

# Supporting Information (SI)

## **Structural polymorphism in the promoter of *pfmrp2* confers tolerance to mefloquine and chloroquine in *Plasmodium falciparum***

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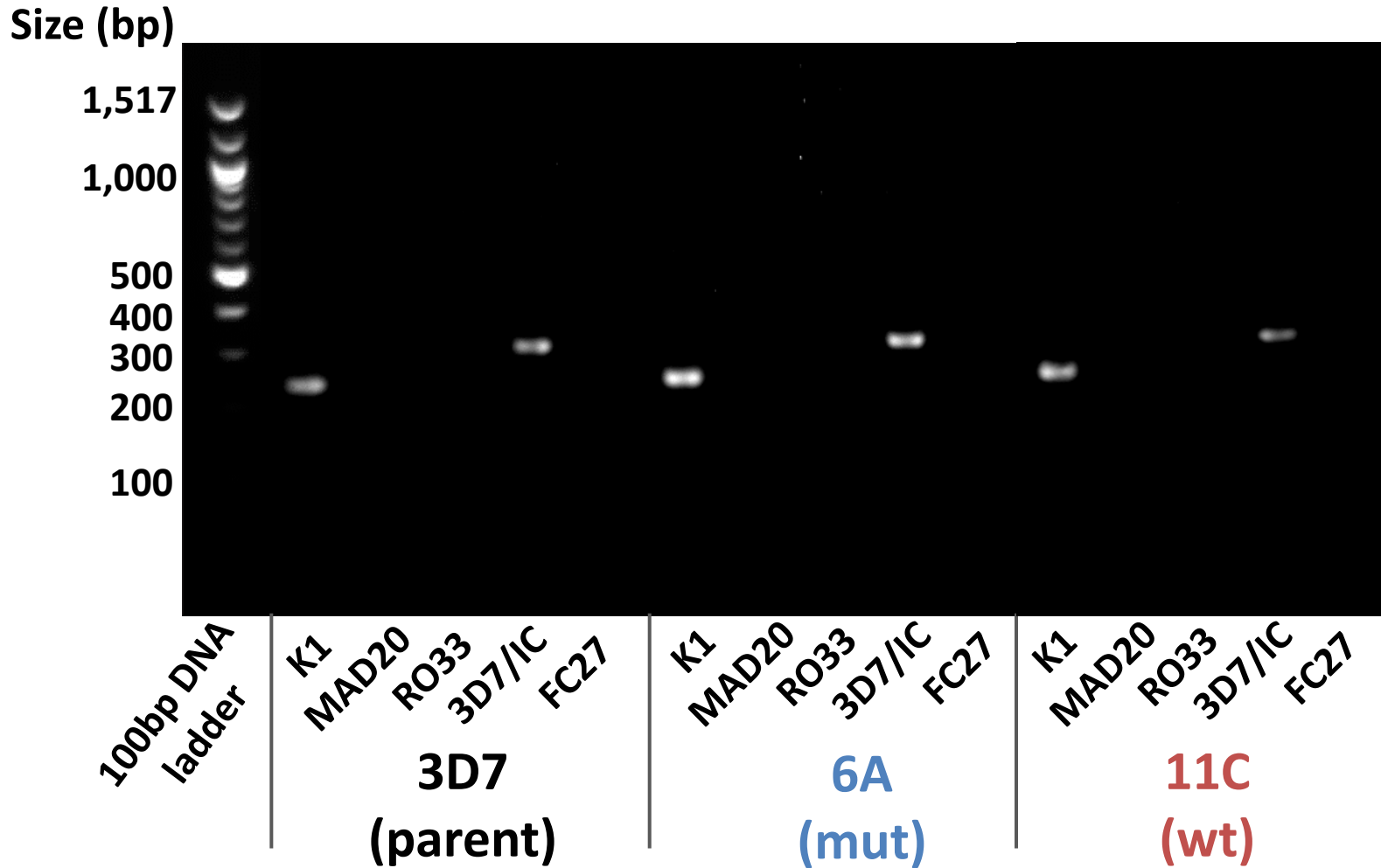
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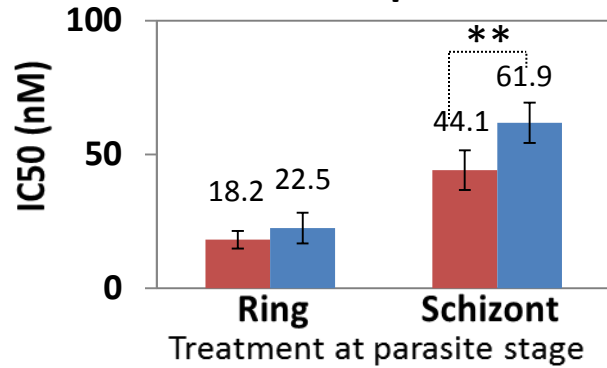
Singapore 637551, Singapore

# Figure S1

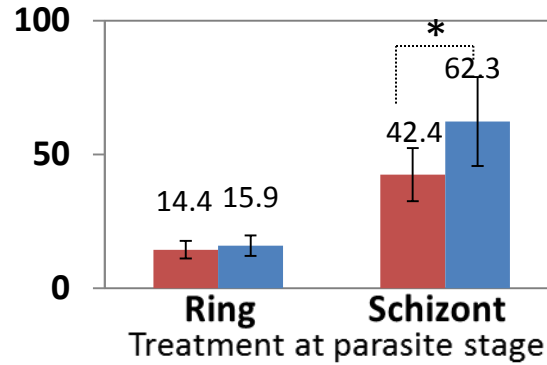


# Figure S2

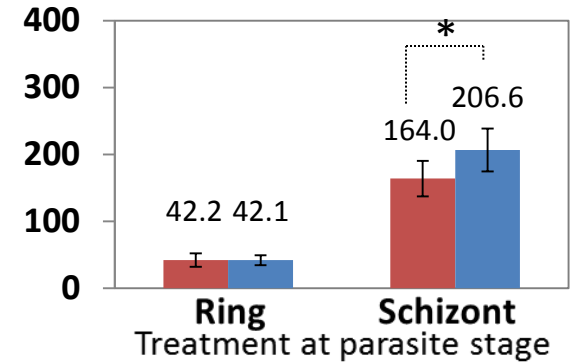
## Mefloquine



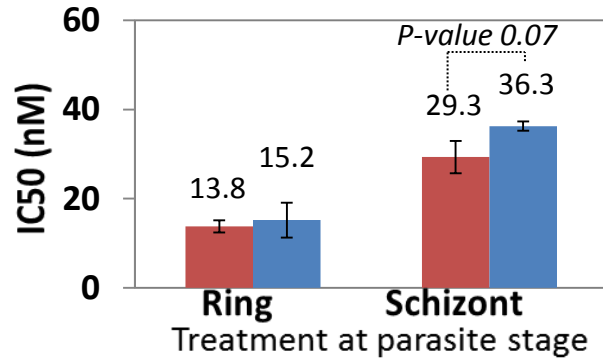
## Chloroquine



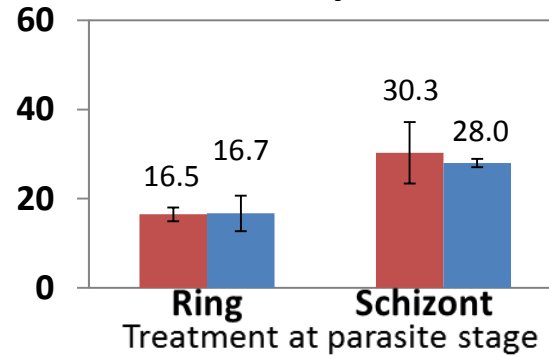
## Quinine



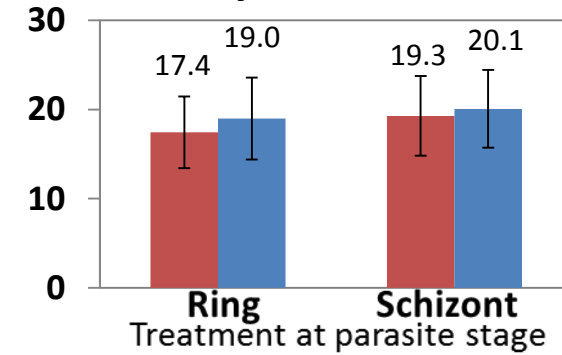
## Lumefantrine



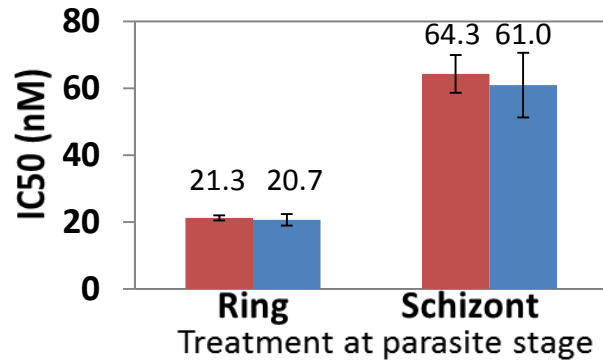
## Amodiaquine



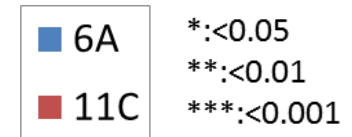
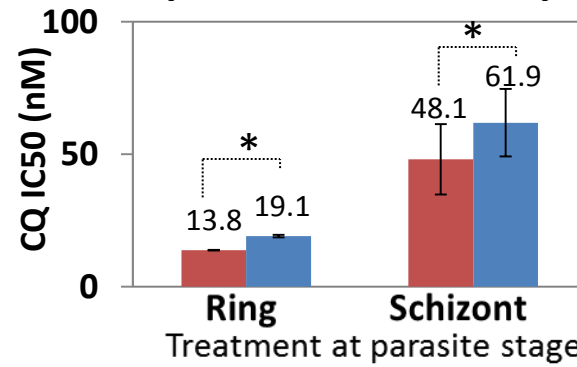
## Pyrimethamine



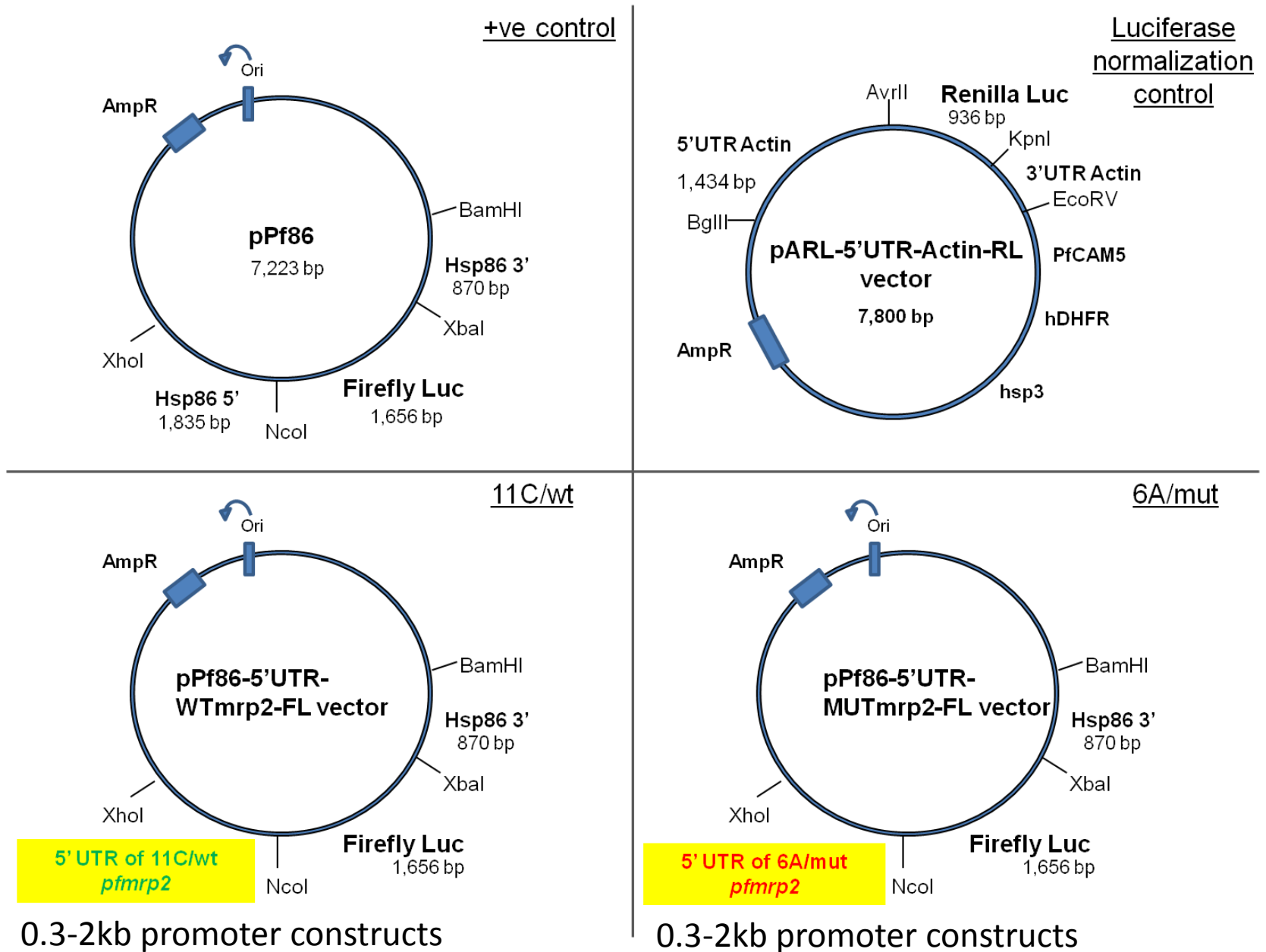
## Artemisinin



## Chloroquine + 0.8uM Verapamil

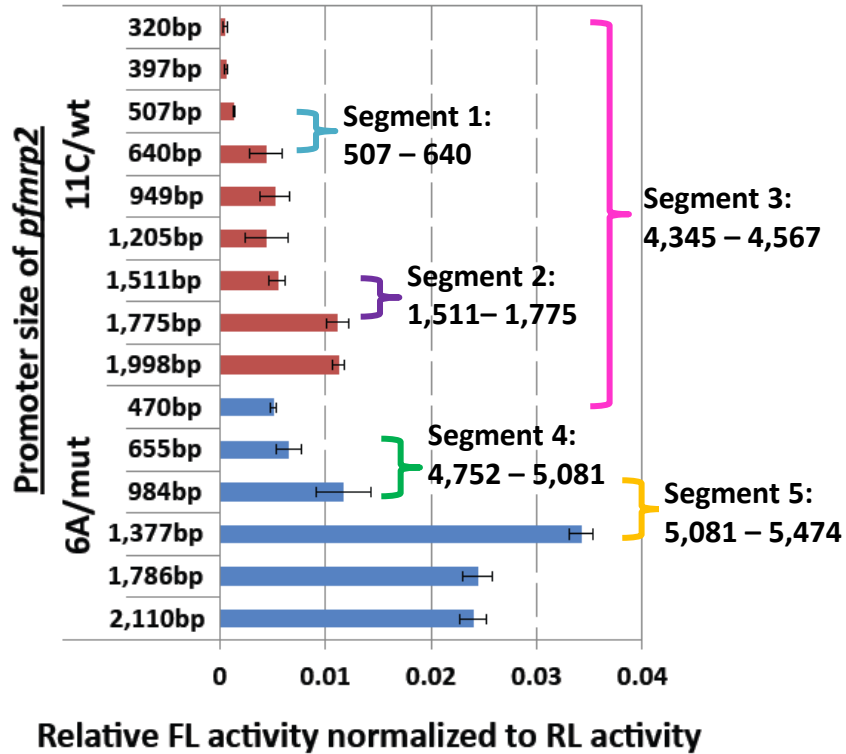


# Figure S3



# Figure S4

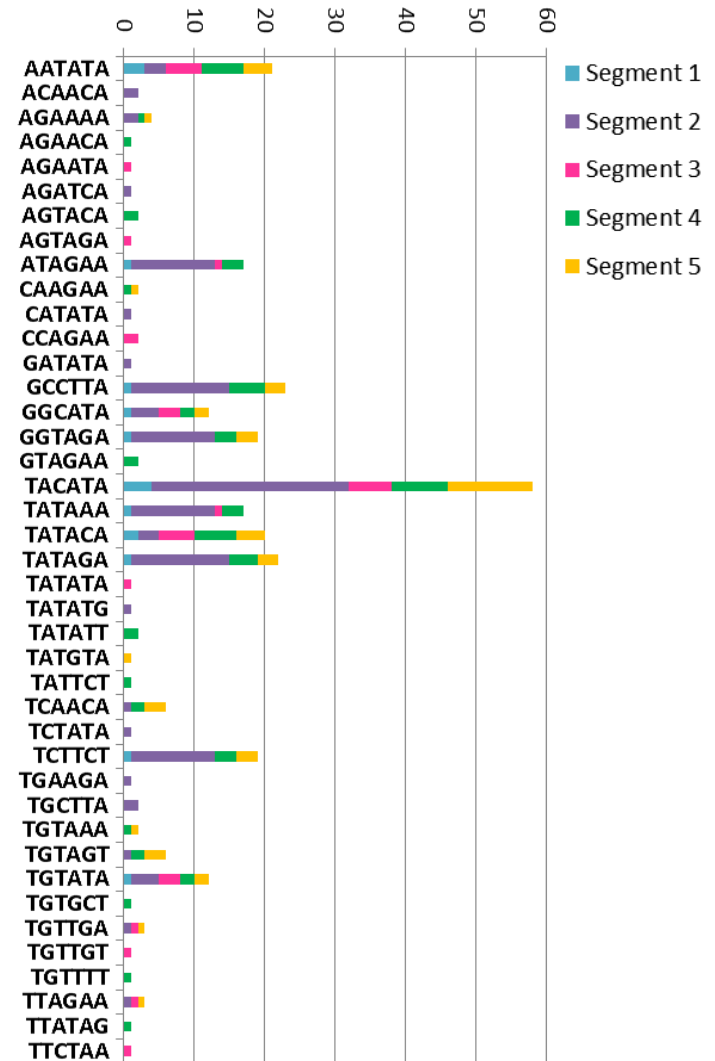
A.



B.

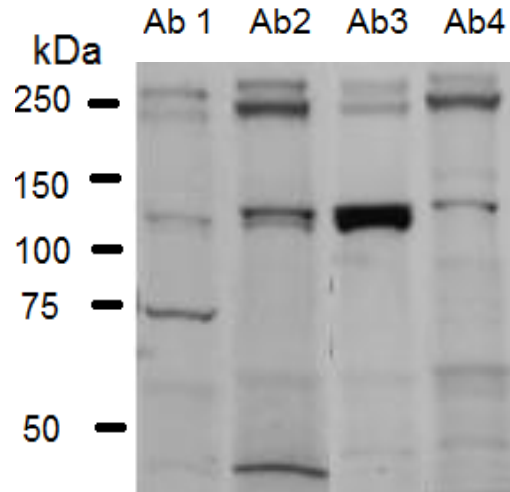
## Motifs present in upstream of PFL1410c

Frequency of occurrence of each motif

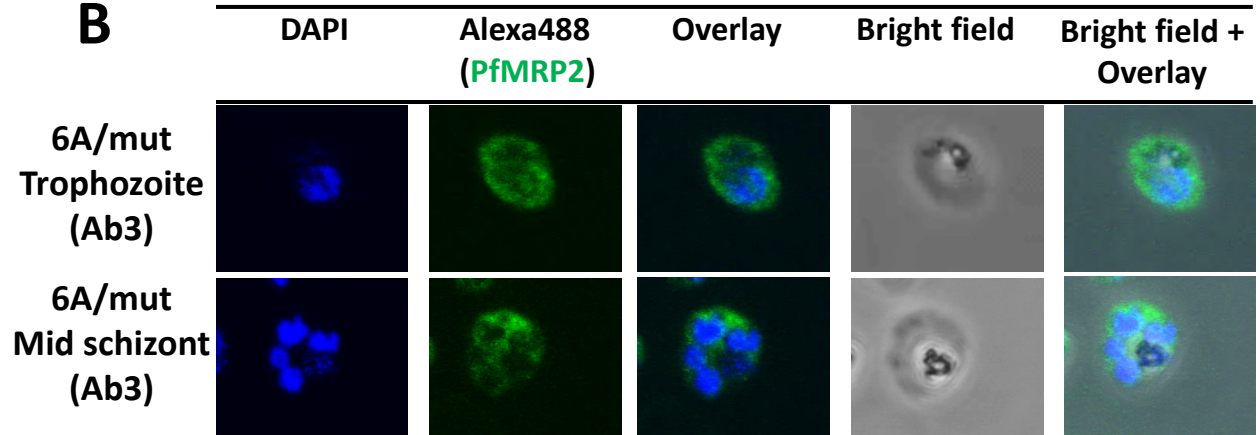


# Figure S5

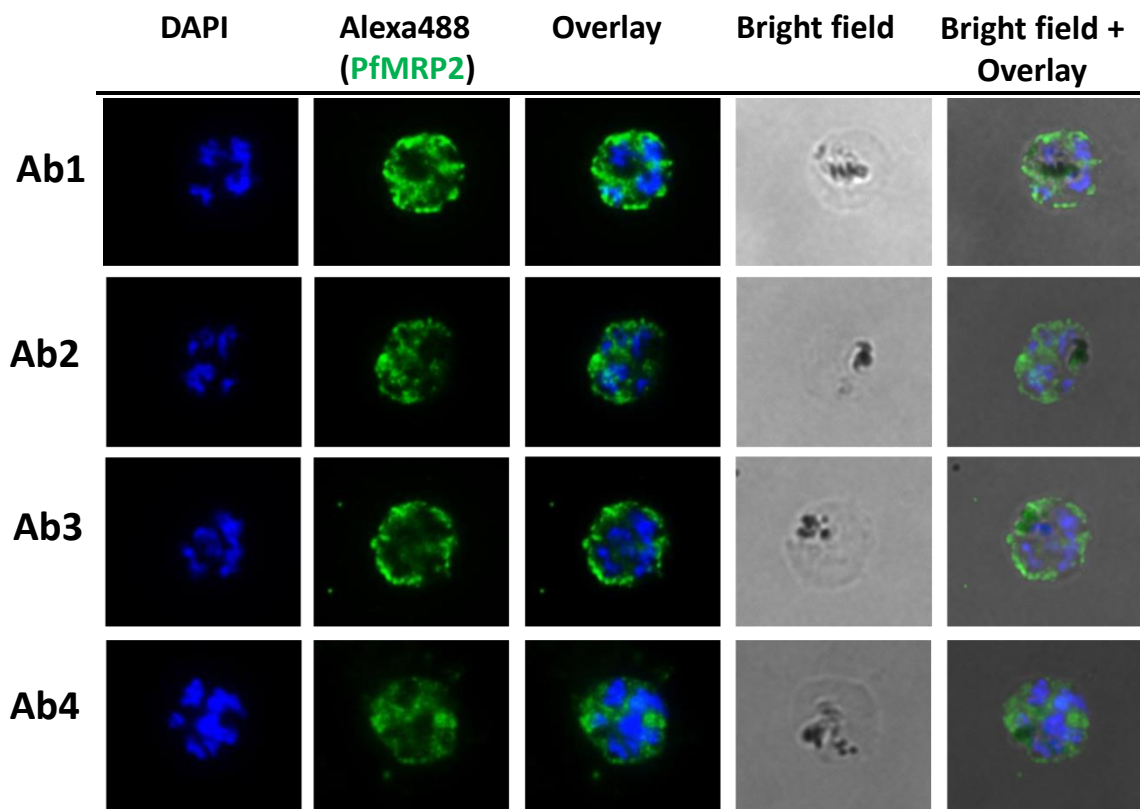
**A**



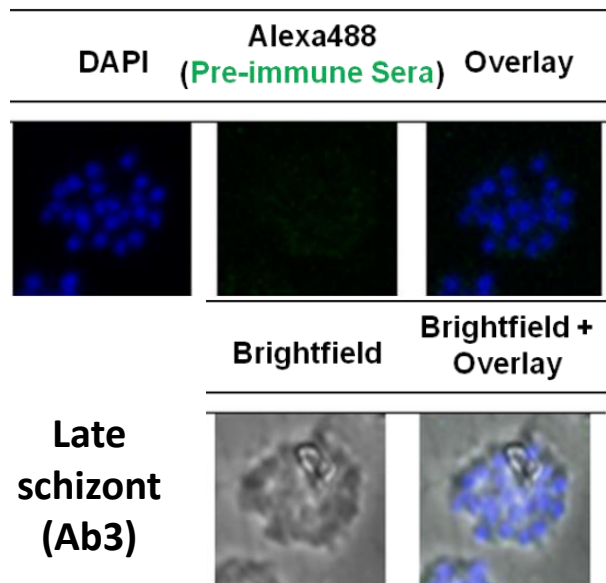
**B**



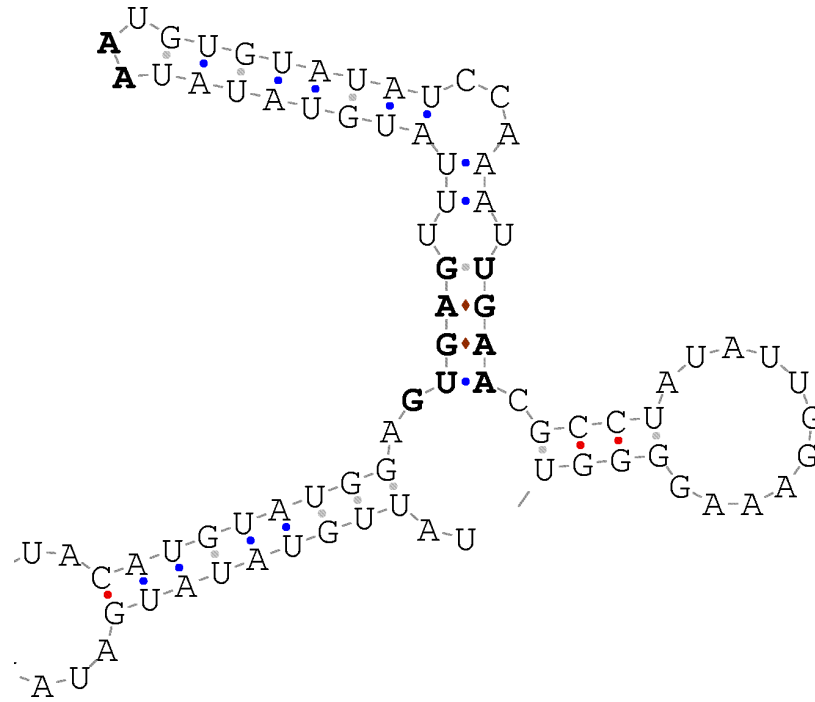
**C**



**D**



# Figure S6



# Table S1

List of the 18 genes significantly associated with CNPs which were detected between clones 6A and 11C (T-score >7.0) and their corresponding CGH log<sub>2</sub> ratios.

\*\* indicates the CNP is detected at the non-coding 5' region of the gene instead of the coding sequence.

Segment #	Chromosome #	Gene associated with CNP	Relative copy number of 6A to 11C	Mean Amplitude in Log <sub>2</sub> ratio (6A/11C)
1	2	PFB0075c:: Plasmodium exported protein (hyp9),	Loss	-4.15
	2	PFB0080c:: Plasmodium exported protein (PHISTb)		
	2	PFB0085c:: DNAJ protein, putative		
	2	PFB0090c:: RESA-like protein with PHIST and DnaJ domains		
	2	PFB0095c:: erythrocyte membrane protein 3		
	2	PFB0100c:: knob-associated histidine-rich protein		
2	4	PFD0630c:: erythrocyte membrane protein 1, PfEMP1	Gain	1.43
3	4	PFD1005c:: erythrocyte membrane protein 1, PfEMP1	Gain	1.03
	4	PFD1010w:: rifin		
	4	PFD1015c:: erythrocyte membrane protein 1, PfEMP1		
4	7	c7rRNA28s:: 28S rRNA	Gain	4.20
5	11	PF11_0480:: sporozoite asparagine-rich protein	Gain	5.51
	11	PF11_0481:: tubulin-tyrosine ligase, putative **		
6	12	PFL0005w:: erythrocyte membrane protein 1, PfEMP1	Loss	-4.28
	12	PFL0010c:: rifin		
	12	PFL0015c:: rifin		
	12	PFL0020w:: erythrocyte membrane protein 1, PfEMP1		
	12	PFL0025c:: rifin		
	12	PFL0030c:: erythrocyte membrane protein 1, PfEMP1		
	12	PFL0035c:: acyl-CoA synthetase, PfACS7		
	12	PFL0040c:: Serine/Threonine protein kinase, FIKK family		
	12	PFL0045c:: Plasmodium exported protein (PHISTc)		
	12	PFL0050c:: Plasmodium exported protein (PHISTb)		
	12	PFL0055c:: RESA-like protein with PHIST and DnaJ domains		
	12	PFL0060w:: Plasmodium exported protein		
12	PFL0065w:: conserved Plasmodium protein			
7	12	PFL1410c:: ABC transporter, (CT family) **	Loss	-3.23
8	13	PF13_0119:: Rab11a, GTPase **	Gain	3.57



# Table S2

## List of the 50 genes associated with the 67 SNPs identified between 6A and 11C.

GeneID	GeneID (PlasmoDB v8.2)	Annotation	Count (DOWNSTREAM)	Count (INTRON)	Count (NON_SYNONYMOUS_CODING)	Count (STOP_GAINED)	Count (SYNONYMOUS_CODING)	Count (UPSTREAM)
PF3D7_0313000	PFC0545c	conserved Plasmodium protein,	0	0	3	0	0	0
PF3D7_0406500	PFD0320c	conserved Plasmodium protein,	0	0	3	0	2	0
PF3D7_1427100	PF14_0250	lipase, putative	0	0	3	0	0	0
PF3D7_0113900	PFA0670c	Plasmodium exported protein (hyp8),	0	0	2	0	0	0
PF3D7_0315500	PFC0675c	mitochondrial ribosomal protein L29/L47 precursor, putative	0	0	1	0	0	0
PF3D7_0424700	PFD1175w	serine/threonine protein kinase, FIKK family	0	0	1	0	0	0
PF3D7_1325400	MAL13P1.137	conserved Plasmodium protein,	0	0	1	0	2	0
PF3D7_1348400	PF13_0254	conserved Plasmodium membrane protein,	0	0	1	0	0	0
PF3D7_1362900	MAL13P1.316	conserved Plasmodium protein,	0	0	1	0	0	0
PF3D7_1466100	PF14_0630	protein serine/threonine phosphatase	0	0	1	0	0	0
PF3D7_1229100	PFL1410c	ABC transporter, (CT family)	0	0	0	1	0	0
PF3D7_0418500	PFD0895c	Bet3 transport protein, putative	0	1	0	0	0	0
PF3D7_0601700	PFF0085w	Plasmodium exported protein (PHISTa), pseudogene	0	1	0	0	0	0
PF3D7_1329100	MAL13P1.148	myosin C	0	1	0	0	0	0
PF3D7_0103400	PFA0170c	zinc-carboxypeptidase, putative	0	0	0	0	1	0
PF3D7_0313600	PFC0570c	conserved Plasmodium protein	0	0	0	0	1	0
PF3D7_0610900	PFF0535c	transcription factor, putative	0	0	0	0	1	0
PF3D7_0618000	PFF0870w	conserved Plasmodium membrane protein,	0	0	0	0	1	0
PF3D7_0831300	MAL8P1.205	Plasmodium exported protein,	0	0	0	0	1	0
PF3D7_1038400	PF10_0374	Pf11-1 protein	0	0	0	0	1	0
PF3D7_0517400	PFE0870w	transcriptional regulator, putative	0	0	0	0	0	1
PF3D7_0632300	PFF1570w	rifin	0	0	0	0	0	1
PF3D7_0833200	MAL7P1.215	rifin	0	0	0	0	0	1
PF3D7_0913700	PFI0670w	conserved Plasmodium protein,	0	0	0	0	0	1
PF3D7_1033700	PF10_0328	bromodomain protein, putative	0	0	0	0	0	1
PF3D7_1224300	PFL1170w	polyadenylate-binding protein, putative	0	0	0	0	0	1
PF3D7_1326800	MAL13P1.365	syntaxin, Qa-SNARE family	0	0	0	0	0	1
PF3D7_1347700	PF13_0253	ethanolamine-phosphate cytidyltransferase, putative	0	0	0	0	0	1
PF3D7_1441000	PF14_0389	conserved Plasmodium protein,	0	0	0	0	0	1
PF3D7_1455000	PF14_0523	protein phosphatase, putative	0	0	0	0	0	1
PF3D7_1465500	PF14_0622	potassium channel protein	0	0	0	0	0	1
PF3D7_0102500	PFA0125c	erythrocyte binding antigen-181	0	0	0	0	0	2
PF3D7_0105400.1	PFA0265c	conserved Plasmodium protein,	0	0	0	0	0	2
PF3D7_0704400	PF07_0017	phosphoinositide-binding protein, putative	0	0	0	0	0	2
PF3D7_0932800	PFI1590c	conserved Plasmodium protein,	0	0	0	0	0	2
PF3D7_1115300	PF11_0161	cysteine proteinase falcipain 2b	0	0	0	0	0	2
PF3D7_0831800	MAL7P1.231	histidine-rich protein II	0	0	0	0	0	3
PF3D7_1228200	PFL1365w	conserved Plasmodium protein,	0	0	0	0	0	4
PF3D7_0209100	PFB0410c	phospholipase A2, putative	1	0	0	0	0	0
PF3D7_0403600	PFD0170c	conserved Plasmodium protein,	1	0	0	0	0	0
PF3D7_0913600	PFI0665w	conserved Plasmodium protein,	1	0	0	0	0	0
PF3D7_1326900	MAL13P1.370	conserved Plasmodium membrane protein,	1	0	0	0	0	0
PF3D7_1343200	PF13_0236	tRNA guanosine-2'-O-methyltransferase, putative	1	0	0	0	0	0
PF3D7_1441100	PF14_0390	conserved Plasmodium protein,	1	0	0	0	0	0
PF3D7_1455100	PF14_0524	protein phosphatase, putative	1	0	0	0	0	0
PF3D7_0105500	PFA0270c	conserved Plasmodium protein,	2	0	0	0	0	0
PF3D7_0704300	PF07_0016	conserved Plasmodium membrane protein,	2	0	0	0	0	0
PF3D7_0932900	PFI1595c	conserved Plasmodium protein,	2	0	0	0	0	0
PF3D7_1115400	PF11_0162	cysteine proteinase falcipain 3	2	0	0	0	0	0
PF3D7_0631200	PFF1515c	erythrocyte membrane protein 1 (PIEMP1), pseudogene	3	0	0	0	0	0

# Table S3

## List of primer sequences used in PCR for investigating polymorphisms in the 5' upstream of *pfmrp2* gene (PFL1410c).

Description (Fw.Rv)	Forward Primer	Reverse Primer
<b>Primers for investigating polymorphisms within the 5'UTR promoter of <i>pfmrp2</i> gene (PFL1410c)</b>		
ORF (13.13)	13_Fw: +504 ACAACATTTGAACCGCT	13_Rv: +1 ATGATGAGACGGAGAAGCG
ORF (14.14)	14_Fw: +447 ATTTGTTGCTGTGTATTGAG	14_Rv: +878 CTGTTGGTTGAATCTTTGCTTTC
5'UTR (1.9)	1_Fw: -20 ACTTTACTATATGGTGATAAGTT	9_Rv: -6212 TATTACACCTTTCTTTACATTTCCGG
5'UTR (1.10)	1_Fw: -20 ACTTTACTATATGGTGATAAGTT	10_Rv: -4284 TTATCAAACCGTATCTCTACTCG
5'UTR (1.12)	1_Fw: -20 ACTTTACTATATGGTGATAAGTT	12_Rv: -10321 AAAGAGAACCACTGAAGGC
5'UTR (2.9)	2_Fw: -295 CTGGGAACCTGGAGGTGCT	9_Rv: -6212 TATTACACCTTTCTTTACATTTCCGG
5'UTR (2.10)	2_Fw: -295 CTGGGAACCTGGAGGTGCT	10_Rv: -4284 TTATCAAACCGTATCTCTACTCG
5'UTR (2.12)	2_Fw: -295 CTGGGAACCTGGAGGTGCT	12_Rv: -10321 AAAGAGAACCACTGAAGGC
5'UTR (3.9)	3_Fw: -844 GTATAAACAGATGCTCAATATA	9_Rv: -6212 TATTACACCTTTCTTTACATTTCCGG
5'UTR (3.10)	3_Fw: -844 GTATAAACAGATGCTCAATATA	10_Rv: -4284 TTATCAAACCGTATCTCTACTCG
5'UTR (3.12)	3_Fw: -844 GTATAAACAGATGCTCAATATA	12_Rv: -10321 1AAAGAGAACCACTGAAGGC
5'UTR (4.9)	4_Fw: -1173 TAAATAAACACAGCTCATACAAATAA	9_Rv: -6212 TATTACACCTTTCTTTACATTTCCGG
5'UTR (4.10)	4_Fw: -1173 TAAATAAACACAGCTCATACAAATAA	10_Rv: -4284 TTATCAAACCGTATCTCTACTCG
5'UTR (4.12)	4_Fw: -1173 TAAATAAACACAGCTCATACAAATAA	12_Rv: -10321 AAAGAGAACCACTGAAGGC
<b>Primers for investigating transcriptional activity of various constructs within the 5' promoter of <i>pfmrp2</i> gene (PFL1410c)</b>		
11C/wt 320bp	ATCGCTCGAGAAGAAATACAGCACCTCCAG -320	ATCGCCATGGAAAAACGGAATCTTTCTAACTTT 0
11C/wt 397bp	ATCGCTCGAGTTTAATTAGTCTCCTCTTTATTTATTATA -397	ATCGCCATGGAAAAACGGAATCTTTCTAACTTT 0
11C/wt 507bp	ATCGCTCGAGTCTAAATATTAACATAGCAGTTTTGA -507	ATCGCCATGGAAAAACGGAATCTTTCTAACTTT 0
11C/wt 640bp	ATCGCTCGAGTTAACATCATAAATATTTATGAAATACG -640	ATCGCCATGGAAAAACGGAATCTTTCTAACTTT 0
11C/wt 949bp	ATCGCTCGAGGAAAAATATTTATTTTGTATTAGAAGG -949	ATCGCCATGGAAAAACGGAATCTTTCTAACTTT 0
11C/wt 1,205bp	ATCGCTCGAGATATGTATTTATTTGTATGAGCTGTG -1205	ATCGCCATGGAAAAACGGAATCTTTCTAACTTT 0
11C/wt 1,511bp	ATCGCTCGAGGTAGTAAATATATATTCTGTTTTGTGCT -1511	ATCGCCATGGAAAAACGGAATCTTTCTAACTTT 0
11C/wt 1,775bp	ATCGCTCGAGGTGAATGTGCCTTATAAACAAC -1775	ATCGCCATGGAAAAACGGAATCTTTCTAACTTT 0
11C/wt 1,998bp	ATCGCTCGAGAAATAGAACAATGGATAAAATCTCTTTG -1998	ATCGCCATGGAAAAACGGAATCTTTCTAACTTT 0
6Amut 470bp	ATCGCTCGAGCTCATATGCCAAGAATTTCTTA -4567	ATCGCCATGGAAAAACGGAATCTTTCTAACTTT 0
6A/mut 655bp	ATCGCTCGAGGGAAGGTATAAATATTTTCAAGAA -4752	ATCGCCATGGAAAAACGGAATCTTTCTAACTTT 0
6A/mut 984bp	ATCGCTCGAGCATTGGAAGTGCATATACTTT -5081	ATCGCCATGGAAAAACGGAATCTTTCTAACTTT 0
6A/mut 1,377bp	ATCGCTCGAGCATACATCCGATGCGC -5474	ATCGCCATGGAAAAACGGAATCTTTCTAACTTT 0
6A/mut 1,786bp	ATCGCTCGAGGCCAGATGAAAAGCTTCTG -5883	ATCGCCATGGAAAAACGGAATCTTTCTAACTTT 0
6A/mut 2,110bp	ATCGCTCGAGACACCTTTCTTTACATTTCCGG -6207	ATCGCCATGGAAAAACGGAATCTTTCTAACTTT 0