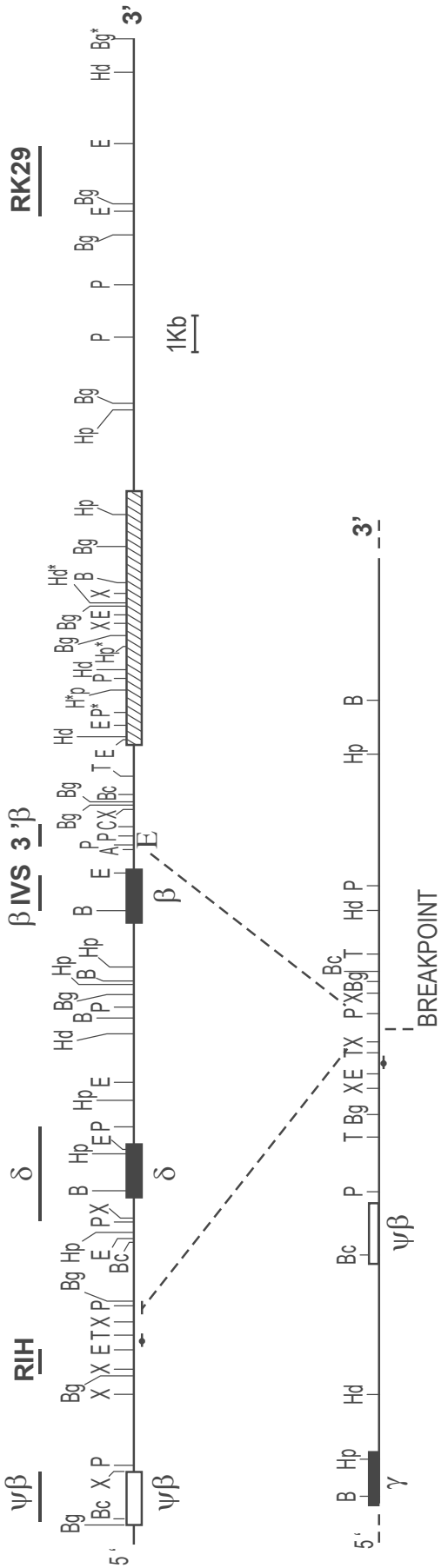


Figure 1

Figure 1A

Figure 1 (cont.)

Figure 1B

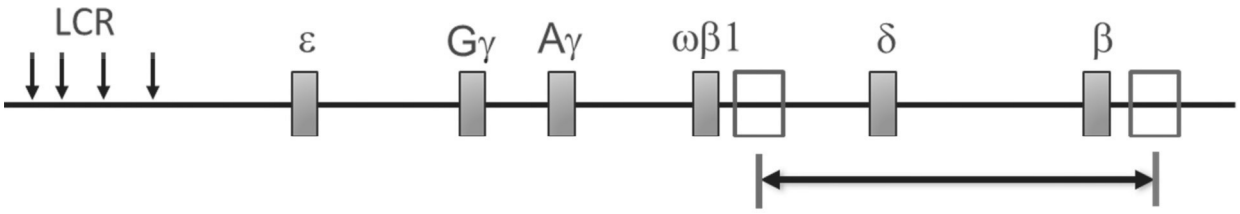


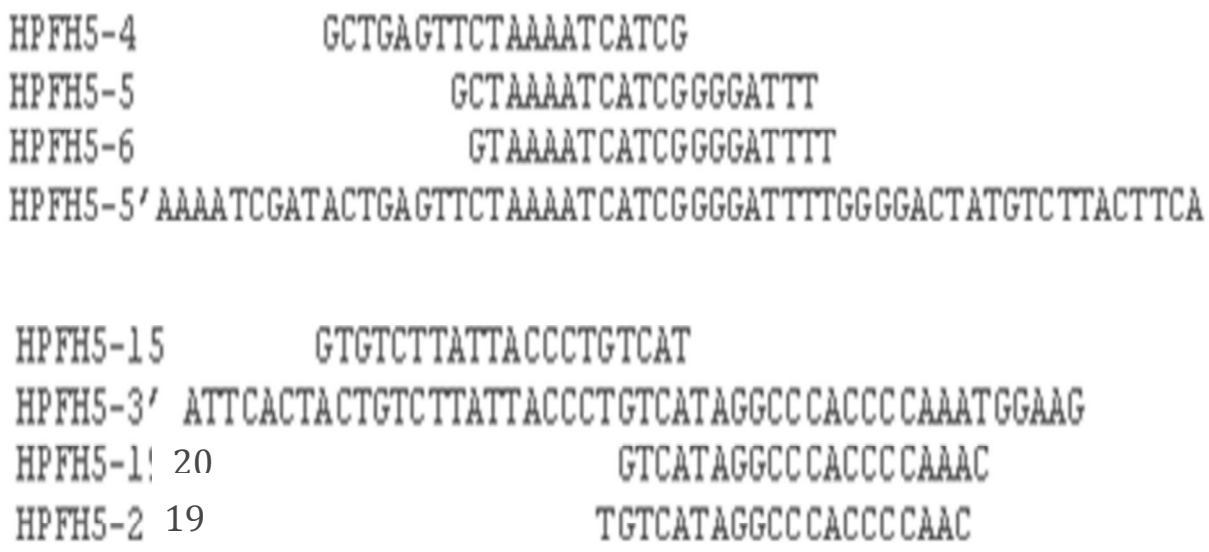
Figure 1C

HPFH5

Guide	Sequence	SEQ ID NO	Location	Cut Site
HPFH5-04	gCTGAGTTCTAAAATCATCG	SEQ ID NO: 4	Chr11:5237756-5237778	Chr11:5237762
HPFH5-15	gTGTCTTATTACCCTGTCAT	SEQ ID NO: 15	Chr11:5224763-5224785	Chr11:5224769
HPFH5-19	gTTGGGGTGGGCCTATGACA	SEQ ID NO: 19	Chr11:5224752-5224774	Chr11:5224768
HPFH5-20	gTTTGGGGTGGGCCTATGAC	SEQ ID NO: 20	Chr11:5224751-5224773	Chr11:5224767
HPFH5_44	gGGTGGGAAAATAGACCAAT	SEQ ID NO: 43	Chr11:5226804-5226826	Chr11:5226820
HPFH5_56	gATCAGAATGGCCCTAGTCT	SEQ ID NO: 55	Chr11:5229841-5229863	Chr11:5229857
HPFH5_73	gAAAGCAAGGGAACCGTACA	SEQ ID NO: 72	Chr11:5232701-5232723	Chr11:5232707
HPFH5_84	gGTGTTTTAGGCTAATATAG	SEQ ID NO: 83	Chr11:5234752-5234774	Chr11:5234768
HPFH5_87	gCATTTGTGGATACTATTAA	SEQ ID NO: 86	Chr11:5235767-5235789	Chr11:5235773
HPFH5_93	gTCTGTTAATTCCAAAGACT	SEQ ID NO: 92	Chr11:5236813-5236835	Chr11:5236829

Figure 1 (cont.)

Figure 1D



HPFH5-4 = SEQ ID NO: 4

HPFH5-5 = SEQ ID NO: 5

HPFH5-6 = SEQ ID NO: 6

HPFH5-5’ = SEQ ID NO: 144

HPFH5-15 = SEQ ID NO: 15

HPFH5-3’ = SEQ ID NO: 145

HPFH5-19 = SEQ ID NO: 19

HPFH5-20 = SEQ ID NO: 20

Figure 2

Figure 2A

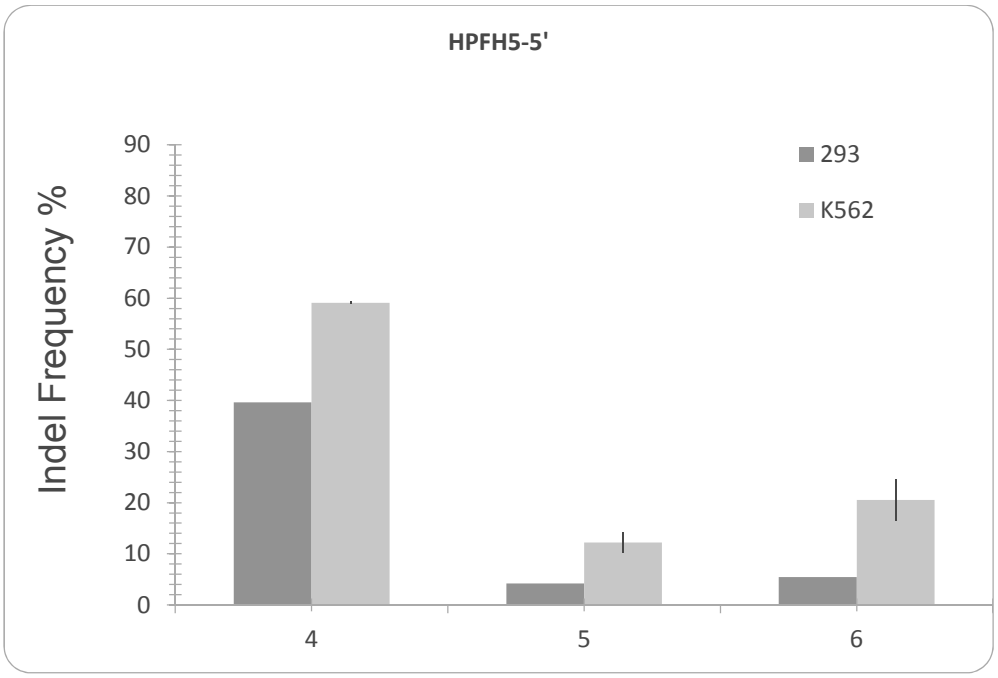


Figure 2B

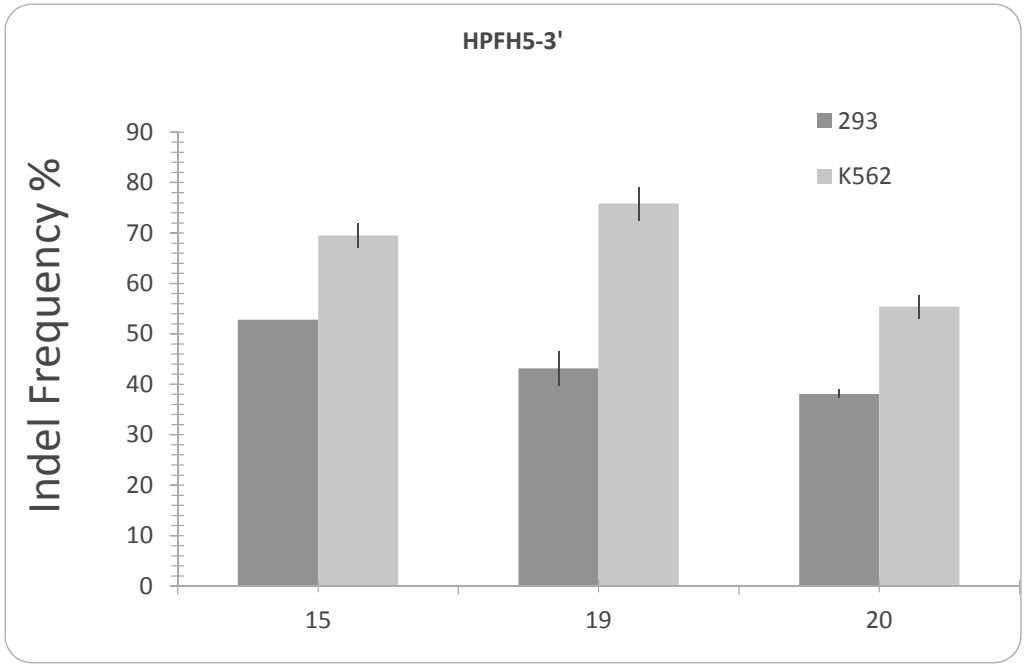


Figure 2 (cont.)

Figure 2C



First line = SEQ ID NO: 146
Second line = SEQ ID NO: 147
Third line = SEQ ID NO: 148
Fourth line = SEQ ID NO: 149
Fifth line = SEQ ID NO: 150
Sixth line = SEQ ID NO: 151

Figure 3

Figure 3A

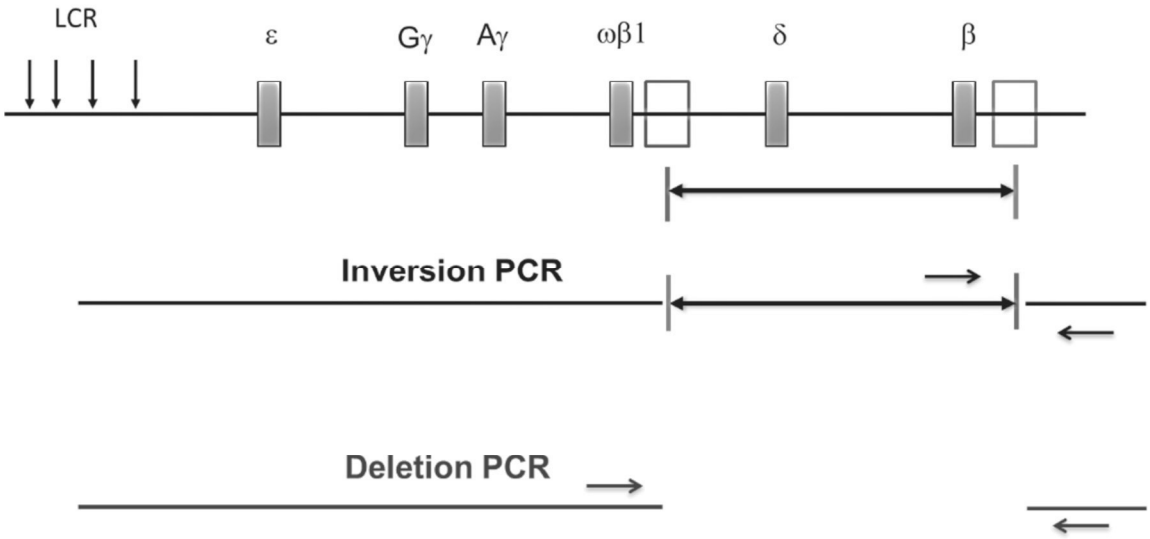
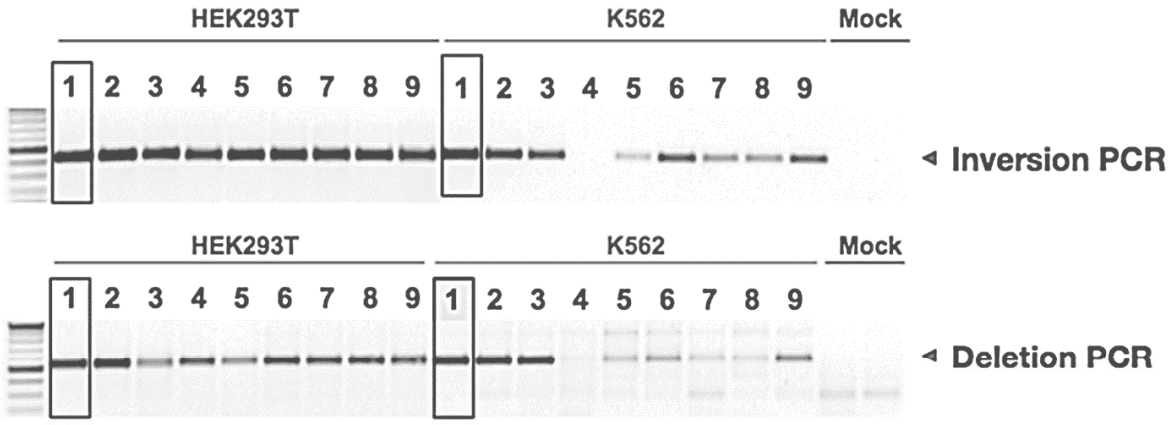


Figure 3B



3' \ 5'	HPFH5-4	HPFH5-5	HPFH5-6
HPFH5-15	1	4	7
HPFH5-19	2	5	8
HPFH5-20	3	6	9

Combinations

Figure 4



First line = SEQ ID NO: 152
Second line = SEQ ID NO: 153
Third line = SEQ ID NO: 154
Fourth line = SEQ ID NO: 155
Fifth line = SEQ ID NO: 156
Sixth line = SEQ ID NO: 157
Seventh line = SEQ ID NO: 158
Eigth line = SEQ ID NO: 159
Ninth line = SEQ ID NO: 160
Tenth line = SEQ ID NO: 161

Figure 5

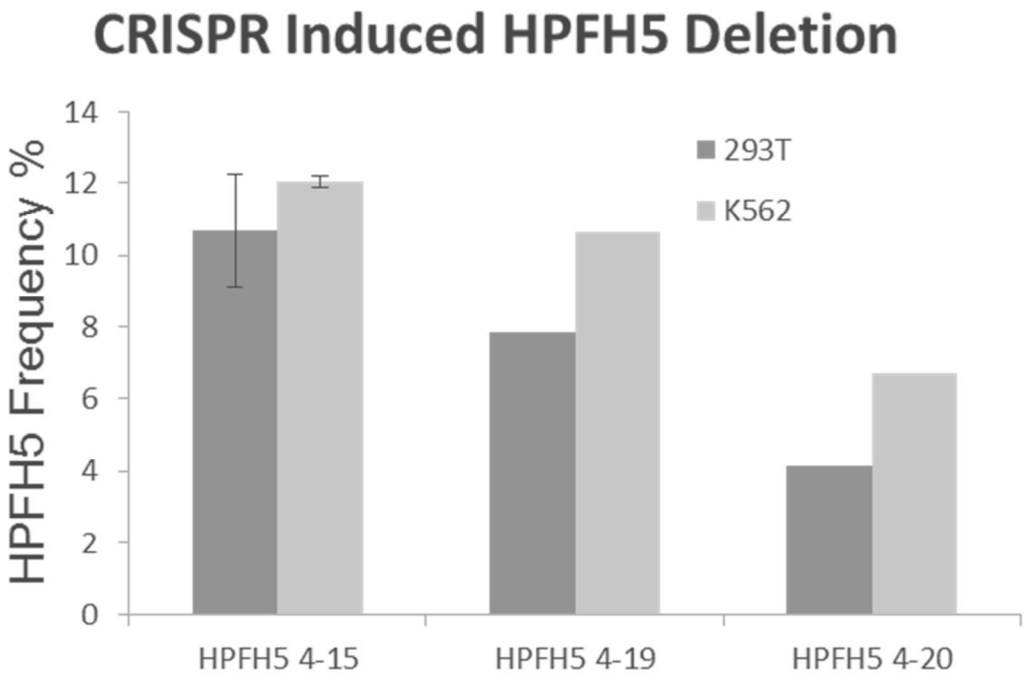

CRISPR Induced HPFH5 Deletion
HPFH5 Frequency %
14
12
10
8
6
4
2
0
293T
K562
HPFH5 4-15
HPFH5 4-19
HPFH5 4-20

Figure 6

Figure 6A

Site	Sequence	Score
HPFH5_4ON	ACTGAGTTCTAAAATCATCGGGG	0
HPFH5_4OT1	CCTGA**TC**TCT**T**AAATCATCGTGG	1.14
HPFH5_15ON	CTGTCTTATTACCCTGTCATAGG	0
HPFH5-15_OT1	TT**TG**CTTATTACCCTGTCATA**A**G	0.32
HPFH5-15_OT2	CTG**AT**TTAT**A**ACCCTGTCATCGG	0.86
HPFH5-15_OT3	ATGT**G**T**C**AT**C**ACCCTGTCATC**A**G	0.92
HPFH5-15_OT4	GTGTCTT**C**TT**T**CCCTGTCATTGG	0.97
HPFH5-15_OT5	GTGTCTT**C**TT**C**CCCTGTCATG**A**G	0.97
HPFH5-15_OT6	T**AC**TCTTATT**C**CCCTGTCATC**A**G	0.98
HPFH5-15_OT7	CT**T**T**T**TTATTA**A**CCTGTCATTGG	1.14
HPFH5-15_OT8	ATG**AG**TTATTA**G**CCTGTCATTGG	1.16
HPFH5-15_OT9	C**AT**TCTTATTAC**A**CTGTCATC**A**G	1.38
HPFH5-15_OT10	T**A**GT**T**TTATTAC**A**CTGTCATC**A**G	1.42
HPFH5-15_OT11	ATGTCTT**GA**TA**G**CCTGTCATA**A**G	1.42

HPFH5_4ON = SEQ ID NO: 162
HPFH5_4OT1 = SEQ ID NO: 163
HPFH5_15ON = SEQ ID NO: 164
HPFH5-15_OT1 = SEQ ID NO: 165
HPFH5-15_OT2 = SEQ ID NO: 166
HPFH5-15_OT3 = SEQ ID NO: 167
HPFH5-15_OT4 = SEQ ID NO: 168
HPFH5-15_OT5 = SEQ ID NO: 169
HPFH5-15_OT6 = SEQ ID NO: 170
HPFH5-15_OT7 = SEQ ID NO: 171
HPFH5-15_OT8 = SEQ ID NO: 172
HPFH5-15_OT9 = SEQ ID NO: 173
HPFH5-15_OT10 = SEQ ID NO: 174
HPFH5-15_OT11 = SEQ ID NO: 175

Figure 6 (cont.)

Figure 6B

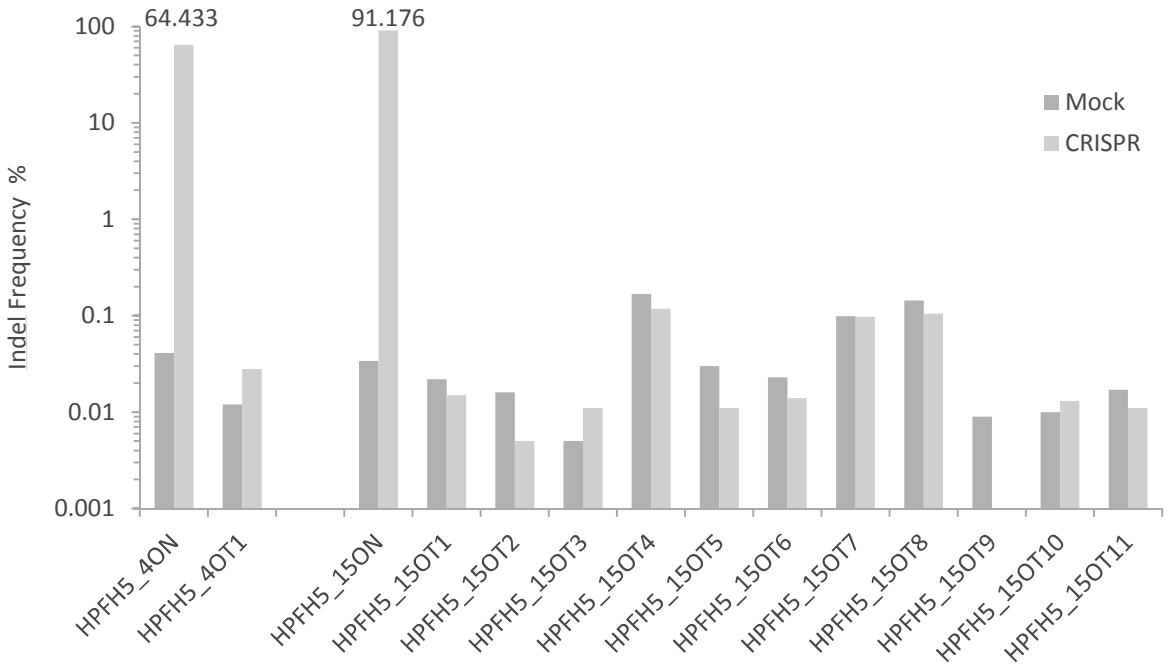


Figure 7

Figure 7A

HPFH5

Guide	Sequence	SEQ ID NO	Location	Cut Site
HPFH5_36	gACAGACCAGCACGTTGCCC	SEQ ID NO: 35	Chr11:5225702-5225724	Chr11:5225718
HPFH5_37	gCAGCTCCTGGGCAACGTGC	SEQ ID NO: 36	Chr11:5225708-5225730	Chr11:5225714
HPFH5_38	gTTAGCAAAAGGGCCTAGCT	SEQ ID NO: 37	Chr11:5225758-5225780	Chr11:5225774
HPFH5_39	gATTATTCTGAGTCCAAGCT	SEQ ID NO: 38	Chr11:5225771-5225793	Chr11:5225777
HPFH5_40	gGCTGCTGGTGGTCTACCCT	SEQ ID NO: 39	Chr11:5226778-5226800	Chr11:5226784
HPFH5_41	gGTAGACCACCAGCAGCCTA	SEQ ID NO: 40	Chr11:5226783-5226805	Chr11:5226799
HPFH5_42	gTAGACCACCAGCAGCCTAA	SEQ ID NO: 41	Chr11:5226784-5226806	Chr11:5226800
HPFH5_43	gCCACCAGCAGCCTAAGGGT	SEQ ID NO: 42	Chr11:5226788-5226810	Chr11:5226804
HPFH5_44	gGGTGGGAAAATAGACCAAT	SEQ ID NO: 43	Chr11:5226804-5226826	Chr11:5226820
HPFH5_45	gCCCAAAGTGTGACTATCAA	SEQ ID NO: 44	Chr11:5227835-5227857	Chr11:5227851
HPFH5_46	gCCCATTGATAGTCACACTT	SEQ ID NO: 45	Chr11:5227837-5227859	Chr11:5227843
HPFH5_47	gCCAAAGTGTGACTATCAAT	SEQ ID NO: 46	Chr11:5227836-5227858	Chr11:5227852
HPFH5_48	gCTATCAATGGGGTAATCAG	SEQ ID NO: 47	Chr11:5227847-5227869	Chr11:5227863
HPFH5_49	gGTAATCAGTGGTGTCAAAT	SEQ ID NO: 48	Chr11:5227858-5227880	Chr11:5227874
HPFH5_50	gACCTGTCTCAACCCTCATC	SEQ ID NO: 49	Chr11:5228644-5228666	Chr11:5228660
HPFH5_51	gACCTGATGAGGGTTGAGAC	SEQ ID NO: 50	Chr11:5228646-5228668	Chr11:5228652
HPFH5_52	gCACACACGCAGAAAGTGTT	SEQ ID NO: 51	Chr11:5228698-5228720	Chr11:5228714
HPFH5_53	gTGGTTCTTCTATGGCTATC	SEQ ID NO: 52	Chr11:5228717-5228739	Chr11:5228733
HPFH5_54	gTGCCTATGTATGATTATAG	SEQ ID NO: 53	Chr11:5228758-5228780	Chr11:5228774
HPFH5_55	gTATCAGAATGGCCCTAGTC	SEQ ID NO: 54	Chr11:5229840-5229862	Chr11:5229856
HPFH5_56	gATCAGAATGGCCCTAGTCT	SEQ ID NO: 55	Chr11:5229841-5229863	Chr11:5229857
HPFH5_57	gTCTAAGTATACCCAGACTA	SEQ ID NO: 56	Chr11:5229852-5229874	Chr11:5229858
HPFH5_58	gCTCTAAGTATACCCAGACT	SEQ ID NO: 57	Chr11:5229853-5229875	Chr11:5229859
HPFH5_59	gCTAGTCTGGGTATACTTAG	SEQ ID NO: 58	Chr11:5229854-5229875	Chr11:5229869
HPFH5_60	gTTCAGTATGTCTGAATGAA	SEQ ID NO: 59	Chr11:5230701-5230723	Chr11:5230707
HPFH5_61	gAAATTAAAGCCAAATCTTG	SEQ ID NO: 60	Chr11:5230786-5230808	Chr11:5230802
HPFH5_62	gGAATTAATTCCTCAAGATT	SEQ ID NO: 61	Chr11:5230796-5230818	Chr11:5230802
HPFH5_63	gTTAAAACAAAGTATAGGAA	SEQ ID NO: 62	Chr11:5230817-5230839	Chr11:5230823
HPFH5_64	gGTACATGTACAAGTTATAT	SEQ ID NO: 63	Chr11:5230858-5230880	Chr11:5230874
HPFH5_65	gACACATTGTCAGTATATTC	SEQ ID NO: 64	Chr11:5231674-5231696	Chr11:5231690
HPFH5_66	gATCCTTCTAATTTTACCTA	SEQ ID NO: 65	Chr11:5231840-5231862	Chr11:5231856
HPFH5_67	gTGCCATAGGTAAAATTAGA	SEQ ID NO: 66	Chr11:5231843-5231865	Chr11:5231849
HPFH5_68	gTGAGCACCATTTTTGCCAT	SEQ ID NO: 67	Chr11:5231856-5231877	Chr11:5231862
HPFH5_69	gATGGCAAAAATGGTGCTCA	SEQ ID NO: 68	Chr11:5231858-5231880	Chr11:5231874
HPFH5_70	gCACCCATTAATGCCTTGTA	SEQ ID NO: 69	Chr11:5232689-5232710	Chr11:5232704
HPFH5_71	gAACCGTACAAGGCATTAAT	SEQ ID NO: 70	Chr11:5232691-5232712	Chr11:5232697

HPFH5_72	gGAACCGTACAAGGCATTAA	SEQ ID NO: 71	Chr11:5232692-5232714	Chr11:5232698
HPFH5_73	gAAAGCAAGGGAACCGTACA	SEQ ID NO: 72	Chr11:5232701-5232723	Chr11:5232707
HPFH5_74	gTCCCTATCTGTAGAGCCTC	SEQ ID NO: 73	Chr11:5232762-5232783	Chr11:5232777
HPFH5_75	gAGCCTCTCCCATACCCATG	SEQ ID NO: 74	Chr11:5233650-5233672	Chr11:5233666
HPFH5_76	gCTCCACATGGGTATGGGAG	SEQ ID NO: 75	Chr11:5233653-5233675	Chr11:5233659
HPFH5_77	gTGTCTCTCCACATGGGTAT	SEQ ID NO: 76	Chr11:5233658-5233680	Chr11:5233664
HPFH5_78	gTTGTCTCTCCACATGGGTA	SEQ ID NO: 77	Chr11:5233659-5233681	Chr11:5233665
HPFH5_79	gTTCTAAGTGCAGAATTAGC	SEQ ID NO: 78	Chr11:5233688-5233710	Chr11:5233704
HPFH5_80	gGCGGTGGGGAGATATGTAG	SEQ ID NO: 79	Chr11:5234677-5234699	Chr11:5234683
HPFH5_81	gTGCTGAAAGAGATGCGGTG	SEQ ID NO: 80	Chr11:5234690-5234712	Chr11:5234696
HPFH5_82	gCTGCTGAAAGAGATGCGGT	SEQ ID NO: 81	Chr11:5234691-5234713	Chr11:5234697
HPFH5_83	gACTGCTGAAAGAGATGCGG	SEQ ID NO: 82	Chr11:5234692-5234714	Chr11:5234698
HPFH5_84	gGTGTTTTAGGCTAATATAG	SEQ ID NO: 83	Chr11:5234752-5234774	Chr11:5234768
HPFH5_85	gTCAAATTTTGGTGGTGATA	SEQ ID NO: 84	Chr11:5235684-5235706	Chr11:5235700
HPFH5_86	gTACAATAGTATAACCCCTT	SEQ ID NO: 85	Chr11:5235740-5235762	Chr11:5235756
HPFH5_87	gCATTTGTGGATACTATTAA	SEQ ID NO: 86	Chr11:5235767-5235789	Chr11:5235773
HPFH5_88	gTAATAGTATCCACAAATGC	SEQ ID NO: 87	Chr11:5235770-5235792	Chr11:5235786
HPFH5_89	gATCAAGCATCCAGCATTTG	SEQ ID NO: 88	Chr11:5235780-5235802	Chr11:5235786
HPFH5_90	gTGTCATTTTTAACAGGTAG	SEQ ID NO: 89	Chr11:5236644-5236666	Chr11:5236650
HPFH5_91	gGTAAATTCTTAAGGCCATG	SEQ ID NO: 90	Chr11:5236773-5236795	Chr11:5236789
HPFH5_92	gGATCAAATAACAGTCCTCA	SEQ ID NO: 91	Chr11:5236788-5236810	Chr11:5236794
HPFH5_93	gTCTGTTAATTCCAAAGACT	SEQ ID NO: 92	Chr11:5236813-5236835	Chr11:5236829
HPFH5_94	gCTGAAATGATTTTACACAT	SEQ ID NO: 93	Chr11:5236859-5236881	Chr11:5236875

Figure 7 (Cont.)

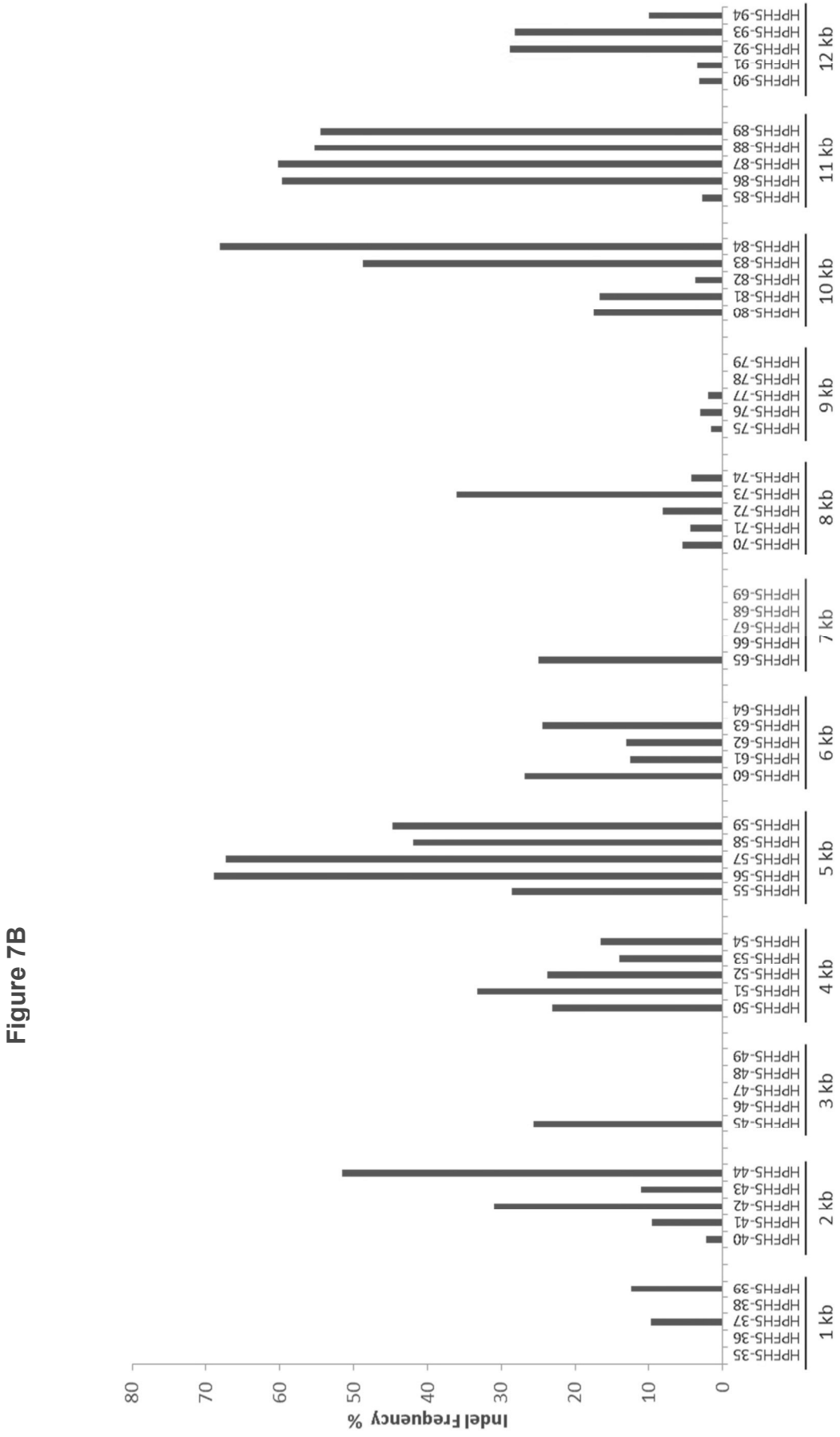


Figure 8

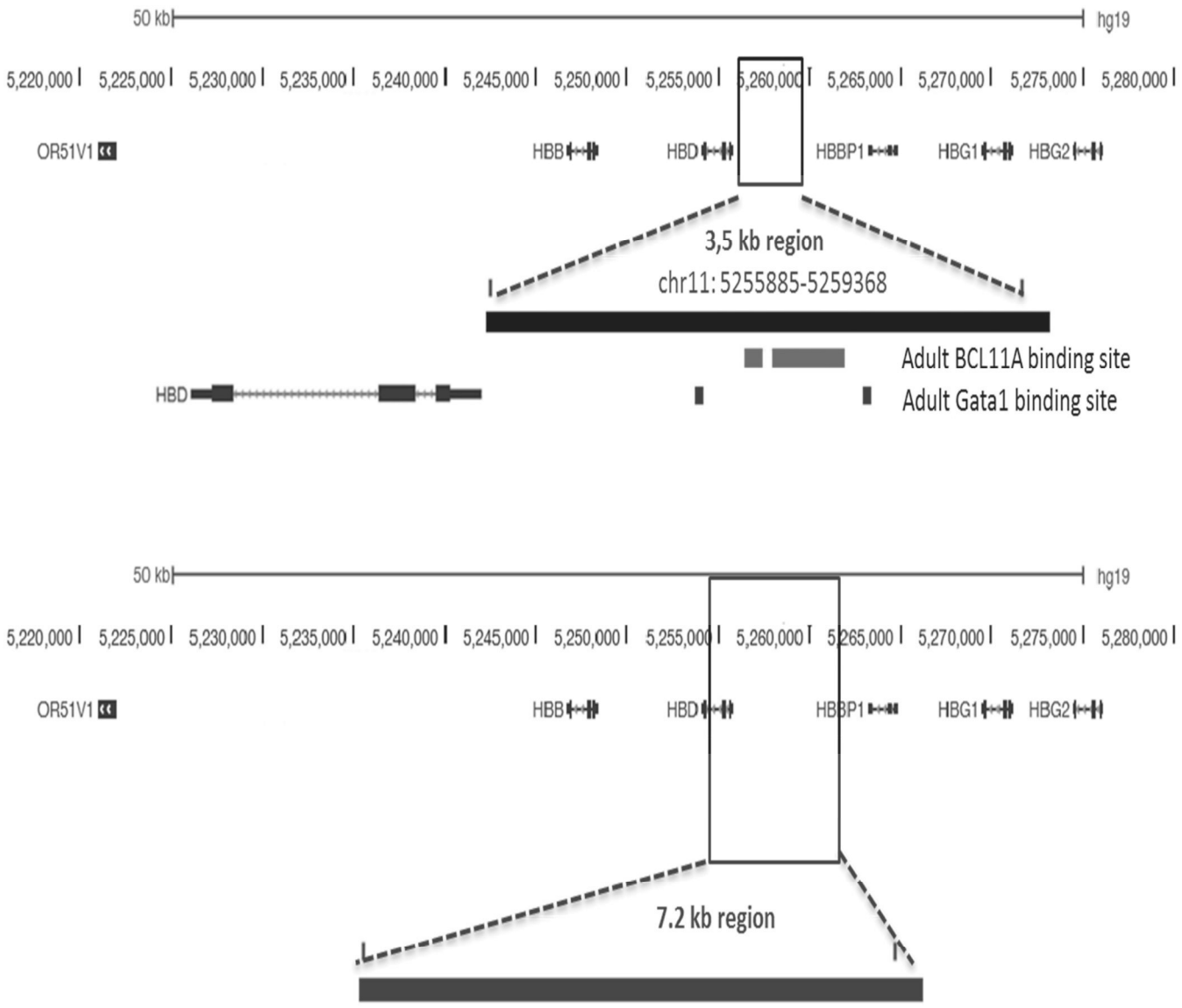

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hg19
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HBG2
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5,270,000
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5,280,000
OR51V1
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HBD
HBBP1
HBG1
HBG2
7.2 kb region

Figure 9

Corfu

Guide	Sequence	SEQ ID NO	Location	Cut Site
HPFHCS-02	gTAGACCACCAGTAATCTGA	SEQ ID NO: 105	Chr11:5234198-5234220	Chr11:5234214
HPFHCS-04	gTGGTATGGGAGGTATACTA	SEQ ID NO: 107	Chr11:5237949-5237971	Chr11:5237965
HPFHCS-06	gGTATACCTCCCATACCATG	SEQ ID NO: 109	Chr11:5237945-5237967	Chr11:5237951
HPFHCL-01	gGTGTGCTGGCCCGCAACTT	SEQ ID NO: 111	Chr11:5233049-5233071	Chr11:5233055
HPFHCL-02	gTGGGGCAGAAGTCGTTGCT	SEQ ID NO: 112	Chr11:5233476-5233498	Chr11:5233482
HPFHCL-08	gCCACTCAAGAGATATGGTG	SEQ ID NO: 118	Chr11:5240337-5240359	Chr11:5240353

Figure 10

Figure 10A

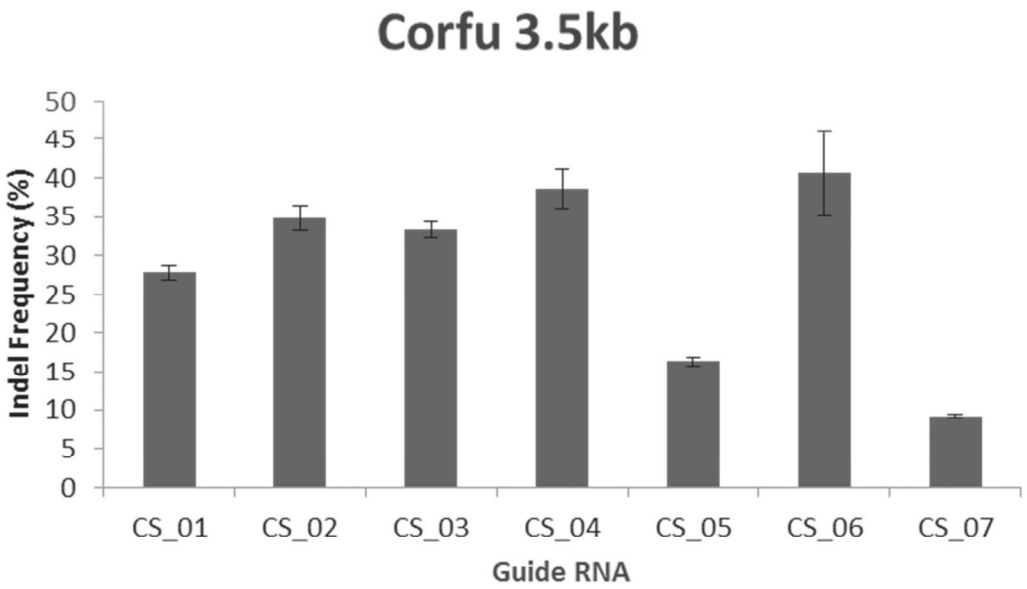


Figure 10B

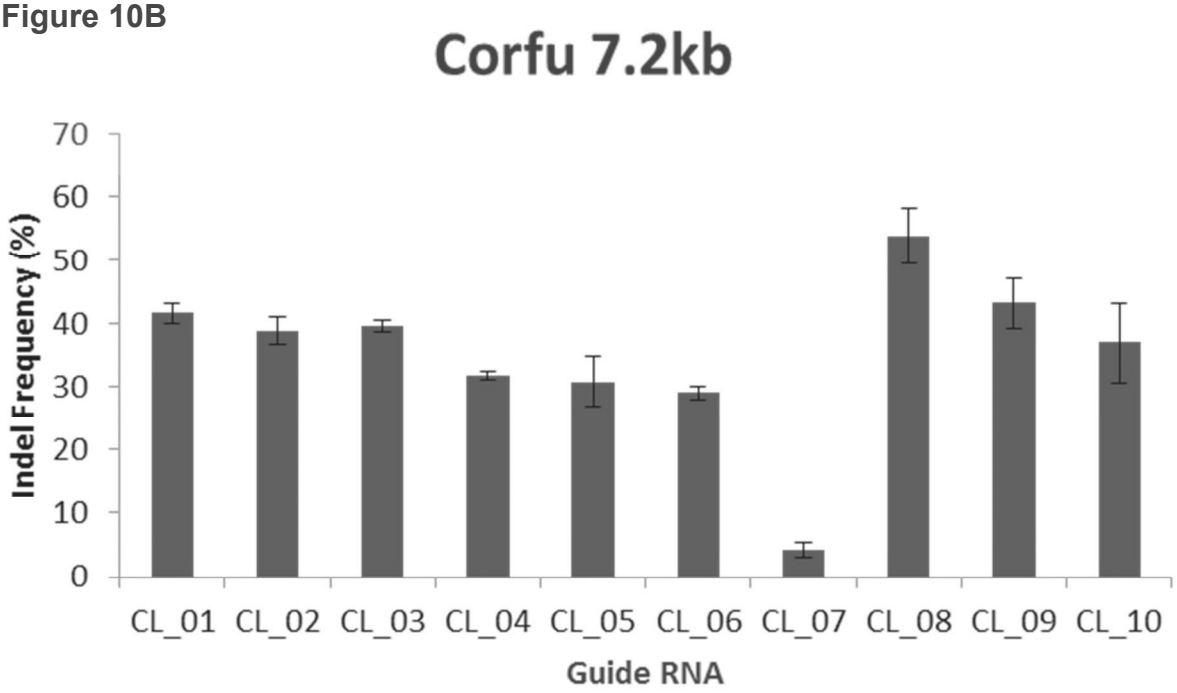


Figure 10C



Figure 11

Figure 11A

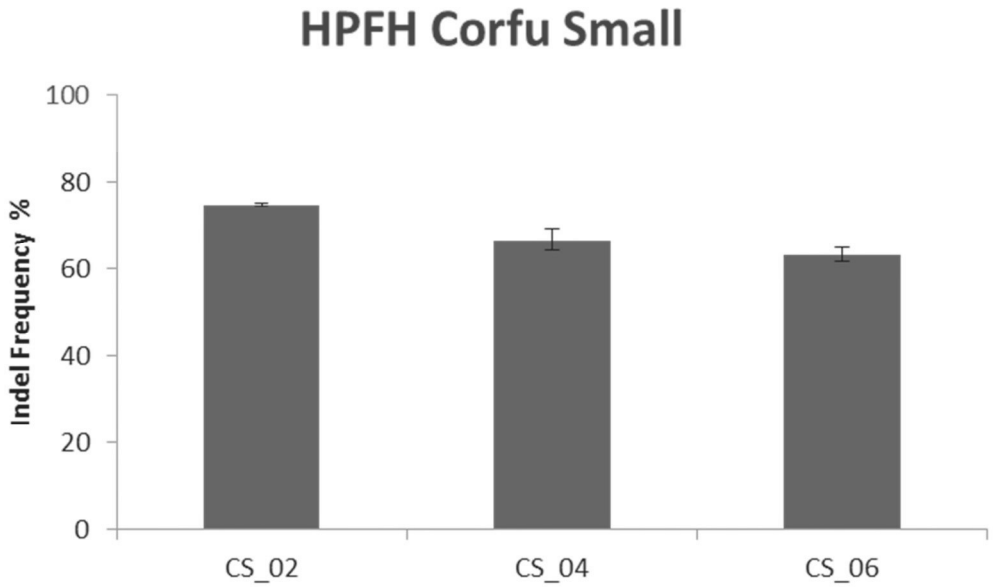


Figure 11B

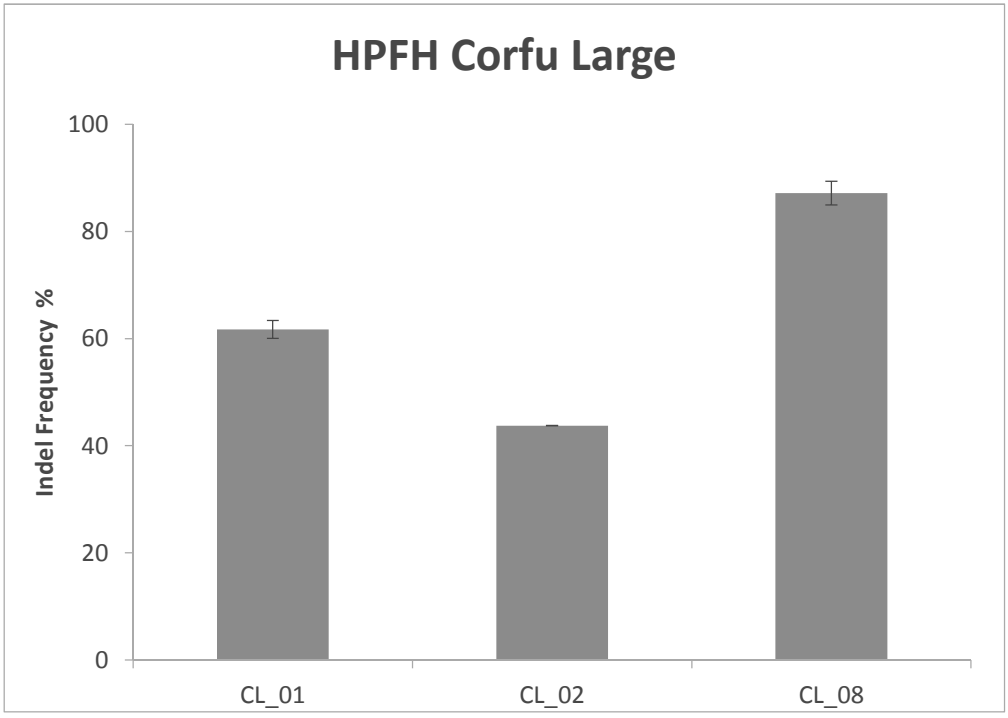


Figure 11C



Figure 12

Figure 12A

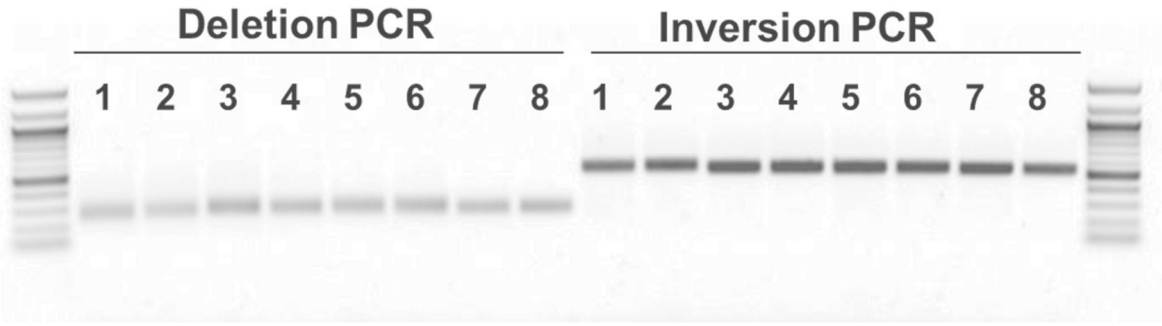


Figure 12B

3' guide		5' guide	
	CS-02	CL_01	CL_02
CS_04	1&2		
CS_06	3&4		
CL_08		5&6	7&8

Figure 13

Figure 13A

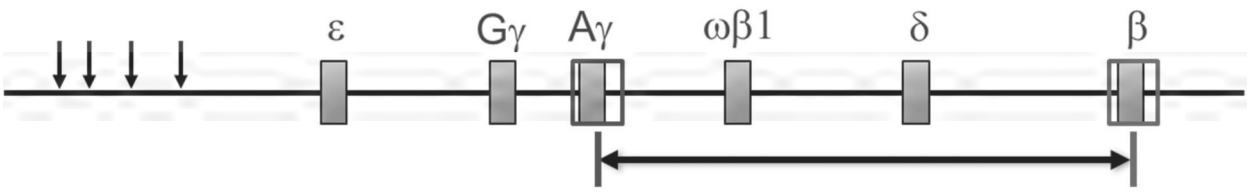


Figure 13B

Kenya

Guide	Sequence	SEQ ID NO	Location	Cut Site
HPFHK-02	gTCTTCAGCCTACAACATAC	SEQ ID NO: 122	Chr11:5248713-5248735	Chr11:5248719
HPFHK-10	gTGCCTAGTACATTACTATT	SEQ ID NO: 130	Chr11:5226235-5226257	Chr11:5226241
HPFHK-14	gACGAATGATTGCATCAGTG	SEQ ID NO: 134	Chr11:5226448-5226470	Chr11:5226454
HPFHK-17	gTTAAGTTCATGTCATAGGA	SEQ ID NO: 137	Chr11:5226507-5226529	Chr11:5226513

Figure 13C

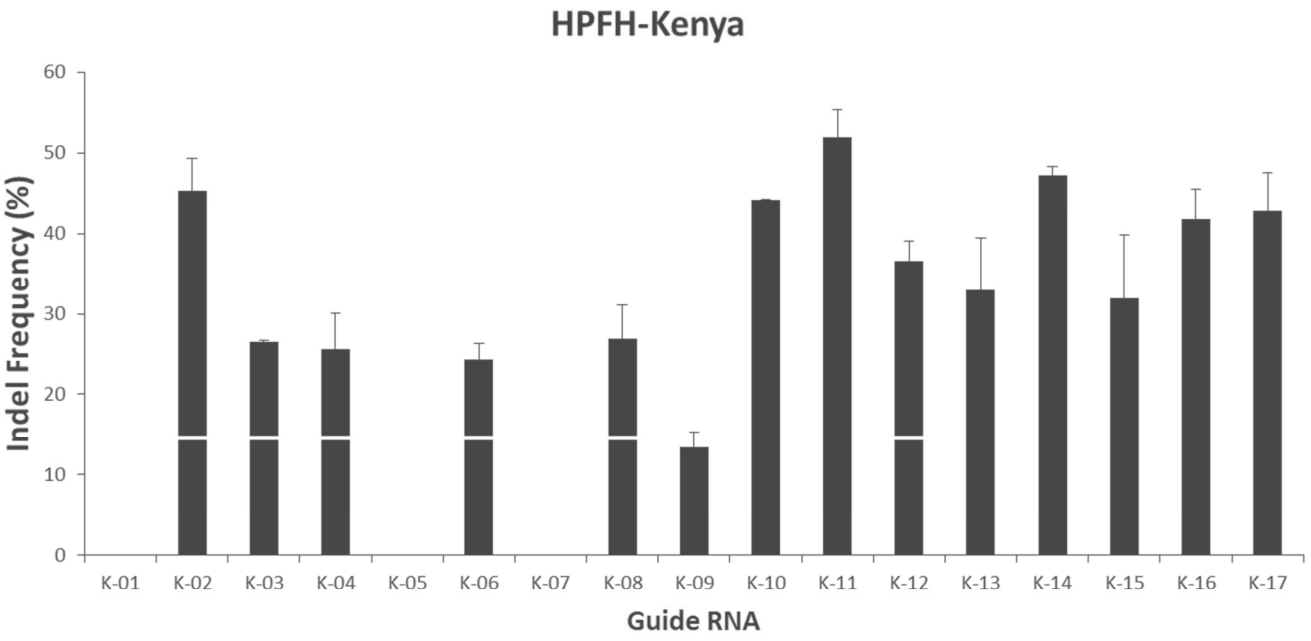
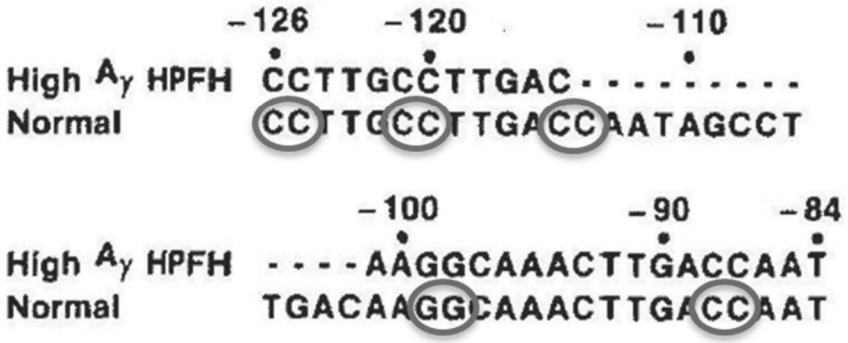


Figure 14

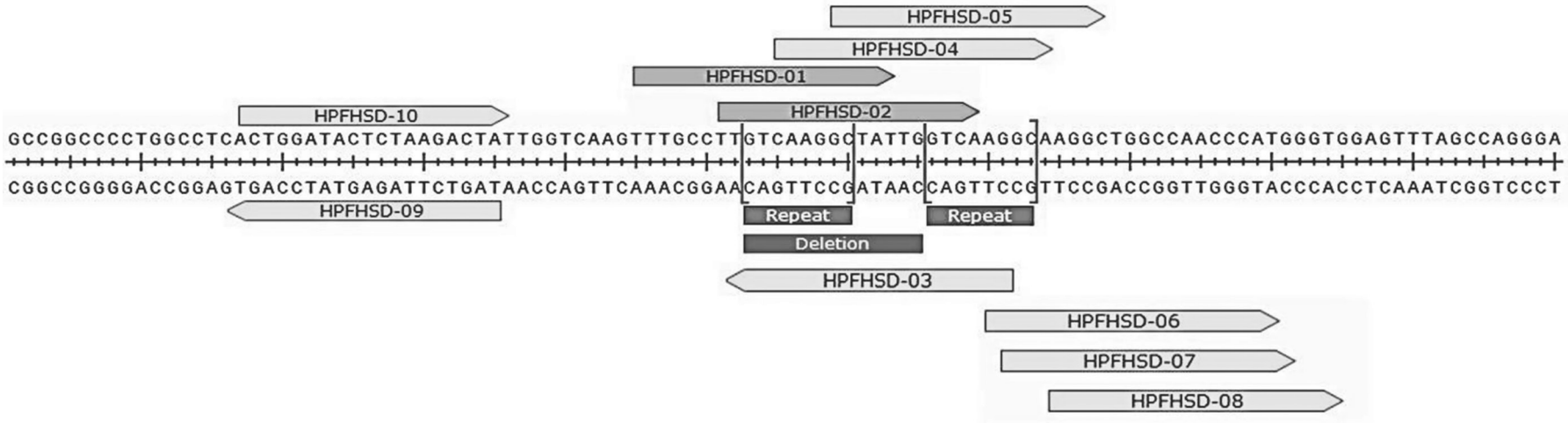
Figure 14A



High $^{A}\gamma$ HPFH (top panel) = SEQ ID NO: 176
Normal (top panel) = SEQ ID NO: 177
High $^{A}\gamma$ HPFH (bottom panel) = SEQ ID NO: 178
Normal (bottom panel) = SEQ ID NO: 179

Figure 14 (cont).

Figure 14B



top sequence = SEQ ID NO: 180

bottom sequence = SEQ ID NO: 181

Figure 14 (Cont.)

Figure 14C

Small Deletion					
Guide	**Sequence**	**Location**	**Cut Site**	**Location**	**Cut Site**
>HPFHSD_01	gTTTGCCTTGTCAAGGCTAT	Chr11:5249950-5249972	Chr11:5249966	Chr11:5254874-5254896	Chr11:5254890
>HPFHSD_02	gTTGTCAAGGCTATTGGTCA	Chr11:5249956-5249978	Chr11:5249972	Chr11:5254880-5254902	Chr11:5254896

HPFHSD_01 = SEQ ID NO: 138
HPFHSD_02 = SEQ ID NO: 139

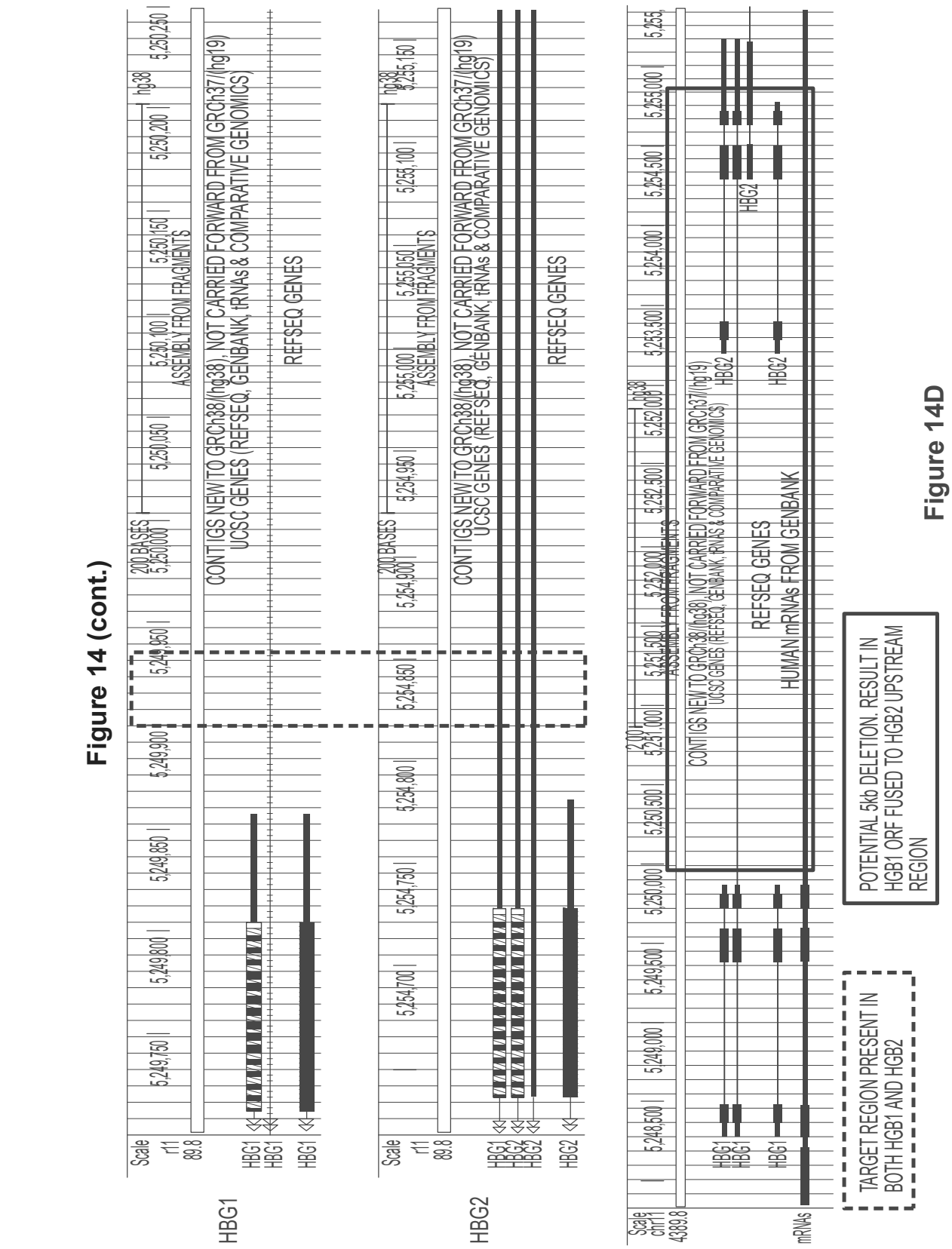

Figure 14 (cont.)
HBG1
HBG2
CONTIGS NEW TO GRCh38/(hg38), NOT CARRIED FORWARD FROM GRCh37/(hg19)
UCSC GENES (REFSEQ, GENBANK, tRNAs & COMPARATIVE GENOMICS)
ASSEMBLY FROM FRAGMENTS
REFSEQ GENES
200 BASES
HBG1
HBG2
mRNAs
HUMAN mRNAs FROM GENBANK
TARGET REGION PRESENT IN BOTH HGB1 AND HGB2
POTENTIAL 5kb DELETION. RESULT IN HGB1 ORF FUSED TO HGB2 UPSTREAM REGION
Figure 14D

Figure 15

Figure 15A

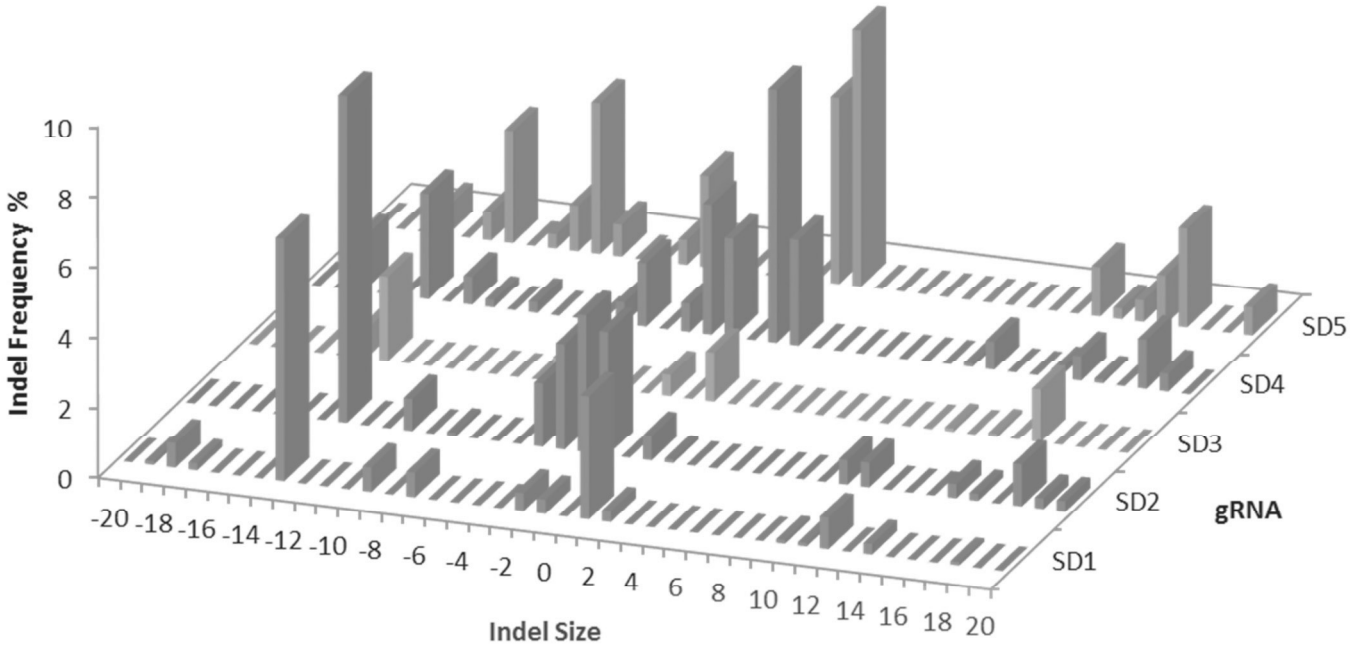


Figure 15B

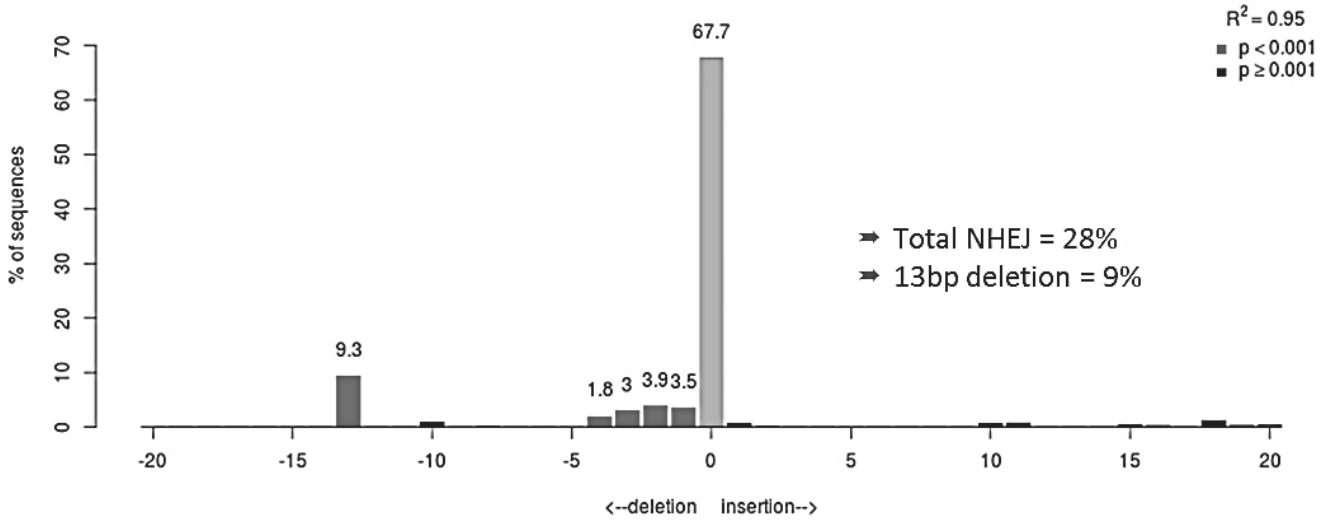


Figure 15 (cont.)

13bp Deletion

AAGACTATTGGTCAAGTTTGCCTT**GTCAAGGC**TATTG**GTCAAGGC**AAGGCTGGCCAACCCATGGGTGGAGTTTAG
AAGACTATTGGTCAAGTTTGCC:::TGGGTGGAGTTTAG
AAGACTATTGGTCAAGTTTGCCTT:::::::::::::GATCAAGGCAAGGCTGGCCAACCCATGGGTGGAGTTTAG
AAGACTATTGGTCAAGTTTGCCTT:::::::::::::GTCAAGGCAAGGCTGGCCAACCCATGGGTGGAGTTTAG
AAGACTATTGGTCAAGTTTGCCTA:::::::::::::GCTGGCCAACCCATGGGTGGAGTTTAG ➡ Alternative
AAGACTATTGGTCAAGTTTGCCTTGTCAAGGC:::::::::AAGGCAAGGCTGGCCAACCCATGGGTGGAGTTTAG "13bp deletion"
AAGACTATTGGTCAAGTTTGCCTTGTCAAGGCT::::::TCAAGGCAAGGCTGGCCAACCCATGGGTGGAGTTTAG
AAGACTATTGGTCAAGTTTGCCTTGTCAAGGCTATT:::CAAGGCAAGGCTGGCCAACCCATGGGTGGAGTTTAG
AAGACTATTGGTCAAGTTTGCCTTGTCAAGGCTATTGG:CAAGGCAAGGCTGGCCAACCCATGGGTGGAGTTTAG

First line = SEQ ID NO: 182
Second line = SEQ ID NO: 183
Third line = SEQ ID NO: 184
Fourth line = SEQ ID NO: 185
Fifth line = SEQ ID NO: 186
Sixth line = SEQ ID NO: 187
Seventh line = SEQ ID NO: 188
Eighth line = SEQ ID NO: 189
Ninth line = SEQ ID NO: 190

Figure 15C

Figure 16

Figure 16A

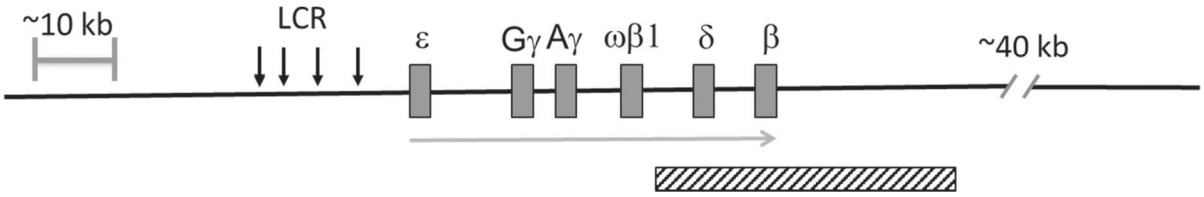


Figure 16B

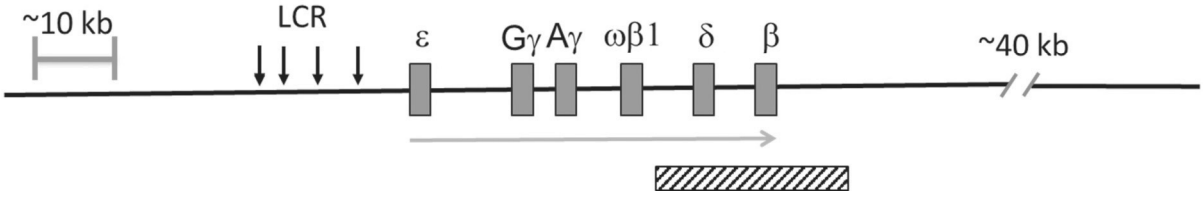


Figure 16C

ggggggcccctttccccacactatctcaatgcaaaTacctgtctgaaacggtccctggctaaactccacccatgggttgg

SEQ ID NO: 191