Supplementary material for:

Incipient functional SARS-CoV-2 diversification identified through neural network haplotype maps

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Figure S1

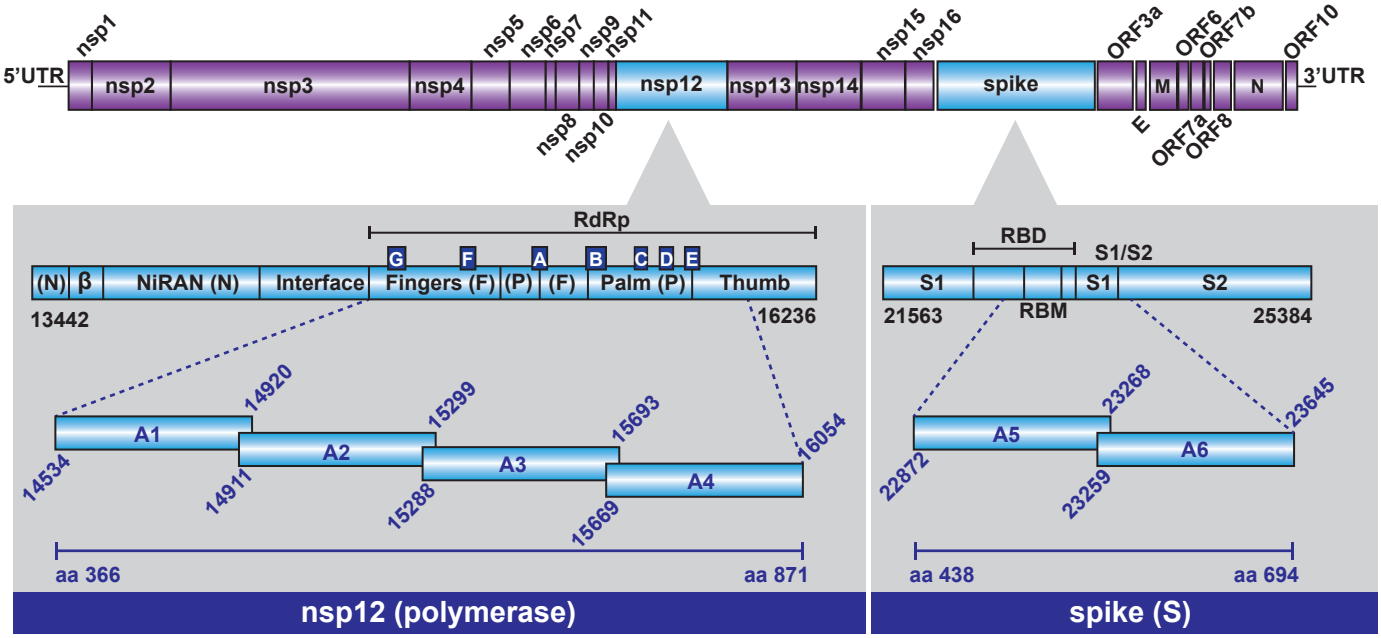
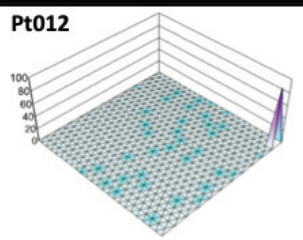


Figure S1. Representation of the SARS-CoV-2 genome and amplicons analyzed by UDS. Top: Scheme of the SARS-CoV-2 genome with location of untranslated regions (UTRs) and encoded proteins. Bottom panels: Amplicons of the nsp12-coding region (left) and of the S-coding region (right), with indication of the relevant nucleotide and amino acid residue numbers (taking as reference the genome with NCBI accession number NC_045512.2), and major functional domains of viral proteins. Scheme based on V'Kovski *et al.*, 2021, Nat Rev Microbiol 19(3):155-170 and Lamkiewicz *et al.*, 2023, Curr Top Microbiol Immunol 439:305-339.

nsp12 A1

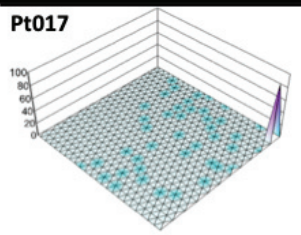
Wu

Pt012



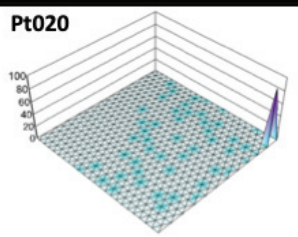
41 haplotypes. 38 peaks

Pt017



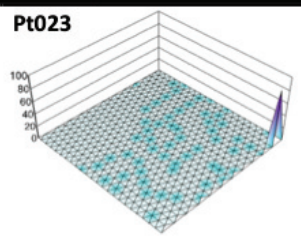
51 haplotypes. 44 peaks

Pt020



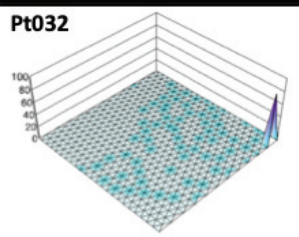
61 haplotypes. 52 peaks

Pt023



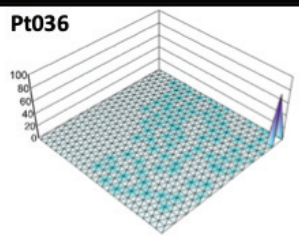
72 haplotypes.62 peaks

Pt032



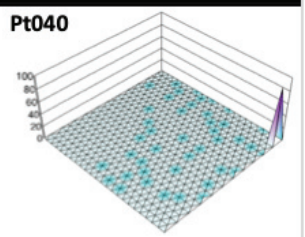
92 haplotypes.72 peaks

Pt036



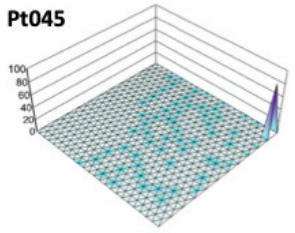
110 haplotypes. 81 peaks

Pt040



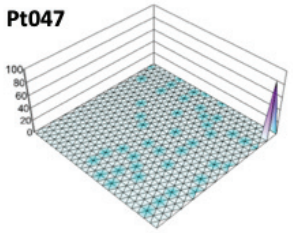
49 haplotypes. 44 peaks

Pt045



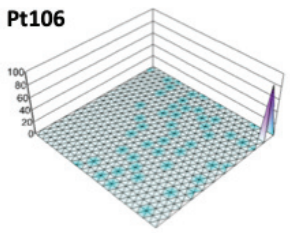
73 haplotypes. 63 peaks

Pt047



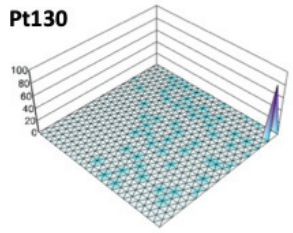
49 haplotypes. 45 peaks

Pt106



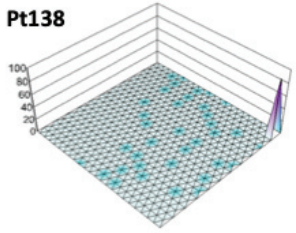
58 haplotypes. 51 peaks

Pt130



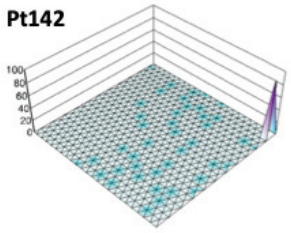
71 haplotypes. 60 peaks

Pt138



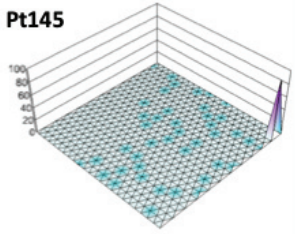
43 haplotypes. 38 peaks

Pt142



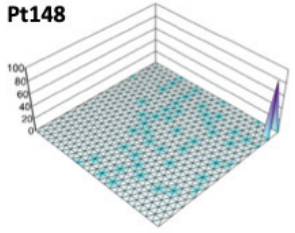
50 haplotypes. 44 peaks

Pt145



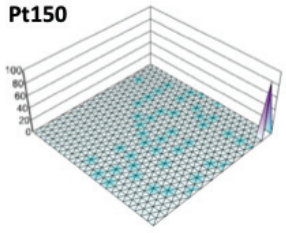
48 haplotypes. 44 peaks

Pt148



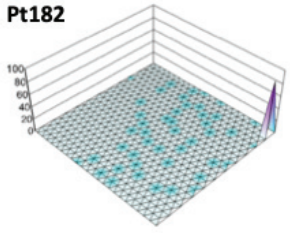
56 haplotypes. 51 peaks

Pt150



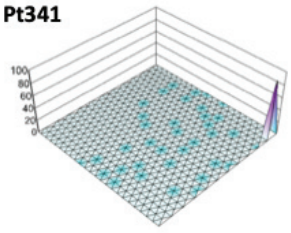
51 haplotypes. 45 peaks

Pt182



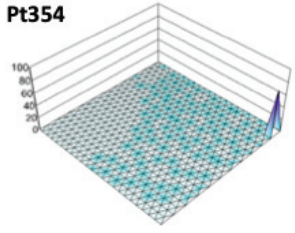
55 haplotypes. 47 peaks

Pt341



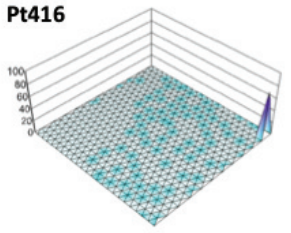
43 haplotypes. 38 peaks

Pt354



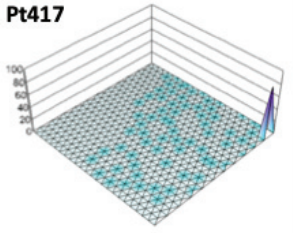
135 haplotypes. 97 peaks

Pt416



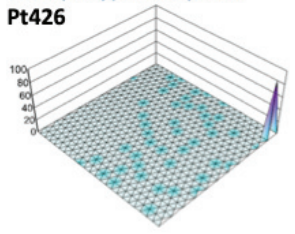
105 haplotypes. 83 peaks

Pt417



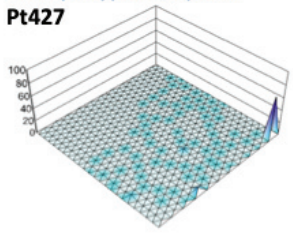
89 haplotypes. 73 peaks

Pt426



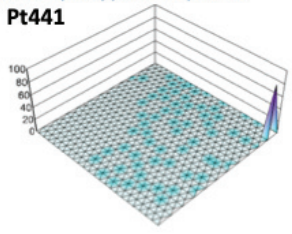
52 haplotypes. 48 peaks

Pt427



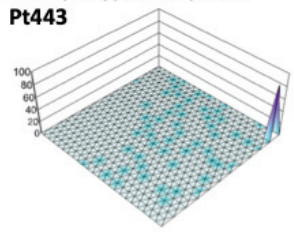
94 haplotypes. 77 peaks

Pt441



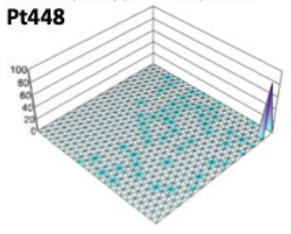
79 haplotypes. 68 peaks

Pt443



66 haplotypes. 58 peaks

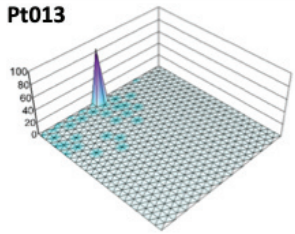
Pt448



61 haplotypes. 55 peaks

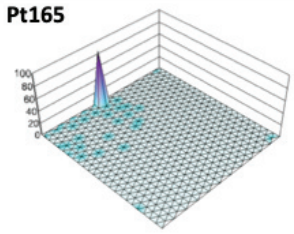
Wu-Mutant(1)

Pt013



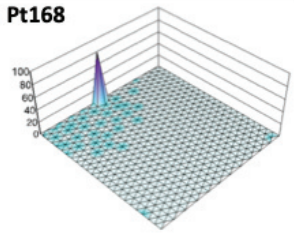
51 haplotypes. 32 peaks

Pt165



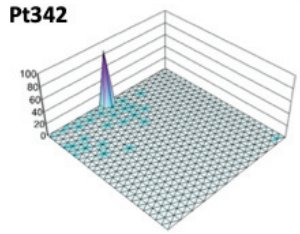
50 haplotypes. 33 peaks

Pt168



71 haplotypes. 40 peaks

Pt342



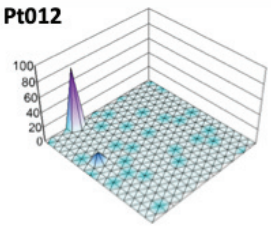
42 haplotypes. 31 peaks

Figure S2

nsp12 A2

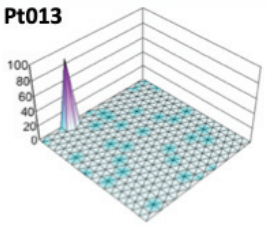
Wu

Pt012



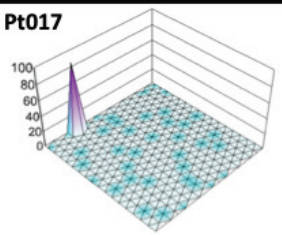
34 haplotypes. 31 peaks

Pt013



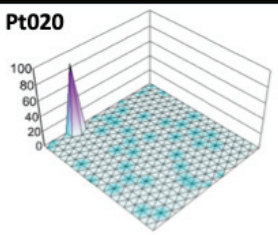
38 haplotypes. 32 peaks

Pt017



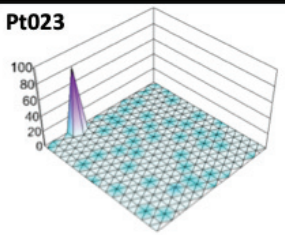
45 haplotypes. 40 peaks

Pt020



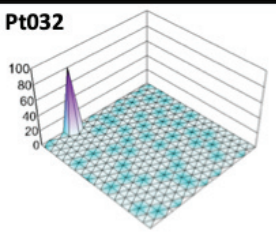
48 haplotypes. 41 peaks

Pt023



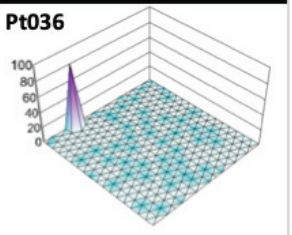
59 haplotypes.49 peaks

Pt032



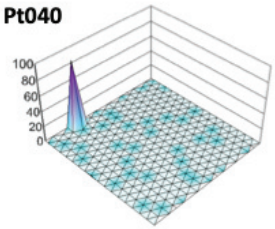
66 haplotypes.54 peaks

Pt036



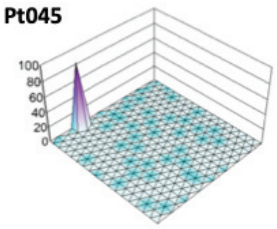
66 haplotypes. 53 peaks

Pt040



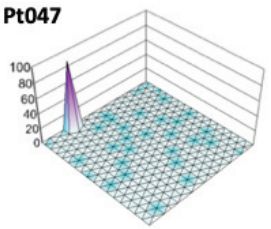
47 haplotypes. 42 peaks

Pt045



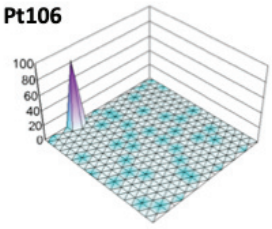
58 haplotypes. 49 peaks

Pt047



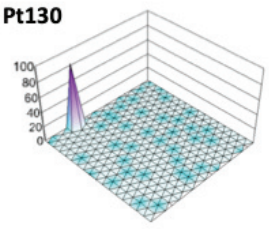
37 haplotypes. 33 peaks

Pt106



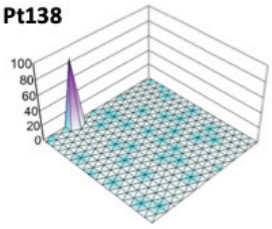
51 haplotypes. 42 peaks

Pt130



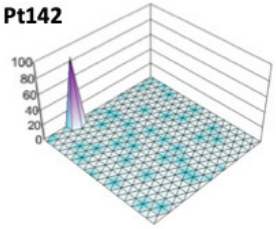
54 haplotypes. 45 peaks

Pt138



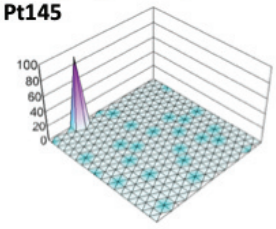
44 haplotypes. 38 peaks

Pt142



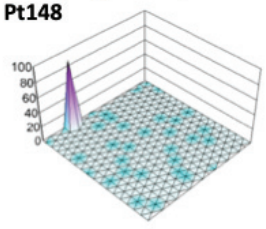
49 haplotypes. 43 peaks

Pt145



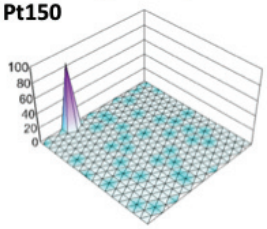
29 haplotypes. 27 peaks

Pt148



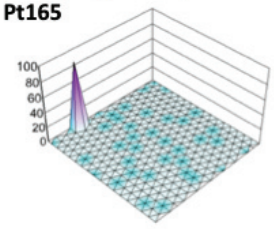
38 haplotypes. 34 peaks

Pt150



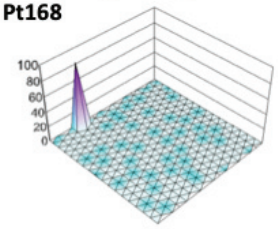
50 haplotypes. 42 peaks

Pt165



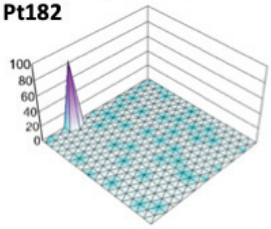
45 haplotypes. 40 peaks

Pt168



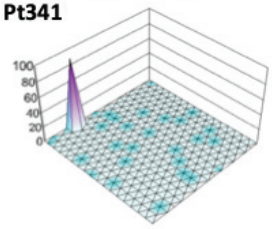
57 haplotypes. 49 peaks

Pt182



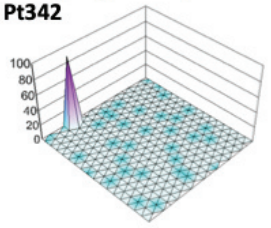
52 haplotypes. 44 peaks

Pt341



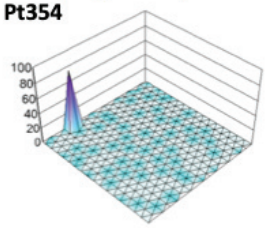
34 haplotypes. 30 peaks

Pt342



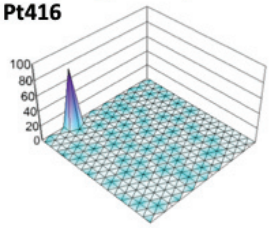
39 haplotypes. 36 peaks

Pt354



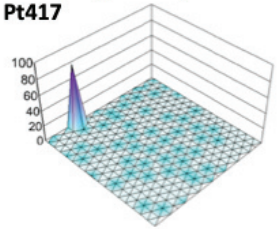
87 haplotypes. 63 peaks

Pt416



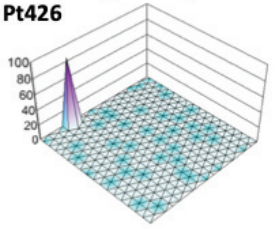
84 haplotypes. 66 peaks

Pt417



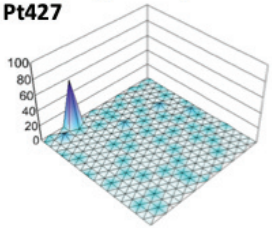
76 haplotypes. 58 peaks

Pt426



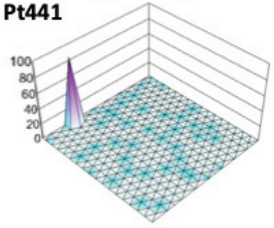
49 haplotypes. 43 peaks

Pt427



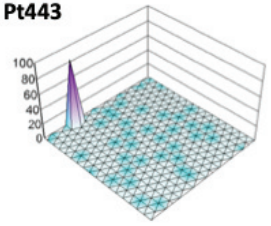
74 haplotypes. 57 peaks

Pt441



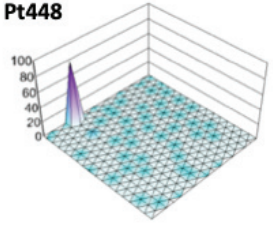
52 haplotypes. 44 peaks

Pt443



53 haplotypes. 44 peaks

Pt448

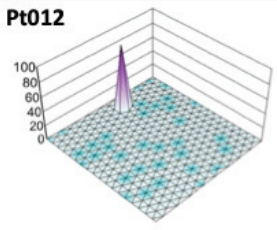


63 haplotypes. 51 peaks

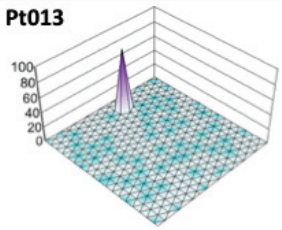
Figure S3

Wu

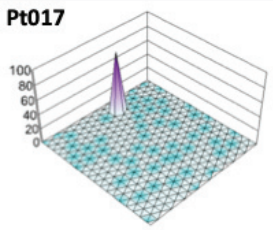
nsp12 A3



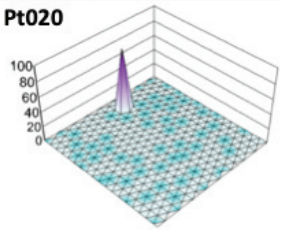
40 haplotypes. 35 peaks



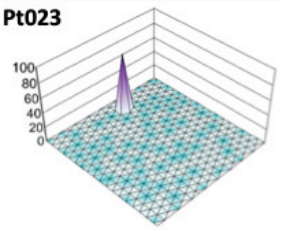
69 haplotypes. 58 peaks



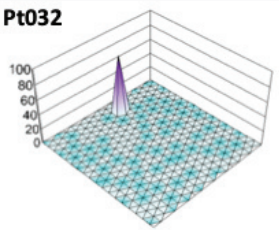
64 haplotypes. 55 peaks



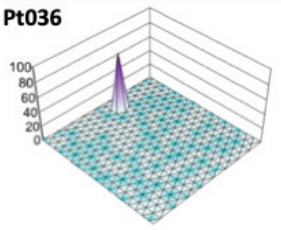
74 haplotypes. 60 peaks



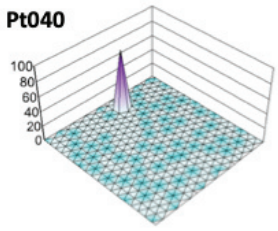
87 haplotypes. 69 peaks



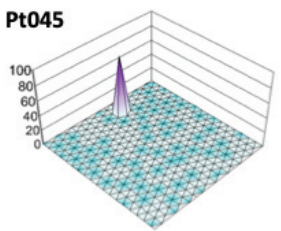
91 haplotypes. 70 peaks



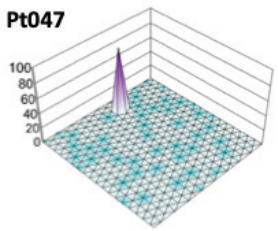
91 haplotypes. 72 peaks



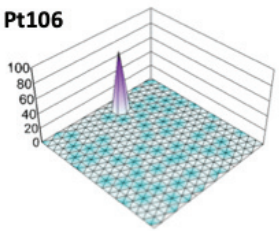
82 haplotypes. 65 peaks



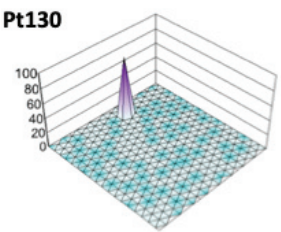
89 haplotypes. 70 peaks



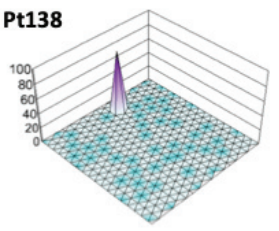
58 haplotypes. 48 peaks



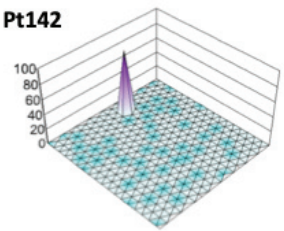
77 haplotypes. 64 peaks



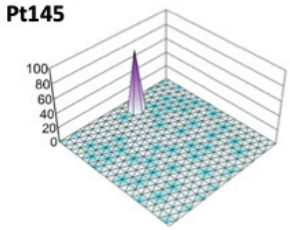
77 haplotypes. 64 peaks



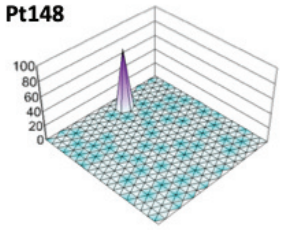
67 haplotypes. 54 peaks



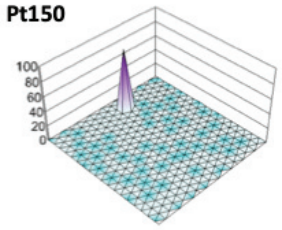
66 haplotypes. 50 peaks



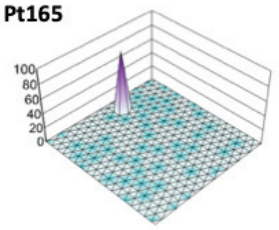
64 haplotypes. 52 peaks



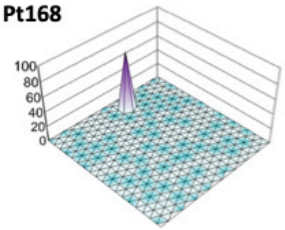
72 haplotypes. 59 peaks



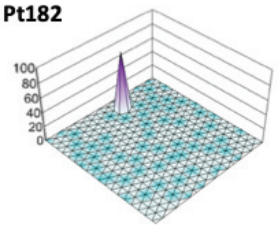
73 haplotypes. 59 peaks



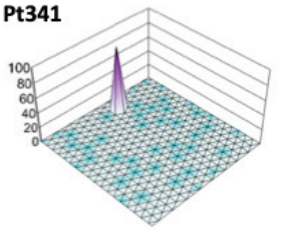
67 haplotypes. 54 peaks



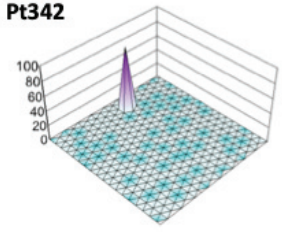
86 haplotypes. 67 peaks



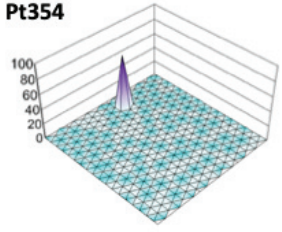
78 haplotypes. 63 peaks



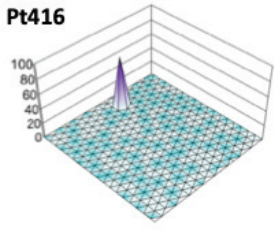
51 haplotypes. 43 peaks



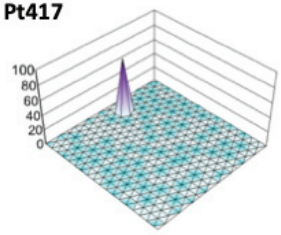
62 haplotypes. 54 peaks



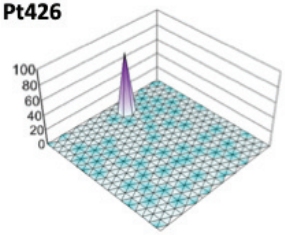
119 haplotypes. 84 peaks



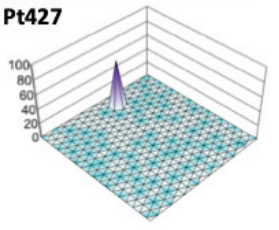
109 haplotypes. 79 peaks



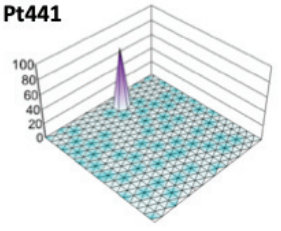
104 haplotypes. 77 peaks



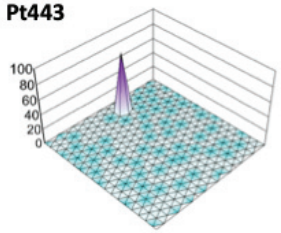
74 haplotypes. 60 peaks



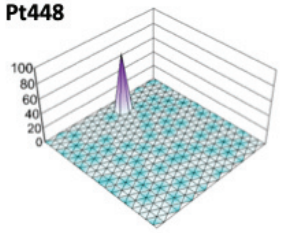
98 haplotypes. 77 peaks



77 haplotypes. 63 peaks



81 haplotypes. 68 peaks



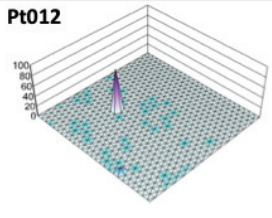
86 haplotypes. 70 peaks

Figure S4

nsp12 A4

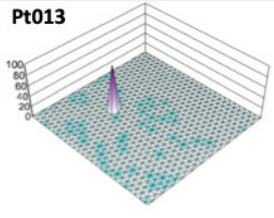
Wu

Pt012



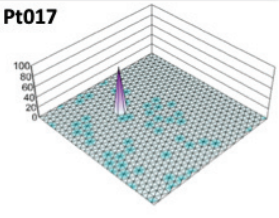
43 haplotypes. 42 peaks

Pt013



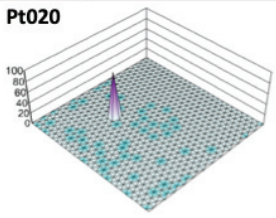
52 haplotypes. 52 peaks

Pt017



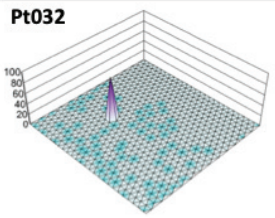
53 haplotypes. 51 peaks

Pt020



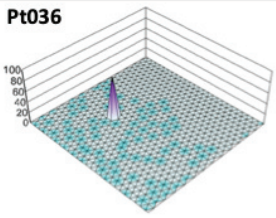
58 haplotypes. 56 peaks

Pt032



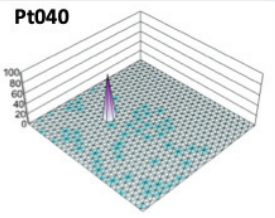
81 haplotypes. 75 peaks

Pt036



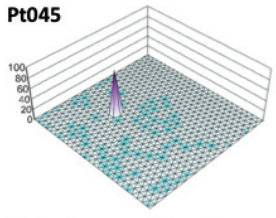
99 haplotypes. 86 peaks

Pt040



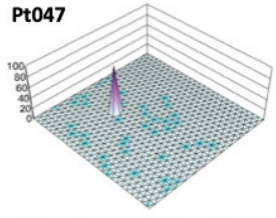
58 haplotypes. 56 peaks

Pt045



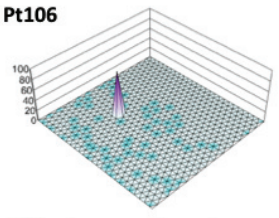
70 haplotypes. 66 peaks

Pt047



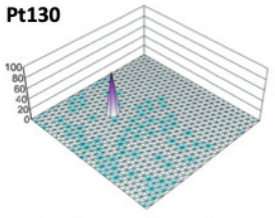
41 haplotypes. 41 peaks

Pt106



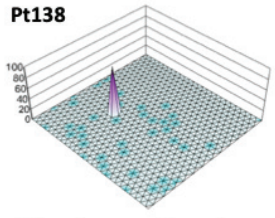
66 haplotypes. 64 peaks

Pt130



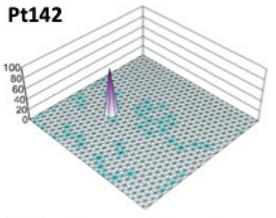
81 haplotypes. 73 peaks

Pt138



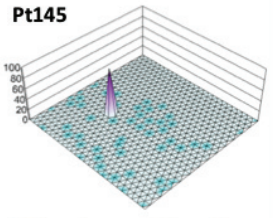
41 haplotypes. 41 peaks

Pt142



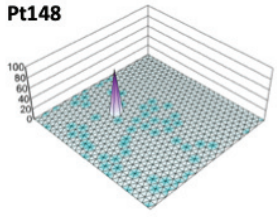
50 haplotypes. 48 peaks

Pt145



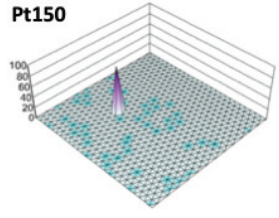
56 haplotypes. 53 peaks

Pt148



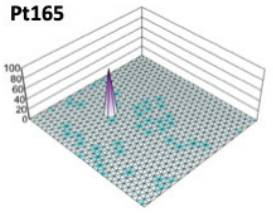
64 haplotypes. 61 peaks

Pt150



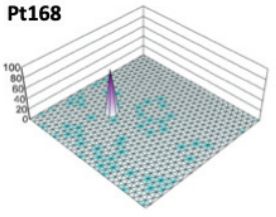
53 haplotypes. 50 peaks

Pt165



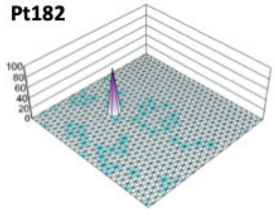
46 haplotypes. 46 peaks

Pt168



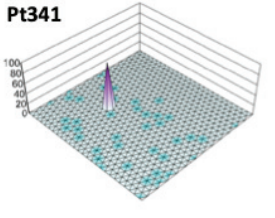
62 haplotypes. 57 peaks

Pt182



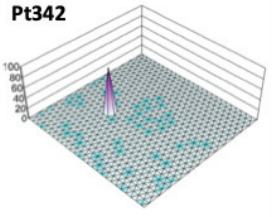
57 haplotypes. 55 peaks

Pt341



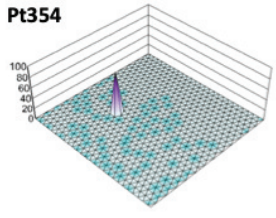
41 haplotypes. 41 peaks

Pt342



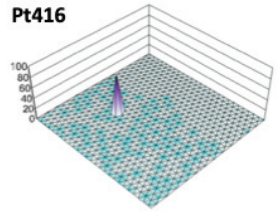
50 haplotypes. 49 peaks

Pt354



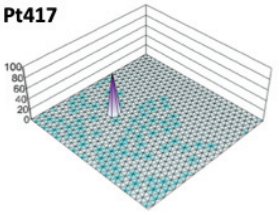
88 haplotypes. 79 peaks

Pt416



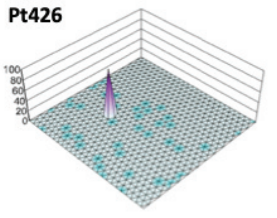
108 haplotypes. 94 peaks

Pt417



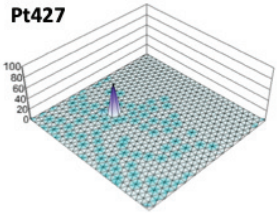
90 haplotypes. 82 peaks

Pt426



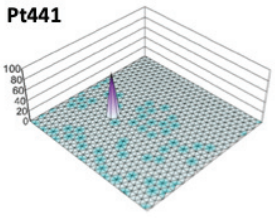
41 haplotypes. 41 peaks

Pt427



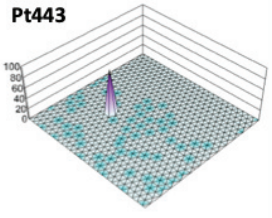
99 haplotypes. 87 peaks

Pt441



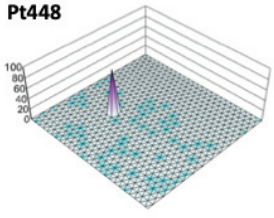
74 haplotypes. 64 peaks

Pt443



68 haplotypes. 64 peaks

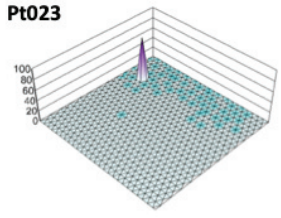
Pt448



62 haplotypes. 59 peaks

Wu-Mutant(2)

Pt023



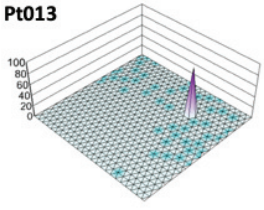
71 haplotypes. 56 peaks

Figure S5

spike A5

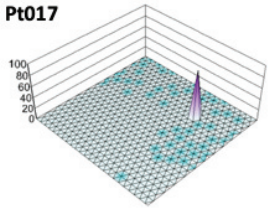
Wu

Pt013



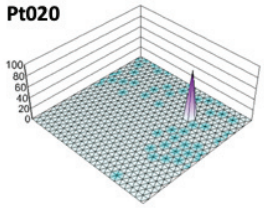
53 haplotypes. 48 peaks

Pt017



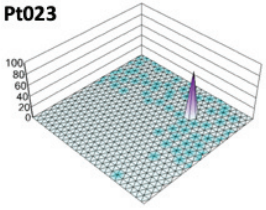
61 haplotypes. 53 peaks

Pt020



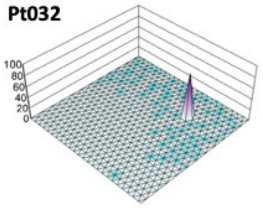
55 haplotypes. 50 peaks

Pt023



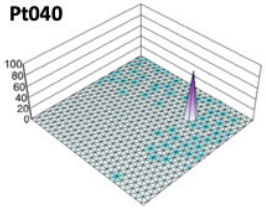
76 haplotypes. 65 peaks

Pt032



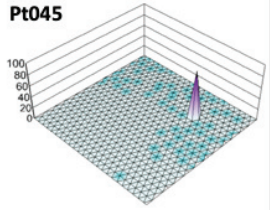
81 haplotypes. 67 peaks

Pt040



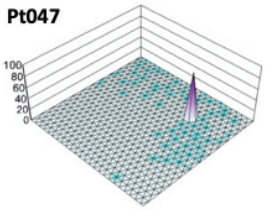
65 haplotypes. 57 peaks

Pt045



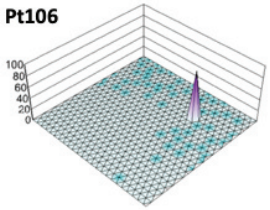
71 haplotypes. 60 peaks

Pt047



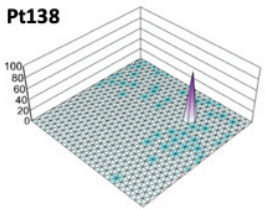
70 haplotypes. 60 peaks

Pt106



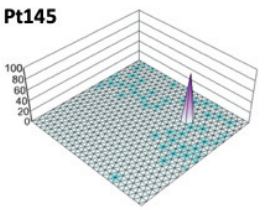
62 haplotypes. 54 peaks

Pt138



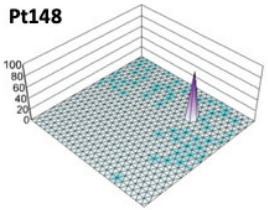
53 haplotypes. 49 peaks

Pt145



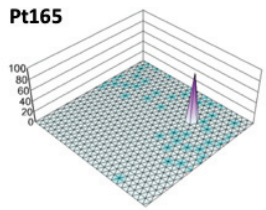
53 haplotypes. 49 peaks

Pt148



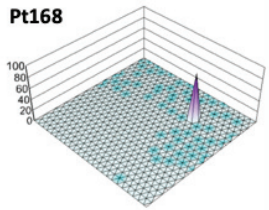
63 haplotypes. 57 peaks

Pt165



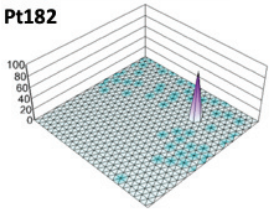
49 haplotypes. 45 peaks

Pt168



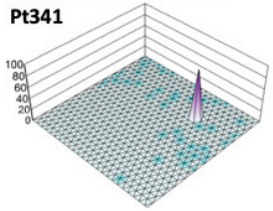
72 haplotypes. 62 peaks

Pt182



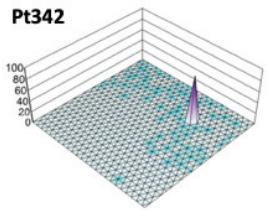
61 haplotypes. 54 peaks

Pt341



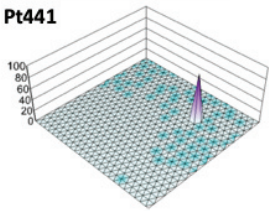
47 haplotypes. 43 peaks

Pt342



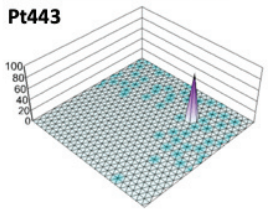
81 haplotypes. 67 peaks

Pt441



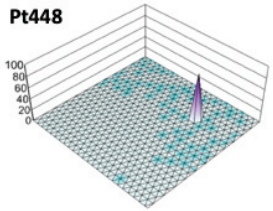
74 haplotypes. 64 peaks

Pt443



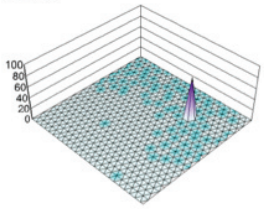
69 haplotypes. 58 peaks

Pt448



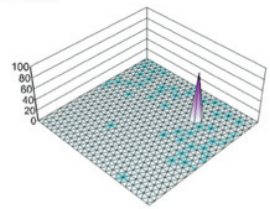
79 haplotypes. 65 peaks

Pt130



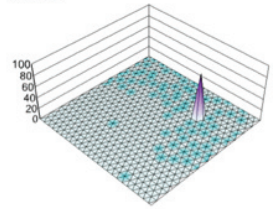
111 haplotypes. 85 peaks

Pt142



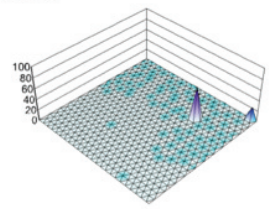
57 haplotypes. 50 peaks

Pt150



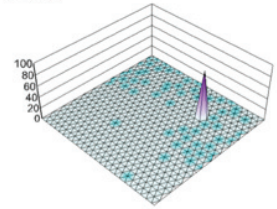
88 haplotypes. 74 peaks

Pt354



100 haplotypes. 81 peaks

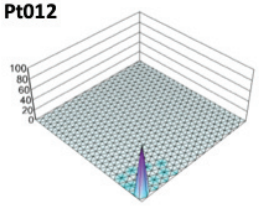
Pt426



68 haplotypes. 60 peaks

Wu-Mutant(3)

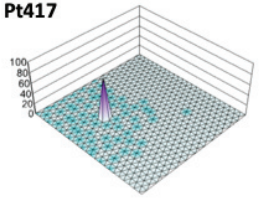
Pt012



39 haplotypes. 16 peaks

Wu-Mutant(4)

Pt417

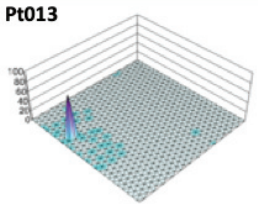


93 haplotypes. 66 peaks

Figure S6

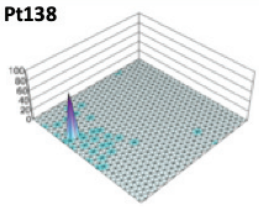
Spike A6

Wu



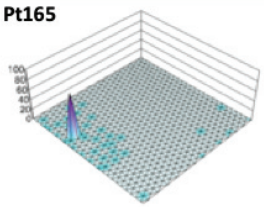
Pt013

56 haplotypes. 38 peaks



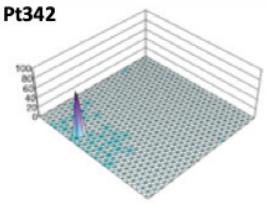
Pt138

46 haplotypes. 33 peaks



Pt165

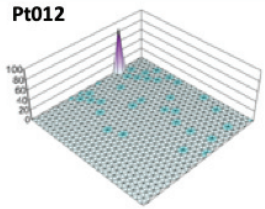
50 haplotypes. 40 peaks



Pt342

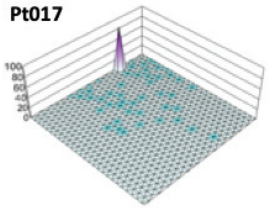
48 haplotypes. 33 peaks

Wu-Mutant(5)



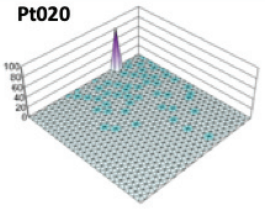
Pt012

37 haplotypes. 35 peaks



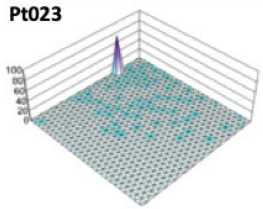
Pt017

57 haplotypes. 50 peaks



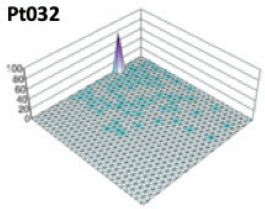
Pt020

66 haplotypes. 53 peaks



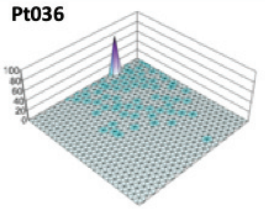
Pt023

93 haplotypes. 73 peaks



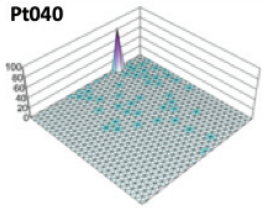
Pt032

90 haplotypes. 69 peaks



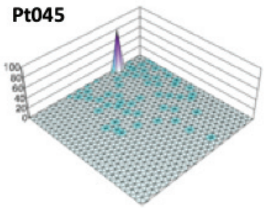
Pt036

100 haplotypes. 70 peaks



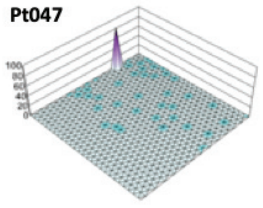
Pt040

60 haplotypes. 51 peaks



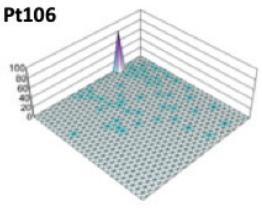
Pt045

77 haplotypes. 59 peaks



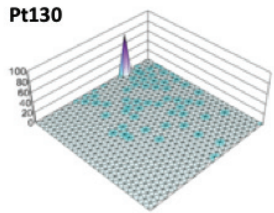
Pt047

50 haplotypes. 44 peaks



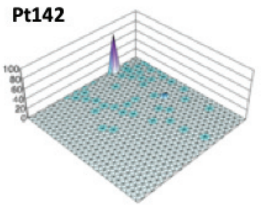
Pt106

67 haplotypes. 57 peaks



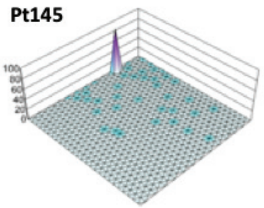
Pt130

79 haplotypes. 62 peaks



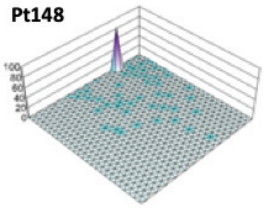
Pt142

55 haplotypes. 48 peaks



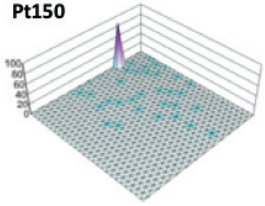
Pt145

48 haplotypes. 43 peaks



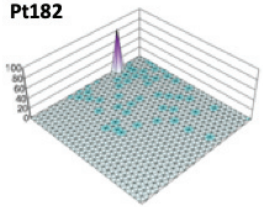
Pt148

63 haplotypes. 53 peaks



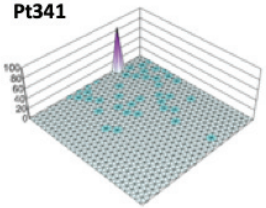
Pt150

46 haplotypes. 40 peaks



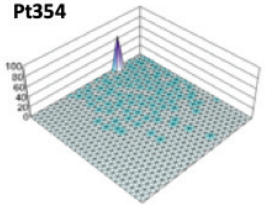
Pt182

59 haplotypes. 53 peaks



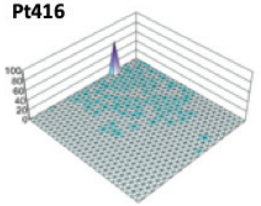
Pt341

45 haplotypes. 40 peaks



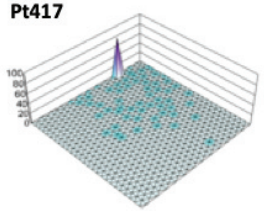
Pt354

139 haplotypes. 94 peaks



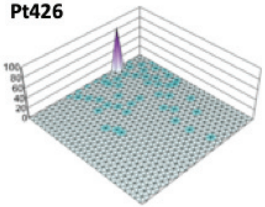
Pt416

110 haplotypes. 82 peaks



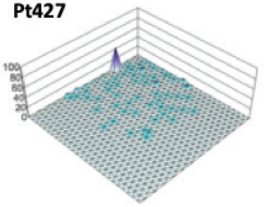
Pt417

88 haplotypes. 63 peaks



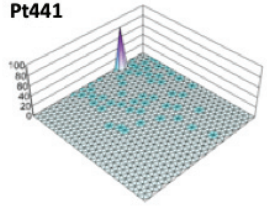
Pt426

59 haplotypes. 50 peaks



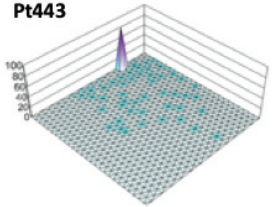
Pt427

79 haplotypes. 63 peaks



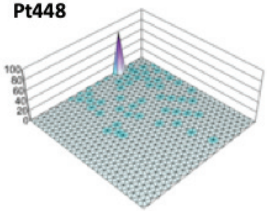
Pt441

67 haplotypes. 55 peaks



Pt443

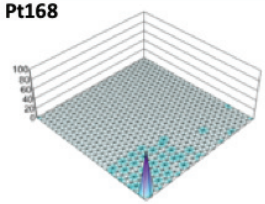
71 haplotypes. 57 peaks



Pt448

73 haplotypes. 56 peaks

Wu-mutant(6)



Pt168

74 haplotypes. 42 peaks

Figure S7

Figures S2 to S7. SOM-derived haplotype maps for each individual amplicon-patient. The coding region and the amplicon number are indicated in the top filled boxes. Patients (Pt) are divided according to the SOM classes that are indicated in the boxes at the left of each panel.

Figure S8

nsp12 A1

Master neuron Wu

Master neuron Wu-Mutant (1)

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	
1		1;1				23;3		5;1			39;2			27;2				10;3		16;1	6;1		41;6	1
2	5;2				20;2			13;3		52;2			8;3			1;1	2;2						29;1	2
3						26;1					1;1			11;1					1;1		6;2		18;3	3
4					2;2			6;1		43;2			29;2			31;2		1;1						4
5		5;2				26;1					16;1			27;2			3;1		39;3		25;2		42;3	5
6	13;2				2;2			15;3		18;1			3;1			27;2								6
7			2;1			13;2		4;1			22;2						23;1			12;1			15;4	7
8	1;1		2;1							15;1				2;1		3;2			3;1			3;2		8
9			1;1			26;1		3;2			15;2	18;1								4;2				9
10						4;1				16;1				32;3			26;1		11;3				27;2	10
11		4;1		7;2				26;1				2;2			5;1					10;1	26;1			11
12	7;3			5;2		9;3		4;1		50;2				13;1			53;3		2;1				1;1	12
13	5;1	10;4						1;1			17;1									1;1				13
14	18;6			4;1		5;2				16;1			29;2		18;1		2;1		1;1			27;2		14
15		4;2					1;1				1;1						38;2			7;1			1;1	15
16	10;3				3;2				1;1							4;1			1;1				25;1	16
17		4;1					6;2			4;1	26;1		24;1				1;1						1;1	17
18	11;3			1;1		1;1			1;1						26;1						26;1		2;1	18
19		4;1					2;1			9;1						49;2			21;1					19
20	4;1		1;1		5;2				4;1			2;1		26;1				10;2			12;1			20
21	10;3					8;3				25;1						6;1			2;1					21
22			3;2		4;1			1;1					26;1		26;1			2;1			7;1		1;1	22
23	16;5			8;2		4;1			16;1		2;1		1;1		1;1		1;1		1;1	1;1	1;1		1;1	23
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	

nsp12 A2

Master neuron Wu

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	
1	58; 4		30; 2		2; 1		1; 1				1; 1		1; 1					1
2					16; 1		3; 1		30; 1	1; 1								2
3	25; 1		5; 1									29; 1					14; 2	3
4	6; 1					5; 2			30; 1		17; 1			30; 1				4
5		13; 1	1; 1				58; 2					33; 2			4; 1			5
6	30; 3				30; 3					25; 2					1; 1			6
7		16, 1	1; 1			8; 1							1; 1				27; 2	7
8	1; 1							55; 2		17; 1		31; 2				5; 1		8
9		30; 1	28; 1		60; 2								30; 1				18; 2	9
10	37; 3						16; 1			3; 1		13; 1			25; 1	29; 1		10
11			35; 2		1; 1			48; 3					8; 1				1; 1	11
12	21; 2						38; 2				7; 1				2; 2			12
13	30; 1	5; 2		1; 1					30; 1			39; 4				1; 1	11; 1	13
14	37; 4					10; 2		1; 1			24; 1			1; 1	1; 1			14
15		1; 1		7; 1			2; 1		1; 1			1; 1				30; 1		15
16	19; 1		1; 1			30; 1					56; 2				27; 2			16
17	44; 3			5; 3		1; 1		48; 3					2; 2				1; 1	17
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	

Neurons that include haplotypes that belong to the SOM class Wu

Neurons that include haplotypes that belong to the SOM class Wu-Mutant (1)

Neurons that include haplotypes that belong to both SOM classes

SOM class Wu-Mutant (1) refers to SOMs whose haplotype in the master neuron differed from Wuhan-Hu-1 in mutation C14805T (Syn).
Found in patients Pt013, Pt165, Pt168 and Pt342

nsp12 A3

Master neuron Wu

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	
1	21; 3		31; 2		15; 1			73; 3			26; 2		9; 2		23; 1			2; 2	1
2	31; 2						27; 2			25; 2									2
3		7; 2			30; 1			5; 1				28; 1				16; 1	1; 1	1; 1	3
4	59; 2			25; 2			45; 2				1; 1				28; 1				4
5		11; 2			32; 2				59; 2			29; 1				30; 1		9; 1	5
6	18; 2			30; 1				26; 1			1; 1				18; 1			1; 1	6
7		28; 1			30; 1				18; 1				32; 2						7
8			30; 1				53; 2					30; 1				3; 1		30; 1	8
9	1; 1			20; 2				24; 1	2; 2				30; 1						9
10	6; 1		27; 2				1; 1				34; 2		24; 1			60; 2			10
11				3; 1					24; 1					1; 1				32; 3	11
12	2; 2		1; 1					5; 1					30; 1			24; 1			12
13					55; 2					29; 1								16; 1	13
14	1; 1			2; 1			47; 2		33; 2			29; 1			29; 2		20; 1		14
15		27; 2			30; 1					1; 1			19; 1					31; 3	15
16	61; 3			29; 1			54; 2		4; 1			60; 2			30; 1		1; 1		16
17		2; 1			29; 1			13; 1		20; 1								2; 1	17
18	69; 4			21; 2			85; 3			13; 2		4; 1		31; 2		3; 2		35; 3	18
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	

nsp12 A4

Master neuron Wu-Mutant (2)

Master neuron Wu

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y	Z	
1		2; 2		1; 1			1; 1		2; 2		1; 1			1; 1		2; 2		1; 1			1; 1					22; 2	1
2	3; 3					1; 1							2; 2		1; 1					1; 1			1; 1				2
3			1; 1				1; 1	1; 1		2; 2						1; 1					1; 1					1; 1	3
4	2; 2					2; 2							3; 3		1; 1			1; 1		1; 1			1; 1				4
5		1; 1		1; 1				2; 2			1; 1					1; 1					1; 1					23; 1	5
6	2; 2					1; 1				1; 1			1; 1		1; 1			1; 1		1; 1				1; 1			6
7				1; 1			1; 1										1; 1				2; 2						7
8	1; 1		1; 1			2; 2			1; 1			12; 1															8
9	1; 1												29; 1				1; 1		1; 1							1; 1	9
10				1; 1		1; 1					26; 1					28; 1											10
11	30; 2							2; 1				24; 1					27; 1			3; 1				29; 1			11
12			3; 1			29; 1					35; 2					29; 1							25; 1			1; 1	12
13	26; 2			39; 2					1; 1			29; 1		32; 2			26; 1							2; 1			13
14								32; 2			1; 1									23; 2		29; 1					14
15		2; 1		2; 2		7; 1						18; 1		27; 1		29; 1		1; 1						12; 1		1; 1	15
16	27; 3			2; 1					30; 1		2; 1									10; 2		2; 1					16
17		25; 1			2; 1		2; 1			29; 1			8; 1		6; 1			1; 1						1; 1			17
18	34; 2			26; 1					4; 1								3; 1				16; 1		5; 1			17; 1	18
19		28; 1			2; 1		12; 1			2; 1				22; 2					10; 2								19
20	1; 1			7; 1					1; 1				1; 1		29; 1			12; 1				1; 1				31; 2	20
21						4; 1				5; 1						29; 1				1; 1				28; 1			21
22	39; 2		1; 1		2; 1			21; 1				6; 1			3; 1				1; 1				14; 1			28; 1	22
23				6; 2		29; 1			29; 1				17; 1			14; 1				29; 1				18; 1			23
24	20; 2		4; 1					30; 2			29; 1	5; 1			29; 1			13; 1				2; 1				7; 1	24
25					6; 2											30; 2			16; 2					2; 2			25
26	1; 1	12; 1		36; 3			15; 1		1; 1		5; 1		42; 3		1; 1			29; 1		3; 1		24; 2				38; 2	26
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y	Z	

Neurons that include haplotypes that belong to the SOM class Wu

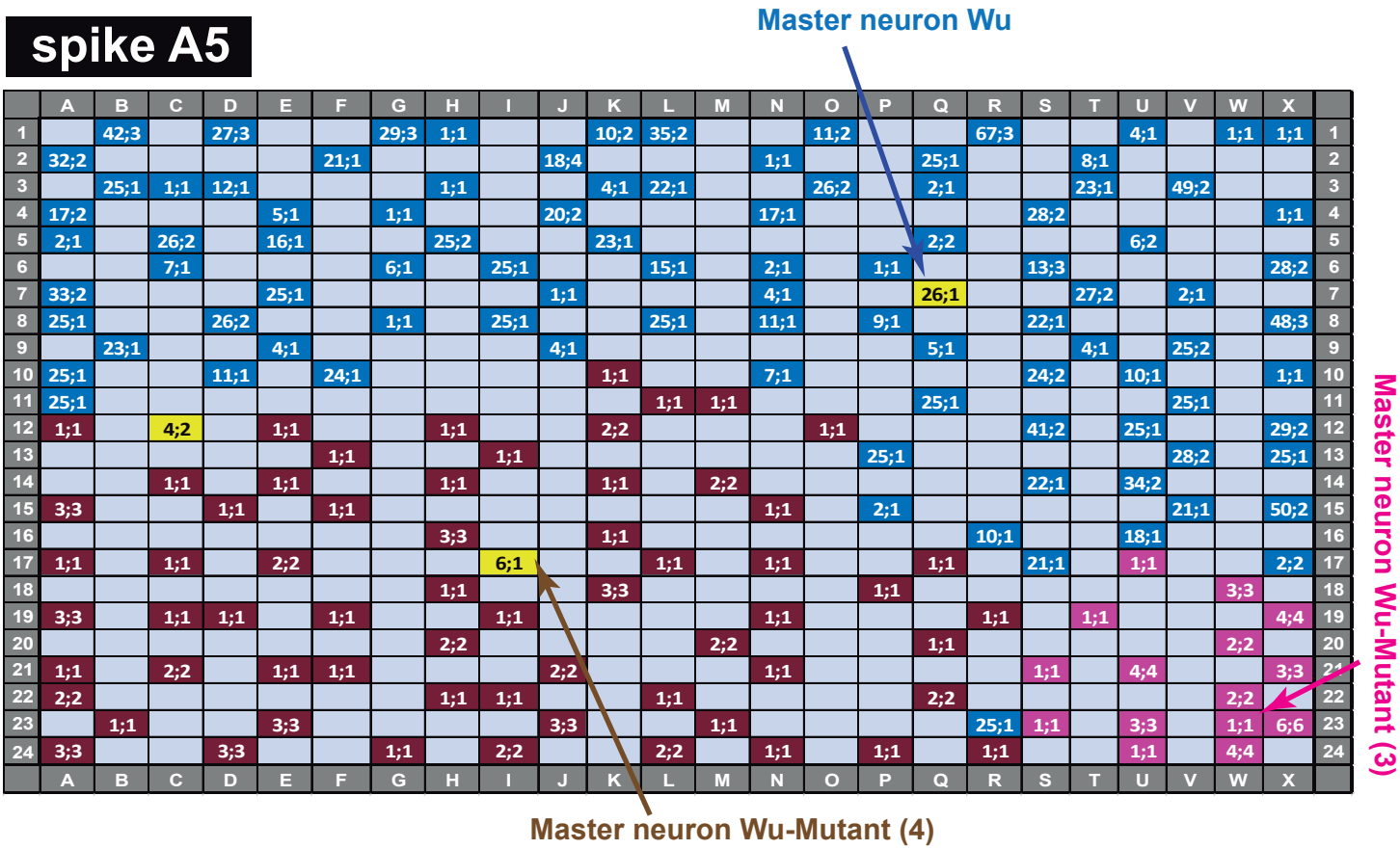
Neurons that include haplotypes that belong to the SOM class Wu-Mutant (2)

Neurons that include haplotypes that belong to both SOM classes

SOM class Wu-Mutant (2) refers to SOMs whose haplotype in the master neuron differed from Wuhan-Hu-1 in mutation G15906T (Q822H).
Found in patient Pt023

Figure S8 (*continued 2*)

spike A5



	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	
1		42;3		27;3			29;3	1;1			10;2	35;2			11;2			67;3			4;1		1;1	1;1	1
2	32;2					21;1				18;4				1;1			25;1			8;1					2
3		25;1	1;1	12;1				1;1			4;1	22;1			26;2		2;1			23;1		49;2			3
4	17;2				5;1		1;1			20;2				17;1					28;2					1;1	4
5	2;1		26;2		16;1			25;2			23;1						2;2				6;2				5
6			7;1				6;1		25;1			15;1		2;1		1;1			13;3					28;2	6
7	33;2				25;1					1;1				4;1			26;1			27;2		2;1			7
8	25;1			26;2			1;1		25;1			25;1		11;1		9;1			22;1					48;3	8
9		23;1			4;1					4;1							5;1			4;1		25;2			9
10	25;1			11;1		24;1					1;1			7;1					24;2		10;1			1;1	10
11	25;1											1;1	1;1				25;1					25;1			11
12	1;1		4;2		1;1			1;1			2;2				1;1				41;2		25;1			29;2	12
13						1;1			1;1							25;1						28;2		25;1	13
14			1;1		1;1			1;1			1;1		2;2						22;1		34;2				14
15	3;3			1;1		1;1								1;1		2;1						21;1		50;2	15
16								3;3			1;1							10;1			18;1				16
17	1;1		1;1		2;2				6;1			1;1		1;1			1;1		21;1		1;1			2;2	17
18								1;1			3;3					1;1							3;3		18
19	3;3		1;1	1;1		1;1			1;1					1;1				1;1		1;1				4;4	19
20								2;2					2;2				1;1						2;2		20
21	1;1		2;2		1;1	1;1				2;2				1;1					1;1		4;4			3;3	21
22	2;2							1;1	1;1			1;1					2;2						2;2		22
23		1;1			3;3					3;3			1;1					25;1	1;1		3;3		1;1	6;6	23
24	3;3			3;3			1;1		2;2			2;2		1;1		1;1		1;1			1;1		4;4		24
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	

Neurons that include haplotypes that belong to the SOM class Wu

Neurons that include haplotypes that belong to the SOM class Wu-Mutant (3)

Neurons that include haplotypes that belong to the SOM class Wu-Mutant (4)

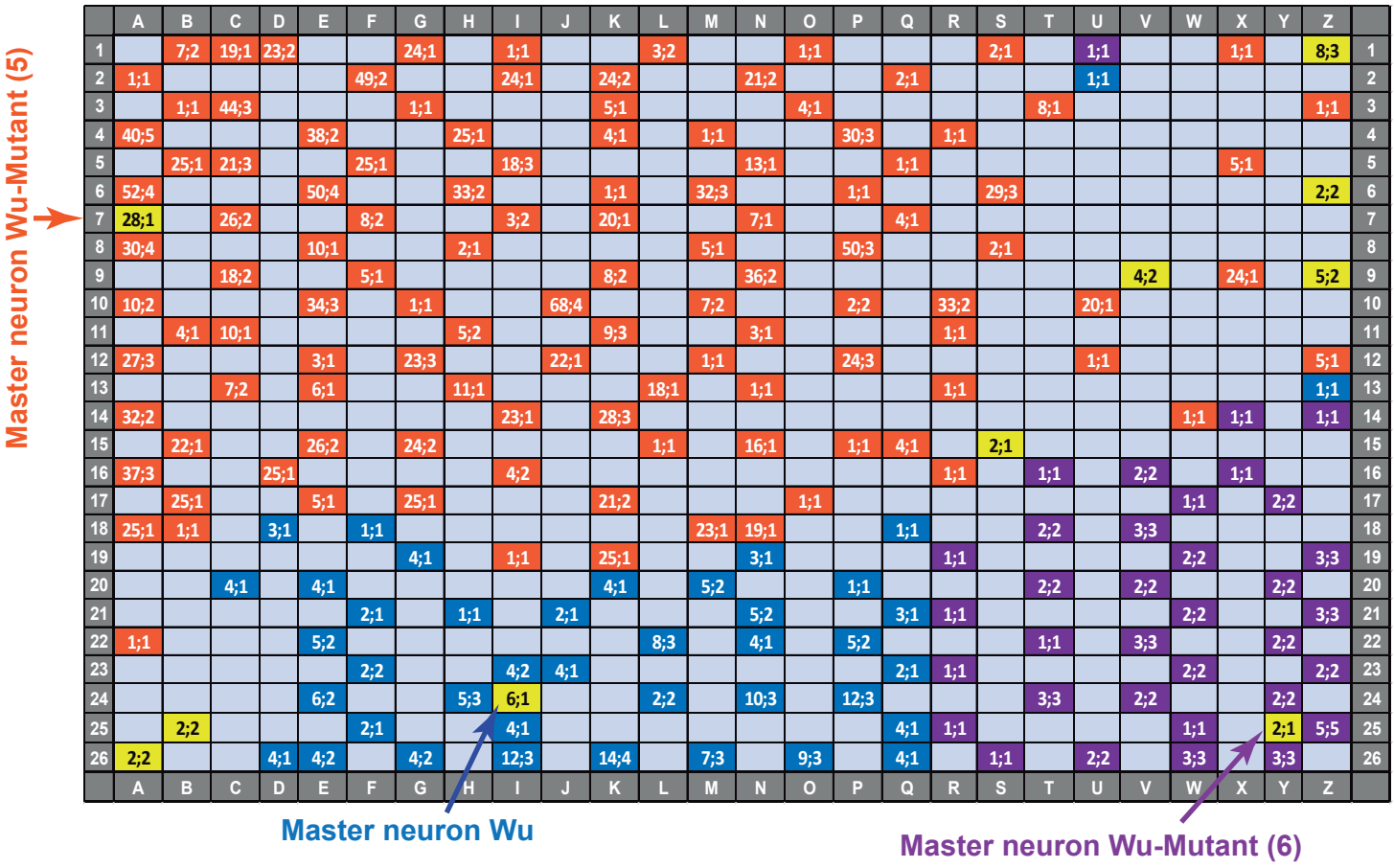
Neurons that include haplotypes that belong to SOM class Wu and a Wu-Mutant

SOM class Wu-Mutant (3) refers to SOMs whose haplotype in the master neuron differed from Wuhan-Hu-1 in mutation C23127T (A522V).
Found in patient Pt012

SOM class Wu-Mutant (4) refers to SOMs whose haplotype in the master neuron differed from Wuhan-Hu-1 in mutation T23042C (S494P).
Found in patient Pt417

Figure S8 (*continued 3*)

spike A6



	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y	Z	
1		7;2	19;1	23;2			24;1		1;1			3;2			1;1				2;1		1;1			1;1		8;3	1
2	1;1					49;2			24;1		24;2			21;2			2;1				1;1						2
3		1;1	44;3				1;1				5;1				4;1					8;1						1;1	3
4	40;5				38;2			25;1			4;1		1;1			30;3		1;1									4
5		25;1	21;3			25;1			18;3					13;1			1;1							5;1			5
6	52;4				50;4			33;2			1;1		32;3			1;1			29;3							2;2	6
7	28;1		26;2			8;2			3;2		20;1			7;1			4;1										7
8	30;4				10;1			2;1					5;1			50;3			2;1								8
9			18;2			5;1					8;2			36;2								4;2		24;1		5;2	9
10	10;2				34;3		1;1			68;4			7;2			2;2		33;2			20;1						10
11		4;1	10;1					5;2			9;3			3;1				1;1									11
12	27;3				3;1		23;3			22;1			1;1			24;3					1;1					5;1	12
13			7;2		6;1			11;1				18;1		1;1				1;1								1;1	13
14	32;2								23;1		28;3												1;1	1;1		1;1	14
15		22;1			26;2		24;2					1;1		16;1		1;1	4;1		2;1								15
16	37;3			25;1					4;2									1;1		1;1		2;2		1;1			16
17		25;1			5;1		25;1				21;2				1;1								1;1		2;2		17
18	25;1	1;1		3;1		1;1							23;1	19;1			1;1			2;2		3;3					18
19							4;1		1;1		25;1			3;1				1;1					2;2			3;3	19
20			4;1		4;1						4;1		5;2			1;1				2;2		2;2			2;2		20
21						2;1		1;1		2;1				5;2			3;1	1;1					2;2			3;3	21
22	1;1				5;2							8;3		4;1		5;2				1;1		3;3			2;2		22
23						2;2			4;2	4;1							2;1	1;1					2;2			2;2	23
24					6;2			5;3	6;1			2;2		10;3		12;3				3;3		2;2			2;2		24
25		2;2				2;1			4;1								4;1	1;1					1;1		2;1	5;5	25
26	2;2			4;1	4;2		4;2		12;3		14;4		7;3		9;3		4;1		1;1		2;2		3;3		3;3		26
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y	Z	

Neurons that include haplotypes that belong to the SOM class Wu

Neurons that include haplotypes that belong to the SOM class Wu-Mutant (5)

Neurons that include haplotypes that belong to the SOM class Wu-Mutant (6)

Neurons that include haplotypes that belong to SOM class Wu and a Wu-Mutant

SOM class Wu-Mutant (5) refers to SOMs whose haplotype in the master neuron differed from Wuhan-Hu-1 in mutation A23403G (D614G).
Found in patients Pt012, Pt017, Pt020, Pt023, Pt032, Pt036, Pt040, Pt045, Pt047, Pt106, Pt130, Pt142, Pt145, Pt148, Pt150, Pt182, Pt341, Pt354, Pt416, Pt417, Pt426, Pt427, Pt441, Pt443 and Pt448

SOM class Wu-Mutant (6) refers to SOMs whose haplotype in the master neuron differed from Wuhan-Hu-1 in mutation C23380T (Syn).
Found in patient Pt168

Figure S8. Representation of composite self-organized haplotype maps of amplicons of the nsp12- (amplicons A1 to A4), and S- (amplicons A5 to A6) coding regions. In each neuron (rectangular cell) the first number indicates the total number of haplotypes in that neuron, and the second number gives the total number of different haplotypes. Neurons that include only haplotypes that belong to the SOM class Wu are depicted in blue. Neurons that include only haplotypes that belong to the SOM class Wu-Mutant (1), Wu-Mutant (2), Wu-Mutant (3), Wu-Mutant (4), Wu-Mutant (5) and Wu-Mutant (6) are depicted in red, green, pink, brown, orange and purple, respectively. Neurons that include haplotypes that belong to SOM class Wu and a Wu-Mutant are depicted in yellow. Mutation (amino acid substitution) relative to Wuhan-Hu-1 genome that define Wu-Mutant classes are indicated. Patients whose master neuron included a Wu-Mutant SOM class are also indicated. Location of Master neurons Wu and Wu-Mutants are highlighted with arrows in each map.

Figure S9

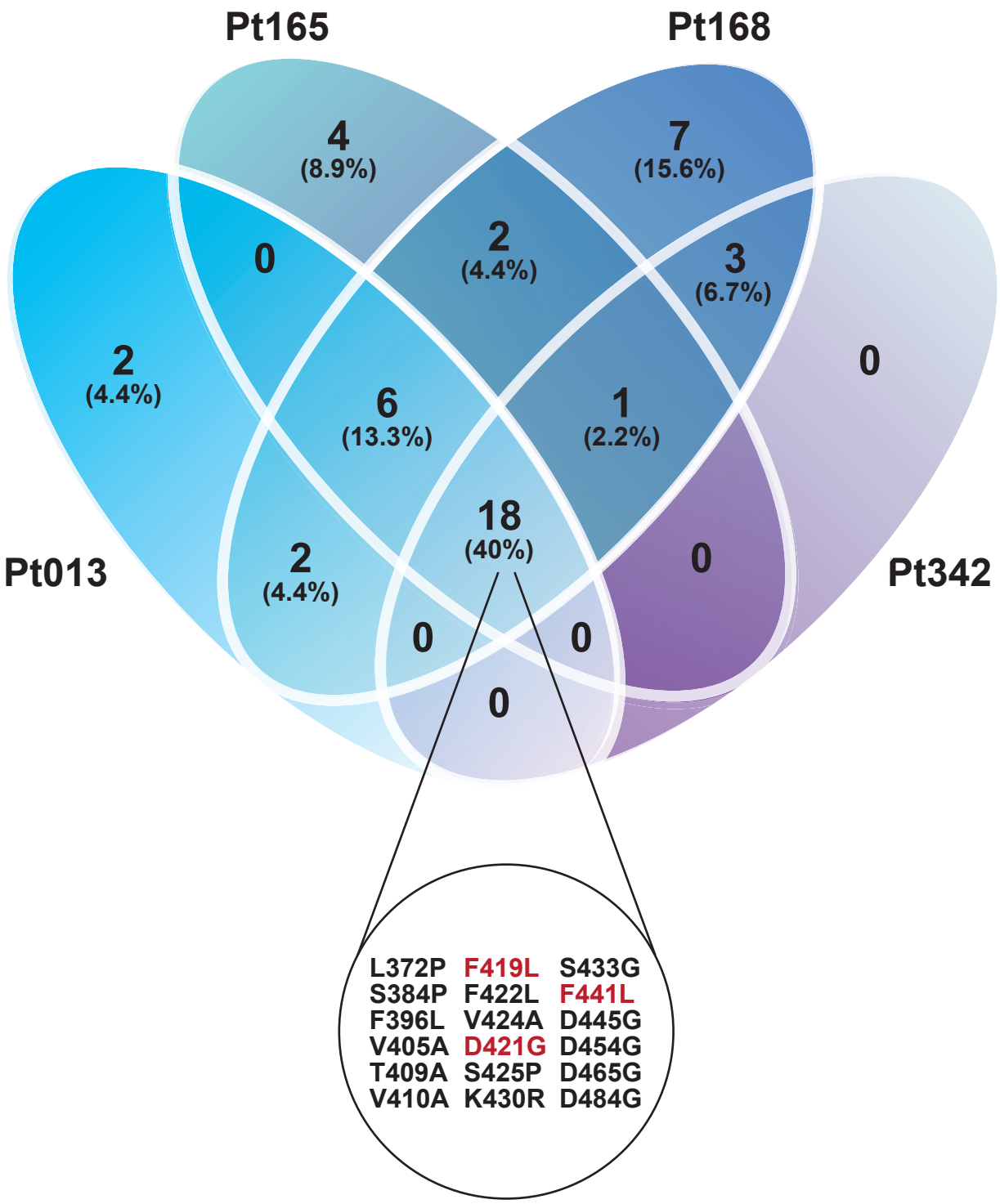


Figure S9. Number and percentage of amino acid substitutions detected in each patient of the SOM class Wu-Mutant (1), represented as a Venn diagram. Substitutions in red were used for functional assays.

Figure S10

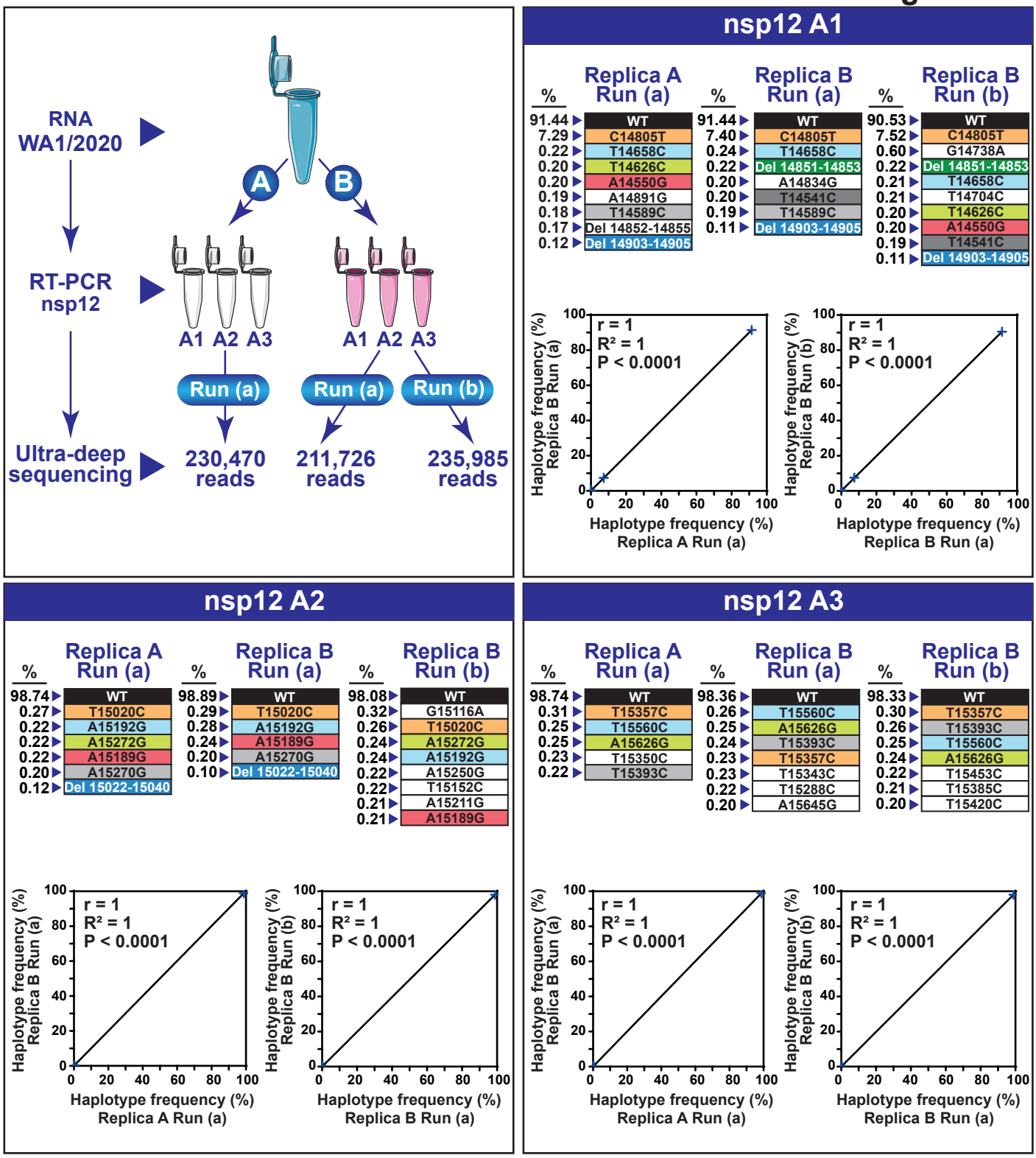


Figure S10. **Test of sample representability of haplotype composition.** The top left panel depictes the experimental design which consisted in the amplification of three nsp12 (polymerase)-coding region amplicons (A1, A2 and A3) of SARS-CoV-2 USA-WA1/2020 viral RNA (replicas A and B) and sequencing of the replica B in a different run. The other three panels show the results obtained for each of the amplicons separately; top, the haplotype composition is depicted; bottom, the axes represent the haplotype frequency obtained; each haplotype is represented by a blue cross and its position in the graphs is given by the intersection of the frequencies obtained by each run. The lines correspond to functions y = 0.9997x + 0.03448 and y = 0.9899x + 0.03040 for amplicon A1, y = 1.001x + 0.01388 and y = 0.9922x - 0.03088 for amplicon A2 and y = 0.9963x – 0.01074 and y = 0.9995x + 0.01520 for amplicon A3.

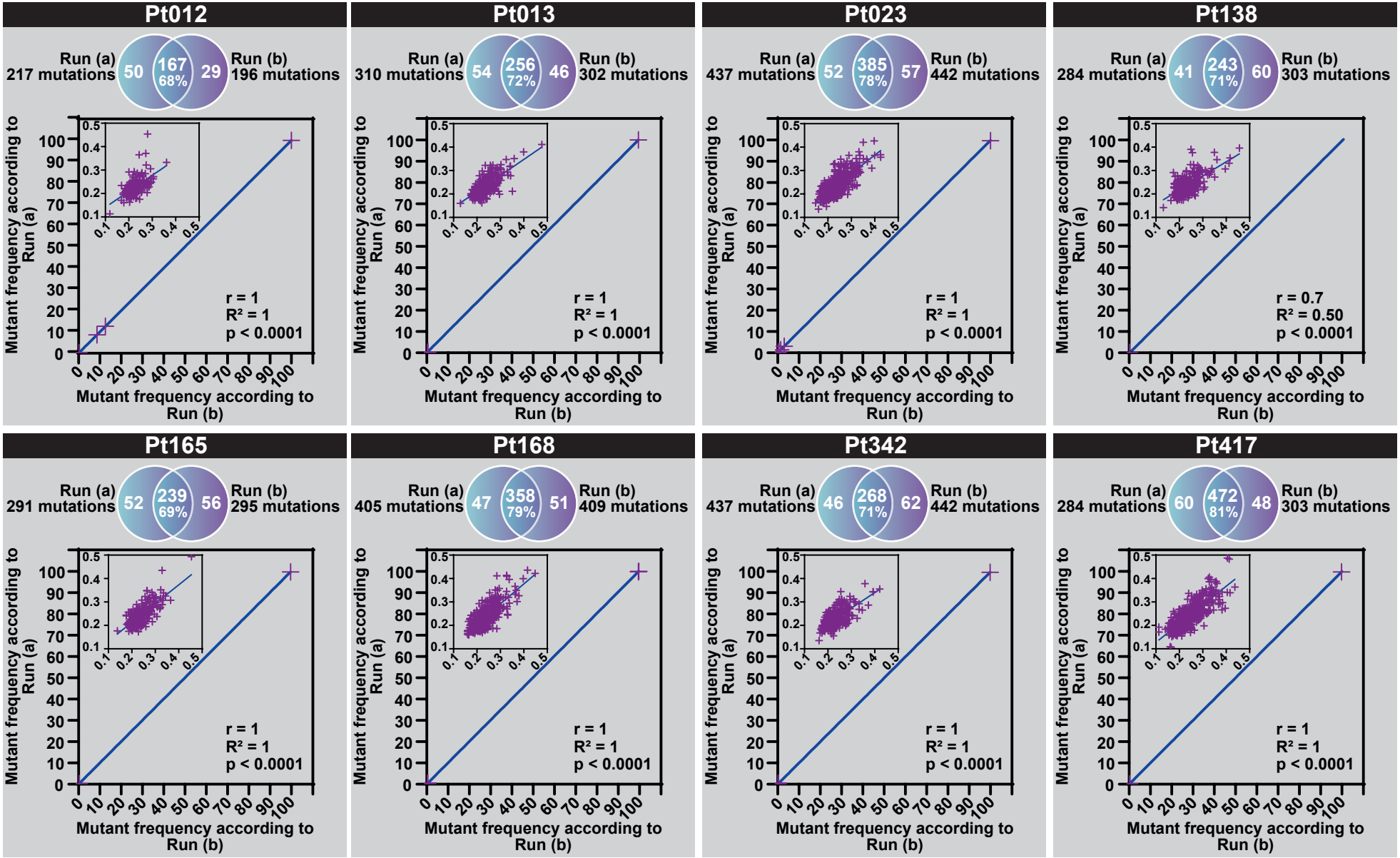


Figure S11. Control of ultra-deep sequencing reproducibility. Six amplicons from 8 patients (Pt012, Pt013, Pt023, Pt138, Pt165, Pt168, Pt342, Pt417) were sequenced a second time [called run (b)], and the results were compared with the first run [called run (a)]. The ordinate axis represents the mutant frequency obtained in run (a). The abscissa axis represents the mutant frequency obtained by the run (b). Each mutation is represented by a purple cross and its position in the graph is given by the intersection of the frequencies obtained by each run. The lines correspond to functions $y = 1.000x + 0.001182$, $y = 1.006x + 0.002637$, $y = 0.9981x + 0.001913$, $y = 0.6732x + 0.07998$, $y = 1.001x + 0.004973$, $y = 1.004x + 0.0008648$, $y = 0.9976x + 0.001988$, and $y = 0.9995x + 0.001075$ for patients Pt012, Pt013, Pt023, Pt138, Pt165, Pt168, Pt342, Pt417, respectively.

Table S1. Demographic and clinical data of the thirty SARS-CoV-2-infected patients included in the study. Patients are divided according to disease severity.

Characteristics	COVID-19 mild (n=10) [a]	COVID-19 moderate (n=10) [b]	COVID-19 exitus (n=10) [c]	TOTAL (n=30)
Age mean ± SD, years	58.40 ± 11.19	78 ± 13.61	81.5 ± 11.97	**72.63 ± 15.74**
Male (%)	3 (30.0%)	3 (30.0%)	3 (30.0%)	**9 (30.0%)**
Female (%)	7 (70.0%)	7 (70.0%)	7 (70.0%)	**21 (70.0%)**
Hypertension (%)	5 (50.0%)	9 (90.0%)	7 (70.0%)	**21 (70.0%)**
Cardiac disease (%)	4 (40.0%)	5 (50.0%)	5 (50.0%)	**14 (46.7%)**
Diabetes (%)	2 (20.0%)	3 (30.0%)	4 (40.0%)	**9 (30.0%)**
Obesity (%)	1 (10.0%)	1 (10.0%)	0 (0%)	**2 (6.7%)**
Dyslipidemia (%)	3 (30.0%)	5 (50.0%)	5 (50.0%)	**13 (43.3%)**
Asthma (%)	3 (30.0%)	2 (20.0%)	1 (10.0%)	**6 (20.0%)**
COPD (%)	1 (10.0%)	2 (20.0%)	0 (0%)	**3 (10.0%)**
Immunosuppression (%)	0 (0%)	0 (0%)	2 (20.0%)	**2 (6.7%)**
Leukemia (%)	1 (10.0%)	0 (0%)	0 (0%)	**1 (3.3%)**
Lymphoma (%)	0 (0%)	1 (10.0%)	4 (40.0%)	**5 (16.7%)**
Hospitalization (%)	0 (0%)	10 (100 %)	10 (100%)	**20 (66.7%)**
ICU admission (%)	0 (0%)	0 (0%)	3 (30.0%)	**3 (10.0%)**
Conventional oxygen therapy (%)	0 (0%)	10 (100 %)	10 (100 %)	**20 (66.7%)**
Invasive mechanical ventilation (%)	0 (0%)	0 (0%)	1 (10.0%)	**1 (3.3%)**
Noninvasive mechanical ventilation (%)	0 (0%)	0 (0%)	5 (50.0%)	**5 (16.7%)**
High flow nasal cannulas (%)	0 (0%)	0 (0%)	4 (40.0%)	**4 (13.3%)**
Corticosteroids (%)	1 (10.0%)	10 (100%)	9 (90.0%)	**20 (66.7%)**
IL-6 (pg/mL) ± SD	56.01 ± 43.5	97.21 ± 147.6	nd	**73.11 ± 106.5**
Survival 90 days after diagnosis (%)	10 (100%)	10 (100%)	0 (0%)	**20 (66.7%)**
Days between swab collection and onset of symptoms ± SD [d]	5.78 ± 4.2	4.89 ± 3.1	4.5 ± 2.6	**5.08 ± 3.3**
Days between swab collection and patient outcome ± SD [e]	na	11.90 ± 5.8	11.2 ± 7.9	**11.55 ± 6.7**
Ct (cycle threshold, which is inversely correlated with viral RNA level) ± SD [f]	25.37 ± 3.9	21.81 ± 2.4	20.38 ± 2.9	**22.29 ± 3.6**

[a] Patients with mild COVID-19: Pt341, Pt342, Pt354, Pt416, Pt417, Pt426, Pt427, Pt441, Pt443 and Pt448.
[b] Patients with moderate COVID-19: Pt106, Pt130, Pt138, Pt142, Pt145, Pt148, Pt150, Pt165, Pt168 and Pt182.
[c] Patients with severe (exitus) COVID-19: Pt012, Pt013, Pt017, Pt020, Pt023, Pt032, Pt036, Pt040, Pt045 and Pt047.

[d] All nasopharyngeal swabs were collected in April 2020, on April 3 for Pt165, Pt416 and Pt426; April 4 for Pt342; April 6 for Pt106, Pt148 and Pt417; April 7 for Pt040, Pt047, Pt130, Pt182, Pt341 and Pt443; April 8 for Pt145; April 9 for Pt020, Pt032 and Pt354; April 11 for Pt023 and Pt441; April 13 for Pt045; April 14 for Pt013, Pt138 and Pt150, April 16 for Pt036, Pt142 and Pt427; April 17 for Pt012; April 18 for Pt017, April 19 for Pt448 and April 22 for Pt017. Onset of symptoms data available for 26 patients.

[e] Data available for 20 patients. The outcome date was established as the date of hospital discharge in the case of moderate patients, and the date of death in the case of exitus patients, respectively. na: not applicable; nd: no data.

[f] The Ct values were: 15.57 for Pt012, 18.67 for Pt013, 18.33 for Pt017, 18.58 for Pt020, 25.36 for Pt023, 20.78 for Pt032, 21.64 for Pt036, 19.03 for Pt040, 22.13 for Pt045, 23.68 for Pt047, 22.21 for Pt106, 25.8 for Pt130, 19.79 for Pt138, 18.89 for Pt142, 23.03 for Pt145, 21.19 for Pt148, 18.3 for Pt150, 20.87 for Pt165, 24.41 for Pt168, 23.64 for Pt182, 18.39 for Pt341, 18.96 for Pt342, 29.11 for Pt354, 28.53 for Pt416, 27.1 for Pt417, 28.46 for Pt426, 27.85 for Pt427, 25.21 for Pt441, 23.61 for Pt443 and 26.51 for Pt448.

Table S2. Mutations and amino acid substitutions identified COVIDSeq analysis in the whole genome in virus from the Madrid cohort.

Region[a]	Mutation[b]	Substitution[c]	Type[d]	Patients
5'UTR	**C241T**	-	-	Pt012, Pt020, Pt023, Pt040, Pt047, Pt150, Pt341, Pt416, Pt441
nsp2	**C2091T**	T429I	Non-Syn	Pt040
nsp3	**C3037T**	F106	Syn	Pt012, Pt020, Pt023, Pt040, Pt047, Pt150, Pt341, Pt416, Pt441
nsp3	**C3540T**	A274V	Non-Syn	Pt416
nsp3	**C4058T**	P447S	Non-Syn	Pt341
nsp3	**T4346C**	S543P	Non-Syn	Pt341
nsp3	**A6293G**	I1192V	Non-Syn	Pt341
nsp3	**G7016T**	G1433C	Non-Syn	Pt416
nsp3	**C7564T**	S1615	Syn	Pt047
nsp4	**C8782T**	S76	Syn	Pt342
nsp4	**T9477A**	F308Y	Non-Syn	Pt342
nsp12	**C14408T**	P323L	Non-Syn	Pt012, Pt020, Pt023, Pt040, Pt047, Pt150, Pt341, Pt416, Pt441
nsp12	**C14805T**	Y455	Syn	Pt342
nsp12	**G15906T**	Q822H	Non-Syn	Pt023
nsp15	**T19839C**	N73	Syn	Pt416
nsp15	**A20268G**	L216	Syn	Pt012, Pt020, Pt023, Pt040, Pt047, Pt150, Pt341, Pt441
nsp16	**C21365T**	P236L	Non-Syn	Pt341
nsp16	**A21405G**	K249	Syn	Pt441
spike	**C23127T**	A522V	Non-Syn	Pt012
spike	**A23403G**	D614G	Non-Syn	Pt012, Pt020, Pt023, Pt040, Pt047, Pt150, Pt341, Pt416, Pt441
spike	**T23599G**	N679K	Non-Syn	Pt416
spike	**C24130A**	N856K	Non-Syn	Pt416
ORF3a	**C25658T**	T89I	Non-Syn	Pt020
ORF3a	**G25979T**	G196V	Non-Syn	Pt342
M	**C27145T**	T208I	Non-Syn	Pt341
ORF8	**T28144C**	L84S	Non-Syn	Pt342
N	**C28313T[e]**	R14C	Non-Syn	Pt441
N	**C28657T**	D128	Syn	Pt342
N	**C28863T**	S197L	Non-Syn	Pt342
N	**G28881T**	R203M	Non-Syn	Pt341
N	**G28881A** **G28882A**	R203K	Non-Syn	Pt416
N	**G28883C**	G204R	Non-Syn	Pt416
N	**C29272T**	Y333	Syn	Pt040
3'UTR	**G29734C**	-	-	Pt047, Pt341

[a] Genomic region.

[b] The SARS-CoV-2 genome residue numbering is according to the NCBI reference sequence (accession number NC_045512.2).

[c] Amino acid residues (single letter code) are numbered from N- to the C- terminus of each region.

[d] Type of mutation: synonymous (Syn); non-synonymous (Non-Syn).

[e] This mutation, which is indicated as non-synonymous for the coding of protein N, is synonymous for ORF9b (amino acid P10).

Table S3. Non-synonymous mutations, corresponding amino acid substitutions (with predicted acceptability and functional effect) identified in the mutant spectra of nsp12 (polymerase) and spike (S) of SARS-CoV-2 from the Madrid cohort.

					Number of patients		
Region[a]	Mutation[b]	Substitution[c]	PAM250[d]	SNAP2[e]	Mild	Moderate	Exitus
nsp12 A1	T14537C	L366P	-3	effect (55)	6	4	7
nsp12 A1	T14543C	F368S	-3	effect (9)	1	0	0
nsp12 A1	C14554T	L372F	2	effect (8)	0	0	1
nsp12 A1	T14555C	L372P	-3	effect (45)	10	9	10
nsp12 A1	T14558C	V373A	0	neutral (-55)	7	1	4
nsp12 A1	T14560C	Y374H	0	effect (62)	1	0	0
nsp12 A1	A14570G	D377G	1	effect (36)	1	0	1
nsp12 A1	C14576T	A379V	0	effect (9)	1	0	0
nsp12 A1	T14579C	M380T	-1	neutral (-46)	7	7	8
nsp12 A1	A14582G	H381R	2	neutral (-57)	3	2	2
nsp12 A1	C14585T	A382V	0	neutral (-94)	1	0	0
nsp12 A1	T14590C	S384P	1	effect (21)	10	10	10
nsp12 A1	A14597G	N386S	1	neutral (-94)	0	1	0
nsp12 A1	T14606C	L389P	-3	effect (59)	1	0	1
nsp12 A1	A14609G	D390G	1	effect (14)	0	0	1
nsp12 A1	A14617G	T393A	1	neutral (-1)	3	1	3
nsp12 A1	T14623C	C395R	-4	effect (71)	9	8	7
nsp12 A1	T14626C	F396L	2	neutral (-86)	10	10	10
nsp12 A1	T14627C	F396S	-3	effect (53)	5	0	4
nsp12 A1	T14629C	S397P	1	effect (56)	1	0	0
nsp12 A1	T14633C	V398A	0	neutral (-73)	2	0	1
nsp12 A1	T14642C	L401P	-3	effect (20)	6	5	6
nsp12 A1	A14647G	N403D	2	neutral (-88)	1	0	0
nsp12 A1	A14648G	N403S	1	neutral (-91)	4	2	1
nsp12 A1	T14654C	V405A	0	neutral (-57)	10	10	10
nsp12 A1	T14659C	F407L	2	neutral (-81)	8	9	9
nsp12 A1	T14660C	F407S	-3	neutral (-40)	1	0	1
nsp12 A1	A14663G	Q408R	1	effect (4)	2	0	0
nsp12 A1	A14665G	T409A	1	neutral (-56)	8	7	9
nsp12 A1	T14669C	V410A	0	neutral (-45)	10	10	10
nsp12 A1	A14671G	K411E	0	effect (44)	7	5	5
nsp12 A1	A14672G	K411R	3	neutral (-87)	1	0	2
nsp12 A1	A14687G	N416S	1	neutral (-39)	4	1	5
nsp12 A1	A14693G	D418G	1	effect (9)	8	10	10
nsp12 A1	T14695C	F419L	2	effect (31)	10	10	10
nsp12 A1	A14702G	D421G	1	neutral (-7)	10	10	10
nsp12 A1	T14704C	F422L	2	neutral (-25)	10	10	10
nsp12 A1	T14711C	V424A	0	neutral (-69)	10	10	10
nsp12 A1	T14713C	S425P	1	neutral (-36)	10	10	10
nsp12 A1	A14717G	K426R	3	neutral (-93)	8	5	7

nsp12 A1	T14722C	F428L	2	neutral (-85)	2	0	2
nsp12 A1	T14723C	F428S	-3	effect (21)	3	0	2
nsp12 A1	T14725C	F429L	2	neutral (-94)	5	0	2
nsp12 A1	A14729G	K430R	3	neutral (-84)	10	10	10
nsp12 A1	A14732G	E431G	0	effect (15)	4	1	4
nsp12 A1	A14737G	S433G	1	neutral (-79)	10	10	10
nsp12 A1	T14740C	S434P	1	neutral (-82)	8	10	9
nsp12 A1	T14744C	V435A	0	neutral (-25)	4	0	2
nsp12 A1	A14747G	E436G	0	neutral (-64)	1	0	2
nsp12 A1	A14756G	H439R	2	effect (56)	4	1	3
nsp12 A1	T14758C	F440L	2	effect (26)	10	10	10
nsp12 A1	T14759C	F440S	-3	effect (35)	2	0	2
nsp12 A1	T14761C	F441L	2	effect (42)	10	10	10
nsp12 A1	T14762C	F441S	-3	effect (56)	1	0	0
nsp12 A1	T14764C	F442L	2	effect (37)	8	5	5
nsp12 A1	T14765C	F442S	-3	effect (26)	1	0	0
nsp12 A1	A14771G	Q444R	1	effect (19)	9	6	5
nsp12 A1	A14774G	D445G	1	effect (20)	10	10	10
nsp12 A1	A14780G	N447S	1	neutral (-92)	3	0	1
nsp12 A1	C14786T	A449V	0	neutral (-21)	1	0	0
nsp12 A1	T14789C	I450T	0	neutral (-46)	4	1	3
nsp12 A1	A14791G	S451G	1	neutral (-47)	8	6	5
nsp12 A1	A14801G	D454G	1	effect (20)	10	10	10
nsp12 A1	A14804G	Y455C	0	effect (27)	1	0	0
nsp12 A1	A14816G	N459S	1	neutral (-22)	1	0	0
nsp12 A1	A14824G	T462A	1	neutral (-41)	7	5	5
nsp12 A1	A14827G	M463V	2	neutral (-27)	1	0	1
nsp12 A1	T14828C	M463T	-1	effect (63)	3	0	0
nsp12 A1	T14830C	C464R	-4	effect (61)	7	7	8
nsp12 A1	A14834G	D465G	1	effect (28)	10	10	10
nsp12 A1	A14836G	I466V	4	neutral (-71)	2	0	0
nsp12 A1	T14837C	I466T	0	effect (5)	5	1	4
nsp12 A1	A14839G	R467G	-3	neutral (-15)	8	7	5
nsp12 A1	A14843G	Q468R	1	effect (30)	4	2	6
nsp12 A1	T14851C	F471L	2	effect (2)	1	0	0
nsp12 A1	T14851G	F471V	-1	neutral (-54)	0	4	1
nsp12 A1	T14855A	V472E	-2	neutral (-36)	0	4	1
nsp12 A1	T14858C	V473A	0	neutral (-52)	2	0	0
nsp12 A1	A14861G	E474G	0	neutral (-7)	2	0	2
nsp12 A1	T14864C	V475A	0	neutral (-23)	2	0	0
nsp12 A1	T14867C	V476A	0	neutral (-54)	3	0	2
nsp12 A1	A14870G	D477G	1	neutral (-30)	9	3	5
nsp12 A1	A14872G	K478E	0	neutral (-51)	1	0	0
nsp12 A1	A14873G	K478R	3	neutral (-77)	10	7	7
nsp12 A1	A14876G	Y479C	0	effect (11)	1	0	0
nsp12 A1	T14878C	F480L	2	neutral (-47)	4	1	1
nsp12 A1	T14879C	F480S	-3	effect (34)	1	0	0
nsp12 A1	A14882G	D481G	1	neutral (-54)	0	0	1
nsp12 A1	A14888G	Y483C	0	effect (42)	2	0	1

nsp12 A1	A14891G	D484G	1	effect (42)	10	10	10
nsp12 A1	T14899C	C487R	-4	neutral (-37)	5	0	1
nsp12 A1	T14903C	I488T	0	effect (2)	2	0	0
nsp12 A1	A14905G	N489D	2	neutral (-77)	1	0	0
nsp12 A1	A14906G	N489S	1	neutral (-97)	1	0	0
nsp12 A1	A14911G	N491D	2	neutral (-72)	3	1	1
nsp12 A1	A14912G	N491S	1	neutral (-89)	1	1	1
nsp12 A1/A2	C14914A	Q492K	1	neutral (-10)	0	0	1
nsp12 A2	T14918C	V493A	0	neutral (-12)	10	10	10
nsp12 A1	A14920G	I494V	4	neutral (-96)	5	3	7
nsp12 A2	T14921C	I494T	0	neutral (-13)	4	1	2
nsp12 A2	G14923A	V495I	4	neutral (-80)	1	0	0
nsp12 A2	T14924C	V495A	0	effect (1)	10	10	10
nsp12 A2	A14930G	N497S	1	effect (6)	3	0	1
nsp12 A2	A14936G	D499G	1	effect (70)	6	5	5
nsp12 A2	T14950C	F504L	2	effect (30)	5	6	2
nsp12 A2	T14951C	F504S	-3	effect (59)	10	9	8
nsp12 A2	T14981C	L514P	-3	neutral (-34)	10	9	9
nsp12 A2	T14986C	Y516H	0	effect (57)	1	0	0
nsp12 A2	A14990G	D517G	1	effect (46)	1	0	0
nsp12 A2	T14992C	S518P	1	effect (3)	1	0	0
nsp12 A2	A14998G	S520G	1	neutral (-80)	7	2	8
nsp12 A2	G15004A	E522K	0	neutral (-55)	1	0	0
nsp12 A2	A15005G	E522G	0	neutral (-18)	10	8	10
nsp12 A2	A15014G	D525G	1	effect (26)	9	10	9
nsp12 A2	C15017T	A526V	0	neutral (-36)	0	0	2
nsp12 A2	T15020C	L527P	-3	effect (74)	9	10	10
nsp12 A2	T15020A	L527H	-2	effect (51)	1	0	0
nsp12 A2	T15022C	F528L	2	effect (23)	1	0	0
nsp12 A2	A15034G	K532E	0	effect (51)	1	0	0
nsp12 A2	T15044C	V535A	0	effect (14)	10	10	10
nsp12 A2	A15046G	I536V	4	neutral (-27)	3	0	5
nsp12 A2	T15047C	I536T	0	neutral (-20)	8	7	2
nsp12 A2	A15058G	T540A	1	effect (27)	2	0	0
nsp12 A2	T15071C	L544P	-3	effect (46)	1	0	0
nsp12 A2	A15074G	K545R	3	effect (36)	7	2	4
nsp12 A2	A15082G	I548V	4	neutral (-35)	1	0	0
nsp12 A2	T15083C	I548T	0	effect (15)	1	0	0
nsp12 A2	A15092G	K551R	3	neutral (-25)	1	0	0
nsp12 A2	A15095G	N552S	1	neutral (-94)	10	10	10
nsp12 A2	C15103T	R555C	-4	effect (68)	1	0	0
nsp12 A2	A15106G	T556A	1	effect (57)	6	0	2
nsp12 A2	C15107T	T556I	0	effect (73)	1	0	0
nsp12 A2	G15109A	V557I	4	neutral (-51)	0	0	1
nsp12 A2	T15110C	V557A	0	effect (22)	0	0	1
nsp12 A2	T15119C	V560A	0	effect (3)	10	10	10
nsp12 A2	T15121C	S561P	1	effect (68)	10	10	10
nsp12 A2	T15125C	I562T	0	effect (20)	10	9	9
nsp12 A2	T15127C	C563R	-4	effect (78)	9	8	7

nsp12 A2	A15136G	M566V	2	effect (22)	2	0	0
nsp12 A2	T15137C	M566T	-1	effect (4)	4	0	1
nsp12 A2	A15139G	T567A	1	neutral (-28)	10	10	10
nsp12 A2	A15143G	N568S	1	neutral (-49)	5	3	6
nsp12 A2	A15145G	R569G	-3	effect (79)	3	0	0
nsp12 A2	A15149G	Q570R	1	neutral (-56)	1	0	0
nsp12 A2	T15151C	F571L	2	neutral (-34)	10	10	10
nsp12 A2	T15152C	F571S	-3	effect (51)	10	10	10
nsp12 A2	A15169G	K577E	0	effect (45)	1	0	0
nsp12 A2	A15175G	I579V	4	neutral (0)	9	9	10
nsp12 A2	A15177G	I579M	2	neutral (-64)	0	0	1
nsp12 A2	A15184G	T582A	1	neutral (-60)	8	6	5
nsp12 A2	A15187G	R583G	-3	effect (81)	2	1	0
nsp12 A2	A15196G	T586A	1	neutral (-39)	1	0	0
nsp12 A2	A15211G	T591A	1	effect (34)	10	10	10
nsp12 A2	A15214G	S592G	1	effect (54)	9	9	7
nsp12 A2	A15218G	K593R	3	effect (57)	1	0	0
nsp12 A2	T15232C	W598R	2	effect (90)	2	1	2
nsp12 A2	A15236G	H599R	2	effect (63)	10	8	7
nsp12 A2	A15238G	N600D	2	neutral (-64)	4	0	4
nsp12 A2	A15239G	N600S	1	neutral (-86)	10	10	10
nsp12 A2	A15241G	M601V	2	neutral (-27)	8	4	5
nsp12 A2	T15242C	M601T	-1	neutral (-10)	1	0	0
nsp12 A2	A15250G	T604A	1	neutral (-62)	9	6	9
nsp12 A2	C15251T	T604I	0	effect (4)	0	0	1
nsp12 A2	T15254C	V605A	0	neutral (-40)	6	2	1
nsp12 A2	A15259G	S607G	1	neutral (-92)	1	0	0
nsp12 A2	A15263G	D608G	1	neutral (-83)	10	10	10
nsp12 A2	A15271G	N611D	2	neutral (-63)	3	0	0
nsp12 A2	A15272G	N611S	1	neutral (-49)	10	10	10
nsp12 A2	A15278G	H613R	2	neutral (-76)	8	10	5
nsp12 A2	T15281C	L614P	-3	effect (48)	1	0	0
nsp12 A3	G15292A	D618N	2	effect (75)	1	0	0
nsp12 A3	A15308G	D623G	1	effect (75)	2	1	4
nsp12 A3	T15317C	M626T	-1	effect (44)	7	6	6
nsp12 A3	A15323G	N628S	1	neutral (-35)	3	0	0
nsp12 A3	A15325G	M629V	2	neutral (-79)	1	0	0
nsp12 A3	T15329C	L630P	-3	effect (61)	10	9	7
nsp12 A3	T15343C	S635P	1	effect (27)	10	10	10
nsp12 A3	T15347C	L636P	-3	effect (39)	10	10	10
nsp12 A3	T15350C	V637A	0	neutral (-7)	10	10	10
nsp12 A3	T15353C	L638P	-3	effect (67)	10	10	10
nsp12 A3	C15358T	R640C	-4	effect (56)	1	0	0
nsp12 A3	A15365G	H642R	2	effect (29)	1	0	0
nsp12 A3	A15370G	T644A	1	neutral (-63)	9	7	8
nsp12 A3	T15373C	C645R	-4	effect (69)	7	6	6
nsp12 A3	T15376C	C646R	-4	effect (47)	7	5	6
nsp12 A3	T15383C	L648S	-3	neutral (-73)	10	10	10
nsp12 A3	T15385C	S649P	1	neutral (-59)	10	10	10

nsp12 A3	A15389G	H650R	2	effect (7)	9	9	10
nsp12 A3	T15394C	F652L	2	neutral (-43)	9	10	10
nsp12 A3	T15395C	F652S	-3	neutral (-11)	1	0	0
nsp12 A3	T15397C	Y653H	0	effect (23)	2	2	0
nsp12 A3	A15413G	E658G	0	effect (62)	10	10	9
nsp12 A3	T15415C	C659R	-4	effect (63)	10	10	9
nsp12 A3	C15419T	A660V	0	neutral (-29)	1	0	0
nsp12 A3	T15425C	V662A	0	effect (16)	1	0	0
nsp12 A3	A15430G	S664G	1	effect (6)	8	8	7
nsp12 A3	A15434G	E665G	0	effect (58)	10	10	9
nsp12 A3	A15436G	M666V	2	neutral (-78)	10	10	10
nsp12 A3	G15439A	V667I	4	effect (32)	1	0	0
nsp12 A3	T15440C	V667A	0	neutral (-19)	10	10	10
nsp12 A3	A15442G	M668V	2	neutral (-54)	3	0	1
nsp12 A3	T15443C	M668T	-1	neutral (-52)	7	8	9
nsp12 A3	T15445C	C669R	-4	effect (50)	10	10	9
nsp12 A3	T15454C	S672P	1	neutral (-2)	8	6	6
nsp12 A3	T15458C	L673P	-3	effect (74)	2	0	0
nsp12 A3	T15460C	Y674H	0	effect (71)	1	0	0
nsp12 A3	T15464C	V675A	0	neutral (-34)	3	0	1
nsp12 A3	A15478G	T680A	1	effect (54)	10	10	10
nsp12 A3	T15481C	S681P	1	effect (72)	10	10	10
nsp12 A3	T15484C	S682P	1	effect (83)	8	6	5
nsp12 A3	A15491G	D684G	1	effect (58)	10	10	10
nsp12 A3	A15496G	T686A	1	effect (41)	7	4	7
nsp12 A3	A15499G	T687A	1	effect (81)	3	0	1
nsp12 A3	C15503T	A688V	0	effect (30)	1	0	0
nsp12 A3	A15506G	Y689C	0	effect (69)	1	0	0
nsp12 A3	T15518C	V693A	0	neutral (-41)	9	7	7
nsp12 A3	A15524G	N695S	1	effect (16)	9	6	8
nsp12 A3	T15527C	I696T	0	neutral (-7)	1	0	1
nsp12 A3	A15533G	Q698R	1	effect (63)	9	10	10
nsp12 A3	T15539C	V700A	0	neutral (-17)	10	10	10
nsp12 A3	A15541G	T701A	1	neutral (-27)	10	10	9
nsp12 A3	A15547G	N703D	2	effect (39)	1	0	0
nsp12 A3	T15551C	V704A	0	effect (4)	1	0	0
nsp12 A3	A15554G	N705S	1	neutral (-71)	3	0	2
nsp12 A3	T15560C	L707P	-3	effect (86)	10	10	10
nsp12 A3	T15565C	S709P	1	effect (39)	9	8	7
nsp12 A3	G15571A	D711H	1	neutral (-56)	1	0	0
nsp12 A3	A15572G	D711G	1	neutral (-55)	9	10	6
nsp12 A3	A15578G	N713S	1	neutral (-85)	9	10	9
nsp12 A3	A15581G	K714R	3	neutral (-81)	1	0	0
nsp12 A3	A15583G	I715V	4	neutral (-85)	5	3	3
nsp12 A3	A15593G	K718R	3	neutral (-88)	8	5	4
nsp12 A3	A15596G	Y719C	0	neutral (-6)	1	0	0
nsp12 A3	T15599C	V720A	0	neutral (-13)	10	6	8
nsp12 A3	A15611G	Q724R	1	effect (20)	4	0	1
nsp12 A3	C15613T	H725Y	0	neutral (-79)	1	0	0

nsp12 A3	A15614G	H725R	2	neutral (-89)	10	10	9
nsp12 A3	A15616G	R726G	-3	neutral (-53)	5	1	2
nsp12 A3	T15620C	L727P	-3	effect (66)	8	9	9
nsp12 A3	T15622C	Y728H	0	effect (47)	1	0	0
nsp12 A3	A15626G	E729G	0	neutral (-16)	10	10	10
nsp12 A3	T15628C	C730R	-4	neutral (-22)	7	1	1
nsp12 A3	T15632C	L731P	-3	effect (67)	7	8	7
nsp12 A3	A15637G	R733G	-3	effect (73)	2	1	1
nsp12 A3	A15641G	N734S	1	neutral (-96)	1	0	0
nsp12 A3	A15647G	D736G	1	neutral (-52)	9	10	10
nsp12 A3	T15650C	V737A	0	neutral (-73)	2	0	1
nsp12 A3	A15653G	D738G	1	effect (36)	10	10	10
nsp12 A3	A15655G	T739A	1	neutral (-86)	10	10	10
nsp12 A3	C15656T	T739I	0	neutral (-69)	0	0	1
nsp12 A3	A15659G	D740G	1	neutral (-27)	10	10	9
nsp12 A3	T15661C	F741L	2	neutral (-54)	6	1	5
nsp12 A3	T15662C	F741S	-3	effect (9)	1	0	0
nsp12 A3	T15665C	V742A	0	neutral (-13)	1	0	0
nsp12 A3	A15667G	N743D	2	neutral (-85)	10	10	10
nsp12 A3	A15671G	E744G	0	neutral (-33)	9	8	10
nsp12 A3/A4	T15673C	F745L	2	effect (23)	10	10	10
nsp12 A4	T15686C	L749S	-3	effect (50)	1	0	0
nsp12 A3	A15692G	K751R	3	effect (39)	3	9	5
nsp12 A4	T15698C	F753S	-3	effect (60)	0	0	1
nsp12 A4	T15700C	S754P	1	effect (6)	10	10	10
nsp12 A4	T15704C	M755T	-1	effect (73)	2	1	0
nsp12 A4	A15706G	M756V	2	neutral (-15)	1	0	1
nsp12 A4	T15707C	M756T	-1	effect (68)	4	2	3
nsp12 A4	A15709G	I757V	4	neutral (-29)	5	1	3
nsp12 A4	A15711G	I757M	2	effect (10)	1	0	0
nsp12 A4	C15712T	L758F	2	neutral (-43)	1	0	0
nsp12 A4	T15713C	L758P	-3	effect (46)	10	10	10
nsp12 A4	T15715C	S759P	1	effect (35)	9	10	10
nsp12 A4	A15719G	D760G	1	effect (55)	7	3	8
nsp12 A4	G15721A	D761N	2	effect (11)	1	0	0
nsp12 A4	T15728C	V763A	0	effect (10)	10	10	10
nsp12 A4	T15731C	V764A	0	neutral (-50)	10	10	10
nsp12 A4	T15733C	C765R	-4	effect (76)	10	10	10
nsp12 A4	T15736C	F766L	2	neutral (-59)	1	0	0
nsp12 A4	T15737C	F766S	-3	effect (37)	3	0	1
nsp12 A4	T15754C	S772P	1	neutral (-88)	10	10	10
nsp12 A4	T15764C	L775P	-3	effect (29)	10	9	8
nsp12 A4	T15767C	V776A	0	neutral (-41)	8	8	7
nsp12 A4	A15772G	S778G	1	neutral (-28)	1	0	1
nsp12 A4	A15779G	K780R	3	neutral (-15)	1	0	0
nsp12 A4	A15782G	N781S	1	neutral (-58)	6	2	4
nsp12 A4	T15784C	F782L	2	effect (57)	9	9	9
nsp12 A4	A15788G	K783R	3	neutral (-85)	3	1	3
nsp12 A4	T15790C	S784P	1	neutral (-66)	9	10	8

nsp12 A4	T15794C	V785A	0	neutral (-73)	10	10	10
nsp12 A4	T15797C	L786P	-3	effect (67)	2	0	2
nsp12 A4	T15802C	Y788H	0	effect (72)	1	0	0
nsp12 A4	A15808G	N790D	2	neutral (-3)	1	0	0
nsp12 A4	A15809G	N790S	1	neutral (-19)	5	3	8
nsp12 A4	T15815C	V792A	0	effect (48)	4	1	2
nsp12 A4	T15821C	M794T	-1	neutral (-22)	0	3	2
nsp12 A4	G15822T	M794I	2	neutral (0)	0	0	1
nsp12 A4	T15823C	S795P	1	neutral (-19)	10	10	10
nsp12 A4	A15827G	E796G	0	effect (29)	8	4	6
nsp12 A4	A15833G	K798R	3	neutral (-7)	9	9	7
nsp12 A4	T15838C	W800R	2	effect (57)	1	0	1
nsp12 A4	G15839A	W800*		effect (41)	1	0	0
nsp12 A4	A15841G	T801A	1	neutral (-45)	10	10	10
nsp12 A4	G15844A	E802K	0	effect (27)	1	0	0
nsp12 A4	A15845G	E802G	0	effect (22)	9	10	10
nsp12 A4	A15847G	T803A	1	neutral (-81)	10	10	10
nsp12 A4	A15851G	D804G	1	effect (21)	10	10	10
nsp12 A4	T15854C	L805P	-3	effect (59)	7	7	8
nsp12 A4	A15860G	K807R	3	neutral (-91)	2	0	0
nsp12 A4	C15868T	H810Y	0	effect (52)	0	0	1
nsp12 A4	A15869G	H810R	2	effect (62)	2	0	0
nsp12 A4	T15880C	S814P	1	effect (27)	10	10	10
nsp12 A4	A15884G	Q815R	1	effect (34)	2	0	0
nsp12 A4	A15887G	H816R	2	neutral (-28)	4	5	5
nsp12 A4	A15892G	M818V	2	neutral (-85)	10	10	10
nsp12 A4	T15896C	L819P	-3	effect (62)	1	0	0
nsp12 A4	T15899C	V820A	0	neutral (-54)	1	0	1
nsp12 A4	A15905G	Q822R	1	neutral (-81)	8	4	6
nsp12 A4	G15906T	Q822H	3	neutral (-85)	0	0	1
nsp12 A4	G15910A	D824N	2	neutral (-12)	1	0	0
nsp12 A4	A15911G	D824G	1	neutral (-50)	7	3	5
nsp12 A4	A15914G	D825G	1	neutral (-69)	1	0	0
nsp12 A4	T15920C	V827A	0	neutral (-53)	10	9	10
nsp12 A4	T15922C	Y828H	0	effect (58)	1	0	0
nsp12 A4	T15926C	L829P	-3	effect (80)	10	10	10
nsp12 A4	A15938G	D833G	1	effect (67)	8	7	9
nsp12 A4	T15943C	S835P	1	effect (10)	2	0	2
nsp12 A4	C15944T	S835L	-3	neutral (0)	2	0	0
nsp12 A4	A15946G	R836G	-3	effect (88)	4	1	1
nsp12 A4	A15949G	I837V	4	neutral (-63)	8	9	5
nsp12 A4	T15964C	C842R	-4	effect (59)	1	0	0
nsp12 A4	T15968C	F843S	-3	neutral (-24)	1	1	0
nsp12 A4	T15971C	V844A	0	effect (10)	1	0	0
nsp12 A4	A15977G	D846G	1	effect (57)	7	7	5
nsp12 A4	A15979G	I847V	4	neutral (-93)	1	0	0
nsp12 A4	T15980C	I847T	0	neutral (-67)	1	1	0
nsp12 A4	A15988G	T850A	1	neutral (-69)	4	6	2
nsp12 A4	A15992G	D851G	1	effect (60)	10	10	10

nsp12 A4	A15997G	T853A	1	neutral (-29)	3	1	1
nsp12 A4	T16001C	L854P	-3	neutral (-43)	1	0	1
nsp12 A4	A16006G	I856V	4	neutral (-86)	10	10	10
nsp12 A4	A16010G	E857G	0	effect (40)	9	8	9
nsp12 A4	T16015C	F859L	2	neutral (-74)	7	8	9
nsp12 A4	T16016C	F859S	-3	effect (1)	3	1	2
nsp12 A4	T16019C	V860A	0	neutral (-37)	3	1	1
nsp12 A4	T16021C	S861P	1	effect (73)	6	4	4
nsp12 A4	C16028T	A863V	0	effect (11)	1	0	0
nsp12 A4	A16030G	I864V	4	neutral (-51)	2	1	0
nsp12 A4	A16034G	D865G	1	effect (81)	8	7	8
nsp12 A4	C16049T	T870I	0	neutral (-81)	0	0	1
nsp12 A4	A16052G	K871R	3	neutral (-86)	1	0	0
spike A5	T22874C	S438P	1	neutral (-50)	8	10	9
spike A5	T22884C	L441P	-3	effect (53)	4	7	4
spike A5	T22889C	S443P	1	neutral (-9)	4	2	3
spike A5	A22893G	K444R	3	neutral (-58)	1	0	0
spike A5	T22896C	V445A	0	neutral (-50)	6	7	3
spike A5	T22917C	L452P	-3	neutral (-16)	8	10	8
spike A5	T22928C	F456L	2	neutral (-67)	3	3	1
spike A5	T22929C	F456S	-3	neutral (-32)	3	2	1
spike A5	A22934G	K458E	0	neutral (-31)	0	2	2
spike A5	A22935G	K458R	3	neutral (-76)	8	10	9
spike A5	T22937C	S459P	1	neutral (-28)	8	10	8
spike A5	T22944C	L461P	-3	effect (76)	8	10	9
spike A5	A22946G	K462E	0	effect (62)	0	1	0
spike A5	T22952C	F464L	2	neutral (-59)	1	0	0
spike A5	A22956G	E465G	0	neutral (-36)	8	10	9
spike A5	A22958G	R466G	-3	effect (11)	8	10	9
spike A5	A22962G	D467G	1	neutral (-14)	8	10	9
spike A5	A22964G	I468V	4	neutral (-88)	0	1	0
spike A5	T22965C	I468T	0	neutral (-23)	1	0	0
spike A5	T22967C	S469P	1	neutral (-48)	1	1	0
spike A5	A22976G	I472V	4	neutral (-95)	4	5	0
spike A5	T22977C	I472T	0	neutral (-70)	3	2	0
spike A5	A22983G	Q474R	1	neutral (-60)	3	5	6
spike A5	C22986T	A475V	0	neutral (-88)	1	0	0
spike A5	A22991G	S477G	1	neutral (-60)	0	0	1
spike A5	A22994G	T478A	1	neutral (-73)	5	5	3
spike A5	C22997T	P479S	1	neutral (-16)	1	0	0
spike A5	A23004G	N481S	1	neutral (-90)	2	1	1
spike A5	T23010C	V483A	0	neutral (-69)	8	8	9
spike A5	T23030C	F490L	2	neutral (-59)	8	10	9
spike A5	T23042C[f]	S494P	1	neutral (-25)	3	3	0
spike A5	A23046G	Y495C	0	effect (4)	0	0	1
spike A5	T23051C	F497L	2	neutral (-79)	3	3	0
spike A5	T23052C	F497S	-3	effect (4)	1	1	0
spike A5	A23055G	Q498R	1	neutral (-52)	1	1	0
spike A5	C23061T	T500I	0	neutral (-6)	1	0	0

spike A5	T23070C	V503A	0	neutral (-55)	7	9	7
spike A5	A23076G	Y505C	0	effect (6)	0	1	0
spike A5	A23079G	Q506R	1	effect (21)	3	2	1
spike A5	A23087G	R509G	-3	neutral (-32)	5	7	5
spike A5	T23100C	L513P	-3	effect (73)	8	10	9
spike A5	T23102C	S514P	1	effect (9)	5	6	8
spike A5	A23109G	E516G	0	neutral (-49)	5	2	1
spike A5	T23112C	L517P	-3	effect (11)	8	10	9
spike A5	A23118G	H519R	2	neutral (-48)	5	3	4
spike A5	C23127T[f]	A522V	0	neutral (-71)	0	0	1
spike A5	A23129G	T523A	1	neutral (-45)	8	8	8
spike A5	T23133C	V524A	0	effect (41)	5	7	8
spike A5	A23148G	K529R	3	neutral (-71)	2	2	2
spike A5	T23150C	S530P	1	neutral (-36)	8	10	9
spike A5	A23153G	T531A	1	neutral (-63)	0	0	1
spike A5	T23163C	V534A	0	neutral (-4)	4	1	4
spike A5	A23168G	N536D	2	neutral (-50)	5	5	1
spike A5	A23169G	N536S	1	neutral (-50)	8	10	9
spike A5	A23172G	K537R	3	neutral (-35)	2	1	0
spike A5	T23178C	V539A	0	effect (3)	8	10	9
spike A5	A23180G	N540D	2	neutral (-68)	0	1	0
spike A5	T23184C	F541S	-3	effect (87)	0	1	0
spike A5	A23187G	N542S	1	neutral (-12)	2	2	0
spike A5	T23189C	F543L	2	neutral (-61)	3	4	3
spike A5	A23193G	N544S	1	neutral (-67)	2	2	0
spike A5	A23201G	T547A	1	effect (12)	5	8	7
spike A5	C23202T	T547I	0	effect (72)	0	0	1
spike A5	A23207G	T549A	1	neutral (-33)	8	9	8
spike A5	T23214C	V551A	0	effect (34)	8	9	9
spike A5	T23217C	L552P	-3	effect (89)	2	0	1
spike A5	A23223G	E554G	0	effect (12)	8	10	9
spike A5	T23225C	S555P	1	effect (31)	7	9	7
spike A5	A23229G	N556S	1	neutral (-56)	7	10	7
spike A5	A23235G	K558R	3	neutral (-86)	0	1	0
spike A5	T23241C	L560P	-3	neutral (-11)	5	5	2
spike A5	T23246C	F562L	2	neutral (-12)	4	3	4
spike A5	T23247C	F562S	-3	effect (21)	3	4	4
spike A5	A23250G	Q563R	1	neutral (-21)	3	2	1
spike A5	A23253G	Q564R	1	effect (15)	0	1	0
spike A5/A6	A23261G	R567G	-3	effect (47)	9	10	8
spike A5/A6	A23265G	D568G	1	neutral (-5)	9	10	9
spike A5	A23267G	I569V	4	neutral (-76)	3	2	0
spike A6	T23268C	I569T	0	neutral (-49)	1	0	0
spike A6	C23271T	A570V	0	neutral (-88)	0	1	0
spike A6	G23273A	D571N	2	neutral (-46)	1	0	0
spike A6	A23274G	D571G	1	neutral (-61)	3	0	0
spike A6	A23276G	T572A	1	neutral (-66)	6	1	4
spike A6	C23280T	T573I	0	neutral (-54)	1	0	0
spike A6	A23283G	D574G	1	neutral (-39)	2	0	1

spike A6	C23286T	A575V	0	neutral (-71)	1	0	0
spike A6	T23289C	V576A	0	neutral (-35)	10	10	10
spike A6	A23295G	D578G	1	effect (42)	4	1	4
spike A6	A23301G	Q580R	1	neutral (-38)	4	5	4
spike A6	G23302T	Q580H	3	neutral (-42)	0	1	0
spike A6	A23303G	T581A	1	effect (42)	9	8	7
spike A6	T23307C	L582P	-3	effect (28)	7	8	8
spike A6	A23310G	E583G	0	neutral (-12)	9	6	9
spike A6	G23311T	E583D	3	neutral (-59)	0	0	1
spike A6	A23312G	I584V	4	neutral (-95)	1	2	2
spike A6	T23313C	I584T	0	neutral (-68)	3	0	1
spike A6	A23319G	D586G	1	effect (5)	9	6	8
spike A6	A23321G	I587V	4	neutral (-74)	1	0	0
spike A6	T23322C	I587T	0	effect (55)	3	0	3
spike A6	T23330C	C590R	-4	effect (93)	8	8	8
spike A6	T23333C	S591P	1	neutral (-25)	9	7	8
spike A6	T23337C	F592S	-3	neutral (-68)	3	0	0
spike A6	T23346C	V595A	0	effect (10)	10	10	10
spike A6	A23348G	S596G	1	effect (49)	0	1	2
spike A6	T23352C	V597A	0	neutral (-50)	10	10	10
spike A6	A23357G	T599A	1	neutral (-21)	3	1	3
spike A6	A23366G	T602A	1	neutral (-65)	10	10	10
spike A6	A23370G	N603S	1	neutral (-20)	1	1	1
spike A6	A23379G	N606S	1	neutral (-68)	4	0	1
spike A6	T23385C	V608A	0	neutral (-59)	9	10	9
spike A6	T23391C	V610A	0	neutral (-7)	10	10	10
spike A6	T23394C	L611P	-3	effect (85)	10	10	10
spike A6	C23399T	Q613*		neutral (-57)	1	0	0
spike A6	A23400G	Q613R	1	neutral (-61)	9	5	7
spike A6	A23403G[f]	D614G	1	neutral (-52)	10	9	10
spike A6	A23403G[f]+T23404C	D614G	1	neutral (-52)	8	6	5
spike A6	T23406C	V615A	0	neutral (-30)	10	8	9
spike A6	A23409G	N616S	1	neutral (-85)	2	3	1
spike A6	T23411C	C617R	-4	effect (84)	7	5	7
spike A6	A23414G	T618A	1	neutral (-60)	10	10	9
spike A6	T23421C	V620A	0	neutral (-12)	10	10	10
spike A6	G23426A	V622I	4	neutral (-56)	1	0	0
spike A6	T23427C	V622A	0	neutral (-50)	8	9	9
spike A6	T23433C	I624T	0	effect (8)	5	2	7
spike A6	A23436G	H625R	2	neutral (-14)	2	0	1
spike A6	A23442G	D627G	1	neutral (-14)	1	0	1
spike A6	A23445G	Q628R	1	neutral (-22)	3	0	1
spike A6	A23446G	Q628G	-1	neutral (0)	1	1	2
spike A6	T23448C	L629P	-3	effect (17)	5	2	4
spike A6	T23459C	W633R	2	effect (75)	3	0	3
spike A6	T23466C	V635A	0	neutral (-16)	10	9	8
spike A6	T23471C	S637P	1	effect (44)	1	0	0
spike A6	A23474G	T638A	1	effect (17)	1	0	1
spike A6	C23475T	T638I	0	effect (66)	1	0	0

spike A6	A23476G	T638M	-1	effect (60)	9	10	8
spike A6	T23480C	S640P	1	neutral (-45)	8	5	8
spike A6	C23481T	S640F	-3	neutral (-14)	1	0	0
spike A6	T23487C	V642A	0	neutral (-53)	10	10	9
spike A6	T23489C	F643L	2	effect (3)	8	6	8
spike A6	A23493G	Q644R	1	effect (34)	2	0	0
spike A6	A23495G	T645A	1	effect (52)	10	10	9
spike A6	T23507C	C649R	-4	effect (91)	3	1	4
spike A6	A23513G	I651V	4	neutral (-86)	1	0	0
spike A6	A23515G	I651M	2	neutral (0)	2	1	2
spike A6	G23517A	G652E	0	effect (78)	1	0	0
spike A6	G23519A	A653T	1	neutral (-75)	1	0	0
spike A6	C23520T	A653V	0	neutral (-91)	1	0	0
spike A6	A23523G	E654G	0	effect (44)	1	0	1
spike A6	A23526G	H655R	2	effect (21)	2	1	3
spike A6	T23529C	V656A	0	neutral (-41)	10	9	10
spike A6	A23531G	N657D	2	neutral (-21)	9	9	9
spike A6	A23532G	N657S	1	neutral (-81)	3	0	3
spike A6	A23535G	N658S	1	neutral (-63)	3	1	4
spike A6	T23537C	S659P	1	effect (23)	5	4	5
spike A6	A23544G	E661G	0	effect (41)	9	5	9
spike A6	T23546C	C662R	-4	effect (92)	4	0	2
spike A6	A23550G	D663G	1	neutral (-8)	10	10	10
spike A6	A23552G	I664V	4	neutral (-60)	2	0	3
spike A6	A23554G	I664M	2	neutral (-75)	1	0	1
spike A6	A23572G	I670M	2	neutral (-45)	1	0	0
spike A6	T23582C	Y674H	0	effect (26)	1	0	0
spike A6	A23586G	Q675R	1	neutral (-15)	7	2	4
spike A6	A23588G	T676A	1	neutral (-29)	10	10	10
spike A6	A23592G	Q677R	1	neutral (-52)	3	1	4
spike A6	A23594G	T678A	1	neutral (-23)	10	10	10
spike A6	A23598G	N679S	1	neutral (-22)	1	0	1
spike A6	T23600C	S680P	1	effect (24)	1	0	2
spike A6	G23607A	R682Q	1	effect (24)	1	0	0
spike A6	C23609T	R683W	2	effect (81)	1	0	0
spike A6	C23615T	R685C	-4	effect (26)	1	0	0
spike A6	A23631G	Q690R	1	neutral (-19)	1	0	0
spike A6	T23633C	S691P	1	neutral (-79)	2	0	0
spike A6	A23636G	I692V	4	neutral (-62)	2	2	3
spike A6	A23639G	I693V	4	neutral (-86)	1	0	0
spike A6	T23645C	Y695H	0	effect (57)	1	0	0

[a] Genomic region and amplicon. The genomic regions covered by each amplicon are depicted in Figure S1 of the Supplementary Material.

[b] The SARS-CoV-2 genome residue numbering is according to the NCBI reference sequence (accession number NC_045512.2).

[c] Amino acid residues (single letter code) are numbered from N- to the C- terminus of nsp12 (polymerase)- and spike-coding regions. Asterisk indicates STOP codon.

[d] PAM250 (accepted point mutation 250) substitution matrix (Feng and Doolittle, Methods in Enzymology 266: 368-382, 1996). PAM250<0, lower acceptability than expected; PAM250=0, acceptability as expected; PAM250>0, acceptability higher than expected.

[e] SNAP2 (Screening for Non-Acceptable Polymorphism 2) prediction score values (Hecht et al, BMC Genomics 2015, 16 Suppl 8:S1). Values between -100 to 0 correspond to neutral substitution and values between 0 to 100 correspond to substitution with an effect.

[f] Mutation detected at frequency of 90-100% counted relative to the Wuhan-Hu-1 NCBI reference sequence (NC_045512.2).

Table S4. Specific oligonucleotides designed to amplify and sequence the nsp12 (polymerase)- and spike-coding regions of SARS-CoV-2, and oligonucleotides used for site mutagenesis (listed at the end).

Primer	Region	Sense	Sequence (5' – 3')	Genome positions[a]	Tm (°C)
nsp12-CoV2-u14511	nsp12	Fw	GGATGTAAACTTACATAGCTCTA	14511-14533	49.9
nsp12-CoV2-d14942	nsp12	Rv	GATTTGTCTAGGTTGTTGACGA	14942-14921	51.1
nsp12-CoV2-u14890	nsp12	Fw	GATGGTGGCTGTATTAATGCT	14890-14910	50.5
nsp12-CoV2-d15320	nsp12	Rv	GGGATGGCTCTATCACATTTA	15320-15300	50.5
nsp12-CoV2-u15268	nsp12	Fw	GAAAACCCTCACCTTATGGG	15268-15287	51.8
nsp12-CoV2-d15717	nsp12	Rv	AGAGAGTATCATCATTGAGAAATG	15717-15694	50.6
nsp12-CoV2-u15646	nsp12	Fw	GATGTTGACACAGACTTTGTGAA	15646-15668	51.7
nsp12-CoV2-d16075	nsp12	Rv	CAGCATACTCCTGATTAGGAT	16075-16055	50.5
spk-CoV2-u22853	spike	Fw	GGCTGCGTTATAGCTTGGA	22853-22871	51.1
spk-CoV2-d23288	spike	Rv	CAGCATCAGTAGTGTCAGCA	23288-23269	51.8
spk-CoV2-u23236	spike	Fw	GTTTCTGCCTTTCCAACAATTTG	23236-23258	51.7
spk-CoV2-d23666	spike	Rv	CTGCACCAAGTGACATAGTGT	23666-23646	52.4
To introduce mutation F419L or D421G[b]	nsp12	Fw	AAGGGCTTTTTCAAAGAAGGTAGCAG		
To introduce mutation F419L[b]	nsp12	Rv	GCTCACGGCAAAATCATACAGATCCTTGTTG		
To introduce mutation D421G[b]	nsp12	Rv	GCTCACGGCAAAGCCATAGAAATCCTTGTTG		
To introduce mutation F441L[b]	nsp12	Fw	GTAATGCAGCCATCAGCGATTATG		
To introduce mutation F441L[b]	nsp12	Rv	CATCCTGTGCAAACAGAAAATGCTTCAGTTCAAC		

[a] Residues are numbered according to the SARS-CoV-2 reference Wuhan-Hu-1 genome (NCBI accession number NC_045512.2).

[b] Oligonucleotides used for site mutagenesis into nsp12-coding region.