

CLAIMS

~~What is claimed is:~~

Claims

1. An isolated antibody that binds to a MS4A4A protein, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises: an HVR-H1 comprising an amino acid sequence of SEQ ID NO:308; an HVR-H2 comprising an amino acid sequence of SEQ ID NO:309; and an HVR-H3 comprising an amino acid sequence of SEQ ID NO:310; and the light chain variable region comprises: an HVR-L1 comprising an amino acid sequence of SEQ ID NO:314; an HVR-L2 comprising an amino acid sequence of SEQ ID NO:315; and an HVR-L3 comprising an amino acid sequence of SEQ ID NO:316.

2. The antibody of claim 1, wherein the antibody comprises a heavy chain variable region, wherein the heavy chain variable region comprises an amino acid sequence of SEQ ID NO: 304.

3. The antibody of claim 1, wherein the antibody comprises a light chain variable region, wherein the light chain variable region comprises an amino acid sequence of SEQ ID NO:305.

4. The antibody of claim 1, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises an amino acid sequence of SEQ ID NO:304, and the light chain variable region comprises an amino acid sequence of SEQ ID NO:305.

5. The antibody of claim 1, wherein the antibody comprises a heavy chain and a light chain, wherein the heavy chain comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 320-327 and the light chain comprises an amino acid sequence of SEQ ID NO:363.

6. The antibody of claim 5, wherein the antibody comprises a heavy chain and a light chain, wherein the heavy chain comprises an amino acid sequence of SEQ ID NOs: 324 or 325 and the light chain comprises an amino acid sequence of SEQ ID NO:363.

7. The antibody of claim 5, wherein the antibody comprises a heavy chain and a light chain, wherein the heavy chain comprises an amino acid sequence of SEQ ID NO: 327 and the light chain comprises an amino acid sequence of SEQ ID NO:363.

8. The antibody of claim 5, wherein the antibody comprises a heavy chain and a light chain, wherein the heavy chain comprises an amino acid sequence of SEQ ID NO: 323 and the light chain comprises an amino acid sequence of SEQ ID NO:363.

9. An isolated antibody that binds to a MS4A4A protein, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises: an HVR-H1 comprising the amino acid sequence of SEQ ID NO:94; an HVR-H2 comprising the amino acid sequence of SEQ ID NO:96; and an HVR-H3 comprising the

amino acid sequence of SEQ ID NO:102; and the light chain variable region comprises: an HVR-L1 comprising the amino acid sequence of SEQ ID NO:104; an HVR-L2 comprising the amino acid sequence of SEQ ID NO:105; and an HVR-L3 comprising the amino acid sequence of SEQ ID NO:107.

10. The antibody of claim 9, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO:14, and the light chain variable region comprises the amino acid sequence of SEQ ID NO:22.

11. The antibody of claim 9, wherein the antibody comprises a heavy chain and a light chain, wherein the heavy chain comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 355-362 and the light chain comprises an amino acid sequence of SEQ ID NO:365.

12. The antibody of claim 11, wherein the antibody comprises a heavy chain and a light chain, wherein the heavy chain comprises an amino acid sequence of SEQ ID NO: 360 and the light chain comprises an amino acid sequence of SEQ ID NO:365.

13. The antibody of claim 11, wherein the antibody comprises a heavy chain and a light chain, wherein the heavy chain comprises an amino acid sequence of SEQ ID NO: 362 and the light chain comprises an amino acid sequence of SEQ ID NO:365.

14. The antibody of claim 11, wherein the antibody comprises a heavy chain and a light chain wherein the heavy chain comprises an amino acid sequence of SEQ ID NO: 358 and the light chain comprises an amino acid sequence of SEQ ID NO:365.

15. An isolated antibody that binds to a MS4A4A protein, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises: an HVR-H1 comprising an amino acid sequence selected from the groups consisting of SEQ ID NOs:94, 108, 116, 146, 147, 308, and 311; an HVR-H2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:95, 96, 97, 98, 99, 110, 111, 117, 118, 119, 120, 121, 122, 149, 150, 151, 152, 153, 309, and 312; and an HVR-H3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:102, 100, 101, 102, 112, 123, 124, 125, 126, 127, 128, 129, 154, 310, and 313; and the light chain variable region comprises: an HVR-L1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:104, 103, 113, 130, 131, 132, 133, 134, 135, 136, 137, 138, 156, 157, 158, 314, and 317; an HVR-L2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:105, 106, 114, 139, 140, 141, 142, 143, 159, 160, 161, 315, and 318; and an HVR-L3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:107, 115, 144, 145, 163, 316, and 319.

~~1. The antibody of claim 1, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises: an HVR-H1 comprising the amino acid sequence of SEQ ID NO:94; an HVR-H2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:96-99; and an HVR-H3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:102, 100, and 101; and the light chain variable region comprises: an HVR-L1~~

comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:104 and 103; an HVR-L2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:105-106; and an HVR-L3 comprising the amino acid sequence of SEQ ID NO:107.

2. ~~The antibody of claim 1, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises: an HVR-H1 comprising the amino acid sequence of SEQ ID NO:108; an HVR-H2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:110-111; and an HVR-H3 comprising the amino acid sequence of SEQ ID NO:112; and the light chain variable region comprises: an HVR-L1 comprising the amino acid sequence of SEQ ID NO:113; an HVR-L2 comprising the amino acid sequence of SEQ ID NO:114; and an HVR-L3 comprising the amino acid sequence of SEQ ID NO:115.~~
3. ~~The antibody of claim 1, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises: an HVR-H1 comprising the amino acid sequence of SEQ ID NO:116; an HVR-H2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:118-122; and an HVR-H3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:123-129; and the light chain variable region comprises: an HVR-L1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:130-138; an HVR-L2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:139-143; and an HVR-L3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:144-145.~~
4. ~~The antibody of claim 1, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises: an HVR-H1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:146-147; an HVR-H2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:149-153; and an HVR-H3 comprising the amino acid sequence of SEQ ID NO:154; and the light chain variable region comprises: an HVR-L1~~

comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:156-158; an HVR-L2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:159-161; and an HVR-L3 comprising the amino acid sequence of SEQ ID NO:163.

5. ~~The antibody of claim 1, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises: an HVR-H1 comprising the amino acid sequence of SEQ ID NO:94; an HVR-H2 comprising the amino acid sequence of SEQ ID NO:96; and an HVR-H3 comprising the amino acid sequence of SEQ ID NO:102; and the light chain variable region comprises: an HVR-L1 comprising the amino acid sequence of SEQ ID NO:104; an HVR-L2 comprising the amino acid sequence of SEQ ID NO:105; and an HVR-L3 comprising the amino acid sequence of SEQ ID NO:107.~~
6. ~~The antibody of claim 1, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises: an HVR-H1 comprising the amino acid sequence of SEQ ID NO:308; an HVR-H2 comprising the amino acid sequence of SEQ ID NO:309; and an HVR-H3 comprising the amino acid sequence of SEQ ID NO:310; and the light chain variable region comprises: an HVR-L1 comprising the amino acid sequence of SEQ ID NO:314; an HVR-L2 comprising the amino acid sequence of SEQ ID NO:315; and an HVR-L3 comprising the amino acid sequence of SEQ ID NO:316.~~
7. ~~The antibody of claim 1, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises: an HVR-H1 comprising the amino acid sequence of SEQ ID NO:311; an HVR-H2 comprising the amino acid sequence of SEQ ID NO:312; and an HVR-H3 comprising the amino acid sequence of SEQ ID NO:313; and the light chain variable region comprises: an HVR-L1 comprising the amino acid sequence of SEQ ID NO:317; an HVR-L2 comprising the amino acid sequence of SEQ ID NO:318; and an HVR-L3 comprising the amino acid sequence of SEQ ID NO:319.~~

8. ~~An antibody that binds to a MS4A4A protein, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises the HVR H1, HVR H2, and HVR H3 of antibody 4A 301, 4A 302, 4A 303, 4A 304, 4A 305, 4A 306, 4A 307, 4A 308, 4A 309, 4A 310, 4A 311, 4A 312, 4A 313, 4A 314, 4A 419, or 4A 450.~~
9. ~~An antibody that binds to a MS4A4A protein, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the light chain variable region comprises the HVR L1, HVR L2, and HVR L3 of antibody 4A 301, 4A 302, 4A 303, 4A 304, 4A 305, 4A 306, 4A 307, 4A 308, 4A 309, 4A 310, 4A 311, 4A 312, 4A 313, 4A 314, 4A 419, or 4A 450.~~
10. ~~An antibody that binds to a MS4A4A protein, wherein the antibody comprises a heavy chain variable region comprising an HVR H1, HVR H2, and HVR H3 and a light chain variable region comprising an HVR L1, HVR L2, and HVR L3, wherein the antibody comprises the HVR H1, HVR H2, HVR H3, HVR L1, HVR L2, and HVR L3 of antibody 4A 301, 4A 302, 4A 303, 4A 304, 4A 305, 4A 306, 4A 307, 4A 308, 4A 309, 4A 310, 4A 311, 4A 312, 4A 313, 4A 314, 4A 419, or 4A 450.~~
11. ~~An antibody that binds to a MS4A4A protein, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises the HVR H1, HVR H2, and HVR H3 of antibody 4A 315, 4A 316, 4A 317, 4A 318, 4A 319, 4A 320, 4A 321, 4A 322, 4A 323, 4A 324, 4A 325, 4A 326, 4A 327, 4A 328, 4A 329, 4A 330, or 4A 331.~~
12. ~~An antibody that binds to a MS4A4A protein, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the light chain variable region comprises the HVR L1, HVR L2, and HVR L3 of antibody 4A 315, 4A 316, 4A 317, 4A 318, 4A 319, 4A 320, 4A 321, 4A 322, 4A 323, 4A 324, 4A 325, 4A 326, 4A 327, 4A 328, 4A 329, 4A 330, or 4A 331.~~

13. ~~An antibody that binds to a MS4A4A protein, wherein the antibody comprises a heavy chain variable region comprising an HVR-H1, HVR-H2, and HVR-H3 and a light chain variable region comprising an HVR-L1, HVR-L2, and HVR-L3, wherein the antibody comprises the HVR-H1, HVR-H2, HVR-H3, HVR-L1, HVR-L2, and HVR-L3 of antibody 4A-315, 4A-316, 4A-317, 4A-318, 4A-319, 4A-320, 4A-321, 4A-322, 4A-323, 4A-324, 4A-325, 4A-326, 4A-327, 4A-328, 4A-329, 4A-330, or 4A-331.~~
14. ~~An antibody that binds to a MS4A4A protein, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises the HVR-H1, HVR-H2, and HVR-H3 of antibody 4A-332, 4A-333, 4A-334, 4A-335, 4A-336, 4A-337, 4A-338, 4A-339, 4A-340, 4A-341, 4A-342, 4A-343, 4A-344, 4A-345, 4A-346, 4A-347, 4A-348, 4A-349, 4A-350, 4A-351, 4A-352, 4A-353, 4A-354, 4A-355, 4A-356, 4A-357, 4A-358, 4A-359, 4A-360, 4A-361, 4A-362, 4A-363, 4A-364, 4A-365, 4A-366, 4A-367, 4A-368, 4A-369, 4A-370, 4A-371, 4A-372, 4A-373, 4A-374, 4A-375, 4A-376, 4A-377, 4A-378, 4A-379, 4A-380, or 4A-381.~~
15. ~~An antibody that binds to a MS4A4A protein, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the light chain variable region comprises the HVR-L1, HVR-L2, and HVR-L3 of antibody 4A-332, 4A-333, 4A-334, 4A-335, 4A-336, 4A-337, 4A-338, 4A-339, 4A-340, 4A-341, 4A-342, 4A-343, 4A-344, 4A-345, 4A-346, 4A-347, 4A-348, 4A-349, 4A-350, 4A-351, 4A-352, 4A-353, 4A-354, 4A-355, 4A-356, 4A-357, 4A-358, 4A-359, 4A-360, 4A-361, 4A-362, 4A-363, 4A-364, 4A-365, 4A-366, 4A-367, 4A-368, 4A-369, 4A-370, 4A-371, 4A-372, 4A-373, 4A-374, 4A-375, 4A-376, 4A-377, 4A-378, 4A-379, 4A-380, or 4A-381.~~
16. ~~An antibody that binds to a MS4A4A protein, wherein the antibody comprises a heavy chain variable region comprising an HVR-H1, HVR-H2, and HVR-H3 and a light chain variable region comprising an HVR-L1, HVR-L2, and HVR-L3, wherein the antibody comprises the HVR-H1, HVR-H2, HVR-H3, HVR-L1, HVR-L2, and HVR-L3 of antibody 4A-332, 4A-333, 4A-334, 4A-335, 4A-336, 4A-337, 4A-338, 4A-339, 4A-340,~~

~~4A-341, 4A-342, 4A-343, 4A-344, 4A-345, 4A-346, 4A-347, 4A-348, 4A-349, 4A-350, 4A-351, 4A-352, 4A-353, 4A-354, 4A-355, 4A-356, 4A-357, 4A-358, 4A-359, 4A-360, 4A-361, 4A-362, 4A-363, 4A-364, 4A-365, 4A-366, 4A-367, 4A-368, 4A-369, 4A-370, 4A-371, 4A-372, 4A-373, 4A-374, 4A-375, 4A-376, 4A-377, 4A-378, 4A-379, 4A-380, or 4A-381.~~

- ~~17. An antibody that binds to a MS4A4A protein, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises the HVR-H1, HVR-H2, and HVR-H3 of antibody 4A-382, 4A-383, 4A-384, 4A-385, 4A-386, 4A-387, 4A-388, 4A-389, or 4A-390.~~
- ~~18. An antibody that binds to a MS4A4A protein, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the light chain variable region comprises the HVR-L1, HVR-L2, and HVR-L3 of antibody 4A-382, 4A-383, 4A-384, 4A-385, 4A-386, 4A-387, 4A-388, 4A-389, or 4A-390.~~
- ~~19. An antibody that binds to a MS4A4A protein, wherein the antibody comprises a heavy chain variable region comprising an HVR-H1, HVR-H2, and HVR-H3 and a light chain variable region comprising an HVR-L1, HVR-L2, and HVR-L3, wherein the antibody comprises the HVR-H1, HVR-H2, HVR-H3, HVR-L1, HVR-L2, and HVR-L3 of antibody 4A-382, 4A-383, 4A-384, 4A-385, 4A-386, 4A-387, 4A-388, 4A-389, or 4A-390.~~
- ~~20. The antibody of claim 1 or claim 9, wherein the antibody comprises a heavy chain variable region, wherein the heavy chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 5-15, 304, and 306.~~
- ~~21. The antibody of claim 1 or claim 12, wherein the antibody comprises a heavy chain variable region, wherein the heavy chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 24-30.~~

22. ~~The antibody of claim 1 or claim 15, wherein the antibody comprises a heavy chain variable region, wherein the heavy chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 40-53.~~

23. ~~The antibody of claim 1 or claim 18, wherein the antibody comprises a heavy chain variable region, wherein the heavy chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 76-84.~~

~~The antibody of claim 1 or claim 10, wherein the antibody comprises a light chain variable region, wherein the light chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 16. The antibody of claim 1, 9, or 15, wherein the antibody is humanized.~~

24. ~~17-22, 305, and 307.~~

25. ~~The antibody of claim 1 or claim 13, wherein the antibody comprises a light chain variable region, wherein the light chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 32-36.~~

26. ~~The antibody of claim 1 or claim 16, wherein the antibody comprises a light chain variable region, wherein the light chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 55-74.~~

27. ~~The antibody of claim 1 or claim 19, wherein the antibody comprises a light chain variable region, wherein the light chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 86-93.~~

28. ~~The antibody of claim 1 or claim 11, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region~~

~~comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 5-15, 304, and 306, and the light chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 17-22, 305, and 307.~~

- ~~29. The antibody of claim 1 or claim 14, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 24-30, and the light chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 32-36.~~
- ~~30. The antibody of claim 1 or claim 17, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 40-53, and the light chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 55-74.~~
- ~~31. The antibody of claim 1 or claim 20, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 76-84, and the light chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 86-93.~~
- ~~32. The antibody of any one of claims 1, 2, 4, 6-11, 21, 25, and 29, wherein the antibody comprises a heavy chain and a light chain, wherein the heavy chain comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 320-343.~~
- ~~33. The antibody of any one of claims 1, 2, 6, 9-11, 21, 25, 29, wherein the antibody comprises a heavy chain and a light chain wherein the heavy chain comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 336-343 and the light chain comprises a light chain variable region comprising the amino acid sequence of SEQ~~

ID NO: 22, optionally wherein the light chain further comprises a constant region comprising the amino acid sequence of SEQ ID NO: 344.

34. — ~~The antibody of any one of claims 1, 7, 9-11, 21, 25, and 29, wherein the antibody comprises a heavy chain and a light chain wherein the heavy chain comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 320-327 and the light chain comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO:305, optionally wherein the light chain further comprises a constant region comprising the amino acid sequence of SEQ ID NO: 344.~~
35. — ~~The antibody of any one of claims 1, 8-11, 21, 25, and 29, wherein the antibody comprises a heavy chain and a light chain wherein the heavy chain comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 328-335 and the light chain comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO:307, optionally wherein the light chain further comprises a constant region comprising the amino acid sequence of SEQ ID NO: 344.~~
36. — ~~The antibody of any one of claims 1, 2, 6, 9-11, 21, 25, and 29, wherein the antibody comprises a heavy chain and a light chain wherein the heavy chain comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 355-362 and the light chain comprises an amino acid sequence of SEQ ID NO:365.~~
37. — ~~The antibody of any one of claims 1, 7, 9-11, 21, 25, and 29, wherein the antibody comprises a heavy chain and a light chain wherein the heavy chain comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 320-327 and the light chain comprises an amino acid sequence of SEQ ID NO:363.~~
38. — ~~The antibody of any one of claims 1, 8-11, 21, 25, and 29, wherein the antibody comprises a heavy chain and a light chain wherein the heavy chain comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 328-335 and the light chain comprises an amino acid sequence of SEQ ID NO:364.~~

39. ~~The antibody of claim 2, wherein the antibody comprises:~~
- ~~a. a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence of SEQ ID NO:94, an HVR-H2 comprising the amino acid sequence of SEQ ID NO:96, and an HVR-H3 comprising the amino acid sequence of SEQ ID NO:102; and the light chain variable region comprises an HVR-L1 comprising the amino acid sequence of SEQ ID NO:104, an HVR-L2 comprising the amino acid sequence of SEQ ID NO:105, and an HVR-L3 comprising the amino acid sequence of SEQ ID NO:107;~~
 - ~~b. a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO:14, and the light chain variable region comprises the amino acid sequence of SEQ ID NO:22; or~~
 - ~~c. a heavy chain and a light chain wherein the heavy chain comprises the amino acid sequence of SEQ ID NO: 359 or 360, and the light chain comprises the amino acid sequence of SEQ ID NO:365.~~
40. ~~The antibody of claim 7, wherein the antibody comprises:~~
- ~~a. a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO:304, and the light chain variable region comprises the amino acid sequence of SEQ ID NO:305; or~~
 - ~~b. a heavy chain and a light chain wherein the heavy chain comprises the amino acid sequence of SEQ ID NO: 324 or 325, and the light chain comprises the amino acid sequence of SEQ ID NO:363.~~
41. ~~The antibody of claim 8, wherein the antibody comprises:~~
- ~~a. a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO:306, and~~

~~the light chain variable region comprises the amino acid sequence of SEQ ID NO:307; or~~

~~b. a heavy chain and a light chain wherein the heavy chain comprises the amino acid sequence of SEQ ID NO: 332 or 333, and the light chain comprises the amino acid sequence of SEQ ID NO:364.~~

~~42. An isolated antibody that binds to a MS4A4A protein, wherein the antibody competitively inhibits binding with one or more of the antibodies of any one of claims 1-42 for binding to MS4A4A.~~

~~43. An isolated antibody that binds to a MS4A4A protein, wherein the antibody binds essentially the same or an overlapping epitope on MS4A4A as the antibody of any one of claims 1-42.~~

~~44. The antibody of claim 44, wherein the antibody binds to one or more amino acid residues within the amino acid sequence SFHHPYCNYYGNSNNCHGTMS (SEQ ID NO:178) of SEQ ID NO:1, wherein the antibody does not bind amino acid residue proline 163 of SEQ ID NO:1.~~

~~45. The antibody of any one of claims 1-42, wherein the antibody binds to extracellular domain 1 of human MS4A4A.~~

~~46. The antibody of any one of claims 1-42, wherein the antibody binds to one or more amino acid residues within the amino acid sequence CMASNTYGSNPIS (SEQ ID NO:177) of SEQ ID NO:1.~~

~~47. The antibody of any one of claims 1-42, wherein the antibody binds to extracellular domain 2 of human MS4A4A.~~

48. — ~~The antibody of any one of claims 1-42, wherein the antibody binds to one or more amino acid residues within the amino acid sequence SFHHPYCNYYGNSNNCHGTMS (SEQ ID NO:178) of SEQ ID NO:1.~~

49. — ~~The antibody of any one of claims 1-49, wherein the antibody is human or humanized.~~

50. — ~~The antibody of any one of claims 1-50, wherein the antibody~~ 16, ~~wherein the antibody~~ (a) decreases cell surface levels of MS4A4A or decreases intracellular levels of MS4A4A.

~~The antibody of any one of claims 1-51, wherein the antibody,~~ (b) increases soluble TREM2 levels, increases membrane TREM2 levels, or increases soluble TREM2 and increases membrane TREM2 levels in myeloid cells. —, and/or (c) reduces expression of M2 cell surface markers on myeloid cells.

51. — ~~18. The antibody of any one of claims 1-52, wherein the antibody reduces expression of M2 cell surface markers on myeloid cells.~~

52. — ~~The antibody of claim 53, wherein the antibody reduces expression of CD200R, Dectin-1, or CD163 on myeloid cells.~~

~~The antibody of any one of claims 1-50~~ 17, wherein the antibody increases mRNA and/or protein expression of gelsolin and/or osteopontin on myeloid cells.

53. — ~~An isolated antibody that binds to a MS4A4A protein, wherein the antibody increases mRNA and/or protein expression of gelsolin and/or osteopontin on myeloid cells.~~

54. — ~~The antibody of claim 56, wherein the myeloid cells are human macrophages.~~

55. — ~~The antibody of claim 56 or 57, wherein the antibody is human or humanized.~~
56. — 19. ~~The antibody of any one of claims 56-58, wherein the antibody binds to the same epitope as an antibody selected from the group consisting of 4A1-18, 4A-25, 4A-214, 4A-21 and 4A-202.~~
57. — ~~The antibody of any one of claims 56-59, wherein the antibody reduces expression of M2 markers on myeloid cells.~~
58. — ~~The antibody of claim 60, wherein the myeloid cells are human macrophages.~~
59. — ~~The antibody of claim 61, wherein the M2 markers are CD200R, Dectin-1, and/or CD163.~~
60. — ~~The antibody of any one of claims 56-62, wherein the antibody increases membrane TREM2 on human macrophages by at least 50%, 90%, 100%, 150%, 200% or 250%.~~
61. — ~~The antibody of any one of claim 56-63, wherein the antibody increases soluble TREM2 in human macrophage supernatant by at least 15%, 20%, 25%, 30%, 40%, 50%, 60%, or 70%.~~
- ~~The antibody of any one of claims 1-64, wherein the antibody is a monoclonal antibody.~~

62. — 20. ~~The antibody of any one of claims 1-65, wherein the antibody binds to human MS4A4A of SEQ ID NO:1.~~

~~The antibody of claim 66~~19, wherein the antibody further binds to cynomolgus monkey MS4A4A of SEQ ID NO:3.

21. The antibody of any one of claims 1-~~67~~4, 9, 10, and 15-20, wherein the antibody is of the IgG class and has an ~~IgG1IgG1~~, IgG2, or IgG4 isotype.

~~63.~~22. The antibody of claim ~~68~~21, wherein the antibody has an ~~IgG1IgG 1~~ isotype.

~~The antibody of claim 69, wherein the antibody and~~ comprises a modified Fc comprising the N325S and L328F mutations according to EU numbering.

23. The antibody of any one of claims 1-~~70~~4, 9, 10, and 15-22, wherein the antibody is an antibody fragment.

24. The antibody of claim ~~71~~23, wherein the antibody fragment is a Fab, ~~Fab'~~, ~~Fab'-Fab'~~, ~~Fab'-SH~~, F(~~ab'-ab'~~)₂, Fv or scFv fragment.

25. The antibody of any one of claims 1-~~72~~24, wherein the antibody is a bispecific antibody recognizing a first antigen and a second antigen.

~~64.~~26. The antibody of claim ~~73~~25, wherein the first antigen is MS4A4A and the second antigen is:
an antigen facilitating transport across the blood-brain-barrier;

27. The antibody of claim 25, wherein the first antigen is MS4A4A, and the second antigen is

(a) an antigen facilitating transport across the blood-brain-barrier selected from the group consisting of transferrin receptor (TR), insulin receptor (HIR), insulin-like growth factor receptor (IGFR), low-density lipoprotein receptor related proteins 1 and 2 (LPR-1 and 2), diphtheria toxin receptor, CRM197, a llama single domain antibody, TMEM 30(A), a protein transduction domain, TAT, Syn-B, penetratin, a poly-arginine peptide, an angiopeptide, and ANG1005;

(b) a disease-causing agent selected from the group consisting of disease-causing peptides or proteins or, disease-causing nucleic acids, wherein the disease-causing nucleic acids are antisense GGCCCC (G2C4) repeat-expansion RNA, the disease-causing proteins are selected from the group consisting of amyloid beta, oligomeric amyloid beta, amyloid beta plaques, amyloid precursor protein or fragments thereof, Tau, IAPP, alpha-synuclein, TDP-43, FUS protein, C9orf72 (chromosome 9 open reading frame 72), c9RAN protein, prion protein, PrPSc, huntingtin, calcitonin, superoxide dismutase, ataxin, ataxin 1, ataxin 2, ataxin 3, ataxin 7, ataxin 8, ataxin 10, Lewy body, atrial natriuretic factor, islet amyloid polypeptide, insulin, apolipoprotein AI, serum amyloid A, medin, prolactin, transthyretin, lysozyme, beta 2 microglobulin, gelsolin, keratoepithelin, cystatin, immunoglobulin light chain AL, S-IBM protein, Repeat-associated non-ATG (RAN) translation products, DiPeptide repeat (DPR) peptides, glycine-alanine (GA) repeat peptides, glycine-proline (GP) repeat peptides, glycine-arginine (GR) repeat peptides, proline-alanine (PA) repeat peptides, ubiquitin, and proline-arginine (PR) repeat peptides;

(c) ligands and/or proteins expressed on immune cells, wherein the ligands and/or proteins selected from the group consisting of CD40, OX40, ICOS, CD28, CD137/4-1BB, CD27, GITR, PD-L1, CTLA-4, PD-L2, PD-1, B7-H3, B7-H4, HVEM, BTLA, KIR, GAL9, TIM3, A2AR, LAG-3, and phosphatidylserine; or

(d) a protein, lipid, polysaccharide, or glycolipid expressed on one or more tumor cells.

28. A pharmaceutical composition comprising the antibody of any one of claims 1-27 and a pharmaceutically acceptable carrier.

29. An isolated nucleic acid comprising a nucleic acid sequence encoding the antibody of any one of ~~the preceding~~ claims 1-27.

~~65. — A vector comprising the nucleic acid of claim 75.~~

30. An isolated host cell comprising the nucleic acid of claim ~~75 or the vector of claim 76~~29.

31. A method of producing an antibody that binds to human MS4A4A, comprising culturing the cell of claim ~~77~~30 so that the antibody is produced.

~~66. —~~32. The ~~method of claim 78, further comprising recovering the antibody produced by the cell.~~

~~67. — A pharmaceutical composition comprising the antibody of any one of claims 1-74 and a pharmaceutically acceptable carrier.~~

~~A method of preventing, reducing risk,~~27 or the pharmaceutical composition of claim 28 for use in treating an individual having a disease, disorder, or injury selected from the group consisting of ~~Alzheimer's disease, late onset Alzheimer's disease, and cognitive impairment, the~~

~~method comprising administering to an individual in need thereof a therapeutically effective amount of the antibody of any one of claims 1-74~~Alzheimer's disease and late onset Alzheimer's disease.

~~68. — A method of preventing, reducing risk, or treating an individual having a disease, disorder, condition, or injury caused by or associated with over expression or increased activity of MS4A4A, the method comprising administering to an individual in need thereof a therapeutically effective amount of the~~33. The antibody of any one of claims 1-74.

~~69. — A method of preventing, reducing risk, or~~27 or the pharmaceutical composition of claim 28 for use in treating an individual having a CSF1R-deficient disease or disorder,~~the method comprising administering to an individual in need thereof a therapeutically effective amount of the antibody of any one of claims 1-74.~~

~~The method of claim 83,~~ wherein the CSF1R-deficient disease or disorder is adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP) or hereditary diffuse leukoencephalopathy with spheroids (HDLS).

~~70. — The method of any one of claims 81-84, further comprising detecting levels of osteopontin, gelsolin, membrane TREM2, and/or soluble TREM2 before and/or after the administration of the antibody.~~