Table S1. Genes differentially expressed in LL-37

Gene[a]	Fold change in LL-37[b]	Product	COG[c]	*p*[d]
Induced in LL-37				
CD630_16180 (clnA)	202.99	ABC-type transport system multidrug-family ATP-binding protein	V	0.023
CD630_16190 (clnB)	192.16	ABC-type transport system multidrug-family permease	-	0.001
CD630_16170 (clnR)	186.82	Transcriptional regulator GntR family	K	0.005
CD630_16100	64.45	conserved hypothetical protein	-	4.2E-04
CD630_16110	34.77	conserved hypothetical protein	-	0.028
CD630_16090	30.62	conserved hypothetical protein	-	0.030
CD630_16070	30.25	ABC-type transport system multidrug-family ATP-binding protein	V	0.011
CD630_12400 (vanZ)	28.43	Teicoplanin resistance protein	V	0.009
CD630_23410 (abfD)	14.81	Gamma-aminobutyrate metabolism dehydratase/isomerase	Q	0.005
CD630_23820	13.76	putative pyridoxal phosphate-dependent transferase	E	0.051
CD630_23810 (iorA)	13.66	Indole pyruvate ferredoxin/flavodoxin oxidoreductase	C	0.007
CD630_23390 (cat2)	13.27	4-hydroxybutyrate CoA transferase	C	0.016
CD630_23400	13.14	uncharacterised protein	-	0.053
CD630_23380 (4hbD)	12.95	4-hydroxybutyrate dehydrogenase	C	0.012
CD630_23420 (sucD)	12.71	Succinate-semialdehyde dehydrogenase	C	0.009
CD630_23430 (cat1)	11.85	Succinyl-CoA:coenzyme A transferase	C	0.007
CD630_23440	10.85	putative membrane protein (butyrate conversion)	R	0.005
CD630_23800 (iorB)	10.81	Indole pyruvate ferredoxin/flavodoxin oxidoreductase	C	0.010
CD630_12382	5.60	Fragment of conserved hypothetical protein	-	0.005
CD630_05500	5.52	putative membrane protein	-	0.053
CD630_18870 (csfU)	5.34	Extracytoplasmic function (ECF) sigma factor	K	0.002
CD630_05490	4.74	conserved hypothetical protein	-	0.049
CD630_18890	4.54	ABC-type transport system multidrug-family ATP-binding protein	V	1.9E-04
CD630_25560	4.24	PTS system fructose/mannitol-family IIAB component	GT	0.019
CD630_16990 (ribE)	4.23	Riboflavin synthase alpha subunit	H	0.035
CD630_04900	4.13	putative sugar-phosphate dehydrogenase	ER	0.049
CD630_04980	4.13	putative cell-division FtsK/SpoIIIE-family protein Tn5397 CTn3-Orf21	D	0.012
CD630_04960	4.13	putative conjugative transposon protein DUF961 family Tn5397 CTn3-Orf23	-	0.039
CD630_33740	3.92	putative conjugative transposon protein Tn916-like CTn7-Orf8	-	0.011
CD630_04970	3.86	putative conjugative transposon protein DUF961 family Tn5397 CTn3-Orf22	-	0.008
CD630_18880 (rsiU)	3.69	Extracytoplasmic function (ECF) anti-sigma factor	-	0.004
CD630_17000 (ribD)	3.65	Riboflavin biosynthesis protein	H	0.018
CD630_05000	3.61	putative antirestriction protein Tn5397 CTn3-Orf18	-	0.012
CD630_18900	3.60	ABC-type transport system multidrug-family permease	-	0.014
CD630_10590 (thlA1)	3.56	Acetoacetyl-CoA thiolase 1	I	0.037
CD630_05060	3.54	Reverse transcriptase/maturase/endonuclease Group II intron	V	0.001
CD630_10580 (hbd)	3.51	3-hydroxybutyryl-CoA dehydrogenase	I	0.045
CD630_04670	3.43	putative hydrolase HAD superfamily subfamily IIB	HR	4.2E-05
CD630_04780 (spaF)	3.43	ABC-type transport system lantibiotic/multidrug-family ATP-binding protein	V	0.015
CD630_33730 (mgtA)	3.39	Magnesium-transporting ATPase P-type Tn916-like CTn7-Orf7	P	0.044
CD630_03580	3.38	putative conjugative transposon protein Tn916-like CTn1-Orf3	-	0.024
CD630_05102	3.35	Fragment of putative conjugative transposon protein Tn5397 CTn3-Orf5	-	6.0E-05
CD630_05101	3.31	putative conjugative transposon protein Tn5397 CTn3-Orf8	-	0.001
CD630_15510 (hisH)	3.29	Imidazole glycerol phosphate synthase subunit	E	0.001
CD630_05103	3.27	putative conjugative transposon protein Tn5397 CTn3-Orf4	-	0.028
CD630_02910	3.25	putative peptidase M20A family	E	0.006
CD630_10560 (etfA3)	3.22	Electron transfer flavoprotein subunit alpha	C	0.027
CD630_16120	3.18	putative amidohydrolase	Q	0.007
CD630_23790 (buk2)	3.13	Butyrate kinase	C	0.013
CD630_15500 (hisB)	3.12	Imidazoleglycerol-phosphate dehydratase	E	0.001
CD630_15540 (hisI)	3.10	Histidine biosynthesis bifunctional protein	E	0.018

CD630_10550 (etfB3)	3.07	Electron transfer flavoproteins subunit beta	C	0.023
CD630_05100	3.07	putative RNA polymerase sigma factor Tn5397 CTn3-Orf7	K	0.001
CD630_18020	3.05	putative hydrolase metallo-beta-lactamase superfamily	R	0.036
CD630_08530 (oppB)	3.02	ABC-type transport system oligopeptide-family permease	EP	0.041
CD630_10570 (crt2)	2.97	3-hydroxybutyryl-CoA dehydratase (Crotonase)	I	0.034
CD630_14240	2.97	conserved hypothetical protein	-	0.001
CD630_05770	2.96	conserved hypothetical protein	R	0.008
CD630_33750 (mgtC)	2.96	Magnesium-transporting ATPase protein Tn916-like CTn7-Orf10	S	0.003
CD630_21640 (ldh)	2.95	L-lactate dehydrogenase	C	0.004
CD630_10540 (bcd2)	2.94	Butyryl-CoA dehydrogenase	I	0.017
CD630_15470 (hisZ)	2.92	ATP phosphoribosyltransferase regulatory subunit	E	0.044
CD630_20140 (ilvD)	2.90	Dihydroxy-acid dehydratase	EG	7.2E-05
CD630_08570 (oppF)	2.88	Fragment of ABC-type transport system oligopeptide-family ATP-binding protein	-	0.029
CD630_15490 (hisC)	2.86	Histidinol-phosphate aminotransferase	E	0.047
CD630_15520 (hisA)	2.80	1-(5-phosphoribosyl)-5-[(5-phosphoribosylamino)m ethylideneamino]imidazole-4-carboxamide isomerase	E	0.044
CD630_16590	2.69	Cation-transporting ATPase	P	0.003
CD630_20270	2.69	N-carbamoyl-L-amino acid hydrolase	E	0.047
CD630_33911	2.66	conserved hypothetical protein	-	0.021
CD630_16310 (sodA)	2.59	spore coat protein-superoxide dismutase (Mn)	P	0.007
CD630_03830	2.58	putative cell-division FtsK/SpoIIIE-family protein Tn916-like CTn1-Orf28	D	0.009
CD630_10860	2.54	putative peptidase M20D family	R	0.033
CD630_21930 (cwp24)	2.54	putative cell wall-binding protein	-	0.047
CD630_20910	2.49	putative xanthine/uracil permease	F	0.010
CD630_17880	2.48	putative membrane protein	-	0.027
CD630_16740	2.47	putative NADPH-dependent FMN reductase	R	0.005
CD630_22330 (asrA)	2.43	Anaerobic sulfite reductase subunit A	C	0.043
CD630_17021 (thiS)	2.41	Thiamine biosynthesis protein	H	0.011
CD630_20280 (racX)	2.39	putative aspartate racemase	M	1.2E-04
CD630_27090	2.37	putative oxidoreductase	I	0.010
CD630_09260	2.36	putative phage protein	-	0.050
CD630_13900	2.35	conserved hypothetical protein DUF819 family	S	2.8E-06
CD630_21270	2.34	putative exported protein	-	0.042
CD630_27840 (cwp6)	2.30	putative N-acetylmuramoyl-L-alanineamidase autolysin	M	0.006
CD630_23090	2.29	conserved hypothetical protein	-	0.014
CD630_04800 (spaG)	2.29	ABC-type transport system lantibiotic/multidrug-family permease	S	0.037
CD630_04890	2.26	putative phosphoribosylaminoimidazole-succinocarb oxamide synthetase	F	0.001
CD630_17151	2.24	conserved hypothetical protein	-	0.016
CD630_15100	2.24	conserved hypothetical protein	-	0.006
CD630_07290 (gcvH)	2.23	Glycine cleavage system H protein	E	0.044
CD630_20751	2.21	conserved hypothetical protein	-	0.018
CD630_16130 (cotA)	2.18	spore coat assembly protein	-	0.022
CD630_10980	2.17	Two-component sensor histidine kinase Tn1549-like CTn4-Orf27	T	4.3E-04
CD630_10850	2.17	putative membrane protein	E	0.015
CD630_15560	2.16	putative polysaccharide deacetylase	G	0.001
CD630_15120 (panC)	2.15	Pantothenate synthetase	H	0.018
CD630_16200	2.15	Transporter Major Facilitator Superfamily (MFS)	G	2.6E-04
CD630_33790	2.14	putative conjugative transposon proteinTn916-like CTn7-Orf15	-	0.006
CD630_29620	2.13	conserved hypothetical protein	-	2.8E-04
CD630_04440 (ortB)	2.09	2-amino-4-ketopentanoate thiolase beta subunit	E	0.013
CD630_17170	2.07	uncharacterised protein	S	0.038
CD630_27250	2.07	putative monogalactosyldiacylglycerol synthase	M	0.020
CD630_25171	2.04	putative phage protein	-	0.001
CD630_19440	2.03	Fragment of conserved hypothetical protein	-	1.4E-04
CD630_26820 (pfo)	2.03	Pyruvate-ferredoxin oxidoreductase	C	0.021
CD630_15660 (ilvB)	2.01	Acetolactate synthase large subunit	EH	0.040
CD630_19670	2.01	uncharacterised protein	-	2.3E-04
Reduced in LL-37				
CD630_23310 (mtlD)	0.12	Mannitol-1-phosphate 5-dehydrogenase	G	4.4E-04

CD630_26140	0.12	uncharacterised protein DegV family	S	0.004
CD630_23320 (mtlF)	0.12	PTS system mannitol-specific EIIA component	G	0.001
CD630_23330 (mtlR)	0.14	Transcription antiterminator PTS operon regulator	K	2.3E-04
CD630_23340 (mtlA)	0.15	PTS system mannitol-specific IICB component	G	2.1E-05
CD630_19120 (eutA)	0.20	Ethanolamine reactivating factor for ammonialyase eutBC	E	0.018
CD630_19150 (eutL)	0.21	Ethanolamine carboxysome structural protein	E	0.003
CD630_31750 (cggR)	0.22	Transcriptional regulator SorC family	K	0.049
CD630_01631	0.22	conserved hypothetical protein	-	4.8E-04
CD630_09950 (serA)	0.23	putative D-3-phosphoglycerate dehydrogenase	HE	0.007
CD630_24291	0.23	putative 4Fe-4S ferredoxin iron-sulfur binding domain protein	C	0.019
CD630_09080	0.23	putative phage protein	-	7.7E-06
CD630_09960	0.24	conserved hypothetical protein	S	0.008
CD630_30270	0.25	PTS system glucose-like IIA component	G	0.021
CD630_19220 (eutN)	0.25	Ethanolamine carboxysome structural protein	QC	0.016
CD630_20160	0.26	conserved hypothetical protein	-	0.034
23S_rRNA	0.27	23S ribosomal RNA	-	0.026
CD630_09360	0.28	putative phage endodeoxyribonuclease RusA-like	L	0.007
CD630_29341	0.29	putative phage protein	-	0.049
CD630_29470	0.30	putative phage protein	-	0.020
CD630_29320	0.30	putative phage protein	-	0.035
CD630_28780 (fhuD)	0.30	ABC-type transport system ferrichrome-specific extracellular solute-binding protein	P	0.004
CD630_14890 (metN)	0.32	ABC-type transport system methionine-specific ATP-binding protein	P	0.035
CD630_14900 (met I)	0.32	ABC-type transport system methionine-specific permease	P	0.034
CD630_16632	0.32	conserved hypothetical protein	-	0.018
CD630_17452	0.34	conserved hypothetical protein	R	0.026
CD630_21710	0.34	Fragment of putative sodium:dicarboxylate symporter	-	0.009
CD630_31360 (bglA7)	0.35	6-phospho-beta-glucosidase	G	0.001
CD630_26640 (murE)	0.35	UDP-N-acetylmuramyl-tripeptide synthetase	M	2.4E-04
CD630_28770 (fhuB)	0.35	ABC-type transport system ferrichrome-specific permease	P	1.5E-04
CD630_36010	0.35	D-alanyl-D-alanine carboxypeptidase M15 family	M	0.013
CD630_31000	0.36	putative C4-dicarboxylate anaerobic carrier Dcu family	S	0.046
CD630_18470	0.36	putative conjugative transposon protein Tn1549-like CTn5-Orf3	-	0.001
CD630_31150 (bglA4)	0.37	6-phospho-beta-glucosidase	G	0.003
CD630_13610	0.37	putative phage protein	-	0.002
CD630_32570	0.37	putative polysaccharide deacetylase	G	0.016
CD630_30340	0.38	Transcriptional regulator TrmB family	K	0.013
CD630_27491	0.38	Autoinducer prepeptide	-	2.5E-05
CD630_25150	0.38	putative L-aspartate-beta-decarboxylase	E	0.043
CD630_27640	0.38	putative hydrolase HAD superfamily IIB subfamily	R	0.003
CD630_26710	0.38	ABC-type transport system ATP-binding protein putative oligopeptide transport system	EP	0.028
CD630_33440	0.39	putative cell-division FtsK/SpoIIIE-family protein Tn916-like CTn6-Orf22	D	0.007
CD630_09340	0.39	putative phage protein	-	0.007
CD630_35370 (phnH)	0.39	putative phosphonate metabolism protein	P	0.007
CD630_31370 (bglF5)	0.39	PTS system beta-glucoside-specific IIAB component	G	0.022
CD630_30360	0.39	Transporter Major Facilitator Superfamily (MFS)	E	0.022
CD630_08450	0.40	putative nuclease	-	0.034
CD630_22010	0.40	Transporter Major Facilitator Superfamily (MFS)	G	0.045
CD630_25090	0.40	putative glycoside hydrolase family 4	G	0.016
CD630_23710 (nadB)	0.40	L-aspartate oxidase (Quinolinate synthetase B)	H	4.3E-04
CD630_23720 (nadA)	0.40	Quinolinate synthetase A	H	0.003
CD630_13640	0.40	putative phage XkdM-like protein	-	0.001
CD630_19180 (eutK)	0.40	Ethanolamine carboxysome strutural protein	QC	0.039
CD630_11540	0.40	Transcriptional regulator PadR family	K	0.025
CD630_03270 (cbiO)	0.40	ABC-type transport system cobalt-specific ATP-binding protein	P	0.003
CD630_05790	0.40	Transcriptional regulator TetR family	K	0.027
CD630_30990	0.40	putative amidohydrolase M20D family	R	0.031

CD630_03260 (cbiQ1)	0.41	ABC-type transport system cobalt-specific permease	P	0.002
CD630_18860	0.41	Transcriptional regulator PadR family	K	0.014
CD630_30720	0.41	conserved hypothetical protein	S	0.019
CD630_03140	0.41	putative membrane protein	S	0.018
CD630_26860	0.41	putative membrane protein	-	0.009
CD630_24620 (grpE)	0.41	HSP-70 cofactor	O	4.5E-04
CD630_29420	0.41	putative phage resolvase/integrase	-	1.4E-04
CD630_11261	0.42	Transcriptional regulator HTH-type	K	0.004
CD630_29400	0.42	putative phage protein	-	0.043
CD630_17540	0.42	ABC-type transport system multidrug-family permease	-	0.018
CD630_03240 (cbiM)	0.42	Cobalamin biosynthesis protein	P	0.009
CD630_23700 (nadC)	0.42	Nicotinate-nucleotide pyrophosphorylase	H	0.002
CD630_06140	0.43	conserved hypothetical protein	-	0.027
CD630_26700	0.43	ABC-type transport system ATP-binding protein putative oligopeptide transport system	E	0.025
CD630_01060 (cwlD)	0.43	Germination-specific N-acetylmuramoyl-L-alanineamidase Autolysin	M	0.009
CD630_26650	0.43	Transcriptional regulator AraC family	K	0.014
CD630_03901	0.43	conserved hypothetical protein	-	0.021
CD630_25160 (ansB)	0.44	L-asparaginase	EJ	0.034
CD630_29360	0.44	putative phage protein	-	0.007
CD630_05670	0.44	uncharacterised protein DegV family	S	0.033
CD630_01250	0.44	putative cell wall endopeptidase	M	0.046
CD630_04090	0.44	putative replication initiation protein Tn1549-like CTn2-Orf2	-	0.029
CD630_29440	0.44	putative phage essential recombination functionprotein	-	0.040
CD630_12700	0.45	Two-component sensor histidine kinase	T	0.001
CD630_30260	0.45	conserved hypothetical protein	TK	0.005
CD630_11710 (etfB4)	0.45	Electron transfer flavoprotein subunit alpha	C	0.008
CD630_29430	0.45	putative phage replication protein	L	0.010
CD630_09170	0.45	putative phage recombination protein Bet	-	6.1E-05
CD630_06240	0.45	putative transcriptional regulator activator	S	0.003
CD630_29710 (bioY)	0.45	Biotin synthase	R	0.012
CD630_01930 (groS)	0.46	chaperonin	O	0.003
CD630_20451	0.46	conserved hypothetical protein	-	1.9E-04
CD630_13450	0.46	Transcriptional regulator PadR family	K	0.002
CD630_26870	0.46	conserved hypothetical protein	-	0.007
CD630_29490	0.46	Transcriptional regulator Phage-type	-	0.005
CD630_05780	0.47	Transporter Major Facilitator Superfamily (MFS)	-	0.004
CD630_18270	0.47	Transcriptional regulator MarR family	K	0.033
CD630_30250	0.47	putative ferredoxin iron-sulphur domain-containing protein	C	0.007
CD630_32090	0.47	Transcriptional regulator PadR family	K	0.006
CD630_00470 (ispD)	0.48	2-C-methyl-D-erythritol 4-phosphatecytidylyltransferase	I	0.029
CD630_21430	0.48	Transcriptional regulator HTH-type	-	0.020
CD630_24610 (dnaK)	0.48	Chaperone protein dnaK (Heat shock protein 70)	O	0.009
CD630_25110	0.48	Transcription antiterminator PTS operon regulator	K	0.026
CD630_32100	0.48	conserved hypothetical protein	E	0.030
CD630_32620 (pstA)	0.48	ABC-type transport system phosphate-specific permease	P	0.045
CD630_25100	0.48	PTS system glucose-like IIBC component	G	0.043
CD630_27880	0.48	putative membrane protein GtrA family	S	0.004
CD630_13720	0.48	putative phage XkdT-like protein	-	2.2E-06
CD630_19210	0.48	putative ethanolamine utilization protein	-	0.017
CD630_10280	0.48	putative signaling protein	TK	0.030
CD630_21510	0.48	putative membrane protein DUF819 family	S	0.006
CD630_23300 (xpt)	0.49	Xanthine phosphoribosyltransferase (XPRTase)	F	0.036
CD630_15800 (hom2)	0.49	Homoserine dehydrogenase	E	0.010
CD630_24630 (hrcA)	0.49	Transcriptional regulator Heat-inducibler epressor	K	0.013
CD630_32220 (sdaB)	0.49	L-serine dehydratase	E	0.005
CD630_27500 (agrB)	0.49	Accessory gene regulator	OTK	0.001
CD630_32600 (phoU)	0.49	Phosphate uptake regulator	P	0.001
CD630_13460	0.50	conserved hypothetical protein DUF1700	S	0.002

CD630_26691	0.50	putative Na(+)/H(+) antiporter	P	0.009
CD630_29330	0.50	Hypothetical protein	J	0.010
CD630_03250 (cbiN)	0.50	ABC-type transport system cobalt-specific extracellular solute-binding protein	P	0.031

[a] Gene accession numbers are given for strain 630.

[b] Ratio of no LL-37/with LL-37 as determined by RNA sequencing analysis of 630Δ*erm* grown in BHIS alone or BHIS supplemented with 2 µg/ml LL-37 as described in Methods. Genes are included in this list if they had ≥ 2-fold increase or decrease in expression and a *P* value ≤ 0.05 by Student's two-tailed t-test.

[c] COG (classification of gene) designations are based on the 2014 COG database. Letter designations correspond to the categories listed in the table below.

[d] *P*-values determined by Student's two-tailed *t*-test.

A	RNA processing and modification
B	Chromatin Structure and dynamics
C	Energy production and conversion
D	Cell cycle control and mitosis
E	Amino Acid metabolism and transport
F	Nucleotide metabolism and transport
G	Carbohydrate metabolism and transport
H	Coenzyme metabolism
I	Lipid metabolism
J	Translation
K	Transcription
L	Replication and repair
M	Cell wall/membrane/envelop biogenesis
N	Cell motility
O	Post-translational modification, protein turnover, chaperone functions
P	Inorganic ion transport and metabolism
Q	Secondary Structure
T	Signal Transduction
U	Intracellular trafficking and secretion
Y	Nuclear structure
Z	Cytoskeleton
R	General Functional Prediction only
S	Function Unknown
-	Unassigned

Table S2. LL-37 MIC and MBC values for *clnR* and *clnAB* mutants

	MIC[a]	MBC[b]
630Δ*erm*	15	20
clnR	15	30
clnAB	15	20

[a] Minimum inhibitory concentration of LL-37 (μg/ml).

[b] Minimum bactericidal concentration of LL-37 (μg/ml).

Table S3. MIC values for *clnR* and *clnAB* mutants in various antimicrobials

	Van[a]	Amp	PmB	Nis
630Δ*erm*	1	4	500	360
clnR	1	4	500	360
clnAB	1	4	500	360

[a] Values shown are µg/ml. Van: vancomycin, Amp: ampicillin, PmB: polymyxin B, Nis: nisin.

Table S4. Genes differentially expressed in a *clnR* mutant in the presence/absence of LL-37

Gene[a]	*clnR*/ WT[b]	Product	COG[c]	*p*[d]
ClnR activates (without LL-37)				
CD630_16632	0.22	conserved hypothetical protein	-	0.003
CD630_23030	0.22	Fragment of putative phage transcriptional repressor	-	0.003
CD630_35370 (phnH)	0.22	putative phosphonate metabolism protein	P	9.0E-05
CD630_19280	0.22	putative membrane protein	D	9.0E-05
CD630_29341	0.23	putative phage protein	-	0.009
CD630_01631	0.24	conserved hypothetical protein	-	0.013
CD630_13700	0.25	putative phage XkdS-like protein	-	0.018
CD630_32770	0.26	PTS system mannose/fructose/sorbose IIC component	G	0.004
CD630_29330	0.32	Hypothetical protein	J	0.005
CD630_04090	0.33	putative replication initiation protein Tn1549-like CTn2-Orf2	-	0.032
CD630_00410	0.33	PTS system galactitol-specific IIA component	GT	2.7E-04
CD630_11980 (spoIIIAG)	0.33	Stage III sporulation protein AG	-	0.001
CD630_07400	0.35	putative pyridoxal phosphate-dependent aminotransferase	E	0.008
CD630_07420	0.37	putative ethanolamine transporter	E	0.003
CD630_36361	0.38	conserved hypothetical protein	-	0.015
CD630_29370	0.39	putative phage protein	-	0.011
CD630_01350	0.41	PTS system lactose/cellobiose-family IIA component	G	0.032
CD630_23260	0.41	PTS system fructose/mannitol family IIBc omponent	G	0.001
CD630_24170	0.42	PTS system Sorbitol-like IIB component	G	0.003
CD630_26870	0.43	conserved hypothetical protein	-	0.002
CD630_01981	0.43	conserved hypothetical protein	-	0.042
CD630_02850	0.44	PTS system mannose/fructose/sorbose IIB component	G	0.001
CD630_29490	0.44	Transcriptional regulator Phage-type	-	3.1E-04
CD630_13630	0.45	putative phage XkdK-like protein	-	0.016
CD630_29360	0.45	putative phage protein	-	0.009
CD630_16490	0.45	ABC-type transport system iron-family ATP-binding protein	P	0.022
CD630_21970	0.46	putative ferredoxin/flavodoxin oxidoreductase	C	0.017
CD630_12332	0.46	conserved hypothetical protein	-	0.034
CD630_26570	0.49	conserved hypothetical protein	-	0.006
CD630_04200	0.49	putative cell surface protein Tn1549-like CTn2-Orf15	R	0.006
CD630_21021	0.49	conserved hypothetical protein	-	0.006
CD630_04880 (orr)	0.50	putative small multidrug resistance SugE-like protein	P	0.041
ClnR represses (without LL-37)				
CD630_16180 (clnA)	57.26	ABC-type transport system multidrug-family ATP-binding protein	V	0.021
CD630_16190 (clnB)	53.69	ABC-type transport system multidrug-family permease	-	0.001
CD630_12400 (vanZ)	21.50	Teicoplanin resistance protein	V	0.017
CD630_33370	3.37	putative membrane protein Tn916-like CTn6-Orf14	B	0.006
CD630_07970	2.96	putative pyruvate carboxyltransferase	E	0.014
CD630_16310 (sodA)	2.70	spore coat protein-superoxide dismutase	P	4.3E-04
CD630_01820	2.47	conserved hypothetical protein	-	0.017
CD630_18840	2.43	conserved hypothetical protein	-	0.042
CD630_22180 (int2)	2.43	Fragment of putative integrase	-	0.042
CD630_03710	2.43	putative conjugative transposon protein Tn916-like CTn1-Orf16	-	0.042
CD630_15111	2.26	conserved hypothetical protein	-	0.037
CD630_16680	2.13	putative membrane protein	-	3.4E-06
CD630_27340	2.09	putative Na+/H+ antiporter NhaC family	C	0.001
CD630_12450	2.08	conserved hypothetical protein	-	0.032
ClnR activates (with LL-37)				
CD630_23540 (grdE)	0.06	Betaine reductase component B subunit	-	0.001
CD630_23520 (grdA)	0.07	Glycine reductase complex selenoprotein A (selenocysteine)	-	1.5E-04
CD630_02850	0.07	PTS system mannose/fructose/sorbose IIB component	G	0.002
CD630_02840	0.08	PTS system mannose/fructose/sorbose IIA component	G	0.005
CD630_23550 (trxA2)	0.09	Thioredoxin 2	O	0.005
CD630_23260	0.09	PTS system fructose/mannitol family IIB component	G	0.008
CD630_02880	0.10	PTS system mannose/fructose/sorbose IIC component	G	3.3E-04
CD630_16080	0.13	ABC-type transport system multidrug-family permease	-	0.003

CD630_02890	0.13	PTS system mannose/fructose/sorbose IID component	G	0.002
CD630_02860	0.13	PTS system mannose/fructose/sorbose IIA component	G	0.014
CD630_16060	0.13	Transcriptional regulator GntR family	K	0.001
CD630_16100	0.13	conserved hypothetical protein	-	0.001
CD630_16110	0.14	conserved hypothetical protein	-	0.003
CD630_02870	0.14	PTS system mannose/fructose/sorbose IIB component	G	0.002
CD630_23570 (grdX)	0.14	putative glycine reductase complex component	-	0.017
CD630_16090	0.15	conserved hypothetical protein	-	0.004
CD630_23560 (trxB3)	0.15	Thioredoxin reductase 3	O	0.018
CD630_23490 (grdC)	0.16	Glycine reductase complex component C	I	0.007
CD630_16070	0.16	ABC-type transport system multidrug-family ATP-binding protein	V	0.003
CD630_20751	0.18	conserved hypothetical protein	-	0.002
CD630_29290	0.18	putative phage protein	-	0.004
CD630_04200	0.20	putative cell surface protein Tn1549-like CTn2-Orf15	R	0.001
CD630_23240	0.21	putative sugar-phosphate dehydrogenase	ER	0.050
CD630_33740	0.21	putative conjugative transposon protein Tn916-like CTn7-Orf8	-	6.2E-05
CD630_23030	0.21	Fragment of putative phage transcriptional repressor	-	0.006
CD630_26000 (cstA)	0.22	Carbon starvation protein	T	1.4E-05
CD630_23810 (iorA)	0.22	Indole pyruvate ferredoxin/flavodoxin oxidoreductase	C	8.8E-05
CD630_04670	0.24	putative hydrolase HAD superfamily subfamily IIB	HR	0.001
CD630_23800 (iorB)	0.24	Indole pyruvate ferredoxin/flavodoxin oxidoreductase	C	4.0E-04
CD630_25990	0.24	putative transcriptional regulator	J	0.040
CD630_02900	0.25	conserved hypothetical protein	-	0.002
CD630_23820	0.26	putative pyridoxal phosphate-dependent transferase	E	0.002
CD630_29410	0.27	putative phage single-strand DNA-binding protein	L	0.037
CD630_16180 (clnA)	0.27	ABC-type transport system multidrug-family ATP-binding protein	V	0.005
CD630_33750 (mgtC)	0.27	Magnesium-transporting ATPase protein Tn916-like CTn7-Orf10	S	0.002
CD630_16190 (clnB)	0.27	ABC-type transport system multidrug-family permease	-	0.011
CD630_33730 (mgtA)	0.27	Magnesium-transporting ATPase P-type Tn916-like CTn7-Orf7	P	0.001
CD630_00330	0.28	putative glycoside hydrolase	G	0.048
CD630_07400	0.28	putative pyridoxal phosphate-dependent aminotransferase	E	0.045
CD630_05490	0.28	conserved hypothetical protein	-	0.001
CD630_33741	0.29	putative conjugative transposon protein Tn916-like CTn7-Orf9	-	0.002
CD630_28130 (garR)	0.30	Tartronate semialdehyde reductase	I	0.042
CD630_29370	0.31	putative phage protein	-	0.001
CD630_00220 (fusA1)	0.31	Elongation factor G	J	0.013
CD630_18570	0.31	putative cell wall hydrolase Tn1549-like CTn5-Orf13	M	0.038
CD630_18880 (rsiU)	0.32	Extracytoplasmic function (ECF) anti-sigma factor	-	0.004
CD630_05000	0.32	putative antirestriction protein Tn5397 CTn3-Orf18	V	0.006
CD630_17970	0.34	Coenzyme A disulfide reductase	R	0.037
CD630_01350	0.34	PTS system lactose/cellobiose-family IIA component	G	0.048
CD630_04960	0.34	putative conjugative transposon protein DUF961 family Tn5397 CTn3-Orf23	-	0.007
CD630_23480 (grdD)	0.34	Glycine reductase complex component C	I	0.015
CD630_04980	0.34	putative cell-division FtsK/SpoIIIE-family protein Tn5397 CTn3-Orf21	D	0.001
CD630_17000 (ribD)	0.35	Riboflavin biosynthesis protein	H	0.014
CD630_28620	0.36	putative peptidase M19 family	E	0.016
CD630_18560	0.36	putative hydrolase Tn1549-like CTn5-Orf12	U	0.002
CD630_15970	0.36	conserved hypothetical protein	-	3.0E-04
CD630_28240	0.36	Fragment of putative membrane protein	-	0.020
CD630_33721	0.36	putative conjugative transposon protein Tn916-like CTn7-Orf5	-	0.004
CD630_04970	0.36	putative conjugative transposon protein DUF961 family Tn5397 CTn3-Orf22	-	0.008
CD630_05103	0.37	putative conjugative transposon proteinTn5397%2CCTn3-Orf4	-	0.013
CD630_04990	0.38	putative replication initiation factor Tn5397 CTn3-Orf20	L	0.001
CD630_22820	0.39	PTS system fructose/mannitol family IIA component	GT	0.024
CD630_04991	0.39	putative conjugative transposon protein Tn5397 CTn3-Orf19	-	0.005
CD630_02910	0.40	putative peptidase M20A family	E	0.009
CD630_16980 (ribBA)	0.40	GTP cyclohydrolase-2 Riboflavin biosynthesis protein	H	0.012
CD630_05100	0.40	putative RNA polymerase sigma factor Tn5397 CTn3-Orf7	K	0.001
CD630_17960	0.40	putative nitrite and sulfite reductase subunit	C	0.044

CD630_05102	0.40	Fragment of putative conjugative transposon protein Tn5397 CTn3-Orf5	-	0.002
CD630_05060	0.41	Reverse transcriptase/maturase/endonuclease Group II intron	V	0.001
CD630_33722	0.41	putative conjugative transposon protein Tn916-like CTn7-Orf6	-	0.002
CD630_23790 (buk2)	0.41	Butyrate kinase	C	2.5E-04
CD630_18870 (csfU)	0.41	Extracytoplasmic function (ECF) sigma factor	K	0.001
CD630_28280	0.41	putative pyridoxal phosphate-dependent transferase	E	0.029
CD630_05101	0.41	putative conjugative transposon protein Tn5397 CTn3-Orf8	-	1.6E-04
CD630_07390	0.42	putative exported protein	-	1.0E-04
CD630_15431	0.43	conserved hypothetical protein	-	0.015
CD630_20750 (pbuX)	0.43	putative xanthine permease	F	0.001
CD630_28110	0.43	conserved hypothetical protein	S	0.010
CD630_08650	0.44	putative ADP-ribose binding protein	R	0.013
CD630_06790	0.45	conserved hypothetical protein	R	0.018
CD630_04890	0.45	putative phosphoribosylaminoimidazole-succinocarboxamide synthetase	F	0.001
CD630_23590	0.46	putative hydrolase HAD superfamily subfamily IIB	R	2.9E-04
CD630_28590	0.46	putative D-aminoacylase	Q	0.018
CD630_18890	0.47	ABC-type transport system multidrug-family ATP-binding protein	V	0.004
CD630_06770 (csfT)	0.47	Extracytoplasmic function (ECF) sigma factor	K	0.001
CD630_21600	0.47	putative membrane protein	V	0.019
CD630_16220	0.47	peptidase propeptide and ypeb domain protein	S	0.034
CD630_24020	0.47	putative cell wall hydrolase phosphatase-associated protein	M	0.008
CD630_18900	0.47	ABC-type transport system multidrug-family permease	O	0.007
CD630_04400 (cwp27)	0.47	putative cell wall binding protein	-	8.9E-05
CD630_29490	0.48	Transcriptional regulator Phage-type	-	0.004
CD630_27080 (aroE2)	0.48	Shikimate dehydrogenase 2	E	8.6E-05
CD630_09370	0.48	putative phage anti-repressor	K	0.012
CD630_25670	0.49	PTS system mannose-specfic IIB component	G	0.009
CD630_05020	0.49	putative ATPase Tn5397 CTn3-Orf16	L	0.002
CD630_29300	0.49	putative phage anti-repressor protein	K	0.012
CD630_27840 (cwp6)	0.49	putative N-acetylmuramoyl-L-alanineamidase autolysin	M	0.002
CD630_01420	0.49	putative RNA-binding protein	J	0.028
CD630_22490	0.50	putative ATPase	R	0.001
CD630_21910	0.50	putative phosphoesterase	ER	0.008
CD630_23090	0.50	conserved hypothetical protein	-	0.039
ClnR represses (with LL-37)				
CD630_26140	7.62	uncharacterised protein DegV family	S	0.017
CD630_06680	4.19	Two-component response regulator	K	0.014
CD630_06690	4.01	Two-component sensor histidine kinase	T	0.011
CD630_27491 (agrD)	3.46	Autoinducer prepeptide	-	0.002
CD630_11920	3.10	Stage III sporulation protein AA	S	0.039
CD630_24291	3.10	putative 4Fe-4S ferredoxin iron-sulfur binding domain protein	C	0.039
CD630_28370	2.74	putative membrane protein	S	0.046
CD630_04370	2.74	Fragment of integrase Tn1549-like CTn2	-	0.046
CD630_09780	2.52	Transcriptional regulator beta-lactams repressor Phage-type	-	0.011
CD630_22290	2.49	putative membrane protein	S	0.049
CD630_10950	2.48	ABC-type transport system multidrug-family permease Tn1549-like CTn4-Orf30	-	0.030
CD630_25150	2.45	putative L-aspartate-beta-decarboxylase	E	0.039
CD630_04640	2.45	putative beta-lactamase-like hydrolase	R	0.018
CD630_26640 (murE)	2.42	UDP-N-acetylmuramyl-tripeptide synthetase	M	0.009
CD630_09950 (serA)	2.40	putative D-3-phosphoglycerate dehydrogenase	HE	0.019
CD630_09960	2.34	conserved hypothetical protein	S	0.015
CD630_21510	2.34	putative membrane protein DUF819 family	S	0.007
CD630_33360	2.32	putative cell wall hydrolase Tn916-like CTn6-Orf13	M	5.0E-04
CD630_01260 (spoIIID)	2.29	Stage III sporulation protein D	-	0.002
CD630_30730	2.24	putative membrane protein	-	0.008
CD630_10970	2.22	ABC-type transport system multidrug-family ATP-binding protein Tn1549-like CTn4-Orf28	V	0.008
CD630_25290	2.18	conserved hypothetical protein	-	0.021
CD630_21710	2.18	Fragment of putative sodium:dicarboxylate symporter	-	0.036

CD630_08220	2.11	ABC-type transport system multidrug-family ATP-binding protein	V	0.016
CD630_26700	2.10	ABC-type transport system ATP-binding protein putative oligopeptide transport system	E	0.031
CD630_25940 (uraA)	2.10	ABC-type transport system uracil-specific permease	F	4.5E-04
CD630_08230	2.05	ABC-type transport system multidrug-family permease	-	0.042
CD630_30230	2.03	conserved hypothetical protein	-	0.034
CD630_23750	2.03	uncharacterised protein	-	0.022

[a] Gene accession numbers are given for strain 630. Gene *CD630_20072 (ermB*) is excluded from these tables because it is an artifact of the insertional disruption used to generate the *clnR* mutant.

[b] Ratio of expression in *clnR* mutant/630Δ*erm*, as determined by RNA sequencing analysis of 630Δ*erm* and *clnR* grown in BHIS alone or BHIS supplemented with 2 μg/ml LL-37 as described in Methods. Fold-change represents the ratio of expression in *clnR*/630Δ*erm* in the condition indicated (with or without LL-37). Genes are included in this list if they had ≥ 2-fold increase or decrease in expression and a *p* value ≤ 0.05 by Student's two-tailed *t*-test.

[c] COG designations are based on the 2014 COG database. Letter designations correspond to the categories listed in the table associated with Table S1.

[d] *p* values determined by Student's two-tailed *t*-test.

Table S5. Genes regulated by both ClnR and LL-37

Gene[a]	**Fold change in LL-37**[b]	***clnR/*WT**[c]	***clnR*/WT (+ LL-37)**[d]	**Product**
CD630_01631	0.22	0.24	1.63	spore coat protein-superoxide dismutase
CD630_02910	3.25	1.32	0.40	putative peptidase M20A family
CD630_04090	0.44	0.33	0.87	putative replication initiation protein Tn1549-like CTn2-Orf2
CD630_04670	3.43	1.44	0.24	putative hydrolase HAD superfamily subfamily IIB
CD630_04890	2.26	1.04	0.45	putative phosphoribosylaminoimidazole-succinocaroxamide synthetase
CD630_04960	4.13	1.19	0.34	putative conjugative transposon protein DUF961 family Tn5397 CTn3-Orf23
CD630_04970	3.86	0.93	0.36	putative conjugative transposon protein DUF961 family Tn5397 CTn3-Orf22
CD630_04980	4.13	0.93	0.34	putative cell-division FtsK/SpoIIIE-family protein Tn5397 CTn3-Orf21
CD630_05000	3.61	1.08	0.32	putative antirestriction protein Tn5397 CTn3-Orf18
CD630_05060	3.54	0.97	0.41	Reverse transcriptase/maturase/endonuclease Group II intron
CD630_05100	3.07	0.79	0.40	putative RNA polymerase sigma factor Tn5397 CTn3-Orf7
CD630_05101	3.31	1.05	0.41	putative conjugative transposon protein Tn5397 CTn3-Orf8
CD630_05102	3.35	0.89	0.40	Fragment of putative conjugative transposon protein Tn5397 CTn3-Orf5
CD630_05103	3.27	1.06	0.37	putative conjugative transposon protein Tn5397 CTn3-Orf4
CD630_05490	4.74	1.15	0.28	conserved hypothetical protein
CD630_05500	5.52	0.81	0.53	putative membrane protein
CD630_09950 (serA)	0.23	1.14	2.40	putative D-3-phosphoglycerate dehydrogenase
CD630_09960	0.24	1.19	2.34	conserved hypothetical protein
CD630_12400 (vanZ)	28.43	21.50	0.74	Teicoplanin resistance protein
CD630_16070	30.25	1.02	0.16	ABC-type transport system multidrug-family ATP-binding protein
CD630_16090	30.62	1.15	0.15	conserved hypothetical protein
CD630_16100	64.45	2.17	0.13	conserved hypothetical protein
CD630_16110	34.77	1.22	0.14	conserved hypothetical protein
CD630_16180 (clnA)	202.99	57.26	0.27	ABC-type transport system multidrug-family ATP-binding protein
CD630_16190 (clnB)	192.16	53.69	0.27	ABC-type transport system multidrug-family permease
CD630_16310 (sodA)	2.59	2.70	0.88	spore coat protein-superoxide dismutase
CD630_16632	0.32	0.22	3.61	conserved hypothetical protein
CD630_17000 (ribD)	3.65	1.11	0.35	Riboflavin biosynthesis protein
CD630_18870 (csfU)	5.34	1.24	0.41	Extracytoplasmic function (ECF) sigma factor
CD630_18880 (rsiU)	3.69	0.95	0.32	Extracytoplasmic function (ECF) anti-sigma factor
CD630_18890	4.54	1.40	0.47	ABC-type transport system multidrug-family ATP-binding protein
CD630_18900	3.60	1.17	0.47	ABC-type transport system multidrug-family permease
CD630_20140 (ilvD)	2.90	1.02	0.53	Dihydroxy-acid dehydratase
CD630_20751	2.21	0.51	0.18	conserved hypothetical protein
CD630_21510	0.48	1.11	2.34	putative membrane protein DUF819 family
CD630_21710	0.34	1.05	2.18	Fragment of putative sodium:dicarboxylate symporter
CD630_22290	0.51	1.02	2.49	putative membrane protein
CD630_23090	2.29	1.03	0.50	conserved hypothetical protein
CD630_23790 (buk2)	3.13	0.81	0.41	Butyrate kinase
CD630_23800 (iorB)	10.81	0.64	0.24	Indole pyruvate ferredoxin/flavodoxin oxidoreductase
CD630_23810 (iorA)	13.66	0.62	0.22	Indole pyruvate ferredoxin/flavodoxin oxidoreductase
CD630_25150	0.38	1.02	2.45	putative L-aspartate-beta-decarboxylase

CD630_26140	0.12	1.18	7.62	uncharacterised protein DegV family
CD630_26640 (murE)	0.35	1.08	2.42	UDP-N-acetylmuramyl-tripeptide synthetase
CD630_26700	0.43	0.91	2.10	ABC-type transport system ATP-binding protein putative oligopeptide transport system
CD630_26870	0.46	0.43	0.79	conserved hypothetical protein
CD630_27491	0.38	0.92	3.46	Autoinducer prepeptide
CD630_27840 (cwp6)	2.30	0.97	0.49	putative N-acetylmuramoyl-L-alanineamidase autolysin
CD630_29330	0.50	0.32	1.45	Hypothetical protein
CD630_29341	0.29	0.23	1.34	putative phage protein
CD630_29360	0.44	0.45	0.57	putative phage protein
CD630_29490	0.46	0.44	0.48	Transcriptional regulator Phage-type
CD630_33730 (mgtA)	3.39	0.78	0.27	Magnesium-transporting ATPase P-type Tn916-like CTn7-Orf7
CD630_33740	3.92	0.76	0.21	putative conjugative transposon protein Tn916-like CTn7-Orf8
CD630_33750 (mgtC)	2.96	0.57	0.27	Magnesium-transporting ATPase protein Tn916-like CTn7-Orf10
CD630_35370 (phnH)	0.39	0.22	1.96	putative phosphonate metabolism protein

[a] Gene accession numbers are given for strain 630. Genes are included in this list if they had ≥ 2-fold increase or decrease in expression and a *p* value ≤ 0.05 by Student's two-tailed *t*-test in both 630Δ*erm* in LL-37 and the *clnR* mutant (either with or without LL-37).

[b] Ratio of no LL-37/with LL-37 as determined by RNA sequencing analysis of 630Δ*erm* grown in BHIS alone or BHIS supplemented with 2 μg/ml LL-37 as described in Methods.

[c] Ratio of expression in *clnR* mutant/expression in 630Δ*erm* as determined by RNA sequencing analysis of strains grown in BHIS alone as described in Methods.

[d] Ratio of expression in *clnR* mutant/expression in 630Δ*erm* as determined by RNA sequencing analysis of strains grown in BHIS supplemented with 2 μg/ml LL-37 as described in Methods.

Table S6. Relative expression of selected RNA-seq transcripts in *clnR* and *clnAB* mutants

	BHIS					+ LL-37 (2 µg/ml)				
Gene	630Δ*erm*	*clnR*	*clnAB*	*clnR* Tn::*clnRAB*	*clnAB* Tn::*clnRAB*	630Δ*erm*	*clnR*	*clnAB*	*clnR* Tn::*clnRAB*	*clnAB* Tn::*clnRAB*
cdd4 (CD630_06670)	1.0 ± 0.0[a]	0.9 ± 0.1	1.1 ± 0.2	0.9 ± 0.2	1.0 ± 0.2	7.1*± 2.4	**915.0***± 30.5	**1672.6*** ± 357	57.2*± 16.1	314.8*± 98.0
vanZ1 (CD630_12400)	1.0 ± 0.0	**25.2** ± 5.5	0.8 ± 0.1	0.8 ± 0.1	0.6 ± 0.0	36.9*± 6.0	**13.4** ± 5.8	**0.9** ± 0.2	**81.5*** ± 7.5	**0.6** ± 0.1
cstA (CD630_26000)	1.0 ± 0.0	0.9 ± 0.2	1.2 ± 0.1	0.6 ± 0.1	0.8 ± 0.2	6.7*± 1.5	2.3 ± 0.5	2.9 ± 1.2	36.3 ± 21.3	1.3 ± 0.2
sigU (csfU; CD630_18870)	1.0 ± 0.0	0.5 ± 0.2	1.3 ± 0.3	0.6 ± 0.1	0.7 ± 0.1	10.5 ± 6.8	2.0 ± 0.6	3.1 ± 1.4	**25.6***± 1.9	0.8 ± 0.1
sigT (csfT; CD630_06770)	1.0 ± 0.0	0.9 ± 0.1	1.0 ± 0.2	1.1 ± 0.1	1.1 ± 0.1	3.6*± 0.1	2.3 ± 1.1	1.2 ± 0.1	**25.3***± 1.7	1.2 ± 0.2
grdA (CD630_23520)	1.0 ± 0.0	0.9 ± 0.1	1.0 ± 0.0	0.9 ± 0.1	1.3 ± 0.2	16.5 ± 10.5	1.4 ± 0.1	1.9* ± 0.1	**1649.2** ± 814.6	1.6 ± 0.2
mtlA (CD630_23340)	1.0 ± 0.0	0.9 ± 0.4	3.3 ± 2.1	0.6 ± 0.2	0.5 ± 0.1	1.0 ± 0.3	1.2 ± 0.7	5.5 ± 4.3	0.6 ± 0.2	0.7 ± 0.4
iorA (CD630_23810)	1.0 ± 0.0	**0.5** ± 0.1	0.7 ± 0.1	0.7 ± 0.0	1.1 ± 0.2	16.8 ± 8.4	2.1*± 0.4	20.5 ± 7.3	**112.4***± 19.9	2.8*± 0.3
CD630_02840	1.0 ± 0.0	1.2 ± 0.1	1.1 ± 0.1	1.1 ± 0.2	1.3 ± 0.2	29.3 ± 18.8	2.2 ± 0.5	2.1* ± 0.2	602.6 ± 455.6	2.8*± 0.1

[a] Relative expression levels were determined by qRT-PCR and are normalized to 630Δ*erm* in BHIS as described in methods. Values shown are the mean of at least 3 biological replicates ± standard error of the mean. Data were analyzed by one-way ANOVA and Dunnett' s multiple comparisons test for comparisons to 630Δ*erm* in the same condition or by Student's *t* test with Holm-Sidak correction for comparisons of the same strain with/without LL-37. Bolded values indicate an adjusted *p* value < 0.05 comparing to 630Δ*erm* in the same condition; * indicates an adjusted *p* value < 0.05 comparing the same strain with/without LL-37.

Table S7. Maximum doubling times for 630Δ*erm*, *clnR, clnAB, clnR* Tn::*clnRAB,* and *clnAB* Tn::*clnRAB* in minimal media supplemented with metabolites, with or without LL-37

		No LL-37	**LL-37[c]**
MM+[a]	**strain**	**Doubling time (min)[b]**	**Doubling time (min)[b]**
--	630Δ*erm*	73.2 ± 3.4	82.2 ± 5.1
	clnR	76.3 ± 2.6	74.1 ± 4.8
	clnAB	73.5 ± 2.3	77.1 ± 5.3
	clnR Tn::*clnRAB*	71.6 ± 2.5	[§]84.8 ± 4.5
	clnAB Tn::*clnRAB*	71.7 ± 2.0	76.4 ± 2.6
Glucose	630Δ*erm*	66.2 ± 3.7	67.7 ± 4.9
	clnR	68.4 ± 3.5	74.0 ± 1.7
	clnAB	*61.4 ± 3.3	62.1 ± 2.2
	clnR Tn::*clnRAB*	64.6 ± 3.7	76.4 ± 5.4
	clnAB Tn::*clnRAB*	63.6 ± 2.5	70.8 ± 4.8
Fructose	630Δ*erm*	64.8 ± 4.1	70.2 ± 3.9
	clnR	70.6 ± 1.7	72.4 ± 0.9
	clnAB	63.9 ± 3.5	65.1 ± 2.0
	clnR Tn::*clnRAB*	67.8 ± 2.5	80.4 ± 7.4
	clnAB Tn::*clnRAB*	67.2 ± 2.6	69.8 ± 2.5
Mannose	630Δ*erm*	71.0 ± 5.2	70.3 ± 5.5
	clnR	70.5 ± 2.9	78.4 ± 4.9
	clnAB	65.6 ± 3.7	66.8 ± 4.5
	clnR Tn::*clnRAB*	72.4 ± 4.6	80.4 ± 8.3
	clnAB Tn::*clnRAB*	68.9 ± 3.4	72.6 ± 3.1
Mannitol	630Δ*erm*	60.0 ± 2.1	69.9 ± 3.4
	clnR	63.7 ± 0.4	67.3 ± 1.5
	clnAB	60.1 ± 3.2	58.3 ± 5.5
	clnR Tn::*clnRAB*	64.5 ± 2.6	75.6 ± 5.3
	clnAB Tn::*clnRAB*	*62.4 ± 0.7	66.4 ± 1.8
NAG	630Δ*erm*	66.6 ± 2.7	[§]91.5 ± 5.7
	clnR	81.8 ± 1.5	86.6 ± 2.5
	clnAB	70.9 ± 0.8	[§]80.3 ± 1.0
	clnR Tn::*clnRAB*	73.6 ± 3.1	111.1 ± 16.5
	clnAB Tn::*clnRAB*	*72.4 ± 1.4	[§]83.6 ± 1.7
EA	630Δ*erm*	78.4 ± 4.0	90.7 ± 7.9
	clnR	*89.9 ± 3.2	84.9 ± 4.6
	clnAB	87.7 ± 7.0	79.6 ± 9.0
	clnR Tn::*clnRAB*	86.2 ± 4.7	93.4 ± 12.2
	clnAB Tn::*clnRAB*	85.9 ± 7.2	84.0 ± 6.7

[a] Strains were grown in MM with additional nutrients as listed: 30mM glucose, 30 mM fructose, 30 mM mannose, 30 mM N-acetylglucosamine (NAG), 30 mM mannitol, 30 mM ethanolamine (EA)

[b] Doubling time was calculated during the 2 hour period of maximal growth after the conclusion of peptide-fueled growth, where $t_d = \ln(2)/\mu$, where $\mu = (\ln(OD_{t2}) - \ln(OD_{t1}))/(t_2 - t_1)$[1, 2]. Values shown are the average of at least three independent experiments ± standard deviation.

[c] LL-37, 0.5 μg/ml

[§] To compare +/- LL-37 for each strain/substrate (across rows), data were analyzed by Student's *t* test ([§]indicates $p < 0.05$).

To compare the growth of strains in each condition (within boxes), data were analyzed by one-way ANOVA with Dunnett's test for multiple comparisons (indicates adjusted $p < 0.05$)

Table S8. Expression of toxin regulation-associated genes

Gene	**Fold-change in expression LL-37**[a, b]
sigD	0.95 ± 0.08
tcdR	1.47 ± 0.44
ilvC[c]	**2.21** ± 0.20
CD0341[d]	2.54 ± 0.59

[a] Fold-change determined by qRT-PCR and normalized to 630Δ*erm* grown in BHIS alone. Concentration of LL-37 = 2 µg/ml. Values are the mean of three replicates ± standard error of the mean.

[b] Bolded values indicate significant difference (*p* value < 0.05) from 630Δ*erm* grown in BHIS without LL-37 and analyzed by Student's two-tailed *t*-test.

[c] *ilvC* indicates CodY activity.

[d] *CD0341* indicates CcpA activity.

Table S9. Plasmids and Strains

Plasmid or Strain		Relevant genotype or features	Source, construction or reference
Strains			
E. coli			
	HB101	F^- *mcrB mrr hsdS20*(r_B^- m_B^-*) recA13 leuB6 ara-14 proA2 lacY1 galK2 xyl-5 mtl-1 rpsL20*	B. Dupuy
	MC101	HB101 pRK24	B. Dupuy
	MC135	HB101 pRK24 pMC123	(McBride and Sonenshein, 2011)
	MC881	HB101 pRK24 pMC616	
	MC932	HB101 pRK24 pMC645	
	MC1122	HB101 pRK24 pMC723	
B. subtilis	BS49	*Tn*916	
	MC951	BS49 *Tn*916::*CD1617-1619*	
C. difficile			
	630	Clinical isolate	[3]
	630Δ*erm*	Erm^S derivative of strain 630	N. Minton [4]
	R20291	Clinical isolate	[5]
	MC324	630Δ*erm* pMC123	(Edwards et al., 2014)
	MC885	630Δ*erm CD1617::ermB*	
	MC935	630Δ*erm CD1618::ermB*	
	MC950	MC885 *Tn*916::*CD1617-1619*	
	MC953	MC935 *Tn*916::*CD1617-1619*	
	MC1123	MC885 pMC123	
	MC1131	MC885 pMC723	
Plasmids	pRK24	Tra$^+$, Mob$^+$; *bla, tet*	[6]
	pCR2.1	*bla, kan*	Invitrogen
	pUC19	Cloning vector; *bla*	[7]
	pCE240	*C. difficile* TargeTron→ construct based on pJIR750ai (group II intron, *ermB::*RAM, *ltrA*); *catP*	C. Ellermeier; [8]
	pSMB47	Tn*916* integrational vector; CmR, ErmR	[9]
	pMC123	*E. coli-C. difficile* shuttle vector; *bla, catP*	
	pMC577	pCR2.1 with *clnR*-targeted intron	
	pMC602	pCE240 with *clnR*-targeted intron	
	pMC616	pMC123 with *clnR*-targeted intron (~nt 127, *ermB::*RAM *ltrA catP*	
	pMC643	pCE240 with *clnA*-targeted intron	
	pMC645	pMC123 with *clnA*-targeted intron (~nt 217, *ermB*::RAM *ltrA catP*	
	pMC649	pSMB47 Tn*916*::*CD1617-1619*	
	pMC723	pMC123 with P$_{clnR}$*::*His-*clnRAB*	

Table S10. Oligonucleotides

Primer	Sequence[a]	Purpose, source, or reference[b]
oMC44	CTAGCTGCTCCTATGTCTCACATC	*rpoC* (*CD0067*) qPCR [10]
oMC45	CCAGTCTCTCCTGGATCAACTA	*rpoC* (*CD0067*) qPCR [10]
oMC112	GGCAAATGTAAGATTTCGTACTCA	*tcdB* (*CD0660*) qPCR [11]
oMC113	TCGACTACAGTATTCTCTGAC	*tcdB* (*CD0660*) qPCR [11]
oMC152	GTTATGGAAGTCAAGGACATGCAC	*ilvC (CD1565*) qPCR [12]
oMC153	GCTTCTGCTACACTCTTAACTTCA	*ilvC (CD1565*) qPCR [12]
oMC178	CTTGAGTTAAATCTTGTGCAGTCA	*csfU (CD1887*) qPCR
oMC179	GGTGATAATAGTGAATGATGCTCGG	*csfU (CD1887*) qPCR
oMC189	TGCCTCTTGTAAAGAGTATAGCA	*sigD (CD0266*) qPCR [11]
oMC190	GCATCAATCAATCCAATGACTCCAC	*sigD (CD0266*) qPCR [11]
oMC242	TCCACAAGGAGCTGTATATGGT	*cdd4 (CD0667)* qPCR
oMC243	GTGGGTTTAGCAAGTCCAAGAA	*cdd4 (CD0667)* qPCR
oMC547	TGGATAGGTGGAGAAGTCAGT	*tcdA (CD0663*) qPCR [11]
oMC548	GCTGTAATGCTTCAGTGGTAGA	*tcdA (CD0663*) qPCR [11]
oMC683	GTATCTGACAACATCAATTGCCTAAA	*CD0341* qPCR [11]
oMC684	TCAGCTTGAGATTCAATTTCTTCATT	*CD0341* qPCR [11]
oMC815	TGGATTCTCTTAAGGAAGAACAATACTTTA	*sigT* (*CD0677*) qPCR [13]
oMC816	CCTTAACTTCATCTACTGAATAACCTTCA	*sigT* (*CD0677*) qPCR [13]
oMC1249	GTCGAGGATCCGATGACAAGTTATTGGAATACACAG	P*spo0A* amplification
oMC1290	GAATGGGAACTTGATAATAACAAACC	check *CD1617-1618* co-transcription; *clnR* (*CD1617*) qPCR
oMC1291	AAGTTCTGTTAGAGCCTTTTGC	check *CD1616-1617* co-transcription; *clnR* (*CD1617*) qPCR
oMC1292	AGGTGTAAACAAGAGTTATGGAAC	check *CD1618-1619* co-transcription; *clnA* (*CD1618*) qPCR
oMC1293	TCTATGGATGGTTTCATTCCATTTATC	check *CD1617-1618* co-transcription; *clnA* (*CD1618*) qPCR
oMC1294	AAGCAAGTGGAAGAATATTTATACCG	*clnB* (*CD1619*) qPCR
oMC1295	ACATTAAATAACCTTCATCCCCC	*clnB* (*CD1619*) qPCR
oMC1297	CACTGCAGTTTTATCCATTTTATAATTC	screening for Targetron insertion in *clnR*
oMC1310	AAAAGCTTTTGCAACCCACGTCGATCGTGAACCGCATCTTCTGGTGCGCCCAGATAGGGT	*clnR (CD1617)* intron retargeting
oMC1311	CAGATTGTACAAATGTGGTGATAACAGATAAGTCCTTCTGCTTAACTTACCTTTCTTTGT	*clnR (CD1617)* intron retargeting
oMC1312	CGCAAGTTTCTAATTTCGGTTTGCGGTCGATAGAGGAAAGTGTCT	*clnR (CD1617)* intron retargeting
oMC1319	AAAAGCTTTTGCAACCCACGTCGATCGTGAAAAAATAGTTTCAGTGCGCCCAGATAGGGT	*clnA (CD1618)* intron retargeting
oMC1320	CAGATTGTACAAATGTGGTGATAACAGATAAGTCGTTTCATATAACTTACCTTTCTTTGT	*clnA (CD1618)* intron retargeting
oMC1321	CGCAAGTTTCTAATTTCGGTTATTTTTCGATAGAGGAAAGTGTCT	*clnA (CD1618)* intron retargeting
oMC1383	GTAGAAGGAGCAGAGGTTGTTT	*grdA (CD2352*) qPCR
oMC1384	TCAGCAGCATCTTTAACTCTGT	*grdA (CD2352*) qPCR
oMC1393	TGAAACCATGAATCTTAGAAGCATAAAC	*vanZ (CD1240)* qPCR
oMC1394	CACATATATCCCAAATGGTACAAATATAGC	*vanZ (CD1240)* qPCR
oMC1410	GTGGGATCCGCTAAAACTTATTACAG	*clnA (CD1618*) cloning
oMC1416	GTGGGATCCAGAAGAACAGTTTAA	P*clnR* cloning
oMC1427	GTTTGGAAAGCCAATGCCAA	check *CD1616-1617* co-transcription
oMC1467	TAGCAGAAGATGCGGAAGTTAAT	*clnR (CD1617*) qPCR
oMC1473	GTTACAAATCTTCCTTTAGTTCTCTGAC	*clnR (CD1617*) qPCR
oMC1476	GCGCATGCATTACTCAAAAGATAGCT	*clnRAB* cloning
oMC1483	CTGGGTCAACACCACCTATAG	verify *clnA (CD1618)* disruption
oMC1493	GTTAGAAGAGCAAATGAGATGATTAAAAGC	*clnA (CD1618*) qPCR
oMC1614	GTGTACTCCACCAGCAAAGA	*cstA* (*CD2600*) qPCR
oMC1615	GCAGGGTTAGGTCCGATATTT	*cstA* (*CD2600*) qPCR
oMC1684	GCGGAATTCCTAAAAAGTAATTGACATATACTTTG	P*clnR* cloning
oMC1689	GTGGGATCCGGCGCCATGCATCACCATCACCATCACATGGAATGGGAACTTGATAATAAC	*clnR* cloning with His-tag

oMC1690	GTGGGCGCCGTTCATGCCTCCTTATTA	P*clnR* cloning
oMC1691	FAM-CTAAAAAGTAATTGACATATACTTTG	P*clnR* amplification with fluorescein
oMC1692	FAM-CATGCCTCCTTATTATATTATTG	P*clnR* amplification with fluorescein
oMC1700	FAM-AGTTTGTGCAGTTTCTGAA	P*iorA* amplification with fluorescein
oMC1701	FAM-ACTACAATTATTAAATTCATAGATG	P*iorA* amplification with fluorescein
oMC1702	FAM-CTCCAAAATACTACATAAATAA	P*mtlA* amplification with fluorescein
oMC1703	FAM-TATATCGATATGATTCCCTTTTG	P*mtlA* amplification with fluorescein
oMC1704	FAM-CAAATTAAAATAAAGCAATTTATA	P*CD1606* amplification with fluorescein
oMC1705	FAM-CTAGTGTATTAATACGATAGTAC	P*CD1606* amplification with fluorescein
oMC1706	FAM-TTGTTTAAGTATTAATTATGAGT	P*csfU* amplification with fluorescein
oMC1707	FAM-CGTCATTATATATAACGATTTATAC	P*csfU* amplification with fluorescein
oMC1710	FAM-ATGTTTCATCCCCTTTTTTAATC	P*cdd4/CD0668* amplification with fluorescein
oMC1711	FAM-CACCCTCCTTTAGTATACC	P*cdd4/CD0668* amplification with fluorescein
oMC1712	FAM-CAATATTAATTTATTTTTAAAAAATAG	P*tcdA* amplification with fluorescein
oMC1713	FAM-AGTATTATTATTTTTGATAATAAATC	P*tcdA* amplification with fluorescein
oMC1714	FAM-CTTGTAATAAAATAAAGATTTAAGTG	P*grdE* amplification with fluorescein
oMC1715	FAM-CACCTCCTGTTATTTAATTTG	P*grdE* amplification with fluorescein
oMC1716	CACCAATAATTTTATTATTTTGTATTATTG	P*spo0A* amplification
oMC1735	AGAAAGATATGAAATACTACAATAGC	P*vanZ* amplification with fluorescein
oMC1736	TAGATTTCATTTATTACCTCCTTAC	P*vanZ* amplification with fluorescein
oMC1737	AGtGaattcgagctcggtacccggggatccCAGAAGAACAGTTTAAACTTTTAAAAG	P*clnR* Gibson assembly
oMC1738	CATTCCATGTGATGGTGATGGTGATGCATggcgccTTCATGCCTCCTTATTATATTAttg	P*clnR* Gibson assembly
oMC1739	CTCCAAAATACTACATAAATAA	P*mtlA* amplifciation
oMC1740	TATATCGATATGATTCCCTTTTG	P*mtlA* amplification
oMC1741	CAAATTAAAATAAAGCAATTTATA	P*CD1606* amplification
oMC1742	CTAGTGTATTAATACGATAGTAC	P*CD1606* amplification
oMC1743	TTGTTTAAGTATTAATTATGAGT	P*csfU* amplification
oMC1744	CGTCATTATATATAACGATTTATAC	P*csfU* amplification
oMC1745	ATGTTTCATCCCCTTTTTTAATC	P*cdd4/CD0668* amplification
oMC1746	CACCCTCCTTTAGTATACC	P*cdd4/CD0668* amplification
oMC1717	TTGAGTACTATAGGTGACCCAATGA	*mtlA (CD2334)* qPCR
oMC1718	CCTCTTTGTCCTGCTATTGCTTTA	*mtlA (CD2334)* qPCR
oMC1719	GGGTAAATGGTGGTATGGTACTTATT	*iorA (CD2381)* qPCR
oMC1720	AGCTTCTTGACTAGTTGATGGTTC	*iorA (CD2381)* qPCR
oMC1754	GGAATAATAGTTATGACTCATGGGAGTT	*CD0284* qPCR
oMC1755	AGTTTAATTGCTGCTGTTCTTTCTG	*CD0284* qPCR
tcdRqF	AGCAAGAAATAACTCAGTAGATGATT	*tcdR (CD0659*) qPCR[14]
tcdRqR	TTATTAAATCTGTTTCTCCCTCTTCA	*tcdR (CD0659*) qPCR[14]

[a] All sequences are listed 5’ to 3’. Underlined sequences denote restriction sites or intron retarget sites.

[b] Abbreviations: qPCR, quantitative PCR

Table S11. Plasmid construct details.

pMC602: The group II intron of pCE240 was targeted to *CD1617* at nucleotide 127 by splicing PCR using primers oMC1310, oMC1311, oMC1312, and EBSu as outlined in the TargeTron users manual (Sigma-Aldrich). The primers for intron retargeting were obtained by using the jpintronator algorithm. The group II *CD1617*-targeted intron was subcloned using the *BsrG*I and *Hind*III sites into pCE240.

pMC616: The 5.45 kb *Sph*I/*Sfo*I fragment from pMC602 was cloned as *Sph*I/*SnaB*I into pMC123.

pMC643: The group II intron of pCE240 was targeted to *CD1618* at nucleotide 217 by splicing PCR using primers oMC1319, oMC1320, oMC1321, and EBSu as outlined in the TargeTron users manual (Sigma-Aldrich). The primers for intron retargeting were obtained by using the jpintronator algorithm. The group II *CD1618*-targeted intron was subcloned using the *BsrG*I and *Hind*III sites into pCE240.

pMC645: The 5.45 kb *Sph*I/*Sfo*I fragment from pMC645 was cloned as *Sph*I/*SnaB*I into pMC123.

pMC649: The coding sequence of *CD1617-1619* and 300 bp upstream of *CD1617* was amplified using oMC1416 and oMC1476 and cloned into pSMB47 as *Bam*HI/*Sph*I.

pMC687: The coding sequence of *CD1234* was amplified with primers oMC1609 and oMC1610 and cloned into pMC211 as *BamH*I/*Pst*I.

pMC723: The *clnRAB* operon was amplified with an N-terminal 6x His tag using primers oMC1689 and oMC1476 and cloned as *BamH*I/*Sph*I into pMC123. Subsequently, P*clnR* (amplified using primers oMC1737 and oMC1738) was cloned by Gibson assembly as *BamH*I/*Sfo*I.

Table S12. Expression of ClnR-dependent genes in the *clnR* mutant complemented with HIS-ClnR.

	BHIS			+ LL-37 (0.5 µg/ml)		
Gene	630Δ*erm* pMC123	*clnR* pMC123	*clnR* pMC123 P*clnR::HIS-clnRAB*	630Δ*erm* pMC123	*clnR* pMC123	*clnR* pMC123 P*clnR::HIS-clnRAB*
clnA (CD630_16180)	1.0 ± 0.0[a]	37.4 ± 6.6	69.4 ± 20.3	81.6 ± 20.5	44.9 ± 8.0	236.5 ± 22.7
vanZ1 (CD630_12400)	1.0 ± 0.0	17.5 ± 2.4	4.1 ± 1.3	15.4. ± 2.8	21.8 ± 1.8	18.6 ± 2.3

[a] Relative expression levels were determined by qRT-PCR and are normalized to 630Δ*erm* + pMC123 in BHIS as described in methods. Values shown are the mean of 3 biological replicates ± standard error of the mean.

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