

CLAIMS

1. A polynucleotide, comprising a polynucleotide sequence encoding a fusion protein comprising a mitochondrial targeting sequence (MTS); a transmembrane domain (TMD); and a Parkin protein or functional variant or fragment thereof.
2. The polynucleotide of claim 1, wherein the MTS is the MTS of PINK1 or a functional variant thereof.
3. The polynucleotide of claim 1 or claim 2, wherein the MTS comprises a mitochondrial processing peptidase (MPP) cleavage site.
4. The polynucleotide of any one of claim 1-3, wherein the MTS comprises a polypeptide sequence at least 95% identical to residues 1-34 of human PINK1:
1 MAVRQALGRG LQLGRALLLR FTGKPGRAYG LGRP (SEQ ID NO: 66).
5. The polynucleotide of claim 4, wherein the MTS comprises a polypeptide sequence at least 95% identical to residues 1-94 of human PINK1:
1 MAVRQALGRG LQLGRALLLR FTGKPGRAYG LGRP GPAAGC
41 VRGERPGWAA GPGAEPFRVG LGLPNRLRFF RQSVAGLAAR
81 LQRQFVVRW GCAG (SEQ ID NO: 65).
6. The polynucleotide of claim 5, wherein the MTS comprises a polypeptide sequence identical to residues 1-94 of human PINK1:
1 MAVRQALGRG LQLGRALLLR FTGKPGRAYG LGRP GPAAGC
41 VRGERPGWAA GPGAEPFRVG LGLPNRLRFF RQSVAGLAAR
81 LQRQFVVRW GCAG (SEQ ID NO: 65).
7. The polynucleotide of any one of claims 1-6, wherein the TMD is the TMD of PINK1 or a functional variant thereof.
8. The polynucleotide of any one of claims 1-7, wherein the TMD comprises a PARL cleavage site.
9. The polynucleotide of any one of claims 1-8, wherein the TMD comprises a polypeptide sequence at least 95% identical to residues 95-110 of human PINK1:
81 PCGRAV FLAFGLGLGL (SEQ ID NO: 67).
10. The polynucleotide of claim 9, wherein the TMD comprises a polypeptide sequence identical to residues 95-110 of human PINK1:
81 PCGRAV FLAFGLGLGL (SEQ ID NO: 67).

11. The polynucleotide of claim 9, wherein the TMD comprises a polypeptide sequence identical to residues 95-110 of human PINK1:
- 81 PCGRAV FLAMGLGLGL (SEQ ID NO: 68).
12. The polynucleotide of any one of claims 1-11, wherein the fusion protein comprises an MTS-TMD fragment of PINK1 or a functional variant thereof.
13. The polynucleotide of claim 12, wherein the MTS-TMD fragment comprises a polypeptide sequence at least 95% identical to residues 1-110 of human PINK1:
- 1 MAVRQALGRG LQLGRALLLR FTGKPGRAYG LGRPGPAAGC
41 VRGERPGWAA GPGAEPRRVG LGLPNRLRFF RQSVAGLAAR
81 LQRQFVVRW GCAGPCGRAV FLAFGLGLGL (SEQ ID NO: 70).
14. The polynucleotide of claim 12, wherein the MTS-TMD fragment comprises a polypeptide sequence identical to residues 1-110 of human PINK1:
- 1 MAVRQALGRG LQLGRALLLR FTGKPGRAYG LGRPGPAAGC
41 VRGERPGWAA GPGAEPRRVG LGLPNRLRFF RQSVAGLAAR
81 LQRQFVVRW GCAGPCGRAV FLAFGLGLGL (SEQ ID NO: 70).
15. The polynucleotide of any one of claims 1-14, wherein the functional variant or fragment thereof is a Δ Parkin protein comprising a deletion of the N-terminal ubiquitin-like (Ubl) domain and optionally a deletion of the Ubl-RING0 interdomain linker sequence.
16. The polynucleotide of claim 15, wherein the Δ Parkin protein comprises a polypeptide sequence at least 95% identical to residues 141-465 of human Parkin F146A+W403A:
- 121 SIYNSAYVYC KGPCQRVQPG
161 KLRVQCSTCR QATLTLTQGP SCWDDVLIPN RMSGECQSPH
201 CPGTSAEFFF KCGAHPTSDK ETSVALHLIA TNSRNITCIT
241 CTDVRSFVLV FQCNSRHVIC LDCFHLYCVT RLNDRQFVHD
281 PQLGYSLPCV AGCPNSLIKE LHHFRILGEE QYNRYQQYGA
321 EECVLQMGGV LCPRPGCGAG LLPEPDQRKV TCEGGNGLGC
361 GFAFCRECKE AYHEGECSAV FEASGTTTQA YRVDERAAEQ
401 ARAEAASKET IKKTTKPCPR CHVPVEKNNG CMHMKCPQPQ
441 CRLEWCWNCG CEWNRVCMGD HWFDV (SEQ ID NO: 73).
17. The polynucleotide of claim 15, wherein the Δ Parkin protein comprises a polypeptide sequence identical to residues 141-465 of human Parkin F146A+W403A:

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121                               SIYNSAYVYC KGPCQRVQPG
161 KLRVQCSTCR QATLTLTQGP SCWDDVLIPN RMSGECQSPH
201 CPGTSAEFFF KCGAHPTSDK ETSVALHLIA TNSRNITCIT
241 CTDVRSPLV FQCNSRHVIC LDCFHLYCVT RLNDRQFVHD
281 PQLGYSLPCV AGCPNSLIKE LHHFRILGEE QYNRYQQYGA
321 EECVLQMGGV LCPRPGCGAG LLPEPDQRKV TCEGGNGLGC
361 GF AFCRECKE AYHEGECSAV FEASGTTTQA YRVDERAAEQ
401 ARAEAASKET IKKTTKPCPR CHVPVEKNGG CMHMKCPQPQ
441 CRLEWCWNCG CEWNRVCMGD HWFDV (SEQ ID NO: 73).

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18. The polynucleotide of claim 15, wherein the Δ Parkin protein comprises a polypeptide sequence at least 95% identical to residues 76-465 of human Parkin F146A+W403A:

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41                               KGQEM
81 NATGGDDPRN AAGGCEREPO SLTRVDLSSS VLPGDSVGLA
121 VILHTDSRKD SPPAGSPAGR SIYNSAYVYC KGPCQRVQPG
161 KLRVQCSTCR QATLTLTQGP SCWDDVLIPN RMSGECQSPH
201 CPGTSAEFFF KCGAHPTSDK ETSVALHLIA TNSRNITCIT
241 CTDVRSPLV FQCNSRHVIC LDCFHLYCVT RLNDRQFVHD
281 PQLGYSLPCV AGCPNSLIKE LHHFRILGEE QYNRYQQYGA
321 EECVLQMGGV LCPRPGCGAG LLPEPDQRKV TCEGGNGLGC
361 GF AFCRECKE AYHEGECSAV FEASGTTTQA YRVDERAAEQ
401 ARAEAASKET IKKTTKPCPR CHVPVEKNGG CMHMKCPQPQ
441 CRLEWCWNCG CEWNRVCMGD HWFDV (SEQ ID NO: 74).

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19. The polynucleotide of claim 15, wherein the Δ Parkin protein comprises a polypeptide sequence identical to residues 76-465 of human Parkin F146A+W403A:

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41                               KGQEM
81 NATGGDDPRN AAGGCEREPO SLTRVDLSSS VLPGDSVGLA
121 VILHTDSRKD SPPAGSPAGR SIYNSAYVYC KGPCQRVQPG
161 KLRVQCSTCR QATLTLTQGP SCWDDVLIPN RMSGECQSPH
201 CPGTSAEFFF KCGAHPTSDK ETSVALHLIA TNSRNITCIT
241 CTDVRSPLV FQCNSRHVIC LDCFHLYCVT RLNDRQFVHD
281 PQLGYSLPCV AGCPNSLIKE LHHFRILGEE QYNRYQQYGA
321 EECVLQMGGV LCPRPGCGAG LLPEPDQRKV TCEGGNGLGC
361 GF AFCRECKE AYHEGECSAV FEASGTTTQA YRVDERAAEQ
401 ARAEAASKET IKKTTKPCPR CHVPVEKNGG CMHMKCPQPQ
441 CRLEWCWNCG CEWNRVCMGD HWFDV (SEQ ID NO: 74).

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20. The polynucleotide of any one of claims 1-19 wherein the fusion protein comprises a polypeptide sequence at least 95% identical to the sequence:

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1  MAVRQALGRG LQLGRALLLR FTGKPGRAYG LGRPGPAAGC
41 VRGERPGWAA GPGAEPRRVG LGLPNRLRFF RQSVAGLAAR
81 LQRQFVVRW GCAGPCGRAV FLAFGLGLGL KGQEMNATGG
121 DDPNAAGGC EREPQSLTRV DLSSSVLP GD SVGLAVILHT
161 DSRKDSPPAG SPAGRSIYNS AYVYCKGPCQ RVQPGKLRVQ
201 CSTCRQATLT LTQGPSCWDD VLIPNRMSGE CQSPHCPGTS
241 AEEFFKCGAH PTSDKETSVA LHLIATNSRN ITCITCTDVR
281 SPVLVFQCNS RHVICLD CFH LYCVTRLNDR QFVHDPQLGY
321 SLPCVAGCPN SLIKELHHFR ILGEEQYNRY QQYGAECEVL
361 QMGGVLCPRP GCGAGLLPEP DQRKVTCEGG NGLGCGFAFC
401 RECKEAYHEG ECSAVFEASG TTTQAYRVDE RAAEQARAEA
441 ASKETIKKTT KPCPRCHVPV EKNGGCMHMK CPQPQCRLEW
481 CWNCGCEWNR VCMGDHWF DV (SEQ ID NO: 75) .

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21. The polynucleotide of any one of claims 1-20, wherein the fusion protein comprises an F146A substitution relative to a reference human Parkin protein sequence of SEQ ID NO: 1.
22. The polynucleotide of any one of claims 1-21, wherein the fusion protein comprises a W403A substitution relative to a reference human Parkin protein sequence of SEQ ID NO: 1.
23. The polynucleotide of any one of claims 1-22, wherein the fusion protein comprises an F463A substitution relative to a reference human Parkin protein sequence of SEQ ID NO: 1.
24. The polynucleotide of any one of claims 1-23, wherein the fusion protein comprises a C457S substitution relative to a reference human Parkin protein sequence of SEQ ID NO: 1.
25. The polynucleotide of claim 22, wherein the fusion protein comprises both an F146A substitution and a W403A substitution relative to a reference human Parkin protein sequence of SEQ ID NO: 1.
26. The polynucleotide of any one of claims 1-25, wherein the fusion protein comprises a F104M substitution relative to a reference human PINK1 protein sequence of SEQ ID NO: 64.
27. The polynucleotide of any one of claims 1-26, wherein the fusion protein comprises both an F146A substitution and a W403A substitution relative to a

reference human Parkin protein sequence of SEQ ID NO: 1, and wherein the fusion protein comprises a F104M substitution relative to a reference human PINK1 protein sequence of SEQ ID NO: 64.

28. The polynucleotide of claim 1, wherein the fusion protein comprises a polypeptide sequence at least 95% identical to the sequence of SEQ ID NO: 97 or 98 and comprises two or more amino acid substitutions selected from F104M, W403A, and F463A,

wherein F104M is relative to a reference human PINK1 protein sequence of SEQ ID NO: 64, W403A is relative to a reference human Parkin protein sequence of SEQ ID NO: 1, and F463A is relative to a reference human Parkin protein sequence of SEQ ID NO: 1.

29. The polynucleotide of claim 1, wherein the fusion protein comprises a polypeptide sequence identical to the sequence any one of SEQ ID NO: 97 or 98 and comprises two or more amino acid substitutions selected from F104M, W403A, and F463A,

wherein F104M is relative to a reference human PINK1 protein sequence of SEQ ID NO: 64, W403A is relative to a reference human Parkin protein sequence of SEQ ID NO: 1, and F463A is relative to a reference human Parkin protein sequence of SEQ ID NO: 1.

30. A vector, comprising the polynucleotide of any one of claims 1-29.
31. The vector of claim 30, wherein the vector is an adeno-associated virus (AAV) vector.
32. The vector of claim 31, wherein the vector comprises an AAV9 capsid or functional variant thereof.
33. The vector of claim 32, wherein the AAV9 capsid shares at least 98%, 99%, or 100% identity to a reference AAV9 capsid.
34. A method of increasing Parkin activity in a cell, comprising contacting the cell with the polynucleotide of any one of claims 1-29 or the vector of any one of claims 30-33.
35. A method of increasing Parkin activity in a subject, comprising administering to the subject the polynucleotide of any one of claims 1-29 or the vector of any one of claims 30-33.
36. The method of claim 34 or claim 35, wherein the cell or subject is deficient in Parkin activity and/or comprises a loss-of-function mutation in Parkin.

37. The method of any one of claims 34-36, wherein Parkin activity comprises one or more of colocalization of Parkin with TOMM2 in response to neurotoxin treatment, ubiquitination of mitochondrial proteins in response to neurotoxin treatment, and increased in Parkin levels in the mitochondrial fraction in response to neurotoxin treatment.
38. A method of promoting survival of a neuron, comprising contacting the neuron with a polynucleotide of any one of claims 1-29 or the vector of any one of claims 30-33.
39. A method of promoting survival of a neuron in a subject, comprising administering to the subject the polynucleotide of any one of claims 1-29 or the vector of any one of claims 30-33.
40. The method of claim 38 or claim 39, wherein the neuron is a dopaminergic neuron.
41. A method of treating a disease or disorder in a subject in need thereof, comprising administering to the subject the polynucleotide of any one of claims 1-29 or the vector of any one of claims 30-33.
42. The method of claim 41, wherein the subject suffers from a genetic deficiency in Parkin expression or function.
43. The method of claim 41 or claim 42, wherein the subject suffers from a genetic deficiency in PINK1 expression or function.
44. The method of any one of claims 41-43, wherein the disease or disorder is Parkinson's disease.
45. The method of claim 44, wherein the Parkinson's disease is early onset Parkinson's disease (EOPD).
46. The method of any one of claims 41-45, wherein the method alleviates one or more symptoms of Parkinson's disease.
47. The method of any one of claims 41-46, wherein the method reduces motor complications associated with neurodegeneration; reduces the need for antiparkinsonian pharmacotherapy, optionally L-DOPA and/or dopaminergic agonists; restores the function of degenerating neurons; and/or protects neurons from degeneration.
48. The method of any one of claims 41-47, wherein the method enhances nigrostriatal function, optionally assessed by [¹⁸F]fluoro-L-dopa positron emission tomography (PET) or DaT-SPECT imaging.

49. The method of any one of claims 41-48, wherein the method improves one or both of the UPDRS or MDS-UPDRS of the subject.
50. A cell comprising the polynucleotide of any one of claims 1-29.
51. A protein encoded by the polynucleotide of any one of claims 1-29.
52. A pharmaceutical composition comprising the vector of any one of claims 30-33 and one or more pharmaceutically acceptable carriers, diluents, or excipients.
53. A kit comprising the vector of any one of claims 30-33 and instructions for use.
54. A recombinant adeno-associated virus (rAAV) virion, comprising a capsid and a vector genome, wherein the vector genome comprises a polynucleotide sequence encoding an activated Parkin protein operatively linked to a promoter.
55. The rAAV virion of claim 55, wherein the activated Parkin protein comprises one or more amino acid substitutions at positions Phe-146, Trp-403, Cys-457, Phe-463, and Asn-273 relative to a reference Parkin protein.
56. The rAAV virion of claim 55, wherein the activated Parkin protein comprises two or more amino acid substitutions at positions Phe-146, Trp-403, Cys-457, Phe-463, and Asn-273 relative to a reference Parkin protein.
57. The rAAV virion of claim 56, wherein the activated Parkin protein comprises amino acid substitutions at positions Phe-146, Trp-403, Cys-457, Phe-463, and Asn-273 relative to a reference Parkin protein.
58. The rAAV virion of any one of claims 54-57, wherein the activated Parkin protein comprises one or more amino acid substitutions selected from F146A, W403A, and/or N273K relative to a reference Parkin protein.
59. The rAAV virion of claim 58, wherein the activated Parkin protein comprises amino acid substitutions F146A and W403A relative to a reference Parkin protein.
60. The rAAV virion of claim 59, wherein the activated Parkin protein comprises amino acid substitutions F146A, N273K, and W403A relative to a reference Parkin protein.

61. The rAAV virion of claim 60, the activated Parkin protein comprises a polypeptide sequence at least 95% identical to human Parkin N273K+W403A+F463A (SEQ ID NO: 93).
62. The rAAV virion of claim 54, wherein the activated Parkin protein comprises a polypeptide sequence identical to human Parkin N273K+W403A+F463A (SEQ ID NO: 93).
63. The rAAV virion of any one of claims 54-60, wherein the Parkin protein is a Δ Parkin protein comprising a deletion of the ubiquitin-like (Ubl) domain.
64. The rAAV virion of claim 63, wherein the Δ Parkin protein comprises a polypeptide sequence at least 95% identical to residues 76-465 of human Parkin F146A+W403A:
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41 KGQEM
81 NATGGDDPRN AAGGCEREPQ SLTRVDLSSS VLPGDSVGLA
121 VILHTDSRKD SPPAGSPAGR SIYNSAYVYC KGPCQRVQPG
161 KLRVQCSTCR QATLTLTQGP SCWDDVLIPN RMSGECQSPH
201 CPGTSAEFFF KCGAHPTSDK ETSVALHLIA TNSRNITCIT
241 CTDVRSPLV FQCNSRHVIC LDCFHLYCVT RLNDRQFVHD
281 PQLGYSLPCV AGCPNSLIKE LHHFRILGEE QYNRYQQYGA
321 EECVLQMGGV LCPRPGCGAG LLPEPDQRKV TCEGGNGLGC
361 GFAFCRECKE AYHEGECSAV FEASGTTTQA YRVDERAAEQ
401 ARAEAASKET IKKTTKPCPR CHVPVEKNGG CMHMKCPQPQ
441 CRLEWCWNCG CEWNRVCMGD HWFDV (SEQ ID NO: 18) .

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65. The rAAV virion of claim 63, wherein the  $\Delta$ Parkin protein comprises a polypeptide sequence identical to residues 76-465 of human Parkin F146A+W403A:
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41                                     KGQEM
81 NATGGDDPRN AAGGCEREPQ SLTRVDLSSS VLPGDSVGLA
121 VILHTDSRKD SPPAGSPAGR SIYNSAYVYC KGPCQRVQPG
161 KLRVQCSTCR QATLTLTQGP SCWDDVLIPN RMSGECQSPH
201 CPGTSAEFFF KCGAHPTSDK ETSVALHLIA TNSRNITCIT
241 CTDVRSPLV FQCNSRHVIC LDCFHLYCVT RLNDRQFVHD
281 PQLGYSLPCV AGCPNSLIKE LHHFRILGEE QYNRYQQYGA
321 EECVLQMGGV LCPRPGCGAG LLPEPDQRKV TCEGGNGLGC

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361 GFAFCRECKE AYHEGECSAV FEASGTTTQA YRVDERAAEQ
401 ARAEAASKET IKKTTKPCPR CHVPVEKNGG CMHMKCPQPQ
441 CRLEWCWNCG CEWNRVCMGD HWFDV (SEQ ID NO: 18).

66. The rAAV virion of any one of claims 54-65, wherein the activated Parkin protein comprises amino acid substitutions at position Cys-431 relative to a reference Parkin protein.
67. The rAAV virion of claim 66, wherein the activated Parkin protein comprises a C431F amino acid substitution relative to a reference Parkin protein.
68. The rAAV virion of any one of claims 54-67, wherein the promoter is a constitutive promoter.
69. The rAAV virion of any one of claims 54-68, wherein the promoter is a CAG promoter.
70. The rAAV virion of any one of claims 54-68, wherein the promoter is a CMV promoter.
71. The rAAV virion of any one of claims 54-67, wherein the promoter is a neuron-specific promoter.
72. The rAAV virion of any one of claims 54-67 or 71, wherein the promoter is a SYN promoter.
73. The rAAV virion of any one of claims 54-72, wherein the vector genome comprises a WPRE element.
74. The rAAV virion of any one of claims 54-73, wherein the vector genome comprises a hGH polyadenylation site.
75. The rAAV virion of any one of claims 54-74, wherein the capsid is an AAV9 capsid or functional variant thereof.
76. The rAAV virion of claim 75, wherein the AAV9 capsid shares at least 98%, 99%, or 100% identity to a reference AAV9 capsid.

77. A method of increasing Parkin activity in a cell, comprising contacting the cell with the rAAV virion of any one of claims 54-76.
78. A method of increasing Parkin activity in a subject, comprising administering to the subject an effective amount of the rAAV virion of any one of claims 54-76.
79. The method of claim 77 or claims 78, wherein the cell or subject is deficient in Parkin activity and/or comprises a loss-of-function mutation in Parkin.
80. The method of any one of claims 77-79, wherein Parkin activity comprises one or more of colocalization of Parkin with TOMM2 in response to neurotoxin treatment, ubiquitination of mitochondrial proteins in response to neurotoxin treatment, and increased in Parkin levels in the mitochondrial fraction in response to neurotoxin treatment.
81. A method of promoting survival of a neuron, comprising contacting the neuron with the rAAV virion of any one of claims 54-76.
82. A method of promoting survival of a neuron in a subject, comprising administering to the subject an effective amount of the rAAV virion of any one of claims 54-76.
83. The method of claim 81 or claim 82, wherein the neuron is a dopaminergic neuron.
84. A method of treating a disease or disorder in a subject in need thereof, comprising administering to the subject an effective amount of the rAAV virion of any one of claims 54-76.
85. The method of claim 84, wherein the subject suffers from a genetic deficiency in Parkin.
86. The method of claim 84, wherein the subject suffers from a genetic deficiency in PINK1.
87. The method of claim 84, wherein the subject suffers from a genetic deficiency in DJ-1.

88. The method of any one of claims 84-87, wherein the disease or disorder is Parkinson's disease.
89. The method of claim 88, wherein the Parkinson's disease is early onset Parkinson's disease (EOPD).
90. The method of any one of claims 84-89, wherein the method alleviates one or more symptoms of Parkinson's disease.
91. The method of any one of claims 84-90, wherein the method reduces motor complications associated with neurodegeneration; reduces the need for antiparkinsonian pharmacotherapy, optionally L-DOPA and/or dopaminergic agonists; restores the function of degenerating neurons; and/or protects neurons from degeneration.
92. The method of any one of claims 84-91, wherein the method enhances nigrostriatal function, optionally assessed by [18F]fluoro-L-dopa positron emission tomography (PET) or DaT-SPECT imaging.
93. The method of any one of claims 84-92, wherein the method improves one or both of the UPDRS or MDS-UPDRS of the subject.
94. A pharmaceutical composition comprising the rAAV virion of any one of claims 54-76 and one or more pharmaceutically acceptable carriers, diluents, or excipients.
95. A kit comprising the rAAV virion of any one of claims 54-76 and instructions for use.
96. A polynucleotide, comprising a polynucleotide sequence encoding an activated Parkin protein.
97. The polynucleotide of claim 96, wherein the activated Parkin protein comprises amino acid substitutions at position Cys-431 relative to a reference Parkin protein.
98. The polynucleotide of claim 96, wherein the activated Parkin protein comprises a C431F amino acid substitution relative to a reference Parkin protein.

99. The polynucleotide of any one of claims 96-98, wherein the activated Parkin protein comprises one or more amino acid substitutions at positions Phe-146, Trp-403, Cys-457, Phe-463, and Asn-273 relative to a reference Parkin protein.
100. The polynucleotide of claim 99, wherein the activated Parkin protein comprises two or more amino acid substitutions at positions Phe-146, Trp-403, Cys-457, Phe-463, and Asn-273 relative to a reference Parkin protein.
101. The polynucleotide of claim 100, wherein the activated Parkin protein comprises amino acid substitutions at positions Phe-146, Trp-403, Cys-457, Phe-463, and Asn-273 relative to a reference Parkin protein.
102. The polynucleotide of any one of claims 96-101, wherein the activated Parkin protein comprises one or more amino acid substitutions selected from F146A, W403A, and/or N273K relative to a reference Parkin protein.
103. The polynucleotide of claim 102, wherein the activated Parkin protein comprises amino acid substitutions F146A and W403A relative to a reference Parkin protein.
104. The polynucleotide of claim 103, wherein the activated Parkin protein comprises amino acid substitutions F146A, N273K, and W403A relative to a reference Parkin protein.
105. The polynucleotide of claim 96, wherein the activated Parkin protein comprises a polypeptide sequence at least 95% identical to human Parkin N273K+W403A+F463A (SEQ ID NO: 93).
106. The polynucleotide of claim 96, wherein the activated Parkin protein comprises a polypeptide sequence identical to human Parkin N273K+W403A+F463A (SEQ ID NO: 93).
107. The polynucleotide of any one of claims 96-104, wherein the Parkin protein is a Δ Parkin protein comprising a deletion of the ubiquitin-like (Ubl) domain.
108. The polynucleotide of any one of claim 107, wherein the Δ Parkin protein comprises a polypeptide sequence at least 95% identical to residues 76-465 of human Parkin F146A+W403A:

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41                                     KGQEM
81 NATGGDDPRN AAGGCEREPEQ SLTRVDLSSS VLPGDSVGLA
121 VILHTDSRKD SPPAGSPAGR SIYNSAYVYC KGPCQRVQPG
161 KLRVQCSTCR QATLTTLTQGP SCWDDVLIPN RMSGECQSPH
201 CPGTSAEFFF KCGAHPTSDK ETSVALHLIA TNSRNITCIT
241 CTDVRSPLV FQCNSRHVIC LDCFHLYCVT RLNDRQFVHD
281 PQLGYSLPCV AGCPNSLIKE LHHFRILGEE QYNRYQQYGA
321 EECVLQMGV LCPRPGCGAG LLPEPDQRKV TCEGGNGLGC
361 GFAFCRECKE AYHEGECSAV FEASGTTTQA YRVDERAAEQ
401 ARAEAASKET IKKTTKPCPR CHVPVEKNGG CMHMKCPQPQ
441 CRLEWCWNCG CEWNRVCMGD HWFDV (SEQ ID NO: 18).

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109. The polynucleotide of claim 108, wherein the Δ Parkin protein comprises a polypeptide sequence identical to residues 76-465 of human Parkin

F146A+W403A:

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41                                     KGQEM
81 NATGGDDPRN AAGGCEREPEQ SLTRVDLSSS VLPGDSVGLA
121 VILHTDSRKD SPPAGSPAGR SIYNSAYVYC KGPCQRVQPG
161 KLRVQCSTCR QATLTTLTQGP SCWDDVLIPN RMSGECQSPH
201 CPGTSAEFFF KCGAHPTSDK ETSVALHLIA TNSRNITCIT
241 CTDVRSPLV FQCNSRHVIC LDCFHLYCVT RLNDRQFVHD
281 PQLGYSLPCV AGCPNSLIKE LHHFRILGEE QYNRYQQYGA
321 EECVLQMGV LCPRPGCGAG LLPEPDQRKV TCEGGNGLGC
361 GFAFCRECKE AYHEGECSAV FEASGTTTQA YRVDERAAEQ
401 ARAEAASKET IKKTTKPCPR CHVPVEKNGG CMHMKCPQPQ
441 CRLEWCWNCG CEWNRVCMGD HWFDV (SEQ ID NO: 18).

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110. The polynucleotide of any one of claims 96-109, wherein the polynucleotide comprises a promoter operably linked to the polynucleotide sequence encoding an activated Parkin protein.
111. The polynucleotide of claim 110, wherein the promoter is a constitutive promoter.
112. The polynucleotide of claim 111, wherein the promoter is a CAG promoter or a CMV promoter.
113. The polynucleotide of claim 110, wherein the promoter is a neuron-specific promoter.

114. The polynucleotide of claim 110 or claim 113, wherein the promoter is a SYN promoter.
115. The polynucleotide of any one of claims 96-114, wherein the polynucleotide comprises a WPRE element.
116. The polynucleotide of any one of claims 96-115, wherein the polynucleotide comprises a hGH polyadenylation site.
117. A vector, comprising the polynucleotide of any one of claims 96-116.
118. The vector of claim 117, wherein the vector is an adeno-associated virus (AAV) vector.
119. The vector of claim 118, wherein the vector comprises an AAV9 capsid or functional variant thereof.
120. The vector of claim 119, wherein the AAV9 capsid shares at least 98%, 99%, or 100% identity to a reference AAV9 capsid.
121. A method of increasing Parkin activity in a cell, comprising contacting the cell with the polynucleotide of any one of claims 96-116 or the vector of any one of claims 117-120.
122. A method of increasing Parkin activity in a subject, comprising administering to the subject the polynucleotide of any one of claims 96-116 or the vector of any one of claims 117-120.
123. The method of claim 121 or claim 122, wherein the cell or subject is deficient in Parkin activity and/or comprises a loss-of-function mutation in Parkin.
124. The method of any one of claims 121-123, wherein Parkin activity comprises one or more of colocalization of Parkin with TOMM2 in response to neurotoxin treatment, ubiquitination of mitochondrial proteins in response to neurotoxin treatment, and increased in Parkin levels in the mitochondrial fraction in response to neurotoxin treatment.

125. A method of promoting survival of a neuron, comprising contacting the neuron with a polynucleotide of any one of claims 96-116 or the vector of any one of claims 117-120.
126. A method of promoting survival of a neuron in a subject, comprising administering to the subject the polynucleotide of any one of claims 96-116 or the vector of any one of claims 117-120.
127. The method of claim 125 or claim 126, wherein the neuron is a dopaminergic neuron.
128. A method of treating a disease or disorder in a subject in need thereof, comprising administering to the subject the polynucleotide of any one of claims 96-116 or the vector of any one of claims 117-120.
129. The method of claim 128, wherein the subject suffers from a genetic deficiency in Parkin expression or function.
130. The method of claim 128 or claim 129, wherein the subject suffers from a genetic deficiency in PINK1 expression or function.
131. The method of any one of claims 128-130, wherein the disease or disorder is Parkinson's disease.
132. The method of claim 131, wherein the Parkinson's disease is early onset Parkinson's disease (EOPD).
133. The method of any one of claims 128-132, wherein the method alleviates one or more symptoms of Parkinson's disease.
134. The method of any one of claims 128-133, wherein the method reduces motor complications associated with neurodegeneration; reduces the need for antiparkinsonian pharmacotherapy, optionally L-DOPA and/or dopaminergic agonists; restores the function of degenerating neurons; and/or protects neurons from degeneration.

135. The method of any one of claims 128-134, wherein the method enhances nigrostriatal function, optionally assessed by [¹⁸F]fluoro-L-dopa positron emission tomography (PET) or DaT-SPECT imaging.
136. The method of any one of claims 128-135, wherein the method improves one or both of the UPDRS or MDS-UPDRS of the subject.
137. A cell comprising the polynucleotide of any one of claims 96-116.
138. A protein encoded by the polynucleotide of any one of claims 96-116.
139. A pharmaceutical composition comprising the vector of any one of claims 117-120 and one or more pharmaceutically acceptable carriers, diluents, or excipients.
140. A kit comprising the vector of any one of claims 117-120 and instructions for use.