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Association between the IL13 rs1800925 (-1112C/T) polymorphism and *Schistosoma mansoni* infection intensity in a population from western Côte d'Ivoire

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ABSTRACT

Intestinal schistosomiasis remains a major public health concern in sub-Saharan Africa. Interindividual variation in infection intensity suggests that host genetic factors, particularly the IL13 rs1800925 (-1112C/T) polymorphism, may influence the Th2 immune response to *Schistosoma mansoni*. This study aimed to investigate the association of this polymorphism with susceptibility to *S. mansoni* infection and infection intensity in a population from western Côte d'Ivoire. A case-control study was conducted among individuals living in an endemic area. Genotyping of the IL13 -1112C/T (rs1800925) polymorphism was performed using the amplification refractory mutation system-polymerase chain reaction (ARMS-PCR). Associations between the polymorphism and both susceptibility to infection and infection intensity were assessed using logistic regression analysis. No significant association was observed between the IL13 rs1800925 polymorphism and susceptibility to *S. mansoni* infection. However, the CT genotype and carriage of the T allele were significantly associated with a reduced risk of high-intensity infection. In addition, children younger than 15 years were at a significantly higher risk of developing heavy-intensity infections. The IL13 rs1800925 polymorphism does not appear to influence susceptibility to *S. mansoni* infection but may contribute to the regulation of parasite burden. These findings highlight the importance of host immunogenetic factors in modulating infection intensity and warrant further large-scale functional studies to clarify the role of this polymorphism in the immune response to intestinal schistosomiasis.

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INTRODUCTION

Schistosomiasis is one of the most widespread neglected tropical diseases worldwide and remains a major public health concern in developing countries, particularly in sub-Saharan Africa (Tavakoli Pirzaman *et al.*, 2024). According to the World Health Organization (WHO), more than 250 million people require preventive chemotherapy for this parasitic disease, the majority of whom live in Africa (Lo *et al.*, 2022). Schistosomiasis is caused by trematodes of the genus *Schistosoma*, with *Schistosoma mansoni* being the main causative agent of intestinal schistosomiasis in sub-Saharan Africa (Hong, 2023). Its transmission is particularly favored in disadvantaged rural areas where access to safe drinking water and adequate sanitation remains limited (Sékéré *et al.*, 2024). In Côte d'Ivoire, despite the implementation of control strategies based on mass praziquantel administration, transmission persists in several endemic foci, particularly in the western part of the country (Sokouri *et al.*, 2024a), highlighting the limitations of current control approaches and the need for a better understanding of the determinants of susceptibility to infection.

Schistosoma mansoni infection exhibits considerable clinical and parasitological variability among exposed individuals. While some individuals develop heavy-intensity infections associated with severe hepatointestinal complications, others maintain low parasite burdens despite similar levels of exposure (Mewamba *et al.*, 2023). This heterogeneity suggests that, beyond environmental and behavioral factors, host genetic determinants play a significant role in regulating infection intensity.

The immune response against helminths is predominantly characterized by T helper 2 (Th2) responses involving several cytokines, including interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-10 (IL-10), and interleukin-13 (IL-13) (Abdel Aziz *et al.*, 2022). Among these cytokines, IL-13 plays a pivotal role in regulating anti-helminth immune responses by contributing to granuloma formation, tissue fibrosis, and effector mechanisms involved in

parasite control (Lekki-Jóźwiak and Baska, 2024). Previous studies have also shown that genetic variations within the *IL13* gene may influence IL-13 expression and alter susceptibility to parasitic infections as well as inflammatory diseases (Junior *et al.*, 2023; Mewamba *et al.*, 2023).

The *IL13* gene, located on chromosome 5q31–q33, harbors several polymorphisms that may affect the transcriptional regulation of the cytokine. Among them, the rs1800925 (-1112C/T) polymorphism, located in the promoter region, has been extensively investigated in inflammatory, allergic, and parasitic diseases (Choto *et al.*, 2021; Gaceja *et al.*, 2023). This functional variant may influence the transcriptional activity of the *IL13* gene and consequently alter IL-13 production, leading to interindividual differences in immune responses (Gaceja *et al.*, 2023). Although several studies have suggested an association between this polymorphism and anti-helminth immune responses, findings remain inconsistent across populations, probably owing to genetic and environmental heterogeneity.

In West Africa, particularly in Côte d'Ivoire, data regarding the involvement of the *IL13* rs1800925 polymorphism in intestinal schistosomiasis remain scarce. In this context, investigating genetic factors associated with infection severity is essential to improve our understanding of the immunopathological mechanisms underlying the disease and to identify potential genetic markers of disease severity. Therefore, the present study aimed to evaluate the association between the *IL13* rs1800925 (-1112C/T) polymorphism and the intensity of *Schistosoma mansoni* infection in a population living in an endemic area of western Côte d'Ivoire.

MATERIALS AND METHODS

Study area

This study was conducted in the Cavally Region, located in western Côte d'Ivoire. The region is part of the Montagnes District and is characterized by high annual rainfall and a dense network of rivers and

other permanent and seasonal water bodies. The climate is humid equatorial, providing favorable ecological conditions for the proliferation of freshwater snails of the genus *Biomphalaria*, the intermediate hosts responsible for the transmission of *Schistosoma mansoni* (Sokouri *et al.*, 2024 b). The local economy is predominantly based on agriculture, including both cash and subsistence crops such as cocoa, coffee, rice, cassava, etc. These agricultural activities are frequently carried out in close contact with freshwater sources, including swamps, lowlands, and irrigated fields, thereby increasing the population's exposure to *S. mansoni* infection. In addition, access to safe drinking water and adequate sanitation remains limited in several rural communities, leading residents to rely on surface water for domestic activities such as bathing, laundry, and water collection. These practices increase human-water contact and contribute to the sustained transmission of intestinal schistosomiasis in the region (Assaré *et al.*, 2026). Owing to its ecological, socioeconomic, and sanitary characteristics, the Cavally Region represents a high-risk area for intestinal schistosomiasis and provides an appropriate setting for investigating factors associated with the intensity of *Schistosoma mansoni* infection.

Study design

This study was a cross-sectional analytical case-control study. Data were collected through surveys conducted between February and December 2020 among the target populations. This approach enabled the comparison of individuals infected with *Schistosoma mansoni* (cases) with uninfected individuals (controls) in order to identify the risk factors associated with the intensity of infection in the study area.

Ethical considerations

This study was conducted as part of a project named TrypanoGEN+, involving several countries, notably Uganda, the Democratic Republic of the Congo (DRC), Cameroon, and Côte d'Ivoire, in the field of intestinal schistosomiasis. The study protocol was

approved by the National Ethics Committee for Life Sciences and Health (Comité National d'Éthique des Sciences de la Vie et de la Santé - CNESVS) under approval number N/Ref: 040-19/MSHP/CNESVS-kp. Approval for the study was also obtained from the relevant regional, departmental, health, village, and educational authorities. Participants who tested positive by the Kato-Katz (KK) method or the POC-CCA test were treated with praziquantel.

Study population

The study population comprised individuals residing in communities located in highly endemic areas for intestinal schistosomiasis in the Cavally Region, Côte d'Ivoire. It included several groups at increased risk of *Schistosoma mansoni* infection, particularly school-aged children, who are especially vulnerable because of their frequent recreational activities and regular contact with surface water (Sokouri *et al.*, 2024 a). Adults living in the same communities were also included; especially those whose daily or occupational activities involved direct exposure to infested water. These included fishermen, farmers working in marshy environments, and individuals engaged in irrigation-related activities. Women were likewise represented, particularly those who routinely used surface water for domestic purposes such as washing clothes, dishes, and collecting water. Overall, the study population encompassed individuals of all age groups and socioeconomic backgrounds living in endemic communities and at potential risk of exposure to *S. mansoni*.

Sample collection

Three types of biological specimens, blood, urine, and stool were collected from each participant for parasitological, serological, and molecular analyses.

Venous blood samples were collected by trained healthcare personnel using standard aseptic venipuncture procedures. Approximately 2 mL of whole blood was drawn into EDTA tubes for subsequent genomic DNA extraction. Immediately after collection, the samples were placed in insulated cool boxes containing ice packs to maintain the cold

chain during transportation. Upon arrival at the laboratory, blood samples were aliquoted into cryovials and stored at -20°C until molecular analysis.

For urine and stool collection, sterile, labeled containers were provided to participants one day before sample collection, together with standardized instructions. Participants were asked to collect approximately 50 mL of the first morning urine and a fresh stool sample sufficient to fill approximately half of the stool container. All specimens were collected the following morning and transported promptly to the laboratory under appropriate conditions for parasitological and serological examination for the diagnosis of schistosomiasis.

Parasitological diagnosis of schistosomiasis

Intestinal schistosomiasis was diagnosed using the Kato-Katz technique, performed in accordance with WHO guidelines (WHO, 2023) and as described by (Sokouri *et al.*, 2024a).

Two duplicate 42-mg thick smears were prepared from each stool sample and examined independently by two microscopists. A sample was classified as positive if at least one *Schistosoma mansoni* egg was detected. Parasite intensity was expressed as eggs per gram (EPG) of feces, calculated by multiplying the number of observed eggs by 24 and averaging the counts across the two readers.

Serological diagnosis (Point-of-care circulating cathodic antigen - POC-CCA)

Serological diagnosis of *Schistosoma mansoni* infection was performed using the Point-of-Care Circulating Cathodic Antigen (POC-CCA) rapid test, which detects circulating cathodic antigen (CCA) secreted by adult worms and excreted in urine (Alemu and Nibret, 2024).

Assays were conducted in accordance with the manufacturer's instructions (ICT Diagnostics, Cape Town, South Africa). For each specimen, two drops of fresh urine were applied to the sample well of the

POC-CCA cassette. Following a 20-minute incubation period to allow complete sample migration and absorption, results were visually interpreted based on the presence or absence of the test line and its color intensity (Sokouri *et al.*, 2024a; Sokouri *et al.*, 2024b). A test was deemed valid if the control line displayed a strong pink coloration; in the absence of a visible control line, the result was considered invalid and the test was repeated.

Furthermore, samples testing positive via the POC-CCA assay underwent quantitative assessment of the circulating cathodic antigen. Following visual interpretation, the cassettes were analyzed using an ESEQuant LR3 reader (Qiagen, Germany) to quantify the CCA concentration present in the urine samples.

Genotyping of the IL-13 -1112C/T (rs1800925) polymorphism

Genomic DNA was extracted from whole blood samples using Qiagen DNA extraction kits according to the manufacturer's instructions. The extracted DNA samples were stored at -20°C until further analysis.

Genotyping of the IL-13 -1112C/T (rs1800925) polymorphism was performed using the Amplification Refractory Mutation System Polymerase Chain Reaction (ARMS-PCR) technique, as previously described by Choto *et al.* (2021). For each DNA sample, two separate PCR reactions were carried out using two allele-specific forward primers targeting the C and T alleles of the polymorphism. The primer sequences were as follows: C allele-specific forward primer (5'-TTCTGGAGGACTTCTAGGAAAAC-3') and T allele-specific forward primer (5'-TTCTGGAGGACTTCTAGGAAAAT-3'). A common reverse primer, IL-13-740R (5'-GGAGATGGGGTCTCACTATG-3'), was used in all reactions. Amplification of the target allele generated a 319-bp PCR product (Fig. 1).

To verify amplification efficiency and minimize false-negative results, an internal amplification control was

included in each reaction. The internal control consisted of a forward primer (5'-TGCCAAGTGGAGCACCCAA-3') and a reverse primer (5'-GCATCTTGCTCTGTGCAGAT-3'), producing a 726-bp amplicon (Fig. 1).

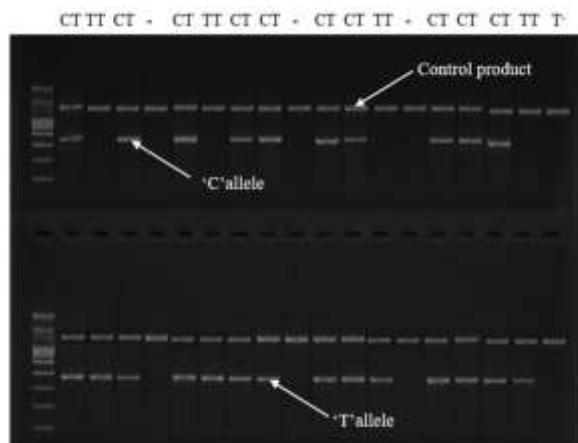


Fig. 1. ARMS-PCR genotyping of the IL-13 -1112C/T polymorphism

The upper gel panel shows the amplification products generated using the C allele-specific primer, whereas the lower gel panel displays the products amplified with the T allele-specific primer. T-: negative control.

PCR amplification was performed in a final reaction volume of 25 μ L containing 9.8 μ L of ultrapure water, 2.5 μ L of 10 $\times$ PCR buffer, 1.5 μ L of MgCl₂ (25 mM), 1 μ L of deoxynucleotide triphosphate (dNTP) mix (10 mM), 0.2 μ L of Taq DNA polymerase, 1.5 μ L each of the allele-specific forward primer (C or T) and the common reverse primer, and 1 μ L each of the internal control forward and reverse primers, all at a concentration of 10 pmol. Finally, 5 μ L of extracted genomic DNA was added to each reaction as the PCR template.

PCR amplification was carried out in a BIO-RAD T100™ Thermal Cycler under the following cycling conditions: an initial denaturation at 94 °C for 2 min, followed by 15 cycles of denaturation at 94 °C for 30 s, annealing at 63 °C for 60 s, and extension at 72 °C for 60 s. This was followed by 20 additional cycles consisting of denaturation at 94 °C for 30 s, annealing at 60 °C for 60 s, and extension at 72 °C for 60 s. A final extension step was performed at 72

°C for 5 min to ensure complete synthesis of the amplified DNA fragments.

Statistical analysis

Statistical analyses were performed using PLINK version 2.0 and R software version 4.6.0.

Pearson's chi-square test was used to compare the observed and expected genotype frequencies under Hardy–Weinberg equilibrium (HWE). Allele and genotype frequencies were calculated by direct allele counting from the genotyping data.

The association between infection intensity and the recorded covariates (age and sex) was assessed using multivariable analysis. Associations between IL-13 genotypes and alleles and the risk of developing intestinal schistosomiasis were evaluated under four genetic inheritance models: recessive, dominant, codominant, and overdominant. Crude and adjusted odds ratios (ORs) were estimated and are presented with their corresponding 95% confidence intervals (95% CIs). Statistical significance was defined as a two-sided *P* value ≤ 0.05 .

RESULTS

Population characteristics

A total of 142 participants were enrolled in the study. Participants ranged in age from 5 to 68 years, with a mean age of 18.9 $\pm$ 16.2 years. The median age was 11 years (interquartile range [IQR]: 9–35 years) (Table 1). Of the study population, 79 participants (55.6%) were male and 63 (44.4%) were female, yielding a male-to-female sex ratio of 1.25 (Table 1).

Association between sociodemographic characteristics and infection intensity

The results of the multivariable logistic regression analysis showed that, after adjustment for sex and age, sex was not significantly associated with infection intensity. Males had a slightly higher likelihood of developing high-intensity infection than females (adjusted OR [aOR] = 1.13; 95% CI: 0.53–2.40); however, this association was not statistically significant (*p* = 0.752; Table 2).

Table 1. Sociodemographic characteristics of the study participants (N = 142)

Variables	Values
Total participants, n	142
Age (years)	
Mean $\pm$ standard deviation	18.9 $\pm$ 16.2
Median (IQR)	11 (9–35)
Range (min–max)	5–68
Sex, n (%)	
Male	79 (55.6)
Female	63 (44.4)
Male/female ratio	1.25

Table 2. Factors associated with infection intensity: Bivariable and multivariable analyses (N = 142)

Variables	Total, n (%)	High-intensity infection, n (%)	Low-intensity infection, n (%)	Crude OR (95 % CI)	p	Adjusted OR (95 % CI)	p
Sex							
Female	63 (44.4)	17 (27.0)	46 (73)	1.00	–	1.00	–
male	79 (55.6)	24 (30.4)	55 (69.6)	1.18 (0.57–2.45)	0.650	1.13 (0.53–2.40)	0.752
Age (years)							
≥ 25	43 (30.3)	6 (14.0)	37 (86)	1.00	–	1.00	–
15–24	8 (5.6)	2 (25.0)	6 (75)	2.06 (0.35–12.24)	0.420	2.03 (0.33–12.52)	0.446
0–14	91 (64.1)	33 (36.3)	58 (63.7)	3.51 (1.33–9.21)	0.011	3.49 (1.33–9.14)	0.011

OR : odds ratios, CI : Confidence interval, p : p-value

Table 3. Allelic and Genotypic Frequencies of the IL13 rs1800925 (–1112C/T) polymorphism in cases and controls and compliance with Hardy–Weinberg Equilibrium

Alleles and genotypes	Phenotypes		Freq gp	HWE	
	Cases (%)	Controls (%)		χ^2	P-value
C	56 (52.83)	52 (52.0)	0.52	–	–
T	50 (47.17)	48 (48.0)	0.48	–	–
CC	25 (32.89)	18 (27.27)	0.31	0.11	> 0,05
TT	20 (26.32)	14 (21.21)	0.24		
CT	31 (40.79)	34 (51.52)	0.45		

Freq gp: Frequency in the general population; C and T: alleles; CC, TT and CT: genotypes; HWE: Hardy–Weinberg equilibrium.

Table 4. Association between genetic models of the IL13 –1112C/T polymorphism and the risk of intestinal schistosomiasis infection

Genetic model	Genotype comparison	Cases n (%)	Controls n (%)	OR	95 % CI	p
Codominant	CC	25 (32.89)	18 (27.27)	Réf	–	–
	CT	31 (40.79)	34 (51.52)	0.66	0.30–1.46	0.31
	TT	20 (26.32)	14 (21.21)	1.03	0.41–2.56	0.95
Dominant	CT + TT vs CC	51 (67.11)	48 (72.73)	0.77	0.36–1.65	0.50
Recessive	TT vs CC + CT	20 (26.32)	14 (21.21)	1.33	0.59–3.01	0.49
overdominant	CT vs CC + TT	31 (40.79)	34 (51.52)	0.65	0.33–1.29	0.22
Allelic	T vs C	71 (46.71)	62 (46.97)	0.99	0.61–1.61	0.98

OR: Odd ratio, CI: Confidence interval, p: p-value

In contrast, age remained a significant predictor of infection intensity. Compared with participants aged 25 years and older, children aged 0–14 years were 3.49 times more likely to develop high-intensity infection (aOR= 3.49; 95% CI: 1.33–9.14; p= 0.011). No significant association was observed among

participants aged 15–24 years (aOR= 2.03; 95% CI: 0.33–12.52; p= 0.446).

Overall, the logistic regression model was statistically significant (likelihood ratio test, p= 0.049), indicating that the variables included in the

model explained a significant proportion of the variability in infection intensity.

Distribution of allelic and genotypic frequencies of the IL13 rs1800925 (–1112C/T) polymorphism and compliance with Hardy–Weinberg equilibrium

The allelic and genotypic frequencies of the IL13 rs1800925 (–1112C/T) polymorphism are presented in Table 3. The frequencies of the C and T alleles were comparable between cases and controls. The C allele was the most frequent in both groups, accounting for 52.83% of alleles in cases and 52.0% in controls. Similarly, the T allele accounted for 47.17% in cases and 48.0% in controls, indicating a very similar allelic distribution between the two groups.

Regarding genotype distribution, the heterozygous CT genotype was the most common in both groups, with frequencies of 40.79% among cases and 51.52% among controls. The homozygous CC and TT genotypes were observed in 32.89% and 26.32% of cases, respectively, compared with 27.27% and 21.21% of controls (Table 3).

Furthermore, the genotype frequencies were consistent with Hardy–Weinberg equilibrium ($\chi^2 = 0.11$; $p > 0.05$), indicating no significant deviation from genetic equilibrium in the study population.

Association of the IL13 rs1800925 (–1112C/T) polymorphism with intestinal schistosomiasis under different genetic models

The association between the IL13 rs1800925 (–1112C/T) polymorphism and susceptibility to intestinal schistosomiasis was evaluated under different genetic models (codominant, dominant, recessive, overdominant, and allelic), as presented in Table 4. None of the genetic models tested showed a statistically significant association between the polymorphism and the risk of developing intestinal schistosomiasis, with all p -values exceeding 0.05. Furthermore, the 95% confidence intervals of the odds ratios consistently included the null value of 1, confirming the absence

of a significant association between this genetic variant and the disease.

Allelic analysis likewise revealed similar frequencies of the T allele in cases and controls (46.71% vs. 46.97%), with no statistically significant difference observed (OR = 0.99; 95% CI: 0.61–1.61; $p = 0.98$).

Association between the IL13 gene polymorphism and the intensity of intestinal schistosomiasis

The association between the IL13 rs1800925 (–1112C/T) polymorphism and the intensity of intestinal schistosomiasis was evaluated under different genetic models, as presented in Table 5. Under the codominant model, individuals carrying the CT genotype were significantly less likely to develop high-intensity infection than those with the CC genotype (OR = 0.28; 95% CI: 0.09–0.89; $p = 0.03$; Table 5). In contrast, no significant association was observed between the TT and CC genotypes (OR = 0.39; 95% CI: 0.11–1.34; $p = 0.13$), although a trend toward a reduced risk of high-intensity infection was noted.

Analysis under the dominant model (CT + TT vs. CC) also revealed a statistically significant association (Table 5). Individuals carrying at least one T allele had an approximately 68% lower risk of developing high-intensity intestinal schistosomiasis than CC homozygotes (OR = 0.32; 95% CI: 0.11–0.92; $p = 0.03$).

In contrast, the recessive model (TT vs. CC + CT) showed no significant association between the TT genotype and infection intensity (OR = 1.02; 95% CI: 0.36–2.92; $p = 0.97$), suggesting that carrying two copies of the T allele does not confer an additional effect on the risk of high-intensity infection.

Finally, the overdominant model (CT vs. CC + TT) indicated a trend toward a protective effect of the CT genotype; however, this association did not reach statistical significance (OR = 0.40; 95% CI: 0.15–1.08; $p = 0.07$; Table 5).

Table 5. Association between genetic models of the IL13 –1112C/T polymorphism and the intensity of intestinal schistosomiasis infection

Genetic model	Genotype comparison	High-intensity infection, n (%)	Low-intensity infection, n (%)	OR (95 % CI)	p
Codominant	CC	18 (72.0)	7 (28.0)	1	–
	CT	13 (41.9)	18 (58.1)	0.28 (0.09–0.89)	0.03
	TT	10 (50.0)	10 (50.0)	0.39 (0.11–1.34)	0.13
Dominant	CT + TT vs CC	23 (45.1)	28 (54.9)	0.32 (0.11–0.92)	0.03
Recessive	TT vs CC + CT	10 (50.0)	10 (50.0)	1.02 (0.36–2.92)	0.97
overdominant	CT vs CC + TT	13 (41.9)	18 (58.1)	0.40 (0.15–1.08)	0.07

OR : Odd ratio, CI : Confidence interval, p : p-value

DISCUSSION

This study aimed to evaluate the association between the IL13 rs1800925 (–1112C/T) polymorphism and both susceptibility to and intensity of *Schistosoma mansoni* infection in a population living in an endemic area of Côte d'Ivoire. The results highlight two main findings. First, age emerged as an independent determinant of high-intensity infection, with children under 15 years showing a significantly higher risk of heavy infection compared with adults. Second, although the IL13 rs1800925 polymorphism was not associated with susceptibility to intestinal schistosomiasis, it appeared to play a role in modulating parasite intensity. These findings support the hypothesis that host genetic factors have a greater influence on infection progression and parasite burden control than on the initial acquisition of infection (Fofana *et al.*, 2023; Ye *et al.*, 2023).

The significant association between younger age and high-intensity infection observed in our study is consistent with epidemiological patterns reported in many endemic regions. School-aged children generally exhibit the highest parasite loads due to more frequent and prolonged contact with contaminated freshwater sources through recreational, domestic, and school-related activities (Assaré *et al.*, 2026; Chanhanga *et al.*, 2023). Furthermore, repeated exposure to the parasite during childhood may promote the gradual development of partial acquired immunity, contributing to a reduction in parasite burden among older individuals (Chanhanga *et al.*, 2023). The World Health Organization considers school-aged children a priority population for schistosomiasis

control interventions, particularly preventive chemotherapy with praziquantel, due to their increased vulnerability to high-intensity infections and associated complications (WHO, 2022). Therefore, the persistence of high-intensity infections among children in our population emphasizes the importance of maintaining targeted control strategies in endemic settings.

Conversely, no significant association was observed between sex and infection intensity after adjustment for potential confounding factors. Although several studies have reported higher parasite intensity among males or boys, these differences appear to be mainly related to variations in exposure to infested water rather than intrinsic biological differences between sexes (Ayabina *et al.*, 2021; Reitzug *et al.*, 2023). Activities such as swimming, fishing, agricultural work, or certain domestic tasks may influence the frequency and duration of contact with contaminated water. Previous studies have shown that sex-related differences often decrease after accounting for behavioral and environmental factors (Trienekens *et al.*, 2022). Our results therefore suggest that, in this population, age and exposure-related factors may play a more important role than sex in determining variation in infection intensity.

Regarding genetic analysis, no significant association was identified between the IL13 rs1800925 (–1112C/T) polymorphism and the risk of developing intestinal schistosomiasis, regardless of the genetic model considered. The similar allelic and genotypic frequencies between cases and controls indicate that this variant is unlikely to represent a major

susceptibility factor for infection in the studied population. This lack of association is not unexpected given the multifactorial nature of susceptibility to parasitic infections. The establishment of *S. mansoni* infection depends on complex interactions between environmental exposure, transmission intensity, parasite characteristics, and multiple host genetic determinants. Therefore, polymorphisms affecting immune cytokines such as IL-4, IL-5, IL-10, IL-13, IFN- γ , and TNF- α , as well as their receptors, likely act collectively to influence immune responses rather than independently (Oyesola *et al.*, 2022; Ye *et al.*, 2023).

However, our study revealed a significant association between the IL13 rs1800925 polymorphism and infection intensity. Individuals carrying the CT genotype had a significantly lower probability of developing high-intensity infection compared with individuals carrying the CC genotype. Similarly, the presence of at least one T allele (CT + TT) was associated with a significantly reduced risk of heavy infection. These findings suggest that this polymorphism may not influence the mechanisms responsible for the initial establishment of infection, but rather those involved in controlling parasite multiplication and *S. mansoni* egg burden.

This observation is biologically plausible considering the central role of IL-13 in type 2 immune responses against helminths. IL-13 contributes to eosinophil activation, IgE production, alternative macrophage activation, as well as parasite-induced tissue repair and remodeling processes (Drurey *et al.*, 2021; Maizels and Gause, 2023). During *S. mansoni* infection, this cytokine also plays a major role in peri-egg granuloma formation and in maintaining the balance between protective immunity and immunopathology. A variation located in the promoter region of the *IL13* gene, such as rs1800925, may modify gene transcriptional activity and consequently influence the magnitude of parasite-specific immune responses (Ye *et al.*, 2023).

An interesting finding of our study was the protective effect observed mainly among

heterozygous CT individuals, whereas the TT genotype was not significantly associated with infection intensity. This pattern may suggest the existence of a heterozygote advantage, which has been described for several genes involved in immune responses. An intermediate level of IL-13 expression may provide an optimal balance between effective parasite control mechanisms and limitation of excessive inflammatory responses that could promote tissue damage. Conversely, insufficient or excessive IL-13 production may be less favorable for controlling parasite burden. However, this hypothesis requires confirmation through functional studies, including measurements of IL-13 concentrations according to genotype. In addition, the lack of association observed under the recessive model may also be explained by the limited number of individuals carrying the TT genotype, reducing the statistical power of the analysis.

The findings of this study contribute significantly to understanding the genetic determinants underlying clinical variation in schistosomiasis. Unlike many previous studies that primarily assess susceptibility to infection, our approach distinguished between two biologically distinct phenotypes: infection acquisition and parasite intensity. This distinction is important because parasite burden represents a major determinant of morbidity risk and chronic complications associated with schistosomiasis.

Nevertheless, several limitations should be considered. The relatively few sample size may have reduced the statistical power required to detect small genetic effects, particularly for less frequent genotypes. Furthermore, only one polymorphism within the *IL13* gene was investigated, whereas immune responses against *S. mansoni* involve a complex network of cytokines and immunological pathways. Future studies involving larger sample sizes, haplotype analyses, gene–gene and gene–environment interaction studies, as well as functional approaches, will be necessary to better understand the genetic mechanisms involved in parasite burden regulation.

CONCLUSION

This study shows that the IL13 rs1800925 (–1112C/T) polymorphism is not associated with susceptibility to *Schistosoma mansoni* infection but may influence infection intensity. Individuals carrying the CT genotype and the T allele had a lower risk of developing high-intensity infection, suggesting a potential role of this variant in regulating parasite burden. Furthermore, children under 15 years of age were significantly more exposed to high-intensity infections, confirming their status as the main at-risk group in endemic areas. These findings highlight the importance of immunogenetic factors in modulating infection intensity and support the need for functional and multicenter studies to further validate the role of the IL13 rs1800925 polymorphism in immune responses against *S. mansoni*.

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