Infection, Genetics and Evolution 65 (2018) 28–34

Contents lists available at ScienceDirect

Infection, Genetics and Evolution

journal homepage: www.elsevier.com/locate/meegid

Research paper

Interleukin-4 and STAT6 promoter polymorphisms but not interleukin-10 or 13 are essential for schistosomiasis and associated disease burden among Nigerian children

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ARTICLE INFO

Keywords:
Interleukin-4
IL-10
IL-13
STAT6
Schistosomiasis
Egg burden
Africa

ABSTRACT

Schistosomiasis is endemic in many parts of rural Africa, with previous reports showing interleukin-13 polymorphisms as drivers of infectivity and disease severity in West Africa while IL-13/IL-4 polymorphisms contributes to patterns of reinfection in East Africa. We have shown that there is a genetic delineation in susceptibility to and severity of infectious diseases in Africa, in addition to sub-continental differences in disease pattern. Therefore, which immunoregulatory biomarkers are essential in driving *S. haematobium* infection or regulate disease burden among Nigerian school children? One hundred and thirty one age and sex-matched schistosome-infected children and 275 uninfected controls, of same ethnicity, recruited from southwestern Nigeria, were screened for variability of cytokine genes, IL-10 (*rs1800872*), IL-13 (*rs7719175*), IL-4 (*rs2243250*) and STAT6 (*rs3024974*), utilizing a polymerase chain reaction-restriction fragment length polymorphism assay. We found no difference in genotypic or allelic frequencies of IL-10 and IL-13 promoter polymorphisms alone or in association with disease. Contrariwise, we report significant differences in the frequencies of IL-4 and STAT6 variants between groups. For IL-4, the rs2243250 T/T variant was significantly different for genotypes (71.6% versus 51.2%; $p < .0004$) and alleles (82.6% versus 71.1%; $p < .001$) between disease and control groups respectively. For STAT6 (*rs3024974*), the frequencies of genotypes C/C and C/T are 75.4% and 24.6%, both showing an association with disease; none of the infected subjects had the T/T variant. Despite minor differences in disease covariates, we found no association between IL-4 and STAT6 variants with age, gender or anemia. However, mean egg count (indicative of disease burden), was regulated based on IL-4 variants, with highest burden in infected subjects with rs2243250 T/T variant (mean egg count: 207.5 eggs/10 ml of urine) versus rs2243250 C/T heterozygotes (mean egg count: 84.3 eggs/10 ml of urine) versus rs2243250 C/C (mean egg count: 127.9 eggs/10 ml of urine). Comparing rs2243250 C/T versus rs2243250 T/T ($p < .008$) or rs2243250 C/C + C/T versus rs2243250 T/T ($p < .016$) reveals an association with disease burden. We conclude that the IL-4 promoter gene is a susceptibility factor for schistosomiasis, and essential to regulate disease burden, with worse disease among carriers of the rs2243250 T/T variant. The absence of the STAT6, *rs3024974T/T* variant among infected subjects reveal the necessity of the STAT6 promoter gene in driving susceptibility to schistosomiasis in Nigeria.

1. Introduction

Schistosomiasis is prevalent in many parts of rural Africa, Latin and South America and Asia, leading to severe morbidity and negative health outcome in many endemic communities, causing disease forms ranging from intestinal to urinary or co-infections, depending on the parasite species and body part where the eggs are deposited. Severity of disease in many cases is related to patient's age, initial immune status

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https://doi.org/10.1016/j.meegid.2018.07.012
Received 24 April 2018; Received in revised form 9 July 2018; Accepted 11 July 2018
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and immune response to infection, with pathologies such as hydronephrosis, hematuria or liver damage. Schistosomiasis is known to drive a Th2 immune response, with high levels of circulating immunoglobulin E and eosinophilis, contributing to the Th1/Th2 balance and associated cytokines. Of significance, infection-associated cytokines are implicated in immune response, with inter-individual variability in cytokine gene polymorphisms influencing response and disease outcome. Such variabilities driven by host genetic diversity of encoding genes has been reported for many types of bacterial, parasitic, viral or autoimmune diseases, especially if such polymorphisms are located in promoter regions, modifying gene transcription and cytokine production in the process (Miteva and Stanilova, 2008; Sam et al., 2015). Previous work on schistosomiasis has established that interleukin-13 (rs7719175) gene promoter polymorphism is associated with *Schistosoma haematobium* infection levels (indicative of disease burden) and identification of a susceptibility haplotype among infected groups in Mali, West Africa (Isnard et al., 2011). Additionally, reports from Uganda, East Africa (Gatlin et al., 2009) identified polymorphisms that are associated with disease, alongside patterns of reinfection in such groups, postulating that single nucleotide polymorphisms of interferon-γ (+874), IL-13 (-1055) and IL-4 (-590 C/T) permit the development of resistant phenotypes to reinfection. Other reports have revealed the importance IL-10 promoter variants in regulating Th2 cytokines in schistosome infections (Adebayo et al., 2017), in a schistosomiasis-malaria co-infection model.

Beyond IL-10 and IL-13 variants driving disease patterns, other promoter gene polymorphisms have been implicated, to some degree, in immune response to urinary schistosomiasis, including IL-4, the signature Th2 cytokine, and signal transducer and activator of transcription 6 (STAT6) (He et al., 2008). Allelic polymorphism of IL-4 gene may affect cytokine synthesis post-infection, becoming potential driver of immunologic pathogenesis in schistosomiasis. STAT6 is a cytosolic protein whose phosphorylation is catalyzed by JAK kinases 1 and 2 (Wurster et al., 2000) and an essential ingredient for the functional responses of Th2 cells, inducing IL-4 and IL-13, in the process. Previous reports have associated STAT6 polymorphisms with the pathogenesis of autoimmune diseases (psoriasis), atopy and asthma (Tarutani, 2013; Lim et al., 2013). However, there is paucity of information on the role of STAT6 variants on schistosome pathogenesis, except reports suggesting major role in driving susceptibility and response to infectious agents (Koukouikila-Koussounda et al., 2013; Amoako-Sakyi et al., 2016), including urinary schistosomiasis (He et al., 2008). We have shown that the susceptibility to, and severity of infectious diseases, are driven by host genetic polymorphism of immunologic markers, displaying significant intra- and interethnic diversities, potentially delineated along sub-regional or sub-continental lines (Thomas et al., 2013; Thakur et al., 2014; Noble et al., 2015; Agyingi et al., 2016; Navarro et al., 2016; Ojurongbe et al., 2017).

Schistosomiasis is prevalent in rural Nigeria, with *S. haematobium* the most common causative agent, displaying varying degree of endemicity, from one part of the country to the other (*World Health Organization (WHO),* 2014). Children are the most commonly infected, including others whose daily activities entail contact with water bodies, contaminated with cercariae, the infective form of the parasite. Given the prevalence and severity of *S. haematobium* infection in rural Nigeria, are there similarities in the patterns of Th2 immunoregulatory biomarkers observed in Mali and Uganda? Alternatively, are these strictly coast-associated patterns between Nigeria (coastal West Africa) and Mali (inland West Africa), region-associated patterns between Nigeria (West Africa) and Uganda (East Africa), or linguistic-associated patterns (Afroasiatic versus Niger-Kordofanian versus Bantu), as postulated (Gomez et al., 2014)? Tangentially, are these biomarkers significant to regulate disease burden or other covariates of infection, individually or in combination? To this end, we elucidated the diversity and frequency of IL-10, IL-13, IL-4 and STAT6 cytokine gene polymorphisms between school-children infected with *S. haematobium* and uninfected control group, recruited from south-western Nigeria, as well as extrapolated potential association between schistosomiasis and covariates of infection (egg burden, age and packed cell volume (PCV) (marker of anemia).

Table 1
General characteristics of study population.

		Sh positive *n* = 131 (%)	*Sh* negative *n* = 275 (%)	*p* value
Gender	Male (%)	71 (54.2)	140 (50.9)	0.595
	Female (%)	60 (45.0)	135 (49.1)	
Age (years)	Range	3–20	3–20	
	Mean ± SD	10.7 ± 3.7	8.4 ± 3.6	< 0.0001
Weight	Mean ± SD	33.7 ± 12.7	25.8 ± 10.0	< 0.0001
PCV	Mean ± SD	36.9 ± 5.3	37.2 ± 5.3	< 0.0001
Parasite	Mean ± SD	178.8 ± 270.3	NA	
Count	Number with heavy infection (≥50 eggs/ 10 ml urine) (%)	77 (57.9)	NA	
	Number with light infection (< 50 eggs/ 10 ml urine) (%)	54 (40.6)	NA	

Sh: *Schistosoma haematobium*; NA: not applicable.

2. Materials and methods

2.1. Study site and subjects

This study was conducted between January and October 2015, among preschool/school age children (age 3–20 years), recruited from Ore community, Osun State, Nigeria. This community was chosen because of reports of schistosome endemicity, and a nearby water body, known to be the site of infection (Morenikeji et al., 2014). Six hundred and twenty-five school children, whose parents/guardian gave informed consent and approved of their involvement participated in this study. Individual demographic information was collected while ages were retrieved from school records (Table 1).

2.2. Urinalysis and screening for S. haematobium

Universal bottles labelled with the corresponding identification number were given to the school children who gave consent to participate in the study to produce urine specimen between 10:00 AM and 2:00 PM, and to be submitted the same day, while research team remain within the school premises. Urine samples were transported to the laboratory for microscopic examination of characteristic *S. haematobium* eggs, using the nucleopore filtration technique (Adebayo et al., 2017). Briefly, 10 ml of well-mixed urine was aspirated and carefully forced through a filter membrane; filter was removed and placed on a slide, covered with cover slip and examined under a light microscope. The number of eggs on the entire filter was counted and recorded as the number of eggs per 10 ml urine. From the total slides, 10% were randomly selected and re-examined by an independent microscopist for quality control. After parasitological testing, the cohort was divided into cases (131 *S. haematobium* positive) and control (494 *S. haematobium* negative). In the control group, DNA extraction and amplification was successfully in only 275 children which were included in the final analysis (Table 1).

2.3. PCR analysis

After sterilization with an alcohol swab, finger prick blood was spotted onto filter paper (GE Healthcare Sciences) from each schistosome patient. Genomic DNA was extracted from filter paper blood spot with the Qiagen Blood Mini Kit (Qiagen Inc., Valencia, CA), with some

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