

CLAIMS

1. An antibody or antigen-binding fragment thereof that binds to a chromosome 9 open
5 reading frame 72 (C9orf72) dipeptide repeat protein (DPR) with a poly-Glycine-
Alanine (GA)₁₅ repeat, wherein the antibody or antigen-binding fragment thereof
comprises:
a heavy chain variable region (VH) comprising VH complementarity determining
10 regions (CDRs) 1, 2, and 3, wherein the VH CDRs 1, 2, and 3 comprise the
amino acid sequences set forth in amino acid positions 32-36 of SEQ ID NO:8,
amino acid positions 51-67 of SEQ ID NO:8, and amino acid positions 100-113
of SEQ ID NO:8, respectively; and
a light chain variable region (VL) comprising VL CDRs 1, 2, and 3, wherein the VL
15 CDRs 1, 2, and 3 comprise the amino acid sequences set forth in amino acid
positions 25-35 of SEQ ID NO:10, amino acid positions 51-57 of SEQ ID
NO:10, and amino acid positions 90-98 of SEQ ID NO:10, respectively.
2. The antibody or antigen-binding fragment thereof of claim 1, wherein the VH
20 comprises an amino acid sequence that is at least 95% identical to the amino acid
sequence of SEQ ID NO:8.
3. The antibody or antigen-binding fragment thereof of claim 1, wherein the VH
comprises the amino acid sequence set forth in SEQ ID NO:8 or a variant of the amino
acid sequence set forth in SEQ ID NO:8 with one amino acid deletion.
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4. The antibody or antigen-binding fragment thereof of claim 1, wherein the VL
comprises an amino acid sequence that is at least 95% identical to the amino acid
sequence of SEQ ID NO:10.
- 30 5. The antibody or antigen-binding fragment thereof of claim 1, wherein the VL
comprises the amino acid sequence set forth in SEQ ID NO:10 or a variant of the
amino acid sequence set forth in SEQ ID NO:10 with one amino acid deletion.

6. The antibody or antigen-binding fragment thereof of claim 1, wherein the VH comprises an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:8, and wherein the VL comprises an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:10.
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7. The antibody or antigen-binding fragment thereof of claim 1, wherein the VH comprises the amino acid sequence set forth in SEQ ID NO:8 or a variant of the amino acid sequence set forth in SEQ ID NO:8 with one amino acid deletion, and wherein the VL comprises the amino acid sequence set forth in SEQ ID NO:10 or a variant of the amino acid sequence set forth in SEQ ID NO:10 with one amino acid deletion.
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8. The antibody or antigen-binding fragment thereof of any one of claims 1 to 7, wherein the antibody comprises an immunoglobulin heavy chain and an immunoglobulin light chain, wherein the immunoglobulin heavy chain comprises a human IgG1 constant region, and wherein the immunoglobulin light chain comprises a human kappa constant region.
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9. The antibody or antigen-binding fragment thereof of any one of claims 1 to 8, which is detectably labeled.
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10. The antibody of claim 9, wherein the detectable label is selected from the group consisting of an enzyme, a radioisotope, a fluorophore, and a heavy metal.
11. A pharmaceutical composition comprising the antibody of any one of claims 1 to 10 and a pharmaceutically acceptable carrier.
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12. A combination for expressing the antibody or antigen-binding fragment thereof of any one of claims 1 to 8, comprising: (i) a polynucleotide encoding a polypeptide comprising the VH of the antibody or antigen-binding fragment thereof of any one of claims 1 to 8; and (ii) a polynucleotide encoding a polypeptide comprising the VL of the antibody or antigen-binding fragment thereof of any one of claims 1 to 8.
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13. The combination of claim 12, wherein each polynucleotide further comprises a heterologous nucleic acid encoding a secretory signal peptide.

14. An expression vector for expressing the antibody or antigen-binding fragment thereof of any one of claims 1 to 8 comprising (i) a promoter operably linked to a polynucleotide encoding a polypeptide comprising the VH of the antibody or antigen-binding fragment thereof of any one of claims 1 to 8; and (ii) a promoter operably linked to a polynucleotide encoding a polypeptide comprising the VL of the antibody or antigen-binding fragment thereof of any one of claims 1 to 8.
15. An expression vector for expressing the antibody or antigen-binding fragment thereof of any one of claims 1 to 8 comprising:
a first polynucleotide encoding a first polypeptide comprising a VH of the antibody or antigen binding fragment thereof of any one of claims 1 to 8; and
a second polynucleotide encoding a second polypeptide comprising a VL of the antibody or antigen binding fragment thereof of any one of claims 1 to 8.
16. A host cell comprising the combination of claim 12 or 13 or the expression vector of claim 14 or 15.
17. A method for preparing the antibody or antigen-binding fragment thereof of any one of claims 1 to 8, the method comprising
(a) culturing the cell of claim 16; and
(b) isolating the antibody or antigen-binding fragment thereof from the culture.
18. Use of the antibody or antigen-binding fragment thereof of any one of claims 1 to 10 in the manufacture of a medicament for diagnosing a disorder associated with DPR protein in a human subject, wherein the diagnosing comprises obtaining a sample from the subject, determining the presence of DPR protein species, or fragments thereof, in the sample from the subject, wherein the presence of the DPR protein species, or fragments thereof, in the sample is determined using the antibody or antigen-binding fragment thereof of any one of claims 1 to 10, wherein the presence of DPR protein species, or fragments thereof, is indicative for amyotrophic lateral sclerosis (ALS) and/or frontotemporal lobar degeneration (FTLD).

19. Use of the antibody or antigen-binding fragment thereof of any one of claims 1 to 10 in the manufacture of a medicament for *in vivo* detection of a poly-GA DPR protein in a human subject, wherein the antibody or antigen-binding fragment thereof is attached to a detectable label.
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20. Use of the antibody or antigen-binding fragment thereof of any one of claims 1 to 8 in the manufacture of a medicament for prophylactic and/or therapeutic treatment of a disease associated with DPR protein or aggregated forms thereof in a human subject.
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21. The use of claim 20, wherein the disease is selected from the group consisting of amyotrophic lateral sclerosis (ALS), Frontotemporal lobar degeneration (FTLD), and FTLD-ALS.
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22. The use of claim 20 or 21, wherein the antibody or antigen-binding fragment thereof is formulated for intrathecal, intravenous, or subcutaneous delivery.
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23. An antibody or antigen-binding fragment thereof that binds to a chromosome 9 open reading frame 72 (C9orf72) dipeptide repeat (DPR) protein with a poly-glycine-alanine (GA)₁₅ repeat, wherein the antibody or antigen-binding fragment thereof comprises:
 - (a) (i) a heavy chain variable region (VH) comprising VH complementarity determining regions (CDRs) 1, 2, and 3, wherein the VH CDRs 1, 2, and 3 comprise the amino acid sequences set forth in amino acid positions 32-36 of SEQ ID NO:2, amino acid positions 51-66 of SEQ ID NO:2, and amino acid positions 99-112 of SEQ ID NO:2, respectively; and (ii) a light chain variable region (VL) comprising VL CDRs 1, 2, and 3, wherein the VL CDRs 1, 2, and 3 comprise the amino acid sequences set forth in amino acid positions 25-40 of SEQ ID NO:4, amino acid positions 56-62 of SEQ ID NO:4, and amino acid positions 95-102 of SEQ ID NO:4, respectively;
 - (b) (i) a VH comprising VH CDRs 1, 2, and 3, wherein the VH CDRs 1, 2, and 3 comprise the amino acid sequences set forth in amino acid positions 32-36 of SEQ ID NO:22, amino acid positions 51-66 of SEQ ID NO:22, and amino acid positions 99-112 of SEQ ID NO:22, respectively; and (ii) a VL comprising VL CDRs 1, 2, and 3, wherein the VL CDRs 1, 2, and 3 comprise the amino acid sequences set forth in amino
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acid positions 25-40 of SEQ ID NO:24, amino acid positions 56-62 of SEQ ID NO:24, and amino acid positions 95-103 of SEQ ID NO:24, respectively; or

(c) (i) a VH comprising VH CDRs 1, 2, and 3, wherein the VH CDRs 1, 2, and 3 comprise the amino acid sequences set forth in amino acid positions 32-38 of SEQ ID NO:30, amino acid positions 53-70 of SEQ ID NO:30, and amino acid positions 103-118 of SEQ ID NO:30, respectively; and (ii) a VL comprising VL CDRs 1, 2, and 3, wherein the VL CDRs 1, 2, and 3 comprise the amino acid sequences set forth in amino acid positions 25-40 of SEQ ID NO:32, amino acid positions 56-62 of SEQ ID NO:32, and amino acid positions 95-103 of SEQ ID NO:32, respectively.

24. An antibody or antigen-binding fragment thereof that binds to a chromosome 9 open reading frame 72 (C9orf72) dipeptide repeat (DPR) protein with a poly-proline-arginine (PR)₁₅ repeat, wherein the antibody or antigen-binding fragment thereof comprises:

(a) (i) a heavy chain variable region (VH) comprising VH complementarity determining regions (CDRs) 1, 2, and 3, wherein the VH CDRs 1, 2, and 3 comprise the amino acid sequences set forth in amino acid positions 32-36 of SEQ ID NO:38, amino acid positions 51-66 of SEQ ID NO:38, and amino acid positions 99-116 of SEQ ID NO:38, respectively; and (ii) a light chain variable region (VL) comprising VL CDRs 1, 2, and 3, wherein the VL CDRs 1, 2, and 3 comprise the amino acid sequences set forth in amino acid positions 25-35 of SEQ ID NO:40, amino acid positions 51-57 of SEQ ID NO:40, and amino acid positions 90-98 of SEQ ID NO:40, respectively; or

(b) (i) a VH comprising VH CDRs 1, 2, and 3, wherein the VH CDRs 1, 2, and 3 comprise the amino acid sequences set forth in amino acid positions 32-36 of SEQ ID NO:80, amino acid positions 51-67 of SEQ ID NO:80, and amino acid positions 100-114 of SEQ ID NO:80, respectively; and (ii) a VL comprising VL CDRs 1, 2, and 3, wherein the VL CDRs 1, 2, and 3 comprise the amino acid sequences set forth in amino acid positions 25-36 of SEQ ID NO:82, amino acid positions 52-58 of SEQ ID NO:82, and amino acid positions 91-95 of SEQ ID NO:82, respectively.

25. An antibody or antigen-binding fragment thereof that binds to a chromosome 9 open reading frame 72 (C9orf72) dipeptide repeat (DPR) protein with a poly-glycine-proline (GP)₁₅ repeat, wherein the antibody or antigen-binding fragment thereof comprises:

(a) (i) a heavy chain variable region (VH) comprising VH complementarity determining regions (CDRs) 1, 2, and 3, wherein the VH CDRs 1, 2, and 3 comprise the amino acid sequences set forth in amino acid positions 32-36 of SEQ ID NO:14, amino acid positions 51-67 of SEQ ID NO:14, and amino acid positions 100-113 of SEQ ID NO:14, respectively; and (ii) a light chain variable region (VL) comprising VL CDRs 1, 2, and 3, wherein the VL CDRs 1, 2, and 3 comprise the amino acid sequences set forth in amino acid positions 25-41 of SEQ ID NO:16, amino acid positions 57-63 of SEQ ID NO:16, and amino acid positions 96-104 of SEQ ID NO:16, respectively;

(b) (i) a VH comprising VH CDRs 1, 2, and 3, wherein the VH CDRs 1, 2, and 3 comprise the amino acid sequences set forth in amino acid positions 32-36 of SEQ ID NO:44, amino acid positions 53-68 of SEQ ID NO:44, and amino acid positions 101-113 of SEQ ID NO:44, respectively; and (ii) a VL comprising VL CDRs 1, 2, and 3, wherein the VL CDRs 1, 2, and 3 comprise the amino acid sequences set forth in amino acid positions 25-35 of SEQ ID NO:46, amino acid positions 51-57 of SEQ ID NO:46, and amino acid positions 90-98 of SEQ ID NO:46, respectively; or

(c) (i) a VH comprising VH CDRs 1, 2, and 3, wherein the VH CDRs 1, 2, and 3 comprise the amino acid sequences set forth in amino acid positions 31-36 of SEQ ID NO:72, amino acid positions 51-67 of SEQ ID NO:72, and amino acid positions 100-116 of SEQ ID NO:72, respectively; and (ii) a VL comprising VL CDRs 1, 2, and 3, wherein the VL CDRs 1, 2, and 3 comprise the amino acid sequences set forth in amino acid positions 25-41 of SEQ ID NO:74, amino acid positions 57-63 of SEQ ID NO:74, and amino acid positions 96-104 of SEQ ID NO:74, respectively.

26. An antibody or antigen-binding fragment thereof that binds to a chromosome 9 open reading frame 72 (C9orf72) dipeptide repeat (DPR) protein with a poly-glycine-arginine (GR)₁₅ repeat, wherein the antibody or antigen-binding fragment thereof comprises:

(a) (i) a heavy chain variable region (VH) comprising VH complementarity determining regions (CDRs) 1, 2, and 3, wherein the VH CDRs 1, 2, and 3 comprise the amino acid sequences set forth in amino acid positions 32-36 of SEQ ID NO:52, amino acid positions 51-67 of SEQ ID NO:52, and amino acid positions 100-118 of SEQ ID NO:52, respectively; and (ii) a light chain variable region (VL) comprising VL CDRs 1, 2, and 3, wherein the VL CDRs 1, 2, and 3 comprise the amino acid sequences set

forth in amino acid positions 25-35 of SEQ ID NO:54, amino acid positions 51-57 of SEQ ID NO:54, and amino acid positions 90-98 of SEQ ID NO:54, respectively; or

(b) (i) a VH comprising VH CDRs 1, 2, and 3, wherein the VH CDRs 1, 2, and 3 comprise the amino acid sequences set forth in amino acid positions 32-36 of SEQ ID NO:58, amino acid positions 51-67 of SEQ ID NO:58, and amino acid positions 100-115 of SEQ ID NO:58, respectively; and (ii) a VL comprising VL CDRs 1, 2, and 3, wherein the VL CDRs 1, 2, and 3 comprise the amino acid sequences set forth in amino acid positions 24-36 of SEQ ID NO:60, amino acid positions 52-58 of SEQ ID NO:60, and amino acid positions 91-101 of SEQ ID NO:60, respectively.

27. An antibody or antigen-binding fragment thereof that binds to a chromosome 9 open reading frame 72 (C9orf72) dipeptide repeat (DPR) protein with a poly-proline-alanine (PA)₁₅ repeat, wherein the antibody or antigen-binding fragment thereof comprises:

(i) a heavy chain variable region (VH) comprising VH complementarity determining regions (CDRs) 1, 2, and 3, wherein the VH CDRs 1, 2, and 3 comprise the amino acid sequences set forth in amino acid positions 32-36 of SEQ ID NO:64, amino acid positions 51-67 of SEQ ID NO:64, and amino acid positions 100-116 of SEQ ID NO:64, respectively; and (ii) a light chain variable region (VL) comprising VL CDRs 1, 2, and 3, wherein the VL CDRs 1, 2, and 3 comprise the amino acid sequences set forth in amino acid positions 25-35 of SEQ ID NO:66, amino acid positions 51-57 of SEQ ID NO:66, and amino acid positions 90-99 of SEQ ID NO:66, respectively.

28. The antibody or antigen-binding fragment thereof of any one of claims 23 to 27, wherein the antibody comprises an immunoglobulin heavy chain and an immunoglobulin light chain, wherein the immunoglobulin heavy chain comprises a human IgG1 constant region, and wherein the immunoglobulin light chain comprises a human kappa constant region.

29. The antibody or antigen-binding fragment thereof of any one of claims 23 to 28, which is detectably labeled.

30. The antibody or antigen-binding fragment thereof of claim 29, wherein the detectable label is selected from the group consisting of an enzyme, a radioisotope, a fluorophore and a heavy metal.

31. A pharmaceutical composition comprising the antibody or antigen-binding fragment thereof of any one of claims 23 to 30 and a pharmaceutically acceptable carrier.
- 5 32. A combination for expressing the antibody or antigen-binding fragment thereof of any one of claims 23 to 28 comprising:
- (i) a polynucleotide encoding a polypeptide comprising the VH of the antibody or antigen-binding fragment thereof of any one of claims 23 to 28; and
- (ii) a polynucleotide encoding a polypeptide comprising the VL of the antibody or antigen-binding fragment thereof of any one of claims 23 to 28.
- 10 33. The combination of claim 32, wherein each polynucleotide further comprises a heterologous nucleic acid encoding a secretory signal peptide.
- 15 34. An expression vector for expressing the antibody or antigen-binding fragment thereof of any one of claims 23 to 28 comprising (i) a promoter operably linked to a polynucleotide encoding a polypeptide comprising the VH of the antibody or antigen-binding fragment thereof of any one of claims 23 to 28; and (ii) a promoter operably linked to a polynucleotide encoding a polypeptide comprising the VL of the antibody or antigen-binding fragment thereof of any one of claims 23 to 28.
- 20 35. An expression vector for expressing the antibody or antigen-binding fragment thereof of any one of claims 23 to 28 comprising:
- a first polynucleotide encoding a first polypeptide comprising a VH of the antibody or antigen binding fragment thereof of any one of claims 23 to 28; and
- 25 a second polynucleotide encoding a second polypeptide comprising a VL of the antibody or antigen binding fragment thereof of any one of claims 23 to 28.
- 30 36. A host cell comprising the combination of claim 32 or 33 or the expression vector of claim 34 or 35.

37. A method for preparing the antibody or antigen-binding fragment thereof of any one of claims 23 to 28, the method comprising:
(a) culturing the cell of claim 36; and
(b) isolating the antibody or antigen-binding fragment thereof from the culture.

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38. Use of the antibody or antigen-binding fragment thereof of any one of claims 1 to 10 in the manufacture of a medicament for diagnosing a disorder associated with DPR protein in a human subject, wherein the diagnosing comprises obtaining a sample from the subject, determining the presence of DPR protein species, or fragments thereof, in the sample from the subject, wherein the presence of the DPR protein species, or fragments thereof, in the sample is determined using the antibody or antigen-binding fragment thereof of any one of claims 23 to 30, wherein the presence of DPR protein species, or fragments thereof, is indicative for amyotrophic lateral sclerosis (ALS) and/or frontotemporal lobar degeneration (FTLD).

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39. Use of the antibody or antigen-binding fragment thereof of claim 23 in the manufacture of a medicament for in vivo detection of a poly-GA DPR protein in a human subject, wherein the antibody or antigen-binding fragment thereof is attached to a detectable label.

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40. Use of the antibody or antigen-binding fragment thereof of claim 24 in the manufacture of a medicament for in vivo detection of a poly-proline-arginine (PR) DPR protein in a human subject, wherein the antibody or antigen-binding fragment thereof is attached to a detectable label.

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41. Use of the antibody or antigen-binding fragment thereof of claim 25 in the manufacture of a medicament for in vivo detection of a poly-glycine-proline (GP) DPR protein in a human subject, wherein the antibody or antigen-binding fragment thereof is attached to a detectable label.

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42. Use of the antibody or antigen-binding fragment thereof of claim 26 in the manufacture of a medicament for in vivo detection of a poly-glycine-arginine (GR) DPR protein in a human subject, wherein the antibody or antigen-binding fragment thereof is attached to a detectable label.

43. Use of the antibody or antigen-binding fragment thereof of claim 27 in the manufacture of a medicament for in vivo detection of a poly-proline-alanine (PA) DPR protein in a human subject, wherein the antibody or antigen-binding fragment thereof is attached to a detectable label.
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44. Use of the antibody or antigen-binding fragment thereof of any one of claims 23 to 30 in the manufacture of a medicament for prophylactic and/or therapeutic treatment of a disease associated with DPR protein or aggregated forms thereof in a human subject.
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45. The use of claim 44, wherein the disease is selected from the group consisting of amyotrophic lateral sclerosis (ALS), frontotemporal lobar degeneration (FTLD), and FTLD-ALS.
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46. The use of claim 44 or 45, wherein the antibody or antigen-binding fragment thereof is formulated for intrathecal, intravenous, or subcutaneous delivery.