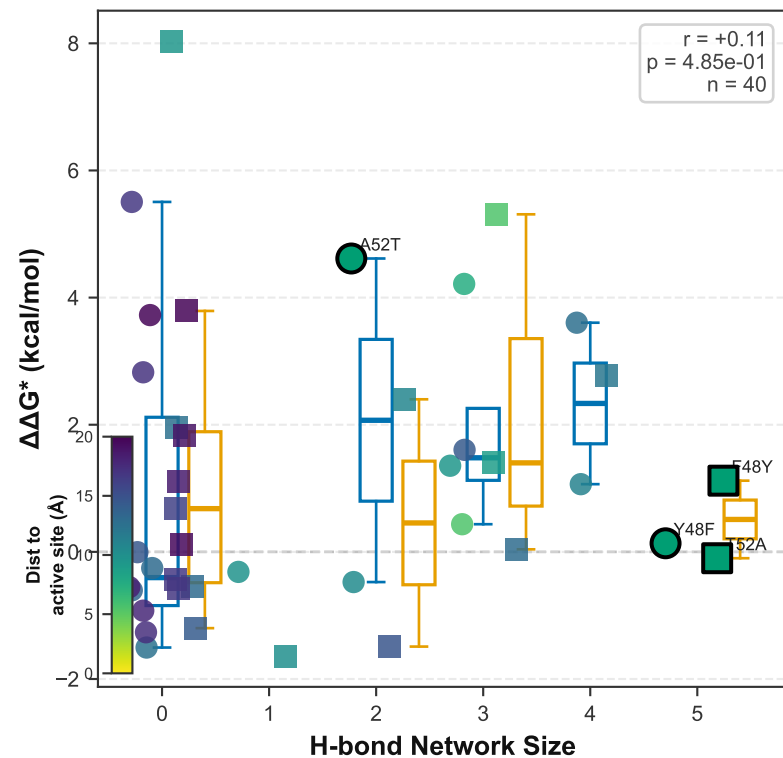


Electrostatic Environment Drives Activation Energetics and Epistasis in GPX6

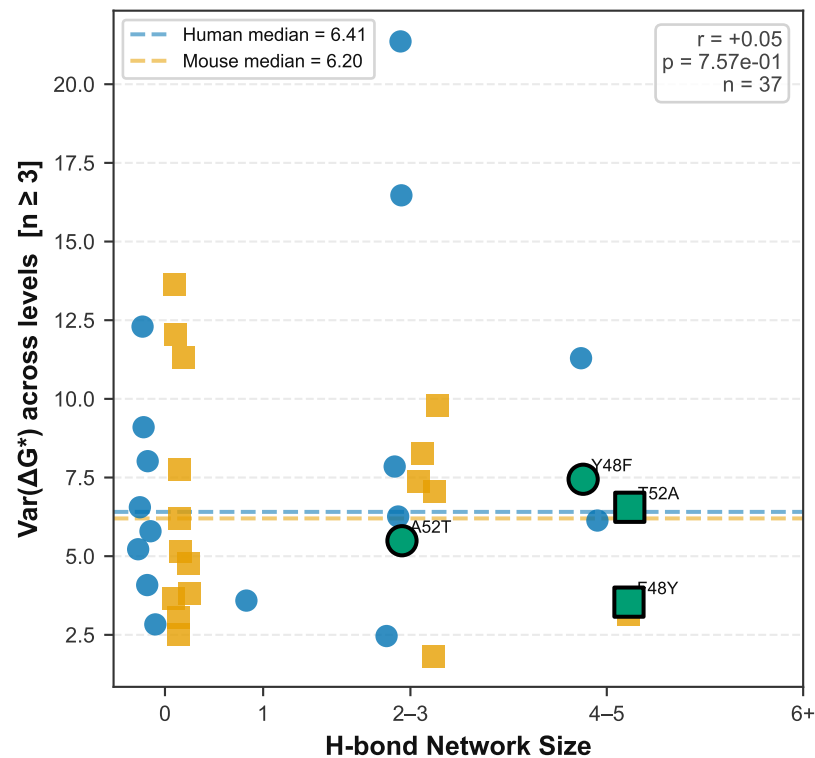
H-bond network size determines $\Delta\Delta G^*$ (Panel A); epistasis (variance across mutation levels, ≥ 3 levels) also scales with H-bonds (Panel B);

Panel C tests whether high-barrier mutants are also more context-dependent. Active-site H-bond mutants (green) are labelled.

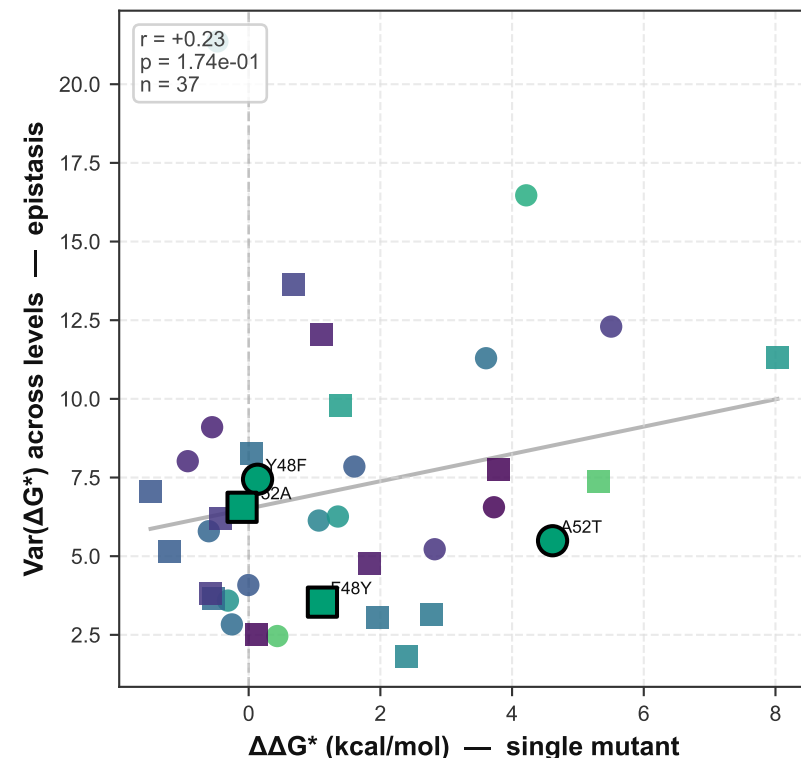
A | H-bonds \rightarrow Activation Barrier



B | H-bonds \rightarrow Epistatic Context-Dependence



C | Activation Barrier vs Epistasis



● Human (circle) ■ Mouse (square) ● Active-site H-bond mutant — OLS regression