



FIG. 1

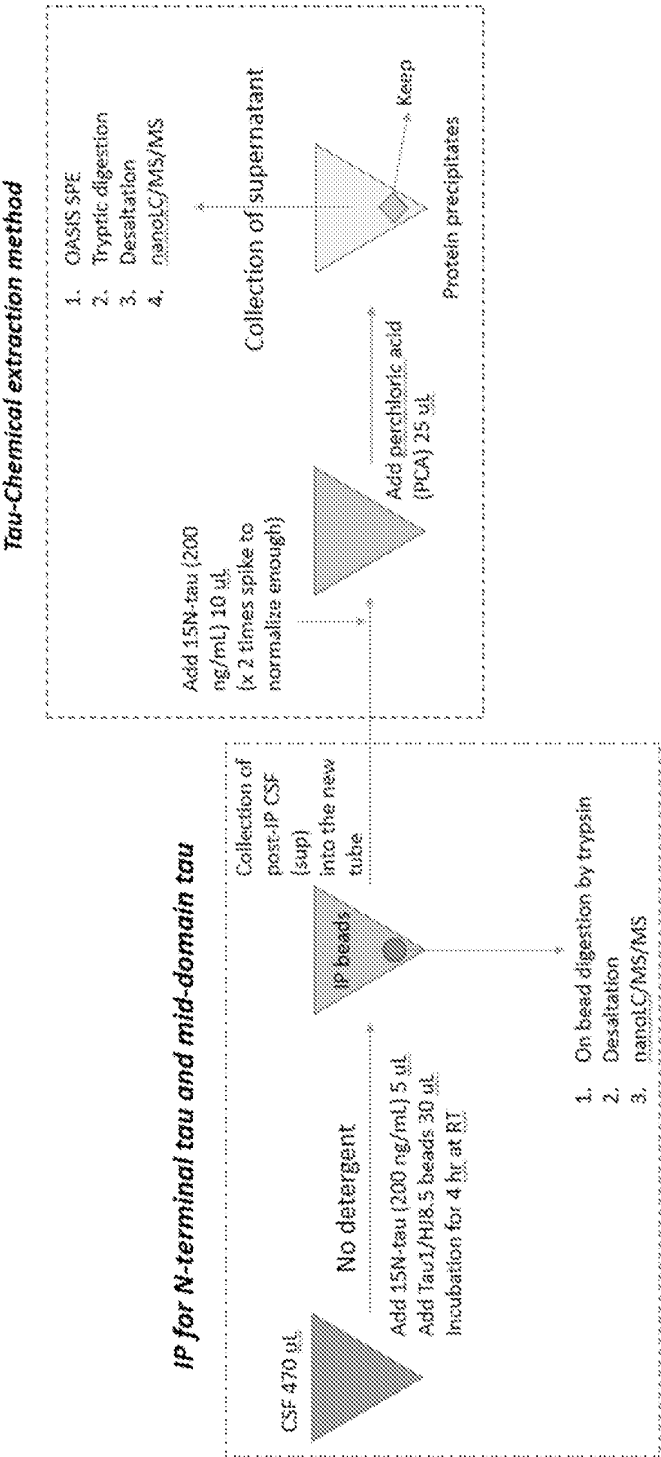


FIG. 2A

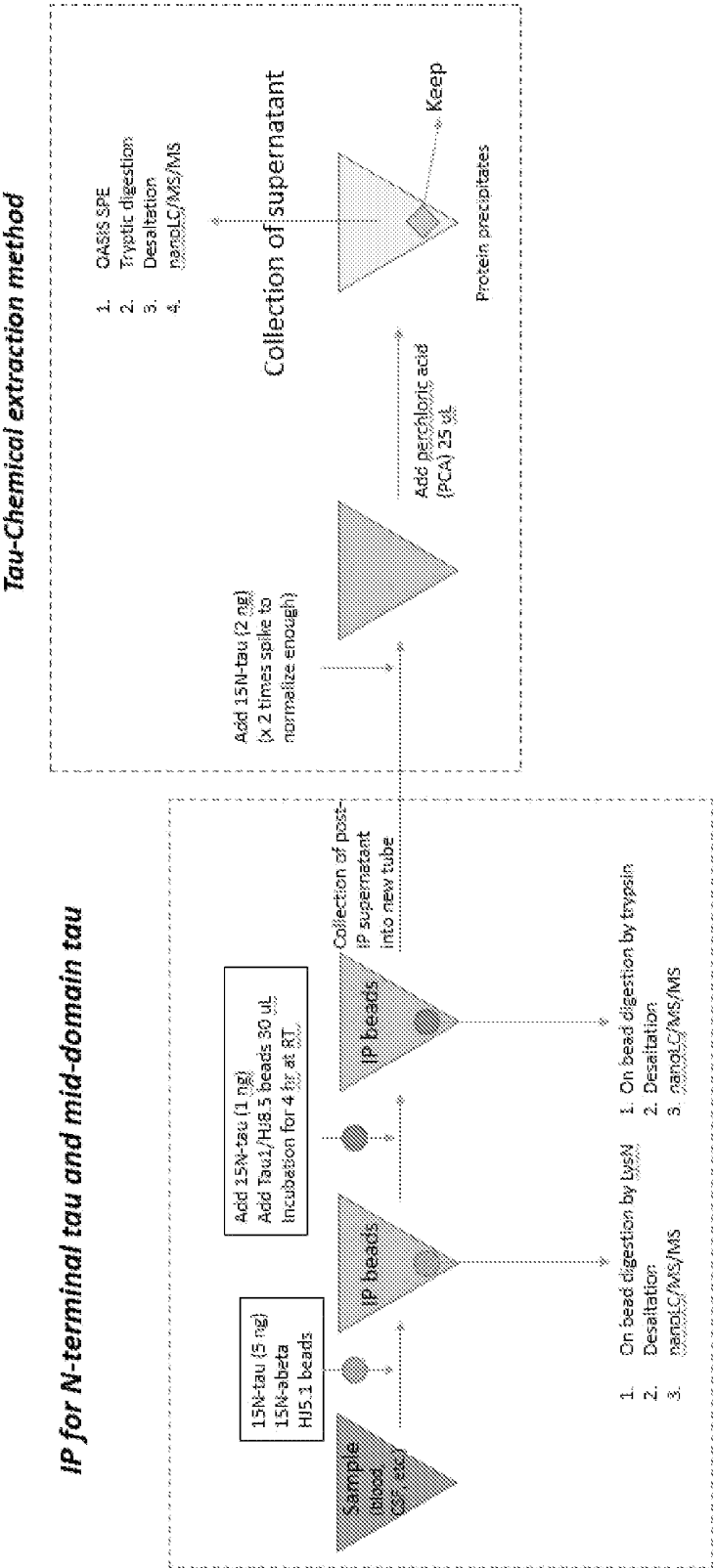


FIG. 2B

MTBR tau assay

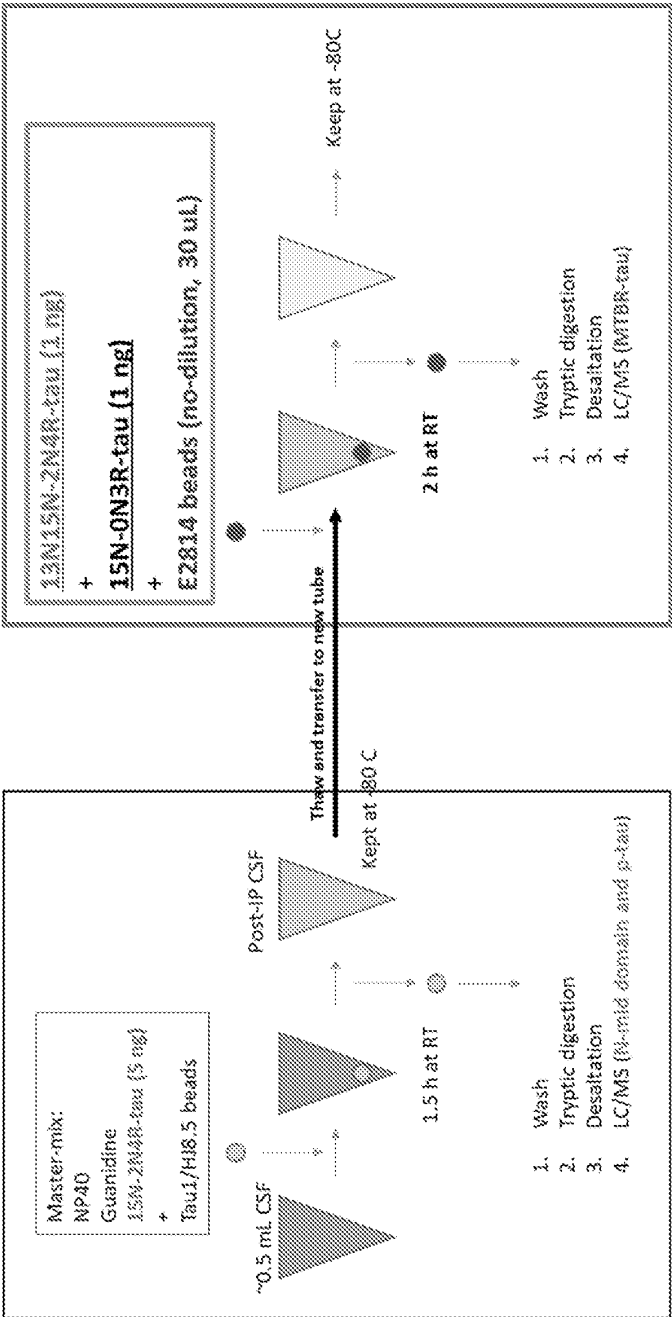


FIG. 4

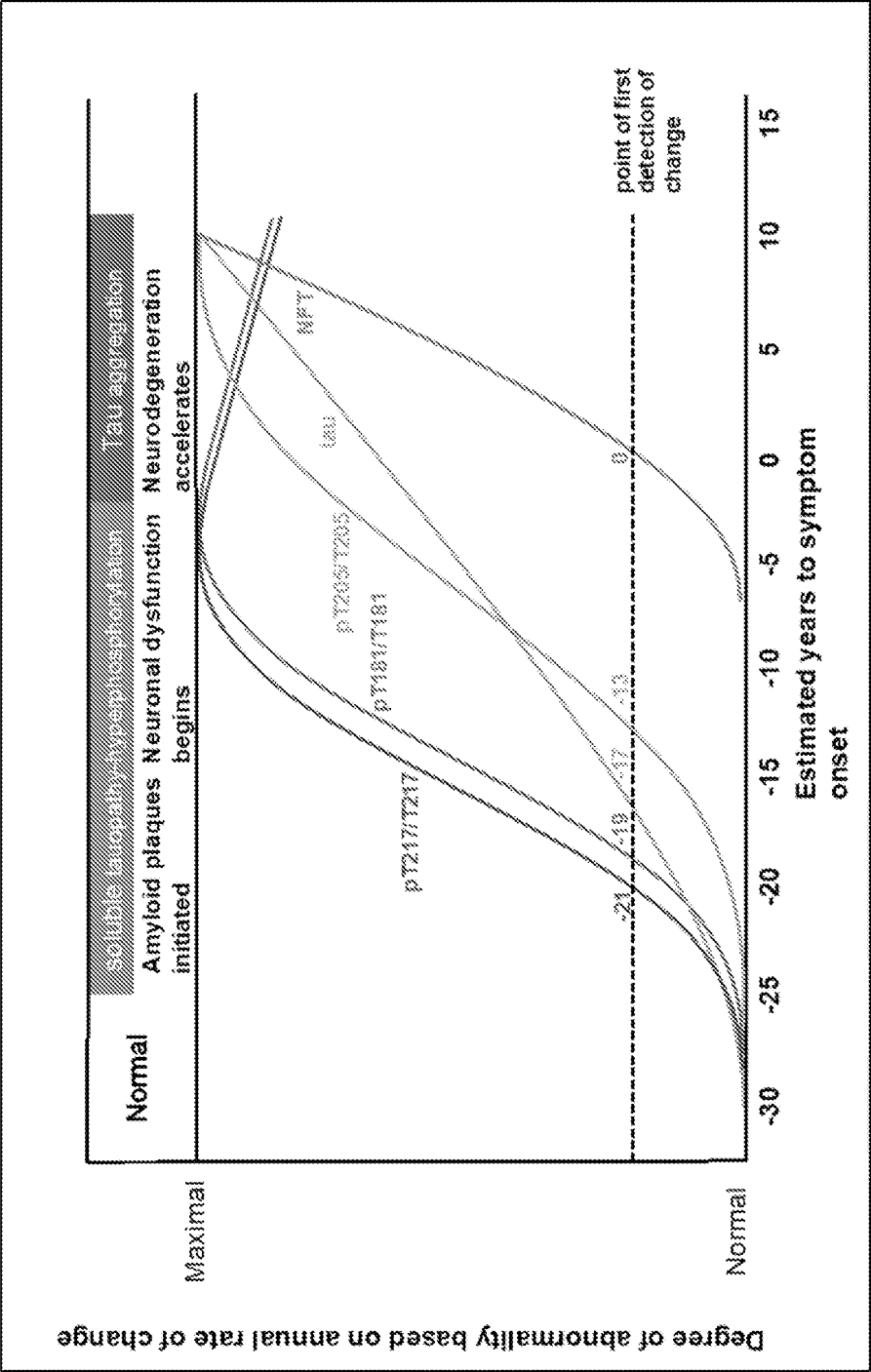


FIG. 5

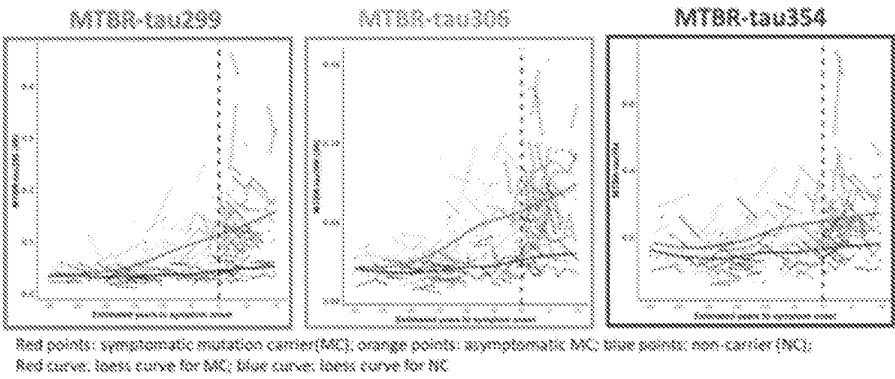


FIG. 6B

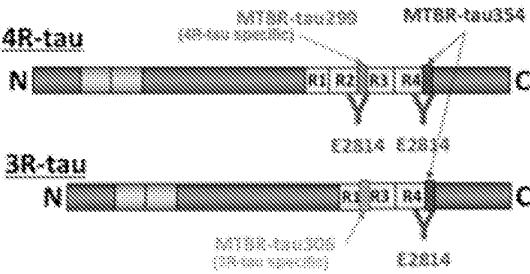


FIG. 6A

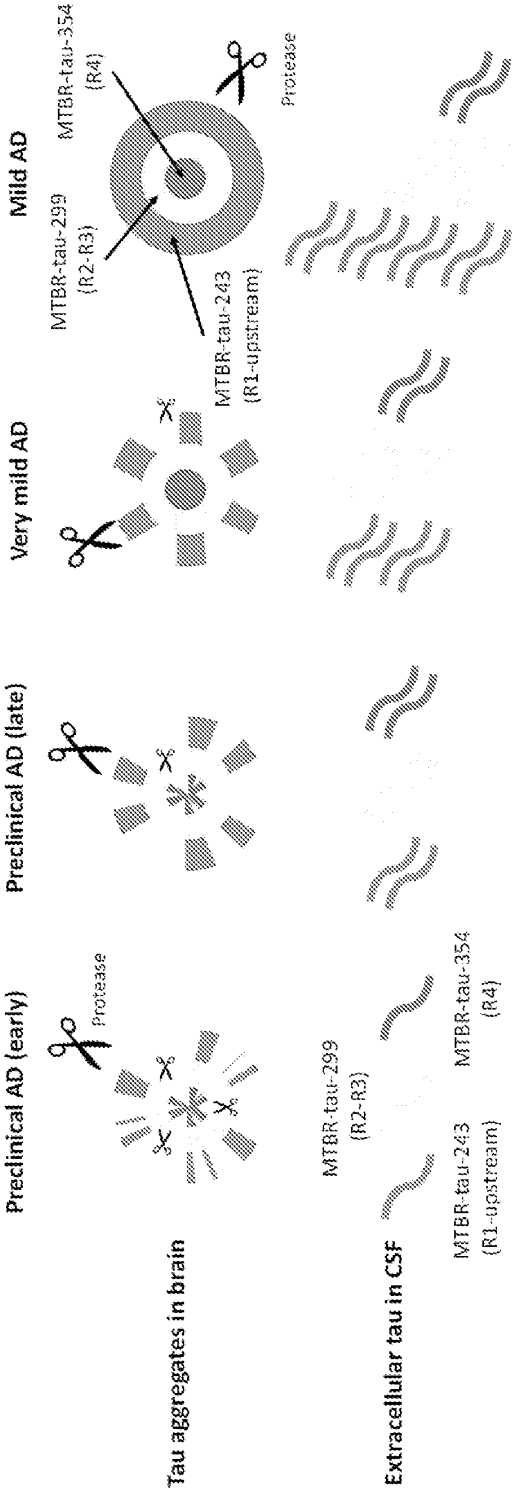


FIG. 7

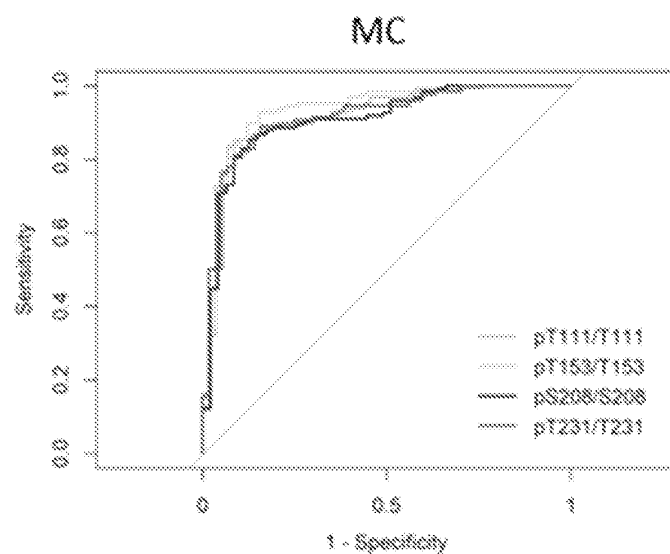


FIG. 8A

Both MC and NC

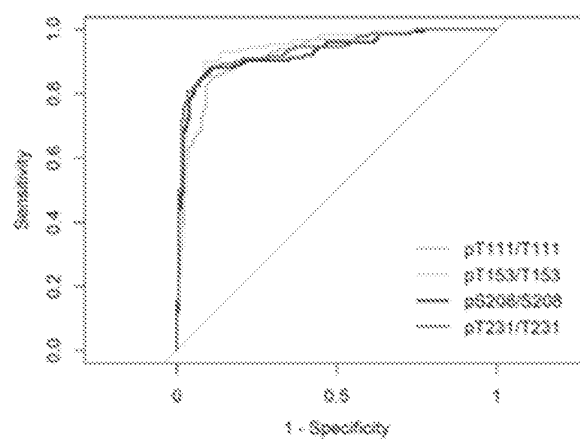


FIG. 8B

ROC and AUC of pTau species in classifying amyloid
PET status (positive, negative)

Variable	AUC	95% Confidence Interval
<i>MC Only</i>		
pT111/T111	0.92	(0.87, 0.96)
pT153/T153	0.93	(0.89, 0.98)
pS208/S208	0.91	(0.86, 0.96)
pT231/T231	0.91	(0.87, 0.96)
<i>MC and NC</i>		
pT111/T111	0.92	(0.89, 0.95)
pT153/T153	0.95	(0.92, 0.97)
pS208/S208	0.93	(0.90, 0.96)
pT231/T231	0.94	(0.91, 0.96)

FIG. 8C

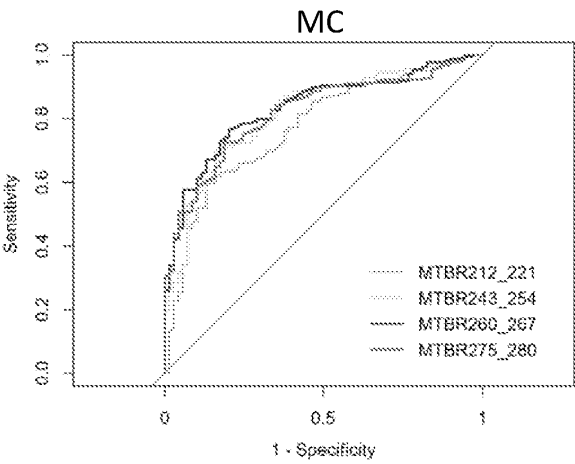


FIG. 9A

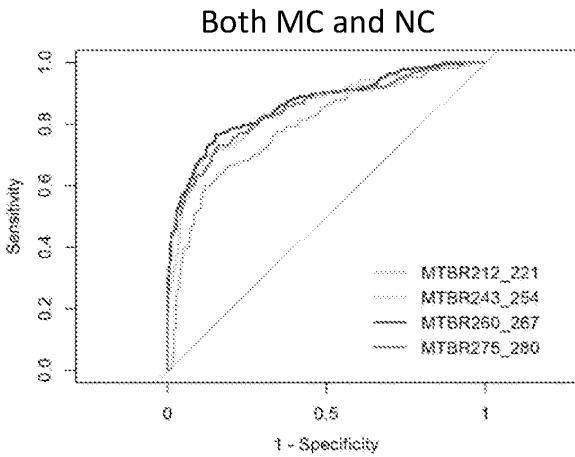


FIG. 9B

ROC and AUC of MTBR-tau species in classifying amyloid PET status (positive, negative)

Variable	AUC	95% Confidence Interval
<i>MC Only</i>		
MTBR212_221	0.77	(0.71, 0.83)
MTBR243_254	0.82	(0.76, 0.87)
MTBR260_267	0.83	(0.78, 0.88)
MTBR275_280	0.82	(0.77, 0.87)
<i>MC and NC</i>		
MTBR212_211	0.79	(0.75, 0.83)
MTBR243_254	0.85	(0.81, 0.88)
MTBR260_267	0.86	(0.83, 0.90)
MTBR275_280	0.85	(0.81, 0.88)

FIG. 9C

MC

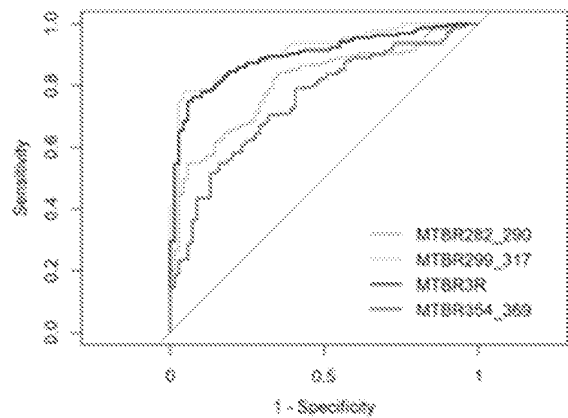


FIG. 10A

Both MC and NC

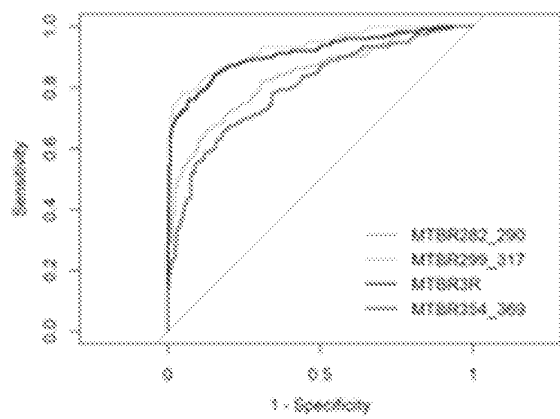


FIG. 10B

ROC and AUC of MTBR-tau species in classifying amyloid PET status (positive, negative)

Variable	AUC	95% Confidence Interval
MC Only		
MTBR282_290	0.81	(0.75, 0.86)
MTBR299_317	0.91	(0.87, 0.94)
MTBR3R	0.80	(0.86, 0.93)
MTBR354_369	0.75	(0.69, 0.81)
MC and NC		
MTBR282_290	0.84	(0.80, 0.87)
MTBR299_317	0.93	(0.91, 0.95)
MTBR3R	0.91	(0.88, 0.94)
MTBR354_369	0.80	(0.76, 0.84)

FIG. 10C

12/75
MC

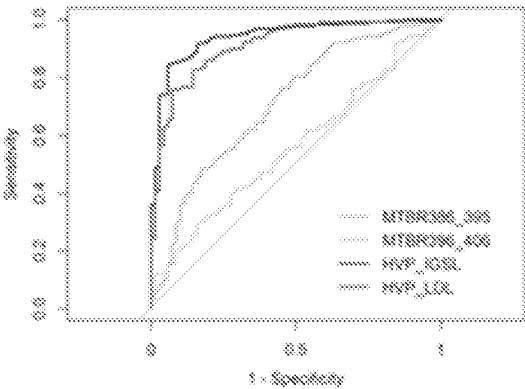


FIG. 11A

Both MC and NC

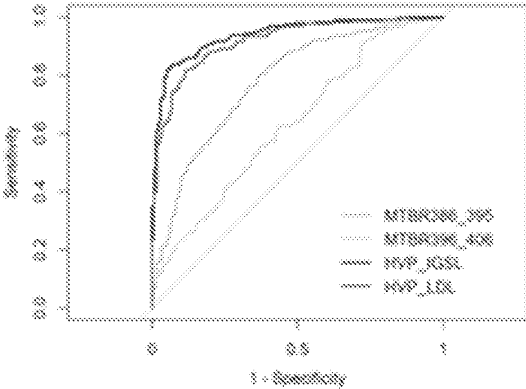


FIG. 11B

ROC and AUC of MTBR-tau species in classifying amyloid PET status (positive, negative)

Variable	AUC	95% Confidence Interval
MC Only		
MTBR386_395	0.71	(0.64, 0.78)
MTBR396_406	0.56	(0.49, 0.64)
HVP_IGSL	0.94	(0.91, 0.97)
HVP_LDL	0.91	(0.87, 0.95)
MC and NC		
MTBR386_395	0.78	(0.74, 0.82)
MTBR396_406	0.63	(0.58, 0.68)
HVP_IGSL	0.94	(0.92, 0.96)
HVP_LDL	0.92	(0.89, 0.94)

FIG. 11C

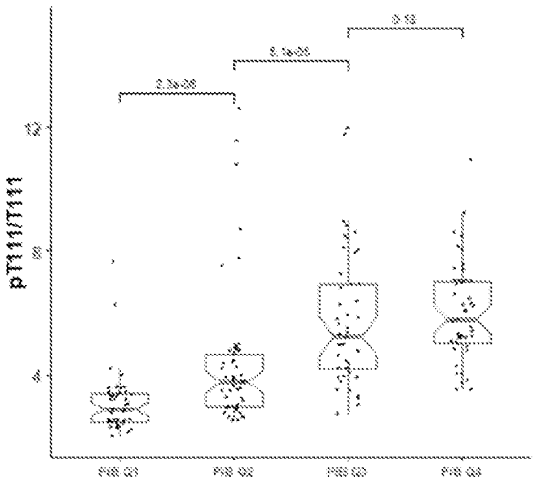


FIG. 12A

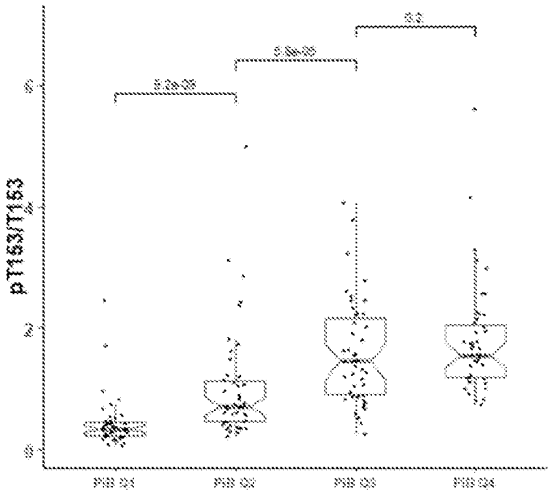


FIG. 12B

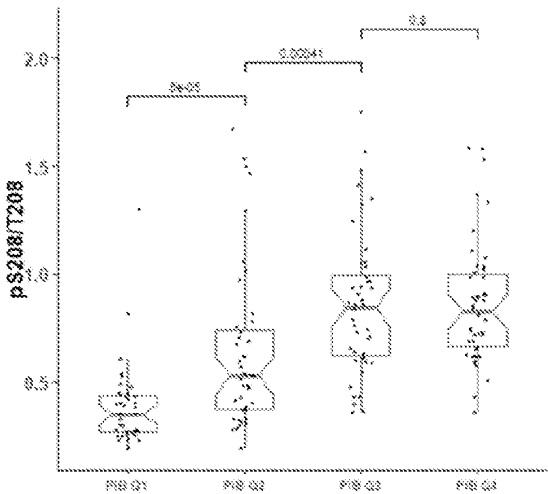


FIG. 12C

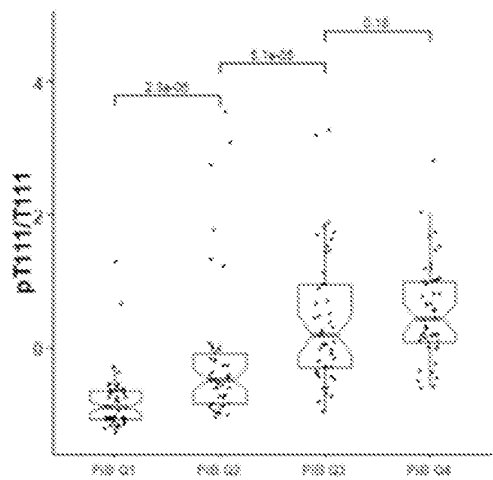


FIG. 12D

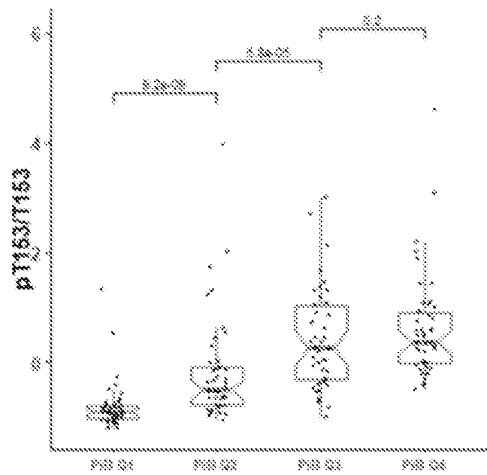


FIG. 12E

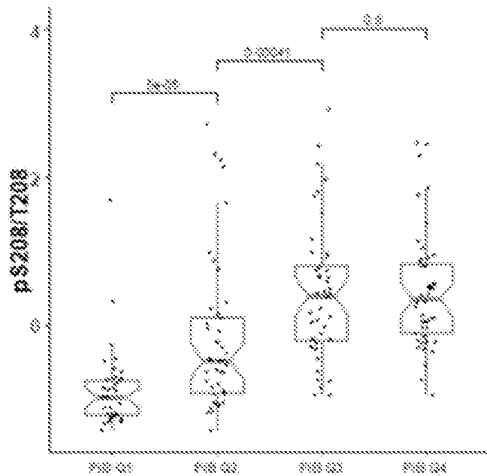


FIG. 12F

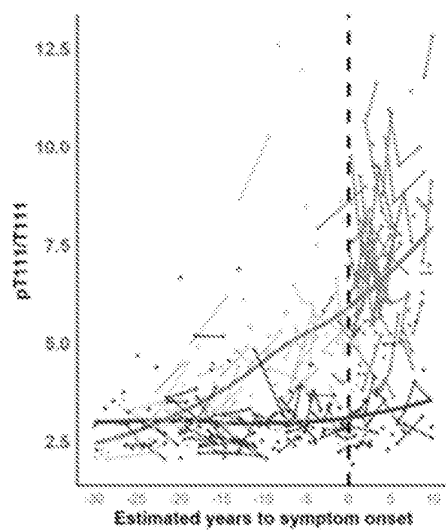


FIG. 13A

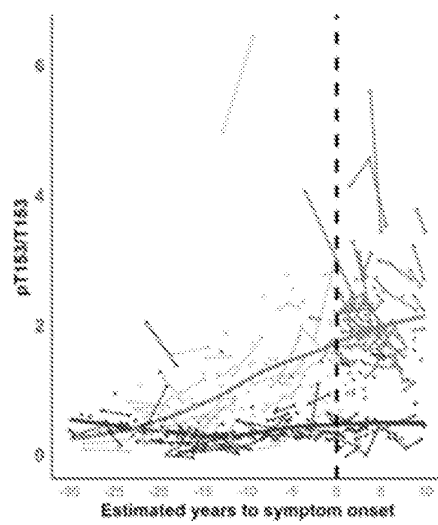


FIG. 13B

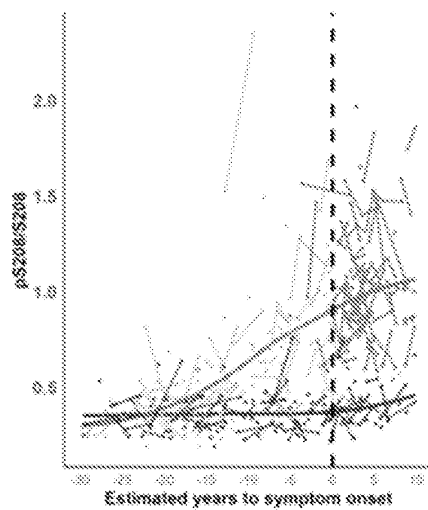


FIG. 13C

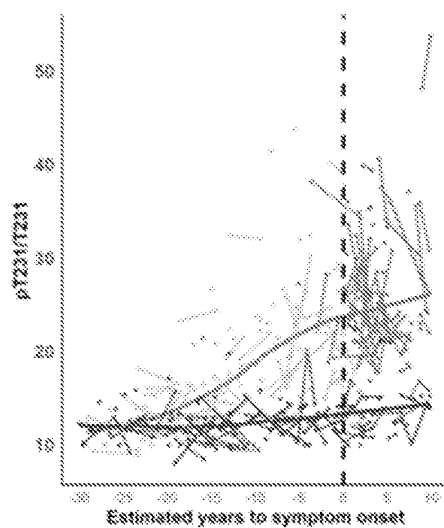


FIG. 13D

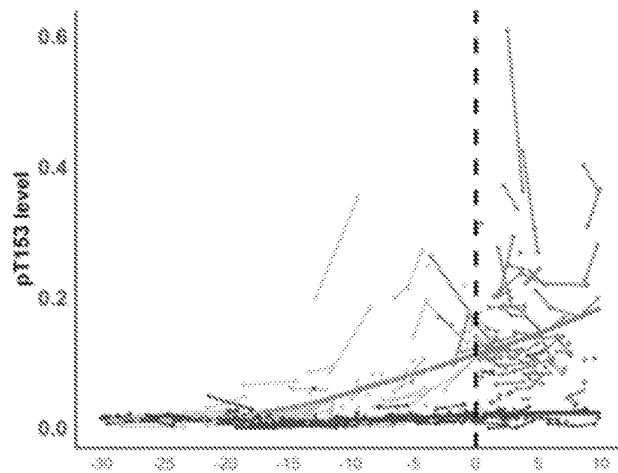


FIG. 13E

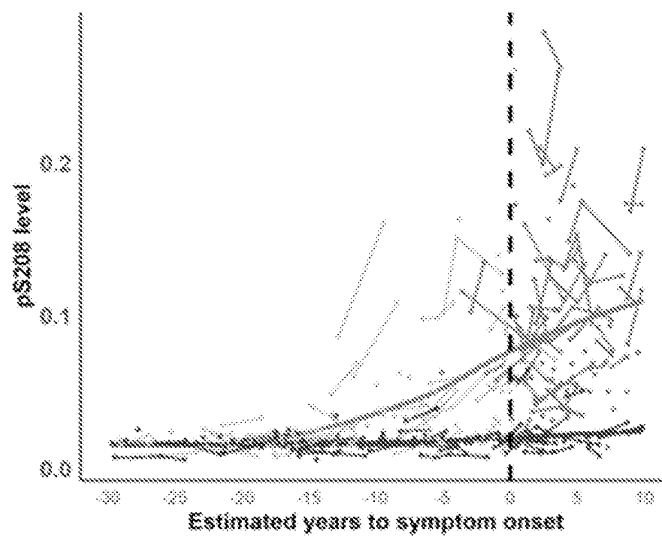


FIG. 13F

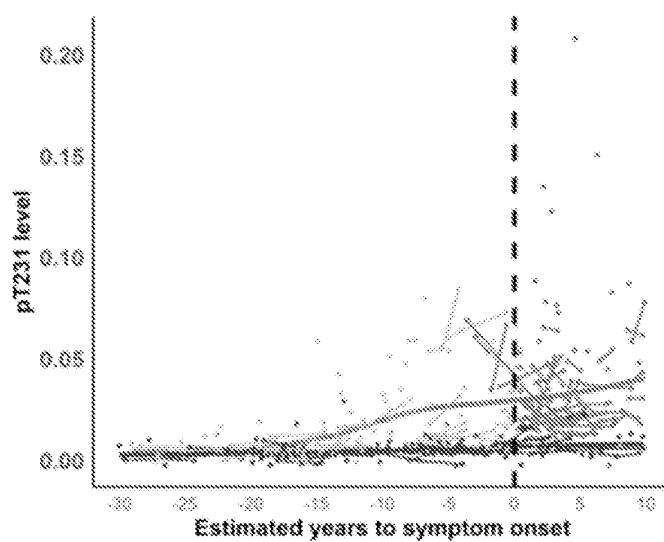


FIG. 13G

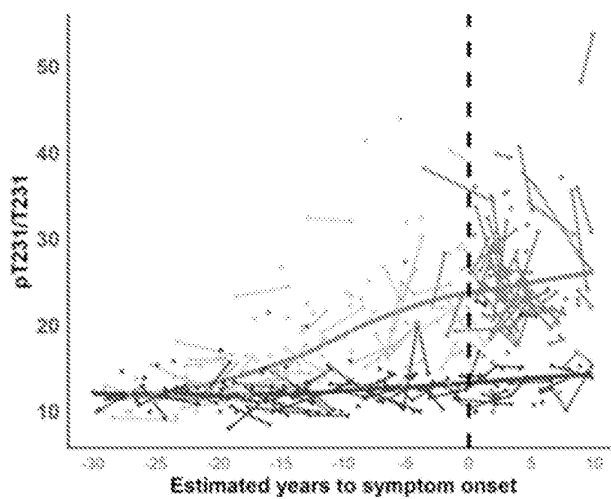


FIG. 13H

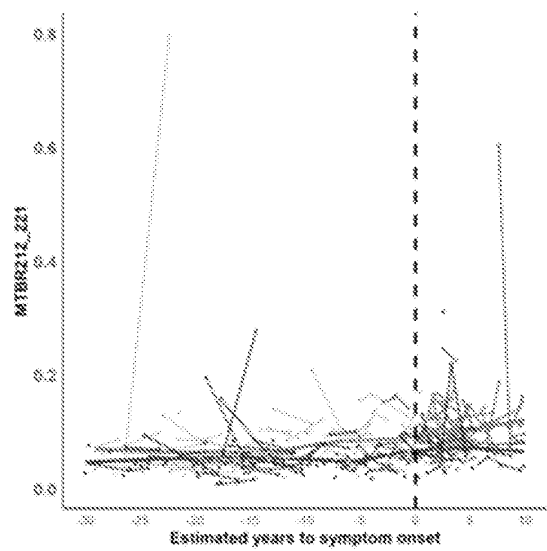


FIG. 13I

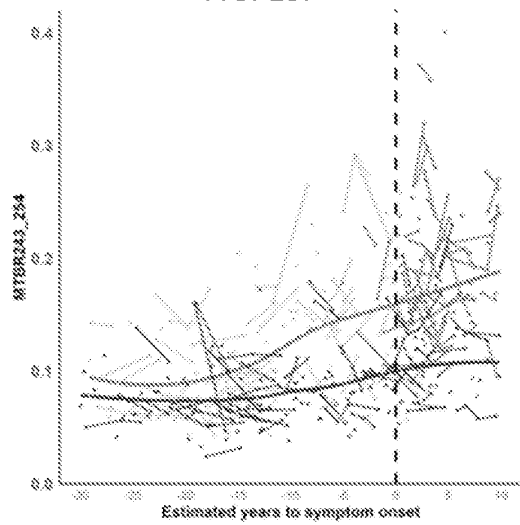


FIG. 13J

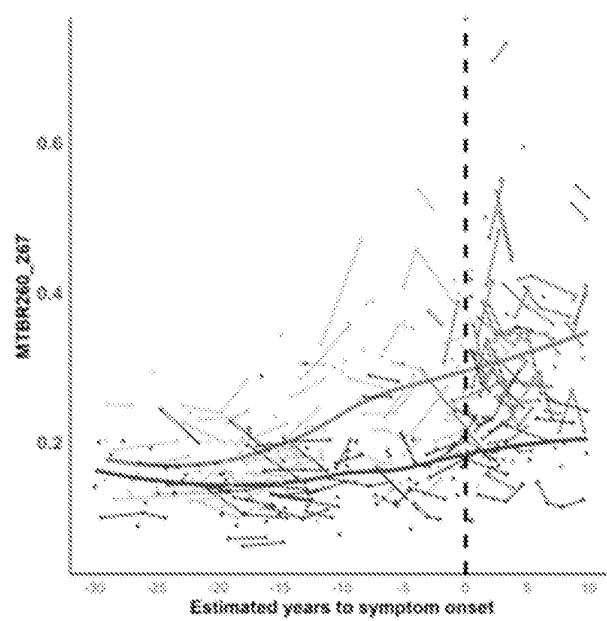


FIG. 13K

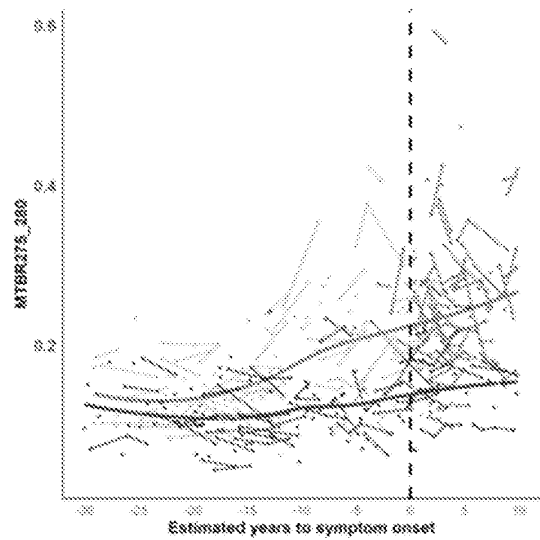


FIG. 13L

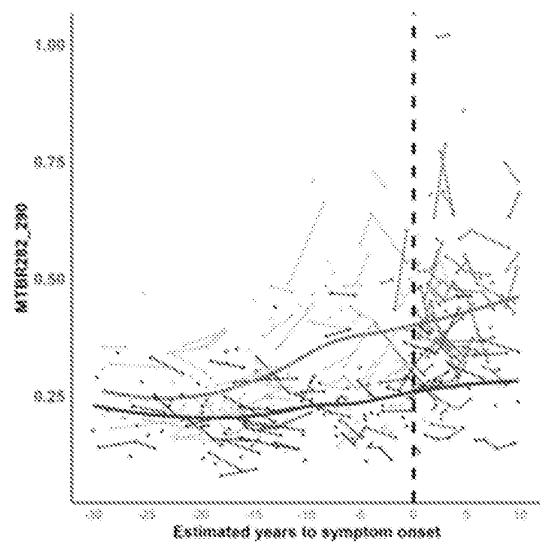


FIG. 13M

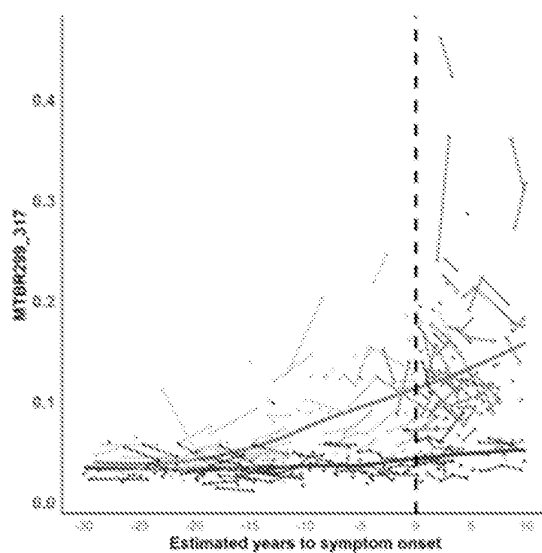


FIG. 13N

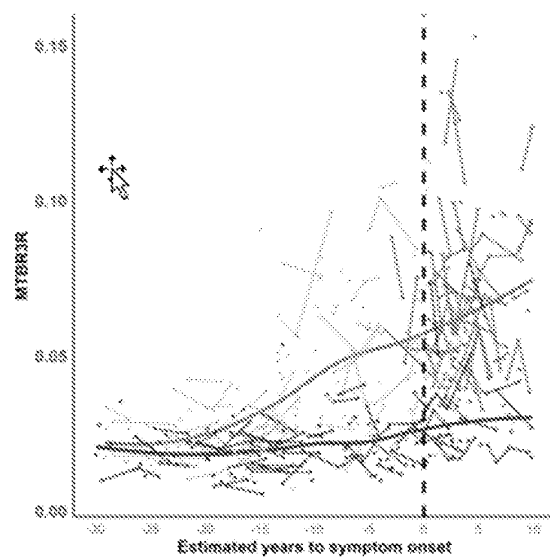


FIG. 13O

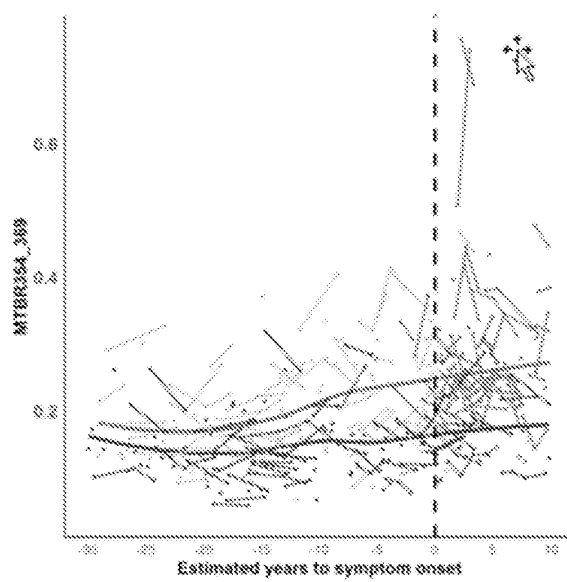


FIG. 13P

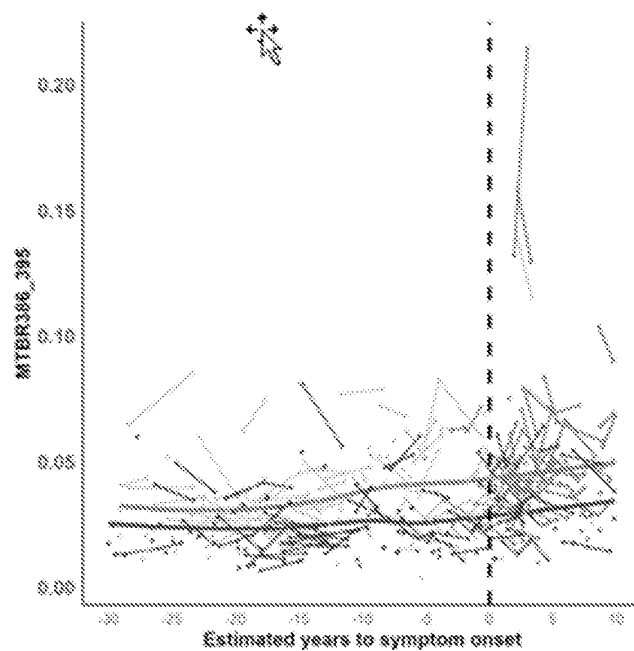


FIG. 13Q

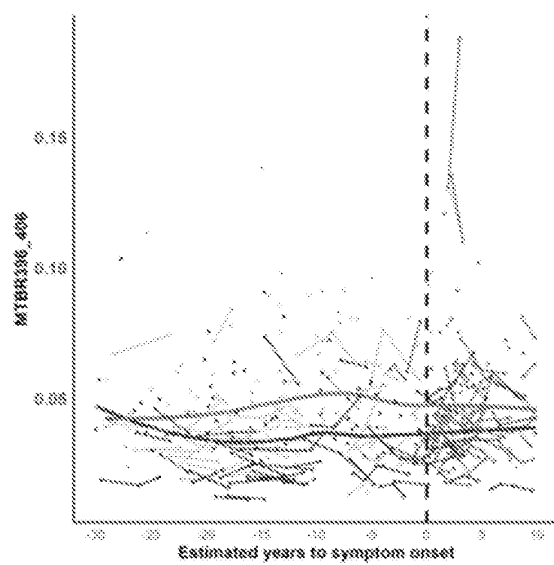


FIG. 13R

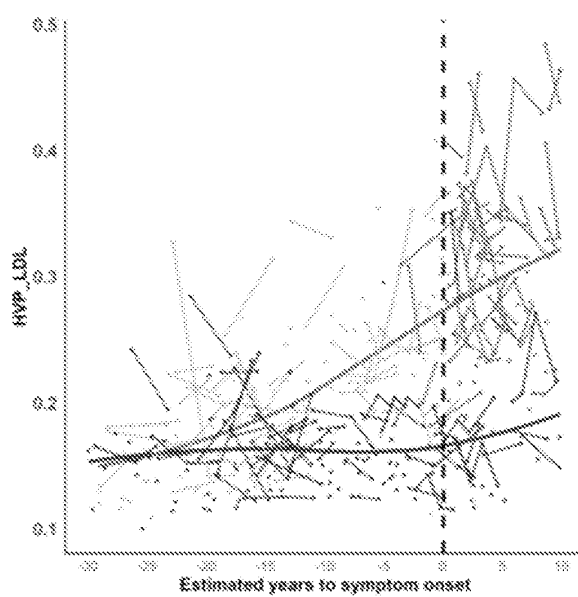


FIG. 13S

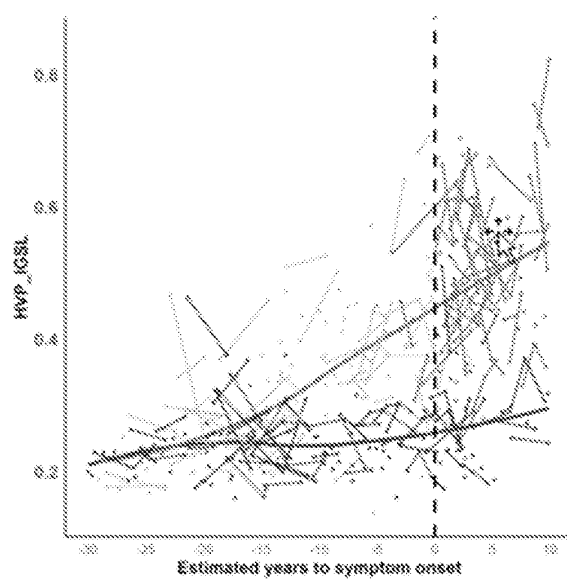


FIG. 13T

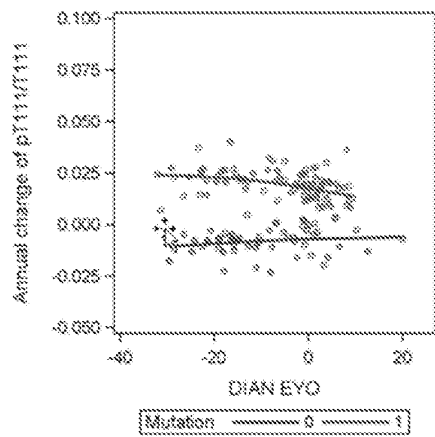


FIG. 14A

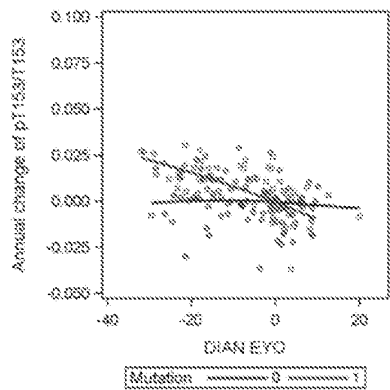


FIG. 14B

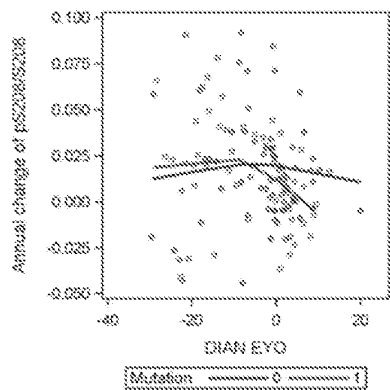


FIG. 14C

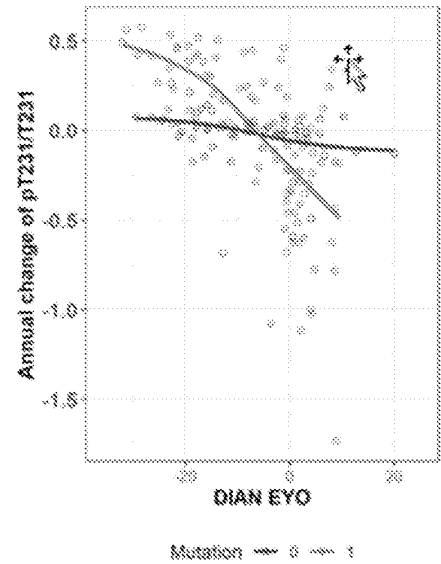


FIG. 14D

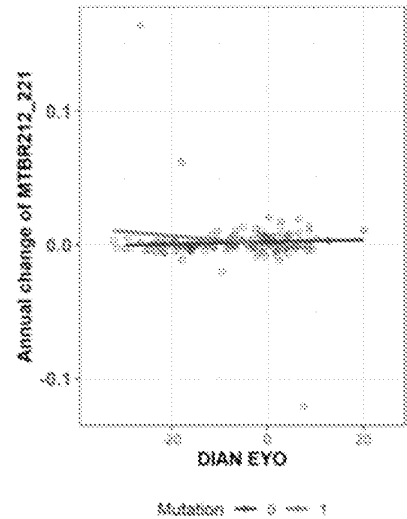


FIG. 14E

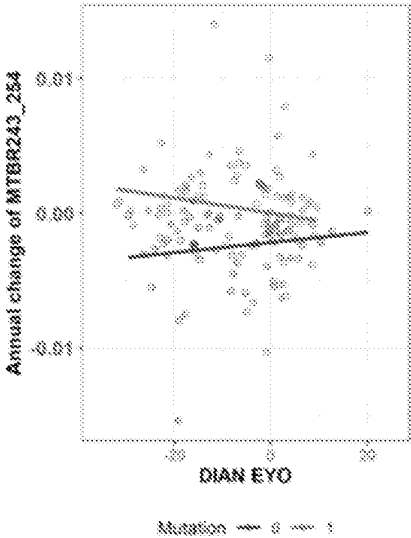


FIG. 14F

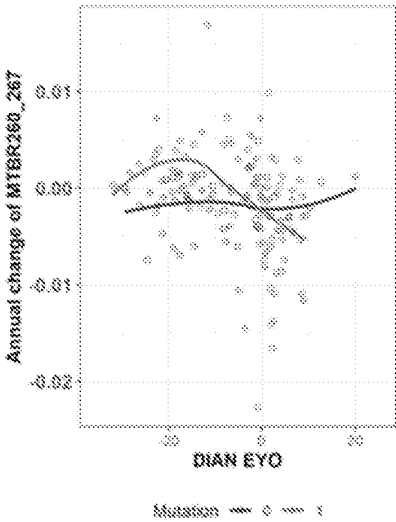


FIG. 14G

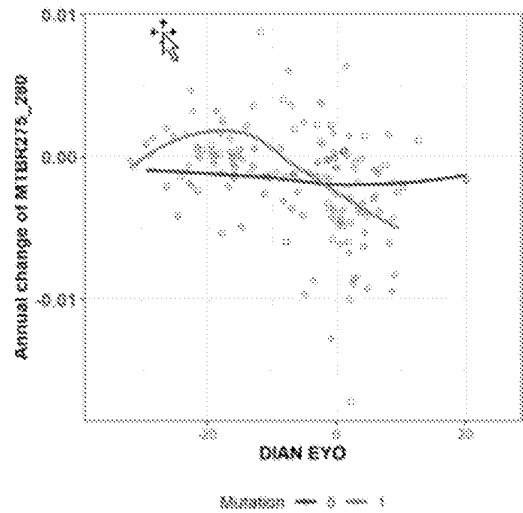


FIG. 14H

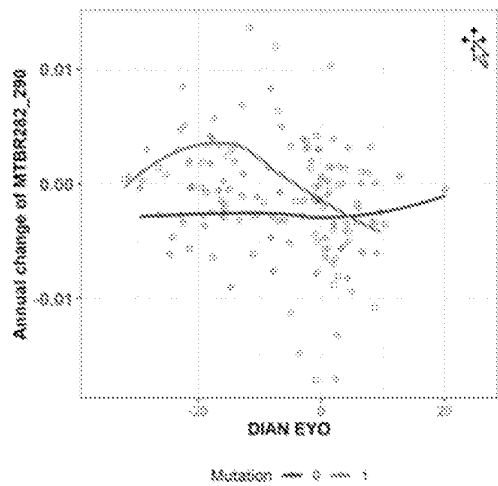


FIG. 14I

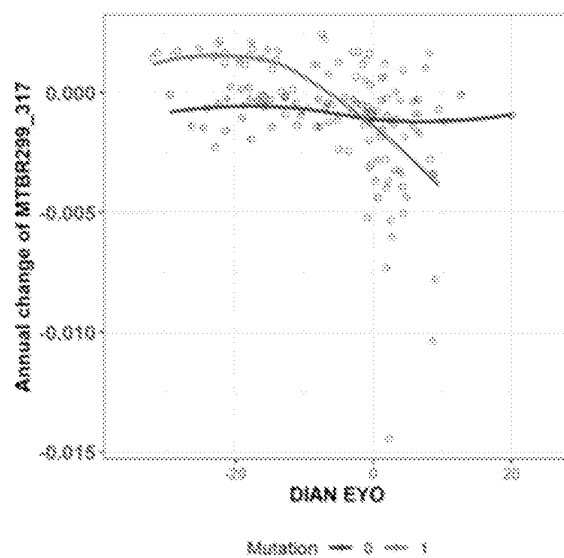


FIG. 14J

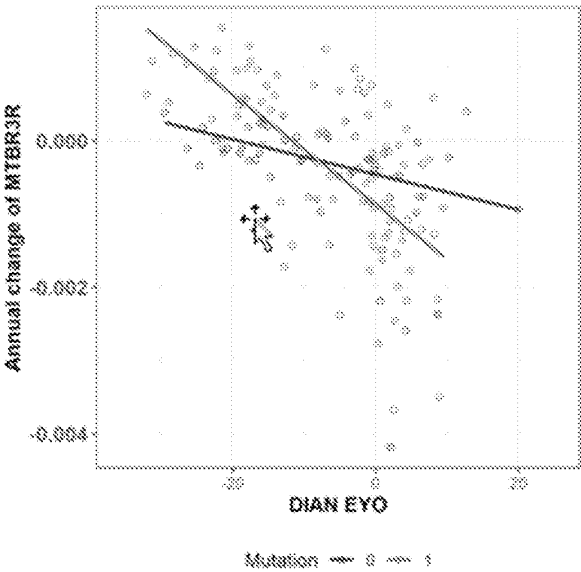


FIG. 14K

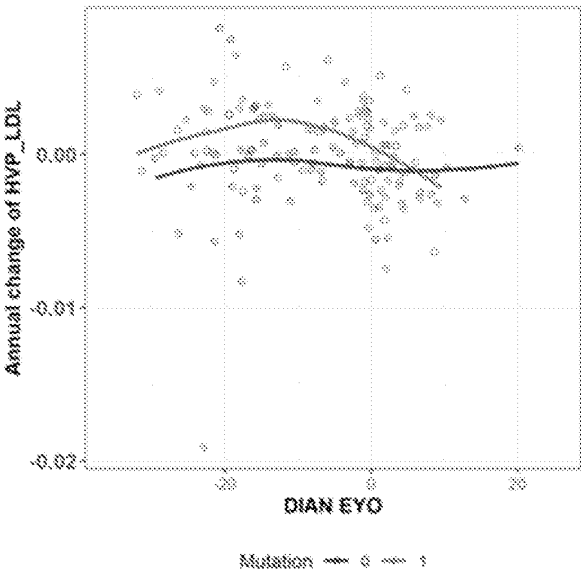


FIG. 14L

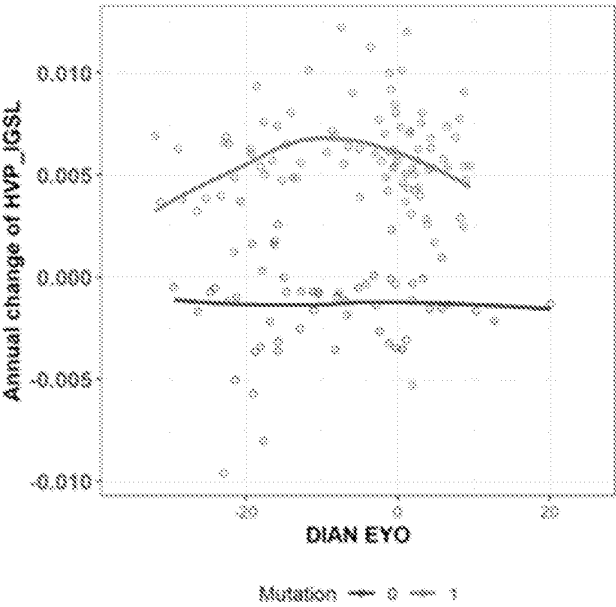


FIG. 14M

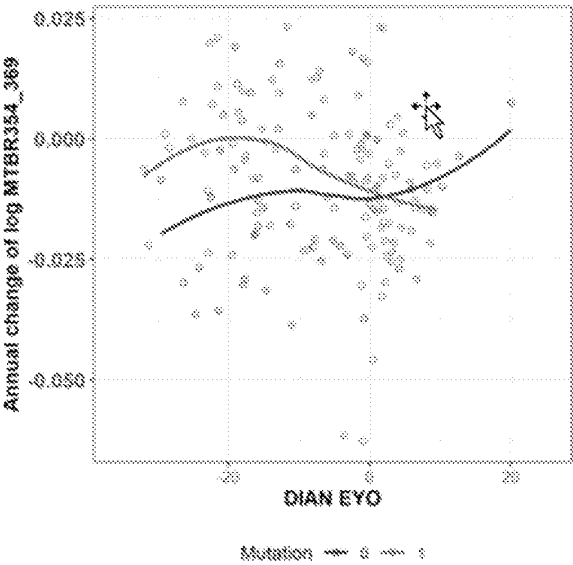


FIG. 14N

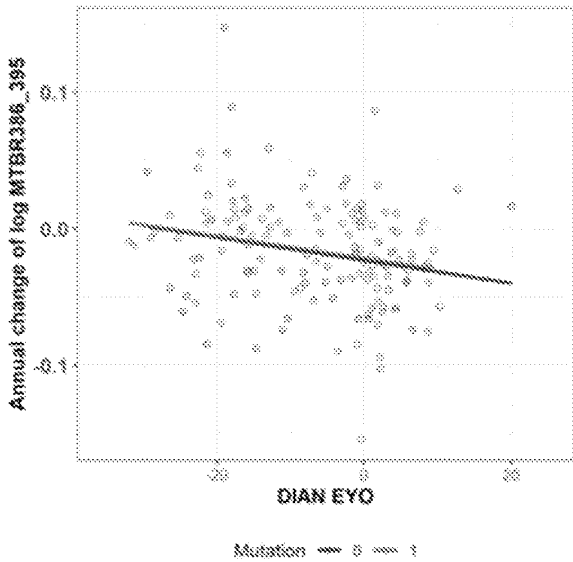


FIG. 14O

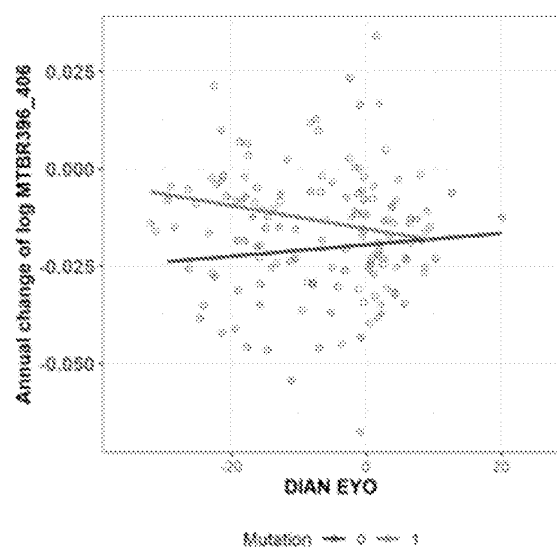


FIG. 14P

Association between baseline biomarkers and the longitudinal rate of change of cognitive composite

Biomarker	Mutation	Estimate	SE	P value
log pT111_T111	MC	-0.200	0.044	<.0001
	NC	0.066	0.111	0.56
sqrt pT153_T153	MC	-0.188	0.041	<.0001
	NC	0.141	0.094	0.14
log pS208_S208	MC	-0.139	0.036	0.0004
	NC	0.013	0.098	0.89

FIG. 15

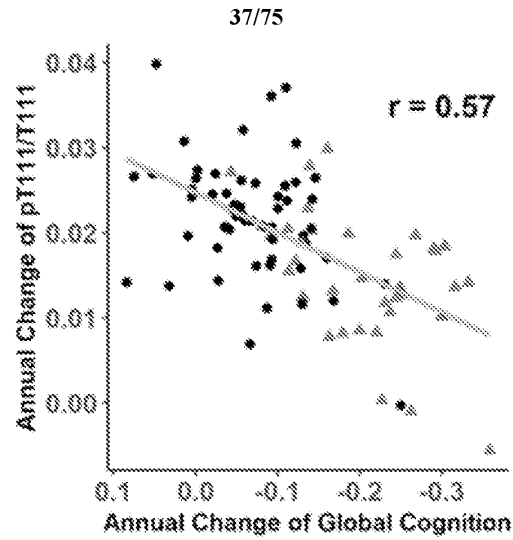


FIG. 16A

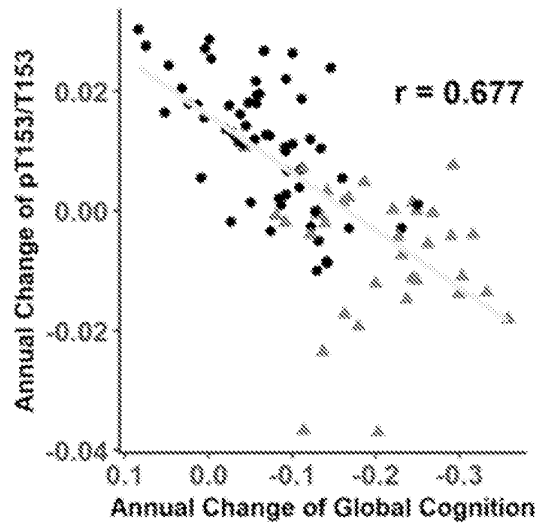


FIG. 16B

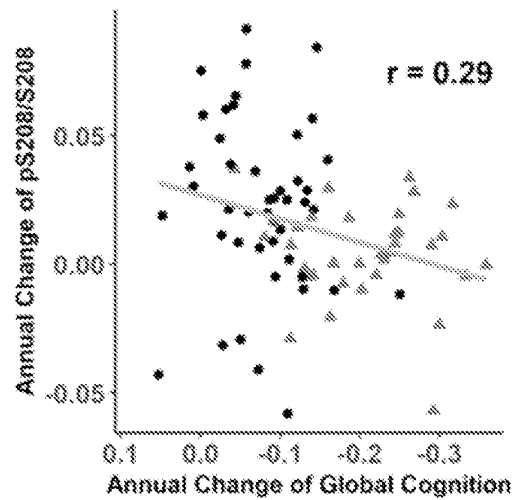


FIG. 16C

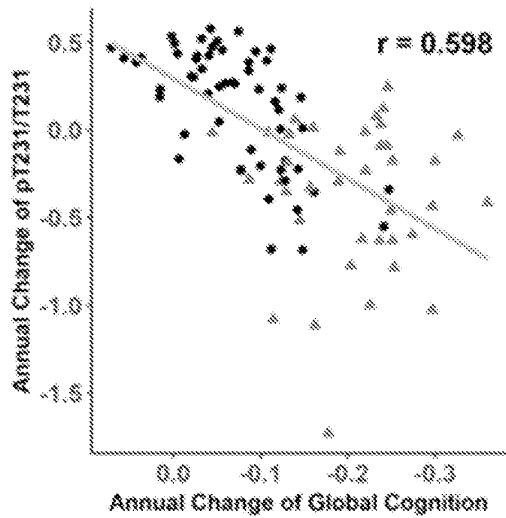


FIG. 16D

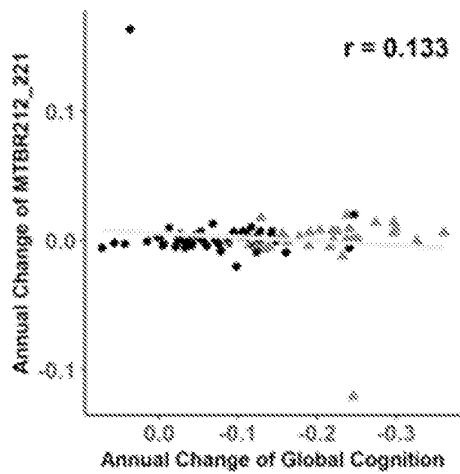


FIG. 16E

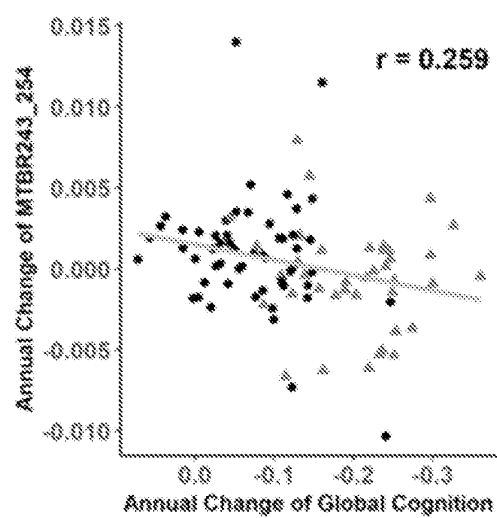


FIG. 16F

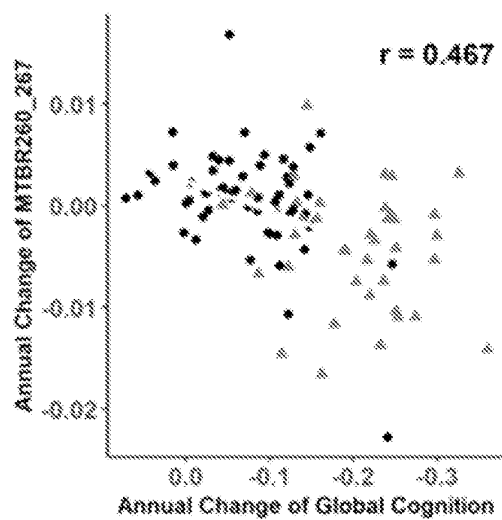


FIG. 16G

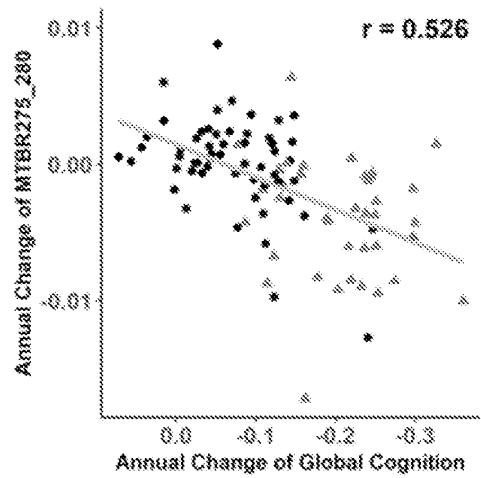


FIG. 16H

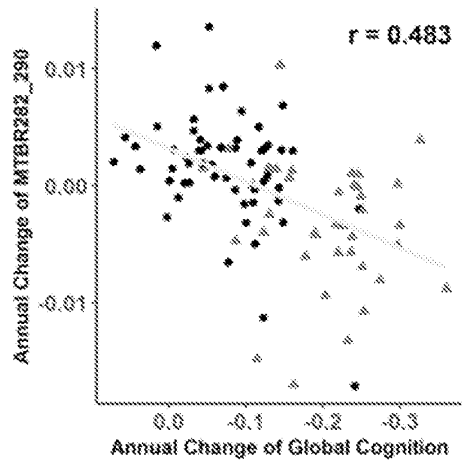


FIG. 16I

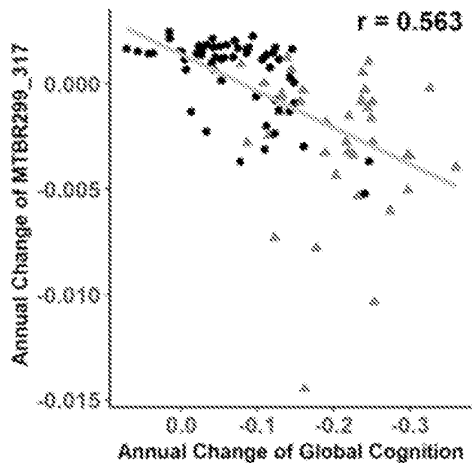


FIG. 16J

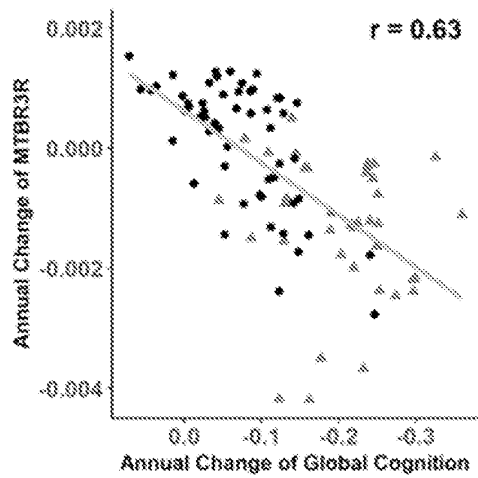


FIG. 16K

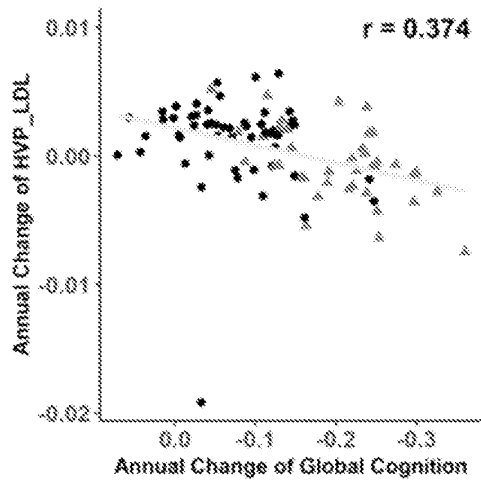


FIG. 16L

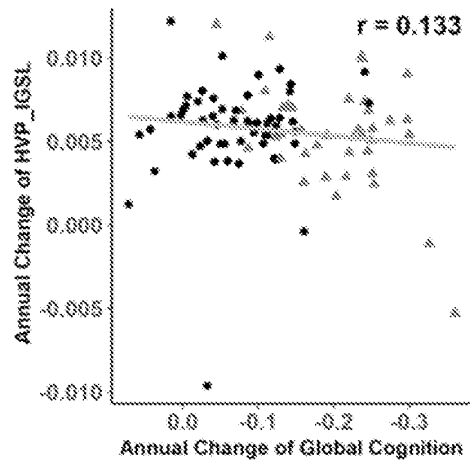


FIG. 16K

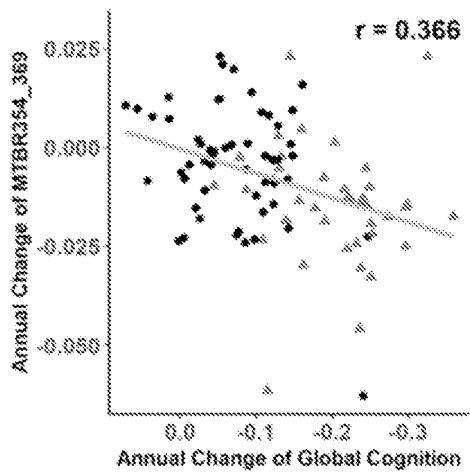


FIG. 16N

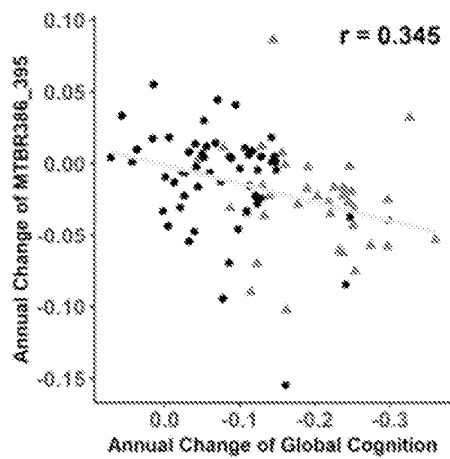


FIG. 16O

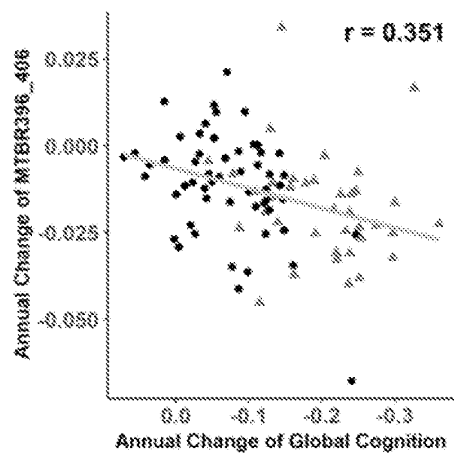


FIG. 16P

Correlation with pT217/T217		Baseline			Annual change		
		pT111/T111	pT153/T153	pS208/S208	pT111/T111	pT153/T153	pS208/S208
all MC	correlation	0.90	0.93	0.87	0.70	0.62	0.37
	p value	<.0001	<.0001	<.0001	<.0001	<.0001	0.0005
	sample size	228	229	213	95	97	86
aMC	correlation	0.86	0.90	0.85	0.55	0.34	0.23
	p value	<.0001	<.0001	<.0001	<.0001	0.01	0.12
	sample size	150	151	137	55	57	46
sMC	correlation	0.68	0.76	0.59	0.60	0.59	0.14
	p value	<.0001	<.0001	<.0001	<.0001	<.0001	0.40
	sample size	78	78	76	40	40	40

Correlation with pT205/T205		Baseline			Annual change		
		pT111/T111	pT153/T153	pS208/S208	pT111/T111	pT153/T153	pS208/S208
all MC	correlation	0.81	0.77	0.83	-0.24	-0.54	-0.10
	p value	<.0001	<.0001	<.0001	0.02	<.0001	0.35
	sample size	228	229	213	95	97	86
aMC	correlation	0.66	0.57	0.72	-0.004	-0.42	0.12
	p value	<.0001	<.0001	<.0001	0.98	0.0010	0.42
	sample size	150	151	137	55	57	46
sMC	correlation	0.64	0.53	0.61	0.07	-0.32	-0.03
	p value	<.0001	<.0001	<.0001	0.65	0.04	0.85
	sample size	78	78	76	40	40	40

FIG. 17A

Correlation with PIB PET cortical mean		Baseline			Annual change	
		pT111/T111	pT153/T153	pS208/S208	pT111/T111	pT153/T153 pS208/S208
all MC	correlation	0.72	0.73	0.64	-0.19	-0.43
	p value	<.0001	<.0001	<.0001	0.13	0.0003
	sample size	174	175	160	65	67
aMC	correlation	0.73	0.75	0.67	-0.11	-0.52
	p value	<.0001	<.0001	<.0001	0.50	0.0003
	sample size	126	127	114	41	43
sMC	correlation	0.14	0.14	0.09	0.03	0.43
	p value	0.35	0.36	0.56	0.88	0.04
	sample size	48	48	46	24	24

Correlation with lumipulse Aβ42/40		Baseline			Annual change	
		pT111/T111	pT153/T153	pS208/S208	pT111/T111	pT153/T153 pS208/S208
all MC	correlation	-0.74	-0.75	-0.72	-0.54	-0.67
	p value	<.0001	<.0001	<.0001	<.0001	<.0001
	sample size	223	224	208	93	95
aMC	correlation	-0.69	-0.72	-0.70	-0.45	-0.65
	p value	<.0001	<.0001	<.0001	0.00	<.0001
	sample size	147	148	134	53	55
sMC	correlation	-0.49	-0.40	-0.43	0.10	-0.15
	p value	<.0001	0.0004	0.0001	0.53	0.37
	sample size	76	76	74	40	40

FIG. 17B

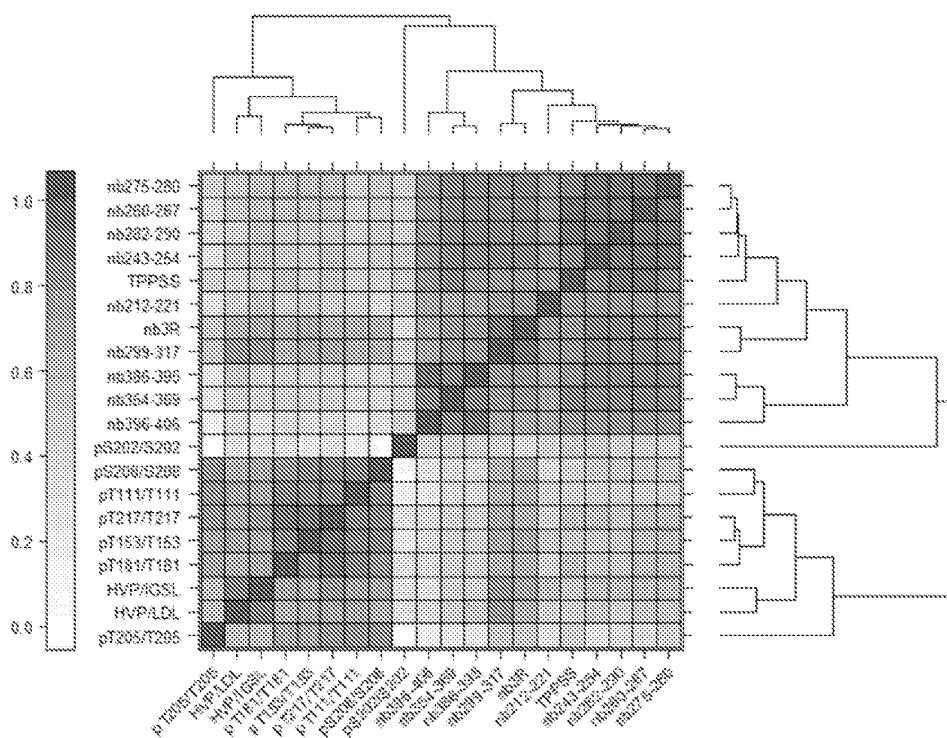


FIG. 18A

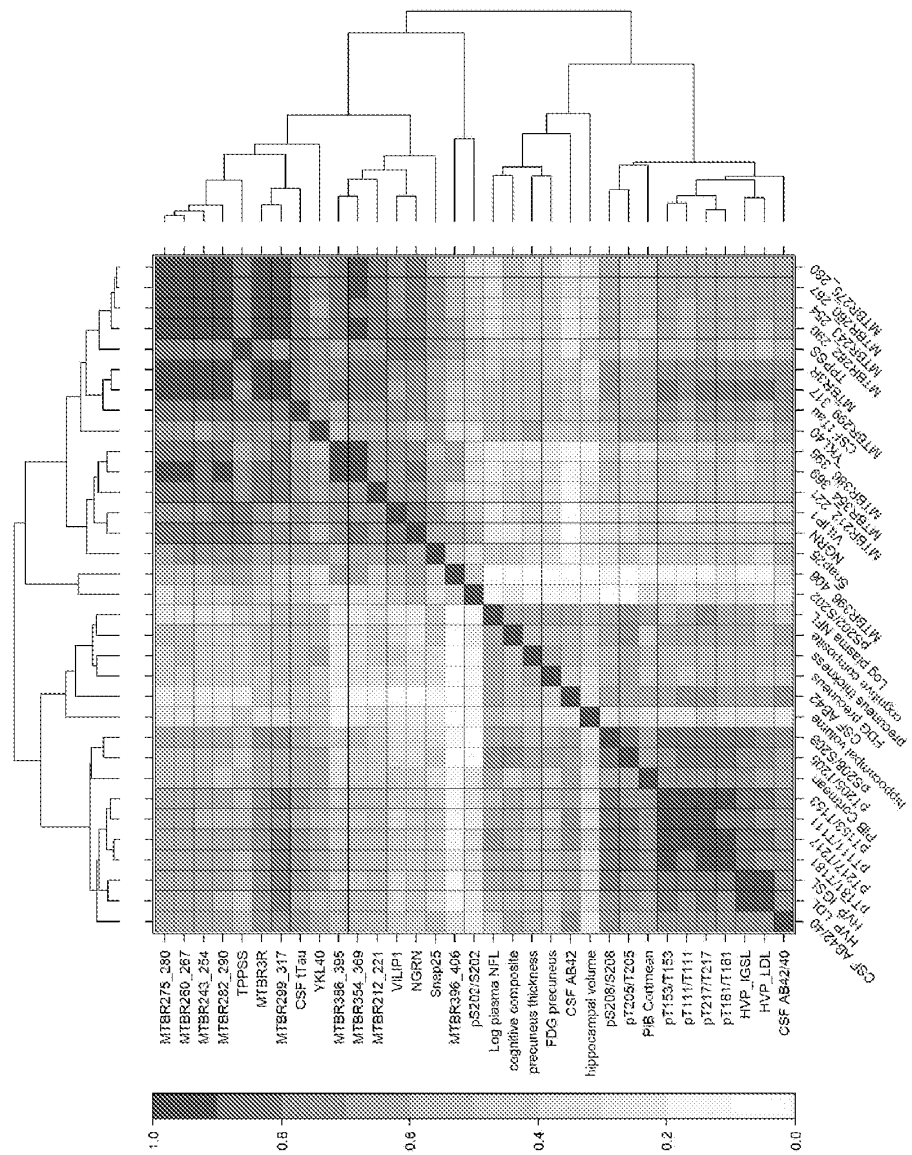


FIG. 18B

Heatmap for the correlations in baseline using asymptomatic MC

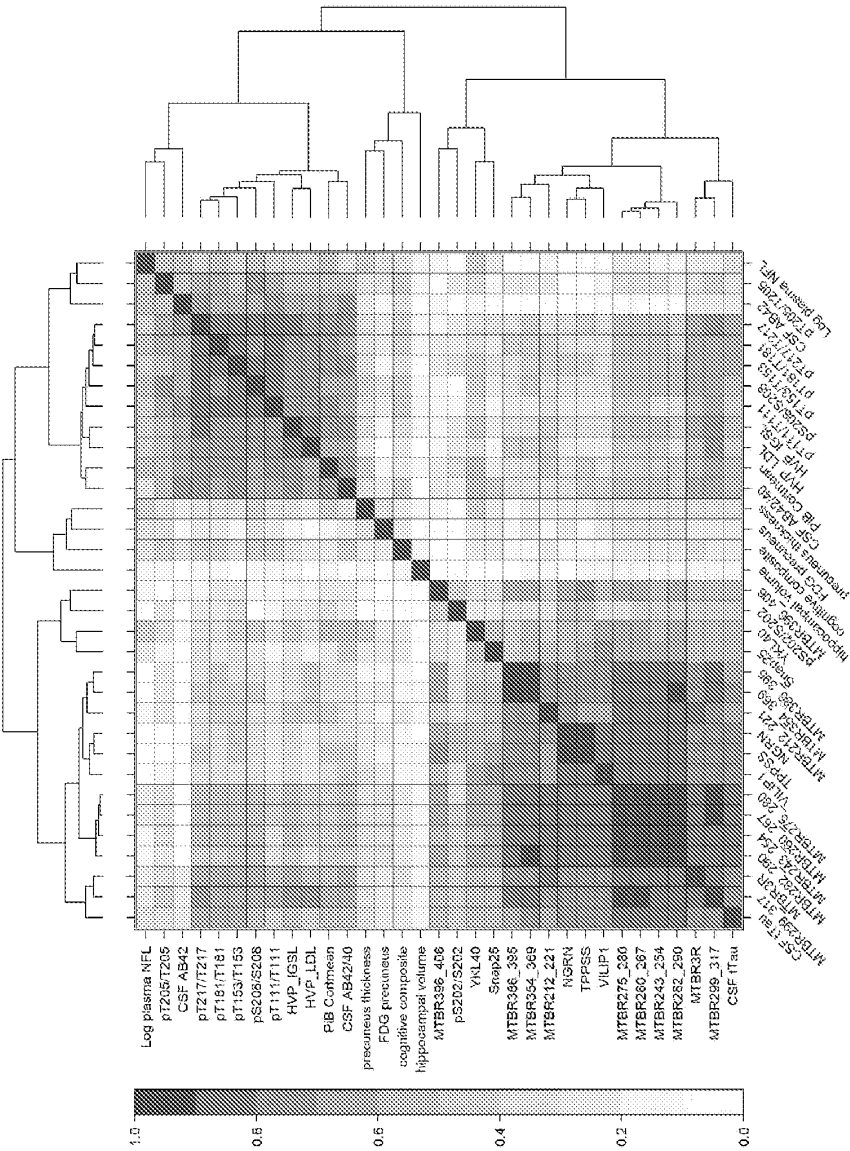


FIG. 18C

Heatmap for the correlations in baseline using NC

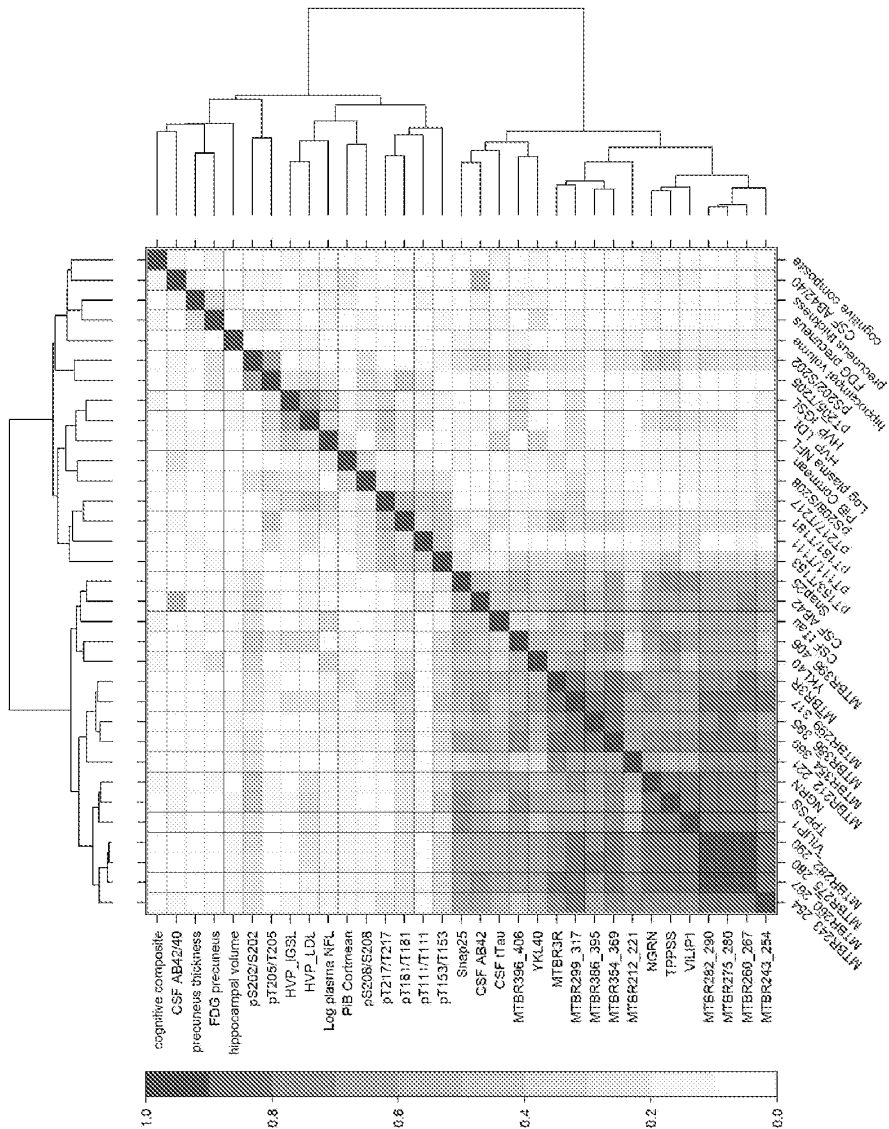


FIG. 18E

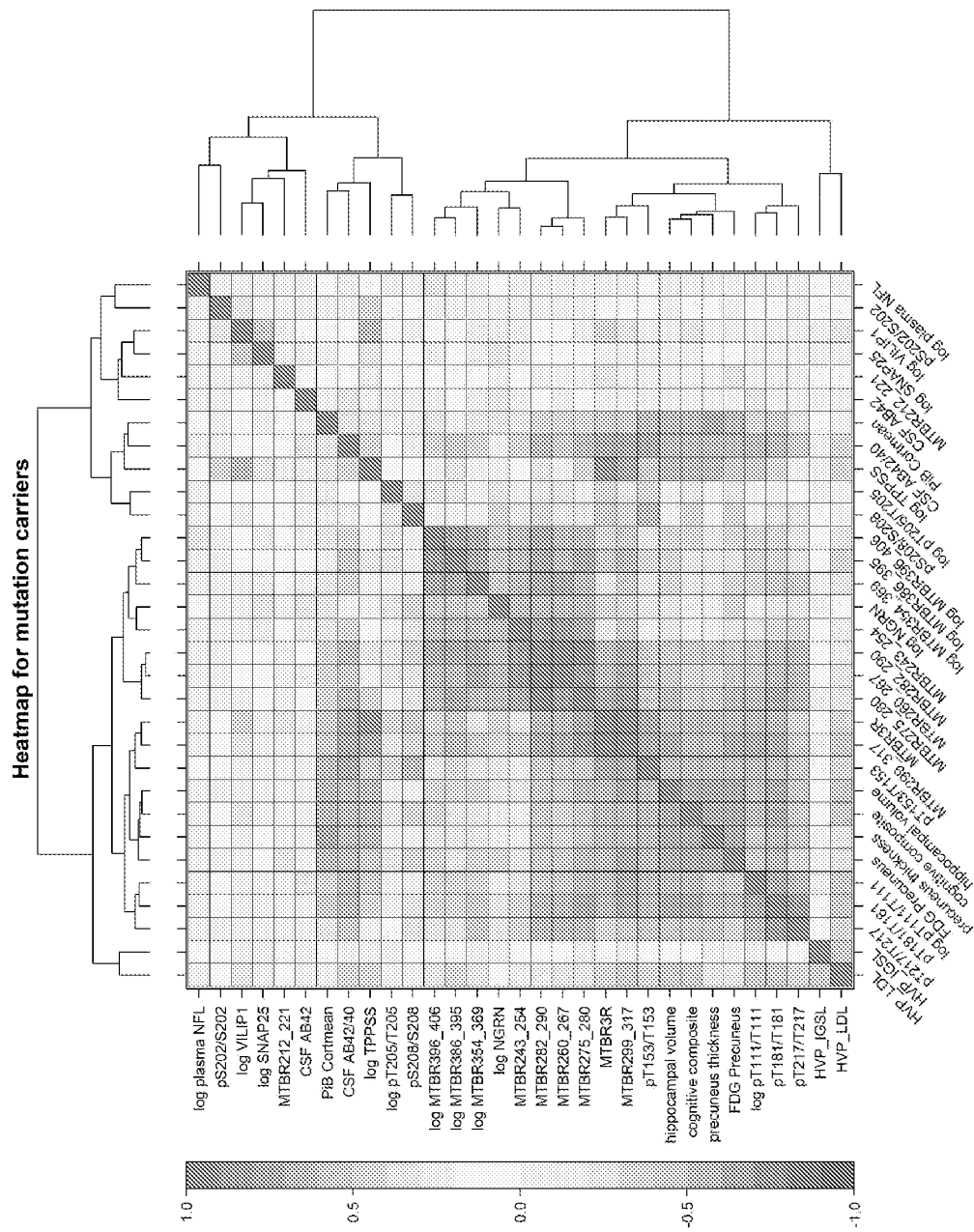


FIG. 18F

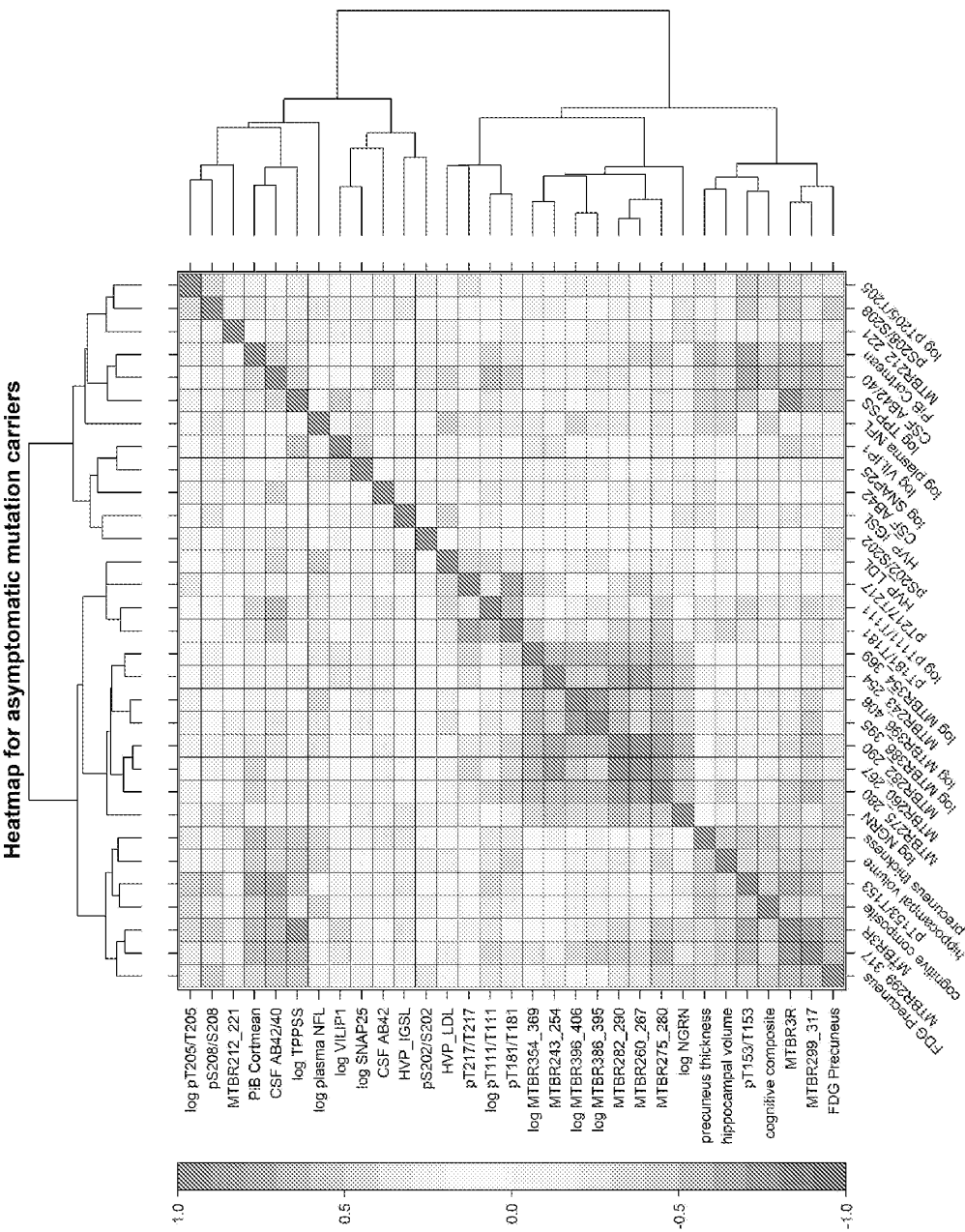


FIG. 18G

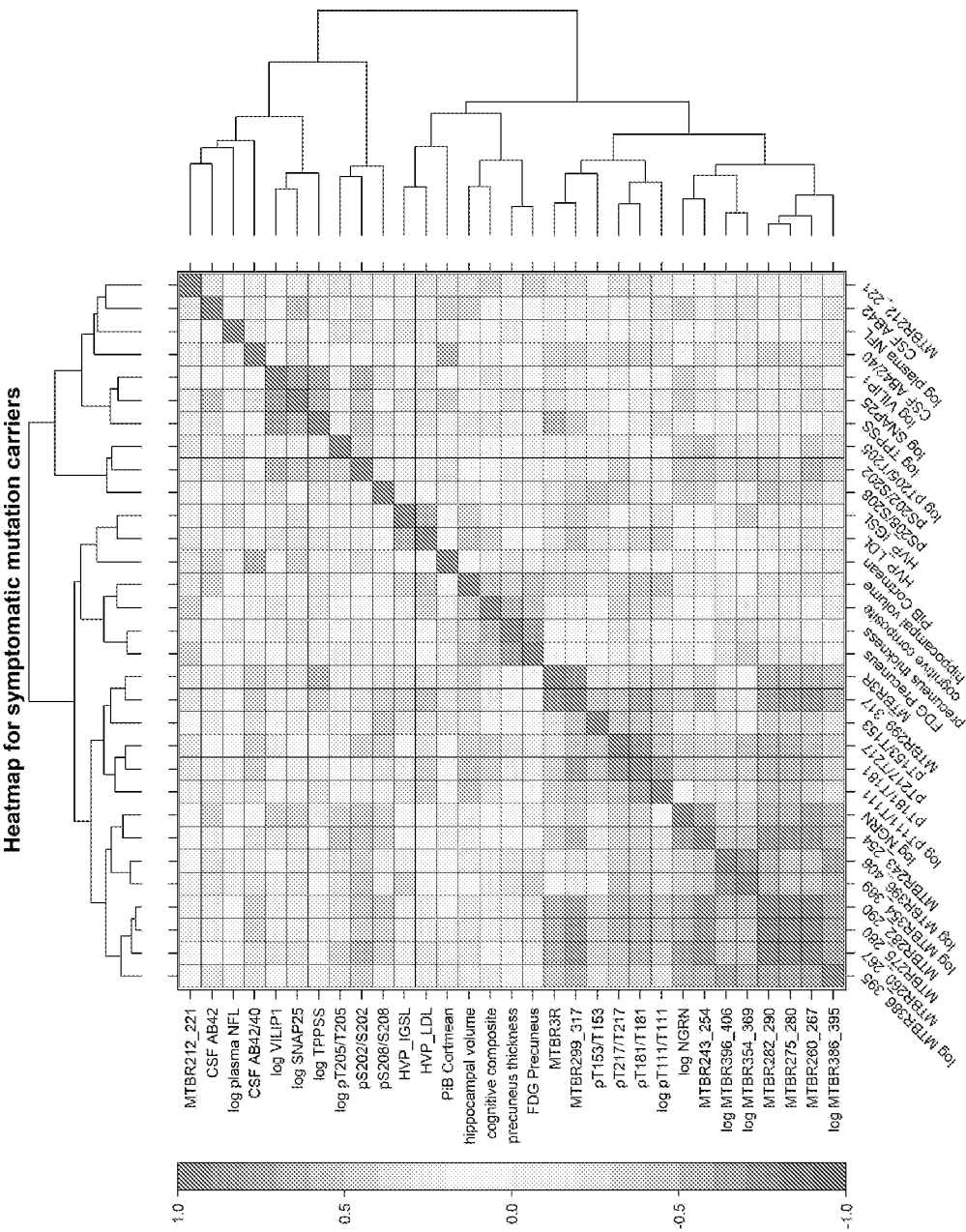


FIG. 18H

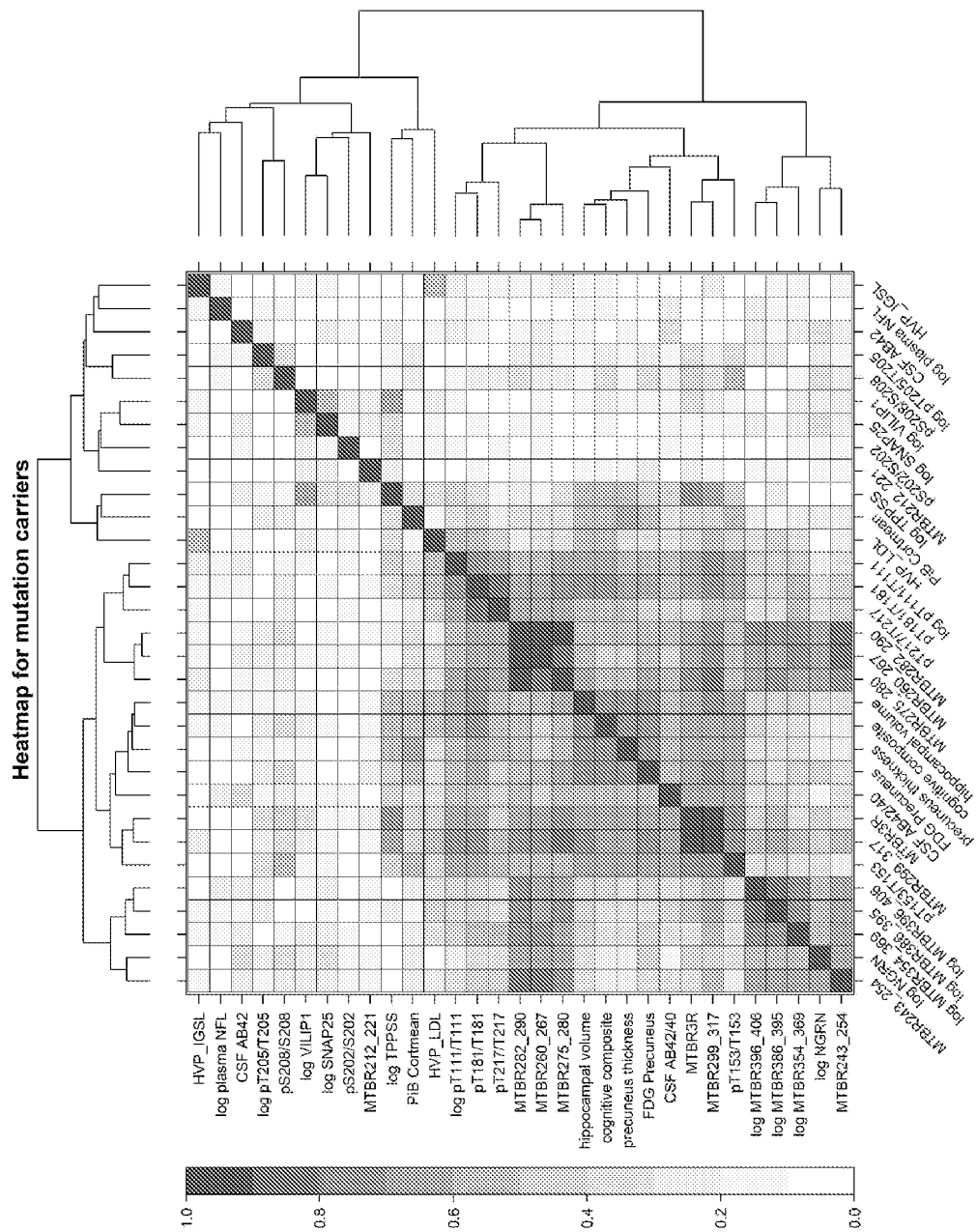


FIG. 18I

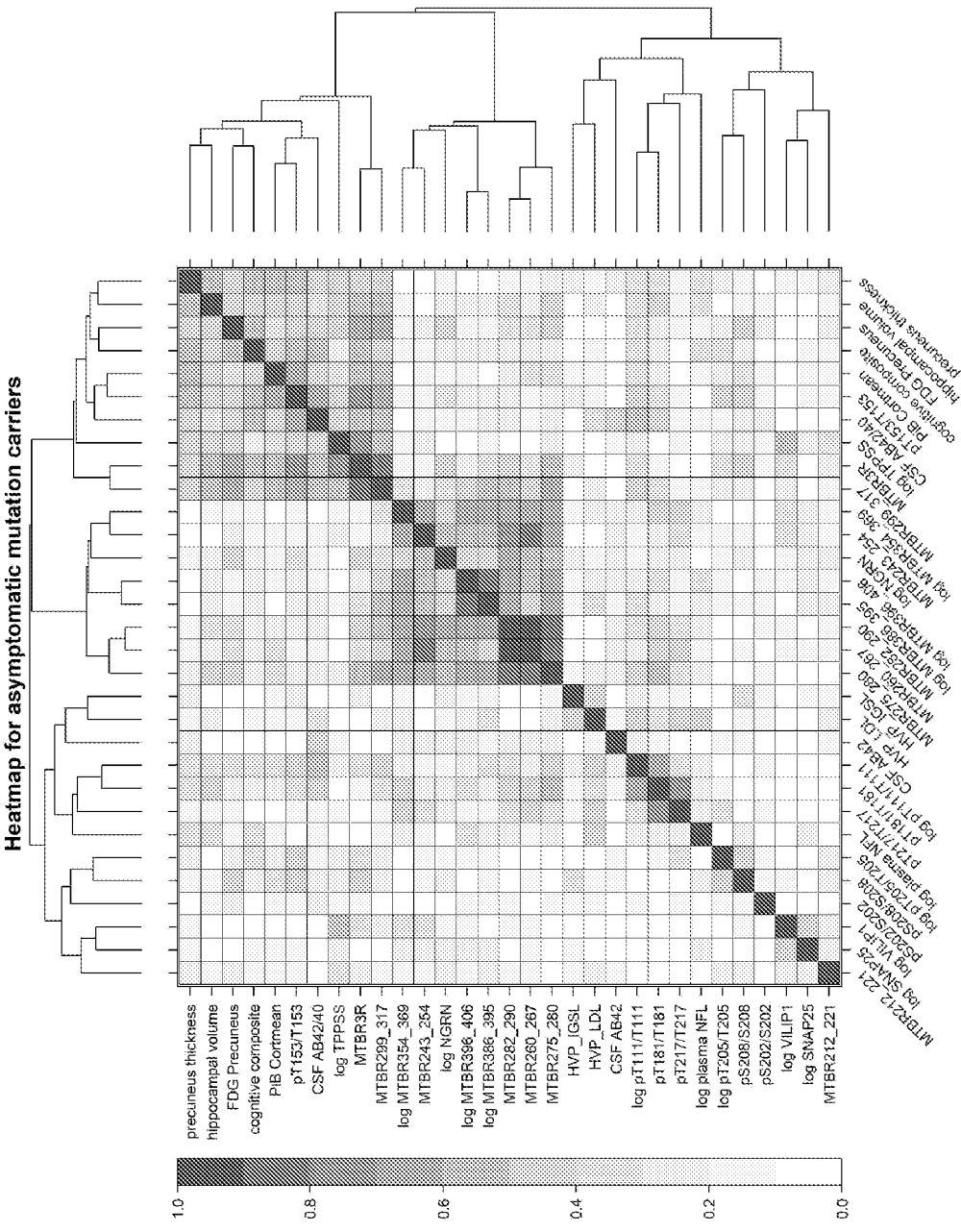


FIG. 18J

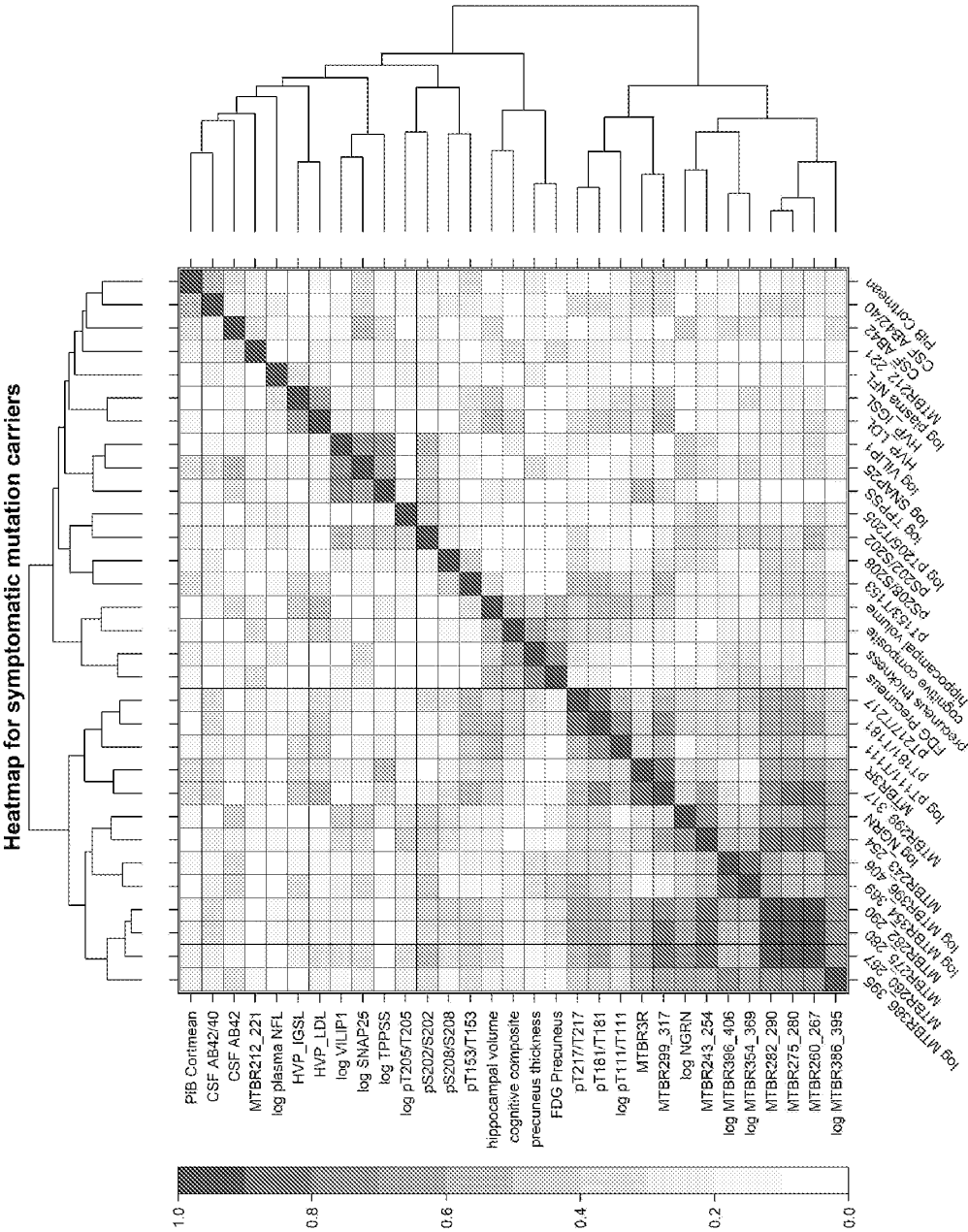


FIG. 18K

All MC baseline

 $R^2 = 0.60$

Parameter	Estimate	Standard Error	t Value	Pr > t	R ² for each biomarker	Semi-partial R ²
Intercept	10.0	2.98	3.35	0.0009		
log_pT205_T205	11.7	1.73	6.76	<.0001	0.52	0.08
log_MTR6212_221	2.9	1.041	2.87	0.0045	0.24	0.01
log_HVP_IQSI	9.6	2.01	4.80	<.0001	0.51	0.04

FIG. 19A

aMC baseline

 $R^2 = 0.47$

Variable	Parameter Estimate	Standard Error	t Value	Pr > t	R ² for each biomarker	Semi-partial R ²
Intercept	-4.85208	4.60561	-1.05	0.2938		
log_pT205_T205	8.59269	2.76535	3.11	0.0023	0.32	0.03471
log_pT217_T217	4.17946	1.24904	3.35	0.0010	0.39	0.04025
log_MTR6212_221	4.85622	1.19306	4.07	<.0001	0.18	0.05956

FIG. 19B

sMC baseline

 $R^2 = 0.12$

Parameter	Estimate	Standard Error	t Value	Pr > t
Intercept	1.787307983	0.65571132	2.73	0.0080
log_pT415_T415	3.922116526	1.23963400	3.16	0.0022

FIG. 19C

EYO group	[-30,-25)	[-25,-20)	[-20,-15)	[-15,-10)	[-10,-5)	[-5,0)	[0,5)	[5,10)	[10,15)
pT217_T217	9	33	38	61	68	88	93	85	100
pT231_T231	10	11	25	61	79	88	90	85	0
pT153_T153	0	11	16	56	79	84	92	95	100
pT181_T181	18	11	13	46	76	88	92	95	100
pS208_S208	0	14	10	46	75	88	86	95	100
HVP_IGSL	0	11	0	43	63	84	83	95	100
MTBR299_317	9	6	3	39	62	68	82	85	100
MTBR3R	0	11	3	38	59	68	78	85	100
pT111_T111	0	0	6	28	48	76	75	90	0
HVP_LDL	0	6	9	18	46	64	78	75	0
MTBR260_267	9	0	0	29	48	56	63	70	100
MTBR275_280	9	6	0	25	52	60	67	70	100
MTBR282_290	9	0	0	25	48	56	58	70	0
pT205_T205	0	0	3	4	28	60	82	86	0
TPP55	9	0	0	25	38	44	69	80	0
MTBR243_254	0	6	0	14	24	40	53	66	0
MTBR212_221	0	11	0	11	31	28	43	50	0
MTBR354_369	16	0	3	18	38	49	35	30	0
MTBR386_385	9	6	3	7	17	20	18	15	0
MTBR396_406	9	0	3	21	31	12	23	5	0

FIG. 20A

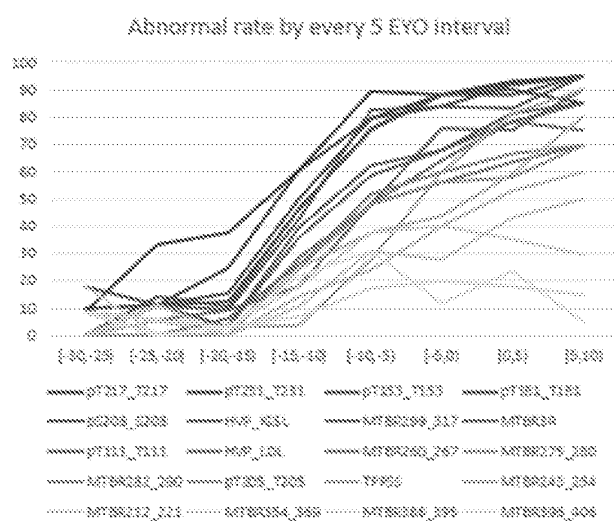


FIG. 20B

Biomarker	EYO [-25, -10]			EYO [-10, 0]			EYO [0, 10]				
	Estimated annual rate of change	SD	MSR	Biomarker	Estimated annual rate of change	SD	MSR	Biomarker	Estimated annual rate of change	SD	MSR
log_pT217_T217	0.067	0.21	0.32	log_pS208_S208	0.063	0.21	0.30	log_pT205_T205	0.016	0.13	0.12
log_pT181_T181	0.019	0.06	0.29	log_pT153_T153	0.099	0.33	0.30	log_pT111_T111	-0.005	0.13	-0.04
log_MTBR_3R	0.049	0.19	0.26	log_pT231_T231	0.043	0.16	0.28	log_TPPSS	-0.010	0.21	-0.05
log_pT231_T231	0.025	0.11	0.23	log_pT205_T205	0.045	0.17	0.26	log_HVP_IGSL	-0.010	0.12	-0.09
log_pT111_T111	0.024	0.12	0.21	log_HVP_IGSL	0.038	0.17	0.22	log_pS208_S208	-0.020	0.15	-0.14
log_MTBR282_290	0.030	0.14	0.21	log_pT217_T217	0.085	0.40	0.21	log_pT217_T217	-0.046	0.32	-0.15
log_MTBR299_317	0.034	0.17	0.19	log_pT111_T111	0.037	0.19	0.20	log_pT153_T153	-0.024	0.14	-0.16
log_MTBR260_267	0.025	0.14	0.19	log_HVP_LDL	0.026	0.15	0.17	log_HVP_LDL	-0.025	0.11	-0.22
log_MTBR354_369	0.024	0.13	0.18	log_pT181_T181	0.020	0.13	0.16	log_MTBR212_221	-0.043	0.18	-0.24
log_MTBR275_280	0.025	0.14	0.18	log_MTBR3R	0.026	0.22	0.12	log_MTBR243_254	-0.044	0.17	-0.26
log_TPPSS	0.024	0.15	0.16	log_MTBR299_317	0.027	0.26	0.11	log_MTBR3R	-0.059	0.18	-0.32
log_MTBR243_254	0.022	0.16	0.14	log_TPPSS	0.014	0.26	0.06	log_MTBR282_290	-0.056	0.16	-0.35
log_HVP_IGSL	0.012	0.10	0.12	log_MTBR282_290	0.000	0.19	0.00	log_MTBR299_317	-0.083	0.23	-0.36
log_MTBR396_406	0.015	0.14	0.11	log_MTBR260_267	-0.003	0.18	-0.01	log_MTBR275_280	-0.061	0.17	-0.37
log_MTBR386_395	0.013	0.14	0.09	log_MTBR243_254	-0.006	0.21	-0.03	log_pT181_T181	-0.029	0.08	-0.38
log_pT205_T205	0.008	0.09	0.09	log_MTBR275_280	-0.009	0.18	-0.05	log_MTBR260_267	-0.058	0.15	-0.39
log_HVP_LDL	0.006	0.10	0.06	log_MTBR396_406	-0.014	0.22	-0.07	log_pT231_T231	-0.043	0.11	-0.40
log_pT153_T153	0.016	0.31	0.05	log_MTBR354_369	-0.015	0.20	-0.08	log_MTBR386_395	-0.087	0.19	-0.46
log_pS208_S208	-0.001	0.21	-0.01	log_MTBR386_395	-0.031	0.22	-0.14	log_MTBR396_406	-0.092	0.18	-0.50
log_MTBR212_221	-0.008	0.16	-0.05	log_MTBR212_221	-0.035	0.22	-0.16	log_MTBR354_369	-0.079	0.16	-0.50

MTBR299_317/MTBR282_290 MTBR299_317/MTBR354_369
HVP/LDL HVP/IGSL

FIG. 21A

sMC

Biomarker	Estimated annual rate of change	SD	MSR*	Biomarker	Estimated annual rate of change	SD	MSR*	Magnitude of MSR
log_pT111_T111	0.02867	0.17491	0.16388	log_MTBR354_369	-0.07859	0.16011	-0.49085	0.49085
log_pT181_T181	0.01548	0.10426	0.14847	log_MTBR396_406	-0.08304	0.18348	-0.45256	0.45256
log_pT231_T231	0.01985	0.15105	0.13143	log_MTBR260_267	-0.06146	0.14787	-0.41564	0.41564
log_pT217_T217	0.05069	0.39886	0.12709	log_MTBR386_395	-0.08041	0.19541	-0.41149	0.41149
log_pT205_T205	0.02020	0.16561	0.12196	log_MTBR275_280	-0.06516	0.16562	-0.39345	0.39345
log_TPPSS	0.02555	0.22582	0.11314	log_MTBR282_290	-0.06100	0.15948	-0.38249	0.38249
log_MTBR3R	0.02685	0.24744	0.10852	log_MTBR3R	-0.06297	0.16914	-0.37231	0.37231
log_HVP_IGSL	0.01695	0.15764	0.10755	log_MTBR299_317	-0.08150	0.21903	-0.37209	0.37209
log_pT153_T153	0.03503	0.37549	0.09329	log_MTBR212_221	-0.05610	0.17125	-0.32759	0.32759
log_MTBR282_290	0.01475	0.17324	0.08515	log_pT181_T181	-0.02539	0.08269	-0.30706	0.30706
log_MTBR299_317	0.01831	0.26167	0.06997	log_pT231_T231	-0.03570	0.12508	-0.28543	0.28543
log_pS208_S208	0.01550	0.24680	0.06281	log_MTBR243_254	-0.04654	0.17569	-0.26487	0.26487
log_MTBR260_267	0.009308	0.17450	0.05334	log_pT205_T205	0.01928	0.12918	0.14925	0.14925
log_MTBR275_280	0.008033	0.17010	0.04722	log_HVP_LDL	-0.01633	0.11107	-0.14699	0.14699
log_MTBR243_254	0.008310	0.20092	0.04136	log_pT217_T217	-0.02392	0.16986	-0.14082	0.14082
log_HVP_LDL	0.003914	0.14052	0.02785	log_pT153_T153	-0.01951	0.14739	-0.13237	0.13237
log_MTBR354_369	0.002702	0.16669	0.01621	log_TPPSS	-0.02115	0.20162	-0.10492	0.10492
log_MTBR396_406	-0.00423	0.17181	-0.02462	log_pS208_S208	-0.01533	0.15598	-0.09826	0.09826
log_MTBR386_395	-0.00779	0.17621	-0.04421	log_pT111_T111	-0.00790	0.13972	-0.05655	0.05655
log_MTBR212_221	-0.01702	0.19957	-0.08527	log_HVP_IGSL	-0.00468	0.11015	-0.04248	0.04248

FIG. 21B

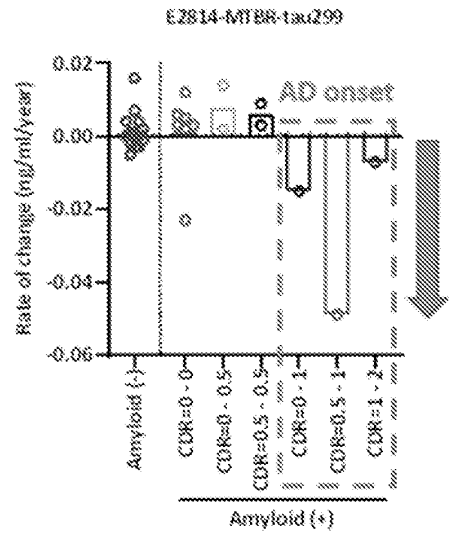


FIG. 22A

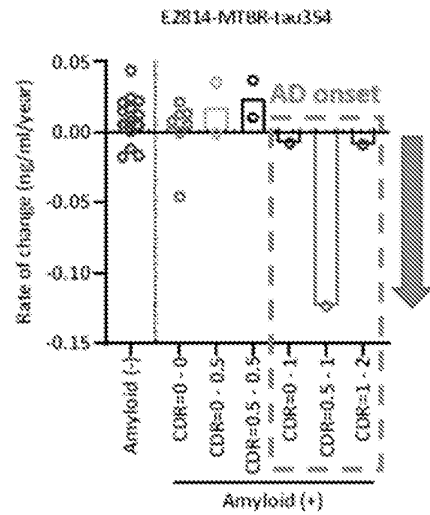


FIG. 22B

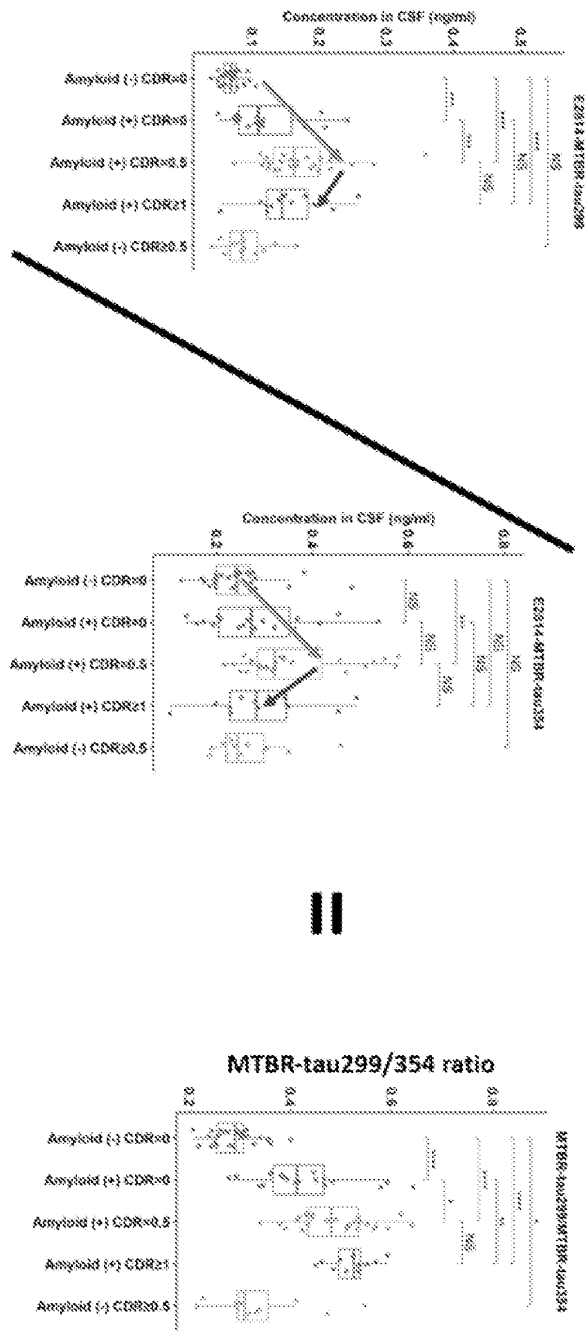


FIG. 23

Spearman $r=0.423$ ($p=0.0009$) for AD

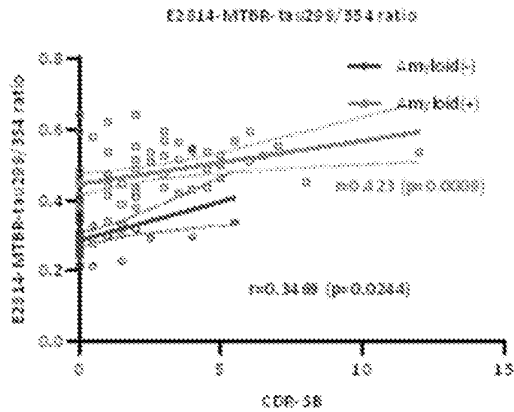


FIG. 24A

Spearman $r=0.384$ ($p=0.0029$) for AD

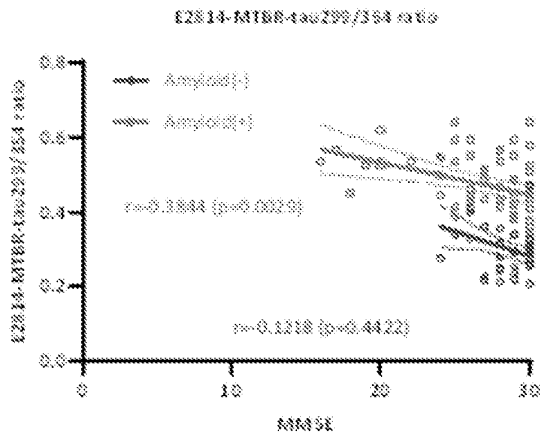


FIG. 24B

Residue (Abbreviated)	Domain	Preparation method	CDR-SB				MMSE			
			Amyloid (-)		Amyloid (+)		Amyloid (-)		Amyloid (+)	
			r	p-value	r	p-value	r	p-value	r	p-value
E2814-MTBR- τ au212	mid-domain	E2814-IP	0.09627	0.5442 (NS)	-0.02827	0.8332 (NS)	0.02417	0.8792 (NS)	-0.1331	0.3191 (NS)
E2814-MTBR- τ au243	upstream of MTBR	E2814-IP	0.08977	0.5718 (NS)	0.06991	0.6021 (NS)	-0.03952	0.8037 (NS)	-0.1709	0.1997 (NS)
E2814-MTBR- τ au260	R1	E2814-IP	0.1998	0.2046 (NS)	0.04242	0.7519 (NS)	-0.06755	0.6708 (NS)	-0.1436	0.2823 (NS)
E2814-MTBR- τ au275	R2-upstream	E2814-IP	0.1786	0.2579 (NS)	0.04654	0.7287 (NS)	-0.11165	0.4624 (NS)	-0.1492	0.2638 (NS)
E2814-MTBR- τ au282	mid-R2	E2814-IP	0.1432	0.3657 (NS)	0.0264	0.8441 (NS)	-0.0666	0.6752 (NS)	-0.1291	0.3341 (NS)
E2814-MTBR- τ au299	R2-downstream to R3	E2814-IP	0.3374	0.0289 (*)	0.2607	0.0481 (*)	-0.2053	0.1922 (NS)	-0.3314	0.0111 (*)
E2814-MTBR- τ au354	R4	E2814-IP	0.1113	0.476 (NS)	0.05977	0.6558 (NS)	-0.1306	0.4096 (NS)	-0.1597	0.2311 (NS)
E2814-MTBR- τ au386	C-terminal	E2814-IP	0.2076	0.187 (NS)	0.08296	0.5359 (NS)	-0.04745	0.7654 (NS)	-0.1675	0.2088 (NS)
E2814-MTBR- τ au396	C-terminal	E2814-IP	0.1295	0.4137 (NS)	-0.109	0.4155 (NS)	-0.08875	0.5762 (NS)	0.02097	0.8758 (NS)
E2814-MTBR- τ au306(3R)	R1 to R3 (3R-specific)	E2814-IP	0.2554	0.1025 (NS)	0.1801	0.176 (NS)	0.04326	0.7856 (NS)	-0.1768	0.1843 (NS)
MTBR- τ au299/354 ratio	R2-downstream to R3 / R3 ratio	E2814-IP	0.3469	0.0244 (*)	0.2221	0.176 (NS)	-0.1218	0.4422	0.1768	0.1843 (NS)

MTBR: microtubule binding region. r: Spearman correlation coefficient

CDR-SB: Clinical Dementia Rating-sum of boxes. MMSE: Mini-Mental State Exam

***p < 0.001, **p < 0.01, *p < 0.05. NS = not significant.

FIG. 25

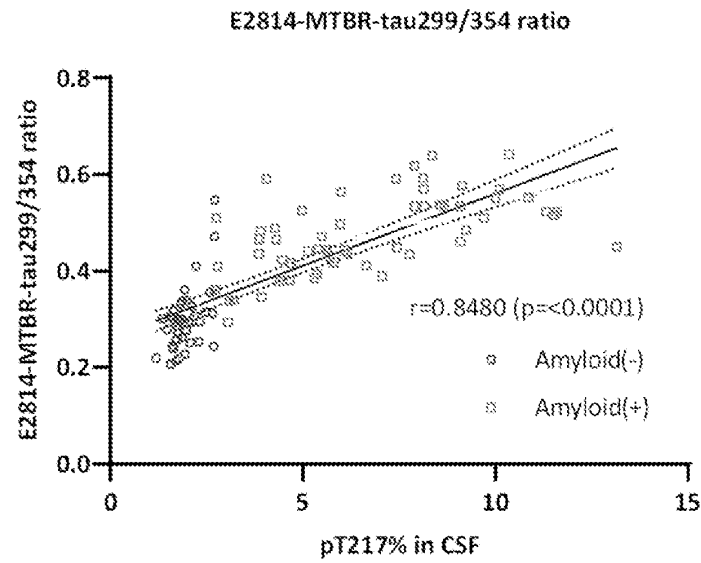


FIG. 26A

	pT217% vs. Amyloid(-)	pT217% vs. Amyloid(+)	pT217% vs. All
Spearman r			
r	0.4222	0.6312	0.8480
95% confidence interval	0.1214 to 0.6514	0.4372 to 0.7691	0.7786 to 0.8969
P value			
P (two-tailed)	0.0060	<0.0001	<0.0001
P value summary	**	****	****
Exact or approximate P value?	Approximate	Approximate	Approximate
Significant? (alpha = 0.05)	Yes	Yes	Yes
Number of XY Pairs	41	57	98

FIG. 26B



FIG. 27A

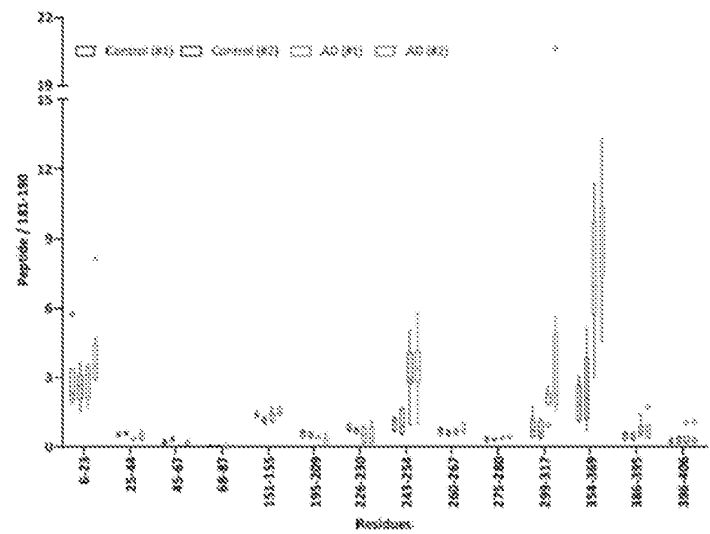


FIG. 27B

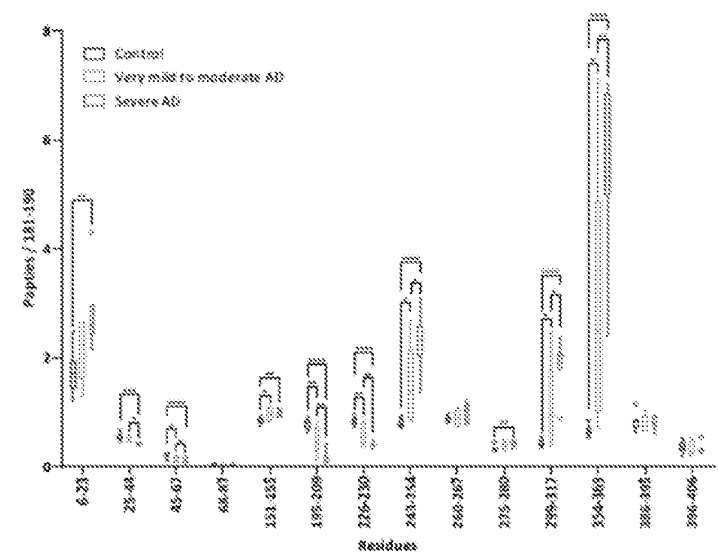
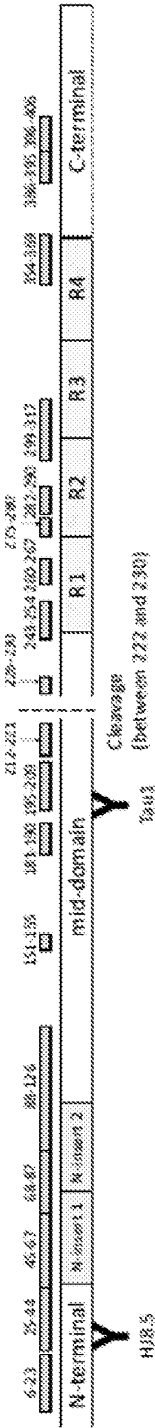


FIG. 27C



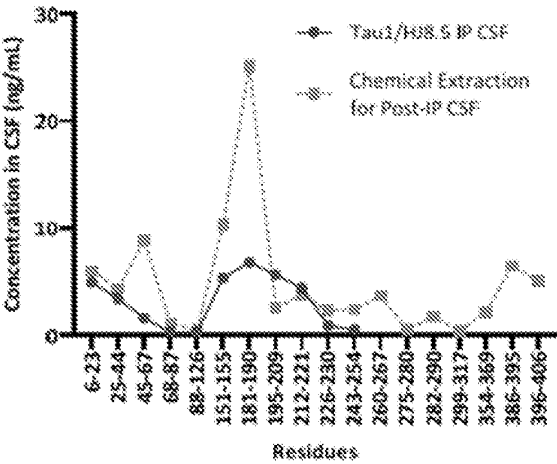


FIG. 28B

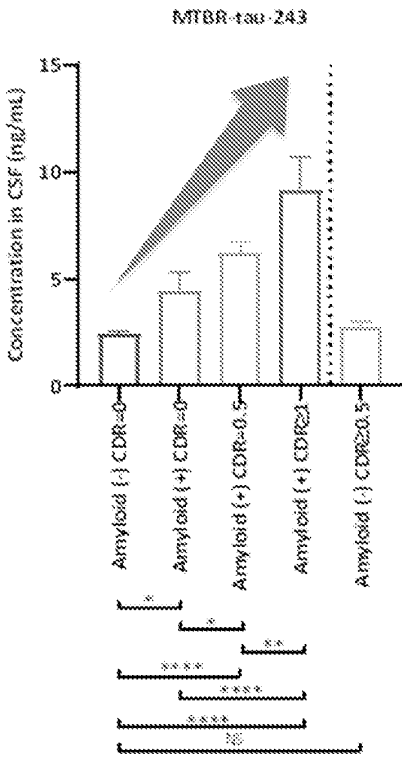


FIG. 29A

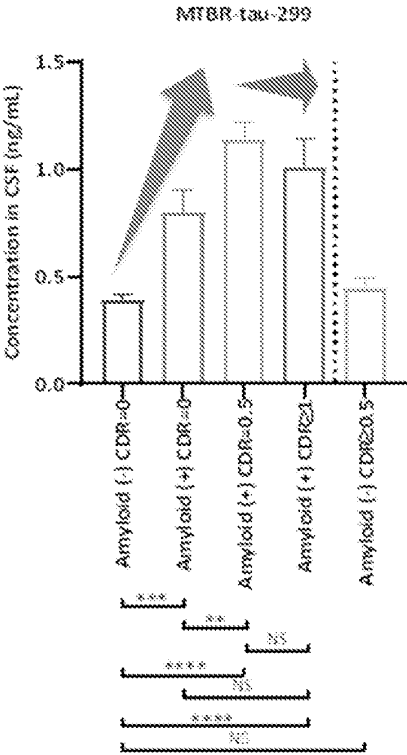


FIG. 29B

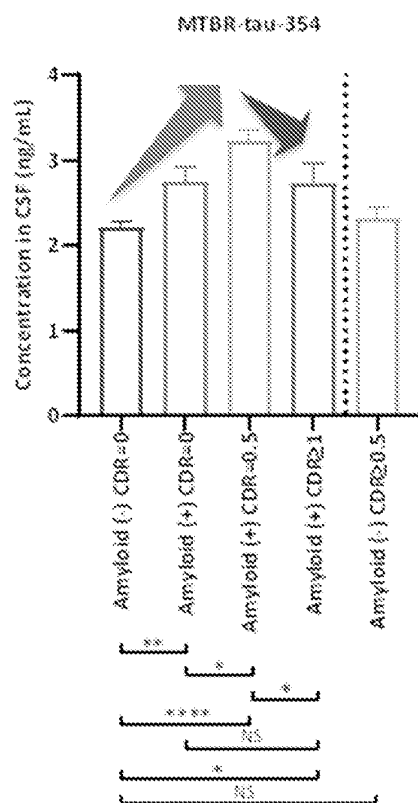
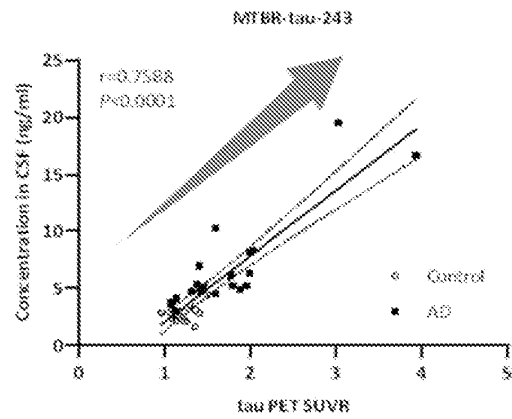


FIG. 29C



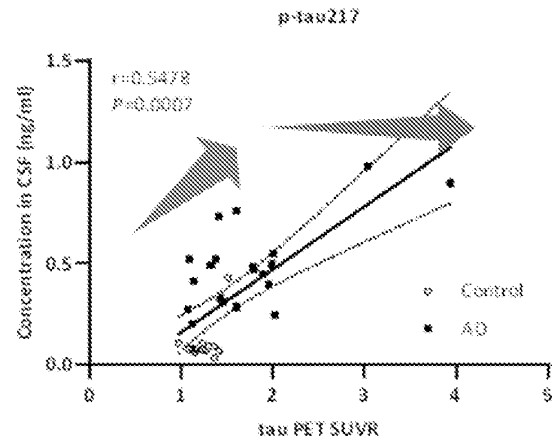


FIG. 30C

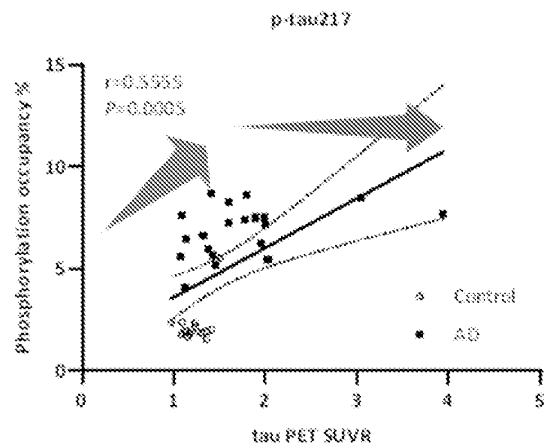


FIG. 30D

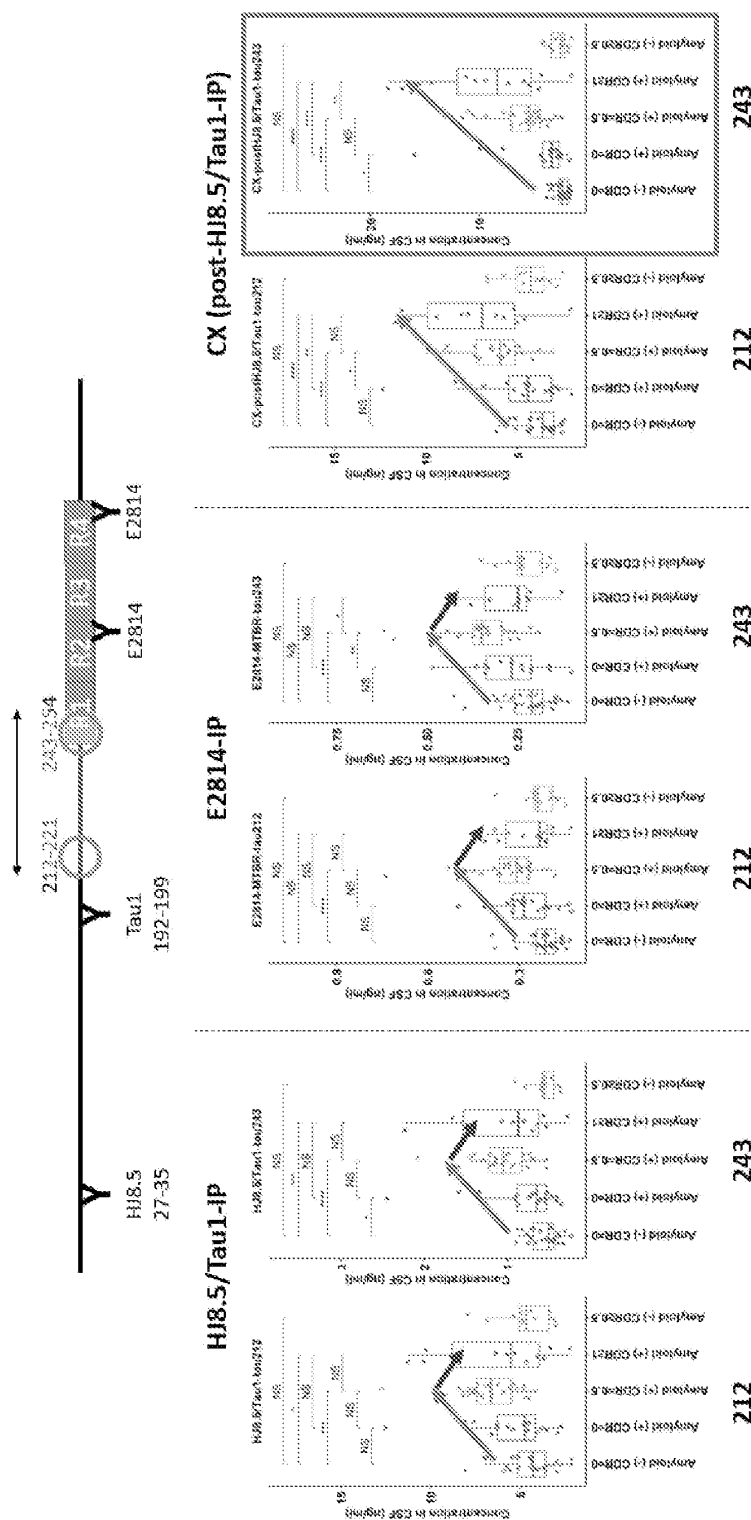


FIG. 32