POlymorphisms in Fc Gamma Receptors and Susceptibility to Malaria in an Endemic Population

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Repeated infections by Plasmodium falciparum result in a humoral response that could reduce disease symptoms and prevent the development of clinical malaria. The principal mechanism underlying this humoral response is that immunoglobulin G (IgG) binds directly to the parasites, thus causing their neutralization. However, the action of antibodies alone is not always sufficient to eliminate pathogens from an organism. One key element involved in the recognition of IgG that plays a crucial role in the destruction of the parasites responsible for spreading malaria is the family of Fc gamma receptors. These receptors are expressed on the surface of immune cells. Several polymorphisms have been detected in the genes encoding these receptors, associated with susceptibility or resistance to malaria in different populations. In this review, we describe identified polymorphisms within the family of Fc gamma receptors and the impact of these variations on the response of a host to infection as well as provide new perspectives for the design of an effective vaccine for malaria.

Keywords: Fc gamma receptors, polymorphism, malaria, immunoglobulin G, susceptibility

INTRODUCTION

Despite the progress made against malaria, this disease remains a major public health concern, particularly in sub-Saharan Africa (sSA) (1). Indeed, 405,000 malaria-related deaths were reported in 2018, with 94% of them in sSA (2). In malaria-endemic regions, there are populations that present some resistance to the disease (3). In fact, Plasmodium falciparum, the main malaria parasite...
in sSA, is considered to be one of the most important evolutionary forces causing the appearance of several alleles giving the host some protection (4). Natural selection is a process explaining how individuals of a species living in a given environment will tend to exhibit a certain suitability for that environment (5). This principle is believed to be the cause of a larger proportion of individuals with the βS allele in sSA compared to those living in Europe. Indeed, although this allele in homozygotes is associated with hemolytic anemia as well as unpredictable episodes of pain and generalized organ damage, all of which could be life-threatening for the carrier, it does appear in heterozygous individuals to be associated with a 90% greater chance of not developing severe malaria (6).

Understanding the mechanism behind the low susceptibility levels of particular individuals to malaria infection could allow us to develop new tools for controlling such infection. Several association studies have revealed human genes that can generate populations some resistance to malaria (7). Such has been the case for Fc gamma receptor (FCGR) genes. These genes are in major part localized in an area that is peripheral to the centromere, specifically in the q23 area of chromosome 1 (8). They constitute, therefore, a cluster encoding a number of proteins involved in recognizing the Fc domains of antibodies that bind pathogenic antigens (9). The implications of specific gene clusters for innate and adaptive immunity are of particular interest for those developing new strategies to control disease.

However, the polymorphisms detected within the FCGR genes have been associated with either susceptibility or resistance to malaria. Indeed, the selection phenomenon induced by a pathogen does not always result in the elimination of alleles conferring susceptibility to the host but very often leads to the maintenance of resistance and susceptibility alleles (10). This process leads, therefore, to genetic variability in the population affected by the phenomenon known as balancing selection. This phenomenon may be the source of the difficulty in establishing, in classical association studies, the real influence of a mutation or an allele on the response to malaria (11). Thus, the same allele could be associated with susceptibility in some cases and resistance in others depending on whether or not another allele having an impact on malaria response is present (12).

The United States Food and Drug Administration first authorized the use of antibodies for certain diseases, including cancer, in 1986 (13). Several antibodies have been tested in clinical trials in an effort to combat human immunodeficiency virus (HIV) infection (14) and no antibodies have been approved for the treatment of malaria treatment as of yet (15). Recent studies, each performed in an animal model, showed that the passive administration of anti-tumor antibodies could induce long-term protection via a mechanism involving the maturation of dendritic cells and the presentation of tumor antigens to T cells (16). If successfully applied to humans, this approach could improve the efficacy of candidate vaccines for the prevention of malaria. It is therefore necessary to identify polymorphisms in FCGR genes that are associated with susceptibility and resistance to malaria in endemic areas.

In this review, we describe the known polymorphisms within the FCGR family of genes and the impact of these variations on the response of the host to infection, as well as provide new perspectives for the design of an effective vaccine against malaria.

**FCGR GENES AND THEIR EVOLUTION**

The FCGR genes are known to form a cluster on human chromosome 1 (17). These genes code for glycoprotein receptors on the surface of immune cells including B cells, macrophages, natural killer (NK) cells and dendritic cells (DCs) (9). Previous research has identified three classes of Fc receptors in humans, including FcγRI, FcγRII and FcγRIII, with each class containing a range of different isoforms. The FcγRI class features the FcγRIA, FcγRIIB and FcγRIC isoforms, while the FcγRII class features the FcγRIIA, FcγRIIB and FcγRIIC isoforms. The FcγRIII class features the FcγRIIIA and FcγRIIIB isoforms (9).

The family of FCGR genes as described by Hargreaves et al. (18) first appeared millions of years ago in our common ancestor with bony fish. FCGR2 and FCGR3 have been hypothesized to be the first genes to appear on the long arm of chromosome 1 (band q23-24) (19, 20). These genes subsequently experienced duplications leading to new isoforms that were initially identical but subsequently diverged, thus giving rise to the FCGR2A and FCGR2B genes prior to the process of divergence that ultimately led to primates (21). In contrast, the FCGR3A and FCGR3B genes are thought to have been generated during the divergence of humans and chimpanzees approximately 6 million years ago (22). Later, the FCGR3B gene experienced structural changes in its promoter and transmembrane regions (22, 23), thus resulting in copy number variations that are characteristic of this gene. The FCGR2C gene may have formed as a result of an unequal crossing over of FCGR2A and FCGR2B genes (21). The FCGR1 gene first appeared after the FCGR2 and FCGR3 genes; the exact period of this event remains unknown although a previous study did show this gene to be absent in the genome of the opossum (19, 20). Maresco et al. (24) further suggested that the ancestor of the FCGR1 genes later experienced a duplication that led to the three isoforms that exist to this day, namely FCGR1A, FCGR1B and FCGR1C. The same authors also hypothesized that an inversion may have initially located FCGR1B in the centromeric area (1p12 area of the chromosome) and later led to the FCGR1A and FCGR1C isoforms located in the 1q21 area of chromosome 1.

**THE STRUCTURE AND FUNCTION OF FC GAMMA RECEPTORS**

Fc gamma receptors can be structurally considered either as activating receptors (such as FcγRI, FcγRIIA, FcγRIIC and FcγRIIIA) that each have an immunoreceptor tyrosine-based
activation motif (ITAM) or inhibitory receptor (FcγRIIB) that contain an immunoreceptor tyrosine-based inhibitory motif (ITIM) (25). These intracytoplasmic regions can either be located on a transducing chain (as is the case of the FcγRI and FcγRIIA receptors) or they may represent an integral component of the receptors (as is the case of FcγRIIA and FcγRIIC). The FcγRIIB receptor, while it interacts with other receptors, is the only receptor that does not adopt a mechanism involving signal transduction. Receptors of the FcγRI family are expressed by monocytes, macrophages, neutrophils and dendritic cells. The FcγRIIA receptor is expressed by the same cells as the FcγRIIB receptor and can also directly activate blood platelets. In addition, the FcγRIIC and FcγRIIIA receptors are able to activate NK cells while FcγRIIB can activate neutrophils and eosinophils (26).

The receptor activation process begins after the antibodies that opsonize parasites are recognized by a specific receptor. This recognition results in an aggregation of the activating receptors that bind the pathogens. This process is then followed a phosphorylation of the two tyrosine (Y) residues of ITAM (the consensus sequence of ITAM motif being Yxx[L/I]x(6–8)Yxx[L/I]; with x representing any amino acid residue) by Src family tyrosine protein kinases (27, 28). This phosphorylation permits the recruitment of two Src-homology 2 (SH2) domains of the Syk tyrosine kinase in the docking sites formed by both phosphotyrosines and the space between them (29–31). Activated receptors are involved in a wide range of activities, including phagocytosis, the respiratory burst, the production of cytokines by macrophages and DCs, antibody-dependent cell cytotoxicity (ADCC), and the degranulation of neutrophils and NK cells (32, 33). However, it has been observed in some specific circumstances that the ITAM motif responsible for activating the receptors could exhibit inhibitory functions, denoted as ITAMI (ITAM-mediated inhibitory signal) (34). This change is due to a particular reaction in which there is phosphorylation of only one of the two tyrosine residues of the receptor in the presence of the kinase Src (35). Two juxtaposed receptors carrying an ITAM motif and each motif having only one of their tyrosine residues phosphorylated would in this case be able to bind tandem SH2 domains of the SH2-domain containing protein tyrosine phosphatase 1 (SHP-1) (34, 35). A binding comparable to that formed between two ITIM motifs and SHP1 is obtained—causing Lyn phosphorylation of tyrosine at position 536 and regulating SHP-1 phosphatase and inhibiting cell activation (36). This particular inhibition of ITAM-like receptors would have as an effect reduction of inflammation in animals and would serve as a basic mechanism for controlling the activation of both FcγRIIA and FcγRIIIA receptors (35, 37).

Another mechanism for the inhibition of the activating receptor involves the inhibitory receptor (FcγRIIB), which presents an ITIM motif with only one tyrosine residue [I/V/L/S]xYxx[L/V] (27). This receptor is highly expressed in B cells and can inhibit the activation of signals induced by B-cell receptors (BCRs) and hence regulate their effects (38). During this process, the ITIM motif, characterized by the presence of a single tyrosine, is phosphorylated by the protein tyrosine kinase (PTK) Src which allows the recruitment of the two SH2 domains from the proteins inositol phosphatase 1 and 2 (SHIP-1 and SHIP-2) (27). This recruitment leads to a cascade of events, in turn leading to inhibition of Ig-calcium flux (39), the dephosphorylation of the activating receptor, and as a result to its inactivation (40). Thus, the inhibitory action of FcγRIIB receptors requires the co-ligation of an inhibitory and activating receptor via an immune complex (27). However, although the scientific community entirely accepts the idea that the FcγRIIB receptor is able to inhibit activating receptors of the BCR type, some studies question the ability of FcγRIIB to inhibit phagocytic activity of myeloid cells (40). Indeed, by an mRNA splicing of exon C1 leading to the form of FcγRIIB called FcγRIIB2 instead of the form FcγRIIB1 of B cells (34), the FcγRIIB receptor can be also expressed in monocytes, macrophages, neutrophils, and dendritic cells. During phagocytosis induced in transfected Chinese hamster fibroblast cells, the inhibitory FcγRIIB receptors have been shown to be at least half as numerous as the activating FcγRIIA receptors (41). However, these authors showed that an equi-proportional amount of the two types of receptors would be required to allow inhibition. The low number of the inhibitory FcγRIIB compared to the activating FcγRIIA receptors could thus affect the ability of FcγRIIB to inhibit the activity of FcγRIIA receptors (41). Do these observations indicate that the preferential mechanism of inhibition of FcγRIIA is that involving the ITAMI? Perhaps, but it could be noticed that some mutations suppressing the inhibitor receptor have been associated with increasing macrophage phagocytosis of Plasmodium (42). Moreover, the mechanism called “inside-out control” and well reviewed by Koenderman et al. (43) could be explained how FcγRIIB apparently in low number succeed to inhibit FcγRIIA’s activity. Indeed, by modulating the affinity, i.e., the strength of the receptor for its ligand, modulating the valency or the engagement of multiple receptors, modulating the interaction with the signal chains, the other receptors, or their localization in the various membranes, it is possible to regulate the function of the receptors. Different mechanisms are therefore involved. FcγRI receptors, which normally bind monomeric antibodies, can be activated and bind immune complexes by the action of the phosphatase PP2A, an enzyme involved in the dephosphorylation of FcγRI receptors, and probably by the lateral movement of the receptor in the membrane (44). For FcγRIIA receptors, the engagement of mitogen-activated protein kinase kinases (MEK-MAPK) has been indicated to be involved in the activation of the receptor (45) as far as the level of expression of the tail of the receptor (46, 47). The expression of the FcγRIIA receptor has been indicated to be influenced by the glycosylation. The review by Koenderman et al. (43) mentioned that an ectopically expressing tail-less version of FcγRIIB could weaken the signal response. Again, some studies have shown that a mutation in FCGR2C genes to a stop codon leads to the expression of FcγRIIB in NK cells with consequences of inhibiting its function (34, 48). Finally, the authors mentioned that “inside-out control” of Fcγ receptors.
could also be achieved by receptors others than Fcγ receptors (toll-like receptor, cytokine/chemokine receptors, glucan receptors) (49–51).

**METHODS FOR IDENTIFYING POLYMORPHISMS IN FCGR GENES**

Several methods have been used to investigate the association between polymorphisms in the FCGR genes and the immune response to malaria. This topic was recently reviewed by Hargreaves et al. (18). The simplest approach uses the polymerase chain reaction (PCR) in combination with restriction enzyme digestion; this process is known as allele-specific restriction enzyme digestion (ASRED) and is able to differentiate alleles and single nucleotide polymorphisms (SNPs) or single nucleotide variants (SNVs). A SNP is a substitution occurring in at least 1% in the general population and an SNV is a variation of a single nucleotide without limitation of frequency (52–54). The advantages of this method are that it is relatively inexpensive and easy to perform (55). However, the high similarity of genes within the same specific cluster can make it very difficult to design primers that are able to amplify specific regions of the target DNA.

An alternative strategy uses the TaqMan assay (Life Technologies, Paisley, UK) to identify SNPs within a family cluster (18). This method uses a probe with a fluorescent dye on the 5′-end, while a nonfluorescent quencher on the 3′-end inhibits the fluorescence. The probe, once added to a sample of human DNA, would hybridize to the target sequence, if present. During the elongation step of the PCR reaction, the Taq polymerase cleaves the 5′-end of the probe, thus liberating the dye from the quencher and fluorescing light that can be detected, thus confirming the efficacy of the reaction. The TaqMan assay has been used successfully to determine the distribution of FCGR2B-rs1050519, FCGR2C-rs3933769 and FCGR3A-rs396991 SNPs in sympatric ethnic groups from Mali (56). This method has also been used to identify insertions and deletions in sequences of DNA. For example, a TaqMan assay was used to identify in the promoter of the NF-κ B1 gene a 94-base pair insertion/deletion polymorphism (rs28362491) that was associated with bladder cancer in the Chinese population (57). This method has also been used to determine the copy number variation (CNV) values of genes; for example, Qi et al. (58) using TaqMan assays observed that low CNVs of FCGR3A and FCGR3B in Chinese patients were associated with systemic lupus erythematosus (SLE). The TaqMan assay clearly has many advantages in that it is relatively inexpensive, uses low quantities of DNA and can be used for a variety of applications. However, the main disadvantage of this method is that the amplicons it produces are very short. This disadvantage represents a serious problem when the target region of the FCGR gene shares a broad homologous domain with another gene within the same cluster, as is the case for both the FCGR2B and FCGR2C genes (18, 59).

The multiplex ligation-dependent probe amplification assay (MLPA) is similar to the TaqMan assay in that it can detect the CNV of a genomic sequence by using a specific probe. However, in the MLPA, the probe contains two separate parts that target the same specific sequence of a gene. Once bound to the target sequence, both parts of the probe are ligated and are amplified by PCR using primers that are located at each end of the probe; CNV can then be quantified from the resultant fluorescence. This method was previously used to investigate variability in all genes located within a specific cluster of Black and Caucasian subjects in the 1000 genomes project (60). However, this method tends to be expensive, because it relies on the co-amplification of multiple genes of interest in one reaction.

Pyrosequencing is based on the introduction of a known nucleotide into the sequencing mix. This known nucleotide is subsequently incorporated into the DNA fragment being sequenced when it encounters a complementary nucleotide in this DNA fragment. This incorporation results in the release of pyrophosphate, which in the presence of firefly luciferase enzyme is converted into adenosine triphosphate (ATP). Since this reaction is luminescent, it can be readily detected. This method is advantageous because it allows for the study of two sequences with high levels of similarity. However, the major drawback of pyrosequencing is that it is not efficient in homopolymeric regions, i.e., genomic sequences that feature the same base sequence but are of different sizes (18, 61).

Next-generation sequencing (NGS) also represents a useful technology for sequencing and differentiating between FcγR gene clusters. Pacific Biosciences, Inc, of California, USA (PacBio) has developed a new technology referred to as Single Molecule, Real-Time (SMRT) Sequencing. This method is a parallelized single-molecule DNA sequencing method and is based on the conversion of a double-stranded piece of DNA into one circular strand by ligating hairpin adaptors at the ends of the sequence. This method was previously used by Hargreaves et al. to sequence the FCGR2B gene in a single 14 kb fragment, but has also been shown to support the sequencing of fragments up to 60 kb in length in one single fragment (18, 62). However, SMRT is associated with a high error rate (13%) and is a low throughput method. In addition, SMRT sequencing tends to be more expensive than other forms of NGS technology.

**POLYMORPHISMS IN FCGR GENES AND THEIR IMPACT ON THE RESPONSE OF A HOST TO MALARIA**

Two classes of FcγRs can be identified on the basis of their affinities for monomeric IgG. The high-affinity class is only composed of the FcγRI receptor, while the class of low-affinity receptors includes both FcγRII (A, B, and C) and FcγRIII (A and B). Because the FcγRI receptor binds with high affinity to monomeric IgG, previous researchers postulated that the receptor might not be able to bind to other immune complexes (63) and has not, therefore, been studied extensively. However, recent studies have highlighted the importance of the FcγRI receptor in immunological responses. In this part of our review, we present an overview of our current understanding of the
complexes. The other two SNVs, rs12078005 (I1301M) and rs142350980 (I338T); the other two are nonsense (rs74315310, R92X; and rs1338887, Q224X). In a recent study, Brandsma et al. (71) investigated the effects of the three non-synonymous SNVs on the function of the FCGR1A receptor in murine models and observed in each case a clear breakdown in the immune response. The first SNP, rs7531523 (V39I) reduced the ability of the FcγRI receptor to bind immune complexes. The other two SNVs, rs12078005 (I301M) and rs1052028 (I338T), reduced FcγRI signaling. These authors also noticed that both SNVs had a low occurrence rate in Dutch individuals. Collectively, this information leads us to hypothesize that the deleterious immune response caused by these variations may have contributed to negative selection during evolution and therefore highlights the importance of the FcγRI receptor in controlling diseases such as malaria.

Indeed, Loughland et al. (72) observed an important expression of FcγRI in intermediate monocytes involved in antibody-mediated phagocytosis of *P. falciparum* (73). These monocytes are much more important in Fulani people than in Mossi people, since the Mossi are more susceptible to malaria (3). It seems therefore, when considering the study of Loughland et al. (72), that the immune system has a tendency to solicit FcγRI in intermediate monocytes to contain infection, as their results confirmed an increase of the expression of intermediate monocytes and FcγRI with the evolution of the disease. However Dobbs et al. (72) observed an association of overexpression of FcγRI receptor in monocytes during acute malaria with a reduction of phagocytosis in comparison with the level observed 6 weeks after the treatment (74). According to the authors, this association could be due to the effect of the inhibitory receptor FcγRIIB and the recruitment of the SHIP phosphatase having a consequence of negatively regulating phagocytosis. But this explanation has not been proved. In another study, McIntosh et al. (75) reported that the transgenic incorporation of the human FcγRI receptor into a mouse model allowed these mice to clear malaria parasites in the presence of IgG1 against merozoite surface protein 19 or anti-MSP19. However, as suggested by Brandsma et al. (71) there must be redundant properties of the activities of the FcγR receptors. Indeed, the occurrence of an SNP in the first extracellular domain-encoding region of the FcγR receptor was shown to lead to a complete loss of the receptor expression without any apparent consequence in the ability of subjects to control infection (48, 68). More studies will be needed to understand the influence of variations in the gene FCGR1 on responses to malaria.

### Genes Encoding Low-Affinity Receptors

Five FCGR genes encode low-affinity receptors for monomeric IgG: FCGR2A, FCGR2B, FCGR3A, and FCGR3B. These genes have lengths ranging from 8.3 kb (for FCGR3A) to 18.9 kb (for FCGR2C) and each gene contains multiple exons (Figure 1). Several SNPs have been reported in low-affinity FCGR genes and associated with the host response to malaria (Table 1).

![Structural map showing the FCGR2 and FCGR3 genes on human chromosome 1q23 and depicting the principal polymorphisms associated with malaria/susceptibility. The coding regions for the FCGR2 and FCGR3 genes are shown in color while the non-coding regions are shown in grey. The 8th exon of the FCGR2C gene is spliced into the FCGR2A and 2C genes (lighter shade). Important SNPs that are associated with disease susceptibility/resistance, along with their patterns of localization, are indicated by arrows. For example, the FCGR2A-131I/H single nucleotide polymorphism occurs in the exon 4 of the gene FCGR2A. The FCGR genes show high levels of sequence homology. The coding regions that exhibit similar sequences are shown in the same color (note that the sequences of the FCGR3A and FCGR3B genes are identical). The directional aspects of different genes are specified by the tips of the arrows; white indicates left to right while green indicates right to left. The first exon of the FCGR2A gene is thus at the left end and the last exon of the FCGR2B gene at the right end of the figure.](image-url)
| Gene  | RefSNP | Variations                  | Effect                                                                 | Outcome | Malaria | Country | Population | Statistic          | P-value | Authors |
|-------|--------|-----------------------------|------------------------------------------------------------------------|---------|---------|---------|------------|---------------------|---------|---------|
| FCGR2A | rs1801274 | RR131 homozygote            | FcγRIIA-RR131 bind IgG2 less efficiently than FcγRIIA-HH131            | Protective | HP      | Kenya   | High vs. low risk group | 17% vs. 34% | 0.0021 | (76)    |
|       | rs1801274 | HH131 homozygote            | HH131 genotype have a greater quantitative activation of the innate immune system can be achieved by a broader repertoire of antibodies, increasing the risk of immunopathology and disease | At risk  | SM      | Gambia  | Severe vs. control | 26.3% vs. 21.7% | 0.034  | (77)    |
|       | rs1801274 | H131 allele                 | FcγRIIA -131H, the only human FcγR capable of binding IgG2 efficiently and that its polymorphism affects the regulation of the production or turnover of the IgG subclass in humans | Protective | CLM     | Asia, Africa | Cases vs. controls | 8,688 vs. 5,706 | 0.009  | (78)    |
| FCGR2B | rs1050501 | TT232 homozygote            | Removed expression of receptor                                          | Protective | SM      | Kenya   | Severe vs. control | 0.784% vs. 0.459% | 7.1 x 10^{-5} | (42)    |
|       |         |                             | Suppress inhibitory effect                                               |          |         |         |            |         |         |         |
|       |         |                             | Increase macrophage phagocytosis                                         |          |         |         |            |         |         |         |
|       |         |                             | Receptor FcγRIIb deficiency associated to less parasitemia in mice (79)  |          |         |         |            |         |         |         |
|       |         |                             | Altering the balance of activating and inhibitory FcγR on immune cells  | At risk  | SM      | Kenya   | Mild vs. severe | 5.3 ± 0.9 vs. 4.3 ± 0.8 | < 0.0001 | (81)    |
|       |         |                             | Prevent excessive immune responses by restricting number of receptors on cell surface |          |         |         |            |         |         |         |
|       |         |                             | Increase production of IFN-γ                                              | At risk  | SMA     | Kenya   | Non SMA vs. SMA | 20.9% vs. 33.3% | 0.009  | (12)    |
|       | Intron  | rs3933769                   | To be determined                                                         | Protective | HP      | Mali    | Fulani vs. Dogon | 76.19% vs. 36.87% | < 0.0001 | (82)    |
|       |         | T allele                    |                                                                        |          |         |         |            |         |         |         |
| FCGR3A | rs396991/ rs5749396 | 158V/1237T (TLR9) haplotype | Increase production of IFN-γ                                              | At risk  | SMA     | Kenya   | Non SMA vs. SMA | 20.9% vs. 33.3% | 0.009  | (12)    |
|       |         | NA2*03/NA2* (N82D) haplotype | Lead to one glycosylation site                                           | At risk  | CLM     | Ghana   | cases vs. controls | 12.5% vs. 04.1% | 0.0092 | (83)    |
|       | rs5030738 | SH allotype                 | May influence ligand epitope                                             | Protective | CLM     | Ghana   | cases vs. controls | 0.67% vs. 0.20% | 0.049  | (83)    |
|       |         |                             | Associated with high FcγRIIb expression level                            |          |         |         |            |         |         |         |
|       | CNV     | CNV > 3 copies              | Overactivation of immune cells                                           | At risk  | SM      | Gabon   | severe vs. mild | 2.8 ± 0.7 vs. 2.3 ± 0.6 | < 0.0001 | (81)    |
|       |         |                             | Create inflammatory disorders and exacerbate symptoms                    |          |         |         |            |         |         |         |
| FCGR2A | rs1801274/ rs403016/ rs447536/ rs448740/ rs428888/ rs2290834 | H131/NA2 haplotype            | To be determined                                                         | At risk  | SMA     | Kenya   | 131H/NA2 vs. non-131H/NA2 | RR=1.47 | 0.020  | (84)    |
|       | rs1801274/ rs403016/ rs447536/ rs448740/ rs428888/ rs2290834 | H131/NA2 haplotype            | Neutrophils with the FcγRIIB-NA2/NA2 genotype show lower activation of FcγRIIb-mediated phagocytosis than those with the FcγRIIb-NA1/NA1 genotype |         |         |         |            |         |         |         |

(Continued)
**TABLE 1** Continued

| Gene RefSNP Variations | Effect | Outcome | Population | Country | Population Statistic | P-value |
|------------------------|--------|---------|------------|---------|----------------------|---------|
| FCGR2A rs1801274/131H/158F/ | May be low binding of cytophilic antibodies due to the diluting effect of guanine (G) base is present in the DNA sequence, the corresponding amino acid residue could either be an arginine (allele R131) or a histidine (allele H131). The receptors encoded by allele H131 have been shown to have better affinities for IgG2 than those encoded by allele R131 (21, 86). The FcγRIIA-H131 receptor has been shown to be capable of binding three different immunoglobulins (IgG1, 2, and 3) more efficiently than has the FcγRIIA-R131 variant. This broad coverage increases the phagocytic capacity of the FcγRIIA-H131 receptors (87). Consequently, researchers have investigated the association between H131R and its potential ability to provide protection against several diseases (88, 89). The first indication that the H131 allele could be involved in providing protection against an infectious disease like malaria came from observing differences in allele frequencies when comparing Asian populations (in which malaria was the primary cause of 19,700 deaths in 2017) and European populations (90). In field studies, 28% of Caucasians (91) were shown to be homozygous for H131 while 71.5% of Asians were shown to be homozygous (92). The H131 allele is therefore more prevalent in Asian populations than in populations like Caucasians who are not subjected to selective pressure. The occurrences of the H131 allele in various African peoples have also been studied. Indeed, the frequencies of the H131 and R131 alleles vary according to ethnic grouping in Africa. Three different studies showed similar distributions of H131 homozygotes (27.37% out of 274 subjects, 32% out of 97 subjects, and 20.45% out of 88 subjects) in Luo and Luhya populations of Kenya and a Yoruba population of Nigeria (56, 60). However, different distributions of the genotype for this SNP were found for different ethnic groups from Ghana (p=0.036), with the frequency of subjects who were homozygous for R131 being higher for the Ga-Adangbe ethnic group than for the Akan, Hausa and Fulani ethnic groups (p=0.01347; Chi square test performed by us and R according to the results given by the authors in the Supplementary Table in SI) (93). In this way, it has been observed that in Mali and Eastern Sudan, the Fulani, who are less susceptible to malaria than other sympatric ethnic groups (94), exhibited a greater frequency of the H131 allele than did a non-Fulani group (95, 96). Association studies were also carried out to assess any possible influence of SNPs on the control of malaria; these studies led to inconclusive findings. While a few of the studies suggested an association between the H131 allele and a protective effect against malaria (95, 96), others have reported an association between this allele and the occurrence of severe or cerebral malaria (77, 85, 96). The R131 allele has also been associated with low parasitemia in western Kenya (76). Finally, a meta-analysis of H131 and R131 suggested a strong association between the FcγRIIA-H131 allele and protection against malaria in Asian and African populations (78). The authors of this meta- | 4.37 vs. 4.12 | 0.009 (56) |
| FCGR3A rs396991/NA1 | Reduced antibody dependent respiratory burst | At risk SMA Kenya | SMA vs. non-SMA | 69.3% vs. 57.5% | 0.036 (56) |
| FCGR3B rs403016/rs447536/rs448740/rs428888/rs2290834 | | | | | |
| FCGR2A rs1801274/131H/158F/ | | | | | |
| Author column: the collecting author of the antigenic diversity at a genetic level. Allotype: The allotype of a particular polymorphism is the amino acid sequence that is encoded by a particular SNP. Haplotype: The haplotype is the combination of allotypes associated with a particular SNP. | | | | | |
| Author: reference of authors of the article that mentioned the variation. | | | | | |
| Authors column: other authors in parentheses. Outcome: The outcome of the study, following the standard naming convention of the population. Country: The country in which the study was conducted. Population: The population in which the sample was studied. | | | | | |
| Meta-analysis of the association between FcγRIIA-H131 allele and protection against malaria in Asian and African populations (78). The authors of this meta- | | | | | |
| FCGR2A rs1801274/131H/158F/ | | | | | |
| FCGR3A rs396991/NA1 | | | | | |
| FCGR3B rs403016/rs447536/rs448740/rs428888/rs2290834 | | | | | |
| FCGR2A rs1801274/131H/158F/ | | | | | |
| FCGR3A rs396991/NA1 | | | | | |
| FCGR3B rs403016/rs447536/rs448740/rs428888/rs2290834 | | | | | |
The FCGR2B Gene
SNP rs1050501 in the FCGR2B gene may be under the influence of evolutionary pressure caused by malaria (98). This SNP leads to the replacement of isoleucine by threonine at position 232 in the transmembrane domain of the protein encoded by the FCGR2B gene. The presence of threonine abrogates the inhibitory function of the receptor, thus leading to the increased phagocytosis of parasites by macrophages (79). Mice deficient in the receptor FcγRIIb have shown on average lower levels of parasitemia and less severe anemia than have non-deficient mice (79). In humans, a higher frequency of the FCGR2B-T232 allele has been observed in Asian and African populations than in the Caucasian population (79, 99, 100). In addition, a cohort study involving Kenyan children revealed that those homozygous for FCGR2B-T232 exhibited lower levels of susceptibility to severe malaria (101).

The FCGR2B gene also presents with a haplotype in the promoter region (-386C -120A) including two SNVs, at codons 386 and 120, responsible for replacing cysteine and alanine with glycine and threonine, respectively (102). This haplotype has been associated with an increased level of gene expression in monocytes, neutrophils and dendritic cells (103, 104). In contrast, Blank et al. (105) showed a relatively high susceptibility of European-Americans homozygous for the first SNV (-386C/C or -343C/C if considering the start of transcription), to systemic lupus erythematosus (SLE), an autoimmune disease. These authors also observed that these individuals had lower expression levels of FcγRIIb receptors on the surface of activated B cells. Investigating the impact of this SNP in the African population would therefore be expected to enhance our understanding of the precise role of the FCGR gene in malaria susceptibility.

The FCGR2C Gene
The FCGR2C gene is often referred to as a chimeric or pseudogene gene because it does not always encode a protein; this characteristic is due to the presence of the mutation Q13X at position 13 in exon 3 of this gene (45, 99). Consequently, the expression of the FCGR2C gene by NK cells is in fact an open reading frame (ORF) due to the substitution of a thymine residue by cytosine, thus resulting in the replacement of a stop codon (TAG) with a glutamine residue (CAG) (26). However, this study found that approximately 20% of Caucasians with an FCGR2C-ORF genotype did not express the FcγRIIc receptor on the surfaces of their NK cells. Indeed, these authors noted the presence, within the splicing site of intron 7, of a second mutation (G → A) that led to another stop codon, and thus the inability to express FcγRIIc receptors on the surface of NK cells.

In contrast to FCGR2A and FCGR2B, the FCGR2C gene leads to a higher level of protein expression in Caucasians than in Africans (in which the FCGR2C-ORF gene is weaker) and Asians (in which the gene is absent) (8, 60). Moreover, van der Heijden et al. (48) mentioned that a nonclassical STOP allele of FCGR2C due to a splice site mutation near exon 7 could promote the expression of FcγRIIb in NK cells. This receptor is not normally detected in these cells. Therefore, the NK cell expression of FcγRIIb has been associated by van der Heijden et al. to an inhibition of the killing activity of FcγRIIia mediated by antibody-dependent cell cytotoxicity. Collectively, this information might suggest that this gene has less influence than the other genes described above on resistance to malaria. This theory is supported by the observation of Gabonese children displaying a higher risk of developing severe malaria when presenting with a high frequency of the FCGR2C gene (81). But, the increased number of copies in FCGR2C concerns only the FCGR2C ORF. This means that an increase in the number of copies of FCGR2C would lead to a possible overexpression of the receptor FcγRIIc in NK cells and then overly high immune activation with a consequence of increasing inflammation, resulting in a more severe form of the disease (8, 80).

Existing data indicate that the precise role of this gene is complex. Indeed, an SNP occurring in intron 7 of the FCGR2C gene, referred to as rs3933769, is far more common in Fulani subjects from Mali than in Dogon subjects (82). As a distinct ethnic group, the Fulani are known to be less susceptible to malaria than are other sympatric ethnic groups (93). This study demonstrated an association between the mutant allele of this SNP and clearance of parasitemia (82). This could highlight the importance of this particular intron in protecting the Fulani people against malaria. Further studies are needed to elucidate the precise role of the FCGR2C gene in the response to malaria.

The FCGR3A Gene
Two polymorphisms in the FCGR3A gene could potentially play a role in providing protection against malaria. The rs396991 polymorphism is a non-synonymous single nucleotide polymorphism from T to G at nucleotide position 559 in the FCGR3A gene. This SNP is responsible for substitution of a phenylalanine for a valine amino acid position 158 of the protein excluding signal peptides (FCGR3A-F/V158) or at position 176 of the full protein (FCGR3A-F/V176) (8). It seems that the wild type (FCGR3A-F/V158) alters the capacity of NK cells to bind the cytphilic antibodies Ig1 and IgG3 (106, 107). Indeed, this allele, combined with FCGR2A-131R and FCGR3B-NA1, was indicated to be associated with high levels of parasitemia in children from western Kenya, while the FCGR2A-131R/
The FCGR3A-158F/FCGR3B-NA2 haplotype was associated with susceptibility to severe malarial anemia (SMA) (56). In contrast, the FCGR3A-158V genotype allows the encoding receptor at the surface of NK cells to bind cytophilic antibodies-coated target cell and therefore the release of cytotoxic effector proteins by NK cells. This activation of NK cells able the death of the target cell (28, 108, 109). However, the influence of SNP V158F on the immune response could be affected by the presence of the -1237T/C SNP in the TLR9 promoter gene (thymine base mutated to cytosine at position -1237 of the TLR9 promoter region) (12). Toll-like receptors (TLRs) are proteins belonging to the family of pattern recognition receptors (PRRs). These proteins are localized specifically in antigen-presenting cells and are involved in the detection of pathogenic molecules. In particular, TLR9 is an intracellular TLR that stimulates immune cells and releases detection of pathogenic molecules. In particular, TLR9 is an intracellular TLR that stimulates immune cells and releases a cytokine involved in the differentiation of naïve T cells from helper T cells but also involved in the production of interferon gamma (IFN-γ) (110). Thus, when associated with FCGR3A-176V, the presence of the variant -1237T would double the risk of developing severe malaria anemia by increasing the production of IFN-γ (12).

Another important polymorphism in the FCGR3A gene is the rs10127939 SNP. This SNP results from the substitution of a g or a, thus replacing leucine by arginine or histidine at amino acid position 66 in the extracellular domain (111, 112). Some authors have shown the SNP L66R/H and the SNP V176F to be associated with a reduced cytotoxic response and IgG binding capacity in the NK cells of patients experiencing recurrent infections with Herpes simplex virus, Epstein-Barr virus or Varicella zoster (111). This observation has led to the speculation that both SNPs should lead to increased levels of susceptibility to different infections and autoimmune diseases (109, 112, 113). However, in a study involving 115 Colombians, neither of these SNPs showed any association with the phenomenon of antibody-dependent cell-mediated cytotoxicity (ADCC) in NK cells (111). However, the authors of this study found a linkage disequilibrium between the SNP L66R/H and the SNP V176F in the FCGR3A gene. Furthermore, the 176FF variant appears to result in alterations to the epitope that would normally interact with IgG1 antibodies (111). Further studies should be undertaken to specifically investigate the effect of these SNPs in a population that is endemic for malaria, as no previous research has been attempted in such a population. Pursuing such studies is particularly important considering the presence of an association between lupus nephritis and the 66R/H/L and 176F variants in African Americans but not in Caucasians (114). Again, it will also be important to study the impact of CNV of this gene on malaria susceptibility as an CNV higher than 2 increases expression of the receptor (40).

The FCGR3B Gene

The FCGR3B gene codes for a receptor that is expressed on neutrophils. Three isoforms of the FcγRIIb receptor have been described, each exhibiting a different ability to bind antibodies (115). These allotypes include several human neutrophil antigens, namely HNA-1a (NA1), HNA-1b (NA2), and HNA-1c (SH) (83). HNA-1a (NA1) and HNA-1b (NA2) are encoded by FCGR3B*1 and FCGR3B*2, respectively (83). Differences between FCGR3B*1 and FCGR3B*2 at five nucleotide positions (c.108C>G; c.114T>C; c.194A>G; c.244A>G; and c.316A>G), which lead to differences at only four different amino acid residues (due to c.114T>C resulting in a synonymous replacement), allow us to distinguish between these two allotypes of the FCGR3B gene. This set of differences leads to the presence of two glycosylation sites in the NA2 allotype. It is likely that these glycosylation sites are responsible for the NA1 allotype being more efficient than the NA2 allotype (116). Indeed, compared to the NA2 allotype, the NA1 allotype has a greater ability to facilitate the phagocytosis of opsonized particles by IgG1 and IgG3 (116). Moreover, when combined with the FCGR2A-H131I allele, the NA2 allotype has been associated with cerebral malaria in Thailand and severe anemia in Kenya (84, 85). Similarly, a variant of the NA2 allotype, NA*203, which has only one glycosylation site, has been associated with susceptibility to malaria in Ghana (83). This variant results in the substitution of asparagine with aspartic acid at position 82 (N82D); and the disruption of receptor function may be due to the loss of a carbohydrate group that is involved in ligand binding affinity and immunogenicity (83, 117, 118). But, it appears also that the final impact of the receptors on immune response would be influenced by glycosylation of IgG depending on whether the glycosylated IgG contains N-glycan (43). Therefore, these inside-out controls of the receptors could be at the origin of discrepancies when trying to assess their role in malaria response.

HNA-1c (SH) is the third most commonly studied allotype of the FCGR3B gene. This allotype is encoded by the allele FCGR3B*3 (83), which differs from the FCGR3B*2 allele by virtue of an SNP at position c.233C>A (rs5030738) resulting in the replacement of alanine with aspartic acid at position 78. The c.233A allele has already been associated with a protective effect against malaria in Ghanaian children (83). Neutrophils from individuals who have this allele appear, according to the research, to be able to bind malaria IgG antibodies more efficiently than those who express the c.233C allele (119). However, another study involving Gabonese children showed that those having a CNV greater than 3 for FCGR3B displayed a significantly higher risk of contracting severe malaria (81). The association between CNV and severe malaria has also been reported for FCGR2C genes. Consequently, it appears that an increase in the expression of the FcγRII gene could lead to the overactivation of immune cells, thus creating inflammatory disorders and exacerbating the symptoms of malaria (81, 120, 121).

FCγ RECEPTORS AND THE DEVELOPMENT OF NEW VACCINE STRATEGIES

Chloroquine resistance, which began in Southeast Asia in the 1960s and then spread to Africa, increasing the number of deaths from malaria, has led to the adoption in several countries since 2005 of artemisinin combination-based therapies (ACTs). However, resistance to artemisinin was reported in Southeast
Asia (2, 122). If this resistance were to spread around the world as did chloroquine resistance, the consequences could be devastating for the countries affected. Also, it is more important than ever to think of new strategies for combating malaria. In particular, the development of an effective vaccine would make it possible to curb the phenomenon of selection of resistant strains, which is very common with antimalarial drugs because of drug pressure. But research to this effect has been complicated by the variability of the antigens carried by the parasite. Thus, the currently most advanced candidate vaccine allows only partial short-term protection against malaria (50% reduction in malaria incidence over 1 year) (123).

Therefore, finding a methodology to boost candidate vaccine antigens would be a welcome solution to the challenges of reaching the goal of eliminating malaria. From this perspective, therapeutic antibodies could offer an avenue. Indeed, Douglas et al. (124) showed that the transfer of neutralizing antiplasmodial antibodies to primates induces protection against Plasmodium falciparum without resorting to treatment. While the quantities used to achieve this test result were large, the study clearly offered a plausible solution. But a limitation of this study was the non-integration of the pathogen destruction mechanism by the activation of complement and the opsonization of particles. As shown by Koenderman et al. (43), it may be possible to reduce the therapeutic doses of antibodies by impeding the inside-out control of FcγR.

Another study identified monoclonal antibodies capable of recognizing different strains of parasites from RIFIN (repetitive interspersed family) proteins which are antigens expressed on the surface of infected red blood cells (125). The variable domains of such antibodies could, according to Shi et al. (15), be used to design a particular antibodies called bispecific antibodies capable of targeting the antigens of interest. These antibodies present another variable domains of the light and heavy chain (VL, VH) (126) that could also be designed to recognize specifically a given FcγR receptor (127, 128). Additionally, these antibodies can also be designed to target the FcγR receptors located on memory T cells or receptors involved in stimulating the presentation of antigens to DCs like FcγRIIA. These DCs in turn activate the memory T cells (16). According to Anania et al. (34), the use of anti-CD3/CD28 could directly stimulate the intracellular and surface expression of FcγRIIA receptors. Thus, a new vaccine strategy against malaria might involve combining both antibodies not linked to the antigens, thereby making it possible for them to not only serve as therapy for an infection in progress but also to induce a long-term response, a “vaccine” effect of antibodies, when they engage memory T cells. These antibodies could boost the efficiency of the candidate antigen vaccines to which they would be linked (15). Therapeutic antibodies would thus serve as a vehicle for candidate antigen vaccines instead of the use of traditional adjuvants.

But one of the obstacles to using therapeutic antibodies is their cost of manufacture, which would not be profitable since these therapeutics would be intended for poor countries where malaria is prevalent. However, as Shi et al. (15) showed, bispecific antibodies can be produced simply and economically by carrying out chemical conjugation or recombinant expression systems.

Hart et al. (129) indicated that certain NK cells that play an important role in malaria resistance do not present FcγR receptors but rather NKG2C (two C-type lectin protein expressed by NK cells) receptors in individuals who at some point in their lives had been infected with cytomegalovirus (representing 81.8% in Africa, (130). Taking this study into account, one could imagine that the antibodies not linked to human complexes of the new vaccine against malaria could be specifically directed against these cells.

Combined, these studies show the seemingly endless possibilities for developing new vaccine strategies against malaria.

**CONCLUSIONS AND PERSPECTIVES**

FcγR receptors modulate the immune response by interacting with the Fc domain of an antibody. This interaction stimulates the activation of innate immune cells and the production of antibodies and is also known to influence the activities of antigen-presenting cells. Therefore, by enhancing our understanding of the functional activity of the FcγR receptors, we may be able to develop new strategies for vaccination. Cancer patients have been screened for polymorphisms in the FCGR genes that encode for FcγR receptors in order to design antibodies in which the Fc domain induces better recognition by immune cells. Individuals with the FCGRA3-158VV genotype have been shown to exhibit better responses to therapeutic antibodies, including rituximab (131). This new concept allows for individualized treatments of patients and leads to better results.

Despite the success associated with passive immunization strategies involving anti-malaria antibodies (15), such techniques have not yet been applied for the clinical treatment of malaria. However, new engineering approaches now allow us to design antibodies against specific epitopes of plasmodial surface antigens (15). In addition, a new form of synthetic IgG has also been developed, referred to as “bispecific diabodies”. These antibodies composed of two antigen binding Fv domains, each with a VH and a VL domains can be designed to specifically recognized a target antigen and be directed to the FcγR receptors of cytotoxic cells in order to increase parasitic clearance (126, 128, 132). Alternatively, one of the antigen binding Fv domains can target antigen-presenting cells instead of cytotoxic cells in order to generate memory T cells and thus promote a long-lasting effect (16). If these new therapeutic approaches are effective, then it may be possible to prevent the spread of malaria altogether. However, as discussed herein, there are many important questions that remain unanswered. Taking the example of the receptor FcγRII, future studies could investigate whether the binding to monomeric antibodies hinders the recognition of the parasite’s antigens and the activation of the receptor for the destruction of immune complexes as currently presumed (133). Also, the prevalence of individuals with the FCGR1 gene lacking exon 5 and its influence in malaria resistance in endemic populations should be studied. Moreover, a different track could be pursued to understand why discrepancies have been often observed regarding the association between certain alleles and protection against malaria. For the gene FCGR2A, for example, future studies should focus on children 10
years and older, to determine the influence of the H131 allele on the production of IgG2, which increases in this age group (9, 134). It will also be important to study the hypomethylation of the gene promoter in African populations. Respectively for FCGR2C and FCGR3A, the influence of the SNP rs3933769, SNPs L66R/H, and SNP V176F should be investigated. Finally, it is important to note that different SNPs in the FCGR cluster have not yet been the target of association studies involving malaria susceptibility or resistance (Table 2). Indeed, further investigations to comprehensively dissect the associations between the FCGR cluster and malaria should be done. But, as the FCGR genes show highly homologous sequences, these studies should use next-generation sequencing and associated bioinformatic analyses.

**AUTHOR CONTRIBUTIONS**

MA wrote the first draft of the review. The other authors (AO, DO, S-PN, and WY) read and made revisions to the first draft and approved the final version for publication. All authors contributed to the article and approved the submitted version.

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these terms.
**GLOSSARY**

| Acronym | Definition |
|---------|------------|
| A base | adenine base |
| SLE | systemic lupus erythematosus |
| 120A | alanine at position 120 |
| 388C | cysteine at position 388 |
| ACT | Artemisinin Combination based Therapy |
| ASRED | allele-specific restriction enzyme digestion |
| ATP | adenosine triphosphate |
| BCR | B-cell receptor |
| C (1, 2 or 3) | cytoplasmic domains |
| CD28 | cluster of differentiation 28, proteins expressed on T cells and also involved in T cell activation |
| CD3 | cluster of differentiation 3, transmembrane protein associated with T cell receptor and zeta-chain (ζ-chain) to able T lymphocytes activation signal |
| CLM | clinical malaria |
| CM | cerebral malaria |
| CNV | copy number variation |
| cp | number of gene copies |
| D (1,2 or 3) | extracellular immunoglobulin-like domains in Fc gamma receptor |
| DCs | dendritic cells |
| DNA | deoxyribonucleic acid |
| EC (1 or 2) | extracellular domains |
| FCGR | genes coding for Fc gamma Receptors |
| FcγR | receptor Fc gamma |
| G → A | guanine base mutated in adenine base |
| G base | guanine base |
| H131R | histidine substitution by arginine |
| HIV | Human Immunodeficiency Virus |
| HNA (NA) | human neutrophil antigen |
| HP | hyper parasitemia |
| I301M | isoleucine substitution in methionine at position 301 |
| I338T | isoleucine substitution in threonine at position 338 |
| IFN-γ | interferon gamma |
| IgG | immunoglobulin G |
| ITAM | immunoreceptor tyrosine-based activation motif |
| ITAMi | ITAM- mediated inhibitory signal |
| ITIM | immunoreceptor tyrosine-based inhibitory motif |
| MAPK | mitogen-activated protein kinase |
| MEK | MAP kinase kinases |
| MLPA | multiplex ligation-dependent probe amplification assay |
| MSP | merozoite surface protein |
| N82D | substitution of asparagine by aspartic acid at position 82 |
| NGS | next generation sequencing |
| NK cells | Natural Killer cells |
| NkG2C | NK cells two C-type lectin protein |
| ORF | open reading frame |
| PGR | polymerase chain reaction |
| PRRs | pattern recognition receptors |
| PTK | protein tyrosine kinase |
| Q13X | glutamine substitution by stop codon in position 13 |
| Q224X | Glutamine substitution by stop codon in position 224 |
| R92X | Arginine substitution by stop codon at position 92 |
| ReSNP | accession number of SNP |
| RfIPF | repetitive interspersed family proteins |
| RR | relative risk |
| S (1 or 2) | signal peptides |
| SH | human neutrophil antigen-1c encoding by FCGR3B*3 allele |
| SH2 | Src-homology 2 domain |
| CHIP | protein inositol phosphatase |
| SHP | protein tyrosine phosphatase |
| SM | severe malaria |
| SMA | severe malaria anemia |
| SMRT | single molecule real time |

(Continued)