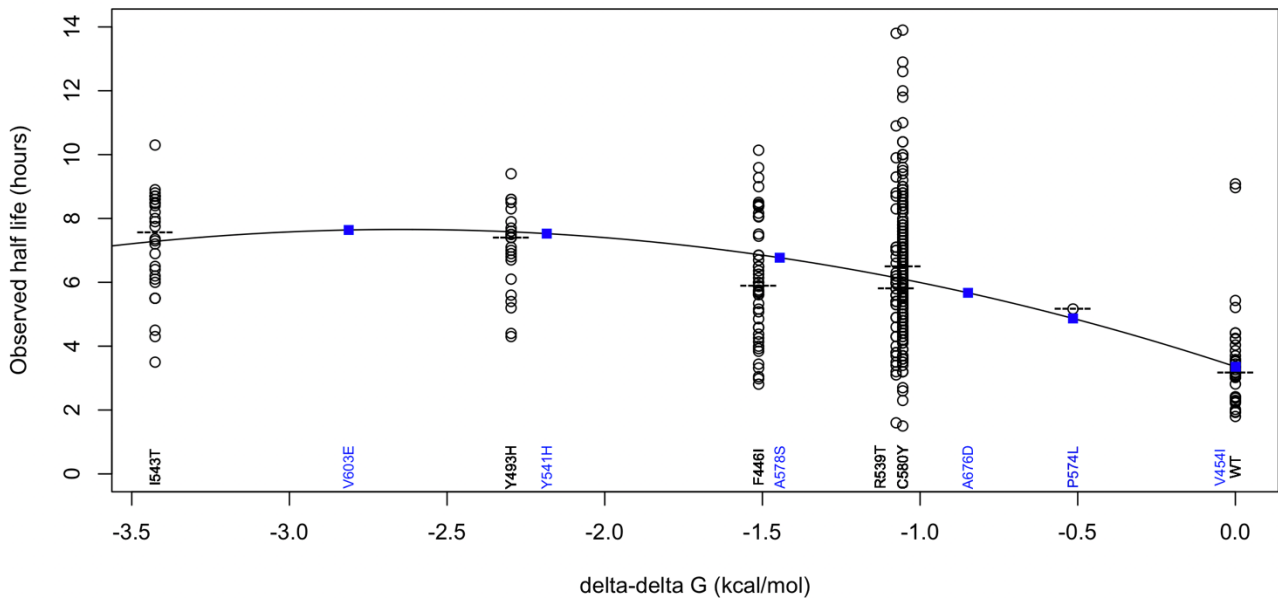


S2 Figure

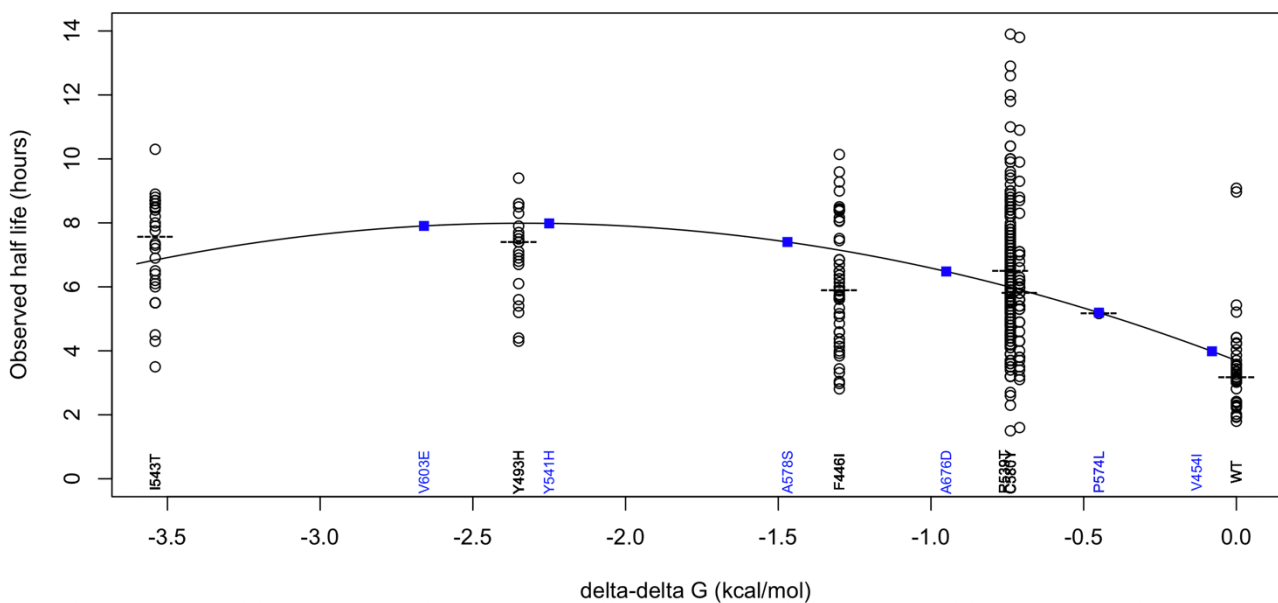
Quadratic relationship between parasitaemia half-life and inferred Delta-delta Gibbs energy (DDG, $\Delta\Delta G$). Predictions (solid squares) for V603E, Y541H, A578S, A676D, P574L, and V454I are presented (blue); WT = wild type; horizontal dashed lines are the medians per mutation

(a) 4YY8b (DUET)



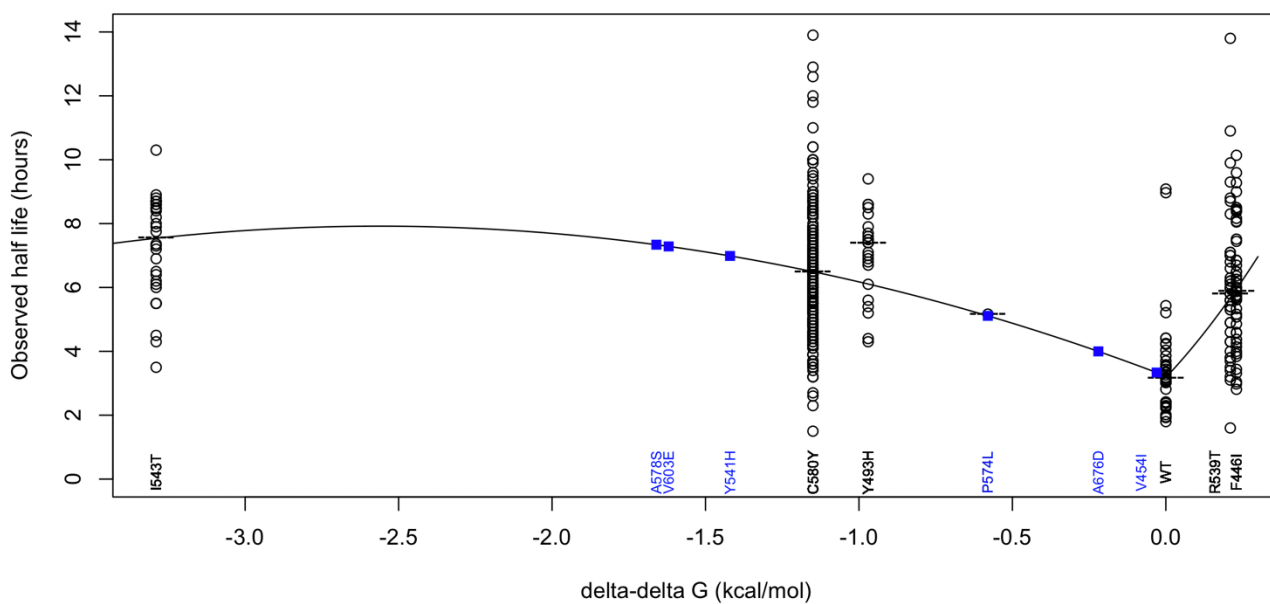
Black line: $3.359 - 3.248 \text{ DDG} - 0.614 \text{ DDG}^2$; adjusted $R^2 = 0.174$; inclusion of quadratic effect ($P < 6 \times 10^{-10}$)

(b) 4ZGCa (DUET)



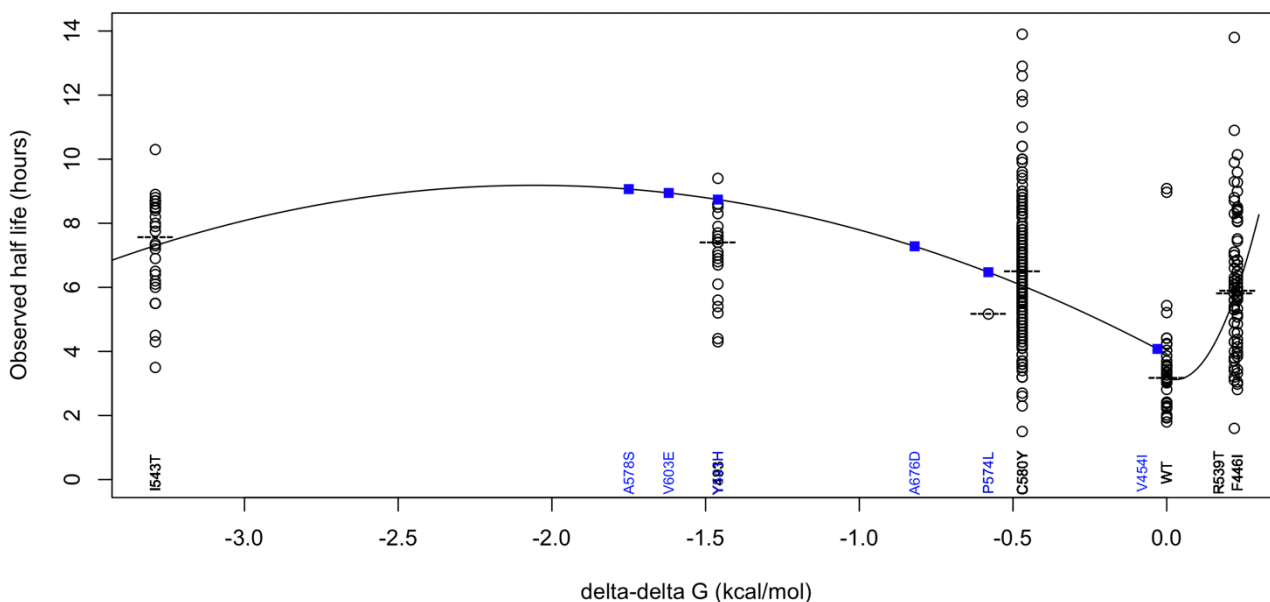
Black line: $3.696 - 3.681 \text{ DDG} - 0.789 \text{ DDG}^2$; adjusted $R^2 = 0.140$; inclusion of quadratic effect ($P < 3 \times 10^{-9}$)

(c) 4YY8b (SDM2)



Black lines: (negative DDG) $3.227 - 3.663 \text{ DDG} - 0.715 \text{ DDG}^2$; (positive DDG) $3.182 + 10.18 \text{ DDG} + 8.087 \text{ DDG}^2$;
adjusted $R^2 = 0.246$; inclusion of quadratic effect ($P < 7 \times 10^{-13}$)

(d) 4ZGCa (SDM2)



Black lines: (negative DDG) $3.926 - 5.109 \text{ DDG} - 1.241 \text{ DDG}^2$; (positive DDG) $3.182 - 4.096 \text{ DDG} + 70.15 \text{ DDG}^2$;
adjusted $R^2 = 0.185$; inclusion of quadratic effect ($P < 2 \times 10^{-12}$)