Claims:

Claim 1. A method for detecting the level of soluble Unc-5 netrin receptor C (UNC5C) in a biological fluid sample obtained from a subject, wherein the method comprises contacting the biological fluid sample with an antibody or antibody fragment thereof which specifically binds to UNC5C protein or a fragment thereof, wherein the antibody binds an epitope located in the extracellular region of UNC5C, wherein the biological fluid sample is a blood or cerebrospinal fluid (CSF) sample, and wherein the antibody comprises a heavy chain variable domain (VH) with the following CDRs:

CDRH1 comprising amino acid sequence SEQ ID NO: 142, 143, 144, 145, 146, 147, 148, or 149;

CDRH2 comprising amino acid sequence SEQ ID NO: 150, 151, 152, 153, 154, 155, 156, 157, or 158; and

CDRH3 comprising amino acid sequence SEQ ID NO: 159, 160, 161, 162, 163, 164, 165, 166, 167, or 168.

Claim 2. A method of determining the effect of a therapeutic compound or composition that affects the level of soluble UNC5C in a subject who has been administered the therapeutic compound or composition, wherein the method comprises determining a level of soluble UNC5C in a biological fluid sample previously obtained from the subject using the method of claim 1.

Claim 3. A method of detecting the presence and/or severity of a neurodegenerative disease in a subject and/or determining whether a subject is likely to be resilient to a neurodegenerative disease, the method comprising:

(a) determining a level of soluble UNC5C in a biological fluid sample previously obtained from the subject using the method of claim 1;

(b) comparing the level of soluble UNC5C and a reference level of soluble UNC5C, wherein the reference level of soluble UNC5C is a level of soluble UNC5C associated with one or more biological fluid samples from respective healthy controls, wherein a healthy control is a subject who has not been diagnosed with a neurodegenerative disease, wherein a higher level of soluble UNC5C in the biological fluid sample relative to the reference level of soluble UNC5C is indicative of the presence of the neurodegenerative disease and/or indicative of the severity of the neurodegenerative disease and/or indicative of the subject being unlikely to be resilient to the neurodegenerative disease, wherein the biological fluid samples from respective healthy controls are blood or CSF samples.

Claim 4. A method of selecting a subject for treatment with a therapeutic compound or composition that affects the level of soluble UNC5C, or for participating in a clinical trial of a therapeutic compound or composition that affects the level of soluble UNC5C, the method comprising:

(a) determining a level of soluble UNC5C in a biological fluid sample previously obtained from the subject using the method of claim 1;

(b) comparing the level of soluble UNC5C and a reference level of soluble UNC5C, wherein the reference level of soluble UNC5C is a level of soluble UNC5C associated with one or more biological fluid samples from respective healthy controls, wherein a healthy control is a subject who has not been diagnosed with a neurodegenerative disease; and

(c) selecting the subject for treatment or for participating in the clinical trial when the level of soluble UNC5C in the biological fluid sample is higher than the reference level of soluble UNC5C;

and wherein the biological fluid samples from respective healthy controls are blood or cerebrospinal fluid (CSF) samples.

Claim 5. The method according to any of claims 1-4, wherein the antibody comprises a VH with the CDRs: SEQ ID NO: 142, 150, and 159; SEQ ID NO: 143, 151, and 160; SEQ ID NO: 144, 152, and 161; SEQ ID NO: 145, 153, and 162; SEQ ID NO: 144, 152, and 163; SEQ ID NO: 143, 154, and 164; SEQ ID NO: 146, 155, and 165; SEQ ID NO: 147, 156, and 166; SEQ ID NO: 148, 157, and 167; or SEQ ID NO: 149, 158, and 168.

Claim 6. The method according to any one of claims 1-5, wherein the antibody has a heavy chain variable domain (VH) with the following framework sequences:

HFWR1 of SEQ ID NO: 205, 209, 212, or 220;

HFWR2 of SEQ ID NO: 206, 210, or 221;

HFWR3 of SEQ ID NO: 207, 211, or 222; and

HFWR4 of SEQ ID NO: 208 or 223;

optionally wherein the antibody has a heavy chain variable domain (VH) with the framework sequences: SEQ ID NO: 205, 206, 207, and 208; SEQ ID NO: 209, 210, 211, and 208; SEQ ID NO: 212, 206, 207, and 208; or SEQ ID NO: 220, 221, 222, and 223;

optionally wherein the antibody has a heavy chain variable domain (VH) with the framework sequences: SEQ ID NO: 205, 206, 207, and 208.

Claim 7. The method according to any one of claims 1-6, wherein:

(a) the antibody has a heavy chain variable domain (VH) with the CDRs and/or the framework sequences of ATL_6532 or ATL_6533, wherein the CDRs are defined according to IMGT, optionally wherein the antibody has a heavy chain variable domain (VH) with the CDRs and/or the framework sequences of ATL_6532, wherein the CDRs are defined according to IMGT; and/or

(b) the antibody has a heavy chain variable domain (VH) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity with a sequence selected from SEQ ID NOs: 124; 125; 126; 129; optionally wherein the antibody has a heavy chain variable domain (VH) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity with a sequence selected from: SEQ ID NO: 124; SEQ ID NO: 125; optionally wherein the antibody has a heavy chain variable domain (VH) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity with SEQ ID NO: 124.

Claim 8. The method according to any of claims 1-7, wherein:

(a) the antibody comprises a light chain variable domain (VL) with the following CDRs:

CDRL1 comprising amino acid sequence SEQ ID NO: 169, 171, or 174;

CDRL2 comprising amino acid sequence EDN or QDN; and

CDRL3 comprising amino acid sequence SEQ ID NO: 186, 187, 188, or 191;

optionally wherein the antibody comprises a VL with the CDRs: SEQ ID NO:171, EDN, and SEQ ID NO:186; SEQ ID NO:169, EDN, and SEQ ID NO:187; SEQ ID NO:169, EDN, and SEQ ID NO:188; or SEQ ID NO:174, QDN, and SEQ ID NO:191;

optionally wherein the antibody comprises a VL with the CDRs: SEQ ID NO:171, EDN, and SEQ ID NO:186; and/or

(b) the antibody has a light chain variable domain (VL) with the following framework sequences:

LFWR1 of SEQ ID NO: 230, 232, 233, or 235;

LFWR2 of SEQ ID NO: 240, 241, 238, or 244;

LFWR3 of SEQ ID NO: 247, 249, 250, or 253; and

LFWR4 of SEQ ID NO: 256 or 258;

optionally wherein the antibody comprises a VL with the FWRs: SEQ ID NO:232, 240, 249, and 258; SEQ ID NO:230, 241, 247, and 256; SEQ ID NO:233, 238, 250, and 256; or SEQ ID NO:235, 244, 253, and 256;

optionally wherein the antibody comprises a VL with the FWRs: SEQ ID NO:232, 240, 249, and 258; and/or

(c) the antibody has a light chain variable domain (VL) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity with a sequence selected from SEQ ID NO: 134; SEQ ID NO: 135; SEQ ID NO: 136; SEQ ID NO: 139;

optionally wherein the antibody has a light chain variable domain (VL) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity with a sequence selected from: SEQ ID NO: 134; SEQ ID NO: 135;

optionally wherein the antibody has a light chain variable domain (VL) comprising a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% sequence identity with SEQ ID NO: 134.

Claim 9. The method according to any one of claims 1-8, wherein:

(a) the antibody specifically binds the second immunoglobulin (Ig2) domain, TSP type-1 (TSP1) domain, and/or TSP type-2 (TSP2) domain of UNC5C protein, optionally wherein the antibody specifically binds the second immunoglobulin (Ig2) domain of UNC5C protein; and/or

(b) the antibody does not compete or cross compete for binding to UNC5C with an antibody comprising the heavy chain variable domain (VH) set forth in SEQ ID NO: 93 and the light chain variable domain (VL) set forth in SEQ ID NO: 94; and/or

(c) the antibody competes or cross competes for binding to UNC5C with an antibody comprising the heavy chain variable domain (VH) set forth in SEQ ID NO: 124 and the light chain variable domain (VL) set forth in SEQ ID NO: 134; and/or

(d) the antibody binds human, mouse and/or cynomolgus monkey UNC5C protein; and/or

(e) the antibody selectively binds to UNC5C over other one or more netrin receptors selected from: Deleted in Colorectal Cancer (DCC), Unc-5 Netrin Receptor A (UNC5A), Unc-5 Netrin Receptor B (UNC5B), Unc-5 Netrin Receptor D (UNC5D).

Claim 10. The method according to any one of claims 1-9, wherein:

(a) the subject is a mammal, optionally wherein the subject is a mouse, monkey, or human, optionally wherein the subject is a human; and/or

(b) the blood sample is selected from a whole blood, plasma or serum sample; and/or

(c) the subject is a patient who has been treated with a therapeutic compound or composition that alters the concentration of soluble UNC5C in the subject's blood and/or CSF, optionally wherein the therapeutic compound is an anti-UNC5C antibody; and/or

(d) the subject is a patient who has been diagnosed with a neurodegenerative disease, optionally wherein the neurodegenerative disease is: (i) a prodromal or preclinical stage neurodegenerative disease; or (ii) a symptomatic or clinical stage neurodegenerative disease, optionally wherein the neurodegenerative disease is selected from amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), Alzheimer's disease (AD), Parkinson's disease (PD), or a prodromal stage thereof, optionally wherein the neurodegenerative disease is ALS.

Claim 11. The method according to any of claims 1-10, wherein the antibody or antibody fragment is used as a capture antibody in an immunoassay, optionally wherein the immunoassay is a sandwich ELISA or a meso scale discovery (MSD) assay, optionally wherein the method further comprises:

detecting UNC5C bound by the capture antibody using a detection probe, wherein the detection probe binds UNC5C, wherein the detection probe is a detection antibody, UNC5C binding protein or ligand, wherein:

(i) the detection probe carries a detectable label; or

(ii) the detection probe is detected using a secondary antibody which binds the detection probe, wherein the secondary antibody carries a detectable label; and

detecting the detectable label to determine the level of soluble UNC5C in the biological fluid sample; wherein:

(a) the detection antibody is a non-human antibody which binds UNC5C; optionally wherein the detection antibody is a polyclonal antibody;
optionally wherein the detection antibody is a goat polyclonal antibody; and/or

(b) the secondary antibody is a non-human polyclonal antibody which binds to antibodies of the species from which the detection antibody is derived;
optionally wherein the detection antibody is a goat antibody, and the secondary antibody is an anti-goat polyclonal antibody;
optionally wherein the secondary antibody is a mouse anti-goat polyclonal antibody or a donkey anti-goat polyclonal antibody; and/or

(c) the detectable label is selected from the group consisting of a fluorescent, chemiluminescent, electrochemiluminescent, radioactive or enzymatically active label; optionally wherein the detectable label is:

(i) an electrochemiluminescent label, optionally a Sulfo-tag, wherein detecting the detectable label comprises applying an electrical current to the electrochemiluminescent label and measuring the luminescence; or

(ii) a horseradish peroxidase (HRP) enzyme, wherein detecting the detectable label comprises contacting the horseradish peroxidase (HRP) enzyme with TMB (3, 3', 5, 5'-tetramethylbenzidine); and measuring the ultraviolet (UV) absorption at 450nm and/or 570nm.

Claim 12. The method according to any one of claims 2 or 4-11, wherein the therapeutic compound is an anti-UNC5C antibody, optionally wherein:

(a) the therapeutic anti-UNC5C antibody binds the first immunoglobulin (Ig1) domain of UNC5C protein; and/or

(b) the therapeutic anti-UNC5C antibody comprises a VH with the CDRs of SEQ ID NO: 20, 22, 23 and a VL with the CDRs of SEQ ID NO: 24, AAS, SEQ ID NO: 40, wherein the CDRs are defined according to IMGT, optionally wherein the therapeutic anti-UNC5C antibody comprises the heavy chain variable domain (VH) set forth in SEQ ID NO: 93 and the light chain variable domain (VL) set forth in SEQ ID NO: 94.

Claim 13. The method according to any of claims 1-2 or 5-12, comprising:

(a) determining a first level of soluble UNC5C in a first biological fluid sample previously obtained from the subject, wherein the first biological fluid sample was obtained prior to administration of a therapeutic compound or composition to the subject;

(b) determining a second level of soluble UNC5C, wherein the second level of soluble UNC5C is:

(i) a reference level, wherein the reference level of soluble UNC5C is a level of soluble UNC5C associated with one or more biological fluid samples from respective healthy controls, wherein a healthy control is a subject who has not been diagnosed with a neurodegenerative disease, or

(ii) a level of soluble UNC5C in a second biological fluid sample previously obtained from the subject, wherein the second biological fluid sample was obtained after administration of the therapeutic compound or composition to the subject; and

(c) comparing the first level of soluble UNC5C and the second level of soluble UNC5C to determine the effect of the therapeutic compound or composition on the level of soluble UNC5C, optionally wherein determining the first level of soluble UNC5C comprises contacting said first biological fluid sample previously obtained from the subject with the

antibody, and/or wherein determining the second level of soluble UNC5C comprises contacting said second biological fluid sample with the antibody.

Claim 14. The method according to any of claims 3-13, wherein determining a level of soluble UNC5C in a biological fluid sample comprises determining a level of total protein in the biological fluid sample; and comparing levels of soluble UNC5C comprises comparing levels of soluble UNC5C normalised to the level of total protein in the respective biological fluid sample, optionally wherein the levels of total protein are determined using a copper-based protein assay, a fluorescence-based protein assay, or a dye-based protein assay, optionally wherein the levels of total protein are determined using a bicinchoninic acid (BCA) assay.

Claim 15. The method according to any of claims 3-14, wherein the healthy control is a subject who has not been diagnosed with amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), Alzheimer’s disease (AD), or Parkinson’s disease (PD).