CLAIMS

1. An anti-TAR-DNA-binding protein 43 kDa (TDP-43) antibody, or a TDP-43 binding fragment thereof, comprising a heavy chain variable domain (VH) and a light chain variable domain (VL), wherein the VH comprises complementarity determining regions (CDRs) H-CDR1, H-CDR2, and H-CDR3, and the VL comprises CDRs L-CDR1, L-CDR2, and L-CDR3, wherein:

> H-CDR1, H-CDR2, and H-CDR3 consist of the amino acid sequence set forth in SEQ ID NOs: 131, 132, and 133, respectively, and L-CDR1, L-CDR2, and L-CDR3 consist of the amino acid sequence set forth in SEQ ID NOs: 135, 136, and 137, respectively.

2. An anti-TAR-DNA-binding protein 43 kDa (TDP-43) antibody, or a TDP-43 binding fragment thereof, comprising a heavy chain variable domain (VH) and a light chain variable domain (VL), wherein:

the VH consists of the amino acid sequence set forth in SEQ ID NO:130, and the VL consists of the amino acid sequence set forth in SEQ ID NO:134.

3. The anti-TDP-43 antibody or TDP-43 binding fragment thereof of claim 1 or 2, which is a human antibody.

4. The anti-TDP-43 antibody or TDP-43 binding fragment thereof of claim 1 or 2, which is a chimeric antibody.

5. The anti-TDP-43 antibody or TDP-43 binding fragment thereof of claim 1 or 2, which is a TDP-43 binding fragment.

6. The anti-TDP-43 antibody or TDP-43 binding fragment thereof of claim 5, wherein the TDP-43 binding fragment is a single chain Fv fragment (scFv), an F(ab') fragment, an F(ab) fragment, or an F(ab')2 fragment.

7. An isolated polynucleotide or polynucleotides comprising a nucleotide sequence or nucleotide sequences encoding the anti-TDP-43 antibody or TDP-43 binding fragment thereof of claim 1 or claim 2.

8. An isolated polynucleotide or polynucleotides encoding an anti-TAR-DNA-binding protein 43 kDa (TDP-43) antibody, or a TDP-43 binding fragment thereof, comprising a nucleotide sequence encoding a heavy chain variable domain (VH) and a nucleotide sequence encoding a light chain variable domain (VL), wherein:

the nucleotide sequence encoding the VH consists of the nucleic acid sequence set forth in SEQ ID NO:275, and the nucleotide sequence encoding the VL consists of the nucleic acid sequence set in SEQ ID NO:276.

9. An isolated vector comprising the polynucleotide or polynucleotides of claim 7 or claim 8.

10. An isolated host cell comprising the polynucleotide or polynucleotides of claim 7 or claim 8, or the vector of claim 9.

11. A method for preparing an anti-TDP-43 antibody or TDP-43-binding fragment thereof, the method comprising:

(a) culturing the host cell of claim 10; and

(b) isolating the anti-TDP-43 antibody or TDP-43-binding fragment thereof from the culture.

12. An isolated anti-TDP-43 antibody or TDP-43-binding fragment thereof obtained by the method of claim 11.

13. The anti-TDP-43 antibody or TDP-43-binding fragment thereof of any one of claims 1 to 6 or 12, which is labeled with a detectable label.

14. The anti-TDP-43 antibody or TDP-43-binding fragment thereof of claim 13, wherein the detectable label is selected from the group consisting of an enzyme, a radioisotope, a fluorophore, and a heavy metal.

15. The anti-TDP-43 antibody or TDP-43-binding fragment thereof of any one of claims 1 to 6 or 12, which is attached to a drug.

16. A pharmaceutical composition comprising the anti-TDP-43 antibody or TDP-43-binding fragment thereof of any one of claims 1 to 6 or 12 to 15, and a pharmaceutically acceptable carrier.

17. A diagnostic composition comprising the anti-TDP-43 antibody or TDP-43-binding fragment thereof of any one of claims 1 to 6 or 12 to 15, and an immuno- or nucleic acid-based diagnostic reagent.

18. A composition comprising an anti-TDP-43 antibody or TDP-43-binding fragment thereof of any one of claims 1 to 6 or 12 to 15 for use in diagnosing, treating, monitoring the progression, or monitoring the response to a treatment of a TDP-43 proteinopathy in a human subject.

19. A method of using level of TDP-43 as an indicator of a TDP-43 proteinopathy in a human subject, the method comprising:

(a) determining the level of TDP-43 in a sample from the subject with the anti-TDP-43 antibody or TDP-43-binding fragment thereof of any one of claims 1 to 6 or 12 to 15 ; and

(b) comparing the level of TDP-43 to a reference standard that indicates the level of TDP-43 in a control subject,
wherein a difference or similarity between the level of TDP-43 in the sample and the reference standard indicates that the subject suffers from a TDP-43 proteinopathy.

20. The composition of claim 18, wherein the TDP-43 proteinopathy is selected from the group consisting of argyrophilic grain disease, Alzheimer's disease, amyotrophic lateral sclerosis (ALS), ALS-Parkinsonism dementia complex of Guam, corticobasal degeneration, Dementia with Lewy bodies, Huntington's disease, Lewy body disease, motor neuron disease, frontotemporal lobar degeneration (FTLD), frontotemporal dementia, frontotemporal lobar degeneration with ubiquitin-positive inclusions, hippocampal sclerosis, inclusion body myopathy, inclusion body myositis, Parkinson's disease, Parkinson's disease dementia, Parkinson-dementia complex in Kii peninsula and Pick's disease.

21. The composition of claim 18, wherein the TDP-43 proteinopathy is selected from the group consisting of Alzheimer's disease, ALS, FTLD, and Parkinson's disease.

22. A composition comprising an anti-TDP-43 antibody or TDP-43-binding fragment thereof of any one of claims 1 to 6 or 12 to 15 for *in vivo* detection or targeting of a therapeutic and/or diagnostic agent to TDP-43 in a human body.

23. The composition of claim 22, wherein the *in vivo* detection comprises positron emission tomography (PET), single photon emission tomography (SPECT), near infrared (NIR) optical imaging or magnetic resonance imaging (MRI).

24. A kit useful in the diagnosis or monitoring the progression of a TDP-43 proteinopathy, said kit characterized by comprising at least one anti-TDP-43 antibody or TDP-43-binding fragment thereof as defined in any one of claims 1 to 6 or 12 to 15.

25. The kit of claim 24, wherein the TDP-43 proteinopathy is selected from the group consisting of Alzheimer's disease, ALS, FTLD, and Parkinson's disease.

26. The method of claim 19, wherein the TDP-43 proteinopathy is selected from the group consisting of argyrophilic grain disease, Alzheimer's disease, amyotrophic lateral sclerosis (ALS), ALS-Parkinsonism dementia complex of Guam, corticobasal degeneration, Dementia with Lewy bodies, Huntington's disease, Lewy body disease, motor neuron disease, frontotemporal lobar degeneration (FTLD), frontotemporal dementia, frontotemporal lobar degeneration with ubiquitin-positive inclusions, hippocampal sclerosis, inclusion body myopathy, inclusion body myositis, Parkinson's disease, Parkinson's disease dementia, Parkinson-dementia complex in Kii peninsula and Pick's disease.

27. The method of claim 19, wherein the TDP-43 proteinopathy is selected from the group consisting of Alzheimer's disease, ALS, FTLD, and Parkinson's disease.