Genetic Resistance to Malaria Is Associated With Greater Enhancement of Immunoglobulin (Ig)M Than IgG Responses to a Broad Array of Plasmodium falciparum Antigens

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Background. People of the Fulani ethnic group are more resistant to malaria compared with genetically distinct ethnic groups, such as the Dogon people, in West Africa, and studies suggest that this resistance is mediated by enhanced antibody responses to Plasmodium falciparum antigens. However, prior studies measured antibody responses to <0.1% of P. falciparum proteins, so whether the Fulani mount an enhanced and broadly reactive immunoglobulin (Ig)M and IgG response to P. falciparum remains unknown. In general, little is known about the extent to which host genetics influence the overall antigen specificity of IgM and IgG responses to natural infections.

Methods. In a cross-sectional study in Mali, we collected plasma from asymptomatic, age-matched Fulani (n = 24) and Dogon (n = 22) adults with or without concurrent P. falciparum infection. We probed plasma against a protein microarray containing 1087 P. falciparum antigens and compared IgM and IgG profiles by ethnicity.

Results. We found that the breadth and magnitude of P. falciparum-specific IgM and IgG responses were significantly higher in the malaria-resistant Fulani versus the malaria-susceptible Dogon, and, unexpectedly, P. falciparum-specific IgM responses more strongly distinguished the 2 ethnic groups.

Conclusions. These findings point to an underappreciated role for IgM in protection from malaria, and they suggest that host genetics may influence the antigen specificity of IgM and IgG responses to infection.

Keywords. antibodies; Dogon; Fulani; malaria; Plasmodium falciparum.

People of the Fulani ethnic group in West Africa are at lower risk of malaria compared with genetically distinct ethnic groups, such as the Dogon people, who live in the same geographic area and are exposed to similar biting rates of Plasmodium falciparum-infected mosquitoes [1]. Because of the strong selective pressure imposed by the mortality associated with P. falciparum infection in children and pregnant women, malaria has had a significant impact on the human genome [2]. However, the classical red blood cell (RBC) variants associated with protection from malaria such as hemoglobin S and C, G6PD deficiency, and ABO blood group polymorphisms do not fully explain the difference in malaria susceptibility between the Fulani and Dogon, because these RBC variants do not appear to be enriched in the Fulani [3]. Although the mechanisms conferring enhanced protection against malaria in the Fulani have yet to be precisely determined, prior studies show that the Fulani tend to have higher levels of P. falciparum-specific immunoglobulin (Ig)M [4] and IgG [1, 4–8] antibodies relative to levels in sympatric ethnic groups—findings consistent with the observation that the Fulani
have a higher percentage of activated memory B cells and plasma cells [9]. However, studies that have compared antibody responses of the Fulani and sympatric ethnic groups measured responses to either crude lysate of blood-stage parasites [1,10] or a very small number of recombinant *P.falciparum* proteins (eg, circumsporozoite protein, thrombospondin-related adhesive protein, and merozoite surface protein 1) [5–7], which together comprise <0.1% of the 5000+ predicted *P. falciparum* proteins. This leaves open the question of whether the Fulani generate a higher and more broadly reactive IgM and IgG response to a wide range of *P. falciparum* antigens—particularly antigens to which antibody responses have been associated with protection from malaria, as shown in other studies [11–14].

In this study, we compared the breadth and magnitude of *P. falciparum*-specific IgM and IgG responses in the Fulani and Dogon ethnic groups with a microarray containing 1087 *P. falciparum* proteins. In particular, we investigated the extent to which host genetic background influences the overall antigen specificity of IgM and IgG responses to a defined pathogen.

**MATERIALS AND METHODS**

**Study Site and Participants**

This study was conducted in Mantéourou, Mali, approximately 850 km north of Bamako [1]. Participants were randomly selected from a cohort study described in detail elsewhere [15,16]. Age-matched adults of the Fulani (n = 24) and Dogon (n = 22) ethnic groups were included. As is typical in Mali, *P. falciparum*-infected adults had no symptoms of malaria when blood smears were prepared. A research team, including a physician, was based in the health center at the study site. The physician conducted a medical history and physical examination at the time of the venipuncture to determine whether signs and symptoms of malaria or other illnesses were present. The physical examination included measurement of axillary temperature and spleen size (graded by the Hackett score). Clinical data were recorded on a standard case report form for each subject.

The Ethics Committee of the Faculty of Medicine, Pharmacy, and Odonto-Stomatolasy at the University of Bamako, Mali approved this study. Written, informed consent was obtained from study participants. Deidentified specimens were obtained from this study for immunological analyses. The National Institutes of Health (NIH) Office of Human Subjects Research Protections determined that the analyses conducted at the NIH on deidentified specimens were excluded from National Institute of Allergy and Infectious Diseases/NIH Institutional Review Board (IRB) review.

Plasma samples from healthy US adults were obtained through the University of California Institute of Clinical and Translational Science (ICTS) Normal Blood Donor program. This program provides a source of normal human blood to University of California investigators whose projects have been approved by the University of California ICTS Scientific Review Committee and the University of California IRB.

**Plasma Isolation**

Blood samples were drawn by venipuncture into sodium citrate-containing cell preparation tubes (BD). Plasma was isolated according to manufacturer’s instructions and kept frozen at –80°C.

**Measurement of *Plasmodium falciparum* Parasitemia**

Thick blood smears were stained with Giemsa solution and counted against 300 leukocytes. *Plasmodium falciparum* densities were recorded as the number of asexual parasites/µL of blood based on an average leukocyte count of 7500/µL. Each smear was evaluated separately by 2 expert microscopists, and discrepancies were resolved by a third expert microscopist.

**Plasmodium falciparum Protein Microarray**

Protein microarrays (Antigen Discovery Inc., Irvine, CA) containing 1087 sequence-verified *P.falciparum* polypeptides were generated using an in vitro transcription translation reaction (RTS 100 Escherichia coli HY kits; Roche) as described previously [17]. Due to gene length, some proteins were printed on the microarray in multiple spots of overlapping polypeptides representing 861 unique full-length *P. falciparum* proteins. The protein expression efficiency of the in vitro reactions was 98.7%. The proteins included were down-selected from larger microarray studies in which these proteins were consistently immunoreactive in adults living in malaria-endemic areas [18,19].

For probing, plasma samples were (1) diluted 1:100 in Protein Array Blocking buffer (Whatman Inc, Sanford, ME) supplemented with DH5α *E. coli* lysate (MCLAB, San Francisco, CA) at 20% (vol/vol) for IgM probing and 10% for IgG and (2) incubated on arrays overnight at 4°C. Preabsorption with *E. coli* lysate is necessary to block anti-*E. coli* antibodies [17]. Microarray slides were then incubated in biotin SP-conjugated affinity-purified goat antihuman IgM (Fc5µ fragment-specific) or IgG (Fcγ fragment-specific) secondary antibodies (Jackson ImmunoResearch, West Grove, PA) and detected with streptavidin-conjugated SureLight P-3 (Columbia Biosciences, Columbia, MD) both diluted 1/400 in blocking buffer without lysate. Slides were washed and air-dried by brief centrifugation. Probed array slides were scanned in a GenePix 4200 confocal laser scanner at a wavelength of 670 nm, at 30% laser power and 300 and 330 photo multiplier tube for IgM and IgG, respectively. The output gray-scale TIFF files generated by the scanner were quantitated using ProScanArray Express software (PerkinElmer, Waltham, MA) with spot-specific background correction.

**Statistical Analysis**

Protein microarray data were analyzed using the R Project for Statistical Computing. Median foreground intensity 635 nm
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RESULTS

Subject Characteristics
Twenty-four Fulani adults and 22 age-matched Dogon adults living in the same village in Mali were included in this study. Demographic data and Plasmodium falciparum infection status of these individuals are shown in Table 1. The median age of Fulani subjects was 37 years (range: 21–57 years) and 38% were female. The median age of Dogon subjects was 39.5 years (range: 22–57 years) and 45% were female. At the time of blood collection, 4 Fulani (17%) and 9 Dogon (41%) were infected with Plasmodium falciparum by blood-smear. Of those infected, median parasite densities for the Fulani and Dogon were 2375 (range: 700–3675) and 2900 (range: 375–4725) asexual parasites/µL, respectively. All subjects were afebrile and asymptomatic at the time of the blood draw.

Breadth of Plasmodium falciparum-Specific Immunoglobulin (Ig)M and IgG Response Is Higher in Fulani Versus Dogon
We first compared the breadth of P. falciparum-specific IgM responses in the Fulani versus Dogon, irrespective of P. falciparum infection status. Breadth was defined for each plasma sample as the number of antigens to which the level of IgM reactivity exceeded 2 SDs above the negative (NoDNA) control. On average, IgM breadth was significantly higher in the Fulani (Figure 1A; Fulani mean: 317 [SD = 253]; Dogon mean: 81 [SD = 89]; P < .001). Among uninfected subjects, IgM breadth was also significantly higher in the Fulani (Figure 1B; Fulani mean: 280 [SD = 243]; Dogon mean: 74 [SD = 117]; P < .001); and likewise, among infected subjects, the average IgM breadth was significantly higher in the Fulani (Figure 1B; Fulani mean: 504 [SD = 429]; Dogon mean: 81 [SD = 89]; P = .011). Although the difference in mean IgM breadth from infected to uninfected subjects was larger in the Fulani (504–317 = 187 antigens) than Dogon (81–77 = 4 antigens), this difference was not significant (P = .75), possibly because of the small number of infected Fulani subjects.

We then examined the breadth of P. falciparum-specific IgG responses for all subjects irrespective of P. falciparum infection status. The average IgG breadth was significantly higher in the Fulani (Figure 1C; Fulani mean: 592 [SD = 253]; Dogon mean: 412 [SD = 204]; P = .014). Among uninfected subjects, IgG breadth was higher in the Fulani, but not significantly so (Figure 1D; Fulani mean: 603 [SD = 251]; Dogon mean: 443 [SD = 207]; P = .30), and among infected subjects, the average IgG breadth was also higher in the Fulani but not significantly so (Figure 1D; Fulani: 534

Table 1. Characteristics of Study Subjects by Ethnic Group

|                | Fulani | Dogon | P Value |
|----------------|--------|-------|---------|
| Age, median in years (range) | 37 (21–57) | 39.5 (22–57) | .77a |
| Gender (% female) | 9 (38%) | 10 (45%) | .77b |
| Plasmodium falciparum smear positive (%) | 4 (17%) | 9 (41%) | .10b |
| Asexual parasites/µL among smear positive, median (range) | 2375 (700–3675) | 2900 (375–4725) | .59a |

a Wilcoxon rank-sum test.  
b Fisher’s exact test.
Contrary to what we observed for IgM, the mean IgG breadth was lower in infected versus uninfected subjects for both the Fulani and Dogon, although the decrease was not significant in either case (Figure 1D). Therefore, the breadth of both IgM and IgG responses was higher in the Fulani versus the Dogon, but the greatest difference between the 2 groups was in the breadth of the IgM response.

**Fulani Immunoglobulin M Exclusively Recognizes a Greater Proportion of *Plasmodium falciparum* Antigens**

We defined IgM and IgG “recognized” antigens as those to which the level of IgM or IgG reactivity, respectively, exceeded 2 SD above the negative control in at least 1 subject. Supplementary Table 1 lists IgM- and IgG-recognized antigens. Of 999 IgM-recognized antigens, both the Fulani and Dogon responded to 565, whereas 432 antigens were exclusively IgM-recognized in the Fulani, and 2 antigens were exclusively IgM-recognized in the Dogon. Eighty-eight antigens were not IgM-recognized in any samples (Figure 2A). Of the 1070 IgG-recognized antigens, both the Fulani and Dogon responded to 1006, whereas 54 were exclusively IgG-recognized in the Fulani, and 10 exclusively IgG-recognized in the Dogon. Only 17 antigens were not IgG-recognized in any samples (Figure 2B). Thus, the Fulani recognized most of the 1087 *P. falciparum* antigens on the protein microarray, and IgM of the Fulani bound to a far greater number of *P. falciparum* antigens than did those of the Dogon (almost half of the antigens recognized by the Fulani IgM samples were not recognized by the Dogon IgM samples). Although a trend to a similar difference in responsiveness was evident in the IgG response, it was far less impressive than that seen with IgM.
Magnitude of Plasmodium falciparum-Specific Immunoglobulin (Ig)M and IgG Responses Is Higher in Fulani Versus Dogon

Next, we compared the overall level of IgM reactivity to the 1087 antigens by ethnicity irrespective of P. falciparum infection status. The sum of positive IgM log2-transformed intensity values was significantly higher in the Fulani (Figure 3A; Fulani mean: 1747 [SD = 617]; Dogon mean: 1339 [SD = 488]; P = .00174). We also compared uninfected subjects and found that the sum of positive IgG log2-intensity values was higher in the uninfected Fulani versus Dogon, but this was not significant (Figure 3D; Fulani mean: 1789 [SD = 626]; Dogon mean: 1400 [SD = 502]; P = .22). Among infected subjects, IgG reactivity was also higher in the Fulani, but this was not significant (Figure 3D; Fulani mean: 1538 [SD = 603]; Dogon mean: 1252 [SD = 483]; P = .83). In contrast to IgM responses, the mean sum of IgG log2-intensities decreased from uninfected to infected subjects in the Fulani and Dogon. Although the decrease was greater for the Fulani (1538–1789 = −251) versus Dogon (1252–1400 = −148), this difference was not significant (P = .96).

Next, we compared the magnitude of IgM and IgG reactivities in the Fulani versus Dogon on an antigen-by-antigen basis using empirical Bayes moderated t tests. Any antigen that was not reactive (mean antigen intensity < mean + 2SD of the NoDNA control spots) in at least 10% of all 46 samples (ie, reactive in at least 5 samples) was removed from individual tests. For IgM data, 697 of 1087 antigens passed the filtering process and 667 antigens (96%) yielded statistically significant differences in IgM log2-intensity between Fulani and Dogon samples (Figure 4A), all of which were higher in the Fulani. For IgG data, 981 of 1087 antigens passed the filtering process, but only 227 (23%) yielded statistically significant differences in IgG log2-intensity between the Fulani and Dogon (Figure 4B), 97% of which were higher in the Fulani.

We then focused on 20 antigens to which antibody levels have been correlated with protection from malaria in studies conducted in other malaria-endemic settings [11–14, 20, 21] (Supplementary Table 2). Of the 19 antigens that passed the IgM reactivity filter described above, the average level of IgM reactivity to each antigen was significantly higher in the Fulani after adjusting for multiple comparisons (Figure 4C). The average level of IgG reactivity was also higher in the Fulani for 17 of 20 antigens, but, in contrast to the IgM response, only 1 of these 17 was statistically significant after adjusting for multiple comparisons (Figure 4D). These data suggest (1) that IgM responses play an underappreciated role in conferring resistance to malaria in the Fulani and (2) that host genetics influence the overall antigen specificity of IgM and IgG responses to malaria.

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DISCUSSION

People of the Fulani ethnic group are at lower risk of malaria compared with ethnic groups such as the Dogon people who live in the same geographic area and are exposed to similar biting rates of *Plasmodium falciparum*-infected mosquitoes [1]. In general, IgG is known to play a critical role in protection from blood-stage malaria, and prior studies using small numbers of *P falciparum* antigens (<0.1% of 5000+ *P falciparum* proteins) have shown that the Fulani tend to have higher IgM and IgG responses [5–7]. The question addressed here is whether the Fulani mount a stronger and more broadly reactive IgM and IgG response to a wide range of *P falciparum* antigens—particularly antigens to which antibody responses have been associated with protection from malaria in other studies [11–14]. In particular, we sought to better understand the extent to which host genetics influences the overall specificity of IgM and IgG responses to infection.

We found that Fulani adults mount a stronger and more broadly reactive IgM and IgG response to a diverse array of *P falciparum* antigens compared with Dogon adults. Moreover, the breadth and magnitude of IgM rather than IgG responses more strongly distinguished the Fulani and Dogon, particularly for responses to blood-stage antigens that were previously associated with protective antibodies [11–14]. This finding suggests that IgM responses play an underappreciated role in protection from malaria.

Surprisingly little is known about the role of IgM in human malaria. The binding of nonimmune or “natural” IgM to the surface of *P falciparum*-infected RBCs (iRBCs) has been implicated in RBC rosetting (binding of iRBCs to uninfected RBCs) and certain severe malaria syndromes [22–25], including
placental malaria [26, 27]. The binding of nonimmune IgM to iRBCs appears to only occur with certain *P. falciparum* strains [24] and is mediated through binding of a particular subset of the parasite variant surface antigen *P. falciparum* erythrocyte membrane protein 1 ( PfEMP1) to the Cµ4 domain of the Fc portion of the human IgM heavy chain [23, 28, 29]. The binding of nonimmune IgM to PfEMP1 on the surface of iRBCs may mask protective IgG epitopes without compromising PfEMP1 function [27]. In contrast, *Plasmodium*-specific IgM has been shown to limit parasite replication in mouse models of malaria [30, 31], but the role of specific IgM in human malaria remains unclear. Our finding in this study—that the breadth and magnitude of IgM rather than IgG responses to *P. falciparum* more strongly distinguish the malaria-resistant Fulani from the susceptible Dogon—suggests that IgM may play a more important role in protection from malaria than previously thought. This observation warrants further longitudinal studies of the role of IgM in natural *P. falciparum* infection, as well as in malaria vaccine trials in the field and in the context of controlled human malaria infection [32, 33]—particularly since both naturally acquired and vaccine-induced immunity to malaria tend to be short-lived in the absence of parasite exposure [34].

The findings of this study also have implications for understanding how host genetic factors shape the specificity of antibody responses to infections. The malaria-resistant Fulani

**Figure 4.** Greater enhancement of immunoglobulin (Ig)M than IgG responses to individual *Plasmodium falciparum* antigens in the Fulani compared with the Dogon. The average magnitude of IgM responses (log2-intensity values) to 697 individual antigens is shown for Fulani and Dogon subjects (A). The average magnitude of IgG responses (log2-intensity) for 981 individual antigens is shown for Fulani and Dogon adults (B). Shown is the average magnitude of IgM (C) and IgG (D) responses (log2-intensity values) for Fulani and Dogon subjects to individual antigens to which IgG levels have been correlated with protection from malaria in other studies. For each plot, the antigens are sorted on the Dogon subjects by decreasing intensity from left to right. Dashed black lines indicate the cutoff for statistically significant differences in antibody reactivity for individual antigens between the Fulani and Dogon. *P* values were determined by empirical Bayes moderated *t* tests from the limma R package library with false-discovery rate adjustments for multiple tests among the antigens. Data are shown as means.
generated a markedly enhanced and more broadly reactive IgM response to malaria compared with the malaria-susceptible Dogon. There are many possible genetic changes that could alter the malaria-specific IgM and IgG repertoires of the Fulani and Dogon, including changes in the V gene repertoire and somatic hypermutation [35] as well as major histocompatibility complex allele profiles. Another possibility is that the selective pressure of malaria led to mutations in the Fulani that inactivated the expression of certain self-antigens that cross-react with *P. falciparum* antigens, allowing the Fulani to maintain B cells that would otherwise be eliminated as autoreactive. In contrast, the malaria-susceptible Dogon may have eliminated these autoreactive but potentially protective IgM⁺ B cells. In support of this hypothesis, a study in mice deficient for the UDP-galactose:β-galactoside-α1-3-galactosyltransferase (α1,3GT) gene—which ablates the expression of the Galα1-3Galβ1-4GlcNAc-R (α-gal) glycan and allows for the production of anti-α-gal antibodies in response to gut commensals—showed that anti-α-gal IgM antibodies target α-gal-expressing *Plasmodium* sporozoites for complement-mediated destruction in the skin after inoculation by *Anopheles* mosquitoes [36]. In this context, we hypothesize that the Fulani may have lost the ability to express certain self-antigens that are also made by pathogens, and as a result they can produce antibodies that other ethnic groups such as the Dogon cannot [37, 38]. What might expand this population of cross-reactive B cells? Although the Fulani are considered to live sympatrically with the Dogon, the diet of the Fulani differs from that of the Dogon, and it includes high amounts of milk and cultured milk products [39]. Such foods may shift the composition of the gut microbiota of the Fulani [40], thereby exposing them to commensals that drive the production of T cell-independent IgM antibodies that cross-react with malaria antigens.

A limitation of this study is the interpretation of antibody breadth, defined for each sample as the number of antigens to which IgM or IgG reactivity exceeded 2 SD above the negative control. It is possible that IgM and IgG antibodies are present in plasma samples at levels below this cutoff, leading to underestimates of breadth in some samples. Additional studies involving serial dilutions of plasma samples will explore this possibility. Another limitation is the lack of data on past *P. falciparum* exposure. It remains possible that the higher IgM and IgG responses of the Fulani are due to more intense and/or recent *P. falciparum* exposure. However, the Fulani and Dogon groups were age-matched and live in sympathy in a small village, and, moreover, IgM and IgG responses were higher in the uninfected Fulani compared with the infected Dogon. It is possible that blood smear-negative subjects harbored subpatent *P. falciparum* infection (polymerase chain reaction [PCR] positive). Unfortunately, only blood smears and plasma were available from these archived samples so PCR was not done. However, the breadth and magnitude of IgM and IgG responses tended to be higher in the blood smear-negative Fulani compared with the blood smear-positive Dogon; therefore, even if the blood smear-negative Fulani were PCR+ (subpatent parasitemia), their antibody responses were higher than the blood smear-positive Dogon who presumably had higher (patent) parasitemias.

**CONCLUSIONS**

In summary, we found that IgM and IgG responses to *P. falciparum* are enhanced and more broadly reactive in the malaria-resistant Fulani compared with the malaria-susceptible Dogon, and, unexpectedly, the breadth and magnitude of the IgM response more strongly distinguished these 2 ethnic groups. These findings suggest that IgM may play an underappreciated role in protection from malaria, and they also raise the intriguing possibility that the selective pressure of malaria has resulted in host genetic polymorphisms that yield more robust and protective IgM responses in certain ethnic groups.

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**Potential conflicts of interest.** P. L. F. has an equity interest in Antigen Discovery, Inc., which is developing products related to the research described in this paper. In addition, this author serves on the advisory board of ADI and receives compensation for these services. The terms of this arrangement have been reviewed and approved by the University of California in accordance with its conflict of interest policies. D. H. D. has an equity interest in Antigen Discovery and receives compensation for services. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been closed.

**Supplementary Material**

Supplementary material is available online at Open Forum Infectious Diseases (http://OpenForumInfectiousDiseases.oxfordjournals.org/).

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