

Table S2: **The ten families with the most significantly ($p < 0.01$) higher or lower number of bi-functional positions than expected by chance.**

Family	overlap	significance
<i>Most significant overlapping families</i>		P-value (right)
Amylase, catalytic domain	1.35	2.2e-16
Tyrosine-dependent oxidoreductases	1.23	2.2e-16
Tandem AAA-ATPase domain	1.32	2.2e-16
Extended AAA-ATPase domain	1.57	2.2e-16
Subtilases	4.35	2.2e-16
Protein kinases, catalytic subunit	1.28	2.2e-16
G proteins	1.34	2.8e-16
Di-heme elbow motif	1.41	5.0e-16
V set domains (antibody variable-like)	1.31	4.8e-15
Glutathione S-transferase, C-terminal	1.60	6.7e-15
<i>Most significant non-overlapping families</i>		P-value (left)
Thi4-like	0.1	8.8e-12
Photosystem I subunits PsaA/PsaB	0.76	5.2e-10
Myeloperoxidase-like	0.23	6.5e-09
Heme-dependent catalases	0.47	1.0e-08
Eukaryotic type heme oxygenase	0.37	1.4e-08
Bacterial photosystem II (L and M)	0.84	2.0e-08
tRNA-guanine transglycosylase	0	1.3e-07
Catalase-peroxidase KatG	0.22	1.8e-07
Undecaprenyl diphosphate synthase	0.14	5.2e-07
MTH1675-like	0.09	7.9e-07

Bi-functional positions refer to alignment positions that bind both small molecules (250-1000 Da) and proteins. The significance of the overlap (Text Eqn 1) is assessed by the Fisher exact test (<http://r-project.org>).