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A Bioinformatics Pipeline for Evaluating Protein Misfolding Impact on the Tertiary Structure in Alzheimer's Disease

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Antigoni Avramouli is a Ph.D. candidate in the Department of Informatics at the Ionian University. She earned a B.S. degree in Molecular Biology and Genetics at the Democritus University of Trace, Greece. She has completed an interdisciplinary Master's of Clinical Applications of Molecular Medicine in University of Thessaly, postgraduate study program of the School of Medicine.

Research Interests

Her research is mainly focused in Neuroinflammation and Neurodegeneration, Neurodegenerative diseases, Oxidative stress, DNA &RNA damage, Molecular pathways, Immunology, Bioinformatics, Genomic Data Science, System Biology.

Protein Misfolding Diseases

Human diseases caused by defects in protein folding, stability and aggregation

Disease	Protein affected	Description
Cystic fibrosis	Cystic fibrosis transmembrane conductance regulator (CFTR)	The ΔPhe508 mutant has wild-type activity, but impaired folding in the endoplasmic reticulum leads to degradation.
α1 Antitrypsin deficiency	α1 Antitrypsin (also known as SERPINA1)	80% of Glu342Lys mutants misfold and are degraded. Pathology is due to aggregation in patients with a reduced degradation rate.
SCAD deficiency	Short-chain acyl-CoA dehydrogenase (SCAD)	Impaired folding of Arg22Trp mutants leads to rapid degradation.
Alzheimer disease	Presenilin, γ-secretase	Mutations cause incorrect cleavage by the γ-secretase protease to produce the amyloid β-peptide; this aggregates into extracellular amyloid plaques.
Parkinson disease	α-Synuclein	Oxidative damage causes misfolding and aggregation. Hereditary forms are linked to deficiency in ubiquitin-mediated degradation.
Huntington disease	Huntingtin	CAG expansions in the Huntingtin gene lead to an abundance of polyglutamine fragments that aggregate and associate non-specifically with other cellular proteins.
Sickle cell anaemia	Haemoglobin	The Glu6Val mutation leads to aggregation in red blood cells.

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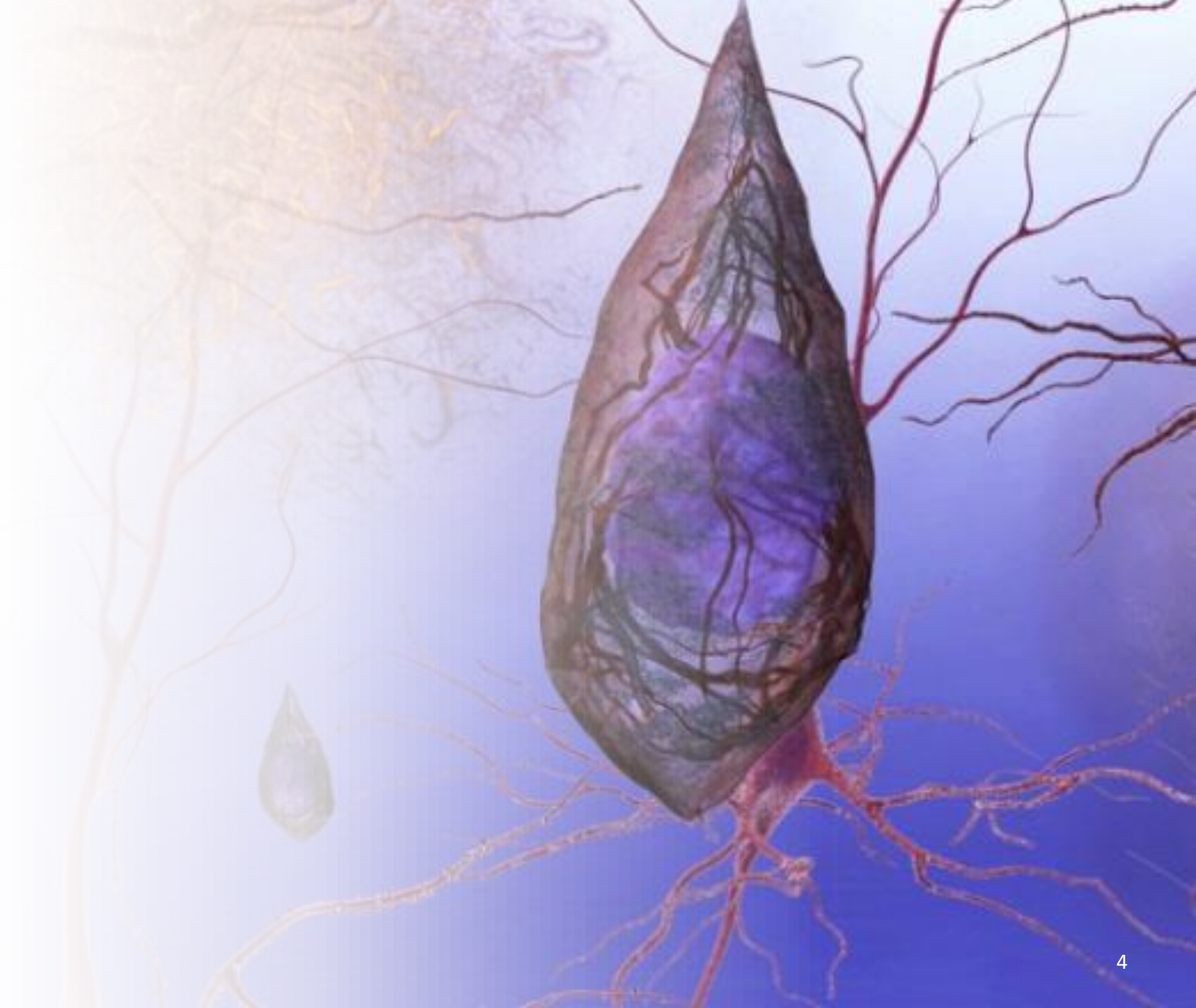
Alzheimer’s Disease is a folding disorder

- Irreversible progressive dementia with long prodromal stages and up to now there is a lack of effective pharmacotherapy options evaluation of the prediction algorithms
- While the clinical symptoms of the disease are defined by cognitive impairment, the causes leading to memory decline are strongly tied to deposits of misfolded protein aggregates.



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PLoS COMPUTATIONAL BIOLOGY

In Silico Analysis of the Apolipoprotein E and the Amyloid β Peptide Interaction: Misfolding Induced by Frustration of the Salt Bridge Network

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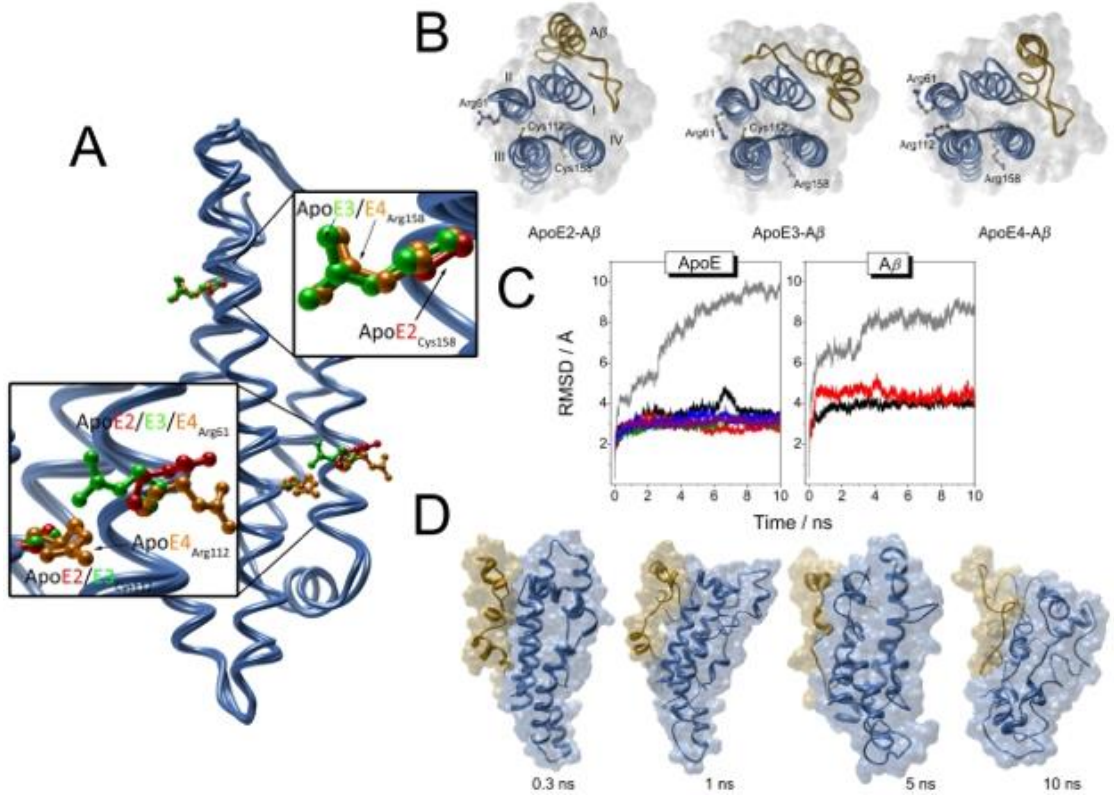
Abstract

The relationship between Apolipoprotein E (ApoE) and the aggregation processes of the amyloid β (Aβ) peptide has been shown to be crucial for Alzheimer's disease (AD). The presence of the ApoE4 isoform is considered to be a contributing risk factor for AD. However, the detailed molecular properties of ApoE4 interacting with the Aβ peptide are unknown, although various mechanisms have been proposed to explain the physiological and pathological role of this relationship. Here, computer simulations have been used to investigate the process of Aβ interaction with the N-terminal domain of the human ApoE isoforms (ApoE2, ApoE3 and ApoE4). Molecular docking combined with molecular dynamics simulations have been undertaken to determine the Aβ peptide binding sites and the relative stability of binding to each of the ApoE isoforms. Our results show that from the several ApoE isoforms investigated, only ApoE4 presents a misfolded intermediate when bound to Aβ. Moreover, the initial α-helix used as the Aβ peptide model structure also becomes unstructured due to the interaction with ApoE4. These structural changes appear to be related to a rearrangement of the salt bridge network in ApoE4, for which we propose a model. It seems plausible that ApoE4 in its partially unfolded state is incapable of performing the clearance of Aβ, thereby promoting amyloid forming processes. Hence, the proposed model can be used to identify potential drug binding sites in the ApoE4-Aβ complex, where the interaction between the two molecules can be inhibited.



Hypothesis

What is the connection between the different isoforms of well-known proteins implicated in the pathogenesis and progression of Alzheimer's Disease?

Could we find a correlation between their misfolded forms and the events occurring at the molecular level?

Methods
Data Consolidation

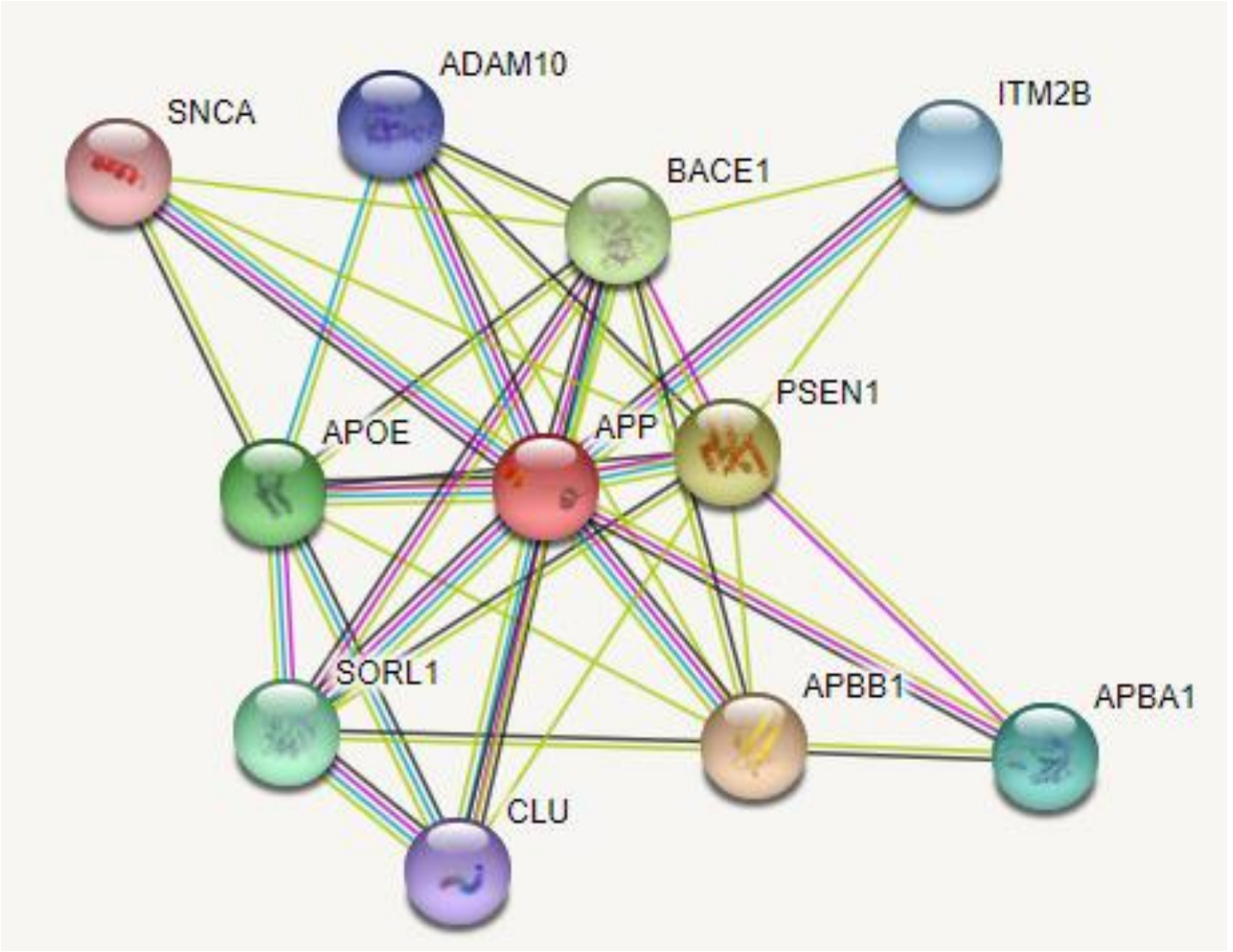
The genetic loci that will be analysed further through protein 3D structure include:

- APP (Amyloid precursor protein),
- PSEN1 (Presenilin one),
- PSEN2 (Presenilin two),
- CLU (Clusterin),
- CR1 (Complement receptor 1),
- PICALM (Phosphatidylinositol binding clathrin assembly protein),
- BIN1 (Myc box- dependent- interacting protein 1),
- ABCA7 (ATP binding cassette transporter 7),
- MS4A (Membrane- spanning 4- domains, subfamily A),
- EPHA1 (Ephrin type-A receptor 1),
- CD33 (CD33 antigen), C
- D2AP (CD2 associated protein),
- SORL1 (Sortilin-related receptor 1),
- TPEM2 (Triggering receptor expressed on myeloid cells 2)

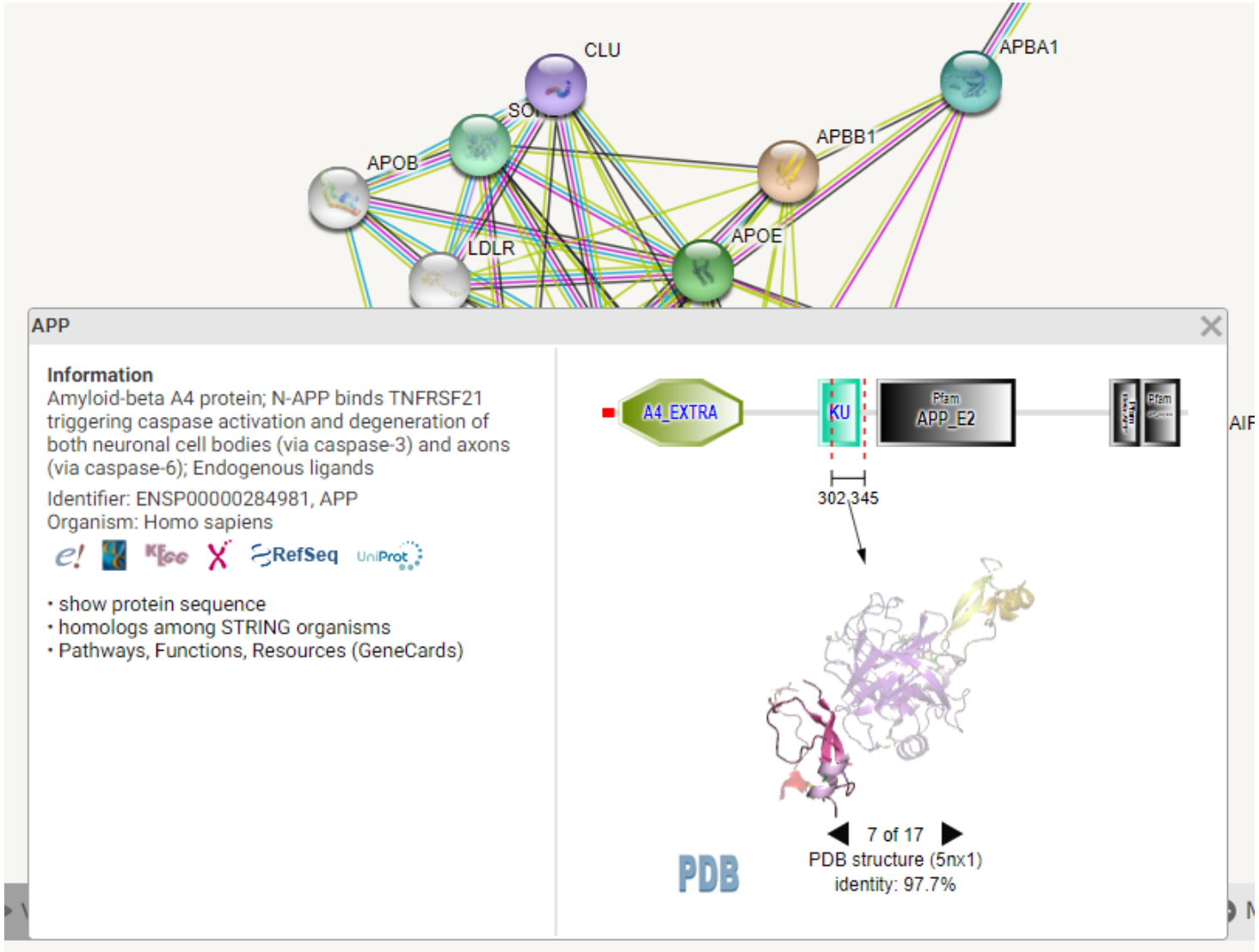
Methods *Evaluation of Protein Structures*

Methodology	Description	How was used
Uniprot	A comprehensive resource for protein sequence and annotation data	To understand the protein function, and the most related protein structures
PolyPhen-2	A tool which predicts possible impact of an amino acid substitution on the structure and function	To understand how mutations affect the structure and function of the protein
iTASSER	A hierarchical approach to protein structure prediction and structure-based function annotation	To predict the mutated and unmutated 3D protein structures
PDBeFold	An interactive service that allows you to identify structures that are similar to that of your reference protein	To compare the mutated and unmutated structures on residues level
CATH / Gene3D	A protein family classification methodology	To identify if there is any relationship between mutations impact and protein families

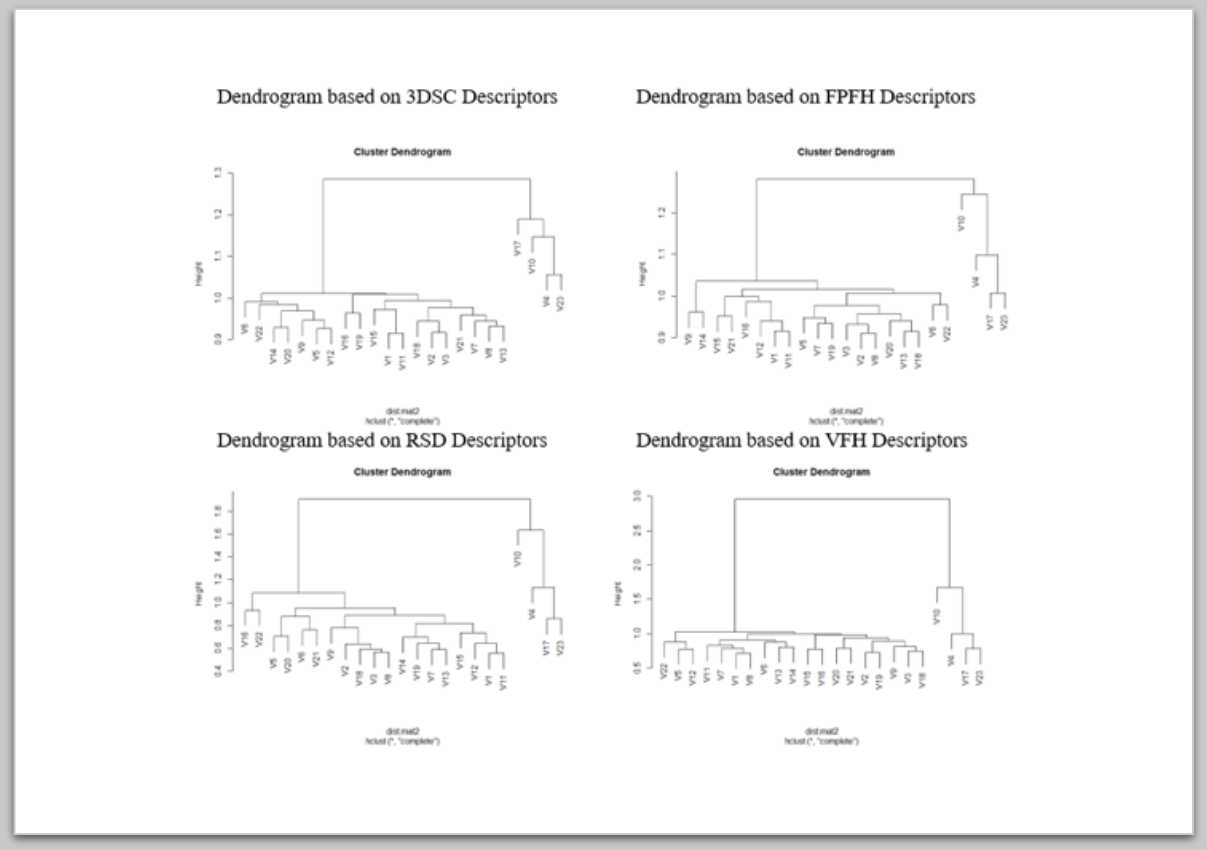
- **Example of APP network in STRING network analysis**

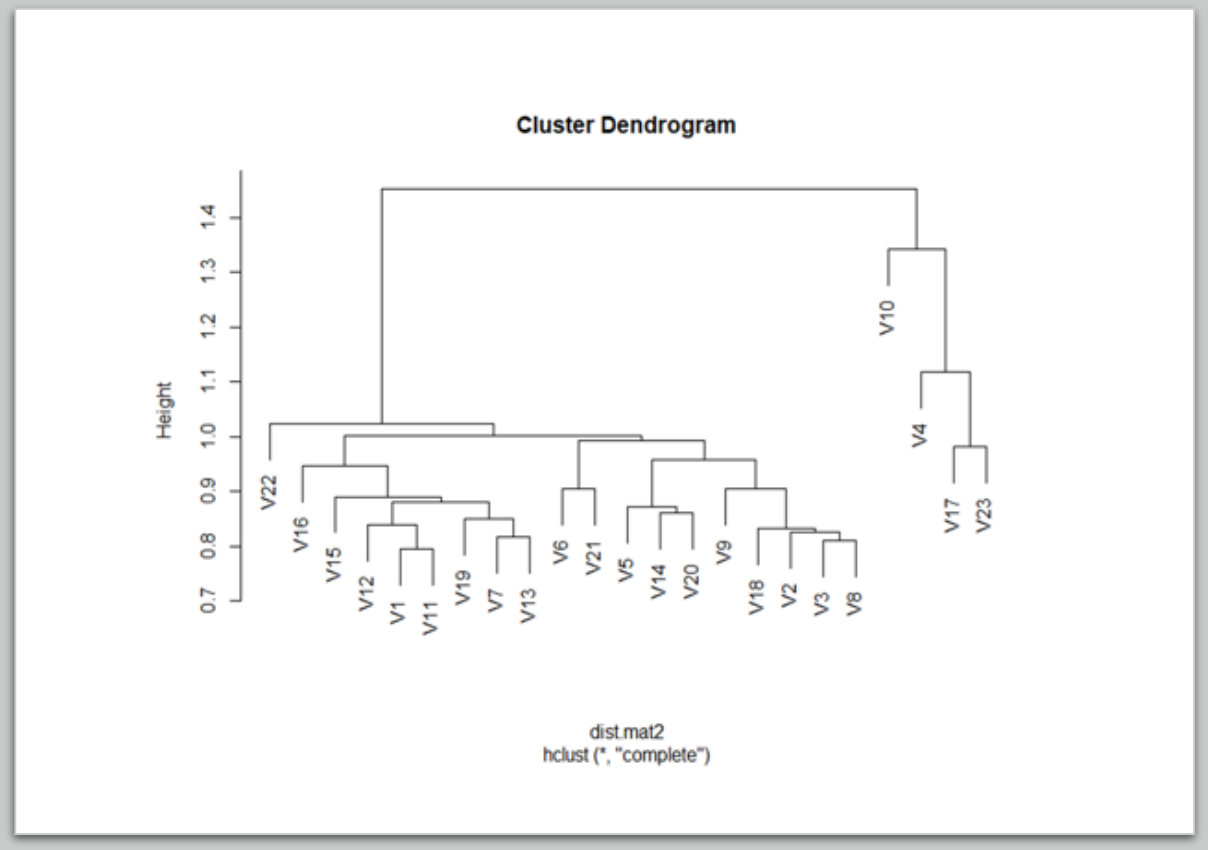


- Structural Analysis of the protein. Each protein is mapped to the experimental determined structures (one or more) included in PDB and PDBe.



STRUCTURAL SIMILARITY and MUTATION analysis IN Alzheimer's disease





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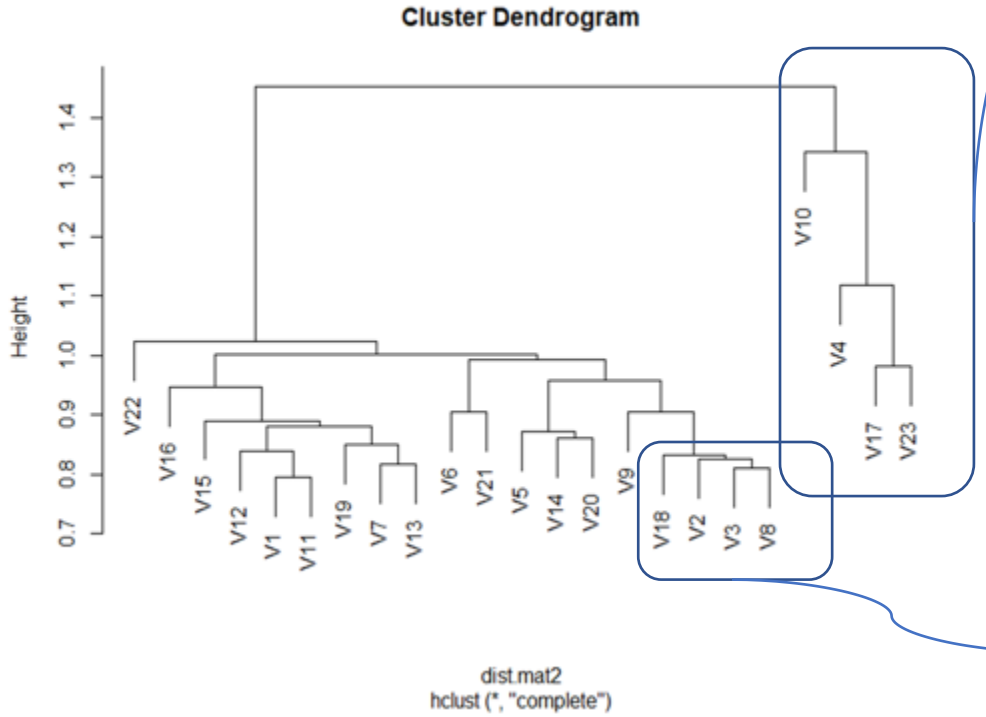

Higher Percentage of structure alteration due to mutation

Mapping	Mutation	Pathogenicity
V17	G378V	AD : Pathogenic
V23	S390N	AD : Pathogenic
V4	I83_M84del	AD : Pathogenic

Mapping	Mutation	Pathogenicity
V8	E120K	AD : Pathogenic
V2	R35Q	AD : Unclear Pathogenicity
V3	I83T	AD : Pathogenic
V18	F386I	AD : Pathogenic

Insights for the pathogenicity of the R35Q mutation

Summary

- Risk prediction standpoint,
- networks exhibiting coexistent genetic variation and biological perturbation would represent prime targets in the development of personalized, burden-based genetic susceptibility tests.
- Therapeutic strategies development
- pathways and networks displaying multi-omics relationships in AD would reduce the search space for rational drug design and may highlight “hub” genes for therapeutic cocktail approaches, such as in the polypharmacy strategies successfully employed for AIDS and various cancers.

> Adv Exp Med Biol. 2020;1195:227-236. doi: 10.1007/978-3-030-32633-3_31.

Alzheimer's Disease: The Role of Mutations in Protein Folding

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Affiliations + expand

PMID: 32468481 DOI: 10.1007/978-3-030-32633-3_31

Abstract

Misfolded proteins result when a protein follows the wrong folding pathway. Accumulation of misfolded proteins can cause disorders, known as amyloid diseases. Unfortunately, some of them are very common. The most prevalent one is Alzheimer's disease. Alzheimer's disease is a neurodegenerative disorder and the commonest form of dementia. The current study aims to assess the impact of somatic mutations in PSEN1 gene. The said mutations are the most common cause of familial Alzheimer's disease. As protein functionality can be affected by mutations, the study of possible alterations in the tertiary structure of proteins may reveal new insights related to the relationship between mutations and protein functions. To examine the effect of mutations, the

Polychronidou E, Avramouli A, Vlamos P. Alzheimer's Disease: The Role of Mutations in Protein Folding. Adv Exp Med Biol. 2020;1195:227-236. doi: 10.1007/978-3-030-32633-3_31. PMID: 32468481.

Thank you!

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