said wild type FVIII, has at least 45.2 to 59.2% GC content, and is at least 94% identical to the sequence of SEQ ID NO:1.

[0009b] In one embodiment, there is provided a Factor VIII (FVIII) encoding nucleic acid variant, wherein the FVIII encoded by said nucleic acid variant comprises a B domain deletion and exhibits greater expression when compared to wild type FVIII comprising a B domain deletion expression, wherein said nucleic acid variant has one or more leucine codons changed to CTG compared to TTA, TTG, CTT, CTC or CTA leucine codons in said wild type FVIII, has at least 45.2 to 59.2% GC content, and is at least 94% identical to the sequence of SEQ ID NO:1.

[0009c] In one embodiment, there is provided the use of the nucleic acid variant as described herein, the expression vector as described herein, or the virus or AAV vector as described herein in the manufacture of a medicament for treating a mammal with hemophilia A.

[0009d] In one embodiment, there is provided the use of the nucleic acid variant as described herein, the expression vector as described herein, or the virus or AAV vector as described herein in the manufacture of a medicament for treating a mammal with hemophilia A, wherein the medicament is to be transferred into a mammalian cell.

[0010] In one embodiment, a Factor VIII (FVIII) encoding nucleic acid variant exhibits greater expression when compared to wild type FVIII expression. In another embodiment, a Factor VIII (FVIII) encoding nucleic acid variant comprises a B domain deletion and exhibits greater expression when compared to wild type FVIII comprising a B domain deletion

WHAT IS CLAIMED IS:

1. A Factor VIII (FVIII) encoding nucleic acid variant, wherein the FVIII encoded by said nucleic acid variant exhibits greater expression when compared to wild type FVIII expression, wherein said nucleic acid variant has one or more leucine codons changed to CTG compared to TTA, TTG, CTT, CTC or CTA leucine codons in said wild type FVIII, has 45.2 to 59.2% GC content, and is at least 94% identical to the sequence of SEQ ID NO:1.

2. A Factor VIII (FVIII) encoding nucleic acid variant, wherein the FVIII encoded by said nucleic acid variant comprises a B domain deletion and exhibits greater expression when compared to wild type FVIII comprising a B domain deletion expression, wherein said nucleic acid variant has one or more leucine codons changed to CTG compared to TTA, TTG, CTT, CTC or CTA leucine codons in said wild type FVIII, has 45.2 to 59.2% GC content, and is at least 94% identical to the sequence of SEQ ID NO:1.

3. The nucleic acid variant as claimed in any of claims 1, 2 and 37, wherein said nucleic acid variant is more efficiently packaged into an adenovirus-associated virus (AAV) vector when compared to packaging of said wild type Factor VIII.

4. The nucleic acid variant as claimed in any of claims 1-3 and 37, wherein said FVIII encoded by said nucleic acid variant exhibits greater clotting activity when compared to said wild type FVIII or when compared to said wild type FVIII comprising a B domain deletion.

5. The nucleic acid variant as claimed in claim 4, wherein said clotting activity is determined by a clotting assay or reduced bleeding in a FVIII assay or FVIII deficiency model.

6. The nucleic acid variant as claimed in any of claims 1-4 and 37, wherein 2-5, 5-10, 10-20, 20-50, 50-100, 100-250, 250-500, 500-750 or 750-850 of the leucine codons are CTG leucine codons modified from TTA, TTG, CTT, CTC or CTA leucine codons.

7. The nucleic acid variant as claimed in any of claims 1-4 and 37, wherein at least 85% of the leucine codons are CTG leucine codons.

8. The nucleic acid variant as claimed in any of claims 1-4 and 37, wherein all of the leucine codons are CTG leucine codons.

9. The nucleic acid variant as claimed in any of claims 1-4 and 37, wherein said nucleic acid variant has one or more lysine codons changed to AAG lysine codons.

10. The nucleic acid variant as claimed in any of claims 1, 2 and 37, wherein said nucleic acid variant has between 50-59%, or 50-56%, or 50-53% GC content.

11. The nucleic acid variant as claimed in any of claims 1-4 and 37, wherein said nucleic acid variant is at least 75% identical to said wild type human FVIII nucleic acid or said wild type human FVIII nucleic acid comprising a B domain deletion.

12. The nucleic acid variant as claimed in any of claims 1-4 and 37, wherein said nucleic acid variant is human FVIII, and/or wherein said wild type FVIII or wild type FVIII comprising a B domain deletion is human FVIII.

13. The nucleic acid variant as claimed in any of claims 1, 2 and 37, wherein said nucleic acid variant comprises any of SEQ ID NOs:1-7 and 9.

14. The nucleic acid variant as claimed in any of claims 1-13 and 37, wherein 1, 2, 3 or all 4 codons encoding a PACE/furin cleavage site is/are deleted.

15. The nucleic acid variant as claimed in any of claims 1-13 and 37, wherein 1, 2, 3 or all 4 codons encoding a PACE/furin cleavage site set forth as HHQR or RHQR from positions 1645-1648 is/are deleted.

16. An expression vector comprising the variant FVIII of any of claims 1-15 and 37.

17. The expression vector of claim 16, selected from the group consisting of an adenovirus-associated virus (AAV) vector, a retroviral vector, an adenoviral vector, a plasmid, or a lentiviral vector.

18. The expression vector of claim 17, wherein said AAV vector comprises an AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, Rh10, Rh74 or AAV-2i8 AAV serotype.

19. The expression vector of claim 16, further comprising an intron, an expression control element, one or more adeno-associated virus (AAV) inverted terminal repeats (ITRs) and/or a filler polynucleotide sequence.

20. The expression vector of claim 19, wherein the intron is within or flanks the variant FVIII, or wherein the expression control element is operably linked to the variant FVIII, or wherein the AAV ITR(s) flanks the 5' or 3' terminus of the variant FVIII, or wherein the filler polynucleotide sequence flanks the 5' or 3'terminus of the variant FVIII.

21. The expression vector of claim 19, wherein the expression control element comprises a constitutive or regulatable control element, or a tissue-specific expression control element or promoter.

22. The expression vector of claim 19, wherein the expression control element comprises an element that confers expression in liver.

23. The expression vector of claim 19, wherein the expression control element comprises a TTR promoter or mutant TTR promoter.

24. The expression vector of claim 23, wherein the mutant TTR promoter comprises SEQ ID NO:8.

25. The expression vector of claim 19, wherein the ITR comprises one or more ITRs of any of: AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, Rh10, Rh74 or AAV-2i8 AAV serotypes, or a combination thereof.

26. A host cell expressing the FVIII encoded by said nucleic acid variant of any of claims 1-15 and 37.

27. A host cell comprising the nucleic acid variant of any of claims 1-15 and 37 or the expression vector of any of claims 16-25.

28. A virus vector comprising the nucleic acid variant of any of claims 1-15 and 37 or the expression vector of any of claims 16-25.

29. An AAV vector comprising the nucleic acid variant of any of claims 1-15 and 37 or the expression vector of any of claims 16-25.

30. The AAV vector of claim 29, wherein the AAV vector comprises a VP1, VP2 and/or VP3 capsid sequence having 75% or more sequence identity to AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, Rh10, Rh74 or AAV-2i8 VP1, VP2 and/or VP3 sequences.

31. The AAV vector of claim 29, wherein the AAV vector comprises a VP1, VP2 and/or VP3 capsid sequence selected from any of: AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, Rh10, Rh74 and AAV-2i8 AAV serotypes.

32. A pharmaceutical composition comprising the nucleic acid variant of any of claims 1-15 and 37, the expression vector of any of claims 16-25, or the virus or AAV vector of any of claims 29-31 in a biologically compatible carrier or excipient, optionally including empty capsid AAV.

33. The nucleic acid variant of any of claims 1-15 and 37, the expression vector of any of claims 16-25, or the virus or AAV vector of any of claims 29-31 encapsulated in a liposome or mixed with phospholipids or micelles.

34. Use of the nucleic acid variant of any of claims 1-15 and 37, the expression vector of any of claims 16-25, or the virus or AAV vector of any of claims 29-31 in the manufacture of a medicament for treating a mammal with hemophilia A, wherein the medicament is to be transferred into a mammalian cell.

35. The use according to claim 34, wherein said mammalian cell is present in the mammal.

36. Use of the nucleic acid variant of any of claims 1-15 and 37, the expression vector of any of claims 16-25, or the virus or AAV vector of any of claims 29-31 in the manufacture of a medicament for treating a mammal with hemophilia A.

37. A Factor VIII (FVIII) encoding nucleic acid variant as claimed in claim 1 or claim 2, wherein said nucleic acid variant exhibits greater expression when compared to expression of wild-type FVIII encoded by GenBank accession number NG 011403.1.

38. The Factor VIII (FVIII) encoding nucleic acid variant as claimed in claim 1 or claim 2, wherein said nucleic acid variant comprises any of SEQ ID NOs:1-7.