Genetic Aspects of Congenital Heart Disease

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RECURRENCES of congenital heart disease (CHD) within the same family have been commonly observed in the Japanese population, as in other races. Several studies were done to elucidate the mode of this familial aggregation in cases of usual CHD (CHD with unknown etiology), excluding those cases which occurred as a part of recognized syndromes (CHD with known etiology). The latter type was in only 24 out of the 1778 cases (1.4%) with established CHD diagnosis admitted to our Institute during the

years of 1967, 1968 and 1971. The etiology of CHD in most cases remains unknown. The genetic patterns of CHD have been investigated in family and twins.

Materials:

Group A: 361 examples of familial aggregation recorded at random among the CHD outpatients diagnosed during the past 14 years.

Group B: 85 pairs of twins, with either or both having CHD.

TABLE 1 RANDOMLY OBSERVED NUMBERS OF FAMILY AGGREGATED CHDs AND CONSANGUINITY (1958–1971)

	Family numbers				Consanguinity
	Sibling	Parent & child	Cousin, aunt & uncle	Total	
VSD	65	26	38	139	22
ASD	26	16	16	58	4
PDA	24	6	4	34	4
TF	8	2	8	18	6
PS	3	3	5	11	2
ECD	3	2	5	10	1
AS	5	4	2	11	0
Dextro, Levocardia	7	1	4	12	3
PMD	32	10	6	48	8
Other CHDs	11	1	8	20	9
Total	184	71	96	361	59

Key Word: Congenital Heart Disease

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Fig.1. Some pedigrees of families with aggregated CHD.

TABLE II OBSERVED FAMILIAL AGGREGATES IN 1754 ADMITTED PATIENTS

	Probands No.	Family No. of affected sib.		Family No. of affected parents		Family No. of affected cousins, uncles & aunts		Total No. of affected relatives		Consanguinity positive	
		No.	%	No.	%	No.	%	No.	%	No.	%
VSD	556	10	(1.79)	5	(0.89)	8	(1.44)	23	(4.11)	11	(1.97)
ASD II	293	6	(2.06)	7	(2.39)	6	(2.06)	19	(6.49)	1	(0.34)
TOF	296	6	(2.03)	3	(1.01)	2	(0.69)	11	(3.71)	5	(1.68)
PDA	139	3	(2.15)	1	(0.72)	0		4	(2.87)	1	(0.72)
PS	63	2	(3.17)	1	(1.58)	2	(3.17)	5	(7.93)	0	
PMD	70	11	(17.1)	0		6	(8.57)	17	(24.3)	2	(2.85)
Other CHDs	337	14	(4.17)	0		10	(2.96)	24	(7.12)	9	(2.69)
	1754	52	(2.97)	17	(0.98)	34	(1.93)	103	(5.87)	29	(1.65)

Group C: 1754 probands with established common CHD diagnoses, examined during the years of 1967, 1968 and 1971.

Group D: One or both of 206 parents with established CHD diagnoses, who had 361 offsprings during the last 7 years (1965–1971).

Group E: 3230 patients of CHD seen at the outpatient clinic during the two years of 1968 and 1969.

CHD cases with known causes—For example chromosomal aberrations, rubella syndrome, single-gene mutants etc.—were excluded from this study. From groups A and B, conditions of aggregation were observed. And from groups C, D and E, CHD recurrence risks were observed; that is, in those cases with a CHD patient in the family, the recurrence risk of CHD in other members of the family was calculated.

TABLE III CHD INCIDENCE IN SIBLINGS
1967, 1968, 1971 admitted patients

	Probands	Affected siblings	
		No.	%
VSD	556	10/709	1.41
ASD II	293	6/450	1.33
TOF	296	6/380	1.58
PDA	139	3/177	1.69
PS	63	2/ 92	2.19
PMD	70	11/197	5.58
Other CHDs	337	14/457	3.06
Total	1754	52/2462	2.11

TABLE IV PARENTS WITH CHD AND
THEIR OFFSPRINGS
1966–1971 admitted patients

	Proband parents	Affected children	
		No.	%
ASD II	126	8/235	3.40
VSD	33	0/ 51	
PDA	18	0/ 26	
PS	9	0/ 14	
TOF	7	0/ 11	
PPH	6	0/ 12	
ECD	4	1/ 7	14.2
Other CHDs	3	0/ 5	
Total	206	9/361	2.49

TABLE V RANDOMLY DIAGNOSED TWINS
WITH CHD
during 14 years (1958–1971)

Zygoty	Concordant pairs	Discordant pairs	Total
	CHD–CHD	Normal–CHD	
Monozygotic	8 (21.6 %)	30	38
Dizygotic	2 (6.99%)	27	29
Unknown	2 (12.5 %)	16	18
Total	12 (14.1 %)	73	85

Table I: Shows the aggregation of 361 families for siblings, parents, uncles, aunts or cousins, classified by common congenital heart disease. The patients were diagnosed at the outpatient clinic during the 14 years of Group A. Figure 1 indicated some examples of the familial aggregation, showing a CHD occurrence extending 2 generations and, in some cases, a thick aggregation even in the same generation. These families seems to follow the autosomal recessive or dominant form.

Table II: Shows the familial aggregation tendency, considered from the patients' familial history. It includes those patients admitted to this Institute during the 3 years of 1967, 1968 and 1971. The familial aggregation of the total number of affected relatives was 103/1754 (5.8%). The recurrence rate observed in siblings was 52/1754 (2.97%), 17/1754 (0.98%) in parents, and 34/1754 (1.93%) in cousins, uncles and aunts.

Table III: In 2462 siblings of the 1754 probands with usual CHD, recurrence was observed in 52 cases (2.11%) this is three times higher than the general population incidence in Japanese (0.7%). Recurrence risks for different types of CHD were 1.41% in VSD, 1.33% in ASDII°, 1.58% in TOF, 1.69% in PDA, 2.19% in PS, 5.5% in primary myocardial disease and 3.06% in other CHD. These statistics demonstrate the contribution of the genetic factor in the etiology of CHD. However, this value is far below the expected recurrence in siblings in autosomal dominant inheritance (50%) and in autosomal recessive inheritance (25%). This study also examined the relationship between parents and their offsprings in order to evaluate the contribution of the genetic factor.

Table IV: As to one or both of the parents with established CHD diagnosed during the past 7 years (1966–1971), 206 parents had 361 offsprings. Of the 361 offsprings, there were 9 CHD cases (2.49%), which is also approximately three times the general population incidence.

Table V: During the past 14 years, we have examined 85 pairs of twins with either or both having CHD. 38 pairs were monozygotic and 29 pairs were dizygotic. The twin study showed the concordance rate to be 21.6% in monozygotic twins, and 6.99% in dizygotic twins. The low concordance rate for the monozygotic twins suggests that genetic mechanisms are not the sole determining factor in CHD. The view that environmental factors are important in the

TABLE VI EXPECTED $\sqrt{P}$ AND OBSERVED RECURRENCE RISK

	No.	%	Estimated population incidence	$\sqrt{P}$	Observed recurrence risk
VSD	1729	53.5	0.374	6.03	1.41
ASD II	586	18.2	0.127	3.56	1.33
TOF	285	8.8	0.061	2.47	1.58
PDA	229	7.1	0.049	2.22	1.69
Other CHDs	401	12.4	0.087	2.91	3.06
Total	3230	100			2.11

Fig.2. Approximation of multifactorial inheritance.

etiology of CHD is supported by the finding that there is not 100% concordance in monozygotic twins. This pattern closely approximates the pattern for multifactorial inheritance proposed by Dr. Wright, S. (1934). A disease which follows this multifactorial inheritance mode is considered to be rather common. The population frequency is between 0.1–1.0%, and the familial aggregation tendency in siblings from 1–5%. Identical twins are affected in 25 to 30% of the cases, and they are influenced by environmental factors. If the population frequency is P , then the occurrence in siblings and other first degree relatives, of a disease transmitted through multifactorial inheritance, is equal to the square root of the

population frequency. We calculated the expected $\sqrt{P}$ from the frequency of each disease for 3230 cases seen in the outpatient clinic in 1968 and 1969. (Table VI) The recurrence risk of common CHD was 2.22–6.63%. This is approximately the same as the actually measured recurrence risk. When expected $\sqrt{P}$ was adapted to the monograph of Newcombe which follows the hypothesis of multifactorial inheritance (Figure 2) our data and Nora's study closely approximated the expected pattern for multifactorial inheritance. The above results strongly support the hypothesis of multifactorial inheritance as the etiology of common CHD.

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