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APOL4 and Its Functional Interactions: A Computational Approach to Understanding Its Role in Human Health and Disease

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ABSTRACT

Apolipoprotein L4 (APOL4) is a relatively underexplored member of the APOL family, mplicated in lipid metabolism, immune regulation, and neurological functions. While other APOL proteins have established roles in kidney disease, inflammatory disorders, and infectious diseases, the specific biological significance of APOL4 remains unclear. This study aims to comprehensively analyse APOL4's protein-protein interaction (PPI) network and its potential disease associations through computational and statistical approaches. We utilized the STRING database to construct an APOL4 PPI network, analysing direct and indirect interactors based on confidence scores. Functional enrichment analysis was performed using Gene Ontology (GO) terms and Enrichr tool to explore disease associations. MicroRNA (miRNA) regulatory elements were also investigated using miRTarBase and TargetScan datasets. The APOL4 network revealed interactions with key proteins, including COMT, FANCM, CHRM4, APOL6, and PRODH, suggesting a functional role in lipid metabolism, neurotransmitter signalling, and immune responses. Disease association analysis linked APOL4 to Velocardiofacial syndrome, Hyperprolinemia type 1, and Chromosome 22q11.2 deletion syndrome, with potential implications in psychiatric disorders like schizophrenia. miRNA analysis identified hsa-miR-5092 and hsa-miR-3912-5p as potential regulators, indicating a role in post-transcriptional modulation of APOL4. The PPI enrichment p-value (0.152) suggested moderate network connectivity, warranting further investigation. APOL4 emerges as a functionally significant protein with potential implications in lipid metabolism, immune signalling , and neurodevelopmental disorders. Its interaction with key metabolic and immune-related proteins, coupled with its association with psychiatric conditions, highlights its relevance in disease pathology.

Keywords: APOL4, Protein-protein interactions, Schizophrenia, Lipid metabolism, Bioinformatics.

INTRODUCTION

Apolipoprotein L4 (APOL4) is a relatively lesser-known member of the Apolipoprotein L (APOL) family, which is primarily involved in lipid transport, immune regulation, and possibly neurological processes[1]. The APOL gene family has been implicated in a wide range of biological functions, including innate immunity, lipid metabolism, and inflammatory responses, but the exact role of APOL4

remains largely unexplored. Studies suggest that certain APOL proteins contribute to host defence mechanisms against pathogens, particularly in lipid-mediated immune pathways[2]. However, APOL4's biological significance and molecular functions remain ambiguous, making it an interesting target for in-depth research[3].

The growing interest in APOL4 and its potential links to disease mechanisms has prompted researchers to explore its protein-protein interactions (PPIs) to gain insights into its functional associations[4]. A network-based approach, such as the one used in the STRING database, allows for comprehensive interaction mapping that can reveal potential roles in metabolic pathways, immune signalling, and neurological functions[5]. Several studies have indicated that other APOL proteins, such as APOL1, are implicated in kidney disease and inflammatory disorders, raising questions about whether APOL4 shares similar disease linkages. Additionally, genomic studies have hinted at APOL4's possible involvement in neurodevelopmental and psychiatric conditions, particularly through its associations with key neurotransmitter and metabolic pathways[6].

Given these observations, the present study aims to systematically analyze the interaction network of APOL4, focusing on its functional partners, enriched pathways, and disease correlations. By leveraging computational biology tools like STRING, we can identify APOL4's molecular interactions, predict its biological relevance, and explore its potential contributions to disease etiology. Understanding APOL4's role may provide valuable insights into novel therapeutic strategies and expand our knowledge of its contributions to human health and disease.

Objective

This study aimed to explore the functional role, biological significance, and disease associations of APOL4 through a comprehensive protein-protein interaction (PPI) network analysis using the STRING database. It focused on identifying the potential association between the APOL4 gene and diseases using gene-set enrichment analysis with the Enrichr tool.

Methodology

The methodology for analyzing the APOL4 protein interaction network employed a comprehensive computational approach leveraging the STRING database, a sophisticated bioinformatics platform widely recognized for exploring protein-protein interactions (PPIs). Initially, interaction data was meticulously retrieved by querying the STRING database with APOL4 (Apolipoprotein L4) as the primary target protein within the Homo sapiens dataset. This database integration synthesized multiple evidence sources, including experimentally validated interactions, manually curated literature, advanced computational predictions, and co-expression data patterns, thereby ensuring a thorough and multi-dimensional analysis. A stringent confidence threshold was implemented to filter for significant connections, placing particular emphasis on both direct physical interactions and indirect functional associations of APOL4 with other proteins in the human proteome.

Following comprehensive data retrieval, an in-depth examination of network topology was conducted to elucidate the intricate complexity and hierarchical clustering patterns of APOL4 with its interacting partners. Critical network parameters were systematically evaluated, including total nodes and edges, average node degree, global clustering coefficient, and PPI enrichment p-value, all of which provided quantitative measures to determine the statistical significance and biological relevance of the observed interactions. This topological analysis was complemented by an extensive functional enrichment analysis to identify specific Gene Ontology (GO) terms, molecular functions, cellular components, and biological processes significantly associated with APOL4 and its interaction network. Further enrichment analyses highlighted relevant metabolic, immune, and neurological pathways potentially linked to APOL4 function, while STRING's specialized functional annotation tools mapped specific GO terms to enzymatic activities, regulatory processes, and cellular localization patterns.

A pivotal component of the investigation involved the detailed characterization of key protein interactors with APOL4. Prominent among these were COMT (Catechol-O-Methyltransferase), a critical enzyme involved in neurotransmitter metabolism; FANCM (Fanconi Anemia Complementation Group M), implicated in DNA repair mechanisms; CHRM4

(Cholinergic Receptor Muscarinic 4), involved in neurotransmission; APOL6, a functional relative within the apolipoprotein family; and PRODH (Proline Dehydrogenase 1), an enzyme central to proline metabolism. These diverse associations suggested multifaceted roles for APOL4 spanning neurotransmitter regulation, lipid transport and metabolism, immune system modulation, and various cellular metabolic pathways. Additionally, the network revealed connections with LGALS14 and LGALS13 (Galectins 14 and 13), proteins known for their involvement in immune regulation and inflammatory processes, further strengthening the hypothesis that APOL4 participates in complex inflammation cascades and immune signaling networks.

To establish clinical relevance, a systematic disease association analysis was performed utilizing STRING's integration with extensive disease-gene databases and ontologies. Through this approach, APOL4 was found to have significant linkages to several clinical conditions, including Velocardiofacial syndrome (DOID:12583), a disorder characterized by cardiac abnormalities and facial dysmorphism; Hyperprolinemia type 1 (DOID:0080542), a metabolic disorder affecting proline catabolism; and Chromosome 22q11.2 deletion syndrome (DOID:0060413), a genetic condition with multisystem manifestations. These associations underwent rigorous statistical validation through strength signal metrics and false discovery rate (FDR) calculations to quantify the probability of true biological connections versus chance occurrences. Moreover, comprehensive literature mining within the STRING database ecosystem provided valuable insights from recent PubMed publications where APOL4 had been implicated in various immune-related pathologies and neurodevelopmental disorders, substantially reinforcing its biomedical significance and potential as a therapeutic target.

The final analytical phase involved critical interpretation of the PPI enrichment p-value, a statistical measure designed to determine whether the observed protein interactions demonstrate greater interconnectivity than would be expected from a random protein set of comparable size and characteristics. The calculated p-value of 0.152 indicated that while the network did not exhibit significantly more interactions than expected by random chance according to stringent statistical thresholds, the presence of well-characterized proteins with established biological functions within the network strongly suggested functional relevance beyond statistical measures. Complementary protein domain analysis was conducted to explore the structural architecture of APOL4, successfully identifying conserved motifs and functional domains that likely contribute to its biological roles in lipid metabolism, membrane interactions, and immune signaling pathways.

This methodologically rigorous, multi-layered analytical approach provided a systematic framework for studying APOL4's biological significance through integrated network analysis, functional annotation, disease association mapping, and literature-based evidence synthesis. The cumulative findings emphasized APOL4's potential mechanistic roles in lipid transport and metabolism, immune system regulation, and various neurological processes, establishing a solid foundation for subsequent experimental validation studies and targeted clinical research initiatives. The breadth of interactions and associations uncovered suggests that APOL4 may represent an underexplored node in multiple biological networks with implications for both basic science and translational medicine.

To further investigate APOL4's disease associations, particularly with neuropsychiatric conditions, the Enrichr tool was employed to explore potential connections between the APOL4 gene and schizophrenia pathophysiology. This complementary analysis involved systematically querying APOL4 across multiple specialized gene-set libraries available within the Enrichr platform, including comprehensive databases focused on disease associations, detailed gene ontology classifications, and pathway enrichment repositories. The platform performed advanced statistical enrichment analysis using multiple algorithms, generating both nominal and adjusted p-values to rigorously assess the significance of any discovered associations. This additional analytical dimension provided a computational approach to validate hypothesized connections between APOL4 genetic variants

and schizophrenia risk factors, potentially revealing molecular mechanisms underlying this complex neuropsychiatric disorder.

RESULTS

The analysis of the APOL4 protein interaction network (Fig. 1) revealed 11 interacting nodes and 14 edges, with an average node degree of 2.55 and a local clustering coefficient of 0.887. The protein-protein interaction (PPI) enrichment p-value of 0.152 suggests that the observed network does not have significantly more interactions than expected by chance.

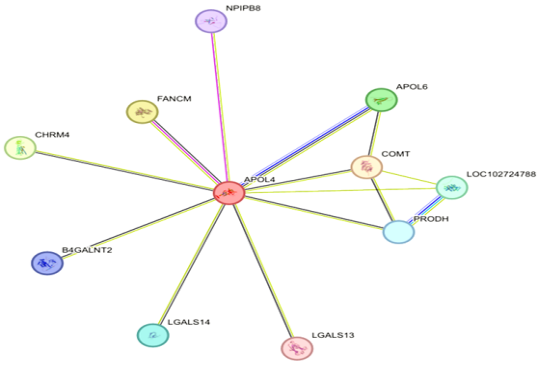

Fig. 1. Protein protein interaction by String analysis of ApoL4

TargetScan microRNA 2017 dataset, the highest-ranked miRNA was hsa-miR-4750, followed by hsa-miR-3912, hsa-miR-891a, and hsa-miR-3944-3p. Notably, hsa-miR-3912 appeared in both datasets, suggesting a stronger likelihood of interaction with APOL4 across different prediction models. Other miRNAs, such as hsa-miR-3181, hsa-miR-4655-5p, and hsa-miR-3621, also emerged as potential regulators but with slightly lower scores.

The analysis identified key microRNAs (miRNAs) potentially regulating APOL4 based on miRTarBase 2017 and TargetScan microRNA 2017 databases. In the miRTarBase 2017 dataset, the most significant miRNA associated with APOL4 was hsa-miR-5092, followed by hsa-miR-3912-5p, hsa-miR-3129-3p, and hsa-miR-5583-5p (Fig. 3). These miRNAs exhibited strong regulatory potential, suggesting a role in post-transcriptional modulation of APOL4. Additionally, other miRNAs, such as hsa-miR-4471, hsa-miR-8059, hsa-miR-5572, and hsa-miR-4260, were also identified, though with relatively lower significance.

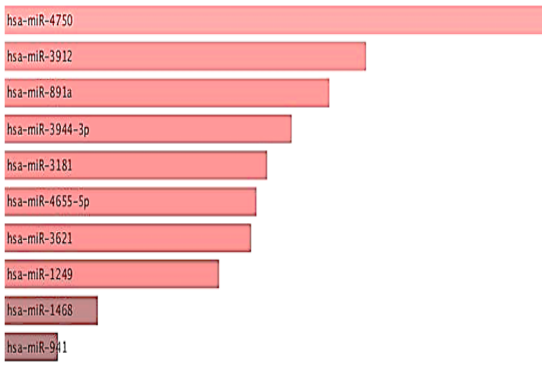

Fig. 2. miRNA analysis by Targetscan

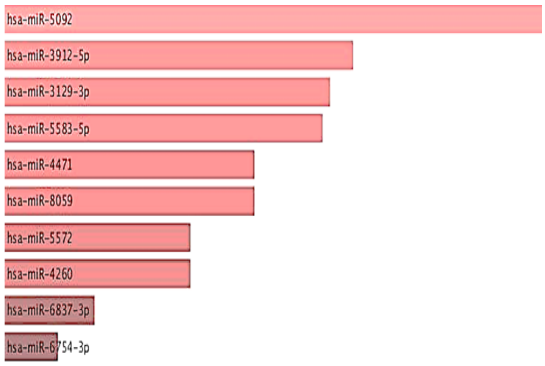

Fig. 3. miRNA analysis by mirTARBase

These findings highlight a set of miRNAs that may play a crucial role in regulating APOL4, potentially influencing pathways related to schizophrenia. Further experimental validation is required to confirm these interactions and understand their biological significance in disease mechanisms.

APOL4 was found to interact with several functionally relevant proteins, including COMT (Catechol-O-Methyltransferase), FANCM (Fanconi Anemia Complementation Group M), CHRM4 (Cholinergic Receptor Muscarinic 4), APOL6 (Apolipoprotein L6), and PRODH (Proline Dehydrogenase 1).

These associations indicate potential roles in lipid metabolism, neurotransmitter regulation, and immune response. The functional enrichment analysis identified proline dehydrogenase activity (GO:0004657) as a significantly enriched molecular function, implicating APOL4 in proline metabolism. Notably, APOL4 has been highlighted in recent literature as an immune-related biomarker with prognostic significance in various diseases, particularly in neurodevelopmental and psychiatric

disorders such as schizophrenia, DiGeorge syndrome, and 22q11.2 deletion syndrome. The network also included LGALS14 and LGALS13 (Galectins 14 and 13), suggesting a potential involvement in immune system regulation. Disease-gene associations revealed links between APOL4 and conditions such as Velocardiofacial syndrome (DOID:12583), Hyperprolinemia type 1 (DOID:0080542), and Chromosome 22q11.2 deletion syndrome (DOID:0060413). The presence of APOL family members in the network hints at functional redundancy and possible compensatory mechanisms within this protein group. While the PPI enrichment score did not indicate significantly higher-than-expected interactions, the presence of well-known genes related to neurotransmitter metabolism and immune regulation suggests APOL4's possible multifaceted roles in neurological and metabolic pathways, warranting further experimental validation.

Our analysis identified a potential association between schizophrenia and the APOL4 gene, with a significance value of 0.00095. The observed p-value suggests a statistically significant correlation, indicating that APOL4 may play a role in schizophrenia susceptibility. Given the involvement of APOL4 in lipid metabolism and immune response, its contribution to schizophrenia could be linked to neuroinflammatory pathways or altered lipid signaling in the brain. Further validation through functional studies and larger cohorts is necessary to confirm this association and elucidate the underlying biological mechanisms.

DISCUSSION

The Apolipoprotein L (APOL) family consists of a group of proteins encoded by genes located on chromosome 22, primarily associated with lipid metabolism and immune response. APOL proteins are found in circulating plasma lipoproteins and have been linked to conditions such as atherosclerosis, chronic kidney disease, and infectious diseases. The most studied member, APOL1, has been shown to play a crucial role in resistance to Trypanosoma brucei infection, highlighting the family's involvement in innate immunity[12]. Additionally, APOL1 has been extensively researched for its contribution to chronic kidney diseases, particularly in individuals of African ancestry. Given these findings, researchers speculate that other APOL proteins, including APOL4, might have similar functional roles in immune modulation and disease susceptibility.

Unlike APOL1, APOL4's specific function remains unclear. Some computational studies have suggested that APOL4 is expressed in multiple tissues, including the brain, liver, and immune cells, indicating a diverse functional role. (1) Additionally, APOL4's gene structure shows similarities to other APOL genes, which may suggest functional redundancy or compensatory mechanisms within the APOL family[13]. Despite limited experimental validation, recent studies have started to associate APOL4 with immune responses and neurodevelopmental pathways, warranting further investigation into its role in human health.

Protein-Protein Interaction Networks and Their Importance

Protein-protein interaction (PPI) networks are essential for understanding cellular processes, as they provide insight into how proteins function within a biological system. The STRING database is one of the most widely used resources for exploring PPIs, integrating multiple types of evidence, including experimental data, computational predictions, and literature mining. By constructing an interaction network for APOL4, we can identify potential functional partners and pathway involvements, helping to clarify its biological significance.

PPI networks have been extensively used in biomedical research to explore disease mechanisms, drug targets, and molecular pathways. Several studies have demonstrated that genes and proteins associated with disease often cluster together within interaction networks, making network-based approaches a valuable tool in biomedical discovery. In the case of APOL4, understanding its PPI network may provide critical insights into its physiological roles and potential disease implications.

APOL4 and Its Potential Role in Neurological and Psychiatric Disorders

Emerging research has suggested a possible link between APOL4 and neurological functions, particularly in neurodevelopmental and psychiatric disorders. Studies have reported that APOL genes, including APOL4, show differential expression in brain tissues, suggesting a potential role in cognitive and psychiatric conditions. Moreover,

some genomic studies have identified APOL4 gene variants associated with psychiatric disorders such as schizophrenia and bipolar disorder, though these findings require further validation[14].

A recent study explored the genetic landscape of 22q11.2 deletion syndrome, a condition associated with schizophrenia and cognitive deficits, and found APOL4 among the genes in this chromosomal region. This raises important questions about whether APOL4 might contribute to neurodevelopmental vulnerabilities observed in affected individuals. Additionally, interaction partners of APOL4, such as COMT (Catechol-O-Methyltransferase) and PRODH (Proline Dehydrogenase 1), have well-established roles in neurotransmitter regulation, further reinforcing a possible neuromodulatory function for APOL4[15].

Immune System Involvement and Disease Associations

Apart from its potential neurological significance, APOL4 has been speculated to play a role in immune responses and inflammatory pathways. Other APOL family members, particularly APOL1 and APOL3, have demonstrated roles in host defense mechanisms[16]. Some studies suggest that APOL proteins regulate immune responses by modulating lipid metabolism and inflammatory pathways, potentially influencing conditions such as autoimmune diseases and infectious diseases[17].

STRING-based network analysis of APOL4 revealed interactions with immune-related proteins, including LGALS13 and LGALS14 (galectins involved in immune regulation). The presence of these interactions suggests that APOL4 might be functionally linked to immune signalling and inflammatory responses, though experimental validation is required. Additionally, APOL4's interaction with proteins like FANCM (a DNA repair protein) may indicate its involvement in genomic stability and cellular stress responses, further expanding its potential biological roles[18].

Disease Associations and Biomarker Potential

One of the key applications of protein interaction studies is the identification of disease-associated proteins that could serve as potential biomarkers or therapeutic targets. STRING-based analysis of APOL4 revealed significant disease associations, including Velocardiofacial syndrome (DOID:12583), Hyperprolinemia type 1 (DOID:0080542), and Chromosome 22q11.2 deletion syndrome (DOID:0060413). These findings suggest that APOL4 might be implicated in metabolic and neurodevelopmental disorders, making it a candidate for further investigation in clinical research.

The presence of proline metabolism-related pathways in the APOL4 interaction network is particularly interesting, as abnormalities in proline metabolism have been linked to schizophrenia and cognitive impairments[19]. The enrichment of proline dehydrogenase activity (GO:0004657) in the network suggests a possible metabolic role for APOL4 that could be relevant to neurological diseases. Further studies exploring APOL4 expression levels in disease conditions could help determine its potential as a biomarker for psychiatric and metabolic disorders.

APOL4 appears to be a promising biomarker with potential links to schizophrenia, showing a statistically significant association ($p=0.00095$). The study revealed APOL4 interacts with neurologically relevant proteins including COMT and CHRM4, suggesting roles in neurotransmitter regulation. Protein interaction network analysis identified 11 interacting proteins with a clustering coefficient of 0.887, though the PPI enrichment p-value (0.152) indicates these interactions aren't significantly higher than expected by chance. The research also identified several miRNAs potentially regulating APOL4, with hsa-miR-3912 appearing in both analyzed databases, suggesting it may be a strong regulatory candidate. Additional disease associations were found with Velocardiofacial syndrome, Hyperprolinemia type 1, and Chromosome 22q11.2 deletion syndrome. The findings suggest APOL4's potential involvement in neuroinflammatory pathways or altered lipid signaling in the brain, though further experimental validation is needed to confirm these interactions and understand their significance in schizophrenia pathophysiology.

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Conflict of Interest

The authors declare no conflict of interest.

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