

CLAIMS

What is claimed is:

1. Use of a therapeutically effective amount of an autophagy-lysosomal pathway modulating agent comprising a gene for gene therapy (GT) for the manufacture of a medicament for preventing, treating, reversing or delaying dementia in a subject wherein the subject is determined to have or be at risk for dementia by virtue of detecting that the subject is heterozygous for a loss-of-function variant in at least one lysosomal gene selected from the group consisting of PPT1, DNAJC5, IDUA, NAGLU, GUSB, and GALC, wherein the gene for gene therapy is a wild-type copy of the lysosomal gene.
2. The use of claim 1, wherein the lysosomal gene is NAGLU.
3. The use of claim 1, wherein the lysosomal gene is GALC.
4. The use of claim 1, wherein the lysosomal gene is PPT1.
5. The use of claim 1, wherein the lysosomal gene is GUSB.
6. The use of claim 1, wherein the lysosomal gene is IDUA.
7. The use of claim 1, wherein the lysosomal gene is DNAJC5.
8. The use of any one of the claims 2-7, wherein the loss-of-function variant is one or more of a deletion, a substitution, or a deletion of the lysosomal gene.
9. The use of any one of the claims 1-7, wherein the dementia is of the Alzheimer's type.

10. Use of a therapeutically effective amount of an autophagy-lysosomal pathway modulating agent comprising a gene for gene therapy (GT) for the manufacture of a medicament for preventing, treating, reversing or delaying Alzheimer's disease in a subject, wherein the subject is determined to have or be at risk for Alzheimer's disease by virtue of detecting that the subject is heterozygous for a loss-of-function variant in at least one lysosomal gene selected from the group consisting of PPT1, DNAJC5, IDUA, NAGLU, GUSB, and GALC, wherein the gene for gene therapy is a wild-type copy of the lysosomal gene.

11. The use of claim 10, wherein the lysosomal gene is NAGLU.

12. The use of claim 10, wherein the lysosomal gene is GALC.

13. The use of claim 10, wherein the lysosomal gene is PPT1.

14. The use of claim 10, wherein the lysosomal gene is GUSB.

15. The use of claim 10, wherein the lysosomal gene is DNAJC5.

16. The use of claim 10, wherein the lysosomal gene is IDUA.

17. The use of any one of the claims 10-16, wherein the loss-of-function variant is one or more of a deletion, a substitution, or a deletion of the at least one lysosomal gene.

18. A method of determining risk for a neurological or neurodegenerative disease, disorder, or condition, associated with APP processing dysfunction in a subject, the method comprising:

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

least one lysosomal gene selected from the group consisting of PPT1, DNAJC5, IDUA, NAGLU, GUSB, and GALC,

wherein if at least one lysosomal gene heterozygous for a loss-of-function variant is detected, it is indicative that the subject is at risk for a neurological or neurodegenerative disease, disorder, or condition associated with APP processing dysfunction.

19. The method of claim 18, wherein the lysosomal gene is PPT1.

20. The method of claim 19, wherein the lysosomal gene is NAGLU.

21. The method of claim 19, wherein the lysosomal gene is DNAJC5.

5 22. The method of claim 19, wherein the lysosomal gene is GUSB.

23. The method of claim 19, wherein the lysosomal gene is GALC.

24. The method of claim 19, wherein the lysosomal gene is IDUA.

10

25. The method of any one of claims 18-24, wherein neurological or neurodegenerative disease, disorder, or condition associated with APP processing dysfunction is Alzheimer's disease.

26. The method of any one of the claims 18-25, wherein the loss-of-function variant is one or more of a deletion, a substitution, or a deletion of the lysosomal gene.

15