Heritable Factors Play a Major Role in Determining Host Responses to *Wuchereria bancrofti* Infection in an Isolated South Pacific Island Population

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Background. It is increasingly recognized that host genetic factors may play an important role in determining the outcome of filarial infections. To test this hypothesis in bancroftian lymphatic filariasis, pedigree data were collected twice during an 18-year period from an isolated Polynesian population living on a Pacific island where lymphatic filariasis is endemic.

Methods. Using variance-component analysis, we examined the contribution of shared genetic and environmental effects on host clinical and immune responses to filarial infection, along with potential confounding determinants.

Results. Sex was found to have a negligible influence on heritability estimates, but shared-household effects accounted for up to 32% of host variability. After accounting for these shared-household effects, heritability estimates suggested that levels of microfilariae and circulating adult worm antigen, as well as host eosinophil and immunoglobulin G antibody responses to larval and adult worm antigens, were highly heritable (range of heritability estimates, 0.15–0.84).

Conclusions. These data provide evidence of a key role for genetic factors in determining the host response to filarial infections in humans and emphasize the complexity of the relationships among the host, parasite, and environment.

Infection with the lymphatic filarial parasites *Brugia malayi* and *Wuchereria bancrofti* affects >120 million persons worldwide and exacts an enormous disease burden on populations in which the parasites are endemic [1]. Clinical disease occurs in a subset of infected individuals with a wide range of manifestations, including lymphadenitis and lymphangitis, lymphatic obstruction or dysfunction (elephantiasis and/or hydrocele), and tropical pulmonary eosinophilia [2]. Most infected individuals have a subclinical infection, often associated with the presence of circulating microfilariae (Mf). In some populations, a third group has been described; these persons, although exposed to the parasite, appear to be resistant to infection ("endemic normal" or "putatively immune") [3]. Immunologically, both subjects with patent filarial infection and those who are exposed but resistant to infection mount vigorous antibody responses to parasite antigen, most uniquely immunoglobulin G4 (IgG4) and immunoglobulin E [4, 5]. In contrast to antibody responses, parasite-specific T cell responses in infected individuals are significantly down-regulated in comparison with those in individuals who are exposed but uninfected [3, 6].

Several explanations have been advanced to explain the variability seen in disease manifestations among

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filaria-infected patients. These include differences in (1) immunologic responsiveness caused by human host factors, such as cytokines and specific regulatory molecules [7, 8]; (2) transmission potential as measured by vector monitoring [9]; (3) in utero exposure to parasite antigens [10, 11]; and (4) modulation of the immune response by parasite factors [12]. However, there is growing recognition that host genetic factors might play an important role in determining both the nature of the responses to filarial infection and the variability observed in pathologic outcome. Previous studies in filaria-endemic regions showed that filarial disease tends to aggregate in families [13, 14] and that Mf levels are attributable to genetic factors after adjustments are made for shared environment [15]. Earlier studies suggested a role for genes associated with the major histocompatibility complex in determining susceptibility to filarial disease and its clinical spectrum [16–18]. More recently, studies in South India [19] linked susceptibility to bancroftian filarial infection to 2 other specific candidate genes; in addition, polymorphisms in the vascular endothelial growth factor A gene have been associated with the occurrence of hydrocele [20]. Indeed, host genetic factors have also been implicated as important determinants in other helminth infections, including schistosomiasis [21, 22] and trichuriasis [23].

To extend these earlier observations, we evaluated the influence of host genetics on clinical outcomes and host immune responses in the population of a small Polynesian island (Mauke) in the Cook Islands, South Pacific. Previous longitudinal [24] and cross-sectional [3, 25–27] studies on Mauke, where subperiodic bancroftian filariasis is endemic, have provided clinical, immunologic, and pedigree data on a highly characterized and largely isolated population over a period of nearly 2 decades. Earlier segregation analyses of a single large, extended Maukean family indicated that their filarial infection patterns were compatible with a recessive genetic model, and no evidence was found for linkage to HLA-A or -B locus specificities [13]. Since then, improved biologic measures of filarial disease have been developed, thus enabling collection of more in-depth information for assessing phenotypic heritability. The results of this study demonstrate that specific clinical and immunologic factors in filarial infection can indeed be recognized as having a distinct, heritable component.

METHODS

Study population. Mauke, in the southern Cook Islands, is a small (26 km^2), flat, volcanic island where subperiodic *W. bancrofti* infection is endemic. Inhabitants (n = 750 in 1974 and n = 627 in 1992) lived in 5 villages (2 coastal, 2 inland, and 1 intermediate) located on the northern tip of the island in an area encompassing 3.2 km^2 (Figure 1). First settled by early Maori Polynesians between the 10th and 14th centuries CE [29], the island had been physically and culturally isolated

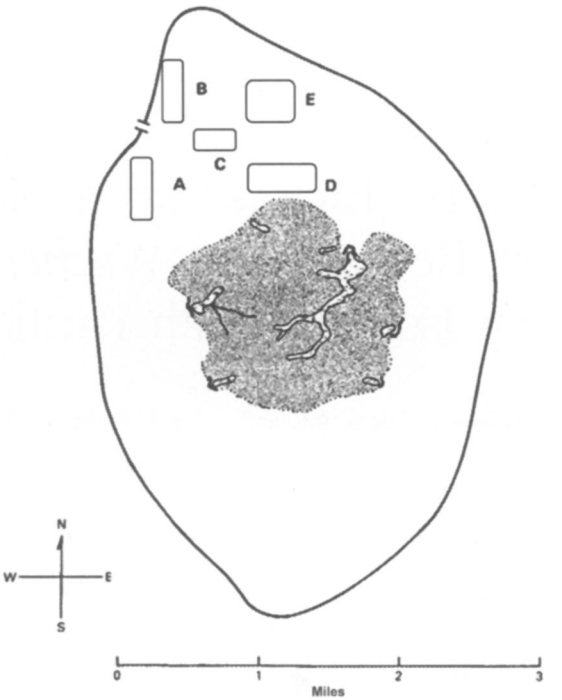

Figure 1. Map of Maukean sampling sites (A–E) and land characteristics. White areas with dots represent swamp region where taro is farmed, and gray densities indicate volcanic rock. Adapted from Ottesen et al [13] and Stoddart et al [28].

because of its geographic remoteness. It is likely that outside contact was, until recently, restricted principally to islanders of the neighboring southern Cook Islands, who shared similar racially homogeneous populations, thus implying minimal human genetic substructure. Indeed, examination of HLA antigens found that, although differences did exist, Maukeans were considerably more similar to other Polynesians than to Pacific Melanesians [25].

The population of Mauke was studied in depth during two 3–4-month periods in 1974–1975 and 1992. Informed consent was obtained for all aspects of the study. Thorough clinical (history, physical examination, and complete blood count), epidemiologic, and parasitologic observations were conducted and extensive pedigree data were collected during both time periods. Assessment of the population determined that only permanent Polynesian residents lived on the island in 1974, with only a few long-term visitors in 1992. Pedigree information was collected by Maukean government-appointed staff [25] and was updated in 1992. Pedigree analysis was conducted in 448 (60%) of 750 individuals in 1974 and in 625 (99.7%) of 627 in 1992.

A pedigree database was constructed, and individual study identification numbers were assigned to each person. Of the 1073 individuals contributing to the database from the second time period, 139 were seen in both 1974 and 1992. These in-

dividuals were assigned a single identifier for the purpose of this study. In a system similar to that of Mäkinen et al [30], study identification numbers were also assigned to deceased individuals with whom a positive relationship with another person (either living or deceased) was confirmed, to reconstruct the pedigree relationships. Household affiliation for each participant was recorded at each collection period. Mauke households were categorized as belonging to 1 of 5 villages (A–E) followed by an individual household number (eg, A1). Where household affiliation could not be verified, the individual was assigned to region F followed by a number (Table 1).

Clinical and parasitologic parameters. Serum and plasma samples were collected at both time periods and stored at −80°C until needed. For this study, 3 clinical or parasitologic measures were used. First, absolute blood eosinophil counts were determined from heparinized blood specimens as the percentage of eosinophils times the total white blood cell count. Second, circulating Mf levels were quantified by filtration of 1 mL of whole blood through a Nucleopore 3-μm polycarbonate filter (Whatman). Third, a quantitative measure of active infection (ie, related to the adult worm burden) was assessed by the level of circulating filarial antigen (CAg) in serum for all samples collected in 1992 and for 361 (81%) of 448 samples collected in 1974 [31]; for this CAg, the Og4C3 enzyme-linked immunosorbent assay (ELISA) (TropBio) was used in accordance with the manufacturer's instructions. Filarial antigen positivity status was also recorded as a binary variable (noted as positive or negative) for each individual, with positive values defined as >32 U/mL in the Og4C3 ELISA, as recommended by the manufacturer. This noncontinuous, qualitative determinant for CAg was used for comparison with the quantitative value determined by the ELISA standard curve.

Antibody responses to defined parasite antigens. Parasite antigens used in this study were saline extracts of the adult (BmA) and microfilarial (MfAg) stages of the related filarial parasite *B. malayi*, produced as described elsewhere [32]. Serum IgG and IgG4 responses to BmA and IgG responses to MfAg were determined by ELISA, as described elsewhere [33]. In addition, IgG responses to 2 immunoreactive larval peptides were measured: peptide 2 (EPQAWCRPNENQSWTD) and peptide 3 (VIERKNNGKLEYSYC) from the *W. bancrofti* abundant larval transcript (ALT2 pep2 and ALT2 pep3, respectively) (Research Technologies Branch, National Institute of Allergy and Infectious Diseases). Briefly, plates were coated with each peptide (10 μg/mL) at 4°C overnight. Plates were then washed and blocked for 1 h at 37°C. After washing, serum samples were added, followed by overnight incubation at 4°C, further washing, and subsequent addition of alkaline phosphatase–conjugated anti–human IgG (Jackson Immunoresearch Laboratories). Plates were developed with alkaline phosphatase substrate tablets (Sigma-Aldrich), and IgG levels (in arbitrary units per milliliter) for each sample were determined from a standard curve (based on a reference pool of patient serum samples).

Statistical and heritability analysis. The distribution of

Table 1. Subject Demographics, by Survey Year

Demographic variable	Subjects, no. (%)		χ^2 (*df*)	*P*[a]
	1974 (*n* = 370)	1992 (*n* = 587)		
Age			17.3 (6)	.007
<10 years	95 (26)	127 (22)		
10–19 years	81 (22)	180 (31)		
20–29 years	38 (10)	79 (13)		
30–39 years	51 (14)	50 (9)		
40–49 years	31 (8)	40 (7)		
50–59 years	38 (10)	51 (9)		
⩾60 years	36 (10)	60 (10)		
Sex			7.35 (1)	.007
Male	164 (44)	313 (53)		
Female	206 (56)	274 (47)		
Household region			49.9 (4)	<.001[b]
A	54 (15)	75 (13)		
B	69 (19)	191 (33)		
C	22 (6)	108 (18)		
D	93 (25)	94 (16)		
E	80 (22)	117 (20)		
F[c]	51 (14)	2 (0)		

[a] Calculated by the χ^2 test for differences in distribution.
[b] Excluding category F.
[c] Individuals not assigned to a particular household.

Table 2. Filarial Antigen and Immune Responses in the Total Population by Year

Response	1974 (n = 370)	1992 (n = 587)
CAg level, antigen units/mL[a]	798.7 (10 to 1.7 × 10^7)	17.2 (10 to 4.2 × 10^6)
Mf level, Mf number/mL[a]	0.9 (0 to 10,000)	0.03 (0 to 1030)
Absolute eosinophil count[a]	935.8 (0 to 1.4 × 10^4)	15.7 (0 to 2640)
IgG4 response to BmA, ng/mL[a]	19,600 (84 to 2.1 × 10^6)	880 (23 to 2.6 × 10^6)
IgG response, U/mL		
BmA	ND	83,700 (2140 to 1.7 × 10^7)
MfAg	ND	48100 (1560 to 1.26 × 10^6)
ALT2 pep2[a]	504 (34 to 2530)	363 (37 to 46,600)
ALT2 pep3[a]	432 (27 to 2630)	216 (15 to 2830)
Antigen positive/total, proportion (%) of subjects	176/362 (49)	88/581 (15)

NOTE. Data are geometric means (ranges), unless otherwise indicated. ALT2 pep2 and ALT2 pep3, peptide 2 and peptide 3 from *Wuchereria bancrofti* abundant larval transcript 2; BmA, antigen from adult *Brugia malayi*; CAg, circulating filarial antigen; IgG, immunoglobulin G; Mf, microfilariae; MfAg, microfilarial antigen; ND, not done.

[a] $P < .001$ for 1974 compared with 1992 statistics.

each immunologic measure was first assessed for normality. Statistical transformations (including rank ordering, Winsorization, and Box-Cox functions) were applied to continuous traits that appeared to be nonnormally distributed, and frequencies are reported for values for binary traits. Categorical variables, including age, sex, and geographic affiliation, were compared for differences in distribution by assessment year, using χ^2 tests. Continuous measures of filarial antigen and immune responses were compared for distributional differences by year and household affiliation, using a 2-sample t test of geometric means and assuming unequal population variances or generalized linear models. These procedures were performed using SAS software (version 9.1; SAS Institute).

Narrow-sense heritability, which estimates the proportion of the total trait variance that could be attributed to additive genetic effects, was also obtained using variance components as implemented in SOLAR (sequential oligogenic linkage analysis routines) software (version 4.1.3; Southwest Foundation for Biomedical Research) [34]. The variance components approach allows for joint consideration of the pedigree members and provides a more stable estimate than the correlation-based estimate of heritability, which allows for only a single relation class to be considered at a time [35]. Heritability estimated from variance components assumes that the trait variability can be broken down into genetic and environmental contributions. Shared environment is further broken down into a specific shared-household effect, based on reports of common household affiliations.

Narrow-sense heritability was assessed using 4 hierarchical models generated for each trait and survey year. These models were (1) no genetic (h^2) or shared-household (c^2) effects, (2) c^2 effects only, (3) h^2 effects only, and (4) h^2 and c^2 joint effects. All models included the additional shared environmental effects beyond those from shared-household effects and therefore canceled out during model comparisons. Model 4 was treated as the full model and was compared with the other 3 models using likelihood ratio tests. These tests are based on 2 times the difference in log likelihood from each model (which approximates a χ^2 statistic with 1 df and assumes a multivariate normal distribution). If the test shows significant differences ($P \leq .05$), then model 4 is a better fit than the reduced model. A larger value of log likelihood corresponds to a poorer-fitting model that is unable to explain trait variability adequately. For a complete analysis, model 2 and model 3 estimates are provided, along with results for the best-fitting model. The effect of potential confounding by age and sex was evaluated by comparing heritability estimates from adjusted and unadjusted models. If heritability estimates from these models differed by >10%, the variable was considered a confounder and retained for heritability estimates.

RESULTS

There were 448 individuals in 1974 and 625 in 1992 who participated in each survey and were included for pedigree analysis. Of those participants, demographic, parasitologic, clinical, and immunologic factors were available for 370 subjects in 1974 and 587 in 1992 (Tables 1 and 2). Therefore, a total of 1073 individuals were included in the pedigree reconstruction, but only the 957 individuals with full demographic data were available for trait descriptive statistics.

The overall age distribution of study participants differed by year ($P = .007$); there were fewer children <10 years old in the 1992 population than in the 1974 population. The proportion of men studied in 1992 was significantly higher than in 1974 (313 [53%] of 587 vs 164 [44%] of 370; $P = .007$). The geographic locations of occupied households differed as well ($P < .001$) (Figure 1). Although the proportion of the population living in coastal area A and inland area E remained stable (for A, 15% in 1974 vs 13% in 1992; for E, 22% vs 20%,

respectively), a greater percentage of individuals studied in 1992 were from coastal area B or midland area C (for B, 33% in 1992 vs 19% in 1974 [$\chi^2 = 22.1$, $df = 1$; $P < .001$]; for C, 18% vs 6%, respectively [$\chi^2 = 30.0$, $df = 1$; $P < .001$]). The proportion of the population in area D did not differ significantly between the 2 study periods.

Reconstruction of family relationships resulted in 20 pedigrees with the following structure: 7 pedigrees with 2 individuals, 5 pedigrees with 3, 3 pedigrees with 4, 2 pedigrees with 5, 1 pedigree with 7, 1 pedigree with 8, and 1 very large pedigree with 723 individuals. This last pedigree had 1672 parent-offspring, 1345 full-sibling, 248 half-sibling, and 2562 avuncular pairs. There were also 140 individuals without self-affiliation to any particular pedigree.

Filarial infection was less prevalent on the island in 1992 than in 1974; geometric mean values for parasitologic indicators (Mf and CAg) were significantly lower in 1992 than in 1974 (Table 2), most likely owing to a one-time treatment of the entire population with diethylcarbamazine in the late 1980s [3]. The rate of CAg positivity decreased from 49% in 1974 to 15% in 1992. In 1974, 87% of households had at least 1 member with infection. Host responsiveness also differed in the 2 populations, with total eosinophil count, IgG4 antibody responses to BmA, and IgG antibody responses to the larval peptides all significantly lower in the 1992 study population. The largest decrease in the antibody responses was observed for the IgG4 response to BmA (geometric mean, 19,600 ng/mL in 1974 vs only 880 ng/mL in 1992).

Heritability and shared-household effect estimates varied by trait as well as by year (Table 3). For subjects in 1974, heritability estimates for levels of CAg, antigen positivity, and Mf levels ranged from 0.46 to 0.58. These values reflect the proportion of variability for each trait attributable to additive genetic effects and were retained in the best model for those traits. Levels of eosinophils, IgG4 antibody to BmA, and IgG antibody to ALT2 pep3 were estimated to have heritability ranging from 0.06 to 0.21; however, the best model found that these terms did not contribute significantly to explaining the overall trait variability. In 1992, heritability estimates for antigen positivity, eosinophil levels, IgG responses to BmA and ALT2 pep2, and IgG4 responses to BmA ranged from 0.15 to 0.84. Mf levels in 1992 were near or at zero for most subjects, resulting in too little trait variability for estimating heritability (h^2) or shared-household (c^2) effects. In 1992 but not in 1974, there was also variability in CAg—and therefore infection intensity—among geographic locations of households (Table 4). The estimated heritability of antigen positivity increased over time (0.46 in 1974 vs 0.84 in 1992) and remained an important predictor of antigen positivity in the best model. The best models for IgG response to BmA indicated that h^2 was not significant. For IgG response to ALT2 pep3 in 1974 and to ALT2 pep2 in 1992, score statistics for the log likelihood indicated a poor model fit on the basis of nonzero score statistics that resulted in unreliable estimates. Age at the time of survey confounded effect estimates and was retained for the reported analyses; however, sex had a negligible effect (data not shown) and was not retained.

The contribution of shared environmental effects due to common household affiliation was less variable in 1974 (c^2, 0–0.18) than in 1992 (c^2, 0–0.50) (Table 3). On the basis of averaging across c^2 values (multiplied by 100 to obtain per-

Table 3. Age-Adjusted Heritability and Household Effects Contributing to Infection and Immune Responses

	1974			1992		
Trait	h^2 [a]	c^2 [a]	Best model	h^2 [a]	c^2 [a]	Best model
CAg level	0.58 (0.11)	0.18 (0.06)	h^2	0.40 (0.09)	0.17 (0.06)	h^2, c^2
Ag positivity	0.46 (0.15)	0.02 (0.09)	h^2	0.84 (0.13)	0.07 (0.03)	h^2
Mf level	0.49 (0.13)	0.13 (0.06)	h^2	...	...	...
Absolute eosinophil count	0.20 (0.13)	0.11 (0.05)	c^2	0.43 (0.11)	0.50 (0.12)	h^2
IgG4 response to BmA	0.21 (0.10)	0.0 (0.07)[b]	None	0.40 (0.10)	0.28 (0.07)	h^2, c^2
IgG response						
BmA	...	...	...	0.18 (0.09)	0.11 (0.04)	c^2
MfAg	...	...	...	0.18 (0.10)	0.10 (0.04)	c^2
ALT2 pep2	0.06 (0.12)	0.08 (0.05)	None	0.31 (0.08)	0.06 (0.03)[c]	h^2
ALT2 pep3	0.19 (0.12)	0.07 (0.05)[c]	None	0.06 (0.07)	0.0	None

NOTE. Values are not given for microfilariae (Mf) level for 1992 because of too few nonzero observations, and values are not given for the immunoglobulin G (IgG) response to antigen from adult *Brugia malayi* (BmA) and microfilarial antigen (MfAg) in 1974 because data were not collected. Ag, antigen; ALT2 pep2 and ALT2 pep3, peptide 2 and peptide 3 from *Wuchereria bancrofti* abundant larval transcript 2; CAg, circulating filarial antigen.

[a] Estimated from models with either heritability (h^2) or shared-household (c^2) effects alone. The best model was determined by likelihood ratio test and by comparison with the full model (h^2 and c^2 joint effects); "none" means that neither term was significant in the model. Percentages are standard errors.

[b] Estimated from the model with both h^2 and c^2 effects.

[c] Score statistic $\geq |0.00|$.

centages) by year, 11% of trait variability in 1974 could be explained by a shared environment, increasing to 21% in 1992. In addition, 18% of observed CAg, 2% of antigen positivity, and 13% of Mf were attributable to shared-household effects in 1974, as reflected by the c^2 values. However, household effects did not contribute significantly to the majority of best models. In contrast, the best models for CAg, IgG response to BmA and MfAg, and IgG4 response to BmA in 1992 did include a shared-household effect.

DISCUSSION

The genetics of immune or autoimmune diseases (eg, asthma [36] and rheumatoid arthritis [37]) has been a subject of research for many years . More recently, reports have described genetic associations in individuals with the widespread but less studied infections caused by parasitic helminths [19–23]. The present study addressed the role played by host genetics in clinical and immune responses to filarial infection in a well-characterized island population for whom bancroftian filariasis is endemic. The population under study was from a relatively isolated island with little genetic exchange outside the population, thus making the findings even more unique.

Especially interesting is the finding that factors related to the presence of the parasite itself (ie, CAg and Mf levels) were strongly attributable to host genetics, particularly in 1974, before any drug intervention had been conducted. CAg levels, which correlate directly with adult worm burdens [38] and Mf levels [31], are influenced by host genetics, and this demonstrates that the burden of infection in individuals is not simply a result of transmission intensity.

Our results also indicate that although host genetics has a significant effect on the outcome of filarial infection, shared environmental conditions (such as household affiliation) may also have an effect on host responses, albeit to a lesser extent. Age was an important confounder in the assessment of genetic and environmental contributions—as might be expected, given that infection level and immune responses to filarial antigens have been shown to fluctuate with age [39, 40]. Other work with this population has also demonstrated a role for prenatal exposure to parasite antigen in the long-term immune response of the host [10]. This factor, although not really a heritable genetic variant or external environmental exposure, may serve as a "modifier" of heritable responses and would be interesting to examine; unfortunately, that would require more mother-child pairs than previously studied.

Estimates of the relative influences that shared genetics and shared-household effects have on filarial traits varied depending on the survey year. Although the one-time, islandwide treatment with diethylcarbamazine in 1987 for all residents >5 years of age did not eliminate filarial infection on the island, it still had the effect of reducing transmission intensity by reducing Mf load [24]. Because a higher prevalence of filarial infection increases the probability of a household having an infected member, discrimination between household and genetic effects on infection becomes more difficult. Indeed, households in 1974 were relatively homogeneous, given that the majority had at least 1 member with infection. Predictably, therefore, the evidence for household effects (from the 1974 data) was weak and implied that a shared environment did not play a prominent role in heritability estimates of infection and immune responses at that time. The effect of environment on trait values became more apparent in 1992 owing to increased heterogeneity for household infection, improving the ability to detect statistical effects due to household affiliation.

Although differences in the estimated heritable and environmental effects between assessments in 1974 and 1992 could result from demographic changes on Mauke, this explanation seems unlikely given the relatively close proximity of the villages (Figure 1). There were undoubtedly microclimate differences among villages leading to differing levels of mosquito breeding (particularly high in inland areas) that might alter exposure; however, the living environment was not necessarily the primary place of exposure to infected, day-biting mosquitoes. Rather, most Maukeans also farmed taro in the inland swampy regions of the island, causing greater and more equivalent ex-

Table 4. Circulating Antigen (CAg) Levels, by Household Sampling Region and Year

	1974		1992	
Household region	No. of subjects	CAg level, geometric mean (range), antigen units/mL	No. of subjects	CAg level, geometric mean (range), antigen units/mL
A	54	446 (10 to 2 × 10^7)	72	11 (10 to 200)
B	67	403 (10 to 2 × 10^6)	187	15 (10 to 5 × 10^5)
C	21	1339 (10 to 4 × 10^6)	103	27 (10 to 4 × 10^5)
D	92	2441 (10 to 4 × 10^6)	77	50 (10 to 9 × 10^5)
E	77	602 (10 to 2 × 10^6)	117	57 (10 to 4 × 10^6)

NOTE. Household regional affiliation was significantly associated with CAg levels in 1992 ($P < .03$) but not in 1974 ($P = .11$).

posure than they otherwise would have had in their respective villages.

The variance-component approach in this analysis allowed for both specification of shared genetic and environmental effects and assessment of confounders [34]. This approach has a distinct advantage over heritability estimation from relative pair intraclass correlations because it can generate valid estimates even in the presence of dominant genetic and environmental effects. Variance-component estimates confirmed that environmental effects were significant, so that relative pair correlation estimates were less useful for estimating heritability in this population [41].

Despite the potential confounders, we were still able to detect heritable traits in the responses to *W. bancrofti* infection because of the presence of a large, extended pedigree on this isolated island, reflecting a highly genetically homogeneous study population. Because the population was primarily from a single family, there were fewer founders contributing genetic variants with potentially different trait effects; rather, there would probably be a more limited set of genetic variants to determine infection and immune responses in this population. The exact degree of genetic isolation of the population conferred by geography remains uncertain. Studies of language suggest that the Cook Islands had been inhabited by an isolated population until a sudden migration of Taiwanese and other Asian people several thousand years ago [42, 43]. Data on Y chromosome haplotypes [44] suggest that the introduction of genetic material to the Cook Islands from outside populations took place over a more protracted period. Even with the influx of genes into the Cook Islands, the number of haplotype variants is low, with a single predominant haplotype indicating less mixture and a more genetically isolated population.

Identification of heritable traits relating to filarial infection and immune responses reaffirms the need for further research to identify genomic characteristics associated with these traits. It would be useful to pursue genomewide studies with both high-throughput polymorphism and epigenomic studies. This approach might also identify host factors generating specific immune responses relevant to protective immunity (as recently seen with another helminth infection [21]), thus leading to the development of more effective vaccine candidates for filarial parasites. Ultimately, knowledge about which genetic factors can predict a host response to these parasites might help tailor future treatment programs as well as enhance our understanding of the relationship between host and parasite in filarial infection.

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