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Familial predisposition to filarial infection – not linked to HLA-A or -B locus specificities

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Summary

Two hundred and twenty-five Polynesians were selected from a larger study population for the evaluation of potential genetic influences on the susceptibility to bancroftian filariasis. Analysis showed that there was significant familial clustering of patients with filariasis and that this clustering was most compatible with genetic transmission of disease susceptibility. The data best fit a model in which the hypothetical gene for filariasis was recessive with a frequency of 0.82 ± 0.15 in the population and a penetrance of 0.62 ± 0.14 . The alternative hypothesis that susceptibility was environmentally (i. e., not genetically) determined was also compatible with the data but was estimated to be 1.9 times less likely to account for the observed findings than the genetic hypothesis. Extensive evaluation of HLA-A and -B locus specificities failed to detect significant linkage either between particular antigen specificities and the clinical manifestations of filariasis or between individual haplotypes (indicated by HLA markers in studies of large families) and the predisposition to filarial infection or disease.

Key words: filariasis; HLA; genetics; families.

Introduction

One of the most intriguing aspects of filarial infections in man is the broad spectrum of clinical manifestations seen in patients in endemic regions. For the

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lymphatic filariases, this spectrum includes asymptomatic states with or without the presence of circulating microfilariae as well as symptomatic conditions such as filarial fevers (lymphadenitis and lymphangitis), chronic lymphatic obstruction (elephantiasis or hydrocoele) and in extreme instances the tropical eosinophilia syndrome (Ottesen, 1980). Additionally, a sizeable proportion (at least 50%) of any endemic population appears not to be infected with the parasite at all. These individuals may be free of infection or have subclinical infection, but current diagnostic techniques are unable to resolve this important problem. Because of this range of host response, however, it has been a persistently interesting question to consider whether identifiable factors can be found that predispose individuals in endemic regions either to acquire or resist infection in the first place or, if infected, to manifest one or another of the clinical expressions of disease. While a number of previous workers have recognized some familial clustering of filarial disease (e. g., Walter, 1974), none have carried out extensive family studies to investigate this issue rigorously.

Largely as a result of genetic studies of the major histocompatibility complex (MHC) in animal models, the analogous genetic loci in man (the HLA region on chromosome 6) is thought to include or to be linked closely to those genes which determine immunologic responses to a wide variety of antigens. Indeed, definition of the HLA antigen profiles of individuals with certain types of diseases (especially autoimmune, rheumatic, dermatologic and neoplastic) has indicated a definite linkage between HLA type and susceptibility to disease (Kaslow and Shaw, 1981). In some instances, the HLA antigen itself seems to identify the disease susceptibility (e. g., antigen B27 in ankylosing spondylitis) and in other instances the association of disease with different HLA antigens in different populations has been felt to indicate segregation of a proximate 'disease gene' with the HLA antigen gene (Kaslow and Shaw, 1981).

The present study was designed to explore the questions of whether or not in human filariasis there is familial predisposition to filarial infection and/or whether disease manifestations are associated in any way with HLA antigens. The population studied consisted of 225 individuals on a South Pacific Island (Mauke) in the Cook Islands group where filariasis due to *Wuchereria bancrofti* is endemic.

Materials and methods

Study population

Mauke is a small, flat volcanic Pacific island surrounded by a coral reef and encompassing about 4½ square miles. Its population is racially homogenous (Polynesian) with few instances of non-Maori intrusion into the islanders' gene pool. At the time of the present study (1974–75) there were no non-Polynesians among the 750 permanent residents of the island. As part of a larger study described in detail elsewhere (Ottesen et al., 1977), 225 persons were evaluated clinically and typed for HLA. Of these, nearly 200 were members of nine major families, each family descending from one or more common ancestor(s) three to six generations ago. Although ancestors were traced

through several generations for many of the persons tested, only one instance of an ancestor shared by husband and wife was documented. Twenty-eight persons either were from off Mauke or were descendants of persons from elsewhere. The detailed evaluation of family relationships was made possible because of the very thorough work of a committee of five inhabitants convened by the government during the year prior to the present study to produce an accurate and extensive series of family trees for the island's inhabitants.

Clinical evaluation

For each individual a thorough physical examination and laboratory evaluation were carried out, as described elsewhere (Ottesen et al., 1977). Microfilaremia was detected with the Nuclepore filter technique (Dennis et al., 1976). Twenty-one patients had evidence of chronic lymphatic pathology caused by filarial infection (8 with elephantiasis and hydrocoele, 3 with elephantiasis alone and 10 with hydrocoele alone). All patients with elephantiasis were older than 59 years old and patients with hydrocoele, older than 47 years. Eighty-one individuals (age 4–71 years) were microfilaremic; five of these also had chronic lymphatic pathology. The remaining 128 islanders (age 1–89 years) though obviously exposed to the mosquito-borne infective larvae, showed no signs of filarial infection and constitute the 'endemic control' population of this study. Information regarding the occurrence of elephantiasis or hydrocoele in the ancestors of these patients was recorded.

HLA test methods

Lymphocytes from freshly drawn peripheral blood samples were prepared for testing in the field using a modification of the Amos lymphocytotoxicity method (Amos et al., 1969) in which lymphocytes were incubated for 20 min with antiserum, washed and then incubated for 30 min with rabbit complement, all at room temperature. Reading was accomplished by the trypan Blue dye exclusion method.

Sixty antisera available from local sources were supplemented by those obtained from colleagues and the NIAID. Sera were selected for optimal reactivity by the technique described above, and each serum was tested in the home laboratory prior to and concurrent with testing the Mauke population. Antisera used in this study were capable of defining 18 A-locus specificities (1, 2, 3, 9, 10, 11, w23, w24, 25, 26, 28, 29, w30, w31, w32, w33, w34, and w36); and 19 B-locus specificities (5, 7, 8, 13, 14, 15, w16, 17, 18, w21, 22, 27, w35, 37, w38, w39, 40, w44, and w45). Most specificities were identified by two or more antisera.

Data analysis

HLA genotypes were assigned to members of each nuclear family, and HLA haplotypes were then traced through the nine major families. Distribution of HLA antigens in diseased individuals (hydrocoele, elephantiasis and/or microfilaremia) was compared with that in disease-free family members. Differences were evaluated for statistical significance with the Fischer exact test, although the usual assumption of nonrandomness did not hold in this population.

Genetic analysis of large multi-case families

Three families contained a sufficient number of affected family members to study potential linkage between HLA and filarial disease with lod score methodology (see below).

First, segregation analysis was carried out on the data from the largest family to determine whether the findings were compatible with a heritable predisposition to disease. The technique employed utilized a "likelihood ratio statistic" developed previously by others (Elston and Stewart, 1974; Kaplan and Elston, unpublished) to study a number of familial diseases (King et al., 1980; Mendel et al., 1978; Spence et al., 1974). It allows testing for evidence of genetic or environmental transmission of disease, comparison of the likelihood of dominant or recessive modes of inheritance, and estimates of gene frequency and penetrance. Findings from the segregation analysis of

the large family were assumed to hold for all three families and the calculated estimates for gene frequency and penetrance, used in subsequent linkage analysis studies.

Linkage analysis utilized the LIPED program (Ott, 1974) to compute lod scores (Cavalli-Sforza and Bodmer, 1970; Ott, 1974) from data of affected families spanning 3 or more generations. A lod score for a particular recombination frequency [$Z(r)$] is the logarithm (base 10) of the ratio between two likelihoods: (1) the likelihood of finding the observed distribution of the disease (filariasis) and HLA types if the disease is caused by a gene linked to HLA and (2) the likelihood of such findings if the gene is not linked to HLA. Lod scores were computed for recombination frequencies which varied between 0.1 and 0.5 and which could differ for males and females. An observed lod score below -1.0 or greater than $+1.0$ can be considered definite evidence against linkage ($p < 0.5$).

Results

Clinical manifestations and HLA markers

Table 1 divides the study population by clinical disease manifestations and records the HLA specificities observed in these individuals. As reported previously (MacQueen et al., 1979), the Mauke population showed relatively restricted HLA polymorphism with five A-locus antigens (2, 11, w24, 26, w34) and four B-locus antigens (w22, 27, w39, 40) accounting for a majority of the HLA-A and -B locus phenotypes. In comparing the frequencies of these antigens between the endemic control population and the various clinical groups of patients with filariasis we were unable to define any HLA specificities which showed statistically significant positive or negative correlation with disease parameters. This lack of significant association was seen both when the clinical groups were considered separately in comparison to the control population as well as when they were analyzed together.

Familial clustering of filarial disease

The issue of potential familial clustering of filarial disease was investigated in two different ways. First, all families with offspring ($n = 27$) were grouped according to whether both, neither, or one parent had evidence of filarial infection (elephantiasis, hydrocoele or microfilaremia). All of the offspring of the families in each category were evaluated for the presence of filarial infection. Because the chronic pathology from lymphatic obstruction manifests itself only late in life in this population (in individuals older than 47 years), the only clinical manifestation of filariasis in the children of these families was microfilaremia. Table 2 shows very clearly the strong association between parents with filariasis and the occurrence of infection in their children. Because one is much more likely to see evidence of filarial infection in older individuals rather than in young children, the offspring in Table 2 are grouped according to age. One can see, however, that the differences observed among the three categories of families are clear regardless of the offspring's age stratification.

Table 1. HLA antigen frequency in study population

		Disease status (# Patients)			
		Elephantiasis (11)	Hydrocoele (18)	Microfilaremia (81)	Endemic controls (128)
A1	0*	0	0	0	1
A2	27	28	43	37	
A3	0	0	4	5	
A9**	0	0	0	1	
A10**	0	0	0	2	
A11	27	28	28	33	
Aw23	0	0	0	1	
Aw24	55	67	70	62	
A25	0	0	0	0	
A26	9	6	15	12	
A28	9	6	0	2	
A29	9	6	0	3	
Aw30	0	0	0	0	
Aw31	0	0	0	1	
Aw32	0	0	0	0	
Aw33	0	0	0	1	
Aw34	36	44	19	21	
Aw36	0	0	0	0	
B5	0	0	0	0	
B7	18	0	7	8	
B8	0	0	0	0	
B13	0	0	5	2	
B14	0	0	0	0	
B15	0	0	2	6	
Bw16**	0	0	0	2	
B17	0	0	1	2	
B18	9	6	0	2	
Bw21	0	0	0	0	
B22	73	67	60	62	
B27	9	6	10	16	
Bw35	0	0	0	2	
B37	0	0	0	0	
Bw38	0	0	2	1	
Bw39	0	17	27	18	
B40	55	61	43	36	
Bw44	9	6	1	6	
Bw45	0	0	0	0	

* Phenotype frequency (%)

** Individuals with these supertypic specificities could not be clearly assigned to the associated subspecificities.

Table 2. Familial predisposition to filarial infection

Filariasis* in parents	Microfilaremia in offspring**			Total (%)
	< 5 y. o.	5–10 y. o.	> 10 y. o.	
Both parents pos.	0/2	7/9	6/14	13/25 (52%)
One parent pos.	1/8	2/20	6/21	9/49 (18%)
Neither parent pos.	0/1	0/5	0/8	0/14 (0%)

* Elephantiasis, hydrocoele or microfilaremia

** Number of microfilaremic children/total number in age group

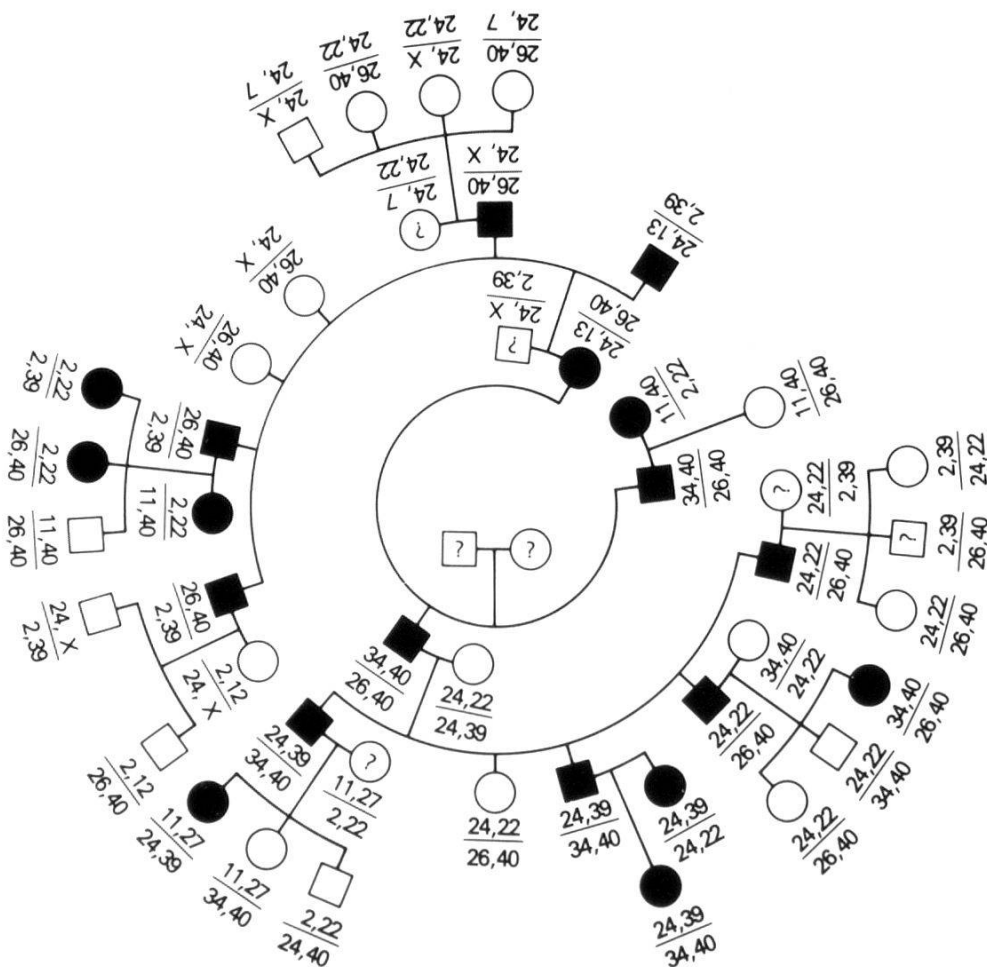


Fig. 1. Pedigree of family 1 showing assigned HLA haplotypes and clinical status of individuals. Males are denoted by squares and females, by circles. The presence of filariasis (either chronic lymphatic pathology or microfilaremia) is indicated by closed symbols, and its absence by open symbols. A "?" within the symbol indicates that the clinical status was unknown. HLA haplotypes (for A- and B-locus antigens) are indicated below the symbols for each individual in the family.

Genetic analyses of affected families

The second approach to the issue of potential familial clustering of filarial disease involved detailed genetic analysis of three major 'superfamilies' composed of 46, 23 and 29 individuals, respectively. Segregation analysis of the largest family (Fig. 1) indicated that the data fit a genetic hypothesis well ($X^2_3 = 0.06$; $p > 0.99$) with slightly greater likelihood that filariasis was recessive rather than dominant (likelihood ratio = 1.36). The gene frequency for the hypothetical "filariasis allele" was estimated to be 0.82 ± 0.15 , a high value probably reflecting the bias of the family's having been selected because of its affected members; the penetrance in individuals homozygous for the allele was estimated to be 0.62 ± 0.14 .

These derived values were then used in the linkage analysis (Table 3). A recombination frequency of 0.5 implies the absence of linkage and since the total lod score for all three families was maximum at a recombination frequency of 0.5 (lod score = 0.0), it was most likely that the filariasis in these families was not linked with HLA-B since $Z(0.0) = -0.21$, an indication that non-linkage is 1.6 times more likely than linkage. Furthermore, varying the recombination frequencies independently for males and females did not alter this conclusion. In order to be certain that these results were not artifacts of an inflated estimate of gene frequency, lod scores for the largest family were also computed first with the gene frequency assumed to be 1/10 of the original estimate and then with the penetrance being 0.9. Table 4 shows that for both assumptions the lod scores were even more negative, a clear indication of the greater likelihood of non-linkage than linkage.

Table 3. Linkage analysis of 3 pedigrees (lod scores)

	Recombination frequency (r)				
	0.1	0.2	0.3	0.4	0.5
<i>Filariasis - HLA-A</i>					
Pedigree 1 (46)*	-0.03**	-0.02	-0.005	-0.001	0.000
Pedigree 2 (23)	+0.09	+0.05	+0.02	+0.006	0.000
Pedigree 3 (29)	-0.08	-0.06	-0.03	-0.009	0.000
<i>Filariasis - HLA-B</i>					
Pedigree 1 (46)	-0.16	-0.08	-0.04	-0.009	0.000
Pedigree 2 (23)	+0.03	+0.02	+0.007	+0.002	0.000
Pedigree 3 (29)	-0.08	-0.06	-0.03	-0.009	0.000
<i>Totals</i>					
HLA-A	-0.02	-0.03	-0.02	-0.004	0.000
HLA-B	-0.21	-0.12	-0.07	-0.001	0.000

* Number of informative family members

** Lod score

Table 4. Lod scores under alternative genetic hypotheses – pedigree 1

	Recombination frequency (r)				
	0.1	0.2	0.3	0.4	0.5
Gene frequency = 0.08					
Penetrance = 0.62					
HLA-A	-0.79*	-0.32	-0.10	-0.02	0.00
HLA-B	-1.25	-0.56	-0.21	-0.05	0.00
Gene frequency = 0.8					
Penetrance = 0.9					
HLA-A	-0.65	-0.29	-0.10	-0.02	0.00
HLA-B	-0.86	-0.42	-0.16	-0.03	0.00

* Lod score

One further type of analysis employed in an effort to demonstrate linkage was the evaluation of HLA specificities in affected siblings whose parents were both HLA heterozygotes. There were eight such sibling pairs in the study population, but their HLA profiles did not significantly differ from those expected in random segregation of the parental haplotypes (data not shown), a finding in distinct contrast to that expected if susceptibility to filariasis were linked to the MHC region.

Potential environmental influences on familial clustering of filariasis

Because children of affected parents do, of course, generally share with their parents a common environment, purely environmental influences (e.g., more intense exposure to mosquitoes carrying infective larvae) could not be excluded from importance in interpreting the data of Table 2. As shown in Fig. 2 the families analyzed in Table 2 were distributed among 5 separate village regions on the island. Though nearly every family farmed taro in the swampy interior of the island, individuals returned each day to their homes in the shore villages (A and B), the inland villages (D and E) or the intermediate village (C). Comparison of the distribution of the three categories of families in Table 2 showed that these families were non-randomly distributed among the villages; instead, 9 of the 12 families whose progeny had filariasis lived in the interior villages D and E (Fig. 2). For this reason and the fact that we have no epidemiologic information about the mosquito populations in these villages, the possibility that environment alone, not genetic inheritance, accounts for the familial predisposition to filariasis seen in Table 2 cannot be ruled out.

Similarly, in the detailed genetic and statistical evaluation of Pedigree # 1 (Fig. 1), the segregation analysis, as described above, indicated a very good fit of the data to a genetic inheritance hypothesis ($X^2_3 = 0.06$; $p > 0.99$). Again,

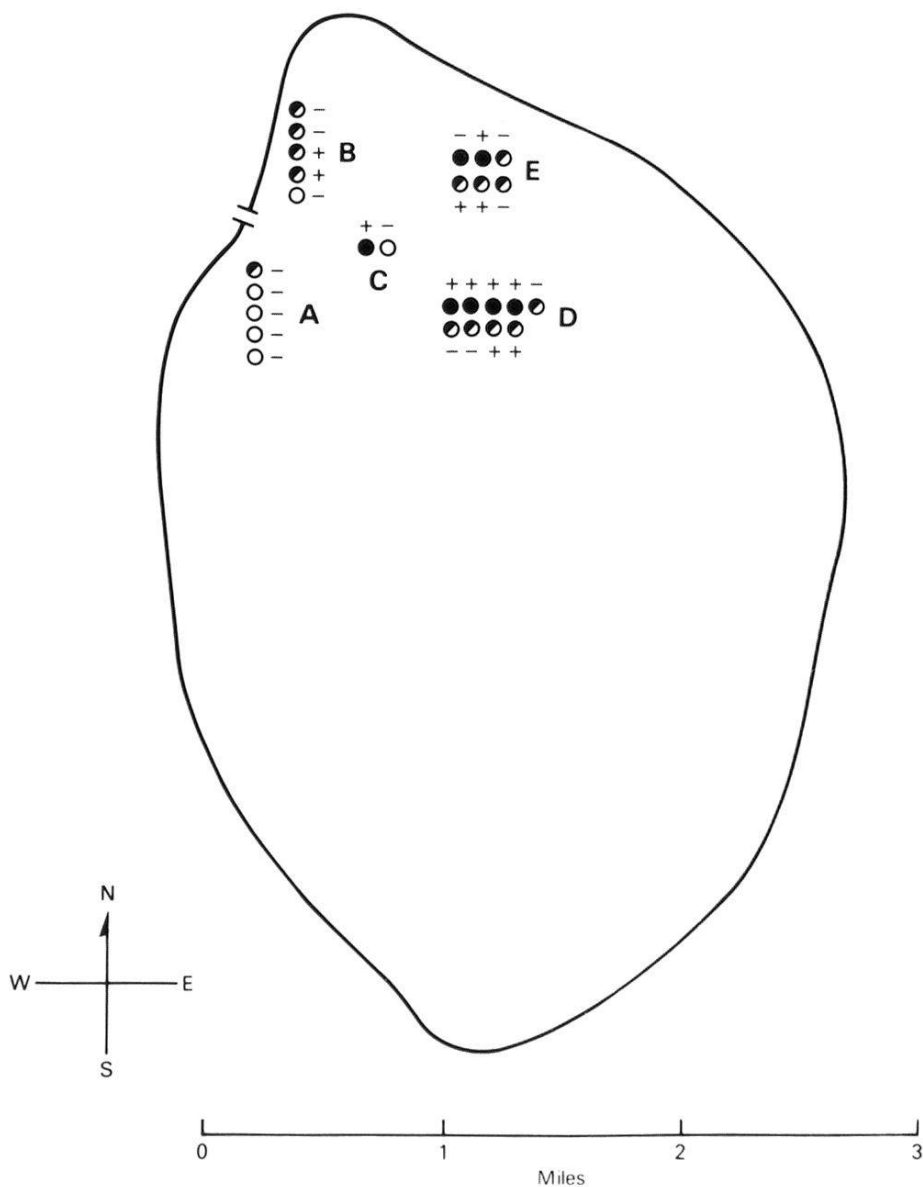


Fig. 2. Map of Mauke showing distribution of households analysed in Table 2 among the island's five villages (A–E). Households where neither parent had filariasis are noted by open circles; those with one affected parent, by half-shaded circles; and those with both parents affected, by closed circles. The '+' or '-' next to each household symbol denotes the presence or absence of filariasis in the offspring of that household.

however, though calculated to be 1.9 times less likely, the alternate hypothesis that an 'environmental' mode of transmission accounted for the observed findings was not able to be excluded ($X^2_3 = 1.33$; $p > 0.2$).

Discussion

Unless disease inheritance is the result of a single gene defect or can be shown to be tightly linked with an identifiable gene product (such as the HLA antigens), it is often extremely difficult to define the subtle influences which the genetic make-up of an individual has on susceptibility to disease. This is espe-

cially true for infectious diseases, as an extraordinary number of variables affect the interactions between host and pathogen. Indeed, while studies of the HLA antigens, presumably because of their close linkage to the immune response (IR) genes, have successfully implicated specific genetic susceptibility to certain types of disease states in man (especially those which are autoimmune or rheumatologic in nature), similar investigations on a wide variety of infectious diseases have been largely unsuccessful (Kaslow and Shaw, 1981). A major reason for this lack of success has been the fact that techniques employed for the analysis of less subtle genetic influences on disease are inadequate for investigating the much more complex systems involving interactions between the host and most infectious pathogens. In general, very large sample sizes of unrelated individuals and/or extensive and detailed family studies of individuals are needed to detect subtle influences of genetic susceptibility to the acquisition or clinical expression of such diseases.

Our present study of 225 Polynesians, mostly comprising nine large family lineages, sought to define potential genetic influences on the susceptibility to bancroftian filariasis in a Pacific population. The analysis showed clearly that, indeed, there was familial clustering of cases of filariasis but it was unable to distinguish with complete certainty whether this clustering was the result of genetic or environmental influences. Analysis of the progeny of filariasis affected parents (Table 2) indicated this familial predisposition to filarial infection quite clearly, but study of the residences of these families revealed a non-random distribution of the houses of the affected families among the island's five villages (Fig. 2). In the absence of further epidemiologic (and entomologic) data, one cannot conclude with complete confidence from the data of Table 2 that the familial predisposition to infection was the result of genetic influences.

Analysis of this same issue, however, by detailed genetic and statistical consideration of three large families totalling 98 individuals (38 with filariasis, and 45 without and 15 unknown¹) showed an extremely good fit of the data to a Mendelian hypothesis and indicated that Mendelian transmission was 1.9 times more likely than environmental transmission to account for our observation. The fact, however, that the calculated penetrance of the "filariasis gene" was only 62% implies that other factors must also be acting to determine the expression of this hypothetical gene. Once again, these other factors could be both genetic (i. e., the influence of still other genes) and/or environmental.

One can conclude with certainty, however, that the present study offered no evidence for association between individuals' HLA antigen specificities and either susceptibility to filarial infection or predisposition to any particular clinical manifestation of this disease. The fact that this conclusion was reached both by analysis of a large number of "unrelated" individuals as well as by extensive

¹ 'Unknown' refers to individuals who married into a family and produced offspring (thereby being "informative") but who could not be evaluated or examined for one reason or another.

and detailed family studies lends further credence to the validity of our observations; still, however, there are at least two reasons why additional studies to confirm these findings should be carried out. First, only HLA-A and -B antigens were analyzed in this study, and it is clear from other studies (e.g., in leprosy [DeVries et al., 1980]) that the more recently defined D/DR locus antigens may be better indicators of linkage between the HLA region and disease susceptibility or expression. Second, since the unique hyper-responsiveness syndrome of filarial infection, tropical eosinophilia, was not found in the population of Mauke, it is impossible from our study to say whether or not this response to bancroftian filariasis is the result of expression of particular IR genes proximate to those coding for the HLA antigens.

Finally, as has been pointed out recently (Grayston and Payne, 1979; Svejgaard et al., 1974; Gart and Nam, 1981; Kaslow and Shaw, 1981), it is important to recognize the particular difficulties inherent in trying to associate genetic influences (including those linked to the HLA antigens) with susceptibility to parasitic and other infectious diseases. Some of these difficulties are illustrated in our present study. It is appropriate to conclude, therefore, that future genetic studies to examine these same issues must be designed to include the following: (1) evaluation of very large numbers of unrelated individuals; (2) analyses of disease linkage with individual haplotypes, possible only in studies of multiple generations of large families with affected individuals; (3) careful clinical assessment of all individuals, with special attention being paid to age-of-onset information which might be helpful in stratifying the population for statistical analyses; (4) the collection of as much relevant epidemiologic information as possible; (5) the extension of genetic linkage studies to markers including but not limited to those associated with HLA and the genes of chromosome 6.

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