Claims

1. A modulatory polynucleotide for decreasing the expression of a huntingtin (HTT) gene comprising an siRNA duplex comprising a sense strand sequence and an antisense strand sequence, wherein the sense strand sequence comprises at least 19 consecutive nucleotides from the nucleotide sequence of SEQ ID NO: 168 or 171, and the antisense strand sequence comprises at least 19 consecutive nucleotides from the nucleotide sequence of SEQ ID NO: 7.

2. The modulatory polynucleotide of claim 1, wherein the sense strand sequence comprises:

(i) 19 or 20 consecutive nucleotides from SEQ ID NO: 168; or

(ii) the nucleotide sequence of SEQ ID NO: 168.

3. The modulatory polynucleotide of claim 1, wherein the sense strand sequence comprises:

(i) 19 or 20 consecutive nucleotides from SEQ ID NO: 171; or

(ii) the nucleotide sequence of SEQ ID NO: 171.

4. The modulatory polynucleotide of claim 1, wherein the antisense strand sequence comprises:

(i) 19 or 20 consecutive nucleotides from SEQ ID NO: 7; or

(ii) the nucleotide sequence of SEQ ID NO: 7.

5. The modulatory polynucleotide of claim 1, which comprises the sense strand sequence of SEQ ID NO: 168 and the antisense sequence of SEQ ID NO: 7.

6. The modulatory polynucleotide of claim 1, which comprises the sense strand sequence of SEQ ID NO: 171 and the antisense sequence of SEQ ID NO: 7.

7. The modulatory polynucleotide of claim 1, wherein the sense strand sequence and the antisense strand sequence are each at least 20, 21, 22, or 23 nucleotides in length.

8. The modulatory polynucleotide of claim 1, wherein the sense strand sequence, the antisense strand sequence, or both the sense strand sequence and the antisense strand sequence comprise a 3’ overhang of at least 1 or 2 nucleotides.

9. The modulatory polynucleotide of claim 1, wherein the antisense strand sequence comprises at least one mismatch relative to a target mRNA sequence.

10. The modulatory polynucleotide of claim 1, wherein the sense strand sequence and the antisense strand sequence comprise a region of complementarity, wherein the region of complementarity is at least 17 nucleotides in length.

11. The modulatory polynucleotide of claim 1, further comprising one, two, or all of:

(i) a first flanking region;

(ii) a loop region; or

(iii) a second flanking region.

12. The modulatory polynucleotide of claim 11, wherein:

(i) the first flanking region comprises the nucleotide sequence of any of SEQ ID NOs: 250-256;

(ii) the loop region comprises the nucleotide sequence of any of SEQ ID NOs: 257264; or

(iii) the second flanking region comprises the nucleotide sequence of any of SEQ ID NOs: 265-269.

13. The modulatory polynucleotide of claim 11, wherein:

(i) the first flanking region comprises the nucleotide sequence of SEQ ID NO: 252; the loop region comprises the nucleotide sequence of SEQ ID NO: 261; and the second flanking region comprises the nucleotide sequence of SEQ ID NO: 265; or

(ii) the first flanking region comprises the nucleotide sequence of SEQ ID NO: 256; the loop region comprises the nucleotide sequence of SEQ ID NO: 264; and the second flanking region comprises the nucleotide sequence of SEQ ID NO: 269.

14. The modulatory polynucleotide of any one of claims 1-13, wherein the modulatory polynucleotide comprises the nucleotide sequence of SEQ ID NO: 349 or 368

15. A modulatory polynucleotide for decreasing the expression of an HTT gene comprising the nucleotide sequence of SEQ ID NO: 349.

16. A modulatory polynucleotide for decreasing the expression of an HTT gene comprising the nucleotide sequence of SEQ ID NO: 368.

17. A modulatory polynucleotide for decreasing the expression of an HTT gene consisting of the nucleotide sequence of SEQ ID NO: 349 or 368.

18. The modulatory polynucleotide of claims 1, wherein the modulatory polynucleotide is a pri-microRNA.

19. An adeno-associated virus (AAV) viral genome comprising a nucleic acid sequence positioned between two inverted terminal repeats (ITRs), wherein said nucleic acid sequence encodes the modulatory polynucleotide of any one of claims 1-13, or 15-18.

20. The AAV viral genome of claim 19, which further comprises one, two, three or all of:

(i) a promoter operably linked to the nucleic acid sequence encoding the modulatory polynucleotide;

(ii) an enhancer;

(iii) an intron region; or

(iv) a poly A signal region.

21. The AAV viral genome of claim 20, wherein:

(i) the promoter comprises a CBA promoter;

(ii) the enhancer comprises a CMV enhancer; or

(iii) the intron comprises an SV40 intron.

22. A recombinant adeno-associated virus (rAAV) particle comprising the AAV viral genome of claim 19, and an AAV capsid.

23. The rAAV particle of claim 22, wherein the AAV capsid is AAV1.

24. A vector comprising the modulatory polynucleotide of any one of claims 1-13 or 15-18.

25. A cell comprising the rAAV particle of claim 22.

26. The cell of claim 25, which is a mammalian cell, a medium spiny neuron, a cortical neuron, or an astrocyte.

27. Use of a pharmaceutical composition comprising the rAAV particle of claim 22, and a pharmaceutically acceptable excipient, in the manufacture of a medicament for treating Huntington's Disease (HD) in a subject.

28. Use of a composition comprising the rAAV particle of claim 22, in the manufacture of a medicament for treating a disease of the central nervous system (CNS) in a subject.

29. Use of a composition comprising the rAAV particle of claim 22, in the manufacture of a medicament for inhibiting the expression of HTT gene in a cell.

30. The use of claim 29 wherein

(i) the cell is a mammalian cell, a medium spiny neuron, a cortical neuron, or an astrocyte;

(ii) the cell is in a subject; or

(iii) the cell is a mammalian cell, a medium spiny neuron, a cortical neuron, or an astrocyte, and the cell is in a subject.

31. The use of claim 30, wherein the subject has Huntington's disease (HD).

32. The use of claim 29, wherein expression of HTT mRNA is inhibited by at least 45%, 50%, 55%, 60%, 65%, 70%, 75%, or 80%.

33. Use of a composition comprising the rAAV particle of claim 22, in the manufacture of a medicament for treating Huntington's Disease (HD) in a subject.

34. The use of claim 33, wherein expression of an HTT gene, mRNA, protein, or a combination thereof, is inhibited in a cell of the central nervous system (CNS) or region of the CNS.

35. The use of claim 34, wherein:

(i) the cell of the CNS comprises a neuron, a medium spiny neuron, an astrocyte, or a combination thereof;

(ii) the region of the CNS is a forebrain region, a midbrain region, a putamen region, a striatum region, a cortex region, a motor cortex region, a somatosensory cortex region, a temporal cortex region, or a combination thereof; or

(iii) the region of the CNS is a putamen region.

36. The use of claim 29, wherein the HTT gene comprises a wild-type HTT gene, mRNA, or protein; an HTT gene, mRNA, or protein comprising at least one mutation; an HTT gene comprising a CAG repeat; or a combination thereof.

37. The use of claim 36, wherein the HTT gene comprising a CAG repeat is a CAG-expanded HTT, comprising at least 36-40 CAG repeats.

38. The use of claim 33, wherein the HD is:

(i) a juvenile form HD;

(ii) an early stage HD;

(iii) a late stage HD;

(iv) a fully penetrant HD, wherein an HTT gene has at least 41 or more CAG repeats;

(v) an incomplete penetrance HD, wherein an HTT gene has 36-40 CAG repeats; or

(vi) an asymptomatic HD.

39. The use of claim 33, wherein the use comprises amelioration of a symptom of HD in the subject, wherein the symptom comprises apathy or lack of initiative, dysphoria, irritability, agitation or anxiety, poor self-care, poor judgment, inflexibility, disinhibition, depression, suicidal ideation euphoria, aggression, delusions, compulsions, hypersexuality, hallucinations, dystonia, speech deterioration, slurred speech, difficulty swallowing, weight loss, bradykinesia, incoordination, cognitive dysfunction, unsteady gait and involuntary movements, CNS deterioration, or a combination thereof.

40. The use of claim 33, wherein the composition is administered:

(i) to the putamen, the thalamus, or both;

(ii) via intraputamenal administration, intrathalamic administration, or both; or

(iii) via intraparenchymal injection.

41. The use of claim 33, wherein the composition is administered to the subject in combination with an additional therapeutic agent suitable for treatment or prevention of HD, wherein the additional therapeutic agent comprises a neuroprotective agent, a dopamine-depleting agent, tetrabenazine, a benzodiazepine, clonazepam, an anticonvulsant, sodium valproate, levetiracetam, levodopa, a skeletal muscle relaxant, baclofen, tizanidine, an inhibitor for acetycholine release at the neuromuscular junction, botulinum toxin, an atypical neuroleptic, olanzapine, quetiapine, risperidone, sulpiride, haloperidol, clozapine, aripiprazole, creatine, selective serotonin reuptake inhibitor (SSRIs), citalopram, fluoxetine, paroxetine, sertraline, mirtazapine, venlafaxine, xopiclone, zolpidem, a mood stabilizer, lithium, IGF-I, GDNF, BDNF, CTNF, VEGF, Colivelin, Xaliproden, Thyrotrophin-releasing hormone, ADNF, or a combination thereof.

42. A composition comprising the rAAV particle of claim 22, for use in inhibiting the expression of HTT gene in a cell.

43. A method of making a rAAV particle, comprising:

(i) providing a cell comprising the AAV viral genome of claim 19 and a nucleic acid encoding a capsid protein; and

(ii) purifying the rAAV particle from the cell.