

CLAIMS

1. An antibody, or an antigen-binding fragment thereof, capable of binding specifically within the E Region of Sortilin as defined by **SEQ ID NO:146**, wherein the antibody or antigen-binding fragment thereof is selected from the group consisting of antibodies (1)-(18):

Antibody (1) is characterized by:

- a. a heavy chain variable domain CDR1 consisting of **SEQ ID NO:1**;
- b. a heavy chain variable domain CDR 2 consisting of **SEQ ID NO:2**;
- c. a heavy chain variable domain CDR 3 consisting of **SEQ ID NO:3**;
- d. a light chain variable domain CDR 1 consisting of **SEQ ID NO:4**;
- e. a light chain variable domain CDR 2 consisting of **SEQ ID NO:5**;
- and
- f. a light chain variable domain CDR 3 consisting of **SEQ ID NO:6**.

Antibody (2) is characterized by:

- a. a heavychain variable domain CDR1 consisting of **SEQ ID NO:7**;
- b. a heavy chain variable domain CDR 2 consisting of **SEQ ID NO:8**;
- c. a heavy chain variable domain CDR 3 consisting of **SEQ ID NO:9**;
- d. a light chain variable domain CDR 1 consisting of **SEQ ID NO:10**;
- e. a light chain variable domain CDR 2 consisting of **SEQ ID NO:11**; and
- f. a light chain variable domain CDR 3 consisting of **SEQ ID NO:12**.

Antibody (3) is characterized by:

- a. a heavy chain variable domain CDR1 consisting of **SEQ ID NO:13**;
- b. a heavy chain variable domain CDR 2 consisting of **SEQ ID NO:14**;
- c. a heavy chain variable domain CDR 3 consisting of **SEQ ID NO:15**;
- d. a light chain variable domain CDR 1 consisting of **SEQ ID NO:16**;
- e. a light chain variable domain CDR 2 consisting of **SEQ ID NO:17**;
- and
- f. a light chain variable domain CDR 3 consisting of **SEQ ID NO:18**.

Antibody (5) is characterized by:

- a. a heavy chain variable domain CDR1 consisting of **SEQ ID NO:25**;
- b. a heavy chain variable domain CDR 2 consisting of **SEQ ID NO:26**;
- c. a heavy chain variable domain CDR 3 consisting of **SEQ ID NO:27**;
- 5 d. a light chain variable domain CDR 1 consisting of **SEQ ID NO:28**;
- e. a light chain variable domain CDR 2 consisting of **SEQ ID NO:29**;
- and
- f. a light chain variable domain CDR 3 consisting of **SEQ ID NO:30**.

10 Antibody (6) is characterized by:

- a. a heavy chain variable domain CDR1 consisting of **SEQ ID NO:31**;
- b. a heavy chain variable domain CDR 2 consisting of **SEQ ID NO:32**;
- c. a heavy chain variable domain CDR 3 consisting of **SEQ ID NO:33**;
- d. a light chain variable domain CDR 1 consisting of **SEQ ID NO:34**;
- 15 e. a light chain variable domain CDR 2 consisting of **SEQ ID NO:35**; and
- f. a light chain variable domain CDR 3 consisting of **SEQ ID NO:36**.

Antibody (7) is characterized by:

- a. a heavy chain variable domain CDR1 consisting of **SEQ ID NO:37**;
- 20 b. a heavy chain variable domain CDR 2 consisting of **SEQ ID NO:38**;
- c. a heavy chain variable domain CDR 3 consisting of **SEQ ID NO:39**;
- d. a light chain variable domain CDR 1 consisting of **SEQ ID NO:40**;
- e. a light chain variable domain CDR 2 consisting of **SEQ ID NO:41**; and
- f. a light chain variable domain CDR 3 consisting of **SEQ ID NO:42**.

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Antibody (8) is characterized by:

- a. a heavy chain variable domain CDR1 consisting of **SEQ ID NO:43**;
- b. a heavy chain variable domain CDR 2 consisting of **SEQ ID NO:44**;
- c. a heavy chain variable domain CDR 3 consisting of **SEQ ID NO:45**;
- 30 d. a light chain variable domain CDR 1 consisting of **SEQ ID NO:46**;
- e. a light chain variable domain CDR 2 consisting of **SEQ ID NO:47** and
- f. a light chain variable domain CDR 3 consisting of **SEQ ID NO:48**.

Antibody (9) is characterized by:

- a. a heavy chain variable domain CDR1 consisting of **SEQ ID NO:49**;
- b. a heavy chain variable domain CDR 2 consisting of **SEQ ID NO:50**;
- 5 c. a heavy chain variable domain CDR 3 consisting of **SEQ ID NO:51**;
- d. a light chain variable domain CDR 1 consisting of **SEQ ID NO:52**;
- e. a light chain variable domain CDR 2 consisting of **SEQ ID NO:53**; and
- f. a light chain variable domain CDR 3 consisting of **SEQ ID NO:54**.

10 Antibody (10) is characterized by:

- a. a heavy chain variable domain CDR1 consisting of **SEQ ID NO:55**;
- b. a heavy chain variable domain CDR 2 consisting of **SEQ ID NO:56**;
- c. a heavy chain variable domain CDR 3 consisting of **SEQ ID NO:57**;
- d. a light chain variable domain CDR 1 consisting of **SEQ ID NO:58**;
- 15 e. a light chain variable domain CDR 2 consisting of **SEQ ID NO:59**; and
- f. a light chain variable domain CDR 3 consisting of **SEQ ID NO:60**.

Antibody (11) is characterized by:

- a. a heavy chain variable domain CDR1 consisting of **SEQ ID NO:61**;
- 20 b. a heavy chain variable domain CDR 2 consisting of **SEQ ID NO:62**;
- c. a heavy chain variable domain CDR 3 consisting of **SEQ ID NO:63**;
- d. a light chain variable domain CDR 1 consisting of **SEQ ID NO:64**;
- e. a light chain variable domain CDR 2 consisting of **SEQ ID NO:65**; and
- f. a light chain variable domain CDR 3 consisting of **SEQ ID NO:66**.

25 Antibody (12) is characterized by:

- a. a heavy chain variable domain CDR1 consisting of **SEQ ID NO:67**;
- b. a heavy chain variable domain CDR 2 consisting of **SEQ ID NO:68**;
- c. a heavy chain variable domain CDR 3 consisting of **SEQ ID NO:69**;
- 30 d. a light chain variable domain CDR 1 consisting of **SEQ ID NO:70**;
- e. a light chain variable domain CDR 2 consisting of **SEQ ID NO:71**; and
- f. a light chain variable domain CDR 3 consisting of **SEQ ID NO:72**.

Antibody (13) is characterized by:

- a. a heavy chain variable domain CDR1 consisting of **SEQ ID NO:73**;
- b. a heavy chain variable domain CDR 2 consisting of **SEQ ID NO:74**;
- 5 c. a heavy chain variable domain CDR 3 consisting of **SEQ ID NO:75**;
- d. a light chain variable domain CDR 1 consisting of **SEQ ID NO:76**;
- e. a light chain variable domain CDR 2 consisting of **SEQ ID NO:77**; and
- f. a light chain variable domain CDR 3 consisting of **SEQ ID NO:78**.

10 Antibody (14) is characterized by:

- a. a heavy chain variable domain CDR1 consisting of **SEQ ID NO:79**;
- b. a heavy chain variable domain CDR 2 consisting of **SEQ ID NO:80**;
- c. a heavy chain variable domain CDR 3 consisting of **SEQ ID NO:81**;
- d. a light chain variable domain CDR 1 consisting of **SEQ ID NO:82**;
- 15 e. a light chain variable domain CDR 2 consisting of **SEQ ID NO:83**; and
- f. a light chain variable domain CDR 3 consisting of **SEQ ID NO:84**.

Antibody (15) is characterized by:

- a. a heavy chain variable domain CDR1 consisting of **SEQ ID NO:85**;
- 20 b. a heavy chain variable domain CDR 2 consisting of **SEQ ID NO:86**;
- c. a heavy chain variable domain CDR 3 consisting of **SEQ ID NO:87**;
- d. a light chain variable domain CDR 1 consisting of **SEQ ID NO:88**;
- e. a light chain variable domain CDR 2 consisting of **SEQ ID NO:89**; and
- f. a light chain variable domain CDR 3 consisting of **SEQ ID NO:90**.

25 Antibody (16) is characterized by:

- a. a heavy chain variable domain CDR1 consisting of **SEQ ID NO:91**;
- b. a heavy chain variable domain CDR 2 consisting of **SEQ ID NO:92**;
- c. a heavy chain variable domain CDR 3 consisting of **SEQ ID NO:93**;
- 30 d. a light chain variable domain CDR 1 consisting of **SEQ ID NO:94**;
- e. a light chain variable domain CDR 2 consisting of **SEQ ID NO:95**; and
- f. a light chain variable domain CDR 3 consisting of **SEQ ID NO:96**.

Antibody (17) is characterized by:

- a. a heavy chain variable domain CDR1 consisting of **SEQ ID NO:97**;
- b. a heavy chain variable domain CDR 2 consisting of **SEQ ID NO:98**;
- 5 c. a heavy chain variable domain CDR 3 consisting of **SEQ ID NO:99**;
- d. a light chain variable domain CDR 1 consisting of **SEQ ID NO:100**;
- e. a light chain variable domain CDR 2 consisting of **SEQ ID NO:101**; and
- f. a light chain variable domain CDR 3 consisting of **SEQ ID NO:102**.

10 Antibody (18) is characterized by:

- a. a heavy chain variable domain CDR1 consisting of **SEQ ID NO:103**;
- b. a heavy chain variable domain CDR 2 consisting of **SEQ ID NO:104**;
- c. a heavy chain variable domain CDR 3 consisting of **SEQ ID NO:105**;
- d. a light chain variable domain CDR 1 consisting of **SEQ ID NO:106**;
- 15 e. a light chain variable domain CDR 2 consisting of **SEQ ID NO:107**; and
- f. a light chain variable domain CDR 3 consisting of **SEQ ID NO:108**.

2. An antibody, or antigen-binding fragment thereof, according to claim 1,
wherein said antibody or antigen-binding fragment is further characterized:

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Antibody (1) is further characterized by a heavy chain variable domain consisting of **SEQ ID NO:109** and/or a light chain variable domain consisting of **SEQ ID NO:110**.

25 Antibody (2) is further characterized by a heavy chain variable domain consisting of **SEQ ID NO:111** and/or a light chain variable domain consisting of **SEQ ID NO:112**.

30 Antibody (3) is further characterized by a heavy chain variable domain consisting of **SEQ ID NO:113** and/or a light chain variable domain consisting of **SEQ ID NO:114**.

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Antibody (5) is further characterized by a heavy chain variable domain consisting of **SEQ ID NO:117** and/or a light chain variable domain consisting of **SEQ ID NO:118**.

5 Antibody (6) is further characterized by a heavy chain variable domain consisting of **SEQ ID NO:119** and/or a light chain variable domain consisting of **SEQ ID NO:120**.

10 Antibody (7) is further characterized by a heavy chain variable domain consisting of **SEQ ID NO:121** and/or a light chain variable domain consisting of **SEQ ID NO:122**.

15 Antibody (8) is further characterized by a heavy chain variable domain consisting of **SEQ ID NO:123** and/or a light chain variable domain consisting of **SEQ ID NO:124**.

20 Antibody (9) is further characterized by a heavy chain variable domain consisting of **SEQ ID NO:125** and/or a light chain variable domain consisting of **SEQ ID NO:126**.

Antibody (10) is further characterized by a heavy chain variable domain consisting of **SEQ ID NO:127** and/or a light chain variable domain consisting of **SEQ ID NO:128**.

25 Antibody (11) is further characterized by a heavy chain variable domain consisting of **SEQ ID NO:129** and/or a light chain variable domain consisting of **SEQ ID NO:130**.

30 Antibody (12) is further characterized by a heavy chain variable domain consisting of **SEQ ID NO:131** and/or a light chain variable domain consisting of **SEQ ID NO:132**.

Antibody (13) is further characterized by a heavy chain variable domain consisting of **SEQ ID NO:133** and/or a light chain variable domain consisting of **SEQ ID NO:134**.

5 Antibody (14) is further characterized by a heavy chain variable domain consisting of **SEQ ID NO:135** and/or a light chain variable domain consisting of **SEQ ID NO:136**.

10 Antibody (15) is further characterized by a heavy chain variable domain consisting of **SEQ ID NO:137** and/or a light chain variable domain consisting of **SEQ ID NO:138**.

15 Antibody (16) is further characterized by a heavy chain variable domain consisting of **SEQ ID NO:139** and/or a light chain variable domain consisting of **SEQ ID NO:140**.

20 Antibody (17) is further characterized by a heavy chain variable domain consisting of **SEQ ID NO:141** and/or a light chain variable domain consisting of **SEQ ID NO:142**.

25 Antibody (18) is further characterized by a heavy chain variable domain consisting of **SEQ ID NO:143** and/or a light chain variable domain consisting of **SEQ ID NO:144**.

30 3. The antibody, or antigen-binding fragment thereof, according to claim 1, wherein the antigen-binding fragment is selected from the group consisting of: an Fv fragment (e.g. single chain Fv or a disulphide-bonded Fv); a Fab-like fragment (e.g. Fab fragment, Fab' fragment or a F(ab)₂ fragment); and a domain antibody (e.g. a single VH variable domain or VL variable domain).

4. The antibody according to any preceding claims, wherein the antibody consists of an intact antibody.
- 5 5. The antibody, or antigen-binding fragment thereof, according to any preceding claims, wherein the antibody is selected from the group consisting of: an antibody of subtype IgG1, IgG2, IgG3 or IgG4.
- 10 6. A preparation comprising the antibody or antigen-binding fragment thereof according to any one of the previous claims, wherein said preparation is substantially free of naturally-arising antibodies that are either not capable of binding to Sortilin or that do not materially alter an anti-Sortilin functionality of the preparation, said functionality being selected from the group consisting of:
- 15 (i) a binding affinity (K_D) for Sortilin;
- (ii) a capability to reduce and/or inhibit clearance of PGRN by Sortilin-expressing cells;
- (iii) a capability to reduce and/or inhibit the endocytosis of PGRN by Sortilin-expressing cells;
- 20 (iv) a capability to increase the amount and/or concentration of PGRN in the plasma in human-Sortilin-expressing knock-in mice; and/or
- (v) a capability, when administered chronically, to provide treatment of frontotemporal dementia (FTD), amyotrophic lateral sclerosis (ALS) or Alzheimer's Disease (AD).
- 25 7. A pharmaceutical composition comprising an antibody, or an antigen-binding fragment thereof, as defined in any of claims 1 to 5, or the preparation of claim 6, and a pharmaceutically-acceptable carrier.
- 30 8. Use of an antibody, or antigen-binding fragment thereof, as defined in any of claims 1 to 5, or the preparation of claim 6, or the pharmaceutical composition of claim 7, for the manufacture of a medicament.

9. Use of the antibody, or antigen-binding fragment thereof, as defined in any of claims 1 to 5, or the preparation of claim 6, or the pharmaceutical composition of claim 7 in the manufacture of a medicament for treating a disease associated with decreased PGRN or decreased functional PGRN levels in the brain of a patient.
10. The use of an antibody, or antigen-binding fragment thereof according to claim 8, or claim 9, wherein the disease is: FTD; ALS; or proteinopathies, such as AD.
11. The use of an antibody, or antigen-binding fragment thereof, according to claim 8, or claim 9, wherein the treatment is chronic, and is preferably for at least 2 weeks, such as at least for 1 month, or at least for 6 months, or at least for 1 year.
12. A kit comprising the antibody, or antigen-binding fragment thereof, as defined in any of claims 1-5, or the preparation of claim 6, or the pharmaceutical composition of claim 7.
13. An antibody, or antigen-binding fragment thereof, as defined in any of claims 1-5 which has been produced or manufactured in a cell line such as a human cell line, a mammal non-human cell line, an insect, yeast or bacterial cell line.
14. The antibody, or antigen binding fragment thereof, according to claim 13 produced in a CHO cell line, HEK cell line, BHK-21 cell line, murine cell line (such as a myeloma cell line), fibrosarcoma cell line, PER.C6 cell line, HKB-11 cell line, CAP cell line and HuH-7 human cell line.