Variant-dependent heterogeneity in amyloid β burden in autosomal dominant Alzheimer's disease: cross-sectional and longitudinal analyses of an observational study

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Lancet Neurol 2022; 21: 140–52

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Summary

Background Insights gained from studying individuals with autosomal dominant Alzheimer's disease have broadly influenced mechanistic hypotheses, biomarker development, and clinical trials in both sporadic and dominantly inherited Alzheimer's disease. Although pathogenic variants causing autosomal dominant Alzheimer's disease are highly penetrant, there is substantial heterogeneity in levels of amyloid β (Aβ) between individuals. We aimed to examine whether this heterogeneity is related to disease progression and to investigate the association with mutation location within *PSEN1*, *PSEN2*, or *APP*.

Methods We did cross-sectional and longitudinal analyses of data from the Dominantly Inherited Alzheimer's Network (DIAN) observational study, which enrols individuals from families affected by autosomal dominant Alzheimer's disease. 340 participants in the DIAN study who were aged 18 years or older, had a history of autosomal dominant Alzheimer's disease in their family, and who were enrolled between September, 2008, and June, 2019, were included in our analysis. 206 participants were carriers of pathogenic mutations in *PSEN1*, *PSEN2*, or *APP*, and 134 were non-carriers. 62 unique pathogenic variants were identified in the cohort and were grouped in two ways. First, we sorted variants in *PSEN1*, *PSEN2*, or *APP* by the affected protein domain. Second, we divided *PSEN1* variants according to position before or after codon 200. We examined variant-dependent variability in Aβ biomarkers, specifically Pittsburgh-Compound-B PET (PiB-PET) signal, levels of CSF Aβ1-42 (Aβ42), and levels of Aβ1-40 (Aβ40).

Findings Cortical and striatal PiB-PET signal showed striking variant-dependent variability using both grouping approaches ($p<0·0001$), despite similar progression on the clinical dementia rating ($p>0·7$), and CSF Aβ42 levels (codon-based grouping: $p=0·49$; domain-based grouping: $p=0·095$). Longitudinal PiB-PET signal also varied across codon-based groups, mirroring cross-sectional analyses.

Interpretation Autosomal dominant Alzheimer's disease pathogenic variants showed highly differential temporal and regional patterns of PiB-PET signal, despite similar functional progression. These findings suggest that although increased PiB-PET signal is generally seen in autosomal dominant Alzheimer's disease, higher levels of PiB-PET signal at an individual level might not reflect more severe or more advanced disease. Our results have high relevance for ongoing clinical trials in autosomal dominant Alzheimer's disease, including those using Aβ PET as a surrogate marker of disease progression. Additionally, and pertinent to both sporadic and autosomal dominant Alzheimer's disease, our results suggest that CSF and PET measures of Aβ levels are not interchangeable and might reflect different Aβ-driven pathobiological processes.

Funding National Institute on Aging, Doris Duke Charitable Foundation, German Center for Neurodegenerative Diseases, Japanese Agency for Medical Research and Development.

Introduction

Biomarkers are starting to have an increasingly important role in the development of treatments for Alzheimer's disease. An example of this increased importance was shown by the accelerated approval of aducanumab by the US Food and Drug Administration in June, 2021—a decision that was based on a noted reduction in amyloid β (Aβ) burden, as shown by Aβ PET signal. People with autosomal dominant Alzheimer's disease have been central to the development of biomarkers for Alzheimer's disease, forming the basis for many animal models of Alzheimer's disease and offered strong support for the amyloid cascade hypothesis of Alzheimer's disease. The nearly complete penetrance and conserved age of symptom onset within families (although with some variability)[1] also provides an understanding of how far

Research in context

Evidence before this study

We searched PubMed from October, 2018, to May, 2021, for relevant articles in English relating to autosomal dominant Alzheimer's disease pathogenic variants that affect amyloid β (Aβ) burden (assessed with both PET and CSF). Search terms included: "dominantly inherited Alzheimer's disease", "autosomal dominant Alzheimer's disease", "amyloid PET", "PSEN1", "PSEN2", "APP", "CSF", "Aβ42", and "Aβ40". Previous studies, particularly those from the Dominantly Inherited Alzheimer's Network (DIAN) and the Alzheimer's Prevention Initiative, have characterised the behaviour of CSF Aβ42 and Aβ PET across a wide spectrum of asymptomatic and symptomatic autosomal dominant Alzheimer's disease. Because of the low diversity of autosomal dominant Alzheimer's disease genotypes and sample size, these studies either did not examine the role of individual pathogenic variants or used broad genotype categories (eg, before or after *PSEN1* codon 200, or all *PSEN1* compared with all *APP* pathogenic variant carriers) in relatively small samples. Combining autosomal dominant Alzheimer's disease pathogenic variant carriers into broad groups (eg, carriers *vs* non-carriers, and *PSEN1* carriers *vs* *APP* carriers) makes it difficult to recognise heterogeneity in Aβ burden between variants and determine the extent to which variations in Aβ burden are mirrored by variations in disease progression.

Added value of this study

We leveraged the unique size and diversity of pathogenic variants present in the DIAN cohort to assess variant-dependent variability in Aβ burden and disease progression in a way that has not previously been possible. The association of PET and CSF Aβ measures with each other and with disease progression could have important implications for ongoing clinical trials in both sporadic and dominantly inherited Alzheimer's disease. This is particularly the case for the use of Aβ PET as a surrogate efficacy marker and proxy for disease stage in ongoing clinical trials. More broadly, the presence of heterogeneity in Aβ measures in autosomal dominant Alzheimer's disease could have mechanistic implications for understanding how pathological Aβ-driven processes promote disease progression in Alzheimer's disease and the extent to which commonly used Alzheimer's disease biomarkers accurately reflect these processes.

Implications of all of the available evidence

Previous studies have suggested that carriers of *PSEN1* pathogenic variants located after codon 200 are more likely to have cerebral amyloid angiopathy, whereas those with variants before codon 200 have shorter disease duration. However, our data suggest that disease progression is very similar in carriers of *PSEN1* variants both before and after codon 200, despite the overall higher levels of Pittsburgh-Compound-B PET (PiB-PET) signal in carriers of *PSEN1* variants before codon 200. Consistent with cross-sectional findings in *PSEN1* carriers, our longitudinal data show higher rates of increase of PiB-PET signal in carriers of *PSEN1* variants before codon 200, particularly during the symptomatic phase of disease. Although previous studies in small and less genetically diverse samples suggest that striatal Aβ accumulation might precede cortical Aβ deposition, our results indicate that this striatal predominant pattern is not universal across autosomal dominant Alzheimer's disease and might be present in only a subset of *PSEN1* pathogenic variants. For many variant groupings, striatal and cortical PiB-PET signal rose in tandem. Additionally, cortical predominant patterns were also observed. Relevant to both sporadic Alzheimer's disease and autosomal dominant Alzheimer's disease, the observed discordance in some variants between CSF and PET measures of Aβ burden raises questions regarding how interchangeable these measures are in assessing an individual's disease stage and potential response to therapy in a clinical trial. Our results could have broader implications for understanding how closely Aβ biomarkers mirror Aβ-related pathogenic processes and the extent to which these biomarkers can be considered surrogate markers of disease progression at an individual level.

along in the disease course an individual with autosomal dominant Alzheimer's disease might be, even if they are asymptomatic. This understanding offers a rare opportunity to examine the temporal course of changes in biomarkers for Alzheimer's disease that culminate in symptom onset, and to identify biomarkers that are most closely tied to cognitive and functional impairment.

PSEN1, *PSEN2*, and *APP* are genes associated with autosomal dominant forms of Alzheimer's disease. More than 300 highly penetrant and pathogenic variants have been identified in these genes, which implicate Aβ production and processing as a central component of Alzheimer's disease pathobiology.[2,3] Genetic variants identified in people with autosomal dominant Alzheimer's disease are believed to drive disease by altering the relative amounts of Aβ peptides that are generated through the processing of *APP*.[4] Lengthier Aβ species (particularly Aβ1-42 [Aβ42] and Aβ1-43 [Aβ43]), which are more prone to aggregation, increase in abundance relative to shorter less aggregation-prone Aβ fragments,[5,6] thereby increasing deposition of fibrillar Aβ in extracellular plaques.[7] However, there is substantial biochemical evidence showing variability in the Aβ peptide profiles produced by different autosomal dominant Alzheimer's disease-causing variants, despite their nearly complete penetrance.[8,9] In turn, this variability in Aβ production and other genotype-dependent changes in γ-secretase function[10–12] might alter the observed biomarker trajectories across variants.

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For more on **DIAN** see https://dian.wustl.edu/

The Dominantly Inherited Alzheimer's Network (DIAN) is an international, multisite observational study that enrols individuals with autosomal dominant Alzheimer's disease and their families.[2] DIAN has gathered data from more than 100 families bearing more than 60 unique pathogenic variants that cause autosomal dominant Alzheimer's disease. The diversity of variants found in the DIAN cohort has offered an opportunity to assess whether variations in biomarker trajectories are present across pathogenic variants.

The effect of pathogenic variants on Aβ burden in people with autosomal dominant Alzheimer's disease, who are either presymptomatic or symptomatic, could improve our understanding of not only autosomal dominant Alzheimer's disease but also sporadic late-onset Alzheimer's disease. Here, we aimed to use data from DIAN to examine variant-dependent variability in CSF and PET measures of Aβ. Since we know with relative certainty that carriers of pathogenic variants will subsequently develop Alzheimer's disease, heterogeneity in Aβ PET and CSF measures might inform our understanding of how precisely these biomarkers reflect Aβ-driven processes that underlie the progression of Alzheimer's disease at an individual level. Therefore, we also aimed to identify variant-specific effects on biomarker trajectories and assess how these variations might be associated with functional decline.

For more on **UniProt** see https://www.uniprot.org/

Methods

Study design

We did cross-sectional and longitudinal analyses of data from participants who were enrolled in the DIAN observational study between September, 2008, and June, 2019.[2,13] We included individuals with pathogenic variants (appendix p 1) and relevant genetic, clinical, imaging, and CSF data. Participants in DIAN provided informed consent in accordance with the local institutional review boards of each participating site. DIAN study procedures have received ethics approval at Washington University (MO, USA) and all of the participating sites.

See Online for appendix

Participants

340 participants (112 families) were included in our analysis, of whom 206 were pathogenic variant carriers and 134 were non-carriers (table). For each participant, the estimated years from symptom onset (EYO) was calculated as their age minus the age at which their family members first showed symptoms of progressive cognitive decline. Negative values for EYO indicate that a participant is younger than their mean familial age of symptom onset and positive values indicate that a participant is older than their mean familial age of onset. A global clinical dementia rating (CDR) score and sum of boxes (SOB) score was obtained for each participant using structured interviews, as previously described.[2]

Procedures

The presence of autosomal dominant Alzheimer's disease pathogenic variants (assessed using Sanger sequencing), and *APOE* genotype (assessed using PCR), were ascertained for all participants in our cohort. This genotyping was done using DNA derived in parallel at the DIAN Genetics Core (Mount Sinai School of Medicine, NY, USA) and the National Cell Repository for Alzheimer's Disease (National Centralized Repository for Alzheimer's Disease and Related Dementias; Indianapolis, IN, USA), as previously described.[2]

To facilitate the assessment of pathogenic variant-dependent variability in Aβ burden, we grouped 62 unique autosomal dominant Alzheimer's disease variants present in our cohort using two approaches (figures 1A–D). First, we grouped individuals by the protein domain in *PSEN1*, *PSEN2*, or *APP* that was affected by the underlying autosomal dominant Alzheimer's disease-causing variant, using annotation available in UniProt. Domain-based groupings with ten or more pathogenic variant carriers were retained as distinct groups for the purposes of statistical modelling, resulting in nine retained domain-based groups (figure 1D). Each domain-based grouping represented at least two families, and all but one represented more than one pathogenic variant (appendix pp 2–3). The *APP* transmembrane domain grouping was mostly comprised of variants at or near the γ-secretase cleavage site (figure 1C). Four *APP* pathogenic variant carriers (including those with variants near the β-secretase cleavage site) were not retained as a distinct group but

	Carriers of pathogenic variants (n=206)	Non-carriers (n=134)
Age, years	38 (10·49), 19 to 65	38 (12·07), 18 to 69
Global CDR		
0 (no dementia)	140 (68%)	129 (96%)
0·5 (questionable dementia)	42 (20%)	5 (4%)
≥1 (mild, moderate, or severe cognitive impairment)	24 (12%)	0 (0%)
Sex		
Female	117 (57%)	79 (59%)
Male	89 (43%)	55 (41%)
EYO, years	−8·28 (10·6), −32·56 to 22·16	−8·26 (12·81), −34·73 to 21·47
Education, years	14·57 (2·88), 6 to 24	15·08 (2·41), 9 to 22
APOE ε4 carrier	65 (32%)	43 (32%)
APOE ε2 carrier	32 (16%)	23 (17%)
Families	112	76
Familial age of symptom onset, years	47 (8), 27 to 77	47 (7), 28 to 62

Data are n (%) or mean (SD), range. CDR=clinical dementia rating. EYO=estimated years from symptom onset.

Table: **Baseline characteristics of participants from the DIAN cohort**

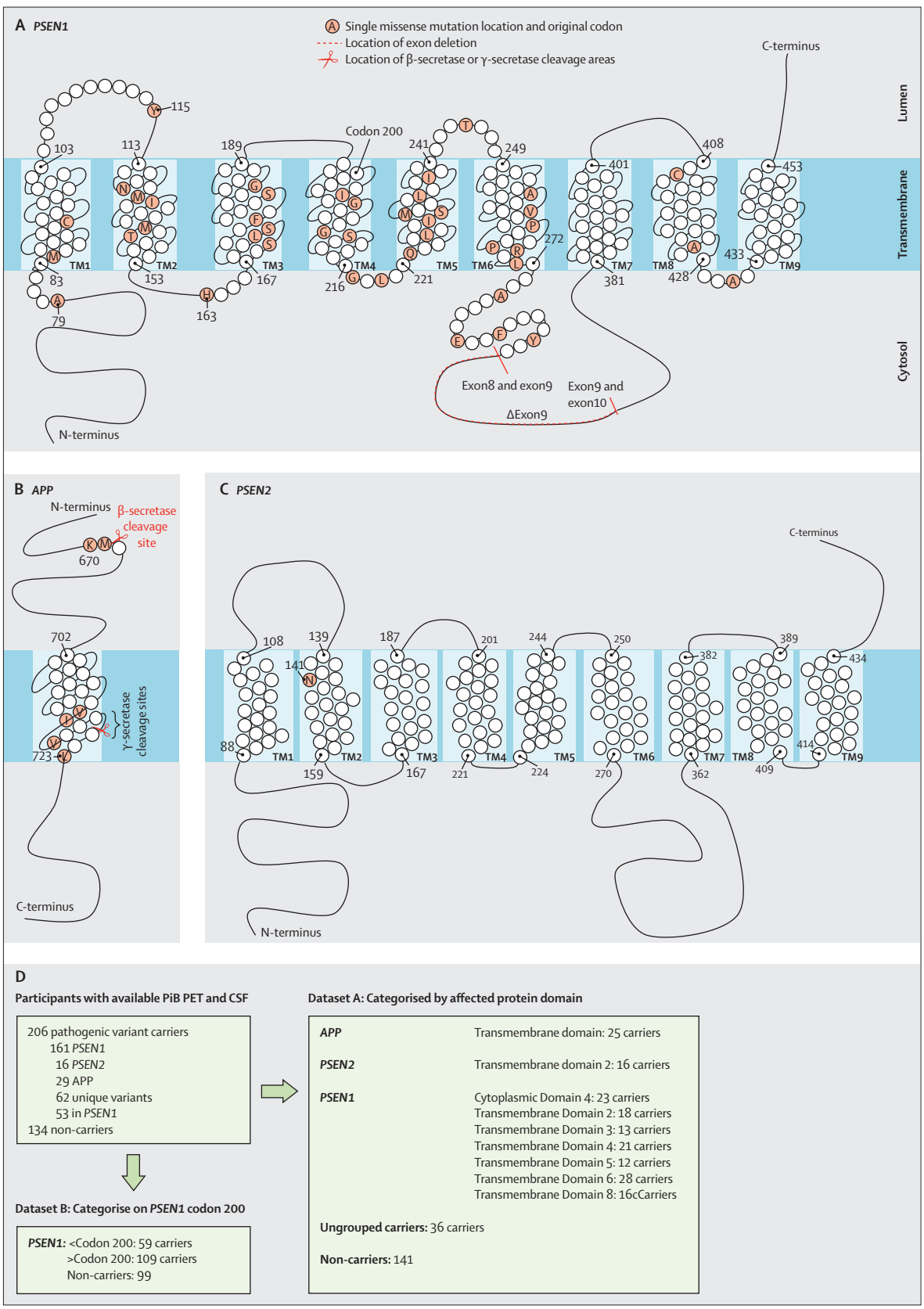

Figure 1: **Categorisation of autosomal dominant Alzheimer's disease pathogenic variants**
The locations of the 62 unique pathogenic variants in *PSEN1*, *PSEN2*, and *APP* in our cohort are represented in panels A–C. Individual variants in *PSEN1*, *PSEN2*, and *APP* were categorised (D) on the basis of the affected protein domain (dataset A) or by whether pathogenic variants were before or after codon 200 in *PSEN1* (dataset B).
In dataset A, only variant categories with ten or more pathogenic variant carriers were retained as distinct groups. Carriers from variant groupings with fewer than ten participants were retained as ungrouped carriers. For dataset B, only *PSEN1* pathogenic variant carriers and their family members were retained in the analysis. Delta symbols refer to deletions. Further detail for variant groupings is shown in the appendix (pp 2–3).
PiB=Pittsburgh-Compound-B. TM=transmembrane domain.

were included with the ungrouped pathogenic variant carriers (figure 1D).

In the second approach, we included only individuals with pathogenic variants in *PSEN1*. These participants were grouped on the basis of whether the underlying variant was before or after codon 200 in *PSEN1*.[14,15] Codon 200 falls within *PSEN1* transmembrane domain 4, but all carriers with transmembrane domain 4 variants in the cohort were in the group after codon 200 (figure 1A). Consequently, carriers of *PSEN1* variants in transmembrane domains 1–3, cytoplasmic domains 1–2, and luminal domains 1–2 were included in the before codon 200 grouping. All remaining *PSEN1* carriers were included in the after codon 200 grouping (figure 1; appendix p 2).

^{11}C-Pittsburgh-Compound-B PET (PiB-PET) was done as previously described.[2,13] Binding was assessed between 40 min and 70 min following PiB bolus and converted to cortical grey matter and dorsal striatal (averaging bilateral caudate and putamen) mean standardised uptake value ratios (SUVRs). Cerebellar grey matter was used as the reference region, and regional spread function-based partial volume correction was done. Sensitivity analyses were done using cortical white matter or brainstem as reference regions. Brain regions were defined using FreeSurfer (version 6.0, Cambridge, MA, USA). Sensitivity analyses showed that the effects reported were not dependent on the reference region (appendix p 4).

CSF was obtained as previously described[2] using procedures consistent with the Alzheimer's Disease Neuroimaging Initiative (Los Angeles, CA, USA). CSF analyses for Aβ1-40 (Aβ40) and Aβ42 were done at the DIAN Biomarker Core (St Louis, MO, USA) using an ELISA (INNOTEST, Innogenetics, Ghent, Belgium).

Statistical analysis

General linear mixed effects models were implemented in R (version 4.0.0) using the *nlme*, *lmer*, *parameters*, and *influence.ME* packages. Satterthwaite approximations were used to calculate degrees of freedom. p values shown are false discovery rate (FDR) adjusted to maintain α less than or equal to 0·05. Domain-based or codon-based variants were grouped by EYO interaction to assess variant-dependent effects across the disease course. Cross-sectional analyses included age, gender, and binarised *APOE* ε4 status (ie, ε4 carrier or non-carrier) as fixed effects and family membership as a random effect. Models using longitudinal data included the same covariates as cross-sectional models and further included terms for a random intercept and slope. A variant grouping by time interaction was included as a fixed effect to assess variant-dependent effects on biomarker trajectories in models using longitudinal data. Locally weighted estimated scatterplot smoothing was used for illustrations. Sensitivity analyses assessing family membership, *APOE* ε4 or *APOE* ε2 genotype, and Alzheimer's disease polygenic risk scores are described in the appendix (p 1).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

We first examined relations between proximity to symptom onset (ie, EYO) and Aβ burden using both PiB-PET and CSF measures. Autosomal dominant Alzheimer's disease pathogenic variant carriers showed significantly lower CSF Aβ42 (β=–16·47 pg/mL per year [95% CI –22·35 to –10·58]; p<0·0001) and higher PiB-PET signal (β=0·06 SUVR per year [0·04 to 0·08]; p<0·0001) with increasing EYO compared with non-carriers (figure 2).

We next assessed whether functional progression of disease varied across variants in autosomal dominant Alzheimer's disease. The mean EYO at study entry was similar across variant groupings (domain F[9, 196]=0·67, p=0·75; codon F[1, 159]=0·18, p=0·71), suggesting that variant groups were statistically similar in terms of their proximity to estimated symptom onset. Progression of functional decline, as assessed using CDR SOB, was also similar across variant groupings (domain-based F[9, 206]=0·79, p=0·68; codon-based F[1, 161]=0·14, p=0·74), suggesting a similar progression of functional impairment across variant groupings (figures 3C, F).

We next examined whether Aβ burden, as measured by PiB-PET, varied across variant groupings during autosomal dominant Alzheimer's disease. Significant variant-dependent variability in the relation between cortical Aβ burden and EYO was observed using the domain-based grouping in autosomal dominant Alzheimer's disease pathogenic variant carriers (variant: grouping by EYO interaction F[9, 170·96]=5·83, p<0·0001; figures 3, 4). Examining this effect more closely, individuals carrying variants affecting *PSEN1* cytoplasmic domain 4 (grouping by EYO interaction F[1, 172·18]=4·24, p=0·031; β=–0·045 [SE 0·020] PiB SUVR per year), *PSEN1* transmembrane domain 6 (F[1, 160·18]=3·98, p=0·047; β=–0·028 [SE 0·014] PiB SUVR per year), and *PSEN1* transmembrane domain 8 (F[1, 126·78]=14·63, p<0·0001; β=–0·053 [SE 0·014] PiB SUVR per year) had less cortical PiB binding in relation to EYO than other pathogenic variant carriers. By contrast, *PSEN1* transmembrane domain 3 (F[1, 156·49]=4·24, p=0·05; β=0·089 [SE 0·043] PiB SUVR per year), *PSEN1* transmembrane 5 (F[1, 198·61]=5·78, p=0·025; β=0·071 [SE 0·029] PiB SUVR per year), and *PSEN2* transmembrane domain 2 (F[1, 98·85]=8·67, p<0·0001; β=0·050 [SE 0·017] PiB SUVR per year) carriers had significantly greater cortical Aβ burden in relation to EYO than other pathogenic variant carriers (figures 3, 4; appendix p 7).

Using the *PSEN1* codon-based grouping, we again observed a significant effect of variant grouping on PiB binding relative to EYO, such that individuals who carried pathogenic variants in *PSEN1* before codon 200

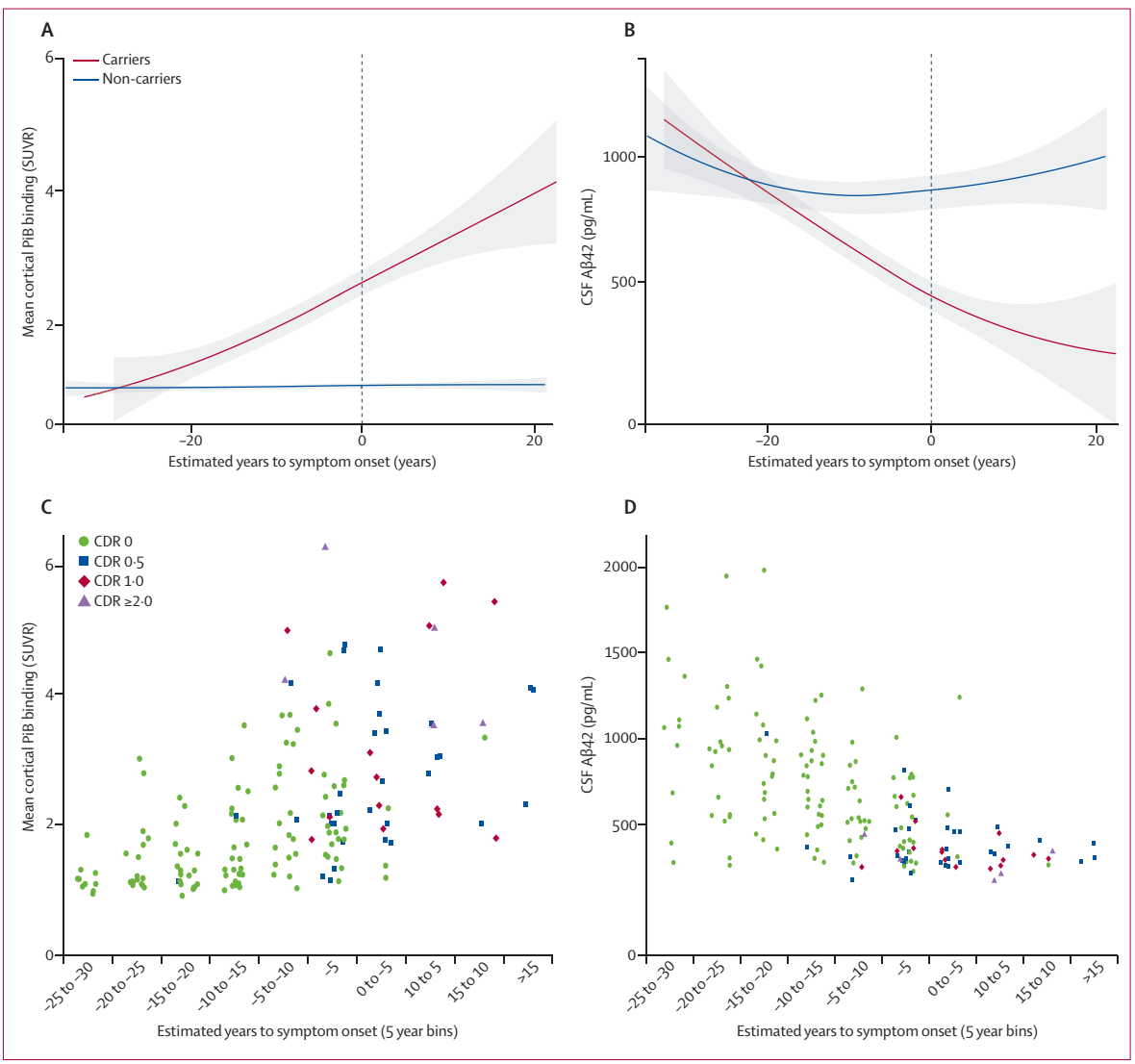

Figure 2: **Trajectories of amyloid β burden across estimated years to symptom onset**
Aβ burden in autosomal dominant Alzheimer's disease pathogenic variant carriers (red line) and non-carriers (blue line) as assessed by PiB-PET (A; cortical mean) and CSF Aβ42 (B). Grey dashed line corresponds to age of expected symptom onset. Shaded areas represent 95% CI. In both PiB-PET and CSF assessments, evidence of increased Aβ burden was seen in pathogenic variant carriers compared with non-carriers at least 10 years before symptom onset. Individual datapoints suggest substantial interindividual variation in Aβ burden measured by PiB-PET (C) and by CSF Aβ42 (D) in pathogenic variant carriers (only carriers shown in panels C and D). Level of impairment is coded with shapes and colours using the clinical dementia rating global score. Aβ=amyloid β. CDR=clinical dementia rating. PiB-PET=Pittsburgh-Compound-B PET. SUVR=standardised uptake value ratio.

had a significantly greater cortical PiB-PET signal with increasing EYO than did those with variants after *PSEN1* codon 200 (codon category by EYO interaction: F[1, 154·99]=21·70, p<0·0001; β=0·065 [SE 0·014] PiB SUVR per year; figure 3). Using a brainstem or white matter reference region instead of cerebellar grey matter yielded similar results for both grouping approaches (appendix p 4), suggesting that variant grouping associations with PiB-PET are not reference region dependent.

We next assessed whether similar variant-dependent differences could be measured by PiB-PET over time. Consistent with cross-sectional findings, carriers of *PSEN1* pathogenic variants before codon 200 had greater longitudinal rates of PiB-PET SUVR increase than did carriers of *PSEN1* pathogenic variants after codon 200 (77 carriers with 187 observations; codon categorisation*time: t(48·44)=4·06, p<0·0001; figure 5A). As clinical trials in autosomal dominant Alzheimer's disease often select participants by EYO range and the presence or absence of symptoms, we repeated these analyses by examining rates of PiB-PET change that were categorised by these parameters (figure 5B). We observed that the rates of PiB change were similar across codon-based groupings in early, asymptomatic phases of autosomal dominant Alzheimer's disease, but that significant

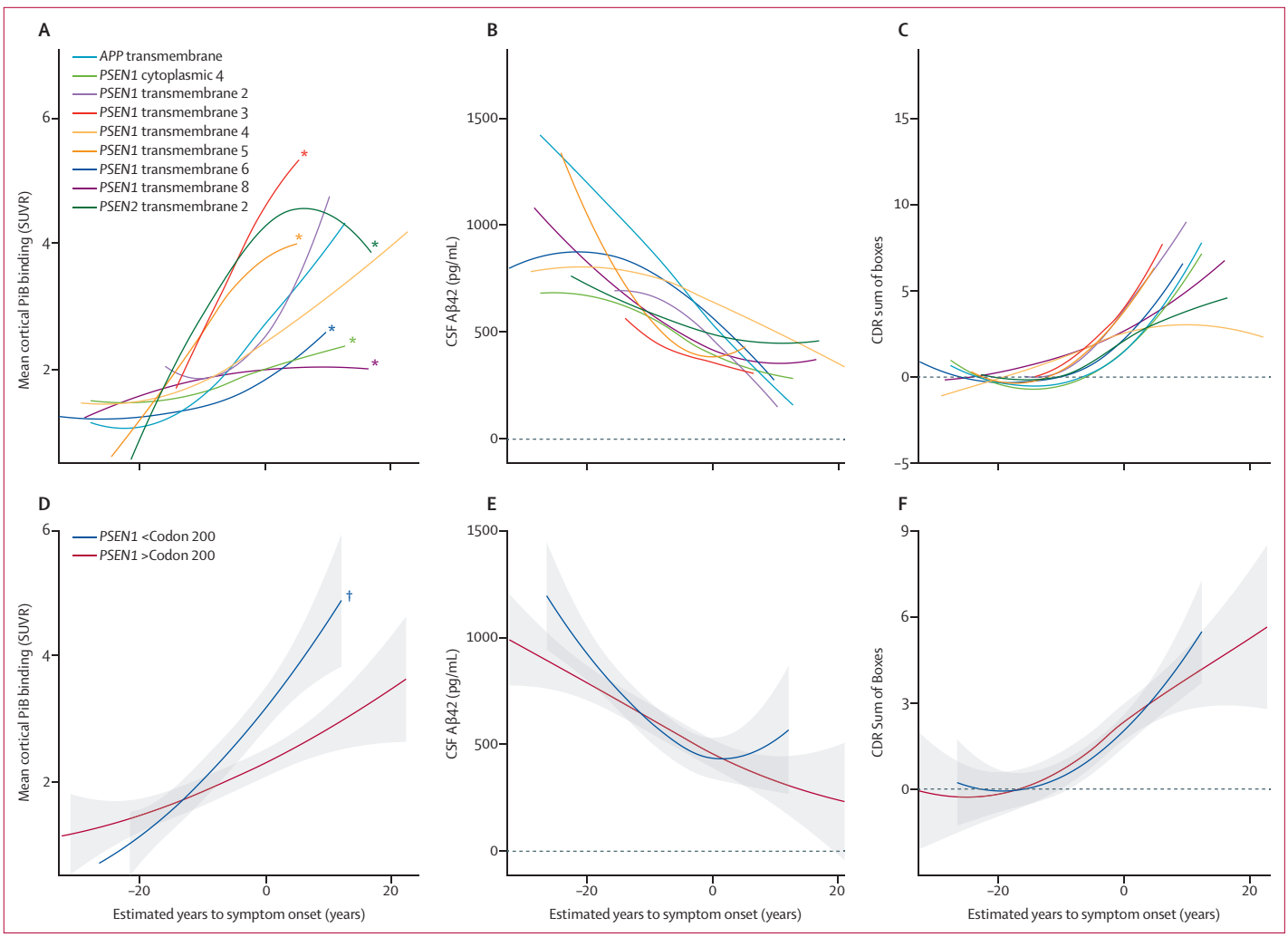

Figure 3: **Amyloid β burden and functional decline considering variant groupings**

Trajectories of PiB-PET (A, D), CSF Aβ42 (B, E), and CDR sum of boxes (C, F) across variant groupings. In panels A–C, individual variants were categorised according to the protein domain affected by the underlying genetic variation. In panels D–F, *PSEN1* pathogenic variant carriers were grouped on the basis of whether the identified variant in *PSEN1* was before or after codon 200. No significant differences between variant groupings were observed in CSF Aβ42 or in CDR sum of boxes (B, C, E, F), but significant variant-dependent variations in Aβ PET signal were observed using both the domain-based and codon-based groupings (A, D; appendix p 7). Aβ=amyloid β. CDR=clinical dementia rating. EYO=estimated years to symptom onset. FDR=false discovery rate. PiB-PET=Pittsburgh-Compound-B PET. SUVR=standardised uptake value ratio. *FDR corrected p≤0·05 for each variant grouping by EYO interaction compared with all other pathogenic variant carriers. †FDR corrected p≤0·0001 for carriers of *PSEN1* variants before codon 200 compared with carriers of variants after codon 200.

variant-dependent variability in Aβ burden was evident in later phases of disease (figure 5). A similar analysis was not done in the domain-based grouping because of insufficient longitudinal data to model all variant groups across the early, late, and symptomatic phases of disease.

We next examined whether variant-based groupings could explain regional variations in striatal versus cortical Aβ burden in pathogenic variant carriers. The relation between EYO and striatal PiB-PET SUVR varied significantly by domain-based grouping (F[9, 167·33]=2·30, p=0·030), as did the relative amounts of cortical and striatal PiB-PET signal (F[9, 296·02]=3·87, p=0·0003; figures 6A, C–K). For most domain-based variant groupings, cortical and striatal PiB-PET signal relative were similar in magnitude. However, striatal or cortical predominant patterns were observed in some variant groups. Specifically, the *PSEN1* transmembrane domain 4 (t[296·02]=–2·09, p=0·048; figure 6G) and *PSEN2* transmembrane 2 (t[296·02]=–2·726, p=0·010; figures 4D, 6K) groupings had significantly greater cortical versus striatal Aβ burden, whereas the *PSEN1* transmembrane 2 (t[296·02]=2·44, p=0·033; figures 4C, 6E; appendix p 8) and *PSEN1* transmembrane domain 8 (t[296·02]=2·16, p=0·042; figures 4G, 6J) groupings showed greater striatal PiB-PET signal than cortical PiB-PET signal. Mirroring the pattern seen with cortical PiB-PET signal, *PSEN1* carriers with pathogenic variants before codon 200 also had greater striatal PiB-PET signal than those with pathogenic variants after codon 200 (t[159·5]=3·92, p=0·0003; figure 6B).

We next examined CSF Aβ42 and Aβ40 using the same variant groupings and approach. Unlike the pattern

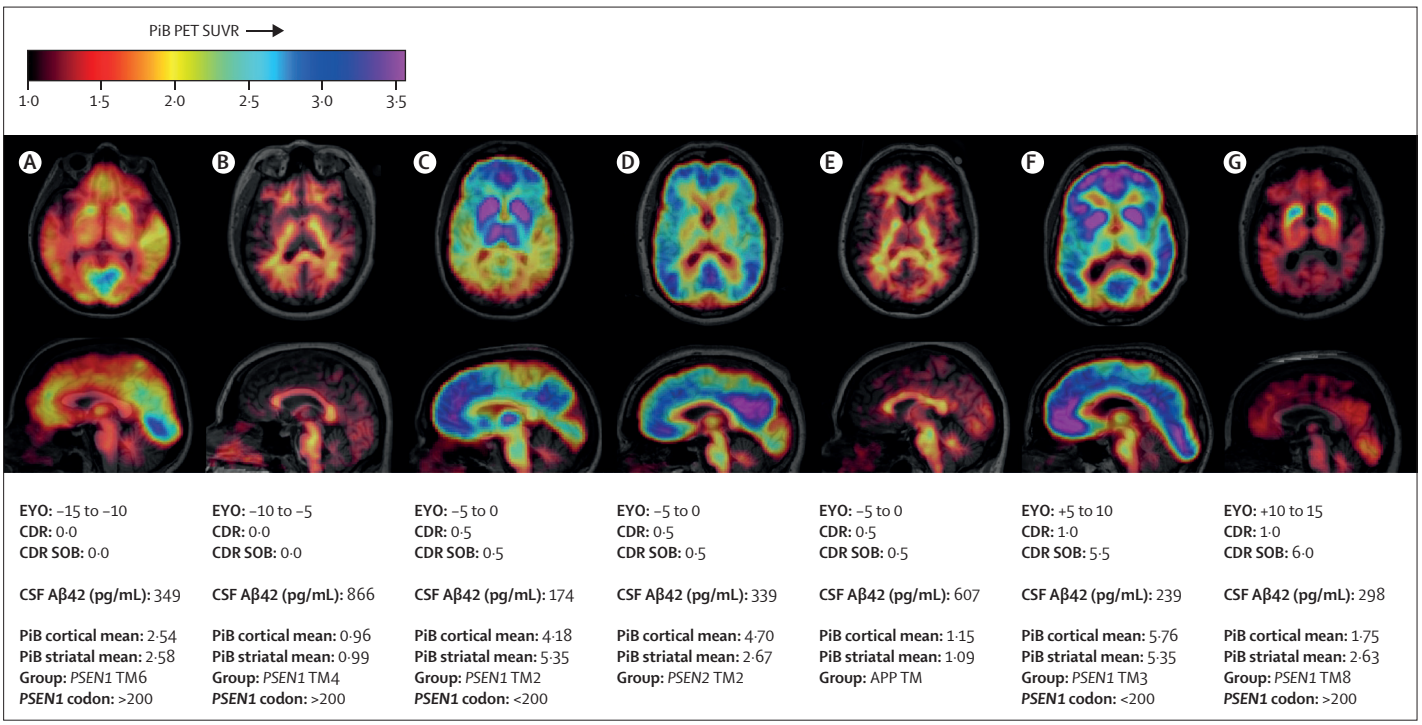

***Figure 4*: Examples of variant-dependent variations in PiB-PET**
PiB-PET images from autosomal dominant Alzheimer's disease pathogenic variant carriers starting from early, presymptomatic stages of disease (left) to later stages with recognised clinical impairment (right), as measured by the global CDR and CDR SOB. Clinical impairment begins from panel C onwards. CSF Aβ42, cortical and striatal mean PiB values, and variant grouping are shown below each image. These images were chosen to show the heterogeneity present in Aβ measures across the course of autosomal dominant Alzheimer's disease. Examples of striatal predominant patterns are shown in the appendix (p8). Aβ=amyloid β. CDR=clinical dementia rating. EYO=estimated years to symptom onset. PiB-PET=Pittsburgh-Compound-B PET. SOB=sum of boxes. SUVR=standardised uptake value ratio. TM=transmembrane domain.

observed with Aβ PET, CSF Aβ42 (figures 2B, D; appendix p 6) did not show variant dependent variability with respect to EYO using either the domain-based (F[9, 151·86]=1·77, p=0·095; figure 3) or codon-based groupings (F[1, 160·94]=0·63, p=0·49; figure 3). The relationship of CSF Aβ42 to PiB-PET varied significantly across variants using the domain-based (F[9, 184·35]=4·85, p<0·0001) but not the *PSEN1* codon 200-based grouping (F[1, 154·99]=0·4059, p=0·59). This finding indicates that that correlations between PET and CSF measures of Aβ vary by the *PSEN1*, *PSEN2*, or *APP* protein domain affected by the underlying pathogenic variant (appendix p 10).

We next examined whether variant-dependent variations in the ratio of Aβ42 and Aβ40 were present. Across all autosomal dominant Alzheimer's disease pathogenic variant carriers, the ratio of Aβ42 to Aβ40 declined with increasing EYO (effect of increasing EYO in carriers: t[198·87]=−2·47, p=0·010). A statistical difference in the ratio of Aβ42 to Aβ40 was seen across variants using the domain-based grouping (F[9, 162·21]=4·34, p<0·0001) and the *PSEN1* codon 200-based grouping (F[1, 143·39]=4·9243, p=0·037). However, including the ratio of Aβ42 to Aβ40 as a covariate did not reduce the effect of variant grouping on PiB-PET SUVR relative to EYO (including the ratio of Aβ42 to Aβ40 as a covariate: domain grouping-by-EYO interaction: F[9, 167·74]=6·138, p<0·0001; codon grouping-by-EYO interaction: F[1, 154·06]=19·63, p<0·0001; appendix pp 9–10). Together, these results indicate that although the ratio of Aβ42 to Aβ40 differs across variant groupings, these differences do not account for the previously observed variant-dependent effects on Aβ PET.

Discussion

The findings of our study of autosomal dominant Alzheimer's disease pathogenic variants showed that Aβ accumulation, as measured by PiB-PET, was highly variable across pathogenic variants grouped by the affected protein domain or by the location of the pathogenic variant in *PSEN1*.[14] However, despite robust associations between variant grouping and Aβ PET changes with respect to EYO, functional decline was similar across variant groupings. In turn, our results suggest that Aβ PET alone might not represent an optimal surrogate marker of disease stage or severity in autosomal dominant Alzheimer's disease. Moreover, consideration of additional biomarkers, particularly measures of soluble Aβ, might be needed in ongoing clinical trials. This consideration includes blood-based measures of the ratio of Aβ42 to Aβ40, which were highly correlated with cognitive benefit or decline in clinical trials of the anti-amyloid agent lecanemab, and have been associated with variations

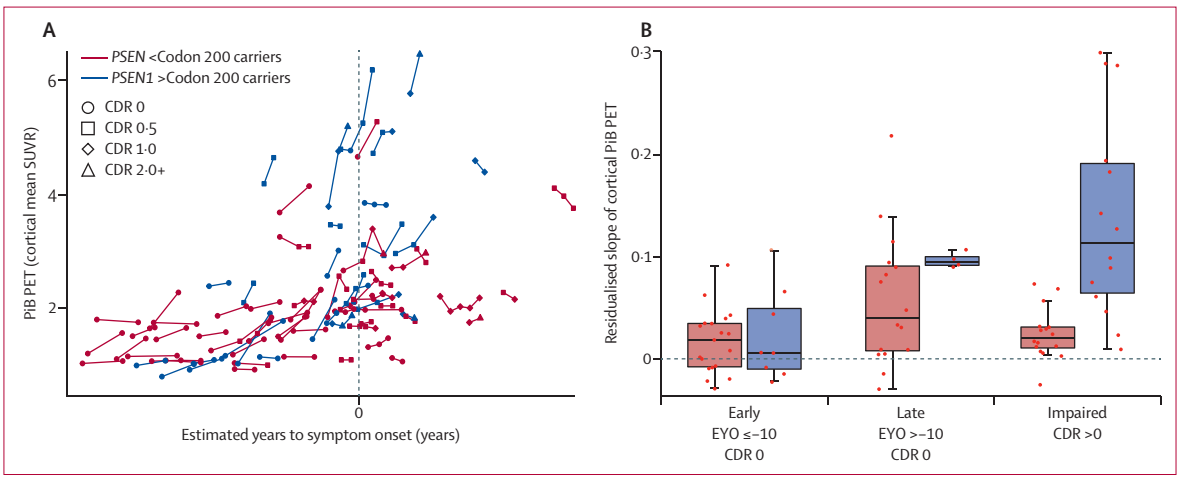

Figure 5: **PiB-PET during longitudinal follow-up**

(A) Individual pathogenic variant carriers are shown. Each datapoint represents a PiB-PET measurement; lines connect observations from the same participant, and symbols show the CDR at each observation at each study visit. (B) To examine how PiB-PET signal varies longitudinally by stage of disease, variant carriers were separated into early asymptomatic, late asymptomatic, and impaired phases of autosomal dominant Alzheimer's disease. Yearly change in PiB-PET signal is shown, which was calculated from the available longitudinal data.The red dots represent slopes for an individual participant. The top of the boxplot shows the 75th percentile. The bottom of the boxplot shows the 25th percentile. Whiskers represent the range; the top and bottom edge of the whisker are the largest and smallest values within 1·5 times the interquartile range. The horizontal line in the box represents the 50th percentile. p values shown are corrected for false discovery rate. CDR=clinical dementia rating. EYO=estimated years to symptom onset. PiB-PET=Pittsburgh-Compound-B PET.

in Aβ PET signal in autosomal dominant Alzheimer's disease.[16,17] Relevant to both sporadic and autosomal dominant Alzheimer's disease, the observed variability between PET and CSF measures of Aβ burden at an individual level suggests that these measures might not be interchangeable in assessing Aβ status nor response to amyloid-targeting therapies.

Regional variations in cortical versus striatal PiB-PET signal in relation to EYO were also seen across pathogenic variants, with most groupings showing similar cortical and striatal PiB-PET signal, but others showing striatal or cortical predominant patterns. At least one study[18] has suggested that Aβ accumulation in autosomal dominant Alzheimer's disease might start in the striatum. This previous study used data from two families with mutations in *PSEN1* transmembrane domain 8. This finding is consistent with those of our study, as *PSEN1* transmembrane domain 8 was among two groupings that showed a striatal predominant pattern of PiB-PET signal. However, this pattern was the exception rather than the rule, as the observations in our study suggest that cortical and striatal PiB-PET signal rise in tandem for many autosomal dominant Alzheimer's disease variants, but that some pathogenic variants can have cortical or striatal predominant patterns.

Although measures of CSF Aβ and Aβ PET are sometimes used interchangeably to assess so-called amyloid positivity,[19] our results provide evidence that these two measures can diverge substantially (figure 4; appendix pp 10–11). More work is needed to determine the biological processes that might alter the commonly observed relation between CSF-based and PET-based measures of Aβ burden, as this divergence could have relevance for clinical and research interpretations of these measures of Alzheimer's disease pathology. This divergence might be due to variant-dependent differences in the production of aggregation-prone Aβ species (particularly Aβ42 and Aβ43) relative to less aggregation-prone, shorter fragments. We observed that variant-dependent variations in Aβ PET signal across the autosomal dominant Alzheimer's disease course do not necessarily correlate with functional decline and are not easily explained by the ratio of Aβ42 and Aβ40 measured in vivo from these same individuals. However, although previous studies have indicated that most autosomal dominant Alzheimer's disease-causing variants lead to an increased production of Aβ42 relative to Aβ40,[4] the mean age of onset for particular *PSEN1* pathogenic variants was not correlated with in vitro production of the ratio of Aβ42 to Aβ40 for that variant.[8] This finding suggests that the ratio of Aβ42 to Aβ40 by itself might not be sufficient to characterise the pathogenicity of a particular disease-causing variant. Accordingly, assessment of other Aβ fragments (particularly Aβ38 and Aβ43) might be needed to better characterise the pathogenicity of individual disease-causing variants. By contrast, work assessing plasma concentrations of Aβ38, Aβ40, and Aβ42 in an autosomal dominant Alzheimer's disease sample suggests that in vivo measures of γ-secretase function are moderately correlated with age of onset within *PSEN1* variant carriers.[16] In addition to examining this issue in a broader set of variants, aspects of γ-secretase function apart from APP processing need to be considered, including alterations in the processing of other γ-secretase substrates and effects on calcium homoeostasis.[7,10,20,21]

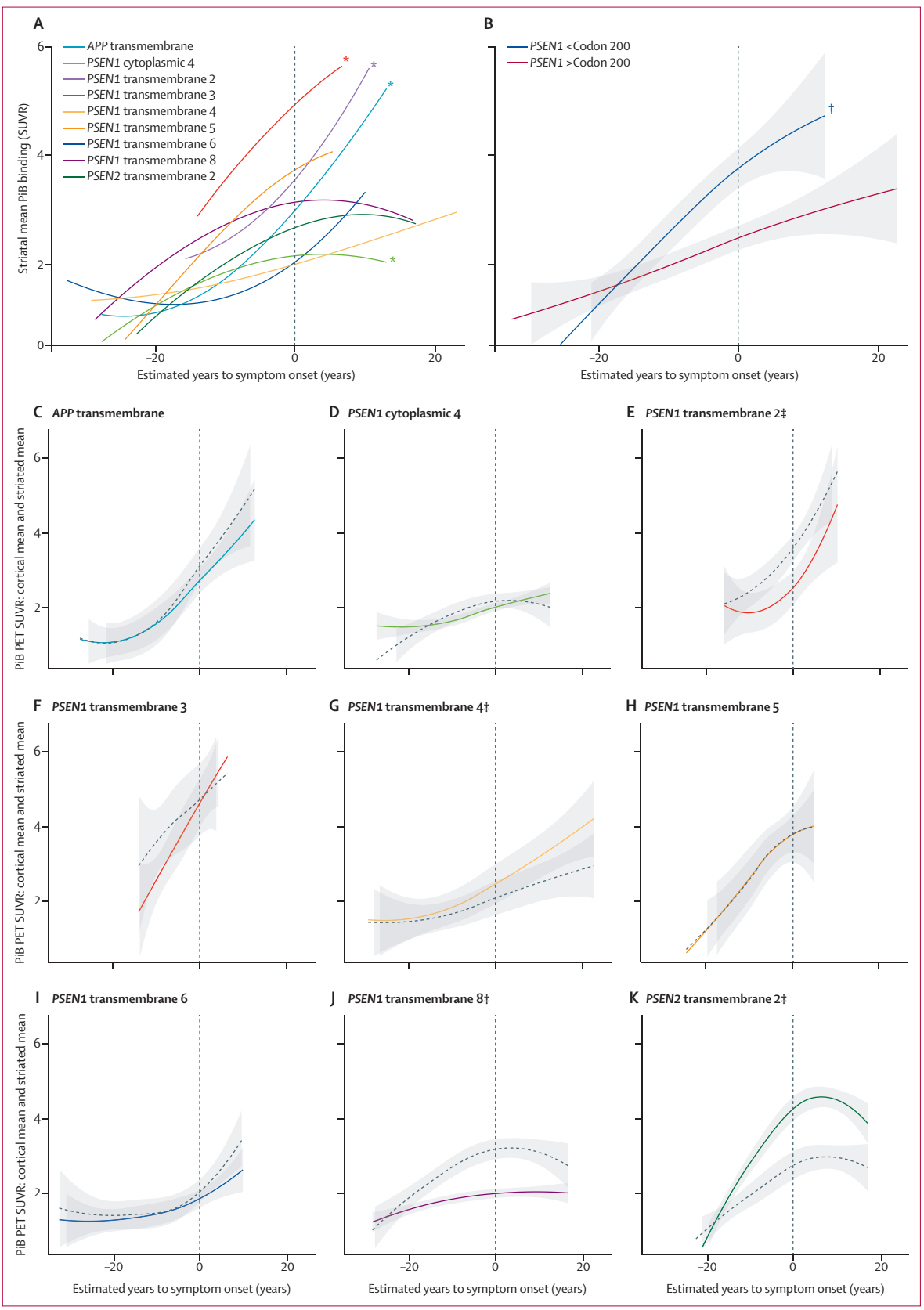

Figure 6: **Variant-dependent variability in regional amyloid burden**
Trajectories of striatal mean PiB SUVR across EYO with pathogenic variants grouped according to affected protein domain (A) or in *PSEN1* carriers with genetic variants before or after codon 200 (B). Individual variant categories from panel A are depicted in panels C–K, with cortical mean shown in coloured solid lines and striatal mean shown in grey dashed lines. EYO=estimated years to symptom onset. PiB-PET=Pittsburgh-Compound-B PET. SUVR=standardised uptake value ratio. *p≤0·05 for main effect of variant grouping relative to other pathogenic variant carriers. †p≤0·0005 for the presence of a codon-based grouping by EYO interaction. ‡p≤0·05 for comparison of cortical to striatal PiB-PET SUVR within each variant grouping. p values are corrected for false discovery rate.

The disconnect between CSF and PET measures of Aβ observed in some variant groupings also raises the possibility that particular pathogenic variants might aggregate Aβ pathology in forms[22–24] that are differentially detectable by Aβ PET. Although further pathological characterisation is needed to address this possibility, this hypothesis would be consistent with what has been seen in a starker form with the *APP* Glu693Gly (Arctic) mutation, in which Aβ deposits appear not to be detectable by PiB, even in advanced states of impairment.[25,26] Alternatively, it could be that the true burden of pathological amyloid across pathogenic variants could itself be variable, despite similarities in rates of functional decline. Regardless of the cause, the potential for discordance between CSF and PET measures of Aβ burden itself raises questions for the interchangeable use of these measures in amyloid, tau, and neurodegeneration (ATN) staging and as surrogate markers of disease progression in both sporadic and autosomal dominant Alzheimer's disease. From a more mechanistic perspective, the high degree of variability in relations between CSF Aβ42 and the the ratio of Aβ42 to Aβ40 with Aβ PET observed here also raises questions regarding the common assumption that CSF Aβ levels are reduced because of sequestration of these peptides within insoluble Aβ plaques.

The strengths of our study include its large sample size and greater diversity of autosomal dominant Alzheimer's disease pathogenic variants relative to other studies. Additionally, the availability of longitudinal PiB-PET data allowed for the verification of cross-sectional patterns in longitudinal data for the codon-based grouping. The need to combine individual variants into groups on the basis of the affected protein domain or location within *PSEN1* (relative to codon 200) reduced the number of comparisons, allowed for a broader range of EYO to be represented, and allowed for potentially more stable statistical estimates because of a greater number of datapoints within each grouping. Additionally, combining variants into groups is likely to have reduced the impact of polygenic effects related to family membership on our results, as all groupings had at least two families contributing data (and most groupings had more than ten families represented; appendix p 2). This observation is especially true for the *PSEN1* codon 200-based groupings, each of which had more than 30 families represented. Consistent with this, adjusting for an International Genetics of Alzheimer's Project-derived polygenic risk score at an individual level did not account for the observed associations between either variant-grouping relative to EYO and Aβ PET signal (appendix p 5). Conversely, the grouping of variants might have diminished variant-dependent effects by causing variants with dissimilar effects on fibrillar Aβ to be included in the same group by virtue of their proximity within the affected gene. However, grouping dissimilar variants together should bias the results away from seeing a significant effect of variant grouping, rather than the observed pattern of robust, variant grouping associated effects.

Several other limitations are important to consider. Although all domain-based groups had at least 14 mutation carriers contributing data, more statistical power within a particular grouping might be needed to observe subtle variant-dependent effects. Related to this concern, although the potential effects of family membership on our results were addressed in sensitivity analyses and by our inclusion of family as a random effect in statistical models, to fully eliminate the possibility of family membership effects will require larger samples in which the same pathogenic variants are present in different genetic and environmental backgrounds. This initial examination of variant-dependent variability in Aβ burden in autosomal dominant Alzheimer's disease made use of variant categories defined a priori on the basis of previous studies (codon 200 grouping) or on the portion of the protein affected by the underlying pathogenic variant (domain-based grouping). Although the biological implications of each pathogenic variant possibly differed on the basis (partly) of the location affected within the resulting protein (eg, within a transmembrane *vs* cytoplasmic domain), further work is necessary to generate data-driven variant groupings and biochemically driven variant groupings that are likely to better cluster biologically similar variants than the groupings used in our study. Lastly, it will be important to extend this work into other imaging and biochemical measures in the DIAN observational study and, particularly, to examine potential variant-dependent changes in biofluid and PET measures of tau pathology when sufficient data of this type become available.

Despite these limitations, our results provide strong evidence that the underlying pathogenic variant is an important determinant of the topography and burden of Aβ deposition in autosomal dominant Alzheimer's disease and, consequently, is important to the success of clinical trials of amyloid-focused treatments in this population. Relevant to both sporadic and autosomal dominant Alzheimer's disease, understanding the underlying biology that might cause measures of CSF Aβ to diverge strongly from PET measures of Aβ burden could help to refine the use of these measures as surrogate markers of Alzheimer's disease progression. More fundamentally, the observed discordance between apparent Aβ burden and stage of disease in autosomal dominant Alzheimer's disease underscores that, although PET and CSF measures of Aβ measures are valuable biomarkers in clinical and translational research in Alzheimer's disease, these widely used biomarkers might not comprehensively and unerringly reflect the essential, amyloid-related pathobiological processes that drive Alzheimer's disease progression at an individual level.

Contributors

JPC and SAS were responsible for doing the literature search. JPC, SAS, EM, BJH, RAS, and KAJ were responsible for designing the study. JPC, SAS, EM, APS, BJH, NJ-M, RF, CDF, KPS, JL, SBB, JHL, AH, JMN, NG-R, HM, SMS, CLM, RM, CMK, CX, CC, BAG, TLSB, NCF, PRS, RJP, AER, BTE, MVF, YJS, AMF, AMG, and RJB were responsible for data collection. JPC, SAS, EM, BJH, and APS were responsible for analysing the data. JPC, SAS, EM, APS, WEK, LL, AMG, KAJ, and RAS were responsible for interpreting the data. JPC, SAS, and APS were responsible for the figures. JPC, SAS, EM, and RAS were responsible for writing the manuscript. JPC, SAS, EM, APS, LL, BJH, NJ-M, RF, CDF, KPS, JL, SBB, JHL, WEK, AH, JMN, NG-R, HM, SMS, CC, CLM, RM, RJP, AER, BTE, MVF, YJS, CMK, CX, BAG, TLSB, NCF, JCM, PRS, AMF, AMG, RJB, KAJ, and RAS were responsible for critically reviewing the manuscript. JPC, SAS, and APS accessed and verified the underlying data. JPC was responsible for submitting the study for publication.

Declaration of interests

JPC has served on medical advisory boards for Otsuka Pharmaceuticals and Humana Healthcare, outside of the submitted work. APS has served on medical advisory boards for Janssen Pharmaceuticals and Biogen, outside of the submitted work. SMS reports consulting to Eisai, Novartis, Genentech, F Hoffmann-La Roche, Gemvax, Avid Radiopharmaceuticals, and Eli Lilly, outside of the submitted work. SMS also serves on steering committees for major biomarker and clinical trials and consortia such as the Alzheimer's Disease Neuroimaging Initiative, the Dominantly Inherited Alzheimer Network (DIAN), Alzheimer's Clinical Trial Consortium, Global Alzheimer's Platform- Network, and Longitudinal Early-onset Alzheimer's disease study, and is a project arm leader for the Dominantly Inherited Alzheimer's Network-Treatment Unit (DIAN-TU) study, outside of the submitted work. WEK is a co-inventor of Pittsburgh-Compound-B (PiB) and, as such, has a financial interest in a license agreement held by GE Healthcare and the University of Pittsburgh (PA, USA) based on the PiB-PET technology used in this manuscript. GE Healthcare provided no grant support for this study and had no role in the design or interpretation of results or preparation of this manuscript. AMF has received research funding from the National Institutes of Health and National Institute on Aging, Biogen, Centene, Fujirebio, and Roche Diagnostics, outside of the submitted work. AMF is a member of the scientific advisory boards for Roche Diagnostics, Genentech, and AbbVie, and also consults for Araclon and Grifols, DiademRes, DiamiR, and Otsuka Pharmaceuticals, outside of the submitted work. RJB has equity ownership interest in C2N Diagnostics and receives royalty income based on technology (ie, stable isotope labelling kinetics and a blood plasma assay) licensed by Washington University (WA, USA) to C2N Diagnostics. RJB receives income from C2N Diagnostics for serving on the scientific advisory board. Washington University, with RJB as co-inventor, has submitted the US non-provisional patent application "Cerebrospinal fluid (CSF) tau rate of phosphorylation measurement to define stages of Alzheimer's disease and monitor brain kinases/phosphatases activity." RJB has received honoraria from Janssen and Pfizer as a speaker, and from Merck and Pfizer as an advisory board member. RJB has been an invited speaker, advisory board member, and consultant for F Hoffman La Roche, an invited speaker and consultant for AC Immune and Janssen, and a consultant for Amgen and Eisai, outside of the submitted work. AMG has consulted for Eisai, Biogen, Pfizer, AbbVie, Cognition Therapeutics, and GSK, outside of the submitted work. AMG also served on the Scientific Advisory Board of Denali Therapeutics (from 2015 to 2018), outside of the submitted work. RAS and KAJ are involved in public-private partnership clinical trials sponsored by the National Institutes of Health and Eli Lilly, which owns the distribution rights to flortaucipir, but they do not have any personal financial relationship with Eli Lilly. NG-R reports grants from Biogen, Abbvie, and Lilly, outside of the submitted work. All other authors declare no competing interests.

Data sharing

Biomarker and cognitive data from the DIAN Observational Study are available by request to RJB at https://dian.wustl.edu/our-research/observational-study/dian-observational-study-investigator-resources/data-request-terms-and-instructions/.

Acknowledgments

Data collection and sharing for this project were supported by the Dominantly Inherited Alzheimer Network (DIAN, grant numbers UF1AG032438, R01AG036694, and K23049087) funded by the National Institute on Aging, the German Center for Neurodegenerative Diseases, partial support by Japanese Agency for the Research and Development, and grants for Dementia from Japan Agency for Medical Research and Development. NJ-M gratefully acknowledges support from an Alzheimer's Association Research Training Fellowship. This manuscript has been reviewed by DIAN Study investigators for scientific content and consistency of data interpretation with previous DIAN Study publications. We acknowledge the altruism of the participants and their families; and DIAN research and support staff at the participating sites for their contributions to this study.

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