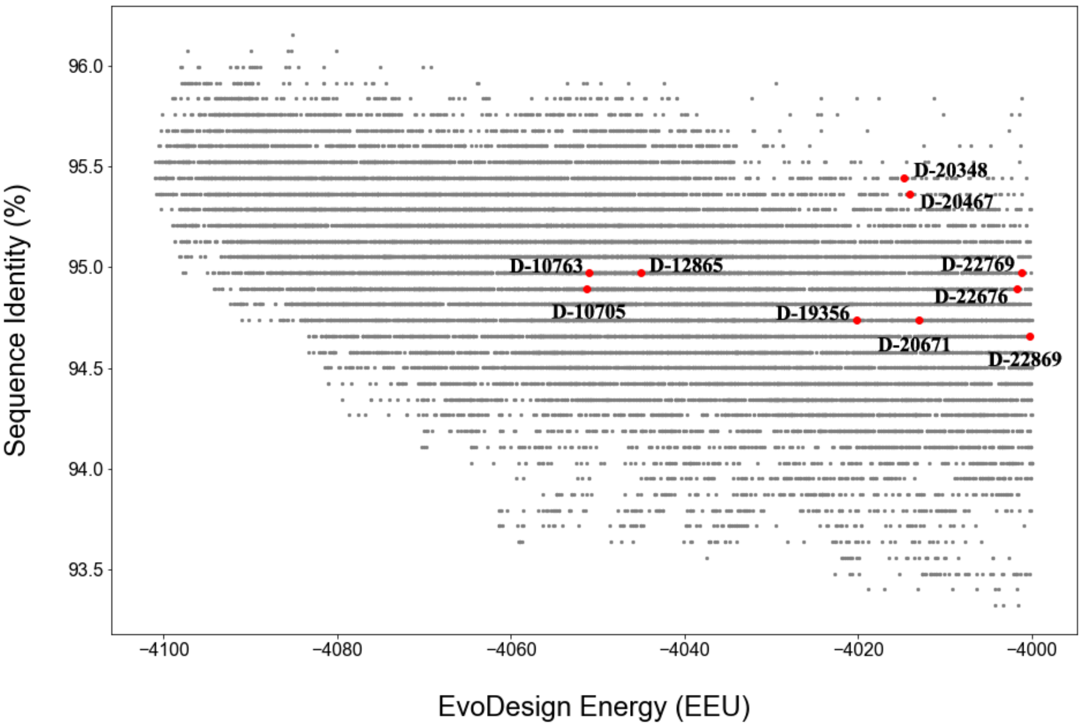
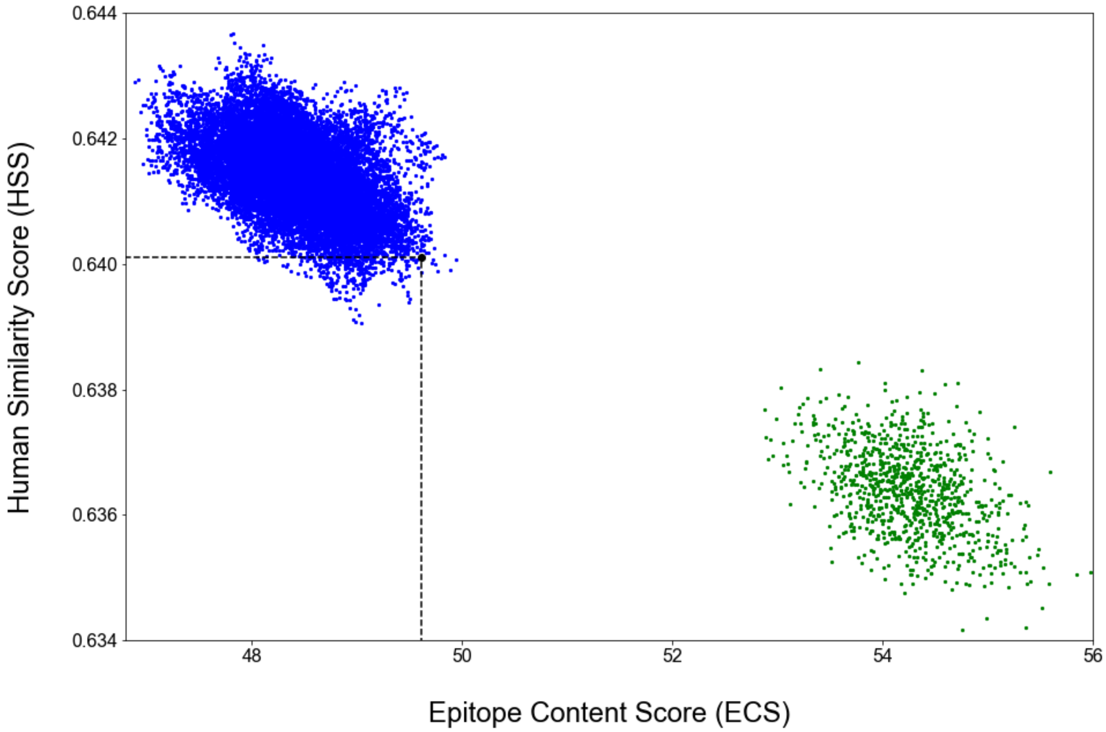


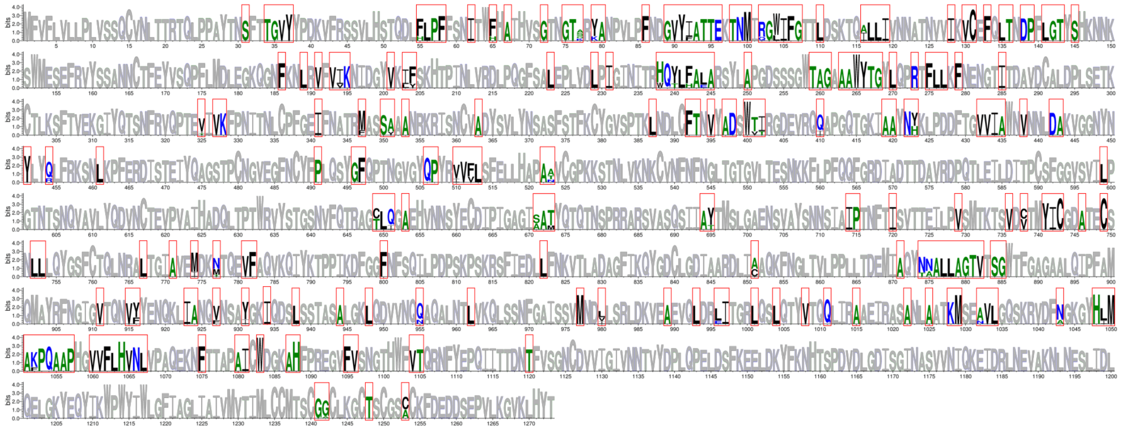
S1 Figure. The EvoDesign energy and sequence identity for designed S proteins.



S2 Figure. The comparison of epitope content score (ECS) and human similarity score (HSS) for designed S proteins between EvoDesign and Rosetta.

A)

B)



S3 Figure. The sequence logo plot of (A) top 10 versus (B) worst 10 S protein designs.

S1 Table. SARS-CoV-2 S protein residues' core, intermediate, and surface definition for EvoDesign.

Residue Positions											
core		intermediate			surface						
31	497	9	473	1078	1	294	520	658	890	1135	1268
34	506	10	474	1082	2	295	521	659	891	1136	1269
35	507	11	480	1090	3	296	524	660	892	1138	1271
36	510	15	488	1093	4	297	525	661	893	1139	1272
37	511	18	489	1094	5	298	526	662	894	1140	1273
55	512	20	492	1097	6	299	527	663	895	1141	
56	513	21	495	1102	7	300	528	665	896	1142	
57	522	24	498	1103	8	301	529	667	897	1143	
58	523	26	508	1106	12	302	530	668	898	1144	
62	599	29	509	1108	13	303	531	676	899	1145	
65	649	33	514	1109	14	304	532	677	900	1146	
67	650	38	515	1110	16	305	533	678	901	1147	
72	651	39	600	1111	17	306	534	679	902	1148	
75	653	44	641	1115	19	307	535	680	903	1149	
76	671	49	645	1116	22	308	536	681	904	1150	
77	672	51	648	1117	23	309	537	682	905	1151	
79	673	53	652	1119	25	310	538	683	906	1152	
80	694	54	656	1127	27	311	539	684	907	1153	
86	695	60	664	1131	28	312	540	685	908	1154	
89	714	63	666	1133	30	313	541	686	909	1155	
90	715	64	669	1137	32	314	542	696	913	1156	
91	720	66	670	1235	40	315	543	697	914	1157	
92	729	68	674	1246	41	316	544	699	917	1158	
93	736	70	675	1261	42	317	545	700	918	1159	
94	738	71	687	1270	43	319	546	701	921	1160	
95	741	78	688		45	320	547	702	922	1161	
96	742	81	689		46	321	548	703	925	1162	
98	743	84	690		47	322	549	704	928	1163	
99	746	97	691		48	323	550	705	929	1164	
100	749	101	692		50	324	551	706	933	1165	
102	752	108	693		52	331	552	707	936	1166	
103	753	111	698		59	332	553	708	937	1167	
104	767	112	713		61	333	554	709	939	1168	
105	771	114	716		69	334	555	710	940	1169	
106	774	115	718		73	335	556	711	941	1170	
107	777	120	722		74	336	557	712	942	1171	
110	781	121	723		82	340	558	717	943	1172	
116	782	123	725		83	343	559	719	946	1173	
117	800	125	726		85	345	560	721	947	1174	
118	822	126	727		87	346	561	724	950	1175	
119	851	127	728		88	354	562	737	953	1176	
128	871	129	730		109	355	563	739	954	1177	
130	874	132	731		113	356	564	740	956	1178	
131	875	137	732		122	357	565	744	957	1179	

133	876	140	733		124	359	566	745	960	1180	
135	877	152	734		134	360	567	747	961	1181	
136	878	154	735		144	364	568	751	963	1182	
138	879	159	748		146	366	569	754	964	1183	
139	880	168	750		147	367	570	755	965	1184	
141	881	172	756		148	369	571	757	967	1185	
142	882	175	760		149	370	572	758	969	1186	
143	884	179	763		150	371	573	759	970	1187	
145	885	182	764		151	372	574	761	971	1188	
186	911	188	766		153	373	575	762	973	1189	
189	915	190	770		155	375	576	765	976	1190	
191	916	192	775		156	376	577	768	978	1191	
193	923	196	778		157	377	578	769	979	1192	
194	924	199	785		158	378	579	772	982	1193	
195	927	205	792		160	381	580	773	983	1194	
201	931	206	797		161	383	581	776	985	1195	
203	934	208	820		162	385	582	779	986	1196	
204	938	210	821		163	386	583	780	987	1197	
223	944	212	823		164	389	584	783	988	1198	
229	948	216	825		165	390	585	784	990	1199	
231	955	217	826		166	405	586	786	991	1200	
238	962	219	829		167	408	587	787	994	1201	
239	977	221	830		169	412	588	788	995	1202	
240	980	222	832		170	413	589	789	998	1203	
241	989	233	833		171	414	590	790	1002	1204	
242	993	235	836		173	415	591	791	1005	1205	
243	996	246	838		174	416	592	793	1006	1206	
244	997	247	839		176	417	593	794	1009	1207	
245	1001	249	840		177	427	594	795	1010	1208	
250	1004	251	850		178	428	595	796	1012	1209	
259	1008	255	856		180	429	596	798	1013	1210	
260	1011	257	857		181	430	597	799	1016	1211	
261	1015	258	858		183	437	598	801	1017	1212	
263	1022	283	859		184	439	601	802	1019	1213	
264	1025	318	860		185	440	602	803	1020	1214	
265	1028	326	863		187	441	603	804	1023	1215	
266	1029	329	865		197	444	604	805	1024	1216	
267	1032	330	866		198	445	605	806	1027	1217	
268	1033	337	867		200	446	606	807	1030	1218	
270	1034	338	870		202	449	607	808	1031	1219	
273	1043	339	873		207	450	608	809	1036	1220	
275	1048	342	883		209	452	609	810	1038	1221	
276	1049	344	910		211	456	610	811	1039	1222	
277	1050	348	912		213	458	611	812	1040	1223	
279	1051	349	919		214	459	612	813	1041	1224	
285	1052	352	920		215	460	613	814	1045	1225	
325	1053	358	926		218	462	614	815	1047	1226	
327	1054	361	930		220	463	615	816	1069	1227	

328	1055	362	932		224	465	616	817	1070	1228	
341	1056	365	935		225	467	617	818	1071	1229	
347	1057	368	945		226	468	618	819	1072	1230	
350	1060	374	949		227	469	619	824	1073	1231	
351	1061	379	951		228	470	620	827	1074	1232	
353	1062	380	952		230	471	621	828	1076	1233	
363	1063	382	958		232	472	622	831	1079	1234	
387	1064	384	959		234	475	623	834	1084	1236	
392	1065	388	966		236	476	624	835	1085	1237	
393	1066	391	968		237	477	625	837	1086	1238	
395	1067	394	972		248	478	626	841	1089	1239	
397	1075	396	974		252	479	627	842	1091	1240	
398	1080	399	975		253	481	628	843	1092	1243	
400	1081	403	981		254	482	629	844	1098	1244	
401	1083	404	984		256	483	630	845	1099	1245	
402	1087	406	992		262	484	631	846	1100	1247	
410	1088	407	999		269	485	632	847	1101	1249	
419	1095	409	1000		271	486	633	848	1107	1250	
420	1096	411	1003		272	487	634	849	1112	1251	
422	1104	418	1007		274	490	635	852	1113	1252	
423	1105	421	1014		278	493	636	853	1114	1254	
432	1120	424	1018		280	494	637	854	1118	1255	
433	1241	425	1021		281	499	638	855	1121	1256	
434	1242	426	1026		282	500	639	861	1122	1257	
435	1248	431	1035		284	501	640	862	1123	1258	
438	1253	436	1037		286	502	642	864	1124	1259	
442		447	1042		287	503	643	868	1125	1260	
443		448	1044		288	504	644	869	1126	1262	
451		453	1046		289	505	646	872	1128	1263	
454		455	1058		290	516	647	886	1129	1264	
461		457	1059		291	517	654	887	1130	1265	
491		464	1068		292	518	655	888	1132	1266	
496		466	1077		293	519	657	889	1134	1267	

S2 Table. Seven human coronavirus S proteins.

Spike Protein ID	Organism	Organism Taxon ID
P59594	Human SARS coronavirus (SARS-CoV) (Severe acute respiratory syndrome coronavirus)	694009
R9UQ53	Middle East respiratory syndrome-related coronavirus	1335626
P15423	Human coronavirus 229E (HCoV-229E)	11137
Q0ZME7	Human coronavirus HKU1 (isolate N5) (HCoV-HKU1) (Strain: Isolate N5)	443241
P36334	Human coronavirus OC43 (HCoV-OC43)	31631
Q6Q1S2	Human coronavirus NL63 (HCoV-NL63)	277944
P0DTC2	Severe acute respiratory syndrome coronavirus 2 (2019-nCoV) (SARS-CoV-2)	2697049

S3 Table. Global S protein mutations compared with the EvoDesign core residues' substitution frequencies.

Position	Original Residue	Reported Mutation	Global Frequency	EvoDesign Residue Def.	EvoDesign Substitution & Frequency
80	D	Y	0.005	Designable (core residue)	unmutated: 0.741 D80N: 0.149 D80A: 0.106 D80S: 0.003
98	S	F	0.007	Designable (core residue)	unmutated: 0.155 S98T: 0.837 S98A: 0.008
5	L	F	0.013	Fixed	---
18	L	F	0.095	Fixed	---
21	R	I	0.007	Fixed	---
68	I	-	0.019	Fixed	---
69	H	-	0.019	Fixed	---
70	V	I	0.019	Fixed	---
144	Y	-	0.005	Fixed	---
176	L	F	0.003	Fixed	---
215	D	H	0.003	Fixed	---
222	A	V	0.194	Fixed	---
253	D	G	0.003	Fixed	---
262	A	S	0.011	Fixed	---
272	P	L	0.007	Fixed	---
439	N	K	0.016	Fixed	---
453	Y	F	0.004	Fixed	---
477	S	N	0.063	Fixed	---
501	N	Y	0.005	Fixed	---
570	A	D	0.004	Fixed	---
583	E	D	0.007	Fixed	---
614	D	G	0.895	Fixed	---
626	A	S	0.004	Fixed	---
655	H	Y	0.004	Fixed	---
681	P	H	0.005	Fixed	---
688	A	V	0.004	Fixed	---
716	T	I	0.004	Fixed	---
723	T	I	0.004	Fixed	---
936	D	Y	0.005	Fixed	---
982	S	A	0.004	Fixed	---
1073	K	N	0.004	Fixed	---
1118	D	H	0.004	Fixed	---
1163	D	Y	0.007	Fixed	---
1167	G	V	0.006	Fixed	---
1263	P	L	0.003	Fixed	---

S4 Table. The intrinsic disorder predisposition of the EvoDesign core residues and their corresponding conservation in terms of Jensen-Shannon Divergence (JSD) scores.

DisProt disorder regions	Top 10 EvoDesign conservation score
67	0.84041
72	0.81773
75	0.79401
76	0.76281
77	0.76185
79	0.81535
80	0.80062
142	0.81402
143	0.84579
145	0.84866
250	0.76164
259	0.83607
260	0.81371
261	0.81059
673	0.8344
851	0.80869
1241	0.80855
1242	0.75916
1248	0.82732
1253	0.80943

S5 Table. The full-length sequences of the top ten designs (in FASTA format).

```
>D_10705
MFVFLVLLPLVSSQCVNLTTRTQLPPAYTNAFTTGVYYPDKVFRSSVLHSTQDLFLPFFSNITWFHAIHV
SGTNGTARYNNPVLPFNDGVYFAATLKTNMIQGWAFGTTLDSKTQSLLIVNNATNVVIKVCEFQYTNDP
F
LGTYSHKNNKSWMESEFRVYSSANNCTFEYVSQPFLMDLEGKQGNFKNLRVFVYKNIDGYFKIYSKHT
PI
NLVRDLPQGFSALEPLVDLPIGINITRFMTIRASSRSYLAPGDSSSGWTAGAAAYYVGYLQPRTFLLKFN
ENGTITDAVDCALDPLSETKCTLKSFTVEKGIYQTSNFRVQPTETIVKFPNITNLCPFGEIFNATRFASS
YAANRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDLCFTNVYADSFVIRGDEVRQIAPGQTGKIA
A
YNMKLPDDFTGVVIAWNVNNLDAKVGGNYNYLYRLFRKSNLKPFERDISTEIYQAGSTPCNGVEGFNC
YF
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FL
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G
AENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDCTMYICGDSTECSNLLLQYGSFCTQLNRALTGI
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LGDIAARDLICAQKFNGLTVLPPLLTDEMIAQYTAALLAGIVTSGWTFGAGAALQIPFAMQMAYRFNGIG
VTQNVYYENQKLIANQFNSAIGKLQDSHSSTASALGKLQDVVNQLAQALNTLVKQLSSNFGAISSVMN
DI
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NV
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>D_10763
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A
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KNLNESLIDLQELGKYEQYIKWPWYIWLGFIAGLIAIVMVTIMLCCMTSCGGCLKGCTSCGSACKFDED
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F
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PI
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NT
FVSGNCDVVIGIVNNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLGDISGINASVVNIQKEIDRLNEVA
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D
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>D_20348
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S6 Table. The predicted MHC-II T cell promiscuous epitopes of the native SARS-CoV-2 S protein.

Epitope	Start	End	Median percentile rank	Binding allele
SLLIVNNATNVVIKV	116	130	6.5	DRB1*03:01;DRB1*07:01;DRB1*15:01;DRB3*01:01;DRB3*02:02;DRB4*01:01
TRFQTLLALHRSYLT	236	250	2.9	DRB1*03:01;DRB1*07:01;DRB1*15:01;DRB3*02:02;DRB4*01:01;DRB5*01:01
REGVFVSNGTHWFVT	1091	1105	9.4	DRB1*03:01;DRB1*07:01;DRB1*15:01;DRB3*01:01;DRB3*02:02;DRB5*01:01
IGINITRFQTLLALH	231	245	17	DRB1*03:01;DRB1*07:01;DRB1*15:01;DRB3*02:02;DRB4*01:01;DRB5*01:01
RFASVYAWNRKRISN	346	360	8.2	DRB1*03:01;DRB1*07:01;DRB1*15:01;DRB3*02:02;DRB4*01:01;DRB5*01:01
QLIRAAEIRASANLA	1011	1025	12	DRB1*03:01;DRB1*07:01;DRB1*15:01;DRB3*02:02;DRB4*01:01;DRB5*01:01
IPFAMQMAYRFNGIG	896	910	3.7	DRB1*03:01;DRB1*07:01;DRB1*15:01;DRB3*01:01;DRB3*02:02;DRB4*01:01;DRB5*01:01
VFNATRFASVYAWNR	341	355	9.3	DRB1*07:01;DRB1*15:01;DRB3*02:02;DRB5*01:01
AEIRASANLAATKMS	1016	1030	7.9	DRB1*03:01;DRB1*07:01;DRB1*15:01;DRB3*02:02;DRB4*01:01;DRB5*01:01
QMAYRFNGIGVTQNV	901	915	19	DRB1*07:01;DRB1*15:01;DRB3*01:01;DRB3*02:02
LPFFSNVTWFHAIHV	56	70	7.3	DRB1*07:01;DRB1*15:01;DRB3*01:01;DRB3*02:02;DRB5*01:01
SVLYNSASFSTFKCY	366	380	18	DRB1*07:01;DRB1*15:01;DRB3*01:01;DRB3*02:02
SIIAYTMSLGAENSV	691	705	4.7	DRB1*07:01;DRB1*15:01;DRB3*02:02;DRB4*01:01;DRB5*01:01
KLIANQFNSAIGKIQ	921	935	18	DRB1*07:01;DRB1*15:01;DRB3*02:02;DRB4*01:01
SFIEDLLFNKVTLAD	816	830	16	DRB1*03:01;DRB1*15:01;DRB3*01:01;DRB3*02:02;DRB4*01:01
TLVKQLSSNFGAISS	961	975	14	DRB1*07:01;DRB1*15:01;DRB3*02:02;DRB4*01:01
YLYRLFRKSNLKPFE	451	465	5.7	DRB1*07:01;DRB1*15:01;DRB3*01:01;DRB3*02:02;DRB4*01:01;DRB5*01:01
SNFRVQPTESIVRFP	316	330	9.9	DRB1*03:01;DRB1*07:01;DRB3*01:01;DRB3*02:02;DRB4*01:01;DRB5*01:01
VYYPDKVFRSSVLHS	36	50	11	DRB1*03:01;DRB1*07:01;DRB1*15:01;DRB3*01:01;DRB3*02:02
EFVFKNIDGYFKIYS	191	205	13	DRB1*03:01;DRB1*07:01;DRB1*15:01;DRB3*01:01;DRB3*02:02;DRB5*01:01
TYVTQQLIRAAEIRA	1006	1020	20	DRB1*07:01;DRB3*02:02;DRB4*01:01;DRB5*01:01
FKIYSKHTPINLVRD	201	215	14	DRB1*07:01;DRB1*15:01;DRB3*02:02;DRB5*01:01
EFRVYSSANNCTFEY	156	170	18	DRB1*07:01;DRB1*15:01;DRB3*01:01;DRB3*02:02
YVGYLQPRTFLLKYN	266	280	13	DRB1*07:01;DRB1*15:01;DRB3*01:01;DRB4*01:01;DRB5*01:01
VQIDRLITGRLQSLQ	991	1005	15	DRB1*03:01;DRB1*15:01;DRB4*01:01;DRB5*01:01
GAALQIPFAMQMAYR	891	905	18	DRB1*07:01;DRB1*15:01;DRB4*01:01;DRB5*01:01
YGSFCTQLNRALTGI	756	770	19	DRB1*07:01;DRB1*15:01;DRB3*02:02;DRB5*01:01
KVFRSSVLHSTQDLF	41	55	17	DRB1*07:01;DRB3*02:02;DRB4*01:01;DRB5*01:01
LLFNKVTLADAGFIK	821	835	17	DRB1*03:01;DRB1*07:01;DRB3*01:01;DRB3*02:02
CAQKFNGLTVLPPLL	851	865	19	DRB1*07:01;DRB1*15:01;DRB3*02:02;DRB5*01:01
VTQNVLYENQKLIAN	911	925	16	DRB1*03:01;DRB1*15:01;DRB3*01:01;DRB3*02:02

VVLSFELLHAPATVC	511	525	19	DRB1*07:01;DRB1*15:01;DRB3*02:02;DRB4*01:01;DRB5*01:01