GENETICS IN HYPERTROPHIC CARDIOMYOPATHY

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INTRODUCTION

The familial nature of idiopathic cardiomyopathy was noted by Evans in his original description. Subsequently, several workers have commented on this aspect, and the terms 'familial' and 'non-familial' have been used. In some families inheritance by an autosomal dominant gene has been suggested. To determine the pattern of inheritance in this disease we have examined all available first-degree relatives of 97 index cases who presented at the National Heart Hospital, the Hammersmith Hospital, or the Middlesex Hospital, between 1963 and 1967.

METHODS

The 97 index cases yielded 617 first-degree relatives. Acceptable information for the diagnosis of cardiomyopathy was obtained in 558 (90%) (Table I). The term 'familial' was used when more than one member of the family was affected. There were 28 such families (29%) and a further 14 (14%) when those diagnosed as 'possible cardiomyopathy' were included. Thus, the familial incidence in this series was between 29% and 43%. Cases were also divided into 'hypertrophic' and 'congestive', according to their clinical features (Table II).

TABLE I

CARDIOMYOPATHY STUDY

		Examined	Unexamined
PARENTS	194	177 (91%)	17
SIBLINGS	295	264 (89%)	31
CHILDREN	128	117 (91%)	11
	617	558 (90%)	59

Details of 617 first-degree relatives who formed the basis of this study.

TABLE II

FAMILIAL INCIDENCE OF IDIOPATHIC CARDIOMYOPATHY

	Familial	Doubtful	Non Familial
HYPERTROPHIC	23	12	41
CONGESTIVE	5	2	14
	28 (29%)	14 (14%)	55 (57%)

The familial incidence of idiopathic cardiomyopathy in the 97 families studied.

GENETIC ANALYSIS

Previous genetic analyses have been based on the familial and non-familial hypothesis, which has suggested a dominant mode of transmission in some cases. No explanation has been offered for the sporadic case, which accounts for the majority of patients with idiopathic cardiomyopathy.

We analysed our material on the pattern of the parental matings which produced the propositi and their siblings. Genetically there were three possibilities: only one parent affected (12 families), neither parent affected (76 families), and both parents affected (1 family). In the remaining 8 families one parent had been diagnosed as 'possible cardiomyopathy', and this group will not be analysed further in this paper.

If we postulate that the condition could be inherited as an autosomal dominant gene, this would account for the 12 families in which one parent was clinically affected and the other normal. Although the affected parents could be homozygous for the dominant gene, they were more likely to be heterozygous for it. In this case half the children (the propositus and his siblings) should be affected. In all the families studied, however, there was at least one affected person, the propositus. Such truncate selection introduces a bias from the expected 1 in 2, increasing the apparent frequency of affected persons. Smith has constructed tables for this type of analysis, and we have used them (Table III). The number of observed cases of cardiomyopathy did not differ significantly from the expected, and we conclude that in these 12 cases the disease was inherited as an autosomal dominant.

TABLE III

ANALYSIS OF 12 AFFECTED × UNAFFECTED MATINGS

No. in Sibship	No. of Families	Observed No. Affected	Expected No. Affected	Variance
2	5	6	6·665	1·110
3	1	3	1·714	0·490
4	2	5	4·266	1·564
5	2	5	5·162	2·164
6	1	2	3·048	1·379
7	1	3	3·528	1·667
	12	24	24·383	8·374

$p > 0.9$

Analysis of the 12 families in which the propositus was the product of the mating between one affected and one unaffected parent.

There were 76 families in which neither parent appeared to be affected, but these included 9 unexamined parents; they and their families were excluded from the subsequent analysis. The remaining 67 propositi could be accounted for either by sporadic cases or by a recessive pattern of inheritance, and we examined the latter possibility. If there was recessive inheritance one would expect 1 in 4 of the offspring to be affected but, once again, truncate selection occurred as only families with at least one affected person (the propositus) were included, thus producing a bias from the expected 1 in 4. The analysis was carried out according to Smith (Table IV). The observed number of affected individuals did not differ from the expected at the 1% level of significance. In fact for all sibships other than those containing 8 children, agreement was very good indeed. We consider this data is consistent with the hypothesis of recessive inheritance in the 67 families studied.

TABLE IV

ANALYSIS OF 67 UNAFFECTED × UNAFFECTED MATINGS

No. in Sibship	No. of Families	Observed No. Affected	Expected No. Affected	Variance	Probability
1	8	8	8·000	0	0
2	23	24	26·289	2·806	>·1
3	5	6	6·485	1·315	>·6
4	10	11	14·630	4·200	>·05
5	6	8	9·834	3·552	>·3
6	3	3	5·475	2·328	>·1
7	2	2	4·040	1·940	>·1
8	4	4	8·892	4·688	>·01
9	3	6	7·299	4·140	>·5
10	2	2	5·298	3·184	>·05
15	1	1	3·801	2·658	>0·5
	67	75	100·043	30·811	>·01

(10 D.o.F.)

Analysis of the 67 families in which the propositus was the product of the mating between two unaffected parents.

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TABLE V

ANALYSIS OF CHILDREN OF HOMOZYGOUS RECESSIVE PROPOSITI

No. of Sibship	No. of Families	Observed No. Affected	Expected No. Affected	Variance
1	1	1	1·000	0
2	2	2	2·666	0·444
3	3	4	5·142	1·470
6	1	2	3·048	1·379
	7	9	11·856	3·293

$p > 0{\cdot}1$

Analysis of the 7 families of homozygous recessive propositi who had at least one affected child.

Throughout this analysis the number of observed cases was consistently lower than the expected number. Factors which may account for this include the strict criteria used before the diagnosis of idiopathic cardiomyopathy was accepted, the exclusion of any case diagnosed as 'possible cardiomyopathy' and the possibility that a number of stillbirths and miscarriages were in fact cases of cardiomyopathy. If the 'possible cardiomyopathies' were added to those clinically diagnosed the observed number increased from 75 to 85, and if the stillbirths and miscarriages were also included the total became 109, compared with the expected 100.

Examining further the hypothesis of recessive inheritance, an analysis was made of the families in which the propositus was considered to be a recessive homozygote and had at least one affected child. The assumption made was that the homozygous recessive propositus had mated with a heterozygote carrying the recessive gene. Under these circumstances 50% of the children should be affected but, once again, the selection was truncate, and the data were analysed according to Smith (Table V). There was good agreement between the observed number of affected siblings and the expected number ($P > 0{\cdot}1$), which gives further support to the hypothesis of recessive inheritance.

SUMMARY

Genetic analysis of 617 first-degree relatives of 97 patients with idiopathic cardiomyopathy suggests that this disease has both dominant and recessive modes of transmission.