

Figure 5—Source Data 1. Lipocone family conserved contextual associations across distinct functional themes.

Function	Family	Genome associations ¹	Phyletic pattern notes ²
Lipid head group exchange reactions	Euk-PTDSS1/2	Phosphatidylserine production	Pan-eukaryotic
	Prok-PTDSS	Archaeophosphatidylserine production	sporadic archaea, bacteria, and viruses
	cpCone-1	Kleisin-ScpA, HTH-ScpB	Patescibacteria
		TM+LemA, TM+TM+MPTase, single cpCone-1 KptA domain fusion	
		LP+Lola, 4TM with β -curl insert, [TM+NLPC/p60]	FCB group
	cpCONE-DUF2585	HslV-Peptidase, GNAT, ClpB-HslU	Alphaproteobacteria
		Glycolate-oxidase-GlcE, glycolate-oxidase-GlcF	
Cardiolipin synthesis	Wok-DUF2238	Synaptojanin-like, [GlycosylTFase-A], [α/β -hydrolase], [NUDIX]	Terrabacteria, Pseudomonadota
		Two-gene associations with diverse phosphatases: Calcineurin, HAD, PAP2	Terrabacteria (sp), other lineages
Modified isoprenoid lipid synthesis	Wok-DUF2238	Carotenoid biosynthesis module, GlycosylTFase-A, NUDIX	Actinomycetota
	YfiM-1	amidophosphoribosyltransferase, UbiA-prenylTFase, RidA deaminase, TM-containing DUF5638, HD, PHP+Ig	Calditrichota, FCB group, Gemmatimonadetes
Lipid head group modifications in peptidoglycan dynamics	VanZ-1 & VanZ-2	peptidoglycan glycosylTFases, D-Ala-D-Ala-peptidases, MurE-synthetase MurD-synthetase, MATE-flippase	Gene neighborhoods in Terrabacteria, FCB group, and Pseudomonadota
Lipid head group modifications in exopolysaccharide metabolism	VanZ-1 & VanZ-2	WaaL-ligase, Wzc-CpsD-N, ElyC	Gene neighborhoods in Terrabacteria, FCB & PVC groups, and Pseudomonadota
Uncharacterized modifications of peptidoglycan and the outer membrane	VanZ-1+VanZ-i	Ferredoxin, α/β -hydrolase lipase, D-Ala-D-Ala-M β L transpeptidase	Betaproteobacteria
	VanZ-2	SprA-N, GCV-H, 2TM+proline-rich-linker+TonB-C, TonB-C+OMP- β -barrel	FCB group
	VanZ-2	ABC ATPase transporter, TM+coiled-coil+Papain-like or gly-gly-peptidase, SP+LTDs	Patescibacteria
Lipocone domains operating in or in transit to the outer membrane	YfiM-Griddle (up to 3 copies)	OMP- β -barrel(f), extended β -hairpin(f), Lola, POTRA, PLUG, TolB-N, Patatin lipase, GlycosylTFase-B, PAP2, LP+Synaptojanin, R-P(f)	Gram-negative bacteria
	YfiM-DUF2279	OMP- β -barrel(f), MltG-endolytic-TGase, LP+Cytochrome-C7, PMM/PGM, GNAT, diaminopimelate-epimerase, Lysozyme	FCB group
	YfiM-DUF2279	OMP- β -barrel(f), GlycosylTFase-A, OMP- β -barrel, SP+PDZ+ClpP-protease	FCB group
	ClaspCone-1	TM(f) or 5TM(f), TULIP(f) or Ig and MPTase(f), [PHP](f), GDSL-Lipase, MBOAT	Pseudomonadota, Planctomycetota
Membrane-anchoring linkage	Skillet-1	Specialized lipobox(f), diverse ligand-binding domains(f): Ig, Jellyroll, β Ps, Concanavalin, OB-fold, SHOCT, MORNs	Bacillota, FCB group, Pseudomonadota

Lipid-associated signaling systems, standalone proteins	VanZ-1	HTH(f), RHH(f), YycI(f), RDD(f), Glyoxylase(f), NPCBM(f)	Widespread, sporadic linkages
	VanZ-2	cNMPDB(f), FHA(f), KTSC(f), Papain(f), TPRs(f), Calcineurin(f), CBD9(f)	
	Skillet-3	Ig(f), β -sandwich(f), helix-grip(f), β Ps(f), MORNs(f), Lipocalin(f), β -barrel(f)	Pseudomonadota, FCB group, Terrabacteria
Lipid-associating signaling systems, multicomponent	VanZ-1	HAAS(f), PadR-HTH	Bacillota
	Skillet-2	helix+TM or ZnR+helix+TM or HTH+L12-ClpS+TM, TetR transcriptional repressor, [HMG-CoA-reductase+GHMP-kinase], [SP+Ig repeats]	Bacteriodota, Bacillota (sp)
	Skillet-DUF2809	wHTH, cytoplasmic-helix+6TM protein. Joined by one or more of: ElyC, CreD, Coq4, Lcp-like, DUF1361, TGase	FCB group, Pseudomonadota (sp)
Antiviral immunity	Min-Wnt	DUF3892(f)	Pseudomonadota (sp)
		3-strand β -meander(f), LP+PPTs, SP+Glycosyl-hydrolase, SP+ β -helix	Bacteroidota
		Standalone	Cyanobacteria
		helical-domain+Pcfj-GNAT(f)	Duplodnaviria
Toxin domains in polymorphic and allied conflict systems	Min-Wnt	SP or LP+tail(f), LP+Imm-BamE or LP+Imm-Jellyroll or Imm-4TM	Terrabacteria, Pseudomonadota, FCB group, Elusimicrobia, Acidobacteria, PVC group (sp), Archaea (sp)
		Polymorphic toxin delivery systems: T1SS, T4SS, T6SS, T7SS, T9SS, DUF4157-MPTase, Immunity proteins as above	
		LP+Cystatin-FD (f), LP+Imm-Jellyroll (dominant) or LP+Imm-BamE	Bacteroidota
	Prok-SAA	Polymorphic toxin delivery systems: T6SS, MuF, TM+[TM+TM+]Imm-SAA or LP+Imm-BamE	Spirochaetota, Nitrospirota, Acidobacteriota, Terrabacteria (sp), PVC group, Pseudomonadota (sp), Fusobacteriota, Bacteriodota (sp)
		PGBD(f), TM+Imm-SAA	Pseudomonadota (sp)
	Prok-TelC	Polymorphic toxin delivery systems: T6SS, T7SS, MPTase-DUF4157, ZU5+vWA core {31064832}, Imm-TipC, Imm-Zu5/vWA	Bacillota, Actinomycetota (sp), Myxococcota (sp), FCB and PVC groups (sp), Pseudomonadota (sp)
		SP+GbpC+MucBP-IG(f), Imm-TipC	Bacillota and Actinomycetota (sp)
		TPM+TPM(f) or TPM+Ig, Imm-4TM	Bacteriodota
	CapCone-1	Polymorphic toxin delivery systems: T6SS (including PsbP/MOG1-like fusion), MPTase-DUF4157, LP+Imm-BamE	Pseudomonadota, PVC group, Terrabacteria (sp), FCB group (sp)
		Cystatin-FD+linker, LP+Imm-BamE	Bacteroidota
	CapCone-2	SP(f), SP+Imm-BamE	Bdellovibrionota, Acidobacteria (sp)

		Polymorphic toxin delivery systems: T6SS, MPTase-DUF4157	Pseudomonadota (sp), FCB group (sp), PVC group (sp), Archaea (sp)
		ANKs(f), SP+Imm-SAS6-N-like- β -sandwich	PVC group (sp), Pseudomonadota (sp)
	ClaspCone-2	Polymorphic toxin delivery systems: T6SS, Imm-4TM	FCB group (sp), PVC group (sp), Pseudomonadota (sp)
	VanZ-1	Polymorphic toxin delivery systems: T6SS	Bacillota
Toxins in predator-prey and other inter-specific conflicts	Min-Wnt	SP+half- β -barrel(f), CC-motif-containing-tail(f), C-terminal helical-extension(f)	Bacteroidota, PVC group, Terrabacteria (sp), Hemichordata, Rotifera, fungi
		Broken-hairpin(f)	Alphaproteobacteria (sp), Duplodnaviria (sp), Terrabacteria (sp)
	CapCone-2	SP(f), Patatin(f), Lipocalin, acyltransferase+TM+TM+TM, SP+ α / β -hydrolase, SP+OMP- β -barrel	Bdellovibrionota, Holophagales, Archangium, Woeseiaceae, Labrenzia, Roseibium
	Prok-SAA	SP+MTPase+Prok-SAA+vWD+Ig+Ig	Gemmatimonadetes (sp), Pseudomonata (sp)
	Skillet	Histidine kinase-Receiver, MPTase, Papain-like, MTases, LysM & other ligand-bindings domains, etc.	Omnitrophica Patescibacteria
	Prok-TelC	NAGPA(f), ligand-binding(f): Ig, CW-repeats, β Ps, β -sandwich, etc.	Bacillota
		PGBD+PGBD+Rv2525c-like-TIM-barrel(f), SP+Ig+Ig*, 3TM-CCDN*, SP+VanY*	Bacillota, fungi (sp), Actinomycetota* (sp)
Resistance to antimicrobial agents	VanZ-1, VanZ-2, Skillet-DUF2809*	VanY, vancomycin resistance modules, D-Ala-D-Ala-M β L*	Terrabacteria, FCB group (sp)*, Pseudomonata (sp)*
	YfiM-1	Thioredoxin, DTW-SPOUT, acetate—CoA-ligase+ATP-grasp+GNAT, HKD fold phosphatidylserine synthetase	Gammaproteobacteria (sp)

¹(f): denotes a domain that is directly fused to the Lipocone family; *: associations present in a phylogenetically restricted subset; [x]: association is not universally observed; GlycosylTFase-A: glycosyltransferase-A; TFase: transferase; TGase: transglycosylase; CW: cell wall; MTase: Methylase; MBL: metallo- β -lactamase; TM: transmembrane; SP: signal peptide; LP: membrane-anchored lipoprotein; T[x]SS: Type-X-secretory system; Imm: immunity protein; β Ps: β -propellers;

²(sp): denotes sporadic distribution in the listed phylogeny; *: phylogenies with restricted associations