

Supplementary Table ST3 Examples of domain families showing low tethering numbers (tethering number ≤ 10).

S.No.	Domain family (Interpro ID)	Brief description of the function of the domain family
1	IPR002176	RuvC, members involved in DNA repair and in the late step of RecE and RecF pathway of recombination. Ruv C cleave cruciform junction, these are structurally analogous to Holliday junction, they can also cleaves Holliday junctions that are formed between gapped circular and linear duplex DNA by the function of RecA protein.
2	IPR001133	NADH:ubiquinone/quinoneoxidoreductase, chain 4L. This entry represents NADH:ubiquinoneoxidoreductase, chain 4L, as well as NADH-quinoneoxidoreductase. In eukaryotes, these enzymes are usually found in the mitochondria or chloroplasts as part of the respiratory-chain NADH dehydrogenase (also known as complex I or NADH-ubiquinone oxidoreductase), an oligomeric enzymatic complex. However, they are also found in bacteria and archaea.
3	IPR015977	Nicotinatephosphoribosyltransferase-like Nicotinatephosphoribosyltransferase (EC:2.4.2.11) is the rate limiting enzyme that catalyses the first reaction in the NAD salvage synthesis. This family also includes Pre-B cell enhancing factor that is a cytokine. This family is related to Quinolinatephosphoribosyltransferase.
4	IPR000271	Ribosomal protein L34 Ribosomal protein L34 is one of the proteins from the large subunit of the prokaryotic ribosome. It is a small basic protein of 44 to 51 amino-acid residues. L34 belongs to a family of Eubacterial ribosomal proteins.
5	IPR002490	V-type ATPase 116kDa subunit family this family consists of the 116kDa V-type ATPase (vacuolar (H ⁺)-ATPases) subunits, as well as V-type ATP synthase subunit i. The 116-kDa subunit is a transmembrane glycoprotein required for the assembly and proton transport activity of the ATPase complex. Several isoforms of the 116-kDa subunit exist, providing a potential role in the differential targeting and regulation of the V-ATPase for specific organelles
6	IPR001653	Diaminopimelateepimerasecatalyses the isomerisation of L,L-diaminopimelate to meso-DAP in the biosynthetic pathway leading from aspartate to lysine. It is a member of the broader family of PLP-independent amino acid racemases. This enzyme is a monomeric protein.
7	IPR000453	Chorismate synthase catalyzes the last of the seven steps in the shikimate pathway which is used in prokaryotes, fungi and plants for the biosynthesis of aromatic amino acids.

8	IPR000028	Chloroperoxidase (CPO), also known as Hemehaloperoxidase, is a ~250 residue long heme-containing glycoprotein that is secreted by various fungi. It catalyzes the hydrogen peroxide-dependent chlorination of cyclopentanedione during the biosynthesis of the antibiotic caldarioymcin. Additionally, hemehaloperoxidase catalyzes the iodination and bromination of a wide range of substrates. This enzyme also catalyzes dehydrogenation reactions. Chloroperoxidase also functions as a catalase, facilitating the decomposition of hydrogen peroxide to oxygen and water. Furthermore, chloroperoxidase catalyzes P450-like oxygen insertion reactions. The capability of chloroperoxidase to perform these diverse reactions makes it one of the most versatile of all known heme proteins
9	IPR000096	The serum amyloid A (SAA) proteins comprise a family of vertebrate proteins that associate predominantly with high density lipoproteins (HDL). Some of these proteins are over expressed during inflammation; thus making SAA a major acute phase reactant. While the major physiological function of SAA is unclear, prolonged elevation of plasma SAA levels, results in a pathological condition, called amyloidosis affecting the liver, kidney and spleen. SAA are proteins of about 110 amino acid residues. The proteins are polymorphic, the various isoforms apparently capable of responding in different ways to different stimuli.
10	IPR000391 ⁺	Aromatic-ring-hydroxylating dioxygenase, β subunit. Involved in the degradation of aromatic compounds by aerobic bacteria by dihydroxylation of the substrate by non-haem iron-containing dioxygenases. Aromatic-ring-hydroxylating dioxygenases oxidise aromatic hydrocarbons and related compounds to cis-arenediols.
11	IPR000471	Interferon $\alpha/\beta/\delta$ proteins producing antiviral and antiproliferative response in cells. On the basis of their sequence interferons are classified into five groups: α , α -II (or Ω), β , δ (or trophoblast). The sequence differences is a potential cause for difference in responses to various inducers, or result in the recognition of different target cell types
12	IPR000549 ⁺	Consists of PSI-G (gene <i>psaG</i>) and PSI-K (gene <i>psaK</i>) proteins which are small hydrophobic proteins of about 7 to 9 Kd and are found to be evolutionary related. They form a part of Photosystem I (PSI) an integral membrane protein complex that uses light energy to mediate electron transfer from plastocyanin to ferredoxin
13	IPR000688	Hydrogenase nickel incorporation protein HypA/HybF, the exact role of these proteins is not yet clear, however some of these proteins are indicated to be required for the incorporation of the nickel ions
14	IPR001185	Large-conductance mechanosensitive channel, Mechanosensitive ion channels (MscL) play a critical role in transducing physical stresses at the cell membrane into an electrochemical response.
15	IPR001690 ⁺	Autoinducer synthesis protein, autoinducers are important mediator of molecular communication in bacterial species.

16	IPR002041 ⁺	Ran GTPase, GTP-binding proteins involved in nucleocytoplasmic transport. Required for the import of proteins into the nucleus and also for RNA export
17	IPR002712	CcdB protein, it is a topoisomerase poison. It is responsible for killing plasmid-free segregants, and interferes with the activity of DNA gyrase
18	IPR002770	Formylmethanofuran: tetrahydromethanopterinformyltransferaseFtr, C-terminal. Ftr involved in C1 metabolism in methanogenicarchaea
19	IPR003207 ⁺	This family contains the small subunit of the trimericdiol dehydratases and glycerol dehydratases. These enzymes are produced by some enterobacteria in response to growth substances
20	IPR003418	Fumaratereductase, D subunit. Fumaratereductase is a membrane-bound flavoenzyme consisting of four subunits. The D subunit is speculated to anchor the catalytic components of the fumarate reductase complex to the cytoplasmic membrane.

⁺ Domain families which predominantly exist as single domains in proteins. Such domain families are considered as genuine single domain entries if more than 90% of the sequence is assigned with the respective domain family