

Supplementary Information

Table S1: Number of samples showing mutations in ORF3a protein

Beginning of the table							
position #	# of Mutations (world)	# of Mutations (India)	% of occurrence (India)	position #	# of Mutations (world)	# of Mutations (India)	% of occurrence (India)
1	0	0	-	35	327	1	0.306
2	126	0	0	36	166	0	0
3	23	0	0	37	319	0	0
4	2	0	0	38	1979	0	0
5	40	3	7.5	39	512	0	0
6	68	1	1.471	40	636	1	0.157
7	120	0	0	41	735	6	0.816
8	13	0	0	42	37308	4	0.011
9	87	0	0	43	89	0	0
10	524	0	0	44	583	0	0
11	61	0	0	45	358	1	0.279
12	331	0	0	46	299	0	0
13	516	2	0.388	47	275	0	0
14	245	0	0	48	170	0	0
15	6746	6	0.0889	49	346	0	0
16	467	3	0.6423	50	118	1	0.847
17	44	0	0	51	186	0	0
18	566	5	0.883	52	232	10	4.310
19	189	1	0.529	53	582	2	0.344
20	189	0	0	54	3442	2	0.058
21	903	2	0.221	55	628	4	0.637
22	456	3	0.658	56	52	0	0
23	1464	2	0.137	57	155611	471	0.303
24	217	0	0	58	1111	1	0.090
25	217	0	0	59	530	2	0.377
26	28662	396	1.382	60	866	0	0
27	2643	0	0	61	63	0	0
28	123	0	0	62	747	0	0
29	207	0	0	63	313	0	0
30	177	0	0	64	240	0	0
31	217	0	0	65	346	5	1.445
32	468	0	0	66	125	1	0.8
33	3529	0	0	67	541	0	0
34	147	0	0	68	1050	0	0

Continuation of Table 1							
position #	# of Mutations (world)	# of Mutations (India)	% of occurrence (India)	position #	# of Mutations (world)	# of Mutations (India)	% of occurrence (India)
69	1050	0	0	109	57	1	1.754
70	35	0	0	110	1243	17	1.368
71	69	0	0	111	10	0	0
72	384	1	0.260	112	817	1	0.122
73	549	1	0.182	113	51	0	0
74	1459	0	0	114	30	0	0
75	183	0	0	115	18	2	11.11
76	58	0	0	116	58	0	0
77	429	5	1.166	117	24	0	0
78	1099	0	0	118	91	0	0
79	10	0	0	119	32	0	0
80	40	3	7.5	120	36	0	0
81	102	0	0	121	20	0	0
82	16	0	0	122	101	0	0
83	185	0	0	123	117	0	0
84	36	0	0	124	66	0	0
85	719	2	0.278	125	455	13	2.857
86	456	1	0.219	126	245	0	0
87	29	0	0	127	309	0	0
88	420	2	0.476	128	463	4	0.864
89	1015	1	0.098	129	365	0	0
90	1123	0	0	130	25	0	0
91	11	0	0	131	6122	6	0.098
92	663	0	0	132	13	0	0
93	286	16	5.594	133	14	0	0
94	413	0	0	134	1513	4	0.264
95	265	2	0.755	135	6	0	0
96	116	0	0	136	40	0	0
97	239	1	0.418	137	25	1	4
98	186	0	0	138	3	0	0
99	1903	0	0	139	10	1	10
100	3228	2	0.062	140	521	1	0.192
101	253	1	0.395	141	5	0	0
102	81	0	0	142	75	0	0
103	427	1	0.234	143	381	1	0.262
104	9158	3	0.033	144	34	0	0
105	44	1	2.273	145	44	0	0
106	693	15	2.345	146	3	1	33.33
107	312	0	0	147	197	0	0
108	1350	2	0.148	148	27	2	7.407

Continuation of Table 1							
position #	# of Mutations (world)	# of Mutations (India)	% of occurrence (India)	position #	# of Mutations (world)	# of Mutations (India)	% of occurrence (India)
149	154	1	0.650	189	109	2	1.835
150	55	0	0	190	33	0	0
151	3111	3	0.096	191	78	0	0
152	58	1	1.724	192	39	0	0
153	96	0	0	193	461	0	0
154	82	0	0	194	21	0	0
155	2261	33	1.460	195	127	0	0
156	23	0	0	196	857	0	0
157	1	0	0	197	51	0	0
158	134	0	0	198	136	0	0
159	209	0	0	199	28	0	0
160	6	0	0	200	34	0	0
161	6	0	0	201	68	0	0
162	113	2	1.770	202	829	0	0
163	162	0	0	203	5	0	0
164	7	0	0	204	30	0	0
165	248	0	0	205	31	0	0
166	974	3	0.308	206	27	0	0
167	8	1	12.5	207	188	0	0
168	35	0	0	208	15	0	0
169	33	0	0	209	55	0	0
170	18	0	0	210	484	2	0.413
171	3147	12	0.381	211	51	0	0
172	51165	5	0.010	212	0	0	-
173	331	6	1.813	213	346	0	0
174	2482	3	0.121	214	1	0	0
175	1519	2	0.132	215	6	0	0
176	407	0	0	216	67	0	0
177	222	1	0.450	217	351	0	0
178	26	0	0	218	90	0	0
179	41	0	0	219	290	0	0
180	2355	1	0.042	220	123	1	0.813
181	114	0	0	221	106	0	0
182	158	10	6.329	222	114	0	0
183	551	0	0	223	5066	37	0.730
184	66	0	0	224	2346	7	0.298
185	708	0	0	225	1107	0	0
186	153	0	-	226	661	1	0.151
187	49	0	0	227	90	1	1.111
188	2581	0	0	228	38	0	0

Continuation of Table 1							
position #	# of Mutations (world)	# of Mutations (India)	% of occurrence (India)	position #	# of Mutations (world)	# of Mutations (India)	% of occurrence (India)
229	368	0	0	255	86	0	0
230	75	0	0	256	310	0	0
231	22	0	0	257	725	1	0.138
232	60	0	0	258	103	0	0
233	4	0	0	259	240	0	0
234	19	0	0	260	330	0	0
235	63	0	0	261	92	0	0
236	828	0	0	262	448	2	0.446
237	87	0	0	263	50	3	6
238	260	3	1.154	264	99	0	0
239	3536	2	0.056	265	62	0	0
240	7589	3	0.040	266	63	1	1.587
241	312	1	1.111	267	784	0	0
242	60	0	0	268	362	1	0.276
243	15	1	6.667	269	455	0	0
244	32	0	0	270	457	0	0
245	66	1	1.515	271	64	0	0
246	49	0	0	272	112	0	0
247	70	0	0	273	102	0	0
248	7	0	0	274	18	1	5.556
249	3	0	0	275	213	3	1.408
250	6	1	16.667	-	-	-	-
251	674	0	0	-	-	-	-
252	147	0	0	-	-	-	-
253	15954	0	0	-	-	-	-
254	748	0	0	-	-	-	-
End of Table							

Table S2: The list of residues forming hydrogen bonds showing maximum occupancy in the three systems are shown. Main and side indicate main chain and side chain hydrogen bonds.

Residue1	Residue2	Occupancy
TYR156'-Side	LYS192'-Main	71.93%±0.0019
ARG134'-Side	ASP155'-Side	70.1%±0.0084
SER205'-Side	ASN144'-Main	67.99%±0.0022
LEU203-Main	ASP210-Main	68.28%±0.0013
SER205-Side	ASN144-Main	67.86%±0.0020
LEU203'-Main	ASP210'-Main	67.97%±0.0010
TYR154-Side	GLU191-Side	61.90%±0.0005
THR89'-Side	LEU85'-Main	61.75%±0.0011
THR89-Side	LEU85-Main	60.97%±0.0021
THR175'-Side	ASP173'-Side	61.7%±0.0036

(a) WT

Residue1	Residue2	Occupancy
TYR212'-Side	THR164'-Main	68.44%±0.0129
SER205'-Side	ASN144'-Main	69.27%±0.0022
SER205-Side	ASN144-Main	68.99%±0.0014
TYR233'-Side	LYS198'-Main	66.44%±0.0006
LEU203-Main	ASP210-Main	66.20%±0.0035
TYR233-Side	LYS198-Main	66.44%±0.0035
LEU203'-Main	ASP210'-Main	66.86%±0.0013
THR89'-Side	LEU85'-Main	63.12%±0.0021
TYR233-Main	ILE167-Main	59.67%±0.0077
THR89-Side	LEU85-Main	61.11%±0.0005

(b) D155Y

Residue1	Residue2	Occupancy
LEU203-Main	ASP210-Main	64.48%±0.0074
LEU203'-Main	ASP210'-Main	63.23%±0.0018
THR89-Side	LEU85'-Main	63.37%±0.0068
TYR233'-Side	LYS198'-Main	61.92%±0.0121
TYR91-Side	PRO42-Main	55.81%±0.0182
SER58'-Side	ALA54'-Main	62.31%±0.0085
THR89-Side	LEU85-Main	59.91%±0.0088
TYR154'-Side	GLU191'-Side	60.33%±0.0072
TYR233-Side	LYS198-Main	59.93%±0.0011
SER58-Side	ALA54-Main	61.28%±0.0027

(c) S171L

Table S3: List of salt bridge interactions in the three systems

Salt Bridge	WT	D155Y	S171L	Salt Bridge	WT	D155Y	S171L
ASP142-LYS61'	✓	✓	✓	ASP199-LYS198	✗	✓	✓
ASP142-LYS75	✓	✓	✓	ASP199'-LYS198'	✓	✓	✓
ASP142-ARG116	✓	✗	✗	ASP210-LYS235	✓	✓	✓
ASP142-ARG122	✗	✓	✓	ASP210'-LYS235'	✓	✓	✓
ASP142-ARG126	✗	✓	✓	ASP238-LYS235	✓	✓	✓
ASP142'-LYS61	✓	✓	✓	ASP238'-LYS235'	✓	✓	✓
ASP142'-ARG122'	✓	✗	✓	GLU181-LYS192	✓	✓	✓
ASP142'-LYS61'	✓	✗	✗	GLU181-LYS67	✗	✗	✓
ASP142'-LYS75'	✓	✓	✓	GLU181-ARG67	✗	✗	✓
ASP142'-ARG116'	✓	✗	✗	GLU181'-LYS192'	✓	✓	✓
ASP142'-LYS75	✓	✗	✓	GLU181'-LYS266	✓	✗	✗
ASP142'-ARG126'	✗	✓	✓	GLU191-ARG68	✓	✓	✓
ASP155-ARG134	✓	✗	✓	GLU191-LYS192	✗	✗	✓
ASP155'-ARG134'	✓	✗	✓	GLU191'-LYS192'	✓	✗	✗
ASP181'-LYS192'	✗	✓	✗	GLU191'-ARG68'	✓	✓	✓
ASP183-LYS192	✓	✓	✓	GLU194-LYS192	✓	✓	✓
ASP183-LYS67	✓	✓	✓	GLU194-LYS198	✗	✗	✓
ASP183-ARG68	✓	✗	✓	GLU194'-LYS192'	✓	✓	✓
ASP183'-LYS67'	✓	✗	✗	GLU226-LYS235'	✓	✗	✗
ASP183'-LYS192'	✗	✗	✓	GLU226'-LYS23	✓	✗	✗
ASP199-LYS1	✓	✗	✗	GLU226'-LYS235	✗	✓	✓

Table S4: List of residues constituting each cluster for WT and the two mutants. The functional domain in which some of the constituent residues fall are indicated within parentheses.

Beginning of the table		
WT	D155Y	S171L
0: ALA51 ALA54 ALA59 GLN57 GLY49 GLY44 ILE47 LEU52 LEU53 LEU41 LEU46 PHE56 PHE43 PRO42 SER40 SER58 SER60 TRP45 VAL50 VAL55 VAL48	0: ALA51 ALA54 ALA59 GLN57 GLY49 GLY44 ILE62 ILE47 LEU52 LEU53 LEU41 LEU46 LYS61 PHE56 PHE43 PRO42 SER40 SER58 SER60 TRP45 VAL50 VAL55 VAL48	0: ALA51 ALA54 ALA59 ASN82 CYS81 GLN57 GLY49 GLY76 GLY44 HIE78 HIE93 ILE47 LEU52 LEU53 LEU41 LEU83 LEU84 LEU85 LEU86 LEU94 LEU95 LEU46 LYS75 PHE56 PHE43 PHE79 PHE87 PRO42 SER40 SER58 SER60 SER92 THR89 TRP45 TYR91 VAL50 VAL55 VAL77 VAL80 VAL88 VAL90 VAL48
1: ALA51' ALA54' ALA59' ASN82' CYS81' GLN57' GLY44' GLY49' GLY76' HIE78' HIE93' ILE47' LEU41' LEU46' LEU52' LEU53' LEU83' LEU84' LEU85' LEU86' LEU94' LEU95' LYS75' PHE43' PHE56' PHE79' PHE87' PRO42' SER40' SER58' SER60' SER92' THR89' TRP45' TYR91' VAL48' VAL50' VAL55' VAL77' VAL80' VAL88' VAL90' (Domain 3)	1: ALA98 ALA99 ASN82 CYS81 GLY76 GLY100 HIE78 HIE93 LEU83 LEU84 LEU85 LEU86 LEU94 LEU95 LEU96 LYS75 PHE79 PHE87 SER92 THR89 TYR91 VAL77 VAL80 VAL88 VAL90 VAL97 (Domain 3)	1: ALA51' ALA52' ALA59' GLN57' GLY44' GLY49' ILE47' ILE62' LEU41' LEU46' LEU52' LEU53' LYS61' PHE43' PHE56' PRO42' SER40' SER58' SER60' TRP45' VAL48' VAL50' VAL55' VAL50' VAL55'
2: ASN82 CYS81 GLY76 HIE78 HIE93 LEU83 LEU84 LEU85 LEU86 LEU94 LEU95 LYS75 PHE79 PHE87 SER92 THR89 TYR91 VAL77 VAL80 VAL88 VAL90	2: ALA51' ALA54' ALA59' GLN57' GLY44' GLY49' ILE47' ILE62' ILE63' LEU41' LEU44' LEU52 LEU53' LYS61' PHE43' PHE56' PRO42' SER40' SER58' SER60' THR64' TRP45' VAL48' VAL50' VAL55'	2: ALA62' ARG68' ASN82' CYS81' GLN70' GLY76' HIE78' HIE93' ILE63' LEU65' LEU71' LEU83 LEU84' LEU85' LEU86' LEU94' LEU95' LYS66' LYS67' LYS75' PHE79' PHE87' SER74' SER92' THR64' THR89' TRP69' TYR91' VAL77' VAL80' VAL88' VAL90'

Continuation of Table S4		
WT	D155Y	S171L
3: ALA88 ALA99 ALA103 ALA110 ARG122 ASN119 GLN116 GLU102 GLY100 ILE118 ILE123 ILE124 LEU96 LEU101 LEU106 LEU108 LEU111 LEU115 MET125 PHE105 PHE114 PHE120 PRO104 SER117 TYR107 TYR109 TYR113 VAL97 VAL112 VAL121 (Domain 3)	3: ALA98' ALA99' ALA103' ALA110' ARG122' ASN119' GLN116' GLU102' GLY100' ILE118' ILE123' ILE124' LEU96' LEU101' LEU106' LEU108' LEU111' LEU115' MET125' PHE105' PHE114' PHE120' PRO104' SER117' TYR107' TYR109' TYR113' VAL97' VAL112' VAL121' (Domain 3)	3: ALA98' ALA99' ALA103' ALA110' ARG122' ASN119' GLN116' GLU102' GLY100' ILE118' ILE123' ILE124' LEU96' LEU101' LEU106' LEU108' LEU109' LEU115' MET125' PHE105' PHE114' PHE120' PRO104' SER117' TYR107' TYR109' TYR113' VAL97' VAL112' VAL121' (Domain 3)
4: ALA88' ALA99' ALA103' ALA110' GLN106' GLU102' GLY100' LEU96' LEU101' LEU106' LEU108' LEU111' LEU115' PHE105' PHE114' PRO104' SER117' TYR107' TYR109' TYR113' VAL97' VAL112' (Domain 3)	4: ALA72' ARG68' ASN82' CYS81' GLN70' GLY76' HIE78' HIE93' LEU65' LEU71' LEU73' LEU83' LEU84' LEU85' LEU86' LEU94' LEU95' LYS66' LYS67' LYS75' PHE79' PHE87' SER74' SER92' THR89' TRP69' TYR91' VAL77' VAL80' VAL88' VAL90' (Domain 3)	4: ALA98 ALA99 ALA103 ALA110 ASN119 GLN116 GLU102 GLY100 ILE118 LEU96 LEU101 LEU101' LEU108 LEU111 LEU115 PHE105 PHE114 PHE120 PRO104 SER117 TYR107 TYR109 TYR113 VAL97 VAL112 VAL121 (Domain 3)
5: ALA72 ARG68 GLN70 ILE62 ILE63 LEU65 LEU71 LEU73 LYS61 LYS66 LYS67 SER74 THR64 TRP69	5: ALA103 ALA11 ARG122 ASN119 GLN116 GLU102 ILE118 ILE123 ILE124 LEU101 LEU106 LEU108 LEU111 LEU115 MET125 PHE105 PHE114 PHE120 PRO104 SER117 TYR107 TYR109 TYR113 VAL112 VAL121 (Domain 3)	5: ALA72 ARG68 GLN70 ILE62 ILE63 LEU65 LEU71 LEU73 LYS61 LYS66 LYS67 SER74 THR64 TRP69
6: ARG122' ARG126' ASN119' ASN119' ASP199' ASP210' ASP238' CYS130' CYS133' CYS200' HIE204' ILE118' ILE123' ILE124' ILE236' LYS132' LYS198' LYS235' MET125' PHE120' PHE207' SER205' SER209' THR208' TRP127' TRP131' TYR206' TYR211' TYR212' VAL121' VAL200' VAL202' VAL237' (Domain 3)	6: ALA72 ARG68 GLN70 ILE63 LEU65 LEU71 LEU73 LYS66 LYS67 SER74 THR64 TRP69	6: ALA143' ARG126' ARG134' ASN137' ASN144' ASN152' ASP142' ASP155' ASP199' ASP210' ASP238' CYS130' CYS133' CYS148' CYS153' CYS157' CYS200' HIE150' HIE204' ILE158' ILE236' LEU127' LEU129' LEU139' LEU140' LEU147' LEU203' LYS132' LYS136' LYS198' LYS235' PHE146' PHE207' PRO138' SER135' SER205'

Continuation of Table S4		
WT	D155Y	S171L
		SER209' THR151' THR208 TRP128' TRP131' TRP149' TYR141' TYR145' TYR154 TYR156' TYR206' TYR211' TYR212' VAL201' VAL202' VAL237' (Domain 4)
7: ALA72' ARG68' GLN70' ILE62' ILE63' LEU65' LEU71' LEU73' LYS61' LEU71' LEU73' LYS61' LYS66' LYS67' SER74' THR64' TRP69'	7: ALA143' ARG126' ARG134' ASN137' ASN144' ASN152' ASN161' ASP142' ASP199' ASP210' ASP238' CYS130' CYS133' CYS148' CYS153' CYS157' CYS200' HIE150' HIE204' ILE158' ILE236' LEU127' LEU129' LEU139' LEU140' LEU147' LEU203' LYS142' LYS146' LYS198' LYS235' PHE146' PHE207' PRO138' PRO159' SER135' SER162' SER165' SER166' SER205' SER209' THR151' THR164' THR208' TRP128' TRP131' TRP149' TYR141' TYR145' TYR154' TYR155' TYR156' TYR160' TYR206' TYR211' TYR212' VAL163' VAL210' VAL202' VAL237' (Domains 3, 4, 5)	7: ASN161' ASN234' ASP222' GLN213' GLN218' GLU226' GLY224' HIE227' ILE167' ILE169' ILE232' LEU214' LEU219' PHE230' PHE231' PRO159' SER162' SER165' SER166' SER216' SER220' THR164' THR170' THR217' THR221' THR223' THR229' TYR160' TYR215' TYR133' VAL163' VAL168' VAL225' VAL228' (Domain 5)
8: ALA143' ARG134' ASN137' ASN144' ASN152' ASN161' ASP143' ASP155' CYS148' CYS153' CYS157' HIE150' ILE158' LEU139' LEU140' LEU147' LYS136' PHE146' PRO138' PRO159' SER135' PRO138' PRO159' SER135' SER162' SER165' SER166' THR151' THR164' TRP149' TYR141' TYR145' TYR154 TYR156' TYR160' VAL163' (Domain 4)	8: ALA143 ARG126 ARG134 ASN144 ASN152 ASN137 ASP142 ASP199 ASP210 ASP238 CYS148 CYS153 CYS157 CYS200 CYS130 CYS133 HIE150 HIE204 ILE158 ILE236 LEU139 LEU140 LEU147 LEU203 LEU127 LEU129 LYS198 LYS235 LYS132 LYS136 PHE146 PHE207 PRO138 SER205 SER209 SER135 THR151 THR208 TRP149 TRP128 TRP131 TYR141 TYR145 TYR154 TYR155 TYR156 TYR206 TYR211	8: ALA143 ARG122 ARG126 ARG134 ASN144 ASN161 ASN137 ASP142 ASP210 ASP238 CYS130 CYS133 HIE204 ILE236 ILE123 ILE124 LEU139 LEU140 LEU203 LEU127 LEU129 LYS235 LYS132 LYS136 MET125 PHE146 PHE207 PRO159 PRO138 SER162 SER205 SER209 SER135 THR208 TRP128 TRP131 TYR141 TYR145 TYR160 TYR206 TYR211 TYR212 VAL201 VAL202 VAL237 (Domains 4, 5)

Continuation of Table S4		
WT	D155Y	S171L
	TYR212 VAL201 VAL202 VAL237 (Domains 3, 4)	
9: ARG134 ASN152 ASP155 ASP173 ASP183 CYS148 CYS153 CYS157 GLN185 GLU181 GLU191 GLU194 GLY172 GLY174 GLY187 GLY188 GLY196 HIE182 HIE182 ILE158 ILE179 ILE186 LEU147 LYS192 PRO178 SER177 SER180 SER195 SER135 THR151 THR175 THR176 THR190 TRP149 TRP193 TYR154 TYR156 TYR184 TYR189 VAL197 (Domain 4)	9: ASP173 ASP183 GLN185 GLU181 GLU191 GLU194 GLY172 GLY174 GLY187 GLY188 GLY196 HIE182 ILE179 ILE186 LYS192 PRO178 SER177 SER180 SER195 THR175 THR176 THR190 TRP193 TYR184 TYR189 VAL197 (Domain 6)	9: ASP173 ASP183 GLN185 GLU181 GLU191 GLY172 GLY174 GLY187 GLY188 HIE182 ILE179 ILE176 LEU171 PRO178 SER177 SER180 THR175 THR176 THR190 TYR184 TYR189 (Domain 6)
10: ARG126 ASN137 ASP152 CYS130 CYS133 LEU139 LEU140 LEU127 LEU129 LYS132 LYS136 PRO138 TRP128 TRP131 TYR141 (Domain 4)	10: ASN161 ASN234 ASP222 GLN213 GLN218 GLU226 GLY224 HIE227 ILE167 ILE169 ILE232 LEU214 LEU219 PHE230 PHE231 PRO159 SER162 SER165 SER166 SER171 SER216 SER220 THR164 THR170 THR217 THR221 THR223 THR229 TYR160 TYR215 TYR233 VAL163 VAL168 VAL225 VAL228 (Domains 5, 6)	10: ASN152 ASP155 ASP199 CYS148 CYS153 CYS157 CYS200 GLU194 GLY196 HIE150 ILE158 LEU147 LYS192 LYS198 SER195 THR151 TRP149 TRP193 TYR154 TYR156 VAL197
11: ASN234 ASP222 GLN213 GLN218 GLU226 GLY224 HIE227 ILE167 ILE169 ILE232 LEU214 LEU219 PHE230 PHE231 SER171 SER216 SER220 THR170 THR217 THR221 THR223 THR229 TYR215 TYR233 VAL168 VAL225 VAL228	11: ASP173' ASP183' GLN185' GLU181' GLU191' GLU194' GLY172' GLY174' GLY187' GLY188' GLY196' HIE182' ILE179' ILE186' LYS192' PRO178' SER177' SER180' SER195' THR175' THR176' THR190' TRP193' TYR184' TYR189' VAL197' (Domain 6)	11: ASN234 ASP222 GLN213 GLN218 GLU226 GLY224 HIE227 ILE167 ILE169 ILE232 LEU214 LEU219 PHE230 PHE231 SER165 SER166 SER216 SER220 THR164 THR170 THR217 THR221 THR223 THR229 TYR215 TYR233 VAL163 VAL168 VAL225 VAL228
12: ALA143 ASN144 ASN161 ASP199 ASP210 ASP238 CYS200 HIE204 ILE237 LEU203 LYS198 LYS235 PHE146 PHE207 PRO159	12: ASN234' ASP222' GLN213' GLN218' GLU226' GLY224' HIE227' ILE167' ILE169' ILE242' LEU214' LEU219 PHE230' PHE231' SER171'	12: ASP173' ASP183' GLN185' GLU181' GLU191' GLU194' GLY172' GLY174' GLY187' GLY188' GLY196' HIE182' ILE179' ILE186' LEU171'

Continuation of Table S4		
WT	D155Y	S171L
SER162 SER165 SER166 SER205 SER209 THR164 THR208 TYR145 TYR160 TYR206 TYR211 TYR212 VAL163 VAL201 VAL202 VAL237 (Domains 4, 5)	SER216' SER220' THR170' THR217' THR221' THR223' THR229' TYR215' TYR233' VAL168' VAL225' VAL228'	LYS192' PRO178' SER177' SER180' SER195' THR175' THR176' THR190' TRP193' TYR184' TYR189' VAL197' (Domain 6)
13: ASP173' ASP183' GLN185' GLU181' GLU191' GLU194' GLY172' GLY174' GLY187' GLY188' GLY196' HIE182' ILE179' ILE186' LYS192' PRO178' SER177' SER180' SER195' THR175' THR176' THR190' TRP193' TYR194' TYR189' VAL197' (Domain 6)		
14: ASN234' ASP222' GLN213' GLN218' GLU226' GLY224' HIE227' ILE167' ILE169' ILE242' LEU214' LEU219' PHE230' PHE231' SER171' SER216' SER220' THR170' THR217' THR221' THR223' THR229' TYR215' TYR233' VAL168' VAL225' VAL228' (Domain 6)		
End of Table		

Table S5: **Rearrangement of constituent interactome clusters.** Every coloured box denotes a range of residues residing in the same cluster. Red bordered rectangles show how some of the residue sequences (coloured boxes) have merged in different combinations to form larger clusters due to increased strength of interactions between them.

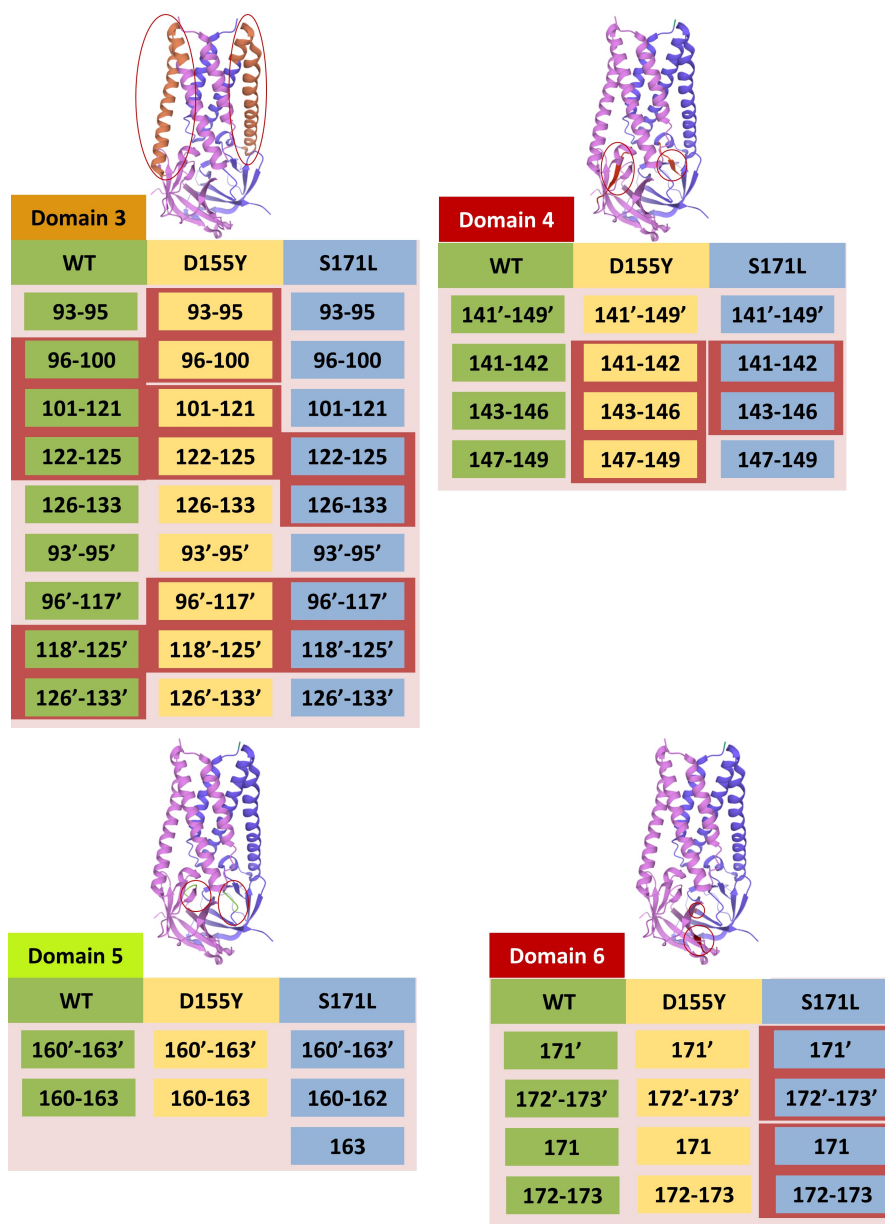


Table S6: The list of PROVEAN scores of selected mutations of ORF3A.

Amino acid Substitution in ORF3a	PROVEAN score*	Variation effect on protein
Q57H	-3.286	Deleterious
W131C	-7.752	Deleterious
W131R	-9.067	Deleterious
D155Y	-6.829	Deleterious
S171L	-2.238	Neutral
G172C	-6.752	Deleterious
G172V	-6.762	Deleterious

* Cutoff value = -2.5

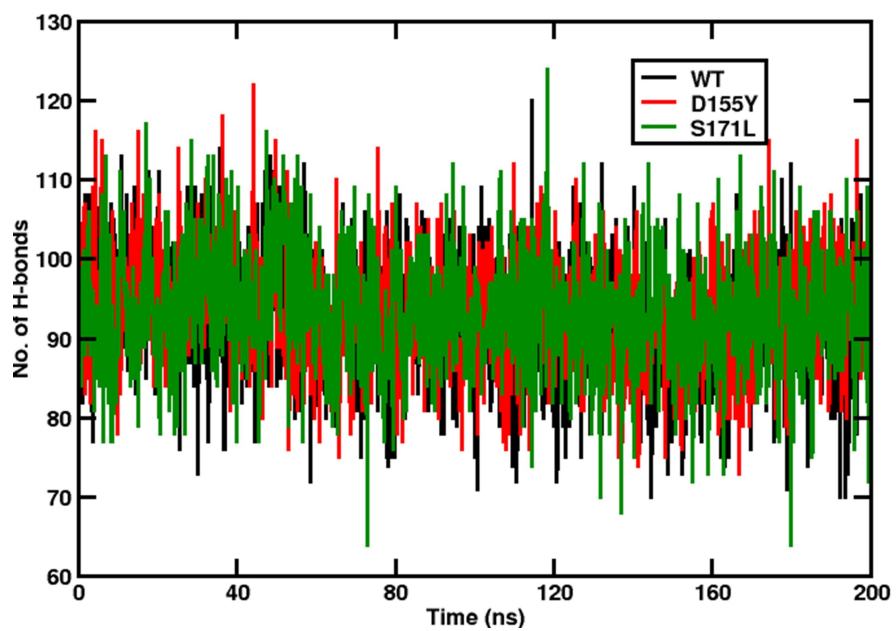
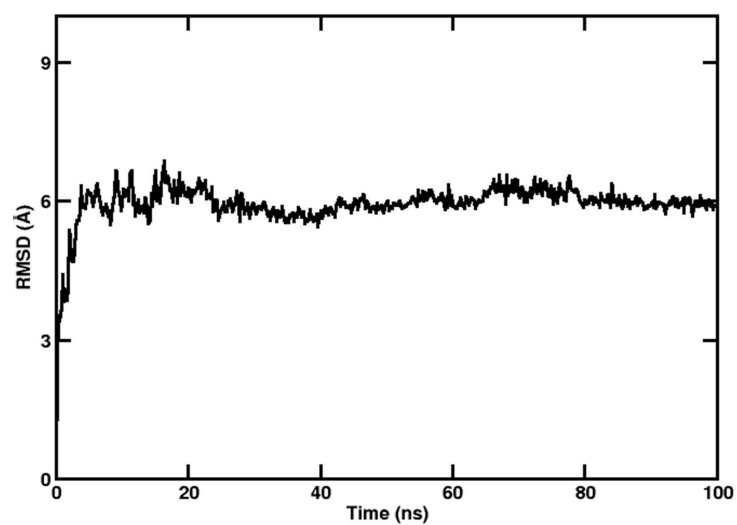
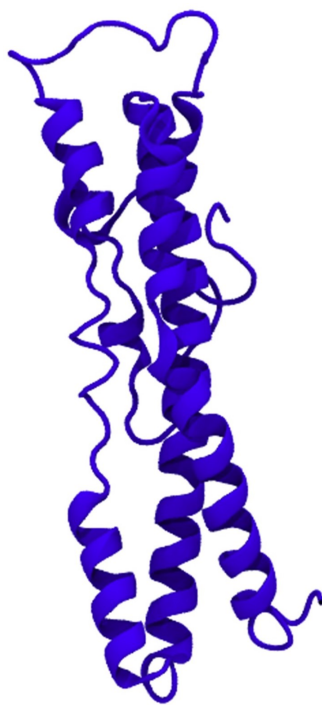


Fig.S1 The time evolution of hydrogen bonds for WT, D155Y and S171L are shown in black, red and green respectively



(a)



(b)

Fig. S2 (a) RMSD of the simulation of apo-caveolin-1 (b) Average structure of Caveolin-1 generated from simulation

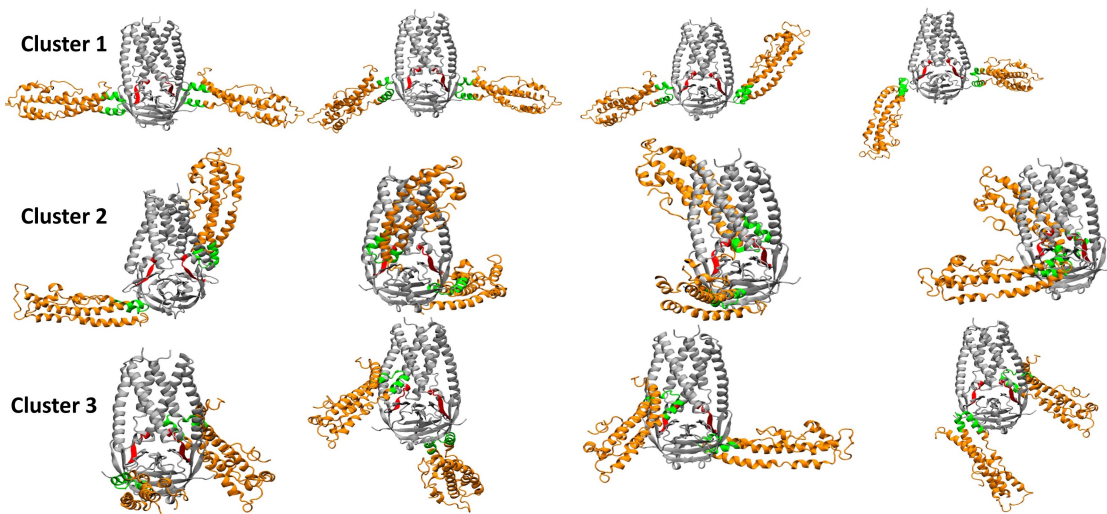


Fig. S3 The probable complexes generated from Haddock

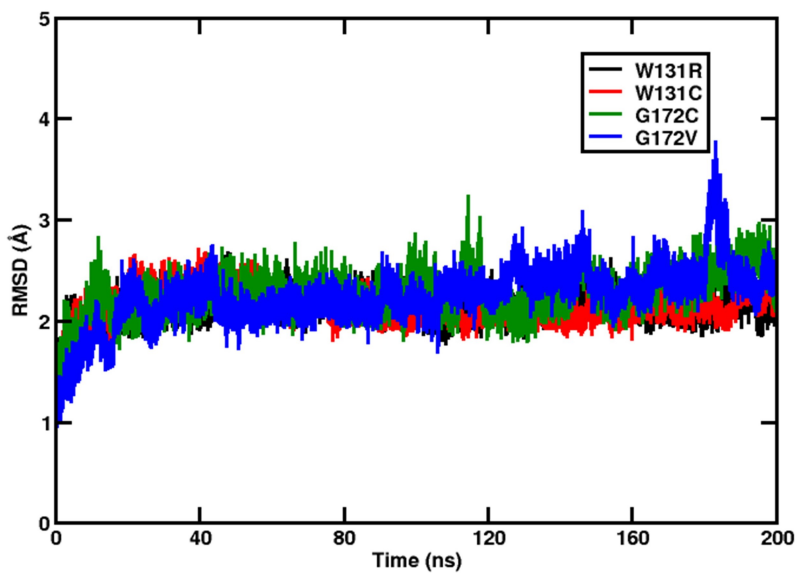


Fig. S4 The time evolution of RMSD of the four other mutants of ORF3a studied

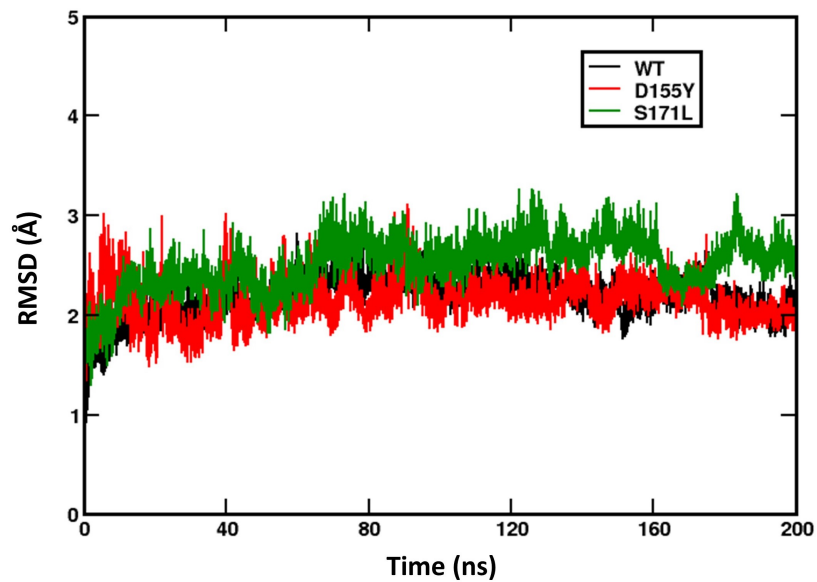


Fig. S5 The time evolution of the RMSD of the ORF3a protein with respect to the starting structure, obtained from the second production run

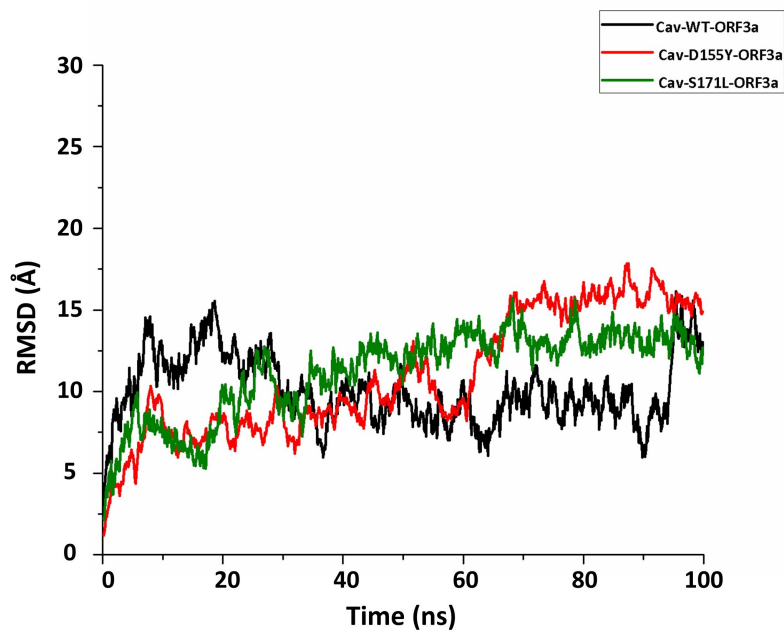


Fig. S6 Stability of the ORF3a-caveolin-1 complex, obtained from the second production run

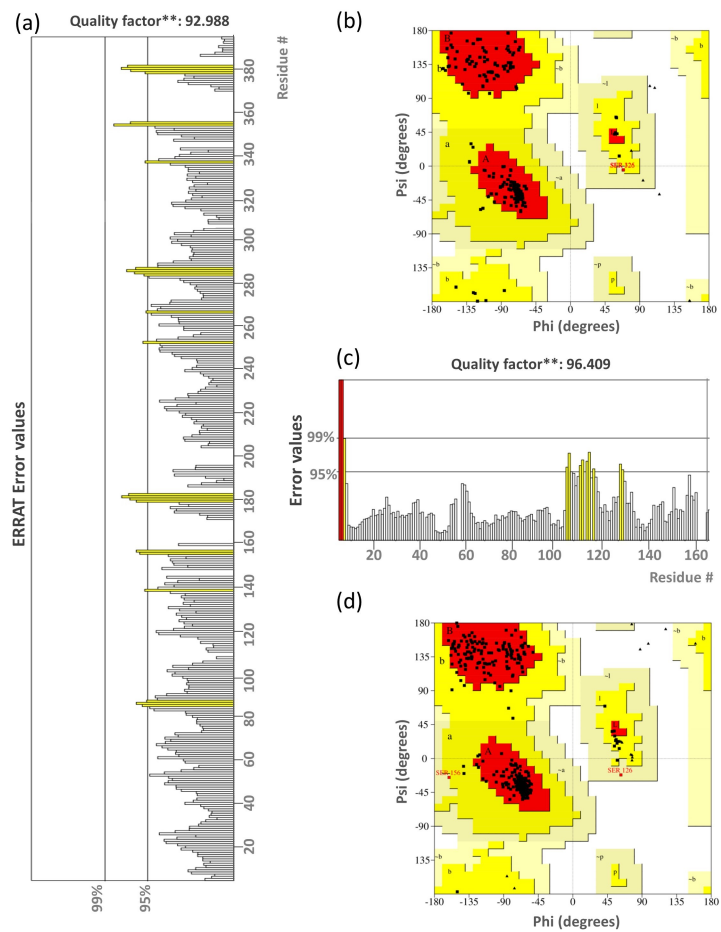


Fig. S7 The ERRAT analysis and Ramachandran Plot of ORF3a