CLAIMS

1. An adeno-associated virus (AAV) viral genome comprising a nucleotide sequence positioned between two inverted terminal repeats (ITRs), wherein the nucleotide sequence encodes a modulatory polynucleotide comprising:

(a) a 5' flanking region comprising the nucleotide sequence of any one of SEQ ID NOs: 1-4;

(b) a loop region comprising the nucleotide sequence of any one of SEQ ID NOs: 5-9; and

(c) a 3' flanking region comprising the nucleotide sequence of any one of SEQ ID NOs: 10-14 or 810.

2. The AAV viral genome of claim 1, wherein:

(a) the 5' flanking region comprises the nucleotide sequence of SEQ ID NO: 2 or SEQ ID NO: 3;

(b) the loop region comprises the nucleotide sequence of SEQ ID NO: 5, SEQ ID NO: 6, or SEQ ID NO: 9; and

(c) the 3' flanking region comprises the nucleotide sequence of SEQ ID NO: 11, SEQ ID NO: 12, or SEQ ID NO: 13.

3. The AAV viral genome of claim 1 or 2, wherein the 5' flanking region comprises the nucleotide sequence of SEQ ID NO: 2, the loop region comprises the nucleotide sequence of SEQ ID NO: 5, and the 3' flanking region comprises the nucleotide sequence of SEQ ID NO: 12.

4. The AAV viral genome of claim 1 or 2, wherein the 5' flanking region comprises the nucleotide sequence of SEQ ID NO: 2, the loop region comprises the nucleotide sequence of SEQ ID NO: 6, and the 3' flanking region comprises the nucleotide sequence of SEQ ID NO: 11.

5. The AAV viral genome of claim 1 or 2, wherein the 5’ flanking region comprises the nucleotide sequence of SEQ ID NO: 2, the loop region comprises the nucleotide sequence of SEQ ID NO: 5, and the 3’ flanking region comprises the nucleotide sequence of SEQ ID NO: 11.

6. The AAV viral genome of claim 1 or 2, wherein the 5’ flanking region comprises the nucleotide sequence of SEQ ID NO: 3, the loop region comprises the nucleotide sequence of SEQ ID NO: 9, and the 3’ flanking region comprises the nucleotide sequence of SEQ ID NO: 13.

7. The AAV viral genome of any one of claims 1-6, further comprising a passenger strand and a guide strand.

8. The AAV viral genome of claim 7, wherein the passenger strand is located between the 5’ flanking region and the loop region and the guide strand is located between the loop region and the 3’ flanking region.

9. The AAV viral genome of claim 7 or 8, wherein:

(i) the passenger strand is between 15-30 nucleotides in length; and/or

(ii) the guide strand is between 15-30 nucleotides in length.

10. The AAV viral genome of any one of claims 7-9, wherein the passenger strand is at least 70% complementary to the guide strand.

11. The AAV viral genome of any one of claims 7-10, wherein the guide strand is at least 70% complementary to a target RNA.

12. The AAV viral genome of claim 11, wherein the target RNA is expressed in a neurologic cell, tissue, or organ.

13. The AAV viral genome of any one of claims 1-12, which further comprises:

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

(ii) an enhancer;

(iii) an intron region; and/or

(iv) a polyadenylation (poly A) region.

14. A recombinant adeno-associated virus (AAV) comprising the AAV viral genome of any one of claims 1-13 and an AAV capsid protein.

15. The recombinant AAV of claim 14, wherein the AAV capsid protein comprises an AAV1 capsid protein or a variant thereof, an AAV5 capsid protein or a variant thereof, or an AAV9 capsid protein or a variant thereof.

16. A cell comprising the AAV viral genome of any one of claims 1-15, or the recombinant AAV of claim 14 or 15.

17. The cell of claim 16, wherein the cell is a human cell, an HEK293 cell, a cell of the central nervous system, a motor neuron, or an astrocyte.

18. A pharmaceutical composition comprising the AAV viral genome of any one of claims 1-13, or the recombinant AAV of claim 14 or 15, and a pharmaceutically acceptable excipient.

19. Use of a composition comprising the AAV genome of any one of claims 1-13, the recombinant AAV of claim 14 or 15, or the pharmaceutical composition of claim 18, in the manufacture of a medicament for treating a disease of the central nervous system in a subject.

20. The use of claim 19, wherein the disease of the central nervous system is Huntington's disease or amyotrophic lateral sclerosis (ALS).

21. The use of claim 19 or 20, wherein the composition is formulated for intravenous administration, intracisternal injection, intravascular administration, and/or intraventricular administration.

22. A composition comprising the AAV viral genome of any one of claims 1-13, the recombinant AAV of claim 14 or 15, or the pharmaceutical composition of claim 18 for use treating a disease of the central nervous system in a subject.

23. The composition for use of claim 22, wherein the disease of the central nervous system is Huntington's disease or amyotrophic lateral sclerosis (ALS).

24. The composition for use of claim 22 or 23, wherein the composition is formulated for intravenous administration, intracisternal injection, intravascular administration, and/or intraventricular administration.