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Supplemental Information

CRISPR/Cas9 Editing of the Mutant Huntingtin Allele In Vitro and In Vivo

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Figure S1: List of SNP-dependent PAMs targeted by different CRISPR systems flanking *HTT* exon-1.

HD PROMOTER TARGETED SNPs

# Variant ID	Sequence Variation	Ref.Allele	Min. allele
rs35631490	GTCTGCGTCAGGGTTTCCTTCTTTT[C/G]CAGCCCCACCCCGCGTGCATCCCAC	C	G

SpCas9_WT (PAM Motif: NRG)

Ref. Allele:

```
                               CGGGGTGGGGCGCACGTAGG
5' GTCTGCGTCAGGGTTTCCTTCTTTTCCAGCCCCACCCCGCGTGCATCCCAC 3'
3' CAGACGCAGTCCCAAAGGAAGAAAAGGTCGGGGTGGGGCGCACGTAGGGTG 5'
                            PAM
```

Minor Allele

```
5' GTCTGCGTCAGGGTTTCCTTCTTTTGCAGCCCCACCCCGCGTGCATCCCAC 3'
3' CAGACGCAGTCCCAAAGGAAGAAAACGTCGGGGTGGGGCGCACGTAGGGTG 5'
```

SpCas9_VQR/EQR (PAM Motif: NGAN-NGNG/NGAG)

Ref. Allele:

```
                              TCGGGGTGGGGCGCACGTAG
5' GTCTGCGTCAGGGTTTCCTTCTTTTCCAGCCCCACCCCGCGTGCATCCCAC 3'
3' CAGACGCAGTCCCAAAGGAAGAAAAGGTCGGGGTGGGGCGCACGTAGGGTG 5'
                           PAM
```

Minor Allele

```
5' GTCTGCGTCAGGGTTTCCTTCTTTTGCAGCCCCACCCCGCGTGCATCCCAC 3'
3' CAGACGCAGTCCCAAAGGAAGAAAACGTCGGGGTGGGGCGCACGTAGGGTG 5'
```

SaCas9(NNGRRT/NNGRR):

Ref. Allele:

```
                               CGGGGTGGGGCGCACGTAGG
5' GTCTGCGTCAGGGTTTCCTTCTTTTCCAGCCCCACCCCGCGTGCATCCCAC 3'
3' CAGACGCAGTCCCAAAGGAAGAAAAGGTCGGGGTGGGGCGCACGTAGGGTG 5'
                           PAM
```

Minor Allele

```
5' GTCTGCGTCAGGGTTTCCTTCTTTTGCAGCCCCACCCCGCGTGCATCCCAC 3'
3' CAGACGCAGTCCCAAAGGAAGAAAACGTCGGGGTGGGGCGCACGTAGGGTG 5'
```

LbCpf1(TTTN/TTCN/CTTN/TCTN/ATTN/TCCN/…):

```
Ref. Allele:
                            PAM
5’ GTCTGCGTCAGGGTTTCCTTCTTTTCCAGCCCCACCCCGCGTGCATCCCAC 3’
3’ CAGACGCAGTCCCAAAGGAAGAAAAGGTCGGGGTGGGGCGCACGTAGGGTG 5’
                               GCCCCACCCCGCGTGCATCC
Minor Allele
5’ GTCTGCGTCAGGGTTTCCTTCTTTTGCAGCCCCACCCCGCGTGCATCCCAC 3’
3’ CAGACGCAGTCCCAAAGGAAGAAAACGTCGGGGTGGGGCGCACGTAGGGTG 5’
```

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# Variant ID	**Sequence Variation**	**Ref.Allele**	**Min. allele**
rs73086139	TCAAGGCCTCTTCTCTCTTCTCGGC[A/G]GGACAGGCACAGGCAGGTGGCCAGG	A	G

SpCas9_VQR/EQR (PAM Motif: NGAN-NGNG/NGAG)

```
Ref. Allele:
5’ TCAAGGCCTCTTCTCTCTTCTCGGCAGGACAGGCACAGGCAGGTGGCCAGG 3’
3’ AGTTCCGGAGAAGAGAGAAGAGCCGTCCTGTCCGTGTCCGTCCACCGGTCC 5’

Minor Allele:
                          PAM
5’ TCAAGGCCTCTTCTCTCTTCTCGGCGGGACAGGCACAGGCAGGTGGCCAGG 3’
3’ AGTTCCGGAGAAGAGAGAAGAGCCGCCCTGTCCGTGTCCGTCCACCGGTCC 5’
       GGCCTCTTCTCTCTTCTCG
```

SpCas9_VRER (PAM Motif: NGCG)

```
Ref. Allele:
5’ TCAAGGCCTCTTCTCTCTTCTCGGCAGGACAGGCACAGGCAGGTGGCCAGG 3’
3’ AGTTCCGGAGAAGAGAGAAGAGCCGTCCTGTCCGTGTCCGTCCACCGGTCC 5’

Minor Allele:
                          PAM
5’ TCAAGGCCTCTTCTCTCTTCTCGGCGGGACAGGCACAGGCAGGTGGCCAGG 3’
3’ AGTTCCGGAGAAGAGAGAAGAGCCGCCCTGTCCGTGTCCGTCCACCGGTCC 5’
```

```
       GGCCTCTTCTCTCTTCTCG


SaCas9(NNGRRT/NNGRR):
Ref. Allele:
5’ TCAAGGCCTCTTCTCTCTTCTCGGCAGGACAGGCACAGGCAGGTGGCCAGG
3’ AGTTCCGGAGAAGAGAGAAGAGCCGTCCTGTCCGTGTCCGTCCACCGGTCC

Minor Allele:
                           PAM
5’ TCAAGGCCTCTTCTCTCTTCTCGGCGGGACAGGCACAGGCAGGTGGCCAGG
3’ AGTTCCGGAGAAGAGAGAAGAGCCGCCCTGTCCGTGTCCGTCCACCGGTCC
       GGCCTCTTCTCTCTTCTCG

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# Variant ID      Sequence Variation                                            Ref.Allele        Min. allele
rs73086140        GCCAGGTGTCATGCTTAGCTCCCCG[C/G]CCAGTGAGATTCTTTCATTTAACAA           C                 G

SpCas9_WT (PAM Motif: NRG)
Ref. Allele:
                               TCACTCTAAGAAAGTAAATT
5’ GCCAGGTGTCATGCTTAGCTCCCCGCCCAGTGAGATTCTTTCATTTAACAA
3’ CGGTCCACAGTACGAATCGAGGGGCGGGTCACTCTAAGAAAGTAAATTGTT
                            PAM
Minor Allele:
                          PAM
5’ GCCAGGTGTCATGCTTAGCTCCCCGGCCAGTGAGATTCTTTCATTTAACAA
3’ CGGTCCACAGTACGAATCGAGGGGCCGGTCACTCTAAGAAAGTAAATTGTT
      AGGTGTCATGCTTAGCTCCC

SpCas9_VQR/EQR (PAM Motif: NGAN-NGNG/NGAG)
Ref. Allele:
                             GGTCACTCTAAGAAAGTAAATT
5’ GCCAGGTGTCATGCTTAGCTCCCCGCCCAGTGAGATTCTTTCATTTAACAA
3’ CGGTCCACAGTACGAATCGAGGGGCGGGTCACTCTAAGAAAGTAAATTGTT
                          PAM
Minor Allele:
```

```
5’ GCCAGGTGTCATGCTTAGCTCCCCGGCCAGTGAGATTCTTTCATTTAACAA
   CGGTCCACAGTACGAATCGAGGGGCCGGTCACTCTAAGAAAGTAAATTGTT
```

SpCas9_VRER (PAM Motif: NGCG)

Ref. Allele:

```
                             GGTCACTCTAAGAAAGTAAATT
5’ GCCAGGTGTCATGCTTAGCTCCCCGCCCAGTGAGATTCTTTCATTTAACAA
3’ CGGTCCACAGTACGAATCGAGGGGCGGGTCACTCTAAGAAAGTAAATTGTT
                          PAM
```

Minor Allele:

```
5’ GCCAGGTGTCATGCTTAGCTCCCCGGCCAGTGAGATTCTTTCATTTAACAA
   CGGTCCACAGTACGAATCGAGGGGCCGGTCACTCTAAGAAAGTAAATTGTT
```

==

# Variant ID	**Sequence Variation**	**Ref.Allele**	**Min. allele**
rs61791259	GATTACAGGCACCTGCCACCATGCC[C/T]GGCTAATTTTTGTATTTTTAGTTGA	C	T

SaCas9 (PAM Motif: NNGRRT)

Ref. Allele:

```
                               GATTAAAAACATAAAAATCA
5’ GATTACAGGCACCTGCCACCATGCCCGGCTAATTTTTGTATTTTTAGTTGA
3’ CTAATGTCCGTGGACGGTGGTACGGGCCGATTAAAAACATAAAAATCAACT
                          PAM
```

Minor Allele:

```
GATTACAGGCACCTGCCACCATGCCTGGCTAATTTTTGTATTTTTAGTTGA
CTAATGTCCGTGGACGGTGGTACGGACCGATTAAAAACATAAAAATCAACT
```

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# Variant ID	**Sequence Variation**	**Ref.Allele**	**Min. allele**
rs61792460	GAGGGTTTCATCTTGTTGGTCAGGC[A/G]GACTTGAACTCCTGACCTCAGGTGA	G	A

SpCas9_VQR/EQR (PAM Motif: NGAN-NGNG/NGAG)

Ref. Allele:

```
                       PAM
GAGGGTTTCATCTTGTTGGTCAGGCGGACTTGAACTCCTGACCTCAGGTGA
CTCCCAAAGTAGAACAACCAGTCCGCCTGAACTTGAGGACTGGAGTCCACT
   GGTTTCATCTTGTTGGTCAG
```

Minor Allele:

```
GAGGGTTTCATCTTGTTGGTCAGGCAGACTTGAACTCCTGACCTCAGGTGA
CTCCCAAAGTAGAACAACCAGTCCGTCTGAACTTGAGGACTGGAGTCCACT
```

SpCas9_VRER (PAM Motif: NGCG)
Ref. Allele:

```
                       PAM
GAGGGTTTCATCTTGTTGGTCAGGCGGACTTGAACTCCTGACCTCAGGTGA
CTCCCAAAGTAGAACAACCAGTCCGCCTGAACTTGAGGACTGGAGTCCACT
   GGTTTCATCTTGTTGGTCAG
```

Minor Allele:

```
GAGGGTTTCATCTTGTTGGTCAGGCAGACTTGAACTCCTGACCTCAGGTGA
CTCCCAAAGTAGAACAACCAGTCCGTCTGAACTTGAGGACTGGAGTCCACT
```

SaCas9(NNGRRT/NNGRR)
Ref. Allele:

```
                        PAM
GAGGGTTTCATCTTGTTGGTCAGGCGGACTTGAACTCCTGACCTCAGGTGA
CTCCCAAAGTAGAACAACCAGTCCGCCTGAACTTGAGGACTGGAGTCCACT
  GGGTTTCATCTTGTTGGTCAG
```

Minor Allele:

```
GAGGGTTTCATCTTGTTGGTCAGGCAGACTTGAACTCCTGACCTCAGGTGA
CTCCCAAAGTAGAACAACCAGTCCGTCTGAACTTGAGGACTGGAGTCCACT
```

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# Variant ID	**Sequence Variation**	**Ref.Allele**	**Min. allele**
rs73086145	GCTGTTTTTTCTTTAGAATGGGGGA[C/G]GTTATCAGGCTCTACATGGTGTGTA	C	G

SpCas9_WT (PAM Motif: NRG)
Ref. Allele:

```
GCTGTTTTTTCTTTAGAATGGGGGACGTTATCAGGCTCTACATGGTGTGTA
```

```
CGACAAAAAAGAAATCTTACCCCCTGCAATAGTCCGAGATGTACCACACAT



Minor Allele
                       PAM
GCTGTTTTTTCTTTAGAATGGGGGAGGTTATCAGGCTCTACATGGTGTGTA
CGACAAAAAAGAAATCTTACCCCCTCCAATAGTCCGAGATGTACCACACAT
   GTTTTTTCTTTAGAATGGGG

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# Variant ID      Sequence Variation                                            Ref.Allele        Min. allele
rs61792461        TCTACATGGTGTGTAGTCGGCTAGC[A/G]TGTTGTAAGCCTTTCCCTGTGTCAC                   A           G

SpCas9_VQR/EQR (PAM Motif: NGAN-NGNG/NGAG)
Ref. Allele:
TCTACATGGTGTGTAGTCGGCTAGCATGTTGTAAGCCTTTCCCTGTGTCAC
AGATGTACCACACATCAGCCGATCGTACAACATTCGGAAAGGGACACAGTG

Minor Allele
                       PAM
TCTACATGGTGTGTAGTCGGCTAGCGTGTTGTAAGCCTTTCCCTGTGTCAC
AGATGTACCACACATCAGCCGATCGCACAACATTCGGAAAGGGACACAGTG
   ACATGGTGTGTAGTCGGCTA

SpCas9_VRER (PAM Motif: NGCG)

Ref. Allele:
TCTACATGGTGTGTAGTCGGCTAGCATGTTGTAAGCCTTTCCCTGTGTCAC
AGATGTACCACACATCAGCCGATCGTACAACATTCGGAAAGGGACACAGTG

Minor Allele
                       PAM
TCTACATGGTGTGTAGTCGGCTAGCGTGTTGTAAGCCTTTCCCTGTGTCAC
AGATGTACCACACATCAGCCGATCGCACAACATTCGGAAAGGGACACAGTG
   ACATGGTGTGTAGTCGGCTA

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```

# Variant ID	Sequence Variation	Ref.Allele	Min. allele
rs61792462	CTGTGTCACAAGTGCTCATCTGGAA[C/G]AGGATTCTAATGACTGCCTGTGGCT	C	G

SpCas9_WT (PAM Motif: NRG)

```
Ref. Allele:
CTGTGTCACAAGTGCTCATCTGGAACAGGATTCTAATGACTGCCTGTGGCT
GACACAGTGTTCACGAGTAGACCTTGTCCTAAGATTACTGACGGACACCGA

Minor Allele
                       PAM
CTGTGTCACAAGTGCTCATCTGGAAGAGGATTCTAATGACTGCCTGTGGCT
GACACAGTGTTCACGAGTAGACCTTCTCCTAAGATTACTGACGGACACCGA
    GTCACAAGTGCTCATCTGG
```

SpCas9_VQR/EQR (PAM Motif: NGAN-NGNG/NGAG)

```
Ref. Allele:
CTGTGTCACAAGTGCTCATCTGGAACAGGATTCTAATGACTGCCTGTGGCT
GACACAGTGTTCACGAGTAGACCTTGTCCTAAGATTACTGACGGACACCGA

Minor Allele
                        PAM
CTGTGTCACAAGTGCTCATCTGGAAGAGGATTCTAATGACTGCCTGTGGCT
GACACAGTGTTCACGAGTAGACCTTCTCCTAAGATTACTGACGGACACCGA
    GTCACAAGTGCTCATCTGGA
```

SaCas9(NNGRRT/NNGRR)

```
Ref. Allele:
CTGTGTCACAAGTGCTCATCTGGAACAGGATTCTAATGACTGCCTGTGGCT
GACACAGTGTTCACGAGTAGACCTTGTCCTAAGATTACTGACGGACACCGA

Minor Allele
                        PAM
CTGTGTCACAAGTGCTCATCTGGAAGAGGATTCTAATGACTGCCTGTGGCT
GACACAGTGTTCACGAGTAGACCTTCTCCTAAGATTACTGACGGACACCGA
    GTCACAAGTGCTCATCTGG
```

LbCpf1(TTTN/TTCN/CTTN/TCTN/ATTN/TCCN/…)

```
Ref. Allele:
CTGTGTCACAAGTGCTCATCTGGAACAGGATTCTAATGACTGCCTGTGGCT
GACACAGTGTTCACGAGTAGACCTTGTCCTAAGATTACTGACGGACACCGA

Minor Allele
GACACAGTGTTCACGAGTAGACC
CTGTGTCACAAGTGCTCATCTGGAAGAGGATTCTAATGACTGCCTGTGGCT
GACACAGTGTTCACGAGTAGACCTTCTCCTAAGATTACTGACGGACACCGA
                       PAM
```

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# Variant ID	Sequence Variation	Ref.Allele	Min. allele
rs61090955	TCATTTTATGTGATTCCTTTCTAGA[A/G]GTACTACTCATTACTTCTGCTTGCA	A	G

SpCas9_WT (PAM Motif: NRG)

```
Ref. Allele:
TCATTTTATGTGATTCCTTTCTAGAAGTACTACTCATTACTTCTGCTTGCA
AGTAAAATACACTAAGGAAAGATCTTCATGATGAGTAATGAAGACGAACGT

Minor Allele
                       PAM
TCATTTTATGTGATTCCTTTCTAGAGGTACTACTCATTACTTCTGCTTGCA
AGTAAAATACACTAAGGAAAGATCTCCATGATGAGTAATGAAGACGAACGT
   TTTTATGTGATTCCTTTCTA
```

LbCpf1(TTTN/TTCN/CTTN/TCTN/ATTN/TCCN/…)

```
Ref. Allele:
 GTAAAATACACTAAGGAAAGA
TCATTTTATGTGATTCCTTTCTAGAAGTACTACTCATTACTTCTGCTTGCA
AGTAAAATACACTAAGGAAAGATCTTCATGATGAGTAATGAAGACGAACGT
                      PAM
Minor Allele
TCATTTTATGTGATTCCTTTCTAGAGGTACTACTCATTACTTCTGCTTGCA
```

```
AGTAAAATACACTAAGGAAAGATCTCCATGATGAGTAATGAAGACGAACGT

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# Variant ID      Sequence Variation                                                Ref.Allele        Min. allele
rs77384845  TAGCTGAAGGAAGGACAGGGACTGT[C/T]ATACACTAGCTAAGAGGCAAACTGC                  C                 T

SpCas9_VQR/EQR (PAM Motif: NGAN-NGNG/NGAG)
Ref. Allele:
                           ATGTGATCGATTCTCCG
TAGCTGAAGGAAGGACAGGGACTGTCATACACTAGCTAAGAGGCAAACTGC
ATCGACTTCCTTCCTGTCCCTGACAGTATGTGATCGATTCTCCGTTTGACG
                        PAM
Minor Allele
TAGCTGAAGGAAGGACAGGGACTGTTATACACTAGCTAAGAGGCAAACTGC
ATCGACTTCCTTCCTGTCCCTGACAATATGTGATCGATTCTCCGTTTGACG

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# Variant ID      Sequence Variation                                                Ref.Allele        Min. allele
rs61792464  TCCCTCATTCAGGTTGATGTCCTAA[C/G]CCCCAGAACCTCAGAATGGGATTGT                        G                 C

SpCas9_WT (PAM Motif: NRG)
Ref. Allele:
                            GGTCTTGGAGTCTTACCCTA
TCCCTCATTCAGGTTGATGTCCTAACCCCCAGAACCTCAGAATGGGATTGT
AGGGAGTAAGTCCAACTACAGGATTGGGGGTCTTGGAGTCTTACCCTAACA
                         PAM
Minor Allele           PAM
TCCCTCATTCAGGTTGATGTCCTAAGCCCCAGAACCTCAGAATGGGATTGT
AGGGAGTAAGTCCAACTACAGGATTCGGGGTCTTGGAGTCTTACCCTAACA
    TCATTCAGGTTGATGTCCT

LbCpf1(TTTN/TTCN/CTTN/TCTN/ATTN/TCCN/…)
Ref. Allele:
TCCCTCATTCAGGTTGATGTCCTAACCCCCAGAACCTCAGAATGGGATTGT
AGGGAGTAAGTCCAACTACAGGATTGGGGGTCTTGGAGTCTTACCCTAACA

Minor Allele
```

```
GGAGTAAGTCCAACTACAGG
TCCCTCATTCAGGTTGATGTCCTAAGCCCCAGAACCTCAGAATGGGATTGT
AGGGAGTAAGTCCAACTACAGGATTCGGGGTCTTGGAGTCTTACCCTAACA
                      PAM
===========================================================================================================

# Variant ID      Sequence Variation                                          Ref.Allele        Min. allele
rs112435590 TCCATGCCAAGAAGGCAACAGAGAG[G/T]GCCAGGGAGACTGAAGTCATACCCT           G                 T

SpCas9_WT (PAM Motif: NRG)
Ref. Allele:
                       PAM
TCCATGCCAAGAAGGCAACAGAGAGGGCCAGGGAGACTGAAGTCATACCCT
AGGTACGGTTCTTCCGTTGTCTCTCCCGGTCCCTCTGACTTCAGTATGGGA
   ATGCCAAGAAGGCAACAGAG

Minor Allele
TCCATGCCAAGAAGGCAACAGAGAGTGCCAGGGAGACTGAAGTCATACCCT
AGGTACGGTTCTTCCGTTGTCTCTCACGGTCCCTCTGACTTCAGTATGGGA

SaCas9(NNGRRT/NNGRR)
Ref. Allele:
                     PAM
TCCATGCCAAGAAGGCAACAGAGAGGGCCAGGGAGACTGAAGTCATACCCT
AGGTACGGTTCTTCCGTTGTCTCTCCCGGTCCCTCTGACTTCAGTATGGGA
TCCATGCCAAGAAGGCAACA
Minor Allele
                     PAM
TCCATGCCAAGAAGGCAACAGAGAGTGCCAGGGAGACTGAAGTCATACCCT
AGGTACGGTTCTTCCGTTGTCTCTCACGGTCCCTCTGACTTCAGTATGGGA
TCCATGCCAAGAAGGCAACA
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# Variant ID      Sequence Variation                                          Ref.Allele        Min. allele
rs111670395 CCCAGGTTCAAGCAATTCTGCCTCA[A/G]CCTCCGGAATAGCTGGGACTACAGG     G     A

SpCas9_WT (PAM Motif: NRG)
Ref. Allele:
                       PAM
```

```
CCCAGGTTCAAGCAATTCTGCCTCAGCCTCCGGAATAGCTGGGACTACAGG
GGGTCCAAGTTCGTTAAGACGGAGTCGGAGGCCTTATCGACCCTGATGTCC
    GGTTCAAGCAATTCTGCCT

Minor Allele
CCCAGGTTCAAGCAATTCTGCCTCAACCTCCGGAATAGCTGGGACTACAGG
GGGTCCAAGTTCGTTAAGACGGAGTTGGAGGCCTTATCGACCCTGATGTCC

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# Variant ID      Sequence Variation                                          Ref.Allele        Min. allele
rs9996199   TGTGGCCTGGCTAAAGTAGGCTTTA[C/G]TGGGCTCCTCTCTGCCTGCATCACC                 C                 G

SpCas9_WT (PAM Motif: NRG)
Ref. Allele:
                            CCGAGGAGAGACGGACG
TGTGGCCTGGCTAAAGTAGGCTTTACTGGGCTCCTCTCTGCCTGCATCACC
ACACCGGACCGATTTCATCCGAAATGACCCGAGGAGAGACGGACGTAGTGG
                         PAM
Minor Allele
                       PAM
TGTGGCCTGGCTAAAGTAGGCTTTAGTGGGCTCCTCTCTGCCTGCATCACC
ACACCGGACCGATTTCATCCGAAATCACCCGAGGAGAGACGGACGTAGTGG
   GGCCTGGCTAAAGTAGGCTT

===========================================================================================================

# Variant ID      Sequence Variation                                          Ref.Allele        Min. allele
rs28431418  CTCCCCGCAGGGCTGTCCGGGTGAG[C/T]ATGGCTCTGGCCACGGGCCAGTGTG     T     C

SaCas9(NNGRRT/NNGRR)
Ref. Allele:
                     PAM
CTCCCCGCAGGGCTGTCCGGGTGAGTATGGCTCTGGCCACGGGCCAGTGTG
GAGGGGCGTCCCGACAGGCCCACTCATACCGAGACCGGTGCCCGGTCACAC
 TCCCCGCAGGGCTGTCCGG

Minor Allele         PAM
CTCCCCGCAGGGCTGTCCGGGTGAGCATGGCTCTGGCCACGGGCCAGTGTG
```

```
GAGGGGCGTCCCGACAGGCCCACTCGTACCGAGACCGGTGCCCGGTCACAC
TCCCCGCAGGGCTGTCCGG
```

```
=============================================================================================================
```

# Variant ID	Sequence Variation	Ref.Allele	Min. allele
rs2857935	GGGCGCAGGCCCATGCGGAAAGGAT[A/C/G]CCCCGCCGACGCCTGGAGCGGGGCG	G	C/T (Rev Strand)

SpCas9_WT (PAM Motif: NRG)

```
Ref. Allele:
                            GGCGGCTGCGGACCTCG
GGGCGCAGGCCCATGCGGAAAGGATCCCCCGCCGACGCCTGGAGCGGGGCG
CCCGCGTCCGGGTACGCCTTTCCTAGGGGGCGGCTGCGGACCTCGCCCCGC
                         PAM
Minor Allele
GGGCGCAGGCCCATGCGGAAAGGATGCCCCGCCGACGCCTGGAGCGGGGCG
CCCGCGTCCGGGTACGCCTTTCCTACGGGGCGGCTGCGGACCTCGCCCCGC
```

SpCas9_VQR/EQR (PAM Motif: NGAN-NGNG/NGAG)

```
Ref. Allele:
                          GGGGCGGCTGCGGACCTCG
GGGCGCAGGCCCATGCGGAAAGGATCCCCCGCCGACGCCTGGAGCGGGGCG
CCCGCGTCCGGGTACGCCTTTCCTAGGGGGCGGCTGCGGACCTCGCCCCGC
                       PAM
Minor Allele
GGGCGCAGGCCCATGCGGAAAGGATGCCCCGCCGACGCCTGGAGCGGGGCG
CCCGCGTCCGGGTACGCCTTTCCTACGGGGCGGCTGCGGACCTCGCCCCGC
```

SaCas9(NNGRRT/NNGRR)

```
Ref. Allele:                   GGCTGCGGACCTCGCCCCG
GGGCGCAGGCCCATGCGGAAAGGATCCCCCGCCGACGCCTGGAGCGGGGCG
CCCGCGTCCGGGTACGCCTTTCCTAGGGGGCGGCTGCGGACCTCGCCCCGC
                           PAM
Minor Allele                   GGCTGCGGACCTCGCCCCG
GGGCGCAGGCCCATGCGGAAAGGATACCCCGCCGACGCCTGGAGCGGGGCG
CCCGCGTCCGGGTACGCCTTTCCTATGGGGCGGCTGCGGACCTCGCCCCGC
                           PAM
```

LbCpf1(TTTN/TTCN/CTTN/TCTN/ATTN/TCCN/…):

```
Ref. Allele:
                        PAM
GGGCGCAGGCCCATGCGGAAAGGATCCCCCGCCGACGCCTGGAGCGGGGCG
CCCGCGTCCGGGTACGCCTTTCCTAGGGGGCGGCTGCGGACCTCGCCCCGC
                            CCGCCGACGCCTGGAGCGGG
Minor Allele
GGGCGCAGGCCCATGCGGAAAGGATACCCCGCCGACGCCTGGAGCGGGGCG
CCCGCGTCCGGGTACGCCTTTCCTATGGGGCGGCTGCGGACCTCGCCCCGC

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# Variant ID      Sequence Variation                                          Ref.Allele        Min. allele
rs149624523 CCCCGCCCCGGCCTCGCCACGCCCC[C/T]ACCTCACCACGCCCCCCGCATCGCC     T     C
```

SaCas9(NNGRRT/NNGRR)

```
Ref. Allele:
CCCCGCCCCGGCCTCGCCACGCCCCTACCTCACCACGCCCCCCGCATCGCC
GGGGCGGGGCCGGAGCGGTGCGGGGATGGAGTGGTGCGGGGGGCGTAGCGG

Minor Allele
                            GAGTGGTGCGGGGGGCGTAG
CCCCGCCCCGGCCTCGCCACGCCCCCACCTCACCACGCCCCCCGCATCGCC
GGGGCGGGGCCGGAGCGGTGCGGGGGTGGAGTGGTGCGGGGGGCGTAGCGG
                        PAM

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# Variant ID      Sequence Variation                                          Ref.Allele        Min. allele
rs13122415  attacagtctcaccacgccccgtcc[C/G]CTCTCCGTTGAGCCCCGCGCCTTCG     C     G
```

SpCas9_WT (PAM Motif: NRG)

```
Ref. Allele:
                            GAGGCAACTCGGGGCGCGG
ATTACAGTCTCACCACGCCCCGTCCCCTCTCCGTTGAGCCCCGCGCCTTCG
```

```
TAATGTCAGAGTGGTGCGGGGCAGGGGAGAGGCAACTCGGGGCGCGGAAGC
                         PAM
```

```
Minor Allele
ATTACAGTCTCACCACGCCCCGTCCGCTCTCCGTTGAGCCCCGCGCCTTCG
TAATGTCAGAGTGGTGCGGGGCAGGCGAGAGGCAACTCGGGGCGCGGAAGC
```

SpCas9_VQR/EQR (PAM Motif: NGAN-NGNG/NGAG)

```
Ref. Allele:
ATTACAGTCTCACCACGCCCCGTCCCCTCTCCGTTGAGCCCCGCGCCTTCG
TAATGTCAGAGTGGTGCGGGGCAGGGGAGAGGCAACTCGGGGCGCGGAAGC
```

```
Minor Allele
                           AGAGGCAACTCGGGGCG
ATTACAGTCTCACCACGCCCCGTCCGCTCTCCGTTGAGCCCCGCGCCTTCG
TAATGTCAGAGTGGTGCGGGGCAGGCGAGAGGCAACTCGGGGCGCGGAAGC
                        PAM
```

SpCas9_VRER (PAM Motif: NGCG)

```
Ref. Allele:
ATTACAGTCTCACCACGCCCCGTCCCCTCTCCGTTGAGCCCCGCGCCTTCG
TAATGTCAGAGTGGTGCGGGGCAGGGGAGAGGCAACTCGGGGCGCGGAAGC
```

```
Minor Allele
                           AGAGGCAACTCGGGGCG
ATTACAGTCTCACCACGCCCCGTCCGCTCTCCGTTGAGCCCCGCGCCTTCG
TAATGTCAGAGTGGTGCGGGGCAGGCGAGAGGCAACTCGGGGCGCGGAAGC
                        PAM
```

SaCas9(NNGRRT/NNGRR)

```
Ref. Allele:
                            GAGGCAACTCGGGGCG
ATTACAGTCTCACCACGCCCCGTCCCCTCTCCGTTGAGCCCCGCGCCTTCG
TAATGTCAGAGTGGTGCGGGGCAGGGGAGAGGCAACTCGGGGCGCGGAAGC
                        PAM
```

```
Minor Allele
ATTACAGTCTCACCACGCCCCGTCCGCTCTCCGTTGAGCCCCGCGCCTTCG
TAATGTCAGAGTGGTGCGGGGCAGGCGAGAGGCAACTCGGGGCGCGGAAGC

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# Variant ID      Sequence Variation                                                Ref.Allele        Min. allele
rs113331544 GGCCTTGCTGTGTGAGGCAGAACCT[-/GCGGGG]GCGGGGGCAGGGGCGGGCTGGTTCC      -     insGCGGGG

SpCas9_VQR/EQR (PAM Motif: NGAN-NGNG/NGAG)
Ref. Allele:
                         PAM
GGCCTTGCTGTGTGAGGCAGAACCTGCGGGGGCAGGGGCGGGCTGGTTCC
CCGGAACGACACACTCCGTCTTGGACGCCCCCGTCCCCGCCCGACCAAGG
      GCTGTGTGAGGCAGAACCT
Minor Allele
                               PAM
GGCCTTGCTGTGTGAGGCAGAACCTGCGGGGGCGGGGGCAGGGGCGGGCTGGTTCC
CCGGAACGACACACTCCGTCTTGGACGCCCCCGCCCCCGTCCCCGCCCGACCAAGG
           GTGAGGCAGAACCTGCGGGG

SpCas9_VRER (PAM Motif: NGCG)
Ref. Allele:
                         PAM
GGCCTTGCTGTGTGAGGCAGAACCTGCGGGGGCAGGGGCGGGCTGGTTCC
CCGGAACGACACACTCCGTCTTGGACGCCCCCGTCCCCGCCCGACCAAGG
      GCTGTGTGAGGCAGAACCT
Minor Allele
                               PAM
GGCCTTGCTGTGTGAGGCAGAACCTGCGGGGGCGGGGGCAGGGGCGGGCTGGTTCC
CCGGAACGACACACTCCGTCTTGGACGCCCCCGCCCCCGTCCCCGCCCGACCAAGG
           GTGAGGCAGAACCTGCGGGG
===========================================================================================================

# Variant ID      Sequence Variation                                                Ref.Allele        Min. allele
rs13132932  TGTGTGAGGCAGAACCTGCGGGGGC[A/G]GGGGCGGGCTGGTTCCCTGGCCAGC                 A                 G


SpCas9_VQR/EQR (PAM Motif: NGAN-NGNG/NGAG)
```

```
Ref. Allele:
TGTGTGAGGCAGAACCTGCGGGGGCAGGGGCGGGCTGGTTCCCTGGCCAGC
ACACACTCCGTCTTGGACGCCCCCGTCCCCGCCCGACCAAGGGACCGGTCG

Minor Allele
                       PAM
TGTGTGAGGCAGAACCTGCGGGGGCGGGGGCGGGCTGGTTCCCTGGCCAGC
ACACACTCCGTCTTGGACGCCCCCGCCCCCGCCCGACCAAGGGACCGGTCG
     GAGGCAGAACCTGCGGGG
```

SpCas9_VRER (PAM Motif: NGCG)

```
Ref. Allele:
TGTGTGAGGCAGAACCTGCGGGGGCAGGGGCGGGCTGGTTCCCTGGCCAGC
ACACACTCCGTCTTGGACGCCCCCGTCCCCGCCCGACCAAGGGACCGGTCG

Minor Allele
                       PAM
TGTGTGAGGCAGAACCTGCGGGGGCGGGGGCGGGCTGGTTCCCTGGCCAGC
ACACACTCCGTCTTGGACGCCCCCGCCCCCGCCCGACCAAGGGACCGGTCG
     GAGGCAGAACCTGCGGGG
```

SaCas9(NNGRRT/NNGRR)

```
Ref. Allele:
TGTGTGAGGCAGAACCTGCGGGGGCAGGGGCGGGCTGGTTCCCTGGCCAGC
ACACACTCCGTCTTGGACGCCCCCGTCCCCGCCCGACCAAGGGACCGGTCG

Minor Allele            PAM
TGTGTGAGGCAGAACCTGCGGGGGCGGGGGCGGGCTGGTTCCCTGGCCAGC
ACACACTCCGTCTTGGACGCCCCCGCCCCCGCCCGACCAAGGGACCGGTCG
   GTGAGGCAGAACCTGCGGGG
```

==

# Variant ID	**Sequence Variation**	**Ref.Allele**	**Min. allele**
rs13102260	AGCGTCTGGGACGCAAGGCGCCGTG[A/G]GGGCTGCCGGGACGGGTCCAAGATG	G	A

SpCas9_WT (PAM Motif: NRG)

```
Ref. Allele:
                       PAM
```

```
AGCGTCTGGGACGCAAGGCGCCGTGGGGGCTGCCGGGACGGGTCCAAGATG
TCGCAGACCCTGCGTTCCGCGGCACCCCCGACGGCCCTGCCCAGGTTCTAC
   GTCTGGGACGCAAGGCGCCG
```

```
Minor Allele
AGCGTCTGGGACGCAAGGCGCCGTGAGGGCTGCCGGGACGGGTCCAAGATG
TCGCAGACCCTGCGTTCCGCGGCACTCCCGACGGCCCTGCCCAGGTTCTAC
```

SpCas9_VQR/EQR (PAM Motif: NGAN-NGNG/NGAG)

```
Ref. Allele:
AGCGTCTGGGACGCAAGGCGCCGTGGGGGCTGCCGGGACGGGTCCAAGATG
TCGCAGACCCTGCGTTCCGCGGCACCCCCGACGGCCCTGCCCAGGTTCTAC
```

```
Minor Allele
                       PAM
AGCGTCTGGGACGCAAGGCGCCGTGAGGGCTGCCGGGACGGGTCCAAGATG
TCGCAGACCCTGCGTTCCGCGGCACTCCCGACGGCCCTGCCCAGGTTCTAC
   GTCTGGGACGCAAGGCGCCG
```

SaCas9(NNGRRT/NNGRR)

```
Ref. Allele:
                         PAM
AGCGTCTGGGACGCAAGGCGCCGTGGGGGCTGCCGGGACGGGTCCAAGATG
TCGCAGACCCTGCGTTCCGCGGCACCCCCGACGGCCCTGCCCAGGTTCTAC
 GCGTCTGGGACGCAAGGCGCCG
```

```
Minor Allele
AGCGTCTGGGACGCAAGGCGCCGTGAGGGCTGCCGGGACGGGTCCAAGATG
TCGCAGACCCTGCGTTCCGCGGCACTCCCGACGGCCCTGCCCAGGTTCTAC
```

```
===========================================================================================================
```

# Variant ID	Sequence Variation		Ref.Allele	Min. allele
rs10009935	CTCACTTGGGTCTTCCCTTGTCCTC[C/T]CGCGAGGGGAGGCAGAGCCTTGTTG	T	C	

SpCas9_WT (PAM Motif: NRG)

Ref. Allele:

```
CTCACTTGGGTCTTCCCTTGTCCTCTCGCGAGGGGAGGCAGAGCCTTGTTG
GAGTGAACCCAGAAGGGAACAGGAGAGCGCTCCCCTCCGTCTCGGAACAAC
```

Minor Allele

```
                            GCTCCCCTCCGTCTCGG
CTCACTTGGGTCTTCCCTTGTCCTCCCGCGAGGGGAGGCAGAGCCTTGTTG
GAGTGAACCCAGAAGGGAACAGGAGGGCGCTCCCCTCCGTCTCGGAACAAC
                         PAM
```

SpCas9_VQR/EQR (PAM Motif: NGAN-NGNG/NGAG)

Ref. Allele:

```
                           CGCTCCCCTCCGTCTCGG
CTCACTTGGGTCTTCCCTTGTCCTCTCGCGAGGGGAGGCAGAGCCTTGTTG
GAGTGAACCCAGAAGGGAACAGGAGAGCGCTCCCCTCCGTCTCGGAACAAC
                        PAM
```

Minor Allele

```
CTCACTTGGGTCTTCCCTTGTCCTCCCGCGAGGGGAGGCAGAGCCTTGTTG
GAGTGAACCCAGAAGGGAACAGGAGGGCGCTCCCCTCCGTCTCGGAACAAC
```

SaCas9(NNGRRT/NNGRR)

Ref. Allele:

```
CTCACTTGGGTCTTCCCTTGTCCTCTCGCGAGGGGAGGCAGAGCCTTGTTG
GAGTGAACCCAGAAGGGAACAGGAGAGCGCTCCCCTCCGTCTCGGAACAAC
```

Minor Allele

```
                            GCTCCCCTCCGTCTCGGAA
CTCACTTGGGTCTTCCCTTGTCCTCCCGCGAGGGGAGGCAGAGCCTTGTTG
GAGTGAACCCAGAAGGGAACAGGAGGGCGCTCCCCTCCGTCTCGGAACAAC
                       PAM
```

# Variant ID	**Sequence Variation**	**Ref.Allele**	**Min. allele**
rs58870770	TGAATGAGTTGTGGTTGCCAAGTAA[-/A]GTGGTGAACTTACGTGGTGATTAAT	A	delA

LbCpf1(TTTN/TTCN/CTTN/TCTN/ATTN/TCCN/…):

Ref. Allele:

CTTACTCAACACCAACGGTTC

```
TGAATGAGTTGTGGTTGCCAAGTAAAGTGGTGAACTTACGTGGTGATTAAT
ACTTACTCAACACCAACGGTTCATTTCACCACTTGAATGCACCACTAATTA
                      PAM


Minor Allele
TGAATGAGTTGTGGTTGCCAAGTAAGTGGTGAACTTACGTGGTGATTAAT
ACTTACTCAACACCAACGGTTCATTCACCACTTGAATGCACCACTAATTA

AsCpf1(TTTN)
Ref. Allele:
 CTTACTCAACACCAACGGTTC
TGAATGAGTTGTGGTTGCCAAGTAAAGTGGTGAACTTACGTGGTGATTAAT
ACTTACTCAACACCAACGGTTCATTTCACCACTTGAATGCACCACTAATTA
                      PAM
Minor Allele
TGAATGAGTTGTGGTTGCCAAGTAAGTGGTGAACTTACGTGGTGATTAAT
ACTTACTCAACACCAACGGTTCATTCACCACTTGAATGCACCACTAATTA

===========================================================================================================

# Variant ID      Sequence Variation                                          Ref.Allele        Min. allele
rs28571971  ACAGTAGGAGTTAGGAAGTACTCTG[C/G]TGCAGTTCAGGCCTTTCTCTTACCT    G     C

SpCas9_WT (PAM Motif: NRG)
Ref. Allele:           PAM
ACAGTAGGAGTTAGGAAGTACTCTGGGTGCAGTTCAGGCCTTTCTCTTACCT
TGTCATCCTCAATCCTTCATGAGACCACGTCAAGTCCGGAAAGAGAATGGA
      GGAGTTAGGAAGTACTC
Minor Allele:
                            GTCAAGTCCGGAAAGAGAATGG
ACAGTAGGAGTTAGGAAGTACTCTGCTGCAGTTCAGGCCTTTCTCTTACCT
TGTCATCCTCAATCCTTCATGAGACGACGTCAAGTCCGGAAAGAGAATGGA
                         PAM
===========================================================================================================

# Variant ID      Sequence Variation                                          Ref.Allele        Min. allele
rs28583447  CAGTAGGAGTTAGGAAGTACTCTGG[C/T]GCAGTTCAGGCCTTTCTCTTACCTC           T                 C
```

SpCas9_VQR/EQR (PAM Motif: NGAN-NGNG/NGAG)

```
Ref. Allele:
CAGTAGGAGTTAGGAAGTACTCTGGTGCAGTTCAGGCCTTTCTCTTACCTC
GTCATCCTCAATCCTTCATGAGACCACGTCAAGTCCGGAAAGAGAATGGAG


Minor Allele:               TCAAGTCCGGAAAGAGAATG
CAGTAGGAGTTAGGAAGTACTCTGGCGCAGTTCAGGCCTTTCTCTTACCTC
GTCATCCTCAATCCTTCATGAGACCGCGTCAAGTCCGGAAAGAGAATGGAG
                         PAM
```

SpCas9_VRER (PAM Motif: NGCG)

```
Ref. Allele:
CAGTAGGAGTTAGGAAGTACTCTGGTGCAGTTCAGGCCTTTCTCTTACCTC
GTCATCCTCAATCCTTCATGAGACCACGTCAAGTCCGGAAAGAGAATGGAG

Minor Allele:           PAM
CAGTAGGAGTTAGGAAGTACTCTGGCGCAGTTCAGGCCTTTCTCTTACCTC
GTCATCCTCAATCCTTCATGAGACCGCGTCAAGTCCGGAAAGAGAATGGAG
     GGAGTTAGGAAGTACTCTG

Minor Allele:               TCAAGTCCGGAAAGAGAATG
CAGTAGGAGTTAGGAAGTACTCTGGCGCAGTTCAGGCCTTTCTCTTACCTC
GTCATCCTCAATCCTTCATGAGACCGCGTCAAGTCCGGAAAGAGAATGGAG
                         PAM
```

===

# Variant ID	**Sequence Variation**	**Ref.Allele**	**Min. allele**
rs28468636	TCTCTTACCTCTCAGTATTCTATTT[C/G]CGATCTGGATGTGTCCCAGATGGCA	C	G

SpCas9_WT (PAM Motif: NRG)

```
Ref. Allele:                TAGACCTACACAGGGTCTA
TCTCTTACCTCTCAGTATTCTATTTCCGATCTGGATGTGTCCCAGATGGCA
AGAGAATGGAGAGTCATAAGATAAAGGCTAGACCTACACAGGGTCTACCGT
                         PAM

Minor Allele
TCTCTTACCTCTCAGTATTCTATTTGCGATCTGGATGTGTCCCAGATGGCA
```

```
AGAGAATGGAGAGTCATAAGATAAACGCTAGACCTACACAGGGTCTACCGT
```

SpCas9_VQR/EQR (PAM Motif: NGAN-NGNG/NGAG)

```
Ref. Allele:
TCTCTTACCTCTCAGTATTCTATTTCCGATCTGGATGTGTCCCAGATGGCA
AGAGAATGGAGAGTCATAAGATAAAGGCTAGACCTACACAGGGTCTACCGT

Minor Allele             PAM
TCTCTTACCTCTCAGTATTCTATTTGCGATCTGGATGTGTCCCAGATGGCA
AGAGAATGGAGAGTCATAAGATAAACGCTAGACCTACACAGGGTCTACCGT
      ACCTCTCAGTATTCTATTT
```

SpCas9_VRER (PAM Motif: NGCG)

```
Ref. Allele:
TCTCTTACCTCTCAGTATTCTATTTCCGATCTGGATGTGTCCCAGATGGCA
AGAGAATGGAGAGTCATAAGATAAAGGCTAGACCTACACAGGGTCTACCGT

Minor Allele             PAM
TCTCTTACCTCTCAGTATTCTATTTGCGATCTGGATGTGTCCCAGATGGCA
AGAGAATGGAGAGTCATAAGATAAACGCTAGACCTACACAGGGTCTACCGT
      ACCTCTCAGTATTCTATTT
```

SaCas9(NNGRRT/NNGRR):

```
Ref. Allele:                TAGACCTACACAGGGTCTA
TCTCTTACCTCTCAGTATTCTATTTCCGATCTGGATGTGTCCCAGATGGCA
AGAGAATGGAGAGTCATAAGATAAAGGCTAGACCTACACAGGGTCTACCGT
                        PAM

Minor Allele
TCTCTTACCTCTCAGTATTCTATTTGCGATCTGGATGTGTCCCAGATGGCA
AGAGAATGGAGAGTCATAAGATAAACGCTAGACCTACACAGGGTCTACCGT
```

LbCpf1(TTTN/TTCN/CTTN/TCTN/ATTN/TCCN/…):

```
Ref. Allele:             PAM
TCTCTTACCTCTCAGTATTCTATTTCCGATCTGGATGTGTCCCAGATGGCA
AGAGAATGGAGAGTCATAAGATAAAGGCTAGACCTACACAGGGTCTACCGT
                            ATCTGGATGTGTCCCAGATG
Minor Allele
```

```
TCTCTTACCTCTCAGTATTCTATTTGCGATCTGGATGTGTCCCAGATGGCA
AGAGAATGGAGAGTCATAAGATAAACGCTAGACCTACACAGGGTCTACCGT

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# Variant ID      Sequence Variation                          Ref.Allele        Min. allele
rs28564368  TATTCTATTTCCGATCTGGATGTGT[A/C]CCAGATGGCATTTGGTAAGAATATC     C     A
```

SpCas9_WT (PAM Motif: NRG)

```
Ref. Allele:                TCTACCGTAAACCATTCTTA
TATTCTATTTCCGATCTGGATGTGTCCCAGATGGCATTTGGTAAGAATATC
ATAAGATAAAGGCTAGACCTACACAGGGTCTACCGTAAACCATTCTTATAG
                         PAM
Minor Allele
TATTCTATTTCCGATCTGGATGTGTACCAGATGGCATTTGGTAAGAATATC
ATAAGATAAAGGCTAGACCTACACATGGTCTACCGTAAACCATTCTTATAG
```

SpCas9_VQR/EQR (PAM Motif: NGAN-NGNG/NGAG)

```
Ref. Allele:               GTCTACCGTAAACCATTCTT
TATTCTATTTCCGATCTGGATGTGTCCCAGATGGCATTTGGTAAGAATATC
ATAAGATAAAGGCTAGACCTACACAGGGTCTACCGTAAACCATTCTTATAG
                       PAM
Minor Allele
TATTCTATTTCCGATCTGGATGTGTACCAGATGGCATTTGGTAAGAATATC
ATAAGATAAAGGCTAGACCTACACATGGTCTACCGTAAACCATTCTTATAG

Ref. Allele:                TCTACCGTAAACCATTCTTA
TATTCTATTTCCGATCTGGATGTGTCCCAGATGGCATTTGGTAAGAATATC
ATAAGATAAAGGCTAGACCTACACAGGGTCTACCGTAAACCATTCTTATAG
                         PAM
Minor Allele
TATTCTATTTCCGATCTGGATGTGTACCAGATGGCATTTGGTAAGAATATC
ATAAGATAAAGGCTAGACCTACACATGGTCTACCGTAAACCATTCTTATAG
```

LbCpf1(TTTN/TTCN/CTTN/TCTN/ATTN/TCCN/…):

```
Ref. Allele:             PAM
TATTCTATTTCCGATCTGGATGTGTCCCAGATGGCATTTGGTAAGAATATC
ATAAGATAAAGGCTAGACCTACACAGGGTCTACCGTAAACCATTCTTATAG
```

```
                            AGATGGCATTTGGTAAGAATAT
Minor Allele
TATTCTATTTCCGATCTGGATGTGTACCAGATGGCATTTGGTAAGAATATC
ATAAGATAAAGGCTAGACCTACACATGGTCTACCGTAAACCATTCTTATAG
```

```
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# Variant ID      Sequence Variation                                            Ref.Allele        Min. allele
rs77173925  GAATAAATTATTCTAAAGGATGGAA[A/G]AACTTTTTGGATATTTGGAGAAATT     A     G
```

SpCas9_WT (PAM Motif: NRG)

```
Ref. Allele:
GAATAAATTATTCTAAAGGATGGAAAAACTTTTTGGATATTTGGAGAAATT
CTTATTTAATAAGATTTCCTACCTTTTTGAAAAACCTATAAACCTCTTTAA

Minor Allele           PAM
GAATAAATTATTCTAAAGGATGGAAGAACTTTTTGGATATTTGGAGAAATT
CTTATTTAATAAGATTTCCTACCTTCTTGAAAAACCTATAAACCTCTTTAA
    AAATTATTCTAAAGGATGG
```

SpCas9_VQR/EQR (PAM Motif: NGAN-NGNG/NGAG)

```
Ref. Allele:
GAATAAATTATTCTAAAGGATGGAAAAACTTTTTGGATATTTGGAGAAATT
CTTATTTAATAAGATTTCCTACCTTTTTGAAAAACCTATAAACCTCTTTAA

Minor Allele             PAM
GAATAAATTATTCTAAAGGATGGAAGAACTTTTTGGATATTTGGAGAAATT
CTTATTTAATAAGATTTCCTACCTTCTTGAAAAACCTATAAACCTCTTTAA
      ATTATTCTAAAGGATGGAA
```

SaCas9(NNGRRT/NNGRR):

```
Ref. Allele:
GAATAAATTATTCTAAAGGATGGAAAAACTTTTTGGATATTTGGAGAAATT
CTTATTTAATAAGATTTCCTACCTTTTTGAAAAACCTATAAACCTCTTTAA

Minor Allele            PAM
GAATAAATTATTCTAAAGGATGGAAGAACTTTTTGGATATTTGGAGAAATT
CTTATTTAATAAGATTTCCTACCTTCTTGAAAAACCTATAAACCTCTTTAA
     AATTATTCTAAAGGATGG
```

```
AsCpf1(TTTN)
Ref. Allele:
   ATTTAATAAGATTTCCTACC
GAATAAATTATTCTAAAGGATGGAAAAACTTTTTGGATATTTGGAGAAATT
CTTATTTAATAAGATTTCCTACCTTTTTGAAAAACCTATAAACCTCTTTAA
                       PAM

Minor Allele
GAATAAATTATTCTAAAGGATGGAAGAACTTTTTGGATATTTGGAGAAATT
CTTATTTAATAAGATTTCCTACCTTCTTGAAAAACCTATAAACCTCTTTAA

===========================================================================================================

# Variant ID      Sequence Variation                                            Ref.Allele       Min. allele
rs3905238   TTGTATCATGTCAATGTATTACTTA[C/T]GCAAAAATAATACATTAAAAAAAAT     A     G (Rev Strand)

SpCas9_VQR/EQR (PAM Motif: NGAN-NGNG/NGAG)
Ref. Allele:
TTGTATCATGTCAATGTATTACTTATGCAAAAATAATACATTAAAAAAAAT
AACATAGTACAGTTACATAATGAATACGTTTTTATTATGTAATTTTTTTTA

Minor Allele                 TTTTATTATGTAATTTTTT
TTGTATCATGTCAATGTATTACTTACGCAAAAATAATACATTAAAAAAAAT
AACATAGTACAGTTACATAATGAATGCGTTTTTATTATGTAATTTTTTTTA
                         PAM

SpCas9_VRER (PAM Motif: NGCG)
Ref. Allele:
TTGTATCATGTCAATGTATTACTTATGCAAAAATAATACATTAAAAAAAAT
AACATAGTACAGTTACATAATGAATACGTTTTTATTATGTAATTTTTTTTA

Minor Allele                 TTTTATTATGTAATTTTTT
TTGTATCATGTCAATGTATTACTTACGCAAAAATAATACATTAAAAAAAAT
AACATAGTACAGTTACATAATGAATGCGTTTTTATTATGTAATTTTTTTTA
                         PAM

===========================================================================================================
```

```
# Variant ID      Sequence Variation                                            Ref.Allele        Min. allele
rs33950430  AGGTATTCACTAATTTTGAGTAACA[-/AACA]CTGCTCACAAAGTTTGGATTTTGGC  AACA  delAACA
```

LbCpf1(TTTN/TTCN/CTTN/TCTN/ATTN/TCCN/…):

```
Ref. Allele:
   ATAAGTGATTAAAACTCATT
AGGTATTCACTAATTTTGAGTAACAAACACTGCTCACAAAGTTTGGATTTTGGC
TCCATAAGTGATTAAAACTCATTGTTTGTGACGAGTGTTTCAAACCTAAAACCG
                        PAM
Minor Allele
AGGTATTCACTAATTTTGAGTAACACTGCTCACAAAGTTTGGATTTTGGC
TCCATAAGTGATTAAAACTCATTGTGACGAGTGTTTCAAACCTAAAACCG
```

AsCpf1(TTTN)

```
Ref. Allele:
   ATAAGTGATTAAAACTCATT
AGGTATTCACTAATTTTGAGTAACAAACACTGCTCACAAAGTTTGGATTTTGGC
TCCATAAGTGATTAAAACTCATTGTTTGTGACGAGTGTTTCAAACCTAAAACCG
                        PAM
Minor Allele
AGGTATTCACTAATTTTGAGTAACACTGCTCACAAAGTTTGGATTTTGGC
TCCATAAGTGATTAAAACTCATTGTGACGAGTGTTTCAAACCTAAAACCG
```

```
==============================================================================================================

# Variant ID      Sequence Variation                                            Ref.Allele        Min. allele
rs28377140  AGGCAATTAATACTTGCTTCTGGCA[C/G]TTTCTTATTCTCCTTCAGATTCCTA       G     C
```

SpCas9_WT (PAM Motif: NRG)

```
Ref. Allele:           PAM
AGGCAATTAATACTTGCTTCTGGCAGTTTCTTATTCTCCTTCAGATTCCTA
TCCGTTAATTATGAACGAAGACCGTCAAAGAATAAGAGGAAGTCTAAGGAT
     ATTAATACTTGCTTCTGG

Minor Allele                AGAATAAGAGGAAGTCTAAGG
```

```
AGGCAATTAATACTTGCTTCTGGCACTTTCTTATTCTCCTTCAGATTCCTA
TCCGTTAATTATGAACGAAGACCGTGAAAGAATAAGAGGAAGTCTAAGGAT
                         PAM
===========================================================================================================

# Variant ID      Sequence Variation                                            Ref.Allele        Min. allele
rs3856973   ttaaaaataaaaataaGTTAACACT[C/T]GATTAACCCTGACATTTCCCTATCC     G     A (Rev strand)

SpCas9_VQR/EQR (PAM Motif: NGAN-NGNG/NGAG)

Ref. Allele:              CTAATTGGGACTGTAAAGGG
TTAAAAATAAAAATAAGTTAACACTCGATTAACCCTGACATTTCCCTATCC
AATTTTTATTTTTATTCAATTGTGAGCTAATTGGGACTGTAAAGGGATAGG
                       PAM
Minor Allele
TTAAAAATAAAAATAAGTTAACACTTGATTAACCCTGACATTTCCCTATCC
AATTTTTATTTTTATTCAATTGTGAACTAATTGGGACTGTAAAGGGATAGG

SaCas9(NNGRRT/NNGRR):
Ref. Allele:                AATTGGGACTGTAAAGGG
TTAAAAATAAAAATAAGTTAACACTCGATTAACCCTGACATTTCCCTATCC
AATTTTTATTTTTATTCAATTGTGAGCTAATTGGGACTGTAAAGGGATAGG
                       PAM
Minor Allele
TTAAAAATAAAAATAAGTTAACACTTGATTAACCCTGACATTTCCCTATCC
AATTTTTATTTTTATTCAATTGTGAACTAATTGGGACTGTAAAGGGATAGG

LbCpf1(TTTN/TTCN/CTTN/TCTN/ATTN/TCCN/…):
Ref. Allele:
TTAAAAATAAAAATAAGTTAACACTCGATTAACCCTGACATTTCCCTATCC
AATTTTTATTTTTATTCAATTGTGAGCTAATTGGGACTGTAAAGGGATAGG

Minor Allele           PAM
TTAAAAATAAAAATAAGTTAACACTTGATTAACCCTGACATTTCCCTATCC
AATTTTTATTTTTATTCAATTGTGAACTAATTGGGACTGTAAAGGGATAGG
                           ATTAACCCTGACATTTCCCTA
===========================================================================================================

# Variant ID      Sequence Variation                                            Ref.Allele        Min. allele
```

```
rs4498089   AGTGTTAACTTATTTTTATTTTTAA[A/G]AAAATTGTTAAGGGCTTTCCAGCAA     A     G
```

SpCas9_WT (PAM Motif: NRG)

```
Ref. Allele:
AGTGTTAACTTATTTTTATTTTTAAAAAAATTGTTAAGGGCTTTCCAGCAA
TCACAATTGAATAAAAATAAAAATTTTTTTAACAATTCCCGAAAGGTCGTT

Minor Allele           PAM
AGTGTTAACTTATTTTTATTTTTAAGAAAATTGTTAAGGGCTTTCCAGCAA
TCACAATTGAATAAAAATAAAAATTCTTTTAACAATTCCCGAAAGGTCGTT
   GTTAACTTATTTTTATTTTT
```

SpCas9_VQR/EQR (PAM Motif: NGAN-NGNG/NGAG)

```
Ref. Allele:
AGTGTTAACTTATTTTTATTTTTAAAAAAATTGTTAAGGGCTTTCCAGCAA
TCACAATTGAATAAAAATAAAAATTTTTTTAACAATTCCCGAAAGGTCGTT

Minor Allele           PAM
AGTGTTAACTTATTTTTATTTTTAAGAAAATTGTTAAGGGCTTTCCAGCAA
TCACAATTGAATAAAAATAAAAATTCTTTTAACAATTCCCGAAAGGTCGTT
   GTTAACTTATTTTTATTTTTA
```

SaCas9(NNGRRT/NNGRR):

```
Ref. Allele:
AGTGTTAACTTATTTTTATTTTTAAAAAAATTGTTAAGGGCTTTCCAGCAA
TCACAATTGAATAAAAATAAAAATTTTTTTAACAATTCCCGAAAGGTCGTT

Minor Allele            PAM
AGTGTTAACTTATTTTTATTTTTAAGAAAATTGTTAAGGGCTTTCCAGCAA
TCACAATTGAATAAAAATAAAAATTCTTTTAACAATTCCCGAAAGGTCGTT
   GTTAACTTATTTTTATTTTT
```

AsCpf1(TTTN)

```
Ref. Allele:
 CACAATTGAATAAAAATAAAA
AGTGTTAACTTATTTTTATTTTTAAAAAAATTGTTAAGGGCTTTCCAGCAA
TCACAATTGAATAAAAATAAAAATTTTTTTAACAATTCCCGAAAGGTCGTT
```

```
                       PAM
Minor Allele
AGTGTTAACTTATTTTTATTTTTAAGAAAATTGTTAAGGGCTTTCCAGCAA
TCACAATTGAATAAAAATAAAAATTCTTTTAACAATTCCCGAAAGGTCGTT

===========================================================================================================


# Variant ID      Sequence Variation                                          Ref.Allele        Min. allele
rs57666989  CTGCAAGCTCCGCTTCCCGAGTTCA[C/T]GCCATTCTCCTGCCTCAGTCTCCCA     C     T

SpCas9_VQR/EQR (PAM Motif: NGAN-NGNG/NGAG)
Ref. Allele:                 TAAGAGGACGGAGTCAGAGGG
CTGCAAGCTCCGCTTCCCGAGTTCACGCCATTCTCCTGCCTCAGTCTCCCA
GACGTTCGAGGCGAAGGGCTCAAGTGCGGTAAGAGGACGGAGTCAGAGGGT
                         PAM
Minor Allele
CTGCAAGCTCCGCTTCCCGAGTTCATGCCATTCTCCTGCCTCAGTCTCCCA
GACGTTCGAGGCGAAGGGCTCAAGTACGGTAAGAGGACGGAGTCAGAGGGT

SpCas9_VRER (PAM Motif: NGCG)
Ref. Allele:                 TAAGAGGACGGAGTCAGAGG
CTGCAAGCTCCGCTTCCCGAGTTCACGCCATTCTCCTGCCTCAGTCTCCCA
GACGTTCGAGGCGAAGGGCTCAAGTGCGGTAAGAGGACGGAGTCAGAGGGT
                         PAM
Minor Allele
CTGCAAGCTCCGCTTCCCGAGTTCATGCCATTCTCCTGCCTCAGTCTCCCA
GACGTTCGAGGCGAAGGGCTCAAGTACGGTAAGAGGACGGAGTCAGAGGGT

===========================================================================================================

# Variant ID      Sequence Variation                                          Ref.Allele        Min. allele
rs10006129  tcttgatctcctgacctcgtcatcc[C/G]ccgaccttgtgatccgcccacctcg     G     C


SpCas9_WT (PAM Motif: NRG)
Ref. Allele:
TCTTGATCTCCTGACCTCGTCATCCGCCGACCTTGTGATCCGCCCACCTCG
AGAACTAGAGGACTGGAGCAGTAGGCGGCTGGAACACTAGGCGGGTGGAGC
```

```
Minor Allele                CTGGAACACTAGGCGGGTGG
TCTTGATCTCCTGACCTCGTCATCCCCCGACCTTGTGATCCGCCCACCTCG
AGAACTAGAGGACTGGAGCAGTAGGGGGCTGGAACACTAGGCGGGTGGAGC
                         PAM
```

SpCas9_VQR/EQR (PAM Motif: NGAN-NGNG/NGAG)

```
Ref. Allele:
TCTTGATCTCCTGACCTCGTCATCCGCCGACCTTGTGATCCGCCCACCTCG
AGAACTAGAGGACTGGAGCAGTAGGCGGCTGGAACACTAGGCGGGTGGAGC

Minor Allele                CTGGAACACTAGGCGGGTGG
TCTTGATCTCCTGACCTCGTCATCCCCCGACCTTGTGATCCGCCCACCTCG
AGAACTAGAGGACTGGAGCAGTAGGGGGCTGGAACACTAGGCGGGTGGAGC
                         PAM
```

SpCas9_VRER (PAM Motif: NGCG)

```
Ref. Allele:                CTGGAACACTAGGCGGGTGG
TCTTGATCTCCTGACCTCGTCATCCGCCGACCTTGTGATCCGCCCACCTCG
AGAACTAGAGGACTGGAGCAGTAGGCGGCTGGAACACTAGGCGGGTGGAGC
                        PAM
Minor Allele
TCTTGATCTCCTGACCTCGTCATCCCCCGACCTTGTGATCCGCCCACCTCG
AGAACTAGAGGACTGGAGCAGTAGGGGGCTGGAACACTAGGCGGGTGGAGC
```

SaCas9(NNGRRT/NNGRR):

```
Ref. Allele:
TCTTGATCTCCTGACCTCGTCATCCGCCGACCTTGTGATCCGCCCACCTCG
AGAACTAGAGGACTGGAGCAGTAGGCGGCTGGAACACTAGGCGGGTGGAGC

Minor Allele                CTGGAACACTAGGCGGGTGG
TCTTGATCTCCTGACCTCGTCATCCCCCGACCTTGTGATCCGCCCACCTCG
AGAACTAGAGGACTGGAGCAGTAGGGGGCTGGAACACTAGGCGGGTGGAGC
                        PAM
```

```
===========================================================================================================
```

```
# Variant ID      Sequence Variation                                          Ref.Allele        Min. allele
rs28696693  GGTAATTTTTGTATTTTTAGTAGAG[A/G]TGGGGTTTTGCCATGATGAGCAGGC     A     G

SpCas9 (PAM Motif: NRG)
Ref. Allele:
GGTAATTTTTGTATTTTTAGTAGAGATGGGGTTTTGCCATGATGAGCAGGC
CCATTAAAAACATAAAAATCATCTCTACCCCAAAACGGTACTACTCGTCCG

Minor Allele           PAM
GGTAATTTTTGTATTTTTAGTAGAGGTGGGGTTTTGCCATGATGAGCAGGC
CCATTAAAAACATAAAAATCATCTCCACCCCAAAACGGTACTACTCGTCCG
    ATTTTTGTATTTTTAGTAG

SpCas9_VQR/EQR (PAM Motif: NGAN-NGNG/NGAG)
Ref. Allele:           PAM
GGTAATTTTTGTATTTTTAGTAGAGATGGGGTTTTGCCATGATGAGCAGGC
CCATTAAAAACATAAAAATCATCTCTACCCCAAAACGGTACTACTCGTCCG
     TTTTTGTATTTTTAGTAG
Minor Allele
GGTAATTTTTGTATTTTTAGTAGAGGTGGGGTTTTGCCATGATGAGCAGGC
CCATTAAAAACATAAAAATCATCTCCACCCCAAAACGGTACTACTCGTCCG

===========================================================================================================

# Variant ID      Sequence Variation                                          Ref.Allele        Min. allele
rs28393280  GGATTTTGAATGCGGAACCAACTGC[A/G]CTTGTTGAACTCTGCTAAGTATAAC     A     G

SpCas9_VQR/EQR (PAM Motif: NGAN-NGNG/NGAG)
Ref. Allele:
GGATTTTGAATGCGGAACCAACTGCACTTGTTGAACTCTGCTAAGTATAAC
CCTAAAACTTACGCCTTGGTTGACGTGAACAACTTGAGACGATTCATATTG

Minor Allele:          PAM
GGATTTTGAATGCGGAACCAACTGCGCTTGTTGAACTCTGCTAAGTATAAC
CCTAAAACTTACGCCTTGGTTGACGCGAACAACTTGAGACGATTCATATTG
```

```
  ATTTTGAATGCGGAACCAAC
```

SpCas9_VRER (PAM Motif: NGCG)

```
Ref. Allele:
GGATTTTGAATGCGGAACCAACTGCACTTGTTGAACTCTGCTAAGTATAAC
CCTAAAACTTACGCCTTGGTTGACGTGAACAACTTGAGACGATTCATATTG

Minor Allele:          PAM
GGATTTTGAATGCGGAACCAACTGCGCTTGTTGAACTCTGCTAAGTATAAC
CCTAAAACTTACGCCTTGGTTGACGCGAACAACTTGAGACGATTCATATTG
  ATTTTGAATGCGGAACCAAC

Minor Allele:               ACAACTTGAGACGATTCAT
GGATTTTGAATGCGGAACCAACTGCGCTTGTTGAACTCTGCTAAGTATAAC
CCTAAAACTTACGCCTTGGTTGACGCGAACAACTTGAGACGATTCATATTG
                        PAM
```

Figure S2: List of sgRNA sequences designed targeting prevalent SNP-dependent PAM upstream *HTT* exon-1, and within *HTT* intron-1.

sgRNA sequences targeting SNP-dependent PAM:

Sequence sgHD1

Complementary guide: 5’GCTCCAGGCGTCGGCGG 3’ (sgHD1) (n=17 nt)
sgRNA expression cassette: hU6 promoter

Major Allele (C): Have a PAM motif on the Positive strand (NGG)

```
GTCGCCCCGCTCCAGGCGTCGGCGGGGGATCCTTTCCGCATGGGCCTGCGCC
CAGCGGGGCGAGGTCCGCAGCCGCCCCCTAGGAAAGGCGTACCCGGACGCGG
        GCTCCAGGCGTCGGCGG
```

Minor Allele (G): Disruption of the PAM motive.

```
GTCGCCCCGCTCCAGGCGTCGGCGGGGCATCCTTTCCGCATGGGCCTGCGCC
CAGCGGGGCGAGGTCCGCAGCCGCCCCGTAGGAAAGGCGTACCCGGACGCGG
```

Sequence sgHD2

Complementary guide: 5’GGCGCGGGGCTCAACGGAG 3’ (sgHD2) (n=19 nt)
sgRNA expression cassette: hU6 promoter

Major Allele (C): Has a PAM motif on the Negative strand (NGG)

```
                           GAGGCAACTCGGGGCGCGG
TTACAGTCTCACCACGCCCCGTCCCCTCTCCGTTGAGCCCCGCGCCTTC
AATGTCAGAGTGGTGCGGGGCAGGGGAGAGGCAACTCGGGGCGCGGAAG
```

Minor Allele (G): Disruption of the PAM motive

```
TTACAGTCTCACCACGCCCCGTCCGCTCTCCGTTGAGCCCCGCGCCTTC
AATGTCAGAGTGGTGCGGGGCAGGCGAGAGGCAACTCGGGGCGCGGAAG
```

Sequence sgHD3

Complementary guide: 5′GTCTGGGACGCAAGGCGCCG3′ (sgHD3) (n=20 nt)
sgRNA expression cassette: hU6 promoter

Major Allele (G): Has a PAM motif on the Positive strand (NGG) Use U6 promoter

```
GCGTCTGGGACGCAAGGCGCCGTGGGGCTGCCGGGACGGGTCCAAGAT
CGCAGACCCTGCGTTCCGCGGCACCCCCGACGGCCCTGCCCAGGTTCTA
  GTCTGGGACGCAAGGCGCCG
```

Minor Allele (A): Loss PAM motif on the Positive strand (NGG) Use U6 promoter

```
GCGTCTGGGACGCAAGGCGCCGTGAGGGCTGCCGGGACGGGTCCAAGAT
CGCAGACCCTGCGTTCCGCGGCACTCCCGACGGCCCTGCCCAGGTTCTA
```

Sequence sgHD4

Complementary guide: 5′ GATGCACGCGGGGTGGGGC 3′ (n=19 nt)
sgRNA expression cassette: hU6 promoter

Major Allele: Has a PAM motif on the negative strand (NGG))

```
                           3′ CGGGGTGGGGCGCACGTAG 5′
5′ TCTGCGTCAGGGTTTCCTTCTTTTCCAGCCCCACCCCGCGTGCATCCCA 3′
3′ AGACGCAGTCCCAAAGGAAGAAAAGGTCGGGGTGGGGCGCACGTAGGGT 5′
```

Minor Allele: SNP produces a Loss of the PAM motif.

```
5′ TCTGCGTCAGGGTTTCCTTCTTTTGCAGCCCCACCCCGCGTGCATCCCA 3′
3′ AGACGCAGTCCCAAAGGAAGAAAACGTCGGGGTGGGGCGCACGTAGGGT
```

Sequence sgHD5g and sgHD5c

Complementary guide: 5’ATTCAGGTTGATGTCCT 3’ (sgHD5g) (n=17 nt)
Complementary guide: 5’ATCCCATTCTGAGGTTCTGG 3 (sgHD5c) (n=20 nt)
sgRNA expression cassette: hH1 promoter

Major Allele: Has a PAM motif on the Positive strand (NAG)

```
5’CCCTCATTCAGGTTGATGTCCTAAGCCCCAGAACCTCAGAATGGGATTG 3’
3’  GGGAGTAAGTCCAACTACAGGATTCGGGGTCTTGGAGTCTTACCCTAAC 5’
       ATTCAGGTTGATGTCCT
```

Minor Allele: generates a PAM motif on the Negative strand (NAG)

```
                             GGTCTTGGAGTCTTACCCTA
5’CCCTCATTCAGGTTGATGTCCTAACCCCCAGAACCTCAGAATGGGATTG 3’
3’GGGAGTAAGTCCAACTACAGGATTGGGGGTCTTGGAGTCTTACCCTAAC 5’
```

Sequence sgHD6c and sgHD6g

Complementary guide: 5’GCAGGCAGAGAGGAGCC 3’ (sgHD6c) (n=17 nt)
Complementary guide: 5’GCCTGGCTAAAGTAGGCTT 3 (sgHD6g) (n=19 nt)
sgRNA expression cassette: hU6 promoter

Major Allele (C): Have a PAM motif on the negative strand (NAG)

```
                              CCGAGGAGAGACGGACG
5’ GTGGCCTGGCTAAAGTAGGCTTTACTGGGCTCCTCTCTGCCTGCATCAC 3’
3’ CACCGGACCGATTTCATCCGAAATGACCCGAGGAGAGACGGACGTAGTG 5’
```

Minor Allele (G): Generates a PAM motif on the Positive strand (NAG)

```
5’ GTGGCCTGGCTAAAGTAGGCTTTAGTGGGCTCCTCTCTGCCTGCATCAC 3’
```

```
3’ CACCGGACCGATTTCATCCGAAATCACCCGAGGAGAGACGGACGTAGTG 5’
      GCCTGGCTAAAGTAGGCTT
```

Sequence sgHDi3

Complementary guide: 5’GCTTTTAGGACGCCTCGG 3’ (sgHDi3) (n=18 nt)

sgRNA expression cassette: hU6 promoter

```
5’ AATGCTTTTAGGACGCCTCGGCGGGAGTGGCGGGCAGGGGGGGGCG 3
3’ TTACGAAAATCCTGCGGAGCCGCCCTCACCGCCCGTCCCCCCCCGC 5’
      GCTTTTAGGACGCCTCGG
```

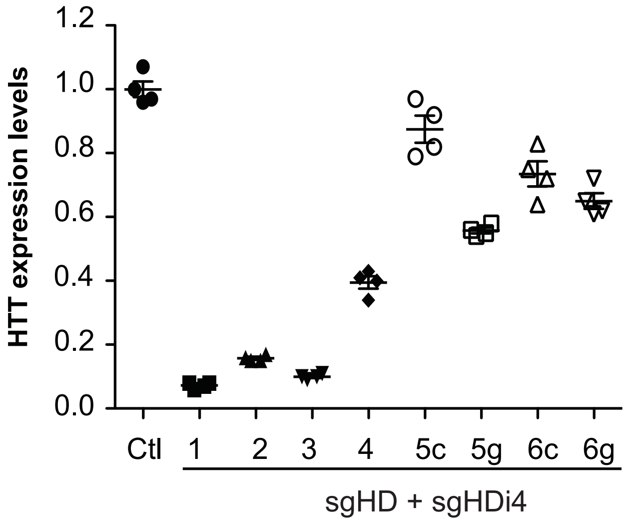
Sequence sgHDi4

Complementary guide: 5’ GCGGGACACTTCGAGAGG 3’ (sgHDi4) (n=18 nt)

sgRNA expression cassette: hU6 promoter

```
5’ GGCGCGGGACACTTCGAGAGGAGGCGGGGTTTGGAGCTGGAGAGATGT 3’
3’ CCGCGCCCTGTGAAGCTCTCCTCCGCCCCAAACCTCGACCTCTCTACA 5’
         GCGGGACACTTCGAGAGG
```

Supplementary Figure 3: Efficacy of SNP-dependent sgHD/SpCas9 complexes in HEK 293 cells using a common intronic sgHDi4 sequences.



Supplementary Figure 4: Sanger sequencing of PCR amplified products after of HTT exon-1 editing.

sgHD1B/i3

```
CGGCTCAGAGTCCACGGCCGGCTGTCGCCCCGCTCCAGGCGTCGGCGGGG--//--ATGCTTTTAGGACGCCTCGGCGGGAGTGGCGGGGCGGGGGGGGCGGGGAGTGAG
CGGCTCAGAGTCCACGGCCGGCTGTCGCCCCGCTCCAGGCGTCG-----------------------------CGGCGGGAGTGGCGGGGCGGGGGGGGCGGGGAGTGAG
CGGCTCAGAGTCCACGGCCGGCTGTCGCCCCGCCCCAGGCGTCG-----------------------------CGGCGGGAGTGGCGGGGCGGGGGGGGCGGGGAGTGAG
CGGCTCAGAGTCCACGGCCGGC-------------------------------------------------------GGGAGTGGCGGGGCGGGGGGGGCGGGGAGTGAG
CGGCTCAGAGTCCACGGCCGGCTGTCGCCCCGCTCCAGGCGTCGG-----------------------------GGCGGGAGTGGCGGGGCGGGGGGGGCGGGGAGTGAG
```

HD promoter sequence upstream sgHD1B

HD intron 1 sequence downstream sgHDi3

sgHD2B/i3

```
CCCATTACAGTCTCACCACGCCCCGTCCCCTCTCCGTTGAGCCCCGCGCC--//--ATGCTTTTAGGACGCCTCGGCGGGAGTGGCGGGGCGGGGGGGGCGGGGAGTGAG
CCCATTACAGTCTCACCACGCCCCGTCCCCTCTCC--------------------------------------CGGCGGGAGTGCGGGGCGGGGGGGGCGGGGAGTGAGG
CCCATTACAGTCTCACCACGCCCCGTCCCCTCTCC-------------------------------------TCGGCGGGAGTGCGGGGCGGGGGGGGCGGGGAGTGAGG
CCCATTACAGTCTCACCACGCCCCGTCCCCTCTCC--------------------------------------CGGCGGGAGTGGCGGGGCGGGGGGGGGCGGGGAGTGA
CCCATTACAGTCTCACCACGCCCCGTCCCCTCTC--------------------------------------GCGGCGGGAGTGGCGGGGCGGGGGGGGCGGGGAGTGAG
```

HD promoter sequence upstream sgHD2B

HD intron 1 sequence downstream sgHDi3

sgHD3B/i3

```
CGCGGCCCCGCCTCCGCCGGCGCAGCGTCTGGGACGCAAGGCGCCGTGG--//--ATGCTTTTAGGACGCCTCGGCGGGAGTGGCGGGGCGGGGGGGGCGGGGAGTGAG
CGCGGCCCCGCCTCCGCCGGCGCAGCGTCTGGG---------------------------------------CGGCGGGAGTGGCGGGGCGGGGGGGGCGGGGAGTGAG
CGCGGCCCCGCCTCCGCCGGCGCAGCGTCTGGGACGCAAGGCG----------------------------TCGGCGGGAGTGGCGGGGCGGGGGGGGCGGGGAGTGAG
CGCGGCCCCGCCTCCGCCGGCGCAGCGTCTGGGACGCAAGGCGA---------------------------TCGGCGGGAGTGGCGGGGCGGGGGGGGCGGGGAGTGAG
TCCGGCCCCGCCTCCGCCGGCGCAGCGTCTGGGACGCAAGGCG-----------------------------CGGCGGGAGTGGCGGGGCGGGGGGGGCGGGGAGTGAG
```

HD promoter sequence upstream sgHD3B

HD intron 1 sequence downstream sgHDi3

sgHD4/i3

```
TGGGGTCTGCGTCAGGGTTTCCTTCTTTTCCAGCCCCACCCCGCGTGCATC--//--ATGCTTTTAGGACGCCTCGGCGGGAGTGGCGGGGCGGGGGGGGCGGGGAGTGAG
TGGGGTCTGCGTCAGGGTTTCCTTCTTTTCCAGCC-------------------------------------------GGGAGTGGCGGGGCGGGGGGGGCGGGGAGTGAG
TGGGGTCTGCGTCAGGGTTTCCTTCTTTTCCAGCC---------------------------------------CGGCGGGAGTGGCGGGGCGGGGGGGGCGGGGAGTGAG
TGGGGTCTGCGTCAGGGTTTCCTTCTTTTCCAGCC---------------------------------------CGGCGGGAGTGGCGGGGCGGGGGGGGCGGGGAGTGAG
TGGGGTCTGCGTCAGGGTTTCCTTCTTTT---------------------------------------------CGGCGGGAGTGGCGGGGCGGGGGGGGCGGGGAGTGAG
```

HD promoter sequence upstream sgHD4

HD intron 1 sequence downstream sgHDi3

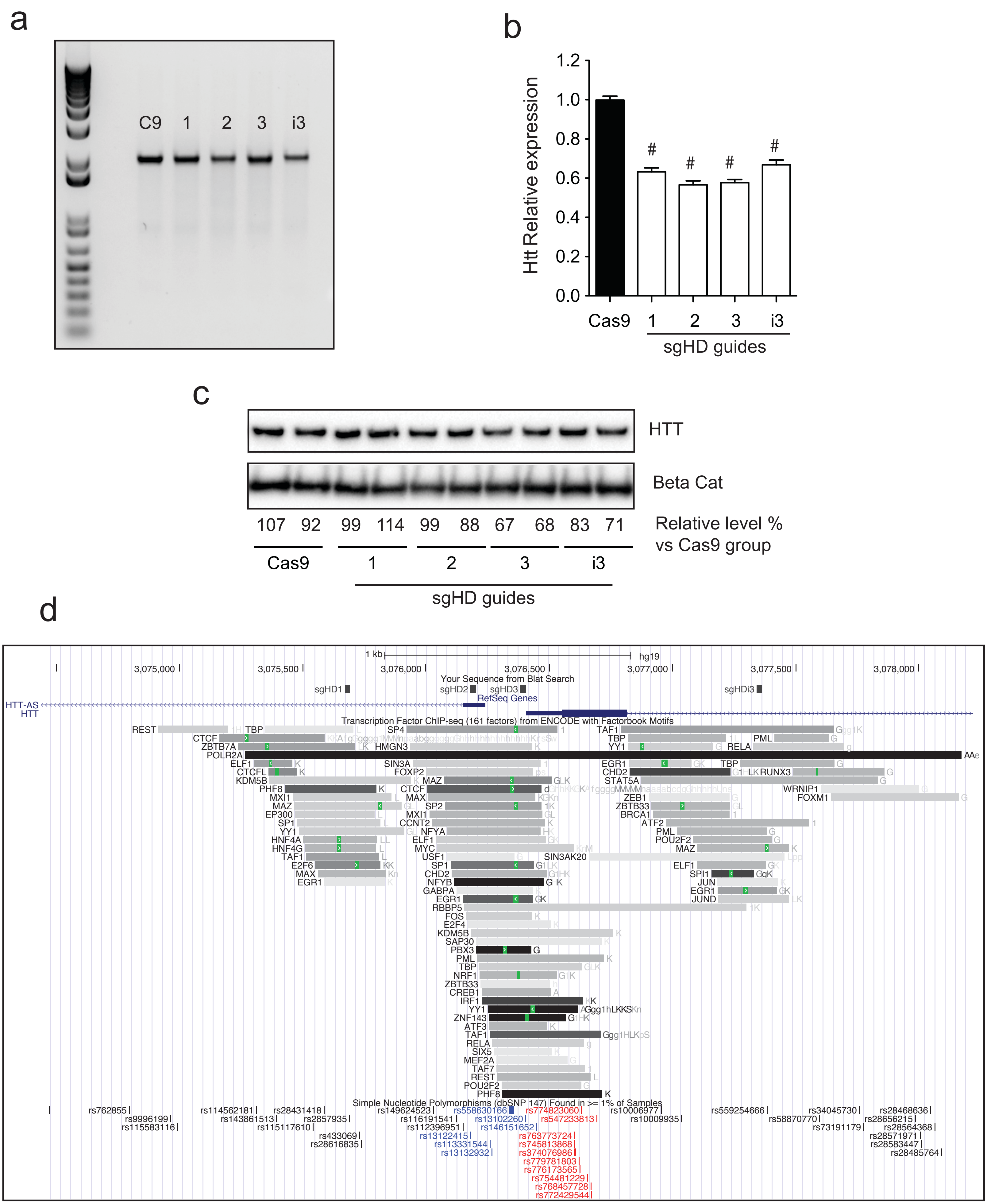
sgHD6C/i3

```
CAGGTGTGGCCTGGCTAAAGTAGGCTTTACTGGGCTCCTCTCTGCCTGCATC--//--ATGCTTTTAGGACGCCTCGGCGGGAGTGGCGGGGCGGGGGGGGCGGGGAGTGAG
CAGGTGTGGCCTGGCTAAAGTAGGCTTTACTGGG-----------------------------------------CGGCGGGAGTGGCGGGGCGGGGGGGGCGGGGAGTGAG
CAGGTGTGGCCTGGCTAAAGTAGGCTTTACTGGGC---------------------------------------TCGGCGGGAGTGGCGGGGCGGGGGGGGCGGGGAGTGAG
CAGGTGTGGCCTGGCTAAAGTAGGCTTTACTGGGC----------------------------------------CGGCGGGAGTGGCGGGGCGGGGGGGGCGGGGAGTGAG
CAGGTGTGGCCTGGCTAAAGTAGGCTTTACTGGGC----------------------------------------CGGCGGGAGTGGCGGGGCGGGGGGGGCGGGGAGTGAG
```

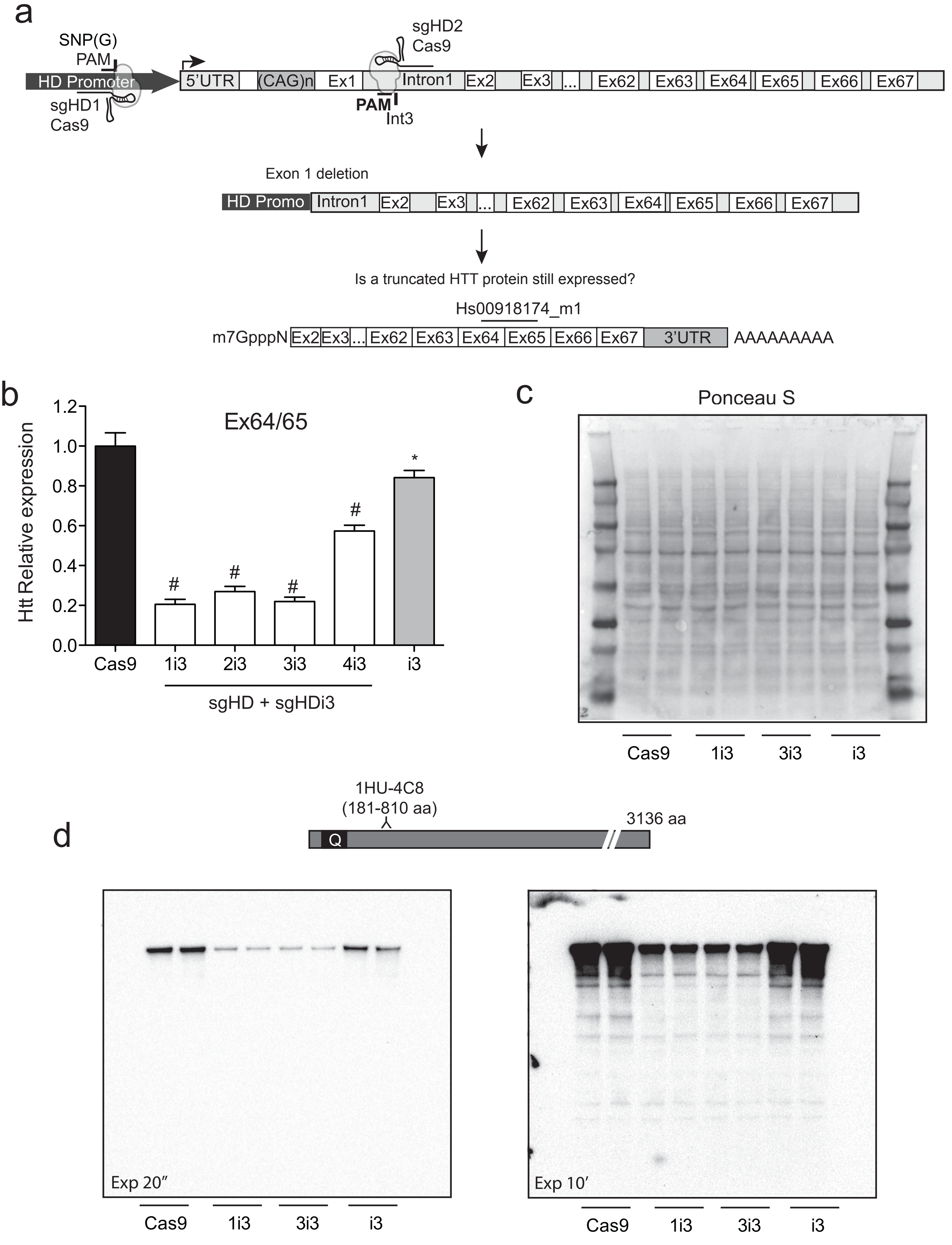
HD promoter sequence upstream sgHD6C

HD intron 1 sequence downstream sgHDi3

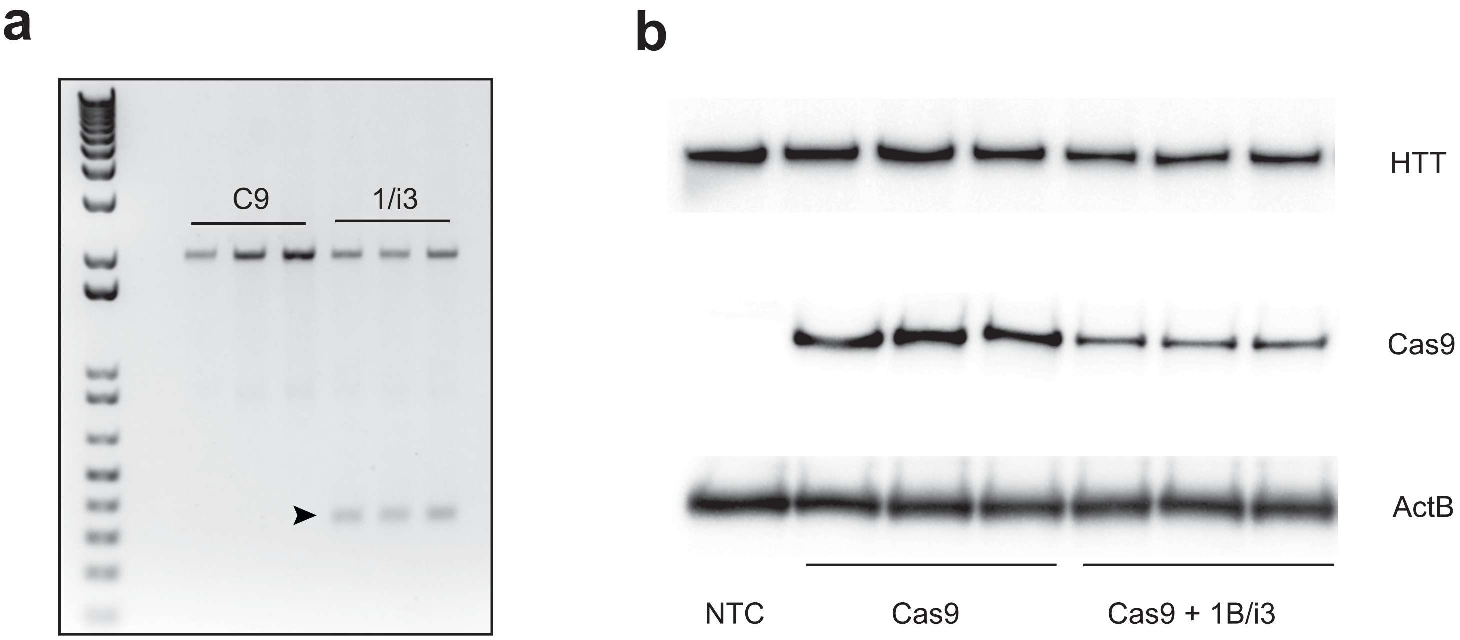
Supplementary Figure 5: Cleavage of single sgHD/SpCas9 complexes in HEK 293 cells.



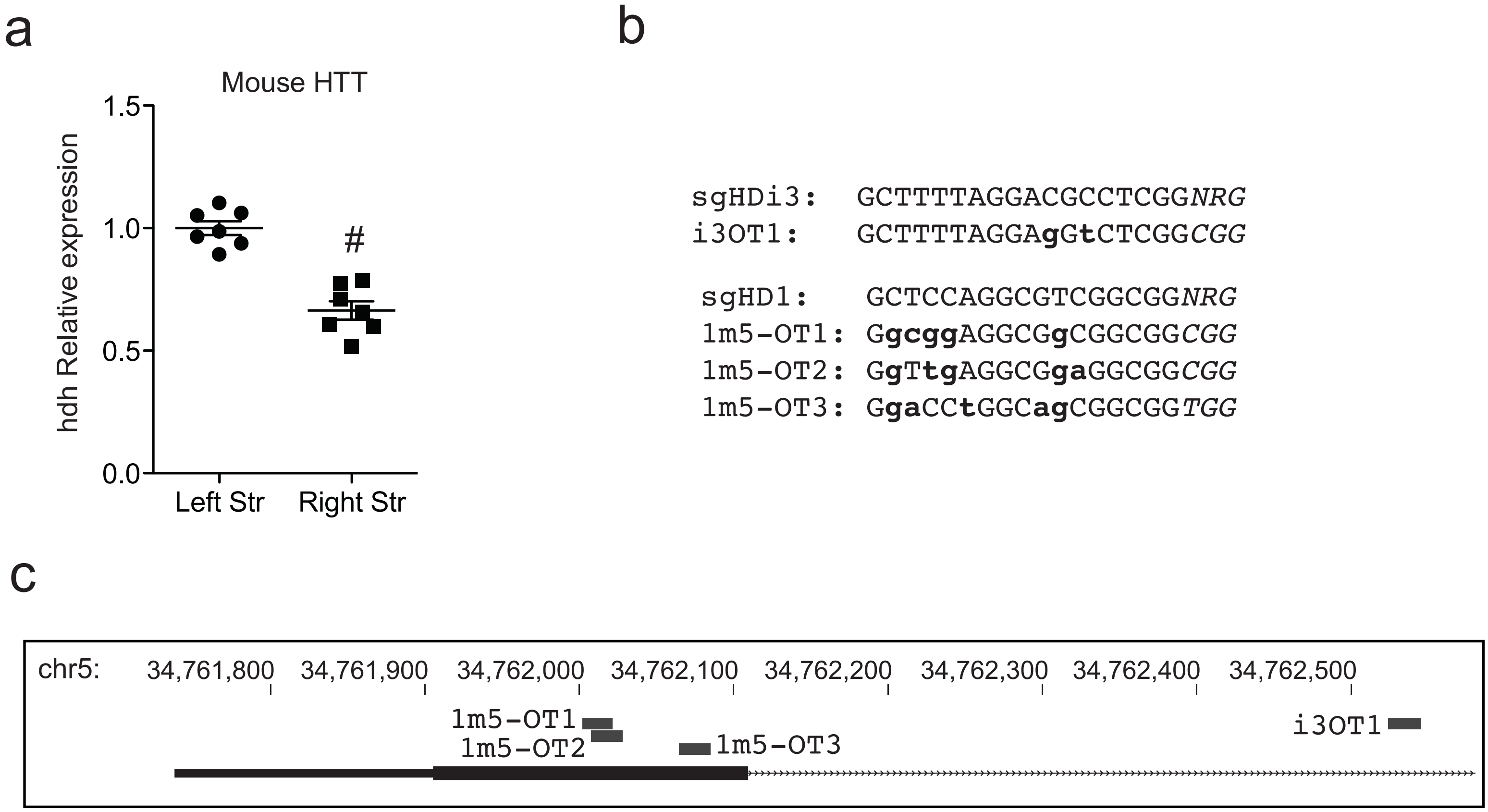
Supplementary Figure 6: C-terminal HTT products are not generated after HTT exon-1 deletion in HEK293 cells.



Supplementary Figure 7: In vitro testing of rAAV2/1 SpCas9 and rAAV2/1 vectors in HEK 293 cells.



Supplementary Figure 8: In vivo gene editing of endogenous mouse HTT allele.



sgHDi3: GCTTTTAGGACGCCTCGG*NRG*
i3OT1: GCTTTTAGGA**g**G**t**CTCGG*CGG*

sgHD1: GCTCCAGGCGTCGGCGG*NRG*
1m5-OT1: G**gcgg**AGGCG**g**CGGCGG*CGG*
1m5-OT2: G**g**T**tg**AGGCG**ga**GGCGG*CGG*
1m5-OT3: G**ga**CC**t**GGC**ag**CGGCGG*TGG*

Table S1: List of the 36 prevalent SNPs flanking *HTT* exon-1 within the critical nucleotide position of the different CRISPR systems analyzed.

			1000 Genome DATA		
# Variant ID	Location	Sequence Variation	Ref.Allele	Min. Allele	MAF >0.05
rs35631490	**Promoter**	**GTCTGCGTCAGGGTTTCCTTCTTTT[C/G]CAGCCCCACCCCGCGTGCATCCCAC**	**C**	**G**	**0.1074**
rs73086139	Promoter	TCAAGGCCTCTTCTCTCTTCTCGGC[A/G]GGACAGGCACAGGCAGGTGGCCAGG	A	G	0.0659
rs73086140	Promoter	GCCAGGTGTCATGCTTAGCTCCCCG[C/G]CCAGTGAGATTCTTTCATTTAACAA	C	G	0.0962
rs113541600	Promoter	TAGGAACCTTATTTCTCTCTCGCTC[-/T]TTTTTTTTTTTTTGAGACAGAGTCT	T	delT	0.2091
rs61791259	Promoter	GATTACAGGCACCTGCCACCATGCC[C/T]GGCTAATTTTTGTATTTTTAGTTGA	C	T	0.0661
rs61792460	Promoter	GAGGGTTTCATCTTGTTGGTCAGGC[A/G]GACTTGAACTCCTGACCTCAGGTGA	G	A	0.0966
rs73086144	Promoter	GCCACTGCGCCTTCATCTCTCTTCT[A/G]TGTATGTGTACGCTGTTTTTTCTTT	G	A	0.0899
rs73086145	Promoter	GCTGTTTTTTCTTTAGAATGGGGGA[C/G]GTTATCAGGCTCTACATGGTGTGTA	C	G	0.0899
rs61792461	Promoter	TCTACATGGTGTGTAGTCGGCTAGC[A/G]TGTTGTAAGCCTTTCCCTGTGTCAC	A	G	0.0901
rs61792462	Promoter	CTGTGTCACAAGTGCTCATCTGGAA[C/G]AGGATTCTAATGACTGCCTGTGGCT	C	G	0.0579
rs61090955	Promoter	TCATTTTATGTGATTCCTTTCTAGA[A/G]GTACTACTCATTACTTCTGCTTGCA	A	G	0.0865
rs77384845	Promoter	TAGCTGAAGGAAGGACAGGGACTGT[C/T]ATACACTAGCTAAGAGGCAAACTGC	C	T	0.0984
rs10011412	Promoter	agctgaaggaaggacagggactgtC[A/G]TACACTAGCTAAGAGGCAAACTGCT	A	G	0.1158
rs61792464	**Promoter**	**TCCCTCATTCAGGTTGATGTCCTAA[C/G]CCCCAGAACCTCAGAATGGGATTGT**	**G**	**C**	**0.1372**
rs112435590	Promoter	TCCATGCCAAGAAGGCAACAGAGAG[G/T]GCCAGGGAGACTGAAGTCATACCCT	G	T	0.0881
rs111670395	Promoter	CCCAGGTTCAAGCAATTCTGCCTCA[A/G]CCTCCGGAATAGCTGGGACTACAGG	G	A	0.0663
rs762855	Promoter	TTGAGAAGGACAGCAGAGAAACAGC[C/T]GTTAGTtcccagttcttgggaggct	G	A (Rev strand)	0.4828
rs9996199	**Promoter**	**TGTGGCCTGGCTAAAGTAGGCTTTA[C/G]TGGGCTCCTCTCTGCCTGCATCACC**	**C**	**G**	**0.1575**
rs143861513	Promoter	TCCGGGGCGCTGCGCTGGGACCGAT[-/G]GGGGGGCGCCAGGCCTGTGGACACC	-	insG	0.0599
rs28431418	Promoter	CTCCCCGCAGGGCTGTCCGGGTGAG[C/T]ATGGCTCTGGCCACGGGCCAGTGTG	T	C	0.1438
rs2857935	**Promoter**	**GGGCGCAGGCCCATGCGGAAAGGAT[A/C/G]CCCCGCCGACGCCTGGAGCGGGGCG**	**G**	**C/T (Rev Strand)**	**0.226**
rs28616835	Promoter	GCGCCCGCGCTCGGCGCCCCCTCCA[C/T]GGCCCCGCCCCGTCCATGGCCCCGT	C	T	0.0839
rs149624523	Promoter	CCCCGCCCCGGCCTCGCCACGCCCC[C/T]ACCTCACCACGCCCCCCGCATCGCC	T	C	0.0927
rs13122415	**Promoter**	**attacagtctcaccacgccccgtcc[C/G]CTCTCCGTTGAGCCCCGCGCCTTCG**	**C**	**G**	**0.1082**
rs113331544	5'UTR	GGCCTTGCTGTGTGAGGCAGAACCT[-/GCGGGG]GCGGGGGCAGGGGCGGGCTGGTTCC	-	insGCGGGG	0.0851
rs13132932	5'UTR	TGTGTGAGGCAGAACCTGCGGGGGC[A/G]GGGGCGGGCTGGTTCCCTGGCCAGC	A	G	0.0727
rs13102260	**5'UTR**	**AGCGTCTGGGACGCAAGGCGCCGTG[A/G]GGGCTGCCGGGACGGGTCCAAGATG**	**G**	**A**	**0.1581**
rs10009935	Intron 1	CTCACTTGGGTCTTCCCTTGTCCTC[C/T]CGCGAGGGGAGGCAGAGCCTTGTTG	T	C	0.0877
rs58870770	Intron 1	TGAATGAGTTGTGGTTGCCAAGTAA[-/A]GTGGTGAACTTACGTGGTGATTAAT	A	delA	0.0845
rs34045730	Intron 1	GAGGTGTACATTTTACCAGTATTCC[A/T]GTCAGGCTTGCCAGAATACGGGGGG	A	T	0.0589
rs28656215	Intron 1	GGAAGTCTGTGTGTCGAGTGTACAG[C/T]AGGAGTTAGGAAGTACTCTGGTGCA	T	C	0.1544
rs28571971	Intron 1	ACAGTAGGAGTTAGGAAGTACTCTG[C/G]TGCAGTTCAGGCCTTTCTCTTACCT	G	C	0.0839
rs28583447	Intron 1	CAGTAGGAGTTAGGAAGTACTCTGG[C/T]GCAGTTCAGGCCTTTCTCTTACCTC	T	C	0.0839
rs28468636	Intron 1	TCTCTTACCTCTCAGTATTCTATTT[C/G]CGATCTGGATGTGTCCCAGATGGCA	C	G	0.0839
rs28564368	Intron 1	TATTCTATTTCCGATCTGGATGTGT[A/C]CCAGATGGCATTTGGTAAGAATATC	C	A	0.0839
rs28485764	Intron 1	GATGGCATTTGGTAAGAATATCTCT[A/G]TTAAGACTGATTAATTTTTAGTAAT	G	A	0.0845
rs77173925	Intron 1	GAATAAATTATTCTAAAGGATGGAA[A/G]AACTTTTTGGATATTTGGAGAAATT	A	G	0.0843
rs3905238	Intron 1	TTGTATCATGTCAATGTATTACTTA[C/T]GCAAAAATAATACATTAAAAAAAAT	A	G (Rev Strand)	0.4443
rs33950430	Intron 1	AGGTATTCACTAATTTTGAGTAACA[-/AACA]CTGCTCACAAAGTTTGGATTTTGGC	AACA	delAACA	0.0835
rs28377140	Intron 1	AGGCAATTAATACTTGCTTCTGGCA[C/G]TTTCTTATTCTCCTTCAGATTCCTA	G	C	0.1064
rs3856973	Intron 1	ttaaaaataaaaataaGTTAACACT[C/T]GATTAACCCTGACATTTCCCTATCC	G	A (Rev strand)	0.4081
rs4498089	Intron 1	AGTGTTAACTTATTTTTATTTTTAA[A/G]AAAATTGTTAAGGGCTTTCCAGCAA	A	G	0.2917
rs112353753	Intron 1	GACATGCACTGCCATGCCTGGGTAA[-/T]TTTTTTTTTTCCCCCGAGACGGAG	T	delT	0.1154
rs57666989	Intron 1	CTGCAAGCTCCGCTTCCCGAGTTCA[C/T]GCCATTCTCCTGCCTCAGTCTCCCA	C	T	0.1424
rs10006129	Intron 1	tcttgatctcctgacctcgtcatcc[C/G]ccgaccttgtgatccgcccacctcg	G	C	0.0845
rs28696693	Intron 1	GGTAATTTTTGTATTTTTAGTAGAG[A/G]TGGGGTTTTGCCATGATGAGCAGGC	A	G	0.0839
rs28393280	Intron 1	GGATTTTGAATGCGGAACCAACTGC[A/G]CTTGTTGAACTCTGCTAAGTATAAC	A	G	0.0717

	SpCas9_WT (NRG)						SpCas9_VQR/EQR (NGAN_NGNG/NGAG)					
	Reference Allele			Minor allele			Reference Allele			Minor allele		
# Variant ID	PAM Motif	Strand	PAM Ref>Min	PAM Motif	Strand	PAM Ref>Min	PAM Motif	Strand	PAM Ref>Min	PAM Motif	Strand	PAM Ref>Min
rs35631490	TGG	Negative	Loss	–	–	–	GGAA	Negative	Loss	–	–	–
rs73086139	–	–	–	–	–	–	–	–	–	GGCG	Positive	Gain
rs73086140	GGG	Negative	Loss	CGG	Positive	Gain	GGCG	Negative	Loss	–	–	–
rs113541600	–	–	–	–	–	–	–	–	–	–	–	–
rs61791259	–	–	–	–	–	–	–	–	–	–	–	–
rs61792460	–	–	–	–	–	–	GGCG	Positive	Loss	–	–	–
rs73086144	–	–	–	–	–	–	–	–	–	–	–	–
rs73086145	–	–	–	GAG	Positive	Gain	–	–	–	–	–	–
rs61792461	–	–	–	–	–	–	–	–	–	AGCG	Positive	Gain
rs61792462	–	–	–	AAG	Positive	Gain	–	–	–	AGAG	Positive	Gain
rs61090955	–	–	–	GAG	Positive	Gain	–	–	–	–	–	–
rs77384845	–	–	–	–	–	–	TGAC	Negative	Loss	–	–	–
rs10011412	–	–	–	–	–	–	–	–	–	–	–	–
rs61792464	GGG	Negative	Loss	AAG	Positive	Gain	–	–	–	–	–	–
rs112435590	AGG	Positive	Loss	–	–	–	–	–	–	–	–	–
rs111670395	CAG	Positive	Loss	–	–	–	–	–	–	–	–	–
rs762855	–	–	–	–	–	–	–	–	–	–	–	–
rs9996199	CAG	Negative	Loss	TAG	Positive	Gain	–	–	–	–	–	–
rs143861513	–	–	–	–	–	–	–	–	–	–	–	–
rs28431418	–	–	–	–	–	–	–	–	–	–	–	–
rs2857935	GGG	Negative	Loss	–	–	–	GGAT	Negative	Loss	–	–	–
rs28616835	–	–	–	–	–	–	–	–	–	–	–	–
rs149624523	–	–	–	–	–	–	–	–	–	–	–	–
rs13122415	AGG	Negative	Loss	–	–	–	GGGG	Positive	Loss	–	–	–
rs113331544	–	–	–	–	–	–	–	–	–	GGCG	Positive	Gain
rs13132932	–	–	–	–	–	–	–	–	–	GGCG	Positive	Gain
rs13102260	TGG	Positive	Loss	–	–	–	–	–	–	TGAG	Positive	Gain
rs10009935	–	–	–	CGG	Negative	Gain	CGAG	Negative	Loss	–	–	–
rs58870770	–	–	–	–	–	–	–	–	–	–	–	–
rs34045730	–	–	–	–	–	–	–	–	–	–	–	–
rs28656215	–	–	–	–	–	–	–	–	–	–	–	–
rs28571971	TGG	Positive	Loss	CAG	Negative	Gain	–	–	–	–	–	–
rs28583447	–	–	–	–	–	–	–	–	–	TGCG	Negative	Gain
rs28468636	CGG	Negative	Loss	–	–	–	–	–	–	TGCG	Positive	Gain
rs28564368	GGG	Negative	Loss	–	–	–	GGAC/TGGG	Neg/Neg	Loss	–	–	–
rs28485764	–	–	–	–	–	–	–	–	–	–	–	–
rs77173925	–	–	–	AAG	Positive	Gain	–	–	–	AGAA	Positive	Gain
rs3905238	–	–	–	–	–	–	–	–	–	TGCG	Negative	Gain
rs33950430	–	–	–	–	–	–	–	–	–	–	–	–
rs28377140	CAG	Positive	Loss	AAG	Negative	Gain	–	–	–	–	–	–
rs3856973	–	–	–	–	–	–	CGAG	Negative	Loss			
rs4498089	–	–	–	AAG	Positive	Gain	–	–	–	AGAA	Positive	Gain
rs112353753	–	–	–	–	–	–	–	–	–	–	–	–
rs57666989	–	–	–	–	–	–	GGCG	Negative	Loss	–	–	–
rs10006129	–	–	–	GGG	Negative	Gain	–	–	–	CGGG	Negative	Gain
rs28696693	–	–	–	AGG	Positive	Gain	AGAT	Positive	Loss	–	–	–
rs28393280	–	–	–	–	–	–	–	–	–	TGCG	Positive	Gain

	SpCas9_VRER (NGCG)						SaCas9 (NNGRRT/NNGRR)					
	Reference Allele			Minor allele			Reference Allele			Minor allele		
# Variant ID	PAM Motif	Strand	PAM Ref>Min	PAM Motif	Strand	PAM Ref>Min	PAM Motif	Strand	PAM Ref>Min	PAM Motif	Strand	PAM Ref>Min
rs35631490	–	–	–	–	–	–	TGGAA	Negative	Loss	–	–	–
rs73086139	–	–	–	GGCG	Positive	Gain	–	–	–	GCGGG	Positive	Gain
rs73086140	GGCG	Negative	Loss	–	–	–	–	–	–	–	–	–
rs113541600	–	–	–	–	–	–	–	–	–	–	–	–
rs61791259	–	–	–	–	–	–	CCGGG	Negative	Loss	–	–	–
rs61792460	GGCG	Positive	Loss	–	–	–	GCGGA	Positive	Loss	–	–	–
rs73086144	–	–	–	–	–	–	–	–	–	–	–	–
rs73086145	–	–	–	–	–	–	–	–	–	–	–	–
rs61792461	–	–	–	AGCG	Positive	Gain	–	–	–	–	–	–
rs61792462	–	–	–	–	–	–	–	–	–	AAGAG	Positive	Gain
rs61090955	–	–	–	–	–	–	–	–	–	–	–	–
rs77384845	–	–	–	–	–	–	–	–	–	–	–	–
rs10011412	–	–	–	–	–	–	–	–	–	–	–	–
rs61792464	–	–	–	–	–	–	–	–	–	–	–	–
rs112435590	–	–	–	–	–	–	GAGAG	Positive	–	GAGAGT	Positive	Gain
rs111670395	–	–	–	–	–	–	–	–	–	–	–	–
rs762855	–	–	–	–	–	–	–	–	–	–	–	–
rs9996199	–	–	–	–	–	–	–	–	–	–	–	–
rs143861513	–	–	–	–	–	–	–	–	–	–	–	–
rs28431418	–	–	–	–	–	–	GTGAGT	Positive	Loss	GTGAG	Positive	–
rs2857935	–	–	–	–	–	–	CGGGG	Negative	–	CGGGGT	Negative	Gain
rs28616835	–	–	–	–	–	–	–	–	–	–	–	–
rs149624523	–	–	–	–	–	–	–	–	–	GTGGG	Negative	Gain
rs13122415	–	–	–	AGCG	Negative	Gain	AGGGG	Negative	Loss	–	–	–
rs113331544	–	–	–	GGCG	Positive	Gain	–	–	–	–	–	–
rs13132932	–	–	–	GGCG	Positive	Gain	–	–	–	GCGGG	Positive	Gain
rs13102260	–	–	–	–	–	–	TGGGG	Positive	Loss	–	–	–
rs10009935	–	–	–	–	–	–	–	–	–	CGGGA	Negative	Gain
rs58870770	–	–	–	–	–	–	–	–	–	–	–	–
rs34045730	–	–	–	–	–	–	–	–	–	–	–	–
rs28656215	–	–	–	–	–	–	–	–	–	–	–	–
rs28571971	–	–	–	–	–	–	–	–	–	–	–	–
rs28583447	–	–	–	GGCG/TGCG	Pos/Neg	Gain	–	–	–	–	–	–
rs28468636	–	–	–	TGCG	Positive	Gain	CGGAA	Negative	Loss	–	–	–
rs28564368	–	–	–	–	–	–	–	–	–	–	–	–
rs28485764	–	–	–	–	–	–	–	–	–	–	–	–
rs77173925	–	–	–	–	–	–	–	–	–	AAGAA	Positive	Gain
rs3905238	–	–	–	TGCG	Negative	Gain	–	–	–	–	–	–
rs33950430	–	–	–	–	–	–	–	–	–	–	–	–
rs28377140	–	–	–	–	–	–	–	–	–	–	–	–
rs3856973	–	–	–	–	–	–	TCGAGT	Negative	Loss	–	–	–
rs4498089	–	–	–	–	–	–	–	–	–	AAGAA	Positive	Gain
rs112353753	–	–	–	–	–	–	–	–	–	–	–	–
rs57666989	GGCG	Negative	Loss	–	–	–	–	–	–	–	–	–
rs10006129	GGCG	Negative	Loss	–	–	–	–	–	–	GGGGG	Negative	Gain
rs28696693	–	–	–	–	–	–	–	–	–	–	–	–
rs28393280	–	–	–	TGCG/AGCG	Pos/Neg	Gain	–	–	–	–	–	–

	LbCpf1 (TTTN/TTCN/CTTN/TCTN/ATTN/TCCN/TTGN/GTTN/CCCN/CCTN...)						AsCpf1(TTTN)					
	Reference Allele			Minor allele			Reference Allele			Minor allele		
# Variant ID	PAM Motif	Strand	PAM Ref>Min	PAM Motif	Strand	PAM Ref>Min	PAM Motif	Strand	PAM Ref>Min	PAM Motif	Strand	PAM Ref>Min
rs35631490	TCCA	Positive	Loss	–	–	–	–	–	–	–	–	–
rs73086139	–	–	–	–	–	–	–	–	–	–	–	–
rs73086140	–	–	–	–	–	–	–	–	–	–	–	–
rs113541600	–	–	–	–	–	–	–	–	–	–	–	–
rs61791259	–	–	–	–	–	–	–	–	–	–	–	–
rs61792460	–	–	–	–	–	–	–	–	–	–	–	–
rs73086144	–	–	–	–	–	–	–	–	–	–	–	–
rs73086145	–	–	–	–	–	–	–	–	–	–	–	–
rs61792461	–	–	–	–	–	–	–	–	–	–	–	–
rs61792462	–	–	–	TCTT	Negative	Gain	–	–	–	–	–	–
rs61090955	–	–	–	–	–	–	–	–	–	–	–	–
rs77384845	–	–	–	–	–	–	–	–	–	–	–	–
rs10011412	–	–	–	–	–	–	–	–	–	–	–	–
rs61792464	–	–	–	–	–	–	–	–	–	–	–	–
rs112435590	–	–	–	–	–	–	–	–	–	–	–	–
rs111670395	–	–	–	–	–	–	–	–	–	–	–	–
rs762855	–	–	–	–	–	–	–	–	–	–	–	–
rs9996199	–	–	–	–	–	–	–	–	–	–	–	–
rs143861513	–	–	–	–	–	–	–	–	–	–	–	–
rs28431418	–	–	–	–	–	–	–	–	–	–	–	–
rs2857935	TCCC	Positive	Loss	–	–	–	–	–	–	–	–	–
rs28616835	–	–	–	–	–	–	–	–	–	–	–	–
rs149624523	–	–	–	–	–	–	–	–	–	–	–	–
rs13122415	–	–	–	–	–	–	–	–	–	–	–	–
rs113331544	–	–	–	–	–	–	–	–	–	–	–	–
rs13132932	–	–	–	–	–	–	–	–	–	–	–	–
rs13102260	–	–	–	–	–	–	–	–	–	–	–	–
rs10009935	–	–	–	–	–	–	–	–	–	–	–	–
rs58870770	–	–	–	–	–	–	TTTA	Negative	Loss	–	–	–
rs34045730	–	–	–	–	–	–	–	–	–	–	–	–
rs28656215	–	–	–	–	–	–	–	–	–	–	–	–
rs28571971	–	–	–	–	–	–	–	–	–	–	–	–
rs28583447	–	–	–	–	–	–	–	–	–	–	–	–
rs28468636	TCCG	Positive	Loss	–	–	–	–	–	–	–	–	–
rs28564368	TCCC	Positive	Loss	–	–	–	–	–	–	–	–	–
rs28485764	–	–	–	–	–	–	–	–	–	–	–	–
rs77173925	–	–	–	–	–	–	TTTT	Negative	Loss	–	–	–
rs3905238	–	–	–	–	–	–	–	–	–	–	–	–
rs33950430	TTTG	Negative	Loss	–	–	–	TTTG	Negative	Loss	–	–	–
rs28377140	–	–	–	–	–	–	–	–	–	–	–	–
rs3856973	–	–	–	–	–	–	–	–	–	–	–	–
rs4498089	–	–	–	–	–	–	TTTA	Negative	Loss	–	–	–
rs112353753	–	–	–	–	–	–	–	–	–	–	–	–
rs57666989	–	–	–	–	–	–	–	–	–	–	–	–
rs10006129	–	–	–	–	–	–	–	–	–	–	–	–
rs28696693	–	–	–	–	–	–	–	–	–	–	–	–
rs28393280	–	–	–	–	–	–	–	–	–	–	–	–

Supplementary Table 2: List of prevalent SNPs upstream human HTT exon-1.

				Allele frequency			
SNP ID	**Variant ID**	**Location**	**SNP**	**Reference**	**1000G MAF**	**Strand**	**PAM**
SNP4	rs35631490	3,071,679	C/G	C=0.8926	G = 0.1074	+	Loss
SNP5	rs61792464	3,073,385	G/C	G=0.8628	C = 0.1372	+	Gain/Loss
SNP6	rs9996199	3,074,965	C/G	C=0.8425	G = 0.1575	+	Gain/Loss
SNP1	rs2857935	3,075,691	C/G/T	C=0.7710	G= 0.2260	-	Loss
SNP2	rs13122415	3,076,181	C/G	C=0.8918	G = 0.1082	+	Loss
SNP3	rs13102260	3,076,405	G/A	G=0.8419	A = 0.1581	+	Loss

Supplementary Table 3: SNP genotyping of 23 HD fibroblast lines.

HD Fibroblast	**CAG repeat**	**SNP1 rs2857935 (C>G/T) 0.226**	**SNP2 rs13122415 (C>G) 0.1082**	**SNP3 rs13102260 (G>A) 0.1581**	**SNP4 rs35631490 (C>G) 0.1074**	**SNP5 rs61792464 (C>G) 0.1372**	**SNP6 rs9996199 (C>G) 0.1575**
GM04723	CAG:72	**C/G**	C	G	C	G	C
GM04869	CAG:50	C	C	G	C	G	C
GM04767	CAG:47	**C/G**	C	G	C	G	C
GM04887	ND	C	C	G	C	G	C
GM04849	ND	C	C	G	C	G	C
GM04689	CAG:46	C	C	G	C	G	C
ND29801	CAG:40	C	C	G	C	G	C
ND29970	CAG:40	**C**	C	**G/A**	C	**G/C**	**G/C**
ND30013	CAG:43	C	C	G	C	G	C
ND30015	CAG:41	**C/G**	C	G	C	G	C
ND30016	CAG:41	**C/G**	C	G	C	G	C
ND30047	CAG:41	**C/G**	C	G	C	G	C
ND30259	CAG:38	C	C	G	C	G	C
ND30422	CAG:40	**C/G**	C	G	C	G	C
ND30626	CAG:41	**C/G**	C	G	C	G	C
ND30967	CAG:43	C	C	G	C	G	C
ND31038	CAG:44	**C/G**	C	G	C	G	C
ND31551	CAG:39	**C/G**	**C/G**	**G/A**	**C/G**	G	**G/C**
ND31846	CAG:40	C	C	G	C	G	C
ND33392	CAG:57	**C/G**	C	G	C	G	C
ND33947	CAG:40	**C/G**	C	G	C	G	C
ND40536	CAG:66	C	C	G	C	G	C
ND40534	CAG:46/26	**C**	C	G	C	G	C

Supplementary Table 4: Genotyping of the nucleotide variation in the mutant and normal allele of HD fibroblast lines heterozygotic for SNP1.

a

			Huntingtin Allele			
HD Fibroblast	**CAG repeat**	**SNP**	**Normal**	**Mutant**	**Targeted**	**Family**
GM04723	CAG:72/17	C/G	G	**C**	Mutant	691
GM04767	CAG:47/18	C/G	G	**C**	Mutant	691
ND30015	CAG:41/20	C/G	G	**C**	Mutant	NINDS3749
ND30016	CAG:41/21	C/G	G	**C**	Mutant	NINDS3749
ND30047	CAG:41/18	C/G	G	**C**	Mutant	NINDS3753
ND30422	CAG:40/18	C/G	G	**C**	Mutant	NINDS3751
ND30626	CAG:41/21	C/G	G	**C**	Mutant	NINDS3752
ND31038	CAG:44/19	C/G	**C**	G	Normal	NINDS3752
ND31551	CAG:39/18	C/G	**C**	G	Normal	Unknown
ND33392	CAG:57/17	C/G	G	**C**	Mutant	NINDS4250
ND33947	CAG:40/18	C/G	G	**C**	Mutant	Unknown

b

SNP1: rs2857935 (C/G/T) PAM: Loss

Major Allele (C): PAM motif on the Positive strand (NGG)

```
                                      PAM
5' GTCGCCCCGCTCCAGGCGTCGGCGGGGGATCCTTTCCGCATGGGCCTGC 3'
3' CAGCGGGGCGAGGTCCGCAGCCGCCCCCTAGGAAAGGCGTACCCGGACG 5'
           5' GCTCCAGGCGTCGGCGG 3'  ▲
```

Minor Allele (G): Disruption of the PAM motive.

```
5' GTCGCCCCGCTCCAGGCGTCGGCGGGGCATCCTTTCCGCATGGGCCTGC 3'
3' CAGCGGGGCGAGGTCCGCAGCCGCCCCGTAGGAAAGGCGTACCCGGACG 5'
                              ▲
```

Minor Allele (T): Disruption of the PAM motive.

```
5' GTCGCCCCGCTCCAGGCGTCGGCGGGGAATCCTTTCCGCATGGGCCTGC 3'
3' CAGCGGGGCGAGGTCCGCAGCCGCCCCTTAGGAAAGGCGTACCCGGACG 5'
                              ▲
```

Table S5

Oligos to generate guide sequences:

Name:	Sequence
PosCRPAS1	caccGCTCCAGGCGTCGGCGG
NegCRPAS1	aaacCCGCCGACGCCTGGAGC
PosCRPAS2	caccGGCGCGGGGCTCAACGGAG
NegCRPAS2	aaacCTCCGTTGAGCCCCGCGCC
PosCRPAS3	caccGTCTGGGACGCAAGGCGCCG
NegCRPAS3	aaacCGGCGCCTTGCGTCCCAGAC
PosCRPAS4	caccGATGCACGCGGGGTGGGGC
NegCRPAS4	aaacGCCCCACCCCGCGTGCATC
PosCRPAS5G	tcccATTCAGGTTGATGTCCT
NegCRPAS5G	aaacAGGACATCAACCTGAAT
PosCRPAS5C	tcccATCCCATTCTGAGGTTCTGG
NegCRPAS5C	aaacCCAGAACCTCAGAATGGGAT
PosCRPAS6C	caccGCAGGCAGAGAGGAGCC
NegCRPAS6C	aaacGGCTCCTCTCTGCCTGC
PosCRPAS6G	caccGCCTGGCTAAAGTAGGCTT
NegCRPAS6G	aaacAAGCCTACTTTAGCCAGGC
PosCRi3	caccGCTTTTAGGACGCCTCGG
NegCRI3	aaacCCGAGGCGTCCTAAAAGC
PosCRi4	caccGCGGGACACTTCGAGAGG
NegCRI4	aaacCCTCTCGAAGTGTCCCGC

Primers to assess cleavage

Name:	Sequence
Fwd1SNP	5’-GAC CAC GCG CAT TCT CT -3’
Fwd4SNP	5'- GGA AAC AGG ACA GAT GAA GGAG- 3'
Fwd5SNP	5'- CAG CTC AGA CGG AAG TGT ATT T-3'
Fwd6SNP	5'-CTC CCA AGA ACT GGG AAC TAA C 3'
Rev3Cleavage	5'-ACC ACC GTG ATC ATG AAC TAA A-3'

Name:	Sequence
Fwd HTT	TCGGTGCAGCGGCTCCTC
Rev HTT	ATGGCGACCCTGGAAAAGCTG
FwdActB	TTCGCGGGCGACGATGC
RevActB	CGTACATGGCTGGGGTGTTG