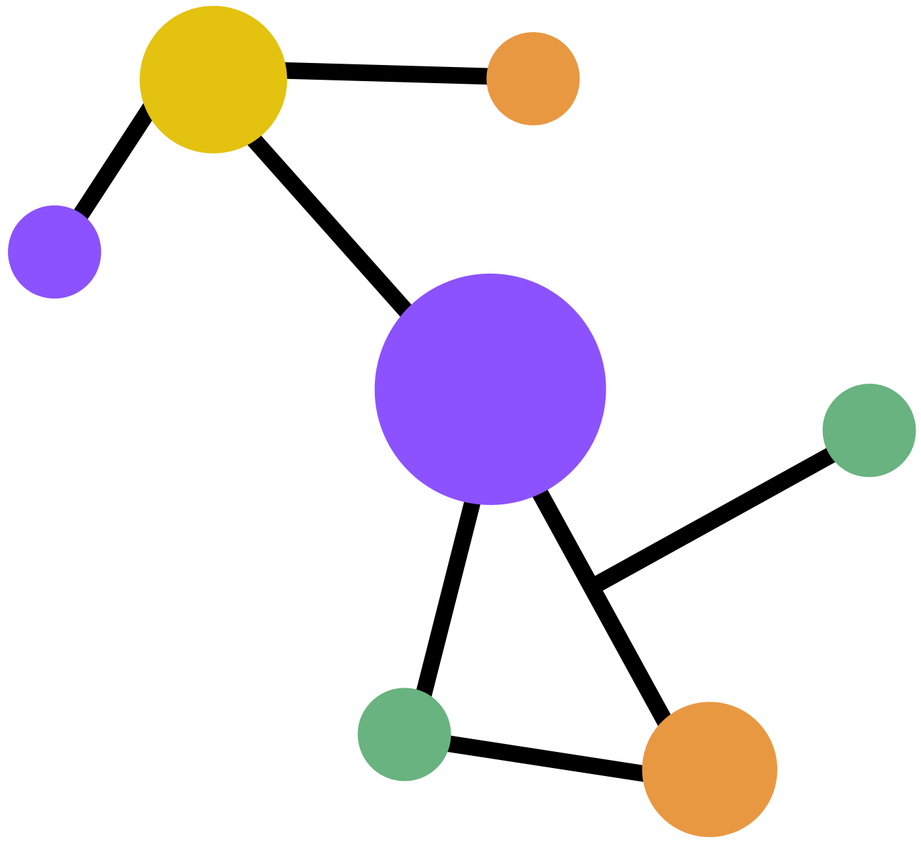
Analysis of the Human Interactome:

Fragilities and their Implications for Alzheimer's Disease



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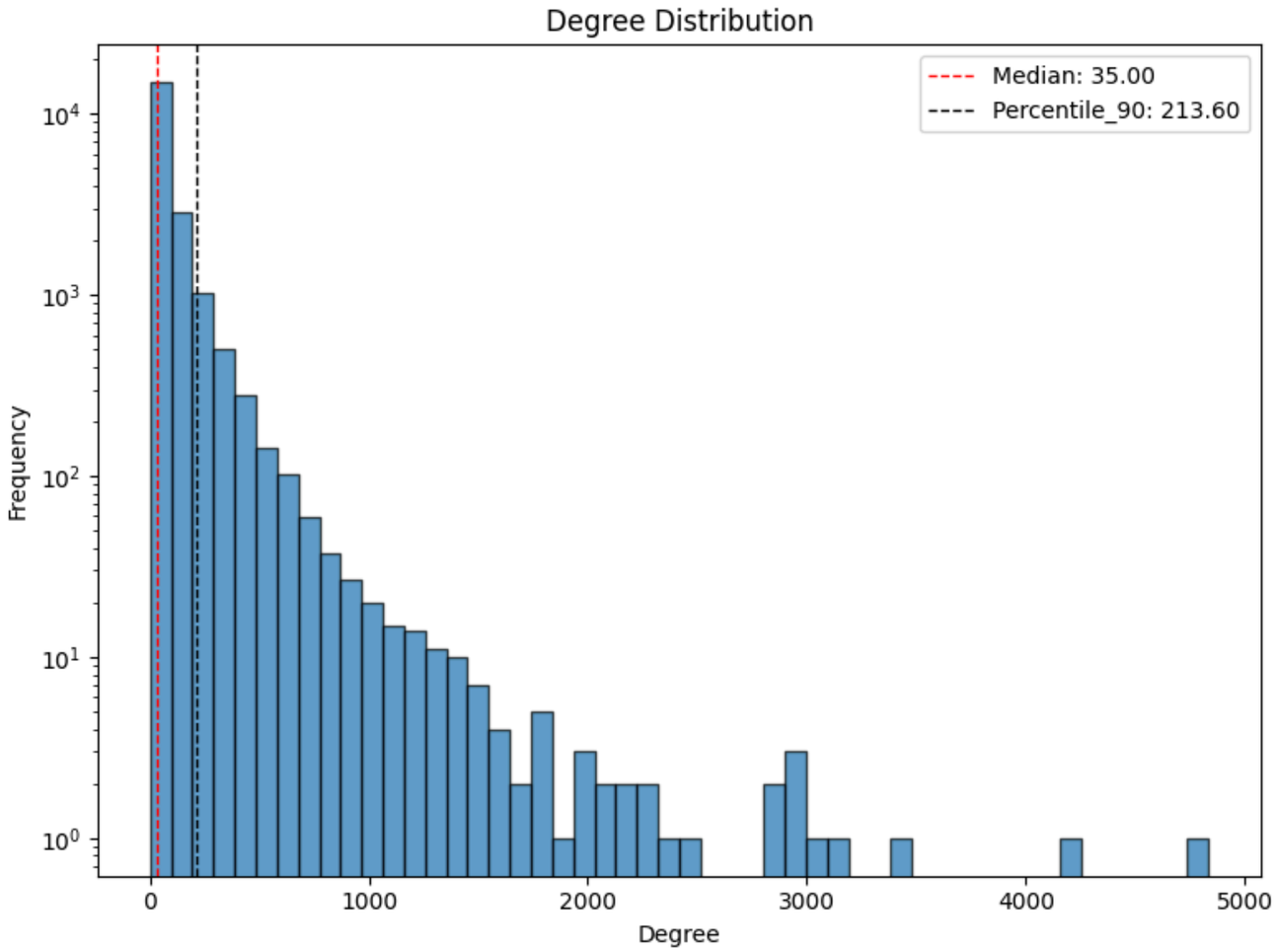
Data Driven Models for Complex Systems

Why Network Analysis in Biology?

- **Human Interactome** ⟶ Maps all genes interactions in the body, forming a network that drives biological processes

- **Goal** ⟶ Identify genetic causes of a disease by analyzing the network and tracing its spread through genes

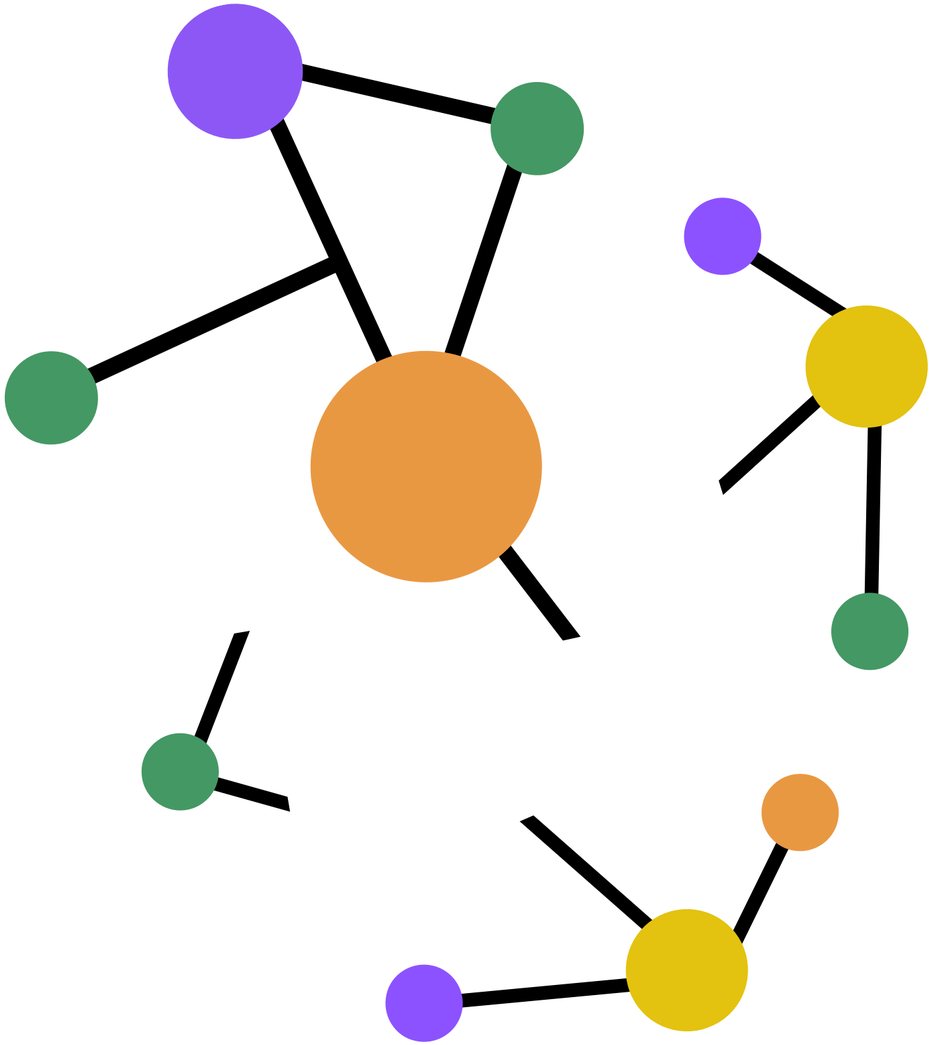
- **Benefits :**
  - **Reveals Fragilities** : Identifies critical genes whose disruption may lead to diseases.
  - **Data-Driven Insights** : Enables modeling of complex systems to predict disease mechanisms and progression.
  - **Therapeutic Potential** : Highlights key interaction points for targeted interventions and drug development.



The Human Interactome

- **Connected** graph
- **Nodes** : 20.045
- **Edges** : 871.700
- **mean**-degree : **86,97**
- **median**-degree : **35**
- only **99** nodes have a degree **> 1000**
- only **19** nodes have a degree **> 2000**
- **Top-5** degree genes :
  - *TRIM67* (4834) - *ZRANB1* (4160) - *PARK2* (3416) - *CUL3* (3146)– *RPA1* (3049)

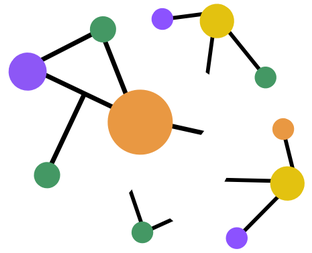
Percolation

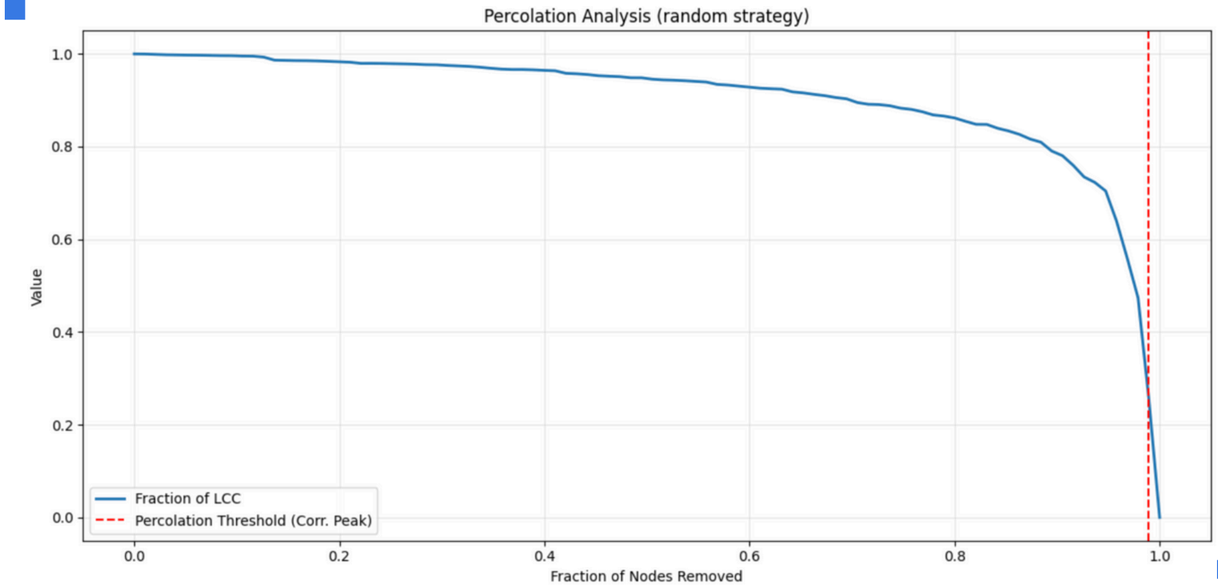


- What is percolation ?
  - Progressive removal of nodes (or edges) from a network to study its structural **robustness**.
- Why do we use it ?
  - To simulate the **impact of mutations** caused by a disease on the interactome, allowing us to identify key proteins whose loss critically affects overall connectivity.
  - We will use site percolation.
- How do we use it ?
  - Two different strategies :
    - Random removal
    - Degree-based removal

Connectivity Analysis

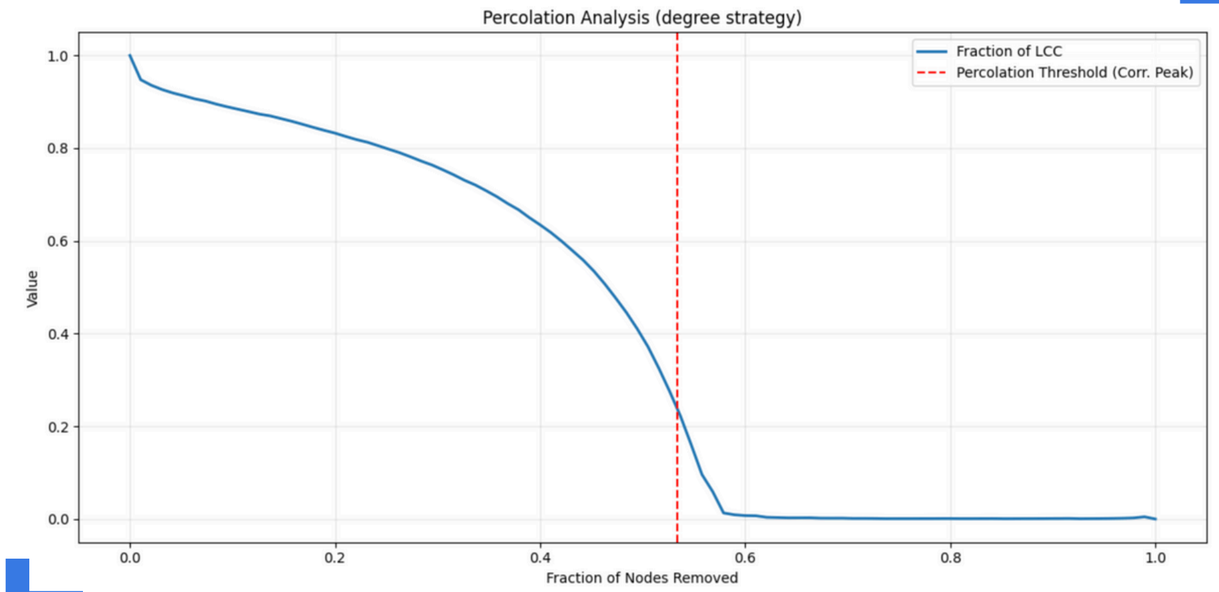
Robustness of the Human Interactome



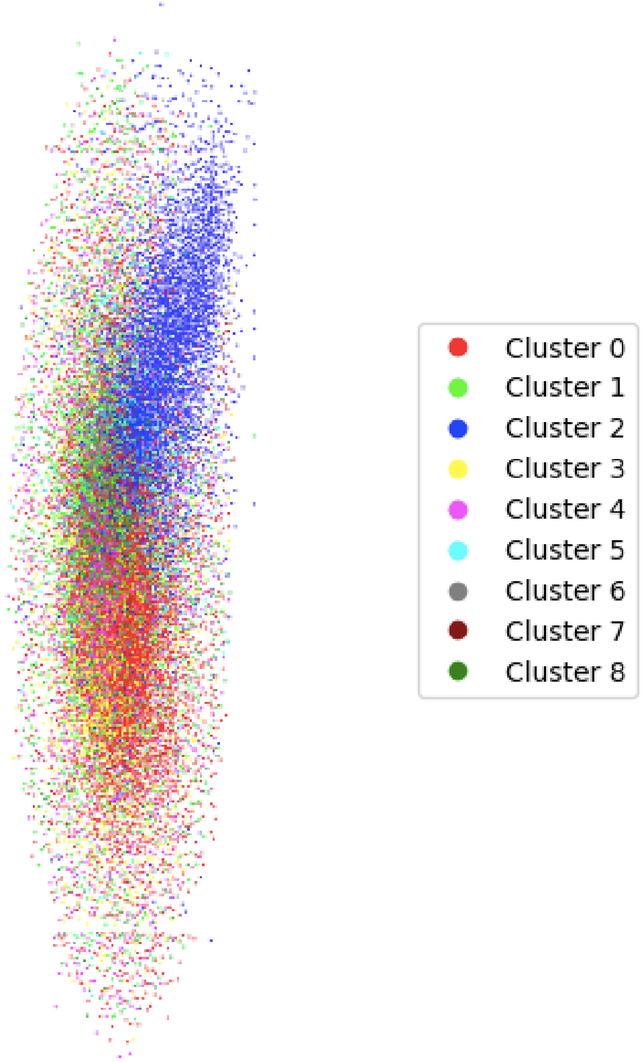


- **Random strategy** ⟶ shows high network's resistance to random attacks.
- Percolation **threshold** = **0.989**

- **Degree-based strategy** ⟶ highlights the network's vulnerability to targeted attacks
- Percolation **threshold** = **0.534**



Communities



Cluster Analysis

- We used the **Louvain method** 100 times to reliably identify optimal gene communities in the interactome.
- **Modularity** : **30%**

- **Community 0** : Involved in cell division processes (27.7%)
- **Community 1** : Involved in protein stabilization (15.9%)
- **Community 2** : Regulation of cytoskeletal structure (23.8%)
- **Community 3** : Control of DNA transcription (12.0%)
- **Community 4** : Responsible for protein synthesis (11.1%)
- **Community 5** : Related to skin and retina health (3.2%)
- **Community 6** : Support energy production in mitochondria (5.0%)
- **Community 7** : Involved in the immune response (0.2%)
- **Community 8** : Basic, unknown, or peripheral roles (1.1%)

Case Study : Alzheimer's disease

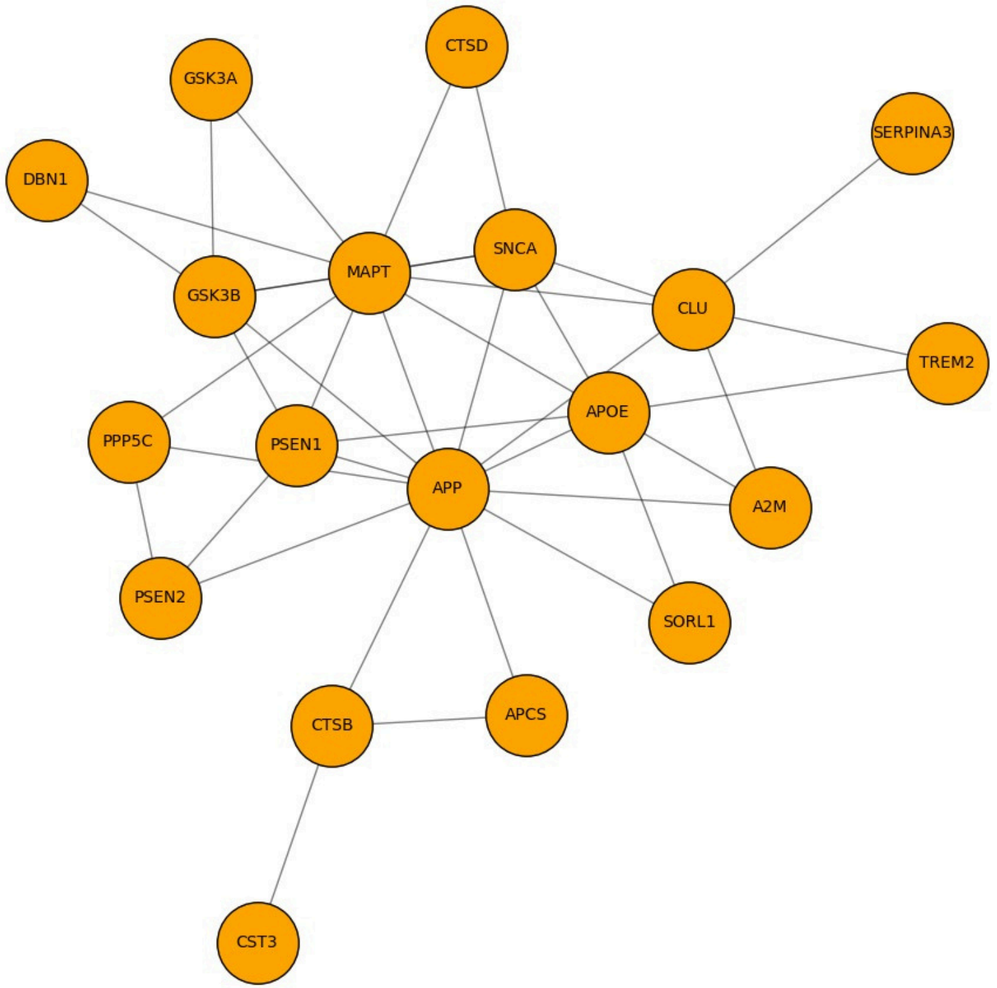
- Neurodegenerative disease causing memory loss and brain cell damage.
- Obtained **genes** related to **Alzheimer's** Disease from the *Jensen Lab* database.

QUESTIONS :

- Does Alzheimer's disease selectively impact **hub genes**, in a way comparable to targeted percolation?

- Can we find other genes related to the disease with **link prediction** algorithms?

- Which **functional classes** of genes are affected by Alzheimer's?



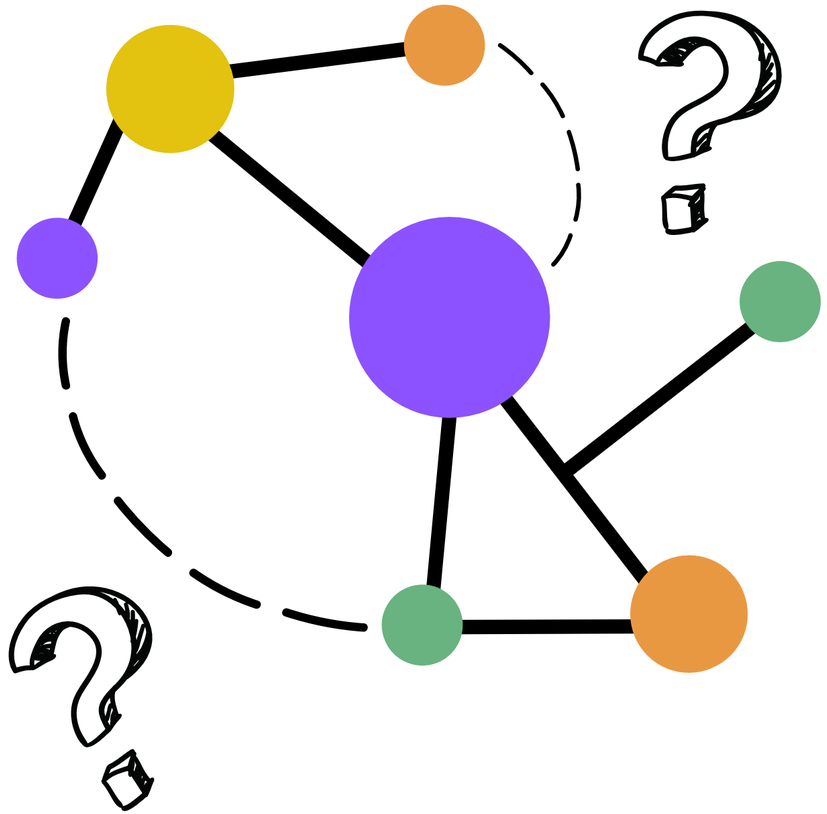
Alzheimer's Effect on the Interactome

High degree nodes in the GDAs

- APP (2323) : Involved in cell division processes (Aids neuron migration)
- SNCA (966) : Involved in protein stabilization (dopamine regulation)
- MAPT (946) : Involved in protein stabilization (mantains neuron structure)
- GSK3B (823) : Involved in protein stabilization (cell signaling)
- GSK3A (446) : Involved in cell division processes (cell growth and signaling)

- **28 Original** Seed Genes → **26** Found in **Interactome**
- Building the Disease Interactome LCC:
  - **19** Genes
  - **39** edges
- Includes genes that have **important network roles** in the PPI graph
- 10 genes are present in Regulation of cytoskeletal structure (cluster 2)
- No genes from Clusters 3,4,7,8

Algorithms



Heat Diffusion

- Heat propagates over the network structure.
- Nearby nodes get influenced proportionally to their proximity and connectivity.
- Heat equation on graphs:

$$h(t) = e^{-Lt}h(0)$$

- L Laplacian Matrix
- $h(t)$ Heat Vector at time t

Random Walk with Restart (RWR)

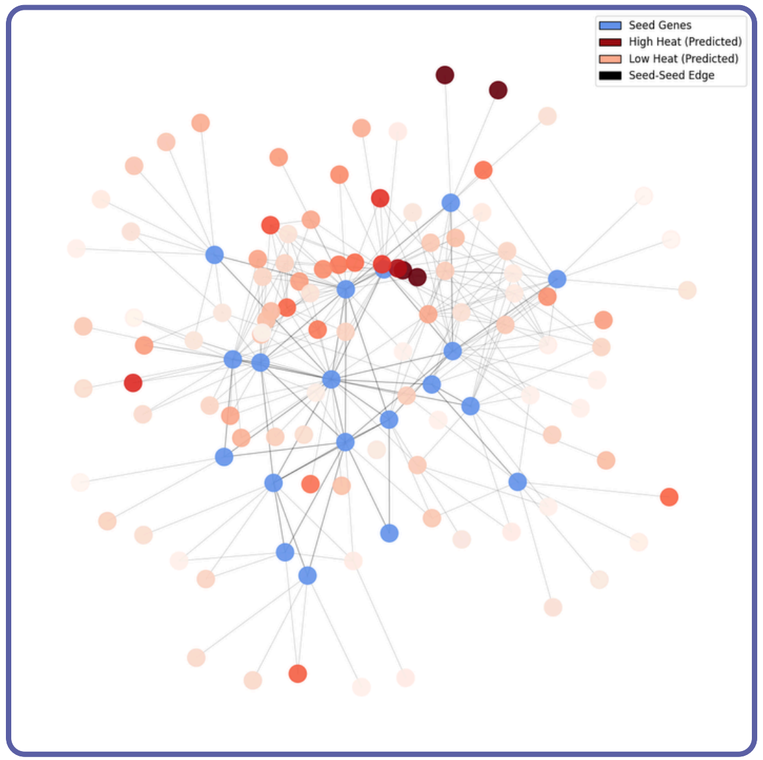
- Probability mass propagates over the network structure.
- Nearby nodes accumulate influence based on their connectivity and proximity to the seed.

$$p(t+1) = (1-\alpha)Pp(t) + \alpha r$$

- P Transition matrix
- r Seed vector
- α Restart Probability
- $p(t)$ Probability vector

Predicted Genes

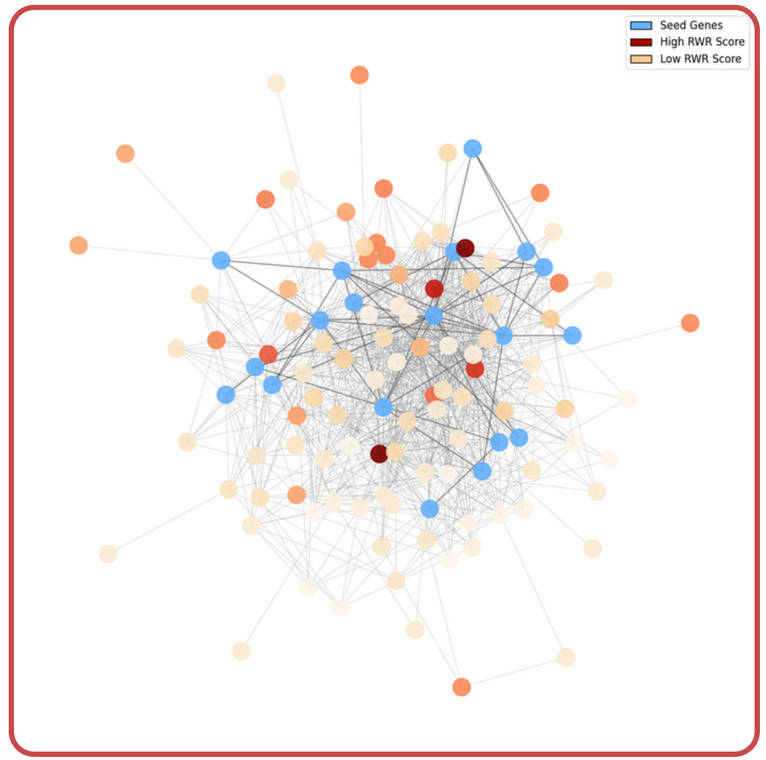
- *Heat Diffusion*
  - **35** genes in **Cluster 2** & **20** genes in **Cluster 3**
  - doesn't include important genes from the PPI



Results

- Computed **100** new **genes** with both algorithms
- **24** genes were found in **common**
- **Heat Diffusion** tends to find high degree genes inside **cluster 3**: (genes that Control DNA transcription)
- **RWR** finds more high degree genes inside **clusters 0** and **1**, which are **hubs** for the interactome graph

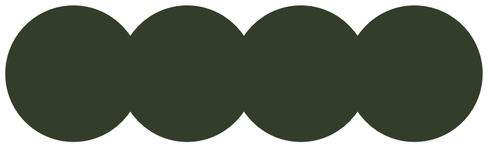
- *Random Walk with Restart*
  - **40** genes present in **Cluster 2**
  - include significative genes in the PPI



Biological Validation

- RWR genes are **highly connected** and involved in general functions like protein stabilization and cell division, suggesting they may **not** be **specific** to **Alzheimer's**.

- Heat Diffusion genes have **lower degree** and have **more disease-specific** roles.



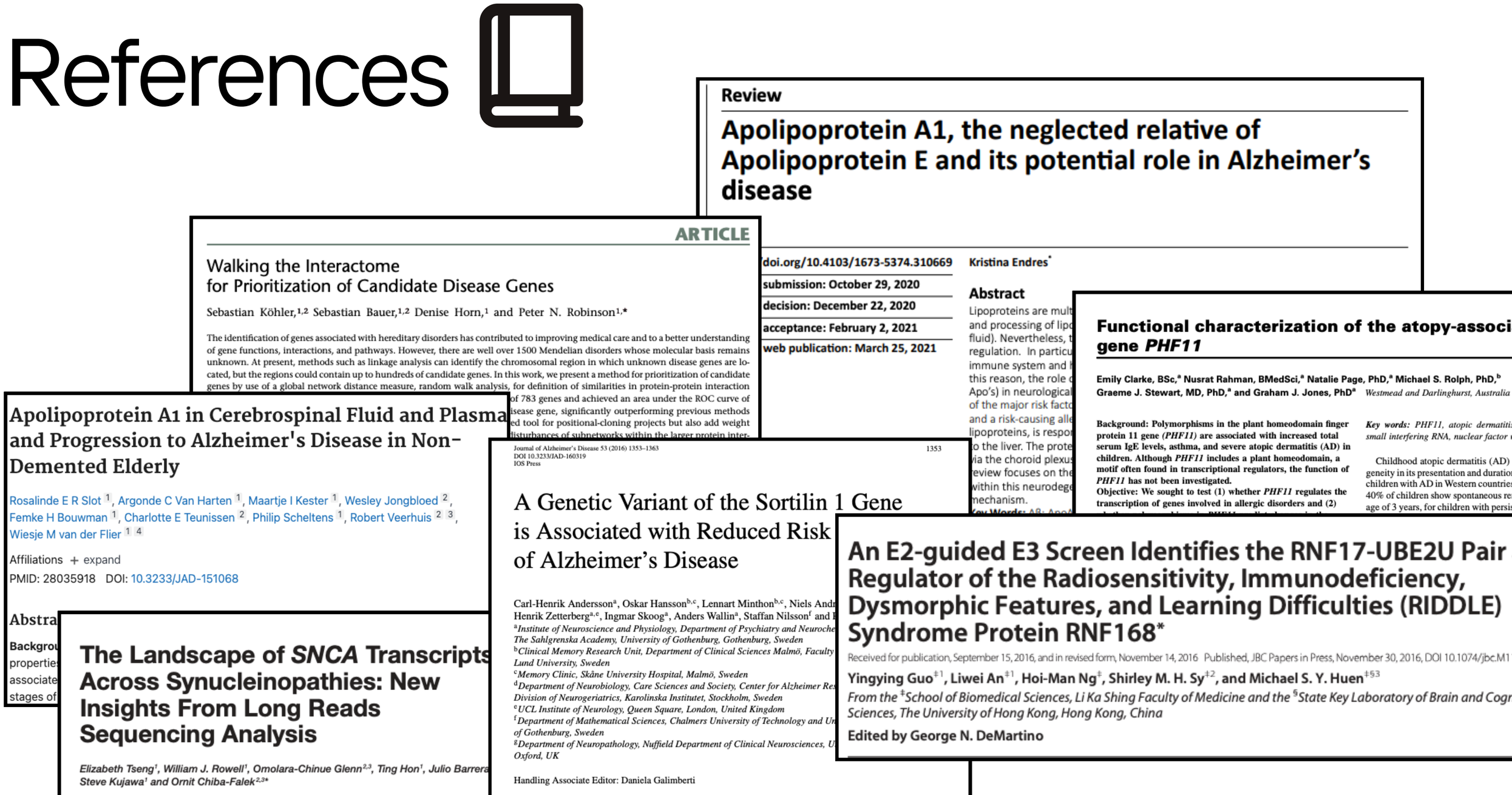
Gene Name	Degree	Function
ZRANB1	4160	Support energy production in mitochondria
CUL3	3146	Involved in cell division processes
RPA1	3049	Involved in protein stabilization
MYC	2964	Responsible for protein synthesis
RPA2	2897	Involved in protein stabilization
TEX101	254	Involved in protein stabilization
SORT1	195	Intracellular trafficking and neurodegeneration
APOA1	178	Helps clear a toxic protein in AD from the brain
UBE2U	138	Neurofibrillary tangles
PHF11	136	Immune modulation and chromatin remodeling

Conclusions

- The Human Interactome is a complex network relying heavily on a small number of hub proteins for stability.
- It is resilient to random disruptions but fragile when these hubs are targeted.
- Its modular structure reflects specialized biological functions.
- In Alzheimer's disease, high-degree nodes like *APP*, *SNCA*, *GSK3B*, *MAPT* and *GSK3A* emerge as key players.
- Link prediction can reveal hidden disease-related genes. Different algorithms provided different results.
- Our research question has been answered : diseases like Alzheimer’s attack the interactome, targeting hub genes to compromise its structure

Appendix

References



Review

Apolipoprotein A1, the neglected relative of Apolipoprotein E and its potential role in Alzheimer's disease

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Abstract

ARTICLE

Walking the Interactome for Prioritization of Candidate Disease Genes

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The identification of genes associated with hereditary disorders has contributed to improving medical care and to a better understanding of gene functions, interactions, and pathways. However, there are well over 1500 Mendelian disorders whose molecular basis remains unknown. At present, methods such as linkage analysis can identify the chromosomal region in which unknown disease genes are located, but the regions could contain up to hundreds of candidate genes. In this work, we present a method for prioritization of candidate genes by use of a global network distance measure, random walk analysis, for definition of similarities in protein-protein interaction

Apolipoprotein A1 in Cerebrospinal Fluid and Plasma and Progression to Alzheimer's Disease in Non-Demented Elderly

Rosalinde E R Slot [1], Argonde C Van Harten [1], Maartje I Kester [1], Wesley Jongbloed [2], Femke H Bouwman [1], Charlotte E Teunissen [2], Philip Scheltens [1], Robert Veerhuis [2 3], Wiesje M van der Flier [1 4]

Affiliations + expand

PMID: 28035918 DOI: 10.3233/JAD-151068

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Functional characterization of the atopy-associ gene *PHF11*

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Background: Polymorphisms in the plant homeodomain finger protein 11 gene *(PHF11)* are associated with increased total serum IgE levels, asthma, and severe atopic dermatitis (AD) in children. Although *PHF11* includes a plant homeodomain, a motif often found in transcriptional regulators, the function of *PHF11* has not been investigated.

Objective: We sought to test (1) whether *PHF11* regulates the transcription of genes involved in allergic disorders and (2)

Key words: PHF11, atopic dermatiti small interfering RNA, nuclear factor

Childhood atopic dermatitis (AD) geneity in its presentation and duratio children with AD in Western countrie 40% of children show spontaneous re age of 3 years, for children with persis

Journal of Alzheimer's Disease 53 (2016) 1353–1363 1353
DOI 10.3233/JAD-160319
IOS Press

A Genetic Variant of the Sortilin 1 Gene is Associated with Reduced Risk of Alzheimer's Disease

Carl-Henrik Andersson[a], Oskar Hansson[b,c], Lennart Minthon[b,c], Niels Andr Henrik Zetterberg[a,c], Ingmar Skoog[a], Anders Wallin[a], Staffan Nilsson[f] and

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Handling Associate Editor: Daniela Galimberti

An E2-guided E3 Screen Identifies the RNF17-UBE2U Pair Regulator of the Radiosensitivity, Immunodeficiency, Dysmorphic Features, and Learning Difficulties (RIDDLE) Syndrome Protein RNF168*

Received for publication, September 15, 2016, and in revised form, November 14, 2016 Published, JBC Papers in Press, November 30, 2016, DOI 10.1074/jbc.M1

Yingying Guo[‡1], Liwei An[‡1], Hoi-Man Ng[‡], Shirley M. H. Sy[‡2], and Michael S. Y. Huen[‡§3]

From the [‡]School of Biomedical Sciences, Li Ka Shing Faculty of Medicine and the [§]State Key Laboratory of Brain and Cogr Sciences, The University of Hong Kong, Hong Kong, China

Edited by George N. DeMartino

The Landscape of *SNCA* Transcripts Across Synucleinopathies: New Insights From Long Reads Sequencing Analysis

*Elizabeth Tseng[1], William J. Rowell[1], Omolara-Chinue Glenn[2,3], Ting Hon[1], Julio Barrera Steve Kujawa[1] and Ornit Chiba-Falek[2,3]**

Thank You