# Optimized detection of disease and treatment effect in preclinical and prodromal autosomal dominant Alzheimer's disease with imaging biomarkers

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## BACKGROUND

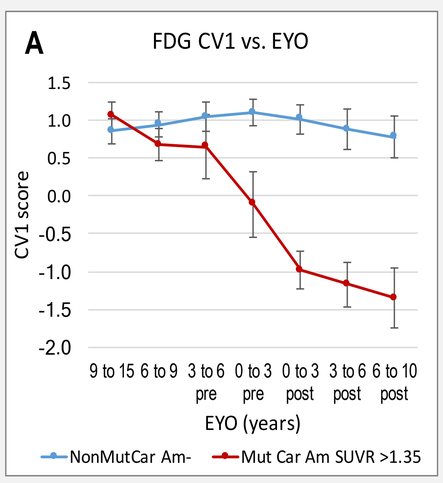
The Dominantly Inherited Alzheimer Network (DIAN) has provided a valuable early onset cohort to provide insight to disease progression and treatment response[1]. Imaging biomarkers have potential to measure longitudinal changes in pathology and neurodegeneration. However, particularly early in disease, levels and rates of change are subtle. Univariate analyses are challenged by signal variability, image noise, and inability to capture network effects. We have developed multivariate machine learning classifiers using MRI, FDG PET, and amyloid PET to optimally detect neurodegenerative and pathological changes.

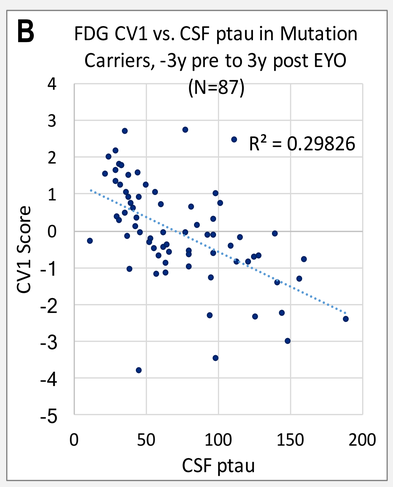
## METHODS

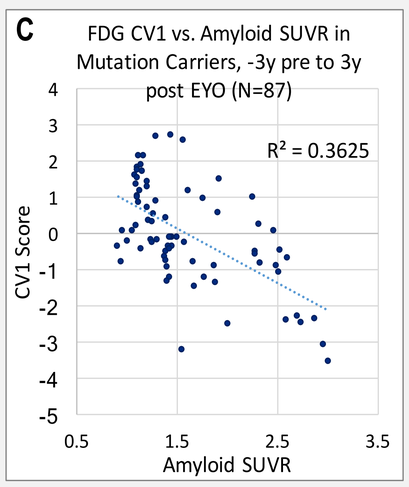
MRI, FDG, and combined classifiers were developed to characterize disease progression using volumetric and cortical thickness values produced by Freesurfer v5.3[2] (MRI) and regional SUVRs measured using Freesurfer masks (FDG). Five age-matched cross-sectional training classes were defined using 78 DIAN subjects based on mutation status, amyloid burden, and estimated years to symptom onset (EYO)[1]. Using the NPAIRS framework[3], Principal Component Analysis was applied followed by Canonical Variates Analysis (CVA) to determine image patterns best differentiating disease stages. Model parameters were optimized through iterative split half data resampling and calculation of reproducibility and prediction. Pattern expression was quantified for each scan as a numeric CV score. Age adjustment was determined using 40 non mutation carrier scans. Scores were generated for an additional 345 scans from 230 independent subjects. These were evaluated vs. EYO, CDR-sum of boxes, MMSE, Logical Memory, PIB SUVR, and CSF Abeta42 and tau by mutation and amyloid groups, and compared to hippocampal volume (adjusted for ICV and age), and to FDG SUVRs in hippocampus, posterior cingulate, and inferior parietal cortex.

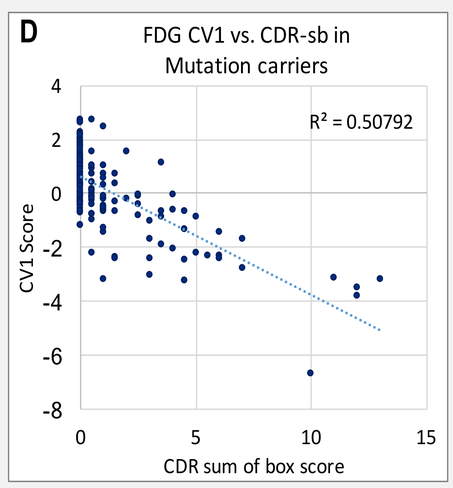
## RESULTS

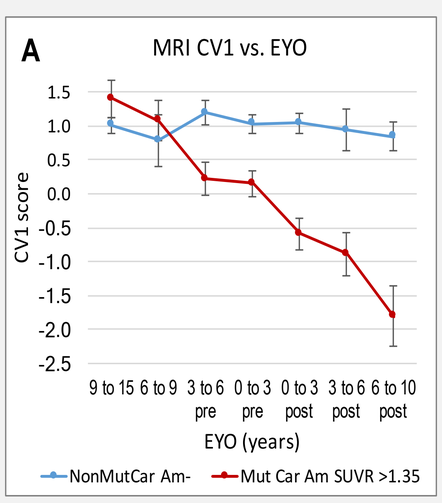
Relationships between FDG (top row) and MRI (bottom row) classifier scores are shown for independent test subjects. FDG and MRI classifier scores are correlated ($R^2$= 0.67). **A)** Amyloid-negative non-mutation carriers (for autosomal dominant AD) with global CDR 0 showed relatively flat CV1 scores regardless of EYO. Mutation carriers declined in classifier score several years prior to EYO (line graph shows amyloid negative non mutation carriers and mutation carriers with an amyloid SUVR >1.35); **B,C)** CV scores correlate with CSF ptau **(B)** and amyloid levels **(C)** in subjects from -3 to +3 years EYO (N=87) where most variability occured; **D)** CV1 scores correlate with clinical endpoints in mutation carriers (N=201 scans from 129 subjects, range -38 years pre to +8 years post EYO).

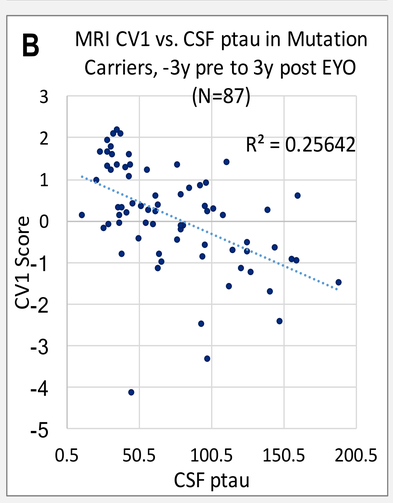


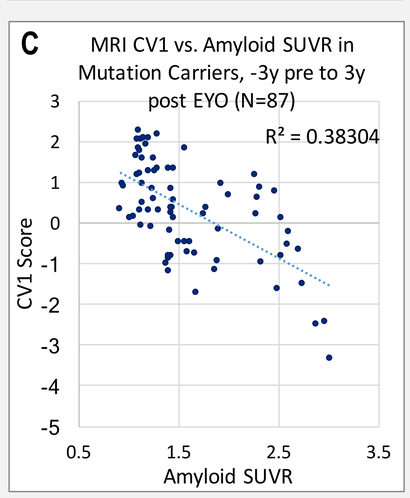



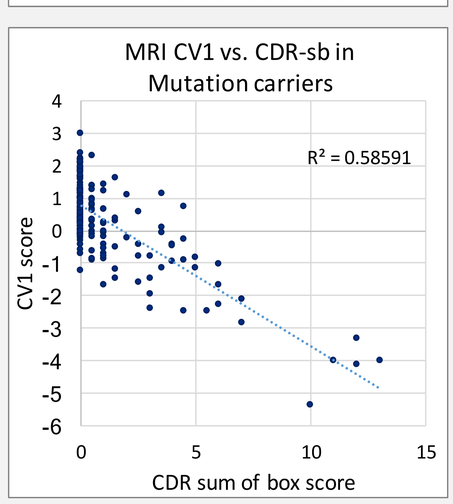



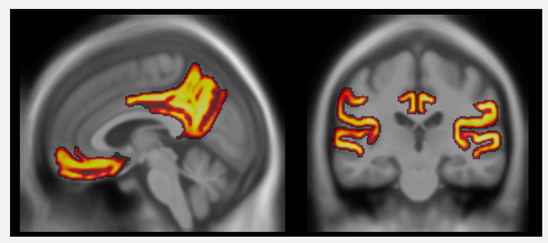



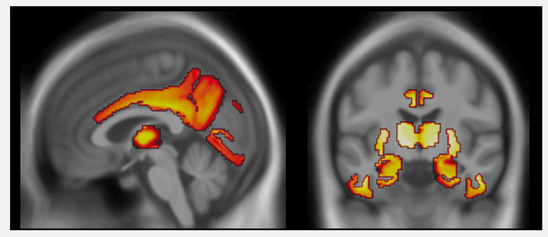




Regions contributing to the CV patterns:

FDG (hypo-metabolism)



MRI (atrophy)



Comparative correlation with clinical endpoints and pathology: $R^2$ values, all p-values significant

| | MRI CV1 | FDG CV1 | Hip Vol | FDG PC | FDG IPL |
|---|---|---|---|---|---|
| CDR-sb | .59 | .51 | .35 | .33 | .46 |
| MMSE | .54 | .44 | .29 | .31 | .50 |
| LogMem | .38 | .39 | .33 | .25 | .38 |
| Am SUVR | .38 | .38 | .17 | .16 | .25 |
| CSF ptau | .26 | .28 | .21 | .17 | .13 |

## DISCUSSION AND CONCLUSIONS

Multivariate MRI and FDG PET classifiers can provide sensitive measures of disease progression in preclinical and prodromal early onset AD. Classifier scores correlate with amyloid SUVR and CSF ptau, helping to differentiate subjects with regard to disease status. Changes precede and continue to correlate with change in clinical endpoints, providing potential metrics for the identification of clinical trial patients most likely to decline, and detection of therapeutic effect.

[1] Benzinger T et al, Proc Natl Acad Sci, 2013; [2] Fischl B et al, Cereb Cortex, 2004; [3] Strother SC et al, 2010, Neuroimage 2002.