Discovering Alzheimer's disease subtypes with imaging and genetic signatures via multi-view weakly-supervised deep clustering

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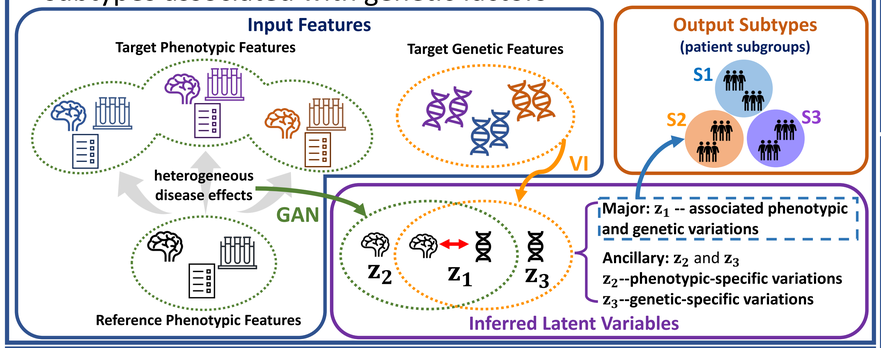
Background: Heterogeneity of AD and machine learning

- Alzheimer's disease and distinct co-pathology causes varying patterns of brain atrophy
- Increasing evidence suggests associations between genetic variants and heterogeneous imaging patterns in brain diseases
- **Machine learning methods** could dissect neuroanatomical heterogeneity and identify genetically-explained disease subtypes with distinct brain phenotypes.

Gene-SGAN Method

- **Gene-SGAN** aims to identify genetically driven disease subtypes from phenotypic and genetic features
- Learn one-to-many mappings through GAN → Capture the heterogeneous brain change patterns related to disease
- Guidance from genetic features through VI → disentangle linked and unlinked phenotypic and genetic features → phenotypic
- subtypes associated with genetic factors

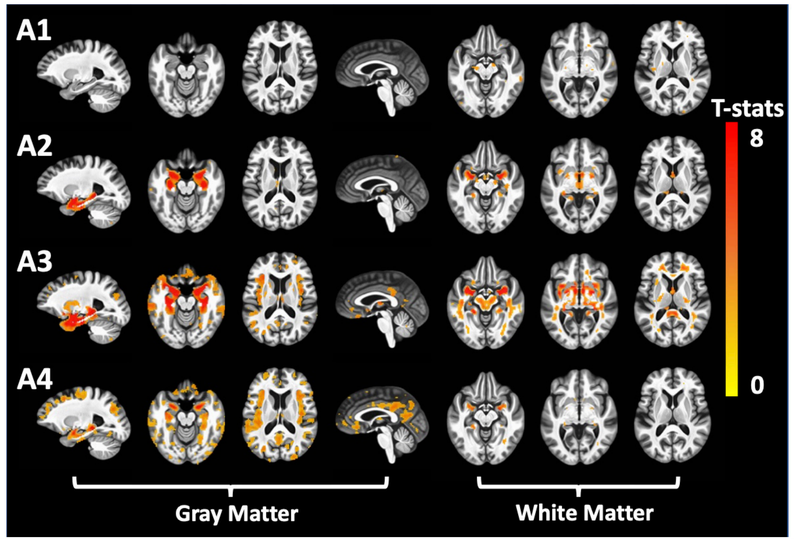


Application of Gene-SGAN to ADNI Dataset

- **Participants:** All CN (Reference) & MCI/AD (Target) participants with WGS data from ADNI were used for model training.
- **Phenotypic features**: imaging ROIs; **Genetic features**: AD-associated SNPs collected from GWAS-Catalog

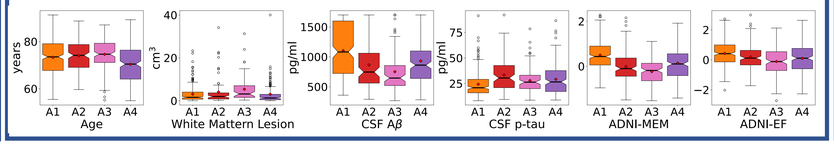
Four subtypes show distinct atrophy patterns

- **A1:** Minimal atrophy (no significant difference from control)
- **A2**: MTL-predominant atrophy
- **A3**: Severe widespread atrophy, including MTL
- **A4**: dominant cortical atrophy , sparing MTL



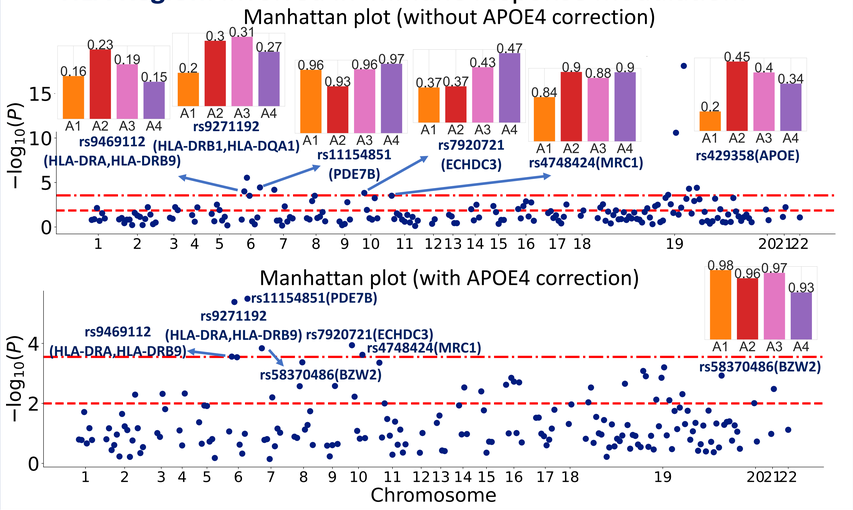
Demographic and Clinical Variables

- **A1**: best cognitive performance and relatively normal CSF-Aβ and CSF-pTau
- **A2:** the most abnormal CSF-pTau
- **A3**: the worst cognitive performance, highest WMH, most abnormal CSF-Aβ
- **A4**: significantly younger than other groups.



Genetic Associations

- The four subtypes reveal significant differences in seven known AD-related genetic variants.
  - **rs429358**: most significant genetic risk factor of AD
  - **rs7920721**: associated with AD among Non-APOE carriers
  - **HLA Region**: involved in immune response modulation.



Differences in CSF/Plasma Biomarkers

- These biomarkers are related to several biological mechanisms contributing to the heterogeneity of AD:
  - Hemostatic functions of the blood-brain barrier Microglial activation or proliferation; Aβ degradation and clearance.