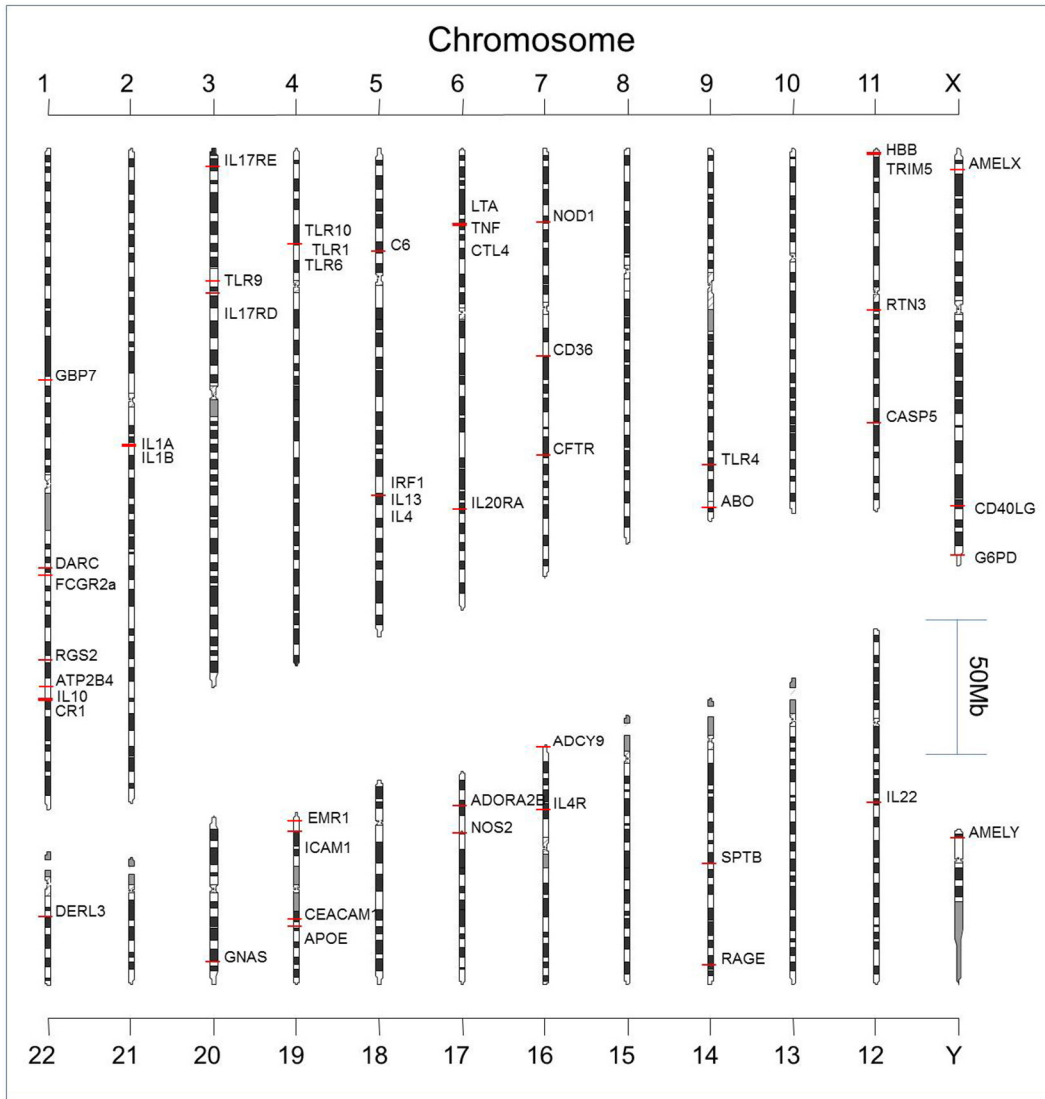


Supplementary Figure 1

Map of the locations of the MalariaGEN Partner Study sites involved in this project.

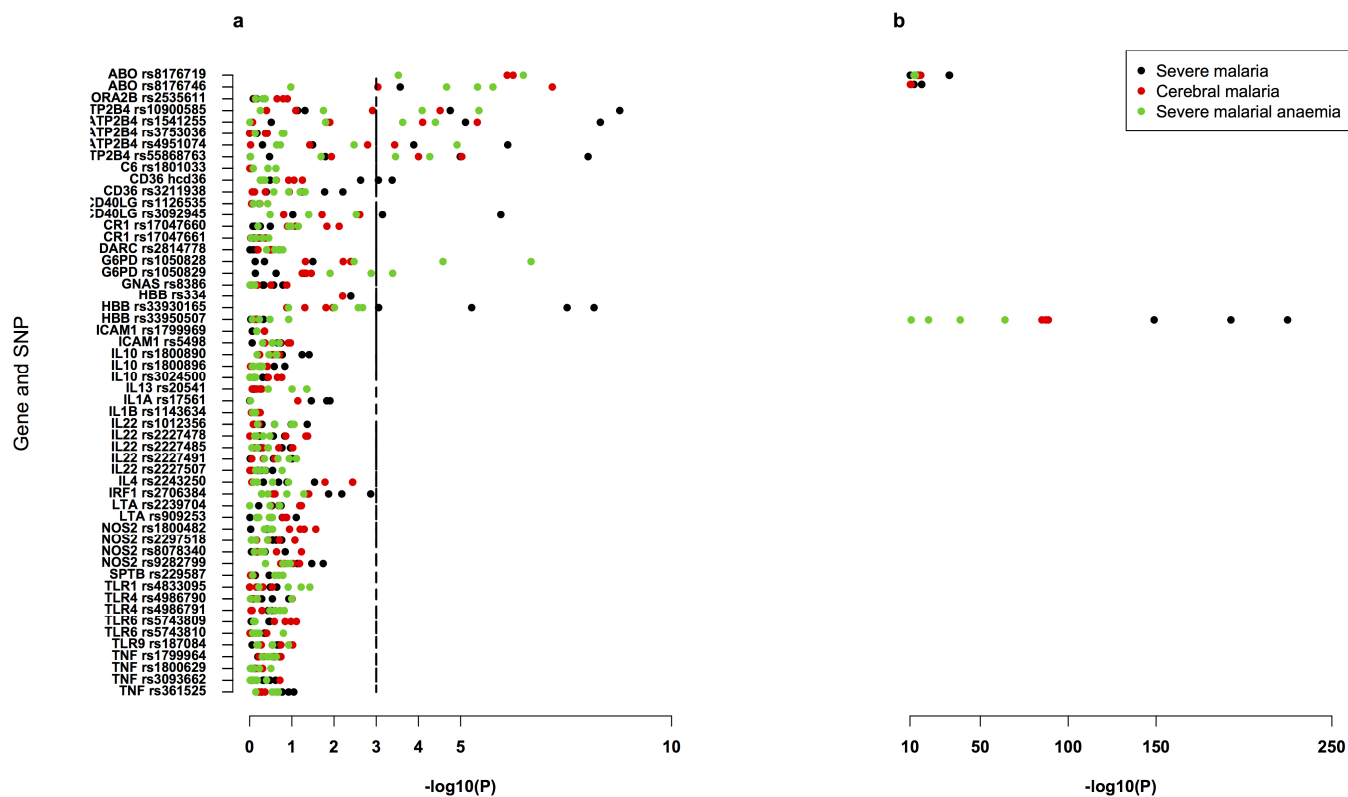
1. UK Resource Centre, Oxford University and Wellcome Trust Sanger Institute. 2. The Gambia, MRC Laboratories, Banjul. 3. Mali, University of Bamako, Bamako. 4. Burkina Faso, Centre National de Recherche et de Formation sur le Paludisme, Ouagadougou. 5. Ghana (Navrongo), Navrongo Memorial Institute for Medical Research with Navrongo Health Research Centre. 6. Ghana (Kumasi), Kwame Nkrumah University of Science and Technology. 7. Nigeria, University of Ibadan. 8. Cameroon, University of Buea. 9. Kenya, KEMRI–Wellcome Research Programme, Kilifi. 10. Tanzania, Joint Malaria Programme, Kilimanjaro Christian Medical Centre, Moshi. 11. Malawi, Blantyre Malaria Project with Malawi-Liverpool–Wellcome Programme. 12. Vietnam, Oxford University Clinical Research Unit, Ho Chi Minh City. 13. Papua New Guinea, Papua New Guinea Institute for Medical Research, Madang. See also **Supplementary Tables 1 and 2**.



Supplementary Figure 2

Chromosomal map of the genes included in Supplementary Tables 5–7.

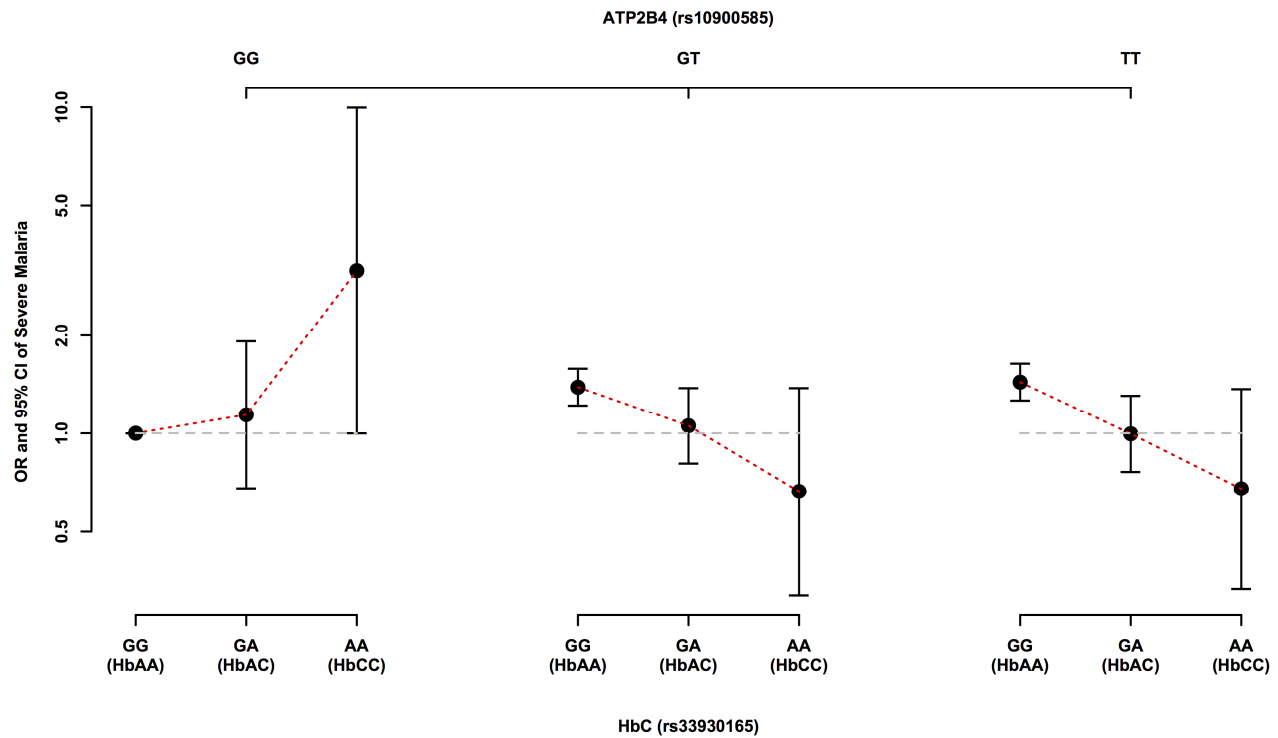
All genes are referenced to GRCh37, dbSNP137 and Ensembl build 73.



Supplementary Figure 3

Distribution of P values from multiple-association analyses at 55 SNPs having a prior association with severe malaria.

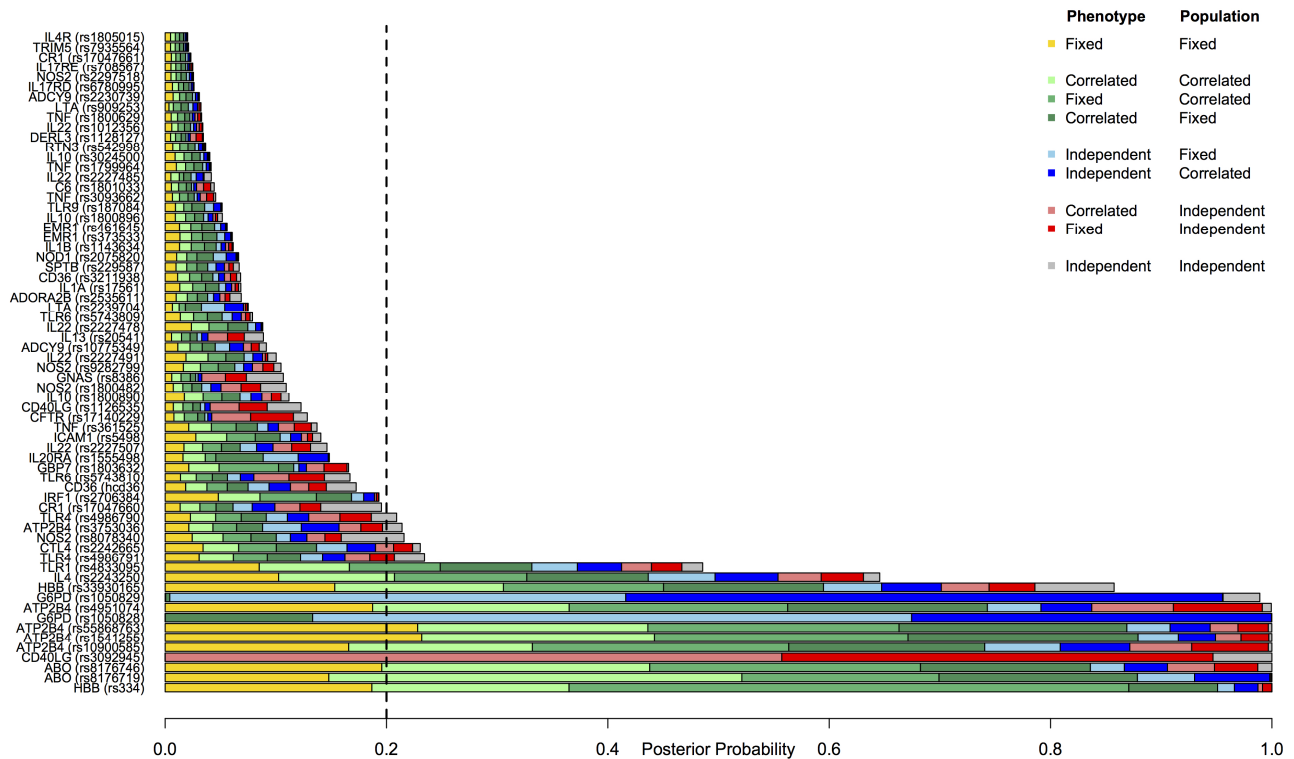
$-\log_{10} P$ values from combined analyses across the 12 contributing Consortium Project 1 study sites for severe malaria and the subtypes cerebral malaria and severe malarial anemia under additive, recessive, dominant and heterozygote advantage models. Results are shown for all individuals combined for (a) $0 < -\log_{10}(P) \leq 10$ and (b) $10 < -\log_{10}(P) < 250$; results are shown in two panels for optimal viewing. The vertical dashed line indicates a P -value threshold of 1×10^{-3} .



Supplementary Figure 4

Forest plots for interaction between *ATP2B4* and HbC for association with severe malaria.

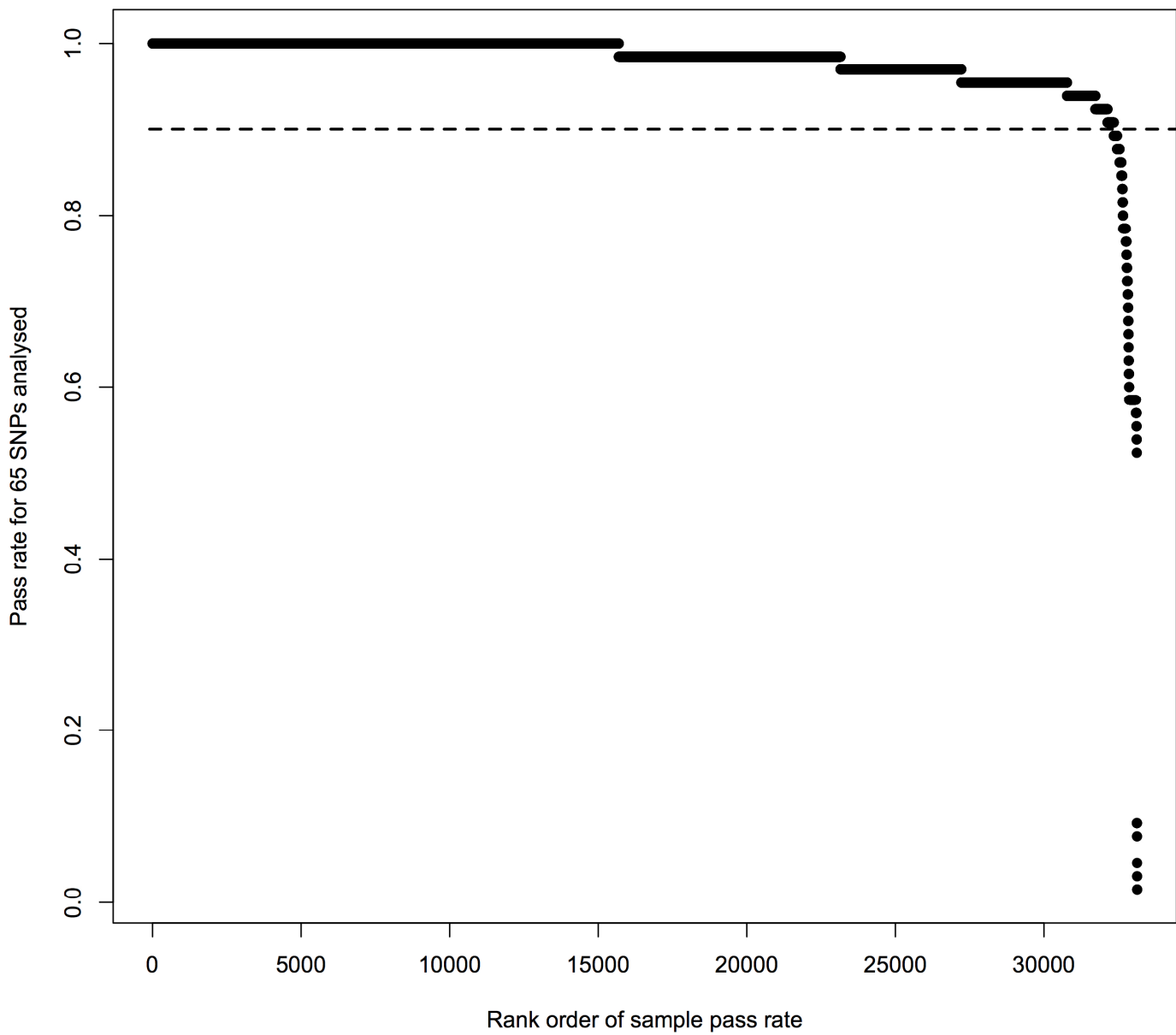
Odds ratios and 95% confidence intervals are shown for the interaction between *ATP2B4* (rs10900585) and HbC (rs33930165) for association with severe malaria in all individuals combined across West African sites (Burkina Faso, The Gambia, Ghana, Mali, Cameroon and Nigeria). Results are adjusted for sex and ancestry. The baseline genotype is GG/GG, representing double ancestral homozygotes. OR = 1, indicating no effect, is highlighted by the gray horizontal dashed line.



Supplementary Figure 5

Genetic heterogeneity of the severe malaria subtypes cerebral malaria and severe malarial anemia within and across African populations for all loci.

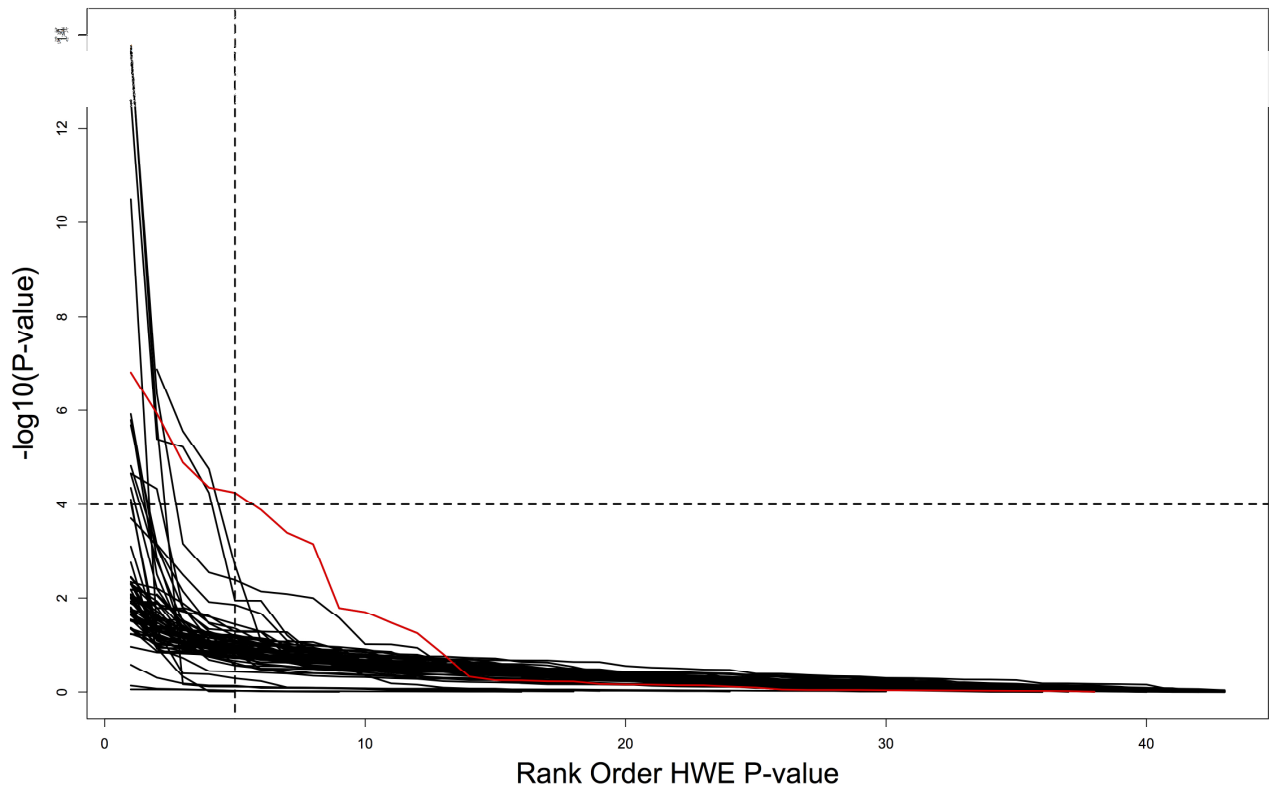
Bar plots show the posterior probability on each of nine models of association where effects on the two subtypes are fixed, independent or correlated within a population combined with being fixed, independent or correlated across all the populations, as indicated by the different colors; the remainder of the posterior probability is on the null model where there is no effect on any of the subtypes. Before seeing the data, the null model is assumed to have 80% probability; the remaining 20% is divided equally among the other models. Approximate Bayes factors (ABFs), calculated as the ratio of the marginal likelihoods of a given model and the null model, are used to compare the evidence between models. (See the Online Methods for details and the specification of priors.) The dashed line at posterior probability = 20% indicates where the combined posterior probability of the non-null models is greater than their combined prior probability.



Supplementary Figure 6

Performance of sample collection across the set of 65 core SNPs (not including *ATP2B4*) successfully genotyped for all samples.

Samples have been ranked in order of pass rate from high to low (x axis) and plotted against their pass rate (y axis). A total of 33,138 samples were assayed, with 32,349 samples achieving a pass rate of $\geq 90\%$ (98% of the sample received).



Supplementary Figure 7

Hardy-Weinberg equilibrium analysis of genotype data by SNP and country/ancestry.

A P value for Hardy-Weinberg equilibrium was calculated for each SNP and country/ancestry, discarding ancestry groups where the chromosome with the minor allele count fell below five (*Forensic Sci. Int.* **149**, 279–286, 2005). X-chromosome SNPs used female genotypes only. At each SNP, the Hardy-Weinberg equilibrium P values calculated for each country/ancestry were transformed to unsigned log values and ranked from high to low. Each line corresponds to a single SNP and shows the transformed P values plotted as a function of their rank. The vertical dashed line at rank 5 represents the threshold for the number of ancestry groups failing the Hardy-Weinberg equilibrium test at a significance level of 1×10^{-4} , a conservative threshold to allow for multiple tests (represented by the dashed horizontal line). Lines crossing into the top right of the area defined by the two dashed lines therefore represent SNPs that failed more than five tests and therefore were removed from further analysis. Using these cutoffs, the TNF c.-376G>A (rs1800750) SNP, indicated by the red line, was removed from further analysis owing to an excess of heterozygotes.

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Supplementary Tables

Country	Institute	Ethics approving institution	Ethics committee	local ID(s)
Gambia	Medical Research Council Unit, The Gambia	MRC Gambia and Gambia Government	MRC/Gambia Government Ethics Committee	SCC 1029v2 SCC670/630
Mali	University of Bamako	University of Bamako, FMPOS, MRTC	FMPOS Research Ethics committee	No/18/FMPOS No/06-18bis/FMPOS
Burkina Faso	Centre National de Recherche et de Formation sur le Paludisme	Ministry of Health & Ministry of Science and Education	Health Research Ethics Committee	No 2007-048
Ghana (Navrongo)	Navrongo Memorial Institute for Medical Research with Navrongo Health Research Centre	Navrongo	Navrongo Institutional Research Committee	NMIMR-IRB CPN 016/01-02 NMIMR-IRB CPN 029/05-06
Ghana (Kumasi)	Kwame Nkrumah University of Science and Technology	Ghana Health Service School Medical Sciences, KNUST	Ghana Health Service Ethics Research Board Committee on Human Research Publication and Ethics	GHS-ERC-03/9/06 CHRP/07/01/06 CHRPE SMS UST dated 24-05-2007
Nigeria	University of Ibadan (UI)	Institute of Child Health, College of Medicine, University of Ibadan	UI/UCh Ethics committee	UI/IRC/06/0034
Cameroon	University of Buea	University of Buea Government of Cameroon	Institutional Research Board Provincial Delegate for Public Health	University of Buea ethical clearance 07-12-2005 D7.1.A/MPH/SWP/PDPH /PS.CH/2340/811
Kenya	KEMRI-Wellcome Research Programme	KEMRI, Kilifi	KEMRI Research Ethics Committee	SCC1192
Tanzania	Joint Malaria Programme, Kilimanjaro Christian Medical Centre	London School of Hygiene and Tropical Medicine National Institute for Medical Research (NIMR), Tanzania	London School of Hygiene and Tropical Medicine Ethics Research Committee NIMR Research Coordinating Committee	4093 NIMR/HQ/R.8a/Vol. IX/513
Malawi	Blantyre Malaria Project with Malawi-Liverpool-Wellcome Programme	University of Malawi, College of Medicine	College of Medicine Research Ethics Committee	P.05/06/442
Viet Nam	Oxford University Clinical Research Unit	Hospital Tropical Diseases	Research Ethics Committee	SECHTD dated 20/04/2006
Papua New Guinea	Papua New Guinea Institute for Medical Research	Government of PNG Papua New Guinea Institutional Research Board	Papua New Guinea Medical Research Advisory Committee Papua New Guinea Institute of Medical Research Institutional Research Board	MRAC No:06.21 IMR IRB 0603
United Kingdom	Oxford University	Oxford University	The Oxford Tropical Research Ethics Committee (OXTREC)	OXTREC 020-06

Supplementary Table 1: Partner sites. Partner sites for MalariaGEN Consortial Project 1 (Genetic Determinants of Resistance to Malaria) with details of the partner institution and local approving bodies. Supplementary Figure 5 shows a map of these Partner sites (<http://www.malariagen.net/projects/cp1>).

Country	Study Design
Gambia	Unmatched Case-Control study. 2801 cases - recruited from hospitals in/near Banjul. 4527 controls - cord blood samples were collected from labour wards of various hospitals primarily in western division of the country. Other samples were sampled from Gambian Biobank blood donors.
Mali	Matched Case-Control study. 510 cases - recruited from a hospital in Bamako. 389 controls - recruited from community, individually matched to cases by age, ethnicity, place of residence & duration of residence
Burkina Faso	Unmatched Case-Control study. 983 cases - recruited from hospitals in Ouagadougou. 816 controls - recruited from rural villages near Ouagadougou
Ghana (Navrongo/Noguchi)	Matched Case-control study. 2459 cases - recruited from hospitals in Kassena-Nankana District. 2129 controls - selected from demographic surveillance system in same district, some frequency & some individually matched to cases by age, gender, location & ethnicity
Ghana (Kumasi)	Unmatched Case-Control study. 1923 cases recruited from hospitals in Kumasi. 2326 controls are cord bloods recruited from labour wards in Kumasi.
Nigeria	Unmatched Case-Control study. 114 cases - recruited from hospitals in Ibadan. 88 controls - recruited from communities in areas surrounding hospitals from which cases recruited
Cameroon	Unmatched Case-Control study. 914 cases - recruited from hospitals/health centres in South-West, Littoral & Central Regions. 914 controls - recruited from schools in South-West Region and blood bank in Central Region
Kenya	Unmatched Case-Control study. 2741 cases - recruited from Kilifi District Hospital. 4183 controls - recruited from demographic surveillance system representative of area in which cases reside
Tanzania	Matched Case-Control study. 501 cases - recruited from a hospital in Muheza. 504 controls - recruited from community, individually matched to cases by ethnicity of at least one parent, electoral ward of residence & age
Malawi	Unmatched Case-Control study. 1815 cases - recruited from a hospital in Blantyre. 3272 controls - cord blood samples taken from same hospital as cases
Viet Nam	Case-control study. 1014 cases - recruited from a hospital in Ho Chi Minh City & provincial hospitals in Southern Vietnam. 2791 controls - recruited from community, individually matched to cases by age, gender, ethnicity & location, & cord blood samples taken from a hospital in Ho Chi Minh City and a hospital in Dong Thap province
PNG	Matched Case-Control study. 658 cases - recruited from main hospital in Madang province. 553 controls - recruited from community, individually matched to cases by ethnicity, age, gender & residence, & from children with chronic minor skin infections presenting to clinics near residence of case, individually matched to cases by age, gender and ethnicity where possible
Total	16433 cases 22492 controls

Supplementary Table 2: Summary study design descriptions of contributing partner studies to MalariaGEN Consortium Project 1 (CP1). Data includes total numbers of cases and controls collected at each site preceding the filtering process as described in the Methods section. Further information for each site and study can be found on the MalariaGEN web site (see URLs)

Study site	Cases			Controls		
	Number	% Males	Age in Years Median(IQR)	Number	% Males	Age in Years Median(IQR)
Gambia	2425	52	3.8(2.2-4.3)	3342	50	0(0-0)
Mali	453	56	3(1.7-3.7)	344	51	3.1(2-3.8)
Burkina Faso	865	57	3.7(2-4.4)	729	52	3(2-2.7)
Ghana (Kumasi)	682	57	1.3(0.9-1.6)	489	56	1.2(0.8-1.4)
Ghana (Navrongo)	1496	54	2(1-2.8)	2042	52	0(0-0)
Nigeria	77	61	2.9(1.6-3.3)	40	45	2.6(1.2-3.1)
Cameroon	621	54	2.1(1.2-3.1)	578	72	21(7.6-19.2)
Kenya	2268	52	2.2(1.2-2.7)	3949	50	0.5(0.4-0.6)
Tanzania	429	53	1.7(1.1-2)	453	45	2.8(2.1-3.1)
Malawi	1388	51	2.8(1.8-3.3)	2697	52	0(0-0)
Viet Nam	794	73	29(22-32.2)	2538	54	0(0-5.1)
Papua New Guinea	392	56	3(2.1-3.4)	240	52	3.3(2.2-3.7)
Total	11890	55	2.8(1.5-5.2)	17441	52	0(0-1.9)

Supplementary Table 3: Descriptive Statistics. Features of severe malaria cases and controls after quality control filtering, as described in the Methods section. IQR, interquartile range.

Study site		Gender: %	Age in years: %	Ethnicity (%)
		M / F / missing	<5 / 5-15 / >15 / missing	
Gambia	Cases	51 / 46 / 3	71 / 29 / 0 / 0.4	Mandinka (32), Jola (15), Fula (13), Wollof (12), Other (28), Not recorded (0.4)
	Controls	44 / 51 / 4	84 / 0.4 / 5 / 11	Mandinka (30), Jola (12), Fula (18), Wollof (13), Other (20), Not recorded (8)
Mali	Cases	55 / 43 / 2	78 / 22 / 0 / 0	Bambara (42), Bambara mixed (9), Malinke (12), Peulh (6), Sarakole (7), Other (25)
	Controls	47 / 48 / 5	77 / 23 / 0 / 0.5	Bambara (46), Bambara mixed (5), Malinke (12), Peulh (6), Sarakole (5), Other (26)
Burkina Faso	Cases	54 / 42 / 4	72 / 28 / 0 / 1	Mossi (100)
	Controls	50 / 48 / 2	99 / 1 / 0 / 0	Mossi (100)
Ghana (Kumasi)	Cases	50 / 44 / 7	84 / 15 / 0 / 0.2	Akans (Ashanti/Eastern) (54), Frafra/Nankana/Grushie/Kusasu (8), Other (36)
	Controls	50 / 46 / 4	100 / 0 / 0 / 0	Akans (Ashanti/Eastern) (66), Frafra/Nankana/Grushie/Kusasu (5), Other (30)
Ghana (Noguchi/Navrongo)	Cases	55 / 42 / 3	100 / 0 / 0 / 0	Kasem (58), Nankam (29), Other (14), Not recorded (0.2)
	Controls	52 / 43 / 5	60 / 0 / 0 / 20	Kasem (55), Nankam (33), Other (12)
Nigeria	Cases	57 / 38 / 5	87 / 13 / 0 / 0	Yoruba (97), Other (3)
	Controls	49 / 41 / 10	75 / 25 / 0 / 0	Yoruba (98), Other (2)
Cameroon	Cases	47 / 43 / 10	74 / 15 / 0.1 / 11	Bantu (38), Semi-Bantu (42), Other (11), Not recorded (9)
	Controls	65 / 33 / 2	7 / 43 / 41 / 9	Bantu (41), Semi-Bantu (40), Other (5), Not recorded (11)
Kenya	Cases	49 / 45 / 7	83 / 11 / 0.04 / 6	Chonyi (23), Giriama (59), Kauma (7), Other (10), Not recorded (0.2)
	Controls	49 / 48 / 3	100 / 0 / 0 / 0	Chonyi (36), Giriama (46), Kauma (11), Other (7)
Tanzania	Cases	51 / 45 / 4	96 / 4 / 0 / 0	Mzigua(26), Mzigua mixed (7), Wasambaa (20), Wasambaa mixed (11), Wabondei (11), Wabondei mixed (7), Other (18)
	Controls	44 / 53 / 3	92 / 8 / 0 / 0	Mzigua (28), Mzigua mixed (5), Wasambaa (20), Wasambaa mixed (10), Wabondei (12), Wabondei (6), Other (18)
Malawi	Cases	50 / 46 / 4	82 / 18 / 0 / 0.5	Malawi (100)
	Controls	47 / 42 / 12	100 / 0 / 0 / 0	Malawi (100)
Viet Nam	Cases	71 / 29 / 1	5 / 6 / 89 / 0	Kinh (88), Other (10), Not recorded (3)
	Controls	51 / 45 / 4	82 / 5 / 13 / 0.3	Kinh (94), Other (6), Not recorded (0.4)
PNG	Cases	55 / 44 / 1	82 / 18 / 0 / 0.2	Madang (67), Madang mixed (6), Sepik (8), Other (9), Not recorded (10)
	Controls	38 / 33 / 30	81 / 18 / 0 / 2	Madang (63), Madang mixed (5), Sepik (7), Other (8), Not recorded (16)
Total	Cases	52 / 43 / 4	78 / 15 / 6 / 2	
	Controls	49 / 46 / 5	88 / 4 / 4 / 5	

Supplementary Table 4: Gender, age and ethnicity of cases and controls collected by each contributing partner study to MalariaGEN Consortium Project 1 (CP1). These data represent the proportions included for analysis following the filtering process (as described in the Methods section). Ethnic groups representing <5% of the site sample set are grouped together as 'Other'.

Gene	Chr	SNP Ref	Alternative Name	Location	Ancestral Allele ^a	Derived Allele	Single Letter code	Mean Frequency (min - max)	References
ATP2B4	1	rs55868763		203652140	C	G	S	0.73(0.62-1)	
ATP2B4	1	rs1541255		203652141	A	G	D	0.27(0-0.38)	
ATP2B4	1	rs10900585		203654024	G	T	K	0.71(0.57-0.98)	1,2
ATP2B4	1	rs4951074		203660781	G	A	R	0.26(0-0.37)	
ATP2B4	1	rs3753036		203677250	G	A	R	0.04(0-0.17)	
CR1	1	rs17047660	McC (McCoy)	207782856	A	G	R	0.26(0.16-0.37)	3-8,9
CR1	1	rs17047661	SI (Swain-Lagley)	207782889	A	G	R	0.72(0.67-0.8)	
DARC	1	rs2814778	Duffy – FyA/FyB	159174683	T	C	Y	0.83 (0.83-1)	10-12
IL10	1	rs3024500		206940831	G	A	R	0.39(0.06-0.55)	13,14
IL10	1	rs1800896		206946897	T	C	Y	0.29(0.06-0.4)	
IL10	1	rs1800890		206949365	A	T	W	0.19(0.04-0.34)	
IL1A	2	rs17561	IL1A G4845T	113537223	C	A	M	0.16(0.05-0.23)	15-17
IL1B	2	rs1143634	IL1B A2	113590390	G	A	R	0.1(0.01-0.24)	
TLR9	3	rs187084		52261031	G	A	R	0.70(0.50-0.77)	18-20
TLR1	4	rs4833095		38799710	C	T	Y	0.15(0.07-0.47)	21
TLR6	4	rs5743810		38830350	G	A	R	0.01(0.01-0.02)	21
TLR6	4	rs5743809		38830514	A	G	R	0.04(0.01-0.08)	
C6	5	rs1801033		41199959	T	G	K	0.48 (0.42-0.60)	22-24
IL13	5	rs20541		131995964	G	A	R	0.23(0.09-0.42)	25
IL4	5	rs2243250	IL-4-589	132009154	C	T	Y	0.76(0.45-0.83)	17,25-27
IRF1	5	rs2706384		131826880	G	T	K	0.44(0.38-0.78)	28
LTA	6	rs2239704	LTA +77	31540141	C	A	M	0.26(0.12-0.46)	17,29-43
LTA	6	rs909253	LTA NCO1	31540313	A	G	R	0.47(0.12-0.56)	
TNF	6	rs1799964	TNFA -1031	31542308	T	C	Y	0.2(0.12-0.41)	31,32,37,40,44-49
TNF	6	rs1800750	TNF-376	31542963	G	A	R	0.04(0.01-0.42)	
TNF	6	rs1800629	TNF -308	31543031	G	A	R	0.11(0.07-0.14)	
TNF	6	rs361525	TNF -238	31543101	G	A	R	0.05(0.01-0.09)	
TNF	6	rs3093662	TNF +851	31544189	A	G	R	0.08(0.01-0.12)	
CD36	7	rs3211938	CD36 T1264G	80300449	T	G	K	0.09(0.02-0.27)	50-56
CD36	7	rs210346212	CD36 G1439C	80302110	G	C	S	0.02(0.01-0.06)	
ABO	9	rs8176746		136131322	G	T	K	0.17(0.13-0.26)	57-59
ABO	9	rs8176719		136132909	C (INS)	- (DEL)	I	0.69(0.59-0.78)	
TLR4	9	rs4986791		120475602	C	T	Y	0.01(0.01-0.02)	18,19,60-64
TLR4	9	rs4986790		120475302	A	G	R	0.06(0.01-0.11)	
HBB	11	rs33950507	HbE	5248173	G (INS)	- (DEL)	I	0.01(0.01-0.04)	65-68
HBB	11	rs334	HbS	5248232	T	A	W	0.07(0.03-0.11)	69-72 73
HBB	11	rs33930165	HbC	5248233	G	A	R	0.03(0.01-0.15)	73-77
IL22	12	rs2227507	IL22+4583	68642647	T	C	Y	0.04(0.01-0.04)	
IL22	12	rs1012356	IL22+2611	68644618	A	T	W	0.51(0.04-0.58)	
IL22	12	rs2227491	IL22+708	68646521	T	C	Y	0.63(0.05-0.71)	78
IL22	12	rs2227485	IL22-485	68647713	G	A	R	0.47(0.05-0.58)	
IL22	12	rs2227478	IL22-1394	68648622	G	A	R	0.67(0.28-0.85)	
SPTB	14	rs229587		65263300	T	C	Y	0.35(0.22-0.61)	79
ADORA2B	17	rs2535611		15861332	C	T	Y	0.07(0.01-0.14)	80
NOS2	17	rs2297518		26096597	G	A	R	0.12(0.05-0.16)	81-86
NOS2	17	rs1800482	NOS2A -954/969	26128509	C	G	S	0.09(0.06-0.12)	
NOS2	17	rs9282799	NOS2A -1173	26128728	G	A	R	0.05(0.03-0.08)	
NOS2	17	rs8078340	NOS2A -1659	26129212	G	A	R	0.2(0.02-0.28)	
ICAM1	19	rs1799969	ICAM1 codon241	10394792	G	A	R	0(0-0)	55,56,87,88
ICAM1	19	rs5498	ICAM1 codon469	10395683	A	G	R	0.14(0.11-0.54)	
GNAS	20	rs8386		57485812	C	T	Y	0.16(0.12-0.27)	89,90
CD40LG	23	rs3092945	CD40LG -727	135729609	T	C	Y	0.27(0.03-0.47)	91-93
CD40LG	23	rs1126535	CD40LG +220	135730555	T	C	Y	0.14(0.08-0.4)	
G6PD	X	rs1050829	G6PD +376	153763492	T	C	Y	0.39 (0.32-0.52)	94-98
G6PD	X	rs1050828	G6PD +202	153764217	C	T	Y	0.15(0.03-0.29)	

Supplementary Table 5: Summary of 55 SNPs selected for analysis due to a known association with malaria and successfully genotyped. Details of SNPs include an alternate name, ancestral or reference allele, the single letter nucleotide code, the mean frequency of the derived allele in controls (with range by ethnicity) plus selected references. All SNPs are referenced to GRCh37, dbSNP137 and Ensembl build 73.

Chr, Chromosome.

^aAncestral allele is assigned from dbSNP137 or, where not available, from human reference sequence Ensembl build 73.

^bNo rs designation.

Gene	Chr	SNP Ref	Alternative Name	Location	Ancestral Allele ^{a,b}	Derived Allele ^b	Single Letter code	Mean Frequency (min - max)	References
GBP7	1	rs1803632		89582690	G	C	S	0.51(0.28-0.75)	25
IL17RD	3	rs6780995		57138419	G	A	R	0.51(0.15-0.61)	99
IL17RE	3	rs708567		9960070	C	T	Y	0.43(0.11-0.71)	99
CTL4	6	rs2242665		31839309	C	T	Y	0.70(0.62-0.82)	
IL20RA	6	rs1555498		137325847	C	T	Y	0.53(0.39-1)	100,101
CFTR	7	rs17140229		117230283	T	C	Y	0.36(0.29-0.45)	102,103
NOD1	7	rs2075820		30492237	C	T	Y	0.38(0.15-0.45)	104,105
RTN3	11	rs542998		63487386	T	C	Y	0.49(0.34-0.98)	
TRIM5	11	rs7935564		5718517	G	A	R	0.42(0.17-0.52)	106
ADCY9	16	rs2230739		4033436	T	C	Y	0.15(0.07-0.39)	80,107
ADCY9	16	rs10775349		4079823	C	G	S	0.30(0.11-0.99)	
IL4R	16	rs1805015		27374180	T	C	Y	0.39(0.11-0.49)	108,109
EMR1	19	rs373533		6919624	C	A	M	0.43(0.31-0.67)	110
EMR1	19	rs461645		6919753	A	G	R	0.57(0.34-0.69)	
DERL3	22	rs1128127		24179132	G	A	R	0.47(0.01-0.60)	
AMELX/AMELY	X	None assigned	Amelogenin_SNP1	11313735	G	A	R	NA	
AMELX/AMELY	X	None assigned	Amelogenin_SNP2	11316106	T	C	Y	NA	
AMELX/AMELY	X	None assigned	Amelogenin_SNP6	11316650	C	A	M	NA	

Supplementary Table 6: Additional genes and SNPs selected for analysis and successfully genotyped. Summary of 18 additional SNPs genotyped, 15 of which were selected due to a non genetic association with severe malaria and 3 of which (in the AMELX/AMELY genes) were selected for gender typing. Details of SNPs include an alternate name, ancestral or reference allele, the single letter nucleotide code, the mean frequency of the derived allele in controls (with range by ethnicity) plus selected references. All SNPs are referenced to GRCh37, dbSNP137 and Ensembl build 73.

Chr, Chromosome.

^aAncestral allele is assigned from dbSNP137 or, where not available, from human reference sequence Ensembl build 73.

^bFor AMELX/AMELY SNPs, ancestral allele column shows X chromosome allele and derived allele column shows Y chromosome allele.

Gene	Chr	SNP Ref	Alternative Name	Location	Ancestral Allele ^{a,b}	Derived Allele ^b	Single Letter code	References
FCGR2a	1	rs1801274	FCGR2a-H131R	161479745	A	G	R	111,112
RGS2	1	rs2179652		192769826	T	C	Y	80,113
TLR10	4	rs1109695 7		38776491	T	G	K	114
TLR1	4	rs5743611		38800214	C	G	S	21
CD36	7	None assigned	CD36_I1444D	80302115	I	D	I	50-56
ABO	9	rs8176747		136131315	C	G	S	57-59
ABO	9	rs8176743		136131415	C	T	Y	57-59
CASP5	11	rs523104		104869708	G	C	S	
SPTB	14	rs77806		65253232	C	T	Y	79
RAGE	14	rs2236493		102695693	C	T	Y	115
MARVELD3	16	rs2334880		71653637	A	G	R	2
ICAM1	19	rs5491	ICAM-1codon29	10385540	A	T	W	55,56,87,88
CEACAM1	19	rs8110904		43031369	A	G	R	116
APOE	19	rs7412	APOE_Arg176Cys	45412079	C	T	Y	117-120
GNAS	20	rs2057291		57472043	G	A	R	89
AMELX/AMELY	X	None assigned	Amelogenin_SNP3	11316131	A	G	R	

Supplementary Table 7: Genes and SNPs selected for genotyping and analyses dropped due to poor genotyping quality. List of 16 additional SNPs, including 1 (in the AMELX/AMELY gene) selected for gender typing, which were dropped as a consequence of poor genotyping quality. Details of SNPs include an alternate name, ancestral or reference allele, the single letter nucleotide code, the mean frequency of the derived allele in controls (with range by ethnicity) plus selected references. All SNPs are referenced to GRCh37, dbSNP137 and Ensembl build 73.

Chr, Chromosome.

^aAncestral allele is assigned from dbSNP137 or, where not available, from human reference sequence Ensembl build 73.

^bFor AMELX/AMELY SNPs, ancestral allele column shows X chromosome allele and derived allele column shows Y chromosome allele.

Gene	Chromosome	SNP Ref	Sample	Best Model ^a	Best Model OR(95% CI)	Best Model P	Heterozygote OR(95% CI)	Derived Homozygote OR(95% CI)	Genotypic P	Frequency (Derived Homozygote/Heterozygote/Ancstral Homozygote)		Alleles	
										Cases	Controls	An	De
ABO	9	rs8176746	All	D	1.25(1.19-1.32)	2.01 X 10 ⁻¹⁷	1.24(1.18-1.31)	1.37(1.2-1.56)	8.19 X 10 ⁻¹⁷	0.2(7512/3817/507)	0.17(11943/4852/565)	C	A
ABO	9	rs8176719	All	R	0.74(0.7-0.78)	4.99 X 10 ⁻³³	0.88(0.81-0.96)	0.67(0.62-0.73)	1.01 X 10 ⁻³³	0.64(1506/5533/4750)	0.69(1700/7215/8238)	I	D
ADCY9	16	rs2230739	All	H	0.94(0.89-1)	0.05	0.94(0.88-1)	0.99(0.85-1.16)	0.15	0.13(9115/2463/290)	0.15(12706/4094/604)	A	G
ADCY9	16	rs10775349	All	R	1.09(0.96-1.24)	0.18	1(0.94-1.06)	1.09(0.96-1.24)	0.4	0.26(7270/3134/1461)	0.3(9884/4518/3000)	C	G
ADORA2B	17	rs2535611	All	A	1.01(0.95-1.08)	0.69	1.01(0.94-1.09)	1.03(0.78-1.36)	0.92	0.08(10044/1629/98)	0.07(14377/2198/130)	T	C
ATP2B4	1	rs55868763	All	D	1.33(1.21-1.47)	9.52 X 10 ⁻⁰⁹	1.31(1.19-1.46)	1.34(1.21-1.49)	5.91 X 10 ⁻⁰⁸	0.71(742/3935/4554)	0.68(1428/5690/6229)	C	G
ATP2B4	1	rs1541255	All	R	0.75(0.68-0.83)	4.87 X 10 ⁻⁰⁹	0.98(0.92-1.04)	0.74(0.67-0.82)	3.10 X 10 ⁻⁰⁸	0.29(4558/3922/743)	0.32(6241/5667/1439)	A	G
ATP2B4	1	rs10900585	All	D	1.32(1.21-1.45)	1.69 X 10 ⁻⁰⁹	1.32(1.2-1.46)	1.33(1.2-1.46)	1.37 X 10 ⁻⁰⁸	0.68(868/4056/4203)	0.66(1644/5722/5737)	G	T
ATP2B4	1	rs4951074	All	R	0.77(0.7-0.86)	7.64 X 10 ⁻⁰⁷	0.98(0.92-1.04)	0.76(0.69-0.85)	4.13 X 10 ⁻⁰⁶	0.29(4365/3605/658)	0.31(6115/5392/1284)	G	A
ATP2B4	1	rs3753036	All	H	0.98(0.87-1.09)	0.67	0.98(0.87-1.09)	0.99(0.64-1.54)	0.91	0.03(9900/540/28)	0.04(14787/1253/81)	G	A
C6	5	rs1801033	All	R	0.99(0.94-1.06)	0.87	1(0.94-1.06)	0.99(0.93-1.07)	0.98	0.46(3418/5885/2531)	0.48(4757/8591/4003)	A	C
CD36	7	rs210346212	All	H	0.67(0.54-0.84)	4.19 X 10 ⁻⁰⁴	0.67(0.54-0.84)	1.74(0.49-6.15)	1.36 X 10 ⁻⁰³	0.01(6374/138/6)	0.02(7252/236/5)	G	C
CD36	7	rs3211938	All	H	0.9(0.83-0.97)	6.17 X 10 ⁻⁰³	0.9(0.84-0.97)	1.08(0.86-1.35)	0.02	0.09(8904/1590/173)	0.09(12291/2178/174)	T	G
CD40LG	X	rs3092945	M	M	0.9(0.83-0.98)	1.04 X 10 ⁻⁰²	n.c. [¶]	n.c. [¶]	n.c. [¶]	0.28(4487/0/1737)	0.27(6449/0/2348)	T	C
CD40LG	X	rs3092945	F	R	0.78(0.69-0.88)	8.93 X 10 ⁻⁰⁵	1.03(0.95-1.12)	0.79(0.7-0.9)	3.63 X 10 ⁻⁰⁴	0.3(2636/2035/513)	0.27(4581/2621/849)	T	C
CD40LG	X	rs3092945	All	R	0.85(0.79-0.91)	1.11 X 10 ⁻⁰⁶	1.11(1.02-1.2)	0.86(0.81-0.92)	2.40 X 10 ⁻⁰⁷	0.29(7123/2035/2250)	0.27(11030/2621/3197)	T	C
CD40LG	X	rs1126535	M	M	1(0.91-1.1)	0.99	n.c. [¶]	n.c. [¶]	n.c. [¶]	0.15(5527/0/948)	0.14(7793/0/1290)	T	C
CD40LG	X	rs1126535	F	R	0.94(0.74-1.19)	0.58	1(0.92-1.1)	0.94(0.74-1.19)	0.86	0.14(3967/1283/126)	0.14(6206/1904/193)	T	C
CD40LG	X	rs1126535	All	R	0.98(0.89-1.07)	0.59	1.03(0.95-1.12)	0.98(0.89-1.07)	0.67	0.14(9494/1283/1074)	0.14(13999/1904/1483)	T	C
CFTR	7	rs17140229	All	H	0.98(0.92-1.04)	0.49	0.98(0.92-1.05)	1.02(0.93-1.12)	0.72	0.38(3314/3963/1234)	0.36(5182/5816/1632)	T	C
CR1	1	rs17047660	All	R	1.05(0.95-1.16)	0.32	1(0.94-1.06)	1.05(0.95-1.16)	0.61	0.27(5669/4132/856)	0.26(8059/5508/1048)	A	G
CR1	1	rs17047661	All	H	1.02(0.96-1.07)	0.56	1.02(0.92-1.13)	1(0.9-1.11)	0.84	0.73(783/4181/5701)	0.72(1159/5820/7633)	A	G
CTL4	6	rs2242665	All	D	0.92(0.85-1)	0.06	0.92(0.84-1.01)	0.92(0.85-1.01)	0.16	0.7(1163/4804/5816)	0.7(1670/7134/8465)	G	A
DARC	1	rs2814778	All	D	4.91(0.4-60.95)	0.2	4.27(0.35-52.71)	4.08(0.32-52.06)	0.5	0.89(1171/44/9691)	0.83(2751/59/13799)	A	G
DERL3	22	rs1128127	All	H	0.98(0.93-1.03)	0.41	0.97(0.91-1.03)	0.98(0.92-1.06)	0.66	0.49(3314/5323/3159)	0.47(5327/7634/4290)	G	A
EMR1	19	rs373533	All	D	1.03(0.98-1.09)	0.28	1.03(0.98-1.09)	1.02(0.95-1.09)	0.51	0.45(3612/5755/2376)	0.43(5667/8256/3280)	G	T
EMR1	19	rs461645	All	R	0.97(0.92-1.02)	0.2	1.02(0.95-1.09)	0.98(0.91-1.05)	0.38	0.55(2413/5784/3650)	0.57(3357/8303/5726)	T	C
G6PD	X	rs1050829	M	M	1.08(1.01-1.17)	0.04	n.c. [¶]	n.c. [¶]	n.c. [¶]	0.4(3396/0/2228)	0.38(4679/0/2869)	T	C
G6PD	X	rs1050829	F	H	0.93(0.86-1)	0.06	0.92(0.85-1)	0.98(0.87-1.1)	0.17	0.38(1921/2285/762)	0.39(2606/3356/1062)	T	C
G6PD	X	rs1050829	All	R	1.06(1-1.13)	0.05	0.94(0.87-1.02)	1.05(0.99-1.12)	0.05	0.39(5317/2285/2990)	0.38(7285/3356/3931)	T	C
G6PD	X	rs1050828	M	M	1.1(0.99-1.22)	0.07	n.c. [¶]	n.c. [¶]	n.c. [¶]	0.15(4811/0/866)	0.15(6483/0/1105)	C	T
G6PD	X	rs1050828	F	H	0.9(0.82-0.99)	0.02	0.9(0.82-0.99)	1.11(0.87-1.42)	0.06	0.14(3705/1152/134)	0.15(5069/1770/174)	C	T
G6PD	X	rs1050828	All	A	1.02(0.97-1.06)	0.15	0.9(0.82-0.98)	1.1(1-1.21)	6.35 X 10 ⁻⁰³	0.15(8516/1152/1000)	0.15(11552/1770/1279)	C	T
GBP7	1	rs1803632	All	A	1.03(0.99-1.07)	0.11	1.03(0.97-1.09)	1.06(0.99-1.14)	0.27	0.49(3170/5725/2965)	0.51(4369/8259/4777)	G	C
GNAS	20	rs8386	All	H	0.96(0.9-1.02)	0.16	0.96(0.9-1.02)	1.04(0.89-1.22)	0.33	0.16(7505/2863/318)	0.16(10246/3995/398)	C	T
HBB	11	rs33950507	All	H	0.99(0.67-1.45)	0.94	1.01(0.68-1.48)	1.4(0.55-3.58)	0.78	0.01(4029/39/8)	0.01(6447/127/27)	G	A
HBB	11	rs334	All	H	0.14(0.12-0.16)	1.62 X 10 ⁻²²⁵	0.14(0.12-0.16)	1.4(1.02-1.92)	7.92 X 10 ⁻²²⁵	0.02(10388/213/84)	0.07(12773/1791/77)	A	T
HBB	11	rs33930165	All	A	0.71(0.63-0.8)	6.87 X 10 ⁻⁰⁹	0.71(0.61-0.82)	0.5(0.34-0.73)	5.13 X 10 ⁻⁰⁸	0.04(6866/445/46)	0.03(9341/515/74)	G	A
ICAM1	19	rs1799969	All	ADH*	0.94(0.45-1.96)	0.86	n.c. [§]	n.c. [§]	n.c. [§]	0(5459/11/0)	0(9294/27/0)	G	A
ICAM1	19	rs5498	All	D	1.04(0.98-1.1)	0.18	1.04(0.98-1.1)	1.03(0.87-1.21)	0.4	0.15(8560/2900/334)	0.14(12716/4164/411)	A	G
IL10	1	rs3024500	All	H	0.98(0.93-1.03)	0.39	0.98(0.92-1.03)	0.99(0.92-1.07)	0.69	0.41(4274/5380/2197)	0.39(6859/7440/3080)	A	G

IL10	1	rs1800896	All	R	0.94(0.87-1.02)	0.15	1.02(0.97-1.08)	0.95(0.87-1.04)	0.27	0.3(5800/4869/1168)	0.29(8946/6734/1723)	T	C
IL10	1	rs1800890	All	R	0.88(0.78-0.99)	0.04	0.98(0.92-1.03)	0.87(0.77-0.99)	0.08	0.19(7740/3647/486)	0.19(11441/5183/784)	A	T
IL13	5	rs20541	All	A	0.99(0.95-1.04)	0.77	0.99(0.93-1.06)	0.98(0.87-1.12)	0.96	0.21(6031/2955/492)	0.23(8778/4974/938)	C	T
IL17RD	3	rs6780995	All	H	1.03(0.98-1.08)	0.29	1.04(0.97-1.11)	1.02(0.95-1.09)	0.51	0.53(2739/5616/3486)	0.51(4680/7806/4890)	G	A
IL17RE	3	rs708567	All	D	1.05(0.99-1.11)	0.08	1.06(1-1.12)	1.04(0.97-1.12)	0.19	0.47(3416/5579/2750)	0.43(5820/7587/3555)	G	A
IL1A	2	rs17561	All	H	1.07(1.02-1.13)	0.01	1.07(1.02-1.14)	1.02(0.88-1.18)	0.04	0.17(8141/3377/361)	0.16(12491/4439/479)	G	T
IL1B	2	rs1143634	All	A	1.05(1-1.11)	0.07	1.05(0.98-1.12)	1.14(0.93-1.4)	0.18	0.12(9216/2457/188)	0.1(13962/3178/215)	C	T
IL20RA	6	rs1555498	All	A	1.02(0.99-1.06)	0.23	1.02(0.96-1.08)	1.05(0.97-1.13)	0.49	0.49(3368/5336/3162)	0.53(4600/7179/5633)	C	T
IL22	12	rs2227507	All	A	0.98(0.89-1.08)	0.65	0.96(0.87-1.06)	1.42(0.74-2.72)	0.41	0.03(9960/708/19)	0.04(13593/1033/20)	T	C
IL22	12	rs1012356	All	D	1.06(1-1.13)	0.04	1.06(1-1.13)	1.06(0.99-1.14)	0.13	0.5(3017/5757/3091)	0.51(4254/8493/4643)	A	T
IL22	12	rs2227491	All	D	1.07(0.99-1.15)	0.1	1.06(0.98-1.14)	1.08(0.99-1.16)	0.21	0.64(1717/5075/4986)	0.63(2505/7684/7080)	T	C
IL22	12	rs2227485	All	H	1.04(0.99-1.09)	0.11	1.05(0.99-1.11)	1.02(0.95-1.09)	0.24	0.46(3495/5705/2627)	0.47(4979/8362/4021)	G	A
IL22	12	rs2227478	All	H	1.04(0.99-1.09)	0.15	1.04(0.96-1.13)	1(0.92-1.09)	0.35	0.65(1562/5209/5089)	0.67(2059/7268/8059)	G	A
IL4	5	rs2243250	All	H	1.06(1.01-1.12)	0.03	1.1(0.99-1.23)	1.04(0.94-1.16)	0.07	0.75(754/4284/6566)	0.76(1101/6094/10066)	C	T
IL4R	16	rs1805015	All	H	0.98(0.93-1.03)	0.48	0.99(0.93-1.05)	1.01(0.94-1.09)	0.73	0.41(4375/5288/2172)	0.39(6872/7570/2912)	T	C
IRF1	5	rs2706384	All	A	0.94(0.91-0.98)	1.35 X 10 ⁻⁰³	0.94(0.89-1)	0.89(0.83-0.96)	0.01	0.42(3964/5423/2137)	0.44(5462/8154/3434)	C	A
LTA	6	rs2239704	All	D	1.04(0.98-1.09)	0.18	1.04(0.98-1.09)	1.04(0.95-1.14)	0.4	0.28(6129/4502/1088)	0.26(9604/6224/1411)	G	T
LTA	6	rs909253	All	A	0.97(0.94-1)	0.08	0.97(0.92-1.03)	0.94(0.87-1.01)	0.21	0.45(3676/5627/2464)	0.47(4997/8355/3853)	T	C
NOD1	7	rs2075820	All	H	1.03(0.98-1.08)	0.21	1.03(0.97-1.08)	0.99(0.92-1.06)	0.43	0.38(4526/5577/1732)	0.38(6692/8105/2597)	G	A
NOS2	17	rs2297518	All	A	0.96(0.91-1.02)	0.17	0.97(0.91-1.03)	0.89(0.73-1.09)	0.35	0.11(9380/2301/159)	0.12(13373/3691/298)	G	A
NOS2	17	rs1800482	All	H	0.97(0.9-1.04)	0.38	0.97(0.9-1.04)	1(0.75-1.34)	0.68	0.09(8916/1644/86)	0.09(12169/2320/120)	G	C
NOS2	17	rs9282799	All	A	1.1(1.02-1.19)	0.02	1.08(0.99-1.18)	1.49(0.98-2.27)	0.03	0.06(9443/1196/51)	0.05(13124/1476/45)	C	T
NOS2	17	rs8078340	All	R	0.92(0.82-1.03)	0.14	1.02(0.96-1.07)	0.92(0.82-1.04)	0.3	0.21(7302/4000/544)	0.2(11224/5365/808)	C	T
RTN3	11	rs542998	All	H	0.97(0.92-1.02)	0.28	0.97(0.91-1.03)	0.99(0.92-1.07)	0.54	0.45(3897/5109/2775)	0.49(5203/7090/4964)	T	C
SPTB	14	rs229587	All	R	1.04(0.96-1.12)	0.34	0.98(0.93-1.04)	1.03(0.95-1.12)	0.52	0.33(5027/4720/1359)	0.35(7361/7416/2348)	T	C
TLR1	4	rs4833095	All	R	1.1(0.94-1.28)	0.23	0.98(0.92-1.04)	1.09(0.93-1.27)	0.36	0.13(9042/2422/314)	0.15(12637/3942/681)	C	T
TLR4	9	rs4986791	All	H	1.12(0.92-1.37)	0.25	1.12(0.92-1.37)	0.29(0.03-2.9)	0.27	0.01(11657/195/1)	0.01(17141/248/3)	C	T
TLR4	9	rs4986790	All	R	0.78(0.58-1.07)	0.12	1.04(0.58-1.12)	0.79(0.58-1.07)	0.18	0.07(10234/1525/75)	0.06(15371/1879/112)	A	G
TLR6	4	rs5743810	All	H	1.09(0.88-1.34)	0.43	1.09(0.88-1.34)	0.87(0.09-8.7)	0.73	0.01(11243/166/1)	0.01(16903/227/3)	C	T
TLR6	4	rs5743809	All	D	1.05(0.95-1.15)	0.33	1.05(0.95-1.15)	1.03(0.63-1.66)	0.62	0.04(10384/922/30)	0.04(15698/1279/43)	T	C
TLR9	3	rs187084	All	R	1.04(0.98-1.09)	0.2	0.99(0.9-1.09)	1.02(0.93-1.13)	0.42	0.71(960/4335/5625)	0.7(1455/6473/7909)	C	T
TNF	6	rs1799964	All	D	1.04(0.98-1.09)	0.18	1.04(0.98-1.09)	1.04(0.92-1.18)	0.41	0.2(7689/3638/506)	0.2(11148/5452/767)	T	C
TNF	6	rs1800629	All	D	1.01(0.95-1.07)	0.76	1.01(0.95-1.07)	1.01(0.82-1.25)	0.95	0.11(9373/2282/172)	0.11(13921/3273/222)	G	A
TNF	6	rs361525	All	H	1.08(0.99-1.17)	0.09	1.07(0.99-1.17)	0.87(0.55-1.37)	0.2	0.05(10704/1125/31)	0.05(15732/1647/55)	G	A
TNF	6	rs3093662	All	H	1.04(0.97-1.12)	0.24	1.04(0.97-1.12)	0.91(0.69-1.21)	0.41	0.08(9954/1798/87)	0.08(14652/2591/143)	A	G
TRIM5	11	rs7935564	All	H	0.98(0.93-1.03)	0.37	0.98(0.93-1.04)	1.01(0.94-1.08)	0.65	0.46(3564/5681/2514)	0.42(5881/8072/3205)	G	A

Supplementary Table 8: All severe malaria association signals. Summary of association signals at all SNPs for *all-severe-malaria* across the 12 contributing Consortium Project 1 study sites. Odds ratios (OR), 95% confidence intervals (95% CI) and p-values (P) are presented for the best model (for autosomal SNPs and for females at X chromosome SNPs this is the model (selected from additive, recessive, dominant or heterozygote advantage) that has the most significant association; for males at X chromosome, this is the male hemizygote model and; for all individuals combined at X chromosome SNPs this is the model (selected from additive, recessive or dominant) that has the most significant association. Heterozygote and homozygote ORs from a genotypic model are also presented. Results are adjusted for HbS (except rs334), gender and ethnicity. Sites at which a SNP was found to be monomorphic were excluded from the analysis. An, ancestral; De, derived; n.c., not calculated. ^aModels are A, additive; D, dominant; H, heterozygote advantage; M, male hemizygote; R, recessive. ^sGenotype counts too small for accurate calculation. ¹Not applicable to male hemizygotes. *Models are equivalent due to zero genotype class.

Gene	Chromosome	SNP Ref	Sample	Best Model [†]	Best Model OR(95% CI)	Best Model P	Heterozygote OR(95% CI)	Derived Homozygote OR(95% CI)	Genotypic P	Frequency (Derived Homozygote/ Heterozygote/Ancstral Homozygote)		Alleles	
										Cases	Controls	An	De
ABO	9	rs8176746	All	A	1.27(1.18-1.36)	2.00 X 10 ⁻¹¹	1.29(1.19-1.4)	1.53(1.25-1.88)	1.38 X 10 ⁻¹⁰	0.2(2148/1049/138)	0.17(11943/4852/565)	C	A
ABO	9	rs8176719	All	R	0.73(0.67-0.79)	8.85 X 10 ⁻¹⁶	0.84(0.74-0.96)	0.63(0.56-0.72)	2.95 X 10 ⁻¹⁶	0.64(415/1537/1373)	0.69(1700/7215/8238)	I	D
ADCY9	16	rs2230739	All	A	0.95(0.87-1.03)	0.23	0.95(0.86-1.05)	0.91(0.7-1.19)	0.49	0.12(2593/675/69)	0.15(12706/4094/604)	A	G
ADCY9	16	rs10775349	All	A	0.97(0.9-1.04)	0.35	0.98(0.9-1.07)	0.9(0.73-1.11)	0.58	0.24(2065/944/327)	0.3(9884/4518/3000)	C	G
ADORA2B	17	rs2535611	All	H	1.09(0.98-1.22)	0.13	1.09(0.98-1.21)	0.94(0.61-1.45)	0.30	0.09(2779/524/27)	0.07(14377/2198/130)	T	C
ATP2B4	1	rs55868763	All	D	1.41(1.21-1.66)	9.35 X 10 ⁻⁰⁶	1.43(1.17-1.77)	1.53(1.25-1.89)	1.48 X 10 ⁻⁰⁴	0.71(137/791/929)	0.68(1428/5690/6229)	C	G
ATP2B4	1	rs1541255	All	R	0.7(0.59-0.82)	4.03 X 10 ⁻⁰⁶	0.93(0.83-1.04)	0.65(0.53-0.79)	1.02 X 10 ⁻⁰⁴	0.29(932/788/137)	0.32(6241/5667/1439)	A	G
ATP2B4	1	rs10900585	All	D	1.35(1.17-1.57)	3.06 X 10 ⁻⁰⁵	1.49(1.22-1.81)	1.58(1.3-1.92)	1.34 X 10 ⁻⁰⁵	0.69(159/816/851)	0.66(1644/5722/5737)	G	T
ATP2B4	1	rs4951074	All	R	0.75(0.64-0.88)	3.66 X 10 ⁻⁰⁴	1(0.89-1.12)	0.64(0.51-0.79)	6.97 X 10 ⁻⁰⁵	0.28(890/762/121)	0.31(6115/5392/1284)	G	A
ATP2B4	1	rs3753036	All	H	0.92(0.76-1.11)	0.38	1.22(0.93-1.59)	1.34(0.3-5.94)	0.36	0.02(1946/72/2)	0.04(14787/1253/81)	G	A
C6	5	rs1801033	All	R	0.99(0.9-1.09)	0.89	1(0.92-1.1)	1(0.89-1.11)	0.99	0.47(942/1667/720)	0.48(4757/8591/4003)	A	C
CD36	7	rs210346212	All	H	0.71(0.49-1.02)	0.06	0.71(0.49-1.02)	4.09(0.86-19.43)	0.04	0.02(1228/37/3)	0.02(7252/236/5)	G	C
CD36	7	rs3211938	All	R	1.35(0.94-1.94)	0.12	0.96(0.85-1.08)	1.33(0.93-1.92)	0.23	0.08(2621/412/42)	0.09(12291/2178/174)	T	G
CD40LG	X	rs3092945	M	M	0.85(0.75-0.97)	1.35 X 10 ⁻⁰²	n.c. [‡]	n.c. [‡]	n.c. [‡]	0.25(1289/0/439)	0.27(6449/0/2348)	T	C
CD40LG	X	rs3092945	F	R	0.9(0.74-1.09)	0.27	1.02(0.9-1.16)	0.91(0.74-1.11)	0.52	0.29(813/576/157)	0.27(4581/2621/849)	T	C
CD40LG	X	rs3092945	All	R	0.85(0.76-0.94)	0	1.07(0.95-1.2)	0.86(0.77-0.95)	4.74 X 10 ⁻⁰³	0.27(2102/576/596)	0.27(11030/2621/3197)	T	C
CD40LG	X	rs1126535	M	M	1.02(0.88-1.19)	0.76	n.c. [‡]	n.c. [‡]	n.c. [‡]	0.15(1495/0/266)	0.14(7793/0/1290)	T	C
CD40LG	X	rs1126535	F	R	0.72(0.48-1.07)	0.09	1.01(0.89-1.15)	0.72(0.48-1.08)	0.24	0.15(1141/396/30)	0.14(6206/1904/193)	T	C
CD40LG	X	rs1126535	All	R	0.96(0.83-1.1)	0.57	1.05(0.93-1.2)	0.96(0.84-1.11)	0.62	0.15(2636/396/296)	0.14(13999/1904/1483)	T	C
CFTR	7	rs17140229	All	D	0.95(0.86-1.05)	0.35	0.95(0.86-1.06)	0.97(0.83-1.13)	0.64	0.35(871/916/255)	0.36(5182/5816/1632)	T	C
CR1	1	rs17047660	All	A	1.09(1.02-1.17)	7.56 X 10 ⁻⁰³	1.09(1-1.19)	1.19(1.02-1.4)	0.03	0.27(1647/1185/248)	0.26(8059/5508/1048)	A	G
CR1	1	rs17047661	All	H	1.03(0.95-1.12)	0.41	1.02(0.88-1.2)	0.99(0.85-1.15)	0.71	0.71(246/1266/1566)	0.72(1159/5820/7633)	A	G
CTL4	6	rs2242665	All	A	0.97(0.92-1.03)	0.39	0.96(0.84-1.11)	0.94(0.82-1.08)	0.68	0.7(319/1375/1624)	0.7(1670/7134/8465)	G	A
DARC	1	rs2814778	All	H	0.72(0.37-1.38)	0.3	n.c. [§]	n.c. [§]	n.c. [§]	0.92(250/11/2960)	0.83(2751/59/13799)	A	G
DERL3	22	rs1128127	All	A	0.99(0.94-1.05)	0.76	0.99(0.9-1.09)	0.98(0.88-1.1)	0.95	0.49(911/1539/865)	0.47(5327/7634/4290)	G	A
EMR1	19	rs373533	All	H	1.07(0.99-1.16)	0.08	1.09(1-1.19)	1.05(0.94-1.17)	0.16	0.46(971/1665/681)	0.43(5667/8256/3280)	G	T
EMR1	19	rs461645	All	H	1.08(1-1.17)	0.05	1.07(0.96-1.18)	0.98(0.87-1.09)	0.12	0.55(675/1675/984)	0.57(3357/8303/5726)	T	C
G6PD	X	rs1050829	M	M	0.92(0.82-1.03)	0.16	n.c. [‡]	n.c. [‡]	n.c. [‡]	0.35(1009/0/553)	0.38(4679/0/2869)	T	C
G6PD	X	rs1050829	F	A	0.93(0.86-1.02)	0.12	0.94(0.83-1.07)	0.87(0.72-1.04)	0.29	0.36(601/703/195)	0.39(2606/3356/1062)	T	C
G6PD	X	rs1050829	All	A	0.95(0.9-1)	0.03	0.95(0.84-1.06)	0.9(0.82-0.99)	0.11	0.36(1610/703/748)	0.38(7285/3356/3931)	T	C
G6PD	X	rs1050828	M	M	0.81(0.68-0.96)	1.39 X 10 ⁻⁰²	n.c. [‡]	n.c. [‡]	n.c. [‡]	0.12(1384/0/191)	0.15(6483/0/1105)	C	T
G6PD	X	rs1050828	F	H	0.87(0.76-1.01)	0.06	0.87(0.76-1.01)	1.04(0.72-1.51)	0.16	0.14(1129/338/39)	0.15(5069/1770/174)	C	T
G6PD	X	rs1050828	All	A	0.91(0.85-0.97)	6.08 X 10 ⁻⁰³	0.86(0.75-0.99)	0.85(0.72-0.99)	0.02	0.13(2513/338/230)	0.15(11552/1770/1279)	C	T
GBP7	1	rs1803632	All	D	1.08(0.98-1.18)	0.11	1.07(0.98-1.18)	1.08(0.97-1.21)	0.28	0.5(835/1640/856)	0.51(4369/8259/4777)	G	C
GNAS	20	rs8386	All	R	1.21(0.95-1.55)	0.13	0.96(0.87-1.05)	1.2(0.94-1.54)	0.22	0.15(2225/773/85)	0.16(10246/3995/398)	C	T
HBB	11	rs33950507	All	H	1.1(0.56-2.15)	0.79	1.11(0.57-2.19)	1.74(0.16-19.46)	0.88	0.01(1091/10/1)	0.01(6447/127/27)	G	A
HBB	11	rs334	All	H	0.11(0.08-0.15)	4.67 X 10 ⁻⁸⁸	0.11(0.08-0.15)	0.3(0.12-0.74)	9.16 X 10 ⁻⁸⁹	0.01(3041/42/5)	0.07(12773/1791/77)	A	T
HBB	11	rs33930165	All	A	0.72(0.56-0.94)	1.07 X 10 ⁻⁰²	0.73(0.54-0.99)	0.5(0.2-1.25)	0.04	0.02(1412/56/5)	0.03(9341/515/74)	G	A
ICAM1	19	rs1799969	All	ADH*	0.59(0.14-2.54)	0.44	n.c. [§]	n.c. [§]	n.c. [§]	0(1982/2/0)	0(9294/27/0)	G	A
ICAM1	19	rs5498	All	A	1.07(0.99-1.15)	0.11	1.07(0.97-1.17)	1.13(0.87-1.47)	0.27	0.14(2435/801/80)	0.14(12716/4164/411)	A	G
IL10	1	rs3024500	All	D	0.94(0.86-1.03)	0.17	0.94(0.86-1.02)	0.96(0.85-1.07)	0.36	0.42(1177/1501/655)	0.39(6859/7440/3080)	A	G

IL10	1	rs1800896	All	R	0.95(0.83-1.07)	0.38	0.98(0.91-1.07)	0.94(0.82-1.07)	0.64	0.32(1586/1377/358)	0.29(8946/6734/1723)	T	C
IL10	1	rs1800890	All	A	0.96(0.89-1.02)	0.2	0.97(0.89-1.05)	0.89(0.74-1.07)	0.39	0.2(2128/1058/148)	0.19(11441/5183/784)	A	T
IL13	5	rs20541	All	H	0.97(0.88-1.07)	0.52	0.97(0.88-1.07)	1(0.82-1.23)	0.81	0.21(1570/773/133)	0.23(8778/4974/938)	C	T
IL17RD	3	rs6780995	All	R	0.94(0.86-1.02)	0.16	1(0.91-1.11)	0.94(0.84-1.05)	0.37	0.54(753/1575/999)	0.51(4680/7806/4890)	G	A
IL17RE	3	rs708567	All	A	1.03(0.97-1.09)	0.33	1.03(0.94-1.13)	1.06(0.95-1.18)	0.61	0.47(988/1566/759)	0.43(5820/7587/3555)	G	A
IL1A	2	rs17561	All	H	1.09(1-1.19)	0.06	1.09(1-1.19)	1(0.8-1.26)	0.16	0.18(2264/976/99)	0.16(12491/4439/479)	G	T
IL1B	2	rs1143634	All	H	1.03(0.93-1.13)	0.56	1.03(0.93-1.13)	0.99(0.7-1.39)	0.84	0.11(2614/681/43)	0.1(13962/3178/215)	C	T
IL20RA	6	rs1555498	All	H	0.97(0.9-1.06)	0.52	0.98(0.9-1.08)	1.02(0.91-1.14)	0.76	0.5(924/1500/912)	0.53(4600/7179/5633)	C	T
IL22	12	rs2227507	All	A	1(0.86-1.16)	0.99	1.01(0.87-1.18)	0.75(0.25-2.22)	0.85	0.04(2742/217/4)	0.04(12811/980/20)	T	C
IL22	12	rs1012356	All	R	1.02(0.94-1.12)	0.6	1.01(0.91-1.11)	1.03(0.92-1.15)	0.86	0.5(835/1632/868)	0.51(4254/8493/4643)	A	T
IL22	12	rs2227491	All	D	1.08(0.96-1.21)	0.21	1.07(0.95-1.21)	1.08(0.96-1.23)	0.44	0.64(453/1488/1369)	0.63(2505/7684/7080)	T	C
IL22	12	rs2227485	All	H	1.07(0.99-1.15)	0.1	1.06(0.96-1.16)	0.97(0.87-1.09)	0.22	0.45(995/1651/684)	0.47(4979/8362/4021)	G	A
IL22	12	rs2227478	All	R	0.92(0.85-1)	0.04	1.04(0.92-1.18)	0.95(0.84-1.08)	0.10	0.64(433/1524/1380)	0.67(2059/7268/8059)	G	A
IL4	5	rs2243250	All	R	0.89(0.82-0.96)	3.61 X 10 ⁻⁰³	1.07(0.9-1.26)	0.94(0.8-1.11)	0.01	0.74(204/1222/1762)	0.76(1101/6094/10066)	C	T
IL4R	16	rs1805015	All	R	1.06(0.96-1.18)	0.23	1(0.92-1.1)	1.07(0.95-1.19)	0.48	0.42(1184/1523/624)	0.39(6872/7570/2912)	T	C
IRF1	5	rs2706384	All	D	0.92(0.85-1)	0.04	0.92(0.85-1.01)	0.9(0.8-1.01)	0.11	0.4(1189/1509/550)	0.44(5462/8154/3434)	C	A
LTA	6	rs2239704	All	A	1.06(1-1.14)	0.06	1.07(0.99-1.17)	1.12(0.96-1.3)	0.16	0.26(1852/1186/268)	0.26(9604/6224/1411)	G	T
LTA	6	rs909253	All	A	0.96(0.91-1.01)	0.13	0.95(0.87-1.04)	0.92(0.82-1.03)	0.31	0.45(1024/1602/693)	0.47(4997/8355/3853)	T	C
NOD1	7	rs2075820	All	H	1.08(1-1.16)	0.06	1.07(0.98-1.16)	0.97(0.86-1.09)	0.16	0.39(1230/1609/486)	0.38(6692/8105/2597)	G	A
NOS2	17	rs2297518	All	R	0.76(0.55-1.05)	0.08	0.97(0.89-1.07)	0.75(0.54-1.04)	0.20	0.12(2569/709/47)	0.12(13341/3684/298)	G	A
NOS2	17	rs1800482	All	A	0.89(0.8-0.99)	0.03	0.91(0.81-1.02)	0.59(0.33-1.05)	0.05	0.08(2613/442/13)	0.09(12169/2320/120)	G	C
NOS2	17	rs9282799	All	A	1.12(0.99-1.27)	0.07	1.1(0.97-1.26)	1.59(0.84-3.03)	0.14	0.06(2741/332/13)	0.05(13124/1476/45)	C	T
NOS2	17	rs8078340	All	R	0.84(0.69-1.01)	0.06	1.04(0.95-1.13)	0.85(0.7-1.03)	0.11	0.22(2012/1168/145)	0.2(11224/5365/808)	C	T
RTN3	11	rs542998	All	H	0.96(0.88-1.04)	0.3	0.96(0.87-1.05)	0.99(0.88-1.12)	0.58	0.45(1112/1448/759)	0.49(5203/7090/4964)	T	C
SPTB	14	rs229587	All	R	1.01(0.9-1.15)	0.82	1(0.92-1.09)	1.01(0.89-1.16)	0.97	0.33(1512/1390/368)	0.35(7361/7416/2348)	T	C
TLR1	4	rs4833095	All	R	1.15(0.89-1.48)	0.29	1.01(0.91-1.12)	1.15(0.89-1.5)	0.56	0.12(2580/662/82)	0.15(12637/3942/681)	C	T
TLR4	9	rs4986791	All	H	0.98(0.7-1.38)	0.93	n.c. [§]	n.c. [§]	n.c. [§]	0.01(828/12/0)	0.01(4187/74/3)	C	T
TLR4	9	rs4986790	All	R	0.63(0.35-1.13)	0.1	1.01(0.9-1.15)	0.62(0.35-1.12)	0.24	0.07(2687/378/13)	0.07(12626/1852/112)	A	G
TLR6	4	rs5743810	All	H	1.01(0.73-1.41)	0.93	n.c. [§]	n.c. [§]	n.c. [§]	0.01(1693/33/0)	0.01(7539/184/3)	C	T
TLR6	4	rs5743809	All	H	1.13(0.99-1.3)	0.08	1.13(0.99-1.29)	0.5(0.19-1.27)	0.06	0.05(2932/311/5)	0.04(15698/1279/43)	T	C
TLR9	3	rs187084	All	R	1.07(0.99-1.17)	0.1	1.01(0.86-1.19)	1.08(0.93-1.27)	0.25	0.72(228/1087/1477)	0.7(1455/6473/7909)	C	T
TNF	6	rs1799964	All	H	1.06(0.97-1.15)	0.18	1.06(0.97-1.15)	0.97(0.8-1.18)	0.39	0.21(2080/1107/141)	0.2(11148/5452/767)	T	C
TNF	6	rs1800629	All	R	1.12(0.81-1.53)	0.49	0.97(0.88-1.07)	1.11(0.81-1.52)	0.65	0.11(2584/629/51)	0.11(13681/3273/222)	G	A
TNF	6	rs361525	All	H	1.05(0.93-1.19)	0.43	1.05(0.93-1.19)	0.81(0.41-1.61)	0.61	0.06(2947/378/10)	0.05(15732/1647/55)	G	A
TNF	6	rs3093662	All	R	0.76(0.49-1.16)	0.19	1.01(0.91-1.12)	0.76(0.49-1.17)	0.42	0.1(2670/588/26)	0.08(14381/2583/143)	A	G
TRIM5	11	rs7935564	All	D	0.93(0.85-1.01)	0.09	0.94(0.85-1.02)	0.92(0.82-1.02)	0.23	0.44(1042/1608/673)	0.42(5881/8072/3205)	G	A

Supplementary Table 9: Cerebral malaria only association signals. Summary of association signals for all SNPs for *cerebral malaria only* across the 12 contributing Consortial Project 1 study sites. Odds ratios (OR), 95% confidence intervals (95% CI) and p-values (P) are presented for the best model (for autosomal SNPs and for females at X chromosome SNPs this is the model (selected from additive, recessive, dominant or heterozygote advantage) that has the most significant association; for males at X chromosome, this is the male hemizygote model and; for all individuals combined at X chromosome SNPs this is the model (selected from additive, recessive or dominant) that has the most significant association. Heterozygote and homozygote ORs from a genotypic model are also presented. Results are adjusted for HbS (except rs334), gender and ethnicity. Sites at which a SNP was found to be monomorphic were excluded from the analysis. An, ancestral; De, derived; n.c., not calculated. ^aModels are A, additive; D, dominant; H, heterozygote advantage; M, male hemizygote; R, recessive. [§]Genotype counts too small for accurate calculation. [¶]Not applicable to male hemizygotes. *Models are equivalent due to zero genotype class.

Gene	Chromosome	SNP Ref	Sample	Best Model ^a	Best Model OR(95% CI)	Best Model P	Heterozygote OR(95% CI)	Derived Homozygote OR(95% CI)	Genotypic P	Frequency (Derived Homozygote/Heterozygote/Ancstral Homozygote)		Alleles	
										Cases	Controls	An	De
ABO	9	rs8176746	All	D	1.28(1.16-1.42)	1.71 X 10 ⁻⁰⁶	1.28(1.15-1.42)	1.34(1.04-1.71)	1.01 X 10 ⁻⁰⁵	0.22(1342/746/97)	0.17(11943/4852/565)	C	A
ABO	9	rs8176719	All	R	0.68(0.62-0.76)	7.97 X 10 ⁻¹⁴	0.9(0.77-1.05)	0.63(0.54-0.74)	3.10 X 10 ⁻¹³	0.62(302/1054/816)	0.69(1700/7215/8238)	I	D
ADCY9	16	rs2230739	All	R	0.9(0.62-1.31)	0.59	0.98(0.87-1.11)	0.9(0.62-1.3)	0.84	0.12(1701/453/39)	0.15(12706/4094/604)	A	G
ADCY9	16	rs10775349	All	R	1.18(0.9-1.54)	0.25	1.02(0.91-1.14)	1.18(0.9-1.56)	0.48	0.23(1396/581/214)	0.3(9884/4518/3000)	C	G
ADORA2B	17	rs2535611	All	A	0.95(0.83-1.08)	0.43	0.95(0.82-1.1)	0.9(0.53-1.54)	0.73	0.07(1865/280/19)	0.07(14377/2198/130)	T	C
ATP2B4	1	rs55868763	All	D	1.48(1.22-1.81)	5.39 X 10 ⁻⁰⁵	1.43(1.17-1.77)	1.53(1.25-1.89)	0.00	0.71(137/791/929)	0.68(1428/5690/6229)	C	G
ATP2B4	1	rs1541255	All	R	0.67(0.55-0.82)	3.96 X 10 ⁻⁰⁵	0.93(0.83-1.04)	0.65(0.53-0.79)	0.00	0.29(932/788/137)	0.32(6241/5667/1439)	A	G
ATP2B4	1	rs10900585	All	D	1.53(1.27-1.84)	3.68 X 10 ⁻⁰⁶	1.49(1.22-1.81)	1.58(1.3-1.92)	1.34 X 10 ⁻⁰⁵	0.69(159/816/851)	0.66(1644/5722/5737)	G	T
ATP2B4	1	rs4951074	All	R	0.64(0.51-0.79)	1.22 X 10 ⁻⁰⁵	1(0.89-1.12)	0.64(0.51-0.79)	6.97 X 10 ⁻⁰⁵	0.28(890/762/121)	0.31(6115/5392/1284)	G	A
ATP2B4	1	rs3753036	All	A	1.21(0.94-1.56)	0.15	1.22(0.93-1.59)	1.34(0.3-5.94)	0.36	0.02(1946/72/2)	0.04(14787/1253/81)	G	A
C6	5	rs1801033	All	D	0.94(0.84-1.04)	0.24	0.94(0.84-1.05)	0.95(0.82-1.09)	0.49	0.45(675/1069/445)	0.48(4757/8591/4003)	A	C
CD36	7	rs210346212	All	H	0.9(0.64-1.27)	0.56	n.c. [§]	n.c. [§]	n.c. [§]	0.03(596/44/0)	0.03(3470/199/5)	G	C
CD36	7	rs3211938	All	A	0.88(0.77-1)	0.05	0.88(0.76-1.03)	0.73(0.44-1.22)	0.14	0.08(1730/287/22)	0.09(12291/2178/174)	T	G
CD40LG	X	rs3092945	M	M	0.87(0.75-1.01)	0.07	n.c. [¶]	n.c. [¶]	n.c. [¶]	0.31(773/0/349)	0.27(6449/0/2348)	T	C
CD40LG	X	rs3092945	F	R	0.71(0.56-0.9)	3.49 X 10 ⁻⁰³	1.13(0.96-1.32)	0.75(0.58-0.97)	4.89 X 10 ⁻⁰³	0.33(424/411/103)	0.27(4581/2621/849)	T	C
CD40LG	X	rs3092945	All	R	0.82(0.73-0.94)	2.97 X 10 ⁻⁰³	1.15(0.98-1.34)	0.84(0.74-0.96)	2.11 X 10 ⁻⁰³	0.32(1197/411/452)	0.27(11030/2621/3197)	T	C
CD40LG	X	rs1126535	M	M	1.05(0.86-1.27)	0.65	n.c. [¶]	n.c. [¶]	n.c. [¶]	0.15(1012/0/178)	0.14(7793/0/1290)	T	C
CD40LG	X	rs1126535	F	R	1.31(0.86-1.99)	0.22	0.96(0.81-1.15)	1.29(0.85-1.97)	0.43	0.15(738/230/34)	0.14(6206/1904/193)	T	C
CD40LG	X	rs1126535	All	R	1.08(0.91-1.27)	0.37	0.96(0.8-1.14)	1.08(0.91-1.27)	0.61	0.15(1750/230/212)	0.14(13999/1904/1483)	T	C
CFTR	7	rs17140229	All	H	0.94(0.84-1.05)	0.27	0.94(0.83-1.06)	0.99(0.84-1.17)	0.54	0.38(694/807/265)	0.36(5182/5816/1632)	T	C
CR1	1	rs17047660	All	D	0.91(0.82-1.01)	0.07	0.91(0.82-1.01)	0.91(0.75-1.11)	0.19	0.28(1065/803/163)	0.26(8059/5508/1048)	A	G
CR1	1	rs17047661	All	D	1.1(0.9-1.35)	0.35	1.1(0.89-1.35)	1.1(0.9-1.36)	0.64	0.75(135/767/1140)	0.72(1159/5820/7633)	A	G
CTL4	6	rs2242665	All	H	0.89(0.81-0.99)	0.03	0.8(0.67-0.95)	0.87(0.74-1.03)	0.03	0.71(214/821/1141)	0.7(1670/7134/8465)	G	A
DARC	1	rs2814778	All	H	1.75(0.83-3.68)	0.16	13.95(0.23-835.58)	8.65(0.13-557.62)	0.22	0.93(150/9/1981)	0.83(2751/59/13799)	A	G
DERL3	22	rs1128127	All	D	0.93(0.82-1.05)	0.23	0.93(0.81-1.05)	0.93(0.81-1.07)	0.48	0.51(588/978/615)	0.47(5327/7634/4290)	G	A
EMR1	19	rs373533	All	R	0.98(0.87-1.11)	0.78	1(0.89-1.11)	0.98(0.85-1.13)	0.96	0.45(667/1057/443)	0.43(5667/8256/3280)	G	T
EMR1	19	rs461645	All	H	1.02(0.92-1.12)	0.75	1.02(0.9-1.16)	1.01(0.88-1.16)	0.94	0.55(449/1065/675)	0.57(3357/8303/5726)	T	C
G6PD	X	rs1050829	M	M	1.23(1.07-1.41)	4.55 X 10 ⁻⁰³	n.c. [¶]	n.c. [¶]	n.c. [¶]	0.42(634/0/468)	0.38(4679/0/2869)	T	C
G6PD	X	rs1050829	F	R	1.23(1.01-1.5)	0.04	1.01(0.86-1.2)	1.24(1-1.54)	0.12	0.41(325/426/167)	0.39(2606/3356/1062)	T	C
G6PD	X	rs1050829	All	R	1.23(1.1-1.38)	4.08 X 10 ⁻⁰⁴	0.99(0.85-1.16)	1.23(1.09-1.38)	2.11 X 10 ⁻⁰³	0.42(959/426/635)	0.38(7285/3356/3931)	T	C
G6PD	X	rs1050828	M	M	1.49(1.24-1.79)	3.55 X 10 ⁻⁰⁵	n.c. [¶]	n.c. [¶]	n.c. [¶]	0.2(894/0/222)	0.15(6483/0/1105)	C	T
G6PD	X	rs1050828	F	R	1.94(1.3-2.89)	1.92 X 10 ⁻⁰³	0.96(0.8-1.16)	1.92(1.28-2.87)	7.51 X 10 ⁻⁰³	0.16(669/215/41)	0.15(5069/1770/174)	C	T
G6PD	X	rs1050828	All	A	1.19(1.1-1.28)	2.62 X 10 ⁻⁰⁵	0.93(0.78-1.12)	1.55(1.31-1.83)	1.66 X 10 ⁻⁰⁶	0.18(1563/215/263)	0.15(11552/1770/1279)	C	T
GBP7	1	rs1803632	All	A	1.05(0.98-1.12)	0.19	1.04(0.92-1.16)	1.1(0.96-1.26)	0.41	0.47(623/1066/503)	0.51(4369/8259/4777)	G	C
GNAS	20	rs8386	All	H	0.98(0.88-1.1)	0.76	0.98(0.88-1.1)	0.99(0.73-1.34)	0.95	0.17(1413/571/61)	0.16(10246/3995/398)	C	T
HBB	11	rs33950507	All	H	1.12(0.31-4.02)	0.87	n.c. [§]	n.c. [§]	n.c. [§]	0.05(28/3/0)	0.04(2383/124/27)	G	A
HBB	11	rs334	All	H	0.11(0.07-0.15)	9.25 X 10 ⁻⁶⁵	0.11(0.08-0.16)	3.91(2.61-5.88)	1.18 X 10 ⁻⁷¹	0.03(1965/31/45)	0.07(12773/1791/77)	A	T
HBB	11	rs33930165	All	A	0.74(0.6-0.9)	2.11 X 10 ⁻⁰³	0.73(0.57-0.92)	0.57(0.28-1.14)	8.73 X 10 ⁻⁰³	0.04(1465/116/10)	0.03(9341/515/74)	G	A
ICAM1	19	rs1799969	All	ADH*	1.33(0.37-4.81)	0.67	n.c. [§]	n.c. [§]	n.c. [§]	0(977/3/0)	0(9294/27/0)	G	A
ICAM1	19	rs5498	All	A	1.07(0.97-1.18)	0.2	1.05(0.94-1.18)	1.2(0.89-1.63)	0.40	0.16(1555/555/78)	0.14(12716/4164/411)	A	G
IL10	1	rs3024500	All	D	0.98(0.88-1.09)	0.72	0.98(0.88-1.09)	0.99(0.85-1.14)	0.93	0.41(769/1031/391)	0.39(6859/7440/3080)	A	G
IL10	1	rs1800896	All	R	0.95(0.8-1.11)	0.5	1(0.9-1.11)	0.94(0.8-1.12)	0.79	0.3(1082/896/209)	0.29(8946/6734/1723)	T	C
IL10	1	rs1800890	All	A	0.95(0.87-1.03)	0.23	0.97(0.87-1.08)	0.85(0.67-1.09)	0.41	0.19(1442/666/85)	0.19(11441/5183/784)	A	T

IL13	5	rs20541	All	D	1.13(1-1.26)	0.04	1.12(0.99-1.26)	1.18(0.91-1.52)	0.12	0.21(1200/582/96)	0.23(8778/4974/938)	C	T
IL17RD	3	rs6780995	All	A	0.98(0.92-1.05)	0.65	0.99(0.87-1.12)	0.97(0.84-1.11)	0.90	0.53(493/1064/634)	0.51(4680/7806/4890)	G	A
IL17RE	3	rs708567	All	H	1.02(0.92-1.12)	0.7	1.02(0.9-1.15)	1(0.87-1.15)	0.93	0.5(568/1044/550)	0.43(5820/7587/3555)	G	A
IL1A	2	rs17561	All	R	1.06(0.81-1.38)	0.67	1(0.89-1.11)	1.06(0.81-1.39)	0.91	0.17(1520/601/74)	0.16(12491/4439/479)	G	T
IL1B	2	rs1143634	All	A	1.02(0.92-1.13)	0.72	1.01(0.9-1.14)	1.08(0.72-1.6)	0.92	0.12(1695/461/33)	0.1(13962/3178/215)	C	T
IL2ORA	6	rs1555498	All	A	1.1(1.02-1.18)	0.01	1.06(0.95-1.19)	1.21(1.05-1.39)	0.03	0.47(635/1042/518)	0.53(4600/7179/5633)	C	T
IL22	12	rs2227507	All	A	0.96(0.79-1.17)	0.72	0.92(0.75-1.13)	2.35(0.76-7.32)	0.29	0.04(1551/110/4)	0.04(12811/980/20)	T	C
IL22	12	rs1012356	All	A	1.06(0.99-1.14)	0.09	1.04(0.92-1.18)	1.13(0.98-1.3)	0.21	0.5(595/1017/582)	0.51(4254/8493/4643)	A	T
IL22	12	rs2227491	All	A	1.07(0.99-1.15)	0.08	1.07(0.91-1.26)	1.14(0.97-1.35)	0.21	0.65(326/883/972)	0.63(2505/7684/7080)	T	C
IL22	12	rs2227485	All	R	1.06(0.94-1.19)	0.36	0.97(0.86-1.09)	1.04(0.9-1.19)	0.59	0.46(679/1004/501)	0.47(4979/8362/4021)	G	A
IL22	12	rs2227478	All	H	1.05(0.95-1.16)	0.33	1.05(0.9-1.23)	1.01(0.86-1.18)	0.62	0.64(303/984/904)	0.67(2059/7268/8059)	G	A
IL4	5	rs2243250	All	D	1.17(0.96-1.42)	0.12	1.19(0.97-1.46)	1.15(0.94-1.4)	0.23	0.74(150/830/1195)	0.76(1101/6094/10066)	C	T
IL4R	16	rs1805015	All	R	1.01(0.89-1.14)	0.88	1(0.89-1.12)	1.01(0.87-1.16)	0.99	0.42(763/1000/422)	0.39(6872/7570/2912)	T	C
IRF1	5	rs2706384	All	R	0.88(0.77-1)	0.05	1(0.89-1.12)	0.88(0.76-1.02)	0.15	0.44(683/1028/408)	0.44(5462/8154/3434)	C	A
LTA	6	rs2239704	All	D	0.93(0.84-1.04)	0.19	0.93(0.83-1.03)	0.96(0.81-1.14)	0.39	0.31(1059/854/237)	0.26(9604/6224/1411)	G	T
LTA	6	rs909253	All	R	1.07(0.95-1.2)	0.29	1.01(0.9-1.14)	1.07(0.93-1.24)	0.56	0.46(680/999/493)	0.47(4997/8355/3853)	T	C
NOD1	7	rs2075820	All	A	0.93(0.87-1)	0.05	0.92(0.82-1.02)	0.87(0.75-1.02)	0.13	0.36(893/997/299)	0.38(6692/8105/2597)	G	A
NOS2	17	rs2297518	All	R	0.81(0.5-1.31)	0.38	1.02(0.9-1.16)	0.81(0.5-1.32)	0.64	0.1(1751/404/21)	0.12(13341/3684/298)	G	A
NOS2	17	rs1800482	All	A	1.07(0.95-1.21)	0.29	1.06(0.92-1.21)	1.23(0.75-2.01)	0.54	0.09(1678/342/21)	0.09(12169/2320/120)	G	C
NOS2	17	rs9282799	All	A	1.13(0.98-1.3)	0.11	1.12(0.96-1.31)	1.4(0.65-3.01)	0.27	0.07(1781/251/9)	0.05(13124/1476/45)	C	T
NOS2	17	rs8078340	All	A	0.97(0.89-1.05)	0.45	0.98(0.88-1.09)	0.92(0.73-1.15)	0.72	0.22(1322/765/103)	0.2(11224/5365/808)	C	T
RTN3	11	rs542998	All	D	0.98(0.89-1.09)	0.74	0.98(0.88-1.1)	0.99(0.85-1.15)	0.94	0.42(770/985/426)	0.49(5203/7090/4964)	T	C
SPTB	14	rs229587	All	D	0.93(0.84-1.03)	0.16	0.92(0.83-1.03)	0.95(0.79-1.13)	0.37	0.31(925/800/207)	0.35(7361/7416/2348)	T	C
TLR1	4	rs4833095	All	H	0.87(0.77-0.99)	0.04	0.88(0.77-1)	1.06(0.72-1.56)	0.11	0.11(1734/393/37)	0.15(12637/3942/681)	C	T
TLR4	9	rs4986791	All	H	1.27(0.89-1.8)	0.19	n.c. ⁵	n.c. ⁵	n.c. ⁵	0.01(867/18/0)	0.01(4187/74/3)	C	T
TLR4	9	rs4986790	All	R	0.63(0.35-1.13)	0.1	1.02(0.89-1.18)	0.63(0.35-1.13)	0.25	0.09(1694/323/16)	0.07(12626/1852/112)	A	G
TLR6	4	rs5743810	All	H	1.04(0.67-1.62)	0.85	1.05(0.67-1.62)	7.29(0.67-79.55)	0.38	0.01(785/14/1)	0.01(7539/184/3)	C	T
TLR6	4	rs5743809	All	A	1.03(0.86-1.23)	0.75	1.02(0.85-1.24)	1.14(0.42-3.1)	0.94	0.04(1892/163/5)	0.04(15698/1279/43)	T	C
TLR9	3	rs187084	All	D	0.87(0.74-1.03)	0.12	0.87(0.73-1.04)	0.87(0.73-1.04)	0.30	0.7(216/852/1091)	0.7(1455/6473/7909)	C	T
TNF	6	rs1799964	All	A	1.06(0.97-1.16)	0.23	1.05(0.94-1.17)	1.14(0.88-1.48)	0.48	0.18(1487/614/87)	0.2(11148/5452/767)	T	C
TNF	6	rs1800629	All	R	0.8(0.52-1.24)	0.31	1.03(0.91-1.17)	0.81(0.52-1.25)	0.54	0.12(1606/435/28)	0.11(13681/3273/222)	G	A
TNF	6	rs361525	All	H	1.12(0.94-1.34)	0.21	1.12(0.94-1.34)	0.86(0.33-2.25)	0.43	0.04(2019/171/5)	0.05(15732/1647/55)	G	A
TNF	6	rs3093662	All	R	1.26(0.75-2.12)	0.4	1.01(0.87-1.16)	1.26(0.75-2.13)	0.69	0.07(1770/270/18)	0.08(14381/2583/143)	A	G
TRIM5	11	rs7935564	All	A	1.01(0.95-1.09)	0.69	1.01(0.9-1.14)	1.03(0.89-1.18)	0.92	0.48(589/1078/487)	0.42(5881/8072/3205)	G	A

Supplementary Table 10: Severe malarial anaemia only association signals. Summary of association signals for all SNPs for *severe malarial anaemia only* across the 12 contributing Consortial Project 1 study sites. Odds ratios (OR), 95% confidence intervals (95% CI) and p-values (P) are presented for the best model (for autosomal SNPs and for females at X chromosome SNPs this is the model (selected from additive, recessive, dominant or heterozygote advantage) that has the most significant association; for males at X chromosome, this is the male hemizygote model and; for all individuals combined at X chromosome SNPs this is the model (selected from additive, recessive or dominant) that has the most significant association. Heterozygote and homozygote ORs from a genotypic model are also presented. Results are adjusted for HbS (except rs334), gender and ethnicity. Sites at which a SNP was found to be monomorphic were excluded from the analysis. An, ancestral; De, derived; n.c., not calculated. ^aModels are A, additive; D, dominant; H, heterozygote advantage; M, male hemizygote; R, recessive. ⁵Genotype counts too small for accurate calculation. ¹Not applicable to male hemizygotes. *Models are equivalent due to zero genotype class.

Sickle Cell Trait Phenotype Site	Heterozygote Frequency (Heterozygote/Total)		OR (95% CI)	P
	Cases	Controls		
Males and Females – Heterozygote Advantage Model				
Severe malaria				
Gambia	0.01 (32/2415)	0.14 (460/3332)	0.09(0.06-0.12)	2.80 X 10 ⁻⁷⁴
Mali	0.01 (4/453)	0.08 (28/344)	0.09(0.03-0.27)	4.08 X 10 ⁻⁰⁸
Burkina Faso	0.02 (21/865)	0.1 (73/729)	0.22(0.14-0.37)	6.94 X 10 ⁻¹¹
Ghana (Navrongo)	0.03 (19/682)	0.1 (50/489)	0.25(0.14-0.43)	7.99 X 10 ⁻⁰⁸
Ghana (Kumasi)	0.02 (32/1495)	0.13 (271/2042)	0.13(0.09-0.2)	4.83 X 10 ⁻³⁵
Nigeria	0.12 (9/77)	0.22 (9/40)	0.46(0.16-1.28)	0.14
Cameroon	0.05 (32/621)	0.17 (99/576)	0.26(0.17-0.4)	3.17 X 10 ⁻¹¹
Kenya	0.03 (57/2261)	0.15 (594/3941)	0.15(0.12-0.2)	6.33 X 10 ⁻⁶⁰
Tanzania	0.01 (5/428)	0.17 (75/452)	0.06(0.02-0.15)	5.31 X 10 ⁻¹⁸
Malawi	0 (2/1388)	0.05 (132/2696)	0.03(0.01-0.11)	1.64 X 10 ⁻²²
All	0.02 (213/10685)	0.12 (1791/14641)	0.14(0.12-0.16)	1.62 X 10 ⁻²²⁵
Cerebral malaria only				
Gambia	0.01 (9/783)	0.14 (460/3332)	0.07(0.04-0.14)	1.10 X 10 ⁻³²
Mali	0 (0/86)	0.08 (28/344)	n.c. [§]	n.c. [§]
Burkina Faso	0 (0/107)	0.1 (73/729)	n.c. [§]	n.c. [§]
Ghana (Navrongo)	0.05 (1/22)	0.1 (50/489)	0.42(0.06-3.21)	0.34
Ghana (Kumasi)	0.01 (3/230)	0.13 (271/2042)	0.1(0.03-0.31)	3.33 X 10 ⁻⁰⁹
Nigeria	0 (0/6)	0.22 (9/40)	n.c. [§]	n.c. [§]
Cameroon	0.05 (2/39)	0.17 (99/576)	0.26(0.06-1.08)	0.02
Kenya	0.03 (25/908)	0.15 (594/3941)	0.17(0.11-0.26)	6.79 X 10 ⁻²⁸
Tanzania	0 (0/34)	0.17 (75/452)	0(0-Inf)	7.73 X 10 ⁻⁰⁴
Malawi	0 (2/873)	0.05 (132/2696)	0.04(0.01-0.18)	7.84 X 10 ⁻¹⁵
All	0.01 (42/3088)	0.12 (1791/14641)	0.11(0.08-0.15)	4.67 X 10 ⁻⁸⁸
Severe malarial anaemia only				
Gambia	0.01 (3/456)	0.14 (460/3332)	0.04(0.01-0.13)	5.48 X 10 ⁻²⁴
Mali	0.01 (1/185)	0.08 (28/344)	0.06(0.01-0.41)	9.55 X 10 ⁻⁰⁶
Burkina Faso	0 (0/39)	0.1 (73/729)	n.c. [§]	n.c. [§]
Ghana (Navrongo)	0.02 (5/248)	0.1 (50/489)	0.18(0.07-0.45)	8.22 X 10 ⁻⁰⁶
Ghana (Kumasi)	0.02 (11/551)	0.13 (271/2042)	0.14(0.07-0.27)	1.07 X 10 ⁻¹⁵
Nigeria	0.38 (3/8)	0.22 (9/40)	1.98(0.39-10.11)	0.42
Cameroon	0.04 (3/82)	0.17 (99/576)	0.18(0.06-0.59)	3.23 X 10 ⁻⁰⁴
Kenya	0.02 (3/158)	0.15 (594/3941)	0.11(0.04-0.36)	5.18 X 10 ⁻⁰⁸
Tanzania	0.01 (2/182)	0.17 (75/452)	0.06(0.01-0.24)	6.83 X 10 ⁻¹⁰
Malawi	0 (0/132)	0.05 (132/2696)	n.c. [§]	n.c. [§]
All	0.02 (31/2041)	0.12 (1791/14641)	0.11(0.07-0.15)	9.25 X 10 ⁻⁶⁵

Supplementary Table 11: HbS All Heterozygous Model. Frequency of cases and controls heterozygous for sickle-cell haemoglobin (HbS) derived from rs334. Odds Ratios (OR), 95% Confidence Intervals (95% CI) and p-values (P) for association of HbS heterozygotes with severe malaria, cerebral malaria only and severe malarial anaemia only for all individuals at each study site and at all study sites combined. Results are adjusted for gender and ethnicity. Sites at which HbS is not present (Vietnam and Papua New Guinea) were excluded from this analysis. Het, Heterozygotes; n.c., not calculated. [§] sample size too small for accurate calculation.

Blood Group O Phenotype Site	Derived Homozygote Frequency (Derived Homozygote/Total)		OR (95% CI)	P
	Cases	Controls		
Males and Females – Recessive Model				
All severe malaria				
Gambia	0.39 (945/2418)	0.46 (1551/3337)	0.75(0.67-0.84)	3.08 X 10 ⁻⁰⁷
Mali	0.29 (131/450)	0.43 (146/340)	0.57(0.42-0.78)	3.15 X 10 ⁻⁰⁴
Burkina Faso	0.37 (321/859)	0.44 (320/721)	0.75(0.61-0.92)	6.30 X 10 ⁻⁰³
Ghana (Navrongo)	0.39 (260/666)	0.4 (193/484)	0.93(0.73-1.19)	0.58
Ghana (Kumasi)	0.37 (547/1478)	0.5 (984/1978)	0.61(0.52-0.7)	1.66 X 10 ⁻¹¹
Nigeria	0.35 (27/77)	0.62 (24/39)	0.31(0.14-0.71)	4.68 X 10 ⁻⁰³
Cameroon	0.44 (267/603)	0.54 (310/570)	0.69(0.54-0.88)	2.46 X 10 ⁻⁰³
Kenya	0.47 (1055/2256)	0.55 (2126/3888)	0.74(0.66-0.82)	2.64 X 10 ⁻⁰⁸
Tanzania	0.44 (188/424)	0.48 (219/452)	0.85(0.64-1.12)	0.25
Malawi	0.43 (600/1385)	0.5 (1297/2603)	0.76(0.66-0.87)	4.05 X 10 ⁻⁰⁵
Vietnam	0.34 (271/789)	0.4 (993/2506)	0.78(0.66-0.93)	4.62 X 10 ⁻⁰³
Papua New Guinea	0.36 (138/384)	0.32 (75/235)	1.22(0.86-1.72)	0.27
All	0.4 (4750/11789)	0.48 (8238/17153)	0.74(0.7-0.78)	4.99 X 10 ⁻³³
Cerebral malaria only				
Gambia	0.4 (311/783)	0.46 (1551/3337)	0.77(0.66-0.91)	1.86 X 10 ⁻⁰³
Mali	0.28 (24/86)	0.43 (146/340)	0.55(0.32-0.94)	0.03
Burkina Faso	0.34 (36/106)	0.44 (320/721)	0.66(0.43-1.01)	5.32 X 10 ⁻⁰²
Ghana (Navrongo)	0.35 (7/20)	0.4 (193/484)	0.73(0.28-1.89)	0.51
Ghana (Kumasi)	0.4 (89/225)	0.5 (984/1978)	0.64(0.47-0.87)	4.02 X 10 ⁻⁰³
Nigeria	0.17 (1/6)	0.62 (24/39)	0.1(0.01-1.06)	0.03
Cameroon	0.43 (16/37)	0.54 (310/570)	0.65(0.33-1.28)	0.21
Kenya	0.48 (437/903)	0.55 (2126/3888)	0.79(0.69-0.92)	2.35 X 10 ⁻⁰³
Tanzania	0.26 (9/34)	0.48 (219/452)	0.35(0.16-0.77)	6.13 X 10 ⁻⁰³
Malawi	0.42 (369/872)	0.5 (1297/2603)	0.73(0.62-0.85)	5.93 X 10 ⁻⁰⁵
Vietnam	0.29 (61/210)	0.4 (993/2506)	0.6(0.44-0.82)	1.00 X 10 ⁻⁰³
Papua New Guinea	0.3 (13/43)	0.32 (75/235)	0.87(0.41-1.81)	0.70
All	0.41 (1373/3325)	0.48 (8238/17153)	0.73(0.67-0.79)	8.85 X 10 ⁻¹⁶
Severe malarial anaemia only				
Gambia	0.36 (165/457)	0.46 (1551/3337)	0.65(0.53-0.8)	3.74 X 10 ⁻⁰⁵
Mali	0.3 (55/184)	0.43 (146/340)	0.61(0.41-0.9)	1.12 X 10 ⁻⁰²
Burkina Faso	0.39 (15/38)	0.44 (320/721)	0.84(0.43-1.64)	0.61
Ghana (Navrongo)	0.4 (96/242)	0.4 (193/484)	0.93(0.68-1.29)	0.68
Ghana (Kumasi)	0.36 (195/549)	0.5 (984/1978)	0.55(0.45-0.69)	5.19 X 10 ⁻⁰⁸
Nigeria	0.5 (4/8)	0.62 (24/39)	0.67(0.14-3.18)	0.61
Cameroon	0.38 (30/78)	0.54 (310/570)	0.55(0.33-0.92)	2.09 X 10 ⁻⁰²
Kenya	0.42 (68/160)	0.55 (2126/3888)	0.62(0.45-0.85)	3.18 X 10 ⁻⁰³
Tanzania	0.42 (74/178)	0.48 (219/452)	0.76(0.53-1.11)	0.15
Malawi	0.48 (63/130)	0.5 (1297/2603)	0.93(0.65-1.33)	0.69
Vietnam	0.38 (11/29)	0.4 (993/2506)	1(0.47-2.15)	1.00
Papua New Guinea	0.34 (40/119)	0.32 (75/235)	1.05(0.65-1.7)	0.85
All	0.38 (816/2172)	0.48 (8238/17153)	0.68(0.62-0.76)	7.97 X 10 ⁻¹⁴

Supplementary Table 12: Blood Group O All Individuals Recessive Model. Frequency of cases and controls homozygous for the derived allele at rs8176719. Odds Ratios (OR), 95% Confidence Intervals (95% CI) and p-values (P) for association of Blood Group O with severe malaria, cerebral malaria only and severe malarial anaemia only for all individuals at each study site and at all study sites combined. Results are adjusted for gender, sickle-cell haemoglobin and ethnicity.

G6PD+202 Phenotype Site	Derived-Allele Frequency (Derived Homozygote/ Heterozygote/Ancestral Homozygote)		OR (95% CI)	P
	Cases	Controls		
Males and Females – Additive Model				
Severe malaria				
Gambia	0.02 (2341/45/32)	0.03 (3202/83/51)	0.9(0.74-1.1)	0.32
Mali	0.17 (345/58/50)	0.17 (263/47/34)	0.99(0.8-1.23)	0.92
Burkina Faso	0.17 (661/116/85)	0.14 (576/91/58)	1.12(0.95-1.32)	0.18
Ghana (Navrongo)	0.21 (490/92/99)	0.19 (353/81/54)	1.08(0.92-1.28)	0.35
Ghana (Kumasi)	0.2 (1093/214/187)	0.18 (1510/299/216)	1.06(0.96-1.18)	0.26
Nigeria	0.14 (63/7/7)	0.28 (22/12/5)	0.53(0.29-0.97)	0.04
Cameroon	0.11 (523/48/47)	0.11 (502/25/51)	1.09(0.89-1.34)	0.41
Kenya	0.19 (1673/311/270)	0.19 (2863/639/438)	1.01(0.93-1.09)	0.85
Tanzania	0.16 (334/49/45)	0.2 (319/85/49)	0.83(0.67-1.03)	0.09
Malawi	0.21 (993/212/178)	0.2 (1942/408/323)	1.03(0.94-1.13)	0.52
All	0.15 (8516/1152/1000)	0.15 (11552/1770/1279)	1.02(0.97-1.06)	0.45
Cerebral malaria only				
Gambia	0.02 (766/9/9)	0.03 (3202/83/51)	0.75(0.53-1.06)	0.10
Mali	0.08 (75/8/3)	0.17 (263/47/34)	0.58(0.35-0.94)	0.03
Burkina Faso	0.16 (78/21/6)	0.14 (576/91/58)	1.05(0.77-1.43)	0.76
Ghana (Navrongo)	0.14 (18/2/2)	0.19 (353/81/54)	0.75(0.34-1.65)	0.47
Ghana (Kumasi)	0.15 (182/28/20)	0.18 (1510/299/216)	0.86(0.68-1.09)	0.21
Nigeria	0.08 (5/1/0)	0.28 (22/12/5)	0.32(0.07-1.36)	0.12
Cameroon	0.06 (36/1/2)	0.11 (502/25/51)	0.71(0.3-1.66)	0.43
Kenya	0.17 (682/135/89)	0.19 (2863/639/438)	0.94(0.84-1.05)	0.26
Tanzania	0.19 (25/5/4)	0.2 (319/85/49)	0.95(0.55-1.63)	0.85
Malawi	0.18 (646/128/95)	0.2 (1942/408/323)	0.94(0.84-1.05)	0.27
All	0.13 (2513/338/230)	0.15 (11552/1770/1279)	0.91(0.85-0.97)	6.08 x 10 ⁻⁰³
Severe malarial anaemia only				
Gambia	0.03 (437/11/9)	0.03 (3202/83/51)	1.11(0.8-1.53)	0.53
Mali	0.22 (133/24/28)	0.17 (263/47/34)	1.18(0.91-1.53)	0.21
Burkina Faso	0.22 (28/5/6)	0.14 (576/91/58)	1.36(0.85-2.18)	0.20
Ghana (Navrongo)	0.24 (174/26/47)	0.19 (353/81/54)	1.22(0.98-1.51)	0.07
Ghana (Kumasi)	0.23 (383/83/85)	0.18 (1510/299/216)	1.19(1.03-1.38)	0.02
Nigeria	0.31 (5/1/2)	0.28 (22/12/5)	1.34(0.39-4.6)	0.65
Cameroon	0.17 (63/8/10)	0.11 (502/25/51)	1.54(1.06-2.22)	0.02
Kenya	0.26 (108/20/32)	0.19 (2863/639/438)	1.32(1.07-1.63)	1.08 x 10 ⁻⁰²
Tanzania	0.15 (147/13/21)	0.2 (319/85/49)	0.81(0.61-1.08)	0.16
Malawi	0.27 (85/24/23)	0.2 (1942/408/323)	1.28(1.02-1.61)	0.03
All	0.18 (1563/215/263)	0.15 (11552/1770/1279)	1.19(1.1-1.28)	2.62 x 10 ⁻⁰⁵

Supplementary Table 13: G6PD+202 Males and Females Additive Model. Frequency of the derived-allele at G6PD+202 (rs1050828) in all cases and controls. Odds ratios (OR), 95% confidence intervals (95% CI) and p-values are presented for association of the derived-allele with all severe malaria, cerebral malaria only and severe malarial anaemia only for all individuals at each study site and at all study sites combined. Results are adjusted for sickle-cell trait and ethnicity. Sites where rs1050828 is not present (Vietnam and Papua New Guinea) were excluded from this analysis.

G6PD+202 Phenotype Site	Derived-Allele Frequency (Derived Hemizygote/Total)		OR (95% CI)	P
	Cases	Controls		
Males – Hemizygote Model				
All severe malaria				
Gambia	0.02 (29/1265)	0.03 (49/1684)	0.81(0.5-1.31)	0.39
Mali	0.18 (47/255)	0.18 (31/174)	0.94(0.56-1.58)	0.82
Burkina Faso	0.15 (75/488)	0.14 (51/375)	1.15(0.78-1.69)	0.49
Ghana (Navrongo)	0.22 (86/386)	0.18 (49/272)	1.29(0.87-1.92)	0.21
Ghana (Kumasi)	0.2 (160/799)	0.18 (184/1051)	1.12(0.87-1.44)	0.38
Nigeria	0.09 (4/47)	0.17 (3/18)	0.32(0.06-1.71)	0.20
Cameroon	0.13 (44/336)	0.11 (48/419)	1.31(0.83-2.07)	0.25
Kenya	0.2 (232/1167)	0.19 (376/1989)	1.13(0.93-1.36)	0.22
Tanzania	0.15 (34/227)	0.19 (39/205)	0.75(0.44-1.27)	0.29
Malawi	0.22 (155/707)	0.2 (275/1401)	1.13(0.91-1.41)	0.28
All	0.15 (866/5677)	0.15 (1105/7588)	1.1(0.99-1.22)	0.07
Cerebral malaria only				
Gambia	0.02 (9/398)	0.03 (49/1684)	0.78(0.37-1.62)	0.49
Mali	0.06 (3/51)	0.18 (31/174)	0.25(0.07-0.92)	0.02
Burkina Faso	0.07 (4/57)	0.14 (51/375)	0.46(0.16-1.33)	0.12
Ghana (Navrongo)	0.08 (1/12)	0.18 (49/272)	0.39(0.05-3.15)	0.32
Ghana (Kumasi)	0.16 (18/116)	0.18 (184/1051)	0.82(0.47-1.44)	0.48
Nigeria	0 (0/4)	0.17 (3/18)	0(0-Inf)	0.16
Cameroon	0.1 (2/20)	0.11 (48/419)	0.94(0.21-4.2)	0.93
Kenya	0.15 (71/465)	0.19 (376/1989)	0.82(0.62-1.08)	0.16
Tanzania	0.18 (3/17)	0.19 (39/205)	1.01(0.26-3.92)	0.99
Malawi	0.18 (80/435)	0.2 (275/1401)	0.91(0.69-1.2)	0.49
All	0.12 (191/1575)	0.15 (1105/7588)	0.81(0.68-0.96)	0.01
Severe malarial anaemia only				
Gambia	0.03 (8/240)	0.03 (49/1684)	1.15(0.53-2.48)	0.73
Mali	0.24 (25/105)	0.18 (31/174)	1.32(0.71-2.47)	0.38
Burkina Faso	0.21 (4/19)	0.14 (51/375)	1.63(0.52-5.12)	0.42
Ghana (Navrongo)	0.25 (38/155)	0.18 (49/272)	1.48(0.9-2.41)	0.12
Ghana (Kumasi)	0.25 (72/289)	0.18 (184/1051)	1.4(0.99-1.97)	0.06
Nigeria	0.25 (1/4)	0.17 (3/18)	1.5(0.1-23.07)	0.77
Cameroon	0.2 (8/40)	0.11 (48/419)	2.58(1.09-6.12)	0.04
Kenya	0.33 (29/89)	0.19 (376/1989)	2.2(1.39-3.5)	1.41 x 10 ⁻⁰³
Tanzania	0.16 (17/108)	0.19 (39/205)	0.9(0.47-1.74)	0.76
Malawi	0.3 (20/67)	0.2 (275/1401)	1.72(1-2.94)	0.06
All	0.2 (222/1116)	0.15 (1105/7588)	1.49(1.24-1.79)	3.55 x 10 ⁻⁰⁵

Supplementary Table 14: G6PD+202 Males Hemizygote Model. Frequency of the derived-allele at G6PD+202 (rs1050828) in male cases and controls Odds ratios (OR), 95% confidence intervals (95% CI) and p-values (P) are presented for association of the derived-allele with severe malaria, cerebral malaria only and severe malarial anaemia only for males at each study site and at all study sites combined. Results are adjusted for sickle-cell trait and ethnicity. Sites where rs1050828 is not present (Vietnam and Papua New Guinea) were excluded from this analysis.

G6PD+202 Phenotype Site	Derived Homozygote Frequency (Derived Homozgote/Total)		OR (95% CI)	P
	Cases	Controls		
Females – Recessive Model				
Severe malaria				
Gambia	0 (3/1153)	0 (2/1652)	n.c. [§]	n.c. [§]
Mali	0.02 (3/198)	0.02 (3/170)	n.c. [§]	n.c. [§]
Burkina Faso	0.03 (10/374)	0.02 (7/350)	1.36(0.5-3.65)	0.54
Ghana (Navrongo)	0.04 (13/295)	0.02 (5/216)	2.39(0.79-7.19)	0.10
Ghana (Kumasi)	0.04 (27/695)	0.03 (32/974)	1.11(0.63-1.95)	0.71
Nigeria	0.1 (3/30)	0.1 (2/21)	n.c. [§]	n.c. [§]
Cameroon	0.01 (3/282)	0.02 (3/159)	n.c. [§]	n.c. [§]
Kenya	0.03 (38/1087)	0.03 (62/1951)	1.16(0.76-1.78)	0.50
Tanzania	0.05 (11/201)	0.04 (10/248)	1.66(0.63-4.34)	0.30
Malawi	0.03 (23/676)	0.04 (48/1272)	0.89(0.53-1.48)	0.65
All	0.03 (134/4991)	0.02 (174/7013)	1.15(0.9-1.46)	0.27
Cerebral malaria only				
Gambia	0 (0/386)	0 (2/1652)	n.c. [§]	n.c. [§]
Mali	0 (0/35)	0.02 (3/170)	n.c. [§]	n.c. [§]
Burkina Faso	0.04 (2/48)	0.02 (7/350)	n.c. [§]	n.c. [§]
Ghana (Navrongo)	0.1 (1/10)	0.02 (5/216)	n.c. [§]	n.c. [§]
Ghana (Kumasi)	0.02 (2/114)	0.03 (32/974)	n.c. [§]	n.c. [§]
Nigeria	0 (0/2)	0.1 (2/21)	n.c. [§]	n.c. [§]
Cameroon	0 (0/19)	0.02 (3/159)	n.c. [§]	n.c. [§]
Kenya	0.04 (18/441)	0.03 (62/1951)	1.4(0.81-2.44)	0.24
Tanzania	0.06 (1/17)	0.04 (10/248)	n.c. [§]	n.c. [§]
Malawi	0.03 (15/434)	0.04 (48/1272)	0.9(0.5-1.63)	0.73
All	0.03 (39/1506)	0.02 (174/7013)	1.09(0.76-1.57)	0.65
Severe malarial anaemia only				
Gambia	0 (1/217)	0 (2/1652)	n.c. [§]	n.c. [§]
Mali	0.04 (3/80)	0.02 (3/170)	n.c. [§]	n.c. [§]
Burkina Faso	0.1 (2/20)	0.02 (7/350)	n.c. [§]	n.c. [§]
Ghana (Navrongo)	0.1 (9/92)	0.02 (5/216)	7.37(2.04-26.67)	1.15 x 10 ⁻⁰³
Ghana (Kumasi)	0.05 (13/262)	0.03 (32/974)	1.31(0.6-2.85)	0.50
Nigeria	0.25 (1/4)	0.1 (2/21)	n.c. [§]	n.c. [§]
Cameroon	0.05 (2/41)	0.02 (3/159)	n.c. [§]	n.c. [§]
Kenya	0.04 (3/71)	0.03 (62/1951)	n.c. [§]	n.c. [§]
Tanzania	0.05 (4/73)	0.04 (10/248)	n.c. [§]	n.c. [§]
Malawi	0.05 (3/65)	0.04 (48/1272)	n.c. [§]	n.c. [§]
All	0.04 (41/925)	0.02 (174/7013)	1.94(1.3-2.89)	1.92 x 10⁻⁰³

Supplementary Table 15: G6PD+202 Females Recessive Model. Frequency of female cases and controls homozygous for the derived-allele at G6PD+202 (rs1050828). Odds ratios (OR), 95% confidence intervals (95% CI) and p-values are presented for association of derived homozygotes with severe malaria, cerebral malaria only and severe malarial anaemia only for females at each study site and at all study sites combined. Results are adjusted for sickle-cell trait and ethnicity. Sites where rs1050828 is not present (Vietnam and Papua New Guinea) were excluded from this analysis. [§] Genotype counts too small for accurate calculation.

G6PD+202 Phenotype Site	Heterozygote Frequency (Heterozgote/Total)		OR (95% CI)	P
	Cases	Controls		
Females – Heterozygote Advantage Model				
Severe malaria				
Gambia	0.04 (45/1153)	0.05 (83/1652)	0.82(0.56-1.21)	0.32
Mali	0.29 (58/198)	0.28 (47/170)	1.02(0.64-1.63)	0.93
Burkina Faso	0.31 (116/374)	0.26 (91/350)	1.23(0.88-1.7)	0.22
Ghana (Navrongo)	0.31 (92/295)	0.38 (81/216)	0.75(0.52-1.09)	0.14
Ghana (Kumasi)	0.31 (214/695)	0.31 (299/974)	1.06(0.85-1.33)	0.62
Nigeria	0.23 (7/30)	0.57 (12/21)	0.23(0.07-0.77)	0.01
Cameroon	0.17 (48/282)	0.16 (25/159)	0.9(0.52-1.56)	0.72
Kenya	0.29 (311/1087)	0.33 (639/1951)	0.82(0.7-0.97)	0.02
Tanzania	0.24 (49/201)	0.34 (85/248)	0.54(0.35-0.85)	6.34 x 10 ⁻⁰³
Malawi	0.31 (212/676)	0.32 (408/1272)	0.98(0.8-1.2)	0.85
All	0.23 (1152/4991)	0.25 (1770/7013)	0.9(0.82-0.99)	0.02
Cerebral malaria only				
Gambia	0.02 (9/386)	0.05 (83/1652)	0.48(0.24-0.98)	0.03
Mali	0.23 (8/35)	0.28 (47/170)	0.79(0.33-1.92)	0.60
Burkina Faso	0.44 (21/48)	0.26 (91/350)	2.08(1.12-3.87)	0.02
Ghana (Navrongo)	0.2 (2/10)	0.38 (81/216)	0.4(0.08-1.94)	0.22
Ghana (Kumasi)	0.25 (28/114)	0.31 (299/974)	0.78(0.48-1.27)	0.31
Nigeria	0.5 (1/2)	0.57 (12/21)	0.89(0.05-16.66)	0.94
Cameroon	0.05 (1/19)	0.16 (25/159)	0.24(0.03-1.93)	0.11
Kenya	0.31 (135/441)	0.33 (639/1951)	0.89(0.71-1.13)	0.34
Tanzania	0.29 (5/17)	0.34 (85/248)	0.69(0.23-2.07)	0.50
Malawi	0.29 (128/434)	0.32 (408/1272)	0.9(0.71-1.14)	0.38
All	0.22 (338/1506)	0.25 (1770/7013)	0.87(0.76-1.01)	0.06
Severe malarial anaemia only				
Gambia	0.05 (11/217)	0.05 (83/1652)	1.06(0.55-2.04)	0.87
Mali	0.3 (24/80)	0.28 (47/170)	1.12(0.61-2.03)	0.72
Burkina Faso	0.25 (5/20)	0.26 (91/350)	0.89(0.31-2.53)	0.83
Ghana (Navrongo)	0.28 (26/92)	0.38 (81/216)	0.66(0.39-1.13)	0.13
Ghana (Kumasi)	0.32 (83/262)	0.31 (299/974)	1.22(0.88-1.68)	0.23
Nigeria	0.25 (1/4)	0.57 (12/21)	0.17(0.01-2.77)	0.17
Cameroon	0.2 (8/41)	0.16 (25/159)	1.14(0.46-2.84)	0.77
Kenya	0.28 (20/71)	0.33 (639/1951)	0.77(0.45-1.33)	0.34
Tanzania	0.18 (13/73)	0.34 (85/248)	0.34(0.17-0.67)	9.81 x 10 ⁻⁰⁴
Malawi	0.37 (24/65)	0.32 (408/1272)	1.26(0.75-2.11)	0.39
All	0.23 (215/925)	0.25 (1770/7013)	0.93(0.77-1.11)	0.42

Supplementary Table 16: G6PD+202 Females Heterozygote Advantage Model. Frequency of female cases and controls heterozygous for the the derived-allele at G6PD+202 (rs1050828). Odds ratios (OR), 95% confidence intervals (95% CI) and p-values are presented for association of heterozygotes with severe malaria, cerebral malaria and severe malarial anaemia for females at each study site and at all study sites combined. Results are adjusted for sickle-cell trait and ethnicity. Sites where rs1050828 is not present (Vietnam and Papua New Guinea) were excluded from this analysis.

G6PD+202		Model Allele Counts		
Phenotype	Cases	Controls	OR (95% CI)	P
Females – All Sites – Heterozygote vs. Homozygous for Ancestral Allele				
All severe malaria	1152/3705	1770/5069	0.9(0.82-0.99)	0.03
Cerebral malaria only	338/1129	1770/5069	0.87(0.76-1.01)	0.06
Severe malarial anaemia only	215/669	01770/5069	0.96(0.8-1.16)	0.68
Females – All Sites – Heterozygote vs. Homozygous for Derived-Allele				
All severe malaria	1152/134	1770/174	0.8(0.62-1.03)	0.09
Cerebral malaria only	338/39	01770/174	0.84(0.57-1.23)	0.38
Severe malarial anaemia only	0.84 (215/41)	1770/174	0.49(0.32-0.75)	1.51 x 10 ⁻⁰³
Females – All Sites – Homozygous for Derived vs. Homozygous for Ancestral Allele				
All severe malaria	134/3705	174/5069	1.1(0.87-1.41)	0.43
Cerebral malaria only	39/1129	174/5069	1.05(0.73-1.52)	0.80
Severe malarial anaemia only	41/669	174/5069	1.88(1.25-2.83)	3.54 x 10 ⁻⁰³

Supplementary Table 17: G6PD+202 Female Various Models. Counts of cases and controls in given model categories at G6PD+202 (rs1050828). Odds ratios (OR), 95% Confidence Intervals (95% CI) and p-values (*P*) are presented for association of G6PD+202 with severe malaria, cerebral malaria only and severe malarial anaemia only in females for various models at all study sites combined. Results are adjusted for sickle-cell trait and ethnicity. Sites where rs1050828 is not present (Vietnam and Papua New Guinea) were excluded from this analysis.

ATP2B4				
Derived-Allele Frequency (Derived Homozygote/ Heterozygote/Ancestral Homozygote)				
Phenotype Site	Cases	Controls	OR (95% CI)	P
Males and Females – Dominant Model				
Severe malaria				
Gambia	0.91 (204/1021/1161)	0.87 (426/1369/1485)	1.61(1.34-1.93)	1.64 X 10 ⁻⁰⁷
Mali	0.92 (35/164/228)	0.92 (25/141/156)	0.97(0.56-1.68)	0.92
Burkina Faso	0.91 (78/377/388)	0.91 (63/292/365)	0.94(0.66-1.34)	0.75
Ghana (Navrongo)	0.94 (34/246/334)	0.97 (5/74/86)	0.52(0.19-1.39)	0.16
Ghana (Kumasi)	0.87 (102/365/294)	0.81 (240/586/405)	1.54(1.16-2.03)	2.32 X 10 ⁻⁰³
Nigeria	0.84 (12/39/25)	0.88 (4/15/15)	0.77(0.22-2.68)	0.68
Cameroon	0.87 (80/264/253)	0.83 (96/240/240)	1.24(0.89-1.74)	0.20
Kenya	0.91 (150/786/688)	0.89 (429/1689/1644)	1.29(1.06-1.58)	1.14 X 10 ⁻⁰²
Tanzania	0.89 (48/199/178)	0.87 (58/211/182)	1.18(0.77-1.81)	0.44
Malawi	0.91 (125/595/654)	0.88 (298/1105/1159)	1.27(1.01-1.58)	0.04
Vietnam	1 (0/33/746)	1 (0/89/2367)	n.c. [§]	n.c. [§]
All	0.9 (868/4056/4203)	0.87 (1644/5722/5737)	1.32(1.21-1.45)	1.69 X 10 ⁻⁰⁹
Cerebral malaria only				
Gambia	0.92 (65/330/380)	0.87 (426/1369/1485)	1.67(1.27-2.21)	1.48 X 10 ⁻⁰⁴
Mali	0.91 (7/35/39)	0.92 (25/141/156)	0.89(0.35-2.26)	0.81
Burkina Faso	0.93 (8/46/53)	0.91 (63/292/365)	1.16(0.54-2.51)	0.70
Ghana (Navrongo)	1 (0/10/9)	0.97 (5/74/86)	n.c. [§]	n.c. [§]
Ghana (Kumasi)	0.86 (16/58/43)	0.81 (240/586/405)	1.43(0.77-2.63)	0.24
Nigeria	0.67 (2/3/1)	0.88 (4/15/15)	0.34(0.04-3.03)	0.35
Cameroon	0.87 (5/14/20)	0.83 (96/240/240)	1.31(0.5-3.47)	0.58
Kenya	0.9 (59/285/266)	0.89 (429/1689/1644)	1.23(0.92-1.65)	0.15
Tanzania	0.88 (4/17/12)	0.87 (58/211/182)	1.2(0.4-3.62)	0.74
Malawi	0.91 (79/370/413)	0.88 (298/1105/1159)	1.26(0.97-1.64)	0.08
Vietnam	1 (0/13/195)	1 (0/89/2367)	n.c. [§]	n.c. [§]
All	0.91 (245/1168/1236)	0.87 (1644/5722/5737)	1.35(1.17-1.57)	3.06 X 10 ⁻⁰⁵
Severe malarial anaemia only				
Gambia	0.93 (33/197/219)	0.87 (426/1369/1485)	1.92(1.32-2.78)	2.25 X 10 ⁻⁰⁴
Mali	0.93 (12/68/95)	0.92 (25/141/156)	1.14(0.55-2.38)	0.73
Burkina Faso	0.89 (4/17/16)	0.91 (63/292/365)	0.79(0.27-2.32)	0.68
Ghana (Navrongo)	0.95 (11/92/122)	0.97 (5/74/86)	0.53(0.16-1.69)	0.27
Ghana (Kumasi)	0.88 (45/189/155)	0.81 (240/586/405)	1.94(1.31-2.86)	4.81 X 10 ⁻⁰⁴
Nigeria	0.5 (4/3/1)	0.88 (4/15/15)	0.12(0.02-0.74)	0.02
Cameroon	0.85 (12/33/34)	0.83 (96/240/240)	1.11(0.56-2.22)	0.76
Kenya	0.92 (12/75/68)	0.89 (429/1689/1644)	1.67(0.9-3.13)	0.08
Tanzania	0.92 (15/84/81)	0.87 (58/211/182)	1.46(0.79-2.72)	0.22
Malawi	0.91 (11/58/60)	0.88 (298/1105/1159)	1.36(0.72-2.55)	0.33
Vietnam	1 (0/1/29)	1 (0/89/2367)	n.c. [§]	n.c. [§]
All	0.91 (159/816/851)	0.87 (1644/5722/5737)	1.53(1.27-1.84)	3.68 X 10 ⁻⁰⁶

Supplementary Table 18: ATP2B4 Males and Females Dominant Model. Frequency of the derived allele at ATP2B4 (rs10900585) in all cases and controls. Odds ratios (OR), 95% confidence intervals (95% CI) and p-values (P) are presented for association of the derived-allele with all severe malaria, cerebral malaria only and severe malarial anaemia only for all individuals at each study site and at all study sites combined. Results are adjusted for sickle-cell trait and ethnicity. Sites at which rs10900585 is monomorphic (Papua New Guinea) were excluded from this analysis. n.c., not calculated. [§] sample size too small for accurate calculation.

CD40LG Phenotype Site	Derived Homozygote Frequency (Derived Homozygote/Total)			
	Cases	Controls	OR (95% CI)	P
Males and Females – Recessive Model				
All severe malaria				
Gambia	0.24 (586/2406)	0.36 (1159/3204)	0.54(0.48-0.61)	2.30 X 10 ⁻²²
Mali	0.25 (114/449)	0.24 (82/335)	0.99(0.7-1.41)	0.96
Burkina Faso	0.24 (205/862)	0.22 (156/720)	1.02(0.79-1.31)	0.89
Ghana (Navrongo)	0.25 (168/675)	0.25 (116/458)	0.93(0.7-1.25)	0.63
Ghana (Kumasi)	0.25 (366/1483)	0.25 (491/1937)	0.92(0.78-1.1)	0.37
Nigeria	0.21 (16/77)	0.31 (12/39)	0.5(0.19-1.35)	0.17
Cameroon	0.2 (120/610)	0.21 (120/576)	1.14(0.84-1.55)	0.39
Kenya	0.18 (406/2258)	0.13 (521/3927)	1.42(1.22-1.65)	7.57 X 10 ⁻⁰⁶
Tanzania	0.15 (63/426)	0.12 (54/444)	1.08(0.71-1.65)	0.73
Malawi	0.15 (206/1372)	0.15 (406/2683)	1.01(0.84-1.22)	0.91
Vietnam	0 (0/790)	0.03 (80/2525)	n.c. [§]	n.c. [§]
All	0.2 (2250/11408)	0.19 (3197/16848)	0.85(0.79-0.91)	1.11 X 10⁻⁰⁶
Cerebral malaria only				
Gambia	0.26 (200/780)	0.36 (1159/3204)	0.6(0.5-0.72)	3.54 X 10 ⁻⁰⁸
Mali	0.29 (25/85)	0.24 (82/335)	1.18(0.68-2.05)	0.56
Burkina Faso	0.21 (22/107)	0.22 (156/720)	0.82(0.48-1.4)	0.47
Ghana (Navrongo)	0.18 (4/22)	0.25 (116/458)	0.64(0.19-2.12)	0.47
Ghana (Kumasi)	0.25 (57/226)	0.25 (491/1937)	0.99(0.69-1.42)	0.96
Nigeria	0.33 (2/6)	0.31 (12/39)	0.8(0.06-11.21)	0.87
Cameroon	0.11 (4/38)	0.21 (120/576)	0.54(0.19-1.59)	0.27
Kenya	0.17 (158/906)	0.13 (521/3927)	1.36(1.1-1.68)	4.19 X 10 ⁻⁰³
Tanzania	0.18 (6/34)	0.12 (54/444)	1.58(0.62-4.05)	0.34
Malawi	0.14 (118/861)	0.15 (406/2683)	0.92(0.73-1.15)	0.46
Vietnam	0 (0/209)	0.03 (80/2525)	n.c. [§]	n.c. [§]
All	0.18 (596/3274)	0.19 (3197/16848)	0.85(0.76-0.94)	2.45 X 10⁻⁰³
Severe malarial anaemia only				
Gambia	0.25 (114/457)	0.36 (1159/3204)	0.56(0.45-0.71)	1.01 X 10 ⁻⁰⁶
Mali	0.23 (42/183)	0.24 (82/335)	0.86(0.55-1.34)	0.51
Burkina Faso	0.23 (9/39)	0.22 (156/720)	1.06(0.48-2.34)	0.89
Ghana (Navrongo)	0.24 (59/245)	0.25 (116/458)	0.79(0.54-1.15)	0.22
Ghana (Kumasi)	0.22 (122/549)	0.25 (491/1937)	0.78(0.6-1.01)	0.06
Nigeria	0.5 (4/8)	0.31 (12/39)	2.36(0.24-23.12)	0.46
Cameroon	0.14 (11/80)	0.21 (120/576)	0.8(0.39-1.62)	0.53
Kenya	0.25 (40/157)	0.13 (521/3927)	2.29(1.51-3.46)	8.64 X 10 ⁻⁰⁵
Tanzania	0.14 (26/181)	0.12 (54/444)	0.9(0.52-1.56)	0.70
Malawi	0.19 (25/130)	0.15 (406/2683)	1.4(0.88-2.22)	0.15
Vietnam	0 (0/31)	0.03 (80/2525)	n.c. [§]	n.c. [§]
All	0.22 (452/2060)	0.19 (3197/16848)	0.82(0.73-0.94)	2.97 X 10⁻⁰³

Supplementary Table 19: CD40LG Females Recessive Model. Frequency of female cases and controls homozygous for the derived allele at CD40LG (rs3092945). Odds ratios (OR), 95% confidence intervals (95% CI) and p-values are presented for association of derived homozygotes with severe malaria, cerebral malaria only and severe malarial anaemia only for females at each study site and at all study sites combined. Results are adjusted for sickle-cell trait and ethnicity. Sites where rs3092945 is not present (Papua New Guinea) were excluded from this analysis. n.c. not calculated. [§] Genotype counts too small for accurate calculation.

Gene 1	Gene 2	SNP 1	SNP 2	Best Model 1 ^a	Best Model 2 ^a	Phenotype	Sample	Genotype Test of Interaction P-value	Best Model Test of Interaction P-value
ATP2B4	HbS	rs1541255	rs334	R	H	SM	F	3.95 X 10 ⁻⁰²	1.01 X 10 ⁻⁰¹
ATP2B4	HbC	rs1541255	rs33930165	R	A	SM	M	3.86 X 10 ⁻⁰²	3.35 X 10 ⁻⁰³
ATP2B4	HbC	rs1541255	rs33930165	R	A	SM	All	4.11 X 10 ⁻⁰³	1.34 X 10 ⁻⁰³
ATP2B4	G6PD	rs1541255	rs1050828	R	A	SM	F	1.92 X 10 ⁻⁰¹	4.23 X 10 ⁻⁰²
ATP2B4	ABO	rs10900585	rs8176746	D	D	SM	All	4.61 X 10 ⁻⁰²	6.47 X 10 ⁻⁰¹
ATP2B4	HbS	rs10900585	rs334	D	H	SM	F	1.12 X 10 ⁻⁰²	3.07 X 10 ⁻⁰¹
ATP2B4	HbC	rs10900585	rs33930165	D	A	SM	M	6.82 X 10 ⁻⁰²	3.34 X 10 ⁻⁰³
ATP2B4	HbC	rs10900585	rs33930165	D	A	SM	All	1.77 X 10 ⁻⁰²	1.27 X 10 ⁻⁰³
ATP2B4	G6PD	rs10900585	rs1050828	D	A	SM	F	2.91 X 10 ⁻⁰¹	3.20 X 10 ⁻⁰²
ABO	CD40LG	rs8176746	rs3092945	D	R	SM	F	6.73 X 10 ⁻⁰²	3.26 X 10 ⁻⁰²
ABO	G6PD	rs8176746	rs1050828	D	A	SM	All	1.04 X 10 ⁻⁰¹	3.28 X 10 ⁻⁰²
HBB	CD40LG	rs33930165	rs3092945	A	R	SM	M	8.07 X 10 ⁻⁰²	2.70 X 10 ⁻⁰²
HBB	CD40LG	rs33930165	rs3092945	A	R	SM	All	2.21 X 10 ⁻⁰²	3.75 X 10 ⁻⁰²
CD40LG	G6PD	rs3092945	rs1050828	R	A	SM	M	2.54 X 10 ⁻⁰²	2.17 X 10 ⁻⁰²
CD40LG	G6PD	rs3092945	rs1050828	R	A	SM	All	2.30 X 10 ⁻⁰²	2.26 X 10 ⁻⁰³
ATP2B4	HbS	rs10900585	rs334	D	H	CM	F	4.48 X 10 ⁻⁰²	1.06 X 10 ⁻⁰¹
ATP2B4	HbC	rs10900585	rs33930165	D	A	CM	All	3.67 X 10 ⁻⁰²	8.48 X 10 ⁻⁰²
ABO	HbS	rs8176746	rs334	D	H	CM	M	4.13 X 10 ⁻⁰²	6.48 X 10 ⁻⁰¹
ABO	HbS	rs8176719	rs334	R	H	CM	M	4.07 X 10 ⁻⁰²	8.19 X 10 ⁻⁰¹
ATP2B4	ABO	rs1541255	rs8176719	R	R	SMA	F	3.16 X 10 ⁻⁰³	6.80 X 10 ⁻⁰¹
ATP2B4	ABO	rs1541255	rs8176719	R	R	SMA	All	2.07 X 10 ⁻⁰²	3.00 X 10 ⁻⁰¹
ATP2B4	HbS	rs1541255	rs334	R	H	SMA	All	2.32 X 10 ⁻⁰¹	4.82 X 10 ⁻⁰²
ATP2B4	HbC	rs1541255	rs33930165	R	A	SMA	F	1.29 X 10 ⁻⁰¹	3.23 X 10 ⁻⁰²
ATP2B4	ABO	rs10900585	rs8176719	D	R	SMA	F	4.27 X 10 ⁻⁰³	6.25 X 10 ⁻⁰¹
ATP2B4	ABO	rs10900585	rs8176719	D	R	SMA	All	3.69 X 10 ⁻⁰³	8.60 X 10 ⁻⁰¹
CD40LG	G6PD	rs3092945	rs1050828	R	A	SMA	All	5.52 X 10 ⁻⁰²	4.60 X 10 ⁻⁰²
ATP2B4	ABO	rs1541255	rs8176719	R	R	SMA	F	3.16 X 10 ⁻⁰³	6.80 X 10 ⁻⁰¹

Supplementary Table 20: Gene-Gene Interaction. Summary of gene-gene interaction signals of association at all pairs of SNPs with $P < 0.05$ in either the “Genotype” test of interaction or the “Best Model” test of interaction for association with severe malaria (SM), cerebral malaria (CM) and severe malarial anaemia (SMA) in males, females and all individuals combined. Results are adjusted for gender and ethnicity. Study sites at which a SNP was monomorphic were excluded from the analysis. Best model for each SNP is selected according to its association with SM for all individuals across all sites in a fixed effect model adjusted for ethnicity and gender.

^aModels are A, Additive; D, Dominant; H, Heterozygote Advantage; R, Recessive.

Cerebral Malaria (CM)	Severe Malarial Anaemia (SMA)	CM OR SMA*	CM AND SMA	CM NOT SMA	SMA NOT CM	NEITHER CM NOR SMA	Not Determined
0	0	0	0	0	0	1	0
0	1	1	0	0	1	0	0
0	n.d.	n.d.	0	0	n.d.	n.d.	1
1	0	1	0	1	0	0	0
1	1	1	1	0	0	0	0
1	n.d.	1	n.d.	n.d.	0	0	1
n.d.	0	n.d.	0	n.d.	0	n.d.	1
n.d.	1	1	n.d.	0	n.d.	0	1
n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	1

Supplementary Table 21: Logic table used to combine the cerebral malaria (CM) and severe malaria anaemia (SMA) phenotypes. Where sufficient data were available to make a NO/YES classification a 0 or 1 was assigned respectively, otherwise not determined (n.d.) was assigned. The resulting classifications for CM and SMA were then combined according to the logic terms; OR, AND, NOT, NOR. Combinations not resulting in a positive classification from the AND, NOT, NOR operations were then classified as 'Not Determined'. This latter group includes all individuals with other severe malaria subtypes and those who may have cerebral malaria or severe malaria anaemia but lack information to classify them.

Header	description
multiplex_code	multiplex number
Assay type	sequenom assay type
rsnumber	rsnumber where assigned
alternate_name	common name for SNP used in the literature
SNP sequence	SNP definition with 15 flanking bases
gene_symbol	HGNC gene name
chromosome	chromosome
position	chromosomal position
stand	chromosome strand with respect to reference genome
1st-PCR	first round PCR primer sequence
2nd-PCR	first round PCR primer sequence
AMP_LEN	amplicon length for first-round PCR
UEP_DIR	universal extension primer direction with respect to SNP sequence
UEP_SEQ	universal extension primer sequence
UEP_MASS	universal extension primer mass (Da)
EXT1_SEQ	allele 1 primer extension product
EXT1_CALL	allele 1 genotype call
EXT1_MASS	allele 1 primer extension product mass (Da)
EXT2_SEQ	allele 2 primer extension product
EXT2_CALL	allele 2 genotype call
EXT2_MASS	allele 2 primer extension product mass (Da)
EXT3_SEQ	allele 3 primer extension product
EXT3_CALL	allele 3 genotype call
EXT3_MASS	allele 3 primer extension product mass (Da)

Supplementary Table 22: Header Dictionary for Supplementary Tables 23 and 24. These headers describe the column information some of which are typically found in a Sequenom Assay Design File. Further details may be found in the Spectrodesigner® assay design software manual (Sequenom® [see URLs]).

Multiplex_Code	Assay_Type	rs_number	alternate_name	SNP_Sequence	gene_symbol	chromosome	position	strand	ref_PCP	alt_PCP	AMP_LEN	UPD_DIR	UPD_SEQ	UPD_MASS	EXT_SEQ	EXT_CALL	EXT_MASS	EXT_SEQ	EXT_CALL	EXT_MASS
W1	IPLEX	rs2227478	IL22-1394	GCAAGTGCACCTG[A/G]AAGGTGCGAACAC	IL22	12	68648622	1	ACGTTGGATGCTGCCACCTTCAACAATG	ACGTTGGATGTGAGATGGCAGCACTAAG	104	R	GTGGTCCGACCTT	4534.9	GTGGTCCGACCTT	G	4782.1	GTGGTCCGACCTT	A	4862
W1	IPLEX	rs361525	TNF-238	ACCCCTCTMRGAT[C/A]GAGGAGGAGGATGG	TNF	6	31543101	1	ACGTTGGATGAAGATCAAGGATACCCCTC	ACGTTGGATGACGGCTCTACACAAATC	115	R	CCCATCTCCCTGCTC	4689	CCCATCTCCCTGCTC	G	4936.2	CCCATCTCCCTGCTC	A	5016.1
W1	IPLEX	rs5498	ICAM-1codon469	GGGAGGTCCACCC[A/G]AGGTGACCGTGAATG	ICAM1	19	10395683	1	ACGTTGGATGCTCAGAGCACTTACCG	ACGTTGGATGTCTCAGATCTTGGAG	115	R	ACATTCACGGTCACT	4801.1	ACATTCACGGTCACT	G	5048.3	ACATTCACGGTCACT	A	5128.2
W1	IPLEX	rs1800890	IL-10-3533	TACTGATTTAAATG[A/T]ATTTTCCAGTGGGG	IL10	1	206949365	1	ACGTTGGATGCTGATTTCCAGTACATCCC	ACGTTGGATGCAAGCCAGATGCATAGTAG	110	R	CCCCACTGGAAAAAT	4819.2	CCCCACTGGAAAAAT	T	5090.4	CCCCACTGGAAAAAT	A	5146.3
W1	IPLEX	rs1800896	IL-10-1082	TATCCCTACTCC[C/T]TCCCAAGAGCCTT	IL10	1	206946897	1	ACGTTGGATGCTCAGAGGCTGGATAG	ACGTTGGATGCAAGCAACACTACTAAGG	111	F	CCTATCCCTACTCC	4977.2	CCTATCCCTACTCC	C	5224.4	CCTATCCCTACTCC	T	5304.3
W1	IPLEX	none assigned	amelogenin_XY_SNP6	CAATGTAAACCTG[C/A]CTCTCTGTTCTCAC	AMELX	X	11316650	1	ACGTTGGATGCTCTGTTGGATGAGT	ACGTTGGATGGGCTGTCAACTAGGAAG	103	F	GCCAAATGGTAACTGC	5179.4	GCCAAATGGTAACTGC	C	5426.6	GCCAAATGGTAACTGC	A	5450.6
W1	IPLEX	rs8386		TGTGGACACTGAGAA[C/T]ATCCCGCTGTGTC	GNAS	20	57485812	1	ACGTTGGATGTGATCGCTGAATGATGC	ACGTTGGATGTCACTTCCCTGCTGGG	98	R	GTGAACACACGGGGAT	5244.4	GTGAACACACGGGGAT	T	5515.6	GTGAACACACGGGGAT	C	5531.6
W1	IPLEX	rs17561	IL1A G4845T	ATCAAGCTAGGT[C/G]TACCTTTAGTCTCC	IL1A	2	113537223	-1	ACGTTGGATGTGATCTGTGATCATGG	ACGTTGGATGTTCACTTGTCTCAGGAAG	96	F	ATCATCAAGCTAGGTCA	5467.6	ATCATCAAGCTAGGTCA	G	5754.8	ATCATCAAGCTAGGTCA	T	5794.7
W1	IPLEX	rs18176719		GGATGCTCTGTGT[G/A]ACCCCTGGCTGGCT	ABO	9	136132909	-1	ACGTTGGATGATGATGATGATGATGATG	ACGTTGGATGTGATGATGATGATGATG	99	F	GAAGGATGCTCTGTGTA	5570.6	GAAGGATGCTCTGTGTA	D	5841.8	GAAGGATGCTCTGTGTA	I	5857.8
W1	IPLEX	rs9282799	NOS2-1173	AGCAAGTGTGGG[A/C]TGGTGAATCAAGGGT	NOS2	17	26128728	-1	ACGTTGGATGTAGGAGAAAGTGAAGAG	ACGTTGGATGTGGACGTTGAGCAAGTG	98	R	HTCACCTTGATCTCAC	5649.7	HTCACCTTGATCTCAC	T	5920.9	HTCACCTTGATCTCAC	C	5936.9
W1	IPLEX	rs334	HBS	TGCACCTGACTCTR[A/T]JGGAGAAGTGCCTG	HBB	11	5248232	-1	ACGTTGGATGCAACTTATCCAGCTCAC	ACGTTGGATGTCAACAGACACCATGGTC	106	R	ctTAACGGCAGACTTCTC	5723.7	ctTAACGGCAGACTTCTC	T	5994.9	ctTAACGGCAGACTTCTC	A	6050.8
W1	IPLEX	rs1800750	TNF-376	GCATCTCTGCGAA[A/G]TAGAAGGAACAAGA	TNF	6	31542963	1	ACGTTGGATGCAAGTCTGTGGCTGTGTC	ACGTTGGATGCTCCAGTCTTAGTCTATC	91	R	GTGGTCTGTTCTCTCAA	5775.8	GTGGTCTGTTCTCTCAA	G	6022.9	GTGGTCTGTTCTCTCAA	A	6102.9
W1	IPLEX	rs229587		AGGCGCTGTTTCA[C/T]TGAGCAGCTGTCTAC	SPTB	14	65263300	1	ACGTTGGATGCAAGTCTGTCCCTTATC	ACGTTGGATGAAGCCCGCAAGAGAGAC	94	F	CACGAGCGCTGGTTTCA	5819.8	CACGAGCGCTGGTTTCA	C	6067	CACGAGCGCTGGTTTCA	T	6146.9
W1	IPLEX	rs1050829	G6PD_plus376	CCAGGTGGGGGAT[C/T]CATGTGGCTGTGAC	G6PD	X	153763492	1	ACGTTGGATGATGATGATGATGATGATG	ACGTTGGATGATGATGATGATGATGATG	105	R	ccccCTCAACAGCACATG	5969.6	ccccCTCAACAGCACATG	T	6238.1	ccccCTCAACAGCACATG	C	6254.1
W1	IPLEX	rs3024500		CTCTCTCTGGGGT[A/G]GGGGTGTGGCTT	IL10	1	206940831	1	ACGTTGGATGAGTGGGTAAGTAACTCTG	ACGTTGGATGCTCTGATCAGTTGGAGC	111	R	ccccGAAGCCAGTACCC	5967.9	ccccGAAGCCAGTACCC	G	6215.1	ccccGAAGCCAGTACCC	A	6295
W1	IPLEX	rs2227485	IL22-485	TGATCTNCTATAGT[G/A]CTGAGTAAGCATTT	IL22	12	68647713	1	ACGTTGGATGCTGAGAAAGAAAGTCCG	ACGTTGGATGGTTTGTCTGATAGAGTTC	116	R	TGACAAAATGCTTACTAC	6085	TGACAAAATGCTTACTAC	G	6332.2	TGACAAAATGCTTACTAC	A	6411.2
W1	IPLEX	rs090253	LTA Ncol	GGGAACAGAGAGAA[C/T]CATGGCAGAAACAG	LTA	6	31540313	-1	ACGTTGGATGCTCTGCTCAACATCTCTG	ACGTTGGATGGTCAAGAAACCCCAAGTGC	115	R	cATTCTCTGTTCTGCGATG	6314.1	cATTCTCTGTTCTGCGATG	T	6585.3	cATTCTCTGTTCTGCGATG	C	6602.3
W1	IPLEX	rs3211938	CD36_T1264G	AAATGTACATATA[G/T]GGTGTAGATC	CD36	7	80300449	1	ACGTTGGATGTGATCTGTGATGCTAG	ACGTTGGATGCTCTGATGAAACCCAGAC	117	R	gTtTCTGATGCTAGCACACC	6372.2	gTtTCTGATGCTAGCACACC	G	6619.3	gTtTCTGATGCTAGCACACC	T	6643.4
W1	IPLEX	rs1799969	ICAM-1codon241	GCTGTCTGGGAC[A/G]GGCTGTCCAGCTG	ICAM1	19	10394792	1	ACGTTGGATGCTAGAGGCTGACGACGAG	ACGTTGGATGAACCTTGGTCCCAAGTGC	120	F	caaGTGCTCTGCTGGAC	6389.1	caaGTGCTCTGCTGGAC	A	6660.3	caaGTGCTCTGCTGGAC	G	6676.4
W1	IPLEX	rs2227491	IL22+708	GACGGCAGCAGCC[C/T]TGTGCTCAACAGT	IL22	12	68646521	1	ACGTTGGATGATCAACCCCAAGCTAAG	ACGTTGGATGCTCCAGCAGCAGCGCC	98	F	ggggTGGACGGCAGCGCC	6458.2	ggggTGGACGGCAGCGCC	C	6705.4	ggggTGGACGGCAGCGCC	T	6785.3
W1	IPLEX	rs3093662	TNF +851	GGAAAGTGAATACAC[A/G]GATGAATGGAGAG	TNF	6	31544189	1	ACGTTGGATGCTGCTGTTTCTCTCTCC	ACGTTGGATGGGAAGAGCTGTTGAATGCC	84	R	ttGTTTTCTCTCCTTCTC	6568.31	ttGTTTTCTCTCCTTCTC	G	6815.5	ttGTTTTCTCTCCTTCTC	A	6895.4
W1	IPLEX	rs17047661	SI (Swain-Lagley)	GTTGAAAATGCAAT[A/G]GAGTACAGGAGATC	CR1	1	207782889	1	ACGTTGGATGCTGGGCTGACATTAATC	ACGTTGGATGATGACAGCTCCAAAGTGT	117	R	aaacCTCTGTTCTGCTGATC	6925.5	aaacCTCTGTTCTGCTGATC	A	7172.7	aaacCTCTGTTCTGCTGATC	A	7252.6
W1	IPLEX	rs1050828	G6PD_plus202	ACGGGCGATGCCA[C/T]GATGAWGTGTTTC	G6PD	X	153764217	1	ACGTTGGATGATGGCTTCTGCCGAAAC	ACGTTGGATGCTCACTGTTGGGATGTC	102	R	ttggGCCGAAAACCTTATC	6928.5	ttggGCCGAAAACCTTATC	T	7199.7	ttggGCCGAAAACCTTATC	C	7215.7
W1	IPLEX	none assigned	CD36_g1439C	TTCACTTACAATT[C/G]CAANNCGCTGAGG	CD36	7	80302110	1	ACGTTGGATGCTCTTCTGATCAACTGG	ACGTTGGATGCTCAACTGACTGCTG	88	F	TAACGTGATCACTTACAATT	6987.6	TAACGTGATCACTTACAATT	C	7234.8	TAACGTGATCACTTACAATT	G	7274.8
W1	IPLEX	rs4986791		GTGATTTGGGACA[C/T]GAGCTAAAGTATT	TLR4	9	120475602	1	ACGTTGGATGAGTGTCTGCTCAAAAGT	ACGTTGGATGGTAATACACCAATGAAGC	96	F	TCTCAAGTGAATTTGGGACAA	7077.6	TCTCAAGTGAATTTGGGACAA	C	7324.8	TCTCAAGTGAATTTGGGACAA	T	7404.7
W1	IPLEX	rs155498		ACAGGTAATAGATA[C/T]GGGCAAAATACATA	IL20RA	6	137325847	1	ACGTTGGATGATGAAATAGCCATCAAGC	ACGTTGGATGCAATCATGAGTTCAAGG	113	F	AAAAAAGAACCGTAATAGATA	7130.7	AAAAAAGAACCGTAATAGATA	G	7377.9	AAAAAAGAACCGTAATAGATA	T	7457.8
W1	IPLEX	rs1799964	TNF-1031	GAGAGCTGAGAGAA[C/T]GAAGGAAGAGCAGG	TNF	6	31542308	1	ACGTTGGATGCTGCTGCTCAACATCTC	ACGTTGGATGGGAGAAAGAAAGAGCTG	112	R	CTCCAGACCTGACTTCTCTC	7421.9	CTCCAGACCTGACTTCTCTC	T	7421.9	CTCCAGACCTGACTTCTCTC	C	7437.9
W1	IPLEX	rs2239704	LTA +77	AGGGCAGGACACTG[C/T]GGCGGTATGCCAA	LTA	6	31540141	-1	ACGTTGGATGCTGCTGCTGGGACTA	ACGTTGGATGAGTGCAGAGGAGCAGG	91	R	gttgCTGCTTGGACTACCGCC	7296.7	gttgCTGCTTGGACTACCGCC	G	7543.9	gttgCTGCTTGGACTACCGCC	T	7567.9
W1	IPLEX	rs2297518		TTCAAGTGAAGGAC[A/G]GATTTCTCAAGTCT	NOS2	17	26096597	1	ACGTTGGATGCTGAGCACTCTGCTTCC	ACGTTGGATGTTGTTGAGCTTCTACG	95	R	gCTCTTCTAGAAGTGAAGAAAT	7359.8	gCTCTTCTAGAAGTGAAGAAAT	A	7607	gCTCTTCTAGAAGTGAAGAAAT	A	7686.9
W1	IPLEX	rs1012356	IL22+2611	GACTTCAATTAAT[C/T]TAATAACTCTTAC	IL22	12	68644618	1	ACGTTGGATGCTTCAACTTCAATTAAC	ACGTTGGATGCCCGCTTCAATTAAC	107	F	ttCCAATTCAGACTTCAATTA	7510.9	ttCCAATTCAGACTTCAATTA	A	7782.1	ttCCAATTCAGACTTCAATTA	T	7838
W1	IPLEX	rs187084		AAAGTCACTGCTT[C/T]AAGAACTGACATTC	TLR9	3	52261031	-1	ACGTTGGATGCTGCTGCTGACTGATG	ACGTTGGATGTAITCCCTGCTGGAATGC	100	F	GATGAGATAAAAGTCACTGCCCT	7659	GATGAGATAAAAGTCACTGCCCT	C	7906.2	GATGAGATAAAAGTCACTGCCCT	T	7986.1
W1	IPLEX	rs2230739		CTCCACAGCTGAT[A/G]AAGAACTCCCGCTG	ADCY9	16	4033436	-1	ACGTTGGATGCTCCGCTCACTCTCC	ACGTTGGATGAGGAGTGGACTAGCAAGC	100	F	ctaCACTCTGCTCCACAGCTTCA	7811.1	ctaCACTCTGCTCCACAGCTTCA	A	8082.3	ctaCACTCTGCTCCACAGCTTCA	G	8098.3
W1	IPLEX	rs2814778	Duffy - FyA/FyB	GCCTGTGCTCAAG[A/G]TAAGAGCAAGGACT	DARC	1	159174683	-1	ACGTTGGATGATCACTGCTGGCCATTAAG	ACGTTGGATGAGACAGCACTGCTGGACG	97	R	TGGCCCTCAATGCTTGGCTCTTA	7879.1	TGGCCCTCAATGCTTGGCTCTTA	G	8126.3	TGGCCCTCAATGCTTGGCTCTTA	A	8206.2
W1	IPLEX	rs2535611		TGTCAGTCACTCT[C/T]TTTTTTTTTTTTTTT	ADORA2B	17	15861332	1	ACGTTGGATGCACTTGTGAACACAGGAC	ACGTTGGATGGAGTGAACCTGTCTCAAG	92	F	gggCCAGAACCTGTCAAGTACACTC	7932.1	gggCCAGAACCTGTCAAGTACACTC	C	8179.3	gggCCAGAACCTGTCAAGTACACTC	T	8259.2
W1	IPLEX	rs4986790		ACTACTACTCGATG[A/G]TATTATGACTTATT	TLR4	9	120475302	1	ACGTTGGATGCTCCAGCAGAAATGAAGAAC	ACGTTGGATGAGCACTACTAGACTATACC	99	R	GTCAACAATAAATAAGTCAATAAT	8291.5	GTCAACAATAAATAAGTCAATAAT	G	8538.7	GTCAACAATAAATAAGTCAATAAT	A	8616.6
W1	IPLEX	rs1805015		CGCAGCTCAGCAAC[C/T]CCCTGACGCTGAC	IL4R	16	27374180	1	ACGTTGGATGCTGCTGCTGCTGCTGAG	ACGTTGGATGCTCTGGCAGCAGGACTG	114	F	CAACCTGCTTCCAGCAGCTTCAAGC	8438.5	CAACCTGCTTCCAGCAGCTTCAAGC	C	8685.7	CAACCTGCTTCCAGCAGCTTCAAGC	T	8765.6
W2	IPLEX	rs3390165	HBC	GTGACCTGACTCT[A/G]WGGAGAGCTCCGGC	HBB	11	5248233	1	ACGTTGGATGCTCAACAGCACTTCACTG	ACGTTGGATGTTCTCCAGCTCTGTC	102	F	GTGCACTGACTCTCA	4503.9	GTGCACTGACTCTCA	A	4775.1	GTGCACTGACTCTCA	G	4791.1
W2	IPLEX	rs1800629	TNF-308	GTTTTGAGGGGATG[A/G]GAGCGGTTGAGCC	TNF	6	31543031	1	ACGTTGGATGCTGATTTGTGTAGGACCC	ACGTTGGATGGGAGCAATAGTTTTGAG	86	R	GGCTGAACCCCTGCTC	4513.9	GGCTGAACCCCTGCTC	G	4761.1	GGCTGAACCCCTGCTC	A	4841
W2	IPLEX	rs2075820		CCAGAGCGGGACCC[A/G]AGGAGTGTGTTGCC	NOD1	7	30492237	-1	ACGTTGGATGCTGCTCTCAAGCACTAC	ACGTTGGATGAAGCGCAGGAGGCAACAA	90	F	aCCAGAGCGGGACCC	4861.2	aCCAGAGCGGGACCC	A	5132.4	aCCAGAGCGGGACCC	G	5148.4
W2	IPLEX	rs242665		TTTCTATGGACCA[C/A]GTTCTCCAGCGCGC	CTLA4	6	31839309	-1	ACGTTGGATGCTGCTGCTCATGCTGATC	ACGTTGGATGGTGGTGGTCTGCTGATC	107	R	AGCGCCGGTGGAGTAA	4971.2	AGCGCCGGTGGAGTAA	G	5218.4	AGCGCCGGTGGAGTAA	A	5298.3
W2	IPLEX	none assigned	amelogenin_XY_SNP1	CAAGTTNACNCT[A/G]CTCTCTCTCTCTC	AMELX	X	11313735	1	ACGTTGGATGCTGCTGCTGCTGCTGAG	ACGTTGGATGTGATCAACAGAGCCAGC	89	R	AGAGGAAGAGAGGAGG	5093.3	AGAGGAAGAGAGGAGG	G	5340.5	AGAGGAAGAGAGGAGG	A	5420.4
W2	IPLEX	rs352140		ATTCAAGGATGACT[A/G]GAGTGGAGGCTGAC	TLR9	3	52231737	-1	ACGTTGGATGATGAGTGGCACTTACAC	ACGTTGGATGGTGTGATGATGAGGCT	99	R	cATTACAGGAGCTACC	5115.3	cATTACAGGAGCTACC	T	5386.5	cATTACAGGAGCTACC	C	5402.5
W2	IPLEX	rs1800482	NOS2-954	AGCTTCAGAGTTC[A/G]ACCAAGTACGACCA	NOS2	17	26128509	-1	ACGTTGGATGCTCAACCCCAAGCTAAT	ACGTTGGATGGGCAACCACTTCAAGCTC	119	R	TTGTTGCTCATGCTGGT	5198.4	TTGTTGCTCATGCTGGT	C	5445.6	TTGTTGCTCATGCTGGT	C	5485.6
W2	IPLEX	rs6780995		AGGAGCAGCTGCTG[A/G]TCTCTGATGTTGCT	IL17RD	3	57138419	1	ACGTTGGATGCTTGGTCTGCTGCTGAG	ACGTTGGATGCTCCCTGGAGAAACATTTG	92	R	GGAGCAAACTACAGAGA	5261.5	GGAGCAAACTACAGAGA	G	5508.6	GGAGCAAACTACAGAGA	A	5588.6
W2	IPLEX	rs542998		CCACAGTGAAGTGG[C/T]TTACTGATGACCA	RTN3	11	63487386	1	ACGTTGGATGCTGCTGCACTTCACTTAC	ACGTTGGATGACTTTGGGTTCTGGAGT	99	R	GGTGTCTACAGTAAA	5274.4	GGTGTCTACAGTAAA	T	5545.7	GGTGTCTACAGTAAA	C	5561.7
W2	IPLEX	rs33950507	HBE	GATGAAGTGGTGTG[A/G]TJAGCCCTGGCCAG	HBB	11	5248173	-1	ACGTTGGATGCTCTTCAACTGCTGTG	ACGTTGGATCAAGGTGAAGTGGATGAG	98	F	ggGATGAAGTGGTGT	5361.5	ggGATGAAGTGGTGT	A	5632.7	ggGATGAAGTGGTGT	G	5648.7
W2	IPLEX	rs17047660	McC (McCoy)	TGTATTTCAACT[A/G]AATGACAGCTCAG	CR1	1	207782856	1	ACGTTGGATGCTCAACTGCTGGAGC	ACGTTGGATGATCAAGTGGTGTGGAGC	99	R	ccccCTGGAGCTGTGCTT	5466.6	ccccCTGGAGCTGTGCTT	G	5713.7	ccccCTGGAGCTGTGCTT	A	5793.6
W2	IPLEX	rs461645																		

Multiplex_code	Assay_type	rsnumber	alternate_name	SNP_sequence	gene_symbol	chromosome	position	strand	5'-PCRP	3'-PCRP	AMP_LEN	AMP_DIR	AMP_SEQ	AMP_MASS	EXT1_SEQ	EXT1_CALL	EXT1_MASS	EXT2_SEQ	EXT2_CALL	EXT2_MASS	EXT3_SEQ	EXT3_CALL	EXT3_MASS
N/A	IPLEX	rs55868763		CTGCCAGACTTCATA[C/G]DGAAGAAAGGATCTA	ATP2B4	1	203652140	1	ACGTTGGATGTTCCACTCAGTCCCCCATC	ACGTTGGATGTAGCCGTCCGAAAGTCTAGAT	101	F	CTCGTGCCAGACTTCATA	5723.7	CTCGTGCCAGACTTCATA	C	5970.9	CTCGTGCCAGACTTCATAG	G	6010.9			
N/A	IPLEX	rs1541255		TGCYAGACTTCATAS[A/G/T]GAAGAAAGGATCT	ATP2B4	1	203652141	1	ACGTTGGATGTTCCACTCAGTCCCCCATC	ACGTTGGATGTAGCCGTCCGAAAGTCTAGAT	101	R	CCGTCCGAAGTCTAGATCCTTTCTTC	7848.1	CCGTCCGAAGTCTAGATCCTTTCTTCC	G	8095.3	CCGTCCGAAGTCTAGATCCTTTCTTCA	T	8119.3	CCGTCCGAAGTCTAGATCCTTTCTTCT	A	8175.2
N/A	IPLEX	rs10900585		AGGAGTCTCACTTT[G/T]TTGCCAGGCAGGCT	ATP2B4	1	203654024	1	ACGTTGGATGTTTGTGAGAAGGAGTC	ACGTTGGATGCCAAGATTGCACCATTCAC	86	F	AGAAGGAGTCTCACTCTT	5498.6	AGAAGGAGTCTCACTCTTG	G	5785.8	AGAAGGAGTCTCACTCTTT	T	5825.7			
N/A	IPLEX	rs4951074		CTGTGACCTRAATC[A/G]ACTGCTTTATCTCTA	ATP2B4	1	203660781	1	ACGTTGGATGTTGCTCCCTATCTGTAGAC	ACGTTGGATGCAAGTTCATCATCTCTGGC	100	R	CTCCTAGAGATAAAGCAGT	5820.8	CTCCTAGAGATAAAGCAGTC	G	6068	CTCCTAGAGATAAAGCAGTT	A	6147.9			
N/A	IPLEX	rs3753036		AAGCATTTCTTTGC[A/G]TAGACACTTAGAGTG	ATP2B4	1	203677250	1	ACGTTGGATGTTCCCAACCCACTCTAAG	ACGTTGGATGTGACCTCATTGTCAATGGC	120	R	aaACCCACTCTAAGTGCTA	6045	aaACCCACTCTAAGTGCTAC	G	6292.1	aaACCCACTCTAAGTGCTAT	A	6372.1			

Supplementary Table 24: Sequenom Assay designs for the ATP2B4 SNPs used in this study (Supplementary Tables 5-7). Header descriptions can be found in Supplementary Table 22. The assays are split into 2 multiplexes (assay groups) defined by the field called 'Multiplex_Code'. The SNP, gene and coordinates are taken from GRCh37, Ensembl build 73 and dbSNP137. Further details may be found in the Spectrodesigner® assay design software manual (Sequenom® [see URLs]).

MODEL	Ancestral Homozygotes	Heterozygotes	Derived Homozygotes
Autosomal chromosomes and female X chromosomes			
GENOTYPE	AA	AB	BB
General	0	1	2
Additive or Additive	0	1	2
Dominant	0	1	1
Recessive	0	0	1
Heterozygote	0	1	0
Het vs Ancestral Hom	0	1	Omitted
Het vs Derived Hom	Omitted	1	0
Ancestral Hom vs Derived Hom	0	Omitted	1
Males X chromosomes			
GENOTYPE	A		B
General	0		2
Additive or Additive	0		2
Dominant	0		1
Recessive	0		1
Heterozygote	n.a.		n.a.
Het vs Ancestral Hom	n.a.		n.a.
Het vs Derived Hom	n.a.		n.a.
Ancestral Hom vs Derived Hom	0		1

Supplementary Table 25: Coding of Alleles for logistic regression analysis with respect to the derived allele. In the general and additive models ancestral-allele homozygotes were coded as 0 for all chromosomes (autosomes and sex chromosomes), heterozygotes were coded as 1 and derived-allele homozygotes were coded as 2 (including the male derived-allele homozygotes so that they are treated equivalent to the female X chromosome derived-allele homozygotes in the analysis). For all other models the genotypes were coded as 0 or 1 depending on the model grouping requirements having 1 with respect to the model and derived allele.

n.a., not applicable to males because heterozygotes are not present.

Supplementary Note:

MalariaGEN Sample Handling Procedures

Sample Archiving:

Sample Collection:

Blood was collected from individuals typically by venupuncture into a non-heparin anti-coagulant (typically EDTA); volumes varied between <1ml to 10ml depending on clinical circumstances and ethical permissions.

DNA extraction:

The blood was processed locally to extract DNA using the local method of choice; either Nucleon™ BACC Genomic DNA Extraction Kits (Gen-Probe Life Sciences Ltd, Tepnel Research Products & Services, Manchester, UK [see URLs]), or Qiagen DNeasy Blood kits (Qiagen, Crawley, UK [see URLs]). Extractions were carried out according to manufacturers' instructions although some local changes may have been made to the protocols to suit local conditions.

Sample Processing:

DNA was shipped frozen to Oxford. After arrival, the sample manifest was confirmed and all samples were relabeled and recoded with new sample_codes according to a standard format bearing no relationship to the original coding. Sample volumes were recorded and the DNA concentrations were measured using the PicoGreen® reagent (Invitrogen, Paisley, UK [see URLs]). An aliquot from each sample was diluted to 20ng/ul where possible to provide a 'working' sample allowing the remaining stock sample to be stored with little disturbance; an aliquot from samples below 20ng/ul was taken and used 'as is'. All DNAs were stored at -80°C in screw-cap tubes with rubber 'O' ring seals (Greiner Bio-One, Stonehouse, UK; 0.5ml skirted tubes #693201-1, lids #366380-1 and 9x9 format boxes #TR81N [see URLs]).

Primer-extension Amplification (PEP):

PEP reaction:

Samples underwent a whole-genome amplification step using Primer-Extension Pre-Amplification as previously described¹²¹. gDNA was diluted to 1ng/ul in 96-well plates (Thermo-Fast® 96-skirted, Thermo Fisher Scientific, UK), leaving 2 to 3 empty wells for water controls.

A PCR reagent mixture of 45ul comprising;

- 2.2ul of 1:10 diluted N15 primers (Genetix Ltd, UK [see URLs]),
- 1.25ul 8mM pooled dNTP's (Sigma-Aldrich, UK [see URLs]),
- 2.5ul 50mM MgCl₂ (Bioline, UK [see URLs]),
- 5ul of 10X BioTaq buffer (Bioline, UK [see URLs]),
- 0.5ul 5U/ul Biotaq polymerase (Bioline [see URLs]),
- 33.55ul MilliQ water (Sigma-Aldrich, UK [see URLs]).

were added to each well of a 96-well skirted PCR plate (Thermo Fisher Scientific). Five microlitres of gDNA (1ng/ul) was added to the PEP PCR mixture and the plates were sealed with Flat-Cap Strips (Thermo fisher Scientific) before thermocycling using a MJ Tetrad (Bio-Rad, UK) with the following programme:

94°C for 3 min;
50 cycles of: 94 °C for 1min,
37 °C for 2 min
Ramp to 55°C at 0.1/sec
55 °C for 4 min

and a final extension of 72°C for 5 min,
maintain at 4°C

PEP DNA was stored neat at -20°C until used.

PEP testing:

Twelve samples were selected at random from the plate of PEP reactions prepared above. PCR reactions were prepared as described below for Sequenom genotyping except that the final reaction volume was 20ul; 1ul of neat PEP was used and a single primer pair designed from an existing iPLEX assay design was used:

forward primer: ACGTTGGATGTCTGTAGTGATGGAGGGATG

reverse primer: ACGTTGGATGGTGTCCCTCTCCCTTGTAAC

Samples were run on 2% Agarose gels to check band intensity and fidelity.

Genotyping:

Platform:

The genotyping methodology chosen was SEQUENOM® iPLEX® Gold which allowed up to 40 SNPs to be designed into a single reaction (multiplex) and for up to 384 samples to be processed on one chip (see URLs). All reagents specific for this process were purchased from SEQUENOM®. Other reagents used were purchased as described below.

SNP sets:

Genotyping was undertaken for all samples upon receipt in Oxford for a set of SNPs designed as part of the QC process or with relevance to malaria.

Our primary SNP set is shown in Supplementary Tables 5, 6 and 7. These were identified from literature searches in publications showing associations of SNPs with malaria infection/disease severity. To these were added assays designed to determine gender by comparing the Amelogenin gene between the X and Y chromosomes¹²². Other SNPs from research being undertaken in the laboratory at the time were added to complete the multiplex design process.

iPLEX design:

Polymorphism sequence information was downloaded from Ensembl (see URLs) and reformatted for the SEQUENOM® assay design process (see URLs). The SEQUENOM® RealSNP™ Assay Database (see URLs) tools ProxSNP and PreEXTEND were used to identify proximal SNPs in the region of the target SNPs and to mask and design first-round PCR primers (Amplicon Design). Multiplex design for the iPLEX methodology was then

undertaken using the MassARRAY[®] Assay Design v3.1 Software. Common settings for assay design included the addition of a universal 10 base 5' sequences and then at least 20 bases of sequence-specific bases. All first round reactions were designed for an average of amplicon of 100-bases pairs and ranging between 80 and 120 bases. Universal extension primers were designed with a mass range of 4500Da to 10,000Da (~15-mer to ~29-mer oligos).

For reasons of economy and processing time, we decided to focus on 2 multiplexes only. These multiplexes were then tested using a panel of CEPH and YRI HapMap DNAs. Poorly performing assays or poor concordance assays were removed from the multiplex.

Details of the final 2 multiplexes are provided in Supplementary Table 23 and additional markers typed for ATP2B4 are provided in Supplementary Table 24 as these were typed separately from the 2 primary multiplexes.

Sample preparation:

PEP DNA samples were diluted 1:10 using a phenol red solution (0.01mg/ml) to aid tracking into 384-well plates (yellow/red to purple colour change); 22.5ul of phenol red solution plated into each well of a 384-well plate and 2.5ul of neat PEP was added. An aliquot of diluted PEP was then immediately used for the first-round PCR reactions as described below. Unused diluted PEP was frozen at -20°C. NB: Diluted PEP kept at 4°C for more than 2 days or freeze-thawed more than twice was discarded as this was found too degraded for genotyping .

iPLEX primers:

All primers were purchased lyophilised from Metabion International AG (Martinsried, Germany [see URLs]).

First-round primers were hydrated at 100 uM and extension primers were hydrated at 300 uM. All primers were stored at -20°C.

First-Round reaction master-mix:

A master-mix comprising the following was prepared for each 384-well plate allowing some extra volume;

- 3.3 ul of each first-round primer (100mM),
- 214.5 ul MgCl₂ (50mM),
- 66 ul dNTPs (25mM pooled),
- 412.5 ul 10X HotStar Taq buffer (Qiagen),
- 132 ul HotStar Taq (5U/ul) (Qiagen) and
- milliQ water to make a final volume of 1980ul.

First-Round Reaction:

PCR master mix (4.5 ul per well) was plated into a 384-well PCR plate (Thermo Fisher Scientific) and 3 ul of 1:10 diluted PEP DNA were added per well. Plates were sealed with Microseal 'A' lids (Bio-Rad) and cycled on an MJ Tetrad with the following conditions:

- 94 °C for 15 min,
- 44 cycles of; 94 °C for 20 sec,
- 56 °C for 30 sec,
- 72 °C for 1 min,
- and 72°C for 3 min
- maintain at 4°C

A 1ul sample from each well of a single row was run on a 2% agarose gel to confirm the PCR had worked prior to further processing.

Shrimp-alkaline Phosphatase treatment:

Unincorporated dNTP's were destroyed by adding 2ul of iPLEX shrimp-alkaline phosphatase (SAP) mixture to 5ul of first-round PCR reaction mixture and incubating at 37 °C for 40 min followed by a denaturation step at 85 °C for 5 min and then cooling to 15°C for 15 min.

Primer-Extension Reaction:

Extension-primer final reaction concentrations were dependent on their molecular mass based on SEQUENOM[®] protocol guidelines;

< 5800Da 0.84 uM,
5800 to 7000Da 1.04 uM,
7000 to 10,000 Da 1.25 uM,
>10,000Da 1.5uM.

Primer extension was carried out in the sample plate by adding 2 ul per well of a mixture containing;

0.2ul iPLEX termination mixture,
0.041ul extension Taq,
0.2ul extension buffer,
Primers (300mM);
 0.025ul per primer up to 5800Da,
 0.0312 ul per primer 5800 to 7000Da,
 0.0375 ul per primer 7000 to 10,000 Da
 0.045 ul per primer >10,000 Da
and water to 2ul.

The final extension reaction volume was 9 ul (5ul first-round reaction, 2ul SAP and 2ul of extension mixture).

Extension cycling was undertaken on an MJ Tetrad using the following conditions:

94 °C for 30 sec,
40 cycles of;
 94°C for 5 sec,
 5 cycles of;
 52 °C for 5 sec,
 80 °C for 5 sec,
then 72°C for 3 min
and 15°C for 15 min.

Plates were processed by adding 6 mg ion-exchange resin per well and 16ul MilliQ water. Plates were sealed, rotated for 30min and then centrifuged to pellet the resin prior to 'spotting' samples onto SpectroCHIPS and running on the Mass-Spectrometer. Data were inspected and genotypes checked using the SEQUENOM[®] Typer 4.03 software. Data were downloaded and stored in a central database where any further curation was undertaken. All genotype data were maintained according to the sequence strand used for the assay design process.

Sequenom Assay details:

Supplementary Tables 22-24 contain information on the primers and assays designs.

Genetic Heterogeneity

To assess evidence for genetic heterogeneity across severe malaria subtypes CM and SMA both within and across populations, we make model comparisons in a Bayesian statistical framework. To facilitate computation, we use Approximate Bayes Factors (ABFs) in place of Bayes factors to estimate the posterior probabilities of each model of association as described in Band et al. ¹²³. The ABF differs from the Bayes Factor in that it depends on an approximation of the marginal likelihood function (up to a constant) by a multivariate normal density. The ABF for each model is calculated as the ratio of the approximate marginal likelihood of that model to that of the null model where the variant has no effect on any of the subtypes; note that the ABF for the null model is then, of course, equal to 1. Under the assumption that exactly one of the models is correct and all models are equally likely *a priori*, the unweighted posterior probability of a given model is calculated as the ABF for that model divided by the sum of the ABFs for all models under consideration. If any of the models are assumed *a priori* to be more likely, then we need to weigh the ABFs accordingly. For example, if, before seeing data, the null model is given 80% probability and the other nine models are assumed equally probable with each other, then the corresponding posterior probabilities are calculated by weighing the ABFs by 0.8 for the null model and $0.2 / 9 = 0.022$ for any other model. (See Supplementary figure 5)

Calculation of the marginal likelihood requires specification of a prior distribution for the SNP effects on each phenotype at each site as well as maximum likelihood (ML) point estimates of these effects with their asymptotic standard errors. Suppose in general that we have P phenotypes and S sites. We assume a multivariate prior distribution for the SNP effects with mean zero and a covariance matrix in block form

$$\Sigma = \sigma^2 \begin{bmatrix} A_{11} & A_{12} & \cdots & A_{1S} \\ A_{12} & A_{22} & \cdots & A_{2S} \\ \vdots & \vdots & \ddots & \vdots \\ A_{1S} & \cdots & \cdots & A_{SS} \end{bmatrix}$$

where

- σ is the standard deviation;
- for $s, t = 1, \dots, S, t \geq s$, A_{st} are matrices of the form

$$A_{ss} = \begin{bmatrix} 1 & \rho_{12}^{ss} & \cdots & \rho_{1P}^{ss} \\ \rho_{12}^{ss} & 1 & \cdots & \rho_{2P}^{ss} \\ \vdots & \vdots & \ddots & \vdots \\ \rho_{1P}^{ss} & \rho_{2P}^{ss} & \cdots & 1 \end{bmatrix} \text{ when } s=t \text{ and } A_{st} = \begin{bmatrix} \rho_{11}^{st} & \rho_{12}^{st} & \cdots & \rho_{1P}^{st} \\ \rho_{12}^{st} & \rho_{22}^{st} & \cdots & \rho_{2P}^{st} \\ \vdots & \vdots & \ddots & \vdots \\ \rho_{1P}^{st} & \rho_{2P}^{st} & \cdots & \rho_{PP}^{st} \end{bmatrix} \text{ when } s \neq t$$

where ρ_{pq}^{st} denotes the prior correlation between phenotype p at site s and phenotype q at site t . Thus A_{ss} represents the prior correlation between effects on phenotypes within a site (phenotypic

heterogeneity) and; A_{st} is the prior correlation between phenotypes across sites (population heterogeneity).

By selecting different prior correlation values within and across sites, we can formally compare different models of effect heterogeneity. In our analyses, we use $\rho_{pq}^{st} = 1, 0.1$, or 0.96 to model fixed, independent and correlated effects respectively. For example, for 3 phenotypes and 2 sites:

- A model with effects fixed within site and correlated across sites

$$A_{11} = A_{22} = \begin{bmatrix} 1 & 1 & 1 \\ 1 & 1 & 1 \\ 1 & 1 & 1 \end{bmatrix} \text{ and } A_{12} = \begin{bmatrix} 0.96 & 0.96 & 0.96 \\ 0.96 & 0.96 & 0.96 \\ 0.96 & 0.96 & 0.96 \end{bmatrix}.$$

- A model with effects correlated within site and independent across sites

$$A_{11} = A_{22} = \begin{bmatrix} 1 & 0.96 & 0.96 \\ 0.96 & 1 & 0.96 \\ 0.96 & 0.96 & 1 \end{bmatrix} \text{ and } A_{12} = \begin{bmatrix} 0.1 & 0.1 & 0.1 \\ 0.1 & 0.1 & 0.1 \\ 0.1 & 0.1 & 0.1 \end{bmatrix}.$$

Let $\hat{\beta}_s = (\hat{\beta}_{s1}, \hat{\beta}_{s2}, \dots, \hat{\beta}_{sP})^t$ be a $P \times 1$ vector of maximum likelihood (ML) estimates, and \mathbf{V}_{β_s} the corresponding $P \times P$ variance-covariance matrix, for the estimated SNP effects on each phenotype at site s , $s = 1, \dots, S$ from a multinomial regression model. We approximate the multinomial likelihood function for site s by the multivariate normal density with mean $\hat{\beta}_s$ and variance-covariance \mathbf{V}_{β_s} . The approximate marginal likelihood is then given (up to a multiplicative constant) by the multivariate normal density evaluated at the ML estimate,

$$f(\hat{\beta}; \mathbf{0}, \mathbf{\Sigma} + \mathbf{V}_{\beta})$$

where

- $\hat{\beta} = (\hat{\beta}_1, \hat{\beta}_2, \dots, \hat{\beta}_S)^t$ is an $(S \times P) \times 1$ vector comprising the estimated effects at each phenotype at each site:
- $\mathbf{0}$ is the null vector.
- \mathbf{V}_{β} is an $(S \times P) \times (S \times P)$ matrix with diagonal blocks comprising the variance covariance matrix for the estimated effects at each site

$$\mathbf{V}_{\beta} = \begin{bmatrix} \mathbf{V}_{\beta_1} & 0 & \dots & 0 \\ 0 & \mathbf{V}_{\beta_2} & \dots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \dots & \mathbf{V}_{\beta_S} \end{bmatrix}$$

The models examined here are similar to those employed by Bellenguez et al.¹²⁴ to look at heterogeneity of effects *within* a single site and by Band et al.¹²³ to look at heterogeneity of effects *across* a site. Here we are extending the method to allow for examination of effects both *within and across* sites.

Contributors to MalariaGEN Consortial Project 1

Listed below are all contributors to the MalariaGEN Consortial Project 1 (Genetic determinants of resistance to malaria). These are grouped by partner site and contributors are listed alphabetically within each site.

Each partner has also provided a more detailed description of their individual study sites. These can be found on the MalariaGEN website (see URLs). Individual links for each partner site are also included.

RESOURCE CENTRE (see URLs)

Jacob Almagro Garcia¹, Sarah Auburn¹, Gavin Band¹, David Barnwell¹, Susan Bull^{1,4}, Susana Campino², Taane G. Clark⁵, Geraldine M. Clarke^{1,3}, Olivia Cook², Victoria Cornelius¹, Rachel Craik¹, Panos Deloukas², Jantina deVries^{1,4}, Andrea Diss¹, Eleanor Drury², Abier Elzein¹, Julie Evans¹, Kathryn Fitzpatrick¹, Angie Green¹, Lee Hart¹, Eliza Hilton¹, Christina Hubbard¹, Catherine Hughes¹, Robert Hutton¹, Anna E. Jeffreys¹, Kimberly J. Johnson¹, Dushyanth Jyothi², Angeliki Kerasidou^{1,4}, Katja Kivinen², Dominic P. Kwiatkowski^{1,2,3}, Si Quang Le¹, Bronwyn MacInnis², Cinzia Malangone², Magnus Manske², Gareth Maslen², Daniel Mead², Marilyn McCreight¹, Alieu Mendy¹, Alistair Miles¹, Sile Molloy¹, Catherine Moyes¹, John O'Brien¹, Michael Parker⁴, Richard Pearson¹, Matti Pirinen¹, Claire Potter¹, Ioannis Ragoussis², Kirk A. Rockett^{1,2,3}, Jane Rogers⁴, Kate Rowlands¹, Valentín Ruano-Rubio¹, Miguel SanJoaquin¹, Nuno Sepúlveda⁵, Shivang Shah¹, Kerrin S. Small¹, Elilan Somaskantharajah², Chris C.A. Spencer^{1,3}, Jim Stalker², Marryat Stevens¹, Yik Ying Teo¹, Aaron Vanderwal¹, Renee Watson¹, Rebecca Wrigley¹

¹Wellcome Trust Centre for Human Genetics, University of Oxford, Roosevelt Drive, Oxford OX3 7BN, UK.

²The Wellcome Trust Sanger Institute, Hinxton, Cambridge CB10 1SA, UK.

³MRC Centre for Genomics and Global Health, University of Oxford, Oxford, UK

⁴The Ethox Centre, Department of Public Health and Primary Health Care/Nuffield Department of Population Health, University of Oxford, Badenoch Rosemary Rue Building, Old Road Campus, Headington, Oxford OX3 7LF, UK.

⁵London School of Hygiene & Tropical Medicine, Keppel Street, London WC1E 7HT, UK.

BANJUL GAMBIA (see URLs)

Ismaela Abubakar⁶, Mohammed Aiyegbo⁷, Abdou Bah⁷, Kalifa A. Bojang⁶, Landing Camara⁷, Abdoulie Camara⁶, Climent Casals-Pascual^{6,8}, Pa Lamin Ceesay⁷, Ndey Ceesay⁷, Ramou Cole-Ceesay⁹, David J. Conway^{6,10}, Simon Correa⁶, Bakary Danso⁶, Yaya Dibba^{6,7}, Augustine Ebonyi⁷, Pamela Esangbedo⁷, Janet Fullah⁷, Jula Jaiteh⁷, Mariatou Jallow⁷, Muminatou Jallow^{6,7}, Kebba Jammeh⁷, Momodou Jasseh⁶, Amie Jobarteh⁷, Haddy Kanyi⁶, Momodou Lamin Keita⁷, Aja Abie Khan⁹, Lamin Manneh⁶, Anthony Mendy⁶, Jalimory Njie⁷, Madi Njie⁶, Sophie Njie⁷, Malick Njie⁷, Haddy Njie⁷, Herbert Obu⁷, Rasaan Olaosebikan⁷, Emmanuel Onykwelu⁷, Margaret Pinder⁶, Oba Rasheed⁷, Kumba Sabally-Ceesay⁹, Abubacar Sadiq⁶, Momodou Saidy-Khan⁶, Horeja Saine⁷, Idrissa Sambou⁶, Giorgio Sirugo⁶, Fatoumatta Sisay-Joof⁶, Bintou Taal⁷, Stanley Usen⁶, Lawrence Yamoah⁶

⁶Medical Research Council Unit, Atlantic Boulevard, Serrekunda, The Gambia.

⁷Royal Victoria Teaching Hospital, Independence Drive, Banjul, The Gambia.

⁸Wellcome Trust Centre for Human Genetics, University of Oxford, Roosevelt Drive, Oxford OX3 7BN, UK.

⁹Department of State for Health and Social Welfare, The Quadrangle, Banjul, The Gambia.

¹⁰Department of Pathogen Molecular Biology, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK.

BAMAKO MALI (see URLs)

Amadou Abathina¹¹, Kariatou Bamba¹¹, Abdoulaye Barry¹¹, Awa Dembele¹¹, Elizabeth Diarra¹¹, Ogobara Doumbo¹¹, Salimata Konate¹¹, Amadou Niangaly¹¹, Belco Poudiougou¹¹, Abdourahmane H. Sall¹¹, Sibiry Sissoko¹¹, Mahamadou A. Thera¹¹, Ousmane Toure¹¹

¹¹Malaria Research and Training Centre, Faculty of Medicine University of Bamako Bamako Mali.

OUAGADOUGOU BURKINA FASO (see URLs)

Germana Bancone¹², Edith C. Bougouma¹³, Amadou T. Konate¹², Valentina D. Mangano¹², David Modiano¹², Issa N. Ouedraogo¹³, Jaques Simporé¹⁴, Sodiomon B. Sirima¹³

¹²University of Rome La Sapienza, Italy.

¹³Centre National de Recherche et de Formation sur le Paludisme (CNRFP), Ouagadougou, Burkina Faso.

¹⁴Centre Médicale St. Camille, Ouagadougou, Burkina Faso.

NAVRONGO GHANA (see URLs)

Lucas N. Amenga-Etego¹⁵, Patrick A. Ansah¹⁵, Nana Akosua Ansah¹⁵, Thomas Anyorigiya¹⁵, Victor Asoala¹⁵, Frank Atuguba¹⁵, Anita Ghansah¹⁶, Abraham V. O. Hodgson¹⁵, Kwadwo A. Koram¹⁶, Nathan Mensah¹⁵, Francis Nkrumah¹⁶, Abraham R. Oduro¹⁵, William O. Rogers¹⁷, Michael D. Wilson¹⁶

¹⁵Navrongo Health Research Centre, Navrongo, Ghana.

¹⁶Noguchi Memorial Institute for Medical Research, Accra, Ghana.

¹⁷Naval Medical Research Unit Three, Cairo, Egypt.

KUMASI GHANA (see URLs)

Tsiri Agbenyega^{18,19}, Alex Osei Akoto^{18,19}, Daniel Ansong^{18,19}, Sampson Antwi¹⁹, Emmanuel Asafo-Agyei¹⁹, Anthony Enimil¹⁹, Jennifer Evans^{20,21}, Alex Owusu Ofori¹⁹, David Sambian¹⁹, Justice Sylverken¹⁹

¹⁸Kwame Nkrumah University of Science and Technology, Ghana.

¹⁹Komfo Anokye Teaching Hospital, Ghana.

²⁰Department of Molecular Medicine, Bernhard Nocht Institute for Tropical Medicine, Postfach 30 41 2, D-20324 Hamburg, Germany.

²¹Kumasi Centre for Collaborative Research, Kumasi, Ghana.

IBADAN NIGERIA (see URLs)

Olukemi Amodu²², Folakemi Anjol Amodu²², Subulade Olaniyan²², Olayemi O. Omotade²², Olajumoke Oni²², Adebola E. Orimadegun²²

²²University of Ibadan, Nigeria.

BUEA CAMEROON (see URLs)

Eric Achidi²³, Judith Anchang-Kimbi²⁴, Tobias Apinjo²⁵, Richard Besingi²³, Eric Mbunwe²³, Regina Mugri²³, Andre Ndi²³, Vincent Titanji²⁵, Clarisse Yafi²⁵

²³Department of Medical Laboratory Sciences, University of Buea, Buea, South West Region, Cameroon.

²⁴Department of Zoology & Animal Physiology, University of Buea, Buea, South West Region, Cameroon.

²⁵Department of Biochemistry & Molecular Biology, University of Buea, Buea, South West Region, Cameroon.

KILIFI KENYA (see URLs)

Evasius Bauni²⁶, Dorcas Kamuya²⁶, Alexander Macharia²⁶, Kevin Marsh²⁶, Vicki Marsh²⁶, Sassy Molyneux²⁶, Carolyne M. Ndila²⁶, Charles Newton²⁶, Daniel H. Opi²⁶, Norbert Peshu²⁶, Sophie Uyoga²⁶, Thomas N. Williams^{26,27}

²⁶KEMRI-Wellcome Trust Research Programme, PO Box 230, Kilifi, Kenya.

²⁷Faculty of Medicine, Department of Medicine, Imperial College, Exhibition Road, London SW7 2AZ, UK.

MOSHI TANZANIA (see URLs)

Chris Drakeley^{28,29}, Sarah Joseph²⁹, Alphaxard Manjurano^{28,29}, Caroline Maxwell²⁹, Frank Mtei²⁸, George Mtove³⁰, Behzad Nadjm²⁹, Hugh Reyburn^{28,29}, Eleanor Riley²⁹, Hannah Wangai²⁸

²⁸Joint Malaria Programme, Kilimanjaro Christian Medical Centre, PO box 2228, Moshi, Tanzania.

²⁹Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, Keppel Street, London, UK.

³⁰National Institute for Medical Research, Amani Centre, Tanga.

BLANTYRE MALAWI (see URLs)

David Kachala³¹, Malcolm Molyneux³¹, Mike Moore³¹, Annie Munthali³¹, Labes Njiragoma³¹, Neema Ntunthama³¹, Vysaul Nyirongo³¹, Paul Pensulo^{31,32}, Ajib Phiri³¹, Terrie Taylor³²

³¹Malawi-Liverpool-Wellcome Trust Clinical Research Programme, College of Medicine, University of Malawi, PO Box 30096, Blantyre, Malawi.

³²Blantyre Malaria Project, College of Medicine, University of Malawi.

HO CHI MINH CITY VIET NAM (see URLs)

Tran Thi Hong Chau³³, Ly Van Chuong³³, Nicholas Day^{34,35}, Sarah J. Dunstan^{34,36,37}, Jeremy Farrar^{34,36}, Tran Tinh Hien^{33,36}, Nguyen T. Hieu³⁸, Nguyen Thi Hoang Mai³³, Sean E. O'Riordan³⁶, Nguyen Hoan Phu^{33,36}, Nguyen Thi Ngoc Quyen³⁶, Cameron P. Simmons^{34,36}, Dinh Xuan Sinh³³, Cao Quang Thai^{33,36}

³³Hospital for Tropical Diseases, 764 Vo Van Kiet, District 5, Ho Chi Minh City, Viet Nam.

³⁴Centre for Tropical Medicine, Nuffield Department of Clinical Medicine, Oxford University, OX3 7LJ, UK.

³⁵Mahidol-Oxford Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok 10400, Thailand.

³⁶Oxford University Clinical Research Unit, 764 Vo Van Kiet, District 5, Ho Chi Minh City, Viet Nam.

³⁷Nossal Institute of Global Health, University of Melbourne, Australia.

³⁸Hung Vuong Hospital, District 5, Ho Chi Minh City, Viet Nam.

MADANG PAPUA NEW GUINEA (see URLs)

Steve Allen³⁹, Angela Allen^{39,40}, Timothy M. E. Davis⁴¹, Harin Karunajeewa⁴², Moses Laman⁴², Laurens Manning^{41,42}, Pascal Michon^{42,43}, Ivo Mueller^{42,44,45}, Peter Siba⁴²

³⁹Swansea University, Swansea, Wales, UK.

⁴⁰Weatherall Institute of Molecular Medicine, Oxford University, Oxford, UK.

⁴¹University of Western Australia, Perth, Australia.

⁴²Papua New Guinea Institute of Medical Research, PO BOX 60, Garoka, EHP441, Papua New Guinea.

⁴³Faculty of Health Sciences, Divine Word University, Madang, Papua New Guinea.

⁴⁴Walter and Eliza Hall Institute of Medical Research, Australia.

⁴⁵Barcelona Centre for International Health Research (CRESIB), Barcelona, Spain.

MalariaGEN Programme Management Committee/Governance Committee (see URLs)

Eric Achidi⁴⁶, Tsiri Agbenyega^{47,48}, Ogobara Doumbo⁴⁹, Jeremy Farrar^{50,51}, Michael Gottlieb⁵², Dominic P. Kwiatkowski^{53,54,55}, Kevin Marsh⁵⁶, Terrie Taylor⁵⁷

⁴⁶Department of Medical Laboratory Sciences, University of Buea, Buea, South West Region, Cameroon.

⁴⁷Komfo Anokye Teaching Hospital, Ghana.

⁴⁸Kwame Nkrumah University of Science and Technology, Ghana.

⁴⁹Malaria Research and Training Centre, Faculty of Medicine University of Bamako Bamako Mali.

⁵⁰Oxford University Clinical Research Unit, 764 Vo Van Kiet, District 5, Ho Chi Minh City, Viet Nam.

⁵¹Centre for Tropical Medicine, Nuffield Department of Clinical Medicine, Oxford University, OX3 7LJ, UK.

⁵²Deputy Director, Science Division, Foundation for the National Institutes of Health, 9650 Rockville Pike, Bethesda, MD 20814, USA.

⁵³Wellcome Trust Centre for Human Genetics, University of Oxford, Roosevelt Drive, Oxford OX3 7BN, UK.

⁵⁴The Wellcome Trust Sanger Institute, Hinxton, Cambridge CB10 1SA, UK.

⁵⁵MRC Centre for Genomics and Global Health, University of Oxford, Oxford, UK

⁵⁶Kemri-Wellcome Trust Research Programme, PO Box 230, Kilifi, Kenya. ⁵⁷Blantyre Malaria Project, College of Medicine, University of Malawi.

URLs.

MalariaGEN partner site details: <http://www.malariagen.net/projects/cp1>;
MalariaGEN Resource Centre: <http://www.malariagen.net/community/resource-centre>;
BANJUL GAMBIA: <http://www.malariagen.net/community/partner-studies/cp1-gambia>;
BAMAKO MALI : <http://www.malariagen.net/community/partner-studies/cp1-mali>;
OUAGADOUGOU BURKINA FASO: <http://www.malariagen.net/community/partner-studies/cp1-burkinafaso>;
NAVRONGO GHANA: <http://www.malariagen.net/community/partner-studies/cp1-ghana-noguchi>;
KUMASI GHANA: <http://www.malariagen.net/community/partner-studies/cp1-ghana-kumasi>;
IBADAN NIGERIA: <http://www.malariagen.net/community/partner-studies/cp1-nigeria>;
BUEA CAMEROON: <http://www.malariagen.net/community/partner-studies/cp1-cameroon>;
KILIFI KENYA: <http://www.malariagen.net/community/partner-studies/cp1-kenya>;
MOSHI TANZANIA: <http://www.malariagen.net/community/partner-studies/cp1-tanzania>;
BLANTYRE MALAWI: <http://www.malariagen.net/community/partner-studies/cp1-malawi>;
HO CHI MINH CITY VIET NAM: <http://www.malariagen.net/community/partner-studies/cp1-vietnam>;
MADANG PAPUA NEW GUINEA: <http://www.malariagen.net/community/partner-studies/cp1-png>
MalariaGEN Programme Management Committee/Governance Committee :
<http://www.malariagen.net/community/ethics-governance/gc>

Tepnel BACC DNA extraction kit: <http://www.gen-probe.com/pdfs/downloads/protocol%20BACC%20123%5B1%5D.pdf>;
Qiagen: <http://www.qiagen.com>;
Invitrogen: <http://www.probes.com>;
Greiner Bio-One: <http://www.greinerbioone.com>;
Genetix Ltd: <http://www.genetix.com>;
Bioline: <http://www.bioline.com>;
Sigma-Aldrich: <https://www.sigmaaldrich.com>;
Sequenom: <http://www.sequenom.com>;
Ensembl: <http://www.ensembl.org>;
RealSNP: <http://www.realsnp.com>;
Metabion: <http://www.metabion.com/home/index.php>.

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