Supplemental Table 1: Demographics and Family Representation in Pathogenic Variant Groupings						
Dataset A:	*# of Pathogenic Variant Carriers/Families*	*# Variants*	*Variants Represented in Domain-Based Grouping*	Baseline EYO (mean years/SD)	Baseline Age (mean years/SD)	Familial Age of Onset (mean years/SD)
APP Transmembrane Domain	25 / 17	6	APP:p.Val715Ala, APP:p.Ile716Phe, APP:p.Ile716Val, APP:p.Val717Ile, APP:p.Val717Leu, APP:p.Leu723Arg	-10.52/11.69	37.72/10.95	48.24/7.68
PSEN2 Transmembrane Domain 2	16 / 2	1	PSEN2:p.Asn141Ile	-11.53/10.09	38.62/9.93	50.16/NA
PSEN1 Cytoplasmic Domain 4	23 / 9	6	PSEN1:p.Ala275Val, PSEN1:p.Glu280Ala, PSEN1:p.Glu280Gly, PSEN1:p.Phe283Leu, PSEN1:p.Tyr288His, PSEN1:exon9del	-6.67/9.05	34.35/8.11	41.02/4.36
PSEN1 Transmembrane Domain 2	18 / 13	8	PSEN1:p.Asn135Ser, PSEN1:p.Asn135Tyr, PSEN1:p.Ile143Thr, PSEN1:p.Met139Ile, PSEN1:p.Met146Ile, PSEN1:p.Met146Leu, PSEN1:p.Met146Val, PSEN1:p.Thr147Ile	-5.50/7.20	32.11/6.27	37.61/6.28
PSEN1 Transmembrane Domain 3	13/ 7	6	PSEN1:p.Ser169Leu, PSEN1:p.Ser170Phe, PSEN1:p.Leu171Pro, PSEN1:p.Phe176Val, PSEN1:p.Ser178Pro, PSEN1:p.Glu184Asp	-6.10/6.13	35.46/8.17	41.56/6.81
PSEN1 Transmembrane Domain 4	21 /14	5	PSEN1:p.Ile202Phe, PSEN1:p.Gly206Ala, PSEN1:p.Gly209Glu, PSEN1:p.Gly209Val, PSEN1:p.Ser212Tyr	-6.86/13.12	43.90/10.86	50.77/8.00
PSEN1 Transmembrane Domain 5	12 / 10	8	PSEN1:p.Gln222His, PSEN1:p.Ile229Phe, PSEN1:p.Leu226Arg, PSEN1:p.Ser230Asn, PSEN1:p.Met233Leu, PSEN1:p.Met233Thr, PSEN1:p.Leu235Val, PSEN1:p.Ile238Met	-8.25/8.89	38.50/9.48	46.75/9.79
PSEN1 Transmembrane Domain 6	28 / 12	7	PSEN1:p.Ala260Gly, PSEN1:p.Ala260Val, PSEN1:p.Val261Phe, PSEN1:p.Pro264Leu, PSEN1:p.Pro267Leu, PSEN1:p.Arg269His, PSEN1:p.Leu271Val	-8.44/11.62	43.57/11.39	52.01/6.24
PSEN1 Transmembrane Domain 8	16 /4	2	PSEN1:p.Cys410Tyr, PSEN1:p.Ala426Pro	-7.24/13.26	37.00/11.71	44.24/5.56
Ungrouped Carriers	34 / 24	12	APP:p.Lys670_Met671delinsAsnLeu, APP:dupplication, PSEN1:p.Ala79Val, PSEN1:p.Met84Val, PSEN1:p.Cys92Ser, PSEN1:p.Phe105Leu, PSEN1:p.Tyr115His, PSEN1:p.His163Arg, PSEN1:p.Gly217Arg, PSEN1:p.Leu219Pro, PSEN1:p.Thr245Pro, PSEN1:p.Ala431Glu	-9.74/10.74	37.18/10.61	46.92/7.53
Dataset B:						
PSEN1 pathogenic variant prior to codon 200	54 / 35	20	*PSEN1* variants in blue (above)	-8.04/9.10	34.93/8.88	42.97/8.31
PSEN1 pathogenic variant after codon 200	107 / 55	33	*PSEN1* variants in red (above)	-7.30/11.10	39.66/10.91	46.96/7.92

Supplemental Table 2: Variant Coding DNA Reference Sequences

Gene	Variant gDNA consequence	Variant cDNA consequence	Variant protein consequence
APP	chr21:g.27269938_27269939delinsGA	c.2010_2011delinsTC	p.Lys670_Met671delinsAsnLeu
APP	chr21:g.27264101A>G	c.2144T>C	p.Val715Ala
APP	chr21:g.27264099T>C	c.2146A>G	p.Ile716Val
APP	chr21:g.27264099T>A	c.2146A>T	p.Ile716Phe
APP	chr21:g.27264096C>T	c.2149G>A	p.Val717Ile
APP	chr21:g.27264096C>G	c.2149G>C	p.Val717Leu
APP	chr21:g.27264077A>C	c.2168T>G	p.Leu723Arg
APP	-	-	dup
PSEN1	chr14:g.73683933G>A	c.1229G>A	p.Cys410Tyr
PSEN1	chr14:g.73685869G>C	c.1276G>C	p.Ala426Pro
PSEN1	chr14:g.73685885C>A	c.1292C>A	p.Ala431Glu
PSEN1	chr14:g.73637653C>T	c.236C>T	p.Ala79Val
PSEN1	chr14:g.73637667A>G	c.250A>G	p.Met84Val
PSEN1	chr14:g.73637691T>A	c.274T>A	p.Cys92Ser
PSEN1	chr14:g.73637730T>C	c.313T>C	p.Phe105Leu
PSEN1	chr14:g.73640278T>C	c.343T>C	p.Tyr115His
PSEN1	chr14:g.73640338A>T	c.403A>T	p.Asn135Tyr
PSEN1	chr14:g.73640339A>G	c.404A>G	p.Asn135Ser
PSEN1	chr14:g.73640352G>C	c.417G>C	p.Met139Ile
PSEN1	chr14:g.73640363T>C	c.428T>C	p.Ile143Thr
PSEN1	chr14:g.73640371A>C	c.436A>C	p.Met146Leu
PSEN1	chr14:g.73640371A>G	c.436A>G	p.Met146Val
PSEN1	chr14:g.73640373G>C	c.438G>C	p.Met146Ile
PSEN1	chr14:g.73640375C>T	c.440C>T	p.Thr147Ile
PSEN1	chr14:g.73653568A>G	c.488A>G	p.His163Arg
PSEN1	chr14:g.73653586C>T	c.506C>T	p.Ser169Leu
PSEN1	chr14:g.73653589C>T	c.509C>T	p.Ser170Phe
PSEN1	chr14:g.73653592T>C	c.512T>C	p.Leu171Pro
PSEN1	chr14:g.73653606T>G	c.526T>G	p.Phe176Val
PSEN1	chr14:g.73653612T>C	c.532T>C	p.Ser178Pro
PSEN1	chr14:g.73659355A>C	c.552A>C	p.Glu184Asp
PSEN1	chr14:g.73659407A>T	c.604A>T	p.Ile202Phe
PSEN1	chr14:g.73659420G>C	c.617G>C	p.Gly206Ala
PSEN1	chr14:g.73659429G>A	c.626G>A	p.Gly209Glu
PSEN1	chr14:g.73659429G>T	c.626G>T	p.Gly209Val
PSEN1	chr14:g.73659438C>A	c.635C>A	p.Ser212Tyr
PSEN1	chr14:g.73659452G>C	c.649G>C	p.Gly217Arg
PSEN1	chr14:g.73659459T>C	c.656T>C	p.Leu219Pro
PSEN1	chr14:g.73659469G>T	c.666G>T	p.Gln222His
PSEN1	chr14:g.73659480T>G	c.677T>G	p.Leu226Arg
PSEN1	chr14:g.73659488A>T	c.685A>T	p.Ile229Phe
PSEN1	chr14:g.73659492G>A	c.689G>A	p.Ser230Asn
PSEN1	chr14:g.73659500A>C	c.697A>C	p.Met233Leu
PSEN1	chr14:g.73659501T>C	c.698T>C	p.Met233Thr
PSEN1	chr14:g.73659506C>G	c.703C>G	p.Leu235Val
PSEN1	chr14:g.73659517C>G	c.714C>G	p.Ile238Met
PSEN1	chr14:g.73659536A>C	c.733A>C	p.Thr245Pro
PSEN1	chr14:g.73664748C>G	c.779C>G	p.Ala260Gly
PSEN1	chr14:g.73664748C>T	c.779C>T	p.Ala260Val
PSEN1	chr14:g.73664750G>T	c.781G>T	p.Val261Phe
PSEN1	chr14:g.73664760C>T	c.791C>T	p.Pro264Leu
PSEN1	chr14:g.73664769C>T	c.800C>T	p.Pro267Leu
PSEN1	chr14:g.73664775G>A	c.806G>A	p.Arg269His
PSEN1	chr14:g.73664780C>G	c.811C>G	p.Leu271Val
PSEN1	chr14:g.73664793C>T	c.824C>T	p.Ala275Val
PSEN1	chr14:g.73664808A>C	c.839A>C	p.Glu280Ala
PSEN1	chr14:g.73664808A>G	c.839A>G	p.Glu280Gly
PSEN1	chr14:g.73664816T>C	c.847T>C	p.Phe283Leu
PSEN1	chr14:g.73664831T>C	c.862T>C	p.Tyr288His
PSEN1	chr14:g.73671096_73676953del5858	c.869-1998_956-1524del5858	p.S290C;T291_S319del
PSEN1	chr14:g.73673093G>A	c.869-1G>A	p.S290C;T291_S319del
PSEN1	chr14:g.73673093G>T	c.869-1G>T	p.S290C;T291_S319del
PSEN2	chr1:g.227073304A>T	c.422A>T	p.Asn141Ile

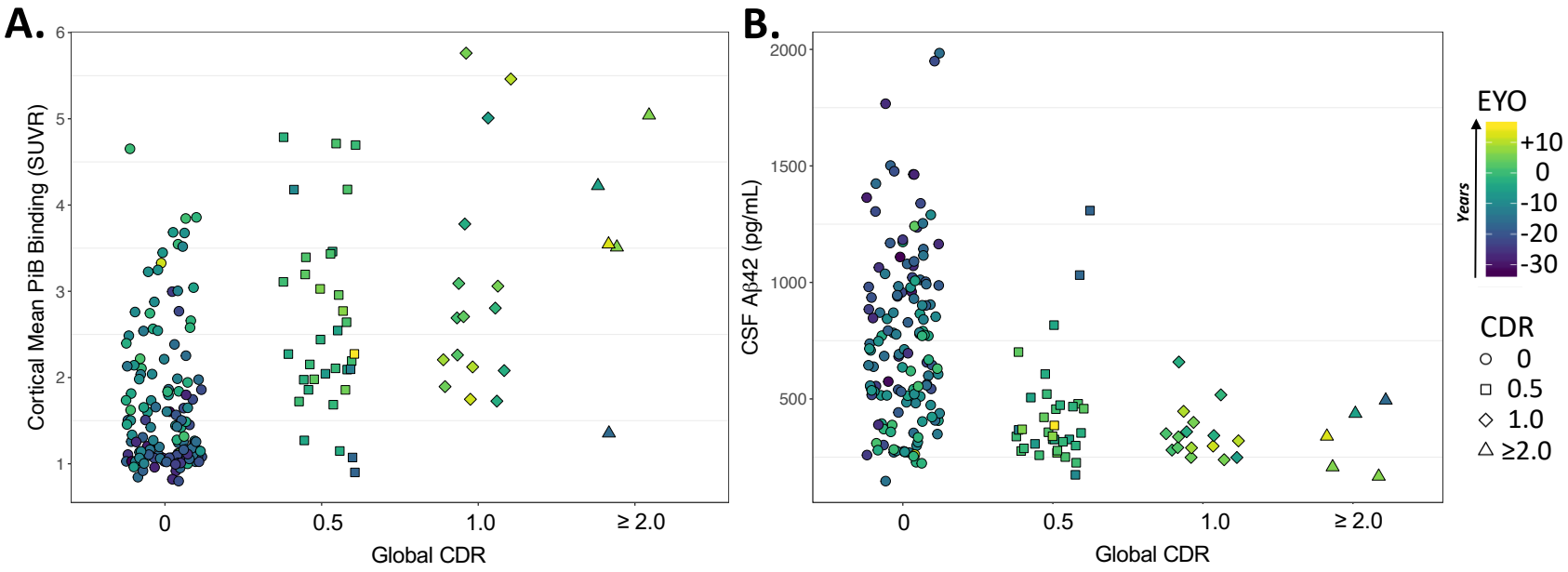
Supplemental Table 3: Effect of Reference Region on PiB PET Findings		
Reference Region:	**Domain-Based Grouping**	**Codon-Based Grouping**
Cerebellar Gray	F(9,170.96) = 5.82, p = 3.32e-7	F(1,154.99) = 21.70, p = 2.24e-6
Brainstem	F(9,173.90) = 4.85, p = 3.13e-6	F(1,156.60) = 9.70, p = 0.0036
White Matter	F(9,173.35) = 5.14, p = 1.69e-5	F(1,154.96) = 11.55, p = 0.0016

P-values shown are FDR corrected

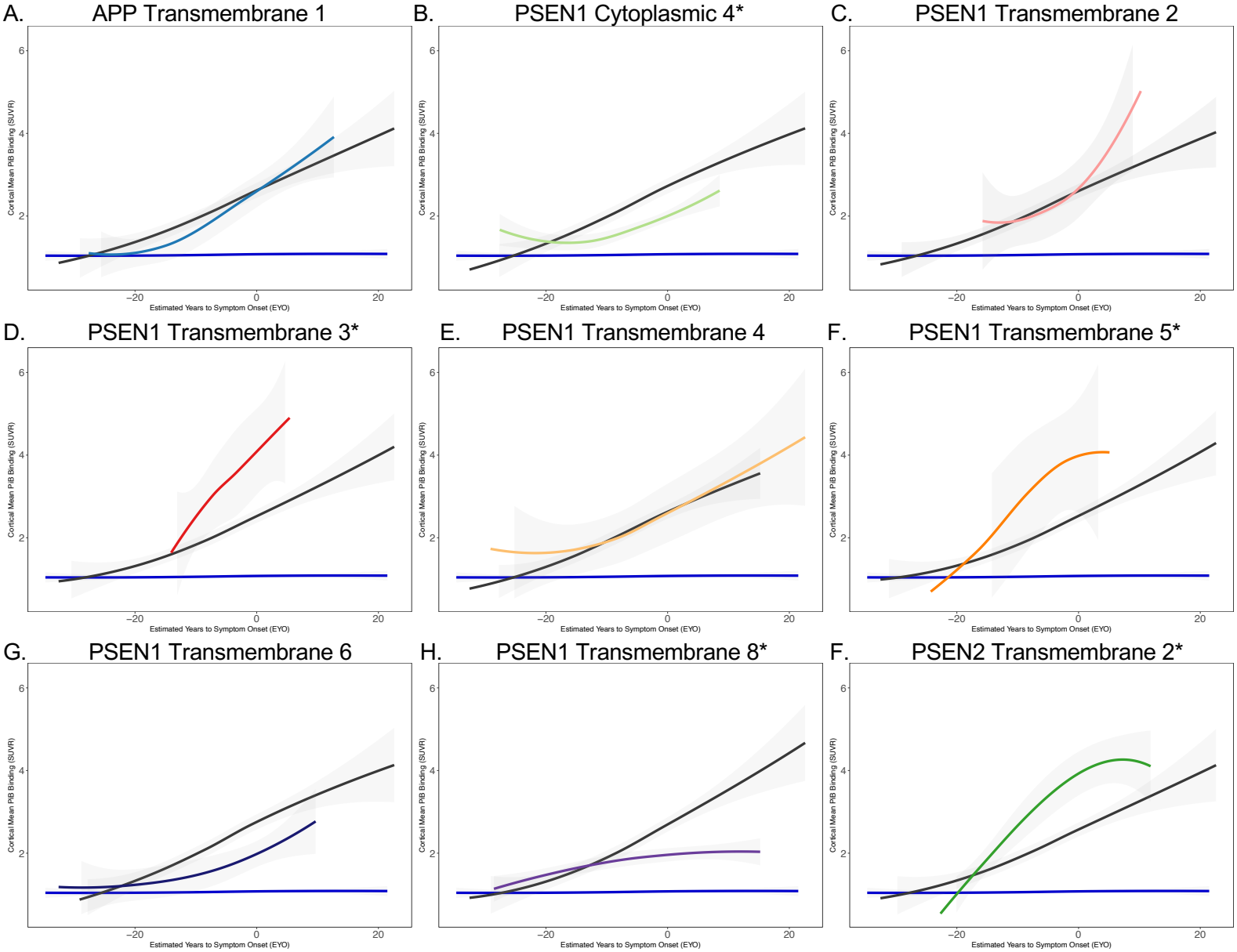
Supplemental Table 4: Sensitivity Analyses Examining Variant Grouping x EYO Associations with Cortical PiB PET SUVR

	Effect of Domain Grouping		*Effect of Codon Grouping*	
	F Value	*p*	*F Value*	*p*
Including All Families and Groupings	F(9, 170.96) = 5.17	p = 3.13e-06	F(1, 154.99) = 21.71	p = 2.24e-05
Excluding Families with Cooks D > 1 SD from mean	F(9, 149.24) = 5.98	p = 3.14e-06	F(1, 145.15) = 24.18	p = 1.22e-05
Excluding *PSEN2* Carriers	F(8, 165.47) = 5.27	p = 2.24e-05	NA	NA
Excluding *APP* Carriers	F(8, 149.28) = 6.32	p = 3.13e-06	NA	NA
Excluding All *APOE* ε4 carriers	F(9, 107.80) = 4.81	p = 5.21e-05	F(1, 104.762) = 15.32	p = 3.23e-04
Excluding All *APOE* ε2 carriers	F(9, 139.53) = 3.18	p = 2.67e-03	F(1, 134.542) = 16.94	p = 1.51e-04
Covarying Weighted Polygenic AD Risk Scores (PRS)	F(9, 164.55) = 5.14	p = 1.70e-05	F(1, 153.69) = 21.13	p = 2.44e-05
Excluding PRS > 1 SD from mean	F(9, 139.61) = 5.68	p = 6.36e-06	F(1, 135.43) = 15.71	p = 2.58e-04

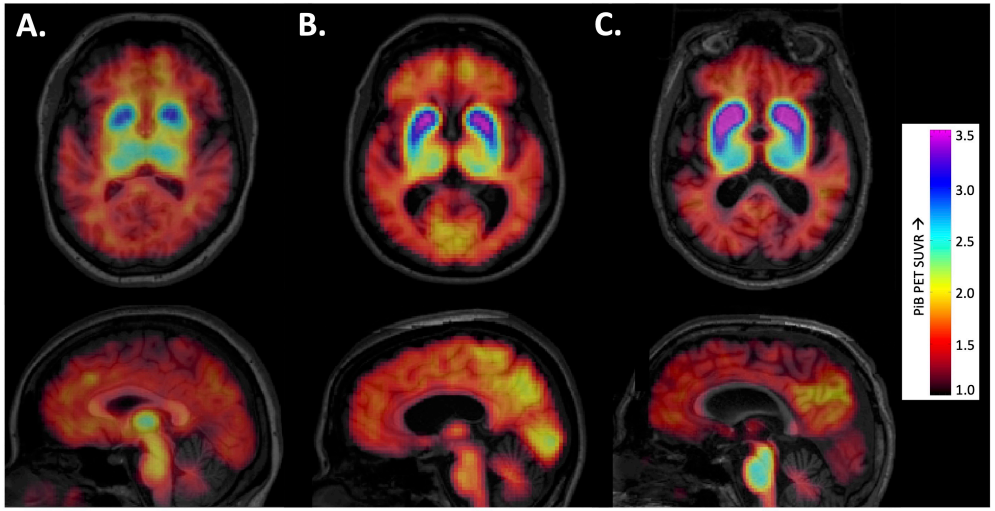
P-values shown are FDR corrected



Supplemental Figure 1: *Amyloid Measures Grouped by Global Clinical Dementia Rating:* Cortical mean PiB PET binding (Panel A) and CSF Aβ42 (Panel B) in autosomal dominant Alzheimer's disease pathogenic variant carriers grouped by global Clinical Dementia Rating (CDR). Color indicates each individual pathogenic variant carrier's estimated years from symptom onset (EYO).

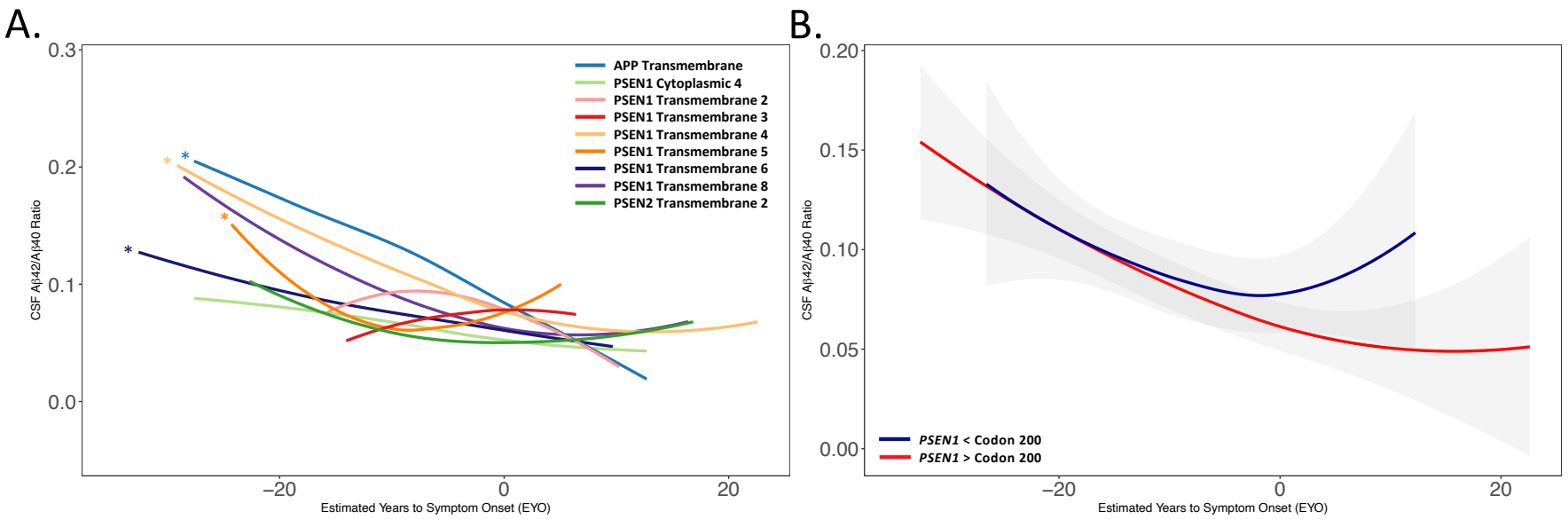


<u>Supplemental Figure 2:</u> *Amyloid Trajectories Differ Across Domain-based Variant Groups*: Cortical mean PiB PET binding across EYO is compared between each domain-based group (colored lines in A-F) and all other pathogenic variant carriers (Black lines). Pathogenic variant non-carriers (Blue line) are shown for illustration purposes and non-carriers were not included in statistical comparisons. * denotes FDR corrected p≤ 0.05 for a significant group by EYO interaction comparing each domain-based group to all other pathogenic variant carriers.

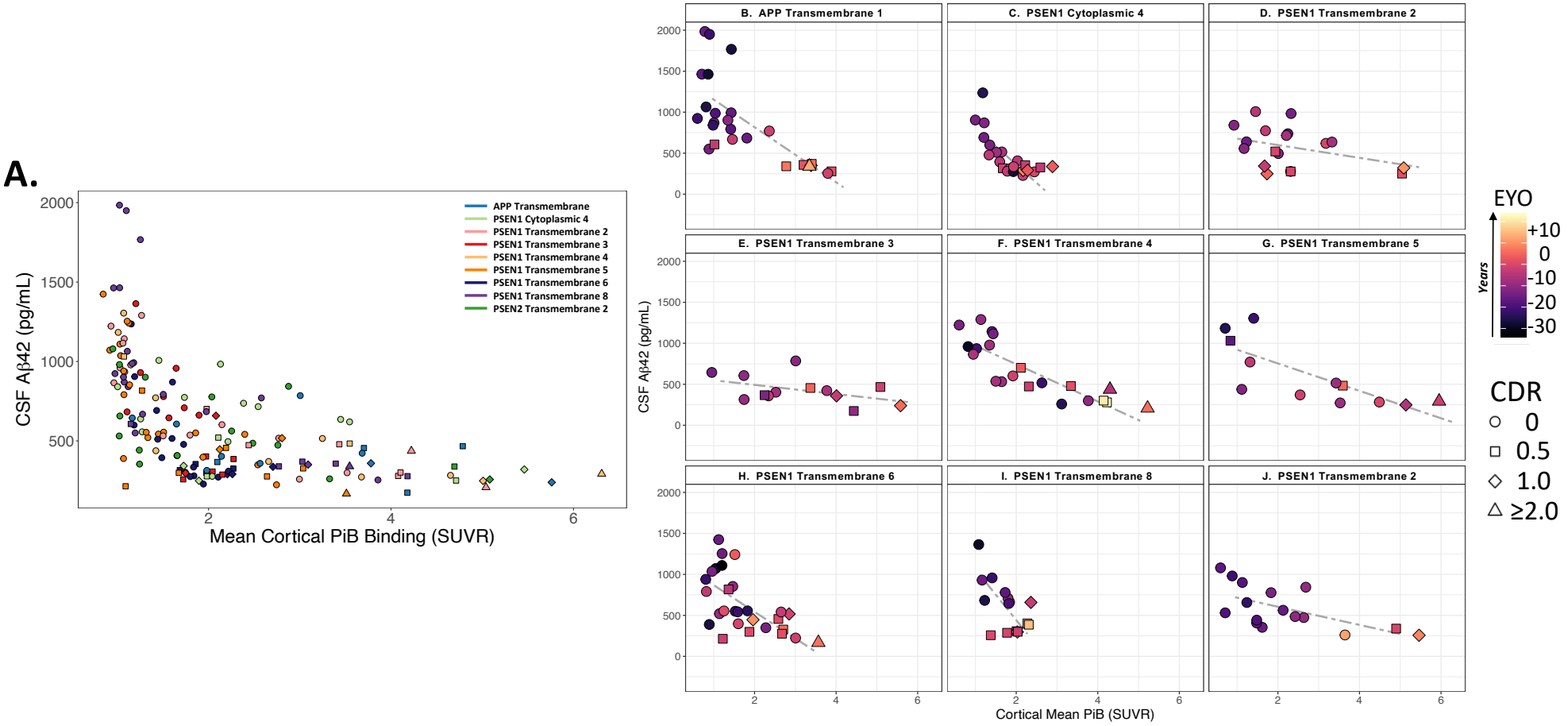


A.	B.	C.
EYO: -25 to -20	**EYO**: -5 to 0	**EYO**: 0 to +5
CDR: 0.0	**CDR**: 0.5	**CDR**: 1.0
CDR SOB: 0.0	**CDR SOB**: 3.0	**CDR SOB**: 5.5
CSF Aβ42 (pg/mL): 550	**CSF Aβ42** (pg/mL): 300	**CSF Aβ42** (pg/mL): 249
PiB Cortical Mean: 1.86	**PiB Cortical Mean:**1.98	**PiB Cortical Mean:** 1.90
PiB Striatal Mean: 3.11	**PiB Striatal Mean**: 3.73	**PiB Striatal Mean**: 4.19
Group: PSEN1 TM6	**Group:** PSEN1 TM8	**Group:** PSEN1 TM2
***PSEN1* Codon:** >200	***PSEN1* Codon:** >200	***PSEN1* Codon:** <200

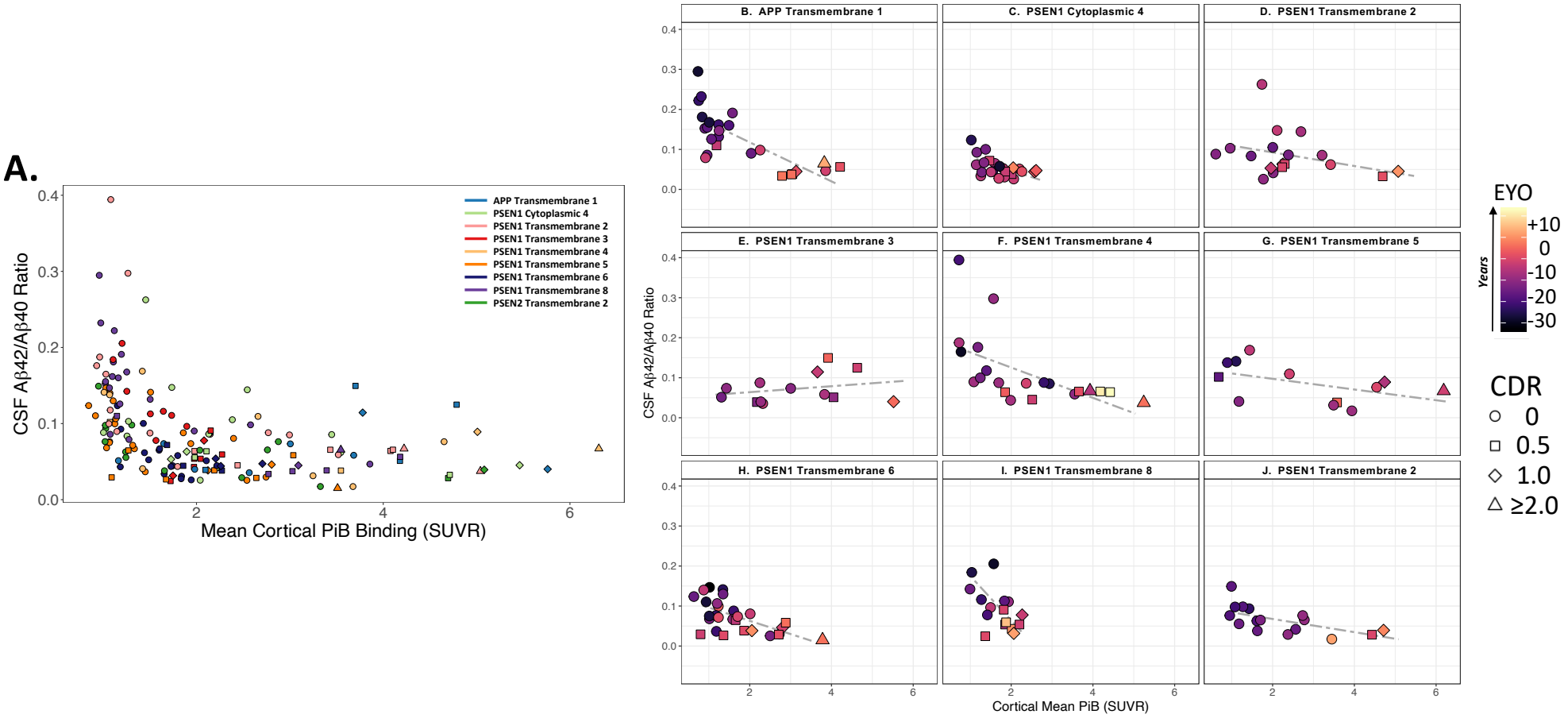
Supplemental Figure 3: *Regional Variability in Amyloid Burden: Examples of Striatal Predominant Patterns.* Three examples across a range of estimated years to symptom onset (EYO) and impairment (Clinical Dementia Rating: CDR; Sum of Boxes: SOB) that show greater striatal compared to cortical amyloid burden as assessed by PiB PET. These images were chosen to demonstrate the heterogeneity present in β-amyloid measures across the course of autosomal dominant Alzheimer's disease. Transmembrane domain abbreviated as TM.



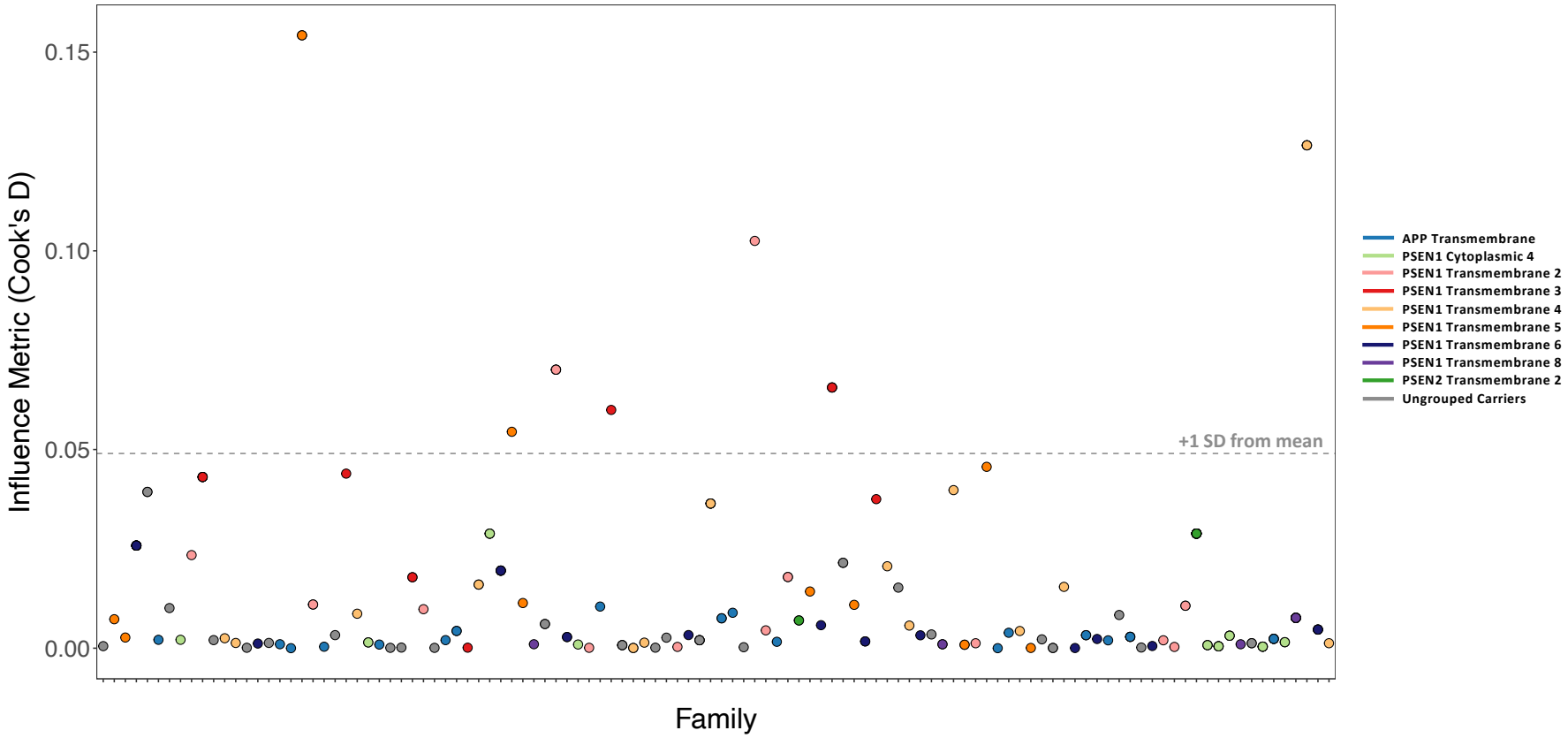
<u>Supplemental Figure 4:</u> *CSF Aβ42/Aβ40 across variant groupings*: Ratios of CSF Aβ42/40 were calculated for domain-based variant groupings (Panel A) and the PSEN1 codon 200 based grouping (Panel B). * denotes FDR corrected $p < 0.05$ for a significant variant group by EYO interaction.



Supplemental Figure 5: *CSF Aβ42 Relative to Amyloid PET, Accounting for Variant Category:* Relationships between CSF Aβ42 and PET based measures of β-amyloid burden were assessed across all domain-based variant groupings (Panel A) and across individual variant groupings (Panels B-J). Only pathogenic variant carriers are shown.



Supplemental Figure 6: *CSF Aβ42/ Aβ40 Ratio Relative to Amyloid PET, Accounting for Variant Category:* Relationships between the CSF Aβ42/40 ratio and PET based measures of β-amyloid burden were assessed across all domain-based variant groupings (Panel A) and across individual variant groupings (Panels B-J). Only pathogenic variant carriers are shown.



Supplemental Figure 7: *Effects of Family Membership on Amyloid PET Results:* Influence metrics were calculated for each family in the sample in models examining associations between PiB PET and domain-based variant groupings. Colors denote each domain-based group. Dashed line indicates 1 standard deviation above the group mean value for the influence metric used (Cook's D).