High Heritability but Uncertain Mode of Inheritance for Total Serum IgE Level and *Schistosoma mansoni* Infection Intensity in a Schistosomiasis-Endemic Brazilian Population

Audrey V. Grant,[1,2] Maria Ilma Araujo,[3] Eduardo Vieira Ponte,[4] Ricardo Riccio Oliveira,[3] Alvaro A. Cruz,[3,4] Kathleen C. Barnes,[1,2] and Terri H. Beaty[1]

[1]Department of Epidemiology, Bloomberg School of Public Health, [2]Division of Allergy and Clinical Immunology, Department of Medicine, the Johns Hopkins University, Baltimore, Maryland; [3]Serviço de Imunologia, Hospital Universitário Professor Edgard Santos, and [4]Program for Control of Asthma and Allergic Rhinitis in Bahia (ProAR), Federal University of Bahia School of Medicine, Salvador, Bahia, Brazil

Background. Evidence of genetic control for total serum IgE (tIgE) level has been reported in multiple populations, although populations with substantial exposure to helminths have yielded lower estimates of heritability, despite evidence suggesting that genes also control a significant portion of the variation in the number of *Schistosoma mansoni* eggs per gram of fecal matter.

Methods. By use of a whole-population ascertainment scheme, 822 individuals were enrolled from a schistosomiasis-endemic area in Conde, Bahia, in Brazil. Heritability was estimated by using an additive polygenic model, and segregation analysis was performed for 2 quantitative traits, tIgE level and egg count.

Results. After adjusting for nongenetic covariates, the heritability of log-transformed tIgE level and log-transformed egg count was estimated at 60% and 31%, respectively. No evidence for a single major gene controlling tIgE level or egg count was observed in segregation analysis for 781 individuals and 403 individuals, respectively, in 318 families, however, which suggests complex biological control.

Conclusions. The high heritability of tIgE level indicates that genetic factors are likely to control tIgE level even in the presence of helminthic infection. Substantial heritability for the burden of *S. mansoni* infection was confirmed in these Brazilian families. Further genetic studies will be needed to dissect the specific genetic factors that underlie these traits.

The worldwide prevalence of schistosomiasis is high—200 million infected individuals—and it occurs where humans come into contact with water that harbors the intermediate snail host for *Schistosoma* species: *S. mansoni* in parts of South America, Africa, and the Middle East; *S. haematobium* in Africa and the Middle East; and *S. japonicum* in China, Southeast Asia, and the Philippines [1]. Although the disease has been successfully eradicated from some regions where it was endemic, control of schistosomiasis is cumbersome, and reinfection after treatment is common [1]. These difficulties have prompted efforts to identify the most susceptible individuals—either those susceptible to greater intensity of infection or more severe disease—to better target treatment and prevention [2].

In atopic individuals (including asthmatics), both helminthic infection and exposure to certain allergens elicit a TH2-mediated immune response and stimulate IgE production [3]. The higher polyclonal total serum IgE (tIgE) level observed in response to helminths include both specific and nonspecific IgE [4, 5]. Similarly,

Received 14 January 2008; accepted 28 April 2008; electronically published XX August 2008.

Potential conflicts of interest: none reported.

Presented in part: 2006 American Academy of Allergy, Asthma and Immunology Annual Meeting, Miami Beach, Florida, 3–7 March 2006 (abstract 1204).

Financial support: Glaxo-Smith-Kline (project WE445 entitled "Immunogenetics of Schistosomiasis and Asthma" to A.V.G., E.V.P., and R.R.O.); National Institutes of Health (grant AI050024); Mary Beryl Patch Turnbull Scholar Program (support to K.C.B.). Some of the results in this paper were obtained by using the Statistical Analysis for Genetic Epidemiology (S.A.G.E.) package, which is supported by a US Public Health Service Resource Grant (RR03655) from the National Center for Research Resources.

Reprints or correspondence: Audrey V. Grant, PhD, Laboratory of Human Genetics of Infectious Diseases, University of Paris René Descartes-INSERM U550, Necker-Enfants Malades Medical School, 156, rue de Vaugirard, 75015 Paris, France, EU (audrey.grant@inserm.fr).

The Journal of Infectious Diseases 2008; 198:xxx

0022-1899/2008/19808-00XX$15.00
DOI: 10.1086/591946

an allergic response is accompanied by an elevated level of IgE specific to environmental allergens, as well as tIgE level [6]. Some evidence, including particularly convincing findings from mouse models [7], suggests allergic reactions are less pronounced in individuals infected with helminths, although both tIgE level and the level of IgE specific to allergens remain high, so areas where helminthic infection is endemic typically have lower levels of allergic disease, compared with areas free of helminths [8–10]. General suppression of allergic responses (including asthma) is partly mediated by regulatory T cells and cytokines such as interleukin (IL)–10 [11–13]. Given these differences in TH2 pathway regulation in the presence of helminthic infection, genetic and environmental components controlling tIgE level in helminthic infection–endemic populations clearly merit further study.

Studies of twin or family-based samples ascertained through atopic disease have confirmed that tIgE level is likely under genetic control, with heritability estimates ranging from 45% to 78% (reviewed in Duffy et al. [14]). In populations exposed to helminths (regardless of helminth infection status), estimates have been considerably lower [15]. Evidence for a genetic basis for the intensity of *S. mansoni* infection in Brazilian populations of African descent have yielded estimates of heritability between 27% and 66% [16–18]. Using families from 5 neighboring villages in the Conde District of Bahia in Brazil (where *S. mansoni* infection is endemic), we investigated the genetic basis for tIgE level as well as intensity of *S. mansoni* infection. We estimated heritability and searched for the best-fitting model of inheritance for 2 related phenotypic traits: tIgE level and intensity of *S. mansoni* infection as measured by fecal egg count.

METHODS

Location. The study was conducted in the rural district of Conde, Bahia—located 200 km north of the city of Salvador—in 5 communities where schistosomiasis is endemic (Buri, Camarao, Genipapo, Sempre Viva, and Cobo). Previous investigations in this region verified the endemicity of schistosomiasis [8–10]. Located on the Atlantic coast, 44 km from the administrative center of Conde, the primary occupation in this area is fishing. Regular, publicly administered mass-treatment campaigns against helminthic infection last occurred during 2001. The population of Brazil represents a mixture of West African, European, and Amerindian ancestral populations, with substantial African admixture in Bahia [19].

Study population. A whole-population ascertainment scheme was implemented and between July and September 2004, we enrolled 822 subjects from an estimated total population of 1700. Local health liaisons informed volunteers about the study, in a concerted effort to reach all households, and volunteers attended the regional public health clinic or a makeshift clinic set up in a school in the 2 larger villages (Cobo and Sempre Viva) or in Buri, which is accessible from the 2 other smaller villages (Genipapo and Camarao). Children under 6 years old were excluded. Blood was collected through venipuncture and serum was separated for measuring tIgE level. Two fecal samples were collected from subjects at an interval of 2–40 days.

Table 1. Relationships for pairs of related individuals in the Brazilian study population.

Relationship, by degree	Count
First	2447
Second	3138
Third	2409
Fourth	805
Fifth	265
Sixth	33
Other	78
Total	9175

All adults provided written consent (or verbal consent recorded by a witness); children gave verbal assent, and written consent for children's participation was obtained from a parent or guardian. The research protocol was approved by institutional review boards at Johns Hopkins University School of Medicine and the Federal University of Bahia and was endorsed by the National Commission for Ethics in Human Research in Brazil.

Pedigree data collection. Key respondents (i.e., mothers of children) were asked to provide name, age, and sex for all of their and their spouse's first-degree relatives living in the schistosomiasis-endemic area. These nuclear families were connected together when individuals from distinct families were found to overlap, and family members were retained if they were either enrolled or were needed to connect branches of the pedigree. The final set of families included 2 large pedigrees with 535 and 310 individuals each, 38 families with 3–36 members and 44 singletons. Counts of relative pairs for first-degree to sixth-degree relationships are presented in table 1. The final set of families was collapsed into 318 nuclear families for certain analyses (described below). A total of 223 individuals appeared more than once in the nuclear family file (e.g., as a parent and as a child in different nuclear families), and sibships ranged in size from 1 to 9.

Biological samples. Stool samples from a total of 631 subjects were tested by using the Kato-Katz method [20, 21] to estimate the number of *S. mansoni* eggs per gram of fecal matter from 3 subsamples taken from 2 independent samples per individual, and the arithmetic mean was calculated for each subject. This test has been shown to give reproducible results when 3–5 exams are performed [21]. A total of 620 individuals had complete data on both samples for *S. mansoni* egg count. The presence or absence of *Ascaris lumbricoides, Trichuris trichiura,* and

hookworm eggs was also determined. A total of 605 individuals had complete data from tests for all helminths. Total serum IgE level was measured using chemiluminescence (Advia Centaur; Bayer) in Salvador, Brazil.

Assessment of water contact. A previously developed environmental exposures questionnaire [22] was administered to quantitate the intensity of exposure to *S. mansoni*. For each of 7 activities (farming, bathing, washing clothes, washing hair, washing dishes, fishing, and playing), each subject was asked to provide a local name for the water source along with the frequency and duration of each activity. Water source names were compiled from all questionnaires and reduced to a nonredundant list, and snails sampled at these sites were tested for cercariae. For water sources positive for cercariae, subjects were classified across all activities into 4 categories to reflect the level of exposure: no exposure, low exposure ($<$ 1 h/week), medium exposure (1–3 h/week), or high exposure (1–3 h/day). Categories were imputed for any individual with missing information about frequency, duration, or water source by using data from those with no missing data ($<$3% subjects had missing information for frequency and/or duration of $\geqslant$1 activities). Smoking status (no smoking exposure, current smoker, or secondary smoke exposure in the household) was also covered by this questionnaire.

Statistical analysis. Analyses of egg count were limited to those with positive egg counts ($n = 273$) or egg counts of 0 but with documented exposure to infested water ($n = 130$). Subjects who were recorded as having no exposure to infested water and who had a negative Kato-Katz result for *S. mansoni* were excluded ($n = 217$). To bring the observed distributions closer to normality, tIgE level and *S. mansoni* egg count + 1 were log-10 transformed. Multiple linear regression models were used to test for association between log-transformed phenotype values and covariates (including sex and age, as well as age squared and age cubed). For tIgE level, we tested other covariates, including smoking status, secondary household smoking exposure, and helminthic infection status. For egg count, association with categorical values was also tested for intensity of contact with infested water, village membership, and type of water-related activity. Residuals from the final models were used to estimate familial correlations, and covariates retained from these analyses were also used to define fixed effects in the variance components models later used to estimate heritability in the segregation analyses.

The mean level of adjusted log(tIgE level) and log(egg count+1) were calculated by age category (6–9 years, 10–14 years, 15–19 years, 20–29 years, 30–39 years, 40–49 years, 50–59 years, 60–69 years, and 70–85 years). For egg count, only 6 individuals fell into the "60–69 years" age group, and these were combined with the "70–85 years" category. The level was also adjusted for covariates other than age. Plots were drawn by using Stata (version 8.2; StataCorp), displaying both means and standard errors.

Familial correlations for relative pairs (marital, parent-offspring, sibling, half-sibling, grandparental, avuncular, and cousin) were calculated by using the family correlations program in S.A.G.E. (2006) Statistical Analysis for Genetic Epidemiology, Release 5.1 (Case Western Reserve University). Heritability analyses were conducted by using the Sequential Oligogenic Linkage Analysis Routines package ([SOLAR] version 2.1.4; Southwest Foundation for Biomedical Research), using variance components models [23]. SOLAR accepts complex pedigree structures including marriage loops and multiple mates. Log-transformed trait values were the dependent variable, and covariates were included as fixed effects. Likelihood ratio tests (LRTs) that compared a model that included an additive genetic variance component and a residual environmental component were compared to a reduced model in which the genetic component was set to 0 provided a formal test for the significance of estimated heritability.

The S.A.G.E. segregation analysis program SEGREG was used to estimate parameters of a general model of inheritance by using class D regressive models for continuous traits for 781 subjects for tIgE level and 403 subjects for *S. mansoni* egg count. The individuals included were those who had complete phenotypic and covariate data, such that each individual was in a nuclear family unit with $\geqslant$1 other individual who also had complete data [24]. A series of models of inheritance were tested including sporadic, environmental, and Mendelian models (dominant and codominant) by setting transmission parameters (τ) that represented the probability of a parent's transmitting an A allele to an offspring for each parental genotype (AA, AB, or BB). Hardy-Weinberg equilibrium was assumed to underlie the distributions of these three putative genotypes in the population when estimating the frequency of the A allele (q_A). The LRT was used to assess the fit of each reduced model against a general unrestricted model. Akaike's information criterion (AIC), defined as $-2\ln L + 2$(number of estimated parameters), was used to identify the most parsimonious model.

RESULTS

Preliminary data analysis. On the basis of data from 620 subjects with data on *S. mansoni* egg count and 605 subjects tested for all helminths in this schistosomiasis-endemic area, the prevalence of schistosomiasis was estimated at 44%, and the overall prevalence of helminthic infection was 83.5%. Infection status, as well as the demographic and clinical characteristics of 822 enrolled subjects are presented in table 2. The mean ($\pm$SD) egg count was 120.54 ($\pm$ 212.2) eggs/g of fecal matter (moderate intensity of infection, according to the World Health Organization scale [25]) for 273 individuals with a positive infection test result, and the mean ($\pm$SD) tIgE level was 3858.57 ($\pm$2944) ng/

Table 2. Demographic and clinical characteristics of the study population from the schistosomiasis-endemic region in the Conde district of Bahia, Brazil.

Characteristic	Value
Male sex	360/822 (43.8)
Age, mean ± SD, years (N = 822)	26.87 ± 18.7
Infected with helminths	505/605 (83.5)
Infected with *Schistosoma mansoni*	273/620 (44.0)
S. mansoni egg count, mean ± SD	
All, eggs/g fecal matter (N = 620)	53.08 ± 152.9
If count >0, eggs/g fecal matter (N = 273)	120.54 ± 212.2
For subjects with water exposure data, eggs/g fecal matter (N = 403)	81.65 ± 183.5
Total serum IgE level, mean ± SD, ng/mL (N = 783)	3859 ± 2944
log-transformed total serum IgE level, mean ± SD (N = 783)	3.40 ± 0.51
Level of exposure to infested water	
Low	135/724 (18.7)
Medium	120/724 (16.6)
High	144/724 (19.9)
Smoking status	
Current smoker	177/806 (22.0)
Household exposure	78/806 (9.7)

NOTE. Data are proportion (%) of subjects, unless otherwise indicated.

mL. When grouped by level of exposure to infested water, 135 subjects had low exposure, 120 had medium exposure, and 144 had high exposure; 325 reported no contact with infested water.

Age, sex, smoking, helminthic infection status, and *S. mansoni* egg count were identified as important covariates for log(tIgE level). For log(egg count+1), age, sex, and categorical exposure variables were retained as predictors, and despite the nonlinear effect of age (figure 1*A*), addition of age-squared or age-cubed terms did not substantially improve the fit of the model. Village of residence and fishing activity were also statistically significant, but other exposure variables absorbed their effect so these were not retained in subsequent analysis.

The profiles of the adjusted log(tIgE level) and log(egg count+1) distributions according to age category are presented in figure 1. For log(tIgE level), there was an overall decline with increasing age, with a dramatic drop from age 6–9 years to 10–14 years. For log(egg count+1), the age profile peaked in the second decade of life, followed by a slow decline through adolescence and beyond.

Familial correlation coefficients. Consistent with genetic control, spousal pairs showed no significant correlation for log(tIgE level) and log(egg count+1) (table 3). A low parent-offspring correlation, compared with sibling correlation, for log(egg count+1)—0.09 versus 0.17—might result from the nonlinear relationship between log(egg count+1) and age shown in figure 1*A*. Offspring were largely children, who had higher egg counts overall (mean [±SD], 84.3 [± 190] eggs/g), siblings were closer in age, and parents (always adults) had much lower mean counts (mean [±SD], 57.4 [± 109] eggs/g). More distant relative pairs showed weak or negative correlations for egg counts. The parent-offspring correlation (SE) was high (0.278 [0.057]) and sibling correlation was lower (0.176 [0.067]) for log(tIgE level). Grandparental correlations were particularly high (0.249) for log(tIgE level).

Heritability. Variance components analysis gave high heritability estimates that were also highly significant (h^2 = 0.574–0.727; P = .014 to P < .001) (table 4) for both traits using all available data (table 4). Estimated heritability for log(tIgE level) and log(egg count + 1) were 0.59 and 0.31, respectively. The proportion of phenotypic variance attributed to covariates was substantial (e.g., 0.23 for log(egg count + 1)). For log(tIgE level), a high kurtosis prevented accurate estimation of the proportion of variance due to these covariates.

Segregation analysis. For log(tIgE level), a comparison between 2 sporadic models (models 1 and 2 in table 5) confirmed there was no significant difference in residual correlations ρ_{PO} and ρ_{SS} (P = .466). A single residual correlation coefficient for first-degree relatives was estimated at 0.267 (±0.04), and all subsequent models kept $\rho_{PO} = \rho_{SS}$. The codominant Mendelian model showed a better fit to these data than the dominant model, the sporadic model, or the environmental-mixed model. A semigeneral dominant model in which τ_{AB} was estimated showed a further improvement, and the estimated transmission from putative heterozygotes was not significantly different from the Mendelian expectation of 50%. The 12-unit difference in log-likelihoods between a Mendelian codominant model and the general model seems to arise from <100% transmission from "AA" parents (under the general model 8, it was 81.6%) and <50% transmission from "AB" parents (under the model 8, it was 36.8%). When the most general model (8 in table 5) was

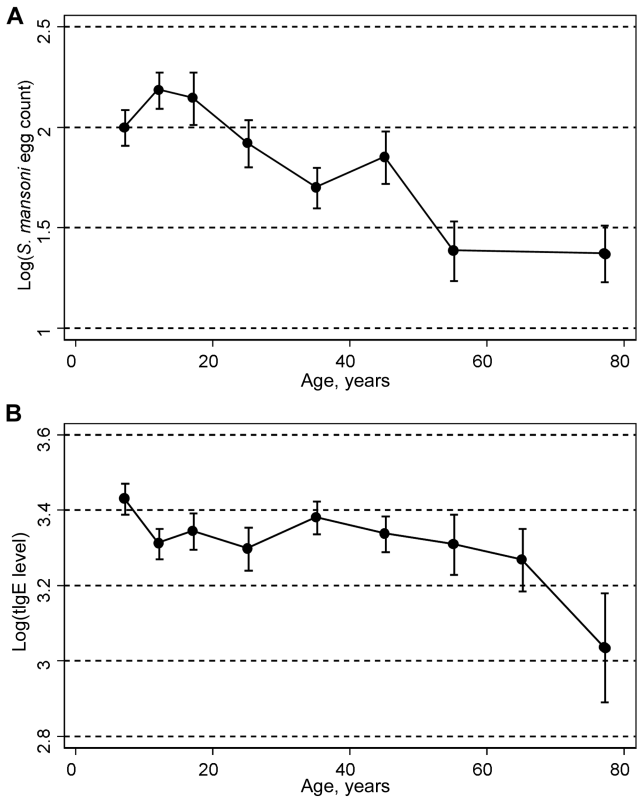

Figure 1. Age profiles for *Schistosoma mansoni* egg count and total serum IgE (tIgE) level, showing mean log-transformed adjusted level by age category; mean levels are displayed at median age. For details about age categories, see Methods. *Bars,* mean ± SE. *A,* Log(*S. mansoni* egg count) adjusted for sex and low, medium, and high exposure to infested water, recentered around the mean level for 20-year-old males without exposure to infested water. *B,* Log(tIgE level) adjusted for sex, smoking, helminthic infection status, and log-transformed *S. mansoni* egg count, recentered around the mean level for uninfected, nonsmoking males at age 20.

used as the reference model, however, all reduced models (1–7) were rejected. Examining the AIC showed that no reduced model could explain these data better than the general model in which the transmission from putative homozygous and heterozygous parents was distinctly lower than expected.

Similarly, for log(egg count+1) (table 6), the LRT comparing single distribution models with one or two correlation coefficients was not statistically significant ($P = .205$). The combined residual correlation coefficient was 0.153 (±0.054). The most general model fit significantly better than any reduced model, and among other models, the environmental model fit best, lending little support for a major gene controlling egg count in these families.

DISCUSSION

Findings from analysis of this Brazilian study population of 822 individuals—with an estimated prevalence of *Schistosoma mansoni* infection of 44%—contribute to previous evidence that host genetic factors control variation in burden of infection as measured by fecal egg count. Although there is a large body of evidence indicating that genetic factors influence tIgE level, these data have come largely from family samples ascertained through atopic disease in industrialized regions. Here, we demonstrate that variation in tIgE level in a population where the main TH2 immune pathway stimulus is helminthic infection also reflects a substantial additive genetic component.

We found a high heritability estimate (59%) for tIgE level under a variance components model after adjusting for nongenetic factors such as age, sex, smoking status, helminth infection status, and *S. mansoni* egg count, which took advantage of most relative pairs in this sample with a complex family structure. This estimate falls in the range of previously reported estimates of 45%–78% in populations in which schistosomiasis is not en-

Table 3. Familial correlation coefficients between relative pairs for log-transformed total serum IgE (tIgE) level and log-transformed *Schistosoma mansoni* egg count.

	tIgE level[a]		*S. mansoni* egg count[b]	
Relative pair	No. of pairs	Correlation (SE)	No. of pairs	Correlation (SE)
Spousal	48	0.050 (0.145)	24	−0.170 (0.209)
Parent-offspring	402	0.278 (0.057)	217	0.093 (0.074)
Sibling	401	0.176 (0.067)	262	0.170 (0.079)
Half sibling	42	0.248 (0.169)	33	−0.075 (0.214)
Grandparent	180	0.249 (0.093)	67	−0.059 (0.126)
Avuncular	625	0.076 (0.070)	408	0.057 (0.061)
Cousin	651	0.139 (0.071)	451	0.013 (0.061)

[a] Adjusted for age, sex, smoking status, helminth infection status, and log-transformed *S. mansoni* egg count.

[b] Adjusted for age, sex, and low, medium, and high exposure to infested water sources.

Table 4. Heritability estimates for log-transformed total serum IgE (tIgE) level and log-transformed *Schistosoma mansoni* egg count, as determined by variance components analysis.

Trait	Covariate (% variance)	h^2 (SE)	*P*
tIgE level[a] ($N = 575$)	NC[c]	0.598 (0.090)	<.0001
S. mansoni egg count [b] ($N = 403$)	0.229	0.311 (0.120)	.0012

NOTE. NC, not calculated.

[a] Adjusted for age, sex, smoking status, helminth infection status, and log-transformed *S. mansoni* egg count.

[b] Adjusted for age, sex, and low, medium, and high exposure to infested water sources.

[c] Because of the high kurtosis of the total IgE level distribution, it was not possible to estimate the proportion of phenotypic variance attributable to covariates.

demic [14]. In other studies involving populations with similar racial characteristics, heritability for tIgE level was 35% (African-Caribbean population [26]) and 60% (African American population [27]). One previous study examining tIgE level in a helminth infection–endemic population revealed familial aggregation of high tIgE levels [28]. In an Indian population, low heritability for tIgE level was attributed to possible helminthic infection that was not tested for in this study population [15]. Our study identified a mean tIgE value of 3859 ng/mL (over 19 times the clinically relevant threshold of 200 ng/mL for atopy), which strongly suggests that variation in tIgE level in this Brazilian population (after adjusting for relevant covariates, including helminthic infection) has a substantial genetic component.

However, segregation analyses of log(tIgE level) failed to identify any distinct single-locus model of inheritance. The most parsimonious model (other than the general) was a Mendelian codominant model, but this did not fit these family data as well as the general model. Although these results do not support a single major model, the strong heritability for log(tIgE level) suggests that multiple genes acting together could explain our results. Given the numerous covariates influencing tIgE level, it is not surprising no single gene could be identified through segregation analysis. Prior investigations have supported a range of genetic models of inheritance for tIgE level, including the following: single Mendelian genes with recessive inheritance [29–31] or codominant inheritance [32], a 2-distribution Mendelian model [33], as well as a more general polygenic model [34]; one study suggested extensive genetic heterogeneity [35]. The lack of consistency in the literature with respect to genetic models raises the possibility of heterogeneity across populations. In this admixed Brazilian population, it is also possible that greater heterogeneity in the population has reduced power to detect a single major gene with clear Mendelian inheritance.

Our evaluation of the intensity of *S. mansoni* infection yielded a substantial heritability estimate (31% for fecal egg count, adjusted for nongenetic covariates), although, again, no single major gene could adequately explain this quantitative phenotype. Although we did not have direct observation of individuals' amount of contact with infested water, our questionnaire did cover a wide variety of common activities that entail possible exposure to the parasite, and the breadth of information allowed us to construct 4 broad but valid intensity categories suitable for statistical analysis. A previous study in a Brazilian population found evidence for a codominant major gene that could explain 66% of variation in egg count (also adjusted for age, sex, and water exposure) [16]. In another Brazilian study, after accounting for shared household effects and other covariates, Bethony et al. found 27%–29% of variance in egg count could be explained genetic effects [17, 18]. A Senegalese study, however, used segregation analysis and found no evidence for a major gene effect [36].

The profile for *S. mansoni* egg count (figure 1*A*) features a peak in infection intensity in the second decade of life, which represents acquisition of natural immunity to infection in adolescence, and this appears to be minimally related to differences in exposure to the parasite in a variety of settings according to age [37, 38]. This natural immunity has been found to track with increased levels of IgE for schistosome-specific antigens within the same age groups and with a shift in the balance between production of schistosome antigen-specific IgG4 and IgE in favor of IgE [39–41]. It does not track with tIgE level, as shown in this study, in which mean level was highest among young children age 6–9 years old and then declined with increasing age. A greater nonspecific component in IgE production, at the expense of schistosome-specific IgE, may result in a less protective humoral immune response in young children, compared with adolescents and adults.

The high heritability estimate obtained for log(tIgE level) in our Brazilian study implies that there are genes controlling tIgE level regardless of the relative proportion of schistosome antigen-specific IgE. Measuring schistosome antigen-specific IgE and IgG4 in the Conde population could allow us to determine the relationship between specific immunoglobulin levels and development of a protective immune response in individuals with schistosomiasis, as well estimating heritabilities for both specific and nonspecific IgE; this work is in progress. Another set of Brazilian families showed a positive sibling correlation for IgE and IgG4 levels specific for egg antigens (but not for crude antigen preparations of eggs or adult worms) [42].

While tIgE level does not appear to directly reflect natural immunity in helminth infection–endemic populations, linkage studies have implicated a locus in chromosome 5q31–q33 in controlling asthma, including 3 studies of tIgE level as a quantitative trait [43–46], and intensity of schistosomiasis infection in Brazilian and Senegalese populations [36, 47, 48]. Because this same chromosomal region was identified for helminthic infection and for atopic phenotypes in a number of independent studies, there may be a common genetic basis for

Table 5. Segregation analysis for log-transformed total IgE level in 1493 individuals (781 with complete phenotype and covariate data) in 318 families.

Model no. and name	μ_{AA}[a]	μ_{AB}[a]	μ_{BB}[a]	σ^2[b]	ρ_{PO}[c]	ρ_{SS}[c]	q_A[d]	τ_{AA}[e]	τ_{AB}[e]	τ_{BB}[e]	$-2 \times \ln L$[f]	AIC	χ^2[g]	df[g]	P[g]
1. Sporadic	3.411 (0.02)	[3.411 (0.02)]	[3.411 (0.02)]	0.194 (0.01)	0.267 (0.04)	[0.267 (0.04)]	. . .	q_A	q_A	q_A	638.5	656.5	150	6	<.0001
2. Familial correlations	3.411 (0.02)	[3.411 (0.02)]	[3.411 (0.02)]	0.193 (0.01)	0.286 (0.04)	0.236 (0.06)	. . .	q_A	q_A	q_A	638.0	658.0	149	5	<.0001
3. Mendelian dominant	2.662 (0.05)	[2.662 (0.05)]	3.545 (0.02)	0.087 (0.01)	0.23 (0.06)	[0.23 (0.06)]	0.08 (0.01)	[1]	[0.5]	[0]	562.8	584.8	74.3	4	<.0001
4. Mendelian codominant	2.461 (0.05)	3.296 (0.04)	3.664 (0.02)	0.065 (0.01)	−0.11 (0.01)	[−0.11 (0.01)]	0.283 (0.03)	[1]	[0.5]	[0]	500.5	524.5	11.9	3	<.0001
5. Environmental mixed	2.140 (0.1)	2.940 (0.06)	3.599 (0.02)	0.067 (0.01)	0.403 (0.08)	[0.403 (0.08)]	0.146 (0.02)	q_A	q_A	q_A	533.7	557.7	45.2	3	<.0001
6. τ_{AB} estimated	2.600 (0.05)	[2.600 (0.05)]	3.547 (0.02)	0.085 (0.01)	0.072 (0.06)	[0.072 (0.06)]	0.074 (0.02)	[1]	0.474 (0.06)	[0]	502.3	526.3	13.7	3	.0010
7. τ_{AB} estimated (codominant)	2.448 (0.04)	3.267 (0.00)	3.668 (0.00)	0.063 (0.00)	−0.11 (0.00)	[−0.11 (0.00)]	0.297 (0.02)	[1]	0.438 (NA)	[0]	499.9	523.9	11.4	2	.0033
8. General	2.309 (0.04)	3.090 (0.04)	3.667 (0.02)	0.043 (0.00)	0.153 (0.09)	[0.153 (0.09)]	0.244 (0.03)	0.816 (0.08)	0.368 (0.05)	0.052 (0.02)	488.5	518.5	. . .	. . .	. . .

NOTE. Covariates included in all models include age, sex, smoking status, helminthic infection status, and log-transformed *Schistosoma mansoni* egg count (means not displayed). Square brackets indicate fixed values; parentheses indicate standard errors. AIC, Akaike information criterion; NA, not available—standard errors could not be estimated; PO, parent-offspring; SS, sibling-sibling.

[a] Genotypic mean for genotype (AA, AB, or BB).
[b] Residual variance of the phenotype.
[c] Familial correlation.
[d] Frequency of allele A, associated with high total IgE level.
[e] Probability of transmitting A allele for each possible parental genotype.
[f] Twice the log of the likelihood of the model
[g] χ^2 test statistic with degrees of freedom and P value evaluating each model against model 8.

Table 6. Segregation analysis for log-transformed *Schistosoma mansoni* egg count in 1493 individuals (403 with complete phenotype and covariate data) in 318 families.

Model no. and name	μ_{AA}[a]	μ_{AB}[a]	μ_{BB}[a]	σ^2[b]	ρ_{PO}[c]	ρ_{SS}[c]	q_A[d]	τ_{AA}[e]	τ_{AB}[e]	τ_{BB}[e]	$-2\times$ lnL[f]	AIC	χ^2[g]	df[g]	P[g]
1. Sporadic	1.283 (0.06)	[1.283 (0.06)]	[1.283 (0.06)]	0.65 (0.05)	0.153 (0.05)	[0.153 (0.05)]	. . .	q_A	q_A	q_A	967.3	983.3	195	6	<.0001
2. Familial correlations	1.282 (0.06)	[1.282 (0.06)]	[1.282 (0.06)]	0.67 (0.05)	0.077 (0.07)	0.295 (0.09)	. . .	q_A	q_A	q_A	963.7	981.7	192	5	<.0001
3. Mendelian dominant	0.722 (0.04)	[0.722 (0.04)]	2.347 (0.05)	0.159 (0.01)	0.067 (0.06)	[0.067 (0.06)]	0.325 (0.03)	[1]	[0.5]	[0]	878.5	898.5	106	4	<.0001
4. Mendelian codominant	0.692 (0.03)	2.255 (0.05)	2.843 (0.10)	0.127 (0.01)	0.049 (0.06)	[0.049 (0.06)]	0.701 (0.03)	[1]	[0.5]	[0]	874.6	896.6	103	3	<.0001
5. Environmental mixed	−0.01 (0.04)	1.404 (0.03)	2.214 (0.04)	0.057 (0.01)	0.027 (0.07)	[0.027 (0.07)]	0.534 (0.02)	q_A	q_A	q_A	790.1	812.1	18.0	3	.0004
6. τ_{AB} estimated	0.718 (0.04)	[0.718 (0.04)]	2.344 (0.05)	0.158 (0.01)	0.064 (0.06)	[0.064 (0.06)]	0.363 (0.03)	[1]	0.413 (0.04)	[0]	874.6	896.6	102	3	<.0001
7. General	−0.003 (0.03)	1.401 (0.03)	2.213 (0.04)	0.056 (0.01)	0.025 (0.07)	[0.025 (0.07)]	0.619 (0.04)	0.714 (0.07)	0.497 (0.08)	0.218 (0.08)	772.1	800.1	. . .	. . .	. . .

NOTE. Covariates included in all models include: age, sex, and low, medium, and high exposure to infested water sources (means not displayed). Square brackets indicate fixed values; parentheses indicate standard errors. AIC, Akaike information criterion; PO, parent-offspring; SS, sibling-sibling.

[a] Genotypic mean for genotype (AA, AB, or BB).
[b] Residual variance of the phenotype.
[c] Familial correlation.
[d] Frequency of allele A, associated with high total IgE level.
[e] Probability of transmitting A allele for each possible parental genotype.
[f] Twice the log of the likelihood of the model.
[g] χ^2 test statistic with degrees of freedom and P value evaluating each model against model 7.

host susceptibility to helminthic infection and atopic disease. Variants in *IL13* located in this region have been associated with intensity of *S. haematobium* infection [49]. Ongoing genotyping studies include variants in the 5q31–q33 region, to determine whether certain variants influence tIgE level, egg count, or both. Genetic dissection of these 2 traits in tandem will allow localization of particular genetic effects that influence aspects of host immunity, or further downstream, influence the outcome of schistosomiasis.

Acknowledgments

We would like to thank the people of the schistosomiasis-endemic area in Conde from Buri, Camarao, Genipapo, Sempre Viva and Cobo for their participation in our study; the health liaisons, Adaliudes Conceição, Luciana Quintela, Ivanice Santos; the public health officers of the main Conde office, Analú Lima, Benivaldo Valber Oliveira Silva, and Iraci Santos Araujo; and students from the Federal University of Bahia who assisted in data collection: Rafael Santana, Roberta Barbosa, Ana Paula Santana, Charlton Barros, Marcele Brandão, Ludmila Almeida, Thiago Cardoso and Daniela Costa. In addition, Leda Alcântara sampled snails and performed parasitological exams.

References

1. King CH, Dickman K, Tisch DJ. Reassessment of the cost of chronic helminthic infection: a meta-analysis of disability-related outcomes in endemic schistosomiasis. Lancet **2005**; 365:1561–9.
2. Quinnell RJ. Genetics of susceptibility to human helminth infection. Int J Parasitol **2003**; 33:1219–31.
3. Pearce EJ, MacDonald AS. The immunobiology of schistosomiasis. Nat Rev Immunol **2002**; 2:499–511.
4. Kojima S, Yokogawa M, Tada T. Raised levels of serum IgE in human helminthiases. Am J Trop Med Hyg **1972**; 21:913–8.
5. Radermecker M, Bekhti A, Poncelet E, Salmon J. Serum IgE levels in protozoal and helminthic infections. Int Arch Allergy Appl Immunol **1974**; 47:285–95.
6. Burrows B, Martinez FD, Halonen M, Barbee RA, Cline MG. Association of asthma with serum IgE levels and skin-test reactivity to allergens. N Engl J Med **1989**; 320:271–7.
7. Maizels RM. Infections and allergy—helminths, hygiene and host immune regulation. Curr Opin Immunol **2005**; 17:656–61.
8. Araujo MI, Lopes AA, Medeiros M, et al. Inverse association between skin response to aeroallergens and *Schistosoma mansoni* infection. Int Arch Allergy Immunol **2000**; 123:145–8.
9. Medeiros M, Jr., Almeida MC, Figueiredo JP, et al. Low frequency of positive skin tests in asthmatic patients infected with *Schistosoma mansoni* exposed to high levels of mite allergens. Pediatr Allergy Immunol **2004**; 15:142–7.
10. Medeiros M, Jr., Figueiredo JP, Almeida MC, et al. *Schistosoma mansoni* infection is associated with a reduced course of asthma. J Allergy Clin Immunol **2003**; 111:947–51.
11. van den Biggelaar AH, van Ree R, Rodrigues LC, et al. Decreased atopy in children infected with *Schistosoma haematobium:* a role for parasite-induced interleukin-10. Lancet **2000**; 356:1723–7.
12. Araujo MI, Hoppe B, Medeiros M, Jr., et al. Impaired T helper 2 response to aeroallergen in helminth-infected patients with asthma. J Infect Dis **2004**; 190:1797–803.
13. Belkaid Y, Blank RB, Suffia I. Natural regulatory T cells and parasites: a common quest for host homeostasis. Immunol Rev **2006**; 212:287–300.
14. Duffy DL. Applying statistical approaches in the dissection of genes versus environment for asthma and allergic disease. Curr Opin Allergy Clin Immunol **2001**; 1:431–4.
15. Parks T, Felix K, Rice T, Subbarao PV, Marimuthu KM, Rao DC. A genetic study of immunoglobulin E and atopic disease based on families ascertained through asthmatic children. Hum Hered **1990**; 40:69–76.
16. Abel L, Demenais F, Prata A, Souza AE, Dessein A. Evidence for the segregation of a major gene in human susceptibility/resistance to infection by *Schistosoma mansoni*. Am J Hum Genet **1991**; 48:959–70.
17. Bethony J, Williams JT, Blangero J, et al. Additive host genetic factors influence fecal egg excretion rates during *Schistosoma mansoni* infection in a rural area in Brazil. Am J Trop Med Hyg **2002**; 67:336–43.
18. Bethony J, Williams JT, Kloos H, et al. Exposure to *Schistosoma mansoni* infection in a rural area in Brazil. II: Household risk factors. Trop Med Int Health **2001**; 6:136–45.
19. Azevedo ES, Fortuna CM, Silva KM, et al. Spread and diversity of human populations in Bahia, Brazil. Hum Biol **1982**; 54:329–41.
20. Katz N, Chaia G. Coprological diagnosis of schistosomiasis. I. Evaluation of quantitative techniques. Rev Inst Med Trop Sao Paulo **1968**; 10: 295–8.
21. Katz N, Coelho PM, Pellegrino J. Evaluation of Kato's quantitative method through the recovery of *Schistosoma mansoni* eggs added to human feces. J Parasitol **1970**; 56:1032–3.
22. Dessein AJ, Begley M, Demeure C, et al. Human resistance to *Schistosoma mansoni* is associated with IgG reactivity to a 37-kDa larval surface antigen. J Immunol **1988**; 140:2727–36.
23. Almasy L, Blangero J. Multipoint quantitative-trait linkage analysis in general pedigrees. Am J Hum Genet **1998**; 62:1198–211.
24. Bonney GE. On the statistical determination of major gene mechanisms in continuous human traits: regressive models. Am J Med Genet **1984**; 18:731–49.
25. World Health Organization. Report of the Scientific Working Group meeting on schistosomiasis. Geneva: World Health Organization, on behalf of the Special Programme for Research and Training in Tropical Diseases, **2006**. Available at: http://www.who.int/tdr/publications/publications/pdf/swg_schisto.pdf. Accessed 13 August 2008.
26. Manolio TA, Barnes KC, Beaty TH, Levett PN, Naidu RP, Wilson AF. Sex differences in heritability of sensitization to *Blomia tropicalis* in asthma using regression of offspring on midparent (ROMP) methods. Hum Genet **2003**; 113:437–46.
27. Mathias RA, Freidhoff LR, Blumenthal MN, et al. Genome-wide linkage analyses of total serum IgE using variance components analysis in asthmatic families. Genet Epidemiol **2001**; 20:340–55.
28. Wahyuni S, Sartono E, Supali T, et al. Clustering of allergic outcomes within families and households in areas endemic for helminth infections. Int Arch Allergy Immunol **2005**; 136:356–64.
29. Gerrard JW, Rao DC, Morton NE. A genetic study of immunoglobulin E. Am J Hum Genet **1978**; 30:46–58.
30. Marsh DG, Bias WB, Ishizaka K. Genetic control of basal serum immunoglobulin E level and its effect on specific reaginic sensitivity. Proc Natl Acad Sci U S A **1974**; 71:3588–92.
31. Meyers DA, Beaty TH, Freidhoff LR, Marsh DG. Inheritance of total serum IgE (basal levels) in man. Am J Hum Genet **1987**; 41:51–62.
32. Meyers DA, Bias WB, Marsh DG. A genetic study of total IgE levels in the Amish. Hum Hered **1982**; 32:15–23.
33. Mathias RA, Beaty TH, Bailey-Wilson JE, Bickel C, Stockton ML, Barnes KC. Inheritance of total serum IgE in the isolated Tangier Island population from Virginia: complexities associated with genealogical depth of pedigrees in segregation analyses. Hum Hered **2005**; 59:228–38.
34. Hasstedt SJ, Meyers DA, Marsh DG. Inheritance of immunoglobulin E: genetic model fitting. Am J Med Genet **1983**; 14:61–6.
35. Blumenthal MN, Namboodiri K, Mendell N, Gleich G, Elston RC, Yunis E. Genetic transmission of serum IgE Levels. Am J Med Genet **1981**; 10: 219–28.
36. Muller-Myhsok B, Stelma FF, Guisse-Sow F, et al. Further evidence suggesting the presence of a locus, on human chromosome 5q31–q33, in-

fluencing the intensity of infection with *Schistosoma mansoni*. Am J Hum Genet **1997**; 61:452–4.
37. Keymer A, Pagel M. Predisposition to helminth infection. In: Schad GA, Warren KS, eds. Hookworm disease: current status and new directions. London: Taylor & Francis, **1990**:177–209.
38. Woolhouse ME. Patterns in parasite epidemiology: the peak shift. Parasitol Today **1998**; 14:428–34.
39. Demeure CE, Rihet P, Abel L, Ouattara M, Bourgois A, Dessein AJ. Resistance to *Schistosoma mansoni* in humans: influence of the IgE/IgG4 balance and IgG2 in immunity to reinfection after chemotherapy. J Infect Dis **1993**; 168:1000–8.
40. Hagan P, Blumenthal UJ, Dunn D, Simpson AJ, Wilkins HA. Human IgE, IgG4 and resistance to reinfection with *Schistosoma haematobium*. Nature **1991**; 349:243–5.
41. Rihet P, Demeure CE, Bourgois A, Prata A, Dessein AJ. Evidence for an association between human resistance to *Schistosoma mansoni* and high anti-larval IgE levels. Eur J Immunol **1991**; 21:2679–86.
42. Bethony J, Silveira AM, Alves-Oliveira LF, et al. Familial resemblance in humoral immune response to defined and crude *Schistosoma mansoni* antigens in an endemic area in Brazil. J Infect Dis **1999**; 180: 1665–73.
43. Marsh DG, Neely JD, Breazeale DR, et al. Linkage analysis of IL4 and other chromosome 5q31.1 markers and total serum immunoglobulin E concentrations. Science **1994**; 264:1152–6.
44. Meyers DA, Postma DS, Panhuysen CI, et al. Evidence for a locus regulating total serum IgE levels mapping to chromosome 5. Genomics **1994**; 23:464–70.
45. Postma DS, Bleecker ER, Amelung PJ, et al. Genetic susceptibility to asthma—bronchial hyperresponsiveness coinherited with a major gene for atopy. N Engl J Med **1995**; 333:894–900.
46. Wills-Karp M, Ewart SL. Time to draw breath: asthma-susceptibility genes are identified. Nat Rev Genet **2004**; 5:376–87.
47. Marquet S, Abel L, Hillaire D, Dessein A. Full results of the genome-wide scan which localises a locus controlling the intensity of infection by *Schistosoma mansoni* on chromosome 5q31–q33. Eur J Hum Genet **1999**; 7:88–97.
48. Marquet S, Abel L, Hillaire D, et al. Genetic localization of a locus controlling the intensity of infection by *Schistosoma mansoni* on chromosome 5q31–q33. Nat Genet **1996**; 14:181–4.
49. Kouriba B, Chevillard C, Bream JH, et al. Analysis of the 5q31–q33 locus shows an association between IL13-1055C/T IL-13-591A/G polymorphisms and *Schistosoma haematobium* infections. J Immunol **2005**; 174:6274–81.