Atrophy Subtypes In Alzheimer's Disease Are Differentially Associated With Alzheimer's Disease Polygenic Risk

01-324

Eleanor O'Brien[1,*], Chenyang Jiang[2,*], Vikram Venkatraghavan[2], Neil Oxtoby[3], Pierrick Bourgeat[4], Betty Tijms[2], Tenielle Porter[1], Simon Laws[1], Andre Altmann[3]

1 Edith Cowan University, Joondalup, Australia, **2** Vrije Universiteit Amsterdam, Amsterdam UMC, Alzheimer Center Amsterdam, Netherlands, **3** UCL Hawkes Institute, UCL, UK, **4** CSIRO, Brisbane, ACT, Australia

Genes influence spatial atrophy patterns observed in Alzheimer's Disease

BACKGROUND

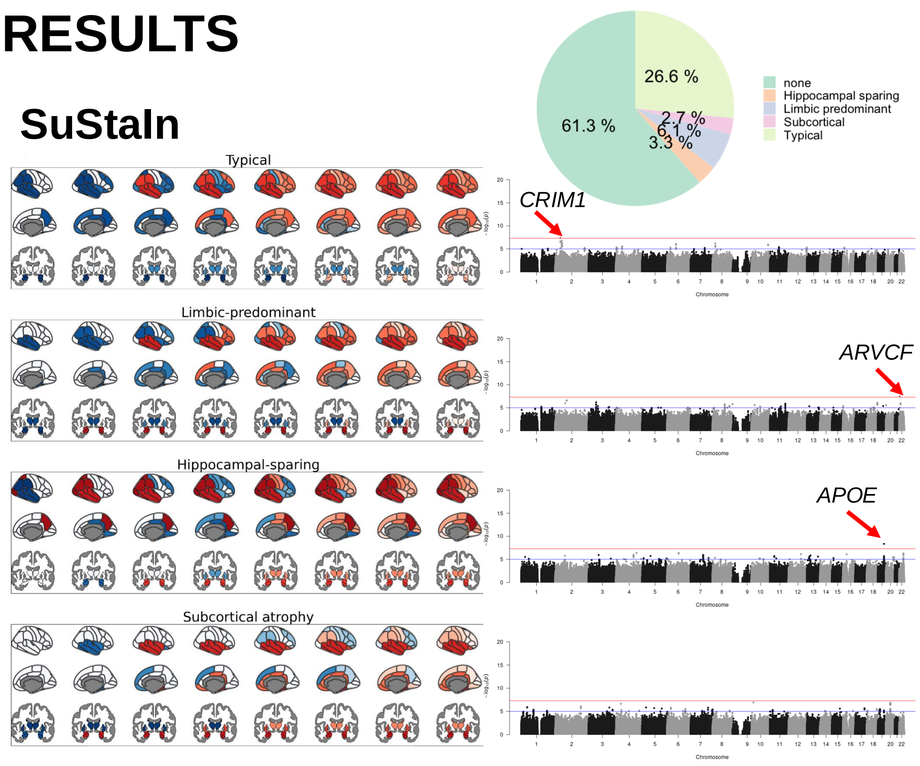
- Alzheimer's disease (AD) is a heterogeneous disorder
- Previous work has identified atrophy subtypes in AD [1,2]
- it remains unclear whether there is a genetic predisposition to develop a specific atrophy subtype
- We investigated the genetic basis of atrophy subtypes using GWAS and AD polygenic risk scores (PRS)

METHODS

1. Study participants from four cohorts: ADNI, AIBL, Amsterdam, UK Biobank (UKBB)
2. T1w MRI processed with FreeSurfer v7.1.1. pipeline to extract cortical and sub-cortical volumes
3. pySuStaIn [3] and Snowphlake [4] were trained on 1195 participants [4] and applied to ~39,000 participants in the four cohorts
4. Genotyping data imputed
5. 1-vs-all GWAS adjusted for age, sex and first 10 PCs
6. PRS: SNP content was harmonized LD pruning in ADNI
7. IGAP2 results [5] and cutoffs 0.5, 1e-5 and 5e-8 used for AD-PRS

RESULTS

SuStaIn



Snowphlake

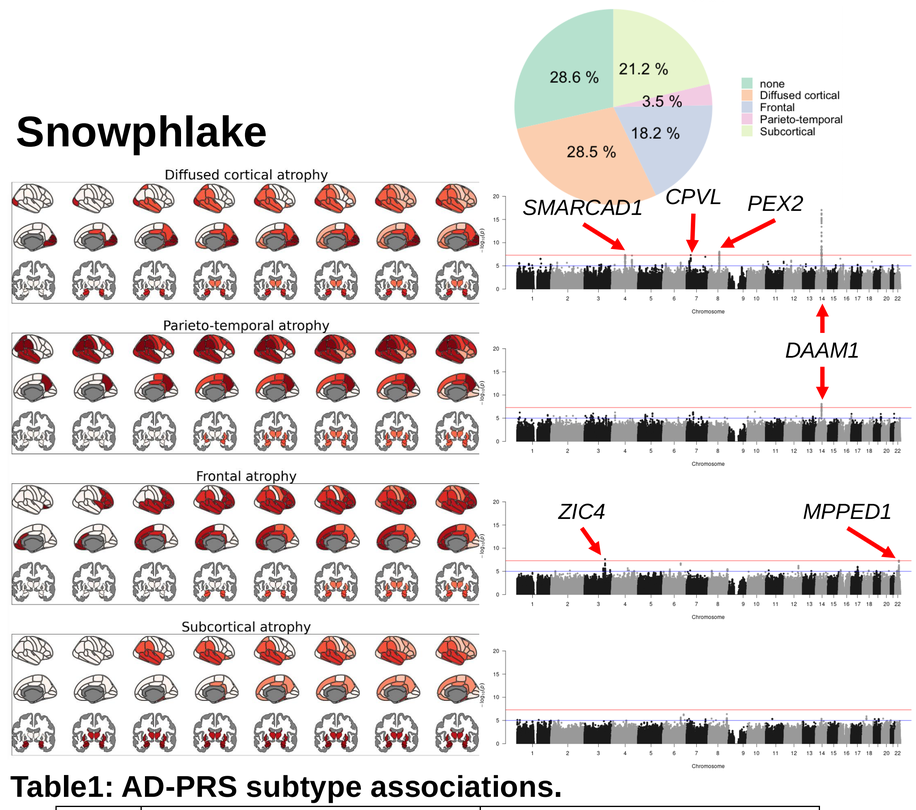


Table1: AD-PRS subtype associations.

	SuStaIn				Snowphlake			
	Hippocampal sparing	Limbic predominant	Subcortical	Typical	Diffuse cortical	Frontal	Parieto-temporal	Subcortical
P=5e-8	-0.048 (0.021); **P=0.021**	0.040 (0.015); **P=0.009**	**0.063 (0.022); P=0.003**	0.006 (0.008); P=0.468	-0.024 (0.008); **P=0.003**	0.016 (0.009); P=0.08	0.002 (0.02); P=0.936	0.020 (0.009); P=0.022
P=1e-5	-0.044 (0.019); **P=0.022**	0.043 (0.014); **P=0.002**	**0.057 (0.02); P=0.004**	0.003 (0.008); P=0.723	-0.021 (0.007); **P=0.005**	0.011 (0.009); P=0.218	0.001 (0.018); P=0.937	0.016 (0.008); P=0.041
P=0.5	-0.004 (0.019); P=0.103	0.003 (0.002); P=0.052	0.000 (0.002); P=0.909	0.000 (0.001); P=0.763	-0.001 (0.001); P=0.354	0.002 (0.001); P=0.111	-0.001 (0.002); P=0.591	0.001 (0.001); P=0.222

Effect sizes (and standard errors) and p-values for the association between subtypes (columns) and PRS at specific thresholds (rows). Bold font indicates FDR-adjusted p-value < 0.05.

Contact: a.altmann@ucl.ac.uk Twitter: @CombineLab

ADDITIONAL INFORMATION

Database	N	SuStaIn	Snowphlake
UKBB	32,399	11,201 (9,290)	22,474 (18,698)
Amsterdam	3,248	2,195 (1,993)	2,707 (1,993)
ADNI	1,981	1,343 (1,140)	1,790 (1,543)
AIBL	996	478 (408)	792 (671)
Total	38,624	15,217 (12,831)	27,763 (22,905)

A large fraction of participants did not show sufficient atrophy to be able to assign an atrophy subtype. Numbers in parentheses indicate participants contributing to genetic studies.

Subtypes:
Naming based on predominant atrophy pattern in early stages. Plots show increasing progress from left to right.
SuStaIn plots show mild atrophy in blue (Z-score 1) and moderate atrophy in red (Z-score 2).
Snowphlake plots depict more severe atrophy in darker red.

Identified loci (P<5e-8)
CRIM1: involved in central nervous system (CNS) development
ARVCF: brain specific gene expression; linked to Velo-Cardio-Facial syndrome; formation of adherens junction complexes; Next to *COMT* locus
APOE: ε4 allele negatively associated with Hippocampal-sparing subtype
SMARCAD1: linked to genetic skin disorders
CPVL: May be involved in the digestion of phagocytosed particles in the lysosome, participation in an inflammatory protease cascade
PEX2: Significant loci is intergenic upstream of the *PEX2* gene. Linked to infantile Refsum disease, a developmental brain disorder.
DAAM1: linked ITM2B-related cerebral amyloid angiopathy-2, also known as familial Danish dementia (FDD); Neuropathological hallmarks include extensive brain atrophy, chronic diffuse encephalopathy, and demyelinated cranial nerves
ZIC4: zinc finger gene; expression specific to cerebellum
MPPED1: Metallophosphoesterase; brain specific expression

References:

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JPND research
EU Joint Programme – Neurodegenerative Disease Research
E-DADS Early Detection of Alzheimer's Disease Subtypes
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