**S2 Table**

**Comparison between observed and predicted median half-life (MHL) of parasitaemia using linear and quadratic ($\Delta\Delta$G) analysis of *PfK13* mutations with the $-\Delta\Delta$G values, based on analysis of crystal structures 4YY8b and S-S linked 4ZGCa using the DUET website.**

Although the linear analysis gave a P value <0.0001, the quadratic analysis was more predictive (F-statistic $P<10^{-9}$), with predictions closer to the observed half-lives, and values for unlinked 4YY8 having marginal improvements over those from S-S linked 4ZGC.

| Model | Mutant | Obs. MHL | DUET $\Delta\Delta$G | Linear MHL* | Quad. MHL* | SDM2 $\Delta\Delta$G | Linear MHL* | Quad. MHL* | Structure | Patients |
|---|---|---|---|---|---|---|---|---|---|---|
| 4YY8b | WT | 3.17 | 0.00 | 5.10 | 3.36 | 0.00 | 5.04 | 3.23/3.18 | | 43 China |
| | F446I | 5.89 | -1.51 | 6.45 | 6.87 | 0.23 | 6.15 | 5.95 | B-STRAND 1b | 49 China |
| | V454I | | 0.001 | 5.11 | 3.36 | -0.03 | 5.07 | 3.34 | LOOP 1b-1c | |
| | V493H | 7.40 | -2.28 | 7.14 | 7.58 | -0.97 | 6.02 | 6.11 | B-STRAND 2b | 24 |
| | R539T | 5.80 | -1.08 | 6.06 | 6.14 | 0.21 | 5.92 | 5.68 | B-STRAND 3b | 45 |
| | Y541H | | -2.18 | 7.04 | 7.53 | -1.42 | 6.48 | 6.99 | B-STRAND 3b | |
| | I543T | 7.56 | -3.43 | 8.14 | 7.29 | -3.29 | 8.38 | 7.54 | B-STRAND 3b | 30 |
| | P574L | 5.17 | -0.52 | 5.56 | 4.87 | -0.58 | 5.63 | 5.11 | LOOP 3d-4a | 7 China |
| | A578S | | -1.45 | 6.39 | 6.77 | -1.66 | 6.72 | 7.34 | LOOP 3d-4a | |
| | C580Y | 6.50 | -1.06 | 6.04 | 6.10 | -1.15 | 6.20 | 6.49 | B-STRAND 4a | 264 |
| | V603E | | -2.81 | 7.59 | 7.64 | -1.62 | 6.68 | 7.29 | B-STRAND 4c | |
| | A676D | | -0.85 | 5.86 | 5.67 | -0.22 | 5.26 | 3.99 | B-STRAND 6a | |
| 4ZGCa | WT | 3.17 | 0.000 | 5.52 | 3.69 | 0.000 | 5.77 | 3.93/3.18 | | 43 China |
| | F446I | 5.89 | -1.30 | 6.39 | 7.15 | 0.23 | 6.10 | 5.95 | B-STRAND 1b | 49 China |
| | V454I | | -0.08 | 5.58 | 3.98 | -0.03 | 5.79 | 4.08 | LOOP 1b-1c | |
| | Y493H | 7.40 | -2.35 | 7.10 | 7.99 | -1.46 | 6.71 | 8.74 | B-STRAND 2b | 24 |
| | R539T | 5.80 | -0.71 | 6.00 | 5.91 | 0.22 | 5.98 | 5.68 | B-STRAND 3b | 45 |
| | Y541H | | -2.25 | 7.04 | 7.98 | -1.46 | 6.71 | 8.74 | B-STRAND 3b | |
| | I543T | 7.56 | -3.54 | 7.90 | 6.84 | -3.29 | 7.88 | 7.30 | B-STRAND 3b | 30 |
| | P574L | 5.17 | -0.45 | 5.83 | 5.19 | -0.58 | 6.14 | 6.47 | LOOP 3d-4a | 7 China |
| | A578S | | -1.47 | 6.51 | 7.40 | -1.75 | 6.89 | 9.07 | LOOP 3d-4a | |
| | C580Y | 6.50 | -0.74 | 6.02 | 5.99 | -0.47 | 6.07 | 6.05 | B-STRAND 4a | 264 |
| | V603E | | -2.66 | 7.31 | 7.90 | -1.62 | 6.81 | 8.95 | B-STRAND 4c | |
| | A676D | | -0.95 | 6.16 | 6.48 | -0.82 | 6.30 | 7.28 | B-STRAND 6a | |

* Predicted