

**Figure 4–source data 2.** List of ten highest % frequency synonymous mutations for each proteostasis environment and passage.

HSF1-Activated									
Passage 2		Passage 9		Passage 11		Passage 19		Passage 23	
Mutation	Freq.	Mutation	Freq.	Mutation	Freq.	Mutation	Freq.	Mutation	Freq.
<b>6555 A/G (Intergenic)</b>	<b>42</b>	<b>6555 A/G (Intergenic)</b>	<b>42</b>	<b>6555 A/G (Intergenic)</b>	<b>43</b>	7689 ggT/ggC (PA 371)	78	6414 aaA/aaG (NP 452)	92
962 atC/atT (HA 316)	8	5202 aaA/aaG (NP 48)	13	5202 aaA/aaG (NP 48)	18	6414 aaA/aaG (NP 452)	60	7689 ggT/ggC (PA 371)	83
4905 caC/caT (NEP 87)	5	1922 ttG/ttA (M1 60)	10	7770 ccT/ccG (PA 398)	16	<b>6555 A/G (Intergenic)</b>	<b>43</b>	<b>6555 A/G (Intergenic)</b>	<b>42</b>
<b>7647 acT/acA (PA 357)</b>	<b>2</b>	<b>2586 taT/taC (M2 52)</b>	<b>10</b>	1922 ttG/ttA (M1 60)	15	1238 ttC/ttT (HA 408)	35	1238 ttC/ttT (HA 408)	30
5109 ggG/ggA (NP 17)	2	<b>6687 gcA/gcG (PA 37)</b>	<b>10</b>	2586 taT/taC (M2 52)	14	2586 taT/taC (M2 52)	34	<b>10867 ttT/ttC (PB1 700)</b>	<b>20</b>
8607 gaA/gaG (PA 677)	2	2411 ccT/ccC (M1 223)	9	<b>6687 gcA/gcG (PA 37)</b>	<b>13</b>	9292 gaT/gaC (PB1 175)	34	9292 gaT/gaC (PB1 175)	20
9131 Cta/Tta (PB1 122)	2	962 atC/atT (HA 316)	7	7689 ggT/ggC (PA 371)	12	9229 ggT/ggC (PB1 154)	19	11135 gaG/gaA (PB2 18)	18
10249 agC/agT (PB1 494)	2	7869 gaC/gaT (PA 431)	7	8721 ttA/ttG (PA 715)	11	5202 aaA/aaG (NP 48)	16	6696 acT/acA (PA 40)	17
		8166 ccG/ccA (PA 530)	7	4223 ctT/ctC (NS1 82)	10	7980 gcC/gcT (PA 468)	12	9229 ggT/ggC (PB1 154)	17
		7689 ggT/ggC (PA 371)	6	7869 gaC/gaT (PA 431)	9	4223 ctT/ctC (NS1 82)	11	<b>8529 gcA/gcC (PA 651)</b>	<b>10</b>
Baseline									
Passage 2		Passage 9		Passage 11		Passage 19		Passage 23	
Mutation	Freq.	Mutation	Freq.	Mutation	Freq.	Mutation	Freq.	Mutation	Freq.
<b>6555 A/G (Intergenic)</b>	<b>43</b>	<b>6555 A/G (Intergenic)</b>	<b>43</b>	<b>6555 A/G (Intergenic)</b>	<b>43</b>	2586 taT/taC (M2 52)	67	11135 gaG/gaA (PB2 18)	95
4905 caC/caT (NEP 87)	14	10960 gaG/gaA (PB1 731)	25	11135 gaG/gaA (PB2 18)	34	11135 gaG/gaA (PB2 18)	63	2586 taT/taC (M2 52)	68
4346 gcA/gcG (NS1 56)	11	4905 caC/caT (NEP 87)	20	4905 caC/caT (NEP 87)	24	2093 ctC/ctA (M1 117)	60	2093 ctC/ctA (M1 117)	63
8217 gaT/gaC (PA 547)	5	4346 gcA/gcG (NS1 56)	16	4346 gcA/gcG (NS1 56)	20	<b>6555 A/G (Intergenic)</b>	<b>44</b>	<b>6555 A/G (Intergenic)</b>	<b>43</b>
6207 agC/agT (NP 383)	4	11109 Ctg/Ttg (PB2 10)	14	10960 gaG/gaA (PB1 731)	20	10444 taT/taC (PB1 559)	21	10444 taT/taC (PB1 559)	42
10024 ttA/ttG (PB1 414)	2	6045 gtG/gtA (NP 329)	12	2586 taT/taC (M2 52)	16	2605 Ctg/Ttg (M2 59)	20	5175 ttC/ttT (NP 39)	26
4409 ctT/ctC (NS1 77)	2	6207 agC/agT (NP 383)	9	8013 gaT/gaC (PA 479)	12	4905 caC/caT (NEP 87)	18	4905 caC/caT (NEP 87)	23
779 ccG/ccA (HA 255)	2	8013 gaT/gaC (PA 479)	8	11109 Ctg/Ttg (PB2 10)	11	4346 gcA/gcG (NS1 56)	15	6630 gaA/gaG (PA 18)	22
<b>7647 acT/acA (PA 357)</b>	<b>2</b>	8217 gaT/gaC (PA 547)	<b>8</b>	8217 gaT/gaC (PA 547)	<b>9</b>	7662 aaA/aaG (PA 362)	<b>13</b>	4346 gcA/gcG (NS1 56)	<b>21</b>

10351 acA/acG (PB1 528)	2	425 acC/acT (HA 137)	7	2093 ctC/ctA (M1 117)	9	8685 aaT/aaC (PA 703)	13	2605 Ctg/Ttg (M2 59)	19
<b>Hsp90-Inhibited</b>									
Passage 2		Passage 9		Passage 11		Passage 19		Passage 23	
Mutation	Freq.	Mutation	Freq.	Mutation	Freq.	Mutation	Freq.	Mutation	Freq.
<b>6555 A/G (Intergenic)</b>	<b>42</b>	<b>6555 A/G (Intergenic)</b>	<b>43</b>	<i>2616 ggG/ggA</i> (M2 62)	51	<i>11135 gaG/gaA</i> (PB2 18)	92	<i>11135 gaG/gaA</i> (PB2 18)	94
2616 ggG/ggA (M2 62)	28	2616 ggG/ggA (M2 62)	38	<b>6555 A/G (Intergenic)</b>	<b>43</b>	<i>2586 taT/taC</i> (M2 52)	83	5592 gcT/gcC (NP 178)	93
2718 ctG/ctA (M2 96)	4	2270 gaG/gaA (M1 176)	34	2270 gaG/gaA (M1 176)	37	2616 ggG/ggA (M2 62)	79	2616 ggG/ggA (M2 62)	90
2297 acG/acA (M1 185)	3	4905 caC/caT (NEP 87)	23	5592 gcT/gcC (NP 178)	24	5592 gcT/gcC (NP 178)	61	1001 acT/acC (HA 329)	58
4361 ggA/ggG (NS1 61)	2	5592 gcT/gcC (NP 178)	11	4905 caC/caT (NEP 87)	22	4905 caC/caT (NEP 87)	45	4905 caC/caT (NEP 87)	56
11135 gaG/gaA (PB2 18)	2	9220 agA/agG (PB1 151)	10	2586 taT/taC (M2 52)	17	<b>6555 A/G (Intergenic)</b>	<b>42</b>	10309 gtG/gtA (PB1 514)	51
4905 caC/caT (NEP 87)	2	2586 taT/taC (M2 52)	7	11135 gaG/gaA (PB2 18)	17	1001 acT/acC (HA 329)	36	2586 taT/taC (M2 52)	44
7647 acT/acA (PA 357)	2	5784 gtG/gtA (NP 242)	4	1694 atT/atC (HA 560)	9	2099 taT/taC (M1 119)	33	5214 taT/taC (NP 52)	43
<b>10249 agC/agT (PB1 494)</b>	<b>2</b>	7902 agG/agA (PA 442)	3	9220 agA/agG (PB1 151)	7	5826 ctC/ctA (NP 256)	19	<b>6555 A/G (Intergenic)</b>	<b>42</b>
		7512 aaA/aaG (PA 312)	3	4436 gcT/gcA (NS1 86)	4	10309 gtG/gtA (PB1 514)	16	2099 taT/taC (M1 119)	22

\*Bolded mutations were observed in 3/3 biological replicates; italicized mutations were observed in 2/3 biological replicates. Top line of mutation description is the nucleotide number (of concatenated influenza genome) and codon mutation; bottom line contains the respective protein and codon number in parentheses. Empty cells indicate that less than ten variants were observed.