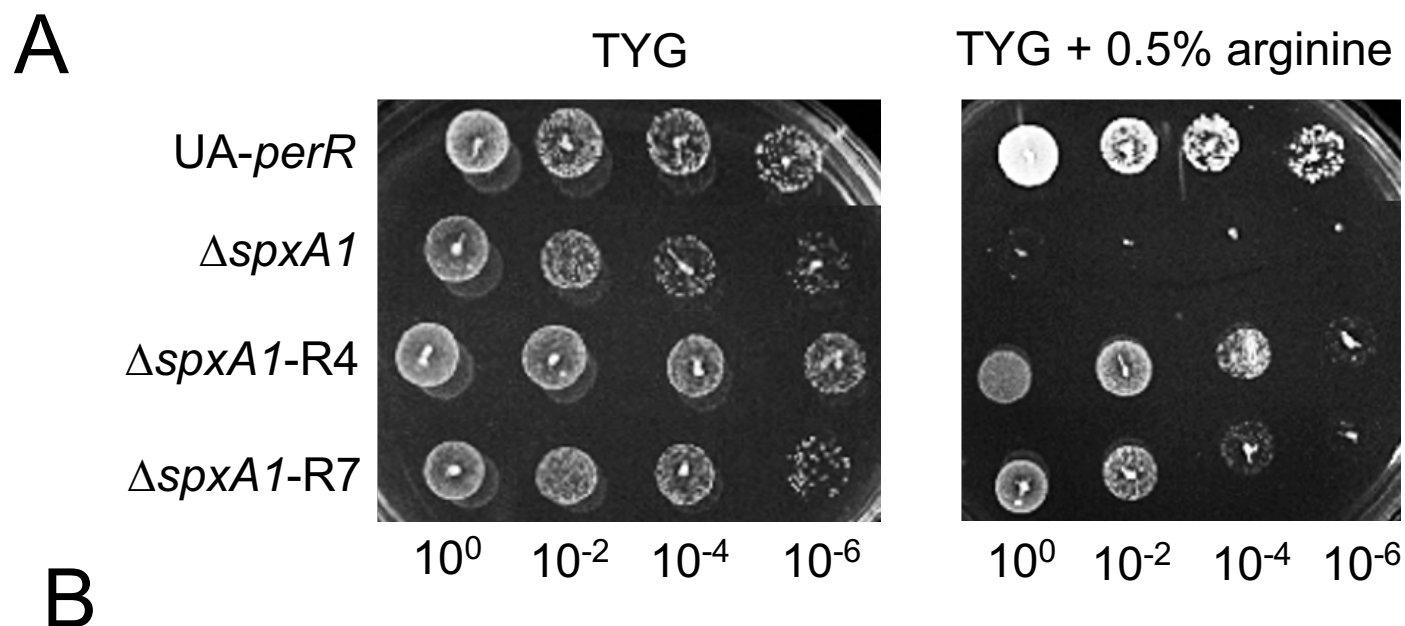


**Figure S1.** Suppressor mutations reverse arginine-sensitive phenotype of  $\Delta spxA1$ . (A) Serial dilutions of overnight cultures of the UA-*perR*,  $\Delta spxA1$ , and  $\Delta spxA1$  arginine-tolerant revertants R4 and R7 spotted onto TYG agar or TYG agar supplemented with 0.5% arginine. The images shown are representative of three independent experiments. (B) WGS of arginine-tolerant revertants uncovered spontaneously-occurring mutations in the *smu997* and *smu998* genes.

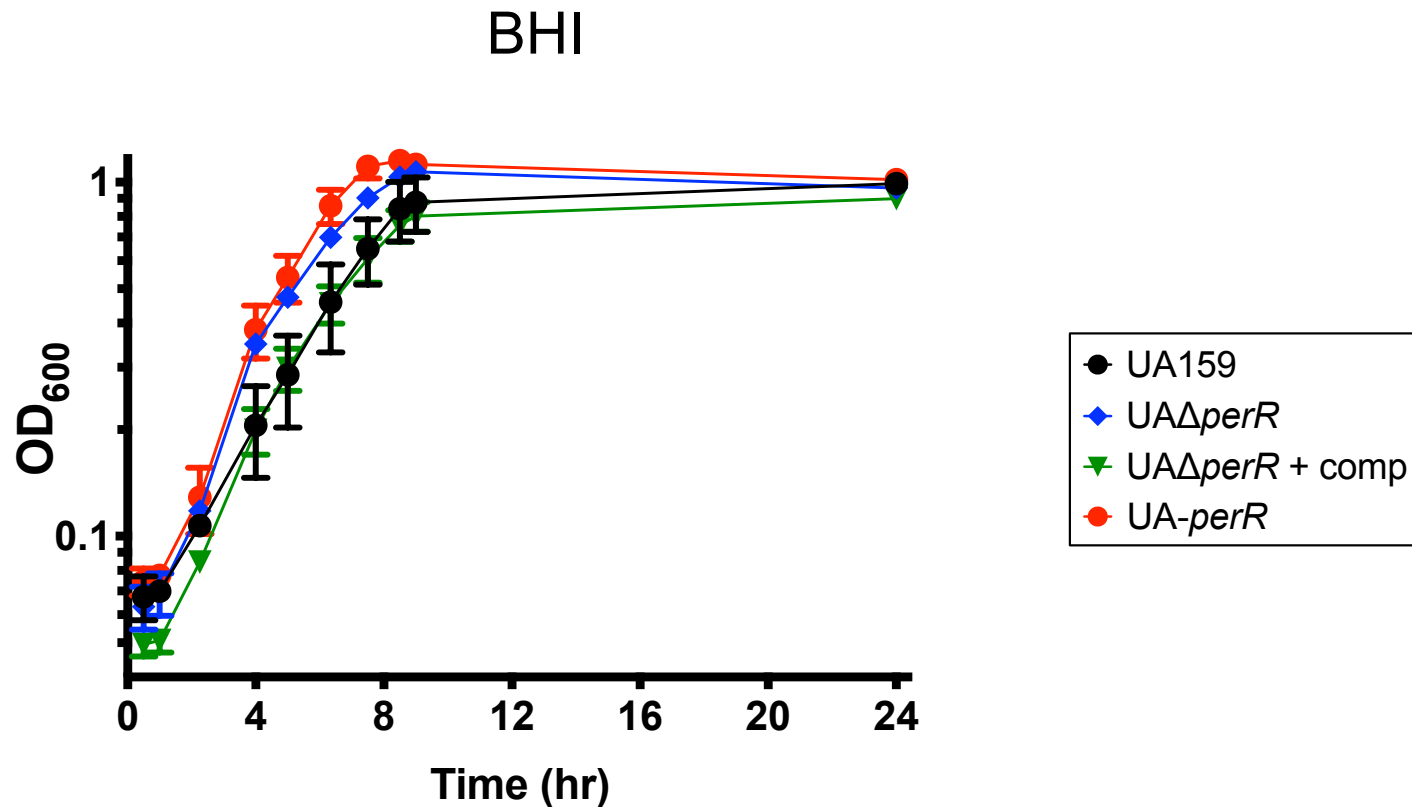


**B**

$\Delta spxA1$ revertant	Gene name	Mutation	Result
R1	smu.998	GCT --> GAT	A19D
R4	smu.997	GAA --> TAA	E94*
R6	smu.997	CAG --> CAT	Q152H
R7	smu.998	TGG --> TGA	W237*

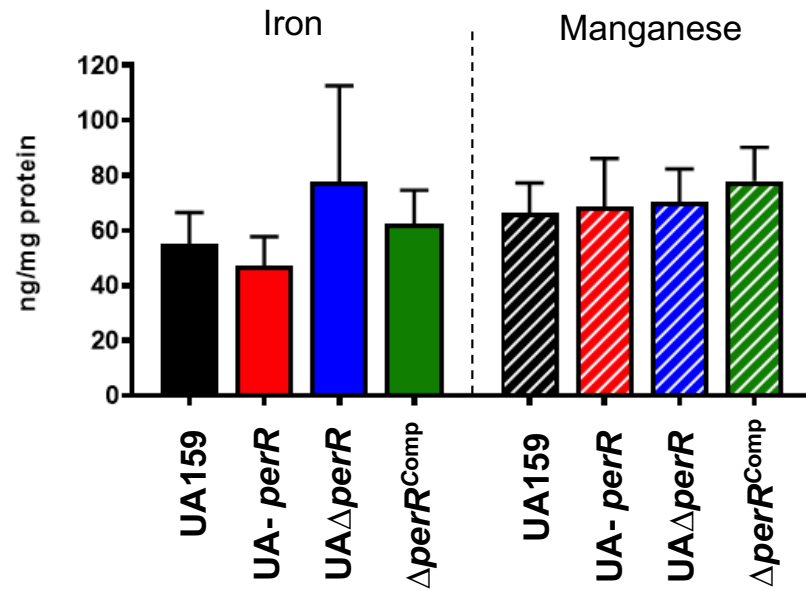


**Figure S3. Strains lacking a functional PerR show a slight growth advantage in a 5% CO<sub>2</sub> atmosphere.** *S. mutans* UA159 (*perR*<sup>+</sup>), UA-*perR* (*perR*<sup>-</sup>), the *perR* deletion mutant strain (UAΔ*perR*) and complemented strain (UAΔ*perR*<sup>Comp</sup>) were grown in BHI medium at 37°C in a 5% CO<sub>2</sub> atmosphere. Data represent averages and standard deviations of results from four independent cultures.

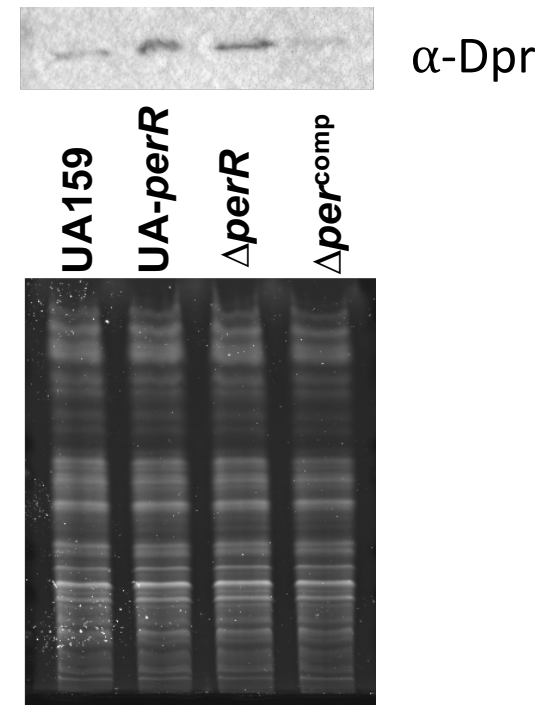


**Figure S4.** (A) Intracellular iron and manganese concentration as determined by ICP-MS analysis. (B) Western-blot analysis of whole cell lysates obtained from mid-log grown BHI cultures using anti-Dpr polyclonal antibody. The loading control stained with SYPRO Ruby is shown below.

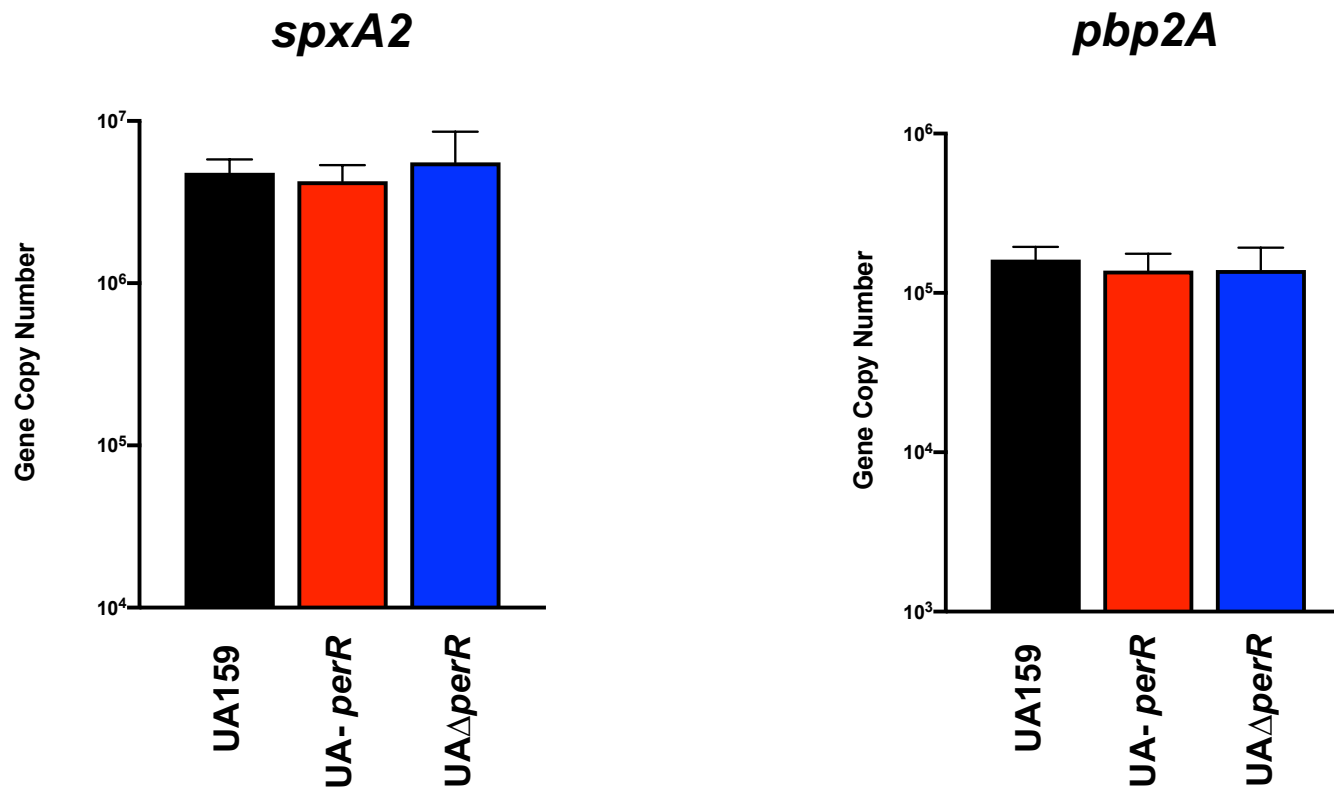
**A**



**B**



**Figure S5.** RT-qPCR analysis of genes lacking putative PerR-binding motifs. Bars represent the gene copy number and represent averages and SDs from three replicate samples. No significant differences were found when expression levels for each strain were compared to that of UA159 by ANOVA.



**Table S1. List of genes differentially expressed in *S. mutans* UA159 following exposure to H<sub>2</sub>O<sub>2</sub> stress as compared to unstressed controls**

<b>Locus</b>	<b>Gene name, function</b>	<b>Fold change</b>	<b>P-value</b>
SMU_0043	conserved hypothetical protein	2.00	1.98E-04
SMU_0044	conserved hypothetical protein	2.04	1.41E-03
SMU_0061	comR, transcriptional regulator	2.92	1.52E-08
SMU_0124	putative transcriptional regulator (MarR family)	3.23	3.52E-06
SMU_0125	conserved hypothetical protein	3.71	5.21E-07
SMU_0127	adhA, acetoin dehydrogenase E1 component alpha subunit	3.30	1.11E-07
SMU_0128	adhB, acetoin dehydrogenase E1 component beta subunit	3.69	9.52E-07
SMU_0129	adhC, dihydrolipoamide S-acetyltransferase	3.77	9.69E-06
SMU_0130	adhD, dihydrolipoamide dehydrogenase	3.88	2.44E-06
SMU_0131	lplA, lipoate-protein ligase	3.68	4.23E-06
SMU_0132	hipO, amino acid amidohydrolase	2.01	5.83E-06
SMU_0143c	def, polypeptide deformylase (PDF)	2.63	2.37E-05
SMU_0144c	possible transcriptional regulator	2.73	2.11E-05
SMU_0150	nImA, non-lantibiotic mutacin IV A	0.41	1.20E-05
SMU_0151	nImB, non-lantibiotic mutacin IV B	0.46	9.96E-06
SMU_0152	hypothetical protein	0.32	1.28E-04
SMU_0153	hypothetical protein	0.30	1.02E-03
SMU_0182	sloA, ABC transporter, ATP-binding protein	0.50	1.25E-05
SMU_0184	sloC, ABC transporter, substrate binding protein	0.45	2.61E-04
SMU_0185	hypothetical protein	0.34	8.08E-07
SMU_0186	sloR, metal-dependent transcriptional regulator	0.50	5.07E-05
SMU_0187c	dusA, tRNA-dihydrouridine synthase	3.07	3.00E-07
SMU_0188c	hsIO, putative 33 kD chaperonin (heat shock protein)	3.09	4.17E-08
SMU_0234	ilvA, threonine dehydratase	2.00	7.62E-06
SMU_0247	sufC, ABC transporter, ATP-binding protein	3.70	9.74E-09
SMU_0248	sufD, ABC transporter permease	3.52	3.55E-08
SMU_0249	sufS, class-V aminotransferase	3.48	4.77E-08
SMU_0250	sufU, nitrogen fixation-like protein	3.73	7.37E-09

SMU_0251	<u>suFB, ABC transporter permease</u>	3.25	9.85E-08
SMU_0260	conserved hypothetical protein	3.16	5.05E-06
SMU_0271	ptxB, PTS enzyme IIB component	2.29	2.75E-07
SMU_0273	rmpD, hexulose-6-phosphate synthase	2.01	2.19E-06
SMU_0274	rmpE, hexulose-6-phosphate isomerase	2.23	7.56E-07
SMU_0275	rmpF, L-ribulose 5-phosphate 4-epimerase	2.16	1.79E-06
SMU_0277	hypothetical protein	0.41	1.03E-04
SMU_0278	hypothetical protein	0.43	2.86E-04
SMU_0279	hypothetical protein	0.35	2.96E-05
SMU_0281	hypothetical protein	0.34	1.46E-06
SMU_0283	hypothetical protein	0.39	1.39E-06
SMU_0284	nlnT, transport and processing of non-lantibiotic mutacins	0.48	1.05E-04
SMU_0285	nlnE, transport and processing of non-lantibiotic mutacins	0.45	6.75E-05
SMU_0328	putative carbonic anhydrase	2.67	1.55E-05
SMU_0329	conserved hypothetical protein	2.39	3.38E-05
SMU_0348	pht, histidine triad (HIT) hydrolase	3.29	4.07E-07
SMU_0349	ksgA, dimethyladenosine transferase	3.20	1.01E-05
SMU_0350	hypothetical protein	3.09	1.21E-05
SMU_0424	copY, negative transcriptional regulator	2.36	2.38E-06
SMU_0426	copA, copper-transporting ATPase	2.27	1.33E-06
SMU_0427	copZ, copper chaperone	2.12	6.99E-05
SMU_0438c	NADPH-dependent glutamate synthase (small subunit)	0.42	2.27E-06
SMU_0463	trxB, thioredoxin reductase	3.37	7.45E-08
SMU_0478	gmk, putative guanylate kinase	2.44	2.81E-07
SMU_0479	rpoZ, DNA-directed RNA polymerase, omega subunit	2.15	4.23E-06
SMU_0486	liaS, two-component sensor histidine kinase	0.50	3.10E-05
SMU_0487	liaR, two-component response regulator	0.50	3.93E-04
SMU_0502	conserved hypothetical protein	0.46	6.97E-04
SMU_0503c	Hypothetical protein	0.46	2.27E-04
SMU_0524	ABC transporter ATP-binding/permease protein	2.53	7.70E-06
SMU_0525	ABC transporter ATP-binding/permease protein	2.44	8.45E-06
SMU_0540	dpr, peroxide resistance protein/iron binding protein	3.97	3.41E-06
SMU_0562	clpE, ATP-dependent protease	2.67	2.09E-07

SMU_0569	feoA, ferrous ion transport protein A	0.45	4.20E-05
SMU_0570	feoB, ferrous ion transport protein B	0.50	3.65E-04
SMU_0593	perR, peroxidase regulator	2.04	2.93E-04
SMU_0594	hypothetical protein	2.38	5.88E-05
SMU_0609	bsp, cell wall protein precursor	0.50	7.29E-04
SMU_0629	soda, superoxide dismutase	4.67	1.24E-06
SMU_0634	queA, tRNA ribosyltransferase-isomerase	2.43	5.15E-05
SMU_0666	argD, N-acetylornithine aminotransferase	2.13	3.08E-04
SMU_0667	nrdf, ribonucleotide reductase, small subunit	2.92	2.92E-07
SMU_0668c	nrda, ribonucleotide reductase, large subunit	2.59	9.43E-06
SMU_0669c	nrh, glutaredoxin	2.79	4.27E-06
SMU_0670	citB, aconitate hydratase; aconitase A	0.43	1.42E-04
SMU_0671	citZ, citrate synthase	0.45	7.41E-05
SMU_0676	gapN, NADP-dependent glyceraldehyde-3-phosphate dehydrogenase	2.64	6.05E-06
SMU_0688	conserved hypothetical protein	0.35	4.31E-04
SMU_0707c	endolysin	2.06	3.42E-06
SMU_0747c	conserved hypothetical protein	2.21	7.20E-05
SMU_0748	hypothetical protein	2.45	8.37E-06
SMU_0764	ahpC, alkyl hydroperoxide reductase, subunit C	5.02	1.00E-08
SMU_0765	ahpF, alkyl hydroperoxide reductase, subunit F	4.72	2.46E-08
SMU_0817	glnH, amino acid ABC transporter, substrate-binding protein	0.49	3.03E-04
SMU_0819	mscL, large conductance mechanosensitive channel	3.01	2.08E-04
SMU_0838	gor, glutathione reductase	4.41	4.40E-07
SMU_0841	folC, putative folyl-polyglutamate synthetase	2.26	1.62E-06
SMU_0842	conserved hypothetical protein	2.16	2.58E-06
SMU_0876	msmR, MSM operon regulatory protein	0.41	1.20E-04
SMU_0877	agal, alpha-galactosidase	0.39	1.11E-03
SMU_0878	msmE, sugar-binding protein	0.42	1.75E-03
SMU_0891	hsdM, DNA methylase	0.48	1.70E-03
SMU_0911c	hypothetical protein	2.15	8.86E-04
SMU_0917c	tetrahydropterin synthase	0.47	7.46E-04
SMU_0921	rcrR, transcriptional regulator	2.32	3.95E-06
SMU_0922	rcrP, ABC transporter ATP-binding protein	2.10	1.05E-05



SMU_0923	rerQ, ABC transporter ATP-binding protein	2.11	6.76E-05
SMU_0924	tpx, thiol peroxidase	6.57	1.94E-06
SMU_0925	cipl, bacteriocin immunity protein	3.45	1.18E-05
SMU_0929c	conserved hypothetical protein	4.75	1.83E-05
SMU_0956	cipl, ATP-dependent Clp protease, ATP-binding subunit	2.16	3.39E-06
SMU_0991	putative ribonucleotide reductase	3.80	5.83E-06
SMU_1071c	conserved hypothetical protein	3.41	1.37E-08
SMU_1073	fhs, formate-tetrahydrofolate ligase	2.68	2.06E-06
SMU_1117	nox, H2O-forming NADH Oxidase	3.83	1.25E-03
SMU_1124	pdp, putative pyrimidine-nucleoside phosphorylase	0.37	6.11E-04
SMU_1125c	conserved hypothetical protein	0.36	2.68E-04
SMU_1208c	hypothetical protein	0.42	8.44E-04
SMU_1209c	hypothetical protein	0.43	1.77E-03
SMU_1210	parE, DNA topoisomerase IV subunit B	0.44	4.97E-06
SMU_1235	thdF, tRNA modification GTPase	2.08	4.92E-05
SMU_1287	transcriptional regulator	2.17	2.94E-05
SMU_1296	yghU, glutathione S-transferase	3.46	1.12E-05
SMU_1297	conserved hypothetical protein, DHH family	3.90	2.51E-09
SMU_1307c	conserved hypothetical protein	0.49	7.54E-04
SMU_1317c	hypothetical protein	0.50	1.53E-04
SMU_1368	hypothetical protein	2.01	1.13E-03
SMU_1394	lepA, putative GTP-binding protein	2.15	5.12E-06
SMU_1395c	Hypothetical protein	2.05	1.74E-03
SMU_1396	gbpC, glucan-binding protein C	2.42	5.49E-06
SMU_1412c	ABC transporter, ATP-binding and permease fusion protein	0.47	7.76E-07
SMU_1451	aldB, alpha-acetolactate decarboxylase	3.16	5.76E-07
SMU_1452	alsS, alpha-acetolactate synthase	2.91	1.14E-06
SMU_1476c	GTP-binding protein	2.31	6.90E-07
SMU_1509	rggD, transcriptional regulator	0.44	1.23E-04
SMU_1519	glnQ, putative amino acid ABC transporter, ATP-binding protein	0.44	2.77E-05
SMU_1520	glnH, amino acid ABC transporter, substrate-binding protein	0.42	2.52E-05
SMU_1523	endA, membrane endonuclease	2.05	2.15E-05
SMU_1524c	hypothetical protein	2.47	2.47E-06

SMU_1525	murA, carboxyvinyltransferase	2.20	1.98E-06
SMU_1563	pacL, putative cation-transporting P-type ATPase	2.17	1.72E-04
SMU_1566	malR, maltose operon transcriptional repressor	2.97	2.18E-07
SMU_1572	murZ, UDP-N-acetylglucosamine 1-carboxyvinyltransferase	2.23	3.49E-05
SMU_1593c	conserved hypothetical protein	2.45	1.95E-05
SMU_1629c	cell division protein	2.20	3.64E-04
SMU_1641c	conserved hypothetical protein	2.11	3.12E-04
SMU_1645	tehB, tellurite resistance protein	3.10	1.67E-07
SMU_1649	exoA, exodeoxyribonuclease III/ Smx nuclease	3.82	2.05E-05
SMU_1650	end3, endonuclease III	2.95	5.40E-05
SMU_1665	livF, branched chain amino acid ABC transporter, ATP-binding protein	2.08	1.28E-05
SMU_1666	livG, branched chain amino acid ABC transporter, ATP-binding protein	2.24	4.82E-06
SMU_1667	livM, branched chain amino acid ABC transporter, permease	2.45	2.01E-06
SMU_1668	livH, putative branched chain amino acid ABC transporter	2.37	1.10E-06
SMU_1669	livK, putative ABC transporter, branched chain amino acid-binding	2.53	1.49E-06
SMU_1692	pflA, pyruvate-formate lyase activating enzyme	3.50	8.51E-08
SMU_1700c	cidB, LrgB-like protein	2.48	1.23E-04
SMU_1701c	cidA, conserved hypothetical protein	2.44	2.17E-04
SMU_1702c	pgpB, phosphatase	3.00	9.96E-05
SMU_1703c	conserved hypothetical protein	3.35	2.19E-05
SMU_1722c	putative integral membrane protein	2.15	3.36E-04
SMU_1750c	hypothetical protein	2.33	1.54E-03
SMU_1753c	CRISPR2-Cas related	2.20	3.50E-05
SMU_1754c	CRISPR2-Cas related	2.44	9.55E-07
SMU_1755c	CRISPR2-Cas related	2.32	9.91E-06
SMU_1757c	CRISPR2-Cas related	2.06	1.45E-05
SMU_1758c	CRISPR2-Cas related	2.56	2.22E-05
SMU_1760c	conserved hypothetical protein	2.85	1.50E-04
SMU_1761c	conserved hypothetical protein	3.10	3.03E-05
SMU_1762c	conserved hypothetical protein	3.67	5.45E-06
SMU_1763c	CRISPR2-Cas related	3.68	8.62E-06
SMU_1764c	conserved hypothetical protein	4.27	6.10E-06
SMU_1787c	preprotein translocase, YajC subunit	3.01	4.62E-06

SMU_1788c	bia, bacterocin transport accessory protein	4.37	2.47E-07
SMU_1812	tpn, transposase	2.52	3.19E-06
SMU_1813	transposase	3.46	7.16E-07
SMU_1814	senK, histidine kinase	2.98	1.35E-07
SMU_1815	senR, response regulator	3.29	6.69E-09
SMU_1849	comEB, deoxycytidylate deaminase; late competence protein	2.50	4.03E-07
SMU_1850	pepP, aminopeptidase P	2.74	5.75E-08
SMU_1851	uvrA, excinuclease ABC subunit A	3.26	7.63E-08
SMU_1865	mutY, A/G-specific adenine glycosylase	3.15	2.95E-07
SMU_1867c	adhB, putative alcohol dehydrogenase	3.60	6.80E-06
SMU_1869	trxA, thioredoxin	4.75	1.02E-05
SMU_1916	comD, histidine kinase of the competence regulon	2.36	1.59E-04
SMU_1917	comE, response regulator	2.48	2.18E-05
SMU_1955	groES, co-chaperonin	2.02	5.00E-05
SMU_1963c	levQ, sugar-binding periplasmic protein	0.48	1.64E-03
SMU_1964c	levR, two-component response regulator	0.43	7.82E-04
SMU_1965c	levS, histidine kinase	0.46	1.15E-04
SMU_1966c	levT, ABC transport ribose-binding protein	0.44	3.21E-04
SMU_1968c	conserved hypothetical protein	0.49	4.20E-04
SMU_1988c	probable DNA binding protein	4.56	3.29E-08
SMU_1993	adcB, zinc ABC transporter, permease	2.11	9.55E-06
SMU_1994	adcC, zinc ABC transport, ATP-binding protein	2.15	4.12E-07
SMU_1995c	adcR, zinc transport transcriptional repressor	2.05	5.96E-06
SMU_2027	transcriptional regulator	2.44	5.96E-06
SMU_2036	pepO, endopeptidase O	2.68	1.40E-04
SMU_2043c	dtd, D-tyrosyl-tRNA deacylase	2.03	2.12E-05
SMU_2044	relA, GTP pyrophosphokinase	2.34	9.76E-08
SMU_2072c	acetyltransferase	0.43	5.41E-04
SMU_2077c	conserved hypothetical protein	2.27	1.74E-06
SMU_2078c	Holliday junction resolvase-like protein	2.03	5.19E-06
SMU_2102	hiss, histidine-tRNA synthetase	3.06	2.33E-07
SMU_2129c	conserved hypothetical protein	2.09	8.08E-04
SMU_2142	rpiA, putative sugar-phosphate isomerase	2.35	5.99E-07



**Table S2. List of genes differentially expressed in *S. mutans* UA~~Aper~~R as compared to UA159**

Locus	Gene name, function	Unstressed		5 min H <sub>2</sub> O <sub>2</sub>	
		Fold change	P-value	Fold change	P-value
SMU_0026	plsX, fatty acid/phospholipid synthesis protein	2.02	1.38E-06	2.02	1.38E-06
SMU_0027	acpP, acyl carrier protein	2.52	1.82E-06	2.52	1.82E-06
SMU_0028	comA, ABC transporter, ATP-binding protein	2.04	1.88E-04	2.04	1.88E-04
SMU_0083	dnaJ, co-chaperone protein DnaJ	2.10	3.72E-05	2.10	3.72E-05
SMU_0087	conserved hypothetical protein	2.08	3.56E-04	2.08	3.56E-04
SMU_0185	hypothetical protein	2.02	2.36E-05	2.97	8.24E-07
SMU_0193c	conserved hypothetical protein	0.31	1.40E-04	0.23	5.10E-05
SMU_0194c	conserved hypothetical protein	0.31	1.37E-05	0.29	2.44E-05
SMU_0195c	hypothetical protein	0.22	2.34E-08	0.25	1.43E-07
SMU_0196c	immunogenic secreted protein (transfer protein)	0.19	4.75E-08	0.17	4.30E-08
SMU_0197c	hypothetical protein	0.21	1.89E-08	0.15	2.58E-09
SMU_0198c	tpn, conjugative transposon protein	0.24	1.35E-07	0.17	2.25E-08
SMU_0199c	hypothetical protein	0.23	7.67E-07	0.13	8.96E-08
SMU_0200c	hypothetical protein	0.21	4.01E-06	0.14	1.47E-06
SMU_0201c	conserved hypothetical protein	0.26	2.41E-06	0.17	2.31E-07
SMU_0202c	Streptococcus-specific protein	0.20	3.87E-07	0.13	9.23E-08
SMU_0204c	hypothetical protein	0.17	7.70E-07	0.10	1.78E-07
SMU_0205c	conserved hypothetical protein	0.17	4.02E-09	0.14	2.95E-09
SMU_0206c	hypothetical protein	0.24	2.36E-06	0.21	2.06E-06
SMU_0207c	transcriptional regulator	0.21	4.95E-07	0.18	3.06E-07
SMU_0208c	DNA binding protein, FtsK/SpoIIIE family	0.19	1.02E-07	0.16	4.75E-08
SMU_0209c	hypothetical protein	0.19	6.46E-06	0.15	3.12E-06
SMU_0210c	hypothetical protein	0.16	8.23E-08	0.13	5.43E-08
SMU_0211c	hypothetical protein	0.26	2.16E-05	0.21	1.26E-05
SMU_0212c	hypothetical protein	0.35	6.15E-04	0.32	5.76E-04
SMU_0213c	hypothetical protein	0.41	1.60E-04	0.39	2.11E-04
SMU_0214c	hypothetical protein	0.28	2.50E-06	0.25	2.87E-06

SMU_0215c	hypothetical protein	0.31	6.94E-05	0.21	1.53E-05
SMU_0216c	hypothetical protein	0.33	1.17E-04	0.27	8.05E-05
SMU_0217c	Streptococcus-specific protein	0.44	1.02E-04	0.43	1.67E-04
SMU_0433	transcriptional regulator			2.01	8.71E-04
SMU_0434	conserved hypothetical protein			2.05	1.89E-03
SMU_0593	perR, peroxidase regulator	0.03	2.92E-11	0.01	7.53E-12
SMU_0594	hypothetical protein	0.12	1.59E-08	0.14	2.19E-08
SMU_0670	citB, aconitate hydratase; aconitase A	0.45	1.45E-04	0.46	4.56E-04
SMU_0700c	gpmb, phosphoglycerate mutase	2.13	2.11E-05	2.28	1.56E-05
SMU_0702c	ydbF, transcriptional regulator			2.34	1.82E-05
SMU_0849	rpmA, 50S ribosomal protein L27			2.22	8.61E-05
SMU_0958	hypothetical protein			2.09	1.59E-03
SMU_1249c	hypothetical protein			2.23	1.72E-03
SMU_1296	yghU, glutathione S-transferase			2.06	2.46E-03
SMU_1319c	conserved hypothetical protein	2.33	6.62E-05	3.55	1.21E-06
SMU_1321c	conserved hypothetical protein	2.04	1.27E-05	2.69	4.29E-07
SMU_1457	mlb, dTDP-glucose-4,6-dehydratase			2.32	2.70E-05
SMU_1502c	conserved hypothetical protein			2.35	2.84E-03
SMU_1750c	hypothetical protein	0.41	1.22E-03	0.46	3.22E-03
SMU_1752c	hypothetical protein	0.30	1.58E-05	0.35	6.54E-05
SMU_1753c	CRISPR2-Cas related	0.38	6.18E-06	0.40	7.75E-06
SMU_1754c	CRISPR2-Cas related	0.40	1.08E-06	0.34	1.28E-07
SMU_1755c	CRISPR2-Cas related	0.38	2.93E-06	0.37	1.95E-06
SMU_1757c	CRISPR2-Cas related	0.44	4.29E-06	0.42	2.10E-06
SMU_1758c	CRISPR2-Cas related	0.40	4.94E-05	0.31	3.27E-06
SMU_1760c	conserved hypothetical protein			0.29	4.33E-05
SMU_1761c	conserved hypothetical protein			0.30	2.11E-05
SMU_1762c	conserved hypothetical protein			0.28	7.72E-06
SMU_1763c	CRISPR2-Cas related	0.39	3.47E-04	0.27	9.51E-06
SMU_1764c	conserved hypothetical protein	0.45	1.36E-03	0.26	1.29E-05
SMU_1907	hypothetical protein			0.48	4.10E-03
SMU_1946	conserved hypothetical protein			2.02	8.38E-04
SMU_1961c	levD, fructose-specific Enzyme IIA component			0.39	3.19E-03

