

WHAT IS CLAIMED IS:

1. A humanized antibody specifically binding to human sortilin, comprising three light chain CDRs and three heavy chain CDRs of:

a mouse antibody characterized by a heavy chain variable region having an amino acid sequence comprising SEQ ID NO:52 and a light chain variable region having an amino acid sequence comprising SEQ ID NO:58, except that position L54 can be L, G, or I;

a mouse antibody characterized by a heavy chain variable region having an amino acid sequence comprising SEQ ID NO:4 and a light chain variable region having an amino acid sequence comprising SEQ ID NO:10;

a mouse antibody characterized by a heavy chain variable region having an amino acid sequence comprising SEQ ID NO:28 and a light chain variable region having an amino acid sequence comprising SEQ ID NO:34;

a mouse antibody characterized by a heavy chain variable region having an amino acid sequence comprising SEQ ID NO:78 and a light chain variable region having an amino acid sequence comprising SEQ ID NO:84;

a mouse antibody characterized by a heavy chain variable region having an amino acid sequence comprising SEQ ID NO:90 and a light chain variable region having an amino acid sequence comprising SEQ ID NO:96;

a mouse antibody characterized by a heavy chain variable region having an amino acid sequence comprising SEQ ID NO:102 and a light chain variable region having an amino acid sequence comprising SEQ ID NO:108;

a mouse antibody characterized by a heavy chain variable region having an amino acid sequence comprising SEQ ID NO:114 and a light chain variable region having an amino acid sequence comprising SEQ ID NO:120;

a mouse antibody characterized by a heavy chain variable region having an amino acid sequence comprising SEQ ID NO:126 and a light chain variable region having an amino acid sequence comprising SEQ ID NO:132;

a mouse antibody characterized by a heavy chain variable region having an amino acid sequence comprising SEQ ID NO:138 and a light chain variable region having an amino acid sequence comprising SEQ ID NO:144; or

a mouse antibody characterized by a heavy chain variable region having an amino acid sequence comprising SEQ ID NO:150 and a light chain variable region having an amino acid sequence comprising SEQ ID NO:156.

2. The humanized antibody of claim 1, wherein the humanized antibody comprises the three light chain CDRs and the three heavy chain CDRs of a mouse antibody characterized by a heavy chain variable region having an amino acid sequence comprising SEQ ID NO:52 and a light chain variable region having an amino acid sequence comprising SEQ ID NO:58, except that position L54 can be L, G, or I.

3. The humanized antibody of claim 2, wherein the humanized antibody comprises a humanized mature heavy chain variable region comprising the three Kabat/Chothia Composite heavy chain CDRs of SEQ ID NOs: 53-55 and a humanized mature light chain variable region comprising the three Kabat/Chothia Composite light chain CDRs of SEQ ID NOs: 59-61, except that position L54 can be L, G, or I.

4. The humanized antibody of claim 2 or 3, comprising a humanized mature heavy chain variable region having an amino acid sequence at least 90% identical to any one of SEQ ID NOs: 190-192, and a humanized mature light chain variable region having an amino acid sequence at least 90% identical to any one of SEQ ID NOs: 196-199.

5. The humanized antibody of claim 4, wherein at least one of the following positions in the VH region is occupied by the amino acid as specified: H49 is occupied by A, H80 is occupied by L or G, H82c is occupied by L or G.

6. The humanized antibody of claim 5, provided position H49 in the VH region is occupied by A.

7. The humanized antibody of claim 5, provided positions H49 and H82c in the VH region are occupied by A and G, respectively.

8. The humanized antibody of claim 5, provided positions H49 and H80 in the VH region are occupied by A and G, respectively.

9. The humanized antibody of claim 4, wherein at least one of the following positions in the VL region is occupied by the amino acid as specified: L43 is A or S, L48 is V, L54 is L, G, or I, L71 is Y, L76 is N or S.

10. The humanized antibody of claim 9, provided positions L48 and L71 in the VL region are occupied by V and Y respectively.

11. The humanized antibody of claim 9, provided positions L43, L48, L71, and L76 in the VL region are occupied by S, V, Y, and S, respectively.

12. The humanized antibody of claim 9, provided positions L43, L48, L54, L71, and L76 in the VL region are occupied by S, V, G, Y, and S, respectively.

13. The humanized antibody of claim 9, provided positions L43, L48, L54, L71, and L76 in the VL region are occupied by S, V, I, Y, and S, respectively.

14. The humanized antibody of claim 4, comprising a humanized mature heavy chain variable region having an amino acid sequence at least 95% identical to at least one of SEQ ID NOs: 190-192 and a humanized mature light chain variable region having an amino acid sequence at least 95% identical to at least one of SEQ ID NOs: 196-199.

15. The humanized antibody of claim 14, wherein the humanized mature heavy chain variable region has an amino acid sequence of any one of SEQ ID NOs: 190-192, and the humanized mature light chain variable region has an amino acid sequence of any one of SEQ ID NOs: 196-199.

16. The humanized antibody of claim 15, wherein:

the humanized mature heavy chain variable region has an amino acid sequence of SEQ ID NO: 190 and the humanized mature light chain variable region has an amino acid sequence of SEQ ID NO: 196;

the humanized mature heavy chain variable region has an amino acid sequence of SEQ ID NO:190 and the humanized mature light chain variable region has an amino acid sequence of SEQ ID NO:197;

the humanized mature heavy chain variable region has an amino acid sequence of SEQ ID NO:190 and the humanized mature light chain variable region has an amino acid sequence of SEQ ID NO:198;

the humanized mature heavy chain variable region has an amino acid sequence of SEQ ID NO:190 and the humanized mature light chain variable region has an amino acid sequence of SEQ ID NO:199;

the humanized mature heavy chain variable region has an amino acid sequence of SEQ ID NO:191 and the humanized mature light chain variable region has an amino acid sequence of SEQ ID NO:196;

the humanized mature heavy chain variable region has an amino acid sequence of SEQ ID NO:191 and the humanized mature light chain variable region has an amino acid sequence of SEQ ID NO:197;

the humanized mature heavy chain variable region has an amino acid sequence of SEQ ID NO: 191 and the humanized mature light chain variable region has an amino acid sequence of SEQ ID NO: 198;

the humanized mature heavy chain variable region has an amino acid sequence of SEQ ID NO:191 and the humanized mature light chain variable region has an amino acid sequence of SEQ ID NO:199;

the humanized mature heavy chain variable region has an amino acid sequence of SEQ ID NO:192 and the humanized mature light chain variable region has an amino acid sequence of SEQ ID NO:196;

the humanized mature heavy chain variable region has an amino acid sequence of SEQ ID NO:192 and the humanized mature light chain variable region has an amino acid sequence of SEQ ID NO:197;

the humanized mature heavy chain variable region has an amino acid sequence of SEQ ID NO:192 and the humanized mature light chain variable region has an amino acid sequence of SEQ ID NO:198; or

the humanized mature heavy chain variable region has an amino acid sequence of SEQ ID NO:192 and the humanized mature light chain variable region has an amino acid sequence of SEQ ID NO:199.

17. The humanized antibody of any one of claims 1-16 that is an intact antibody.

18. The humanized antibody of any one of claims 1-16 that is a binding fragment.

19. The humanized antibody of any one of claims 1-18, wherein the humanized antibody has an isotype of human IgG1.

20. The humanized antibody of any one of claims 14-16, wherein the humanized mature light chain variable region is fused to a light chain constant region and the humanized mature heavy chain variable region is fused to a heavy chain constant region.

21. The humanized antibody of claim 20, wherein the heavy chain constant region is a mutant form of a natural human heavy chain constant region which has reduced binding to a Fcγ receptor relative to the natural human heavy chain constant region.

22. The humanized antibody of claim 20, wherein the heavy chain constant region is a mutant form of a natural human heavy chain constant region which has enhanced binding to a neonatal Fcγ receptor relative to the natural human heavy chain constant region.

23. The humanized antibody of claim 20, comprising:

a heavy chain of SEQ ID NO: 244 and a light chain of SEQ ID NO: 245;

a heavy chain of SEQ ID NO: 246 and a light chain of SEQ ID NO: 247;

a heavy chain of SEQ ID NO: 248 and a light chain of SEQ ID NO: 249;

a heavy chain of SEQ ID NO: 250 and a light chain of SEQ ID NO: 245;

a heavy chain of SEQ ID NO:251 and a light chain of SEQ ID NO:247; or

a heavy chain of SEQ ID NO: 252 and a light chain of SEQ ID NO: 249.

24. The humanized antibody of any one of claims 1-18 and 20-23, wherein the humanized antibody has a human IgG2 or IgG4 isotype.

25. A pharmaceutical composition comprising the humanized antibody of any one of claims 1-24 and a pharmaceutically-acceptable carrier.

26. A nucleic acid encoding a heavy chain and/or light chain of the humanized antibody of any one of claims 1-24.

27. A method of humanizing a mouse antibody, the method comprising:

(a) selecting one or more acceptor antibody sequences;

(b) identifying amino acid residues of the mouse antibody to be retained;

(c) synthesizing a nucleic acid encoding a humanized heavy chain comprising CDRs of the mouse antibody heavy chain and a nucleic acid encoding a humanized light chain comprising CDRs of the mouse antibody light chain; and

(d) expressing the nucleic acids in a host cell to produce a humanized antibody;

wherein the mouse antibody is characterized by:

a mature heavy chain variable region of SEQ ID NO: 52 and a mature light chain variable region of SEQ ID NO: 58;

a mature heavy chain variable region of SEQ ID NO: 4 and a mature light chain variable region of SEQ ID NO: 10;

a mature heavy chain variable region of SEQ ID NO: 28 and a mature light chain variable region of SEQ ID NO: 34;

a mature heavy chain variable region of SEQ ID NO: 78 and a mature light chain variable region of SEQ ID NO: 84;

a mature heavy chain variable region of SEQ ID NO: 90 and a mature light chain variable region of SEQ ID NO: 96;

a mature heavy chain variable region of SEQ ID NO: 102 and a mature light chain variable region of SEQ ID NO: 108;

a mature heavy chain variable region of SEQ ID NO: 114 and a mature light chain variable region of SEQ ID NO: 120;

a mature heavy chain variable region of SEQ ID NO: 126 and a mature light chain variable region of SEQ ID NO: 132;

a mature heavy chain variable region of SEQ ID NO: 138 and a mature light chain variable region of SEQ ID NO: 144; or

a mature heavy chain variable region of SEQ ID NO: 150 and a mature light chain variable region of SEQ ID NO: 156.

28. A method of producing a humanized, chimeric, or veneered antibody, the method comprising:

(a) culturing cells transformed with nucleic acids encoding the heavy and light chains of the antibody, so that the cells secrete the antibody; and

(b) purifying the antibody from cell culture media;

wherein the antibody is a humanized antibody of any one of claims 1-24.

29. A method of producing a cell line producing a humanized, chimeric, or veneered antibody, the method comprising:

(a) introducing a vector encoding heavy and light chains of an antibody and a selectable marker into cells;

(b) propagating the cells under conditions to select for cells having increased copy number of the vector;

(c) isolating single cells from the selected cells; and

(d) banking cells cloned from a single cell selected based on yield of antibody;

wherein the antibody is a humanized antibody of any one of claims 1-24.

30. Use of the humanized antibody of any one of claims 1-24 in the manufacture of a medicament for increasing progranulin levels in a subject having or at risk of developing a disease or disorder associated with changes in progranulin levels.

31. Use of the humanized antibody of any one of claims 1-24 in the manufacture of a medicament for treating or effecting prophylaxis of a disease or disorder associated with changes in progranulin levels in a subject.

32. The use of claim 31, wherein the disease or disorder associated with changes in progranulin levels is frontotemporal dementia, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Batten disease, a neurodegenerative disorder, or a neurodegenerative disorder associated with aging.

33. Use of the humanized antibody of any one of claims 1-24 in the manufacture of a medicament for detecting sortilin in a subject having or at risk of a disease associated with a disease or disorder associated with changes in progranulin levels.