

Supplement

The closed eye harbors a unique microbiome in dry eye disease

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Supplemental Fig S1.

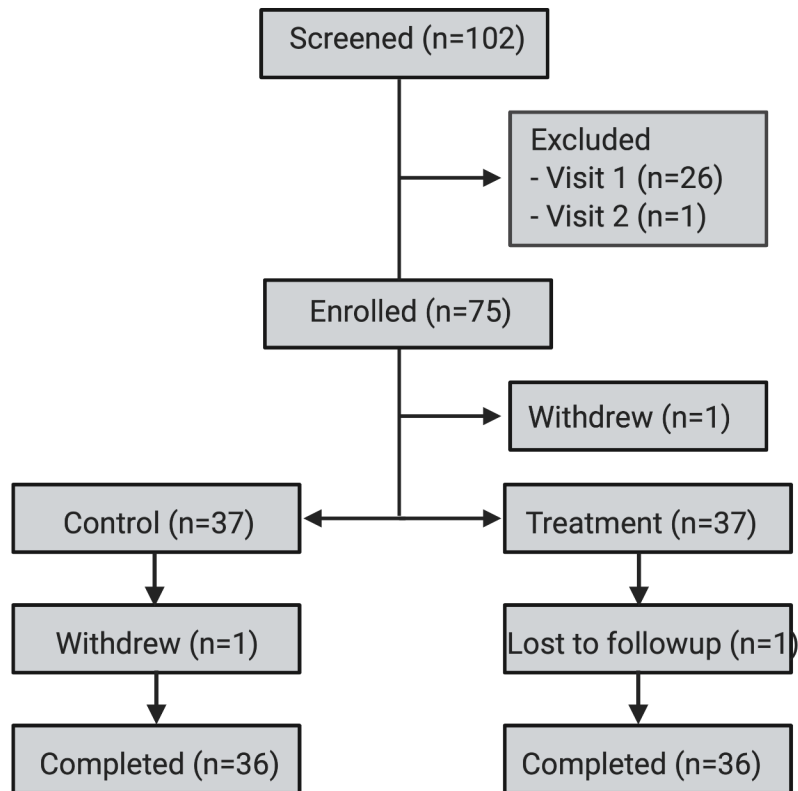


Fig. S1. Consolidated standards of reporting trials subject allocation diagram.
CONSORT subject allocation diagram. Figure generated by BioRender.

Supplemental Fig S2.

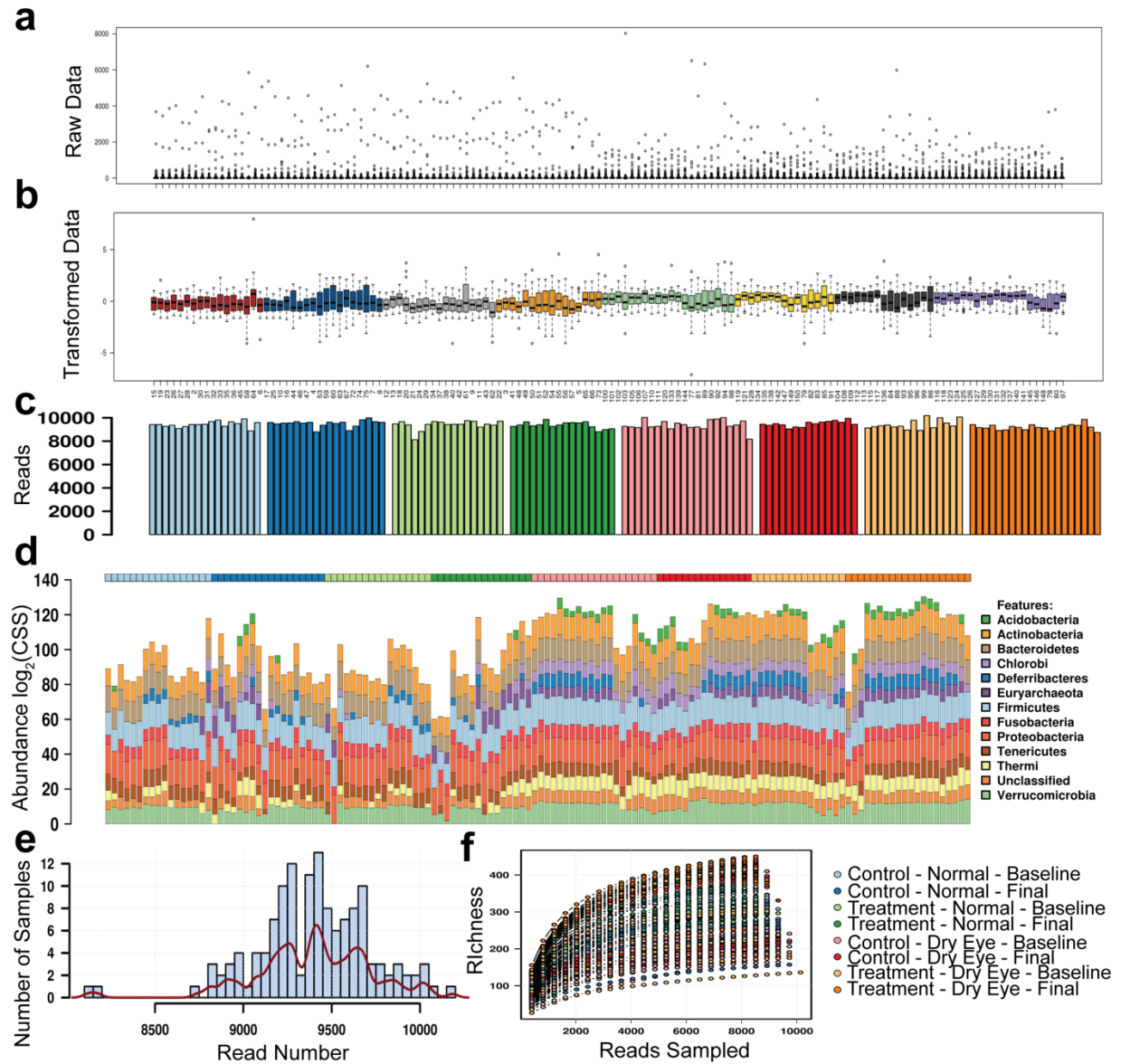


Fig. S2. Read depth and quality are consistent across clinical groupings.

- (a) Raw sequencing data.
- (b) Log₂-transformed relative abundance.
- (c) Sequencing depth.
- (d) Relative abundance at the phylum level.
- (e) Sequence reads per sample.
- (f) Read depth.

Supplemental Fig. S3.

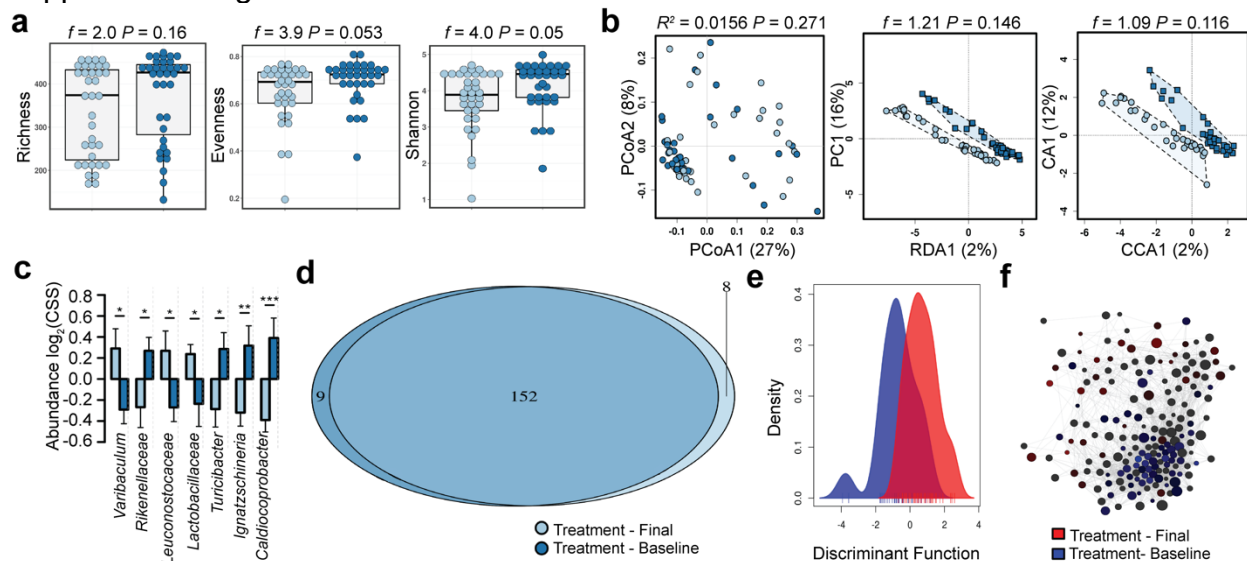


Fig. S3. Limited changes occur in the dry eye microbiome with daily eye rinse.

- (a) Alpha diversity.
 (b) Beta diversity.
 (c) Relative abundance of bacterial genera. Two-way ANOVA, * $P = 0.05$, ** $P = 0.01$, *** $P = 0.001$.
 (d) Core microbiome analysis.
 (e) Discriminant analysis of principal components.
 (f) Spearman network analysis at the genus level.

Supplemental Fig. S4

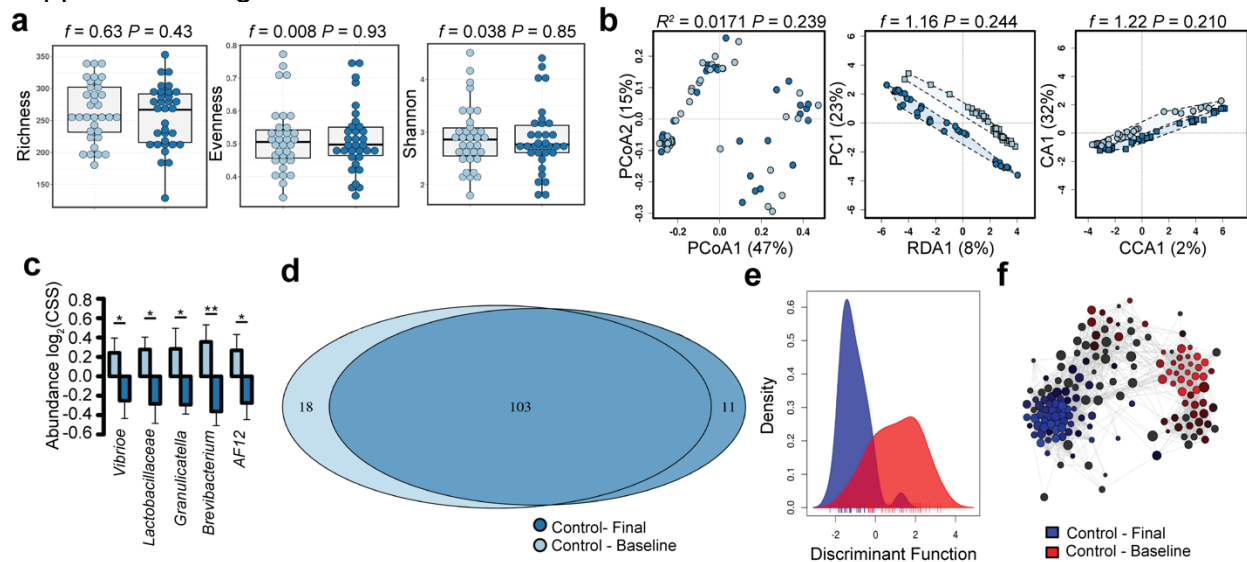


Fig. S4. Limited changes occur in the normal eye microbiome with eye rinse.

- (a) Alpha diversity.
 (b) Beta diversity.
 (c) Relative abundance of bacterial orders. Two-way ANOVA, * $P = 0.05$, ** $P = 0.01$, *** $P = 0.001$.
 (d) Core microbiome analysis.
 (e) Discriminant analysis of principal components.
 (f) Spearman network analysis at the genus level.

Supplemental Fig. S5.

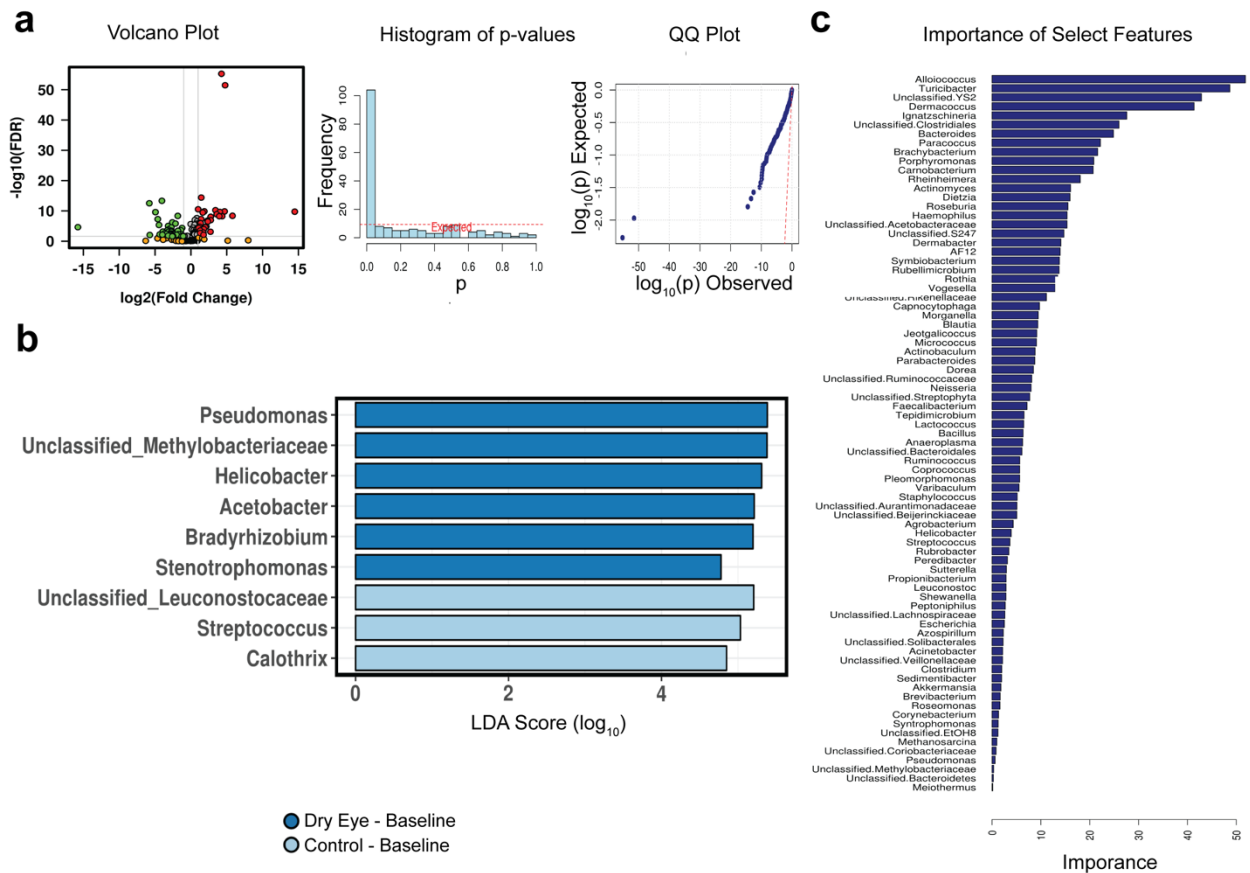


Fig. S5. The acquisition of unique taxa separates the dry from the normal eye at baseline.

- (a) Negative binomial distribution (DESeq2 function).
 (b) Linear discriminant analysis of effect size (LEfSe).
 (c) Variable importance analysis of random forest classifier.

Supplemental Fig. S6.

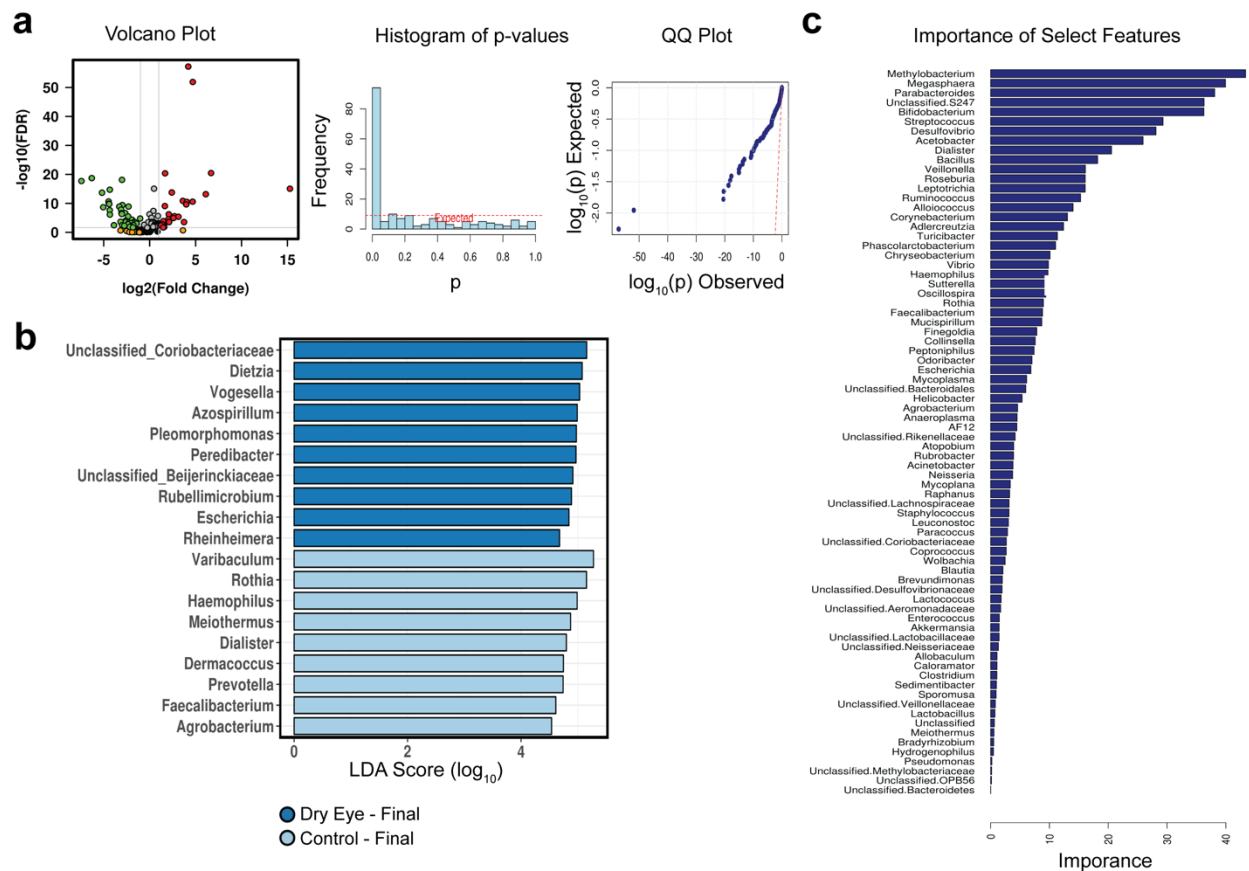


Fig. S6. Additional unique taxa separate the dry from the normal eye after a month.

- (a) Negative binomial distribution (DESeq2 function).
 (b) Linear discriminant analysis of effect size (LEfSe).
 (c) Variable importance analysis of random forest classifier.

Supplemental Table 1.

	Normal		Dry Eye	
	Normal	Mild	Moderate	Severe
DEQ5	≤ 5	≤ 5	≥ 6	≥ 12
Phenol Red	All of the below:		At least one of the following:	
Thread, mm	> 10, bilateral	> 10, bilateral	< 10, one eye	< 10, one eye
NIKBUT, s	> 5, bilateral	> 5, bilateral	< 10, one eye	< 5, one eye
InflammaDry	Negative, both eyes	Positive, one or both eyes	Positive, one or both eyes	Positive, one or both eyes

Supplemental Table 2.

Taxa (genus)	P (biological condition)	Adjusted P (Bonferroni)	FDR
<i>Unclassified.OPB56</i>	< 1E-22	< 1E-22	< 1E-22
<i>Unclassified.Methylobacteriaceae</i>	< 1E-22	1E-21	2.00E-22
<i>Unclassified.Bacteroidetes</i>	< 1E-22	< 1E-22	< 1E-22
<i>Pseudomonas</i>	< 1E-22	< 1E-22	< 1E-22
<i>Meiothermus</i>	< 1E-22	< 1E-22	< 1E-22
<i>Hydrogenophilus</i>	2.5E-19	4.6E-17	7.7E-18
<i>Unclassified.Chitinophagaceae</i>	7.6E-19	1.4E-16	2E-17
<i>Bradyrhizobium</i>	6E-18	1.1E-15	1.4E-16
<i>Unclassified</i>	3.6E-16	6.6E-14	7.4E-15
<i>Unclassified.Aeromonadaceae</i>	7.2E-16	1.3E-13	1.3E-14
<i>Raphanus</i>	2.7E-15	5E-13	4.5E-14
<i>Unclassified.Coriobacteriaceae</i>	1.4E-14	2.6E-12	2.1E-13
<i>Unclassified.Desulfovibrionaceae</i>	4.8E-13	8.8E-11	6.8E-12
<i>Brevundimonas</i>	5.8E-12	1.1E-09	7.6E-11
<i>Lactobacillus</i>	5.4E-11	9.9E-09	6.6E-10
<i>Leuconostoc</i>	1.7E-10	0.000000031	0.000000002
<i>Allobaculum</i>	5.9E-10	0.00000011	6.4E-09
<i>Unclassified.Beijerinckiaceae</i>	1.1E-09	0.0000002	0.000000011
<i>Unclassified.Aurantimonadaceae</i>	1.4E-09	0.00000026	0.000000014
<i>Shewanella</i>	1.8E-09	0.00000033	0.000000015
<i>Corynebacterium</i>	1.8E-09	0.00000033	0.000000015
<i>Acinetobacter</i>	1.8E-09	0.00000033	0.000000015
<i>Roseomonas</i>	2.2E-09	0.0000004	0.000000018
<i>Phenylobacterium</i>	4.7E-09	0.00000086	0.000000036
<i>Azospirillum</i>	5.8E-09	0.0000011	0.000000043
<i>Aerococcus</i>	0.000000025	0.0000046	0.00000018
<i>Lysobacter</i>	0.000000043	0.0000079	0.00000029
<i>Pleomorphomonas</i>	0.000000063	0.000012	0.00000041
<i>Brevibacterium</i>	0.000000068	0.000013	0.00000043
<i>Morganella</i>	0.000000094	0.000017	0.00000058
<i>Symbiobacterium</i>	0.000000097	0.000018	0.00000058
<i>Peredibacter</i>	0.0000001	0.000018	0.00000058
<i>Bacillus</i>	0.00000012	0.000022	0.00000067
<i>Unclassified.Solibacterales</i>	0.00000024	0.000044	0.0000013
<i>Jeotgalicoccus</i>	0.00000031	0.000057	0.0000016
<i>Sedimentibacter</i>	0.00000088	0.00016	0.0000045
<i>Caloramator</i>	0.000001	0.00018	0.000005

<i>Wolbachia</i>	0.0000012	0.00022	0.0000058
<i>Unclassified.Caulobacteraceae</i>	0.0000013	0.00024	0.0000061
<i>Streptococcus</i>	0.0000022	0.0004	0.00001
<i>Unclassified.Veillonellaceae</i>	0.0000024	0.00044	0.000011
<i>Unclassified.Neisseriaceae</i>	0.0000041	0.00075	0.000018
<i>Mycoplasma</i>	0.0000043	0.00079	0.000018
<i>Mucispirillum</i>	0.0000046	0.00085	0.000019
<i>Sporomusa</i>	0.0000056	0.001	0.000023
<i>Caldicoprobacter</i>	0.0000077	0.0014	0.000031
<i>Caldinitratiruptor</i>	0.000013	0.0024	0.000051
<i>Akkermansia</i>	0.000015	0.0028	0.000058
<i>Anaerococcus</i>	0.000018	0.0033	0.000068
<i>Leptotrichia</i>	0.000024	0.0044	0.000088
<i>Devosia</i>	0.000025	0.0046	0.00009
<i>Unclassified.Halanaerobiales</i>	0.000027	0.005	0.000096
<i>Neisseria</i>	0.000032	0.0059	0.00011
<i>Balneimonas</i>	0.000033	0.0061	0.00011
<i>Unclassified.Lactobacillaceae</i>	0.000038	0.007	0.00013
<i>Methanosarcina</i>	0.000045	0.0083	0.00015
<i>Desulfosporosinus</i>	0.000048	0.0088	0.00015
<i>Dietzia</i>	0.000087	0.016	0.00028
<i>Lactococcus</i>	0.000093	0.017	0.00029
<i>Unclassified.MLE112</i>	0.00012	0.022	0.00037
<i>Ruminococcus</i>	0.00015	0.028	0.00045
<i>Gordonia</i>	0.00015	0.028	0.00045
<i>Mycoplasma</i>	0.00018	0.033	0.00053
<i>Sutterella</i>	0.00019	0.035	0.00055
<i>Paenibacillus</i>	0.00025	0.046	0.0007
<i>Finegoldia</i>	0.00025	0.046	0.0007
<i>Unclassified.Paenibacillaceae</i>	0.00027	0.05	0.00074
<i>Rubrobacter</i>	0.00032	0.059	0.00087
<i>Helicobacter</i>	0.0004	0.074	0.0011
<i>Unclassified.EtOH8</i>	0.00046	0.085	0.0012
<i>Actinobaculum</i>	0.00056	0.1	0.0015
<i>Micrococcus</i>	0.00063	0.12	0.0016
<i>Lutispora</i>	0.00078	0.14	0.002
<i>Brachybacterium</i>	0.00088	0.16	0.0022
<i>Sphingobium</i>	0.0011	0.2	0.0027
<i>Vogesella</i>	0.0012	0.22	0.0029
<i>Unclassified.Lachnospiraceae</i>	0.0013	0.24	0.003

<i>Unclassified.Clostridiales</i>	0.0013	0.24	0.003
<i>Staphylococcus</i>	0.0013	0.24	0.003
<i>Moraxella</i>	0.0013	0.24	0.003
<i>Propionibacterium</i>	0.0015	0.28	0.0034
<i>Unclassified.Bacillales</i>	0.0017	0.31	0.0038
<i>Agrobacterium</i>	0.0018	0.33	0.004
<i>Rothia</i>	0.002	0.37	0.0044
<i>Unclassified.Barnesiellaceae</i>	0.0021	0.39	0.0045
<i>Unclassified.Acetobacteraceae</i>	0.0021	0.39	0.0045
<i>Alloiococcus</i>	0.0026	0.48	0.0055
<i>Unclassified.Aerococcaceae</i>	0.0029	0.53	0.0061
<i>Peptostreptococcus</i>	0.0034	0.63	0.007
<i>Escherichia</i>	0.0037	0.68	0.0076
<i>Coprococcus</i>	0.0048	0.88	0.0096
<i>Adlercreutzia</i>	0.0048	0.88	0.0096
<i>Oscillospira</i>	0.0052	0.96	0.01
<i>Comamonas</i>	0.0063	1	0.012
<i>Clostridium</i>	0.0067	1	0.013
<i>Unclassified.ML615J28</i>	0.0068	1	0.013
<i>Unclassified.Rikenellaceae</i>	0.0083	1	0.016
<i>Syntrophomonas</i>	0.009	1	0.017
<i>Unclassified.Ruminococcaceae</i>	0.01	1	0.019
<i>SMB53</i>	0.011	1	0.02
<i>Vibrio</i>	0.012	1	0.022
<i>Paraprevotella</i>	0.012	1	0.022
<i>Bacteroides</i>	0.014	1	0.025
<i>Unclassified.S247</i>	0.016	1	0.028
<i>Pantoea</i>	0.016	1	0.028
<i>Paracoccus</i>	0.018	1	0.031
<i>Haemophilus</i>	0.018	1	0.031
<i>Unclassified.03196G20</i>	0.02	1	0.034
<i>Rubellimicrobium</i>	0.021	1	0.035
<i>Peptoniphilus</i>	0.022	1	0.037
<i>Blautia</i>	0.023	1	0.038
<i>Candidatus_Arthromitus</i>	0.028	1	0.046
<i>Citrobacter</i>	0.034	1	0.055
<i>Veillonella</i>	0.035	1	0.056
<i>Capnocytophaga</i>	0.036	1	0.058
<i>Parabacteroides</i>	0.037	1	0.058
<i>Lachnospira</i>	0.037	1	0.058

<i>Roseburia</i>	0.04	1	0.062
<i>Anaeroplasma</i>	0.047	1	0.073
<i>Unclassified.Streptophyta</i>	0.049	1	0.074
<i>Unclassified.Gemellaceae</i>	0.049	1	0.074
<i>Enterococcus</i>	0.049	1	0.074
<i>Turicibacter</i>	0.05	1	0.074
<i>AF12</i>	0.05	1	0.074
<i>Collinsella</i>	0.059	1	0.086
<i>Chryseobacterium</i>	0.059	1	0.086
<i>Eubacterium</i>	0.063	1	0.091
<i>Kocuria</i>	0.067	1	0.096
<i>Desulfovibrio</i>	0.073	1	0.1
<i>Pelosinus</i>	0.079	1	0.11
<i>Faecalibacterium</i>	0.08	1	0.11
<i>Eikenella</i>	0.08	1	0.11
<i>Phascolarctobacterium</i>	0.087	1	0.12
<i>WAL_1855D</i>	0.096	1	0.13
<i>Arthrobacter</i>	0.11	1	0.15
<i>Shuttleworthia</i>	0.13	1	0.17
<i>Selenomonas</i>	0.13	1	0.17
<i>Actinomyces</i>	0.13	1	0.17
<i>Bifidobacterium</i>	0.14	1	0.19
<i>Lautropia</i>	0.15	1	0.2
<i>Unclassified.RF32</i>	0.16	1	0.21
<i>Sneathia</i>	0.16	1	0.21
<i>Phyllobacterium</i>	0.17	1	0.22
<i>Granulicatella</i>	0.17	1	0.22
<i>Varibaculum</i>	0.18	1	0.23
<i>Abiotrophia</i>	0.18	1	0.23
<i>Unclassified.Erysipelotrichaceae</i>	0.19	1	0.24
<i>Dorea</i>	0.19	1	0.24
<i>Dermabacter</i>	0.2	1	0.25
<i>X168</i>	0.24	1	0.29
<i>Unclassified.Bacteroidales</i>	0.24	1	0.29
<i>Achromobacter</i>	0.26	1	0.31
<i>Geobacter</i>	0.28	1	0.34
<i>Calothrix</i>	0.32	1	0.38
<i>Megasphaera</i>	0.33	1	0.39
<i>Aggregatibacter</i>	0.34	1	0.4
<i>Rheinheimera</i>	0.39	1	0.45

<i>Facklamia</i>	0.39	1	0.45
<i>Acetobacter</i>	0.39	1	0.45
<i>Dermaococcus</i>	0.43	1	0.49
<i>Stenotrophomonas</i>	0.46	1	0.53
<i>Unclassified.YS2</i>	0.47	1	0.53
<i>Enhydrobacter</i>	0.47	1	0.53
<i>Odoribacter</i>	0.49	1	0.55
<i>Dehalobacterium</i>	0.49	1	0.55
<i>Anaerostipes</i>	0.54	1	0.6
<i>Carnobacterium</i>	0.56	1	0.62
<i>Porphyromonas</i>	0.58	1	0.63
<i>Bilophila</i>	0.58	1	0.63
<i>rc44</i>	0.59	1	0.64
<i>Salinispora</i>	0.61	1	0.65
<i>Chroococcidiopsis</i>	0.61	1	0.65
<i>Prevotella</i>	0.62	1	0.66
<i>Atopobium</i>	0.64	1	0.68
<i>Fusobacterium</i>	0.68	1	0.71
<i>Campylobacter</i>	0.69	1	0.72
<i>Acidaminococcus</i>	0.75	1	0.78
<i>Methylobacterium</i>	0.79	1	0.82
<i>Mycobacterium</i>	0.89	1	0.91
<i>Proteus</i>	0.9	1	0.92
<i>Sphingomonas</i>	0.91	1	0.93
<i>Janthinobacterium</i>	0.92	1	0.93
<i>Dialister</i>	0.93	1	0.94
<i>Tissierella_Soehngenia</i>	0.95	1	0.95

Supplemental Table 3.

Taxa	P Assignment	FDR Assignment	P adjusted Assignment
<i>Unclassified.OPB56</i>	< 1E-22	< 1E-22	< 1E-22
<i>Unclassified.Bacteroidetes</i>	< 1E-22	< 1E-22	< 1E-22
<i>Pseudomonas</i>	< 1E-22	< 1E-22	1E-22
<i>Meiothermus</i>	< 1E-22	2E-22	9E-22
<i>Unclassified.Methylobacteriaceae</i>	2E-22	6.3E-21	3.1E-20
<i>Hydrogenophilus</i>	5.8E-18	1.8E-16	1E-15
<i>Unclassified.Chitinophagaceae</i>	7.1E-18	1.9E-16	1.3E-15
<i>Bradyrhizobium</i>	1.4E-16	3.2E-15	2.5E-14
<i>Unclassified</i>	7.9E-15	1.6E-13	1.4E-12

<i>Unclassified.Aeromonadaceae</i>	1.1E-14	2E-13	1.9E-12
<i>Raphanus</i>	6.4E-14	1.1E-12	1.1E-11
<i>Unclassified.Coriobacteriaceae</i>	2.4E-13	3.7E-12	4.2E-11
<i>Unclassified.Desulfovibrionaceae</i>	8.6E-12	1.2E-10	1.5E-09
<i>Brevundimonas</i>	1.2E-10	1.6E-09	0.000000021
<i>Lactobacillus</i>	4.7E-10	5.8E-09	0.00000008
<i>Unclassified.Aurantimonadaceae</i>	0.000000002	0.000000023	0.000000034
<i>Allobaculum</i>	2.9E-09	0.000000031	0.000000049
<i>Leuconostoc</i>	3.1E-09	0.000000032	0.000000052
<i>Unclassified.Beijerinckiaceae</i>	0.000000009	0.000000087	0.00000015
<i>Corynebacterium</i>	0.000000021	0.00000019	0.00000035
<i>Shewanella</i>	0.000000023	0.0000002	0.00000038
<i>Acinetobacter</i>	0.000000028	0.00000023	0.00000046
<i>Azospirillum</i>	0.000000057	0.00000046	0.00000092
<i>Phenyllobacterium</i>	0.000000068	0.00000052	0.0000011
<i>Roseomonas</i>	0.00000012	0.00000088	0.0000019
<i>Bacillus</i>	0.00000023	0.0000016	0.0000037
<i>Lysobacter</i>	0.00000025	0.0000017	0.000004
<i>Aerococcus</i>	0.00000033	0.0000022	0.0000052
<i>Pleomorphomonas</i>	0.0000006	0.0000038	0.0000094
<i>Morganella</i>	0.00000094	0.0000058	0.000015
<i>Peredibacter</i>	0.00000099	0.0000059	0.000015
<i>Brevibacterium</i>	0.0000022	0.000013	0.000034
<i>Symbiobacterium</i>	0.0000024	0.000013	0.000036
<i>Unclassified.Solibacterales</i>	0.0000033	0.000018	0.00005
<i>Unclassified.Caulobacteraceae</i>	0.0000096	0.00005	0.00014
<i>Wolbachia</i>	0.000014	0.00007	0.00021
<i>Streptococcus</i>	0.000014	0.00007	0.00021
<i>Akkermansia</i>	0.000018	0.000087	0.00026
<i>Mycoplana</i>	0.000024	0.00011	0.00035
<i>Jeotgalicoccus</i>	0.000033	0.00015	0.00048
<i>Mucispirillum</i>	0.000051	0.00023	0.00073
<i>Unclassified.Neisseriaceae</i>	0.000069	0.0003	0.00099
<i>Caldinitratiruptor</i>	0.00012	0.00051	0.017
<i>Leptotrichia</i>	0.00018	0.00075	0.025
<i>Unclassified.Lactobacillaceae</i>	0.00019	0.00076	0.027
<i>Balneimonas</i>	0.00019	0.00076	0.027
<i>Devosia</i>	0.00024	0.00094	0.033
<i>Neisseria</i>	0.00029	0.0011	0.04
<i>Ruminococcus</i>	0.00056	0.0021	0.076

<i>Lactococcus</i>	0.0008	0.0029	0.11
<i>Dietzia</i>	0.0008	0.0029	0.11
<i>Anaerococcus</i>	0.00089	0.0031	0.12
<i>Sutterella</i>	0.0014	0.0049	0.18
<i>Mycoplasma</i>	0.0019	0.0064	0.25
<i>Finegoldia</i>	0.0019	0.0064	0.25
<i>Unclassified.Veillonellaceae</i>	0.002	0.0066	0.26
<i>Paenibacillus</i>	0.0023	0.0073	0.29
<i>Caloramator</i>	0.0023	0.0073	0.29
<i>Gordonia</i>	0.0024	0.0075	0.3
<i>Rubrobacter</i>	0.0026	0.008	0.32
<i>Unclassified.Halanaerobiales</i>	0.0038	0.011	0.47
<i>Caldicoprobacter</i>	0.0038	0.011	0.47
<i>Helicobacter</i>	0.004	0.012	0.49
<i>Actinobaculum</i>	0.0044	0.013	0.53
<i>Micrococcus</i>	0.0048	0.014	0.58
<i>Sporomusa</i>	0.0052	0.014	0.62
<i>Brachybacterium</i>	0.0076	0.021	0.9
<i>Sedimentibacter</i>	0.0082	0.022	0.96
<i>Unclassified.Lachnospiraceae</i>	0.0084	0.022	0.97
<i>Unclassified.MLE112</i>	0.0089	0.023	1
<i>Staphylococcus</i>	0.0096	0.025	1
<i>Vogesella</i>	0.0099	0.025	1
<i>Desulfosporosinus</i>	0.01	0.025	1
<i>Unclassified.Clostridiales</i>	0.011	0.027	1
<i>Unclassified.Acetobacteraceae</i>	0.012	0.029	1
<i>Unclassified.Aerococcaceae</i>	0.013	0.031	1
<i>Propionibacterium</i>	0.014	0.033	1
<i>Agrobacterium</i>	0.014	0.033	1
<i>Unclassified.Paenibacillaceae</i>	0.015	0.034	1
<i>Rothia</i>	0.015	0.034	1
<i>Moraxella</i>	0.015	0.034	1
<i>Unclassified.Bacillales</i>	0.018	0.04	1
<i>Alloiococcus</i>	0.018	0.04	1
<i>Peptostreptococcus</i>	0.025	0.055	1
<i>Escherichia</i>	0.028	0.061	1
<i>Coprococcus</i>	0.03	0.064	1
<i>Adlercreutzia</i>	0.031	0.066	1
<i>Unclassified.Barnesiellaceae</i>	0.032	0.067	1
<i>Sphingobium</i>	0.041	0.084	1

<i>Comamonas</i>	0.041	0.084	1
<i>Unclassified.EtOH8</i>	0.046	0.092	1
<i>Bacteroides</i>	0.046	0.092	1
<i>Oscillospira</i>	0.049	0.097	1
<i>Vibrio</i>	0.05	0.098	1
<i>Unclassified.Rikenellaceae</i>	0.055	0.11	1
<i>Methanosarcina</i>	0.06	0.12	1
<i>Unclassified.Ruminococcaceae</i>	0.065	0.12	1
<i>Unclassified.S247</i>	0.073	0.14	1
<i>Blautia</i>	0.083	0.15	1
<i>Lutispora</i>	0.098	0.18	1
<i>Veillonella</i>	0.1	0.18	1
<i>SMB53</i>	0.1	0.18	1
<i>Haemophilus</i>	0.1	0.18	1
<i>Rubellimicrobium</i>	0.11	0.19	1
<i>Paraprevotella</i>	0.11	0.19	1
<i>Unclassified.ML615J28</i>	0.12	0.2	1
<i>Paracoccus</i>	0.12	0.2	1
<i>Anaeroplasma</i>	0.12	0.2	1
<i>Candidatus_Arthromitus</i>	0.14	0.24	1
<i>Pantoea</i>	0.15	0.25	1
<i>Faecalibacterium</i>	0.15	0.25	1
<i>Peptoniphilus</i>	0.16	0.26	1
<i>Parabacteroides</i>	0.18	0.29	1
<i>Syntrophomonas</i>	0.19	0.31	1
<i>Lachnospira</i>	0.2	0.32	1
<i>Capnocytophaga</i>	0.2	0.32	1
<i>Turicibacter</i>	0.21	0.33	1
<i>Roseburia</i>	0.22	0.34	1
<i>Unclassified.Bacteroidales</i>	0.23	0.35	1
<i>Phascolarctobacterium</i>	0.23	0.35	1
<i>Unclassified.Gemellaceae</i>	0.24	0.36	1
<i>Collinsella</i>	0.25	0.38	1
<i>Eubacterium</i>	0.28	0.41	1
<i>Chryseobacterium</i>	0.28	0.41	1
<i>AF12</i>	0.28	0.41	1
<i>Unclassified.Streptophyta</i>	0.29	0.42	1
<i>Unclassified.03196G20</i>	0.3	0.43	1
<i>Dorea</i>	0.32	0.46	1
<i>Desulfovibrio</i>	0.37	0.53	1

<i>WAL_1855D</i>	0.4	0.57	1
<i>Enterococcus</i>	0.44	0.61	1
<i>Eikenella</i>	0.44	0.61	1
<i>Bifidobacterium</i>	0.44	0.61	1
<i>Citrobacter</i>	0.45	0.62	1
<i>Kocuria</i>	0.48	0.65	1
<i>Shuttleworthia</i>	0.49	0.65	1
<i>Clostridium</i>	0.49	0.65	1
<i>Arthrobacter</i>	0.49	0.65	1
<i>Actinomyces</i>	0.55	0.73	1
<i>Selenomonas</i>	0.57	0.74	1
<i>Lautropia</i>	0.57	0.74	1
<i>Unclassified.Erysipelotrichaceae</i>	0.58	0.75	1
<i>Prevotella</i>	0.58	0.75	1
<i>Sneathia</i>	0.59	0.75	1
<i>Unclassified.RF32</i>	0.6	0.76	1
<i>Varibaculum</i>	0.62	0.78	1
<i>Granulicatella</i>	0.62	0.78	1
<i>Abiotrophia</i>	0.64	0.8	1
<i>Pelosinus</i>	0.67	0.83	1
<i>Dermabacter</i>	0.76	0.93	1
<i>Achromobacter</i>	0.8	0.97	1
<i>Calothrix</i>	0.84	1	1
<i>Geobacter</i>	0.85	1	1
<i>Rheinheimera</i>	0.87	1	1
<i>Megasphaera</i>	0.87	1	1
<i>Bilophila</i>	0.9	1	1
<i>X168</i>	0.91	1	1
<i>Acetobacter</i>	0.92	1	1
<i>Dermacoccus</i>	0.93	1	1
<i>Stenotrophomonas</i>	0.94	1	1
<i>rc44</i>	0.95	1	1
<i>Unclassified.YS2</i>	0.97	1	1
<i>Odoribacter</i>	0.97	1	1
<i>Facklamia</i>	0.97	1	1
<i>Enhydrobacter</i>	0.97	1	1
<i>Phyllobacterium</i>	0.98	1	1
<i>Dehalobacterium</i>	0.98	1	1
<i>Tissierella_Soehngenina</i>	1	1	1
<i>Sphingomonas</i>	1	1	1

<i>Salinispora</i>	1	1	1
<i>Proteus</i>	1	1	1
<i>Porphyromonas</i>	1	1	1
<i>Mycobacterium</i>	1	1	1
<i>Methylobacterium</i>	1	1	1
<i>Janthinobacterium</i>	1	1	1
<i>Fusobacterium</i>	1	1	1
<i>Dialister</i>	1	1	1
<i>Chroococcidiopsis</i>	1	1	1
<i>Carnobacterium</i>	1	1	1
<i>Campylobacter</i>	1	1	1
<i>Atopobium</i>	1	1	1
<i>Anaerostipes</i>	1	1	1
<i>Aggregatibacter</i>	1	1	1
<i>Acidaminococcus</i>	1	1	1

Supplemental Table 4.

Taxa (Genus)	Fold Change	P (DESeq2)	Adjusted P (Bonferroni)	FDR
<i>Unclassified.Methylobacteriaceae</i>	25.81	< 1E-22	< 1E-22	< 1E-22
<i>Pseudomonas</i>	18.38	< 1E-22	< 1E-22	< 1E-22
<i>Azospirillum</i>	102.9	3.5E-21	6.3E-19	1.9E-19
<i>Bradyrhizobium</i>	3.2	4.3E-21	7.8E-19	1.9E-19
<i>Unclassified.Coriobacteriaceae</i>	-78.88	1.9E-19	3.5E-17	7E-18
<i>Unclassified.Bacteroidetes</i>	-8.057	7.7E-19	1.4E-16	2.3E-17
<i>Unclassified</i>	1.389	8.8E-16	1.6E-13	1.8E-14
<i>Unclassified.Beijerinckiaceae</i>	39600	9E-16	1.6E-13	1.8E-14
<i>Unclassified.Aeromonadaceae</i>	-20.23	2E-15	3.7E-13	3.7E-14
<i>Agrobacterium</i>	5.308	1.8E-14	3.3E-12	3E-13
<i>Unclassified.Desulfovibrionaceae</i>	-36.35	2.1E-14	3.8E-12	3.2E-13
<i>Phenylobacterium</i>	69	7E-14	1.3E-11	9.8E-13
<i>Lysobacter</i>	12.23	1.3E-11	2.4E-09	1.7E-10
<i>Allobaculum</i>	-22.21	2.2E-11	3.9E-09	2.6E-10
<i>Peredibacter</i>	25.57	2.5E-11	4.5E-09	2.8E-10
<i>Unclassified.Aurantimonadaceae</i>	16.52	2.9E-11	5.3E-09	3.1E-10
<i>Roseomonas</i>	-21.81	1.1E-10	0.000000021	1.2E-09
<i>Mucispirillum</i>	-21.21	1.7E-10	0.000000031	1.6E-09
<i>Unclassified.Caulobacteraceae</i>	15.83	2.3E-10	0.000000042	2.1E-09
<i>Akkermansia</i>	-7.868	3.9E-10	0.00000007	3.3E-09

<i>Mycoplana</i>	3.14	8.5E-10	0.00000015	0.000000007
<i>Meiothermus</i>	-9.829	1.3E-09	0.00000023	9.7E-09
<i>Corynebacterium</i>	-4.932	1.3E-09	0.00000023	9.7E-09
<i>Brevundimonas</i>	-33.23	2.2E-09	0.00000004	0.000000016
<i>Brevibacterium</i>	-8.647	0.000000014	0.00000026	0.00000001
<i>Unclassified.Chitinophagaceae</i>	-20.34	0.000000024	0.00000044	0.000000016
<i>Escherichia</i>	1.325	0.000000041	0.00000074	0.000000026
<i>Hydrogenophilus</i>	-6.369	0.000000022	0.000004	0.00000014
<i>Unclassified.OPB56</i>	-8.359	0.000000024	0.0000043	0.00000014
<i>Leuconostoc</i>	-8.183	0.00000005	0.0000091	0.00000029
<i>Unclassified.Lachnospiraceae</i>	-1.012	0.000000058	0.0001	0.00000032
<i>Methanosarcina</i>	4.233	0.000000059	0.00011	0.00000032
<i>Shewanella</i>	-20.13	0.000000079	0.00014	0.00000042
<i>Clostridium</i>	1.871	0.00000023	0.00042	0.0000012
<i>Unclassified.EtOH8</i>	6.491	0.00000027	0.00049	0.0000014
<i>Morganella</i>	-5.069	0.00000036	0.00065	0.0000018
<i>Pleomorphomonas</i>	8.764	0.00000044	0.00079	0.0000021
<i>Ruminococcus</i>	1.151	0.00000097	0.0018	0.0000045
<i>Balneimonas</i>	6.021	0.0000012	0.0022	0.0000054
<i>Vibrio</i>	-2.046	0.0000018	0.0033	0.0000081
<i>Lutispora</i>	4.099	0.0000033	0.0061	0.000014
<i>Anaerococcus</i>	-3.812	0.0000045	0.0081	0.000019
<i>Jeotgalicoccus</i>	-6.116	0.0001	0.019	0.000043
<i>Paraprevotella</i>	2.8	0.00014	0.026	0.000058
<i>Aerococcus</i>	-8.985	0.00023	0.042	0.0009
<i>Vogesella</i>	4.328	0.00024	0.043	0.0009
<i>Propionibacterium</i>	-3.183	0.00024	0.043	0.0009
<i>Rubrobacter</i>	-6.067	0.00025	0.046	0.00093
<i>Coprococcus</i>	1.133	0.00026	0.046	0.00093
<i>Unclassified.Halanaerobiales</i>	4.103	0.00029	0.053	0.001
<i>Unclassified.Acetobacteraceae</i>	13.38	0.0003	0.054	0.001
<i>Rubellimicrobium</i>	4.332	0.0003	0.054	0.001
<i>Unclassified.Ruminococcaceae</i>	1.386	0.00031	0.056	0.001
<i>Gordonia</i>	-1.118	0.00034	0.061	0.0011
<i>Rheinheimera</i>	1.18	0.00036	0.065	0.0012
<i>Lactobacillus</i>	-4.775	0.00046	0.083	0.0015
<i>Lactococcus</i>	-3.43	0.00056	0.1	0.0018
<i>Dorea</i>	1.36	0.00062	0.11	0.0019
<i>Sporomusa</i>	1.93	0.00064	0.12	0.0019
<i>Dietzia</i>	-4.13	0.00068	0.12	0.002

<i>Citrobacter</i>	1.767	0.00094	0.17	0.0027
<i>Streptococcus</i>	-2.691	0.001	0.18	0.0029
<i>Anaeroplasma</i>	1.15	0.001	0.18	0.0029
<i>Odoribacter</i>	1.734	0.0013	0.24	0.0037
<i>Syntrophomonas</i>	2.622	0.0017	0.3	0.0046
<i>Neisseria</i>	-5.043	0.0017	0.32	0.0047
<i>Unclassified.Bacteroidales</i>	1.442	0.0023	0.41	0.0061
<i>Caloramator</i>	1.715	0.0026	0.47	0.0068
<i>Alloiococcus</i>	-1.518	0.0026	0.47	0.0068
<i>Helicobacter</i>	-3.416	0.0031	0.57	0.008
<i>Actinobaculum</i>	-7.919	0.0034	0.62	0.0086
<i>Sedimentibacter</i>	1.655	0.0035	0.64	0.0087
<i>Ignatzschineria</i>	-14.77	0.0036	0.64	0.0087
<i>Pantoea</i>	2.364	0.0039	0.71	0.0094
<i>Unclassified.Solibacterales</i>	-6.776	0.005	0.91	0.012
<i>Collinsella</i>	1.413	0.0051	0.92	0.012
<i>Adlercreutzia</i>	-4.107	0.0073	1	0.017
<i>Unclassified.Veillonellaceae</i>	1.702	0.008	1	0.018
<i>Varibaculum</i>	1.724	0.0083	1	0.019
<i>Phascolarctobacterium</i>	1.498	0.01	1	0.023
<i>Faecalibacterium</i>	1.302	0.012	1	0.026
<i>Arthrobacter</i>	-4.483	0.012	1	0.027
<i>Mycoplasma</i>	2.988	0.015	1	0.032
<i>Sphingobium</i>	-3.533	0.019	1	0.04
<i>Kocuria</i>	2.79	0.021	1	0.043
<i>Unclassified.Rikenellaceae</i>	-1.203	0.022	1	0.046
<i>Roseburia</i>	-1.083	0.025	1	0.052
<i>Unclassified.Lactobacillaceae</i>	-3.374	0.027	1	0.055
<i>Pelosinus</i>	-1.596	0.03	1	0.061
<i>AF12</i>	1.225	0.036	1	0.072
<i>Acinetobacter</i>	-3.148	0.038	1	0.075
<i>Geobacter</i>	1.062	0.045	1	0.087
<i>Unclassified.Neisseriaceae</i>	-1.398	0.047	1	0.09
<i>Paracoccus</i>	-1.053	0.054	1	0.1
<i>Enterococcus</i>	-1.179	0.066	1	0.13
<i>Leptotrichia</i>	-3.279	0.076	1	0.14
<i>Parabacteroides</i>	-1.922	0.081	1	0.15
<i>Sutterella</i>	-5.098	0.088	1	0.16
<i>Unclassified.Paenibacillaceae</i>	-1.196	0.11	1	0.19
<i>Symbiobacterium</i>	-4.816	0.11	1	0.2

<i>Staphylococcus</i>	-1.869	0.12	1	0.21
<i>Enhydrobacter</i>	-2.418	0.12	1	0.21
<i>Chryseobacterium</i>	-2.675	0.12	1	0.22
<i>Sphingomonas</i>	-1.643	0.13	1	0.23
<i>Haemophilus</i>	-2.023	0.13	1	0.22
<i>Wolbachia</i>	-2.859	0.14	1	0.23
<i>Aggregatibacter</i>	1.088	0.14	1	0.24
<i>Oscillospira</i>	-1.383	0.15	1	0.25
<i>Phyllobacterium</i>	-1.332	0.16	1	0.26
<i>Mycobacterium</i>	-1.512	0.16	1	0.26
<i>Rothia</i>	-2.088	0.17	1	0.27
<i>Pelotomaculum</i>	-1.032	0.17	1	0.27
<i>Unclassified.Streptophyta</i>	-3.172	0.18	1	0.28
<i>Dialister</i>	1.108	0.19	1	0.29
<i>Desulfosporosinus</i>	-1.338	0.19	1	0.29
<i>Chroococcidiopsis</i>	12.31	0.2	1	0.31
<i>Unclassified.RF39</i>	-1.258	0.21	1	0.32
<i>Carnobacterium</i>	-1.16	0.21	1	0.32
<i>Tepidimicrobium</i>	1.105	0.22	1	0.33
<i>Lautropia</i>	-9.06	0.23	1	0.34
<i>Achromobacter</i>	-1.664	0.23	1	0.34
<i>Unclassified.YS2</i>	-3.569	0.25	1	0.36
<i>Unclassified.Gemellaceae</i>	-2.135	0.25	1	0.36
<i>Capnocytophaga</i>	-1.13	0.25	1	0.36
<i>Tissierella_Soehngen</i>	-1.76	0.28	1	0.41
<i>Bilophila</i>	-1.311	0.29	1	0.42
<i>Unclassified.Erysipelotrichaceae</i>	1.091	0.34	1	0.48
<i>Methylobacterium</i>	-1.533	0.34	1	0.48
<i>Bifidobacterium</i>	-1.596	0.34	1	0.48
<i>Bacteroides</i>	-1.707	0.35	1	0.49
<i>Unclassified.OPB54</i>	-5.676	0.36	1	0.49
<i>Burkholderia</i>	-2.341	0.37	1	0.51
<i>Lachnospira</i>	-1.483	0.38	1	0.51
<i>Facklamia</i>	-1.657	0.39	1	0.52
<i>Desulfovibrio</i>	-1.809	0.39	1	0.52
<i>Unclassified.MLE112</i>	-3.853	0.4	1	0.53
<i>WAL_1855D</i>	-2.038	0.41	1	0.54
<i>Fusobacterium</i>	-1.756	0.41	1	0.54
<i>Megasphaera</i>	-2.338	0.43	1	0.56
<i>Blautia</i>	-1.234	0.43	1	0.56

<i>Campylobacter</i>	-1.373	0.44	1	0.56
<i>Dermabacter</i>	-4.032	0.45	1	0.57
<i>Proteus</i>	-1.954	0.47	1	0.59
<i>Acidaminococcus</i>	-1.064	0.49	1	0.61
<i>Micrococcus</i>	-2.801	0.52	1	0.65
<i>Sneathia</i>	-2.198	0.56	1	0.69
<i>rc44</i>	1.815	0.57	1	0.7
<i>Veillonella</i>	-1.787	0.59	1	0.72
<i>Turicibacter</i>	-2	0.6	1	0.72
<i>Peptostreptococcus</i>	-2.727	0.6	1	0.72
<i>Dermaococcus</i>	-2.61	0.6	1	0.72
<i>Stenotrophomonas</i>	-2.086	0.63	1	0.74
<i>Unclassified.S247</i>	-1.464	0.65	1	0.76
<i>Unclassified.Bacillales</i>	-1.809	0.66	1	0.76
<i>Finegoldia</i>	-3.337	0.66	1	0.76
<i>Eikenella</i>	-1.672	0.66	1	0.76
<i>Candidatus_Arthromitus</i>	-2.061	0.68	1	0.78
<i>Janthinobacterium</i>	-1.921	0.69	1	0.79
<i>Moraxella</i>	-1.631	0.71	1	0.8
<i>Unclassified.ML615J28</i>	-1.871	0.72	1	0.8
<i>SMB53</i>	-2.048	0.72	1	0.8
<i>Dehalobacterium</i>	-2.649	0.73	1	0.81
<i>Prevotella</i>	-1.739	0.75	1	0.83
<i>Brachybacterium</i>	-2.333	0.76	1	0.84
<i>Peptoniphilus</i>	-2.596	0.78	1	0.85
<i>Anaerostipes</i>	1.011	0.81	1	0.88
<i>Unclassified.03196G20</i>	-4.599	0.82	1	0.88
<i>Unclassified.RF32</i>	-1.961	0.85	1	0.9
<i>Caldicoprobacter</i>	-2.043	0.85	1	0.9
<i>Shuttleworthia</i>	-2.217	0.86	1	0.9
<i>Pseudoxanthomonas</i>	-3.164	0.86	1	0.9
<i>Actinomyces</i>	-1.658	0.86	1	0.9
<i>Selenomonas</i>	-3.757	0.89	1	0.93
<i>Comamonas</i>	-2.271	0.9	1	0.93
<i>Porphyromonas</i>	-1.242	0.94	1	0.97
<i>Acetobacter</i>	-2.159	0.95	1	0.98
<i>Brevibacillus</i>	-2.066	0.96	1	0.98
<i>Atopobium</i>	-1.961	0.97	1	0.98