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COMPLEX DATA IN HEALTH

Studying Alzheimer's Disease

Authors:

Emanuele Alberti
Leandro Duarte
Ottavia Biagi

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Introduction

For this assignment, we were assigned to study **Alzheimer's Disease (AD)**. The following identifiers were provided: UMLS CUI C0002395, NCIt code C2866, recommended protein Apolipoprotein E (UniProt: P02649), transcriptome dataset GSE300079, and image dataset from OASIS (Kaggle).

1 Medical Terminologies and Semantic Datasets

1.1 Disease General Information

We explored biomedical databases to gather standardized information about Alzheimer's Disease.

NCBI MedGen (UID: 1853) provides the following definition: “*A degenerative disease of the brain that causes dementia, which is a gradual loss of memory, judgment, and ability to function. This disorder usually appears in people older than age 65, but less common forms of the disease appear earlier in adulthood.*” The disease is classified as *Disease or Syndrome* with concept ID C0002395. The directly associated gene is APP (21q21.3), with related genes including APOE, PSEN1, PSEN2, ABCA7, MPO, and PLA2U [1].

NCBI MeSH (ID: D000544) describes AD as a degenerative brain disease with insidious onset of dementia, impairment of memory, judgment, and attention span, followed by apraxias and global loss of cognitive abilities. Pathologically, it is marked by senile plaques, neurofibrillary tangles, and neuropil threads [2].

ICD-10 classifies AD under code G30, with subtypes: G30.0 (early onset, before age 65), G30.1 (late onset, after age 65), G30.8 (other), and G30.9 (unspecified) [3].

Orphanet (ORPHA:1020) describes Early-onset autosomal dominant Alzheimer disease (EOAD), representing less than 1% of all AD cases, caused by mutations in PSEN1 (69%), APP (13%), or PSEN2 (2%) [4].

Table 1 summarizes the disease codifications across vocabularies.

Table 1: Alzheimer's Disease codifications across medical vocabularies [1, 2, 3, 5, 6, 7, 8, 4].

Vocabulary	Code
UMLS CUI	C0002395
MedGen UID	1853
MeSH	D000544
ICD-10	G30
SNOMED CT	26929004
NCIt	C2866
OMIM	104300, 516000
Orphanet	ORPHA:238616, ORPHA:1020
MONDO	MONDO:0004975
HPO	HP:0002511

1.2 SPARQL Query Results

We queried the NCIt SPARQL endpoint (<https://shared.semantics.cancer.gov/sparql>) to retrieve annotation properties for Alzheimer's Disease (code C2866) [6]. The query extracted the preferred label, synonyms, definition, semantic type, and UMLS CUI.

Summary of SPARQL Findings: The query retrieved annotation properties for NCIt code C2866. The disease is classified under semantic type “Mental or Behavioral Dysfunction” and maps to UMLS CUI C0002395. Seven synonyms were identified, including “Alzheimer’s Dementia”, “Alzheimer Disease”, and “Alzheimer dementia”. The definition describes AD as a progressive neurodegenerative disease characterized by nerve cell death leading to loss of cognitive function such as memory and language.

2 Bioinformatics

2.1 Disease Genes

We identified three main genetic factors linked to Alzheimer’s disease from NCBI MedGen [1]: APP and PSEN1, when mutated, can directly cause rare, early-onset familial forms of the disease. APOE primarily affects an individual’s risk for the more common late-onset form.

APP (Amyloid Precursor Protein) – NCBI Gene ID: 351, chromosome 21q21.3. The APP gene provides the blueprint for amyloid precursor protein. This protein is cut into smaller fragments, including amyloid-beta ($A\beta$), which is a key component of the plaques observed in the brains of Alzheimer’s patients [9, 10]. Certain APP mutations or extra copies of the gene lead to an overproduction or more “sticky” forms of $A\beta$, which promotes plaque buildup and can directly cause early-onset familial Alzheimer’s disease [9].

PSEN1 (Presenilin 1) – NCBI Gene ID: 5663, chromosome 14q24.2. PSEN1 encodes presenilin-1, which is the catalytic core of the γ -secretase enzyme. This enzyme performs the final cut of APP to release $A\beta$. Mutations in PSEN1 typically alter this cutting process, leading to the production of more of the longer, aggregation-prone $A\beta$ peptides. This makes PSEN1 the most common genetic cause of autosomal-dominant early-onset Alzheimer’s, with symptoms often beginning before age 65, and sometimes even before 40 [11, 12].

APOE (Apolipoprotein E) – NCBI Gene ID: 348, chromosome 19q13.32. APOE produces apolipoprotein E, a protein that assists in transporting fats and cholesterol within the body and brain [13]. Its common variants ($\varepsilon 2$, $\varepsilon 3$, $\varepsilon 4$) differ in how they manage $A\beta$ and brain lipid metabolism. Carrying the $\varepsilon 4$ form increases the risk of late-onset Alzheimer’s in a dose-dependent manner, while the $\varepsilon 2$ variant tends to lower this risk. APOE primarily acts as a risk modifier; individuals with the $\varepsilon 4$ allele may never develop Alzheimer’s, and conversely, those without it can still develop the disease [13, 14].

Gene Sequence: Following the assignment recommendation, the APOE mRNA FASTA sequence (RefSeq: NM_000041.4) is provided in Appendix A [15].

2.2 Proteins

We analyzed Apolipoprotein E (APOE), the recommended protein for this assignment, using UniProt accession P02649 [16].

Function: APOE is an apolipoprotein that associates with lipid particles and transports lipids between organs via plasma and interstitial fluids. It is a core component of plasma lipoproteins (chylomicrons, VLDL, IDL, HDL) and participates in their production, conversion, and clearance. APOE binds to cellular receptors (LDLR, LRP1, LRP2, LRP8, VLDLR) that mediate uptake of APOE-containing lipoprotein particles. The protein plays a role in cholesterol homeostasis through reverse cholesterol transport and regulates lipid transport in the central nervous system, affecting neuron survival and sprouting [16].

Role in Alzheimer’s Disease: The APOE*4 allele is associated with late-onset familial and sporadic Alzheimer disease. Risk for AD increases from 20% to 90% and mean age at onset decreases

from 84 to 68 years with increasing number of APOE*4 alleles. [16].

Protein Sequence: The APOE protein sequence (317 amino acids) was retrieved from UniProt and is provided in Appendix B.

Molecular Interactions: APOE does not interact with DNA or RNA. The protein primarily interacts with lipids through its C-terminal domain (residues 222-299), which binds phospholipids and cholesterol in lipoprotein particles. The N-terminal domain (residues 1-191) contains the LDLR-binding region (residues 134-150) that mediates receptor-mediated cellular uptake of lipoproteins. APOE also binds heparin and heparan sulfate proteoglycans on cell surfaces through its N-terminal domain [16].

Protein Structures: We obtained protein structures from classical experimental methods and computational prediction.

Figure 1 shows the four structures obtained from classical methods and AlphaFold prediction.

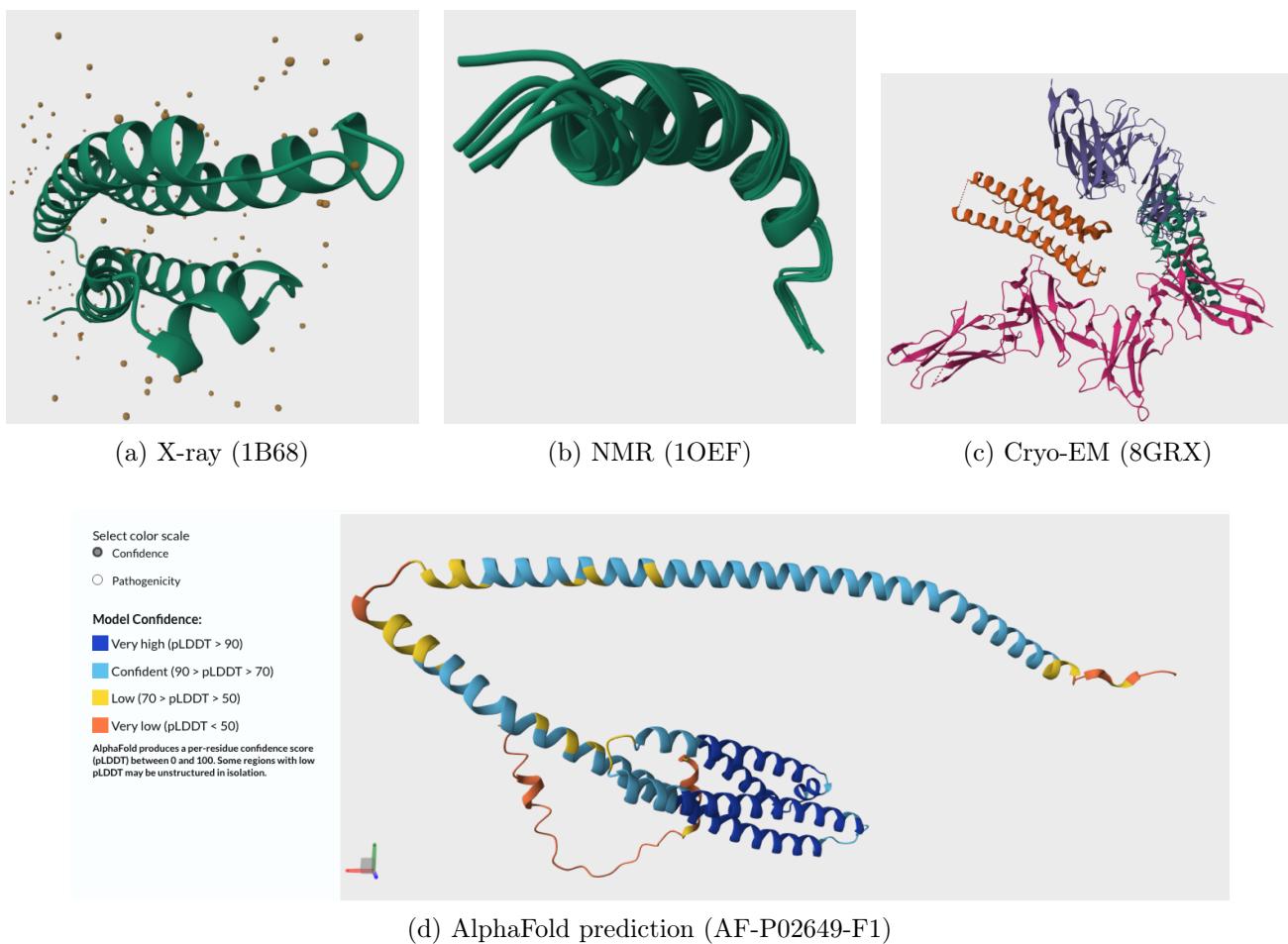


Figure 1: APOE protein structures from different determination methods [17, 18, 19, 20].

Structural Comparison: The X-ray structure displays a static, well-defined conformation typical of crystallographic methods, capturing residues 19-209. Crystallography freezes the protein in a single state, producing a clean ribbon structure. The NMR structure shows multiple overlapping conformations (appearing as a bundle of strands), representing an ensemble of solution-state structures for residues 281-304. NMR captures protein dynamics in solution, resulting in multiple overlaid structures. The Cryo-EM structure presents a complete assembly (residues 41-180), revealing protein organization in a near-native frozen state. AlphaFold predicts the full-length structure (1-317), displayed as a single ribbon colored by confidence: blue indicates high confidence, cyan for confident regions, yellow for low confidence, and orange for very low confidence. Classical methods provide fragmented views of specific domains, while AlphaFold offers a complete structure prediction across the entire sequence.

A APOE Gene FASTA Sequence

>NM_000041.4 Homo sapiens apolipoprotein E (APOE), transcript variant 2, mRNA
CTACTCAGCCCCAGCGGAGGTGAAGGACGTCTTCCCCAGGAGCCGACTGGCAATCACAGGCAGGAAGA
TGAAGGTTCTGTGGGCTCGTTGCTGGTCACATTCCCTGGCAGGATGCCAGGCCAAGGTGGAGCAAGCGGT
GGAGACAGAGCCGGAGCCCGAGCTGCCAGCAGACCGAGTGGCAGAGCGGCCAGCGCTGGGAAGTGGCA
CTGGGTCGCTTTGGGATTACCTGCCCTGGGTGCAGACACTGTCTGAGCAGGTGCAGGAGGAGCTGCTCA
GCTCCCAGGTACCCAGGAAGTGAGGGCGCTATGGACGAGACCATGAAGGAGTTGAAGGCCTACAAATC
GGAAGTGGAGGAACAAGTGACCCCGTGGCGAGGAGACGCCGACGGCTGTCCAAGGAGCTGCAGGCG
GCGCAGGCCGGCTGGCGCGACATGGAGGACGTGTGCCGCTGGTCAGTACCGCGGCGAGGTGC
AGGCCATGCTCGGCCAGAGCACCGAGGAGCTGGGGTGCCTCGCCTCCACCTGCGCAAGCTGCGTAA
GCGGCTCCTCCCGATGCCGATGACCTGCAGAACGCCCTGGCAGTGTACAGGCCGGGCCGAGGGC
GCCGAGCGCGGCCCTAGGCCATCCCGAGGCCCTGGGCCCTGGTGGAACAGGGCCGCGTGCAGGCCG
CCACTGTGGGCTCCCTGGCCGGCCAGCGCTACAGGAGCGGCCAGGCCCTGGGGGAGCGGGCTGCGCG
GCGGATGGAGGAGATGGGAGCCGGACCGCAGCAGATAACGCCCTGAGGCCAGGCCCTCCAGGCCCTCAAGA
GCTGGTTCGAGCCCCTGGTGGAAAGACATGCAGGCCAGTGGCCGGCTGGTGGAGAACGGTGCAGGCTGC
CGTGGGACCAGGCCGCCCTGTGCCAGCGACAATCACTGAACGCCGAAGCCTGCAGCCATGCGACCC
CACGCCACCCCGTGCCTCTGCCCTCGCAGCCTGCAGCGGAGACCCCTGTCCCCGCCAGCCGTCC
CCTGGGTGGACCCTAGTTAATAAGATTACCAAGTTCACGCA

B Apolipoprotein E FASTA Sequence

>sp|P02649|APOE_HUMAN Apolipoprotein E OS=Homo sapiens OX=9606 GN=APOE PE=1 SV=1
MKVLAALLVTFLAGCQAKVEQAVETEPEPELRRQQTEWQSGQRWELALGRFWDYLRWVQT
LSEQVQEELLSSQVTQELRALMDETMKELKAYKSELEEQLTPVAEETRARLSKELQAAQA
RLGADMEDVCGRNVQYRGEVQAMLGGSTEELRVLASHLRKLRKLLRDADDLQKRLAVY
QAGAREGAERGLSAIRERLGPLVEQGRVRAATVGSLAGQPLQERAQAWGERLRARMEEMG
SRTRDRLDEVKEQVAEVRAKLEEQQIRLQAEAFQARLKSWFEPLOEDMQRQWAGLVEK
VQAAVGTSAAPVPSDNH

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