The Global Regulator $CodY_{St}$ in *Streptococcus thermophilus* Controls the Metabolic Network for

Escalating Growth in the Milk Environment

Running title: $CodY_{St}$ in *Streptococcus thermophilus*

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Table. S1 The CodY$_{St}$-box in genes

Genes	+/-	Location	P-value	Sequences containing CodY$_{St}$-box
ortholog of STND_1818	+	174	4.76e-08	TATGTGTAGAAATTTTCTGACAATTATGCTACAAT
ortholog of STND_1813	+	89	4.76e-08	GAATTACAGAAATATTCCGAAAATTCATTGATATT
ortholog of STND_0590	-	112	7.35e-08	GTTATTTTGCAAAATTCTGACAATTATTTTATAAG
ortholog of STND_0733	+	239	1.38e-07	ACCAATTCAGATTATTCTGAAAATTGTTTTAGGA
ortholog of STND_1308	+	180	1.51e-07	ATATTTATATAATTTTCCGAAAATTCTATCTTTTT
ortholog of STND_0811	-	146	2.21e-07	ATTATAGCAAAATATTCAGAAAATTGAAACATATA
ortholog of STND_0425	+	197	2.21e-07	ACTTGACAATAAGATTCTGAAAATTTATACTATTC
ortholog of STND_0466	+	122	2.81e-07	AAATGGCAGAAATATTCTGTCAATTACGATAGAAA
ortholog of STND_0352	+	137	2.81e-07	TATGATTGACAATTTTCTGATAATTCTGTAACCTA
ortholog of STND_0370	-	154	3.42e-07	CAATTATAGCAAAATTCTGATAATTTGTCACATTG
ortholog of STND_0154	+	221	3.70e-07	ATAGATTGCTATTTTTCTGAAAATTGTGATACAAT
ortholog of STND_1235	-	132	6.77e-07	CAAGTTTATGAAAATTCTGACGATTAAACAAGTAG
ortholog of STND_1212	-	147	1.16e-06	TTAAATGAGTAGTATTCAGAAAATTTTGACAAAAA
ortholog of STND_1528	-	137	1.42e-06	AGATGTCAAGAATTTTCTGTTAATTCGACAATTC
ortholog of STND_0611	+	120	2.08e-06	TGTCTTTTTGAAAATTTTGAAAATTAAGTCACAAA
ortholog of STND_0733	+	198	3.42e-06	AGCTATTGAAATTATTCCAACAATTGTGTAAAATG

Table S2 The effect of the global regulator $CodY_{St}$ on the transcription of *gdhA*

ST2017/ST2017Δ*codY*	Transcriptome	RT-qPCR
gdhA	3.3[a]	2.8±0.2

[a] p-value=8.60E-58, FDR=1.61E-56

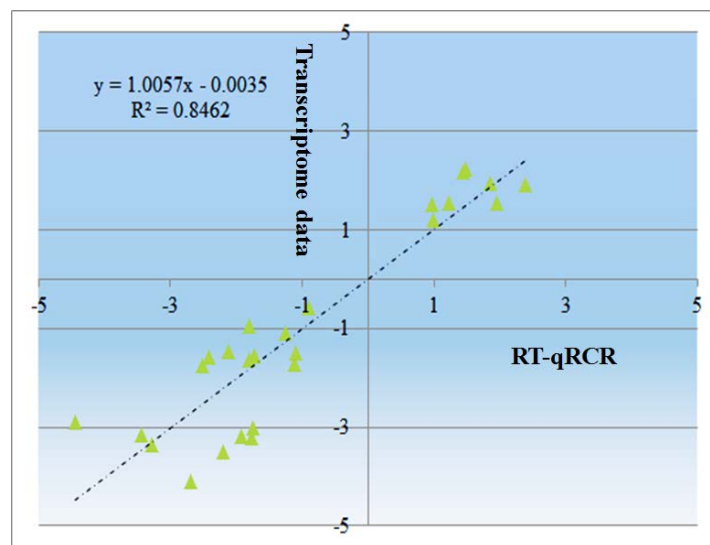| ST2017/ST2017ΔcodY			ST2017/ST2017ΔcodY		
log2(Fold_change) normalized			log2(Fold_change) normalized		
Genes	RT-qPCR	Transcritpome	Genes	RT-qPCR	Transcritpome
ortholog of STND_0027	2.39	1.92	*ortholog of STND_0425*	-2.52	-1.74
ortholog of STND_0113	1.44	2.15	*ortholog of STND_0433*	0.97	1.50
ortholog of STND_0115	1.84	1.94	*ortholog of STND_0611*	-2.11	-1.46
ortholog of STND_0119	-1.72	-1.54	*ortholog of STND_0658*	-2.20	-3.50
ortholog of STND_0135	1.21	1.52	*ortholog of STND_0782*	1.48	2.23
ortholog of STND_0154	-2.41	-1.58	*ortholog of STND_0811*	-4.45	-2.88
ortholog of STND_0182	-1.75	-3.01	*ortholog of STND_1004*	-1.80	-1.64
ortholog of STND_0202	-1.80	-0.94	*ortholog of STND_1007*	-1.76	-3.22
ortholog of STND_0203	-1.93	-3.17	*ortholog of STND_1212*	-1.09	-1.50
ortholog of STND_0204	-1.26	-1.10	*ortholog of STND_1346*	1.95	1.54
ortholog of STND_0306	-0.91	-0.58	*ortholog of STND_1569*	-2.69	-4.11
ortholog of STND_0307	-1.11	-1.73	*ortholog of STND_1785*	0.99	1.20
ortholog of STND_0352	-3.28	-3.34	*ortholog of STND_1813*	-3.43	-3.15

Fig. S1 Scatter plot comparative analysis of transcriptome and RT-qPCR experiments. Each data point represents the logarithmic ratio of the signal intensity determined for 26 CodY$_{St}$-regulated genes (*orthologs of STND_0027, STND_0113, STND_0115, STND_0119, STND_0135, STND_0154, STND_0182, STND_0202, STND_0203, STND_0204, STND_0306, STND_0307, STND_0352, STND_0425, STND_0433, STND_0611, STND_0658, STND_0782, STND_0811, STND_1004, STND_1007, STND_1212, STND_1346, STND_1569, STND_1785, STND_1813*) for the wild-type and the *codY* mutant strains, as determined by both RT-qPCR and transcriptome analyses. R^2, Pearson correlation coefficient.
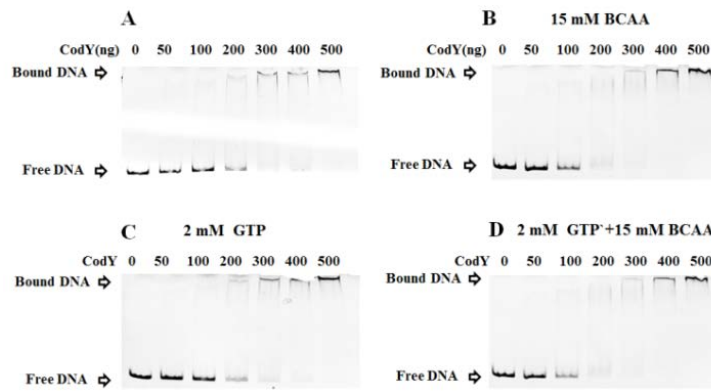
Fig. S2

Fig. S2 Effects of BCAA and GTP on CodY$_{St}$ binding to *gdhA* promoter region. A 253-bp DNA fragment containing the *gdhA* promoter region (100 ng) was incubated with or without various concentrations of CodY$_{St}$ protein from *S. thermophilus* ST2017 in the presence or not of 15 mM of BCAA, 2 mM of GTP, or both and analyzed on non-denaturing polyacrylamide gel electrophoresis.