Supporting Information

NMR analysis of the human saliva metabolome distinguishes dementia patients from matched controls

João Figueira[a], Pär Jonsson[b], Annelie Nordin Adolfsson[c], Rolf Adolfsson[c], Lars Nyberg[d] and Anders Öhman[a,*]

[a]Department of Pharmacology and Clinical Neuroscience, Umeå University, SE – 901 85 Umeå, [b]Department of Chemistry, Umeå University, SE – 901 87 Umeå, [c]Department of Clinical Sciences, Psychiatry, Umeå University, SE – 901 85 Umeå, [d]Departments of Radiation Sciences and Integrative Medical Biology, Umeå University, SE – 901 87, Umeå, Sweden.

[*]Correspondence to: Anders Öhman

E-mail: anders.ohman01@umu.se

Phone: +46 (0)70 5955136

Fax: +46 (0)90 143107

Table S-1. Univariate and multivariate statistical analysis of metabolites in filtrated whole saliva. For each metabolite, the average concentration (PQN normalized) and standard error for the dementia and control groups in SS1+SS3 are listed, as well as the fold-changes and *p*-values from the Mann–Whitney U-test in the pair-wise comparisons. Weight values (w*) of the metabolites used in the initial OPLS-DA model of SS1+SS3 are also included. Metabolites with *p*-values below 0.05 and significant weight values w* are indicated with an asterisk.

Metabolite	Dementia *Mean ± SEM [mM]*	Control *Mean ± SEM [mM]*	Dementia versus Controls		
			fold change	*Mann–Whitney U-test, p*	*w**
2-Aminoadipate	0.5083 ± 0.0311	0.5089 ± 0.0187	0.99	0.290	
2-Hydroxyisobutyrate	0.0152 ± 0.0020	0.0197 ± 0.0032	0.77	0.390	
2-Hydroxyisovalerate	0.0191 ± 0.0031	0.0208 ± 0.0028	0.92	0.412	
2-Oxoglutarate	0.0845 ± 0.0033	0.0831 ± 0.0023	1.02	0.440	
4-Hydroxyphenylacetate	0.0558 ± 0.0062	0.0520 ± 0.0051	1.07	0.213	−0.04
Acetate	9.4878 ± 0.4117	7.6043 ± 0.2546	1.25	2e−05*	0.44 *
Acetoacetate	0.0408 ± 0.0017	0.0452 ± 0.0066	0.90	0.216	0.05
Acetone	0.0456 ± 0.0051	0.0622 ± 0.0084	0.73	0.379	0.04
Adenine	0.0312 ± 0.0030	0.0311 ± 0.0029	1.00	0.207	
Alanine	0.2174 ± 0.0125	0.1933 ± 0.0076	1.12	0.071	−0.12
Anserine	0.0237 ± 0.0033	0.0222 ± 0.0012	1.07	0.076	−0.03
Aspartate	0.0847 ± 0.0039	0.0816 ± 0.0026	1.04	0.158	
Butyrate	0.1943 ± 0.0137	0.1775 ± 0.0105	1.09	0.040*	−0.13
Caffeine	0.0306 ± 0.0026	0.0285 ± 0.0015	1.07	0.207	−0.02
Choline	0.0513 ± 0.0030	0.0615 ± 0.0033	0.83	0.080	0.16
Creatine	0.0780 ± 0.0039	0.0842 ± 0.0025	0.93	0.058	0.08
Dimethyl sulfone	0.0383 ± 0.0032	0.0471 ± 0.0021	0.81	0.005*	0.33 *
Dimethylamine	0.0105 ± 0.0005	0.011 ± 0.0004	0.96	0.344	0.09
Ethanol	0.1249 ± 0.0120	0.1145 ± 0.0085	1.09	0.078	−0.06
Formate	0.7512 ± 0.1173	0.7517 ± 0.0780	1.00	0.435	0.01
Fucose	0.0930 ± 0.0120	0.0758 ± 0.0067	1.23	0.125	−0.11
Glucitol	0.1672 ± 0.0287	0.6228 ± 0.1726	0.27	0.204	
Glucose	0.1825 ± 0.0361	0.5719 ± 0.1649	0.32	0.255	0.13
Glycerol	0.7225 ± 0.0866	0.9179 ± 0.0708	0.79	0.040*	0.20 *
Glycine	0.4214 ± 0.0344	0.4541 ± 0.0428	0.93	0.499	0.04
Histamine	0.0484 ± 0.0041	0.0386 ± 0.0019	1.26	0.019*	0.30 *
Isoleucine	0.0690 ± 0.0061	0.0558 ± 0.0026	1.24	0.021*	−0.22
Lactate	1.1788 ± 0.3198	2.6417 ± 0.5047	0.45	0.093	0.17
Leucine	0.1174 ± 0.0111	0.0917 ± 0.0044	1.28	0.055	−0.24
Methanol	0.0654 ± 0.0072	0.0562 ± 0.0048	1.16	0.011*	−0.04
Methylamine	0.0166 ± 0.0016	0.0169 ± 0.0008	0.98	0.171	−0.02
O-Phosphocholine	0.0095 ± 0.0010	0.0189 ± 0.0034	0.50	0.063	0.16
Ornithine	0.1650 ± 0.0116	0.1425 ± 0.0052	1.16	0.029*	−0.10
Phenylacetate	0.0450 ± 0.0045	0.0398 ± 0.0024	1.13	0.152	0.01
Proline	0.3114 ± 0.0257	0.3187 ± 0.0181	0.98	0.492	0.07
Propionate	1.9501 ± 0.1593	1.4443 ± 0.0720	1.35	0.002*	0.34 *
Putrescine	0.1463 ± 0.0131	0.1206 ± 0.0062	1.21	0.048*	−0.19
Pyruvate	0.0860 ± 0.0089	0.0872 ± 0.0071	0.99	0.330	0.08
Sarcosine	0.0144 ± 0.0010	0.0148 ± 0.0007	0.97	0.230	−0.02
Succinate	0.0986 ± 0.0148	0.1584 ± 0.0170	0.62	0.008*	0.18 *
Taurine	0.1860 ± 0.0083	0.2647 ± 0.0189	0.70	0.007*	0.20 *
Trimethylamine	0.0071 ± 0.0018	0.0069 ± 0.0006	1.03	0.119	−0.05
Valine	0.0805 ± 0.0072	0.0712 ± 0.0038	1.13	0.340	−0.18
Xanthine	0.0524 ± 0.0070	0.0477 ± 0.0028	1.10	0.131	-0.04

Table S-2. Univariate and multivariate statistical analysis of metabolites in filtrated whole saliva. For each metabolite, the average concentration (PQN normalized) and standard error for the pre-dementia and control groups in SS2 are listed, as well as the fold-changes and *p*-values from the Mann–Whitney U-test in the pair-wise comparisons. Weight values (w*) from the OPLS-DA model generated with seven metabolites are also included. Metabolites with *p*-values below 0.05 are indicated with an asterisk.

Metabolite	Pre-dementia Mean ± SEM [mM]	Control Mean ± SEM [mM]	Pre-dementia versus Controls fold change	Mann–Whitney U-test, p	w*
2-Aminoadipate	0.6450 ± 0.0310	0.6465 ± 0.0208	1.00	0.447	
2-Hydroxyisobutyrate	0.0090 ± 0.0005	0.0107 ± 0.0008	0.84	0.284	
2-Hydroxyisovalerate	0.0223 ± 0.0059	0.0202 ± 0.0022	1.10	0.140	
2-Oxoglutarate	0.0765 ± 0.0035	0.0807 ± 0.0033	0.95	0.401	
4-Hydroxyphenylacetate	0.0387 ± 0.0024	0.0427 ± 0.0038	0.91	0.240	
Acetate	8.6509 ± 0.2810	8.5282 ± 0.2024	1.01	0.302	−0.17
Acetoacetate	0.0415 ± 0.0016	0.0401 ± 0.0014	1.04	0.498	
Acetone	0.0422 ± 0.0047	0.0297 ± 0.0019	1.42	0.057	
Adenine	0.0468 ± 0.0057	0.0488 ± 0.0024	0.96	0.142	
Alanine	0.2300 ± 0.0130	0.2158 ± 0.0076	1.06	0.307	
Anserine	0.0252 ± 0.0012	0.0284 ± 0.0011	0.88	0.054	
Aspartate	0.1023 ± 0.0052	0.0958 ± 0.0026	1.07	0.300	
Butyrate	0.1875 ± 0.0123	0.1812 ± 0.0071	1.04	0.456	
Caffeine	0.0202 ± 0.0011	0.0208 ± 0.0010	0.97	0.452	
Choline	0.0582 ± 0.0030	0.0555 ± 0.0025	1.05	0.031*	
Creatine	0.0606 ± 0.0024	0.0631 ± 0.0024	0.96	0.414	
Dimethyl sulfone	0.0416 ± 0.0028	0.0394 ± 0.0016	1.06	0.286	−0.07
Dimethylamine	0.0094 ± 0.0007	0.0087 ± 0.0003	1.08	0.388	
Ethanol	0.1195 ± 0.0455	0.0850 ± 0.0042	1.40	0.435	
Formate	0.7492 ± 0.0779	0.8060 ± 0.0699	0.92	0.119	
Fucose	0.1040 ± 0.0069	0.1140 ± 0.0038	0.91	0.002*	
Glucitol	0.7236 ± 0.5035	0.5273 ± 0.2349	1.37	0.115	
Glucose	0.4500 ± 0.0554	0.6165 ± 0.1033	0.73	0.306	
Glycerol	0.8813 ± 0.0690	0.9501 ± 0.0647	0.93	0.317	0.27
Glycine	0.4437 ± 0.0259	0.4770 ± 0.0210	0.93	0.336	
Histamine	0.0353 ± 0.0019	0.0352 ± 0.0016	1.00	0.248	0.02
Isoleucine	0.0630 ± 0.0050	0.0635 ± 0.0027	0.99	0.259	
Lactate	1.2829 ± 0.2337	1.4043 ± 0.2234	0.91	0.002*	
Leucine	0.0991 ± 0.0066	0.1089 ± 0.0042	0.91	0.195	
Methanol	0.0439 ± 0.0028	0.0460 ± 0.0025	0.95	0.369	
Methylamine	0.0180 ± 0.0010	0.0178 ± 0.0008	1.01	0.497	
O-Phosphocholine	0.0112 ± 0.0012	0.0099 ± 0.0007	1.13	0.197	
Ornithine	0.1140 ± 0.0064	0.1243 ± 0.0044	0.92	0.039*	
Phenylacetate	0.0460 ± 0.0037	0.0453 ± 0.0019	1.02	0.498	
Proline	0.3587 ± 0.0247	0.3803 ± 0.0220	0.94	0.226	
Propionate	1.7380 ± 0.0908	1.5998 ± 0.0641	1.09	0.041*	−0.76
Putrescine	0.1316 ± 0.0093	0.1304 ± 0.0047	1.01	0.347	
Pyruvate	0.0583 ± 0.0055	0.0581 ± 0.0023	1.00	0.323	
Sarcosine	0.0145 ± 0.0007	0.0141 ± 0.0004	1.03	0.352	
Succinate	0.1466 ± 0.0151	0.1327 ± 0.0116	1.10	0.012*	−0.55
Taurine	0.2020 ± 0.0096	0.2024 ± 0.0087	1.00	0.275	−0.11
Trimethylamine	0.0084 ± 0.0009	0.0087 ± 0.0006	0.97	0.284	
Valine	0.0649 ± 0.0066	0.0709 ± 0.0034	0.92	0.098	
Xanthine	0.0592 ± 0.0037	0.0680 ± 0.0036	0.87	0.212	