

S2 Table – Highly conserved cofactor biosynthesis genes in prokaryotic genomes. Essentiality is given as the number of datasets in DEG (out of 36) in which each gene is essential. Conservation is given as the percentage of the 79 genomes where a significant homolog for this gene was found. The description is that of the corresponding annotated ORF in the genome of *E. coli* K12. Biosynthesized cofactors were manually retrieved from the detailed information available in the Metacyc database.

Gene Name	Conservation	Description	Cofactor	Essentiality (DEG)
gltX	100%	Glutamate-tRNA ligase	Heme	28
sufC	100%	Probable ATP-dependent transporter SufC	FeS clusters	2
sufS	98.7%	cysteine desulfurase, stimulated by SufE; selenocysteine lyase, PLP-dependent	FeS clusters	2
iscS	97.5%	cysteine desulfurase (tRNA sulfurtransferase), PLP-dependent	FeS clusters	10
entA	97.5%	2,3-dihydro-2,3-dihydroxybenzoate dehydrogenase	siderophores	0
ispB	96.2%	octaprenyl diphosphate synthase	quinones	12
ispA	96.2%	geranyltranstransferase	quinones	9
ispU	96.2%	undecaprenyl pyrophosphate synthase	quinones	2
glyA	94.9%	serine hydroxymethyltransferase	Folates	14
hemL	94.9%	glutamate-1-semialdehyde aminotransferase (aminomutase)	porphyrins	14
bioA	94.9%	7,8-diaminopelargonic acid synthase, PLP-dependent	Biotin	3
folD	94.9%	Bifunctional protein FOLD	Folates	19
dxs	92.4%	1-deoxyxylulose-5-phosphate synthase, thiamine triphosphate-binding, FAD-requiring	thiamine; isoprenoids;	16
nadK	92.4%	NAD kinase	nad/nadp	0
pdxB	92.4%	erythronate-4-phosphate dehydrogenase	pyridoxal-5-p	2
pabA	92.4%	aminodeoxychorismate synthase, subunit II	Folates	0
epd	92.4%	D-erythrose 4-phosphate dehydrogenase	pyridoxal-5-p	1
gor	91.1%	glutathione oxidoreductase	glutathione	2
ribB	91.1%	3,4-dihydroxy-2-butanone-4-phosphate synthase	riboflavin	5
ribF	91.1%	bifunctional riboflavin kinase/FAD synthetase	flavins	15
ribD	89.9%	fused diaminohydroxyphosphoribosylamino pyrimidine deaminase and 5-amino-6-(5-phosphoribosylamino) uracil reductase	riboflavin	8
ribE	89.9%	riboflavin synthase beta chain	riboflavin	7
entC	89.9%	isochorismate synthase 1	terpenoids	1
ligA	89.9%	DNA ligase, NAD(+)-dependent	?	23
folC	88.6%	bifunctional folylpolyglutamate synthase/ dihydrofolate synthase	Folates	9
coaD	88.6%	pantetheine-phosphate adenylyltransferase	CoA	22
folP	88.6%	7,8-dihydropteroate synthase	folates	7
ribC	88.6%	riboflavin synthase, alpha subunit	riboflavin	3