Original article

Elucidation of hub genes and pathway associated with gut microbiome dysbiosis-linked irritable bowel disease and Alzheimer's disease via data analytic approaches

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Abstract

Background: Recent studies have highlighted the relationship between gut microbiome and Alzheimer's disease (AD), revealing how gut microbial balance impacts conditions ranging from inflammatory bowel diseases to neurological disorders. The emerging field of the gut-brain axis suggests that the production of microbial metabolites influences AD progression. However, there is limited understanding of molecular mechanisms involved in neurological disease when gut microbiome dysbiosis occurs, especially in irritable bowel disease (IBD).
Objective: This study aimed to identify hub genes and pathways associated with gut microbiome dysbiosis in IBD and AD through data analytics approaches.
Methods: Public gene expression datasets on gut microbiome dysbiosis, and AD were obtained from the GEO and pre-processed for gene symbol annotation. Differentially expressed genes were identified with $P < 0.05$ and Log2FC ≥ 1. Functional genomics analysis using DAVID ($P < 0.05$ and FDR < 0.05) was performed. Validated protein-protein interactions for differentially expressed genes ($P < 0.05$) were integrated into a comprehensive network using GeneMANIA and STRING.
Results: In total, AD and inflammatory bowel disease samples shared 1,715 genes in common. The top 10 common hub genes involved in positive regulation of leukocyte activation (CLEC7A, VNN1, SASH3, IL33, CD6, NFKBIZ, AIF1, ZBTB1, SIRBP1, LILRB1) were selected from the protein-protein interactions based on their top scores.
Conclusion: This study discovered that AD and IBD share hub genes in their pathogenesis mainly through positive regulation of leukocyte activation in the gut-brain axis that involves immune cell trafficking associated with inflammatory activation in IBD and microglia activation in AD, leading to neuroinflammation and neurodegeneration. The finding provides an insight into anti-neuroinflammatory therapeutic development targeting genes and molecular pathways within GBA.

Keywords: Functional gastrointestinal disorders, gut-brain axis, gut dysregulation, inflammatory bowel disease.

The gut-brain axis (GBA), a complex network of bi-directional communication between the central and the enteric nervous system, has been implicated in the plethora of health issues.[1] One approach to define gut health is as a state of physical and mental well-being characterized by the absence of gastrointestinal (GI) complaints and absence of indications or risks of bowel disease.[2] A balanced gut-brain axis is essential for fostering a symbiotic relationship with the gut microbiota, thereby facilitating crucial biological functions such as nutrient absorption, vitamin synthesis, and defense against pathogens.[2] However, this balance can be disturbed by many factors, including chronic stress, poor diet, or antibiotic misuse, leading to a dysregulated state characterized by increased intestinal permeability and systemic inflammation.[3,4] This dysregulated state will lead to the development of functional gastrointestinal diseases (FGIDs).[3,4]

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FGIDs are a range of disorders, such as irritable bowel syndrome, functional dyspepsia, or functional constipation, characterized by chronic or recurrent GI symptoms, which are closely associated with GBA dysregulation.[5] Altered communications within this GBA can trigger a cascade of negative physiological responses such as abnormal gut motility, visceral hypersensitivity, and anomalous secretion patterns, which in turn exacerbates the FGID's symptoms.[6] Furthermore, several scientific studies suggest repercussions of this GBA dysregulation transcend the limitations of the gastrointestinal tract, having a substantial impact on brain health.[6, 7] For instance, the persistent inflammation, byproduct of gut dysregulation, has been implicated in promoting neuroinflammation and neurodegeneration, affecting the structural and functional integrity of the brain.[7] Current research suggests that the disrupted gut microbiota can influence brain health through the productions of metabolites and endotoxins which are potentially amyloidogenic, a distinctive feature of Alzheimer's disease (AD).[7-11] Thus, a direct link has been found between altered gut microbiota and the worsening of Alzheimer's symptoms, indicating a possible function for the gut-brain axis in the etiopathogenesis and progression of AD.[7-11] Though several correlations and mechanisms have been proposed, direct causation remains elusive, especially the molecular association in IBD and AD through bidirectional GBA. Hence, it is worth elucidating the gene signatures and molecular pathways associated with gut microbiome dysbiosis in IBD and AD through data analytics approaches, so that could provide a new insights gut-brain axis to bridge IBD and AD, as well as contribute to therapeutic development.

Materials and methods

This study was reviewed and approved by the Institutional Review Board of IMU University (4.11/JCM-265/2023) on 18th May 2023.

Data selection and identification

The publicly available gene expression datasets were obtained from Gene Expression Omnibus (GEO) using specific keywords such as "gut microbiome dysbiosis", "Alzheimer's disease", "gut dysregulation", "microbiome composition", "gut-brain axis", "gut-brain signaling", and "functional gastrointestinal disorders". These searches identified relevant datasets of which four datasets (GSE118553, GSE63063, GSE36701and GSE13367) were selected for further analysis, based on the diseased samples and normal samples in each dataset, respectively.[12-15]

Pre-processing of datasets

The selected datasets underwent internal and external validation to ensure data comparability across different platforms. The internal validation involved K-Fold cross-validation, bootstrapping, and cross-validation with feature selection that includes identifying the normal control and diseased samples in the datasets. Then, the genes were annotated to the datasets by consolidating gene symbols from different platforms used by the respective datasets. The platform and datasets were cross validated to ensure the accuracy of the gene annotation before further data processing. Normalization was performed between normal control and diseased samples to identify the differentially expressed genes within the respective datasets.

Feature selections

Differentially expressed genes (DEGs) were identified within each dataset using specific criteria ($P < 0.05$ and $\text{Log2FC} \geq 1$). This specific criterion threshold was selected to capture genes that may exhibit moderate but relevant changes in expression, aligning with the exploratory nature of the research and the desire to cast a broad network of potential differentially expressed genes. Functional genomics analysis was carried out on the selected DEGs using the Database for Annotation, Visualization, and Integrated Discovery (DAVID) through a linear regression approach, with statistical significance defined as $P < 0.05$, Benjamin-corrected value < 0.05 and false discovery rates (FDR) < 0.05.

Predictive model development

The DEGs identified in functional genomics analysis were further subjected to study the alterations in pathway activity and biological features through a predictive protein-protein interactions (PPIs) model with significance ($P < 0.05$) using GeneMANIA and STRING. In GeneMANIA, a pathway network was plotted between the DEGs of AD and IBD, whereas in STRING, a co-expression network was plotted with a confidence level of 0.7. This network aimed to unveil specific patterns or sets of genes that are indicative of or associated with biological conditions or processes associated with gut microbiome dysbiosis-linked IBD and AD, providing insights into potential pathogenic mechanisms.

Results

Identification of commonly shared DEGs between AD and IBD

Following preprocessing and datasets validation, sets of differentially expressed genes (DEGs) were produced. A total of 1399 DEGs were obtained from IBD samples, and 11970 DEGs were obtained from AD samples, while a total of 1,715 commonly shared DEGs were observed.

Functional genomics analysis

Functional genomics analysis was conducted employing DAVID to elucidate the functional attributes of the 1,715 identified DEGs **(Figure 1)**. In the realm of molecular function (MF), the most substantial category, characterized by 1,295 genes, centered around protein binding (GO:0005515). This cohort featured prominent genes like OAS2, XRN1, ALAS1, NT5C2, and AZI2. Within the cellular component (CC) domain, 683 genes were ascribed to the cytosol (GO:0005829) category. Notable representatives encompassed AKAP13, ARF4, APIP, BLNK, and AHI1. Furthermore, the biological processes (BP) category exhibited 183 genes primarily linked to signal transduction (GO:0007165). Among these genes were HTR3A, ATM, CCL23, DEK, and JAK2. The functional genomic analysis reveals that the 1,715 identified DEGs are associated with specific molecular functions, cellular components, and biological processes, which aid in potential roles and functions of these DEGs.

The co-expression network analysis of IBD and AD

The genes corresponding to the top 10 GO categories, including MF, BP, and CC, were subjected to further analysis using the STRING database. The genes were selected based on specific criteria of $P < 0.05$, Benjamin-corrected value < 0.05, and FDR < 0.05. The co-expression network analysis in STRING,

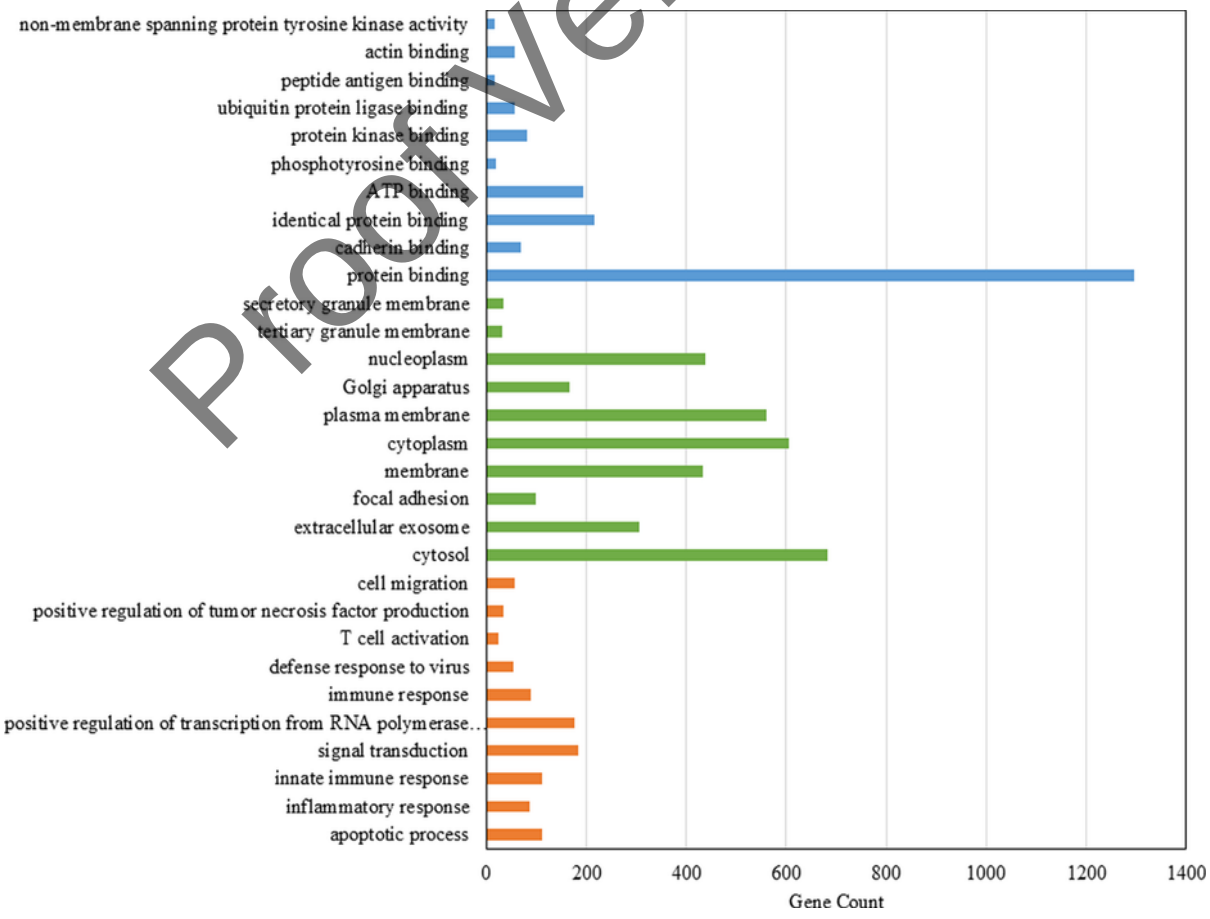

Figure 1. Functional genomics analysis of the differentially expressed genes among irritable bowel disease and Alzheimer's disease. Orange - biological processes; Green – cellular components; Blue - molecular function.

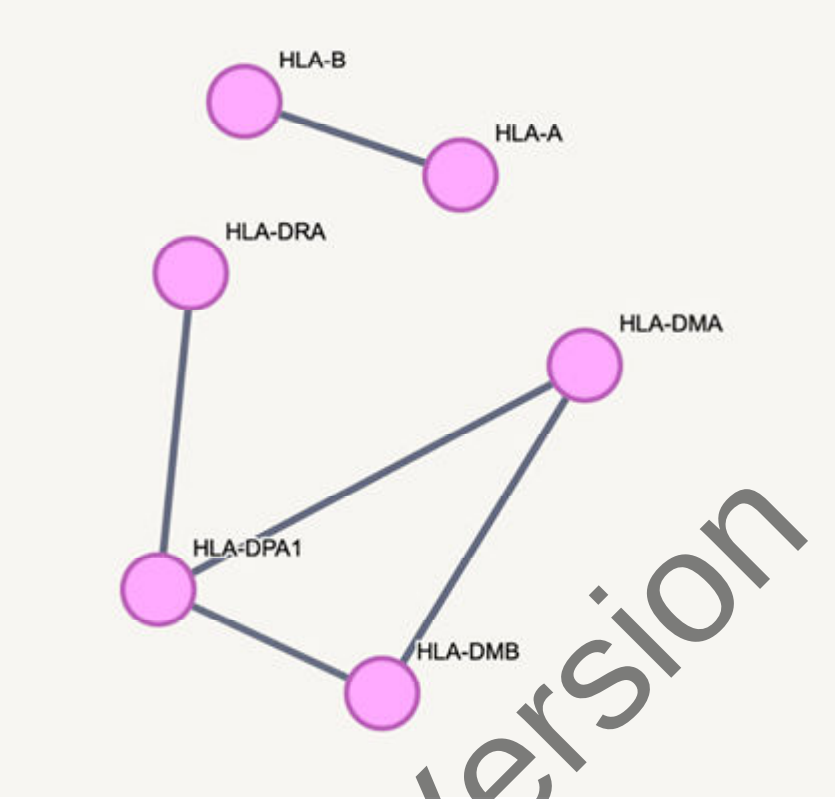

Figure 2. Co-expression network analysis of irritable bowel disease and Alzheimer's disease associated with MHC class II activity.

Table 1. Gene interactions associated with positive regulation of cell activation.

Gene 1	Gene 2	Weight
IL17A	IL17RA	1.000
TNFSF18	TNFRSF18	1.000
TNFRSF1A	DAP	1.000
TNFAIP3	TAX1BP1	1.000
CD244	CD48	1.000
TNFRSF8	TNFSF8	0.927
PATZ1	RNF4	0.904
CSTA	TFAP2C	0.888
TAP1	TAPBP	0.834
LCP2	WAS	0.831
AIP	AHR	0.746
CASP1	NLRP1	0.715

which reveals that commonly shared DEGs are mainly associated with MHC (major histocompatibility complex) class II activity through Human Leukocyte Antigen (HLA) family **(Figure 2).**

The predictive protein-protein interaction pathway analysis of IBD and AD

GeneMANIA was used to generate a protein-protein interaction (PPI) network using genes identified in functional genomics analysis. The network reveals a high degree of association between both diseases, especially in the regulation of the leukocyte activation signaling pathway. **Table 1** provides a list of gene networks associated with the positive regulation of cell activation, and the listed gene networks exhibit high confidence in the functional association between the genes.

Discussion

Identification of commonly shared DEGs between AD and IBD

This present study engages datasets involving AD (GSE118553 and GSE63063) and IBD-related (GSE36701 and GSE13367) to explore the potential hub genes and pathways involved in GBA. Extending the bimodal relationship, it can be postulated that AD and IBD may influence each other through shared biological processes and mechanisms contributed by GBA's bidirectional unique features. AD is primarily characterized by neurodegeneration and cognitive decline, but emerging research suggests that it may also have systemic effects on the immune system and GI tract.[16] This is especially significant given that many of the discovered DEGs may be involved in immune response regulation, inflammation, and gut-brain axis interactions. On the other hand, IBD is a chronic inflammatory condition of the GI tract, which includes ulcerative colitis (UC) and Crohn's disease (CD), but emerging research indicates that it can also impact the central nervous system (CNS) and cognitive function.[17, 18] This impact may be mediated by the release of pro-inflammatory cytokines, which could potentially affect brain function and contribute to the development or exacerbation of AD.[16]

Functional genomics analysis of the differentially expressed genes among IBD and AD

The functional genomics analysis of the DEGs among IBD and AD revealed extensive biological pathway dysregulation. The study highlights that these two distinct diseases share pathophysiological mechanisms rooted primarily in immune system dysregulation, especially inflammatory dysregulation, through BP, MF, and CC. In terms of biological processes, both AD and IBD exhibit altered cell migration, which is essential for immune cell trafficking and inflammation.[19,20] This altered migration pattern can lead to immune cell infiltration within the brain, resulting in a microenvironment characterized by chronic inflammation and neuroinflammation.[21] This, in turn, results in activation of microglia, culminating in the release of pro-inflammatory molecules that can inflict harm upon neurons.[22] Elevated tumor necrosis factor-alpha (TNF-α) production, a hallmark pro-inflammatory cytokine is present. Within the AD context, the heightened TNF-α level serves as a catalyst for chronic brain inflammation, which results in the initiation of cascade events leading to neurodegeneration.[23] The involvement of T-cell activation, a hallmark of maladaptive immunity in both AD and IBD.[18, 24] In AD, dysregulated T-cell activation can result in the release of cytotoxic molecules, exerting damage upon neurons.[18,24] While in IBD, this can result in increased intestinal permeability, allowing the translocation of luminal microbial products, such as bacterial endotoxins, into the bloodstream.[19] The enriched genes related to defense against viruses illustrated in this study suggest viral infections as potential triggers. The virus enters the brain causing neuronal death or activating antiviral responses that result in neuroinflammation and AD pathology.[25] Systemic infections like cytomegalovirus can directly damage the intestinal mucosa, resulting in compromise of the integrity of the gut barrier, allowing the translocation of microbial products and antigens into the lamina propria in IBD.[26] In addition, genes associated with RNA polymerase II-driven transcription and signal transduction emphasize extensive molecular regulation and signaling alterations in these diseases. Dysregulated transcriptional activation in IBD can lead to an influx of activated immune cells into the gut mucosa, where they contribute to tissue damage and inflammation.[27] While dysregulated signal transduction in AD can lead to the survival of dysfunctional neurons or the apoptosis of healthy neurons. [28] Discrepancies in apoptotic process can indicate propagation of inflammation or induce tissue damage. Evidence of caspase activation and altered expression of apoptotic proteins postulated apoptosis is a potential neuronal cell death mechanism.[28,29] Besides that, increased apoptosis is noted in the inflamed mucosa of IBD patients.[30]

This present study underscores the significant overlap in molecular functions such as "protein binding", "cadherin binding", "identical protein binding" and "actin binding", which indicates that there is a commonality in altered protein interactions between these diseases. These disruptions in cellular adhesion suggested a link to disrupted signaling pathways involving genes like TNF and nuclear factor-kappa B (NF-κB), leading to sustained inflammation in IBD[31], as well as aberrant protein interactions involving genes such as APP, PSEN1, and MAPT contribute to the formation of beta-amyloid (Aβ) plaques and tau tangles, a hallmark of AD_pathogenesis.[28, 29] Furthermore, molecular functions like "ATP binding", "phosphotyrosine binding", "protein kinase binding", and "non-membrane spanning protein tyrosine kinase activity" also suggest dysregulated signaling pathways.

For example, genes such as JAK2 and STAT3 can contribute to persistent immune activation and inflammation in IBD.[32] In AD, genes such as MAPK1, MAPK3, and GSK3B may be implicated in aberrant signaling, leading to neuronal cell death and cognitive decline.[33, 34] The presence of "ubiquitin protein ligase binding" suggests alterations in protein regulation, particularly ubiquitination. In both IBD and AD, genes like UBE2D1, UBE2D3, and UBE2N could be involved in the dysregulation of protein turnover.[35] This dysfunction may lead to the accumulation of aberrant proteins, such as pro-inflammatory mediators in IBD and Aβ and tau in AD.[36, 37] The presence of "peptide antigen binding" suggests the involvement of immune system in both conditions. Genes like HLA-DQB1 and HLA-DRB1 are involved in antigen presentation and immunity regulation, leading to inflammation in IBD.[38] Immune-related genes like CD33, and TREM 2 regulate microglial function and phagocytosis, impacting Aβ accumulation and subsequent neuroinflammation.[39]

The cellular components analysis in this study reveals a common potential pathogenesis in both IBD and AD through GBA, such as aberrant secretory process and barrier integrity dysfunction. The secretory granule membrane plays a crucial roles in Aâ peptide secretion.[40, 41] The amyloid precursor protein (APP) processed in the Golgi apparatus undergoes sequential cleavages, which involve the beta-site APP-cleaving enzyme 1 (BACE1) and the γ-secretase complex (composed of presenilin 1 and 2, encoded by PSEN1 and PSEN2 genes).[40, 41] Dysregulation of these processes results in abnormal Aβ accumulation and developed neuroinflammation, subsequently neurodegeneration as observed in AD pathogenesis.[40, 41] The tertiary granule membrane reflects altered vesicle trafficking, possibly involving genes related to vesicle transport like VPS35 and VPS36, that can control the level of Aβ peptides.[42] Whereas in IBD, the secretory granules are involved in the release of pro-inflammatory mediators by neutrophils, influenced by genes such as interleukin (IL)-6 and TNF-α.[18, 19] These pro-inflammatory mediators contribute to inflammatory activation in the gut microenvironment. The neuronal plasma membrane and focal adhesions are involved in tissue integrity, and abnormalities in the Neurexin 1 (NRXN1) gene are linked to synaptic dysfunction.[43-45] Overexpression or mutation of the NRXN1 gene is postulated to diminish synaptic plasticity, resulting in memory impairment.[43] The focal adhesions are involved with epithelial adhesion and migration, commonly associated with genes like ITGA6, which has the ability to induce very-early-onset IBD.[46, 47] In addition, the Golgi dysfunction can affect mucin processing due to MUC2 mutations.[48, 49] Impairment in mucus production could affect the intestinal barrier stability, favoring bacterial entry, resulting in microbiome dysbiosis.[49] The changes in nucleoplasm can affect transcriptional regulation of the apolipoprotein E (APOE) gene, influencing Aβ aggregation and neuroinflammation.[40, 50] The alterations in the neuronal plasma membrane can affect synaptic function, with the APOE gene contributing to synaptic plasticity and tau protein abnormalities which impacts membrane stability and cytoplasmic changes which are driven by tau protein, microtubule stabilization and disruption.[44, 45] The extracellular exosome can promote Aβ aggregation and then accelerate the formation of amyloid plaques.[51] In addition, the changes in nucleoplasm may impact tissue repair genes such as NOD2, associated with autophagy dysfunction in the intestines.[30] The plasma membrane is involved in maintaining the integrity of the intestinal epithelial barrier components, such as E-cadherin (CDH1) and tight junction proteins.[3, 52] The cytoplasmic processes often involve cytokine signaling pathways driven by genes like IL-6 and TNF-α.[19, 27]

Co-expression network analysis of IBD and AD associated with MHC Class II activity

In IBD, a key finding is increased epithelial MHC class II expression in response to initial microbial colonization. MHC class II molecules are important for presenting exogenous antigens to immune cells, especially CD4+ T cells, to initiate adaptive responses.[53] Inappropriate immune responses which typically involve activation of CD4+ T cells, particularly Th1 and Th17 subsets of interferon-gamma (IFN-γ) and interleukins (IL-17, IL-21, IL-21.IL-22, IL-26).[53, 54] This suggests that early microbial colonization of the gut induces expression of MHC class II molecules in epithelial cells, which may lead to presentation of microbial antigens to CD4+ T cells.[53, 54] Furthermore, studies have highlighted the importance of histone deacetylase 3 (HDAC3), an enzyme involved in gene regulation, especially for the maintenance of MHC class II expression in intestinal epithelial cells.[53, 55] Loss of HDAC3 reduces MHC class II expression and impairs the regulation of commensal specific CD4+ T cells, leading to an

imbalance between regulatory T cells (Tregs) and pro-inflammatory Th17 cells, with a shift to Th17 dominance. Notably, patients with active IBD are known to have commensal-specific CD4+ T cells that secrete large amounts of IL-17.[53]

Several studies have deduced that a few factors link gut microbiota to AD, such as the role of *Escherichia coli (E. coli)*-derived neurotoxins, the presence of bacterial amyloids, and microbiome-driven alterations in microglial function and neuroinflammation.[55] These studies point out the role of MHC class II molecules in mediating the interactions between the gut microbiota and AD-related neuroinflammation. *E.coli*-derived neurotoxins in Proteobacteria are implicated in neuropathology in AD. These neurotoxins can induce the release of pro-inflammatory cytokines, contributing to systemic inflammation and exacerbating AD pathology.[56] Furthermore, bacterial amyloids produced by various bacterial strains share structural similarities with CNS amyloid.[57, 58] These bacterial amyloids could potentially prime the immune system and induce the misfolding of host proteins, including Aβ in humans.[9, 10, 58] In addition, Aβ deposition may initially occur in the gastrointestinal tract, migrate via the vagus nerve to the brain through the GBA, leading to cognitive impairment.[58] Moreover, activated microglia and reactive astrocytes are characteristic features of neuroinflammation.[55, 58, 59] Dysfunctional microglia, prone to chronic activation, can contribute to neural network damage as the disease progresses.[55]

Protein-protein interaction pathway analysis of IBD and AD associated with positive regulation of leukocyte activation

Protein-protein interaction network highlights the intricate process governing the initiation of immune activation in IBD, driven by a network of genes primarily involved in immune regulation and inflammation. This multifaceted process commences with an inciting event, encompassing genetic predisposition, environmental factors, or infections.[3, 16, 60, 61] This initial trigger disrupts the delicate equilibrium within the gut microbiome, leading to a state of dysbiosis characterized by an excessive presence of pathogenic bacteria at the expense of beneficial ones.[61, 62] This dysbiosis sets the stage for immune activation to unfold. Two key genes, NFKBIZ and CD6, play prominent roles in this cascade.[63, 64] The altered microbial composition subsequently triggers the release of pro-inflammatory cytokines and chemokines, a response orchestrated by genes like CLEC7A and IL-33, as immune cells strive to counteract these changes.[64, 65] This dysregulation of the microbiota and the ensuing immune reactions collectively establish an environment of chronic inflammation within the gastrointestinal tract, perpetuating tissue damage and disrupting the delicate balance of the gut's immune ecosystem.[61] The cascade of immune activation is driven by the recognition of bacterial antigens by antigen-presenting cells, such as dendritic cells and macrophages, which sense and present these antigens to T-cells with a notable emphasis on effector T-cells such as Th1 and Th17.[53, 54] Upon activation, these T-cells subsets produce great quantities of pro-inflammatory cytokines, including TNF-α and IL-17, which then amplifies the inflammatory cascade.[54, 55, 59]

As chronic inflammation is a recognized risk factor for AD, the immune activation seen in IBD may exacerbate or accelerate the development of AD in susceptible individuals.[16, 66] The accumulation of Aâ plaques and neuroinflammation is an AD hallmark.[21] Genetic variants linked to AD such as NR4A3, CD74 and TNFSF13 may contribute to immune activation in the brain.[67-69] Recent studies suggest that T-cells, including CD4+ T-cells could infiltrate the brain in AD by crossing blood brain barrier.[21] This neuroinflammatory process can have systemic impacts through GBA due to the impaired intestinal barrier caused by microbiome dysbiosis, affecting intestinal permeability and subsequently crossing the blood brain barrier.[8, 56] Dysregulation of genes like CD6 is associated with both IBD and AD, and may mediate communication between the CNS and the gut, which then impacts gut function and microbiota composition, potentially contributing to IBD.[9, 63] In addition, interactions were identified in GeneMANIA, offering insights into the interconnected molecular pathways that contribute to the bidirectional pathogenesis of IBD and AD.

Among these interactions, IL-17A and IL-17RA are involved in the IL-17 signaling pathway, known for its role in inflammation, which can potentially link IBD-induced gut inflammation to systemic inflammation associated with AD.[18, 19] Similarly, studies suggested TNFSF18 and TNFRSF18 are key players in T-cell regulation, hinting at a connection between dysregulated immune responses in IBD and AD.[70, 71] TNFRSF1A and DAP interactions are

implicated in inflammation, reflecting chronic inflammation shared between both conditions. TNFAIP3 and TAX1BP1 govern NF-κB regulation, contributing to sustained NF-κB activation, a common denominator in IBD and AD.[72, 73] CD244 and CD48 interactions are suggestive of dysfunctional NK and T cells, common in both diseases.[74, 75] TNFRSF8 and TNFSF8 interactions may participate in monocyte-mediated inflammation in IBD.[76] PATZ1 and RNF4 interactions influence gene expression, possibly affecting immune dysregulation and inflammation in both conditions.[77-79] Cystatin A (CSTA) and transcription factor AP-2 gamma (TFAP2C) interactions impact protease inhibition and transcriptional regulation; it was suggested that this may a gene expression in epithelial and Tau protein, which is relevant to IBD and AD.[80, 81] TAP1 and TAPBP interactions are pivotal in antigen presentation, potentially leading to abnormal immune responses in both diseases.[82] LCP2 and WAS interactions in T-cell signaling may contribute to immune dysregulation seen in IBD and AD.[83, 84] AIP and AHR interactions influence aryl hydrocarbon receptor signaling, impacting immune responses and inflammation in both diseases.[85-87] Finally, CASP1 and NLRP1 interactions are linked to inflammasome activation, which contributes to excessive inflammation in both IBD and AD.[88, 89] However, data analytics approaches still possess their own limitations, and further studies such as *in-vitro* analysis, are still required to verify the current findings **(Figure 3).**

Conclusion

This study postulated that the 10 top DEGs are potentially associated with immune system dysregulation, mainly positive regulation of leukocyte activation. This association would be mediated by the bidirectional GBA between IBD and AD, which is likely involving dysregulated inflammatory responses, such as immune cell trafficking associated with inflammatory activation in IBD and microglia activation in AD, that could lead to neuroinflammation

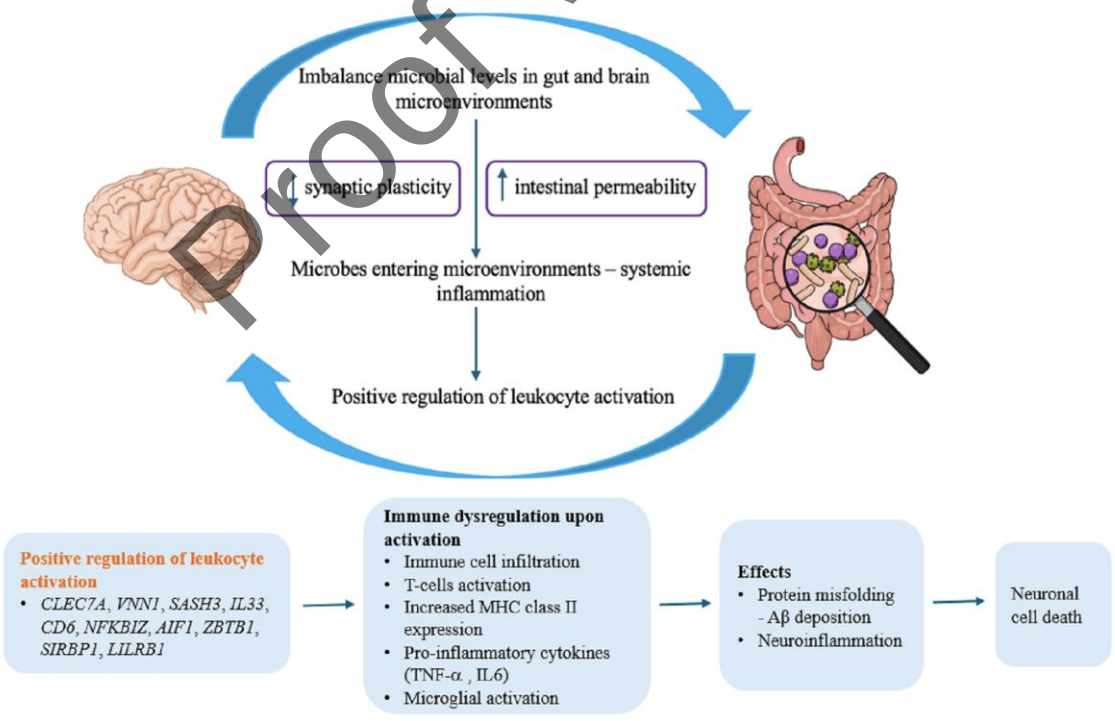

Figure 3. AD and IBD shares pathogenesis mainly through positive regulation of leukocyte activation in gut-brain axis. AD, Alzheimer's disease; IBD, irritable bowel disease.

and neurodegeneration. The data generated in this study provides potential insight into AD therapeutic development by targeting the hub gene and molecular pathways associated with gut microbiome dysbiosis-linked IBD through GBA.

Author contributions

PAR, YPW, EXT, and APKL contributed substantially to the concept and design of this study, acquiring the data, reviewing the literature, and its analysis and interpretation. The authors also contributed substantially to acquiring the data, drafting the manuscript, and editing the manuscript critically for important intellectual content. All authors approved the final version submitted for publication and took responsibility for statements made in the published article.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

Data sharing statement

The data that support the findings of the present study are available from the corresponding author upon request.

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