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A simulative deep learning model of SNP interactions on chromosome 19 for predicting Alzheimer's disease risk and rates of disease progression

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Abstract

Background: Identifying genetic patterns that contribute to Alzheimer's disease (AD) is important not only for pre-symptomatic risk assessment but also for building personalized therapeutic strategies.

Methods: We implemented a novel simulative deep learning model to chromosome 19 genetic data from the ADNI and the ImaGene datasets. The model quantified the contribution of each single nucleotide polymorphism (SNP) and their epistatic impact on the likelihood of AD by using the occlusion method. The top 35 AD-risk SNPs in chromosome 19 were identified, and their ability in predicting the rate of AD progression was analyzed.

Results: Rs561311966 (*APOC1*) and rs2229918 (*ERCC1/CD3EAP*) were recognized as the most powerful AD-risk factors influencing AD risk. The top 35 chromosome 19 AD-risk SNPs were significant predictors of AD progression.

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Conflicts of Interest

We have no conflicts of interest to disclose. Please refer ICMJE forms for detailed information.

Discussion: The model successfully estimated the contribution of AD-risk SNPs, which accounts for AD progression at the individual level. This can help in building preventive precision medicine.

Keywords

Alzheimer's disease; Genetics; and Deep learning

Background

Alzheimer's disease (AD) is a neurodegenerative condition that causes irreversible cognitive dysfunction [1, 2]. About 6.2 million Americans aged 65 or older have been diagnosed with AD [3]. This number is expected to reach 88 million in the U.S. and 152 million worldwide by 2050. Despite the ever-increasing prevalence, a pharmacological treatment that could reverse AD has not been successfully developed. This raises the importance o f preventive medicine. In recent decades, many disease-specific biomarkers have been developed using cerebrospinal fluid (CSF), plasma, and neuroimaging [4] that detect the disease during presymptomatic stages [5–7]. Yet only genetic factors can identify one's AD risk prior to any disease activity rendering primary prevention possible.

Despite its simple composition, with only 4 nucleotide variants, deoxyribonucleic acid (DNA) stores the unique information of enormous inter- and intra-species variability. The genetic code is determined by single nucleotide polymorphisms (SNPs) order and location, their spatial relation to each other, and their epistatic interactions with other SNPs [8–10]. Genome-wide association study (GWAS) methods were used to identify AD-related SNPs by group comparison of individuals with dementia and individuals who are cognitively unimpaired (CU) [11–15]. However, GWAS does not take epistatic interactions into account. Multiple regression approaches with the *apolipoprotein E* (*APOE) ε4* haplotype, the most significant sporadic AD risk factor, together with numerous additional AD risk SNPs identified by GWAS approaches and polygenic risk scores (PGRS), were developed to better explain heritability and identify the genetic architecture of AD [16–19]. They, however, explain only part of the disease heritability suggesting that additional risk SNPs and critical information on interaction effects are missing.

Data-driven methods (e.g., machine and deep learning models) are cutting-edge tools for pattern recognition and have been applied to GWAS data [20–24]. These methods have identified new AD-linked SNPs, but so far these methods still fall short in correctly estimating the impact of AD risk and protective variants at the individual level. There are likely several reasons for suboptimal estimates of risk. First, to avoid overfitting [25], most machine/deep learning models rely on pre-determined feature selection methods for SNP data reduction based on assumptions and/or prior knowledge. This approach restricts scientific discovery by eliminating data linked to the outcome of interest that is yet to be discovered. Second, deep learning methods in genetics have considered only individual variants but not their potential interactions or positional information.

The goal of this study was to identify the chromosome 19 chromosomal risk impact score (CRIS) at the individual level attributable to individual SNPs and their interactions with each

other by developing a novel deep-learning model. Using a single chromosome significantly reduces the computational burden in order to explore the feasibility and effectiveness of this type of model. Chromosome 19 is well known to include many AD-linked genes including *APOE*, apolipoprotein C1 (*APOC1*), and Translocase of Outer Mitochondrial Membrane 40 (*TOMM40*), which can provide us with a sufficient resource to qualify our model's results. Our novel deep-learning framework utilized all 266,161 GWAS SNPs on chromosome 19 in the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset [26]. We used an end-to-end, a quantitative approach without imposing feature selection methods or pre-assumptions. The model's capability for predicting AD pathology and disease progression was studied by examining the CRIS associations with the rate of cognitive decline and CSF amyloid beta and tau protein changes over time.

Methods

Participants and data division:

We used the GWAS chromosome 19 data for 457 unique ADNI participants classified as CU and 313 diagnosed with dementia due to AD (hereafter referred to as "AD"). 382 were ADNI1 and 388 ADNI2 participants, which used Illumina Human 610-Quad BeadChip and Illumina Human Omni Express BeadChip as the genotyping platform, respectively. We randomly divided the total dataset (N=770) into 60% train (N=462), 20% validation (N=154), and 20% test (N=154) sets (Table 1) [27, 28] used to train the model, tune the hyper-parameters and test its performance, respectively. For the details in how the data was processed, please refer to S.1 Data format in supplementary materials.

Model architecture:

We implemented the Capsule Network (CapsNet) [29, 30] to examine SNP-SNP interactions considering the positional relations between SNPs. CapsNet has two significant features: 1) primary capsule layers and 2) dynamic routing algorithms. The primary capsule layer is a multi-dimensional convolutional layer that enables the identification not only of the specific contribution of each SNP but also its spatial relation with other SNPs. The dynamic routing algorithm is applied between primary capsule layers. It connects lower-level primary capsules encapsulating a finer AD-risk pattern, to higher-level primary capsules encapsulating a broader AD-risk pattern. The model produces the likelihood of being AD vs. CU at the last capsule layer, the Class capsule layer (S.Fig 1). A higher likelihood of AD than CU results in a predicted AD participant (pADp) and conversely a higher likelihood of CU than AD predicted CU participants (pCUp) (S.3 Prediction scores of Capsule Network). The model was modified to have a smaller complexity and was trained with multiple regularization methods (S.4 Hyperparameters for the model) to manage overfitting.

Identification of AD and CU contributing SNPs and their CRIS:

We used occlusion maps as a feature visualization method to interpret the model [31]. Occlusion mapping is a technique that measures the change in the prediction scores when a single or a group of features (in our case an AD-risk SNP or a group of AD-risk SNPs) are masked (S.Fig 2). A decrease in psAD due to occlusion indicates that the respective SNP plays a role in AD and vice versa. We sequentially and individually occluded 266,161 SNPs

for each participant. We averaged the occlusion results and ranked the SNP based on the corresponding change in psAD and psCU (S.Fig 3). The top 35 AD and CU SNPs, showing the greatest decrease in psAD for pADp or psCU for pCUp were identified (S.5 Occlusion maps for SNPs, S.Table 2–4). The change in psAD essentially indicates the individual SNP contribution to the CRIS.

To test for epistatic interactions, we tested how the co-occlusion of each possible combination of 2 SNPs from the top 35 AD or top 35 CU SNPs affected the prediction results. If the prediction score change was higher or lower than the sum of prediction changes of each individual SNP, we concluded that there was an interaction (amplification or attenuation) between them (S.Fig 4). In our final experiment, we substituted each of the top 35 AD and CU SNPs with the other biologically plausible genotype and measured the corresponding psAD change whereby simulating genetic editing technologies such as CRISPR.

Predicting AD progression in multiple linear regression:

We utilized multiple linear regression to estimate the ability of the top 35 AD SNPs and their interactions to predict the rate of cognitive decline and the rate of CSF Aβ and tau protein changes for pADp. Sex, age, education, and *APOE ε4* genotypes were used as covariates. To avoid the degree of freedom exceeding the number of samples, we restrained the number of SNPs to 3 plus their 4 interaction terms. Every possible combination of 3 SNPs within the top 35 AD SNPs was tested. We used composite scores for the memory, language, executive and visuospatial domains [32–34]. The CSF measures included changes in amyloid beta (Aβ), total tau (tTau), phosphorylated tau (pTau), Aβ/tTau, and Aβ/pTau [35]. The rate of change (slope) in cognitive and CSF measures was calculated by dividing all available longitudinal measures by their follow-up time period on a yearly scale (S.Table 5&6).

Implementing deep learning pipeline to the external dataset:

We replicated our model using independent GWAS data from the Imaging and Genetic Biomarkers for AD (ImaGene) study (see S.Table 7 for participant demographics and comparisons to the ADNI sample). SNP genotyping in ImaGene was completed using Illumina 1M chips. The ImaGene study enrolled and followed longitudinally a total of 159 participants (52 CU and 107 MCI) for 5 years. Our analyses included 22 participants who converted to AD dementia from both CU or MCI during 5-year follow-up as AD participants and 28 CU participants who remained CU over the same period as CU participants. These inclusion criteria resulted in 50 participants for our external test dataset.

Results

Deep learning model performance:

Our deep learning prediction model achieved an accuracy of 68.18% [specificity=72.04%, sensitivity=62.30%, area under the curve (AUC)=0.67, equal error rate=0.37 (S.Fig 1)]. Given that the test set of 154 subjects contained 93 CU participants, a random guess of pCUp would produce 60.39% classification accuracy. Also, in the test set, 63.93%

of AD participants as opposed to 30.11% of CU participants were *APOE ε4* carriers. Hence, with *APOE* information alone, we could achieve a CU vs. AD accuracy of 67.53% (specificity=69.9%, sensitivity=63.9%). Therefore, our model performed slightly better both than the random guess and the *APOE* model achieving an accuracy. For the model validation results, please refer to S.6 Deep learning model performance validation. We further implemented three different machine learning models, support vector machine, decision tree, and random forest, as comparison to demonstrate that our deep learning model outperforms conventional machine learning models (S.Table 8).

The top 35 AD SNPs and their epistatic interactions:

Among the 35 AD SNPs, 7 belonged to *APOC1* and another 7 to *TOMM40*. Additionally, we observed 5 SNPs from Zinc Finger Protein 473 (*ZNF473*) and 3 SNPs from Vaccina-Related Kinase Serine/Threonine Kinase 3 (*VRK3*) (Table 3, left panel). Co-occlusion of two AD SNPs at a time resulted in 574 and 358 amplification and 21 and 170 attenuation interactions of pADp and pCUp, respectively (S.Table 9). It must be noted that the two *APOE* SNPs, rs429358 and rs7412, were not detected as AD-risk SNPs (S.7 Assessment of APOE as a contributing factor for AD risk). For CU SNPs, please refer to S.8 The top 35 CU SNPs and their interactions.

Significance of the top 35 AD SNPs in predictions: Sixty-four test set participants with higher psAD than psCU were classified as pADp. The mean prediction gap between psAD and psCU for these participants was 0.147 with a standard deviation of 0.065. If all the top 35 AD chromosome 19 SNPs were occluded, the average decrease in psAD and increase in psCU were 0.292 (29.2%) and 0.137 (13.7%), respectively. With all 35 AD SNPs occluded, all originally predicted pADp were predicted as pCUp (S.Fig 5). Therefore, we concluded that the top AD SNPs have dominant power in making prediction results. For CU SNPs, please refer to the S.9 Significance of the top 35 CU SNPs in predictions.

Analysis of the AD SNPs for predicting pADp:

Rs56131196 (*APOC1*) was the most significant SNP for pADp. Occluding it produced CRIS of −0.023, i.e., −2.3% likelihood of AD. Rs56131196 (*APOC1*) also showed the strongest interactions with other SNPs. The co-occlusion of rs56131196 (*APOC1*) and rs144311893 (*APOC1*) produced a CRIS of −0.045 (−4.5%). The greatest CRIS amplification occurred when rs147510483 (*VRK3*) and rs149633759 (*VRK3*) were occluded together. Their individual CRIS were −0.002 (−0.2%) and −0.004 (−0.4%), respectively, but when they were removed simultaneously, a −0.010 (i.e., −1%) CRIS was observed. The greatest attenuation was observed when rs60229698 (*VRK3*) and rs149633759 (*VRK3*) were occluded together. Each SNPs resulted in −0.004 (0.4%) CRIS, yet when removed together, we observed still only a −0.004 (−0.4%) CRIS (S.Fig 6&7). For CU SNPs, please refer to S.10 Analysis of the CU SNPs for predicting pCUp.

Independent Dataset Validation:

Only 206,756 of the 266,161 SNPs available in ADNI (Illumina Human 610-Quad and Omni Express BeadChip arrays) were available in ImaGene (Illumina 1M array, S.Table 10). Despite the missing 59,405 SNPs, 26 out of the top 35 ADNI pADp SNPs were

also identified as strong AD-contributing SNPs in the ImaGene dataset (S.Table 11). Rs56131196 (*APOC1*) and rs2229918 (Repair Cross Complementation Group 1/CD3e Molecule Associated Protein; *ERCC1/CD3EAP*) were detected as the most and the second most significant AD SNPs with respect to pADp and pCUp. (S.Table 12–14). Based on this external validation we concluded that our deep learning model reliably identifies AD-contributing SNPs.

Genotype replacement of the most powerful AD SNPs:

Rs56131196 (*APOC1*) was recognized as the most powerful individual pADp SNP and the 4th most powerful pCUp SNP. 79.69% of pADp had an adenine/guanine (A/G) genotype while about 88.89% of pCUp had the reference, G/G genotype at this locus. Rs56131196 A/G had 6 interactions stronger than 0.003 with other AD SNPs located in *APOC1/APOC1P1, TOMM40, and ERCC1/CD3EAP* (S.Fig 8&9) that further decreased psAD when replaced. Replacing rs56131196 A/G with G/G in pADp decreased psAD by 0.079 (7.9%). This led to about 36% of pADp now being predicted as pCUp (S.Fig 16). For pCUp, please refer to S.11 Analysis of the CU SNPs for predicting pCUp.

Relating CRIS of 3 AD SNPs to the rate of cognitive decline:

We hypothesized that the CRIS derived from the top 35 AD SNPs would associate with the rate of cognitive decline in the pADp. The CRIS of 3 SNPs in the top 35 AD SNPs was utilized due to the degree of freedom issue. The 3 AD SNPs used for each cognitive measure are presented in S.Table 16. SNPs in *APOC1*, *APOC2*, *ZNF473*, *VRK3*, and *TOMM40* were used. We found that their CRIS was significantly correlated with the rate of cognitive decline ($p<0.05$, r^2-adjusted=0.19–0.43). The weakest association was observed for the memory domain and the highest for the executive function domain (Table 4 and S.Table 17).

Relating CRIS of 3 AD SNPs to CSF biomarker changes:

The 3 AD SNPs used for each CSF measure are presented in S.Table 16. The main, as well as interactive effects of the 3 selected AD SNPs on longitudinal changes of CSF biomarkers, were examined using the approach outlined above. SNPs in *APOC1*, *APOC2*, *TOMM40*, and *ERCC1* were used. All regression models were significant ($p<0.05$, r^2-adjusted=0.89–0.99). The strongest prediction was seen for Aβ/pTau and the weakest for tTau (Table 5).

Discussion

We report a novel deep-learning framework derived from 266,161 SNPs from chromosome 19 in a hypothesis-free manner. To our knowledge, the Capsule network approach is the first model that allows for the exploration of the epistatic interactions between AD-risk or protective SNPs. Our model determined SNPs from previously recognized AD genomic regions including *APOC1, TOMM40, and VRK3* as well as novel regions (S.Table 2–4). Rs56131196 (*APOC1*) and rs2229918 (*ERCC1/CD3EAP*) were identified as the most powerful AD-risk SNPs for pADp and pCUp, respectively. We qualified these findings with prior medical knowledge.

APOC1 resulted in the most substantive change in predicting AD and CU if occluded. Rs56131196 from *APOC1* has been previously identified as an *APOE ε4*-independent AD-risk factor associated with hippocampal atrophy [36]. Many research groups have spotlighted the association between *APOC1* and cognitive performance in AD [37–40]. In terms of the interactive effects between SNPs in *APOC1* and *TOMM40* (S.Fig 6), Prendecki et al. reported that defects in *APOC1*, in addition to the *TOMM40* gene, increase oxidative stress and have an *APOE ε4*-independent effect on AD progression [41].

The top *APOE* SNP - rs439401, ranked as the 47th pADp SNP with CRIS=−0.003 (−0.3%). This SNP has been previously associated with AD [42, 43]. Surprisingly, rs429358 and rs7412, commonly used to define the *APOE ε4* haplotype, were not determined as powerful predictive features. *APOE ε4* haplotype did not affect prediction changes when occluded nor epistatic effects with any other SNPs in chromosome 19 when co-occluded, indicating that it did not contribute to model's predictive performance (S.7 Assessment of APOE as a contributing factor for AD risk). Replacement of rs429358 and/or rs7412 showed no change in CRIS and no amplification or attenuation effects. This was a consistent finding across three separate models, 5 non-overlapping test sets from ADNI (S.6 Deep learning model performance validation), and one independent data set (ImaGene). *APOE*, however, was strongly collinear with the model's prediction results. This is most likely explained by the strong linkage disequilibrium of *APOE* with *APOC1* (S.Fig 17).

The occlusion of rs2229918 (*ERCC1/CD3EAP*) decreased psAD in pCUp the most, i.e., pCUp subjects were more likely to be diagnosed with AD when this SNP was occluded. *ERCC1* is known to play a role in DNA repair. A previous study reported that deficient ERCC1 protein leads to imbalance between DNA repair and oxidative stress and neurodegeneration [44]. *ERCC1* $^{\Delta/-}$ mice showed neuronal apoptosis and synaptic plasticity deficits in the hippocampus and accelerated age-dependent cognitive decline [45–50]. *CD3EAP* has differential hippocampal expression in AD vs. healthy controls [51, 52].

As an interactive effect, SNPs in *VRK3* were found to have the strongest amplification effect in pADp, while for pCUp, SNPs *APOC1* showed the most powerful interaction (S.9 Analysis of the CU SNPs for predicting pCUp). For the attenuation effect, *VRK3* and *ERCC1* showed the highest attenuated impact for pADp and pCUp, respectively. *VRK3* was also known to progress AD via oxidative stress-induced cyclin-dependent kinase 5 (*CDK5*) [53].

Top AD SNPs determined by our model, however, did not include genome-wide significant SNPs from the three latest GWAS research [13–15]. This is due to the differences in diversity of race, population size, and AD-risk factor identification process. GWAS identified AD-risk factor by examining the association between genotype and phenotype. The three latest GWAS research suggested in total 16 AD-risk SNPs in chromosome 19 excluding *APOE* haplotype (S.Table 19). On the other hand, our deep learning model examined the genetic variants as well as their epistatic interactions. We quantified the impact of previously suggested GWAS AD-risk factors and found that their contribution to our model's predictive performance is minimal (S.Table 19). Therefore, we concluded that epistatic interactions play a more significant role than genetic variant itself in recognizing

AD-risk factors. This indicates that epistatic effects provided a more powerful contribution in increasing the model's performance than the GWAS variants including *APOE* haplotype.

Our next goal was to demonstrate that AD-risk SNPs identified by the deep learning model and their CRIS associate with AD progression. We were able to demonstrate that a small number of SNPs (in this case 3) out of the 35 powerfully associated with CSF biomarker changes over time and also show modest association with decline across all cognitive domains. All regression models were significant, which implies two points: 1) the over-fitting issue was well-handled and 2) our model determined AD-risk SNPs that account for biological as well as clinical AD progression.

Several strengths and limitations of our approach should be recognized. One of the novelties of this research lies in the examination of SNP-SNP interactions. Statistical GWAS approaches disregard SNP-SNP interactions. It is highly likely that the positional information and variability in spatial relationships between SNPs and/or SNP sequences is a major component of the missing heritability. CapsNet is capable of analyzing positional relations between AD-risk SNPs leading to the use of spatial and positional information in our predictive model. This enables the individual inspection of each SNP regardless of the given SNP's linkage disequilibrium.

The model developed here as a proof-of-concept study utilized GWAS data from a single chromosome. We believed that the restrictive information of input data, i.e., chromosome 19, limited the model's predictive performance. A future study utilizing multiple/all chromosomes will perform better and allow the identification of powerful epistatic interactions within and between chromosomes. Using more comprehensive input data will provide sufficient information, i.e., AD-genetic risk factors as well as their epistatic interactions, to explain the genetic nature of AD. Combining all risk variants in a data-driven algorithm and defining a genome-wide polygenic risk score is our goal for the future.

No single dataset is fully representative of the population. Hence, the biological interpretation originating from the weight matrix at the lowest validation loss in our dataset might not optimally align with the full breadth of observations in nature. One could postulate that implementing a different model on a different dataset subjected to different pre-processing might identify different features. To minimize this risk and increase our confidence in the results, we validated the findings through three different model architectures, 5 internal train/validation/test sets, and in an external dataset and produced similar outcomes.

Identifying epistatic interactions between SNPs in different chromosomes was beyond the scope of this research. In a future study, we will aim to utilize GWAS data of all 23 chromosomes, build a comprehensive polygenic risk score and map out the entire genetic architecture of AD.

In summary, we implemented the novel capsule network, which examines the interactive effects between SNPs. Our model captured the variability of not only the individual SNPs but also their positional relations. We identified and ranked the top 35 AD-predictive GWAS SNPs on chromosome 19 by studying their individual contribution as well as their epistatic

effects. We used the occlusion method in a fully quantitative manner without imposing any feature selection methods. Lastly, we estimated the change of the likelihood of AD that one could expect from gene-editing technology such as CRISPR by replacing genotypes at certain SNPs. This CRISPR simulation technique could provide useful insight into the primary prevention or disease modification opportunities that could be achieved through gene editing.

In conclusion, our hypothesis-free deep learning approach identified potential AD-risk SNPs which might bring us closer to a full understanding of AD's heritability and personalized genome-level risk assessment. Our approach shows promise for clinical implementation as an AD-risk assessment tool and for presymptomatic clinical trial enrichment with patients at high likelihood for AD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Consent Statement

The UCLA Institutional Review Boards approved the study. All ImaGene participants or their legally authorized representatives provided informed consent for data collection and publication according to the Declaration of Helsinki, U.S. federal regulations, local state laws and regulations, and policies of the UCLA IRB.

ADNI enrolls participants between the ages of 55 and 90 who are recruited at 57 sites in the United States and Canada. After obtaining informed consent, participants undergo a series of initial tests that are repeated at intervals over subsequent years, including a clinical evaluation, neuropsychological tests, genetic testing, lumbar puncture, and MRI and PET scans.

Systematic review: Previous in-silico genetic research utilized data-driven methods, i.e., machine and deep learning models, to identify Alzheimer's disease (AD) genetic risk factors. While these models presented new AD-linked single nucleotide morphisms (SNPs), they fall short in providing epistatic impacts of potential AD-risk SNPs.

Interpretation: The manuscript proposes a novel framework that can translate the predictive performance of the deep learning model into genetic findings. Our model was developed to examine the epistatic interactions between SNPs in chromosome 19 and thereby quantify the hypothesis-free polygenic risk impact of AD-risk SNPs in the individual. AD-risk SNPs determined by the model were consistent with prior medical knowledge and can help in building a pre-symptomatic genetic risk assessment.

Future directions: The manuscript provides directions for future studies: (1) visualizing overall genetic architectures of AD throughout all 23 chromosomes. (2) identifying the role of underrecognized AD-risk SNPs in clinical and biological AD progression.

Table 1.

Demographic and clinical comparisons of Alzheimer's disease (AD) and cognitively unimpaired (CU) participants as well as the train, validation, and test set in the Alzheimer's disease neuroimaging initiative (ADNI) dataset. Cognitive composite scores were provided by the Crane group. Pairwise chi-square and t-tests between the train, validation, and test sets regarding age and education, sex, *APOE ε4*, and diagnosis distribution found no significant differences (S.Table 1).

	AD (N=457)	CU (N=313)	Train (N=452)	Validation (N=154)	Test (N=154)
Age, mean (SD), years	74.7 (7.8)	74.1 (5.7)	74.3 (6.5)	74.6 (6.9)	74.3 (6.7)
Education, mean (SD), years	15.2 (3.0)	16.4 (2.7)	15.9 (2.8)	15.8 (3.1)	16.0 (2.8)
Diagnosis (% AD)	100%	0%	40.7%	41.6%	39.6%
Sex (% Male)	56.9%	50.6%	52.6%	52.6%	55.2%
APOE ε4 (% APOE ε4+)	63.9%	26.7%	41.8%	40.3%	43.5%
Race (% White)	98.7%	98.7%	98.7%	98.7%	98.7%
Aβ baseline, mean (SD), pg/ml	656.4 (285.6)	965.8 (375.5)	827.7 (374.5)	852.7 (389.5)	783.2 (337.8)
Rate of Aβ change, mean (SD), pg/ml/year	−26.4 (98.6)	−20.25 (105.7)	−23.5 (89.2)	−20.9 (80.4)	−20.9 (153.4)
tTau baseline, mean (SD), pg/ml	354.3 (140.0)	254.8 (98.0)	300.9 (128.9)	286.5 (126.3)	287.4 (120.0)
Rate of tTau change, mean (SD), pg/ml/year	8.0 (31.2)	6.3 (14.2)	5.2 (19.6)	7.9 (17.7)	10.0 (25.5)
pTau baseline, mean (SD), pg/ml	35.1 (15.3)	23.8 (10.5)	29.0 (14.1)	27.5 (13.7)	27.7 (13.2)
Rate of pTau change, mean (SD), pg/ml/year	−0.2 (3.0)	0.6 (1.3)	0.3 (2.1)	0.5 (2.0)	0.4 (1.6)
Aβ/tTau ratio baseline, mean (SD)	2.2 (1.7)	4.6 (2.6)	3.4 (2.5)	3.8 (2.6)	3.5 (2.5)
Rate of Aβ/tTau change, mean (SD)	−0.1 (0.4)	−0.2 (0.5)	−0.1 (0.4)	−0.2 (0.3)	−0.2 (0.8)
Aβ/pTau ratio baseline, mean (SD)	23.6 (20.4)	51.5 (31.0)	37.9 (29.9)	41.6 (31.7)	38.2 (28.9)
Rate of Aβ/pTau change, mean (SD)	−1.1 (5.3)	−1.7 (5.7)	−0.1 (0.4)	−0.1 (0.3)	−0.1 (0.7)
MEM baseline, mean (SD)	−0.9 (0.5)	1.0 (0.6)	0.2 (1.1)	0.3 (1.0)	0.2 (1.1)
Rate of MEM change, mean (SD)	−0.2 (0.4)	−0.0 (0.2)	−0.1 (0.3)	−0.1 (0.3)	−0.1 (0.3)
LAN baseline, mean (SD)	−0.8 (0.9)	0.8 (0.7)	0.2 (1.1)	0.3 (1.1)	0.2 (1.1)
Rate of LAN change, mean (SD)	−0.4 (0.6)	−0.0 (0.2)	−0.2 (0.5)	−0.1 (0.5)	−0.2 (0.5)
EF baseline, mean (SD)	−0.9 (0.9)	0.8 (0.8)	0.1 (1.2)	0.2 (1.1)	0.0 (1.3)
Rate of EF change, mean (SD)	−0.3 (0.6)	−0.0 (0.3)	−0.2 (0.5)	−0.1 (0.4)	−0.2 (0.5)
VS baseline, mean (SD)	−0.6 (0.9)	0.2 (0.6)	−0.1 (0.87)	−0.0 (0.8)	−0.1 (0.9)
Rate of VS change, mean (SD)	−0.3 (0.9)	−0.1 (0.4)	−0.2 (0.7)	−0.1 (0.7)	−0.2 (0.7)

Table 2.

Distribution of *APOE ε4* carrier for the predicted AD and CU participants. The model's prediction results and *APOE ε4* distribution is strongly associated.

	***APOE ε4* +/+**	***APOE ε4* +/−**	***APOE ε4* −/−**	**N**
pCUp	0	6	84	90
pADp	11	50	3	64

Table 3.

Genes that include AD and CU SNPs. *APOC1* and *VRK3* feature both risk and protective SNPs. Linkage disequilibrium between these SNPs, as well as APOE haplotype SNPs, was presented in S.Fig 15.

Top 35 AD SNPs				Top 35 CU SNPs				
APOC1	**TOMM40**	**ZNF473**	**VRK3**	**ERCC1**	**ZNF714**	**LOC 105372326**	**ZNF208**	**APOC1**
rs144311893	rs78245864	rs28372420	rs149633759	rs3212986	rs546840781	rs143835282	rs2359812	rs4420638
rs139136389	rs1038026	rs10425282	rs60229698	rs62109562	rs73024674	rs563728461	rs4456632	rs56131196
rs12721051	rs141864196	rs146272735	rs147510483	rs59228959	rs143553695	rs79534448	rs4550595	
rs12721056	rs112019714	rs10406823	rs182296059	rs3212989	rs73024685	rs117384953		
rs1064725	rs117264457	rs11083997		rs28586606	rs139001424			*VRK3*
rs56131196	rs149311267		*APOC2*	rs2336219	rs73024675			rs56934989
rs12721046	rs116977783	*ERCC1*	rs12709887	rs3212985	rs143211742			
		rs2229918	rs1130742	rs12984195				
			rs7257095					
Others				Others				
rs147817461	rs138451097	rs3745513	rs140962335	rs554404582	rs190058096	rs574395670	rs11670070	rs140965804
rs8103298	rs182542361	rs117529462	rs73923361	rs617761	rs553334631	rs138603379	rs846884	rs143994597

Table 4.

Multiple linear regression relating 3 out of the top 35 AD SNPs to the rate of cognitive decline, i.e., memory (MEM), language (LAN), executive functioning (EF), and visuospatial (VS) composite score change. The changes in psAD due to the occlusion of these SNPs are presented with $CRIS_j$, where i ranges from 1 to 3 representing 3 SNPs. Their interaction terms are also presented.

	Intercept	Sex	Age	Edu	*APOE* E4	$CRIS_1$	$CRIS_2$	$CRIS_3$	$CRIS_{1:2}$	$CRIS_{1:3}$	$CRIS_{2:3}$	$CRIS_{1:2:3}$	*N*
			*			***			**	*		**	
ΔMEM	3.6E−02	−1.2E−02	9.3E−04	−3.5E−04	−1.9E−02	1.5E+01	1.4E+01	2.1E+01	2.7E+03	3.2E+03	3.9E+03	6.2E+05	62
			*		*		**				***	**	
ΔLAN	−5.8E−02	−8.9E−03	1.5E−03	−1.4E−03	−5.1E−02	3.3E+00	−4.5E+00	−7.5E+00	−1.3E+02	−4.8E+01	−1.9E+03	−1.0E+05	61
	*					***			***	*			
ΔEF	−5.1E−01	1.1E−02	1.2E−03	−3.5E−03	−2.5E−02	−4.7E+01	−9.6E+01	−4.4E+01	−1.2E+04	−6.2E+03	9.1E+02	−1.1E+06	62
				**		*	***		**		*	*	
ΔVS	1.1E−01	2.9E−02	−9.4E−04	−8.8E−03	−3.9E−02	−8.9E+00	−1.3E+01	−1.5E+01	−1.0E+03	−1.5E+03	−1.6E+03	−1.5E+05	60

*** :$p<0.001$

** :$p<0.01$, and

* :$p<0.05$

Table 5.

Multiple linear regression model relating the 3 out of the top 35 AD SNPs to the rate of CSF biomarker changes over time. Changes in psAD due to the occlusion of these SNPs are presented with $CRIS_i$, where i ranges from 1 to 3 representing 3 SNPs. Their interaction terms are also presented.

	Intercept	**Sex**	**Age**	**Edu**	***APOE4***	**$CRIS_1$**	**$CRIS_2$**	**$CRIS_3$**	**$CRIS_{1:2}$**	**$CRIS_{1:3}$**	**$CRIS_{2:3}$**	**$CRIS_{1:2:3}$**	***N***	
	***		***			***	***	***	***	***	***	***		
ΔAβ	3.0E+02	−2.1E+00	−5.1E−01	−6.7E−02	1.1E+00	1.9E+04	9.7E+04	6.9E+04	7.6E+06	5.3E+06	2.4E+07	1.9E+09	18	.9
				*	*		*	*	*		*			
ΔtTau	1.5E+01	−9.6E−02	−6.2E−02	3.3E−01	2.3E+00	1.2E+03	2.7E+03	9.1E+03	2.9E+05	6.3E+05	1.3E+06	1.1E+08	18	.8
		**		***	**	**	**			**	**	*		
ΔpTau	2.6E−01	2.6E−01	5.5E−04	−1.0E−01	−4.6E−01	7.0E+02	−8.0E+02	−1.1E+02	2.2E+04	2.4E+05	−2.0E+05	9.8E+06	18	.8
ΔAβ/ tTau	2.0E−02	*** 1.5E−02	*** −2.3E−03	*** −3.2E−03	*** −2.8E−02	*** −5.5E+01	*** −3.2E+01	*** −4.2E+01	*** −1.0E+04	*** −1.0E+04	*** −7.4E+03	*** −1.9E+06	18	.9
ΔAβ/ pTau	*** 1.2E+01	*** −1.5E−01	−1.1E−03	*** 5.3E−02	*** 4.1E−01	*** 6.0E+02	*** 1.2E+03	*** 2.5E+03	*** 5.6E+04	*** 1.1E+05	*** 2.3E+05	*** 1.0E+07	18	.9

*** :$p<0.001$

** :$p<0.01$, and

* :$p<0.05$