Table S1. Parameters used for 10-fold cross-validation

PPQ Susceptibility	Lambda	Family
PSA	0.6375	Poisson
IC50	0.5354	Gaussian
IC90	1.2246	Gaussian
AUC	3.0373	Poisson

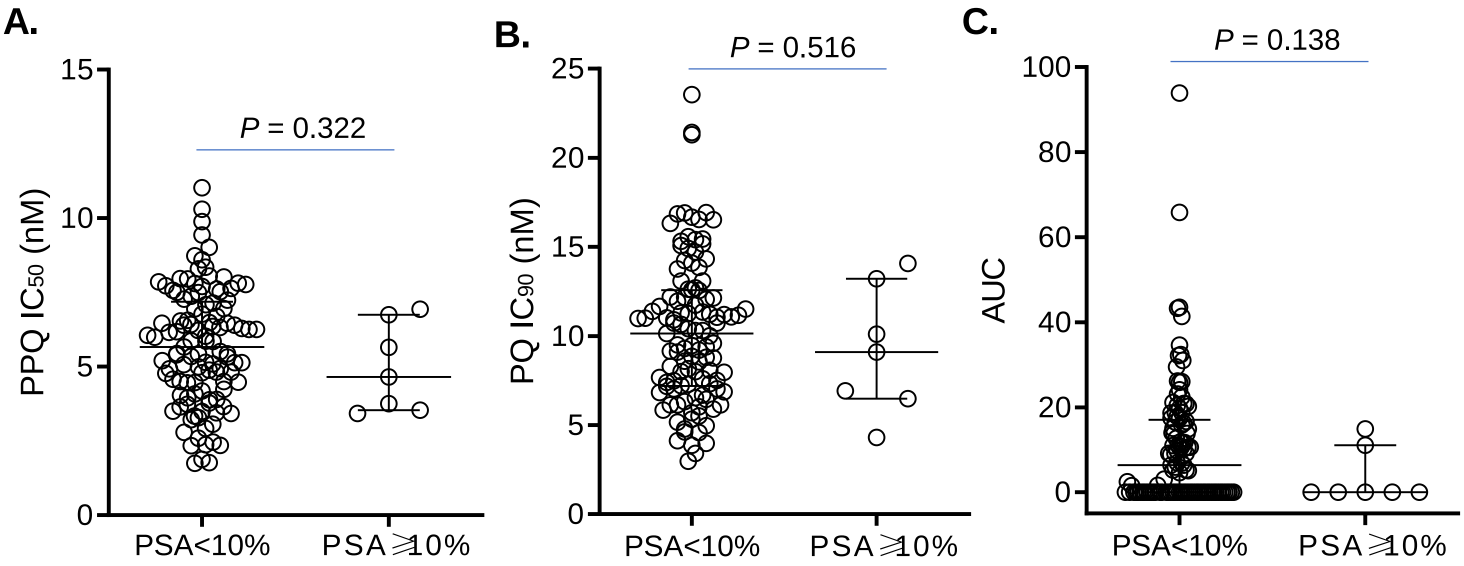

Fig. S1. Comparison of IC_{50}, IC_{90} and AUC values among parasite isolates with PSA values of <10% and ≥10%. Lines represent the median and interquartile range. *P* values were based on Mann-Whitney *U* test.

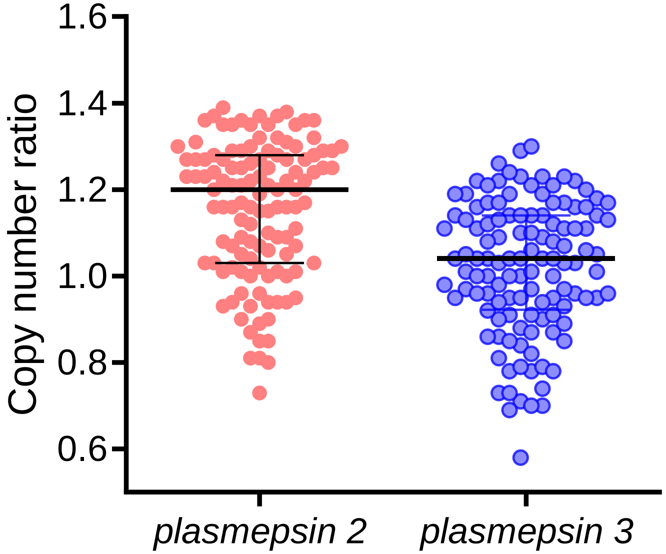

Fig. S2. Determination of *plasmepsin 2/3* amplification by real-time PCR. *Plasmepsin 2/3* copy number was calculated by the $2^{-\Delta C_t}$ method using *β-tubulin* as the internal reference gene. 3D7 was included as a control. Copy number ≥ 1.5 was defined as an amplification of the gene.

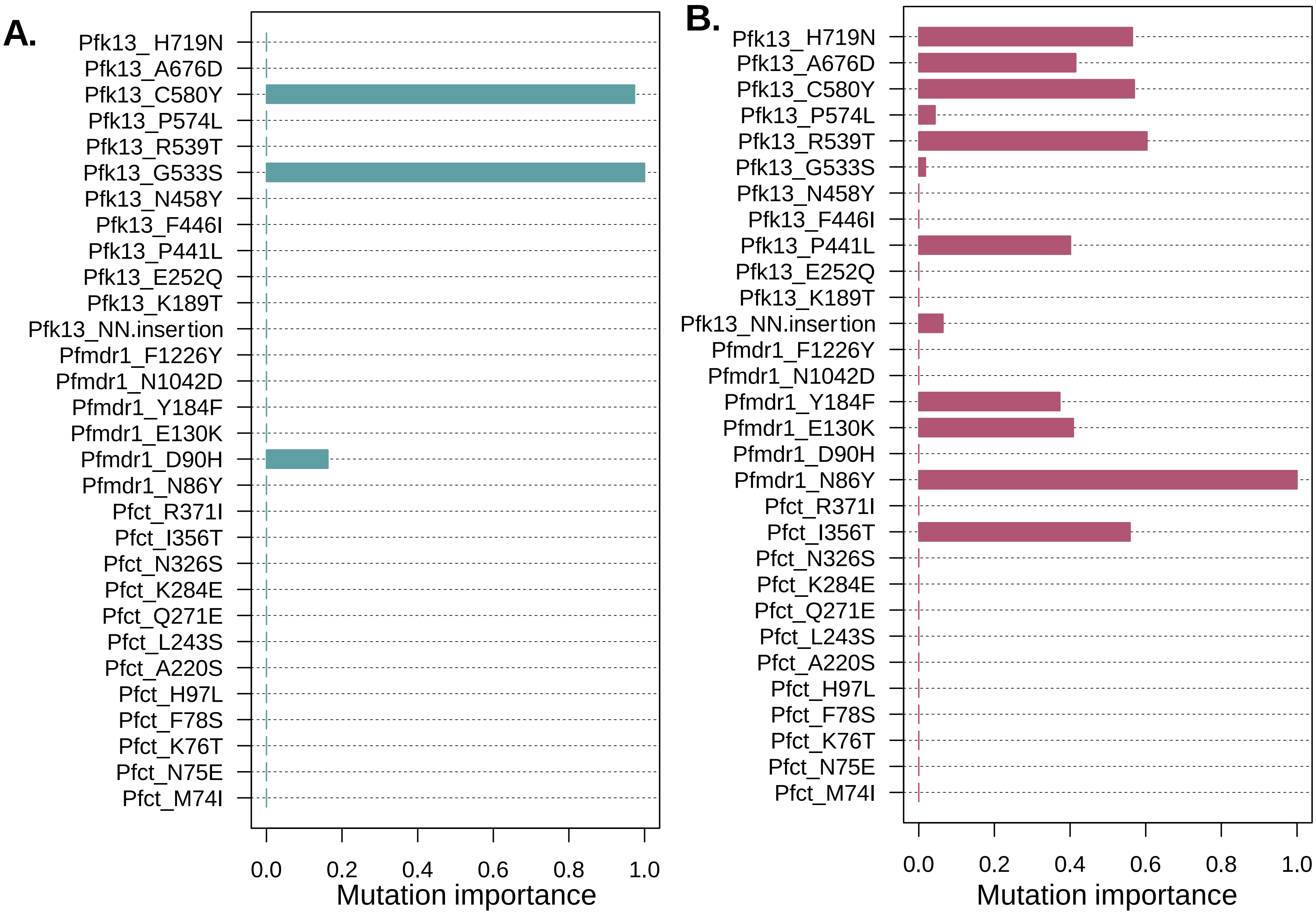

Fig. S3. The associations between mutation markers and the PPQ IC_{50} (**A**) and PSA (**B**) values. The absolute coefficient from Lasso regression is used to measure association intensity and normalized as the fraction of the highest absolute coefficient.

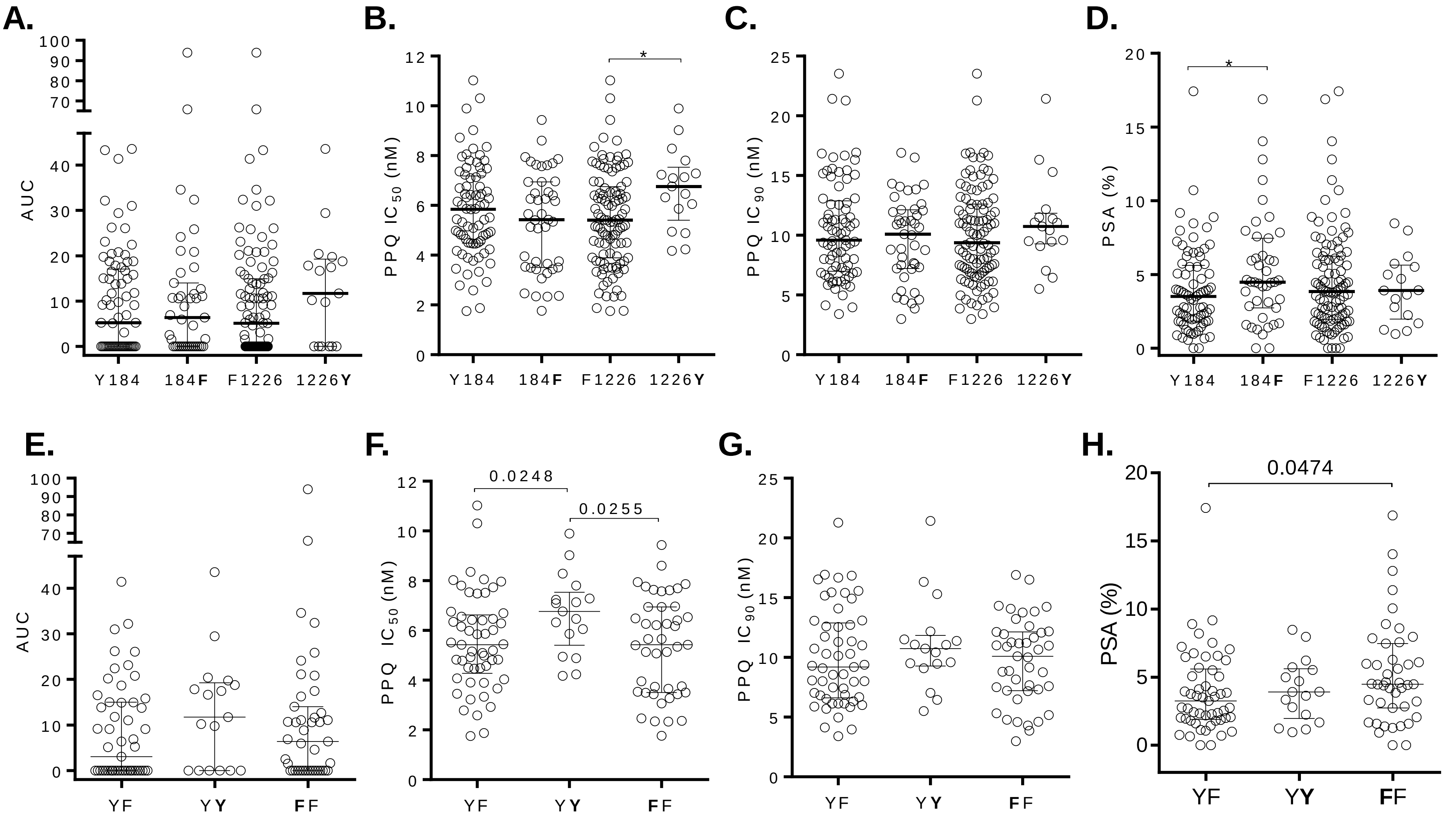

Fig. S4. Comparisons of in vitro piperaquine susceptibility (AUC, IC_{50}, IC_{90} and PSA) between parasites with wild-type and pfmdr1 mutations (highlighted in bold). Upper panels show comparisons at individual amino acids, while lower panels show comparison among different haplotypes at 184 and 1226 positions (Y184/F1226, Y184/1226**Y**, and 184**F/**1226F). Only mutations or haplotypes exceeding 5% frequency were included in the analysis. AUC, area under curve. Horizontal lines indicate median ± interquartile range. Significant *P* values are indicated or marked with * to indicate *P* < 0.05 (Mann-Whitney U test).

Table S2. Longitudinal prevalence of non-synonymous mutations and haplotypes of the *Pfmdr1* gene

	Amina acid position	Prevalence of isolates [n (%)] 2007 (n=17)	2008 (n=19)	2009 (n=14)	2010-2012 (n=7)	2013 (n=36)	2014-2016 (n=27)	Total (n=120)	*P* value*
SNP	N86**Y**	0	0	0	0	1 (2.8)	1 (3.7)	2 (1.7)	0.86
	D90**H**	0	0	0	0	0	1 (3.7)	1 (0.8)	0.6274
	E130**K**	0	0	0	0	2 (5.6)	0	2 (1.7)	0.4477
	Y184**F**	5 (29.4)	5 (26.3)	4 (28.6)	0	16 (44.4)	13 (48.1)	43 (35.8)	0.1442
	N1042**D**	0	0	3 (21.4)	0	0	0	3 (2.5)	0.0003
	F1226**Y**	0	0	0	0	5 (13.9)	12 (44.4)	17 (14.2)	<0.0001
Haplotype	WT	12 (70.6)	14 (73.7)	7 (50.0)	7 (100.0)	12 (33.3)	1 (3.7)	53 (44.2)	<0.0001
	YDEYNF	0	0	0	0	1 (2.8)	0	1 (0.8)	0.7985
	ND**K**YNF	0	0	0	0	2 (5.6)	0	2 (1.7)	0.4477
	NDE**F**NF	5 (29.4)	5 (26.3)	4 (28.6)	0	16 (44.4)	13 (48.1)	43 (35.8)	0.1442
	NDEY**D**F	0	0	3 (21.4)	0	0	0	3 (2.5)	0.0003
	NDEYN**Y**	0	0	0	0	5 (13.9)	12 (44.4)	17 (14.2)	<0.0001
	YHEYNF	0	0	0	0	0	1 (3.7)	1 (0.8)	0.6274

* Chi-square test.