

Supplementary Material

Comparative Analysis of Rumen Bacterial Profiles and Functions during Adaption to Different Phenology (Regreen vs. Grassy) in Alpine Merino Sheep with Two Growing Stages on an Alpine Meadow

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Supplementary Table S1. Common forage nutrient composition in different phenological periods (% DM basis)¹.

Item ²	Regreen stage	Grassy stage	SEM ³	P-value
OM	92.41	90.16	1.049	0.01
Ash	7.59	8.67	0.032	0.01
CP	10.24	12.74	0.315	0.01
NDF	57.24	63.72	1.775	0.24
ADF	29.15	28.36	0.858	0.23

¹ The data of forage nutrient composition were obtained from Zhang et al. [24].

² OM, organic matter; CP, crude protein; NDF, neutral detergent fiber; ADF, acid detergent fiber.

³ SEM, standard error of means.

Supplementary Table S2. The relative abundance of Kyoto Encyclopedia of Genes and Genomes (KEGGs) genes in rumen microbiome of hoggets (H) of grazing Alpine Merino sheep under different phonological periods.

Class3_name	Regreen stage	Grassy stage	SEM ¹	<i>P</i> -value
2-Oxocarboxylic acid metabolism	1.688	1.665	0.004	0.083
ABC transporters	3.072	2.893	0.037	0.123
AMPK signaling pathway	0.153	0.152	0.001	0.967
Adipocytokine signaling pathway	0.106	0.108	0.002	0.680
African trypanosomiasis	0.001	0.001	<0.001	0.274
Alanine, aspartate and glutamate metabolism	1.609	1.654	0.005	0.040
Alcoholism	0	0	<0.001	0.129
Alzheimer's disease	0.071	0.072	<0.001	0.683

Amino sugar and nucleotide sugar metabolism	1.957	1.975	0.006	0.327
Aminoacyl-tRNA biosynthesis	1.758	1.733	0.004	0.084
Aminobenzoate degradation	0.146	0.146	0.001	0.700
Amoebiasis	0.012	0.007	0.001	0.045
Amphetamine addiction	0	0	<0.001	0.128
Amyotrophic lateral sclerosis (ALS)	0.016	0.020	<0.001	0.046
Antigen processing and presentation	0.063	0.067	<0.001	0.047
Apoptosis	0	0	<0.001	0.092
Arachidonic acid metabolism	0.039	0.042	0.001	0.419
Arginine and proline metabolism	1.528	1.520	0.003	0.326
Ascorbate and aldarate metabolism	0.127	0.123	0.001	0.311
Atrazine degradation	0.015	0.010	0.001	0.048
Bacterial chemotaxis	0.921	0.859	0.020	0.313

Bacterial invasion of epithelial cells	0.001	0.001	<0.001	0.251
Bacterial secretion system	0.804	0.816	0.004	0.289
Basal transcription factors	0.004	0.002	<0.001	0.282
Base excision repair	0.605	0.600	0.001	0.143
Benzoate degradation	0.239	0.218	0.003	0.045
Betalain biosynthesis	0	0	<0.001	0.048
Bile secretion	0	0	<0.001	0.084
Biosynthesis of amino acids	7.412	7.379	0.010	0.268
Biosynthesis of ansamycins	0.160	0.148	0.003	0.145
Biosynthesis of siderophore group nonribosomal peptides	0.012	0.014	0.001	0.278
Biosynthesis of type II polyketide products	0	0	<0.001	0.150
Biosynthesis of unsaturated fatty acids	0.155	0.139	0.001	0.017

Biosynthesis of vancomycin group antibiotics	0.100	0.107	0.001	0.011
Biotin metabolism	0.566	0.580	0.003	0.131
Bisphenol degradation	0.103	0.095	0.001	0.045
Butanoate metabolism	0.886	0.850	0.005	0.056
Butirosin and neomycin biosynthesis	0.127	0.132	0.001	0.092
C5-Branched dibasic acid metabolism	0.519	0.514	0.002	0.396
Caprolactam degradation	0.017	0.012	0.001	0.108
Carbapenem biosynthesis	0.134	0.135	0.001	0.443
Carbohydrate digestion and absorption	0.025	0.030	0.001	0.048
Carbon fixation in photosynthetic organisms	0.828	0.832	0.002	0.546
Carbon fixation pathways in prokaryotes	1.559	1.560	0.009	0.975
Carbon metabolism	4.321	4.295	0.008	0.272
Cardiac muscle contraction	0	0	<0.001	0.090

Carotenoid biosynthesis	0.002	0.001	<0.001	0.084
Cell cycle - Caulobacter	0.768	0.784	0.003	0.092
Central carbon metabolism in cancer	0.466	0.466	0.002	0.957
Chagas disease (American trypanosomiasis)	0	0	<0.001	0.398
Chemical carcinogenesis	0.005	0.002	<0.001	0.134
Chloroalkane and chloroalkene degradation	0.219	0.187	0.005	0.086
Chlorocyclohexane and chlorobenzene degradation	0.006	0.003	<0.001	0.010
Choline metabolism in cancer	0.014	0.011	0.001	0.265
Citrate cycle (TCA cycle)	0.893	0.917	0.011	0.422
Cocaine addiction	0	0	<0.001	0.127
Cyanoamino acid metabolism	0.502	0.536	0.007	0.129
Cysteine and methionine metabolism	1.454	1.449	0.002	0.379
D-Alanine metabolism	0.154	0.153	0.001	0.784

D-Arginine and D-ornithine metabolism	0.003	0.003	<0.001	0.668
D-Glutamine and D-glutamate metabolism	0.232	0.236	0.001	0.336
DNA replication	0.997	1.008	0.003	0.266
Degradation of aromatic compounds	0.096	0.082	0.003	0.140
Dioxin degradation	0.009	0.009	<0.001	0.846
Dopaminergic synapse	0	0	<0.001	0.126
Drug metabolism - cytochrome P450	0.012	0.008	0.001	0.046
Drug metabolism - other enzymes	0.481	0.492	0.003	0.174
Endocytosis	0	0	<0.001	0.089
Epithelial cell signaling in Helicobacter pylori infection	0.137	0.142	0.001	0.045
Epstein-Barr virus infection	0.003	0.002	<0.001	0.336
Estrogen signaling pathway	0.063	0.067	<0.001	0.046
Ether lipid metabolism	0.001	0	<0.001	0.544

Ethylbenzene degradation	0.072	0.076	0.001	0.142
Fanconi anemia pathway	0.003	0.002	<0.001	0.333
Fatty acid biosynthesis	0.731	0.706	0.004	0.090
Fatty acid degradation	0.273	0.243	0.004	0.047
Fatty acid metabolism	0.826	0.779	0.005	0.045
Fc gamma R-mediated phagocytosis	0	0	<0.001	0.088
Flagellar assembly	0.803	0.761	0.020	0.456
Flavone and flavonol biosynthesis	0.011	0.011	0.001	0.923
Flavonoid biosynthesis	0	0	<0.001	0.982
Fluorobenzoate degradation	0.001	0.001	<0.001	0.046
Folate biosynthesis	0.619	0.643	0.007	0.254
FoxO signaling pathway	0.054	0.062	0.001	0.094
Fructose and mannose metabolism	1.277	1.259	0.007	0.383

GABAergic synapse	0.161	0.163	0.001	0.559
Galactose metabolism	1.216	1.288	0.009	0.046
Geraniol degradation	0.059	0.060	0.002	0.849
Glutamatergic synapse	0.147	0.144	0.001	0.081
Glutathione metabolism	0.245	0.244	0.002	0.830
Glycerolipid metabolism	0.602	0.606	0.004	0.690
Glycerophospholipid metabolism	0.872	0.871	0.004	0.922
Glycine, serine and threonine metabolism	1.464	1.505	0.007	0.091
Glycolysis / Gluconeogenesis	1.515	1.483	0.004	0.045
Glycosaminoglycan degradation	0.115	0.148	0.004	0.044
Glycosphingolipid biosynthesis - ganglio series	0.089	0.118	0.003	0.046
Glycosphingolipid biosynthesis - globo series	0.194	0.229	0.004	0.044
Glyoxylate and dicarboxylate metabolism	1.000	1.007	0.003	0.441

GnRH signaling pathway	0	0	<0.001	0.087
HIF-1 signaling pathway	0.164	0.161	0.001	0.414
Histidine metabolism	0.733	0.727	0.002	0.415
Homologous recombination	1.429	1.445	0.004	0.147
Huntington's disease	0.036	0.040	0.001	0.190
Indole alkaloid biosynthesis	0	0	<0.001	0.046
Inositol phosphate metabolism	0.111	0.107	0.001	0.225
Insulin signaling pathway	0.107	0.108	0.001	0.850
Isoflavonoid biosynthesis	0.001	0	<0.001	0.412
Isoquinoline alkaloid biosynthesis	0.088	0.090	0.001	0.562
Legionellosis	0.238	0.242	0.001	0.463
Limonene and pinene degradation	0.128	0.126	0.002	0.732
Linoleic acid metabolism	0.092	0.087	0.001	0.079

Lipoic acid metabolism	0.038	0.044	0.001	0.119
Lipopolysaccharide biosynthesis	0.382	0.455	0.014	0.105
Lysine biosynthesis	0.938	0.936	0.001	0.578
Lysine degradation	0.156	0.146	0.002	0.175
Lysosome	0.166	0.205	0.004	0.043
MAPK signaling pathway - yeast	0.073	0.077	0.001	0.230
Meiosis - yeast	0.009	0.008	<0.001	0.479
Metabolism of xenobiotics by cytochrome P450	0.012	0.008	0.001	0.049
Methane metabolism	1.339	1.316	0.004	0.106
MicroRNAs in cancer	0.123	0.121	0.001	0.664
Mineral absorption	0.009	0.007	<0.001	0.049
Mismatch repair	1.237	1.247	0.002	0.101
N-Glycan biosynthesis	0.053	0.054	0.001	0.891

NOD-like receptor signaling pathway	0.064	0.067	<0.001	0.049
Naphthalene degradation	0.066	0.053	0.002	0.084
Nicotinate and nicotinamide metabolism	0.700	0.718	0.004	0.137
Nitrogen metabolism	0.593	0.591	0.002	0.728
Nitrotoluene degradation	0.119	0.096	0.003	0.048
Non-alcoholic fatty liver disease (NAFLD)	0	0	<0.001	0.086
Non-homologous end-joining	0.002	0.002	<0.001	0.467
Nonribosomal peptide structures	0.009	0.008	0.001	0.679
Novobiocin biosynthesis	0.191	0.185	0.001	0.046
Nucleotide excision repair	0.597	0.597	0.001	0.978
One carbon pool by folate	1.001	1.030	0.005	0.093
Other glycan degradation	0.440	0.524	0.009	0.041
Oxidative phosphorylation	1.703	1.762	0.015	0.185

PI3K-Akt signaling pathway	0.068	0.070	0.001	0.286
PPAR signaling pathway	0.151	0.147	0.001	0.410
Pantothenate and CoA biosynthesis	1.005	1.016	0.002	0.133
Parkinson's disease	0	0	<0.001	0.085
Pathways in cancer	0.074	0.076	0.001	0.326
Penicillin and cephalosporin biosynthesis	0.008	0.005	<0.001	0.075
Pentose and glucuronate interconversions	0.631	0.649	0.006	0.311
Pentose phosphate pathway	1.132	1.095	0.007	0.132
Peptidoglycan biosynthesis	1.215	1.205	0.003	0.286
Peroxisome	0.268	0.280	0.003	0.176
Pertussis	0.025	0.032	0.001	0.056
Phenylalanine metabolism	0.348	0.333	0.002	0.040
Phenylalanine, tyrosine and tryptophan biosynthesis	1.387	1.403	0.004	0.241

Phenylpropanoid biosynthesis	0.309	0.336	0.006	0.166
Phosphatidylinositol signaling system	0.109	0.111	0.001	0.351
Phosphonate and phosphinate metabolism	0.100	0.106	0.001	0.045
Phosphotransferase system (PTS)	0.344	0.289	0.011	0.147
Photosynthesis	0.600	0.621	0.004	0.129
Plant-pathogen interaction	0.195	0.203	0.002	0.225
Polycyclic aromatic hydrocarbon degradation	0.001	0	<0.001	0.022
Polyketide sugar unit biosynthesis	0.327	0.343	0.001	0.015
Porphyrin and chlorophyll metabolism	1.087	1.026	0.009	0.065
Primary bile acid biosynthesis	0.039	0.045	0.001	0.090
Primary immunodeficiency	0.054	0.060	0.001	0.047
Prion diseases	0.001	0.001	<0.001	0.050
Progesterone-mediated oocyte maturation	0.063	0.067	<0.001	0.046

Prolactin signaling pathway	0.034	0.031	0.001	0.228
Propanoate metabolism	0.767	0.715	0.007	0.048
Prostate cancer	0.063	0.067	<0.001	0.045
Proteasome	0.003	0.002	<0.001	0.331
Protein digestion and absorption	0.035	0.044	0.002	0.086
Protein export	0.925	0.928	0.003	0.727
Protein processing in endoplasmic reticulum	0.112	0.116	0.002	0.441
Proteoglycans in cancer	0.070	0.071	<0.001	0.379
Proximal tubule bicarbonate reclamation	0.027	0.028	0.001	0.603
Purine metabolism	3.071	3.102	0.008	0.198
Pyrimidine metabolism	2.782	2.818	0.007	0.129
Pyruvate metabolism	1.477	1.419	0.010	0.084
RIG-I-like receptor signaling pathway	0	0	<0.001	0.044

RNA degradation	0.847	0.861	0.001	0.023
RNA polymerase	0.235	0.229	0.002	0.195
RNA transport	0.196	0.187	0.002	0.140
Ras signaling pathway	0	0	<0.001	0.084
Renal cell carcinoma	0.011	0.010	<0.001	0.371
Renin-angiotensin system	0	0	<0.001	0.157
Retinol metabolism	0.019	0.019	0.001	0.849
Retrograde endocannabinoid signaling	0	0	<0.001	0.149
Riboflavin metabolism	0.443	0.461	0.004	0.140
Ribosome	3.635	3.666	0.014	0.454
Ribosome biogenesis in eukaryotes	0.071	0.071	<0.001	0.509
Salmonella infection	0.070	0.072	0.002	0.731
Secondary bile acid biosynthesis	0.039	0.045	0.001	0.089

Selenocompound metabolism	0.521	0.523	0.002	0.738
Serotonergic synapse	0	0	<0.001	0.124
Sesquiterpenoid and triterpenoid biosynthesis	0.001	0.001	<0.001	0.049
Sphingolipid metabolism	0.311	0.353	0.005	0.046
Sphingolipid signaling pathway	0	0	<0.001	0.042
Staphylococcus aureus infection	0.012	0.011	0.002	0.880
Starch and sucrose metabolism	1.605	1.668	0.016	0.215
Steroid biosynthesis	0.001	0.001	<0.001	0.297
Steroid degradation	0	0	<0.001	0.427
Steroid hormone biosynthesis	0.003	0.002	<0.001	0.170
Stilbenoid, diarylheptanoid and gingerol biosynthesis	0.001	0	<0.001	0.009
Streptomycin biosynthesis	0.509	0.530	0.002	0.043
Styrene degradation	0.023	0.017	0.001	0.084

Sulfur metabolism	0.333	0.332	0.005	0.953
Sulfur relay system	0.317	0.286	0.004	0.047
Synaptic vesicle cycle	0	0	<0.001	0.148
Synthesis and degradation of ketone bodies	0.037	0.029	0.001	0.063
Taurine and hypotaurine metabolism	0.177	0.178	0.001	0.879
Terpenoid backbone biosynthesis	0.885	0.878	0.003	0.405
Tetracycline biosynthesis	0.136	0.119	0.003	0.122
Thiamine metabolism	0.660	0.640	0.004	0.128
Thyroid hormone synthesis	0.039	0.042	0.001	0.406
Toluene degradation	0.003	0.002	<0.001	0.472
Tropane, piperidine and pyridine alkaloid biosynthesis	0.175	0.173	0.001	0.560
Tryptophan metabolism	0.145	0.132	0.003	0.195
Tuberculosis	0.221	0.219	0.001	0.162

Two-component system	2.067	1.942	0.028	0.151
Type I diabetes mellitus	0.084	0.089	0.001	0.048
Type II diabetes mellitus	0.071	0.073	<0.001	0.080
Tyrosine metabolism	0.281	0.273	0.002	0.274
Ubiquinone and other terpenoid-quinone biosynthesis	0.244	0.294	0.009	0.091
Valine, leucine and isoleucine biosynthesis	0.880	0.870	0.002	0.085
Valine, leucine and isoleucine degradation	0.303	0.304	0.005	0.953
Vancomycin resistance	0.410	0.406	0.001	0.100
Various types of N-glycan biosynthesis	0.003	0.002	<0.001	0.325
Vasopressin-regulated water reabsorption	0	0	<0.001	0.147
Vibrio cholerae pathogenic cycle	0.106	0.107	0.001	0.842
Viral carcinogenesis	0.072	0.072	0.001	0.733
Vitamin B6 metabolism	0.297	0.314	0.002	0.046

Xylene degradation	0.011	0.011	<0.001	0.894
Zeatin biosynthesis	0.080	0.083	0.001	0.252
alpha-Linolenic acid metabolism	0.001	0.002	<0.001	0.444
beta-Alanine metabolism	0.216	0.222	0.002	0.331
beta-Lactam resistance	0.413	0.453	0.006	0.061
cAMP signaling pathway	0	0	<0.001	0.083

¹ SEM, standard error of means.

Supplementary Table S3. The relative abundance of Kyoto Encyclopedia of Genes and Genomes (KEGGs) genes in rumen microbiome of rams (R) of grazing Alpine Merino sheep under different phonological periods.

Class3_name	Regreen stage	Grassy stage	SEM ¹	<i>P</i> -value
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ABC transporters	2.861	2.920	0.041	0.703

AMPK signaling pathway	0.146	0.148	0.001	0.569
Adipocytokine signaling pathway	0.116	0.109	0.002	0.208
African trypanosomiasis	0.001	0.001	<0.001	0.888
Alanine, aspartate and glutamate metabolism	1.620	1.644	0.006	0.237
Alcoholism	0	0	<0.001	0.880
Alzheimer's disease	0.073	0.072	<0.001	0.319
Amino sugar and nucleotide sugar metabolism	1.932	1.967	0.004	0.047
Aminoacyl-tRNA biosynthesis	1.774	1.754	0.004	0.143
Aminobenzoate degradation	0.150	0.145	0.002	0.373
Amoebiasis	0.012	0.007	<0.001	0.096
Amphetamine addiction	0	0	<0.001	0.875
Amyotrophic lateral sclerosis (ALS)	0.018	0.019	0.001	0.540
Antigen processing and presentation	0.063	0.065	<0.001	0.192

Apoptosis	0	0	<0.001	0.220
Arachidonic acid metabolism	0.040	0.040	0.001	0.971
Arginine and proline metabolism	1.534	1.520	0.002	0.095
Ascorbate and aldarate metabolism	0.129	0.127	0.001	0.664
Atrazine degradation	0.014	0.011	0.001	0.363
Bacterial chemotaxis	0.792	0.860	0.020	0.300
Bacterial invasion of epithelial cells	0.001	0.001	<0.001	0.977
Bacterial secretion system	0.821	0.824	0.003	0.796
Basal transcription factors	0.006	0.004	<0.001	0.125
Base excision repair	0.609	0.601	0.001	0.163
Benzoate degradation	0.239	0.218	0.002	0.068
Betalain biosynthesis	0	0	<0.001	0.993
Bile secretion	0	0	<0.001	0.115

Biosynthesis of amino acids	7.371	7.345	0.012	0.531
Biosynthesis of ansamycins	0.150	0.149	0.002	0.919
Biosynthesis of siderophore group nonribosomal peptides	0.014	0.014	0.001	0.984
Biosynthesis of type II polyketide products	0	0	<0.001	0.939
Biosynthesis of unsaturated fatty acids	0.161	0.146	0.002	0.046
Biosynthesis of vancomycin group antibiotics	0.100	0.108	0.001	0.095
Biotin metabolism	0.585	0.592	0.004	0.625
Bisphenol degradation	0.101	0.095	0.001	0.083
Butanoate metabolism	0.881	0.846	0.004	0.093
Butirosin and neomycin biosynthesis	0.125	0.129	0.001	0.291
C5-Branched dibasic acid metabolism	0.517	0.514	0.002	0.740
Caprolactam degradation	0.023	0.017	0.001	0.119

Carbapenem biosynthesis	0.136	0.136	<0.001	0.790
Carbohydrate digestion and absorption	0.023	0.029	0.001	0.079
Carbon fixation in photosynthetic organisms	0.827	0.832	0.002	0.316
Carbon fixation pathways in prokaryotes	1.607	1.555	0.007	0.087
Carbon metabolism	4.358	4.285	0.004	0.002
Cardiac muscle contraction	0	0	<0.001	0.218
Carotenoid biosynthesis	0.002	0.002	<0.001	0.811
Cell cycle - Caulobacter	0.778	0.788	0.003	0.306
Central carbon metabolism in cancer	0.458	0.460	0.002	0.853
Chagas disease (American trypanosomiasis)	0.001	0.001	<0.001	0.413
Chemical carcinogenesis	0.007	0.004	<0.001	0.124
Chloroalkane and chloroalkene degradation	0.219	0.194	0.004	0.112
Chlorocyclohexane and chlorobenzene degradation	0.006	0.004	<0.001	0.040

Choline metabolism in cancer	0.013	0.013	0.001	0.963
Citrate cycle (TCA cycle)	0.961	0.935	0.009	0.380
Cocaine addiction	0	0	<0.001	0.871
Cyanoamino acid metabolism	0.490	0.524	0.005	0.126
Cysteine and methionine metabolism	1.453	1.450	0.002	0.738
D-Alanine metabolism	0.153	0.154	0.001	0.858
D-Arginine and D-ornithine metabolism	0.002	0.004	<0.001	0.114
D-Glutamine and D-glutamate metabolism	0.236	0.238	0.001	0.755
DNA replication	1.014	1.007	0.003	0.469
Degradation of aromatic compounds	0.094	0.082	0.002	0.125
Dioxin degradation	0.008	0.010	<0.001	0.118
Dopaminergic synapse	0	0	<0.001	0.867
Drug metabolism - cytochrome P450	0.015	0.011	0.001	0.102

Drug metabolism - other enzymes	0.481	0.479	0.001	0.788
Endocytosis	0	0	<0.001	0.216
Epithelial cell signaling in Helicobacter pylori infection	0.135	0.140	0.001	0.085
Epstein-Barr virus infection	0.005	0.003	<0.001	0.075
Estrogen signaling pathway	0.063	0.065	<0.001	0.190
Ether lipid metabolism	0	0	<0.001	0.183
Ethylbenzene degradation	0.074	0.073	0.002	0.871
Fanconi anemia pathway	0.005	0.003	<0.001	0.072
Fatty acid biosynthesis	0.752	0.712	0.005	0.053
Fatty acid degradation	0.292	0.256	0.003	0.031
Fatty acid metabolism	0.853	0.792	0.006	0.033
Fc gamma R-mediated phagocytosis	0	0	<0.001	0.213
Flagellar assembly	0.671	0.749	0.018	0.202

Flavone and flavonol biosynthesis	0.009	0.011	0.001	0.164
Flavonoid biosynthesis	0	0	<0.001	0.623
Fluorobenzoate degradation	0.002	0.001	<0.001	0.397
Folate biosynthesis	0.652	0.652	0.006	0.991
FoxO signaling pathway	0.061	0.063	0.001	0.850
Fructose and mannose metabolism	1.270	1.247	0.007	0.302
GABAergic synapse	0.164	0.159	0.001	0.102
Galactose metabolism	1.172	1.249	0.008	0.061
Geraniol degradation	0.074	0.067	0.002	0.390
Glutamatergic synapse	0.149	0.142	<0.001	0.000
Glutathione metabolism	0.252	0.249	0.002	0.661
Glycerolipid metabolism	0.579	0.598	0.003	0.103
Glycerophospholipid metabolism	0.860	0.874	0.003	0.208

Glycine, serine and threonine metabolism	1.477	1.494	0.005	0.306
Glycolysis / Gluconeogenesis	1.514	1.485	0.003	0.036
Glycosaminoglycan degradation	0.127	0.141	0.004	0.292
Glycosphingolipid biosynthesis - ganglio series	0.101	0.112	0.003	0.361
Glycosphingolipid biosynthesis - globo series	0.201	0.220	0.004	0.205
Glyoxylate and dicarboxylate metabolism	1.001	1.002	0.004	0.936
GnRH signaling pathway	0	0	<0.001	0.211
HIF-1 signaling pathway	0.169	0.167	0.001	0.380
Histidine metabolism	0.738	0.731	0.003	0.587
Homologous recombination	1.444	1.445	0.004	0.980
Huntington's disease	0.040	0.041	0.001	0.859
Indole alkaloid biosynthesis	0	0	<0.001	0.989
Inositol phosphate metabolism	0.118	0.112	0.001	0.141

Insulin signaling pathway	0.104	0.106	0.001	0.660
Isoflavonoid biosynthesis	0.001	0.001	<0.001	0.655
Isoquinoline alkaloid biosynthesis	0.088	0.089	0.001	0.432
Legionellosis	0.240	0.244	0.001	0.387
Limonene and pinene degradation	0.138	0.129	0.002	0.244
Linoleic acid metabolism	0.091	0.087	0.001	0.111
Lipoic acid metabolism	0.044	0.046	0.001	0.742
Lipopolysaccharide biosynthesis	0.425	0.472	0.008	0.124
Lysine biosynthesis	0.943	0.929	0.001	0.050
Lysine degradation	0.166	0.154	0.002	0.075
Lysosome	0.178	0.197	0.005	0.291
MAPK signaling pathway - yeast	0.077	0.077	0.001	0.889
Meiosis - yeast	0.011	0.011	0.001	0.872

Metabolism of xenobiotics by cytochrome P450	0.015	0.011	0.001	0.100
Methane metabolism	1.341	1.312	0.003	0.049
MicroRNAs in cancer	0.122	0.117	0.001	0.211
Mineral absorption	0.008	0.007	<0.001	0.300
Mismatch repair	1.235	1.240	0.002	0.537
N-Glycan biosynthesis	0.059	0.057	0.001	0.462
NOD-like receptor signaling pathway	0.064	0.066	<0.001	0.210
Naphthalene degradation	0.065	0.053	0.002	0.054
Nicotinate and nicotinamide metabolism	0.725	0.717	0.005	0.627
Nitrogen metabolism	0.586	0.590	0.002	0.642
Nitrotoluene degradation	0.114	0.100	0.003	0.143
Non-alcoholic fatty liver disease (NAFLD)	0	0	<0.001	0.209
Non-homologous end-joining	0.003	0.002	<0.001	0.381

Nonribosomal peptide structures	0.008	0.009	<0.001	0.486
Novobiocin biosynthesis	0.190	0.187	0.001	0.414
Nucleotide excision repair	0.600	0.599	0.001	0.440
One carbon pool by folate	1.021	1.022	0.004	0.974
Other glycan degradation	0.451	0.503	0.009	0.143
Oxidative phosphorylation	1.788	1.775	0.015	0.859
PI3K-Akt signaling pathway	0.068	0.068	0.001	0.988
PPAR signaling pathway	0.158	0.149	0.002	0.126
Pantothenate and CoA biosynthesis	1.008	1.013	0.001	0.165
Parkinson's disease	0	0	<0.001	0.207
Pathways in cancer	0.073	0.076	0.001	0.159
Penicillin and cephalosporin biosynthesis	0.008	0.006	<0.001	0.259
Pentose and glucuronate interconversions	0.614	0.635	0.005	0.302

Pentose phosphate pathway	1.105	1.095	0.006	0.661
Peptidoglycan biosynthesis	1.228	1.209	0.004	0.164
Peroxisome	0.286	0.281	0.003	0.597
Pertussis	0.029	0.033	0.001	0.308
Phenylalanine metabolism	0.355	0.339	0.003	0.091
Phenylalanine, tyrosine and tryptophan biosynthesis	1.382	1.399	0.004	0.178
Phenylpropanoid biosynthesis	0.299	0.328	0.005	0.165
Phosphatidylinositol signaling system	0.112	0.114	0.001	0.327
Phosphonate and phosphinate metabolism	0.098	0.105	0.001	0.107
Phosphotransferase system (PTS)	0.313	0.291	0.008	0.424
Photosynthesis	0.584	0.612	0.005	0.116
Plant-pathogen interaction	0.181	0.198	0.001	0.020
Polycyclic aromatic hydrocarbon degradation	0.001	0.001	<0.001	0.307

Polyketide sugar unit biosynthesis	0.330	0.342	0.003	0.225
Porphyrin and chlorophyll metabolism	1.034	1.059	0.013	0.643
Primary bile acid biosynthesis	0.035	0.043	0.001	0.115
Primary immunodeficiency	0.053	0.058	0.001	0.110
Prion diseases	0.001	0.001	<0.001	0.043
Progesterone-mediated oocyte maturation	0.063	0.065	<0.001	0.187
Prolactin signaling pathway	0.029	0.030	0.001	0.982
Propanoate metabolism	0.756	0.721	0.005	0.093
Prostate cancer	0.063	0.065	<0.001	0.185
Proteasome	0.005	0.003	<0.001	0.070
Protein digestion and absorption	0.040	0.043	0.001	0.538
Protein export	0.946	0.933	0.002	0.144
Protein processing in endoplasmic reticulum	0.123	0.121	0.002	0.758

Proteoglycans in cancer	0.071	0.071	<0.001	0.262
Proximal tubule bicarbonate reclamation	0.029	0.028	0.001	0.903
Purine metabolism	3.097	3.112	0.007	0.538
Pyrimidine metabolism	2.806	2.801	0.006	0.858
Pyruvate metabolism	1.489	1.415	0.004	0.022
RIG-I-like receptor signaling pathway	0	0	<0.001	0.102
RNA degradation	0.849	0.859	0.002	0.113
RNA polymerase	0.238	0.231	0.002	0.211
RNA transport	0.195	0.191	0.001	0.302
Ras signaling pathway	0	0	<0.001	0.205
Renal cell carcinoma	0.010	0.011	0.001	0.737
Renin-angiotensin system	0	0	<0.001	0.292
Retinol metabolism	0.021	0.020	0.001	0.626

Retrograde endocannabinoid signaling	0	0	<0.001	0.935
Riboflavin metabolism	0.453	0.467	0.003	0.137
Ribosome	3.715	3.679	0.012	0.331
Ribosome biogenesis in eukaryotes	0.073	0.073	<0.001	0.910
Salmonella infection	0.057	0.070	0.001	0.041
Secondary bile acid biosynthesis	0.035	0.042	0.001	0.116
Selenocompound metabolism	0.512	0.531	0.002	0.025
Serotonergic synapse	0	0	<0.001	0.862
Sesquiterpenoid and triterpenoid biosynthesis	0.002	0.001	<0.001	0.914
Sphingolipid metabolism	0.310	0.341	0.004	0.113
Sphingolipid signaling pathway	0	0	<0.001	0.871
Staphylococcus aureus infection	0.011	0.012	0.001	0.793
Starch and sucrose metabolism	1.534	1.627	0.013	0.102

Steroid biosynthesis	0.001	0.001	<0.001	0.912
Steroid degradation	0	0	<0.001	0.361
Steroid hormone biosynthesis	0.004	0.003	<0.001	0.549
Stilbenoid, diarylheptanoid and gingerol biosynthesis	0.001	0.001	<0.001	0.317
Streptomycin biosynthesis	0.515	0.530	0.003	0.264
Styrene degradation	0.021	0.017	0.001	0.160
Sulfur metabolism	0.321	0.342	0.004	0.124
Sulfur relay system	0.316	0.297	0.003	0.076
Synaptic vesicle cycle	0	0	<0.001	0.931
Synthesis and degradation of ketone bodies	0.038	0.030	0.001	0.050
Taurine and hypotaurine metabolism	0.181	0.174	0.001	0.039
Terpenoid backbone biosynthesis	0.899	0.883	0.003	0.138
Tetracycline biosynthesis	0.131	0.114	0.002	0.038

Thiamine metabolism	0.643	0.638	0.005	0.862
Thyroid hormone synthesis	0.040	0.041	0.002	0.936
Toluene degradation	0.003	0.003	<0.001	0.870
Tropane, piperidine and pyridine alkaloid biosynthesis	0.175	0.172	0.001	0.254
Tryptophan metabolism	0.160	0.143	0.002	0.048
Tuberculosis	0.224	0.219	0.001	0.093
Two-component system	1.922	1.955	0.027	0.755
Type I diabetes mellitus	0.087	0.088	0.001	0.665
Type II diabetes mellitus	0.071	0.071	<0.001	0.873
Tyrosine metabolism	0.283	0.272	0.003	0.220
Ubiquinone and other terpenoid-quinone biosynthesis	0.282	0.301	0.009	0.548
Valine, leucine and isoleucine biosynthesis	0.876	0.864	0.002	0.142
Valine, leucine and isoleucine degradation	0.327	0.320	0.004	0.640

Vancomycin resistance	0.413	0.404	0.001	0.047
Various types of N-glycan biosynthesis	0.005	0.003	<0.001	0.077
Vasopressin-regulated water reabsorption	0	0	<0.001	0.926
Vibrio cholerae pathogenic cycle	0.102	0.104	0.001	0.662
Viral carcinogenesis	0.075	0.071	0.001	0.076
Vitamin B6 metabolism	0.304	0.314	0.002	0.225
Xylene degradation	0.010	0.012	<0.001	0.185
Zeatin biosynthesis	0.083	0.083	0.001	0.914
alpha-Linolenic acid metabolism	0.002	0.002	<0.001	0.701
beta-Alanine metabolism	0.226	0.229	0.002	0.693
beta-Lactam resistance	0.433	0.451	0.005	0.278
cAMP signaling pathway	0	0	<0.001	0.203

¹ SEM, standard error of means.