Functional Polymorphisms in *IL13* Are Protective against High *Schistosoma mansoni* Infection Intensity in a Brazilian Population

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**Abstract**

**Background:** *IL-13* is a signature cytokine of the helper T cell type 2 (TH2) pathway whichunderlies host defense to helminthic infection and activates production of IgE in both parasitized populations and in urban settings after allergen exposure.

**Methodology/Principal Findings:** Two functional polymorphisms in *IL13*, rs1800925 (c.1-1111C>T) and rs20541 (or R130Q) were previously found to be associated with *Schistosoma hematobium* infection intensity. They have not been thoroughly explored in *S. mansoni*-endemic populations, however, and were selected along with 5 tagging SNPs for genotyping in 812 individuals in 318 nuclear families from a schistosomiasis-endemic area of Conde, Bahia, in Brazil. Regression models using GEE to account for family membership and family-based quantitative transmission disequilibrium tests (QTDT) were used to evaluate associations with total serum IgE (tIgE) levels and *S. mansoni* fecal egg counts adjusted for non-genetic covariates. We identified a protective effect for the T allele at rs20541 (P = 0.005) against high *S. mansoni* egg counts, corroborated by QTDT (P = 0.014). Our findings also suggested evidence for protective effects for the T allele at rs1800925 and A allele at rs2066960 after GEE analysis only (P = 0.050, 0.0002).

**Conclusions/Significance:** The two functional variants in *IL13* are protective against high *S. mansoni* egg counts. These markers showed no evidence of association with tIgE levels, unlike tIgE levels previously studied in non-parasitized or atopic study populations.

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**Introduction**

The worldwide prevalence of schistosomiasis is high at 200 million infected individuals, creating a substantial public health burden. [1] Schistosomiasis occurs in areas where humans come into contact with water harboring the intermediate snail host for *Schistosoma mansoni* in parts of South America, Africa and the Middle East; *S. haematobium* in Africa and the Middle East; or *S. japonicum* in China, South-East Asia and the Philippines. [1] Infection occurs when cercariae burrow directly through the skin, maturing into the adult form in the portal vasculature. Females lay eggs which traverse into the intestine (*S. mansoni* and *S. japonicum*) or the bladder (*S. haematobium*). [2] Control of schistosomiasis is cumbersome, and reinfection after treatment is common. [1] These obstacles have motivated research to better understand schistosomiasis host immunity to identify those individuals susceptible to greatest intensity of infection for targeted treatment and prevention. [3,4]

Host immune response to infection involves differentiation of helper T cells into two major subtypes known as TH1 and TH2 cells. While TH1 cells elicit cellular immunity against intracellular bacteria and viruses, infection by helminths (including *S. mansoni*) induces a TH2 humoral response, accompanied by release of the cytokines IL-4, IL-5 and IL-13. Although effector mechanisms of TH2 activation in parasitic disease are not fully understood, these result in acquired immunity through antibody-dependent cellular cytotoxicity mediated by production of IgE antibodies and eosinophils. [2,3] Activation of TH2 immunity also underlies atopic diseases, including asthma, in response to stimulation by innocuous allergens. The cytokine IL-13 is involved in immunoglobulin class switching to immunoglobulin E (IgE) and in airway hypersensitivity, mucus hypersecretion, and inflammation of the
bowel. [6,7] IgE production is thought to have evolved as a protective feature in host defense against helminthes [2], but total serum IgE (tIgE) levels have been widely studied as a surrogate endophenotype relating to atopic disease [8], although it is seldom studied in the context of helminthic infection.

Considerable evidence points to a genetic basis for variation in tIgE levels in urban populations [9,10] and we have previously reported high heritability for tIgE levels in a schistosomiasis-endemic Brazilian population, as well as for burden of infection by S. mansoni, measured by fecal egg counts. [11] To explore specific genetic factors underlying this heritability, we focused on variation in IL13 located in the 5q31-q33 region. Linkage studies have identified the 5q31-q33 region as a locus influencing tIgE levels in populations of high-income countries [12], as well as intensity of parasite infection in Brazilian [13] and Senegalese [14] schistosomiasis-endemic populations. In terms of specific variants, the T allele at the promoter polymorphism rs1800925 (or c.-1111C>T) [8] and the T allele at the non-synonymous coding variant rs20541 [8] (or R130Q where the T allele creates an amino acid change and the T allele at the non-synonymous coding variant rs20541 associated with higher tIgE levels. These variants in IL13 were higher in IL-13Gln-bearing individuals. [17] Thus, both residue was more active than the Arg form, and serum levels of IL-13 containing the variant Gln were reported among non-atopic individuals of European ancestry. Functional studies have demonstrated increased binding of nuclear proteins to the IL13 promoter region when the T allele at rs1800925 was present. [15,16] IL-13 containing the variant Gln residue was more active than the Arg form, and serum levels of IL-13 were higher in IL-13Gln-bearing individuals. [17] Thus, both variants increase amount or activity of IL-13 and as expected are associated with higher tIgE levels. These variants in IL13 have also been explored in schistosomiasis-endemic populations. In particular, rs1800925 and rs20541 were protective against high S. hematobium infection intensity [18] and rs1800925 against high S. mansoni intensity, [19] for alleles associated with elevated tIgE levels in urban setting studies.

We investigated associations between these and other variants in IL13, covering the full gene (including rs1800925 and rs20541), for two quantitative traits (tIgE levels and S. mansoni egg counts) in a Brazilian population endemic for schistosomiasis. IL13 variants have not been previously tested for association with tIgE levels in a parasitized population. Measured tIgE levels represent activation of TH2 immunity largely in response to infection by helminths, and S. mansoni egg counts (corresponding to worm burden) represent the impact of host immunity or overall effectiveness of schistosomiasis host immunity (including TH2 activation and effector mechanisms). Therefore we were able to investigate the influence of IL13 variation on two key aspects of S. mansoni host immunity.

Methods

Ethics Statement

The research protocol was approved by Institutional Review Boards (IRBs) 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. In accord with the protocol, all subjects enrolled in the study gave written consent when possible or oral consent in the case of subjects unable to read or to provide a written signature. The protocol for providing consent thus covered the full target population which includes some individuals who are literate and others who are illiterate. Children gave their assent, and a parent or a legal guardian provided written or oral consent. Oral consent was documented by a witness able to provide a written signature on a separate line incorporated into the consent form for this purpose specifically approved by the IRBs at Johns Hopkins University School of Medicine and the Federal University of Bahia.

Study Design and Clinical Characteristics

This study was performed on a Brazilian study population from a schistosomiasis-endemic area of Conde, Bahia conducted between July and September 2004 (as described previously). [11] A total of 812 subjects were enrolled based on a whole-population ascertainment scheme, comprising two large families of 535 and 510 individuals each, 30 families with three to 36 members, and 44 singletons. These pedigrees were broken down into 318 nuclear families, and connecting individuals were duplicated when performing family-based association tests, or assigned to one family for GEE regression tests. S. mansoni egg counts on 397 individuals from 3–5 stool samples per individual were obtained using the Kato-Katz method [20,21] and egg count means were calculated for all available samples, while presence of Ascaris lumbricoides, Trichuris trichiura, and hookworm eggs was also measured. Total serum IgE levels were measured on 572 individuals using chemiluminescence (ADVIA Centaur Bayer Corporation) in Salvador, Brazil. The raw values of tIgE levels were adjusted for non-genetic covariates (sex, age, smoking history, and infection by other helminths) and S. mansoni egg counts were adjusted for sex, age, and exposure to infested water, and tests of genetic association were conducted on residuals.

SNP Selection

In addition to the two functional polymorphisms rs1800925 and rs20541, coverage of the full gene was assured based on detailed evaluation of linkage disequilibrium from an IL13 sequencing study. Tarazona-Santos and Tishkoff identified five haplotype tagging single nucleotide polymorphisms (SNPs) in IL13 through sequencing based on West African, South American (with a strong Amerindian component) and European populations. [22] Thus, to best reflect the admixed Brazilian study population (derived from West African, European and Amerindian ancestral populations, with substantial African ancestry in the state of Bahia [23]), these five additional SNPs covering the gene were selected for genotyping, bringing the total to 7 SNPs. SNPs with a minor allele frequency (MAF) of 10% or below were excluded. Linkage disequilibrium (LD) bins were defined as groups of SNPs with pairwise r²>0.8. Genotyping of these 7 SNPs was conducted using the TaqMan probe-based 5′ nuclease assays (Applied Biosystems, Foster City, CA, USA). If an assay failed on a sample, this was repeated up to three times.

Statistical Methods

As described previously, the two quantitative traits were initially log-10 transformed and adjusted for non-genetic covariates so genetic effects on remaining variation could be assessed. Thus, log10-transformed values of tIgE levels were adjusted for age, sex, smoking status, household smoking exposure and helminthic infection status using STATA 8.2 (StataCorp. StataCorp LP. College Station, TX). [11] Similarly, log-10 transformed S. mansoni egg counts were adjusted for age, sex and four categories of exposure to infested water. [11] Associations between the 7 selected markers and the two quantitative traits were tested under an additive model, which has been shown to perform well even when the true genetic model is not additive (i.e. dominant or recessive) using two approaches, first regression-based GEE methodology which considers the nuclear family as a cluster, [24] and second using variance components models implemented in QTDT (quantitative
Results

Clinical characteristics for the 812 subjects, including 222 founders are described in detail elsewhere. [11,27] There were fewer male than female participants (44.2% males), and the mean age of the population was 27 years. The proportion of subjects infected by any helminth was 83.5%, the proportion infected with S. mansoni was 48.9%. Geometric means for all subjects, including infected and uninfected individuals, for adjusted tIgE levels and S. mansoni egg counts were 251.9 ng/mL (Standard deviation (SD): 2.7; range: 4.5 to 28020 ng/mL) and 15.5 count/g fecal matter (SD: 6.5; range: 0 to 1579 count/g fecal matter), respectively.

Genotyping call rates for the 7 IL13 SNPs ranged from 90 to 99%. Mendelian inconsistencies were identified using Sib-Pair v.1.00a17 (http://www.qimr.edu.au/davidID/), and underlying genotypes by SNP and nuclear family were set as missing. All 7 SNPs were found to be in Hardy-Weinberg equilibrium among unrelated founders (P>0.001). The final set of 7 SNPs with allele frequencies are displayed in Table 1. All but two markers had a MAF >0.1.

Table 1. The 7 IL13 SNPs among 222 founders in the Brazilian study sample.

| Marker     | Chr    | Chr Position | Functional       | Allele | MAF      |
|------------|--------|--------------|------------------|--------|----------|
| rs2066960  | 5      | 132022334    | Intron 1         | C/T    | 0.098    |
| rs20541    | 5      | 132023863    | Exon 4           | C/T    | 0.206    |
| rs1900925  | 5      | 132020708    | 5’ UTR           | C/T    | 0.313    |
| rs2069743  | 5      | 132021174    | 5’ UTR           | C/T    | 0.202    |
| rs2066960  | 5      | 132022334    | Intron 1         | C/A    | 0.098    |
| rs20541    | 5      | 132023863    | Exon 4           | G/C    | 0.098    |
| rs1295685  | 5      | 132023742    | Intron 3         | G/A    | 0.449    |
| rs20669750 | 5      | 132024946    | Exon 4           | G/C    | 0.098    |

Abbreviations: SNP, single-nucleotide polymorphism; UTR, untranslated region; MAF, minor allele frequency; Chr, chromosome. Chromosomal position according to db126; major and minor alleles in Brazilian data before and after forward slash, respectively, ancestral allele according to db126 data underlined. Atopy-related SNPs are indicated in bold and tagging SNPs that are not atopy-related are in regular font.

Pairwise LD based on the D’ statistic was calculated using HaploView (http://www-genome.wi.mit.edu/personal/jcbarrett/haplo) among founders as shown in Figure 1. LD blocks were defined using Gabriel et al.’s algorithm, and there were two LD blocks, one in the promoter region and one in exon 4. [28]

Table 2 summarizes GEE regression analyses of residual tIgE levels and S. mansoni egg counts on genotype, after adjustment for non-genetic factors. QTDT association test results are displayed in Table 3. Alleles T, A and T at the three SNPs (rs1800925, rs2066960, and rs20541 respectively, spanning the promoter to the exon 4 region) showed evidence of association with low levels of S. mansoni egg counts (P = 0.05, 0.0002, and 0.005, respectively) based on GEE regression (Table 2). For these SNPs, the major allele increased risk while the minor allele was protective against high burden of infection. Association of S. mansoni egg counts with the non-synonymous coding SNP rs20541 was supported by QTDT analysis (P = 0.014). Geometric means were 7.1, 13.4 and 17.5 count/g fecal matter for individuals with the TT, CT and CC genotypes respectively at rs20541. The promoter SNP rs1800925 showed the same direction of association for GEE regression, although without statistical significance (Table 3). No associations were found for tIgE levels, however. This absence of association with tIgE levels is unlikely to merely result from low statistical power as our previous work on the same Brazilian study population, similarly investigating variants in the promoter region in a TH2-pathway cytokine gene, identified statistically significant associations between atopy-related SNPs in IL10 and tIgE levels. [27]

Figure 1. Pairwise linkage disequilibrium (LD) within Haploview using the D’ statistic for IL13. Intensity of shading indicates the degree of confidence in the D’ value. Dark filled squares indicate a D’ value of 1. Untranslated regions are indicated with black bars, exons with dark gray bars and introns with light gray bars. Exons are numbered from 5’ to 3’.

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suggesting this signal is likely to be independent although replication will be required to confirm this finding.

**Discussion**

Genetic associations observed for functional polymorphisms, rs1800925 and rs20541, which are protective against high *S. mansoni* egg counts in our Brazilian study population, support evidence for a protective effect against high infection intensity for alleles associated with atopic disease, and as previously observed in a population endemic for the *S. haematobium* species of schistosomes. For the SNP rs20541, the protective effect of the T allele was identified using both family-based QTDT analysis and GEE regression, while for the SNP rs1800925, statistical significance of the protective effect at the T allele was achieved using GEE regression only. Given the MAF for SNP rs1800925 in our study, statistical power for detecting the association using regression was substantial: it was close to 80% while power was under 40% for the 247 informative trios. Thus, the lack of association using QTDT can be explained by insufficient power, and our finding of association for rs1800925 using GEE regression remains credible given higher statistical power inherent in regression-based methods for similar sample sizes. In the literature, in a Malian population infected with *S. haematobium*, the T allele at rs1800925 was protective against higher infection levels (*P* = 0.01), [18] and in a subsequent investigation of the promoter region, no other marker showed a greater protective effect within the full study population. [30] Also in this Malian study, in a family-based analysis, the T allele at rs20541 was found to be preferentially transmitted to offspring in the highest 10% of *S. haematobium* infection intensity. [19] A recent Kenyan study on a population infected with *S. mansoni* showed heterozygotes at rs1800925 were resistant to reinfection, but this finding specific to the heterozygous genotype class is biologically difficult to interpret and may reflect the small sample size. [19] Thus our study extends previous findings of association of the T allele at rs1800925 and the T allele at rs20541 with high *S. haematobium* infection intensity to high *S. mansoni* infection intensity.

From studies in industrialized populations, considerable evidence points to some influence by variants in the IL13 promoter, in particular rs1800925 and rs20541, on risk of atopy among European and Asian ancestry cohorts. [9] The T allele at rs1800925 was associated with asthma and atopy among European Americans and Europeans, [31,32] and the T allele at rs20541 was associated with bronchial asthma among Europeans. [33] The T alleles for both SNPs were the risk alleles for atopy, while we have shown these are protective against high burden of *S. mansoni* infection in this highly parasitized Brazilian study of an admixed population. Our data are consistent with an evolutionary hypothesis proposing the TH2 pathway developed, at least in part, as a mechanism to protect humans (and their ancestors) from helminthic infection, and certain genetic risk factors for atopic disease are a vestige of this selective process. [34].

**Table 2.** Generalized Estimating Equation association tests for individual SNPs with tlgE levels (N = 572) and *Schistosoma mansoni* egg counts (N = 397) under the additive model.

| Marker   | Allele | tlgE       | S.m. egg count |
|----------|--------|------------|----------------|
|          |        | *P*        | Dir           | *P*        | Dir           |
| rs1800925 | T      | 0.408      | neg           | 0.050a      | neg           |
| rs2069743 | G      | 0.351      | neg           | 0.084       | neg           |
| rs2066960 | A      | 0.066      | pos           | 0.0002b     | neg           |
| rs1295686 | A      | 0.045      | pos           | 0.706       | neg           |
| rs20541   | T      | 0.779      | neg           | 0.005d      | neg           |
| rs1295685 | T      | 0.157      | neg           | 0.014       | neg           |
| rs2069750 | C      | 0.473      | pos           | 0.392       | neg           |

Abbreviations: Dir, direction of association; pos, positive; neg, negative. 
*a*Log(10)-transformed values adjusted for age, sex, and smoking, and helminthic infection status. 
*b*Log(10)-transformed values adjusted for age, sex, and low, medium and high exposure to infested water sources. 
*c*P-values and direction of association with high values are given for the beta-coefficient for the minor allele under the additive model. 
*d*P-values are statistically significant with *x* = 0.05 for atopy-related SNPs (bold) and *x* = 0.005 for tagging SNPs that are not atopy-related (unbolded).

**Table 3.** QTDT association results for individual IL13 SNPs with tlgE levels and *Schistosoma mansoni* egg count.

| Marker   | Allele | tlgE       | S.m. egg count |
|----------|--------|------------|----------------|
|          |        | *X*2       | P        | Dir   | *X*2       | P    | Dir   |
| rs1800925 | T      | 1.28       | 0.258    | neg   | 247/686    | 0.09 | 0.768 | neg   |
| rs2069743 | G      | 0.27       | 0.605    | neg   | 149/703    | 1.49 | 0.222 | pos   |
| rs2066960 | A      | 0.82       | 0.365    | pos   | 154/691    | 0.17 | 0.676 | neg   |
| rs1295686 | A      | 0.02       | 0.876    | pos   | 256/693    | 1.05 | 0.305 | neg   |
| rs20541   | T      | 0.22       | 0.639    | neg   | 184/680    | 5.99 | 0.014 | neg   |
| rs1295685 | T      | 0.02       | 0.882    | neg   | 144/711    | 1.31 | 0.252 | neg   |
| rs2069750 | C      | 0.54       | 0.463    | neg   | 129/661    | 0.22 | 0.637 | pos   |

Abbreviations: Dir, direction of association; pos, positive; neg, negative; N offspring, number of informative offspring over number of offspring evaluated; neg, negative; pos, positive; QTDT, quantitative transmission disequilibrium test; S.m. count, *Schistosoma mansoni* egg count per gram of fecal matter; SNP, single-nucleotide polymorphism; tlgE, total serum IgE.

*Note:* Significant values are in bold typeface (**).
The lack of association between \textit{IL13} variants and tIgE levels in this Brazilian parasitized study population can be evaluated in the context of previous findings in industrialized populations where tIgE levels have been studied among different groups, such as atopic individuals who have been exposed to allergens, non-atopic individuals, or the general population. Specifically, in a linkage study identifying the 5q31-q33 region for tIgE levels, the signal was only present in the subset of the population among individuals where no IgE specific to antigens was detected. [35] Similarly, in genetic association studies focusing on \textit{IL13} variants, associations have been identified for tIgE levels among non-atopic individuals or the general population, but rarely among atopic individuals. [8] For example, in the large British 1958 Birth Cohort following 4,570 individuals from the general population, basal tIgE means significantly differed between genotypes at both rs1800925 and rs20541. [36] The helminth-endemic setting of the present Brazilian study population meant tIgE levels reflected a mixture of IgE specific to \textit{S. mansoni} and IgE specific to other helminths or antigens. Basal IgE levels without any antigenic stimulation, which are conditions under which we would expect to detect association with \textit{IL13} polymorphisms based on the literature as discussed above, cannot be measured in a helminth-endemic setting by definition. Thus, the finding of no associations between \textit{IL13} polymorphisms and tIgE levels in this Brazilian study is consistent with studies conducted in populations of industrialized communities.

In our Brazilian study population, the age profile for \textit{S. mansoni} egg counts features a characteristic peak in infection intensity at 15 years, which represents acquisition of natural immunity to infection in adolescence shown previously. [11] For tIgE levels, a different pattern was observed and mean values were highest among young children aged 6–9 years, and then declined with increasing age. We therefore performed association analyses across SNPs on subsets of independent individuals from the full study population comprising children under 15 years and individuals over 15 years of age. No differences in evidence for association were observed in the two subsets (data not shown). Thus, evaluating our data in the context of the literature suggests IL-13 acts most strongly on TH2 pathway effector mechanisms (as reflected in statistical associations with \textit{S. mansoni} egg counts) rather than on TH2 pathway activation (as reflected by lack of association with tIgE levels). It is also possible IL-13 acts during only early TH2 activation in an antigen-specific manner, but IgE levels specific against schistosomiasis antigens were not available in this Brazilian study.

The two quantitative traits, tIgE levels, representing TH2 pathway activation, and \textit{S. mansoni} egg counts, reflecting global impact of TH2 effector mechanisms and helminth host immunity, provided a unique opportunity for genetic dissection of the TH2 pathway in the context of schistosomiasis endemicity. In summary, we have found significant associations between two well-known functional variants and \textit{S. mansoni} egg counts, and a striking lack of association with tIgE levels. Since the functional effect of both variants on the gene product, IL-13, is to increase its amount or activity, this finding suggests IL-13 functions to increase anti-helminth immunity, and functional variants may be an evolutionary vestige of selective forces that result in atopic phenotypes in modern, industrialized settings. Our evaluation of \textit{IL13} variation has demonstrated TH2 pathway genes shown to carry variants that impact on atopic disease are good candidates to evaluate determinants of host immunity to helminthic infections. Moreover, genetic association studies in schistosomiasis-endemic populations allow further fine dissection of the TH2 pathway and its role in disease, both helminthic and atopic.

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Author Contributions

Conceived and designed the experiments: AVG MIA KCB AAC THB. Performed the experiments: AVG RRO EVP PG. Analyzed the data: AVG. Contributed reagents/materials/analysis tools: MIA AAC KCB. Wrote the paper: AVG THB.

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