17] including cell type specific delivery, the efficiency of homologous recombination, and the frequency of on-target repair errors and off-target editing. Moreover, at >6 kb per transcript, the sodium channel coding region of *SCN1A* exceeds the capacity of AAV thus limiting the utility of the rapid pace of advancing AAV therapies for tissue specific gene replacement. Thus, there are limited clinical options for *SCN1A* LOF associated with Dravet Syndrome, and the therapeutic pipeline remains thin. The compositions and methods described herein address this and other deficiencies in the art.

SUMMARY

The compositions and methods described herein have a broad range of applications, providing potential disease modifying therapies for a range of haploinsufficiency disorders. The key advantage of this mRNA regulon approach is that it is 100% agnostic to mutation type and location by stabilizing the mRNA of the wild-type (WT) allele. The potential to reengineer these approaches for other indications is high and facile.

Thus, provided herein are fusion proteins comprising: an RNA effector protein that targets mRNA(s) of an active allele of a gene associated with a haploinsufficiency disorder; and a regulon moiety that stimulates and/or stabilizes the mRNA(s). In one aspect, the present disclosure refers to a fusion protein comprising: an RNA effector protein that targets an endogenous mRNA(s) of an active allele of a gene associated with a haploinsufficiency disorder, wherein the RNA effector protein is a catalytically inactive Cas protein; and

a regulon moiety that stimulates and/or stabilizes the endogenous mRNA(s).

In some examples, the RNA effector protein is a Cas effector protein selected from the group consisting of Cas9, Cas12, Cas13, and Cas14. In some examples, the RNA effector protein is Cas13b. In some examples, the Cas effector protein is a catalytically inactive Cas protein.

In some examples, the regulon moiety is PABPC1 or NAT10.

In some examples, the fusion proteins further comprise a linker and/or a spacer.

In some examples, the fusion proteins further comprise a nuclear export signal and/or an epitope tag.

In some examples, the RNA effector protein is N terminal to the regulon moiety. In some examples, the RNA effector protein is C terminal to the regulon moiety.

In some examples, the fusion proteins comprise or consist of SEQ ID NO: 48 or SEQ ID NO: 49 or a polypeptide having at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% sequence identity to SEQ ID NO: 48 or SEQ ID NO: 49.

Also provided herein are polynucleotides encoding any one of the fusion proteins described herein. In one aspect, the present disclosure refers to a polynucleotide encoding the fusion protein as described herein. Also provided herein are vectors comprising any one of the polynucleotides described herein. In another aspect, the present disclosure refers to a vector comprising the polynucleotide as described herein. Also provided herein are cells comprising any one of the vectors described herein. In yet another example, the present disclosure refers to a cell comprising the vector as described herein.

Also provided herein are systems comprising: a fusion protein comprising: an RNA effector protein that targets mRNA(s) of an active allele of a gene associated with a haploinsufficiency disorder; and a regulon moiety that stimulates and/or stabilizes the mRNA(s); and a gRNA that forms a complex with the RNA effector protein and comprises a complementarity region that hybridizes with the mRNA(s) of the active allele. In one aspect, the present disclosure refers to a system comprising: a fusion protein of the disclosure; and a gRNA that forms a complex with the RNA effector protein and comprises a complementarity region that hybridizes with the endogenous mRNA(s) of the active allele.

In some examples, the RNA effector protein is a Cas effector protein selected from the group consisting of Cas9, Cas12, Cas13, and Cas14. In some examples, the Cas effector protein is Cas13b. In some examples, the Cas effector protein is a catalytically inactive Cas effector protein.

In some examples, the regulon moiety is PABPC1 or NAT10.

In some examples, the fusion protein further comprises a linker and/or a spacer. In some examples, the fusion protein further comprises a nuclear export signal and/or an epitope tag.

In some examples, the RNA effector protein is N terminal to the regulon moiety. In some examples, the RNA effector protein is C terminal to the regulon moiety.

In some examples, the fusion protein comprises or consists of SEQ ID NO: 48 or SEQ ID NO: 49 or a polypeptide having at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% sequence identity to SEQ ID NO: 48 or SEQ ID NO: 49.

In some examples, the gRNA targets an mRNA encoding MeCP2, SCN1A, SYNGAP1, SHANK3, CHD2, or PTEN. In some examples, the gRNA comprises a complementarity region designed to hybridize to an mRNA selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16 , SEQ ID NO: 17, SEQ ID NO: 18, and combinations thereof. In some examples, the gRNA comprises a complementarity region designed to hybridize to an mRNA selected from the group consisting of SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 10, SEQ ID NO: 15, SEQ ID NO: 17, and combinations thereof.

In some examples, the gRNA comprises a complementarity region designed to hybridize to an mRNA encoding an amino acid selected from the group consisting of SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, and combinations thereof.

In some examples, the gRNA comprises a complementarity region designed to hybridize to an mRNA selected from the group consisting of SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID

NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36, and combinations thereof.

In some examples, the gRNA comprises a complementarity region designed to hybridize to an mRNA encoding an amino acid selected from the group consisting of SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 41, and combinations thereof.

In some examples, the gRNA is selected from the group consisting of SEQ ID NO: 55, SEQ ID NO: 56, SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID NO: 61, SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 64, SEQ ID NO: 65, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 68, SEQ ID NO: 69, SEQ ID NO: 70, SEQ ID NO: 71, and SEQ ID NO: 72.

Also provided herein are one or more polynucleotide(s) encoding any one of the systems described herein. In one aspect, the present disclosure refers to one or more polynucleotide(s) encoding the system as described herein. Also provided herein are one or more vector(s) comprising any one of the polynucleotide(s) described herein. In another aspect, the present disclosure refers to one or more vector(s) comprising the polynucleotide(s) as described herein. Also provided herein are cells comprising any one of the vector(s) described herein. In yet another example, the present disclosure refers to a cell comprising the vector(s) as described herein.

Also provided herein are complexes comprising: a fusion protein comprising: an RNA effector protein that targets mRNA(s) of an active allele of a gene associated with a haploinsufficiency disorder; and a regulon moiety that stimulates and/or stabilizes the mRNA(s), bound to a gRNA comprising a complementarity region that hybridizes with the mRNA(s) of the active allele. In one aspect, the present disclosure refers to a complex comprising: a fusion protein comprising: an RNA effector protein that targets mRNA(s) of an active allele of a gene associated with a haploinsufficiency disorder; and a regulon moiety that stimulates and/or stabilizes the mRNA(s), bound to a gRNA comprising a complementarity region that hybridizes with the mRNA(s) of the active allele.

In some examples, the RNA effector protein is dCas13b and the regulon moiety is PABP1 or NAT10.

In some examples, the gRNA comprises a complementarity region designed to hybridize to an mRNA selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16 , SEQ ID NO: 17, SEQ ID NO: 18, and combinations thereof. In some examples, the gRNA comprises a complementarity region designed to hybridize to an mRNA selected from the group consisting of SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 10, SEQ ID NO: 15, SEQ ID NO: 17, and combinations thereof.

In some examples, the gRNA comprises a complementarity region designed to hybridize to an mRNA encoding an amino acid selected from the group consisting of SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, and combinations thereof.

In some examples, the gRNA comprises a complementarity region designed to hybridize to an mRNA selected from the group consisting of SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36, and combinations thereof.

In some examples, the gRNA comprises a complementarity region designed to hybridize to an mRNA encoding SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 41, and combinations thereof.

Also provided herein are complexes comprising: a fusion protein comprising: an RNA effector protein that targets mRNA(s) of an active allele of a gene associated with a haploinsufficiency disorder; and a regulon moiety that stimulates and/or stabilizes the mRNA(s), bound to a gRNA and the mRNA. In one aspect, the present disclosure refers to a complex comprising: a fusion protein comprising: an RNA effector protein that targets an endogenous mRNA(s) of an active allele of a gene associated with a haploinsufficiency disorder, wherein the RNA effector protein is a catalytically inactive Cas protein; and a regulon moiety that stimulates and/or stabilizes the endogenous mRNA(s), bound to a gRNA and the endogenous mRNA.

In some examples, the RNA effector protein is dCas13b and the regulon moiety is PABP1 or NAT10.

In some examples, the mRNA is selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16 , SEQ ID NO: 17, SEQ ID NO: 18, and combinations thereof. In some examples, the mRNA encodes an amino acid selected from the group consisting of SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 10, SEQ ID NO: 15, SEQ ID NO: 17, and combinations thereof.

In some examples, the mRNA is selected from the group consisting of SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, and combinations thereof.

In some examples, the mRNA is selected from the group consisting of SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36, and combinations thereof.

In some examples, the mRNA encodes an amino acid selected from the group consisting of is selected from the group consisting of SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 41, and combinations thereof.

Also provided herein are pharmaceutical compositions comprising: any one of the fusion proteins or systems described herein. In some examples, the pharmaceutical compositions further comprise a pharmaceutically acceptable carrier.

In one aspect, the present disclosure refers to a pharmaceutical composition comprising: the fusion protein or system as described herein or one or more polynucleotide(s) encoding the fusion protein as described herein or system as described herein.

Also provided herein are pharmaceutical compositions comprising: one or more nucleic acids encoding any one of the fusion proteins or systems described herein. In one example, the present disclosure refers to a pharmaceutical composition comprising: one or more nucleic acids encoding the fusion protein or system as described herein.

Also provided herein are viral vectors comprising one or more nucleic acids encoding any one of the fusion proteins or systems described herein. In one aspect, the present disclosure refers to a viral vector comprising one or more nucleic acids encoding the fusion protein or system as described herein. In some examples, the viral vector is an adeno-associated viral vector.

Also provided herein are nanoparticles or liposomes comprising any one of the fusion proteins or systems described herein or one or more nucleic acids encoding any one of the fusion proteins or systems described herein. In one aspect, the present disclosure refers to a nanoparticle or liposome comprising the fusion protein or system as described herein or one or more polynucleotides encoding the fusion protein or system as described herein.

Also provided herein are methods of stimulating or stabilizing mRNA(s), the method comprising: contacting the mRNA(s) with any one of the fusion proteins or systems described herein. In some examples, the method is carried out, in vitro, in vivo, or ex vivo. In one aspect, the present disclosure refers to an *in vitro* method of stimulating or stabilizing endogenous mRNA(s), the method comprising: contacting the endogenous mRNA(s) with the fusion protein or system as described herein. In another aspect, the present disclosure refers to use of the fusion protein or system as described herein in the manufacture of a medicament for stimulating or stabilizing endogenous mRNA(s), wherein the medicament is to be contacted with the endogenous mRNA(s) *in vivo* or *ex vivo*.

Also provided herein are methods of treating or preventing a haploinsufficiency disorder in a subject, the method comprising: administering to the subject a fusion protein or a nucleic acid encoding a fusion protein comprising: an RNA effector protein that targets mRNA(s) of an active allele of a gene associated with a haploinsufficiency disorder; and a regulon moiety that stimulates and/or stabilizes the mRNA(s); and a gRNA or a nucleic acid encoding a gRNA designed to form a complex with the RNA effector protein and comprising a complementarity region designed to hybridize with the mRNA of the active allele. In one aspect, the present disclosure refers to use of a fusion protein or a nucleic acid encoding a fusion protein comprising: an RNA effector protein that targets endogenous mRNA(s) of an active allele of a gene associated with a haploinsufficiency disorder, wherein the RNA effector protein is a catalytically inactive Cas protein; and a regulon moiety that stimulates and/or stabilizes the endogenous mRNA(s); and a gRNA or a nucleic acid encoding a gRNA designed to form a complex with the RNA effector protein and comprising a complementarity region designed to hybridize with the endogenous mRNA of the active allele in the manufacture of a medicament for treating or preventing a haploinsufficiency disorder in a subject.

In some examples, the RNA effector protein is a Cas effector protein selected from the group consisting of a Cas9, Cas12, Cas13, and Cas14. In some examples, the Cas effector protein is Cas13b. In some examples, the Cas effector protein is a catalytically inactive Cas protein.

In some examples, the regulon moiety is PABPC1 or NAT10.

In some examples, the fusion protein further comprises a linker and/or a spacer. In some examples, the fusion protein further comprises a nuclear export signal and/or an epitope tag.

In some examples, the RNA effector protein is N terminal to the regulon moiety. In some examples, the RNA effector protein is C terminal to the regulon moiety.

In some examples, the fusion protein comprises or consists of SEQ ID NO: 48 or SEQ ID NO: 49 or a polypeptide having at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% sequence identity to SEQ ID NO: 48 or SEQ ID NO: 49.

In some examples, the haploinsufficiency disorder is selected from the group consisting from 5qsyndrome,Adams-Oliver syndrome 1, Adams-Oliver syndrome 3, Adams-Oliver syndrome 5,Adams-Oliver syndrome 6, Alagille syndrome 1, Autoimmune lymphoproliferative syndrome type IA, Autoimmune lymphoproliferative syndrome type V,

WHAT IS CLAIMED IS:

1. A fusion protein comprising:

an RNA effector protein that targets an endogenous mRNA(s) of an active allele of a gene associated with a haploinsufficiency disorder, wherein the RNA effector protein is a catalytically inactive Cas protein; and

a regulon moiety that stimulates and/or stabilizes the endogenous mRNA(s).

2. The fusion protein of claim 1, wherein the RNA effector protein is a catalytically inactive Cas9, Cas12, Cas13, or Cas14.

3. The fusion protein of any one of the preceding claims, wherein the regulon moiety is PABPC1 or NAT10.

4. The fusion protein of any one of the preceding claims, further comprising a linker, a spacer, a nuclear export signal, and/or an epitope tag.

5. The fusion protein of any one of the preceding claims, wherein the RNA effector protein is N terminal to the regulon moiety.

6. The fusion protein of any one of the preceding claims, wherein the RNA effector protein is C terminal to the regulon moiety.

7. The fusion protein of claim 1 comprising or consisting of SEQ ID NO: 48 or SEQ ID NO: 49 or a polypeptide having at least 80% sequence identity to SEQ ID NO: 48 or SEQ ID NO: 49.

8. A polynucleotide encoding the fusion protein of any one of the preceding claims.

9. A vector comprising the polynucleotide of claim 8.

10. A system comprising:

a fusion protein of any one of claims 1-7; and

a gRNA that forms a complex with the RNA effector protein and comprises a complementarity region that hybridizes with the endogenous mRNA(s) of the active allele.

11. The system of claim 10, wherein the gRNA targets an endogenous mRNA encoding MeCP2, SCN1A, SYNGAP1, SHANK3, CHD2, or PTEN.

12. One or more polynucleotide(s) encoding the system of claim 10 or claim 11.

13. One or more vector(s) comprising the polynucleotide(s) of claim 12.

14. A complex comprising:

a fusion protein comprising:

an RNA effector protein that targets an endogenous mRNA(s) of an active allele of a gene associated with a haploinsufficiency disorder, wherein the RNA effector protein is a catalytically inactive Cas protein; and

a regulon moiety that stimulates and/or stabilizes the endogenous mRNA(s),

bound to a gRNA comprising a complementarity region that hybridizes with the endogenous mRNA(s) of the active allele.

15. The complex of claim 14, wherein the RNA effector protein is dCas13b and the regulon moiety is PABP1 or NAT10.

16. A complex comprising:

a fusion protein comprising:

an RNA effector protein that targets an endogenous mRNA(s) of an active allele of a gene associated with a haploinsufficiency disorder, wherein the RNA effector protein is a catalytically inactive Cas protein; and

a regulon moiety that stimulates and/or stabilizes the endogenous mRNA(s),

bound to a gRNA and the endogenous mRNA.

17. The complex of claim 16, wherein the RNA effector protein is dCas13b and the regulon moiety is PABP1 or NAT10.

18. A pharmaceutical composition comprising:

the fusion protein of any one of claims 1-7 or system of any one of claims 10-11, or

one or more polynucleotide(s) encoding the fusion protein of any one of claims 1-7 or system of any one of claims 10-11.

19. The pharmaceutical composition of claim 18, further comprising a pharmaceutically acceptable carrier.

20. A viral vector comprising one or more nucleic acids encoding the fusion protein of any one of claims 1-7 or system of any one of claims 10-11.

21. The viral vector of claim 20, wherein the viral vector is an adeno-associated viral vector.

22. A nanoparticle or liposome comprising the fusion protein of any one of claims 1-7 or system of any one of claims 10-11 or one or more polynucleotide(s) encoding the fusion protein of any one of claims 1-7or system of any one of claims 10-11.

23. An in vitro method of stimulating or stabilizing endogenous mRNA(s), the method comprising:

contacting the endogenous mRNA(s) with the fusion protein of any one of claims 1-7 or system of any one of claims 10-11.

24. Use of the fusion protein of any one of claims 1-7 or system of any one of claims 10-11 in the manufacture of a medicament for stimulating or stabilizing endogenous mRNA(s), wherein the medicament is to be contacted with the endogenous mRNA(s) *in vivo* or *ex vivo*.

25. Use of a fusion protein or a nucleic acid encoding a fusion protein comprising:

an RNA effector protein that targets endogenous mRNA(s) of an active allele of a gene associated with a haploinsufficiency disorder, wherein the RNA effector protein is a catalytically inactive Cas protein; and

a regulon moiety that stimulates and/or stabilizes the endogenous mRNA(s); and

a gRNA or a nucleic acid encoding a gRNA designed to form a complex with the RNA effector protein and comprising a complementarity region designed to hybridize with the endogenous mRNA of the active allele

in the manufacture of a medicament for treating or preventing a haploinsufficiency disorder in a subject.

26. The use of claim 25, wherein the RNA effector protein is a catalytically inactive Cas9, Cas12, Cas13, or Cas14.

27. The use of any one of claims 25-26, wherein the regulon moiety is PABPC1 or NAT10.

28. The use of any one of claims 25-27, wherein the haploinsufficiency disorder is selected from the group consisting from of 5q syndrome, Adams-Oliver syndrome 1, Adams-Oliver syndrome 3, Adams-Oliver syndrome 5, Adams-Oliver syndrome 6, Alagille syndrome 1, Autoimmune lymphoproliferative syndrome type IA, Autoimmune lymphoproliferative syndrome type V, Autosomal dominant deafness-2A, brain malformations with or without urinary tract defects (BRMUTD), Carney complex type 1, CHARGE syndrome, cleidocranial dysplasia, Currarino syndrome, Denys-Drash syndrome/Frasier syndrome, Developmental delay, intellectual disability, obesity, and dysmorphic features(DIDOD), DiGeorge syndrome (TBX1-associated), Dravet syndrome, Duane-radial ray syndrome, Ehlers-Danlos syndrome (classic-like), Ehlers-Danlos syndrome (vascular type), Feingold syndrome 1, Frontotemporal lobar degeneration with TDP43 inclusions (FTLD-TDP),GRN-related, GLUT I deficiency syndrome, Greig cephalopolysyndactyly syndrome, Hereditary hemorrhagic telangiectasia type 1, Holoprosencephaly 3, Holoprosencephaly 4 ,Holoprosencephaly 5, Holt-Oram syndrome, Hypoparathyroidism, sensorineural deafness, and renal disease (HDR), Kleefstra syndrome 1, Klippel-Trenaunay syndrome (AAGF-related), Leri-Weill dyschondrosteosis, Marfan syndrome, Mental retardation and distinctive facial features with or without cardiac defects (MRFACD), Mental retardation, autosomal dominant 1, autosomal dominant 19, autosomal dominant 29, Nail-patella syndrome (NPS), Phelan-McDermid syndrome, Pitt-Hopkins syndrome, Primary pulmonary hypertension 1, Rett syndrome (congenital variant), Smith-Magenis syndrome (RAI1 associated), Sotos syndrome 1, Sotos syndrome 2, Stickler syndrome type I, Supravalvular aortic stenosis, SYNGAP1-related intellectual disability, Treacher Collins syndrome, Trichorhinophalangeal syndrome type I, Ulnar-mammary syndrome, van der Woude syndrome1, Waardenburg syndrome type 1, Waardenburg syndrome type 2A, and Waardenburg syndrometype 4C.

29. The use of any one of claims 25-27, wherein the haploinsufficiency disorder is a CNS haploinsufficiency disorder.

30. The use of claim 29, wherein the CNS haploinsufficiency disorder is selected from the group consisting of episodic ataxia, familial hemiplegia migraine, CDKL5 deficiency disorder, CHD2 myoclonic encephalopathy, familial focal epilepsy with variable loci, FOXG1 syndrome, benign familial neonatal seizures, Rett syndrome, Dravat syndrome, SCN2A-epileptic encephalopathy, SCN2A-developmental encephalopathy, SCN8A-epileptic encephalopathy, SC8A familial infantile epilepsy, early infantile epileptic encephalopathy, myoclonic-atonic epilepsy, early infantile epileptic encephalopathy, SYNGAP1-related intellectual disability, tuberous sclerosis, Lennox-Gastaut Syndrome, FoxG1 syndrome, KCNQ2-related epileptic encephalopathy, PCDH19-related epilepsy, SLC6A1-related myoclonic-astatic epilepsy, STXBP1-related epileptic encephalopathy, SYNGAP1 syndrome, and combinations thereof.

31. The use of any one of claims 25-27, wherein the haploinsufficiency disorder is Dravet Syndrome or Rett syndrome.

32. The use of any one of claims 25-27, wherein the subject has a haploinsufficiency in a gene selected from the group consisting of *AGGFI, ARHGAP31, BMPR2, CHD7, COL2Al, COL3Al, CTLA4, CTNNBI, DLL4, EHMTI, ELN, ENG, FAS, FBNI, FOXGI, GATA3, GLI3, GRN, IRF6, JAGI, KCNQ4, LMXIB, MBD5,MED13L, MITF, MNXI, MYCN, NFIA, NFIX, NOTCH1, NSDI, PAX3, PHIP, PRKARIA, RAI1, RBPJ, RPS14, RUNX2, SALL4, SCNIA, SETBPI, SHANK3, SHH, SHOX,SLC2Al/GLUT1, SOXI0, SYNGAPI, TBXI, TBX3, TBX5, TCF4, TCOFI, TGIFI, TNXB,TRPSI, WTI, ZIC2,* and combinations thereof.

33. The use of any one of claims 25-27, wherein the subject has a mutation selected from the list in Table 4 and combinations thereof.

34. The use of any one of claims 25-27, wherein the subject has a mutation selected from the list in Table 6 and combinations thereof.

35. The use of any one of claims 25-34, wherein the subject is a mammal.

36. The use of claim 35, wherein the subject is a human.

37. The use of any one of claims 25-36, wherein the fusion protein and gRNA are to be administered as part of a pharmaceutical composition.

38. The use of any one of claims 25-36, wherein a viral vector comprising nucleic acid sequence(s) encoding the fusion protein and gRNA is to be administered to the subject.

39. The use of any one of claims 25-36, wherein a nanoparticle or liposome comprising the fusion protein and gRNA or nucleic acid sequence(s) encoding the fusion protein and gRNA is to be administered to the subject.