

CLAIMS

What is claimed is:

1. Use of a therapeutically effective amount of an autophagy-lysosomal pathway modulating agent comprising an enzyme for enzyme replacement therapy (ERT), a gene for gene therapy (GT), a composition for gene editing, hematopoietic stem cells for hematopoietic stem cell transplantation (HSCT), a stop codon read through drug, a small molecule for substrate reduction therapy (SRT), or any combination thereof for the manufacture of a medicament for preventing, treating, reversing or delaying a neurological or neurodegenerative disease, disorder, or condition in a subject determined to have or be at risk for a neurological or neurodegenerative disease, disorder, or condition by virtue of detecting at least one lysosomal gene comprising a loss-of-function variant in the subject, wherein the subject is heterozygous for a loss-of-function variant.

2. The use of claim 1, wherein the at least one lysosomal gene comprising a loss-of-function variant is CTNS, MAN2B1, MFSD8, GLB1, GALNS, NAGLU, CLN3, GNPTAB, SGSH, CLN8, NPC1, TPP1, DNAJC5, MANBA, PPT1, SMPD1, GAA, HGSNAT, GNS, CTSA, HEXB, or any combination thereof.

3. The use of claim 1, wherein the lysosomal gene comprising a loss-of-function variant is AGA, ARSA, ARSB, ASAH1, CLN2 (TPP1), CLN3, CLN5, CLN6, CLN8, CTNS, CTSA, CTSD, CTSK, FUCA1, GAA, GALC, GALNS, GLA, GLB1, GM2A, GNPTAB, GNPTG, GNS, GUSB, HEXA, HEXB, HGSNAT, HYAL1, IDS, IDUA, KCTD7, LAMP2, LIPA, MAN2B1, MANBA, MCOLN1, MFSD8, NAGA, NAGLU, NEU1, NPC1, NPC2, PPT1, PSAP, SGSH, SLC17A5, SMPD1, SUMF1, CHIT1, ATP13A2, CTSF, DNAJC5, GRN, or any combination thereof.

4. The use of claim 1, wherein the lysosomal gene comprising a loss-of-function variant is NEU1, NAGLU, GLB1, MANBA, MAN2B1, HGSNAT, IDS, PPT1, GNS, or any combination thereof.

5. The use of claim 1, wherein the lysosomal gene comprising a loss-of-function variant is GALC, ACD, or any combination thereof.

6. The use of claim 1, wherein the subject is haploinsufficient for or is a heterozygous variant in a lysosomal gene comprising a loss-of-function variant of NAGLU, PPT1, Csp-a, or any combination thereof.

7. The use claim 1, wherein the lysosomal gene comprising a loss-of-function variant is SGSH, NAGLU, HGSNAT, GNS, or any combination thereof.

8. The use of any one of the claims 2-7, wherein the loss-of-function variant is one or more variants is a deletion, a substitution, or a deletion of the lysosomal gene.

9. The use of claim 1, wherein the neurological or neurodegenerative disease, disorder, or condition is APP processing dysfunction.

10. The use of claim 1, wherein the neurological or neurodegenerative disease, disorder, or condition is Alzheimer's disease (AD).

11. The use of claim 1, wherein the subject is suspected of having dementia, Alzheimer's disease (AD), Parkinson's disease (PD), frontotemporal dementia (FTD), Creutzfeldt–Jakob disease, motor neuron disease, a polyglutamine disorder, Huntington's disease, familial amyloid polyneuropathy (FAP), Lewy body dementia, or multiple system atrophy.

12. Use of a therapeutically effective amount of an autophagy-lysosomal pathway modulating agent comprising an enzyme for enzyme replacement therapy (ERT), a gene for gene therapy (GT), a composition for gene editing, hematopoietic stem cells for hematopoietic stem cell transplantation (HSCT), a stop codon read through drug, a small molecule for substrate reduction therapy

(SRT), or any combination thereof, for the manufacture of a medicament for preventing, treating, reversing, or delaying the onset of a neurological disease, disorder, or condition in a subject determined to have or be at risk for a neurological or neurodegenerative disease, disorder, or condition by virtue of detecting at least one lysosomal gene comprising a loss-of-function variant, wherein the subject is heterozygous for the loss-of-function variant.

13. The use of claim 12, wherein the at least one lysosomal gene comprising a loss-of-function variant is CTNS, MAN2B1, MFSD8, GLB1, GALNS, NAGLU, CLN3, GNPTAB, SGSH, CLN8, NPC1, TPP1, DNAJC5, MANBA, PPT1, SMPD1, GAA, HGSNAT, GNS, CTSA, HEXB, or any combination thereof.

14. The use of claim 12, wherein the at least one lysosomal gene comprising a loss-of-function variant is AGA, ARSA, ARSB, ASAH1, CLN2 (TPP1), CLN3, CLN5, CLN6, CLN8, CTNS, CTSA, CTSD, CTSK, FUCA1, GAA, GALC, GALNS, GLA, GLB1, GM2A, GNPTAB, GNPTG, GNS, GUSB, HEXA, HEXB, HGSNAT, HYAL1, IDS, IDUA, KCTD7, LAMP2, LIPA, MAN2B1, MANBA, MCOLN1, MFSD8, NAGA, NAGLU, NEU1, NPC1, NPC2, PPT1, PSAP, SGSH, SLC17A5, SMPD1, SUMF1, CHIT1, ATP13A2, CTSF, DNAJC5, GRN, or any combination thereof.

15. The use of claim 12, wherein the lysosomal gene comprising a loss-of-function variant is NEU1, NAGLU, GLB1, MANBA, MAN2B1, HGSNAT, IDS, PPT1, GNS, or any combination thereof.

16. The use of claim 12, wherein the lysosomal gene comprising a loss-of-function variant is GALC, ACD, or any combination thereof.

17. The use of claim 12, wherein the subject is haploinsufficient for or is a heterozygous variant in a lysosomal gene comprising a loss-of-function variant of NAGLU, PPT1, Csp-a, or any combination thereof.

18. The use of claim 12, wherein the lysosomal gene comprising a loss-of-function variant is SGSH, NAGLU, HGSNAT, GNS, or any combination thereof.

19. The use of any one of the claims 13-18, wherein the loss-of-function variant is one or more variants is a deletion, a substitution, or a deletion of the lysosomal gene.

20. The use of claim 12, wherein the neurological or neurodegenerative disease, disorder, or condition is APP processing dysfunction.

21. The use of claim 12, wherein the neurological or neurodegenerative disease, disorder, or condition is Alzheimer's disease (AD).

22. The use of claim 12, wherein the subject is suspected of having dementia, Alzheimer's disease (AD), Parkinson's disease (PD), frontotemporal dementia (FTD), Creutzfeldt–Jakob disease, motor neuron disease, a polyglutamine disorder, Huntington's disease, familial amyloid polyneuropathy (FAP), Lewy body dementia, or multiple system atrophy.

23. Use of a therapeutically effective amount of an autophagy-lysosomal pathway modulating agent comprising an enzyme for enzyme replacement therapy (ERT), a gene for gene therapy (GT), a composition for gene editing, hematopoietic stem cells for hematopoietic stem cell transplantation (HSCT), a stop codon read through drug, a small molecule for substrate reduction therapy (SRT), or any combination thereof, for the manufacture of a medicament for preventing, treating, reversing or delaying Alzheimer's disease in a subject determined to have or be at risk for Alzheimer's disease by virtue of detecting at least one lysosomal gene comprising a loss-of-function variant in the subject, wherein the subject is heterozygous for a loss-of-function variant.

24. The use of claim 23, wherein the at least one lysosomal gene comprising a loss-of-function variant is CTNS, MAN2B1, MFSD8, GLB1, GALNS, NAGLU, CLN3, GNPTAB, SGSH, CLN8, NPC1, TPP1, DNAJC5, MANBA, PPT1, SMPD1, GAA, HGSNAT, GNS, CTSA, HEXB, or any combination thereof.

25. The use of claim 23, wherein the at least one lysosomal gene comprising a loss-of-function variant is AGA, ARSA, ARSB, ASAH1, CLN2 (TPP1), CLN3, CLN5, CLN6, CLN8, CTNS, CTSA, CTSD, CTSK, FUCA1, GAA, GALC, GALNS, GLA, GLB1, GM2A, GNPTAB, GNPTG, GNS, GUSB, HEXA, HEXB, HGSNAT, HYAL1, IDS, IDUA, KCTD7, LAMP2, LIPA, MAN2B1, MANBA, MCOLN1, MFSD8, NAGA, NAGLU, NEU1, NPC1, NPC2, PPT1, PSAP, SGSH, SLC17A5, SMPD1, SUMF1, CHIT1, ATP13A2, CTSF, DNAJC5, GRN, or any combination thereof.

26. The use of claim 23, wherein the at least one lysosomal gene comprising a loss-of-function variant is NEU1, NAGLU, GLB1, MANBA, MAN2B1, HGSNAT, IDS, PPT1, GNS, or any combination thereof.

27. The use of claim 23, wherein the at least one lysosomal gene comprising a loss-of-function variant is GALC, ACD, or any combination thereof.

28. The use of claim 23, wherein the subject is haploinsufficient for or has a heterozygous variant in a lysosomal gene comprising a loss-of-function variant of NAGLU, PPT1, Csp-a, or any combination thereof.

29. The use of claim 23, wherein the at least one lysosomal gene comprising a loss-of-function variant is SGSH, NAGLU, HGSNAT, GNS, or any combination thereof.

30. The use of any one of the claims 24-29, wherein the loss-of-function variant is one or more variants is a deletion, a substitution, or a deletion of the at least one lysosomal gene.

31. A method of determining risk for a neurological or neurodegenerative disease, disorder, or condition, in a subject not afflicted with a lysosomal storage disease, the method comprising:

detecting in a biological sample obtained from the subject the presence of at least one lysosomal gene comprising a loss-of-function variant wherein the subject is heterozygous for the lysosomal gene variant, and

determining the subject is at risk for neurological or neurodegenerative disease, disorder, or condition when at least one lysosomal gene comprising a loss-of-function variant is detected.

32. The method of claim 31, wherein the lysosomal gene or at least one lysosomal gene comprising a loss-of-function variant is:

(i) CTNS, MAN2B1, MFSD8, GLB1, GALNS, NAGLU, CLN3, GNPTAB, SGSH, CLN8, NPC1, TPP1, DNAJC5, MANBA, PPT1, SMPD1, GAA, HGSNAT, GNS, CTSA, HEXB, or any combination thereof;

(ii) NEU1, NAGLU, GLB1, MANBA, MAN2B1, HGSNAT, IDS, PPT1, GNS, or any combination thereof;

(iii) GALC, ACD, or any combination thereof;

(iv) AGA, ARSA, ARSB, ASAH1, CLN2 (TPP1), CLN3, CLN5, CLN6, CLN8, CTNS, CTSA, CTSD, CTSK, FUCA1, GAA, GALC, GALNS, GLA, GLB1, GM2A, GNPTAB, GNPTG, GNS, GUSB, HEXA, HEXB, HGSNAT, HYAL1, IDS, IDUA, KCTD7, LAMP2, LIPA, MAN2B1, MANBA, MCOLN1, MFSD8, NAGA, NAGLU, NEU1, NPC1, NPC2, PPT1, PSAP, SGSH, SLC17A5, SMPD1, SUMF1, CHIT1, ATP13A2, CTSF, DNAJC5, or any combination thereof;

(v) NAGLU, PPT1, Csp-a, or any combination thereof; or

(vi) SGSH, NAGLU, HGSNAT, GNS, or any combination thereof.