

SEQUENCE LISTING

<110> Regeneron Pharmaceuticals, Inc.

<120> CRISPR/CAS DROPOUT SCREENING PLATFORM TO REVEAL GENETIC
VULNERABILITIES ASSOCIATED WITH TAU AGGREGATION

<130> 057766-544640

<150> US 62/820,101

<151> 2019-03-18

<160> 43

<170> PatentIn version 3.5

<210> 1

<211> 31

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

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Gln	Thr	Ala	Pro	Val	Pro	Met	Pro	Asp	Leu	Lys	Asn	Val	Lys	Ser	Lys
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Ile	Gly	Ser	Thr	Glu	Asn	Leu	Lys	His	Gln	Pro	Gly	Gly	Gly	Lys
			20					25					30	

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Val	Gln	Ile	Ile	Asn	Lys	Lys	Leu	Asp	Leu	Ser	Asn	Val	Gln	Ser	Lys
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Cys	Gly	Ser	Lys	Asp	Asn	Ile	Lys	His	Val	Pro	Gly	Gly	Gly	Ser
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Val Gln Ile Val Tyr Lys Pro Val Asp Leu Ser Lys Val Thr Ser Lys
1 5 10 15

Cys Gly Ser Leu Gly Asn Ile His His Lys Pro Gly Gly Gly Gln
20 25 30

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Val Glu Val Lys Ser Glu Lys Leu Asp Phe Lys Asp Arg Val Gln Ser
1 5 10 15

Lys Ile Gly Ser Leu Asp Asn Ile Thr His Val Pro Gly Gly Gly Asn
20 25 30

<210> 5

<211> 93

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gagaacctga agcaccagcc gggaggcgagg aag 93

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 gataatatca aacacgtccc gggaggcggc agt 93

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 <212> DNA
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 ggcaacatcc atcataaacc aggaggtggc cag 93

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 ctggacaata tcaccacgt ccctggcgga ggaaat 96

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 <211> 133
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 <223> Synthetic

<400> 9

Leu Gln Thr Ala Pro Val Pro Met Pro Asp Leu Lys Asn Val Lys Ser
 1 5 10 15

Lys Ile Gly Ser Thr Glu Asn Leu Lys His Gln Pro Gly Gly Gly Lys
 20 25 30

Val Gln Ile Ile Asn Lys Lys Leu Asp Leu Ser Asn Val Gln Ser Lys
 35 40 45

Cys Gly Ser Lys Asp Asn Ile Lys His Val Pro Gly Gly Gly Ser Val
 50 55 60

Gln Ile Val Tyr Lys Pro Val Asp Leu Ser Lys Val Thr Ser Lys Cys
 65 70 75 80

Gly Ser Leu Gly Asn Ile His His Lys Pro Gly Gly Gly Gln Val Glu
 85 90 95

Val Lys Ser Glu Lys Leu Asp Phe Lys Asp Arg Val Gln Ser Lys Ile
 100 105 110

Gly Ser Leu Asp Asn Ile Thr His Val Pro Gly Gly Gly Asn Lys Lys
 115 120 125

Ile Glu Thr His Lys
 130

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 ggctcattag gcaacatcca tcataaacca ggaggtggcc aggtggaagt aaaatctgag 300
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 <212> PRT
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<400> 11

Leu Gln Thr Ala Pro Val Pro Met Pro Asp Leu Lys Asn Val Lys Ser
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Lys Ile Gly Ser Thr Glu Asn Leu Lys His Gln Pro Gly Gly Gly Lys
20 25 30

Val Gln Ile Ile Asn Lys Lys Leu Asp Leu Ser Asn Val Gln Ser Lys
35 40 45

Cys Gly Ser Lys Asp Asn Ile Lys His Val Ser Gly Gly Gly Ser Val
50 55 60

Gln Ile Val Tyr Lys Pro Val Asp Leu Ser Lys Val Thr Ser Lys Cys
65 70 75 80

Gly Ser Leu Gly Asn Ile His His Lys Pro Gly Gly Gly Gln Val Glu
85 90 95

Val Lys Ser Glu Lys Leu Asp Phe Lys Asp Arg Val Gln Ser Lys Ile
100 105 110

Gly Ser Leu Asp Asn Ile Thr His Val Pro Gly Gly Gly Asn Lys Lys
115 120 125

Ile Glu Thr His Lys
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<212> DNA

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gatcttagca acgtccagtc caagtgtggc tcaaaggata atatcaaaca cgtctcggga 180

ggcggcagtg tgcaaatagt ctacaaacca gttgacctga gcaaggtgac ctccaagtgt 240
 ggctcattag gcaacatcca tcataaacca ggaggtggcc aggtggaagt aaaatctgag 300
 aagcttgact tcaaggacag agtccagtcg aagattgggt ccctggacaa tatcaccac 360
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Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu Val
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Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly Glu
 20 25 30

Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile Cys
 35 40 45

Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr Leu
 50 55 60

Thr Trp Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys Gln
 65 70 75 80

His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu Arg
 85 90 95

Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu Val
 100 105 110

Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly Ile
 115 120 125

Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr Asn
 130 135 140

Tyr Ile Ser His Asn Val Tyr Ile Thr Ala Asp Lys Gln Lys Asn Gly
145 150 155 160

Ile Lys Ala Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser Val
165 170 175

Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly Pro
180 185 190

Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu Ser
195 200 205

Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe Val
210 215 220

Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys
225 230 235

<210> 14
<211> 714
<212> DNA
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ctggagtaca actacatcag ccacaacgtc tatatcaccg ccgacaagca gaagaacggc 480
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ctgagcaccc agtccgccct gagcaaagac cccaacgaga agcgcgatca catggtcctg 660

ctggagttcg tgaccgccgc cgggatcact ctcggcatgg acgagctgta caag

714

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Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu Val
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Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly Glu
20 25 30

Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile Cys
35 40 45

Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr Phe
50 55 60

Gly Tyr Gly Leu Gln Cys Phe Ala Arg Tyr Pro Asp His Met Lys Gln
65 70 75 80

His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu Arg
85 90 95

Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu Val
100 105 110

Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly Ile
115 120 125

Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr Asn
130 135 140

Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn Gly
145 150 155 160

Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser Val
165 170 175

Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly Pro
180 185 190

Val Leu Leu Pro Asp Asn His Tyr Leu Ser Tyr Gln Ser Ala Leu Ser
195 200 205

Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe Val
210 215 220

Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu
225 230 235

<210> 16
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<212> DNA
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<223> Synthetic

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aagctgaccc tgaagttcat ctgcaccacc ggcaagctgc ccgtgccctg gcccaccctc 180
gtgaccacct tcggctacgg cctgcagtgc ttgcccgtc accccgacca catgaagcag 240
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aaggacgacg gcaactacaa gaccgcgcc gaggtgaagt tcgagggcga caccctggtg 360
aaccgcatcg agctgaaggg catcgacttc aaggaggacg gcaacatcct ggggcacaag 420
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atcaaggtga acttcaagat ccgccacaac atcgaggacg gcagcgtgca gctcgccgac 540
cactaccagc agaacacccc catcggcgac ggccccgtgc tgctgcccga caaccactac 600
ctgagctacc agtccgccct gagcaaagac cccaacgaga agcgcgatca catggtcctg 660
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ggcaccgagu cggugcu 77

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<211> 82

<212> RNA

<213> Artificial Sequence

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<400> 18

guuggaacca uucaaacag cauagcaagu uaaaauaagg cuaguccguu aucaacuuga 60

aaaaguggca ccgagucggu gc 82

<210> 19

<211> 76

<212> RNA

<213> Artificial Sequence

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<223> Synthetic

<400> 19

guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc cguuaucaac uugaaaaagu 60

ggcaccgagu cggugc 76

<210> 20

<211> 86

<212> RNA

<213> Artificial Sequence

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<400> 20

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uugaaaaagu ggcaccgagu cggugc 86

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<211> 1392

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<222> (1)..(1384)
<223> Cas9

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<222> (1385)..(1392)
<223> FLAG

<400> 21

Met Asp Lys Lys Tyr Ser Ile Gly Leu Asp Ile Gly Thr Asn Ser Val
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Gly Trp Ala Val Ile Thr Asp Glu Tyr Lys Val Pro Ser Lys Lys Phe
20 25 30

Lys Val Leu Gly Asn Thr Asp Arg His Ser Ile Lys Lys Asn Leu Ile
35 40 45

Gly Ala Leu Leu Phe Asp Ser Gly Glu Thr Ala Glu Ala Thr Arg Leu
50 55 60

Lys Arg Thr Ala Arg Arg Arg Tyr Thr Arg Arg Lys Asn Arg Ile Cys
65 70 75 80

Tyr Leu Gln Glu Ile Phe Ser Asn Glu Met Ala Lys Val Asp Asp Ser
85 90 95

Phe Phe His Arg Leu Glu Glu Ser Phe Leu Val Glu Glu Asp Lys Lys
100 105 110

His Glu Arg His Pro Ile Phe Gly Asn Ile Val Asp Glu Val Ala Tyr
115 120 125

His Glu Lys Tyr Pro Thr Ile Tyr His Leu Arg Lys Lys Leu Val Asp
130 135 140

Ser Thr Asp Lys Ala Asp Leu Arg Leu Ile Tyr Leu Ala Leu Ala His
 145 150 155 160

Met Ile Lys Phe Arg Gly His Phe Leu Ile Glu Gly Asp Leu Asn Pro
 165 170 175

Asp Asn Ser Asp Val Asp Lys Leu Phe Ile Gln Leu Val Gln Thr Tyr
 180 185 190

Asn Gln Leu Phe Glu Glu Asn Pro Ile Asn Ala Ser Gly Val Asp Ala
 195 200 205

Lys Ala Ile Leu Ser Ala Arg Leu Ser Lys Ser Arg Arg Leu Glu Asn
 210 215 220

Leu Ile Ala Gln Leu Pro Gly Glu Lys Lys Asn Gly Leu Phe Gly Asn
 225 230 235 240

Leu Ile Ala Leu Ser Leu Gly Leu Thr Pro Asn Phe Lys Ser Asn Phe
 245 250 255

Asp Leu Ala Glu Asp Ala Lys Leu Gln Leu Ser Lys Asp Thr Tyr Asp
 260 265 270

Asp Asp Leu Asp Asn Leu Leu Ala Gln Ile Gly Asp Gln Tyr Ala Asp
 275 280 285

Leu Phe Leu Ala Ala Lys Asn Leu Ser Asp Ala Ile Leu Leu Ser Asp
 290 295 300

Ile Leu Arg Val Asn Thr Glu Ile Thr Lys Ala Pro Leu Ser Ala Ser
 305 310 315 320

Met Ile Lys Arg Tyr Asp Glu His His Gln Asp Leu Thr Leu Leu Lys
 325 330 335

Ala Leu Val Arg Gln Gln Leu Pro Glu Lys Tyr Lys Glu Ile Phe Phe
 340 345 350

Asp Gln Ser Lys Asn Gly Tyr Ala Gly Tyr Ile Asp Gly Gly Ala Ser
 355 360 365

Gln Glu Glu Phe Tyr Lys Phe Ile Lys Pro Ile Leu Glu Lys Met Asp
370 375 380

Gly Thr Glu Glu Leu Leu Val Lys Leu Asn Arg Glu Asp Leu Leu Arg
385 390 395 400

Lys Gln Arg Thr Phe Asp Asn Gly Ser Ile Pro His Gln Ile His Leu
405 410 415

Gly Glu Leu His Ala Ile Leu Arg Arg Gln Glu Asp Phe Tyr Pro Phe
420 425 430

Leu Lys Asp Asn Arg Glu Lys Ile Glu Lys Ile Leu Thr Phe Arg Ile
435 440 445

Pro Tyr Tyr Val Gly Pro Leu Ala Arg Gly Asn Ser Arg Phe Ala Trp
450 455 460

Met Thr Arg Lys Ser Glu Glu Thr Ile Thr Pro Trp Asn Phe Glu Glu
465 470 475 480

Val Val Asp Lys Gly Ala Ser Ala Gln Ser Phe Ile Glu Arg Met Thr
485 490 495

Asn Phe Asp Lys Asn Leu Pro Asn Glu Lys Val Leu Pro Lys His Ser
500 505 510

Leu Leu Tyr Glu Tyr Phe Thr Val Tyr Asn Glu Leu Thr Lys Val Lys
515 520 525

Tyr Val Thr Glu Gly Met Arg Lys Pro Ala Phe Leu Ser Gly Glu Gln
530 535 540

Lys Lys Ala Ile Val Asp Leu Leu Phe Lys Thr Asn Arg Lys Val Thr
545 550 555 560

Val Lys Gln Leu Lys Glu Asp Tyr Phe Lys Lys Ile Glu Cys Phe Asp
565 570 575

Ser Val Glu Ile Ser Gly Val Glu Asp Arg Phe Asn Ala Ser Leu Gly
580 585 590

Thr Tyr His Asp Leu Leu Lys Ile Ile Lys Asp Lys Asp Phe Leu Asp
595 600 605

Asn Glu Glu Asn Glu Asp Ile Leu Glu Asp Ile Val Leu Thr Leu Thr
610 615 620

Leu Phe Glu Asp Arg Glu Met Ile Glu Glu Arg Leu Lys Thr Tyr Ala
625 630 635 640

His Leu Phe Asp Asp Lys Val Met Lys Gln Leu Lys Arg Arg Arg Tyr
645 650 655

Thr Gly Trp Gly Arg Leu Ser Arg Lys Leu Ile Asn Gly Ile Arg Asp
660 665 670

Lys Gln Ser Gly Lys Thr Ile Leu Asp Phe Leu Lys Ser Asp Gly Phe
675 680 685

Ala Asn Arg Asn Phe Met Gln Leu Ile His Asp Asp Ser Leu Thr Phe
690 695 700

Lys Glu Asp Ile Gln Lys Ala Gln Val Ser Gly Gln Gly Asp Ser Leu
705 710 715 720

His Glu His Ile Ala Asn Leu Ala Gly Ser Pro Ala Ile Lys Lys Gly
725 730 735

Ile Leu Gln Thr Val Lys Val Val Asp Glu Leu Val Lys Val Met Gly
740 745 750

Arg His Lys Pro Glu Asn Ile Val Ile Glu Met Ala Arg Glu Asn Gln
755 760 765

Thr Thr Gln Lys Gly Gln Lys Asn Ser Arg Glu Arg Met Lys Arg Ile
770 775 780

Glu Glu Gly Ile Lys Glu Leu Gly Ser Gln Ile Leu Lys Glu His Pro
785 790 795 800

Val Glu Asn Thr Gln Leu Gln Asn Glu Lys Leu Tyr Leu Tyr Tyr Leu

805										810					815				
Gln	Asn	Gly	Arg	Asp	Met	Tyr	Val	Asp	Gln	Glu	Leu	Asp	Ile	Asn	Arg				
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Leu	Ser	Asp	Tyr	Asp	Val	Asp	His	Ile	Val	Pro	Gln	Ser	Phe	Leu	Lys				
		835					840					845							
Asp	Asp	Ser	Ile	Asp	Asn	Lys	Val	Leu	Thr	Arg	Ser	Asp	Lys	Asn	Arg				
	850					855					860								
Gly	Lys	Ser	Asp	Asn	Val	Pro	Ser	Glu	Glu	Val	Val	Lys	Lys	Met	Lys				
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Asn	Tyr	Trp	Arg	Gln	Leu	Leu	Asn	Ala	Lys	Leu	Ile	Thr	Gln	Arg	Lys				
				885					890					895					
Phe	Asp	Asn	Leu	Thr	Lys	Ala	Glu	Arg	Gly	Gly	Leu	Ser	Glu	Leu	Asp				
			900					905					910						
Lys	Ala	Gly	Phe	Ile	Lys	Arg	Gln	Leu	Val	Glu	Thr	Arg	Gln	Ile	Thr				
	915						920					925							
Lys	His	Val	Ala	Gln	Ile	Leu	Asp	Ser	Arg	Met	Asn	Thr	Lys	Tyr	Asp				
	930					935					940								
Glu	Asn	Asp	Lys	Leu	Ile	Arg	Glu	Val	Lys	Val	Ile	Thr	Leu	Lys	Ser				
945					950					955					960				
Lys	Leu	Val	Ser	Asp	Phe	Arg	Lys	Asp	Phe	Gln	Phe	Tyr	Lys	Val	Arg				
				965					970					975					
Glu	Ile	Asn	Asn	Tyr	His	His	Ala	His	Asp	Ala	Tyr	Leu	Asn	Ala	Val				
			980					985					990						
Val	Gly	Thr	Ala	Leu	Ile	Lys	Lys	Tyr	Pro	Lys	Leu	Glu	Ser	Glu	Phe				
		995					1000					1005							
Val	Tyr	Gly	Asp	Tyr	Lys	Val	Tyr	Asp	Val	Arg	Lys	Met	Ile	Ala					
	1010					1015					1020								

Lys	Ser	Glu	Gln	Glu	Ile	Gly	Lys	Ala	Thr	Ala	Lys	Tyr	Phe	Phe
1025						1030					1035			
Tyr	Ser	Asn	Ile	Met	Asn	Phe	Phe	Lys	Thr	Glu	Ile	Thr	Leu	Ala
1040						1045					1050			
Asn	Gly	Glu	Ile	Arg	Lys	Arg	Pro	Leu	Ile	Glu	Thr	Asn	Gly	Glu
1055						1060					1065			
Thr	Gly	Glu	Ile	Val	Trp	Asp	Lys	Gly	Arg	Asp	Phe	Ala	Thr	Val
1070						1075					1080			
Arg	Lys	Val	Leu	Ser	Met	Pro	Gln	Val	Asn	Ile	Val	Lys	Lys	Thr
1085						1090					1095			
Glu	Val	Gln	Thr	Gly	Gly	Phe	Ser	Lys	Glu	Ser	Ile	Leu	Pro	Lys
1100						1105					1110			
Arg	Asn	Ser	Asp	Lys	Leu	Ile	Ala	Arg	Lys	Lys	Asp	Trp	Asp	Pro
1115						1120					1125			
Lys	Lys	Tyr	Gly	Gly	Phe	Asp	Ser	Pro	Thr	Val	Ala	Tyr	Ser	Val
1130						1135					1140			
Leu	Val	Val	Ala	Lys	Val	Glu	Lys	Gly	Lys	Ser	Lys	Lys	Leu	Lys
1145						1150					1155			
Ser	Val	Lys	Glu	Leu	Leu	Gly	Ile	Thr	Ile	Met	Glu	Arg	Ser	Ser
1160						1165					1170			
Phe	Glu	Lys	Asn	Pro	Ile	Asp	Phe	Leu	Glu	Ala	Lys	Gly	Tyr	Lys
1175						1180					1185			
Glu	Val	Lys	Lys	Asp	Leu	Ile	Ile	Lys	Leu	Pro	Lys	Tyr	Ser	Leu
1190						1195					1200			
Phe	Glu	Leu	Glu	Asn	Gly	Arg	Lys	Arg	Met	Leu	Ala	Ser	Ala	Gly
1205						1210					1215			
Glu	Leu	Gln	Lys	Gly	Asn	Glu	Leu	Ala	Leu	Pro	Ser	Lys	Tyr	Val
1220						1225					1230			

Asn Phe Leu Tyr Leu Ala Ser His Tyr Glu Lys Leu Lys Gly Ser
1235 1240 1245

Pro Glu Asp Asn Glu Gln Lys Gln Leu Phe Val Glu Gln His Lys
1250 1255 1260

His Tyr Leu Asp Glu Ile Ile Glu Gln Ile Ser Glu Phe Ser Lys
1265 1270 1275

Arg Val Ile Leu Ala Asp Ala Asn Leu Asp Lys Val Leu Ser Ala
1280 1285 1290

Tyr Asn Lys His Arg Asp Lys Pro Ile Arg Glu Gln Ala Glu Asn
1295 1300 1305

Ile Ile His Leu Phe Thr Leu Thr Asn Leu Gly Ala Pro Ala Ala
1310 1315 1320

Phe Lys Tyr Phe Asp Thr Thr Ile Asp Arg Lys Arg Tyr Thr Ser
1325 1330 1335

Thr Lys Glu Val Leu Asp Ala Thr Leu Ile His Gln Ser Ile Thr
1340 1345 1350

Gly Leu Tyr Glu Thr Arg Ile Asp Leu Ser Gln Leu Gly Gly Asp
1355 1360 1365

Lys Arg Pro Ala Ala Thr Lys Lys Ala Gly Gln Ala Lys Lys Lys
1370 1375 1380

Lys Asp Tyr Lys Asp Asp Asp Asp Lys
1385 1390

<210> 22
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<212> DNA
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<221> misc_feature
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<223> Cas9

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<222> (4153)..(4176)
<223> FLAG

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cacagcatca agaagaacct gatcggagcc ctgctgttcg acagcggcga aacagccgag 180
gccacccggc tgaagagaac cgccagaaga agatacacca gacggaagaa ccggatctgc 240
tatctgcaag agatcttcag caacgagatg gccaaaggtgg acgacagctt cttccacaga 300
ctggaagagt cttcctggt ggaagaggat aagaagcacg agcggcaccc catcttcggc 360
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16

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 gugcuuu 67

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35 40 45

Lys Val Leu Gly Asn Thr Asp Arg His Ser Ile Lys Lys Asn Leu Ile
50 55 60

Gly Ala Leu Leu Phe Asp Ser Gly Glu Thr Ala Glu Ala Thr Arg Leu
65 70 75 80

Lys Arg Thr Ala Arg Arg Arg Tyr Thr Arg Arg Lys Asn Arg Ile Cys
85 90 95

Tyr Leu Gln Glu Ile Phe Ser Asn Glu Met Ala Lys Val Asp Asp Ser
100 105 110

Phe Phe His Arg Leu Glu Glu Ser Phe Leu Val Glu Glu Asp Lys Lys
115 120 125

His Glu Arg His Pro Ile Phe Gly Asn Ile Val Asp Glu Val Ala Tyr
130 135 140

His Glu Lys Tyr Pro Thr Ile Tyr His Leu Arg Lys Lys Leu Val Asp
145 150 155 160

Ser Thr Asp Lys Ala Asp Leu Arg Leu Ile Tyr Leu Ala Leu Ala His
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Met Ile Lys Phe Arg Gly His Phe Leu Ile Glu Gly Asp Leu Asn Pro
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Asp Asn Ser Asp Val Asp Lys Leu Phe Ile Gln Leu Val Gln Thr Tyr
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Asn Gln Leu Phe Glu Glu Asn Pro Ile Asn Ala Ser Gly Val Asp Ala
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Lys Ala Ile Leu Ser Ala Arg Leu Ser Lys Ser Arg Arg Leu Glu Asn
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Leu Ile Ala Leu Ser Leu Gly Leu Thr Pro Asn Phe Lys Ser Asn Phe
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Asp Leu Ala Glu Asp Ala Lys Leu Gln Leu Ser Lys Asp Thr Tyr Asp
275 280 285

Asp Asp Leu Asp Asn Leu Leu Ala Gln Ile Gly Asp Gln Tyr Ala Asp
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Leu Phe Leu Ala Ala Lys Asn Leu Ser Asp Ala Ile Leu Leu Ser Asp
305 310 315 320

Ile Leu Arg Val Asn Thr Glu Ile Thr Lys Ala Pro Leu Ser Ala Ser
325 330 335

Met Ile Lys Arg Tyr Asp Glu His His Gln Asp Leu Thr Leu Leu Lys
340 345 350

Ala Leu Val Arg Gln Gln Leu Pro Glu Lys Tyr Lys Glu Ile Phe Phe
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Asp Gln Ser Lys Asn Gly Tyr Ala Gly Tyr Ile Asp Gly Gly Ala Ser
370 375 380

Gln Glu Glu Phe Tyr Lys Phe Ile Lys Pro Ile Leu Glu Lys Met Asp
385 390 395 400

Gly Thr Glu Glu Leu Leu Val Lys Leu Asn Arg Glu Asp Leu Leu Arg
405 410 415

Lys Gln Arg Thr Phe Asp Asn Gly Ser Ile Pro His Gln Ile His Leu
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Gly Glu Leu His Ala Ile Leu Arg Arg Gln Glu Asp Phe Tyr Pro Phe
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Leu Lys Asp Asn Arg Glu Lys Ile Glu Lys Ile Leu Thr Phe Arg Ile
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Pro Tyr Tyr Val Gly Pro Leu Ala Arg Gly Asn Ser Arg Phe Ala Trp
465 470 475 480

Met Thr Arg Lys Ser Glu Glu Thr Ile Thr Pro Trp Asn Phe Glu Glu
485 490 495

Val Val Asp Lys Gly Ala Ser Ala Gln Ser Phe Ile Glu Arg Met Thr
500 505 510

Asn Phe Asp Lys Asn Leu Pro Asn Glu Lys Val Leu Pro Lys His Ser
515 520 525

Leu Leu Tyr Glu Tyr Phe Thr Val Tyr Asn Glu Leu Thr Lys Val Lys
530 535 540

Tyr Val Thr Glu Gly Met Arg Lys Pro Ala Phe Leu Ser Gly Glu Gln
545 550 555 560

Lys Lys Ala Ile Val Asp Leu Leu Phe Lys Thr Asn Arg Lys Val Thr
565 570 575

Val Lys Gln Leu Lys Glu Asp Tyr Phe Lys Lys Ile Glu Cys Phe Asp
580 585 590

Ser Val Glu Ile Ser Gly Val Glu Asp Arg Phe Asn Ala Ser Leu Gly
595 600 605

Thr Tyr His Asp Leu Leu Lys Ile Ile Lys Asp Lys Asp Phe Leu Asp
610 615 620

Asn Glu Glu Asn Glu Asp Ile Leu Glu Asp Ile Val Leu Thr Leu Thr
625 630 635 640

Leu Phe Glu Asp Arg Glu Met Ile Glu Glu Arg Leu Lys Thr Tyr Ala
645 650 655

His Leu Phe Asp Asp Lys Val Met Lys Gln Leu Lys Arg Arg Arg Tyr
660 665 670

Thr Gly Trp Gly Arg Leu Ser Arg Lys Leu Ile Asn Gly Ile Arg Asp
675 680 685

Lys Gln Ser Gly Lys Thr Ile Leu Asp Phe Leu Lys Ser Asp Gly Phe
Page 27

690

695

700

Ala Asn Arg Asn Phe Met Gln Leu Ile His Asp Asp Ser Leu Thr Phe
705 710 715 720

Lys Glu Asp Ile Gln Lys Ala Gln Val Ser Gly Gln Gly Asp Ser Leu
725 730 735

His Glu His Ile Ala Asn Leu Ala Gly Ser Pro Ala Ile Lys Lys Gly
740 745 750

Ile Leu Gln Thr Val Lys Val Val Asp Glu Leu Val Lys Val Met Gly
755 760 765

Arg His Lys Pro Glu Asn Ile Val Ile Glu Met Ala Arg Glu Asn Gln
770 775 780

Thr Thr Gln Lys Gly Gln Lys Asn Ser Arg Glu Arg Met Lys Arg Ile
785 790 795 800

Glu Glu Gly Ile Lys Glu Leu Gly Ser Gln Ile Leu Lys Glu His Pro
805 810 815

Val Glu Asn Thr Gln Leu Gln Asn Glu Lys Leu Tyr Leu Tyr Tyr Leu
820 825 830

Gln Asn Gly Arg Asp Met Tyr Val Asp Gln Glu Leu Asp Ile Asn Arg
835 840 845

Leu Ser Asp Tyr Asp Val Asp His Ile Val Pro Gln Ser Phe Leu Lys
850 855 860

Asp Asp Ser Ile Asp Asn Lys Val Leu Thr Arg Ser Asp Lys Ala Arg
865 870 875 880

Gly Lys Ser Asp Asn Val Pro Ser Glu Glu Val Val Lys Lys Met Lys
885 890 895

Asn Tyr Trp Arg Gln Leu Leu Asn Ala Lys Leu Ile Thr Gln Arg Lys
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Phe Asp Asn Leu Thr Lys Ala Glu Arg Gly Gly Leu Ser Glu Leu Asp
915 920 925

Lys Ala Gly Phe Ile Lys Arg Gln Leu Val Glu Thr Arg Gln Ile Thr
930 935 940

Lys His Val Ala Gln Ile Leu Asp Ser Arg Met Asn Thr Lys Tyr Asp
945 950 955 960

Glu Asn Asp Lys Leu Ile Arg Glu Val Lys Val Ile Thr Leu Lys Ser
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Lys Leu Val Ser Asp Phe Arg Lys Asp Phe Gln Phe Tyr Lys Val Arg
980 985 990

Glu Ile Asn Asn Tyr His His Ala His Asp Ala Tyr Leu Asn Ala Val
995 1000 1005

Val Gly Thr Ala Leu Ile Lys Lys Tyr Pro Lys Leu Glu Ser Glu
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Phe Val Tyr Gly Asp Tyr Lys Val Tyr Asp Val Arg Lys Met Ile
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Phe Tyr Ser Asn Ile Met Asn Phe Phe Lys Thr Glu Ile Thr Leu
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Ala Asn Gly Glu Ile Arg Lys Arg Pro Leu Ile Glu Thr Asn Gly
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Glu Thr Gly Glu Ile Val Trp Asp Lys Gly Arg Asp Phe Ala Thr
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Val Arg Lys Val Leu Ser Met Pro Gln Val Asn Ile Val Lys Lys
1100 1105 1110

Thr Glu Val Gln Thr Gly Gly Phe Ser Lys Glu Ser Ile Leu Pro
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Lys Arg Asn Ser Asp Lys Leu Ile Ala Arg Lys Lys Asp Trp Asp
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 Pro Lys Lys Tyr Gly Gly Phe Asp Ser Pro Thr Val Ala Tyr Ser
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 Val Leu Val Val Ala Lys Val Glu Lys Gly Lys Ser Lys Lys Leu
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 Lys Ser Val Lys Glu Leu Leu Gly Ile Thr Ile Met Glu Arg Ser
 1175 1180 1185
 Ser Phe Glu Lys Asn Pro Ile Asp Phe Leu Glu Ala Lys Gly Tyr
 1190 1195 1200
 Lys Glu Val Lys Lys Asp Leu Ile Ile Lys Leu Pro Lys Tyr Ser
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 Leu Phe Glu Leu Glu Asn Gly Arg Lys Arg Met Leu Ala Ser Ala
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 Gly Glu Leu Gln Lys Gly Asn Glu Leu Ala Leu Pro Ser Lys Tyr
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 Val Asn Phe Leu Tyr Leu Ala Ser His Tyr Glu Lys Leu Lys Gly
 1250 1255 1260
 Ser Pro Glu Asp Asn Glu Gln Lys Gln Leu Phe Val Glu Gln His
 1265 1270 1275
 Lys His Tyr Leu Asp Glu Ile Ile Glu Gln Ile Ser Glu Phe Ser
 1280 1285 1290
 Lys Arg Val Ile Leu Ala Asp Ala Asn Leu Asp Lys Val Leu Ser
 1295 1300 1305
 Ala Tyr Asn Lys His Arg Asp Lys Pro Ile Arg Glu Gln Ala Glu
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 Asn Ile Ile His Leu Phe Thr Leu Thr Asn Leu Gly Ala Pro Ala
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Ala Phe Lys Tyr Phe Asp Thr Thr Ile Asp Arg Lys Arg Tyr Thr
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Ser Thr Lys Glu Val Leu Asp Ala Thr Leu Ile His Gln Ser Ile
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Thr Gly Leu Tyr Glu Thr Arg Ile Asp Leu Ser Gln Leu Gly Gly
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Asp Ser Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
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Gly Gly Ser Gly Pro Lys Lys Lys Arg Lys Val Ala Ala Ala Gly
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Ser Gly Arg Ala Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu
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Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser
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35 40 45

Val Arg Gln Ser Ser Ala Gln Lys Arg Lys Tyr Thr Ile Lys Val Glu
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Val Pro Lys Val Ala Thr Gln Thr Val Gly Gly Val Glu Leu Pro Val
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Ala Ala Trp Arg Ser Tyr Leu Asn Met Glu Leu Thr Ile Pro Ile Phe
85 90 95

Ala Thr Asn Ser Asp Cys Glu Leu Ile Val Lys Ala Met Gln Gly Leu
100 105 110

Leu Lys Asp Gly Asn Pro Ile Pro Ser Ala Ile Ala Ala Asn Ser Gly
115 120 125

Ile Tyr Ser Ala Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
130 135 140

Gly Gly Ser Gly Pro Lys Lys Lys Arg Lys Val Ala Ala Ala Gly Ser
145 150 155 160

Pro Ser Gly Gln Ile Ser Asn Gln Ala Leu Ala Leu Ala Pro Ser Ser

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Leu	Ala	Gln	Pro	Pro	Ala	Pro	Ala	Pro	Val	Leu	Thr	Pro	Gly	Pro	Pro	
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Gln	Ser	Leu	Ser	Ala	Pro	Val	Pro	Lys	Ser	Thr	Gln	Ala	Gly	Glu	Gly	
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Thr	Leu	Ser	Glu	Ala	Leu	Leu	His	Leu	Gln	Phe	Asp	Ala	Asp	Glu	Asp	
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Val	Ser	Met	Ser	His	Ser	Thr	Ala	Glu	Pro	Met	Leu	Met	Glu	Tyr	Pro	
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Glu	Ala	Ile	Thr	Arg	Leu	Val	Thr	Gly	Ser	Gln	Arg	Pro	Pro	Asp	Pro	
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Pro	Asp	Met	Ser	Leu	Pro	Asp	Leu	Asp	Ser	Ser	Leu	Ala	Ser	Ile	Gln	
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Ser Ser Pro Asp Ser Gly Lys Gln Leu Val His Tyr Thr Ala Gln Pro
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Leu Phe Leu Leu Asp Pro Gly Ser Val Asp Thr Gly Ser Asn Asp Leu
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Pro Val Leu Phe Glu Leu Gly Glu Gly Ser Tyr Phe Ser Glu Gly Asp
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Val Pro Lys Val Ala Thr Gln Thr Val Gly Gly Val Glu Leu Pro Val
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