deficiencies of the protein in patients afflicted with FA. Adeno-associated viruses (AAVs) have emerged as one of the most widely studied and utilized viral particles for delivery of therapeutically effective polypeptides to mammalian cells. *See, e.g.*, Tratschin et al., Mol. Cell Biol., 5(11):3251-3260 (1985) and Grimm et al., Hum. Gene Ther., 10(15):2445-2450 (1999), the contents of each of which are incorporated herein by reference in their entirety. As such, this modality is well suited to exploitation toward treatment of FA and the delivery of frataxin and frataxin related proteins and peptides.

SUMMARY

[0009] In one aspect, the present disclosure provides an adeno-associated virus (AAV) viral genome comprising an engineered promoter and a nucleotide sequence encoding a frataxin (FXN) protein, wherein the engineered promoter consists of a nucleotide sequence that has at least 90% sequence identity to SEQ ID NO: 1742. In some examples, the present disclosure provides AAV viral genomes comprising at least one inverted terminal repeat (ITR) and a payload region, wherein the payload region encodes a frataxin protein. In some examples, the AAV viral genome comprises a 5' ITR, an engineered promoter, a payload region, and a 3' ITR. The encoded frataxin protein may be a human (*Homo sapiens*) frataxin, a cynomolgus monkey (*Macaca fascicularis*) frataxin, or a rhesus monkey (*Macaca mulatta*) frataxin, a synthetic (non-naturally occurring) frataxin, or a derivative thereof, e.g., a variant that retains one or more function of a wild-type frataxin. In some examples, the frataxin protein may be at least partially humanized.

[0010] The engineered promoter of the AAV viral genome may be derived from a cytomegalovirus (CMV) promoter, a chicken β-actin (CBA) promoter, or a frataxin (FXN) promoter. In some examples, the engineered promoter is a promoter variant or a derivative of a parent promoter sequence.

[0011] In some examples, the engineered promoter is derived from a CMV promoter.

[0012] In some examples, the engineered promoter is derived from a CBA promoter.

[0013] In some examples, the engineered promoter is derived from a FXN promoter.

[0014] An engineered promoter of the AAV viral genome as described herein, may comprise a sequence as given by any of SEQ ID NO: 1734-1777. In some examples, the engineered promoter comprises a sequence having at least 90% sequence identity to any of SEQ ID NO: 1734-1777. In some examples, the engineered promoter comprises a sequence having at least 95% sequence identity to any of SEQ ID NO: 1734-1777. In some examples, the engineered promoter comprises a sequence having at least 99% sequence identity to any of SEQ ID NO: 1734-1777. In some examples, the engineered promoter may consist of any of SEQ ID NO: 1734-1777. In some examples, the engineered promoter is derived from a CMV promoter and may comprise a sequence as given by any of SEQ ID NO: 1743-1751, 1767, and 1772-1774. In some examples, the engineered promoter comprises SEQ ID NO: 1777. In some examples, the engineered promoter is derived from a CBA promoter and may comprise

a sequence as given by any of SEQ ID NO: 1734-1742, 1760-1766, 1768, and 1775-1776. In some examples, the engineered promoter is derived from a FXN promoter and may comprise a sequence as given by any of SEQ ID NO: 1752-1759 and 1769-1770.

[0015] In some examples, the engineered promoter comprises a sequence as given by SEQ ID NO: 1738. In some examples, the engineered promoter comprises a sequence which has at least 90% sequence identity to SEQ ID NO: 1738. In some examples, the engineered promoter comprises a sequence which has at least 95% sequence identity to SEQ ID NO: 1738. In some examples, the engineered promoter comprises a sequence which has at least 99% sequence identity to SEQ ID NO: 1738. In some examples, the engineered promoter consists of SEQ ID NO: 1738.

[0016] In some examples, the engineered promoter comprises a sequence as given by SEQ ID NO: 1740. In some examples, the engineered promoter comprises a sequence which has at least 90% sequence identity to SEQ ID NO: 1740. In some examples, the engineered promoter comprises a sequence which has at least 95% sequence identity to SEQ ID NO: 1740. In some examples, the engineered promoter comprises a sequence which has at least 99% sequence identity to SEQ ID NO: 1740. In some examples, the engineered promoter consists of SEQ ID NO: 1740.

[0017] In some examples, the engineered promoter comprises a sequence as given by SEQ ID NO: 1742. In some examples, the engineered promoter comprises a sequence which has at least 90% sequence identity to SEQ ID NO: 1742. In some examples, the engineered promoter comprises a sequence which has at least 95% sequence identity to SEQ ID NO: 1742. In some examples, the engineered promoter comprises a sequence which has at least 99% sequence identity to SEQ ID NO: 1742. In some examples, the engineered promoter consists of SEQ ID NO: 1742.

[0018] In some examples, the engineered promoter comprises a sequence as given by SEQ ID NO: 1750. In some examples, the engineered promoter comprises a sequence which has at least 90% sequence identity to SEQ ID NO: 1750. In some examples, the engineered promoter comprises a sequence which has at least 95% sequence identity to SEQ ID NO: 1750. In some examples, the engineered promoter comprises a sequence which has at least 99% sequence identity to SEQ ID NO: 1750. In some examples, the engineered promoter consists of SEQ ID NO: 1750.

[0019] In some examples, the engineered promoter comprises a sequence as given by SEQ ID NO: 1756. In some examples, the engineered promoter comprises a sequence which has at least 90% sequence identity to SEQ ID NO: 1756. In some examples, the engineered

promoter comprises a sequence which has at least 95% sequence identity to SEQ ID NO: 1756. In some examples, the engineered promoter comprises a sequence which has at least 99% sequence identity to SEQ ID NO: 1756. In some examples, the engineered promoter consists of SEQ ID NO: 1756.

[0020] An engineered promoter as described herein, may have a length of 50-1400 nucleotides (nt). In some examples, the engineered promoter is derived from a CMV promoter and is 50-700 nt in length. In, some examples, the engineered promoter is derived from a CMV promoter and is 109 nt in length. In some examples, the engineered promoter is derived from a CBA promoter and is 100-700 nt in length. In some examples, the engineered promoter is derived from a CBA promoter and is 100-400 nt in length. In some examples, the engineered promoter is derived from a CBA promoter and is 100 nt in length. In some examples, the engineered promoter is derived from a CBA promoter and is 200-350 nt in length. In some examples, the engineered promoter is derived from a CBA promoter and is 260 nt in length. In some examples, the engineered promoter is derived from a CBA promoter and is 332 nt in length. In some examples, the engineered promoter is derived from a FXN promoter and is 200-1400 nt in length. In some examples, the engineered promoter is 950-1150 nt in length. In some examples, the engineered promoter is derived from a FXN promoter and is 1060 nt in length.

[0021] In some examples, the engineered promoter comprises an enhancer region.

[0022] Engineered promoters and payload regions encoding frataxin may be incorporated into an AAV viral genome.

[0023] In some examples, the AAV viral genome comprises, in addition to an engineered promoter and a payload region, a 5’ ITR, an enhancer, an intron, at least one miR binding site (e.g., one, two, or three miR binding sites), a polyA sequence, a filler sequence and a 3’ ITR. In some examples, the AAV viral genome comprises multiple miR binding sites (an “miR binding site series”) that may appear consecutively or separated by one or more nucleotides. In some examples, the 5’ ITR and/or the 3’ ITR is an AAV2 ITR.

[0024] In some examples, the viral genome comprises at least one ITR sequence. In some examples, the ITR may be an AAV2 ITR. In some examples, the 5’ ITR may be an AAV2 ITR. In some examples, the 3’ ITR may be an AAV2 ITR. In some examples, the 5’ and/or the 3’ ITR may be 141 nt in length. In some examples, the 5’ ITR comprises a sequence at least 95%, at least 99%, or 100% identical to SEQ ID NO: 1811. In some examples, the 3’ ITR comprises a sequence at least 95%, at least 99%, or 100% identical to SEQ ID NO: 1812.

[0025] In some examples, an ITR to ITR sequence comprises an intron/exon region. In some examples, the intron/exon region may be an enhancer sequence. As a non-limiting example, an enhancer sequence may comprise two or more subcomponents, such as, but not limited to, an ie1 exon (e.g., exon 1), an ie1 intron (e.g., intron 1), a human beta-globin intron (e.g., intron 2), and/or a human beta globin exon (e.g., exon 3), or a fragment thereof. In some examples, the intron/exon region comprises a sequence at least 90%, at least 95%, at least 99%, or 100% identical to a sequence as given by any of SEQ ID NOs: 1815-1821. In some examples, the enhancer comprises a sequence at least 90%, at least 95%, at least 99%, or 100% identical to a sequence as given by any of SEQ ID NOs: 1815-1821. In some examples, the enhancer comprises a sequence at least 90%, at least 95%, at least 99%, or 100% identical to SEQ ID NO: 1777. In some examples, the intron/exon region comprises one or more human beta-globin sequences, e.g., a sequence at least 90%, at least 95%, at least 99%, or 100% identical to SEQ ID NOs: 1820 and/or 1821. In some examples, the intron may comprise a sequence as given by any of SEQ ID NO: 1815-1821. In some examples, the intron has a sequence at least 90%, at least 95%, at leas 99%, or 100% identical to SEQ ID NO: 1816. In some examples, the intron may consist of SEQ ID NO: 1816.

[0026] In some examples, a miR binding site series comprises at least one miR122 binding site sequence. In some examples, the at least one miR122 binding site comprises a sequence at least 90%, at least 95%, at least 99%, or 100% identical to SEQ ID NO: 1827. In some examples, the at least one miR122 binding site consists of SEQ ID NO: 1827. In some examples, the AAV vector genome comprises three copies of a miR122 binding site, e.g., three copies of SEQ ID NO: 1827 or a variant thereof having at least 90% sequence identity. In some examples, the miR binding site series may comprise a sequence having at least 90%, at least 95%, at least 99%, or 100% identical to SEQ ID NO: 1826. In some examples, the miR binding site series may consist of SEQ ID NO: 1826.

[0027] In some examples, the polyA sequence is a human growth hormone (hGH) polyA sequence. In some examples, the viral genome comprises a hGH polyA sequence at least 90%, at least 95%, at least 99%, or 100% identical to SEQ ID NO: 1828. In some examples, the polyA sequence consists of SEQ ID NO: 1828.

[0028] In some examples, the AAV viral genome further comprises a filler sequence, e.g., an albumin filler sequence. In some examples, the filler sequence may comprise a sequence at least 90%, at least 95%, at least 99%, or 100% identical to a sequence as given by any of SEQ ID NOs: 1829-1842. In some examples, the filler sequence may comprise a sequence at least 90%, at least 95%, at least 99% or 100% identical to SEQ ID NO: 1838. In some examples,

the filler sequence may consist of SEQ ID NO: 1838. In some examples, the filler sequence may comprise a sequence at least 90%, at least 95%, at least 99% or 100% identical to SEQ ID NO: 1839. In some examples, the filler sequence may consist of SEQ ID NO: 1839. In some examples, the filler sequence may comprise a sequence at least 90%, at least 95%, at least 99% or 100% identical to SEQ ID NO: 1840. In some examples, the filler sequence may consist of SEQ ID NO: 1840. In some examples, the filler sequence may comprise a sequence at least 90%, at least 95%, at least 99% or 100% identical to SEQ ID NO: 1841. In some examples, the filler sequence may consist of SEQ ID NO: 1841.

[0029] In some examples, an AAV viral genome may comprise a sequence as given by any of SEQ ID NO: 1778-1810. In some examples, the AAV viral genome comprises a sequence that has at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% sequence identity to any of SEQ ID NO: 1778-1810. In some examples, the AAV viral genome comprises a sequence that has 80-85%, 80-90%, 80-95%, 80-99%, 80-100%, 90-95%, 90-99%, or 90-100% sequence identity to any of SEQ ID NOs: 1778-1810. An AAV viral genome wherein the encoded frataxin is a *Cynomolgus sp*. frataxin may comprise a sequence as given by any of SEQ ID NO: 1778-1795. In some examples, the AAV viral genome comprises a sequence that has at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% sequence identity to any of SEQ ID NO: 1778-1795. In some examples, the AAV viral genome comprises a sequence that has 80-85%, 80-90%, 80-95%, 80-99%, 80-100%, 90-95%, 90-99%, or 90-100% sequence identity to any of SEQ ID NOs: 1778-1795. An AAV viral genome wherein the encoded frataxin is a human frataxin may comprise a sequence as given by any of SEQ ID NO: 1796-1810. In some examples, the AAV viral genome comprises a sequence that has at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% sequence identity to any of SEQ ID NO: 1796-1810. In some examples, the AAV viral genome comprises a sequence that has 80-85%, 80-90%, 80-95%, 80-99%, 80-100%, 90-95%, 90-99%, or 90-100% sequence identity to any of SEQ ID NOs: 1796-1810.

[0030] In another aspect, the present disclosure provides an adeno-associated virus (AAV) viral genome, comprising a nucleotide sequence that has at least 90% sequence identity to SEQ ID NO: 1797. In yet another aspect, the present disclosure provides an adeno-associated virus (AAV) viral genome comprising the nucleotide sequence of SEQ ID NO: 1797.

In some examples, the AAV viral genome may comprise a sequence at least 90%, at least 95%, at least 99% or 100% identical to SEQ ID NO: 1797. In some examples, the AAV viral genome may consist of SEQ ID NO: 1797. In some examples, the AAV viral genome may comprise a sequence at least 90%, at least 95%, at least 99% or 100% identical to SEQ ID NO: 1801. In some examples, the AAV viral genome may consist of SEQ ID NO: 1801. In some examples, the AAV viral genome may comprise a sequence at least 90%, at least 95%, at least 99% or 100% identical to SEQ ID NO: 1808. In some examples, the AAV viral genome may consist of SEQ ID NO: 1808. In some examples, the AAV viral genome

may comprise a sequence at least 90%, at least 95%, at least 99% or 100% identical to SEQ ID NO: 1809. In some examples, the AAV viral genome may consist of SEQ ID NO: 1809.

[0031] In some examples, a payload region of an AAV vector genome encoding frataxin comprises a nucleic acid sequence at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to a sequence as given by any of SEQ ID NOs: 1822-1824. In some examples, a payload region of an AAV vector genome encoding frataxin comprises a nucleic acid sequence as given by any of SEQ ID NOs: 1822-1824. In some examples, the nucleic acid sequence encoding frataxin comprises SEQ ID NO: 1822. In some examples, the nucleic acid sequence encoding frataxin comprises SEQ ID NO: 1823. In some examples, the nucleic acid sequence encoding frataxin comprises SEQ ID NO: 1824. In some examples, the nucleic acid sequence encoding frataxin comprises a fragment of SEQ ID NO: 1728, 1729, or 1730, or a variant thereof having at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% sequence identity thereto. In some examples, the nucleic acid sequence encoding frataxin comprises a fragment of SEQ ID NO: 1728. In some examples, the nucleic acid sequence encoding frataxin comprises nucleotides 221-853 of SEQ ID NO: 1728.

[0032] In some examples, a payload region of an AAV vector genome comprises a nucleic acid sequence that encodes a frataxin polypeptide having at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% sequence identity to SEQ ID NO: 1725, 1726, or 1727. In some examples, a payload region of an AAV vector genome comprises a nucleic acid sequence that encodes a frataxin polypeptide of SEQ ID NO: 1725, 1726, or 1727. In some examples the AAV vector genome comprises a nucleic acid sequence that encodes a frataxin polypeptide comprising SEQ ID NO: 1725. In some examples, a payload region of an AAV vector genome comprises a nucleic acid sequence that encodes a frataxin polypeptide having at least 80%, 85%, 90%, 95%, or 99% sequence identity to SEQ ID NO: 1731, 1732, or 1733. In some examples, a payload region of an AAV vector genome comprises a nucleic acid sequence that encodes a frataxin polypeptide of SEQ ID NO: 1731, 1732, or 1733.

[0033] In a further aspect, the present disclosure provides an adeno-associated virus (AAV) particle comprising the AAV viral genome as disclosed herein. In yet another aspect, the present disclosure provides a cell comprising the AAV viral genome as disclosed herein or the AAV particle as disclosed herein.

Viral genomes comprising engineered promoters or promoter variants may be incorporated into an AAV particle, wherein the AAV particle comprises a viral genome and a capsid. In some examples, the capsid comprises a sequence as shown in Table 1 or is selected from the group consisting of SEQ ID NO: 1-1724. Non-limiting examples of capsids include AAV9, AAV9 K449R, AAVPHP.B, AAVPHP.N, VOY101 (having an amino acid sequence of SEQ ID NO: 1 and/or having a nucleic acid sequence of SEQ ID NO: 1722), and/or VOY201 (having an amino acid sequence of SEQ ID NO: 1724 and/or having a nucleic acid sequence of SEQ ID NO: 1723). In some examples, the capsid is encoded by a nucleic acid

sequence selected from SEQ ID NO: 4, 135, 1722, and 1723. In some examples, the capsid may have an amino acid sequence as given by any of SEQ ID NO: 1, 2, 3, 9, 136, or 1724. In some examples, the capsid comprises an amino acid sequence as given by SEQ ID NO: 136. In some examples, the capsid comprises an amino acid sequence encoded by a nucleic acid sequence as given by SEQ ID NO: 135. In some examples, the capsid comprises an amino acid sequence as given by SEQ ID NO: 9. In some examples, the capsid comprises an amino acid sequence as given by SEQ ID NO: 3. In some examples, the capsid comprises an amino acid sequence encoded by a nucleic acid sequence as given by SEQ ID NO: 4. In some examples, the capsid comprises an amino acid sequence as given by SEQ ID NO: 2. In some examples, the capsid comprises an amino acid sequence as given by SEQ ID NO: 1. In some examples, the capsid comprises an amino acid sequence encoded by a nucleic acid sequence as given by SEQ ID NO: 1722. In some examples, the capsid comprises an amino acid sequence encoded by a nucleic acid sequence as given by SEQ ID NO: 1723. In some examples, the capsid comprises an amino acid sequence as given by SEQ ID NO: 1724.

[0034] In a further aspect, the present disclosure provides a pharmaceutical composition comprising the AAV particle as disclosed herein and a pharmaceutically acceptable excipient. In some examples, the AAV particles described herein may be used in a pharmaceutical composition. In some examples, the pharmaceutical composition comprises sodium chloride, sodium phosphate, potassium chloride, potassium phosphate and poloxamer 188. In some examples, the pharmaceutical composition comprises 192 mM sodium chloride, 10 mM sodium phosphate, 2.7 mM potassium chloride, 2 mM potassium phosphate and 0.001% poloxamer 188 (v/v). In some examples, the sodium phosphate of the composition is dibasic. In some examples, the potassium phosphate of the composition is monobasic. In some examples, the pH of the pharmaceutical composition is between 7.3-7.7. In some examples, the pH of the pharmaceutical composition is 7.4

[0035] In some examples, the AAV particle may comprise a vector genome as given by SEQ ID NO: 1797 and a VOY101 capsid. In some examples, a pharmaceutical composition comprising the AAV particle comprising a vector genome given by SEQ ID NO: 1797 and a VOY101 capsid, comprises sodium chloride, sodium phosphate, potassium chloride, potassium phosphate and poloxamer 188; optionally wherein the pharmaceutical composition comprises192 mM sodium chloride, 10 mM sodium phosphate, 2.7 mM potassium chloride, 2 mM potassium phosphate and 0.001% poloxamer 188 (v/v), and wherein the pH of the composition is 7.4.

[0036] In some examples, the AAV particle may comprise a vector genome as given by SEQ ID NO: 1801 and a VOY101 capsid. In some examples, a pharmaceutical composition comprising the AAV particle comprising a vector genome given by SEQ ID NO: 1801 and a

VOY101 capsid, comprises sodium chloride, sodium phosphate, potassium chloride, potassium phosphate and poloxamer 188; optionally wherein the pharmaceutical composition comprises192 mM sodium chloride, 10 mM sodium phosphate, 2.7 mM potassium chloride, 2 mM potassium phosphate and 0.001% poloxamer 188 (v/v), and wherein the pH of the composition is 7.4.

[0037] In some examples, the AAV particle may comprise a vector genome as given by SEQ ID NO: 1808 and a VOY101 capsid. In some examples, a pharmaceutical composition comprising the AAV particle comprising a vector genome given by SEQ ID NO: 1808 and a VOY101 capsid, comprises sodium chloride, sodium phosphate, potassium chloride, potassium phosphate and poloxamer 188; optionally wherein the pharmaceutical composition comprises192 mM sodium chloride, 10 mM sodium phosphate, 2.7 mM potassium chloride, 2 mM potassium phosphate and 0.001% poloxamer 188 (v/v), and wherein the pH of the composition is 7.4.

[0038] In some examples, the AAV particle may comprise a vector genome as given by SEQ ID NO: 1809 and a VOY101 capsid. In some examples, a pharmaceutical composition comprising the AAV particle comprising a vector genome given by SEQ ID NO: 1809 and a VOY101 capsid, comprises sodium chloride, sodium phosphate, potassium chloride, potassium phosphate and poloxamer 188; optionally wherein the pharmaceutical composition comprises192 mM sodium chloride, 10 mM sodium phosphate, 2.7 mM potassium chloride, 2 mM potassium phosphate and 0.001% poloxamer 188 (v/v), and wherein the pH of the composition is 7.4.

[0039] Pharmaceutical compositions and/or the AAV particles of this disclosure may be used to treat a neurological or neuromuscular disorder, such as, but not limited to Friedreich's Ataxia.

[0040] In a further aspect, the present disclosure provides the AAV particle as disclosed herein or the pharmaceutical composition as disclosed herein for use in therapy. In yet another aspect, the present disclosure provides a use of the pharmaceutical composition as disclosed herein or the AAV particle as disclosed herein in the manufacture of a medicament for the treatment of a disorder associated with decreased frataxin protein levels. In yet another aspect, the present disclosure provides a use of the pharmaceutical composition as disclosed herein or the AAV particle as disclosed herein in the manufacture of a medicament for the delivery of a nucleic acid encoding a frataxin protein to a subject for the treatment of a disorder associated with decreased frataxin protein levels.

In yet another aspect, the present disclosure provides a use of the pharmaceutical composition as disclosed herein or the AAV particle as disclosed herein in the manufacture of a medicament for increasing frataxin protein in a subject for the treatment of a disorder associated with decreased frataxin protein levels. In some examples, AAV particles of the present disclosure are used to treat a disorder or condition associated with decreased frataxin expression or protein levels. In some examples, the disorder or condition associated with decreased frataxin expression or protein levels is a neurological or neuromuscular disorder. In some examples, the disorder or condition associated with decreased frataxin protein levels is FA or frataxin deficiency. In some examples, administration of AAV particles may result in enhanced frataxin expression in a target cell to a level 0.5-3x (e.g., 0.5-1x, 1-1.5x, 1.5-2x, 2-2.5x, 2.5-3x) of frataxin expression in an equivalent target cell of a normal subject not suffering from a disorder associated with decreased frataxin levels. In some examples, administration of AAV particles may result in frataxin expression in a target cell of approximately 5.5-32.8 ng/mg protein.

CLAIMS

1. An adeno-associated virus (AAV) viral genome comprising an engineered promoter and a nucleotide sequence encoding a frataxin protein, wherein the engineered promoter consists of a nucleotide sequence that has at least 90% sequence identity to SEQ ID NO: 1742.

2. The AAV viral genome of claim 1, wherein the engineered promoter consists of a nucleotide sequence that has at least 95% sequence identity to SEQ ID NO: 1742.

3. The AAV viral genome of claim 1 or claim 2, wherein the engineered promoter consists of a nucleotide sequence that has at least 99% sequence identity to SEQ ID NO: 1742.

4. The AAV viral genome of any one of claims 1-3, wherein the engineered promoter consists of the nucleotide sequence of SEQ ID NO: 1742.

5. The AAV viral genome of any one of claims 1-4, wherein the frataxin protein comprises the amino acid sequence of any one of SEQ ID NO: 1725, SEQ ID NO: 1726, and SEQ ID NO: 1727, or an amino acid sequence that has at least 80% sequence identity to any one of SEQ ID NO: 1725, SEQ ID NO: 1726, and SEQ ID NO: 1727.

6. The AAV viral genome of claim 5, wherein the frataxin protein comprises the amino acid sequence of SEQ ID NO: 1725.

7. The AAV viral genome of any one of claims 1-6, wherein the nucleotide sequence encoding the frataxin protein comprises nucleotides 221-853 of SEQ ID NO: 1728.

8. The AAV viral genome of any one of claims 1-7, wherein the nucleotide sequence encoding the frataxin protein comprises a nucleotide sequence that has at least 80% sequence identity to SEQ ID NO: 1823 or SEQ ID NO: 1824.

9. The AAV viral genome of any one of claims 1-8, wherein the nucleotide sequence encoding the frataxin protein comprises a nucleotide sequence that has at least 90% sequence identity to SEQ ID NO: 1823 or SEQ ID NO: 1824.

10. The AAV viral genome of any one of claims 1-9, wherein the nucleotide sequence encoding the frataxin protein comprises a nucleotide sequence that has at least 95% sequence identity to SEQ ID NO: 1823 or SEQ ID NO: 1824.

11. The AAV viral genome of any one of claims 1-10, wherein the nucleotide sequence encoding the frataxin protein comprises SEQ ID NO: 1823 or SEQ ID NO: 1824.

12. The AAV viral genome of any one of claims 1-11, wherein the nucleotide sequence encoding the frataxin protein consists of the nucleotide sequence of SEQ ID NO: 1823 or SEQ ID NO: 1824.

13. The AAV viral genome of any one of claims 1-12, further comprising a 5’ inverted terminal repeat (ITR) and/or a 3’ ITR.

14. The AAV viral genome of claim 13, wherein the 5' ITR is an AAV2 ITR and/or the 3' ITR is an AAV2 ITR.

15. The AAV viral genome of any one of claims 1-14, further comprising an intron, a polyadenylation (polyA) sequence, and/or a filler sequence.

16. The AAV viral genome of claim 15, wherein the intron comprises an enhancer sequence.

17. The AAV viral genome of any one of claims 1-16, further comprising the nucleotide sequence of SEQ ID NO: 1827 or a nucleotide sequence that has at least 90% sequence identity thereto.

18. The AAV viral genome of any one of claims 1-4, further wherein the nucleic acid sequence encoding the frataxin protein has at least 90% identity to the nucleotide sequence of SEQ ID NO: 1824, and wherein the AAV viral genome further comprises:

(i) a nucleotide sequence that has at least 95% sequence identity to SEQ ID NO: 1811;

(ii) a nucleotide sequence that has at least 90% sequence identity to SEQ ID NO: 1816;

(iii) a nucleotide sequence that has at least 90% identity to SEQ ID NO: 1826 or SEQ ID NO: 1827;

(iv) a nucleotide sequence that has at least 90% sequence identity to SEQ ID NO: 1828;

(v) a nucleotide sequence that has at least 90% sequence identity to SEQ ID NO: 1841, and/or;

(vi) a nucleotide sequence that has at least 95% sequence identity to SEQ ID NO: 1812.

19. The AAV viral genome of any one of claims 1-18, wherein the AAV viral genome comprises:

(i) the nucleotide sequence of SEQ ID NO: 1811;

(ii) the nucleotide sequence of SEQ ID NO: 1816;

(iii) the nucleotide sequence of SEQ ID NO: 1824;

(iv) the nucleotide sequence of SEQ ID NO: 1826 or SEQ ID NO: 1827;

(v) the nucleotide sequence of SEQ ID NO: 1828;

(vi) the nucleotide sequence of SEQ ID NO: 1841; and/or

(vii) the nucleotide sequence of SEQ ID NO: 1812.

20. The AAV viral genome of any one of claims 1-19, which comprises the nucleotide sequence of SEQ ID NO: 1797, or a nucleotide sequence at least 95% identical thereto.

21. An adeno-associated virus (AAV) viral genome, comprising a nucleotide sequence that has at least 90% sequence identity to SEQ ID NO: 1797.

22. An adeno-associated virus (AAV) viral genome comprising the nucleotide sequence of SEQ ID NO: 1797.

23. An adeno-associated virus (AAV) particle comprising the AAV viral genome of any one of claims 1-22.

24. The AAV particle of claim 23, which comprises an AAV capsid protein, wherein the AAV capsid protein comprises an AAV9 capsid protein or variant thereof, or an AAV capsid protein or variant thereof.

25. A cell comprising the AAV viral genome of any one of claims 1-21 or the AAV particle of claim 23 or 24.

26. A pharmaceutical composition comprising the AAV particle of claim 23 and a pharmaceutically acceptable excipient.

27. The AAV particle of claim 23 or the pharmaceutical composition of claim 26 for use in therapy.

28. Use of the pharmaceutical composition of claim 26 or the AAV particle of claim 23 in the manufacture of a medicament for the treatment of a disorder associated with decreased frataxin protein levels.

29. The use of claim 28, wherein the disorder associated with decreased frataxin protein levels is Friedreich’s Ataxia.

30. Use of the pharmaceutical composition of claim 26 or the AAV particle of claim 23 in the manufacture of a medicament for the delivery of a nucleic acid encoding a frataxin protein to a subject for the treatment of a disorder associated with decreased frataxin protein levels.

31. Use of the pharmaceutical composition of claim 26 or the AAV particle of claim 23 in the manufacture of a medicament for increasing frataxin protein in a subject for the treatment of a disorder associated with decreased frataxin protein levels.

32. The use of any one of claims 28-31, wherein the AAV particle or pharmaceutical composition is formulated for intravenous administration.

33. The use of any one of claims 30-32, wherein the subject has a neurological or neuromuscular disorder.

34. The use of any one of claims 30-33, wherein the subject has Friedreich's ataxia (FA).