

WHAT IS CLAIMED IS:

1. A progranulin variant comprising a sequence having at least 90% identity to SEQ ID NO:2 and a sequence defined by $X_1X_2X_3$ at the positions corresponding to residues 574 to 576 of SEQ ID NO:2, wherein X_1 , X_2 , and X_3 are each independently an amino acid and together are not QLL.

2. The progranulin variant of claim 1, wherein the progranulin variant has at least 95% identity to SEQ ID NO:2.

3. The progranulin variant of claim 1 or 2, wherein the progranulin variant has at least 98% identity to SEQ ID NO:2.

4. The progranulin variant of any one of claims 1 to 3, wherein the progranulin variant has at least 99% identity to SEQ ID NO:2.

5. The progranulin variant of claim 1, wherein the progranulin variant comprises a sequence having at least 95% identity to SEQ ID NO:2.

6. The progranulin variant of claim 1 or 5, wherein the progranulin variant comprises a sequence having at least 98% identity to SEQ ID NO:2.

7. The progranulin variant of any one of claims 1, 5, and 6, wherein the progranulin variant comprises a sequence having at least 99% identity to SEQ ID NO:2.

8. The progranulin variant of any one of claims 1 to 7, wherein the progranulin variant has the sequence of:

TRCPDGQFCPVACCLDPGGASYSCCRPLLDKWPTTLRHLGGPCQVDAHCSAGHSCI
FTVSGTSSCCPFPEAVACGDGHHCCPRGFHCSADGRSCFQRSGNNSVGAIQCPDSQF
ECPDFSTCCVMVDGSGWCCPMPQASCCEDRVHCCPHGAFCDLVHTRCITPTGTHPL
AKKLPAQRTNRAVALSSVMCPDARSRCPDGSTCCELP SGKYGCCPMPNATCCSDH
LHCCPQDTVCDLIQSKCLSKENATTDLLTKLPAHTVGDVKCDMEVSCPDGYTCCRL
QSGAWGCCPFTQAVCCEDHIHCCPAGFTCDTQKGTCEQGPHQVPWMEKAPAHLSLP
DPQALKRDVPCDNVSSCPSSDTCCQLTSGEWGCCPIPEAVCCSDHQHCCPQGYTCVA
EGQCQRGSEIVAGLEKMPARRASLSHPRDIGCDQHTSCPVGQTCCPSLGGSWACCQL
PHAVCCEDRQHCCPAGYTCNVKARSCEKEVVSQAQPATFLARSPHVGVDVECGEG
HFCHDNQTCCRDNRQGWACCPYRQGVCCADRRHCCPAGFRCAARGTKCLRREAPR
WDAPLRDPALRX $_1X_2X_3$ (SEQ ID NO:3).

9. The progranulin variant of any one of claims 1 to 8, wherein X_1 is R, H, K, D, E, S, T, N, Q, L, F, Y, P, or V.

10. The progranulin variant of any one of claims 1 to 9, wherein X_2 is H, K, D, E, S, T, N, Q, G, P, A, Y, V, I, F, L, or R.

11. The progranulin variant of any one of claims 1 to 10, wherein X_3 is L, Y, or P.

12. The progranulin variant of any one of claims 1 to 11, wherein $X_1X_2X_3$ is X_1IL , X_1FL , X_1QL , PX_2L , QX_2L , or VX_2L .

13. The progranulin variant of any one of claims 1 to 11, wherein $X_1X_2X_3$ is X_1X_2L .

14. The progranulin variant of claim 13, wherein X_2 is A, R, N, D, C, Q, E, G, H, I, K, M, F, P, S, T, W, Y, or V.

15. The progranulin variant of any one of claims 1 to 11, wherein $X_1X_2X_3$ is PIL, PFL, QQL, VVL, or VTL.

16. The progranulin variant of any one of claims 1 to 11, wherein $X_1X_2X_3$ is PPL, PYL, QQL, QHL, or QRL.

17. A progranulin variant comprising a sequence having at least 90% identity to SEQ ID NO:2 and a sequence defined by Y_1Y_2QLL (SEQ ID NO:137) that is adjacent and C-terminal to the position corresponding to residue 576 of SEQ ID NO:2, wherein Y_1 is L or absent, and Y_2 is R or absent.

18. The progranulin variant of claim 17, wherein the progranulin variant comprises the sequence:

TRCPDGQFCPVACCLDPGGASYSCCRPLLDKWPTTLRHLGGPCQVDAHCSAGHSCI
FTVSGTSSCCPFPEAVACGDGHHCCPRGFHCSADGRSCFQRSGNNSVGAIQCPDSQF
ECPDFSTCCVMVDGSWGCCPMPQASCCEDRVHCCPHGAFCDLVHTRCITPTGTHPL
AKKLPAQRTNRAVALSSVMCPDARSRCPDGSTCCELPSGKYGCCPMPNATCCSDH
LHCCPQDQTVCDLIQSKCLSKENATTDLLTKLPAHTVGDVKCDMEVSCPDGYTCCRL
QSGAWGCCPFTQAVCCEDHIHCCPAGFTCDTQKGTCEQGPHQVPWMEKAPAHLSLP
DPQALKRDVPCDNVSSCPSSDTCCQLTSGEWGCCPIPEAVCCSDHQHCCPQGYTCVA
EGQCQRGSEIVAGLEKMPARRASLSHPRDIGCDQHTSCPVGQTCCPSLGGSWACCQL

PHAVCCEDRQHCCPAGYTCNVKARSCEKEVVSAQPATFLARSPHVGVDVECGEG
HFCHDNQTCCRDNRQGWACCPYRQGVCCADRRHCCPAGFRCAARGTKCLRREAPR
WDAPLRDPALRQLLY₁Y₂QLL (SEQ ID NO:55),

wherein Y₁ is L or absent, and Y₂ is R or absent.

19. The progranulin variant of claim 17 or 18, wherein Y₁ is L.
20. The progranulin variant of any one of claims 17 to 19, wherein Y₂ is R.
21. The progranulin variant of claim 17 or 18, wherein Y₁ and Y₂ are both absent.
22. A polypeptide comprising a progranulin variant that comprises a sequence having at least 90% identity to SEQ ID NO:2 and a sequence defined by X₁X₂X₃ at the positions corresponding to residues 574 to 576 of SEQ ID NO:2, wherein X₁, X₂, and X₃ are each independently an amino acid and together are not QLL.
23. The polypeptide of claim 22, wherein the progranulin variant has at least 95% identity to SEQ ID NO:2.
24. The polypeptide of claim 22 or 23, wherein the progranulin variant has at least 98% identity to SEQ ID NO:2.
25. The polypeptide of any one of claims 22 to 24, wherein the progranulin variant has at least 99% identity to SEQ ID NO:2.
26. The polypeptide of any one of claims 22 to 25, wherein the progranulin variant has the sequence of:

TRCPDGQFCPVACCLDPGGASYSCCRPLLDKWPTTLRHLGGPCQVDAHCSAGHSCI
FTVSGTSSCCPFPEAVACGDGHHCCPRGFHCSADGRSCFQRSGNNSVGAIQCPDSQF
ECPDFSTCCVMVDGSGCCPMPQASCCEDRVHCCPHGAFCDLVHTRCITPTGTHPL
AKKLPAQRTNRAVALSSVMCPDARSRCPDGSTCCELPSGKYGCCPMPNATCCSDH
LHCCPQDQTVCDLIQSKCLSKENATTDLLTKLPAHTVGDVKCDMEVSCPDGYTCCRL
QSGAWGCCPFTQAVCCEDHIHCCPAGFTCDTQKGTCEQGPHQVPWMEKAPAHLSLP
DPQALKRDVPCDNVSSCPSSDTCCQLTSGEWGCCPIPEAVCCSDHQHCCPQGYTCVA
EGQCQRGSEIVAGLEKMPARRASLSHPRDIGCDQHTSCPVGQTCCPSLGGSWACCQL
PHAVCCEDRQHCCPAGYTCNVKARSCEKEVVSAQPATFLARSPHVGVDVECGEG
HFCHDNQTCCRDNRQGWACCPYRQGVCCADRRHCCPAGFRCAARGTKCLRREAPR
WDAPLRDPALRX₁X₂X₃ (SEQ ID NO:3).

27. The polypeptide of any one of claims 22 to 26, wherein X₁ is R, H, K, D, E, S, T, N, Q, L, F, Y, P, or V.

28. The polypeptide of any one of claims 22 to 27, wherein X_2 is H, K, D, E, S, T, N, Q, G, P, A, Y, V, I, F, L, or R.
29. The polypeptide of any one of claims 22 to 28, wherein X_3 is L, Y, or P.
30. The polypeptide of any one of claims 22 to 29, wherein $X_1X_2X_3$ is X_1IL , X_1FL , or X_1QL .
31. The polypeptide of any one of claims 22 to 29, wherein $X_1X_2X_3$ is PX_2L , QX_2L , or VX_2L .
32. The polypeptide of any one of claims 22 to 29, wherein $X_1X_2X_3$ is X_1X_2L .
33. The polypeptide of claim 32, wherein X_2 is A, R, N, D, C, Q, E, G, H, I, K, M, F, P, S, T, W, Y, or V.
34. The polypeptide of any one of claims 22 to 30, wherein $X_1X_2X_3$ is PIL.
35. The polypeptide of any one of claims 22 to 30, wherein $X_1X_2X_3$ is PFL.
36. The polypeptide of any one of claims 22 to 30, wherein $X_1X_2X_3$ is QQL.
37. The polypeptide of any one of claims 22 to 29 and 31, wherein $X_1X_2X_3$ is VVL.
38. The polypeptide of any one of claims 22 to 29 and 31, wherein $X_1X_2X_3$ is VTL.
39. The polypeptide of any one of claims 22 to 29 and 31, wherein $X_1X_2X_3$ is PPL.
40. The polypeptide of any one of claims 22 to 29 and 31, wherein $X_1X_2X_3$ is PYL.
41. The polypeptide of any one of claims 22 to 29 and 31, wherein $X_1X_2X_3$ is QRL.

42. The polypeptide of any one of claims 22 to 29 and 31, wherein $X_1X_2X_3$ is QHL.

43. A polypeptide comprising a progranulin variant that comprises a sequence having at least 90% identity to SEQ ID NO:2 and a sequence defined by Y_1Y_2QLL (SEQ ID NO:137) that is adjacent and C-terminal to the position corresponding to residue 576 of SEQ ID NO:2, wherein Y_1 is L or absent, and Y_2 is R or absent.

44. The polypeptide of claim 43, wherein the progranulin variant comprises the sequence:

TRCPDGQFCPVACCLDPGGASYSCCRPLLDKWPTTLRHLGGPCQVDAHCSAGHSCI
FTVSGTSSCCPFPEAVACGDGHHCCPRGFHCSADGRSCFQRSGNNSVGAIQCPDSQF
ECPDFSTCCVMVDGSWGCCPMPQASCCEDRVHCCPHGAFCDLVHTRCITPTGTHPL
AKKLPAQRTNRAVALSSVMCPDARSRCPDGSTCCELPSGKYGCCPMPNATCCSDH
LHCCPQDTVCDLIQSKCLSKENATTDLLTKLPAHTVGDVKCDMEVSCPDGYTCCRL
QSGAWGCCPFTQAVCCEDHIHCCPAGFTCDTQKGTCEQGPVWMEKAPAHLSLP
DPQALKRDVPCDNVSSCPSSDTCCQLTSGEWGCCPIPEAVCCSDHQHCCPQGYTCVA
EGQCQRGSEIVAGLEKMPARRASLSHPRDIGCDQHTSCPVGQTCCPSLGGSWACCQL
PHAVCCEDRQHCCPAGYTCNVKARSCEKEVVSAPATFLARSPHVGVDVECGEG
HFCHDNQTCCRDNRQGWACCPYRQGVCCADRRHCCPAGFRCAARGTKCLRREAPR
WDAPLRDPALRQLLY₁Y₂QLL (SEQ ID NO:55),

wherein Y_1 is L or absent, and Y_2 is R or absent.

45. The polypeptide of claim 44, wherein Y_1 is L.

46. The polypeptide of any one of claims 43 to 45, wherein Y_2 is R.

47. The polypeptide of claim 43 or 44, wherein Y_1 and Y_2 are both absent.

48. The polypeptide of any one of claims 22 to 47, further comprising an Fc polypeptide that is linked to the progranulin variant.

49. The polypeptide of claim 48, wherein the N-terminus or C-terminus of the Fc polypeptide is linked to the progranulin variant.

50. The polypeptide of claim 48 or 49, wherein the Fc polypeptide is linked to the progranulin variant by a peptide bond or by a polypeptide linker.

51. The polypeptide of claim 50, wherein the polypeptide linker is 1 to 50 amino acids in length.

52. The polypeptide of claim 50 or 51, wherein the polypeptide linker is a flexible polypeptide linker.

53. The polypeptide of claim 52, wherein the flexible polypeptide linker is a glycine-rich linker.

54. The polypeptide of claim 53, wherein the glycine-rich linker is G₄S (SEQ ID NO:90) or (G₄S)₂ (SEQ ID NO:91).

55. The polypeptide of any one of claims 48 to 54, wherein the Fc polypeptide comprises a sequence selected from the group consisting of SEQ ID NOS:64-67.

56. The polypeptide of any one of claims 48 to 54, wherein the Fc polypeptide is a modified Fc polypeptide that specifically binds to a transferrin receptor.

57. The polypeptide of claim 56, wherein the Fc polypeptide comprises a sequence selected from the group consisting of SEQ ID NOS:68-87 and 129-132.

58. The polypeptide of claim 57, wherein the Fc polypeptide comprises a sequence selected from SEQ ID NOS:70, 75, 80, 85, and 129-132.

59. A fusion protein comprising:
(a) a progranulin variant of any one of claims 1 to 21;
(b) a first Fc polypeptide that is linked to the progranulin variant of (a); and
(c) a second Fc polypeptide that forms an Fc polypeptide dimer with the first Fc polypeptide.

60. The fusion protein of claim 59, wherein the second Fc polypeptide is linked to a second progranulin variant of any one of claims 1 to 21.

61. The fusion protein of claim 59 or 60, wherein the first Fc polypeptide is linked to the progranulin variant by a peptide bond or by a polypeptide linker and/or the second Fc polypeptide is linked to the progranulin variant by a peptide bond or by a polypeptide linker.

62. The fusion protein of claim 61, wherein the polypeptide linker is 1 to 50 amino acids in length.

63. The fusion protein of claim 61 or 62, wherein the polypeptide linker is a flexible polypeptide linker.

64. The fusion protein of claim 63, wherein the flexible polypeptide linker is a glycine-rich linker.

65. The fusion protein of claim 64, wherein the glycine-rich linker is G₄S (SEQ ID NO:90) or (G₄S)₂ (SEQ ID NO:91).

66. The fusion protein of any one of claims 59 to 65, wherein the C-terminus of the first Fc polypeptide is linked to the the N-terminus of the progranulin, and/or the C-terminus of the second Fc polypeptide is linked to the N-terminus of the progranulin variant.

67. The fusion protein of any one of claims 59 to 66, wherein the first Fc polypeptide or the second Fc polypeptide specifically binds to a transferrin receptor.

68. The fusion protein of any one of claims 59 to 67, wherein the first Fc polypeptide and the second Fc polypeptide each comprise modifications that promote heterodimerization.

69. The fusion protein of claim 68, wherein:

(i) the first Fc polypeptide comprises a T366W substitution and the second Fc polypeptide comprises T366S, L368A, and Y407V substitutions, according to EU numbering; or

(ii) the first Fc polypeptide comprises T366S, L368A, and Y407V substitutions and the second Fc polypeptide comprises a T366W substitution, according to EU numbering.

70. The fusion protein of any one of claims 59 to 69, wherein the first Fc polypeptide and/or the second Fc polypeptide independently comprises modifications that reduce effector function.

71. The fusion protein of claim 70, wherein the modifications that reduce effector function are L234A and L235A substitutions, according to EU numbering.

72. The fusion protein of any one of claims 59 to 71, wherein the first Fc polypeptide comprises a sequence selected from the group consisting of SEQ ID NOS:64-67.

73. The fusion protein of any one of claims 59 to 72, wherein the second Fc polypeptide comprises a sequence selected from the group consisting of SEQ ID NOS:68-87 and 129-132.

74. The fusion protein of claim 73, wherein the second Fc polypeptide comprises a sequence selected from the group consisting of SEQ ID NOS:70, 75, 80, 85, and 129-132.

75. The fusion protein of any one of claims 59 to 74, wherein a hinge region or a portion thereof is linked to the first Fc polypeptide and/or the second Fc polypeptide.

76. The fusion protein of any one of claims 59 to 75, wherein the first Fc polypeptide linked to the progranulin variant comprises the sequence of SEQ ID NO:98, and the second Fc polypeptide comprises the sequence of SEQ ID NO:75.

77. The fusion protein of any one of claims 59 to 75, wherein the first Fc polypeptide linked to the progranulin variant comprises the sequence of SEQ ID NO:98, and the second Fc polypeptide comprises the sequence of SEQ ID NO:130.

78. The fusion protein of any one of claims 59 to 75, wherein the first Fc polypeptide linked to the progranulin variant comprises the sequence of SEQ ID NO:99, and the second Fc polypeptide the sequence of SEQ ID NO:75.

79. The fusion protein of any one of claims 59 to 75, wherein the first Fc polypeptide linked to the progranulin variant comprises the sequence of SEQ ID NO:99, and the second Fc polypeptide the sequence of SEQ ID NO:130.

80. The fusion protein of any one of claims 59 to 75, wherein the first Fc polypeptide linked to the progranulin variant comprises the sequence of SEQ ID NO:100, and the second Fc polypeptide comprises the sequence of SEQ ID NO:75.

81. The fusion protein of any one of claims 59 to 75, wherein the first Fc polypeptide linked to the progranulin variant comprises the sequence of SEQ ID NO:100, and the second Fc polypeptide comprises the sequence of SEQ ID NO:130.

82. The fusion protein of any one of claims 59 to 75, wherein the first Fc polypeptide linked to the progranulin variant comprises the sequence of SEQ ID NO:101, and the second Fc polypeptide comprises the sequence of SEQ ID NO:75.

83. The fusion protein of any one of claims 59 to 75, wherein the first Fc polypeptide linked to the progranulin variant comprises the sequence of SEQ ID NO:101, and the second Fc polypeptide comprises the sequence of SEQ ID NO:130.

84. The fusion protein of any one of claims 59 to 75, wherein the first Fc polypeptide linked to the progranulin variant comprises the sequence of SEQ ID NO:102, and the second Fc polypeptide comprises the sequence of SEQ ID NO:75.

85. The fusion protein of any one of claims 59 to 75, wherein the first Fc polypeptide linked to the progranulin variant comprises the sequence of SEQ ID NO:102, and the second Fc polypeptide comprises the sequence of SEQ ID NO:130.

86. The fusion protein of any one of claims 59 to 75, wherein the first Fc polypeptide linked to the progranulin variant comprises the sequence of SEQ ID NO:123, and the second Fc polypeptide comprises the sequence of SEQ ID NO:75.

87. The fusion protein of any one of claims 59 to 75, wherein the first Fc polypeptide linked to the progranulin variant comprises the sequence of SEQ ID NO:123, and the second Fc polypeptide comprises the sequence of SEQ ID NO:130.

88. The fusion protein of any one of claims 59 to 75, wherein the first Fc polypeptide linked to the progranulin variant comprises the sequence of SEQ ID NO:124, and the second Fc polypeptide comprises the sequence of SEQ ID NO:75.

89. The fusion protein of any one of claims 59 to 75, wherein the first Fc polypeptide linked to the progranulin variant comprises the sequence of SEQ ID NO:124, and the second Fc polypeptide comprises the sequence of SEQ ID NO:130.

90. The fusion protein of any one of claims 59 to 75, wherein the first Fc polypeptide linked to the progranulin variant comprises the sequence of SEQ ID NO:125, and the second Fc polypeptide comprises the sequence of SEQ ID NO:75.

91. The fusion protein of any one of claims 59 to 75, wherein the first Fc polypeptide linked to the progranulin variant comprises the sequence of SEQ ID NO:125, and the second Fc polypeptide comprises the sequence of SEQ ID NO:130.

92. The fusion protein of any one of claims 59 to 75, wherein the first Fc polypeptide linked to the progranulin variant comprises the sequence of SEQ ID NO:126, and the second Fc polypeptide comprises the sequence of SEQ ID NO:75.

93. The fusion protein of any one of claims 59 to 75, wherein the first Fc polypeptide linked to the progranulin variant comprises the sequence of SEQ ID NO:126, and the second Fc polypeptide comprises the sequence of SEQ ID NO:130.

94. The fusion protein of any one of claims 59 to 93, wherein the fusion protein is produced in a Chinese Hamster Ovary (CHO) cell.

95. The fusion protein of claim 94, wherein the fusion protein is purified substantially as described in Example 1.

96. The fusion protein of any one of claims 59 to 95, wherein more than 50% of the progranulin variants in the first polypeptides of the fusion proteins are not truncated at the C-terminus.

97. The fusion protein of any one of claims 59 to 96, wherein the K_D value for sortilin binding of the fusion protein is less than about 100 nM.

98. The fusion protein of any one of claims 59 to 97, wherein the EC_{50} for sortilin binding of the fusion protein is less than about 25 nM.

99. The fusion protein of claim 98, wherein the EC_{50} is measured by ELISA.

100. The fusion protein of claim 99, wherein the ELISA assay is carried out substantially as described in Example 4.

101. The fusion protein of any one of claims 59 to 100, wherein the EC_{50} for sortilin binding of the fusion protein exhibits less than 10-fold decrease in sortilin binding relative to a reference fusion protein, wherein the reference fusion protein comprises (i) a first

polypeptide comprising SEQ ID NO:2 and (ii) a second Fc polypeptide that forms an Fc polypeptide dimer with the first Fc polypeptide.

102. The fusion protein of any one of claims 59 to 101, wherein the EC₅₀ for sortilin binding of the fusion protein exhibits less than 10-fold decrease in sortilin binding relative to a reference fusion protein, wherein the reference fusion protein comprises (i) a first polypeptide comprising SEQ ID NO:108 and (ii) a second Fc polypeptide that forms an Fc polypeptide dimer with the first Fc polypeptide.

103. The fusion protein of claim 101 or 102, wherein the reference fusion protein is produced in a HEK cell.

104. The fusion protein of claim 103, wherein the reference fusion protein is purified substantially as described in Example 1.

105. A pharmaceutical composition comprising the progranulin variant of any one of claims 1 to 21, the polypeptide of any one of claims 22 to 58, or the fusion protein of any one of claims 59 to 104, and a pharmaceutically acceptable carrier.

106. A pharmaceutical composition comprising a plurality of the fusion protein of any one of claims 59 to 104 and a pharmaceutically acceptable carrier.

107. The pharmaceutical composition of claim 106, wherein more than 50% of the plurality of the fusion protein comprises an intact C-terminus in the progranulin variant of the fusion protein.

108. A method of treating a subject having a neurodegenerative disease, atherosclerosis, a disorder associated with TDP-43, age-related macular degeneration (AMD), or a progranulin-associated disorder, the method comprising administering the progranulin variant of any one of claims 1 to 21, the polypeptide of any one of claims 22 to 58, the fusion protein of any one of claims 59 to 104, or the pharmaceutical composition of any one of claims 105 to 107 to the subject.

109. A method of increasing the amount of a progranulin or a variant thereof in a subject, the method comprising administering the progranulin variant of any one of claims 1 to 21, the polypeptide of any one of claims 22 to 58, the fusion protein of any one of claims 59 to 104, or the pharmaceutical composition of any one of claims 105 to 107 to the subject.

110. A method of decreasing cathepsin D activity in a subject, the method comprising administering the progranulin variant of any one of claims 1 to 21, the polypeptide of any one of claims 22 to 58, the fusion protein of any one of claims 59 to 104, or the pharmaceutical composition of any one of claims 105 to 107 to the subject.

111. A method of increasing lysosomal degradation in a subject having a progranulin-associated disorder, the method comprising administering the progranulin variant of any one of claims 1 to 21, the polypeptide of any one of claims 22 to 58, the fusion protein of any one of claims 59 to 104, or the pharmaceutical composition of any one of claims 105 to 107 to the subject.

112. A method of improving or rescuing lysosomal function in a subject having a progranulin-associated disorder, the method comprising administering the progranulin variant of any one of claims 1 to 21, the polypeptide of any one of claims 22 to 58, the fusion protein of any one of claims 59 to 104, or the pharmaceutical composition of any one of claims 105 to 107 to the subject.

113. The method of any of claims 109 to 112, wherein the subject has a neurodegenerative disease, atherosclerosis, a disorder associated with TDP-43, or AMD.

114. The method of any one of claims 108 to 113, wherein the subject has a neurodegenerative disease.

115. The method of claim 114, wherein the neurodegenerative disease is selected from the group consisting of frontotemporal dementia (FTD), neuronal ceroid lipofuscinosis (NCL), Niemann-Pick disease type A (NPA), Niemann-Pick disease type B (NPB), Niemann-Pick disease type C (NPC), C9ORF72-associated amyotrophic lateral sclerosis (ALS)/FTD, sporadic ALS, Alzheimer's disease (AD), Gaucher's disease, and Parkinson's disease.

116. The method of claim 115, wherein the neurodegenerative disease is FTD.

117. The method of any one of claims 108 to 116, wherein the subject has a mutation in a gene encoding the progranulin.

118. A polynucleotide comprising a nucleic acid sequence encoding the progranulin variant of any one of claims 1 to 21 or the polypeptide of any one of claims 22 to 58.

119. A vector comprising the polynucleotide of claim 118.

120. A host cell comprising the polynucleotide of claim 118 or the vector of claim 119.

121. The host cell of claim 120, further comprising a polynucleotide comprising a nucleic acid sequence encoding a second Fc polypeptide.

122. The host cell of claim 121, wherein the second Fc polypeptide has a sequence selected from any one of SEQ ID NOs: 61 and 64-87.

123. A method for producing a polypeptide, comprising culturing a host cell under conditions in which the polypeptide encoded by the polynucleotide of claim 118 is expressed.