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Exploring the Basis of Phenotypic Diversity in Alzheimer's Disease

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Introduction

Alzheimer's Disease (AD) as the most common type of dementia affects more than 50 million people around the world. Therefore, it is important to recognise the phenotypic diversity of AD and detect the disease early to try out various specific treatments.

The hallmarks for the diagnosis of AD are both phosphorylated-Tau aggregates in neurons and amyloid-β (Aβ) parernchymal pathology[1]. The progressions of tau (Braak and Braak stages) and Aβ (Thal Phase) are shown in Figure 1.

Besides the vast majorities of sporadic AD, some early-onset familial AD cases are caused by autosomal dominant gene mutations. Mutations from three genes are found essential so far: *APP* (*amyloid precursor protein*), *PSEN1* (*presenilin-1*), and *PSEN2* (*presenilin-2*)[2].

AD as the most common type of dementia has been long known to exhibit cognitive impairment. However, not all Alzheimer's cases demonstrate the stereotypical amnestic problems at first. The pathologies started developing from different brain regions might refer to other non-classic clinical phenotypes, including Corticobasal Syndrome (CBS), behavioural variant of Frontotemporal Dementia (bvFTD), Posterior Cortical Atrophy (PCA), and Progressive Aphasia (PPA).

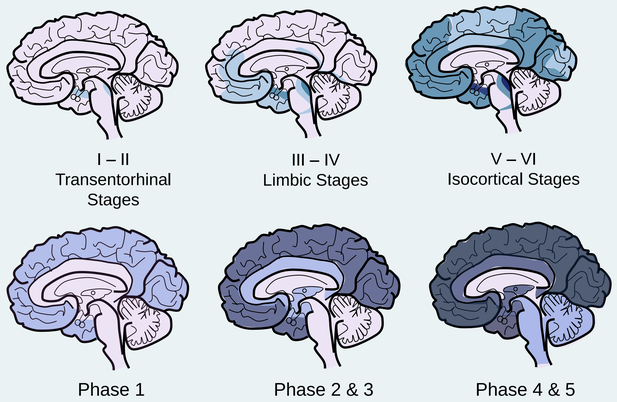


Figure 1. *Upper panel (green): Braak and Braak staging of neurofibrillary tangles (NFTs) / neuropil threads (NTs). Lower panel (blue): Thal phasing of amyloid deposits.*

Reference: **1.** HYMAN, B. T. et al. 2012. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. *Alzheimer's Dement*, 8, 1-13. **2.** PIACERI, I., et al. 2013. Genetics of familial and sporadic Alzheimer's disease. *Front Biosci (Elite Ed)*, 5, 167-77. **3.** PETERSEN, C. et al. 2019. Alzheimer's disease clinical variants show distinct regional patterns of neurofibrillary tangle accumulation. *Acta Neuropathol*, 138, 597-612.

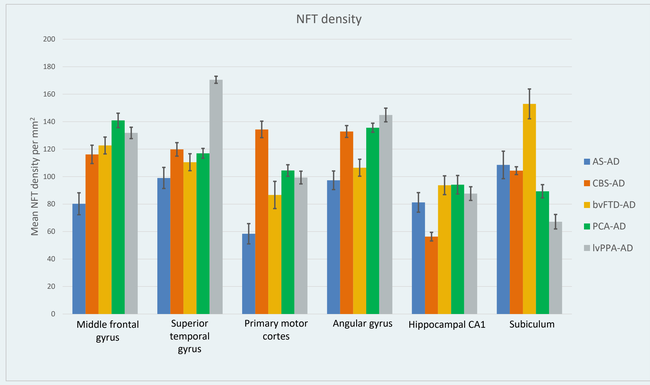
	Phenotypes	Characteristics	Onset Age	Gender Preference	Selective Vulnerability		
					p-tau	Aβ	Genetic
Typical	**Amnestic Syndrome (AS)**	▪ Impaired learning ability ▪ Memory (episodic and semantic) retrival dysfunction	60s	▪ Females > Males ▪ Equal severity	▪ Relatively mild in cortical areas at the beginning	▪ Follows Thal phasing	*APP* *PSEN1* *PSEN2* *ApoE4* (risk factor)
Atypical	**Corticobasal Syndrome (CBS)**	▪ Parkinsonism with limb apraxia and cortical sensory loss	50 - 70	▪ Not reported	▪ Primary motor cortex ▪ Frontal gyrus ▪ Angular gyrus ▪ Somatosensory cortex	▪ Depend on the presence of *ApoE4*	*PSEN1* *ApoE4*
Atypical	**Behavioural Variant of Frontotemporal Dementia (bvFTD)**	▪ Personality changes ▪ Social disinhibition ▪ Impulsivity ▪ Obsessive-compulsive behaviours	50-60	▪ Men > Women	▪ Subiculum ▪ Middle frontal gyrus	▪ Substantia nigra ▪ Basal ganglia	*PSEN1* *PSEN2* *ApoE4*
Atypical	**Posterior Cortical Atrophy (PCA)**	▪ Predominant visuospatial deficits	50-65	▪ No a unitised gender prevalence	▪ Angular gyrus ▪ Middle frontal gyrus	▪ Occipito-parieto-temporal junction	*PSEN1* *PSEN2* *ApoE4*
Atypical	**Primary Progressive Aphasia (PPA)**	▪ Progressive impairment in language functions ▪ Three subtyes: Semantic, Non-fluent, and Logopenic PPA. ▪ Logopenic is the one most significantly associated with AD.	60s	▪ Males > Females ▪ Females have greater damage	▪ Temporal and parietal cortices ▪ Superior temporal gyrus ▪ Angular gyrus ▪ Inferior parietal cortex	▪ No significant difference	*APP* *PSEN1* *ApoE4*

Table 1. *Summary of clinical presentations of AD. The characteristics, including clinical symptoms, age of onset, gender prevalence, and regional vulnerability are summarised.*

Selective Regional Vulnerability and Phenotypic Diversity

The characteristics including clinical symptoms, age of onset, gender prevalence, and selective vulnerability of the phenotypes are summarized in Table 1. The tauopathy of each phenotype, which is discussed by considerable research, is demonstrated in Figure 2. Complementary information is discussed in the following[3].

AS-AD
- ❖ Tauopathy: entorhinal → limbic → isocortical
- ❖ There is no direct evidence suggesting familial cases for AS-AD. The inheritable factors listed in Table 1 are considered as in familial AD cases.



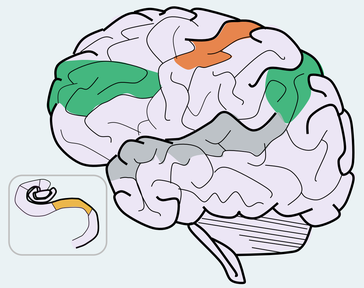


Figure 2. *The involvement of brain regions bearing tauopathy in diverse phenotypes. The areas showing most significant differences are mapped in the right panel. NFT: neurofibrillary tangle.*

CBS-AD
- ❖ Amyloid deposits: for *ApoE4* carriers, the density and distribution of Aβ aggregates are problematic
- ❖ Elevated total CSF tau levels
- ❖ Greater neuronal loss in the substantia nigra; ventricular enlargement; atrophy in occipital cortex and perirolandic region
- ❖ Genetics: *PSEN1* [*p.Gly378Val, p.Phe283Leu, Leu85Pro*]; *ApoE4* [influence Aβ distribution and tau progression]

bvFTD-AD
- ❖ Tauopathy: those develop in subiculum might influence functions of hypothalamic-pituitary-adrenal axis
- ❖ CSF studies: conflicts between evidence, unable to draw a strong argument
- ❖ Genetics: *ApoE4* [severer brain atrophy in different brain regions compared to AS-AD]

PCA-AD
- ❖ Others: hippocampal volume is larger but cortical gray matter volume of parietal and occipital lobes are smaller
- ❖ Genetics: *PSEN1* [*I211M, Q223R, Leu424Pro*]; *PSEN2* [*M239I*]; *ApoE4* [greater grey matter loss in posterior cingulate cortex]

PPA-AD
- ❖ CSF studies: both p-tau and total-tau levels are higher
- ❖ Genetics: *APP* [*Val604Met*]; *PSEN1* [Not specified whether link to AD]; *ApoE4* [heavying Aβ burden]

Conclusion

- ❖ The diverse clinical phenotypes of AD share similar pathogenesis and genetic factors
- ❖ Each phenotype has divergent patterns of pathological distribution.
- ❖ Firm conclusion can not be drawn because of inconsistency between research.
- ❖ Future research
  - ❖ Address more on differences in amyloid deposition patterns with confirmation of underlying disease.
  - ❖ CSF biomarkers as new emerging diagnosis tools are also worth to investigate and set up a standard to identify atypical phenotypes.
  - ❖ More evidence and meta-analysis on genetic factors are suggested.