

Table S1: Substitutions that arose over 5% frequency after each passage

Protein	Passage	H1N1			
		WT	I38L	I38T	E199D
PB2	1	N71I	V734E	K738N	K738N
		K738N*	K738N		
	2	K738N	N/A	K738N	K738N
	3	N/A [†]	N/A	N/A	K738N
PB1	1	N/A	N/A	N/A	L753I
	2	N/A	N/A	N/A	N/A
	3	N/A	N/A	N/A	N/A
PA	1	N/A	D394N	N/A	E26K
	2	N/A	D394N	N/A	N/A
	3	I38L	D394N	N/A	N/A
HA	1	N/A	N/A	N/A	HA2 S215A
	2	N/A	N/A	N/A	N/A
	3	N/A	N/A	N/A	N/A
HA2	1	N/A	N/A	N/A	N/A
	2	N/A	N/A	N/A	N/A
	3	N/A	N/A	N/A	N/A
NA	1	N/A	N/A	N/A	N/A
	2	N/A	N/A	N/A	N/A
	3	N/A	N/A	N/A	N/A
NP	1	N/A	N/A	N/A	N/A
	2	N/A	N/A	N/A	N/A
	3	N/A	N/A	N/A	N/A
M1	1	N/A	N/A	N/A	N/A
	2	N/A	N/A	N/A	N/A
	3	N/A	N/A	N/A	N/A
M2	1	N/A	N/A	N/A	N/A
	2	N/A	N/A	N/A	N/A
	3	N/A	N/A	N/A	N/A
NS	1	N/A	N/A	N/A	N/A
	2	N/A	N/A	N/A	N/A
	3	N/A	N/A	N/A	N/A

*Bolted subsitutions indicate common substitutions between WT and MUT virus

[†]N/A: Not applicable; No substitutions were observed in the viral protein after passage

Substitutions that arose over 5% frequency after each passage

Protein	Passage	H3N2	
		WT	I38T
	1	R213G	T21K
		D309G	H27N
		D506G	I30K
		A569T	G37E
		Y592N	Y55C
		L733S	D60H
			E65K
			E69Stop
			R70K
			E72K
			Q73K
			G74E
			G75K
			S79N/R
			Y111N/Stop
			P112T/Q
			D120E
			E171K
			L177G
			E191K
			T215K
			L232F
			Q236H
			R299Stop
			D309N
			R318K
			F325I
			S336A
			V338I
			E343K
			L352S
			I354K
			E358Stop
			G359V
			G367R/E
			G388E
			I411L
			K412T
			A413T/G
			G459E
			M483L
			L502F
			D506Y
			N510I

PB2			L512Stop
			S519R
			E520K
			N548K
			T549I
			Y550D
			W552R
			I553F
			Q563K
			W564L
			Y572Stop
			E576K
			M645I
			R646K
			R664K
			T666K
			G669R/E
			P679Q
			E712K
			A717T/E
			L725I
			I726F/S
			Q728H
			G729V
			D730E/V
			M735I/L
			K736N/Stop
			R737L
			L738N
			D746H
	2	N/A [†]	L20I/Q
			T21K
			T23P
			D26N
			H27N
			I30K
			G74E
			G75K
			P169S
			E188K
			E191K
			E192K
			P219Q
			V267E
			R268K
			E305K
			Q306K

			T333K
			E342K
			E343K
			I354K
			T666K
			L675Stop
			N723I
			Q728K
			D730E/V
			V731G
			V734E
			M735I
			R737P/L
			L738N
	3	N/A	E305G/Stop
			G367R
			Q433H
			Y572F
			Q728K
		C770R	A140S
			A14E
			A349V
			A453E
			E109D
			E178K
			E256K
			E390K
			E60K
			F185V/C/L
			F412L
			G234D
			G513V/Stop
			G622E
			H634Q
			I18K
			I248N
			I392K
			I674F
			I750F
			K237N
			K578Stop
			L163Q
			L236I/Stop
			L550M
			L675R
			M246I
			M317L

PB1	1		M409I
			M546K
			N134K
			N16K
			N425I
			N58K
			N641K
			N671D
			N676K
			P394H
			P454T/Q
			P596Q
			Q186K/H
			Q247K
			Q268L
			Q313K
			Q367K
			Q460K
			Q48L
			R135K/Stop
			R187K
			R233K
			S173Stop
			S19R
			S633R
			T132A
			T20K
			T307A
			T366K
			T36A
			T432N
			T434K
			T543P
			T59K
			T677K
			V421L
			V640E
			W437Stop
			Y253N
			Y355C
			Y555Stop
			E277K
			E311K
			E383K
			E636K
			E78K
			F185L

	2	N/A	I181K
			I219K
			I342K
			I552N
			L218I/Q
			L271I
			L576Q
			N276K
			N312K
			N346K
			N536K
			P369H
			P596Q
			Q313K
			Q549K
			Q567K
			R187K
			R287G
			S384T/Stop
			T110K
			T20K
			T21K
			T385K
			T677K
	3	P369A	E256K
		S704Stop	G594R
		Y436Stop	I389T
			L258I
			S261R
		L42W	C7S
		E43Q	C10S
		D108N	N14K
		K134E	E15K
		P238L	G20E
		G372E	N25K
		E430V	Q27K
		I486R	Stop49R
		Y722H	T50K
			V65D
			Q77K
			N78K
			S84R
			Q106K
			Stop132K
			E135K
			G147E
			H171Q

PA

1

	T173K
	R174K
	P180T
	R188Q
	E215Q
	P249L
	F253L
	D256V
	N261I/K
	Q262K
	N306T
	R320Q
	G322V
	F325Y/L
	M331I
	R337K
	A339S
	D350N
	W365Stop
	H380Q
	E384Stop
	R390Q
	L415M
	E435V
	H460N
	N484K
	Stop485K
	A489E
	I494L
	E524K
	Stop526L
	A527D
	T543N
	Y554Stop
	V557L
	N568K
	E569K
	Stop590W
	E598K
	Q602K
	R610K
	H614N
	C662F
	S676C
	L692P
	A695S
	L703P

			Y705Stop	
			F717L	
	2	N/A	C7S	
			A20E	
			M21K/I	
			D27N	
			N33K	
			I178K	
			R179K	
			Q180K	
			E181K	
			E195K	
			I268N	
			Y277F	
			G372E	
			E377K	
			L500F	
			Y501F	
			L550I/Q	
			T567K	
			S571Stop	
			E604K	
			Q654K	
			V669F	
			L701F	
	3	N/A	C7S	
		1	N/A	D7E
				H18N
				N22D
				V26E
				T28S/K
				A106V
F120Y/L				
N121K				
G129Stop				
T131S				
A138S				
H156Q				
L157I/Stop				
L164Stop				
M168K/I				
P169T/Q				
N170K				
N171Y/K				
E172K				
H183Q				
G200V				

HA1			T206N
			Q211L
			P215T
			N216D
			I217T
			Q327K/L
			A334E
			A336E
			G337C
			G342R
			W343L
	2	T135R	G5R/E
		P254H	D7E
		R261Stop	P169T/Q
			N170K
			N171K
			E172K
			T206N
			R208K
			I236K
			Q295E
	Q327K		
3	N/A	C100R	
	1	N/A	M3I
			V4L
			G6C
			W7R
			Q20K
			D23H
			N32K
			Q33K
			N46H
			F49I
			E53D
			K54I
			E55K/V
			E60V
			G61V
			V70D
			T93K
			E114K
			F124L
			I138N
			R139K
			N140K
			H145N
			V147I

HA2			Q158K
			I159N
			S176F
2	N/A		C185F
			V186F
			L188F
3	N/A		L189F
			N31K
			Q32K
1	N/A		G42E
			E46K
			R61K
			H91N/Q
			T92K
			R106K
			T107K
			E113K
			F123L
			R138K
			V146I
			I158N
			L182F
			C184F
			V185F
			A186S/G/V
			L187F
			K27R
			Y71H
			A131S
			A237E
			C333Stop
			D112N/E
			D72E
			E114K/Stop
			E115K/Stop
			E11D
			E14K/D
			E294K
			E454K
			E455K
			E64K
			E81K
			G356E
			G5S
			I116K
			I257L
			I347N

NP			I63K
			I96M
	2		K198R/N
			L143F
			M137I
			M13I
			N124K
			P283T
			P419Q
			Q235K
			Q308K
			R117T
			R31K
			S310G
			T62K
			Y111N/Stop
			Y289N
			Y52N
		A251T	M13I
		V280A	E14K/D
		N417D	G102V
			Y111F
			D112N/E
			E113K
			I116K
			R117T
			Y120R
			D128G
			R195K
			T215K
			R216K
			Q235K
			E244K
			G295E
			H324Q
			P419Q
			E454K
			E455K
	3	N/A	Y496H
			S14P
			L15H
			V33E
			P46Q
			Q49K
			E54K
			P55T/Q
			T56K

NA	1	N/A	I58K
			R60K
			E74K
			H168Y
			G196W
			A201S/E
			N208Y/I
			R210S
			L211H
			E221K
			S266C
			V303E
			D304N/E
			I305K
			R327T
			C337S
			E344K
			G357R/E
			E375K
			F377I
			Q395L
			R430K
			V445L
			C447F
			G448C
	2	N2I	S18F
		K80E	M24I
		W87R	Q25K
		E343Stop	S101F
		S367N	T138K
			L140I/Q
			N141K
			H168Y
			E221K
			C318G
			R327K
			E344K
			G363E
			R364K
			E375K
			I392K
			S411F
			V412F
			R430K
			E433K
			V445L
			C447F

	3	N/A	E476K/A/D
			L321I
			S332P
			R430G
			G461E
M1	1	N/A	E23G
			E44K
			T48K
			K57T
			I131K
			Y132N/Stop
			R210M
			Q238K
			Stop253S
			R259H
			Y261H
			W263L
			A266E
			L267I
			Q285H
	2	E6K	P50Q
		E152D	V63C
		M203K/L	Y132N/Stop
		D268V	V138E
		S275C	N177K
			R178K
			E201D
			Stop289K
			C313R
	3	N/A	
M2	1	E14V	D24H
		L46V	A30T
			G34W
			H37N/Q
			K56I
	2	N/A	
	3	N/A	
NS	1	N/A	Q21K
			D44G
			T48S
			E56K
			T57A
			G58C
			L80F
			S97Stop
			N102Y
			K110Stop

			N111Y
			Q113L/H
			W117C
			S119C
			N123Y/I
	2	N/A	Q21K
			V23I/E
			D24N
			L77I/H
			I90K
			N101I
			E112D
			D173N
	3	N/A	V111A

*Bolted substitutions indicate common substitutions between WT and mutant virus

†N/A: Not applicable; No substitutions were observed in the viral protein after passage

Substitutions that arose over 5% frequency after each passage

Protein	Passage	IBV	
		WT	I38T
		V21E	L22Stop
		L22Stop*	Q24K
		Q24K	T25K
		T25K	Y30Stop
		D28N/E	I32K
		Q29K	I77K
		Y30N/Stop	Q78K
		N31K	T81K
		I32K	E155K
		I33K	E190K
		R34K	I200K
		R40K	S276Stop
		L47Stop	L332Q
		M49I	Q354K
		L72F	I388K
		G76E	M396K/I
		I77K	L399F/Stop
		Q78K	R443K/I
		L79I/H	S490C/I
		T81K	T500K
		E155K	L505Stop
		E190K	I506K
		R192K	I616K
		E193K	E666K
		I200K	E716K
		F230Y/L	G733E
		I231K	
		E232K	
		R243K	
		S276T/Stop	
		E284K	
		R324T/I	
		Q325K	
		R334K	
		F340Y/L	
		Q354K	
		I375K	
		L376I/Stop	
		R382K	
		L387Q	
		I388K	
		D395E	
		M396K/I	
		L399F/Stop	
		I400K	

L430Stop	
Q437K	
R443K/I	
M469I	
V480E	
V481I/E	
T482K	
S490C/I	
S491F	
S504N/R	
L505I/Stop	
I506K	
G541E	
T542K	
T543N	
E545K	
L546P	
Q548K	
Q552E	
W553C	
G568Stop	
E570K	
I584K	
A597S	
Q603K	
I616K	
G646R/E	
E647K	
T665K	
E666K	
E716K	
L720I/Q	
V738I	
L22M/Stop	A597S
Q24K	D395E
T25K	E155K
Y30N/Stop	E190K
N31K	E193K
I32K	E232K
I33K	E284K
R34K	E647K
G76E	E666K
I77K	E716K
Q78K	F230Y/L
L79I/H	F340L
T81K	F489L
E155K	F615L
E190K	G646R/E
R192K	G733E

PB2

2

E193K	I200K
M199I	I231K
I200K	I32K
F230Y/L	I33K
I231K	I375K
E232K	I388K
S276T/Stop	I400K
V283E	I506K
E284K	I616K
L319Q	I77K
L332I/Q	L22M/Stop
R334K	L319Q
F340L	L332I/Q
Q354K	L376I/Stop
I375K	L387I/Q
L376I/Stop	L399F/Stop
L387I/Q	L505Stop
I388K	L79I/H
D395E	M199I
M396K/I	M396K/I
L399F/Stop	N31K
I400K	Q24K
Q437K	Q354K
R443K/I	Q603K
V481I/E	Q78K
T482K	R192K
S490C/I	R334K
L505Stop	R34K
I506K	R40K
T542K	R443K/I
T543N	S276T/Stop
E545K	S407F
A597S	S490C
Q603K	T25K
F615L	T482K
I616K	T542K
G646E	T665K
E647K	T81K
T665K	V481I/E
E666K	Y30N/Stop
E716K	Y772N/Stop
G733E	
L22Stop	A597S
Q24K	D395E
T25K	D683E
Y30N/Stop	E155K
N31K	E190K
I32K	E232K
I33K	E284K

R34K	E545K
R40K	E647K
I77K	E666K
Q78K	E684K
L79I/H	E685K
T81K	E716K
E155K	F230Y/L
E190K	F340L
R192K	F615L
E193K	G646R/E
M199I	G733E
I200K	I200K
F230Y/L	I231K
I231K	I32K
E232K	I33K
S276T/Stop	I375K
V283E	I388K
E284K	I400K
L319Q/I	I499K
L332I/Q	I506K
R334K	I616K
F340L	I77K
Q354K	L22M/Stop
I375K	L332I/Q
L376I/Stop	L376I/Stop
L387I/Q	L399F/Stop
I388K	L505Stop
D395E	L79I/H
M396K/I	M199I
L399F/Stop	M396K/I
I400K	N31K
R443K/I	Q24K
V481I/E	Q354K
T482K	Q603K
F489L	Q78K
S490C	R334K
T500K	R34K
L505Stop	R443K/I
I506K	S276T/Stop
T542K	S490C
T543N	T25K
A597S	T482K
Q603K	T500K
F615L	T542K
I616K	T543N
G646R/E	T665K
E647K	T81K
T665K	V481I/E
E666K	Y30N/Stop

		E716K	
		A140P	E399K
		A259D/T	G431E
		A387E/S	I187K
		A452E	I218N
		A543E	I547K
		A744D	N432K
		C469Y	Q548K
		C560F	R196K
		C63Stop	R238K
		D175N/E	T39K
		D553V	Y217Stop
		D76N/E	Y381Stop
		E178K/D	Y619Stop
		E383K/V	
		E384K	
		E399K	
		E618K	
		E696Stop	
		E740Stop	
		E748Stop	
		E75K	
		G431E	
		G525E	
		G53E	
		H38Q	
		H745L	
		I201K	
		I357K	
		K185Stop	
		K188Stop	
		K347N	
		K360I	
		K362I/Stop	
		L404F	
		M356I/K	
		N186I	
		N432H/K	
		N535K	
		N581K	
		P138H	
		Q168K	
		Q367K	
		Q544K	
		Q548H/K	
		Q686K	
		R203K	
		R238K	
		R316K	

PB1

2

R380S	
R555M	
R733I	
S291G	
S359N/R	
Stop753L/K	
T301R	
T358K	
T361K	
T385K	
T39K	
T492K	
T64K	
T667N	
T69K	
V252L	
V450F	
Y619N/Stop	
H38Q	A259T/D
T39K	A543E
E75K	D616N
D76N/E	D643N/E
L143Stop	D76N/E
T145K	E277K
V184I/E	E399K
N186K	E75K
I187K	G431E
R196K	G525E
R203K	G53E
V208E	H38Q
I218N	I187K
L236Q	I218N
R238K	I325K
V252L	I427N
A259T/D	I528K
R316K	I529K
R324K	I644K
I325K	L143I/Stop
S359N/R	L236Q
T361K	L779P
N397K	N186K
E398K	N397K
E399K	N432K
I427N	N51K
N432K	Q104K
L436Stop	Q544K
I474K	Q548K
E485K	Q686K
G525E	R203K

T527K	R238K
I528K	R316K
I529K	R324K
Q548K	R722K
S565Y	S359N/R
G569R/E	T145K
R571K	T361K
D616N	T39K
D643E	T64K
I644K	V184I/E
Q686K	V252L
R722K	V450F
T752K	Y217Stop
Stop753K	Y381Stop
Y619N/Stop	
A259T/D	A259T/D
A447S/V	A543E
A543E	D616N
D616N	D643N/E
D643E/N	D76N/E
D76N/E/H	E379K
E379K	E399K
E399K	E75K
E75K/D	G431E
G431E	G525E
G525E	H38Q
I187K	I187K
I218N	I218N
I325K	I325K
I474K	I528K
I528K	I529K
I529K	I644K
I644K	L143I/Stop
L236Q/I	L236Q/I
L436Stop	L378Stop
N186K	L436Stop
N195K	N144K
N432K	N186K
N51K	N432K
N77K	Q544K
Q544K	Q548K
Q548K	Q686K
Q686K	R196K
R196K	R203K
R203K	R238K
R238K	R316K
R324K	R324K
R571K	R571K
R705K	R722K

		R722K	S359N/R
		S359N/R	Stop753K
		Stop753K	T145K
		T145K	T146K
		T20K	T361K
		T361K	T39K
		T39K	T752K
		T752K	V184I/E
		V184I/E	V252L
		V252L	V450F
		Y381N/Stop	Y381N/Stop
		Y619Stop	Y619Stop
		A306T/D	E137K
		C45S	E194K
		C603Stop	E224K
		D109G	E26A
		D261N	E329G
		D670N/E	E621K
		E193K	E65K
		E194K	E70K
		E224K	G622E
		E23K	I375K
		E240K	I38T
		E260K	M376K/I
		E26K	N745K
		E29Stop	Q583K
		E308K	Q595K
		E311K	Q71K
		E333K	R671K
		E378K	Stop727K
		E468K	Stop742K
		E550K	T20K
		E621K	V625E
		E65K	W133Stop
		E70K	Y476N/Stop
		F36I	
		G225E	
		G498C	
		G622R/E	
		G68E	
		I239K	
		I375K	
		I48K	
		L249Stop	
		L35I	
		L466Stop	
		L641F	
		L668I/Stop	
		M376K/I	

PA

2

N332K	
N395K	
N467K	
P322Q	
P534T/Q	
Q566K	
Q71K	
R241K	
R634I	
R671K	
S299Y	
S415N/R	
S436N/R	
T20K	
T414K	
V403D	
V47E	
W133R/Stop	
W259C	
Y476Stop	
Y497F	
Y683F	
D670N/E	E137K
E137K	E165K
E165K	E193K
E193K	E194K
E194K	E26K
E26K	E308K
E308K	E329G
E333K	E333K
E378K	E378K
E65K	E621K
E70K	E65K
E710K	E70K
E726K	G225E
F709L	G622E
G622R/E	I375K
G681E	I38T
I375K	I48K
I48K	M376K/I
L249Stop	N745K
L624I/Q	P322Q
L641F	Q583K
L668I/Stop	Q595K
M376K/I	Q71K
N19K	R241K
N332K	R671K
N395K	S415N/R
N444Y	Stop727K

P254H	Stop742K
P322Q	T20K
P534T/Q	T414K
Q583K	V47E
Q595K	V625E
Q71K	W133Stop
R241K	Y476N/Stop
R438K	
R439K	
R671K	
S415N/R	
Stop727K	
T20K	
T414K	
V443F	
V47E	
V625I/E	
W133Stop	
Y476N/Stop	
D231E	D670E/N
D670N/E	E137K
E137K	E165K
E165K	E176K
E193K	E193K
E194K	E194K
E308K	E26K
E378K	E308K
E65K	E329G
E70K	E468K
E710K	E65K
F709L	E70K
G622R/E	E710K
G681E	F709L
I325K	G622E/R
I347K	G681E
I375K	I38T
I48K	L624I/Q
I723K	L641F
L624I/Q	L668I/Stop
L641F	M376I/K
L668I/Stop	N444Y
M376K/I	N467K
N19K	P322Q
N395K	P534Q
P322Q	Q595K
P534Q	Q71K
Q583K	R241K
Q595K	R438K
Q71K	R439K

HA1		R241K	R671K
		R438K	S415N/R
		R439K	Stop727K
		R671K	T20K
		S415N/R	T414K
		Stop727K	V443F
		T20K	V625E/I
		T414K	W133Stop
		V625I/E	Y476N/Stop
		W133Stop	
		Y476N/Stop	
	1	A154E	E183K
		D100E	E184K
		D185E	N165K
		E183K	N303K
		E184K	T47K
		E86K	
		G218V	
		G258E/R	
		K344Stop	
		L343Stop	
		N303K	
		P171Q	
		P269R	
		P31Q	
		Q186K	
		R101K	
		S148N/R	
		T102K	
		T147N	
		T221S	
		T257K	
		T259K	
		T47K	
	2	D100E	D100E
		D163E	D163E
		E183K	D185E/N
		E184K	E183K
		E232K	E184K
		E235K	E232K
		N164K	E235K
		N165K	N164K
		N303K	N165K
		P36Q	N303K
		Q233K	Q186K
		Q263K	Q233K
		R101K	Q263K
		T102K	R101K
		T234K	S148R

		T37K	T102K
		T47K	T37K
	3		T47K
		D100E	A42E
		D163E	D100E
		E183K	D163E
		E184K	D185E/N
		E232K	E183K
		E235K	E184K
		I7K	E232K
		N164K	E235K
		N165K	N164K
		Q186K	N165K
		Q233K	P36T/Q
		Q263K	Q186K
		R101K	Q233K
		T102K	R101K
		T37K	T102K
		T47K	T234K
			T37K
			T47K
	1	C219F	H142Q
		E105K	I107K
		E43K	I108K
		E82K	I48K
		E97K	T49K
		G106E/R	V217F
		G225E	
		I107K	
		I108K	
		I208F	
		I48K	
		I96K	
		M211L	
		N46K	
		Q42K	
		Q95K	
		S163F	
		S196Y	
		S220Y	
		T49K	
		V131I	
		V200E	
		V209F	
		V217F	
		V60E/I	
		Y210F	
		D215E/N	D215E/N
		E43K	E43K

HA2	2	E97K	E97K
		G106E/R	G106E/R
		G225E	H142N/Q
		H142N/Q	I107K
		I107K	I108K
		I108K	I208F
		I48K	I48K
		I96K	I96K
		M211L	N46K
		N46K	Q42K
		Q42K	Q95K
		Q95K	T49K
		T49K	V200E
		V131I	V217F
		V200E	V60E/I
		V217F	
		Y210F	
		D215E/N	D215E/N
		E43K	E43K
		E97K	E97K
		G106E/R	G106E/R
		H142N/Q	G225E
		I107K	H142N/Q
		I108K	I107K
		I48K	I108K
		I96K	I208F
		N46K	I48K
		Q42K	I96K
		Q95K	M211L
		T49K	N46K
		V131I	Q42K
		V200E	Q95K
		V209F	T49K
		V217F	V209F
		V60E/I	V217F
			Y210F
		A366E	D161E
		D566H	E140K
		E104K	E278K
		E140K	E88K
		E74K	I75K
		E88D	N43K
		G193E	T244N
		G219E	L592V
		G246E	
		G259E	
		I271N	
		I565K	
		I75K	

NP	1	L194Q	
		L558H	
		M94L	
		N499K	
		N563K	
		P326H	
		P72T/Q	
		Q92K	
		R105K	
		R236Stop	
		R325M	
		R373K	
		R482K	
		R483K	
		S212Stop	
		S330N/R	
		S42R	
		S562T	
		Stop561K	
		T122S	
		T73K	
		V138F	
		V328E	
		V355D	
		V481I/E	
		Y560N/Stop	
	2	D161N/E	S42A
		D380E	N43K
		E278K	E74K
		E74K	I75K
		E88K	E88K
		G219E	H147Q
		I75K	N148K
		L194Q	D161N/E
		L372I/Stop	R170K
		L414I/Stop	E176K
		N148K	T180K
		N286K	L194Q
		N43K	G219E
		R105K	E278K
		R304K	N286K
		R373K	S303R
		R482K	L372I/Stop
		R483K	R373K
		S303R	D380E
		S42R	R482K
		Y560N	R483K
			V496D
		Y560N/Stop	

			Stop561K
			S562R
			N563K
3		D15E	S42A
		D161N/E	N43K
		D380E	E74K
		E143K	I75K
		E144K	E88K
		E278K	R105K
		E74K	E143K
		E88K	E144K
		G219E	H147Q
		I169K	N148K
		I75K	D161N/E
		L194Q	R170K
		L403Stop	T180K
		L414I/Stop	L194Q
		N148K	G219E
		N43K	R235K
		P72Q	E278K
		R116K	S303R
		R170K	R304K
		R482K	L372I/Stop
		R483K	R373K
		S42R	D380E
		Stop561K	Q383K
		Y277Stop	L414I/Stop
		Y560N/Stop	Y560N/Stop
			Stop561K
			N563K
		Y30N	T43K
		L38Q	E44K
		S41Stop	I45K
		S42T	G108R/E
		T43K	R147K
		E44K	E148K
		I45K	D149N/E
		E105K	R150K
		G108R/E	N151K
		I115K	I204K
		P124Q	N219K
		G145V	E226K
		R147K	I262K
		E148K	I262K
		R150K	N284K
		N151K	I333K
		K152N	
		P165Q	
		I204K	

NA	1	T213R	
		Y214N	
		L222Q	
		T224K	
		Q225K	
		E226K	
		Y237F	
		L238F	
		I261K	
		I262K	
		P267S	
		E272K	
		E275K	
		E276K	
		N284K	
		A298T/E	
		L305Stop	
		S332R	
		I333K	
		Q355K	
		R356K	
		R367Q	
		T368K	
		I372N	
	2	Stop39K	L38Q
		H42Q	S42T/Stop
		N44Q	T43K
		Stop46K	E44K
		Y86F	I45K
		P107T/Q	L85F
		G108R/E	T106N
		I114K	G108R/E
		I115K	I114K
		D194N/E	I115K
		R150K	D149N
		N151K	R150K
		I204K	N151K
		N219K	I204K
		Y237F	N219K
		L238F	Y237F
		I261K	L238F
		I262K	I261K
		E264K	I262K
		N284K	E264K
		A298T/E	N284K
		L305I/Stop	A298T/E
		I333K	L305T/Stop
		R356K	I333K
		L372Q	R356K

		I415K	I415K
		D417N/E	D417N/E
	3	E418K	
		L38Q	L38Q
		S42T/Stop	S42T/Stop
		T43K	T43K
		E44K	E44K
		I45K	I45K
		L85F	L85F
		G108R/E	G108R/E
		I114K	I114K
		I115K	I115K
		E148K	E148K
		D149E	D149E
		R150K	R150K
		N151K	N151K
		I204K	I204K
		E226K	E226K
		Y237F	Y237F
		I261K	I261K
		I262K	I262K
		E264K	E264K
		N284K	N284K
		L305I/Stop	L305I/Stop
		I333K	I333K
NB	1	I32K	N45K
		F43L	R46K
		I44N	N47K
		N45K	
		R46K	
		N47K	
	2	I44N	I44N
		N45K	N45K
		R46K	R46K
		N47K	N47K
		I88F	I88F
	3	I44N	I44N
		N45K	N45K
		R46K	R46K
		N47K	N47K
		I88F	I88F
		E196K	E23K
		E36K	G191E
		G191E	Q154K
		G193V	T91K
		I46K	
		I55K	
		K68I/Stop	
		L67F/Stop	

M	1	M177L	
		N48K	
		Q154K	
		Q219K	
		Q56K	
		R74K	
		S218R	
		T88K	
		T91K	
	2	A22E	A22E
		A25E/T	A25E/T
		E23K	D71Y
		E26K	E23K
		I46K	E26K
		L24I/Q	G191E
		N48K	I46K
		Q154K	K68I/Stop
		Q219K	L24I/Q
		R74K	L67F
		S218R	N48K
		T88K	Q154K
		T91K	Q219K
			S218R
			T88K
			T91K
	3	A22E	A22E
		A25E/T	A25E/T
		E23K	A90E
		E26K	D71Y
		G191E	E23K
		I46K	E26K
		K68I/Stop	G191E
		L24Q	I46K
		L67F	K68I/Stop
		N48K	L24I/Q
		Q154K	L67F
		Q219K	N48K
		R101K	Q154K
		R74K	Q219K
		S218R	R101K
		T88K	S218R
		T91K	T88K
			T91K
		E104Stop	D47E
		E63K	E106K
		E79D	E107K
		E93D	L15Stop
		H19N	T48K
		H84Q	

MB	1	I14F	
		I49K	
		I95K	
		I96K	
		L103F	
		M37I	
		Q61K	
		S91F	
		T48K	
		T69K	
		Y60Stop	
	2	E63K	C11F
		I49K	D47E
		L10F	E106K
		M37I	E107K
		Q61K	I49K
		R106K	L114Stop
		R107K	L15Stop
		T48K	M37I
		Y60Stop	Q61K
			T48K
			Y60Stop
	3	D47E	D47E
		E63K	E106K
		L15Stop	E107K
		M37I	E63K
		N48K	I49K
		Q61K	L110Stop
		R106K	M37I
		R107K	Q61K
		T48K	T48K
		Y60Stop	Y60Stop
	1	A257E/G	L51Q
		A258S	N151K
		A95S	N152K
		E144K	R53K
		E168K	R58K
		E245D	V163I/E
		E249D	E259K
		E32K	
		F100V	
		I159K	
		I175K	
		I255L	
		K253N	
		L185F	
		N152K	
		P142Q	
		P254Q	

NS1		Q157K	
		R217T	
		S252Stop	
		T174K	
		T260S	
		V163I/E	
		V262G	
		V82I/E	
		W36R/C	
		Y116Stop	
		Y121C	
		Y31Stop	
	2	E168K	E259K
		I159K	I159K
		I175K	I175K
		I59K	I59K
		L51I/Q	L51I/Q
		N151K	N151K
		N152K	N152K
		R53K	R53K
		R58K	R58K
		S57Stop	S57Stop
		S69N/R	S69R
	3	E168K	E259K
		I159K	I159K
		I175K	I175K
		I59K	I59K
		L51I/Q	L51I/Q
		N151K	N151K
		N152K	N152K
		Q214K	R53K
		R53K	R58K
		R58K	S57Stop
		S57Stop	S69N/R
		S69N/R	V163I
		V163I/E	
NS1	1	D78Y	D79E
		D79E/N	I93K
		D96Y	
		F37Y	
		I93K	
		K31T	
		K41N	
		L29Stop	
		L82F	
		Q34L/K	
		Q36H/K	
		Q39K/E/H	
		R76K	

		S27I	
		S35I	
		V87E	
		W44G	
	2	D79E	D79E
		E259K	I93K
		I93K	L72F
		L73F	L73F
		Y71F	Y71F
	3	D79E	D79E
			I93K

* Bolded substitutions indicate common substitutions between WT and mutant virus

† N/A: Not applicable; No substitutions were observed in the viral protein after passage