

Association with soluble TREM2

Name	N	AAF	Effect (95% CI)	P value
11:60302703:A:G	19,467 16,173 3,281	29.2%	-0.30 (-0.31, -0.29)	2.2e-307
11:60160949:G:A	39,742 1,768 19	2.2%	-0.47 (-0.51, -0.43)	3e-127
11:603335639:T:C	18,394 18,615 4,520	33.1%	-0.11 (-0.13, -0.10)	1.8e-77
11:60392235:G:T	21,504 16,766 3,259	28.0%	-0.05 (-0.07, -0.04)	1.8e-16
11:60385111:G:A	18,506 16,589 3,826	31.1%	0.07 (0.06, 0.08)	8.2e-29
11:60254475:G:A	16,041 19,601 5,887	37.7%	0.40 (0.39, 0.41)	2.2e-307
11:60173126:T:A	15,122 18,277 5,511	37.6%	0.40 (0.39, 0.41)	2.2e-307
11:60280507:G:A	41,288 241 0	0.29%	0.20 (0.09, 0.30)	3e-04
11:60181585:A:G	36,728 2,164 29	2.9%	0.02 (-0.02, 0.05)	0.315
11:60173027:C:T	38,576 339 0	0.44%	0.62 (0.54, 0.71)	5.8e-44

Figure 1

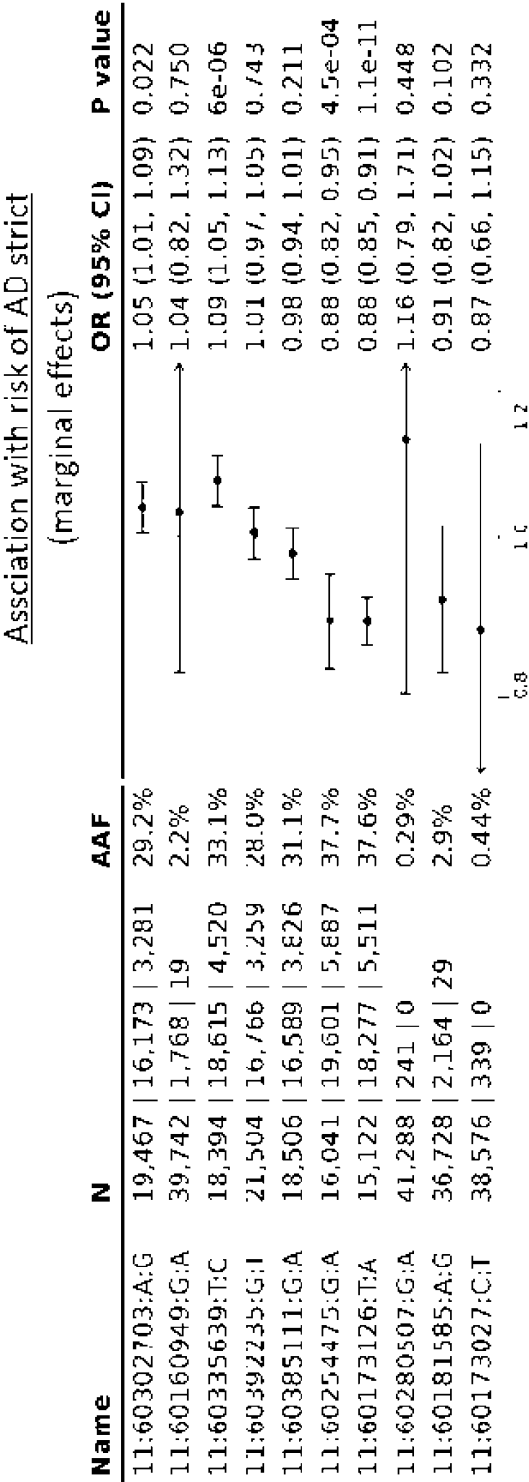


Figure 1 (cont.)

Association with soluble TREM2

Name	N	AAF	(joint effects)		
			Effect (95% CI)	P joint	
11:60302703:A:G	19,467	16,173 3,281	29.2%	-0.28 (-0.29, -0.26)	1.10e-193
11:60160949:G:A	39,742	1,768 19	2.2%	-0.18 (-0.22, -0.14)	3.56e-21
11:60335639:T:C	18,394	18,615 4,520	33.1%	-0.06 (-0.08, -0.04)	1.06e-09
11:60392235:G:T	21,504	16,766 3,259	28.0%	-0.04 (-0.05, -0.02)	2.86e-08
11:6038511:G:A	18,506	16,589 3,826	31.1%	0.05 (0.04, 0.06)	5.72e-13
11:60254475:G:A	16,041	19,601 5,887	37.7%	0.08 (0.06, 0.11)	4.01e-11
11:60173126:T:A	15,122	18,277 5,511	37.6%	0.26 (0.24, 0.28)	5.71e-143
11:60280507:G:A	41,288	241 0	0.29%	0.29 (0.19, 0.39)	1.10e-08
11:60181585:A:G	36,728	2,164 29	2.9%	0.34 (0.31, 0.38)	1.24e-87
11:60173027:C:T	38,576	339 0	0.44%	0.92 (0.83, 1.00)	6.07e-107



Figure 2

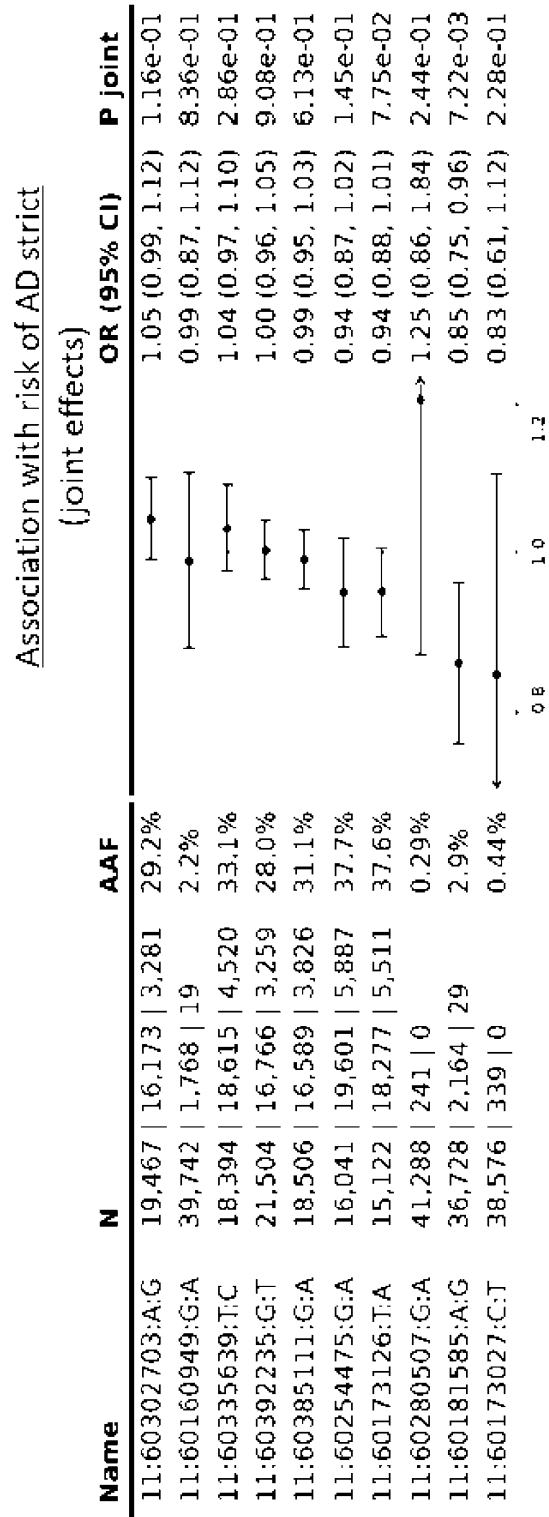


Figure 2 (cont.)

SUSIE cred. set (conditional PIP)	Variant	Joint effect on TREM2 protein in SD units [95% CI]	P-value	N RR RA AA	AAF
2 (1.0)	11:60302703:A:G	-0.28 (-0.29, -0.26)	5.05E-192	20711 17299 3519	0.29
1(1.0)	11:60173126:T:A	0.26 (0.24, 0.28)	4.50E-142	16122 19550 5857	0.38
3 (1.0)	11:60173027:C:T	0.91 (0.83, 0.99)	1.18E-105	41169 360 0	0.004
4 (1.0)	11:60181585:A:G	0.34 (0.31, 0.38)	3.42E-87	39192 2304 33	0.03
8 (0.2)	11:60160949:G:A	-0.18 (-0.22, -0.15)	2.81E-21	39742 1768 19	0.02
-	11:60385111:G:A	0.05 (0.03, 0.06)	7.91E-13	19738 17695 4096	0.31
-	11:60254475:G:A	0.08 (0.06, 0.11)	2.56E-11	16041 19601 5887	0.38
-	11:60335639:T:C	-0.06 (-0.08, -0.04)	1.16E-09	18394 18615 4520	0.33
-	11:60280507:G:A	0.29 (0.19, 0.39)	1.81E-08	41288 241 0	0.003
-	11:60392235:G:T	-0.04 (-0.05, -0.02)	2.53E-08	21504 16766 3259	0.28

Figure 3

SUSIE cred. set (conditional PIP)	Variant	LD ($r^2>0.95$) with coding variant? (undefined if exact variant)	Colocalization with eQTL ($r^2>0.95$ with sentinel eQTL)?
2 (1.0)	11:60302703:A>G	MS4A4A :Met178Val	MS4A4A (macrophages)
1 (1.0)	11:60173126:T>A	MS4A6A :Thr185Ser	-
3 (1.0)	11:60173027:C>T	MS4A6A :splice donor[LoF]	
4 (1.0)	11:60191585:A>G	MS4A6A :Ile76Thr	-
8 (0.2)	11:60150949:G>A	MS4A2:Glu23>gly	Lower MS4A6A (blood, lung; isoQTL in macrophages)
-	11:60385111:G>A		MS4A7 (isoQTL in blood and macrophages)
-	11:60254475:G>A	-	Lower MS4A4A (blood)
	11:60335639:T>C	MS4A6:missense(3)	MS4A4A (monocytes)
-	11:60280507:G>A	-	Lower MS4A4A (Liver)
-	11:60302235:C>T	MS4A14:Asn177Tyr	MS4A14 (blood, monocytes, liver), MS4A1 (blood), MS4A7 (blood, DCs)

Figure 3 (cont.)

A)

Effect on soluble IREM2 (UKB plasma)
(effects conditional on 9 pOTLs, EUR ancestry)

Effect in NPX raw unit (95% CI)	P-value	RR RA AA
0.735 (0.178, 1.292)	0.009	38914 7 0
0.700 (0.179, 1.221)	0.008	38913 8 0
0.430 (0.249, 0.611)	3.4x10 ⁻⁶	38855 66 0
0.767 (0.410, 1.125)	2.54x10 ⁻⁵	38904 17 0

MS4A4A variant	AAF
Burden pLoF MAF<1%	0.007
11:60173027:C:T (splice donor.missense)	0.004
(frame shift, exon 4/8)	0.002
Burden pLoF MAF<0.1%	0.0002

Effect on MS4A4A mRNA levels (GHS liver)
[marginal effects, EUR ancestry]

Effect (95% CI)	P-value	RR RA AA
-0.335 (-0.440, 0.230)	3.62E-10	1899 29 0
0.035 (0.190, 0.489)	8.84E-06	1913 19 4 0
-1.055 (-1.216, -0.893)	1.80E-37	1916 12 0
-	-	-

Figure 4

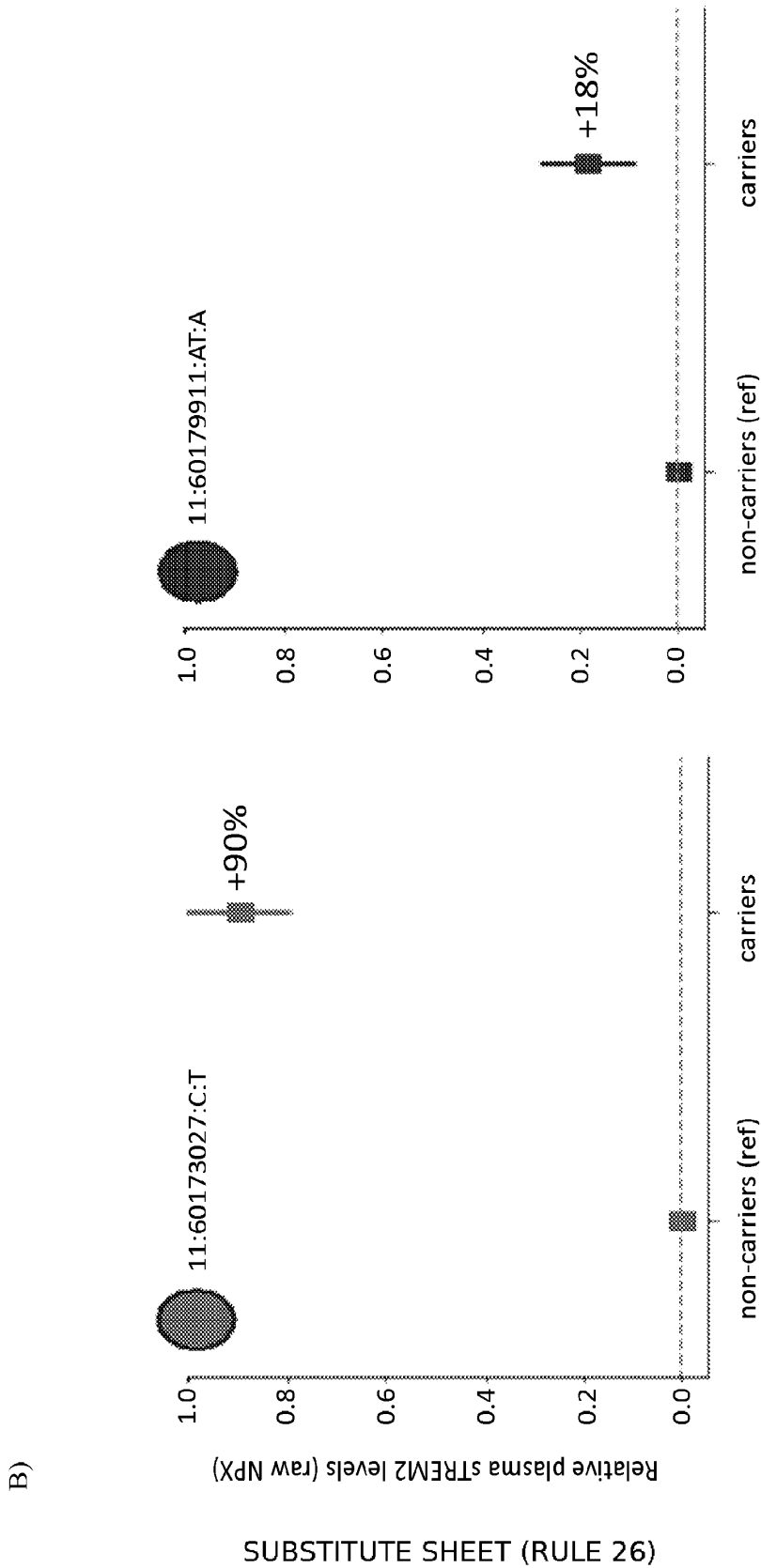


Figure 4 (cont.)

B)

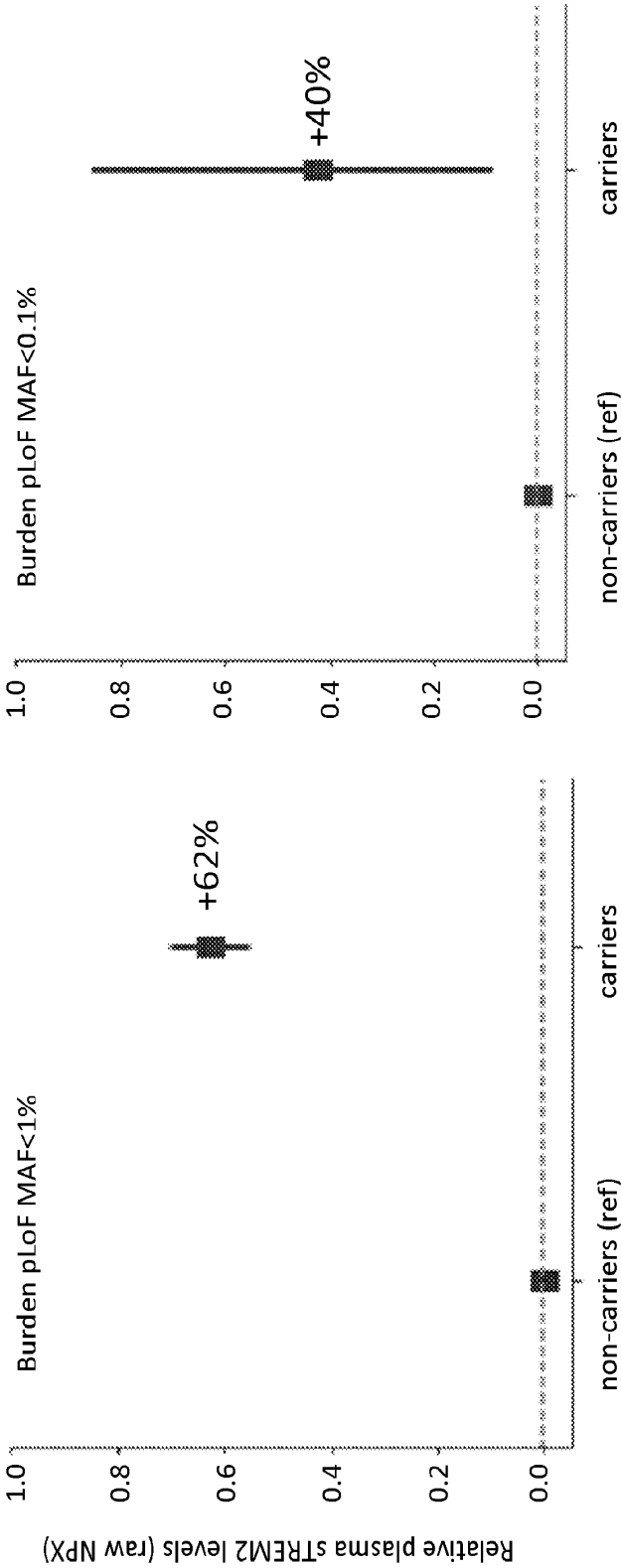


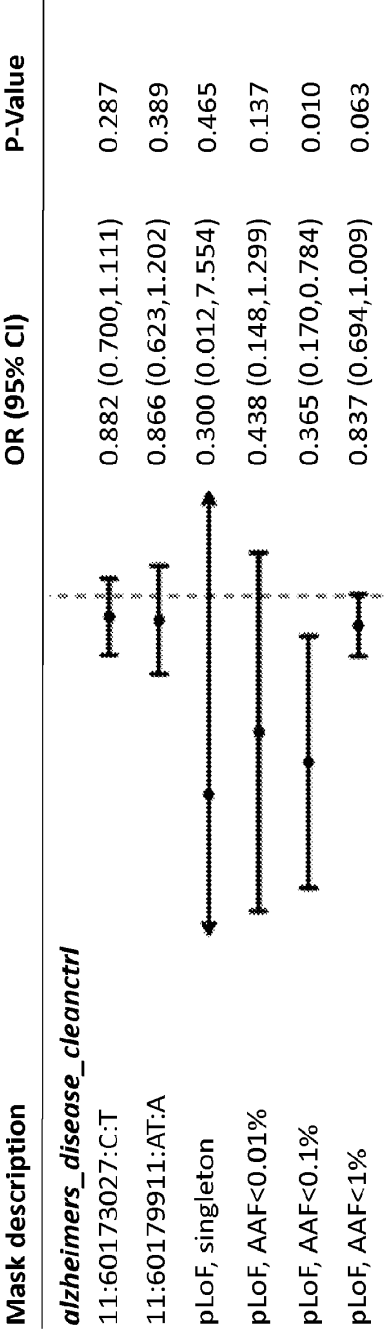
Figure 4 (cont.)

Mask description	Cases Ref/Het/Hom	Controls Ref/Het/Hom	AAF
<i>alzheimers_disease_broad_fmhx</i>			
11:60173027:C:T	80,068 / 629 / 2	830,946 / 6,139 / 15	0.38%
11:60179911:AT:A	80,449 / 250 / 0	834,200 / 2,895 / 5	0.20%
pLoF, singleton	76,009 / 1 / 0	808,494 / 45 / 0	0.003%
pLoF, AAF<0.01%	75,985 / 25 / 0	808,192 / 347 / 0	0.021%
pLoF, AAF<0.1%	75,969 / 41 / 0	807,931 / 608 / 0	0.037%
pLoF, AAF<1%	75,122 / 886 / 2	798,647 / 9,869 / 23	0.61%

Mask description	OR (95% CI)	P-Value
<i>alzheimers_disease_broad_fmhx</i>		
11:60173027:C:T	0.936 (0.860,1.020)	0.132
11:60179911:AT:A	0.854 (0.747,0.976)	0.020
pLoF, singleton	0.795 (0.234,2.697)	0.713
pLoF, AAF<0.01%	0.993 (0.645,1.528)	0.974
pLoF, AAF<0.1%	0.954 (0.685,1.328)	0.779
pLoF, AAF<1%	0.911 (0.850,0.977)	0.009

Figure 5

Mask description	Cases Ref/Het/Hom	Controls Ref/Het/Hom	AAF
<i>alzheimers_disease_cleanctrl</i>			
11:60173027:C:T	9,930 / 72 / 0	881,399 / 6,722 / 19	0.38%
11:60179911:AT:A	10,107 / 35 / 0	918,754 / 3,312 / 7	0.18%
pLoF, singleton	9,729 / 0 / 0	835,084 / 40 / 0	0.002%
pLoF, AAF<0.01%	10,141 / 1 / 0	921,696 / 385 / 0	0.021%
pLoF, AAF<0.1%	10,141 / 1 / 0	921,332 / 749 / 0	0.040%
pLoF, AAF<1%	10,033 / 109 / 0	911,140 / 10,914 / 27	0.59%



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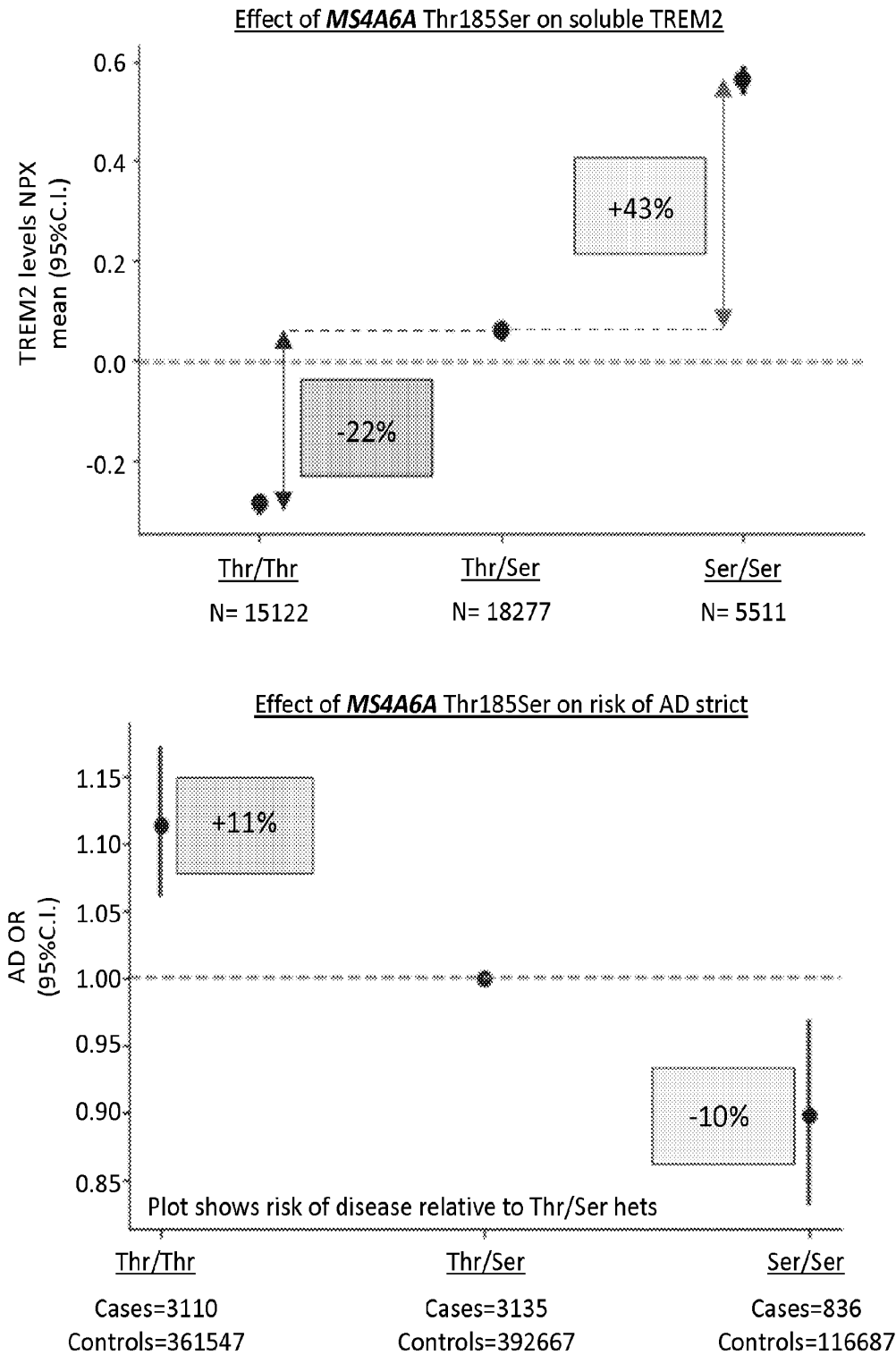


Figure 6

SUBSTITUTE SHEET (RULE 26)

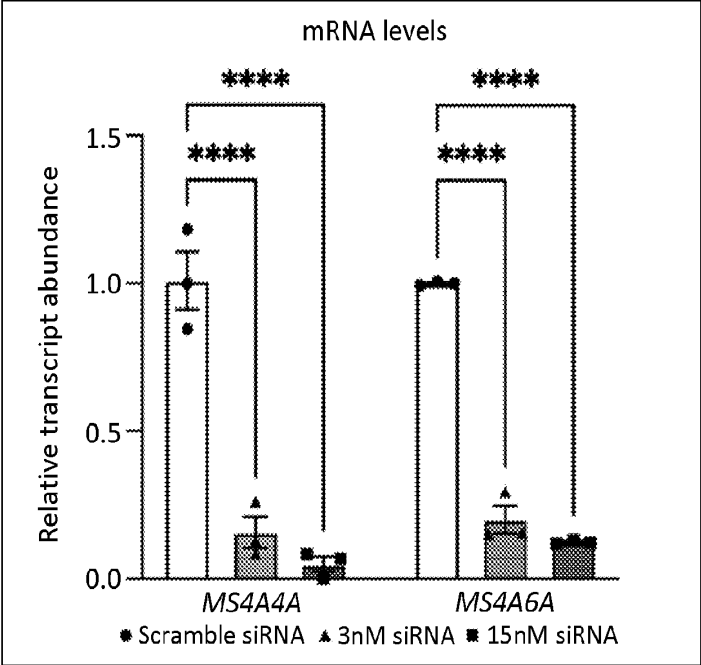
Effect of *MS4A6A* rare pLoF variants on risk of AD strict

Genotype for <i>MS4A6A</i> Thr185Ser	Odds Ratio for AD strict (95% C.I.)	P-value	N cases RR RA AA	N controls RR RA AA
Overall	0.84 (0.66,1.06)	0.14	6591 72 1	6999 719 29 73
Thr185Ser	0.73 (0.50,1.07)	0.10	2804 26 1	2705 48 3696 16
TTT/TTT	0.81 (0.57,1.16)	0.25	2982 33 0	3286 64 4180 0
TTT/TTT	0.77 (0.60,1.00)	0.05	5786 39 1	5992 12 7876 16
TTT/TTT	1.37 (0.79,2.39)	0.26	797 13 0	100164 11148 7

*AD ~ MS4A6A_Thr185Ser x MS4A6A_pLoF **
Interaction P-value = 0.11; both Thr185Ser and pLoF <0.05 significant after interaction

Figure 6 (cont.)

siRNA transfection leads to robust MS4A4A and MS4A6A knockdown



Knockdown of MS4A4A or MS4A6A potentiates TREM2-dependent Syk phosphorylation

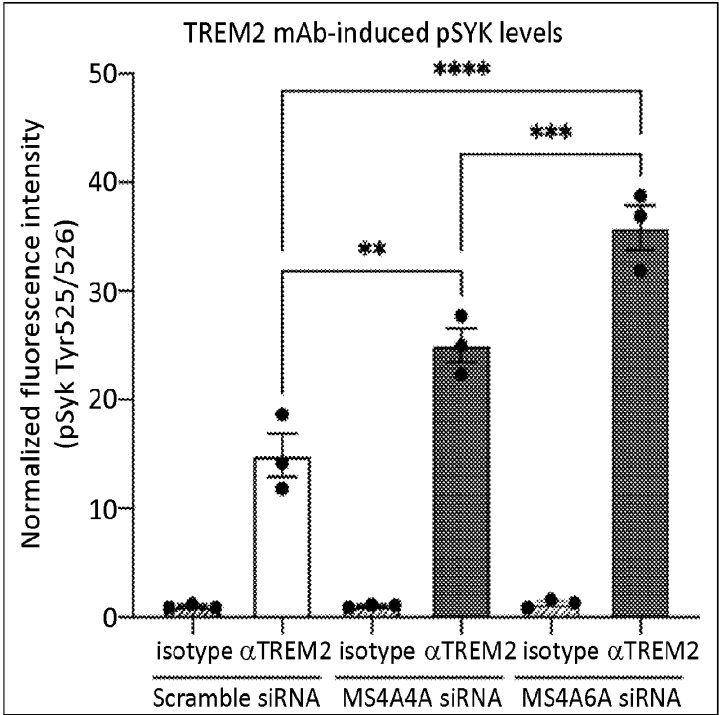


Figure 7

Trend towards decreased A β deposition in KO

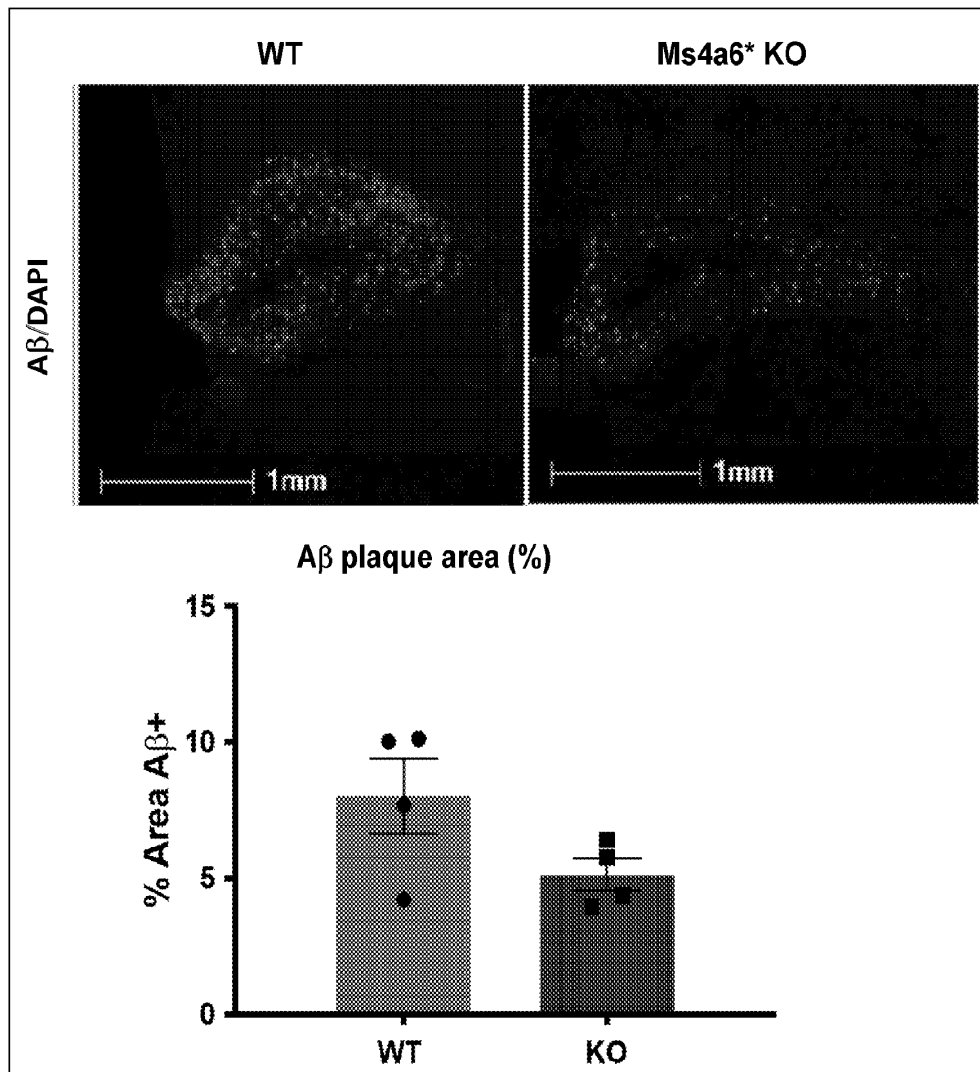


Figure 8

SUBSTITUTE SHEET (RULE 26)

Decreased clustering of microglia per plaque in KO

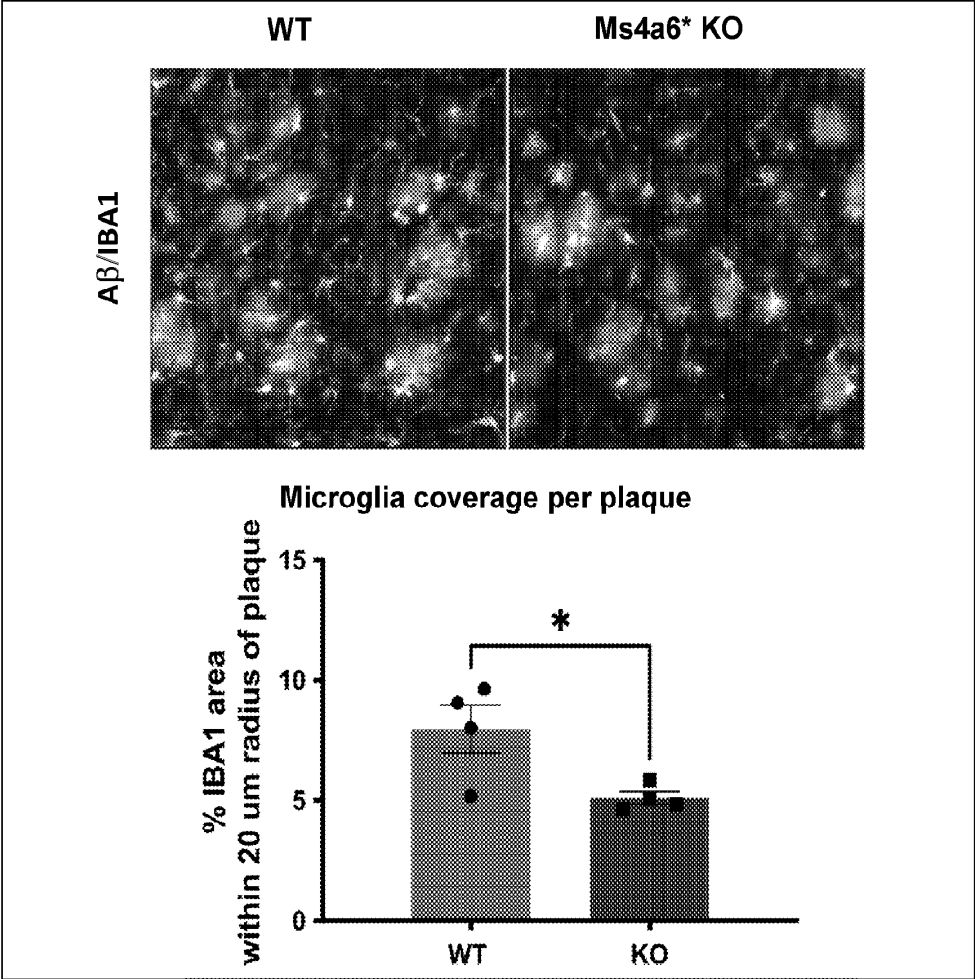


Figure 8 (cont.)

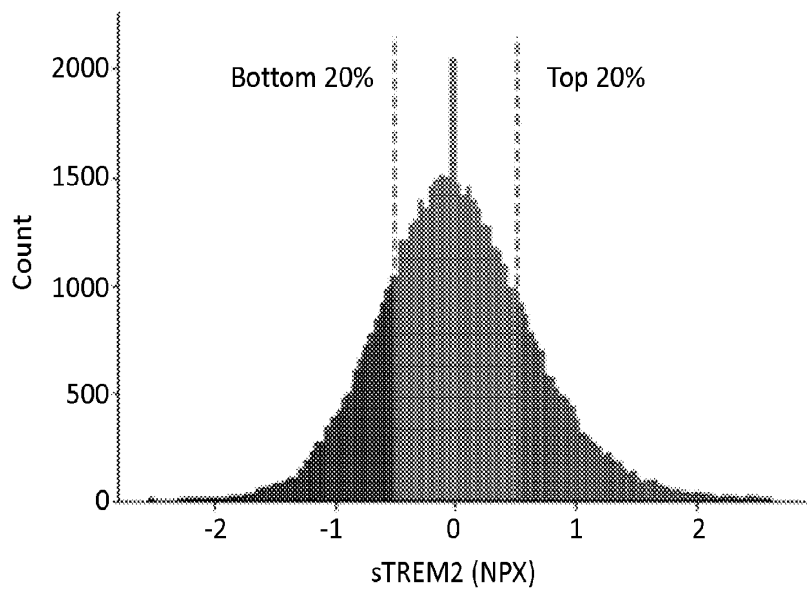
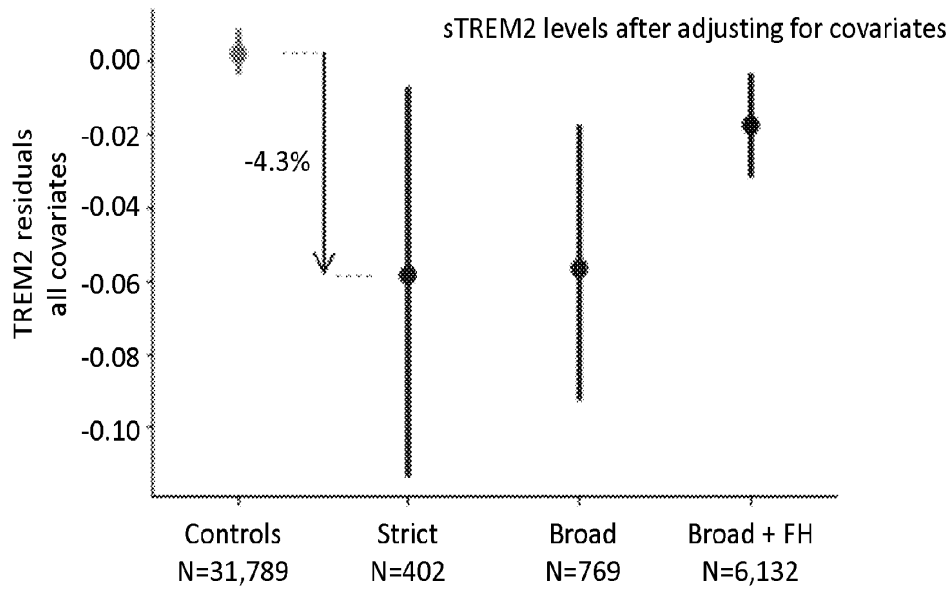


Figure 9

Alzheimer's disease (AD) definition	Odds Ratio per raw unit* increase in soluble TREM2 (95% C.I.)	P-value	N cases	N controls
AD strict	0.78 (0.64,0.94)	0.009	402	31,789
AD broad	0.80 (0.70,0.92)	0.002	769	31,789
AD broad + FH	0.93 (0.88,0.98)	0.005	6132	31,789

** A unit increase in raw NPX scale equals a two-fold difference in OLINK's detection units (2¹)

Figure 9 (cont.)

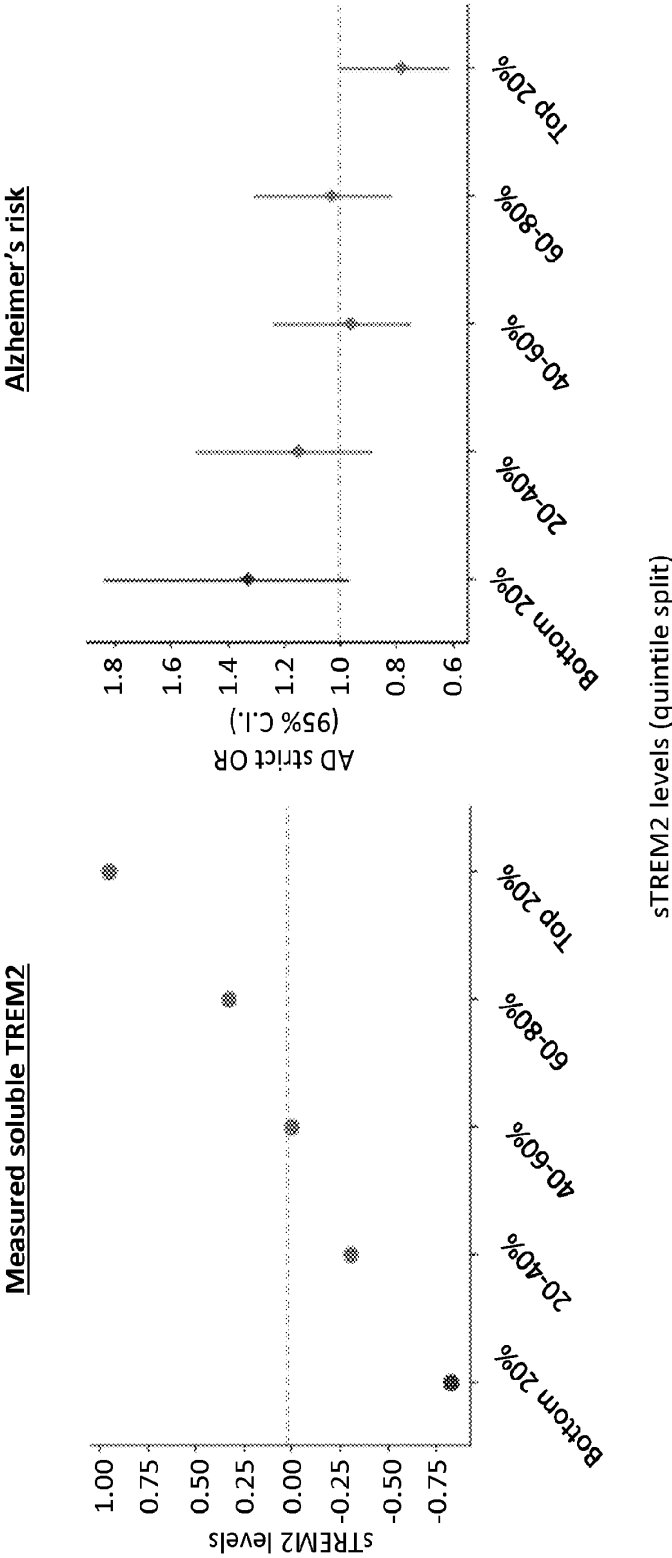


Figure 9 (cont.)

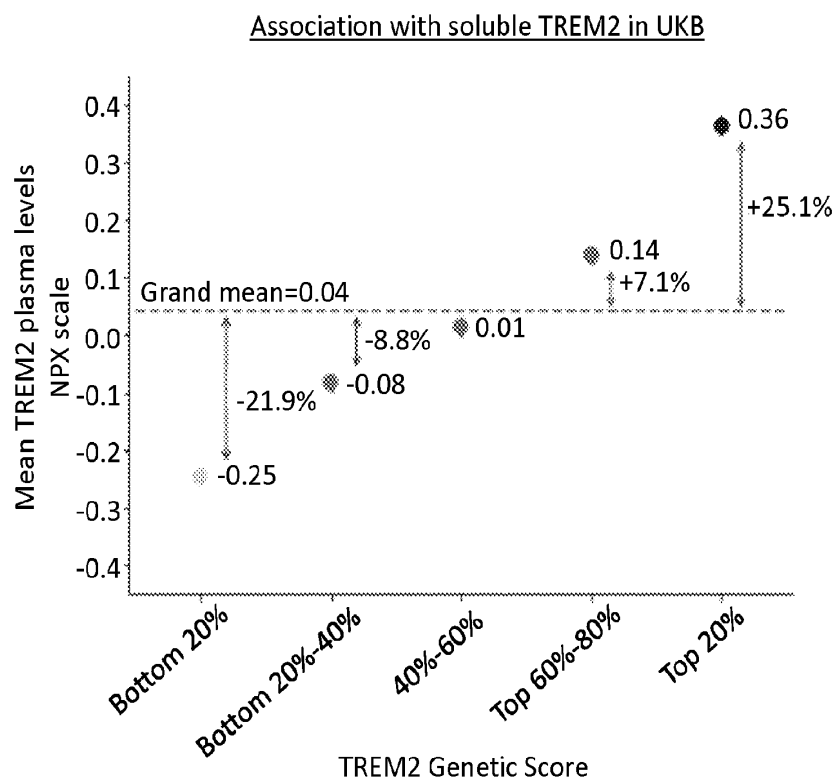
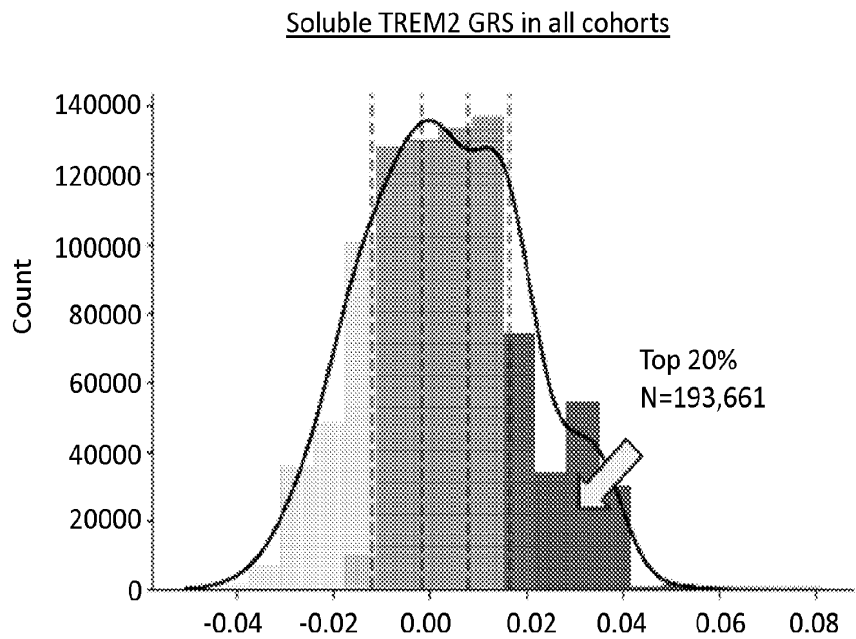


Figure 10

SUBSTITUTE SHEET (RULE 26)

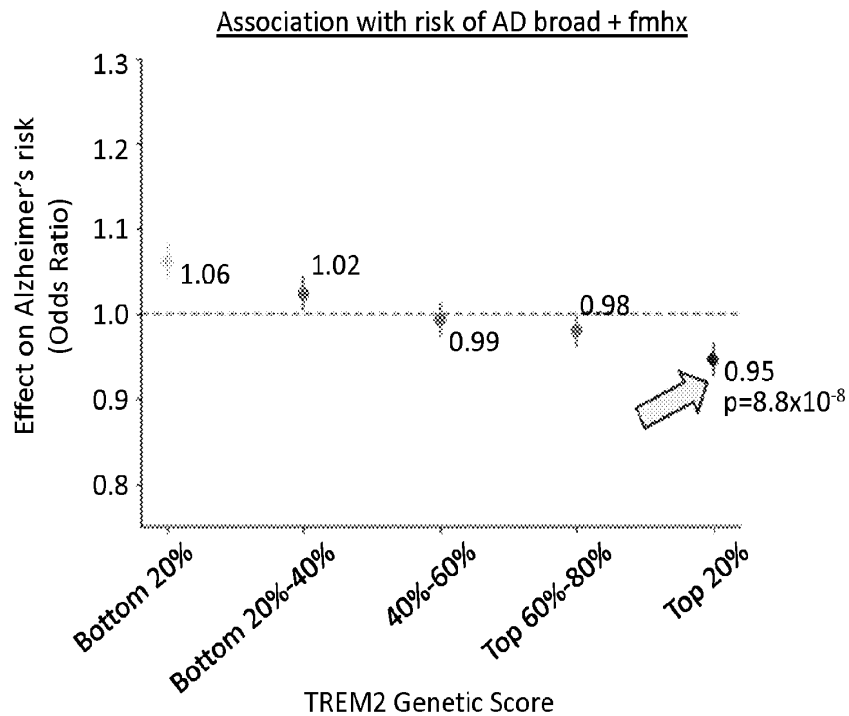
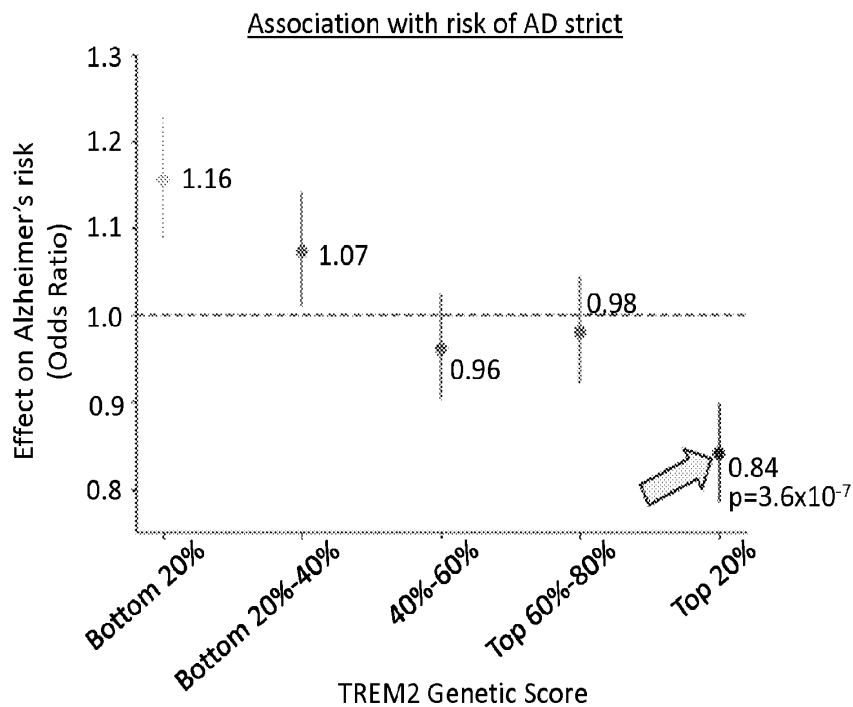


Figure 10 (cont.)

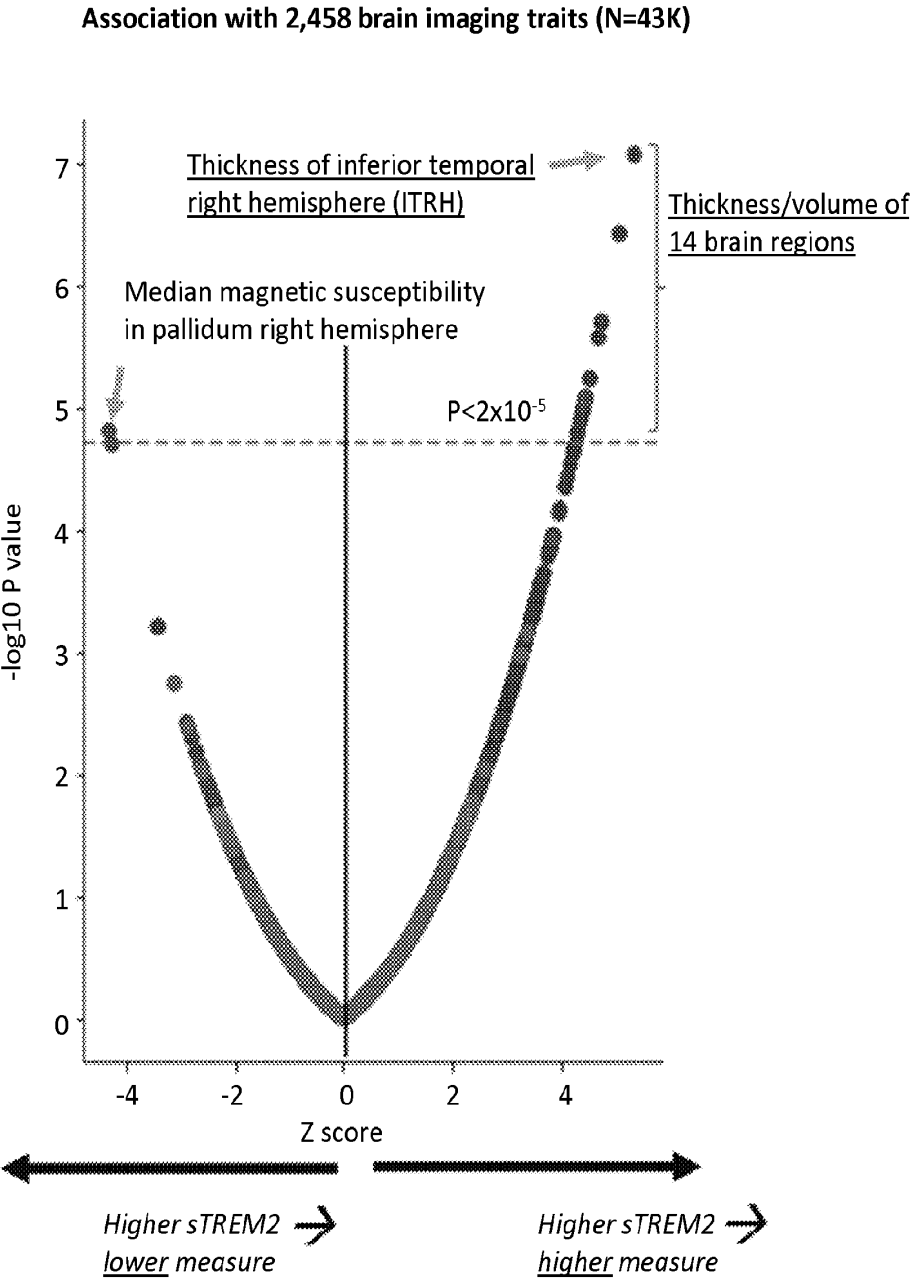


Figure 11

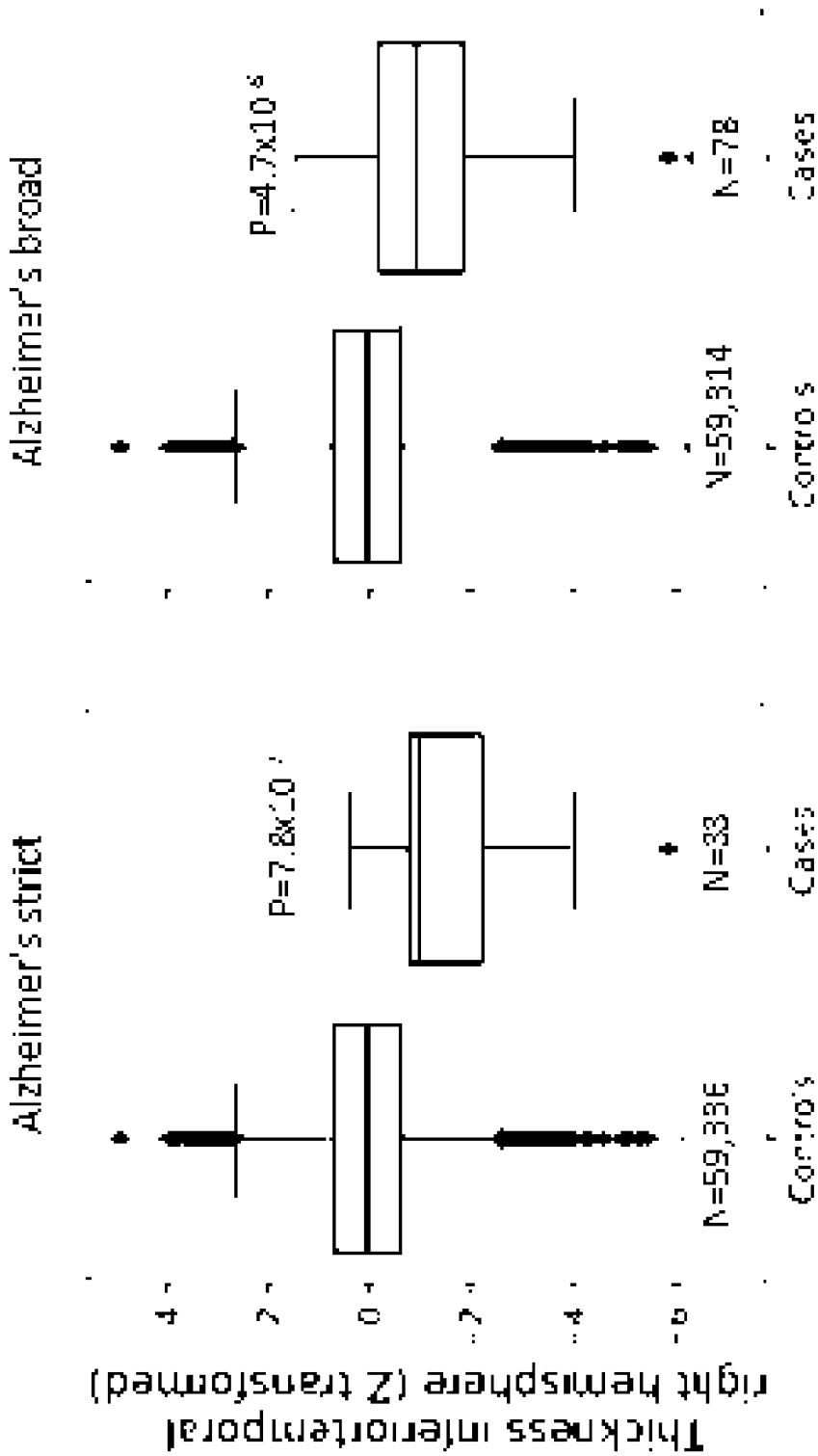


Figure 11 (cont.)

MS4A6A missense variant 11:60173126:T:A (Thr185Ser) mimicks MS4A6A pLoF effects across the proteome

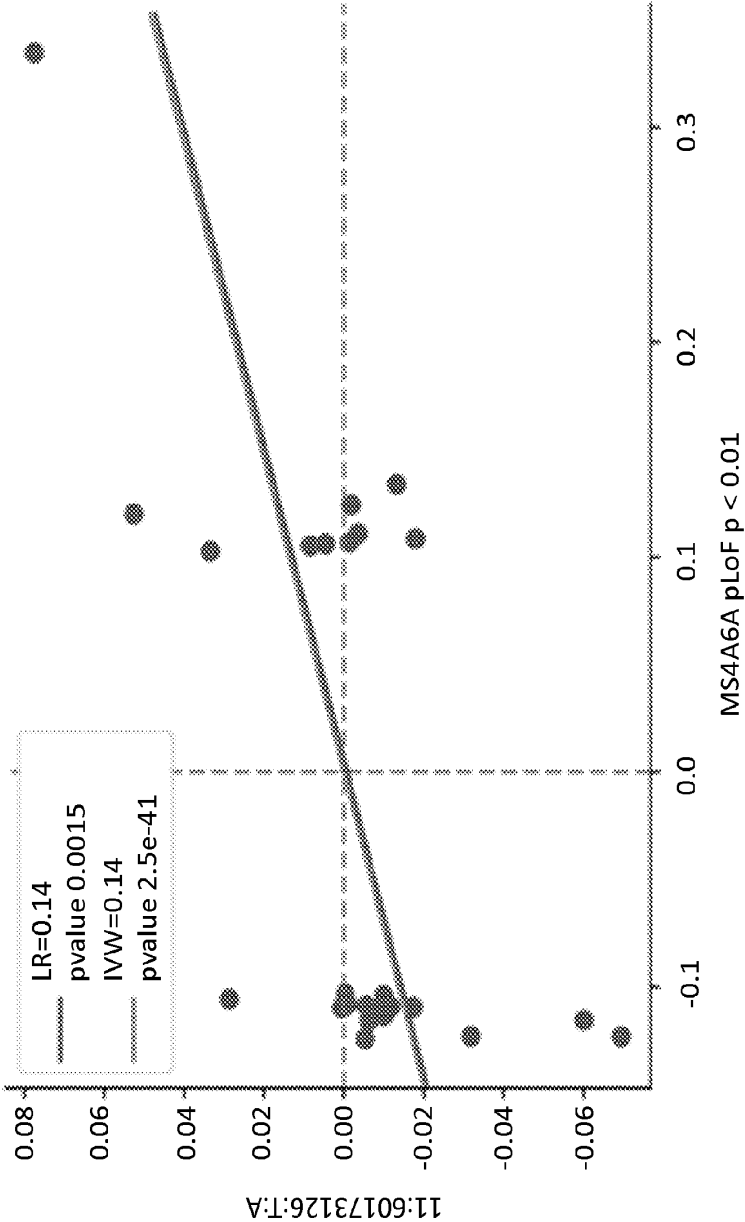
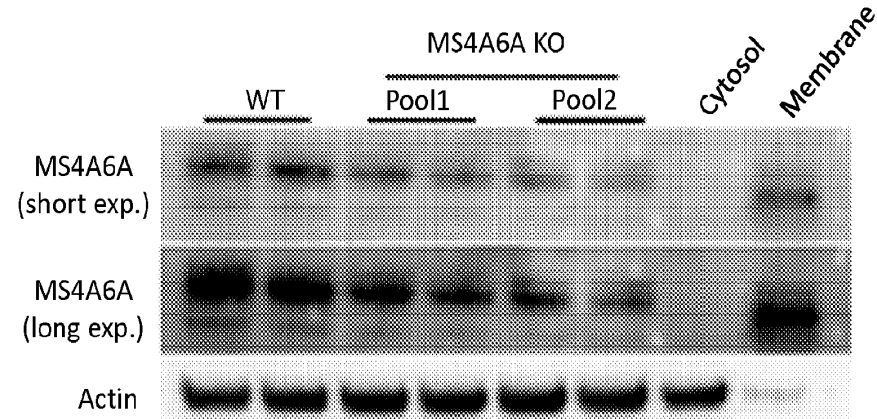


Figure 12

A)



B)

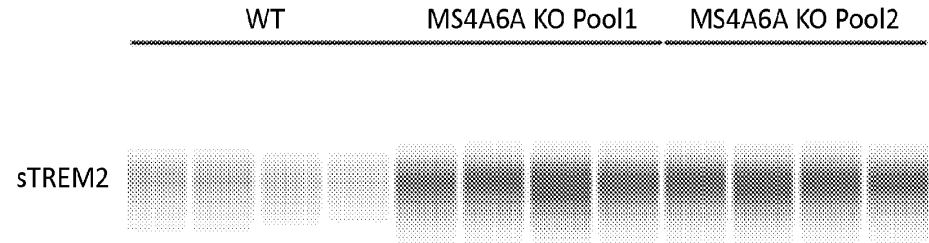
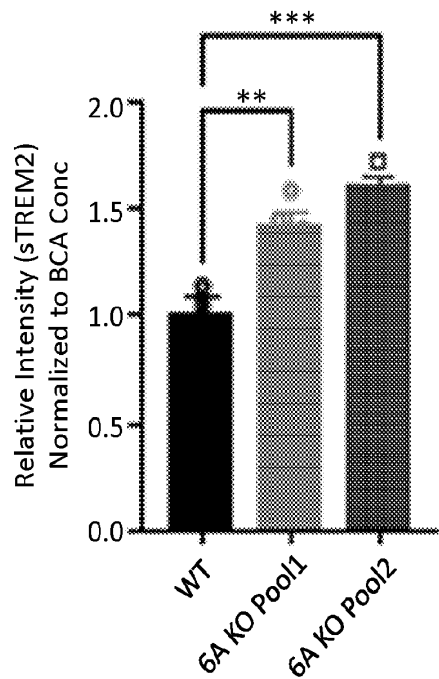


Figure 13

C)



D)

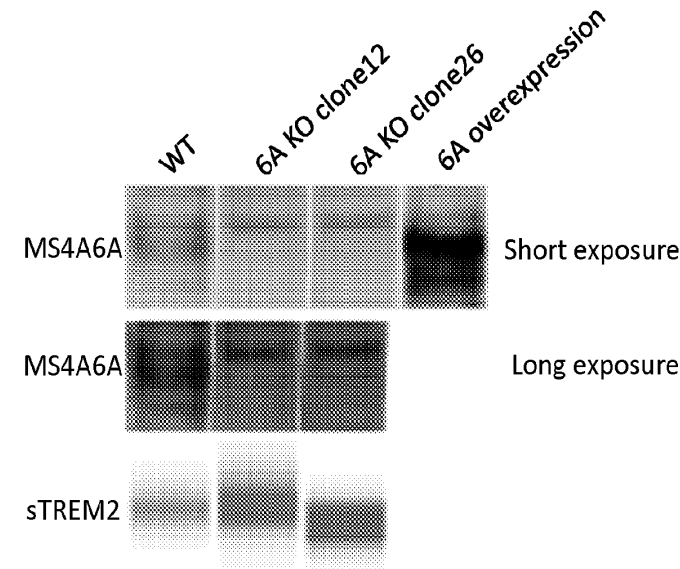


Figure 13 (cont.)