

Claims

- [Claim 1] A polynucleotide, comprising the following base sequences:
(a) a base sequence encoding a fusion protein of a nuclease-deficient CRISPR effector protein and a transcription repressor, and
(b) a base sequence encoding a guide RNA targeting a continuous region of 18 to 24 nucleotides in length in a region set forth in SEQ ID NO: 54, 55, 56, 57, 68, 153 or 97 in the expression regulatory region of human MAPT gene.
- [Claim 2] The polynucleotide according to claim 1, wherein the base sequence encoding the guide RNA comprises the base sequence set forth in SEQ ID NO: 54, 55, 56, 57, 68, 153 or 97, or the base sequence set forth in SEQ ID NO: 54, 55, 56, 57, 68, 153 or 97 in which 1 to 3 bases are deleted, substituted, inserted, and/or added.
- [Claim 3] The polynucleotide according to claim 1 or 2, comprising at least two different base sequences encoding the guide RNA.
- [Claim 4] The polynucleotide according to any one of claims 1 to 3, wherein the transcriptional repressor is selected from the group KRAB, MeCP2, SIN3A, HDT1, MBD2B, NIPPI1, and HP1A.
- [Claim 5] The polynucleotide according to claim 4, wherein the transcriptional repressor is KRAB.
- [Claim 6] The polynucleotide according to any one of claims 1 to 5, wherein the nuclease-deficient CRISPR effector protein is dCas9.
- [Claim 7] The polynucleotide according to claim 6, wherein the dCas9 is derived from *Staphylococcus aureus*.
- [Claim 8] The polynucleotide according to any one of claims 1 to 7, further comprising a promoter sequence for the base sequence encoding the guide RNA and/or a promoter sequence for the base sequence encoding the fusion protein of the nuclease-deficient CRISPR effector protein and the transcriptional repressor.
- [Claim 9] The polynucleotide according to claim 8, wherein the promoter sequence for the base sequence encoding the guide RNA is selected from the group U6 promoter, SNR6 promoter, SNR52 promoter, SCR1 promoter, RPR1 promoter, U3 promoter, and H1 promoter.
- [Claim 10] The polynucleotide according to claim 9, wherein the promoter sequence for the base sequence encoding the guide RNA is U6 promoter.
- [Claim 11] The polynucleotide according to any one of claims 8 to 10, wherein the

- promoter sequence for the base sequence encoding the fusion protein of the nuclease-deficient CRISPR effector protein and the transcriptional repressor is a ubiquitous promoter or a neuron specific promoter.
- [Claim 12] The polynucleotide according to claim 11, wherein the ubiquitous promoter is selected from the group EFS promoter, CMV promoter and CAG promoter.
- [Claim 13] A vector comprising a polynucleotide according to any one of claims 1 to 12.
- [Claim 14] The vector according to claim 13, wherein the vector is a plasmid vector or a viral vector.
- [Claim 15] The vector according to claim 14, wherein the viral vector is selected from the group adeno-associated virus (AAV) vector, adenovirus vector, and lentivirus vector.
- [Claim 16] The vector according to claim 15, wherein the AAV vector is selected from the group AAV1, AAV2, AAV6, AAV7, AAV8, AAV9, Anc80, AAV₅₈₇MTP, AAV₅₈₈MTP, AAV-B1, AAVM41, and AAVrh74.
- [Claim 17] The vector according to claim 16, wherein the AAV vector is AAV9.
- [Claim 18] A pharmaceutical composition comprising a polynucleotide according to any one of claims 1 to 12 or a vector according to any one of claims 13 to 17.
- [Claim 19] The pharmaceutical composition according to claim 18 for treating or preventing Alzheimer's disease.
- [Claim 20] A method for treating or preventing Alzheimer's disease, comprising administering a polynucleotide according to any one of claims 1 to 12, or a vector of any one of claims 13 to 17, to a subject in need thereof.