What is claimed is:

1. A polynucleotide comprising a human UBE3A open reading frame, wherein the human UBE3A open reading frame encodes human UBE3A short isoform and long isoform, optionally wherein the human UBE3A long isoform is human UBE3A long isoform 2 or human UBE3A long isoform 3,

wherein the human UBE3A open reading frame comprises one or more nucleotide modifications to reduce expression of the long isoform as compared to expression of native ORF which lacks the one or more nucleotide modifications to reduce expression and/or wherein the human UBE3A open reading frame comprises one or more nucleotide modifications to enhance expression of the short isoform, and

wherein the polynucleotide comprises a first Kozak sequence comprising SEQ ID NO: 6 operably linked to coding sequences for the long isoform and a second Kozak sequence comprising SEQ ID NO: 8 operably linked to coding sequence for the short isoform.

2. The polynucleotide of claim 1, wherein the expression of the long isoform is reduced by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 95% as compared to native ORF not comprising nucleotide modifications to reduce expression, and/or optionally wherein the expression of the short isoform is enhanced by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 95% as compared to native ORF not comprising nucleotide modifications to enhance expression.

3. The polynucleotide of claim 1 or 2, wherein the human UBE3A open reading frame comprises one or more nucleotide modifications to encode expression of the short isoform at a ratio of 1:1 to 15:1, as compared to expression of the long isoform.

4. The polynucleotide of any one of claims 1-3, wherein the human UBE3A open reading frame is codon-optimized for expression in a human cell, optionally wherein the human UBE3A open reading frame is codon-optimized for intracellular or non-secretory expression in a human cell.

5. The polynucleotide of any one of claims 1-4, wherein the human UBE3A open reading

frame comprises the nucleotide sequence of SEQ ID NO:9, SEQ ID NO:26, or SEQ ID NO:27, or a nucleotide sequence having at least about 70% identity thereto.

6. An expression cassette comprising the polynucleotide of any one of claims 1-5.

7. The expression cassette of claim 6, wherein the human UBE3A open reading frame is operably linked to a promoter and/or a polyadenylation signal, optionally, wherein the promoter is a neuron-specific promoter, optionally a human synapsin promoter, and/or optionally wherein the polyadenylation signal is a bovine growth hormone (bGH) polyadenylation signal (bGHpA).

8. The expression cassette of claim 6 or 7, further comprising at least one adeno-associated virus (AAV) inverted terminal repeat (ITR), optionally two AAV ITRs, optionally wherein the AAV ITRs are selected from the group consisting of AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, AAV12 and AAV13 ITRs.

9. The expression cassette of any one of claims 6-8, wherein the expression cassette comprises an AAV2 ITR; a human synapsin promoter; the human UBE3A open reading frame comprising human UBE3A short isoform and long isoform 3 further comprising one or more Kozak sequences comprising, consisting essentially of, or consisting of SEQ ID NO:6 and/or SEQ ID NO:8; a bGHpA; and an AAV2 ITR, optionally comprising the nucleotide sequence of SEQ ID NO:14 or a sequence at least about 90% identical thereto.

10. A vector comprising the polynucleotide of any one of claims 1-5 or the expression cassette of any one of claims 8-11, optionally wherein the vector is a neuro-tropic vector, optionally wherein the vector is a viral vector, optionally an AAV vector such as AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, AAV12 AAV13, or any combination or derivative thereof.

11. A transformed cell comprising the polynucleotide of any one of claims 1-5, the expression cassette of any one of claims 6-9, and/or the vector of claim 10, optionally wherein the polynucleotide, expression cassette, and/or vector is stably incorporated into the cell genome.

12. A pharmaceutical composition comprising the polynucleotide of any one of claims 1-5, the expression cassette of any one of claims 6-9, and/or the vector of claim 10, and/or the transformed cell of claim 11 in a pharmaceutically acceptable carrier.

13. The polynucleotide of any one of claims 1-5, expression cassette of any one of claims 6-9, vector of claim 10, transformed cell of claim 11, and/or pharmaceutical composition of claim 12, for use in therapy.

14. Use of the polynucleotide of any one of claims 1-5, expression cassette of any one of claims 6-9, vector of claim 10, transformed cell of claim 11, and/or pharmaceutical composition of claim 12, in the manufacture of a medicament for treating Angelman Syndrome, comprising the subject to be administered the medicament, such that the UBE3A open reading frame is expressed in the subject.

15. The polynucleotide, expression cassette, vector, transformed cell, and/or pharmaceutical composition for use of claim 13, or the use according to claim 14, wherein the human UBE3A short isoform is expressed at a ratio of 1:1 to 15:1 as compared to expression of the long isoform, optionally wherein the subject exhibits symptoms of the disease prior to delivery of the polynucleotide, expression cassette, vector, transformed cell, pharmaceutical composition, and/or the medicament, optionally wherein the polynucleotide, expression cassette, vector, transformed cell, pharmaceutical composition, and/or the medicament is to be delivered *in utero*, optionally wherein the subject is a human, optionally wherein the polynucleotide, expression cassette, vector, transformed cell, pharmaceutical composition, and/or the medicament is to be delivered to the nervous system of the subject optionally at a dose of at least about 10^2, 10^3, 10^4, 10^5, 10^6, 10^7, 10^8, 10^9, 10^{10}, 10^{11}, 10^{12}, 10^{13}, 10^{14}, 10^{15} or 10^{16} viral genomes/kilogram, optionally from 10^8-10^{14} viral genomes/kilogram, optionally delivered by intravenous, intrathecal, intracerebral, intra-cisterna magna, intraparenchymal, intracerebroventricular, intranasal, intra-aural, intra-ocular, or peri-ocular delivery, or any combination thereof.