TABLE S1
A list of the 216 proteins

PDB	EC Class	SCOP	Chain	Nsites[1]	Year	Resolution (Å)	R.value	Nseq[2]
132L	3.02.01.0017	a+b	A	124	1993	1.8	0.173	300
13PK	2.07.02.0003	a/b	A	415	1996	2.5	0.221	300
1A26	2.04.02.0030	a, a+b	A	351	1998	2.25	0.168	300
1A2T	3.01.31.0001	b	A	134	1998	1.96	0.169	300
1A4L	5.99.01.0002	a/b	A	349	1998	2.6	0.185	300
1A65	1.10.03.0002	b, b, b	A	504	1998	2.23	0.16	300
1A8H	6.01.01.0010	a, a/b	A	500	1998	2	0.205	300
1A8S	1.11.01.0010	a/b	A	273	1998	1.8	0.173	300
1AF7	2.01.01.0080	a, a/b	A	274	1997	2	0.2	300
1AGM	3.02.01.0003	a	A	470	1994	2.3	0.124	300
1AGY	3.01.01.0000	a/b	A	197	1997	1.15	0.175	300
1AH7	3.01.04.0003	a	A	245	1997	1.5	0.203	83
1AJ0	2.05.01.0015	a/b	A	282	1997	2	0.206	300
1AK0	3.01.30.0001	a	A	264	1997	1.8	0.207	300
1AKO	3.01.11.0002	a+b	A	268	1997	1.7	0.169	300
1AMY	3.02.01.0001	b, a/b	A	403	1994	2.8	0.153	300
1AQ2	4.01.01.0049	a/b, a/b	A	534	1997	1.9	0.218	300
1AQL	3.01.01.0013	a/b	A	532	1997	2.8	0.211	300
1AST	3.04.24.0021	a+b	A	200	1993	1.8	0.158	300
1B04	6.05.01.0002	a+b	A	310	1998	2.8	0.23	300
1B2R	1.18.01.0002	b, a/b	A	295	1998	1.8	0.19	300
1BBS	3.04.23.0015	b	A	325	1992	2.8	0.196	300
1BF2	3.02.01.0068	b, b, a/b	A	750	1998	2	0.161	300
1BG0	2.07.03.0003	a, a+b	A	356	1998	1.86	0.196	300
1BH2	na	a, a/b	A	315	1998	2.1	0.19	300
1BOL	2.07.01.0068	a+b	A	222	1998	2	0.185	300
1BP2	3.01.01.0004	a	A	123	1981	1.7	0.171	300
1BQC	3.02.01.0078	a/b	A	302	1998	1.5	0.119	300
1BS0	2.03.01.0047	a/b	A	383	1998	1.65	0.178	300
1BS4	3.05.01.0088	a+b	A	168	1998	1.9	0.193	300
1BS9	3.01.01.0006	a/b	A	207	1998	1.1	0.123	300
1BT1	1.10.03.0001	a	A	336	1998	2.7	0.168	300
1BU7	1.06.02.0004	a	A	455	1998	1.65	0.197	300
1BVV	3.02.01.0008	b	A	185	1998	1.8	0.189	300
1BVZ	3.02.01.0135	b, b, a/b	A	585	1998	2.6	0.196	300
1BWL	1.06.99.0001	a/b	A	399	1998	2.7	0.19	300
1BWZ	5.01.01.0007	a+b, a+b	A	274	1998	2.72	0.19	300
1BYA	3.02.01.0002	a/b	A	491	1994	2.2	0.169	137
1BZC	3.01.03.0048	a/b	A	297	1998	2.35	0.204	300
1C82	4.02.02.0001	a, b, b	A	719	2000	1.7	0.215	244
1CA2	4.02.01.0001	b	A	256	1989	2	0.173	300
1CB8	4.02.02.0005	a, b, b	A	674	1999	1.9	0.195	240
1CBX	3.04.17.0001	a/b	A	307	1991	2	0.166	300

1CDG	2.04.01.0019	b, b, b, a/b	A	686	1993	2	0.164	300
1CEL	3.02.01.0091	b	A	433	1994	1.8	0.181	239
1CHD	3.01.01.0061	a/b	A	198	1995	1.75	0.182	300
1CHK	3.02.01.0132	a+b	B	238	1995	2.4	0.181	73
1CM0	2.03.01.0048	a+b	A	162	1999	2.3	0.223	300
1CNS	3.04.23.0004	a+b	A	243	1995	1.91	0.186	300
1COY	1.01.03.0006	a/b, a+b	A	501	1993	1.8	0.159	300
1CQQ	2.07.07.0048	b	A	180	1999	1.85	0.218	194
1CVR	3.04.22.0037	b, a/b	A	432	1999	2	0.163	134
1CWY	2.04.01.0025	a/b	A	500	1999	2	0.19	300
1CZ1	3.02.01.0058	a/b	A	394	1999	1.85	0.166	300
1CZF	3.02.01.0015	b	A	335	1999	1.68	0.166	300
1D1Q	3.01.03.0002	a/b	A	159	1999	1.7	0.17	300
1D4C	1.03.99.0001	a, a/b, a+b	A	570	1999	2.9	0.21	300
1D6O	5.02.01.0008	a+b	A	107	1999	1.85	0.192	300
1DDJ	3.04.21.0007	b	A	247	1999	2	0.194	300
1DGK	2.07.01.0001	a/b, a/b, a/b, a/b	N	898	1999	2.8	0.258	60
1DGS	6.05.01.0002	a, b, a+b	A	581	1999	2.9	0.228	300
1DIN	3.01.01.0045	a/b	A	233	1996	1.8	0.15	300
1DNP	4.01.99.0003	a, a/b	A	469	1995	2.3	0.172	300
1DVE	1.14.99.0003	a	A	214	2000	2.4	0.214	300
1E0C	2.08.01.0001	a/b, a/b	A	270	2000	1.8	0.18	300
1E1A	3.01.08.0002	b	A	312	2000	1.8	0.1763	300
1E6E	1.18.01.0002	a/b, a/b	A	457	2000	2.3	0.222	300
1EB6	3.04.24.0039	a+b	A	177	2001	1	0.104	225
1EH5	3.01.02.0022	a/b	A	279	2000	2.5	0.226	300
1EUG	3.02.02.0003	a/b	A	225	1998	1.6	0.194	300
1EUU	3.02.01.0018	b, b, b	A	601	1996	2.5	0.228	300
1EX1	3.02.01.0058	a/b, a/b	A	602	1998	2.2	0.17	300
1EXN	3.01.11.0003	a, a/b	A	267	1997	2.5	0.227	300
1EXP	3.02.01.0008	a/b	A	312	1996	1.8	0.208	300
1EYP	5.05.01.0006	a+b	A	212	2000	2.5	0.249	272
1FF3	1.08.04.0006	a+b	A	210	2000	1.9	0.195	300
1FGH	4.02.01.0003	a/b, a/b	A	753	1996	2.05	0.177	300
1FHL	3.02.01.0089	a/b	A	334	2000	2.3	0.166	300
1FOA	2.04.01.0101	a/b	A	342	2000	1.8	0.185	200
1G24	2.04.02.0000	a+b	A	211	2000	1.7	0.24	241
1G6T	2.05.01.0019	a+b	A	427	2000	1.6	0.155	300
1G8O	2.04.01.0087	a/b	A	287	2000	2.3	0.274	98
1GA8	2.04.01.0044	a/b	A	271	2000	2	0.189	300
1GAL	1.01.03.0004	a/b, a+b	A	581	1992	2.3	0.181	300
1GCU	1.03.01.0024	a/b, a+b	A	292	2000	1.4	0.219	300
1GOG	1.01.03.0009	b, b, b	A	639	1993	1.9	0.17	300
1GP5	1.14.11.0019	b	A	346	2001	2.2	0.204	300
1GQ8	3.01.01.0011	b	A	318	2001	1.75	0.181	300
1H19	3.03.02.0006	a, b, a+b	A	610	2002	2.1	0.184	300

1H3I	2.01.01.0043	b, b	A	293	2002	2.1	0.21	300
1HKA	2.07.06.0003	a+b	A	158	1998	1.5	0.182	300
1HPL	3.01.01.0003	b, a/b	A	448	1993	2.3	0.159	300
1HPM	3.06.01.0003	a/b, a/b	A	378	1995	1.7	0.205	300
1HQC	3.06.01.0003	a, a/b	A	314	2000	3.2	0.263	300
1I1E	3.04.24.0069	b, b, a+b, Coiled coil proteins	A	1287	2001	2.5	0.217	32
1I1I	3.04.24.0016	a+b	P	665	2001	2.3	0.224	300
1I9A	5.03.03.0002	a+b	A	175	2001	2.5	0.229	300
1IDJ	4.02.02.0010	b	A	359	1996	2.4	0.16	300
1IG8	2.07.01.0001	a/b, a/b	A	469	2001	2.2	0.162	300
1IM5	3.05.01.0019	a/b	A	179	2001	1.65	0.152	300
1INP	3.01.03.0057	multi-domain	A	400	1994	2.3	0.198	300
1IU4	2.03.02.0013	a+b	A	331	2002	2.4	0.199	8
1J00	3.01.02.0000	a/b	A	176	2002	2	0.239	300
1J09	6.01.01.0017	a, a/b	A	468	2002	1.8	0.199	300
1JH6	3.01.04.0000	a+b	A	181	2001	1.8	0.192	282
1JMS	2.07.07.0031	a, a, a+b	A	360	2001	2.36	0.214	300
1JOA	1.11.01.0001	a/b, a/b, a+b	A	446	1996	2.8	0.179	300
1JS4	3.02.01.0004	a, b	A	605	1997	2	0.199	300
1K30	2.03.01.0015	a/b	A	363	2001	1.9	0.186	48
1KL7	4.02.03.0001	a/b	A	503	2001	2.7	0.201	300
1KNP	1.04.03.0016	a, a/b, a+b	A	529	2001	2.6	0.23	300
1L1D	1.08.04.0006	b	A	142	2002	1.85	0.207	300
1L1L	1.17.04.0002	a/b	A	717	2002	1.75	0.223	300
1L6P	1.08.01.0008	b	A	121	2002	1.65	0.141	300
1L7N	3.01.03.0003	a/b	A	207	2002	1.8	0.191	300
1L7Q	3.01.01.0001	b, a/b	A	571	2002	1.76	0.183	300
1L8T	2.07.01.0095	a+b	A	263	2002	2.4	0.234	300
1L9X	3.04.19.0009	a/b	A	288	2002	1.6	0.181	300
1LBA	3.05.01.0028	a+b	A	146	1993	2.2	0.19	300
1LBU	3.04.17.0008	a, a+b	A	213	1996	1.8	0.164	300
1LDM	1.01.01.0027	a/b, a+b	A	329	1987	2.1	0.173	300
1LJL	1.03.99.0001	a/b	A	130	2002	2.01	0.214	300
1LVH	5.04.02.0006	a/b	A	220	2002	2.3	0.243	300
1M53	5.04.99.0011	b, a/b	A	556	2002	2.2	0.194	300
1MBB	1.01.01.0158	a+b, a+b	A	340	1995	2.3	0.238	300
1MJ9	2.03.01.0048	a+b	A	273	2002	2.5	0.232	300
1MLA	2.03.01.0039	a/b, a+b	A	305	1995	1.5	0.184	300
1MRQ	1.03.01.0020	a/b	A	323	2002	1.59	0.173	300
1MUD	3.02.02.0000	a	A	225	1998	1.8	0.192	300
1MUG	3.02.02.0000	a/b	A	165	1998	1.8	0.198	300
1NDH	1.06.02.0002	b, a/b	A	270	1994	2.1	0.223	300
1NDI	2.03.01.0007	a/b, a/b	A	596	2002	2.3	0.27	300
1NLU	3.04.21.0100	a/b	A	368	2003	1.3	0.164	300
1O8A	3.04.15.0001	a+b	A	574	2002	2	0.18	300

1O98	5.04.02.0001	a/b, a/b	A	509	2002	1.4	0.19	300
1OBA	3.02.01.0017	b, a/b	A	338	2003	2.45	0.205	300
1OG1	2.04.02.0031	a+b	A	223	2003	2	0.202	165
1OGO	3.02.01.0011	b, b	X	572	2003	1.65	0.188	161
1OJ4	2.07.01.0148	a+b, a+b	A	277	2003	2.01	0.1655	300
1ONR	2.02.01.0002	a/b	A	316	1996	1.87	0.201	300
1OPM	1.14.17.0003	b, b	A	310	1999	2.1	0.2	275
1OXA	1.00.00.0000	a	A	403	1995	2.1	0.196	300
1OYG	2.04.01.0010	b	A	440	2003	1.5	0.165	114
1P1X	4.01.02.0004	a/b	A	250	2003	0.99	0.143	300
1P3D	6.03.02.0008	a/b, a/b, a/b	A	449	2003	1.7	0.168	300
1P5D	5.04.02.0008	a/b, a/b, a/b, a+b	X	454	2003	1.6	0.156	300
1PA9	3.01.03.0048	a/b	A	279	2003	2	0.226	300
1PII	4.01.01.0048	a/b, a/b	A	452	1991	2	0.173	286
1PKN	2.07.01.0040	b, a/b, a/b	A	514	1994	2.9	0.191	300
1PMI	5.03.01.0008	b	A	440	1996	1.7	0.184	300
1PP4	3.01.01.0000	a/b	A	233	2003	2.5	0.182	300
1PS9	1.03.01.0034	a/b, a/b, a/b	A	671	2003	2.2	0.203	300
1PTD	4.06.01.0013	a/b	A	296	1995	2.6	0.187	300
1PUD	2.04.02.0029	a/b	A	372	1996	1.85	0.19	300
1PYL	3.01.04.0008	a+b	A	96	2003	1.51	0.149	223
1Q91	3.01.03.0005	a/b	A	194	2003	1.6	0.186	300
1QAM	2.01.01.0048	a/b	A	235	1999	2.2	0.221	300
1QAZ	3.05.01.0045	a	A	351	1999	1.78	0.18	300
1QBA	3.02.01.0052	b, b, a/b, a+b	A	858	1996	1.85	0.139	300
1QFM	3.04.21.0026	b, a/b	A	705	1999	1.4	0.19	300
1QGX	3.01.03.0007	multi-domain	A	354	1999	1.6	0.197	300
1QJE	1.21.03.0001	b	A	327	1999	1.35	0.131	300
1QK2	3.02.01.0091	a/b	A	363	1999	2	0.189	295
1QV0	1.13.12.0005	a	A	185	2003	1.1	0.134	300
1QWN	3.02.01.0114	a, b, a/b	A	1014	2003	1.2	0.175	300
1R1J	3.04.24.0011	a+b	A	696	2003	2.35	0.222	300
1R44	3.04.13.0000	a+b	A	202	2003	2.25	0.254	300
1R4Z	3.01.01.0003	a/b	A	179	2003	1.8	0.177	300
1RBN	3.01.27.0005	a+b	A	124	1994	2.1	0.166	292
1RDD	3.01.26.0004	a/b	A	155	1993	2.8	0.19	300
1RU4	4.02.02.0002	b	A	400	2003	1.6	0.167	300
1S3I	1.05.01.0006	b, a/b	A	307	2004	2.3	0.242	300
1S95	3.01.03.0016	a+b	A	324	2004	1.6	0.169	300
1SCA	3.04.21.0062	a/b	A	274	1993	2	0.156	300
1SLL	4.02.02.0015	b, b	A	679	1997	2	0.167	184
1SML	3.05.02.0006	a+b	A	266	1998	1.7	0.18	300
1SNZ	5.01.03.0003	b	A	344	2004	2.2	0.172	300
1TAH	3.01.01.0003	a/b	B	318	1993	3	0.159	300
1TLP	3.04.24.0027	a+b	E	316	1987	2.3	0.174	300
1U3F	6.03.03.0002	a/b	A	164	2004	2.5	0.223	300

1U5U	4.02.01.0092	multi-domain	A	366	2004	2	0.196	300
1UAS	3.02.01.0022	b, a/b	A	362	2003	1.5	0.16	300
1UN1	2.04.01.0207	b	A	267	2003	2.1	0.206	300
1VID	2.01.01.0006	a/b	A	213	1996	2	0.194	300
1VLB	1.02.99.0007	a, a+b, a+b, a+b	A	907	2004	1.28	0.148	300
1VNC	1.11.01.0010	a	A	576	1995	2.1	0.2	126
1VQ1	2.01.01.0000	a/b	A	263	2004	2.8	0.208	300
1W0H	3.01.00.0000	a/b	A	194	2004	1.59	0.168	300
1XQW	3.04.11.0005	na	A	290	2004	2	0.248	300
1Y9M	3.02.01.0080	b, b	A	517	2004	1.89	0.165	300
1YON	1.01.01.0169	a, a/b	A	292	2005	1.95	0.166	300
1YSC	3.04.16.0005	a/b	A	421	1994	2.8	0.162	300
1ZE1	4.02.01.0070	b, a+b	A	308	2005	2.9	0.235	300
1ZIO	2.07.04.0003	a/b, Small proteins	A	217	1996	1.96	0.161	300
206L	3.02.01.0017	a+b	A	162	1996	1.75	0.17	300
2A0N	4.01.03.0000	a/b	A	251	2005	1.64	0.167	300
2ABK	4.02.99.0018	a	A	211	1995	1.85	0.185	300
2ACY	3.06.01.0007	a+b	A	98	1996	1.8	0.179	300
2AYH	3.02.01.0073	b	A	214	1995	1.6	0.143	300
2CPO	1.11.01.0010	a, a	A	298	1996	2.1	0.186	158
2CPU	3.02.01.0001	b, a/b	A	495	1999	2	0.167	300
2DLN	6.03.02.0004	a/b, a+b	A	306	1994	2.3	0.172	300
2EBN	3.02.01.0096	a/b	A	285	1994	2	0.158	300
2ENG	3.02.01.0004	b	A	205	1995	1.5	0.105	120
2F61	3.02.01.0045	b, a/b	A	497	2005	2.5	0.196	300
2F9R	3.01.04.0041	na	A	285	2005	1.85	0.187	174
2NLR	3.02.01.0004	b	A	222	1998	1.2	0.112	259
2NMT	2.03.01.0097	a+b, a+b	A	422	1998	2.9	0.228	181
2PEC	4.02.02.0002	b	A	352	1994	2.2	0.18	300
2PIA	1.00.00.0000	b, a/b, a+b	A	321	1993	2	0.186	300
2PTH	3.01.01.0029	a/b	A	193	1997	1.2	0.196	300
2SQC	5.04.99.0017	a, a	A	623	1998	2	0.153	300
2THI	2.05.01.0002	a/b	A	362	1998	2.5	0.195	300
2TPS	2.05.01.0003	a/b	A	226	1999	1.25	0.181	300
5EAT	4.02.03.0009	a, a	A	532	1997	2.8	0.24	300
7ATJ	1.11.01.0007	a	A	305	1999	1.47	0.16	300

[1] Number of sites in each protein sequence

[2] Number of sequence in the MSA profile of each protein

TABLE S2

Comparison between sequence variability measures using RSA as reference

ref.	x1	x2	Δ[1]	T[2]	Paired.T[3]	%[4]	Binomial[5]	d[6]	W[7]	Paired.W[8]
RSA^T	*CS*	*ET*	0.006	1.3	0.096628	51.9	0.316985	0.002	12249	0.282008
	CS	*KBSP*	0.050	8.3	5.31E-15	72.7	9.26E-12	0.059	18573	4.53E-14
	CS	*VTSP*	0.051	8.4	2.44E-15	73.6	1.23E-12	0.060	18697	1.62E-14
	CS	*EN*	0.194	18.1	2.25E-45	95.4	4.92E-49	0.186	23230	2.97E-36
	ET	*KBSP*	0.044	8.1	1.66E-14	74.1	4.32E-13	0.057	18862	3.98E-15
	ET	*VTSP*	0.045	8.4	3.60E-15	74.1	4.32E-13	0.058	18965	1.64E-15
	ET	*EN*	0.188	17.3	7.33E-43	94.0	2.51E-45	0.184	23118	1.37E-35
	KBSP	*VTSP*	0.001	2.0	0.021100	50.9	0.419158	0.001	12196	0.301792
	KBSP	*EN*	0.144	12.8	1.47E-28	84.7	1.10E-26	0.127	21986	3.02E-29
	VTSP	*EN*	0.143	12.6	5.78E-28	84.7	1.10E-26	0.127	21862	1.36E-28

[1] Difference between the mean correlations of ref with x1 and x2
[2] T-value derived by T test with paired variables
[3] P-value derived by T test with paired variables for x1 > x2
[4] The proportion of cases for which x1 > x2
[5] P-value derived by Binomial test for x1 > x2
[6] Difference between the median correlations of ref with x1 and x2
[7] W-value derived by Wilcoxon matched-paired signed-rank test
[8] P-value derived by Wilcoxon matched-paired signed-rank test for x1 > x2

Table S3

Comparison between sequence variability measures using WCN as reference

ref.	x1	x2	Δ[1]	T[2]	Paired.T[3]	%[4]	Binomial[5]	d[6]	W[7]	Paired.W[8]
WCN	*CS*	*ET*	0.000	0.0	0.514733	42.6	0.987740	-0.001	10306	0.937732
	CS	*KBSP*	0.041	6.5	3.53E-10	68.5	2.72E-08	0.052	17360	4.26E-10
	CS	*VTSP*	0.041	6.4	4.25E-10	69.4	5.37E-09	0.053	17338	4.95E-10
	CS	*EN*	0.196	15.9	1.63E-38	93.5	3.66E-44	0.175	22976	9.29E-35
	ET	*KBSP*	0.041	6.4	3.84E-10	72.7	9.26E-12	0.053	17931	7.11E-12
	ET	*VTSP*	0.042	6.5	3.31E-10	72.2	2.46E-11	0.054	17858	1.22E-11
	ET	*EN*	0.196	15.5	2.45E-37	93.1	4.96E-43	0.176	22799	9.77E-34
	KBSP	*VTSP*	0.000	0.1	0.461592	40.3	0.998329	0.001	9805	0.981275
	KBSP	*EN*	0.154	11.9	1.04E-25	86.1	5.56E-29	0.124	21810	2.55E-28
	VTSP	*EN*	0.154	11.8	1.52E-25	83.3	1.59E-24	0.123	21715	7.96E-28

[1] Difference between the mean correlations of ref with x1 and x2
[2] T-value derived by T test with paired variables
[3] P-value derived by T test with paired variables for x1 > x2
[4] The proportion of cases for which x1 > x2
[5] P-value derived by Binomial test for x1 > x2
[6] Difference between the median correlations of ref with x1 and x2
[7] W-value derived by Wilcoxon matched-paired signed-rank test
[8] P-value derived by Wilcoxon matched-paired signed-rank test for x1 > x2

TABLE S4

Comparison between SA profiles using sequence variability measures as reference

ref.	x1	x2	Δ[1]	T[2]	Paired.T[3]	%[4]	Binomial[5]	d[6]	W[7]	Paired.W[8]
CS	RSA^T	RSA^M	0.001	3.5	3.34E-04	63.9	2.69E-05	0.006	15267	5.70E-05
	RSA^T	RSA^R	0.001	3.4	4.21E-04	65.3	4.19E-06	0.005	15111	1.13E-04
	RSA^T	ASA	0.008	4.2	1.83E-05	60.2	1.67E-03	0.009	15375	3.50E-05
	RSA^M	RSA^R	0.000	0.1	0.470690	47.2	0.811776	-0.001	10876	0.820210
	RSA^M	ASA	0.007	3.3	5.73E-04	60.2	1.67E-03	0.002	14615	8.17E-04
	RSA^R	ASA	0.007	3.3	5.69E-04	59.3	3.91E-03	0.004	14688	6.21E-04
ET	RSA^T	RSA^M	0.001	3.5	2.63E-04	61.1	6.65E-04	0.000	14946	2.24E-04
	RSA^T	RSA^R	0.001	3.8	1.06E-04	60.2	1.67E-03	0.002	14949	2.22E-04
	RSA^T	ASA	0.011	6.0	4.85E-09	65.3	4.19E-06	0.014	17033	3.75E-09
	RSA^M	RSA^R	0.000	1.0	0.162618	48.6	0.683015	0.002	12013	0.374389
	RSA^M	ASA	0.009	4.9	8.73E-07	62.0	2.46E-04	0.014	16322	2.78E-07
	RSA^R	ASA	0.009	4.8	1.28E-06	62.5	1.45E-04	0.013	16251	4.14E-07
KBSP	RSA^T	RSA^M	0.003	9.6	1.25E-18	77.3	1.46E-16	0.003	19443	2.23E-17
	RSA^T	RSA^R	0.003	9.5	2.03E-18	75.9	5.21E-15	0.003	19497	1.35E-17
	RSA^T	ASA	0.012	6.4	4.24E-10	68.1	5.94E-08	0.008	17530	1.31E-10
	RSA^M	RSA^R	0.000	-0.3	0.632773	45.4	0.923561	0.000	11168	0.725292
	RSA^M	ASA	0.009	4.5	6.13E-06	64.4	1.48E-05	0.005	16211	5.16E-07
	RSA^R	ASA	0.009	4.5	4.91E-06	63.0	8.44E-05	0.005	16214	5.08E-07
VTSP	RSA^T	RSA^M	0.003	9.8	3.12E-19	77.3	1.46E-16	0.003	19549	8.32E-18
	RSA^T	RSA^R	0.003	9.7	5.49E-19	76.9	4.94E-16	0.004	19647	3.30E-18
	RSA^T	ASA	0.012	6.4	5.84E-10	67.1	2.66E-07	0.008	17500	1.62E-10
	RSA^M	RSA^R	0.000	-0.4	0.641680	45.4	0.923561	0.000	11122	0.741720
	RSA^M	ASA	0.008	4.4	8.54E-06	63.9	2.69E-05	0.005	16149	7.25E-07
	RSA^R	ASA	0.008	4.5	6.84E-06	62.5	1.45E-04	0.004	16173	6.36E-07
EN	ASA	RSA^T	0.006	3.1	1.01E-03	62.5	1.45E-04	0.011	15025	1.62E-04
	ASA	RSA^M	0.007	3.5	3.09E-04	63.4	4.81E-05	0.015	15416	2.90E-05
	ASA	RSA^R	0.007	3.5	2.44E-04	64.4	1.48E-05	0.014	15456	2.41E-05
	RSA^T	RSA^M	0.001	3.0	1.73E-03	64.8	7.93E-06	0.004	14982	1.93E-04
	RSA^T	RSA^R	0.001	3.3	5.31E-04	64.8	7.93E-06	0.003	15345	4.01E-05
	RSA^M	RSA^R	0.000	1.1	0.141269	54.2	0.123666	-0.001	12503	0.196803

[1] Difference between the mean correlations of ref with x1 and x2
[2] T-value derived by T test with paired variables
[3] P-value derived by T test with paired variables for x1 > x2
[4] The proportion of cases for which x1 > x2
[5] P-value derived by Binomial test for x1 > x2
[6] Difference between the median correlations of ref with x1 and x2
[7] W-value derived by Wilcoxon matched-paired signed-rank test
[8] P-value derived by Wilcoxon matched-paired signed-rank test for x1 > x2

TABLE S5
Mean Pearson correlations between $CN_{cut\text{-}off}$ and sequence profiles

Profile	CS	ET	KBSP	VTSP	EN
CN_9	0.5324	0.5277	0.4913	0.4909	0.3617
CN_{10}	0.5589	0.5513	0.5126	0.5123	0.3847
CN_{11}	0.5648	0.5565	0.5233	0.5233	0.3846
CN_{12}	0.5768	0.5695	0.5321	0.5321	0.3959
CN_{13}	0.5820	0.5765	0.5383	0.5383	0.4004
CN_{14}	0.5859	0.5818	0.5430	0.5430	0.4054
CN_{15}	0.5862	0.5832	0.5449	0.5450	0.4073
CN_{16}	0.5888	0.5867	0.5474	0.5476	0.4113
CN_{17}	0.5918	0.5905	0.5491	0.5493	0.4155
CN_{18}	0.5951	0.5945	0.5506	0.5508	0.4198
CN_{19}	0.5958	0.5956	0.5500	0.5502	0.4217
CN_{20}	0.5952	0.5954	0.5484	0.5485	0.4223
CN_{21}	0.5948	0.5953	0.5468	0.5469	0.4215
CN_{22}	0.5933	0.5942	0.5444	0.5445	0.4195
CN_{23}	0.5898	0.5914	0.5409	0.5410	0.4157
CN_{24}	0.5864	0.5884	0.5368	0.5368	0.4116
CN_{25}	0.5815	0.5838	0.5316	0.5316	0.4056
CN_{26}	0.5768	0.5793	0.5265	0.5264	0.3999
CN_{27}	0.5706	0.5735	0.5202	0.5201	0.3927
CN_{28}	0.5639	0.5672	0.5138	0.5136	0.3848
CN_{29}	0.5566	0.5601	0.5063	0.5061	0.3766
CN_{30}	0.5483	0.5520	0.4984	0.4981	0.3675

TABLE S6

Comparison between LPD profiles using sequence variability measures as reference

ref.	x1	x2	Δ[1]	T[2]	Paired.T[3]	%[4]	Binomial[5]	d[6]	W[7]	Paired.W[8]
CS			0.013	5.8	1.51E-08	67.1	2.66E-07	0.015	16954	6.23E-09
ET			0.013	5.7	2.02E-08	64.4	1.48E-05	0.014	16730	2.52E-08
KBSP	WCN	CN*	0.017	8.0	4.52E-14	70.4	9.73E-10	0.023	18269	5.27E-13
VTSP			0.016	7.9	9.44E-14	70.8	4.01E-10	0.018	18197	9.27E-13
EN			-0.009	-3.5	0.999683	38.4	0.999754	0.001	8386	0.999855

[1] Difference between the mean correlations of ref with x1 and x2
[2] T-value derived by T test with paired variables
[3] P-value derived by T test with paired variables for x1 > x2
[4] The proportion of cases for which x1 > x2
[5] P-value derived by Binomial test for x1 > x2
[6] Difference between the median correlations of ref with x1 and x2
[7] W-value derived by Wilcoxon matched-paired signed-rank test
[8] P-value derived by Wilcoxon matched-paired signed-rank test for x1 > x2

TABLE S7

Comparison between WCN and RSA^T using sequence variability measures as reference

ref.	x1	x2	Δ[1]	T[2]	Paired.T[3]	%[4]	Binomial[5]	d[6]	W[7]	Paired.W[8]
CS			0.049	11.9	9.91E-26	79.2	8.65E-19	0.057	20388	2.10E-21
ET			0.056	12.3	4.45E-27	79.6	2.24E-19	0.059	20606	2.13E-22
KBSP	WCN	RSA^T	0.059	12.4	2.03E-27	81.9	1.70E-22	0.064	20719	6.37E-23
VTSP			0.060	12.6	4.56E-28	82.9	7.78E-24	0.063	20805	2.52E-23
EN			0.048	10.3	1.07E-20	77.3	1.46E-16	0.067	19760	1.12E-18

[1] Difference between the mean correlations of ref with x1 and x2
[2] T-value derived by T test with paired variables
[3] P-value derived by T test with paired variables for x1 > x2
[4] The proportion of cases for which x1 > x2
[5] P-value derived by Binomial test for x1 > x2
[6] Difference between the median correlations of ref with x1 and x2
[7] W-value derived by Wilcoxon matched-paired signed-rank test
[8] P-value derived by Wilcoxon matched-paired signed-rank test for x1 > x2

FIGURE S1

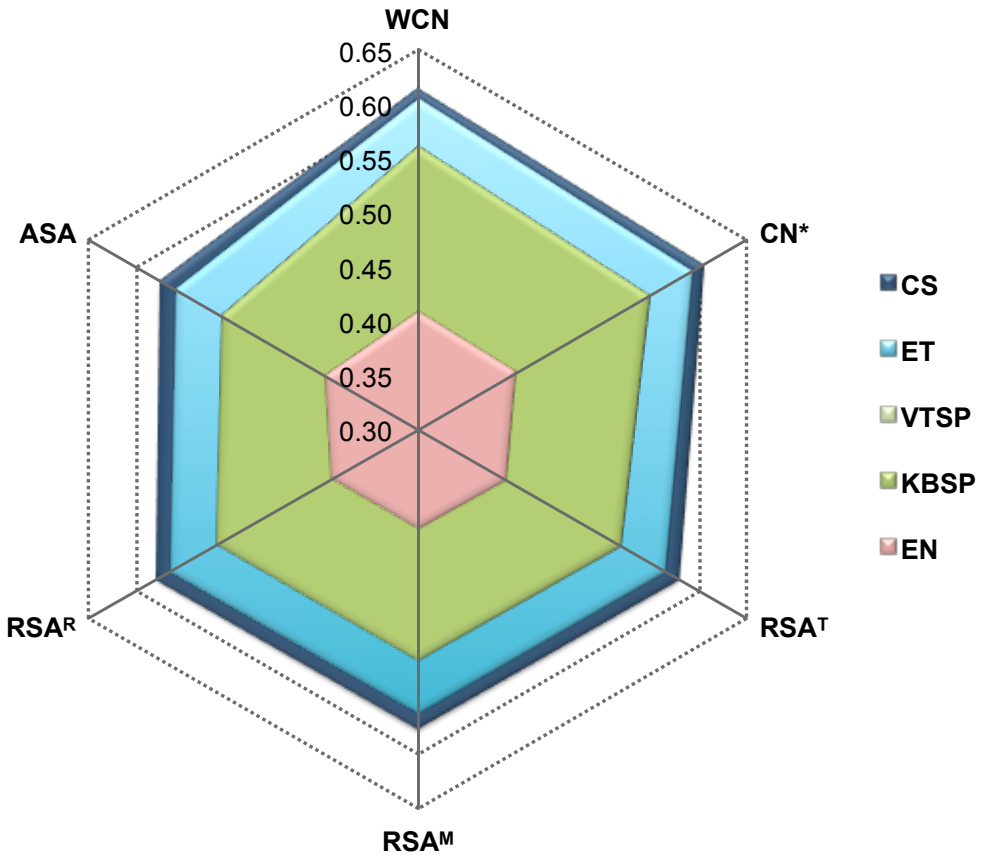

Figure S1: Comparison of sequence variability profiles by their average Spearman's correlation coefficients with different structural profiles. The sequence variability scores (listed in the figure legend) are: ConSurf rate of evolution (CS), Evolutionary Trace score (ET), Karlin & Brocchieri Sum-of-Pairs score (KBSP), Valdar & Thornton Sum-of-Pairs score (VTSP), and Entropy (EN). The structural properties (the apices of the hexagon) are: Weighted Contact Number (WCN), Contact Number (CN), Relative Solvent Accessibility (RSA), and Absolute Solvent Accessibility (ASA). The asterisk mark on CN means that the cut-off radius was chosen to maximize each CN-sequence average correlation. The cut-off radii for CS, ET, KBSP, VTSP and EN are 19Å, 19Å, 18Å, 18Å and 20Å, respectively. Superscript letters distinguish RSA profiles obtained using different methods.

FIGURE S2

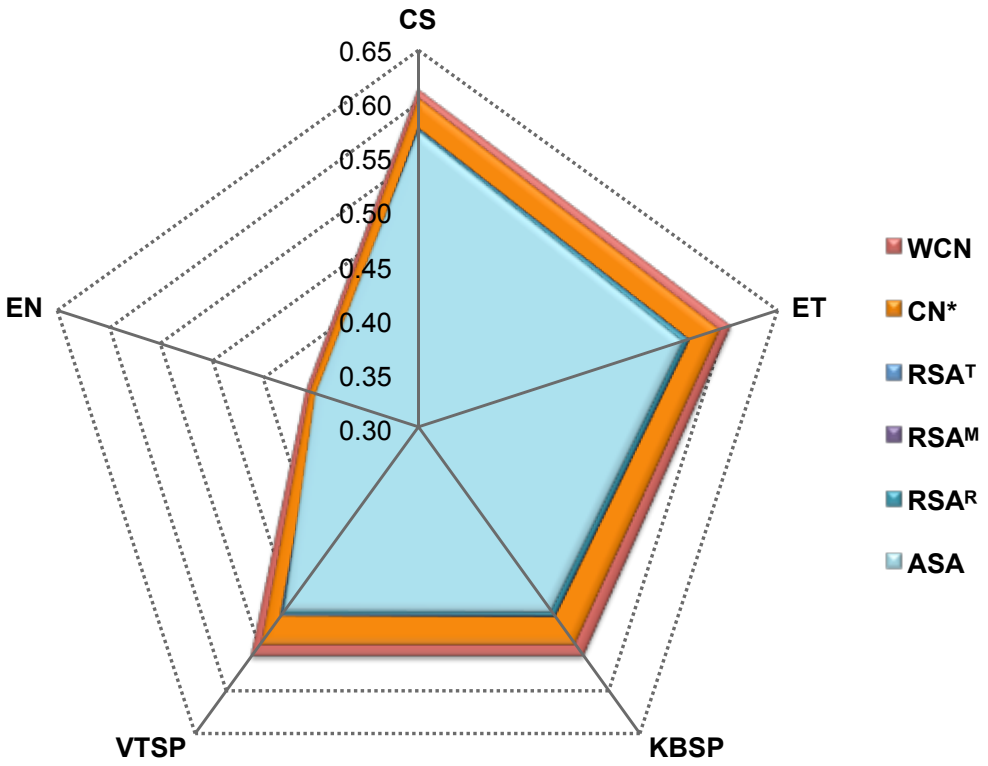

Figure S2: Comparison of structural profiles by their average Spearman's correlation coefficients with different sequence variability profiles. The sequence variability measures (the axes of the pentagon) are: ConSurf rate of evolution (CS), Evolutionary Trace score (ET), Karlin & Brocchieri Sum-of-Pairs score (KBSP), Valdar & Thornton Sum-of-Pairs score (VTSP), and Entropy (EN). The structural properties (listed in the figure legend) are: Weighted Contact Number (WCN), Contact Number (CN), Relative Solvent Accessibility (RSA), and Absolute Solvent Accessibility (ASA). The asterisk mark on CN means that the cut-off radius was chosen to maximize each CN-sequence average correlation. The cut-off radii for CS, ET, KBSP, VTSP and EN are 19Å, 19Å, 18Å, 18Å and 20Å, respectively. Superscript letters distinguish RSA profiles obtained using different methods.

FIGURE S3

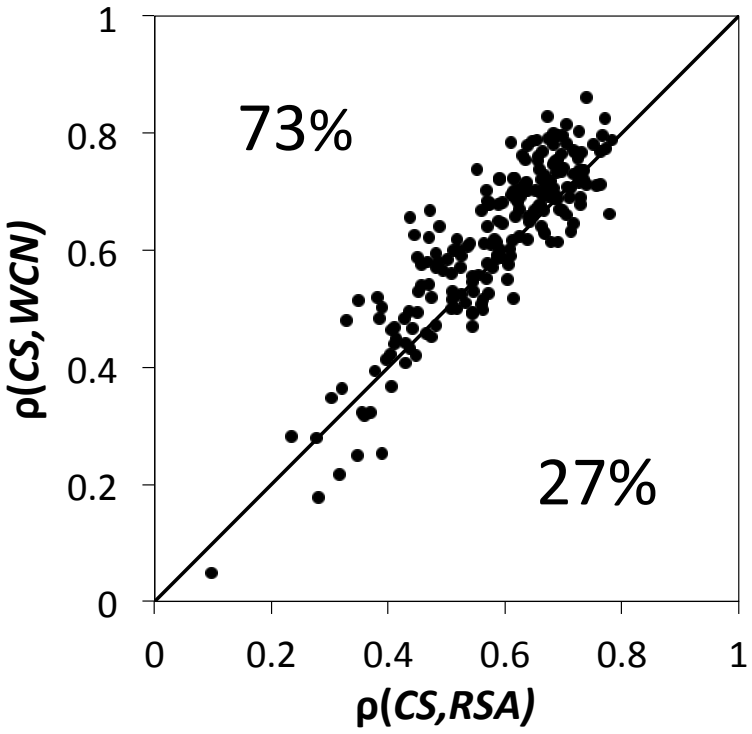

Figure S3: Local Packing Density vs. Solvent Accessibility as determinants of site-specific evolutionary rates with Spearman's correlation coefficient. Points above (below) the diagonal are proteins for which WCN (RSA^T) correlates better than RSA^T (WCN) with the site-specific rates of amino acid substitution as estimated using the phylogenetic-based approach ConSurf (CS). The percentages of points above and below the diagonals are shown.

TABLE S8

Mean structure-sequence Spearman's correlations

Property	Profile	*CS*	*ET*	*KBSP*	*VTSP*	*EN*
LPD	WCN	0.614	0.605	0.561	0.561	0.408
	CN*	0.604	0.593	0.547	0.547	0.405
SA	RSA^T	0.577	0.564	0.516	0.515	0.394
	RSA^M	0.576	0.563	0.514	0.513	0.393
	RSA^R	0.576	0.563	0.514	0.513	0.393
	ASA	0.573	0.558	0.509	0.508	0.399

*For each sequence variability profile, the cut-off distance of CN was chosen to maximize the CN-sequence average correlation coefficients. The cut-off radii for CS, ET, KBSP, VTSP and EN are 19Å, 19Å, 18Å, 18Å and 20Å, respectively. Values are the structure-sequence Pearson correlation coefficients averaged over all proteins of the dataset.

TABLE S9

Mean Spearman's correlations between sequence variability measures using RSA as reference

ref.	x1	x2	Δ[1]	T[2]	Paired.T[3]	%[4]	Binomial[5]	d[6]	W[7]	Paired.W[8]
RSA^T	*CS*	*ET*	0.013	3.1	1.26E-03	55.6	0.058695	0.020	14061	5.43E-03
	CS	*KBSP*	0.061	11.3	8.20E-24	78.2	1.19E-17	0.070	20326	3.98E-21
	CS	*VTSP*	0.062	11.3	5.87E-24	77.8	4.22E-17	0.072	20340	3.45E-21
	CS	*EN*	0.183	18.4	2.04E-46	95.8	2.36E-50	0.186	23297	1.18E-36
	ET	*KBSP*	0.048	8.9	9.43E-17	74.5	1.49E-13	0.051	19372	4.30E-17
	ET	*VTSP*	0.049	9.1	2.61E-17	75.0	4.98E-14	0.052	19454	2.02E-17
	ET	*EN*	0.170	17.3	8.89E-43	92.6	6.26E-42	0.166	23150	8.86E-36
	KBSP	*VTSP*	0.001	2.6	5.11E-03	51.4	0.366894	0.001	12700	0.142913
	KBSP	*EN*	0.122	12.0	3.85E-26	83.3	1.59E-24	0.116	21793	3.13E-28
	VTSP	*EN*	0.121	11.9	1.42E-25	82.9	7.78E-24	0.114	21670	1.36E-27

[1] Difference between the mean correlations of ref with x1 and x2
[2] T-value derived by T test with paired variables
[3] P-value derived by T test with paired variables for x1 > x2
[4] The proportion of cases for which x1 > x2
[5] P-value derived by Binomial test for x1 > x2
[6] Difference between the median correlations of ref with x1 and x2
[7] W-value derived by Wilcoxon matched-paired signed-rank test
[8] P-value derived by Wilcoxon matched-paired signed-rank test for x1 > x2

Table S10

Mean Spearman's correlations between sequence variability measures using WCN as reference

ref.	x1	x2	Δ[1]	T[2]	Paired.T[3]	%[4]	Binomial[5]	d[6]	W[7]	Paired.W[8]
WCN	*CS*	*ET*	0.009	1.9	0.026554	46.3	0.876334	0.015	12376	0.237307
	CS	*KBSP*	0.053	8.4	2.25E-15	70.8	4.01E-10	0.067	18553	5.34E-14
	CS	*VTSP*	0.054	8.4	2.31E-15	71.8	6.37E-11	0.068	18538	6.05E-14
	CS	*EN*	0.206	18.1	2.17E-45	95.8	2.36E-50	0.207	23238	2.66E-36
	ET	*KBSP*	0.044	6.6	1.60E-10	67.1	2.66E-07	0.052	17814	1.70E-11
	ET	*VTSP*	0.045	6.7	1.08E-10	66.7	5.46E-07	0.053	17806	1.80E-11
	ET	*EN*	0.197	17.0	4.24E-42	94.4	1.59E-46	0.192	23013	5.65E-35
	KBSP	*VTSP*	0.000	1.0	0.152483	44.9	0.941305	0.002	10906	0.811529
	KBSP	*EN*	0.153	12.7	4.17E-28	86.6	8.86E-30	0.140	22056	1.28E-29
	VTSP	*EN*	0.152	12.6	7.14E-28	86.1	5.56E-29	0.138	21993	2.77E-29

[1] Difference between the mean correlations of ref with x1 and x2
[2] T-value derived by T test with paired variables
[3] P-value derived by T test with paired variables for x1 > x2
[4] The proportion of cases for which x1 > x2
[5] P-value derived by Binomial test for x1 > x2
[6] Difference between the median correlations of ref with x1 and x2
[7] W-value derived by Wilcoxon matched-paired signed-rank test
[8] P-value derived by Wilcoxon matched-paired signed-rank test for x1 > x2

TABLE S11

Comparison mean Spearman's correlations between SA profiles using sequence variability measures as reference

ref.	x1	x2	Δ[1]	T[2]	Paired.T[3]	%[4]	Binomial[5]	d[6]	W[7]	Paired.W[8]
CS	RSA^T	RSA^M	0.001	3.1	9.63E-04	64.4	1.48E-05	0.004	15128	1.05E-04
	RSA^T	RSA^R	0.001	3.1	9.65E-04	60.6	1.06E-03	0.005	14953	2.18E-04
	RSA^T	ASA	0.004	2.4	9.41E-03	59.3	3.91E-03	0.001	14075	5.20E-03
	RSA^M	RSA^R	0.000	0.0	0.514708	46.3	0.876334	0.001	11062	0.762357
	RSA^M	ASA	0.003	1.6	0.054505	56.9	0.024111	-0.003	13390	0.034558
	RSA^R	ASA	0.003	1.6	0.052425	55.6	0.058695	-0.003	13412	0.032768
ET	RSA^T	RSA^M	0.001	1.7	0.047994	54.2	0.123666	0.002	13329	0.039945
	RSA^T	RSA^R	0.001	2.0	0.021647	55.1	0.076439	0.003	13654	0.017657
	RSA^T	ASA	0.006	3.8	1.02E-04	59.3	3.91E-03	0.002	15266	5.72E-05
	RSA^M	RSA^R	0.000	0.9	0.175332	49.5	0.580842	0.001	12219	0.293130
	RSA^M	ASA	0.005	3.2	7.10E-04	58.8	5.82E-03	0.000	14910	2.60E-04
	RSA^R	ASA	0.005	3.2	8.96E-04	57.9	0.012260	0.000	14799	4.04E-04
KBSP	RSA^T	RSA^M	0.002	7.7	2.96E-13	72.7	9.26E-12	0.002	18540	5.95E-14
	RSA^T	RSA^R	0.002	7.1	9.99E-12	69.9	2.31E-09	0.002	17854	1.26E-11
	RSA^T	ASA	0.007	4.3	1.50E-05	65.7	2.17E-06	0.005	15988	1.72E-06
	RSA^M	RSA^R	0.000	-0.4	0.663093	46.3	0.876334	0.000	10947	0.799254
	RSA^M	ASA	0.005	2.9	1.95E-03	62.0	2.46E-04	0.004	14806	3.93E-04
	RSA^R	ASA	0.005	3.0	1.62E-03	62.0	2.46E-04	0.004	14775	4.44E-04
VTSP	RSA^T	RSA^M	0.002	7.8	1.43E-13	73.6	1.23E-12	0.002	18619	3.10E-14
	RSA^T	RSA^R	0.002	7.2	4.66E-12	69.9	2.31E-09	0.002	17995	4.39E-12
	RSA^T	ASA	0.007	4.2	1.75E-05	65.7	2.17E-06	0.000	15936	2.26E-06
	RSA^M	RSA^R	0.000	-0.4	0.644904	46.3	0.876334	0.000	10981	0.788720
	RSA^M	ASA	0.005	2.9	2.23E-03	62.5	1.45E-04	-0.002	14769	4.55E-04
	RSA^R	ASA	0.005	2.9	1.88E-03	63.0	8.44E-05	-0.001	14741	5.07E-04
EN	ASA	RSA^T	0.005	3.4	4.64E-04	61.6	4.08E-04	0.012	15048	1.47E-04
	ASA	RSA^M	0.006	3.5	2.42E-04	59.7	2.58E-03	0.011	15207	7.43E-05
	ASA	RSA^R	0.006	3.6	1.90E-04	61.1	6.65E-04	0.010	15241	6.39E-05
	RSA^T	RSA^M	0.001	2.2	0.016007	63.4	4.81E-05	-0.001	14384	1.87E-03
	RSA^T	RSA^R	0.001	2.5	7.43E-03	60.6	1.06E-03	-0.002	14173	3.80E-03
	RSA^M	RSA^R	0.000	0.8	0.201854	51.4	0.366894	-0.001	12423	0.221808

[1] Difference between the mean correlations of ref with x1 and x2
[2] T-value derived by T test with paired variables
[3] P-value derived by T test with paired variables for x1 > x2
[4] The proportion of cases for which x1 > x2
[5] P-value derived by Binomial test for x1 > x2
[6] Difference between the median correlations of ref with x1 and x2
[7] W-value derived by Wilcoxon matched-paired signed-rank test
[8] P-value derived by Wilcoxon matched-paired signed-rank test for x1 > x2

TABLE S12

Mean Spearman correlations between $CN_{cut\text{-}off}$ and sequence profiles

Profile	CS	ET	KBSP	VTSP	EN
CN_9	0.5375	0.5271	0.4892	0.4884	0.3651
CN_{10}	0.5631	0.5497	0.5104	0.5097	0.3856
CN_{11}	0.5685	0.5549	0.5210	0.5207	0.3844
CN_{12}	0.5810	0.5677	0.5305	0.5301	0.3931
CN_{13}	0.5856	0.5737	0.5360	0.5357	0.3950
CN_{14}	0.5905	0.5794	0.5409	0.5405	0.3973
CN_{15}	0.5909	0.5802	0.5421	0.5418	0.3962
CN_{16}	0.5939	0.5837	0.5444	0.5441	0.3976
CN_{17}	0.5980	0.5879	0.5460	0.5457	0.4002
CN_{18}	0.6023	0.5922	0.5469	0.5465	0.4033
CN_{19}	0.6037	0.5934	0.5457	0.5453	0.4045
CN_{20}	0.6035	0.5931	0.5437	0.5432	0.4048
CN_{21}	0.6029	0.5925	0.5412	0.5406	0.4039
CN_{22}	0.6020	0.5916	0.5385	0.5379	0.4025
CN_{23}	0.5993	0.5893	0.5351	0.5345	0.4000
CN_{24}	0.5963	0.5866	0.5312	0.5306	0.3976
CN_{25}	0.5924	0.5832	0.5265	0.5258	0.3939
CN_{26}	0.5888	0.5799	0.5219	0.5213	0.3910
CN_{27}	0.5837	0.5751	0.5160	0.5153	0.3863
CN_{28}	0.5783	0.5703	0.5105	0.5098	0.3822
CN_{29}	0.5726	0.5648	0.5040	0.5033	0.3779
CN_{30}	0.5665	0.5589	0.4976	0.4968	0.3734

TABLE S13

Comparison mean Spearman's correlations between LPD profiles using sequence variability measures as reference

ref.	x1	x2	Δ[1]	T[2]	Paired.T[3]	%[4]	Binomial[5]	d[6]	W[7]	Paired.W[8]
CS			0.011	4.9	1.01E-06	66.2	1.10E-06	0.017	16517	9.04E-08
ET			0.012	5.2	2.04E-07	65.3	4.19E-06	0.024	16571	6.57E-08
KBSP	WCN	CN*	0.014	6.6	1.86E-10	66.7	5.46E-07	0.015	17386	3.57E-10
VTSP			0.014	6.6	2.05E-10	67.6	1.27E-07	0.013	17401	3.22E-10
EN			0.003	1.4	0.076363	53.2	0.188224	0.007	13086	0.068498

[1] Difference between the mean correlations of ref with x1 and x2
[2] T-value derived by T test with paired variables
[3] P-value derived by T test with paired variables for x1 > x2
[4] The proportion of cases for which x1 > x2
[5] P-value derived by Binomial test for x1 > x2
[6] Difference between the median correlations of ref with x1 and x2
[7] W-value derived by Wilcoxon matched-paired signed-rank test
[8] P-value derived by Wilcoxon matched-paired signed-rank test for x1 > x2

TABLE S14

Comparison mean Spearman's correlations between WCN and RSA^T using sequence variability measures as reference

ref.	x1	x2	Δ[1]	T[2]	Paired.T[3]	%[4]	Binomial[5]	d[6]	W[7]	Paired.W[8]
CS			0.037	8.4	3.67E-15	72.7	9.26E-12	0.045	18437	1.38E-13
ET			0.041	8.8	2.45E-16	75.9	5.21E-15	0.050	18860	4.05E-15
KBSP	WCN	RSA^T	0.045	9.5	1.58E-18	75.0	4.98E-14	0.049	19452	2.06E-17
VTSP			0.046	9.7	6.42E-19	75.9	5.21E-15	0.048	19547	8.47E-18
EN			0.014	3.2	7.77E-04	56.5	0.032972	0.024	14495	1.27E-03

[1] Difference between the mean correlations of ref with x1 and x2
[2] T-value derived by T test with paired variables
[3] P-value derived by T test with paired variables for x1 > x2
[4] The proportion of cases for which x1 > x2
[5] P-value derived by Binomial test for x1 > x2
[6] Difference between the median correlations of ref with x1 and x2
[7] W-value derived by Wilcoxon matched-paired signed-rank test
[8] P-value derived by Wilcoxon matched-paired signed-rank test for x1 > x2

TABLE S15

Variance partitioning of Spearman's correlations

Fit	Contribution	R^2	%
CS~WCN+RSA^T	Total	0.420±0.010	100
	Common	0.332±0.009	76.43±1.37
	Unique WCN	0.069±0.004	16.85±1.04
	Unique RSA^T	0.020±0.002	6.72±0.84

NOTE: Fit is the bivariate linear fit considered, R^2 is the explained variance averaged over the dataset of 216 enzymes ± its standard deviation, % is the proportion of explained variance accounted for by the given contribution.