

Table S1. Over-represented functions in the metagenome of Enamel and Dentin caries samples. p- and q-values are indicated for the comparison of frequencies between the two samples at the hierarchical level 2 of the SEED functional classification system (Meyer et al. 2008), by an application of the FDR method modified for metagenomic data (White et al. 2009). Only statistically significant differences in gene functions are shown, which are color-coded for clarity.

Name	mean(ENAMEL)	mean(DENTIN)	pvalue	qvalue
Oxygen and light sensor PpaA-PpsR	0.00E+00	2.5464 e-05	4.27E-02	1.60E-01
Sulfate reduction-associated complexes	0.00E+00	2.5464 e-05	4.27E-02	1.60E-01
Bacterial cytostatics, differentiation factors and antibiotics	1.31E-04	1.993 e-05	3.23E-03	2.57E-02
Bacteriocins, ribosomally synthesized antibacterial peptides	1.46E-04	2.36E-04	4.21E-02	1.60E-01
SigmaB stress response regulation	1.54E-04	2.95E-04	3.33E-02	1.41E-01
CBSS-316273.3.peg.922	1.78E-04	7.3631 e-05	1.52E-02	8.03E-02
Cyanate hydrolysis	1.78E-04	3.69E-04	1.94E-03	1.68E-02
Flavocytochrome C	1.81E-04	8.6363 e-05	3.58E-02	1.42E-01
Cold shock	1.81E-04	7.086 e-05	1.55E-02	8.03E-02
Aerotolerance operon in Bacteroides and potentially orthologous operons in other organisms	1.86E-04	5.16E-04	6.3932 e-08	2.0902 e-06
Phage shock protein (psp) operon	2.50E-04	1.01E-04	5.05E-03	3.66E-02
CBSS-159087.4.peg.2189	2.56E-04	9.9696 e-06	4.7785 e-08	1.7576 e-06
Muconate lactonizing enzyme family	3.15E-04	1.69E-04	1.90E-02	9.20E-02
Allantoin Utilization	3.70E-04	5.62E-04	1.56E-02	8.03E-02
Hfl operon	4.22E-04	6.14E-04	4.29E-02	1.60E-01
Ferrous iron transporter EfeUOB, low-pH-induced	4.34E-04	1.50E-04	5.9610 e-06	1.35E-04
Two-component regulatory systems in Campylobacter	4.40E-04	8.73E-04	1.7407 e-06	4.6565 e-05
Dissimilatory nitrite reductase	4.43E-04	2.67E-04	1.98E-02	9.38E-02
Adenosyl nucleosidases	5.48E-04	9.58E-04	4.8208 e-05	7.09E-04
Iron acquisition in Streptococcus	5.50E-04	7.31E-04	1.39E-02	7.56E-02
Acid stress	5.85E-04	2.50E-04	9.726 e-05	1.36E-03
Sporulation-associated proteins with broader functions	6.26E-04	3.56E-04	5.96E-03	3.90E-02
CBSS-211586.1.peg.3133	6.32E-04	1.10E-03	3.3697 e-05	5.22E-04
Flavo-haemoglobin	6.58E-04	4.21E-04	2.82E-03	2.37E-02
Allophanate hydrolase 2 and Biotin carboxylase cluster	7.86E-04	5.24E-04	1.01E-02	5.81E-02
Biogenesis of c-type cytochromes	7.89E-04	1.12E-03	1.10E-03	1.08E-02
CBSS-316057.3.peg.3521	8.59E-04	6.28E-04	2.08E-02	9.56E-02
Proteorhodopsin	8.59E-04	5.87E-04	7.91E-03	4.85E-02
YjeE	1.09E-03	1.52E-03	4.14E-03	3.12E-02
Bacterial Chemotaxis	1.10E-03	1.78E-03	3.8655 e-07	1.1374 e-05
P uptake (cyanobacteria)	1.14E-03	1.61E-03	5.05E-04	5.50E-03
Heme, hemin uptake and utilization systems in GramNegatives	1.34E-03	1.02E-03	2.05E-02	9.56E-02
Stringent Response, (p)ppGpp metabolism	1.41E-03	1.02E-03	5.32E-03	3.66E-02
CBSS-320372.3.peg.6046	1.42E-03	1.77E-03	9.93E-03	5.81E-02
Murein Hydrolases	1.43E-03	1.76E-03	4.60E-02	1.65E-01
High affinity phosphate transporter and control of PHO regulon	1.44E-03	1.78E-03	2.92E-02	1.28E-01
CRISPs	1.44E-03	1.90E-03	2.95E-03	2.41E-02
Soluble cytochromes and functionally related electron carriers	1.53E-03	1.22E-03	3.45E-02	1.41E-01
Galactosylceramide and Sulfatide metabolism	1.76E-03	2.08E-03	2.25E-02	1.02E-01
Transposable elements	2.10E-03	2.87E-03	2.2363 e-05	3.87E-04
Gram-Positive cell wall components	2.20E-03	3.01E-03	8.6398 e-06	1.82E-04
Riboflavin, FMN, FAD	2.26E-03	2.61E-03	2.97E-02	1.29E-01
ECF class transporters	2.38E-03	3.08E-03	2.12E-04	2.65E-03
CBSS-281090.3.peg.464	2.39E-03	2.77E-03	4.93E-02	1.75E-01
Inorganic sulfur assimilation	2.68E-03	2.05E-03	3.39E-04	3.99E-03
Quinone cofactors	2.85E-03	2.27E-03	1.70E-03	1.61E-02
ZZ gjo need homes	3.11E-03	2.65E-03	3.39E-02	1.41E-01
Electron accepting reactions	3.30E-03	2.61E-03	1.87E-03	1.67E-02
Nitrate and nitrite ammonification	3.37E-03	2.89E-03	1.12E-02	6.33E-02
Coenzyme A	3.38E-03	3.00E-03	4.56E-02	1.65E-01
Biosynthesis of galactoglycans and related lipopolysaccharides	3.54E-03	4.02E-03	3.97E-02	1.56E-01
Flagellar motility in Prokaryota	3.73E-03	5.88E-03	8.4156 e-18	8.2543 e-16
CBSS-196620.1.peg.2477	4.19E-03	3.70E-03	2.52E-02	1.12E-01
UDP-N-acetylmuramate from Fructose-6-phosphate Biosynthesis	4.36E-03	3.81E-03	4.36E-02	1.61E-01
Ton and Tol transport systems	4.66E-03	5.31E-03	3.42E-03	2.64E-02
Histidine Metabolism	4.73E-03	3.91E-03	4.85E-04	5.49E-03
NAD and NADP	5.38E-03	7.51E-03	1.4287 e-12	8.4083 e-11
Polysaccharides	5.40E-03	6.60E-03	1.1681 e-05	2.15E-04
Iron acquisition in Vibrio	5.40E-03	6.59E-03	4.6813 e-06	1.15E-04
Glutamine, glutamate, aspartate, asparagine; ammonia assimilation	6.26E-03	7.42E-03	1.84E-04	2.46E-03
Organic acids	7.16E-03	5.84E-03	9.3409 e-06	1.83E-04
Heat shock	7.58E-03	6.80E-03	1.26E-02	6.99E-02
Electron donating reactions	9.50E-03	8.71E-03	6.96E-03	4.45E-02
Arginine; urea cycle, polyamines	9.57E-03	8.84E-03	3.41E-02	1.41E-01
Branched-chain amino acids	1.12E-02	1.00E-02	8.48E-04	8.92E-03
Tetrapyrroles	1.28E-02	1.05E-02	1.4539 e-08	6.1118 e-07
Monosaccharides	1.40E-02	1.87E-02	2.4384 e-23	3.5875 e-21
Di- and oligosaccharides	1.66E-02	1.98E-02	3.9877 e-11	1.9556 e-09
Sugar utilization in Thermotogales	1.89E-02	2.30E-02	2.477 e-14	1.8221 e-12
Lysine, threonine, methionine, and cysteine	2.50E-02	2.36E-02	1.90E-02	9.20E-02
DNA repair	2.66E-02	2.86E-02	8.81E-04	8.94E-03
Phages, Prophages	2.75E-02	1.61E-02	6.0848 e-96	1.7901 e-93
Protein biosynthesis	6.78E-02	6.51E-02	5.69E-03	3.80E-02
Carbon storage regulator	1.1649 e-05	8.9727 e-05	2.16E-04	2.65E-03
carbazol degradation cluster	2.6212 e-05	1.01E-04	5.35E-03	3.66E-02
Bile hydrolysis related cluster	2.9124 e-06	4.9848 e-05	1.87E-03	1.67E-02
Pseudouridine catabolism	2.9124 e-06	9.0808 e-05	2.4406 e-05	3.99E-04
Iron Scavenging cluster in Thermus	2.9124 e-06	4.2641 e-05	7.61E-03	4.76E-02
Dessication stress	5.2424 e-05	0.00E+00	3.52E-02	1.42E-01
Tricarboxylate transport system	5.8249 e-05	1.62E-04	9.01E-03	5.41E-02
beta-glucuronide utilization	5.8249 e-06	3.9878 e-05	1.91E-02	9.20E-02
Sulfur oxidation	8.1549 e-05	1.93E-04	5.19E-03	3.66E-02

Table S2. Clinical data of the studied samples. The number at the end of each sample code correspond to the tooth from which the active caries sample was extracted. “P” indicates a Dental Plaque sample and WS indicates that several “White Spot” lesions from the same individual were pooled. Oral Health Index (OHI) values correspond to: 0: No plaque is observed; 1: Plaque adheres to the probe; 2: Plaque is observed in the gum region; 3: Plaque is observed in 2/3 of the tooth. Gingival Index values correspond to: 0: Healthy gingiva; 1: mild inflammation; 2: Induced bleeding; 3: Spontaneous bleeding. Brush habits are indicated by the number of tooth brushes per day. DMF index values are separately shown, indicating the number of Decayed, Missing and Filled teeth. Caries severity values correspond to: 1. Initial Caries. No clinically detectable loss of substance; 2. Enamel Caries. Demonstrable loss of tooth substance in pits, fissures, or on smooth surfaces, but no softened floor or wall or undermined enamel; 3. dentin caries; detectably softened yellowish floor, undermined enamel, or a softened wall; 4. Deep dentin caries; no bleeding observed when taking sample, lack of pulp exposure, absence of apical radiological area.

SAMPLE	GENDER	AGE	OHI	GINGIVAL INDEX	BRUSH	DECAYED	FILLED	MISSING	SEVERITY
CA.001 3.8	M	51	3	2	0	5	0	11	4
CA.002 2.5	F	61	2	2	0	2	3	15	2
CA.005 4.7	F	42	2	1	1	7	1	2	3
CA.005 1.6	F	42	2	1	1	7	1	2	3
CA.006 2.2	F	49	3	3	0	6	0	2	4
CA.006 4.5	F	49	3	3	0	6	0	2	4
CA.007 4.3	F	45	3	2	0	9	0	13	4
CA.009 P	F	28	0	0	2	3	2	3	0
CA.011 1.2	F	24	0	1	1	17	0	0	3
CA.011 2.6	F	24	0	1	1	17	0	0	4
CA.011 P	F	24	0	1	1	17	0	0	0
CA.011 4.6	F	24	0	1	1	17	0	0	3
CA.013 P	M	21	3	3	0	21	0	0	0
CA.013 2.3	M	21	3	3	0	21	0	0	4
CA.013 2.1	M	21	3	3	0	21	0	0	3
CA.013 1.3	M	21	3	3	0	21	0	0	4
CA.017 WS	M	18	0	1	2	17	5	0	1
CA.017 P	M	18	0	1	2	17	5	0	0
CA1.01 1.2	M	38	1	1	1	5	14	0	1
CA1.01 2.3	M	38	1	1	1	5	14	0	1
CA.021 4.6	F	25	0	0	3	8	8	0	1
CA.022 1.3	F	27	1	1	3	2	2	5	1