CLAIMS

What is claimed is:

1. A polynucleotide encoding a CRISPR interference (CRISPRi) platform comprising a single guide RNA (sgRNA) and a fusion polypeptide, wherein the fusion polypeptide further comprises a catalytically inactive Cas9 (dCas9 or iCas9) fused to an epigenetic repressor.

2. The polynucleotide of claim 1, wherein the sgRNA is under control of the U6 promoter.

3. The polynucleotide of claim 1, wherein the sgRNA targets the DUX4 locus.

4. The polynucleotide of any one of claims 1-3, wherein the fusion polypeptide is under control of a skeletal muscle-specific regulatory cassette.

5. The polynucleotide of any one of claims 1-4, wherein the catalytically inactive Cas9 is a dSaCas9.

6. The polynucleotide of any one of claims 1-5, wherein the epigenetic repressor is selected from the group consisting of HP1α, HP1γ, the chromo shadow domain and C-terminal extension region of HP1α or HP1γ, MeCP2 transcription repression domain (TRD), and SUV39H1 SET domain.

7. The polynucleotide of any one of claims 1-6, wherein the sgRNA comprises SEQ ID NO: 38, 39, 40, 41, 42, or 43.

8. The polynucleotide of any one of claims 1-6, wherein the fusion polypeptide comprises any one of SEQ ID NOs: 1-4.

9. The polynucleotide of any one of claims 1-6, wherein the polynucleotide comprises any one of SEQ ID NOs: 48-55.

10. A vector comprising a polynucleotide encoding a CRISPRi platform comprising a sgRNA and a fusion polypeptide, wherein the fusion polypeptide further comprises a catalytically inactive Cas9 (dCas9 or iCas9) fused to an epigenetic repressor.

11. The vector of claim 10, wherein the sgRNA is under control of the U6 promoter.

12. The vector of claim 10, wherein the sgRNA targets the DUX4 locus.

13. The vector of any one of claims 10-12, wherein the fusion polypeptide is under control of a skeletal muscle-specific regulatory cassette.

14. The vector of any one of claims 10-13, wherein the catalytically inactive Cas9 is a dSaCas9.

15. The vector of any one of claims 10-14, wherein the epigenetic repressor is selected from the group consisting of a HP1α, HP1γ, the chromo shadow domain and C-terminal extension region of HP1α or HP1γ, MeCP2 transcription repression domain (TRD), and SUV39H1 SET domains.

16. The vector of any one of claims 10-15, wherein the sgRNA comprises a nucleic acid selected from the group comprising SEQ ID NOs: 38, 39, 40, 41, 42, or 43.

17. The vector of any one of claims 10-16, wherein the fusion polypeptide comprises any one of SEQ ID NOs: 1-4.

18. The vector of any one of claims 10-17, wherein the polynucleotide comprises any one of SEQ ID NOs: 48-55.

19. The vector of any one of claims 10-18, wherein the vector is an adeno-associated viral (AAV) vector.

20. The vector of any one of claims 10-19, wherein the vector comprises any one of SEQ ID NOs: 48-55.

21. A method of treating facioscapulohumeral muscular dystrophy (FSHD) in a subject in need thereof, the method comprising administering to the subject an effective amount of a repressor of DUX4 gene expression, wherein the repressor decreases DUX4 gene expression in the skeletal muscle cells of the subject, thereby treating the disorder.

22. The method of claim 21 wherein the DUX4 repressor is polynucleotide comprising a CRISPRi platform comprising a sgRNA and a fusion polypeptide, wherein the fusion polypeptide further comprises a dCas9 fused to an epigenetic repressor.

23. The method of any one of claims 21-22, wherein the sgRNA targets the DUX4 locus.

24. The method of any one of claims 21-23, wherein the sgRNA comprises a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 38, 39, 40, 41, 42, or 43.

25. The method of any one of claims 21-24, wherein the dCas9 is a dSaCas9.

26. The method of any one of claims 21-25, wherein the epigenetic repressor is selected from the group consisting of HP1α, HP1γ, the chromo shadow domain and C-terminal extension region of HP1α or HP1γ, MeCP2 transcription repression domain (TRD), and SUV39H1 SET domains.

27. The method of any one of claims 21-26, wherein the fusion polypeptide is encoded by a polynucleotide comprising any one of SEQ ID NOs: 1-4.

28. The method of any one of claims 21-27, wherein the polynucleotide comprises any one of SEQ ID NOs: 48-55.

29. The method of any one of claims 21-28, wherein the subject is a mammal.

30. The method of claim 29, wherein the mammal is a human.

31. A method of treating FSHD in a subject in need thereof, the method comprising administering to the subject an effective amount of the vector of any one of claims 10-20.

32. The method of claim 31, wherein the subject is a mammal.

33. The method of claim 32, wherein the mammal is a human.

CLAIMS

What is claimed is:

1. A polynucleotide encoding a CRISPR interference (CRISPRi) platform comprising a single guide RNA (sgRNA) and a fusion polypeptide, wherein the fusion polypeptide further comprises a catalytically inactive Cas9 (dCas9 or iCas9), preferably dSaCas9 fused to an epigenetic repressor.

2. The polynucleotide of claim 1, wherein the sgRNA is under control of the U6 promoter.

3. The polynucleotide of claim 1, wherein the sgRNA targets the DUX4 locus.

4. The polynucleotide of any one of claims 1-3, wherein the fusion polypeptide is under control of a skeletal muscle-specific regulatory cassette.

5. The polynucleotide of any one of claims 1- 4, wherein the epigenetic repressor is selected from the group consisting of HP1α, HP1γ, the chromo shadow domain and C-terminal extension region of HP1α or HP1γ, MeCP2 transcription repression domain (TRD), and SUV39H1 SET domain.

6. The polynucleotide of any one of claims 1-5, wherein:

    a) the sgRNA comprises SEQ ID NO: 38, 39, 40, 41, 42, or 43;

    b) the fusion polypeptide comprises any one of SEQ ID NOs: 1-4; and/or

    c) the polynucleotide comprises any one of SEQ ID NOs: 48-55.

7. A vector comprising a polynucleotide of any one of claims 1-6.

8. The vector of claim 7, wherein the vector is an adeno-associated viral (AAV) vector.

9. The vector of claims 7 or 8, wherein the vector comprises any one of SEQ ID NOs: 48-55.

10. Use of a repressor of DUX4 gene expression in the manufacture of a medicament for treating facioscapulohumeral muscular dystrophy (FSHD) in a subject in need thereof, wherein the repressor decreases DUX4 gene expression in the skeletal muscle cells of the subject, thereby treating the disorder.

11. The use according to claim 10, wherein the DUX4 repressor is polynucleotide comprising a CRISPRi platform comprising a sgRNA and a fusion polypeptide, wherein the fusion polypeptide further comprises a dCas9, preferably a sSaCas9, fused to an epigenetic repressor.

12. The use according to claims 10 or 11, wherein the sgRNA targets the DUX4 locus.

13. The use according to any one of claims 10-12, wherein the sgRNA comprises a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 38, 39, 40, 41, 42, or 43.

14. The use according to any one of claims 10-13, wherein the epigenetic repressor is selected from the group consisting of HP1α, HP1γ, the chromo shadow domain and C-terminal extension region of HP1α or HP1γ, MeCP2 transcription repression domain (TRD), and SUV39H1 SET domains.

15. The use according to any one of claims 10-14, wherein the fusion polypeptide is encoded by a polynucleotide comprising any one of SEQ ID NOs: 1-4, and/or the polynucleotide comprises any one of SEQ ID NOs: 48-55.

16. Use of the vector of any one of claims 7-9 in the manufacture of a medicament for treating FSHD in a subject in need thereof.

17. The use according to any one of claims 10-15 or 16, wherein the subject is a mammal, preferably the mammal is a human.

18. The polynucleotide of any one of claims 1-6 or the vector of any one of claims 7-9 for use in therapy.