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■ RESEARCH ARTICLE

Toward Defining Molecular Signature of Alzheimer's Disease Using a Network-Based Systems Biology Approach

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ABSTRACT: Alzheimer's Disease (AD) is a complex multifactorial disease that does not yet have a cure. Although many statistical and computational methods have been effective in its early prediction and prognosis, our understanding of the biological mechanisms of the disease is far from satisfactory. Due to the complex nature of the disease and the lack of diversity in existing data, a multimodal systems biology approach is best suited to elucidate the etiology of the disease while abstracting variant differences among populations of different ethnicities. Although Alzheimer's is a complex disease with many contributing factors, genetic risks have been shown to have a significant impact on its manifestation. Using a systems biology approach, this paper uses graph theory, network analysis, omics data integration, and visualization to develop a functionally coherent AD module. This genetic tool, combined with other existing biomarkers and predictive algorithms, can enhance the accuracy of AD early prediction and prognosis.

KEYWORDS: Computational Biology and Bioinformatics; Computational Neuroscience; Alzheimer's.

■ Introduction

Alzheimer's Disease (AD) is the sixth cause of death in the United States and the only one among the top ten that cannot be cured or prevented at this time. The number of people affected by AD is projected to reach 8.4 million by 2030, and the projected cost associated with dementia is $1.1 trillion by 2050.[1]

As opposed to normal aging, Alzheimer's disease (AD) is a neurodegenerative disease that progresses silently many years before symptom onset. The silent preclinical stage of the disease is characterized by the accumulation of beta-amyloid beta (Aβ) plaques outside the cell and intracellular neurofibrillary tau tangles in the brain.

Alzheimer's progresses in many stages, including Early Mild Cognitive Impairment, Late Mild Cognitive Impairment, and eventually dementia. Predicting if and when a patient will transition from one stage to the next is important for precision medicine, better patient outcomes, and is more efficient for clinical trial screening and drug development.

Many statistical and computational methods have been developed for predicting the development of Alzheimer's disease from the preclinical stage and predicting the speed of progression from MCI to dementia. Deep learning methods have been at the forefront of such efforts, and many Neural Network (NN) based models, like Convolution Neural Networks (CNN) and Generative Adversarial Networks (GAN), have been developed with varying prediction accuracies.[2-4] Other methods were based on calculating Polygenic Risk Score (PRS) from the subject's genotype data for early prediction of their susceptibility to developing AD.[5]

PRS are statistical methods that have proven useful for AD prediction and prognosis, especially when combined with other biomarkers. However, they have limitations. The score calculation is dependent on significant single nucleotide polymorphisms (SNPs) that are defined in the study and does not include rare variants, which limits its ability to capture the whole genomic picture of the disease, especially if the condition is polygenic, like AD. In AD, like all complex diseases, synergistic and non-linear interactions must be captured while estimating the genetic risk factor, which cannot be accounted for using PRS since it assumes linear, additive relationships. Due to that, PRS is more sensitive to the lack of diversity in the data, where most subjects are of European ethnicity. At the same time, AD is more prevalent in Asian, Hispanic, and African ethnicities.[5] As a result, this paper seeks to use more ethnically diverse datasets to derive a common signature and to establish a method that can be used as diverse datasets continue to be produced.

AD has a complex nature; multiple modifiable and non-modifiable genetic and non-genetic factors and multiple pathways synergistically contribute to the disease. This calls for using multimodalities for AD detection and prognosis, which are superior to single-modality methods.[6-8] Hence, integrating multiple complementary markers of preclinical stage AD and its progression with a robust predictive model optimizes early detection and management and supports effective drug development. This paper seeks to contribute to one of these modalities by establishing a method for uncovering diversity-insensitive molecular signatures for AD.

Focusing on the genetic factors alone, every level of genetic data, going from the finest granularity to the coarsest, gives a different perspective on the underpinnings of the disease. So, a multi-omics integration of genetic data (e.g., genomic, transcriptomic, proteomic, epi-genomic, etc.) and a holistic systems biology approach is warranted to get a comprehensive view of the underlying mechanisms of the disease. Integrating

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ing multi-level omics data is a promising way to shed light on biological pathways beyond the potential of a single layer of omics data. Although Alzheimer's is a complex disease that isn't solely dictated by genetic factors, the previous use of genetic methods to calculate risk indicates that genetics play a large role.[5]

Using a system biology approach, this paper uses graph theory, omics data integration, and visualization to develop a functionally coherent AD module. This novel genetic tool, combined with other biomarkers and predictive algorithms, can be useful in enhancing the accuracy of AD early prediction and prognosis.

Methods

Data:

The data used is the significant SNPs (at $p < 10^{-5}$) associated with AD, as published by the International Genomics of Alzheimer's Project (IGAP).[9] This is a large two-stage study based on genome-wide association studies (GWAS) on individuals of European ancestry. In stage 1, IGAP used genotyped and imputed data on 7,055,881 SNPs to meta-analyze four previously-published GWAS datasets consisting of 17,008 Alzheimer's disease cases and 37,154 controls (The European Alzheimer's Disease Initiative – EADI the Alzheimer Disease Genetics Consortium – ADGC The Cohorts for Heart and Aging Research in Genomic Epidemiology consortium – CHARGE The Genetic and Environmental Risk in AD consortium – GERAD). In stage 2, 11,632 SNPs were genotyped and tested for association in an independent set of 8,572 Alzheimer's disease cases and 11,312 controls. Finally, a meta-analysis was performed, combining results from stages 1 & 2. The institutional review boards of all participating institutions approved the procedures for IGAP sub-studies. Written informed consent was obtained from all participants or surrogates.[6]

SNPs in Linkage Disequilibrium (LD):

Linkage disequilibrium is the phenomenon where certain combinations of genetic variants or alleles occur together more frequently than would be predicted from their individual frequencies in a population. It is important for genetic analyses because it helps identify genetic markers linked to diseases and traits, thereby facilitating the mapping of genes and understanding the genetic basis of complex diseases. To find SNPs in linkage disequilibrium (LD) with our AD-associated SNPs, we input the AD-associated SNPs into SNPsnap for LD search using HapMap3 release two datasets.[10,11] For this purpose, we use the European panel (CEU). r^2 is a key measure used to understand the genetic link (linkage disequilibrium) between two biallelic markers. The metric calculates the squared correlation between the presence or absence of a specific allele at two different genetic locations.[12] We consider two SNPs to be in linkage disequilibrium (LD) if their r^2 value is at least 0.5 and they are located within 500 kilobases (Kbs) of each other on the genome as they are standard figures. The r^2 threshold ensures a strong correlation, indicating that these SNPs are inherited together more often than expected by chance. The distance criterion reflects that closely located genes on a chromosome are less likely to be separated during recombination, making this combination of criteria both statistically significant and biologically relevant for identifying meaningful genetic associations. Different criteria would lead to different associated genetic markers.

Mapping SNPs to Genes:

SNPs themselves don't give much useful information and aren't relevant to a molecular signature, so they must be mapped to genes. To map SNPs to genes, all RefSeq transcripts for hg38 assembly are downloaded from the UCSC Table browser and extended 100kb upstream and 10kb downstream.[13] Refseq IDs are translated to HGNC symbols. SNPs are mapped to their positions on hg38 assembly through biomaRt and are intersected with gene coordinates.[12] Such intersections result in an AD-associated gene list.

Mapping Genes to Biological Functions:

Then, these genes must be mapped to their biological functions for understandability. To identify biological processes enriched in AD-associated SNPs, we use enrichment analysis of the AD-associated gene set using the WebGestalt R package.[14,15] Biological Process terms are used, and the False Discovery Rate (FDR) threshold is set to 5%.

Network Analysis:

We feed the loci that are found to be associated with the disease to the Prix-Fixe network analysis tool.[16] The Prix-Fixe tool uses a network-based disease-associated subnetwork identification algorithm that uses genome-scale shared function networks to identify the most functionally coherent subnetwork of genes spanning the disease-associated loci. Using shared function networks as a reference, the algorithm evaluates gene combinations, constraining the choice of one gene from each disease-associated locus for their shared function. It is similar to choosing compatible food items from a prix fixe restaurant menu, with one dish from each course. The algorithm outputs a list of genes with their disease association scores, such that the top-scored genes constitute the most coherent disease-associated subnetwork.

The prioritized gene list is then fed into NetworkAnalyst for AD-associated Protein-Protein Interaction network development and visualization **(Figure 1)** and the corresponding Gene Regulatory Network and miRNA networks **(Figure 2)**.[17] In AD, investigating protein-protein interactions (PPIs) is pivotal for elucidating the underlying molecular mechanisms driving the disease's pathogenesis. These interactions, encompassing the physical binding between proteins, are instrumental in mediating AD progression. High-frequency PPIs within the AD context signify proteins with central roles in cellular pathways, potentially acting as prime therapeutic targets or biomarkers for early detection. Consequently, the study of PPIs, particularly those characterized by high interaction strength or frequency, is essential for identifying crucial nodes within the complex network of cellular interactions that could be leveraged for therapeutic advantage in Alzheimer's Disease.

Results

Name	Degree
PICALM	205
INPP5D	198
CLU	133
CD2AP	123
BIN1	113
MS4A6A	100
RIN3	95
FERMT2	87
MS4A4A	72
SPPL2A	58

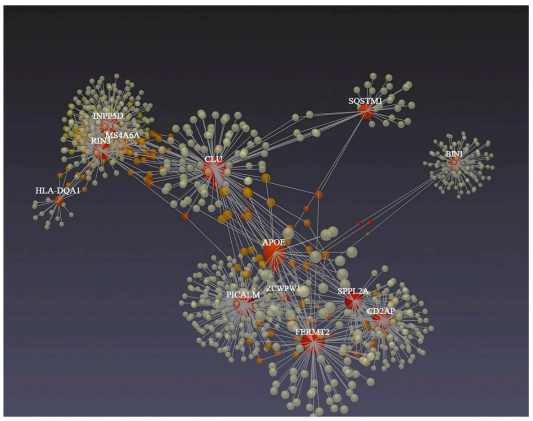

Figure 1: AD-associated Protein Interaction Network. The network represents the interaction between proteins encoded by genes harboring significant AD-associated loci. Hub proteins are shown in red. The associated table outlines the proteins with the highest degrees of connectivity.

Name	Degree	Betweenness
ZCWP1	131	17673.81
ABCA7	113	12801.92
SQSTM1	75	6018.805
INPP5D	41	4170.409
PTK2B	32	2252.065
APOE	29	1467.853
CASS4	28	1766.804
CD2AP	28	1503.882

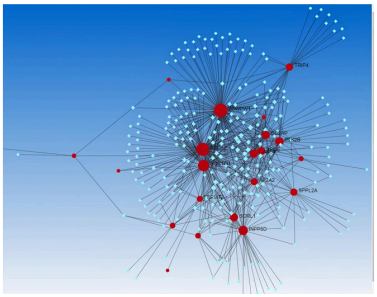

Figure 2: Gene Regulatory Network. The GRN shows the regulatory relationships between transcription factors (TFs) in cyan color and their binding sites of mRNA in red.

Name	Degree
CELF1	208
SPPL2A	114
SLC24A4	109
CD2AP	75
CLU	69
SCIMP	50
SQSTM1	27

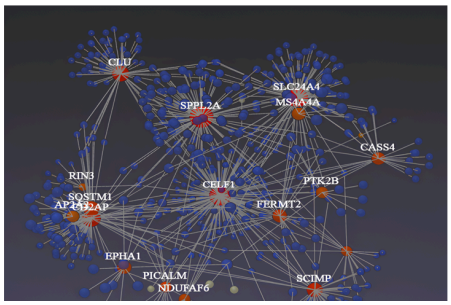

Figure 3: miRNA network. The miRNA network shows the many-to-many relationships between microRNA (miRNA) in blue color, TFs in yellow, and target genes in red.

Network Analysis:

Protein Interaction Network:

The hub protein-coding genes that play an important role in the molecular etiology underlying AD are shown in Figure 1 and are colored in red. From a graph theory perspective, hub genes have a higher than average degree, meaning a high number of edges connecting it to other genes, which implies importance. Figures 2 and 3 show the most important protein-coding genes that harbor significant AD loci, with their connections, representing interactions, to other genes presumably related based on the "guilt-by-association" principle.

For example, the highest degree node in the network represents the gene *PICALM*, with 205 interactions with other genes. *PICALM* contributes to amyloid plaque load in the brain via its effect on α-Beta metabolism.[18] *INPP5D* is an AD risk factor restricting microglial responses in amyloid pathology.[19] Another example is the *CLU* gene, which, when changed or mutated, is associated with an increased risk of AD.[20]

Gene Regulatory Network:

The Gene Regulatory Network (GRN) associated with AD is shown in **Figure 2**. The GRN shows the regulatory relationships between transcription factors (TFs) and their binding sites of mRNA. The TFs govern certain expression levels of mRNA and their resulting proteins. The GRN shows the most significant network of genes associated with AD and their TFs. For example, the hub genes *ZCWPW1* and *ABCA7* have the highest degrees and betweenness centrality, which means they interact with the highest number of TFs, indicating the central roles both genes play in association with AD, which is in concordance with previous findings.[21,22]

miRNA Network:

The miRNA network for the brain tissue associated with AD is shown in **Figure 3**. The network shows the many-to-many relationships between microRNA (miRNA) and target genes to illuminate the miRNA regulatory mechanisms underlying AD. *CELF1* has the highest degree in this network, which shows that AD polymorphisms highly regulate its expression.[23] Additionally, *SPPL2A*, the second highest degree in our miRNA network, is involved in the non-canonical shedding of TNF-α.[24]

Pathway Enrichment Analysis:

The pathway enrichment analysis (PEA) results are shown in Table 1. The top 15 biological functions overrepresented in the set of genes that harbor AD-associated loci are ranked by significance in descending order. The significance threshold is the probability of the null hypothesis being true (p-value) < 0.05 and False Discovery Rate (FDR) < 0.05.

For example, the results show the programmed cell death-receptor 1 (PD-1) signaling pathway as the most significant in the AD-associated set of genes tested in this study. PD-1 blockade reduces glycogen synthase kinase 3β activity (*GSK3β*) and tau hyper-phosphorylation in AD mouse models, and the immune regulation of the PD1/PDL1 axis is closely involved in AD.[25] The top most significant pathways (PD-1 signaling, interferon-gamma signaling phosphorylation of CD3 and TCR ZETA chains, translocation of ZAP-70 to Immunological synapse) belong to the interferon-gamma signaling, which regulates several biological processes that are primarily known to regulate inflammation and cell-mediated immune responses, including regulation of innate and acquired immune response, apoptosis and cell cycle and are well associated to AD.[27]

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Table 1: Pathway Analysis Results. Pathways that involve biological functions overrepresented in genes that harbor loci significantly associated with AD are ranked in descending order by significance.

Pathway name	P-Value
PD-1 signaling	0.004
Translocation of ZAP-70 to Immunological synapse	0.005
RUNX1 and FOXP3 control the development of regulatory T lymphocytes (Tregs)	0.011
Phosphorylation of CD3 and TCR zeta chains	0.012
MECP2 regulates transcription factors	0.012
MHC class II antigen presentation	0.017
Terminal pathway of complement	0.024
Clathrin-mediated endocytosis	0.025
EPH-ephrin-mediated repulsion of cells	0.027
Downstream TCR signaling	0.028
Plasma lipoprotein clearance	0.032
WNT5A-dependent internalization of FZD2, FZD5 and ROR2	0.035
Defective SLC24A4 causes hypo-mineralized amelogenesis imperfecta (AI)	0.040
TRKA activation by NGF	0.042
Nef Mediated CD8 Down-regulation	0.050

Discussion

To understand the mechanisms underlying a complex disease like AD, a systems biology approach becomes essential to integrate all important players. It also mitigates, to some extent, the lack of ethnic diversity in the existing genomics data of AD, making the study results less sensitive to variations in genomic variants between different populations. The network-based approach for analyzing and visualizing the etiology of AD is very suitable as it integrates various types of information and makes it intuitive and easily interpretable. This paper uses systems biology, network analysis, and graph theoretical measures to elucidate the etiology of AD and develop a functional signature to be used as a genetic tool together with other biomarkers to enhance the accuracy of AD prediction and prognosis and improve clinical trial recruitment to accelerate drug discovery. The results illustrate that the PD-1 signaling pathway and Translocation of ZAP-70 to immunological synapse are the most significant across ethnic cohorts. In other words, these pathways are highly associated with Alzheimer's regardless of the patient's ethnicity. Knowing such pathways is important to improve genetic risk analysis so that they're inclusive and accurate for various populations. The paper's primary focus, however, is establishing systems biology as a way to reveal complex patterns at different levels of genetic data. While the paper focuses on the method, applying the same method on more extensive and more diverse datasets, as they become available, will result in a sharper picture of the disease and an updated signature of AD. By using datasets with more ethnic diversity than predecessors, this paper takes the next step towards a diversity-insensitive signature of Alzheimer's.

However, the established method isn't without limitations. Firstly, the effectiveness of systems biology and network analyses heavily depends on the quality and comprehensiveness of the existing datasets, which are often limited by current technological and methodological constraints. Additionally, while this method aims to overcome the issue of ethnic diversity in genetic studies, it still requires significant enhancement in the representation of diverse populations in datasets to truly achieve inclusive and universally applicable genetic insights. Furthermore, the complexity of integrating various types of data poses a challenge in accurately interpreting the results, which necessitates advanced computational tools and expertise. Finally, the method was only tested on AD and not other neurodegenerative diseases.

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