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(54) **THERAPEUTIC USES OF GENOME EDITING WITH CRISPR/CAS SYSTEMS**

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Related U.S. Application Data

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(57) **ABSTRACT**

Disclosed herein are methods, compositions, and kits for high efficiency, site-specific genomic editing of cells for treating or preventing genetic blood disorders.

Specification includes a Sequence Listing.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	20	43248474	+	GCTTCTCTGAACCAACGAGCAGG	1	2	17	SEQ ID NO. 1
(N20)NGG	20	43248475	+	CTTCTCTGAACCAACGAGCAGGG	2	3	21	SEQ ID NO. 2
(N20)NGG	20	43248463	-	AGAGGTTCTGCCCTGCTCGTTGG	1	2	19	SEQ ID NO. 3
(N20)NGG	20	43248481	-	TGGAGGAGTGGCGTCTTCAGAGG	1	3	36	SEQ ID NO. 4
(N20)NGG	20	43248951	+	GCCTTTCCAGAACATCAATGCGG	1	3	35	SEQ ID NO. 5
(N20)NGG	20	43248986	+	TCCTCCCAGAAGATGAAAAGAGG	1	8	88	SEQ ID NO. 6
(N20)NGG	20	43248987	+	CCTCCCAGAAGATGAAAAGAGGG	1	8	120	SEQ ID NO. 7
(N20)NGG	20	43249018	+	GACCTGCTCTATAAAGCCTATGG	1	3	20	SEQ ID NO. 8
(N20)NGG	20	43249019	+	ACCTGCTCTATAAAGCCTATGGG	1	5	24	SEQ ID NO. 9
(N20)NGG	20	43249042	+	ATGCCACCTTCAGCCTCTGCAGG	2	6	74	SEQ ID NO. 10
(N20)NGG	20	43249046	+	CACCTTCAGCCTCTGCAGGTAGG	1	5	86	SEQ ID NO. 11
(N20)NGG	20	43249057	+	TCTGCAGGTAGGTTCCTGTCTGG	1	2	32	SEQ ID NO. 12
(N20)NGG	20	43249058	+	CTGCAGGTAGGTTCCTGTCTGGG	3	10	82	SEQ ID NO. 13
(N20)NGG	20	43249065	+	TAGGTTCCTGTCTGGGCTTCTGG	1	1	40	SEQ ID NO. 14
(N20)NGG	20	43249066	+	AGGTTCCTGTCTGGGCTTCTGGG	1	5	66	SEQ ID NO. 15
(N20)NGG	20	43248921	-	ATGTTCTGGAAAGGCCAGAATGG	1	2	78	SEQ ID NO. 16
(N20)NGG	20	43248930	-	GCCGCATTGATGTTCTGGAAAGG	1	2	17	SEQ ID NO. 17
(N20)NGG	20	43248935	-	ATTTGGCCGCATTGATGTTCTGG	1	1	9	SEQ ID NO. 18
(N20)NGG	20	43248952	-	TTCTGGGAGGAAACTAGATTTGG	1	6	76	SEQ ID NO. 19
(N20)NGG	20	43248965	-	CCCTCTTTTCATCTTCTGGGAGG	3	7	75	SEQ ID NO. 20
(N20)NGG	20	43248968	-	GCTCCCTCTTTTCATCTTCTGGG	2	10	106	SEQ ID NO. 21
(N20)NGG	20	43248969	-	AGCTCCCTCTTTTCATCTTCTGG	1	6	99	SEQ ID NO. 22
(N20)NGG	20	43248998	-	TCCCATAGGCTTTATAGAGCAGG	1	2	13	SEQ ID NO. 23
(N20)NGG	20	43249012	-	GGCTGAAGGTGGCATCCCATAGG	1	2	34	SEQ ID NO. 24
(N20)NGG	20	43249023	-	CTACCTGCAGAGGCTGAAGGTGG	1	7	86	SEQ ID NO. 25
(N20)NGG	20	43249026	-	AACCTACCTGCAGAGGCTGAAGG	1	4	42	SEQ ID NO. 26
(N20)NGG	20	43249033	-	AGACAGGAACCTACCTGCAGAGG	2	9	79	SEQ ID NO. 27
(N20)NGG	20	43249658	+	TCTCCTCCTCCCTCTTCTGCAGG	4	24	329	SEQ ID NO. 28
(N20)NGG	20	43249674	+	CTGCAGGCTCAAAAATGACCAGG	1	5	39	SEQ ID NO. 29
(N20)NGG	20	43249725	+	GCTCATCTTCAAGTCCACCCTGG	1	1	26	SEQ ID NO. 30
(N20)NGG	20	43249751	+	CTGATTACCAGATGACCAAACGG	1	4	33	SEQ ID NO. 31

FIG. 1

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	20	43249752	+	TGATTACCAGATGACCAAACGGG	1	2	21	SEQ ID NO. 32
(N20)NGG	20	43249758	+	CCAGATGACCAAACGGGACATGG	1	1	20	SEQ ID NO. 33
(N20)NGG	20	43249759	+	CAGATGACCAAACGGGACATGGG	1	2	14	SEQ ID NO. 34
(N20)NGG	20	43249773	+	GGACATGGGCTTTACTGAAGAGG	1	3	29	SEQ ID NO. 35
(N20)NGG	20	43249784	+	TTACTGAAGAGGAGTTTAAAAGG	1	4	74	SEQ ID NO. 36
(N20)NGG	20	43249788	+	TGAAGAGGAGTTTAAAAGGCTGG	1	6	79	SEQ ID NO. 37
(N20)NGG	20	43249795	+	GAGTTTAAAAGGCTGGTGAGTGG	3	6	46	SEQ ID NO. 38
(N20)NGG	20	43249796	+	AGTTTAAAAGGCTGGTGAGTGGG	1	6	48	SEQ ID NO. 39
(N20)NGG	20	43249811	+	TGAGTGGGTGTGAGCCATACTGG	1	1	16	SEQ ID NO. 40
(N20)NGG	20	43249639	-	GAGCCTGCAGAAGAGGGAGGAGG	4	21	222	SEQ ID NO. 41
(N20)NGG	20	43249642	-	TTTGAGCCTGCAGAAGAGGGAGG	1	6	78	SEQ ID NO. 42
(N20)NGG	20	43249645	-	ATTTTTGAGCCTGCAGAAGAGGG	1	10	102	SEQ ID NO. 43
(N20)NGG	20	43249646	-	CATTTTTGAGCCTGCAGAAGAGG	1	8	72	SEQ ID NO. 44
(N20)NGG	20	43249670	-	TGTTGAGCGAGTAGTTAGCCTGG	1	1	4	SEQ ID NO. 45
(N20)NGG	20	43249700	-	GGGTGGACTTGAAGATGAGCGGG	1	4	28	SEQ ID NO. 46
(N20)NGG	20	43249701	-	AGGGTGGACTTGAAGATGAGCGG	2	7	80	SEQ ID NO. 47
(N20)NGG	20	43249717	-	CTGGTAATCAGTGTCCAGGGTGG	1	4	27	SEQ ID NO. 48
(N20)NGG	20	43249720	-	CATCTGGTAATCAGTGTCCAGGG	1	2	30	SEQ ID NO. 49
(N20)NGG	20	43249721	-	TCATCTGGTAATCAGTGTCCAGG	1	2	25	SEQ ID NO. 50
(N20)NGG	20	43249736	-	CCATGTCCCGTTTGGTCATCTGG	1	1	8	SEQ ID NO. 51
(N20)NGG	20	43249744	-	AGTAAAGCCCATGTCCCGTTTGG	1	1	6	SEQ ID NO. 52
(N20)NGG	20	43251239	+	TGCTCTTCCAGATCTGCCCCTGG	2	5	61	SEQ ID NO. 53
(N20)NGG	20	43251256	+	CCCTGGTCCAGCTACCTCACTGG	2	5	30	SEQ ID NO. 54
(N20)NGG	20	43251263	+	CCAGCTACCTCACTGGTGCCTGG	1	5	42	SEQ ID NO. 55
(N20)NGG	20	43251270	+	CCTCACTGGTGCCTGGAAGCCGG	1	8	72	SEQ ID NO. 56
(N20)NGG	20	43251276	+	TGGTGCCTGGAAGCCGGACACGG	1	3	32	SEQ ID NO. 57
(N20)NGG	20	43251293	+	ACACGGAGCATGCAGTCATTCGG	1	1	25	SEQ ID NO. 58
(N20)NGG	20	43251311	+	TTCGGTGAGCTCTGTTCCCCTGG	1	2	25	SEQ ID NO. 59
(N20)NGG	20	43251312	+	TCGGTGAGCTCTGTTCCCCTGGG	1	1	18	SEQ ID NO. 60
(N20)NGG	20	43251204	-	TGGAAGAGCAGGTGTGTGGCTGG	1	6	147	SEQ ID NO. 61
(N20)NGG	20	43251208	-	GATCTGGAAGAGCAGGTGTGTGG	1	11	97	SEQ ID NO. 62

FIG. 1 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	20	43251215	-	AGGGGCAGATCTGGAAGAGCAGG	1	8	82	SEQ ID NO. 63
(N20)NGG	20	43251224	-	AGCTGGACCAGGGGCAGATCTGG	1	4	62	SEQ ID NO. 64
(N20)NGG	20	43251233	-	CAGTGAGGTAGCTGGACCAGGGG	1	4	65	SEQ ID NO. 65
(N20)NGG	20	43251234	-	CCAGTGAGGTAGCTGGACCAGGG	1	2	47	SEQ ID NO. 66
(N20)NGG	20	43251235	-	ACCAGTGAGGTAGCTGGACCAGG	1	4	35	SEQ ID NO. 67
(N20)NGG	20	43251241	-	CCAGGCACCAGTGAGGTAGCTGG	1	5	53	SEQ ID NO. 68
(N20)NGG	20	43251248	-	CCGGCTTCCAGGCACCAGTGAGG	1	2	49	SEQ ID NO. 69
(N20)NGG	20	43251259	-	ATGCTCCGTGTCCGGCTTCCAGG	1	1	10	SEQ ID NO. 70
(N20)NGG	20	43251267	-	ATGACTGCATGCTCCGTGTCCGG	2	3	36	SEQ ID NO. 71
(N20)NGG	20	43251469	+	GCTCTATTCTGCTTCTCTACAGG	1	4	34	SEQ ID NO. 72
(N20)NGG	20	43251475	+	TTCTGCTTCTCTACAGGCTGTGG	1	11	100	SEQ ID NO. 73
(N20)NGG	20	43251495	+	TGGACATACTCAAGACAGAGCGG	1	2	48	SEQ ID NO. 74
(N20)NGG	20	43251499	+	CATACTCAAGACAGAGCGGCTGG	1	3	14	SEQ ID NO. 75
(N20)NGG	20	43251500	+	ATACTCAAGACAGAGCGGCTGGG	1	1	16	SEQ ID NO. 76
(N20)NGG	20	43251506	+	AAGACAGAGCGGCTGGGACACGG	1	9	81	SEQ ID NO. 77
(N20)NGG	20	43251520	+	GGGACACGGCTACCACACCCTGG	1	1	15	SEQ ID NO. 78
(N20)NGG	20	43251529	+	CTACCACACCCTGGAAGACCAGG	1	3	42	SEQ ID NO. 79
(N20)NGG	20	43251543	+	AAGACCAGGCCCTTTATAACAGG	1	3	34	SEQ ID NO. 80
(N20)NGG	20	43251549	+	AGGCCCTTTATAACAGGCTGCGG	1	2	25	SEQ ID NO. 81
(N20)NGG	20	43251553	+	CCTTTATAACAGGCTGCGGCAGG	1	2	16	SEQ ID NO. 82
(N20)NGG	20	43251571	+	GCAGGAAAACATGCACTTCGAGG	1	4	26	SEQ ID NO. 83
(N20)NGG	20	43251578	+	AACATGCACTTCGAGGTAAGCGG	1	1	14	SEQ ID NO. 84
(N20)NGG	20	43251579	+	ACATGCACTTCGAGGTAAGCGGG	1	1	10	SEQ ID NO. 85
(N20)NGG	20	43251584	+	CACTTCGAGGTAAGCGGGCCAGG	1	1	7	SEQ ID NO. 86
(N20)NGG	20	43251585	+	ACTTCGAGGTAAGCGGGCCAGGG	1	1	9	SEQ ID NO. 87
(N20)NGG	20	43251590	+	GAGGTAAGCGGGCCAGGGAGTGG	2	6	85	SEQ ID NO. 88
(N20)NGG	20	43251591	+	AGGTAAGCGGGCCAGGGAGTGGG	1	2	38	SEQ ID NO. 89
(N20)NGG	20	43251592	+	GGTAAGCGGGCCAGGGAGTGGGG	1	3	47	SEQ ID NO. 90
(N20)NGG	20	43251595	+	AAGCGGGCCAGGGAGTGGGGAGG	2	10	143	SEQ ID NO. 91
(N20)NGG	20	43251510	-	GGGCCTGGTCTTCCAGGGTGTGG	1	5	82	SEQ ID NO. 92
(N20)NGG	20	43251515	-	ATAAAGGGCCTGGTCTTCCAGGG	2	5	38	SEQ ID NO. 93

FIG. 1 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	20	43251516	-	TATAAAGGGCCTGGTCTTCCAGG	1	3	20	SEQ ID NO. 94
(N20)NGG	20	43251525	-	GCAGCCTGTTATAAAGGGCCTGG	1	4	23	SEQ ID NO. 95
(N20)NGG	20	43251530	-	CTGCCGCAGCCTGTTATAAAGGG	1	1	13	SEQ ID NO. 96
(N20)NGG	20	43251531	-	CCTGCCGCAGCCTGTTATAAAGG	1	1	7	SEQ ID NO. 97
(N20)NGG	20	43251647	+	GACCTGGCTCTCCCCCTTCCAGG	1	5	127	SEQ ID NO. 98
(N20)NGG	20	43251650	+	CTGGCTCTCCCCCTTCCAGGAGG	1	4	116	SEQ ID NO. 99
(N20)NGG	20	43251663	+	TTCCAGGAGGCTGTGAAGAGCGG	3	7	125	SEQ ID NO. 100
(N20)NGG	20	43251687	+	ATTCACCGTACTGTCCACGCCGG	1	2	47	SEQ ID NO. 101
(N20)NGG	20	43251688	+	TTCACCGTACTGTCCACGCCGGG	1	1	11	SEQ ID NO. 102
(N20)NGG	20	43251689	+	TCACCGTACTGTCCACGCCGGGG	1	1	2	SEQ ID NO. 103
(N20)NGG	20	43251692	+	CCGTACTGTCCACGCCGGGGAGG	1	1	3	SEQ ID NO. 104
(N20)NGG	20	43251695	+	TACTGTCCACGCCGGGGAGGTGG	1	1	4	SEQ ID NO. 105
(N20)NGG	20	43251696	+	ACTGTCCACGCCGGGGAGGTGGG	1	1	11	SEQ ID NO. 106
(N20)NGG	20	43251701	+	CCACGCCGGGGAGGTGGGCTCGG	1	6	45	SEQ ID NO. 107
(N20)NGG	20	43251719	+	CTCGGCCGAAGTAGTAAAAGAGG	1	2	6	SEQ ID NO. 108
(N20)NGG	20	43251724	+	CCGAAGTAGTAAAAGAGGTGAGG	1	1	13	SEQ ID NO. 109
(N20)NGG	20	43251725	+	CGAAGTAGTAAAAGAGGTGAGGG	1	2	51	SEQ ID NO. 110
(N20)NGG	20	43251730	+	TAGTAAAAGAGGTGAGGGCCTGG	1	3	44	SEQ ID NO. 111
(N20)NGG	20	43251731	+	AGTAAAAGAGGTGAGGGCCTGGG	1	2	55	SEQ ID NO. 112
(N20)NGG	20	43251735	+	AAAGAGGTGAGGGCCTGGGCTGG	2	15	136	SEQ ID NO. 113
(N20)NGG	20	43251741	+	GTGAGGGCCTGGGCTGGCCATGG	3	11	158	SEQ ID NO. 114
(N20)NGG	20	43251742	+	TGAGGGCCTGGGCTGGCCATGGG	2	10	99	SEQ ID NO. 115
(N20)NGG	20	43251743	+	GAGGGCCTGGGCTGGCCATGGGG	1	17	142	SEQ ID NO. 116
(N20)NGG	20	43251627	-	CTCCTGGAAGGGGGAGAGCCAGG	2	7	106	SEQ ID NO. 117
(N20)NGG	20	43251636	-	CTTCACAGCCTCCTGGAAGGGGG	1	7	115	SEQ ID NO. 118
(N20)NGG	20	43251637	-	TCTTCACAGCCTCCTGGAAGGGG	1	7	86	SEQ ID NO. 119
(N20)NGG	20	43251638	-	CTCTTCACAGCCTCCTGGAAGGG	1	9	79	SEQ ID NO. 120
(N20)NGG	20	43251639	-	GCTCTTCACAGCCTCCTGGAAGG	1	5	96	SEQ ID NO. 121
(N20)NGG	20	43251643	-	TGCCGCTCTTCACAGCCTCCTGG	1	3	39	SEQ ID NO. 122
(N20)NGG	20	43251670	-	CCTCCCCGGCGTGGACAGTACGG	1	1	6	SEQ ID NO. 123
(N20)NGG	20	43251679	-	CCGAGCCCACCTCCCCGGCGTGG	1	5	37	SEQ ID NO. 124

FIG. 1 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	20	43251684	-	TTCGGCCGAGCCCACCTCCCCGG	1	3	19	SEQ ID NO. 125
(N20)NGG	20	43251702	-	CCTCACCTCTTTTACTACTTCGG	1	4	46	SEQ ID NO. 126
(N20)NGG	20	43252846	+	TGGGCATCTCGCCCACAGACTGG	1	2	13	SEQ ID NO. 127
(N20)NGG	20	43252856	+	GCCCACAGACTGGTCCCCCAAGG	1	6	43	SEQ ID NO. 128
(N20)NGG	20	43252859	+	CACAGACTGGTCCCCCAAGGTGG	1	1	37	SEQ ID NO. 129
(N20)NGG	20	43252862	+	AGACTGGTCCCCCAAGGTGGTGG	1	2	36	SEQ ID NO. 130
(N20)NGG	20	43252895	+	GAAGTACCAGCAGCAGACCGTGG	1	1	34	SEQ ID NO. 131
(N20)NGG	20	43252910	+	GACCGTGGTAGCCATTGACCTGG	1	1	10	SEQ ID NO. 132
(N20)NGG	20	43252914	+	GTGGTAGCCATTGACCTGGCTGG	1	2	21	SEQ ID NO. 133
(N20)NGG	20	43252932	+	GCTGGAGATGAGACCATCCCAGG	1	4	44	SEQ ID NO. 134
(N20)NGG	20	43252950	+	CCAGGAAGCAGCCTCTTGCCTGG	2	11	127	SEQ ID NO. 135
(N20)NGG	20	43252961	+	CCTCTTGCCTGGACATGTCCAGG	1	4	42	SEQ ID NO. 136
(N20)NGG	20	43252970	+	TGGACATGTCCAGGCCTACCAGG	1	3	18	SEQ ID NO. 137
(N20)NGG	20	43252973	+	ACATGTCCAGGCCTACCAGGTGG	1	6	45	SEQ ID NO. 138
(N20)NGG	20	43252974	+	CATGTCCAGGCCTACCAGGTGGG	1	4	24	SEQ ID NO. 139
(N20)NGG	20	43252987	+	ACCAGGTGGGTCCTGTGAGAAGG	1	6	35	SEQ ID NO. 140
(N20)NGG	20	43252992	+	GTGGGTCCTGTGAGAAGGAATGG	1	14	148	SEQ ID NO. 141
(N20)NGG	20	43252818	-	TGTGGGCGAGATGCCCACCCAGG	1	3	19	SEQ ID NO. 142
(N20)NGG	20	43252835	-	ACCTTGGGGGACCAGTCTGTGGG	1	2	23	SEQ ID NO. 143
(N20)NGG	20	43252836	-	CACCTTGGGGGACCAGTCTGTGG	1	3	29	SEQ ID NO. 144
(N20)NGG	20	43252848	-	ACACAGCTCCACCACCTTGGGGG	1	5	37	SEQ ID NO. 145
(N20)NGG	20	43252849	-	TACACAGCTCCACCACCTTGGGG	1	2	24	SEQ ID NO. 146
(N20)NGG	20	43252850	-	TTACACAGCTCCACCACCTTGGG	1	1	34	SEQ ID NO. 147
(N20)NGG	20	43252851	-	CTTACACAGCTCCACCACCTTGG	1	3	29	SEQ ID NO. 148
(N20)NGG	20	43252879	-	TGGCTACCACGGTCTGCTGCTGG	1	3	22	SEQ ID NO. 149
(N20)NGG	20	43252890	-	AGCCAGGTCAATGGCTACCACGG	1	2	24	SEQ ID NO. 150
(N20)NGG	20	43252899	-	CTCATCTCCAGCCAGGTCAATGG	1	7	131	SEQ ID NO. 151
(N20)NGG	20	43252906	-	GGATGGTCTCATCTCCAGCCAGG	1	2	44	SEQ ID NO. 152
(N20)NGG	20	43252923	-	CAAGAGGCTGCTTCCTGGGATGG	3	8	86	SEQ ID NO. 153
(N20)NGG	20	43252927	-	CAGGCAAGAGGCTGCTTCCTGGG	2	7	85	SEQ ID NO. 154
(N20)NGG	20	43252928	-	CCAGGCAAGAGGCTGCTTCCTGG	1	7	113	SEQ ID NO. 155

FIG. 1 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	20	43252939	-	CCTGGACATGTCCAGGCAAGAGG	1	2	50	SEQ ID NO. 156
(N20)NGG	20	43252946	-	TGGTAGGCCTGGACATGTCCAGG	1	2	17	SEQ ID NO. 157
(N20)NGG	20	43252957	-	CAGGACCCACCTGGTAGGCCTGG	1	3	33	SEQ ID NO. 158
(N20)NGG	20	43252962	-	TCTCACAGGACCCACCTGGTAGG	1	2	28	SEQ ID NO. 159
(N20)NGG	20	43252966	-	TCCTTCTCACAGGACCCACCTGG	1	6	55	SEQ ID NO. 160
(N20)NGG	20	43254211	+	CTACTCCTCTCCTCACACAGAGG	1	5	119	SEQ ID NO. 161
(N20)NGG	20	43254212	+	TACTCCTCTCCTCACACAGAGGG	1	10	105	SEQ ID NO. 162
(N20)NGG	20	43254213	+	ACTCCTCTCCTCACACAGAGGGG	1	6	66	SEQ ID NO. 163
(N20)NGG	20	43254231	+	AGGGGACCTCACCCCAGACGAGG	1	1	26	SEQ ID NO. 164
(N20)NGG	20	43254234	+	GGACCTCACCCCAGACGAGGTGG	1	1	21	SEQ ID NO. 165
(N20)NGG	20	43254237	+	CCTCACCCCAGACGAGGTGGTGG	1	2	40	SEQ ID NO. 166
(N20)NGG	20	43254246	+	AGACGAGGTGGTGGCCCTAGTGG	1	2	24	SEQ ID NO. 167
(N20)NGG	20	43254247	+	GACGAGGTGGTGGCCCTAGTGGG	1	2	13	SEQ ID NO. 168
(N20)NGG	20	43254252	+	GGTGGTGGCCCTAGTGGGCCAGG	1	2	48	SEQ ID NO. 169
(N20)NGG	20	43254253	+	GTGGTGGCCCTAGTGGGCCAGGG	1	3	40	SEQ ID NO. 170
(N20)NGG	20	43254261	+	CCTAGTGGGCCAGGGCCTGCAGG	1	4	43	SEQ ID NO. 171
(N20)NGG	20	43254264	+	AGTGGGCCAGGGCCTGCAGGAGG	3	14	163	SEQ ID NO. 172
(N20)NGG	20	43254265	+	GTGGGCCAGGGCCTGCAGGAGGG	1	14	225	SEQ ID NO. 173
(N20)NGG	20	43254266	+	TGGGCCAGGGCCTGCAGGAGGGG	2	18	238	SEQ ID NO. 174
(N20)NGG	20	43254267	+	GGGCCAGGGCCTGCAGGAGGGGG	2	32	318	SEQ ID NO. 175
(N20)NGG	20	43254280	+	CAGGAGGGGGAGCGAGACTTCGG	1	2	39	SEQ ID NO. 176
(N20)NGG	20	43254281	+	AGGAGGGGGAGCGAGACTTCGGG	1	2	35	SEQ ID NO. 177
(N20)NGG	20	43254282	+	GGAGGGGGAGCGAGACTTCGGGG	1	1	29	SEQ ID NO. 178
(N20)NGG	20	43254288	+	GGAGCGAGACTTCGGGGTCAAGG	1	2	20	SEQ ID NO. 179
(N20)NGG	20	43254293	+	GAGACTTCGGGGTCAAGGCCCGG	1	2	18	SEQ ID NO. 180
(N20)NGG	20	43254333	+	GCGCCACCAGCCCAGTGAGTAGG	1	1	15	SEQ ID NO. 181
(N20)NGG	20	43254187	-	TCTGTGTGAGGAGAGGAGTAGGG	1	10	104	SEQ ID NO. 182
(N20)NGG	20	43254188	-	CTCTGTGTGAGGAGAGGAGTAGG	2	11	148	SEQ ID NO. 183
(N20)NGG	20	43254194	-	GGTCCCCTCTGTGTGAGGAGAGG	1	4	52	SEQ ID NO. 184
(N20)NGG	20	43254199	-	GGTGAGGTCCCCTCTGTGTGAGG	1	3	51	SEQ ID NO. 185
(N20)NGG	20	43254215	-	CCACCACCTCGTCTGGGGTGAGG	1	4	100	SEQ ID NO. 186

FIG. 1 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	20	43254220	-	TAGGGCCACCACCTCGTCTGGGG	1	1	11	SEQ ID NO. 187
(N20)NGG	20	43254221	-	CTAGGGCCACCACCTCGTCTGGG	1	2	16	SEQ ID NO. 188
(N20)NGG	20	43254222	-	ACTAGGGCCACCACCTCGTCTGG	1	1	17	SEQ ID NO. 189
(N20)NGG	20	43254238	-	CTGCAGGCCCTGGCCCACTAGGG	1	7	54	SEQ ID NO. 190
(N20)NGG	20	43254239	-	CCTGCAGGCCCTGGCCCACTAGG	3	5	89	SEQ ID NO. 191
(N20)NGG	20	43254248	-	GCTCCCCCTCCTGCAGGCCCTGG	1	17	186	SEQ ID NO. 192
(N20)NGG	20	43254254	-	AGTCTCGCTCCCCCTCCTGCAGG	1	4	38	SEQ ID NO. 193
(N20)NGG	20	43254289	-	CATGCAGCACAGGATGGACCGGG	1	3	34	SEQ ID NO. 194
(N20)NGG	20	43254290	-	GCATGCAGCACAGGATGGACCGG	1	3	42	SEQ ID NO. 195
(N20)NGG	20	43254295	-	GTGGCGCATGCAGCACAGGATGG	1	3	62	SEQ ID NO. 196
(N20)NGG	20	43254299	-	GCTGGTGGCGCATGCAGCACAGG	1	1	22	SEQ ID NO. 197
(N20)NGG	20	43254314	-	GATCCTACTCACTGGGCTGGTGG	1	2	32	SEQ ID NO. 198
(N20)NGG	20	43254317	-	GGTGATCCTACTCACTGGGCTGG	1	2	13	SEQ ID NO. 199
(N20)NGG	20	43254321	-	GGGCGGTGATCCTACTCACTGGG	1	1	10	SEQ ID NO. 200
(N20)NGG	20	43254322	-	AGGGCGGTGATCCTACTCACTGG	1	1	14	SEQ ID NO. 201
(N20)NGG	20	43255096	+	AACCCCTTTCTTCCCTTCCCAGG	1	11	148	SEQ ID NO. 202
(N20)NGG	20	43255097	+	ACCCCTTTCTTCCCTTCCCAGGG	5	16	156	SEQ ID NO. 203
(N20)NGG	20	43255098	+	CCCCTTTCTTCCCTTCCCAGGGG	1	18	215	SEQ ID NO. 204
(N20)NGG	20	43255105	+	CTTCCCTTCCCAGGGGCTGCCGG	1	15	150	SEQ ID NO. 205
(N20)NGG	20	43255106	+	TTCCCTTCCCAGGGGCTGCCGGG	2	11	144	SEQ ID NO. 206
(N20)NGG	20	43255109	+	CCTTCCCAGGGGCTGCCGGGAGG	2	15	134	SEQ ID NO. 207
(N20)NGG	20	43255120	+	GCTGCCGGGAGGCTATCAAAAGG	1	2	9	SEQ ID NO. 208
(N20)NGG	20	43255148	+	CTATGAGTTTGTAGAGATGAAGG	1	2	59	SEQ ID NO. 209
(N20)NGG	20	43255157	+	TGTAGAGATGAAGGCCAAAGAGG	1	7	68	SEQ ID NO. 210
(N20)NGG	20	43255158	+	GTAGAGATGAAGGCCAAAGAGGG	1	10	86	SEQ ID NO. 211
(N20)NGG	20	43255163	+	GATGAAGGCCAAAGAGGGCGTGG	1	1	33	SEQ ID NO. 212
(N20)NGG	20	43255172	+	CAAAGAGGGCGTGGTGTATGTGG	1	3	17	SEQ ID NO. 213
(N20)NGG	20	43255175	+	AGAGGGCGTGGTGTATGTGGAGG	1	3	39	SEQ ID NO. 214
(N20)NGG	20	43255180	+	GCGTGGTGTATGTGGAGGTGCGG	1	3	88	SEQ ID NO. 215
(N20)NGG	20	43255199	+	GCGGTACAGTCCGCACCTGCTGG	1	1	2	SEQ ID NO. 216
(N20)NGG	20	43255214	+	CCTGCTGGCCAACTCCAAAGTGG	1	3	32	SEQ ID NO. 217

FIG. 1 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	20	43255228	+	CCAAAGTGGAGCCAATCCCCTGG	2	5	22	SEQ ID NO. 218
(N20)NGG	20	43255235	+	GGAGCCAATCCCCTGGAACCAGG	1	1	30	SEQ ID NO. 219
(N20)NGG	20	43255250	+	GAACCAGGCTGAGTGAGTGATGG	1	4	65	SEQ ID NO. 220
(N20)NGG	20	43255251	+	AACCAGGCTGAGTGAGTGATGGG	1	3	48	SEQ ID NO. 221
(N20)NGG	20	43255256	+	GGCTGAGTGAGTGATGGGCCTGG	1	2	70	SEQ ID NO. 222
(N20)NGG	20	43255260	+	GAGTGAGTGATGGGCCTGGAAGG	1	7	91	SEQ ID NO. 223
(N20)NGG	20	43255261	+	AGTGAGTGATGGGCCTGGAAGGG	2	8	97	SEQ ID NO. 224
(N20)NGG	20	43255262	+	GTGAGTGATGGGCCTGGAAGGGG	1	9	107	SEQ ID NO. 225
(N20)NGG	20	43255071	-	GGGAAGGGAAGAAAGGGGTTGGG	2	22	449	SEQ ID NO. 226
(N20)NGG	20	43255072	-	TGGGAAGGGAAGAAAGGGGTTGG	3	32	451	SEQ ID NO. 227
(N20)NGG	20	43255076	-	CCCCTGGGAAGGGAAGAAAGGGG	2	23	175	SEQ ID NO. 228
(N20)NGG	20	43255077	-	GCCCCTGGGAAGGGAAGAAAGGG	2	13	169	SEQ ID NO. 229
(N20)NGG	20	43255078	-	AGCCCCTGGGAAGGGAAGAAAGG	1	22	197	SEQ ID NO. 230
(N20)NGG	20	43255086	-	CTCCCGGCAGCCCCTGGGAAGGG	2	7	127	SEQ ID NO. 231
(N20)NGG	20	43255087	-	CCTCCCGGCAGCCCCTGGGAAGG	2	11	137	SEQ ID NO. 232
(N20)NGG	20	43255091	-	ATAGCCTCCCGGCAGCCCCTGGG	1	2	20	SEQ ID NO. 233
(N20)NGG	20	43255092	-	GATAGCCTCCCGGCAGCCCCTGG	1	1	15	SEQ ID NO. 234
(N20)NGG	20	43255102	-	CGATCCTTTTGATAGCCTCCCGG	1	1	11	SEQ ID NO. 235
(N20)NGG	20	43255125	-	CTTCATCTCTACAAACTCATAGG	3	5	67	SEQ ID NO. 236
(N20)NGG	20	43255149	-	CACATACACCACGCCCTCTTTGG	1	1	15	SEQ ID NO. 237
(N20)NGG	20	43255187	-	TTGGAGTTGGCCAGCAGGTGCGG	1	5	56	SEQ ID NO. 238
(N20)NGG	20	43255192	-	CCACTTTGGAGTTGGCCAGCAGG	1	3	26	SEQ ID NO. 239
(N20)NGG	20	43255200	-	GATTGGCTCCACTTTGGAGTTGG	1	5	22	SEQ ID NO. 240
(N20)NGG	20	43255206	-	CCAGGGGATTGGCTCCACTTTGG	1	2	18	SEQ ID NO. 241
(N20)NGG	20	43255217	-	TCAGCCTGGTTCCAGGGGATTGG	1	4	79	SEQ ID NO. 242
(N20)NGG	20	43255222	-	CTCACTCAGCCTGGTTCCAGGGG	1	5	69	SEQ ID NO. 243
(N20)NGG	20	43255223	-	ACTCACTCAGCCTGGTTCCAGGG	1	7	79	SEQ ID NO. 244
(N20)NGG	20	43255224	-	CACTCACTCAGCCTGGTTCCAGG	1	3	62	SEQ ID NO. 245
(N20)NGG	20	43255231	-	GGCCCATCACTCACTCAGCCTGG	1	2	39	SEQ ID NO. 246
(N20)NGG	20	43257687	+	CCACTCACTGTTTTGTTTCCAGG	1	5	76	SEQ ID NO. 247
(N20)NGG	20	43257690	+	CTCACTGTTTTGTTTCCAGGAGG	1	6	88	SEQ ID NO. 248

FIG. 1 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	20	43257695	+	TGTTTTGTTTCCAGGAGGAGAGG	1	7	117	SEQ ID NO. 249
(N20)NGG	20	43257696	+	GTTTTGTTTCCAGGAGGAGAGGG	1	11	95	SEQ ID NO. 250
(N20)NGG	20	43257724	+	CCTCCCAGCTAACACAGCAGAGG	1	5	52	SEQ ID NO. 251
(N20)NGG	20	43257725	+	CTCCCAGCTAACACAGCAGAGGG	1	5	66	SEQ ID NO. 252
(N20)NGG	20	43257726	+	TCCCAGCTAACACAGCAGAGGGG	1	7	53	SEQ ID NO. 253
(N20)NGG	20	43257743	+	GAGGGGCTGCTGAACGTCATTGG	1	1	28	SEQ ID NO. 254
(N20)NGG	20	43257748	+	GCTGCTGAACGTCATTGGCATGG	1	2	26	SEQ ID NO. 255
(N20)NGG	20	43257778	+	GCTCACCCTTCCAGACTTCCTGG	2	5	47	SEQ ID NO. 256
(N20)NGG	20	43257832	+	GTGAGTTGCCCCCAACCCACAGG	1	2	28	SEQ ID NO. 257
(N20)NGG	20	43257662	-	GGAAACAAAACAGTGAGTGGTGG	2	9	97	SEQ ID NO. 258
(N20)NGG	20	43257665	-	CCTGGAAACAAAACAGTGAGTGG	1	5	106	SEQ ID NO. 259
(N20)NGG	20	43257683	-	GAGGGCGATCCCTCTCCTCCTGG	2	4	21	SEQ ID NO. 260
(N20)NGG	20	43257701	-	CTCTGCTGTGTTAGCTGGGAGGG	1	7	73	SEQ ID NO. 261
(N20)NGG	20	43257702	-	CCTCTGCTGTGTTAGCTGGGAGG	1	4	56	SEQ ID NO. 262
(N20)NGG	20	43257705	-	GCCCCTCTGCTGTGTTAGCTGGG	1	3	34	SEQ ID NO. 263
(N20)NGG	20	43257706	-	AGCCCCTCTGCTGTGTTAGCTGG	1	4	32	SEQ ID NO. 264
(N20)NGG	20	43257754	-	AGGAAGTCTGGAAGGGTGAGCGG	1	8	158	SEQ ID NO. 265
(N20)NGG	20	43257761	-	CTTGGCCAGGAAGTCTGGAAGGG	1	2	37	SEQ ID NO. 266
(N20)NGG	20	43257762	-	ACTTGGCCAGGAAGTCTGGAAGG	1	4	48	SEQ ID NO. 267
(N20)NGG	20	43257766	-	TCAAACTTGGCCAGGAAGTCTGG	1	4	39	SEQ ID NO. 268
(N20)NGG	20	43257774	-	TGTAGTAGTCAAACTTGGCCAGG	1	1	16	SEQ ID NO. 269
(N20)NGG	20	43257779	-	AGGCATGTAGTAGTCAAACTTGG	1	3	33	SEQ ID NO. 270
(N20)NGG	20	43257799	-	GGGGCAACTCACGCGATAGCAGG	1	1	2	SEQ ID NO. 271
(N20)NGG	20	43264867	+	TCTTCCCCCTGCCCCCTTGCAGG	1	11	106	SEQ ID NO. 272
(N20)NGG	20	43264870	+	TCCCCCTGCCCCCTTGCAGGTGG	1	5	90	SEQ ID NO. 273
(N20)NGG	20	43264892	+	GAACTGCATGTCCACCTAGACGG	1	1	25	SEQ ID NO. 274
(N20)NGG	20	43264925	+	CCTGAAACCATCTTATACTATGG	1	5	49	SEQ ID NO. 275
(N20)NGG	20	43264929	+	AAACCATCTTATACTATGGCAGG	1	2	23	SEQ ID NO. 276
(N20)NGG	20	43264849	-	TCCACCTGCAAGGGGGCAGGGGG	1	12	174	SEQ ID NO. 277
(N20)NGG	20	43264850	-	TTCCACCTGCAAGGGGGCAGGGG	1	5	64	SEQ ID NO. 278
(N20)NGG	20	43264851	-	GTTCCACCTGCAAGGGGGCAGGG	1	6	42	SEQ ID NO. 279

FIG. 1 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	20	43264852	-	AGTTCCACCTGCAAGGGGGCAGG	1	1	41	SEQ ID NO. 280
(N20)NGG	20	43264856	-	ATGCAGTTCCACCTGCAAGGGGG	1	4	33	SEQ ID NO. 281
(N20)NGG	20	43264857	-	CATGCAGTTCCACCTGCAAGGGG	1	2	29	SEQ ID NO. 282
(N20)NGG	20	43264858	-	ACATGCAGTTCCACCTGCAAGGG	1	1	38	SEQ ID NO. 283
(N20)NGG	20	43264859	-	GACATGCAGTTCCACCTGCAAGG	1	2	51	SEQ ID NO. 284
(N20)NGG	20	43264881	-	GCTTGATGGATCCGTCTAGGTGG	1	2	5	SEQ ID NO. 285
(N20)NGG	20	43264884	-	CAGGCTTGATGGATCCGTCTAGG	1	1	5	SEQ ID NO. 286
(N20)NGG	20	43264895	-	TAAGATGGTTTCAGGCTTGATGG	1	1	26	SEQ ID NO. 287
(N20)NGG	20	43264903	-	CCATAGTATAAGATGGTTTCAGG	1	1	23	SEQ ID NO. 288
(N20)NGG	20	43264910	-	TTACCTGCCATAGTATAAGATGG	1	5	28	SEQ ID NO. 289
(N20)NGG	20	43280218	+	CGGGGCGCACGAGGGCACCATGG	1	1	14	SEQ ID NO. 290
(N20)NGG	20	43280261	+	AAGCCCAAAGTGAGCGCGCGCGG	1	1	7	SEQ ID NO. 291
(N20)NGG	20	43280262	+	AGCCCAAAGTGAGCGCGCGCGGG	1	1	4	SEQ ID NO. 292
(N20)NGG	20	43280263	+	GCCCAAAGTGAGCGCGCGCGGGG	1	1	8	SEQ ID NO. 293
(N20)NGG	20	43280264	+	CCCAAAGTGAGCGCGCGCGGGGG	1	1	11	SEQ ID NO. 294
(N20)NGG	20	43280270	+	GTGAGCGCGCGCGGGGGCTCCGG	1	3	41	SEQ ID NO. 295
(N20)NGG	20	43280271	+	TGAGCGCGCGCGGGGGCTCCGGG	1	3	24	SEQ ID NO. 296
(N20)NGG	20	43280272	+	GAGCGCGCGCGGGGGCTCCGGGG	1	3	44	SEQ ID NO. 297
(N20)NGG	20	43280195	-	CATGGTGCCCTCGTGCGCCCCGG	1	2	15	SEQ ID NO. 298
(N20)NGG	20	43280213	-	GAAGGCGGGCGTCTGGGCCATGG	1	2	26	SEQ ID NO. 299
(N20)NGG	20	43280219	-	CTTGTCGAAGGCGGGCGTCTGGG	1	1	6	SEQ ID NO. 300
(N20)NGG	20	43280220	-	GCTTGTCGAAGGCGGGCGTCTGG	1	1	9	SEQ ID NO. 301
(N20)NGG	20	43280227	-	ACTTTGGGCTTGTCGAAGGCGGG	1	2	17	SEQ ID NO. 302
(N20)NGG	20	43280228	-	CACTTTGGGCTTGTCGAAGGCGG	1	2	18	SEQ ID NO. 303
(N20)NGG	20	43280231	-	GCTCACTTTGGGCTTGTCGAAGG	1	1	21	SEQ ID NO. 304
(N20)NGG	20	43280242	-	CCCCCGCGCGCGCTCACTTTGGG	1	1	9	SEQ ID NO. 305
(N20)NGG	20	43280243	-	GCCCCCGCGCGCGCTCACTTTGG	2	6	11	SEQ ID NO. 306

FIG. 1 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target site sequence with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	1	33476443	+	TATTTCAGCCTAGTATCAGAAGG	1	2	38	SEQ ID NO. 307
(N20)NGG	1	33476448	+	CAGCCTAGTATCAGAAGGCCAGG	2	4	49	SEQ ID NO. 308
(N20)NGG	1	33476415	-	GATACTAGGCTGAAATAGAGAGG	1	2	28	SEQ ID NO. 309
(N20)NGG	1	33476429	-	TCGCCTGGCCTTCTGATACTAGG	2	3	20	SEQ ID NO. 310
(N20)NGG	1	33478814	+	TCTTCCTGTTCTCAGATCACCGG	4	452	2834	SEQ ID NO. 311
(N20)NGG	1	33478815	+	CTTCCTGTTCTCAGATCACCGGG	2	5	408	SEQ ID NO. 312
(N20)NGG	1	33478816	+	TTCCTGTTCTCAGATCACCGGGG	1	1	25	SEQ ID NO. 313
(N20)NGG	1	33478852	+	TCGATCAGATGATAATGAAAAGG	2	3	34	SEQ ID NO. 314
(N20)NGG	1	33478914	+	CCCCACTCATAGAGTACTACAGG	2	2	8	SEQ ID NO. 315
(N20)NGG	1	33478920	+	TCATAGAGTACTACAGGAAACGG	2	2	44	SEQ ID NO. 316
(N20)NGG	1	33478921	+	CATAGAGTACTACAGGAAACGGG	2	2	35	SEQ ID NO. 317
(N20)NGG	1	33478922	+	ATAGAGTACTACAGGAAACGGGG	2	2	26	SEQ ID NO. 318
(N20)NGG	1	33478923	+	TAGAGTACTACAGGAAACGGGGG	2	3	11	SEQ ID NO. 319
(N20)NGG	1	33479014	+	CAAAGCCACATGTAAAGACTTGG	1	6	64	SEQ ID NO. 320
(N20)NGG	1	33478796	-	TTCCCCGGTGATCTGAGAACAGG	1	1	13	SEQ ID NO. 321
(N20)NGG	1	33478811	-	TCGACGGATCAAGGGTTCCCCGG	2	2	2	SEQ ID NO. 322
(N20)NGG	1	33478819	-	TCATCTGATCGACGGATCAAGGG	2	2	4	SEQ ID NO. 323
(N20)NGG	1	33478820	-	ATCATCTGATCGACGGATCAAGG	2	3	9	SEQ ID NO. 324
(N20)NGG	1	33478827	-	TTTCATTATCATCTGATCGACGG	2	3	41	SEQ ID NO. 325
(N20)NGG	1	33478853	-	GGCTTGCAGGCGGATTTTCAAGG	1	3	16	SEQ ID NO. 326
(N20)NGG	1	33478863	-	GAGTGTGGTAGGCTTGCAGGCGG	2	4	44	SEQ ID NO. 327
(N20)NGG	1	33478866	-	TTTGAGTGTGGTAGGCTTGCAGG	2	2	17	SEQ ID NO. 328
(N20)NGG	1	33478874	-	TGGGGTGGTTTGAGTGTGGTAGG	2	6	77	SEQ ID NO. 329
(N20)NGG	1	33478878	-	TGAGTGGGGTGGTTTGAGTGTGG	2	5	86	SEQ ID NO. 330
(N20)NGG	1	33478889	-	GTAGTACTCTATGAGTGGGGTGG	2	2	15	SEQ ID NO. 331
(N20)NGG	1	33478892	-	CCTGTAGTACTCTATGAGTGGGG	2	2	16	SEQ ID NO. 332
(N20)NGG	1	33478893	-	TCCTGTAGTACTCTATGAGTGGG	2	2	16	SEQ ID NO. 333
(N20)NGG	1	33478894	-	TTCCTGTAGTACTCTATGAGTGG	2	3	23	SEQ ID NO. 334
(N20)NGG	1	33478926	-	GGGATGCATCGATGGCGGAGTGG	1	2	11	SEQ ID NO. 335
(N20)NGG	1	33478931	-	GGTCTGGGATGCATCGATGGCGG	2	2	43	SEQ ID NO. 336
(N20)NGG	1	33478934	-	GGGGGTCTGGGATGCATCGATGG	1	4	26	SEQ ID NO. 337
(N20)NGG	1	33478946	-	GAACACGACATCGGGGGTCTGGG	2	2	3	SEQ ID NO. 338
(N20)NGG	1	33478947	-	CGAACACGACATCGGGGGTCTGG	2	2	3	SEQ ID NO. 339
(N20)NGG	1	33478952	-	GCTTGCGAACACGACATCGGGGG	2	2	3	SEQ ID NO. 340
(N20)NGG	1	33478953	-	TGCTTGCGAACACGACATCGGGG	2	3	4	SEQ ID NO. 341
(N20)NGG	1	33478954	-	ATGCTTGCGAACACGACATCGGG	2	2	37	SEQ ID NO. 342
(N20)NGG	1	33478955	-	GATGCTTGCGAACACGACATCGG	2	2	5	SEQ ID NO. 343
(N20)NGG	1	33478977	-	TGGCTTTGGAGAAGGCTGCTAGG	3	9	93	SEQ ID NO. 344

FIG. 2

site type	site_chromosome	site_start_nucleotide	site_strand	target site sequence with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	1	33478985	-	TTTACATGTGGCTTTGGAGAAGG	2	4	94	SEQ ID NO. 345
(N20)NGG	1	33478991	-	CAAGTCTTTACATGTGGCTTTGG	2	3	39	SEQ ID NO. 346
(N20)NGG	1	33478997	-	CATAACCAAGTCTTTACATGTGG	1	1	29	SEQ ID NO. 347
(N20)NGG	1	33480122	+	ATATTCATTTGCTGTCTTTCAGG	1	3	129	SEQ ID NO. 348
(N20)NGG	1	33480142	+	AGGCTGATTCACCCCAAGAGTGG	1	1	23	SEQ ID NO. 349
(N20)NGG	1	33480159	+	GAGTGGCCGTTCCTACCACGAGG	2	2	6	SEQ ID NO. 350
(N20)NGG	1	33480209	+	AAGATGACGTATGTAAACTCAGG	1	1	11	SEQ ID NO. 351
(N20)NGG	1	33480131	-	GGTAGGAACGGCCACTCTTGGGG	2	2	15	SEQ ID NO. 352
(N20)NGG	1	33480132	-	TGGTAGGAACGGCCACTCTTGGG	2	2	13	SEQ ID NO. 353
(N20)NGG	1	33480133	-	GTGGTAGGAACGGCCACTCTTGG	2	2	62	SEQ ID NO. 354
(N20)NGG	1	33480143	-	TGAACTCCTCGTGGTAGGAACGG	2	3	20	SEQ ID NO. 355
(N20)NGG	1	33480148	-	AGGGTTGAACTCCTCGTGGTAGG	2	2	10	SEQ ID NO. 356
(N20)NGG	1	33480152	-	TTGGAGGGTTGAACTCCTCGTGG	2	2	11	SEQ ID NO. 357
(N20)NGG	1	33480167	-	CTTTCATGGGCTCTTTTGGAGGG	2	6	59	SEQ ID NO. 358
(N20)NGG	1	33480168	-	TCTTTCATGGGCTCTTTTGGAGG	2	4	62	SEQ ID NO. 359
(N20)NGG	1	33480171	-	TCATCTTTCATGGGCTCTTTTGG	2	4	61	SEQ ID NO. 360
(N20)NGG	1	33480180	-	TTACATACGTCATCTTTCATGGG	1	1	28	SEQ ID NO. 361
(N20)NGG	1	33480181	-	TTTACATACGTCATCTTTCATGG	1	3	43	SEQ ID NO. 362
(N20)NGG	1	33486982	+	TTTACAGCTCGATGACCTCATGG	1	2	15	SEQ ID NO. 363
(N20)NGG	1	33486990	+	TCGATGACCTCATGGAGAAGAGG	3	4	27	SEQ ID NO. 364
(N20)NGG	1	33487058	+	CTGCTGATCCGAAGAATCACAGG	2	3	23	SEQ ID NO. 365
(N20)NGG	1	33487062	+	TGATCCGAAGAATCACAGGAAGG	2	2	27	SEQ ID NO. 366
(N20)NGG	1	33487079	+	GGAAGGTATTTGTCCCTTGAAGG	1	2	30	SEQ ID NO. 367
(N20)NGG	1	33486949	-	TCGAGCTGTAAAAGAATGTGTGG	1	1	22	SEQ ID NO. 368
(N20)NGG	1	33486975	-	TCTCTTTCCTCTTCTCCATGAGG	4	20	282	SEQ ID NO. 369
(N20)NGG	1	33487026	-	TTCGGATCAGCAGAGAGTCTGGG	2	4	14	SEQ ID NO. 370
(N20)NGG	1	33487027	-	CTTCGGATCAGCAGAGAGTCTGG	2	3	16	SEQ ID NO. 371
(N20)NGG	1	33487044	-	AATACCTTCCTGTGATTCTTCGG	1	5	70	SEQ ID NO. 372
(N20)NGG	1	33487193	+	CTATTTTGTTCCTAACTTCCAGG	1	2	84	SEQ ID NO. 373
(N20)NGG	1	33487208	+	CTTCCAGGTGAGTGATGAAATGG	1	6	75	SEQ ID NO. 374
(N20)NGG	1	33487214	+	GGTGAGTGATGAAATGGTAGTGG	3	5	43	SEQ ID NO. 375
(N20)NGG	1	33487235	+	GGAGCTCATTGAGAAGAATTTGG	3	4	77	SEQ ID NO. 376
(N20)NGG	1	33487257	+	GAGACCCCCTTGTGCAAAAATGG	2	4	39	SEQ ID NO. 377
(N20)NGG	1	33487268	+	GTGCAAAAATGGTTTTCTTCTGG	3	7	58	SEQ ID NO. 378
(N20)NGG	1	33487272	+	AAAAATGGTTTTCTTCTGGATGG	3	8	176	SEQ ID NO. 379
(N20)NGG	1	33487282	+	TTCTTCTGGATGGCTTCCCTCGG	3	18	115	SEQ ID NO. 380
(N20)NGG	1	33487291	+	ATGGCTTCCCTCGGACTGTGAGG	3	4	29	SEQ ID NO. 381
(N20)NGG	1	33487295	+	CTTCCCTCGGACTGTGAGGCAGG	3	5	27	SEQ ID NO. 382

FIG. 2 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target site sequence with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	1	33487304	+	GACTGTGAGGCAGGCAGAAATGG	3	13	146	SEQ ID NO. 383
(N20)NGG	1	33487307	+	TGTGAGGCAGGCAGAAATGGTGG	1	19	158	SEQ ID NO. 384
(N20)NGG	1	33487308	+	GTGAGGCAGGCAGAAATGGTGGG	1	6	94	SEQ ID NO. 385
(N20)NGG	1	33487181	-	TCATCACTCACCTGGAAGTTAGG	1	3	50	SEQ ID NO. 386
(N20)NGG	1	33487189	-	CTACCATTTCATCACTCACCTGG	4	5	32	SEQ ID NO. 387
(N20)NGG	1	33487239	-	AAAACCATTTTTGCACAAGGGGG	3	5	70	SEQ ID NO. 388
(N20)NGG	1	33487240	-	GAAAACCATTTTTGCACAAGGGG	3	5	73	SEQ ID NO. 389
(N20)NGG	1	33487241	-	AGAAAACCATTTTTGCACAAGGG	3	12	122	SEQ ID NO. 390
(N20)NGG	1	33487242	-	AAGAAAACCATTTTTGCACAAGG	3	6	134	SEQ ID NO. 391
(N20)NGG	1	33487276	-	CTGCCTGCCTCACAGTCCGAGGG	3	14	388	SEQ ID NO. 392
(N20)NGG	1	33487277	-	TCTGCCTGCCTCACAGTCCGAGG	3	8	84	SEQ ID NO. 393
(N20)NGG	1	33490042	+	GTTTTTGTCTTCCTCTCTGTAGG	1	18	183	SEQ ID NO. 394
(N20)NGG	1	33490054	+	CTCTCTGTAGGCACCCAGATTGG	1	2	25	SEQ ID NO. 395
(N20)NGG	1	33490088	+	TGTGTCTGCCATTTAGCTACTGG	2	6	41	SEQ ID NO. 396
(N20)NGG	1	33490089	+	GTGTCTGCCATTTAGCTACTGGG	2	7	36	SEQ ID NO. 397
(N20)NGG	1	33490090	+	TGTCTGCCATTTAGCTACTGGGG	3	4	44	SEQ ID NO. 398
(N20)NGG	1	33490101	+	TAGCTACTGGGGACATGCTGAGG	2	3	37	SEQ ID NO. 399
(N20)NGG	1	33490102	+	AGCTACTGGGGACATGCTGAGGG	2	4	51	SEQ ID NO. 400
(N20)NGG	1	33490108	+	TGGGGACATGCTGAGGGCCATGG	3	8	96	SEQ ID NO. 401
(N20)NGG	1	33490111	+	GGACATGCTGAGGGCCATGGTGG	3	6	74	SEQ ID NO. 402
(N20)NGG	1	33490118	+	CTGAGGGCCATGGTGGCTTCTGG	4	12	93	SEQ ID NO. 403
(N20)NGG	1	33490130	+	GTGGCTTCTGGCTCAGAGCTAGG	4	8	79	SEQ ID NO. 404
(N20)NGG	1	33490144	+	AGAGCTAGGAAAAAAGCTGAAGG	2	6	111	SEQ ID NO. 405
(N20)NGG	1	33490153	+	AAAAAAGCTGAAGGCAACTATGG	5	16	175	SEQ ID NO. 406
(N20)NGG	1	33490160	+	CTGAAGGCAACTATGGATGCTGG	3	3	27	SEQ ID NO. 407
(N20)NGG	1	33490161	+	TGAAGGCAACTATGGATGCTGGG	3	6	32	SEQ ID NO. 408
(N20)NGG	1	33490168	+	AACTATGGATGCTGGGAAACTGG	3	5	44	SEQ ID NO. 409
(N20)NGG	1	33490172	+	ATGGATGCTGGGAAACTGGTAGG	4	6	72	SEQ ID NO. 410
(N20)NGG	1	33490177	+	TGCTGGGAAACTGGTAGGTTTGG	1	2	41	SEQ ID NO. 411
(N20)NGG	1	33490180	+	TGGGAAACTGGTAGGTTTGGTGG	1	3	43	SEQ ID NO. 412
(N20)NGG	1	33490031	-	CAATCTGGGTGCCTACAGAGAGG	1	1	22	SEQ ID NO. 413
(N20)NGG	1	33490045	-	CAGAAGTTTTCAGCCAATCTGGG	3	4	65	SEQ ID NO. 414
(N20)NGG	1	33490046	-	ACAGAAGTTTTCAGCCAATCTGG	3	8	40	SEQ ID NO. 415
(N20)NGG	1	33490074	-	GCATGTCCCCAGTAGCTAAATGG	2	4	24	SEQ ID NO. 416
(N20)NGG	1	33490103	-	CTCTGAGCCAGAAGCCACCATGG	5	13	113	SEQ ID NO. 417
(N20)NGG	1	33502333	+	GTGGCAGTGAGAGACTTCGGCGG	2	4	28	SEQ ID NO. 418
(N20)NGG	1	33502339	+	GTGAGAGACTTCGGCGGACATGG	2	3	8	SEQ ID NO. 419
(N20)NGG	1	33502357	+	CATGGCTCCCAGCGTGCCAGCGG	3	6	37	SEQ ID NO. 420

FIG. 2 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target site sequence with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	1	33502379	+	GCAGAACCCGAGTATCCTAAAGG	3	3	19	SEQ ID NO. 421
(N20)NGG	1	33502386	+	CCGAGTATCCTAAAGGCATCCGG	2	4	9	SEQ ID NO. 422
(N20)NGG	1	33502387	+	CGAGTATCCTAAAGGCATCCGGG	2	2	10	SEQ ID NO. 423
(N20)NGG	1	33502399	+	AGGCATCCGGGCCGTGCTGCTGG	2	2	13	SEQ ID NO. 424
(N20)NGG	1	33502400	+	GGCATCCGGGCCGTGCTGCTGGG	2	2	12	SEQ ID NO. 425
(N20)NGG	1	33502401	+	GCATCCGGGCCGTGCTGCTGGGG	2	3	22	SEQ ID NO. 426
(N20)NGG	1	33502409	+	GCCGTGCTGCTGGGGCCTCCCGG	3	5	80	SEQ ID NO. 427
(N20)NGG	1	33502410	+	CCGTGCTGCTGGGGCCTCCCGGG	3	14	165	SEQ ID NO. 428
(N20)NGG	1	33502411	+	CGTGCTGCTGGGGCCTCCCGGGG	2	3	50	SEQ ID NO. 429
(N20)NGG	1	33502415	+	CTGCTGGGGCCTCCCGGGGCCGG	3	27	142	SEQ ID NO. 430
(N20)NGG	1	33502421	+	GGGCCTCCCGGGGCCGGTAAAGG	3	5	22	SEQ ID NO. 431
(N20)NGG	1	33502422	+	GGCCTCCCGGGGCCGGTAAAGGG	1	3	15	SEQ ID NO. 432
(N20)NGG	1	33502429	+	CGGGGCCGGTAAAGGGACCCAGG	1	3	11	SEQ ID NO. 433
(N20)NGG	1	33502436	+	GGTAAAGGGACCCAGGTGAGCGG	1	3	55	SEQ ID NO. 434
(N20)NGG	1	33502440	+	AAGGGACCCAGGTGAGCGGCAGG	1	1	29	SEQ ID NO. 435
(N20)NGG	1	33502445	+	ACCCAGGTGAGCGGCAGGACTGG	1	3	43	SEQ ID NO. 436
(N20)NGG	1	33502446	+	CCCAGGTGAGCGGCAGGACTGGG	1	7	55	SEQ ID NO. 437
(N20)NGG	1	33502451	+	GTGAGCGGCAGGACTGGGCTTGG	1	5	101	SEQ ID NO. 438
(N20)NGG	1	33502342	-	GGTTCTGCCGCTGGCACGCTGGG	3	3	16	SEQ ID NO. 439
(N20)NGG	1	33502343	-	GGGTTCTGCCGCTGGCACGCTGG	3	3	14	SEQ ID NO. 440
(N20)NGG	1	33502351	-	GGATACTCGGGTTCTGCCGCTGG	3	3	9	SEQ ID NO. 441
(N20)NGG	1	33502363	-	CGGATGCCTTTAGGATACTCGGG	2	2	11	SEQ ID NO. 442
(N20)NGG	1	33502364	-	CCGGATGCCTTTAGGATACTCGG	2	3	12	SEQ ID NO. 443
(N20)NGG	1	33502372	-	AGCACGGCCCGGATGCCTTTAGG	2	2	17	SEQ ID NO. 444
(N20)NGG	1	33502383	-	GAGGCCCCAGCAGCACGGCCCGG	3	7	90	SEQ ID NO. 445
(N20)NGG	1	33502388	-	CCCGGGAGGCCCCAGCAGCACGG	3	9	114	SEQ ID NO. 446
(N20)NGG	1	33502402	-	GTCCCTTTACCGGCCCCGGGAGG	1	3	13	SEQ ID NO. 447
(N20)NGG	1	33502405	-	TGGGTCCCTTTACCGGCCCCGGG	1	6	19	SEQ ID NO. 448
(N20)NGG	1	33502406	-	CTGGGTCCCTTTACCGGCCCCGG	2	4	16	SEQ ID NO. 449
(N20)NGG	1	33502412	-	GCTCACCTGGGTCCCTTTACCGG	1	2	24	SEQ ID NO. 450
(N20)NGG	1	33502424	-	CCCAGTCCTGCCGCTCACCTGGG	2	7	62	SEQ ID NO. 451
(N20)NGG	1	33502425	-	GCCCAGTCCTGCCGCTCACCTGG	1	1	46	SEQ ID NO. 452

FIG. 2 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	11	118209916	+	GATGCTCAGTACAGCCACCTTGG	1	1	32	SEQ ID NO. 453
(N20)NGG	11	118209919	+	GCTCAGTACAGCCACCTTGGAGG	1	4	47	SEQ ID NO. 454
(N20)NGG	11	118209926	+	ACAGCCACCTTGGAGGAAACTGG	1	3	56	SEQ ID NO. 455
(N20)NGG	11	118209927	+	CAGCCACCTTGGAGGAAACTGGG	1	6	70	SEQ ID NO. 456
(N20)NGG	11	118209932	+	ACCTTGGAGGAAACTGGGCTCGG	1	7	61	SEQ ID NO. 457
(N20)NGG	11	118209953	+	GGAACAAGTGAACCTGAGACTGG	1	1	31	SEQ ID NO. 458
(N20)NGG	11	118209956	+	ACAAGTGAACCTGAGACTGGTGG	1	1	29	SEQ ID NO. 459
(N20)NGG	11	118209852	-	TAAGAGAGGAGAAGAGAAAACGG	6	116	1279	SEQ ID NO. 460
(N20)NGG	11	118209866	-	GATCTCGGAGGGGCTAAGAGAGG	1	2	45	SEQ ID NO. 461
(N20)NGG	11	118209876	-	GCATCATCTCGATCTCGGAGGGG	1	1	9	SEQ ID NO. 462
(N20)NGG	11	118209877	-	AGCATCATCTCGATCTCGGAGGG	1	1	5	SEQ ID NO. 463
(N20)NGG	11	118209878	-	GAGCATCATCTCGATCTCGGAGG	1	1	4	SEQ ID NO. 464
(N20)NGG	11	118209881	-	ACTGAGCATCATCTCGATCTCGG	1	2	10	SEQ ID NO. 465
(N20)NGG	11	118209908	-	GAGCCCAGTTTCCTCCAAGGTGG	1	4	48	SEQ ID NO. 466
(N20)NGG	11	118209911	-	TCCGAGCCCAGTTTCCTCCAAGG	1	3	44	SEQ ID NO. 467
(N20)NGG	11	118209943	-	TTCTAGAAGCCACCAGTCTCAGG	1	6	53	SEQ ID NO. 468
(N20)NGG	11	118210190	+	CCGACACACAAGCTCTGTTGAGG	1	1	13	SEQ ID NO. 469
(N20)NGG	11	118210200	+	AGCTCTGTTGAGGAATGACCAGG	1	3	27	SEQ ID NO. 470
(N20)NGG	11	118210209	+	GAGGAATGACCAGGTCTATCAGG	1	1	23	SEQ ID NO. 471
(N20)NGG	11	118210221	+	GGTCTATCAGGTGAGCGTTGAGG	1	1	10	SEQ ID NO. 472
(N20)NGG	11	118210222	+	GTCTATCAGGTGAGCGTTGAGGG	1	1	15	SEQ ID NO. 473
(N20)NGG	11	118210223	+	TCTATCAGGTGAGCGTTGAGGGG	1	2	18	SEQ ID NO. 474
(N20)NGG	11	118210227	+	TCAGGTGAGCGTTGAGGGGAAGG	1	8	42	SEQ ID NO. 475
(N20)NGG	11	118210230	+	GGTGAGCGTTGAGGGGAAGGAGG	1	4	95	SEQ ID NO. 476
(N20)NGG	11	118210168	-	CCTCAACAGAGCTTGTGTGTCGG	1	4	26	SEQ ID NO. 477
(N20)NGG	11	118210196	-	CAACGCTCACCTGATAGACCTGG	1	3	11	SEQ ID NO. 478
(N20)NGG	11	118210506	+	CACAGTGTGCCAGAGCTGTGTGG	1	12	110	SEQ ID NO. 479
(N20)NGG	11	118210512	+	GTGCCAGAGCTGTGTGGAGCTGG	1	6	58	SEQ ID NO. 480
(N20)NGG	11	118210527	+	GGAGCTGGATCCAGCCACCGTGG	1	3	32	SEQ ID NO. 481
(N20)NGG	11	118210531	+	CTGGATCCAGCCACCGTGGCTGG	1	2	43	SEQ ID NO. 482
(N20)NGG	11	118210575	+	TGCCACTCTGCTCCTTGCTTTGG	2	5	71	SEQ ID NO. 483
(N20)NGG	11	118210576	+	GCCACTCTGCTCCTTGCTTTGGG	1	3	60	SEQ ID NO. 484
(N20)NGG	11	118210594	+	TTGGGAGTCTTCTGCTTTGCTGG	1	2	44	SEQ ID NO. 485

FIG. 3

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	11	118210606	+	TGCTTTGCTGGACATGAGACTGG	1	2	47	SEQ ID NO. 486
(N20)NGG	11	118210610	+	TTGCTGGACATGAGACTGGAAGG	1	5	66	SEQ ID NO. 487
(N20)NGG	11	118210618	+	CATGAGACTGGAAGGCTGTCTGG	1	2	38	SEQ ID NO. 488
(N20)NGG	11	118210619	+	ATGAGACTGGAAGGCTGTCTGGG	1	4	51	SEQ ID NO. 489
(N20)NGG	11	118210620	+	TGAGACTGGAAGGCTGTCTGGGG	1	4	76	SEQ ID NO. 490
(N20)NGG	11	118210621	+	GAGACTGGAAGGCTGTCTGGGGG	1	7	78	SEQ ID NO. 491
(N20)NGG	11	118210628	+	GAAGGCTGTCTGGGGGTTAGTGG	1	4	51	SEQ ID NO. 492
(N20)NGG	11	118210465	-	TGTGGGGGAAGGGAGGAGAGAGG	9	73	815	SEQ ID NO. 493
(N20)NGG	11	118210472	-	GGCACACTGTGGGGGAAGGGAGG	1	7	129	SEQ ID NO. 494
(N20)NGG	11	118210475	-	TCTGGCACACTGTGGGGGAAGGG	1	4	46	SEQ ID NO. 495
(N20)NGG	11	118210476	-	CTCTGGCACACTGTGGGGGAAGG	1	1	51	SEQ ID NO. 496
(N20)NGG	11	118210480	-	ACAGCTCTGGCACACTGTGGGGG	1	7	59	SEQ ID NO. 497
(N20)NGG	11	118210481	-	CACAGCTCTGGCACACTGTGGGG	1	4	70	SEQ ID NO. 498
(N20)NGG	11	118210482	-	ACACAGCTCTGGCACACTGTGGG	2	6	59	SEQ ID NO. 499
(N20)NGG	11	118210483	-	CACACAGCTCTGGCACACTGTGG	2	9	112	SEQ ID NO. 500
(N20)NGG	11	118210493	-	GATCCAGCTCCACACAGCTCTGG	1	4	45	SEQ ID NO. 501
(N20)NGG	11	118210515	-	ATGATGCCAGCCACGGTGGCTGG	1	2	54	SEQ ID NO. 502
(N20)NGG	11	118210519	-	GACAATGATGCCAGCCACGGTGG	1	5	65	SEQ ID NO. 503
(N20)NGG	11	118210522	-	AGTGACAATGATGCCAGCCACGG	1	3	47	SEQ ID NO. 504
(N20)NGG	11	118210555	-	TCCCAAAGCAAGGAGCAGAGTGG	1	8	105	SEQ ID NO. 505
(N20)NGG	11	118210565	-	AGCAGAAGACTCCCAAAGCAAGG	1	7	54	SEQ ID NO. 506
(N20)NGG	11	118211115	+	CCCCTTCAAGATACCTATAGAGG	1	2	22	SEQ ID NO. 507
(N20)NGG	11	118211124	+	GATACCTATAGAGGAACTTGAGG	1	1	15	SEQ ID NO. 508
(N20)NGG	11	118211162	+	ATTGCAATACCAGCATCACATGG	1	4	44	SEQ ID NO. 509
(N20)NGG	11	118211163	+	TTGCAATACCAGCATCACATGGG	1	1	32	SEQ ID NO. 510
(N20)NGG	11	118211169	+	TACCAGCATCACATGGGTAGAGG	1	4	70	SEQ ID NO. 511
(N20)NGG	11	118211170	+	ACCAGCATCACATGGGTAGAGGG	1	2	37	SEQ ID NO. 512
(N20)NGG	11	118211175	+	CATCACATGGGTAGAGGGAACGG	1	4	69	SEQ ID NO. 513
(N20)NGG	11	118211178	+	CACATGGGTAGAGGGAACGGTGG	1	2	38	SEQ ID NO. 514
(N20)NGG	11	118211179	+	ACATGGGTAGAGGGAACGGTGGG	1	3	29	SEQ ID NO. 515
(N20)NGG	11	118211208	+	GCTCTCAGACATTACAAGACTGG	1	4	31	SEQ ID NO. 516
(N20)NGG	11	118211214	+	AGACATTACAAGACTGGACCTGG	1	1	27	SEQ ID NO. 517
(N20)NGG	11	118211215	+	GACATTACAAGACTGGACCTGGG	1	1	18	SEQ ID NO. 518

FIG. 3 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	11	118211229	+	GGACCTGGGAAAACGCATCCTGG	1	1	17	SEQ ID NO. 519
(N20)NGG	11	118211239	+	AAACGCATCCTGGACCCACGAGG	1	1	5	SEQ ID NO. 520
(N20)NGG	11	118211249	+	TGGACCCACGAGGAATATATAGG	1	2	13	SEQ ID NO. 521
(N20)NGG	11	118211257	+	CGAGGAATATATAGGTGTAATGG	1	1	22	SEQ ID NO. 522
(N20)NGG	11	118211258	+	GAGGAATATATAGGTGTAATGGG	1	1	51	SEQ ID NO. 523
(N20)NGG	11	118211274	+	TAATGGGACAGATATATACAAGG	1	9	142	SEQ ID NO. 524
(N20)NGG	11	118211331	+	TACGTGCTTCCTGAACCCTTTGG	1	2	14	SEQ ID NO. 525
(N20)NGG	11	118211332	+	ACGTGCTTCCTGAACCCTTTGGG	1	1	17	SEQ ID NO. 526
(N20)NGG	11	118211080	-	CTTGAAGGGGCTCACTAAAGGGG	1	1	20	SEQ ID NO. 527
(N20)NGG	11	118211081	-	TCTTGAAGGGGCTCACTAAAGGG	1	2	23	SEQ ID NO. 528
(N20)NGG	11	118211082	-	ATCTTGAAGGGGCTCACTAAAGG	1	2	15	SEQ ID NO. 529
(N20)NGG	11	118211093	-	CCTCTATAGGTATCTTGAAGGGG	1	1	18	SEQ ID NO. 530
(N20)NGG	11	118211094	-	TCCTCTATAGGTATCTTGAAGGG	1	3	21	SEQ ID NO. 531
(N20)NGG	11	118211095	-	TTCCTCTATAGGTATCTTGAAGG	1	1	33	SEQ ID NO. 532
(N20)NGG	11	118211106	-	CTGTCCTCAAGTTCCTCTATAGG	1	3	35	SEQ ID NO. 533
(N20)NGG	11	118211149	-	TCCCTCTACCCATGTGATGCTGG	1	1	54	SEQ ID NO. 534
(N20)NGG	11	118211210	-	GGTCCAGGATGCGTTTTCCCAGG	1	3	19	SEQ ID NO. 535
(N20)NGG	11	118211225	-	TATATATTCCTCGTGGGTCCAGG	1	1	11	SEQ ID NO. 536
(N20)NGG	11	118211231	-	TACACCTATATATTCCTCGTGGG	1	1	9	SEQ ID NO. 537
(N20)NGG	11	118211232	-	TTACACCTATATATTCCTCGTGG	1	2	34	SEQ ID NO. 538
(N20)NGG	11	118211287	-	ACTTCGATAATGAACTTGCACGG	1	1	14	SEQ ID NO. 539
(N20)NGG	11	118213264	+	TCTACTGGATGAGTTCCGCTGGG	1	1	9	SEQ ID NO. 540
(N20)NGG	11	118213270	+	GGATGAGTTCCGCTGGGAGATGG	1	3	31	SEQ ID NO. 541
(N20)NGG	11	118213292	+	GAACATAGCACGTTTCTCTCTGG	1	1	17	SEQ ID NO. 542
(N20)NGG	11	118213297	+	TAGCACGTTTCTCTCTGGCCTGG	1	4	39	SEQ ID NO. 543
(N20)NGG	11	118213303	+	GTTTCTCTCTGGCCTGGTACTGG	1	2	19	SEQ ID NO. 544
(N20)NGG	11	118213322	+	CTGGCTACCCTTCTCTCGCAAGG	2	5	27	SEQ ID NO. 545
(N20)NGG	11	118213327	+	TACCCTTCTCTCGCAAGGTAAGG	1	2	12	SEQ ID NO. 546
(N20)NGG	11	118213337	+	TCGCAAGGTAAGGCTACTCCAGG	1	1	4	SEQ ID NO. 547
(N20)NGG	11	118213340	+	CAAGGTAAGGCTACTCCAGGTGG	1	2	30	SEQ ID NO. 548
(N20)NGG	11	118213341	+	AAGGTAAGGCTACTCCAGGTGGG	1	2	29	SEQ ID NO. 549
(N20)NGG	11	118213344	+	GTAAGGCTACTCCAGGTGGGTGG	1	3	26	SEQ ID NO. 550
(N20)NGG	11	118213345	+	TAAGGCTACTCCAGGTGGGTGGG	1	2	24	SEQ ID NO. 551

FIG. 3 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	11	118213346	+	AAGGCTACTCCAGGTGGGTGGGG	1	2	27	SEQ ID NO. 552
(N20)NGG	11	118213257	-	TGCTATGTTCCATCTCCCAGCGG	1	4	57	SEQ ID NO. 553
(N20)NGG	11	118213293	-	AGAGAAGGGTAGCCAGTACCAGG	1	4	38	SEQ ID NO. 554
(N20)NGG	11	118213307	-	AGCCTTACCTTGCGAGAGAAGGG	1	1	14	SEQ ID NO. 555
(N20)NGG	11	118213308	-	TAGCCTTACCTTGCGAGAAGG	1	1	9	SEQ ID NO. 556

FIG. 3 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	10	14950408	+	CTGTTTTGTTTGTCCCACAGAGG	3	7	100	SEQ ID NO. 557
(N20)NGG	10	14950411	+	TTTTGTTTGTCCCACAGAGGAGG	1	8	95	SEQ ID NO. 558
(N20)NGG	10	14950455	+	ATCCTCTGCCAATACCTTTAAGG	1	4	37	SEQ ID NO. 559
(N20)NGG	10	14950474	+	AAGGCACAAAGTTCCATACCCGG	1	1	31	SEQ ID NO. 560
(N20)NGG	10	14950492	+	CCCGGAAACTTTTCACCCTGAGG	1	2	12	SEQ ID NO. 561
(N20)NGG	10	14950550	+	GAAAAACTGAGACAAACCCCAGG	1	6	60	SEQ ID NO. 562
(N20)NGG	10	14950640	+	AGTGAAAGTGAAGAAGAAGTAGG	1	14	197	SEQ ID NO. 563
(N20)NGG	10	14950661	+	GGAATCCCAGCTTCACTGCAAGG	1	3	67	SEQ ID NO. 564
(N20)NGG	10	14950669	+	AGCTTCACTGCAAGGAGATCTGG	1	2	28	SEQ ID NO. 565
(N20)NGG	10	14950670	+	GCTTCACTGCAAGGAGATCTGGG	1	4	40	SEQ ID NO. 566
(N20)NGG	10	14950693	+	CTCTGTACTTCACCTGCAAAAGG	1	3	51	SEQ ID NO. 567
(N20)NGG	10	14950700	+	CTTCACCTGCAAAAGGCTGATGG	1	2	53	SEQ ID NO. 568
(N20)NGG	10	14950701	+	TTCACCTGCAAAAGGCTGATGGG	1	4	44	SEQ ID NO. 569
(N20)NGG	10	14950702	+	TCACCTGCAAAAGGCTGATGGGG	1	5	52	SEQ ID NO. 570
(N20)NGG	10	14950716	+	CTGATGGGGATGTACCCCAGTGG	1	2	23	SEQ ID NO. 571
(N20)NGG	10	14950717	+	TGATGGGGATGTACCCCAGTGGG	1	1	21	SEQ ID NO. 572
(N20)NGG	10	14950762	+	TGAAATCACAGATGAGAGTTTGG	2	4	66	SEQ ID NO. 573
(N20)NGG	10	14950786	+	AAACTTCCCTTCCTCCACAGTGG	1	4	85	SEQ ID NO. 574
(N20)NGG	10	14950790	+	TTCCCTTCCTCCACAGTGGCAGG	1	7	90	SEQ ID NO. 575
(N20)NGG	10	14950791	+	TCCCTTCCTCCACAGTGGCAGGG	1	6	83	SEQ ID NO. 576
(N20)NGG	10	14950792	+	CCCTTCCTCCACAGTGGCAGGGG	1	8	112	SEQ ID NO. 577
(N20)NGG	10	14950793	+	CCTTCCTCCACAGTGGCAGGGGG	3	8	98	SEQ ID NO. 578
(N20)NGG	10	14950829	+	AAGCTTTTCAGTGACTCTGATGG	1	3	63	SEQ ID NO. 579
(N20)NGG	10	14950889	+	TCAACACACATAACAGAACAAGG	1	4	82	SEQ ID NO. 580
(N20)NGG	10	14950898	+	ATAACAGAACAAGGAAGTCAAGG	1	10	104	SEQ ID NO. 581
(N20)NGG	10	14950902	+	CAGAACAAGGAAGTCAAGGCTGG	1	6	74	SEQ ID NO. 582
(N20)NGG	10	14950903	+	AGAACAAGGAAGTCAAGGCTGGG	1	14	244	SEQ ID NO. 583
(N20)NGG	10	14950952	+	TCTTCCCAAGAGAGAAACAGTGG	1	7	125	SEQ ID NO. 584
(N20)NGG	10	14950953	+	CTTCCCAAGAGAGAAACAGTGGG	1	5	98	SEQ ID NO. 585
(N20)NGG	10	14950954	+	TTCCCAAGAGAGAAACAGTGGGG	1	6	70	SEQ ID NO. 586
(N20)NGG	10	14950969	+	CAGTGGGGATATTACTTCCTTGG	1	1	30	SEQ ID NO. 587
(N20)NGG	10	14951023	+	GAATATTCCTGCCTCTCTCATGG	1	4	39	SEQ ID NO. 588
(N20)NGG	10	14951047	+	ACAAAATGTAATTTGCCCAAAGG	2	12	88	SEQ ID NO. 589

FIG. 4

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	10	14951105	+	GTGACAATAGTTCCTAGTACTGG	1	1	19	SEQ ID NO. 590
(N20)NGG	10	14951146	+	CAGTGAGACACATATACCCGAGG	1	2	8	SEQ ID NO. 591
(N20)NGG	10	14951272	+	ACAATATTTATATGAGAAGCTGG	1	5	70	SEQ ID NO. 592
(N20)NGG	10	14951279	+	TTATATGAGAAGCTGGCAACTGG	1	3	39	SEQ ID NO. 593
(N20)NGG	10	14950385	-	CTCTGTGGGACAAACAAAACAGG	1	5	76	SEQ ID NO. 594
(N20)NGG	10	14950399	-	TAGTCATCTTCCTCCTCTGTGGG	1	6	82	SEQ ID NO. 595
(N20)NGG	10	14950400	-	ATAGTCATCTTCCTCCTCTGTGG	1	5	77	SEQ ID NO. 596
(N20)NGG	10	14950435	-	TGCCTTAAAGGTATTGGCAGAGG	1	3	28	SEQ ID NO. 597
(N20)NGG	10	14950441	-	ACTTTGTGCCTTAAAGGTATTGG	1	2	37	SEQ ID NO. 598
(N20)NGG	10	14950447	-	TATGGAACTTTGTGCCTTAAAGG	1	3	49	SEQ ID NO. 599
(N20)NGG	10	14950465	-	GGGTGAAAAGTTTCCGGGTATGG	1	1	17	SEQ ID NO. 600
(N20)NGG	10	14950470	-	CCTCAGGGTGAAAAGTTTCCGGG	1	6	69	SEQ ID NO. 601
(N20)NGG	10	14950471	-	ACCTCAGGGTGAAAAGTTTCCGG	4	6	46	SEQ ID NO. 602
(N20)NGG	10	14950485	-	CAGTCATTGAAAATACCTCAGGG	1	2	52	SEQ ID NO. 603
(N20)NGG	10	14950486	-	GCAGTCATTGAAAATACCTCAGG	1	2	29	SEQ ID NO. 604
(N20)NGG	10	14950525	-	GGGGTTTGTCTCAGTTTTTCAGG	1	4	48	SEQ ID NO. 605
(N20)NGG	10	14950544	-	CTCTGCTCTGCAGCATCCTGGGG	2	17	132	SEQ ID NO. 606
(N20)NGG	10	14950545	-	ACTCTGCTCTGCAGCATCCTGGG	3	10	93	SEQ ID NO. 607
(N20)NGG	10	14950546	-	CACTCTGCTCTGCAGCATCCTGG	1	9	79	SEQ ID NO. 608
(N20)NGG	10	14950613	-	TTCTTCTTCACTTTCACTGTTGG	1	10	150	SEQ ID NO. 609
(N20)NGG	10	14950644	-	GATCTCCTTGCAGTGAAGCTGGG	1	2	33	SEQ ID NO. 610
(N20)NGG	10	14950645	-	AGATCTCCTTGCAGTGAAGCTGG	1	4	45	SEQ ID NO. 611
(N20)NGG	10	14950683	-	CATCCCCATCAGCCTTTTGCAGG	1	6	57	SEQ ID NO. 612
(N20)NGG	10	14950708	-	TTAAAGAATACTTCCCACTGGGG	1	6	67	SEQ ID NO. 613
(N20)NGG	10	14950709	-	TTTAAAGAATACTTCCCACTGGG	1	4	89	SEQ ID NO. 614
(N20)NGG	10	14950710	-	TTTTAAAGAATACTTCCCACTGG	2	9	108	SEQ ID NO. 615
(N20)NGG	10	14950770	-	CCCCTGCCACTGTGGAGGAAGGG	1	5	68	SEQ ID NO. 616
(N20)NGG	10	14950771	-	CCCCCTGCCACTGTGGAGGAAGG	1	4	70	SEQ ID NO. 617
(N20)NGG	10	14950775	-	AGATCCCCCTGCCACTGTGGAGG	1	3	43	SEQ ID NO. 618
(N20)NGG	10	14950778	-	CTGAGATCCCCCTGCCACTGTGG	1	3	67	SEQ ID NO. 619
(N20)NGG	10	14950804	-	TCAGAGTCACTGAAAAGCTTTGG	1	6	66	SEQ ID NO. 620
(N20)NGG	10	14950847	-	TGACTGGGAAGAATTCTGGGAGG	1	4	86	SEQ ID NO. 621
(N20)NGG	10	14950850	-	TGTTGACTGGGAAGAATTCTGGG	1	6	74	SEQ ID NO. 622

FIG. 4 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	10	14950851	-	GTGTTGACTGGGAAGAATTCTGG	1	4	57	SEQ ID NO. 623
(N20)NGG	10	14950862	-	TTCTGTTATGTGTGTTGACTGGG	1	7	48	SEQ ID NO. 624
(N20)NGG	10	14950863	-	GTTCTGTTATGTGTGTTGACTGG	1	2	37	SEQ ID NO. 625
(N20)NGG	10	14950908	-	ATAACAAAACAGTATCAGATTGG	1	7	120	SEQ ID NO. 626
(N20)NGG	10	14950934	-	ATCCCCACTGTTTCTCTCTTGGG	1	4	83	SEQ ID NO. 627
(N20)NGG	10	14950935	-	TATCCCCACTGTTTCTCTCTTGG	1	4	66	SEQ ID NO. 628
(N20)NGG	10	14950964	-	TCTGTAGTCAGCTTTGTCCAAGG	1	2	46	SEQ ID NO. 629
(N20)NGG	10	14950987	-	GGAATATTCTCTTTGATTGTTGG	1	1	64	SEQ ID NO. 630
(N20)NGG	10	14951008	-	TTTTGTTCCATGAGAGAGGCAGG	1	3	41	SEQ ID NO. 631
(N20)NGG	10	14951012	-	TACATTTTGTTCCATGAGAGAGG	1	3	70	SEQ ID NO. 632
(N20)NGG	10	14951040	-	AATCAGAGTAAGTATCCTTTGGG	1	5	70	SEQ ID NO. 633
(N20)NGG	10	14951041	-	AAATCAGAGTAAGTATCCTTTGG	1	4	59	SEQ ID NO. 634
(N20)NGG	10	14951095	-	GTAGTTGGTTCTCCAGTACTAGG	1	2	33	SEQ ID NO. 635
(N20)NGG	10	14951110	-	GTCTCACTGCTTAGAGTAGTTGG	1	1	19	SEQ ID NO. 636
(N20)NGG	10	14951140	-	TTTAGCAAACTTTTTTCCTCGGG	1	10	106	SEQ ID NO. 637
(N20)NGG	10	14951141	-	ATTTAGCAAACTTTTTTCCTCGG	2	9	151	SEQ ID NO. 638
(N20)NGG	10	14951183	-	TTCAAAATCAGAAGAGCTCTGGG	1	4	77	SEQ ID NO. 639
(N20)NGG	10	14951184	-	CTTCAAAATCAGAAGAGCTCTGG	1	3	62	SEQ ID NO. 640
(N20)NGG	10	14951209	-	AACTCAGCTTCTGGAGTTGAGGG	1	9	165	SEQ ID NO. 641
(N20)NGG	10	14951210	-	TAACTCAGCTTCTGGAGTTGAGG	1	3	77	SEQ ID NO. 642
(N20)NGG	10	14951218	-	CGTTTAGGTAACTCAGCTTCTGG	1	2	12	SEQ ID NO. 643
(N20)NGG	10	14951233	-	TATTGTAAATGCTCTCGTTTAGG	1	3	37	SEQ ID NO. 644
(N20)NGG	10	14951324	-	TTGAAACGCTTTGAATTCTTAGG	2	6	54	SEQ ID NO. 645
(N20)NGG	10	14961754	+	TCAGCTTAAAGCCTTTATGCCGG	1	4	22	SEQ ID NO. 646
(N20)NGG	10	14961770	+	ATGCCGGTCTTCCCAAAGTACGG	1	2	11	SEQ ID NO. 647
(N20)NGG	10	14961791	+	GGAGCCAAAGTATAAACCACTGG	1	2	33	SEQ ID NO. 648
(N20)NGG	10	14961792	+	GAGCCAAAGTATAAACCACTGGG	1	3	43	SEQ ID NO. 649
(N20)NGG	10	14961831	+	AGAACAGTTCACCGAGACTCAGG	1	1	17	SEQ ID NO. 650
(N20)NGG	10	14961843	+	CGAGACTCAGGTAAGAAAAATGG	1	3	71	SEQ ID NO. 651
(N20)NGG	10	14961849	+	TCAGGTAAGAAAAATGGTCCTGG	1	3	48	SEQ ID NO. 652
(N20)NGG	10	14961850	+	CAGGTAAGAAAAATGGTCCTGGG	1	7	69	SEQ ID NO. 653
(N20)NGG	10	14961743	-	CTTTGGGAAGACCGGCATAAAGG	1	2	8	SEQ ID NO. 654
(N20)NGG	10	14961751	-	GCTCCGTACTTTGGGAAGACCGG	1	4	91	SEQ ID NO. 655

FIG. 4 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	10	14961759	-	ATACTTTGGCTCCGTACTTTGGG	1	3	20	SEQ ID NO. 656
(N20)NGG	10	14961760	-	TATACTTTGGCTCCGTACTTTGG	1	1	8	SEQ ID NO. 657
(N20)NGG	10	14961773	-	TTTCCCAGTGGTTTATACTTTGG	1	4	78	SEQ ID NO. 658
(N20)NGG	10	14961785	-	GCTCTCTTCAGTTTTCCCAGTGG	1	9	90	SEQ ID NO. 659
(N20)NGG	10	14961820	-	CATTTTTCTTACCTGAGTCTCGG	2	10	114	SEQ ID NO. 660
(N20)NGG	10	14965040	+	TATCCAAATGTCATTCCAGTTGG	1	3	53	SEQ ID NO. 661
(N20)NGG	10	14965051	+	CATTCCAGTTGGCACAACTATGG	1	2	25	SEQ ID NO. 662
(N20)NGG	10	14965082	+	GTCGAAATGTGAGTAGTCACTGG	1	1	9	SEQ ID NO. 663
(N20)NGG	10	14965088	+	ATGTGAGTAGTCACTGGTTGTGG	1	4	27	SEQ ID NO. 664
(N20)NGG	10	14965089	+	TGTGAGTAGTCACTGGTTGTGGG	2	2	28	SEQ ID NO. 665
(N20)NGG	10	14964956	-	CTAGAAAAAGGAAAATCACATGG	3	15	312	SEQ ID NO. 666
(N20)NGG	10	14964968	-	GAAATCTTTAATCTAGAAAAAGG	2	19	176	SEQ ID NO. 667
(N20)NGG	10	14964999	-	GATATGCGTTCACAGGACAGAGG	1	2	12	SEQ ID NO. 668
(N20)NGG	10	14965006	-	ACATTTGGATATGCGTTCACAGG	1	1	13	SEQ ID NO. 669
(N20)NGG	10	14965021	-	GTGCCAACTGGAATGACATTTGG	1	1	33	SEQ ID NO. 670
(N20)NGG	10	14965033	-	TTATCCATAGTTGTGCCAACTGG	1	2	22	SEQ ID NO. 671
(N20)NGG	10	14968841	+	TTGTGTTTTCACTTCCCTTTAGG	2	12	229	SEQ ID NO. 672
(N20)NGG	10	14968846	+	TTTTCACTTCCCTTTAGGACTGG	1	2	54	SEQ ID NO. 673
(N20)NGG	10	14968896	+	TTTTCACTCCTCCTACAGTGAGG	1	1	51	SEQ ID NO. 674
(N20)NGG	10	14968903	+	TCCTCCTACAGTGAGGTAAGAGG	1	2	27	SEQ ID NO. 675
(N20)NGG	10	14968833	-	GAACTCTCTCCAGTCCTAAAGGG	1	4	27	SEQ ID NO. 676
(N20)NGG	10	14968834	-	TGAACTCTCTCCAGTCCTAAAGG	1	1	28	SEQ ID NO. 677
(N20)NGG	10	14968882	-	TCCTCTTACCTCACTGTAGGAGG	2	2	44	SEQ ID NO. 678
(N20)NGG	10	14968885	-	GGATCCTCTTACCTCACTGTAGG	1	5	33	SEQ ID NO. 679
(N20)NGG	10	14970014	+	CTATGCTTTTTATCTTTTTTAGG	1	55	838	SEQ ID NO. 680
(N20)NGG	10	14970020	+	TTTTTATCTTTTTTAGGCAGAGG	2	43	1301	SEQ ID NO. 681
(N20)NGG	10	14970034	+	AGGCAGAGGAATATTTTCAGTGG	2	9	115	SEQ ID NO. 682
(N20)NGG	10	14970051	+	CAGTGGAGCAAATTACCCTGTGG	1	3	35	SEQ ID NO. 683
(N20)NGG	10	14970112	+	GCATTAAGCCATCCACCATGTGG	1	2	21	SEQ ID NO. 684
(N20)NGG	10	14970117	+	AAGCCATCCACCATGTGGTTTGG	1	4	38	SEQ ID NO. 685
(N20)NGG	10	14970124	+	CCACCATGTGGTTTGGAGAAAGG	1	7	49	SEQ ID NO. 686
(N20)NGG	10	14970151	+	GAAAAACAAATGTAATTGTGAGG	2	11	216	SEQ ID NO. 687
(N20)NGG	10	14970171	+	AGGTAAGAGAGCAATATCATAGG	1	1	33	SEQ ID NO. 688

FIG. 4 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	10	14970044	-	TTTCTGGAAGTAATTCCACAGGG	2	8	107	SEQ ID NO. 689
(N20)NGG	10	14970045	-	ATTTCTGGAAGTAATTCCACAGG	2	5	67	SEQ ID NO. 690
(N20)NGG	10	14970060	-	GTGGAGTGGAATTCTATTTCTGG	1	1	38	SEQ ID NO. 691
(N20)NGG	10	14970074	-	TTAATGCTGATTATGTGGAGTGG	1	1	60	SEQ ID NO. 692
(N20)NGG	10	14970079	-	ATGGCTTAATGCTGATTATGTGG	1	8	65	SEQ ID NO. 693
(N20)NGG	10	14970098	-	TCTCCAAACCACATGGTGGATGG	1	4	51	SEQ ID NO. 694
(N20)NGG	10	14970102	-	CCTTTCTCCAAACCACATGGTGG	1	9	53	SEQ ID NO. 695
(N20)NGG	10	14970105	-	GCTCCTTTCTCCAAACCACATGG	2	10	84	SEQ ID NO. 696
(N20)NGG	10	14974852	+	ATGTATGTATTATTTGCCTTAGG	1	7	147	SEQ ID NO. 697
(N20)NGG	10	14974881	+	TGAATAAGCTAGACATGTTTAGG	2	4	58	SEQ ID NO. 698
(N20)NGG	10	14974944	+	ACACTCAGATCCATGCATGCCGG	2	5	43	SEQ ID NO. 699
(N20)NGG	10	14974954	+	CCATGCATGCCGGCATCCCAAGG	1	2	34	SEQ ID NO. 700
(N20)NGG	10	14974846	-	AGCTTATTCACATGAACCTAAGG	1	5	45	SEQ ID NO. 701
(N20)NGG	10	14974888	-	GTGAGATGATGAAGGATCTCAGG	2	4	58	SEQ ID NO. 702
(N20)NGG	10	14974896	-	GGTCTGTTGTGAGATGATGAAGG	2	6	47	SEQ ID NO. 703
(N20)NGG	10	14974917	-	ATGCATGGATCTGAGTGTTGCGG	2	6	47	SEQ ID NO. 704
(N20)NGG	10	14974932	-	CCTTGGGATGCCGGCATGCATGG	1	1	23	SEQ ID NO. 705
(N20)NGG	10	14974941	-	GCACACGTACCTTGGGATGCCGG	1	1	7	SEQ ID NO. 706
(N20)NGG	10	14974948	-	ATCACTTGCACACGTACCTTGGG	1	1	10	SEQ ID NO. 707
(N20)NGG	10	14974949	-	AATCACTTGCACACGTACCTTGG	1	1	22	SEQ ID NO. 708
(N20)NGG	10	14976378	+	GTCTCTTTAAAATCCTGTCTAGG	2	6	86	SEQ ID NO. 709
(N20)NGG	10	14976381	+	TCTTTAAAATCCTGTCTAGGAGG	2	6	64	SEQ ID NO. 710
(N20)NGG	10	14976394	+	GTCTAGGAGGAGTGTTTAAGTGG	2	2	30	SEQ ID NO. 711
(N20)NGG	10	14976408	+	TTTAAGTGGAGTCTTAGAGCTGG	2	2	35	SEQ ID NO. 712
(N20)NGG	10	14976419	+	TCTTAGAGCTGGTCCGAAGCTGG	1	3	9	SEQ ID NO. 713
(N20)NGG	10	14976428	+	TGGTCCGAAGCTGGATCACTCGG	1	2	8	SEQ ID NO. 714
(N20)NGG	10	14976449	+	GGAGCCCGTACCATGTTGTGTGG	1	2	13	SEQ ID NO. 715
(N20)NGG	10	14976465	+	TGTGTGGCTGAACTGCAAAGCGG	2	5	52	SEQ ID NO. 716
(N20)NGG	10	14976472	+	CTGAACTGCAAAGCGGCTTATGG	3	3	31	SEQ ID NO. 717
(N20)NGG	10	14976511	+	ACCAACCTTAGTGAAGAATTAGG	2	4	32	SEQ ID NO. 718
(N20)NGG	10	14976519	+	TAGTGAAGAATTAGGAGTCCAGG	2	5	35	SEQ ID NO. 719
(N20)NGG	10	14976524	+	AAGAATTAGGAGTCCAGGTATGG	2	6	86	SEQ ID NO. 720
(N20)NGG	10	14976369	-	CTTAAACACTCCTCCTAGACAGG	2	4	25	SEQ ID NO. 721

FIG. 4 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	10	14976410	-	GGCTCCGAGTGATCCAGCTTCGG	1	3	22	SEQ ID NO. 722
(N20)NGG	10	14976431	-	TCAGCCACACAACATGGTACGGG	2	8	158	SEQ ID NO. 723
(N20)NGG	10	14976432	-	TTCAGCCACACAACATGGTACGG	2	4	30	SEQ ID NO. 724
(N20)NGG	10	14976437	-	TGCAGTTCAGCCACACAACATGG	2	3	60	SEQ ID NO. 725
(N20)NGG	10	14976490	-	TCCTAATTCTTCACTAAGGTTGG	2	6	37	SEQ ID NO. 726
(N20)NGG	10	14976494	-	GGACTCCTAATTCTTCACTAAGG	2	2	18	SEQ ID NO. 727
(N20)NGG	10	14976515	-	GAATGAACAGTCACCATACCTGG	2	6	26	SEQ ID NO. 728
(N20)NGG	10	14976729	+	AGACATCCAAAGTGTATATTTGG	2	6	50	SEQ ID NO. 729
(N20)NGG	10	14976773	+	GATTTTACCAAATTCCAAGTCGG	4	8	74	SEQ ID NO. 730
(N20)NGG	10	14976774	+	ATTTTACCAAATTCCAAGTCGGG	2	5	52	SEQ ID NO. 731
(N20)NGG	10	14976787	+	CCAAGTCGGGTAAGTCTGCCTGG	2	2	14	SEQ ID NO. 732
(N20)NGG	10	14976790	+	AGTCGGGTAAGTCTGCCTGGAGG	2	4	29	SEQ ID NO. 733
(N20)NGG	10	14976796	+	GTAAGTCTGCCTGGAGGAACAGG	2	5	41	SEQ ID NO. 734
(N20)NGG	10	14976797	+	TAAGTCTGCCTGGAGGAACAGGG	2	3	53	SEQ ID NO. 735
(N20)NGG	10	14976713	-	TAGTATCCAAATATACACTTTGG	2	8	49	SEQ ID NO. 736
(N20)NGG	10	14976747	-	CTTGGAATTTGGTAAAATCTTGG	3	13	87	SEQ ID NO. 737
(N20)NGG	10	14976758	-	GACTTACCCGACTTGGAATTTGG	2	2	15	SEQ ID NO. 738
(N20)NGG	10	14976765	-	CCAGGCAGACTTACCCGACTTGG	2	2	16	SEQ ID NO. 739
(N20)NGG	10	14977461	+	CTGGGATATATTTCTTTTTCAGG	2	7	140	SEQ ID NO. 740
(N20)NGG	10	14977474	+	CTTTTTCAGGTTTTTATTTCAGG	3	21	378	SEQ ID NO. 741
(N20)NGG	10	14977475	+	TTTTTCAGGTTTTTATTTCAGGG	5	53	552	SEQ ID NO. 742
(N20)NGG	10	14977484	+	TTTTTATTTCAGGGCAATAATGG	2	11	217	SEQ ID NO. 743
(N20)NGG	10	14977502	+	AATGGAACTGTCCTGTACACAGG	1	6	36	SEQ ID NO. 744
(N20)NGG	10	14977516	+	GTACACAGGAGACTTCAGATTGG	2	3	44	SEQ ID NO. 745
(N20)NGG	10	14977523	+	GGAGACTTCAGATTGGCGCAAGG	1	3	15	SEQ ID NO. 746
(N20)NGG	10	14977540	+	GCAAGGAGAAGCTGCTAGAATGG	3	7	73	SEQ ID NO. 747
(N20)NGG	10	14977556	+	AGAATGGAGCTTCTGCACTCCGG	2	5	95	SEQ ID NO. 748
(N20)NGG	10	14977557	+	GAATGGAGCTTCTGCACTCCGGG	2	2	36	SEQ ID NO. 749
(N20)NGG	10	14977558	+	AATGGAGCTTCTGCACTCCGGGG	2	2	17	SEQ ID NO. 750
(N20)NGG	10	14977559	+	ATGGAGCTTCTGCACTCCGGGGG	2	3	20	SEQ ID NO. 751
(N20)NGG	10	14977563	+	AGCTTCTGCACTCCGGGGGCAGG	2	4	36	SEQ ID NO. 752
(N20)NGG	10	14977569	+	TGCACTCCGGGGGCAGGTACTGG	2	5	19	SEQ ID NO. 753
(N20)NGG	10	14977570	+	GCACTCCGGGGGCAGGTACTGGG	2	2	11	SEQ ID NO. 754

FIG. 4 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	10	14977581	+	GCAGGTACTGGGCCTCGTATAGG	2	3	14	SEQ ID NO. 755
(N20)NGG	10	14977491	-	ATCTGAAGTCTCCTGTGTACAGG	2	4	39	SEQ ID NO. 756
(N20)NGG	10	14977553	-	CGAGGCCCAGTACCTGCCCCCGG	2	4	57	SEQ ID NO. 757
(N20)NGG	10	14978539	+	TTCTTTATTTTCTTTTTAGAAGG	15	1012	20720	SEQ ID NO. 758
(N20)NGG	10	14978570	+	GTTGTGACTCTCTTACCAGCTGG	1	2	25	SEQ ID NO. 759
(N20)NGG	10	14978581	+	CTTACCAGCTGGTCACTGTCCGG	1	2	23	SEQ ID NO. 760
(N20)NGG	10	14978582	+	TTACCAGCTGGTCACTGTCCGGG	1	3	29	SEQ ID NO. 761
(N20)NGG	10	14978597	+	TGTCCGGGATCAGTTATGTAAGG	1	1	4	SEQ ID NO. 762
(N20)NGG	10	14978598	+	GTCCGGGATCAGTTATGTAAGGG	1	1	6	SEQ ID NO. 763
(N20)NGG	10	14978599	+	TCCGGGATCAGTTATGTAAGGGG	1	1	9	SEQ ID NO. 764
(N20)NGG	10	14978600	+	CCGGGATCAGTTATGTAAGGGGG	1	1	7	SEQ ID NO. 765
(N20)NGG	10	14978563	-	GATCCCGGACAGTGACCAGCTGG	1	1	11	SEQ ID NO. 766
(N20)NGG	10	14978578	-	CCCCCTTACATAACTGATCCCGG	1	1	5	SEQ ID NO. 767
(N20)NGG	10	14981850	+	TCCTACCCAGATATCTTTAGTGG	2	4	28	SEQ ID NO. 768
(N20)NGG	10	14981863	+	TCTTTAGTGGATGAAGCATCAGG	2	2	30	SEQ ID NO. 769
(N20)NGG	10	14981868	+	AGTGGATGAAGCATCAGGAGAGG	2	7	68	SEQ ID NO. 770
(N20)NGG	10	14981829	-	TCCACTAAAGATATCTGGGTAGG	2	4	31	SEQ ID NO. 771
(N20)NGG	10	14981833	-	TTCATCCACTAAAGATATCTGGG	2	4	48	SEQ ID NO. 772
(N20)NGG	10	14981834	-	CTTCATCCACTAAAGATATCTGG	2	2	29	SEQ ID NO. 773
(N20)NGG	10	14987110	+	CTTTTTTCCTTTCAGCTTGAAGG	1	8	175	SEQ ID NO. 774
(N20)NGG	10	14987140	+	ATACTGTTCACCTGTGACTAAGG	1	1	23	SEQ ID NO. 775
(N20)NGG	10	14987175	+	CGAGCCCGAAATACAGATTTTGG	1	1	14	SEQ ID NO. 776
(N20)NGG	10	14987095	-	AGATAAACCTTCAAGCTGAAAGG	1	5	44	SEQ ID NO. 777
(N20)NGG	10	14987128	-	AACAACAACTCCTTAGTCACAGG	1	1	17	SEQ ID NO. 778
(N20)NGG	10	14987157	-	TCTTCCAAAATCTGTATTTCGGG	1	16	173	SEQ ID NO. 779
(N20)NGG	10	14987158	-	TTCTTCCAAAATCTGTATTTCGG	4	19	226	SEQ ID NO. 780
(N20)NGG	10	14991046	+	TTGTTTTTAGATCACATGAAAGG	1	6	109	SEQ ID NO. 781
(N20)NGG	10	14991074	+	GAGCCCCTACCTTGAAAAGAAGG	1	6	40	SEQ ID NO. 782
(N20)NGG	10	14991078	+	CCCTACCTTGAAAAGAAGGTTGG	1	2	29	SEQ ID NO. 783
(N20)NGG	10	14991086	+	TGAAAAGAAGGTTGGAGTGCAGG	1	3	60	SEQ ID NO. 784
(N20)NGG	10	14991055	-	CAACCTTCTTTTCAAGGTAGGGG	1	2	64	SEQ ID NO. 785
(N20)NGG	10	14991056	-	CCAACCTTCTTTTCAAGGTAGGG	1	3	43	SEQ ID NO. 786
(N20)NGG	10	14991057	-	TCCAACCTTCTTTTCAAGGTAGG	2	6	53	SEQ ID NO. 787

FIG. 4 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	10	14991061	-	GCACTCCAACCTTCTTTTCAAGG	2	2	45	SEQ ID NO. 788
(N20)NGG	10	14995915	+	CGGCGCTATGAGTTCTTTCGAGG	1	1	2	SEQ ID NO. 789
(N20)NGG	10	14995916	+	GGCGCTATGAGTTCTTTCGAGGG	1	1	4	SEQ ID NO. 790
(N20)NGG	10	14995917	+	GCGCTATGAGTTCTTTCGAGGGG	1	1	8	SEQ ID NO. 791
(N20)NGG	10	14995924	+	GAGTTCTTTCGAGGGGCAGATGG	1	2	33	SEQ ID NO. 792
(N20)NGG	10	14995962	+	TCTCCATAGACCGCTTCGATAGG	1	1	5	SEQ ID NO. 793
(N20)NGG	10	14995963	+	CTCCATAGACCGCTTCGATAGGG	1	1	1	SEQ ID NO. 794
(N20)NGG	10	14995974	+	GCTTCGATAGGGAGAACCTGAGG	1	1	9	SEQ ID NO. 795
(N20)NGG	10	14995975	+	CTTCGATAGGGAGAACCTGAGGG	1	1	9	SEQ ID NO. 796
(N20)NGG	10	14996009	+	TTCCTGTCCCACTGCCACAAAGG	1	6	52	SEQ ID NO. 797
(N20)NGG	10	14996018	+	CACTGCCACAAAGGTGAGTGAGG	1	4	42	SEQ ID NO. 798
(N20)NGG	10	14996019	+	ACTGCCACAAAGGTGAGTGAGGG	1	5	56	SEQ ID NO. 799
(N20)NGG	10	14995875	-	CGCCGCCGATCCCAGAGTCCGGG	1	1	13	SEQ ID NO. 800
(N20)NGG	10	14995876	-	GCGCCGCCGATCCCAGAGTCCGG	1	1	10	SEQ ID NO. 801
(N20)NGG	10	14995925	-	TATGGAGATAGTTGGATACTCGG	1	1	25	SEQ ID NO. 802
(N20)NGG	10	14995933	-	AAGCGGTCTATGGAGATAGTTGG	1	1	10	SEQ ID NO. 803
(N20)NGG	10	14995943	-	CTCCCTATCGAAGCGGTCTATGG	1	1	2	SEQ ID NO. 804
(N20)NGG	10	14995950	-	TCAGGTTCTCCCTATCGAAGCGG	1	2	10	SEQ ID NO. 805
(N20)NGG	10	14995968	-	GGAAGTAGGCGCGGGCCCTCAGG	1	1	18	SEQ ID NO. 806
(N20)NGG	10	14995976	-	GTGGGACAGGAAGTAGGCGCGGG	1	5	51	SEQ ID NO. 807
(N20)NGG	10	14995977	-	AGTGGGACAGGAAGTAGGCGCGG	1	4	48	SEQ ID NO. 808
(N20)NGG	10	14995982	-	GTGGCAGTGGGACAGGAAGTAGG	1	5	123	SEQ ID NO. 809
(N20)NGG	10	14995989	-	CACCTTTGTGGCAGTGGGACAGG	1	4	35	SEQ ID NO. 810
(N20)NGG	10	14995994	-	TCACTCACCTTTGTGGCAGTGGG	1	4	43	SEQ ID NO. 811
(N20)NGG	10	14995995	-	CTCACTCACCTTTGTGGCAGTGG	1	6	55	SEQ ID NO. 812
(N20)NGG	10	14996001	-	GCAGCCCTCACTCACCTTTGTGG	1	6	73	SEQ ID NO. 813

FIG. 4 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	11	5246833	+	TATCTTCCTCCCACAGCTCCTGG	1	6	114	SEQ ID NO. 814
(N20)NGG	11	5246834	+	ATCTTCCTCCCACAGCTCCTGGG	2	14	155	SEQ ID NO. 815
(N20)NGG	11	5246845	+	ACAGCTCCTGGGCAACGTGCTGG	1	6	44	SEQ ID NO. 816
(N20)NGG	11	5246857	+	CAACGTGCTGGTCTGTGTGCTGG	1	5	25	SEQ ID NO. 817
(N20)NGG	11	5246870	+	TGTGTGCTGGCCCATCACTTTGG	1	2	47	SEQ ID NO. 818
(N20)NGG	11	5246896	+	AGAATTCACCCCACCAGTGCAGG	1	3	31	SEQ ID NO. 819
(N20)NGG	11	5246914	+	GCAGGCTGCCTATCAGAAAGTGG	2	5	34	SEQ ID NO. 820
(N20)NGG	11	5246917	+	GGCTGCCTATCAGAAAGTGGTGG	2	5	50	SEQ ID NO. 821
(N20)NGG	11	5246921	+	GCCTATCAGAAAGTGGTGGCTGG	2	7	86	SEQ ID NO. 822
(N20)NGG	11	5246926	+	TCAGAAAGTGGTGGCTGGTGTGG	3	6	74	SEQ ID NO. 823
(N20)NGG	11	5246938	+	GGCTGGTGTGGCTAATGCCCTGG	2	5	34	SEQ ID NO. 824
(N20)NGG	11	5246806	-	AGCTGTGGGAGGAAGATAAGAGG	1	9	146	SEQ ID NO. 825
(N20)NGG	11	5246817	-	CGTTGCCCAGGAGCTGTGGGAGG	1	4	62	SEQ ID NO. 826
(N20)NGG	11	5246820	-	GCACGTTGCCCAGGAGCTGTGGG	1	3	39	SEQ ID NO. 827
(N20)NGG	11	5246821	-	AGCACGTTGCCCAGGAGCTGTGG	1	3	57	SEQ ID NO. 828
(N20)NGG	11	5246829	-	CACAGACCAGCACGTTGCCCAGG	1	3	26	SEQ ID NO. 829
(N20)NGG	11	5246858	-	GAATTCTTTGCCAAAGTGATGGG	1	6	77	SEQ ID NO. 830
(N20)NGG	11	5246859	-	TGAATTCTTTGCCAAAGTGATGG	1	6	102	SEQ ID NO. 831
(N20)NGG	11	5246882	-	ATAGGCAGCCTGCACTGGTGGGG	1	2	25	SEQ ID NO. 832
(N20)NGG	11	5246883	-	GATAGGCAGCCTGCACTGGTGGG	1	2	30	SEQ ID NO. 833
(N20)NGG	11	5246884	-	TGATAGGCAGCCTGCACTGGTGG	1	3	28	SEQ ID NO. 834
(N20)NGG	11	5246887	-	TTCTGATAGGCAGCCTGCACTGG	1	3	35	SEQ ID NO. 835
(N20)NGG	11	5246900	-	ACCAGCCACCACTTTCTGATAGG	2	4	59	SEQ ID NO. 836
(N20)NGG	11	5246933	-	TTAGTGATACTTGTGGGCCAGGG	1	3	27	SEQ ID NO. 837
(N20)NGG	11	5246934	-	CTTAGTGATACTTGTGGGCCAGG	1	1	22	SEQ ID NO. 838
(N20)NGG	11	5246939	-	GCGAGCTTAGTGATACTTGTGGG	1	1	1	SEQ ID NO. 839
(N20)NGG	11	5246940	-	AGCGAGCTTAGTGATACTTGTGG	1	1	8	SEQ ID NO. 840
(N20)NGG	11	5247806	+	TGGTCTATTTTCCCACCCTTAGG	2	6	54	SEQ ID NO. 841
(N20)NGG	11	5247813	+	TTTTCCCACCCTTAGGCTGCTGG	1	2	40	SEQ ID NO. 842
(N20)NGG	11	5247816	+	TCCCACCCTTAGGCTGCTGGTGG	1	7	50	SEQ ID NO. 843
(N20)NGG	11	5247827	+	GGCTGCTGGTGGTCTACCCTTGG	1	1	34	SEQ ID NO. 844
(N20)NGG	11	5247836	+	TGGTCTACCCTTGGACCCAGAGG	2	6	27	SEQ ID NO. 845
(N20)NGG	11	5247853	+	CAGAGGTTCTTTGAGTCCTTTGG	2	2	55	SEQ ID NO. 846

FIG. 5

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	11	5247854	+	AGAGGTTCTTTGAGTCCTTTGGG	3	5	87	SEQ ID NO. 847
(N20)NGG	11	5247855	+	GAGGTTCTTTGAGTCCTTTGGGG	2	8	65	SEQ ID NO. 848
(N20)NGG	11	5247882	+	GTCCACTCCTGATGCTGTTATGG	2	6	50	SEQ ID NO. 849
(N20)NGG	11	5247883	+	TCCACTCCTGATGCTGTTATGGG	2	4	33	SEQ ID NO. 850
(N20)NGG	11	5247894	+	TGCTGTTATGGGCAACCCTAAGG	2	4	23	SEQ ID NO. 851
(N20)NGG	11	5247900	+	TATGGGCAACCCTAAGGTGAAGG	2	3	23	SEQ ID NO. 852
(N20)NGG	11	5247907	+	AACCCTAAGGTGAAGGCTCATGG	2	4	31	SEQ ID NO. 853
(N20)NGG	11	5247922	+	GCTCATGGCAAGAAAGTGCTCGG	2	6	45	SEQ ID NO. 854
(N20)NGG	11	5247937	+	GTGCTCGGTGCCTTTAGTGATGG	2	4	20	SEQ ID NO. 855
(N20)NGG	11	5247942	+	CGGTGCCTTTAGTGATGGCCTGG	2	3	23	SEQ ID NO. 856
(N20)NGG	11	5247951	+	TAGTGATGGCCTGGCTCACCTGG	2	5	29	SEQ ID NO. 857
(N20)NGG	11	5247963	+	GGCTCACCTGGACAACCTCAAGG	2	2	29	SEQ ID NO. 858
(N20)NGG	11	5247964	+	GCTCACCTGGACAACCTCAAGGG	2	3	40	SEQ ID NO. 859
(N20)NGG	11	5248011	+	GCACTGTGACAAGCTGCACGTGG	6	7	23	SEQ ID NO. 860
(N20)NGG	11	5248028	+	ACGTGGATCCTGAGAACTTCAGG	5	6	18	SEQ ID NO. 861
(N20)NGG	11	5248029	+	CGTGGATCCTGAGAACTTCAGGG	5	6	21	SEQ ID NO. 862
(N20)NGG	11	5248040	+	AGAACTTCAGGGTGAGTCTATGG	1	15	83	SEQ ID NO. 863
(N20)NGG	11	5248041	+	GAACTTCAGGGTGAGTCTATGGG	1	5	32	SEQ ID NO. 864
(N20)NGG	11	5247795	-	ACCACCAGCAGCCTAAGGGTGGG	1	1	26	SEQ ID NO. 865
(N20)NGG	11	5247796	-	GACCACCAGCAGCCTAAGGGTGG	1	4	36	SEQ ID NO. 866
(N20)NGG	11	5247799	-	GTAGACCACCAGCAGCCTAAGGG	1	2	24	SEQ ID NO. 867
(N20)NGG	11	5247800	-	GGTAGACCACCAGCAGCCTAAGG	1	2	20	SEQ ID NO. 868
(N20)NGG	11	5247821	-	CAAAGAACCTCTGGGTCCAAGGG	4	8	41	SEQ ID NO. 869
(N20)NGG	11	5247822	-	TCAAAGAACCTCTGGGTCCAAGG	5	11	32	SEQ ID NO. 870
(N20)NGG	11	5247829	-	AAAGGACTCAAAGAACCTCTGGG	2	7	59	SEQ ID NO. 871
(N20)NGG	11	5247830	-	CAAAGGACTCAAAGAACCTCTGG	2	6	61	SEQ ID NO. 872
(N20)NGG	11	5247847	-	AGGAGTGGACAGATCCCCAAAGG	2	3	38	SEQ ID NO. 873
(N20)NGG	11	5247862	-	GCCCATAACAGCATCAGGAGTGG	2	2	42	SEQ ID NO. 874
(N20)NGG	11	5247867	-	GGGTTGCCCATAACAGCATCAGG	2	2	11	SEQ ID NO. 875
(N20)NGG	11	5247887	-	TGCCATGAGCCTTCACCTTAGGG	2	2	32	SEQ ID NO. 876
(N20)NGG	11	5247888	-	TTGCCATGAGCCTTCACCTTAGG	2	4	35	SEQ ID NO. 877
(N20)NGG	11	5247925	-	GTGAGCCAGGCCATCACTAAAGG	2	2	23	SEQ ID NO. 878
(N20)NGG	11	5247938	-	TGAGGTTGTCCAGGTGAGCCAGG	2	7	55	SEQ ID NO. 879

FIG. 5 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	11	5247947	-	AGGTGCCCTTGAGGTTGTCCAGG	2	3	19	SEQ ID NO. 880
(N20)NGG	11	5247956	-	GTGTGGCAAAGGTGCCCTTGAGG	1	2	36	SEQ ID NO. 881
(N20)NGG	11	5247967	-	CAGCTCACTCAGTGTGGCAAAGG	1	4	40	SEQ ID NO. 882
(N20)NGG	11	5247973	-	ACAGTGCAGCTCACTCAGTGTGG	2	8	46	SEQ ID NO. 883
(N20)NGG	11	5248014	-	AGACTCACCCTGAAGTTCTCAGG	2	7	74	SEQ ID NO. 884
(N20)NGG	11	5248162	+	GCAACCTCAAACAGACACCATGG	2	3	35	SEQ ID NO. 885
(N20)NGG	11	5248180	+	CATGGTGCATCTGACTCCTGAGG	2	6	43	SEQ ID NO. 886
(N20)NGG	11	5248206	+	AGTCTGCCGTTACTGCCCTGTGG	1	3	20	SEQ ID NO. 887
(N20)NGG	11	5248207	+	GTCTGCCGTTACTGCCCTGTGGG	1	2	12	SEQ ID NO. 888
(N20)NGG	11	5248208	+	TCTGCCGTTACTGCCCTGTGGGG	1	3	32	SEQ ID NO. 889
(N20)NGG	11	5248213	+	CGTTACTGCCCTGTGGGGCAAGG	1	2	18	SEQ ID NO. 890
(N20)NGG	11	5248222	+	CCTGTGGGGCAAGGTGAACGTGG	4	5	33	SEQ ID NO. 891
(N20)NGG	11	5248232	+	AAGGTGAACGTGGATGAAGTTGG	1	3	34	SEQ ID NO. 892
(N20)NGG	11	5248235	+	GTGAACGTGGATGAAGTTGGTGG	2	9	139	SEQ ID NO. 893
(N20)NGG	11	5248240	+	CGTGGATGAAGTTGGTGGTGAGG	2	4	30	SEQ ID NO. 894
(N20)NGG	11	5248246	+	TGAAGTTGGTGGTGAGGCCCTGG	2	5	49	SEQ ID NO. 895
(N20)NGG	11	5248247	+	GAAGTTGGTGGTGAGGCCCTGGG	2	5	46	SEQ ID NO. 896
(N20)NGG	11	5248251	+	TTGGTGGTGAGGCCCTGGGCAGG	2	13	109	SEQ ID NO. 897
(N20)NGG	11	5248255	+	TGGTGAGGCCCTGGGCAGGTTGG	3	14	130	SEQ ID NO. 898
(N20)NGG	11	5248263	+	CCCTGGGCAGGTTGGTATCAAGG	2	2	38	SEQ ID NO. 899
(N20)NGG	11	5248275	+	TGGTATCAAGGTTACAAGACAGG	1	5	45	SEQ ID NO. 900
(N20)NGG	11	5248144	-	TGCACCATGGTGTCTGTTTGAGG	2	5	45	SEQ ID NO. 901
(N20)NGG	11	5248157	-	CTCAGGAGTCAGATGCACCATGG	2	7	85	SEQ ID NO. 902
(N20)NGG	11	5248174	-	GTAACGGCAGACTTCTCCTCAGG	1	1	11	SEQ ID NO. 903
(N20)NGG	11	5248190	-	CTTGCCCCACAGGGCAGTAACGG	1	2	48	SEQ ID NO. 904
(N20)NGG	11	5248199	-	CACGTTCACCTTGCCCCACAGGG	2	4	22	SEQ ID NO. 905
(N20)NGG	11	5248200	-	CCACGTTCACCTTGCCCCACAGG	4	5	26	SEQ ID NO. 906
(N20)NGG	11	5248241	-	CCTTGATACCAACCTGCCCAGGG	2	2	16	SEQ ID NO. 907
(N20)NGG	11	5248242	-	ACCTTGATACCAACCTGCCCAGG	2	2	20	SEQ ID NO. 908

FIG. 5 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	X	70327585	+	ACCTGGACATATCTGTCTTTAGG	1	4	62	SEQ ID NO. 909
(N20)NGG	X	70327590	+	GACATATCTGTCTTTAGGCCTGG	1	2	39	SEQ ID NO. 910
(N20)NGG	X	70327595	+	ATCTGTCTTTAGGCCTGGAGTGG	1	2	52	SEQ ID NO. 911
(N20)NGG	X	70327606	+	GGCCTGGAGTGGTGTGTCTAAGG	1	4	54	SEQ ID NO. 912
(N20)NGG	X	70327607	+	GCCTGGAGTGGTGTGTCTAAGGG	1	2	45	SEQ ID NO. 913
(N20)NGG	X	70327612	+	GAGTGGTGTGTCTAAGGGACTGG	1	1	32	SEQ ID NO. 914
(N20)NGG	X	70327676	+	GTCAGTGAGATTCCCCCAAAAGG	1	2	30	SEQ ID NO. 915
(N20)NGG	X	70327679	+	AGTGAGATTCCCCCAAAAGGAGG	1	4	51	SEQ ID NO. 916
(N20)NGG	X	70327680	+	GTGAGATTCCCCCAAAAGGAGGG	1	2	59	SEQ ID NO. 917
(N20)NGG	X	70327681	+	TGAGATTCCCCCAAAAGGAGGGG	1	3	53	SEQ ID NO. 918
(N20)NGG	X	70327688	+	CCCCCAAAAGGAGGGGCCCTTGG	1	3	28	SEQ ID NO. 919
(N20)NGG	X	70327689	+	CCCCAAAAGGAGGGGCCCTTGGG	1	1	33	SEQ ID NO. 920
(N20)NGG	X	70327690	+	CCCAAAAGGAGGGGCCCTTGGGG	1	3	33	SEQ ID NO. 921
(N20)NGG	X	70327693	+	AAAAGGAGGGGCCCTTGGGGAGG	1	3	95	SEQ ID NO. 922
(N20)NGG	X	70327694	+	AAAGGAGGGGCCCTTGGGGAGGG	1	10	110	SEQ ID NO. 923
(N20)NGG	X	70327695	+	AAGGAGGGGCCCTTGGGGAGGGG	2	8	140	SEQ ID NO. 924
(N20)NGG	X	70327700	+	GGGGCCCTTGGGGAGGGGCCTGG	1	30	212	SEQ ID NO. 925
(N20)NGG	X	70327701	+	GGGCCCTTGGGGAGGGGCCTGGG	1	16	187	SEQ ID NO. 926
(N20)NGG	X	70327702	+	GGCCCTTGGGGAGGGGCCTGGGG	4	30	206	SEQ ID NO. 927
(N20)NGG	X	70327734	+	GCAACCAGCATAGCCCCTACTGG	1	3	14	SEQ ID NO. 928
(N20)NGG	X	70327735	+	CAACCAGCATAGCCCCTACTGGG	1	1	13	SEQ ID NO. 929
(N20)NGG	X	70327564	-	GCCTAAAGACAGATATGTCCAGG	1	1	24	SEQ ID NO. 930
(N20)NGG	X	70327586	-	TCCCTTAGACACACCACTCCAGG	1	3	26	SEQ ID NO. 931
(N20)NGG	X	70327627	-	CAGAGTCGTTCACTGTAGTCTGG	1	2	69	SEQ ID NO. 932
(N20)NGG	X	70327650	-	TTGGGGGAATCTCACTGACGAGG	1	2	16	SEQ ID NO. 933
(N20)NGG	X	70327666	-	CCAAGGGCCCCTCCTTTTGGGGG	1	4	39	SEQ ID NO. 934
(N20)NGG	X	70327667	-	CCCAAGGGCCCCTCCTTTTGGGG	1	4	51	SEQ ID NO. 935
(N20)NGG	X	70327668	-	CCCCAAGGGCCCCTCCTTTTGGG	1	4	44	SEQ ID NO. 936
(N20)NGG	X	70327669	-	TCCCCAAGGGCCCCTCCTTTTGG	1	2	53	SEQ ID NO. 937
(N20)NGG	X	70327682	-	GGCCCCAGGCCCCTCCCCAAGGG	2	10	147	SEQ ID NO. 938
(N20)NGG	X	70327683	-	AGGCCCCAGGCCCCTCCCCAAGG	5	22	285	SEQ ID NO. 939
(N20)NGG	X	70327696	-	TGGTTGCATGGGGAGGCCCCAGG	1	1	74	SEQ ID NO. 940
(N20)NGG	X	70327703	-	GCTATGCTGGTTGCATGGGGAGG	1	3	22	SEQ ID NO. 941
(N20)NGG	X	70327706	-	GGGGCTATGCTGGTTGCATGGGG	1	1	26	SEQ ID NO. 942

FIG. 6

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	X	70327707	-	AGGGGCTATGCTGGTTGCATGGG	1	3	29	SEQ ID NO. 943
(N20)NGG	X	70327708	-	TAGGGGCTATGCTGGTTGCATGG	1	3	28	SEQ ID NO. 944
(N20)NGG	X	70327716	-	GGGCCCAGTAGGGGCTATGCTGG	1	1	20	SEQ ID NO. 945
(N20)NGG	X	70327725	-	AACATGGGGGGGCCCAGTAGGGG	1	1	23	SEQ ID NO. 946
(N20)NGG	X	70327726	-	TAACATGGGGGGGCCCAGTAGGG	1	1	6	SEQ ID NO. 947
(N20)NGG	X	70327727	-	GTAACATGGGGGGGCCCAGTAGG	1	1	15	SEQ ID NO. 948
(N20)NGG	X	70327736	-	CTTTAGGGTGTAACATGGGGGGG	1	1	19	SEQ ID NO. 949
(N20)NGG	X	70327737	-	GCTTTAGGGTGTAACATGGGGGG	1	2	17	SEQ ID NO. 950
(N20)NGG	X	70327738	-	GGCTTTAGGGTGTAACATGGGGG	1	1	16	SEQ ID NO. 951
(N20)NGG	X	70327739	-	AGGCTTTAGGGTGTAACATGGGG	1	2	23	SEQ ID NO. 952
(N20)NGG	X	70327740	-	CAGGCTTTAGGGTGTAACATGGG	1	1	17	SEQ ID NO. 953
(N20)NGG	X	70327741	-	TCAGGCTTTAGGGTGTAACATGG	1	2	24	SEQ ID NO. 954
(N20)NGG	X	70327751	-	GGTTCAGGTTTCAGGCTTTAGGG	1	2	50	SEQ ID NO. 955
(N20)NGG	X	70327752	-	GGGTTCAGGTTTCAGGCTTTAGG	1	7	64	SEQ ID NO. 956
(N20)NGG	X	70327759	-	AGGATTGGGGTTCAGGTTTCAGG	1	3	35	SEQ ID NO. 957
(N20)NGG	X	70327766	-	CTGTCAGAGGATTGGGGTTCAGG	1	6	51	SEQ ID NO. 958
(N20)NGG	X	70327772	-	GTTCTTCTGTCAGAGGATTGGGG	1	3	46	SEQ ID NO. 959
(N20)NGG	X	70327773	-	GGTTCTTCTGTCAGAGGATTGGG	1	4	33	SEQ ID NO. 960
(N20)NGG	X	70328126	+	CTCCCTCTTTCTCCCCTGTCAGG	1	15	220	SEQ ID NO. 961
(N20)NGG	X	70328163	+	TCCCACCCTGAAGAACCTAGAGG	1	2	23	SEQ ID NO. 962
(N20)NGG	X	70328185	+	GATCTTGTTACTGAATACCACGG	1	3	34	SEQ ID NO. 963
(N20)NGG	X	70328186	+	ATCTTGTTACTGAATACCACGGG	1	2	24	SEQ ID NO. 964
(N20)NGG	X	70328196	+	TGAATACCACGGGAACTTTTCGG	1	2	17	SEQ ID NO. 965
(N20)NGG	X	70328106	-	GTCCTGACAGGGGAGAAAGAGGG	1	6	137	SEQ ID NO. 966
(N20)NGG	X	70328107	-	CGTCCTGACAGGGGAGAAAGAGG	1	5	48	SEQ ID NO. 967
(N20)NGG	X	70328116	-	TCGGGGCATCGTCCTGACAGGGG	1	1	8	SEQ ID NO. 968
(N20)NGG	X	70328117	-	TTCGGGGCATCGTCCTGACAGGG	1	1	7	SEQ ID NO. 969
(N20)NGG	X	70328118	-	ATTCGGGGCATCGTCCTGACAGG	1	1	2	SEQ ID NO. 970
(N20)NGG	X	70328133	-	TTCTTCAGGGTGGGAATTCGGGG	1	1	33	SEQ ID NO. 971
(N20)NGG	X	70328134	-	GTTCTTCAGGGTGGGAATTCGGG	2	3	62	SEQ ID NO. 972
(N20)NGG	X	70328135	-	GGTTCTTCAGGGTGGGAATTCGG	1	6	42	SEQ ID NO. 973
(N20)NGG	X	70328142	-	TCCTCTAGGTTCTTCAGGGTGGG	1	2	39	SEQ ID NO. 974
(N20)NGG	X	70328143	-	ATCCTCTAGGTTCTTCAGGGTGG	1	2	36	SEQ ID NO. 975
(N20)NGG	X	70328146	-	AAGATCCTCTAGGTTCTTCAGGG	1	2	48	SEQ ID NO. 976

FIG. 6 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	X	70328147	-	CAAGATCCTCTAGGTTCTTCAGG	1	2	54	SEQ ID NO. 977
(N20)NGG	X	70328156	-	ATTCAGTAACAAGATCCTCTAGG	1	4	33	SEQ ID NO. 978
(N20)NGG	X	70328180	-	TTCTCACCGAAAAGTTCCCGTGG	1	1	9	SEQ ID NO. 979
(N20)NGG	X	70328471	+	GAATCCTTTCCTGTTTGCATTGG	1	4	54	SEQ ID NO. 980
(N20)NGG	X	70328480	+	CCTGTTTGCATTGGAAGCCGTGG	2	3	18	SEQ ID NO. 981
(N20)NGG	X	70328493	+	GAAGCCGTGGTTATCTCTGTTGG	1	1	16	SEQ ID NO. 982
(N20)NGG	X	70328501	+	GGTTATCTCTGTTGGCTCCATGG	1	1	36	SEQ ID NO. 983
(N20)NGG	X	70328502	+	GTTATCTCTGTTGGCTCCATGGG	1	5	55	SEQ ID NO. 984
(N20)NGG	X	70328536	+	GCCTTCTCTGTGTGTATTTCTGG	1	2	83	SEQ ID NO. 985
(N20)NGG	X	70328540	+	TCTCTGTGTGTATTTCTGGCTGG	2	9	112	SEQ ID NO. 986
(N20)NGG	X	70328545	+	GTGTGTATTTCTGGCTGGAACGG	1	5	78	SEQ ID NO. 987
(N20)NGG	X	70328555	+	CTGGCTGGAACGGTGAGATTTGG	1	3	14	SEQ ID NO. 988
(N20)NGG	X	70328453	-	GCTTCCAATGCAAACAGGAAAGG	1	1	54	SEQ ID NO. 989
(N20)NGG	X	70328458	-	CCACGGCTTCCAATGCAAACAGG	2	3	18	SEQ ID NO. 990
(N20)NGG	X	70328475	-	GGAGCCAACAGAGATAACCACGG	1	3	43	SEQ ID NO. 991
(N20)NGG	X	70328496	-	AAGGCTGATAATCAATCCCATGG	1	2	29	SEQ ID NO. 992
(N20)NGG	X	70328515	-	GCCAGAAATACACACAGAGAAGG	1	16	277	SEQ ID NO. 993
(N20)NGG	X	70329077	+	CCTCATCCTCTTTCTCCTCAAGG	2	27	343	SEQ ID NO. 994
(N20)NGG	X	70329089	+	TCTCCTCAAGGAACAATCAGTGG	1	1	33	SEQ ID NO. 995
(N20)NGG	X	70329122	+	TAAGTTCTCCTTGCCTAGTGTGG	1	2	29	SEQ ID NO. 996
(N20)NGG	X	70329126	+	TTCTCCTTGCCTAGTGTGGATGG	1	4	66	SEQ ID NO. 997
(N20)NGG	X	70329127	+	TCTCCTTGCCTAGTGTGGATGGG	1	4	32	SEQ ID NO. 998
(N20)NGG	X	70329154	+	AACGCTACACGTTTCGTGTTCGG	1	1	2	SEQ ID NO. 999
(N20)NGG	X	70329177	+	AGCCGCTTTAACCCACTCTGTGG	1	1	10	SEQ ID NO. 1000
(N20)NGG	X	70329193	+	TCTGTGGAAGTGCTCAGCATTGG	2	5	51	SEQ ID NO. 1001
(N20)NGG	X	70329202	+	GTGCTCAGCATTGGAGTGAATGG	1	2	36	SEQ ID NO. 1002
(N20)NGG	X	70329220	+	AATGGAGCCACCCAATCCACTGG	1	2	23	SEQ ID NO. 1003
(N20)NGG	X	70329221	+	ATGGAGCCACCCAATCCACTGGG	1	1	24	SEQ ID NO. 1004
(N20)NGG	X	70329222	+	TGGAGCCACCCAATCCACTGGGG	1	1	46	SEQ ID NO. 1005
(N20)NGG	X	70329223	+	GGAGCCACCCAATCCACTGGGGG	1	1	36	SEQ ID NO. 1006
(N20)NGG	X	70329240	+	TGGGGGAGCAATACTTCAAAAGG	1	1	29	SEQ ID NO. 1007
(N20)NGG	X	70329248	+	CAATACTTCAAAAGGTAAAATGG	2	7	167	SEQ ID NO. 1008
(N20)NGG	X	70329249	+	AATACTTCAAAAGGTAAAATGGG	2	11	213	SEQ ID NO. 1009
(N20)NGG	X	70329054	-	CTTGAGGAGAAAGAGGATGAGGG	2	10	183	SEQ ID NO. 1010

FIG. 6 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	X	70329055	-	CCTTGAGGAGAAAGAGGATGAGG	1	16	187	SEQ ID NO. 1011
(N20)NGG	X	70329061	-	ATTGTTCCTTGAGGAGAAAGAGG	1	5	77	SEQ ID NO. 1012
(N20)NGG	X	70329070	-	AATCCACTGATTGTTCCTTGAGG	1	3	31	SEQ ID NO. 1013
(N20)NGG	X	70329108	-	CTGCCCATCCACACTAGGCAAGG	1	6	51	SEQ ID NO. 1014
(N20)NGG	X	70329113	-	CGTTTCTGCCCATCCACACTAGG	1	1	18	SEQ ID NO. 1015
(N20)NGG	X	70329157	-	TTCCACAGAGTGGGTTAAAGCGG	1	1	39	SEQ ID NO. 1016
(N20)NGG	X	70329166	-	GCTGAGCACTTCCACAGAGTGGG	1	3	36	SEQ ID NO. 1017
(N20)NGG	X	70329167	-	TGCTGAGCACTTCCACAGAGTGG	2	8	90	SEQ ID NO. 1018
(N20)NGG	X	70329205	-	TGCTCCCCCAGTGGATTGGGTGG	1	4	50	SEQ ID NO. 1019
(N20)NGG	X	70329208	-	TATTGCTCCCCCAGTGGATTGGG	1	3	20	SEQ ID NO. 1020
(N20)NGG	X	70329209	-	GTATTGCTCCCCCAGTGGATTGG	1	2	18	SEQ ID NO. 1021
(N20)NGG	X	70329214	-	TTGAAGTATTGCTCCCCCAGTGG	1	1	18	SEQ ID NO. 1022
(N20)NGG	X	70330015	+	ACATATCTCCAGTGATCCCCTGG	1	3	31	SEQ ID NO. 1023
(N20)NGG	X	70330016	+	CATATCTCCAGTGATCCCCTGGG	1	1	31	SEQ ID NO. 1024
(N20)NGG	X	70330072	+	AATCCCAGCTAGAACTGAACTGG	1	4	32	SEQ ID NO. 1025
(N20)NGG	X	70330100	+	CAGATTCTTGAACCACTGTTTGC	1	4	44	SEQ ID NO. 1026
(N20)NGG	X	70330109	+	GAACCACTGTTTGGAGCACTTGG	1	3	36	SEQ ID NO. 1027
(N20)NGG	X	70330120	+	TGGAGCACTTGGTGCAGTACCGG	1	3	23	SEQ ID NO. 1028
(N20)NGG	X	70330129	+	TGGTGCAGTACCGGACTGACTGG	1	2	8	SEQ ID NO. 1029
(N20)NGG	X	70330130	+	GGTGCAGTACCGGACTGACTGGG	1	1	1	SEQ ID NO. 1030
(N20)NGG	X	70330141	+	GGACTGACTGGGACCACAGCTGG	1	4	50	SEQ ID NO. 1031
(N20)NGG	X	70330157	+	CAGCTGGACTGTGAGTGACTAGG	1	2	57	SEQ ID NO. 1032
(N20)NGG	X	70330158	+	AGCTGGACTGTGAGTGACTAGGG	1	2	35	SEQ ID NO. 1033
(N20)NGG	X	70329981	-	TGGAGATATGTGTGCATATGTGG	1	11	182	SEQ ID NO. 1034
(N20)NGG	X	70330001	-	TCTGGAGCCCAGGGGATCACTGG	1	2	61	SEQ ID NO. 1035
(N20)NGG	X	70330009	-	TTAGGTTCTCTGGAGCCCAGGGG	1	8	215	SEQ ID NO. 1036
(N20)NGG	X	70330010	-	GTTAGGTTCTCTGGAGCCCAGGG	1	4	40	SEQ ID NO. 1037
(N20)NGG	X	70330011	-	TGTTAGGTTCTCTGGAGCCCAGG	1	4	112	SEQ ID NO. 1038
(N20)NGG	X	70330019	-	TTGTGAAGTGTTAGGTTCTCTGG	1	1	31	SEQ ID NO. 1039
(N20)NGG	X	70330027	-	CACTCAGTTTGTGAAGTGTTAGG	1	3	36	SEQ ID NO. 1040
(N20)NGG	X	70330053	-	GTTCCAGTTCAGTTCTAGCTGGG	1	2	29	SEQ ID NO. 1041
(N20)NGG	X	70330054	-	TGTTCCAGTTCAGTTCTAGCTGG	1	2	21	SEQ ID NO. 1042
(N20)NGG	X	70330090	-	GCACCAAGTGCTCCAAACAGTGG	1	2	25	SEQ ID NO. 1043
(N20)NGG	X	70330117	-	AGCTGTGGTCCCAGTCAGTCCGG	1	16	472	SEQ ID NO. 1044

FIG. 6 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	X	70330132	-	AGTCACTCACAGTCCAGCTGTGG	1	5	52	SEQ ID NO. 1045
(N20)NGG	X	70330353	+	CCTTCCAACCTTTCTCCTCTAGG	1	8	135	SEQ ID NO. 1046
(N20)NGG	X	70330366	+	CTCCTCTAGGTACAAGAACTCGG	1	1	26	SEQ ID NO. 1047
(N20)NGG	X	70330424	+	TTCTCTGAAGAAATCACTTCTGG	2	8	90	SEQ ID NO. 1048
(N20)NGG	X	70330444	+	TGGCTGTCAGTTGCAAAAAAAGG	1	2	57	SEQ ID NO. 1049
(N20)NGG	X	70330483	+	AACATTTGTTGTTCAGCTCCAGG	1	4	43	SEQ ID NO. 1050
(N20)NGG	X	70330491	+	TTGTTCAGCTCCAGGACCCACGG	1	4	38	SEQ ID NO. 1051
(N20)NGG	X	70330492	+	TGTTCAGCTCCAGGACCCACGGG	1	2	39	SEQ ID NO. 1052
(N20)NGG	X	70330500	+	TCCAGGACCCACGGGAACCCAGG	1	6	53	SEQ ID NO. 1053
(N20)NGG	X	70330507	+	CCCACGGGAACCCAGGAGACAGG	1	1	42	SEQ ID NO. 1054
(N20)NGG	X	70330537	+	GATGCTAAAACTGCAGAATCTGG	2	7	55	SEQ ID NO. 1055
(N20)NGG	X	70330538	+	ATGCTAAAACTGCAGAATCTGGG	3	20	217	SEQ ID NO. 1056
(N20)NGG	X	70330546	+	ACTGCAGAATCTGGGTAATTTGG	1	2	48	SEQ ID NO. 1057
(N20)NGG	X	70330555	+	TCTGGGTAATTTGGAAAGAAAGG	9	482	8109	SEQ ID NO. 1058
(N20)NGG	X	70330556	+	CTGGGTAATTTGGAAAGAAAGGG	126	2902	13176	SEQ ID NO. 1059
(N20)NGG	X	70330331	-	CCTAGAGGAGAAAGGTTGGAAGG	1	5	75	SEQ ID NO. 1060
(N20)NGG	X	70330335	-	TGTACCTAGAGGAGAAAGGTTGG	1	4	52	SEQ ID NO. 1061
(N20)NGG	X	70330339	-	TTCTTGTACCTAGAGGAGAAAGG	1	2	43	SEQ ID NO. 1062
(N20)NGG	X	70330346	-	ATCCGAGTTCTTGTACCTAGAGG	1	1	7	SEQ ID NO. 1063
(N20)NGG	X	70330380	-	ATAGATAGTGGCTGCACTTCTGG	1	2	21	SEQ ID NO. 1064
(N20)NGG	X	70330392	-	TTTCTTCAGAGAATAGATAGTGG	1	6	86	SEQ ID NO. 1065
(N20)NGG	X	70330449	-	CAACAAATGTTTGGTAGAGGTGG	1	4	64	SEQ ID NO. 1066
(N20)NGG	X	70330452	-	GAACAACAAATGTTTGGTAGAGG	1	5	45	SEQ ID NO. 1067
(N20)NGG	X	70330458	-	GGAGCTGAACAACAAATGTTTGG	1	1	48	SEQ ID NO. 1068
(N20)NGG	X	70330479	-	TCCTGGGTTCCCGTGGGTCCTGG	1	2	68	SEQ ID NO. 1069
(N20)NGG	X	70330485	-	CCTGTCTCCTGGGTTCCCGTGGG	1	2	111	SEQ ID NO. 1070
(N20)NGG	X	70330486	-	GCCTGTCTCCTGGGTTCCCGTGG	1	6	77	SEQ ID NO. 1071
(N20)NGG	X	70330495	-	ATCTGTGTGGCCTGTCTCCTGGG	1	7	72	SEQ ID NO. 1072
(N20)NGG	X	70330496	-	CATCTGTGTGGCCTGTCTCCTGG	1	5	62	SEQ ID NO. 1073
(N20)NGG	X	70330508	-	CTGCAGTTTTAGCATCTGTGTGG	1	10	89	SEQ ID NO. 1074
(N20)NGG	X	70330808	+	TTCCACTCTGCCCCTCCCAGAGG	3	7	115	SEQ ID NO. 1075
(N20)NGG	X	70330852	+	TCGAGTACATGAATTGCACTTGG	1	1	9	SEQ ID NO. 1076
(N20)NGG	X	70330900	+	CCAACCTCACTCTGCATTATTGG	1	6	42	SEQ ID NO. 1077
(N20)NGG	X	70330910	+	TCTGCATTATTGGTATGAGAAGG	1	4	36	SEQ ID NO. 1078

FIG. 6 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	X	70330911	+	CTGCATTATTGGTATGAGAAGGG	1	2	42	SEQ ID NO. 1079
(N20)NGG	X	70330917	+	TATTGGTATGAGAAGGGACGAGG	1	2	23	SEQ ID NO. 1080
(N20)NGG	X	70330918	+	ATTGGTATGAGAAGGGACGAGGG	1	1	23	SEQ ID NO. 1081
(N20)NGG	X	70330919	+	TTGGTATGAGAAGGGACGAGGGG	1	3	25	SEQ ID NO. 1082
(N20)NGG	X	70330920	+	TGGTATGAGAAGGGACGAGGGGG	2	6	57	SEQ ID NO. 1083
(N20)NGG	X	70330923	+	TATGAGAAGGGACGAGGGGGAGG	1	6	62	SEQ ID NO. 1084
(N20)NGG	X	70330924	+	ATGAGAAGGGACGAGGGGGAGGG	1	5	168	SEQ ID NO. 1085
(N20)NGG	X	70330723	-	CTAGATTGGGGAGAAAATGAAGG	1	8	128	SEQ ID NO. 1086
(N20)NGG	X	70330735	-	TCAGGAAGAAATCTAGATTGGGG	1	8	83	SEQ ID NO. 1087
(N20)NGG	X	70330736	-	GTCAGGAAGAAATCTAGATTGGG	1	3	68	SEQ ID NO. 1088
(N20)NGG	X	70330737	-	GGTCAGGAAGAAATCTAGATTGG	1	3	50	SEQ ID NO. 1089
(N20)NGG	X	70330753	-	AGTCAGTGGGCATAGTGGTCAGG	1	2	42	SEQ ID NO. 1090
(N20)NGG	X	70330758	-	GAGGGAGTCAGTGGGCATAGTGG	1	4	82	SEQ ID NO. 1091
(N20)NGG	X	70330766	-	GAAACACTGAGGGAGTCAGTGGG	1	2	68	SEQ ID NO. 1092
(N20)NGG	X	70330767	-	GGAAACACTGAGGGAGTCAGTGG	1	6	81	SEQ ID NO. 1093
(N20)NGG	X	70330776	-	GGGCAGAGTGGAAACACTGAGGG	2	6	93	SEQ ID NO. 1094
(N20)NGG	X	70330777	-	GGGGCAGAGTGGAAACACTGAGG	2	8	95	SEQ ID NO. 1095
(N20)NGG	X	70330788	-	AACCTCTGGGAGGGGCAGAGTGG	1	6	132	SEQ ID NO. 1096
(N20)NGG	X	70330796	-	AAACACTGAACCTCTGGGAGGGG	1	3	46	SEQ ID NO. 1097
(N20)NGG	X	70330797	-	AAAACACTGAACCTCTGGGAGGG	1	4	63	SEQ ID NO. 1098
(N20)NGG	X	70330798	-	CAAAACACTGAACCTCTGGGAGG	1	8	69	SEQ ID NO. 1099
(N20)NGG	X	70330801	-	ACACAAAACACTGAACCTCTGGG	1	11	102	SEQ ID NO. 1100
(N20)NGG	X	70330802	-	AACACAAAACACTGAACCTCTGG	1	4	92	SEQ ID NO. 1101
(N20)NGG	X	70330868	-	AGAGTGAGGTTGGTAGGCTGGGG	1	6	61	SEQ ID NO. 1102
(N20)NGG	X	70330869	-	CAGAGTGAGGTTGGTAGGCTGGG	1	2	33	SEQ ID NO. 1103
(N20)NGG	X	70330870	-	GCAGAGTGAGGTTGGTAGGCTGG	1	5	37	SEQ ID NO. 1104
(N20)NGG	X	70330874	-	TAATGCAGAGTGAGGTTGGTAGG	1	1	32	SEQ ID NO. 1105
(N20)NGG	X	70330878	-	CCAATAATGCAGAGTGAGGTTGG	1	5	31	SEQ ID NO. 1106
(N20)NGG	X	70330882	-	CATACCAATAATGCAGAGTGAGG	1	3	28	SEQ ID NO. 1107
(N20)NGG	X	70331331	+	ATTCCTGCAGCTGCCCCTGCTGG	1	8	110	SEQ ID NO. 1108
(N20)NGG	X	70331332	+	TTCCTGCAGCTGCCCCTGCTGGG	2	21	144	SEQ ID NO. 1109
(N20)NGG	X	70331337	+	GCAGCTGCCCCTGCTGGGAGTGG	1	15	206	SEQ ID NO. 1110
(N20)NGG	X	70331338	+	CAGCTGCCCCTGCTGGGAGTGGG	2	13	196	SEQ ID NO. 1111
(N20)NGG	X	70331339	+	AGCTGCCCCTGCTGGGAGTGGGG	1	8	162	SEQ ID NO. 1112

FIG. 6 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	X	70331368	+	ACGACAATTCTGACGCCCAATGG	1	1	3	SEQ ID NO. 1113
(N20)NGG	X	70331369	+	CGACAATTCTGACGCCCAATGGG	1	1	5	SEQ ID NO. 1114
(N20)NGG	X	70331389	+	GGGAATGAAGACACCACAGCTGG	1	5	59	SEQ ID NO. 1115
(N20)NGG	X	70331392	+	AATGAAGACACCACAGCTGGTGG	3	9	74	SEQ ID NO. 1116
(N20)NGG	X	70331393	+	ATGAAGACACCACAGCTGGTGGG	1	7	54	SEQ ID NO. 1117
(N20)NGG	X	70331401	+	ACCACAGCTGGTGGGAAATCTGG	1	2	34	SEQ ID NO. 1118
(N20)NGG	X	70331402	+	CCACAGCTGGTGGGAAATCTGGG	1	6	105	SEQ ID NO. 1119
(N20)NGG	X	70331407	+	GCTGGTGGGAAATCTGGGACTGG	2	8	64	SEQ ID NO. 1120
(N20)NGG	X	70331410	+	GGTGGGAAATCTGGGACTGGAGG	1	4	96	SEQ ID NO. 1121
(N20)NGG	X	70331411	+	GTGGGAAATCTGGGACTGGAGGG	2	7	66	SEQ ID NO. 1122
(N20)NGG	X	70331412	+	TGGGAAATCTGGGACTGGAGGGG	1	8	95	SEQ ID NO. 1123
(N20)NGG	X	70331413	+	GGGAAATCTGGGACTGGAGGGGG	1	4	101	SEQ ID NO. 1124
(N20)NGG	X	70331250	-	GCGCTTGCTCTTCATTCCCTGGG	1	2	21	SEQ ID NO. 1125
(N20)NGG	X	70331251	-	GGCGCTTGCTCTTCATTCCCTGG	1	1	23	SEQ ID NO. 1126
(N20)NGG	X	70331272	-	TGGTAATGATGGCTTCAACATGG	2	4	44	SEQ ID NO. 1127
(N20)NGG	X	70331283	-	AGGGATGTGAATGGTAATGATGG	1	5	65	SEQ ID NO. 1128
(N20)NGG	X	70331292	-	AGGAATAAGAGGGATGTGAATGG	1	11	130	SEQ ID NO. 1129
(N20)NGG	X	70331302	-	GGGCAGCTGCAGGAATAAGAGGG	1	4	71	SEQ ID NO. 1130
(N20)NGG	X	70331303	-	GGGGCAGCTGCAGGAATAAGAGG	1	4	82	SEQ ID NO. 1131
(N20)NGG	X	70331312	-	CTCCCAGCAGGGGCAGCTGCAGG	3	44	380	SEQ ID NO. 1132
(N20)NGG	X	70331322	-	TTCAGCCCCACTCCCAGCAGGGG	1	12	114	SEQ ID NO. 1133
(N20)NGG	X	70331323	-	GTTCAGCCCCACTCCCAGCAGGG	2	8	74	SEQ ID NO. 1134
(N20)NGG	X	70331324	-	TGTTCAGCCCCACTCCCAGCAGG	1	4	89	SEQ ID NO. 1135
(N20)NGG	X	70331361	-	GTGGTGTCTTCATTCCCATTGGG	1	8	113	SEQ ID NO. 1136
(N20)NGG	X	70331362	-	TGTGGTGTCTTCATTCCCATTGG	4	45	242	SEQ ID NO. 1137
(N20)NGG	X	70331380	-	CCCAGATTTCCCACCAGCTGTGG	1	7	101	SEQ ID NO. 1138

FIG. 6 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	5	35857092	+	TCTCTCAGAATGACAATTCTAGG	1	5	65	SEQ ID NO. 1139
(N20)NGG	5	35857104	+	ACAATTCTAGGTACAACTTTTGG	1	1	53	SEQ ID NO. 1140
(N20)NGG	5	35857109	+	TCTAGGTACAACTTTTGGCATGG	1	2	25	SEQ ID NO. 1141
(N20)NGG	5	35857137	+	TCTTTACTTCAAGTCGTTTCTGG	1	3	24	SEQ ID NO. 1142
(N20)NGG	5	35857146	+	CAAGTCGTTTCTGGAGAAAGTGG	1	3	41	SEQ ID NO. 1143
(N20)NGG	5	35857161	+	GAAAGTGGCTATGCTCAAAATGG	1	5	49	SEQ ID NO. 1144
(N20)NGG	5	35860953	+	CTGCATGTTTGTTCCTCCCCAGG	1	7	138	SEQ ID NO. 1145
(N20)NGG	5	35860961	+	TTGTTCCTCCCCAGGAGACTTGG	1	4	43	SEQ ID NO. 1146
(N20)NGG	5	35860976	+	AGACTTGGAAGATGCAGAACTGG	1	3	89	SEQ ID NO. 1147
(N20)NGG	5	35861009	+	ATTCTCATGCTATAGCCAGTTGG	1	1	24	SEQ ID NO. 1148
(N20)NGG	5	35861019	+	TATAGCCAGTTGGAAGTGAATGG	1	4	44	SEQ ID NO. 1149
(N20)NGG	5	35861051	+	CTCACTGACCTGTGCTTTTGAGG	1	3	45	SEQ ID NO. 1150
(N20)NGG	5	35861078	+	AGATGTCAACATCACCAATCTGG	1	2	27	SEQ ID NO. 1151
(N20)NGG	5	35861092	+	CCAATCTGGAATTTGAAATATGG	1	6	84	SEQ ID NO. 1152
(N20)NGG	5	35861097	+	CTGGAATTTGAAATATGGTGAGG	1	3	67	SEQ ID NO. 1153
(N20)NGG	5	35861098	+	TGGAATTTGAAATATGGTGAGGG	1	4	109	SEQ ID NO. 1154
(N20)NGG	5	35861102	+	ATTTGAAATATGGTGAGGGATGG	1	6	107	SEQ ID NO. 1155
(N20)NGG	5	35861105	+	TGAAATATGGTGAGGGATGGTGG	1	2	79	SEQ ID NO. 1156
(N20)NGG	5	35861114	+	GTGAGGGATGGTGGTTTTAATGG	1	3	47	SEQ ID NO. 1157
(N20)NGG	5	35860944	-	ATCTTCCAAGTCTCCTGGGGAGG	2	7	42	SEQ ID NO. 1158
(N20)NGG	5	35860947	-	TGCATCTTCCAAGTCTCCTGGGG	1	6	71	SEQ ID NO. 1159
(N20)NGG	5	35860948	-	CTGCATCTTCCAAGTCTCCTGGG	1	5	70	SEQ ID NO. 1160
(N20)NGG	5	35860949	-	TCTGCATCTTCCAAGTCTCCTGG	1	8	86	SEQ ID NO. 1161
(N20)NGG	5	35861002	-	GCGATCCATTCACTTCCAACTGG	1	4	82	SEQ ID NO. 1162
(N20)NGG	5	35861037	-	ATCTGGGTCCTCAAAAGCACAGG	1	2	34	SEQ ID NO. 1163
(N20)NGG	5	35861053	-	GATTGGTGATGTTGACATCTGGG	1	3	36	SEQ ID NO. 1164
(N20)NGG	5	35861054	-	AGATTGGTGATGTTGACATCTGG	1	4	28	SEQ ID NO. 1165
(N20)NGG	5	35861070	-	CCATATTTCAAATTCCAGATTGG	1	5	91	SEQ ID NO. 1166
(N20)NGG	5	35867409	+	TCCCCTTTTTATTCCTACAGTGG	1	3	68	SEQ ID NO. 1167
(N20)NGG	5	35867410	+	CCCCTTTTTATTCCTACAGTGGG	1	5	52	SEQ ID NO. 1168
(N20)NGG	5	35867411	+	CCCTTTTTATTCCTACAGTGGGG	1	9	56	SEQ ID NO. 1169
(N20)NGG	5	35867420	+	TTCCTACAGTGGGGCCCTCGTGG	1	1	11	SEQ ID NO. 1170
(N20)NGG	5	35867423	+	CTACAGTGGGGCCCTCGTGGAGG	1	3	22	SEQ ID NO. 1171
(N20)NGG	5	35867443	+	AGGTAAAGTGCCTGAATTTCAGG	1	3	47	SEQ ID NO. 1172

FIG. 7

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	5	35867493	+	ACAAAGAAATTCTTACTGATTGG	1	4	81	SEQ ID NO. 1173
(N20)NGG	5	35867516	+	AAAGAGCAATATATGTGTGAAGG	2	9	100	SEQ ID NO. 1174
(N20)NGG	5	35867520	+	AGCAATATATGTGTGAAGGTTGG	2	2	37	SEQ ID NO. 1175
(N20)NGG	5	35867565	+	AAAATAGACCTAACCACTATAGG	1	3	38	SEQ ID NO. 1176
(N20)NGG	5	35867388	-	CCCACTGTAGGAATAAAAAGGGG	1	2	57	SEQ ID NO. 1177
(N20)NGG	5	35867389	-	CCCCACTGTAGGAATAAAAAGGG	1	5	66	SEQ ID NO. 1178
(N20)NGG	5	35867390	-	GCCCCACTGTAGGAATAAAAAGG	1	5	43	SEQ ID NO. 1179
(N20)NGG	5	35867400	-	CTCCACGAGGGCCCCACTGTAGG	1	1	30	SEQ ID NO. 1180
(N20)NGG	5	35867412	-	CAGGCACTTTACCTCCACGAGGG	1	1	17	SEQ ID NO. 1181
(N20)NGG	5	35867413	-	TCAGGCACTTTACCTCCACGAGG	1	2	20	SEQ ID NO. 1182
(N20)NGG	5	35867431	-	CTTGTAGTTTCCTGAAATTCAGG	1	1	70	SEQ ID NO. 1183
(N20)NGG	5	35867535	-	GGTTAGGTCTATTTTTTTTGCAGG	1	1	35	SEQ ID NO. 1184
(N20)NGG	5	35867551	-	ACTTCTTACCTATAGTGGTTAGG	1	1	33	SEQ ID NO. 1185
(N20)NGG	5	35867556	-	ATACAACTTCTTACCTATAGTGG	2	3	57	SEQ ID NO. 1186
(N20)NGG	5	35871168	+	TTCTTTTCCAGTTAAACCTGAGG	1	6	90	SEQ ID NO. 1187
(N20)NGG	5	35871197	+	TTGACCTGAGTGTCGTCTATCGG	1	3	13	SEQ ID NO. 1188
(N20)NGG	5	35871198	+	TGACCTGAGTGTCGTCTATCGGG	1	4	13	SEQ ID NO. 1189
(N20)NGG	5	35871202	+	CTGAGTGTCGTCTATCGGGAAGG	1	1	3	SEQ ID NO. 1190
(N20)NGG	5	35871219	+	GGAAGGAGCCAATGACTTTGTGG	1	3	70	SEQ ID NO. 1191
(N20)NGG	5	35871291	+	GCACGATGTAGCTTACCGCCAGG	1	1	1	SEQ ID NO. 1192
(N20)NGG	5	35871297	+	TGTAGCTTACCGCCAGGAAAAGG	1	2	11	SEQ ID NO. 1193
(N20)NGG	5	35871311	+	AGGAAAAGGATGAAAACAAATGG	2	48	722	SEQ ID NO. 1194
(N20)NGG	5	35871315	+	AAAGGATGAAAACAAATGGACGG	3	70	1031	SEQ ID NO. 1195
(N20)NGG	5	35871153	-	AAAGGAGCCTCAGGTTTAACTGG	1	3	24	SEQ ID NO. 1196
(N20)NGG	5	35871162	-	CTCAGGTCAAAAGGAGCCTCAGG	1	2	45	SEQ ID NO. 1197
(N20)NGG	5	35871171	-	TAGACGACACTCAGGTCAAAAGG	1	3	13	SEQ ID NO. 1198
(N20)NGG	5	35871179	-	CTTCCCGATAGACGACACTCAGG	1	1	2	SEQ ID NO. 1199
(N20)NGG	5	35871205	-	AAATGTCACCACAAAGTCATTGG	1	3	80	SEQ ID NO. 1200
(N20)NGG	5	35871284	-	TGTTTTCATCCTTTTCCTGGCGG	1	10	151	SEQ ID NO. 1201
(N20)NGG	5	35871287	-	ATTTGTTTTCATCCTTTTCCTGG	2	10	217	SEQ ID NO. 1202
(N20)NGG	5	35873635	+	CCTGCAGAGAAAGCTCCAACCGG	1	5	50	SEQ ID NO. 1203
(N20)NGG	5	35873687	+	ATCCCTGATCACTATTTTAAAGG	1	3	48	SEQ ID NO. 1204
(N20)NGG	5	35873694	+	ATCACTATTTTAAAGGCTTCTGG	2	3	68	SEQ ID NO. 1205
(N20)NGG	5	35873703	+	TTAAAGGCTTCTGGAGTGAATGG	1	6	109	SEQ ID NO. 1206

FIG. 7 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	5	35873750	+	CCAGAGATCAATAATAGCTCAGG	1	3	26	SEQ ID NO. 1207
(N20)NGG	5	35873755	+	GATCAATAATAGCTCAGGTAAGG	1	2	20	SEQ ID NO. 1208
(N20)NGG	5	35873760	+	ATAATAGCTCAGGTAAGGAATGG	1	9	58	SEQ ID NO. 1209
(N20)NGG	5	35873763	+	ATAGCTCAGGTAAGGAATGGTGG	1	2	47	SEQ ID NO. 1210
(N20)NGG	5	35873594	-	CAGGAGTGTCAGCTTTGTGCTGG	1	8	52	SEQ ID NO. 1211
(N20)NGG	5	35873613	-	CCGGTTGGAGCTTTCTCTGCAGG	1	1	17	SEQ ID NO. 1212
(N20)NGG	5	35873628	-	TCTCATACATTGCTGCCGGTTGG	1	5	57	SEQ ID NO. 1213
(N20)NGG	5	35873632	-	TTAATCTCATACATTGCTGCCGG	1	9	114	SEQ ID NO. 1214
(N20)NGG	5	35873663	-	TTTAAAATAGTGATCAGGGATGG	2	9	131	SEQ ID NO. 1215
(N20)NGG	5	35873667	-	AGCCTTTAAAATAGTGATCAGGG	1	11	135	SEQ ID NO. 1216
(N20)NGG	5	35873668	-	AAGCCTTTAAAATAGTGATCAGG	1	6	66	SEQ ID NO. 1217
(N20)NGG	5	35873707	-	GGAGTTCTGAAGTAATAACTTGG	1	4	31	SEQ ID NO. 1218
(N20)NGG	5	35873728	-	CCTGAGCTATTATTGATCTCTGG	1	1	25	SEQ ID NO. 1219
(N20)NGG	5	35874550	+	ACAATCTATTCTTGCTTTCCAGG	1	10	59	SEQ ID NO. 1220
(N20)NGG	5	35874551	+	CAATCTATTCTTGCTTTCCAGGG	1	8	70	SEQ ID NO. 1221
(N20)NGG	5	35874552	+	AATCTATTCTTGCTTTCCAGGGG	2	7	77	SEQ ID NO. 1222
(N20)NGG	5	35874558	+	TTCTTGCTTTCCAGGGGAGATGG	1	11	89	SEQ ID NO. 1223
(N20)NGG	5	35874612	+	TTTTTTCTCTGTCGCTCTGTTGG	1	9	192	SEQ ID NO. 1224
(N20)NGG	5	35874621	+	TGTCGCTCTGTTGGTCATCTTGG	1	1	26	SEQ ID NO. 1225
(N20)NGG	5	35874635	+	TCATCTTGGCCTGTGTGTTATGG	1	4	46	SEQ ID NO. 1226
(N20)NGG	5	35874644	+	CCTGTGTGTTATGGAAAAAAAGG	1	7	98	SEQ ID NO. 1227
(N20)NGG	5	35874526	-	TGGAAAGCAAGAATAGATTGTGG	2	5	129	SEQ ID NO. 1228
(N20)NGG	5	35874546	-	AAGATAGGATCCATCTCCCCTGG	1	3	27	SEQ ID NO. 1229
(N20)NGG	5	35874561	-	ATGCTGATGGTTAGTAAGATAGG	1	2	30	SEQ ID NO. 1230
(N20)NGG	5	35874574	-	GAAAAAACTCAAAATGCTGATGG	1	14	200	SEQ ID NO. 1231
(N20)NGG	5	35874622	-	CCTTTTTTTCCATAACACACAGG	1	1	75	SEQ ID NO. 1232
(N20)NGG	5	35875613	+	TATCAATGTTCTCTGATTTCAGG	1	12	84	SEQ ID NO. 1233
(N20)NGG	5	35875631	+	TCAGGATTAAGCCTATCGTATGG	1	1	5	SEQ ID NO. 1234
(N20)NGG	5	35875662	+	CCCCGATCATAAGAAGACTCTGG	1	1	6	SEQ ID NO. 1235
(N20)NGG	5	35875702	+	CCAAGAAAAGTGAGTGTTTTTGG	1	17	122	SEQ ID NO. 1236
(N20)NGG	5	35875620	-	GGGAGACTGGGCCATACGATAGG	1	1	6	SEQ ID NO. 1237
(N20)NGG	5	35875632	-	TTCTTATGATCGGGGAGACTGGG	1	2	26	SEQ ID NO. 1238
(N20)NGG	5	35875633	-	CTTCTTATGATCGGGGAGACTGG	1	1	11	SEQ ID NO. 1239
(N20)NGG	5	35875640	-	CCAGAGTCTTCTTATGATCGGGG	1	1	12	SEQ ID NO. 1240

FIG. 7 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	5	35875641	-	TCCAGAGTCTTCTTATGATCGGG	1	2	27	SEQ ID NO. 1241
(N20)NGG	5	35875642	-	TTCCAGAGTCTTCTTATGATCGG	1	5	82	SEQ ID NO. 1242
(N20)NGG	5	35875680	-	CCAAAAACACTCACTTTTCTTGG	1	5	106	SEQ ID NO. 1243
(N20)NGG	5	35876120	+	TTTCAATCCTGAAAGTTTCCTGG	1	7	96	SEQ ID NO. 1244
(N20)NGG	5	35876137	+	TCCTGGACTGCCAGATTCATAGG	1	1	37	SEQ ID NO. 1245
(N20)NGG	5	35876138	+	CCTGGACTGCCAGATTCATAGGG	1	2	39	SEQ ID NO. 1246
(N20)NGG	5	35876141	+	GGACTGCCAGATTCATAGGGTGG	1	1	22	SEQ ID NO. 1247
(N20)NGG	5	35876168	+	CATTCAAGCTAGAGATGAAGTGG	1	2	50	SEQ ID NO. 1248
(N20)NGG	5	35876172	+	CAAGCTAGAGATGAAGTGGAAGG	2	4	66	SEQ ID NO. 1249
(N20)NGG	5	35876224	+	TAGAAGAATCTGAGAAGCAGAGG	3	17	163	SEQ ID NO. 1250
(N20)NGG	5	35876229	+	GAATCTGAGAAGCAGAGGCTTGG	1	12	241	SEQ ID NO. 1251
(N20)NGG	5	35876232	+	TCTGAGAAGCAGAGGCTTGGAGG	2	9	113	SEQ ID NO. 1252
(N20)NGG	5	35876233	+	CTGAGAAGCAGAGGCTTGGAGGG	1	17	193	SEQ ID NO. 1253
(N20)NGG	5	35876234	+	TGAGAAGCAGAGGCTTGGAGGGG	5	27	261	SEQ ID NO. 1254
(N20)NGG	5	35876264	+	GAGCCCCAACTGCCCATCTGAGG	1	6	53	SEQ ID NO. 1255
(N20)NGG	5	35876292	+	GTCATCACTCCAGAAAGCTTTGG	1	2	35	SEQ ID NO. 1256
(N20)NGG	5	35876318	+	AGATTCATCCCTCACATGCCTGG	1	1	43	SEQ ID NO. 1257
(N20)NGG	5	35876322	+	TCATCCCTCACATGCCTGGCTGG	1	4	69	SEQ ID NO. 1258
(N20)NGG	5	35876323	+	CATCCCTCACATGCCTGGCTGGG	1	5	91	SEQ ID NO. 1259
(N20)NGG	5	35876365	+	CCCCTATTCTCTCCTCTTCCAGG	3	15	178	SEQ ID NO. 1260
(N20)NGG	5	35876380	+	CTTCCAGGTCCCTAGACTGCAGG	1	3	69	SEQ ID NO. 1261
(N20)NGG	5	35876381	+	TTCCAGGTCCCTAGACTGCAGGG	1	8	143	SEQ ID NO. 1262
(N20)NGG	5	35876388	+	TCCCTAGACTGCAGGGAGAGTGG	1	3	75	SEQ ID NO. 1263
(N20)NGG	5	35876397	+	TGCAGGGAGAGTGGCAAGAATGG	1	13	157	SEQ ID NO. 1264
(N20)NGG	5	35876398	+	GCAGGGAGAGTGGCAAGAATGGG	1	7	94	SEQ ID NO. 1265
(N20)NGG	5	35876414	+	GAATGGGCCTCATGTGTACCAGG	1	2	18	SEQ ID NO. 1266
(N20)NGG	5	35876433	+	CAGGACCTCCTGCTTAGCCTTGG	2	37	129	SEQ ID NO. 1267
(N20)NGG	5	35876434	+	AGGACCTCCTGCTTAGCCTTGGG	2	4	43	SEQ ID NO. 1268
(N20)NGG	5	35876478	+	CCTCCATTTTCTCTCCAATCTGG	1	7	95	SEQ ID NO. 1269
(N20)NGG	5	35876507	+	GACATTGAACCCAGTTGCTCAGG	1	6	37	SEQ ID NO. 1270
(N20)NGG	5	35876508	+	ACATTGAACCCAGTTGCTCAGGG	1	4	49	SEQ ID NO. 1271
(N20)NGG	5	35876531	+	TCAGCCCATTCTTACTTCCCTGG	1	5	54	SEQ ID NO. 1272
(N20)NGG	5	35876532	+	CAGCCCATTCTTACTTCCCTGGG	1	2	59	SEQ ID NO. 1273
(N20)NGG	5	35876061	-	CTGCACAGAAAAAGGAGAAAGGG	2	26	307	SEQ ID NO. 1274

FIG. 7 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	5	35876062	-	TCTGCACAGAAAAAGGAGAAAGG	2	15	207	SEQ ID NO. 1275
(N20)NGG	5	35876069	-	TTTAAATTCTGCACAGAAAAAGG	2	22	385	SEQ ID NO. 1276
(N20)NGG	5	35876105	-	TGGCAGTCCAGGAAACTTTCAGG	1	3	25	SEQ ID NO. 1277
(N20)NGG	5	35876116	-	CCCTATGAATCTGGCAGTCCAGG	1	2	39	SEQ ID NO. 1278
(N20)NGG	5	35876125	-	TGTCATCCACCCTATGAATCTGG	1	2	8	SEQ ID NO. 1279
(N20)NGG	5	35876192	-	TCAGATTCTTCTAGTTGCTGAGG	1	4	66	SEQ ID NO. 1280
(N20)NGG	5	35876245	-	CATCCTCAGATGGGCAGTTGGGG	1	2	52	SEQ ID NO. 1281
(N20)NGG	5	35876246	-	ACATCCTCAGATGGGCAGTTGGG	1	2	33	SEQ ID NO. 1282
(N20)NGG	5	35876247	-	TACATCCTCAGATGGGCAGTTGG	1	2	36	SEQ ID NO. 1283
(N20)NGG	5	35876254	-	TGATGACTACATCCTCAGATGGG	1	3	25	SEQ ID NO. 1284
(N20)NGG	5	35876255	-	GTGATGACTACATCCTCAGATGG	2	3	23	SEQ ID NO. 1285
(N20)NGG	5	35876279	-	GAATCTCTTCCAAAGCTTTCTGG	2	9	69	SEQ ID NO. 1286
(N20)NGG	5	35876304	-	ATTCCCAGCCAGGCATGTGAGGG	1	6	54	SEQ ID NO. 1287
(N20)NGG	5	35876305	-	CATTCCCAGCCAGGCATGTGAGG	1	9	61	SEQ ID NO. 1288
(N20)NGG	5	35876314	-	ATGCACTGACATTCCCAGCCAGG	1	4	42	SEQ ID NO. 1289
(N20)NGG	5	35876343	-	CCTGGAAGAGGAGAGAATAGGGG	2	10	144	SEQ ID NO. 1290
(N20)NGG	5	35876344	-	ACCTGGAAGAGGAGAGAATAGGG	1	7	142	SEQ ID NO. 1291
(N20)NGG	5	35876345	-	GACCTGGAAGAGGAGAGAATAGG	1	7	150	SEQ ID NO. 1292
(N20)NGG	5	35876355	-	GCAGTCTAGGGACCTGGAAGAGG	1	5	109	SEQ ID NO. 1293
(N20)NGG	5	35876361	-	CTCCCTGCAGTCTAGGGACCTGG	1	2	69	SEQ ID NO. 1294
(N20)NGG	5	35876367	-	GCCACTCTCCCTGCAGTCTAGGG	1	2	38	SEQ ID NO. 1295
(N20)NGG	5	35876368	-	TGCCACTCTCCCTGCAGTCTAGG	1	4	71	SEQ ID NO. 1296
(N20)NGG	5	35876399	-	AGGAGGTCCTGGTACACATGAGG	1	2	43	SEQ ID NO. 1297
(N20)NGG	5	35876410	-	CAAGGCTAAGCAGGAGGTCCTGG	1	2	28	SEQ ID NO. 1298
(N20)NGG	5	35876416	-	TAGTCCCAAGGCTAAGCAGGAGG	1	3	35	SEQ ID NO. 1299
(N20)NGG	5	35876419	-	TTGTAGTCCCAAGGCTAAGCAGG	1	1	21	SEQ ID NO. 1300
(N20)NGG	5	35876428	-	GCGTGCTGTTTGTAGTCCCAAGG	1	1	9	SEQ ID NO. 1301
(N20)NGG	5	35876453	-	GATTGGAGAGAAAATGGAGGGGG	1	19	192	SEQ ID NO. 1302
(N20)NGG	5	35876454	-	AGATTGGAGAGAAAATGGAGGGG	2	24	394	SEQ ID NO. 1303
(N20)NGG	5	35876455	-	CAGATTGGAGAGAAAATGGAGGG	4	13	191	SEQ ID NO. 1304
(N20)NGG	5	35876456	-	CCAGATTGGAGAGAAAATGGAGG	1	6	115	SEQ ID NO. 1305
(N20)NGG	5	35876459	-	ATTCCAGATTGGAGAGAAAATGG	2	11	145	SEQ ID NO. 1306
(N20)NGG	5	35876470	-	TCAATGTCAGGATTCCAGATTGG	1	4	39	SEQ ID NO. 1307
(N20)NGG	5	35876482	-	GAGCAACTGGGTTCAATGTCAGG	1	3	20	SEQ ID NO. 1308

FIG. 7 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	5	35876494	-	TGGGCTGACCCTGAGCAACTGGG	1	4	36	SEQ ID NO. 1309
(N20)NGG	5	35876495	-	ATGGGCTGACCCTGAGCAACTGG	1	3	39	SEQ ID NO. 1310
(N20)NGG	5	35876513	-	GATCCCAGGGAAGTAAGAATGGG	1	7	81	SEQ ID NO. 1311
(N20)NGG	5	35876514	-	TGATCCCAGGGAAGTAAGAATGG	1	18	211	SEQ ID NO. 1312
(N20)NGG	5	35876526	-	TTCTTCTTGATTTTGATCCCAGGG	1	2	82	SEQ ID NO. 1313
(N20)NGG	5	35876527	-	CTTCTTCTTGATTTTGATCCCAGG	1	7	173	SEQ ID NO. 1314
(N20)NGG	5	35876559	-	GTTTTGGTAGAAGCTGGACATGG	1	5	131	SEQ ID NO. 1315
(N20)NGG	5	35876565	-	TCACTGGTTTTTGGTAGAAGCTGG	1	5	53	SEQ ID NO. 1316
(N20)NGG	5	35876575	-	TTCTTACACTTCACTGGTTTTTGG	1	7	62	SEQ ID NO. 1317
(N20)NGG	5	35876581	-	CTGGGTTTCTTACACTTCACTGG	1	1	37	SEQ ID NO. 1318

FIG. 7 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	19	17937551	+	TTATCTGTCCCCCGCCCCTCAGG	1	2	35	SEQ ID NO. 1319
(N20)NGG	19	17937577	+	ACGAGCTCATGAAGCTGTGCTGG	1	3	13	SEQ ID NO. 1320
(N20)NGG	19	17937578	+	CGAGCTCATGAAGCTGTGCTGGG	1	3	18	SEQ ID NO. 1321
(N20)NGG	19	17937593	+	GTGCTGGGCCCCTAGCCCACAGG	1	5	61	SEQ ID NO. 1322
(N20)NGG	19	17937598	+	GGGCCCCTAGCCCACAGGACCGG	1	4	83	SEQ ID NO. 1323
(N20)NGG	19	17937617	+	CCGGCCATCATTCAGCGCCCTGG	1	1	7	SEQ ID NO. 1324
(N20)NGG	19	17937618	+	CGGCCATCATTCAGCGCCCTGGG	1	2	3	SEQ ID NO. 1325
(N20)NGG	19	17937629	+	CAGCGCCCTGGGCCCCCAGCTGG	1	9	113	SEQ ID NO. 1326
(N20)NGG	19	17937640	+	GCCCCCAGCTGGACATGCTGTGG	1	3	74	SEQ ID NO. 1327
(N20)NGG	19	17937645	+	CAGCTGGACATGCTGTGGAGCGG	1	8	69	SEQ ID NO. 1328
(N20)NGG	19	17937652	+	ACATGCTGTGGAGCGGAAGCCGG	1	1	25	SEQ ID NO. 1329
(N20)NGG	19	17937653	+	CATGCTGTGGAGCGGAAGCCGGG	1	5	28	SEQ ID NO. 1330
(N20)NGG	19	17937654	+	ATGCTGTGGAGCGGAAGCCGGGG	1	2	18	SEQ ID NO. 1331
(N20)NGG	19	17937655	+	TGCTGTGGAGCGGAAGCCGGGGG	1	1	21	SEQ ID NO. 1332
(N20)NGG	19	17937689	+	TGCCTTCACTGCTCACCCAGAGG	1	2	60	SEQ ID NO. 1333
(N20)NGG	19	17937690	+	GCCTTCACTGCTCACCCAGAGGG	1	7	51	SEQ ID NO. 1334
(N20)NGG	19	17937739	+	AGCTCCTGCCCGCAGACCTCTGG	1	6	64	SEQ ID NO. 1335
(N20)NGG	19	17937526	-	GAGGGGCGGGGGACAGATAATGG	1	8	99	SEQ ID NO. 1336
(N20)NGG	19	17937537	-	CTCGTGAACCTGAGGGGCGGGGG	1	63	1843	SEQ ID NO. 1337
(N20)NGG	19	17937538	-	GCTCGTGAACCTGAGGGGCGGGG	1	5	100	SEQ ID NO. 1338
(N20)NGG	19	17937539	-	AGCTCGTGAACCTGAGGGGCGGG	1	3	36	SEQ ID NO. 1339
(N20)NGG	19	17937540	-	GAGCTCGTGAACCTGAGGGGCGG	1	1	22	SEQ ID NO. 1340
(N20)NGG	19	17937543	-	CATGAGCTCGTGAACCTGAGGGG	1	1	9	SEQ ID NO. 1341
(N20)NGG	19	17937544	-	TCATGAGCTCGTGAACCTGAGGG	1	1	13	SEQ ID NO. 1342
(N20)NGG	19	17937545	-	TTCATGAGCTCGTGAACCTGAGG	1	3	19	SEQ ID NO. 1343
(N20)NGG	19	17937579	-	TGGCCGGTCCTGTGGGCTAGGGG	1	5	18	SEQ ID NO. 1344
(N20)NGG	19	17937580	-	ATGGCCGGTCCTGTGGGCTAGGG	1	1	14	SEQ ID NO. 1345
(N20)NGG	19	17937581	-	GATGGCCGGTCCTGTGGGCTAGG	1	1	22	SEQ ID NO. 1346
(N20)NGG	19	17937586	-	TGAATGATGGCCGGTCCTGTGGG	1	7	93	SEQ ID NO. 1347
(N20)NGG	19	17937587	-	CTGAATGATGGCCGGTCCTGTGG	1	2	16	SEQ ID NO. 1348
(N20)NGG	19	17937595	-	CCAGGGCGCTGAATGATGGCCGG	1	1	12	SEQ ID NO. 1349
(N20)NGG	19	17937599	-	GGGCCCAGGGCGCTGAATGATGG	1	3	33	SEQ ID NO. 1350
(N20)NGG	19	17937612	-	CATGTCCAGCTGGGGGCCCAGGG	1	7	59	SEQ ID NO. 1351

FIG. 8

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	19	17937613	-	GCATGTCCAGCTGGGGGCCCAGG	1	6	70	SEQ ID NO. 1352
(N20)NGG	19	17937619	-	TCCACAGCATGTCCAGCTGGGGG	1	5	67	SEQ ID NO. 1353
(N20)NGG	19	17937620	-	CTCCACAGCATGTCCAGCTGGGG	1	2	71	SEQ ID NO. 1354
(N20)NGG	19	17937621	-	GCTCCACAGCATGTCCAGCTGGG	1	3	37	SEQ ID NO. 1355
(N20)NGG	19	17937622	-	CGCTCCACAGCATGTCCAGCTGG	1	2	28	SEQ ID NO. 1356
(N20)NGG	19	17937649	-	AGGCATGAGTCTCACACCCCCGG	1	5	38	SEQ ID NO. 1357
(N20)NGG	19	17937669	-	GCCCTCTGGGTGAGCAGTGAAGG	1	4	62	SEQ ID NO. 1358
(N20)NGG	19	17937682	-	GGGAGTGGTGTTTGCCCTCTGGG	1	2	42	SEQ ID NO. 1359
(N20)NGG	19	17937683	-	AGGGAGTGGTGTTTGCCCTCTGG	1	4	49	SEQ ID NO. 1360
(N20)NGG	19	17937697	-	GCTATGAAAAGGACAGGGAGTGG	1	6	89	SEQ ID NO. 1361
(N20)NGG	19	17937702	-	CAGGAGCTATGAAAAGGACAGGG	2	6	79	SEQ ID NO. 1362
(N20)NGG	19	17937703	-	GCAGGAGCTATGAAAAGGACAGG	1	4	47	SEQ ID NO. 1363
(N20)NGG	19	17937708	-	TGCGGGCAGGAGCTATGAAAAGG	1	4	28	SEQ ID NO. 1364
(N20)NGG	19	17937721	-	TAATCCAGAGGTCTGCGGGCAGG	1	1	21	SEQ ID NO. 1365
(N20)NGG	19	17940916	+	ATGCGCTCCTCCTTGGCTCCAGG	1	6	33	SEQ ID NO. 1366
(N20)NGG	19	17940927	+	CTTGGCTCCAGGAGTTCCTGCGG	1	9	84	SEQ ID NO. 1367
(N20)NGG	19	17940934	+	CCAGGAGTTCCTGCGGATGATGG	1	3	27	SEQ ID NO. 1368
(N20)NGG	19	17940935	+	CAGGAGTTCCTGCGGATGATGGG	1	1	17	SEQ ID NO. 1369
(N20)NGG	19	17940945	+	TGCGGATGATGGGATGTGAGCGG	1	2	38	SEQ ID NO. 1370
(N20)NGG	19	17940946	+	GCGGATGATGGGATGTGAGCGGG	1	1	19	SEQ ID NO. 1371
(N20)NGG	19	17940973	+	CCCCGCCCTCTGCCGCCTCTTGG	1	8	80	SEQ ID NO. 1372
(N20)NGG	19	17940982	+	CTGCCGCCTCTTGGAACTGCTGG	1	3	29	SEQ ID NO. 1373
(N20)NGG	19	17940985	+	CCGCCTCTTGGAACTGCTGGAGG	2	5	31	SEQ ID NO. 1374
(N20)NGG	19	17940988	+	CCTCTTGGAACTGCTGGAGGAGG	1	6	63	SEQ ID NO. 1375
(N20)NGG	19	17940989	+	CTCTTGGAACTGCTGGAGGAGGG	1	3	67	SEQ ID NO. 1376
(N20)NGG	19	17940996	+	AACTGCTGGAGGAGGGCCAGAGG	2	8	91	SEQ ID NO. 1377
(N20)NGG	19	17941003	+	GGAGGAGGGCCAGAGGCTGCCGG	2	24	274	SEQ ID NO. 1378
(N20)NGG	19	17941027	+	GCCTCCTGCCTGCCCTGCTGAGG	5	32	242	SEQ ID NO. 1379
(N20)NGG	19	17941040	+	CCTGCTGAGGTGAGCGCCGCAGG	1	1	26	SEQ ID NO. 1380
(N20)NGG	19	17941041	+	CTGCTGAGGTGAGCGCCGCAGGG	1	2	17	SEQ ID NO. 1381
(N20)NGG	19	17940901	-	AGGAACTCCTGGAGCCAAGGAGG	1	4	96	SEQ ID NO. 1382
(N20)NGG	19	17940904	-	CGCAGGAACTCCTGGAGCCAAGG	1	5	67	SEQ ID NO. 1383
(N20)NGG	19	17940912	-	CCATCATCCGCAGGAACTCCTGG	1	1	21	SEQ ID NO. 1384

FIG. 8 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	19	17940921	-	GCTCACATCCCATCATCCGCAGG	1	1	10	SEQ ID NO. 1385
(N20)NGG	19	17940951	-	CCAAGAGGCGGCAGAGGGCGGGG	1	4	58	SEQ ID NO. 1386
(N20)NGG	19	17940952	-	TCCAAGAGGCGGCAGAGGGCGGG	1	2	46	SEQ ID NO. 1387
(N20)NGG	19	17940953	-	TTCCAAGAGGCGGCAGAGGGCGG	2	3	53	SEQ ID NO. 1388
(N20)NGG	19	17940956	-	CAGTTCCAAGAGGCGGCAGAGGG	1	3	33	SEQ ID NO. 1389
(N20)NGG	19	17940957	-	GCAGTTCCAAGAGGCGGCAGAGG	1	2	34	SEQ ID NO. 1390
(N20)NGG	19	17940963	-	CCTCCAGCAGTTCCAAGAGGCGG	1	6	49	SEQ ID NO. 1391
(N20)NGG	19	17940966	-	CCTCCTCCAGCAGTTCCAAGAGG	1	6	64	SEQ ID NO. 1392
(N20)NGG	19	17940990	-	CAGGAGGCGCCGGCAGCCTCTGG	1	4	60	SEQ ID NO. 1393
(N20)NGG	19	17941000	-	GCAGGGCAGGCAGGAGGCGCCGG	2	28	284	SEQ ID NO. 1394
(N20)NGG	19	17941006	-	ACCTCAGCAGGGCAGGCAGGAGG	2	9	170	SEQ ID NO. 1395
(N20)NGG	19	17941009	-	CTCACCTCAGCAGGGCAGGCAGG	1	7	82	SEQ ID NO. 1396
(N20)NGG	19	17941013	-	GGCGCTCACCTCAGCAGGGCAGG	1	2	30	SEQ ID NO. 1397
(N20)NGG	19	17941017	-	CTGCGGCGCTCACCTCAGCAGGG	1	3	15	SEQ ID NO. 1398
(N20)NGG	19	17941018	-	CCTGCGGCGCTCACCTCAGCAGG	1	1	25	SEQ ID NO. 1399
(N20)NGG	19	17941311	+	CAAGACCTTGTCCCCTCTCCAGG	2	4	63	SEQ ID NO. 1400
(N20)NGG	19	17941333	+	GTATGCCCCCGAATCCCTCTCGG	1	1	11	SEQ ID NO. 1401
(N20)NGG	19	17941365	+	TCTCTCGCCAGTCAGACGTCTGG	1	2	9	SEQ ID NO. 1402
(N20)NGG	19	17941373	+	CAGTCAGACGTCTGGAGCTTCGG	1	5	39	SEQ ID NO. 1403
(N20)NGG	19	17941374	+	AGTCAGACGTCTGGAGCTTCGGG	1	1	15	SEQ ID NO. 1404
(N20)NGG	19	17941375	+	GTCAGACGTCTGGAGCTTCGGGG	1	1	7	SEQ ID NO. 1405
(N20)NGG	19	17941426	+	CGACAAAAGCTGCAGCCCCTCGG	1	2	34	SEQ ID NO. 1406
(N20)NGG	19	17941437	+	GCAGCCCCTCGGCCGTGAGTCGG	1	2	31	SEQ ID NO. 1407
(N20)NGG	19	17941294	-	GCATACCTGGAGAGGGGACAAGG	1	3	70	SEQ ID NO. 1408
(N20)NGG	19	17941300	-	TCGGGGGCATACCTGGAGAGGGG	1	2	25	SEQ ID NO. 1409
(N20)NGG	19	17941301	-	TTCGGGGGCATACCTGGAGAGGG	1	1	24	SEQ ID NO. 1410
(N20)NGG	19	17941302	-	ATTCGGGGGCATACCTGGAGAGG	1	1	11	SEQ ID NO. 1411
(N20)NGG	19	17941307	-	GAGGGATTCGGGGGCATACCTGG	1	2	14	SEQ ID NO. 1412
(N20)NGG	19	17941316	-	GTTGTCCGAGAGGGATTCGGGGG	1	1	3	SEQ ID NO. 1413
(N20)NGG	19	17941317	-	TGTTGTCCGAGAGGGATTCGGGG	1	1	4	SEQ ID NO. 1414
(N20)NGG	19	17941318	-	ATGTTGTCCGAGAGGGATTCGGG	1	1	7	SEQ ID NO. 1415
(N20)NGG	19	17941319	-	GATGTTGTCCGAGAGGGATTCGG	1	1	13	SEQ ID NO. 1416
(N20)NGG	19	17941325	-	AGAGAAGATGTTGTCCGAGAGGG	1	2	32	SEQ ID NO. 1417

FIG. 8 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	19	17941326	-	GAGAGAAGATGTTGTCCGAGAGG	1	4	26	SEQ ID NO. 1418
(N20)NGG	19	17941350	-	CGAAGCTCCAGACGTCTGACTGG	1	1	4	SEQ ID NO. 1419
(N20)NGG	19	17941380	-	AGTAGGTGAAGAGCTCGTACAGG	1	2	6	SEQ ID NO. 1420
(N20)NGG	19	17941397	-	GCTGCAGCTTTTGTCGCAGTAGG	1	1	17	SEQ ID NO. 1421
(N20)NGG	19	17941419	-	GAAGCCGACTCACGGCCGAGGGG	1	1	3	SEQ ID NO. 1422
(N20)NGG	19	17941420	-	GGAAGCCGACTCACGGCCGAGGG	1	1	3	SEQ ID NO. 1423
(N20)NGG	19	17941421	-	GGGAAGCCGACTCACGGCCGAGG	1	1	4	SEQ ID NO. 1424
(N20)NGG	19	17941427	-	GGCTCTGGGAAGCCGACTCACGG	1	4	34	SEQ ID NO. 1425
(N20)NGG	19	17942036	+	CGCTCACACCGCCCGCCCGCAGG	2	5	26	SEQ ID NO. 1426
(N20)NGG	19	17942037	+	GCTCACACCGCCCGCCCGCAGGG	1	5	22	SEQ ID NO. 1427
(N20)NGG	19	17942042	+	CACCGCCCGCCCGCAGGGCATGG	1	2	35	SEQ ID NO. 1428
(N20)NGG	19	17942051	+	CCCGCAGGGCATGGAGTACCTGG	1	3	21	SEQ ID NO. 1429
(N20)NGG	19	17942052	+	CCGCAGGGCATGGAGTACCTGGG	1	4	24	SEQ ID NO. 1430
(N20)NGG	19	17942081	+	CCGCTGCGTGCACCGCGACCTGG	1	1	11	SEQ ID NO. 1431
(N20)NGG	19	17942102	+	GGCCGCCCGAAACATCCTCGTGG	1	1	6	SEQ ID NO. 1432
(N20)NGG	19	17942111	+	AAACATCCTCGTGGAGAGCGAGG	1	1	5	SEQ ID NO. 1433
(N20)NGG	19	17942136	+	CACGTCAAGATCGCTGACTTCGG	2	6	15	SEQ ID NO. 1434
(N20)NGG	19	17942177	+	GCTTGACAAAGACTACTACGTGG	1	1	9	SEQ ID NO. 1435
(N20)NGG	19	17942190	+	TACTACGTGGTCCGCGAGCCAGG	1	1	3	SEQ ID NO. 1436
(N20)NGG	19	17942209	+	CAGGCCAGAGCCCCATTTTCTGG	1	7	63	SEQ ID NO. 1437
(N20)NGG	19	17942212	+	GCCAGAGCCCCATTTTCTGGTGG	1	4	52	SEQ ID NO. 1438
(N20)NGG	19	17942213	+	CCAGAGCCCCATTTTCTGGTGGG	1	5	52	SEQ ID NO. 1439
(N20)NGG	19	17942214	+	CAGAGCCCCATTTTCTGGTGGGG	1	3	56	SEQ ID NO. 1440
(N20)NGG	19	17942228	+	CTGGTGGGGAACCCGCGCCTAGG	1	1	19	SEQ ID NO. 1441
(N20)NGG	19	17942022	-	CTCCATGCCCTGCGGGCGGGCGG	1	2	37	SEQ ID NO. 1442
(N20)NGG	19	17942025	-	GTACTCCATGCCCTGCGGGCGGG	1	1	17	SEQ ID NO. 1443
(N20)NGG	19	17942026	-	GGTACTCCATGCCCTGCGGGCGG	1	2	17	SEQ ID NO. 1444
(N20)NGG	19	17942029	-	CCAGGTACTCCATGCCCTGCGGG	1	3	54	SEQ ID NO. 1445
(N20)NGG	19	17942030	-	CCCAGGTACTCCATGCCCTGCGG	1	3	70	SEQ ID NO. 1446
(N20)NGG	19	17942047	-	GCACGCAGCGGCGGGAGCCCAGG	1	3	42	SEQ ID NO. 1447
(N20)NGG	19	17942055	-	GTCGCGGTGCACGCAGCGGCGGG	1	1	6	SEQ ID NO. 1448
(N20)NGG	19	17942056	-	GGTCGCGGTGCACGCAGCGGCGG	1	1	8	SEQ ID NO. 1449
(N20)NGG	19	17942059	-	CCAGGTCGCGGTGCACGCAGCGG	1	1	15	SEQ ID NO. 1450

FIG. 8 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	19	17942071	-	TGTTTCGGGCGGCCAGGTCGCGG	2	2	10	SEQ ID NO. 1451
(N20)NGG	19	17942077	-	CGAGGATGTTTCGGGCGGCCAGG	1	6	13	SEQ ID NO. 1452
(N20)NGG	19	17942082	-	CTCCACGAGGATGTTTCGGGCGG	1	2	14	SEQ ID NO. 1453
(N20)NGG	19	17942085	-	GCTCTCCACGAGGATGTTTCGGG	1	1	17	SEQ ID NO. 1454
(N20)NGG	19	17942086	-	CGCTCTCCACGAGGATGTTTCGG	1	1	7	SEQ ID NO. 1455
(N20)NGG	19	17942095	-	CGTGTGCCTCGCTCTCCACGAGG	1	1	13	SEQ ID NO. 1456
(N20)NGG	19	17942137	-	CAAGCGGCAGCAGCTTAGCTAGG	1	1	32	SEQ ID NO. 1457
(N20)NGG	19	17942153	-	ACGTAGTAGTCTTTGTCAAGCGG	1	1	12	SEQ ID NO. 1458
(N20)NGG	19	17942179	-	TGGGGCTCTGGCCTGGCTCGCGG	2	5	79	SEQ ID NO. 1459
(N20)NGG	19	17942186	-	CAGAAAATGGGGCTCTGGCCTGG	1	7	80	SEQ ID NO. 1460
(N20)NGG	19	17942191	-	CCCACCAGAAAATGGGGCTCTGG	1	5	46	SEQ ID NO. 1461
(N20)NGG	19	17942197	-	GGGTTCCCCACCAGAAAATGGGG	1	2	32	SEQ ID NO. 1462
(N20)NGG	19	17942198	-	CGGGTTCCCCACCAGAAAATGGG	1	3	19	SEQ ID NO. 1463
(N20)NGG	19	17942199	-	GCGGGTTCCCCACCAGAAAATGG	1	1	17	SEQ ID NO. 1464
(N20)NGG	19	17942482	+	TGACAGATCCTGCCTTCTCCAGG	1	4	66	SEQ ID NO. 1465
(N20)NGG	19	17942498	+	CTCCAGGCCGCCAGAGCCTGCGG	1	12	92	SEQ ID NO. 1466
(N20)NGG	19	17942502	+	AGGCCGCCAGAGCCTGCGGCTGG	2	3	29	SEQ ID NO. 1467
(N20)NGG	19	17942508	+	CCAGAGCCTGCGGCTGGTCATGG	1	4	75	SEQ ID NO. 1468
(N20)NGG	19	17942524	+	GTCATGGAGTACCTGCCCAGCGG	1	4	41	SEQ ID NO. 1469
(N20)NGG	19	17942549	+	GCTTGCGCGACTTCCTGCAGCGG	1	1	12	SEQ ID NO. 1470
(N20)NGG	19	17942607	+	CTATTCCTCGCAGATCTGCAAGG	1	2	14	SEQ ID NO. 1471
(N20)NGG	19	17942614	+	TCGCAGATCTGCAAGGTGCGAGG	1	3	14	SEQ ID NO. 1472
(N20)NGG	19	17942615	+	CGCAGATCTGCAAGGTGCGAGGG	1	1	9	SEQ ID NO. 1473
(N20)NGG	19	17942616	+	GCAGATCTGCAAGGTGCGAGGGG	1	3	25	SEQ ID NO. 1474
(N20)NGG	19	17942617	+	CAGATCTGCAAGGTGCGAGGGGG	1	2	28	SEQ ID NO. 1475
(N20)NGG	19	17942625	+	CAAGGTGCGAGGGGGCGCCCCGG	1	1	25	SEQ ID NO. 1476
(N20)NGG	19	17942626	+	AAGGTGCGAGGGGGCGCCCCGGG	1	2	16	SEQ ID NO. 1477
(N20)NGG	19	17942468	-	TCTGGCGGCCTGGAGAAGGCAGG	1	20	75	SEQ ID NO. 1478
(N20)NGG	19	17942472	-	AGGCTCTGGCGGCCTGGAGAAGG	1	10	74	SEQ ID NO. 1479
(N20)NGG	19	17942478	-	AGCCGCAGGCTCTGGCGGCCTGG	1	3	36	SEQ ID NO. 1480
(N20)NGG	19	17942483	-	TGACCAGCCGCAGGCTCTGGCGG	1	5	49	SEQ ID NO. 1481
(N20)NGG	19	17942486	-	CCATGACCAGCCGCAGGCTCTGG	1	1	29	SEQ ID NO. 1482
(N20)NGG	19	17942492	-	GGTACTCCATGACCAGCCGCAGG	1	1	10	SEQ ID NO. 1483

FIG. 8 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	19	17942513	-	CGCGCAAGCAGCCGCTGGGCAGG	1	1	8	SEQ ID NO. 1484
(N20)NGG	19	17942517	-	AAGTCGCGCAAGCAGCCGCTGGG	1	1	3	SEQ ID NO. 1485
(N20)NGG	19	17942518	-	GAAGTCGCGCAAGCAGCCGCTGG	1	1	1	SEQ ID NO. 1486
(N20)NGG	19	17942540	-	GGCGCGCGCGGTGCCGCTGCAGG	1	2	38	SEQ ID NO. 1487
(N20)NGG	19	17942552	-	GGCTGGCATCGAGGCGCGCGCGG	1	4	15	SEQ ID NO. 1488
(N20)NGG	19	17942561	-	GAAGGAGGCGGCTGGCATCGAGG	1	2	28	SEQ ID NO. 1489
(N20)NGG	19	17942569	-	GGAATAGAGAAGGAGGCGGCTGG	1	5	66	SEQ ID NO. 1490
(N20)NGG	19	17942573	-	GCGAGGAATAGAGAAGGAGGCGG	1	9	243	SEQ ID NO. 1491
(N20)NGG	19	17942576	-	TCTGCGAGGAATAGAGAAGGAGG	1	4	45	SEQ ID NO. 1492
(N20)NGG	19	17942579	-	AGATCTGCGAGGAATAGAGAAGG	1	6	38	SEQ ID NO. 1493
(N20)NGG	19	17942590	-	TCGCACCTTGCAGATCTGCGAGG	1	1	11	SEQ ID NO. 1494
(N20)NGG	19	17943327	+	CATCAGTCCCGCTATCCCCCAGG	1	1	10	SEQ ID NO. 1495
(N20)NGG	19	17943328	+	ATCAGTCCCGCTATCCCCCAGGG	1	1	14	SEQ ID NO. 1496
(N20)NGG	19	17943337	+	GCTATCCCCCAGGGCAACTTTGG	1	1	20	SEQ ID NO. 1497
(N20)NGG	19	17943345	+	CCAGGGCAACTTTGGCAGCGTGG	1	2	17	SEQ ID NO. 1498
(N20)NGG	19	17943370	+	CTGTGCCGCTATGACCCGCTAGG	1	1	6	SEQ ID NO. 1499
(N20)NGG	19	17943382	+	GACCCGCTAGGCGACAATACAGG	1	1	3	SEQ ID NO. 1500
(N20)NGG	19	17943390	+	AGGCGACAATACAGGTGCCCTGG	1	2	10	SEQ ID NO. 1501
(N20)NGG	19	17943393	+	CGACAATACAGGTGCCCTGGTGG	1	2	12	SEQ ID NO. 1502
(N20)NGG	19	17943418	+	GTGAAACAGCTGCAGCACAGCGG	1	3	70	SEQ ID NO. 1503
(N20)NGG	19	17943419	+	TGAAACAGCTGCAGCACAGCGGG	2	4	97	SEQ ID NO. 1504
(N20)NGG	19	17943434	+	ACAGCGGGCCAGACCAGCAGAGG	1	1	33	SEQ ID NO. 1505
(N20)NGG	19	17943435	+	CAGCGGGCCAGACCAGCAGAGGG	1	3	30	SEQ ID NO. 1506
(N20)NGG	19	17943446	+	ACCAGCAGAGGGACTTTCAGCGG	1	5	71	SEQ ID NO. 1507
(N20)NGG	19	17943447	+	CCAGCAGAGGGACTTTCAGCGGG	1	5	65	SEQ ID NO. 1508
(N20)NGG	19	17943499	+	GATTTCATTGTCAAGTATCGTGG	1	2	15	SEQ ID NO. 1509
(N20)NGG	19	17943511	+	AAGTATCGTGGTGTCAGCTATGG	1	1	20	SEQ ID NO. 1510
(N20)NGG	19	17943516	+	TCGTGGTGTCAGCTATGGCCCGG	1	3	19	SEQ ID NO. 1511
(N20)NGG	19	17943517	+	CGTGGTGTCAGCTATGGCCCGGG	2	11	26	SEQ ID NO. 1512
(N20)NGG	19	17943532	+	GGCCCGGGTGAGCCAGCTCCCGG	1	2	50	SEQ ID NO. 1513
(N20)NGG	19	17943312	-	AAGTTGCCCTGGGGGATAGCGGG	1	1	16	SEQ ID NO. 1514
(N20)NGG	19	17943313	-	AAAGTTGCCCTGGGGGATAGCGG	1	3	37	SEQ ID NO. 1515
(N20)NGG	19	17943320	-	CGCTGCCAAAGTTGCCCTGGGGG	1	1	18	SEQ ID NO. 1516

FIG. 8 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	19	17943321	-	ACGCTGCCAAAGTTGCCCTGGGG	1	2	22	SEQ ID NO. 1517
(N20)NGG	19	17943322	-	CACGCTGCCAAAGTTGCCCTGGG	1	1	13	SEQ ID NO. 1518
(N20)NGG	19	17943323	-	CCACGCTGCCAAAGTTGCCCTGG	1	2	18	SEQ ID NO. 1519
(N20)NGG	19	17943353	-	TGTCGCCTAGCGGGTCATAGCGG	1	1	4	SEQ ID NO. 1520
(N20)NGG	19	17943362	-	CACCTGTATTGTCGCCTAGCGGG	1	1	5	SEQ ID NO. 1521
(N20)NGG	19	17943363	-	GCACCTGTATTGTCGCCTAGCGG	1	1	5	SEQ ID NO. 1522
(N20)NGG	19	17943385	-	CAGCTGTTTCACGGCCACCAGGG	1	3	21	SEQ ID NO. 1523
(N20)NGG	19	17943386	-	GCAGCTGTTTCACGGCCACCAGG	1	3	17	SEQ ID NO. 1524
(N20)NGG	19	17943394	-	GCTGTGCTGCAGCTGTTTCACGG	2	3	57	SEQ ID NO. 1525
(N20)NGG	19	17943420	-	TGAAAGTCCCTCTGCTGGTCTGG	1	4	42	SEQ ID NO. 1526
(N20)NGG	19	17943425	-	CCCGCTGAAAGTCCCTCTGCTGG	1	2	15	SEQ ID NO. 1527
(N20)NGG	19	17943458	-	AATCACTGTGCAGTGCTTTGAGG	1	1	73	SEQ ID NO. 1528
(N20)NGG	19	17943512	-	ATCCGGGAGCTGGCTCACCCGGG	1	2	19	SEQ ID NO. 1529
(N20)NGG	19	17943513	-	CATCCGGGAGCTGGCTCACCCGG	1	3	24	SEQ ID NO. 1530
(N20)NGG	19	17943628	+	CTCCTCTCAGACCCCACACCTGG	3	14	136	SEQ ID NO. 1531
(N20)NGG	19	17943636	+	AGACCCCACACCTGGTGCCCTGG	2	7	51	SEQ ID NO. 1532
(N20)NGG	19	17943649	+	GGTGCCCTGGCACCTCGTGATGG	1	1	17	SEQ ID NO. 1533
(N20)NGG	19	17943650	+	GTGCCCTGGCACCTCGTGATGGG	1	2	9	SEQ ID NO. 1534
(N20)NGG	19	17943656	+	TGGCACCTCGTGATGGGCTGTGG	1	1	27	SEQ ID NO. 1535
(N20)NGG	19	17943661	+	CCTCGTGATGGGCTGTGGAATGG	2	4	24	SEQ ID NO. 1536
(N20)NGG	19	17943702	+	CCAAGACCCCACGATCTTCGAGG	1	1	5	SEQ ID NO. 1537
(N20)NGG	19	17943732	+	CCTCAAGTACATCTCACAGCTGG	1	3	38	SEQ ID NO. 1538
(N20)NGG	19	17943733	+	CTCAAGTACATCTCACAGCTGGG	1	3	43	SEQ ID NO. 1539
(N20)NGG	19	17943738	+	GTACATCTCACAGCTGGGCAAGG	1	2	51	SEQ ID NO. 1540
(N20)NGG	19	17943743	+	TCTCACAGCTGGGCAAGGTAAGG	1	5	66	SEQ ID NO. 1541
(N20)NGG	19	17943746	+	CACAGCTGGGCAAGGTAAGGTGG	2	7	85	SEQ ID NO. 1542
(N20)NGG	19	17943747	+	ACAGCTGGGCAAGGTAAGGTGGG	1	2	45	SEQ ID NO. 1543
(N20)NGG	19	17943751	+	CTGGGCAAGGTAAGGTGGGCAGG	1	4	67	SEQ ID NO. 1544
(N20)NGG	19	17943752	+	TGGGCAAGGTAAGGTGGGCAGGG	1	5	107	SEQ ID NO. 1545
(N20)NGG	19	17943757	+	AAGGTAAGGTGGGCAGGGCCAGG	2	9	141	SEQ ID NO. 1546
(N20)NGG	19	17943758	+	AGGTAAGGTGGGCAGGGCCAGGG	3	15	128	SEQ ID NO. 1547
(N20)NGG	19	17943761	+	TAAGGTGGGCAGGGCCAGGGTGG	1	11	220	SEQ ID NO. 1548
(N20)NGG	19	17943762	+	AAGGTGGGCAGGGCCAGGGTGGG	2	25	282	SEQ ID NO. 1549

FIG. 8 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	19	17943574	-	TGGGGTGGGGGCATGGGCAGTGG	6	54	656	SEQ ID NO. 1550
(N20)NGG	19	17943580	-	ATAGTCTGGGGTGGGGGCATGGG	1	5	88	SEQ ID NO. 1551
(N20)NGG	19	17943581	-	CATAGTCTGGGGTGGGGGCATGG	1	10	133	SEQ ID NO. 1552
(N20)NGG	19	17943586	-	GAGCTCATAGTCTGGGGTGGGGG	3	10	112	SEQ ID NO. 1553
(N20)NGG	19	17943587	-	GGAGCTCATAGTCTGGGGTGGGG	2	12	80	SEQ ID NO. 1554
(N20)NGG	19	17943588	-	AGGAGCTCATAGTCTGGGGTGGG	1	13	121	SEQ ID NO. 1555
(N20)NGG	19	17943589	-	GAGGAGCTCATAGTCTGGGGTGG	1	14	149	SEQ ID NO. 1556
(N20)NGG	19	17943592	-	TGAGAGGAGCTCATAGTCTGGGG	1	3	54	SEQ ID NO. 1557
(N20)NGG	19	17943593	-	CTGAGAGGAGCTCATAGTCTGGG	1	4	51	SEQ ID NO. 1558
(N20)NGG	19	17943594	-	TCTGAGAGGAGCTCATAGTCTGG	1	5	48	SEQ ID NO. 1559
(N20)NGG	19	17943608	-	CACCAGGTGTGGGGTCTGAGAGG	1	6	70	SEQ ID NO. 1560
(N20)NGG	19	17943617	-	GTGCCAGGGCACCAGGTGTGGGG	4	14	64	SEQ ID NO. 1561
(N20)NGG	19	17943618	-	GGTGCCAGGGCACCAGGTGTGGG	3	11	64	SEQ ID NO. 1562
(N20)NGG	19	17943619	-	AGGTGCCAGGGCACCAGGTGTGG	2	6	82	SEQ ID NO. 1563
(N20)NGG	19	17943624	-	TCACGAGGTGCCAGGGCACCAGG	1	1	23	SEQ ID NO. 1564
(N20)NGG	19	17943631	-	CAGCCCATCACGAGGTGCCAGGG	1	2	21	SEQ ID NO. 1565
(N20)NGG	19	17943632	-	ACAGCCCATCACGAGGTGCCAGG	1	3	11	SEQ ID NO. 1566
(N20)NGG	19	17943639	-	CCATTCCACAGCCCATCACGAGG	2	3	24	SEQ ID NO. 1567
(N20)NGG	19	17943664	-	GTCTTGGCAGGCATAGAGCTGGG	1	3	36	SEQ ID NO. 1568
(N20)NGG	19	17943665	-	GGTCTTGGCAGGCATAGAGCTGG	2	5	53	SEQ ID NO. 1569
(N20)NGG	19	17943676	-	GAAGATCGTGGGGTCTTGGCAGG	1	2	24	SEQ ID NO. 1570
(N20)NGG	19	17943680	-	CCTCGAAGATCGTGGGGTCTTGG	1	1	7	SEQ ID NO. 1571
(N20)NGG	19	17943686	-	GTCTCTCCTCGAAGATCGTGGGG	1	2	5	SEQ ID NO. 1572
(N20)NGG	19	17943687	-	TGTCTCTCCTCGAAGATCGTGGG	1	1	6	SEQ ID NO. 1573
(N20)NGG	19	17943688	-	GTGTCTCTCCTCGAAGATCGTGG	1	2	7	SEQ ID NO. 1574
(N20)NGG	19	17943710	-	CCAGCTGTGAGATGTACTTGAGG	1	2	37	SEQ ID NO. 1575
(N20)NGG	19	17945397	+	TCAGAAACTCCAATTTTATGAGG	1	7	86	SEQ ID NO. 1576
(N20)NGG	19	17945402	+	AACTCCAATTTTATGAGGACCGG	1	3	40	SEQ ID NO. 1577
(N20)NGG	19	17945415	+	TGAGGACCGGCAGCAGCTGCCGG	1	6	66	SEQ ID NO. 1578
(N20)NGG	19	17945426	+	AGCAGCTGCCGGCCCCCAAGTGG	1	1	43	SEQ ID NO. 1579
(N20)NGG	19	17945436	+	GGCCCCCAAGTGGACAGAGCTGG	1	4	67	SEQ ID NO. 1580
(N20)NGG	19	17945460	+	CCTGCTGATTCAACAGTGCATGG	1	3	37	SEQ ID NO. 1581
(N20)NGG	19	17945472	+	ACAGTGCATGGCCTATGAGCCGG	1	2	32	SEQ ID NO. 1582

FIG. 8 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	19	17945480	+	TGGCCTATGAGCCGGTCCAGAGG	1	2	15	SEQ ID NO. 1583
(N20)NGG	19	17945530	+	CTCAATAGCCTCATCTCTTCAGG	1	2	45	SEQ ID NO. 1584
(N20)NGG	19	17945540	+	TCATCTCTTCAGGTGCCCGCTGG	1	2	16	SEQ ID NO. 1585
(N20)NGG	19	17945541	+	CATCTCTTCAGGTGCCCGCTGGG	2	2	25	SEQ ID NO. 1586
(N20)NGG	19	17945545	+	TCTTCAGGTGCCCGCTGGGACGG	2	2	27	SEQ ID NO. 1587
(N20)NGG	19	17945546	+	CTTCAGGTGCCCGCTGGGACGGG	1	3	24	SEQ ID NO. 1588
(N20)NGG	19	17945550	+	AGGTGCCCGCTGGGACGGGTTGG	1	2	12	SEQ ID NO. 1589
(N20)NGG	19	17945551	+	GGTGCCCGCTGGGACGGGTTGGG	1	2	18	SEQ ID NO. 1590
(N20)NGG	19	17945554	+	GCCCGCTGGGACGGGTTGGGTGG	1	1	22	SEQ ID NO. 1591
(N20)NGG	19	17945356	-	CTGAGGGTGAGAGGAGCAGTCGG	1	6	131	SEQ ID NO. 1592
(N20)NGG	19	17945365	-	TTGGAGTTTCTGAGGGTGAGAGG	1	10	100	SEQ ID NO. 1593
(N20)NGG	19	17945372	-	CATAAAATTGGAGTTTCTGAGGG	1	8	117	SEQ ID NO. 1594
(N20)NGG	19	17945373	-	TCATAAAATTGGAGTTTCTGAGG	1	10	88	SEQ ID NO. 1595
(N20)NGG	19	17945384	-	GCTGCCGGTCCTCATAAAATTGG	1	2	12	SEQ ID NO. 1596
(N20)NGG	19	17945399	-	TGGGGGCCGGCAGCTGCTGCCGG	1	8	83	SEQ ID NO. 1597
(N20)NGG	19	17945412	-	AGCTCTGTCCACTTGGGGGCCGG	1	4	66	SEQ ID NO. 1598
(N20)NGG	19	17945416	-	GGCCAGCTCTGTCCACTTGGGGG	1	11	71	SEQ ID NO. 1599
(N20)NGG	19	17945417	-	GGGCCAGCTCTGTCCACTTGGGG	1	5	58	SEQ ID NO. 1600
(N20)NGG	19	17945418	-	AGGGCCAGCTCTGTCCACTTGGG	1	7	74	SEQ ID NO. 1601
(N20)NGG	19	17945419	-	CAGGGCCAGCTCTGTCCACTTGG	2	7	118	SEQ ID NO. 1602
(N20)NGG	19	17945437	-	CATGCACTGTTGAATCAGCAGGG	1	3	32	SEQ ID NO. 1603
(N20)NGG	19	17945438	-	CCATGCACTGTTGAATCAGCAGG	2	2	27	SEQ ID NO. 1604
(N20)NGG	19	17945461	-	GGGCCTCTGGACCGGCTCATAGG	1	2	19	SEQ ID NO. 1605
(N20)NGG	19	17945469	-	CGGAAGGAGGGCCTCTGGACCGG	1	2	23	SEQ ID NO. 1606
(N20)NGG	19	17945474	-	CGGCTCGGAAGGAGGGCCTCTGG	1	2	12	SEQ ID NO. 1607
(N20)NGG	19	17945481	-	CGAATGACGGCTCGGAAGGAGGG	1	1	4	SEQ ID NO. 1608
(N20)NGG	19	17945482	-	ACGAATGACGGCTCGGAAGGAGG	1	1	4	SEQ ID NO. 1609
(N20)NGG	19	17945485	-	GTCACGAATGACGGCTCGGAAGG	1	1	1	SEQ ID NO. 1610
(N20)NGG	19	17945489	-	TGAGGTCACGAATGACGGCTCGG	1	1	9	SEQ ID NO. 1611
(N20)NGG	19	17945494	-	GCTATTGAGGTCACGAATGACGG	1	1	15	SEQ ID NO. 1612
(N20)NGG	19	17945507	-	CTGAAGAGATGAGGCTATTGAGG	1	3	54	SEQ ID NO. 1613
(N20)NGG	19	17945516	-	AGCGGGCACCTGAAGAGATGAGG	1	3	26	SEQ ID NO. 1614
(N20)NGG	19	17945673	+	TTCCCTCAGTGCTCACCGACAGG	1	1	25	SEQ ID NO. 1615

FIG. 8 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	19	17945682	+	TGCTCACCGACAGGATCCCCTGG	1	2	14	SEQ ID NO. 1616
(N20)NGG	19	17945683	+	GCTCACCGACAGGATCCCCTGGG	1	2	12	SEQ ID NO. 1617
(N20)NGG	19	17945686	+	CACCGACAGGATCCCCTGGGTGG	1	2	16	SEQ ID NO. 1618
(N20)NGG	19	17945703	+	GGGTGGCCCCCGAGTGTCTCCGG	1	1	13	SEQ ID NO. 1619
(N20)NGG	19	17945704	+	GGTGGCCCCCGAGTGTCTCCGGG	1	2	27	SEQ ID NO. 1620
(N20)NGG	19	17945707	+	GGCCCCCGAGTGTCTCCGGGAGG	1	2	24	SEQ ID NO. 1621
(N20)NGG	19	17945725	+	GGAGGCGCAGACACTTAGCTTGG	1	1	9	SEQ ID NO. 1622
(N20)NGG	19	17945739	+	TTAGCTTGGAAGCTGACAAGTGG	1	2	29	SEQ ID NO. 1623
(N20)NGG	19	17945740	+	TAGCTTGGAAGCTGACAAGTGGG	1	5	33	SEQ ID NO. 1624
(N20)NGG	19	17945741	+	AGCTTGGAAGCTGACAAGTGGGG	1	3	47	SEQ ID NO. 1625
(N20)NGG	19	17945747	+	GAAGCTGACAAGTGGGGCTTCGG	1	2	38	SEQ ID NO. 1626
(N20)NGG	19	17945755	+	CAAGTGGGGCTTCGGCGCCACGG	1	1	8	SEQ ID NO. 1627
(N20)NGG	19	17945760	+	GGGGCTTCGGCGCCACGGTCTGG	1	1	9	SEQ ID NO. 1628
(N20)NGG	19	17945761	+	GGGCTTCGGCGCCACGGTCTGGG	1	1	8	SEQ ID NO. 1629
(N20)NGG	19	17945774	+	ACGGTCTGGGAAGTGTTTAGTGG	1	1	16	SEQ ID NO. 1630
(N20)NGG	19	17945800	+	CACCATGCCCATCAGTGCCCTGG	1	8	63	SEQ ID NO. 1631
(N20)NGG	19	17945812	+	CAGTGCCCTGGATCCTGCTAAGG	1	4	51	SEQ ID NO. 1632
(N20)NGG	19	17945830	+	TAAGGTCAGAGCCCCTCACCCGG	1	2	38	SEQ ID NO. 1633
(N20)NGG	19	17945836	+	CAGAGCCCCTCACCCGGCATCGG	1	3	43	SEQ ID NO. 1634
(N20)NGG	19	17945635	-	GAGGGAATGAAAGTGGGATCAGG	1	7	74	SEQ ID NO. 1635
(N20)NGG	19	17945641	-	AGCACTGAGGGAATGAAAGTGGG	1	8	86	SEQ ID NO. 1636
(N20)NGG	19	17945642	-	GAGCACTGAGGGAATGAAAGTGG	1	8	106	SEQ ID NO. 1637
(N20)NGG	19	17945653	-	ATCCTGTCGGTGAGCACTGAGGG	1	1	16	SEQ ID NO. 1638
(N20)NGG	19	17945654	-	GATCCTGTCGGTGAGCACTGAGG	1	2	15	SEQ ID NO. 1639
(N20)NGG	19	17945666	-	GGCCACCCAGGGGATCCTGTCGG	1	2	36	SEQ ID NO. 1640
(N20)NGG	19	17945676	-	GACACTCGGGGGCCACCCAGGGG	1	2	18	SEQ ID NO. 1641
(N20)NGG	19	17945677	-	AGACACTCGGGGGCCACCCAGGG	1	1	25	SEQ ID NO. 1642
(N20)NGG	19	17945678	-	GAGACACTCGGGGGCCACCCAGG	1	1	16	SEQ ID NO. 1643
(N20)NGG	19	17945687	-	CGCCTCCCGGAGACACTCGGGGG	1	2	11	SEQ ID NO. 1644
(N20)NGG	19	17945688	-	GCGCCTCCCGGAGACACTCGGGG	1	2	13	SEQ ID NO. 1645
(N20)NGG	19	17945689	-	TGCGCCTCCCGGAGACACTCGGG	1	1	14	SEQ ID NO. 1646
(N20)NGG	19	17945690	-	CTGCGCCTCCCGGAGACACTCGG	1	2	32	SEQ ID NO. 1647
(N20)NGG	19	17945700	-	AGCTAAGTGTCTGCGCCTCCCGG	1	1	11	SEQ ID NO. 1648

FIG. 8 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	19	17945750	-	ACTAAACACTTCCCAGACCGTGG	1	2	14	SEQ ID NO. 1649
(N20)NGG	19	17945780	-	ATCCAGGGCACTGATGGGCATGG	1	5	64	SEQ ID NO. 1650
(N20)NGG	19	17945785	-	GCAGGATCCAGGGCACTGATGGG	2	7	75	SEQ ID NO. 1651
(N20)NGG	19	17945786	-	AGCAGGATCCAGGGCACTGATGG	1	10	73	SEQ ID NO. 1652
(N20)NGG	19	17945795	-	TCTGACCTTAGCAGGATCCAGGG	1	1	26	SEQ ID NO. 1653
(N20)NGG	19	17945796	-	CTCTGACCTTAGCAGGATCCAGG	1	2	25	SEQ ID NO. 1654
(N20)NGG	19	17945803	-	TGAGGGGCTCTGACCTTAGCAGG	1	3	36	SEQ ID NO. 1655
(N20)NGG	19	17945891	+	TTCCTGTGTCTGGCCCCCTTAGG	1	6	38	SEQ ID NO. 1656
(N20)NGG	19	17945894	+	CTGTGTCTGGCCCCCTTAGGAGG	1	2	37	SEQ ID NO. 1657
(N20)NGG	19	17945901	+	TGGCCCCCTTAGGAGGACAAAGG	1	1	26	SEQ ID NO. 1658
(N20)NGG	19	17945913	+	GAGGACAAAGGCCTGCCCCATGG	1	1	82	SEQ ID NO. 1659
(N20)NGG	19	17945929	+	CCCATGGCAATGTCTCTGCCCGG	1	4	46	SEQ ID NO. 1660
(N20)NGG	19	17945933	+	TGGCAATGTCTCTGCCCGGAAGG	1	3	31	SEQ ID NO. 1661
(N20)NGG	19	17945942	+	CTCTGCCCGGAAGGTGCTCCTGG	3	3	60	SEQ ID NO. 1662
(N20)NGG	19	17945947	+	CCCGGAAGGTGCTCCTGGCTCGG	1	4	52	SEQ ID NO. 1663
(N20)NGG	19	17945948	+	CCGGAAGGTGCTCCTGGCTCGGG	1	3	33	SEQ ID NO. 1664
(N20)NGG	19	17945951	+	GAAGGTGCTCCTGGCTCGGGAGG	1	2	38	SEQ ID NO. 1665
(N20)NGG	19	17945952	+	AAGGTGCTCCTGGCTCGGGAGGG	1	2	32	SEQ ID NO. 1666
(N20)NGG	19	17945953	+	AGGTGCTCCTGGCTCGGGAGGGG	1	2	58	SEQ ID NO. 1667
(N20)NGG	19	17945954	+	GGTGCTCCTGGCTCGGGAGGGGG	1	4	61	SEQ ID NO. 1668
(N20)NGG	19	17945961	+	CTGGCTCGGGAGGGGGCTGATGG	1	6	71	SEQ ID NO. 1669
(N20)NGG	19	17945962	+	TGGCTCGGGAGGGGGCTGATGGG	1	2	41	SEQ ID NO. 1670
(N20)NGG	19	17945994	+	TTCATCAAGCTGAGTGACCCTGG	3	5	37	SEQ ID NO. 1671
(N20)NGG	19	17945995	+	TCATCAAGCTGAGTGACCCTGGG	1	4	59	SEQ ID NO. 1672
(N20)NGG	19	17945996	+	CATCAAGCTGAGTGACCCTGGGG	1	8	61	SEQ ID NO. 1673
(N20)NGG	19	17946020	+	CAGCCCCGCTGTGTTAAGCCTGG	1	1	11	SEQ ID NO. 1674
(N20)NGG	19	17946035	+	AAGCCTGGAGAGTAAGTTCCTGG	1	2	32	SEQ ID NO. 1675
(N20)NGG	19	17946038	+	CCTGGAGAGTAAGTTCCTGGAGG	2	9	56	SEQ ID NO. 1676
(N20)NGG	19	17946041	+	GGAGAGTAAGTTCCTGGAGGTGG	1	7	79	SEQ ID NO. 1677
(N20)NGG	19	17946044	+	GAGTAAGTTCCTGGAGGTGGAGG	3	4	90	SEQ ID NO. 1678
(N20)NGG	19	17946047	+	TAAGTTCCTGGAGGTGGAGGAGG	1	9	103	SEQ ID NO. 1679
(N20)NGG	19	17946048	+	AAGTTCCTGGAGGTGGAGGAGGG	2	10	150	SEQ ID NO. 1680
(N20)NGG	19	17945871	-	CTCCTAAGGGGGCCAGACACAGG	1	1	23	SEQ ID NO. 1681

FIG. 8 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	19	17945882	-	AGGCCTTTGTCCTCCTAAGGGGG	1	5	27	SEQ ID NO. 1682
(N20)NGG	19	17945883	-	CAGGCCTTTGTCCTCCTAAGGGG	1	4	42	SEQ ID NO. 1683
(N20)NGG	19	17945884	-	GCAGGCCTTTGTCCTCCTAAGGG	1	3	34	SEQ ID NO. 1684
(N20)NGG	19	17945885	-	GGCAGGCCTTTGTCCTCCTAAGG	1	1	35	SEQ ID NO. 1685
(N20)NGG	19	17945902	-	CAGAGACATTGCCATGGGGCAGG	1	2	74	SEQ ID NO. 1686
(N20)NGG	19	17945906	-	CGGGCAGAGACATTGCCATGGGG	1	1	22	SEQ ID NO. 1687
(N20)NGG	19	17945907	-	CCGGGCAGAGACATTGCCATGGG	1	1	13	SEQ ID NO. 1688
(N20)NGG	19	17945908	-	TCCGGGCAGAGACATTGCCATGG	2	3	22	SEQ ID NO. 1689
(N20)NGG	19	17945925	-	CCGAGCCAGGAGCACCTTCCGGG	2	3	29	SEQ ID NO. 1690
(N20)NGG	19	17945926	-	CCCGAGCCAGGAGCACCTTCCGG	1	3	26	SEQ ID NO. 1691
(N20)NGG	19	17945938	-	CATCAGCCCCCTCCCGAGCCAGG	1	5	56	SEQ ID NO. 1692
(N20)NGG	19	17945965	-	CACTCAGCTTGATGAAGGGCGGG	1	4	36	SEQ ID NO. 1693
(N20)NGG	19	17945966	-	TCACTCAGCTTGATGAAGGGCGG	1	3	36	SEQ ID NO. 1694
(N20)NGG	19	17945969	-	GGGTCACTCAGCTTGATGAAGGG	3	3	19	SEQ ID NO. 1695
(N20)NGG	19	17945970	-	AGGGTCACTCAGCTTGATGAAGG	2	4	44	SEQ ID NO. 1696
(N20)NGG	19	17945989	-	ACACAGCGGGGCTGACCCCAGGG	1	2	31	SEQ ID NO. 1697
(N20)NGG	19	17945990	-	AACACAGCGGGGCTGACCCCAGG	1	2	18	SEQ ID NO. 1698
(N20)NGG	19	17946001	-	TCTCCAGGCTTAACACAGCGGGG	1	1	24	SEQ ID NO. 1699
(N20)NGG	19	17946002	-	CTCTCCAGGCTTAACACAGCGGG	1	3	26	SEQ ID NO. 1700
(N20)NGG	19	17946003	-	ACTCTCCAGGCTTAACACAGCGG	1	3	46	SEQ ID NO. 1701
(N20)NGG	19	17946016	-	CCTCCAGGAACTTACTCTCCAGG	2	7	64	SEQ ID NO. 1702
(N20)NGG	19	17946732	+	GCCTCTCCCTGCTGCCAACCAGG	1	8	88	SEQ ID NO. 1703
(N20)NGG	19	17946740	+	CTGCTGCCAACCAGGCACCATGG	1	8	71	SEQ ID NO. 1704
(N20)NGG	19	17946746	+	CCAACCAGGCACCATGGTGCAGG	1	5	43	SEQ ID NO. 1705
(N20)NGG	19	17946761	+	GGTGCAGGAATTTGTACACCTGG	1	2	22	SEQ ID NO. 1706
(N20)NGG	19	17946762	+	GTGCAGGAATTTGTACACCTGGG	1	1	28	SEQ ID NO. 1707
(N20)NGG	19	17946763	+	TGCAGGAATTTGTACACCTGGGG	1	2	33	SEQ ID NO. 1708
(N20)NGG	19	17946764	+	GCAGGAATTTGTACACCTGGGGG	1	2	26	SEQ ID NO. 1709
(N20)NGG	19	17946792	+	GACATGTATCTGCGAAAACGTGG	1	1	8	SEQ ID NO. 1710
(N20)NGG	19	17946800	+	TCTGCGAAAACGTGGCCACCTGG	1	1	9	SEQ ID NO. 1711
(N20)NGG	19	17946814	+	GCCACCTGGTGCCAGCCAGCTGG	1	7	83	SEQ ID NO. 1712
(N20)NGG	19	17946824	+	GCCAGCCAGCTGGAAGCTGCAGG	2	7	88	SEQ ID NO. 1713
(N20)NGG	19	17946827	+	AGCCAGCTGGAAGCTGCAGGTGG	1	9	117	SEQ ID NO. 1714

FIG. 8 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	19	17946839	+	GCTGCAGGTGGTCAAACAGCTGG	1	6	63	SEQ ID NO. 1715
(N20)NGG	19	17946860	+	GGCCTACGCCCTCAACTATCTGG	1	1	4	SEQ ID NO. 1716
(N20)NGG	19	17946707	-	GGTTGGCAGCAGGGAGAGGCGGG	1	17	229	SEQ ID NO. 1717
(N20)NGG	19	17946708	-	TGGTTGGCAGCAGGGAGAGGCGG	1	27	393	SEQ ID NO. 1718
(N20)NGG	19	17946711	-	GCCTGGTTGGCAGCAGGGAGAGG	1	14	135	SEQ ID NO. 1719
(N20)NGG	19	17946716	-	ATGGTGCCTGGTTGGCAGCAGGG	1	2	48	SEQ ID NO. 1720
(N20)NGG	19	17946717	-	CATGGTGCCTGGTTGGCAGCAGG	1	5	66	SEQ ID NO. 1721
(N20)NGG	19	17946724	-	CCTGCACCATGGTGCCTGGTTGG	1	5	83	SEQ ID NO. 1722
(N20)NGG	19	17946728	-	AATTCCTGCACCATGGTGCCTGG	1	2	26	SEQ ID NO. 1723
(N20)NGG	19	17946735	-	GTGTACAAATTCCTGCACCATGG	1	1	32	SEQ ID NO. 1724
(N20)NGG	19	17946757	-	GATACATGTCTATGGCCCCCAGG	1	3	18	SEQ ID NO. 1725
(N20)NGG	19	17946765	-	TTTTCGCAGATACATGTCTATGG	1	2	18	SEQ ID NO. 1726
(N20)NGG	19	17946793	-	TCCAGCTGGCTGGCACCAGGTGG	1	5	80	SEQ ID NO. 1727
(N20)NGG	19	17946796	-	GCTTCCAGCTGGCTGGCACCAGG	1	5	88	SEQ ID NO. 1728
(N20)NGG	19	17946803	-	ACCTGCAGCTTCCAGCTGGCTGG	1	3	63	SEQ ID NO. 1729
(N20)NGG	19	17946807	-	GACCACCTGCAGCTTCCAGCTGG	1	4	56	SEQ ID NO. 1730
(N20)NGG	19	17946840	-	CACCAGATAGTTGAGGGCGTAGG	1	1	12	SEQ ID NO. 1731
(N20)NGG	19	17946846	-	AGCACTCACCAGATAGTTGAGGG	1	3	35	SEQ ID NO. 1732
(N20)NGG	19	17946847	-	GAGCACTCACCAGATAGTTGAGG	1	1	26	SEQ ID NO. 1733
(N20)NGG	19	17947946	+	CCACCTTCCCCAGTCATTCCTGG	1	9	117	SEQ ID NO. 1734
(N20)NGG	19	17947981	+	TGATGAGCCAAGTGTCGTACCGG	1	1	12	SEQ ID NO. 1735
(N20)NGG	19	17948001	+	CGGCATCTCGTGCTGCTCCACGG	1	2	13	SEQ ID NO. 1736
(N20)NGG	19	17948012	+	GCTGCTCCACGGCGTGTGCATGG	1	1	20	SEQ ID NO. 1737
(N20)NGG	19	17948016	+	CTCCACGGCGTGTGCATGGCTGG	1	2	12	SEQ ID NO. 1738
(N20)NGG	19	17947918	-	ATGACTGGGGAAGGTGGGAAGGG	2	9	149	SEQ ID NO. 1739
(N20)NGG	19	17947919	-	AATGACTGGGGAAGGTGGGAAGG	1	9	154	SEQ ID NO. 1740
(N20)NGG	19	17947923	-	CAGGAATGACTGGGGAAGGTGGG	1	11	118	SEQ ID NO. 1741
(N20)NGG	19	17947924	-	CCAGGAATGACTGGGGAAGGTGG	2	12	157	SEQ ID NO. 1742
(N20)NGG	19	17947927	-	CTTCCAGGAATGACTGGGGAAGG	2	7	86	SEQ ID NO. 1743
(N20)NGG	19	17947931	-	GCTGCTTCCAGGAATGACTGGGG	1	10	75	SEQ ID NO. 1744
(N20)NGG	19	17947932	-	CGCTGCTTCCAGGAATGACTGGG	1	2	27	SEQ ID NO. 1745
(N20)NGG	19	17947933	-	TCGCTGCTTCCAGGAATGACTGG	1	3	24	SEQ ID NO. 1746
(N20)NGG	19	17947942	-	TCATCAAGCTCGCTGCTTCCAGG	1	4	23	SEQ ID NO. 1747

FIG. 8 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	19	17947966	-	CGAGATGCCGGTACGACACTTGG	1	1	3	SEQ ID NO. 1748
(N20)NGG	19	17947978	-	CGTGGAGCAGCACGAGATGCCGG	1	2	16	SEQ ID NO. 1749
(N20)NGG	19	17947996	-	CTCCAGCCATGCACACGCCGTGG	1	3	26	SEQ ID NO. 1750
(N20)NGG	19	17948752	+	CACCATTCAGCATGAGAACCTGG	1	2	23	SEQ ID NO. 1751
(N20)NGG	19	17948753	+	ACCATTCAGCATGAGAACCTGGG	1	2	30	SEQ ID NO. 1752
(N20)NGG	19	17948759	+	CAGCATGAGAACCTGGGCCATGG	1	4	58	SEQ ID NO. 1753
(N20)NGG	19	17948760	+	AGCATGAGAACCTGGGCCATGGG	1	3	36	SEQ ID NO. 1754
(N20)NGG	19	17948781	+	GGTCCTTCACCAAGATTTACCGG	1	2	23	SEQ ID NO. 1755
(N20)NGG	19	17948782	+	GTCCTTCACCAAGATTTACCGGG	1	2	32	SEQ ID NO. 1756
(N20)NGG	19	17948783	+	TCCTTCACCAAGATTTACCGGGG	1	1	16	SEQ ID NO. 1757
(N20)NGG	19	17948797	+	TTACCGGGGCTGTCGCCATGAGG	1	1	5	SEQ ID NO. 1758
(N20)NGG	19	17948800	+	CCGGGGCTGTCGCCATGAGGTGG	1	3	21	SEQ ID NO. 1759
(N20)NGG	19	17948803	+	GGGCTGTCGCCATGAGGTGGTGG	1	3	38	SEQ ID NO. 1760
(N20)NGG	19	17948807	+	TGTCGCCATGAGGTGGTGGATGG	1	1	19	SEQ ID NO. 1761
(N20)NGG	19	17948808	+	GTCGCCATGAGGTGGTGGATGGG	1	1	13	SEQ ID NO. 1762
(N20)NGG	19	17948809	+	TCGCCATGAGGTGGTGGATGGGG	1	2	25	SEQ ID NO. 1763
(N20)NGG	19	17948812	+	CCATGAGGTGGTGGATGGGGAGG	2	14	159	SEQ ID NO. 1764
(N20)NGG	19	17948827	+	TGGGGAGGCCCGAAAGACAGAGG	1	3	36	SEQ ID NO. 1765
(N20)NGG	19	17948839	+	AAAGACAGAGGTGCTGCTGAAGG	1	5	101	SEQ ID NO. 1766
(N20)NGG	19	17948845	+	AGAGGTGCTGCTGAAGGTCATGG	1	7	105	SEQ ID NO. 1767
(N20)NGG	19	17948869	+	TGCCAAGCACAAGAACTGCATGG	1	3	52	SEQ ID NO. 1768
(N20)NGG	19	17948872	+	CAAGCACAAGAACTGCATGGAGG	1	26	858	SEQ ID NO. 1769
(N20)NGG	19	17948886	+	GCATGGAGGTGAGAGCAATGTGG	1	3	66	SEQ ID NO. 1770
(N20)NGG	19	17948725	-	TTCTCATGCTGAATGGTGAGGGG	2	4	48	SEQ ID NO. 1771
(N20)NGG	19	17948726	-	GTTCTCATGCTGAATGGTGAGGG	1	8	52	SEQ ID NO. 1772
(N20)NGG	19	17948727	-	GGTTCTCATGCTGAATGGTGAGG	1	5	36	SEQ ID NO. 1773
(N20)NGG	19	17948732	-	GCCCAGGTTCTCATGCTGAATGG	1	1	35	SEQ ID NO. 1774
(N20)NGG	19	17948748	-	TGGTGAAGGACCCATGGCCCAGG	1	1	41	SEQ ID NO. 1775
(N20)NGG	19	17948754	-	AAATCTTGGTGAAGGACCCATGG	1	5	45	SEQ ID NO. 1776
(N20)NGG	19	17948762	-	GCCCCGGTAAATCTTGGTGAAGG	1	1	8	SEQ ID NO. 1777
(N20)NGG	19	17948768	-	GCGACAGCCCCGGTAAATCTTGG	1	1	6	SEQ ID NO. 1778
(N20)NGG	19	17948778	-	CCACCTCATGGCGACAGCCCCGG	1	2	31	SEQ ID NO. 1779
(N20)NGG	19	17948790	-	CCTCCCCATCCACCACCTCATGG	5	17	178	SEQ ID NO. 1780

FIG. 8 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	19	17948813	-	CAGCAGCACCTCTGTCTTTCGGG	1	6	85	SEQ ID NO. 1781
(N20)NGG	19	17948814	-	TCAGCAGCACCTCTGTCTTTCGG	1	5	70	SEQ ID NO. 1782
(N20)NGG	19	17948849	-	CTCCATGCAGTTCTTGTGCTTGG	1	12	406	SEQ ID NO. 1783
(N20)NGG	19	17949091	+	AGAAAAGTCCAACCTGATCGTGG	1	1	20	SEQ ID NO. 1784
(N20)NGG	19	17949101	+	AACCTGATCGTGGTCCAGAGAGG	1	1	6	SEQ ID NO. 1785
(N20)NGG	19	17949127	+	CAGCCCACCCACATCATCCTTGG	1	8	83	SEQ ID NO. 1786
(N20)NGG	19	17949193	+	CAAGATCCCTGCTGACAGCCTGG	1	2	54	SEQ ID NO. 1787
(N20)NGG	19	17949198	+	TCCCTGCTGACAGCCTGGAGTGG	1	8	92	SEQ ID NO. 1788
(N20)NGG	19	17949199	+	CCCTGCTGACAGCCTGGAGTGGG	1	8	92	SEQ ID NO. 1789
(N20)NGG	19	17949206	+	GACAGCCTGGAGTGGGTAAGAGG	1	4	56	SEQ ID NO. 1790
(N20)NGG	19	17949212	+	CTGGAGTGGGTAAGAGGCCCTGG	1	3	58	SEQ ID NO. 1791
(N20)NGG	19	17949213	+	TGGAGTGGGTAAGAGGCCCTGGG	2	4	45	SEQ ID NO. 1792
(N20)NGG	19	17949221	+	GTAAGAGGCCCTGGGAAATGAGG	1	8	122	SEQ ID NO. 1793
(N20)NGG	19	17949051	-	TTTCTATGGGGAGAGGATGAGGG	1	12	105	SEQ ID NO. 1794
(N20)NGG	19	17949052	-	TTTTCTATGGGGAGAGGATGAGG	2	9	112	SEQ ID NO. 1795
(N20)NGG	19	17949058	-	TTGGACTTTTCTATGGGGAGAGG	1	4	44	SEQ ID NO. 1796
(N20)NGG	19	17949063	-	TCAGGTTGGACTTTTCTATGGGG	1	3	31	SEQ ID NO. 1797
(N20)NGG	19	17949064	-	ATCAGGTTGGACTTTTCTATGGG	2	2	30	SEQ ID NO. 1798
(N20)NGG	19	17949065	-	GATCAGGTTGGACTTTTCTATGG	1	5	40	SEQ ID NO. 1799
(N20)NGG	19	17949077	-	TCTCTGGACCACGATCAGGTTGG	1	1	8	SEQ ID NO. 1800
(N20)NGG	19	17949081	-	GACCTCTCTGGACCACGATCAGG	1	1	5	SEQ ID NO. 1801
(N20)NGG	19	17949093	-	TGGGTGGGCTGTGACCTCTCTGG	1	5	54	SEQ ID NO. 1802
(N20)NGG	19	17949108	-	GAACCAAGGATGATGTGGGTGGG	1	3	40	SEQ ID NO. 1803
(N20)NGG	19	17949109	-	TGAACCAAGGATGATGTGGGTGG	1	2	45	SEQ ID NO. 1804
(N20)NGG	19	17949112	-	GGCTGAACCAAGGATGATGTGGG	1	2	27	SEQ ID NO. 1805
(N20)NGG	19	17949113	-	GGGCTGAACCAAGGATGATGTGG	1	2	43	SEQ ID NO. 1806
(N20)NGG	19	17949122	-	TTGGGATTGGGGCTGAACCAAGG	1	1	34	SEQ ID NO. 1807
(N20)NGG	19	17949133	-	CTCAGCTGGTATTGGGATTGGGG	1	2	33	SEQ ID NO. 1808
(N20)NGG	19	17949134	-	ACTCAGCTGGTATTGGGATTGGG	1	2	30	SEQ ID NO. 1809
(N20)NGG	19	17949135	-	GACTCAGCTGGTATTGGGATTGG	1	3	19	SEQ ID NO. 1810
(N20)NGG	19	17949140	-	CATCTGACTCAGCTGGTATTGGG	1	2	29	SEQ ID NO. 1811
(N20)NGG	19	17949141	-	TCATCTGACTCAGCTGGTATTGG	1	1	25	SEQ ID NO. 1812
(N20)NGG	19	17949147	-	GAAATGTCATCTGACTCAGCTGG	1	4	172	SEQ ID NO. 1813

FIG. 8 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	19	17949177	-	CCCACTCCAGGCTGTCAGCAGGG	1	9	108	SEQ ID NO. 1814
(N20)NGG	19	17949178	-	ACCCACTCCAGGCTGTCAGCAGG	1	9	61	SEQ ID NO. 1815
(N20)NGG	19	17949189	-	CAGGGCCTCTTACCCACTCCAGG	1	4	54	SEQ ID NO. 1816
(N20)NGG	19	17950295	+	TCTTCTTTGCAGAACCCCCTTGG	1	4	45	SEQ ID NO. 1817
(N20)NGG	19	17950309	+	CCCCCTTGGTCCTGATTATAAGG	1	2	19	SEQ ID NO. 1818
(N20)NGG	19	17950310	+	CCCCTTGGTCCTGATTATAAGGG	1	3	38	SEQ ID NO. 1819
(N20)NGG	19	17950323	+	ATTATAAGGGCTGCCTCATCCGG	1	4	23	SEQ ID NO. 1820
(N20)NGG	19	17950337	+	CTCATCCGGCGCAGCCCCACAGG	1	1	15	SEQ ID NO. 1821
(N20)NGG	19	17950351	+	CCCCACAGGAACCTTCCTTCTGG	1	8	59	SEQ ID NO. 1822
(N20)NGG	19	17950355	+	ACAGGAACCTTCCTTCTGGTTGG	1	3	37	SEQ ID NO. 1823
(N20)NGG	19	17950393	+	CAGCAGTCTTCGAGAGCTCCTGG	1	5	27	SEQ ID NO. 1824
(N20)NGG	19	17950404	+	GAGAGCTCCTGGCAACCTGCTGG	2	7	66	SEQ ID NO. 1825
(N20)NGG	19	17950405	+	AGAGCTCCTGGCAACCTGCTGGG	1	2	41	SEQ ID NO. 1826
(N20)NGG	19	17950409	+	CTCCTGGCAACCTGCTGGGATGG	1	4	58	SEQ ID NO. 1827
(N20)NGG	19	17950410	+	TCCTGGCAACCTGCTGGGATGGG	1	1	49	SEQ ID NO. 1828
(N20)NGG	19	17950411	+	CCTGGCAACCTGCTGGGATGGGG	1	3	57	SEQ ID NO. 1829
(N20)NGG	19	17950412	+	CTGGCAACCTGCTGGGATGGGGG	1	4	56	SEQ ID NO. 1830
(N20)NGG	19	17950413	+	TGGCAACCTGCTGGGATGGGGGG	1	3	58	SEQ ID NO. 1831
(N20)NGG	19	17950427	+	GATGGGGGGCTGCACGTAGATGG	1	5	18	SEQ ID NO. 1832
(N20)NGG	19	17950428	+	ATGGGGGGCTGCACGTAGATGGG	1	1	6	SEQ ID NO. 1833
(N20)NGG	19	17950429	+	TGGGGGGCTGCACGTAGATGGGG	1	1	24	SEQ ID NO. 1834
(N20)NGG	19	17950432	+	GGGGCTGCACGTAGATGGGGTGG	1	6	41	SEQ ID NO. 1835
(N20)NGG	19	17950472	+	TGCTGTATCCCCAGACCCAAAGG	1	9	97	SEQ ID NO. 1836
(N20)NGG	19	17950492	+	AGGTGAGCCCCTTCCTCCCCTGG	2	6	93	SEQ ID NO. 1837
(N20)NGG	19	17950269	-	GGGGGTTCTGCAAAGAAGAGTGG	1	4	75	SEQ ID NO. 1838
(N20)NGG	19	17950287	-	CCTTATAATCAGGACCAAGGGGG	1	3	56	SEQ ID NO. 1839
(N20)NGG	19	17950288	-	CCCTTATAATCAGGACCAAGGGG	1	3	28	SEQ ID NO. 1840
(N20)NGG	19	17950289	-	GCCCTTATAATCAGGACCAAGGG	1	1	34	SEQ ID NO. 1841
(N20)NGG	19	17950290	-	AGCCCTTATAATCAGGACCAAGG	1	2	18	SEQ ID NO. 1842
(N20)NGG	19	17950297	-	ATGAGGCAGCCCTTATAATCAGG	1	2	19	SEQ ID NO. 1843
(N20)NGG	19	17950314	-	CTGTGGGGCTGCGCCGGATGAGG	1	4	27	SEQ ID NO. 1844
(N20)NGG	19	17950320	-	AGGTTCCTGTGGGGCTGCGCCGG	1	5	44	SEQ ID NO. 1845
(N20)NGG	19	17950329	-	CCAGAAGGAAGGTTCCTGTGGGG	1	3	70	SEQ ID NO. 1846

FIG. 8 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	19	17950330	-	ACCAGAAGGAAGGTTCCTGTGGG	1	3	50	SEQ ID NO. 1847
(N20)NGG	19	17950331	-	AACCAGAAGGAAGGTTCCTGTGG	1	5	83	SEQ ID NO. 1848
(N20)NGG	19	17950340	-	GCTGAGGCCAACCAGAAGGAAGG	1	2	60	SEQ ID NO. 1849
(N20)NGG	19	17950344	-	GTCGGCTGAGGCCAACCAGAAGG	1	1	16	SEQ ID NO. 1850
(N20)NGG	19	17950356	-	GACTGCTGTGGGGTCGGCTGAGG	1	11	462	SEQ ID NO. 1851
(N20)NGG	19	17950362	-	CTCGAAGACTGCTGTGGGGTCGG	1	2	25	SEQ ID NO. 1852
(N20)NGG	19	17950366	-	AGCTCTCGAAGACTGCTGTGGGG	1	3	21	SEQ ID NO. 1853
(N20)NGG	19	17950367	-	GAGCTCTCGAAGACTGCTGTGGG	1	2	26	SEQ ID NO. 1854
(N20)NGG	19	17950368	-	GGAGCTCTCGAAGACTGCTGTGG	1	3	31	SEQ ID NO. 1855
(N20)NGG	19	17950389	-	CCCCATCCCAGCAGGTTGCCAGG	1	2	68	SEQ ID NO. 1856
(N20)NGG	19	17950397	-	GTGCAGCCCCCCATCCCAGCAGG	2	6	62	SEQ ID NO. 1857
(N20)NGG	19	17950439	-	GGGGATACAGCAGGAAGTGAGGG	3	16	147	SEQ ID NO. 1858
(N20)NGG	19	17950440	-	TGGGGATACAGCAGGAAGTGAGG	2	22	135	SEQ ID NO. 1859
(N20)NGG	19	17950448	-	TTTGGGTCTGGGGATACAGCAGG	1	1	76	SEQ ID NO. 1860
(N20)NGG	19	17950458	-	GGGGCTCACCTTTGGGTCTGGGG	1	3	51	SEQ ID NO. 1861
(N20)NGG	19	17950459	-	AGGGGCTCACCTTTGGGTCTGGG	1	3	37	SEQ ID NO. 1862
(N20)NGG	19	17950460	-	AAGGGGCTCACCTTTGGGTCTGG	1	3	14	SEQ ID NO. 1863
(N20)NGG	19	17950465	-	GGAGGAAGGGGCTCACCTTTGGG	1	8	53	SEQ ID NO. 1864
(N20)NGG	19	17950466	-	GGGAGGAAGGGGCTCACCTTTGG	1	5	64	SEQ ID NO. 1865
(N20)NGG	19	17951042	+	TCTCACCTTCCCCCACAGTCTGG	1	5	72	SEQ ID NO. 1866
(N20)NGG	19	17951070	+	GCCATCAACAAGCTCAAGACTGG	1	3	33	SEQ ID NO. 1867
(N20)NGG	19	17951071	+	CCATCAACAAGCTCAAGACTGGG	1	5	52	SEQ ID NO. 1868
(N20)NGG	19	17951072	+	CATCAACAAGCTCAAGACTGGGG	1	4	42	SEQ ID NO. 1869
(N20)NGG	19	17951073	+	ATCAACAAGCTCAAGACTGGGGG	1	3	35	SEQ ID NO. 1870
(N20)NGG	19	17951085	+	AAGACTGGGGGCTCACGTCCTGG	1	1	19	SEQ ID NO. 1871
(N20)NGG	19	17951114	+	TGTTCTCCGCCGCAGCCCCCAGG	1	4	26	SEQ ID NO. 1872
(N20)NGG	19	17951150	+	CCTCCTCACTGTCTGTGTCCAGG	1	8	102	SEQ ID NO. 1873
(N20)NGG	19	17951154	+	CTCACTGTCTGTGTCCAGGTCGG	3	8	76	SEQ ID NO. 1874
(N20)NGG	19	17951166	+	GTCCAGGTCGGTCTACTGCTAGG	1	2	10	SEQ ID NO. 1875
(N20)NGG	19	17951167	+	TCCAGGTCGGTCTACTGCTAGGG	1	2	13	SEQ ID NO. 1876
(N20)NGG	19	17951170	+	AGGTCGGTCTACTGCTAGGGTGG	1	1	6	SEQ ID NO. 1877
(N20)NGG	19	17951171	+	GGTCGGTCTACTGCTAGGGTGGG	1	1	3	SEQ ID NO. 1878
(N20)NGG	19	17951017	-	GACTGTGGGGGAAGGTGAGAGGG	1	8	176	SEQ ID NO. 1879

FIG. 8 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	19	17951018	-	AGACTGTGGGGGAAGGTGAGAGG	1	12	195	SEQ ID NO. 1880
(N20)NGG	19	17951025	-	AAAGTCCAGACTGTGGGGGAAGG	2	5	65	SEQ ID NO. 1881
(N20)NGG	19	17951029	-	TGGCAAAGTCCAGACTGTGGGGG	1	7	80	SEQ ID NO. 1882
(N20)NGG	19	17951030	-	ATGGCAAAGTCCAGACTGTGGGG	1	3	54	SEQ ID NO. 1883
(N20)NGG	19	17951031	-	GATGGCAAAGTCCAGACTGTGGG	1	6	52	SEQ ID NO. 1884
(N20)NGG	19	17951032	-	TGATGGCAAAGTCCAGACTGTGG	1	11	64	SEQ ID NO. 1885
(N20)NGG	19	17951049	-	CCCAGTCTTGAGCTTGTTGATGG	1	2	30	SEQ ID NO. 1886
(N20)NGG	19	17951081	-	CGGCGGAGAACATAGGAGCCAGG	1	1	6	SEQ ID NO. 1887
(N20)NGG	19	17951088	-	GGGGCTGCGGCGGAGAACATAGG	1	1	15	SEQ ID NO. 1888
(N20)NGG	19	17951098	-	CAAAGTCCTGGGGGCTGCGGCGG	1	8	72	SEQ ID NO. 1889
(N20)NGG	19	17951101	-	TGTCAAAGTCCTGGGGGCTGCGG	1	10	141	SEQ ID NO. 1890
(N20)NGG	19	17951107	-	GGAAGCTGTCAAAGTCCTGGGGG	1	9	85	SEQ ID NO. 1891
(N20)NGG	19	17951108	-	AGGAAGCTGTCAAAGTCCTGGGG	1	5	81	SEQ ID NO. 1892
(N20)NGG	19	17951109	-	GAGGAAGCTGTCAAAGTCCTGGG	1	2	57	SEQ ID NO. 1893
(N20)NGG	19	17951110	-	GGAGGAAGCTGTCAAAGTCCTGG	1	1	49	SEQ ID NO. 1894
(N20)NGG	19	17951128	-	CCTGGACACAGACAGTGAGGAGG	1	6	106	SEQ ID NO. 1895
(N20)NGG	19	17951131	-	CGACCTGGACACAGACAGTGAGG	1	3	26	SEQ ID NO. 1896
(N20)NGG	19	17951146	-	ACCCTAGCAGTAGACCGACCTGG	1	1	6	SEQ ID NO. 1897
(N20)NGG	19	17952197	+	CTCTGACGCTTGTCCCTCGCAGG	1	1	10	SEQ ID NO. 1898
(N20)NGG	19	17952200	+	TGACGCTTGTCCCTCGCAGGAGG	1	1	6	SEQ ID NO. 1899
(N20)NGG	19	17952213	+	TCGCAGGAGGCCGAGTTCCCAGG	1	1	16	SEQ ID NO. 1900
(N20)NGG	19	17952214	+	CGCAGGAGGCCGAGTTCCCAGGG	1	4	28	SEQ ID NO. 1901
(N20)NGG	19	17952224	+	CGAGTTCCCAGGGCTGCCCGAGG	1	2	39	SEQ ID NO. 1902
(N20)NGG	19	17952239	+	GCCCGAGGCTCTGTCGTTCGTGG	1	1	6	SEQ ID NO. 1903
(N20)NGG	19	17952248	+	TCTGTCGTTCGTGGCGCTCGTGG	1	1	4	SEQ ID NO. 1904
(N20)NGG	19	17952252	+	TCGTTCGTGGCGCTCGTGGACGG	1	1	6	SEQ ID NO. 1905
(N20)NGG	19	17952262	+	CGCTCGTGGACGGCTACTTCCGG	1	1	2	SEQ ID NO. 1906
(N20)NGG	19	17952272	+	CGGCTACTTCCGGCTGACCACGG	1	1	14	SEQ ID NO. 1907
(N20)NGG	19	17952296	+	CTCCCAGCACTTCTTCTGCAAGG	1	6	100	SEQ ID NO. 1908
(N20)NGG	19	17952299	+	CCAGCACTTCTTCTGCAAGGAGG	1	4	54	SEQ ID NO. 1909
(N20)NGG	19	17952302	+	GCACTTCTTCTGCAAGGAGGTGG	1	4	43	SEQ ID NO. 1910
(N20)NGG	19	17952313	+	GCAAGGAGGTGGCACCGCCGAGG	1	1	19	SEQ ID NO. 1911
(N20)NGG	19	17952320	+	GGTGGCACCGCCGAGGCTGCTGG	1	4	29	SEQ ID NO. 1912

FIG. 8 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	19	17952323	+	GGCACCGCCGAGGCTGCTGGAGG	1	2	49	SEQ ID NO. 1913
(N20)NGG	19	17952329	+	GCCGAGGCTGCTGGAGGAAGTGG	3	15	162	SEQ ID NO. 1914
(N20)NGG	19	17952345	+	GAAGTGGCCGAGCAGTGCCACGG	1	1	29	SEQ ID NO. 1915
(N20)NGG	19	17952360	+	TGCCACGGCCCCATCACGTAAGG	1	2	10	SEQ ID NO. 1916
(N20)NGG	19	17952379	+	AAGGACCTGTCCCCCATTCCCGG	1	1	32	SEQ ID NO. 1917
(N20)NGG	19	17952188	-	GGGAACTCGGCCTCCTGCGAGGG	1	1	8	SEQ ID NO. 1918
(N20)NGG	19	17952189	-	TGGGAACTCGGCCTCCTGCGAGG	1	2	22	SEQ ID NO. 1919
(N20)NGG	19	17952201	-	CTCGGGCAGCCCTGGGAACTCGG	1	3	54	SEQ ID NO. 1920
(N20)NGG	19	17952208	-	ACAGAGCCTCGGGCAGCCCTGGG	1	8	75	SEQ ID NO. 1921
(N20)NGG	19	17952209	-	GACAGAGCCTCGGGCAGCCCTGG	2	7	70	SEQ ID NO. 1922
(N20)NGG	19	17952218	-	GCCACGAACGACAGAGCCTCGGG	1	1	21	SEQ ID NO. 1923
(N20)NGG	19	17952219	-	CGCCACGAACGACAGAGCCTCGG	1	1	9	SEQ ID NO. 1924
(N20)NGG	19	17952259	-	GCTGGGAGTCCGTGGTCAGCCGG	1	2	33	SEQ ID NO. 1925
(N20)NGG	19	17952267	-	GAAGAAGTGCTGGGAGTCCGTGG	1	1	41	SEQ ID NO. 1926
(N20)NGG	19	17952276	-	CTCCTTGCAGAAGAAGTGCTGGG	1	5	51	SEQ ID NO. 1927
(N20)NGG	19	17952277	-	CCTCCTTGCAGAAGAAGTGCTGG	1	3	46	SEQ ID NO. 1928
(N20)NGG	19	17952305	-	ACTTCCTCCAGCAGCCTCGGCGG	1	4	58	SEQ ID NO. 1929
(N20)NGG	19	17952308	-	GCCACTTCCTCCAGCAGCCTCGG	1	12	123	SEQ ID NO. 1930
(N20)NGG	19	17952330	-	GATGGGGCCGTGGCACTGCTCGG	1	2	21	SEQ ID NO. 1931
(N20)NGG	19	17952340	-	GTCCTTACGTGATGGGGCCGTGG	1	1	7	SEQ ID NO. 1932
(N20)NGG	19	17952346	-	GGACAGGTCCTTACGTGATGGGG	1	1	9	SEQ ID NO. 1933
(N20)NGG	19	17952347	-	GGGACAGGTCCTTACGTGATGGG	1	1	13	SEQ ID NO. 1934
(N20)NGG	19	17952348	-	GGGGACAGGTCCTTACGTGATGG	1	2	13	SEQ ID NO. 1935
(N20)NGG	19	17952448	+	CGGTACTCCCCCTCCTTCCCAGG	1	3	41	SEQ ID NO. 1936
(N20)NGG	19	17952502	+	CGTAGACATTAGCATCAAGCAGG	1	1	9	SEQ ID NO. 1937
(N20)NGG	19	17952515	+	ATCAAGCAGGCCCCGCGCGTTGG	1	2	4	SEQ ID NO. 1938
(N20)NGG	19	17952520	+	GCAGGCCCCGCGCGTTGGCCCGG	1	2	16	SEQ ID NO. 1939
(N20)NGG	19	17952524	+	GCCCCGCGCGTTGGCCCGGCCGG	1	2	15	SEQ ID NO. 1940
(N20)NGG	19	17952538	+	CCCGGCCGGAGAGCACCGCCTGG	1	2	30	SEQ ID NO. 1941
(N20)NGG	19	17952552	+	ACCGCCTGGTCACTGTTACCAGG	1	1	4	SEQ ID NO. 1942
(N20)NGG	19	17952574	+	GACAGACAACCAGATTTTAGTGG	1	3	47	SEQ ID NO. 1943
(N20)NGG	19	17952575	+	ACAGACAACCAGATTTTAGTGGG	1	3	37	SEQ ID NO. 1944
(N20)NGG	19	17952581	+	AACCAGATTTTAGTGGGTGCAGG	2	3	31	SEQ ID NO. 1945

FIG. 8 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	19	17952433	-	TGGAGGACCTGGGAAGGAGGGGG	1	22	279	SEQ ID NO. 1946
(N20)NGG	19	17952434	-	CTGGAGGACCTGGGAAGGAGGGG	2	15	206	SEQ ID NO. 1947
(N20)NGG	19	17952435	-	GCTGGAGGACCTGGGAAGGAGGG	1	7	167	SEQ ID NO. 1948
(N20)NGG	19	17952436	-	GGCTGGAGGACCTGGGAAGGAGG	1	14	219	SEQ ID NO. 1949
(N20)NGG	19	17952439	-	AAGGGCTGGAGGACCTGGGAAGG	2	11	124	SEQ ID NO. 1950
(N20)NGG	19	17952443	-	GCAGAAGGGCTGGAGGACCTGGG	1	6	100	SEQ ID NO. 1951
(N20)NGG	19	17952444	-	CGCAGAAGGGCTGGAGGACCTGG	1	7	57	SEQ ID NO. 1952
(N20)NGG	19	17952450	-	GAAAGTCGCAGAAGGGCTGGAGG	1	2	35	SEQ ID NO. 1953
(N20)NGG	19	17952453	-	CTGGAAAGTCGCAGAAGGGCTGG	1	1	26	SEQ ID NO. 1954
(N20)NGG	19	17952457	-	ATTTCTGGAAAGTCGCAGAAGGG	1	3	44	SEQ ID NO. 1955
(N20)NGG	19	17952458	-	GATTTCTGGAAAGTCGCAGAAGG	1	2	37	SEQ ID NO. 1956
(N20)NGG	19	17952472	-	ATGCTAATGTCTACGATTTCTGG	1	1	16	SEQ ID NO. 1957
(N20)NGG	19	17952503	-	TCCGGCCGGGCCAACGCGCGGGG	1	1	9	SEQ ID NO. 1958
(N20)NGG	19	17952504	-	CTCCGGCCGGGCCAACGCGCGGG	1	1	13	SEQ ID NO. 1959
(N20)NGG	19	17952505	-	TCTCCGGCCGGGCCAACGCGCGG	1	1	11	SEQ ID NO. 1960
(N20)NGG	19	17952516	-	CCAGGCGGTGCTCTCCGGCCGGG	1	2	34	SEQ ID NO. 1961
(N20)NGG	19	17952517	-	ACCAGGCGGTGCTCTCCGGCCGG	1	1	16	SEQ ID NO. 1962
(N20)NGG	19	17952521	-	AGTGACCAGGCGGTGCTCTCCGG	1	2	20	SEQ ID NO. 1963
(N20)NGG	19	17952531	-	TCCTGGTAACAGTGACCAGGCGG	1	3	35	SEQ ID NO. 1964
(N20)NGG	19	17952534	-	CTGTCCTGGTAACAGTGACCAGG	1	1	37	SEQ ID NO. 1965
(N20)NGG	19	17952548	-	TAAAATCTGGTTGTCTGTCCTGG	1	3	37	SEQ ID NO. 1966
(N20)NGG	19	17952561	-	ATCCTGCACCCACTAAAATCTGG	1	1	30	SEQ ID NO. 1967
(N20)NGG	19	17953131	+	CTCCAACCCCTGCAGCTACAAGG	1	5	78	SEQ ID NO. 1968
(N20)NGG	19	17953167	+	AAGCCTGCGCGACCTGATCCAGG	1	1	7	SEQ ID NO. 1969
(N20)NGG	19	17953168	+	AGCCTGCGCGACCTGATCCAGGG	1	3	22	SEQ ID NO. 1970
(N20)NGG	19	17953187	+	AGGGCCTGAGCTTCGTGACGCGG	1	1	11	SEQ ID NO. 1971
(N20)NGG	19	17953190	+	GCCTGAGCTTCGTGACGCGGAGG	1	1	3	SEQ ID NO. 1972
(N20)NGG	19	17953199	+	TCGTGACGCGGAGGCGTATTCGG	1	1	1	SEQ ID NO. 1973
(N20)NGG	19	17953202	+	TGACGCGGAGGCGTATTCGGAGG	1	1	3	SEQ ID NO. 1974
(N20)NGG	19	17953206	+	GCGGAGGCGTATTCGGAGGACGG	1	1	7	SEQ ID NO. 1975
(N20)NGG	19	17953230	+	GCGCAGAGCCCTGCGCCGCGTGG	1	2	32	SEQ ID NO. 1976
(N20)NGG	19	17953242	+	GCGCCGCGTGGCCGCCTGCCAGG	1	3	27	SEQ ID NO. 1977
(N20)NGG	19	17953250	+	TGGCCGCCTGCCAGGCAGACCGG	3	3	29	SEQ ID NO. 1978

FIG. 8 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	19	17953263	+	GGCAGACCGGCACTCGCTCATGG	1	1	9	SEQ ID NO. 1979
(N20)NGG	19	17953278	+	GCTCATGGCCAAGTACATCATGG	2	4	39	SEQ ID NO. 1980
(N20)NGG	19	17953284	+	GGCCAAGTACATCATGGACCTGG	1	1	13	SEQ ID NO. 1981
(N20)NGG	19	17953289	+	AGTACATCATGGACCTGGAGCGG	1	1	34	SEQ ID NO. 1982
(N20)NGG	19	17953293	+	CATCATGGACCTGGAGCGGCTGG	1	5	22	SEQ ID NO. 1983
(N20)NGG	19	17953303	+	CTGGAGCGGCTGGATCCAGCCGG	1	3	46	SEQ ID NO. 1984
(N20)NGG	19	17953304	+	TGGAGCGGCTGGATCCAGCCGGG	2	4	44	SEQ ID NO. 1985
(N20)NGG	19	17953305	+	GGAGCGGCTGGATCCAGCCGGGG	1	6	33	SEQ ID NO. 1986
(N20)NGG	19	17953326	+	GGCCGCCGAGACCTTCCACGTGG	1	1	8	SEQ ID NO. 1987
(N20)NGG	19	17953327	+	GCCGCCGAGACCTTCCACGTGGG	1	1	5	SEQ ID NO. 1988
(N20)NGG	19	17953336	+	ACCTTCCACGTGGGCCTCCCTGG	2	11	234	SEQ ID NO. 1989
(N20)NGG	19	17953337	+	CCTTCCACGTGGGCCTCCCTGGG	2	30	1326	SEQ ID NO. 1990
(N20)NGG	19	17953338	+	CTTCCACGTGGGCCTCCCTGGGG	1	2	74	SEQ ID NO. 1991
(N20)NGG	19	17953345	+	GTGGGCCTCCCTGGGGCCCTTGG	1	6	132	SEQ ID NO. 1992
(N20)NGG	19	17953348	+	GGCCTCCCTGGGGCCCTTGGTGG	1	7	129	SEQ ID NO. 1993
(N20)NGG	19	17953357	+	GGGGCCCTTGGTGGCCACGACGG	1	2	33	SEQ ID NO. 1994
(N20)NGG	19	17953358	+	GGGCCCTTGGTGGCCACGACGGG	1	5	23	SEQ ID NO. 1995
(N20)NGG	19	17953362	+	CCTTGGTGGCCACGACGGGCTGG	1	3	26	SEQ ID NO. 1996
(N20)NGG	19	17953363	+	CTTGGTGGCCACGACGGGCTGGG	1	1	11	SEQ ID NO. 1997
(N20)NGG	19	17953364	+	TTGGTGGCCACGACGGGCTGGGG	1	3	26	SEQ ID NO. 1998
(N20)NGG	19	17953377	+	CGGGCTGGGGCTGCTCCGCGTGG	1	5	51	SEQ ID NO. 1999
(N20)NGG	19	17953381	+	CTGGGGCTGCTCCGCGTGGCTGG	1	3	49	SEQ ID NO. 2000
(N20)NGG	19	17953387	+	CTGCTCCGCGTGGCTGGTGACGG	1	1	35	SEQ ID NO. 2001
(N20)NGG	19	17953390	+	CTCCGCGTGGCTGGTGACGGCGG	1	1	15	SEQ ID NO. 2002
(N20)NGG	19	17953400	+	CTGGTGACGGCGGCATCGCCTGG	1	2	5	SEQ ID NO. 2003
(N20)NGG	19	17953407	+	CGGCGGCATCGCCTGGACCCAGG	1	1	13	SEQ ID NO. 2004
(N20)NGG	19	17953408	+	GGCGGCATCGCCTGGACCCAGGG	1	1	17	SEQ ID NO. 2005
(N20)NGG	19	17953416	+	CGCCTGGACCCAGGGAGAACAGG	1	3	29	SEQ ID NO. 2006
(N20)NGG	19	17953419	+	CTGGACCCAGGGAGAACAGGAGG	2	13	137	SEQ ID NO. 2007
(N20)NGG	19	17953424	+	CCCAGGGAGAACAGGAGGTGAGG	1	7	157	SEQ ID NO. 2008
(N20)NGG	19	17953425	+	CCAGGGAGAACAGGAGGTGAGGG	2	9	149	SEQ ID NO. 2009
(N20)NGG	19	17953428	+	GGGAGAACAGGAGGTGAGGGCGG	3	33	396	SEQ ID NO. 2010
(N20)NGG	19	17953441	+	GTGAGGGCGGACTCCCCCGCTGG	1	2	12	SEQ ID NO. 2011

FIG. 8 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	19	17953442	+	TGAGGGCGGACTCCCCCGCTGGG	1	1	9	SEQ ID NO. 2012
(N20)NGG	19	17953102	-	GCTGCAGGGGTTGGAGGGGAGGG	2	23	266	SEQ ID NO. 2013
(N20)NGG	19	17953103	-	AGCTGCAGGGGTTGGAGGGGAGG	1	19	260	SEQ ID NO. 2014
(N20)NGG	19	17953106	-	TGTAGCTGCAGGGGTTGGAGGGG	1	7	99	SEQ ID NO. 2015
(N20)NGG	19	17953107	-	TTGTAGCTGCAGGGGTTGGAGGG	1	2	61	SEQ ID NO. 2016
(N20)NGG	19	17953108	-	CTTGTAGCTGCAGGGGTTGGAGG	1	6	56	SEQ ID NO. 2017
(N20)NGG	19	17953111	-	GGCCTTGTAGCTGCAGGGGTTGG	1	4	54	SEQ ID NO. 2018
(N20)NGG	19	17953115	-	GGCAGGCCTTGTAGCTGCAGGGG	1	5	51	SEQ ID NO. 2019
(N20)NGG	19	17953116	-	AGGCAGGCCTTGTAGCTGCAGGG	1	3	43	SEQ ID NO. 2020
(N20)NGG	19	17953117	-	TAGGCAGGCCTTGTAGCTGCAGG	1	2	32	SEQ ID NO. 2021
(N20)NGG	19	17953132	-	GCGCAGGCTTGGGGGTAGGCAGG	1	4	37	SEQ ID NO. 2022
(N20)NGG	19	17953136	-	GGTCGCGCAGGCTTGGGGGTAGG	1	2	28	SEQ ID NO. 2023
(N20)NGG	19	17953140	-	ATCAGGTCGCGCAGGCTTGGGGG	1	1	5	SEQ ID NO. 2024
(N20)NGG	19	17953141	-	GATCAGGTCGCGCAGGCTTGGGG	1	1	10	SEQ ID NO. 2025
(N20)NGG	19	17953142	-	GGATCAGGTCGCGCAGGCTTGGG	1	1	11	SEQ ID NO. 2026
(N20)NGG	19	17953143	-	TGGATCAGGTCGCGCAGGCTTGG	1	1	4	SEQ ID NO. 2027
(N20)NGG	19	17953148	-	GGCCCTGGATCAGGTCGCGCAGG	1	3	8	SEQ ID NO. 2028
(N20)NGG	19	17953157	-	CGAAGCTCAGGCCCTGGATCAGG	1	3	34	SEQ ID NO. 2029
(N20)NGG	19	17953163	-	GCGTCACGAAGCTCAGGCCCTGG	1	1	13	SEQ ID NO. 2030
(N20)NGG	19	17953169	-	GCCTCCGCGTCACGAAGCTCAGG	1	1	25	SEQ ID NO. 2031
(N20)NGG	19	17953216	-	GCAGGCGGCCACGCGGCGCAGGG	1	3	21	SEQ ID NO. 2032
(N20)NGG	19	17953217	-	GGCAGGCGGCCACGCGGCGCAGG	1	3	35	SEQ ID NO. 2033
(N20)NGG	19	17953223	-	CTGCCTGGCAGGCGGCCACGCGG	2	8	56	SEQ ID NO. 2034
(N20)NGG	19	17953231	-	GTGCCGGTCTGCCTGGCAGGCGG	1	2	37	SEQ ID NO. 2035
(N20)NGG	19	17953234	-	CGAGTGCCGGTCTGCCTGGCAGG	1	2	14	SEQ ID NO. 2036
(N20)NGG	19	17953238	-	TGAGCGAGTGCCGGTCTGCCTGG	1	1	9	SEQ ID NO. 2037
(N20)NGG	19	17953247	-	ACTTGGCCATGAGCGAGTGCCGG	1	2	8	SEQ ID NO. 2038
(N20)NGG	19	17953264	-	CTCCAGGTCCATGATGTACTTGG	1	4	29	SEQ ID NO. 2039
(N20)NGG	19	17953280	-	CGGCTGGATCCAGCCGCTCCAGG	2	5	33	SEQ ID NO. 2040
(N20)NGG	19	17953296	-	AAGGTCTCGGCGGCCCCGGCTGG	1	2	12	SEQ ID NO. 2041
(N20)NGG	19	17953300	-	GTGGAAGGTCTCGGCGGCCCCGG	1	2	11	SEQ ID NO. 2042
(N20)NGG	19	17953306	-	GCCCACGTGGAAGGTCTCGGCGG	1	2	12	SEQ ID NO. 2043
(N20)NGG	19	17953309	-	GAGGCCCACGTGGAAGGTCTCGG	1	2	30	SEQ ID NO. 2044

FIG. 8 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	19	17953315	-	CCCAGGGAGGCCCACGTGGAAGG	1	4	102	SEQ ID NO. 2045
(N20)NGG	19	17953319	-	GGGCCCCAGGGAGGCCCACGTGG	2	8	88	SEQ ID NO. 2046
(N20)NGG	19	17953328	-	GGCCACCAAGGGCCCCAGGGAGG	1	8	112	SEQ ID NO. 2047
(N20)NGG	19	17953331	-	CGTGGCCACCAAGGGCCCCAGGG	1	6	45	SEQ ID NO. 2048
(N20)NGG	19	17953332	-	TCGTGGCCACCAAGGGCCCCAGG	1	3	42	SEQ ID NO. 2049
(N20)NGG	19	17953339	-	CAGCCCGTCGTGGCCACCAAGGG	1	1	46	SEQ ID NO. 2050
(N20)NGG	19	17953340	-	CCAGCCCGTCGTGGCCACCAAGG	1	4	59	SEQ ID NO. 2051
(N20)NGG	19	17953349	-	GGAGCAGCCCCAGCCCGTCGTGG	1	6	49	SEQ ID NO. 2052
(N20)NGG	19	17953370	-	TGCCGCCGTCACCAGCCACGCGG	1	1	14	SEQ ID NO. 2053
(N20)NGG	19	17953396	-	CTCCTGTTCTCCCTGGGTCCAGG	2	9	115	SEQ ID NO. 2054
(N20)NGG	19	17953402	-	CCTCACCTCCTGTTCTCCCTGGG	1	7	141	SEQ ID NO. 2055
(N20)NGG	19	17953403	-	CCCTCACCTCCTGTTCTCCCTGG	1	9	145	SEQ ID NO. 2056
(N20)NGG	19	17953850	+	CCCCCAGCACCGCAGTGACCTGG	1	5	53	SEQ ID NO. 2057
(N20)NGG	19	17953857	+	CACCGCAGTGACCTGGTGAGTGG	1	2	32	SEQ ID NO. 2058
(N20)NGG	19	17953858	+	ACCGCAGTGACCTGGTGAGTGGG	1	2	15	SEQ ID NO. 2059
(N20)NGG	19	17953871	+	GGTGAGTGGGCGCCTCCCCGTGG	1	4	34	SEQ ID NO. 2060
(N20)NGG	19	17953872	+	GTGAGTGGGCGCCTCCCCGTGGG	1	1	10	SEQ ID NO. 2061
(N20)NGG	19	17953886	+	CCCCGTGGGCCTCAGTCTCAAGG	1	6	39	SEQ ID NO. 2062
(N20)NGG	19	17953892	+	GGGCCTCAGTCTCAAGGAGCAGG	1	2	44	SEQ ID NO. 2063
(N20)NGG	19	17953893	+	GGCCTCAGTCTCAAGGAGCAGGG	1	2	36	SEQ ID NO. 2064
(N20)NGG	19	17953910	+	GCAGGGTGAGTGTCTCAGCCTGG	1	6	70	SEQ ID NO. 2065
(N20)NGG	19	17953919	+	GTGTCTCAGCCTGGCCGTGTTGG	1	4	32	SEQ ID NO. 2066
(N20)NGG	19	17953925	+	CAGCCTGGCCGTGTTGGACCTGG	1	10	30	SEQ ID NO. 2067
(N20)NGG	19	17953930	+	TGGCCGTGTTGGACCTGGCCCGG	1	1	15	SEQ ID NO. 2068
(N20)NGG	19	17953934	+	CGTGTTGGACCTGGCCCGGATGG	1	2	8	SEQ ID NO. 2069
(N20)NGG	19	17953946	+	GGCCCGGATGGCGCGAGAGCAGG	1	1	10	SEQ ID NO. 2070
(N20)NGG	19	17953954	+	TGGCGCGAGAGCAGGCCCAGCGG	1	4	34	SEQ ID NO. 2071
(N20)NGG	19	17953958	+	GCGAGAGCAGGCCCAGCGGCCGG	1	3	47	SEQ ID NO. 2072
(N20)NGG	19	17953959	+	CGAGAGCAGGCCCAGCGGCCGGG	1	9	45	SEQ ID NO. 2073
(N20)NGG	19	17953981	+	GAGAGCTGCTGAAGACTGTCAGG	1	3	36	SEQ ID NO. 2074
(N20)NGG	19	17953995	+	ACTGTCAGGTGAGAGCCACCAGG	2	5	65	SEQ ID NO. 2075
(N20)NGG	19	17954001	+	AGGTGAGAGCCACCAGGCTGTGG	3	27	432	SEQ ID NO. 2076
(N20)NGG	19	17954002	+	GGTGAGAGCCACCAGGCTGTGGG	1	5	69	SEQ ID NO. 2077

FIG. 8 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	19	17954003	+	GTGAGAGCCACCAGGCTGTGGGG	1	8	71	SEQ ID NO. 2078
(N20)NGG	19	17953816	-	GGTGCTGGGGGGCCGCCACAGGG	1	2	29	SEQ ID NO. 2079
(N20)NGG	19	17953817	-	CGGTGCTGGGGGGCCGCCACAGG	1	1	23	SEQ ID NO. 2080
(N20)NGG	19	17953827	-	CAGGTCACTGCGGTGCTGGGGGG	1	4	41	SEQ ID NO. 2081
(N20)NGG	19	17953828	-	CCAGGTCACTGCGGTGCTGGGGG	1	4	52	SEQ ID NO. 2082
(N20)NGG	19	17953829	-	ACCAGGTCACTGCGGTGCTGGGG	1	4	24	SEQ ID NO. 2083
(N20)NGG	19	17953830	-	CACCAGGTCACTGCGGTGCTGGG	1	1	29	SEQ ID NO. 2084
(N20)NGG	19	17953831	-	TCACCAGGTCACTGCGGTGCTGG	1	1	17	SEQ ID NO. 2085
(N20)NGG	19	17953837	-	GCCCACTCACCAGGTCACTGCGG	1	5	45	SEQ ID NO. 2086
(N20)NGG	19	17953846	-	CGGGGAGGCGCCCACTCACCAGG	1	3	35	SEQ ID NO. 2087
(N20)NGG	19	17953861	-	TGAGACTGAGGCCCACGGGGAGG	1	5	104	SEQ ID NO. 2088
(N20)NGG	19	17953864	-	CCTTGAGACTGAGGCCCACGGGG	1	4	29	SEQ ID NO. 2089
(N20)NGG	19	17953865	-	TCCTTGAGACTGAGGCCCACGGG	2	2	41	SEQ ID NO. 2090
(N20)NGG	19	17953866	-	CTCCTTGAGACTGAGGCCCACGG	2	8	69	SEQ ID NO. 2091
(N20)NGG	19	17953873	-	CACCCTGCTCCTTGAGACTGAGG	1	2	40	SEQ ID NO. 2092
(N20)NGG	19	17953906	-	GGGCCAGGTCCAACACGGCCAGG	1	2	24	SEQ ID NO. 2093
(N20)NGG	19	17953911	-	CATCCGGGCCAGGTCCAACACGG	1	2	19	SEQ ID NO. 2094
(N20)NGG	19	17953921	-	GCTCTCGCGCCATCCGGGCCAGG	1	1	6	SEQ ID NO. 2095
(N20)NGG	19	17953926	-	GGCCTGCTCTCGCGCCATCCGGG	1	1	16	SEQ ID NO. 2096
(N20)NGG	19	17953927	-	GGGCCTGCTCTCGCGCCATCCGG	1	2	12	SEQ ID NO. 2097
(N20)NGG	19	17953947	-	CAGCAGCTCTCCCGGCCGCTGGG	1	1	38	SEQ ID NO. 2098
(N20)NGG	19	17953948	-	TCAGCAGCTCTCCCGGCCGCTGG	1	1	25	SEQ ID NO. 2099
(N20)NGG	19	17953955	-	ACAGTCTTCAGCAGCTCTCCCGG	1	4	45	SEQ ID NO. 2100
(N20)NGG	19	17954206	+	ACAGCTTTTACTTCCCCAATTGG	1	5	52	SEQ ID NO. 2101
(N20)NGG	19	17954211	+	TTTTACTTCCCCAATTGGTTTGG	1	3	55	SEQ ID NO. 2102
(N20)NGG	19	17954212	+	TTTACTTCCCCAATTGGTTTGGG	1	2	32	SEQ ID NO. 2103
(N20)NGG	19	17954216	+	CTTCCCCAATTGGTTTGGGCTGG	1	1	14	SEQ ID NO. 2104
(N20)NGG	19	17954235	+	CTGGAGAAGTGCCACCGCTTCGG	1	2	13	SEQ ID NO. 2105
(N20)NGG	19	17954236	+	TGGAGAAGTGCCACCGCTTCGGG	1	2	14	SEQ ID NO. 2106
(N20)NGG	19	17954246	+	CCACCGCTTCGGGCTACGCAAGG	1	1	2	SEQ ID NO. 2107
(N20)NGG	19	17954252	+	CTTCGGGCTACGCAAGGATTTGG	1	2	4	SEQ ID NO. 2108
(N20)NGG	19	17954282	+	TATCCTTGACCTGCCAGTCCTGG	1	2	28	SEQ ID NO. 2109
(N20)NGG	19	17954300	+	CCTGGAGCACCTCTTTGCCCAGG	1	7	57	SEQ ID NO. 2110

FIG. 8 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	19	17954303	+	GGAGCACCTCTTTGCCCAGGTGG	1	4	46	SEQ ID NO. 2111
(N20)NGG	19	17954304	+	GAGCACCTCTTTGCCCAGGTGGG	1	6	43	SEQ ID NO. 2112
(N20)NGG	19	17954305	+	AGCACCTCTTTGCCCAGGTGGGG	1	7	64	SEQ ID NO. 2113
(N20)NGG	19	17954315	+	TGCCCAGGTGGGGTTCTGCCTGG	3	4	64	SEQ ID NO. 2114
(N20)NGG	19	17954316	+	GCCCAGGTGGGGTTCTGCCTGGG	2	4	58	SEQ ID NO. 2115
(N20)NGG	19	17954317	+	CCCAGGTGGGGTTCTGCCTGGGG	2	7	75	SEQ ID NO. 2116
(N20)NGG	19	17954163	-	GTGAGGAGAGGAGAGAACCCTGG	1	6	147	SEQ ID NO. 2117
(N20)NGG	19	17954175	-	GAAGTAAAAGCTGTGAGGAGAGG	1	7	74	SEQ ID NO. 2118
(N20)NGG	19	17954180	-	TTGGGGAAGTAAAAGCTGTGAGG	1	6	70	SEQ ID NO. 2119
(N20)NGG	19	17954197	-	TCTCCAGCCCAAACCAATTGGGG	1	1	40	SEQ ID NO. 2120
(N20)NGG	19	17954198	-	TTCTCCAGCCCAAACCAATTGGG	1	3	53	SEQ ID NO. 2121
(N20)NGG	19	17954199	-	CTTCTCCAGCCCAAACCAATTGG	1	3	46	SEQ ID NO. 2122
(N20)NGG	19	17954224	-	CCTTGCGTAGCCCGAAGCGGTGG	1	1	5	SEQ ID NO. 2123
(N20)NGG	19	17954227	-	AATCCTTGCGTAGCCCGAAGCGG	1	1	3	SEQ ID NO. 2124
(N20)NGG	19	17954253	-	TGGCAGGTCAAGGATAGCACTGG	1	1	40	SEQ ID NO. 2125
(N20)NGG	19	17954263	-	GCTCCAGGACTGGCAGGTCAAGG	1	3	62	SEQ ID NO. 2126
(N20)NGG	19	17954269	-	AGAGGTGCTCCAGGACTGGCAGG	1	4	60	SEQ ID NO. 2127
(N20)NGG	19	17954273	-	GCAAAGAGGTGCTCCAGGACTGG	1	2	34	SEQ ID NO. 2128
(N20)NGG	19	17954278	-	CCTGGGCAAAGAGGTGCTCCAGG	1	3	54	SEQ ID NO. 2129
(N20)NGG	19	17954287	-	AGAACCCCACCTGGGCAAAGAGG	2	2	46	SEQ ID NO. 2130
(N20)NGG	19	17954295	-	CCCCAGGCAGAACCCCACCTGGG	2	6	89	SEQ ID NO. 2131
(N20)NGG	19	17954296	-	ACCCCAGGCAGAACCCCACCTGG	1	4	61	SEQ ID NO. 2132
(N20)NGG	19	17954585	+	CTGATGGGACCATCCCCTGTAGG	1	2	22	SEQ ID NO. 2133
(N20)NGG	19	17954620	+	GTACCACTCCCTCTTTGCTCTGG	1	2	24	SEQ ID NO. 2134
(N20)NGG	19	17954626	+	CTCCCTCTTTGCTCTGGCCACGG	1	2	126	SEQ ID NO. 2135
(N20)NGG	19	17954629	+	CCTCTTTGCTCTGGCCACGGAGG	1	1	45	SEQ ID NO. 2136
(N20)NGG	19	17954643	+	CCACGGAGGACCTGTCCTGCTGG	1	1	24	SEQ ID NO. 2137
(N20)NGG	19	17954671	+	CCCGAGCCACATCTTCTCCGTGG	1	3	17	SEQ ID NO. 2138
(N20)NGG	19	17954674	+	GAGCCACATCTTCTCCGTGGAGG	1	2	23	SEQ ID NO. 2139
(N20)NGG	19	17954703	+	GCACCCAAGTCCTGCTGTACAGG	1	4	22	SEQ ID NO. 2140
(N20)NGG	19	17954709	+	AAGTCCTGCTGTACAGGATTCGG	1	1	32	SEQ ID NO. 2141
(N20)NGG	19	17954713	+	CCTGCTGTACAGGATTCGGTAGG	1	1	8	SEQ ID NO. 2142
(N20)NGG	19	17954572	-	GGCAGGATGCCTACAGGGGATGG	1	3	71	SEQ ID NO. 2143

FIG. 8 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	19	17954576	-	CACAGGCAGGATGCCTACAGGGG	1	8	69	SEQ ID NO. 2144
(N20)NGG	19	17954577	-	ACACAGGCAGGATGCCTACAGGG	1	5	54	SEQ ID NO. 2145
(N20)NGG	19	17954578	-	TACACAGGCAGGATGCCTACAGG	1	2	20	SEQ ID NO. 2146
(N20)NGG	19	17954589	-	AGAGGGAGTGGTACACAGGCAGG	1	5	64	SEQ ID NO. 2147
(N20)NGG	19	17954593	-	GCAAAGAGGGAGTGGTACACAGG	1	3	32	SEQ ID NO. 2148
(N20)NGG	19	17954601	-	TGGCCAGAGCAAAGAGGGAGTGG	2	15	482	SEQ ID NO. 2149
(N20)NGG	19	17954606	-	CTCCGTGGCCAGAGCAAAGAGGG	1	2	39	SEQ ID NO. 2150
(N20)NGG	19	17954607	-	CCTCCGTGGCCAGAGCAAAGAGG	1	7	41	SEQ ID NO. 2151
(N20)NGG	19	17954621	-	CCAGCAGGACAGGTCCTCCGTGG	1	1	32	SEQ ID NO. 2152
(N20)NGG	19	17954631	-	TCGGGGGGAACCAGCAGGACAGG	1	1	20	SEQ ID NO. 2153
(N20)NGG	19	17954636	-	GTGGCTCGGGGGGAACCAGCAGG	1	2	25	SEQ ID NO. 2154
(N20)NGG	19	17954646	-	CGGAGAAGATGTGGCTCGGGGGG	1	1	21	SEQ ID NO. 2155
(N20)NGG	19	17954647	-	ACGGAGAAGATGTGGCTCGGGGG	1	2	17	SEQ ID NO. 2156
(N20)NGG	19	17954648	-	CACGGAGAAGATGTGGCTCGGGG	1	2	12	SEQ ID NO. 2157
(N20)NGG	19	17954649	-	CCACGGAGAAGATGTGGCTCGGG	1	4	25	SEQ ID NO. 2158
(N20)NGG	19	17954650	-	TCCACGGAGAAGATGTGGCTCGG	1	3	31	SEQ ID NO. 2159
(N20)NGG	19	17954655	-	CATCCTCCACGGAGAAGATGTGG	1	2	32	SEQ ID NO. 2160
(N20)NGG	19	17954666	-	TTGGGTGCTGGCATCCTCCACGG	1	3	53	SEQ ID NO. 2161
(N20)NGG	19	17954678	-	GTACAGCAGGACTTGGGTGCTGG	1	3	38	SEQ ID NO. 2162
(N20)NGG	19	17954684	-	AATCCTGTACAGCAGGACTTGGG	1	2	38	SEQ ID NO. 2163
(N20)NGG	19	17954685	-	GAATCCTGTACAGCAGGACTTGG	1	2	25	SEQ ID NO. 2164
(N20)NGG	19	17954691	-	CCTACCGAATCCTGTACAGCAGG	1	1	2	SEQ ID NO. 2165
(N20)NGG	19	17955045	+	CCCCAGGCAAGTTGCACTCATGG	1	4	47	SEQ ID NO. 2166
(N20)NGG	19	17955105	+	TTCATGCAGCCTCTTGTCCACGG	1	2	48	SEQ ID NO. 2167
(N20)NGG	19	17955108	+	ATGCAGCCTCTTGTCCACGGAGG	1	2	13	SEQ ID NO. 2168
(N20)NGG	19	17955112	+	AGCCTCTTGTCCACGGAGGCTGG	1	1	19	SEQ ID NO. 2169
(N20)NGG	19	17955140	+	TGCATGTGCTGCTGCCCGCTCGG	1	2	22	SEQ ID NO. 2170
(N20)NGG	19	17955141	+	GCATGTGCTGCTGCCCGCTCGGG	1	3	27	SEQ ID NO. 2171
(N20)NGG	19	17955142	+	CATGTGCTGCTGCCCGCTCGGGG	1	2	7	SEQ ID NO. 2172
(N20)NGG	19	17955148	+	CTGCTGCCCGCTCGGGGCCCCGG	1	4	52	SEQ ID NO. 2173
(N20)NGG	19	17955149	+	TGCTGCCCGCTCGGGGCCCCGGG	1	1	51	SEQ ID NO. 2174
(N20)NGG	19	17955178	+	CAGCGCCTATCTTTCTCCTTTGG	1	2	27	SEQ ID NO. 2175
(N20)NGG	19	17955179	+	AGCGCCTATCTTTCTCCTTTGGG	1	2	23	SEQ ID NO. 2176

FIG. 8 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	19	17955180	+	GCGCCTATCTTTCTCCTTTGGGG	1	1	20	SEQ ID NO. 2177
(N20)NGG	19	17955189	+	TTTCTCCTTTGGGGACCACTTGG	1	3	51	SEQ ID NO. 2178
(N20)NGG	19	17955195	+	CTTTGGGGACCACTTGGCTGAGG	1	4	72	SEQ ID NO. 2179
(N20)NGG	19	17955210	+	GGCTGAGGACCTGTGCGTGCAGG	1	4	33	SEQ ID NO. 2180
(N20)NGG	19	17955219	+	CCTGTGCGTGCAGGCTGCCAAGG	1	4	40	SEQ ID NO. 2181
(N20)NGG	19	17955226	+	GTGCAGGCTGCCAAGGCCAGCGG	1	10	130	SEQ ID NO. 2182
(N20)NGG	19	17955244	+	AGCGGTGAGTGCATCCCTAGTGG	2	2	6	SEQ ID NO. 2183
(N20)NGG	19	17955249	+	TGAGTGCATCCCTAGTGGATCGG	1	2	31	SEQ ID NO. 2184
(N20)NGG	19	17955250	+	GAGTGCATCCCTAGTGGATCGGG	1	1	10	SEQ ID NO. 2185
(N20)NGG	19	17955023	-	CCATGAGTGCAACTTGCCTGGGG	1	12	546	SEQ ID NO. 2186
(N20)NGG	19	17955024	-	GCCATGAGTGCAACTTGCCTGGG	1	9	338	SEQ ID NO. 2187
(N20)NGG	19	17955025	-	TGCCATGAGTGCAACTTGCCTGG	1	3	34	SEQ ID NO. 2188
(N20)NGG	19	17955048	-	AGGGGCGTCTCTTCACTTGGAGG	1	1	17	SEQ ID NO. 2189
(N20)NGG	19	17955051	-	ATCAGGGGCGTCTCTTCACTTGG	1	1	12	SEQ ID NO. 2190
(N20)NGG	19	17955066	-	CATGAACGCTGAGGGATCAGGGG	1	2	19	SEQ ID NO. 2191
(N20)NGG	19	17955067	-	GCATGAACGCTGAGGGATCAGGG	1	1	23	SEQ ID NO. 2192
(N20)NGG	19	17955068	-	TGCATGAACGCTGAGGGATCAGG	1	1	21	SEQ ID NO. 2193
(N20)NGG	19	17955074	-	AGAGGCTGCATGAACGCTGAGGG	1	2	24	SEQ ID NO. 2194
(N20)NGG	19	17955075	-	AAGAGGCTGCATGAACGCTGAGG	1	2	34	SEQ ID NO. 2195
(N20)NGG	19	17955092	-	CACCAGCCTCCGTGGACAAGAGG	1	3	27	SEQ ID NO. 2196
(N20)NGG	19	17955100	-	ATGCAGGGCACCAGCCTCCGTGG	1	3	36	SEQ ID NO. 2197
(N20)NGG	19	17955115	-	AGCGGGCAGCAGCACATGCAGGG	2	4	58	SEQ ID NO. 2198
(N20)NGG	19	17955116	-	GAGCGGGCAGCAGCACATGCAGG	1	3	47	SEQ ID NO. 2199
(N20)NGG	19	17955132	-	GGGGGCCCGGGGCCCCGAGCGGG	1	13	120	SEQ ID NO. 2200
(N20)NGG	19	17955133	-	GGGGGGCCCGGGGCCCCGAGCGG	1	8	125	SEQ ID NO. 2201
(N20)NGG	19	17955143	-	ATAGGCGCTGGGGGGGCCCGGGG	1	2	13	SEQ ID NO. 2202
(N20)NGG	19	17955144	-	GATAGGCGCTGGGGGGGCCCGGG	1	2	33	SEQ ID NO. 2203
(N20)NGG	19	17955145	-	AGATAGGCGCTGGGGGGGCCCGG	1	1	26	SEQ ID NO. 2204
(N20)NGG	19	17955150	-	GAGAAAGATAGGCGCTGGGGGGG	1	1	45	SEQ ID NO. 2205
(N20)NGG	19	17955151	-	GGAGAAAGATAGGCGCTGGGGGG	1	9	159	SEQ ID NO. 2206
(N20)NGG	19	17955152	-	AGGAGAAAGATAGGCGCTGGGGG	1	3	129	SEQ ID NO. 2207
(N20)NGG	19	17955153	-	AAGGAGAAAGATAGGCGCTGGGG	1	5	50	SEQ ID NO. 2208
(N20)NGG	19	17955154	-	AAAGGAGAAAGATAGGCGCTGGG	1	5	45	SEQ ID NO. 2209

FIG. 8 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	19	17955155	-	CAAAGGAGAAAGATAGGCGCTGG	1	2	48	SEQ ID NO. 2210
(N20)NGG	19	17955161	-	GGTCCCCAAAGGAGAAAGATAGG	1	7	46	SEQ ID NO. 2211
(N20)NGG	19	17955172	-	CTCAGCCAAGTGGTCCCCAAAGG	1	5	40	SEQ ID NO. 2212
(N20)NGG	19	17955182	-	CGCACAGGTCCTCAGCCAAGTGG	1	3	20	SEQ ID NO. 2213
(N20)NGG	19	17955197	-	CCTTGGCAGCCTGCACGCACAGG	1	5	30	SEQ ID NO. 2214
(N20)NGG	19	17955214	-	GATGCACTCACCGCTGGCCTTGG	1	1	22	SEQ ID NO. 2215
(N20)NGG	19	17955220	-	ACTAGGGATGCACTCACCGCTGG	1	2	4	SEQ ID NO. 2216

FIG. 8 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	13	108860971	+	GAACGAATACAGAAAAGTAAAGG	1	4	132	SEQ ID NO. 2217
(N20)NGG	13	108860999	+	CAGAAAAAATCAGACACTTCAGG	2	4	102	SEQ ID NO. 2218
(N20)NGG	13	108861000	+	AGAAAAAATCAGACACTTCAGGG	1	7	193	SEQ ID NO. 2219
(N20)NGG	13	108861017	+	TCAGGGAATTTTTAGATTCTTGG	1	4	97	SEQ ID NO. 2220
(N20)NGG	13	108861120	+	TCAGCTAGAAAGAGAGAGAATGG	1	24	320	SEQ ID NO. 2221
(N20)NGG	13	108861127	+	GAAAGAGAGAGAATGGCCTATGG	1	9	187	SEQ ID NO. 2222
(N20)NGG	13	108861187	+	TTGCTTAATTTACCTAGAGATGG	1	3	71	SEQ ID NO. 2223
(N20)NGG	13	108861229	+	TTAAACTACAGAACACCCACTGG	1	2	40	SEQ ID NO. 2224
(N20)NGG	13	108861238	+	AGAACACCCACTGGAACTCATGG	1	5	43	SEQ ID NO. 2225
(N20)NGG	13	108861247	+	ACTGGAACTCATGGAGATGCTGG	1	3	54	SEQ ID NO. 2226
(N20)NGG	13	108861301	+	AAGCCAAGATGTTTACAGAAAGG	1	8	83	SEQ ID NO. 2227
(N20)NGG	13	108861434	+	GTTCAGCACTTGAGCAAAAGTGG	2	4	30	SEQ ID NO. 2228
(N20)NGG	13	108861443	+	TTGAGCAAAAGTGGCTTATACGG	1	1	42	SEQ ID NO. 2229
(N20)NGG	13	108861456	+	GCTTATACGGATGATCATAAAGG	1	2	11	SEQ ID NO. 2230
(N20)NGG	13	108861469	+	ATCATAAAGGATTTAAAGCTTGG	1	7	76	SEQ ID NO. 2231
(N20)NGG	13	108861543	+	GCATAATGTCACTACAGATCTGG	1	2	17	SEQ ID NO. 2232
(N20)NGG	13	108861557	+	CAGATCTGGAAAAAGTCTGTAGG	1	5	67	SEQ ID NO. 2233
(N20)NGG	13	108861580	+	CAACTGCATGATCCTTCTGTAGG	1	3	22	SEQ ID NO. 2234
(N20)NGG	13	108861663	+	AGATATTGAGCACATTGAGAAGG	1	3	47	SEQ ID NO. 2235
(N20)NGG	13	108861706	+	TACATAGAAACCAAGCTAGATGG	1	3	65	SEQ ID NO. 2236
(N20)NGG	13	108861733	+	CGTATGCAAATGCACAAAGATGG	1	6	63	SEQ ID NO. 2237
(N20)NGG	13	108861763	+	TATAAATACTTCTCTCGAAATGG	1	3	55	SEQ ID NO. 2238
(N20)NGG	13	108861787	+	TATAACTACACTGATCAGTTTGG	1	3	28	SEQ ID NO. 2239
(N20)NGG	13	108861805	+	TTTGGTGCTTCTCCTACTGAAGG	1	3	41	SEQ ID NO. 2240
(N20)NGG	13	108861868	+	ATACAAATCTGTATTCTTGATGG	1	4	80	SEQ ID NO. 2241
(N20)NGG	13	108861879	+	TATTCTTGATGGTGAGATGATGG	1	5	52	SEQ ID NO. 2242
(N20)NGG	13	108861915	+	TACACAAACTTTCATGCAAAAGG	1	6	92	SEQ ID NO. 2243
(N20)NGG	13	108861916	+	ACACAAACTTTCATGCAAAAGGG	1	9	109	SEQ ID NO. 2244
(N20)NGG	13	108861942	+	TAAGTTTGATATTAAAAGAATGG	1	13	223	SEQ ID NO. 2245
(N20)NGG	13	108861948	+	TGATATTAAAAGAATGGTAGAGG	1	7	109	SEQ ID NO. 2246
(N20)NGG	13	108861993	+	TTGTGTTTTTGATGTATTGATGG	1	8	188	SEQ ID NO. 2247
(N20)NGG	13	108862012	+	ATGGTTAATAATAAAAAGCTAGG	1	10	140	SEQ ID NO. 2248
(N20)NGG	13	108862013	+	TGGTTAATAATAAAAAGCTAGGG	1	5	129	SEQ ID NO. 2249
(N20)NGG	13	108862034	+	GGCATGAGACTCTGAGAAAGAGG	2	6	82	SEQ ID NO. 2250

FIG. 9

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	13	108862072	+	AGTATTTTTACACCAATTCCAGG	2	2	72	SEQ ID NO. 2251
(N20)NGG	13	108862161	+	AGCAATAGATAAAAGAGAAGAGG	1	13	203	SEQ ID NO. 2252
(N20)NGG	13	108862162	+	GCAATAGATAAAAGAGAAGAGGG	2	13	232	SEQ ID NO. 2253
(N20)NGG	13	108862170	+	TAAAAGAGAAGAGGGAATTATGG	1	13	241	SEQ ID NO. 2254
(N20)NGG	13	108862210	+	ATCTACAAGCCAGACAAAAGAGG	2	10	219	SEQ ID NO. 2255
(N20)NGG	13	108862216	+	AAGCCAGACAAAAGAGGTGAAGG	2	13	147	SEQ ID NO. 2256
(N20)NGG	13	108862217	+	AGCCAGACAAAAGAGGTGAAGGG	1	7	94	SEQ ID NO. 2257
(N20)NGG	13	108862220	+	CAGACAAAAGAGGTGAAGGGTGG	1	5	107	SEQ ID NO. 2258
(N20)NGG	13	108862249	+	ATTAAACCAGAGTATGTCAGTGG	1	4	25	SEQ ID NO. 2259
(N20)NGG	13	108862257	+	AGAGTATGTCAGTGGACTAATGG	1	3	40	SEQ ID NO. 2260
(N20)NGG	13	108862266	+	CAGTGGACTAATGGATGAATTGG	2	6	92	SEQ ID NO. 2261
(N20)NGG	13	108862282	+	GAATTGGACATTTTAATTGTTGG	1	8	108	SEQ ID NO. 2262
(N20)NGG	13	108862285	+	TTGGACATTTTAATTGTTGGAGG	1	5	89	SEQ ID NO. 2263
(N20)NGG	13	108862292	+	TTTTAATTGTTGGAGGATATTGG	1	3	107	SEQ ID NO. 2264
(N20)NGG	13	108862293	+	TTTAATTGTTGGAGGATATTGGG	1	7	118	SEQ ID NO. 2265
(N20)NGG	13	108862294	+	TTAATTGTTGGAGGATATTGGGG	1	4	60	SEQ ID NO. 2266
(N20)NGG	13	108862300	+	GTTGGAGGATATTGGGGTAAAGG	1	4	35	SEQ ID NO. 2267
(N20)NGG	13	108862307	+	GATATTGGGGTAAAGGATCACGG	1	2	25	SEQ ID NO. 2268
(N20)NGG	13	108862308	+	ATATTGGGGTAAAGGATCACGGG	1	3	23	SEQ ID NO. 2269
(N20)NGG	13	108862309	+	TATTGGGGTAAAGGATCACGGGG	1	2	16	SEQ ID NO. 2270
(N20)NGG	13	108862312	+	TGGGGTAAAGGATCACGGGGTGG	1	2	18	SEQ ID NO. 2271
(N20)NGG	13	108862360	+	GTAGCAGAGAAGCCCCCTCCTGG	1	2	35	SEQ ID NO. 2272
(N20)NGG	13	108862399	+	TTTCATACTCTCTCTCGTGTTGG	1	2	23	SEQ ID NO. 2273
(N20)NGG	13	108862400	+	TTCATACTCTCTCTCGTGTTGGG	1	1	30	SEQ ID NO. 2274
(N20)NGG	13	108862405	+	ACTCTCTCTCGTGTTGGGTCTGG	1	1	13	SEQ ID NO. 2275
(N20)NGG	13	108862434	+	CATGAAAGAACTGTATGATCTGG	1	2	41	SEQ ID NO. 2276
(N20)NGG	13	108862435	+	ATGAAAGAACTGTATGATCTGGG	1	4	76	SEQ ID NO. 2277
(N20)NGG	13	108862446	+	GTATGATCTGGGTTTGAAATTGG	1	2	51	SEQ ID NO. 2278
(N20)NGG	13	108862457	+	GTTTGAAATTGGCCAAGTATTGG	1	5	44	SEQ ID NO. 2279
(N20)NGG	13	108862501	+	CCACCAAGCAGCATTTTATGTGG	1	3	44	SEQ ID NO. 2280
(N20)NGG	13	108862597	+	CCCAGTGATATGTATAAAACTGG	1	4	34	SEQ ID NO. 2281
(N20)NGG	13	108862644	+	TGAAAAGATAAGAGATGACAAGG	1	10	202	SEQ ID NO. 2282
(N20)NGG	13	108862649	+	AGATAAGAGATGACAAGGAGTGG	2	11	152	SEQ ID NO. 2283
(N20)NGG	13	108862668	+	GTGGCATGAGTGCATGACCCTGG	1	1	50	SEQ ID NO. 2284

FIG. 9 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	13	108862688	+	TGGACGACCTAGAACAACTTAGG	1	2	8	SEQ ID NO. 2285
(N20)NGG	13	108862689	+	GGACGACCTAGAACAACTTAGGG	1	2	6	SEQ ID NO. 2286
(N20)NGG	13	108862690	+	GACGACCTAGAACAACTTAGGGG	1	1	12	SEQ ID NO. 2287
(N20)NGG	13	108862691	+	ACGACCTAGAACAACTTAGGGGG	1	1	14	SEQ ID NO. 2288
(N20)NGG	13	108862695	+	CCTAGAACAACTTAGGGGGAAGG	1	1	21	SEQ ID NO. 2289
(N20)NGG	13	108862702	+	CAACTTAGGGGGAAGGCATCTGG	1	4	59	SEQ ID NO. 2290
(N20)NGG	13	108862732	+	GCATCTAAACACCTTTATATAGG	1	4	38	SEQ ID NO. 2291
(N20)NGG	13	108862735	+	TCTAAACACCTTTATATAGGTGG	1	2	40	SEQ ID NO. 2292
(N20)NGG	13	108862763	+	ATGAACCACAAGAAAAAAAGCGG	1	8	286	SEQ ID NO. 2293
(N20)NGG	13	108862795	+	CCAAAGATGAAGAAAGTTATTGG	1	10	120	SEQ ID NO. 2294
(N20)NGG	13	108862885	+	GTAGAGTTTTGTGTTATGAGTGG	1	2	38	SEQ ID NO. 2295
(N20)NGG	13	108862914	+	TAGCCAGCCAAAGCCTGACCTGG	1	2	19	SEQ ID NO. 2296
(N20)NGG	13	108862936	+	GAGAACAGAATTGCAGAATTTGG	1	8	110	SEQ ID NO. 2297
(N20)NGG	13	108862939	+	AACAGAATTGCAGAATTTGGTGG	1	6	106	SEQ ID NO. 2298
(N20)NGG	13	108862960	+	GGTTATATAGTACAAAATCCAGG	1	2	21	SEQ ID NO. 2299
(N20)NGG	13	108862987	+	GACACGTACTGTGTAATTCCAGG	1	1	13	SEQ ID NO. 2300
(N20)NGG	13	108862988	+	ACACGTACTGTGTAATTGCAGGG	1	2	19	SEQ ID NO. 2301
(N20)NGG	13	108863054	+	ATGATGTTGTCAAGCCTGCATGG	1	5	38	SEQ ID NO. 2302
(N20)NGG	13	108863093	+	AGACCAAAAGCTTTGTACCATGG	1	3	40	SEQ ID NO. 2303
(N20)NGG	13	108863164	+	GCCCGTGAATATGATTGCTATGG	1	2	7	SEQ ID NO. 2304
(N20)NGG	13	108863205	+	TACAGACTTGAACCAACTGAAGG	1	1	38	SEQ ID NO. 2305
(N20)NGG	13	108863218	+	CAACTGAAGGAAGTATTCTCAGG	1	1	41	SEQ ID NO. 2306
(N20)NGG	13	108863256	+	CGAGCAGACTCCTGAAGAAATGG	1	2	37	SEQ ID NO. 2307
(N20)NGG	13	108863285	+	TGATTGCTGATTTAGAATATCGG	1	4	88	SEQ ID NO. 2308
(N20)NGG	13	108863294	+	ATTTAGAATATCGGTATTCCTGG	1	1	18	SEQ ID NO. 2309
(N20)NGG	13	108863295	+	TTTAGAATATCGGTATTCCTGGG	1	2	27	SEQ ID NO. 2310
(N20)NGG	13	108863340	+	TCGACGCCACACCGTTTATTTGG	1	1	2	SEQ ID NO. 2311
(N20)NGG	13	108863382	+	TGACCTGAGTACCAAAAATGAGG	1	3	33	SEQ ID NO. 2312
(N20)NGG	13	108863383	+	GACCTGAGTACCAAAAATGAGGG	1	2	32	SEQ ID NO. 2313
(N20)NGG	13	108863384	+	ACCTGAGTACCAAAAATGAGGGG	1	5	34	SEQ ID NO. 2314
(N20)NGG	13	108863390	+	GTACCAAAAATGAGGGGACAAGG	2	2	41	SEQ ID NO. 2315
(N20)NGG	13	108863409	+	AAGGTTAGCTATTAAAGCCTTGG	1	4	27	SEQ ID NO. 2316
(N20)NGG	13	108863417	+	CTATTAAAGCCTTGGAGCTTCGG	1	2	31	SEQ ID NO. 2317
(N20)NGG	13	108863425	+	GCCTTGGAGCTTCGGTTTCATGG	1	3	18	SEQ ID NO. 2318

FIG. 9 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	13	108863454	+	AGTAGTTTCTTGTTTAGCTGAGG	1	5	47	SEQ ID NO. 2319
(N20)NGG	13	108863455	+	GTAGTTTCTTGTTTAGCTGAGGG	1	4	51	SEQ ID NO. 2320
(N20)NGG	13	108863476	+	GGAGTGTCTCATGTAATAATTGG	1	2	29	SEQ ID NO. 2321
(N20)NGG	13	108863477	+	GAGTGTCTCATGTAATAATTGGG	1	7	48	SEQ ID NO. 2322
(N20)NGG	13	108863478	+	AGTGTCTCATGTAATAATTGGGG	1	6	62	SEQ ID NO. 2323
(N20)NGG	13	108863558	+	TTAAAATCCTAAAAGAAAGTTGG	2	22	272	SEQ ID NO. 2324
(N20)NGG	13	108863559	+	TAAAATCCTAAAAGAAAGTTGGG	2	14	269	SEQ ID NO. 2325
(N20)NGG	13	108860887	-	AACAGTTTGTGAAGTTTGTGAGG	1	6	80	SEQ ID NO. 2326
(N20)NGG	13	108860922	-	GTTGAACACAAATCTGCAAAAGG	1	6	72	SEQ ID NO. 2327
(N20)NGG	13	108861047	-	AAGAGTCTGTGACATCTTTGTGG	1	5	70	SEQ ID NO. 2328
(N20)NGG	13	108861075	-	GGAAGAATTAGTCTCATTGCTGG	1	2	28	SEQ ID NO. 2329
(N20)NGG	13	108861096	-	ATTCTCTCTCTTTCTAGCTGAGG	1	10	144	SEQ ID NO. 2330
(N20)NGG	13	108861121	-	CATAGTTTCTTTAATTCCATAGG	1	15	131	SEQ ID NO. 2331
(N20)NGG	13	108861177	-	AGGGCATCTTTTCCATCTCTAGG	1	4	72	SEQ ID NO. 2332
(N20)NGG	13	108861196	-	TCTGTAGTTTAAAAGTTTGAGGG	1	14	139	SEQ ID NO. 2333
(N20)NGG	13	108861197	-	TTCTGTAGTTTAAAAGTTTGAGG	1	12	235	SEQ ID NO. 2334
(N20)NGG	13	108861222	-	GCATCTCCATGAGTTCCAGTGGG	1	1	33	SEQ ID NO. 2335
(N20)NGG	13	108861223	-	AGCATCTCCATGAGTTCCAGTGG	1	4	57	SEQ ID NO. 2336
(N20)NGG	13	108861282	-	CTTCCTTTCTGTAAACATCTTGG	2	9	100	SEQ ID NO. 2337
(N20)NGG	13	108861310	-	AAGGTCGTTTACTTGCTGTATGG	1	1	14	SEQ ID NO. 2338
(N20)NGG	13	108861329	-	TGCTGGCAATTGAGTCTAAAAGG	1	2	27	SEQ ID NO. 2339
(N20)NGG	13	108861346	-	TCTTTTAGCAGAATTATTGCTGG	1	5	61	SEQ ID NO. 2340
(N20)NGG	13	108861374	-	GAAGAAGGCTCTTTTTTATTAGG	1	4	98	SEQ ID NO. 2341
(N20)NGG	13	108861389	-	TCTGAGTTATAAGTTGAAGAAGG	1	2	58	SEQ ID NO. 2342
(N20)NGG	13	108861570	-	ATATCACTGAGTCCTACAGAAGG	1	4	39	SEQ ID NO. 2343
(N20)NGG	13	108861621	-	TCTGCAATAGCAGCTAGCATTGG	1	1	31	SEQ ID NO. 2344
(N20)NGG	13	108861694	-	CATACGTTCACCATCTAGCTTGG	1	1	15	SEQ ID NO. 2345
(N20)NGG	13	108861795	-	GGGGTAAGAGAACCTTCAGTAGG	1	1	18	SEQ ID NO. 2346
(N20)NGG	13	108861814	-	GAATGCATTATGAATGAATGGGG	2	21	230	SEQ ID NO. 2347
(N20)NGG	13	108861815	-	TGAATGCATTATGAATGAATGGG	2	32	329	SEQ ID NO. 2348
(N20)NGG	13	108861816	-	TTGAATGCATTATGAATGAATGG	1	10	174	SEQ ID NO. 2349
(N20)NGG	13	108861880	-	AGTTTGTGTATTAGGATTATAGG	1	3	41	SEQ ID NO. 2350
(N20)NGG	13	108861888	-	TGCATGAAAGTTTGTGTATTAGG	1	5	76	SEQ ID NO. 2351
(N20)NGG	13	108862062	-	ATTTCTATTCTACCTGGAATTGG	1	5	154	SEQ ID NO. 2352

FIG. 9 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	13	108862068	-	TGCACTATTTCTATTCTACCTGG	1	4	37	SEQ ID NO. 2353
(N20)NGG	13	108862179	-	TCTGGCTTGTAGATGGATAGAGG	1	5	35	SEQ ID NO. 2354
(N20)NGG	13	108862186	-	TCTTTTGTCTGGCTTGTAGATGG	1	4	81	SEQ ID NO. 2355
(N20)NGG	13	108862197	-	CACCCTTCACCTCTTTTGTCTGG	1	8	33	SEQ ID NO. 2356
(N20)NGG	13	108862233	-	ATTAGTCCACTGACATACTCTGG	1	2	24	SEQ ID NO. 2357
(N20)NGG	13	108862350	-	GATGGCTTCTCACCAGGAGGGGG	1	9	121	SEQ ID NO. 2358
(N20)NGG	13	108862351	-	AGATGGCTTCTCACCAGGAGGGG	1	4	53	SEQ ID NO. 2359
(N20)NGG	13	108862352	-	CAGATGGCTTCTCACCAGGAGGG	2	8	60	SEQ ID NO. 2360
(N20)NGG	13	108862353	-	ACAGATGGCTTCTCACCAGGAGG	2	5	74	SEQ ID NO. 2361
(N20)NGG	13	108862356	-	AACACAGATGGCTTCTCACCAGG	1	5	49	SEQ ID NO. 2362
(N20)NGG	13	108862368	-	GAGAGAGTATGAAACACAGATGG	1	15	279	SEQ ID NO. 2363
(N20)NGG	13	108862411	-	CAGATCATACAGTTCTTTCATGG	1	5	51	SEQ ID NO. 2364
(N20)NGG	13	108862447	-	ATGAAAAGGCTTCCAATACTTGG	1	1	36	SEQ ID NO. 2365
(N20)NGG	13	108862461	-	GGTGGAGCTTTTCTATGAAAAGG	1	4	45	SEQ ID NO. 2366
(N20)NGG	13	108862479	-	CCACATAAAATGCTGCTTGGTGG	1	2	44	SEQ ID NO. 2367
(N20)NGG	13	108862482	-	GTTCCACATAAAATGCTGCTTGG	1	2	44	SEQ ID NO. 2368
(N20)NGG	13	108862512	-	CAAGGTTCAATGTATACTTCTGG	1	2	24	SEQ ID NO. 2369
(N20)NGG	13	108862530	-	TGAACAATGACAGAATTACAAGG	1	8	103	SEQ ID NO. 2370
(N20)NGG	13	108862575	-	CCAGTTTTATACATATCACTGGG	1	3	54	SEQ ID NO. 2371
(N20)NGG	13	108862576	-	GCCAGTTTTATACATATCACTGG	1	2	26	SEQ ID NO. 2372
(N20)NGG	13	108862603	-	TTCAATTCGTGGAAAACGCAAGG	1	2	13	SEQ ID NO. 2373
(N20)NGG	13	108862614	-	TCTCTTATCTTTTCAATTCGTGG	1	3	54	SEQ ID NO. 2374
(N20)NGG	13	108862663	-	AAGTTGTTCTAGGTCGTCCAGGG	1	2	9	SEQ ID NO. 2375
(N20)NGG	13	108862664	-	TAAGTTGTTCTAGGTCGTCCAGG	1	1	8	SEQ ID NO. 2376
(N20)NGG	13	108862673	-	CCTTCCCCCTAAGTTGTTCTAGG	1	4	40	SEQ ID NO. 2377
(N20)NGG	13	108862721	-	CATCATCACCACCTATATAAAGG	1	6	43	SEQ ID NO. 2378
(N20)NGG	13	108862746	-	GCTTTCCGCTTTTTTTCTTGTGG	1	4	72	SEQ ID NO. 2379
(N20)NGG	13	108862771	-	AATAACTTTCTTCATCTTTGGGG	3	14	170	SEQ ID NO. 2380
(N20)NGG	13	108862772	-	CAATAACTTTCTTCATCTTTGGG	1	13	151	SEQ ID NO. 2381
(N20)NGG	13	108862773	-	CCAATAACTTTCTTCATCTTTGG	1	5	82	SEQ ID NO. 2382
(N20)NGG	13	108862818	-	TTGTTAACGTTAGTAAGGTTAGG	1	2	14	SEQ ID NO. 2383
(N20)NGG	13	108862823	-	AAATTTTGTTAACGTTAGTAAGG	1	3	83	SEQ ID NO. 2384
(N20)NGG	13	108862895	-	TCTCCAGGTCAGGCTTTGGCTGG	1	2	36	SEQ ID NO. 2385
(N20)NGG	13	108862899	-	CTGTTCTCCAGGTCAGGCTTTGG	1	4	47	SEQ ID NO. 2386

FIG. 9 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	13	108862905	-	GCAATTCTGTTCTCCAGGTCAGG	1	4	30	SEQ ID NO. 2387
(N20)NGG	13	108862910	-	ATTCTGCAATTCTGTTCTCCAGG	1	4	92	SEQ ID NO. 2388
(N20)NGG	13	108862956	-	ACACAGTACGTGTCTGGGCCTGG	1	3	21	SEQ ID NO. 2389
(N20)NGG	13	108862961	-	CAATTACACAGTACGTGTCTGGG	1	2	21	SEQ ID NO. 2390
(N20)NGG	13	108862962	-	GCAATTACACAGTACGTGTCTGG	1	3	12	SEQ ID NO. 2391
(N20)NGG	13	108863046	-	AAACATTCTAAAAGCCATGCAGG	2	5	51	SEQ ID NO. 2392
(N20)NGG	13	108863074	-	CTGCCATGGTACAAAGCTTTTGG	1	2	31	SEQ ID NO. 2393
(N20)NGG	13	108863088	-	ATCATAAAGCGAGGCTGCCATGG	1	1	14	SEQ ID NO. 2394
(N20)NGG	13	108863097	-	CACATATGAATCATAAAGCGAGG	1	2	22	SEQ ID NO. 2395
(N20)NGG	13	108863120	-	CAAAATGTTCTTTGGTTGATGGG	1	8	84	SEQ ID NO. 2396
(N20)NGG	13	108863121	-	GCAAAATGTTCTTTGGTTGATGG	1	5	77	SEQ ID NO. 2397
(N20)NGG	13	108863128	-	TTCACGGGCAAAATGTTCTTTGG	1	2	19	SEQ ID NO. 2398
(N20)NGG	13	108863143	-	ACCATAGCAATCATATTCACGGG	1	1	26	SEQ ID NO. 2399
(N20)NGG	13	108863144	-	CACCATAGCAATCATATTCACGG	1	4	44	SEQ ID NO. 2400
(N20)NGG	13	108863195	-	CTGAGAATACTTCCTTCAGTTGG	1	2	48	SEQ ID NO. 2401
(N20)NGG	13	108863244	-	ATCAGAGAAGCCATTTCTTCAGG	1	3	79	SEQ ID NO. 2402
(N20)NGG	13	108863290	-	ACTGAGAGGAGAGCAATCCCAGG	1	2	43	SEQ ID NO. 2403
(N20)NGG	13	108863304	-	TGGCGTCGAAACATACTGAGAGG	1	1	3	SEQ ID NO. 2404
(N20)NGG	13	108863324	-	ACGAGTCCAAATAAACGGTGTGG	1	1	4	SEQ ID NO. 2405
(N20)NGG	13	108863329	-	AGCATACGAGTCCAAATAAACGG	1	1	16	SEQ ID NO. 2406
(N20)NGG	13	108863363	-	TCCCCTCATTTTTGGTACTCAGG	1	3	46	SEQ ID NO. 2407
(N20)NGG	13	108863371	-	TAACCTTGTCCCCTCATTTTTGG	1	2	42	SEQ ID NO. 2408
(N20)NGG	13	108863404	-	TCCATGAAACCGAAGCTCCAAGG	1	3	21	SEQ ID NO. 2409
(N20)NGG	13	108863543	-	CAGTTACCCAACTTTCTTTTAGG	1	3	56	SEQ ID NO. 2410

FIG. 9 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	2	219941102	+	ACTTGGGTTCCCTTTTTTCTAGG	1	3	85	SEQ ID NO. 2411
(N20)NGG	2	219941103	+	CTTGGGTTCCCTTTTTTCTAGGG	1	4	98	SEQ ID NO. 2412
(N20)NGG	2	219941112	+	CCTTTTTTCTAGGGTACTTCAGG	1	5	42	SEQ ID NO. 2413
(N20)NGG	2	219941141	+	GCAGAGACCTCAGCTGTCAAAGG	2	7	49	SEQ ID NO. 2414
(N20)NGG	2	219941149	+	CTCAGCTGTCAAAGGTCAAGAGG	1	5	67	SEQ ID NO. 2415
(N20)NGG	2	219941161	+	AGGTCAAGAGGAAGAAGCCAAGG	1	12	171	SEQ ID NO. 2416
(N20)NGG	2	219941162	+	GGTCAAGAGGAAGAAGCCAAGGG	1	9	103	SEQ ID NO. 2417
(N20)NGG	2	219941163	+	GTCAAGAGGAAGAAGCCAAGGGG	1	6	120	SEQ ID NO. 2418
(N20)NGG	2	219941186	+	TCTCTTCAGTTAATCTGTTGTGG	1	2	51	SEQ ID NO. 2419
(N20)NGG	2	219941201	+	TGTTGTGGCCTCAGCTGCTGAGG	2	5	75	SEQ ID NO. 2420
(N20)NGG	2	219941089	-	CTGAAGTACCCTAGAAAAAAGGG	2	2	53	SEQ ID NO. 2421
(N20)NGG	2	219941090	-	CCTGAAGTACCCTAGAAAAAAGG	1	5	44	SEQ ID NO. 2422
(N20)NGG	2	219941113	-	ACAGCTGAGGTCTCTGCAGAGGG	1	13	200	SEQ ID NO. 2423
(N20)NGG	2	219941114	-	GACAGCTGAGGTCTCTGCAGAGG	3	7	90	SEQ ID NO. 2424
(N20)NGG	2	219941126	-	CTCTTGACCTTTGACAGCTGAGG	2	5	47	SEQ ID NO. 2425
(N20)NGG	2	219941156	-	GATTAACTGAAGAGACCCCTTGG	1	1	16	SEQ ID NO. 2426
(N20)NGG	2	219941967	+	CTCTTGATCTTTCTGATTTCAGG	1	5	119	SEQ ID NO. 2427
(N20)NGG	2	219942003	+	TCAAACAGTGCTTCCCTGCAAGG	1	3	57	SEQ ID NO. 2428
(N20)NGG	2	219942041	+	TGTAAACCAGCCAGAACAACTGG	1	4	61	SEQ ID NO. 2429
(N20)NGG	2	219942086	+	AGCACCTGAGAAAGAGTCCACGG	1	2	66	SEQ ID NO. 2430
(N20)NGG	2	219942108	+	GTGAGTCATGAGCAGCTTCCTGG	1	1	30	SEQ ID NO. 2431
(N20)NGG	2	219941972	-	GAAGCACTGTTTGAGGTATGAGG	1	3	40	SEQ ID NO. 2432
(N20)NGG	2	219941979	-	TTGCAGGGAAGCACTGTTTGAGG	1	2	54	SEQ ID NO. 2433
(N20)NGG	2	219941994	-	TTGGCTATCGATTCCTTGCAGGG	1	2	7	SEQ ID NO. 2434
(N20)NGG	2	219941995	-	ATTGGCTATCGATTCCTTGCAGG	1	1	30	SEQ ID NO. 2435
(N20)NGG	2	219942013	-	GTTCTGGCTGGTTTACACATTGG	1	3	38	SEQ ID NO. 2436
(N20)NGG	2	219942025	-	AGGAGACCAGTTGTTCTGGCTGG	1	1	31	SEQ ID NO. 2437
(N20)NGG	2	219942029	-	GCTGAGGAGACCAGTTGTTCTGG	1	1	23	SEQ ID NO. 2438
(N20)NGG	2	219942045	-	TGCTGAGAGGGTTGGGGCTGAGG	1	12	181	SEQ ID NO. 2439
(N20)NGG	2	219942051	-	CTCAGGTGCTGAGAGGGTTGGGG	1	7	79	SEQ ID NO. 2440
(N20)NGG	2	219942052	-	TCTCAGGTGCTGAGAGGGTTGGG	1	2	73	SEQ ID NO. 2441
(N20)NGG	2	219942053	-	TTCTCAGGTGCTGAGAGGGTTGG	1	6	74	SEQ ID NO. 2442
(N20)NGG	2	219942057	-	CTCTTTCTCAGGTGCTGAGAGGG	1	3	80	SEQ ID NO. 2443
(N20)NGG	2	219942058	-	ACTCTTTCTCAGGTGCTGAGAGG	1	2	58	SEQ ID NO. 2444

FIG. 10

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	2	219942068	-	CTCACCGTGGACTCTTTCTCAGG	1	2	39	SEQ ID NO. 2445
(N20)NGG	2	219942081	-	AAGCTGCTCATGACTCACCGTGG	1	1	9	SEQ ID NO. 2446
(N20)NGG	2	219942822	+	TCTCTTACAGAAACTGCCAGAGG	1	5	60	SEQ ID NO. 2447
(N20)NGG	2	219942835	+	CTGCCAGAGGCATGCAGCATTGG	1	2	42	SEQ ID NO. 2448
(N20)NGG	2	219942841	+	GAGGCATGCAGCATTGGTGATGG	1	6	90	SEQ ID NO. 2449
(N20)NGG	2	219942867	+	GCCCTTTGTCATGAATCTGCAGG	1	2	33	SEQ ID NO. 2450
(N20)NGG	2	219942879	+	GAATCTGCAGGATCTGTATATGG	1	5	31	SEQ ID NO. 2451
(N20)NGG	2	219942897	+	TATGGCAGTCACCACACAAGAGG	1	3	28	SEQ ID NO. 2452
(N20)NGG	2	219942906	+	CACCACACAAGAGGTCCAAGTGG	1	2	32	SEQ ID NO. 2453
(N20)NGG	2	219942907	+	ACCACACAAGAGGTCCAAGTGGG	1	2	30	SEQ ID NO. 2454
(N20)NGG	2	219942922	+	CAAGTGGGACAGAAGCATCAAGG	1	3	52	SEQ ID NO. 2455
(N20)NGG	2	219942928	+	GGACAGAAGCATCAAGGCGCTGG	1	2	24	SEQ ID NO. 2456
(N20)NGG	2	219942943	+	GGCGCTGGTGAGCCCTCCAGAGG	1	1	30	SEQ ID NO. 2457
(N20)NGG	2	219942950	+	GTGAGCCCTCCAGAGGTACCCGG	1	1	23	SEQ ID NO. 2458
(N20)NGG	2	219942796	-	TGGCAGTTTCTGTAAGAGAGAGG	1	3	78	SEQ ID NO. 2459
(N20)NGG	2	219942816	-	TCACCAATGCTGCATGCCTCTGG	1	2	32	SEQ ID NO. 2460
(N20)NGG	2	219942846	-	TCCTGCAGATTCATGACAAAGGG	1	2	47	SEQ ID NO. 2461
(N20)NGG	2	219942847	-	ATCCTGCAGATTCATGACAAAGG	1	2	32	SEQ ID NO. 2462
(N20)NGG	2	219942886	-	TCCCACTTGGACCTCTTGTGTGG	1	2	60	SEQ ID NO. 2463
(N20)NGG	2	219942899	-	CTTGATGCTTCTGTCCCACTTGG	1	3	31	SEQ ID NO. 2464
(N20)NGG	2	220011442	+	ATTTGAAGAAAATTCCTTCTTGG	1	15	228	SEQ ID NO. 2465
(N20)NGG	2	220011460	+	CTTGGAACAATTTATGATAGAGG	1	5	45	SEQ ID NO. 2466
(N20)NGG	2	220011465	+	AACAATTTATGATAGAGGTAAGG	1	2	83	SEQ ID NO. 2467
(N20)NGG	2	220011387	-	TCAATCGATCTGTAATAAGAAGG	1	1	25	SEQ ID NO. 2468
(N20)NGG	2	220011418	-	AAGAAGGAATTTTCTTCAAATGG	1	16	274	SEQ ID NO. 2469
(N20)NGG	2	220011434	-	TATCATAAATTGTTCCAAGAAGG	1	5	55	SEQ ID NO. 2470
(N20)NGG	2	220012378	+	ATTGATATCTCTTCCCTCAAAGG	1	1	67	SEQ ID NO. 2471
(N20)NGG	2	220012408	+	ACATTTGATTCGTCCTCTGATGG	1	2	14	SEQ ID NO. 2472
(N20)NGG	2	220012409	+	CATTTGATTCGTCCTCTGATGGG	1	3	17	SEQ ID NO. 2473
(N20)NGG	2	220012420	+	TCCTCTGATGGGCATGAGTCTGG	1	1	44	SEQ ID NO. 2474
(N20)NGG	2	220012440	+	TGGCATTACAGTGCCAAGTGAGG	1	4	37	SEQ ID NO. 2475
(N20)NGG	2	220012441	+	GGCATTACAGTGCCAAGTGAGGG	1	1	26	SEQ ID NO. 2476
(N20)NGG	2	220012492	+	CCTAGAGATCCAAGACTACCAGG	1	1	12	SEQ ID NO. 2477
(N20)NGG	2	220012499	+	ATCCAAGACTACCAGGAGAGTGG	1	4	42	SEQ ID NO. 2478

FIG. 10 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	2	220012500	+	TCCAAGACTACCAGGAGAGTGGG	1	6	44	SEQ ID NO. 2479
(N20)NGG	2	220012501	+	CCAAGACTACCAGGAGAGTGGGG	2	4	44	SEQ ID NO. 2480
(N20)NGG	2	220012517	+	AGTGGGGCTACGCTGATTCGAGG	1	1	5	SEQ ID NO. 2481
(N20)NGG	2	220012524	+	CTACGCTGATTCGAGGTAAGAGG	1	1	5	SEQ ID NO. 2482
(N20)NGG	2	220012534	+	TCGAGGTAAGAGGACATTCTTGG	1	2	55	SEQ ID NO. 2483
(N20)NGG	2	220012537	+	AGGTAAGAGGACATTCTTGGAGG	1	3	66	SEQ ID NO. 2484
(N20)NGG	2	220012369	-	AAATGTTGGGAGACCTTTGAGGG	1	5	66	SEQ ID NO. 2485
(N20)NGG	2	220012370	-	CAAATGTTGGGAGACCTTTGAGG	1	2	43	SEQ ID NO. 2486
(N20)NGG	2	220012382	-	CAGAGGACGAATCAAATGTTGGG	1	3	22	SEQ ID NO. 2487
(N20)NGG	2	220012383	-	TCAGAGGACGAATCAAATGTTGG	1	2	23	SEQ ID NO. 2488
(N20)NGG	2	220012399	-	GCCAGACTCATGCCCATCAGAGG	1	3	33	SEQ ID NO. 2489
(N20)NGG	2	220012431	-	ACGTTGCTAGCTCCCTCACTTGG	1	2	16	SEQ ID NO. 2490
(N20)NGG	2	220012470	-	CCTGGTAGTCTTGGATCTCTAGG	1	1	25	SEQ ID NO. 2491
(N20)NGG	2	220012479	-	CCCCACTCTCCTGGTAGTCTTGG	1	5	37	SEQ ID NO. 2492
(N20)NGG	2	220012488	-	TCAGCGTAGCCCCACTCTCCTGG	1	3	63	SEQ ID NO. 2493
(N20)NGG	2	220022193	+	TGTACCACTGCTCTCTCTTTAGG	1	6	57	SEQ ID NO. 2494
(N20)NGG	2	220022207	+	CTCTTTAGGAGCTGAACAAGCGG	1	4	43	SEQ ID NO. 2495
(N20)NGG	2	220022244	+	TGCAGCTTTCCTCTGTCATTTGG	1	5	67	SEQ ID NO. 2496
(N20)NGG	2	220022271	+	TCTCCTTCGCCCATTGTTGAAGG	3	13	95	SEQ ID NO. 2497
(N20)NGG	2	220022316	+	TACCTTCTCCTGTGATTGTGTGG	4	70	594	SEQ ID NO. 2498
(N20)NGG	2	220022336	+	TGGCAGATGCACTGATTCTACGG	1	3	32	SEQ ID NO. 2499
(N20)NGG	2	220022337	+	GGCAGATGCACTGATTCTACGGG	1	2	19	SEQ ID NO. 2500
(N20)NGG	2	220022356	+	CGGGTGCGAAGTGAGCTCTCTGG	1	2	6	SEQ ID NO. 2501
(N20)NGG	2	220022372	+	TCTCTGGCCTCCCCTTCTATTGG	1	6	82	SEQ ID NO. 2502
(N20)NGG	2	220022406	+	CATGCTAGCTAGTCCTTCCCTGG	1	2	15	SEQ ID NO. 2503
(N20)NGG	2	220022426	+	TGGTAAGTGTAATTCGAATGTGG	1	2	12	SEQ ID NO. 2504
(N20)NGG	2	220022427	+	GGTAAGTGTAATTCGAATGTGGG	1	3	19	SEQ ID NO. 2505
(N20)NGG	2	220022428	+	GTAAGTGTAATTCGAATGTGGGG	1	2	19	SEQ ID NO. 2506
(N20)NGG	2	220022175	-	AGCTCCTAAAGAGAGAGCAGTGG	2	4	69	SEQ ID NO. 2507
(N20)NGG	2	220022217	-	TGACAGAGGAAAGCTGCAGGAGG	2	11	120	SEQ ID NO. 2508
(N20)NGG	2	220022220	-	AAATGACAGAGGAAAGCTGCAGG	4	9	110	SEQ ID NO. 2509
(N20)NGG	2	220022231	-	GGAGATTATCCAAATGACAGAGG	1	4	45	SEQ ID NO. 2510
(N20)NGG	2	220022252	-	CGTCCTTCAACAATGGGCGAAGG	1	1	4	SEQ ID NO. 2511
(N20)NGG	2	220022258	-	GAGCAGCGTCCTTCAACAATGGG	1	1	13	SEQ ID NO. 2512

FIG. 10 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	2	220022259	-	TGAGCAGCGTCCTTCAACAATGG	1	2	9	SEQ ID NO. 2513
(N20)NGG	2	220022282	-	AGGAGAAGGTAGCTTCGCTAGGG	1	1	10	SEQ ID NO. 2514
(N20)NGG	2	220022283	-	CAGGAGAAGGTAGCTTCGCTAGG	1	2	18	SEQ ID NO. 2515
(N20)NGG	2	220022296	-	TGCCACACAATCACAGGAGAAGG	1	6	119	SEQ ID NO. 2516
(N20)NGG	2	220022302	-	TGCATCTGCCACACAATCACAGG	1	3	26	SEQ ID NO. 2517
(N20)NGG	2	220022357	-	GGAAATTCCAATAGAAGGGGAGG	1	3	48	SEQ ID NO. 2518
(N20)NGG	2	220022360	-	AGTGGAAATTCCAATAGAAGGGG	2	4	68	SEQ ID NO. 2519
(N20)NGG	2	220022361	-	CAGTGGAAATTCCAATAGAAGGG	1	4	79	SEQ ID NO. 2520
(N20)NGG	2	220022362	-	GCAGTGGAAATTCCAATAGAAGG	1	3	33	SEQ ID NO. 2521
(N20)NGG	2	220022378	-	AAGGACTAGCTAGCATGCAGTGG	1	1	20	SEQ ID NO. 2522
(N20)NGG	2	220022397	-	CGAATTACACTTACCAGGGAAGG	1	1	14	SEQ ID NO. 2523
(N20)NGG	2	220022401	-	CATTCGAATTACACTTACCAGGG	1	2	21	SEQ ID NO. 2524
(N20)NGG	2	220022402	-	ACATTCGAATTACACTTACCAGG	1	3	14	SEQ ID NO. 2525
(N20)NGG	2	220022910	+	AATGAGGACTTTTTTGCAGATGG	1	5	99	SEQ ID NO. 2526
(N20)NGG	2	220022919	+	TTTTTTGCAGATGGAAGAACTGG	1	7	146	SEQ ID NO. 2527
(N20)NGG	2	220022926	+	CAGATGGAAGAACTGGAGCAAGG	2	19	216	SEQ ID NO. 2528
(N20)NGG	2	220022945	+	AAGGCCTGTTGATGCAGCCATGG	1	5	40	SEQ ID NO. 2529
(N20)NGG	2	220022946	+	AGGCCTGTTGATGCAGCCATGGG	1	1	29	SEQ ID NO. 2530
(N20)NGG	2	220022951	+	TGTTGATGCAGCCATGGGCGTGG	1	2	17	SEQ ID NO. 2531
(N20)NGG	2	220022979	+	GCTTGCAGAGAACTCCCTCTTGG	1	3	30	SEQ ID NO. 2532
(N20)NGG	2	220022985	+	AGAGAACTCCCTCTTGGCCAAGG	1	10	95	SEQ ID NO. 2533
(N20)NGG	2	220023003	+	CAAGGTTTTTATCACCAAGCAGG	1	1	20	SEQ ID NO. 2534
(N20)NGG	2	220023004	+	AAGGTTTTTATCACCAAGCAGGG	1	3	55	SEQ ID NO. 2535
(N20)NGG	2	220023018	+	CAAGCAGGGCTATGCCTTGTTGG	1	1	25	SEQ ID NO. 2536
(N20)NGG	2	220023036	+	GTTGGTTTCAGATCTTCAACAGG	1	1	28	SEQ ID NO. 2537
(N20)NGG	2	220023041	+	TTTCAGATCTTCAACAGGTGTGG	1	2	31	SEQ ID NO. 2538
(N20)NGG	2	220023051	+	TCAACAGGTGTGGCATGAACAGG	1	2	38	SEQ ID NO. 2539
(N20)NGG	2	220023054	+	ACAGGTGTGGCATGAACAGGTGG	1	3	58	SEQ ID NO. 2540
(N20)NGG	2	220023066	+	TGAACAGGTGGACACTAGTGTGG	1	1	19	SEQ ID NO. 2541
(N20)NGG	2	220023084	+	TGTGGTCAGCCAGCGAGCCAAGG	1	4	39	SEQ ID NO. 2542
(N20)NGG	2	220023095	+	AGCGAGCCAAGGTAAGTATGAGG	1	1	14	SEQ ID NO. 2543
(N20)NGG	2	220022927	-	ACGCCCATGGCTGCATCAACAGG	1	1	14	SEQ ID NO. 2544
(N20)NGG	2	220022940	-	GCAAGCTGTAGCCACGCCCATGG	1	1	17	SEQ ID NO. 2545
(N20)NGG	2	220022971	-	GATAAAAACCTTGGCCAAGAGGG	1	2	40	SEQ ID NO. 2546

FIG. 10 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	2	220022972	-	TGATAAAAACCTTGGCCAAGAGG	1	2	40	SEQ ID NO. 2547
(N20)NGG	2	220022980	-	CTGCTTGGTGATAAAAACCTTGG	1	1	33	SEQ ID NO. 2548
(N20)NGG	2	220022995	-	CAACAAGGCATAGCCCTGCTTGG	1	2	27	SEQ ID NO. 2549
(N20)NGG	2	220023010	-	TTGAAGATCTGAAACCAACAAGG	1	3	66	SEQ ID NO. 2550
(N20)NGG	2	220023071	-	TCATACTTACCTTGGCTCGCTGG	1	1	6	SEQ ID NO. 2551
(N20)NGG	2	220023079	-	ACTTCTCCTCATACTTACCTTGG	1	2	35	SEQ ID NO. 2552

FIG. 10 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	14	20937686	+	AGAAGGCGTCTGCGAGACCATGG	1	1	13	SEQ ID NO. 2553
(N20)NGG	14	20937693	+	GTCTGCGAGACCATGGAGAACGG	1	2	21	SEQ ID NO. 2554
(N20)NGG	14	20937694	+	TCTGCGAGACCATGGAGAACGGG	1	2	25	SEQ ID NO. 2555
(N20)NGG	14	20937699	+	GAGACCATGGAGAACGGGTGAGG	1	3	40	SEQ ID NO. 2556
(N20)NGG	14	20937702	+	ACCATGGAGAACGGGTGAGGAGG	1	3	41	SEQ ID NO. 2557
(N20)NGG	14	20937703	+	CCATGGAGAACGGGTGAGGAGGG	1	2	47	SEQ ID NO. 2558
(N20)NGG	14	20937710	+	GAACGGGTGAGGAGGGCACCAGG	1	4	36	SEQ ID NO. 2559
(N20)NGG	14	20937718	+	GAGGAGGGCACCAGGCCCGCAGG	1	5	57	SEQ ID NO. 2560
(N20)NGG	14	20937681	-	CCCTCCTCACCCGTTCTCCATGG	1	4	50	SEQ ID NO. 2561
(N20)NGG	14	20940502	+	ATTATAAGAACACTGCAGAATGG	2	12	138	SEQ ID NO. 2562
(N20)NGG	14	20940549	+	CCTCAAGTTGCAATAATCTGTGG	1	1	37	SEQ ID NO. 2563
(N20)NGG	14	20940555	+	GTTGCAATAATCTGTGGTTCTGG	1	5	26	SEQ ID NO. 2564
(N20)NGG	14	20940561	+	ATAATCTGTGGTTCTGGATTAGG	1	2	54	SEQ ID NO. 2565
(N20)NGG	14	20940564	+	ATCTGTGGTTCTGGATTAGGAGG	1	5	39	SEQ ID NO. 2566
(N20)NGG	14	20940587	+	TCTGACTGATAAATTAACTCAGG	2	3	41	SEQ ID NO. 2567
(N20)NGG	14	20940606	+	CAGGCCCAGATCTTTGACTACGG	1	2	42	SEQ ID NO. 2568
(N20)NGG	14	20940636	+	CCCAACTTTCCCCGAAGTACAGG	1	1	17	SEQ ID NO. 2569
(N20)NGG	14	20940642	+	TTTCCCCGAAGTACAGGTACTGG	1	2	31	SEQ ID NO. 2570
(N20)NGG	14	20940647	+	CCGAAGTACAGGTACTGGCAAGG	1	2	14	SEQ ID NO. 2571
(N20)NGG	14	20940648	+	CGAAGTACAGGTACTGGCAAGGG	1	1	15	SEQ ID NO. 2572
(N20)NGG	14	20940655	+	CAGGTACTGGCAAGGGAAAGTGG	1	2	87	SEQ ID NO. 2573
(N20)NGG	14	20940656	+	AGGTACTGGCAAGGGAAAGTGGG	1	4	61	SEQ ID NO. 2574
(N20)NGG	14	20940657	+	GGTACTGGCAAGGGAAAGTGGGG	1	5	69	SEQ ID NO. 2575
(N20)NGG	14	20940443	-	CTGGGGGAGAAAAAATATCAAGG	1	10	154	SEQ ID NO. 2576
(N20)NGG	14	20940459	-	ATCTTCATAGGTGTATCTGGGGG	1	1	33	SEQ ID NO. 2577
(N20)NGG	14	20940460	-	AATCTTCATAGGTGTATCTGGGG	1	2	39	SEQ ID NO. 2578
(N20)NGG	14	20940461	-	TAATCTTCATAGGTGTATCTGGG	1	6	47	SEQ ID NO. 2579
(N20)NGG	14	20940462	-	ATAATCTTCATAGGTGTATCTGG	1	3	36	SEQ ID NO. 2580
(N20)NGG	14	20940471	-	AGTGTTCTTATAATCTTCATAGG	1	1	75	SEQ ID NO. 2581
(N20)NGG	14	20940523	-	AGATTATTGCAACTTGAGGTCGG	1	7	57	SEQ ID NO. 2582
(N20)NGG	14	20940527	-	CCACAGATTATTGCAACTTGAGG	1	7	61	SEQ ID NO. 2583
(N20)NGG	14	20940588	-	TTCACCGTAGTCAAAGATCTGGG	1	1	11	SEQ ID NO. 2584
(N20)NGG	14	20940589	-	TTTCACCGTAGTCAAAGATCTGG	1	1	20	SEQ ID NO. 2585
(N20)NGG	14	20940613	-	CTGTACTTCGGGGAAAGTTGGGG	1	1	14	SEQ ID NO. 2586

FIG. 11

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	14	20940614	-	CCTGTACTTCGGGGAAAGTTGGG	1	1	12	SEQ ID NO. 2587
(N20)NGG	14	20940615	-	ACCTGTACTTCGGGGAAAGTTGG	1	1	10	SEQ ID NO. 2588
(N20)NGG	14	20940623	-	TTGCCAGTACCTGTACTTCGGGG	1	2	13	SEQ ID NO. 2589
(N20)NGG	14	20940624	-	CTTGCCAGTACCTGTACTTCGGG	1	2	22	SEQ ID NO. 2590
(N20)NGG	14	20940625	-	CCTTGCCAGTACCTGTACTTCGG	1	4	33	SEQ ID NO. 2591
(N20)NGG	14	20942636	+	TCTGTTTTGTATACAGTGCCAGG	1	3	59	SEQ ID NO. 2592
(N20)NGG	14	20942645	+	TATACAGTGCCAGGTCATGCTGG	1	1	17	SEQ ID NO. 2593
(N20)NGG	14	20942653	+	GCCAGGTCATGCTGGCCGACTGG	1	1	7	SEQ ID NO. 2594
(N20)NGG	14	20942660	+	CATGCTGGCCGACTGGTGTTTGG	1	2	16	SEQ ID NO. 2595
(N20)NGG	14	20942661	+	ATGCTGGCCGACTGGTGTTTGGG	1	3	16	SEQ ID NO. 2596
(N20)NGG	14	20942672	+	CTGGTGTTTGGGTTCCTGAATGG	2	4	41	SEQ ID NO. 2597
(N20)NGG	14	20942676	+	TGTTTGGGTTCCTGAATGGCAGG	1	9	44	SEQ ID NO. 2598
(N20)NGG	14	20942677	+	GTTTGGGTTCCTGAATGGCAGGG	2	2	43	SEQ ID NO. 2599
(N20)NGG	14	20942695	+	CAGGGCCTGTGTGATGATGCAGG	1	2	66	SEQ ID NO. 2600
(N20)NGG	14	20942696	+	AGGGCCTGTGTGATGATGCAGGG	1	3	46	SEQ ID NO. 2601
(N20)NGG	14	20942700	+	CCTGTGTGATGATGCAGGGCAGG	1	3	43	SEQ ID NO. 2602
(N20)NGG	14	20942717	+	GGCAGGTTCCACATGTATGAAGG	1	1	23	SEQ ID NO. 2603
(N20)NGG	14	20942718	+	GCAGGTTCCACATGTATGAAGGG	1	2	38	SEQ ID NO. 2604
(N20)NGG	14	20942730	+	TGTATGAAGGGTACCCACTCTGG	1	1	14	SEQ ID NO. 2605
(N20)NGG	14	20942734	+	TGAAGGGTACCCACTCTGGAAGG	1	2	24	SEQ ID NO. 2606
(N20)NGG	14	20942745	+	CACTCTGGAAGGTAAGTCAGAGG	2	7	158	SEQ ID NO. 2607
(N20)NGG	14	20942746	+	ACTCTGGAAGGTAAGTCAGAGGG	1	8	112	SEQ ID NO. 2608
(N20)NGG	14	20942751	+	GGAAGGTAAGTCAGAGGGATAGG	1	4	63	SEQ ID NO. 2609
(N20)NGG	14	20942756	+	GTAAGTCAGAGGGATAGGTCCGG	2	2	29	SEQ ID NO. 2610
(N20)NGG	14	20942632	-	ACCAGTCGGCCAGCATGACCTGG	1	1	8	SEQ ID NO. 2611
(N20)NGG	14	20942646	-	TCAGGAACCCAAACACCAGTCGG	2	2	31	SEQ ID NO. 2612
(N20)NGG	14	20942664	-	TCACACAGGCCCTGCCATTCAGG	1	4	46	SEQ ID NO. 2613
(N20)NGG	14	20942678	-	CCTGCCCTGCATCATCACACAGG	1	5	47	SEQ ID NO. 2614
(N20)NGG	14	20942703	-	GTGGGTACCCTTCATACATGTGG	1	1	12	SEQ ID NO. 2615
(N20)NGG	14	20942721	-	TCTGACTTACCTTCCAGAGTGGG	1	5	48	SEQ ID NO. 2616
(N20)NGG	14	20942722	-	CTCTGACTTACCTTCCAGAGTGG	1	6	92	SEQ ID NO. 2617
(N20)NGG	14	20942931	+	TTTCGGATTGTTTGCTTCGAAGG	1	2	17	SEQ ID NO. 2618
(N20)NGG	14	20942948	+	CGAAGGTGACATTCCCAGTGAGG	1	1	23	SEQ ID NO. 2619
(N20)NGG	14	20942949	+	GAAGGTGACATTCCCAGTGAGGG	1	6	55	SEQ ID NO. 2620

FIG. 11 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	14	20942964	+	AGTGAGGGTTTTCCACCTTCTGG	3	7	40	SEQ ID NO. 2621
(N20)NGG	14	20942965	+	GTGAGGGTTTTCCACCTTCTGGG	1	3	32	SEQ ID NO. 2622
(N20)NGG	14	20942970	+	GGTTTTCCACCTTCTGGGTGTGG	2	3	33	SEQ ID NO. 2623
(N20)NGG	14	20942979	+	CCTTCTGGGTGTGGACACCCTGG	1	8	59	SEQ ID NO. 2624
(N20)NGG	14	20942998	+	CTGGTAGTCACCAATGCAGCAGG	1	1	21	SEQ ID NO. 2625
(N20)NGG	14	20943001	+	GTAGTCACCAATGCAGCAGGAGG	1	1	22	SEQ ID NO. 2626
(N20)NGG	14	20943002	+	TAGTCACCAATGCAGCAGGAGGG	1	1	35	SEQ ID NO. 2627
(N20)NGG	14	20943021	+	AGGGCTGAACCCCAAGTTTGAGG	1	6	51	SEQ ID NO. 2628
(N20)NGG	14	20943025	+	CTGAACCCCAAGTTTGAGGTTGG	1	7	48	SEQ ID NO. 2629
(N20)NGG	14	20943064	+	CGTGACCATATCAACCTACCTGG	1	1	11	SEQ ID NO. 2630
(N20)NGG	14	20943073	+	ATCAACCTACCTGGTTTCAGTGG	1	4	25	SEQ ID NO. 2631
(N20)NGG	14	20943091	+	AGTGGTCAGAACCCTCTCAGAGG	1	2	29	SEQ ID NO. 2632
(N20)NGG	14	20943092	+	GTGGTCAGAACCCTCTCAGAGGG	1	2	48	SEQ ID NO. 2633
(N20)NGG	14	20943107	+	TCAGAGGGCCCAATGATGAAAGG	1	3	26	SEQ ID NO. 2634
(N20)NGG	14	20942939	-	GAAGGTGGAAAACCCTCACTGGG	3	6	47	SEQ ID NO. 2635
(N20)NGG	14	20942940	-	AGAAGGTGGAAAACCCTCACTGG	1	3	41	SEQ ID NO. 2636
(N20)NGG	14	20942954	-	GGGTGTCCACACCCAGAAGGTGG	1	3	75	SEQ ID NO. 2637
(N20)NGG	14	20942957	-	CCAGGGTGTCCACACCCAGAAGG	2	4	66	SEQ ID NO. 2638
(N20)NGG	14	20942974	-	TGCTGCATTGGTGACTACCAGGG	1	4	24	SEQ ID NO. 2639
(N20)NGG	14	20942975	-	CTGCTGCATTGGTGACTACCAGG	1	3	23	SEQ ID NO. 2640
(N20)NGG	14	20942986	-	GTTCAGCCCTCCTGCTGCATTGG	1	6	37	SEQ ID NO. 2641
(N20)NGG	14	20943008	-	TATCTCCAACCTCAAACTTGGGG	1	2	45	SEQ ID NO. 2642
(N20)NGG	14	20943009	-	ATATCTCCAACCTCAAACTTGGG	1	2	35	SEQ ID NO. 2643
(N20)NGG	14	20943010	-	GATATCTCCAACCTCAAACTTGG	1	1	33	SEQ ID NO. 2644
(N20)NGG	14	20943041	-	CAGGTAGGTTGATATGGTCACGG	1	3	24	SEQ ID NO. 2645
(N20)NGG	14	20943047	-	TGAAACCAGGTAGGTTGATATGG	1	3	25	SEQ ID NO. 2646
(N20)NGG	14	20943056	-	TCTGACCACTGAAACCAGGTAGG	1	6	45	SEQ ID NO. 2647
(N20)NGG	14	20943060	-	GGGTTCTGACCACTGAAACCAGG	1	2	20	SEQ ID NO. 2648
(N20)NGG	14	20943080	-	CATCATTGGGCCCTCTGAGAGGG	1	2	20	SEQ ID NO. 2649
(N20)NGG	14	20943081	-	TCATCATTGGGCCCTCTGAGAGG	1	1	27	SEQ ID NO. 2650
(N20)NGG	14	20943093	-	CATACATACCTTTCATCATTGGG	1	3	50	SEQ ID NO. 2651
(N20)NGG	14	20943094	-	ACATACATACCTTTCATCATTGG	1	4	52	SEQ ID NO. 2652
(N20)NGG	14	20943220	+	GATAATTCAACCTGTGTCCTAGG	1	2	32	SEQ ID NO. 2653
(N20)NGG	14	20943225	+	TTCAACCTGTGTCCTAGGTTTGG	1	3	40	SEQ ID NO. 2654

FIG. 11 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	14	20943262	+	CCATGTCTGATGCCTACGACCGG	1	2	10	SEQ ID NO. 2655
(N20)NGG	14	20943271	+	ATGCCTACGACCGGACTATGAGG	1	1	3	SEQ ID NO. 2656
(N20)NGG	14	20943277	+	ACGACCGGACTATGAGGCAGAGG	1	1	9	SEQ ID NO. 2657
(N20)NGG	14	20943278	+	CGACCGGACTATGAGGCAGAGGG	1	1	9	SEQ ID NO. 2658
(N20)NGG	14	20943292	+	GGCAGAGGGCTCTCAGTACCTGG	1	4	36	SEQ ID NO. 2659
(N20)NGG	14	20943302	+	TCTCAGTACCTGGAAACAAATGG	1	5	70	SEQ ID NO. 2660
(N20)NGG	14	20943303	+	CTCAGTACCTGGAAACAAATGGG	1	2	54	SEQ ID NO. 2661
(N20)NGG	14	20943304	+	TCAGTACCTGGAAACAAATGGGG	1	5	60	SEQ ID NO. 2662
(N20)NGG	14	20943305	+	CAGTACCTGGAAACAAATGGGGG	1	8	49	SEQ ID NO. 2663
(N20)NGG	14	20943323	+	GGGGGAGCAACGTGAGCTACAGG	1	1	5	SEQ ID NO. 2664
(N20)NGG	14	20943327	+	GAGCAACGTGAGCTACAGGAAGG	1	3	20	SEQ ID NO. 2665
(N20)NGG	14	20943341	+	ACAGGAAGGCACCTATGTGATGG	2	5	29	SEQ ID NO. 2666
(N20)NGG	14	20943344	+	GGAAGGCACCTATGTGATGGTGG	1	4	41	SEQ ID NO. 2667
(N20)NGG	14	20943348	+	GGCACCTATGTGATGGTGGCAGG	1	1	26	SEQ ID NO. 2668
(N20)NGG	14	20943368	+	AGGCCCCAGCTTTGAGACTGTGG	1	7	96	SEQ ID NO. 2669
(N20)NGG	14	20943395	+	ATGTCGTGTGCTGCAGAAGCTGG	1	2	37	SEQ ID NO. 2670
(N20)NGG	14	20943396	+	TGTCGTGTGCTGCAGAAGCTGGG	1	4	25	SEQ ID NO. 2671
(N20)NGG	14	20943411	+	AAGCTGGGAGCAGACGCTGTTGG	1	2	38	SEQ ID NO. 2672
(N20)NGG	14	20943419	+	AGCAGACGCTGTTGGTGAGAAGG	1	3	35	SEQ ID NO. 2673
(N20)NGG	14	20943420	+	GCAGACGCTGTTGGTGAGAAGGG	1	2	37	SEQ ID NO. 2674
(N20)NGG	14	20943421	+	CAGACGCTGTTGGTGAGAAGGGG	1	2	39	SEQ ID NO. 2675
(N20)NGG	14	20943428	+	TGTTGGTGAGAAGGGGAATTTGG	1	9	109	SEQ ID NO. 2676
(N20)NGG	14	20943432	+	GGTGAGAAGGGGAATTTGGCTGG	1	5	57	SEQ ID NO. 2677
(N20)NGG	14	20943208	-	GATCTCCAAACCTAGGACACAGG	1	1	22	SEQ ID NO. 2678
(N20)NGG	14	20943215	-	GGGAAACGATCTCCAAACCTAGG	1	1	10	SEQ ID NO. 2679
(N20)NGG	14	20943235	-	CGTAGGCATCAGACATGGCAGGG	1	1	17	SEQ ID NO. 2680
(N20)NGG	14	20943236	-	TCGTAGGCATCAGACATGGCAGG	1	2	17	SEQ ID NO. 2681
(N20)NGG	14	20943240	-	CCGGTCGTAGGCATCAGACATGG	1	1	4	SEQ ID NO. 2682
(N20)NGG	14	20943252	-	CTGCCTCATAGTCCGGTCGTAGG	1	1	6	SEQ ID NO. 2683
(N20)NGG	14	20943259	-	GAGCCCTCTGCCTCATAGTCCGG	1	3	26	SEQ ID NO. 2684
(N20)NGG	14	20943288	-	TTGCTCCCCCATTTGTTTCCAGG	1	5	49	SEQ ID NO. 2685
(N20)NGG	14	20943330	-	GGGGCCTGCCACCATCACATAGG	1	2	43	SEQ ID NO. 2686
(N20)NGG	14	20943349	-	CTGCCACAGTCTCAAAGCTGGGG	1	3	74	SEQ ID NO. 2687
(N20)NGG	14	20943350	-	TCTGCCACAGTCTCAAAGCTGGG	1	4	55	SEQ ID NO. 2688

FIG. 11 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	14	20943351	-	TTCTGCCACAGTCTCAAAGCTGG	1	7	50	SEQ ID NO. 2689
(N20)NGG	14	20944542	+	TTTCCATCTTTCTCACTATCAGG	1	13	112	SEQ ID NO. 2690
(N20)NGG	14	20944576	+	TACCAGAAGTTATCGTTGCACGG	1	3	9	SEQ ID NO. 2691
(N20)NGG	14	20944584	+	GTTATCGTTGCACGGCACTGTGG	1	1	10	SEQ ID NO. 2692
(N20)NGG	14	20944599	+	CACTGTGGACTTCGAGTCTTTGG	1	2	23	SEQ ID NO. 2693
(N20)NGG	14	20944622	+	CTTCTCACTCATCACTAACAAGG	2	3	48	SEQ ID NO. 2694
(N20)NGG	14	20944631	+	CATCACTAACAAGGTCATCATGG	2	6	50	SEQ ID NO. 2695
(N20)NGG	14	20944646	+	CATCATGGATTATGAAAGCCTGG	3	10	43	SEQ ID NO. 2696
(N20)NGG	14	20944652	+	GGATTATGAAAGCCTGGAGAAGG	2	4	62	SEQ ID NO. 2697
(N20)NGG	14	20944680	+	CATGAAGAAGTCTTAGCAGCTGG	2	5	31	SEQ ID NO. 2698
(N20)NGG	14	20944703	+	CAAACAAGCTGCACAGAAATTGG	2	5	57	SEQ ID NO. 2699
(N20)NGG	14	20944727	+	ACAGTTTGTCTCCATTCTTATGG	2	5	60	SEQ ID NO. 2700
(N20)NGG	14	20944769	+	CAAAGCCAGTTGACCTGCCTTGG	1	3	39	SEQ ID NO. 2701
(N20)NGG	14	20944779	+	TGACCTGCCTTGGAGTCGTCTGG	1	1	14	SEQ ID NO. 2702
(N20)NGG	14	20944523	-	ATGCCTGATAGTGAGAAAGATGG	1	5	60	SEQ ID NO. 2703
(N20)NGG	14	20944556	-	TGCCGTGCAACGATAACTTCTGG	1	1	6	SEQ ID NO. 2704
(N20)NGG	14	20944642	-	CTTCATGGTTGGCCTTCTCCAGG	1	1	32	SEQ ID NO. 2705
(N20)NGG	14	20944653	-	TGCTAAGACTTCTTCATGGTTGG	2	4	30	SEQ ID NO. 2706
(N20)NGG	14	20944657	-	CAGCTGCTAAGACTTCTTCATGG	1	5	56	SEQ ID NO. 2707
(N20)NGG	14	20944716	-	TGGAATGCTGGCCATAAGAATGG	1	4	47	SEQ ID NO. 2708
(N20)NGG	14	20944728	-	TTTGTCAGGGAGTGGAATGCTGG	1	4	51	SEQ ID NO. 2709
(N20)NGG	14	20944736	-	CAACTGGCTTTGTCAGGGAGTGG	1	2	44	SEQ ID NO. 2710
(N20)NGG	14	20944741	-	CAGGTCAACTGGCTTTGTCAGGG	1	4	36	SEQ ID NO. 2711
(N20)NGG	14	20944742	-	GCAGGTCAACTGGCTTTGTCAGG	1	1	22	SEQ ID NO. 2712
(N20)NGG	14	20944752	-	CGACTCCAAGGCAGGTCAACTGG	1	1	13	SEQ ID NO. 2713
(N20)NGG	14	20944760	-	ATGCCAGACGACTCCAAGGCAGG	1	1	10	SEQ ID NO. 2714

FIG. 11 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	8	48686749	+	TTCCAGTGATGAGCTACTCCTGG	1	3	23	SEQ ID NO. 2715
(N20)NGG	8	48686750	+	TCCAGTGATGAGCTACTCCTGGG	1	2	19	SEQ ID NO. 2716
(N20)NGG	8	48686761	+	GCTACTCCTGGGTCATGAGAAGG	1	1	24	SEQ ID NO. 2717
(N20)NGG	8	48686785	+	CCCTGCCTTCAGAGACTATGTGG	1	6	64	SEQ ID NO. 2718
(N20)NGG	8	48686791	+	CTTCAGAGACTATGTGGCTGTGG	1	3	39	SEQ ID NO. 2719
(N20)NGG	8	48686798	+	GACTATGTGGCTGTGGCACGAGG	1	2	27	SEQ ID NO. 2720
(N20)NGG	8	48686840	+	CGTGCCCAAGAACCAGAGAGTGG	2	5	35	SEQ ID NO. 2721
(N20)NGG	8	48686841	+	GTGCCCAAGAACCAGAGAGTGGG	2	4	44	SEQ ID NO. 2722
(N20)NGG	8	48686875	+	GACTCAAGTGAAGTGCCTGATGG	1	2	29	SEQ ID NO. 2723
(N20)NGG	8	48686881	+	AGTGAAGTGCCTGATGGACCAGG	1	3	51	SEQ ID NO. 2724
(N20)NGG	8	48686903	+	GCAACAGACCCCAACATCCTTGG	1	7	44	SEQ ID NO. 2725
(N20)NGG	8	48686913	+	CCAACATCCTTGGCAGAACCTGG	1	2	46	SEQ ID NO. 2726
(N20)NGG	8	48686914	+	CAACATCCTTGGCAGAACCTGGG	1	4	41	SEQ ID NO. 2727
(N20)NGG	8	48686918	+	ATCCTTGGCAGAACCTGGGAAGG	1	3	53	SEQ ID NO. 2728
(N20)NGG	8	48686922	+	TTGGCAGAACCTGGGAAGGATGG	1	12	201	SEQ ID NO. 2729
(N20)NGG	8	48686923	+	TGGCAGAACCTGGGAAGGATGGG	1	4	78	SEQ ID NO. 2730
(N20)NGG	8	48686931	+	CCTGGGAAGGATGGGAGCCCTGG	2	13	133	SEQ ID NO. 2731
(N20)NGG	8	48686939	+	GGATGGGAGCCCTGGATGTGAGG	1	9	87	SEQ ID NO. 2732
(N20)NGG	8	48686946	+	AGCCCTGGATGTGAGGTCTGTGG	2	12	178	SEQ ID NO. 2733
(N20)NGG	8	48686947	+	GCCCTGGATGTGAGGTCTGTGGG	1	5	45	SEQ ID NO. 2734
(N20)NGG	8	48686729	-	ACCCAGGAGTAGCTCATCACTGG	1	1	23	SEQ ID NO. 2735
(N20)NGG	8	48686745	-	CAGGGGCCTTCTCATGACCCAGG	1	5	41	SEQ ID NO. 2736
(N20)NGG	8	48686762	-	CACATAGTCTCTGAAGGCAGGGG	1	1	97	SEQ ID NO. 2737
(N20)NGG	8	48686763	-	CCACATAGTCTCTGAAGGCAGGG	2	5	40	SEQ ID NO. 2738
(N20)NGG	8	48686764	-	GCCACATAGTCTCTGAAGGCAGG	1	2	28	SEQ ID NO. 2739
(N20)NGG	8	48686768	-	CACAGCCACATAGTCTCTGAAGG	1	4	39	SEQ ID NO. 2740
(N20)NGG	8	48686822	-	AAGCCCACTCTCTGGTTCTTGGG	1	6	53	SEQ ID NO. 2741
(N20)NGG	8	48686823	-	AAAGCCCACTCTCTGGTTCTTGG	2	6	91	SEQ ID NO. 2742
(N20)NGG	8	48686830	-	TCTTCTGAAAGCCCACTCTCTGG	1	3	57	SEQ ID NO. 2743
(N20)NGG	8	48686868	-	GGTCTGTTGCCTGGTCCATCAGG	1	1	14	SEQ ID NO. 2744
(N20)NGG	8	48686877	-	GGATGTTGGGGTCTGTTGCCTGG	1	1	28	SEQ ID NO. 2745
(N20)NGG	8	48686889	-	AGGTTCTGCCAAGGATGTTGGGG	1	2	42	SEQ ID NO. 2746
(N20)NGG	8	48686890	-	CAGGTTCTGCCAAGGATGTTGGG	1	2	79	SEQ ID NO. 2747

FIG. 12

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	8	48686891	-	CCAGGTTCTGCCAAGGATGTTGG	2	8	62	SEQ ID NO. 2748
(N20)NGG	8	48686898	-	ATCCTTCCCAGGTTCTGCCAAGG	1	4	65	SEQ ID NO. 2749
(N20)NGG	8	48686909	-	CCAGGGCTCCCATCCTTCCCAGG	2	11	112	SEQ ID NO. 2750
(N20)NGG	8	48686926	-	TCCCACAGACCTCACATCCAGGG	2	4	162	SEQ ID NO. 2751
(N20)NGG	8	48686927	-	CTCCCACAGACCTCACATCCAGG	1	11	200	SEQ ID NO. 2752
(N20)NGG	8	48689432	+	GAACAGAAAATGCTGAAAAAAGG	1	14	354	SEQ ID NO. 2753
(N20)NGG	8	48689435	+	CAGAAAATGCTGAAAAAAGGAGG	1	15	204	SEQ ID NO. 2754
(N20)NGG	8	48689436	+	AGAAAATGCTGAAAAAAGGAGGG	3	26	403	SEQ ID NO. 2755
(N20)NGG	8	48689442	+	TGCTGAAAAAAGGAGGGTCATGG	1	4	67	SEQ ID NO. 2756
(N20)NGG	8	48689475	+	TAAATGTTGCTGAAAAAAATTGG	3	49	626	SEQ ID NO. 2757
(N20)NGG	8	48689519	+	TACGCTAAGAGAAAGTTAGCAGG	1	2	14	SEQ ID NO. 2758
(N20)NGG	8	48689544	+	CCAATCCAGCAGTCATTACTTGG	1	4	28	SEQ ID NO. 2759
(N20)NGG	8	48689562	+	CTTGGTAAGATTTTTATATGTGG	1	5	95	SEQ ID NO. 2760
(N20)NGG	8	48689478	-	CGTAACATATTTTCTGTCGGGGG	1	1	7	SEQ ID NO. 2761
(N20)NGG	8	48689479	-	GCGTAACATATTTTCTGTCGGGG	1	3	16	SEQ ID NO. 2762
(N20)NGG	8	48689480	-	AGCGTAACATATTTTCTGTCGGG	2	12	185	SEQ ID NO. 2763
(N20)NGG	8	48689481	-	TAGCGTAACATATTTTCTGTCGG	1	2	40	SEQ ID NO. 2764
(N20)NGG	8	48689522	-	CCAAGTAATGACTGCTGGATTGG	1	3	25	SEQ ID NO. 2765
(N20)NGG	8	48689527	-	TCTTACCAAGTAATGACTGCTGG	1	3	21	SEQ ID NO. 2766
(N20)NGG	8	48690278	+	TCCCTGAGTTGATGCCTTTTCGG	2	5	57	SEQ ID NO. 2767
(N20)NGG	8	48690324	+	GATGTTACCAATGAAAGAAACGG	2	10	154	SEQ ID NO. 2768
(N20)NGG	8	48690325	+	ATGTTACCAATGAAAGAAACGGG	3	19	266	SEQ ID NO. 2769
(N20)NGG	8	48690345	+	GGGCCTTATGTACAGCATCATGG	1	4	31	SEQ ID NO. 2770
(N20)NGG	8	48690359	+	GCATCATGGTACACGCACTCCGG	1	1	8	SEQ ID NO. 2771
(N20)NGG	8	48690360	+	CATCATGGTACACGCACTCCGGG	1	1	8	SEQ ID NO. 2772
(N20)NGG	8	48690379	+	CGGGCCTTCCGCTCAGACCCTGG	1	1	22	SEQ ID NO. 2773
(N20)NGG	8	48690399	+	TGGCCTGCTCACCAACACCATGG	1	2	38	SEQ ID NO. 2774
(N20)NGG	8	48690414	+	CACCATGGATGTGTTTGTCAAGG	1	3	47	SEQ ID NO. 2775
(N20)NGG	8	48690431	+	TCAAGGAGCCCTCCTTTGATTGG	1	3	47	SEQ ID NO. 2776
(N20)NGG	8	48690439	+	CCCTCCTTTGATTGGAAAGTAGG	1	6	31	SEQ ID NO. 2777
(N20)NGG	8	48690224	-	ACTAAACAAGAAAAAAGGCAAGG	1	20	401	SEQ ID NO. 2778
(N20)NGG	8	48690229	-	CAGAAACTAAACAAGAAAAAAGG	2	47	851	SEQ ID NO. 2779
(N20)NGG	8	48690252	-	AAAGGCATCAACTCAGGGACTGG	1	3	36	SEQ ID NO. 2780

FIG. 12 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	8	48690257	-	GCCGAAAAGGCATCAACTCAGGG	1	1	12	SEQ ID NO. 2781
(N20)NGG	8	48690258	-	AGCCGAAAAGGCATCAACTCAGG	1	2	15	SEQ ID NO. 2782
(N20)NGG	8	48690270	-	AACTGGCGAGTTAGCCGAAAAGG	1	1	3	SEQ ID NO. 2783
(N20)NGG	8	48690287	-	GTAACATCAGATTGATAAACTGG	1	7	35	SEQ ID NO. 2784
(N20)NGG	8	48690309	-	ATAAGGCCCGTTTCTTTCATTGG	1	2	23	SEQ ID NO. 2785
(N20)NGG	8	48690326	-	GTACCATGATGCTGTACATAAGG	1	2	25	SEQ ID NO. 2786
(N20)NGG	8	48690356	-	CAGGGTCTGAGCGGAAGGCCCGG	1	3	35	SEQ ID NO. 2787
(N20)NGG	8	48690361	-	CAGGCCAGGGTCTGAGCGGAAGG	1	4	60	SEQ ID NO. 2788
(N20)NGG	8	48690365	-	TGAGCAGGCCAGGGTCTGAGCGG	1	14	94	SEQ ID NO. 2789
(N20)NGG	8	48690374	-	TGGTGTTGGTGAGCAGGCCAGGG	1	4	52	SEQ ID NO. 2790
(N20)NGG	8	48690375	-	ATGGTGTTGGTGAGCAGGCCAGG	1	3	64	SEQ ID NO. 2791
(N20)NGG	8	48690380	-	CATCCATGGTGTTGGTGAGCAGG	1	1	22	SEQ ID NO. 2792
(N20)NGG	8	48690388	-	GACAAACACATCCATGGTGTTGG	1	2	42	SEQ ID NO. 2793
(N20)NGG	8	48690394	-	CTCCTTGACAAACACATCCATGG	2	3	53	SEQ ID NO. 2794
(N20)NGG	8	48690417	-	CCTACTTTCCAATCAAAGGAGGG	1	1	35	SEQ ID NO. 2795
(N20)NGG	8	48690418	-	ACCTACTTTCCAATCAAAGGAGG	2	2	33	SEQ ID NO. 2796
(N20)NGG	8	48690421	-	AAAACCTACTTTCCAATCAAAGG	2	4	68	SEQ ID NO. 2797
(N20)NGG	8	48691019	+	CACAGCTGTGTCTCTTTTGTAGG	1	5	67	SEQ ID NO. 2798
(N20)NGG	8	48691022	+	AGCTGTGTCTCTTTTGTAGGCGG	1	5	50	SEQ ID NO. 2799
(N20)NGG	8	48691023	+	GCTGTGTCTCTTTTGTAGGCGGG	1	3	42	SEQ ID NO. 2800
(N20)NGG	8	48691034	+	TTTGTAGGCGGGCCTTCGTGAGG	1	1	9	SEQ ID NO. 2801
(N20)NGG	8	48691053	+	GAGGATGAGTACAAGCCCTGAGG	1	2	34	SEQ ID NO. 2802
(N20)NGG	8	48691062	+	TACAAGCCCTGAGGCTTTCCTGG	2	5	39	SEQ ID NO. 2803
(N20)NGG	8	48691115	+	CTCTGATATGCATCAGCCACTGG	1	1	28	SEQ ID NO. 2804
(N20)NGG	8	48691123	+	TGCATCAGCCACTGGATCCTCGG	1	2	37	SEQ ID NO. 2805
(N20)NGG	8	48691124	+	GCATCAGCCACTGGATCCTCGGG	1	2	36	SEQ ID NO. 2806
(N20)NGG	8	48691129	+	AGCCACTGGATCCTCGGGATTGG	1	1	11	SEQ ID NO. 2807
(N20)NGG	8	48691155	+	CAGACATCTGAACAACTTTATGG	2	3	37	SEQ ID NO. 2808
(N20)NGG	8	48691158	+	ACATCTGAACAACTTTATGGTGG	1	3	54	SEQ ID NO. 2809
(N20)NGG	8	48691164	+	GAACAACTTTATGGTGGCCATGG	1	4	30	SEQ ID NO. 2810
(N20)NGG	8	48691171	+	TTTATGGTGGCCATGGAGACTGG	1	5	49	SEQ ID NO. 2811
(N20)NGG	8	48691174	+	ATGGTGGCCATGGAGACTGGCGG	1	10	88	SEQ ID NO. 2812
(N20)NGG	8	48691183	+	ATGGAGACTGGCGGCGTGATCGG	1	2	7	SEQ ID NO. 2813

FIG. 12 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	8	48691184	+	TGGAGACTGGCGGCGTGATCGGG	1	1	16	SEQ ID NO. 2814
(N20)NGG	8	48691195	+	GGCGTGATCGGGATCGACTTTGG	1	1	3	SEQ ID NO. 2815
(N20)NGG	8	48691196	+	GCGTGATCGGGATCGACTTTGGG	1	1	1	SEQ ID NO. 2816
(N20)NGG	8	48691207	+	ATCGACTTTGGGCATGCGTTTGG	1	1	5	SEQ ID NO. 2817
(N20)NGG	8	48691221	+	TGCGTTTGGATCCGCTACACAGG	1	1	3	SEQ ID NO. 2818
(N20)NGG	8	48690994	-	ACAAAAGAGACACAGCTGTGCGG	1	7	106	SEQ ID NO. 2819
(N20)NGG	8	48691024	-	GCTTGTACTCATCCTCACGAAGG	1	2	8	SEQ ID NO. 2820
(N20)NGG	8	48691046	-	GGAGCGCCAGGAAAGCCTCAGGG	1	3	39	SEQ ID NO. 2821
(N20)NGG	8	48691047	-	CGGAGCGCCAGGAAAGCCTCAGG	1	1	24	SEQ ID NO. 2822
(N20)NGG	8	48691058	-	CGAAGTGGGAGCGGAGCGCCAGG	1	2	15	SEQ ID NO. 2823
(N20)NGG	8	48691067	-	GAGAGCTGGCGAAGTGGGAGCGG	1	6	91	SEQ ID NO. 2824
(N20)NGG	8	48691072	-	AGCGTGAGAGCTGGCGAAGTGGG	1	1	12	SEQ ID NO. 2825
(N20)NGG	8	48691073	-	GAGCGTGAGAGCTGGCGAAGTGG	1	1	26	SEQ ID NO. 2826
(N20)NGG	8	48691081	-	GCATATCAGAGCGTGAGAGCTGG	1	2	27	SEQ ID NO. 2827
(N20)NGG	8	48691109	-	CTCCAATCCCGAGGATCCAGTGG	1	2	23	SEQ ID NO. 2828
(N20)NGG	8	48691118	-	GATGTCTGTCTCCAATCCCGAGG	1	2	21	SEQ ID NO. 2829
(N20)NGG	8	48691159	-	GATCACGCCGCCAGTCTCCATGG	1	1	5	SEQ ID NO. 2830
(N20)NGG	8	48691210	-	CAGCAAGTGCACCTGTGTAGCGG	1	1	24	SEQ ID NO. 2831
(N20)NGG	8	48691288	+	TGTTTCTATTATTAAATCATAGG	1	13	240	SEQ ID NO. 2832
(N20)NGG	8	48691289	+	GTTTCTATTATTAAATCATAGGG	2	4	146	SEQ ID NO. 2833
(N20)NGG	8	48691290	+	TTTCTATTATTAAATCATAGGGG	1	10	202	SEQ ID NO. 2834
(N20)NGG	8	48691343	-	ACTTACTTTAAGAGATCAGCAGG	1	11	45	SEQ ID NO. 2835
(N20)NGG	8	48691573	+	TCTCACTCATTAGTGATCCCAGG	1	2	28	SEQ ID NO. 2836
(N20)NGG	8	48691574	+	CTCACTCATTAGTGATCCCAGGG	1	3	36	SEQ ID NO. 2837
(N20)NGG	8	48691600	+	CGCCGTGTGAATATAAAGATTGG	1	2	5	SEQ ID NO. 2838
(N20)NGG	8	48691617	+	GATTGGCTGACAAAAATGTCAGG	3	9	59	SEQ ID NO. 2839
(N20)NGG	8	48691632	+	ATGTCAGGAAAACATGATGTTGG	2	6	92	SEQ ID NO. 2840
(N20)NGG	8	48691663	+	TGCTAATGTATAAGTAAGTTTGG	1	1	39	SEQ ID NO. 2841
(N20)NGG	8	48691544	-	TCACTAATGAGTGAGAAAAGGGG	1	10	154	SEQ ID NO. 2842
(N20)NGG	8	48691545	-	ATCACTAATGAGTGAGAAAAGGG	1	5	139	SEQ ID NO. 2843
(N20)NGG	8	48691546	-	GATCACTAATGAGTGAGAAAAGG	1	5	66	SEQ ID NO. 2844
(N20)NGG	8	48691568	-	TATTCACACGGCGGTGCCCTGGG	1	1	7	SEQ ID NO. 2845
(N20)NGG	8	48691569	-	ATATTCACACGGCGGTGCCCTGG	1	1	4	SEQ ID NO. 2846

FIG. 12 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	8	48691577	-	CAATCTTTATATTCACACGGCGG	1	2	18	SEQ ID NO. 2847
(N20)NGG	8	48691580	-	AGCCAATCTTTATATTCACACGG	1	2	65	SEQ ID NO. 2848
(N20)NGG	8	48694722	+	AACCTTTTATTCTCCCTTTCAGG	1	4	95	SEQ ID NO. 2849
(N20)NGG	8	48694727	+	TTTATTCTCCCTTTCAGGTTAGG	1	4	118	SEQ ID NO. 2850
(N20)NGG	8	48694740	+	TCAGGTTAGGATTAATTGAGTGG	1	4	46	SEQ ID NO. 2851
(N20)NGG	8	48694765	+	TGAAAATACTGTTACCTTGAAGG	1	10	83	SEQ ID NO. 2852
(N20)NGG	8	48694795	+	TTTGAACACCATGTCCCAAGAGG	2	3	38	SEQ ID NO. 2853
(N20)NGG	8	48694801	+	CACCATGTCCCAAGAGGAGAAGG	1	7	62	SEQ ID NO. 2854
(N20)NGG	8	48694804	+	CATGTCCCAAGAGGAGAAGGCGG	1	7	94	SEQ ID NO. 2855
(N20)NGG	8	48694815	+	AGGAGAAGGCGGCTTACCTGAGG	1	2	39	SEQ ID NO. 2856
(N20)NGG	8	48694820	+	AAGGCGGCTTACCTGAGGTAAGG	1	10	658	SEQ ID NO. 2857
(N20)NGG	8	48694821	+	AGGCGGCTTACCTGAGGTAAGGG	1	10	637	SEQ ID NO. 2858
(N20)NGG	8	48694824	+	CGGCTTACCTGAGGTAAGGGCGG	1	2	21	SEQ ID NO. 2859
(N20)NGG	8	48694702	-	AACCTGAAAGGGAGAATAAAAGG	1	4	134	SEQ ID NO. 2860
(N20)NGG	8	48694713	-	CAATTAATCCTAACCTGAAAGGG	1	3	48	SEQ ID NO. 2861
(N20)NGG	8	48694714	-	TCAATTAATCCTAACCTGAAAGG	1	2	41	SEQ ID NO. 2862
(N20)NGG	8	48694757	-	GTTCAAAAGAAGGTCCTTCAAGG	1	3	31	SEQ ID NO. 2863
(N20)NGG	8	48694767	-	GGGACATGGTGTTCAAAAGAAGG	1	3	53	SEQ ID NO. 2864
(N20)NGG	8	48694781	-	CGCCTTCTCCTCTTGGGACATGG	1	4	36	SEQ ID NO. 2865
(N20)NGG	8	48694787	-	GTAAGCCGCCTTCTCCTCTTGGG	1	1	16	SEQ ID NO. 2866
(N20)NGG	8	48694788	-	GGTAAGCCGCCTTCTCCTCTTGG	1	2	18	SEQ ID NO. 2867
(N20)NGG	8	48694809	-	CGTGTGGCCGCCCTTACCTCAGG	1	3	10	SEQ ID NO. 2868
(N20)NGG	8	48694938	+	GATGACATTCTGATTTTTGAAGG	1	5	91	SEQ ID NO. 2869
(N20)NGG	8	48694950	+	ATTTTTGAAGGTGACAGTCATGG	1	3	71	SEQ ID NO. 2870
(N20)NGG	8	48694964	+	CAGTCATGGCGTCTCTGCGAAGG	1	1	7	SEQ ID NO. 2871
(N20)NGG	8	48694987	+	CCCAAGCGCATCATCATCCGTGG	1	1	2	SEQ ID NO. 2872
(N20)NGG	8	48695000	+	TCATCCGTGGCCATGACGAGAGG	1	2	9	SEQ ID NO. 2873
(N20)NGG	8	48695001	+	CATCCGTGGCCATGACGAGAGGG	1	1	12	SEQ ID NO. 2874
(N20)NGG	8	48695016	+	CGAGAGGGAACACCCTTTCCTGG	1	3	16	SEQ ID NO. 2875
(N20)NGG	8	48695022	+	GGAACACCCTTTCCTGGTGAAGG	1	7	82	SEQ ID NO. 2876
(N20)NGG	8	48695023	+	GAACACCCTTTCCTGGTGAAGGG	1	5	53	SEQ ID NO. 2877
(N20)NGG	8	48695026	+	CACCCTTTCCTGGTGAAGGGTGG	1	5	84	SEQ ID NO. 2878
(N20)NGG	8	48695031	+	TTTCCTGGTGAAGGGTGGCGAGG	1	1	38	SEQ ID NO. 2879

FIG. 12 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	8	48695039	+	TGAAGGGTGGCGAGGACCTGCGG	1	3	40	SEQ ID NO. 2880
(N20)NGG	8	48695043	+	GGGTGGCGAGGACCTGCGGCAGG	1	1	38	SEQ ID NO. 2881
(N20)NGG	8	48695055	+	CCTGCGGCAGGACCAGCGCGTGG	1	6	32	SEQ ID NO. 2882
(N20)NGG	8	48695070	+	GCGCGTGGAGCAGCTCTTCCAGG	1	3	24	SEQ ID NO. 2883
(N20)NGG	8	48695080	+	CAGCTCTTCCAGGTCATGAATGG	1	6	56	SEQ ID NO. 2884
(N20)NGG	8	48695081	+	AGCTCTTCCAGGTCATGAATGGG	1	2	50	SEQ ID NO. 2885
(N20)NGG	8	48695088	+	CCAGGTCATGAATGGGATCCTGG	1	3	32	SEQ ID NO. 2886
(N20)NGG	8	48695114	+	AAGACTCCGCCTGCAGCCAGAGG	1	3	37	SEQ ID NO. 2887
(N20)NGG	8	48695115	+	AGACTCCGCCTGCAGCCAGAGGG	1	2	26	SEQ ID NO. 2888
(N20)NGG	8	48695129	+	GCCAGAGGGCCCTGCAGCTGAGG	1	16	148	SEQ ID NO. 2889
(N20)NGG	8	48695159	+	GCGTTGTGCCCATGACCTCCAGG	1	1	10	SEQ ID NO. 2890
(N20)NGG	8	48695170	+	ATGACCTCCAGGTAACTGCCAGG	2	5	28	SEQ ID NO. 2891
(N20)NGG	8	48694965	-	CCACGGATGATGATGCGCTTGGG	1	1	4	SEQ ID NO. 2892
(N20)NGG	8	48694966	-	GCCACGGATGATGATGCGCTTGG	1	1	10	SEQ ID NO. 2893
(N20)NGG	8	48694982	-	GTTCCCTCTCGTCATGGCCACGG	1	1	9	SEQ ID NO. 2894
(N20)NGG	8	48694988	-	AAGGGTGTTCCCTCTCGTCATGG	1	1	15	SEQ ID NO. 2895
(N20)NGG	8	48695006	-	CGCCACCCTTCACCAGGAAAGGG	1	2	36	SEQ ID NO. 2896
(N20)NGG	8	48695007	-	TCGCCACCCTTCACCAGGAAAGG	1	2	25	SEQ ID NO. 2897
(N20)NGG	8	48695012	-	GGTCCTCGCCACCCTTCACCAGG	1	1	37	SEQ ID NO. 2898
(N20)NGG	8	48695033	-	CCACGCGCTGGTCCTGCCGCAGG	1	4	24	SEQ ID NO. 2899
(N20)NGG	8	48695045	-	GGAAGAGCTGCTCCACGCGCTGG	1	2	23	SEQ ID NO. 2900
(N20)NGG	8	48695066	-	CCAGGATCCCATTCATGACCTGG	1	4	44	SEQ ID NO. 2901
(N20)NGG	8	48695084	-	TGCAGGCGGAGTCTTGGGCCAGG	1	2	36	SEQ ID NO. 2902
(N20)NGG	8	48695089	-	CTGGCTGCAGGCGGAGTCTTGGG	1	4	34	SEQ ID NO. 2903
(N20)NGG	8	48695090	-	TCTGGCTGCAGGCGGAGTCTTGG	2	2	41	SEQ ID NO. 2904
(N20)NGG	8	48695098	-	CAGGGCCCTCTGGCTGCAGGCGG	1	11	187	SEQ ID NO. 2905
(N20)NGG	8	48695101	-	CTGCAGGGCCCTCTGGCTGCAGG	2	18	161	SEQ ID NO. 2906
(N20)NGG	8	48695108	-	TCCTCAGCTGCAGGGCCCTCTGG	1	12	121	SEQ ID NO. 2907
(N20)NGG	8	48695116	-	GCTATAGGTCCTCAGCTGCAGGG	1	2	18	SEQ ID NO. 2908
(N20)NGG	8	48695117	-	CGCTATAGGTCCTCAGCTGCAGG	1	1	14	SEQ ID NO. 2909
(N20)NGG	8	48695131	-	GGTCATGGGCACAACGCTATAGG	1	1	9	SEQ ID NO. 2910
(N20)NGG	8	48695145	-	GGCAGTTACCTGGAGGTCATGGG	1	5	55	SEQ ID NO. 2911
(N20)NGG	8	48695146	-	TGGCAGTTACCTGGAGGTCATGG	1	6	46	SEQ ID NO. 2912

FIG. 12 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	8	48695152	-	GCAGCCTGGCAGTTACCTGGAGG	1	7	62	SEQ ID NO. 2913
(N20)NGG	8	48695155	-	GGAGCAGCCTGGCAGTTACCTGG	1	4	45	SEQ ID NO. 2914
(N20)NGG	8	48696302	+	GCAAGGTTCTGGTTTGTTTTAGG	1	2	59	SEQ ID NO. 2915
(N20)NGG	8	48696314	+	TTTGTTTTAGGTCAGTATGACGG	1	7	84	SEQ ID NO. 2916
(N20)NGG	8	48696318	+	TTTTAGGTCAGTATGACGGTAGG	1	1	8	SEQ ID NO. 2917
(N20)NGG	8	48696319	+	TTTAGGTCAGTATGACGGTAGGG	1	3	11	SEQ ID NO. 2918
(N20)NGG	8	48696320	+	TTAGGTCAGTATGACGGTAGGGG	1	1	8	SEQ ID NO. 2919
(N20)NGG	8	48696356	+	GAGTACCACGTGCGAATCGCCGG	1	1	2	SEQ ID NO. 2920
(N20)NGG	8	48696357	+	AGTACCACGTGCGAATCGCCGGG	1	1	3	SEQ ID NO. 2921
(N20)NGG	8	48696369	+	GAATCGCCGGGTTTGATGAGCGG	1	1	4	SEQ ID NO. 2922
(N20)NGG	8	48696370	+	AATCGCCGGGTTTGATGAGCGGG	1	1	3	SEQ ID NO. 2923
(N20)NGG	8	48696374	+	GCCGGGTTTGATGAGCGGGTAGG	1	1	8	SEQ ID NO. 2924
(N20)NGG	8	48696381	+	TTGATGAGCGGGTAGGTGTGAGG	1	3	46	SEQ ID NO. 2925
(N20)NGG	8	48696382	+	TGATGAGCGGGTAGGTGTGAGGG	1	1	20	SEQ ID NO. 2926
(N20)NGG	8	48696325	-	CGCACGTGGTACTCTGGCAATGG	1	1	10	SEQ ID NO. 2927
(N20)NGG	8	48696331	-	GCGATTCGCACGTGGTACTCTGG	1	1	5	SEQ ID NO. 2928
(N20)NGG	8	48696339	-	CAAACCCGGCGATTCGCACGTGG	1	1	1	SEQ ID NO. 2929
(N20)NGG	8	48696353	-	ACCTACCCGCTCATCAAACCCGG	1	1	6	SEQ ID NO. 2930
(N20)NGG	8	48697680	+	TCTTACTAATTTCAGACTTTTGG	1	7	117	SEQ ID NO. 2931
(N20)NGG	8	48697704	+	AAAGAATTTGATAAACATTTTGG	2	20	413	SEQ ID NO. 2932
(N20)NGG	8	48697705	+	AAGAATTTGATAAACATTTTGGG	1	26	397	SEQ ID NO. 2933
(N20)NGG	8	48697710	+	TTTGATAAACATTTTGGGAAAGG	1	14	188	SEQ ID NO. 2934
(N20)NGG	8	48697713	+	GATAAACATTTTGGGAAAGGAGG	1	11	192	SEQ ID NO. 2935
(N20)NGG	8	48697803	+	AACAAAGACTCAAAGCCCCCTGG	1	5	32	SEQ ID NO. 2936
(N20)NGG	8	48697804	+	ACAAAGACTCAAAGCCCCCTGGG	1	3	28	SEQ ID NO. 2937
(N20)NGG	8	48697828	+	ATCTGAAAGAATGTTCACCCTGG	1	2	43	SEQ ID NO. 2938
(N20)NGG	8	48697847	+	CTGGATGAGCGACTTCAAAGTGG	1	2	18	SEQ ID NO. 2939
(N20)NGG	8	48697868	+	GGAGTTCCTGAGAAATGAGCTGG	1	5	56	SEQ ID NO. 2940
(N20)NGG	8	48697878	+	AGAAATGAGCTGGAGATTCCCGG	1	3	62	SEQ ID NO. 2941
(N20)NGG	8	48697894	+	TTCCCGGTGAGTTAACCTCCAGG	1	2	12	SEQ ID NO. 2942
(N20)NGG	8	48697895	+	TCCCGGTGAGTTAACCTCCAGGG	1	1	6	SEQ ID NO. 2943
(N20)NGG	8	48697896	+	CCCGGTGAGTTAACCTCCAGGGG	1	1	7	SEQ ID NO. 2944
(N20)NGG	8	48697758	-	CATTTTTAAAAGTAGCATGTTGG	2	14	210	SEQ ID NO. 2945

FIG. 12 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	8	48697796	-	CATTCTTTCAGATTCCCAGGGGG	3	10	80	SEQ ID NO. 2946
(N20)NGG	8	48697797	-	ACATTCTTTCAGATTCCCAGGGG	1	8	82	SEQ ID NO. 2947
(N20)NGG	8	48697798	-	AACATTCTTTCAGATTCCCAGGG	1	6	85	SEQ ID NO. 2948
(N20)NGG	8	48697799	-	GAACATTCTTTCAGATTCCCAGG	1	4	65	SEQ ID NO. 2949
(N20)NGG	8	48697823	-	ACTTTGAAGTCGCTCATCCAGGG	1	3	17	SEQ ID NO. 2950
(N20)NGG	8	48697824	-	CACTTTGAAGTCGCTCATCCAGG	1	1	9	SEQ ID NO. 2951
(N20)NGG	8	48697852	-	GAATCTCCAGCTCATTTCTCAGG	1	6	53	SEQ ID NO. 2952
(N20)NGG	8	48697874	-	CCCCTGGAGGTTAACTCACCGGG	1	1	19	SEQ ID NO. 2953
(N20)NGG	8	48697875	-	ACCCCTGGAGGTTAACTCACCGG	1	1	12	SEQ ID NO. 2954
(N20)NGG	8	48701466	+	TACTTTTTTTTTCCCCTGACAGG	2	15	278	SEQ ID NO. 2955
(N20)NGG	8	48701471	+	TTTTTTTCCCCTGACAGGATTGG	2	10	115	SEQ ID NO. 2956
(N20)NGG	8	48701559	+	TGAAAGAATGTATGCAGCCTTGG	1	5	69	SEQ ID NO. 2957
(N20)NGG	8	48701560	+	GAAAGAATGTATGCAGCCTTGGG	2	6	73	SEQ ID NO. 2958
(N20)NGG	8	48701571	+	TGCAGCCTTGGGTGACCCAAAGG	1	1	34	SEQ ID NO. 2959
(N20)NGG	8	48701578	+	TTGGGTGACCCAAAGGCTCCAGG	1	1	22	SEQ ID NO. 2960
(N20)NGG	8	48701583	+	TGACCCAAAGGCTCCAGGCCTGG	1	6	51	SEQ ID NO. 2961
(N20)NGG	8	48701584	+	GACCCAAAGGCTCCAGGCCTGGG	1	7	60	SEQ ID NO. 2962
(N20)NGG	8	48701585	+	ACCCAAAGGCTCCAGGCCTGGGG	1	7	91	SEQ ID NO. 2963
(N20)NGG	8	48701586	+	CCCAAAGGCTCCAGGCCTGGGGG	2	9	103	SEQ ID NO. 2964
(N20)NGG	8	48701597	+	CAGGCCTGGGGGCCTTTAGAAGG	3	7	59	SEQ ID NO. 2965
(N20)NGG	8	48701610	+	CTTTAGAAGGAAGTTTATTCAGG	1	3	78	SEQ ID NO. 2966
(N20)NGG	8	48701615	+	GAAGGAAGTTTATTCAGGTATGG	1	4	69	SEQ ID NO. 2967
(N20)NGG	8	48701620	+	AAGTTTATTCAGGTATGGACTGG	1	2	19	SEQ ID NO. 2968
(N20)NGG	8	48701456	-	CATTGCTCCAATCCTGTCAGGGG	1	3	38	SEQ ID NO. 2969
(N20)NGG	8	48701457	-	TCATTGCTCCAATCCTGTCAGGG	1	3	21	SEQ ID NO. 2970
(N20)NGG	8	48701458	-	ATCATTGCTCCAATCCTGTCAGG	1	2	36	SEQ ID NO. 2971
(N20)NGG	8	48701503	-	AATGTTTTTTTTATTTACAGGGG	1	47	1234	SEQ ID NO. 2972
(N20)NGG	8	48701504	-	CAATGTTTTTTTTATTTACAGGG	1	22	559	SEQ ID NO. 2973
(N20)NGG	8	48701505	-	TCAATGTTTTTTTTATTTACAGG	1	14	413	SEQ ID NO. 2974
(N20)NGG	8	48701554	-	TGGAGCCTTTGGGTCACCCAAGG	1	4	40	SEQ ID NO. 2975
(N20)NGG	8	48701564	-	CCCCCAGGCCTGGAGCCTTTGGG	2	8	86	SEQ ID NO. 2976
(N20)NGG	8	48701565	-	GCCCCCAGGCCTGGAGCCTTTGG	1	10	133	SEQ ID NO. 2977
(N20)NGG	8	48701574	-	CTTCTAAAGGCCCCCAGGCCTGG	1	3	36	SEQ ID NO. 2978

FIG. 12 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	8	48701579	-	ACTTCCTTCTAAAGGCCCCCAGG	1	2	39	SEQ ID NO. 2979
(N20)NGG	8	48701587	-	CTGAATAAACTTCCTTCTAAAGG	1	4	60	SEQ ID NO. 2980
(N20)NGG	8	48701711	+	CTTTGTAAATTTTTTTAAATAGG	3	81	973	SEQ ID NO. 2981
(N20)NGG	8	48701727	+	AAATAGGATTAAAAGTAAGTTGG	1	6	140	SEQ ID NO. 2982
(N20)NGG	8	48701734	+	ATTAAAAGTAAGTTGGATCAAGG	1	8	84	SEQ ID NO. 2983
(N20)NGG	8	48701737	+	AAAAGTAAGTTGGATCAAGGAGG	1	4	54	SEQ ID NO. 2984
(N20)NGG	8	48701799	+	TAATCCTGAACTGCTCTTTAAGG	1	3	37	SEQ ID NO. 2985
(N20)NGG	8	48701813	+	TCTTTAAGGTAATGATAGAACGG	1	4	110	SEQ ID NO. 2986
(N20)NGG	8	48701820	+	GGTAATGATAGAACGGCTTCTGG	1	1	3	SEQ ID NO. 2987
(N20)NGG	8	48701761	-	AGGATTAGAGAGCTGATCTAAGG	1	2	27	SEQ ID NO. 2988
(N20)NGG	8	48701781	-	ATTACCTTAAAGAGCAGTTCAGG	1	1	37	SEQ ID NO. 2989
(N20)NGG	8	48706870	+	AGATCTCTTCCGTTCCCTGCTGG	1	1	22	SEQ ID NO. 2990
(N20)NGG	8	48706885	+	CCTGCTGGCAGTTCATCAGCTGG	1	2	28	SEQ ID NO. 2991
(N20)NGG	8	48706898	+	CATCAGCTGGATCAGCCACATGG	1	6	39	SEQ ID NO. 2992
(N20)NGG	8	48706901	+	CAGCTGGATCAGCCACATGGTGG	1	3	53	SEQ ID NO. 2993
(N20)NGG	8	48706910	+	CAGCCACATGGTGGCCTTACTGG	1	5	51	SEQ ID NO. 2994
(N20)NGG	8	48706946	+	CGTTGCTGTTCAGCACTCTGTGG	1	3	17	SEQ ID NO. 2995
(N20)NGG	8	48706973	+	AATCACTGATAACTACCCGCAGG	1	1	6	SEQ ID NO. 2996
(N20)NGG	8	48707021	+	CAGCGAAAGCTATTCCTTCAAGG	1	2	21	SEQ ID NO. 2997
(N20)NGG	8	48707034	+	TCCTTCAAGGATACTTCTACTGG	1	2	23	SEQ ID NO. 2998
(N20)NGG	8	48707048	+	TTCTACTGGTCATAAGAATAAGG	1	1	31	SEQ ID NO. 2999
(N20)NGG	8	48707057	+	TCATAAGAATAAGGAGTTTGTGG	1	3	66	SEQ ID NO. 3000
(N20)NGG	8	48707062	+	AGAATAAGGAGTTTGTGGCAAGG	1	7	95	SEQ ID NO. 3001
(N20)NGG	8	48707066	+	TAAGGAGTTTGTGGCAAGGTAGG	1	3	51	SEQ ID NO. 3002
(N20)NGG	8	48707081	+	AAGGTAGGTAATATTACAGAAGG	2	5	71	SEQ ID NO. 3003
(N20)NGG	8	48706857	-	GATGAACTGCCAGCAGGGAACGG	2	4	64	SEQ ID NO. 3004
(N20)NGG	8	48706862	-	CAGCTGATGAACTGCCAGCAGGG	1	2	78	SEQ ID NO. 3005
(N20)NGG	8	48706863	-	CCAGCTGATGAACTGCCAGCAGG	1	2	35	SEQ ID NO. 3006
(N20)NGG	8	48706891	-	TGTCCAGTAAGGCCACCATGTGG	1	3	31	SEQ ID NO. 3007
(N20)NGG	8	48706902	-	GGCTTGGTCTTTGTCCAGTAAGG	1	3	28	SEQ ID NO. 3008
(N20)NGG	8	48706918	-	AGTGCTGAACAGCAACGGCTTGG	1	2	14	SEQ ID NO. 3009
(N20)NGG	8	48706923	-	CACAGAGTGCTGAACAGCAACGG	1	6	66	SEQ ID NO. 3010
(N20)NGG	8	48706966	-	AGGGATAAACAATAGCCTGCGGG	1	1	24	SEQ ID NO. 3011

FIG. 12 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	8	48706967	-	AAGGGATAAACAATAGCCTGCGG	1	5	37	SEQ ID NO. 3012
(N20)NGG	8	48706985	-	CTTTCGCTGCTTATGATGAAGGG	1	1	11	SEQ ID NO. 3013
(N20)NGG	8	48706986	-	GCTTTCGCTGCTTATGATGAAGG	1	1	15	SEQ ID NO. 3014
(N20)NGG	8	48707013	-	ACCAGTAGAAGTATCCTTGAAGG	1	1	18	SEQ ID NO. 3015
(N20)NGG	8	48710820	+	TATTGATTCTGCAGAACTGCAGG	1	2	62	SEQ ID NO. 3016
(N20)NGG	8	48710838	+	GCAGGCGTATCCAGCACTTGTGG	1	2	12	SEQ ID NO. 3017
(N20)NGG	8	48710841	+	GGCGTATCCAGCACTTGTGGTGG	1	1	3	SEQ ID NO. 3018
(N20)NGG	8	48710921	+	GATTACTTCAGATTATAGAACGG	1	5	80	SEQ ID NO. 3019
(N20)NGG	8	48710931	+	GATTATAGAACGGTATCCAGAGG	1	1	10	SEQ ID NO. 3020
(N20)NGG	8	48710958	+	TTTGAGCCTCATGACAAAAGAGG	1	4	43	SEQ ID NO. 3021
(N20)NGG	8	48710962	+	AGCCTCATGACAAAAGAGGTTGG	1	3	30	SEQ ID NO. 3022
(N20)NGG	8	48710980	+	GTTGGTGTCTTTATTCTACTTGG	1	2	45	SEQ ID NO. 3023
(N20)NGG	8	48710788	-	TGCAGAATCAATAACTATCAAGG	2	3	45	SEQ ID NO. 3024
(N20)NGG	8	48710826	-	ATTTTCTCCACCACAAGTGCTGG	1	1	39	SEQ ID NO. 3025
(N20)NGG	8	48710872	-	AAACTTCAATCTGGCTTCATTGG	1	3	56	SEQ ID NO. 3026
(N20)NGG	8	48710881	-	TAATCTAGGAAACTTCAATCTGG	1	3	49	SEQ ID NO. 3027
(N20)NGG	8	48710895	-	TCTATAATCTGAAGTAATCTAGG	2	6	57	SEQ ID NO. 3028
(N20)NGG	8	48710925	-	ATGAGGCTCAAAGTCTCCTCTGG	1	2	36	SEQ ID NO. 3029
(N20)NGG	8	48710942	-	CACCAACCTCTTTTGTCATGAGG	1	3	37	SEQ ID NO. 3030
(N20)NGG	8	48711770	+	TTTAGGTCTCTGTGAATTCCAGG	1	2	50	SEQ ID NO. 3031
(N20)NGG	8	48711779	+	CTGTGAATTCCAGGTGATCGCGG	1	3	22	SEQ ID NO. 3032
(N20)NGG	8	48711780	+	TGTGAATTCCAGGTGATCGCGGG	1	2	16	SEQ ID NO. 3033
(N20)NGG	8	48711815	+	AGCATTCCAGCACCTCTCTGAGG	1	4	50	SEQ ID NO. 3034
(N20)NGG	8	48711824	+	GCACCTCTCTGAGGCTGTGCAGG	1	1	68	SEQ ID NO. 3035
(N20)NGG	8	48711827	+	CCTCTCTGAGGCTGTGCAGGCGG	1	12	134	SEQ ID NO. 3036
(N20)NGG	8	48711833	+	TGAGGCTGTGCAGGCGGCTGAGG	1	6	97	SEQ ID NO. 3037
(N20)NGG	8	48711836	+	GGCTGTGCAGGCGGCTGAGGAGG	1	37	893	SEQ ID NO. 3038
(N20)NGG	8	48711839	+	TGTGCAGGCGGCTGAGGAGGAGG	1	18	407	SEQ ID NO. 3039
(N20)NGG	8	48711856	+	AGGAGGCCCAGCCTCCCTCCTGG	6	14	129	SEQ ID NO. 3040
(N20)NGG	8	48711864	+	CAGCCTCCCTCCTGGAGCTGTGG	3	18	180	SEQ ID NO. 3041
(N20)NGG	8	48711865	+	AGCCTCCCTCCTGGAGCTGTGGG	2	14	98	SEQ ID NO. 3042
(N20)NGG	8	48711876	+	TGGAGCTGTGGGCCTGCAGCTGG	2	14	122	SEQ ID NO. 3043
(N20)NGG	8	48711877	+	GGAGCTGTGGGCCTGCAGCTGGG	1	19	138	SEQ ID NO. 3044

FIG. 12 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	8	48711878	+	GAGCTGTGGGCCTGCAGCTGGGG	1	10	148	SEQ ID NO. 3045
(N20)NGG	8	48711902	+	GATTGATGCTTACATGACGCTGG	1	1	7	SEQ ID NO. 3046
(N20)NGG	8	48711932	+	CTGTGACCAACAGCTGCGCAAGG	1	2	29	SEQ ID NO. 3047
(N20)NGG	8	48711935	+	TGACCAACAGCTGCGCAAGGAGG	1	2	23	SEQ ID NO. 3048
(N20)NGG	8	48711951	+	AAGGAGGAAGAGAATGCATCAGG	1	6	147	SEQ ID NO. 3049
(N20)NGG	8	48711766	-	GGTACAGACCCGCGATCACCTGG	1	1	3	SEQ ID NO. 3050
(N20)NGG	8	48711787	-	AGAGGTGCTGGAATGCTCTCTGG	1	4	32	SEQ ID NO. 3051
(N20)NGG	8	48711799	-	GCACAGCCTCAGAGAGGTGCTGG	1	4	84	SEQ ID NO. 3052
(N20)NGG	8	48711805	-	CCGCCTGCACAGCCTCAGAGAGG	1	3	61	SEQ ID NO. 3053
(N20)NGG	8	48711840	-	ACAGCTCCAGGAGGGAGGCTGGG	2	13	114	SEQ ID NO. 3054
(N20)NGG	8	48711841	-	CACAGCTCCAGGAGGGAGGCTGG	2	14	149	SEQ ID NO. 3055
(N20)NGG	8	48711845	-	GGCCCACAGCTCCAGGAGGGAGG	1	18	172	SEQ ID NO. 3056
(N20)NGG	8	48711848	-	GCAGGCCCACAGCTCCAGGAGGG	1	8	101	SEQ ID NO. 3057
(N20)NGG	8	48711849	-	TGCAGGCCCACAGCTCCAGGAGG	2	11	104	SEQ ID NO. 3058
(N20)NGG	8	48711852	-	AGCTGCAGGCCCACAGCTCCAGG	2	17	119	SEQ ID NO. 3059
(N20)NGG	8	48711866	-	GCATCAATCACCCCAGCTGCAGG	1	1	32	SEQ ID NO. 3060
(N20)NGG	8	48711916	-	CTTCCTCCTTGCGCAGCTGTTGG	1	2	55	SEQ ID NO. 3061
(N20)NGG	8	48713394	+	CTACTTAAGCAAAAATATTCTGG	1	7	87	SEQ ID NO. 3062
(N20)NGG	8	48713421	+	CCGTGACCAGAACATTCTCTTGG	2	6	31	SEQ ID NO. 3063
(N20)NGG	8	48713422	+	CGTGACCAGAACATTCTCTTGGG	1	5	33	SEQ ID NO. 3064
(N20)NGG	8	48713435	+	TTCTCTTGGGTACAACTTACAGG	1	3	35	SEQ ID NO. 3065
(N20)NGG	8	48713487	+	AGCCTGCCTTGCTGAAATCGAGG	1	2	21	SEQ ID NO. 3066
(N20)NGG	8	48713490	+	CTGCCTTGCTGAAATCGAGGAGG	1	1	24	SEQ ID NO. 3067
(N20)NGG	8	48713496	+	TGCTGAAATCGAGGAGGACAAGG	1	3	23	SEQ ID NO. 3068
(N20)NGG	8	48713521	+	AGAAGAATCTTAGAGCTTTCTGG	1	6	67	SEQ ID NO. 3069
(N20)NGG	8	48713535	+	GCTTTCTGGATCCAGTTCAGAGG	1	2	39	SEQ ID NO. 3070
(N20)NGG	8	48713547	+	CAGTTCAGAGGATTCAGAGAAGG	1	5	92	SEQ ID NO. 3071
(N20)NGG	8	48713556	+	GGATTCAGAGAAGGTAATACTGG	1	3	47	SEQ ID NO. 3072
(N20)NGG	8	48713559	+	TTCAGAGAAGGTAATACTGGAGG	1	4	64	SEQ ID NO. 3073
(N20)NGG	8	48713346	-	GACACGTTGTTCTCATCTGTTGG	1	2	26	SEQ ID NO. 3074
(N20)NGG	8	48713399	-	CCAAGAGAATGTTCTGGTCACGG	1	7	53	SEQ ID NO. 3075
(N20)NGG	8	48713405	-	TTGTACCCAAGAGAATGTTCTGG	1	3	36	SEQ ID NO. 3076
(N20)NGG	8	48713463	-	TCGATTTCAGCAAGGCAGGCTGG	1	2	17	SEQ ID NO. 3077

FIG. 12 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	8	48713467	-	CTCCTCGATTTCAGCAAGGCAGG	1	1	19	SEQ ID NO. 3078
(N20)NGG	8	48713471	-	TGTCCTCCTCGATTTCAGCAAGG	1	2	17	SEQ ID NO. 3079
(N20)NGG	8	48713524	-	CTTCTCTGAATCCTCTGAACTGG	2	5	57	SEQ ID NO. 3080
(N20)NGG	8	48715899	+	ACTTGCTATGAAACTACTGAAGG	1	4	45	SEQ ID NO. 3081
(N20)NGG	8	48715934	+	AGTCAAAAACCAGAGACGATTGG	1	2	43	SEQ ID NO. 3082
(N20)NGG	8	48715938	+	AAAAACCAGAGACGATTGGCTGG	1	3	30	SEQ ID NO. 3083
(N20)NGG	8	48715946	+	GAGACGATTGGCTGGTGAGCTGG	1	1	30	SEQ ID NO. 3084
(N20)NGG	8	48715947	+	AGACGATTGGCTGGTGAGCTGGG	1	2	21	SEQ ID NO. 3085
(N20)NGG	8	48715979	+	ACTGCCGCCTGAGCCACTGCCGG	1	3	39	SEQ ID NO. 3086
(N20)NGG	8	48715985	+	GCCTGAGCCACTGCCGGAGCCGG	1	20	98	SEQ ID NO. 3087
(N20)NGG	8	48715992	+	CCACTGCCGGAGCCGGTCCCAGG	1	2	14	SEQ ID NO. 3088
(N20)NGG	8	48715993	+	CACTGCCGGAGCCGGTCCCAGGG	1	3	24	SEQ ID NO. 3089
(N20)NGG	8	48716007	+	GTCCCAGGGCTGCTCTGAGCAGG	2	15	239	SEQ ID NO. 3090
(N20)NGG	8	48716040	+	GCTGAAAACAGTCTCTTTGTTGG	1	7	89	SEQ ID NO. 3091
(N20)NGG	8	48716041	+	CTGAAAACAGTCTCTTTGTTGGG	1	8	89	SEQ ID NO. 3092
(N20)NGG	8	48715921	-	GCTCACCAGCCAATCGTCTCTGG	1	1	14	SEQ ID NO. 3093
(N20)NGG	8	48715961	-	GGCTCCGGCAGTGGCTCAGGCGG	1	20	66	SEQ ID NO. 3094
(N20)NGG	8	48715964	-	ACCGGCTCCGGCAGTGGCTCAGG	1	4	40	SEQ ID NO. 3095
(N20)NGG	8	48715970	-	CCTGGGACCGGCTCCGGCAGTGG	1	5	33	SEQ ID NO. 3096
(N20)NGG	8	48715976	-	AGCAGCCCTGGGACCGGCTCCGG	1	3	56	SEQ ID NO. 3097
(N20)NGG	8	48715982	-	GCTCAGAGCAGCCCTGGGACCGG	1	7	141	SEQ ID NO. 3098
(N20)NGG	8	48715987	-	CACCTGCTCAGAGCAGCCCTGGG	2	11	145	SEQ ID NO. 3099
(N20)NGG	8	48715988	-	GCACCTGCTCAGAGCAGCCCTGG	1	5	98	SEQ ID NO. 3100
(N20)NGG	8	48719722	+	TTTCTTTCTCAGCAAAATAGAGG	2	19	253	SEQ ID NO. 3101
(N20)NGG	8	48719764	+	AGAAGATAATAGTATGAATGTGG	1	6	95	SEQ ID NO. 3102
(N20)NGG	8	48719774	+	AGTATGAATGTGGATCAAGATGG	2	3	58	SEQ ID NO. 3103
(N20)NGG	8	48719790	+	AAGATGGAGACCCCAGTGACAGG	1	3	40	SEQ ID NO. 3104
(N20)NGG	8	48719794	+	TGGAGACCCCAGTGACAGGATGG	2	9	81	SEQ ID NO. 3105
(N20)NGG	8	48719809	+	CAGGATGGAAGTGCAAGAGCAGG	2	8	126	SEQ ID NO. 3106
(N20)NGG	8	48719835	+	AAGATATCAGCTCCCTGATCAGG	1	1	23	SEQ ID NO. 3107
(N20)NGG	8	48719880	+	TGAAGATGATAGACAGTGCCCGG	1	3	40	SEQ ID NO. 3108
(N20)NGG	8	48719887	+	GATAGACAGTGCCCGGAAGCAGG	1	1	11	SEQ ID NO. 3109
(N20)NGG	8	48719890	+	AGACAGTGCCCGGAAGCAGGTGG	1	4	45	SEQ ID NO. 3110

FIG. 12 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	8	48719891	+	GACAGTGCCCGGAAGCAGGTGGG	1	2	29	SEQ ID NO. 3111
(N20)NGG	8	48719732	-	ACTATTATCTTCTGGAAGAGGGG	1	10	71	SEQ ID NO. 3112
(N20)NGG	8	48719733	-	TACTATTATCTTCTGGAAGAGGG	1	4	79	SEQ ID NO. 3113
(N20)NGG	8	48719734	-	ATACTATTATCTTCTGGAAGAGG	1	3	56	SEQ ID NO. 3114
(N20)NGG	8	48719740	-	ACATTCATACTATTATCTTCTGG	1	6	173	SEQ ID NO. 3115
(N20)NGG	8	48719778	-	GCACTTCCATCCTGTCACTGGGG	1	3	33	SEQ ID NO. 3116
(N20)NGG	8	48719779	-	TGCACTTCCATCCTGTCACTGGG	1	2	25	SEQ ID NO. 3117
(N20)NGG	8	48719780	-	TTGCACTTCCATCCTGTCACTGG	2	4	26	SEQ ID NO. 3118
(N20)NGG	8	48719825	-	AAACTTGCAACTCCTGATCAGGG	1	1	30	SEQ ID NO. 3119
(N20)NGG	8	48719826	-	AAAACTTGCAACTCCTGATCAGG	1	3	23	SEQ ID NO. 3120
(N20)NGG	8	48719849	-	GTCTATCATCTTCATTTTCATGG	1	10	115	SEQ ID NO. 3121
(N20)NGG	8	48719876	-	ACGAGTACCCACCTGCTTCCGGG	1	1	11	SEQ ID NO. 3122
(N20)NGG	8	48719877	-	CACGAGTACCCACCTGCTTCCGG	1	1	12	SEQ ID NO. 3123
(N20)NGG	8	48730010	+	CACCCTCTAATACTATTTTTAGG	1	4	61	SEQ ID NO. 3124
(N20)NGG	8	48730056	+	TTAAGAGACTTCTGAACACCTGG	1	5	47	SEQ ID NO. 3125
(N20)NGG	8	48730084	+	CAGATATCCAGATGCTAAAATGG	1	2	78	SEQ ID NO. 3126
(N20)NGG	8	48730101	+	AAATGGACCCAATGAACATCTGG	1	3	67	SEQ ID NO. 3127
(N20)NGG	8	48730102	+	AATGGACCCAATGAACATCTGGG	1	3	39	SEQ ID NO. 3128
(N20)NGG	8	48730122	+	GGGATGACATCATCACAAATCGG	1	2	37	SEQ ID NO. 3129
(N20)NGG	8	48730132	+	CATCACAAATCGGTAAGACGTGG	1	1	9	SEQ ID NO. 3130
(N20)NGG	8	48729990	-	TGCCTAAAAATAGTATTAGAGGG	1	4	74	SEQ ID NO. 3131
(N20)NGG	8	48729991	-	TTGCCTAAAAATAGTATTAGAGG	1	2	75	SEQ ID NO. 3132
(N20)NGG	8	48730030	-	GTGTTCAGAAGTCTCTTAAGGGG	1	3	45	SEQ ID NO. 3133
(N20)NGG	8	48730031	-	GGTGTTCAGAAGTCTCTTAAGGG	1	3	34	SEQ ID NO. 3134
(N20)NGG	8	48730032	-	AGGTGTTCAGAAGTCTCTTAAGG	1	8	49	SEQ ID NO. 3135
(N20)NGG	8	48730052	-	ATCTGGATATCTGTTTGTCCAGG	1	6	143	SEQ ID NO. 3136
(N20)NGG	8	48730069	-	ATTGGGTCCATTTTAGCATCTGG	1	1	19	SEQ ID NO. 3137
(N20)NGG	8	48730086	-	TGTCATCCCAGATGTTCATTGGG	1	3	30	SEQ ID NO. 3138
(N20)NGG	8	48730087	-	ATGTCATCCCAGATGTTCATTGG	1	1	34	SEQ ID NO. 3139
(N20)NGG	8	48732025	+	CACCAAATTGCAGTCTGTACAGG	1	1	26	SEQ ID NO. 3140
(N20)NGG	8	48732043	+	ACAGGCTTTAACAGAAATTCAGG	1	2	51	SEQ ID NO. 3141
(N20)NGG	8	48732071	+	ATCAGCTTTATAAGCAAACAAGG	1	4	65	SEQ ID NO. 3142
(N20)NGG	8	48732087	+	AACAAGGTAATTTTTTTCATCGG	1	17	171	SEQ ID NO. 3143

FIG. 12 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	8	48731982	-	TGAGTCTACTTTGGTGTAAGAGG	1	3	26	SEQ ID NO. 3144
(N20)NGG	8	48731991	-	GCAATTTGGTGAGTCTACTTTGG	1	4	21	SEQ ID NO. 3145
(N20)NGG	8	48732005	-	AGCCTGTACAGACTGCAATTTGG	1	3	21	SEQ ID NO. 3146
(N20)NGG	8	48733279	+	AGTATATTTTTATGTTCCTTAGG	3	21	253	SEQ ID NO. 3147
(N20)NGG	8	48733330	+	CAAGCTGAAGCTGCTGCTCCAGG	2	13	138	SEQ ID NO. 3148
(N20)NGG	8	48733331	+	AAGCTGAAGCTGCTGCTCCAGGG	4	30	315	SEQ ID NO. 3149
(N20)NGG	8	48733336	+	GAAGCTGCTGCTCCAGGGAGAGG	2	9	186	SEQ ID NO. 3150
(N20)NGG	8	48733379	+	TTTATTGACAAAGCTATGCACGG	1	6	76	SEQ ID NO. 3151
(N20)NGG	8	48733380	+	TTATTGACAAAGCTATGCACGGG	1	1	29	SEQ ID NO. 3152
(N20)NGG	8	48733381	+	TATTGACAAAGCTATGCACGGGG	1	1	18	SEQ ID NO. 3153
(N20)NGG	8	48733393	+	TATGCACGGGGAGCTCCAGAAGG	1	5	26	SEQ ID NO. 3154
(N20)NGG	8	48733484	+	GCCAAATATTACATTCAAAATGG	1	7	127	SEQ ID NO. 3155
(N20)NGG	8	48733504	+	TGGCATTCAGAGTTTTATGCAGG	1	4	34	SEQ ID NO. 3156
(N20)NGG	8	48733273	-	TAAGGTAGATATGTTTCCTAAGG	1	3	54	SEQ ID NO. 3157
(N20)NGG	8	48733291	-	AGCTTGCTGCGGATCATGTAAGG	1	1	7	SEQ ID NO. 3158
(N20)NGG	8	48733302	-	GCAGCAGCTTCAGCTTGCTGCGG	1	8	96	SEQ ID NO. 3159
(N20)NGG	8	48733326	-	GGGACTGGTCAGCCTCTCCCTGG	1	4	41	SEQ ID NO. 3160
(N20)NGG	8	48733341	-	CAATAAATGTCAGCAGGGACTGG	1	5	56	SEQ ID NO. 3161
(N20)NGG	8	48733346	-	TTTGTCAATAAATGTCAGCAGGG	1	7	80	SEQ ID NO. 3162
(N20)NGG	8	48733347	-	CTTTGTCAATAAATGTCAGCAGG	1	6	51	SEQ ID NO. 3163
(N20)NGG	8	48733386	-	GAAGCTCTAGAATCGCCTTCTGG	1	1	14	SEQ ID NO. 3164
(N20)NGG	8	48733437	-	TGTCAACATCATCTTGCAGGAGG	1	1	37	SEQ ID NO. 3165
(N20)NGG	8	48733440	-	CTCTGTCAACATCATCTTGCAGG	1	3	41	SEQ ID NO. 3166
(N20)NGG	8	48733463	-	GCCATTTTGAATGTAATATTTGG	1	4	97	SEQ ID NO. 3167
(N20)NGG	8	48734164	+	TTTATTAACTTTTCTCCACTAGG	1	9	169	SEQ ID NO. 3168
(N20)NGG	8	48734184	+	AGGCTCTCAATAAACAAGACTGG	1	3	34	SEQ ID NO. 3169
(N20)NGG	8	48734185	+	GGCTCTCAATAAACAAGACTGGG	1	5	31	SEQ ID NO. 3170
(N20)NGG	8	48734192	+	AATAAACAAGACTGGGTAGATGG	1	5	73	SEQ ID NO. 3171
(N20)NGG	8	48734215	+	TGAGCCCACAGAAGCCGAGAAGG	1	5	67	SEQ ID NO. 3172
(N20)NGG	8	48734223	+	CAGAAGCCGAGAAGGATTTTTGG	1	3	40	SEQ ID NO. 3173
(N20)NGG	8	48734224	+	AGAAGCCGAGAAGGATTTTTGGG	1	2	44	SEQ ID NO. 3174
(N20)NGG	8	48734265	+	GTTACAACCACCTTGCTGAGTGG	2	3	22	SEQ ID NO. 3175
(N20)NGG	8	48734334	+	CCCCAGACCTAAATAAAATCTGG	1	2	38	SEQ ID NO. 3176

FIG. 12 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	8	48734353	+	CTGGAGTGAACCATTTTATCAGG	1	5	41	SEQ ID NO. 3177
(N20)NGG	8	48734356	+	GAGTGAACCATTTTATCAGGTGG	1	2	42	SEQ ID NO. 3178
(N20)NGG	8	48734357	+	AGTGAACCATTTTATCAGGTGGG	1	3	42	SEQ ID NO. 3179
(N20)NGG	8	48734157	-	CTTGTTTATTGAGAGCCTAGTGG	1	2	39	SEQ ID NO. 3180
(N20)NGG	8	48734197	-	AAATCCTTCTCGGCTTCTGTGGG	1	2	29	SEQ ID NO. 3181
(N20)NGG	8	48734198	-	AAAATCCTTCTCGGCTTCTGTGG	1	1	39	SEQ ID NO. 3182
(N20)NGG	8	48734207	-	AAGTTCCCAAAAATCCTTCTCGG	1	4	67	SEQ ID NO. 3183
(N20)NGG	8	48734234	-	AAGGTGGTTGTAACAGTCAAGGG	1	3	29	SEQ ID NO. 3184
(N20)NGG	8	48734235	-	CAAGGTGGTTGTAACAGTCAAGG	1	2	39	SEQ ID NO. 3185
(N20)NGG	8	48734250	-	GTGATTTCCACTCAGCAAGGTGG	1	2	36	SEQ ID NO. 3186
(N20)NGG	8	48734253	-	CAAGTGATTTCCACTCAGCAAGG	1	2	36	SEQ ID NO. 3187
(N20)NGG	8	48734291	-	GGGGTTCTCACTGTCTATACTGG	1	1	24	SEQ ID NO. 3188
(N20)NGG	8	48734310	-	AGATTTTATTTAGGTCTGGGGGG	1	2	44	SEQ ID NO. 3189
(N20)NGG	8	48734311	-	CAGATTTTATTTAGGTCTGGGGG	2	3	58	SEQ ID NO. 3190
(N20)NGG	8	48734312	-	CCAGATTTTATTTAGGTCTGGGG	1	1	49	SEQ ID NO. 3191
(N20)NGG	8	48734313	-	TCCAGATTTTATTTAGGTCTGGG	1	3	83	SEQ ID NO. 3192
(N20)NGG	8	48734314	-	CTCCAGATTTTATTTAGGTCTGG	1	5	43	SEQ ID NO. 3193
(N20)NGG	8	48734319	-	GTTCACTCCAGATTTTATTTAGG	2	6	102	SEQ ID NO. 3194
(N20)NGG	8	48734341	-	ATTTTACCCACCTGATAAAATGG	1	5	95	SEQ ID NO. 3195
(N20)NGG	8	48736418	+	GCCTTTTTGATTTGTTTTGTAGG	1	19	440	SEQ ID NO. 3196
(N20)NGG	8	48736435	+	TGTAGGCTGTATAGATCAATTGG	1	2	24	SEQ ID NO. 3197
(N20)NGG	8	48736456	+	GGAGAATACGACGTCCTCCGTGG	1	1	3	SEQ ID NO. 3198
(N20)NGG	8	48736457	+	GAGAATACGACGTCCTCCGTGGG	1	1	2	SEQ ID NO. 3199
(N20)NGG	8	48736477	+	GGGATTTTTACCAGTGAGATAGG	1	5	46	SEQ ID NO. 3200
(N20)NGG	8	48736557	+	AGCTGCTAAGCAGTATGATGAGG	1	3	41	SEQ ID NO. 3201
(N20)NGG	8	48736573	+	GATGAGGTAAAATTGATCTCTGG	1	2	48	SEQ ID NO. 3202
(N20)NGG	8	48736397	-	GCCTACAAAACAAATCAAAAAGG	1	12	260	SEQ ID NO. 3203
(N20)NGG	8	48736448	-	CACTGGTAAAAATCCCACGGAGG	1	2	19	SEQ ID NO. 3204
(N20)NGG	8	48736451	-	TCTCACTGGTAAAAATCCCACGG	1	7	62	SEQ ID NO. 3205
(N20)NGG	8	48736465	-	TTGCTTTGTTCCTATCTCACTGG	2	3	79	SEQ ID NO. 3206
(N20)NGG	8	48736516	-	AGCTTCAGAATAATCACTTCTGG	1	3	60	SEQ ID NO. 3207
(N20)NGG	8	48739216	+	GGTTGTATGTGTGGTTTCACAGG	1	2	41	SEQ ID NO. 3208
(N20)NGG	8	48739261	+	CCTGCTGAGCCTCGACCCAGCGG	1	2	42	SEQ ID NO. 3209

FIG. 12 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	8	48739274	+	GACCCAGCGGCTGTTAGCGCTGG	1	1	3	SEQ ID NO. 3210
(N20)NGG	8	48739282	+	GGCTGTTAGCGCTGGTTGCCTGG	1	1	6	SEQ ID NO. 3211
(N20)NGG	8	48739303	+	GGCCAGCCTACAGCAGCCCGTGG	1	2	30	SEQ ID NO. 3212
(N20)NGG	8	48739304	+	GCCAGCCTACAGCAGCCCGTGGG	1	2	17	SEQ ID NO. 3213
(N20)NGG	8	48739321	+	CGTGGGCATCCGCCTGCTAGAGG	1	6	20	SEQ ID NO. 3214
(N20)NGG	8	48739324	+	GGGCATCCGCCTGCTAGAGGAGG	1	8	30	SEQ ID NO. 3215
(N20)NGG	8	48739373	+	CTGCCTGCCAAGCGAGTCCGTGG	1	1	8	SEQ ID NO. 3216
(N20)NGG	8	48739374	+	TGCCTGCCAAGCGAGTCCGTGGG	1	1	5	SEQ ID NO. 3217
(N20)NGG	8	48739378	+	TGCCAAGCGAGTCCGTGGGAAGG	1	1	9	SEQ ID NO. 3218
(N20)NGG	8	48739407	+	TCCCTCCTGATGTCCTCAGATGG	1	2	55	SEQ ID NO. 3219
(N20)NGG	8	48739408	+	CCCTCCTGATGTCCTCAGATGGG	1	3	39	SEQ ID NO. 3220
(N20)NGG	8	48739411	+	TCCTGATGTCCTCAGATGGGTGG	1	5	46	SEQ ID NO. 3221
(N20)NGG	8	48739433	+	GAGCTTGCTAAGTAAGTGTGAGG	1	6	26	SEQ ID NO. 3222
(N20)NGG	8	48739438	+	TGCTAAGTAAGTGTGAGGTCAGG	1	1	35	SEQ ID NO. 3223
(N20)NGG	8	48739238	-	CGCTGGGTCGAGGCTCAGCAGGG	1	1	26	SEQ ID NO. 3224
(N20)NGG	8	48739239	-	CCGCTGGGTCGAGGCTCAGCAGG	1	1	17	SEQ ID NO. 3225
(N20)NGG	8	48739248	-	CGCTAACAGCCGCTGGGTCGAGG	1	1	2	SEQ ID NO. 3226
(N20)NGG	8	48739254	-	AACCAGCGCTAACAGCCGCTGGG	1	1	4	SEQ ID NO. 3227
(N20)NGG	8	48739255	-	CAACCAGCGCTAACAGCCGCTGG	1	2	4	SEQ ID NO. 3228
(N20)NGG	8	48739278	-	CGGGCTGCTGTAGGCTGGCCAGG	1	2	26	SEQ ID NO. 3229
(N20)NGG	8	48739283	-	GCCCACGGGCTGCTGTAGGCTGG	1	1	25	SEQ ID NO. 3230
(N20)NGG	8	48739287	-	GGATGCCCACGGGCTGCTGTAGG	1	2	38	SEQ ID NO. 3231
(N20)NGG	8	48739297	-	TCTAGCAGGCGGATGCCCACGGG	1	3	28	SEQ ID NO. 3232
(N20)NGG	8	48739298	-	CTCTAGCAGGCGGATGCCCACGG	1	7	13	SEQ ID NO. 3233
(N20)NGG	8	48739308	-	GCAGAGCCTCCTCTAGCAGGCGG	1	5	72	SEQ ID NO. 3234
(N20)NGG	8	48739311	-	GGAGCAGAGCCTCCTCTAGCAGG	1	4	43	SEQ ID NO. 3235
(N20)NGG	8	48739332	-	GCAGCTCAGCAGGCAGCAGGCGG	2	14	212	SEQ ID NO. 3236
(N20)NGG	8	48739335	-	CAGGCAGCTCAGCAGGCAGCAGG	2	28	218	SEQ ID NO. 3237
(N20)NGG	8	48739342	-	CGCTTGGCAGGCAGCTCAGCAGG	2	5	47	SEQ ID NO. 3238
(N20)NGG	8	48739354	-	TTCCCACGGACTCGCTTGGCAGG	1	1	7	SEQ ID NO. 3239
(N20)NGG	8	48739358	-	GGCCTTCCCACGGACTCGCTTGG	1	2	6	SEQ ID NO. 3240
(N20)NGG	8	48739368	-	GAGGGAGGCGGGCCTTCCCACGG	2	5	57	SEQ ID NO. 3241
(N20)NGG	8	48739379	-	GAGGACATCAGGAGGGAGGCGGG	1	7	124	SEQ ID NO. 3242

FIG. 12 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	8	48739380	-	TGAGGACATCAGGAGGGAGGCGG	2	17	168	SEQ ID NO. 3243
(N20)NGG	8	48739383	-	ATCTGAGGACATCAGGAGGGAGG	1	3	71	SEQ ID NO. 3244
(N20)NGG	8	48739386	-	CCCATCTGAGGACATCAGGAGGG	1	2	52	SEQ ID NO. 3245
(N20)NGG	8	48739387	-	ACCCATCTGAGGACATCAGGAGG	1	1	33	SEQ ID NO. 3246
(N20)NGG	8	48739390	-	TCCACCCATCTGAGGACATCAGG	1	1	35	SEQ ID NO. 3247
(N20)NGG	8	48739398	-	TAGCAAGCTCCACCCATCTGAGG	1	2	24	SEQ ID NO. 3248
(N20)NGG	8	48740730	+	TTGTTTTGAATTTTTTACAGAGG	1	38	467	SEQ ID NO. 3249
(N20)NGG	8	48740731	+	TGTTTTGAATTTTTTACAGAGGG	3	24	669	SEQ ID NO. 3250
(N20)NGG	8	48740774	+	CTCTTTAGCAGCTTGTTTTCTGG	1	6	55	SEQ ID NO. 3251
(N20)NGG	8	48740791	+	TTCTGGAATTTTGAAAGAGATGG	3	15	244	SEQ ID NO. 3252
(N20)NGG	8	48740908	+	ACCCTTTGTCTCTTGTATTCAGG	1	3	89	SEQ ID NO. 3253
(N20)NGG	8	48740733	-	AGAGCTGTTTTGCAATTATTGGG	2	4	87	SEQ ID NO. 3254
(N20)NGG	8	48740734	-	AAGAGCTGTTTTGCAATTATTGG	1	5	73	SEQ ID NO. 3255
(N20)NGG	8	48740867	-	GGGTGGAAAGAAAGAGAAGGTGG	6	51	772	SEQ ID NO. 3256
(N20)NGG	8	48740870	-	AAAGGGTGGAAAGAAAGAGAAGG	4	94	1695	SEQ ID NO. 3257
(N20)NGG	8	48740884	-	TGAATACAAGAGACAAAGGGTGG	1	5	118	SEQ ID NO. 3258
(N20)NGG	8	48740887	-	ACCTGAATACAAGAGACAAAGGG	1	2	67	SEQ ID NO. 3259
(N20)NGG	8	48740888	-	TACCTGAATACAAGAGACAAAGG	1	6	51	SEQ ID NO. 3260
(N20)NGG	8	48743165	+	TCTTTGGTTCTGGTGCTTATAGG	1	2	51	SEQ ID NO. 3261
(N20)NGG	8	48743195	+	GAGTGAGTTAAAAATGAAGCAGG	1	4	76	SEQ ID NO. 3262
(N20)NGG	8	48743204	+	AAAAATGAAGCAGGATGCCCAGG	1	3	93	SEQ ID NO. 3263
(N20)NGG	8	48743227	+	TCGTTCTGTACAGAAGCTACCGG	1	1	13	SEQ ID NO. 3264
(N20)NGG	8	48743232	+	CTGTACAGAAGCTACCGGCACGG	1	3	14	SEQ ID NO. 3265
(N20)NGG	8	48743285	+	CAGCCTCATCACCCCGTTACAGG	1	2	18	SEQ ID NO. 3266
(N20)NGG	8	48743291	+	CATCACCCCGTTACAGGCCGTGG	1	1	28	SEQ ID NO. 3267
(N20)NGG	8	48743297	+	CCCGTTACAGGCCGTGGCCCAGG	1	1	5	SEQ ID NO. 3268
(N20)NGG	8	48743199	-	GCTTCTGTACAGAACGACCTGGG	1	1	19	SEQ ID NO. 3269
(N20)NGG	8	48743200	-	AGCTTCTGTACAGAACGACCTGG	1	1	7	SEQ ID NO. 3270
(N20)NGG	8	48743224	-	TGTCAGGAAGGTCTCCGTGCCGG	1	3	23	SEQ ID NO. 3271
(N20)NGG	8	48743236	-	GCTTGATCTGAATGTCAGGAAGG	1	5	42	SEQ ID NO. 3272
(N20)NGG	8	48743240	-	CTGTGCTTGATCTGAATGTCAGG	1	2	28	SEQ ID NO. 3273
(N20)NGG	8	48743266	-	CGGCCTGTAACGGGGTGATGAGG	1	1	7	SEQ ID NO. 3274
(N20)NGG	8	48743274	-	CTGGGCCACGGCCTGTAACGGGG	1	1	8	SEQ ID NO. 3275

FIG. 12 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	8	48743275	-	CCTGGGCCACGGCCTGTAACGGG	1	1	31	SEQ ID NO. 3276
(N20)NGG	8	48743276	-	ACCTGGGCCACGGCCTGTAACGG	1	2	11	SEQ ID NO. 3277
(N20)NGG	8	48743286	-	GCAAAAACTGACCTGGGCCACGG	1	3	40	SEQ ID NO. 3278
(N20)NGG	8	48743292	-	GCAGCGGCAAAAACTGACCTGGG	1	2	19	SEQ ID NO. 3279
(N20)NGG	8	48743293	-	CGCAGCGGCAAAAACTGACCTGG	1	1	12	SEQ ID NO. 3280
(N20)NGG	8	48744374	+	TGGGCCTGCTTTCCCTCTCCAGG	1	8	68	SEQ ID NO. 3281
(N20)NGG	8	48744379	+	CTGCTTTCCCTCTCCAGGTGCGG	2	12	111	SEQ ID NO. 3282
(N20)NGG	8	48744383	+	TTTCCCTCTCCAGGTGCGGCCGG	1	2	30	SEQ ID NO. 3283
(N20)NGG	8	48744387	+	CCTCTCCAGGTGCGGCCGGCCGG	1	3	25	SEQ ID NO. 3284
(N20)NGG	8	48744391	+	TCCAGGTGCGGCCGGCCGGACGG	1	2	23	SEQ ID NO. 3285
(N20)NGG	8	48744414	+	ACCTACTACGACTGCGCAGACGG	1	1	5	SEQ ID NO. 3286
(N20)NGG	8	48744423	+	GACTGCGCAGACGGTTTATGAGG	1	1	3	SEQ ID NO. 3287
(N20)NGG	8	48744424	+	ACTGCGCAGACGGTTTATGAGGG	1	1	2	SEQ ID NO. 3288
(N20)NGG	8	48744430	+	CAGACGGTTTATGAGGGACCAGG	1	1	10	SEQ ID NO. 3289
(N20)NGG	8	48744461	+	AGTTTGATGTATGCCAGAAAAGG	1	1	77	SEQ ID NO. 3290
(N20)NGG	8	48744487	+	TGCTGAGCAAAAACGAGAGAAGG	1	4	56	SEQ ID NO. 3291
(N20)NGG	8	48744356	-	CGCACCTGGAGAGGGAAAGCAGG	1	3	41	SEQ ID NO. 3292
(N20)NGG	8	48744364	-	CGGCCGGCCGCACCTGGAGAGGG	1	4	22	SEQ ID NO. 3293
(N20)NGG	8	48744365	-	CCGGCCGGCCGCACCTGGAGAGG	1	3	35	SEQ ID NO. 3294
(N20)NGG	8	48744370	-	TCCGTCCGGCCGGCCGCACCTGG	1	2	25	SEQ ID NO. 3295
(N20)NGG	8	48744380	-	TCGTAGTAGGTCCGTCCGGCCGG	1	1	1	SEQ ID NO. 3296
(N20)NGG	8	48744384	-	GCAGTCGTAGTAGGTCCGTCCGG	1	1	1	SEQ ID NO. 3297
(N20)NGG	8	48744393	-	ACCGTCTGCGCAGTCGTAGTAGG	1	1	3	SEQ ID NO. 3298
(N20)NGG	8	48744426	-	ACATCAAACTGAGCTTCTCCTGG	1	3	41	SEQ ID NO. 3299
(N20)NGG	8	48744452	-	TTGCTCAGCAACGCCTTTTCTGG	1	2	26	SEQ ID NO. 3300
(N20)NGG	8	48746759	+	CTCTGATTGCATGTCACAGATGG	1	2	46	SEQ ID NO. 3301
(N20)NGG	8	48746778	+	ATGGAAGAAGCTCATTTGATTGG	1	2	51	SEQ ID NO. 3302
(N20)NGG	8	48746786	+	AGCTCATTTGATTGGCTGACCGG	1	1	28	SEQ ID NO. 3303
(N20)NGG	8	48746787	+	GCTCATTTGATTGGCTGACCGGG	1	1	13	SEQ ID NO. 3304
(N20)NGG	8	48746806	+	CGGGAGCAGCACTGACCCGCTGG	2	2	18	SEQ ID NO. 3305
(N20)NGG	8	48746856	+	CCTTGCTGTTTGCCCACAAGAGG	1	4	45	SEQ ID NO. 3306
(N20)NGG	8	48746865	+	TTGCCCACAAGAGGAGTGAAAGG	1	3	47	SEQ ID NO. 3307
(N20)NGG	8	48746893	+	GAGAGCACCCTTGAAGTCAGTGG	1	2	38	SEQ ID NO. 3308

FIG. 12 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	8	48746894	+	AGAGCACCCTTGAAGTCAGTGGG	1	1	29	SEQ ID NO. 3309
(N20)NGG	8	48746895	+	GAGCACCCTTGAAGTCAGTGGGG	1	1	36	SEQ ID NO. 3310
(N20)NGG	8	48746906	+	AAGTCAGTGGGGCCTGATTTTGG	1	1	40	SEQ ID NO. 3311
(N20)NGG	8	48746907	+	AGTCAGTGGGGCCTGATTTTGGG	1	1	42	SEQ ID NO. 3312
(N20)NGG	8	48746916	+	GGCCTGATTTTGGGAAAAAAAGG	1	4	82	SEQ ID NO. 3313
(N20)NGG	8	48746920	+	TGATTTTGGGAAAAAAAGGCTGG	2	11	128	SEQ ID NO. 3314
(N20)NGG	8	48746921	+	GATTTTGGGAAAAAAAGGCTGGG	1	9	103	SEQ ID NO. 3315
(N20)NGG	8	48746930	+	AAAAAAAGGCTGGGCCTTCCAGG	1	6	87	SEQ ID NO. 3316
(N20)NGG	8	48746931	+	AAAAAAGGCTGGGCCTTCCAGGG	1	3	46	SEQ ID NO. 3317
(N20)NGG	8	48746932	+	AAAAAGGCTGGGCCTTCCAGGGG	2	3	54	SEQ ID NO. 3318
(N20)NGG	8	48746938	+	GCTGGGCCTTCCAGGGGACGAGG	1	6	58	SEQ ID NO. 3319
(N20)NGG	8	48746941	+	GGGCCTTCCAGGGGACGAGGTGG	1	5	63	SEQ ID NO. 3320
(N20)NGG	8	48746957	+	GAGGTGGATAACAAAGTGAAAGG	1	3	104	SEQ ID NO. 3321
(N20)NGG	8	48746965	+	TAACAAAGTGAAAGGTAAGCTGG	1	7	64	SEQ ID NO. 3322
(N20)NGG	8	48746966	+	AACAAAGTGAAAGGTAAGCTGGG	1	8	103	SEQ ID NO. 3323
(N20)NGG	8	48746734	-	TCTGTGACATGCAATCAGAGAGG	1	2	56	SEQ ID NO. 3324
(N20)NGG	8	48746783	-	CAGCGGGTCAGTGCTGCTCCCGG	1	3	31	SEQ ID NO. 3325
(N20)NGG	8	48746799	-	GACTGGTGTGGTCGACCAGCGGG	1	1	5	SEQ ID NO. 3326
(N20)NGG	8	48746800	-	GGACTGGTGTGGTCGACCAGCGG	1	2	11	SEQ ID NO. 3327
(N20)NGG	8	48746811	-	AGTCAGATGAGGGACTGGTGTGG	1	4	64	SEQ ID NO. 3328
(N20)NGG	8	48746816	-	CAAGGAGTCAGATGAGGGACTGG	2	2	50	SEQ ID NO. 3329
(N20)NGG	8	48746821	-	AACAGCAAGGAGTCAGATGAGGG	1	5	57	SEQ ID NO. 3330
(N20)NGG	8	48746822	-	AAACAGCAAGGAGTCAGATGAGG	2	5	103	SEQ ID NO. 3331
(N20)NGG	8	48746834	-	CCTCTTGTGGGCAAACAGCAAGG	1	1	45	SEQ ID NO. 3332
(N20)NGG	8	48746846	-	TAACCTTTCACTCCTCTTGTGGG	1	4	51	SEQ ID NO. 3333
(N20)NGG	8	48746847	-	GTAACCTTTCACTCCTCTTGTGG	1	1	20	SEQ ID NO. 3334
(N20)NGG	8	48746878	-	TCAGGCCCCACTGACTTCAAGGG	1	5	50	SEQ ID NO. 3335
(N20)NGG	8	48746879	-	ATCAGGCCCCACTGACTTCAAGG	1	3	47	SEQ ID NO. 3336
(N20)NGG	8	48746896	-	AGCCTTTTTTTCCCAAAATCAGG	1	6	84	SEQ ID NO. 3337
(N20)NGG	8	48746922	-	TATCCACCTCGTCCCCTGGAAGG	1	2	13	SEQ ID NO. 3338
(N20)NGG	8	48746926	-	TTGTTATCCACCTCGTCCCCTGG	1	1	18	SEQ ID NO. 3339
(N20)NGG	8	48748898	+	TTTGAAACTTTCTTATGTACAGG	1	5	95	SEQ ID NO. 3340
(N20)NGG	8	48748921	+	AATATACCATTGATTCTGATTGG	2	2	58	SEQ ID NO. 3341

FIG. 12 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	8	48748958	+	TGTTCTCACTCCGATGTTTGTGG	1	2	18	SEQ ID NO. 3342
(N20)NGG	8	48748967	+	TCCGATGTTTGTGGAGACCCAGG	1	3	17	SEQ ID NO. 3343
(N20)NGG	8	48748976	+	TGTGGAGACCCAGGCCTCCCAGG	1	11	71	SEQ ID NO. 3344
(N20)NGG	8	48748977	+	GTGGAGACCCAGGCCTCCCAGGG	2	8	79	SEQ ID NO. 3345
(N20)NGG	8	48749000	+	CACTCTCCAGACCCGTACCCAGG	1	3	19	SEQ ID NO. 3346
(N20)NGG	8	48749004	+	CTCCAGACCCGTACCCAGGAAGG	1	2	27	SEQ ID NO. 3347
(N20)NGG	8	48749005	+	TCCAGACCCGTACCCAGGAAGGG	1	2	41	SEQ ID NO. 3348
(N20)NGG	8	48749023	+	AAGGGTCCCTCTCAGCTCGCTGG	1	3	26	SEQ ID NO. 3349
(N20)NGG	8	48749030	+	CCTCTCAGCTCGCTGGCCAGTGG	1	3	38	SEQ ID NO. 3350
(N20)NGG	8	48749034	+	TCAGCTCGCTGGCCAGTGGCAGG	1	3	26	SEQ ID NO. 3351
(N20)NGG	8	48749035	+	CAGCTCGCTGGCCAGTGGCAGGG	2	10	62	SEQ ID NO. 3352
(N20)NGG	8	48749044	+	GGCCAGTGGCAGGGCAGATAAGG	1	6	71	SEQ ID NO. 3353
(N20)NGG	8	48749045	+	GCCAGTGGCAGGGCAGATAAGGG	1	7	75	SEQ ID NO. 3354
(N20)NGG	8	48749088	+	TTCACACTGACACAGACTGCAGG	2	2	53	SEQ ID NO. 3355
(N20)NGG	8	48749110	+	GTAACAGTGACCCTGCCCGCTGG	1	1	13	SEQ ID NO. 3356
(N20)NGG	8	48748905	-	GAAACGCCAATCAGAATCAATGG	1	2	35	SEQ ID NO. 3357
(N20)NGG	8	48748927	-	TCGGAGTGAGAACAGTACTTCGG	1	3	19	SEQ ID NO. 3358
(N20)NGG	8	48748946	-	GCCTGGGTCTCCACAAACATCGG	2	4	55	SEQ ID NO. 3359
(N20)NGG	8	48748962	-	GAGAGTGCCCTGGGAGGCCTGGG	1	6	76	SEQ ID NO. 3360
(N20)NGG	8	48748963	-	GGAGAGTGCCCTGGGAGGCCTGG	1	13	140	SEQ ID NO. 3361
(N20)NGG	8	48748968	-	GGTCTGGAGAGTGCCCTGGGAGG	1	5	107	SEQ ID NO. 3362
(N20)NGG	8	48748971	-	ACGGGTCTGGAGAGTGCCCTGGG	1	1	22	SEQ ID NO. 3363
(N20)NGG	8	48748972	-	TACGGGTCTGGAGAGTGCCCTGG	1	1	12	SEQ ID NO. 3364
(N20)NGG	8	48748984	-	ACCCTTCCTGGGTACGGGTCTGG	1	1	17	SEQ ID NO. 3365
(N20)NGG	8	48748989	-	GAGGGACCCTTCCTGGGTACGGG	1	3	35	SEQ ID NO. 3366
(N20)NGG	8	48748990	-	AGAGGGACCCTTCCTGGGTACGG	1	3	41	SEQ ID NO. 3367
(N20)NGG	8	48748995	-	AGCTGAGAGGGACCCTTCCTGGG	1	4	47	SEQ ID NO. 3368
(N20)NGG	8	48748996	-	GAGCTGAGAGGGACCCTTCCTGG	1	6	49	SEQ ID NO. 3369
(N20)NGG	8	48749007	-	CACTGGCCAGCGAGCTGAGAGGG	1	5	25	SEQ ID NO. 3370
(N20)NGG	8	48749008	-	CCACTGGCCAGCGAGCTGAGAGG	1	2	38	SEQ ID NO. 3371
(N20)NGG	8	48749024	-	GCCCTTATCTGCCCTGCCACTGG	1	3	44	SEQ ID NO. 3372
(N20)NGG	8	48749046	-	GAAGTCATGCTGCTGCTGGGTGG	1	9	71	SEQ ID NO. 3373
(N20)NGG	8	48749049	-	TGTGAAGTCATGCTGCTGCTGGG	1	2	53	SEQ ID NO. 3374

FIG. 12 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	8	48749050	-	GTGTGAAGTCATGCTGCTGCTGG	1	3	34	SEQ ID NO. 3375
(N20)NGG	8	48749793	+	GATTAATTATTCGAAATTTCTGG	1	2	34	SEQ ID NO. 3376
(N20)NGG	8	48749808	+	ATTTCTGGAGCCATGAAACTAGG	1	5	94	SEQ ID NO. 3377
(N20)NGG	8	48749827	+	TAGGTTACCTTCAAATACCTTGG	1	1	22	SEQ ID NO. 3378
(N20)NGG	8	48749832	+	TACCTTCAAATACCTTGGACCGG	1	1	27	SEQ ID NO. 3379
(N20)NGG	8	48749839	+	AAATACCTTGGACCGGTTGCTGG	1	1	6	SEQ ID NO. 3380
(N20)NGG	8	48749980	+	TCTGTCAGAATGCGAATTTCAGG	1	1	22	SEQ ID NO. 3381
(N20)NGG	8	48749988	+	AATGCGAATTTCAGGTAATGTGG	1	5	40	SEQ ID NO. 3382
(N20)NGG	8	48749796	-	TTGAAGGTAACCTAGTTTCATGG	1	3	31	SEQ ID NO. 3383
(N20)NGG	8	48749812	-	AACCGGTCCAAGGTATTTGAAGG	1	1	6	SEQ ID NO. 3384
(N20)NGG	8	48749822	-	TAGTGCCAGCAACCGGTCCAAGG	1	1	10	SEQ ID NO. 3385
(N20)NGG	8	48749829	-	AGGAATTTAGTGCCAGCAACCGG	1	5	51	SEQ ID NO. 3386
(N20)NGG	8	48749849	-	TTCTATCTTAGGAGAATATAAGG	1	5	95	SEQ ID NO. 3387
(N20)NGG	8	48749860	-	AAAAAGTGCACTTCTATCTTAGG	1	4	72	SEQ ID NO. 3388
(N20)NGG	8	48749915	-	TGGATAATCTGGGCTCATGCTGG	1	2	12	SEQ ID NO. 3389
(N20)NGG	8	48749925	-	ACATGGGGTTTGGATAATCTGGG	2	2	30	SEQ ID NO. 3390
(N20)NGG	8	48749926	-	AACATGGGGTTTGGATAATCTGG	1	4	28	SEQ ID NO. 3391
(N20)NGG	8	48749935	-	GGATGCTCGAACATGGGGTTTGG	1	3	14	SEQ ID NO. 3392
(N20)NGG	8	48749940	-	ACAGAGGATGCTCGAACATGGGG	1	1	18	SEQ ID NO. 3393
(N20)NGG	8	48749941	-	GACAGAGGATGCTCGAACATGGG	1	1	6	SEQ ID NO. 3394
(N20)NGG	8	48749942	-	TGACAGAGGATGCTCGAACATGG	1	2	14	SEQ ID NO. 3395
(N20)NGG	8	48749956	-	TGAAATTCGCATTCTGACAGAGG	1	2	25	SEQ ID NO. 3396
(N20)NGG	8	48751742	+	TGAGACAGATAATGACTCCCAGG	1	4	36	SEQ ID NO. 3397
(N20)NGG	8	48751757	+	CTCCCAGGAAATATTTAAGTTGG	1	4	69	SEQ ID NO. 3398
(N20)NGG	8	48751779	+	GCAAAAGATGTGCTGATTCAAGG	1	1	50	SEQ ID NO. 3399
(N20)NGG	8	48751800	+	GGATTGATCGATGAGAACCCTGG	1	1	5	SEQ ID NO. 3400
(N20)NGG	8	48751822	+	GACTTCAGTACGTGAATAACTGG	1	4	17	SEQ ID NO. 3401
(N20)NGG	8	48751823	+	ACTTCAGTACGTGAATAACTGGG	1	2	16	SEQ ID NO. 3402
(N20)NGG	8	48751827	+	CAGTACGTGAATAACTGGGCTGG	1	1	6	SEQ ID NO. 3403
(N20)NGG	8	48751828	+	AGTACGTGAATAACTGGGCTGGG	1	1	14	SEQ ID NO. 3404
(N20)NGG	8	48751712	-	TCATTATCTGTCTCACTTTCTGG	1	29	133	SEQ ID NO. 3405
(N20)NGG	8	48751737	-	TGCCAACTTAAATATTTCCTGGG	1	2	82	SEQ ID NO. 3406
(N20)NGG	8	48751738	-	TTGCCAACTTAAATATTTCCTGG	1	6	76	SEQ ID NO. 3407

FIG. 12 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	8	48751795	-	TATTCACGTACTGAAGTCCAGGG	1	1	16	SEQ ID NO. 3408
(N20)NGG	8	48751796	-	TTATTCACGTACTGAAGTCCAGG	1	1	14	SEQ ID NO. 3409
(N20)NGG	8	48752604	+	TGAAAGACAAAAAGTATGTTTGG	2	14	184	SEQ ID NO. 3410
(N20)NGG	8	48752673	+	AGAACTTCTGAACCCCGTTGTGG	1	2	15	SEQ ID NO. 3411
(N20)NGG	8	48752705	+	CCCATCCTTCTACAACATGTAGG	1	3	24	SEQ ID NO. 3412
(N20)NGG	8	48752706	+	CCATCCTTCTACAACATGTAGGG	2	4	28	SEQ ID NO. 3413
(N20)NGG	8	48752732	+	AAATGTATAATATTCTCATGTGG	2	11	185	SEQ ID NO. 3414
(N20)NGG	8	48752750	+	TGTGGATTCATGATAATTACAGG	1	3	31	SEQ ID NO. 3415
(N20)NGG	8	48752569	-	TTGTCTTTCATCATCTCTATGGG	2	7	124	SEQ ID NO. 3416
(N20)NGG	8	48752570	-	TTTGTCTTTCATCATCTCTATGG	3	12	151	SEQ ID NO. 3417
(N20)NGG	8	48752625	-	AGTTCTACTGGTTTTAACTTTGG	1	4	62	SEQ ID NO. 3418
(N20)NGG	8	48752637	-	AGAAGTTCTCGGAGTTCTACTGG	1	3	26	SEQ ID NO. 3419
(N20)NGG	8	48752648	-	CAACGGGGTTCAGAAGTTCTCGG	1	1	11	SEQ ID NO. 3420
(N20)NGG	8	48752663	-	GGGAAACGAATTCCACAACGGGG	1	1	7	SEQ ID NO. 3421
(N20)NGG	8	48752664	-	TGGGAAACGAATTCCACAACGGG	1	1	20	SEQ ID NO. 3422
(N20)NGG	8	48752665	-	ATGGGAAACGAATTCCACAACGG	1	1	25	SEQ ID NO. 3423
(N20)NGG	8	48752683	-	CCTACATGTTGTAGAAGGATGGG	1	1	28	SEQ ID NO. 3424
(N20)NGG	8	48752684	-	CCCTACATGTTGTAGAAGGATGG	1	3	39	SEQ ID NO. 3425
(N20)NGG	8	48752688	-	TGTTCCCTACATGTTGTAGAAGG	1	4	34	SEQ ID NO. 3426
(N20)NGG	8	48761714	+	CACCAGTTCCCTTCCCCGCCAGG	1	3	48	SEQ ID NO. 3427
(N20)NGG	8	48761755	+	TTTCTGCTGCCAAAATTTCATGG	1	5	114	SEQ ID NO. 3428
(N20)NGG	8	48761778	+	AGTGTTGAAAACACTCTGTCTGG	1	2	35	SEQ ID NO. 3429
(N20)NGG	8	48761781	+	GTTGAAAACACTCTGTCTGGAGG	1	8	93	SEQ ID NO. 3430
(N20)NGG	8	48761784	+	GAAAACACTCTGTCTGGAGGTGG	1	4	68	SEQ ID NO. 3431
(N20)NGG	8	48761799	+	GGAGGTGGTACTTTGTCGTGTGG	1	2	25	SEQ ID NO. 3432
(N20)NGG	8	48761802	+	GGTGGTACTTTGTCGTGTGGAGG	1	1	8	SEQ ID NO. 3433
(N20)NGG	8	48761803	+	GTGGTACTTTGTCGTGTGGAGGG	1	1	16	SEQ ID NO. 3434
(N20)NGG	8	48761838	+	GTACTTCCAGTTAAAGAGCAAGG	1	4	77	SEQ ID NO. 3435
(N20)NGG	8	48761864	+	TCGTTCAAGTCATGAGACATAGG	1	3	20	SEQ ID NO. 3436
(N20)NGG	8	48761694	-	AACCTGGCGGGGAAGGGAACTGG	1	4	36	SEQ ID NO. 3437
(N20)NGG	8	48761700	-	TTCATGAACCTGGCGGGGAAGGG	1	2	28	SEQ ID NO. 3438
(N20)NGG	8	48761701	-	ATTCATGAACCTGGCGGGGAAGG	1	2	16	SEQ ID NO. 3439
(N20)NGG	8	48761705	-	CAGCATTCATGAACCTGGCGGGG	1	2	36	SEQ ID NO. 3440

FIG. 12 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	8	48761706	-	ACAGCATTCATGAACCTGGCGGG	1	2	50	SEQ ID NO. 3441
(N20)NGG	8	48761707	-	CACAGCATTCATGAACCTGGCGG	2	15	179	SEQ ID NO. 3442
(N20)NGG	8	48761710	-	GAACACAGCATTCATGAACCTGG	1	7	49	SEQ ID NO. 3443
(N20)NGG	8	48761742	-	TTCAACACTCCATGAAATTTTGG	1	2	60	SEQ ID NO. 3444
(N20)NGG	8	48761822	-	CGAAGTCCTTGCTCTTTAACTGG	2	3	19	SEQ ID NO. 3445
(N20)NGG	8	48761945	+	AAACTTAATTTTTCAGATACTGG	1	12	154	SEQ ID NO. 3446
(N20)NGG	8	48761948	+	CTTAATTTTTCAGATACTGGAGG	1	2	75	SEQ ID NO. 3447
(N20)NGG	8	48761966	+	GGAGGAGTCTCTGTGTGAACTGG	1	3	99	SEQ ID NO. 3448
(N20)NGG	8	48762002	+	GAAGCAACATCAGAATACTATGG	1	1	45	SEQ ID NO. 3449
(N20)NGG	8	48762005	+	GCAACATCAGAATACTATGGAGG	1	3	34	SEQ ID NO. 3450
(N20)NGG	8	48762064	+	GCTTCCCTCCTCTTGCAGACAGG	1	4	48	SEQ ID NO. 3451
(N20)NGG	8	48762069	+	CCTCCTCTTGCAGACAGGTATGG	1	2	33	SEQ ID NO. 3452
(N20)NGG	8	48762070	+	CTCCTCTTGCAGACAGGTATGGG	1	2	21	SEQ ID NO. 3453
(N20)NGG	8	48762079	+	CAGACAGGTATGGGCTGTCCAGG	1	2	36	SEQ ID NO. 3454
(N20)NGG	8	48762080	+	AGACAGGTATGGGCTGTCCAGGG	1	2	32	SEQ ID NO. 3455
(N20)NGG	8	48762036	-	TGCAAGAGGAGGGAAGCTCTTGG	1	6	49	SEQ ID NO. 3456
(N20)NGG	8	48762046	-	CATACCTGTCTGCAAGAGGAGGG	1	3	29	SEQ ID NO. 3457
(N20)NGG	8	48762047	-	CCATACCTGTCTGCAAGAGGAGG	1	2	40	SEQ ID NO. 3458
(N20)NGG	8	48762050	-	AGCCCATACCTGTCTGCAAGAGG	1	2	25	SEQ ID NO. 3459
(N20)NGG	8	48765243	+	TGTTTATTGTAGATACTTCCAGG	1	14	73	SEQ ID NO. 3460
(N20)NGG	8	48765249	+	TTGTAGATACTTCCAGGCTTTGG	1	2	27	SEQ ID NO. 3461
(N20)NGG	8	48765310	+	GCCGCTGCAGCAGAAGTTCTAGG	1	2	25	SEQ ID NO. 3462
(N20)NGG	8	48765333	+	ACTTATACTTCGATATGTTATGG	1	2	23	SEQ ID NO. 3463
(N20)NGG	8	48765239	-	ACATATTATTCACCAAAGCCTGG	1	3	54	SEQ ID NO. 3464
(N20)NGG	8	48765262	-	CACTTCTTTATATCTTACAAAGG	1	3	83	SEQ ID NO. 3465
(N20)NGG	8	48765289	-	TCCTAGAACTTCTGCTGCAGCGG	1	4	71	SEQ ID NO. 3466
(N20)NGG	8	48766643	+	CTCCTTTGTGCTTATGTTTCAGG	3	8	74	SEQ ID NO. 3467
(N20)NGG	8	48766666	+	TTAATATTTGAAAAGTTTTCCGG	3	30	414	SEQ ID NO. 3468
(N20)NGG	8	48766699	+	AATTCTAAAGACAACTCAGTAGG	1	7	92	SEQ ID NO. 3469
(N20)NGG	8	48766700	+	ATTCTAAAGACAACTCAGTAGGG	1	6	74	SEQ ID NO. 3470
(N20)NGG	8	48766714	+	TCAGTAGGGATTCAATTGCTAGG	1	2	25	SEQ ID NO. 3471
(N20)NGG	8	48766725	+	TCAATTGCTAGGCATCGTGATGG	1	2	12	SEQ ID NO. 3472
(N20)NGG	8	48766759	+	CCTCCCTATGACCCACAGTGTGG	1	5	40	SEQ ID NO. 3473

FIG. 12 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	8	48766623	-	AACCTGAAACATAAGCACAAAGG	1	4	105	SEQ ID NO. 3474
(N20)NGG	8	48766663	-	TTTAGAATTAGGATCTTTACCGG	1	11	138	SEQ ID NO. 3475
(N20)NGG	8	48766674	-	ACTGAGTTGTCTTTAGAATTAGG	1	4	65	SEQ ID NO. 3476
(N20)NGG	8	48766726	-	GTCATAGGGAGGCAGGTCATTGG	1	1	30	SEQ ID NO. 3477
(N20)NGG	8	48766733	-	ACTGTGGGTCATAGGGAGGCAGG	1	1	47	SEQ ID NO. 3478
(N20)NGG	8	48766737	-	CCACACTGTGGGTCATAGGGAGG	1	5	35	SEQ ID NO. 3479
(N20)NGG	8	48766740	-	ATGCCACACTGTGGGTCATAGGG	1	7	33	SEQ ID NO. 3480
(N20)NGG	8	48766741	-	GATGCCACACTGTGGGTCATAGG	1	2	36	SEQ ID NO. 3481
(N20)NGG	8	48766748	-	TACTCTGGATGCCACACTGTGGG	1	1	35	SEQ ID NO. 3482
(N20)NGG	8	48766749	-	CTACTCTGGATGCCACACTGTGG	1	2	41	SEQ ID NO. 3483
(N20)NGG	8	48766763	-	CAAACACGTACTCGCTACTCTGG	1	1	2	SEQ ID NO. 3484
(N20)NGG	8	48767782	+	CAGAATTTCTGTACCTTTTCAGG	1	9	243	SEQ ID NO. 3485
(N20)NGG	8	48767783	+	AGAATTTCTGTACCTTTTCAGGG	1	8	278	SEQ ID NO. 3486
(N20)NGG	8	48767784	+	GAATTTCTGTACCTTTTCAGGGG	1	11	112	SEQ ID NO. 3487
(N20)NGG	8	48767785	+	AATTTCTGTACCTTTTCAGGGGG	1	9	110	SEQ ID NO. 3488
(N20)NGG	8	48767907	+	TAAAGACCCTTGTCGAGTGCTGG	1	1	10	SEQ ID NO. 3489
(N20)NGG	8	48767911	+	GACCCTTGTCGAGTGCTGGAAGG	1	1	10	SEQ ID NO. 3490
(N20)NGG	8	48767934	+	ATTGTTTATCCATCCCTTATAGG	1	5	57	SEQ ID NO. 3491
(N20)NGG	8	48767946	+	TCCCTTATAGGTATGTTTACTGG	1	3	22	SEQ ID NO. 3492
(N20)NGG	8	48767773	-	TCTTTAGGGACCCCCTGAAAAGG	1	1	26	SEQ ID NO. 3493
(N20)NGG	8	48767787	-	TTGCTAACACTTCATCTTTAGGG	1	5	57	SEQ ID NO. 3494
(N20)NGG	8	48767788	-	TTTGCTAACACTTCATCTTTAGG	1	3	81	SEQ ID NO. 3495
(N20)NGG	8	48767826	-	GATGAAAGACATGTTTCATTAGG	1	6	92	SEQ ID NO. 3496
(N20)NGG	8	48767848	-	TGTCTAAACACAGCTCTTTTTGG	1	1	59	SEQ ID NO. 3497
(N20)NGG	8	48767874	-	CAAGGGTCTTTATAATTTCAAGG	1	7	88	SEQ ID NO. 3498
(N20)NGG	8	48767891	-	ATCCTTCCAGCACTCGACAAGGG	1	2	12	SEQ ID NO. 3499
(N20)NGG	8	48767892	-	AATCCTTCCAGCACTCGACAAGG	1	1	19	SEQ ID NO. 3500
(N20)NGG	8	48767921	-	GTAAACATACCTATAAGGGATGG	1	2	25	SEQ ID NO. 3501
(N20)NGG	8	48767925	-	ACCAGTAAACATACCTATAAGGG	1	1	33	SEQ ID NO. 3502
(N20)NGG	8	48767926	-	AACCAGTAAACATACCTATAAGG	1	5	51	SEQ ID NO. 3503
(N20)NGG	8	48769716	+	TGACTTTTACATCCTCTTGTAGG	1	7	62	SEQ ID NO. 3504
(N20)NGG	8	48769742	+	TTCGCCCTTACGCGAAGCACTGG	1	1	1	SEQ ID NO. 3505
(N20)NGG	8	48769764	+	GCTTAGCCCCTTGCTGCAGCTGG	1	2	28	SEQ ID NO. 3506

FIG. 12 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	8	48769783	+	CTGGCTGCTTCTGAAAACAATGG	2	12	98	SEQ ID NO. 3507
(N20)NGG	8	48769786	+	GCTGCTTCTGAAAACAATGGAGG	1	6	80	SEQ ID NO. 3508
(N20)NGG	8	48769792	+	TCTGAAAACAATGGAGGAGAAGG	1	13	150	SEQ ID NO. 3509
(N20)NGG	8	48769806	+	AGGAGAAGGAATTCACTACATGG	1	5	110	SEQ ID NO. 3510
(N20)NGG	8	48769809	+	AGAAGGAATTCACTACATGGTGG	1	2	66	SEQ ID NO. 3511
(N20)NGG	8	48769821	+	CTACATGGTGGTTGAGATAGTGG	1	3	47	SEQ ID NO. 3512
(N20)NGG	8	48769838	+	TAGTGGCCACTATTCTTTCATGG	1	4	31	SEQ ID NO. 3513
(N20)NGG	8	48769843	+	GCCACTATTCTTTCATGGACAGG	1	1	13	SEQ ID NO. 3514
(N20)NGG	8	48769848	+	TATTCTTTCATGGACAGGCTTGG	1	4	42	SEQ ID NO. 3515
(N20)NGG	8	48769865	+	GCTTGGCCACTCCAACAGTAAGG	1	2	18	SEQ ID NO. 3516
(N20)NGG	8	48769706	-	AAGGGCGAAAGACCTACAAGAGG	1	1	19	SEQ ID NO. 3517
(N20)NGG	8	48769724	-	TAAGCCAGTGCTTCGCGTAAGGG	1	1	3	SEQ ID NO. 3518
(N20)NGG	8	48769725	-	CTAAGCCAGTGCTTCGCGTAAGG	1	1	7	SEQ ID NO. 3519
(N20)NGG	8	48769748	-	AAGCAGCCAGCTGCAGCAAGGGG	1	3	83	SEQ ID NO. 3520
(N20)NGG	8	48769749	-	GAAGCAGCCAGCTGCAGCAAGGG	3	11	92	SEQ ID NO. 3521
(N20)NGG	8	48769750	-	AGAAGCAGCCAGCTGCAGCAAGG	1	6	114	SEQ ID NO. 3522
(N20)NGG	8	48769822	-	GCCTGTCCATGAAAGAATAGTGG	1	1	25	SEQ ID NO. 3523
(N20)NGG	8	48769849	-	ATCAATCCTTACTGTTGGAGTGG	1	1	22	SEQ ID NO. 3524
(N20)NGG	8	48769854	-	GATGCATCAATCCTTACTGTTGG	1	1	23	SEQ ID NO. 3525
(N20)NGG	8	48771076	+	AATTTTGAATGTTTTATTTTAGG	2	82	1250	SEQ ID NO. 3526
(N20)NGG	8	48771105	+	TGCCAAGAGATCTTCCTTCTTGG	1	4	62	SEQ ID NO. 3527
(N20)NGG	8	48771122	+	TCTTGGATGAAATTCCTCCATGG	1	5	66	SEQ ID NO. 3528
(N20)NGG	8	48771130	+	GAAATTCCTCCATGGCAAACTGG	1	2	34	SEQ ID NO. 3529
(N20)NGG	8	48771131	+	AAATTCCTCCATGGCAAACTGGG	1	1	40	SEQ ID NO. 3530
(N20)NGG	8	48771196	+	GCTTGTTATTAATACAGAAGAGG	1	3	56	SEQ ID NO. 3531
(N20)NGG	8	48771085	-	ATCCAAGAAGGAAGATCTCTTGG	1	1	70	SEQ ID NO. 3532
(N20)NGG	8	48771097	-	TGGAGGAATTTCATCCAAGAAGG	2	7	77	SEQ ID NO. 3533
(N20)NGG	8	48771114	-	GATTTCCCAGTTTGCCATGGAGG	1	4	27	SEQ ID NO. 3534
(N20)NGG	8	48771117	-	TTGGATTTCCCAGTTTGCCATGG	1	4	70	SEQ ID NO. 3535
(N20)NGG	8	48771136	-	CGGATATTTAATGGTACTATTGG	1	1	17	SEQ ID NO. 3536
(N20)NGG	8	48771145	-	AAGAAGAGACGGATATTTAATGG	1	2	74	SEQ ID NO. 3537
(N20)NGG	8	48771156	-	CAAGCTTGGCTAAGAAGAGACGG	1	9	65	SEQ ID NO. 3538
(N20)NGG	8	48771170	-	TTCTGTATTAATAACAAGCTTGG	2	4	79	SEQ ID NO. 3539

FIG. 12 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	8	48771409	+	TCCTGGGCCCTCCCTTTCGCAGG	1	12	59	SEQ ID NO. 3540
(N20)NGG	8	48771417	+	CCTCCCTTTCGCAGGAGCAGCGG	1	4	40	SEQ ID NO. 3541
(N20)NGG	8	48771418	+	CTCCCTTTCGCAGGAGCAGCGGG	1	4	41	SEQ ID NO. 3542
(N20)NGG	8	48771427	+	GCAGGAGCAGCGGGACCCCACGG	1	5	67	SEQ ID NO. 3543
(N20)NGG	8	48771445	+	CACGGTGCATGATGATGTGCTGG	1	2	10	SEQ ID NO. 3544
(N20)NGG	8	48771451	+	GCATGATGATGTGCTGGAGCTGG	2	2	33	SEQ ID NO. 3545
(N20)NGG	8	48771457	+	TGATGTGCTGGAGCTGGAGATGG	1	8	102	SEQ ID NO. 3546
(N20)NGG	8	48771471	+	TGGAGATGGACGAGCTCAATCGG	1	2	30	SEQ ID NO. 3547
(N20)NGG	8	48771484	+	GCTCAATCGGCATGAGTGCATGG	1	1	7	SEQ ID NO. 3548
(N20)NGG	8	48771496	+	TGAGTGCATGGCGCCCCTGACGG	1	1	14	SEQ ID NO. 3549
(N20)NGG	8	48771502	+	CATGGCGCCCCTGACGGCCCTGG	1	1	14	SEQ ID NO. 3550
(N20)NGG	8	48771526	+	CAAGCACATGCACAGAAGCCTGG	1	3	95	SEQ ID NO. 3551
(N20)NGG	8	48771527	+	AAGCACATGCACAGAAGCCTGGG	1	2	71	SEQ ID NO. 3552
(N20)NGG	8	48771539	+	AGAAGCCTGGGCCCGCCTCAAGG	1	1	36	SEQ ID NO. 3553
(N20)NGG	8	48771547	+	GGGCCCGCCTCAAGGAGAAGAGG	1	2	33	SEQ ID NO. 3554
(N20)NGG	8	48771388	-	TCCTGCGAAAGGGAGGGCCCAGG	1	2	39	SEQ ID NO. 3555
(N20)NGG	8	48771394	-	CGCTGCTCCTGCGAAAGGGAGGG	1	3	21	SEQ ID NO. 3556
(N20)NGG	8	48771395	-	CCGCTGCTCCTGCGAAAGGGAGG	1	2	19	SEQ ID NO. 3557
(N20)NGG	8	48771398	-	GTCCCGCTGCTCCTGCGAAAGGG	1	2	16	SEQ ID NO. 3558
(N20)NGG	8	48771399	-	GGTCCCGCTGCTCCTGCGAAAGG	1	3	19	SEQ ID NO. 3559
(N20)NGG	8	48771420	-	GCACATCATCATGCACCGTGGGG	1	2	9	SEQ ID NO. 3560
(N20)NGG	8	48771421	-	AGCACATCATCATGCACCGTGGG	1	2	12	SEQ ID NO. 3561
(N20)NGG	8	48771422	-	CAGCACATCATCATGCACCGTGG	1	2	11	SEQ ID NO. 3562
(N20)NGG	8	48771487	-	TGCTTGACCAGGGCCGTCAGGGG	1	1	19	SEQ ID NO. 3563
(N20)NGG	8	48771488	-	GTGCTTGACCAGGGCCGTCAGGG	1	2	13	SEQ ID NO. 3564
(N20)NGG	8	48771489	-	TGTGCTTGACCAGGGCCGTCAGG	1	1	7	SEQ ID NO. 3565
(N20)NGG	8	48771497	-	TCTGTGCATGTGCTTGACCAGGG	1	3	59	SEQ ID NO. 3566
(N20)NGG	8	48771498	-	TTCTGTGCATGTGCTTGACCAGG	1	3	47	SEQ ID NO. 3567
(N20)NGG	8	48771522	-	CTTCTCCTTGAGGCGGGCCCAGG	1	4	34	SEQ ID NO. 3568
(N20)NGG	8	48771528	-	GCACCTCTTCTCCTTGAGGCGGG	1	4	34	SEQ ID NO. 3569
(N20)NGG	8	48771529	-	AGCACCTCTTCTCCTTGAGGCGG	1	3	58	SEQ ID NO. 3570
(N20)NGG	8	48771532	-	AAAAGCACCTCTTCTCCTTGAGG	1	5	79	SEQ ID NO. 3571
(N20)NGG	8	48772174	+	CTCCTTTTTTATATTTCAGATGG	2	15	386	SEQ ID NO. 3572

FIG. 12 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	8	48772206	+	TATGTCTTCCCTGTCATATTTGG	1	6	55	SEQ ID NO. 3573
(N20)NGG	8	48772227	+	GGCAGACAGTACCCTGAGTGAGG	1	5	35	SEQ ID NO. 3574
(N20)NGG	8	48772255	+	AGTCAATTTGATTTCTCAACCGG	1	5	62	SEQ ID NO. 3575
(N20)NGG	8	48772303	+	CAAGACCCTAGACCTGCCACTGG	1	3	55	SEQ ID NO. 3576
(N20)NGG	8	48772313	+	GACCTGCCACTGGTCGTTTTCGG	1	1	6	SEQ ID NO. 3577
(N20)NGG	8	48772319	+	CCACTGGTCGTTTTCGGAGACGG	1	2	9	SEQ ID NO. 3578
(N20)NGG	8	48772320	+	CACTGGTCGTTTTCGGAGACGGG	1	1	5	SEQ ID NO. 3579
(N20)NGG	8	48772154	-	GACCATCTGAAATATAAAAAAGG	1	5	183	SEQ ID NO. 3580
(N20)NGG	8	48772176	-	GACAGGGAAGACATATAGGAAGG	1	8	70	SEQ ID NO. 3581
(N20)NGG	8	48772180	-	ATATGACAGGGAAGACATATAGG	1	2	55	SEQ ID NO. 3582
(N20)NGG	8	48772192	-	ACTGTCTGCCAAATATGACAGGG	1	3	47	SEQ ID NO. 3583
(N20)NGG	8	48772193	-	TACTGTCTGCCAAATATGACAGG	1	4	37	SEQ ID NO. 3584
(N20)NGG	8	48772216	-	TTGACTCATTTCCTCACTCAGGG	1	8	81	SEQ ID NO. 3585
(N20)NGG	8	48772217	-	ATTGACTCATTTCCTCACTCAGG	1	5	81	SEQ ID NO. 3586
(N20)NGG	8	48772252	-	GTATGAATAGCTCTGAACTCCGG	1	1	28	SEQ ID NO. 3587
(N20)NGG	8	48772279	-	AGTGGCAGGTCTAGGGTCTTGGG	1	1	26	SEQ ID NO. 3588
(N20)NGG	8	48772280	-	CAGTGGCAGGTCTAGGGTCTTGG	1	2	41	SEQ ID NO. 3589
(N20)NGG	8	48772286	-	AACGACCAGTGGCAGGTCTAGGG	1	1	5	SEQ ID NO. 3590
(N20)NGG	8	48772287	-	AAACGACCAGTGGCAGGTCTAGG	1	1	15	SEQ ID NO. 3591
(N20)NGG	8	48772293	-	CTCCGAAAACGACCAGTGGCAGG	1	1	3	SEQ ID NO. 3592
(N20)NGG	8	48772297	-	CCGTCTCCGAAAACGACCAGTGG	1	1	3	SEQ ID NO. 3593
(N20)NGG	8	48773459	+	GTTTATTTGTTCTTCCCAATAGG	1	2	105	SEQ ID NO. 3594
(N20)NGG	8	48773468	+	TTCTTCCCAATAGGTTCCTATGG	1	2	38	SEQ ID NO. 3595
(N20)NGG	8	48773497	+	AGAAAAAGTACATTGAAATTAGG	1	19	349	SEQ ID NO. 3596
(N20)NGG	8	48773523	+	GAAGCCAGAGAAGCAGCAAATGG	1	14	212	SEQ ID NO. 3597
(N20)NGG	8	48773524	+	AAGCCAGAGAAGCAGCAAATGGG	2	7	141	SEQ ID NO. 3598
(N20)NGG	8	48773525	+	AGCCAGAGAAGCAGCAAATGGGG	1	9	150	SEQ ID NO. 3599
(N20)NGG	8	48773532	+	GAAGCAGCAAATGGGGATTCAGG	1	7	39	SEQ ID NO. 3600
(N20)NGG	8	48773536	+	CAGCAAATGGGGATTCAGGTAGG	1	2	43	SEQ ID NO. 3601
(N20)NGG	8	48773451	-	TCTTTCCATAGGAACCTATTGGG	1	3	50	SEQ ID NO. 3602
(N20)NGG	8	48773452	-	TTCTTTCCATAGGAACCTATTGG	1	3	42	SEQ ID NO. 3603
(N20)NGG	8	48773462	-	TACTTTTTCTTTCTTTCCATAGG	5	51	869	SEQ ID NO. 3604
(N20)NGG	8	48773505	-	ATCCCCATTTGCTGCTTCTCTGG	1	3	52	SEQ ID NO. 3605

FIG. 12 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	8	48774688	+	TAATTTTCCTGTAGAAGTTGAGG	1	8	83	SEQ ID NO. 3606
(N20)NGG	8	48774651	-	GAAAATTATAGCGGCGCTTCAGG	1	1	2	SEQ ID NO. 3607
(N20)NGG	8	48774660	-	CTTCTACAGGAAAATTATAGCGG	1	3	50	SEQ ID NO. 3608
(N20)NGG	8	48774673	-	TCACTCACCTCAACTTCTACAGG	1	2	33	SEQ ID NO. 3609
(N20)NGG	8	48774964	+	CGATGCATTTACAGAGAACATGG	1	2	25	SEQ ID NO. 3610
(N20)NGG	8	48774968	+	GCATTTACAGAGAACATGGCAGG	1	6	58	SEQ ID NO. 3611
(N20)NGG	8	48774985	+	GGCAGGAGAGAATCAGCTGCTGG	1	5	74	SEQ ID NO. 3612
(N20)NGG	8	48774990	+	GAGAGAATCAGCTGCTGGAGAGG	1	7	88	SEQ ID NO. 3613
(N20)NGG	8	48775073	+	AATGAGTTAAAATTTTACCAAGG	1	14	204	SEQ ID NO. 3614
(N20)NGG	8	48775102	+	GTTTAGTGAAAAACCAGAAAAGG	2	12	108	SEQ ID NO. 3615
(N20)NGG	8	48775106	+	AGTGAAAAACCAGAAAAGGTAGG	1	10	137	SEQ ID NO. 3616
(N20)NGG	8	48775118	+	GAAAAGGTAGGCCACTCCTACGG	1	1	31	SEQ ID NO. 3617
(N20)NGG	8	48775002	-	CGCAGTTGTATGCTGCACAATGG	1	5	16	SEQ ID NO. 3618
(N20)NGG	8	48775025	-	GACACAGCAGATGACAGATATGG	1	6	62	SEQ ID NO. 3619
(N20)NGG	8	48775068	-	TTTCACTAAACAGAAAACCTTGG	3	6	131	SEQ ID NO. 3620
(N20)NGG	8	48775093	-	TAGGAGTGGCCTACCTTTTCTGG	1	2	14	SEQ ID NO. 3621
(N20)NGG	8	48776001	+	TACTCAAATCACCAAGAAGATGG	1	5	106	SEQ ID NO. 3622
(N20)NGG	8	48776002	+	ACTCAAATCACCAAGAAGATGGG	1	5	87	SEQ ID NO. 3623
(N20)NGG	8	48776064	+	CAAAGATGATGTTCATGCTAAGG	1	2	46	SEQ ID NO. 3624
(N20)NGG	8	48776092	+	AAAATTAATCAAGTTTTCCATGG	1	16	209	SEQ ID NO. 3625
(N20)NGG	8	48776110	+	CATGGCTCGTGTATTACAGAAGG	1	1	14	SEQ ID NO. 3626
(N20)NGG	8	48776159	+	AGTAAGATTTTACTTAATTTTGG	1	19	212	SEQ ID NO. 3627
(N20)NGG	8	48775948	-	AGATTCATTTAGCTTCAAAAAGG	1	7	113	SEQ ID NO. 3628
(N20)NGG	8	48775972	-	CTTGGTGATTTGAGTATCAAAGG	1	4	37	SEQ ID NO. 3629
(N20)NGG	8	48775990	-	CTTATAGTAGCCCATCTTCTTGG	1	2	16	SEQ ID NO. 3630
(N20)NGG	8	48776036	-	CATGAACATCATCTTTGGGAAGG	1	2	53	SEQ ID NO. 3631
(N20)NGG	8	48776040	-	TTAGCATGAACATCATCTTTGGG	1	7	75	SEQ ID NO. 3632
(N20)NGG	8	48776041	-	CTTAGCATGAACATCATCTTTGG	1	4	43	SEQ ID NO. 3633
(N20)NGG	8	48776087	-	CTTCTGTAATACACGAGCCATGG	1	2	12	SEQ ID NO. 3634
(N20)NGG	8	48777116	+	TAATTTTATCTTGTTTTCTTAGG	2	39	787	SEQ ID NO. 3635
(N20)NGG	8	48777117	+	AATTTTATCTTGTTTTCTTAGGG	3	43	561	SEQ ID NO. 3636
(N20)NGG	8	48777118	+	ATTTTATCTTGTTTTCTTAGGGG	2	25	472	SEQ ID NO. 3637
(N20)NGG	8	48777139	+	GGTTCATGTGTCACACAAGTAGG	1	1	27	SEQ ID NO. 3638

FIG. 12 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	8	48777147	+	TGTCACACAAGTAGGCCTTCTGG	1	3	26	SEQ ID NO. 3639
(N20)NGG	8	48777170	+	AAAGCGTGTATGAAATGTTCAGG	1	1	15	SEQ ID NO. 3640
(N20)NGG	8	48777174	+	CGTGTATGAAATGTTCAGGAAGG	2	9	99	SEQ ID NO. 3641
(N20)NGG	8	48777213	+	TTTCACACGCCAGTCCTTTGTGG	1	1	18	SEQ ID NO. 3642
(N20)NGG	8	48777239	+	GCTCCCTCCTCACTCTGCTGTGG	2	13	147	SEQ ID NO. 3643
(N20)NGG	8	48777252	+	TCTGCTGTGGCACTGTAGCCTGG	1	4	58	SEQ ID NO. 3644
(N20)NGG	8	48777285	+	AGAATTCTTCAGCACAATTGTGG	1	2	52	SEQ ID NO. 3645
(N20)NGG	8	48777288	+	ATTCTTCAGCACAATTGTGGTGG	2	3	39	SEQ ID NO. 3646
(N20)NGG	8	48777314	+	CCATTGATGTGTTGAAGTCCAGG	1	3	62	SEQ ID NO. 3647
(N20)NGG	8	48777324	+	GTTGAAGTCCAGGTTTACAAAGG	1	2	29	SEQ ID NO. 3648
(N20)NGG	8	48777140	-	TTTCATACACGCTTTCCAGAAGG	1	4	28	SEQ ID NO. 3649
(N20)NGG	8	48777179	-	GGCGTGTGAAACTTAGGCGGGGG	1	3	6	SEQ ID NO. 3650
(N20)NGG	8	48777180	-	TGGCGTGTGAAACTTAGGCGGGG	1	1	4	SEQ ID NO. 3651
(N20)NGG	8	48777181	-	CTGGCGTGTGAAACTTAGGCGGG	1	1	16	SEQ ID NO. 3652
(N20)NGG	8	48777182	-	ACTGGCGTGTGAAACTTAGGCGG	2	3	14	SEQ ID NO. 3653
(N20)NGG	8	48777185	-	AGGACTGGCGTGTGAAACTTAGG	1	2	8	SEQ ID NO. 3654
(N20)NGG	8	48777200	-	GGGAGCGGTCCACAAAGGACTGG	1	2	10	SEQ ID NO. 3655
(N20)NGG	8	48777205	-	GAGGAGGGAGCGGTCCACAAAGG	1	2	48	SEQ ID NO. 3656
(N20)NGG	8	48777215	-	ACAGCAGAGTGAGGAGGGAGCGG	1	30	331	SEQ ID NO. 3657
(N20)NGG	8	48777220	-	GTGCCACAGCAGAGTGAGGAGGG	1	9	88	SEQ ID NO. 3658
(N20)NGG	8	48777221	-	AGTGCCACAGCAGAGTGAGGAGG	1	6	74	SEQ ID NO. 3659
(N20)NGG	8	48777224	-	TACAGTGCCACAGCAGAGTGAGG	1	3	41	SEQ ID NO. 3660
(N20)NGG	8	48777248	-	AGAATTCTCTCAAAGCATCCAGG	1	3	51	SEQ ID NO. 3661
(N20)NGG	8	48777292	-	CCTGGACTTCAACACATCAATGG	1	2	33	SEQ ID NO. 3662
(N20)NGG	8	48777310	-	GTATGATACCTTTGTAAACCTGG	1	2	23	SEQ ID NO. 3663
(N20)NGG	8	48790299	+	TTTCTAGTTTCTAGATGCATTGG	1	5	96	SEQ ID NO. 3664
(N20)NGG	8	48790326	+	ATCTCAAAGCCCTATGTTGTTGG	1	1	25	SEQ ID NO. 3665
(N20)NGG	8	48790352	+	TGATGACAGAAGTTCTTTGTCGG	2	4	59	SEQ ID NO. 3666
(N20)NGG	8	48790353	+	GATGACAGAAGTTCTTTGTCGGG	1	3	36	SEQ ID NO. 3667
(N20)NGG	8	48790371	+	TCGGGAACAGCAGCATGTCATGG	1	1	17	SEQ ID NO. 3668
(N20)NGG	8	48790397	+	AATTATTTCAATCCAGTTTCAGG	2	6	114	SEQ ID NO. 3669
(N20)NGG	8	48790400	+	TATTTCAATCCAGTTTCAGGAGG	1	1	55	SEQ ID NO. 3670
(N20)NGG	8	48790412	+	GTTTCAGGAGGATTGCCAGAAGG	1	2	26	SEQ ID NO. 3671

FIG. 12 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	8	48790425	+	TGCCAGAAGGTAAGTCATTCTGG	1	2	39	SEQ ID NO. 3672
(N20)NGG	8	48790430	+	GAAGGTAAGTCATTCTGGCCTGG	1	5	28	SEQ ID NO. 3673
(N20)NGG	8	48790431	+	AAGGTAAGTCATTCTGGCCTGGG	1	2	44	SEQ ID NO. 3674
(N20)NGG	8	48790313	-	TCATCAATTCCAACAACATAGGG	1	1	58	SEQ ID NO. 3675
(N20)NGG	8	48790314	-	GTCATCAATTCCAACAACATAGG	1	2	32	SEQ ID NO. 3676
(N20)NGG	8	48790387	-	TCTGGCAATCCTCCTGAAACTGG	1	2	19	SEQ ID NO. 3677
(N20)NGG	8	48790405	-	GGCCAGAATGACTTACCTTCTGG	1	3	28	SEQ ID NO. 3678
(N20)NGG	8	48792051	+	TTATGTCTGTCTTGCTCCACAGG	1	5	79	SEQ ID NO. 3679
(N20)NGG	8	48792052	+	TATGTCTGTCTTGCTCCACAGGG	1	6	71	SEQ ID NO. 3680
(N20)NGG	8	48792094	+	CCATTCTTCACCAGCCTCACTGG	1	7	88	SEQ ID NO. 3681
(N20)NGG	8	48792097	+	TTCTTCACCAGCCTCACTGGAGG	1	6	80	SEQ ID NO. 3682
(N20)NGG	8	48792105	+	CAGCCTCACTGGAGGCAGTCTGG	1	2	56	SEQ ID NO. 3683
(N20)NGG	8	48792108	+	CCTCACTGGAGGCAGTCTGGAGG	1	8	65	SEQ ID NO. 3684
(N20)NGG	8	48792126	+	GGAGGAACTTAGACGTGTTCTGG	1	2	11	SEQ ID NO. 3685
(N20)NGG	8	48792164	+	CTCACTTCCCCATGCAGTCCAGG	2	6	45	SEQ ID NO. 3686
(N20)NGG	8	48792165	+	TCACTTCCCCATGCAGTCCAGGG	2	2	48	SEQ ID NO. 3687
(N20)NGG	8	48792178	+	CAGTCCAGGGAATTTCCTCCAGG	1	3	60	SEQ ID NO. 3688
(N20)NGG	8	48792188	+	AATTTCCTCCAGGAACTCCGCGG	1	2	25	SEQ ID NO. 3689
(N20)NGG	8	48792204	+	TCCGCGGTTCAATAATTATGTGG	1	1	5	SEQ ID NO. 3690
(N20)NGG	8	48792219	+	TTATGTGGACTGCATGAAAAAGG	1	4	44	SEQ ID NO. 3691
(N20)NGG	8	48792045	-	AGAGTGACAGCTTGGCCCTGTGG	1	6	58	SEQ ID NO. 3692
(N20)NGG	8	48792053	-	ATGGAAGAAGAGTGACAGCTTGG	1	5	75	SEQ ID NO. 3693
(N20)NGG	8	48792072	-	CCAGTGAGGCTGGTGAAGAATGG	1	11	115	SEQ ID NO. 3694
(N20)NGG	8	48792082	-	CAGACTGCCTCCAGTGAGGCTGG	1	2	39	SEQ ID NO. 3695
(N20)NGG	8	48792086	-	CCTCCAGACTGCCTCCAGTGAGG	2	7	58	SEQ ID NO. 3696
(N20)NGG	8	48792149	-	GAAATTCCCTGGACTGCATGGGG	1	3	33	SEQ ID NO. 3697
(N20)NGG	8	48792150	-	GGAAATTCCCTGGACTGCATGGG	1	3	24	SEQ ID NO. 3698
(N20)NGG	8	48792151	-	AGGAAATTCCCTGGACTGCATGG	1	5	49	SEQ ID NO. 3699
(N20)NGG	8	48792160	-	AGTTCCTGGAGGAAATTCCCTGG	1	5	30	SEQ ID NO. 3700
(N20)NGG	8	48792171	-	TTGAACCGCGGAGTTCCTGGAGG	1	3	16	SEQ ID NO. 3701
(N20)NGG	8	48792174	-	TTATTGAACCGCGGAGTTCCTGG	1	1	3	SEQ ID NO. 3702
(N20)NGG	8	48792183	-	TCCACATAATTATTGAACCGCGG	1	1	12	SEQ ID NO. 3703
(N20)NGG	8	48794010	+	GTATCTTTTAATACAAGTCATGG	1	3	58	SEQ ID NO. 3704

FIG. 12 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	8	48794066	+	TCTACTTGCTGACACAAAGCTGG	1	2	39	SEQ ID NO. 3705
(N20)NGG	8	48794081	+	AAAGCTGGATCTACATTTAAAGG	1	4	64	SEQ ID NO. 3706
(N20)NGG	8	48793951	-	AAAGGAAGGAAAAGAAAAACAGG	16	314	5097	SEQ ID NO. 3707
(N20)NGG	8	48793965	-	AGATGAATCAATCTAAAGGAAGG	1	5	137	SEQ ID NO. 3708
(N20)NGG	8	48793969	-	ATACAGATGAATCAATCTAAAGG	1	4	92	SEQ ID NO. 3709
(N20)NGG	8	48794017	-	TATATGTTGTAAAGACTTCAGGG	1	2	86	SEQ ID NO. 3710
(N20)NGG	8	48794018	-	ATATATGTTGTAAAGACTTCAGG	1	6	66	SEQ ID NO. 3711
(N20)NGG	8	48794472	+	ACTCACAACGAAATTGTCTCAGG	1	2	16	SEQ ID NO. 3712
(N20)NGG	8	48794491	+	CAGGTGAGTGCCGTTTTGAACGG	1	1	17	SEQ ID NO. 3713
(N20)NGG	8	48794513	+	GCATGTTAGACCAGAGCTTCAGG	1	1	21	SEQ ID NO. 3714
(N20)NGG	8	48794514	+	CATGTTAGACCAGAGCTTCAGGG	1	1	30	SEQ ID NO. 3715
(N20)NGG	8	48794539	+	CGAGCAAACCAGAAACACCAAGG	1	3	39	SEQ ID NO. 3716
(N20)NGG	8	48794573	+	CGACTACAATTCTGCAACACTGG	1	2	10	SEQ ID NO. 3717
(N20)NGG	8	48794591	+	ACTGGAAGAAGTGTGATTCATGG	1	2	62	SEQ ID NO. 3718
(N20)NGG	8	48794594	+	GGAAGAAGTGTGATTCATGGTGG	1	6	100	SEQ ID NO. 3719
(N20)NGG	8	48794595	+	GAAGAAGTGTGATTCATGGTGGG	1	4	68	SEQ ID NO. 3720
(N20)NGG	8	48794625	+	TTCCCCTCTCGAAACTAAAATGG	1	1	30	SEQ ID NO. 3721
(N20)NGG	8	48794634	+	CGAAACTAAAATGGCAGTGCTGG	1	1	15	SEQ ID NO. 3722
(N20)NGG	8	48794643	+	AATGGCAGTGCTGGCCTTACTGG	1	6	50	SEQ ID NO. 3723
(N20)NGG	8	48794658	+	CTTACTGGCAAAAATTTTACAGG	1	3	63	SEQ ID NO. 3724
(N20)NGG	8	48794479	-	GTCTAACATGCCGTTCAAAACGG	1	1	7	SEQ ID NO. 3725
(N20)NGG	8	48794501	-	TTGCTCGCTCCCTGAAGCTCTGG	1	2	27	SEQ ID NO. 3726
(N20)NGG	8	48794525	-	GTTTCAGTCCTTGGTGTTTCTGG	1	7	69	SEQ ID NO. 3727
(N20)NGG	8	48794534	-	TAGTCGCAAGTTTCAGTCCTTGG	1	1	14	SEQ ID NO. 3728
(N20)NGG	8	48794596	-	AGTTTCGAGAGGGGAATCTTTGG	1	1	17	SEQ ID NO. 3729
(N20)NGG	8	48794605	-	TGCCATTTTAGTTTCGAGAGGGG	1	3	22	SEQ ID NO. 3730
(N20)NGG	8	48794606	-	CTGCCATTTTAGTTTCGAGAGGG	1	1	22	SEQ ID NO. 3731
(N20)NGG	8	48794607	-	ACTGCCATTTTAGTTTCGAGAGG	1	1	24	SEQ ID NO. 3732
(N20)NGG	8	48794635	-	CTGTAAAATTTTTGCCAGTAAGG	2	5	93	SEQ ID NO. 3733
(N20)NGG	8	48798540	+	GAGTCTTCTCCTGAACCCAGCGG	1	4	63	SEQ ID NO. 3734
(N20)NGG	8	48798552	+	GAACCCAGCGGTGCTGTCCACGG	1	2	25	SEQ ID NO. 3735
(N20)NGG	8	48798561	+	GGTGCTGTCCACGGCGTCCTTGG	1	2	19	SEQ ID NO. 3736
(N20)NGG	8	48798562	+	GTGCTGTCCACGGCGTCCTTGGG	1	1	5	SEQ ID NO. 3737

FIG. 12 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	8	48798573	+	GGCGTCCTTGGGCAGCTCACAGG	1	4	27	SEQ ID NO. 3738
(N20)NGG	8	48798574	+	GCGTCCTTGGGCAGCTCACAGGG	1	5	35	SEQ ID NO. 3739
(N20)NGG	8	48798598	+	AGCGTCATCCACTTCTCCCATGG	1	1	20	SEQ ID NO. 3740
(N20)NGG	8	48798599	+	GCGTCATCCACTTCTCCCATGGG	1	2	13	SEQ ID NO. 3741
(N20)NGG	8	48798600	+	CGTCATCCACTTCTCCCATGGGG	1	2	28	SEQ ID NO. 3742
(N20)NGG	8	48798639	+	GTTCTCAGAAACGATCAACACGG	1	4	50	SEQ ID NO. 3743
(N20)NGG	8	48798657	+	CACGGAATTATTGAAAAATCTGG	1	2	61	SEQ ID NO. 3744
(N20)NGG	8	48798672	+	AAATCTGGATCTTGCTGTATTGG	1	6	96	SEQ ID NO. 3745
(N20)NGG	8	48798693	+	GGAGCTCATGCAGTCTTCAGTGG	1	1	55	SEQ ID NO. 3746
(N20)NGG	8	48798708	+	TTCAGTGGATAATACCAAAATGG	2	8	63	SEQ ID NO. 3747
(N20)NGG	8	48798488	-	GCTCACACTGGGAAAAAGAAAGG	1	7	95	SEQ ID NO. 3748
(N20)NGG	8	48798499	-	ACTCACAAGGCGCTCACACTGGG	1	2	17	SEQ ID NO. 3749
(N20)NGG	8	48798500	-	GACTCACAAGGCGCTCACACTGG	1	1	8	SEQ ID NO. 3750
(N20)NGG	8	48798512	-	GGTTCAGGAGAAGACTCACAAGG	1	2	46	SEQ ID NO. 3751
(N20)NGG	8	48798527	-	TGGACAGCACCGCTGGGTTCAGG	1	3	36	SEQ ID NO. 3752
(N20)NGG	8	48798533	-	ACGCCGTGGACAGCACCGCTGGG	1	1	8	SEQ ID NO. 3753
(N20)NGG	8	48798534	-	GACGCCGTGGACAGCACCGCTGG	1	2	6	SEQ ID NO. 3754
(N20)NGG	8	48798547	-	TGAGCTGCCCAAGGACGCCGTGG	1	2	26	SEQ ID NO. 3755
(N20)NGG	8	48798556	-	GCTGCCCTGTGAGCTGCCCAAGG	3	9	101	SEQ ID NO. 3756
(N20)NGG	8	48798584	-	AATACTCCCCATGGGAGAAGTGG	1	2	37	SEQ ID NO. 3757
(N20)NGG	8	48798592	-	GCTATAGAAATACTCCCCATGGG	1	3	21	SEQ ID NO. 3758
(N20)NGG	8	48798593	-	AGCTATAGAAATACTCCCCATGG	1	2	34	SEQ ID NO. 3759
(N20)NGG	8	48798700	-	GGGAAACTTTGTTACCATTTTGG	1	4	53	SEQ ID NO. 3760
(N20)NGG	8	48800132	+	ACAGATTTGCATCATTCTGTTGG	3	10	73	SEQ ID NO. 3761
(N20)NGG	8	48800152	+	TGGCACAGAACTTCTTTCCCTGG	1	7	55	SEQ ID NO. 3762
(N20)NGG	8	48800162	+	CTTCTTTCCCTGGTTTATAAAGG	1	3	111	SEQ ID NO. 3763
(N20)NGG	8	48800174	+	GTTTATAAAGGCATTGCCCCTGG	1	1	27	SEQ ID NO. 3764
(N20)NGG	8	48800224	+	AGACCTCAGTTGTAAGCAGCTGG	1	4	21	SEQ ID NO. 3765
(N20)NGG	8	48800231	+	AGTTGTAAGCAGCTGGCCAGCGG	1	3	27	SEQ ID NO. 3766
(N20)NGG	8	48800239	+	GCAGCTGGCCAGCGGACTTCTGG	1	2	26	SEQ ID NO. 3767
(N20)NGG	8	48800258	+	CTGGAGTTAGCCTTTGCTTTTGG	1	3	44	SEQ ID NO. 3768
(N20)NGG	8	48800261	+	GAGTTAGCCTTTGCTTTTGGAGG	1	4	52	SEQ ID NO. 3769
(N20)NGG	8	48800266	+	AGCCTTTGCTTTTGGAGGACTGG	1	1	43	SEQ ID NO. 3770

FIG. 12 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	8	48800270	+	TTTGCTTTTGGAGGACTGGTAGG	1	3	49	SEQ ID NO. 3771
(N20)NGG	8	48800099	-	ATGCAAATCTGTGGACTAAAAGG	1	3	62	SEQ ID NO. 3772
(N20)NGG	8	48800108	-	AACAGAATGATGCAAATCTGTGG	1	6	89	SEQ ID NO. 3773
(N20)NGG	8	48800147	-	GGCAATGCCTTTATAAACCAGGG	1	2	45	SEQ ID NO. 3774
(N20)NGG	8	48800148	-	GGGCAATGCCTTTATAAACCAGG	1	1	31	SEQ ID NO. 3775
(N20)NGG	8	48800168	-	ACACTGTCTCTCATCTCCAGGGG	1	3	83	SEQ ID NO. 3776
(N20)NGG	8	48800169	-	GACACTGTCTCTCATCTCCAGGG	1	6	89	SEQ ID NO. 3777
(N20)NGG	8	48800170	-	AGACACTGTCTCTCATCTCCAGG	1	3	99	SEQ ID NO. 3778
(N20)NGG	8	48800194	-	TTACAACTGAGGTCTAGAGAAGG	1	3	50	SEQ ID NO. 3779
(N20)NGG	8	48800205	-	TGGCCAGCTGCTTACAACTGAGG	1	1	35	SEQ ID NO. 3780
(N20)NGG	8	48800225	-	GGCTAACTCCAGAAGTCCGCTGG	1	1	51	SEQ ID NO. 3781
(N20)NGG	8	48800246	-	TACCAGTCCTCCAAAAGCAAAGG	1	3	49	SEQ ID NO. 3782
(N20)NGG	8	48801085	+	TTGTCACATGGCCAGCATTGAGG	1	2	44	SEQ ID NO. 3783
(N20)NGG	8	48801110	+	CTTTGTGCCGTCAACTTGTATGG	1	1	11	SEQ ID NO. 3784
(N20)NGG	8	48801127	+	GTATGGCCCTGACGCGCAAGTGG	1	1	4	SEQ ID NO. 3785
(N20)NGG	8	48801132	+	GCCCTGACGCGCAAGTGGACAGG	1	1	1	SEQ ID NO. 3786
(N20)NGG	8	48801138	+	ACGCGCAAGTGGACAGGAGCAGG	1	1	4	SEQ ID NO. 3787
(N20)NGG	8	48801142	+	GCAAGTGGACAGGAGCAGGCTGG	1	5	85	SEQ ID NO. 3788
(N20)NGG	8	48801182	+	TGTAAACAGCTTCACAGAGCTGG	1	4	64	SEQ ID NO. 3789
(N20)NGG	8	48801183	+	GTAAACAGCTTCACAGAGCTGGG	1	3	49	SEQ ID NO. 3790
(N20)NGG	8	48801211	+	GCATAATATATTACCGTCTCAGG	1	2	16	SEQ ID NO. 3791
(N20)NGG	8	48801074	-	GGCACAAAGCTCCTCAATGCTGG	1	1	18	SEQ ID NO. 3792
(N20)NGG	8	48801095	-	GTCAGGGCCATACAAGTTGACGG	1	1	18	SEQ ID NO. 3793
(N20)NGG	8	48801111	-	TCCTGTCCACTTGCGCGTCAGGG	1	1	8	SEQ ID NO. 3794
(N20)NGG	8	48801112	-	CTCCTGTCCACTTGCGCGTCAGG	1	1	7	SEQ ID NO. 3795
(N20)NGG	8	48801158	-	AGCTCTGTGAAGCTGTTTACAGG	1	2	42	SEQ ID NO. 3796
(N20)NGG	8	48801202	-	TAAGTTATAGTTACCTGAGACGG	1	2	38	SEQ ID NO. 3797
(N20)NGG	8	48801586	+	TCTGTTACAGCTCCTGAAGAAGG	1	3	92	SEQ ID NO. 3798
(N20)NGG	8	48801619	+	TACACACCTGATGAGAGTCCTGG	1	4	20	SEQ ID NO. 3799
(N20)NGG	8	48801650	+	CTGTGTGAGCCCGCAAGCATAGG	1	2	29	SEQ ID NO. 3800
(N20)NGG	8	48801662	+	GCAAGCATAGGTTTCAACATCGG	1	1	26	SEQ ID NO. 3801
(N20)NGG	8	48801673	+	TTTCAACATCGGAGACGTCCAGG	1	1	3	SEQ ID NO. 3802
(N20)NGG	8	48801679	+	CATCGGAGACGTCCAGGTTATGG	1	1	13	SEQ ID NO. 3803

FIG. 12 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	8	48801783	+	GAGAGAAAATAACAGCACAGAGG	1	9	175	SEQ ID NO. 3804
(N20)NGG	8	48801786	+	AGAAAATAACAGCACAGAGGTGG	2	12	229	SEQ ID NO. 3805
(N20)NGG	8	48801787	+	GAAAATAACAGCACAGAGGTGGG	1	15	119	SEQ ID NO. 3806
(N20)NGG	8	48801794	+	ACAGCACAGAGGTGGGTACTTGG	1	4	50	SEQ ID NO. 3807
(N20)NGG	8	48801795	+	CAGCACAGAGGTGGGTACTTGGG	1	4	52	SEQ ID NO. 3808
(N20)NGG	8	48801805	+	GTGGGTACTTGGGTCACAATCGG	1	1	14	SEQ ID NO. 3809
(N20)NGG	8	48801806	+	TGGGTACTTGGGTCACAATCGGG	1	3	30	SEQ ID NO. 3810
(N20)NGG	8	48801807	+	GGGTACTTGGGTCACAATCGGGG	1	2	8	SEQ ID NO. 3811
(N20)NGG	8	48801576	-	TATTACACAAGTCCTTCTTCAGG	1	3	37	SEQ ID NO. 3812
(N20)NGG	8	48801603	-	TCTGCACCAGGACTCTCATCAGG	1	3	38	SEQ ID NO. 3813
(N20)NGG	8	48801615	-	GCTCACACAGCGTCTGCACCAGG	1	2	36	SEQ ID NO. 3814
(N20)NGG	8	48801637	-	ATGTTGAAACCTATGCTTGCGGG	1	1	23	SEQ ID NO. 3815
(N20)NGG	8	48801638	-	GATGTTGAAACCTATGCTTGCGG	1	4	17	SEQ ID NO. 3816
(N20)NGG	8	48801669	-	CAGGAAGATGAGCCATAACCTGG	2	8	38	SEQ ID NO. 3817
(N20)NGG	8	48801688	-	ATCAGATTCACACAAACATCAGG	2	4	70	SEQ ID NO. 3818
(N20)NGG	8	48801728	-	CTCTAGGATATCTTTGTATGGGG	1	1	35	SEQ ID NO. 3819
(N20)NGG	8	48801729	-	TCTCTAGGATATCTTTGTATGGG	1	7	60	SEQ ID NO. 3820
(N20)NGG	8	48801730	-	GTCTCTAGGATATCTTTGTATGG	1	2	32	SEQ ID NO. 3821
(N20)NGG	8	48801744	-	TCTCTCTCAGATGGGTCTCTAGG	1	1	39	SEQ ID NO. 3822
(N20)NGG	8	48801752	-	TGTTATTTTCTCTCTCAGATGGG	1	13	157	SEQ ID NO. 3823
(N20)NGG	8	48801753	-	CTGTTATTTTCTCTCTCAGATGG	3	13	162	SEQ ID NO. 3824
(N20)NGG	8	48802817	+	ACTTTAATATAATTGCTTCTAGG	3	18	179	SEQ ID NO. 3825
(N20)NGG	8	48802852	+	GTCTTCACTTTTGAAAGCAGTGG	1	5	82	SEQ ID NO. 3826
(N20)NGG	8	48802910	+	ATAGCAGCAGAAAAGTGCTTTGG	2	5	105	SEQ ID NO. 3827
(N20)NGG	8	48802916	+	GCAGAAAAGTGCTTTGGCACTGG	1	1	30	SEQ ID NO. 3828
(N20)NGG	8	48802917	+	CAGAAAAGTGCTTTGGCACTGGG	1	3	49	SEQ ID NO. 3829
(N20)NGG	8	48802918	+	AGAAAAGTGCTTTGGCACTGGGG	2	4	61	SEQ ID NO. 3830
(N20)NGG	8	48802925	+	TGCTTTGGCACTGGGGCAGCAGG	2	5	51	SEQ ID NO. 3831
(N20)NGG	8	48802948	+	TAACAGAACAAGCCCACAAGAGG	1	3	40	SEQ ID NO. 3832
(N20)NGG	8	48802949	+	AACAGAACAAGCCCACAAGAGGG	1	4	62	SEQ ID NO. 3833
(N20)NGG	8	48802956	+	CAAGCCCACAAGAGGGAGAAAGG	1	5	71	SEQ ID NO. 3834
(N20)NGG	8	48802984	+	CTACAGCAAATGCACCGTTGTGG	1	2	8	SEQ ID NO. 3835
(N20)NGG	8	48802989	+	GCAAATGCACCGTTGTGGTCCGG	1	1	13	SEQ ID NO. 3836

FIG. 12 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	8	48802996	+	CACCGTTGTGGTCCGGATTATGG	1	2	4	SEQ ID NO. 3837
(N20)NGG	8	48803029	+	GACTCTGCTAAACACCTCCCCGG	1	2	27	SEQ ID NO. 3838
(N20)NGG	8	48803033	+	CTGCTAAACACCTCCCCGGAAGG	1	1	15	SEQ ID NO. 3839
(N20)NGG	8	48803037	+	TAAACACCTCCCCGGAAGGATGG	1	1	35	SEQ ID NO. 3840
(N20)NGG	8	48803041	+	CACCTCCCCGGAAGGATGGAAGG	1	1	31	SEQ ID NO. 3841
(N20)NGG	8	48803045	+	TCCCCGGAAGGATGGAAGGTAGG	1	2	29	SEQ ID NO. 3842
(N20)NGG	8	48803064	+	TAGGCTGCTCTGTTAATTTGAGG	1	3	32	SEQ ID NO. 3843
(N20)NGG	8	48802826	-	TGCTTTCAAAAGTGAAGACTGGG	1	8	102	SEQ ID NO. 3844
(N20)NGG	8	48802827	-	CTGCTTTCAAAAGTGAAGACTGG	1	2	82	SEQ ID NO. 3845
(N20)NGG	8	48802874	-	TGCTGCTATAATGTCATGCATGG	1	1	57	SEQ ID NO. 3846
(N20)NGG	8	48802938	-	TGTACCTTTCTCCCTCTTGTGGG	1	5	80	SEQ ID NO. 3847
(N20)NGG	8	48802939	-	TTGTACCTTTCTCCCTCTTGTGG	1	6	82	SEQ ID NO. 3848
(N20)NGG	8	48802976	-	CTCCATAATCCGGACCACAACGG	1	1	8	SEQ ID NO. 3849
(N20)NGG	8	48802986	-	TCGTGGTAAACTCCATAATCCGG	1	2	10	SEQ ID NO. 3850
(N20)NGG	8	48803003	-	GGAGGTGTTTAGCAGAGTCGTGG	1	1	16	SEQ ID NO. 3851
(N20)NGG	8	48803021	-	TACCTTCCATCCTTCCGGGGAGG	1	1	18	SEQ ID NO. 3852
(N20)NGG	8	48803024	-	GCCTACCTTCCATCCTTCCGGGG	1	2	25	SEQ ID NO. 3853
(N20)NGG	8	48803025	-	AGCCTACCTTCCATCCTTCCGGG	1	11	84	SEQ ID NO. 3854
(N20)NGG	8	48803026	-	CAGCCTACCTTCCATCCTTCCGG	1	6	71	SEQ ID NO. 3855
(N20)NGG	8	48805699	+	TTAATTTTGTTTCTTTTTAAAGG	6	183	2613	SEQ ID NO. 3856
(N20)NGG	8	48805721	+	GCAACAGATCCCCTAATTTGTGG	1	4	25	SEQ ID NO. 3857
(N20)NGG	8	48805740	+	GTGGCTGAAAGATGTTCTCAAGG	1	2	48	SEQ ID NO. 3858
(N20)NGG	8	48805747	+	AAAGATGTTCTCAAGGAAGAAGG	1	8	138	SEQ ID NO. 3859
(N20)NGG	8	48805776	+	TTTTCTCATCAACACCTTTGAGG	2	7	90	SEQ ID NO. 3860
(N20)NGG	8	48805777	+	TTTCTCATCAACACCTTTGAGGG	1	7	88	SEQ ID NO. 3861
(N20)NGG	8	48805778	+	TTCTCATCAACACCTTTGAGGGG	1	3	53	SEQ ID NO. 3862
(N20)NGG	8	48805779	+	TCTCATCAACACCTTTGAGGGGG	1	3	41	SEQ ID NO. 3863
(N20)NGG	8	48805780	+	CTCATCAACACCTTTGAGGGGGG	2	5	35	SEQ ID NO. 3864
(N20)NGG	8	48805783	+	ATCAACACCTTTGAGGGGGGTGG	1	4	32	SEQ ID NO. 3865
(N20)NGG	8	48805789	+	ACCTTTGAGGGGGGTGGCTGTGG	1	3	51	SEQ ID NO. 3866
(N20)NGG	8	48805800	+	GGGTGGCTGTGGCCAGCCCTCGG	3	11	127	SEQ ID NO. 3867
(N20)NGG	8	48805801	+	GGTGGCTGTGGCCAGCCCTCGGG	2	8	104	SEQ ID NO. 3868
(N20)NGG	8	48805809	+	TGGCCAGCCCTCGGGCATCCTGG	2	3	38	SEQ ID NO. 3869

FIG. 12 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	8	48805834	+	CAGCCCACCCTCTTGTACTTCGG	2	3	34	SEQ ID NO. 3870
(N20)NGG	8	48805835	+	AGCCCACCCTCTTGTACTTCGGG	1	1	23	SEQ ID NO. 3871
(N20)NGG	8	48805836	+	GCCCACCCTCTTGTACTTCGGGG	1	2	22	SEQ ID NO. 3872
(N20)NGG	8	48805837	+	CCCACCCTCTTGTACTTCGGGGG	1	2	27	SEQ ID NO. 3873
(N20)NGG	8	48805853	+	TCGGGGGCCATTCAGCCTGCAGG	1	1	12	SEQ ID NO. 3874
(N20)NGG	8	48805867	+	GCCTGCAGGCCACGCTATGCTGG	1	1	36	SEQ ID NO. 3875
(N20)NGG	8	48805871	+	GCAGGCCACGCTATGCTGGCTGG	1	1	10	SEQ ID NO. 3876
(N20)NGG	8	48805883	+	ATGCTGGCTGGACCTGCTCCTGG	1	5	48	SEQ ID NO. 3877
(N20)NGG	8	48805892	+	GGACCTGCTCCTGGCCGCGTTGG	1	1	17	SEQ ID NO. 3878
(N20)NGG	8	48805914	+	GAGTGCTACAACACGTTCATTGG	1	1	10	SEQ ID NO. 3879
(N20)NGG	8	48805929	+	TTCATTGGCGAGAGAACTGTAGG	1	3	16	SEQ ID NO. 3880
(N20)NGG	8	48805940	+	GAGAACTGTAGGAGCGCTCCAGG	1	1	9	SEQ ID NO. 3881
(N20)NGG	8	48805947	+	GTAGGAGCGCTCCAGGTCCTAGG	1	1	16	SEQ ID NO. 3882
(N20)NGG	8	48805951	+	GAGCGCTCCAGGTCCTAGGTAGG	1	2	15	SEQ ID NO. 3883
(N20)NGG	8	48805971	+	AGGTCACCCTTGCCTTATTCTGG	1	6	87	SEQ ID NO. 3884
(N20)NGG	8	48805708	-	ATCTTTCAGCCACAAATTAGGGG	2	6	56	SEQ ID NO. 3885
(N20)NGG	8	48805709	-	CATCTTTCAGCCACAAATTAGGG	2	5	53	SEQ ID NO. 3886
(N20)NGG	8	48805710	-	ACATCTTTCAGCCACAAATTAGG	1	4	58	SEQ ID NO. 3887
(N20)NGG	8	48805768	-	GCCACAGCCACCCCCCTCAAAGG	2	2	67	SEQ ID NO. 3888
(N20)NGG	8	48805790	-	GGGCCAGGATGCCCGAGGGCTGG	2	6	61	SEQ ID NO. 3889
(N20)NGG	8	48805794	-	GGCTGGGCCAGGATGCCCGAGGG	1	2	45	SEQ ID NO. 3890
(N20)NGG	8	48805795	-	GGGCTGGGCCAGGATGCCCGAGG	1	8	103	SEQ ID NO. 3891
(N20)NGG	8	48805805	-	ACAAGAGGGTGGGCTGGGCCAGG	1	12	157	SEQ ID NO. 3892
(N20)NGG	8	48805810	-	GAAGTACAAGAGGGTGGGCTGGG	2	5	49	SEQ ID NO. 3893
(N20)NGG	8	48805811	-	CGAAGTACAAGAGGGTGGGCTGG	1	2	27	SEQ ID NO. 3894
(N20)NGG	8	48805815	-	CCCCCGAAGTACAAGAGGGTGGG	1	1	5	SEQ ID NO. 3895
(N20)NGG	8	48805816	-	GCCCCCGAAGTACAAGAGGGTGG	1	1	9	SEQ ID NO. 3896
(N20)NGG	8	48805819	-	ATGGCCCCCGAAGTACAAGAGGG	1	1	14	SEQ ID NO. 3897
(N20)NGG	8	48805820	-	AATGGCCCCCGAAGTACAAGAGG	1	1	13	SEQ ID NO. 3898
(N20)NGG	8	48805838	-	AGCGTGGCCTGCAGGCTGAATGG	1	2	29	SEQ ID NO. 3899
(N20)NGG	8	48805846	-	GCCAGCATAGCGTGGCCTGCAGG	1	3	22	SEQ ID NO. 3900
(N20)NGG	8	48805854	-	CAGGTCCAGCCAGCATAGCGTGG	1	1	17	SEQ ID NO. 3901
(N20)NGG	8	48805873	-	ACTCCAACGCGGCCAGGAGCAGG	1	1	16	SEQ ID NO. 3902

FIG. 12 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	8	48805879	-	TGTAGCACTCCAACGCGGCCAGG	1	1	6	SEQ ID NO. 3903
(N20)NGG	8	48805884	-	CGTGTTGTAGCACTCCAACGCGG	1	1	8	SEQ ID NO. 3904
(N20)NGG	8	48805936	-	AGGGTGACCTACCTAGGACCTGG	1	1	11	SEQ ID NO. 3905
(N20)NGG	8	48805942	-	AAGGCAAGGGTGACCTACCTAGG	1	1	24	SEQ ID NO. 3906
(N20)NGG	8	48809722	+	AGTATGCTGTCTCTGTGCAGAGG	1	2	56	SEQ ID NO. 3907
(N20)NGG	8	48809754	+	TTCCGCATCATTGTGTTTATTGG	1	1	28	SEQ ID NO. 3908
(N20)NGG	8	48809760	+	ATCATTGTGTTTATTGGATCTGG	1	3	46	SEQ ID NO. 3909
(N20)NGG	8	48809768	+	GTTTATTGGATCTGGTCAAGTGG	1	2	25	SEQ ID NO. 3910
(N20)NGG	8	48809785	+	AAGTGGCTTTTAGCTCATTGTGG	1	1	31	SEQ ID NO. 3911
(N20)NGG	8	48809786	+	AGTGGCTTTTAGCTCATTGTGGG	1	1	36	SEQ ID NO. 3912
(N20)NGG	8	48809789	+	GGCTTTTAGCTCATTGTGGGAGG	1	1	28	SEQ ID NO. 3913
(N20)NGG	8	48809854	+	AAATTCGTTCCTTTATTGCCAGG	1	3	34	SEQ ID NO. 3914
(N20)NGG	8	48809859	+	CGTTCCTTTATTGCCAGGTATGG	1	1	14	SEQ ID NO. 3915
(N20)NGG	8	48809727	-	AAACACAATGATGCGGAAGGTGG	1	2	25	SEQ ID NO. 3916
(N20)NGG	8	48809730	-	AATAAACACAATGATGCGGAAGG	1	2	31	SEQ ID NO. 3917
(N20)NGG	8	48809734	-	ATCCAATAAACACAATGATGCGG	1	1	59	SEQ ID NO. 3918
(N20)NGG	8	48809790	-	TTGTGTCGACATTCTGTCTGGGG	1	3	47	SEQ ID NO. 3919
(N20)NGG	8	48809791	-	TTTGTGTCGACATTCTGTCTGGG	1	1	31	SEQ ID NO. 3920
(N20)NGG	8	48809792	-	ATTTGTGTCGACATTCTGTCTGG	1	1	16	SEQ ID NO. 3921
(N20)NGG	8	48809815	-	GAATTTATAAAAGAGTTCAATGG	1	5	162	SEQ ID NO. 3922
(N20)NGG	8	48809841	-	ATTACCATACCTGGCAATAAAGG	1	5	55	SEQ ID NO. 3923
(N20)NGG	8	48809850	-	GATATACAGATTACCATACCTGG	1	3	19	SEQ ID NO. 3924
(N20)NGG	8	48811029	+	ATGTCTCTGTACTTGAGAACAGG	1	5	46	SEQ ID NO. 3925
(N20)NGG	8	48811129	+	CAAAGAAACGACGTTTGCCGCGG	1	2	6	SEQ ID NO. 3926
(N20)NGG	8	48811133	+	GAAACGACGTTTGCCGCGGTAGG	1	1	1	SEQ ID NO. 3927
(N20)NGG	8	48811053	-	GATGCGGCATAGGTGATCAATGG	1	1	13	SEQ ID NO. 3928
(N20)NGG	8	48811063	-	TCTTTTCAATGATGCGGCATAGG	1	1	22	SEQ ID NO. 3929
(N20)NGG	8	48811069	-	CATGCTTCTTTTCAATGATGCGG	1	4	58	SEQ ID NO. 3930
(N20)NGG	8	48811124	-	GGAAGCAAGATCACCTACCGCGG	1	1	18	SEQ ID NO. 3931
(N20)NGG	8	48812932	+	TTTCCTATTCTTTATTTTACAGG	2	25	352	SEQ ID NO. 3932
(N20)NGG	8	48812933	+	TTCCTATTCTTTATTTTACAGGG	2	12	304	SEQ ID NO. 3933
(N20)NGG	8	48812948	+	TTACAGGGAAGAAGAGTCTCTGG	1	3	52	SEQ ID NO. 3934
(N20)NGG	8	48812951	+	CAGGGAAGAAGAGTCTCTGGTGG	1	7	112	SEQ ID NO. 3935

FIG. 12 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	8	48812975	+	ACAGTTTGTGTTTGAAGCCTTGG	1	6	56	SEQ ID NO. 3936
(N20)NGG	8	48812987	+	TGAAGCCTTGGTGATATACATGG	1	2	33	SEQ ID NO. 3937
(N20)NGG	8	48812996	+	GGTGATATACATGGAGAGTCTGG	1	1	11	SEQ ID NO. 3938
(N20)NGG	8	48813027	+	CATGCAGATGAGAAGTCCTTAGG	1	2	55	SEQ ID NO. 3939
(N20)NGG	8	48812913	-	TTCCCTGTAAAATAAAGAATAGG	2	16	246	SEQ ID NO. 3940
(N20)NGG	8	48812970	-	ACTCTCCATGTATATCACCAAGG	1	1	24	SEQ ID NO. 3941
(N20)NGG	8	48812997	-	CTTCTCATCTGCATGTGCTAAGG	1	2	63	SEQ ID NO. 3942
(N20)NGG	8	48813021	-	ACTGAAGCAAAACGTACCTAAGG	1	1	25	SEQ ID NO. 3943
(N20)NGG	8	48815128	+	AGGTCTCTTTGTTTTGTTTCAGG	1	15	192	SEQ ID NO. 3944
(N20)NGG	8	48815132	+	CTCTTTGTTTTGTTTCAGGATGG	1	11	201	SEQ ID NO. 3945
(N20)NGG	8	48815140	+	TTTGTTTCAGGATGGAATTGTGG	1	4	85	SEQ ID NO. 3946
(N20)NGG	8	48815174	+	AGTACTTTAAGAGATTTTTGTGG	2	7	119	SEQ ID NO. 3947
(N20)NGG	8	48815178	+	CTTTAAGAGATTTTTGTGGTCGG	1	7	99	SEQ ID NO. 3948
(N20)NGG	8	48815202	+	GTATTCGAGAATTCCTTAAATGG	1	2	18	SEQ ID NO. 3949
(N20)NGG	8	48815233	+	GCAAATAACACCACAGCAGCAGG	1	3	39	SEQ ID NO. 3950
(N20)NGG	8	48815310	+	TTCACCCCAATGCTTTCAAGAGG	1	2	40	SEQ ID NO. 3951
(N20)NGG	8	48815314	+	CCCCAATGCTTTCAAGAGGCTGG	1	3	23	SEQ ID NO. 3952
(N20)NGG	8	48815315	+	CCCAATGCTTTCAAGAGGCTGGG	1	2	56	SEQ ID NO. 3953
(N20)NGG	8	48815346	+	TTGCCTTTAATAATATCTACAGG	1	5	70	SEQ ID NO. 3954
(N20)NGG	8	48815347	+	TGCCTTTAATAATATCTACAGGG	1	5	105	SEQ ID NO. 3955
(N20)NGG	8	48815355	+	ATAATATCTACAGGGAATTCAGG	1	4	53	SEQ ID NO. 3956
(N20)NGG	8	48815142	-	CTCTTAAAGTACTGTCAACAGGG	1	3	40	SEQ ID NO. 3957
(N20)NGG	8	48815143	-	TCTCTTAAAGTACTGTCAACAGG	1	3	27	SEQ ID NO. 3958
(N20)NGG	8	48815193	-	TTTGCTTAATGGACCATTTAAGG	1	4	43	SEQ ID NO. 3959
(N20)NGG	8	48815204	-	CTGTGGTGTTATTTGCTTAATGG	2	4	63	SEQ ID NO. 3960
(N20)NGG	8	48815221	-	GGACTCTTCTCCTGCTGCTGTGG	1	9	70	SEQ ID NO. 3961
(N20)NGG	8	48815242	-	AAAAGCGATTTGGTGTTTACTGG	1	2	23	SEQ ID NO. 3962
(N20)NGG	8	48815252	-	AAGTCGCTTGAAAAGCGATTTGG	1	1	6	SEQ ID NO. 3963
(N20)NGG	8	48815280	-	AAGCATTGGGGTGAAGCGCAAGG	1	1	20	SEQ ID NO. 3964
(N20)NGG	8	48815292	-	CCAGCCTCTTGAAAGCATTGGGG	1	2	39	SEQ ID NO. 3965
(N20)NGG	8	48815293	-	CCCAGCCTCTTGAAAGCATTGGG	1	5	60	SEQ ID NO. 3966
(N20)NGG	8	48815294	-	TCCCAGCCTCTTGAAAGCATTGG	2	5	147	SEQ ID NO. 3967
(N20)NGG	8	48815327	-	TTCCCTGTAGATATTATTAAAGG	1	6	82	SEQ ID NO. 3968

FIG. 12 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	8	48817428	+	TTTAATGGTATTGTTTCTTCAGG	2	61	604	SEQ ID NO. 3969
(N20)NGG	8	48817436	+	TATTGTTTCTTCAGGTGACAAGG	1	1	63	SEQ ID NO. 3970
(N20)NGG	8	48817475	+	TAGTTATGCAGCTGATTCACTGG	1	2	13	SEQ ID NO. 3971
(N20)NGG	8	48817506	+	CAACAAGAAATTTGAAAGTCAGG	1	4	108	SEQ ID NO. 3972
(N20)NGG	8	48817536	+	TGCCTTACTAGAAGCTATATTGG	1	3	16	SEQ ID NO. 3973
(N20)NGG	8	48817449	-	TGAATCAGCTGCATAACTAGTGG	1	2	35	SEQ ID NO. 3974
(N20)NGG	8	48817516	-	TACCAATATAGCTTCTAGTAAGG	1	1	16	SEQ ID NO. 3975
(N20)NGG	8	48824969	+	CTGACCTCCTGGTCTGTTTTAGG	1	4	54	SEQ ID NO. 3976
(N20)NGG	8	48824999	+	CTGTGAACTTTTACATAGCATGG	1	3	50	SEQ ID NO. 3977
(N20)NGG	8	48825014	+	TAGCATGGTTATGTTTATGTTGG	1	2	59	SEQ ID NO. 3978
(N20)NGG	8	48825015	+	AGCATGGTTATGTTTATGTTGGG	1	3	54	SEQ ID NO. 3979
(N20)NGG	8	48825039	+	AAAGCCACGCAGATGCCAGAAGG	1	5	55	SEQ ID NO. 3980
(N20)NGG	8	48825040	+	AAGCCACGCAGATGCCAGAAGGG	1	4	72	SEQ ID NO. 3981
(N20)NGG	8	48825041	+	AGCCACGCAGATGCCAGAAGGGG	1	4	67	SEQ ID NO. 3982
(N20)NGG	8	48825042	+	GCCACGCAGATGCCAGAAGGGGG	1	4	46	SEQ ID NO. 3983
(N20)NGG	8	48825047	+	GCAGATGCCAGAAGGGGGACAGG	1	3	57	SEQ ID NO. 3984
(N20)NGG	8	48825048	+	CAGATGCCAGAAGGGGGACAGGG	2	5	71	SEQ ID NO. 3985
(N20)NGG	8	48825079	+	CCATGTACCAGCTCTATAAGCGG	1	3	21	SEQ ID NO. 3986
(N20)NGG	8	48825122	+	ACTTGCGTGTGATGTTGATCAGG	1	2	11	SEQ ID NO. 3987
(N20)NGG	8	48825127	+	CGTGTGATGTTGATCAGGTAAGG	1	2	7	SEQ ID NO. 3988
(N20)NGG	8	48825128	+	GTGTGATGTTGATCAGGTAAGGG	1	2	30	SEQ ID NO. 3989
(N20)NGG	8	48824951	-	GCAACCTAAAACAGACCAGGAGG	1	3	25	SEQ ID NO. 3990
(N20)NGG	8	48824954	-	GCTGCAACCTAAAACAGACCAGG	1	3	23	SEQ ID NO. 3991
(N20)NGG	8	48824976	-	CATGCTATGTAAAAGTTCACAGG	1	4	51	SEQ ID NO. 3992
(N20)NGG	8	48825021	-	TCCCCCTTCTGGCATCTGCGTGG	1	2	22	SEQ ID NO. 3993
(N20)NGG	8	48825032	-	GGGGCTCCCTGTCCCCCTTCTGG	1	5	68	SEQ ID NO. 3994
(N20)NGG	8	48825051	-	ATAGAGCTGGTACATGGGTGGGG	1	1	24	SEQ ID NO. 3995
(N20)NGG	8	48825052	-	TATAGAGCTGGTACATGGGTGGG	1	2	22	SEQ ID NO. 3996
(N20)NGG	8	48825053	-	TTATAGAGCTGGTACATGGGTGG	1	1	20	SEQ ID NO. 3997
(N20)NGG	8	48825056	-	CGCTTATAGAGCTGGTACATGGG	1	1	7	SEQ ID NO. 3998
(N20)NGG	8	48825057	-	CCGCTTATAGAGCTGGTACATGG	1	1	4	SEQ ID NO. 3999
(N20)NGG	8	48825064	-	GAAACGTCCGCTTATAGAGCTGG	1	1	2	SEQ ID NO. 4000
(N20)NGG	8	48825086	-	CACGCAAGTCGAAGCAGCACAGG	1	2	8	SEQ ID NO. 4001

FIG. 12 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	8	48826495	+	TGAGATGATGAAGAGCTATGTGG	1	11	69	SEQ ID NO. 4002
(N20)NGG	8	48826500	+	TGATGAAGAGCTATGTGGCCTGG	1	1	39	SEQ ID NO. 4003
(N20)NGG	8	48826501	+	GATGAAGAGCTATGTGGCCTGGG	1	8	59	SEQ ID NO. 4004
(N20)NGG	8	48826515	+	TGGCCTGGGACAGAGAGAAGCGG	2	9	195	SEQ ID NO. 4005
(N20)NGG	8	48826564	+	GATGAAACCTGTCATTTTCCTGG	1	5	54	SEQ ID NO. 4006
(N20)NGG	8	48826466	-	GCTCTTCATCATCTCATCTGAGG	2	3	57	SEQ ID NO. 4007
(N20)NGG	8	48826496	-	CAGCCGCTTCTCTCTGTCCCAGG	2	10	95	SEQ ID NO. 4008
(N20)NGG	8	48826531	-	ACAGGTTTCATCTCTCTAAAGGG	1	4	54	SEQ ID NO. 4009
(N20)NGG	8	48826532	-	GACAGGTTTCATCTCTCTAAAGG	1	6	34	SEQ ID NO. 4010
(N20)NGG	8	48826549	-	AACACATCCAGGAAAATGACAGG	1	5	92	SEQ ID NO. 4011
(N20)NGG	8	48826560	-	CTCGAGGCAGGAACACATCCAGG	1	2	33	SEQ ID NO. 4012
(N20)NGG	8	48826572	-	CTAATTCTGTGACTCGAGGCAGG	1	1	50	SEQ ID NO. 4013
(N20)NGG	8	48826576	-	AGCGCTAATTCTGTGACTCGAGG	1	2	7	SEQ ID NO. 4014
(N20)NGG	8	48826604	-	TACTTTAGTTTGTCTGTCACTGG	1	1	37	SEQ ID NO. 4015
(N20)NGG	8	48827939	+	ATTAGAGTAGTACAAATGCTTGG	1	2	32	SEQ ID NO. 4016
(N20)NGG	8	48827948	+	GTACAAATGCTTGGATCTCTAGG	1	4	29	SEQ ID NO. 4017
(N20)NGG	8	48827951	+	CAAATGCTTGGATCTCTAGGAGG	1	10	204	SEQ ID NO. 4018
(N20)NGG	8	48827978	+	ATAAACAAAAATCTTCTGACAGG	1	8	137	SEQ ID NO. 4019
(N20)NGG	8	48827900	-	TCTAATTCTTATTTCTTCTAAGG	2	22	266	SEQ ID NO. 4020
(N20)NGG	8	48830855	+	TAGATGAGACCAAGAATAACTGG	1	2	47	SEQ ID NO. 4021
(N20)NGG	8	48830856	+	AGATGAGACCAAGAATAACTGGG	1	6	61	SEQ ID NO. 4022
(N20)NGG	8	48830876	+	GGGAAGTGTCAGCTCTTTCTCGG	1	6	57	SEQ ID NO. 4023
(N20)NGG	8	48830877	+	GGAAGTGTCAGCTCTTTCTCGGG	1	4	50	SEQ ID NO. 4024
(N20)NGG	8	48830890	+	CTTTCTCGGGCTGCCCAGAAAGG	1	5	36	SEQ ID NO. 4025
(N20)NGG	8	48830904	+	CCAGAAAGGATTTAATAAAGTGG	1	5	118	SEQ ID NO. 4026
(N20)NGG	8	48830842	-	TGACACTTCCCAGTTATTCTTGG	1	1	42	SEQ ID NO. 4027
(N20)NGG	8	48830881	-	CACTTTATTAAATCCTTTCTGGG	2	5	135	SEQ ID NO. 4028
(N20)NGG	8	48830882	-	CCACTTTATTAAATCCTTTCTGG	1	7	63	SEQ ID NO. 4029
(N20)NGG	8	48830933	-	AAGGACTTCTTACTGATGAAAGG	1	7	51	SEQ ID NO. 4030
(N20)NGG	8	48839756	+	TGTTTGTATTAACATACAGATGG	1	7	123	SEQ ID NO. 4031
(N20)NGG	8	48839768	+	CATACAGATGGCTTTCAAACTGG	1	2	36	SEQ ID NO. 4032
(N20)NGG	8	48839769	+	ATACAGATGGCTTTCAAACTGGG	1	4	66	SEQ ID NO. 4033
(N20)NGG	8	48839789	+	GGGCCTGAGCTATACCCCCTTGG	1	4	20	SEQ ID NO. 4034

FIG. 12 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	8	48839799	+	TATACCCCCTTGGCAGAAGTAGG	1	1	14	SEQ ID NO. 4035
(N20)NGG	8	48839821	+	GCCTGAATGCTCTAGAAGAATGG	1	3	32	SEQ ID NO. 4036
(N20)NGG	8	48839882	+	CAAAGACATTCTCCCCTGCCTGG	1	2	42	SEQ ID NO. 4037
(N20)NGG	8	48839886	+	GACATTCTCCCCTGCCTGGATGG	1	6	51	SEQ ID NO. 4038
(N20)NGG	8	48839913	+	CTGAAGACTTCAGCCTTGTCAGG	1	4	39	SEQ ID NO. 4039
(N20)NGG	8	48839770	-	CTGCCAAGGGGGTATAGCTCAGG	1	2	11	SEQ ID NO. 4040
(N20)NGG	8	48839781	-	CAGGCCTACTTCTGCCAAGGGGG	1	1	33	SEQ ID NO. 4041
(N20)NGG	8	48839782	-	TCAGGCCTACTTCTGCCAAGGGG	1	1	31	SEQ ID NO. 4042
(N20)NGG	8	48839783	-	TTCAGGCCTACTTCTGCCAAGGG	1	1	28	SEQ ID NO. 4043
(N20)NGG	8	48839784	-	ATTCAGGCCTACTTCTGCCAAGG	1	2	32	SEQ ID NO. 4044
(N20)NGG	8	48839800	-	ACCATTCTTCTAGAGCATTCAGG	1	1	30	SEQ ID NO. 4045
(N20)NGG	8	48839852	-	GGGAGAATGTCTTTGTAATAAGG	1	5	68	SEQ ID NO. 4046
(N20)NGG	8	48839872	-	TCAGGTATCCATCCAGGCAGGGG	1	3	40	SEQ ID NO. 4047
(N20)NGG	8	48839873	-	TTCAGGTATCCATCCAGGCAGGG	1	3	36	SEQ ID NO. 4048
(N20)NGG	8	48839874	-	CTTCAGGTATCCATCCAGGCAGG	1	1	23	SEQ ID NO. 4049
(N20)NGG	8	48839878	-	AAGTCTTCAGGTATCCATCCAGG	1	2	27	SEQ ID NO. 4050
(N20)NGG	8	48839890	-	CTGACAAGGCTGAAGTCTTCAGG	1	4	37	SEQ ID NO. 4051
(N20)NGG	8	48839904	-	CTTCTAAACATTACCTGACAAGG	1	2	39	SEQ ID NO. 4052
(N20)NGG	8	48840330	+	TACTGTCTTCTTTCTTGTTAAGG	1	12	166	SEQ ID NO. 4053
(N20)NGG	8	48840333	+	TGTCTTCTTTCTTGTTAAGGTGG	1	7	123	SEQ ID NO. 4054
(N20)NGG	8	48840369	+	GCAGTACAAAGATGAACTTTTGG	2	3	51	SEQ ID NO. 4055
(N20)NGG	8	48840450	+	AGCCTACGTTCCTGCACTGCAGG	1	1	10	SEQ ID NO. 4056
(N20)NGG	8	48840454	+	TACGTTCCTGCACTGCAGGTAGG	1	2	15	SEQ ID NO. 4057
(N20)NGG	8	48840370	-	CAGAAGAAAGGTCAAACAAGAGG	1	5	107	SEQ ID NO. 4058
(N20)NGG	8	48840382	-	GTGTGGCAAGGACAGAAGAAAGG	2	7	158	SEQ ID NO. 4059
(N20)NGG	8	48840394	-	TTCAATGATGTTGTGTGGCAAGG	1	2	55	SEQ ID NO. 4060
(N20)NGG	8	48840399	-	TCGAGTTCAATGATGTTGTGTGG	1	2	9	SEQ ID NO. 4061
(N20)NGG	8	48840430	-	TACCTGCAGTGCAGGAACGTAGG	1	1	18	SEQ ID NO. 4062
(N20)NGG	8	48840438	-	ACAACGCCTACCTGCAGTGCAGG	1	2	12	SEQ ID NO. 4063
(N20)NGG	8	48841651	+	AACTTGCTGTTTTATTTGACAGG	2	10	99	SEQ ID NO. 4064
(N20)NGG	8	48841652	+	ACTTGCTGTTTTATTTGACAGGG	1	7	108	SEQ ID NO. 4065
(N20)NGG	8	48841730	+	TTTGCTTTATTTGTGAAATTTGG	1	15	363	SEQ ID NO. 4066
(N20)NGG	8	48841738	+	ATTTGTGAAATTTGGCAAAGAGG	2	13	136	SEQ ID NO. 4067

FIG. 12 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	8	48841660	-	GGAGAGTGTTTCAGACTCTTTGG	1	3	33	SEQ ID NO. 4068
(N20)NGG	8	48841681	-	GAATACTTTTCTGGGTCTTCAGG	1	7	46	SEQ ID NO. 4069
(N20)NGG	8	48841689	-	CAAAGCAAGAATACTTTTCTGGG	2	4	143	SEQ ID NO. 4070
(N20)NGG	8	48841690	-	GCAAAGCAAGAATACTTTTCTGG	1	5	62	SEQ ID NO. 4071
(N20)NGG	8	48842454	+	AAGCAGAATTTTTTGAACCATGG	2	31	630	SEQ ID NO. 4072
(N20)NGG	8	48842455	+	AGCAGAATTTTTTGAACCATGGG	1	3	137	SEQ ID NO. 4073
(N20)NGG	8	48842496	+	AATTAATTTTGCAATCTACAAGG	1	5	116	SEQ ID NO. 4074
(N20)NGG	8	48842513	+	ACAAGGTTGCCCCTCATCAGTGG	1	3	19	SEQ ID NO. 4075
(N20)NGG	8	48842572	+	CAAGAAAATAAAATATTTCGAGG	1	20	306	SEQ ID NO. 4076
(N20)NGG	8	48842589	+	TCGAGGTGAGTCTTTCTTGCAGG	2	4	38	SEQ ID NO. 4077
(N20)NGG	8	48842421	-	AAAATTCTGCTTGTTTCTCAGGG	1	13	160	SEQ ID NO. 4078
(N20)NGG	8	48842422	-	AAAAATTCTGCTTGTTTCTCAGG	1	5	118	SEQ ID NO. 4079
(N20)NGG	8	48842449	-	TATGAAAATGAGTACACCCATGG	1	5	50	SEQ ID NO. 4080
(N20)NGG	8	48842500	-	TTGTAGAAACCACTGATGAGGGG	1	7	49	SEQ ID NO. 4081
(N20)NGG	8	48842501	-	TTTGTAGAAACCACTGATGAGGG	1	4	90	SEQ ID NO. 4082
(N20)NGG	8	48842502	-	ATTTGTAGAAACCACTGATGAGG	1	5	61	SEQ ID NO. 4083
(N20)NGG	8	48842549	-	CTCGAAATATTTTATTTTCTTGG	1	21	221	SEQ ID NO. 4084
(N20)NGG	8	48843235	+	CTACAATTACTCTTTAAGAATGG	1	3	78	SEQ ID NO. 4085
(N20)NGG	8	48843243	+	ACTCTTTAAGAATGGAGATGAGG	1	7	67	SEQ ID NO. 4086
(N20)NGG	8	48843250	+	AAGAATGGAGATGAGGCGCCTGG	1	4	41	SEQ ID NO. 4087
(N20)NGG	8	48843257	+	GAGATGAGGCGCCTGGTGTTTGG	1	3	31	SEQ ID NO. 4088
(N20)NGG	8	48843282	+	GATCCCAACTTCAGATCCAGCGG	2	2	31	SEQ ID NO. 4089
(N20)NGG	8	48843318	+	AGCTAAACCTAAAGATTTTTCGG	1	9	84	SEQ ID NO. 4090
(N20)NGG	8	48843333	+	TTTTTCGGCTTTCATTAACCTGG	1	2	33	SEQ ID NO. 4091
(N20)NGG	8	48843336	+	TTCGGCTTTCATTAACCTGGTGG	1	2	18	SEQ ID NO. 4092
(N20)NGG	8	48843347	+	TTAACCTGGTGGAATTTTGCAGG	1	4	41	SEQ ID NO. 4093
(N20)NGG	8	48843354	+	GGTGGAATTTTGCAGGTATTTGG	1	4	39	SEQ ID NO. 4094
(N20)NGG	8	48843246	-	GTTGGGATCATCCAAACACCAGG	1	2	24	SEQ ID NO. 4095
(N20)NGG	8	48843263	-	TAGCCGCTGGATCTGAAGTTGGG	1	1	10	SEQ ID NO. 4096
(N20)NGG	8	48843264	-	TTAGCCGCTGGATCTGAAGTTGG	1	1	14	SEQ ID NO. 4097
(N20)NGG	8	48843276	-	GCTGGATGCAAGTTAGCCGCTGG	1	1	5	SEQ ID NO. 4098
(N20)NGG	8	48843294	-	GAAAAATCTTTAGGTTTAGCTGG	1	1	57	SEQ ID NO. 4099
(N20)NGG	8	48843303	-	ATGAAAGCCGAAAAATCTTTAGG	1	2	39	SEQ ID NO. 4100

FIG. 12 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	8	48843329	-	AATACCTGCAAAATTCCACCAGG	1	3	53	SEQ ID NO. 4101
(N20)NGG	8	48845579	+	TATTGTTTTTCTTTATTTAAAGG	1	63	1249	SEQ ID NO. 4102
(N20)NGG	8	48845693	+	TTTGAAGATTGTTGAGAAATTGG	1	6	137	SEQ ID NO. 4103
(N20)NGG	8	48845721	+	ACACTTGAAATACAGACTGTTGG	1	3	40	SEQ ID NO. 4104
(N20)NGG	8	48845722	+	CACTTGAAATACAGACTGTTGGG	1	2	54	SEQ ID NO. 4105
(N20)NGG	8	48845723	+	ACTTGAAATACAGACTGTTGGGG	1	4	53	SEQ ID NO. 4106
(N20)NGG	8	48845732	+	ACAGACTGTTGGGGAACAAGAGG	1	4	66	SEQ ID NO. 4107
(N20)NGG	8	48845619	-	ATGATTCAGACTTTCACTGGAGG	1	1	44	SEQ ID NO. 4108
(N20)NGG	8	48845622	-	TAAATGATTCAGACTTTCACTGG	1	5	68	SEQ ID NO. 4109
(N20)NGG	8	48845667	-	TTTCTCAACAATCTTCAAAACGG	1	7	153	SEQ ID NO. 4110
(N20)NGG	8	48846524	+	GTCATGCTGTCTTTCTGGCCAGG	1	1	29	SEQ ID NO. 4111
(N20)NGG	8	48846525	+	TCATGCTGTCTTTCTGGCCAGGG	1	7	81	SEQ ID NO. 4112
(N20)NGG	8	48846561	+	TCTGAAGACCACCGTGCTTCAGG	1	2	22	SEQ ID NO. 4113
(N20)NGG	8	48846562	+	CTGAAGACCACCGTGCTTCAGGG	1	2	16	SEQ ID NO. 4114
(N20)NGG	8	48846563	+	TGAAGACCACCGTGCTTCAGGGG	1	1	18	SEQ ID NO. 4115
(N20)NGG	8	48846576	+	GCTTCAGGGGAAGTCAGAACTGG	1	5	37	SEQ ID NO. 4116
(N20)NGG	8	48846583	+	GGGAAGTCAGAACTGGCAAATGG	1	7	71	SEQ ID NO. 4117
(N20)NGG	8	48846587	+	AGTCAGAACTGGCAAATGGAAGG	1	6	60	SEQ ID NO. 4118
(N20)NGG	8	48846611	+	GCCCACATACAAAGACTACGTGG	1	1	11	SEQ ID NO. 4119
(N20)NGG	8	48846650	+	CCTGAGCTCTGACCAGATGATGG	2	5	79	SEQ ID NO. 4120
(N20)NGG	8	48846520	-	CAGATTCAGACTCAGGGCCCTGG	1	11	80	SEQ ID NO. 4121
(N20)NGG	8	48846526	-	GGTCTTCAGATTCAGACTCAGGG	1	6	78	SEQ ID NO. 4122
(N20)NGG	8	48846527	-	TGGTCTTCAGATTCAGACTCAGG	1	4	50	SEQ ID NO. 4123
(N20)NGG	8	48846547	-	TGACTTCCCCTGAAGCACGGTGG	1	1	20	SEQ ID NO. 4124
(N20)NGG	8	48846550	-	TTCTGACTTCCCCTGAAGCACGG	1	6	77	SEQ ID NO. 4125
(N20)NGG	8	48846590	-	TCCACGTAGTCTTTGTATGTGGG	1	2	18	SEQ ID NO. 4126
(N20)NGG	8	48846591	-	ATCCACGTAGTCTTTGTATGTGG	1	2	11	SEQ ID NO. 4127
(N20)NGG	8	48846628	-	CCATCATCTGGTCAGAGCTCAGG	1	3	26	SEQ ID NO. 4128
(N20)NGG	8	48846640	-	TGGTAAATGTTACCATCATCTGG	2	3	48	SEQ ID NO. 4129
(N20)NGG	8	48847576	+	TTTTCTTTTTTCAGTGCATCAGG	1	14	294	SEQ ID NO. 4130
(N20)NGG	8	48847577	+	TTTCTTTTTTCAGTGCATCAGGG	2	19	285	SEQ ID NO. 4131
(N20)NGG	8	48847606	+	CAGAATATGTTCTAAACCAGTGG	2	4	56	SEQ ID NO. 4132
(N20)NGG	8	48847618	+	TAAACCAGTGGTCCTTCCAAAGG	1	2	27	SEQ ID NO. 4133

FIG. 12 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	8	48847600	-	TTTACCTTTGGAAGGACCACTGG	1	4	57	SEQ ID NO. 4134
(N20)NGG	8	48847608	-	ATTCAGAATTTACCTTTGGAAGG	1	6	102	SEQ ID NO. 4135
(N20)NGG	8	48847612	-	TTAAATTCAGAATTTACCTTTGG	1	13	150	SEQ ID NO. 4136
(N20)NGG	8	48848291	+	GTTTGCTGATTATTTCCGGTAGG	1	2	15	SEQ ID NO. 4137
(N20)NGG	8	48848300	+	TTATTTCCGGTAGGTTCCTGAGG	1	1	21	SEQ ID NO. 4138
(N20)NGG	8	48848318	+	TGAGGTGTATACTCCAGTTCTGG	1	1	22	SEQ ID NO. 4139
(N20)NGG	8	48848330	+	TCCAGTTCTGGAGCACCTCGTGG	1	1	20	SEQ ID NO. 4140
(N20)NGG	8	48848378	+	GTACAGTCCAAAAATGCAGCTGG	1	1	30	SEQ ID NO. 4141
(N20)NGG	8	48848402	+	GTGTTGCAGAGCCATAGTGAAGG	1	2	27	SEQ ID NO. 4142
(N20)NGG	8	48848417	+	AGTGAAGGTGTTCCTAGCTTTGG	1	2	24	SEQ ID NO. 4143
(N20)NGG	8	48848427	+	TTCCTAGCTTTGGCAGCAAAAGG	1	5	56	SEQ ID NO. 4144
(N20)NGG	8	48848428	+	TCCTAGCTTTGGCAGCAAAAGGG	1	7	62	SEQ ID NO. 4145
(N20)NGG	8	48848440	+	CAGCAAAAGGGCCAGTTCTCAGG	1	3	45	SEQ ID NO. 4146
(N20)NGG	8	48848459	+	CAGGAATTGCATTAGTACTGTGG	1	2	53	SEQ ID NO. 4147
(N20)NGG	8	48848460	+	AGGAATTGCATTAGTACTGTGGG	1	2	49	SEQ ID NO. 4148
(N20)NGG	8	48848284	-	TATACACCTCAGGAACCTACCGG	1	2	14	SEQ ID NO. 4149
(N20)NGG	8	48848294	-	AGAACTGGAGTATACACCTCAGG	1	2	22	SEQ ID NO. 4150
(N20)NGG	8	48848309	-	ACCACGAGGTGCTCCAGAACTGG	1	4	9	SEQ ID NO. 4151
(N20)NGG	8	48848323	-	TGTCTATCTGCATCACCACGAGG	1	2	13	SEQ ID NO. 4152
(N20)NGG	8	48848350	-	GCATTTTTGGACTGTACTGTGGG	1	2	23	SEQ ID NO. 4153
(N20)NGG	8	48848351	-	TGCATTTTTGGACTGTACTGTGG	1	4	39	SEQ ID NO. 4154
(N20)NGG	8	48848363	-	CAACACACCAGCTGCATTTTTGG	2	5	47	SEQ ID NO. 4155
(N20)NGG	8	48848391	-	AGCTAGGAACACCTTCACTATGG	1	1	19	SEQ ID NO. 4156
(N20)NGG	8	48848407	-	GCCCTTTTGCTGCCAAAGCTAGG	2	4	48	SEQ ID NO. 4157
(N20)NGG	8	48848429	-	CTAATGCAATTCCTGAGAACTGG	2	5	31	SEQ ID NO. 4158
(N20)NGG	8	48848921	+	ACCTTTTCTAAAGCCGTGCAAGG	1	2	19	SEQ ID NO. 4159
(N20)NGG	8	48849006	+	TTCCTCACCCAGACAGACACTGG	1	2	48	SEQ ID NO. 4160
(N20)NGG	8	48848900	-	ACCTTGCACGGCTTTAGAAAAGG	1	3	13	SEQ ID NO. 4161
(N20)NGG	8	48848912	-	TTTGCGTTTATAACCTTGCACGG	1	1	29	SEQ ID NO. 4162
(N20)NGG	8	48848986	-	CACCAGTGTCTGTCTGGGTGAGG	1	6	146	SEQ ID NO. 4163
(N20)NGG	8	48848991	-	GTCGTCACCAGTGTCTGTCTGGG	1	2	9	SEQ ID NO. 4164
(N20)NGG	8	48848992	-	GGTCGTCACCAGTGTCTGTCTGG	1	1	13	SEQ ID NO. 4165
(N20)NGG	8	48849013	-	AGCTTGGCATCTGATAAACACGG	1	6	38	SEQ ID NO. 4166

FIG. 12 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	8	48849029	-	GCAACAGACTGGAGGAAGCTTGG	1	3	62	SEQ ID NO. 4167
(N20)NGG	8	48849037	-	AGACGCTTGCAACAGACTGGAGG	1	3	15	SEQ ID NO. 4168
(N20)NGG	8	48849040	-	GCAAGACGCTTGCAACAGACTGG	1	1	11	SEQ ID NO. 4169
(N20)NGG	8	48849067	-	TTAGTTCACTTACTGTGTCAAGG	1	5	63	SEQ ID NO. 4170
(N20)NGG	8	48852110	+	AATAAATATTATGTATTTGCAGG	3	18	262	SEQ ID NO. 4171
(N20)NGG	8	48852122	+	GTATTTGCAGGTTTCTAATATGG	1	6	100	SEQ ID NO. 4172
(N20)NGG	8	48852125	+	TTTGCAGGTTTCTAATATGGTGG	1	4	49	SEQ ID NO. 4173
(N20)NGG	8	48852170	+	AAATAAACTGCAGTACTTTATGG	1	6	143	SEQ ID NO. 4174
(N20)NGG	8	48852183	+	TACTTTATGGAGCAGTTTTATGG	1	6	154	SEQ ID NO. 4175
(N20)NGG	8	48852200	+	TTATGGAATCATCAGAAATGTGG	1	2	66	SEQ ID NO. 4176
(N20)NGG	8	48852215	+	AAATGTGGATTCGAACAACAAGG	1	3	35	SEQ ID NO. 4177
(N20)NGG	8	48852237	+	GAGTTATCTATTGCTATCCGTGG	1	1	5	SEQ ID NO. 4178
(N20)NGG	8	48852243	+	TCTATTGCTATCCGTGGATATGG	1	2	10	SEQ ID NO. 4179
(N20)NGG	8	48852255	+	CGTGGATATGGACTTTTTGCAGG	1	2	6	SEQ ID NO. 4180
(N20)NGG	8	48852232	-	CTGCAAAAAGTCCATATCCACGG	1	2	43	SEQ ID NO. 4181
(N20)NGG	8	48855771	+	ATGGCATTTGCATTTGCAGCTGG	1	4	65	SEQ ID NO. 4182
(N20)NGG	8	48855821	+	TCAGTTTAGCACCTGCCTTCTGG	1	5	37	SEQ ID NO. 4183
(N20)NGG	8	48855859	+	TATTTGAAGTCTTGTTAAAGTGG	1	9	113	SEQ ID NO. 4184
(N20)NGG	8	48855908	+	AAAAGCTGCACTTTCAGCCCTGG	1	3	58	SEQ ID NO. 4185
(N20)NGG	8	48855926	+	CCTGGAATCCTTTCTGAAACAGG	2	13	97	SEQ ID NO. 4186
(N20)NGG	8	48855778	-	GAGATGCATGCAGGGCAAATAGG	1	3	33	SEQ ID NO. 4187
(N20)NGG	8	48855786	-	GCTAAACTGAGATGCATGCAGGG	1	1	16	SEQ ID NO. 4188
(N20)NGG	8	48855787	-	TGCTAAACTGAGATGCATGCAGG	1	1	21	SEQ ID NO. 4189
(N20)NGG	8	48855810	-	CACGTAGTTGTCCAGAAGGCAGG	1	1	11	SEQ ID NO. 4190
(N20)NGG	8	48855814	-	GAGACACGTAGTTGTCCAGAAGG	1	2	10	SEQ ID NO. 4191
(N20)NGG	8	48855864	-	TTTCAATTCTACATTTGTGTGGG	2	8	158	SEQ ID NO. 4192
(N20)NGG	8	48855865	-	TTTTCAATTCTACATTTGTGTGG	1	10	148	SEQ ID NO. 4193
(N20)NGG	8	48855903	-	CTGTTTCAGAAAGGATTCCAGGG	1	7	72	SEQ ID NO. 4194
(N20)NGG	8	48855904	-	CCTGTTTCAGAAAGGATTCCAGG	1	5	60	SEQ ID NO. 4195
(N20)NGG	8	48855912	-	TTGTGGTACCTGTTTCAGAAAGG	1	1	35	SEQ ID NO. 4196
(N20)NGG	8	48856443	+	AAGAGATATGCTGTGCCCTCAGG	1	3	35	SEQ ID NO. 4197
(N20)NGG	8	48856447	+	GATATGCTGTGCCCTCAGGTAGG	1	2	21	SEQ ID NO. 4198
(N20)NGG	8	48856465	+	GTAGGATTCTGTTTATAATGAGG	2	6	58	SEQ ID NO. 4199

FIG. 12 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	8	48856436	-	ATAAACAGAATCCTACCTGAGGG	1	3	56	SEQ ID NO. 4200
(N20)NGG	8	48856437	-	TATAAACAGAATCCTACCTGAGG	1	3	45	SEQ ID NO. 4201
(N20)NGG	8	48856549	+	CCCTAGATCCCCAGACTTCAAGG	1	5	61	SEQ ID NO. 4202
(N20)NGG	8	48856550	+	CCTAGATCCCCAGACTTCAAGGG	1	1	27	SEQ ID NO. 4203
(N20)NGG	8	48856574	+	GATTTTTAATTTTGTACTAAAGG	1	12	240	SEQ ID NO. 4204
(N20)NGG	8	48856589	+	ACTAAAGGCAATTCGTCCTCAGG	1	2	10	SEQ ID NO. 4205
(N20)NGG	8	48856593	+	AAGGCAATTCGTCCTCAGGTAGG	1	3	11	SEQ ID NO. 4206
(N20)NGG	8	48856527	-	CCTTGAAGTCTGGGGATCTAGGG	1	1	35	SEQ ID NO. 4207
(N20)NGG	8	48856528	-	CCCTTGAAGTCTGGGGATCTAGG	1	2	43	SEQ ID NO. 4208
(N20)NGG	8	48856535	-	AAAATCTCCCTTGAAGTCTGGGG	1	4	74	SEQ ID NO. 4209
(N20)NGG	8	48856536	-	AAAAATCTCCCTTGAAGTCTGGG	1	2	76	SEQ ID NO. 4210
(N20)NGG	8	48856537	-	TAAAAATCTCCCTTGAAGTCTGG	1	3	64	SEQ ID NO. 4211
(N20)NGG	8	48856583	-	AGTAATATTAATCCTACCTGAGG	1	2	42	SEQ ID NO. 4212
(N20)NGG	8	48866218	+	AGAGCCCAAACTACCTGTTCTGG	1	3	21	SEQ ID NO. 4213
(N20)NGG	8	48866222	+	CCCAAACTACCTGTTCTGGCAGG	1	3	26	SEQ ID NO. 4214
(N20)NGG	8	48866233	+	TGTTCTGGCAGGATGTCTGAAGG	2	2	31	SEQ ID NO. 4215
(N20)NGG	8	48866234	+	GTTCTGGCAGGATGTCTGAAGGG	1	5	78	SEQ ID NO. 4216
(N20)NGG	8	48866235	+	TTCTGGCAGGATGTCTGAAGGGG	1	3	60	SEQ ID NO. 4217
(N20)NGG	8	48866272	+	GTGCAACTTCACTAAGTCCATGG	1	3	17	SEQ ID NO. 4218
(N20)NGG	8	48866279	+	TTCACTAAGTCCATGGAAGAAGG	2	15	82	SEQ ID NO. 4219
(N20)NGG	8	48866289	+	CCATGGAAGAAGGTATTGCTTGG	1	3	32	SEQ ID NO. 4220
(N20)NGG	8	48866200	-	CCTGCCAGAACAGGTAGTTTGGG	2	3	20	SEQ ID NO. 4221
(N20)NGG	8	48866201	-	TCCTGCCAGAACAGGTAGTTTGG	3	4	21	SEQ ID NO. 4222
(N20)NGG	8	48866209	-	TTCAGACATCCTGCCAGAACAGG	1	3	37	SEQ ID NO. 4223
(N20)NGG	8	48866240	-	AGTGAAGTTGCACAGAAGTGAGG	2	6	91	SEQ ID NO. 4224
(N20)NGG	8	48866267	-	CCAAGCAATACCTTCTTCCATGG	2	6	41	SEQ ID NO. 4225
(N20)NGG	8	48866393	+	GAAAAAGTATATGAGCTCCTAGG	1	1	63	SEQ ID NO. 4226
(N20)NGG	8	48866401	+	ATATGAGCTCCTAGGATTATTGG	1	5	34	SEQ ID NO. 4227
(N20)NGG	8	48866402	+	TATGAGCTCCTAGGATTATTGGG	2	4	33	SEQ ID NO. 4228
(N20)NGG	8	48866461	+	AAACCTGTTCCGCGCTTTTCTGG	1	1	10	SEQ ID NO. 4229
(N20)NGG	8	48866462	+	AACCTGTTCCGCGCTTTTCTGGG	1	2	11	SEQ ID NO. 4230
(N20)NGG	8	48866479	+	TCTGGGTGAACTTAAGACCCAGG	1	2	19	SEQ ID NO. 4231
(N20)NGG	8	48866388	-	GAACTTCACCCAATAATCCTAGG	1	1	21	SEQ ID NO. 4232

FIG. 12 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	8	48866413	-	GCATTATTTATCATCTCACTAGG	1	6	60	SEQ ID NO. 4233
(N20)NGG	8	48866442	-	CACCCAGAAAAGCGCGGAACAGG	1	1	8	SEQ ID NO. 4234
(N20)NGG	8	48866448	-	TAAGTTCACCCAGAAAAGCGCGG	1	2	21	SEQ ID NO. 4235
(N20)NGG	8	48866474	-	TCATAAAGTTCATCATACCTGGG	1	4	38	SEQ ID NO. 4236
(N20)NGG	8	48866475	-	GTCATAAAGTTCATCATACCTGG	1	2	23	SEQ ID NO. 4237
(N20)NGG	8	48866930	+	TTTTAGAAGTTCTAGACTCATGG	1	5	86	SEQ ID NO. 4238
(N20)NGG	8	48866946	+	CTCATGGATGAATTTAAAATTGG	1	9	111	SEQ ID NO. 4239
(N20)NGG	8	48866970	+	GAATTATTTAGTAAATTCTATGG	2	6	170	SEQ ID NO. 4240
(N20)NGG	8	48867006	+	AAAAAAAAAATACCAGATACAGG	9	181	2285	SEQ ID NO. 4241
(N20)NGG	8	48866996	-	AAATGCATCTCACCTGTATCTGG	1	3	35	SEQ ID NO. 4242
(N20)NGG	8	48868493	+	TAAATGTAAAATTCCAGCCCTGG	3	11	94	SEQ ID NO. 4243
(N20)NGG	8	48868508	+	AGCCCTGGACCTTCTTATTAAGG	3	7	43	SEQ ID NO. 4244
(N20)NGG	8	48868428	-	AACACTGGTACAAGTGTTCTAGG	1	7	53	SEQ ID NO. 4245
(N20)NGG	8	48868443	-	TCTATCTTTTGTATAAACACTGG	4	6	81	SEQ ID NO. 4246
(N20)NGG	8	48868484	-	TTAATAAGAAGGTCCAGGGCTGG	2	6	50	SEQ ID NO. 4247
(N20)NGG	8	48868488	-	TACCTTAATAAGAAGGTCCAGGG	1	3	33	SEQ ID NO. 4248
(N20)NGG	8	48868489	-	TTACCTTAATAAGAAGGTCCAGG	1	1	29	SEQ ID NO. 4249
(N20)NGG	8	48868495	-	ACATAATTACCTTAATAAGAAGG	1	4	86	SEQ ID NO. 4250
(N20)NGG	8	48869787	+	ATGTATTTTCTTAGAAAAAATGG	5	45	588	SEQ ID NO. 4251
(N20)NGG	8	48869788	+	TGTATTTTCTTAGAAAAAATGGG	2	29	518	SEQ ID NO. 4252
(N20)NGG	8	48869823	+	ACCTTACTCTGTTGAAATTAAGG	1	2	36	SEQ ID NO. 4253
(N20)NGG	8	48869753	-	AGAAAATACATAAAAACTTTAGG	2	29	537	SEQ ID NO. 4254
(N20)NGG	8	48869789	-	CAGAGTAAGGTGCGATCTTCTGG	1	1	8	SEQ ID NO. 4255
(N20)NGG	8	48869802	-	ACCTTAATTTCAACAGAGTAAGG	1	1	47	SEQ ID NO. 4256
(N20)NGG	8	48869950	+	TTAGTTTTTTCCAGAGATTTCGG	2	12	158	SEQ ID NO. 4257
(N20)NGG	8	48869969	+	TCGGTTTGCTTGTATTTGTCCGG	2	5	89	SEQ ID NO. 4258
(N20)NGG	8	48870008	+	TTGAAGTAAGTTGACAATTTTGG	1	5	73	SEQ ID NO. 4259
(N20)NGG	8	48869938	-	TACAAGCAAACCGAAATCTCTGG	1	4	14	SEQ ID NO. 4260
(N20)NGG	8	48869966	-	CAATACTGTTGAGTGACTTCCGG	3	3	30	SEQ ID NO. 4261
(N20)NGG	8	48872530	+	CGCGCGGGAGCGGGACTCGGCGG	1	2	20	SEQ ID NO. 4262
(N20)NGG	8	48872535	+	GGGAGCGGGACTCGGCGGCATGG	1	2	34	SEQ ID NO. 4263
(N20)NGG	8	48872538	+	AGCGGGACTCGGCGGCATGGCGG	1	2	8	SEQ ID NO. 4264
(N20)NGG	8	48872539	+	GCGGGACTCGGCGGCATGGCGGG	1	1	11	SEQ ID NO. 4265

FIG. 12 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	8	48872545	+	CTCGGCGGCATGGCGGGCTCCGG	1	2	11	SEQ ID NO. 4266
(N20)NGG	8	48872551	+	GGCATGGCGGGCTCCGGAGCCGG	1	2	26	SEQ ID NO. 4267
(N20)NGG	8	48872573	+	GTGTGCGTTGCTCCCTGCTGCGG	1	4	47	SEQ ID NO. 4268
(N20)NGG	8	48872580	+	TTGCTCCCTGCTGCGGCTGCAGG	1	4	73	SEQ ID NO. 4269
(N20)NGG	8	48872598	+	GCAGGAGACCTTGTCCGCTGCGG	1	2	14	SEQ ID NO. 4270
(N20)NGG	8	48872608	+	TTGTCCGCTGCGGACCGCTGCGG	1	1	5	SEQ ID NO. 4271
(N20)NGG	8	48872619	+	GGACCGCTGCGGTGCTGCCCTGG	1	1	23	SEQ ID NO. 4272
(N20)NGG	8	48872623	+	CGCTGCGGTGCTGCCCTGGCCGG	1	4	30	SEQ ID NO. 4273
(N20)NGG	8	48872641	+	GCCGGTCATCAACTGATCCGCGG	1	1	1	SEQ ID NO. 4274
(N20)NGG	8	48872646	+	TCATCAACTGATCCGCGGCCTGG	1	1	5	SEQ ID NO. 4275
(N20)NGG	8	48872647	+	CATCAACTGATCCGCGGCCTGGG	1	1	64	SEQ ID NO. 4276
(N20)NGG	8	48872648	+	ATCAACTGATCCGCGGCCTGGGG	1	1	3	SEQ ID NO. 4277
(N20)NGG	8	48872652	+	ACTGATCCGCGGCCTGGGGCAGG	1	1	23	SEQ ID NO. 4278
(N20)NGG	8	48872679	+	CGTCCTGAGCAGCAGCCCCGCGG	1	3	29	SEQ ID NO. 4279
(N20)NGG	8	48872685	+	GAGCAGCAGCCCCGCGGTGCTGG	2	5	34	SEQ ID NO. 4280
(N20)NGG	8	48872686	+	AGCAGCAGCCCCGCGGTGCTGGG	1	4	35	SEQ ID NO. 4281
(N20)NGG	8	48872689	+	AGCAGCCCCGCGGTGCTGGGTGG	1	4	57	SEQ ID NO. 4282
(N20)NGG	8	48872690	+	GCAGCCCCGCGGTGCTGGGTGGG	1	2	36	SEQ ID NO. 4283
(N20)NGG	8	48872696	+	CCGCGGTGCTGGGTGGGTACCGG	2	7	22	SEQ ID NO. 4284
(N20)NGG	8	48872706	+	GGGTGGGTACCGGCCCGAGCTGG	1	3	18	SEQ ID NO. 4285
(N20)NGG	8	48872707	+	GGTGGGTACCGGCCCGAGCTGGG	1	2	6	SEQ ID NO. 4286
(N20)NGG	8	48872542	-	GGAGCAACGCACACCGGCTCCGG	1	2	15	SEQ ID NO. 4287
(N20)NGG	8	48872548	-	CAGCAGGGAGCAACGCACACCGG	2	9	105	SEQ ID NO. 4288
(N20)NGG	8	48872563	-	GGTCTCCTGCAGCCGCAGCAGGG	1	4	51	SEQ ID NO. 4289
(N20)NGG	8	48872564	-	AGGTCTCCTGCAGCCGCAGCAGG	1	3	50	SEQ ID NO. 4290
(N20)NGG	8	48872584	-	GCAGCGGTCCGCAGCGGACAAGG	1	1	5	SEQ ID NO. 4291
(N20)NGG	8	48872590	-	AGCACCGCAGCGGTCCGCAGCGG	1	1	10	SEQ ID NO. 4292
(N20)NGG	8	48872600	-	CGGCCAGGGCAGCACCGCAGCGG	2	3	40	SEQ ID NO. 4293
(N20)NGG	8	48872614	-	GATCAGTTGATGACCGGCCAGGG	1	1	8	SEQ ID NO. 4294
(N20)NGG	8	48872615	-	GGATCAGTTGATGACCGGCCAGG	1	2	15	SEQ ID NO. 4295
(N20)NGG	8	48872620	-	GCCGCGGATCAGTTGATGACCGG	1	1	4	SEQ ID NO. 4296
(N20)NGG	8	48872636	-	CGCATTCCTGCCCCAGGCCGCGG	1	1	33	SEQ ID NO. 4297
(N20)NGG	8	48872642	-	TCAGGACGCATTCCTGCCCCAGG	1	4	31	SEQ ID NO. 4298

FIG. 12 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	8	48872660	-	GCACCGCGGGGCTGCTGCTCAGG	1	1	32	SEQ ID NO. 4299
(N20)NGG	8	48872672	-	GGTACCCACCCAGCACCGCGGGG	1	3	18	SEQ ID NO. 4300
(N20)NGG	8	48872673	-	CGGTACCCACCCAGCACCGCGGG	1	5	15	SEQ ID NO. 4301
(N20)NGG	8	48872674	-	CCGGTACCCACCCAGCACCGCGG	1	2	16	SEQ ID NO. 4302

FIG. 12 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	11	36594881	+	AGCCTCTTTCCCACCCACCTTGG	1	8	94	SEQ ID NO. 4303
(N20)NGG	11	36594882	+	GCCTCTTTCCCACCCACCTTGGG	1	2	65	SEQ ID NO. 4304
(N20)NGG	11	36594937	+	CACATATTAAATTTTCAGAATGG	1	20	258	SEQ ID NO. 4305
(N20)NGG	11	36594955	+	AATGGAAATTTAAGCTGTTCCGG	1	7	80	SEQ ID NO. 4306
(N20)NGG	11	36594956	+	ATGGAAATTTAAGCTGTTCCGGG	1	13	156	SEQ ID NO. 4307
(N20)NGG	11	36594995	+	GACACCTGAAGAAGCTCAAAAGG	1	2	47	SEQ ID NO. 4308
(N20)NGG	11	36595004	+	AGAAGCTCAAAAGGAAAAGAAGG	3	24	430	SEQ ID NO. 4309
(N20)NGG	11	36595016	+	GGAAAAGAAGGATTCCTTTGAGG	1	8	108	SEQ ID NO. 4310
(N20)NGG	11	36595017	+	GAAAAGAAGGATTCCTTTGAGGG	1	11	268	SEQ ID NO. 4311
(N20)NGG	11	36595018	+	AAAAGAAGGATTCCTTTGAGGGG	1	7	95	SEQ ID NO. 4312
(N20)NGG	11	36595031	+	CTTTGAGGGGAAACCCTCTCTGG	1	3	23	SEQ ID NO. 4313
(N20)NGG	11	36595052	+	GGAGCAATCTCCAGCAGTCCTGG	1	1	24	SEQ ID NO. 4314
(N20)NGG	11	36595058	+	ATCTCCAGCAGTCCTGGACAAGG	1	3	46	SEQ ID NO. 4315
(N20)NGG	11	36595065	+	GCAGTCCTGGACAAGGCTGATGG	1	2	44	SEQ ID NO. 4316
(N20)NGG	11	36595149	+	CACGACAACGAGAAAGCAAGAGG	1	1	19	SEQ ID NO. 4317
(N20)NGG	11	36595197	+	CGACATCTCTGCCGCATCTGTGG	1	1	9	SEQ ID NO. 4318
(N20)NGG	11	36595198	+	GACATCTCTGCCGCATCTGTGGG	1	1	14	SEQ ID NO. 4319
(N20)NGG	11	36595228	+	TTAGAGCTGATGAGCACAACAGG	1	2	26	SEQ ID NO. 4320
(N20)NGG	11	36595245	+	AACAGGAGATATCCAGTCCATGG	1	2	83	SEQ ID NO. 4321
(N20)NGG	11	36595253	+	ATATCCAGTCCATGGTCCTGTGG	1	3	21	SEQ ID NO. 4322
(N20)NGG	11	36595257	+	CCAGTCCATGGTCCTGTGGATGG	1	5	41	SEQ ID NO. 4323
(N20)NGG	11	36595269	+	CCTGTGGATGGTAAAACCCTAGG	1	3	43	SEQ ID NO. 4324
(N20)NGG	11	36595286	+	CCTAGGCCTTTTACGAAAGAAGG	1	1	24	SEQ ID NO. 4325
(N20)NGG	11	36595306	+	AGGAAAAGAGAGCTACTTCCTGG	1	2	55	SEQ ID NO. 4326
(N20)NGG	11	36595310	+	AAAGAGAGCTACTTCCTGGCCGG	1	2	48	SEQ ID NO. 4327
(N20)NGG	11	36595325	+	CTGGCCGGACCTCATTGCCAAGG	1	1	18	SEQ ID NO. 4328
(N20)NGG	11	36595333	+	ACCTCATTGCCAAGGTTTTCCGG	1	4	35	SEQ ID NO. 4329
(N20)NGG	11	36595346	+	GGTTTTCCGGATCGATGTGAAGG	1	1	1	SEQ ID NO. 4330
(N20)NGG	11	36595393	+	CTGAGTTCTGCCATAACTGCTGG	1	2	40	SEQ ID NO. 4331
(N20)NGG	11	36595408	+	ACTGCTGGAGCATCATGCACAGG	1	4	26	SEQ ID NO. 4332
(N20)NGG	11	36595433	+	GTTTAGCAGTGCCCCATGTGAGG	1	1	13	SEQ ID NO. 4333
(N20)NGG	11	36595447	+	CATGTGAGGTTTACTTCCCGAGG	1	1	12	SEQ ID NO. 4334
(N20)NGG	11	36595460	+	CTTCCCGAGGAACGTGACCATGG	1	3	24	SEQ ID NO. 4335

FIG. 13

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	11	36595465	+	CGAGGAACGTGACCATGGAGTGG	1	2	15	SEQ ID NO. 4336
(N20)NGG	11	36595510	+	ACATCTGCAACACTGCCCGTCGG	1	1	12	SEQ ID NO. 4337
(N20)NGG	11	36595511	+	CATCTGCAACACTGCCCGTCGGG	1	1	9	SEQ ID NO. 4338
(N20)NGG	11	36595512	+	ATCTGCAACACTGCCCGTCGGGG	1	1	10	SEQ ID NO. 4339
(N20)NGG	11	36595522	+	CTGCCCGTCGGGGACTCAAGAGG	1	1	14	SEQ ID NO. 4340
(N20)NGG	11	36595616	+	TCAGCACAAGAGAAGAGCTCAGG	1	6	78	SEQ ID NO. 4341
(N20)NGG	11	36595621	+	ACAAGAGAAGAGCTCAGGCAAGG	1	9	140	SEQ ID NO. 4342
(N20)NGG	11	36595634	+	TCAGGCAAGGATCAGCAGCAAGG	1	2	57	SEQ ID NO. 4343
(N20)NGG	11	36595697	+	TAGTACCAAGCTCCTTGCAGTGG	1	2	25	SEQ ID NO. 4344
(N20)NGG	11	36595754	+	CCAGATCTGTGAACACATTCTGG	2	6	47	SEQ ID NO. 4345
(N20)NGG	11	36595766	+	ACACATTCTGGCTGACCCTGTGG	1	4	40	SEQ ID NO. 4346
(N20)NGG	11	36595795	+	ACTGTAAGCATGTCTTTTGCCGG	1	6	108	SEQ ID NO. 4347
(N20)NGG	11	36595796	+	CTGTAAGCATGTCTTTTGCCGGG	1	2	51	SEQ ID NO. 4348
(N20)NGG	11	36595826	+	TCTCAGATGCCTCAAAGTCATGG	1	4	63	SEQ ID NO. 4349
(N20)NGG	11	36595827	+	CTCAGATGCCTCAAAGTCATGGG	1	3	49	SEQ ID NO. 4350
(N20)NGG	11	36595874	+	TCCATGCTTCCCTACTGACCTGG	1	2	33	SEQ ID NO. 4351
(N20)NGG	11	36595919	+	GAGCGTCTTGAATTCCCTGATGG	1	1	19	SEQ ID NO. 4352
(N20)NGG	11	36595949	+	TCCAGCAAAAGAGTGCAATGAGG	1	4	46	SEQ ID NO. 4353
(N20)NGG	11	36595952	+	AGCAAAAGAGTGCAATGAGGAGG	2	4	92	SEQ ID NO. 4354
(N20)NGG	11	36595961	+	GTGCAATGAGGAGGTCAGTTTGG	1	3	36	SEQ ID NO. 4355
(N20)NGG	11	36595994	+	TCACCACATCTCAAGTCACAAGG	1	2	48	SEQ ID NO. 4356
(N20)NGG	11	36596028	+	ATTTTTGTGCACATTAATAAAGG	1	11	171	SEQ ID NO. 4357
(N20)NGG	11	36596029	+	TTTTTGTGCACATTAATAAAGGG	1	9	142	SEQ ID NO. 4358
(N20)NGG	11	36596030	+	TTTTGTGCACATTAATAAAGGGG	1	4	85	SEQ ID NO. 4359
(N20)NGG	11	36596031	+	TTTGTGCACATTAATAAAGGGGG	1	3	57	SEQ ID NO. 4360
(N20)NGG	11	36596035	+	TGCACATTAATAAAGGGGGCCGG	1	1	18	SEQ ID NO. 4361
(N20)NGG	11	36596065	+	AACATCTTCTGTCGCTGACTCGG	1	1	21	SEQ ID NO. 4362
(N20)NGG	11	36596083	+	CTCGGAGAGCTCAGAAGCACCGG	1	2	28	SEQ ID NO. 4363
(N20)NGG	11	36596089	+	GAGCTCAGAAGCACCGGCTGAGG	2	5	54	SEQ ID NO. 4364
(N20)NGG	11	36596090	+	AGCTCAGAAGCACCGGCTGAGGG	2	4	23	SEQ ID NO. 4365
(N20)NGG	11	36596133	+	GCCTTTGCTGACAAAGAAGAAGG	1	4	63	SEQ ID NO. 4366
(N20)NGG	11	36596136	+	TTTGCTGACAAAGAAGAAGGTGG	2	11	153	SEQ ID NO. 4367
(N20)NGG	11	36596174	+	GTGCATGACCTTGTTCCTGCTGG	1	2	26	SEQ ID NO. 4368

FIG. 13 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	11	36596182	+	CCTTGTTCCTGCTGGCTCTGAGG	1	19	168	SEQ ID NO. 4369
(N20)NGG	11	36596183	+	CTTGTTCCTGCTGGCTCTGAGGG	1	8	75	SEQ ID NO. 4370
(N20)NGG	11	36596188	+	TCCTGCTGGCTCTGAGGGCGAGG	1	6	64	SEQ ID NO. 4371
(N20)NGG	11	36596200	+	TGAGGGCGAGGAATGAGCACAGG	1	4	38	SEQ ID NO. 4372
(N20)NGG	11	36596216	+	GCACAGGCAAGCTGATGAGCTGG	1	5	35	SEQ ID NO. 4373
(N20)NGG	11	36596219	+	CAGGCAAGCTGATGAGCTGGAGG	1	5	67	SEQ ID NO. 4374
(N20)NGG	11	36596231	+	TGAGCTGGAGGCCATCATGCAGG	1	8	235	SEQ ID NO. 4375
(N20)NGG	11	36596232	+	GAGCTGGAGGCCATCATGCAGGG	3	247	3384	SEQ ID NO. 4376
(N20)NGG	11	36596237	+	GGAGGCCATCATGCAGGGAAAGG	1	1	66	SEQ ID NO. 4377
(N20)NGG	11	36596238	+	GAGGCCATCATGCAGGGAAAGGG	1	6	65	SEQ ID NO. 4378
(N20)NGG	11	36596244	+	ATCATGCAGGGAAAGGGCTCTGG	1	3	42	SEQ ID NO. 4379
(N20)NGG	11	36596267	+	CCTGCAGCCAGCTGTTTGCTTGG	2	7	76	SEQ ID NO. 4380
(N20)NGG	11	36596320	+	GTCAGTACCACAAGATGTACAGG	1	1	13	SEQ ID NO. 4381
(N20)NGG	11	36596340	+	AGGACTGTGAAAGCCATCACAGG	1	2	41	SEQ ID NO. 4382
(N20)NGG	11	36596341	+	GGACTGTGAAAGCCATCACAGGG	1	2	33	SEQ ID NO. 4383
(N20)NGG	11	36596374	+	TTCAGCCTTTGCATGCCCTTCGG	1	5	58	SEQ ID NO. 4384
(N20)NGG	11	36596387	+	TGCCCTTCGGAATGCTGAGAAGG	1	2	41	SEQ ID NO. 4385
(N20)NGG	11	36596400	+	GCTGAGAAGGTACTTCTGCCAGG	1	2	53	SEQ ID NO. 4386
(N20)NGG	11	36596419	+	CAGGCTACCACCACTTTGAGTGG	2	2	37	SEQ ID NO. 4387
(N20)NGG	11	36596460	+	GTGTCTTCCAGCACTGATGTTGG	1	3	41	SEQ ID NO. 4388
(N20)NGG	11	36596472	+	ACTGATGTTGGCATTATTGATGG	2	13	67	SEQ ID NO. 4389
(N20)NGG	11	36596473	+	CTGATGTTGGCATTATTGATGGG	1	7	68	SEQ ID NO. 4390
(N20)NGG	11	36596481	+	GGCATTATTGATGGGCTGTCTGG	1	2	25	SEQ ID NO. 4391
(N20)NGG	11	36596498	+	GTCTGGACTATCATCCTCTGTGG	1	2	17	SEQ ID NO. 4392
(N20)NGG	11	36596513	+	CTCTGTGGATGATTACCCAGTGG	1	3	31	SEQ ID NO. 4393
(N20)NGG	11	36596530	+	CAGTGGACACCATTGCAAAGAGG	1	3	39	SEQ ID NO. 4394
(N20)NGG	11	36596552	+	GTTCCGCTATGATTCAGCTTTGG	1	1	12	SEQ ID NO. 4395
(N20)NGG	11	36596567	+	AGCTTTGGTGTCTGCTTTGATGG	2	7	76	SEQ ID NO. 4396
(N20)NGG	11	36596573	+	GGTGTCTGCTTTGATGGACATGG	1	3	44	SEQ ID NO. 4397
(N20)NGG	11	36596588	+	GGACATGGAAGAAGACATCTTGG	1	3	73	SEQ ID NO. 4398
(N20)NGG	11	36596592	+	ATGGAAGAAGACATCTTGGAAGG	1	3	87	SEQ ID NO. 4399
(N20)NGG	11	36596628	+	GACCTTGATGATTACCTGAATGG	1	3	23	SEQ ID NO. 4400
(N20)NGG	11	36596642	+	CCTGAATGGCCCCTTCACTGTGG	1	3	46	SEQ ID NO. 4401

FIG. 13 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	11	36596645	+	GAATGGCCCCTTCACTGTGGTGG	1	1	31	SEQ ID NO. 4402
(N20)NGG	11	36596651	+	CCCCTTCACTGTGGTGGTGAAGG	1	2	62	SEQ ID NO. 4403
(N20)NGG	11	36596664	+	GTGGTGAAGGAGTCTTGTGATGG	1	2	30	SEQ ID NO. 4404
(N20)NGG	11	36596669	+	GAAGGAGTCTTGTGATGGAATGG	2	5	69	SEQ ID NO. 4405
(N20)NGG	11	36596670	+	AAGGAGTCTTGTGATGGAATGGG	1	4	63	SEQ ID NO. 4406
(N20)NGG	11	36596691	+	GGAGACGTGAGTGAGAAGCATGG	1	2	58	SEQ ID NO. 4407
(N20)NGG	11	36596692	+	GAGACGTGAGTGAGAAGCATGGG	1	3	33	SEQ ID NO. 4408
(N20)NGG	11	36596697	+	GTGAGTGAGAAGCATGGGAGTGG	1	5	111	SEQ ID NO. 4409
(N20)NGG	11	36596698	+	TGAGTGAGAAGCATGGGAGTGGG	1	6	95	SEQ ID NO. 4410
(N20)NGG	11	36596717	+	TGGGCCTGTAGTTCCAGAAAAGG	1	4	62	SEQ ID NO. 4411
(N20)NGG	11	36596840	+	CAAGCCATTGTGCCTTATGCTGG	1	4	34	SEQ ID NO. 4412
(N20)NGG	11	36596899	+	TGAGTCCTCTCATTGCTGAGAGG	1	12	64	SEQ ID NO. 4413
(N20)NGG	11	36596900	+	GAGTCCTCTCATTGCTGAGAGGG	1	4	47	SEQ ID NO. 4414
(N20)NGG	11	36596903	+	TCCTCTCATTGCTGAGAGGGAGG	1	5	58	SEQ ID NO. 4415
(N20)NGG	11	36596936	+	CAGTGAATTAATGCTTGAGCTGG	1	3	44	SEQ ID NO. 4416
(N20)NGG	11	36596937	+	AGTGAATTAATGCTTGAGCTGGG	1	2	71	SEQ ID NO. 4417
(N20)NGG	11	36596940	+	GAATTAATGCTTGAGCTGGGAGG	1	3	74	SEQ ID NO. 4418
(N20)NGG	11	36596950	+	TTGAGCTGGGAGGCATTCTCCGG	1	2	44	SEQ ID NO. 4419
(N20)NGG	11	36596971	+	GGACTTTCAAGTTCATCTTCAGG	1	3	48	SEQ ID NO. 4420
(N20)NGG	11	36596972	+	GACTTTCAAGTTCATCTTCAGGG	1	4	98	SEQ ID NO. 4421
(N20)NGG	11	36596973	+	ACTTTCAAGTTCATCTTCAGGGG	1	7	69	SEQ ID NO. 4422
(N20)NGG	11	36596979	+	AAGTTCATCTTCAGGGGCACCGG	1	3	35	SEQ ID NO. 4423
(N20)NGG	11	36597001	+	GCTATGATGAAAAACTTGTGCGG	1	2	53	SEQ ID NO. 4424
(N20)NGG	11	36597002	+	CTATGATGAAAAACTTGTGCGGG	1	2	42	SEQ ID NO. 4425
(N20)NGG	11	36597008	+	TGAAAAACTTGTGCGGGAAGTGG	1	2	18	SEQ ID NO. 4426
(N20)NGG	11	36597012	+	AAACTTGTGCGGGAAGTGGAAGG	1	1	20	SEQ ID NO. 4427
(N20)NGG	11	36597020	+	GCGGGAAGTGGAAGGCCTCGAGG	1	1	27	SEQ ID NO. 4428
(N20)NGG	11	36597027	+	GTGGAAGGCCTCGAGGCTTCTGG	1	1	17	SEQ ID NO. 4429
(N20)NGG	11	36597068	+	TCTTTGTGATGCCACCCGTCTGG	1	2	16	SEQ ID NO. 4430
(N20)NGG	11	36597125	+	CAGAAGCCATGCTGAGAACCTGG	3	7	92	SEQ ID NO. 4431
(N20)NGG	11	36597137	+	TGAGAACCTGGAACGTTATGAGG	1	1	10	SEQ ID NO. 4432
(N20)NGG	11	36597142	+	ACCTGGAACGTTATGAGGTCTGG	1	2	11	SEQ ID NO. 4433
(N20)NGG	11	36597170	+	CAACCCTTACCATGAGTCTGTGG	1	1	19	SEQ ID NO. 4434

FIG. 13 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	11	36597181	+	ATGAGTCTGTGGAAGAACTGCGG	1	4	75	SEQ ID NO. 4435
(N20)NGG	11	36597182	+	TGAGTCTGTGGAAGAACTGCGGG	1	4	70	SEQ ID NO. 4436
(N20)NGG	11	36597187	+	CTGTGGAAGAACTGCGGGATCGG	1	1	26	SEQ ID NO. 4437
(N20)NGG	11	36597188	+	TGTGGAAGAACTGCGGGATCGGG	1	1	16	SEQ ID NO. 4438
(N20)NGG	11	36597195	+	GAACTGCGGGATCGGGTGAAAGG	1	1	29	SEQ ID NO. 4439
(N20)NGG	11	36597196	+	AACTGCGGGATCGGGTGAAAGGG	1	1	5	SEQ ID NO. 4440
(N20)NGG	11	36597197	+	ACTGCGGGATCGGGTGAAAGGGG	1	1	10	SEQ ID NO. 4441
(N20)NGG	11	36597258	+	GATGCACTCCACTGTGACATTGG	1	2	33	SEQ ID NO. 4442
(N20)NGG	11	36597300	+	AAGATCTTCCAGCTAGAGATAGG	1	3	39	SEQ ID NO. 4443
(N20)NGG	11	36597301	+	AGATCTTCCAGCTAGAGATAGGG	1	6	55	SEQ ID NO. 4444
(N20)NGG	11	36597302	+	GATCTTCCAGCTAGAGATAGGGG	2	5	50	SEQ ID NO. 4445
(N20)NGG	11	36597335	+	GAATCCCAATGCTTCCAAAGAGG	1	2	31	SEQ ID NO. 4446
(N20)NGG	11	36597340	+	CCAATGCTTCCAAAGAGGAAAGG	1	7	60	SEQ ID NO. 4447
(N20)NGG	11	36597346	+	CTTCCAAAGAGGAAAGGAAAAGG	1	41	458	SEQ ID NO. 4448
(N20)NGG	11	36597349	+	CCAAAGAGGAAAGGAAAAGGTGG	2	39	523	SEQ ID NO. 4449
(N20)NGG	11	36597353	+	AGAGGAAAGGAAAAGGTGGCAGG	3	11	305	SEQ ID NO. 4450
(N20)NGG	11	36597362	+	GAAAAGGTGGCAGGCCACACTGG	1	5	53	SEQ ID NO. 4451
(N20)NGG	11	36597376	+	CCACACTGGACAAGCATCTCCGG	1	3	24	SEQ ID NO. 4452
(N20)NGG	11	36597406	+	TGAACCTCAAACCAATCATGAGG	1	1	35	SEQ ID NO. 4453
(N20)NGG	11	36597414	+	AAACCAATCATGAGGATGAATGG	1	5	72	SEQ ID NO. 4454
(N20)NGG	11	36597427	+	GGATGAATGGCAACTTTGCCAGG	1	3	24	SEQ ID NO. 4455
(N20)NGG	11	36597452	+	GCTCATGACCAAAGAGACTGTGG	1	2	39	SEQ ID NO. 4456
(N20)NGG	11	36597482	+	TTGTGAGTTAATTCCTTCCGAGG	1	1	16	SEQ ID NO. 4457
(N20)NGG	11	36597487	+	AGTTAATTCCTTCCGAGGAGAGG	1	1	13	SEQ ID NO. 4458
(N20)NGG	11	36597494	+	TCCTTCCGAGGAGAGGCACGAGG	1	1	28	SEQ ID NO. 4459
(N20)NGG	11	36597502	+	AGGAGAGGCACGAGGCTCTGAGG	1	3	69	SEQ ID NO. 4460
(N20)NGG	11	36597503	+	GGAGAGGCACGAGGCTCTGAGGG	1	1	43	SEQ ID NO. 4461
(N20)NGG	11	36597512	+	CGAGGCTCTGAGGGAGCTGATGG	1	3	43	SEQ ID NO. 4462
(N20)NGG	11	36597541	+	ACCTGAAGATGAAACCAGTATGG	1	3	36	SEQ ID NO. 4463
(N20)NGG	11	36597643	+	TTTCTACGAAGTTCAAGTATAGG	1	2	51	SEQ ID NO. 4464
(N20)NGG	11	36597650	+	GAAGTTCAAGTATAGGTATGAGG	2	3	35	SEQ ID NO. 4465
(N20)NGG	11	36597651	+	AAGTTCAAGTATAGGTATGAGGG	1	3	35	SEQ ID NO. 4466
(N20)NGG	11	36597683	+	CAATTATTTTCACAAAACCCTGG	1	5	94	SEQ ID NO. 4467

FIG. 13 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	11	36597709	+	ATGTTCCTGAAATTATTGAGAGG	1	4	79	SEQ ID NO. 4468
(N20)NGG	11	36597710	+	TGTTCCTGAAATTATTGAGAGGG	1	8	155	SEQ ID NO. 4469
(N20)NGG	11	36597714	+	CCTGAAATTATTGAGAGGGATGG	1	2	50	SEQ ID NO. 4470
(N20)NGG	11	36597723	+	ATTGAGAGGGATGGCTCCATTGG	1	2	17	SEQ ID NO. 4471
(N20)NGG	11	36597724	+	TTGAGAGGGATGGCTCCATTGGG	1	1	17	SEQ ID NO. 4472
(N20)NGG	11	36597725	+	TGAGAGGGATGGCTCCATTGGGG	1	4	41	SEQ ID NO. 4473
(N20)NGG	11	36597730	+	GGGATGGCTCCATTGGGGCATGG	1	4	21	SEQ ID NO. 4474
(N20)NGG	11	36597731	+	GGATGGCTCCATTGGGGCATGGG	1	1	19	SEQ ID NO. 4475
(N20)NGG	11	36597740	+	CATTGGGGCATGGGCAAGTGAGG	1	3	33	SEQ ID NO. 4476
(N20)NGG	11	36597741	+	ATTGGGGCATGGGCAAGTGAGGG	1	3	41	SEQ ID NO. 4477
(N20)NGG	11	36597753	+	GCAAGTGAGGGAAATGAGTCTGG	1	5	114	SEQ ID NO. 4478
(N20)NGG	11	36597769	+	AGTCTGGTAACAAACTGTTTAGG	1	4	43	SEQ ID NO. 4479
(N20)NGG	11	36597778	+	ACAAACTGTTTAGGCGCTTCCGG	1	1	16	SEQ ID NO. 4480
(N20)NGG	11	36597793	+	GCTTCCGGAAAATGAATGCCAGG	1	1	17	SEQ ID NO. 4481
(N20)NGG	11	36597815	+	GCAGTCCAAATGCTATGAGATGG	1	3	34	SEQ ID NO. 4482
(N20)NGG	11	36597838	+	AAGATGTCCTGAAACACCACTGG	1	1	36	SEQ ID NO. 4483
(N20)NGG	11	36597900	+	CATAATGCATTAAAAACCTCTGG	1	3	60	SEQ ID NO. 4484
(N20)NGG	11	36597901	+	ATAATGCATTAAAAACCTCTGGG	2	8	86	SEQ ID NO. 4485
(N20)NGG	11	36597920	+	TGGGTTTACCATGAACCCTCAGG	1	3	17	SEQ ID NO. 4486
(N20)NGG	11	36597930	+	ATGAACCCTCAGGCAAGCTTAGG	1	2	27	SEQ ID NO. 4487
(N20)NGG	11	36597931	+	TGAACCCTCAGGCAAGCTTAGGG	1	1	17	SEQ ID NO. 4488
(N20)NGG	11	36597932	+	GAACCCTCAGGCAAGCTTAGGGG	1	2	16	SEQ ID NO. 4489
(N20)NGG	11	36597942	+	GCAAGCTTAGGGGACCCATTAGG	1	2	12	SEQ ID NO. 4490
(N20)NGG	11	36597950	+	AGGGGACCCATTAGGCATAGAGG	1	3	22	SEQ ID NO. 4491
(N20)NGG	11	36597959	+	ATTAGGCATAGAGGACTCTCTGG	1	1	20	SEQ ID NO. 4492
(N20)NGG	11	36597977	+	TCTGGAAAGCCAAGATTCAATGG	1	7	61	SEQ ID NO. 4493
(N20)NGG	11	36594861	-	TCCCAAGGTGGGTGGGAAAGAGG	1	6	90	SEQ ID NO. 4494
(N20)NGG	11	36594868	-	AACTGAGTCCCAAGGTGGGTGGG	1	6	113	SEQ ID NO. 4495
(N20)NGG	11	36594869	-	GAACTGAGTCCCAAGGTGGGTGG	2	6	82	SEQ ID NO. 4496
(N20)NGG	11	36594872	-	GCAGAACTGAGTCCCAAGGTGGG	1	4	61	SEQ ID NO. 4497
(N20)NGG	11	36594873	-	GGCAGAACTGAGTCCCAAGGTGG	1	6	100	SEQ ID NO. 4498
(N20)NGG	11	36594876	-	TGGGGCAGAACTGAGTCCCAAGG	1	5	98	SEQ ID NO. 4499
(N20)NGG	11	36594894	-	TGGGTGCTGAATTTCATCTGGGG	2	8	65	SEQ ID NO. 4500

FIG. 13 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	11	36594895	-	GTGGGTGCTGAATTTCATCTGGG	2	2	49	SEQ ID NO. 4501
(N20)NGG	11	36594896	-	TGTGGGTGCTGAATTTCATCTGG	1	4	38	SEQ ID NO. 4502
(N20)NGG	11	36594913	-	ATTCTGAAAATTTAATATGTGGG	1	22	290	SEQ ID NO. 4503
(N20)NGG	11	36594914	-	CATTCTGAAAATTTAATATGTGG	3	11	173	SEQ ID NO. 4504
(N20)NGG	11	36594952	-	TCTTTTCAAAGGATCTCACCCGG	1	2	51	SEQ ID NO. 4505
(N20)NGG	11	36594963	-	TTCTTCAGGTGTCTTTTCAAAGG	2	12	161	SEQ ID NO. 4506
(N20)NGG	11	36594977	-	TTTTCCTTTTGAGCTTCTTCAGG	1	11	187	SEQ ID NO. 4507
(N20)NGG	11	36595008	-	CAGAGAGGGTTTCCCCTCAAAGG	1	4	28	SEQ ID NO. 4508
(N20)NGG	11	36595022	-	GCTGGAGATTGCTCCAGAGAGGG	1	4	56	SEQ ID NO. 4509
(N20)NGG	11	36595023	-	TGCTGGAGATTGCTCCAGAGAGG	1	2	43	SEQ ID NO. 4510
(N20)NGG	11	36595040	-	TCAGCCTTGTCCAGGACTGCTGG	1	4	49	SEQ ID NO. 4511
(N20)NGG	11	36595048	-	TCTGACCATCAGCCTTGTCCAGG	2	2	47	SEQ ID NO. 4512
(N20)NGG	11	36595073	-	AACAATGGCTGAGTTGGGACTGG	1	5	52	SEQ ID NO. 4513
(N20)NGG	11	36595078	-	CTTTTAACAATGGCTGAGTTGGG	1	6	95	SEQ ID NO. 4514
(N20)NGG	11	36595079	-	GCTTTTAACAATGGCTGAGTTGG	1	3	58	SEQ ID NO. 4515
(N20)NGG	11	36595088	-	TTAGGGTGGGCTTTTAACAATGG	1	2	34	SEQ ID NO. 4516
(N20)NGG	11	36595101	-	TTTCTTTGAAAACTTAGGGTGGG	1	13	130	SEQ ID NO. 4517
(N20)NGG	11	36595102	-	ATTTCTTTGAAAACTTAGGGTGG	1	5	108	SEQ ID NO. 4518
(N20)NGG	11	36595105	-	GAAATTTCTTTGAAAACTTAGGG	2	22	293	SEQ ID NO. 4519
(N20)NGG	11	36595106	-	TGAAATTTCTTTGAAAACTTAGG	1	22	312	SEQ ID NO. 4520
(N20)NGG	11	36595159	-	GATGTCGAAGGTTGGCTTGATGG	1	3	18	SEQ ID NO. 4521
(N20)NGG	11	36595167	-	GCGGCAGAGATGTCGAAGGTTGG	1	1	6	SEQ ID NO. 4522
(N20)NGG	11	36595171	-	AGATGCGGCAGAGATGTCGAAGG	1	2	15	SEQ ID NO. 4523
(N20)NGG	11	36595186	-	TAAAAGAATTCCCACAGATGCGG	1	7	91	SEQ ID NO. 4524
(N20)NGG	11	36595235	-	CCATCCACAGGACCATGGACTGG	1	5	75	SEQ ID NO. 4525
(N20)NGG	11	36595240	-	TTTTACCATCCACAGGACCATGG	1	3	46	SEQ ID NO. 4526
(N20)NGG	11	36595247	-	CCTAGGGTTTTACCATCCACAGG	1	2	16	SEQ ID NO. 4527
(N20)NGG	11	36595263	-	CTTCTTTCGTAAAAGGCCTAGGG	1	5	27	SEQ ID NO. 4528
(N20)NGG	11	36595264	-	CCTTCTTTCGTAAAAGGCCTAGG	1	1	19	SEQ ID NO. 4529
(N20)NGG	11	36595270	-	TCTTTTCCTTCTTTCGTAAAAGG	1	10	194	SEQ ID NO. 4530
(N20)NGG	11	36595302	-	CTTGGCAATGAGGTCCGGCCAGG	1	1	10	SEQ ID NO. 4531
(N20)NGG	11	36595307	-	AAAACCTTGGCAATGAGGTCCGG	1	4	52	SEQ ID NO. 4532
(N20)NGG	11	36595312	-	TCCGGAAAACCTTGGCAATGAGG	1	1	12	SEQ ID NO. 4533

FIG. 13 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	11	36595320	-	CACATCGATCCGGAAAACCTTGG	1	2	6	SEQ ID NO. 4534
(N20)NGG	11	36595330	-	CATCTGCCTTCACATCGATCCGG	1	2	11	SEQ ID NO. 4535
(N20)NGG	11	36595363	-	TATGGCAGAACTCAGTGGGGTGG	1	1	59	SEQ ID NO. 4536
(N20)NGG	11	36595366	-	AGTTATGGCAGAACTCAGTGGGG	1	4	34	SEQ ID NO. 4537
(N20)NGG	11	36595367	-	CAGTTATGGCAGAACTCAGTGGG	1	3	39	SEQ ID NO. 4538
(N20)NGG	11	36595368	-	GCAGTTATGGCAGAACTCAGTGG	1	4	57	SEQ ID NO. 4539
(N20)NGG	11	36595381	-	GCATGATGCTCCAGCAGTTATGG	1	1	19	SEQ ID NO. 4540
(N20)NGG	11	36595422	-	CGGGAAGTAAACCTCACATGGGG	1	1	16	SEQ ID NO. 4541
(N20)NGG	11	36595423	-	TCGGGAAGTAAACCTCACATGGG	1	2	18	SEQ ID NO. 4542
(N20)NGG	11	36595424	-	CTCGGGAAGTAAACCTCACATGG	1	3	16	SEQ ID NO. 4543
(N20)NGG	11	36595441	-	ACTCCATGGTCACGTTCCTCGGG	1	5	19	SEQ ID NO. 4544
(N20)NGG	11	36595442	-	CACTCCATGGTCACGTTCCTCGG	1	3	28	SEQ ID NO. 4545
(N20)NGG	11	36595455	-	TGTGTGGGGGTGCCACTCCATGG	1	4	35	SEQ ID NO. 4546
(N20)NGG	11	36595468	-	TGTCACAGGATGGTGTGTGGGGG	2	5	97	SEQ ID NO. 4547
(N20)NGG	11	36595469	-	ATGTCACAGGATGGTGTGTGGGG	1	5	63	SEQ ID NO. 4548
(N20)NGG	11	36595470	-	GATGTCACAGGATGGTGTGTGGG	1	4	48	SEQ ID NO. 4549
(N20)NGG	11	36595471	-	AGATGTCACAGGATGGTGTGTGG	1	5	57	SEQ ID NO. 4550
(N20)NGG	11	36595478	-	GTGTTGCAGATGTCACAGGATGG	1	8	106	SEQ ID NO. 4551
(N20)NGG	11	36595482	-	GGCAGTGTTGCAGATGTCACAGG	2	2	39	SEQ ID NO. 4552
(N20)NGG	11	36595503	-	CTTCCTCTTGAGTCCCCGACGGG	1	3	13	SEQ ID NO. 4553
(N20)NGG	11	36595504	-	TCTTCCTCTTGAGTCCCCGACGG	1	2	24	SEQ ID NO. 4554
(N20)NGG	11	36595535	-	TTTTTGCTGAGCTGCAAGTTTGG	1	2	52	SEQ ID NO. 4555
(N20)NGG	11	36595576	-	GCTGACGGGCTTGTCTTGCTTGG	1	3	74	SEQ ID NO. 4556
(N20)NGG	11	36595590	-	AGCTCTTCTCTTGTGCTGACGGG	2	3	38	SEQ ID NO. 4557
(N20)NGG	11	36595591	-	GAGCTCTTCTCTTGTGCTGACGG	1	2	44	SEQ ID NO. 4558
(N20)NGG	11	36595653	-	AAGATGTATCTTACTGCAGTTGG	1	2	43	SEQ ID NO. 4559
(N20)NGG	11	36595680	-	GAAGTCCACTGCAAGGAGCTTGG	1	3	26	SEQ ID NO. 4560
(N20)NGG	11	36595687	-	GCTCTGGGAAGTCCACTGCAAGG	1	4	41	SEQ ID NO. 4561
(N20)NGG	11	36595702	-	TGGATTTCACAAAGTGCTCTGGG	1	2	66	SEQ ID NO. 4562
(N20)NGG	11	36595703	-	ATGGATTTCACAAAGTGCTCTGG	1	3	41	SEQ ID NO. 4563
(N20)NGG	11	36595722	-	TTCACAGATCTGGCAGGAGATGG	1	13	151	SEQ ID NO. 4564
(N20)NGG	11	36595728	-	AATGTGTTCACAGATCTGGCAGG	1	4	43	SEQ ID NO. 4565
(N20)NGG	11	36595732	-	CCAGAATGTGTTCACAGATCTGG	2	6	47	SEQ ID NO. 4566

FIG. 13 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	11	36595759	-	GCTTACAGTTGGTCTCCACAGGG	1	1	23	SEQ ID NO. 4567
(N20)NGG	11	36595760	-	TGCTTACAGTTGGTCTCCACAGG	1	1	20	SEQ ID NO. 4568
(N20)NGG	11	36595770	-	GCAAAAGACATGCTTACAGTTGG	1	2	51	SEQ ID NO. 4569
(N20)NGG	11	36595792	-	GGCATCTGAGAATGCAGACCCGG	1	5	50	SEQ ID NO. 4570
(N20)NGG	11	36595813	-	AATAGCTGCCCATGACTTTGAGG	1	7	48	SEQ ID NO. 4571
(N20)NGG	11	36595838	-	AAGCATGGATATCGGCAAGAGGG	1	1	23	SEQ ID NO. 4572
(N20)NGG	11	36595839	-	GAAGCATGGATATCGGCAAGAGG	1	2	22	SEQ ID NO. 4573
(N20)NGG	11	36595846	-	CAGTAGGGAAGCATGGATATCGG	1	2	47	SEQ ID NO. 4574
(N20)NGG	11	36595853	-	TCCAGGTCAGTAGGGAAGCATGG	1	5	59	SEQ ID NO. 4575
(N20)NGG	11	36595861	-	CTGGACTCTCCAGGTCAGTAGGG	1	3	39	SEQ ID NO. 4576
(N20)NGG	11	36595862	-	ACTGGACTCTCCAGGTCAGTAGG	2	5	17	SEQ ID NO. 4577
(N20)NGG	11	36595870	-	AGGACTTCACTGGACTCTCCAGG	1	3	35	SEQ ID NO. 4578
(N20)NGG	11	36595880	-	ACGCTCAGAAAGGACTTCACTGG	1	1	22	SEQ ID NO. 4579
(N20)NGG	11	36595890	-	GGAATTCAAGACGCTCAGAAAGG	1	1	23	SEQ ID NO. 4580
(N20)NGG	11	36595911	-	TGCTGGACATTTCACCATCAGGG	1	3	48	SEQ ID NO. 4581
(N20)NGG	11	36595912	-	TTGCTGGACATTTCACCATCAGG	1	2	30	SEQ ID NO. 4582
(N20)NGG	11	36595928	-	TCCTCATTGCACTCTTTTGCTGG	1	3	33	SEQ ID NO. 4583
(N20)NGG	11	36595975	-	ATTCCTTGTGACTTGAGATGTGG	1	3	32	SEQ ID NO. 4584
(N20)NGG	11	36596032	-	ACAGAAGATGTTGGCGGGGCCGG	1	2	60	SEQ ID NO. 4585
(N20)NGG	11	36596036	-	AGCGACAGAAGATGTTGGCGGGG	1	2	21	SEQ ID NO. 4586
(N20)NGG	11	36596037	-	CAGCGACAGAAGATGTTGGCGGG	1	2	23	SEQ ID NO. 4587
(N20)NGG	11	36596038	-	TCAGCGACAGAAGATGTTGGCGG	1	2	30	SEQ ID NO. 4588
(N20)NGG	11	36596041	-	GAGTCAGCGACAGAAGATGTTGG	1	8	54	SEQ ID NO. 4589
(N20)NGG	11	36596080	-	GCAGCTTGAGCTCCCTCAGCCGG	1	3	40	SEQ ID NO. 4590
(N20)NGG	11	36596112	-	ACCTTCTTCTTTGTCAGCAAAGG	1	4	50	SEQ ID NO. 4591
(N20)NGG	11	36596148	-	CAGGAACAAGGTCATGCACACGG	1	4	56	SEQ ID NO. 4592
(N20)NGG	11	36596160	-	CCTCAGAGCCAGCAGGAACAAGG	2	19	201	SEQ ID NO. 4593
(N20)NGG	11	36596167	-	TCCTCGCCCTCAGAGCCAGCAGG	1	2	41	SEQ ID NO. 4594
(N20)NGG	11	36596220	-	AGAGCCCTTTCCCTGCATGATGG	1	1	46	SEQ ID NO. 4595
(N20)NGG	11	36596245	-	CCAAGCAAACAGCTGGCTGCAGG	3	4	45	SEQ ID NO. 4596
(N20)NGG	11	36596252	-	CGGATGGCCAAGCAAACAGCTGG	1	1	16	SEQ ID NO. 4597
(N20)NGG	11	36596268	-	GAGGAAGGTGTTGACACGGATGG	1	3	37	SEQ ID NO. 4598
(N20)NGG	11	36596272	-	AGCTGAGGAAGGTGTTGACACGG	1	5	72	SEQ ID NO. 4599

FIG. 13 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	11	36596283	-	GTACTGACTGCAGCTGAGGAAGG	1	7	57	SEQ ID NO. 4600
(N20)NGG	11	36596287	-	TGTGGTACTGACTGCAGCTGAGG	1	5	65	SEQ ID NO. 4601
(N20)NGG	11	36596305	-	TCACAGTCCTGTACATCTTGTGG	1	2	36	SEQ ID NO. 4602
(N20)NGG	11	36596331	-	AAAAATCTGTCTCCCTGTGATGG	1	2	100	SEQ ID NO. 4603
(N20)NGG	11	36596357	-	GCATTCCGAAGGGCATGCAAAGG	1	1	10	SEQ ID NO. 4604
(N20)NGG	11	36596367	-	TACCTTCTCAGCATTCCGAAGGG	1	1	35	SEQ ID NO. 4605
(N20)NGG	11	36596368	-	GTACCTTCTCAGCATTCCGAAGG	1	1	11	SEQ ID NO. 4606
(N20)NGG	11	36596396	-	CACTCAAAGTGGTGGTAGCCTGG	2	3	19	SEQ ID NO. 4607
(N20)NGG	11	36596404	-	GTGGCTGCCACTCAAAGTGGTGG	1	1	30	SEQ ID NO. 4608
(N20)NGG	11	36596407	-	GAGGTGGCTGCCACTCAAAGTGG	1	5	53	SEQ ID NO. 4609
(N20)NGG	11	36596423	-	GAAGACACATTCTTCAGAGGTGG	1	4	82	SEQ ID NO. 4610
(N20)NGG	11	36596426	-	CTGGAAGACACATTCTTCAGAGG	2	5	70	SEQ ID NO. 4611
(N20)NGG	11	36596445	-	AATAATGCCAACATCAGTGCTGG	1	4	41	SEQ ID NO. 4612
(N20)NGG	11	36596490	-	CACTGGGTAATCATCCACAGAGG	2	2	27	SEQ ID NO. 4613
(N20)NGG	11	36596506	-	TCTTTGCAATGGTGTCCACTGGG	1	5	24	SEQ ID NO. 4614
(N20)NGG	11	36596507	-	CTCTTTGCAATGGTGTCCACTGG	1	2	24	SEQ ID NO. 4615
(N20)NGG	11	36596517	-	ATAGCGGAACCTCTTTGCAATGG	1	1	10	SEQ ID NO. 4616
(N20)NGG	11	36596533	-	ACACCAAAGCTGAATCATAGCGG	1	2	35	SEQ ID NO. 4617
(N20)NGG	11	36596601	-	CAGGTAATCATCAAGGTCTTGGG	1	1	26	SEQ ID NO. 4618
(N20)NGG	11	36596602	-	TCAGGTAATCATCAAGGTCTTGG	1	3	33	SEQ ID NO. 4619
(N20)NGG	11	36596608	-	GGCCATTCAGGTAATCATCAAGG	1	1	17	SEQ ID NO. 4620
(N20)NGG	11	36596620	-	CCACAGTGAAGGGGCCATTCAGG	1	3	33	SEQ ID NO. 4621
(N20)NGG	11	36596629	-	CCTTCACCACCACAGTGAAGGGG	1	3	62	SEQ ID NO. 4622
(N20)NGG	11	36596630	-	TCCTTCACCACCACAGTGAAGGG	1	2	52	SEQ ID NO. 4623
(N20)NGG	11	36596631	-	CTCCTTCACCACCACAGTGAAGG	1	5	79	SEQ ID NO. 4624
(N20)NGG	11	36596699	-	ACTGCCTTTTCTGGAACTACAGG	2	2	53	SEQ ID NO. 4625
(N20)NGG	11	36596708	-	GAAAAACGGACTGCCTTTTCTGG	1	1	27	SEQ ID NO. 4626
(N20)NGG	11	36596722	-	TCATGATTGTGAATGAAAAACGG	1	8	141	SEQ ID NO. 4627
(N20)NGG	11	36596757	-	TTTCACATTCTGAGAGCTGTGGG	1	4	66	SEQ ID NO. 4628
(N20)NGG	11	36596758	-	CTTTCACATTCTGAGAGCTGTGG	3	9	85	SEQ ID NO. 4629
(N20)NGG	11	36596793	-	ACACAGTTCAGAGTTAGGTTTGG	1	4	32	SEQ ID NO. 4630
(N20)NGG	11	36596798	-	TTGCAACACAGTTCAGAGTTAGG	2	11	62	SEQ ID NO. 4631
(N20)NGG	11	36596822	-	TCTGCCAGCATAAGGCACAATGG	1	2	34	SEQ ID NO. 4632

FIG. 13 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	11	36596830	-	CAGACTCATCTGCCAGCATAAGG	1	1	36	SEQ ID NO. 4633
(N20)NGG	11	36596854	-	GGATGGCAGTCAGCGTCTCGTGG	1	3	11	SEQ ID NO. 4634
(N20)NGG	11	36596871	-	AGCAATGAGAGGACTCAGGATGG	1	5	97	SEQ ID NO. 4635
(N20)NGG	11	36596875	-	TCTCAGCAATGAGAGGACTCAGG	1	2	55	SEQ ID NO. 4636
(N20)NGG	11	36596882	-	GCCTCCCTCTCAGCAATGAGAGG	1	2	42	SEQ ID NO. 4637
(N20)NGG	11	36596904	-	CATTAATTCACTGCTCTTCATGG	1	4	108	SEQ ID NO. 4638
(N20)NGG	11	36596947	-	TGAAGATGAACTTGAAAGTCCGG	1	2	94	SEQ ID NO. 4639
(N20)NGG	11	36596976	-	CACAAGTTTTTCATCATAGCCGG	1	1	28	SEQ ID NO. 4640
(N20)NGG	11	36597013	-	AGACTGAGCCAGAAGCCTCGAGG	1	3	42	SEQ ID NO. 4641
(N20)NGG	11	36597057	-	TTGAGAGGCTTCCAGACGGGTGG	1	3	30	SEQ ID NO. 4642
(N20)NGG	11	36597060	-	ATTTTGAGAGGCTTCCAGACGGG	1	4	31	SEQ ID NO. 4643
(N20)NGG	11	36597061	-	GATTTTGAGAGGCTTCCAGACGG	1	5	64	SEQ ID NO. 4644
(N20)NGG	11	36597072	-	GTGGAAGACAAGATTTTGAGAGG	1	3	81	SEQ ID NO. 4645
(N20)NGG	11	36597091	-	CATGGCTTCTGGTTATAGAGTGG	1	6	44	SEQ ID NO. 4646
(N20)NGG	11	36597102	-	CAGGTTCTCAGCATGGCTTCTGG	1	5	76	SEQ ID NO. 4647
(N20)NGG	11	36597109	-	AACGTTCCAGGTTCTCAGCATGG	1	3	20	SEQ ID NO. 4648
(N20)NGG	11	36597121	-	GCCAGACCTCATAACGTTCCAGG	1	1	11	SEQ ID NO. 4649
(N20)NGG	11	36597147	-	CACAGACTCATGGTAAGGGTTGG	1	2	29	SEQ ID NO. 4650
(N20)NGG	11	36597151	-	CTTCCACAGACTCATGGTAAGGG	1	5	41	SEQ ID NO. 4651
(N20)NGG	11	36597152	-	TCTTCCACAGACTCATGGTAAGG	1	5	38	SEQ ID NO. 4652
(N20)NGG	11	36597157	-	GCAGTTCTTCCACAGACTCATGG	1	5	54	SEQ ID NO. 4653
(N20)NGG	11	36597209	-	GAAGGGACTGTCTCAATGAAAGG	1	3	40	SEQ ID NO. 4654
(N20)NGG	11	36597226	-	AGTGGAGTGCATCTATGGAAGGG	1	2	31	SEQ ID NO. 4655
(N20)NGG	11	36597227	-	CAGTGGAGTGCATCTATGGAAGG	1	2	21	SEQ ID NO. 4656
(N20)NGG	11	36597231	-	GTCACAGTGGAGTGCATCTATGG	1	9	59	SEQ ID NO. 4657
(N20)NGG	11	36597244	-	CTGCATTGCCAATGTCACAGTGG	1	5	50	SEQ ID NO. 4658
(N20)NGG	11	36597286	-	ACACTTCCCCTATCTCTAGCTGG	1	1	24	SEQ ID NO. 4659
(N20)NGG	11	36597317	-	CTTTCCTCTTTGGAAGCATTGGG	1	7	102	SEQ ID NO. 4660
(N20)NGG	11	36597318	-	CCTTTCCTCTTTGGAAGCATTGG	1	3	74	SEQ ID NO. 4661
(N20)NGG	11	36597327	-	CCACCTTTTCCTTTCCTCTTTGG	3	18	318	SEQ ID NO. 4662
(N20)NGG	11	36597354	-	CCGGAGATGCTTGTCCAGTGTGG	1	1	11	SEQ ID NO. 4663
(N20)NGG	11	36597373	-	GTTTGAGGTTCATCTTCTTCCGG	1	5	47	SEQ ID NO. 4664
(N20)NGG	11	36597388	-	TCATCCTCATGATTGGTTTGAGG	1	3	36	SEQ ID NO. 4665

FIG. 13 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	11	36597395	-	TTGCCATTCATCCTCATGATTGG	1	2	34	SEQ ID NO. 4666
(N20)NGG	11	36597423	-	CTCTTTGGTCATGAGCTTCCTGG	1	5	59	SEQ ID NO. 4667
(N20)NGG	11	36597438	-	AACTGCATCCACAGTCTCTTTGG	1	6	70	SEQ ID NO. 4668
(N20)NGG	11	36597473	-	GCCTCGTGCCTCTCCTCGGAAGG	1	3	21	SEQ ID NO. 4669
(N20)NGG	11	36597477	-	CAGAGCCTCGTGCCTCTCCTCGG	1	4	45	SEQ ID NO. 4670
(N20)NGG	11	36597520	-	GCCATACTGGTTTCATCTTCAGG	1	1	32	SEQ ID NO. 4671
(N20)NGG	11	36597533	-	GGGCATGATGATCGCCATACTGG	1	2	5	SEQ ID NO. 4672
(N20)NGG	11	36597553	-	ATTCTGGGCACTCTTTAGCAGGG	1	2	35	SEQ ID NO. 4673
(N20)NGG	11	36597554	-	GATTCTGGGCACTCTTTAGCAGG	2	4	32	SEQ ID NO. 4674
(N20)NGG	11	36597568	-	TGTACTGGCAGAGGGATTCTGGG	1	2	31	SEQ ID NO. 4675
(N20)NGG	11	36597569	-	CTGTACTGGCAGAGGGATTCTGG	1	1	23	SEQ ID NO. 4676
(N20)NGG	11	36597576	-	ATTGAAACTGTACTGGCAGAGGG	1	3	38	SEQ ID NO. 4677
(N20)NGG	11	36597577	-	AATTGAAACTGTACTGGCAGAGG	1	7	44	SEQ ID NO. 4678
(N20)NGG	11	36597583	-	GCTGTGAATTGAAACTGTACTGG	1	1	19	SEQ ID NO. 4679
(N20)NGG	11	36597619	-	TATACTTGAACTTCGTAGAAAGG	1	1	37	SEQ ID NO. 4680
(N20)NGG	11	36597660	-	CAGGGTTTTGTGAAAATAATTGG	1	7	98	SEQ ID NO. 4681
(N20)NGG	11	36597678	-	AATTTCAGGAACATGGGCCAGGG	1	4	44	SEQ ID NO. 4682
(N20)NGG	11	36597679	-	TAATTTCAGGAACATGGGCCAGG	1	3	36	SEQ ID NO. 4683
(N20)NGG	11	36597684	-	CTCAATAATTTCAGGAACATGGG	1	4	74	SEQ ID NO. 4684
(N20)NGG	11	36597685	-	TCTCAATAATTTCAGGAACATGG	1	9	114	SEQ ID NO. 4685
(N20)NGG	11	36597692	-	CCATCCCTCTCAATAATTTCAGG	1	2	35	SEQ ID NO. 4686
(N20)NGG	11	36597717	-	CTCACTTGCCCATGCCCCAATGG	1	3	38	SEQ ID NO. 4687
(N20)NGG	11	36597775	-	ACTGCCTGGCATTCATTTTCCGG	1	4	45	SEQ ID NO. 4688
(N20)NGG	11	36597789	-	CTCATAGCATTTGGACTGCCTGG	1	1	18	SEQ ID NO. 4689
(N20)NGG	11	36597798	-	ATCTTCCATCTCATAGCATTTGG	1	4	51	SEQ ID NO. 4690
(N20)NGG	11	36597823	-	TGTACAACCAGTGGTGTTTCAGG	1	1	24	SEQ ID NO. 4691
(N20)NGG	11	36597832	-	ATTTGGAGGTGTACAACCAGTGG	1	1	24	SEQ ID NO. 4692
(N20)NGG	11	36597846	-	AAACTTCTGGAGGTATTTGGAGG	1	6	76	SEQ ID NO. 4693
(N20)NGG	11	36597849	-	CATAAACTTCTGGAGGTATTTGG	1	2	42	SEQ ID NO. 4694
(N20)NGG	11	36597856	-	GAGCATTCATAAACTTCTGGAGG	1	5	79	SEQ ID NO. 4695
(N20)NGG	11	36597859	-	TATGAGCATTCATAAACTTCTGG	1	4	38	SEQ ID NO. 4696
(N20)NGG	11	36597894	-	AGGGTTCATGGTAAACCCAGAGG	1	6	39	SEQ ID NO. 4697
(N20)NGG	11	36597906	-	TAAGCTTGCCTGAGGGTTCATGG	1	1	25	SEQ ID NO. 4698

FIG. 13 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	11	36597913	-	GGTCCCCTAAGCTTGCCTGAGGG	1	2	21	SEQ ID NO. 4699
(N20)NGG	11	36597914	-	GGGTCCCCTAAGCTTGCCTGAGG	1	3	18	SEQ ID NO. 4700
(N20)NGG	11	36597934	-	GAGAGTCCTCTATGCCTAATGGG	1	1	9	SEQ ID NO. 4701
(N20)NGG	11	36597935	-	AGAGAGTCCTCTATGCCTAATGG	1	3	21	SEQ ID NO. 4702

FIG. 13 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	11	36614186	+	AACATAGCCTTAATTCAGCCAGG	1	3	29	SEQ ID NO. 4703
(N20)NGG	11	36614210	+	TTCTCACTGATGAATTTTGATGG	1	24	221	SEQ ID NO. 4704
(N20)NGG	11	36614228	+	GATGGACAAGTTTTCTTCTTTGG	1	4	80	SEQ ID NO. 4705
(N20)NGG	11	36614237	+	GTTTTCTTCTTTGGACAAAAAGG	1	13	170	SEQ ID NO. 4706
(N20)NGG	11	36614241	+	TCTTCTTTGGACAAAAAGGCTGG	1	8	67	SEQ ID NO. 4707
(N20)NGG	11	36614264	+	CCCAAAAGATCCTGCCCCACTGG	1	3	46	SEQ ID NO. 4708
(N20)NGG	11	36614278	+	CCCCACTGGAGTTTTCCATCTGG	1	4	38	SEQ ID NO. 4709
(N20)NGG	11	36614326	+	GAAGCCTACAATTTTCTCTAAGG	1	5	38	SEQ ID NO. 4710
(N20)NGG	11	36614378	+	CCAGCCACTTGCACATTCAAAGG	1	3	30	SEQ ID NO. 4711
(N20)NGG	11	36614386	+	TTGCACATTCAAAGGCAGCTTGG	2	3	40	SEQ ID NO. 4712
(N20)NGG	11	36614417	+	AAGCATCAATACATCATCCATGG	1	2	28	SEQ ID NO. 4713
(N20)NGG	11	36614420	+	CATCAATACATCATCCATGGAGG	1	1	22	SEQ ID NO. 4714
(N20)NGG	11	36614421	+	ATCAATACATCATCCATGGAGGG	1	3	30	SEQ ID NO. 4715
(N20)NGG	11	36614440	+	AGGGAAAACACCAAACAATGAGG	1	3	105	SEQ ID NO. 4716
(N20)NGG	11	36614491	+	TGTTTGCAAGAACAACAAAAAGG	1	16	224	SEQ ID NO. 4717
(N20)NGG	11	36614521	+	TCGCTGCACAGAGAAAGACTTGG	1	2	30	SEQ ID NO. 4718
(N20)NGG	11	36614525	+	TGCACAGAGAAAGACTTGGTAGG	1	4	54	SEQ ID NO. 4719
(N20)NGG	11	36614549	+	GATGTTCCTGAAGCCAGATATGG	1	8	46	SEQ ID NO. 4720
(N20)NGG	11	36614566	+	ATATGGTCATTCCATTAATGTGG	1	4	45	SEQ ID NO. 4721
(N20)NGG	11	36614579	+	ATTAATGTGGTGTACAGCCGAGG	1	1	8	SEQ ID NO. 4722
(N20)NGG	11	36614580	+	TTAATGTGGTGTACAGCCGAGGG	1	1	11	SEQ ID NO. 4723
(N20)NGG	11	36614590	+	GTACAGCCGAGGGAAAAGTATGG	1	5	223	SEQ ID NO. 4724
(N20)NGG	11	36614591	+	TACAGCCGAGGGAAAAGTATGGG	1	2	20	SEQ ID NO. 4725
(N20)NGG	11	36614603	+	AAAAGTATGGGTGTTCTCTTTGG	1	2	60	SEQ ID NO. 4726
(N20)NGG	11	36614606	+	AGTATGGGTGTTCTCTTTGGAGG	1	2	40	SEQ ID NO. 4727
(N20)NGG	11	36614649	+	CCCACAGAACCACAGAAAAATGG	2	11	170	SEQ ID NO. 4728
(N20)NGG	11	36614686	+	CTGCCTGCCCTGTGTTTTCCTGG	3	8	106	SEQ ID NO. 4729
(N20)NGG	11	36614689	+	CCTGCCCTGTGTTTTCCTGGTGG	1	8	117	SEQ ID NO. 4730
(N20)NGG	11	36614702	+	TTCCTGGTGGATTTTGAATTTGG	1	3	72	SEQ ID NO. 4731
(N20)NGG	11	36614703	+	TCCTGGTGGATTTTGAATTTGGG	1	7	123	SEQ ID NO. 4732
(N20)NGG	11	36614737	+	ATACATTCTTCCAGAACTTCAGG	1	5	73	SEQ ID NO. 4733
(N20)NGG	11	36614741	+	ATTCTTCCAGAACTTCAGGATGG	1	4	73	SEQ ID NO. 4734
(N20)NGG	11	36614742	+	TTCTTCCAGAACTTCAGGATGGG	1	4	69	SEQ ID NO. 4735

FIG. 14

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	11	36614792	+	AATGACACCATCTATATTTTAGG	1	18	113	SEQ ID NO. 4736
(N20)NGG	11	36614795	+	GACACCATCTATATTTTAGGAGG	1	3	49	SEQ ID NO. 4737
(N20)NGG	11	36614820	+	ATTCACTTGCCAATAATATCCGG	1	2	47	SEQ ID NO. 4738
(N20)NGG	11	36614844	+	CTGCCAACCTGTACAGAATAAGG	1	3	42	SEQ ID NO. 4739
(N20)NGG	11	36614845	+	TGCCAACCTGTACAGAATAAGGG	1	2	36	SEQ ID NO. 4740
(N20)NGG	11	36614860	+	AATAAGGGTTGATCTTCCCCTGG	1	2	22	SEQ ID NO. 4741
(N20)NGG	11	36614861	+	ATAAGGGTTGATCTTCCCCTGGG	1	1	27	SEQ ID NO. 4742
(N20)NGG	11	36614894	+	GTGAATTGCACAGTCTTGCCAGG	1	2	25	SEQ ID NO. 4743
(N20)NGG	11	36614897	+	AATTGCACAGTCTTGCCAGGAGG	1	5	39	SEQ ID NO. 4744
(N20)NGG	11	36614957	+	AATGATGAATTTGTTATTGTTGG	2	8	158	SEQ ID NO. 4745
(N20)NGG	11	36614960	+	GATGAATTTGTTATTGTTGGTGG	1	6	90	SEQ ID NO. 4746
(N20)NGG	11	36615013	+	CTGCAACATCATCTCTTTAGAGG	1	5	78	SEQ ID NO. 4747
(N20)NGG	11	36615040	+	CAAGATAGAAATTCGTGAGATGG	1	5	34	SEQ ID NO. 4748
(N20)NGG	11	36615054	+	GTGAGATGGAGACCCCAGATTGG	1	1	40	SEQ ID NO. 4749
(N20)NGG	11	36615084	+	ACATTAAGCACAGCAAGATATGG	1	7	62	SEQ ID NO. 4750
(N20)NGG	11	36615089	+	AAGCACAGCAAGATATGGTTTGG	1	2	49	SEQ ID NO. 4751
(N20)NGG	11	36615100	+	GATATGGTTTGGAAGCAACATGG	1	2	48	SEQ ID NO. 4752
(N20)NGG	11	36615101	+	ATATGGTTTGGAAGCAACATGGG	1	3	96	SEQ ID NO. 4753
(N20)NGG	11	36615107	+	TTTGGAAGCAACATGGGAAATGG	1	8	210	SEQ ID NO. 4754
(N20)NGG	11	36615122	+	GGAAATGGAACTGTTTTTCTTGG	1	14	119	SEQ ID NO. 4755
(N20)NGG	11	36615131	+	ACTGTTTTTCTTGGCATACCAGG	1	2	51	SEQ ID NO. 4756
(N20)NGG	11	36615158	+	AATAAACAAGTTGTTTCAGAAGG	2	6	109	SEQ ID NO. 4757
(N20)NGG	11	36615251	+	CAAACATCAACAGAAGATCCAGG	1	4	57	SEQ ID NO. 4758
(N20)NGG	11	36615252	+	AAACATCAACAGAAGATCCAGGG	1	8	97	SEQ ID NO. 4759
(N20)NGG	11	36615253	+	AACATCAACAGAAGATCCAGGGG	1	4	72	SEQ ID NO. 4760
(N20)NGG	11	36615317	+	GCAGAAGCAAATAGTTTTGATGG	1	3	92	SEQ ID NO. 4761
(N20)NGG	11	36615374	+	GAAGAAGATGAGTCTGAGACAGG	1	7	125	SEQ ID NO. 4762
(N20)NGG	11	36615381	+	ATGAGTCTGAGACAGGCTACTGG	1	2	29	SEQ ID NO. 4763
(N20)NGG	11	36615409	+	ATGCTGCCCTACTTGTGATGTGG	1	5	48	SEQ ID NO. 4764
(N20)NGG	11	36615423	+	GTGATGTGGATATCAACACTTGG	1	5	19	SEQ ID NO. 4765
(N20)NGG	11	36615424	+	TGATGTGGATATCAACACTTGGG	1	1	31	SEQ ID NO. 4766
(N20)NGG	11	36615479	+	GCCATGATCTACTGCTCTCATGG	1	3	39	SEQ ID NO. 4767
(N20)NGG	11	36615480	+	CCATGATCTACTGCTCTCATGGG	1	2	31	SEQ ID NO. 4768

FIG. 14 cont.

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	11	36615481	+	CATGATCTACTGCTCTCATGGGG	1	3	22	SEQ ID NO. 4769
(N20)NGG	11	36615485	+	ATCTACTGCTCTCATGGGGATGG	1	2	37	SEQ ID NO. 4770
(N20)NGG	11	36615486	+	TCTACTGCTCTCATGGGGATGGG	1	3	34	SEQ ID NO. 4771
(N20)NGG	11	36615492	+	GCTCTCATGGGGATGGGCACTGG	1	3	36	SEQ ID NO. 4772
(N20)NGG	11	36615493	+	CTCTCATGGGGATGGGCACTGGG	2	3	45	SEQ ID NO. 4773
(N20)NGG	11	36615511	+	CTGGGTCCATGCTCAGTGCATGG	1	4	50	SEQ ID NO. 4774
(N20)NGG	11	36615517	+	CCATGCTCAGTGCATGGATCTGG	1	3	34	SEQ ID NO. 4775
(N20)NGG	11	36615548	+	ACACTCATCCATCTGTCAGCAGG	1	7	46	SEQ ID NO. 4776
(N20)NGG	11	36615580	+	GTATTACTGCAATGAGCATGTGG	1	4	77	SEQ ID NO. 4777
(N20)NGG	11	36615659	+	ATGAAATCCCTCCGTAAAAAAGG	1	3	25	SEQ ID NO. 4778
(N20)NGG	11	36615665	+	TCCCTCCGTAAAAAAGGTTCTGG	1	1	10	SEQ ID NO. 4779
(N20)NGG	11	36615705	+	CCAAGAAATCCTTTCTTAGAAGG	1	5	71	SEQ ID NO. 4780
(N20)NGG	11	36614171	-	TGAGAAGCCTGGCTGAATTAAGG	1	5	54	SEQ ID NO. 4781
(N20)NGG	11	36614182	-	AAATTCATCAGTGAGAAGCCTGG	2	3	61	SEQ ID NO. 4782
(N20)NGG	11	36614242	-	CCAGTGGGGCAGGATCTTTTGGG	1	3	50	SEQ ID NO. 4783
(N20)NGG	11	36614243	-	TCCAGTGGGGCAGGATCTTTTGG	1	1	27	SEQ ID NO. 4784
(N20)NGG	11	36614252	-	ATGGAAAACTCCAGTGGGGCAGG	1	6	47	SEQ ID NO. 4785
(N20)NGG	11	36614256	-	CCAGATGGAAAACTCCAGTGGGG	1	3	58	SEQ ID NO. 4786
(N20)NGG	11	36614257	-	TCCAGATGGAAAACTCCAGTGGG	1	3	70	SEQ ID NO. 4787
(N20)NGG	11	36614258	-	ATCCAGATGGAAAACTCCAGTGG	1	7	85	SEQ ID NO. 4788
(N20)NGG	11	36614271	-	GGTTATGCTTTACATCCAGATGG	1	2	21	SEQ ID NO. 4789
(N20)NGG	11	36614292	-	TTGTAGGCTTCAGTTTGACATGG	1	3	44	SEQ ID NO. 4790
(N20)NGG	11	36614308	-	GAATCCTTAGAGAAAATTGTAGG	1	6	86	SEQ ID NO. 4791
(N20)NGG	11	36614330	-	GCGAAGAGGAGGGAGGTAGCAGG	1	9	101	SEQ ID NO. 4792
(N20)NGG	11	36614337	-	CTGGGTAGCGAAGAGGAGGGAGG	1	6	94	SEQ ID NO. 4793
(N20)NGG	11	36614340	-	TGGCTGGGTAGCGAAGAGGAGGG	1	3	67	SEQ ID NO. 4794
(N20)NGG	11	36614341	-	GTGGCTGGGTAGCGAAGAGGAGG	1	4	55	SEQ ID NO. 4795
(N20)NGG	11	36614344	-	CAAGTGGCTGGGTAGCGAAGAGG	1	3	21	SEQ ID NO. 4796
(N20)NGG	11	36614355	-	CTTTGAATGTGCAAGTGGCTGGG	1	4	37	SEQ ID NO. 4797
(N20)NGG	11	36614356	-	CCTTTGAATGTGCAAGTGGCTGG	1	2	29	SEQ ID NO. 4798
(N20)NGG	11	36614360	-	GCTGCCTTTGAATGTGCAAGTGG	1	7	72	SEQ ID NO. 4799
(N20)NGG	11	36614412	-	TGTTTGGTGTTTTCCCTCCATGG	1	5	88	SEQ ID NO. 4800
(N20)NGG	11	36614428	-	TTATCTGAAACCTCATTGTTTGG	1	7	60	SEQ ID NO. 4801

FIG. 14 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	11	36614533	-	GAATGACCATATCTGGCTTCAGG	2	3	36	SEQ ID NO. 4802
(N20)NGG	11	36614540	-	ATTAATGGAATGACCATATCTGG	1	2	35	SEQ ID NO. 4803
(N20)NGG	11	36614555	-	TCGGCTGTACACCACATTAATGG	1	2	5	SEQ ID NO. 4804
(N20)NGG	11	36614574	-	GAACACCCATACTTTTCCCTCGG	1	2	29	SEQ ID NO. 4805
(N20)NGG	11	36614620	-	TCTGTGGTTCTGTGGGTAGAAGG	1	5	78	SEQ ID NO. 4806
(N20)NGG	11	36614627	-	CCATTTTTCTGTGGTTCTGTGGG	1	6	144	SEQ ID NO. 4807
(N20)NGG	11	36614628	-	TCCATTTTTCTGTGGTTCTGTGG	1	9	120	SEQ ID NO. 4808
(N20)NGG	11	36614636	-	TACACTATTCCATTTTTCTGTGG	1	8	105	SEQ ID NO. 4809
(N20)NGG	11	36614667	-	CCACCAGGAAAACACAGGGCAGG	1	7	95	SEQ ID NO. 4810
(N20)NGG	11	36614671	-	AAATCCACCAGGAAAACACAGGG	1	12	140	SEQ ID NO. 4811
(N20)NGG	11	36614672	-	AAAATCCACCAGGAAAACACAGG	1	8	96	SEQ ID NO. 4812
(N20)NGG	11	36614682	-	ACCCAAATTCAAAATCCACCAGG	1	6	79	SEQ ID NO. 4813
(N20)NGG	11	36614725	-	GATAGCCCATCCTGAAGTTCTGG	1	1	16	SEQ ID NO. 4814
(N20)NGG	11	36614765	-	AATATAGATGGTGTCATTTTTGG	1	3	110	SEQ ID NO. 4815
(N20)NGG	11	36614777	-	ATGTCCTCCTAAAATATAGATGG	2	8	100	SEQ ID NO. 4816
(N20)NGG	11	36614807	-	GTTGGCAGGCCGGATATTATTGG	1	1	7	SEQ ID NO. 4817
(N20)NGG	11	36614817	-	TTCTGTACAGGTTGGCAGGCCGG	1	8	194	SEQ ID NO. 4818
(N20)NGG	11	36614821	-	CTTATTCTGTACAGGTTGGCAGG	1	1	23	SEQ ID NO. 4819
(N20)NGG	11	36614825	-	AACCCTTATTCTGTACAGGTTGG	1	2	21	SEQ ID NO. 4820
(N20)NGG	11	36614829	-	GATCAACCCTTATTCTGTACAGG	1	1	11	SEQ ID NO. 4821
(N20)NGG	11	36614854	-	TTCACAGCTGGGCTACCCAGGGG	2	4	54	SEQ ID NO. 4822
(N20)NGG	11	36614855	-	ATTCACAGCTGGGCTACCCAGGG	1	1	32	SEQ ID NO. 4823
(N20)NGG	11	36614856	-	AATTCACAGCTGGGCTACCCAGG	1	2	25	SEQ ID NO. 4824
(N20)NGG	11	36614865	-	AGACTGTGCAATTCACAGCTGGG	1	1	42	SEQ ID NO. 4825
(N20)NGG	11	36614866	-	AAGACTGTGCAATTCACAGCTGG	1	2	43	SEQ ID NO. 4826
(N20)NGG	11	36614890	-	CTGGAGACAGAGATTCCTCCTGG	1	4	80	SEQ ID NO. 4827
(N20)NGG	11	36614909	-	AGTTTGAGTCAGGATTGCACTGG	1	4	23	SEQ ID NO. 4828
(N20)NGG	11	36614919	-	CATCATTGTTAGTTTGAGTCAGG	1	1	31	SEQ ID NO. 4829
(N20)NGG	11	36615044	-	AATGTCTGGGGTCCAATCTGGGG	1	5	30	SEQ ID NO. 4830
(N20)NGG	11	36615045	-	TAATGTCTGGGGTCCAATCTGGG	1	3	22	SEQ ID NO. 4831
(N20)NGG	11	36615046	-	TTAATGTCTGGGGTCCAATCTGG	1	2	21	SEQ ID NO. 4832
(N20)NGG	11	36615056	-	CTTGCTGTGCTTAATGTCTGGGG	1	5	54	SEQ ID NO. 4833
(N20)NGG	11	36615057	-	TCTTGCTGTGCTTAATGTCTGGG	1	2	70	SEQ ID NO. 4834

FIG. 14 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	11	36615058	-	ATCTTGCTGTGCTTAATGTCTGG	1	1	36	SEQ ID NO. 4835
(N20)NGG	11	36615127	-	ACAACTTGTTTATTGTCTCCTGG	1	5	70	SEQ ID NO. 4836
(N20)NGG	11	36615247	-	TCAAAGGGAGTGGAATCCCCTGG	1	3	23	SEQ ID NO. 4837
(N20)NGG	11	36615257	-	TTCAGAGTCTTCAAAGGGAGTGG	1	6	79	SEQ ID NO. 4838
(N20)NGG	11	36615262	-	AATTCTTCAGAGTCTTCAAAGGG	1	13	151	SEQ ID NO. 4839
(N20)NGG	11	36615263	-	AAATTCTTCAGAGTCTTCAAAGG	1	7	122	SEQ ID NO. 4840
(N20)NGG	11	36615335	-	TTCTTCATCATCTTCATTATAGG	2	21	338	SEQ ID NO. 4841
(N20)NGG	11	36615393	-	TGATATCCACATCACAAGTAGGG	1	2	30	SEQ ID NO. 4842
(N20)NGG	11	36615394	-	TTGATATCCACATCACAAGTAGG	1	5	26	SEQ ID NO. 4843
(N20)NGG	11	36615427	-	TTGAGCTCAGTTGAATAGAATGG	1	3	42	SEQ ID NO. 4844
(N20)NGG	11	36615454	-	TGAGAGCAGTAGATCATGGCGGG	1	3	43	SEQ ID NO. 4845
(N20)NGG	11	36615455	-	ATGAGAGCAGTAGATCATGGCGG	1	4	44	SEQ ID NO. 4846
(N20)NGG	11	36615458	-	CCCATGAGAGCAGTAGATCATGG	1	3	29	SEQ ID NO. 4847
(N20)NGG	11	36615495	-	CCAGATCCATGCACTGAGCATGG	1	1	44	SEQ ID NO. 4848
(N20)NGG	11	36615534	-	TGTTGCTTCCTGCTGACAGATGG	1	3	89	SEQ ID NO. 4849
(N20)NGG	11	36615604	-	TTTAAGGGTAGGACTCTTTGGGG	1	2	36	SEQ ID NO. 4850
(N20)NGG	11	36615605	-	TTTTAAGGGTAGGACTCTTTGGG	1	8	46	SEQ ID NO. 4851
(N20)NGG	11	36615606	-	TTTTTAAGGGTAGGACTCTTTGG	1	2	54	SEQ ID NO. 4852
(N20)NGG	11	36615615	-	TTGGAGGCTTTTTTAAGGGTAGG	1	5	52	SEQ ID NO. 4853
(N20)NGG	11	36615619	-	TTCATTGGAGGCTTTTTTAAGGG	2	9	98	SEQ ID NO. 4854
(N20)NGG	11	36615620	-	TTTCATTGGAGGCTTTTTTAAGG	2	11	101	SEQ ID NO. 4855
(N20)NGG	11	36615631	-	TTACGGAGGGATTTCATTGGAGG	1	2	11	SEQ ID NO. 4856
(N20)NGG	11	36615634	-	TTTTTACGGAGGGATTTCATTGG	1	3	24	SEQ ID NO. 4857
(N20)NGG	11	36615644	-	TCCAGAACCTTTTTTACGGAGGG	1	1	20	SEQ ID NO. 4858
(N20)NGG	11	36615645	-	TTCCAGAACCTTTTTTACGGAGG	1	2	19	SEQ ID NO. 4859
(N20)NGG	11	36615648	-	TTTTTCCAGAACCTTTTTTACGG	1	12	219	SEQ ID NO. 4860
(N20)NGG	11	36615679	-	CTAAGAAAGGATTTCTTGGCAGG	2	4	86	SEQ ID NO. 4861
(N20)NGG	11	36615683	-	CCTTCTAAGAAAGGATTTCTTGG	1	8	100	SEQ ID NO. 4862
(N20)NGG	11	36615692	-	ATCAAACAACCTTCTAAGAAAGG	1	5	63	SEQ ID NO. 4863

FIG. 14 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	2	98340496	+	GCAGGTTTCGGGAGGCCCAGGGG	1	3	38	SEQ ID NO. 4864
(N20)NGG	2	98340514	+	AGGGGCGATGCCAGACCCCGCGG	1	1	18	SEQ ID NO. 4865
(N20)NGG	2	98340536	+	GCGCACCTGCCCTTCTTCTACGG	1	1	16	SEQ ID NO. 4866
(N20)NGG	2	98340556	+	CGGCAGCATCTCGCGTGCCGAGG	1	1	5	SEQ ID NO. 4867
(N20)NGG	2	98340562	+	CATCTCGCGTGCCGAGGCCGAGG	1	1	3	SEQ ID NO. 4868
(N20)NGG	2	98340577	+	GGCCGAGGAGCACCTGAAGCTGG	1	5	72	SEQ ID NO. 4869
(N20)NGG	2	98340580	+	CGAGGAGCACCTGAAGCTGGCGG	1	17	373	SEQ ID NO. 4870
(N20)NGG	2	98340581	+	GAGGAGCACCTGAAGCTGGCGGG	1	11	352	SEQ ID NO. 4871
(N20)NGG	2	98340586	+	GCACCTGAAGCTGGCGGGCATGG	1	3	69	SEQ ID NO. 4872
(N20)NGG	2	98340589	+	CCTGAAGCTGGCGGGCATGGCGG	1	2	52	SEQ ID NO. 4873
(N20)NGG	2	98340593	+	AAGCTGGCGGGCATGGCGGACGG	1	2	20	SEQ ID NO. 4874
(N20)NGG	2	98340594	+	AGCTGGCGGGCATGGCGGACGGG	1	2	18	SEQ ID NO. 4875
(N20)NGG	2	98340628	+	GCGCCAGTGCCTGCGCTCGCTGG	1	2	13	SEQ ID NO. 4876
(N20)NGG	2	98340629	+	CGCCAGTGCCTGCGCTCGCTGGG	1	2	17	SEQ ID NO. 4877
(N20)NGG	2	98340632	+	CAGTGCCTGCGCTCGCTGGGCGG	1	1	19	SEQ ID NO. 4878
(N20)NGG	2	98340698	+	CCCATCGAGCGCCAGCTCAACGG	1	3	14	SEQ ID NO. 4879
(N20)NGG	2	98340716	+	AACGGCACCTACGCCATTGCCGG	1	2	4	SEQ ID NO. 4880
(N20)NGG	2	98340719	+	GGCACCTACGCCATTGCCGGCGG	2	2	10	SEQ ID NO. 4881
(N20)NGG	2	98340734	+	GCCGGCGGCAAAGCGCACTGTGG	1	2	10	SEQ ID NO. 4882
(N20)NGG	2	98340739	+	CGGCAAAGCGCACTGTGGACCGG	1	1	7	SEQ ID NO. 4883
(N20)NGG	2	98340776	+	TTCTACTCGCGCGACCCCGACGG	1	1	1	SEQ ID NO. 4884
(N20)NGG	2	98340777	+	TCTACTCGCGCGACCCCGACGGG	1	1	1	SEQ ID NO. 4885
(N20)NGG	2	98340810	+	ACCTGCGCAAGCCGTGCAACCGG	1	1	9	SEQ ID NO. 4886
(N20)NGG	2	98340817	+	CAAGCCGTGCAACCGGCCGTCGG	1	1	3	SEQ ID NO. 4887
(N20)NGG	2	98340818	+	AAGCCGTGCAACCGGCCGTCGGG	1	1	1	SEQ ID NO. 4888
(N20)NGG	2	98340835	+	GTCGGGCCTCGAGCCGCAGCCGG	1	21	58	SEQ ID NO. 4889
(N20)NGG	2	98340836	+	TCGGGCCTCGAGCCGCAGCCGGG	1	20	58	SEQ ID NO. 4890
(N20)NGG	2	98340837	+	CGGGCCTCGAGCCGCAGCCGGGG	1	2	49	SEQ ID NO. 4891
(N20)NGG	2	98340838	+	GGGCCTCGAGCCGCAGCCGGGGG	1	22	81	SEQ ID NO. 4892
(N20)NGG	2	98340865	+	CGACTGCCTGCGAGACGCCATGG	1	1	8	SEQ ID NO. 4893
(N20)NGG	2	98340891	+	GTGACTACGTGCGCCAGACGTGG	1	1	3	SEQ ID NO. 4894
(N20)NGG	2	98340898	+	CGTGCGCCAGACGTGGAAGCTGG	1	1	6	SEQ ID NO. 4895
(N20)NGG	2	98340901	+	GCGCCAGACGTGGAAGCTGGAGG	1	1	18	SEQ ID NO. 4896

FIG. 15

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	2	98340917	+	CTGGAGGTGAGAGCGCAGCCTGG	1	2	78	SEQ ID NO. 4897
(N20)NGG	2	98340918	+	TGGAGGTGAGAGCGCAGCCTGGG	1	6	72	SEQ ID NO. 4898
(N20)NGG	2	98340919	+	GGAGGTGAGAGCGCAGCCTGGGG	1	6	109	SEQ ID NO. 4899
(N20)NGG	2	98340924	+	TGAGAGCGCAGCCTGGGGCGCGG	1	1	51	SEQ ID NO. 4900
(N20)NGG	2	98340925	+	GAGAGCGCAGCCTGGGGCGCGGG	1	5	53	SEQ ID NO. 4901
(N20)NGG	2	98340489	-	CGGGGTCTGGCATCGCCCCTGGG	1	3	22	SEQ ID NO. 4902
(N20)NGG	2	98340490	-	GCGGGGTCTGGCATCGCCCCTGG	1	1	13	SEQ ID NO. 4903
(N20)NGG	2	98340502	-	GGCAGGTGCGCCGCGGGGTCTGG	1	2	34	SEQ ID NO. 4904
(N20)NGG	2	98340507	-	AGAAGGGCAGGTGCGCCGCGGGG	1	1	23	SEQ ID NO. 4905
(N20)NGG	2	98340508	-	AAGAAGGGCAGGTGCGCCGCGGG	1	3	19	SEQ ID NO. 4906
(N20)NGG	2	98340509	-	GAAGAAGGGCAGGTGCGCCGCGG	1	5	35	SEQ ID NO. 4907
(N20)NGG	2	98340519	-	TGCTGCCGTAGAAGAAGGGCAGG	1	1	24	SEQ ID NO. 4908
(N20)NGG	2	98340523	-	GAGATGCTGCCGTAGAAGAAGGG	1	3	41	SEQ ID NO. 4909
(N20)NGG	2	98340524	-	CGAGATGCTGCCGTAGAAGAAGG	1	1	10	SEQ ID NO. 4910
(N20)NGG	2	98340551	-	CTTCAGGTGCTCCTCGGCCTCGG	1	5	94	SEQ ID NO. 4911
(N20)NGG	2	98340557	-	CGCCAGCTTCAGGTGCTCCTCGG	1	3	47	SEQ ID NO. 4912
(N20)NGG	2	98340567	-	CCGCCATGCCCGCCAGCTTCAGG	1	1	34	SEQ ID NO. 4913
(N20)NGG	2	98340600	-	AGCGCAGGCACTGGCGCAGCAGG	1	2	21	SEQ ID NO. 4914
(N20)NGG	2	98340609	-	CGCCCAGCGAGCGCAGGCACTGG	1	1	18	SEQ ID NO. 4915
(N20)NGG	2	98340615	-	CATAGCCGCCCAGCGAGCGCAGG	1	1	7	SEQ ID NO. 4916
(N20)NGG	2	98340666	-	GGCGCTCGATGGGAAAGTGGTGG	1	2	17	SEQ ID NO. 4917
(N20)NGG	2	98340669	-	GCTGGCGCTCGATGGGAAAGTGG	1	2	8	SEQ ID NO. 4918
(N20)NGG	2	98340676	-	CCGTTGAGCTGGCGCTCGATGGG	1	1	3	SEQ ID NO. 4919
(N20)NGG	2	98340677	-	GCCGTTGAGCTGGCGCTCGATGG	1	1	9	SEQ ID NO. 4920
(N20)NGG	2	98340687	-	TGGCGTAGGTGCCGTTGAGCTGG	1	1	11	SEQ ID NO. 4921
(N20)NGG	2	98340701	-	TTTGCCGCCGGCAATGGCGTAGG	1	1	2	SEQ ID NO. 4922
(N20)NGG	2	98340707	-	GTGCGCTTTGCCGCCGGCAATGG	1	1	1	SEQ ID NO. 4923
(N20)NGG	2	98340713	-	TCCACAGTGCGCTTTGCCGCCGG	1	2	15	SEQ ID NO. 4924
(N20)NGG	2	98340736	-	TAGAACTCGCAGAGCTCTGCCGG	1	2	17	SEQ ID NO. 4925
(N20)NGG	2	98340768	-	GGTTGCAGGGCAGCCCGTCGGGG	1	2	14	SEQ ID NO. 4926
(N20)NGG	2	98340769	-	AGGTTGCAGGGCAGCCCGTCGGG	1	1	20	SEQ ID NO. 4927
(N20)NGG	2	98340770	-	CAGGTTGCAGGGCAGCCCGTCGG	1	4	23	SEQ ID NO. 4928
(N20)NGG	2	98340781	-	CACGGCTTGCGCAGGTTGCAGGG	1	1	10	SEQ ID NO. 4929

FIG. 15 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	2	98340782	-	GCACGGCTTGCGCAGGTTGCAGG	1	1	8	SEQ ID NO. 4930
(N20)NGG	2	98340789	-	GCCGGTTGCACGGCTTGCGCAGG	1	1	5	SEQ ID NO. 4931
(N20)NGG	2	98340799	-	AGGCCCGACGGCCGGTTGCACGG	1	1	4	SEQ ID NO. 4932
(N20)NGG	2	98340807	-	GCGGCTCGAGGCCCGACGGCCGG	1	1	12	SEQ ID NO. 4933
(N20)NGG	2	98340811	-	GGCTGCGGCTCGAGGCCCGACGG	1	2	28	SEQ ID NO. 4934
(N20)NGG	2	98340819	-	AGACCCCCGGCTGCGGCTCGAGG	1	3	13	SEQ ID NO. 4935
(N20)NGG	2	98340826	-	CAGTCGAAGACCCCCGGCTGCGG	1	2	7	SEQ ID NO. 4936
(N20)NGG	2	98340832	-	CGCAGGCAGTCGAAGACCCCCGG	1	1	12	SEQ ID NO. 4937
(N20)NGG	2	98340849	-	CACGCACCATGGCGTCTCGCAGG	1	1	9	SEQ ID NO. 4938
(N20)NGG	2	98340860	-	GCGCACGTAGTCACGCACCATGG	1	1	4	SEQ ID NO. 4939
(N20)NGG	2	98340882	-	TCACCTCCAGCTTCCACGTCTGG	2	3	41	SEQ ID NO. 4940
(N20)NGG	2	98341554	+	CTCCTCGCCTCTCCTTTTCTAGG	1	7	162	SEQ ID NO. 4941
(N20)NGG	2	98341555	+	TCCTCGCCTCTCCTTTTCTAGGG	1	2	71	SEQ ID NO. 4942
(N20)NGG	2	98341560	+	GCCTCTCCTTTTCTAGGGCGAGG	1	1	33	SEQ ID NO. 4943
(N20)NGG	2	98341566	+	CCTTTTCTAGGGCGAGGCCCTGG	1	4	21	SEQ ID NO. 4944
(N20)NGG	2	98341572	+	CTAGGGCGAGGCCCTGGAGCAGG	1	2	38	SEQ ID NO. 4945
(N20)NGG	2	98341587	+	GGAGCAGGCCATCATCAGCCAGG	1	5	39	SEQ ID NO. 4946
(N20)NGG	2	98341596	+	CATCATCAGCCAGGCCCCGCAGG	1	2	32	SEQ ID NO. 4947
(N20)NGG	2	98341599	+	CATCAGCCAGGCCCCGCAGGTGG	2	6	80	SEQ ID NO. 4948
(N20)NGG	2	98341620	+	GGAGAAGCTCATTGCTACGACGG	1	2	19	SEQ ID NO. 4949
(N20)NGG	2	98341631	+	TTGCTACGACGGCCCACGAGCGG	1	1	1	SEQ ID NO. 4950
(N20)NGG	2	98341640	+	CGGCCCACGAGCGGATGCCCTGG	1	1	4	SEQ ID NO. 4951
(N20)NGG	2	98341665	+	CCACAGCAGCCTGACGCGTGAGG	1	2	24	SEQ ID NO. 4952
(N20)NGG	2	98341668	+	CAGCAGCCTGACGCGTGAGGAGG	2	3	18	SEQ ID NO. 4953
(N20)NGG	2	98341690	+	GCCGAGCGCAAACTTTACTCTGG	1	1	3	SEQ ID NO. 4954
(N20)NGG	2	98341691	+	CCGAGCGCAAACTTTACTCTGGG	1	1	2	SEQ ID NO. 4955
(N20)NGG	2	98341692	+	CGAGCGCAAACTTTACTCTGGGG	1	1	5	SEQ ID NO. 4956
(N20)NGG	2	98341705	+	TACTCTGGGGCGCAGACCGACGG	1	1	6	SEQ ID NO. 4957
(N20)NGG	2	98341722	+	CGACGGCAAGTTCCTGTATGTGG	1	4	7	SEQ ID NO. 4958
(N20)NGG	2	98341723	+	GACGGCAAGTTCCTGTATGTGGG	1	1	9	SEQ ID NO. 4959
(N20)NGG	2	98341724	+	ACGGCAAGTTCCTGTATGTGGGG	1	3	16	SEQ ID NO. 4960
(N20)NGG	2	98341729	+	AAGTTCCTGTATGTGGGGCCCGG	1	2	26	SEQ ID NO. 4961
(N20)NGG	2	98341730	+	AGTTCCTGTATGTGGGGCCCGGG	1	4	45	SEQ ID NO. 4962

FIG. 15 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	2	98341736	+	TGTATGTGGGGCCCGGGATTTGG	1	2	26	SEQ ID NO. 4963
(N20)NGG	2	98341737	+	GTATGTGGGGCCCGGGATTTGGG	1	2	21	SEQ ID NO. 4964
(N20)NGG	2	98341531	-	CTAGAAAAGGAGAGGCGAGGAGG	1	6	100	SEQ ID NO. 4965
(N20)NGG	2	98341534	-	GCCCTAGAAAAGGAGAGGCGAGG	1	1	30	SEQ ID NO. 4966
(N20)NGG	2	98341539	-	GCCTCGCCCTAGAAAAGGAGAGG	1	2	23	SEQ ID NO. 4967
(N20)NGG	2	98341544	-	CCAGGGCCTCGCCCTAGAAAAGG	1	3	30	SEQ ID NO. 4968
(N20)NGG	2	98341561	-	GCTGATGATGGCCTGCTCCAGGG	3	6	53	SEQ ID NO. 4969
(N20)NGG	2	98341562	-	GGCTGATGATGGCCTGCTCCAGG	1	7	52	SEQ ID NO. 4970
(N20)NGG	2	98341573	-	CTGCGGGGCCTGGCTGATGATGG	1	1	41	SEQ ID NO. 4971
(N20)NGG	2	98341583	-	GCTTCTCCACCTGCGGGGCCTGG	1	7	75	SEQ ID NO. 4972
(N20)NGG	2	98341588	-	AATGAGCTTCTCCACCTGCGGGG	1	2	33	SEQ ID NO. 4973
(N20)NGG	2	98341589	-	CAATGAGCTTCTCCACCTGCGGG	2	11	57	SEQ ID NO. 4974
(N20)NGG	2	98341590	-	GCAATGAGCTTCTCCACCTGCGG	2	6	33	SEQ ID NO. 4975
(N20)NGG	2	98341621	-	GTACCAGGGCATCCGCTCGTGGG	1	1	5	SEQ ID NO. 4976
(N20)NGG	2	98341622	-	GGTACCAGGGCATCCGCTCGTGG	1	1	9	SEQ ID NO. 4977
(N20)NGG	2	98341635	-	GTCAGGCTGCTGTGGTACCAGGG	1	2	53	SEQ ID NO. 4978
(N20)NGG	2	98341636	-	CGTCAGGCTGCTGTGGTACCAGG	1	2	49	SEQ ID NO. 4979
(N20)NGG	2	98341643	-	CCTCACGCGTCAGGCTGCTGTGG	1	2	25	SEQ ID NO. 4980
(N20)NGG	2	98341652	-	GCTCGGCCTCCTCACGCGTCAGG	1	4	9	SEQ ID NO. 4981
(N20)NGG	2	98341669	-	CCCAGAGTAAAGTTTGCGCTCGG	1	1	6	SEQ ID NO. 4982
(N20)NGG	2	98341699	-	CACATACAGGAACTTGCCGTCGG	1	2	19	SEQ ID NO. 4983
(N20)NGG	2	98341712	-	AAATCCCGGGCCCCACATACAGG	1	2	12	SEQ ID NO. 4984
(N20)NGG	2	98349345	+	ATCCCCTCCCTTCCCCTGCCAGG	1	19	323	SEQ ID NO. 4985
(N20)NGG	2	98349351	+	TCCCTTCCCCTGCCAGGCTGAGG	4	40	380	SEQ ID NO. 4986
(N20)NGG	2	98349357	+	CCCCTGCCAGGCTGAGGCCGCGG	1	8	116	SEQ ID NO. 4987
(N20)NGG	2	98349361	+	TGCCAGGCTGAGGCCGCGGAAGG	1	2	53	SEQ ID NO. 4988
(N20)NGG	2	98349367	+	GCTGAGGCCGCGGAAGGAGCAGG	1	4	92	SEQ ID NO. 4989
(N20)NGG	2	98349368	+	CTGAGGCCGCGGAAGGAGCAGGG	1	4	72	SEQ ID NO. 4990
(N20)NGG	2	98349395	+	TACGCCCTGTCCCTCATCTATGG	1	1	10	SEQ ID NO. 4991
(N20)NGG	2	98349396	+	ACGCCCTGTCCCTCATCTATGGG	1	1	12	SEQ ID NO. 4992
(N20)NGG	2	98349403	+	GTCCCTCATCTATGGGAAGACGG	1	4	37	SEQ ID NO. 4993
(N20)NGG	2	98349433	+	CTACCTCATCAGCCAAGACAAGG	1	1	45	SEQ ID NO. 4994
(N20)NGG	2	98349436	+	CCTCATCAGCCAAGACAAGGCGG	2	4	58	SEQ ID NO. 4995

FIG. 15 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	2	98349437	+	CTCATCAGCCAAGACAAGGCGGG	1	4	45	SEQ ID NO. 4996
(N20)NGG	2	98349457	+	GGGCAAGTACTGCATTCCCGAGG	1	2	10	SEQ ID NO. 4997
(N20)NGG	2	98349458	+	GGCAAGTACTGCATTCCCGAGGG	1	2	12	SEQ ID NO. 4998
(N20)NGG	2	98349480	+	GCACCAAGTTTGACACGCTCTGG	1	1	6	SEQ ID NO. 4999
(N20)NGG	2	98349484	+	CAAGTTTGACACGCTCTGGCAGG	1	2	14	SEQ ID NO. 5000
(N20)NGG	2	98349488	+	TTTGACACGCTCTGGCAGGTAGG	1	1	18	SEQ ID NO. 5001
(N20)NGG	2	98349325	-	AGCCTGGCAGGGGAAGGGAGGGG	2	25	373	SEQ ID NO. 5002
(N20)NGG	2	98349326	-	CAGCCTGGCAGGGGAAGGGAGGG	3	31	429	SEQ ID NO. 5003
(N20)NGG	2	98349327	-	TCAGCCTGGCAGGGGAAGGGAGG	3	26	293	SEQ ID NO. 5004
(N20)NGG	2	98349330	-	GCCTCAGCCTGGCAGGGGAAGGG	1	17	236	SEQ ID NO. 5005
(N20)NGG	2	98349331	-	GGCCTCAGCCTGGCAGGGGAAGG	1	20	289	SEQ ID NO. 5006
(N20)NGG	2	98349335	-	CCGCGGCCTCAGCCTGGCAGGGG	1	8	55	SEQ ID NO. 5007
(N20)NGG	2	98349336	-	TCCGCGGCCTCAGCCTGGCAGGG	1	6	108	SEQ ID NO. 5008
(N20)NGG	2	98349337	-	TTCCGCGGCCTCAGCCTGGCAGG	1	2	211	SEQ ID NO. 5009
(N20)NGG	2	98349341	-	CTCCTTCCGCGGCCTCAGCCTGG	2	3	38	SEQ ID NO. 5010
(N20)NGG	2	98349352	-	TATGTGCCCTGCTCCTTCCGCGG	1	1	23	SEQ ID NO. 5011
(N20)NGG	2	98349377	-	CTTCCCATAGATGAGGGACAGGG	1	4	42	SEQ ID NO. 5012
(N20)NGG	2	98349378	-	TCTTCCCATAGATGAGGGACAGG	1	4	39	SEQ ID NO. 5013
(N20)NGG	2	98349383	-	CACCGTCTTCCCATAGATGAGGG	1	2	15	SEQ ID NO. 5014
(N20)NGG	2	98349384	-	ACACCGTCTTCCCATAGATGAGG	1	2	16	SEQ ID NO. 5015
(N20)NGG	2	98349408	-	TGTCTTGGCTGATGAGGTAGTGG	1	1	46	SEQ ID NO. 5016
(N20)NGG	2	98349414	-	CCGCCTTGTCTTGGCTGATGAGG	1	3	27	SEQ ID NO. 5017
(N20)NGG	2	98349423	-	AGTACTTGCCCGCCTTGTCTTGG	1	2	7	SEQ ID NO. 5018
(N20)NGG	2	98349451	-	GTGTCAAACTTGGTGCCCTCGGG	1	2	24	SEQ ID NO. 5019
(N20)NGG	2	98349452	-	CGTGTCAAACTTGGTGCCCTCGG	1	1	9	SEQ ID NO. 5020
(N20)NGG	2	98349461	-	CTGCCAGAGCGTGTCAAACTTGG	1	1	11	SEQ ID NO. 5021
(N20)NGG	2	98349590	+	AGCTGCCTGCTCCCTGCAGCTGG	3	18	173	SEQ ID NO. 5022
(N20)NGG	2	98349593	+	TGCCTGCTCCCTGCAGCTGGTGG	2	17	246	SEQ ID NO. 5023
(N20)NGG	2	98349611	+	GGTGGAGTATCTGAAGCTGAAGG	1	2	37	SEQ ID NO. 5024
(N20)NGG	2	98349614	+	GGAGTATCTGAAGCTGAAGGCGG	1	8	102	SEQ ID NO. 5025
(N20)NGG	2	98349618	+	TATCTGAAGCTGAAGGCGGACGG	1	1	26	SEQ ID NO. 5026
(N20)NGG	2	98349619	+	ATCTGAAGCTGAAGGCGGACGGG	1	1	15	SEQ ID NO. 5027
(N20)NGG	2	98349638	+	CGGGCTCATCTACTGCCTGAAGG	1	2	15	SEQ ID NO. 5028

FIG. 15 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	2	98349641	+	GCTCATCTACTGCCTGAAGGAGG	1	1	25	SEQ ID NO. 5029
(N20)NGG	2	98349675	+	AGCAGTGCCAGCAACGCCTCAGG	1	2	25	SEQ ID NO. 5030
(N20)NGG	2	98349681	+	GCCAGCAACGCCTCAGGTGACGG	1	2	27	SEQ ID NO. 5031
(N20)NGG	2	98349688	+	ACGCCTCAGGTGACGGCAGCAGG	1	2	18	SEQ ID NO. 5032
(N20)NGG	2	98349691	+	CCTCAGGTGACGGCAGCAGGCGG	1	8	67	SEQ ID NO. 5033
(N20)NGG	2	98349692	+	CTCAGGTGACGGCAGCAGGCGGG	1	5	55	SEQ ID NO. 5034
(N20)NGG	2	98349695	+	AGGTGACGGCAGCAGGCGGGCGG	1	1	57	SEQ ID NO. 5035
(N20)NGG	2	98349696	+	GGTGACGGCAGCAGGCGGGCGGG	1	3	65	SEQ ID NO. 5036
(N20)NGG	2	98349699	+	GACGGCAGCAGGCGGGCGGGCGG	1	8	90	SEQ ID NO. 5037
(N20)NGG	2	98349573	-	CTCCACCAGCTGCAGGGAGCAGG	1	9	119	SEQ ID NO. 5038
(N20)NGG	2	98349579	-	CAGATACTCCACCAGCTGCAGGG	1	6	51	SEQ ID NO. 5039
(N20)NGG	2	98349580	-	TCAGATACTCCACCAGCTGCAGG	1	2	30	SEQ ID NO. 5040
(N20)NGG	2	98349631	-	TGTTGGGGCAGGCCTCCTTCAGG	1	3	55	SEQ ID NO. 5041
(N20)NGG	2	98349642	-	GCTGGCACTGCTGTTGGGGCAGG	2	14	102	SEQ ID NO. 5042
(N20)NGG	2	98349646	-	CGTTGCTGGCACTGCTGTTGGGG	1	3	37	SEQ ID NO. 5043
(N20)NGG	2	98349647	-	GCGTTGCTGGCACTGCTGTTGGG	1	2	10	SEQ ID NO. 5044
(N20)NGG	2	98349648	-	GGCGTTGCTGGCACTGCTGTTGG	1	2	37	SEQ ID NO. 5045
(N20)NGG	2	98349660	-	GCCGTCACCTGAGGCGTTGCTGG	1	3	7	SEQ ID NO. 5046
(N20)NGG	2	98349669	-	CCGCCTGCTGCCGTCACCTGAGG	1	2	41	SEQ ID NO. 5047
(N20)NGG	2	98349759	+	ACTGTCCCTTCTGCTCCCCCAGG	2	2	83	SEQ ID NO. 5048
(N20)NGG	2	98349760	+	CTGTCCCTTCTGCTCCCCCAGGG	1	15	191	SEQ ID NO. 5049
(N20)NGG	2	98349761	+	TGTCCCTTCTGCTCCCCCAGGGG	1	9	119	SEQ ID NO. 5050
(N20)NGG	2	98349814	+	CCACGTTGACTCATGTGAGTTGG	1	1	15	SEQ ID NO. 5051
(N20)NGG	2	98349815	+	CACGTTGACTCATGTGAGTTGGG	1	1	21	SEQ ID NO. 5052
(N20)NGG	2	98349816	+	ACGTTGACTCATGTGAGTTGGGG	1	1	11	SEQ ID NO. 5053
(N20)NGG	2	98349817	+	CGTTGACTCATGTGAGTTGGGGG	1	1	14	SEQ ID NO. 5054
(N20)NGG	2	98349824	+	TCATGTGAGTTGGGGGCACCTGG	1	3	19	SEQ ID NO. 5055
(N20)NGG	2	98349742	-	CAGCCCCTGGGGGAGCAGAAGGG	3	9	111	SEQ ID NO. 5056
(N20)NGG	2	98349743	-	GCAGCCCCTGGGGGAGCAGAAGG	1	17	144	SEQ ID NO. 5057
(N20)NGG	2	98349752	-	GTGGGAGCAGCAGCCCCTGGGGG	2	13	169	SEQ ID NO. 5058
(N20)NGG	2	98349753	-	TGTGGGAGCAGCAGCCCCTGGGG	4	17	142	SEQ ID NO. 5059
(N20)NGG	2	98349754	-	GTGTGGGAGCAGCAGCCCCTGGG	2	10	79	SEQ ID NO. 5060
(N20)NGG	2	98349755	-	AGTGTGGGAGCAGCAGCCCCTGG	1	7	80	SEQ ID NO. 5061

FIG. 15 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	2	98349770	-	GATGGGTGGGCTGGGAGTGTGGG	1	13	158	SEQ ID NO. 5062
(N20)NGG	2	98349771	-	GGATGGGTGGGCTGGGAGTGTGG	3	30	323	SEQ ID NO. 5063
(N20)NGG	2	98349778	-	TCAACGTGGATGGGTGGGCTGGG	1	3	15	SEQ ID NO. 5064
(N20)NGG	2	98349779	-	GTCAACGTGGATGGGTGGGCTGG	1	1	22	SEQ ID NO. 5065
(N20)NGG	2	98349783	-	ATGAGTCAACGTGGATGGGTGGG	1	2	16	SEQ ID NO. 5066
(N20)NGG	2	98349784	-	CATGAGTCAACGTGGATGGGTGG	1	2	20	SEQ ID NO. 5067
(N20)NGG	2	98349787	-	TCACATGAGTCAACGTGGATGGG	1	2	22	SEQ ID NO. 5068
(N20)NGG	2	98349788	-	CTCACATGAGTCAACGTGGATGG	1	1	29	SEQ ID NO. 5069
(N20)NGG	2	98349792	-	CCAACTCACATGAGTCAACGTGG	1	1	14	SEQ ID NO. 5070
(N20)NGG	2	98350040	+	ATCGACACCCTCAACTCAGATGG	1	1	8	SEQ ID NO. 5071
(N20)NGG	2	98350058	+	GATGGATACACCCCTGAGCCAGG	1	2	16	SEQ ID NO. 5072
(N20)NGG	2	98350065	+	ACACCCCTGAGCCAGGTGAGCGG	2	9	67	SEQ ID NO. 5073
(N20)NGG	2	98350066	+	CACCCCTGAGCCAGGTGAGCGGG	1	7	84	SEQ ID NO. 5074
(N20)NGG	2	98350072	+	TGAGCCAGGTGAGCGGGCAGAGG	3	13	83	SEQ ID NO. 5075
(N20)NGG	2	98350075	+	GCCAGGTGAGCGGGCAGAGGTGG	1	7	113	SEQ ID NO. 5076
(N20)NGG	2	98350076	+	CCAGGTGAGCGGGCAGAGGTGGG	1	5	102	SEQ ID NO. 5077
(N20)NGG	2	98350077	+	CAGGTGAGCGGGCAGAGGTGGGG	1	21	161	SEQ ID NO. 5078
(N20)NGG	2	98349982	-	TAAAGGCCACAGGGTCAGCAAGG	1	5	59	SEQ ID NO. 5079
(N20)NGG	2	98349991	-	CTCTGAGGCTAAAGGCCACAGGG	1	1	57	SEQ ID NO. 5080
(N20)NGG	2	98349992	-	TCTCTGAGGCTAAAGGCCACAGG	1	5	54	SEQ ID NO. 5081
(N20)NGG	2	98349999	-	CGATTCGTCTCTGAGGCTAAAGG	1	1	6	SEQ ID NO. 5082
(N20)NGG	2	98350006	-	AGGGTGTCGATTCGTCTCTGAGG	1	1	9	SEQ ID NO. 5083
(N20)NGG	2	98350025	-	GGTGTATCCATCTGAGTTGAGGG	1	2	18	SEQ ID NO. 5084
(N20)NGG	2	98350026	-	GGGTGTATCCATCTGAGTTGAGG	2	2	13	SEQ ID NO. 5085
(N20)NGG	2	98350046	-	TGCCCGCTCACCTGGCTCAGGGG	2	10	61	SEQ ID NO. 5086
(N20)NGG	2	98350047	-	CTGCCCGCTCACCTGGCTCAGGG	5	7	48	SEQ ID NO. 5087
(N20)NGG	2	98350048	-	TCTGCCCGCTCACCTGGCTCAGG	1	3	45	SEQ ID NO. 5088
(N20)NGG	2	98350054	-	CCCACCTCTGCCCGCTCACCTGG	1	6	108	SEQ ID NO. 5089
(N20)NGG	2	98351010	+	TAACGTCCCCAGACAAACCGCGG	1	1	10	SEQ ID NO. 5090
(N20)NGG	2	98351023	+	CAAACCGCGGCCGATGCCCATGG	1	1	3	SEQ ID NO. 5091
(N20)NGG	2	98351062	+	GAGCCCCTACAGCGACCCAGAGG	1	4	27	SEQ ID NO. 5092
(N20)NGG	2	98351071	+	CAGCGACCCAGAGGAGCTCAAGG	2	2	45	SEQ ID NO. 5093
(N20)NGG	2	98351126	+	CTCATAGCTGACATTGAACTTGG	1	9	44	SEQ ID NO. 5094

FIG. 15 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	2	98351132	+	GCTGACATTGAACTTGGCTGCGG	1	5	51	SEQ ID NO. 5095
(N20)NGG	2	98351141	+	GAACTTGGCTGCGGCAACTTTGG	1	1	18	SEQ ID NO. 5096
(N20)NGG	2	98351155	+	CAACTTTGGCTCAGTGCGCCAGG	1	1	10	SEQ ID NO. 5097
(N20)NGG	2	98351156	+	AACTTTGGCTCAGTGCGCCAGGG	1	1	9	SEQ ID NO. 5098
(N20)NGG	2	98351180	+	GTGTACCGCATGCGCAAGTATGG	1	1	2	SEQ ID NO. 5099
(N20)NGG	2	98351195	+	AAGTATGGCCGCCCCTGCCGTGG	1	1	5	SEQ ID NO. 5100
(N20)NGG	2	98351198	+	TATGGCCGCCCCTGCCGTGGTGG	1	1	8	SEQ ID NO. 5101
(N20)NGG	2	98351199	+	ATGGCCGCCCCTGCCGTGGTGGG	1	1	11	SEQ ID NO. 5102
(N20)NGG	2	98350965	-	TGCGTGCTGGGCACACACAGCGG	2	11	66	SEQ ID NO. 5103
(N20)NGG	2	98350977	-	CTGGGGACGTTATGCGTGCTGGG	1	1	5	SEQ ID NO. 5104
(N20)NGG	2	98350978	-	TCTGGGGACGTTATGCGTGCTGG	1	1	4	SEQ ID NO. 5105
(N20)NGG	2	98350994	-	CATCGGCCGCGGTTTGTCTGGGG	1	1	4	SEQ ID NO. 5106
(N20)NGG	2	98350995	-	GCATCGGCCGCGGTTTGTCTGGG	1	1	1	SEQ ID NO. 5107
(N20)NGG	2	98350996	-	GGCATCGGCCGCGGTTTGTCTGG	1	1	4	SEQ ID NO. 5108
(N20)NGG	2	98351005	-	GTGTCCATGGGCATCGGCCGCGG	1	2	14	SEQ ID NO. 5109
(N20)NGG	2	98351011	-	ACGCTCGTGTCCATGGGCATCGG	1	3	8	SEQ ID NO. 5110
(N20)NGG	2	98351017	-	TCATACACGCTCGTGTCCATGGG	1	1	3	SEQ ID NO. 5111
(N20)NGG	2	98351018	-	CTCATACACGCTCGTGTCCATGG	1	1	4	SEQ ID NO. 5112
(N20)NGG	2	98351043	-	GCTCCTCTGGGTCGCTGTAGGGG	1	1	17	SEQ ID NO. 5113
(N20)NGG	2	98351044	-	AGCTCCTCTGGGTCGCTGTAGGG	1	1	14	SEQ ID NO. 5114
(N20)NGG	2	98351045	-	GAGCTCCTCTGGGTCGCTGTAGG	1	1	18	SEQ ID NO. 5115
(N20)NGG	2	98351055	-	TCTTGTCCTTGAGCTCCTCTGGG	2	4	50	SEQ ID NO. 5116
(N20)NGG	2	98351056	-	TTCTTGTCCTTGAGCTCCTCTGG	1	4	76	SEQ ID NO. 5117
(N20)NGG	2	98351085	-	TGAGGAGGTTATCGCGCTTCAGG	1	1	5	SEQ ID NO. 5118
(N20)NGG	2	98351100	-	GTTCAATGTCAGCTATGAGGAGG	2	2	39	SEQ ID NO. 5119
(N20)NGG	2	98351103	-	CAAGTTCAATGTCAGCTATGAGG	1	4	82	SEQ ID NO. 5120
(N20)NGG	2	98351151	-	TGCGCATGCGGTACACGCCCTGG	1	1	6	SEQ ID NO. 5121
(N20)NGG	2	98351163	-	GGCGGCCATACTTGCGCATGCGG	1	1	3	SEQ ID NO. 5122
(N20)NGG	2	98351712	+	CTCCCGTGGCCGGGTCGGGCAGG	1	4	22	SEQ ID NO. 5123
(N20)NGG	2	98351728	+	GGGCAGGAAGCAGATCGACGTGG	1	1	11	SEQ ID NO. 5124
(N20)NGG	2	98351737	+	GCAGATCGACGTGGCCATCAAGG	1	1	12	SEQ ID NO. 5125
(N20)NGG	2	98351749	+	GGCCATCAAGGTGCTGAAGCAGG	1	3	46	SEQ ID NO. 5126
(N20)NGG	2	98351750	+	GCCATCAAGGTGCTGAAGCAGGG	1	4	59	SEQ ID NO. 5127

FIG. 15 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	2	98351755	+	CAAGGTGCTGAAGCAGGGCACGG	1	6	83	SEQ ID NO. 5128
(N20)NGG	2	98351761	+	GCTGAAGCAGGGCACGGAGAAGG	1	5	75	SEQ ID NO. 5129
(N20)NGG	2	98351770	+	GGGCACGGAGAAGGCAGACACGG	2	6	109	SEQ ID NO. 5130
(N20)NGG	2	98351788	+	CACGGAAGAGATGATGCGCGAGG	1	1	6	SEQ ID NO. 5131
(N20)NGG	2	98351809	+	GGCGCAGATCATGCACCAGCTGG	1	1	11	SEQ ID NO. 5132
(N20)NGG	2	98351829	+	TGGACAACCCCTACATCGTGCGG	2	2	12	SEQ ID NO. 5133
(N20)NGG	2	98351837	+	CCCTACATCGTGCGGCTCATTGG	1	2	8	SEQ ID NO. 5134
(N20)NGG	2	98351848	+	GCGGCTCATTGGCGTCTGCCAGG	1	1	7	SEQ ID NO. 5135
(N20)NGG	2	98351854	+	CATTGGCGTCTGCCAGGCCGAGG	1	1	13	SEQ ID NO. 5136
(N20)NGG	2	98351866	+	CCAGGCCGAGGCCCTCATGCTGG	1	4	40	SEQ ID NO. 5137
(N20)NGG	2	98351872	+	CGAGGCCCTCATGCTGGTCATGG	1	5	28	SEQ ID NO. 5138
(N20)NGG	2	98351878	+	CCTCATGCTGGTCATGGAGATGG	1	3	47	SEQ ID NO. 5139
(N20)NGG	2	98351882	+	ATGCTGGTCATGGAGATGGCTGG	1	5	46	SEQ ID NO. 5140
(N20)NGG	2	98351883	+	TGCTGGTCATGGAGATGGCTGGG	1	2	54	SEQ ID NO. 5141
(N20)NGG	2	98351884	+	GCTGGTCATGGAGATGGCTGGGG	1	6	80	SEQ ID NO. 5142
(N20)NGG	2	98351885	+	CTGGTCATGGAGATGGCTGGGGG	1	4	70	SEQ ID NO. 5143
(N20)NGG	2	98351888	+	GTCATGGAGATGGCTGGGGGCGG	1	7	115	SEQ ID NO. 5144
(N20)NGG	2	98351889	+	TCATGGAGATGGCTGGGGGCGGG	1	8	89	SEQ ID NO. 5145
(N20)NGG	2	98351908	+	CGGGCCGCTGCACAAGTTCCTGG	1	2	7	SEQ ID NO. 5146
(N20)NGG	2	98351912	+	CCGCTGCACAAGTTCCTGGTCGG	1	1	14	SEQ ID NO. 5147
(N20)NGG	2	98351919	+	ACAAGTTCCTGGTCGGCAAGAGG	1	2	23	SEQ ID NO. 5148
(N20)NGG	2	98351929	+	GGTCGGCAAGAGGTGAGCACCGG	1	5	15	SEQ ID NO. 5149
(N20)NGG	2	98351930	+	GTCGGCAAGAGGTGAGCACCGGG	1	1	16	SEQ ID NO. 5150
(N20)NGG	2	98351933	+	GGCAAGAGGTGAGCACCGGGTGG	1	6	79	SEQ ID NO. 5151
(N20)NGG	2	98351934	+	GCAAGAGGTGAGCACCGGGTGGG	2	52	403	SEQ ID NO. 5152
(N20)NGG	2	98351939	+	AGGTGAGCACCGGGTGGGCCCGG	2	3	70	SEQ ID NO. 5153
(N20)NGG	2	98351689	-	CTGCCCGACCCGGCCACGGGAGG	1	4	29	SEQ ID NO. 5154
(N20)NGG	2	98351692	-	TTCCTGCCCGACCCGGCCACGGG	1	3	22	SEQ ID NO. 5155
(N20)NGG	2	98351693	-	CTTCCTGCCCGACCCGGCCACGG	1	2	31	SEQ ID NO. 5156
(N20)NGG	2	98351699	-	GATCTGCTTCCTGCCCGACCCGG	1	2	16	SEQ ID NO. 5157
(N20)NGG	2	98351729	-	GCCCTGCTTCAGCACCTTGATGG	1	12	54	SEQ ID NO. 5158
(N20)NGG	2	98351802	-	CGATGTAGGGGTTGTCCAGCTGG	1	2	14	SEQ ID NO. 5159
(N20)NGG	2	98351814	-	CAATGAGCCGCACGATGTAGGGG	1	2	10	SEQ ID NO. 5160

FIG. 15 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	2	98351815	-	CCAATGAGCCGCACGATGTAGGG	1	2	7	SEQ ID NO. 5161
(N20)NGG	2	98351816	-	GCCAATGAGCCGCACGATGTAGG	1	2	6	SEQ ID NO. 5162
(N20)NGG	2	98351844	-	CCAGCATGAGGGCCTCGGCCTGG	2	4	42	SEQ ID NO. 5163
(N20)NGG	2	98351849	-	CATGACCAGCATGAGGGCCTCGG	5	9	61	SEQ ID NO. 5164
(N20)NGG	2	98351855	-	CATCTCCATGACCAGCATGAGGG	1	6	51	SEQ ID NO. 5165
(N20)NGG	2	98351856	-	CCATCTCCATGACCAGCATGAGG	1	3	58	SEQ ID NO. 5166
(N20)NGG	2	98351890	-	CCGACCAGGAACTTGTGCAGCGG	1	1	11	SEQ ID NO. 5167
(N20)NGG	2	98351904	-	GTGCTCACCTCTTGCCGACCAGG	1	2	13	SEQ ID NO. 5168
(N20)NGG	2	98353935	+	CCCGCCTTCCCCGCCACCCCAGG	1	18	237	SEQ ID NO. 5169
(N20)NGG	2	98353936	+	CCGCCTTCCCCGCCACCCCAGGG	1	12	127	SEQ ID NO. 5170
(N20)NGG	2	98353939	+	CCTTCCCCGCCACCCCAGGGAGG	1	18	120	SEQ ID NO. 5171
(N20)NGG	2	98353960	+	GGAGATCCCTGTGAGCAATGTGG	1	2	40	SEQ ID NO. 5172
(N20)NGG	2	98353978	+	TGTGGCCGAGCTGCTGCACCAGG	1	4	32	SEQ ID NO. 5173
(N20)NGG	2	98353987	+	GCTGCTGCACCAGGTGTCCATGG	1	4	54	SEQ ID NO. 5174
(N20)NGG	2	98353988	+	CTGCTGCACCAGGTGTCCATGGG	1	3	44	SEQ ID NO. 5175
(N20)NGG	2	98353989	+	TGCTGCACCAGGTGTCCATGGGG	1	2	43	SEQ ID NO. 5176
(N20)NGG	2	98354002	+	GTCCATGGGGATGAAGTACCTGG	1	1	14	SEQ ID NO. 5177
(N20)NGG	2	98354005	+	CATGGGGATGAAGTACCTGGAGG	1	5	46	SEQ ID NO. 5178
(N20)NGG	2	98354032	+	GAACTTTGTGCACCGTGACCTGG	2	5	25	SEQ ID NO. 5179
(N20)NGG	2	98354035	+	CTTTGTGCACCGTGACCTGGCGG	1	3	28	SEQ ID NO. 5180
(N20)NGG	2	98354053	+	GGCGGCCCGCAACGTCCTGCTGG	1	1	10	SEQ ID NO. 5181
(N20)NGG	2	98354061	+	GCAACGTCCTGCTGGTTAACCGG	1	1	5	SEQ ID NO. 5182
(N20)NGG	2	98354087	+	TACGCCAAGATCAGCGACTTTGG	1	2	4	SEQ ID NO. 5183
(N20)NGG	2	98354104	+	CTTTGGCCTCTCCAAAGCACTGG	3	15	103	SEQ ID NO. 5184
(N20)NGG	2	98354105	+	TTTGGCCTCTCCAAAGCACTGGG	2	15	169	SEQ ID NO. 5185
(N20)NGG	2	98353912	-	CTGGGGTGGCGGGGAAGGCGGGG	2	10	188	SEQ ID NO. 5186
(N20)NGG	2	98353913	-	CCTGGGGTGGCGGGGAAGGCGGG	1	11	172	SEQ ID NO. 5187
(N20)NGG	2	98353914	-	CCCTGGGGTGGCGGGGAAGGCGG	1	13	216	SEQ ID NO. 5188
(N20)NGG	2	98353917	-	CCTCCCTGGGGTGGCGGGGAAGG	1	14	129	SEQ ID NO. 5189
(N20)NGG	2	98353921	-	ATCTCCTCCCTGGGGTGGCGGGG	1	3	59	SEQ ID NO. 5190
(N20)NGG	2	98353922	-	GATCTCCTCCCTGGGGTGGCGGG	1	3	48	SEQ ID NO. 5191
(N20)NGG	2	98353923	-	GGATCTCCTCCCTGGGGTGGCGG	1	8	75	SEQ ID NO. 5192
(N20)NGG	2	98353926	-	CAGGGATCTCCTCCCTGGGGTGG	3	6	79	SEQ ID NO. 5193

FIG. 15 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	2	98353929	-	TCACAGGGATCTCCTCCCTGGGG	1	4	63	SEQ ID NO. 5194
(N20)NGG	2	98353930	-	CTCACAGGGATCTCCTCCCTGGG	1	4	54	SEQ ID NO. 5195
(N20)NGG	2	98353931	-	GCTCACAGGGATCTCCTCCCTGG	1	3	66	SEQ ID NO. 5196
(N20)NGG	2	98353944	-	GCTCGGCCACATTGCTCACAGGG	1	2	15	SEQ ID NO. 5197
(N20)NGG	2	98353945	-	AGCTCGGCCACATTGCTCACAGG	1	2	11	SEQ ID NO. 5198
(N20)NGG	2	98353961	-	GGACACCTGGTGCAGCAGCTCGG	1	1	44	SEQ ID NO. 5199
(N20)NGG	2	98353974	-	ACTTCATCCCCATGGACACCTGG	1	1	34	SEQ ID NO. 5200
(N20)NGG	2	98353982	-	CTCCAGGTACTTCATCCCCATGG	1	3	62	SEQ ID NO. 5201
(N20)NGG	2	98353998	-	GCACAAAGTTCTTCTCCTCCAGG	1	1	59	SEQ ID NO. 5202
(N20)NGG	2	98354022	-	CGTTGCGGGCCGCCAGGTCACGG	1	4	17	SEQ ID NO. 5203
(N20)NGG	2	98354028	-	GCAGGACGTTGCGGGCCGCCAGG	1	2	12	SEQ ID NO. 5204
(N20)NGG	2	98354036	-	GTTAACCAGCAGGACGTTGCGGG	1	1	8	SEQ ID NO. 5205
(N20)NGG	2	98354037	-	GGTTAACCAGCAGGACGTTGCGG	1	2	13	SEQ ID NO. 5206
(N20)NGG	2	98354046	-	CGTAGTGCCGGTTAACCAGCAGG	1	1	4	SEQ ID NO. 5207
(N20)NGG	2	98354058	-	CGCTGATCTTGGCGTAGTGCCGG	1	1	5	SEQ ID NO. 5208
(N20)NGG	2	98354069	-	GAGGCCAAAGTCGCTGATCTTGG	1	4	21	SEQ ID NO. 5209
(N20)NGG	2	98354088	-	CGGCACCCAGTGCTTTGGAGAGG	1	1	22	SEQ ID NO. 5210
(N20)NGG	2	98354093	-	GTCGTCGGCACCCAGTGCTTTGG	1	1	2	SEQ ID NO. 5211
(N20)NGG	2	98354108	-	TACAGTGTAGTAGCTGTCGTCGG	1	1	6	SEQ ID NO. 5212
(N20)NGG	2	98354219	+	AGCAGCATCTCCCCCTCCCCAGG	1	12	172	SEQ ID NO. 5213
(N20)NGG	2	98354232	+	CCTCCCCAGGCCCGCTCAGCAGG	2	5	89	SEQ ID NO. 5214
(N20)NGG	2	98354233	+	CTCCCCAGGCCCGCTCAGCAGGG	2	3	65	SEQ ID NO. 5215
(N20)NGG	2	98354239	+	AGGCCCGCTCAGCAGGGAAGTGG	1	9	57	SEQ ID NO. 5216
(N20)NGG	2	98354251	+	CAGGGAAGTGGCCGCTCAAGTGG	1	2	25	SEQ ID NO. 5217
(N20)NGG	2	98354305	+	TCTCCAGCCGCAGCGATGTCTGG	1	1	16	SEQ ID NO. 5218
(N20)NGG	2	98354313	+	CGCAGCGATGTCTGGAGCTATGG	1	3	16	SEQ ID NO. 5219
(N20)NGG	2	98354314	+	GCAGCGATGTCTGGAGCTATGGG	1	1	18	SEQ ID NO. 5220
(N20)NGG	2	98354315	+	CAGCGATGTCTGGAGCTATGGGG	1	2	22	SEQ ID NO. 5221
(N20)NGG	2	98354326	+	GGAGCTATGGGGTCACCATGTGG	1	4	27	SEQ ID NO. 5222
(N20)NGG	2	98354327	+	GAGCTATGGGGTCACCATGTGGG	1	4	146	SEQ ID NO. 5223
(N20)NGG	2	98354330	+	CTATGGGGTCACCATGTGGGAGG	1	4	33	SEQ ID NO. 5224
(N20)NGG	2	98354343	+	ATGTGGGAGGCCTTGTCCTACGG	1	4	43	SEQ ID NO. 5225
(N20)NGG	2	98354360	+	CTACGGCCAGAAGCCCTACAAGG	1	1	15	SEQ ID NO. 5226

FIG. 15 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	2	98354364	+	GGCCAGAAGCCCTACAAGGCAGG	1	1	28	SEQ ID NO. 5227
(N20)NGG	2	98354369	+	GAAGCCCTACAAGGCAGGCGCGG	1	1	29	SEQ ID NO. 5228
(N20)NGG	2	98354370	+	AAGCCCTACAAGGCAGGCGCGGG	1	3	29	SEQ ID NO. 5229
(N20)NGG	2	98354376	+	TACAAGGCAGGCGCGGGCAGAGG	1	1	24	SEQ ID NO. 5230
(N20)NGG	2	98354380	+	AGGCAGGCGCGGGCAGAGGCAGG	2	10	164	SEQ ID NO. 5231
(N20)NGG	2	98354383	+	CAGGCGCGGGCAGAGGCAGGTGG	1	13	325	SEQ ID NO. 5232
(N20)NGG	2	98354384	+	AGGCGCGGGCAGAGGCAGGTGGG	2	7	89	SEQ ID NO. 5233
(N20)NGG	2	98354195	-	TGGGGAGGGGGAGATGCTGCTGG	2	16	233	SEQ ID NO. 5234
(N20)NGG	2	98354207	-	GCTGAGCGGGCCTGGGGAGGGGG	1	11	178	SEQ ID NO. 5235
(N20)NGG	2	98354208	-	TGCTGAGCGGGCCTGGGGAGGGG	1	6	97	SEQ ID NO. 5236
(N20)NGG	2	98354209	-	CTGCTGAGCGGGCCTGGGGAGGG	1	8	98	SEQ ID NO. 5237
(N20)NGG	2	98354210	-	CCTGCTGAGCGGGCCTGGGGAGG	2	6	88	SEQ ID NO. 5238
(N20)NGG	2	98354213	-	TTCCCTGCTGAGCGGGCCTGGGG	2	5	35	SEQ ID NO. 5239
(N20)NGG	2	98354214	-	CTTCCCTGCTGAGCGGGCCTGGG	1	4	29	SEQ ID NO. 5240
(N20)NGG	2	98354215	-	ACTTCCCTGCTGAGCGGGCCTGG	2	3	19	SEQ ID NO. 5241
(N20)NGG	2	98354220	-	CGGCCACTTCCCTGCTGAGCGGG	1	7	53	SEQ ID NO. 5242
(N20)NGG	2	98354221	-	GCGGCCACTTCCCTGCTGAGCGG	1	2	38	SEQ ID NO. 5243
(N20)NGG	2	98354240	-	TCGGGTGCGTACCACTTGAGCGG	1	1	3	SEQ ID NO. 5244
(N20)NGG	2	98354258	-	TTGCGGAAGTTGATGCATTCGGG	1	1	8	SEQ ID NO. 5245
(N20)NGG	2	98354259	-	CTTGCGGAAGTTGATGCATTCGG	1	1	14	SEQ ID NO. 5246
(N20)NGG	2	98354275	-	CGCTGCGGCTGGAGAACTTGCGG	1	2	28	SEQ ID NO. 5247
(N20)NGG	2	98354286	-	GCTCCAGACATCGCTGCGGCTGG	1	1	18	SEQ ID NO. 5248
(N20)NGG	2	98354290	-	CATAGCTCCAGACATCGCTGCGG	1	3	32	SEQ ID NO. 5249
(N20)NGG	2	98354319	-	GTAGGACAAGGCCTCCCACATGG	1	5	35	SEQ ID NO. 5250
(N20)NGG	2	98354331	-	GGGCTTCTGGCCGTAGGACAAGG	1	1	13	SEQ ID NO. 5251
(N20)NGG	2	98354337	-	CTTGTAGGGCTTCTGGCCGTAGG	1	2	30	SEQ ID NO. 5252
(N20)NGG	2	98354344	-	CGCCTGCCTTGTAGGGCTTCTGG	1	4	32	SEQ ID NO. 5253
(N20)NGG	2	98354351	-	CTGCCCGCGCCTGCCTTGTAGGG	1	1	16	SEQ ID NO. 5254
(N20)NGG	2	98354352	-	TCTGCCCGCGCCTGCCTTGTAGG	1	1	13	SEQ ID NO. 5255
(N20)NGG	2	98354467	+	CGGCTTGAGCAGAAGATGAAAGG	1	1	28	SEQ ID NO. 5256
(N20)NGG	2	98354468	+	GGCTTGAGCAGAAGATGAAAGGG	1	4	67	SEQ ID NO. 5257
(N20)NGG	2	98354472	+	TGAGCAGAAGATGAAAGGGCCGG	1	13	112	SEQ ID NO. 5258
(N20)NGG	2	98354475	+	GCAGAAGATGAAAGGGCCGGAGG	1	5	89	SEQ ID NO. 5259

FIG. 15 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	2	98354481	+	GATGAAAGGGCCGGAGGTCATGG	1	3	32	SEQ ID NO. 5260
(N20)NGG	2	98354496	+	GGTCATGGCCTTCATCGAGCAGG	1	1	11	SEQ ID NO. 5261
(N20)NGG	2	98354497	+	GTCATGGCCTTCATCGAGCAGGG	2	3	15	SEQ ID NO. 5262
(N20)NGG	2	98354504	+	CCTTCATCGAGCAGGGCAAGCGG	1	1	22	SEQ ID NO. 5263
(N20)NGG	2	98354508	+	CATCGAGCAGGGCAAGCGGATGG	1	1	9	SEQ ID NO. 5264
(N20)NGG	2	98354561	+	ACGCACTCATGAGTGACTGCTGG	1	2	16	SEQ ID NO. 5265
(N20)NGG	2	98354583	+	GATCTACAAGTGAGTGCCAGTGG	1	1	24	SEQ ID NO. 5266
(N20)NGG	2	98354584	+	ATCTACAAGTGAGTGCCAGTGGG	1	1	15	SEQ ID NO. 5267
(N20)NGG	2	98354585	+	TCTACAAGTGAGTGCCAGTGGGG	1	3	24	SEQ ID NO. 5268
(N20)NGG	2	98354588	+	ACAAGTGAGTGCCAGTGGGGAGG	1	5	47	SEQ ID NO. 5269
(N20)NGG	2	98354589	+	CAAGTGAGTGCCAGTGGGGAGGG	2	8	87	SEQ ID NO. 5270
(N20)NGG	2	98354590	+	AAGTGAGTGCCAGTGGGGAGGGG	1	9	90	SEQ ID NO. 5271
(N20)NGG	2	98354442	-	TTCATCTTCTGCTCAAGCCGGGG	1	2	24	SEQ ID NO. 5272
(N20)NGG	2	98354443	-	TTTCATCTTCTGCTCAAGCCGGG	1	2	63	SEQ ID NO. 5273
(N20)NGG	2	98354444	-	CTTTCATCTTCTGCTCAAGCCGG	1	4	60	SEQ ID NO. 5274
(N20)NGG	2	98354469	-	TCGATGAAGGCCATGACCTCCGG	1	2	22	SEQ ID NO. 5275
(N20)NGG	2	98354482	-	CCGCTTGCCCTGCTCGATGAAGG	1	1	8	SEQ ID NO. 5276
(N20)NGG	2	98354513	-	GTTCGGGTGGACACTCTGGTGGG	1	2	11	SEQ ID NO. 5277
(N20)NGG	2	98354514	-	AGTTCGGGTGGACACTCTGGTGG	1	1	12	SEQ ID NO. 5278
(N20)NGG	2	98354517	-	TACAGTTCGGGTGGACACTCTGG	1	1	6	SEQ ID NO. 5279
(N20)NGG	2	98354526	-	ATGAGTGCGTACAGTTCGGGTGG	1	3	8	SEQ ID NO. 5280
(N20)NGG	2	98354529	-	CTCATGAGTGCGTACAGTTCGGG	1	1	10	SEQ ID NO. 5281
(N20)NGG	2	98354530	-	ACTCATGAGTGCGTACAGTTCGG	1	1	8	SEQ ID NO. 5282
(N20)NGG	2	98355837	+	GGATGTACCCCACGCCCCACAGG	1	1	14	SEQ ID NO. 5283
(N20)NGG	2	98355840	+	TGTACCCCACGCCCCACAGGTGG	1	2	36	SEQ ID NO. 5284
(N20)NGG	2	98355841	+	GTACCCCACGCCCCACAGGTGGG	1	1	27	SEQ ID NO. 5285
(N20)NGG	2	98355844	+	CCCCACGCCCCACAGGTGGGAGG	1	6	68	SEQ ID NO. 5286
(N20)NGG	2	98355868	+	TCGCCCCGACTTCCTGACCGTGG	1	1	11	SEQ ID NO. 5287
(N20)NGG	2	98355901	+	GCGAGCCTGTTACTACAGCCTGG	1	2	9	SEQ ID NO. 5288
(N20)NGG	2	98355910	+	TTACTACAGCCTGGCCAGCAAGG	1	23	811	SEQ ID NO. 5289
(N20)NGG	2	98355913	+	CTACAGCCTGGCCAGCAAGGTGG	1	8	291	SEQ ID NO. 5290
(N20)NGG	2	98355917	+	AGCCTGGCCAGCAAGGTGGAAGG	1	21	551	SEQ ID NO. 5291
(N20)NGG	2	98355918	+	GCCTGGCCAGCAAGGTGGAAGGG	1	18	453	SEQ ID NO. 5292

FIG. 15 cont.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches	
(N20)NGG	2	98355926	+	AGCAAGGTGGAAGGGCCCCCAGG	1	3	41	SEQ ID NO. 5293
(N20)NGG	2	98355940	+	GCCCCCAGGCAGCACACAGAAGG	3	6	109	SEQ ID NO. 5294
(N20)NGG	2	98355946	+	AGGCAGCACACAGAAGGCTGAGG	1	9	127	SEQ ID NO. 5295
(N20)NGG	2	98355976	+	TGCCTGAGCTCCCGCTGCCCAGG	2	5	59	SEQ ID NO. 5296
(N20)NGG	2	98355977	+	GCCTGAGCTCCCGCTGCCCAGGG	1	10	89	SEQ ID NO. 5297
(N20)NGG	2	98355978	+	CCTGAGCTCCCGCTGCCCAGGGG	1	6	83	SEQ ID NO. 5298
(N20)NGG	2	98355812	-	GTGGGGCGTGGGGTACATCCAGG	1	1	28	SEQ ID NO. 5299
(N20)NGG	2	98355822	-	CCTCCCACCTGTGGGGCGTGGGG	1	3	58	SEQ ID NO. 5300
(N20)NGG	2	98355823	-	TCCTCCCACCTGTGGGGCGTGGG	1	2	33	SEQ ID NO. 5301
(N20)NGG	2	98355824	-	ATCCTCCCACCTGTGGGGCGTGG	1	2	30	SEQ ID NO. 5302
(N20)NGG	2	98355829	-	GGGCGATCCTCCCACCTGTGGGG	1	1	27	SEQ ID NO. 5303
(N20)NGG	2	98355830	-	GGGGCGATCCTCCCACCTGTGGG	1	2	16	SEQ ID NO. 5304
(N20)NGG	2	98355831	-	CGGGGCGATCCTCCCACCTGTGG	1	2	28	SEQ ID NO. 5305
(N20)NGG	2	98355849	-	GCTCCACGGTCAGGAAGTCGGGG	1	1	13	SEQ ID NO. 5306
(N20)NGG	2	98355850	-	TGCTCCACGGTCAGGAAGTCGGG	1	2	15	SEQ ID NO. 5307
(N20)NGG	2	98355851	-	CTGCTCCACGGTCAGGAAGTCGG	1	2	26	SEQ ID NO. 5308
(N20)NGG	2	98355858	-	GCATGCGCTGCTCCACGGTCAGG	1	2	9	SEQ ID NO. 5309
(N20)NGG	2	98355863	-	GGCTCGCATGCGCTGCTCCACGG	1	2	11	SEQ ID NO. 5310
(N20)NGG	2	98355884	-	GCTGGCCAGGCTGTAGTAACAGG	1	2	38	SEQ ID NO. 5311
(N20)NGG	2	98355897	-	GCCCTTCCACCTTGCTGGCCAGG	1	5	65	SEQ ID NO. 5312
(N20)NGG	2	98355902	-	TGGGGGCCCTTCCACCTTGCTGG	1	3	41	SEQ ID NO. 5313
(N20)NGG	2	98355919	-	GCCTTCTGTGTGCTGCCTGGGGG	1	5	102	SEQ ID NO. 5314
(N20)NGG	2	98355920	-	AGCCTTCTGTGTGCTGCCTGGGG	1	6	93	SEQ ID NO. 5315
(N20)NGG	2	98355921	-	CAGCCTTCTGTGTGCTGCCTGGG	1	7	119	SEQ ID NO. 5316
(N20)NGG	2	98355922	-	TCAGCCTTCTGTGTGCTGCCTGG	1	5	76	SEQ ID NO. 5317
(N20)NGG	2	98355950	-	GGCAGCGGGAGCTCAGGCACAGG	1	6	57	SEQ ID NO. 5318
(N20)NGG	2	98355956	-	CCCCTGGGCAGCGGGAGCTCAGG	1	3	66	SEQ ID NO. 5319

FIG. 15 cont.

1 MDKKYSIGLD IGTNSVGWAV ITDEYKVPSK KFKVLGNTDR HSIKKNLIGA LLFDSGETAE

61 ATRLKRTARR RYTRRKNRIC YLQEIFSNEM AKVDDSFFHR LEESFLVEED KKHERHPIFG

121 NIVDEVAYHE KYPTIYHLRK KLVDSTDKAD LRLIYLALAH MIKFRGHFLI EGDLNPDNSD

181 VDKLFIQLVQ TYNQLFEENP INASGVDAKA ILSARLSKSR RLENLIAQLP GEKKNGLFGN

241 LIALSLGLTP NFKSNFDLAE DAKLQLSKDT YDDDLDNLLA QIGDQYADLF LAAKNLSDAI

301 LLSDILRVNT EITKAPLSAS MIKRYDEHHQ DLTLLKALVR QQLPEKYKEI FFDQSKNGYA

361 GYIDGGASQE EFYKFIKPIL EKMDGTEELL VKLNREDLLR KQRTFDNGSI PHQIHLGELH

421 AILRRQEDFY PFLKDNREKI EKILTFRIPY YVGPLARGNS RFAWMTRKSE ETITPWNFEE

481 VVDKGASAQS FIERMTNFDK NLPNEKVLPK HSLLYEYFTV YNELTKVKYV TEGMRKPAFL

541 SGEQKKAIVD LLFKTNRKVT VKQLKEDYFK KIECFDSVEI SGVEDRFNAS LGTYHDLLKI

601 IKDKDFLDNE ENEDILEDIV LTLTLFEDRE MIEERLKTYA HLFDDKVMKQ LKRRRYTGWG

661 RLSRKLINGI RDKQSGKTIL DFLKSDGFAN RNFMQLIHDD SLTFKEDIQK AQVSGQGDSL

721 HEHIANLAGS PAIKKGILQT VKVVDELVKV MGRHKPENIV IEMARENQTT QKGQKNSRER

781 MKRIEEGIKE LGSQILKEHP VENTQLQNEK LYLYYLQNGR DMYVDQELDI NRLSDYDVDH

841 IVPQSFLKDD SIDNKVLTRS DKNRGKSDNV PSEEVVKKMK NYWRQLLNAK LITQRKFDNL

901 TKAERGGLSE LDKAGFIKRQ LVETRQITKH VAQILDSRMN TKYDENDKLI REVKVITLKS

961 KLVSDFRKDF QFYKVREINN YHHAHDAYLN AVVGTALIKK YPKLESEFVY GDYKVYDVRK

1021 MIAKSEQEIG KATAKYFFYS NIMNFFKTEI TLANGEIRKR PLIETNGETG EIVWDKGRDF

1081 ATVRKVLSMP QVNIVKKTEV QTGGFSKESI LPKRNSDKLI ARKKDWDPKK YGGFDSPTVA

1141 YSVLVVAKVE KGKSKKLKSV KELLGITIME RSSFEKNPID FLEAKGYKEV KKDLIIKLPK

1201 YSLFELENGR KRMLASAGEL QKGNELALPS KYVNFLYLAS HYEKLKGSPE DNEQKQLFVE

1261 QHKHYLDEII EQISEFSKRV ILADANLDKV LSAYNKHRDK PIREQAENII HLFTLTNLGA

1321 PAAFKYFDTT IDRKRYTSTK EVLDATLIHQ SITGLYETRI DLSQLGGD (SEQ ID NO: 5320)

FIG. 16

FIG. 17A)



FIG. 17B)

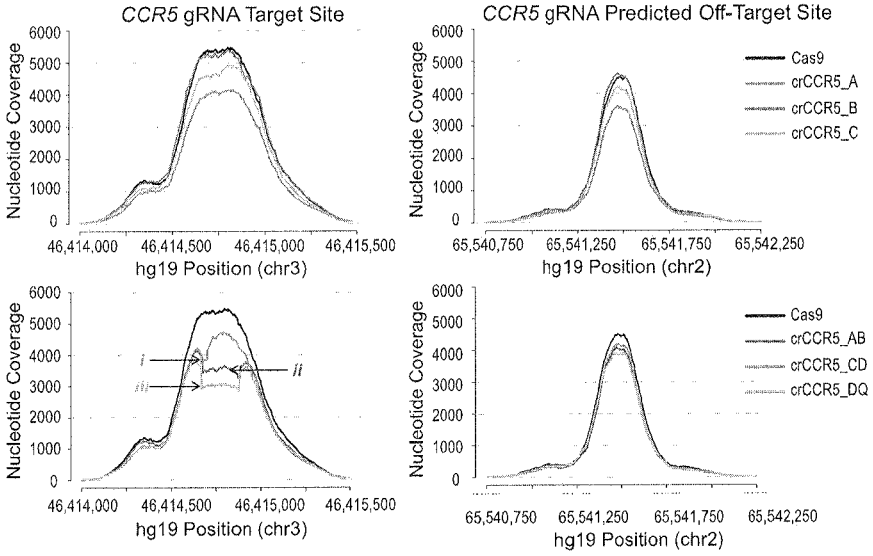


FIG. 17C)

	crCCR5					
Mutation Class	**A**	**B**	**C**	**AB**	**CD**	**DQ**
Predicted deletion	-	-	-	19.95%	20.45%	42.13%
Small InDel	5.10%	13.54%	13.30%	3.06%	0.50%	2.95%
Inversion	-	-	-	3.12%	-	2.48%
Single Nucleotide Substitution	0.03%	0.02%	0.00%	0.05%	0.15%	0.04%
Others	0.66%	3.09%	3.72%	0.05%	0.08%	0.39%
Total On-Target	**5.79%**	**16.65%**	**17.02%**	**26.23%**	**21.19%**	**47.99%**

FIG. 17D)

crCCR5	Off-Target Sites		N-Fold Enrichment of Reads with Variants (Treatment compared to Control)			
	Total Sites	*Significant Sites**	*Off-Target InDel*	*Off-Target Other*	*Off-Target Combined*	***On-Target Combined*****
A	19	0	0.83	1.16	1.06	**39.87**
B	30	1*	1.14*	1.28	1.22	**63**
C	23	0	1.07	0.94	0.96	**23.78**
D	18	0	1.08	0.84	0.88	**40.35**
Q	36	0	0.98	0.78	0.85	**57.66**

FIGS. 17A-17D

FIG. 18A)

crCCR5_A: GCTGCCGCCCAGTGGGACTTTGG (SEQ ID NO: 5335)
"""""""CCR2: **A**CTG**T**C**T**CCC**T**GT**A**G**AA****AC**TGG (SEQ ID NO: 5336)

crCCR5_B: GATCTGGTAAAGATGATTCCTGG (SEQ ID NO: 5337)
"""""""CCR2: **C**AT**TT****A**GTAAAGATGATTCCTGG (SEQ ID NO: 5338)

crCCR5_C: ACAATGTGTCAACTCTTGACAGG (SEQ ID NO: 5339)
"""""""CCR2: **G**CA**TTTTCTGTT**CTC-TGA-AG**T** (SEQ ID NO: 5340)

crCCR5_D: TCACTATGC-TGCCGCCCAGTGG (SEQ ID NO: 5341)
"""""""CCR2: TCACTA**G**GCATGC**T**GCC-AG**A**G**C** (SEQ ID NO: 5342)

crCCR5_Q: GCTGTGTTTGCGTCTCTCCCAGG (SEQ ID NO: 5343)
"""""""CCR2: GCTGTGTTTGC**TT**CT**G**TCCCAGG (SEQ ID NO: 5344)

FIG. 18B)

Mutation	crCCR5 treatment								
	B			AB			A		
	Reads Supporting Mutation	*Total Reads at Site*	*Frequency*	*Reads Supporting Mutation*	*Total Reads at Site*	*Frequency*	*Reads Supporting Mutation*	*Total Reads at Site*	*Frequency*
One Base Insertion	30	5,963	0.50%	2	5,339	0.04%	0	4,678	0.00%
Two Base Insertion	0	5963	0.00%	1	5,339	0.02%	0	4,678	0.00%
One Base Deletion	5	5,963	0.08%	9	5,339	0.17%	4	4,678	0.09%
Two Base Deletion	1	5,963	0.02%	1	5,339	0.02%	0	4,678	0.00%
Total	**36**	5,963	**0.60%**	**13**	5,339	**0.24%**	**4**	**4,678**	**0.09%**

FIGS. 18A-18B

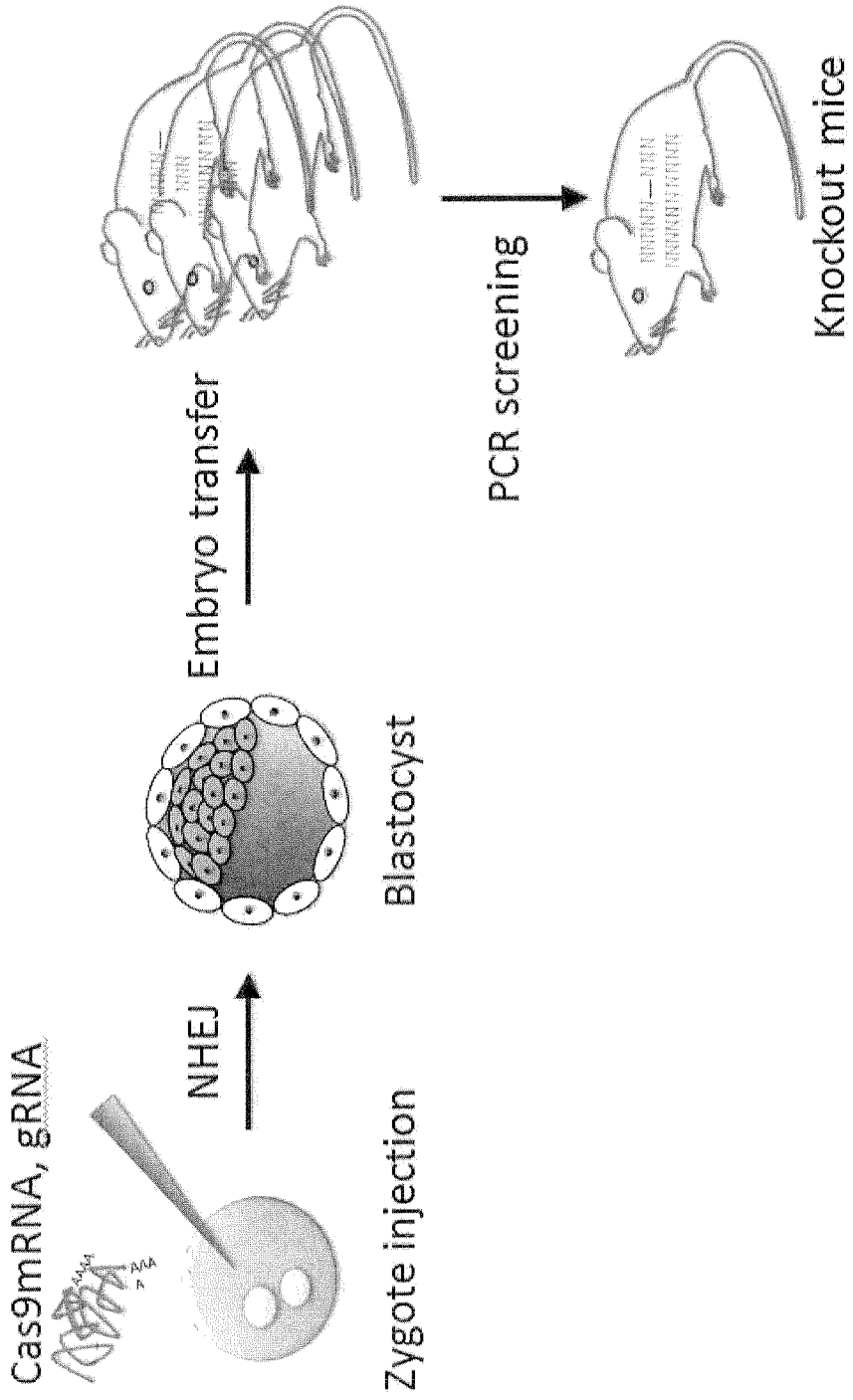

Cas9mRNA, gRNA
NHEJ
Zygote injection
Blastocyst
Embryo transfer
PCR screening
Knockout mice

FIG 19A

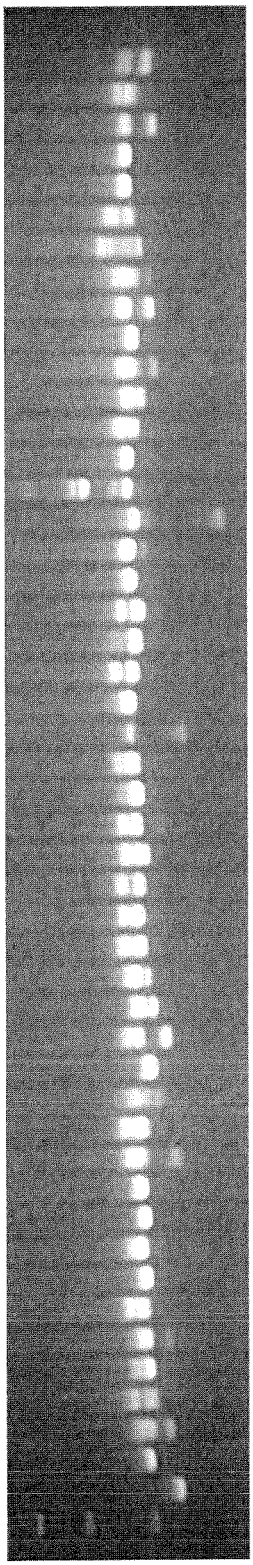


FIG 19B

Table T1 Predicted gRNA mapping in Ensembl GRCh37v71

Site	Chr	Start	End	Sequence	
guideD_OT15	1	7,721,536	7,721,559	CTCCCTGGGCTGCACCATAGTGA	SEQ ID NO. 5356
guideB_OT23	1	26,857,084	26,857,107	GACCTTGTGAAGATGATTCCTGG	SEQ ID NO. 5357
guideB_OT17	1	40,109,230	40,109,253	GATCTGGGGAAGAGGATTCCAGG	SEQ ID NO. 5358
guideC_OT7	1	88,021,569	88,021,592	AGATTGTGTATACTCTTGACTAG	SEQ ID NO. 5359
guideB_OT6	1	95,257,842	95,257,865	CCAGGAATCATCTCTACGATATC	SEQ ID NO. 5360
guideB_OT26	1	95,257,842	95,257,865	CCAGGAATCATCTCTACGATATC	SEQ ID NO. 5361
guideB_OT11	1	102,027,511	102,027,534	CCTGGAATTCTCTTTACTAGATC	SEQ ID NO. 5362
guideQ_OT35	1	109,838,856	109,838,879	CCGGGGAGAGGCGCGGACACAGC	SEQ ID NO. 5363
guideQ_OT10	1	234,728,097	234,728,120	CCAGGGAGAGACGGAACCAAAAC	SEQ ID NO. 5364
guideB_OT22	2	34,792,091	34,792,114	GATCTGATACAGATGATTCATGG	SEQ ID NO. 5365
guideB_OT2	2	55,610,332	55,610,355	CTGGGAATCATCTTTACAAGATG	SEQ ID NO. 5366
guideD_OT4	2	65,541,463	65,541,486	TGAATATCCTGTCGCCCAGTCAG	SEQ ID NO. 5367
guideP_OT6	2	87,822,849	87,822,872	CCACCCAAGTGATCACTCTTCCT	SEQ ID NO. 5368
guideP_OT7	2	87,822,849	87,822,871	AGGAAGAGTGATCACTTGGGTGG	SEQ ID NO. 5369
guideQ_OT4	2	105,475,698	105,475,721	TCTGTGTTTTTGTCTCTCCCCAG	SEQ ID NO. 5370
guideQ_OT32	2	105,475,698	105,475,721	TCTGTGTTTTTGTCTCTCCCCAG	SEQ ID NO. 5371
guideP_OT7	2	112,185,053	112,185,076	AGGAAGAGTGATCACTTGGGTGG	SEQ ID NO. 5372
guideP_OT6	2	112,185,053	112,185,075	CCACCCAAGTGATCACTCTTCCT	SEQ ID NO. 5373
guideB_OT4	2	113,069,812	113,069,835	CTAGGAATCATCTTCCCCAGATG	SEQ ID NO. 5374
guideB_OT7	2	175,176,760	175,176,783	TCTGTGGAAAAGATGATTCCAAG	SEQ ID NO. 5375
guideB_OT10	2	225,356,045	225,356,068	GTTCTTGTTAAGATGATTCCTGG	SEQ ID NO. 5376
guideB_OT21	2	225,356,045	225,356,068	GTTCTTGTTAAGATGATTCCTGG	SEQ ID NO. 5377
guideP_OT3	2	239,253,476	239,253,499	GGCATGTTTCATCACTTGGGGGG	SEQ ID NO. 5378
guideB_OT14	2	239,332,511	239,332,534	GGGCTGGTAAAGATGTTTCCAGG	SEQ ID NO. 5379
guideP_OT20	3	46,399,495	46,399,518	GACAAGTGTGATCACCTGGTTGG	SEQ ID NO. 5380
guideQ_OT15	3	46,399,520	46,399,543	GCTGTGTTTGCTTCTGTCCCAGG	SEQ ID NO. 5381

FIG. 20

guideB_OT5	3	46,399,538	46,399,561	CCAGGAATCATCTTTACTAAATG	SEQ ID NO. 5382
guideB_OT24	3	46,399,538	46,399,561	CCAGGAATCATCTTTACTAAATG	SEQ ID NO. 5383
guideD_TARGET	3	46,414,654	46,414,677	TCACTATGCTGCCGCCCAGTGGG	SEQ ID NO. 5384
guideA_TARGET	3	46,414,661	46,414,684	GCTGCCGCCCAGTGGGACTTTGG	SEQ ID NO. 5385
guideC_TARGET	3	46,414,688	46,414,711	ACAATGTGTCAACTCTTGACAGG	SEQ ID NO. 5386
guideP_TARGET	3	46,414,834	46,414,857	GACAAGTGTGATCACTTGGGTGG	SEQ ID NO. 5387
guideQ_TARGET	3	46,414,859	46,414,882	GCTGTGTTTGCGTCTCTCCCAGG	SEQ ID NO. 5388
guideB_TARGET	3	46,414,877	46,414,900	CCAGGAATCATCTTTACCAGATC	SEQ ID NO. 5389
guideC_OT6	3	51,505,036	51,505,059	ACAAGGGGTCAACTCTGGACAAG	SEQ ID NO. 5390
guideC_OT12	3	51,505,036	51,505,059	ACAAGGGGTCAACTCTGGACAAG	SEQ ID NO. 5391
guideD_OT5	3	53,110,172	53,110,195	CCCACTGGGCTGCAGCATCCTGG	SEQ ID NO. 5392
guideQ_OT28	3	64,142,989	64,143,012	CCAGCGCGTGACGCAAACACAGC	SEQ ID NO. 5393
guideC_OT21	3	94,180,887	94,180,910	ACAATGTGTCACCTTTTAACTGG	SEQ ID NO. 5394
guideC_OT13	3	162,087,348	162,087,371	ACAATATTTCAACACTTGACAAG	SEQ ID NO. 5395
guideB_OT8	4	85,489,957	85,489,980	CTTGGAGTCATCTTTGCCACATC	SEQ ID NO. 5396
guideP_OT24	4	104,977,831	104,977,854	GACAAGCGTGATCCCATGGGGAG	SEQ ID NO. 5397
guideP_OT17	4	136,511,965	136,511,988	CCTCCCAAGTAATCACCCTTTTC	SEQ ID NO. 5398
guideA_OT10	5	13,378,669	13,378,692	CCCAAGTCCCACTGGCAGGTGGC	SEQ ID NO. 5399
guideC_OT2	5	32,668,507	32,668,530	GCTATGTGTTAACTCTTGACAAG	SEQ ID NO. 5400
guideC_OT11	5	32,668,507	32,668,530	GCTATGTGTTAACTCTTGACAAG	SEQ ID NO. 5401
guideD_OT13	5	112,310,301	112,310,324	CCACTATGGTGCCTCCCAGTCAG	SEQ ID NO. 5402
guideD_OT17	5	154,708,103	154,708,126	TCACTCTGCTGCTGTCCAGTGGG	SEQ ID NO. 5403
guideD_OT1	5	157,424,997	157,425,020	ACTCTGTCCTGCCGCCCAGTGAG	SEQ ID NO. 5404
guideB_OT3	6	50,082,676	50,082,699	CTTGGAATCATCTCTACCTGATT	SEQ ID NO. 5405
guideA_OT7	6	95,560,697	95,560,720	CCCAAGTCCCACTGGGTGACATG	SEQ ID NO. 5406
guideQ_OT23	6	149,309,103	149,309,126	CTAAGGAGAGAGGCACACACAGC	SEQ ID NO. 5407
guideQ_OT1	6	151,120,563	151,120,586	CCAGGGAGGGACGCAAACCCAGC	SEQ ID NO. 5408
guideQ_OT24	6	151,120,563	151,120,586	CCAGGGAGGGACGCAAACCCAGC	SEQ ID NO. 5409
guideP_OT13	7	9,489,995	9,490,018	CTTCTCAAGTGATCCCACTGGTC	SEQ ID NO. 5410

FIG. 20 cont.

guideQ_OT19	7	19,938,370	19,938,393	CCTGAGAGAGAAGCAAACACAGA	SEQ ID NO. 5411
guideQ_OT13	7	26,697,753	26,697,776	CTTAGGAAAGACGCAAACATAGC	SEQ ID NO. 5412
guideC_OT4	7	88,108,793	88,108,816	ACATTGATTAAACTCTTGACTAG	SEQ ID NO. 5413
guideC_OT9	7	120,487,950	120,487,973	ACAAAGTTTAAACTCTTGAGCAG	SEQ ID NO. 5414
guideP_OT2	7	140,990,691	140,990,714	CTTCCCAAGTGATTACACTTTAT	SEQ ID NO. 5415
guideD_OT16	7	141,828,674	141,828,697	CCCACTGGGGCGCAGCCTAGTGA	SEQ ID NO. 5416
guideC_OT8	7	145,843,581	145,843,604	CTTGTCAAGATTTGCCACATTAT	SEQ ID NO. 5417
guideC_OT14	7	145,843,581	145,843,604	CTTGTCAAGATTTGCCACATTAT	SEQ ID NO. 5418
guideQ_OT17	7	158,285,285	158,285,308	CCTTGGTGAGAGGCAAACACAGC	SEQ ID NO. 5419
guideD_OT9	8	1,379,562	1,379,585	CCTACTGGGCGTCAGCACTGTGT	SEQ ID NO. 5420
guideD_OT18	8	23,095,380	23,095,403	TCACTATGCAGCACCCCAGTGGG	SEQ ID NO. 5421
guideB_OT28	8	104,258,547	104,258,570	CCAGGCATCTTCTTTACCAGCTC	SEQ ID NO. 5422
guideD_OT6	8	142,638,679	142,638,702	CTCACTGGGCTGCAGCATTGGGG	SEQ ID NO. 5423
guideQ_OT2	9	2,427,359	2,427,382	CCAGGGAGAGACGCAGAAACAAC	SEQ ID NO. 5424
guideQ_OT27	9	2,427,359	2,427,382	CCAGGGAGAGACGCAGAAACAAC	SEQ ID NO. 5425
guideP_OT8	9	42,760,292	42,760,314	TACATGAGTAATCACTTGGGGAG	SEQ ID NO. 5426
guideP_OT9	9	42,760,292	42,760,314	CTCCCCAAGTGATTACTCATGTA	SEQ ID NO. 5427
guideP_OT10	9	42,760,292	42,760,314	CTCCCCAAGTGATTACTCATGTA	SEQ ID NO. 5428
guideP_OT8	9	69,769,168	69,769,190	TACATGAGTAATCACTTGGGGAG	SEQ ID NO. 5429
guideP_OT9	9	69,769,168	69,769,190	CTCCCCAAGTGATTACTCATGTA	SEQ ID NO. 5430
guideP_OT10	9	69,769,168	69,769,190	CTCCCCAAGTGATTACTCATGTA	SEQ ID NO. 5431
guideP_OT8	9	70,135,845	70,135,867	TACATGAGTAATCACTTGGGGAG	SEQ ID NO. 5432
guideP_OT9	9	70,135,845	70,135,867	CTCCCCAAGTGATTACTCATGTA	SEQ ID NO. 5433
guideP_OT10	9	70,135,845	70,135,867	CTCCCCAAGTGATTACTCATGTA	SEQ ID NO. 5434
guideP_OT8	9	70,386,317	70,386,340	TACATGAGTAATCACTTGGGGAG	SEQ ID NO. 5435
guideP_OT9	9	70,386,317	70,386,339	CTCCCCAAGTGATTACTCATGTA	SEQ ID NO. 5436
guideP_OT10	9	70,386,317	70,386,339	CTCCCCAAGTGATTACTCATGTA	SEQ ID NO. 5437
guideP_OT1	9	80,982,901	80,982,924	CAGAGGTGTGATCACTTGGGCAG	SEQ ID NO. 5438
guideP_OT21	9	80,982,901	80,982,924	CAGAGGTGTGATCACTTGGGCAG	SEQ ID NO. 5439

FIG. 20 cont.

guideP_OT5	9	117,954,855	117,954,878	CTTCCCATGTGATAACACTTGTC	SEQ ID NO. 5440
guideP_OT11	9	117,954,855	117,954,878	CTTCCCATGTGATAACACTTGTC	SEQ ID NO. 5441
guideQ_OT20	10	3,031,086	3,031,109	CCTGAGAGAGAGGCAAACACATC	SEQ ID NO. 5442
guideB_OT19	10	20,040,235	20,040,258	CCACGAATCCTCTTTACCAAATC	SEQ ID NO. 5443
guideP_OT9	10	42,689,588	42,689,611	CTCCCCAAGTGATTACTCATGTA	SEQ ID NO. 5444
guideP_OT8	10	42,689,588	42,689,610	TACATGAGTAATCACTTGGGGAG	SEQ ID NO. 5445
guideP_OT10	10	42,689,588	42,689,610	CTCCCCAAGTGATTACTCATGTA	SEQ ID NO. 5446
guideQ_OT9	10	47,655,769	47,655,792	CCTGAGGGTGCGTCTCTCCCGGG	SEQ ID NO. 5447
guideQ_OT7	10	77,358,062	77,358,085	GCTGTGTGCTCGTCTCTCCCTGG	SEQ ID NO. 5448
guideQ_OT31	10	77,358,062	77,358,085	GCTGTGTGCTCGTCTCTCCCTGG	SEQ ID NO. 5449
guideA_OT15	10	88,295,312	88,295,335	GCTGCGGCCCAGCGGGACCTGGG	SEQ ID NO. 5450
guideQ_OT34	10	98,895,438	98,895,461	GCTGTACTTGGGTCTCTCCCCAG	SEQ ID NO. 5451
guideQ_OT8	10	117,958,114	117,958,137	GCCGTGTTTTCCTCTCTCCCAAG	SEQ ID NO. 5452
guideQ_OT11	10	117,958,114	117,958,137	GCCGTGTTTTCCTCTCTCCCAAG	SEQ ID NO. 5453
guideD_OT7	10	129,722,982	129,723,005	CCCACTGGGCTGCAGAATACAGA	SEQ ID NO. 5454
guideP_OT25	10	131,328,679	131,328,702	CCCCCCAGGAGATCACATTTGTC	SEQ ID NO. 5455
guideA_OT16	11	2,952,375	2,952,398	GCTGCCGGACAGTGGGACCTGGG	SEQ ID NO. 5456
guideD_OT14	11	36,441,686	36,441,709	CTGACTGGACGGCACCTTAGTGA	SEQ ID NO. 5457
guideQ_OT25	11	45,632,027	45,632,050	GCTGTCTTTTCCTCTCTCCCTGG	SEQ ID NO. 5458
guideB_OT25	11	58,575,305	58,575,328	CCAGAAATAATCTTTACCAGCTC	SEQ ID NO. 5459
guideQ_OT22	11	62,783,309	62,783,332	GCTGTGTTTGTGCCTCCCCCAGG	SEQ ID NO. 5460
guideC_OT10	11	77,709,742	77,709,765	ACAATGTGTTGGCTCTTGACTAG	SEQ ID NO. 5461
guideC_OT19	11	77,709,742	77,709,765	ACAATGTGTTGGCTCTTGACTAG	SEQ ID NO. 5462
guideP_OT26	11	115,496,055	115,496,078	GACAAGTCTGATCATTTTGGGGG	SEQ ID NO. 5463
guideQ_OT26	12	4,379,332	4,379,355	CCACGGAGAAACACAAACACAGC	SEQ ID NO. 5464
guideC_OT1	12	12,976,312	12,976,335	AAAATGTGTCAACTCTTGATTAG	SEQ ID NO. 5465
guideC_OT16	12	12,976,312	12,976,335	AAAATGTGTCAACTCTTGATTAG	SEQ ID NO. 5466
guideQ_OT21	12	19,270,661	19,270,684	TCTGTGTTTGCCTCTCTCTCAGG	SEQ ID NO. 5467
guideC_OT18	12	53,711,726	53,711,749	ACAATGTGCCAGCTCTGGACTAG	SEQ ID NO. 5468

FIG. 20 cont.

guideP_OT12	12	81,881,220	81,881,243	GACAAGTATGAGCACTTGGTAAG	SEQ ID NO. 5469
guideP_OT14	12	94,428,361	94,428,384	GACTAGTGTGTTCTCTTGGGAAG	SEQ ID NO. 5470
guideP_OT4	12	98,582,748	98,582,771	GACATGTGTAAACACTTGGGAAG	SEQ ID NO. 5471
guideP_OT16	12	98,582,748	98,582,771	GACATGTGTAAACACTTGGGAAG	SEQ ID NO. 5472
guideA_OT3	12	108,460,819	108,460,842	CCAAAGTCCCACTGGGTGACATC	SEQ ID NO. 5473
guideA_OT13	12	108,460,819	108,460,842	CCAAAGTCCCACTGGGTGACATC	SEQ ID NO. 5474
guideQ_OT18	13	20,693,503	20,693,526	CCTGTGAGAGGCTCAAACACAGC	SEQ ID NO. 5475
guideA_OT9	13	21,047,396	21,047,419	CCGCAGTCCCACTGTGCGGCACC	SEQ ID NO. 5476
guideA_OT14	13	21,047,396	21,047,419	CCGCAGTCCCACTGTGCGGCACC	SEQ ID NO. 5477
guideP_OT22	13	25,242,593	25,242,616	GACAAGTGTGTTCACTTCTGCAG	SEQ ID NO. 5478
guideB_OT15	13	42,388,792	42,388,815	GATTTGGGAAAGATCATTCCAGG	SEQ ID NO. 5479
guideB_OT9	13	69,477,970	69,477,993	GCTTTGGTAAAGTTGATTCCTAG	SEQ ID NO. 5480
guideC_OT5	13	94,575,221	94,575,244	AAACTGTGATAACTCTTGACTGG	SEQ ID NO. 5481
guideA_OT6	14	56,740,798	56,740,821	CCTAAGTCCCACTGGCCGAAAGT	SEQ ID NO. 5482
guideB_OT20	14	73,729,934	73,729,957	GTTCTGGTCAAGATGACTCCTGG	SEQ ID NO. 5483
guideA_OT17	14	76,844,953	76,844,976	CCCAGGACCCACTGGGCAGCAGC	SEQ ID NO. 5484
guideC_OT3	14	98,955,845	98,955,868	AAAATCTGTCAACTCTTGAATAG	SEQ ID NO. 5485
guideC_OT17	14	98,955,845	98,955,868	AAAATCTGTCAACTCTTGAATAG	SEQ ID NO. 5486
guideC_OT23	14	103,419,411	103,419,434	CTCATCAGGAGTGGACACATTGT	SEQ ID NO. 5487
guideQ_OT30	14	105,212,041	105,212,064	CCAGGGGGACACGCAAACACTGC	SEQ ID NO. 5488
guideD_OT11	15	27,937,804	27,937,827	TCACTTTGCTGCCAGCCAGTTGG	SEQ ID NO. 5489
guideA_OT8	15	28,812,084	28,812,107	CTGAAGTCCCACTGGGTGGGTGT	SEQ ID NO. 5490
guideA_OT4	15	30,815,609	30,815,631	GCACCAGCCCAGTGGGACTTCAG	SEQ ID NO. 5491
guideA_OT5	15	30,815,609	30,815,631	GCACCAGCCCAGTGGGACTTCAG	SEQ ID NO. 5492
guideA_OT4	15	32,776,439	32,776,462	GCACCAGCCCAGTGGGACTTCAG	SEQ ID NO. 5493
guideA_OT5	15	32,776,439	32,776,462	GCACCAGCCCAGTGGGACTTCAG	SEQ ID NO. 5494
guideQ_OT29	15	58,817,723	58,817,746	CCAGGGAAAGAGGCAAGCACAGC	SEQ ID NO. 5495
guideD_OT3	16	17,377,804	17,377,827	CCACTATACACCCGCCCAGTCAG	SEQ ID NO. 5496
guideD_OT10	16	34,381,274	34,381,297	CCATTGTGCTGCCGCCCAGCCAG	SEQ ID NO. 5497

FIG. 20 cont.

guideB_OT1	16	66,123,576	66,123,599	GATCTGGAAGAGATGATTCCAAG	SEQ ID NO. 5498
guideQ_OT36	17	11,833,418	11,833,441	CCCGGGAGGGAGGCAAAAACAGC	SEQ ID NO. 5499
guideQ_OT6	17	18,078,932	18,078,955	GCTGAGTCTGGGTCTCTCCCCAG	SEQ ID NO. 5500
guideQ_OT33	17	18,078,932	18,078,955	GCTGAGTCTGGGTCTCTCCCCAG	SEQ ID NO. 5501
guideB_OT12	17	21,284,881	21,284,903	CCTGGAATGTTCTTTCCCAGATC	SEQ ID NO. 5502
guideB_OT13	17	21,284,881	21,284,903	CCTGGAATGTTCTTTCCCAGATC	SEQ ID NO. 5503
guideP_OT23	17	59,879,562	59,879,585	GACAGGTGTGAGCACTTTGGGAG	SEQ ID NO. 5504
guideP_OT18	17	65,415,053	65,415,076	GACACTTGTGATGACTTGGGTAG	SEQ ID NO. 5505
guideQ_OT5	18	11,204,603	11,204,626	CTTTGGAGAGACGCAGACACTGC	SEQ ID NO. 5506
guideQ_OT12	18	11,204,603	11,204,626	CTTTGGAGAGACGCAGACACTGC	SEQ ID NO. 5507
guideB_OT12	18	12,705,728	12,705,751	CCTGGAATGTTCTTTCCCAGATC	SEQ ID NO. 5508
guideB_OT13	18	12,705,728	12,705,751	CCTGGAATGTTCTTTCCCAGATC	SEQ ID NO. 5509
guideP_OT19	18	41,187,999	41,188,022	CTACCCAAGTGTTCATATTTGTC	SEQ ID NO. 5510
guideB_OT27	18	69,924,495	69,924,518	CCAGAAATCATGTTTACCAGCTC	SEQ ID NO. 5511
guideA_OT2	19	35,800,794	35,800,817	CTGGAGTCCCACTGCGCGGCAGC	SEQ ID NO. 5512
guideQ_OT14	20	23,302,200	23,302,223	CCTGGGAAAGGCGCAAACACAGC	SEQ ID NO. 5513
guideB_OT18	20	23,472,840	23,472,863	GATCTGATAAAGGTGAGTCCAGG	SEQ ID NO. 5514
guideD_OT2	20	37,102,053	37,102,076	GCAAGTTGCTGCCGCCCAGTGGG	SEQ ID NO. 5515
guideP_OT8	21	9,588,789	9,588,811	TACATGAGTAATCACTTGGGGAG	SEQ ID NO. 5516
guideP_OT9	21	9,588,789	9,588,811	CTCCCCAAGTGATTACTCATGTA	SEQ ID NO. 5517
guideP_OT10	21	9,588,789	9,588,811	CTCCCCAAGTGATTACTCATGTA	SEQ ID NO. 5518
guideQ_OT3	21	32,760,114	32,760,137	GCAGTGTGTGGGTCTCTCCCAGG	SEQ ID NO. 5519
guideQ_OT16	21	32,760,114	32,760,137	GCAGTGTGTGGGTCTCTCCCAGG	SEQ ID NO. 5520
guideP_OT8	22	17,376,827	17,376,849	TACATGAGTAATCACTTGGGGAG	SEQ ID NO. 5521
guideP_OT9	22	17,376,827	17,376,849	CTCCCCAAGTGATTACTCATGTA	SEQ ID NO. 5522
guideP_OT10	22	17,376,827	17,376,849	CTCCCCAAGTGATTACTCATGTA	SEQ ID NO. 5523
guideA_OT12	22	30,136,704	30,136,727	CCAAAGTCGCACTGGCCTGCAGC	SEQ ID NO. 5524
guideB_OT16	22	45,907,886	45,907,909	GATCTGGGAGAGAAGATTCCAGG	SEQ ID NO. 5525
guideC_OT20	X	6,258,801	6,258,824	CCAGAAAAGAGTTGACACATAGT	SEQ ID NO. 5526

FIG. 20 cont.

guideC_OT15	X	21,926,730	21,926,753	CCTGCCAAGGGTTGACACATGGT	SEQ ID NO. 5527
guideP_OT15	X	32,405,319	32,405,342	GACAAGTGTCATAACTTTGGAAG	SEQ ID NO. 5528
guideC_OT22	X	64,736,013	64,736,036	ATAATGTGTCAACCCTGGACCAG	SEQ ID NO. 5529
guideA_OT1	X	70,836,963	70,836,986	CCAAAGACCCACTGGACGGCAGC	SEQ ID NO. 5530
guideA_OT11	X	70,836,963	70,836,986	CCAAAGACCCACTGGACGGCAGC	SEQ ID NO. 5531
guideD_OT8	X	106,847,189	106,847,212	CCAACTGGCCGGCAGCCTGGTGA	SEQ ID NO. 5532
guideD_OT12	X	106,847,189	106,847,212	CCAACTGGCCGGCAGCCTGGTGA	SEQ ID NO. 5533

FIG. 20 cont.

Table T2. Guide Pair crCCR5_A+B On-Target Alleles

Allele	Cas9 Guide Site	Sequence	Split Reads (+) Strand	Split Reads (-) Strand	Split Reads TOTAL	Estimated Allele Frequency
Reference	A (Distal)	TATGCTGCCGCCCAGTGGGACTTTGGAAATACAATGTGTCAACTC	1836	1728	3564	76.78% (SEQ ID NO. 5534)
Reference	B (Proximal)	GGCTGTGTTTGCGTCTCTCCCAGGAATCATCTTTACCAGATCTCA	1340	1753	3093	73.80% (SEQ ID NO. 5535)
206bp deletion	AB (Both)	TATGCTGCCGCCCAGTGGGA | ATCATCTTTACCAGATCTCAAAAAG	411	411	822	18.61% (SEQ ID NOS. 5536, 5537)
205bp inversion	AB (Both)	GAGTTGACACATTGTATTTCCAAAG | ATCATCTTTACCAGATCTCA TATGCTGCCGCCCAGTGGGA | TCCTGGGAGAGACGCAAACACAGCC	60	78	138	3.12% (SEQ ID NOS. 5538, 5539) (SEQ ID NOS. 5540, 5541)
1bp deletion	B (Proximal)	TGGCTGTGTTTGCGTCTCTCCCAGG | ATCATCTTTACCAGATCTCA	23	27	50	1.19% (SEQ ID NOS. 5542, 5543)
206bp deletion with C insertion at break	AB (Both)	TATGCTGCCGCCCAGTGGGA | CATCATCTTTACCAGATCTCAAAAA	19	8	27	0.61% (SEQ ID NOS. 5544, 5545)
1bp deletion	A (Distal)	TATGCTGCCGCCCAGTGGGA | TTTGGAAATACAATGTGTCAACTCT	14	11	25	0.54% (SEQ ID NOS. 5546, 5547)
207bp deletion	AB (Both)	TATGCTGCCGCCCAGTGGGA | TCATCTTTACCAGATCTCAAAAAGA	10	8	18	0.41% (SEQ ID NOS. 5548, 5549)
A insertion	B (Proximal)	GCTGTGTTTGCGTCTCTCCCAGGAA | ATCATCTTTACCAGATCTCA	7	8	15	0.36% (SEQ ID NOS. 5550, 5551)
A insertion	A (Distal)	TATGCTGCCGCCCAGTGGGA | ACTTTGGAAATACAATGTGTCAACT	4	7	11	0.24% (SEQ ID NOS. 5552, 5553)
3bp deletion	A (Distal)	TATGCTGCCGCCCAGTGGGA | TGGAAATACAATGTGTCAACTCTTG	7	0	7	0.15% (SEQ ID NOS. 5554, 5555)
2bp deletion	B (Proximal)	GTGGCTGTGTTTGCGTCTCTCCCAG | ATCATCTTTACCAGATCTCA	4	2	6	0.14% (SEQ ID NOS. 5556, 5557)
TC insertion	A (Distal)	TATGCTGCCGCCCAGTGGGA | TCCTTTGGAAATACAATGTGTCAAC	3	3	6	0.13% (SEQ ID NOS. 5558, 5559)
209bp deletion	AB (Both)	TATGCTGCCGCCCAGTGGGA | ATCTTTACCAGATCTCAAAAAGAAG	1	4	5	0.11% (SEQ ID NOS. 5560, 5561)
4bp deletion	B (Proximal)	TGGTGGCTGTGTTTGCGTCTCTCCC | ATCATCTTTACCAGATCTCA	4	0	4	0.10% (SEQ ID NOS. 5562, 5563)
205bp deletion	AB (Both)	TATGCTGCCGCCCAGTGGGA | AATCATCTTTACCAGATCTCAAAAA	2	2	4	0.09% (SEQ ID NOS. 5564, 5565)
206bp deletion with A insertion at break	AB (Both)	TCACTATGCTGCCGCCCAGTGGGAA | ATCATCTTTACCAGATCTCA	2	2	4	0.09% (SEQ ID NOS. 5566, 5567)
12bp deletion	A (Distal)	TATGCTGCCGCCCAGTGGGA | AATGTGTCAACTCTTGACAGGGCTC	4	0	4	0.09% (SEQ ID NOS. 5568, 5569)
2bp deletion	A (Distal)	TATGCTGCCGCCCAGTGGGA | TTGGAAATACAATGTGTCAACTCTT	2	1	3	0.06% (SEQ ID NOS. 5570, 5571)

FIG. 21

Unidentifiable novel sequence insertion	B (Proximal)	GAGTTACATGATCCCCCATGTTGTG | ATCATCTTTACCAGATCTCA	2	0	2	0.05% (SEQ ID NOS. 5572, 5573)
5bp deletion	B (Proximal)	GTGGTGGCTGTGTTTGCGTCTCCCC | ATCATCTTTACCAGATCTCA	1	0	1	0.02% (SEQ ID NOS. 5574, 5575)
A->T transversion	B (Proximal)	GGCTGTGTTTGCGTCTCTCCCAGGTATCATCTTTACCAGATCTCA	0	1	1	0.02% (SEQ ID NOS. 5576)
208bp deletion	AB (Both)	TATGCTGCCGCCCAGTGGGA | CATCTTTACCAGATCTCAAAAAGAA	1	0	1	0.02% (SEQ ID NOS. 5577, 5578)
7bp deletion	A (Distal)	TATGCTGCCGCCCAGTGGGA | AATACAATGTGTCAACTCTTGACAG	0	1	1	0.02% (SEQ ID NOS. 5579, 5580)
8bp deletion	A (Distal)	TATGCTGCCGCCCAGTGGGA | ATACAATGTGTCAACTCTTGACAGG	0	1	1	0.02% (SEQ ID NOS. 5581, 5582)
C->T transition	A (Distal)	TATGCTGCCGCCCAGTGGGATTTTGGAAATACAATGTTTCAACTC	1	0	1	0.02% (SEQ ID NOS. 5583)

FIG. 21 cont.

Table T3. Guide Pair crCCR5_C+D On-Target Alleles

Allele	Cas9 Guide Site	Sequence	Split Reads (+) Strand	Split Reads (-) Strand	Split Reads TOTAL	Estimated Allele Frequency	
Reference	C (Proximal)	ATACAATGTGTCAACTCTTGACAGGGCTCTATTTTATAGGCTTCT	1704	1457	3161	79.72%	(SEQ ID NO. 5584)
Reference	D (Distal)	GGCTCACTATGCTGCCGCCCAGTGGGACTTTGGAAATACAATGTG	1659	1459	3118	78.64%	(SEQ ID NO. 5585)
35bp deletion	CD (Both)	GGCTCACTATGCTGCCGCCC | GACAGGGCTCTATTTTATAGGCTTC	310	270	580	14.63%	(SEQ ID NO. 5586, 5587)
34bp deletion	CD (Both)	GGCTCACTATGCTGCCGCCC | TGACAGGGCTCTATTTTATAGGCTT	97	99	196	4.94%	(SEQ ID NO. 5588, 5589)
33bp deletion	CD (Both)	GGCTCACTATGCTGCCGCCC | TTGACAGGGCTCTATTTTATAGGCT	23	11	34	0.86%	(SEQ ID NO. 5590, 5591)
1bp deletion	C (Proximal)	AATACAATGTGTCAACTCT | GACAGGGCTCTATTTTATAGGCTTCT	6	3	9	0.23%	(SEQ ID NO. 5592, 5593)
T->G transversion 1bp 5' of PAM	D (Distal)	GGCTCACTATGCTGCCGCCCAGGGGGACTTTGGAAATACAATGTG	3	0	3	0.08%	(SEQ ID NO. 5594)
3bp deletion	D (Distal)	GGCTCACTATGCTGCCGCCC | GGGACTTTGGAAATACAATGTGTCA	3	0	3	0.08%	(SEQ ID NO. 5595, 5596)
Unidentifiable novel sequence insertion	C (Proximal)	CCGGCAAACAAACCACCGC | GACAGGGCTCTATTTTATAGGCTTCT	3	0	3	0.08%	(SEQ ID NO. 5597, 5598)
3bp deletion	C (Proximal)	GAAATACAATGTGTCAACT | GACAGGGCTCTATTTTATAGGCTTCT	3	0	3	0.08%	(SEQ ID NO. 5599, 5600)
5bp deletion	C (Proximal)	TCACTATACAATGTGTCAAGAC | AGGGCTCTATTTTATAGGCTTCT	2	0	2	0.05%	(SEQ ID NO. 5601, 5602)
2bp deletion	C (Proximal)	AAATACAATGTGTCAACTC | GACAGGGCTCTATTTTATAGGCTTCT	0	2	2	0.05%	(SEQ ID NO. 5603, 5604)
34bp deletion; breaks offset 1bp 3' of both Cas9 sites	CD (Both)	GGCTCACTATGCTGCCGCCC | AACAGGGCTCTATTTTATAGGCTTC	1	0	1	0.03%	(SEQ ID NO. 5605, 5606)
G->A transition middle base of PAM	C (Proximal)	ATACAATGTGTCAACTCTTGACAAGGCTCTATTTTATAGGCTTCT	1	0	1	0.03%	(SEQ ID NO. 5607)
19bp deletion	C (Proximal)	CCCAGTGGGACTTTGGAAAA | ACAGGGCTCTATTTTATAGGCTTCT	1	0	1	0.03%	(SEQ ID NO. 5608, 5609)
T->C transition 2bp 5' of Cas9 site	C (Proximal)	ATACAATGTGTCAACTCCT | GACAGGGCTCTATTTTATAGGCTTCT	1	0	1	0.03%	(SEQ ID NO. 5610, 5611)
T->C transition	C (Proximal)	ATACAATGTGTCAACTCTC | GACAGGGCTCTATTTTATAGGCTTCT	0	1	1	0.03%	(SEQ ID NO. 5612, 5613)

FIG. 22

Table T4. Guide Pair crCCR5_D+Q On-Target Alleles

Allele	Cas9 Guide Site	Sequence	Split Reads (+) Strand	Split Reads (-) Strand	Split Reads TOTAL	Estimated Allele Frequency	
Reference	D (Distal)	GGCTCACTATGCTGCCGCCCAGTGGGACTTTGGAAATACAATGTG	1662	1261	2923	54.53%	(SEQ ID NO. 5614)
Reference	Q (Proximal)	GGGTGGTGGCTGTGTTTGCGTCTCTCCCAGGAATCATCTTTACCA	1296	1535	2831	52.82%	(SEQ ID NO. 5615)
205bp deletion	DQ (Both)	TTCTGGGCTCACTATGCTGCCGCCC | CCCAGGAATCATCTTTACCA	332	269	601	11.21%	(SEQ ID NO. 5616, 5617)
205bp deletion	DQ (Both)	GGCTCACTATGCTGCCGCCC | CCCAGGAATCATCTTTACCAGATCT	321	248	569	10.62%	(SEQ ID NO. 5618, 5619)
204bp deletion	DQ (Both)	GGCTCACTATGCTGCCGCCC | TCCCAGGAATCATCTTTACCAGATC	235	278	513	9.57%	(SEQ ID NO. 5620, 5621)
204bp deletion	DQ (Both)	TCTGGGCTCACTATGCTGCCGCCCT | CCCAGGAATCATCTTTACCA	223	273	496	9.25%	(SEQ ID NO. 5622, 5623)
205bp inversion	DQ (Both)	GGCTCACTATGCTGCCGCCC | AGAGACGCAAACACAGCCACCACCC CACATTGTATTTCCAAAGTCCCACT | CCCAGGAATCATCTTTACCA	48	41	89	1.66%	(SEQ ID NO. 5624, 5625) (SEQ ID NO. 5626, 5627)
19bp deletion	D (Distal)	GGCTCACTATGCTGCCGCCC | AATGTGTCAACTCTTGACAGGGCTC	41	24	65	1.21%	(SEQ ID NO. 5628, 5629)
206bp inversion	DQ (Both)	GGCTCACTATGCTGCCGCCC | AGAGACGCAAACACAGCCACCACCC ACATTGTATTTCCAAAGTCCCACTT | CCCAGGAATCATCTTTACCA	26	18	44	0.82%	(SEQ ID NO. 5630, 5631) (SEQ ID NO. 5632, 5633)
T insertion	D (Distal)	GGCTCACTATGCTGCCGCCC | TAGTGGGACTTTGGAAATACAATGT	8	9	17	0.32%	(SEQ ID NO. 5634, 5635)
T insertion	Q (Proximal)	GGTGGTGGCTGTGTTTGCGTCTCTT | CCCAGGAATCATCTTTACCA	7	8	15	0.28%	(SEQ ID NO. 5636, 5637)
206bp deletion	DQ (Both)	CTTCTGGGCTCACTATGCTGCCGCC | CCCAGGAATCATCTTTACCA	4	9	13	0.24%	(SEQ ID NO. 5638, 5639)
Unidentifiable novel sequence insertion	Q (Proximal)	GCTGTTTCCTGTGTGAAATTGTTAT | CCCAGGAATCATCTTTACCA	5	7	12	0.22%	(SEQ ID NO. 5640, 5641)
208bp deletion	DQ (Both)	CCCTTCTGGGCTCACTATGCTGCCG | CCCAGGAATCATCTTTACCA	4	6	10	0.19%	(SEQ ID NO. 5642, 5643)
208bp deletion	DQ (Both)	GGCTCACTATGCTGCCGCCC | AGGAATCATCTTTACCAGATCTCAA	4	5	9	0.17%	(SEQ ID NO. 5644, 5645)
207bp deletion	DQ (Both)	GGCTCACTATGCTGCCGCCC | CCAGGAATCATCTTTACCAGATCTC	2	7	9	0.17%	(SEQ ID NO. 5646, 5647)
109bp deletion w/ TTA insertion	D (Distal)	GGCTCACTATGCTGCCGCCC | TTACTGTCGTCCATGCTGTGTTTGC	5	3	8	0.15%	(SEQ ID NO. 5648, 5649)
205bp deletion	DQ (Both)	TTCTGGGCTCACTATGCTGCCGCC | TCCCAGGAATCATCTTTACCA	4	3	7	0.13%	(SEQ ID NO. 5650, 5651)
219bp deletion	DQ (Both)	GGCTCACTATGCTGCCGCCC | TTACCAGATCTCAAAAAGAAGGTCT	3	4	7	0.13%	(SEQ ID NO. 5652, 5653)
Unidentifiable novel sequence insertion	D (Distal)	GGCTCACTATGCTGCCGCCC | TGTATACCGTCGACCTCTAGCTAGA	3	3	6	0.11%	(SEQ ID NO. 5654, 5655)
C insertion	D (Distal)	GGCTCACTATGCTGCCGCCC | CAGTGGGACTTTGGAAATACAATGT	2	3	5	0.09%	(SEQ ID NO. 5656, 5657)
2bp deletion	D (Distal)	GGCTCACTATGCTGCCGCCC | TGGGACTTTGGAAATACAATGTGTC	2	3	5	0.09%	(SEQ ID NO. 5658, 5659)
14bp deletion	D (Distal)	GGCTCACTATGCTGCCGCCC | AATACAATGTGTCAACTCTTGACAG	0	5	5	0.09%	(SEQ ID NO. 5660, 5661)
202bp deletion	DQ (Both)	GGCTCACTATGCTGCCGCCC | TCTCCCAGGAATCATCTTTACCAGA	0	5	5	0.09%	(SEQ ID NO. 5662, 5663)
202bp deletion	DQ (Both)	TGGGCTCACTATGCTGCCGCCCTCT | CCCAGGAATCATCTTTACCA	0	5	5	0.09%	(SEQ ID NO. 5664, 5665)
215bp deletion	DQ (Both)	TACTGTCCCCTTCTGGGCTCACTAT | CCCAGGAATCATCTTTACCA	2	2	4	0.07%	(SEQ ID NO. 5666, 5667)

FIG. 23

1bp deletion	Q (Proximal)	TGGGTGGTGGCTGTGTTTGCGTCTT | CCCAGGAATCATCTTTACCA	2	2	4	0.07% (SEQ ID NO. 5668, 5669)
4bp deletion	Q (Proximal)	ACTTGGGTGGTGGCTGTGTTTGCGT | CCCAGGAATCATCTTTACCA	1	3	4	0.07% (SEQ ID NO. 5670, 5671)
A insertion	D (Distal)	GGCTCACTATGCTGCCGCCC | AAGTGGGACTTTGGAAATACAATGT	3	0	3	0.06% (SEQ ID NO. 5672, 5673)
1bp deletion	D (Distal)	GGCTCACTATGCTGCCGCCC | GTGGGACTTTGGAAATACAATGTGT	3	0	3	0.06% (SEQ ID NO. 5674, 5675)
72bp deletion	D (Distal)	GGCTCACTATGCTGCCGCCC | TCTTCATCATCCTCCTGACAATCGA	3	0	3	0.06% (SEQ ID NO. 5676, 5677)
48bp deletion	D (Distal)	GGCTCACTATGCTGCCGCCC | TTATAGGCTTCTTCTCTGGAATCTT	3	0	3	0.06% (SEQ ID NO. 5678, 5679)
Unidentifiable novel sequence insertion	Q (Proximal)	TTCTTCGATCAGTCTAAAAATGGCT | CCCAGGAATCATCTTTACCA	3	0	3	0.06% (SEQ ID NO. 5680, 5681)
214bp deletion	DQ (Both)	GGCTCACTATGCTGCCGCCC | CATCTTTACCAGATCTCAAAAAGAA	2	1	3	0.06% (SEQ ID NO. 5682, 5683)
50bp deletion	D (Distal)	GGCTCACTATGCTGCCGCCC | AATAGGCTTCTTCTCTGGAATCTTC	0	3	3	0.06% (SEQ ID NO. 5684, 5685)
152bp deletion	D (Distal)	GGCTCACTATGCTGCCGCCC | TTTGGGGTGGTGACAAGTGTGATCA	0	3	3	0.06% (SEQ ID NO. 5686, 5687)
181bp deletion	DQ (Both)	GGCTCACTATGCTGCCGCCC | TTAAAAGCCAGGACGGTCACCTTTG	0	3	3	0.06% (SEQ ID NO. 5688, 5689)
192bp deletion	DQ (Both)	GGCTCACTATGCTGCCGCCC | TGTTTGCGTCTCTCCCAGGAATCAT	1	1	2	0.04% (SEQ ID NO. 5690, 5691)
13bp deletion	Q (Proximal)	AGTGTGATCACTTGGGTGGTGGCTG | CCCAGGAATCATCTTTACCA	1	1	2	0.04% (SEQ ID NO. 5692, 5693)
62bp deletion	D (Distal)	GGCTCACTATGCTGCCGCCC | TCTGGAATCTTCTTCATCATCCTCC	0	2	2	0.04% (SEQ ID NO. 5694, 5695)
A->T transversion	D (Distal)	GGCTCACTATGCTGCCGCCCTGTGGGACTTTGGAAATACAATGTG	0	2	2	0.04% (SEQ ID NO. 5696)
8bp deletion	D (Distal)	GGCTCACTATGCTGCCGCCC | TTTGGAAATACAATGTGTCAACTCT	1	0	1	0.02% (SEQ ID NO. 5697, 5698)
195bp deletion	DQ (Both)	GGCTCACTATGCTGCCGCCC | CCCAAGAATCATCTTTACCAGATCT	1	0	1	0.02% (SEQ ID NO. 5699, 5700)
207bp deletion	DQ (Both)	CCTTCTGGGCTCACTATGCTGCCGC | CCCAGGAATCATCTTTACCA	1	0	1	0.02% (SEQ ID NO. 5701, 5702)
1bp deletion	Q (Proximal)	TGGGTGGTGGCTGTGTTTGCGTCTC | CCCAGGAATCATCTTTACCA	1	0	1	0.02% (SEQ ID NO. 5703, 5704)
17bp deletion	D (Distal)	GGCTCACTATGCTGCCGCCC | ACAATGTGTCAACTCTTGACAGGGC	0	1	1	0.02% (SEQ ID NO. 5705, 5706)
A deletion	D (Distal)	GGCTCACTATGCTGCCGCCC | GTGGGACTTTGGAAATTCAATGTGT	0	1	1	0.02% (SEQ ID NO. 5707, 5708)
205bp deletion w/ G insertion	DQ (Both)	GGCTCACTATGCTGCCGCCC | GCCCAGGAATCATCTTTACCAGATC	0	1	1	0.02% (SEQ ID NO. 5709, 5710)
187bp deletion w/ 1bp deletion 1bp 5' of proximal guide PAM	DQ (Both)	GGCTCACTATGCTGCCGCCC | GGCTGTGTTTGCGTCTCTCCAGGAA	0	1	1	0.02% (SEQ ID NO. 5711, 5712)
218bp deletion	DQ (Both)	TCTTACTGTCCCCTTCTGCGTCTCT | CCCAGGAATCATCTTTACCA	0	1	1	0.02% (SEQ ID NO. 5713, 5714)
C insertion	Q (Proximal)	GGTGGTGGCTGTGTTTGCGTCTCTC | CCCAGGAATCATCTTTACCA	0	1	1	0.02% (SEQ ID NO. 5715, 5716)

FIG. 23 cont.

Table 5. Off-Target Sites with Statistically Significant Mutational Burden

Guide	Degenerate Sequence	Predicted Binding Site			Fisher's Exact Test *p*		N-Fold Enrichment		
		Chr	*Start*	*End*	*InDel*	*Split*	*InDel*	*Split*	
B	CCAGGAATCATCTTTACTAAATG	3	46,399,538	46,399,561	4.4x10^-13	1.0000	3.51	0.47	(SEQ ID NO. 5717)
B	CCAGGCATCTTCTTTACCAGCTC	8	104,258,547	104,258,570	0.0165	1.0000	1.93	0.45	(SEQ ID NO. 5718)
C	AAAATGTGTCAACTCTTGATTAG	12	12,976,312	12,976,335	0.0361	1.0000	1.56	0.27	(SEQ ID NO. 5719)
C	AAAATGTGTCAACTCTTGATTAG	12	12,976,312	12,976,335	0.0361	1.0000	1.56	0.27	(SEQ ID NO. 5720)
C	CCCACTGGGCTGCAGAATACAGA	10	129,722,982	129,723,005	0.0338	0.9996	1.82	0.50	(SEQ ID NO. 5721)
Q	TCTGTGTTTGCCTCTCTCTCAGG	12	19,270,661	19,270,684	0.0086	1.0000	2.08	0.20	(SEQ ID NO. 5722)
Q	CCCGGGAGGGAGGCAAAAACAGC	17	11,833,418	11,833,441	0.0083	1.0000	2.24	0.20	(SEQ ID NO. 5723)

FIG. 24

Table T6. Comparison of On- and Off-Target Mutational Burdens

gRNA	gRNA Combinations Tested	On-Target Site		Most Significant Off-Target Site	
		Mutation Frequency	Variant Read Enrichment (Treatment vs. Control)	Variant Read Enrichment (Treatment vs. Control)	Fisher's Exact *p* (Treatment vs Control)
A	A, AB	5.79%	58.59	1.84	0.1616
B	B, AB	16.65%	51.02	3.51	4.416x10^-13
C	C, CD	17.02%	30.88	1.56	0.0361
D	D, CD, DQ	26.23%	57.64	1.82	0.0338
Q	DQ	21.19%	46.84	2.24	0.0083

FIG. 25

THERAPEUTIC USES OF GENOME EDITING WITH CRISPR/CAS SYSTEMS

RELATED APPLICATIONS

[0001] This application is a continuation of U.S. application Ser. No. 14/509,924, filed Oct. 8, 2014, which is a continuation-in-part of PCT Application No. PCT/US2014/46034, filed Jul. 9, 2014, which claims the benefit of U.S. Provisional Application No. 61/844,333, filed on Jul. 9, 2013, and 61/869,369, filed on Aug. 23, 2013. The entire teachings of the above applications are incorporated herein by reference.

GOVERNMENT SUPPORT

[0002] This invention was made with government support under HL118744, HL098364, DK095384 and HL107440 awarded by the National Institutes of Health. The government has certain rights in the invention.

BACKGROUND OF THE INVENTION

[0003] Clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated (Cas) systems are a new class of genome-editing tools that target desired genomic sites in mammalian cells. Recently published type II CRISPR/Cas systems use Cas9 nuclease that is targeted to a genomic site by complexing with a synthetic guide RNA that hybridizes to a 20-nucleotide DNA sequence and immediately preceding an NGG motif recognized by Cas9 (thus, a $(N)_{20}$NGG target DNA sequence). This results in a double-strand break three nucleotides upstream of the NGG motif. The double strand break instigates either non-homologous end-joining, which is error-prone and conducive to frame-shift mutations that knock out gene alleles, or homology-directed repair, which can be exploited with the use of an exogenously introduced double-strand or single-strand DNA repair template to knock in or correct a mutation in the genome. Thus, CRISPR/Cas systems could be useful tools for therapeutic applications, but unfortunately prior published reports have demonstrated an efficiency of allele targeting of only 2%-4% in human stem cells (Mali et al., *Science* 339:823-826 (2013)).

SUMMARY OF THE INVENTION

[0004] Work described herein demonstrates methods of allele targeting using CRISPR/Cas systems resulting in mutant cells with efficiencies of up to 80%. These vastly improved methods permit CRISPR/Cas systems to be utilized effectively for the first time for therapeutic purposes. Methods of delivery of CRISPR/Cas systems to human stem cells are provided. In addition, methods of specifically identifying useful RNA guide sequences are provided, along with particular guide sequences useful in targeting specific genes (e.g., ADA, AK2, CD3D, DCLRE1C, IL2RG, IL7R, JAK3, LIG4, NHEJ1, PNP, PRKDC, RAG1, RAG2, ZAP70 and HBB). Moreover, methods of treatment (e.g., severe combined immunodeficiency, sickle cell disease, e.g., sickle cell anemia, beta thalassemia, etc.) utilizing the compositions and methods disclosed herein are provided. In some aspects, disclosed herein is a method for altering a target severe combined immunodeficiency (SCID)-associated polynucleotide sequence in a cell comprising contacting the SCID-associated polynucleotide sequence with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target SCID-associated polynucleotide sequence, wherein the target SCID-associated polynucleotide sequence is cleaved.

[0005] In some aspects, disclosed herein is a method for treating or preventing a disorder associated with expression of a SCID-associated polynucleotide sequence in a subject, the method comprising (a) altering a target SCID-associated polynucleotide sequence in a cell ex vivo by contacting the SCID-associated polynucleotide sequence with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target SCID-associated polynucleotide sequence, wherein the target SCID-associated polynucleotide sequence is cleaved, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the SCID-associated polynucleotide sequence.

[0006] In some aspects, disclosed herein is a method for treating or preventing a disorder associated with expression of a SCID-associated polynucleotide sequence in a subject, the method comprising altering a target SCID-associated polynucleotide sequence in a cell by contacting the SCID-associated polynucleotide sequence with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target SCID-associated polynucleotide sequence, and wherein the target SCID-associated polynucleotide sequence is cleaved, thereby treating or preventing a disorder associated with expression of the SCID-associated polynucleotide sequence.

[0007] In some aspects, disclosed herein is a method for simultaneously altering multiple target SCID-associated polynucleotide sequences in a cell comprising contacting the SCID-associated polynucleotide sequences with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target SCID-associated polynucleotide sequences, wherein the target SCID-associated polynucleotide sequences are cleaved.

[0008] In some aspects, disclosed herein is a method for treating or preventing a disorder associated with expression of SCID-associated polynucleotide sequences in a subject, the method comprising (a) altering target SCID-associated polynucleotide sequences in a cell ex vivo by contacting the SCID-associated polynucleotide sequences with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target SCID-associated polynucleotide sequences, wherein the target SCID-associated polynucleotide sequences are cleaved, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the SCID-associated polynucleotide sequences.

[0009] In some aspects, disclosed herein is a method for treating or preventing a disorder associated with expression of SCID-associated polynucleotide sequences in a subject, the method comprising altering target SCID-associated polynucleotide sequences in a cell by contacting the SCID-

associated polynucleotide sequences with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target moieties of the target SCID-associated polynucleotide sequences, and wherein the target SCID-associated polynucleotide sequences are cleaved, thereby treating or preventing a disorder associated with expression of the SCID-associated polynucleotide sequences.

[0010] In some aspects, disclosed herein is a method for altering a target sickle cell disease (SCD)-associated polynucleotide sequence in a cell comprising contacting the SCD-associated polynucleotide sequence with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target SCD-associated polynucleotide sequence, wherein the target SCD-associated polynucleotide sequence is cleaved.

[0011] In some aspects, disclosed herein is a method for treating or preventing a disorder associated with expression of a SCD-associated polynucleotide sequence in a subject, the method comprising (a) altering a target SCD-associated polynucleotide sequence in a cell ex vivo by contacting the SCD-associated polynucleotide sequence with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target SCD-associated polynucleotide sequence, wherein the target SCD-associated polynucleotide sequence is cleaved, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the SCD-associated polynucleotide sequence.

[0012] In some aspects, disclosed herein is a method for treating or preventing a disorder associated with expression of a SCD-associated polynucleotide sequence in a subject, the method comprising altering a target SCD-associated polynucleotide sequence in a cell by contacting the SCD-associated polynucleotide sequence with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target SCD-associated polynucleotide sequence, and wherein the target SCD-associated polynucleotide sequence is cleaved, thereby treating or preventing a disorder associated with expression of the SCD-associated polynucleotide sequence.

[0013] In some aspects, disclosed herein is a method for simultaneously altering multiple target SCD-associated polynucleotide sequences in a cell comprising contacting the SCD-associated polynucleotide sequences with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target SCD-associated polynucleotide sequences, wherein the target SCD-associated polynucleotide sequences are cleaved.

[0014] In some aspects, disclosed herein is a method for treating or preventing a disorder associated with expression of SCD-associated polynucleotide sequences in a subject, the method comprising (a) altering target SCD-associated polynucleotide sequences in a cell ex vivo by contacting the SCD-associated polynucleotide sequences with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target SCD-associated polynucleotide sequences, wherein the target SCD-associated polynucleotide sequences are cleaved, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the SCD-associated polynucleotide sequences.

[0015] In some aspects, disclosed herein is a method for treating or preventing a disorder associated with expression of SCD-associated polynucleotide sequences in a subject, the method comprising altering target SCD-associated polynucleotide sequences in a cell by contacting the SCD-associated polynucleotide sequences with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target moieties of the target SCD-associated polynucleotide sequences, and wherein the target SCD-associated polynucleotide sequences are cleaved, thereby treating or preventing a disorder associated with expression of the SCD-associated polynucleotide sequences.

[0016] In some aspects, disclosed herein is a method for altering a target beta thalassemia-associated polynucleotide sequence in a cell comprising contacting the beta thalassemia-associated polynucleotide sequence with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target beta thalassemia-associated polynucleotide sequence, wherein the target beta thalassemia-associated polynucleotide sequence is cleaved.

[0017] In some aspects, disclosed herein is a method for treating or preventing a disorder associated with expression of a beta thalassemia-associated polynucleotide sequence in a subject, the method comprising (a) altering a target beta thalassemia-associated polynucleotide sequence in a cell ex vivo by contacting the beta thalassemia-associated polynucleotide sequence with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target beta thalassemia-associated polynucleotide sequence, wherein the target beta thalassemia-associated polynucleotide sequence is cleaved, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the beta thalassemia-associated polynucleotide sequence.

[0018] In some aspects, disclosed herein is a method for treating or preventing a disorder associated with expression of a beta thalassemia-associated polynucleotide sequence in a subject, the method comprising altering a target beta thalassemia-associated polynucleotide sequence in a cell by contacting the beta thalassemia-associated polynucleotide sequence with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target beta thalassemia-associated polynucleotide sequence, and wherein the target beta thalassemia-associated polynucleotide sequence is cleaved, thereby treating or preventing a disorder associated with expression of the beta thalassemia-associated polynucleotide sequence.

[0019] In some aspects, disclosed herein is a method for simultaneously altering multiple target beta thalassemia-associated polynucleotide sequences in a cell comprising contacting the beta thalassemia-associated polynucleotide sequences with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target beta thalassemia-associated polynucleotide sequences, wherein the target beta thalassemia-associated polynucleotide sequences are cleaved.

[0020] In some aspects, disclosed herein is a method for treating or preventing a disorder associated with expression of beta thalassemia-associated polynucleotide sequences in a subject, the method comprising (a) altering target beta thalassemia-associated polynucleotide sequences in a cell ex vivo by contacting the beta thalassemia-associated polynucleotide sequences with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target beta thalassemia-associated polynucleotide sequences, wherein the target beta thalassemia-associated polynucleotide sequences are cleaved, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the beta thalassemia-associated polynucleotide sequences.

[0021] In some aspects, disclosed herein is a method for treating or preventing a disorder associated with expression of beta thalassemia-associated polynucleotide sequences in a subject, the method comprising altering target beta thalassemia-associated polynucleotide sequences in a cell by contacting the beta thalassemia-associated polynucleotide sequences with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target moieties of the target beta thalassemia-associated polynucleotide sequences, and wherein the target beta thalassemia-associated polynucleotide sequences are cleaved, thereby treating or preventing a disorder associated with expression of the beta thalassemia-associated polynucleotide sequences.

[0022] In some embodiments, the Cas protein is *Streptococcus pyogenes* Cas9 protein or a functional portion thereof. In some embodiments, the functional portion comprises a combination of operably linked Cas9 protein functional domains selected from the group consisting of a DNA binding domain, at least one RNA binding domain, a helicase domain, and an endonuclease domain. In some embodiments, the functional domains form a complex. In some embodiments, the Cas protein is Cas9 protein from any bacterial species or functional portion thereof. In some embodiments, the functional portion comprises a combination of operably linked Cas9 protein functional domains selected from the group consisting of a DNA binding domain, at least one RNA binding domain, a helicase domain, and an endonuclease domain. In some embodiments, the functional domains form a complex.

[0023] In some embodiments, the Cas protein is complexed with the one to two ribonucleic acids. In some embodiments, the Cas protein is complexed with the multiple ribonucleic acids.

[0024] In some embodiments, the target motif is a 20-nucleotide DNA sequence. In some embodiments, each target motif is a 20-nucleotide DNA sequence. In some embodiments, the target motif is a 20-nucleotide DNA sequence beginning with G and immediately precedes an NGG motif recognized by the Cas protein. In some embodiments, each target motif is a 20-nucleotide DNA sequence beginning with G and immediately precedes an NGG motif recognized by the Cas protein. In some embodiments, the target motif is a 20-nucleotide DNA sequence and immediately precedes an NGG motif recognized by the Cas protein. In some embodiments, each target motif is a 20-nucleotide DNA sequence and immediately precedes an NGG motif recognized by the Cas protein. In some embodiments, the target motif is $G(N)_{19}NGG$. In some embodiments, each target motif is $G(N)_{19}NGG$. In some embodiments, the target motif is $(N)_{20}NGG$. In some embodiments, each target motif is $(N)_{20}NGG$.

[0025] In some embodiments, the target polynucleotide sequence is cleaved such that a double-strand break results. In some embodiments, each target polynucleotide sequence is cleaved such that a double-strand break results. In some embodiments, the target polynucleotide sequence is cleaved such that a single-strand break results. In some embodiments, each target polynucleotide sequence is cleaved such that a single-strand break results.

[0026] In some embodiments, the alteration is an indel. In some embodiments, the alteration results in reduced expression of the target polynucleotide sequence. In some embodiments, the alteration results in reduced expression of the target polynucleotide sequences. In some embodiments, the alteration results in a knock out of the target polynucleotide sequence. In some embodiments, the alteration results in a knock out of the target polynucleotide sequences. In some embodiments, the alteration results in correction of the target polynucleotide sequence from an undesired sequence to a desired sequence. In some embodiments, the alteration results in correction of the target polynucleotide sequences from undesired sequences to desired sequences. In some embodiments, the alteration is a homozygous alteration. In some embodiments, each alteration is a homozygous alteration.

[0027] In some embodiments, subsequent to cleavage of the target polynucleotide sequence, homology-directed repair occurs. In some embodiments, homology-directed repair is performed using an exogenously introduced DNA repair template. In some embodiments, the exogenously introduced DNA repair template is single-stranded. In some embodiments, the exogenously introduced DNA repair template is double-stranded. In some embodiments, subsequent to cleavage of the target polynucleotide sequences, homology-directed repair occurs. In some embodiments, homology-directed repair is performed using an exogenously introduced DNA repair template. In some embodiments, the exogenously introduced DNA repair template is single-stranded. In some embodiments, the exogenously introduced DNA repair template is double-stranded.

[0028] In some embodiments, the cell is a peripheral blood cell. In some embodiments, the cell is a stem cell or a pluripotent cell. In some embodiments, the cell is a hematopoietic stem cell. In some embodiments, the cell is a $CD34^+$ cell. In some embodiments, the cell is a $CD34^+$ mobilized peripheral blood cell. In some embodiments, the cell is a $CD34^+$ cord blood cell. In some embodiments, the cell is a $CD34^+$ bone marrow cell. In some embodiments, the cell is a $CD34^+CD38$-Lineage-$CD90^+CD45RA^-$cell.

[0029] In some embodiments, the target polynucleotide sequence is ADA. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **1** or at least a 12 nucleotide fragment thereof. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **1** or at least a 12 nucleotide fragment thereof.

[0030] In some embodiments, the target polynucleotide sequence is AK2. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **2** or at least a 12 nucleotide fragment thereof. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **2** or at least a 12 nucleotide fragment thereof.

[0031] In some embodiments, the target polynucleotide sequence is CD3D. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **3** or at least a 12 nucleotide fragment thereof. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **3** or at least a 12 nucleotide fragment thereof.

[0032] In some embodiments, the target polynucleotide sequence is DCLRE1C. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **4** or at least a 12 nucleotide fragment thereof. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **4** or at least a 12 nucleotide fragment thereof.

[0033] In some embodiments, the target polynucleotide sequence is IL2RG. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **6** or at least a 12 nucleotide fragment thereof. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **6** or at least a 12 nucleotide fragment thereof.

[0034] In some embodiments, the target polynucleotide sequence is IL7R. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **7** or at least a 12 nucleotide fragment thereof. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **7** or at least a 12 nucleotide fragment thereof.

[0035] In some embodiments, the target polynucleotide sequence is JAK3. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **8** or at least a 12 nucleotide fragment thereof. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **8** or at least a 12 nucleotide fragment thereof.

[0036] In some embodiments, the target polynucleotide sequence is LIG4. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **9** or at least a 12 nucleotide fragment thereof. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **9** or at least a 12 nucleotide fragment thereof.

[0037] In some embodiments, the target polynucleotide sequence is NHEJ1. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **10** or at least a 12 nucleotide fragment thereof. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **10** or at least a 12 nucleotide fragment thereof.

[0038] In some embodiments, the target polynucleotide sequence is PNP. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **11** or at least a 12 nucleotide fragment thereof. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **11** or at least a 12 nucleotide fragment thereof.

[0039] In some embodiments, the target polynucleotide sequence is PRKDC. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **12** or at least a 12 nucleotide fragment thereof. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **12** or at least a 12 nucleotide fragment thereof.

[0040] In some embodiments, the target polynucleotide sequence is RAG1. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **13** or at least a 12 nucleotide fragment thereof. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **13** or at least a 12 nucleotide fragment thereof.

[0041] In some embodiments, the target polynucleotide sequence is RAG2. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **14** or at least a 12 nucleotide fragment thereof. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide

mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **14** or at least a 12 nucleotide fragment thereof.

[0042] In some embodiments, the target polynucleotide sequence is ZAP70. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **15** or at least a 12 nucleotide fragment thereof. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **15** or at least a 12 nucleotide fragment thereof.

[0043] In some embodiments, the target polynucleotide sequence is HBB. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **5** or at least a 12 nucleotide fragment thereof. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **5** or at least a 12 nucleotide fragment thereof. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321) or at least a 12 nucleotide fragment thereof. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to ribonucleic acid sequence GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321) or at least a 12 nucleotide fragment thereof.

[0044] In some embodiments, the target polynucleotide sequences comprise multiple different portions of ADA. In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **1** or at least 12 nucleotide fragments thereof. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **1** or at least 12 nucleotide fragments thereof.

[0045] In some embodiments, the target polynucleotide sequences comprise multiple different portions of AK2. In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **2** or at least 12 nucleotide fragments thereof. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **2** or at least 12 nucleotide fragments thereof.

[0046] In some embodiments, the target polynucleotide sequences comprise multiple different portions of CD3D. In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **3** or at least 12 nucleotide fragments thereof. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **3** or at least 12 nucleotide fragments thereof.

[0047] In some embodiments, the target polynucleotide sequences comprise multiple different portions of DCLRE1C. In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **4** or at least 12 nucleotide fragments thereof. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **4** or at least 12 nucleotide fragments thereof.

[0048] In some embodiments, the target polynucleotide sequences comprise multiple different portions of IL2RG. In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **6** or at least 12 nucleotide fragments thereof. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **6** or at least 12 nucleotide fragments thereof.

[0049] In some embodiments, the target polynucleotide sequences comprise multiple different portions of IL7R. In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **7** or at least 12 nucleotide fragments thereof. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **7** or at least 12 nucleotide fragments thereof.

[0050] In some embodiments, the target polynucleotide sequences comprise multiple different portions of JAK3. In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **8** or at least 12 nucleotide fragments thereof. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **8** or at least 12 nucleotide fragments thereof.

[0051] In some embodiments, the target polynucleotide sequences comprise multiple different portions of LIG4. In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **9** or at least 12 nucleotide fragments thereof. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **9** or at least 12 nucleotide fragments thereof.

[0052] In some embodiments, the target polynucleotide sequences comprise multiple different portions of NHEJ1. In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **10** or at least 12 nucleotide fragments thereof. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different

sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **10** or at least 12 nucleotide fragments thereof.

[0053] In some embodiments, the target polynucleotide sequences comprise multiple different portions of PNP. In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **11** or at least 12 nucleotide fragments thereof. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **11** or at least 12 nucleotide fragments thereof.

[0054] In some embodiments, the target polynucleotide sequences comprise multiple different portions of PRKDC. In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **12** or at least 12 nucleotide fragments thereof. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **12** or at least 12 nucleotide fragments thereof.

[0055] In some embodiments, the target polynucleotide sequences comprise multiple different portions of RAG1. In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **13** or at least 12 nucleotide fragments thereof. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **13** or at least 12 nucleotide fragments thereof.

[0056] In some embodiments, the target polynucleotide sequences comprise multiple different portions of RAG2. In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **14** or at least 12 nucleotide fragments thereof. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **14** or at least 12 nucleotide fragments thereof.

[0057] In some embodiments, the target polynucleotide sequences comprise multiple different portions of ZAP70. In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **15** or at least 12 nucleotide fragments thereof. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **15** or at least 12 nucleotide fragments thereof.

[0058] In some embodiments, the target polynucleotide sequences comprise multiple different portions of HBB. In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **5** or at least 12 nucleotide fragments thereof. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **5** or at least 12 nucleotide fragments thereof.

[0059] In some embodiments, the target polynucleotide sequences comprise at least a portion of any combination of target polynucleotide sequences selected from the group consisting of ADA, AK2, CD3D, DCLRE1C, IL2RG, IL7R, JAK3, LIG4, NHEJ1, PNP, PRKDC, RAG1, RAG2, and ZAP70. In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of FIGS. **1-15** or at least a 12 nucleotide fragment thereof. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of FIGS. **1-15** or at least a 12 nucleotide fragment thereof.

[0060] In some embodiments, the disorder is SCID. In some embodiments, the disorder is sickle cell disease. In some embodiments, the disorder is beta thalassemia.

[0061] In some embodiments, the one to two ribonucleic acids are designed to hybridize to a target motif immediately adjacent to a deoxyribonucleic acid motif recognized by the Cas protein. In some embodiments, each of the one to two ribonucleic acids are designed to hybridize to target motifs immediately adjacent to deoxyribonucleic acid motifs recognized by the Cas protein which flank a mutant allele located between the target motifs. In some embodiments, the multiple ribonucleic acids are designed to hybridize to target motifs immediately adjacent to deoxyribonucleic acid motifs recognized by the Cas protein. In some embodiments, the multiple ribonucleic acids are designed to hybridize to target motifs immediately adjacent to deoxyribonucleic acid motifs recognized by the Cas protein which flank mutant alleles located between the target motifs. In some embodiments, the one to two ribonucleic acids are selected to minimize hybridization with nucleic acid sequences other than the target polynucleotide sequence. In some embodiments, the multiple ribonucleic acids are selected to minimize hybridization with nucleic acid sequences other than the target polynucleotide sequence. In some embodiments, the target motif is selected such that it contains at least two mismatches when compared with all other genomic nucleotide sequences in the cell. In some embodiments, each target motif is selected such that it contains at least two mismatches when compared with all other genomic nucleotide sequences in the cell. In some embodiments, the target motif is selected such that it contains at least one mismatch when compared with all other genomic nucleotide sequences in the cell. In some embodiments, the target motif is selected such that it contains at least one mismatch when compared with all other genomic nucleotide sequences in the cell. In some embodiments, the one to two ribonucleic acids hybridize to a target motif that it contains at least two mismatches when compared with all other genomic nucleotide sequences in the cell. In some embodiments, each of the multiple ribonucleic acids hybridize to target motifs that contain at least two mismatches when compared with all other genomic nucleotide sequences in the cell. In some embodiments, the one to two ribonucleic acids hybridize to a target motif that contains at least one mismatch when compared with all other genomic nucleotide sequences in the cell. In

some embodiments, each of the multiple ribonucleic acids hybridize to target motifs that contain at least one mismatch when compared with all other genomic nucleotide sequences in the cell.

[0062] In some embodiments, the Cas protein and the one to two ribonucleic acids are contained in a nanoparticle. In some embodiments, the Cas protein and the one to two ribonucleic acids are contained in a lipid nanoparticle. In some embodiments, the lipid nanoparticle comprises at least one of a cationic lipid, a neutral lipid, an amino lipid, a sterol, and a PEG or PEG-modified lipid. In some embodiments, the cationic lipid is selected from the group consisting of ALNY-100, C12-200, DODAC, DDAB, DOTAP, DOTMA, DODMA, DLinDMA, DLenDMA, DLin-C-DAP, DLin-DAC, DLin-MA, DLinDAP, DLin-S-DMA, DLin-2-DMAP, DLin-TMA.C1, DLin-TAP.C1, DLin-MPZ, DLinAP, DOAP, DLin-EG-DMA, DLinDMA, DLin-K-DMA, DLin-KC2-DMA, DLin-M-C3-DMA, KC2, MC3, DOTAP.C1, DOSPA, DOGS, DOPE, DODAP, DMRIE, XTC, and mixtures thereof. In some embodiments, the neutral lipid is selected from the group consisting of DPSC, DPPC, POPC, DOPE, SM, and mixtures thereof. In some embodiments, the PEG-modified lipid is selected from the group consisting of PEG-DMG, PEG-CerC14, PEG-CerC20, and mixtures thereof. In some embodiments, the Cas protein and the multiple ribonucleic acids are contained in nanoparticles. In some embodiments, the Cas protein and the multiple ribonucleic acids are contained in lipid nanoparticles. In some embodiments, the lipid nanoparticles comprise at least one of a cationic lipid, a neutral lipid, an amino lipid, a sterol, and a PEG or PEG-modified lipid. In some embodiments, the cationic lipid is selected from the group consisting of ALNY-100, C12-200, DODAC, DDAB, DOTAP, DOTMA, DODMA, DLinDMA, DLenDMA, DLin-C-DAP, DLin-DAC, DLin-MA, DLinDAP, DLin-S-DMA, DLin-2-DMAP, DLin-TMA.C1, DLin-TAP.C1, DLin-MPZ, DLinAP, DOAP, DLin-EG-DMA, DLinDMA, DLin-K-DMA, DLin-KC2-DMA, DLin-M-C3-DMA, KC2, MC3, DOTAP.C1, DOSPA, DOGS, DOPE, DODAP, DMRIE, XTC, and mixtures thereof. In some embodiments, the neutral lipid is selected from the group consisting of DPSC, DPPC, POPC, DOPE, SM, and mixtures thereof. In some embodiments, the PEG-modified lipid is selected from the group consisting of PEG-DMG, PEG-CerC14, PEG-CerC20, and mixtures thereof.

[0063] In some embodiments, the efficiency of alteration at each loci is from about 50% to about 80%. In some embodiments, the efficiency of alteration is at least about 5%. In some embodiments, the efficiency of alteration is at least about 10%. In some embodiments, the efficiency of alteration is from about 50% to about 80%.

[0064] In some embodiments, the Cas protein is encoded by a modified nucleic acid. In some embodiments, the modified nucleic acid comprises a ribonucleic acid containing at least one modified nucleotide selected from the group consisting of pseudouridine, 5-methylcytodine, 2-thio-uridine, 5-methyluridine-5'-triphosphate, 4-thiouridine-5'-triphosphate, 5,6-dihydrouridine-5'-triphosphate, and 5-azauridine-5'-triphosphate. In some embodiments, at least one of the ribonucleic acids is a modified ribonucleic acid comprising one to two modified nucleotides selected from the group consisting of pseudouridine, 5-methylcytodine, 2-thio-uridine, 5-methyluridine-5'-triphosphate, 4-thiouridine-5'-triphosphate, 5,6-dihydrouridine-5'-triphosphate, and 5-azauridine-5'-triphosphate.

[0065] In some embodiments, any of the Cas protein or the ribonucleic acids are expressed from a plasmid. In some embodiments, any of the Cas protein or the ribonucleic acids are expressed using a promoter optimized for increased expression in stem cells. In some embodiments, the promoter is selected from the group consisting of a Cytomegalovirus (CMV) early enhancer element and a chicken beta-actin promoter, a chicken beta-actin promoter, an elongation factor-1 alpha promoter, and a ubiquitin promoter.

[0066] In some embodiments, the method further comprises selecting cells that express the Cas protein. In some embodiments, selecting cells comprises FACS. In some embodiments, FACs is used to select cells which co-express Cas and a fluorescent protein selected from the group consisting of green fluorescent protein and red fluorescent protein.

[0067] In some aspects, disclosed herein is a method for altering a target SCID-associated polynucleotide sequence in a cell comprising contacting the SCID-associated polynucleotide sequence in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target SCID-associated polynucleotide sequence, wherein the target SCID-associated polynucleotide sequence is cleaved, and wherein the efficiency of alteration of cells that express Cas protein is from about 8% to about 80%.

[0068] In some aspects, disclosed herein is a method for altering a target SCD-associated polynucleotide sequence in a cell comprising contacting the SCD-associated polynucleotide sequence in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target SCD-associated polynucleotide sequence, wherein the target SCD-associated polynucleotide sequence is cleaved, and wherein the efficiency of alteration of cells that express Cas protein is from about 8% to about 80%.

[0069] In some aspects, disclosed herein is a method for altering a target beta thalassemia-associated polynucleotide sequence in a cell comprising contacting the beta thalassemia-associated polynucleotide sequence in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target beta thalassemia-associated polynucleotide sequence, wherein the target beta thalassemia-associated polynucleotide sequence is cleaved, and wherein the efficiency of alteration of cells that express Cas protein is from about 8% to about 80%.

[0070] In some aspects, disclosed herein is a method for treating or preventing a disorder associated with expression of a SCID-associated polynucleotide sequence in a subject, the method comprising (a) altering a target SCID-associated

polynucleotide sequence in a cell ex vivo by contacting the SCID-associated polynucleotide sequence in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target SCID-associated polynucleotide sequence, wherein the target SCID-associated polynucleotide sequence is cleaved, and wherein the efficiency of alteration is from about 8% to about 80%, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the SCID-associated polynucleotide sequence.

[0071] In some aspects, disclosed herein is a method for treating or preventing a disorder associated with expression of a SCD-associated polynucleotide sequence in a subject, the method comprising (a) altering a target SCD-associated polynucleotide sequence in a cell ex vivo by contacting the SCD-associated polynucleotide sequence in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target SCD-associated polynucleotide sequence, wherein the target SCD-associated polynucleotide sequence is cleaved, and wherein the efficiency of alteration is from about 8% to about 80%, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the SCD-associated polynucleotide sequence.

[0072] In some aspects, disclosed herein is a method for treating or preventing a disorder associated with expression of a beta thalassemia-associated polynucleotide sequence in a subject, the method comprising (a) altering a target beta thalassemia-associated polynucleotide sequence in a cell ex vivo by contacting the beta thalassemia-associated polynucleotide sequence in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target beta thalassemia-associated polynucleotide sequence, wherein the target beta thalassemia-associated polynucleotide sequence is cleaved, and wherein the efficiency of alteration is from about 8% to about 80%, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the beta thalassemia-associated polynucleotide sequence.

[0073] In some aspects, disclosed herein is a method for simultaneously altering multiple target SCID-associated polynucleotide sequences in a cell comprising contacting the SCID-associated polynucleotide sequences in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target SCID-associated polynucleotide sequences, wherein the target SCID-associated polynucleotide sequences are cleaved, and wherein the efficiency of alteration of cells that express Cas protein is from about 8% to about 80%.

[0074] In some aspects, disclosed herein is a method for simultaneously altering multiple target SCD-associated polynucleotide sequences in a cell comprising contacting the SCD-associated polynucleotide sequences in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target SCD-associated polynucleotide sequences, wherein the target SCD-associated polynucleotide sequences are cleaved, and wherein the efficiency of alteration of cells that express Cas protein is from about 8% to about 80%.

[0075] In some aspects, disclosed herein is a method for simultaneously altering multiple target beta thalassemia-associated polynucleotide sequences in a cell comprising contacting the beta thalassemia-associated polynucleotide sequences in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target beta thalassemia-associated polynucleotide sequences, wherein the target beta thalassemia-associated polynucleotide sequences are cleaved, and wherein the efficiency of alteration of cells that express Cas protein is from about 8% to about 80%.

[0076] In some aspects, disclosed herein is a method for treating or preventing a disorder associated with expression of SCID-associated polynucleotide sequences in a subject, the method comprising (a) altering target SCID-associated polynucleotide sequences in a cell ex vivo by contacting the SCID-associated polynucleotide sequences in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target SCID-associated polynucleotide sequences, wherein the target SCID-associated polynucleotide sequences are cleaved, and wherein the efficiency of alteration of cells that express Cas protein is from about 8% to about 80%, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the SCID-associated polynucleotide sequences.

[0077] In some aspects, disclosed herein is a method for treating or preventing a disorder associated with expression of SCD-associated polynucleotide sequences in a subject, the method comprising (a) altering target SCD-associated polynucleotide sequences in a cell ex vivo by contacting the SCD-associated polynucleotide sequences in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target SCD-associated polynucleotide sequences, wherein the target SCD-associated polynucleotide sequences are cleaved, and wherein the

efficiency of alteration of cells that express Cas protein is from about 8% to about 80%, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the SCD-associated polynucleotide sequences.

[0078] In some aspects, disclosed herein is a method for treating or preventing a disorder associated with expression of beta thalassemia-associated polynucleotide sequences in a subject, the method comprising (a) altering target beta thalassemia-associated polynucleotide sequences in a cell ex vivo by contacting the beta thalassemia-associated polynucleotide sequences in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target SCID-associated polynucleotide sequences, wherein the target beta thalassemia-associated polynucleotide sequences are cleaved, and wherein the efficiency of alteration of cells that express Cas protein is from about 8% to about 80%, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the beta thalassemia-associated polynucleotide sequences.

[0079] In some aspects, disclosed herein is a composition, comprising at least one ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of FIGS. **1-15** or at least a 12 nucleotide fragment thereof.

[0080] In some aspects, disclosed herein is a composition, comprising at least one ribonucleic acid comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIGS. **1-15** or at least a 12 nucleotide fragment thereof.

[0081] In some embodiments, the at least one ribonucleic acid is contained in a nanoparticle. In some embodiments, the at least one ribonucleic acid is contained in a lipid nanoparticle. In some embodiments, the lipid nanoparticle comprises at least one of a cationic lipid, a neutral lipid, an amino lipid, a sterol, and a PEG or PEG-modified lipid. In some embodiments, the cationic lipid is selected from the group consisting of ALNY-100, C12-200, DODAC, DDAB, DOTAP, DOTMA, DODMA, DLinDMA, DLenDMA, DLin-C-DAP, DLin-DAC, DLin-MA, DLinDAP, DLin-S-DMA, DLin-2-DMAP, DLin-TMA.C1, DLin-TAP.C1, DLin-MPZ, DLinAP, DOAP, DLin-EG-DMA, DLinDMA, DLin-K-DMA, DLin-KC2-DMA, DLin-M-C3-DMA, KC2, MC3, DOTAP.C1, DOSPA, DOGS, DOPE, DODAP, DMRIE, XTC, and mixtures thereof. In some embodiments, the neutral lipid is selected from the group consisting of DPSC, DPPC, POPC, DOPE, SM, and mixtures thereof. In some embodiments, the PEG-modified lipid is selected from the group consisting of PEG-DMG, PEG-CerC14, PEG-CerC20, and mixtures thereof. In some embodiments, at least one of the ribonucleic acids is a modified ribonucleic acid comprising one to two modified nucleotides selected from the group consisting of pseudouridine, 5-methylcytodine, 2-thio-uridine, 5-methyluridine-5'-triphosphate, 4-thiouridine-5'-triphosphate, 5,6-dihydrouridine-5'-triphosphate, and 5-azauridine-5'-triphosphate.

[0082] In some embodiments, a composition further comprises a nucleic acid sequence encoding a Cas protein.

[0083] In some embodiments, a composition further comprises a nucleic acid sequence encoding a Cas9 protein or a functional portion thereof. In some embodiments, the nucleic acid comprises a modified ribonucleic acid comprising at least one modified nucleotide selected from the group consisting of pseudouridine, 5-methylcytodine, 2-thio-uridine, 5-methyluridine-5'-triphosphate, 4-thiouridine-5'-triphosphate, 5,6-dihydrouridine-5'-triphosphate, and 5-azauridine-5'-triphosphate.

[0084] In some aspects, disclosed herein is a composition, comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of FIGS. **1-15** or at least a 12 nucleotide fragment thereof.

[0085] In some aspects, disclosed herein is a composition, n comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid sequence comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIGS. **1-15** or at least a 12 nucleotide fragment thereof.

[0086] In some embodiments, the composition further comprises a nucleic acid sequence encoding a fluorescent protein selected from the group consisting of green fluorescent protein and red fluorescent protein. In some embodiments, the composition further comprises a promoter operably linked to the chimeric nucleic acid. In some embodiments, the promoter is optimized for increased expression in human stem cells. In some embodiments, the promoter is selected from the group consisting of a Cytomegalovirus (CMV) early enhancer element and a chicken beta-actin promoter, a chicken beta-actin promoter, an elongation factor-1 alpha promoter, and a ubiquitin promoter.

[0087] In some embodiments, the chimeric nucleic acid is contained in a nanoparticle. In some embodiments, the chimeric nucleic acid is contained in a lipid nanoparticle. In some embodiments, the lipid nanoparticle comprises at least one of a cationic lipid, a neutral lipid, an amino lipid, a sterol, and a PEG or PEG-modified lipid. In some embodiments, the cationic lipid is selected from the group consisting of ALNY-100, C12-200, DODAC, DDAB, DOTAP, DOTMA, DODMA, DLinDMA, DLenDMA, DLin-C-DAP, DLin-DAC, DLin-MA, DLinDAP, DLin-S-DMA, DLin-2-DMAP, DLin-TMA.C1, DLin-TAP.C1, DLin-MPZ, DLinAP, DOAP, DLin-EG-DMA, DLinDMA, DLin-K-DMA, DLin-KC2-DMA, DLin-M-C3-DMA, KC2, MC3, DOTAP.C1, DOSPA, DOGS, DOPE, DODAP, DMRIE, XTC, and mixtures thereof. In some embodiments, the neutral lipid is selected from the group consisting of DPSC, DPPC, POPC, DOPE, SM, and mixtures thereof. In some embodiments, the PEG-modified lipid is selected from the group consisting of PEG-DMG, PEG-CerC14, PEG-CerC20, and mixtures thereof. In some embodiments, the chimeric nucleic acid comprises at least one modified nucleotide selected from the group consisting of pseudouridine, 5-methylcytodine, 2-thio-uridine, 5-methyluridine-5'-triphosphate, 4-thiouridine-5'-triphosphate, 5,6-dihydrouridine-5'-triphosphate, and 5-azauridine-5'-triphosphate.

[0088] In some embodiments, the Cas protein comprises a Cas9 protein or a functional portion thereof.

[0089] In some aspects, disclosed herein is a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9

protein, and at least one ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of FIGS. **1-15**, a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of FIGS. **1-15** or at least a 12 nucleotide fragment thereof.

[0090] In some embodiments, the kit further comprises one or more cell lines, cultures, or populations selected from the group consisting of human pluripotent cells, primary human cells, and non-transformed cells. In some embodiments, the kit further comprises a DNA repair template selected from the group consisting of an ADA DNA repair template, a AK2 DNA repair template, a CD3D DNA repair template, a DCLRE1C DNA repair template, a IL2RG DNA repair template, IL7R DNA repair template, a JAK3 DNA repair template, a LIG4 DNA repair template, a NHEJ1 DNA repair template, a PNP DNA repair template, a PRKDC DNA repair template, a RAG1 DNA repair template, a RAG2 DNA repair template, a ZAP70 DNA repair template, and a HBB DNA repair template.

[0091] In some aspects, the disclosure provides a composition comprising at least one ribonucleic acid having a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321) or at least a 12 nucleotide fragment thereof. In some aspects, the disclosure provides a composition comprising at least one ribonucleic acid comprising a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321) or at least a 12 nucleotide fragment thereof. In some embodiments, the at least one ribonucleic acid is contained in a nanoparticle. In some embodiments, the at least one ribonucleic acid is contained in a lipid nanoparticle. In some embodiments, the lipid nanoparticle comprises at least one of a cationic lipid, a neutral lipid, an amino lipid, a sterol, and a PEG or PEG-modified lipid. In some embodiments, the cationic lipid is selected from the group consisting of ALNY-100, C12-200, DODAC, DDAB, DOTAP, DOTMA, DODMA, DLinDMA, DLenDMA, DLin-C-DAP, DLin-DAC, DLin-MA, DLinDAP, DLin-S-DMA, DLin-2-DMAP, DLin-TMA.C1, DLin-TAP.C1, DLin-MPZ, DLinAP, DOAP, DLin-EG-DMA, DLinDMA, DLin-K-DMA, DLin-KC2-DMA, DLin-M-C3-DMA, KC2, MC3, DOTAP.C1, DOSPA, DOGS, DOPE, DODAP, DMRIE, XTC, and mixtures thereof. In some embodiments, the neutral lipid is selected from the group consisting of DPSC, DPPC, POPC, DOPE, SM, and mixtures thereof. In some embodiments, the PEG-modified lipid is selected from the group consisting of PEG-DMG, PEG-CerC14, PEG-CerC20, and mixtures thereof. In some embodiments, at least one of the ribonucleic acids is a modified ribonucleic acid comprising one to two modified nucleotides selected from the group consisting of pseudouridine, 5-methylcytodine, 2-thio-uridine, 5-methyluridine-5'-triphosphate, 4-thiouridine-5'-triphosphate, 5,6-dihydrouridine-5'-triphosphate, and 5-azauridine-5'-triphosphate. In some embodiments, the composition includes a nucleic acid sequence encoding a Cas protein. In some embodiments, the composition includes a nucleic acid sequence encoding a Cas9 protein or a functional portion thereof. In some embodiments, the nucleic acid comprises a modified ribonucleic acid comprising at least one modified nucleotide selected from the group consisting of pseudouridine, 5-methylcytodine, 2-thio-uridine, 5-methyluridine-5'-triphosphate, 4-thiouridine-5'-triphosphate, 5,6-dihydrouridine-5'-triphosphate, and 5-azauridine-5'-triphosphate.

[0092] In some aspects, the disclosure provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid having a ribonucleic acid sequences of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321) or at least a 12 nucleotide fragment thereof. In some aspects, the disclosure provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid sequence comprising a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321) or at least a 12 nucleotide fragment thereof. In some embodiments, the composition includes a nucleic acid sequence encoding a fluorescent protein selected from the group consisting of green fluorescent protein and red fluorescent protein. In some embodiments, the composition includes a promoter operably linked to the chimeric nucleic acid. In some embodiments, the promoter is optimized for increased expression in human stem cells. In some embodiments, the promoter is selected from the group consisting of a Cytomegalovirus (CMV) early enhancer element and a chicken beta-actin promoter, a chicken beta-actin promoter, an elongation factor-1 alpha promoter, and a ubiquitin promoter. In some embodiments, the chimeric nucleic acid is contained in a nanoparticle. In some embodiments, the chimeric nucleic acid is contained in a lipid nanoparticle. In some embodiments, the lipid nanoparticle comprises at least one of a cationic lipid, a neutral lipid, an amino lipid, a sterol, and a PEG or PEG-modified lipid. In some embodiments, the cationic lipid is selected from the group consisting of ALNY-100, C12-200, DODAC, DDAB, DOTAP, DOTMA, DODMA, DLinDMA, DLenDMA, DLin-C-DAP, DLin-DAC, DLin-MA, DLinDAP, DLin-S-DMA, DLin-2-DMAP, DLin-TMA.C1, DLin-TAP.C1, DLin-MPZ, DLinAP, DOAP, DLin-EG-DMA, DLinDMA, DLin-K-DMA, DLin-KC2-DMA, DLin-M-C3-DMA, KC2, MC3, DOTAP.C1, DOSPA, DOGS, DOPE, DODAP, DMRIE, XTC, and mixtures thereof. In some embodiments, the neutral lipid is selected from the group consisting of DPSC, DPPC, POPC, DOPE, SM, and mixtures thereof. In some embodiments, the PEG-modified lipid is selected from the group consisting of PEG-DMG, PEG-CerC14, PEG-CerC20, and mixtures thereof. In some embodiments, the chimeric nucleic acid comprises at least one modified nucleotide selected from the group consisting of pseudouridine, 5-methylcytodine, 2-thio-uridine, 5-methyluridine-5'-triphosphate, 4-thiouridine-5'-triphosphate, 5,6-dihydrouridine-5'-triphosphate, and 5-azauridine-5'-triphosphate. In some embodiments, the Cas protein comprises a Cas9 protein or a functional portion thereof.

[0093] In some aspects, the disclosure provides a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321), a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321) or at least a 12 nucleotide fragment thereof. In some embodiments, the kit includes one or more cell lines, cultures, or populations selected from the group consisting of human pluripotent cells, primary human

cells, and non-transformed cells. In some embodiments, the kit includes a HBB DNA repair template.

BRIEF DESCRIPTION OF THE DRAWINGS

[0094] FIG. **1** shows exemplary guide RNA sequences useful when the target polynucleotide sequence is human ADA.

[0095] FIG. **2** shows exemplary guide RNA sequences useful when the target polynucleotide sequence is human AK2.

[0096] FIG. **3** shows exemplary guide RNA sequences useful when the target polynucleotide sequence is human CD3D.

[0097] FIG. **4** shows exemplary guide RNA sequences useful when the target polynucleotide sequence is human DCLRE1C.

[0098] FIG. **5** shows exemplary guide RNA sequences useful when the target polynucleotide sequence is human HBB.

[0099] FIG. **6** shows exemplary guide RNA sequences useful when the target polynucleotide sequence is human IL2RG.

[0100] FIG. **7** shows exemplary guide RNA sequences useful when the target polynucleotide sequence is human IL7R.

[0101] FIG. **8** shows exemplary guide RNA sequences useful when the target polynucleotide sequence is human JAK3.

[0102] FIG. **9** shows exemplary guide RNA sequences useful when the target polynucleotide sequence is human LIG4.

[0103] FIG. **10** shows exemplary guide RNA sequences useful when the target polynucleotide sequence is human NHEJ1.

[0104] FIG. **11** shows exemplary guide RNA sequences useful when the target polynucleotide sequence is human PNP.

[0105] FIG. **12** shows exemplary guide RNA sequences useful when the target polynucleotide sequence is human PRKDC.

[0106] FIG. **13** shows exemplary guide RNA sequences useful when the target polynucleotide sequence is human RAG1.

[0107] FIG. **14** shows exemplary guide RNA sequences useful when the target polynucleotide sequence is human RAG2.

[0108] FIG. **15** shows exemplary guide RNA sequences useful when the target polynucleotide sequence is human ZAP70.

[0109] FIG. **16** shows an exemplary amino acid sequence of a Cas protein. Yellow highlights indicate Ruv-C-like domain. Underlining indicates HNH nuclease domain.

[0110] FIGS. **17**A, **17**B, **17**C and **17**D demonstrate targeted capture and extremely deep sequencing of on-target and predicted off-target sites in CD34+ HPSCs. FIG. **17**A is a schematic overview of targeted capture and deep sequencing of on-target and predicted off-target sites (red bar). A 500 bp flanking cutting site (in yellow) were included in sequence analysis for detection of structural rearrangements, including translocations. Probe sets are indicated in blue. FIG. **17**B features plots showing consistent sequencing depth coverage at both on-target (left panel) and off-target (right panel) sites, achieving a coverage exceeding 3,000× for all on-target sites. Decrease in sequencing depth at the on-target sites in dual-gRNA libraries is marked by arrow, supporting predicted deletions (bottom left; i=35 bp, ii=205 bp, iii=205 bp). FIG. **17**C is a Table depicting the precise estimation of on-target mutation allele frequencies by capture sequencing. Notably, the observed rate of effective null mutation exceeds previous estimates by PCR validation of predictable deletions, as smaller InDels and inversions also occur at appreciable frequencies. FIG. **17**D is a Table depicting the estimation of mutation frequencies at predicted off-target sites (*One off-target site was statistically different from controls following correction for multiple comparisons; $p \leq 7.6 \times 10^{-11}$). N-fold enrichment is determined based on the ratio of non-reference reads in treated libraries compared to untreated library. Each value represents the average of all off-target sites for a given single gRNA or dual-gRNA experiment. Enrichment of 1 is equivalent to baseline (untreated control). **For reference to on-target enrichments, on-target combined represents the proportion of non-reference reads (including single and dual-gRNA treatments using a given gRNA) to total reads at on-target sites in treatment compared to control.

[0111] FIGS. **18**A and **18**B demonstrate potential off-target sites identified in CCR5 homologue CCR2 and analysis of events detected at the single off-target site in which mutagenesis was significantly detected above background. FIG. **18**A depicts a sequence alignment of CCR5 gRNAs utilized in this study in relation to the closest homologous sequence in CCR2 showing mismatched nucleotides in bold. Noteworthy is the fact that guide crCCR5_B, which yielded the sole significantly detected off-target mutagenesis in CCR2 (detailed in panel B), has 3 nucleotide mismatches, which are distal to the PAM (underlined) and seed (grey box) sequences. FIG. **18**B is a Table depicting in-depth analyses of all sequence reads at the single off-target site in which mutagenesis was significantly detected above background in both capture libraries treated with the associated gRNA (B; libraries treated with single gRNA crCCR5_B & dual-gRNA crCCR5_A+B), as well as the library treated with gRNA crCCR5_A as a comparison. Total off-target mutation frequency at this site was 0.6% in the single gRNA treatment (crCCR5_B) and notably decreased to 0.24% in the dual gRNA treatment (crCCR5_A+B) in which gRNA plasmid concentration of each gRNA was half of that utilized in single gRNA treatments.

[0112] FIGS. **19**A and **19**B demonstrate the generation of Fgm knockout mice by a CRISPR/Cas system employing a modified Cas9 mRNA. FIG. **19**A is a schematic illustrating the steps employed to generate Fgm knockout mice using the CRISPR/Cas system employing the Cas9 modified RNA. FIG. **19**B shows part of a gel picture depicting results from PCR screening of surviving pups for genetic mutations resulting from genomic editing using the CRISPR/Cas system and the modified Cas9 mRNA.

[0113] FIG. **20** shows predicted gRNA mapping in Ensembl GRCh37v71.

[0114] FIG. **21** shows guide pair crCCR5_A+B on-target alleles.

[0115] FIG. **22** shows guide pair crCCR5_C+D on-target alleles.

[0116] FIG. **23** shows guide pair crCCR5_D+Q on-target alleles.

[0117] FIG. **24** shows off-target sites with statistically significant mutational burden.

[0118] FIG. **25** shows a comparison of on- and off-target mutational burdens.

DETAILED DESCRIPTION OF THE INVENTION

[0119] Work described herein demonstrates methods of allele targeting using CRISPR/Cas systems resulting in mutant cells with efficiencies of up to 80%. These vastly improved methods permit CRISPR/Cas systems to be utilized effectively for the first time for therapeutic purposes. Methods of delivery of CRISPR/Cas systems to human stem cells are provided. In addition, methods of specifically identifying useful RNA guide sequences are provided, along with particular guide sequences useful in targeting specific genes (e.g., ADA, AK2, CD3D, DCLRE1C, HBB, IL2RG, IL7R, JAK3, LIG4, NHEJ1, PNP, PRKDC, RAG1, RAG2, and ZAP70). Moreover, methods of treatment (e.g., methods of treating severe combined immunodeficiency, sickle cell disease, and beta thalassemia) utilizing the compositions and methods disclosed herein are provided.

[0120] In one aspect, the present invention provides methods for altering target polynucleotide sequences in a cell.

[0121] In certain embodiments, the target polynucleotide sequence is a severe combined immunodeficiency (SCID)-associated polynucleotide sequence. In such embodiments, a method for altering a target polynucleotide sequence in a cell comprises a method for altering a target SCID-associated polynucleotide sequence. As used herein, "severe combined immunodeficiency-associated polynucleotide sequence" and "SCID-associated polynucleotide sequence" are used interchangeably to refer to a polynucleotide sequence of a gene displaying one or more mutations associated with SCID. As used herein "severe combined immunodeficiency" and "SCID" refer to a genetic disorder characterized by dysfunctional T-lymphocytes causing a defective antibody response due to either a direct involvement with B lymphocytes or aberrant B lymphocyte activation resulting from non-functional T-helper cells. SCID encompasses dysfunctional B and T cell responses of the adaptive immune system due to mutations in one or more genes, including, but not limited to, ADA, AK2, CD3D, DCLRE1C, IL2RG, IL7R, JAK3, LIG4, NHEJ1, PNP, PRKDC, RAG1, RAG2, and ZAP70. As such, a "SCID-associated polynucleotide sequence" encompasses nucleotide sequences of any of these genes along with variant or mutant forms thereof.

[0122] An exemplary method for altering a target severe combined immunodeficiency (SCID)-associated polynucleotide sequence in a cell comprises contacting the SCID-associated polynucleotide sequence with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target SCID-associated polynucleotide sequence, wherein the target SCID associated polynucleotide sequence is cleaved. In some embodiments, the efficiency of alteration of cells that express Cas protein is from about 50% to about 80%.

[0123] In some embodiments, the SCID-associated polynucleotide sequence is adenosine deaminase (ADA) or a variant thereof. An exemplary ADA sequence is a human ADA sequence (NCBI Gene ID: 100). Those skilled in the art will appreciate that the guide sequences shown in FIG. **1** can be used with the CRISPR/Cas systems of the present invention to alter target polynucleotide sequences of human ADA.

[0124] It should also be appreciated that altering a target polynucleotide sequence of ADA can be used to treat any abnormal phenotype associated with an altered ADA polynucleotide sequence. Table 1 below shows gene phenotype relationships identified by the Online Mendelian Inheritance in Man® (OMIM®) database. Further information regarding a phenotype listed in Table 1 is publicly accessible by querying OMIM for the search term "ADA" and then clicking on a hyperlink in the "Phenotype MIM number" column corresponding to the phenotype listed.

TABLE 1

ADA Gene Phenotype Relationships

Location	Phenotype	Phenotype MIM number
20q13.12	Adenosine deaminase deficiency, partial	102700
	Severe combined immunodeficiency due to ADA deficiency	102700

[0125] In some embodiments, the SCID-associated polynucleotide sequence is adenylate kinase 2 (AK2) or a variant thereof. An exemplary AK2 sequence is a human AK2 sequence (NCBI Gene ID: 204, also known as ADK2 and AK 2). In some embodiments, the human AK2 sequence comprises all or a portion of AK2 coding sequence 1. In some embodiments, the human AK2 sequence comprises all or a portion of AK2 coding sequence 2. In some embodiments, the human AK2 sequence comprises all or a portion of AK2 coding sequence 3. Those skilled in the art will appreciate that the guide sequences shown in FIGS. **2**, **3** and **4** can be used with the CRISPR/Cas systems of the present invention to alter target polynucleotide sequences of human AK2, and in particular human AK2 coding sequences 1, 2 and 3, respectively.

[0126] It should also be appreciated that altering a target polynucleotide sequence of AK2 can be used to treat any abnormal phenotype associated with an altered AK2 polynucleotide sequence. Table 2 below shows gene phenotype relationships identified by the OMIM® database. Further information regarding a phenotype listed in Table 2 is publicly accessible by querying OMIM for the search term "AK2" and then clicking on a hyperlink in the "Phenotype MIM number" column corresponding to the phenotype listed.

TABLE 2

AK2 Gene Phenotype Relationships

Location	Phenotype	Phenotype MIM number
1p35.1	Reticular dysgenesis	267500

[0127] In some embodiments, the SCID-associated polynucleotide sequence is CD3 antigen, delta subunit (CD3D) or a variant thereof. An exemplary CD3D sequence is a human CD3D sequence (NCBI Gene ID: 915, also known as T3D and CD3-DELTA). In some embodiments, the human CD3D sequence comprises all or a portion of CD3D coding sequence 1. In some embodiments, the human CD3D

sequence comprises all or a portion of CD3D coding sequence 2. Those skilled in the art will appreciate that the guide sequences shown in FIGS. **5** and **6** can be used with the CRISPR/Cas systems of the present invention to alter target polynucleotide sequences of human CD3D, and in particular human CD3D coding sequences 1 and 2, respectively.

[0128] It should also be appreciated that altering a target polynucleotide sequence of CD3D can be used to treat any abnormal phenotype associated with an altered CD3D polynucleotide sequence. Table 3 below shows gene phenotype relationships identified by the OMIM® database. Further information regarding a phenotype listed in Table 3 is publicly accessible by querying OMIM for the search term "CD3D" and then clicking on a hyperlink in the "Phenotype MIM number" column corresponding to the phenotype listed.

TABLE 3

CD3D Gene Phenotype Relationships

Location	Phenotype	Phenotype MIM number
11q23.3	Severe combined immunodeficiency, T cell-negative, B-cell/natural killer-cell positive	608971

[0129] In some embodiments, the SCID-associated polynucleotide sequence is DNA cross-link repair protein 1C (DCLRE1C) or a variant thereof. An exemplary DCLRE1C sequence is a human DCLRE1C sequence (NCBI Gene ID: 64421, also known as SCIDA, SNM1C, A-SCID, hSNM1C, RS-SCID, DCLRE1C). In some embodiments, the human DCLRE1C sequence comprises all or a portion of DCLRE1C coding sequence 1. In some embodiments, the human DCLRE1C sequence comprises all or a portion of DCLRE1C coding sequence 2. In some embodiments, the human DCLRE1C sequence comprises all or a portion of DCLRE1C coding sequence 3. In some embodiments, the human DCLRE1C sequence comprises all or a portion of DCLRE1C coding sequence 4. Those skilled in the art will appreciate that the guide sequences shown in FIGS. **7**, **8**, **9**, and **10** can be used with the CRISPR/Cas systems of the present invention to alter target polynucleotide sequences of human DCLRE1C, and in particular human DCLRE1C coding sequences 1, 2, 3, and 4, respectively.

[0130] It should also be appreciated that altering a target polynucleotide sequence of DCLRE1C can be used to treat any abnormal phenotype associated with an altered DCLRE1C polynucleotide sequence. Table 4 below shows gene phenotype relationships identified by the OMIM® database. Further information regarding a phenotype listed in Table 4 is publicly accessible by querying OMIM for the search term "DCLRE1C" and then clicking on a hyperlink in the "Phenotype MIM number" column corresponding to the phenotype listed.

TABLE 4

DCLRE1C Gene Phenotype Relationships

Location	Phenotype	Phenotype MIM number
10p13	Omenn syndrome	603554
	Severe combined immunodeficiency, Athabascan type	602450

[0131] In some embodiments, the SCID-associated polynucleotide sequence is interleukin 2 receptor, gamma (IL2RG) or a variant thereof. An exemplary IL2RG sequence is a human IL2RG sequence (NCBI Gene ID: 3561, also known as P64; CIDX; IMD4; CD132; SCIDX; IL-2RG; and SCIDX1). Those skilled in the art will appreciate that the guide sequences shown in FIG. **12** can be used with the CRISPR/Cas systems of the present invention to alter target polynucleotide sequences of human IL2RG.

[0132] It should also be appreciated that altering a target polynucleotide sequence of IL2RG can be used to treat any abnormal phenotype associated with an altered IL2RG polynucleotide sequence. Table 5 below shows gene phenotype relationships identified by the OMIM® database. Further information regarding a phenotype listed in Table 5 is publicly accessible by querying OMIM for the search term "IL2RG" and then clicking on a hyperlink in the "Phenotype MIM number" column corresponding to the phenotype listed.

TABLE 5

IL2RG Gene Phenotype Relationships

Location	Phenotype	Phenotype MIM number
Xq13.1	Combined immunodeficiency, X-linked, moderate	312863
	Severe combined immunodeficiency, X-linked	300400

[0133] In some embodiments, the SCID-associated polynucleotide sequence is interleukin 7 receptor (IL7R) or a variant thereof. An exemplary IL7R sequence is a human IL7R sequence (NCBI Gene ID: 3575, also known as ILRA, CD127, IL7RA, CDW127, IL-7R-alpha). Those skilled in the art will appreciate that the guide sequences shown in FIG. **13** can be used with the CRISPR/Cas systems of the present invention to alter target polynucleotide sequences of human IL7R.

[0134] It should also be appreciated that altering a target polynucleotide sequence of IL7R can be used to treat any abnormal phenotype associated with an altered IL7R polynucleotide sequence. Table 6 below shows gene phenotype relationships identified by the OMIM® database. Further information regarding a phenotype listed in Table 6 is publicly accessible by querying OMIM for the search term "IL7R" and then clicking on a hyperlink in the "Phenotype MIM number" column corresponding to the phenotype listed.

TABLE 6

IL7R Gene Phenotype Relationships

Location	Phenotype	Phenotype MIM number
5p13.2	Severe combined immunodeficiency, T-cell negative, B-cell/natural killer cell-positive type	608971

[0135] In some embodiments, the SCID-associated polynucleotide sequence is Janus kinase 3(JAK3) or a variant thereof. An exemplary JAK3 sequence is a human JAK3 sequence (NCBI Gene ID: 3718, also known as JAKL; LJAK; JAK-3; L-JAK; JAK3_HUMAN). Those skilled in the art will appreciate that the guide sequences shown in FIG. **14** can be used with the CRISPR/Cas systems of the present invention to alter target polynucleotide sequences of human JAK3.

[0136] It should also be appreciated that altering a target polynucleotide sequence of JAK3 can be used to treat any abnormal phenotype associated with an altered JAK3 polynucleotide sequence. Table 7 below shows gene phenotype relationships identified by the OMIM® database. Further information regarding a phenotype listed in Table 7 is publicly available by querying OMIM for the search term "JAK3" and then clicking on a hyperlink in the "Phenotype MIM number" column corresponding to the phenotype listed.

TABLE 7

JAK3 Gene Phenotype Relationships

Location	Phenotype	Phenotype MIM number
19p13.11	SCID, autosomal recessive, T-negative/B-positive type	600802

[0137] In some embodiments, the SCID-associated polynucleotide sequence is ligase IV, DNA, ATP-dependent (LIG4) or a variant thereof. An exemplary LIG4 sequence is a human LIG4 sequence (NCBI Gene ID: 3981). In some embodiments, the human LIG4 sequence comprises all or a portion of LIG4 coding sequence 1. In some embodiments, the human LIG4 sequence comprises all or a portion of LIG4 coding sequence 2. In some embodiments, the human LIG4 sequence comprises all or a portion of LIG4 coding sequence 3. Those skilled in the art will appreciate that the guide sequences shown in FIGS. **15**, **16**, and **17** can be used with the CRISPR/Cas systems of the present invention to alter target polynucleotide sequences of human LIG4, and in particular human LIG4 coding sequences 1, 2, and 3, respectively.

[0138] It should also be appreciated that altering a target polynucleotide sequence of LIG4 can be used to treat any abnormal phenotype associated with an altered LIG4 polynucleotide sequence. Table 8 below shows gene phenotype relationships identified by the OMIM® database. Further information regarding a phenotype listed in Table 8 is publicly accessible by querying OMIM for the search term "LIG4" and then clicking on a hyperlink in the "Phenotype MIM number" column corresponding to the phenotype listed.

TABLE 8

LIG4 Gene Phenotype Relationships

Location	Phenotype	Phenotype MIM number
13q33.3	LIG4 syndrome	606593
	Severe combined immunodeficiency with sensitivity to ionizing radiation	602450
	{Multiple myeloma, resistance to}	254500

[0139] In some embodiments, the SCID-associated polynucleotide sequence is nonhomologous end-joining factor 1 (NHEJ1) or a variant thereof. An exemplary NHEJ1 sequence is the human NHEJ1 sequence (NCBI Gene ID: 79840, also known as XLF). Those skilled in the art will appreciate that the guide sequences shown in FIG. **18** can be used with the CRISPR/Cas systems of the present invention to alter target polynucleotide sequences of human NHEJ1.

[0140] It should also be appreciated that altering a target polynucleotide sequence of NHEJ1 can be used to treat any abnormal phenotype associated with an altered NHEJ1 polynucleotide sequence. Table 9 below shows gene phenotype relationships identified by the OMIM® database. Further information regarding a phenotype listed in Table 9 is publicly accessible by querying OMIM for the search term "NHEJ1" and then clicking on a hyperlink in the "Phenotype MIM number" column corresponding to the phenotype listed.

TABLE 9

NHEJ1 Gene Phenotype Relationships

Location	Phenotype	Phenotype MIM number
2q35	Severe combined immunodeficiency with microcephaly, growth retardation, and sensitivity to ionizing radiation	611291

[0141] In some embodiments, the SCID-associated polynucleotide sequence is a purine nucleoside phosphorylase sequence (PNP) or a variant thereof. An exemplary PNP sequence is human PNP (NCBI Gene ID: 4860, also known as NP, PUNP, and PR01837). Those skilled in the art will appreciate that the guide sequences shown in FIG. **19** can be used with the CRISPR/Cas systems of the present invention to alter target polynucleotide sequences of human PNP.

[0142] It should also be appreciated that altering a target polynucleotide sequence of PNP can be used to treat any abnormal phenotype associated with an altered PNP polynucleotide sequence. Table 10 below shows gene phenotype relationships identified by the OMIM® database. Further information regarding a phenotype listed in Table 10 is publicly accessible by querying OMIM for the search term "PNP" and then clicking on a hyperlink in the "Phenotype MIM number" column corresponding to the phenotype listed.

TABLE 10

PNP Gene Phenotype Relationships

Location	Phenotype	Phenotype MIM number
14q11.2	Immunodeficiency due to purine nucleoside phosphorylase deficiency	613179

[0143] In some embodiments, the SCID-associated polynucleotide sequence is a protein kinase, DNA activated, catalytic polypeptide sequence (PRKDC) or a variant thereof. An exemplary PRKDC sequence is human PRKDC (NCBI Gene ID: 5591, also known as HYRC; p350; DNAPK; DNPK1; HYRC1; XRCC7; and DNA-PKcs). In some embodiments, the human PRKDC sequence comprises all or a portion of PRKDC coding sequence 1. In some embodiments, the human PRKDC sequence comprises all or a portion of PRKDC coding sequence 2. Those skilled in the art will appreciate that the guide sequences shown in FIGS. **20** and **21** can be used with the CRISPR/Cas systems of the present invention to alter target polynucleotide sequences of human PRKDC, and in particular human PRKDC coding sequences 1 and 2, respectively.

[0144] It should also be appreciated that altering a target polynucleotide sequence of PRKDC can be used to treat any abnormal phenotype associated with an altered PRKDC polynucleotide sequence. In some embodiments, the phenotype associated with an altered PRKDC polynucleotide sequence is SCID. In some embodiments, the phenotype associated with an altered PRKDC polynucleotide sequence is radiosensitivity in xeroderma pigmentosum (Abbaszadeh et al., A novel splice variant of the DNA-PKcs gene is associated with clinical and cellular radiosensitivity in a patient with xeroderma pigmentosum. J Med Genet. 2010; 47(3):176-81).

[0145] In some embodiments, the SCID-associated polynucleotide sequence is a recombination activating gene 1 sequence (RAG1) or a variant thereof. An exemplary RAG1 sequence is human RAG1 (NCBI Gene ID: 5896, also known as RAG-1 and RNF74). Those skilled in the art will appreciate that the guide sequences shown in FIG. **22** can be used with the CRISPR/Cas systems of the present invention to alter target polynucleotide sequences of human RAG1.

[0146] It should also be appreciated that altering a target polynucleotide sequence of RAG1 can be used to treat any abnormal phenotype associated with an altered RAG1 polynucleotide sequence. Table 11 below shows gene phenotype relationships identified by the OMIM® database. Further information regarding a phenotype listed in Table 11 is publicly accessible by querying OMIM for the search term "RAG1" and then clicking on a hyperlink in the "Phenotype MIM number" column corresponding to the phenotype listed.

TABLE 11

RAG1 Gene Phenotype Relationships

Location	Phenotype	Phenotype MIM number
11p12	Alpha/beta T-cell lymphopenia with gamma/delta T-cell expansion, severe cytomegalovirus infection, and autoimmunity	609889
	Combined cellular and humoral immune defects with granulomas	233650
	Omenn syndrome	603554
	Severe combined immunodeficiency, B cell-negative	601457

[0147] In some embodiments, the SCID-associated polynucleotide sequence is a recombination activating gene 2 sequence (RAG2) or a variant thereof. An exemplary RAG2 sequence is human RAG2 (NCBI Gene ID: 5897, also known as RAG-2). In some embodiments, the human RAG2 sequence comprises all or a portion of human RAG2 coding sequence 1. In some embodiments, the human RAG2 sequence comprises all or a portion of human RAG2 coding sequence 2. In some embodiments, the human RAG2 sequence comprises all or a portion of human RAG2 coding sequence 3. Those skilled in the art will appreciate that the guide sequences shown in FIGS. **23**, **24** and **25** can be used with the CRISPR/Cas systems of the present invention to alter target polynucleotide sequences of human RAG2, and in particular human RAG2 coding sequences 1, 2 and 3, respectively.

[0148] It should also be appreciated that altering a target polynucleotide sequence of RAG2 can be used to treat any abnormal phenotype associated with an altered RAG2 polynucleotide sequence. Table 12 below shows gene phenotype relationships identified by the OMIM® database. Further information regarding a phenotype listed in Table 12 is publicly accessible by querying OMIM for the search term "RAG2" and then clicking on a hyperlink in the "Phenotype MIM number" column corresponding to the phenotype listed.

TABLE 12

RAG2 Gene Phenotype Relationships

Location	Phenotype	Phenotype MIM number
11p12	Combined cellular and humoral immune defects with granulomas	233650
	Omenn syndrome	603554
	Severe combined immunodeficiency, B cell-negative	601457

[0149] In some embodiments, the SCID-associated polynucleotide sequence is a zeta-chain-associated protein kinase sequence (ZAP70) or a variant thereof. An exemplary ZAP70 sequence is human ZAP70 (NCBI Gene ID: 7535, also known as SRK; STD; TZK; STCD; and ZAP-70). In some embodiments, the human ZAP70 sequence comprises all or a portion of human ZAP70 coding sequence 1. In some embodiments, the human ZAP70 sequence comprises all or a portion of human ZAP70 coding sequence 2. Those skilled in the art will appreciate that the guide sequences shown in FIGS. **26** and **27** can be used with the CRISPR/Cas systems

of the present invention to alter target polynucleotide sequences of human ZAP70, and in particular human ZAP70 coding sequences 1 and 2, respectively.

[0150] It should also be appreciated that altering a target polynucleotide sequence of ZAP70 can be used to treat any abnormal phenotype associated with an altered ZAP70 polynucleotide sequence. Table 13 below shows gene phenotype relationships identified by the OMIM® database. Further information regarding a phenotype listed in Table 13 is publicly accessible by querying OMIM for the search term "ZAP70" and then clicking on a hyperlink in the "Phenotype MIM number" column corresponding to the phenotype listed.

TABLE 13

ZAP 70 Gene Phenotype Relationships

Location	Phenotype	Phenotype MIM number
2q11.2	Selective T-cell defect	269840

[0151] In some embodiments, the target polynucleotide sequence is hemoglobin beta ("HBB") (e.g., human hemoglobin beta, NCBI Gene ID: 3043) or a variant thereof. Those skilled in the art will appreciate that the guide sequences shown in FIG. **11** can be used with the CRISPR/Cas systems of the present invention to alter target polynucleotide sequences of human HBB.

[0152] It should also be appreciated that altering a target polynucleotide sequence of HBB can be used to treat any abnormal phenotype associated with an altered HBB polynucleotide sequence. Table 14 below shows gene phenotype relationships as identified by the OMIM® database. Further information regarding a phenotype listed in Table 14 is publicly accessible by querying OMIM for the search term "HBB" and then clicking on a hyperlink in the "Phenotype MIM number" column corresponding to the phenotype listed.

TABLE 14

HBB Gene Phenotype Relationships

Location	Phenotype	Phenotype MIM number
11p15.4	Delta-beta thalassemia	141749
	Erythremias, beta-	
	Heinz body anemias, beta-	140700
	Hereditary persistence of fetal hemoglobin	141749
	Methemoglobinemias, beta-	
	Sickle cell anemia	603903
	Thalassemia-beta, dominant inclusion-body	603902
	Thalassemias, beta-	613985
	{Malaria, resistance to}	611162

[0153] Normal adult hemoglobin is a tetramer that consists of two alpha chains and two beta chains. HBB determines the structure of the beta chains of hemoglobin. HBB mutations are associated with sickle cell diseases and/or beta thalassemia. For example, sickle cell anemia is caused by mutant beta globin. The absence of the beta chain results in beta-zero thalassemia. Diminished amounts of detectable beta globin results in beta-plus-thalassemia. Exemplary mutant forms of HBB involved in sickle cell disease are Hemoglobin S (Glu6Val), Hemoglobin C (Glu6Lys), Hemoglobin D (Glu121Gln), and Hemoglobin O (Glu121Lys).

[0154] Insertion of an L1 retrotransposable fragment within the IVS-II of the beta-globin gene results in beta°-thal. This represents a form of beta thalassemia in which the beta globin gene expresses full length beta-globin transcripts at levels equal to about 15% of the total beta-globin mRNA.

[0155] In some embodiments, a method for altering a target polynucleotide sequence in a cell comprises a method for altering a target sickle cell disease (SCD)-associated polynucleotide sequence. As used herein, "sickle cell disease-associated polynucleotide sequence" or "SCD-associated polynucleotide sequence" are used interchangeably to refer to a polynucleotide sequence of the HBB gene displaying one or more HBB mutations associated with SCD. As used herein, "sickle cell disease" refers to a group of symptomatic disorders involving mutations in HBB and defined by the presence of hemoglobin S (Hb S). Normal hemoglobin is a heterotetramer consisting of two alpha-hemoglobin and two beta-hemoglobin chains. Point mutations in HBB cause hemoglobin S to result, for example a point mutation changing the sixth amino acid in the beta-hemoglobin chain from glutamic acid to valine (Glu6Val). Sickle cell anemia (homogzygous HbSS) is an example of a sickle cell disease which makes up between 60-70% of reported sickle cell disease in the United States. Examples of other forms of sickle cell disease are due to coinhereitance of Hb S with various mutant beta-globin chain variants, including sickle-hemoglobin C disease (Hb SC), and two different types of sickle beta thalassemia (Hb Sβ^+_thalassemia and Hb S Pβ_thalassemia).

[0156] An exemplary method for altering a target sickle cell disease (SCD)-associated polynucleotide sequence in a cell comprises contacting the SCD-associated polynucleotide sequence with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target SCD-associated polynucleotide sequence, wherein the target SCD-associated polynucleotide sequence is cleaved. In some embodiments of this and other aspects, the efficiency of alteration of cells that express Cas protein is from about 50% to about 80%.

[0157] In some embodiments, a method for altering a target polynucleotide sequence in a cell comprises a method for altering a target beta thalassemia-associated polynucleotide sequence. As used herein, "beta thalassemia-associated polynucleotide sequence" refers to a polynucleotide sequence of the HBB gene displaying one or more HBB mutations associated with beta thalassemia. As used herein, "beta thalassemia" refers to inherited autosomal recessive diseases characterized by decreased production of the hemoglobin subunit beta (e.g., hemoglobin beta chain) that are caused by over 200 different HBB mutations. As will be appreciated by the skilled artisan, HBB mutations resulting in beta thalassemia include non-deletional HBB mutants, deletional HBB mutants, and HBB mutants resulting from transposable elements. Table 15 below illustrates exemplary non-deletional HBB mutations.

TABLE 15

Non-deletional HBB mutations associated with beta thalassemia

−101 (C−>T)
−92 (C−>T)
−90 (C−>T)
−88 (C−>A)
−88 (C−>T)
−87 (C−>A)
−87 (C−>G)
−87 (C−>T)
−86 (C−>A)
−86 (C−>G)
−32 (C−>A)
−31 (A−>C)
−31 (A−>G)
−30 (T−>A)
−30 (T−>C)
−29 (A−>G)
−28 (A−>C)
−28 (A−>G)
CAP +1(A−>C)
5'UTR; +10(−T)
5'UTR; +22 (G−>A)
5'UTR; +33 (C−>G)
5'UTR; +43 to +40(−AAAC)
Initiation codon ATG−>GTG
Initiation codon ATG−>ACG
Initiation codon ATG−>AGG
Initiation codon ATG−>ATA
Initiation codon ATG−>ATC
Initiation codon ATG−>ATT
Codon 1 (−G); GTG(Val)−>−TG
Codons 2/3/4 (−9 bp; +31 bp); (see below)
Codon 5 (−CT); CCT(Pro)−>C--
Codon 6 (−A); GAG(Glu)−>G-G
Codon 8 (−AA); AAG(Lys)−>--G
Codons 8/9 (+G); AAG. TCT(Lys; Ser)−>AAG•G•TCT
Codons 9/10 (+T); TCT•GCC(Ser; Ala)−>TCT•T•GCC
Codon 10 (C−>A); GCC(Ala)−>GCA(Ala)
Codon 11 (−T); GTT(Val)−>GT-
Codons 14/15 (+G);
Codon 15 (G−>A); TGG(Trp)−>TAG(stop codon)
Codon 15 (G−>A); TGG(Trp)−>TGA(stop codon)
Codon 15 (−T); TGG(Trp)−>−GG
Codon 16 (−C); GGC(Gly)−>GG-
Codon 17 (A−>T); AAG(Lys)−>TAG(stop codon)
Codon 19 (A−>G); AAC(Asn)−>AGC(Ser)
Codon 22 (A−>C); GAA(Glu)−>GCA(Ala) (not listed in Table I; this mutation is likely not associated with thalassemia)
Codon 22 (G−>T); GAA(Glu)−>TAA(stop codon)
Codons 22/23/24 (GAA•GTT•GGT; Glu•Val•Gly); deletion of −AAGTTGG
Codon 24; GGT(Gly); (−G; +CAC)
Codon 24 (T−>A); GGT(Gly)−>GGA(Gly)
Codons 24/25 (−GGT); GGT•GGT(Gly-Gly)−>---•GGT(Gly)
Codons 25/26 (+T); GGT•GAG(Gly-Glu)−>GGT•T•GAG(Gly-Term)
Codon 26 (GAG−>AAG)
Codon 26 (G−>T); GAG(Glu)−>TAG(stop codon)
Codon 26 (+T); GAG(Glu)−>GTAG
Codon 27 (G−>T); GCC(Ala)−>TCC(Ser)
Codons 27/28 (+C); GCC•CTG(Ala•Ser)−>GCC•C•CTG
Codon 28 (−C); CTG(Leu)−>−TG
Codon 28 (T−>G); CTG(Leu)−>CGG(Arg)
Codons 28/29 (−G); CTG•GGC(Leu•Gly)−>CTG•−GC
IVS-I (−3) or codon 29 (C−>T); GGC(Gly)−>GGT(Gly)
IVS-I (−2) or codon 30 (A−>G); AG^GTTGGT−>GG^GTTGGT
IVS-I (−1) or codon 30 (G−>A); AG^GTTGGT−>AA^GTTGGT
IVS-I (−1) or codon 30 (G−>C); AG^GTTGGT−>AC^GTTGGT
IVS-I-1 (G−>A); AG^GTTGGT−>AGATTGGT
IVS-I-1 (G−>T); AG^GTTGGT−>AGTTTGGT
IVS-I-2 (T−>A); AG^GTTGGT−>AGGATGGT
IVS-I-2 (T−>C); AG^GTTGGT−>AGACTGGT
IVS-I-2 (T−>G); AG^GTTGGT−>AGGGTGGT
IVS-I-5 (G−>A)
IVS-I-5 (G−>A) plus the 7,201 bp deletion involving part of the delta gene; the Corfu deletion (deltabeta-thal)
IVS-I-5 (G−>C)
IVS-I-5 (G−>T)

TABLE 15-continued

Non-deletional HBB mutations associated with beta thalassemia

IVS-I-6 (T->C); the Portuguese type
IVS-I-110 (G->A)
IVS-I-116 (T->G)
IVS-I-128 (T->G); TTAG^GCTG->TGAG^GCTG
IVS-I-130 (G->A); TTAG^GCTG->TTAA^GCTG
IVS-I-130 (G->C); TTAG^GCTG->TTAC^GCTG
Codon 30 (AGG->AGC) [IVS-I-130 (+1)]
IVS-I, 3' end; -17 bp
Codon 31 (-C); CTG->-TG
Codons 31/32 (+CGG)
Codon 32 (T->A) CTG->CAG; codon 98 (G->A) GTG->ATG
Codons 33/34 (-GTG); GTG•GTC(Val-Val)->GTC•---(Val)
Codon 35 (C->A); TAC->TAA (Tyr->Term codon)
Codon 35 (-C); TAC(Tyr)->TA-
Codons 36/37 (-T); CCT•TGG(Pro-Trp)->CCT•-GG
Codon 37 (G->A); TGG(Trp)->TGA(stop codon)
Codons 37/38/39 (-7 nts)
Codons 38/39 (-C); ACC•CAG(Thr•Gln)->ACC•-AG
Codons 38/39 (-CC); ACC•CAG(Thr-Glu)->A--•CAG
Codon 39 (C->T); CAG(Gln)->TAG(stop codon)
Codon 40 (-G); AGG(Arg)->AG-
Codons 40/41 (+T); AGG•TTC(Arg-Phe)->AGG•T•TTC
Codon 41 (-C); TTC(Phe)->TT-
Codons 41/42 (-TTCT); TTC•TTT(Phe-Phe)->--- -TT
Codons 42/43 (+G); TTT•GAG(Phe•Glu)->TTT•G•GAG
Codons 42/43 (+T) TTT•GAG(Phe•Glu)->TTT•TGA•G(Phe; stop codon)
Codon 43 (G->T); GAG(Glu)->TAG (stop codon)
Codon 44 (-C); TCC(Ser)->TC-
Codon 45 (-T); TTT(Phe)->-TT
Codon 47 (+A); GAT(Asp)->GAA(Glu)•T
Codons 47/48 (+ATCT); GAT•CTG(Asp-Leu)->GAT•CTATCTG
Codon 51 (-C); CCT(Pro)->-CT
53/54 (+G); GCT•GTT(Ala-Val)->GCT•G•GTT
Codon 54 (-T); GTT(Val)->GT-
Codons 54/55 (+A); GTT•ATG(Val•Met)->GTT•A•ATG
Codons 56/57/58/59/60 (GGC•AAC•CCT•AAG•GTG) (SEQ ID NO: 5345); duplication of 14 bp
Codons 57/58 (+C); AAC•CCT(Asn•Pro)->AAC•C•CCT
Codon 59 (-A); AAG(Lys)->-AG
Codon 60 (T->A); GTG(Val)->GAG(Glu)
Codon 61 (A->T); AAG(Lys)->TAG(stop codon)
Codon 64 (-G); GGC(Gly)->-GC
Codon 67 (-TG); GTG(Val)->--G
Codons 71/72 (+A); TTT•AGT(Phe•Ser)->TTT•A•AGT
Codons 71/72 (+T); TTT•AGT(Phe•Ser)->TTT•T•AGT
Codons 72/73; -AGTGA, +T; AGT•GAT(Ser-Asp)->--- -TT
Codons 74/75 (-C); GGC•CTG(Gly• Leu)->GG--CTG
Codon 76 (-C); GCT(Ala)->G-T
Codons 82/83 (-G); AAG•GGC(Lys•Gly)->AAG•-GC
Codons 84/85 (+C); ACC•TTT(Thr• Phe)->ACC•C•TTT
Codons 84/85/86 (+T); ACC•TTT•GCC(Thr•Phe•Ala)->ACC•TTT•T•GCC
Codon 88 (+T); CTG(Leu)->CTTG
Codons 89/90 (-GT); AGT•GAG(Ser•Glu)->A--•GAG
Codon 90 (G->T); GAG(Glu)->TAG(stop codon)
Codon 94 (+TG); GAC(Asp)->GTGAC
Codon 95 (+A); AAG(Lys)->AAAG
Codon 100; -CTT, +TCTGAGAACTT
IVS-II-1 (G->A);
IVS-II-1 (G->C);
IVS-II-2,3 (+11, -2); insertion of 11 bp (5'-ACGTTCT CTGA-3') (SEQ ID NO: 5346) and deletion of GA (nts 2 and 3 of IVS-II) between positions 1 and 4 of IVS-II
IVS-II-4,5 (-AG);
IVS-II-5 (G->C)
IVS-II-654 (C->T); AAGGCAATA->AAG^GTAATA
IVS-II-705 (T->G); GATGTAAGA->GAG^GTAAGA
IVS-II-745 (C->G); CAGCACCAT->CAG^GTACCAT
IVS-II-837 (T->G);
IVS-II-843 (T->G);
IVS-II-844 (C->G);
IVS-II-848 (C->A);
IVS-II-848 (C->G);
IVS-II-849 (A->C);
IVS-II-849 (A->G);
IVS-II-850 (-G);
IVS-II-850 (G->A);

TABLE 15-continued

Non-deletional HBB mutations associated with beta thalassemia
IVS-II-850 (G->C);
IVS-II-850 (G->T);
Codons 106/107 (+G); CTG•GGC(Leu•Gly)->CTG•G•GC
Codons 108/109/110/111/112 (-12 bp);
Codon 109 (-G); GTG(Val)->-TG
Codon 110 (T->C); CTG(Leu)->CCG(Pro)
Codon 112 (T->A); TGT(Cys)->TGA(stop codon)
Codon 114 (T->C); CTG(Leu)->CCG(Pro)
Codon 114 (-CT; +G); CTG(Leu)->-GG
Codon 115 (C->A); GCC(Ala)->GAC(Asp)
Codons 120/121 (+A); AAA•GAA(Lys-Glu)->AAA•A•GAA
Codon 121 (G->T); GAA(Glu)->TAA(stop codon)
Codon 123 (-A); ACC(Thr)->-CC
Codons 123/124/125 (-ACCCCACC); ACC•CCA•CCA(Thr•Pro•Pro)->--- --- --A
Codon 124 (-A); CCA(Pro)->CC-
Codon 125 (-A); CCA(Pro)->CC-
Codons 124/125/126 (+CCA); CCA•CCA•GTG(Pro•Pro•Val) (SEQ ID NO: 5347)->CCA•CCA•CCA•GTG (Pro•Pro•Pro•Val) (SEQ ID NO: 5348)
Codon 126 (-T); GTG(Val)->G-G
Codon 126 (T->G); GTG(Val)->GGG(Gly)
Codons 126-131 (Val-Gln-Ala-Ala-Thr-Gln (SEQ ID NO: 5349)) (-17 bp); GTG•GAG•GCT•GCC•TAT•CAG (SEQ ID NO: 5350) ->G
Codon 127 (A->C); CAG(Gln)->CCG(Pro)
Codon 127 (A->G); CAG(Gln)->CGG(Arg)
Codon 127 (C->T); CAG(Gln)->TAG(stop codon)
Codons 127/128 (-AGG); CAG•GCT(Gln•Ala)->C-- -CT(Pro)
Codons 128/129 (-4 bp, -GCTG; +5 bp, +CCACA)
Codons 132-135 (-11 bp, -AAAGTGGTGGC) (SEQ ID NO: 5351)
Codons 134/135/136/137 [-(G)TGGCTGGTGT(G) (SEQ ID NO: 5352) and +(G)GCAG(G)]; GTG•GCT•GGT•GTG (SEQ ID NO: 5353) (Val-Ala-Gly-Val) (SEQ ID NO: 5354) ->GGC•AGG(Gly-Arg)
+1480 (C->G); also known as 3' terminating codon +6 (C->G)
3' UTR (-GCATCTGGATTCT) (SEQ ID NO: 5355) 13 bp deletion between positions +1565 to +1577 (the numbers are relative to the Cap site)
T->C; 12 nts 5' to the poly A site or +1570 (the number is relative to the Cap site)
Poly A (T->C); AATAAA->AACAAA
Poly A (A->G); AATAAA->AATGAA
Poly A (A->G); AATAAA->AATAGA
Poly A (A->G); AATAAA->AATAAG
Poly A (-AT or -TA); AATAAA->A--AAA
Poly A (-AATAA); AATAAA->-----A

[0158] Those skilled in the art will also appreciate that a variety of deletional beta thalassemia alleles exist, which tend to be prevalent in certain at-risk populations. Examples of such deletional beta thalassemia alleles include, but are not limited to, a 25 bp deletion, a 44 bp deletion, a 105 bp deletion, a 290 bp deletion, a 532 bp deletion, a 619 bp deletion, a 1,393 bp deletion, a 1,605 bp deletion ("Croatian deletion"), a 3,485 bp deletion ("Thai deletion"), a 4,237 bp deletion ("Czech deletion"), a 7.6 kb deletion ("Turkish deletion"); a 10,329 bp deletion ("Asian Indian deletion"), a 12,023 bp deletion ("Australian deletion"); a 12,620 bp deletion ("Dutch deletion"), a 27 kb deletion ("Southeast Asian deletion"), a 45 kb deletion ("Filipino deletion"), and a 65 kb deletion ("Italian deletion"). Those skilled in the art will be able to retrieve the corresponding nucleic acid and protein sequences corresponding to these deletions from publicly available sources (e.g., A Syllabus of Thalassemia Mutations (1997) by Titus H. J. Huisman, et al. published by The Sickle Cell Anemia Foundation in Augusta, Ga., USA, available online at http://globin.cse.psu.edu/html/huisman/thals/I-b.entries.html).

[0159] An exemplary method for altering a target beta thalassemia-associated polynucleotide sequence in a cell comprises contacting the beta thalassemia-associated polynucleotide sequence with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target beta thalassemia-associated polynucleotide sequence, wherein the target beta thalassemia associated polynucleotide sequence is cleaved. In some embodiments of this and other aspects, the efficiency of alteration of cells that express Cas protein is from about 50% to about 80%.

[0160] As used herein, the term "contacting" (i.e., contacting a polynucleotide sequence with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and/or ribonucleic acids) is intended to include incubating the Cas protein and/or the ribonucleic acids in the cell together in vitro (e.g., adding the Cas protein or nucleic acid encoding the Cas protein to cells in culture). In some embodiments, the term "contacting" is not intended to include the in vivo exposure of cells to the Cas protein and/or ribonucleic acids as disclosed herein that may occur naturally in a microorganism (i.e., bacteria). The step of contacting a target polynucleotide sequence with a Cas protein and/or ribonucleic acids as disclosed herein can be conducted in any suitable manner. For example, the cells may be treated in adherent culture, or in suspension culture. It is understood that the cells contacted with a Cas protein and/or ribonucleic acids as disclosed herein can also be simultaneously or subsequently contacted with another

agent, such as a growth factor or other differentiation agent or environments to stabilize the cells, or to differentiate the cells further.

[0161] In another aspect, the present invention provides a method for treating or preventing a disorder associated with expression of a polynucleotide sequence in a subject.

[0162] The terms "treat", "treating", "treatment", etc., as applied to an isolated cell, include subjecting the cell to any kind of process or condition or performing any kind of manipulation or procedure on the cell. As applied to a subject, the terms refer to providing medical or surgical attention, care, or management to an individual. The individual is usually ill or injured, or at increased risk of becoming ill relative to an average member of the population and in need of such attention, care, or management.

[0163] As used herein, the term "treating" and "treatment" refers to administering to a subject an effective amount of a composition so that the subject has a reduction in at least one symptom of the disease or an improvement in the disease, for example, beneficial or desired clinical results. For purposes of this invention, beneficial or desired clinical results include, but are not limited to, alleviation of one or more symptoms, diminishment of extent of disease, stabilized (i.e., not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable. Treating can refer to prolonging survival as compared to expected survival if not receiving treatment. Thus, one of skill in the art realizes that a treatment may improve the disease condition, but may not be a complete cure for the disease. As used herein, the term "treatment" includes prophylaxis. Alternatively, treatment is "effective" if the progression of a disease is reduced or halted. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment. Those in need of treatment include those already diagnosed with a disorder associated with expression of a polynucleotide sequence, as well as those likely to develop such a disorder due to genetic susceptibility or other factors.

[0164] By "treatment", "prevention" or "amelioration" of a disease or disorder is meant delaying or preventing the onset of such a disease or disorder, reversing, alleviating, ameliorating, inhibiting, slowing down or stopping the progression, aggravation or deterioration the progression or severity of a condition associated with such a disease or disorder. In one embodiment, the symptoms of a disease or disorder are alleviated by at least 5%, at least 10%, at least 20%, at least 30%, at least 40%, or at least 50%.

[0165] In some embodiments, a method for treating or preventing a disorder associated with expression of a polynucleotide sequence comprises a method for treating or preventing a disorder associated with expression of a SCID-associated polynucleotide sequence.

[0166] An exemplary method for treating or preventing a disorder associated with expression of a SCID-associated polynucleotide sequence in a subject comprises (a) altering a target SCID-associated polynucleotide sequence in a cell ex vivo by contacting the SCID-associated polynucleotide sequence with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target SCID-associated polynucleotide sequence, wherein the target SCD-associated polynucleotide sequence is cleaved, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the SCID-associated polynucleotide sequence. In some embodiments of this and other aspects, the efficiency of alteration of cells that express Cas protein is from about 50% to about 80%.

[0167] An exemplary method for treating or preventing a disorder associated with expression of a SCID-associated polynucleotide sequence in a subject comprises altering a target SCID-associated polynucleotide sequence in a cell by contacting the SCID-associated polynucleotide sequence with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target SCID-associated polynucleotide sequence, and wherein the target SCID-associated polynucleotide sequence is cleaved, thereby treating or preventing a disorder associated with expression of the SCID-associated polynucleotide sequence.

[0168] In some embodiments, a method for treating or preventing a disorder associated with expression of a polynucleotide sequence comprises a method for treating or preventing a disorder associated with expression of a SCD-associated polynucleotide sequence.

[0169] An exemplary method for treating or preventing a disorder associated with expression of a SCD-associated polynucleotide sequence in a subject comprises (a) altering a target SCD-associated polynucleotide sequence in a cell ex vivo by contacting the SCD-associated polynucleotide sequence with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target SCD-associated polynucleotide sequence, wherein the target SCD-associated polynucleotide sequence is cleaved, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the SCD-associated polynucleotide sequence. In some embodiments of this and other aspects, the efficiency of alteration of cells that express Cas protein is from about 50% to about 80%.

[0170] An exemplary method for treating or preventing a disorder associated with expression of a SCD-associated polynucleotide sequence in a subject comprises altering a target SCD-associated polynucleotide sequence in a cell by contacting the SCD-associated polynucleotide sequence with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target SCD-associated polynucleotide sequence, and wherein the target SCD-associated polynucleotide sequence is cleaved, thereby treating or preventing a disorder associated with expression of the SCD-associated polynucleotide sequence.

[0171] In some embodiments, a method for treating or preventing a disorder associated with expression of a polynucleotide sequence comprises a method for treating or preventing a disorder associated with expression of a beta thalassemia-associated polynucleotide sequence.

[0172] An exemplary method for treating or preventing a disorder associated with expression of a beta thalassemia-associated polynucleotide sequence in a subject comprises (a) altering a target beta thalassemia-associated polynucleotide sequence in a cell ex vivo by contacting the beta

thalassemia-associated polynucleotide sequence with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target beta thalassemia-associated polynucleotide sequence, wherein the target beta thalassemia-associated polynucleotide sequence is cleaved, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the beta thalassemia-associated polynucleotide sequence. In some embodiments of this and other aspects, the efficiency of alteration of cells that express Cas protein is from about 50% to about 80%.

[0173] An exemplary method for treating or preventing a disorder associated with expression of a beta thalassemia-associated polynucleotide sequence in a subject comprises altering a target beta thalassemia-associated polynucleotide sequence in a cell by contacting the beta thalassemia-associated polynucleotide sequence with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target beta thalassemia-associated polynucleotide sequence, and wherein the target beta thalassemia-associated polynucleotide sequence is cleaved, thereby treating or preventing a disorder associated with expression of the beta thalassemia-associated polynucleotide sequence.

[0174] The present invention contemplates altering target polynucleotide sequences in any manner which is available to the skilled artisan utilizing a CRISPR/Cas system of the present invention. Any CRISPR/Cas system that is capable of altering a target polynucleotide sequence in a cell can be used. Such CRISPR-Cas systems can employ a variety of Cas proteins (Haft et al. *PLoS Comput Biol.* 2005; 1(6)e60). The molecular machinery of such Cas proteins that allows the CRISPR/Cas system to alter target polynucleotide sequences in cells include RNA binding proteins, endo- and exo-nucleases, helicases, and polymerases. In some embodiments, the CRISPR/Cas system is a CRISPR type I system. In some embodiments, the CRISPR/Cas system is a CRISPR type II system.

[0175] The CRISPR/Cas systems of the present invention can be used to alter a target polynucleotide sequence in a cell. The present invention contemplates altering target polynucleotide sequences in a cell for any purpose. In some embodiments, the target polynucleotide sequence in a cell is altered to produce a mutant cell. As used herein, a "mutant cell" refers to a cell with a resulting genotype that differs from its original genotype. In some instances, a "mutant cell" exhibits a mutant phenotype, for example when a normally functioning gene is altered using the CRISPR/Cas systems of the present invention. In other instances, a "mutant cell" exhibits a wild-type phenotype, for example when a CRISPR/Cas system of the present invention is used to correct a mutant genotype. In exemplary embodiments, a mutant cell exhibits a wild-type ADA phenotype. In exemplary embodiments, a mutant cell exhibits a wild-type AK2 phenotype. In exemplary embodiments, a mutant cell exhibits a wild-type CD3D phenotype. In exemplary embodiments, a mutant cell exhibits a wild-type DCLRE1C phenotype. In exemplary embodiments, a mutant cell exhibits a wild-type IL2RG phenotype. In exemplary embodiments, a mutant cell exhibits a wild-type IL7R phenotype. In exemplary embodiments, a mutant cell exhibits a wild-type JAK3 phenotype. In exemplary embodiments, a mutant cell exhibits a wild-type LIG4 phenotype. In exemplary embodiments, a mutant cell exhibits a wild-type NHEJ1 phenotype. In exemplary embodiments, a mutant cell exhibits a wild-type PNP phenotype. In exemplary embodiments, a mutant cell exhibits a wild-type PRKDC phenotype. In exemplary embodiments, a mutant cell exhibits a wild-type RAG1 phenotype. In exemplary embodiments, a mutant cell exhibits a wild-type RAG2 phenotype. In exemplary embodiments, a mutant cell exhibits a wild-type ZAP70 phenotype. In exemplary embodiments, a mutant cell exhibits a wild-type HBB phenotype. In some embodiments, the target polynucleotide sequence in a cell is altered to correct or repair a genetic mutation (e.g., to restore a normal phenotype to the cell). In an exemplary embodiment, a target SCID-associated polynucleotide sequence in a cell is altered to correct or repair one or more ADA mutations involved in SCID. In an exemplary embodiment, a target SCID-associated polynucleotide sequence in a cell is altered to correct or repair one or more AK2 mutations involved in SCID. In an exemplary embodiment, a target SCID-associated polynucleotide sequence in a cell is altered to correct or repair one or more CD3D mutations involved in SCID. In an exemplary embodiment, a target SCID-associated polynucleotide sequence in a cell is altered to correct or repair one or more DCRE1C mutations involved in SCID. In an exemplary embodiment, a target SCID-associated polynucleotide sequence in a cell is altered to correct or repair one or more IL2RG mutations involved in SCID. In an exemplary embodiment, a target SCID-associated polynucleotide sequence in a cell is altered to correct or repair one or more IL7R mutations involved in SCID. In an exemplary embodiment, a target SCID-associated polynucleotide sequence in a cell is altered to correct or repair one or more JAK3 mutations involved in SCID. In an exemplary embodiment, a target SCID-associated polynucleotide sequence in a cell is altered to correct or repair one or more LIG4 mutations involved in SCID. In an exemplary embodiment, a target SCID-associated polynucleotide sequence in a cell is altered to correct or repair one or more NHEJ1 mutations involved in SCID. In an exemplary embodiment, a target SCID-associated polynucleotide sequence in a cell is altered to correct or repair one or more PNP mutations involved in SCID. In an exemplary embodiment, a target SCID-associated polynucleotide sequence in a cell is altered to correct or repair one or more PRKDC mutations involved in SCID. In an exemplary embodiment, a target SCID-associated polynucleotide sequence in a cell is altered to correct or repair one or more RAG1 mutations involved in SCID. In an exemplary embodiment, a target SCID-associated polynucleotide sequence in a cell is altered to correct or repair one or more RAG2 mutations involved in SCID. In an exemplary embodiment, a target SCID-associated polynucleotide sequence in a cell is altered to correct or repair one or more ZAP70 mutations involved in SCID. In an exemplary embodiment, a target SCD-associated polynucleotide sequence in a cell is altered to correct or repair one or more HBB mutations involved in SCD. In an exemplary embodiment, a target SCD-associated polynucleotide sequence in a cell is altered to correct or repair one or more HBB mutations involved in SCD. In another exemplary embodiment, a target beta thalassemia-associated polynucle-

otide sequence in a cell is altered to correct or repair one or more HBB mutations involved in beta thalassemia. In some embodiments, the target polynucleotide sequence in a cell is altered to induce a genetic mutation (e.g., to disrupt the function of a gene or genomic element).

[0176] In some embodiments, the alteration is an indel. As used herein, "indel" refers to a mutation resulting from an insertion, deletion, or a combination thereof. As will be appreciated by those skilled in the art, an indel in a coding region of a genomic sequence will result in a frameshift mutation, unless the length of the indel is a multiple of three. In some embodiments, the alteration is a point mutation. As used herein, "point mutation" refers to a substitution that replaces one of the nucleotides. A CRISPR/Cas system of the present invention can be used to induce an indel of any length or a point mutation in a target polynucleotide sequence.

[0177] In some embodiments, the alteration results in a knock out of the target polynucleotide sequence or a portion thereof. Knocking out a target polynucleotide sequence or a portion thereof using a CRISPR/Cas system of the present invention can be useful for a variety of applications. For example, knocking out a target polynucleotide sequence in a cell can be performed in vitro for research purposes. For ex vivo or in vivo purposes, knocking out a target polynucleotide sequence in a cell can be useful for treating or preventing a disorder associated with expression of the target polynucleotide sequence.

[0178] As used herein, "knock out" includes deleting all or a portion of the target polynucleotide sequence in a way that interferes with the function of the target polynucleotide sequence. For example, a knock out can be achieved by altering a target polynucleotide sequence by inducing an indel in the target polynucleotide sequence in a functional domain of the target polynucleotide sequence (e.g., a DNA binding domain). Those skilled in the art will readily appreciate how to use the CRISPR/Cas systems of the present invention to knock out a target polynucleotide sequence or a portion thereof based upon the details described herein.

[0179] In some embodiments, the alteration results in reduced expression of the target polynucleotide sequence. The terms "decrease," "reduced," "reduction," and "decrease" are all used herein generally to mean a decrease by a statistically significant amount. However, for avoidance of doubt, decrease," "reduced," "reduction," "decrease" means a decrease by at least 10% as compared to a reference level, for example a decrease by at least about 20%, or at least about 30%, or at least about 40%, or at least about 50%, or at least about 60%, or at least about 70%, or at least about 80%, or at least about 90% or up to and including a 100% decrease (i.e. absent level as compared to a reference sample), or any decrease between 10-100% as compared to a reference level.

[0180] In some embodiments, the alteration results in increased expression of the target polynucleotide sequence. The terms "increased", "increase" or "enhance" or "activate" are all used herein to generally mean an increase by a statically significant amount; for the avoidance of any doubt, the terms "increased", "increase" or "enhance" or "activate" means an increase of at least 10% as compared to a reference level, for example an increase of at least about 20%, or at least about 30%, or at least about 40%, or at least about 50%, or at least about 60%, or at least about 70%, or at least about 80%, or at least about 90% or up to and including a 100% increase or any increase between 10-100% as compared to a reference level, or at least about a 2-fold, or at least about a 3-fold, or at least about a 4-fold, or at least about a 5-fold or at least about a 10-fold increase, or any increase between 2-fold and 10-fold or greater as compared to a reference level.

[0181] The term "statistically significant" or "significantly" refers to statistical significance and generally means a two standard deviation (2SD) below normal, or lower, concentration of the marker. The term refers to statistical evidence that there is a difference. It is defined as the probability of making a decision to reject the null hypothesis when the null hypothesis is actually true. The decision is often made using the p-value.

[0182] In some embodiments, the alteration is a homozygous alteration. In some embodiments, the alteration is a heterozygous alteration.

[0183] In some embodiments, the alteration results in correction of the target polynucleotide sequence from an undesired sequence to a desired sequence. The CRISPR/Cas systems of the present invention can be used to correct any type of mutation or error in a target polynucleotide sequence. For example, the CRISPR/Cas systems of the present invention can be used to insert a nucleotide sequence that is missing from a target polynucleotide sequence due to a deletion. The CRISPR/Cas systems of the present invention can also be used to delete or excise a nucleotide sequence from a target polynucleotide sequence due to an insertion mutation. In some instances, the CRISPR/Cas systems of the present invention can be used to replace an incorrect nucleotide sequence with a correct nucleotide sequence (e.g., to restore function to a target polynucleotide sequence that is impaired due to a loss of function mutation, i.e., a SNP).

[0184] In exemplary embodiments, the CRISPR/Cas systems of the present invention can be used to replace mutant ADA polynucleotide sequences with wild-type ADA polynucleotide sequences.

[0185] In exemplary embodiments, the CRISPR/Cas systems of the present invention can be used to replace mutant AK2 polynucleotide sequences with wild-type AK2 polynucleotide sequences.

[0186] In exemplary embodiments, the CRISPR/Cas systems of the present invention can be used to replace mutant CD3D polynucleotide sequences with wild-type CD3D polynucleotide sequences.

[0187] In exemplary embodiments, the CRISPR/Cas systems of the present invention can be used to replace mutant DCLRE1C polynucleotide sequences with wild-type DCLRE1C polynucleotide sequences.

[0188] In exemplary embodiments, the CRISPR/Cas systems of the present invention can be used to replace mutant IL2RG polynucleotide sequences with wild-type IL2RG polynucleotide sequences.

[0189] In exemplary embodiments, the CRISPR/Cas systems of the present invention can be used to replace mutant IL7R polynucleotide sequences with wild-type IL7R polynucleotide sequences.

[0190] In exemplary embodiments, the CRISPR/Cas systems of the present invention can be used to replace mutant JAK3 polynucleotide sequences with wild-type JAK3 polynucleotide sequences.

[0191] In exemplary embodiments, the CRISPR/Cas systems of the present invention can be used to replace mutant LIG4 polynucleotide sequences with wild-type LIG4 polynucleotide sequences.

[0192] In exemplary embodiments, the CRISPR/Cas systems of the present invention can be used to replace mutant NHEJ1 polynucleotide sequences with wild-type NHEJ1 polynucleotide sequences.

[0193] In exemplary embodiments, the CRISPR/Cas systems of the present invention can be used to replace mutant PNP polynucleotide sequences with wild-type PNP polynucleotide sequences.

[0194] In exemplary embodiments, the CRISPR/Cas systems of the present invention can be used to replace mutant PRKDC polynucleotide sequences with wild-type PRKDC polynucleotide sequences.

[0195] In exemplary embodiments, the CRISPR/Cas systems of the present invention can be used to replace mutant RAG1 polynucleotide sequences with wild-type RAG1 polynucleotide sequences.

[0196] In exemplary embodiments, the CRISPR/Cas systems of the present invention can be used to replace mutant RAG2 polynucleotide sequences with wild-type RAG2 polynucleotide sequences.

[0197] In exemplary embodiments, the CRISPR/Cas systems of the present invention can be used to replace mutant ZAP70 polynucleotide sequences with wild-type ZAP70 polynucleotide sequences.

[0198] In exemplary embodiments, the CRISPR/Cas systems of the present invention can be used to replace mutant HBB polynucleotide sequences with wild-type HBB polynucleotide sequences.

[0199] The CRISPR/Cas systems of the present invention can alter target polynucleotides with surprisingly high efficiency as compared to conventional CRISPR/Cas systems. In certain embodiments, the efficiency of alteration is at least about 5%. In certain embodiments, the efficiency of alteration is at least about 10%. In certain embodiments, the efficiency of alteration is from about 10% to about 80%. In certain embodiments, the efficiency of alteration is from about 30% to about 80%. In certain embodiments, the efficiency of alteration is from about 50% to about 80%. In some embodiments, the efficiency of alteration is greater than or equal to about 80%.

[0200] The CRISPR/Cas systems of the present invention can be used to alter any target polynucleotide sequence in a cell. Those skilled in the art will readily appreciate that desirable target polynucleotide sequences to be altered in any particular cell may correspond to any genomic sequence for which expression of the genomic sequence is associated with a disorder or otherwise facilitates entry of a pathogen into the cell. For example, a desirable target polynucleotide sequence to alter in a cell may be a polynucleotide sequence corresponding to a genomic sequence which contains a disease associated single polynucleotide polymorphism (e.g., sickle cell disease, e.g., sickle cell anemia). In such example, the CRISPR/Cas systems of the present invention can be used to correct the disease associated SNP by replacing it with a wild-type allele (e.g., replacing a Glu6Val SNP in hemoglobin S to Val6Glu, a Glu6Lys SNP in hemoglobin C to Lys6Glu, a Glu121Gln SNP in hemoglobin D to Gln121Glu, a Glu121Lys SNP in hemoglobin O to Lys121Glu). As another example, a polynucleotide sequence of a target gene which is responsible for entry or proliferation of a pathogen into a cell may be a suitable target for deletion or insertion to disrupt the function of the target gene to prevent the pathogen from entering the cell or proliferating inside the cell.

[0201] In some embodiments, the target polynucleotide sequence is a genomic sequence. In some embodiments, the target polynucleotide sequence is a human genomic sequence. In some embodiments, the target polynucleotide sequence is a mammalian genomic sequence. In some embodiments, the target polynucleotide sequence is a vertebrate genomic sequence. In some embodiments, the target sequence is a mutant or variant genomic sequence (e.g., a ADA mutant, a AK2 mutant, a CD3D mutant, a DCLRE1C mutant, a IL2RG mutant, a IL7R mutant, a JAK3 mutant, a LIG4 mutant, a NHEJ1 mutant, a PNP mutant, a PRKDC mutant, a RAG1 mutant, a RAG2 mutant, a ZAP70 mutant, a HBB mutant). In some embodiments, the target polynucleotide sequence is a human genomic mutant or variant sequence (e.g., ADA, AK2, CD3D, DCLRE1C, IL2RG, IL7R, JAK3, LIG4, NHEJ1, PNP, PRKDC, RAG1, RAG2, ZAP70, HBB). In some embodiments, the target polynucleotide sequence is a mutant or variant mammalian genomic sequence. In some embodiments, the target polynucleotide sequence is a mammalian mutant or variant genomic sequence.

[0202] In some embodiments, a target polynucleotide sequence is a pathogenic genomic sequence. Exemplary pathogenic genomic sequences include, but are not limited to a viral genomic sequence, a bacterial genomic sequence, a fungal genomic sequence, a toxin genomic sequence, or a parasitic genomic sequence. In such embodiments, the CRISPR/Cas systems of the present invention can be used to disrupt the function of a pathogen (e.g., to treat or prevent an infection by the pathogen) by cleaving a genomic sequence of the pathogen (e.g., a genomic sequence that is critical for entry into a cell, or responsible for multiplication, growth or survival once the pathogen is inside a cell).

[0203] In some embodiments, the target polynucleotide sequence is an SCID-associated polynucleotide sequence.

[0204] In some embodiments, the target polynucleotide sequence is ADA or a portion thereof. In some embodiments, the target polynucleotide sequence is a variant of ADA or a portion thereof. In some embodiments, the target polynucleotide sequence is a homolog of ADA or a portion thereof. In some embodiments, the target polynucleotide sequence is an ortholog of ADA or a portion thereof.

[0205] In some embodiments, the target polynucleotide sequence is AK2 or a portion thereof. In some embodiments, the target polynucleotide sequence is a variant of AK2 or a portion thereof. In some embodiments, the target polynucleotide sequence is AK2 coding sequence 1 or a portion thereof. In some embodiments, the target polynucleotide sequence is AK2 coding sequence 2 or a portion thereof. In some embodiments, the target polynucleotide sequence is AK2 coding sequence 3 or a portion thereof. In some embodiments, the target polynucleotide sequence is a homolog of AK2 or a portion thereof. In some embodiments, the target polynucleotide sequence is an ortholog of AK2 or a portion thereof.

[0206] In some embodiments, the target polynucleotide sequence is CD3D or a portion thereof. In some embodiments, the target polynucleotide sequence is a variant of CD3D or a portion thereof. In some embodiments, the target polynucleotide sequence is CD3D coding sequence 1 or a

portion thereof. In some embodiments, the target polynucleotide sequence is CD3D coding sequence 2 or a portion thereof. In some embodiments, the target polynucleotide sequence is a homolog of CD3D or a portion thereof. In some embodiments, the target polynucleotide sequence is an ortholog of CD3D or a portion thereof.

[0207] In some embodiments, the target polynucleotide sequence is DCLRE1C or a portion thereof. In some embodiments, the target polynucleotide sequence is a variant of DCLRE1C or a portion thereof. In some embodiments, the target polynucleotide sequence is DCLRE1C coding sequence 1 or a portion thereof. In some embodiments, the target polynucleotide sequence is DCLRE1C coding sequence 1 or a portion thereof. In some embodiments, the target polynucleotide sequence is DCLRE1C coding sequence 2 or a portion thereof. In some embodiments, the target polynucleotide sequence is DCLRE1C coding sequence 3 or a portion thereof. In some embodiments, the target polynucleotide sequence is DCLRE1C coding sequence 4 or a portion thereof. In some embodiments, the target polynucleotide sequence is a homolog of DCLRE1C or a portion thereof. In some embodiments, the target polynucleotide sequence is an ortholog of DCLRE1C or a portion thereof.

[0208] In some embodiments, the target polynucleotide sequence is IL2RG or a portion thereof. In some embodiments, the target polynucleotide sequence is a variant of IL2RG or a portion thereof. In some embodiments, the target polynucleotide sequence is a homolog of IL2RG or a portion thereof. In some embodiments, the target polynucleotide sequence is an ortholog of IL2RG or a portion thereof.

[0209] In some embodiments, the target polynucleotide sequence is IL7R or a portion thereof. In some embodiments, the target polynucleotide sequence is a variant of IL7R or a portion thereof. In some embodiments, the target polynucleotide sequence is a homolog of IL7R or a portion thereof. In some embodiments, the target polynucleotide sequence is an ortholog of IL7R or a portion thereof.

[0210] In some embodiments, the target polynucleotide sequence is JAK3 or a portion thereof. In some embodiments, the target polynucleotide sequence is a variant of JAK3 or a portion thereof. In some embodiments, the target polynucleotide sequence is a homolog of JAK3 or a portion thereof. In some embodiments, the target polynucleotide sequence is an ortholog of JAK3 or a portion thereof.

[0211] In some embodiments, the target polynucleotide sequence is LIG4 or a portion thereof. In some embodiments, the target polynucleotide sequence is a variant of LIG4 or a portion thereof. In some embodiments, the target polynucleotide sequence is LIG4 coding sequence 1 or a portion thereof. In some embodiments, the target polynucleotide sequence is LIG4 coding sequence 2 or a portion thereof. In some embodiments, the target polynucleotide sequence is LIG4 coding sequence 3 or a portion thereof. In some embodiments, the target polynucleotide sequence is a homolog of LIG4 or a portion thereof. In some embodiments, the target polynucleotide sequence is an ortholog of LIG4 or a portion thereof.

[0212] In some embodiments, the target polynucleotide sequence is NHEJ1 or a portion thereof. In some embodiments, the target polynucleotide sequence is a variant of NHEJ1 or a portion thereof. In some embodiments, the target polynucleotide sequence is a homolog of NHEJ1 or a portion thereof. In some embodiments, the target polynucleotide sequence is an ortholog of NHEJ1 or a portion thereof.

[0213] In some embodiments, the target polynucleotide sequence is PNP or a portion thereof. In some embodiments, the target polynucleotide sequence is a variant of PNP or a portion thereof. In some embodiments, the target polynucleotide sequence is a homolog of PNP or a portion thereof. In some embodiments, the target polynucleotide sequence is an ortholog of PNP or a portion thereof.

[0214] In some embodiments, the target polynucleotide sequence is PRKDC or a portion thereof. In some embodiments, the target polynucleotide sequence is a variant of PRKDC or a portion thereof. In some embodiments, the target polynucleotide sequence is PRKDC coding sequence 1 or a portion thereof. In some embodiments, the target polynucleotide sequence is PRKDC coding sequence 2 or a portion thereof. In some embodiments, the target polynucleotide sequence is a homolog of PRKDC or a portion thereof. In some embodiments, the target polynucleotide sequence is an ortholog of PRKDC or a portion thereof.

[0215] In some embodiments, the target polynucleotide sequence is RAG1 or a portion thereof. In some embodiments, the target polynucleotide sequence is a variant of RAG1 or a portion thereof. In some embodiments, the target polynucleotide sequence is a homolog of RAG1 or a portion thereof. In some embodiments, the target polynucleotide sequence is an ortholog of RAG1 or a portion thereof.

[0216] In some embodiments, the target polynucleotide sequence is RAG2 or a portion thereof. In some embodiments, the target polynucleotide sequence is a variant of RAG2 or a portion thereof. In some embodiments, the target polynucleotide sequence is RAG2 coding sequence 1 or a portion thereof. In some embodiments, the target polynucleotide sequence is RAG2 coding sequence 2 or a portion thereof. In some embodiments, the target polynucleotide sequence is RAG2 coding sequence 3 or a portion thereof. In some embodiments, the target polynucleotide sequence is a homolog of RAG2 or a portion thereof. In some embodiments, the target polynucleotide sequence is an ortholog of RAG2 or a portion thereof.

[0217] In some embodiments, the target polynucleotide sequence is ZAP70 or a portion thereof. In some embodiments, the target polynucleotide sequence is a variant of ZAP70 or a portion thereof. In some embodiments, the target polynucleotide sequence is ZAP70 coding sequence 1 or a portion thereof. In some embodiments, the target polynucleotide sequence is ZAP70 coding sequence 2 or a portion thereof. In some embodiments, the target polynucleotide sequence is a homolog of ZAP70 or a portion thereof. In some embodiments, the target polynucleotide sequence is an ortholog of ZAP70 or a portion thereof.

[0218] In some embodiments, the target polynucleotide sequence is a SCD-associated polynucleotide sequence (e.g., a mutant form of HBB; NCBI Gene ID: 3043) or a portion thereof. In some embodiments, the target polynucleotide sequence is a mutant homolog of a SCD-associated polynucleotide sequence (e.g., a mutated homolog of HBB) or a portion thereof. In some embodiments, the target polynucleotide sequence is a mutant ortholog of a SCD-associated polynucleotide sequence (e.g., a mutated ortholog of HBB) or a portion thereof.

[0219] In some embodiments, the target polynucleotide sequence is a beta thalassemia-associated polynucleotide sequence (e.g., a mutant form of HBB).

[0220] In some embodiments, the target polynucleotide sequence is a mutant homolog of a beta thalassemia-associated polynucleotide sequence (e.g., a mutated homolog of HBB) or a portion thereof. In some embodiments, the target polynucleotide sequence is a mutant ortholog of a beta thalassemia-associated polynucleotide sequence (e.g., a mutated ortholog of HBB) or a portion thereof. The relevant portions of these target polynucleotide sequences correspond to the guide sequences shown in FIGS. **1**, **2-4**, **5-6**, **7-10**, **12**, **13**, **14**, **15-17**, **18**, **19**, **20-21**, **22**, **23-25**, **26-27**, and **11**, respectively.

[0221] It should be appreciated that the CRISPR/Cas systems of the present invention can cleave target polynucleotide sequences in a variety of ways. In some embodiments, the target polynucleotide sequence is cleaved such that a double-strand break results. In some embodiments, the target polynucleotide sequence is cleaved such that a single-strand break results.

[0222] The methods of the present invention can be used to alter any target polynucleotide sequence in a cell, as long as the target polynucleotide sequence in the cell contains a suitable target motif that allows at least one ribonucleic acid of the CRISPR/Cas system to direct the Cas protein to and hybridize to the target motif. Those skilled in the art will appreciate that the target motif for targeting a particular polynucleotide depends on the CRISPR/Cas system being used, and the sequence of the polynucleotide to be targeted.

[0223] In some embodiments, the target motif is at least 20 bp in length. In some embodiments, the target motif is a 20-nucleotide DNA sequence. In some embodiments, the target motif is a 20-nucleotide DNA sequence beginning with G and immediately precedes an NGG motif recognized by the Cas protein. In some embodiments, the target motif is $G(N)_{19}NGG$. In some embodiments, the target motif is a 20-nucleotide DNA sequence and immediately precedes an NGG motif recognized by the Cas protein. In some embodiments, the target motif is $(N)_{20}NGG$. It is to be understood that the type of target motif for each of the ADA, AK2, CD3D, DCLRE1C, HBB, IL2RG, IL7R, JAK3, LIG4, NHEJ1, PNP, PRKDC, RAG1, RAG2, and ZAP70 target polynucleotide sequences can be found in the "site_type" column of FIGS. **1**, **2-4**, **5-6**, **7-10**, **11**, **12**, **13**, **14**, **15-17**, **18**, **19**, **20-21**, **22**, **23-25**, and **26-27**, respectively.

[0224] The target motifs of the present invention can be selected to minimize off-target effects of the CRISPR/Cas systems of the present invention. In some embodiments, the target motif is selected such that it contains at least two mismatches when compared with all other genomic nucleotide sequences in the cell. In some embodiments, the target motif is selected such that it contains at least one mismatch when compared with all other genomic nucleotide sequences in the cell. Those skilled in the art will appreciate that a variety of techniques can be used to select suitable target motifs for minimizing off-target effects (e.g., bioinformatics analyses).

[0225] In some embodiments, the CRISPR/Cas systems of the present invention utilize homology-directed repair to correct target polynucleotide sequences. In some embodiments, subsequent to cleavage of the target polynucleotide sequence, homology-directed repair occurs. In some embodiments, homology-directed repair is performed using an exogenously introduced DNA repair template. The exogenously introduced DNA repair template can be single-stranded or double-stranded. The DNA repair template can be of any length. Those skilled in the art will appreciate that the length of any particular DNA repair template will depend on the target polynucleotide sequence that is to be corrected. The DNA repair template can be designed to repair or replace any target polynucleotide sequence, particularly target polynucleotide sequences comprising disease associated polymorphisms (e.g., SNPs). For example, homology-directed repair of a mutant allele comprising such SNPs can be achieved with a CRISPR/Cas system by selecting two target motifs which flank the mutant allele, and an designing a DNA repair template to match the wild-type allele.

[0226] In an exemplary embodiment, a cleaved target SCID-associated polynucleotide associated sequence is corrected by homology-directed repair utilizing a corresponding normal wild-type gene sequence as a DNA repair template.

[0227] In an exemplary embodiment, a cleaved target SCID-associated polynucleotide associated sequence (i.e., mutant ADA) is corrected by homology-directed repair utilizing a normal wild-type ADA sequence or portions thereof as a DNA repair template.

[0228] In an exemplary embodiment, a cleaved target SCID-associated polynucleotide associated sequence (i.e., mutant AK2) is corrected by homology-directed repair utilizing a normal wild-type AK2 sequence (e.g., wild-type AK2 coding sequence 1, AK2 coding sequence 2, and AK2 coding sequence 3 or portions thereof) as a DNA repair template.

[0229] In an exemplary embodiment, a cleaved target SCID-associated polynucleotide associated sequence (i.e., mutant CD3D) is corrected by homology-directed repair utilizing a normal wild-type CD3D sequence (e.g., wild-type CD3D coding sequence 1, and CD3D coding sequence 2 or portions thereof) as a DNA repair template.

[0230] In an exemplary embodiment, a cleaved target SCID-associated polynucleotide associated sequence (i.e., mutant DCLRE1C) is corrected by homology-directed repair utilizing a normal wild-type DCLRE1C sequence (e.g., wild-type DCLRE1C coding sequence 1, DCLRE1C coding sequence 2, DCLRE1C coding sequence 3, and DCLRE1C coding sequence 4 or portions thereof) as a DNA repair template.

[0231] In an exemplary embodiment, a cleaved target SCID-associated polynucleotide associated sequence (i.e., mutant IL2RG) is corrected by homology-directed repair utilizing a normal wild-type IL2RG sequence or portions thereof as a DNA repair template.

[0232] In an exemplary embodiment, a cleaved target SCID-associated polynucleotide associated sequence (i.e., mutant IL7R) is corrected by homology-directed repair utilizing a normal wild-type IL7R sequence or portions thereof as a DNA repair template.

[0233] In an exemplary embodiment, a cleaved target SCID-associated polynucleotide associated sequence (i.e., mutant JAK3) is corrected by homology-directed repair utilizing a normal wild-type JAK3 sequence or portions thereof as a DNA repair template.

[0234] In an exemplary embodiment, a cleaved target SCID-associated polynucleotide associated sequence (i.e., mutant LIG4) is corrected by homology-directed repair utilizing a normal wild-type LIG4 sequence (e.g., wild-type LIG4 coding sequence 1, LIG4 coding sequence 2, LIG4 coding sequence 3, or portions thereof) as a DNA repair template.

[0235] In an exemplary embodiment, a cleaved target SCID-associated polynucleotide associated sequence (i.e., mutant NHEJ1) is corrected by homology-directed repair utilizing a normal wild-type NHEJ1 sequence or portions thereof as a DNA repair template.

[0236] In an exemplary embodiment, a cleaved target SCID-associated polynucleotide associated sequence (i.e., mutant PNP) is corrected by homology-directed repair utilizing a normal wild-type PNP sequence or portions thereof as a DNA repair template.

[0237] In an exemplary embodiment, a cleaved target SCID-associated polynucleotide associated sequence (i.e., mutant PRKDC) is corrected by homology-directed repair utilizing a normal wild-type PRKDC sequence (e.g., wild-type PRKDC coding sequence 1, PRKDC coding sequence 2, or portions thereof) as a DNA repair template.

[0238] In an exemplary embodiment, a cleaved target SCID-associated polynucleotide associated sequence (i.e., mutant RAG1) is corrected by homology-directed repair utilizing a normal wild-type RAG1 sequence or portions thereof as a DNA repair template.

[0239] In an exemplary embodiment, a cleaved target SCID-associated polynucleotide associated sequence (i.e., mutant RAG2) is corrected by homology-directed repair utilizing a normal wild-type RAG2 sequence (e.g., wild-type RAG2 coding sequence 1, RAG2 coding sequence 2, RAG2 coding sequence 3, or portions thereof) as a DNA repair template.

[0240] In an exemplary embodiment, a cleaved target SCID-associated polynucleotide associated sequence (i.e., mutant ZAP70) is corrected by homology-directed repair utilizing a normal wild-type ZAP70 sequence (e.g., wild-type ZAP70 coding sequence 1, ZAP70 coding sequence 2, or portions thereof) as a DNA repair template.

[0241] In an exemplary embodiment, a cleaved target SCD-associated polynucleotide associated sequence is corrected by homology-directed repair utilizing a normal wild-type HBB sequence or portions thereof as a DNA repair template.

[0242] In an exemplary embodiment, a cleaved target beta thalassemia-associated polynucleotide associated sequence is corrected by homology-directed repair utilizing a normal wild-type HBB sequence or portions thereof as a DNA repair template.

[0243] In some embodiments, a CRISPR/Cas system of the present invention includes a Cas protein and at least one to two one ribonucleic acids that are capable of directing the Cas protein to and hybridizing to a target motif of a target polynucleotide sequence.

[0244] As used herein, "protein" and "polypeptide" are used interchangeably to refer to a series of amino acid residues joined by peptide bonds (i.e., a polymer of amino acids) and include modified amino acids (e.g., phosphorylated, glycated, glycosolated, etc.) and amino acid analogs. Exemplary polypeptides or proteins include gene products, naturally occurring proteins, homologs, paralogs, fragments and other equivalents, variants, and analogs of the above.

[0245] In some embodiments, a Cas protein comprises one or more amino acid substitutions or modifications. In some embodiments, the one or more amino acid substitutions comprises a conservative amino acid substitution. In some instances, substitutions and/or modifications can prevent or reduce proteolytic degradation and/or extend the half-life of the polypeptide in a cell. In some embodiments, the Cas protein can comprise a peptide bond replacement (e.g., urea, thiourea, carbamate, sulfonyl urea, etc.). In some embodiments, the Cas protein can comprise a naturally occurring amino acid. In some embodiments, the Cas protein can comprise an alternative amino acid (e.g., D-amino acids, beta-amino acids, homocysteine, phosphoserine, etc.). In some embodiments, a Cas protein can comprise a modification to include a moiety (e.g., PEGylation, glycosylation, lipidation, acetylation, end-capping, etc.).

[0246] In some embodiments, a Cas protein comprises a core Cas protein. Exemplary Cas core proteins include, but are not limited to Cas1, Cas2, Cas3, Cas4, Cas5, Cas6, Cas7, Cas8 and Cas9. In some embodiments, a Cas protein comprises a Cas protein of an *E. coli* subtype (also known as CASS2). Exemplary Cas proteins of the *E. Coli* subtype include, but are not limited to Cse1, Cse2, Cse3, Cse4, and Cas5e. In some embodiments, a Cas protein comprises a Cas protein of the Ypest subtype (also known as CASS3). Exemplary Cas proteins of the Ypest subtype include, but are not limited to Csy1, Csy2, Csy3, and Csy4. In some embodiments, a Cas protein comprises a Cas protein of the Nmeni subtype (also known as CASS4). Exemplary Cas proteins of the Nmeni subtype include, but are not limited to Csn1 and Csn2. In some embodiments, a Cas protein comprises a Cas protein of the Dvulg subtype (also known as CASS 1). Exemplary Cas proteins of the Dvulg subtype include Csd1, Csd2, and Cas5d. In some embodiments, a Cas protein comprises a Cas protein of the Tneap subtype (also known as CASS7). Exemplary Cas proteins of the Tneap subtype include, but are not limited to, Cst1, Cst2, Cas5t. In some embodiments, a Cas protein comprises a Cas protein of the Hmari subtype. Exemplary Cas proteins of the Hmari subtype include, but are not limited to Csh1, Csh2, and Cas5h. In some embodiments, a Cas protein comprises a Cas protein of the Apern subtype (also known as CASS5). Exemplary Cas proteins of the Apern subtype include, but are not limited to Csa1, Csa2, Csa3, Csa4, Csa5, and Cas5a. In some embodiments, a Cas protein comprises a Cas protein of the Mtube subtype (also known as CASS6). Exemplary Cas proteins of the Mtube subtype include, but are not limited to Csm1, Csm2, Csm3, Csm4, and Csm5. In some embodiments, a Cas protein comprises a RAMP module Cas protein. Exemplary RAMP module Cas proteins include, but are not limited to, Cmr1, Cmr2, Cmr3, Cmr4, Cmr5, and Cmr6.

[0247] In some embodiments, the Cas protein is a *Streptococcus pyogenes* Cas9 protein or a functional portion thereof. In some embodiments, the Cas protein is Cas9 protein from any bacterial species or functional portion thereof. Cas9 protein is a member of the type II CRISPR systems which typically include a trans-coded small RNA (tracrRNA), endogenous ribonuclease 3 (rnc) and a Cas protein. Cas 9 protein (also known as CRISPR-associated endonuclease Cas9/Csn1) is a polypeptide comprising 1368 amino acids. An exemplary amino acid sequence of a Cas9 protein (SEQ ID NO: 298) is shown in FIG. **28**. Cas 9 contains 2 enconuclease domains, including an RuvC-like domain (residues 7-22, 759-766 and 982-989) which cleaves target DNA that is noncomplementary to crRNA, and an HNH nuclease domain (residues 810-872) which cleave target DNA complementary to crRNA. In FIG. **28**, the RuvC-like domain is highlighted in yellow and the HNH nuclease domain is underlined.

[0248] As used herein, "functional portion" refers to a portion of a peptide which retains its ability to complex with

at least one ribonucleic acid (e.g., guide RNA (gRNA)) and cleave a target polynucleotide sequence. In some embodiments, the functional portion comprises a combination of operably linked Cas9 protein functional domains selected from the group consisting of a DNA binding domain, at least one RNA binding domain, a helicase domain, and an endonuclease domain. In some embodiments, the functional domains form a complex.

[0249] In some embodiments, a functional portion of the Cas9 protein comprises a functional portion of a RuvC-like domain. In some embodiments, a functional portion of the Cas9 protein comprises a functional portion of the HNH nuclease domain.

[0250] It should be appreciated that the present invention contemplates various of ways of contacting a target polynucleotide sequence with a Cas protein (e.g., Cas9). In some embodiments, exogenous Cas protein can be introduced into the cell in polypeptide form. In certain embodiments, Cas proteins can be conjugated to or fused to a cell-penetrating polypeptide or cell-penetrating peptide. As used herein, "cell-penetrating polypeptide" and "cell-penetrating peptide" refers to a polypeptide or peptide, respectively, which facilitates the uptake of molecule into a cell. The cell-penetrating polypeptides can contain a detectable label.

[0251] In certain embodiments, Cas proteins can be conjugated to or fused to a charged protein (e.g., that carries a positive, negative or overall neutral electric charge). Such linkage may be covalent. In some embodiments, the Cas protein can be fused to a superpositively charged GFP to significantly increase the ability of the Cas protein to penetrate a cell (Cronican et al. *ACS Chem Biol.* 2010; 5(8): 747-52).

[0252] In certain embodiments, the Cas protein can be fused to a protein transduction domain (PTD) to facilitate its entry into a cell. Exemplary PTDs include Tat, oligoarginine, and penetratin.

[0253] In some embodiments, the Cas9 protein comprises a Cas9 polypeptide fused to a cell-penetrating peptide. In some embodiments, the Cas9 protein comprises a Cas9 polypeptide fused to a PTD. In some embodiments, the Cas9 protein comprises a Cas9 polypeptide fused to a tat domain. In some embodiments, the Cas9 protein comprises a Cas9 polypeptide fused to an oligoarginine domain. In some embodiments, the Cas9 protein comprises a Cas9 polypeptide fused to a penetratin domain. In some embodiments, the Cas9 protein comprises a Cas9 polypeptide fused to a superpositively charged GFP.

[0254] In some embodiments, the Cas protein can be introduced into a cell containing the target polynucleotide sequence in the form of a nucleic acid encoding the Cas protein (e.g., Cas9). The process of introducing the nucleic acids into cells can be achieved by any suitable technique. Suitable techniques include calcium phosphate or lipid-mediated transfection, electroporation, and transduction or infection using a viral vector. In some embodiments, the nucleic acid comprises DNA. In some embodiments, the nucleic acid comprises a modified DNA, as described herein. In some embodiments, the nucleic acid comprises mRNA. In some embodiments, the nucleic acid comprises a modified mRNA, as described herein (e.g., a synthetic, modified mRNA).

[0255] In some embodiments, the Cas protein is complexed with the one to two ribonucleic acids. In some embodiments, the Cas protein and the one to two ribonucleic acids are contained in a nanoparticle. In some embodiments, the Cas protein and the one to two ribonucleic acids are contained in a lipid nanoparticle, as described herein. In some embodiments, the Cas protein is encoded by a modified nucleic acid, as described herein (e.g., a synthetic, modified mRNA).

[0256] The methods of the present invention contemplate the use of any ribonucleic acid that is capable of directing a Cas protein to and hybridizing to a target motif of a target polynucleotide sequence. In some embodiments, at least one of the ribonucleic acids comprises tracrRNA. In some embodiments, at least one of the ribonucleic acids comprises CRISPR RNA (crRNA). In some embodiments, at least one of the ribonucleic acids comprises a guide RNA that directs the Cas protein to and hybridizes to a target motif of the target polynucleotide sequence in a cell.

[0257] The ribonucleic acids of the present invention can be selected to hybridize to a variety of different target motifs, depending on the particular CRISPR/Cas system employed, and the sequence of the target polynucleotide, as will be appreciated by those skilled in the art. The one to two ribonucleic acids can also be selected to minimize hybridization with nucleic acid sequences other than the target polynucleotide sequence. In some embodiments, the one to two ribonucleic acids hybridize to a target motif that contains at least two mismatches when compared with all other genomic nucleotide sequences in the cell. In some embodiments, the one to two ribonucleic acids hybridize to a target motif that contains at least one mismatch when compared with all other genomic nucleotide sequences in the cell. In some embodiments, the one to two ribonucleic acids are designed to hybridize to a target motif immediately adjacent to a deoxyribonucleic acid motif recognized by the Cas protein. In some embodiments, each of the one to two ribonucleic acids are designed to hybridize to target motifs immediately adjacent to deoxyribonucleic acid motifs recognized by the Cas protein which flank a mutant allele located between the target motifs.

[0258] In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequence of GTAACGGCAGACTTCTCCAC (SEQ ID NO: 5322). In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). It should be appreciated that the former sequence is the protospacer sequence in the guide RNA, whereas the latter sequence is the protospacer plus the PAM.

[0259] In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **1**.

[0260] In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **1**.

[0261] In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **2**. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **2**.

[0262] In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **3**. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **3**.

[0263] In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **4**. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **4**.

[0264] In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **5**. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **5**.

[0265] In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **6**. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **6**.

[0266] In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **7**. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **7**.

[0267] In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **8**. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **8**.

[0268] In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **9**. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **9**.

[0269] In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **10**. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **10**.

[0270] In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **11**. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **11**.

[0271] In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **12**. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **12**.

[0272] In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **13**. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **13**.

[0273] In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **14**. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **14**.

[0274] In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **15**. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **15**.

[0275] In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above do not include the 3 nucleotide NGG sequence. For example, if the target site sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one of the one to two ribonucleic acid sequences is GATGCTCAGTACAGCCACCT (SEQ ID NO: 5324). As another example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5325), a ribonucleic acid sequence with a single nucleotide mismatch which does not include the 3 nucleotide NGG sequence is GATGCTGAGTACAGCCACCT (SEQ ID NO: 5326), with the italicized G being the mismatched nucleotide. Those skilled in the art will appreciate, however, that the single nucleotide mismatch can comprise any nucleotide in the ribonucleic acid, e.g., the first nucleotide, the second nucleotide, the third nucleotide, the fourth nucleotide, the fifth nucleotide, the sixth nucleotide, the seventh nucleotide, the eighth nucleotide, the ninth nucleotide, the tenth nucleotide, the eleventh nucleotide, the twelfth nucleotide, the thirteenth nucleotide, the fourteenth nucleotide, the fifteenth nucleotide, the sixteenth nucleotide, the seventeenth nucleotide, the eighteenth nucleotide, the nineteenth nucleotide, or the twentieth nucleotide of the ribonucleic acid.

[0276] In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 12 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 12 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequences of the at least one of the one

to two ribonucleic acids described above comprise at least a 12 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 12 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTC-CACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one of the one to two ribonucleic acids which comprises at least a 12 nucleotide fragment is GTACAGCCACCT (SEQ ID NO: 5327).

[0277] In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 13 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 13 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15** In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 13 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 13 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTC-CACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one of the one to two ribonucleic acids which comprises at least a 13 nucleotide fragment is AGTACAGCCACCT (SEQ ID NO: 5328).

[0278] In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 14 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 14 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 14 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 14 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTC-CACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one of the one to two ribonucleic acids which comprises at least a 14 nucleotide fragment is CAGTACAGCCACCT (SEQ ID NO: 5329).

[0279] In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 15 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 15 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 15 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 15 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTC-CACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one of the one to two ribonucleic acids which comprises at least a 15 nucleotide fragment is TCAGTACAGCCACCT (SEQ ID NO: 5330).

[0280] In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 16 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 16 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 16 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 16 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTC-CACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one of the one to two ribonucleic acids which comprises at least a 16 nucleotide fragment is CTCAGTACAGCCACCT (SEQ ID NO: 5331).

[0281] In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 17 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 17 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 17 nucleotide fragment of a ribonucleic acid sequence of any of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO:

5321). In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 17 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTC-CACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one of the one to two ribonucleic acids which comprises at least a 17 nucleotide fragment is GCTCAGTACAGCCACCT (SEQ ID NO: 5332).

[0282] In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 18 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 18 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 18 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 18 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTC-CACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one of the one to two ribonucleic acids which comprises at least a 18 nucleotide fragment is TGCTCAGTACAGCCACCT (SEQ ID NO: 5333).

[0283] In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 19 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 19 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 19 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 19 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTC-CACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one of the one to two ribonucleic acids which comprises at least a 19 nucleotide fragment is ATGCTCAGTACAGCCACCT (SEQ ID NO: 5334).

[0284] In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 20 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 20 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 20 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 20 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTC-CACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one of the one to two ribonucleic acids which comprises at least a 20 nucleotide fragment is GATGCTCAGTACAGC-CACCT (SEQ ID NO: 5324).

[0285] The present invention also contemplates multiplex genomic editing. Those skilled in the art will appreciate that the description above with respect to genomic editing of a single gene is equally applicable to the multiplex genomic editing embodiments described below.

[0286] In another aspect, the present invention provides a method for simultaneously altering multiple target polynucleotide sequences in a cell.

[0287] In some embodiments, a method for simultaneously altering multiple target polynucleotide sequences in a cell comprises a method for simultaneously altering multiple target SCID-associated polynucleotides in a cell.

[0288] An exemplary method for simultaneously altering multiple target SCID-associated polynucleotide sequences in a cell comprises contacting the SCID-associated polynucleotide sequences with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target SCID-associated polynucleotide sequences, wherein the target SCID-associated polynucleotide sequences are cleaved. In some embodiments, the efficiency of alteration of cells that express Cas protein is from about 50% to about 80%.

[0289] In some embodiments, a method for simultaneously altering multiple target polynucleotide sequences in a cell comprises a method for simultaneously altering multiple target SCD-associated polynucleotides in a cell.

[0290] An exemplary method for simultaneously altering multiple target SCD-associated polynucleotide sequences in a cell comprises contacting the SCD-associated polynucleotide sequences with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target SCD-associated polynucleotide sequences, wherein the target SCD-associated polynucleotide sequences are cleaved. In some embodiments, the efficiency of alteration of cells that express Cas protein is from about 50% to about 80%.

[0291] In some embodiments, a method for simultaneously altering multiple target polynucleotide sequences in a cell comprises a method for simultaneously altering multiple target beta thalassemia-associated polynucleotides in a cell.

[0292] An exemplary method for simultaneously altering multiple target beta thalassemia-associated polynucleotide sequences in a cell comprises contacting the polynucleotide sequences with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target beta thalassemia-associated polynucleotide sequences, wherein the target beta thalassemia-associated polynucleotide sequences are cleaved. In some embodiments, the efficiency of alteration of cells that express Cas protein is from about 50% to about 80%.

[0293] In yet another aspect, the present invention provides a method for treating or preventing a disorder associated with expression of polynucleotide sequences in a subject.

[0294] In some embodiments, a method for treating or preventing a disorder associated with expression of polynucleotide sequences in a subject comprises a method for treating or preventing a disorder associated with expression of SCID-associated polynucleotide sequences in a subject.

[0295] An exemplary method for treating or preventing a disorder associated with expression of SCID-associated polynucleotide sequences in a subject comprises (a) altering target SCID-associated polynucleotide sequences in a cell ex vivo by contacting the SCID-associated polynucleotide sequences with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target SCID-associated polynucleotide sequences, wherein the target SCID-associated polynucleotide sequences are cleaved, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the SCID-associated polynucleotide sequences. In some embodiments, the efficiency of alteration of cells that express Cas protein is from about 50% to about 80%. In some embodiments, the method includes the step of contacting, before the step of introducing the cell into the subject, the cleaved SCID-associated polynucleotide sequences with an exogenously introduced DNA repair template comprising a corresponding wild-type or normal polynucleotide sequence, thereby allowing homology-directed repair to replace the cleaved SCID-associated polynucleotide sequence with the wild-type or normal gene sequence.

[0296] In embodiments in which the target SCID-associated polynucleotide sequences comprise ADA polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal ADA polynucleotide sequence.

[0297] In embodiments in which the target SCID-associated polynucleotide sequences comprise AK2 polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal AK2 polynucleotide sequence.

[0298] In embodiments in which the target SCID-associated polynucleotide sequences comprise CD3D polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal CD3D polynucleotide sequence.

[0299] In embodiments in which the target SCID-associated polynucleotide sequences comprise DCLRE1C polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal DCLRE1C polynucleotide sequence.

[0300] In embodiments in which the target SCID-associated polynucleotide sequences comprise IL2RG polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal IL2RG polynucleotide sequence.

[0301] In embodiments in which the target SCID-associated polynucleotide sequences comprise IL7R polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal IL7R polynucleotide sequence.

[0302] In embodiments in which the target SCID-associated polynucleotide sequences comprise JAK3 polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal JAK3 polynucleotide sequence.

[0303] In embodiments in which the target SCID-associated polynucleotide sequences comprise LIG4 polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal LIG4 polynucleotide sequence.

[0304] In embodiments in which the target SCID-associated polynucleotide sequences comprise NHEJ1 polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal NHEJ1 polynucleotide sequence.

[0305] In embodiments in which the target SCID-associated polynucleotide sequences comprise PNP polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal PNP polynucleotide sequence.

[0306] In embodiments in which the target SCID-associated polynucleotide sequences comprise PRKDC polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal PRKDC polynucleotide sequence.

[0307] In embodiments in which the target SCID-associated polynucleotide sequences comprise RAG1 polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal RAG1 polynucleotide sequence.

[0308] In embodiments in which the target SCID-associated polynucleotide sequences comprise RAG2 polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal RAG2 polynucleotide sequence.

[0309] In embodiments in which the target SCID-associated polynucleotide sequences comprise ZAP70 polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal ZAP70 polynucleotide sequence.

[0310] In some embodiments, a method for treating or preventing a disorder associated with expression of polynucleotide sequences in a subject comprises a method for treating or preventing a disorder associated with expression of SCD-associated polynucleotide sequences in a subject.

[0311] An exemplary method for treating or preventing a disorder associated with expression of SCD-associated polynucleotide sequences in a subject comprises (a) altering target SCD-associated polynucleotide sequences in a cell ex vivo by contacting the SCD-associated polynucleotide sequences with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribo-

nucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target SCD-associated polynucleotide sequences, wherein the target SCD-associated polynucleotide sequences are cleaved, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the SCD-associated polynucleotide sequences. In some embodiments, the efficiency of alteration of cells that express Cas protein is from about 50% to about 80%. In some embodiments, the method includes the step of contacting, before the step of introducing the cell into the subject, the cleaved SCD-associated polynucleotide sequences with an exogenously introduced DNA repair template comprising a normal HBB sequence, thereby allowing homology-directed repair to replace the cleaved SCD-associated polynucleotide sequence with the normal HBB sequence.

[0312] In some embodiments, a method for treating or preventing a disorder associated with expression of polynucleotide sequences in a subject comprises a method for treating or preventing a disorder associated with expression of beta thalassemia-associated polynucleotide sequences in a subject.

[0313] An exemplary method for treating or preventing a disorder associated with expression of beta thalassemia-associated polynucleotide sequences in a subject comprises (a) altering target beta thalassemia-associated polynucleotide sequences in a cell ex vivo by contacting the beta thalassemia-associated polynucleotide sequences with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target beta thalassemia-associated polynucleotide sequences, wherein the target beta thalassemia-associated polynucleotide sequences are cleaved, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the beta thalassemia-associated polynucleotide sequences. In some embodiments, the efficiency of alteration of cells that express Cas protein is from about 50% to about 80%,

[0314] In some embodiments, the method includes the step of contacting, before the step of introducing the cell into the subject, the cleaved beta thalassemia-associated polynucleotide sequences with an exogenously introduced DNA repair template comprising a normal HBB sequence, thereby allowing homology-directed repair to replace the cleaved beta thalassemia-associated polynucleotide sequence with the normal HBB sequence.

[0315] As used herein, the terms "administering," "introducing" and "transplanting" are used interchangeably in the context of the placement of cells, e.g. cells described herein comprising a target polynucleotide sequence altered according to the methods of the invention into a subject, by a method or route which results in at least partial localization of the introduced cells at a desired site. The cells can be implanted directly to the desired site, or alternatively be administered by any appropriate route which results in delivery to a desired location in the subject where at least a portion of the implanted cells or components of the cells remain viable. The period of viability of the cells after administration to a subject can be as short as a few hours, e.g. twenty-four hours, to a few days, to as long as several years. In some instances, the cells can also be administered a location other than the desired site, such as in the liver or subcutaneously, for example, in a capsule to maintain the implanted cells at the implant location and avoid migration of the implanted cells.

[0316] For ex vivo methods, cells can include autologous cells, i.e., a cell or cells taken from a subject who is in need of altering a target polynucleotide sequence in the cell or cells (i.e., the donor and recipient are the same individual). Autologous cells have the advantage of avoiding any immunologically-based rejection of the cells. Alternatively, the cells can be heterologous, e.g., taken from a donor. The second subject can be of the same or different species. Typically, when the cells come from a donor, they will be from a donor who is sufficiently immunologically compatible with the recipient, i.e., will not be subject to transplant rejection, to lessen or remove the need for immunosuppression. In some embodiments, the cells are taken from a xenogeneic source, i.e., a non-human mammal that has been genetically engineered to be sufficiently immunologically compatible with the recipient, or the recipient's species. Methods for determining immunological compatibility are known in the art, and include tissue typing to assess donor-recipient compatibility for HLA and ABO determinants. See, e.g., *Transplantation Immunology*, Bach and Auchincloss, Eds. (Wiley, John & Sons, Incorporated 1994).

[0317] Any suitable cell culture media can be used for ex vivo methods of the invention.

[0318] Another exemplary method for treating or preventing a disorder associated with expression of SCID-associated polynucleotide sequences in a subject comprises altering target SCID-associated polynucleotide sequences in a cell by contacting the SCID-associated polynucleotide sequences with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target moieties of the target SCID-associated polynucleotide sequences, and wherein the target SCID-associated polynucleotide sequences are cleaved, thereby treating or preventing a disorder associated with expression of the polynucleotide sequences.

[0319] In some embodiments, the method includes the step of contacting the cleaved SCID-associated polynucleotide sequences with an exogenously introduced DNA repair template comprising a corresponding wild-type or normal polynucleotide sequence, thereby allowing homology-directed repair to replace the cleaved SCID-associated polynucleotide sequence with the corresponding wild-type or normal polynucleotide sequence.

[0320] In embodiments in which the target SCID-associated polynucleotide sequences comprise ADA polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal ADA polynucleotide sequence.

[0321] In embodiments in which the target SCID-associated polynucleotide sequences comprise AK2 polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal AK2 polynucleotide sequence.

[0322] In embodiments in which the target SCID-associated polynucleotide sequences comprise CD3D polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal CD3D polynucleotide sequence.

[0323] In embodiments in which the target SCID-associated polynucleotide sequences comprise DCLRE1C poly-

nucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal DCLRE1C polynucleotide sequence.

[0324] In embodiments in which the target SCID-associated polynucleotide sequences comprise IL2RG polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal IL2RG polynucleotide sequence.

[0325] In embodiments in which the target SCID-associated polynucleotide sequences comprise IL7R polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal IL7R polynucleotide sequence.

[0326] In embodiments in which the target SCID-associated polynucleotide sequences comprise JAK3 polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal JAK3 polynucleotide sequence.

[0327] In embodiments in which the target SCID-associated polynucleotide sequences comprise LIG4 polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal LIG4 polynucleotide sequence.

[0328] In embodiments in which the target SCID-associated polynucleotide sequences comprise NHEJ1 polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal NHEJ1 polynucleotide sequence.

[0329] In embodiments in which the target SCID-associated polynucleotide sequences comprise PNP polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal PNP polynucleotide sequence.

[0330] In embodiments in which the target SCID-associated polynucleotide sequences comprise PRKDC polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal PRKDC polynucleotide sequence.

[0331] In embodiments in which the target SCID-associated polynucleotide sequences comprise RAG1 polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal RAG1 polynucleotide sequence.

[0332] In embodiments in which the target SCID-associated polynucleotide sequences comprise RAG2 polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal RAG2 polynucleotide sequence.

[0333] In embodiments in which the target SCID-associated polynucleotide sequences comprise ZAP70 polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal ZAP70 polynucleotide sequence.

[0334] Another exemplary method for treating or preventing a disorder associated with expression of SCD-associated polynucleotide sequences in a subject comprises altering target SCD-associated polynucleotide sequences in a cell by contacting the SCD-associated polynucleotide sequences with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target moieties of the target SCD-associated polynucleotide sequences, and wherein the target SCD-associated polynucleotide sequences are cleaved, thereby treating or preventing a disorder associated with expression of the polynucleotide sequences.

[0335] In some embodiments, the method includes the step of contacting the cleaved SCD-associated polynucleotide sequences with an exogenously introduced DNA repair template comprising a normal HBB sequence, thereby allowing homology-directed repair to replace the cleaved SCD-associated polynucleotide sequence with the normal HBB sequence.

[0336] Another exemplary method for treating or preventing a disorder associated with expression of beta thalassemia-associated polynucleotide sequences in a subject comprises altering target beta thalassemia-associated polynucleotide sequences in a cell by contacting the beta thalassemia-associated polynucleotide sequences with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target moieties of the target beta thalassemia-associated polynucleotide sequences, and wherein the target beta thalassemia-associated polynucleotide sequences are cleaved, thereby treating or preventing a disorder associated with expression of the beta thalassemia-associated polynucleotide sequences.

[0337] In some embodiments, the method includes the step of contacting the cleaved beta thalassemia-associated polynucleotide sequences with an exogenously introduced DNA repair template comprising a normal HBB sequence, thereby allowing homology-directed repair to replace the cleaved beta thalassemia-associated polynucleotide sequence with the normal HBB sequence.

[0338] The terms "subject" and "individual" are used interchangeably herein, and refer to an animal, for example, a human from whom cells can be obtained and/or to whom treatment, including prophylactic treatment, with the cells as described herein, is provided. For treatment of those infections, conditions or disease states which are specific for a specific animal such as a human subject, the term subject refers to that specific animal. The "non-human animals" and "non-human mammals" as used interchangeably herein, includes mammals such as rats, mice, rabbits, sheep, cats, dogs, cows, pigs, and non-human primates. The term "subject" also encompasses any vertebrate including but not limited to mammals, reptiles, amphibians and fish. However, advantageously, the subject is a mammal such as a human, or other mammals such as a domesticated mammal, e.g. dog, cat, horse, and the like, or production mammal, e.g. cow, sheep, pig, and the like.

[0339] In some embodiments, the alteration results in reduced expression of the target polynucleotide sequences. In exemplary embodiments, the alteration results in reduced expression of the target SCID-associated polynucleotide sequences. In exemplary embodiments, the alteration results in reduced expression of the target ADA polynucleotide sequences. In exemplary embodiments, the alteration results in reduced expression of the target AK2 polynucleotide sequences. In exemplary embodiments, the alteration results in reduced expression of the target CD3D polynucleotide sequences. In exemplary embodiments, the alteration results in reduced expression of the target DCLRE1C polynucleotide sequences. In exemplary embodiments, the alteration results in reduced expression of the target IL2RG polynucleotide sequences. In exemplary embodiments, the alteration results in reduced expression of the target IL7R polynucle-

otide sequences. In exemplary embodiments, the alteration results in reduced expression of the target JAK3 polynucleotide sequences. In exemplary embodiments, the alteration results in reduced expression of the target LIG4 polynucleotide sequences. In exemplary embodiments, the alteration results in reduced expression of the target NHEJ1 polynucleotide sequences. In exemplary embodiments, the alteration results in reduced expression of the target PNP polynucleotide sequences. In exemplary embodiments, the alteration results in reduced expression of the target PRKDC polynucleotide sequences. In exemplary embodiments, the alteration results in reduced expression of the target RAG1 polynucleotide sequences. In exemplary embodiments, the alteration results in reduced expression of the target RAG2 polynucleotide sequences. In exemplary embodiments, the alteration results in reduced expression of the target ZAP70 polynucleotide sequences. In exemplary embodiments, the alteration results in reduced expression of the target SCD-associated polynucleotide sequences. In exemplary embodiments, the alteration results in reduced expression of the target beta thalassemia-associated polynucleotide sequences. In some embodiments, the alteration results in a knock out of the target polynucleotide sequences. In exemplary embodiments, the alteration results in a knock out of the target SCID-associated polynucleotide sequences. In exemplary embodiments, the alteration results in a knock out of the target ADA polynucleotide sequences. In exemplary embodiments, the alteration results in a knock out of the target AK2 polynucleotide sequences. In exemplary embodiments, the alteration results in a knock out of the target CD3D polynucleotide sequences. In exemplary embodiments, the alteration results in a knock out of the target DCLRE1C polynucleotide sequences. In exemplary embodiments, the alteration results in a knock out of the target IL2RG polynucleotide sequences. In exemplary embodiments, the alteration results in a knock out of the target IL7R polynucleotide sequences. In exemplary embodiments, the alteration results in a knock out of the target JAK3 polynucleotide sequences. In exemplary embodiments, the alteration results in a knock out of the target LIG4 polynucleotide sequences. In exemplary embodiments, the alteration results in a knock out of the target NHEJ1 polynucleotide sequences. In exemplary embodiments, the alteration results in a knock out of the target PNP polynucleotide sequences. In exemplary embodiments, the alteration results in a knock out of the target PRKDC polynucleotide sequences. In exemplary embodiments, the alteration results in a knock out of the target RAG1 polynucleotide sequences. In exemplary embodiments, the alteration results in a knock out of the target RAG2 polynucleotide sequences. In exemplary embodiments, the alteration results in a knock out of the target ZAP70 polynucleotide sequences. In exemplary embodiments, the alteration results in a knock out of the target SCD-associated polynucleotide sequences. In exemplary embodiments, the alteration results in a knock out of the target beta thalassemia-associated polynucleotide sequences.

[0340] In some embodiments, the alteration results in correction of the target polynucleotide sequences from undesired sequences to desired sequences. In exemplary embodiments, the alteration results in correction of the target SCID-associated polynucleotide sequences to corresponding normal wild-type polynucleotide sequences. In exemplary embodiments, the alteration results in correction of the target SCID-associated polynucleotide sequences to corresponding normal wild-type ADA sequences. In exemplary embodiments, the alteration results in correction of the target SCID-associated polynucleotide sequences to corresponding normal wild-type AK2 sequences. In exemplary embodiments, the alteration results in correction of the target SCID-associated polynucleotide sequences to corresponding normal wild-type CD3D sequences. In exemplary embodiments, the alteration results in correction of the target SCID-associated polynucleotide sequences to corresponding normal wild-type DCLRE1C sequences. In exemplary embodiments, the alteration results in correction of the target SCID-associated polynucleotide sequences to corresponding normal wild-type IL2RG sequences In exemplary embodiments, the alteration results in correction of the target SCID-associated polynucleotide sequences to corresponding normal wild-type IL7R sequences. In exemplary embodiments, the alteration results in correction of the target SCID-associated polynucleotide sequences to corresponding normal wild-type JAK3 sequences. In exemplary embodiments, the alteration results in correction of the target SCID-associated polynucleotide sequences to corresponding normal wild-type LIG4 sequences. In exemplary embodiments, the alteration results in correction of the target SCID-associated polynucleotide sequences to corresponding normal wild-type NHEJ1 sequences. In exemplary embodiments, the alteration results in correction of the target SCID-associated polynucleotide sequences to corresponding normal wild-type PNP sequences. In exemplary embodiments, the alteration results in correction of the target SCID-associated polynucleotide sequences to corresponding normal wild-type PRKDC sequences. In exemplary embodiments, the alteration results in correction of the target SCID-associated polynucleotide sequences to corresponding normal wild-type RAG1 sequences. In exemplary embodiments, the alteration results in correction of the target SCID-associated polynucleotide sequences to corresponding normal wild-type RAG2 sequences. In exemplary embodiments, the alteration results in correction of the target SCID-associated polynucleotide sequences to corresponding normal wild-type ZAP70 sequences. In exemplary embodiments, the alteration results in correction of the target SCD-associated polynucleotide sequences to normal wild-type HBB sequences. In exemplary embodiments, the alteration results in correction of the target beta thalassemia-associated polynucleotide sequences to normal wild-type HBB sequences. In some embodiments, each alteration is a homozygous alteration. In some embodiments, the efficiency of alteration at each loci is from about 5% to about 80%. In some embodiments, the efficiency of alteration at each loci is from about 10% to about 80%. In some embodiments, the efficiency of alteration at each loci is from about 30% to about 80%. In some embodiments, the efficiency of alteration at each loci is from about 50% to about 80%. In some embodiments, the efficiency of alteration at each loci is from greater than or equal to about 80%.

[0341] In some embodiments, each target polynucleotide sequence is cleaved such that a double-strand break results. In some embodiments, each target polynucleotide sequence is cleaved such that a single-strand break results.

[0342] In some embodiments, the target polynucleotide sequences comprise multiple different portions of ADA

(e.g., one or more mutations in the ADA gene). In some embodiments, the target polynucleotide sequences comprise at least a portion of ADA.

[0343] In some embodiments, the target polynucleotide sequences comprise multiple different portions of AK2 (e.g., one or more mutations in the AK2 gene). In some embodiments, the target polynucleotide sequences comprise at least a portion of AK2.

[0344] In some embodiments, the target polynucleotide sequences comprise multiple different portions of CD3D (e.g., one or more mutations in the CD3D gene). In some embodiments, the target polynucleotide sequences comprise at least a portion of CD3D.

[0345] In some embodiments, the target polynucleotide sequences comprise multiple different portions of DCLRE1C (e.g., one or more mutations in the DCLRE1C gene). In some embodiments, the target polynucleotide sequences comprise at least a portion of DCLRE1C.

[0346] In some embodiments, the target polynucleotide sequences comprise multiple different portions of IL2RG (e.g., one or more mutations in the IL2RG gene). In some embodiments, the target polynucleotide sequences comprise at least a portion of IL2RG.

[0347] In some embodiments, the target polynucleotide sequences comprise multiple different portions of IL7R (e.g., one or more mutations in the IL7R gene). In some embodiments, the target polynucleotide sequences comprise at least a portion of IL7R.

[0348] In some embodiments, the target polynucleotide sequences comprise multiple different portions of JAK3 (e.g., one or more mutations in the JAK3 gene). In some embodiments, the target polynucleotide sequences comprise at least a portion of JAK3.

[0349] In some embodiments, the target polynucleotide sequences comprise multiple different portions of LIG4 (e.g., one or more mutations in the LIG4 gene). In some embodiments, the target polynucleotide sequences comprise at least a portion of LIG4.

[0350] In some embodiments, the target polynucleotide sequences comprise multiple different portions of NHEJ1 (e.g., one or more mutations in the NHEJ1 gene). In some embodiments, the target polynucleotide sequences comprise at least a portion of NHEJ1.

[0351] In some embodiments, the target polynucleotide sequences comprise multiple different portions of PNP (e.g., one or more mutations in the PNP gene). In some embodiments, the target polynucleotide sequences comprise at least a portion of PNP.

[0352] In some embodiments, the target polynucleotide sequences comprise multiple different portions of PRKDC (e.g., one or more mutations in the PRKDC gene). In some embodiments, the target polynucleotide sequences comprise at least a portion of PRKDC.

[0353] In some embodiments, the target polynucleotide sequences comprise multiple different portions of RAG1 (e.g., one or more mutations in the RAG1 gene). In some embodiments, the target polynucleotide sequences comprise at least a portion of RAG1.

[0354] In some embodiments, the target polynucleotide sequences comprise multiple different portions of RAG2 (e.g., one or more mutations in the RAG2 gene). In some embodiments, the target polynucleotide sequences comprise at least a portion of RAG2.

[0355] In some embodiments, the target polynucleotide sequences comprise multiple different portions of ZAP70 (e.g., one or more mutations in the ZAP70 gene). In some embodiments, the target polynucleotide sequences comprise at least a portion of ZAP70.

[0356] In some embodiments, the target polynucleotide sequences comprise multiple different portions of HBB (e.g., one or more mutations in the HBB gene). In some embodiments, the target polynucleotide sequences comprise at least a portion of HBB.

[0357] In some embodiments, each target motif is a 20-nucleotide DNA sequence. In some embodiments, each target motif is a 20-nucleotide DNA sequence beginning with G and immediately precedes an NGG motif recognized by the Cas protein. In some embodiments, each target motif is a 20-nucleotide DNA sequence and immediately precedes an NGG motif recognized by the Cas protein. In some embodiments, each target motif is G(N)19NGG. In some embodiments, each target motif is (N)20NGG. In some embodiments, each target motif is selected such that it contains at least two mismatches when compared with all other genomic nucleotide sequences in the cell. In some embodiments, each target motif is selected such that it contains at least two mismatches when compared with all other genomic nucleotide sequences in the cell.

[0358] In some embodiments, subsequent to cleavage of the target polynucleotide sequences, homology-directed repair occurs. In some embodiments, homology-directed repair is performed using an exogenously introduced DNA repair template. In some embodiments, the exogenously introduced DNA repair template is single-stranded. In some embodiments, the exogenously introduced DNA repair template is double-stranded.

[0359] In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type ADA sequence. In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type ADA sequence corresponding to the mutant ADA sequence comprising the SCID-associated polynucleotide sequence.

[0360] In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type AK2 sequence. In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type AK2 sequence corresponding to the mutant AK2 sequence comprising the SCID-associated polynucleotide sequence.

[0361] In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type CD3D sequence. In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type CD3D sequence corresponding to the mutant CD3D sequence comprising the SCID-associated polynucleotide sequence.

[0362] In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type DCLRE1C sequence. In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type DCLRE1C sequence corresponding to the mutant DCLRE1C sequence comprising the SCID-associated polynucleotide sequence.

[0363] In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type IL2RG sequence. In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type IL2RG sequence corresponding to the mutant IL2RG sequence comprising the SCID-associated polynucleotide sequence.

[0364] In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type IL7R sequence. In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type IL7R sequence corresponding to the mutant IL7R sequence comprising the SCID-associated polynucleotide sequence.

[0365] In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type JAK3 sequence. In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type JAK3 sequence corresponding to the mutant JAK3 sequence comprising the SCID-associated polynucleotide sequence.

[0366] In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type LIG4 sequence. In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type LIG4 sequence corresponding to the mutant LIG4 sequence comprising the SCID-associated polynucleotide sequence.

[0367] In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type NHEJ1 sequence. In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type NHEJ1 sequence corresponding to the mutant NHEJ1 sequence comprising the SCID-associated polynucleotide sequence.

[0368] In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type PNP sequence. In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type PNP sequence corresponding to the mutant PNP sequence comprising the SCID-associated polynucleotide sequence.

[0369] In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type PRKDC sequence. In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type PRKDC sequence corresponding to the mutant PRKDC sequence comprising the SCID-associated polynucleotide sequence.

[0370] In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type RAG1 sequence. In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type RAG1 sequence corresponding to the mutant RAG1 sequence comprising the SCID-associated polynucleotide sequence.

[0371] In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type RAG2 sequence. In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type RAG2 sequence corresponding to the mutant RAG2 sequence comprising the SCID-associated polynucleotide sequence.

[0372] In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type ZAP70 sequence. In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type ZAP70 sequence corresponding to the mutant ZAP70 sequence comprising the SCID-associated polynucleotide sequence.

[0373] In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type HBB sequence. In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type HBB sequence corresponding to the mutant HBB sequence comprising the SCD-associated polynucleotide sequence. In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type HBB sequence corresponding to the mutant HBB sequence comprising the beta thalassemia-associated polynucleotide sequence.

[0374] In some embodiments, the Cas protein (e.g., Cas9) is complexed with the multiple ribonucleic acids. In some embodiments, the Cas protein and the multiple ribonucleic acids are contained in nanoparticles, as described herein. In some embodiments, the Cas protein and the multiple ribonucleic acids are contained in lipid nanoparticles, as described herein. In some embodiments, a nucleic acid encoding a Cas protein and the multiple ribonucleic acids are contained in nanoparticles. In some embodiments, a nucleic acid encoding a Cas protein and the multiple ribonucleic acids are contained in lipid nanoparticles, as described herein. In some embodiments, a modified, synthetic mRNA encoding a Cas protein as described herein, and multiple ribonucleic acids at least one of which comprises a modified, synthetic RNA as described herein, are contained in lipid nanoparticles. In some embodiments, a modified, synthetic mRNA encoding a Cas9 protein as described herein, and multiple ribonucleic acids at least one of which comprises a modified, synthetic RNA as described herein, are contained in lipid nanoparticles.

[0375] In some embodiments, the multiple ribonucleic acids are selected to minimize hybridization with nucleic acid sequences other than the target polynucleotide sequence (e.g., multiple alterations of a single target polynucleotide sequence). In some embodiments, the multiple ribonucleic acids are selected to minimize hybridization with nucleic acid sequences other than the target polynucleotide sequences (e.g., one or more alterations of multiple target polynucleotide sequences). In some embodiments, each of the multiple ribonucleic acids hybridize to target motifs that contain at least two mismatches when compared with all other genomic nucleotide sequences in the cell. In some embodiments, each of the multiple ribonucleic acids hybridize to target motifs that contain at least one mismatch when compared with all other genomic nucleotide sequences in the cell. In some embodiments, each of the multiple ribonucleic acids are designed to hybridize to target motifs immediately adjacent to deoxyribonucleic acid motifs recognized by the Cas protein. In some embodiments, each of the multiple ribonucleic acids are designed to hybridize to target motifs immediately adjacent to deoxyribonucleic acid motifs recognized by the Cas protein which flank mutant alleles located between the target motifs.

[0376] In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **1**. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **1**.

[0377] In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **2**. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **2**.

[0378] In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **3**. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide

mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **3**.

[0379] In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **4**. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **4**.

[0380] In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **5**. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **5**.

[0381] In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **6**. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **6**.

[0382] In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **7**. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **7**.

[0383] In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **8**. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **8**.

[0384] In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **9**. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **9**.

[0385] In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **9**. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **9**.

[0386] In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **10**. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **10**.

[0387] In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **11**. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **11**.

[0388] In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **12**. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **12**.

[0389] In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **13**. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **13**.

[0390] In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **14**. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **14**.

[0391] In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **15**. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **15**.

[0392] In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of FIGS. **1-15** and combinations thereof. In some embodiments, the different sequences of the multiple ribonucleic acids described above do not include the 3 nucleotide NGG sequence.

[0393] For example, if a target site sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), a sequence of the multiple ribonucleic acids is GATGCTCAGTACAGCCACCT (SEQ ID NO: 5324). As another example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), a sequence with a single nucleotide mismatch which does not include the 3 nucleotide NGG sequence is GATGCTGAGTACAGCCACCT (SEQ ID NO: 5326), with the italicized G being the mismatched nucleotide. Those skilled in the art will appreciate, however, that the single nucleotide mismatch can comprise any nucleotide in the ribonucleic acid, e.g., the first nucleotide, the second nucleotide, the third nucleotide, the fourth nucleotide, the fifth nucleotide, the sixth nucleotide, the seventh nucleotide, the eighth nucleotide, the ninth nucleotide, the tenth nucleotide, the eleventh nucleotide, the twelfth nucleotide, the thirteenth nucleotide, the fourteenth nucleotide, the fifteenth nucleotide, the sixteenth nucleotide, the seventeenth nucleotide, the eighteenth nucleotide, the nineteenth nucleotide, or the twentieth nucleotide of the ribonucleic acid.

[0394] In some embodiments, the different sequences of the multiple ribonucleic acids described above comprise at least 12 nucleotide fragments of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the different sequences of the multiple ribonucleic acids described above comprise at least 12 nucleotide fragments sequences with

single nucleotide mismatches to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. For example, if a target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), a different sequence of the multiple ribonucleic acids comprising at least a 12 nucleotide fragment with single nucleotide mismatch comprises GTACAGCCACCT (SEQ ID NO: 5327).

[0395] In some embodiments, the different sequences of the multiple ribonucleic acids described above comprise at least 13 nucleotide fragments of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the different sequences of the multiple ribonucleic acids described above comprise at least 13 nucleotide fragments sequences with single nucleotide mismatches to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. For example, if a target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), a different sequence of the multiple ribonucleic acids comprising at least a 13 nucleotide fragment with single nucleotide mismatch comprises AGTACAGCCACCT (SEQ ID NO: 5328).

[0396] In some embodiments, the different sequences of the multiple ribonucleic acids described above comprise at least 14 nucleotide fragments of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the different sequences of the multiple ribonucleic acids described above comprise at least 14 nucleotide fragments sequences with single nucleotide mismatches to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. For example, if a target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), a different sequence of the multiple ribonucleic acids comprising at least a 14 nucleotide fragment with single nucleotide mismatch comprises CAGTACAGCCACCT (SEQ ID NO: 5329).

[0397] In some embodiments, the different sequences of the multiple ribonucleic acids described above comprise at least 15 nucleotide fragments of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the different sequences of the multiple ribonucleic acids described above comprise at least 15 nucleotide fragments sequences with single nucleotide mismatches to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. For example, if a target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), a different sequence of the multiple ribonucleic acids comprising at least a 15 nucleotide fragment with single nucleotide mismatch comprises TCAGTACAGCCACCT (SEQ ID NO: 5330).

[0398] In some embodiments, the different sequences of the multiple ribonucleic acids described above comprise at least 16 nucleotide fragments of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the different sequences of the multiple ribonucleic acids described above comprise at least 16 nucleotide fragments sequences with single nucleotide mismatches to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. For example, if a target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), a different sequence of the multiple ribonucleic acids comprising at least a 16 nucleotide fragment with single nucleotide mismatch comprises CTCAGTACAGCCACCT (SEQ ID NO: 5331).

[0399] In some embodiments, the different sequences of the multiple ribonucleic acids described above comprise at least 17 nucleotide fragments of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the different sequences of the multiple ribonucleic acids described above comprise at least 17 nucleotide fragments sequences with single nucleotide mismatches to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. For example, if a target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), a different sequence of the multiple ribonucleic acids comprising at least a 17 nucleotide fragment with single nucleotide mismatch comprises GCTCAGTACAGCCACCT (SEQ ID NO: 5332).

[0400] In some embodiments, the different sequences of the multiple ribonucleic acids described above comprise at least 18 nucleotide fragments of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the different sequences of the multiple ribonucleic acids described above comprise at least 18 nucleotide fragments sequences with single nucleotide mismatches to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. For example, if a target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), a different sequence of the multiple ribonucleic acids comprising at least a 18 nucleotide fragment with single nucleotide mismatch comprises TGCTCAGTACAGCCACCT (SEQ ID NO: 5333).

[0401] In some embodiments, the different sequences of the multiple ribonucleic acids described above comprise at least 19 nucleotide fragments of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the different sequences of the multiple ribonucleic acids described above comprise at least 19 nucleotide fragments sequences with single nucleotide mismatches to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. For example, if a target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), a different sequence of the multiple ribonucleic acids comprising at least a 19 nucleotide fragment with single nucleotide mismatch comprises ATGCTCAGTACAGCCACCT (SEQ ID NO: 5334).

[0402] In some embodiments, the different sequences of the multiple ribonucleic acids described above comprise at least 20 nucleotide fragments of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the different sequences of the multiple ribonucleic acids described above comprise at least 20 nucleotide fragments sequences with single nucleotide mismatches to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. For example, if a target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), a different sequence of the multiple ribonucleic acids comprising at least a 12 nucleotide fragment with single nucleotide mismatch comprises GATGCTCAGTACAGCCACCT (SEQ ID NO: 5324).

[0403] It should be appreciated that any of the Cas protein or the ribonucleic acids can be expressed from a plasmid. In some embodiments, any of the Cas protein or the ribonucleic acids are expressed using a promoter optimized for increased expression in stem cells (e.g., human stem cells). In some embodiments, the promoter is selected from the group consisting of a Cytomegalovirus (CMV) early enhancer element and a chicken beta-actin promoter, a

chicken beta-actin promoter, an elongation factor-1 alpha promoter, and a ubiquitin promoter.

[0404] In some embodiments, the methods of the present invention further comprise selecting cells that express the Cas protein. The present invention contemplates any suitable method for selecting cells. In some embodiments, selecting cells comprises FACS. In some embodiments, FACs is used to select cells which co-express Cas and a fluorescent protein selected from the group consisting of green fluorescent protein and red fluorescent protein.

[0405] The present invention contemplates treating and/or preventing a variety of disorders which are associated with expression of a target polynucleotide sequences. It should be appreciated that the methods and compositions described herein can be used to treat or prevent disorders associated with increased expression of a target polynucleotide sequence, as well as decreased expression of a target polynucleotide sequence in a cell. Increased and decreased expression of a target polynucleotide sequence includes circumstances where the expression levels of the target polynucleotide sequence are increased or decreased, respectively, as well as circumstances in which the function and/or level of activity of an expression product of the target polynucleotide sequence increases or decreases, respectively, compared to normal expression and/or activity levels. Those skilled in the art will appreciate that treating or preventing a disorder associated with increased expression of a target polynucleotide sequence can be assessed by determining whether the levels and/or activity of the target polynucleotide sequence (or an expression product thereof) are decreased in a relevant cell after employing a method or administering a composition described herein. The skilled artisan will also appreciate that treating or preventing a disorder associated with decreased expression of a target polynucleotide sequence can be assessed by determining whether the levels and/or activity of the target polynucleotide sequence (or an expression product thereof) are increased in the relevant cell after employing a method or administering a composition described herein.

[0406] In some embodiments, the disorder is a genetic disorder. In some embodiments, the disorder is a monogenic disorder. In some embodiments, the disorder is a multigenic disorder. In some embodiments, the disorder is a disorder associated with one or more SNPs. Exemplary disorders associated with one or more SNPs include a complex disease described in U.S. Pat. No. 7,627,436, Alzheimer's disease as described in PCT International Application Publication No. WO/2009/112882, inflammatory diseases as described in U.S. Patent Application Publication No. 2011/0039918, polycystic ovary syndrome as described in U.S. Patent Application Publication No. 2012/0309642, cardiovascular disease as described in U.S. Pat. No. 7,732,139, Huntington's disease as described in U.S. Patent Application Publication No. 2012/0136039, thromboembolic disease as described in European Patent Application Publication No. EP2535424, neurovascular diseases as described in PCT International Application Publication No. WO/2012/001613, psychosis as described in U.S. Patent Application Publication No. 2010/0292211, multiple sclerosis as described in U.S. Patent Application Publication No. 2011/0319288, schizopherenia, schizoaffective disorder, and bipolar disorder as described in PCT International Application Publication No. WO/2006/023719A2, bipolar disorder and other ailments as described in U.S. Patent Application Publication No. U.S. 2011/0104674, colorectal cancer as described in PCT International Application Publication No. WO/2006/104370A1, a disorder associated with a SNP adjacent to the AKT1 gene locus as described in U.S. Patent Application Publication No. U.S. 2006/0204969, an eating disorder as described in PCT International Application Publication No. WO/2003/012143A1, autoimmune disease as described in U.S. Patent Application Publication No. U.S. 2007/0269827, fibrostenosing disease in patients with Chrohn's disease as described in U.S. Pat. No. 7,790,370, and Parkinson's disease as described in U.S. Pat. No. 8,187,811, each of which is incorporated herein by reference in its entirety. Other disorders associated with one or more SNPs which can be treated or prevented according to the methods of the present invention will be apparent to the skilled artisan.

[0407] In some embodiments, the disorder is severe combined immunodeficiency. In some embodiments, the disorder is X-linked moderate combined immunodeficiency. In some embodiments, the disorder is X-linked severe combined immunodeficiency. In some embodiments, the disorder is adenosine deaminase deficiency or SCID associated with adenosine deaminase deficiency. In some embodiments, the disorder is Athabascan type SCID. In some embodiments, the disorder is T cell-negative, B-cell/natural killer cell-positive SCID. In some embodiments, the disorder is T-negative/B-positive type autosomal recessive SCID. In some embodiments, the disorder is SCID with sensitivity to ionizing radiation. In some embodiments, the disorder is SCID with microcephaly, growth retardation, and sensitivity to ionizing radiation. In some embodiments, the disorder is reticular dysgenesis. In some embodiments, the disorder is LIG4 syndrome. In some embodiments, the disorder is alpha/beta T-cell lymphopenia with gamma/delta T-cell expansion, severe cytomegalovirus infection, and autoimmunity. In some embodiments, the disorder is combined cellular and humoral immune defects with granulomas. In some embodiments, the disorder is B cell-negative SCID. In some embodiments, the disorder is a selective T-cell defect or selective T-cell defect associated with SCID. In some embodiments, the disorder is purine nucleoside phosphorylase deficiency or SCID associated with purine nucleoside phosphorylase deficiency. In some embodiments, the disorder is Omenn syndrome. In some embodiments, the disorder is bare lymphocyte syndrome. In some embodiments, the disorder is SCID associated with JAK3 mutation. In some embodiments, the disorder is SCID associated with DCLRE1C mutation. In some embodiments, the disorder is a disorder listed in any one of the Gene Phenotype Relationship tables listed herein. In some embodiments, the disorder is sickle cell anemia. In some embodiments, the disorder is sickle cell disease. In some embodiments, the disorder is sickle cell anemia. In some embodiments, the disorder is sickle beta thalassemia. In some embodiments, the disorder is beta thalassemia.

[0408] The methods of the present invention are capable of altering target polynucleotide sequences in a variety of different cells. In some embodiments, the methods of the present invention are used to alter target polynucleotide sequences in cells ex vivo for subsequent introduction into a subject. In some embodiments, the methods of the present invention can be used to alter target polynucleotide sequences in cells in vivo. In some embodiments, the cell is a peripheral blood cell. In some embodiments, the cell is a

stem cell or a pluripotent cell. In some embodiments, the cell is a hematopoietic stem cell. In some embodiments, the cell is a CD34+ cell. In some embodiments, the cell is a CD34+ mobilized peripheral blood cell. In some embodiments, the cell is a CD34+ cord blood cell. In some embodiments, the cell is a CD34+ bone marrow cell. In some embodiments, the cell is a CD34+CD38-Lineage-CD90+CD45RA− cell. In some embodiments, the cell is a hepatocyte. In some embodiments, the cell is a human pluripotent cell. In some embodiments, the cell is a primary human cell. In some embodiments, the cell is a non-transformed cell. In some embodiments, the cell is not a cancer cell. In some embodiments, the cell is not a tumor cell. In some embodiments, the cell is not a transformed cell.

[0409] In some aspects, the present invention provides a method for altering a target SCID-associated polynucleotide sequence in a cell comprising contacting the SCID-associated polynucleotide sequence in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target SCID-associated polynucleotide sequence, wherein the target SCID-associated polynucleotide sequence is cleaved, and wherein the efficiency of alteration of cells that express Cas protein is from about 8% to about 80%.

[0410] In some aspects, the present invention provides a method for altering a target SCD-associated polynucleotide sequence in a cell comprising contacting the SCD-associated polynucleotide sequence in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target SCD-associated polynucleotide sequence, wherein the target SCD-associated polynucleotide sequence is cleaved, and wherein the efficiency of alteration of cells that express Cas protein is from about 8% to about 80%.

[0411] In some aspects, the present invention provides a method for altering a target beta thalassemia-associated polynucleotide sequence in a cell comprising contacting the beta thalassemia-associated polynucleotide sequence in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target beta thalassemia-associated polynucleotide sequence, wherein the target beta thalassemia-associated polynucleotide sequence is cleaved, and wherein the efficiency of alteration of cells that express Cas protein is from about 8% to about 80%.

[0412] In some aspects, the present invention provides a method for treating or preventing a disorder associated with expression of a SCID-associated polynucleotide sequence in a subject, the method comprising (a) altering a target SCID-associated polynucleotide sequence in a cell ex vivo by contacting the SCID-associated polynucleotide sequence in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target SCID-associated polynucleotide sequence, wherein the target SCID-associated polynucleotide sequence is cleaved, and wherein the efficiency of alteration is from about 8% to about 80%, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the SCID-associated polynucleotide sequence.

[0413] In some embodiments, the method includes the step of contacting, before the step of introducing the cell into the subject, the cleaved SCID-associated polynucleotide sequences with an exogenously introduced DNA repair template comprising a corresponding normal or wild-type polynucleotide sequence, thereby allowing homology-directed repair to replace the cleaved SCID-associated polynucleotide sequence with the corresponding normal or wild type polynucleotide sequence. In embodiments in which the target SCID-associated polynucleotide sequences comprise ADA polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal ADA polynucleotide sequence.

[0414] In embodiments in which the target SCID-associated polynucleotide sequences comprise AK2 polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal AK2 polynucleotide sequence.

[0415] In embodiments in which the target SCID-associated polynucleotide sequences comprise CD3D polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal CD3D polynucleotide sequence.

[0416] In embodiments in which the target SCID-associated polynucleotide sequences comprise DCLRE1C polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal DCLRE1C polynucleotide sequence.

[0417] In embodiments in which the target SCID-associated polynucleotide sequences comprise IL2RG polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal IL2RG polynucleotide sequence.

[0418] In embodiments in which the target SCID-associated polynucleotide sequences comprise IL7R polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal IL7R polynucleotide sequence.

[0419] In embodiments in which the target SCID-associated polynucleotide sequences comprise JAK3 polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal JAK3 polynucleotide sequence.

[0420] In embodiments in which the target SCID-associated polynucleotide sequences comprise LIG4 polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal LIG4 polynucleotide sequence.

[0421] In embodiments in which the target SCID-associated polynucleotide sequences comprise NHEJ1 polynucleotide sequences, the exogenously introduced DNA repair

template comprises a corresponding wild-type or normal NHEJ1 polynucleotide sequence.

[0422] In embodiments in which the target SCID-associated polynucleotide sequences comprise PNP polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal PNP polynucleotide sequence.

[0423] In embodiments in which the target SCID-associated polynucleotide sequences comprise PRKDC polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal PRKDC polynucleotide sequence.

[0424] In embodiments in which the target SCID-associated polynucleotide sequences comprise RAG1 polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal RAG1 polynucleotide sequence.

[0425] In embodiments in which the target SCID-associated polynucleotide sequences comprise RAG2 polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal RAG2 polynucleotide sequence.

[0426] In embodiments in which the target SCID-associated polynucleotide sequences comprise ZAP70 polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal ZAP70 polynucleotide sequence.

[0427] In some aspects, the present invention provides a method for treating or preventing a disorder associated with expression of a SCD-associated polynucleotide sequence in a subject, the method comprising (a) altering a target SCD-associated polynucleotide sequence in a cell ex vivo by contacting the SCD-associated polynucleotide sequence in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target SCD-associated polynucleotide sequence, wherein the target SCD-associated polynucleotide sequence is cleaved, and wherein the efficiency of alteration is from about 8% to about 80%, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the SCD-associated polynucleotide sequence.

[0428] In some embodiments, the method includes the step of contacting, before the step of introducing the cell into the subject, the cleaved SCD-associated polynucleotide sequences with an exogenously introduced DNA repair template comprising a normal HBB sequence, thereby allowing homology-directed repair to replace the cleaved SCD-associated polynucleotide sequence with the normal HBB sequence.

[0429] In some aspects, the present invention provides a method for treating or preventing a disorder associated with expression of a beta thalassemia-associated polynucleotide sequence in a subject, the method comprising (a) altering a target beta thalassemia-associated polynucleotide sequence in a cell ex vivo by contacting the beta thalassemia-associated polynucleotide sequence in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target beta thalassemia-associated polynucleotide sequence, wherein the target beta thalassemia-associated polynucleotide sequence is cleaved, and wherein the efficiency of alteration is from about 8% to about 80%, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the beta thalassemia-associated polynucleotide sequence.

[0430] In some embodiments, the method includes the step of contacting, before the step of introducing the cell into the subject, the cleaved beta thalassemia-associated polynucleotide sequences with an exogenously introduced DNA repair template comprising a normal HBB sequence, thereby allowing homology-directed repair to replace the cleaved beta thalassemia-associated polynucleotide sequence with the normal HBB sequence.

[0431] In some aspects, the present invention provides a method for simultaneously altering multiple target SCID-associated polynucleotide sequences in a cell comprising contacting the SCID-associated polynucleotide sequences in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target SCID-associated polynucleotide sequences, wherein the target SCD-associated polynucleotide sequences are cleaved, and wherein the efficiency of alteration of cells that express Cas protein is from about 8% to about 80%.

[0432] In some embodiments, the method includes the step of contacting the cleaved target SCID-associated polynucleotide sequences with an exogenously introduced DNA repair template comprising a corresponding normal or wild-type sequence (e.g., of a ADA gene, a AK2 gene, a CD3D gene, a DCLRE1C gene, a IL2RG gene, IL7R gene, a LIG4 gene, a NHEJ1 gene, a PNP gene, a PRKDC gene, a RAG1 gene, a RAG2 gene, a ZAP70 gene), thereby allowing homology-directed repair to replace the mutant portion of the cleaved SCID-associated polynucleotide sequence with the corresponding normal or wild-type sequence (e.g., of the ADA gene, the AK2 gene, the CD3D gene, the DCLRE1C gene, the IL2RG gene, the IL7R gene, the LIG4 gene, the NHEJ1 gene, the PNP gene, the PRKDC gene, the RAG1 gene, the RAG2 gene, the ZAP70 gene).

[0433] In some aspects, the present invention provides a method for simultaneously altering multiple target SCD-associated polynucleotide sequences in a cell comprising contacting the SCD-associated polynucleotide sequences in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target SCD-associated polynucleotide sequences, wherein the target SCD-associated polynucleotide sequences are cleaved, and wherein the efficiency of alteration of cells that express Cas protein is from about 8% to about 80%.

[0434] In some embodiments, the method includes the step of contacting the cleaved target SCD-associated polynucleotide sequences with an exogenously introduced DNA repair template comprising a normal HBB sequence, thereby

allowing homology-directed repair to replace the mutant portion of the cleaved SCD-associated polynucleotide sequence with the normal HBB sequence.

[0435] In some aspects, the present invention provides a method for simultaneously altering multiple target beta thalassemia-associated polynucleotide sequences in a cell comprising contacting the beta thalassemia-associated polynucleotide sequences in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target beta thalassemia-associated polynucleotide sequences, wherein the target beta thalassemia-associated polynucleotide sequences are cleaved, and wherein the efficiency of alteration of cells that express Cas protein is from about 8% to about 80%.

[0436] In some embodiments, the method includes the step of contacting the cleaved target beta thalassemia-associated polynucleotide sequences with an exogenously introduced DNA repair template comprising a normal HBB sequence, thereby allowing homology-directed repair to replace the mutant portion of the cleaved beta thalassemia-associated polynucleotide sequence with the normal HBB sequence.

[0437] In some aspects, the present invention provides a method for treating or preventing a disorder associated with expression of SCID-associated polynucleotide sequences in a subject, the method comprising (a) altering target SCID-associated polynucleotide sequences in a cell ex vivo by contacting the SCD-associated polynucleotide sequences in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target SCID-associated polynucleotide sequences, wherein the target SCID-associated polynucleotide sequences are cleaved, and wherein the efficiency of alteration of cells that express Cas protein is from about 8% to about 80%, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the SCID-associated polynucleotide sequences.

[0438] In some embodiments, the method includes the step of contacting, before the step of introducing the cell into the subject, the cleaved SCID-associated polynucleotide sequences with an exogenously introduced DNA repair template comprising a corresponding normal or wild-type sequence (e.g., of a ADA gene, a AK2 gene, a CD3D gene, a DCLRE1C gene, a IL2RG gene, a IL7R gene, a LIG4 gene, a NHEJ1 gene, a PNP gene, a PRKDC gene, a RAG1 gene, a RAG2 gene, a ZAP70 gene), thereby allowing homology-directed repair to replace the cleaved SCD-associated polynucleotide sequence with the normal or wild-type sequence (e.g., of the ADA gene, the AK2 gene, the CD3D gene, the DCLRE1C gene, the IL2RG gene, the IL7R gene, the LIG4 gene, the NHEJ1 gene, the PNP gene, the PRKDC gene, the RAG1 gene, the RAG2 gene, the ZAP70 gene).

[0439] In some aspects, the present invention provides a method for treating or preventing a disorder associated with expression of SCD-associated polynucleotide sequences in a subject, the method comprising (a) altering target SCD-associated polynucleotide sequences in a cell ex vivo by contacting the SCD-associated polynucleotide sequences in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target SCD-associated polynucleotide sequences, wherein the target SCD-associated polynucleotide sequences are cleaved, and wherein the efficiency of alteration of cells that express Cas protein is from about 8% to about 80%, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the SCD-associated polynucleotide sequences.

[0440] In some embodiments, the method includes the step of contacting, before the step of introducing the cell into the subject, the cleaved SCD-associated polynucleotide sequences with an exogenously introduced DNA repair template comprising a normal HBB sequence, thereby allowing homology-directed repair to replace the cleaved SCD-associated polynucleotide sequence with the normal HBB sequence.

[0441] In some aspects, the present invention provides a method for treating or preventing a disorder associated with expression of beta thalassemia-associated polynucleotide sequences in a subject, the method comprising (a) altering target beta thalassemia-associated polynucleotide sequences in a cell ex vivo by contacting the beta thalassemia-associated polynucleotide sequences in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target beta thalassemia-associated polynucleotide sequences, wherein the target beta thalassemia-associated polynucleotide sequences are cleaved, and wherein the efficiency of alteration of cells that express Cas protein is from about 8% to about 80%, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the beta thalassemia-associated polynucleotide sequences.

[0442] In some embodiments, the method includes the step of contacting, before the step of introducing the cell into the subject, the cleaved beta thalassemia-associated polynucleotide sequences with an exogenously introduced DNA repair template comprising a normal HBB sequence, thereby allowing homology-directed repair to replace the cleaved beta thalassemia-associated polynucleotide sequence with the normal HBB sequence.

[0443] The present invention also provides compositions comprising Cas proteins of the present invention or functional portions thereof, nucleic acids encoding the Cas proteins or functional portions thereof, and ribonucleic acid sequences which direct Cas proteins to and hybridize to target motifs of target polynucleotides in a cell.

[0444] For administration to a subject, a composition as disclosed herein can be administered to a subject, for example in pharmaceutically acceptable compositions. Pharmaceutically acceptable compositions comprise a therapeutically-effective amount of a Cas protein of the present invention or functional portion thereof, nucleic acids encoding the Cas proteins (e.g., modified, synthetic mRNA), and

ribonucleic acid sequences which direct Cas proteins to and hybridize, formulated together with one or more pharmaceutically acceptable carriers (additives) and/or diluents.

[0445] As described in detail below, the pharmaceutical compositions of the present invention can be specially formulated for administration in solid or liquid form, including those adapted for the following: (1) oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), lozenges, dragees, capsules, pills, tablets (e.g., those targeted for buccal, sublingual, and systemic absorption), boluses, powders, granules, pastes for application to the tongue; (2) parenteral administration, for example, by subcutaneous, intramuscular, intravenous or epidural injection as, for example, a sterile solution or suspension, or sustained-release formulation; (3) topical application, for example, as a cream, ointment, or a controlled-release patch or spray applied to the skin; (4) intravaginally or intrarectally, for example, as a pessary, cream or foam; (5) sublingually; (6) ocularly; (7) transdermally; (8) transmucosally; or (9) nasally. Additionally, compounds can be implanted into a patient or injected using a drug delivery system. See, for example, Urquhart, et al., Ann. Rev. Pharmacol. Toxicol. 24: 199-236 (1984); Lewis, ed. "Controlled Release of Pesticides and Pharmaceuticals" (Plenum Press, New York, 1981); U.S. Pat. No. 3,773,919; and U.S. Pat. No. 35 3,270,960.

[0446] As used here, the term "pharmaceutically acceptable" refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0447] As used here, the term "pharmaceutically-acceptable carrier" means a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, manufacturing aid (e.g., lubricant, talc magnesium, calcium or zinc stearate, or steric acid), or solvent encapsulating material, involved in carrying or transporting the subject compound from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically-acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, methylcellulose, ethyl cellulose, microcrystalline cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) lubricating agents, such as magnesium stearate, sodium lauryl sulfate and talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol (PEG); (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) pH buffered solutions; (21) polyesters, polycarbonates and/or polyanhydrides; (22) bulking agents, such as polypeptides and amino acids (23) serum component, such as serum albumin, HDL and LDL; (22) C2-C12 alcohols, such as ethanol; and (23) other non-toxic compatible substances employed in pharmaceutical formulations. Wetting agents, coloring agents, release agents, coating agents, sweetening agents, flavoring agents, perfuming agents, preservative and antioxidants can also be present in the formulation. The terms such as "excipient", "carrier", "pharmaceutically acceptable carrier" or the like are used interchangeably herein.

[0448] The phrase "therapeutically-effective amount" as used herein in respect to a Cas protein and/or ribonucleic acids described herein means that amount of relevant protein and/or ribonucleic acid, or composition comprising the same which is effective for producing some desired therapeutic effect in at least a sub-population of cells in an animal at a reasonable benefit/risk ratio applicable to any medical treatment. For example, an amount administered to a subject that is sufficient to produce a statistically significant, measurable change in at least one symptom of sickle cell anemia (e.g., reduced red blood cell count.). Determination of a therapeutically effective amount is well within the capability of those skilled in the art. Generally, a therapeutically effective amount can vary with the subject's history, age, condition, sex, as well as the severity and type of the medical condition in the subject, and administration of other pharmaceutically active agents.

[0449] As used herein, the term "administer" refers to the placement of a composition into a subject by a method or route which results in at least partial localization of the composition at a desired site such that desired effect is produced. A compound or composition described herein can be administered by any appropriate route known in the art including, but not limited to, oral or parenteral routes, including intravenous, intramuscular, subcutaneous, transdermal, airway (aerosol), pulmonary, nasal, rectal, and topical (including buccal and sublingual) administration.

[0450] Exemplary modes of administration include, but are not limited to, injection, infusion, instillation, inhalation, or ingestion. "Injection" includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intraventricular, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, sub capsular, subarachnoid, intraspinal, intracerebro spinal, and intrasternal injection and infusion. In preferred embodiments, the compositions are administered by intravenous infusion or injection.

[0451] In some aspects, the present invention provides a composition comprising at least one ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **1**.

[0452] In some aspects, the present invention provides a composition comprising at least one ribonucleic acid comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **1**.

[0453] In some aspects, the present invention provides a composition comprising at least one ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **2**.

[0454] In some aspects, the present invention provides a composition comprising at least one ribonucleic acid comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **2**.

[0455] In some aspects, the present invention provides a composition comprising at least one ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **3**. In some aspects, the present invention provides a composition comprising at least one ribonucleic acid comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **3**.

[0456] In some aspects, the present invention provides a composition comprising at least one ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **4**. In some aspects, the present invention provides a composition comprising at least one ribonucleic acid comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **4**.

[0457] In some aspects, the present invention provides a composition comprising at least one ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **5**. In some aspects, the present invention provides a composition comprising at least one ribonucleic acid comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **5**.

[0458] In some aspects, the present invention provides a composition comprising at least one ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **6**. In some aspects, the present invention provides a composition comprising at least one ribonucleic acid comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **6**.

[0459] In some aspects, the present invention provides a composition comprising at least one ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **7**. In some aspects, the present invention provides a composition comprising at least one ribonucleic acid comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **7**.

[0460] In some aspects, the present invention provides a composition comprising at least one ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **8**. In some aspects, the present invention provides a composition comprising at least one ribonucleic acid comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **8**.

[0461] In some aspects, the present invention provides a composition comprising at least one ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **9**. In some aspects, the present invention provides a composition comprising at least one ribonucleic acid comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **9**.

[0462] In some aspects, the present invention provides a composition comprising at least one ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **10**. In some aspects, the present invention provides a composition comprising at least one ribonucleic acid comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **10**.

[0463] In some aspects, the present invention provides a composition comprising at least one ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **11**. In some aspects, the present invention provides a composition comprising at least one ribonucleic acid comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **11**.

[0464] In some aspects, the present invention provides a composition comprising at least one ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **12**. In some aspects, the present invention provides a composition comprising at least one ribonucleic acid comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **12**.

[0465] In some aspects, the present invention provides a composition comprising at least one ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **13**. In some aspects, the present invention provides a composition comprising at least one ribonucleic acid comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **13**.

[0466] In some aspects, the present invention provides a composition comprising at least one ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **14**. In some aspects, the present invention provides a composition comprising at least one ribonucleic acid comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **14**.

[0467] In some aspects, the present invention provides a composition comprising at least one ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **15**. In some aspects, the present invention provides a composition comprising at least one ribonucleic acid comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **15**.

[0468] In some aspects, the present invention provides a composition comprising at least one ribonucleic acid having a ribonucleic acid sequences of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). In some aspects, the present invention provides a composition comprising at least one ribonucleic acid comprising a sequence with a single nucleotide mismatch to ribonucleic acid sequences of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). In some embodiments, the at least one ribonucleic acid sequences described above do not include the 3 nucleotide NGG sequence.

[0469] For example, if the target site sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one ribonucleic acid sequence is GATGCTCAGTACAGCCACCT (SEQ ID NO: 5324). As another example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), a ribonucleic acid sequence with a single nucleotide mismatch which does not include the 3 nucleotide NGG sequence is GATGCTGAGTACAGCCACCT (SEQ ID NO: 5326), with the italicized G being the mismatched nucleotide. Those skilled in the art will appreciate, however, that the single nucleotide mismatch can comprise any nucleotide in the ribonucleic acid, e.g., the first nucleotide, the second nucleo-

tide, the third nucleotide, the fourth nucleotide, the fifth nucleotide, the sixth nucleotide, the seventh nucleotide, the eighth nucleotide, the ninth nucleotide, the tenth nucleotide, the eleventh nucleotide, the twelfth nucleotide, the thirteenth nucleotide, the fourteenth nucleotide, the fifteenth nucleotide, the sixteenth nucleotide, the seventeenth nucleotide, the eighteenth nucleotide, the nineteenth nucleotide, or the twentieth nucleotide of the ribonucleic acid.

[0470] In some embodiments, the at least one ribonucleic acid described above comprises at least a 12 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the at least one ribonucleic acid described above comprises at least a 12 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the at least one ribonucleic acid described above comprises at least a 12 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). In some embodiments, the at least one ribonucleic acid described above comprises at least a 12 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of any of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 12 nucleotide fragment is GTACAGCCACCT (SEQ ID NO: 5327).

[0471] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 13 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 13 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 13 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 13 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 13 nucleotide fragment is AGTACAGCCACCT (SEQ ID NO: 5328).

[0472] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 14 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 14 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 14 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 14 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 14 nucleotide fragment is CAGTACAGCCACCT (SEQ ID NO: 5329).

[0473] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 15 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 15 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 15 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 15 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 15 nucleotide fragment is TCAGTACAGCCACCT (SEQ ID NO: 5330).

[0474] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprise at least a 16 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 16 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprise at least a 16 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 16 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 16 nucleotide fragment is CTCAGTACAGCCACCT (SEQ ID NO: 5331).

[0475] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 17 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 17 nucleotide fragment of a sequence with a single nucleotide mismatch to

a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 17 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 17 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 17 nucleotide fragment is GCTCAGTACAGCCACCT (SEQ ID NO: 5332).

[0476] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 18 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 18 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 18 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 18 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 18 nucleotide fragment is TGCTCAGTACAGCCACCT (SEQ ID NO: 5333).

[0477] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprise at least a 19 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 19 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprise at least a 19 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 19 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 19 nucleotide fragment is ATGCTCAGTACAGCCACCT (SEQ ID NO: 5334).

[0478] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 20 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 20 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 20 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 20 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 20 nucleotide fragment is GATGCTCAGTACAGCCACCT (SEQ ID NO: 5324).

[0479] In some embodiments, the at least one ribonucleic acid in the composition is contained in a nanoparticle. In some embodiments, the at least one ribonucleic acid is contained in a lipid nanoparticle. In some embodiments, the lipid nanoparticle comprises at least one of a cationic lipid, a neutral lipid, an amino lipid, a sterol, and a PEG or PEG-modified lipid.

[0480] In some embodiments, at least one of the ribonucleic acids in the composition is a modified ribonucleic acid as described herein (e.g., a synthetic, modified ribonucleic acid, e.g., comprising one to two modified nucleotides selected from the group consisting of pseudouridine, 5-methylcytodine, 2-thio-uridine, 5-methyluridine-5'-triphosphate, 4-thiouridine-5'-triphosphate, 5,6-dihydrouridine-5'-triphosphate, and 5-azauridine-5'-triphosphate, or any other modified nucleotides or modifications described herein).

[0481] In some embodiments, a composition of the present invention comprises a nucleic acid sequence encoding a Cas protein. In some embodiments, a composition of the present invention comprises nucleic acid sequence encoding Cas9 protein or a functional portion thereof.

[0482] In some embodiments, the nucleic acid encoding the Cas protein (e.g., Cas9) comprises a modified ribonucleic acid as described herein (e.g., a synthetic, modified mRNA described herein, e.g., comprising at least one modified nucleotide selected from the group consisting of pseudouridine, 5-methylcytodine, 2-thio-uridine, 5-methyluridine-5'-triphosphate, 4-thiouridine-5'-triphosphate, 5,6-dihydrouridine-5'-triphosphate, and 5-azauridine-5'-triphosphate or any other modified nucleotides or modifications described herein).

[0483] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **1**.

[0484] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one

additional ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **2**.

[0485] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **3**.

[0486] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **4**.

[0487] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **5**.

[0488] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **6**.

[0489] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **7**.

[0490] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **8**.

[0491] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **9**.

[0492] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **10**.

[0493] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **11**.

[0494] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **12**.

[0495] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **13**.

[0496] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **14**.

[0497] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **15**.

[0498] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid having a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321).

[0499] In some embodiments, the at least one additional ribonucleic acid sequences described above do not include the 3 nucleotide NGG sequence.

[0500] For example, if the target site sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one additional ribonucleic acid is GATGCTCAGTACAGCCACCT (SEQ ID NO: 5324). As another example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), a ribonucleic acid sequence with a single nucleotide mismatch which does not include the 3 nucleotide NGG sequence is GATGCTGAGTACAGCCACCT (SEQ ID NO: 5326), with the italicized G being the mismatched nucleotide. Those skilled in the art will appreciate, however, that the single nucleotide mismatch can comprise any nucleotide in the ribonucleic acid, e.g., the first nucleotide, the second nucleotide, the third nucleotide, the fourth nucleotide, the fifth nucleotide, the sixth nucleotide, the seventh nucleotide, the eighth nucleotide, the ninth nucleotide, the tenth nucleotide, the eleventh nucleotide, the twelfth nucleotide, the thirteenth nucleotide, the fourteenth nucleotide, the fifteenth nucleotide, the sixteenth nucleotide, the seventeenth nucleotide, the eighteenth nucleotide, the nineteenth nucleotide, or the twentieth nucleotide of the ribonucleic acid.

[0501] In some embodiments, the at least one additional ribonucleic acid described above comprises at least a 12 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the at least one additional ribonucleic acid described above comprises at least a 12 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the at least one additional ribonucleic acid described above comprises at least a 12 nucleotide fragment of a ribonucleic acid sequence of any of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). In some embodiments, the at least one additional ribonucleic acid described above comprises at least a 12 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCA-

GACTTCTCCACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCAGTACAGCCACCT-TGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one additional ribonucleic acid which comprises at least a 12 nucleotide fragment is GTACAGCCACCT (SEQ ID NO: 5327).

[0502] In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 13 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 13 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 13 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTC-CACAGG (SEQ ID NO: 5321). In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 13 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCA-GACTTCTCCACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCAGTACAGCCACCT-TGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one additional ribonucleic acid which comprises at least a 13 nucleotide fragment is AGTACAGCCACCT (SEQ ID NO: 5328).

[0503] In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 14 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 14 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 14 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTC-CACAGG (SEQ ID NO: 5321). In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 14 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCA-GACTTCTCCACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCAGTACAGCCACCT-TGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one additional ribonucleic acid which comprises at least a 14 nucleotide fragment is CAGTACAGCCACCT (SEQ ID NO: 5329).

[0504] In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 15 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 15 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 15 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTC-CACAGG (SEQ ID NO: 5321). In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 15 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCA-GACTTCTCCACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCAGTACAGCCACCT-TGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one additional ribonucleic acid which comprises at least a 15 nucleotide fragment is TCAGTACAGCCACCT (SEQ ID NO: 5330).

[0505] In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprise at least a 16 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 16 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprise at least a 16 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTC-CACAGG (SEQ ID NO: 5321). In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 16 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCA-GACTTCTCCACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCAGTACAGCCACCT-TGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one additional ribonucleic acid which comprises at least a 16 nucleotide fragment is CTCAGTACAGC-CACCT (SEQ ID NO: 5331).

[0506] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 17 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 17 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 17 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 17 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one additional ribonucleic acid which comprises at least a 17 nucleotide fragment is GCTCAGTACAGCCACCT (SEQ ID NO: 5332).

[0507] In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid

described above comprises at least a 18 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 18 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 18 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 18 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one additional ribonucleic acid which comprises at least a 18 nucleotide fragment is TGCTCAGTACAGCCACCT (SEQ ID NO: 5333).

[0508] In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprise at least a 19 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 19 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprise at least a 19 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 19 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one additional ribonucleic acid which comprises at least a 19 nucleotide fragment is ATGCTCAGTACAGCCACCT (SEQ ID NO: 5334).

[0509] In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 20 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 20 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 20 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 20 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one additional ribonucleic acid which comprises at least a 20 nucleotide fragment is GATGCTCAGTACAGCCACCT (SEQ ID NO: 5324).

[0510] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid sequence comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **1**.

[0511] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid sequence comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **2**.

[0512] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid sequence comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **3**.

[0513] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid sequence comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **4**.

[0514] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid sequence comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **5**.

[0515] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid sequence comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **6**.

[0516] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid sequence comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **7**.

[0517] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid sequence comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **8**.

[0518] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising

a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid sequence comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **9**.

[0519] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid sequence comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **10**.

[0520] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid sequence comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **11**.

[0521] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid sequence comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **12**.

[0522] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid sequence comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **13**.

[0523] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid sequence comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **14**.

[0524] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid sequence comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **15**.

[0525] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid sequence comprising a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321).

[0526] In some embodiments, the at least one additional ribonucleic acid sequences described above do not include the 3 nucleotide NGG sequence. For example, if the target site sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one additional ribonucleic acid is GATGCTCAGTACAGCCACCT (SEQ ID NO: 5324). As another example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), a ribonucleic acid sequence with a single nucleotide mismatch which does not include the 3 nucleotide NGG sequence is GATGCTGAGTACAGCCACCT (SEQ ID NO: 5326), with the italicized G being the mismatched nucleotide. Those skilled in the art will appreciate, however, that the single nucleotide mismatch can comprise any nucleotide in the ribonucleic acid, e.g., the first nucleotide, the second nucleotide, the third nucleotide, the fourth nucleotide, the fifth nucleotide, the sixth nucleotide, the seventh nucleotide, the eighth nucleotide, the ninth nucleotide, the tenth nucleotide, the eleventh nucleotide, the twelfth nucleotide, the thirteenth nucleotide, the fourteenth nucleotide, the fifteenth nucleotide, the sixteenth nucleotide, the seventeenth nucleotide, the eighteenth nucleotide, the nineteenth nucleotide, or the twentieth nucleotide of the ribonucleic acid.

[0527] In some embodiments, the at least one additional ribonucleic acid described above comprises at least a 12 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the at least one additional ribonucleic acid described above comprises at least a 12 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the at least one additional ribonucleic acid described above comprises at least a 12 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). In some embodiments, the at least one additional ribonucleic acid described above comprises at least a 12 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one additional ribonucleic acid which comprises at least a 12 nucleotide fragment is GTACAGCCACCT (SEQ ID NO: 5327).

[0528] In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 13 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 13 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 13 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 13 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one additional ribonucleic acid which comprises at least a 13 nucleotide fragment is AGTACAGCCACCT (SEQ ID NO: 5328).

[0529] In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 14 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some

embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 14 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 14 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 14 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one additional ribonucleic acid which comprises at least a 14 nucleotide fragment is CAGTACAGCCACCT (SEQ ID NO: 5329).

[0530] In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 15 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 15 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 15 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 15 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one additional ribonucleic acid which comprises at least a 15 nucleotide fragment is TCAGTACAGCCACCT (SEQ ID NO: 5330).

[0531] In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprise at least a 16 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 16 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprise at least a 16 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 16 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one additional ribonucleic acid which comprises at least a 16 nucleotide fragment is CTCAGTACAGCCACCT (SEQ ID NO: 5331).

[0532] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 17 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 17 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 17 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 17 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one additional ribonucleic acid which comprises at least a 17 nucleotide fragment is GCTCAGTACAGCCACCT (SEQ ID NO: 5332).

[0533] In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 18 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 18 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 18 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 18 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one additional ribonucleic acid which comprises at least a 18 nucleotide fragment is TGCTCAGTACAGCCACCT (SEQ ID NO: 5333).

[0534] In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprise at least a 19 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 19 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprise at least a 19 nucleotide fragment of a

ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 19 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one additional ribonucleic acid which comprises at least a 19 nucleotide fragment is ATGCTCAGTACAGCCACCT (SEQ ID NO: 5334).

[0535] In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 20 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 20 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 20 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 20 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one additional ribonucleic acid which comprises at least a 20 nucleotide fragment is GATGCTCAGTACAGCCACCT (SEQ ID NO: 5324).

[0536] In some embodiments, a composition of the present invention comprises a nucleic acid sequence encoding a fluorescent protein selected from the group consisting of green fluorescent protein and red fluorescent protein. In some embodiments, a composition of the present invention comprises a promoter operably linked to the chimeric nucleic acid. In some embodiments, the promoter is optimized for increased expression in human stem cells. In some embodiments, the promoter is selected from the group consisting of a Cytomegalovirus (CMV) early enhancer element and a chicken beta-actin promoter, a chicken beta-actin promoter, an elongation factor-1 alpha promoter, and a ubiquitin promoter.

[0537] In some embodiments, the chimeric nucleic acid is contained in a nanoparticle. In some embodiments, the chimeric nucleic acid is contained in a lipid nanoparticle as described herein. In some embodiments, the chimeric nucleic acid comprises at least one modified nucleotide described herein. In some embodiments, the Cas protein comprises a Cas9 protein or a functional portion thereof.

[0538] For in vivo methods, a therapeutically effective amount of a composition described herein can be administered to a subject. Methods of administering compositions to a subject are known in the art and easily available to one of skill in the art.

[0539] In some embodiments, a composition described herein includes one or more additional pharmaceutically active agents for treating or preventing the disorder associated with expression of the target polynucleotide sequence.

[0540] The present invention also provides kits for practicing any of the methods of the present invention, as well as kits comprising the compositions of the present invention, and instructions for using the kits for altering target polynucleotide sequences in a cell.

[0541] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **1**.

[0542] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **2**.

[0543] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **3**.

[0544] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **4**.

[0545] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **5**.

[0546] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **6**.

[0547] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **7**.

[0548] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **8**.

[0549] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **9**.

[0550] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the

Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **10**.

[0551] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **11**.

[0552] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **12**.

[0553] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **13**.

[0554] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **14**.

[0555] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **15**.

[0556] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence having a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321).

[0557] In some embodiments, the at least one ribonucleic acid sequences described above do not include the 3 nucleotide NGG sequence. For example, if the target site sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one ribonucleic acid sequence is GATGCTCAGTACAGCCACCT (SEQ ID NO: 5324). As another example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), a ribonucleic acid sequence with a single nucleotide mismatch which does not include the 3 nucleotide NGG sequence is GATGCTGAGTACAGCCACCT (SEQ ID NO: 5326), with the italicized G being the mismatched nucleotide. Those skilled in the art will appreciate, however, that the single nucleotide mismatch can comprise any nucleotide in the ribonucleic acid, e.g., the first nucleotide, the second nucleotide, the third nucleotide, the fourth nucleotide, the fifth nucleotide, the sixth nucleotide, the seventh nucleotide, the eighth nucleotide, the ninth nucleotide, the tenth nucleotide, the eleventh nucleotide, the twelfth nucleotide, the thirteenth nucleotide, the fourteenth nucleotide, the fifteenth nucleotide, the sixteenth nucleotide, the seventeenth nucleotide, the eighteenth nucleotide, the nineteenth nucleotide, or the twentieth nucleotide of the ribonucleic acid.

[0558] In some embodiments, the at least one ribonucleic acid described above comprises at least a 12 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the at least one ribonucleic acid described above comprises at least a 12 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the at least one ribonucleic acid described above comprises at least a 12 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). In some embodiments, the at least one ribonucleic acid described above comprises at least a 12 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 12 nucleotide fragment is GTACAGCCACCT (SEQ ID NO: 5327).

[0559] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 13 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 13 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 13 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 13 nucleotide fragment of a sequence with a single nucleotide mismatch to f a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 13 nucleotide fragment is AGTACAGCCACCT (SEQ ID NO: 5328).

[0560] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 14 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 14 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 14 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 14 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribo-

nucleic acid sequence of the at least one ribonucleic acid which comprises at least a 14 nucleotide fragment is CAGTACAGCCACCT (SEQ ID NO: 5329).

[0561] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 15 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 15 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 15 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 15 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 15 nucleotide fragment is TCAGTACAGCCACCT (SEQ ID NO: 5330).

[0562] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprise at least a 16 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 16 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprise at least a 16 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 16 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 16 nucleotide fragment is CTCAGTACAGCCACCT (SEQ ID NO: 5331).

[0563] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 17 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 17 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 17 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 17 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 17 nucleotide fragment is GCTCAGTACAGCCACCT (SEQ ID NO: 5332).

[0564] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 18 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 18 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 18 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 18 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 18 nucleotide fragment is TGCTCAGTACAGCCACCT (SEQ ID NO: 5333).

[0565] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprise at least a 19 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 19 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprise at least a 19 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 19 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 19 nucleotide fragment is ATGCTCAGTACAGCCACCT (SEQ ID NO: 5334).

[0566] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 20 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 20 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least

one ribonucleic acid described above comprises at least a 20 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 20 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 20 nucleotide fragment is GATGCTCAGTACAGCCACCT (SEQ ID NO: 5324).

[0567] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **1**, and any combination thereof.

[0568] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **2**, and any combination thereof.

[0569] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **3**, and any combination thereof.

[0570] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **4**, and any combination thereof.

[0571] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **5**, and any combination thereof.

[0572] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **6**, and any combination thereof.

[0573] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **7**, and any combination thereof.

[0574] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **8**, and any combination thereof.

[0575] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **9**, and any combination thereof.

[0576] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **10**, and any combination thereof.

[0577] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **11**, and any combination thereof.

[0578] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **12**, and any combination thereof.

[0579] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **13**, and any combination thereof.

[0580] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **14**, and any combination thereof.

[0581] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of FIG. **15**, and any combination thereof.

[0582] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321).

[0583] In some embodiments, the at least one ribonucleic acid sequences with the single nucleotide mismatches described above do not include the 3 nucleotide NGG

sequence. For example, if the target site sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one ribonucleic acid sequence is GATGCTCAGTACAGCCACCT (SEQ ID NO: 5324). As another example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), a ribonucleic acid sequence with a single nucleotide mismatch which does not include the 3 nucleotide NGG sequence is GATGCTGAGTACAGCCACCT (SEQ ID NO: 5326), with the italicized G being the mismatched nucleotide. Those skilled in the art will appreciate, however, that the single nucleotide mismatch can comprise any nucleotide in the ribonucleic acid, e.g., the first nucleotide, the second nucleotide, the third nucleotide, the fourth nucleotide, the fifth nucleotide, the sixth nucleotide, the seventh nucleotide, the eighth nucleotide, the ninth nucleotide, the tenth nucleotide, the eleventh nucleotide, the twelfth nucleotide, the thirteenth nucleotide, the fourteenth nucleotide, the fifteenth nucleotide, the sixteenth nucleotide, the seventeenth nucleotide, the eighteenth nucleotide, the nineteenth nucleotide, or the twentieth nucleotide of the ribonucleic acid.

[0584] In some embodiments, the at least one ribonucleic acid described above comprises at least a 12 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the at least one ribonucleic acid described above comprises at least a 12 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the at least one ribonucleic acid described above comprises at least a 12 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). In some embodiments, the at least one ribonucleic acid described above comprises at least a 12 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 12 nucleotide fragment is GTACAGCCACCT (SEQ ID NO: 5327).

[0585] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 13 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 13 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 13 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 13 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 13 nucleotide fragment is AGTACAGCCACCT (SEQ ID NO: 5328).

[0586] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 14 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 14 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 14 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 14 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 14 nucleotide fragment is CAGTACAGCCACCT (SEQ ID NO: 5329).

[0587] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 15 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 15 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 15 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 15 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 15 nucleotide fragment is TCAGTACAGCCACCT (SEQ ID NO: 5330).

[0588] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprise at least a 16 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 16 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprise at least a 16 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 16 nucleotide fragment of a sequence with

a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCA-GTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 16 nucleotide fragment is CTCA-GTACAGCCACCT (SEQ ID NO: 5331).

[0589] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 17 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 17 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 17 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 17 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCA-GTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 17 nucleotide fragment is GCTCAGTACAGCCACCT (SEQ ID NO: 5332).

[0590] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 18 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 18 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 18 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 18 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCA-GTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 18 nucleotide fragment is TGCTCAGTACAGCCACCT (SEQ ID NO: 5333).

[0591] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprise at least a 19 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 19 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprise at least a 19 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 19 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCA-GTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 19 nucleotide fragment is ATGCTCAGTACAGCCACCT (SEQ ID NO: 5334).

[0592] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 20 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 20 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 20 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 20 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). For example, if the target sequence is GATGCTCA-GTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 20 nucleotide fragment is GAT-GCTCAGTACAGCCACCT (SEQ ID NO: 5324).

[0593] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of at least one ribonucleic acid sequence of FIG. **1** and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence of FIG. **1**, and combinations thereof.

[0594] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of at least one ribonucleic acid sequence of FIG. **2** and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence of FIG. **2**, and combinations thereof.

[0595] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of at least one ribonucleic acid sequence of FIG. **3** and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence of FIG. **3**, and combinations thereof.

[0596] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of at least one ribonucleic

acid sequence of FIG. **4** and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence of FIG. **4**, and combinations thereof.

[0597] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of at least one ribonucleic acid sequence of FIG. **5** and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence of FIG. **5**, and combinations thereof.

[0598] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of at least one ribonucleic acid sequence of FIG. **6** and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence of FIG. **6**, and combinations thereof.

[0599] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of at least one ribonucleic acid sequence of FIG. **7** and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence of FIG. **7**, and combinations thereof.

[0600] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of at least one ribonucleic acid sequence of FIG. **8** and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence of FIG. **8**, and combinations thereof.

[0601] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of at least one ribonucleic acid sequence of FIG. **9** and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence of FIG. **9**, and combinations thereof.

[0602] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of at least one ribonucleic acid sequence of FIG. **10** and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence of FIG. **10**, and combinations thereof.

[0603] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of at least one ribonucleic acid sequence of FIG. **11** and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence of FIG. **11**, and combinations thereof.

[0604] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of at least one ribonucleic acid sequence of FIG. **12** and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence of FIG. **12**, and combinations thereof.

[0605] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of at least one ribonucleic acid sequence of FIG. **13** and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence of FIG. **13**, and combinations thereof.

[0606] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of at least one ribonucleic acid sequence of FIG. **14** and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence of FIG. **14**, and combinations thereof.

[0607] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of at least one ribonucleic acid sequence of FIG. **15** and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence of FIG. **15**, and combinations thereof.

[0608] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of at least one ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321) and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321).

[0609] In some embodiments, the at least one ribonucleic acid sequences described above do not include the 3 nucleotide NGG sequence. For example, if the target site sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one ribonucleic acid sequence is GATGCTCAGTACAGCCACCT (SEQ ID NO: 5324). As another example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), a ribonucleic acid sequence with a single nucleotide mismatch which does not include the 3 nucleotide NGG sequence is GATGCTGAGTACAGCCACCT (SEQ ID NO: 5326), with the italicized G being the mismatched nucleotide. Those skilled in the art will appreciate, however, that the single nucleotide mismatch can comprise any nucleotide in the ribonucleic acid, e.g., the first nucleotide, the second nucleotide, the third nucleotide, the fourth nucleotide, the fifth nucleotide, the sixth nucleotide, the seventh nucleotide, the eighth nucleotide, the ninth nucleotide, the tenth nucleotide, the eleventh nucleotide, the twelfth nucleotide, the thirteenth nucleotide, the fourteenth nucleotide, the fifteenth nucleotide, the sixteenth nucleotide, the seventeenth nucleotide, the eighteenth nucleotide, the nineteenth nucleotide, or the twentieth nucleotide of the ribonucleic acid.

[0610] In some embodiments, the at least one ribonucleic acid described above comprises at least a 12 nucleotide fragment of a ribonucleic acid sequence of any of FIGS.

1-15. In some embodiments, the at least one ribonucleic acid described above comprises at least a 12 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15** For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 12 nucleotide fragment is GTACAGCCACCT (SEQ ID NO: 5327).

[0611] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 13 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 13 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 13 nucleotide fragment is AGTACAGCCACCT (SEQ ID NO: 5328).

[0612] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 14 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 14 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 14 nucleotide fragment is CAGTACAGCCACCT (SEQ ID NO: 5329).

[0613] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 15 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 15 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 15 nucleotide fragment is TCAGTACAGCCACCT (SEQ ID NO: 5330).

[0614] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprise at least a 16 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 16 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 16 nucleotide fragment is CTCAGTACAGCCACCT (SEQ ID NO: 5331).

[0615] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 17 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 17 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 17 nucleotide fragment is GCTCAGTACAGCCACCT (SEQ ID NO: 5332).

[0616] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 18 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 18 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 18 nucleotide fragment is TGCTCAGTACAGCCACCT (SEQ ID NO: 5333).

[0617] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprise at least a 19 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 19 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 19 nucleotide fragment is ATGCTCAGTACAGCCACCT (SEQ ID NO: 5334).

[0618] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 20 nucleotide fragment of a ribonucleic acid sequence of any of FIGS. **1-15**. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 20 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of FIGS. **1-15**. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG (SEQ ID NO: 5323), the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 20 nucleotide fragment is GATGCTCAGTACAGCCACCT (SEQ ID NO: 5324).

[0619] In some embodiments, the at least one ribonucleic acid described above comprises at least a 12 nucleotide fragment, at least a 13 nucleotide fragment, at least a 14 nucleotide fragment, at least a 15 nucleotide fragment, at least a 16 nucleotide fragment, at least a 17 nucleotide

fragment, at least an 18 nucleotide fragment, at least a 19 nucleotide fragment, or at least a 20 nucleotide sequence of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321). In some embodiments, the at least one ribonucleic acid described above comprises at least a 12, at least a 13, at least a 14, at least a 15, at least a, at least a 17, at least an 18, at least a 19, or at least a 20 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG (SEQ ID NO: 5321).

[0620] In some embodiments, the kit comprises one or more cell lines, cultures, or populations selected from the group consisting of human pluripotent cells, primary human cells, and non-transformed cells. In some embodiments, the kit comprises a DNA repair template.

[0621] In some embodiments, the DNA repair template comprises one or more normal or wild-type ADA gene sequences. In some embodiments, the DNA repair template comprises one or more normal or wild-type DNA sequences that correspond to mutant ADA sequences to be cleaved from target SCID-associated polynucleotide sequences.

[0622] In some embodiments, the DNA repair template comprises one or more normal or wild-type AK2 gene sequences. In some embodiments, the DNA repair template comprises one or more normal or wild-type DNA sequences that correspond to mutant AK2 sequences to be cleaved from target SCID-associated polynucleotide sequences.

[0623] In some embodiments, the DNA repair template comprises one or more normal or wild-type CD3D gene sequences. In some embodiments, the DNA repair template comprises one or more normal or wild-type DNA sequences that correspond to mutant CD3D sequences to be cleaved from target SCID-associated polynucleotide sequences.

[0624] In some embodiments, the DNA repair template comprises one or more normal or wild-type DCLRE1C gene sequences. In some embodiments, the DNA repair template comprises one or more normal or wild-type DNA sequences that correspond to mutant DCLRE1C sequences to be cleaved from target SCID-associated polynucleotide sequences.

[0625] In some embodiments, the DNA repair template comprises one or more normal or wild-type IL2RG gene sequences. In some embodiments, the DNA repair template comprises one or more normal or wild-type DNA sequences that correspond to mutant IL2RG sequences to be cleaved from target SCID-associated polynucleotide sequences.

[0626] In some embodiments, the DNA repair template comprises one or more normal or wild-type IL7R gene sequences. In some embodiments, the DNA repair template comprises one or more normal or wild-type DNA sequences that correspond to mutant IL7R sequences to be cleaved from target SCID-associated polynucleotide sequences.

[0627] In some embodiments, the DNA repair template comprises one or more normal or wild-type JAK3 gene sequences. In some embodiments, the DNA repair template comprises one or more normal or wild-type DNA sequences that correspond to mutant JAK3 sequences to be cleaved from target SCID-associated polynucleotide sequences.

[0628] In some embodiments, the DNA repair template comprises one or more normal or wild-type NHEJ1 gene sequences. In some embodiments, the DNA repair template comprises one or more normal or wild-type DNA sequences that correspond to mutant NHEJ1 sequences to be cleaved from target SCID-associated polynucleotide sequences.

[0629] In some embodiments, the DNA repair template comprises one or more normal or wild-type PNP gene sequences. In some embodiments, the DNA repair template comprises one or more normal or wild-type DNA sequences that correspond to mutant PNP sequences to be cleaved from target SCID-associated polynucleotide sequences.

[0630] In some embodiments, the DNA repair template comprises one or more normal or wild-type PRKDC gene sequences. In some embodiments, the DNA repair template comprises one or more normal or wild-type DNA sequences that correspond to mutant PRKDC sequences to be cleaved from target SCID-associated polynucleotide sequences.

[0631] In some embodiments, the DNA repair template comprises one or more normal or wild-type RAG1 gene sequences. In some embodiments, the DNA repair template comprises one or more normal or wild-type DNA sequences that correspond to mutant RAG1 sequences to be cleaved from target SCID-associated polynucleotide sequences.

[0632] In some embodiments, the DNA repair template comprises one or more normal or wild-type RAG2 gene sequences. In some embodiments, the DNA repair template comprises one or more normal or wild-type DNA sequences that correspond to mutant RAG2 sequences to be cleaved from target SCID-associated polynucleotide sequences.

[0633] In some embodiments, the DNA repair template comprises one or more normal or wild-type ZAP70 gene sequences. In some embodiments, the DNA repair template comprises one or more normal or wild-type DNA sequences that correspond to mutant ZAP70 sequences to be cleaved from target SCID-associated polynucleotide sequences.

[0634] In some embodiments, the DNA repair template comprises one or more normal or wild-type HBB gene sequences. In some embodiments, the DNA repair template comprises one or more normal or wild-type DNA sequences that correspond to mutant HBB sequences to be cleaved from target SCD-associated polynucleotide sequences.

[0635] In some embodiments, the DNA repair template comprises one or more normal or wild-type DNA sequences that correspond to mutant HBB sequences to be cleaved from target beta thalassemia-associated polynucleotide sequences.

[0636] It should be appreciated that the methods, compositions, and kits of the present invention may employ nanoparticles or lipid nanoparticles as a vehicle for delivering, or introducing a Cas protein and/or a ribonucleic acid of the present invention into a cell.

[0637] In some embodiments, the lipid nanoparticle comprises at least one of a cationic lipid, a neutral lipid, an amino lipid, a sterol, and a PEG or PEG-modified lipid.

[0638] The cationic lipid may be, for example, N,N-dioleyl-N,N-dimethylammonium chloride (DODAC), N,N-distearyl-N,N-dimethylammonium bromide (DDAB), N—(I-(2,3-dioleoyloxy)propyl)-N,N,N-trimethylammonium chloride (DOTAP), N—(I-(2,3-dioleyloxy)propyl)-N,N,N-trimethylammonium chloride (DOTMA), N,N-dimethyl-2,3-dioleyloxy)propylamine (DODMA), 1,2-DiLinoleyloxy-N,N-dimethylaminopropane (DLinDMA), 1,2-Dilinolenyloxy-N,N-dimethylaminopropane (DLenDMA), 1,2-Dilinoleylcarbamoyloxy-3-dimethylaminopropane (DLin-C-DAP), 1,2-Dilinoleyoxy-3-(dimethylamino)acetoxypropane (DLin-DAC), 1,2-Dilinoleyoxy-3-morpholinopropane (DLin-MA), 1,2-Dilinoleoyl-3-dimethylaminopropane (DLinDAP), 1,2-Dilinoleylthio-3-dimethylaminopropane (DLin-S-DMA), 1-Linoleoyl-2-

linoleyloxy-3-dimethylaminopropane (DLin-2-DMAP), 1,2-Dilinoleyloxy-3-trimethylaminopropane chloride salt (DLin-TMA.C1), 1,2-Dilinoleoyl-3-trimethylaminopropane chloride salt (DLin-TAP.C1), 1,2-Dilinoleyloxy-3-(N-methylpiperazino)propane (DLin-MPZ), or 3-(N,N-Dilinoleylamino)-1,2-propanediol (DLinAP), 3-(N,N-Dioleylamino)-1,2-propanedio (DOAP), 1,2-Dilinoleyloxo-3-(2-N,N-dimethylamino)ethoxypropane (DLin-EG-DMA), 1,2-Dilinolenyloxy-N,N-dimethylaminopropane (DLinDMA), 2,2-Dilinoleyl-4-dimethylaminomethyl-[1,3]-dioxolane (DLin-K-DMA) or analogs thereof, (3aR,5s,6aS)-N,N-dimethyl-2,2-di((9Z,12Z)-octadeca-9,12-dienyl)tetrahydro-3aH-cyclopenta[d][1,3]dioxol-5-amine (ALNY-100), (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate (MC3), or a mixture thereof.

[0639] Other cationic lipids, which carry a net positive charge at about physiological pH, in addition to those specifically described above, may also be included in lipid particles of the invention. Such cationic lipids include, but are not limited to, N,N-dioleyl-N,N-dimethylammonium chloride ("DODAC"); N-(2,3-dioleyloxy)propyl-N,N—N-triethylammonium chloride ("DOTMA"); N,N-distearyl-N,N-dimethylammonium bromide ("DDAB"); N-(2,3-dioleoyloxy)propyl)-N,N,N-trimethylammonium chloride ("DOTAP"); 1,2-Dioleyloxy-3-trimethylaminopropane chloride salt ("DOTAP.Cl"); 3.beta.-(N—(N',N'-dimethylaminoethane)-carbamoyl)cholesterol ("DC-Chol"), N-(1-(2,3-dioleyloxy)propyl)-N-2-(sperminecarboxamido)ethyl)-N,N-dimethyl-ammonium trifluoracetate ("DOSPA"), dioctadecylamidoglycyl carboxyspermine ("DOGS"), 1,2-dileoyl-sn-3-phosphoethanolamine ("DOPE"), 1,2-dioleoyl-3-dimethylammonium propane ("DODAP"), N,N-dimethyl-2,3-dioleyloxy)propylamine ("DODMA"), and N-(1,2-dimyristyloxyprop-3-yl)-N,N-dimethyl-N-hydroxyethyl ammonium bromide ("DMRIE"), and mixtures thereof. Additionally, a number of commercial preparations of cationic lipids can be used, such as, e.g., LIPOFECTIN (including DOTMA and DOPE, available from GIBCO/BRL), and LIPOFECTAMINE (comprising DOSPA and DOPE, available from GIBCO/BRL). In particular embodiments, a cationic lipid is an amino lipid.

[0640] As used herein, the term "amino lipid" is meant to include those lipids having one or two fatty acid or fatty alkyl chains and an amino head group (including an alkylamino or dialkylamino group) that may be protonated to form a cationic lipid at physiological pH.

[0641] Other amino lipids would include those having alternative fatty acid groups and other dialkylamino groups, including those in which the alkyl substituents are different (e.g., N-ethyl-N-methylamino-, N-propyl-N-ethylamino- and the like). For those embodiments in which R^{11} and R^{12} are both long chain alkyl or acyl groups, they can be the same or different. In general, amino lipids having less saturated acyl chains are more easily sized, particularly when the complexes must be sized below about 0.3 microns, for purposes of filter sterilization. Amino lipids containing unsaturated fatty acids with carbon chain lengths in the range of C_{14} to C_{22} are preferred. Other scaffolds can also be used to separate the amino group and the fatty acid or fatty alkyl portion of the amino lipid. Suitable scaffolds are known to those of skill in the art.

[0642] Specific examples of PEG-modified lipids (or lipid-polyoxyethylene conjugates) that are useful in the present invention can have a variety of "anchoring" lipid portions to secure the PEG portion to the surface of the lipid vesicle. Examples of suitable PEG-modified lipids include PEG-modified phosphatidylethanolamine and phosphatidic acid, PEG-ceramide conjugates (e.g., PEG-CerC14 or PEG-CerC20) which are described in U.S. Pat. No. 5,820,873, incorporated herein by reference, PEG-modified dialkylamines and PEG-modified 1,2-diacyloxypropan-3-amines. Particularly preferred are PEG-modified diacylglycerols and dialkylglycerols.

[0643] Examples of suitable neutral lipid include DPSC, DPPC, POPC, DOPE, SM, and mixtures thereof.

[0644] As used herein "nucleic acid," in its broadest sense, includes any compound and/or substance that comprise a polymer of nucleotides linked via a phosphodiester bond. Exemplary nucleic acids include ribonucleic acids (RNAs), deoxyribonucleic acids (DNAs), threose nucleic acids (TNAs), glycol nucleic acids (GNAs), peptide nucleic acids (PNAs), locked nucleic acids (LNAs) or hybrids thereof. They may also include RNAi-inducing agents, RNAi agents, siRNAs, shRNAs, miRNAs, antisense RNAs, ribozymes, catalytic DNA, tRNA, RNAs that induce triple helix formation, aptamers, vectors, etc. In some embodiments, the nucleic acid encoding the Cas protein is an mRNA. In some embodiments, the Cas protein is encoded by a modified nucleic acid (e.g., a synthetic, modified mRNA described herein).

[0645] The present invention contemplates the use of any nucleic acid modification available to the skilled artisan. The nucleic acids of the present invention can include any number of modifications. In some embodiments, the nucleic acid comprises one or more modifications selected from the group consisting of pyridin-4-one ribonucleoside, 5-aza-uridine, 2-thio-5-aza-uridine, 2-thiouridine, 4-thio-pseudouridine, 2-thio-pseudouridine, 5-hydroxyuridine, 3-methyluridine, 5-carboxymethyl-uridine, 1-carboxymethyl-pseudouridine, 5-propynyl-uridine, 1-propynyl-pseudouridine, 5-taurinomethyluridine, 1-taurinomethyl-pseudouridine, 5-taurinomethyl-2-thio-uridine, 1-taurinomethyl-4-thio-uridine, 5-methyl-uridine, 1-methyl-pseudouridine, 4-thio-1-methyl-pseudouridine, 2-thio-1-methyl-pseudouridine, 1-methyl-1-deaza-pseudouridine, 2-thio-1-methyl-1-deaza-pseudouridine, dihydrouridine, dihydropseudouridine, 2-thio-dihydrouridine, 2-thio-dihydropseudouridine, 2-methoxyuridine, 2-methoxy-4-thio-uridine, 4-methoxy-pseudouridine, 4-methoxy-2-thio-pseudouridine, 5-aza-cytidine, pseudoisocytidine, 3-methyl-cytidine, N4-acetylcytidine, 5-formylcytidine, N4-methylcytidine, 5-hydroxymethylcytidine, 1-methyl-pseudoisocytidine, pyrrolo-cytidine, pyrrolo-pseudoisocytidine, 2-thio-cytidine, 2-thio-5-methyl-cytidine, 4-thio-pseudoisocytidine, 4-thio-1-methyl-pseudoisocytidine, 4-thio-1-methyl-1-deaza-pseudoisocytidine, 1-methyl-1-deaza-pseudoisocytidine, zebularine, 5-aza-zebularine, 5-methyl-zebularine, 5-aza-2-thio-zebularine, 2-thio-zebularine, 2-methoxy-cytidine, 2-methoxy-5-methyl-cytidine, 4-methoxy-pseudoisocytidine, 4-methoxy-1-methyl-pseudoisocytidine, 2-aminopurine, 2,6-diaminopurine, 7-deaza-adenine, 7-deaza-8-aza-adenine, 7-deaza-2-aminopurine, 7-deaza-8-aza-2-aminopurine, 7-deaza-2,6-diaminopurine, 7-deaza-8-aza-2,6-diaminopurine, 1-methyladenosine, N6-methyladenosine, N6-isopentenyladenosine, N6-(cis-hydroxyisopentenyl)adenosine, 2-methylthio-N6-(cis-hydroxyisopentenyl)adenosine, N6-glycinylcarbamoyladenosine, N6-threonylcarbamoyladenosine, 2-methylthio-

N6-threonyl carbamoyladenosine, N6,N6-dimethyladenosine, 7-methyladenine, 2-methylthio-adenine, and 2-methoxy-adenine, inosine, 1-methyl-inosine, wyosine, wybutosine, 7-deaza-guanosine, 7-deaza-8-aza-guanosine, 6-thio-guanosine, 6-thio-7-deaza-guanosine, 6-thio-7-deaza-8-aza-guanosine, 7-methyl-guanosine, 6-thio-7-methyl-guanosine, 7-methylinosine, 6-methoxy-guanosine, 1-methylguanosine, N2-methylguanosine, N2,N2-dimethylguanosine, 8-oxo-guanosine, 7-methyl-8-oxo-guanosine, 1-methyl-6-thio-guanosine, N2-methyl-6-thio-guanosine, and N2,N2-dimethyl-6-thio-guanosine, and combinations thereof.

[0646] Preparation of modified nucleosides and nucleotides used in the manufacture or synthesis of modified RNAs of the present invention can involve the protection and deprotection of various chemical groups. The need for protection and deprotection, and the selection of appropriate protecting groups can be readily determined by one skilled in the art.

[0647] The chemistry of protecting groups can be found, for example, in Greene, et al., Protective Groups in Organic Synthesis, 2d. Ed., Wiley & Sons, 1991, which is incorporated herein by reference in its entirety.

[0648] Modified nucleosides and nucleotides can be prepared according to the synthetic methods described in Ogata et al. Journal of Organic Chemistry 74:2585-2588, 2009; Purmal et al. Nucleic Acids Research 22(1): 72-78, 1994; Fukuhara et al. Biochemistry 1(4): 563-568, 1962; and Xu et al. Tetrahedron 48(9): 1729-1740, 1992, each of which are incorporated by reference in their entirety.

[0649] Modified nucleic acids (e.g., ribonucleic acids) need not be uniformly modified along the entire length of the molecule. Different nucleotide modifications and/or backbone structures may exist at various positions in the nucleic acid. One of ordinary skill in the art will appreciate that the nucleotide analogs or other modification(s) may be located at any position(s) of a nucleic acid such that the function of the nucleic acid is not substantially decreased. A modification may also be a 5' or 3' terminal modification. The nucleic acids may contain at a minimum one and at maximum 100% modified nucleotides, or any intervening percentage, such as at least 50% modified nucleotides, at least 80% modified nucleotides, or at least 90% modified nucleotides.

[0650] In some embodiments, at least one of the one to two ribonucleic acids is a modified ribonucleic acid. In some embodiments, each of the one to two ribonucleic acids is a modified ribonucleic acid. In some embodiments, at least one of the multiple ribonucleic acids is a modified ribonucleic acid. In some embodiments, a plurality of the multiple ribonucleic acids are modified. In some embodiments, each of the multiple ribonucleic acids are modified. Those skilled in the art will appreciate that the modified ribonucleic acids can include one or more of the nucleic acid modification described herein.

[0651] In some aspects, provided herein are synthetic, modified RNA molecules encoding polypeptides, where the synthetic, modified RNA molecules comprise one or more modifications, such that introducing the synthetic, modified RNA molecules to a cell results in a reduced innate immune response relative to a cell contacted with synthetic RNA molecules encoding the polypeptides not comprising the one or more modifications. In some embodiments, the Cas protein comprises a synthetic, modified RNA molecule encoding a Cas protein. In some embodiments, the Cas protein comprises a synthetic, modified RNA molecule encoding a Cas9 protein.

[0652] The synthetic, modified RNAs described herein include modifications to prevent rapid degradation by endo- and exo-nucleases and to avoid or reduce the cell's innate immune or interferon response to the RNA. Modifications include, but are not limited to, for example, (a) end modifications, e.g., 5' end modifications (phosphorylation dephosphorylation, conjugation, inverted linkages, etc.), 3' end modifications (conjugation, DNA nucleotides, inverted linkages, etc.), (b) base modifications, e.g., replacement with modified bases, stabilizing bases, destabilizing bases, or bases that base pair with an expanded repertoire of partners, or conjugated bases, (c) sugar modifications (e.g., at the 2' position or 4' position) or replacement of the sugar, as well as (d) internucleoside linkage modifications, including modification or replacement of the phosphodiester linkages. To the extent that such modifications interfere with translation (i.e., results in a reduction of 50% or more in translation relative to the lack of the modification—e.g., in a rabbit reticulocyte in vitro translation assay), the modification is not suitable for the methods and compositions described herein. Specific examples of synthetic, modified RNA compositions useful with the methods described herein include, but are not limited to, RNA molecules containing modified or non-natural internucleoside linkages. Synthetic, modified RNAs having modified internucleoside linkages include, among others, those that do not have a phosphorus atom in the internucleoside linkage. In other embodiments, the synthetic, modified RNA has a phosphorus atom in its internucleoside linkage(s).

[0653] Non-limiting examples of modified internucleoside linkages include phosphorothioates, chiral phosphorothioates, phosphorodithioates, phosphotriesters, aminoalkylphosphotriesters, methyl and other alkyl phosphonates including 3'-alkylene phosphonates and chiral phosphonates, phosphinates, phosphoramidates including 3'-amino phosphoramidate and aminoalkylphosphoramidates, thionophosphoramidates, thionoalkylphosphonates, thionoalkylphosphotriesters, and boranophosphates having normal 3'-5' linkages, 2'-5' linked analogs of these, and those) having inverted polarity wherein the adjacent pairs of nucleoside units are linked 3'-5' to 5'-3' or 2'-5' to 5'-2'. Various salts, mixed salts and free acid forms are also included.

[0654] Representative U.S. patents that teach the preparation of the above phosphorus-containing linkages include, but are not limited to, U.S. Pat. Nos. 3,687,808; 4,469,863; 4,476,301; 5,023,243; 5,177,195; 5,188,897; 5,264,423; 5,276,019; 5,278,302; 5,286,717; 5,321,131; 5,399,676; 5,405,939; 5,453,496; 5,455,233; 5,466,677; 5,476,925; 5,519,126; 5,536,821; 5,541,316; 5,550,111; 5,563,253; 5,571,799; 5,587,361; 5,625,050; 6,028,188; 6,124,445; 6,160,109; 6,169,170; 6,172,209; 6,239,265; 6,277,603; 6,326,199; 6,346,614; 6,444,423; 6,531,590; 6,534,639; 6,608,035; 6,683,167; 6,858,715; 6,867,294; 6,878,805; 7,015,315; 7,041,816; 7,273,933; 7,321,029; and U.S. Pat. RE 39464, each of which is herein incorporated by reference in its entirety.

[0655] Modified internucleoside linkages that do not include a phosphorus atom therein have internucleoside linkages that are formed by short chain alkyl or cycloalkyl internucleoside linkages, mixed heteroatoms and alkyl or cycloalkyl internucleoside linkages, or one or more short

chain heteroatomic or heterocyclic internucleoside linkages. These include those having morpholino linkages (formed in part from the sugar portion of a nucleoside); siloxane backbones; sulfide, sulfoxide and sulfone backbones; formacetyl and thioformacetyl backbones; methylene formacetyl and thioformacetyl backbones; alkene containing backbones; sulfamate backbones; methyleneimino and methylenehydrazino backbones; sulfonate and sulfonamide backbones; amide backbones; and others having mixed N, O, S and CH2 component parts.

[0656] Representative U.S. patents that teach the preparation of modified oligonucleosides include, but are not limited to, U.S. Pat. Nos. 5,034,506; 5,166,315; 5,185,444; 5,214,134; 5,216,141; 5,235,033; 5,64,562; 5,264,564; 5,405,938; 5,434,257; 5,466,677; 5,470,967; 5,489,677; 5,541,307; 5,561,225; 5,596,086; 5,602,240; 5,608,046; 5,610,289; 5,618,704; 5,623,070; 5,663,312; 5,633,360; 5,677,437; and 5,677,439, each of which is herein incorporated by reference in its entirety.

[0657] Some embodiments of the synthetic, modified RNAs described herein include nucleic acids with phosphorothioate internucleoside linkages and oligonucleosides with heteroatom internucleoside linkage, and in particular —CH2-NH—CH2-, —CH2-N(CH3)-O—CH2-[known as a methylene (methylimino) or MMI], —CH2-O—N(CH3)-CH2-, —CH2-N(CH3)-N(CH3)-CH2- and —N(CH3)-CH2-CH2-[wherein the native phosphodiester internucleoside linkage is represented as —O—P—O—CH2-] of the above-referenced U.S. Pat. No. 5,489,677, and the amide backbones of the above-referenced U.S. Pat. No. 5,602,240, both of which are herein incorporated by reference in their entirety. In some embodiments, the nucleic acid sequences featured herein have morpholino backbone structures of the above-referenced U.S. Pat. No. 5,034,506, herein incorporated by reference in its entirety.

[0658] Synthetic, modified RNAs described herein can also contain one or more substituted sugar moieties. The nucleic acids featured herein can include one of the following at the 2' position: H (deoxyribose); OH (ribose); F; O-, S-, or N-alkyl; O-, S-, or N-alkenyl; O-, S- or N-alkynyl; or O-alkyl-O-alkyl, wherein the alkyl, alkenyl and alkynyl can be substituted or unsubstituted C1 to C10 alkyl or C2 to C10 alkenyl and alkynyl. Exemplary modifications include O[(CH2)nO]mCH3, O(CH2).nOCH3, O(CH2)nNH2, O(CH2)nCH3, O(CH2)nONH2, and O(CH2)nON[(CH2)nCH3)]2, where n and m are from 1 to about 10. In some embodiments, synthetic, modified RNAs include one of the following at the 2' position: C1 to C10 lower alkyl, substituted lower alkyl, alkaryl, aralkyl, O-alkaryl or O-aralkyl, SH, SCH3, OCN, Cl, Br, CN, CF3, OCF3, SOCH3, SO2CH3, ONO2, NO2, N3, NH2, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, a reporter group, an intercalator, a group for improving the pharmacokinetic properties of an RNA, or a group for improving the pharmacodynamic properties of a synthetic, modified RNA, and other substituents having similar properties. In some embodiments, the modification includes a 2' methoxyethoxy (2'-O—CH2CH2OCH3, also known as 2'-O-(2-methoxyethyl) or 2'-MOE) (Martin et al., Helv. Chim. Acta, 1995, 78:486-504) i.e., an alkoxy-alkoxy group. Another exemplary modification is 2'-dimethylaminooxyethoxy, i.e., a O(CH2)20N(CH3)2 group, also known as 2'-DMAOE, and 2'-dimethylaminoethoxyethoxy (also known in the art as 2'-O-dimethylaminoethoxyethyl or 2'-DMAEOE), i.e., 2'-O—CH2-O—CH2-N(CH2)2.

[0659] Other modifications include 2'-methoxy (2'-OCH3), 2'-aminopropoxy (2'-OCH2CH2CH2NH2) and 2'-fluoro (2'-F). Similar modifications can also be made at other positions on the nucleic acid sequence, particularly the 3' position of the sugar on the 3' terminal nucleotide or in 2'-5' linked nucleotides and the 5' position of 5' terminal nucleotide. A synthetic, modified RNA can also have sugar mimetics such as cyclobutyl moieties in place of the pentofuranosyl sugar. Representative U.S. patents that teach the preparation of such modified sugar structures include, but are not limited to, U.S. Pat. Nos. 4,981,957; 5,118,800; 5,319,080; 5,359,044; 5,393,878; 5,446,137; 5,466,786; 5,514,785; 5,519,134; 5,567,811; 5,576,427; 5,591,722; 5,597,909; 5,610,300; 5,627,053; 5,639,873; 5,646,265; 5,658,873; 5,670,633; and 5,700,920, certain of which are commonly owned with the instant application, and each of which is herein incorporated by reference in its entirety.

[0660] As non-limiting examples, synthetic, modified RNAs described herein can include at least one modified nucleoside including a 2'-O-methyl modified nucleoside, a nucleoside comprising a 5' phosphorothioate group, a 2'-amino-modified nucleoside, 2'-alkyl-modified nucleoside, morpholino nucleoside, a phosphoramidate or a non-natural base comprising nucleoside, or any combination thereof.

[0661] In some embodiments of this aspect and all other such aspects described herein, the at least one modified nucleoside is selected from the group consisting of 5-methylcytidine (5mC), N6-methyladenosine (m6A), 3,2'-O-dimethyluridine (m4U), 2-thiouridine (s2U), 2' fluorouridine, pseudouridine, 2'-O-methyluridine (Um), 2' deoxyuridine (2' dU), 4-thiouridine (s4U), 5-methyluridine (m5U), 2'-O-methyladenosine (m6A), N6,2'-O-dimethyladenosine (m6Am), N6,N6,2'-O-trimethyladenosine (m62Am), 2'-O-methylcytidine (Cm), 7-methylguanosine (m7G), 2'-O-methylguanosine (Gm), N2,7-dimethylguanosine (m2,7G), N2,N2,7-trimethylguanosine (m2,2,7G), and inosine (I).

[0662] Alternatively, a synthetic, modified RNA can comprise at least two modified nucleosides, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 15, at least 20 or more, up to the entire length of the nucleotide. At a minimum, a synthetic, modified RNA molecule comprising at least one modified nucleoside comprises a single nucleoside with a modification as described herein. It is not necessary for all positions in a given synthetic, modified RNA to be uniformly modified, and in fact more than one of the aforementioned modifications can be incorporated in a single synthetic, modified RNA or even at a single nucleoside within a synthetic, modified RNA. However, it is preferred, but not absolutely necessary, that each occurrence of a given nucleoside in a molecule is modified (e.g., each cytosine is a modified cytosine e.g., 5mC). However, it is also contemplated that different occurrences of the same nucleoside can be modified in a different way in a given synthetic, modified RNA molecule (e.g., some cytosines modified as 5mC, others modified as 2'-O-methylcytidine or other cytosine analog). The modifications need not be the same for each of a plurality of modified nucleosides in a synthetic, modified RNA. Furthermore, in some embodiments of the aspects described herein, a synthetic, modified RNA comprises at least two different modified nucleosides. In some such preferred embodiments of the aspects described herein, the at least two different modified

nucleosides are 5-methylcytidine and pseudouridine. A synthetic, modified RNA can also contain a mixture of both modified and unmodified nucleosides.

[0663] As used herein, "unmodified" or "natural" nucleosides or nucleobases include the purine bases adenine (A) and guanine (G), and the pyrimidine bases thymine (T), cytosine (C) and uracil (U). In some embodiments, a synthetic, modified RNA comprises at least one nucleoside ("base") modification or substitution. Modified nucleosides include other synthetic and natural nucleobases such as inosine, xanthine, hypoxanthine, nubularine, isoguanisine, tubercidine, 2-(halo)adenine, 2-(alkyl)adenine, 2-(propyl) adenine, 2 (amino)adenine, 2-(aminoalkyl)adenine, 2 (aminopropyl)adenine, 2 (methylthio) N6 (isopentenyl)adenine, 6 (alkyl)adenine, 6 (methyl)adenine, 7 (deaza)adenine, 8 (alkenyl)adenine, 8-(alkyl)adenine, 8 (alkynyl)adenine, 8 (amino)adenine, 8-(halo)adenine, 8-(hydroxyl) adenine, 8 (thioalkyl)adenine, 8-(thiol)adenine, N6-(isopentyl)adenine, N6 (methyl)adenine, N6, N6 (dimethyl) adenine, 2-(alkyl)guanine, 2 (propyl)guanine, 6-(alkyl) guanine, 6 (methyl)guanine, 7 (alkyl)guanine, 7 (methyl) guanine, 7 (deaza)guanine, 8 (alkyl)guanine, 8-(alkenyl) guanine, 8 (alkynyl)guanine, 8-(amino)guanine, 8 (halo) guanine, 8-(hydroxyl)guanine, 8 (thioalkyl)guanine, 8-(thiol)guanine, N (methyl)guanine, 2-(thio)cytosine, 3 (deaza) 5 (aza)cytosine, 3-(alkyl)cytosine, 3 (methyl)cytosine, 5-(alkyl)cytosine, 5-(alkynyl)cytosine, 5 (halo)cytosine, 5 (methyl)cytosine, 5 (propynyl)cytosine, 5 (propynyl) cytosine, 5 (trifluoromethyl)cytosine, 6-(azo)cytosine, N4 (acetyl)cytosine, 3 (3 amino-3 carboxypropyl)uracil, 2-(thio)uracil, 5 (methyl) 2 (thio)uracil, 5 (methylaminomethyl)-2 (thio)uracil, 4-(thio)uracil, 5 (methyl) 4 (thio)uracil, 5 (methylaminomethyl)-4 (thio)uracil, 5 (methyl) 2,4 (dithio)uracil, 5 (methylaminomethyl)-2,4 (dithio)uracil, 5 (2-aminopropyl)uracil, 5-(alkyl)uracil, 5-(alkynyl)uracil, 5-(allylamino)uracil, 5 (aminoallyl)uracil, 5 (aminoalkyl) uracil, 5 (guanidiniumalkyl)uracil, 5 (1,3-diazole-1-alkyl) uracil, 5-(cyanoalkyl)uracil, 5-(dialkylaminoalkyl)uracil, 5 (dimethylaminoalkyl)uracil, 5-(halo)uracil, 5-(methoxy)uracil, uracil-5 oxyacetic acid, 5 (methoxycarbonylmethyl)-2-(thio)uracil, 5 (methoxycarbonyl-methyl)uracil, 5 (propynyl)uracil, 5 (propynyl)uracil, 5 (trifluoromethyl)uracil, 6 (azo) uracil, dihydrouracil, N3 (methyl)uracil, 5-uracil (i.e., pseudouracil), 2 (thio)pseudouracil,4 (thio)pseudouracil,2, 4-(dithio)psuedouracil, 5-(alkyl)pseudouracil, 5-(methyl) pseudouracil, 5-(alkyl)-2-(thio)pseudouracil, 5-(methyl)-2-(thio)pseudouracil, 5-(alkyl)-4 (thio)pseudouracil, 5-(methyl)-4 (thio)pseudouracil, 5-(alkyl)-2,4 (dithio) pseudouracil, 5-(methyl)-2,4 (dithio)pseudouracil, 1 substituted pseudouracil, 1 substituted 2(thio)-pseudouracil, 1 substituted 4 (thio)pseudouracil, 1 substituted 2,4-(dithio) pseudouracil, 1 (aminocarbonylethylenyl)-pseudouracil, 1 (aminocarbonylethylenyl)-2(thio)-pseudouracil, 1 (aminocarbonylethylenyl)-4 (thio)pseudouracil, 1 (aminocarbonylethylenyl)-2,4-(dithio)pseudouracil, 1 (aminoalkylaminocarbonylethylenyl)-pseudouracil, 1 (aminoalkylaminocarbonylethylenyl)-2(thio)-pseudouracil, 1 (aminoalkylaminocarbonylethylenyl)-4 (thio)pseudouracil, 1 (aminoalkylaminocarbonylethylenyl)-2,4-(dithio) pseudouracil, 1,3-(diaza)-2-(oxo)-phenoxazin-1-yl, 1-(aza)-2-(thio)-3-(aza)-phenoxazin-1-yl, 1,3-(diaza)-2-(oxo)-phenthiazin-1-yl, 1-(aza)-2-(thio)-3-(aza)-phenthiazin-1-yl, 7-substituted 1,3-(diaza)-2-(oxo)-phenoxazin-1-yl, 7-substituted 1-(aza)-2-(thio)-3-(aza)-phenoxazin-1-yl, 7-substituted 1,3-(diaza)-2-(oxo)-phenthiazin-1-yl, 7-substituted 1-(aza)-2-(thio)-3-(aza)-phenthiazin-1-yl, 7-(aminoalkylhydroxy)-1,3-(diaza)-2-(oxo)-phenoxazin-1-yl, 7-(aminoalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenoxazin-1-yl, 7-(aminoalkylhydroxy)-1,3-(diaza)-2-(oxo)-phenthiazin-1-yl, 7-(aminoalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenthiazin-1-yl, 7-(guanidiniumalkylhydroxy)-1,3-(diaza)-2-(oxo)-phenoxazin-1-yl, 7-(guanidiniumalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenoxazin-1-yl, 7-(guanidiniumalkylhydroxy)-1,3-(diaza)-2-(oxo)-phenthiazin-1-yl, 7-(guanidiniumalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenthiazin-1-yl, 1,3,5-(triaza)-2,6-(dioxa)-naphthalene, inosine, xanthine, hypoxanthine, nubularine, tubercidine, isoguanisine, inosinyl, 2-aza-inosinyl, 7-deaza-inosinyl, nitroimidazolyl, nitropyrazolyl, nitrobenzimidazolyl, nitroindazolyl, aminoindolyl, pyrrolopyrimidinyl, 3-(methyl)isocarbostyrilyl, 5-(methyl)isocarbostyrilyl, 3-(methyl)-7-(propynyl)isocarbostyrilyl, 7-(aza)indolyl, 6-(methyl)-7-(aza)indolyl, imidizopyridinyl, 9-(methyl)-imidizopyridinyl, pyrrolopyrizinyl, isocarbostyrilyl, 7-(propynyl)isocarbostyrilyl, propynyl-7-(aza)indolyl, 2,4,5-(trimethyl)phenyl, 4-(methyl)indolyl, 4,6-(dimethyl)indolyl, phenyl, napthalenyl, anthracenyl, phenanthracenyl, pyrenyl, stilbenzyl, tetracenyl, pentacenyl, difluorotolyl, 4-(fluoro)-6-(methyl)benzimidazole, 4-(methyl)benzimidazole, 6-(azo) thymine, 2-pyridinone, 5 nitroindole, 3 nitropyrrole, 6-(aza) pyrimidine, 2 (amino)purine, 2,6-(diamino)purine, 5 substituted pyrimidines, N2-substituted purines, N6-substituted purines, 06-substituted purines, substituted 1,2,4-triazoles, pyrrolo-pyrimidin-2-on-3-yl, 6-phenyl-pyrrolo-pyrimidin-2-on-3-yl, para-substituted-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl, ortho-substituted-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl, bis-ortho-substituted-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl, para-(aminoalkylhydroxy)-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl, ortho-(aminoalkylhydroxy)-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl, bis-ortho-(aminoalkylhydroxy)-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl, pyridopyrimidin-3-yl, 2-oxo-7-amino-pyridopyrimidin-3-yl, 2-oxo-pyridopyrimidine-3-yl, or any O-alkylated or N-alkylated derivatives thereof. Modified nucleosides also include natural bases that comprise conjugated moieties, e.g. a ligand. As discussed herein above, the RNA containing the modified nucleosides must be translatable in a host cell (i.e., does not prevent translation of the polypeptide encoded by the modified RNA). For example, transcripts containing s2U and m6A are translated poorly in rabbit reticulocyte lysates, while pseudouridine, m5U, and m5C are compatible with efficient translation. In addition, it is known in the art that 2'-fluoro-modified bases useful for increasing nuclease resistance of a transcript, leads to very inefficient translation. Translation can be assayed by one of ordinary skill in the art using e.g., a rabbit reticulocyte lysate translation assay.

[0664] Further modified nucleobases include those disclosed in U.S. Pat. No. 3,687,808, those disclosed in Modified Nucleosides in Biochemistry, Biotechnology and Medicine, Herdewijn, P. ed. Wiley-VCH, 2008; those disclosed in Int. Appl. No. PCT/US09/038,425, filed Mar. 26, 2009; those disclosed in The Concise Encyclopedia Of Polymer Science And Engineering, pages 858-859, Kroschwitz, J. I., ed. John Wiley & Sons, 1990, and those disclosed by Englisch et al., Angewandte Chemie, International Edition, 1991, 30, 613.

[0665] Representative U.S. patents that teach the preparation of certain of the above noted modified nucleobases as well as other modified nucleobases include, but are not limited to, the above noted U.S. Pat. No. 3,687,808, as well as U.S. Pat. Nos. 4,845,205; 5,130,30; 5,134,066; 5,175,273; 5,367,066; 5,432,272; 5,457,187; 5,457,191; 5,459,255; 5,484,908; 5,502,177; 5,525,711; 5,552,540; 5,587,469; 5,594,121, 5,596,091; 5,614,617; 5,681,941; 6,015,886; 6,147,200; 6,166,197; 6,222,025; 6,235,887; 6,380,368; 6,528,640; 6,639,062; 6,617,438; 7,045,610; 7,427,672; and 7,495,088, each of which is herein incorporated by reference in its entirety, and U.S. Pat. No. 5,750,692, also herein incorporated by reference in its entirety.

[0666] Another modification for use with the synthetic, modified RNAs described herein involves chemically linking to the RNA one or more ligands, moieties or conjugates that enhance the activity, cellular distribution or cellular uptake of the RNA. Ligands can be particularly useful where, for example, a synthetic, modified RNA is administered in vivo. Such moieties include but are not limited to lipid moieties such as a cholesterol moiety (Letsinger et al., Proc. Natl. Acid. Sci. USA, 1989, 86: 6553-6556, herein incorporated by reference in its entirety), cholic acid (Manoharan et al., Biorg. Med. Chem. Let., 1994, 4:1053-1060, herein incorporated by reference in its entirety), a thioether, e.g., beryl-S-tritylthiol (Manoharan et al., Ann. N.Y. Acad. Sci., 1992, 660:306-309; Manoharan et al., Biorg. Med. Chem. Let., 1993, 3:2765-2770, each of which is herein incorporated by reference in its entirety), a thiocholesterol (Oberhauser et al., Nucl. Acids Res., 1992, 20:533-538, herein incorporated by reference in its entirety), an aliphatic chain, e.g., dodecandiol or undecyl residues (Saison-Behmoaras et al., EMBO J, 1991, 10:1111-1118; Kabanov et al., FEBS Lett., 1990, 259:327-330; Svinarchuk et al., Biochimie, 1993, 75:49-54, each of which is herein incorporated by reference in its entirety), a phospholipid, e.g., di-hexadecyl-rac-glycerol or triethyl-ammonium 1,2-di-O-hexadecyl-rac-glycero-3-phosphonate (Manoharan et al., Tetrahedron Lett., 1995, 36:3651-3654; Shea et al., Nucl. Acids Res., 1990, 18:3777-3783, each of which is herein incorporated by reference in its entirety), a polyamine or a polyethylene glycol chain (Manoharan et al., Nucleosides & Nucleotides, 1995, 14:969-973, herein incorporated by reference in its entirety), or adamantane acetic acid (Manoharan et al., Tetrahedron Lett., 1995, 36:3651-3654, herein incorporated by reference in its entirety), a palmityl moiety (Mishra et al., Biochim. Biophys. Acta, 1995, 1264:229-237, herein incorporated by reference in its entirety), or an octadecylamine or hexylamino-carbonyloxycholesterol moiety (Crooke et al., J. Pharmacol. Exp. Ther., 1996, 277:923-937, herein incorporated by reference in its entirety).

[0667] The synthetic, modified RNAs described herein can further comprise a 5' cap. In some embodiments of the aspects described herein, the synthetic, modified RNAs comprise a 5' cap comprising a modified guanine nucleotide that is linked to the 5' end of an RNA molecule using a 5'-5' triphosphate linkage. As used herein, the term "5' cap" is also intended to encompass other 5' cap analogs including, e.g., 5' diguanosine cap, tetraphosphate cap analogs having a methylene-bis(phosphonate) moiety (see e.g., Rydzik, A M et al., (2009) Org Biomol Chem 7(22):4763-76), dinucleotide cap analogs having a phosphorothioate modification (see e.g., Kowalska, J. et al., (2008) RNA 14(6):1119-1131), cap analogs having a sulfur substitution for a non-bridging oxygen (see e.g., Grudzien-Nogalska, E. et al., (2007) RNA 13(10): 1745-1755), N7-benzylated dinucleoside tetraphosphate analogs (see e.g., Grudzien, E. et al., (2004) RNA 10(9):1479-1487), or anti-reverse cap analogs (see e.g., Jemielity, J. et al., (2003) RNA 9(9): 1108-1122 and Stepinski, J. et al., (2001) RNA 7(10):1486-1495). In one such embodiment, the 5' cap analog is a 5' diguanosine cap. In some embodiments, the synthetic, modified RNA does not comprise a 5' triphosphate.

[0668] The 5' cap is important for recognition and attachment of an mRNA to a ribosome to initiate translation. The 5' cap also protects the synthetic, modified RNA from 5' exonuclease mediated degradation. It is not an absolute requirement that a synthetic, modified RNA comprise a 5' cap, and thus in other embodiments the synthetic, modified RNAs lack a 5' cap. However, due to the longer half-life of synthetic, modified RNAs comprising a 5' cap and the increased efficiency of translation, synthetic, modified RNAs comprising a 5' cap are preferred herein.

[0669] The synthetic, modified RNAs described herein can further comprise a 5' and/or 3' untranslated region (UTR). Untranslated regions are regions of the RNA before the start codon (5') and after the stop codon (3'), and are therefore not translated by the translation machinery. Modification of an RNA molecule with one or more untranslated regions can improve the stability of an mRNA, since the untranslated regions can interfere with ribonucleases and other proteins involved in RNA degradation. In addition, modification of an RNA with a 5' and/or 3' untranslated region can enhance translational efficiency by binding proteins that alter ribosome binding to an mRNA. Modification of an RNA with a 3' UTR can be used to maintain a cytoplasmic localization of the RNA, permitting translation to occur in the cytoplasm of the cell. In one embodiment, the synthetic, modified RNAs described herein do not comprise a 5' or 3' UTR. In another embodiment, the synthetic, modified RNAs comprise either a 5' or 3' UTR. In another embodiment, the synthetic, modified RNAs described herein comprise both a 5' and a 3' UTR. In one embodiment, the 5' and/or 3' UTR is selected from an mRNA known to have high stability in the cell (e.g., a murine alpha-globin 3' UTR). In some embodiments, the 5' UTR, the 3' UTR, or both comprise one or more modified nucleosides.

[0670] In some embodiments, the synthetic, modified RNAs described herein further comprise a Kozak sequence. The "Kozak sequence" refers to a sequence on eukaryotic mRNA having the consensus (gcc)gccRccAUGG SEQ ID NO: 1481, where R is a purine (adenine or guanine) three bases upstream of the start codon (AUG), which is followed by another 'G'. The Kozak consensus sequence is recognized by the ribosome to initiate translation of a polypeptide. Typically, initiation occurs at the first AUG codon encountered by the translation machinery that is proximal to the 5' end of the transcript. However, in some cases, this AUG codon can be bypassed in a process called leaky scanning. The presence of a Kozak sequence near the AUG codon will strengthen that codon as the initiating site of translation, such that translation of the correct polypeptide occurs. Furthermore, addition of a Kozak sequence to a synthetic, modified RNA will promote more efficient translation, even if there is no ambiguity regarding the start codon. Thus, in some embodiments, the synthetic, modified RNAs described herein further comprise a Kozak consensus sequence at the

desired site for initiation of translation to produce the correct length polypeptide. In some such embodiments, the Kozak sequence comprises one or more modified nucleosides.

[0671] In some embodiments, the synthetic, modified RNAs described herein further comprise a "poly (A) tail", which refers to a 3' homopolymeric tail of adenine nucleotides, which can vary in length (e.g., at least 5 adenine nucleotides) and can be up to several hundred adenine nucleotides). The inclusion of a 3' poly(A) tail can protect the synthetic, modified RNA from degradation in the cell, and also facilitates extra-nuclear localization to enhance translation efficiency. In some embodiments, the poly(A) tail comprises between 1 and 500 adenine nucleotides; in other embodiments the poly(A) tail comprises at least 5, at least 10, at least 20, at least 30, at least 40, at least 50, at least 60, at least 70, at least 80, at least 90, at least 100, at least 110, at least 120, at least 130, at least 140, at least 150, at least 160, at least 170, at least 180, at least 190, at least 200, at least 225, at least 250, at least 275, at least 300, at least 325, at least 350, at least 375, at least 400, at least 425, at least 450, at least 475, at least 500 adenine nucleotides or more. In one embodiment, the poly(A) tail comprises between 1 and 150 adenine nucleotides. In another embodiment, the poly(A) tail comprises between 90 and 120 adenine nucleotides. In some such embodiments, the poly(A) tail comprises one or more modified nucleosides.

[0672] It is contemplated that one or more modifications to the synthetic, modified RNAs described herein permit greater stability of the synthetic, modified RNA in a cell. To the extent that such modifications permit translation and either reduce or do not exacerbate a cell's innate immune or interferon response to the synthetic, modified RNA with the modification, such modifications are specifically contemplated for use herein. Generally, the greater the stability of a synthetic, modified RNA, the more protein can be produced from that synthetic, modified RNA. Typically, the presence of AU-rich regions in mammalian mRNAs tend to destabilize transcripts, as cellular proteins are recruited to AU-rich regions to stimulate removal of the poly(A) tail of the transcript. Loss of a poly(A) tail of a synthetic, modified RNA can result in increased RNA degradation. Thus, in one embodiment, a synthetic, modified RNA as described herein does not comprise an AU-rich region. In particular, it is preferred that the 3' UTR substantially lacks AUUUA sequence elements.

[0673] In one embodiment, a ligand alters the cellular uptake, intracellular targeting or half-life of a synthetic, modified RNA into which it is incorporated. In some embodiments a ligand provides an enhanced affinity for a selected target, e.g., molecule, cell or cell type, intracellular compartment, e.g., mitochondria, cytoplasm, peroxisome, lysosome, as, e.g., compared to a composition absent such a ligand. Preferred ligands do not interfere with expression of a polypeptide from the synthetic, modified RNA.

[0674] Ligands can include a naturally occurring substance, such as a protein (e.g., human serum albumin (HSA), low-density lipoprotein (LDL), or globulin); carbohydrate (e.g., a dextran, pullulan, chitin, chitosan, inulin, cyclodextrin or hyaluronic acid); or a lipid. The ligand can also be a recombinant or synthetic molecule, such as a synthetic polymer, e.g., a synthetic polyamino acid. Examples of polyamino acids include polylysine (PLL), poly L aspartic acid, poly L-glutamic acid, styrene-maleic acid anhydride copolymer, poly(L-lactide-co-glycolied) copolymer, divinyl ether-maleic anhydride copolymer, N-(2-hydroxypropyl) methacrylamide copolymer (HMPA), polyethylene glycol (PEG), polyvinyl alcohol (PVA), polyurethane, poly(2-ethylacryllic acid), N-isopropylacrylamide polymers, or polyphosphazine. Example of polyamines include: polyethylenimine, polylysine (PLL), spermine, spermidine, polyamine, pseudopeptide-polyamine, peptidomimetic polyamine, dendrimer polyamine, arginine, amidine, protamine, cationic lipid, cationic porphyrin, quaternary salt of a polyamine, or an alpha helical peptide.

[0675] Ligands can also include targeting groups, e.g., a cell targeting agent, (e.g., a lectin, glycoprotein, lipid or protein), or an antibody, that binds to a specified cell type such as a fibroblast cell. A targeting group can be, for example, a thyrotropin, melanotropin, lectin, glycoprotein, surfactant protein A, Mucin carbohydrate, multivalent lactose, multivalent galactose, N-acetyl-galactosamine, N-acetyl-glucosamine multivalent mannose, multivalent fucose, glycosylated polyaminoacids, multivalent galactose, transferrin, bisphosphonate, polyglutamate, polyaspartate, a lipid, cholesterol, a steroid, bile acid, folate, vitamin B 12, biotin, or an RGD peptide or RGD peptide mimetic, among others.

[0676] Other examples of ligands include dyes, intercalating agents (e.g. acridines), cross-linkers (e.g. psoralene, mitomycin C), porphyrins (TPPC4, texaphyrin, Sapphyrin), polycyclic aromatic hydrocarbons (e.g., phenazine, dihydrophenazine), artificial endonucleases (e.g. EDTA), lipophilic molecules, e.g., cholesterol, cholic acid, adamantane acetic acid, 1-pyrene butyric acid, dihydrotestosterone, 1,3-Bis-O (hexadecyl)glycerol, geranyloxyhexyl group, hexadecylglycerol, borneol, menthol, 1,3-propanediol, heptadecyl group, palmitic acid, myristic acid,O3-(oleoyl)lithocholic acid, O3-(oleoyl)cholenic acid, dimethoxytrityl, or phenoxazine) and peptide conjugates (e.g., antennapedia peptide, Tat peptide), alkylating agents, amino, mercapto, PEG (e.g., PEG-40K), MPEG, [MPEG]2, polyamino, alkyl, substituted alkyl, radiolabeled markers, enzymes, haptens (e.g. biotin), and transport/absorption facilitators (e.g., aspirin, vitamin E, folic acid).

[0677] Ligands can be proteins, e.g., glycoproteins, or peptides, e.g., molecules having a specific affinity for a co-ligand, or antibodies e.g., an antibody, that binds to a specified cell type such as a fibroblast cell, or other cell useful in the production of polypeptides. Ligands can also include hormones and hormone receptors. They can also include non-peptidic species, such as lipids, lectins, carbohydrates, vitamins, cofactors, multivalent lactose, multivalent galactose, N-acetyl-galactosamine, N-acetyl-glucosamine multivalent mannose, or multivalent fucose.

[0678] The ligand can be a substance, e.g., a drug, which can increase the uptake of the synthetic, modified RNA or a composition thereof into the cell, for example, by disrupting the cell's cytoskeleton, e.g., by disrupting the cell's microtubules, microfilaments, and/or intermediate filaments. The drug can be, for example, taxol, vincristine, vinblastine, cytochalasin, nocodazole, japlakinolide, latrunculin A, phalloidin, swinholide A, indanocine, or myoservin.

[0679] One exemplary ligand is a lipid or lipid-based molecule. A lipid or lipid-based ligand can (a) increase resistance to degradation, and/or (b) increase targeting or transport into a target cell or cell membrane. A lipid based ligand can be used to modulate, e.g., binding of the modified RNA composition to a target cell.

[0680] In another aspect, the ligand is a moiety, e.g., a vitamin, which is taken up by a host cell. Exemplary vitamins include vitamin A, E, and K. Other exemplary vitamins include B vitamin, e.g., folic acid, B 12, riboflavin, biotin, pyridoxal or other vitamins or nutrients taken up, for example, by cancer cells. Also included are HSA and low density lipoprotein (LDL).

[0681] In another aspect, the ligand is a cell-permeation agent, preferably a helical cell-permeation agent. Preferably, the agent is amphipathic. An exemplary agent is a peptide such as tat or antennopedia. If the agent is a peptide, it can be modified, including a peptidylmimetic, invertomers, non-peptide or pseudo-peptide linkages, and use of D-amino acids. The helical agent is preferably an alpha-helical agent, which preferably has a lipophilic and a lipophobic phase.

[0682] A "cell permeation peptide" is capable of permeating a cell, e.g., a microbial cell, such as a bacterial or fungal cell, or a mammalian cell, such as a human cell. A microbial cell-permeating peptide can be, for example, an α-helical linear peptide (e.g., LL-37 or Ceropin P1), a disulfide bond-containing peptide (e.g., α-defensin, β-defensin or bactenecin), or a peptide containing only one or two dominating amino acids (e.g., PR-39 or indolicidin). For example, a cell permeation peptide can be a bipartite amphipathic peptide, such as MPG, which is derived from the fusion peptide domain of HIV-1 gp41 and the NLS of SV40 large T antigen (Simeoni et al., Nucl. Acids Res. 31:2717-2724, 2003).

[0683] The synthetic, modified RNAs described herein can be synthesized and/or modified by methods well established in the art, such as those described in "Current Protocols in Nucleic Acid Chemistry," Beaucage, S. L. et al. (Edrs.), John Wiley & Sons, Inc., New York, N.Y., USA, which is hereby incorporated herein by reference in its entirety. Transcription methods are described further herein in the Examples.

[0684] In one embodiment of the aspects described herein, a template for a synthetic, modified RNA is synthesized using "splint-mediated ligation," which allows for the rapid synthesis of DNA constructs by controlled concatenation of long oligos and/or dsDNA PCR products and without the need to introduce restriction sites at the joining regions. It can be used to add generic untranslated regions (UTRs) to the coding sequences of genes during T7 template generation. Splint mediated ligation can also be used to add nuclear localization sequences to an open reading frame, and to make dominant-negative constructs with point mutations starting from a wild-type open reading frame. Briefly, single-stranded and/or denatured dsDNA components are annealed to splint oligos which bring the desired ends into conjunction, the ends are ligated by a thermostable DNA ligase and the desired constructs amplified by PCR. A synthetic, modified RNA is then synthesized from the template using an RNA polymerase in vitro. After synthesis of a synthetic, modified RNA is complete, the DNA template is removed from the transcription reaction prior to use with the methods described herein.

[0685] In some embodiments of these aspects, the synthetic, modified RNAs are further treated with an alkaline phosphatase.

[0686] One skilled in the art readily appreciates that the present invention is well adapted to carry out the objects and obtain the ends and advantages mentioned, as well as those inherent therein. The details of the description and the examples herein are representative of certain embodiments, are exemplary, and are not intended as limitations on the scope of the invention. Modifications therein and other uses will occur to those skilled in the art. These modifications are encompassed within the spirit of the invention. It will be readily apparent to a person skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the scope and spirit of the invention.

[0687] The articles "a" and "an" as used herein in the specification and in the claims, unless clearly indicated to the contrary, should be understood to include the plural referents. Claims or descriptions that include "or" between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The invention includes embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given product or process. The invention also includes embodiments in which more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process. Furthermore, it is to be understood that the invention provides all variations, combinations, and permutations in which one or more limitations, elements, clauses, descriptive terms, etc., from one or more of the listed claims is introduced into another claim dependent on the same base claim (or, as relevant, any other claim) unless otherwise indicated or unless it would be evident to one of ordinary skill in the art that a contradiction or inconsistency would arise. It is contemplated that all embodiments described herein are applicable to all different aspects of the invention where appropriate. It is also contemplated that any of the embodiments or aspects can be freely combined with one or more other such embodiments or aspects whenever appropriate. Where elements are presented as lists, e.g., in Markush group or similar format, it is to be understood that each subgroup of the elements is also disclosed, and any element(s) can be removed from the group. It should be understood that, in general, where the invention, or aspects of the invention, is/are referred to as comprising particular elements, features, etc., certain embodiments of the invention or aspects of the invention consist, or consist essentially of, such elements, features, etc. For purposes of simplicity those embodiments have not in every case been specifically set forth in so many words herein. It should also be understood that any embodiment or aspect of the invention can be explicitly excluded from the claims, regardless of whether the specific exclusion is recited in the specification. For example, any one or more active agents, additives, ingredients, optional agents, types of organism, disorders, subjects, or combinations thereof, can be excluded.

[0688] Where the claims or description relate to a composition of matter, it is to be understood that methods of making or using the composition of matter according to any of the methods disclosed herein, and methods of using the composition of matter for any of the purposes disclosed herein are aspects of the invention, unless otherwise indicated or unless it would be evident to one of ordinary skill in the art that a contradiction or inconsistency would arise. Where the claims or description relate to a method, e.g., it is to be understood that methods of making compositions useful for performing the method, and products produced

according to the method, are aspects of the invention, unless otherwise indicated or unless it would be evident to one of ordinary skill in the art that a contradiction or inconsistency would arise.

[0689] Where ranges are given herein, the invention includes embodiments in which the endpoints are included, embodiments in which both endpoints are excluded, and embodiments in which one endpoint is included and the other is excluded. It should be assumed that both endpoints are included unless indicated otherwise. Furthermore, it is to be understood that unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or subrange within the stated ranges in different embodiments of the invention, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise. It is also understood that where a series of numerical values is stated herein, the invention includes embodiments that relate analogously to any intervening value or range defined by any two values in the series, and that the lowest value may be taken as a minimum and the greatest value may be taken as a maximum. Numerical values, as used herein, include values expressed as percentages. For any embodiment of the invention in which a numerical value is prefaced by "about" or "approximately", the invention includes an embodiment in which the exact value is recited. For any embodiment of the invention in which a numerical value is not prefaced by "about" or "approximately", the invention includes an embodiment in which the value is prefaced by "about" or "approximately".

[0690] Approximately" or "about" generally includes numbers that fall within a range of 1% or in some embodiments within a range of 5% of a number or in some embodiments within a range of 10% of a number in either direction (greater than or less than the number) unless otherwise stated or otherwise evident from the context (except where such number would impermissibly exceed 100% of a possible value). It should be understood that, unless clearly indicated to the contrary, in any methods claimed herein that include more than one act, the order of the acts of the method is not necessarily limited to the order in which the acts of the method are recited, but the invention includes embodiments in which the order is so limited. It should also be understood that unless otherwise indicated or evident from the context, any product or composition described herein may be considered "isolated".

[0691] As used herein the term "comprising" or "comprises" is used in reference to compositions, methods, and respective component(s) thereof, that are essential to the invention, yet open to the inclusion of unspecified elements, whether essential or not.

[0692] As used herein the term "consisting essentially of" refers to those elements required for a given embodiment. The term permits the presence of additional elements that do not materially affect the basic and novel or functional characteristic(s) of that embodiment of the invention.

[0693] The term "consisting of" refers to compositions, methods, and respective components thereof as described herein, which are exclusive of any element not recited in that description of the embodiment.

EXAMPLES

Example 1

[0694] Transcription activator-like effector nucleases (TALENs) bind as a pair around a genomic site, in which a double-strand break (DSB) is introduced by a dimer of FokI nuclease domains. The use of a TALEN genome-editing system to rapidly and efficiently generate mutant alleles of 15 different genes in human pluripotent stem cells (hPSCs) as a means of performing rigorous disease modeling was recently reported (Ding et al., Cell Stem Cell 12:238-251 (2013)); the proportions of clones bearing at least one mutant allele ranged from 2%-34%.

[0695] As described below, the relative efficacies of CRISPRs and TALENs targeting the same genomic sites in the same hPSC lines was assessed with the use of the same delivery platform described previously (Ding et al., Cell Stem Cell 12:238-251 (2013)). In the TALEN genome-editing system, the CAG promoter was used to co-translate (via a viral 2A peptide) each TALEN with green fluorescent protein (GFP) or red fluorescent protein (RFP). For CRISPRs, a human codon-optimized Cas9 gene was subcloned with a C-terminal nuclear localization signal (Mali et al., Science 339:823-826 (2013)) into the same CAG expression plasmid with GFP, and the guide RNA (gRNA) was separately expressed from a plasmid with the human U6 polymerase III promoter (Mali et al., Science 339:823-826 (2013)). The 20-nucleotide protospacer sequence for each gRNA was introduced using polymerase chain reaction (PCR)-based methods. Whether using TALENs or CRISPRs, equal amounts of the two plasmids were co-electroporated into hPSCs (either 25 μg of each plasmid, or 12.5 μg of each plasmid along with 25 μg of a DNA repair template if attempting knock-in) followed by fluorescence-activated cell sorting (FACS) after 24-48 hours, clonal expansion of single cells, and screening for mutations at the genomic target site via PCR.

[0696] gRNAs were designed matching G(N)19NGG sequences in seven loci in six genes (AKT2, CELSR2, CIITA, GLUT4, LINC00116, and SORT1) previously successfully targeted with TALENs (Ding et al., Cell Stem Cell 12:238-251 (2013)) and one additional locus in LDLR. In this system, CRISPRs consistently and substantially outperformed TALENs across loci and hPSC lines (see Table S1). The TALENs yielded clones with at least one mutant allele at efficiencies of 0%-34%, but matched CRISPRs yielded mutant clones at efficiencies of 51%-79% (Table S1). Just as with TALENs, CRISPRs produced a variety of indels of sizes ranging from one nucleotide to several dozen nucleotides in size, centered on the predicted cleavage sites, suggesting that non-homologous end-joining mutagenesis occurs in the same way regardless of whether CRISPRs or TALENs are used. Moreover, CRISPRs readily generated homozygous mutant clones (7%-25% of all clones; Table S1) as discerned by sequencing.

[0697] Knock-in of E17K mutations into AKT2 was also attempted using a 67-nucleotide single-stranded DNA oligonucleotide as previously described (Ding et al., Cell Stem Cell 12:238-251 (2013)). Although the predicted CRISPR cleavage site lay 11 and 13 nucleotides from the point mutations, respectively, the CRISPR yielded knock-in clones at a rate of 11%, whereas TALENs yielded only 1.6% (Table S1).

TABLE S1

Targeting Efficiency of CRISPRs Versus TALENs in Human Pluripotent Stem Cells

Gene	Chromosome: Position (Start of Target Sequence)	Target Sequence[a]	Cell Line[b]	TALENs Efficiency (Mutants/ Clones Screened)[c]	Efficiency (Mutants/Clones Screened)[c]	CRISPRs Effi-ciency of Homo-zygous Mutants
AKT2	chr19:40762982	TCCCTTCCTGCCTCATTTCAGGTGAATACA TCAAGACCTGGAGGCCA	HUES 9	8.9% (17/192)	(SEQ ID NO: 335)	
AKT2	chr19:40762982	TCCCTT**CCT**GCC|TCATTTCAGGTGAATAC ATCAAGACCTGGAGGCCA	HUES 9	(SEQ ID NO: 336)	60.6% (86/142)	12.7% (18/142)
CELSR2	chr1:109817568	TGCTGGCTCGGCTGCCCTGAGGTTGCTCAA TCAAGCACAGGTTTCAA	HUES 1	3.5% (18/506)	(SEQ ID NO: 337)	
CELSR2	chr1:109817568	TGCTGGCTCGGCTGCCCTGAGGTTGCTCAA TCAAG|CAC**AGG**TTTCAA	HUES 1	(SEQ ID NO: 338)	66.2% (45/68)	7.4% (5/68)
CIITA	chr16:10989200	TAACAGCGATGCTGACCCCCTGTGCCTCTA CCACTTCTATGACCAGA	BJ-RiPS	12.7% (37/292)	(SEQ ID NO: 339)	
CIITA	chr16:10989206	CGATGCTGACCCCCTGTGCCTCTA**CCA** CTT|CTATGACCAGATGGACC	BJ-RiPS	(SEQ ID NO: 340)	78.7% (96/122)	11.5% (14/122)
GLUT4	chr17:7186601	TGGTCCTTGCTGTGTTCTCTGCGGTGCTTG GCTCCCTGCAGTTTGGGTA	HUES 9	33.5% (52/155)	(SEQ ID NO: 341)	
GLUT4	chr17:7186601	TGGTCCTTGCTGTGTTCT|CTGCGGTGCTT GGCTCCCTGCAGTTTGGGTA	HUES 9	(SEQ ID NO: 342)	66.5% (123/185)	24.9% (46/185)
LDLR	chr19:11210899	TGGGCGACAGATGCGAAAGAAACGAGTTC CAGTGCCAAGACGGGAAA	HUES 9	0% (0/568)	(SEQ ID NO: 343)	
LDLR	chr19:11210917	GAAACGAGTTCCAGTGCCAAGACGGGAAAT GCATCTCCTAC|AAG**TGG**	HUES 9	(SEQ ID NO: 344)	51.1% (90/176)	8.0% (14/176)
LINC00116	ch2:110970090	TCAGAGAGGACACTGCAGTTGTCCGTGCTT AGTAGCCTTCGCTTCTGGA	HUES 9	29.5% (26/88)	(SEQ ID NO: 345)	
LINC00116	ch2:110970090	TCAGAGAGGACATGCAGTTGTCCGTGCTAG TAGCCTTCGC|TTCTGGA	HUES 9	(SEQ ID NO: 346)	57.4% (93/162)	8.6% (14/162)
SORT1 exon 2	chr1:109912203	TGATGATCTCAGAGGCTCAGTATCCTTGTC CTGGGTTGGAGATAGCA	HUES 1	22.2% (128/576)	(SEQ ID NO: 347)	
SORT1 exon 2	chr1:109912203	TGATGATCTCAGAGGCTCAGTATCCTTG| TCC**TGG**GTTGGAGATAGCA	HUES 1	(SEQ ID NO: 348)	68.5% (100/146)	13.0% (19/146)
SORT1 exon 3	chr1:109910069	TGGTAATTATGACTTTTGGACAGTCCAAGC TATATCGAAGGTGAGATCA	HUES 9	10.9% (21/192)	(SEQ ID NO: 349)	
SORT1 exon 3	chr1:109910069	TGGTAATTATGACTTTTGGACAGTCCAAG CTATAT|CGAAGGTGAGATCA	HUES 9	(SEQ ID NO: 350)	75.9% (148/195)	10.3% (20/195)
AKT2 E17K	chr19:40762982	TCCCTTCCTGCCTCATTTCAGGTGA**A**TA CATCAAGACCTGGAGGCCA	HUES 9	1.6% (3/192)[d]	(SEQ ID NO: 351)	
AKT2 E17K	chr19:40762982	TC**CCT**GCC|TCATTTCAGGTGA**A**TACATC AAGACCTGGAGGCCA	HUES 9	(SEQ ID NO: 352)	10.6% (10/94)[d]	1.1% (1/94)[d]
AKT2 off-target	chr5:22683972	CTATGCCCTGCC|TCATTTCAGGTGAAGAT GAAATCCCTGGAGCTTGG	HUES 9	(SEQ ID NO: 363)	0% (0/142)	0% (0/142)

[a]For TALENs, the binding sites are indicated with underlines, with the cleavage site predicted to be midway between the binding sites; for CRISPRs, the protospacer is underlined, the NGG motif is in bold (may be on the antisense strand), and the predicted cleavage site is indicated with "|", for the AKT2 E17K target sequence, the sites of the knock-in mutations are indicated in bold/italics; for the AKT2 off-target site, the two mismatches in the protospacer are indicated in bold/italics

[b]HUES 1 and HUES 9 are human embryonic stem cell lines; BJ-RiPS is an induced pluripotent stem cell line

[c]Mutants include single heterozygotes, compound heterozygotes, and homozygous mutants; TALEN data is from Table 1 of Ding et al. (2013),with the exception of LDLR

[d]Successfully inserted E17K knock-in mutations into an AKT2 allele(s) using single-stranded DNA oligonucleotide (refer to FIG. 3 of Ding et al., 2013)

[0698] It is worth noting that the requirement for a G(N) 19NGG target sequence somewhat limits site selection. Because either DNA strand can be targeted, a target sequence occurs on average every 32 basepairs. This is no

barrier for gene knockout, where any coding sequence can be targeted, but it may present difficulties when trying to knock in or correct a mutation at a specific location. However, the requirement for a G at the start of the protospacer is dictated by the use of the U6 promoter to express the gRNA, and alternative CRISPR/Cas systems can relieve this requirement (Cong et al., Science 339:819-823 (2013)). This allows for the use of (N)20NGG target sequences, which are found on average every 8 basepairs.

[0699] In addition, the extent of CRISPR off-target effects remains to be defined and is highly sequence-dependent. Previous analyses have suggested that one-nucleotide mismatches in the first half of the protospacer are better tolerated than mismatches in second half (Jinek et al., Science 337:816-821 (2012); Cong et al., Science 339:819-823 (2013)). For the AKT2 sequence, there is a two-mismatch sequence differing at nucleotides 1 and 3, in the more "tolerant" half of the protospacer. Zero clones were obtained with mutations at this potential off-target site, as compared to 61% at the on-target site (Table S1). For one of the SORT1 sequences, use of a different human pluripotent stem cell line in which a single nucleotide polymorphism results in a one-nucleotide mismatch at the target site yielded mutant clones at an efficiency of 42%, compared to 66% in the original cell line. Thus, judicious selection of target sites is necessary to minimize systematic off-target effects; target sites with perfect-match or single-nucleotide-mismatch sequences elsewhere in the genome should be avoided.

[0700] From a practical standpoint, CRISPRs are easier to implement than TALENs. Each TALEN pair must be constructed de novo, whereas for CRISPRs the Cas9 component is fixed and the gRNA requires only swapping of the 20-nucleotide protospacer. Given this consideration and the demonstration herein of substantially increased efficiency as a result of replacing TALENs with CRISPRs in an otherwise identical system, CRISPRs appear to be a very powerful and broadly applicable tool for genome editing, particularly in a therapeutic context.

Example 2: Modified Cas9 mRNA Functions to Efficiently Introduce On-Target Mutations

[0701] The inventors generated Figment (Fgm) knockout mice by CRIPSR/Cas9 gene editing utilizing a modified Cas9 mRNA. Fgm is a coding gene within the long noncoding RNA Lnc-Rap-5 (referred to herein as Fgm (Lnc-Rap-5; see Sun et al., "Long noncoding RNAs regulate adipogenesis," *PNAS;* 2013; 110(9):3387-3392, incorporated herein by reference in its entirety). The guide RNA (gRNA) sequence employed in this example was: 5' gaggcgaaagccactagcac 3'. The modified Cas9 mRNA used in this example was made using an in vitro transcription reaction in which pseudouridine and 5-methyl-cytosine were reacted with unmodified nucleotides and randomly integrated into the resulting modified Cas9 mRNA. An exemplary protocol for generating Fgm knockout mice using CRISPR/Cas9 gene editing utilizing a modified Cas9mRNA is shown in FIG. **19**A. As shown in FIG. **19**A, 100 ng/l of the resulting modified Cas9 mRNA and 50 ng/l of the guide RNA noted above targeting Fgm (Lnc-Rap-5) were injected into 250 C57BL/6 mouse zygotes that were subsequently transferred to pseudo-pregnant mice and after weening screened for mutations by PCR. As shown in the gel pictured in FIG. **19**B, PCR screening revealed 63 mutant animals out of 65. These results indicate that modified Cas9 mRNA functions in vivo to efficiently (i.e., 97% efficiency) introduce on target mutations in mammals.

Example 3: Mutational Analysis of Genome Edited Hematopoietic Stem-Progenitor Cells (HSPCs) by Target Capture Deep Sequencing

[0702] CRISPR/Cas9 has previously been shown to generate off-target mutations to varying degrees depending upon experimental setting and cell type (Cho et al., 2014; Cradick et al., 2013; Fu et al., 2013; Fu et al., 2014; Hruscha et al., 2013; Lin et al., 2014). To examine this in primary $CD34^+$ HSPCs we performed target capture sequencing, of $CD34^+$ HSPCs-mPB subjected to CRISPR/Cas9 CCR5-editing. Experimental design included capture of each gRNA target site (n=6) and predicted off-target sites (n=172) with expanded capture intervals of 500 base pairs flanking each site to ensure accurate detection of any genetic lesion occurring at or near the selected sites (FIGS. **17**A and **20**). We have previously shown that this approach can also capture structural variation breakpoints, such as translocations and inversions, in proximity to the capture site (Talkowski et al., 2011) (See supplemental text and methods for detailed description). Sorted $CD34^+$ HSPCs treated with Cas9 alone or in combination with multiple single gRNA (crCCR5_A, crCCR5_B, or crCCR5_C) or dual gRNA combinations (crCCR5_A+B, crCCR5_C+D, or crCCR5_D+Q) were sequenced to a mean target coverage of 3,390× across each 23 bp gRNA sequence and PAM (range 379.6×-7,969.5×)(FIG. **17**B). Analysis of the resulting data revealed highly efficacious on-target mutagenesis with a diverse array of mutated sequence variants observed in both single-gRNA and dual-gRNA treatments (FIG. **17**C). As expected we detected small InDels of up to 10 bp in addition to varying single nucleotide substitutions at the predicted target sites in the single-gRNA libraries. Strikingly, in each dual-gRNA library, no fewer than 15 alternate mutant alleles were observed at either one of the gRNA sites (FIGS. **21**-**23**). Notably, the extreme sequencing depth of our analysis permitted estimation of mutation frequency for each particular variant, including mutations that were observed in only a few hundredths of a percent of the sample sequenced (FIG. **24**). Predicted deletions (i.e. deletions spanning between the two gRNA target sites) were the most common mutations observed (crCCR5_A+B: 19.95%; crCCR5_C+D: 20.45%; crCCR5_D+Q: 42.13%), while small InDels (crCCR5_A+B: 3.06%; crCCR5_C+D: 0.50%; crCCR5_D+Q: 2.95%) were also frequent (FIG. **17**C). Interestingly, for two dual gRNA combinations (crCCR5_A+B and crCCR5_D+Q) we also observed inversions between the two predicted Cas9 cleavage sites (crCCR5_A+B: 3.06%; crCCR5_D+Q: 2.48%). The most efficacious dual gRNA combination crCCR5_D+Q led to mutations in approximately 48% of the captured sequence reads (FIG. **17**C).

[0703] We next examined the capture sequence reads at predicted off-target sites in the genome (FIG. **20**). An N-fold enrichment analysis was performed, wherein we compared the total number of non-reference sequencing reads at each predicted off-target site in gRNA treated and control (Cas9 only) samples. This analysis generated a ratio where 1.0 indicates an equivalent number of non-reference sequence reads in both treated and control samples, values less than 1.0 indicate fewer non-reference reads in treated samples, and values greater than 1.0 indicate a greater number of

non-reference reads in treated samples (see supplementary materials for additional details) (FIG. **17**D). Strikingly, this analysis showed that the mean enrichment of mutations at off-target sites in all the gRNA-treated samples compared to control closely conformed to the null hypothesis (i.e., 0.99-fold enrichment compared to controls) indicating that off-target mutation events were extremely rare. Indeed, statistical evaluation of all captured off-target sites yielded a single site (1/172; 0.6%) in the sample treated with gRNA crCCR5_B alone that passed multiple test correction for a statistically significant enrichment for off-target InDels in the gRNA crCCR5_B treated libraries versus control ($p \leq 7.6 \times 10^{-11}$) (FIGS. **24**-**25**). When we scrutinized the sequencing reads from the only statistically significant off-target site, which was located in the highly homologous CCR2 gene (FIG. **18**A), we found that all sequence variants (36 out of 5,963 total reads) were one or two base InDels, (FIG. **18**B). Of note, the other sample in which gRNA crCCR5_B was used (in combination with gRNA crCCR5_A) only 13 out of 5,339 reads supported mutation, however these events did not meet statistical significance above control or samples treated with other gRNAs (FIG. **18**B, FIG. **24**). Thus, off-target mutagenesis was exceedingly rare and moreover, the use of two gRNAs in combination did not increase the very low incidence of off-target mutagenesis. We also performed targeted analyses for structural variation at all sites and though we could easily detect on-target inversions in dual gRNA combination crCCR5_A+B and crCCR5_D+Q, there was no evidence for inversion or translocation at any off-target sites in any of the treatments. These data indicate that on-target mutagenesis efficiency was very high, and further that off-target mutagenesis was extremely infrequent for both single- and dual gRNA treatments.

[0704] Discussion

[0705] Our mutational analysis revealed highly efficacious mutagenesis of on-target sites in $CD34^+$ HSPCs. Single gRNAs generated a range of mutations with the vast majority comprised of small InDels. In contrast, dual gRNA combinations largely led to predicted deletions through a diverse array of mutations including InDels and even inversions were detected. Importantly, we only identified one statistically significant off-target site in the highly homologous CCR2 gene, which occurred in one out of 6 experimental settings (gRNA crCCR5_B alone). Sequence analysis of gRNA crCCR5_B in comparison to the identified off-target site in CCR2 indicated that it perfectly matched in the seed region and contained 3 sequence mismatches at the 5' end of the gRNA sequence (positions 1, 4 and 6). This data is consistent with previous studies showing that mismatches in the 5' proximal end of the gRNA are well tolerated by Cas9 (Lin et al., 2014; Wu et al., 2014). Our data therefore supports the idea that judicious guide design is critical for minimizing off-target mutations. Of note, our very deep sequencing analysis enabled detection of the sole off-target event we describe, whereas sequence analysis performed at lower sequencing depth—such as 50× coverage that has been used in previous off-target analyses (Smith et al., 2014; Suzuki et al., 2014; Veres et al., 2014)—would have been unable to detect this event. Overall, our analysis of CRISPR/Cas9 mutational activity in $CD34^+$ HSPCs revealed very high on-target mutation rates and extremely low incidence of off-target mutagenesis.

[0706] Off-Target Prediction and Capture Sequencing

[0707] Degenerate gRNA off-target sequences were predicted for each gRNA targeting CCR5 using the CRISPR Design off-target prediction tool (Hsu et al., 2013). Off-target sequences were further supplemented by alignment of each gRNA to the human genome using BOWTIE of which all results up to and including 3 mismatches were added to the total off-target list (Langmead et al., 2009). All instances of each predicted off-target sequence existent in the human genome reference build GRCh37v71 were recorded (FIG. **20**). Each guide RNA target site (n=6) and predicted off-target site (n=172) was selected for capture sequencing using the Agilent SureSelectXT Target Enrichment System. Capture intervals were expanded by approximately 500 bp in both the 5' and 3' directions to ensure exhaustive capture of the targeted region and detection of any genetic lesion occurring at or near a predicted gRNA on- or off-target site, as we have previously shown accurate capability to detect translocations and inversions using targeted capture of probes in proximity to a rearrangement breakpoint using a CapBP procedure as described (Talkowski et al., 2011). Probes were tiled with 60-fold greater density over each predicted 23 bp on- or off-target gRNA binding site than the flanking kilobase of sequence. Isogenic $CD34^+$ HSPCs-mPB were transfected with CRISPR/Cas9 plasmids (one Cas9 only-treated control group, three treatment groups transfected with a single gRNA, and three treatment groups transfected with dual gRNAs). Sorted $CD34^+$ genome edited HSPCs were cultured for two weeks prior to DNA isolation. Capture libraries were prepared from DNA extracted from seven treatment groups. Capture libraries were sequenced as 101 bp paired-end reads on an Illumina HiSeq2000 platform.

[0708] NGS Data Processing and Computational Analysis

[0709] Read pairs were aligned to GRCh37v71 with BwaMEM v0.7.10-r789 (Li, arXiv 2013). Alignments were processed using PicardTools and SAMBLASTER (Faust and Hall, 2014). The Genome Analysis Toolkit (GATK) v3.1-1-g07a4bf8 was applied for base quality score recalibration, insertion/deletion (InDel) realignment, duplicate removal, and single nucleotide variant (SNV) and InDel discovery and genotyping per published best-practice protocols (McKenna et al, Genome Res 2010; DePristo et al, Nat Genet 2011; Van der Auwera et al, 2013). SNVs and InDels were annotated using ANNOVAR (Wang et al., 2010). Structural variants (SVs) were detected with LUMPY v0.2.5 considering both anomalous pair and split read evidence at a minimum call weight threshold of 7 and an evidence set score ≤0.05 (Layer et al., 2014). Candidate copy number variants (CNVs) were further statistically assessed by Student's t-test for a concomitant change in depth of coverage across the putative CNV. As a final exhaustive measure, each on- and off-target site was manually scrutinized in each capture library for evidence supporting predictable mutagenesis that is not detectable by the computational algorithms due to low levels of mosaicism in the sequenced population.

[0710] Evaluation of Off-Target Mutation Frequency

[0711] A statistical framework was developed to assess off-target mutational burden for each gRNA. For each off-target site (n=172), all reads with at least one nucleotide of overlap with that 23 bp off-target site were collected and their CIGAR information was tabulated into categories as follows: reads representing small InDels (CIGAR contains at least one "I" or "D"), reads potentially representative of

other rearrangements (CIGAR contains at least one "S" or "H"), and reads reflecting reference sequence (CIGAR did not match either of the two former categories). Such counts were gathered at all 172 sites in all seven libraries and were further pooled to form comparison groups of "treatment" libraries (transfected gRNA matches corresponding off-target site gRNA) and "control" libraries (transfected gRNA does not match corresponding off-target site gRNA). Next, at each off-target site, relative n-fold enrichment of each read classification between treatment and control libraries was evaluated. Finally, a one-tailed Fisher's Exact Test was performed to assess the statistical significance of enrichment of variant reads in treatments versus controls at each off-target site, followed by Bonferroni correction to retain an experiment-wide significance threshold of α=0.05.

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SEQUENCE LISTING

The patent application contains a lengthy "Sequence Listing" section. A copy of the "Sequence Listing" is available in electronic form from the USPTO web site (http://seqdata.uspto.gov/?pageRequest=docDetail&DocID=US20200048659A1). An electronic copy of the "Sequence Listing" will also be available from the USPTO upon request and payment of the fee set forth in 37 CFR 1.19(b)(3).

1.-**12**. (canceled)

13. A method for altering a target beta thalassemia-associated polynucleotide sequence in a cell comprising contacting the beta thalassemia-associated polynucleotide sequence with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target beta thalassemia-associated polynucleotide sequence, wherein the target beta thalassemia-associated polynucleotide sequence is cleaved, and wherein the efficiency of alteration is from about 50% to about 80%.

14.-**18**. (canceled)

19. The method according to claim **13**, wherein the Cas protein is *Streptococcus pyogenes* Cas9 protein or a functional portion thereof selected from the group consisting of a DNA binding domain, at least one RNA binding domain, a helicase domain, and an endonuclease domain.

20.-**21**. (canceled)

22. The method according to claim **13**, wherein the Cas protein is Cas9 protein from any bacterial species or functional portion thereof selected from the group consisting of a DNA binding domain, at least one RNA binding domain, a helicase domain, and an endonuclease domain.

23.-**24**. (canceled)

25. The method according to claim **13**, wherein the Cas protein is complexed with the one to two ribonucleic acids.

26.-**32**. (canceled)

33. The method according to claim **13**, wherein the target motif is G(N)19NGG.

34.-**41**. (canceled)

42. The method according to claim **13**, wherein the alteration results in reduced expression of the target polynucleotide sequence, a knock out of the target polynucleotide sequence, or correction of the target polynucleotide sequence from an undesired sequence to a desired sequence.

43.-**57**. (canceled)

58. The method according to claim **13**, wherein the cell is selected from the group consisting of a peripheral blood cell, a stem cell, a pluripotent cell, a hematopoietic stem cell, a CD34+ cell, a CD34+ mobilized peripheral blood cell, a CD34+ cord blood cell, a CD34+ bone marrow cell, a $CD34^{+}CD38$-Lineage-$CD90^{+}CD45RA^{-}$ cell, a primary human cell, a non-transformed human cell, and combinations thereof.

59.-**107**. (canceled)

108. The method according to claim **13**, wherein the target polynucleotide sequence is HBB.

109. The method according to claim **108**, wherein at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of SEQ ID NOS. 814-908, or at least a 12 nucleotide fragment thereof.

110. The method according to claim **108**, wherein at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of SEQ ID NOS. 814-908, or at least a 12 nucleotide fragment thereof.

111.-**173**. (canceled)

174. The method according to claim **13**, wherein the one to two ribonucleic acids hybridize to a target motif that

contains at least one mismatch when compared with all other genomic nucleotide sequences in the cell.

175.-**193**. (canceled)

194. The method according to claim **13**, wherein at least one of the ribonucleic acids is a modified ribonucleic acid comprising one to two modified nucleotides selected from the group consisting of pseudouridine, 5-methylcytodine, 2-thio-uridine, 5-methyluridine-5'-triphosphate, 4-thiouridine-5'-triphosphate, 5,6-dihydrouridine-5'-triphosphate, and 5-azauridine-5'-triphosphate.

195.-**272**. (canceled)

273. The method according to claim **13**, wherein the cell was selected for Cas protein expression.

274. The method according to claim **13**, wherein the target motif of the target beta thalassemia-associated polynucleotide sequence comprises nucleotides located between position 5246806 and position 5248263 of human chromosome 11.

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