The Genetics of Human Schistosomiasis Infection Intensity and Liver Disease: A Review

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Schistosomiasis remains the fourth most prevalent parasitic disease affecting over 200 million people worldwide. Control efforts have focussed on the disruption of the life cycle targeting the parasite, vector and human host. Parasite burdens are highly skewed, and the majority of eggs are shed into the environment by a minority of the infected population. Most morbidity results from hepatic fibrosis leading to portal hypertension and is not well-correlated with worm burden. Genetics as well as environmental factors may play a role in these skewed distributions and understanding the genetic risk factors for intensity of infection and morbidity may help improve control measures. In this review, we focus on how genetic factors may influence parasite load, hepatic fibrosis and portal hypertension. We found 28 studies on the genetics of human infection and 20 studies on the genetics of pathology in humans. *S. mansonii* and *S. haematobium* infection intensity have been showed to be controlled by a major quantitative trait locus SM1, on chromosome 5q31-q33 containing several genes involved in the Th2 immune response, and three other loci of smaller effect on chromosomes 1, 6, and 7. The most common pathology associated with schistosomiasis is hepatic and portal vein fibroses and the SM2 quantitative trait locus on chromosome six has been linked to intensity of fibrosis. Although there has been an emphasis on Th2 cytokines in candidate gene studies, we found that four of the five QTL regions contain Th17 immune response pathway genes that have been included in schistosomiasis studies: *IL17B* and *IL12B* in SM1, *IL17A* and *IL17F* in 6p21-q2, *IL6R* in 1p21-q23 and *IL22RA2* in SM2. The Th17 pathway is known to be involved in response to schistosome infection and hepatic fibrosis but variants in this pathway have not been tested for any effect on the regulation of these phenotypes. These should be priorities for future studies.

Keywords: schistosomiasis, fibrosis, Th17, intensity of infection, QTL, linkage
INTRODUCTION

Schistosomiasis is caused by digenic trematodes of the genus Schistosoma with Schistosoma mansoni and Schistosoma haematobium causing the majority of human infections. Adult parasites live in the veins around the gut and bladder and eggs are excreted in feces or urine and infect snails in fresh water. Parasite numbers are amplified in the snail intermediate host and human infective stages then emerge that can penetrate human skin when people enter the water. Schistosomiasis induces human infective stages then emerge that can penetrate human skin and eventually cause liver and bladder fibrosis and eventually colorectal cancer (1). Although exposure to water infected with the infective schistosome cercariae is the main risk factor for schistosomiasis there is considerable variation in infection intensity between people with similar exposures and schistosomiasis cases aggregate in families, some of this variation has been attributed to the genetics of the human immune response (2–4).

A review of the genetics of human susceptibility to schistosomiasis related fibrosis has been published recently (5), but there has been no review of the genetics of schistosomiasis infection since 2008 (2).

A fundamental understanding of the genetics of schistosomiasis susceptibility and high worm load may contribute to rational design of interventions, including vaccines (6). For example, it has recently been shown that a set of 32 SNPs in 10 genes can predict susceptibility to severe hepatic disease among Brazilians with 63% sensitivity and 90% specificity (5).

In the present review of the genetics of human susceptibility to schistosomiasis we focus on loci associated with egg/worm burden and hepatic fibrosis.

We therefore present an updated review of the genes and variants that have been found associated with schistosomiasis infection intensity and liver disease, together with a review of genes within QTL that could be prioritized for future analyses. We have excluded the HLA region since we have only identified one study of genes in this region since they were last reviewed (7, 8).

Epidemiology and Treatment

The disease affects almost 240 million people, and 700 million are at risk of infection in 74 countries, the majority being in Africa, Asia and South America (9, 10). Between 3 and 56 million disability-adjusted life years (DALYs) are lost per annum and 280,000 deaths per annum have been attributed to effects of schistosomiasis (11–13). Approximately 85% of infections occur in sub-Saharan Africa and at least 90% of people requiring treatment for schistosomiasis live in Africa (14). Schistosomiasis can also be associated with chronic anemia, childhood growth stunting, protein calorie malnutrition, cognitive disability, and poor school performance (15–20).

Control of schistosomiasis has continued to rely mainly on mass drug administration (MDA) of school-aged children using the anti-schistosomal drug praziquantel (PZQ) (21, 22). Although this strategy has reduced morbidity, the impact on prevalence has been more limited, because praziquantel does not kill immature schistosomes (23, 24), coverage remains restricted and only school age children are routinely treated. Vaccines are in development but phase three trials have not been successful (25).

Immune Responses During Schistosome Infections

Immune responses to penetrating and migrating Schistosoma larvae (schistosomula) and maturing adults are predominantly Th1 (26). Excretory/secretory Schistosoma antigens damage host barrier cells which release alarmins, activate innate cells and induce proinflammatory cytokines (IL1B, IL6, IL17, TNF, and IFNG) (27). About 6 weeks after infection, Schistosoma eggs are deposited in tissues (the liver and the intestine or the bladder) and trigger an expansion of Th2 cells (28). Schistosoma egg antigens also directly bind receptors on antigen presenting cells inhibiting IL12 production and consequently Th1 responses (29). Th2 responses can also be induced independently of egg deposition as infection with single sex schistosomes induce pre-patent IL4 production by CD4+ T cells (30). Schistosome specific Th2 responses are downmodulated in long-standing infections (31) and this is associated with a development of regulatory cells producing IL10 and transforming growth factor beta (TGFβ). This not only allows the parasite to survive in the host and minimize host tissue damage but also modulates host immune responses to unrelated antigens including allergens, self-antigens, and vaccines.

Schistosome egg secretions are highly antigenic (31) and typically induce polarized granulomatous Th2 responses (32). Granulomas form around eggs lodged in tissues to protect tissue cells (33) but persistent host CD4 T2 cell mediated responses to parasite eggs cause fibrosis (34). The pro-fibrotic Th2 cytokine IL13 is associated with periportal fibrosis in humans (35). Beyond Th2 cytokine responses, intensified hepatic granulomatous inflammation in S. mansoni infected mice is associated with high levels of IL17 and controlled by IFNG (36). In human schistosomiasis, IL17 producing CD4 T helper cells are associated with ultrasound textural abnormalities while T regulatory cells are associated with reductions in this pathology (37).

Phenotypes

Schistosomal Fecal Egg Count and Worm Burden

Studies of the human genetics of susceptibility to schistosomiasis have focussed on two classes of phenotype; infection associated phenotypes and pathology related phenotypes. Infection associated phenotypes are usually egg counts or worm burden estimates but sometimes total IgG as a marker of the immune response (38). Eggs counts are obtained by the Kato Katz (KK) method for S. mansoni and by urine filtration for S. haematobium and worm burdens are estimated by measuring the circulating cathodic antigen (CCA) in urine or circulating anodic antigen (CAA) in plasma (39) that are produced by adult worms.

Approximately 80% of the environmental egg burden from helminths including schistosomes, derives from ~20% of the cases (40). For example 22 out of 119 Kenyan school children had developed high S. mansoni egg burden (>100 eggs per gram of feces) 12 months after treatment, whilst 70 children still had low (<30 epg) egg burdens (41) and this effect was not correlated with
Schistosomiasis Associated Hepatic and Periportal Fibrosis and Portal Vein Hypertension

Although schistosomes cause a wide range of symptoms and fibrotic lesions can form around egg granulomas in many tissues, the main indicator of *S. mansoni* and *S. japonicum* pathology is hepatic fibrosis (HF) and periportal fibrosis (PPF) (52). WHO guidelines provide scoring scales for HF and PPF (53) and both scales are used as phenotypes in genetic research (54). HF and PPF is caused by extracellular matrix forming around schistosome eggs. In the hepatic portal vein this can lead to portal hypertension (PH) (55, 56), ultimately, some patients with PH die of internal bleeding, superinfections, or heart or kidney failure. *S. haematobium* is associated with bladder cancer and *S. mansoni* may be associated with hepatocellular carcinoma (57) but genetic studies of the pathology of schistosomiasis have focussed almost exclusively on hepatic and periportal fibrosis and in this review all references to pathology are to these closely related conditions unless otherwise indicated. Fibrosis can be measured by ultrasound scan, although there are concerns about the accuracy and reproducibility of ultrasound (58); additional markers and protocols for grading pathology are being developed but are not well-validated (59–61).

Heritability of Schistosomiasis Infection Risk

Heritability, the proportion of risk attributable to genetic variation, must be substantial to be detectable. A summary of heritability estimates for schistosomiasis are shown in Table 1. Studies in Brazil (62–64); Kenya (46); and China (65, 66) have each estimated similar proportions of the variance of *S. mansoni* egg count that are attributable to genetic variation, with additive heritability (h²) estimates of 23–31%. However, there were striking differences in the two estimates for heritability of infection with *S. japonicum* in China using variance components (VC) (0 & 58%) (Table 1), which have been discussed by others (2).

Linkage Studies for Schistosoma Egg Count

The initial study of the genetics of human schistosomiasis used segregation analysis, which determines whether the distribution of the disease on family pedigrees is consistent with the presence of a major gene (3). This study demonstrated the presence of a major gene which was subsequently named SM1 and located on chromosome five by parametric linkage analysis (4). A major gene has alleles that cause a difference in phenotype between family members that is large enough to be able to categorize individuals as carriers or non-carriers on the basis of phenotype alone (67) and parametric linkage analysis requires estimates of the disease allele frequency and penetrance of the phenotype for the three possible genotypes.

The SM1 quantitative trait locus (QTL) on chromosome 5 5q31-q33 for *S. mansoni* fecal egg count was the first QTL to be mapped in humans for any infectious disease (Table 2, Figure 1) (4). The great success of this study was partially attributable to the very large effect size of the SM1 locus (66% of the variance after accounting for water contact, age and sex). This is in striking contrast to the very modest proportions of the variance explained by most loci identified by GWAS in which loci rarely explain more than 10% of the variance of the trait that is not attributable to covariates (96). Three further loci (1p22.2, 7q36 and 21q22–22-qter) had evidence of association and contained genes known to be involved in the response to schistosomes but did not achieve genome wide significance (68). A reanalysis of the same data controlling for SM1 genotype identified additional genome wide significant loci at 1p21-q23 and 6p21-q21 (Table 2, Figure 1) (69), since the effect of these loci was small in comparison to the effect of SM1, they were only identifiable when using SM1 genotype as a parameter of the model.

A further study on a Senegalese population, by the same group that conducted the original study in Brazil, confirmed an association at the SM1 locus. However, the effect was not as strong and the association could only be demonstrated by non-parametric pedigree tests for an effect at the SM1 locus (70). Non-parametric analysis requires no prior knowledge of the disease allele frequency or the disease penetrance of the different genotypes.

**GENOME WIDE LINKAGE STUDIES DISCOVER SCHISTOSOMIASIS SUSCEPTIBILITY LOCI**

The reviews of linkage and candidate gene studies of schistosomiasis are broken down into two sections by phenotype: (1) studies of infection status, which is usually determined by egg count in urine or feces and (2) studies of pathology which is mainly periportal fibrosis determined by ultra-sound. Relevant publications were identified by searching PubMed using the terms in Supplementary Table 1.
TABLE 1 | Heritability estimates for genetic component of risk of schistosomiasis in different populations.

| Parasite     | Phenotype | Country and district | Heritability estimate and method eg $h^2$ | References |
|--------------|-----------|----------------------|------------------------------------------|------------|
| S. mansoni   | Egg count | Brazil, Minas Gerais | 23% ($h^2$)                              | (62)       |
| S. mansoni   | Egg count | Brazil, Minas Gerais | 27% (VC)                                 | (63)       |
| S. mansoni   | Egg count | Brazil, Bahia        | 31% (VC)                                 | (64)       |
| S. mansoni   | IgE       | Brazil, Bahia        | 59% (VC)                                 | (64)       |
| S. haematobium| Egg count| Kenya, Coast         | 9% ($h^2$)                               | (46)       |
| S. haematobium| Bladder  | Kenya, Coast         | 14% ($h^2$)                              | (46)       |
| S. japonicum | Infection | China, Jiangxi      | 58% (VC)                                 | (65)       |
| S. japonicum | Infection | China Sichuan       | 0% (VC)                                  | (66)       |

$h^2$ additive heritability, VC variance components.

TABLE 2 | Loci associated with S. mansoni infection discovered by linkage studies.

| Phenotypes   | Locus name | 5' Marker (Position) | 3' Marker (Position) | References | Candidate genes, Tested (Untested) |
|--------------|------------|----------------------|----------------------|------------|-----------------------------------|
| Egg count    | SM1 5q31-q33 | D5S642 (128Mb)       | D5S412 (158Mb)       | (4, 68–70) | IL4, IL5, IL9, IL13, IL17A, IL17C |
| Egg count    | 1p21-q23   | D1S236 (65Mb)        | D1S196 (168Mb)       | (69)       | IL6R, CRP                         |
| Egg count    | 6p21-q21   | D6S271 (43Mb)        | D6S283 (67Mb)        | (69)       | VEGFA, IL17A, IL17C               |
| Hepatic fibrosis | SM2 6q22-q23 | D6S1009 (137Mb)    | D6S310 (142Mb)       | (71)       | CTGF, IFNGR1, IL22RA2             |
| Egg count    | 7q35-q36   | D7S483 (152Mb)       | D7S550 (156Mb)       | (69)       | TRB, NOS3, SHH                    |

Marker positions are shown in GRCh37 co-ordinates. Candidate genes that have been found associated with the phenotype are shown in bold (Tables 3, 4). Other plausible candidates (See Figure 2) in the regions are in brackets. Genes associated with the T$_1$h 17 response are underlined. These loci are shown graphically in Figures 1, 2.

Linkage Studies Identify QTL for Pathology That Are Independent of QTL for Parasite Burden

A study in Sudan found that 12% of the study population had moderate or advanced fibrosis and that half of these also had portal hypertension (97). A linkage study of four candidate gene regions in the same population identified a locus (SM2) on chromosome six near the interferon-gamma receptor (IFNGR1) associated with hepatic fibrosis (Table 2, Figure 1) (98). Fifty percentage of people with risk alleles at SM2 had some continuous thickening of periportal vein branches within 19 years of coming to live within the study area. IFNG is strongly anti-fibrogenic and polymorphisms in IFNGR1 could plausibly regulate fibrosis. No linkage was found with the SM1 locus suggesting that control of infection and pathology were independent. The SM2 locus at 6q22-q23 did not overlap either the HLA region on chromosome six or the 6p21-q21 region that was associated with S. mansoni worm burden in Brazil (69) (Table 2, Figure 1).

The SM2 locus was replicated in a linkage study of 11 candidate gene regions in Egypt where 32.7% of individuals 11 years and older had significant fibrosis and rs1327475 in IFNGR1 was significantly associated with severe PPF. In contrast to the earlier study in Sudan, this study found a weak association with the T$_1$h2 cytokine cluster (IL4, IL13) in SM1 (54), suggesting that worm burden does contribute to risk of pathology. There is evidence for a potentially protective role of a high IFNG response to schistosome infection, consistent with the anti-fibrogenic properties of IFNG [reviewed by Abath et al. (99)] and a SNP in IFNG has been associated with time to reinfection (Table 3) (72). Consequently, it appears that the variation in the IFNG system is involved in both the outcome of infection and pathology. Variation in IFNGR1 has only been shown to be involved in the development of pathology but it has yet to be tested in a candidate gene study for effect on infection response.

ANNOTATION OF GENES IN QTL REGIONS

Very few genes were known in the 5 QTL regions for schistosomiasis (Table 2) at the time that the QTL were discovered, and we are not aware of any attempts to identify the genes that are responsible for the QTL effect. Hundreds of genes are now known in these loci, each of which could potentially regulate the phenotype and we prepared a short list of the most likely candidates in each region. In order to discover which genes in each schistosomiasis QTL region might be involved in the response to schistosomiasis we used a custom Perl script to search...
PubMed with terms for schistosomiasis and each gene name and its aliases and obtained a count of the number of publications returned as detailed in Supplementary Table 4.

We assumed that the genes that are most likely to be the QTL genes will already have been shown to be involved in the response to schistosome infection. In order to identify these genes, we systematically searched PubMed for papers that included terms for schistosomiasis and each of the gene names in the 5 QTL regions in Table 2 or their synonyms (Supplementary Table 4). The genes that have been mentioned most frequently in the abstract of a paper that also mentions schistosomiasis and that are in one of the QTL are shown in Figure 2, Table 2. A complete list of all genes that are in the QTL and that have been studied in the context of schistosomiasis is in Supplementary Table 4. The number of papers shown in Figure 2 is an indicator of the genes most commonly associated with schistosomiasis in these regions. The genes with the largest literature were the Tg2 cytokine genes originally identified by Marquet (4) in SM1 (IL3, IL4, IL5, IL9, and IL13), that each had between 17 and 511 publications associated with schistosomiasis. Only CSF1 and TRB...
TABLE 3 | SNP which have been found to be associated with schistosomiasis infection phenotypes in candidate gene studies.

| SNP          | Gene   | Phenotype | Parasite | Neg refs | Pos refs |
|--------------|--------|-----------|----------|----------|----------|
| rs2430561    | IFNG   | T2R       | Sm       | none     | (72)     |
| rs3024495    | IL10   | FEC       | Sm       | None     | (39)*    |
| rs180086     | IL10   | IgE       | Sm       | None     | (38)     |
| rs1800871    | IL10   | IgE       | Sm       | None     | (38)*    |
| rs1800872    | IL10   | IgE       | Sm       | None     | (38)*    |
| IL10(−1082/−8 19/−592) | IL10   | UEC       | Sh       | (73)     | (74)*    |
| rs20541      | IL13   | FEC       | Sm       | (75, 76) | (77)     |
| rs2066960    | IL13   | FEC       | Sm       | (78)     | (77)     |
| rs7719175    | IL13   | UEC       | Sh       | (73)     | (79)*    |
| rs2069743    | IL13   | UEC       | Sh       | (78)     | (80)     |
| rs1800925    | IL13   | UEC, FEC, T2R | Sh, Sm | None     | (72, 77–79)* |
| rs2243250    | IL4    | UEC, T2R  | Sh       | None     | (73), (72)* |
| rs2079103    | IL5    | IF        | Sj       | None     | (75)*    |
| rs27069399   | IL5    | IF        | Sj       | None     | (75)*    |
| rs3024974    | STAT6  | UEC       | Sh       | None     | (73)*    |
| rs324013     | STAT6  | UEC       | Sh       | None     | (78)*    |
| rs733618     | CTLA4  | UEC       | Sh       | None     | (81)     |
| rs11571316   | CTLA4  | UEC       | Sh       | None     | (81)     |
| rs231775     | CTLA4  | UEC       | Sh       | None     | (81)     |
| rs3124952    | FCN2   | UEC       | Sh       | None     | (82)     |
| rs17514186   | FCN2   | UEC       | Sh       | None     | (82)     |
| rs7567833    | COLECC1 | UEC     | Sh       | None     | (83)     |
| COLECC1*TCCA |        |           |         |          |          |
| Blood group D |        |           |         |          |          |
| rs748822072  | RNASE3 |           | Sm      | None     | (85)     |

LCI that have been found associated with schistosomiasis in more than one study are shown in bold. * Loci that are not significant after Bonferroni correction. IL10 (−1082/−8 19/−592) = a haplotype of rs1800870, rs1800871 and rs1800872. COLECC1*TCCA is a haplotype of rs1864480 (−676T/C), rs4849953 (−472T/C), rs6714770 (−469C>G), and (−275C>T). Blood Group O is most commonly defined by genotypes at three SNP rs8176719, rs8176746(CC), rs8176747(GG). IF, Infection Frequency; T2R, Time to Reinfection; UEC, Urine Egg Count; FEC, Fecal Egg Count; Sh, S. haematobium; Sm, S. mansoni; Sj, S. japonicum. “Pos refs” column contains citations for the studies that showed a significant association with phenotype and “Neg refs” column contains citations of studies that failed to show a significant association at that locus.

(beta T cell receptor) were identified as candidate genes by the original authors in the 1p21-q23 and 7q35-q36 egg burden loci (69) and IFNGR1 was the candidate gene that was used for the linkage study at SM2 (98). The large literature on T\textsubscript{h} cytokines and schistosomiasis is expected given the important role of this pathway in response to egg antigens and the development of pathology. The T\textsubscript{h} cytokines in SM1 are therefore credible candidate genes at this locus.

Our annotation of these QTL also revealed the presence of T\textsubscript{h}1 related genes in four of the five QTL: IL17B and IL12B in SM1, IL22RA2 in SM2, IL17A and IL17F in 6p21-q21 and IL6R in 1p21-q23. Although IL12B (IL12p40) in SM1 is primarily known as a T\textsubscript{h}1 cytokine it is also a component of the heterodimeric IL23 cytokine which is important for T\textsubscript{h}17 maintenance and expansion (100) and IL6 is important in T\textsubscript{h}17 T helper cell differentiation (101). IL17 cytokines are involved in regulation of worm and egg burdens as well as the development of fibrosis and granuloma in response to eggs (102). The presence of T\textsubscript{h}17 related cytokines in four of the five QTL suggests that variation in this system may also contribute to variation in outcome of infection in addition to that caused by variation in the T\textsubscript{h}2 system.

CANDIDATE GENE STUDIES

Infection Status and Intensity

We have identified 28 candidate gene studies of Schistosoma infection or worm burden that reported associations between 24 loci in eleven candidate genes and seven different phenotypes (Table 3, Supplementary Tables 2, 3). The genes with associations were IFNG, IL10, IL13, IL4, IL5, STAT6, CTLA4, FCN2, COLECC11, ABO, and RNASE3. These genes were all chosen because their protein products were known to be involved in the response to infection. One study of MASP2 (103) and one on LTA (104) only reported negative results and are not included in Table 3. We have not attempted any formal meta-analysis since few loci were replicated and there were important differences in study design and data reporting in the studies of loci that were replicated, making any meta-analysis hard to interpret.
Schistosome eggs induce granulomatous T<sub>H</sub>2 responses (IL4, IL5, IL9, IL10, and IL13) (32) and antigen-specific IgG1, IgG4, and IgE (105). The SM1 region on chromosome five identified by Marquet et al. (4) (Figure 1) included the prototypical T<sub>H</sub>2 cytokines IL4, IL5, IL9, and IL13; these are strong candidates for the QTL gene(s) and SNP and all except IL9 have been found associated with schistosomiasis in candidate gene studies (Table 3). IL13 and IL4 regulate STAT6 expression which in turn...
regulates IgE class switching (106) and STAT6 variants are also associated with schistosomiasis (Table 3). IL13, IL4, IL5, and STAT6 are also involved in regulation of the T1,2 response to schistosomiasis (72, 75, 77–80).

T1,1 cytokines and IFNG in particular are involved in the resistance to the immature worms. Studies of mice and ex vivo human PBMC have shown that IFNG levels increase in response to schistosome antigens and are correlated with resistance or tolerance to infection (27, 107, 108) and a candidate gene study found an association between the IFNG SNP rs2430561 and time to reinfection (72). IL10 and CTLA4 downregulate immune responses in long standing infections (31). COLECC11 and FCN2 are involved in the innate immune response, they both bind to specific pathogen-associated molecular patterns (PAMPs) on the pathogen surface and stimulate the complement lectin cascade, thereby clearing the pathogens by opsonization (82, 83). ABO regulates blood group and a meta-analysis found evidence for a protective effect for blood group O (84). RNASE3 also known as eosinophil cationic protein (ECP) is a secretory protein of eosinophil granulocytes that efficiently kills the larval stage of S. mansoni (85).

The Ensembl Variant Effect Predictor was used to provide functional annotations for these variants (Supplementary Table 5). In the functional annotation only rs231775 in CTLA4 and rs20541 in IL13 were predicted to have an effect on function. Both of which were non-synonymous variants and were classified as risk factors by ClinVar (109), although SIFT (110), and Polyphen (111) predicted the effect of these SNP would be benign. Other SNP had no predicted effects on function, possibly because they are not functional but are linked to functional SNP nearby. However, the functional annotation cannot detect all functional variants and experimental work has shown that IL13 expression is regulated by rs1800925 (112). Further detailed studies will be required to determine which of the SNP are truly functional and which are not functional but still potentially useful markers for risk of schistosomiasis.

Pathology: Hepatic and Periportal Fibrosis
It has been noted since at least 1974 that the development of severe fibrosis is clustered in families and is not well-correlated with intensity of infection suggesting that the mechanisms regulating infection intensity and pathology are not closely coupled (5). We found 20 studies which identified associations with schistosomiasis related pathology at 46 candidate SNP or haplotypes in 21 genes outside the HLA complex (Table 4, Supplementary Table 2). Few of the studies applied any multiple testing corrections and 15 out of the 43 associations would not be significant after a Bonferroni correction (Table 4).

There are sixteen genes for which an effect has only been reported for fibrosis and not for infection: APOE, CCN2, HSPA5, IFNGR1, IL22RA2, MAPKAP1, IL1RL1, TNFA, mTOR, AKT2, TGFBR1, TGFBR2, ACVRL1, SMAD9, and SMAD3 (Tables 3, 4). Five genes have been associated with both fibrosis and intensity of infection (RNASE3, IL4, IL10, IFNGI, and IL13). Four genes were associated with fibrosis in more than one population: IFNGR1, IL22RA2, CCN2, and MAPKAP1 (Table 4), the two former genes are also in the SM2 QTL (55, 71, 86, 90, 93). Although these sixteen genes have not been tested for associations with infection status or intensity it is plausible that some of them are only associated with pathology. All of these genes except APOE and IL1RL1 have been associated with the regulation of fibrosis (Table 4) and variation in these may regulate risk of pathology irrespective of intensity of infection.

The Ensembl Variant Effect Predictor was used to provide functional annotations for the SNP in Table 4 (Supplementary Table 5). Two non-synonymous SNP in APOE (rs7412 and rs429358) were predicted by ClinVar to be a risk factor, pathogenic and involved in drug response (109), the rs7412 SNP was also predicted to be deleterious or damaging by SIFT (110) and Polyphen (111). A non-coding SNP in LTA (rs1800629) was predicted to be related to drug response by ClinVar (109) and a non-coding SNP (rs1800872) in IL10 was predicted to be a risk factor by ClinVar. Other SNP in Table 4 did not have functional annotations, and many may be marker SNP that are linked to functional variants rather than functional themselves.

A recent study found that just 32 SNPs could predict who gets severe hepatic fibrosis in Brazil with 63% sensitivity and 90% specificity (5). This review emphasized the importance of TGFB signaling pathway and IL22. TGFβ is also involved in the differentiation of T17 cells (113), and together with SMAD regulates T17 in response to another worm infection Echinococcus multilocularis (114) providing further justification for systematic investigation of the role of variants in the T1,17 pathway in differences in response to infection. IL22 and IL17 are co-expressed by T17 CD4+ T cells and polymorphisms have been associated with hepatic fibrosis in the IL22 receptor IL22RA2 (5, 90). IL22 also has protective effects on the intestinal epithelium against toxic bacterial products (5).

Associations With the HLA Region
The HLA region is associated with response to many communicable and non-communicable diseases. The importance of CD4+ T helper cells in the response to schistosomiasis, and the role of HLA class II alleles in recruiting these, suggests that variation in the HLA region may play an important role in control of schistosome infections. However, associations were not found in this region in the whole genome linkage scans either for worm burden or pathology (4, 68, 71).

Two reviews reported 17 and 18 studies, respectively, of associations of HLA markers with schistosomiasis induced PPF (7, 8), but surprisingly we could not find any studies of HLA genes and worm burden (Table 3, Supplementary Table 3). We have found only one study of genes in the HLA region and schistosomiasis that has been published in the 9 years since those reviews. A SNP in Major histocompatibility complex class I chain-related A (MICA) was associated with liver fibrosis in a Han Chinese population (76).

It has been emphasized that the problems of extensive linkage disequilibrium within the HLA region, the small sizes of the studies reviewed, the allelic diversity and large variations in allele frequencies between populations mean that these studies may not replicate in different populations and need further confirmation.

Raw Text
### TABLE 4 | SNP which have been found to be associated with schistosomiasis pathology related phenotypes in candidate gene studies.

| SNP          | Gene     | Phenotype | Species | Not associated | Associated | References |
|--------------|----------|-----------|---------|----------------|------------|------------|
| rs1327475    | IFNGR1   | HF        | Sm      | NA             | Egypt      | (54)       |
| rs2243250a   | IL4      | HF        | Sm      | NA             | Egypt      | (54)       |
| rs1056854    | TGFβ1    | HF        | Sm      | NA             | Egypt*     | (54)       |
| rs373880612  | IFNG     | PPF, HF, PH | Sm   | NA             | Sudan*     | (55)       |
| rs1861494    | IFNG     | PPF, HF, PH | Sm   | NA             | Sudan*     | (55)       |
| IFN-gR1 (1q22-q23) |   |            |         |                |            |            |
| rs3037970    | CCN2(CTGF) | HF, PH   | Sj,Sm   | China          | Sudan      | (71)       |
|             |          |           |         | Brazil         |            |            |
| rs1257705    | CCN2(CTGF) | HF, PH   | Sj,Sm   | Sudan          | Brazil*    | (86)       |
| rs2151532    | CCN2(CTGF) | HF, PH   | Sj,Sm   | China          | China*     | (54, 86)   |
| rs9402373    | CCN2(CTGF) | HF, PH   | Sj,Sm   | NA             | 2 China*   | (86)       |
|             |          |           |         | Sudan          | Brazil*    |            |
| rs9399005    | CCN2(CTGF) | HF, PH   | Sj      | China          | China*     | (86)       |
| rs6918698    | CCN2(CTGF) | HF, PH   | Sj,Sm   | China          | China*     | (86)       |
| rs1931002    | CCN2(CTGF) | HF, PH   | Sj      | China          | China      | (86)       |
| rs12526196   | CCN2(CTGF) | HF, PH   | Sj,Sm   | Sudan          | Brazil*    | (86)       |
|             |          |           |         |                |            |            |
| rs1800925C-  | IL13     | HF, PH    | Sj      | NA             | China*     | (87)       |
| rs20541A3    |          |           |         |                |            |            |
| rs18009253    | IL13     | HF PH     | Sj,Sm   | NA             | Brazil*    | (58)       |
| rs12712135   | ST2 (IL1RL1) | IL1RL1 | Sj,Sm   | NA             | China      | (58)       |
| rs1420101    | ST2 (IL1RL1) | IL1RL1 | Sj,Sm   | NA             | Brazil      | (58)       |
| rs6543119    | ST2 (IL1RL1) | IL1RL1 | Sj,Sm   | NA             | China      | (58)       |
| rs7412, rs429358 | APOE3   |         |         | NA             | Brazil      | (90)       |
| rs6570136    | IL22RA2  | HF, PH    | Sj,Sm   | NA             | China*     | (90)       |
| rs7774663    | IL22RA2  | HF, PH    | Sj,Sm   | NA             | 2 China*   | (90)       |
| rs2064501    | IL22RA2  | HF, PH, IL22 | Sj,Sm | NA             | Brazil*    | (90)       |
| rs11154915   | IL22RA2  | HF, PH, IL22 | Sj,Sm | China          | Brazil      | (90)       |
| rs7749054    | IL22RA2  | HF, PH, IL22 level | Sj,Sm | China          | Brazil*    | (90)       |
| rs1800870    | IL10     | PPF       | Sm      | NA             | Brazil      | (91)       |
| IL10 (-1082/-819/-592)³ | |         |         |                |            |            |
| rs1800629    | TNFA     | PPF, TNFA | Sm      | NA             | Brazil      | (92)       |
| rs10118570   | MAPKAP1  | PPF, infection | Sj    | NA             | 2 China     | (92)       |
| rs391957     | HSPA5    | HF, infection | Sj    | NA             | China       | (93)       |
| rs17025963   | TGFβR2   | HF        | Sm      | NA             | Brazil      | (93)       |
| rs185882198  |          |           |         |                |            |            |
| rs1090915    |          |           |         |                |            |            |

(Continued)
from larger studies (7). However, some alleles of HLA class II loci DQA1, DQB1 and DRB1 and HLA class I HLA-A and HLA-B were associated with PPF in a meta-analysis that combined evidence from 2 to 3 studies for each allele evaluated (8) and these associations may be robust.

**DISCUSSION**

**Replication of Candidate Gene Studies for Infection**

Few of the candidate gene studies shown in Tables 3, 4 applied correction for testing multiple SNPs and the 32 associations that would not remain significant after such a correction are indicated by asterisks. The lack of Bonferroni corrections suggests that some of these studies will not replicate and, for some of these loci, there are studies that have not replicated the association (Tables 3, 4), although this is often when using a different phenotype. Notably, half of these studies that did not replicate an association were at loci that were significant after a Bonferroni correction.

There are many instances of failures to replicate candidate gene studies. One review found that only 6 out of 166 associations replicated in more than 75% of studies, although 97 of the 166 associations (58%) were reproduced in at least one study (115). Failure to replicate can be due to the initial observation being due to random variation in allele frequencies between test and control samples (a type one error). However, genuine associations can fail to replicate because of linkage between the marker SNP and the functional SNP varying between populations, small study sizes, variable penetrance, population variation at modifier loci, (occult) population stratification within study populations or differences in allele frequencies between populations leading to type two errors. In addition, it is also possible for different SNP in the same gene to be associated with infection (Table 3). Studies of classical HLA loci have been excluded since they have been fully reviewed elsewhere (7, 8). This has been done to ensure that studies of classical HLA loci are not overrepresented in this analysis, as these loci are known to be strongly associated with infection (39).

**The Th17 Pathway Has Been Neglected in Schistosomiasis Association Studies**

Since the Th2 pathway is the dominant response to helminth infections and is the main pathway for response to egg antigens...
(28, 30), genes in this pathway have been well-represented in association studies (Tables 3, 4) and these have confirmed the importance of variation in this pathway for outcome of infection. However, the Th1 and Th17 pathways are also important, particularly in the early stages of the infection (26, 29, 36, 37). Variants in IL17F and IL17RA have been found associated with cerebral malaria (118) and similar variation may contribute to the outcome of schistosome infection. Our annotation of QTL, with the genes that have published associations with schistosomiasis, revealed an excess of Th17 pathway genes in these QTL (Figures 1, 2). There have been no association studies to test candidate gene hypothesis for three out of the five QTL (Table 2) and there are Th17 genes in four of the five QTL (underlined in Table 2), which could be priorities for future association studies.

It is possible that variation in other Th17 pathway genes outside of the QTL also contribute to variation in response to infection. A KEGG pathway diagram of Th17 cell differentiation and a list of 108 genes in this pathway is shown in Supplementary Table 6. We have obtained a list of the 1,742,019 SNP in these genes from dbSNP and kept the 1,052 SNP that were predicted to be “pathogenic” by ClinVar, irrespective of minor allele frequency (Supplementary Table 7). We also kept SNP with minor allele frequency > 5% and that had any of the following functional classifications: splice acceptor variant, stop gained, initiator codon variant, stop lost, splice donor variant, missense variant, terminator codon variant, frameshift variant. This left a list of 2,701 SNP in the Th17 pathway which are most likely to have an effect on function and that could be priorities for further testing (Supplementary Table 7).

**Which Are the Optimal Study Designs to Discover Susceptibility Loci?**

Approaches for discovering susceptibility loci for parasitic infections have been reviewed previously (119). The major approaches are association studies in unrelated individuals and linkage studies within families, the merits of which have been evaluated by Abel and Dessein (120). We noted in this review that family based designs were the first to discover QTL loci in schistosomiasis (4), and these were followed up with considerable success by candidate gene studies in these QTL. Schistosomiasis affected communities are frequently geographical clusters of related individuals where case control studies can be confounded by cryptic relatedness. In contrast family-based association studies exploit this relatedness by estimating disequilibrium in transmission of alleles within families.

Schistosomiasis is also an excellent setting for family-based linkage studies of infection intensity because children are the most heavily infected; therefore, parents are often available for genotyping to create complete families, unlike adult onset diseases. However, it is more difficult to collect full families for complications of chronic schistosomiasis such as fibrosis that affect adults. Whole genome linkage studies have only been undertaken on two populations, one in Brazil and one in Senegal, further studies to identify loci regulating intensity of infection in additional populations should be undertaken and could enlarge our understanding of the mechanisms of response to infection. It has already been shown that 32 SNP can be used to identify those at highest risk of developing pathology after *S. mansoni* infection (5). If the 20% of the people that shed 80% of the eggs could also be identified they could be targeted for regular treatment which could dramatically reduce the number of eggs in the environment and the pressure of infection on the whole community.

**CONCLUSION**

Despite the remarkable success of the early linkage studies that identified major QTL loci, no further whole genome scans for association have been conducted and the QTL genes underlying these loci have not been definitively identified. All subsequent studies have been candidate gene linkage and association studies focussing on genes within the QTL regions SM1, SM2, and the T3,2 pathway that are hypothesized to play a role in schistosomiasis progression. No candidate gene studies have attempted to identify QTL genes in three of the QTL for *S. mansoni* egg count (Table 2). This review has presented evidence that the T3,17 pathway has been overlooked in studies of the genetics of schistosomiasis and should be prioritized in future investigations of susceptibility genes.

The rapid development of genotyping technologies makes large scale genomic studies easier than ever, provided that well-characterized samples can be obtained. The studies of Dessein et al. (86) on populations from China, Sudan and Brazil have demonstrated the value of replicating analyses in multiple populations and similar replication is needed for other candidate SNP and genes.

**AUTHOR CONTRIBUTIONS**

GS and EMa conceived the review. EMe and ON wrote the draft and collected all the relevant literature. HN significantly reviewed the draft and analyzed QTL data. ME contributed to the draft and collected all the relevant literature. All authors read and approved the final manuscript.

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THE TRYPANOGEN+ RESEARCH GROUP OF THE H3AFRICA CONSORTIUM

Membership of the TrypanoGen+ research group is available at http://www.trypanogen.net/

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2021.613468/full#supplementary-material

Supplementary Table 1 | Search strategy: Summary of PubMed search strategy.

REFERENCES

1. Ismail HAHA, Hong ST, Babiker ATEB, Hassan RMAE, Sulaiman MAZ, Jeong HG, et al. Prevalence, risk factors, and clinical manifestations of schistosomiasis among school children in the White Nile River basin, Sudan. Parasites Vectors. (2014) 7:478. doi: 10.1186/s13071-014-0478-6

2. Bethony JM, Quinnell RJ. Genetic epidemiology of human schistosomiasis in Brazil. Acta Trop. (2008) 108:166–174. doi: 10.1016/j.actatropica.2007.11.008

3. 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.

4. Marquet S, Abel L, Hillaire D, Dessein H, Kalil J, Feingold J, et al. Genetic localization of a locus controlling the intensity of infection by Schistosoma mansoni on chromosome 3q31-q33. Nat Genet. (1996) 14:181–4. doi: 10.1038/ng1096-181

5. Alsallaq RA, Gurarie D, Ndeffo Mbah M, Galvani A, King C. Quantitative assessment of the impact of partially protective anti-schistosomiasis vaccines. PLoS Negl Trop Dis. (2018) 12:e0005524. doi: 10.1371/journal.pntd.0005524

6. Steinmann P, Keiser J, Bos R, Tanner M, Utzinger J. Schistosomiasis. Lancet. (2006) 368:2197–223. doi: 10.1016/S0140-6736(05)60099-2

7. Koukounari A, Gabrielli AF, Toure S, Boivin D, Lévéque C, Besançon D, et al. Schistosomiasis and neglected tropical diseases: towards integrated and sustainable control and a word of caution. Parasitology. (2014) 141:1749–56. doi: 10.1017/S0031662214001259

8. van der Werf MJ, de Vlas SJ, Brooker S, Looman CWN, Nagelkerke NJD, Habermann IDF, et al. Quantification of clinical morbidity associated with schistosome infection in sub-Saharan Africa. Acta Trop. (2003) 86:125–39. doi: 10.1016/S0001-706X(03)00029-9

9. Ghalgha NGC, Silué KD, Ba O, Ba H, Tian-Bi NTY, Yapi GY, et al. Prevalence and seasonal transmission of Schistosoma haematobium infection among school-aged children in Kaedi town, southern Mauritania. Parasites Vectors. (2017) 10:353. doi: 10.1186/s13071-017-2284-4

10. Cheever AW, Gaydos CA, Phelan J, Milligan G, Chen C. The economic burden of schistosomiasis. Parasites Vectors. (2014) 7:524. doi: 10.1186/1756-3305-7-524

11. Zinsl J, Litz S, Schelling A, Utzinger J, Steinmann P. Schistosomiasis. Lancet Infect Dis. (2014) 14:857–67. doi: 10.1016/S1473-3099(14)70152-8

12. Kretschmard B, Homan J, Mathin G, Utzinger J, Steinmann P. Schistosomiasis. Parasites Vectors. (2015) 8:7. doi: 10.1186/s13071-015-1071-x

13. van der Werf MJ, de Vlas SJ, Brooker S, Looman CWN, Nagelkerke NJD, Habermann IDF, et al. Quantification of clinical morbidity associated with schistosome infection in sub-Saharan Africa. Acta Trop. (2003) 86:125–39. doi: 10.1016/S0001-706X(03)00029-9

14. Ghalgha NGC, Silué KD, Ba O, Ba H, Tian-Bi NTY, Yapi GY, et al. Prevalence and seasonal transmission of Schistosoma haematobium infection among school-aged children in Kaedi town, southern Mauritania. Parasites Vectors. (2017) 10:353. doi: 10.1186/s13071-017-2284-4

15. Ezeama AE, Friedman JF, Acosta IP, Bellinger DC, Langdon GC, Manalo DL, et al. Helminth infection and cognitive impairment among filipino children. Am J Trop Med Hyg. (2005) 72:540–8. doi: 10.4269/ajtmh.2005.72.540

16. Ezeama AE, Bustinjudy AL, Nkwata AK, Martínez L, Pabalan N, Boivin MJ, et al. Cognitive deficits and educational loss in children with schistosome infection—a systematic review and meta-analysis. PLoS Negl Trop Dis. (2018) 12:e0005524. doi: 10.1371/journal.pntd.0005524

17. Friedman JR, Kanzaria HK, McGarvey ST. Human schistosomiasis and anemia: the relationship and potential mechanisms. Trends Parasitol. (2005) 21:386–92. doi: 10.1016/j.pt.2005.06.006

18. King CH, Dangerfield-Cha M. The unacknowledged impact of chronic schistosomiasis. Chronic Illn. (2008) 4:65–79. doi: 10.1177/1358802007071087

19. 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. doi: 10.1016/S0140-6736(05)66457-4

20. Koulkounari A, Gabrielli AF, Toure S, Bosque- Olivera E, Zhang Y, Sellin B, et al. Schistosoma haematobium infection and morbidity before and after large-scale administration of praziquantel in Burkina Faso. J Infect Dis. (2007) 196:569–69. doi: 10.1086/520515

21. Utzinger J, Raso G, Brooker S, De Savigny D, Tanner M, Ornberg N, et al. Schistosomiasis and neglected tropical diseases: towards integrated and sustainable control and a word of caution. Parasitology. (2009) 136:1859–74. doi: 10.1017/S0031866109991600

22. Evan Scor W. Water-based interventions for schistosomiasis control. Pathogens Global Health. (2014) 108:246–54. doi: 10.1179/2047773214Y.0000000149

23. Ross AGP, Olveda RM, Li Y. An audacious goal: the elimination of schistosomiasis in our lifetime through mass drug administration. Lancet. (2015) 385:2220–1. doi: 10.1016/S0140-6736(14)61417-3

24. Ezeama AE, Friedman JF, Acosta IP, Bellinger DC, Langdon GC, Manalo DL, et al. Helminth infection and cognitive impairment among filipino children. Am J Trop Med Hyg. (2005) 72:540–8. doi: 10.4269/ajtmh.2005.72.540

25. King CH, Dangerfield-Cha M. The unacknowledged impact of chronic schistosomiasis. Chronic Illn. (2008) 4:65–79. doi: 10.1177/1358802007071087

26. Egesa M, Lubyayi L, Tukahebwa EM, Bagaya BS, Chalmers IW, Wilson S, et al. Schistosomiasis and neglected tropical diseases: towards integrated and sustainable control and a word of caution. Parasitology. (2014) 141:1749–56. doi: 10.1017/S0031662214001259

27. Perrigoue JG, Marshall FA, Artis D. On the hunt for helminths: innate immune cells in the recognition and response to helminth parasites. Cellular Microbiology. (2008) 10:1757–1764. doi: 10.1111/j.1462-5822.2008.01174.x

Supplementary Table 2 | All included references: Papers included in the review.

Supplementary Table 3 | Details of Refs Populations, study design, phenotypes, and effects from studies.

Supplementary Table 4 | Genes in QTL. List of genes in QTL regions with lists of publications associated with each gene and schistosomiasis.

Supplementary Table 5 | VEP SNP Annotations. Functional annotation of SNP from candidate genes studies with the Ensembl Variant Effect predictor.

Supplementary Table 6 | TH17 genes. List of Genes in TH17 pathway with KEGG pathway diagram.

Supplementary Table 7 | TH17 SNP. List of potentially function SNP in genes in the TH17 pathway.
28. Grycz JM, Pearce E, Cheever A, Caulada ZA, Caspar P, Heiny S, et al. Egg deposition is the major stimulus for the production of Th2 cytokines in murine schistosomiasis mansoni. *J Immunol*. (1991) 146:1322–7.

29. Pearce EJ, M Kane C, Sun JF, Taylor J, McKee AS, Cervi L. Th2 response polarization during infection with the helminth parasite *Schistosoma mansoni*. *Immunol Rev*. (2004) 201:117–26. doi: 10.1111/j.0105-2896.2004.00187.x

30. de Oliveira Fraga LA, Torrero MN, Tocheva AS, Mitre E, Davies SJ. Induction of type 2 responses by schistosome worms during prepatent infection. *J Infect Dis*. (2010) 201:464–72. doi: 10.1086/649841

31. Joseph S, Jones FM, Kimani G, Mwatha JK, Kamau T, Kazibwe F, et al. Wilkins HA, Goll PH, Marshall TF, Moore PJ. Dynamics of *Schistosoma* 43. Kaplan MH, Whitfield JR, Boros DL. Th2 Cells are required for the 41. Butterworth AE, Capron M, Cordingley JS, Dalton PR, Dunne DW, 37. Mbow M, Larkin BM, Meurs L, Wammes LJ, de Jong SE, Labuda LA, et al. 33. Kaplan MH, Whitfield JR, Boros DL. Th2 Cells are required for the 45. Warren KS. Regulation of the prevalence and intensity of schistosomiasis in man: immunology or ecology? *J Infect Dis*. (1973) 127:595–609. doi: 10.1093/infdis/127.5.595

32. Lopes EP, Martins JRM, et al. New index for the diagnosis of *Schistosoma mansoni* eggs, drives Th2 responses. *J Exp Med*. (2009) 206:1673–80. doi: 10.1084/jem.20082460

33. Alves Oliveira LF, Moreno EC, Gazzinelli A, Martins-Filho OA, Silveira AMS, Gazzinelli A, et al. Cytokine production associated with periportal fibrosis during chronic schistosomiasis mansoni in humans. *Infect Immun*. (2006) 74:1215–21. doi: 10.1128/IAI.74.2.1215–2121.2006

34. Ruttytki LI, Stadecker MJ. Exacerbated egg-induced immunopathology in murine Schistosoma mansoni infection is primarily mediated by IL-17 and restrained by IFN-γ. *Eur J Immunol*. (2011) 41:2677–87. doi: 10.1002/eji.201041327

35. McManus DP, Dunne DW, Sacko M, Utzinger J, Vennervald BJ, Zhou XN. Schistosomiasis. *Nat Rev Dis Primers*. (2018) 4:138. doi: 10.1038/s41572-018-0013-8

36. Richter,J, Hatz,C, Campagne,G, Bequist,N, Jenkins,J. Ultrasonow in Schistosomiasis. *A Practical Guide to the Standardized Use of Ultrasonography for the Assessment of Schistosomiasis-Related Morbidity*. Niamey: WHO. (2000).

37. Corstjens PLAM, De Dood CJ, Kornelis D, Tjon Kon Fat EM, Wilson RA, Kariuki TM, et al. Tools for diagnosis, monitoring and screening of *Schistosoma* infections utilizing lateral-flow based assays and upconverting phosphor labels, *Parasitolology*. (2014) 141:1841–55. doi: 10.1002/spp2.1400662

38. Wooldhouse MEJ, Dye C, Etard JE, Smith T, Charlwood JD, Garnett GP, et al. Heterogeneities in the transmission of infectious agents: implications for the design of control programs. *PNAS*. (1997) 94:338–42. doi: 10.1073/pnas.94.1.338

39. Butterworth AE, Capron M, Cordingly JS, Dalton PR, Dunne DW, Kariuki HC, et al. Immunity after treatment of human *Schistosoma mansoni* infections utilizing lateral-flow based diagnostics. *Acta Radiol Open*. (2016) 5:2058460116686392. doi: 10.1177/2058460116686392

40. Wilkins HA, Goll PH, Marshall TF, Moore PJ. Dynamics of *Schistosoma mansoni* infection in a Gambian community. III. Acquisition and loss of infection. *Trans R Soc Trop Med Hyg*. (1984) 78:227–32. doi: 10.1097/00000035-9203(84)90283-9

41. 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.

42. Wilkins HA, Goll PH, Marshall TF, Moore PJ. Dynamics of *Schistosoma haematobium* infection in a Gambian community. III. Acquisition and loss of infection. *Trans R Soc Trop Med Hyg*. (1984) 78:227–32. doi: 10.1097/00000035-9203(84)90283-9

43. Bradley DJ, McCullough FS. Egg output stability and the epidemiology of *Schistosoma haematobium*. II. An analysis of the epidemiology of endemic *S. haematobium*. *Trans R Soc Trop Med Hyg*. (1973) 67:491–500. doi: 10.1097/00000035-9203(73)9080-1

44. Warren KS. Regulation of the prevalence and intensity of schistosomiasis in man: immunology or ecology? *J Infect Dis*. (1973) 127:595–609. doi: 10.1093/infdis/127.5.595

45. King CH, Kariuki HC, Kadzo H, Kocht DK, Magak P, Ouma JH, et al. Low heritable component of risk for infection intensity and infection-associated disease in urinary schistosomiasis among Wadigo village populations in Coast province, Kenya. *Am J Trop Med Hyg*. (2004) 70:57–62. doi: 10.4269/ajtmh.2004.70.57

46. Mbow M, Larkin BM, Meurs L, Wammes LJ, de Jong SE, Labuda LA, et al. Immunity after treatment of human immunity to schistosomiasis? *Infect Immun*. (2012) 80:4264–70. doi: 10.1128/IAI.00641-12

47. Demeure CE, Riher 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. doi: 10.1093/infdis/168.4.1000

48. Figueiredo JP, Oliveira RR, Cardoso LS, Barnes KC, Grant AV, Carvalho EM, et al. Adult worm-specific IgE/IgG4 balance is associated with low infection levels of *Schistosoma mansoni* in an endemic area. *Parasite Immunol*. (2012) 34:604–10. doi: 10.1111/pim.12001

49. Barreto AVMS, Alecrim VM, Medeiros TB de, Domingues ALC, Pereira TA, Syn WK, Pereira FEL, Lambertucci JR, Secor WE, Diehl AM. Serum osteopontin is a biomarker of severe fibrosis and portal hypertension in human and murine Schistosomiasis. *Int J Parasitol*. (2016) 46:829–32. doi: 10.1016/j.ijpara.2016.08.004
62. Pullan RL, Bethony JM, Geiger SM, Correa-Oliveira R, Brooker S, Quinnell RJ. Human helminth coinfection: no evidence of common genetic control of hookworm and Schistosoma mansoni infection intensity in a Brazilian community. Int J Parasitol. (2010) 40:299–306. doi: 10.1016/j.ijpara.2009.08.002

63. Gazzinelli A, Coelho L, Alves-Fraga L, Soares-Filho B, Williams-Blangero S, Bethony J, et al. Additive host genetic factors influence fecal egg excretion rates during Schistosoma mansoni infection in a rural area in Brazil. Am J Med Hyg. (2002) 67:336–43. doi: 10.4269/ajtmh.2002.67.336

64. Grant AV, Araujo MI, Ponte EV, Oliveira RR, Cruz AA, Barnes KC, et al. High heritability but uncertain mode of inheritance for total serum IgE level and Schistosoma mansoni infection intensity in a Schistosomiasis-Endemic Brazilian Population. J Infect Dis. (2008) 198:1227–36. doi: 10.1086/591946

65. Ellis MK, McManus DP. Familial aggregation of human helminth infection in the Poyang lake area of China with a focus on genetic susceptibility to schistosomiasis japonica and associated markers of disease. Parasitology. (2009) 136:699–712. doi: 10.1017/S003118200900612X

66. Spear RC, Zhong B, Kouch J, Seto EYW, Hubbard A. Genetic and environmental differences in the mountainous transmission areas of China. Am J Trop Med Hyg. (2005) 73:1145–50. doi: 10.4269/ajtmh.2005.73.1145

67. King, R.C, Stransfield, W.D. Dictionary of Genetics. Oxford: Oxford University Press. (1998).

68. King, R.C, Stransfield, W.D. Dictionary of Genetics. Oxford: Oxford University Press. (1998).

69. Müller-Myhsok B, Stelma FF, Guissé-Sow F, Muntau B, Thye T, Zinn-Justin A, Marquet S, Hillaire D, Dessein A, Abel L. Genome scan for genetic variation influencing the intensity of infection in a rural area in China. J Infect Dis. (2007) 196:2321–8. doi: 10.1086/503595

70. Gatlin MR, Black CL, Mwinzi PN, Secor WE, Karanja DM, Colley DG. An IL-13 promoter polymorphism associated with liver fibrosis in patients with Schistosoma japonicum infection. J Infect Dis. (2012) 206:662–70. doi: 10.1093/infdis/jis396

71. Antony JS, Ojurongbe O, Kremsner PG, Velavan TP. Lectin complement protein C11 (CL-K1) and susceptibility to urinary schistosomiasis. PLoS Negl Trop Dis. (2015) 9:e0003647. doi: 10.1371/journal.pntd.0003647

72. Tiongo RE, Paragas NA, Dominguez MJ, Lasta SL, Pandak JC, Pineda-Cortel MR. ABO blood group antigens may be associated with increased susceptibility to schistosomiasis: a systematic review and meta-analysis. J Helminthol. (2018) 94:e211. doi: 10.1017/S0022191X18001116

73. Ouf EA, Ojurongbe O, Akindele AA, Sina-Agbaje OR, Van Tong H, Adeyeye AO, et al. Ficolin-2 Levels and FCN2 genetic polymorphisms as a susceptibility factor in schistosomiasis. J Infect Dis. (2012) 206:662–70. doi: 10.1093/infdis/jis396

74. Long X, Daya M, Zhao J, Raafael N, Liang H, Potee J, et al. The role of ST2 and ST2 genetic variants in schistosomiasis. J Allergy Clin Immunol. (2017) 140:1416–22.e6. doi: 10.1016/j.jaci.2016.12.069

75. Martins da Fonseca CS, Pimenta Filho AA, dos Santos RS, da Silva CA, Domingues ACL, Owen JS, et al. Human plasma lipid modulation in schistosomiasis mansoni depends on apolipoprotein E polymorphism. PLoS ONE. (2014) 9:e101964. doi: 10.1371/journal.pone.0101964

76. Sertorio M, Hou X, Carmo RF, Dessein H, Cabantous S, Abdelwahed M, et al. Human plasma lipid modulation in schistosomiasis mansoni depends on apolipoprotein E polymorphism. PLoS ONE. (2014) 9:e101964. doi: 10.1371/journal.pone.0101964

77. Zhu X, Zhang J, Fan W, Gong Y, Yan J, Yuan Z, et al. MAPKAP1 rs10118570 polymorphism is associated with anti-infection and anti-fibroregeneration of urinary schistosomiasis japonica. Genet Test Mol Biomarkers. (2014) 18:646–50. doi: 10.1089/gene.2014.0098

78. Oliveira JB, Silva PCV, Vasconcelos LM, Gomes AV, Coelho MRC, Cahu GG, et al. Influence of polymorphism (-G308A) TNF-α on the peripheral fibrosis regression of schistosomiasis after specific treatment. Genet Test Mol Biomarkers. (2015) 19:598–603. doi: 10.1089/gene.2015.0091

79. Zheng Z, Li H, Yang L, Lu Y, Liu J, Sun Y, et al. IL-10 and IL-22 Polymorphisms in J. Immunol. (2012) 188:1188–97. doi: 10.4049/jimmunol.1200405

80. Long X, Daya M, Zhao J, Raafael N, Liang H, Potee J, et al. The role of ST2 and ST2 genetic variants in schistosomiasis. J Allergy Clin Immunol. (2017) 140:1416–22.e6. doi: 10.1016/j.jaci.2016.12.069

81. Martins da Fonseca CS, Pimenta Filho AA, dos Santos RS, da Silva CA, Domingues ACL, Owen JS, et al. Human plasma lipid modulation in schistosomiasis mansoni depends on apolipoprotein E polymorphism. PLoS ONE. (2014) 9:e101964. doi: 10.1371/journal.pone.0101964

82. Sertorio M, Hou X, Carmo RF, Dessein H, Cabantous S, Abdelwahed M, et al. Human plasma lipid modulation in schistosomiasis mansoni depends on apolipoprotein E polymorphism. PLoS ONE. (2014) 9:e101964. doi: 10.1371/journal.pone.0101964

83. Zhu X, Zhang J, Fan W, Gong Y, Yan J, Yuan Z, et al. MAPKAP1 rs10118570 polymorphism is associated with anti-infection and anti-fibroregeneration of urinary schistosomiasis japonica. Genet Test Mol Biomarkers. (2014) 18:646–50. doi: 10.1089/gene.2014.0098

84. Oliveira JB, Silva PCV, Vasconcelos LM, Gomes AV, Coelho MRC, Cahu GG, et al. Influence of polymorphism (-G308A) TNF-α on the peripheral fibrosis regression of schistosomiasis after specific treatment. Genet Test Mol Biomarkers. (2015) 19:598–603. doi: 10.1089/gene.2015.0091
95. Xiao Q, Yu H, Zhu X. The associations of hub gene polymorphisms in PI3K/AKT/mTOR pathway and Schistosomiasis japonica infection and hepatic fibrosis. Infect Genet Evol. (2020) 85:104423. doi: 10.1016/j.meegid.2020.104423
96. Manolio TA, Collins FS, Cox NJ, Goldstein DB, Hindorff LA, Hunter DJ, et al. Finding the missing heritability of complex diseases. Nature. (2009) 461:747–53. doi: 10.1038/nature08494
97. Mohamed-Ali Q, Elwali NE, Abdelhameed AA, Mergani A, Rahoud S, Elagib KE, et al. Susceptibility to periporal (Symmers) fibrosis in human Schistosoma mansoni infections: evidence that intensity and duration of infection, gender, and inherited factors are critical in disease progression. J Infect Dis. (1999) 180:1298–306. doi: 10.1086/314999
98. Desein AJ, Marquet S, Henri S, El Wali NE, Hillaire D, Rodrigues V, et al. Infection and disease in human Schistosoma mansoni are under distinct major gene control. Microbes Infect. (1999) 1:561–7. doi: 10.1016/S1286-4579(99)80096-3
99. Abath FGC, Morais CNL, Montenegro CEL, Wynn TA, Montenegro SML. Immunopathogenetic mechanisms in schistosomiasis: what can be learnt from human studies? Trends Parasitol. (2006) 22:85–91. doi: 10.1016/j.pt.2005.12.004
100. Schön MP, Erpenbeck L. The Interleukin-23/Interleukin-17 axis links infection, gender, and inherited factors are critical in disease progression. Front Immunol. (2018) 9:1323. doi: 10.3389/fimmu.2018.01323
101. Kimura A, Kishimoto T. IL-6: Regulator of Treg/Th17 balance. Eur J Immunol. (2011) 50:87–96. doi: 10.1007/s12026-011-8205-2
102. Mohamed-Ali Q, Elwali NE, Abdelhameed AA, Mergani A, Rahoud S, Elagib KE, et al. Low MBL-associated serine protease 2 (MASP-2) levels correlate with urogenital schistosomiasis in Nigerian children. Trop Med Int Health. (2015) 20:1311–9. doi: 10.1111/tmi.12551
103. Elsammak MY, Al-Sharkaweey RM, Ragab MS, Amin GM, Kandil MH. The Interleukin-13 promoter polymorphism associated with increased risk of allergic asthma. Genes Immun. (1999) 1:61–65. doi: 10.1038/sj.gei.636360
104. Elagib KE, et al. Susceptibility to periportal (Symmers) fibrosis in human Schistosoma mansoni infection and hepatic fibrosis. Infect Genet Evol. (2020) 85:104423. doi: 10.1016/j.meegid.2020.104423
105. Goenka S, Kaplan MH. Transcriptional regulation by STAT6. Nucleic Acids Res. (2012) 40:W452–7. doi: 10.1093/nar/gks539
106. Adzhubei IA, Schmidt S, Peshkin L, Ramensky VE, Gerasimova A, Bork P, et al. A method and server for predicting damaging missense mutations. Nat Methods. (2010) 7:248–249. doi: 10.1038/nmeth0410-248
107. van der Pouw Kraan T, van Veen A, Boeije L, van Tuyl S, de Groot E, Stapel S, et al. An IL-13 promoter polymorphism associated with increased risk of allergic asthma. Genes Immun. (1999) 1:61–65. doi: 10.1038/sj.gei.636360
108. Fonseca CT, Oliveira SC, Alves CC. Eliminating schistosomes through vaccination: what are the best immune weapons? Front Immunol. (2015) 6:1–8. doi: 10.3389/fimmu.2015.00095
109. Landrum MJ, Lee JM, Benson M, Brown GR, Chao C, Chitipiralla S, et al. ClinVar: improving access to variant interpretations and supporting evidence. Nucleic Acids Res. (2018) 46:D1062–7. doi: 10.1093/nar/gkx1153
110. Sim N-L, Kumar P, Hu J, Henikoff S, Schneider G, Ng PC. SIFT web server: predicting effects of amino acid substitutions on proteins. Nucleic Acids Res. (2012) 40:W452–7. doi: 10.1093/nar/gks539

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