

Functional dysbiosis within dental plaque microbiota in cleft lip and palate patients

K. Funahashi, T. Shiba, T. Watanabe, K. Muramoto, Y. Takeuchi, T. Ogawa, Y. Izumi, T. Sekizaki, I. Nakagawa and K. Moriyama

Supplementary Material

Supplementary Results

Functional profiles estimated from mRNA reads using BLASTX and various databases

In addition to conducting functional assignment by using the MG-RAST, the mRNA reads were further assigned by using the NCBI nr and two databases of virulence genes (i.e., VFDB and MvirDB) using BLASTX. Before the assignment, all reads were categorized into $210,290 \pm 78,421$ clusters, and the clusters derived from 16S rRNA genes were removed to obtain $175,144 \pm 80,587$ clusters of mRNA reads (Table S1). The mRNA reads were assigned $37,706 \pm 7,014$ gene functions in the CLP group and $39,279 \pm 15,047$ functions in the control group based on the NCBI nr. The genes encoding hypothetical protein in the NCBI nr accounted for nearly one-half of all functions in abundance in each group (47.2% in the CLP group and 47.4% in the control group). The group-specific functions were 3.5% in the CLP group and 4.9% in the control group. The most predominant gene encoding a protein with known function among the group-specific functions was only 0.038% in the CLP group (for RNA-dependent RNA polymerase) and 0.012% in the control group (for sanguinicin K11 precursor protein). The functional profiles assigned using the NCBI nr were not significantly different between the groups ($R = -0.075$ and $P = 0.58$, based on the ANOSIM; Figure S4).

The mRNA reads were assigned $1,234 \pm 179.3$ gene functions in the CLP group and $1,284 \pm 475.4$ functions in the control group based on the VFDB, and $1,300 \pm 157.7$ functions in the CLP group and $1,342 \pm 434.5$ functions in the control group based on the MvirDB (Table S1). The elongation factor, surface-anchored fimbrial subunit, glyceraldehyde-3-phosphate dehydrogenase, and phosphopyruvate hydratase in the VFDB were predominant and were nearly 20% in abundance in both groups (Table S7). The group-specific functions in the VFDB were quite few (2.4% in the CLP group and 2.8% in the control group). The most predominant function among the group-specific functions was only 0.075% in the CLP group (for fimbrial protein P9-2 pilin) and 0.079% in the control group (for manganese ABC transporter substrate-binding protein). In the MvirDB, the translation initiation factor, 50S ribosomal protein, pyruvate formate lyase, ATP-binding protein, and surface-anchored fimbrial subunit were predominant and accounted for more than 10% in both groups (Table S8). As in the VFDB, the group-specific functions in the MvirDB were quite few (2.3% in the CLP group and 2.5% in the control group). The most predominant function among the group-specific functions was only 0.052% in the CLP group (for transcription antitermination factor) and 0.285% in the control group (for type IV pilin). The functional profiles assigned based on the VFDB and MvirDB were not significantly different between the groups (VFDB: $R = -0.053$ and $P = 0.56$; MvirDB: $R = 0.16$ and $P = 0.10$, based on the ANOSIM; Figure S4).

Supplementary Figures

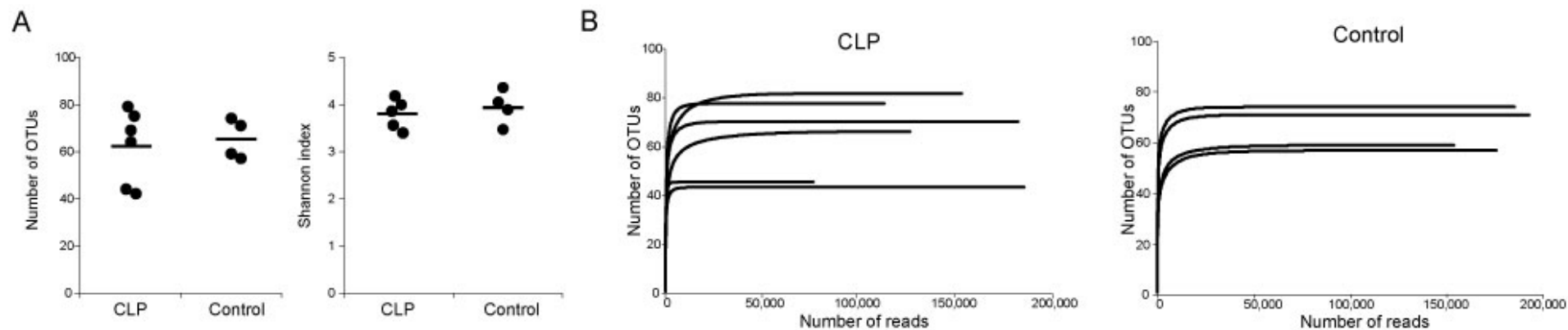


Figure S1. Number of OTUs, Shannon's diversity index, and rarefaction curves. (A) The number of OTUs and Shannon's diversity index for each participant are shown in the scatter graphs. The horizontal bars indicate the mean values among the participants. (B) A rarefaction curve for each participant is shown with the range of horizontal axis from 0 to the number of reads in the corresponding participant.

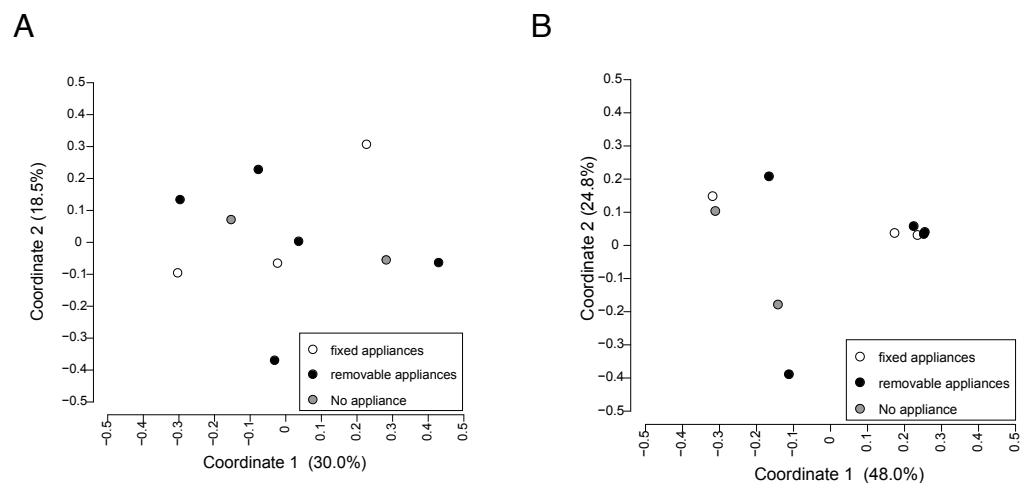


Figure S2. PCoA plots with information of appliances. The bacterial composition estimated from 16S rRNA and mRNA reads are shown in (A) and (B), respectively. Participants with fixed and removable appliances are indicated by open and filled circles, respectively, and participants without any appliances are indicated by gray circles.

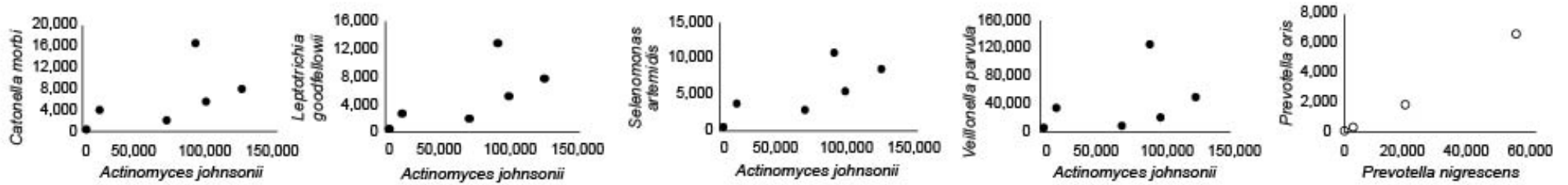


Figure S3. Scatter graphs of mRNA abundances for pairs of interacting core taxa. The CLP patients and control participants are indicated by filled and open circles, respectively.

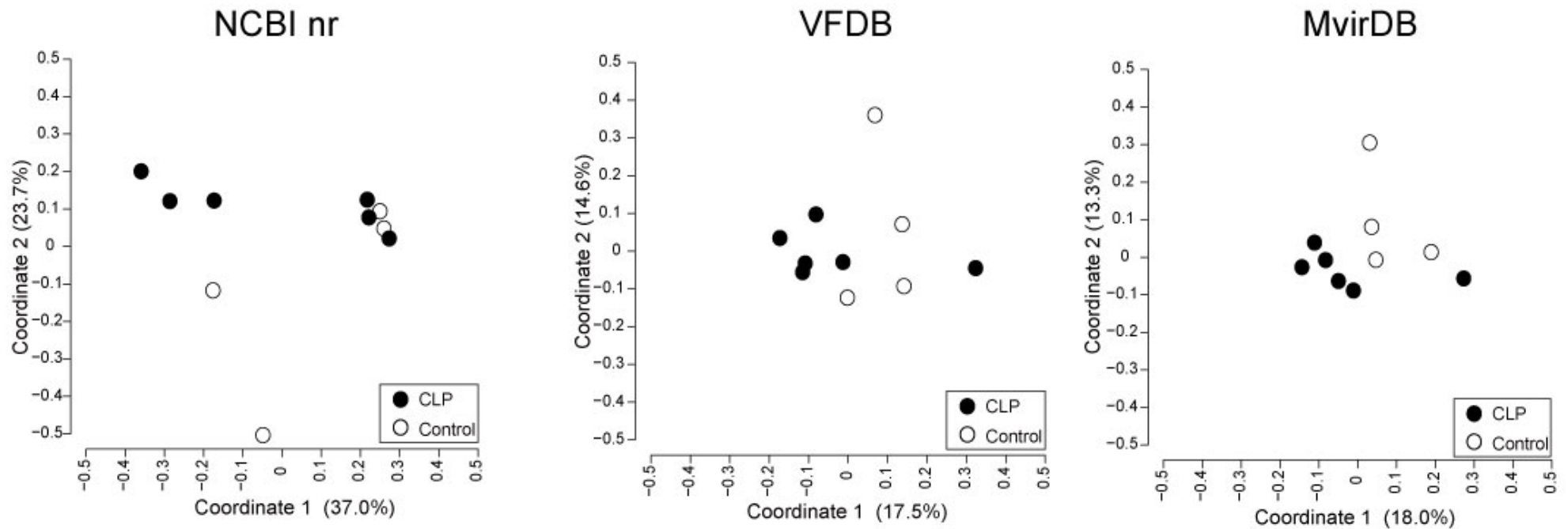


Figure S4. PCoA plots for the functional profiles assigned using BLASTX. First coordinates in PCoA for the functional profiles assigned by using the NCBI nr, VFDB, and MvirDB are plotted with second coordinates in the scatter graphs. The CLP patients and control participants are indicated by filled and open circles, respectively.

Supplementary Tables

Table S1. Summary of Illumina MiSeq reads and the derived data.

Sample name	Number of reads					Number of formed clusters		Number of assigned functions				
	Raw	Preprocessed		EMIRGE	MG-RAST	All	mRNA	SEED	KEGG	NCBI nr	VFDB	MvirDB
		Paired	Unpaired									
CLP1	3,886,942	3,241,544	219,821	57,498	774,136	284,914	243,230	17,421	16,302	36,508	1,367	1,412
CLP2	5,932,626	5,005,270	351,103	405,306	747,449	191,697	137,170	7,479	7,527	28,536	1,094	1,168
CLP3	5,398,948	4,530,979	385,671	277,902	703,790	184,543	167,892	8,026	7,837	32,733	1,212	1,301
CLP4	7,054,912	5,876,240	510,428	350,420	966,679	283,627	262,607	14,279	13,601	37,474	1,486	1,498
CLP5	4,051,374	3,131,673	446,209	130,207	422,111	102,720	53,982	3,961	3,594	42,805	991	1,070
CLP6	4,447,902	3,360,050	523,921	138,199	669,497	198,626	168,842	10,364	10,117	48,177	1,255	1,348
C1	4,960,774	4,136,023	277,602	346,092	583,074	145,333	91,835	4,090	3,839	17,905	925	988
C2	5,233,586	4,449,558	345,749	254,016	992,930	367,024	323,040	35,898	29,717	52,605	1,969	1,956
C3	7,210,598	6,161,642	442,006	273,893	788,363	172,714	153,670	5,239	4,818	40,814	1,006	1,089
C4	5,514,144	4,309,251	576,140	160,140	704,580	171,697	149,170	8,072	7,452	45,791	1,234	1,333

Table S2. Rank distribution of species assigned for the rc-rRNA OTUs (relative abundance per participant).

CLP				Control			
Species	Group-specificity	Mean (%)	Standard deviation	Species	Group-specificity	Mean (%)	Standard deviation
<i>Corynebacterium matruchotii</i>	Common	9.041	6.154	<i>Neisseria sicca</i>	Common	9.613	12.153
<i>Leptotrichia wadei</i>	Common	5.514	3.757	<i>Corynebacterium matruchotii</i>	Common	5.188	3.486
<i>Capnocytophaga granulosa</i>	Common	5.493	7.438	<i>Cardiobacterium hominis</i>	Common	5.091	5.108
<i>Leptotrichia buccalis</i>	Common	4.526	4.838	<i>Capnocytophaga granulosa</i>	Common	4.987	8.101
<i>Streptococcus sanguinis</i>	Common	2.909	3.476	<i>Leptotrichia buccalis</i>	Common	3.826	5.293
<i>Cardiobacterium hominis</i>	Common	2.891	1.692	<i>Neisseria flavescens</i>	Common	3.275	6.549
<i>Fusobacterium nucleatum</i>	Common	2.724	3.153	<i>Haemophilus parainfluenzae</i>	Common	3.208	4.916
<i>Neisseria sicca</i>	Common	2.152	3.334	<i>Lachnoanaerobaculum umeaense</i>	Common	2.823	2.760
<i>Actinomyces naeslundii</i>	Common	2.002	2.582	<i>Moraxella catarrhalis</i>	Common	2.802	3.456
<i>Neisseria oralis</i>	Common	1.993	4.251	<i>Fusobacterium nucleatum</i>	Common	2.320	2.058
<i>Campylobacter showae</i>	Common	1.818	2.305	<i>Actinomyces naeslundii</i>	Common	2.212	1.629
<i>Leptotrichia hofstadii</i>	Common	1.756	3.177	<i>Streptococcus oralis</i>	Specific	2.146	2.741
<i>Neisseria mucosa</i>	Common	1.726	4.191	<i>Streptococcus mitis</i>	Common	1.221	1.623
<i>Actinomyces massiliensis</i>	Common	1.560	0.827	<i>Neisseria subflava</i>	Common	1.189	1.427
<i>Lautropia mirabilis</i>	Common	1.510	2.941	<i>Campylobacter showae</i>	Common	1.172	2.165
<i>Actinomyces dentalis</i>	Common	1.364	2.197	<i>Lautropia mirabilis</i>	Common	1.156	0.526
<i>Capnocytophaga leadbetteri</i>	Common	1.174	1.512	<i>Neisseria elongata</i>	Common	1.069	1.500
<i>Leptotrichia shahii</i>	Common	1.012	1.823	<i>Corynebacterium durum</i>	Common	1.049	1.097
<i>Moraxella catarrhalis</i>	Common	0.973	1.917	<i>Abiotrophia defectiva</i>	Common	1.048	0.452
<i>Selenomonas sputigena</i>	Common	0.954	0.846	<i>Streptococcus cristatus</i>	Common	1.034	2.068
<i>Veillonella dispar</i>	Common	0.851	0.558	<i>Neisseria mucosa</i>	Common	1.025	1.509
<i>Kingella denitrificans</i>	Common	0.833	1.882	<i>Capnocytophaga leadbetteri</i>	Common	0.948	1.270
<i>Haemophilus parainfluenzae</i>	Common	0.751	1.232	<i>Actinomyces oris</i>	Common	0.897	0.864
<i>Actinomyces oris</i>	Common	0.749	1.790	<i>Rothia dentocariosa</i>	Common	0.839	1.153
<i>Campylobacter gracilis</i>	Common	0.710	0.638	<i>Capnocytophaga sputigena</i>	Common	0.777	0.829
<i>Streptococcus dentisani</i>	Common	0.700	1.022	<i>Actinomyces dentalis</i>	Common	0.747	1.169
<i>Corynebacterium durum</i>	Common	0.617	0.755	<i>Actinomyces massiliensis</i>	Common	0.682	0.642

<i>Rothia aerea</i>	Common	0.614	0.810	<i>Veillonella dispar</i>	Common	0.646	0.549
<i>Neisseria elongata</i>	Common	0.589	0.667	<i>Capnocytophaga gingivalis</i>	Common	0.613	0.691
<i>Neisseria subflava</i>	Common	0.548	1.195	<i>Leptotrichia shahii</i>	Common	0.599	1.198
<i>Cardiobacterium valvarum</i>	Common	0.533	0.747	<i>Granulicatella adiacens</i>	Common	0.507	0.548
<i>Actinomyces johnsonii</i>	Common	0.523	0.788	<i>Streptococcus sanguinis</i>	Common	0.453	0.523
<i>Actinomyces georgiae</i>	Specific	0.515	1.262	<i>Leptotrichia hofstadii</i>	Common	0.452	0.709
<i>Lachnoanaerobaculum umeaense</i>	Common	0.467	0.726	<i>Fusobacterium periodonticum</i>	Common	0.429	0.754
<i>Rothia dentocariosa</i>	Common	0.455	0.571	<i>Porphyromonas catoniae</i>	Common	0.422	0.618
<i>Lachnoanaerobaculum saburreum</i>	Common	0.455	1.114	<i>Neisseria pharyngis</i>	Specific	0.418	0.833
<i>Abiotrophia defectiva</i>	Common	0.445	1.014	<i>Kingella denitrificans</i>	Common	0.415	0.206
<i>Capnocytophaga ochracea</i>	Specific	0.443	1.085	<i>Gemella haemolysans</i>	Common	0.376	0.510
<i>Capnocytophaga sputigena</i>	Common	0.412	0.531	<i>Streptococcus lactarius</i>	Common	0.366	0.732
<i>Porphyromonas catoniae</i>	Common	0.345	0.609	<i>Actinomyces odontolyticus</i>	Common	0.346	0.419
<i>Kingella oralis</i>	Common	0.342	0.317	<i>Veillonella parvula</i>	Common	0.343	0.625
<i>Leptotrichia hongkongensis</i>	Common	0.326	0.698	<i>Ottowia sp.</i>	Common	0.334	0.465
<i>Streptococcus mutans</i>	Common	0.297	0.720	<i>Gemella morbillorum</i>	Common	0.304	0.272
<i>Actinomyces gerencseriae</i>	Common	0.296	0.402	<i>Streptococcus gordonii</i>	Common	0.304	0.608
<i>Granulicatella adiacens</i>	Common	0.289	0.277	<i>Leptotrichia wadei</i>	Common	0.287	0.575
<i>Neisseria polysaccharea</i>	Specific	0.284	0.695	<i>Enterococcus italicus</i>	Specific	0.286	0.320
<i>Actinomyces viscosus</i>	Specific	0.247	0.604	<i>Veillonella atypica</i>	Common	0.283	0.433
<i>Fusobacterium naviforme</i>	Specific	0.235	0.575	<i>Propionibacterium propionicum</i>	Common	0.263	0.143
<i>Streptococcus lactarius</i>	Common	0.184	0.451	<i>Rothia aerea</i>	Common	0.236	0.168
<i>Prevotella oulorum</i>	Common	0.182	0.191	<i>Leptotrichia hongkongensis</i>	Common	0.227	0.187
<i>Gemella morbillorum</i>	Common	0.181	0.109	<i>Prevotella melaninogenica</i>	Common	0.225	0.234
<i>Selenomonas flueggei</i>	Specific	0.165	0.298	<i>Neisseria oralis</i>	Common	0.211	0.250
<i>Stomatobaculum longum</i>	Common	0.161	0.262	<i>Selenomonas sputigena</i>	Common	0.166	0.190
<i>Propionibacterium propionicum</i>	Common	0.154	0.107	<i>Gemella sanguinis</i>	Common	0.144	0.288
<i>Selenomonas noxia</i>	Common	0.144	0.312	<i>Centipeda periodontii</i>	Common	0.142	0.284
<i>Gemella sanguinis</i>	Common	0.120	0.186	<i>Streptococcus anginosus</i>	Common	0.140	0.211
<i>Prevotella nigrescens</i>	Common	0.112	0.109	<i>Actinomyces johnsonii</i>	Common	0.139	0.259
<i>Streptococcus mitis</i>	Common	0.111	0.235	<i>Cardiobacterium valvarum</i>	Common	0.131	0.249

<i>Neisseria flava</i>	Specific	0.104	0.166	<i>Campylobacter concisus</i>	Common	0.129	0.117
<i>Veillonella atypica</i>	Common	0.103	0.208	<i>Selenomonas infelix</i>	Common	0.118	0.236
<i>Streptococcus oligofermentans</i>	Common	0.099	0.243	<i>Campylobacter gracilis</i>	Common	0.117	0.234
<i>Lactobacillus vaginalis</i>	Specific	0.095	0.233	<i>Kingella oralis</i>	Common	0.102	0.071
<i>Selenomonas infelix</i>	Common	0.087	0.121	<i>Prevotella nigrescens</i>	Common	0.097	0.104
<i>Capnocytophaga gingivalis</i>	Common	0.081	0.121	<i>Lachnoanaerobaculum saburreum</i>	Common	0.093	0.187
<i>Neisseria flavescens</i>	Common	0.079	0.140	<i>Aggregatibacter paraphrophilus</i>	Common	0.083	0.166
<i>Campylobacter concisus</i>	Common	0.077	0.096	<i>Catonella morbi</i>	Common	0.082	0.107
<i>Prevotella scopos</i>	Specific	0.073	0.180	<i>Actinomyces gerencseriae</i>	Common	0.078	0.103
<i>Fusobacterium periodonticum</i>	Common	0.073	0.136	<i>Selenomonas noxia</i>	Common	0.071	0.102
<i>Atopobium parvulum</i>	Specific	0.072	0.174	<i>Streptococcus parasanguinis</i>	Common	0.068	0.136
<i>Veillonella parvula</i>	Common	0.071	0.084	<i>Eikenella corrodens</i>	Common	0.065	0.130
<i>Actinomyces odontolyticus</i>	Common	0.069	0.110	<i>Selenomonas artemidis</i>	Common	0.057	0.093
<i>Streptococcus tigurinus</i>	Specific	0.064	0.125	<i>Actinomyces israelii</i>	Specific	0.043	0.086
<i>Actinomyces timonensis</i>	Specific	0.061	0.106	<i>Mitsuokella multacida</i>	Specific	0.031	0.062
<i>Prevotella melaninogenica</i>	Common	0.060	0.043	<i>Prevotella oulorum</i>	Common	0.030	0.027
<i>Granulicatella elegans</i>	Common	0.057	0.141	<i>Porphyromonas endodontalis</i>	Specific	0.030	0.061
<i>Aggregatibacter segnis</i>	Common	0.056	0.137	<i>Megasphaera micronuciformis</i>	Common	0.030	0.060
<i>Streptococcus anginosus</i>	Common	0.044	0.107	<i>Prevotella pallens</i>	Common	0.029	0.038
<i>Gemella haemolysans</i>	Common	0.040	0.055	<i>Aggregatibacter segnis</i>	Common	0.027	0.055
<i>Catonella morbi</i>	Common	0.040	0.038	<i>Granulicatella elegans</i>	Common	0.026	0.019
<i>Centipeda periodontii</i>	Common	0.038	0.042	<i>Prevotella saccharolytica</i>	Common	0.026	0.029
<i>Prevotella maculosa</i>	Common	0.038	0.055	<i>Streptococcus oligofermentans</i>	Common	0.024	0.048
<i>Selenomonas artemidis</i>	Common	0.034	0.048	<i>Johnsonella ignava</i>	Common	0.023	0.046
<i>Dialister invisus</i>	Common	0.034	0.069	<i>Stomatobaculum longum</i>	Common	0.020	0.036
<i>Prevotella micans</i>	Common	0.034	0.042	<i>Streptococcus intermedius</i>	Common	0.017	0.022
<i>Johnsonella ignava</i>	Common	0.033	0.079	<i>Solobacterium moorei</i>	Common	0.014	0.016
<i>Prevotella veroralis</i>	Common	0.033	0.071	<i>Dialister invisus</i>	Common	0.012	0.014
<i>Prevotella saccharolytica</i>	Common	0.028	0.018	<i>Prevotella denticola</i>	Common	0.011	0.019
<i>Prevotella salivae</i>	Common	0.028	0.041	<i>Veillonella denticariosi</i>	Common	0.011	0.023
<i>Leptotrichia goodfellowii</i>	Common	0.028	0.039	<i>Streptococcus mutans</i>	Common	0.010	0.011

<i>Streptococcus cristatus</i>	Common	0.025	0.061	<i>Prevotella maculosa</i>	Common	0.010	0.008
<i>Streptococcus parasanguinis</i>	Common	0.022	0.055	<i>Streptococcus dentisani</i>	Common	0.009	0.018
<i>Streptococcus gordonii</i>	Common	0.019	0.048	<i>Treponema socranskii</i>	Common	0.009	0.011
<i>Prevotella denticola</i>	Common	0.019	0.037	<i>Oribacterium parvum</i>	Specific	0.008	0.017
<i>Prevotella intermedia</i>	Specific	0.018	0.045	<i>Capnocytophaga haemolytica</i>	Specific	0.008	0.007
<i>Prevotella oris</i>	Common	0.016	0.019	<i>Prevotella salivae</i>	Common	0.008	0.017
<i>Eikenella corrodens</i>	Common	0.016	0.038	<i>Haemophilus parahaemolyticus</i>	Specific	0.008	0.016
<i>Streptococcus intermedius</i>	Common	0.016	0.025	<i>Prevotella micans</i>	Common	0.007	0.009
<i>Megasphaera micronuciformis</i>	Common	0.015	0.023	<i>Prevotella oris</i>	Common	0.007	0.009
<i>Alloprevotella tanneriae</i>	Specific	0.014	0.014	<i>Oribacterium sinus</i>	Common	0.006	0.009
<i>Lactobacillus fermentum</i>	Specific	0.013	0.033	<i>Mogibacterium diversum</i>	Common	0.005	0.006
<i>Aggregatibacter paraphrophilus</i>	Common	0.013	0.033	<i>Alloprevotella rava</i>	Specific	0.004	0.005
<i>Rothia mucilaginosa</i>	Specific	0.013	0.032	<i>Parvimonas micra</i>	Common	0.003	0.007
<i>Selenomonas diana</i>	Specific	0.012	0.031	<i>Prevotella loescheii</i>	Specific	0.003	0.006
<i>Atopobium rimae</i>	Common	0.011	0.023	<i>Erysipelothrix tonsillarum</i>	Specific	0.003	0.005
<i>Streptococcus salivarius</i>	Specific	0.011	0.026	<i>Haemophilus paraphrohaemolyticus</i>	Specific	0.002	0.004
<i>Prevotella nanceiensis</i>	Common	0.008	0.013	<i>Haemophilus haemolyticus</i>	Common	0.002	0.004
<i>Aggregatibacter aphrophilus</i>	Specific	0.008	0.019	<i>Leptotrichia goodfellowii</i>	Common	0.002	0.004
<i>Oribacterium sinus</i>	Common	0.007	0.017	<i>Atopobium rimae</i>	Common	0.002	0.003
<i>Ottowia</i> sp.	Common	0.006	0.015	<i>Enterococcus durans</i>	Common	0.002	0.003
<i>Treponema socranskii</i>	Common	0.004	0.005	<i>Prevotella veroralis</i>	Common	0.001	0.003
<i>Sneathia amnii</i>	Specific	0.004	0.009	<i>Prevotella nanceiensis</i>	Common	0.001	0.003
<i>Solobacterium moorei</i>	Common	0.004	0.006	Unclassified sp.	Common	25.76	7.045
<i>Scardovia wiggisiae</i>	Specific	0.003	0.008				
<i>Prevotella marshii</i>	Specific	0.003	0.007				
<i>Bifidobacterium dentium</i>	Specific	0.003	0.008				
<i>Mogibacterium diversum</i>	Common	0.003	0.008				
<i>Oribacterium asaccharolyticum</i>	Specific	0.003	0.007				
<i>Shuttleworthia satelles</i>	Specific	0.002	0.006				
<i>Parvimonas micra</i>	Common	0.002	0.006				
<i>Haemophilus haemolyticus</i>	Common	0.002	0.006				

<i>Prevotella pallens</i>	Common	0.002	0.004
<i>Lactobacillus rhamnosus</i>	Specific	0.002	0.005
<i>Anaeroglobus geminatus</i>	Specific	0.002	0.004
<i>Veillonella denticariosi</i>	Common	0.002	0.005
<i>Mycoplasma salivarium</i>	Specific	0.001	0.002
<i>Prevotella pleuritidis</i>	Specific	0.001	0.002
<i>Enterococcus durans</i>	Common	0.001	0.001
Unclassified sp.	Common	29.36	4.937

Table S3. Rank distribution of the level-1 SEED subsystem functions assigned for the mRNA reads (relative abundance per participant).

CLP			Control		
Function	Mean	Standard deviation	Function	Mean	Standard deviation
Protein Metabolism	24.727	2.963	Carbohydrates	21.035	6.015
Carbohydrates	15.629	1.305	Protein Metabolism	16.721	2.711
Clustering-based subsystems	11.805	0.664	Clustering-based subsystems	11.466	1.954
Amino Acids and Derivatives	6.951	0.754	Amino Acids and Derivatives	7.344	0.721
Miscellaneous	4.543	0.745	Cofactors, Vitamins, Prosthetic Groups, Pigments	4.620	0.501
Cofactors, Vitamins, Prosthetic Groups, Pigments	4.440	0.303	Respiration	4.346	0.944
RNA Metabolism	4.177	0.209	Miscellaneous	4.182	1.328
Membrane Transport	3.731	1.183	RNA Metabolism	3.960	1.078
Nucleosides and Nucleotides	3.399	0.364	Membrane Transport	3.830	0.634
Respiration	3.253	0.507	Cell Wall and Capsule	3.802	0.795
DNA Metabolism	3.229	0.868	Nucleosides and Nucleotides	3.493	0.783
Stress Response	2.828	0.459	DNA Metabolism	3.249	1.297
Cell Wall and Capsule	2.547	0.225	Stress Response	2.253	0.435
Fatty Acids, Lipids, and Isoprenoids	1.459	0.311	Virulence, Disease and Defense	1.668	0.374
Virulence, Disease and Defense	1.433	0.145	Fatty Acids, Lipids, and Isoprenoids	1.605	0.268
Phages, Prophages, Transposable elements, Plasmids	0.983	0.292	Iron acquisition and metabolism	1.194	0.795
Nitrogen Metabolism	0.863	0.378	Cell Division and Cell Cycle	0.978	0.343
Cell Division and Cell Cycle	0.804	0.148	Nitrogen Metabolism	0.937	0.572
Iron acquisition and metabolism	0.800	0.224	Phages, Prophages, Transposable elements, Plasmids	0.756	0.123
Phosphorus Metabolism	0.515	0.132	Regulation and Cell signaling	0.602	0.149
Sulfur Metabolism	0.503	0.134	Sulfur Metabolism	0.466	0.204
Regulation and Cell signaling	0.495	0.175	Phosphorus Metabolism	0.459	0.220
Motility and Chemotaxis	0.283	0.072	Motility and Chemotaxis	0.381	0.191
Metabolism of Aromatic Compounds	0.278	0.155	Metabolism of Aromatic Compounds	0.324	0.104
Potassium Metabolism	0.130	0.100	Potassium Metabolism	0.135	0.068
Secondary Metabolism	0.097	0.044	Secondary Metabolism	0.106	0.076

Dormancy and Sporulation 0.076 0.034
Photosynthesis 0.023 0.035

Dormancy and Sporulation 0.075 0.057
Photosynthesis 0.016 0.020

Table S4. Rank distribution of the level-2 KEGG functions assigned for the mRNA reads (relative abundance per participant).

CLP				Control			
Function	Group-specificity	Mean	Standard deviation	Function	Group-specificity	Mean	Standard deviation
Translation	Common	20.45	2.903	Carbohydrate metabolism	Common	16.41	2.439
Amino acid metabolism	Common	14.09	1.218	Amino acid metabolism	Common	15.29	0.817
Carbohydrate metabolism	Common	13.24	0.669	Translation	Common	15.16	2.272
Membrane transport	Common	9.654	0.805	Membrane transport	Common	10.02	1.382
Signal transduction	Common	5.490	0.661	Signal transduction	Common	5.862	1.180
Metabolism of cofactors and vitamins	Common	4.506	0.513	Energy metabolism	Common	5.034	0.704
Energy metabolism	Common	4.482	0.562	Metabolism of cofactors and vitamins	Common	4.932	1.382
Nucleotide metabolism	Common	4.471	0.726	Nucleotide metabolism	Common	4.278	0.654
Replication and repair	Common	4.168	0.974	Replication and repair	Common	4.104	1.320
Folding	Common	3.075	0.680	Lipid metabolism	Common	2.946	0.510
Environmental Adaptation	Common	3.035	0.788	Folding	Common	2.578	0.349
Transcription	Common	2.900	0.225	Transcription	Common	2.446	0.183
Lipid metabolism	Common	2.359	0.238	Glycan biosynthesis and metabolism	Common	1.850	0.562
Cell growth and death	Common	1.589	0.441	Environmental Adaptation	Common	1.782	0.546
Glycan biosynthesis and metabolism	Common	1.525	0.163	Cell growth and death	Common	1.332	0.339
Metabolism of terpenoids and polyketides	Common	0.859	0.211	Metabolism of terpenoids and polyketides	Common	0.919	0.209
Transport and catabolism	Common	0.795	0.193	Biosynthesis of Other Secondary Metabolites	Common	0.892	0.198
Biosynthesis of Other Secondary Metabolites	Common	0.717	0.138	Transport and catabolism	Common	0.868	0.195
Metabolism of other amino acids	Common	0.692	0.053	Infectious diseases	Common	0.863	0.120
Cancers	Common	0.571	0.164	Metabolism of other amino acids	Common	0.862	0.271
Cell motility	Common	0.534	0.104	Cell motility	Common	0.672	0.300
Infectious diseases	Common	0.533	0.078	Cancers	Common	0.527	0.253
Xenobiotics biodegradation and metabolism	Common	0.104	0.055	Xenobiotics biodegradation and metabolism	Common	0.162	0.035

Immune diseases	Common	0.063	0.067	Digestive system	Common	0.078	0.053
Digestive system	Common	0.041	0.031	Immune diseases	Common	0.054	0.061
Neurodegenerative diseases	Specific	0.014	0.020	Endocrine system	Common	0.054	0.032
Endocrine system	Common	0.014	0.013	Immune system	Specific	0.010	0.021
Cell communication	Common	0.005	0.011	Cell communication	Common	0.007	0.008
Substance dependence	Specific	0.002	0.006				
Development	Specific	0.002	0.005				

Table S5. Rank distribution of the top 50 species assigned for the mRNA reads (relative abundance per participant).

CLP			Control		
Species	Mean	Standard deviation	Species	Mean	Standard deviation
<i>Corynebacterium matruchotii</i>	4.906	3.735	<i>Leptotrichia hofstadii</i>	4.089	4.282
<i>Leptotrichia hofstadii</i>	4.582	2.971	<i>Corynebacterium matruchotii</i>	3.150	2.663
<i>Actinomyces</i> sp.	3.421	2.128	<i>Actinomyces</i> sp.	2.873	1.656
<i>Fusobacterium nucleatum</i>	2.872	1.440	<i>Actinomyces naeslundii</i>	2.576	1.015
<i>Actinomyces naeslundii</i>	2.838	1.082	<i>Streptococcus pneumoniae</i>	2.549	0.901
<i>Capnocytophaga</i> sp.	2.385	1.341	<i>Fusobacterium nucleatum</i>	2.548	1.852
<i>Actinomyces johnsonii</i>	2.151	2.634	<i>Capnocytophaga</i> sp.	2.475	1.286
<i>Tannerella</i> sp.	2.147	1.906	<i>Streptococcus</i> sp.	2.307	2.569
<i>Leptotrichia</i> sp.	1.965	0.338	<i>Neisseria</i> sp.	2.169	2.477
<i>Prevotella</i> sp.	1.831	0.996	<i>Actinobaculum</i> sp.	1.865	3.130
<i>Mycobacterium tuberculosis</i>	1.819	1.656	<i>Streptococcus oralis</i>	1.731	2.233
<i>Streptococcus pneumoniae</i>	1.770	1.011	<i>Mycobacterium tuberculosis</i>	1.713	1.918
<i>Selenomonas</i> sp.	1.369	0.746	<i>Actinomyces oris</i>	1.480	0.870
<i>Actinomyces oris</i>	1.320	0.632	<i>Leptotrichia</i> sp.	1.457	0.555
<i>Actinomyces massiliensis</i>	1.226	0.707	<i>Streptococcus sanguinis</i>	1.344	0.036
Unclassified sp.	1.106	0.803	<i>Prevotella</i> sp.	1.232	0.850
<i>Rhodococcus</i> sp.	1.082	0.979	<i>Veillonella</i> sp.	1.137	1.036
<i>Lachnoanaerobaculum saburreum</i>	1.031	0.778	<i>Porphyromonas</i> sp.	1.109	1.070
<i>Streptomyces</i> sp.	1.016	1.057	Unclassified sp.	1.071	1.005
<i>Corynebacterium pseudogenitalium</i>	1.011	1.264	<i>Tannerella</i> sp.	1.070	1.340
<i>Selenomonas noxia</i>	0.992	0.786	<i>Neisseria meningitidis</i>	1.052	0.614
<i>Bifidobacterium adolescentis</i>	0.964	0.869	<i>Rhodococcus</i> sp.	0.991	1.150
<i>Ruminococcus torques</i>	0.902	0.829	<i>Veillonella parvula</i>	0.965	0.977
<i>Propionibacterium acnes</i>	0.877	1.012	<i>Streptomyces</i> sp.	0.897	1.092
<i>Staphylococcus aureus</i>	0.871	0.794	<i>Corynebacterium durum</i>	0.877	0.836
<i>Corynebacterium efficiens</i>	0.854	0.893	<i>Actinomyces massiliensis</i>	0.845	0.633
<i>Streptococcus</i> sp.	0.851	0.321	<i>Ruminococcus torques</i>	0.838	0.970

<i>Neisseria</i> sp.	0.836	0.582	<i>Corynebacterium pseudogenitalium</i>	0.787	1.014
<i>Actinomyces dentalis</i>	0.779	0.648	<i>Bifidobacterium adolescentis</i>	0.774	0.900
<i>Leptotrichia wadei</i>	0.752	0.619	<i>Haemophilusparainfluenzae</i>	0.772	0.830
<i>Veillonella</i> sp.	0.722	0.097	<i>Staphylococcus aureus</i>	0.710	0.860
<i>Pseudopropionibacterium propionicum</i>	0.698	0.662	<i>Corynebacterium efficiens</i>	0.690	0.815
<i>Streptococcus sanguinis</i>	0.685	0.532	<i>Veillonella dispar</i>	0.679	0.620
<i>Daphnia magna</i>	0.669	0.610	<i>Actinomyces odontolyticus</i>	0.672	0.498
<i>Neisseria meningitidis</i>	0.634	0.121	<i>Cardiobacterium hominis</i>	0.671	0.644
<i>Olsenella</i> sp.	0.634	0.583	<i>Streptococcus gordonii</i>	0.661	0.881
<i>Veillonella parvula</i>	0.613	0.251	<i>Propionibacterium acnes</i>	0.617	0.711
<i>Streptococcus oralis</i>	0.602	0.268	<i>Porphyromonas catoniae</i>	0.612	0.881
<i>Porphyromonas</i> sp.	0.558	0.263	<i>Capnocytophaga gingivalis</i>	0.603	0.347
<i>Campylobacter showae</i>	0.554	0.566	<i>Neisseria sicca</i>	0.573	0.878
<i>Ruminococcus gnavus</i>	0.549	0.505	<i>Pseudopropionibacterium propionicum</i>	0.566	0.547
<i>Actinomyces odontolyticus</i>	0.537	0.227	<i>Daphnia magna</i>	0.564	0.685
<i>Nocardia asteroides</i>	0.511	0.725	<i>Streptococcus mitis</i>	0.517	0.577
<i>Campylobacter jejuni</i>	0.448	0.374	<i>Selenomonas</i> sp.	0.497	0.283
<i>Cardiobacterium hominis</i>	0.422	0.210	<i>Ruminococcus gnavus</i>	0.490	0.565
<i>Capnocytophaga ochracea</i>	0.410	0.384	<i>Abiotrophia</i> sp.	0.487	0.568
<i>Actinomyces turicensis</i>	0.402	0.419	<i>Neisseria elongata</i>	0.481	0.457
<i>Blautia obeum</i>	0.401	0.367	<i>Lautropia mirabilis</i>	0.471	0.373
<i>Veillonella dispar</i>	0.400	0.088	<i>Capnocytophaga granulosa</i>	0.464	0.289
<i>Fusobacterium</i> sp.	0.400	0.269	<i>Abiotrophia defectiva</i>	0.462	0.437

Table S6. Rank distribution of VTiF (mean RPKM values among the participants and the mRNA-to-rRNA ratio).

CLP				Control			
Species	rc-rRNA	mRNA	log2 mRNA-to-rRNA ratio	Species	rc-rRNA	mRNA	log2 mRNA-to-rRNA ratio
<i>Enterococcus durans</i>	1.2	2132.6	10.81	<i>Haemophilus haemolyticus</i>	4.2	8079.4	10.91
<i>Lactobacillus rhamnosus</i>	3.9	6519.9	10.70	<i>Prevotella loescheii</i>	6.6	6497.1	9.95
<i>Haemophilus haemolyticus</i>	6.0	7702.1	10.31	<i>Enterococcus durans</i>	3.4	2421.7	9.49
<i>Lactobacillus fermentum</i>	26.5	16924.4	9.32	<i>Leptotrichia goodfellowii</i>	4.1	2795.8	9.43
<i>Treponema socranskii</i>	8.8	4998.8	9.15	<i>Leptotrichia hofstadii</i>	1168.4	411882	8.46
<i>Streptococcus salivarius</i>	27.2	13784.4	8.99	<i>Streptococcus intermedius</i>	37.5	10647.1	8.15
<i>Prevotella pallens</i>	4.8	2126.7	8.79	<i>Oribacterium sinus</i>	15.2	3886.9	8.00
<i>Aggregatibacter aphrophilus</i>	14.3	5883.0	8.69	<i>Stomatobaculum longum</i>	53.7	13088.0	7.93
<i>Actinomyces odontolyticus</i>	118.3	43568.5	8.52	<i>Prevotella veroralis</i>	3.1	668.1	7.75
<i>Veillonella parvula</i>	116.9	40951.6	8.45	<i>Prevotella oris</i>	18.0	2233.0	6.96
<i>Streptococcus gordonii</i>	50.1	16859.6	8.40	<i>Parvimonas micra</i>	7.4	873.5	6.88
<i>Streptococcus intermedius</i>	37.9	11772.5	8.28	<i>Lachnoanaerobaculum saburreum</i>	210.2	23158.6	6.78
<i>Streptococcus cristatus</i>	47.3	13332.4	8.14	<i>Selenomonas noxia</i>	182.1	18586.5	6.67
<i>Eikenella corrodens</i>	30.7	8047.6	8.03	<i>Dialister invisus</i>	30.8	2989.9	6.60
<i>Solobacterium moorei</i>	7.7	1943.7	7.97	<i>Prevotella nigrescens</i>	246.5	18887.2	6.26
<i>Centipeda periodontii</i>	81.2	20222.8	7.96	<i>Treponema socranskii</i>	23.2	1771.8	6.25
<i>Oribacterium sinus</i>	15.6	3712.6	7.89	<i>Streptococcus sanguinis</i>	1055.0	76975.6	6.19
<i>Prevotella pleuritidis</i>	2.0	400.6	7.64	<i>Prevotella maculosa</i>	23.9	1571.7	6.04
<i>Leptotrichia hofstadii</i>	2453.6	422558	7.43	<i>Kingella oralis</i>	236.3	13156.7	5.80
<i>Dialister invisus</i>	43.7	6535.9	7.23	<i>Prevotella saccharolytica</i>	62.9	3488.8	5.79
<i>Prevotella saccharolytica</i>	52.8	7956.2	7.23	<i>Prevotella salivae</i>	19.9	1080.8	5.76
<i>Capnocytophaga gingivalis</i>	151.9	21037.5	7.11	<i>Actinomyces odontolyticus</i>	759.6	40572.8	5.74
<i>Parvimonas micra</i>	6.2	804.8	7.02	<i>Atopobium rimae</i>	4.5	239.2	5.73
<i>Selenomonas noxia</i>	320.4	41595.9	7.02	<i>Actinomyces gerencseriae</i>	198.1	10405.9	5.72
<i>Prevotella marshii</i>	6.6	782.7	6.88	<i>Veillonella parvula</i>	717.1	34755.7	5.60
<i>Prevotella nigrescens</i>	205.2	23879.6	6.86	<i>Johnsonella ignava</i>	55.9	2450.2	5.46
<i>Leptotrichia goodfellowii</i>	44.8	5080.1	6.83	<i>Solobacterium moorei</i>	32.8	1436.8	5.45

<i>Prevotella maculosa</i>	56.8	5775.0	6.67	<i>Centipeda periodontii</i>	378.1	16272.0	5.43
<i>Prevotella oris</i>	37.6	3511.1	6.55	<i>Streptococcus mutans</i>	21.6	932.0	5.43
<i>Prevotella veroralis</i>	38.8	3637.0	6.55	<i>Fusobacterium nucleatum</i>	5421.8	222092	5.36
<i>Prevotella micans</i>	51.0	4524.7	6.47	<i>Campylobacter gracilis</i>	310.7	12356.7	5.31
<i>Streptococcus anginosus</i>	85.6	7521.2	6.46	<i>Capnocytophaga haemolytica</i>	19.0	717.9	5.24
<i>Ottowia</i> sp.	11.8	983.7	6.38	<i>Eikenella corrodens</i>	156.3	5694.5	5.19
<i>Actinomyces johnsonii</i>	773.8	64192.7	6.37	<i>Actinomyces johnsonii</i>	331.1	11541.7	5.12
<i>Catonella morbi</i>	78.2	6157.2	6.30	<i>Actinomyces israelii</i>	88.6	2909.1	5.04
<i>Selenomonas artemidis</i>	81.7	5375.9	6.04	<i>Streptococcus gordonii</i>	629.1	19427.8	4.95
<i>Anaeroglobus geminatus</i>	3.9	240.4	5.93	<i>Prevotella denticola</i>	27.5	842.9	4.94
<i>Johnsonella ignava</i>	64.8	3678.3	5.83	<i>Prevotella oulorum</i>	75.7	2279.2	4.91
<i>Prevotella melaninogenica</i>	136.9	7658.6	5.81	<i>Rothia aeria</i>	564.1	15569.3	4.79
<i>Lachnoanaerobaculum saburreum</i>	1014.4	54952.1	5.76	<i>Actinomyces massiliensis</i>	1610.4	41295.6	4.68
<i>Streptococcus mitis</i>	288.3	15237.8	5.72	<i>Prevotella nanceiensis</i>	2.9	73.8	4.68
<i>Prevotella intermedia</i>	49.6	2587.9	5.71	<i>Actinomyces oris</i>	2174.8	53884.4	4.63
<i>Fusobacterium nucleatum</i>	4637.5	241619	5.70	<i>Prevotella pallens</i>	72.2	1676.9	4.54
<i>Neisseria flavescens</i>	155.8	7783.3	5.64	<i>Haemophilus paraphrohaemolyticus</i>	4.6	96.0	4.38
<i>Actinomyces oris</i>	1665.9	82469.1	5.63	<i>Aggregatibacter segnis</i>	56.8	1174.0	4.37
<i>Oribacterium asaccharolyticum</i>	6.0	293.5	5.62	<i>Actinomyces naeslundii</i>	5360.9	105885	4.30
<i>Prevotella denticola</i>	39.0	1920.8	5.62	<i>Selenomonas artemidis</i>	134.2	2617.4	4.29
<i>Fusobacterium periodonticum</i>	138.6	5959.1	5.43	<i>Oribacterium parvum</i>	19.0	355.9	4.22
<i>Campylobacter concisus</i>	180.6	7560.7	5.39	<i>Streptococcus anginosus</i>	364.8	6741.9	4.21
<i>Selenomonas flueggei</i>	232.2	9499.4	5.35	<i>Catonella morbi</i>	200.3	3649.1	4.19
<i>Alloprevotella tanneriae</i>	30.0	1154.7	5.27	<i>Prevotella micans</i>	18.8	340.4	4.18
<i>Prevotella salivae</i>	59.6	2295.2	5.27	<i>Leptotrichia wadei</i>	763.8	12120.2	3.99
<i>Prevotella oulorum</i>	307.3	11711.7	5.25	<i>Capnocytophaga gingivalis</i>	1406.4	22049.4	3.97
<i>Selenomonas infelix</i>	173.4	6561.8	5.24	<i>Veillonella dispar</i>	1520.4	23347.1	3.94
<i>Actinomyces naeslundii</i>	4401.6	148917	5.08	<i>Campylobacter concisus</i>	321.7	4581.7	3.83
<i>Aggregatibacter segnis</i>	124.7	3796.8	4.93	<i>Selenomonas infelix</i>	283.3	3864.6	3.77

<i>Stomatobaculum longum</i>	352.4	10558.8	4.91	<i>Alloprevotella rava</i>	10.6	144.3	3.76
<i>Gemella morbillorum</i>	344.9	10231.3	4.89	<i>Granulicatella elegans</i>	62.4	831.3	3.74
<i>Actinomyces viscosus</i>	634.8	18355.2	4.85	<i>Selenomonas sputigena</i>	415.5	4840.3	3.54
<i>Gemella haemolysans</i>	102.6	2937.4	4.84	<i>Cardiobacterium valvarum</i>	344.8	3951.6	3.52
<i>Scardovia wiggsiae</i>	6.7	170.2	4.66	<i>Prevotella melaninogenica</i>	567.0	6078.6	3.42
<i>Bifidobacterium dentium</i>	6.4	154.0	4.58	<i>Porphyromonas catoniae</i>	1000.7	10529.6	3.40
<i>Actinomyces gerencseriae</i>	664.3	15556.3	4.55	<i>Streptococcus oralis</i>	4861.0	50371.1	3.37
<i>Megasphaera micronuciformis</i>	34.1	721.0	4.40	<i>Corynebacterium matruchotii</i>	12768.0	121702	3.25
<i>Actinomyces massiliensis</i>	3586.1	67149.2	4.23	<i>Gemella morbillorum</i>	705.2	5936.1	3.07
<i>Shuttleworthia satelles</i>	4.9	91.6	4.23	<i>Corynebacterium durum</i>	2276.9	16501.9	2.86
<i>Prevotella scopos</i>	163.6	2894.6	4.14	<i>Capnocytophaga sputigena</i>	1692.4	10960.1	2.70
<i>Atopobium rimae</i>	22.0	352.1	4.00	<i>Actinomyces dentalis</i>	1949.8	12381.7	2.67
<i>Rothia mucilaginosa</i>	33.7	511.3	3.92	<i>Abiotrophia defectiva</i>	2462.5	11744.0	2.25
<i>Capnocytophaga ochracea</i>	1140.2	16417.5	3.85	<i>Kingella denitrificans</i>	939.6	4392.8	2.23
<i>Capnocytophaga sputigena</i>	1040.6	14754.8	3.83	<i>Lautropia mirabilis</i>	2687.5	12154.8	2.18
<i>Actinomyces dentalis</i>	2544.0	35162.7	3.79	<i>Streptococcus mitis</i>	3152.0	13847.4	2.14
<i>Veillonella dispar</i>	1820.8	25202.7	3.79	<i>Haemophilus parahaemolyticus</i>	18.9	77.6	2.04
<i>Campylobacter gracilis</i>	1440.2	19572.0	3.76	<i>Neisseria elongata</i>	2518.4	10161.4	2.01
<i>Kingella oralis</i>	820.0	10869.2	3.73	<i>Granulicatella adiacens</i>	1116.5	4368.2	1.97
<i>Corynebacterium durum</i>	1436.8	17903.9	3.64	<i>Haemophilus parainfluenzae</i>	6872.5	25308.2	1.88
<i>Haemophilus parainfluenzae</i>	1909.7	23518.0	3.62	<i>Rothia dentocariosa</i>	1796.0	6616.0	1.88
<i>Porphyromonas catoniae</i>	853.7	10248.8	3.59	<i>Fusobacterium periodonticum</i>	1041.0	3666.2	1.82
<i>Corynebacterium matruchotii</i>	18244.8	219299	3.59	<i>Gemella haemolysans</i>	835.6	2825.6	1.76
<i>Rothia aeria</i>	1257.9	15017.9	3.58	<i>Streptococcus cristatus</i>	2749.1	9147.2	1.73
<i>Streptococcus sanguinis</i>	7271.1	75543.2	3.38	<i>Mitsuokella multacida</i>	82.8	239.9	1.54
<i>Streptococcus mutans</i>	585.2	5496.8	3.23	<i>Gemella sanguinis</i>	346.2	960.9	1.47
<i>Cardiobacterium valvarum</i>	1003.3	9146.8	3.19	<i>Megasphaera micronuciformis</i>	79.8	203.0	1.35
<i>Veillonella atypica</i>	254.7	2306.6	3.18	<i>Ottowia sp.</i>	765.1	1809.0	1.24
<i>Actinomyces timonensis</i>	130.5	991.3	2.93	<i>Capnocytophaga granulosa</i>	11111.9	24260.7	1.13
<i>Neisseria elongata</i>	1413.3	10485.1	2.89	<i>Neisseria mucosa</i>	2634.5	5564.8	1.08
<i>Abiotrophia defectiva</i>	1185.4	8756.8	2.88	<i>Leptotrichia shahii</i>	1439.5	2773.5	0.95

<i>Prevotella nanceiensis</i>	19.9	132.9	2.74	<i>Veillonella atypica</i>	739.1	1364.9	0.88
<i>Granulicatella adiacens</i>	642.8	4248.6	2.72	<i>Campylobacter showae</i>	2800.8	4908.9	0.81
<i>Campylobacter showae</i>	3175.0	20021.6	2.66	<i>Cardiobacterium hominis</i>	12059.3	20247.5	0.75
<i>Selenomonas sputigena</i>	1697.2	10022.3	2.56	<i>Porphyromonas endodontalis</i>	73.0	69.5	-0.07
<i>Gemella sanguinis</i>	248.2	1384.1	2.48	<i>Neisseria flavescens</i>	7378.1	6103.7	-0.27
<i>Mycoplasma salivarium</i>	2.4	12.3	2.38	<i>Neisseria sicca</i>	21237.3	9226.0	-1.20
<i>Rothia dentocariosa</i>	1010.7	5202.1	2.36	<i>Neisseria subflava</i>	2752.1	1170.1	-1.23
<i>Granulicatella elegans</i>	154.5	728.9	2.24	<i>Leptotrichia buccalis</i>	9911.7	3342.4	-1.57
<i>Cardiobacterium hominis</i>	6377.1	28956.1	2.18	<i>Moraxella catarrhalis</i>	6386.8	1206.6	-2.40
<i>Actinomyces georgiae</i>	1148.8	5178.4	2.17	<i>Streptococcus lactarius</i>	879.2	79.2	-3.47
<i>Leptotrichia shahii</i>	1768.2	7331.0	2.05	<i>Leptotrichia hongkongensis</i>	523.8	41.3	-3.67
<i>Atopobium parvulum</i>	141.3	543.5	1.94	<i>Veillonella denticariosi</i>	23.3	1.3	-4.16
<i>Leptotrichia wadei</i>	10393.8	32457.5	1.64	<i>Neisseria oralis</i>	528.6	11.0	-5.59
<i>Capnocytophaga granulosa</i>	11270.5	32781.1	1.54	<i>Neisseria pharyngis</i>	1004.6	18.4	-5.77
<i>Lautropia mirabilis</i>	3884.1	10912.6	1.49				
<i>Neisseria subflava</i>	671.4	1557.1	1.21				
<i>Neisseria sicca</i>	4789.3	10371.3	1.11				
<i>Kingella denitrificans</i>	2221.4	4539.1	1.03				
<i>Leptotrichia buccalis</i>	7514.9	13263.2	0.82				
<i>Neisseria polysaccharea</i>	729.7	862.6	0.24				
<i>Lactobacillus vaginalis</i>	186.5	170.2	-0.13				
<i>Neisseria mucosa</i>	4624.7	3996.8	-0.21				
<i>Moraxella catarrhalis</i>	2478.3	1393.9	-0.83				
<i>Leptotrichia hongkongensis</i>	841.2	132.4	-2.67				
<i>Neisseria flava</i>	216.7	31.7	-2.77				
<i>Streptococcus lactarius</i>	474.3	64.9	-2.87				
<i>Neisseria oralis</i>	5009.2	13.6	-8.52				

Table S7. Rank distribution of the top 50 VFDB functions assigned for the mRNA reads (relative abundance per participant).

CLP				Control			
Function	Group-specificity	Mean	Standard deviation	Function	Group-specificity	Mean	Standard deviation
elongation factor Tu	Common	4.988	1.235	elongation factor Tu	Common	3.429	1.171
translation elongation factor Tu	Common	4.049	1.567	glyceraldehyde-3-phosphate dehydrogenase	Common	3.175	1.534
surface-anchored fimbrial subunit	Common	3.741	3.033	surface-anchored fimbrial subunit	Common	3.002	2.324
glyceraldehyde-3-phosphate dehydrogenase	Common	3.352	0.924	hypothetical protein	Common	2.944	0.790
hypothetical protein	Common	2.890	0.421	translation elongation factor Tu	Common	2.840	1.115
glyceraldehyde-3-phosphate dehydrogenase, type I	Common	2.535	0.772	phosphopyruvate hydratase	Common	2.797	1.776
phosphopyruvate hydratase	Common	2.333	0.819	glyceraldehyde-3-phosphate dehydrogenase, type I	Common	2.286	1.342
Unspecified	Common	1.656	0.411	Unspecified	Common	1.886	0.480
Elongation factor Tu	Common	1.609	0.660	type IV pilin structural subunit	Common	1.714	2.980
FimP	Common	1.428	2.022	molecular chaperone DnaK	Common	1.121	0.310
chaperonin GroEL	Common	1.311	0.816	ATP-dependent Clp protease proteolytic subunit	Common	1.113	0.233
ATP-dependent Clp protease proteolytic subunit	Common	1.260	0.304	Elongation factor Tu	Common	0.988	0.303
molecular chaperone DnaK	Common	1.259	0.732	FimP	Common	0.868	0.564
endopeptidase Clp ATP-binding chain C	Common	0.862	0.336	chaperonin GroEL	Common	0.819	0.284
Glyceraldehyde 3-phosphate dehydrogenase, putative	Common	0.775	0.587	ABC transporter ATP-binding protein	Common	0.811	0.235
ABC transporter ATP-binding protein	Common	0.718	0.177	enolase	Common	0.790	0.457
enolase	Common	0.685	0.213	endopeptidase Clp ATP-binding chain C	Common	0.696	0.122
3-oxoacyl-ACP reductase	Common	0.664	0.168	acyl carrier protein	Common	0.586	0.229

RNA polymerase sigma factor	Common	0.572	0.124	Glyceraldehyde 3-phosphate dehydrogenase, putative	Common	0.581	0.275
acyl carrier protein	Common	0.538	0.239	3-oxoacyl-ACP reductase	Common	0.579	0.111
ABC transporter ATP-binding protein AatC	Common	0.530	0.241	UDP-glucose 4-epimerase	Common	0.541	0.265
oligopeptide ABC transporter, permease component	Common	0.492	0.149	phaseolotoxin-insensitive ornithine carbamoyltransferase	Common	0.509	0.156
UDP-glucose 4-epimerase	Common	0.440	0.113	SpaH-type pili major subunit SpaH	Common	0.492	0.797
two-component system response regulator	Common	0.438	0.245	oligopeptide ABC transporter, permease component	Common	0.483	0.133
ABC transporter, ATP-binding protein	Common	0.403	0.182	ABC transporter, ATP-binding protein	Common	0.481	0.176
serine/threonine protein kinase	Common	0.396	0.086	superoxide dismutase	Common	0.475	0.114
glutamine synthetase	Common	0.389	0.143	ABC transporter ATP-binding protein AatC	Common	0.436	0.102
superoxide dismutase	Common	0.387	0.155	Dot/Icm type IV secretion system effector LirB	Common	0.432	0.153
immunogenic lipoprotein A	Common	0.374	0.156	Enolase, putative	Common	0.430	0.216
Enolase, putative	Common	0.371	0.111	flagellin subunit	Common	0.428	0.388
Uncharacterized conserved phage related protein	Common	0.362	0.728	RNA polymerase sigma factor	Common	0.421	0.048
undecaprenyl diphosphate synthase	Common	0.361	0.149	porin, major outer membrane protein P.I	Common	0.377	0.256
type IV pilin structural subunit	Common	0.360	0.761	fimbrial protein MS11-D1 precursor	Common	0.375	0.551
phaseolotoxin-insensitive ornithine carbamoyltransferase	Common	0.356	0.146	ABC transporter-like protein	Common	0.333	0.215
glucose-6-phosphate isomerase	Common	0.349	0.137	undecaprenyl diphosphate synthase	Common	0.328	0.051
drugs-transport transmembrane ATP-binding protein ABC transporter	Common	0.338	0.270	immunogenic lipoprotein A	Common	0.326	0.175
alkyl hydroperoxide reductase C protein AhpC	Common	0.331	0.191	nucleoside diphosphate kinase	Common	0.321	0.077
macrophage infectivity potentiator	Common	0.309	0.314	glucose-6-phosphate isomerase	Common	0.318	0.039

synthase II	Common	0.285	0.047	serine/threonine protein kinase	Common	0.316	0.070
unknown	Common	0.279	0.184	Uncharacterized conserved phage related protein	Common	0.291	0.259
(3R)-hydroxymyristoyl ACP dehydratase	Common	0.273	0.134	outer membrane protein A	Common	0.283	0.143
flagellin subunit	Common	0.273	0.159	dTDP-glucose 4,6-dehydratase	Common	0.283	0.091
dTDP-glucose 4,6-dehydratase	Common	0.260	0.101	Porphobilinogen synthase	Common	0.280	0.112
two component transcriptional regulator, winged helix family	Common	0.252	0.129	histidine transport system permease protein HisQ	Common	0.273	0.098
nitrate reductase subunit alpha	Common	0.252	0.077	macrophage infectivity potentiator	Common	0.268	0.025
outer membrane protein A	Common	0.248	0.174	invasion associated secreted endopeptidase	Common	0.267	0.375
glutamine synthetase, type I	Common	0.247	0.114	synthase II	Common	0.266	0.121
Dot/Icm type IV secretion system effector LirB	Common	0.236	0.152	alkyl hydroperoxide reductase	Common	0.260	0.197
Collagen-binding protein A	Common	0.232	0.301	trifunctional thioredoxin/methionine sulfoxide reductase A/B protein	Common	0.257	0.163
UDP-galactopyranose mutase	Common	0.229	0.085	glutamine synthetase	Common	0.250	0.115

Table S8. Rank distribution of the top 50 MvirDB functions assigned for the mRNA reads (relative abundance per participant).

CLP				Control			
Function	Group-specificity	Mean	Standard deviation	Function	Group-specificity	Mean	Standard deviation
translation initiation factor IF-1	Common	4.347	1.396	translation initiation factor IF-1	Common	2.200	0.852
50S ribosomal protein L13	Common	2.798	0.678	pyruvate formate lyase I	Common	1.939	0.722
RecName: Full=50S ribosomal protein L6;	Common	2.158	0.915	hypothetical protein	Common	1.758	0.879
pyruvate formate lyase I	Common	1.954	0.591	50S ribosomal protein L13	Common	1.744	0.532
ABC transporter, ATP-binding protein	Common	1.355	0.272	surface-anchored fimbrial subunit	Common	1.502	1.697
surface-anchored fimbrial subunit	Common	1.191	0.816	RecName: Full=50S ribosomal protein L6;	Common	1.371	0.484
chaperonin GroEL	Common	1.026	0.616	ABC transporter, ATP-binding protein	Common	1.292	0.209
hypothetical protein	Common	1.010	0.320	ABC-type transporter, ATPase component	Common	0.969	0.496
30S ribosomal protein S9	Common	0.970	0.339	30S ribosomal protein S9	Common	0.862	0.291
ATP-dependent Clp protease proteolytic subunit	Common	0.914	0.198	ATP-dependent Clp protease proteolytic subunit	Common	0.805	0.177
fructose-bisphosphate aldolase	Common	0.834	0.475	fructose-bisphosphate aldolase	Common	0.753	0.490
DNA-directed RNA polymerase subunit beta`	Common	0.787	0.142	oligopeptide ABC transporter, ATP-binding protein	Common	0.702	0.088
molecular chaperone DnaK	Common	0.767	0.369	chaperonin GroEL	Common	0.696	0.153
DNA-directed RNA polymerase subunit beta	Common	0.761	0.058	RecName: Full=Major outer membrane protein P.IB; Short=Protein IB; Short=PIB; AltName: Full=Porin; Flags: Precursor;	Common	0.673	0.343
glutamate dehydrogenase	Common	0.728	0.288	glutamate dehydrogenase	Common	0.665	0.229
oligopeptide ABC transporter, ATP-binding protein	Common	0.716	0.122	molecular chaperone DnaK	Common	0.662	0.232
ABC-type transporter, ATPase component	Common	0.676	0.284	ABC-type transporter, permease component	Common	0.633	0.369

hypothetical protein gbs0131	Common	0.659	0.178	DNA-directed RNA polymerase subunit beta	Common	0.632	0.115
RecName: Full=Preprotein translocase subunit secY;	Common	0.639	0.151	hypothetical protein gbs0131	Common	0.603	0.178
protein found in conjugate transposon	Common	0.618	0.551	DNA-directed RNA polymerase subunit beta`	Common	0.584	0.043
30S ribosomal protein S1	Common	0.607	0.134	30S ribosomal protein S1	Common	0.577	0.168
RecName: Full=ATP-dependent Clp protease ATP-binding subunit ClpX;	Common	0.548	0.064	RecName: Full=Acetate kinase; EC=2.7.2.1; AltName: Full=Acetokinase;	Common	0.567	0.053
hypothetical protein gbs0137	Common	0.539	0.136	protein found in conjugate transposon	Common	0.562	0.378
thioredoxin reductase	Common	0.539	0.137	RecName: Full=Outer membrane protein P.III; AltName: Full=Gonococcal protein III; Short=PIII; Flags: Precursor;	Common	0.521	0.150
pyruvate kinase	Common	0.505	0.198	hypothetical protein gbs0130	Common	0.510	0.487
RecName: Full=Acetate kinase; EC=2.7.2.1; AltName: Full=Acetokinase;	Common	0.498	0.089	putative ABC transporter ATP-binding protein	Common	0.509	0.092
RecName: Full=Protein translocase subunit SecY;	Common	0.497	0.148	ABC-type transporter, periplasmic component	Common	0.508	0.427
glucose-1-phosphate thymidyltransferase	Common	0.495	0.190	ornithine carbamoyltransferase 2, chain F; CP4-6 prophage	Common	0.501	0.159
alkyl hydroperoxide reductase subunit C	Common	0.486	0.284	triosephosphate isomerase	Common	0.498	0.126
30S ribosomal protein S15	Common	0.452	0.157	RecName: Full=ATP-dependent Clp protease ATP-binding subunit ClpX;	Common	0.491	0.080
tetracycline resistance protein	Common	0.451	0.184	RecName: Full=Preprotein translocase subunit secY;	Common	0.460	0.103
polynucleotide phosphorylase/polyadenylase	Common	0.446	0.051	thioredoxin reductase	Common	0.453	0.163

ABC-type transporter, permease component	Common	0.425	0.213	glucose-1-phosphate thymidyltransferase	Common	0.447	0.059
putative ABC transporter ATP-binding protein	Common	0.417	0.128	pyruvate kinase	Common	0.423	0.200
glutamine synthetase GLNA1 glutamine synthase GS-I	Common	0.413	0.105	P60 extracellular protein, invasion associated protein Iap	Common	0.422	0.615
RecName: Full=Outer membrane protein P.III; AltName: Full=Gonococcal protein III; Short=PIII; Flags: Precursor;	Common	0.403	0.484	thioredoxin	Common	0.410	0.156
ABC transporter, permease protein	Common	0.399	0.166	ribose-phosphate pyrophosphokinase	Common	0.377	0.058
hypothetical protein gbs0141	Common	0.387	0.205	IS1480 transposase	Common	0.371	0.467
endopeptidase Clp ATP-binding chain C	Common	0.376	0.096	RecName: Full=Protein translocase subunit SecY;	Common	0.354	0.061
SubName: Full=ClpB protein;	Common	0.375	0.175	30S ribosomal protein S15	Common	0.353	0.179
hypothetical protein lin0097	Common	0.372	0.144	alkyl hydroperoxide reductase subunit C	Common	0.353	0.390
pyruvate formate lyase-activating enzyme 1	Common	0.366	0.078	phosphoserine aminotransferase	Common	0.346	0.124
ornithine carbamoyltransferase 2, chain F; CP4-6 prophage	Common	0.366	0.141	methylmalonyl-CoA mutase	Common	0.345	0.093
thioredoxin	Common	0.350	0.196	SubName: Full=ClpB protein;	Common	0.341	0.083
RecName: Full=Major outer membrane protein P.IB; Short=Protein IB; Short=PIB; AltName: Full=Porin; Flags: Precursor;	Common	0.347	0.357	cold shock protein CspC	Common	0.341	0.374
ribose-phosphate pyrophosphokinase	Common	0.329	0.071	hypothetical protein gbs0137	Common	0.333	0.132
hypothetical protein SAG0145	Common	0.326	0.103	ABC transporter, permease protein	Common	0.331	0.058
putative lysil-tRNA synthetase LysU	Common	0.320	0.087	ribose ABC transporter ATP-binding protein	Common	0.330	0.086
RNA polymerase sigma factor	Common	0.318	0.091	seryl-tRNA synthetase	Common	0.329	0.110
triosephosphate isomerase	Common	0.313	0.066	polynucleotide	Common	0.323	0.059

