

Table S1. Number of unique structures in each Thioredoxin-like Clan family

PFAM model	Sequences with structures ¹	Count of structures
AhpC-TSA	24	42
ArsC	4	13
Calsequestrin	3	4
DSBA	5	24
DUF1687	1	1
DUF836	2	3
DUF953	2	2
ERp29_N	2	6
GSHPx	7	8
GST_N	67	216
Glutaredoxin	18	30
HyaE	3	3
OST3_OST6	0	0
Phosducin	2	4
Redoxin	16	22
SCO1-SenC	4	15
SH3BGR	4	6
T4_deiodinase	0	0
Thioredoxin	41	131
None ²	12	33
Total	217	563

¹For each PDB ID, a structure is counted once for each unique chain sequence containing a Trx fold.

²33 chains included in this analysis exhibited a Trx fold, but did not align to a PFAM Thioredoxin-like Clan model with a score better than the gathering threshold.

Table S2. Number of sequences in each Thioredoxin-like Clan family

PFAM model	Max 40% identical sequences ¹	All sequences
AhpC-TSA	692	4,655
ArsC	82	1,626
Calsequestrin	3	40
DSBA	410	2,085
DUF1687	8	29
DUF836	87	419
DUF953	21	71
ERp29_N	5	16
GSHPx	65	1,230
GST_N	664	6,378
Glutaredoxin	347	2,811
HyaE	17	81
OST3_OST6	30	112
Phosducin	29	239
Redoxin	359	2,539
SCO1-SenC	207	929
SH3BGR	24	86
T4_deiodinase	10	93
Thioredoxin	996	5,635
None ²	26	132
Total	4,082	29,206

¹The total of 29,206 sequences with a Trx fold (see Methods) can be reduced to 4,082 sequences that are longer than 60 amino acids and are no more than 40% identical.

²132 Trx fold sequences included in this analysis did not align to a PFAM Thioredoxin-like Clan model with a score better than the gathering threshold.

Table S3. Network edges from Fig. 4 due to sequence similarity outside of the domain of interest

Additional domain responsible for similarity	Anchoring group 1	Anchoring group 2
Kinase	Single GST (Fig. 5: J)	Single peroxiredoxin (Fig. 5: P); uncharacterized Grx
Peptide methionine sulfoxide reductase	Cytochrome maturation-like proteins (Fig. 5: R)	Glutaredoxins (Fig. 5: I)
NB-ARC (ATP-binding domain shared by plant resistance gene produces, cell death regulators in animals)	Single DsbA-like protein (Fig. 5: B)	Single Thioredoxin-like protein (Fig. 5: G)
Glutaredoxin ¹	Atypical Prx PRX5_HAEIN (Fig. 5: Q)	Glutaredoxin GLRX3_ECOLI (~Fig. 5: I)

¹In this case, the atypical peroxiredoxin from *H. influenzae* is fused to a glutaredoxin domain (PRX5_HAEIN). The peroxiredoxin domain is connected by many edges to the other atypical peroxiredoxins, and there is an additional edge representing a significant alignment between just the glutaredoxin domain of PRX5_HAEIN and *E. coli* Grx 3.