis with probe CRI-L436 was uninformative in family C (no informative individuals). This probe detected one recombinant in five informative individuals in family D. Significant negative LOD scores (less than −2) were achieved with probe L329 for family C and probe pSC14 for family D at

Table II. Two-Point Linkage Analysis of Families with FHC

Family	Probe	Recombination fraction						
		0	0.05	0.1	0.15	0.2	0.3	0.4
A	L436	10.70	9.80	8.85	7.87	6.83	4.60	2.16
	L329	−0.73	1.80	1.88	1.80	1.65	1.23	0.68
	pSC14	4.62	4.16	3.69	3.22	2.74	1.79	0.86
B	L436	0.78	0.76	0.69	0.61	0.51	0.28	0.10
	L329	−0.27	−0.04	0.05	0.10	0.11	0.08	0.03
	pSC14	4.35	3.98	3.59	3.18	2.74	1.81	0.82
C	L436	0	0	0	0	0	0	0
	L329	−3.82	−1.65	−1.08	−0.73	−0.49	−0.19	−0.05
	pSC14	−1.46	−0.93	−0.64	−0.44	−0.30	−0.12	−0.02
D	L436	−0.14	0.09	0.19	0.24	0.24	0.19	0.10
	L329	−1.15	−0.57	−.031	−0.16	−0.09	−0.04	−0.01
	pSC14	−4.21	−1.28	−0.76	−0.49	−0.33	−0.16	−0.06

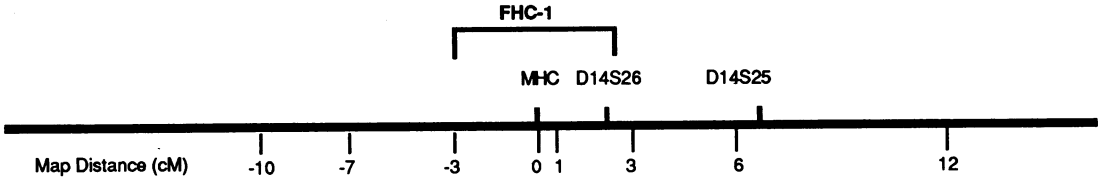
Two-point linkage analysis of four families with probes CRI-L436, CRI-L329 and pSC14. LOD scores are presented at various recombination distances and were calculated using the MLINK computer program with an assigned penetrance of 0.95 and published gene frequencies (see Methods).

0 cM (Fig. 1), suggesting that the gene defect responsible FHC in members of these families is not located on chromosome 14 band q11-12.

Multipoint analysis allows for the determination of disease linkage to a set of marker loci whose relative locations are known (18). Thus, multipoint analysis provides an estimation of the likelihood that the disease gene is located at a given position with respect to a map of known loci. Multipoint analysis was performed using the following order of loci: MHC-D14S26-D14S25 (the most likely order of these loci) (7). Fig. 2 shows a table of multipoint LOD scores and a linkage map of the FHC-1 locus.

Genetic heterogeneity is demonstrated when there is discordance in the inheritance (or lack of co-inheritance) of a disease locus and DNA marker loci in different families. The admixture test of heterogeneity (5) examines the hypothesis that there are two groups of families, one that is linked to the marker locus and another that is not, and compares it with the hypothesis that the marker locus (or loci) is linked to the disease in all the families. The admixture test performed with families A, B, C, and D revealed that the probability of obtaining the observed results, if individuals in all four families were affected by defects in a single genetic locus, was less than 1 in 10,000, (χ^2 = 14.50 with one degree of freedom) demon-

Map Distance (cM)	-10	-7	-3	0	1	3	6	12	Probability*
Family A	10.85	11.64	12.39	13.13	13.07	12.67	10.7	10.47	>.99
Family B	3.62	3.88	4.14	4.39	4.29	4.17	3.07	2.69	>.99
Family C	-0.27	-0.67	-1.35	-4.65	-2.6	-1.62	-1.07	-0.14	<.0001
Family D	-0.92	-1.18	-1.54	-2.08	-2.14	-2.32	-3.26	-1.42	<.0085



* Probability of Linkage to FHC-1

Figure 2. Multipoint linkage analyses for four families with FHC. LOD scores were determined using the LINKMAP computer program; the probability of genetic heterogeneity was calculated using the HOMOG computer program (see Methods). A schematic map of chromosome 14q1 is shown. Loci MHC (β myosin heavy chain, identified by pSC14), D14S26 (identified by probe CRI-L436), and D14S25 (identified by probe CRI-L329), are indicated with map distances (cM) determined by linkage analyses. The zero point is arbitrarily defined as the place of maximum combined LOD score for the linked families A and B, and predicts the most likely (95% confidence) location for the FHC-1 gene.

strating that FHC is genetically heterogeneous in these families. The admixture test further allows calculation of a posterior odds of linkage, which defines the probability that one of the study families is linked to particular marker loci (Fig. 2). Thus, the genetic defect responsible for FHC in members of families A or B is linked to FHC-1 (odds greater than 99 in 100), while the defect responsible for FHC in members of families C or D is not linked to FHC-1 (odds less than 7 in 1,000).

Discussion

Familial hypertrophic cardiomyopathy is a heterogeneous disease by clinical, echocardiographic, and pathologic criteria (1, 9, 10). The results of this study conclusively demonstrate that FHC is a genetically heterogeneous disease as well. Using three DNA probes from chromosome 14 band q1, we have shown that the genetic defect responsible for FHC in members of families A and B is closely linked to this region of chromosome 14. However, the probability that the gene defect responsible for the disease in members of two other families (C and D) maps to FHC-1 is less than 1 in 10,000. We have designated the FHC locus on chromosome 14 q11-12 as FHC-1 and anticipate that there will be other FHC loci identified elsewhere in the genome.

The location and number of other FHC loci remains uncertain. The data presented do not suggest how many other genes, unlinked to the FHC-1 locus, can cause disease. At present we cannot determine whether the gene responsible for FHC in affected members of family C is the same as the disease gene in affected individuals of family D. Further, since a limited number of families have been genetically analyzed to date, it is currently unclear if one locus predominates in causing FHC. Development of more closely linked, informative probes will facilitate analyses in many more families.

Genetic heterogeneity does not explain the variable clinical expression of FHC. There are no obvious objective features of the disease in affected members from families A and B that distinguish them from affected members from families C and D. The minor clinical and echocardiographic differences demonstrated above should be viewed with caution, considering the small numbers of affected individuals analyzed. The variability of symptoms and diagnostic findings within these four families is as great as the interfamily variability and suggests that the range of clinical expression of this disease is not explained by unique causative genes or by particular mutations within responsible genes. Diverse manifestations of this disease in individuals within the same family suggest that developmental, physiologic, or hormonal factors regulate disease expression independent of the genetic etiology.

Evidence that FHC is genetically heterogeneous will be of importance to clinical geneticists. Prenatal or presymptomatic diagnosis of many single-gene disorders is now possible using linked genetic probes; conditions such as Huntington's disease can now be diagnosed with a high degree of accuracy in members of affected families (21). However, these conditions exhibit genetic homogeneity and hence genetic studies done in one family can be extrapolated to other unrelated families. With FHC, it will be necessary to determine if the defective gene in an affected family exhibits linkage to FHC-1 before genetic testing can be performed.

Our data demonstrate that defects in at least two different genes can cause FHC. We speculate that these separate genes encode peptides with related functions. For example, another genetically heterogeneous disorder, thalassemia, can be caused by mutations of either the α or β globin genes (22). While these genes are located on chromosomes 16 and 11, respectively, the function of the globin gene products are closely related. We speculate that FHC gene(s) at other loci may similarly have a gene product or function related to that of FHC-1. We further anticipate that isolation and characterization of one FHC gene will facilitate identification of other FHC genes. Elucidation of the protein encoded by the FHC-1 gene and other FHC gene(s) should greatly improve our understanding of the molecular basis of the pathophysiology of hypertrophic cardiomyopathy.

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